THE SYNTHESIS OF 5-SUBSTITUTED HYDANTOINS

Ross George Murray

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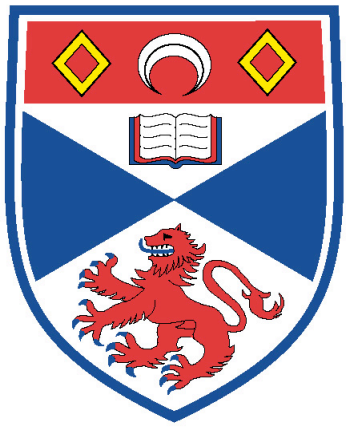
The Synthesis of 5-Substituted Hydantoins



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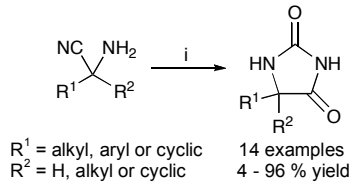
Supervisor: Dr Stuart J. Conway

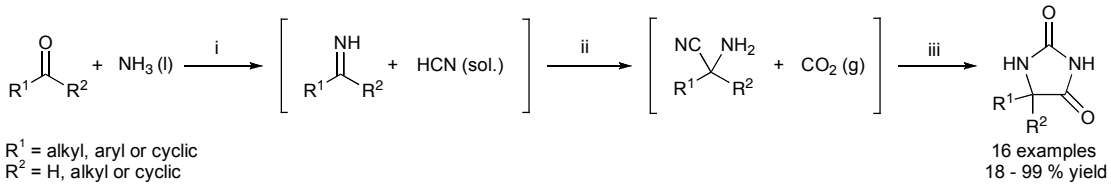
Abstract

The Bucherer-Bergs reaction is a classical multi-component reaction that yields hydantoins, which can be hydrolysed to afford α-amino acids. Hydantoins have many uses in modern organic synthesis, and this moiety has been included in a number of therapeutic agents, which have a wide range of biological activities. Herein, we report a mild synthesis of 5- and 5,5-substituted hydantoins from α-aminonitriles using Hünig's base and carbon dioxide (Scheme **1**). This reaction can be performed in excellent yields, using a variety of organic solvents and is applicable to a range of substrates.



Scheme 1 - Recently developed conditions for the transformation of α-aminonitriles to hydantoins. *Reagents and conditions:* (i) Hünig's base (3 equiv.), CO_2 (g), CH_2Cl_2, RT.

In an extension to the above methodology, a one-pot Lewis acid-catalysed synthesis of hydantoins from ketones has also been developed and optimised in organic media. This reaction can be performed in excellent yields and is suitable for the synthesis of 5- and 5,5-substituted hydantoins (Scheme **2**).



Scheme 2 - Recently developed conditions for the one-pot Lewis acid-catalysed synthesis of hydantoins from ketones. *Reagents and conditions:* (i) $Ga(OTf)_3$ (0.1 equiv.), CH_2Cl_2, - 78 °C, 3 h. (ii) HCN (sol.) (2 equiv.), - 78 °C to RT, 20 h. (iii) Hünig's base (3 equiv.), RT.

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List of Abbreviations

AcOH	acetic acid
AKR	aldo-keto reductase
ALR	aldose reductase
BINOL	1,1'-bis-2-naphthol
cAMP	cyclic adenosine monophosphate
CB	cannabinoid receptor
CDI	carbonyldiimidazole
CNS	central nervous system
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
GPCRs	G-protein-coupled receptors
HLE	human leukocyte elastase
HMBC	heteronuclear multiple bond correlation
^{1}H NMR	proton nuclear magnetic resonance
5-HT	5-hydroxytryptamine
Hünigs base	*N*,*N*-diisopropylethylamine
LFA	lymphocyte function-associated antigen
MCR	multi-component reaction
MeOH	methanol
mGluRs	metabotropic glutamate receptors
MMP	matrix-metallo protein
MW	microwave
NMDA	*N*-methyl-D-aspartate
NR3C4	nuclear human receptor 3C4
PCR	physiological calcium release
[Pd]	palladium
Pd/C	palladium on carbon

PDE	phosphodiesterase
PhMe	toluene
PMA	phophomolybdic acid
PPE	polyphosphoric ester
ppm	parts per million
psi	pound per square inch
py	pyridine
RT	room temperature
RyR	ryanodine receptor
salen	(*R*,*R*)-*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine
SARs	structure activity relationships
$scCO_2$	supercritical CO_2
sp.	sponge
SR	sarcoplasmic reticulum
t-Boc	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	trimethylpropane
TMS	tetramethylsilane
TMSCN	trimethylsilyl cyanide
tolyl	4'-methylphenyl
t_r	retention time
TsCl	tosyl chloride

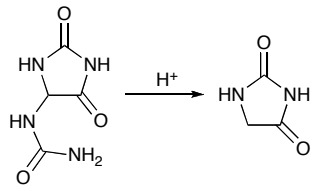
Introduction

1 Introduction

1.1 Hydantoin Chemistry and Natural Occurrence

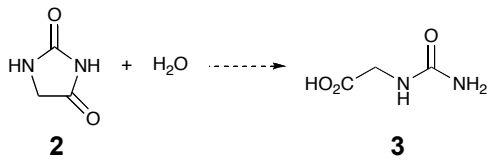
1.1.1 Discovery

The compound hydantoin, or imidazolidine-2,4-dione **2**, was first isolated by Nobel laureate, Adolph von Baeyer, in 1861 from the *hyd*rogenolysis of all*antoin* **1** (Scheme **1**).[1]



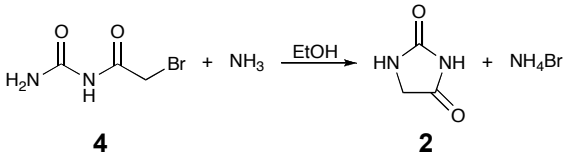
Scheme 1 - Example of Baeyer's synthesis of hydantoin **2** from allantoin **1**.

Several early acyclic structures for hydantoin were proposed, however, Strecker surmised, in 1870, that since ureido (or hydantoic) acid **3** (product of base-catalysed hydrolysis of hydantoin) contains two hydrogen atoms and one oxygen atom more than hydantoin, the ureido acid must result from the cleavage of the cyclic species **2** with the simultaneous addition of water (Scheme **2**).[1,2]



Scheme 2 - Strecker's proposed structures of hydantoin **2** and hydantoic acid **3**.[2]

Further studies by Baeyer also demonstrated that hydantoin could be obtained from bromoacetylurea **4** and Strecker noted that this transformation was best explained through the cyclic ureide representation of hydantoin (Scheme **3**).[2]



Scheme 3 - Baeyer's synthesis of hydantoin **2** from bromoacetylurea **4**.[2]

1.1.2 Hydantoins

Over the last 150 years hydantoin-containing compounds have become increasingly important in the chemical and pharmaceutical industries. Current methodology allows the synthesis of chiral compounds with up to four different points of diversity, through solution- or solid-phase methodologies.[1,3] This technology makes hydantoins highly desirable and interesting scaffolds for further synthetic elaborations. The general compound shown details the possible structures and substitution patterns of hydantoins (Figure **1**).

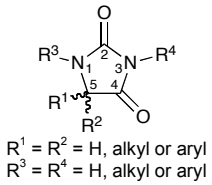
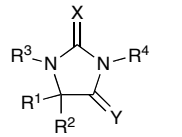


Figure 1 - General structure showing the various points of diversity of the hydantoin scaffold.

Hydantoins are rigid, 5-membered heterocycles that are stable in dilute acid but will form ureido acid salts in basic solution. Generally, hydantoins with substitutents in the *N*-1 and/or the *N*-3 positions are less reactive to hydrolysing or oxidising agents,[2] indicating the increased stability of such derivatives. Hydantoins bearing no *N*-3 substitutents are weakly acidic; hydantoin **2** (Scheme **1**) has a dissociation constant comparable to that of phenol or hydrocyanic acid ($pK_a \sim 9$ or 10). This acidic character is a result of the dissociation of the *N*-3 proton and delocalisation of the negative charge over the two neighbouring carbonyl groups.[2,3]

1.1.3 Thiohydantoins

Closely related analogues of hydantoins are the thiohydantoins, which may have one or both of the carbonyl oxygen atoms exchanged for a sulfur atom. These compounds undergo analogous reactions in the presence of similar reagents.[2] The exchange of oxygen for sulfur gives rise to 2-thio, 4-thio or 2,4-dithio derivatives (Figure **2**) and methodology exists for the mutual interconversion of thiohydantoins and hydantoins with relative ease.[4,5] Of the thiohydantoins, 2-thiohydantoins are the most notable with a large number of medicinal and industrial applications.[6]



$R_1 = R_2 =$ H, alkyl or aryl
$R_3 = R_4 =$ H or alkyl
X = O or S
Y = O or S

Figure 2 - General formulae of 2-thio, 4-thio, or 2,4-dithiohydantoins.

1.1.4 Natural Occurrence of Hydantoins

The hydantoin moiety can be found widely in alkaloids isolated from marine organisms (and to a lesser extent bacteria) and many hydantoin containing alkaloids have been shown to have interesting biological profiles for the treatment of various disorders.[1] Figure **3** shows some of these alkaloids, where examples include the cytotoxic aplysinopsins[7] **5** (*Thorecta* sp.); this range of compounds have also been shown to inhibit neurotransmission.[8] (*E*)-Axinohydantoin **6** (from *Axinella* sp.) and related compounds have been shown to inhibit protein kinase C.[9] The closely related alkaloids mukanadin B **8** (from *Agelas* sp.) and midpacamide **9** (from *Agelas mauritiana*) are members of the oroidin family of alkaloids, which have many therapeutic applications, such as kinase inhibition or antiviral and antifungal activity.[10] The first naturally occurring spironucleoside, (+)-hydantocidin **7** (from *Streptomyces hygroscopicus*) was isolated by fermentation from soil samples collected from Japan in 1990.[11] This compound is a potent non-selective herbicidal natural product which is active in plant growth regulation and shows low toxicity towards mammals.[11,12]

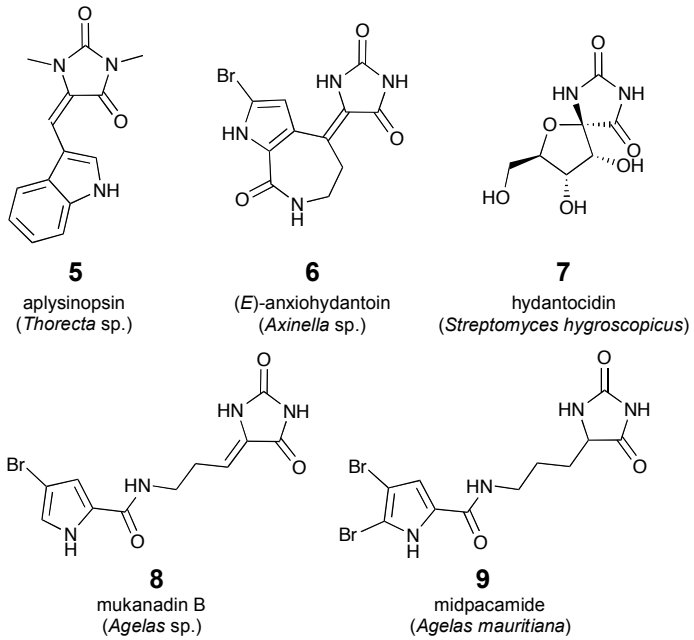


Figure 3 - Hydantoin-containing natural products.[7-12]

1.2 Uses of Hydantoins

1.2.1 Pharmaceutical/Biological Properties

The medicinal uses of hydantoin-containing compounds has become an active area of research in recent years, with novel derivatives being synthesised and tested for activity against various disorders.[1] The hydantoin ring itself possesses no biological activity, but 5- and 5,5-substituted derivatives have a wide range of therapeutic applications.[3] Traditionally hydantoin derivatives have been used as hypnotics, anticonvulsants, antiarrhythmics or as antibacterial agents.[1] The first application of a hydantoin-containing compound as a medicine was the hypnotic nirvanol **10** (Figure **4**), synthesised by Wernecke (1916).[2] This compound was initially reported to possess similar activity to phenylbarbital **11**, with less toxic side effects. However, it was later found that continued use of nirvanol did result in toxic side effects and the drug is now considered a narcotic agent.[1]

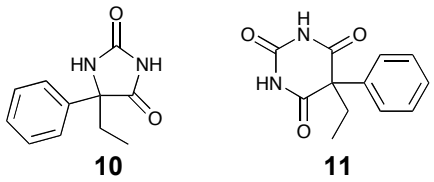


Figure 4 - Example of the structures of nirvanol **10** and phenylbarbital **11**.

The most well known medicinal use of a hydantoin is as the drug phenytoin, which is the sodium salt of 5,5-diphenyl imidazolidine-2,4-dione **12** (Figure **5**). This

compound has a regulatory effect on the central nervous system (CNS) and has been applied successfully to epilepsy sufferers for more than 60 years as an anticonvulsant for the control of grand mal and psychomotor epilepsy. Merrit and Putnam first identified that phenytoin was effective against induced seizures in cats and since becoming available for clinical use it has been applied as the drug of choice for treatment of tonic-clonic seizures.[2]

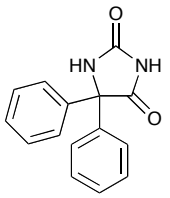


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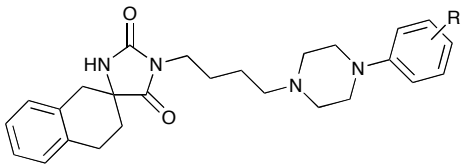
Figure 5 - The structure of phenytoin.

As with nirvanol, phenytoin also suffers from some serious side-effects which include hallucinations, fever, slurred speech and loss of balance; in addition, this drug cannot be administered to patients who are diabetic or have liver disease. Even though this drug has been used for many years, work continues on the synthesis and determination of the structure activity relationships (SARs) of phenytoin derivatives in order to alleviate these problems.[13] However, despite these side effects the drug has recently found a host of new applications due to its antiviral, neuro-protective and cardio-protective properties.[3,14,15]

The neurotransmitter serotonin or 5-hydroxytryptamine (5-HT) regulates the activity of the CNS through a number of receptor sub-types and plays an important role in a wide range of physiological systems. The ability of drugs to act selectively at certain 5-HT receptor subtypes is believed to be effective in the treatment of epilepsy and mood disorders. Pawlowski and co-workers have recently synthesised a range of β-tetralonohydantoins (Figure **6**), which demonstrated high affinity for the 5-HT_{1A} receptor and moderate-to-high affinity for the 5-HT_{2A} receptor.[16]



R = H, 2-OMe, 3-Cl, 2-F, 4-F or 3-CF_3

Figure 6 - The structure of a range of high affinity 5-HT active compounds.[16]

Dantrolene **13** (Figure **7**) is used clinically in the treatment of malignant hyperthermia and inhibits abnormal Ca^{2+} release from the sarcoplasmic reticulum (SR) and physiological Ca^{2+} release (PCR) from skeletal muscle. PCR is controlled by the ryanodine receptor (RyR1)[17] and once malignant hypothermia is triggered, it results in massive intracellular release of Ca^{2+}.[18] Both muscle contraction and relaxation are controlled by the cytoplasmic concentration of Ca^{2+} and derivatives of dantrolene have been synthesised to probe the intracellular release of Ca^{2+} with the aim of determining the Ca^{2+} regulatory systems of muscle cells.[19]

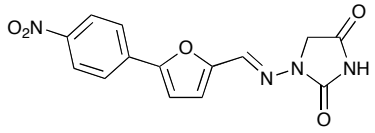


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Figure 7 - The structure of the dantrolene **13**.[19]

An important anti-inflammatory agent is BIRT377 **14** (Figure **8**), which is a potent antagonist of lymphocyte function-associated antigen-1 (LFA-1). The interaction between this enzyme and its ligands (cellular adhesion molecules) play a critical role in leukocyte adhesion. A leukocyte adhesion deficiency can result in poor inflammatory reponses, however, in the case of overactive immune or inflammatory reponses, anti-inflammatory agents like the hydantoin **14** may have great potential applications towards the treatment of autoimmune diseases.[20]

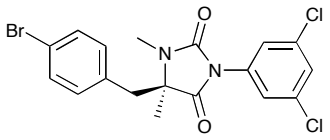

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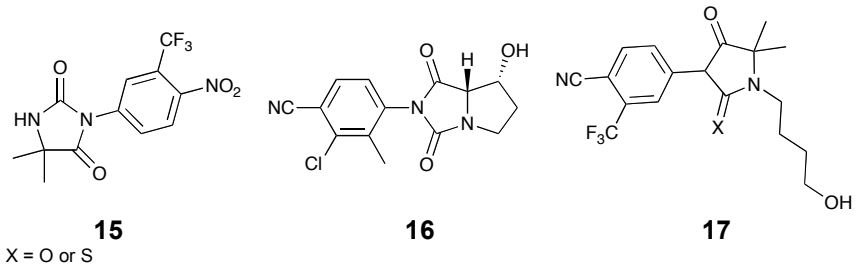
Figure 8 - The structure of the anti-inflammatory agent, BIRT377.

The androgen receptor (NR3C4) is a ligand-binding transcription factor in the nuclear hormone receptor super-family. This receptor is a key molecular target in the growth and progression of prostate cancer as androgen receptor expression is frequently observed in primary and metastatic prostate cancers.[21,22] The receptor is activated by the binding of the androgens, testosterone and dihydrotestosterone; this signals the growth of prostate cancer cells. Androgen receptor agonists and antagonists have been shown to have a variety of biological applications[23] and recent work has shown that a range of hydantoin-based antagonists have promising

activity for the treatment of advanced prostate cancer, these compounds include nilutamide **15**, BMS-564929 **16** and RU 59063 **17** (Figure **9**).

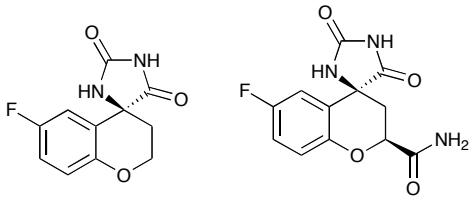


15 **16** **17**

X = O or S

Figure 9 - The structures of promising anti-androgen hydantoin-containing analogues.[22, 23]

Hydantoin-containing compounds have been used to treat the onset of degenerative complications of diabetes, such as neuropathy, nephropathy, retinopathy, cataract formation and cardiovascular disease.[24] Sorbinil **18** (Figure **10**) is an orally active aldose reductase (ALR) inhibitor that contains a spirohydantoin skeleton.[1] Aldose reductase (ALR) belongs to the keto-reductase (AKR) superfamily of enzymes that are responsible for regulation of pro-inflammatory response; the synthesis of metabolically important compounds (like prostaglandins); and the modification of steroids *in vivo*.[25] Aldose reductase is the first enzyme in the polyol pathway, which catalyses the reduction of the aldehyde of glucose to sorbinil, and it is accepted that the polyol pathway plays an important role in the development of degenerative disorders associated with diabetes.[24] The closely related analogue fidarestat **19** has been used to probe binding to ALR1 and ALR2 by these types of compounds.[25]



18 **19**

Figure 10 - The structure of aldose reductase inhibitors sorbinil **18** and fidarestat **19**.[25]

There are many more biological targets that hydantoin containing compounds show activity for, this includes a range of *N*-3 alkyl substituted 5,5-diphenyl hydantoins and thiohydantoins which have a high affinity for the CB_1 cannabinoid receptors.[26] This work is useful for understanding the endocannabinoid system of G-protein coupled receptors (GPCRs). Hydantoin containing compounds have also been found to be inhibitors of matrix metalloproteinases (MMPs),[27] human leukocyte

elastase (HLE),[28] platelet aggregation[29] and of phosphodiesterase type 5 (PDE 5) induced muscle dysfunction.[30]

1.2.3 Other Applications

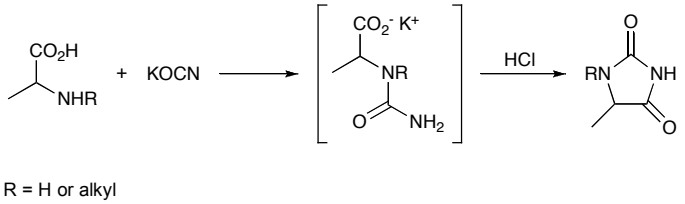
Hydantoins, thiohydantoins and their substitution products also have a number of non-medical uses. In synthesis, hydantoins are important precursors to natural and unnatural α-amino acids, which are vital for the production of pharmaceuticals, agrochemicals and fine chemicals. Hydantoins have also been shown to be effective chiral auxiliaries that promote the synthesis of optically active compounds at the β-position of an acyl group with excellent diastereoselectivity.[31]

In industry, hydantoins, thiohydantoins and their substitution products are used as catalysts and stabiliser agents in polymer chemistry. Other polymers such as epoxy resins, moulds and lacquers have all been developed containing hydantoin moieties while chlorinated hydantoins have been used as bleaching agents, antiseptics and germicides.[2,3]

1.3 Methods of Preparation

1.3.1 Classical Methods of Synthesis

There are many different methods of synthesising hydantoins, depending on the choice of starting materials, however, there are a few classical methods that are still commonly employed. Urech reported the first general method for the synthesis of 5-monosubstituted hydantoins in 1873, where α-amino acids are reacted with potassium cyanate to give α-ureido acids (Scheme **4**). These intermediates are cyclised, under acidic conditions, to yield the desired hydantoins.[1]

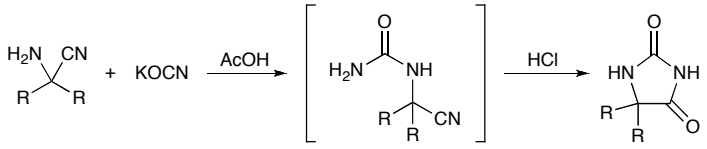


R = H or alkyl

Scheme 4 - The Urech method of synthesising 5-monosubstituted hydantoins.[2]

Small alkyl groups are tolerated on the nitrogen atom of the starting material, which means that a limited range of *N*-1 substituted hydantoins can also be prepared using this method.[2] This methodology was optimised further by Read, in 1922, for the preparation of 5,5-disubstituted hydantoins from α-aminonitriles. The intermediate α-

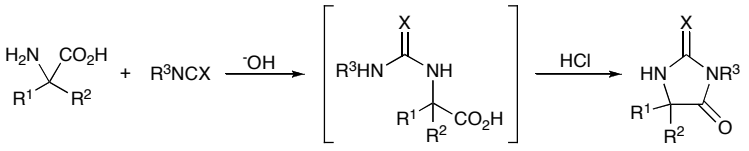
ureido nitrile cyclises under acidic conditions to provide the corresponding hydantoin (Scheme **5**).[32]



R = H, alkyl or aryl

Scheme 5 - The Read method of synthesising 5,5-disubstituted hydantoins.[1,2]

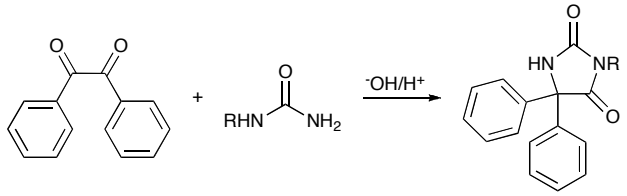
A similar reaction may be performed with α-amino acids and alkyl or aryl isocyanates (or isothiocyanates). The resultant α-ureido (or α-thioureido) acid is cyclised under acidic conditions to furnish the desired *N*-3 substituted hydantoin, or 2-thiohydantoin (Scheme **6**).[2]



R^1 = H, alkyl or aryl
R^2 = alkyl or aryl
R^3 = alkyl or aryl
X = O or S

Scheme 6 - General method for the synthesis of *N*-3 substituted hydantoins or 2-thiohydantoins.[2]

Other classical methods based on the reaction of α-amino acids (or cyanohydrins) with urea are well known.[2,3] However, the condensation of urea with α-dicarbonyl compounds and the Bucherer-Bergs reaction probably represent the most important classical methods employed for the synthesis of hydantoins.[1]



20
R = H, alkyl, aryl

Scheme 7 - Example of the Biltz synthesis of phenytoin.[33]

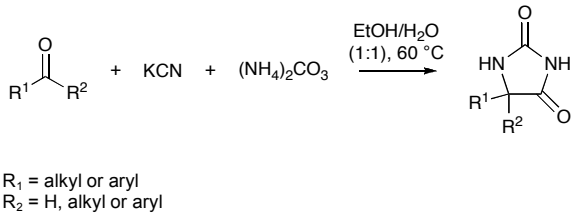
The condensation of benzil **20** and urea(s) is thought to take place through a benzil/benzilic acid type rearrangement,[33] and not a pinacol rearrangement as had been suggested in the early literature.[34] This method is suitable for the synthesis of a range of *N*-3 and/or 5,5-diaryl substituted hydantoins and 2-thiohydantoins, with

the medicinally important derivative phenytoin used as an example (Scheme **7**). This method has been used to produce isotopically labelled derivatives of phenytoin, which are important for metabolic studies.[35]

1.3.2 The Bucherer-Bergs Reaction

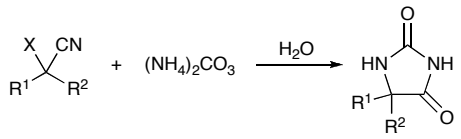
1.3.2.1 Development

The Bucherer-Bergs reaction produces 5- or 5,5-substituted hydantoins *via* a multi-component reaction (MCR) involving carbonyl groups, potassium cyanide and ammonium carbonate (Scheme **8**). The Bucherer-Bergs reaction and other MCRs are convergent reactions, in which three or more starting materials react to form a product, with the product exhibiting functionality from each of the starting materials.



Scheme 8 - Example of the Bucherer-Bergs synthesis of hydantoins.[1-3]

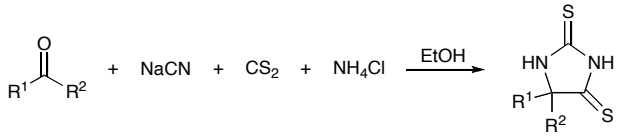
The Bucherer-Bergs reaction has been known since 1934 and is considered to be a general method for the synthesis of 5-substituted hydantoins.[1-3] Reactions of this type were first reported by Ciamician and Silber (1905),[36] but it was work carried out by Bergs that led to a more desirable and shorter route. The Bergs reaction (1929) involved the condensation of carbonyl compounds with the salts, KCN and $(NH_4)_2CO_3$ under a high pressure of CO_2 at 80 °C. This procedure was further modified by Bucherer (1934),[3,36,37] who found that the use of high pressure CO_2 was unnecessary and that the optimum solvent was a water/ethanol (1:1) system (Scheme **8**).[3] Henze found that these modifications increased the substrate range of the reaction where carbonyl derivatives such as ketones, aldehydes, semicarbazones, thiosemicarbazones, oximes, azines, phenylhydrazones, imidazolidines and azomethines were all readily converted into hydantoins using this methodology.[36,38] Bucherer also noted that α-aminonitriles and cyanohydrins were transformed, in excellent yield, to hydantoins in aqueous solution using only ammonium carbonate (Scheme **9**).[39]



R^1 = alkyl or aryl
R^2 = H, alkyl or aryl
X = NH_2 or OH

Scheme 9 - Example of the Bucherer synthesis of hydantoins from α-aminonitriles and cyanohydrins.[39]

Carrington modified the conditions to allow the synthesis of 4-thio and 2,4-dithiohydantoins.[40,41] It was found that substitution of ammonium carbonate for ammonium thiocarbonate gave 4-thiohydantoins and that using carbon disulfide (CS_2), ammonium chloride (NH_4Cl) and sodium cyanide (NaCN) affords 2,4-dithiohydantoins (Scheme **10**).

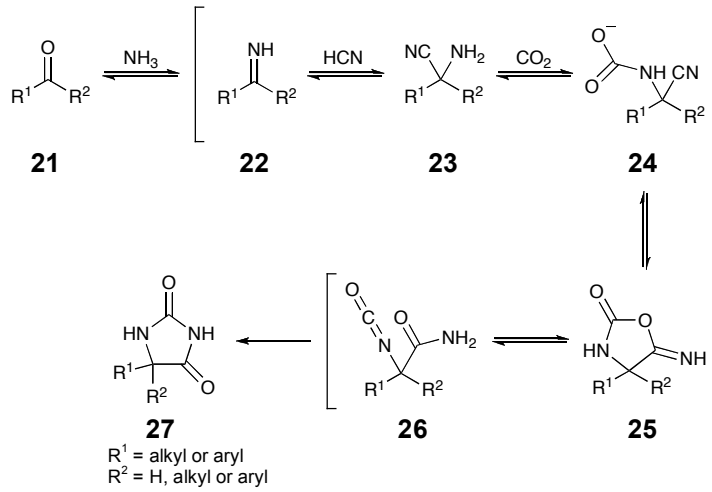


R^1 = alkyl or aryl
R^2 = H, alkyl or aryl

Scheme 10 - Example of the Carrington modification of the Bucherer-Bergs reaction.[41]

1.3.2.2 Mechanism of the Bucherer-Bergs Reaction

Bucherer proposed that the reaction mechanism proceeded initially through the formation of a cyanohydrin and not an imine, however, later thermodynamic and kinetic studies by Commeryas and co-workers[36,37] revealed that the process begins with the formation of the imine **22**, through condensation of a ketone **21** (or aldehyde) and ammonia. The imine **22** undergoes hydrocyantion to furnish the α-aminonitrile **23**, which further reacts with CO_2 to give the intermediate, α-carboxyaminonitrile **24**. This step is followed by intramolecular cyclisation to give 5-imino-2-oxazolidinone **25**, which rearranges to the isocyanatamide intermediate **26**. This intermediate then undergoes cyclisation to give either 5- or 5,5-substitued hydantoins **27** (Scheme **11**).[36,37]

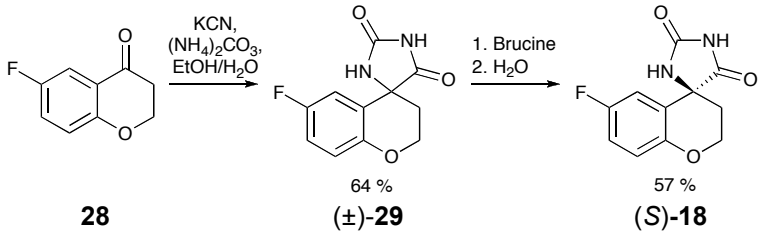


Scheme 11 - The intermediates of the Bucherer-Bergs reaction as proposed by Commeyras and co-workers.[36,37]

Commeyras states that the key intermediate is the α-aminonitrile **23**, which is in equilibrium with the α-carboxyaminonitrile **24**. The stability of the carbamate is dependant on the pH and the concentration of CO_2 in solution. The synthesis of the α-aminonitrile **23** is considered to be the fast step, which is followed by slow formation of the hydantoin **27**. The cyclisation of the carbamate **24** was shown to be the rate-determining step at pH < 9. However, at higher pH the reaction is controlled by fast partitioning of the cyclic intermediate **25** between the α-carboxyaminonitrile **24** and the isocyantamide **26** intermediates.[36,37]

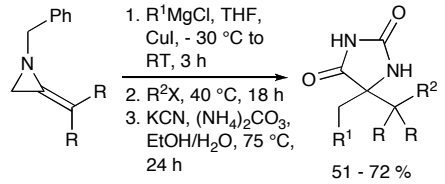
1.3.2.3 Uses of the Bucherer-Bergs Reaction

The Bucherer-Bergs reaction is routinely used for the synthesis of medicinal and industrially important compounds. The reaction has been employed for the industrial production of methionine[37] and the work of Koóš and Mičová has shown that the reaction can be used in carbohydrate chemistry to synthesise novel spironucleosides which may have important biological activity (see Section 1.3.7.1).[42-44] Sarges and co-workers employed the Bucherer-Bergs reaction to synthesise the aldose reductase inhibitor sorbinil **18** from benzopyranone **28** (Scheme **12**).[45] The racemic hydantoin product is then optically resolved using brucine. The chiral resolution occurs as the free base of brucine forms a crystalline complex with sorbinil, whereas the enantiomer of sorbinil only forms the complex with brucine hydrochloride.[45]



Scheme 12 - Conditions employed by Sarges and co-workers for the synthesis of sorbinil.[45]

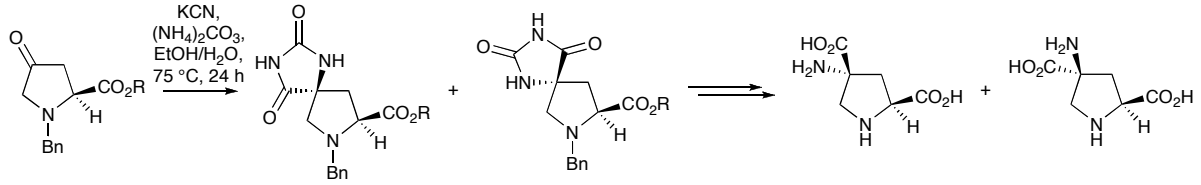
A recent variation of the Bucherer-Bergs reaction which involves the use of organometallic reagents has been reported by Shipman and co-workers (Scheme **13**).[46-48] The process involves generating imine derivatives from methyleneaziridines. *In situ* reaction with the Bucherer-Bergs reagents (KCN, $(NH_4)_2CO_3$ and EtOH) generates three new C-C bonds in the highly branched 5,5-disubstituted hydantoins.



R = H or Me
R^1 = alkyl or aryl
R^2 = alkyl or aryl
X = halogen

Scheme 13 - Conditions employed by Shipman and co-workers for the synthesis of 5,5-disubstituted hydantoins.[46-48]

Tanaka also used the Bucherer-Bergs reaction to synthesise all four diastereoisomers of 4-amino-4-carboxyproline. Scheme **14** demonstrates the synthesis of two of the diastereoisomers; by using the other enantiomer of the ketone, all four diastereoisomers are produced. The diacid products are conformationally restricted analogues of L-glutamic acid, which is one of the major excitatory neurotransmitters in the mammalian CNS. These analogues can be used to probe the requirements for receptor binding of the excitatory amino acid at the active site of the *N*-methyl-D-aspartate (NMDA) receptor.[49]



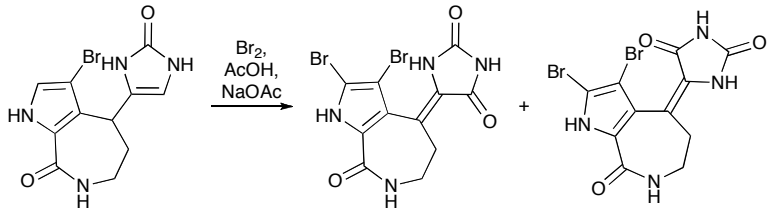
R = Me, Et, *i*-Pr or *t*-Bu.

Scheme 14 - Example of the synthesis of diastereoisomers of 4-amino-4-carboxyproline by Tanaka and co-workers.[49]

1.3.4 Other Syntheses of Hydantoins

1.3.4.1 Conversion of Heterocyclic Compounds to Hydantoins

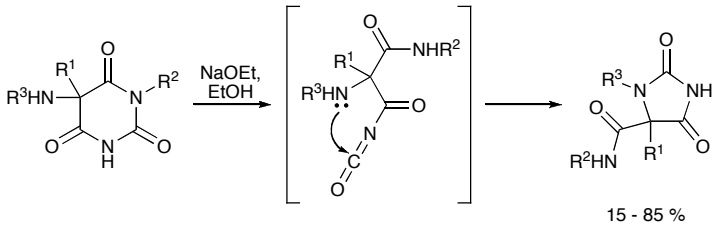
The conversion of other heterocyclic compounds to hydantoins is well known,[2] and can be achieved from 3- or 5-membered heterocycles or from larger heterocycles *via* rearrangement reactions.[1] An example of the conversion of a 5-membered heterocycle to a hydantoin was reported by Sosa and co-workers in the synthesis of axinohydantoin derivatives (Scheme **15**).[9] Pyrroloazepinone **30**, containing a 2-imidazolone group was prepared and oxidised with bromine to furnish the two bromoaxinohydantoin regioisomers, **31** and **32** (*E*/*Z* 45/55).



30 (*Z*)-**31** (*E*)-**32**

Scheme 15 - The synthesis of both regioisomers of bromoaxinohydantoin, highlighting the conversion of 2-imidazolone to hydantoin.[9]

Similarly Gütschow has demonstrated that aminobarbituric acids rearrange, with ring contraction, to give 1,5,5-trisubstituted hydantoins (Scheme **16**).[50] Other rearrangements from pyrimidine derivatives and purines are also known.[1]

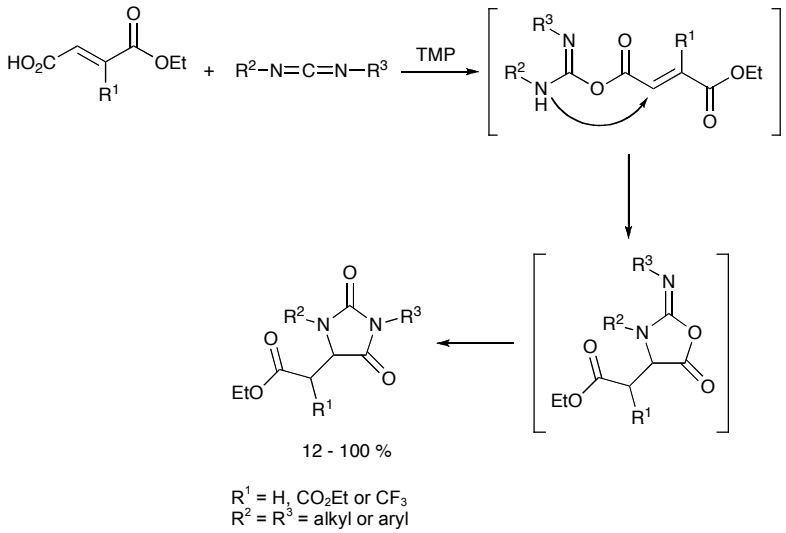


$R^1 = R^2 = R^3$ = alkyl of aryl

Scheme 16 - Example of the aminobarbituric acid/hydantoin rearrangement.[50]

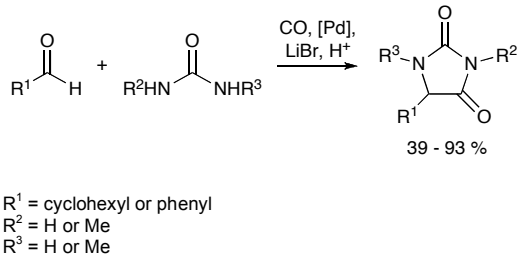
1.3.4.2 Other Methods

The synthesis of hydantoins can be achieved from many different starting materials and by utilising various organic reactions, or combination of reactions. A recent one-pot synthesis reported by Zanda and co-workers demonstrated the synthesis of 1,3,5-trisubstituted hydantoins by a regiospecific, domino condensation/aza michael/*O* to *N* acyl migration of carbodiimides with activated α,β-unsaturated carboxylic acids (Scheme **17**).[51]



Scheme 17 - Example of a new one-pot synthesis of hydantoins, developed by Zanda and co-workers.[51]

Another novel approach for the synthesis of hydantoins, involving a palladium carbonylation reaction, has been developed with the aim of finding new methodology for the synthesis of amino acids. Beller and co-workers have developed an aminocarbonylation reaction where a range of aldehydes and ureas are reacted in the presence of a palladium catalyst; this effects the synthesis of 5-, 3,5- or 1,3,5-substituted hydantoins, depending on the substitution of the urea starting material (Scheme **18**).[52]

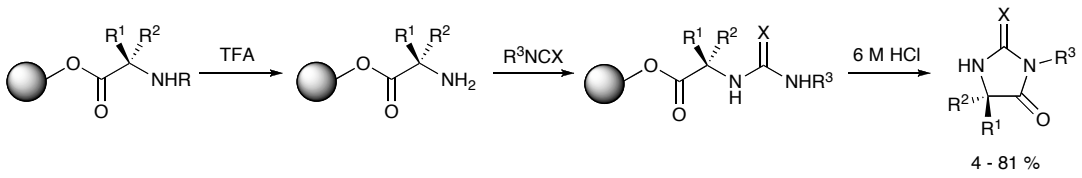


Scheme 18 - Example of Beller's palladium catalysed synthesis of 1,3,5-trisubstituted hydantoins.[52]

1.3.5 Solid Phase Synthesis of Hydantoins

The rapid generation of structurally diverse heterocycles by solid phase synthesis, with the aim of generating new lead compounds for high throughput screening, has become popular in the last 20 years. The hydantoin is an ideal candidate for the generation of combinatorial libraries due to its ease of handling and the diverse substitution patterns that can be achieved in the hydantoin products. The majority of these reactions employ dipeptides as acyclic precursors with cyclisation and cleavage from the solid support typically occuring by either a cycloelimination strategy (cyclisation and simultaneous cleavage) or by separate cyclisation and subsequent cleavage steps. The synthesis of hydantoins from a variety of different solid supports, employing either ester, carbamate or amide linkages has been well documented.[1]

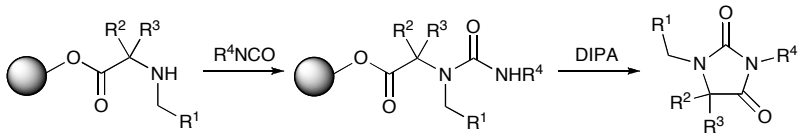
The first reported synthesis of hydantoins and 2-thiohydantoins, *via* solid phase methodology, was described by DeWitt and co-workers who prepared a library of 40 hydantoins using a three-step pathway (Scheme **19**).[53] A range of polystyrene resin, ester-linked amino acids were reacted with isocyanates to give resin bound α-ureido acids. Strongly acidic conditions promoted *N*-cyclisation and simultaneous cleavage of the hydantoin from the resin.



R = *t*-Boc
R_1 = alkyl or aryl
R_2 = H, alkyl or aryl
R_3 = alkyl or aryl
X = O or S.

Scheme 19 - Conditions employed by DeWitt and co-workers for the first demonstration of solid-phase hydantoin synthesis.[53]

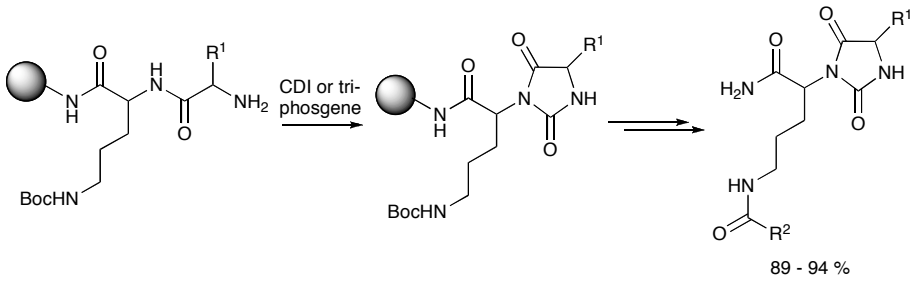
A milder, basic cycloelimination strategy was applied by Kim and co-workers using neat diisopropylamine. This allowed the solid phase synthesis of hydantoins with acid labile groups attached at the substituent positions (Scheme **20**).[54]



R^1 = alkyl or aryl
R^2 = H, alkyl or aryl
R^3 = alkyl or aryl
R^4 = alkyl or aryl

Scheme 20 - Conditions employed by Kim and co-workers for the basic cycloelimination of hydantoins from solid supports.[54]

The cyclisation of the amino amide intermediate, to form resin-bound hydantoins, followed by a separate cleavage step from an amide linked solid support was demonstrated by Nefzi and co-workers.[55,56] The amino acid is reacted with triphosgene or carbonyldiimidazole (CDI) to generate an isocyanate intermediate, which undergoes ring closure to give the hydantoin (Scheme **21**). A separate step involving HF/anisole cleaves the hydantoin from the solid support.



R^1 = alkyl, aryl or alcohol
R^2 = alkyl or aryl

Scheme 21 - Conditions employed by Nefzi and co-workers for the separate cyclisation and cleavage of hydantoins from solid supports.[55,56]

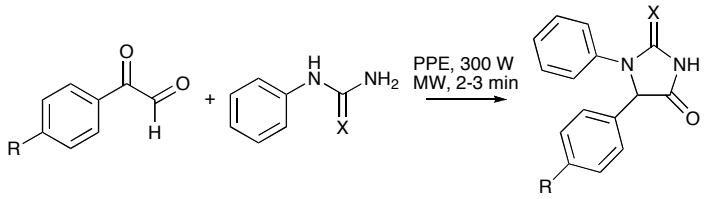
The solid phase synthesis of hydantoins, employing various elimination and release strategies under mild conditions, has been demonstrated to be a practical method for the synthesis of libraries of hydantoins in excellent yield.

1.3.6 Microwave-Assisted Synthesis of Hydantoins

The application of microwave irradiation technology to the synthesis of organic molecules has been known for some time and has become an increasingly popular method of performing organic synthesis due to the dramatic increases in rates of reaction, coupled with increased yields and in some cases, cleaner reaction conditions.[57,58] Microwave-assisted organic synthesis is now an integral part of combinatorial synthesis and drug discovery processes. The use of this technology

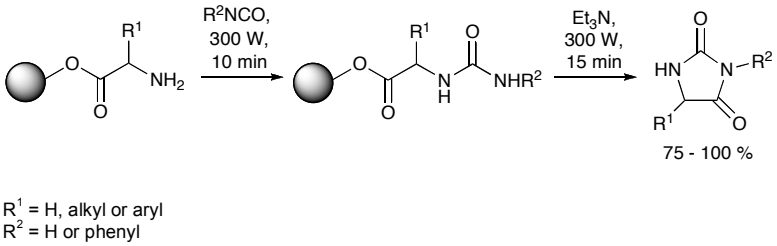
has been applied to the development of efficient methodologies for the production of hydantoins for drug discovery.[59]

The synthesis of 1,5-disubstituted hydantoins, and thiohydantoins, has been reported by Paul and co-workers employing solvent-free microwave-assisted reaction conditions, where a range or arylglyoxals are reacted with phenylureas (or thiophenylureas) using polyphosporic ester (PPE) as reaction mediator (Scheme **22**).[60]



Scheme 22 - Conditions employed by Paul and co-workers for the solvent-free microwave-assisted synthesis of hydantoins.[60]

Parrot and co-workers used an ester-linked solid support for the synthesis of hydantoins from resin bound α-amino acids using microwave-assisted methodology (Scheme **23**). In this process the synthesis of the α-ureido acid intermediate and the cycloelimination reaction was enhanced through use of microwave heating to cleanly synthesise the corresponding hydantoins.[59]



Scheme 23 - Conditions employed by Parrot and co-workers for the solid phase microwave-assisted synthesis of hydantoins.[59]

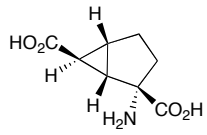
The microwave-assisted synthesis of hydantoins can be performed from a number of staring materials under a variety of conditions and this is an efficient and expediant method for the production of a range of hydantoins.

1.3.7 Asymmetric Synthesis of Hydantoins

The asymmetric synthesis of hydantoins as yet cannot be performed directly from achiral starting materials, however, two methods may be employed for the isolation

of enantiomerically enriched hydantoins. These methods are based on either (1) the separation or preferential synthesis of diastereoisomers or (2) synthesis from chiral starting materials. The synthesis of mixtures of diastereoisomers often gives a low yield of the desired product, coupled with difficult purification procedures, therefore new methods for the asymmetric synthesis of hydantoins are desirable. In order to develop more efficient methods for the synthesis of enantiomerically enriched hydantoins, synthesis from chiral and achiral starting materials has become an active area of research in recent years.[1,3]

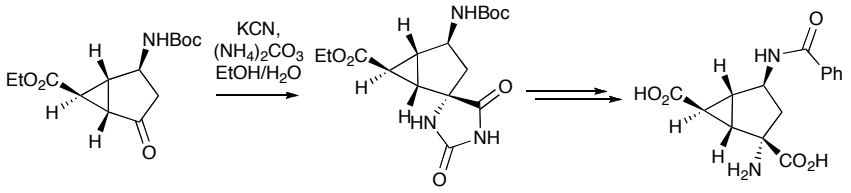
1.3.7.1 Synthesis and Separation of Diastereoisomers



33

Figure 11 - The structure of LY354740.

The asymmetric synthesis of hydantoins *via* the separation of mixtures of diastereoisomers has been applied to the synthesis of various α-amino acid derivatives. LY354740 (**33**) (Figure **11**) shows promising anxiolytic properties and is a conformationally constrained analogue of glutamate, which is a potent agonist for group II cyclic adenosine mono-phosphate (cAMP)-coupled metabotropic glutamate receptors (mGluRs).[61] Miller recently described the synthesis of 4-acylamino analogues of LY354740 through the diastereoselective synthesis of α-amino acids from hydantoins.[62] The isolation of the desired hydantoin diastereoisomer **35** occurred in 60 % (96 % ee) *via* a Bucherer-Bergs reaction from ketone **34**. The hydantoin was later hydrolysed to the corresponding α-amino acid **36** (Scheme **24**).

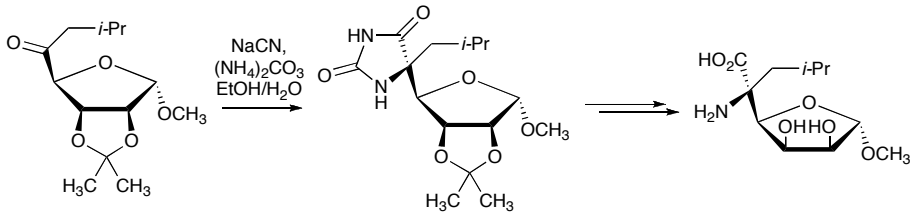


34 **35** **36**

Scheme 24 - The synthesis of 4-acylamino analogues of LY354740.[62]

Kóoš and Mičová described another example of the synthesis of enantiomerically-enriched hydantoins *via* separation of diastereoisomers for the synthesis of sugar α-amino acids, which again utilised the Bucherer-Bergs reaction. Prior to this work,

only a very limited number of sugar derivatives had been applied to the Bucherer-Bergs reaction. With the aim of developing new glycosidase inhibitors, compound **38** was synthesised in poor yield from ketone **37** and only moderate diastereoisomeric excess (de 4/1). Further transformations furnished the sugar α-amino acid **39** (Scheme **25**).[43]

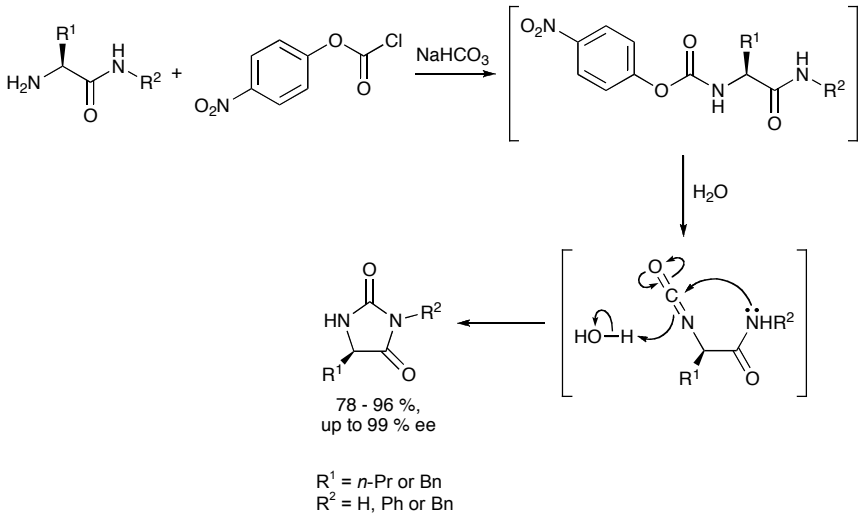


37 **38** **39**

Scheme 25 - The synthesis of novel sugar α-amino acids, *via* diastereoselective separation of hydantoins.[43]

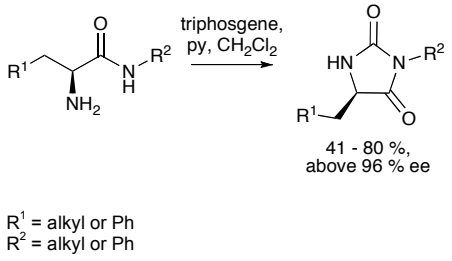
1.3.7.3 Synthesis from Chiral Starting Materials

The synthesis of enantiopure hyantoins *via* solid-phase methodology has already been demonstrated from resin bound enantiopure staring materials (see Section 1.3.5). In an analogous solution-based reaction Suyama and co-workers used enantiopure α-amino amides to generate an isocyanatamide intermediate, which readily cyclised to give optically pure 3,5-disubstituted hydantoins in high enantiomeric excess (Scheme **26**).[63] The formation of the nitrophenyl carbamate is essential as these compounds readily generate isocyanates under basic conditions. The compound cyclises through intramoleculer attack by the amide nitrogen to give the hydantoin product with stereochemistry retained throughout.



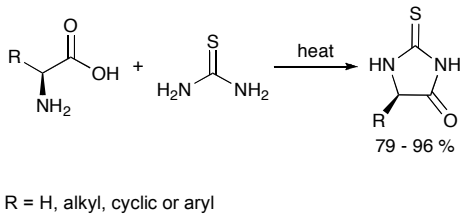
Scheme 26 - Conditions employed by Suyama and co-workers for the synthesis of optically pure hydantoins.[63]

Cuny and co-workers reported another similar method, where enantiomerically pure α-amino amides were reacted with triphosgene to furnish hydantoins with excellent enantiomeric excess (Scheme **27**).[64]



Scheme 27 - Conditions utlilised by Cuny and co-workers for the synthesis of optically pure hydantoins.[64]

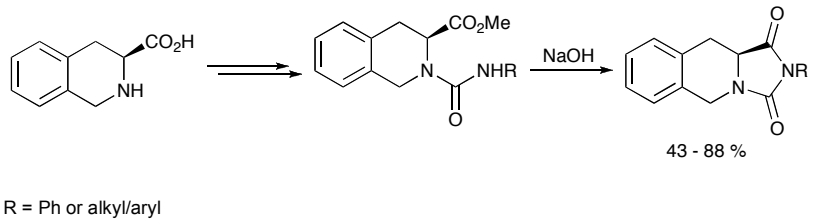
Wang and co-workers have developed a simple solvent free synthesis of enantiopure 2-thiohydantoins through reaction of α-amino acids and thiourea (Scheme **28**).[6]



Scheme 28 - Conditions utlilised by Wang and co-workers for the synthesis of optically pure 2-thiohydantoins.[6]

With the hope of combining bulky aromatic moieties with hydantoins, Charton and co-workers developed a solution phase synthesis of a range of enantiomerically

pure tetrahydroisoquinolone-hydantoins for drug discovery (Scheme **29**).[65] The process began with tetrahydroisoquinoline-carboxylic acid, which was transformed to the urea/ester intermediate in 4 steps. Cyclisation, under basic conditions furnished the desired polycyclic product.

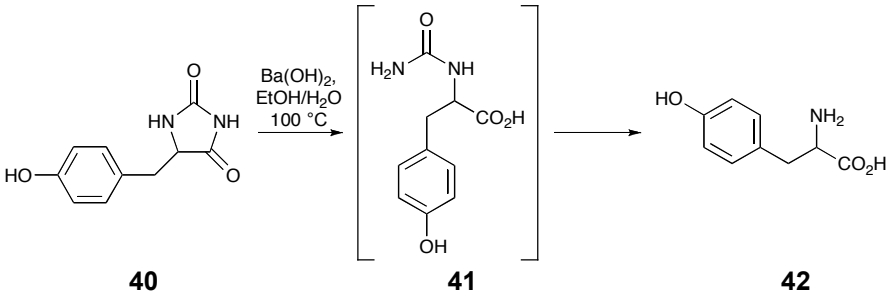


Scheme 29 - Conditions employed by Charton and co-workers for the synthesis of optically pure tetrahydroisoquioline-hydantoin derivatives.[65]

1.4 Reactivity of Hydantoins

1.4.1 Hydrolysis of Hydantoins

The production of α-amino acids is possible from the hydrolysis of hydantoins (or thiohydantoins) in either acidic or basic media, or by enzymes. Hydantoins readily hydrolyse in base, however, acidic conditions need to be more extreme. For base catalysed hydrolysis of hydantoin **40**, the initial product is the ureido acid **41** (or thioureido acid), which is further hydrolysed to an α-amino acid, like tyrosine **42** (Scheme **30**).[1-3] The reaction can also be applied to *N*-1 substituted hydantoins, for the synthesis of corresponding *N*-substituted α-amino acids. This is an extremely important reaction as it can be used to produce unnatural α-amino acids that cannot be synthesised by any other means.

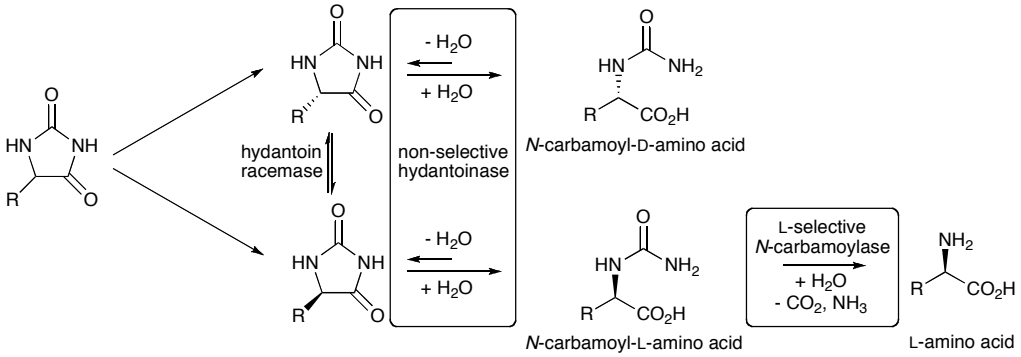


40 **41** **42**

Scheme 30 - Example of the hydrolysis of a hydantoin in basic media to give (±)-tyrosine **42**.[2]

The production of enantiomerically pure α-amino acids by enzymatic biocatalytic conversion of racemic 5-mono substituted hydantoins, in certain bacteria, has been known for some time and has great potential applications in the production of natural and unnatural α-amino acids.[66] The biocatalytic pathway involves two consecutive

hydrolysis steps: a non-selective hydantoinase, and a selective *N*-carbamoylamino acid amidohydrolyase that furnishes the desired α-amino acid enantiomer. Depending on the desired enantiomer, this process may be fine tuned to produce either D- or L-α-amino acids. This pathway may also contain a hydantoin racemase enzyme, which means that theoretically a 100 % conversion of racemic hydantoins to enantiopure α-amino acids may be achieved (Scheme **31**).[66,67]

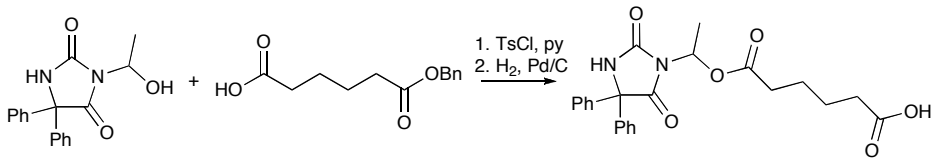


Scheme 31 - Example of the biocatalytic conversion of racemic hydantoins to enantiomerically pure α-amino acids.[67]

The hydrolysis of hydantoins is an extremely important transformation, which may be performed reliably with the use of enzymes or solution-based reagents to produce the industrially important products, α-amino acids.

1.4.2 *N*-Alkylation of Hydantoins

The introduction of substitutents at the *N*-3 position of the hydantoin ring may be accomplished with ease using alkyl halides in alkaline solution. However, the synthesis of *N*-1 monosubstituted hydantoins cannot be achieved through direct alkylation unless the C-5 position is an alkene.[2] The favourable position of the *N*-3 nitrogen between the two activating carbonyl groups explains this pattern of reactivity. Alkylation reactions at the *N*-3 position have also been carried out *via* a Mitsunobu coupling and hydantoins containing only an *N*-1 substituent can be prepared through a suitable protecting group strategy.[1,2,68] The alkylation of hydantoin derivatives is important as the pharmaceutical properties of hydantoins can be varied significantly due to the introduction of substituents at either nitrogen position. An example of this is the synthesis of potential water-soluble *N*-3-substituted derivatives of phenytoin (**45**) from hydantoin **43** and mono-protected acid **44** by Bosch and co-workers (Scheme **32**).[69]

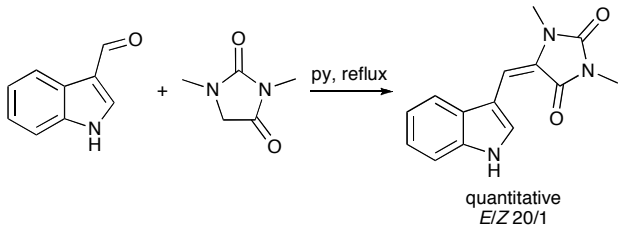


43 **44** **45**

Scheme 32 - Example of the synthesis of potential water-soluble derivatives of phenytoin by Bosch and co-workers.[69]

1.4.3 Aldol-Type Reactions

The synthesis of C-5 unsaturated hydantoin (or 2-thiohydantoin) derivatives can be achieved by reacting aromatic aldehydes with hydantoins bearing no substituents at the C-5 position. This reaction can be performed under either very acidic conditions[2] or by refluxing in pyridine.[1] This type of reaction was used by Pietra and co-workers to synthesise aplysinospsin **5** by reacting the indole **46** with *N*,*N*-dimethyl imidazolidine-2,4-dione **47** (Scheme **33**).[70]

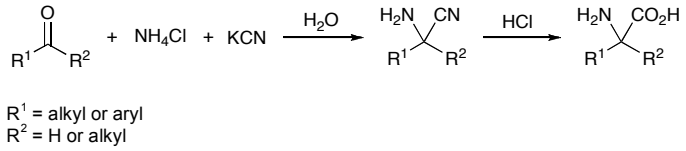


46 **47** (*E*)-**5**

Scheme 33 - Example of the synthesis of aplysinospsin **5** by Pietra and co-workers.[70]

1.5 The Strecker Reaction

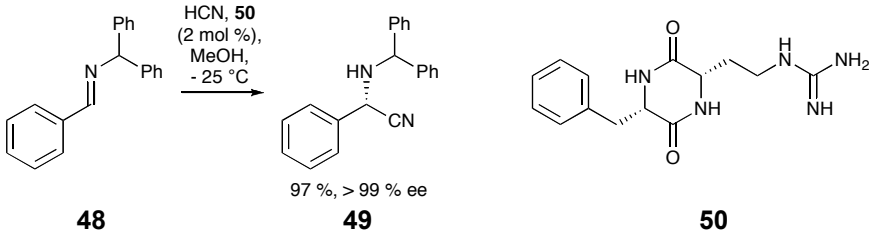
The Strecker reaction (1850) involves the condensation of an aldehyde (or ketone) with ammonia and a cyanide source to give an α-aminonitrile, and is closely related to the Bucherer-Bergs reaction. This reaction is one of the classical methods of preparing α-amino acids as α-aminonitriles can be readily hydrolysed in a separate step to provide the corresponding α-amino acids (Scheme **34**). The product of the Strecker reaction is also one of the intermediates in the Bucherer-Bergs synthesis, and the recent successful development of various asymmetric Strecker conditions,[71] has increased the need to attempt an asymmetric modification to the Bucherer-Bergs reaction.



Scheme 34 - Example of the Strecker synthesis of α-aminonitriles and α-amino acids.

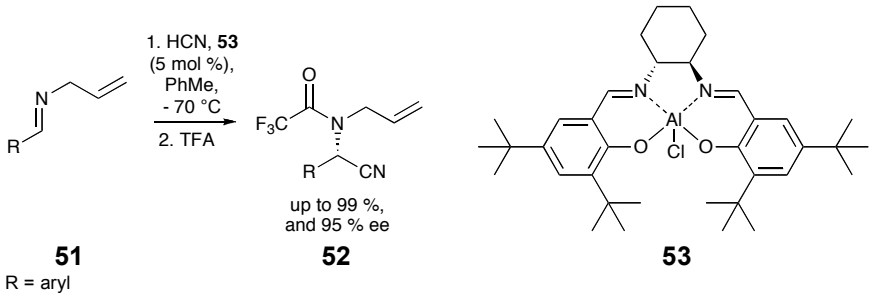
Due to the importance of natural and unnatural α-amino acids (see Section 1.2.3), recent research on the Strecker reaction by many leading scientists, has resulted in the development of a catalytic asymmetric Strecker reaction, where the use of both organic and metal-based chiral Lewis acid catalysts has led to a high-yielding process with outstanding enantioselectivity.[71]

The first asymmetric Strecker reaction was reported by Lipton and co-workers (1996)[72] (Scheme **35**), where a chiral diketopiperazine catalyst **50** was employed to convert aldimines **48** to *N*-substituted α-aminonitriles **49**.



Scheme 35 - Example of the catalyst and conditions Lipton and co-workers used for the development of an asymmetric Strecker reaction.[72]

Since the work of Lipton, many research groups have published similar work noting the conversion of aldehydes and (acyclic or cyclic) ketones to *N*-substituted α-aminonitriles with outsanding yield and enantiomeric excess using a range of organocatalysts. Jacobsen and co-workers developed the first example that employed a metal-based chiral Lewis acid catalyst (an aluminium salen chloride complex **53**) which achieved similarly high yields and enantiomeric excess as the organocatalytic processes (Scheme **36**).[73] Since the work of Jacobsen, the groups of Shibasaki, Hovedya and Vallée have also developed metallo-catalysed reaction systems.[71]



51
R = aryl

52

53

Scheme 36 - Example of the metallo-catalyst and conditions Jacobsen and co-workers used for the development of an asymmetric Strecker reaction.[73]

1.6 Summary

Since the isolation of the first hydantoin by Baeyer in 1861, this group of compounds has been studied extensively. Compounds that possess a hydantoin moiety can be chiral and may possess a varied pattern of substitution, which makes these compounds appealing synthetic targets. Hydantoin-containing alkaloids have been isolated from many marine bio-organisms, and these derivatives have demonstrated novel biological activity. An important application of a hydantoin is as the drug phenytoin, which has been the first choice treatment for certain convulsive disorders for over 60 years. Hydantoin-containing compounds have been developed to treat a vast assortment of medical conditions including viruses, heart problems, cancer, inflammatory response, diabetes, Ca^{2+} cellular control as well as possessing inhibitory action towards a host of CNS processes. Synthetically hydantoins can be hydrolysed to α-amino acids, which have many key medical and industrial applications. Other derivatives have been used as antibacterial agents, herbicides and bleaching agents.

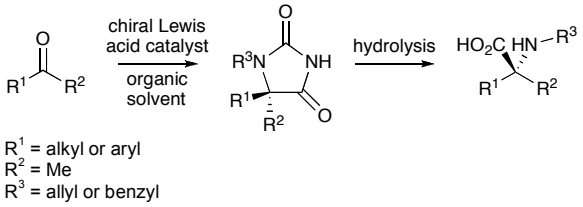
There are many classical methods of synthesising hydantoins, with the Bucherer-Bergs reaction considered to be a general MCR for the synthesis of 5- or 5,5-substituted hydantoins from aldehydes or ketones. This reaction is still frequently applied to the synthesis of novel hydantoin compounds, and new variations of the reaction continue to be developed. The rapid generation of libraries of structurally diverse hydantoins through the use of solid phase and microwave-assisted synthesis has been of great use in drug discovery programs, while new one-pot reactions involving organometallic reagents or palladium catalysis demonstrate the continuing scientific interest in the synthesis of hydantoins. The synthesis of enantiomerically enriched hydantoins has been shown to be possible by solid phase methodology, by the separation of mixtures of diastereoisomers or by synthesis from chiral starting materials, however, the asymmetric synthesis of hydantoins from achiral starting materials has yet to be realised.

Results and Discussion (Part One)

2 Results and Discussion (part one)

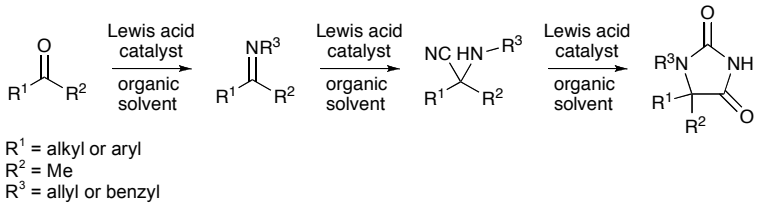
2.1 Aims of the Project

The overall aim of this project was to develop a Lewis acid-catalysed asymmetric variation of the Bucherer-Bergs reaction. As yet, only substrate-controlled versions of the Bucherer-Bergs reaction have been reported concerning the synthesis of enantiomerically enriched hydantoins and their corresponding α-amino acids (see Section **1.3.7**). It was proposed that the use of a chiral Lewis acid catalyst would furnish enantiomerically enriched products from achiral ketones through either a one-pot or stepwise reaction sequence (Scheme **37**).



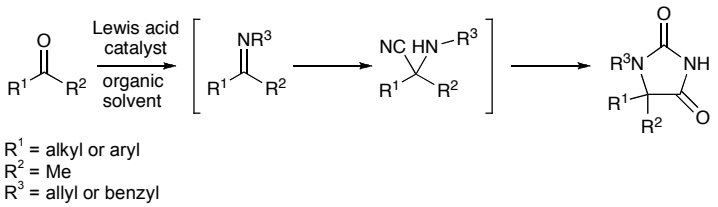
Scheme 37 - The proposed chiral Lewis acid-catalysed synthesis of enantiomerically enriched hydantoins and α-amino acids.

In order to develop the proposed methodology, the Bucherer-Bergs reaction would be divided into three stages. The imine and α-aminonitrile are accepted intermediates in the synthesis of hydantoins through the Bucherer-Bergs reaction[36,37] and the Lewis acid-catalysed synthesis of each these compounds will be investigated as a stepwise series of reactions in organic media (Scheme **38**). As the synthesis of the α-aminonitrile involves the production of a quaternary carbon centre, it is proposed that the use of a chiral Lewis acid catalyst at this stage would give enantiomerically enriched α-aminonitriles and subsequent hydantoins.



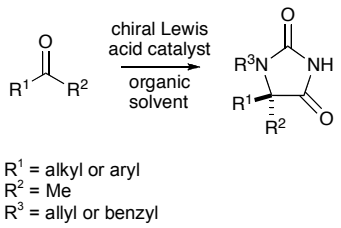
Scheme 38 - The proposed investigation of the stepwise synthesis of each of the intermediates in the Bucherer-Bergs reaction.

It would be operationally convenient if this series of reactions could be optimised into a one-pot procedure for the synthesis of hydantoins (Scheme **39**).



Scheme 39 - The proposed Lewis acid-catalysed one-pot synthesis of hydantoins.

Once suitable racemic conditions have been identified, a chiral Lewis acid catalyst will be applied to the developed methodology in order to determine if enantiomerically enriched hydantoins can be synthesised either directly or indirectly from the achiral substrates (Scheme **40**).



Scheme 40 - The proposed chiral Lewis acid-catalysed synthesis of hydantoins.

The successful development of this methodology would be significant, as this would offer a new method of synthesising biologically important enantiomerically enriched hydantoins and α-amino acids.

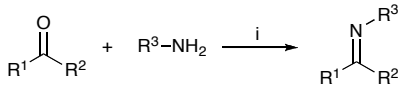
2.2 Existing Methodology

The initial aim was to investigate and optimise a reliable method for the synthesis of a range of imines and α-aminonitriles. Imines and α-aminonitriles that possess no *N*-substituent are unstable and difficult to handle, therefore the synthesis of *N*-substituted imines and α-aminonitriles would be examined. The inclusion of the *N*-substituent would give rise to the synthesis of 1-*N*-protected hydantoins that may be transformed with relative ease to hydantoins with up to four points of diversity. For the synthesis of medicinally important 5,5-disubstituted hydantoins, the desired imines must be derived from ketone starting materials. The use of these substrates may be synthetically challenging as ketones are known to react poorly with primary amines, even in the presence of a Lewis acid catalyst. Ketones that possess large aryl and small alkyl functionality on either side of the carbonyl group would be desired as the greater difference between the size of these groups ensures greater selectivity during asymmetric reactions.[71] Jacobsen, [73-78] Corey[71] and others[71] have

reported the synthesis of *N*-substituted imines and α-aminonitriles. From this work, toluene was selected as a suitable solvent and titanium (IV) chloride was identified from the literature as a Lewis acid that has been employed to catalyse a range of reactions involving imines.[79-83]

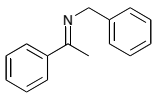
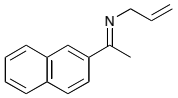
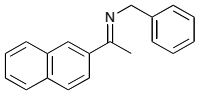
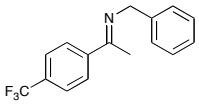
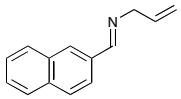
2.3 Investigation of the Synthesis of a Range of *N*-Substituted Imines

Initially, simple substrates were employed to begin with, where acetophenone and benzylamine were reacted to form *N*-benzyl(1-phenylethylidene)amine **54** using titanium (IV) chloride as Lewis acid catalyst, following a method described by Armesto and co-workers.[84] These conditions were further employed to investigate the synthesis of a range of imines (Scheme **41**, Table **1**).



R_1 = Ph, naphthyl or 4'-CF_3Ph.
R_2 = H or Me.
R_3 = allyl or benzyl.

Scheme 41 - The investigation of the synthesis of a range of imines. *Reagents and conditions:* (i) Amine (1.5 equiv.), $TiCl_4$ (0 or 0.02 equiv.) or EtOH (0.5 equiv.), 4 Å mol. sieves, PhMe, RT.

Imine	Compound No.	Conditions	Purification	Conversion (%)[a]	Yield (%)
	**54**	$TiCl_4$, 20 h	crystallised from hexane	65	52
	**55**	$TiCl_4$, 3 h	crystallised from hexane	94	82
		$TiCl_4$, 20 h	crystallised from hexane	90	87[b]
		140 h	no product formed	no product formed	no product formed
	**56**	$TiCl_4$, 22 h	crystallised from hexane	65	60
	**57**	$TiCl_4$, 20 h	conc. under reduced pressure	99	82
	**58**	EtOH, 16 h	crystallised from hexane	100	58

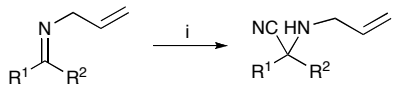
[a] As judged by ^{1}H NMR spectroscopy. [b] Performed on a 20 g scale.

Table 1 - The conditions used for the synthesis of a range of imines.

The synthesis of a range of imines was successful and moderate to excellent conversions and yields were achieved. It was found that crystallisation from hexanes was the best method for purifiying these products. The ketimines all displayed a ~20/1 ratio of stereoisomers, as judged by ^{1}H NMR spectroscopy. It was noted that TLC analysis of the progress of the imine-forming reactions was inconclusive, so all reactions of this type were monitored by ^{1}H NMR spectroscopy. The imine **55** was synthesised in high yield and the reaction could be performed in similar yield on a large scale. Due to the ease of synthesis and isolation, imine **55** would be used in further synthetic steps. Concerning imine **55**, it was demonstrated that no product was formed in the absence of a Lewis acid. The synthesis of the other ketimines proceeded smoothly and could be carried out with ease. The aldehyde-derived α-aminonitrile **58** was synthesised without a Lewis acid, as only ethanol is required to catalyse the reaction. A full conversion was noted, however, it is believed that the moderate yield is a result of product degradation during purification. This range of substrates was used to investigate the synthesis of α-aminonitriles.

2.4 Investigation of the Synthesis of *N*-Substituted α-Aminonitriles

A method reported by Jacobsen noted the transformation of *N*-substituted imines to α-aminonitriles in mild conditions (Scheme **42**).[76] The Jacobsen reaction involves pre-generating a solution of hydrogen cyanide, from TMSCN and methanol, and adding this to the reaction solution. It was hoped that this method would be amenable to Lewis acid-catalysis as this would leave the possibility of developing a chiral Lewis acid-catalysed procedure for the synthesis of enantiomerically enriched products. The exact Jacobsen procedure was attempted before any Lewis acid was included in the reaction conditions (Table **2**).



R^1 = naphthyl
R^2 = Me or H

Scheme 42 - The investigation of the Jacobsen conditions used for the synthesis of α-aminonitriles. *Reagents and conditions:* (i) HCN (sol.) (1.5 equiv.), $TiCl_4$ (0 or 0.02 equiv.), PhMe, 5 °C, for yields see Table **2**.

R^1	R^2	Compound No.	Time (h)	Lewis Acid	Yield (%)
naphthyl	Me	**59**	10	-	93
naphthyl	Me		24	$TiCl_4$	79
naphthyl	Me		40	$TiCl_4$	88[a]
naphthyl	H	**60**	16	$TiCl_4$	90

[a] Reaction performed on a 5 g scale.

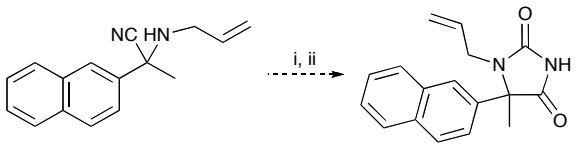
Table 2 - Jacobsen's conditions used for the synthesis of a range of α-aminonitriles.

The synthesis of α-aminonitrile **59** with no Lewis acid proceeded smoothly and the product was isolated in excellent yield. The next step was to investigate if the synthesis could be enhanced with the inclusion of a Lewis acid catalyst. The reaction was performed with titanium (IV) chloride on a larger scale than the uncatalysed reaction, however, it was disappointing that this did not lead to a higher yielding or shorter process. This reaction was repeated and a similar outcome was noted. This demonstrates that titanium (IV) chloride does not catalyse the synthesis of α-aminonitriles. It is expected that the use of a more active catalyst would enhance the transformation of imines to α-aminonitriles, as was noted by Jacobsen

when using the aluminium (salen) chloride catalyst to perform the exact same operation.[84] The Lewis acid-catalysed reaction was also performed using the aldehyde derived imine, *N*-(allyl)-naphthalen-2-ylmethyleneamine **58**. This use of this substrate resulted in an excellent yield of the desired α-aminonitrile **60**.

2.5 Investigation of the Synthesis of Hydantoins from *N*-Substituted α-Aminonitriles

The first attempt at transforming an α-aminonitrile to a hydantoin was performed by passing CO_2 (g) (from dry-ice sublimation) through the reaction solution, in the presence of titanium (IV) chloride (Scheme **43**).



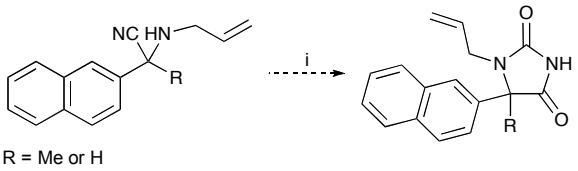
59 **61**

Scheme 43 - The investigation of the synthesis of hydantoin **61** from α-aminonitrile **59**, under a constant flux of CO_2 (g). *Reagents and conditions:* (i) CO_2 (g), $TiCl_4$ (0.04 equiv.), PhMe, RT, 40 h, no product. (ii) CO_2 (g), $TiCl_4$ (0.40 equiv.), CH_2Cl_2, reflux, 50 h, no product.

The expected hydantoin **61** was not synthesised using the conditions described after an extended reaction time. Similar conditions were attempted again with the reaction being performed under reflux in dichoromethane, however, after an extended reaction time (50 h) no transformation was noted. These two examples represent the first attempts at synthesising hydantoins from α-aminonitriles and demonstrate that the desired substrate would not transform as readily as was hoped. Therefore other methods of introducing CO_2 to the reaction solution were investigated.

2.5.1 High Pressure CO_2 Reactions

It is assumed that a higher concentration of CO_2 in the reaction solution would be more favourable for the synthesis of hydantoins. Therefore the synthesis of hydantoins from α-aminonitriles under a high pressure of CO_2 (g) was investigated; it was believed that a high pressure of CO_2 in a sealed system would deliver more CO_2 to the stirred reaction solution. These reactions were carried out in an autoclave in the presence of a titanium (IV) chloride, under 100 psi of CO_2 (g) (Scheme **44**, Table **3**).



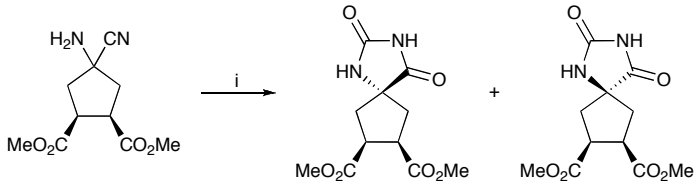
Scheme 44 - The investigation of the synthesis of hydantoins from α-aminonitriles, under a high pressure of CO_2 (g). *Reagents and conditions:* (i) CO_2 (g) (100 psi), PhMe, other conditions see Table **3**.

R	Compound No.	Temp. (°C)	Time (h)	Catalyst	Outcome
Me	**59**	RT	24	$TiCl_4$ (0.25 equiv.)	no product formed
Me		100	24	$TiCl_4$ (0.50 equiv.)	no product formed
Me		100	48	$TiCl_4$ (0.50 equiv.)	no product formed
H	**60**	RT	48	$TiCl_4$ (0.50 equiv.)	no product formed
Me	**59**	100	48	H_2O (2.00 equiv.)	no product formed

Table 3 - The investigation of the synthesis of hydantoins from α-aminonitriles, under a high pressure of CO_2 (g).

The first reaction involved using ambient conditions, but did not yield any hydantoin. The conditions were attempted again with heat and more catalyst, but these conditions did not produce any hydantoin. The aldehyde-derived α-aminonitrile **60** was attempted in order to investigate if the reaction would proceed with this type of substrate. Using similar conditions it was also found that no hydantoin was isolated. Exchanging the Lewis acid for water also had a similar outcome on the reaction. It was found that none of the high-pressure conditions led to the synthesis of the desired hydantoins, and another method of introducing CO_2 to the reaction would have to be investigated.

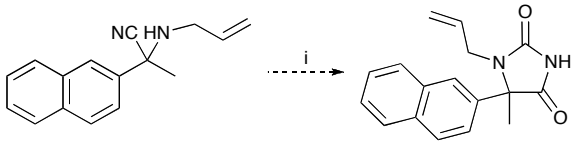
2.5.2 Ammonium Carbonate Reactions



62 **63** **64**

Scheme 45 - The conditions used to synthesise hydantoins **63** and **64**, reported by Acher and co-workers.[86] *Reagents and conditions:* (i) $(NH_4)_2CO_3$ (1.1 equiv.), H_2O, RT, 30 h, 70 % yield.

A method described by Acher and co-workers was attempted where an α-aminonitrile **62** was transformed to a mixture of hydantoin diastereoisomers (**63** and **64**) in good yield using $(NH_4)_2CO_3$ in water (Scheme **45**).[86] This method delivers CO_2 directly to the reaction solution and was performed by Acher with an α-aminonitrile that had no *N*-substituent. It was anticipated that these conditions would be suitable for the transformation of *N*-substituted α-aminonitriles to hydantoins (Scheme **46**, Table **4**).



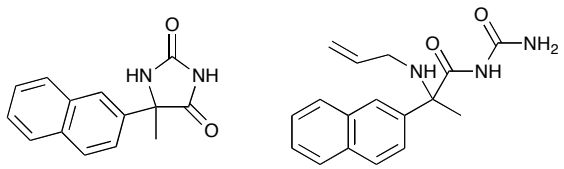
59 **61**

Scheme 46 - The investigation of the synthesis of hydantoin **61**, using ammonium carbonate. *Reagents and conditions:* (i) $(NH_4)_2CO_3$ (1.1 equiv.), other conditions see Table **4**.

Solvent	Lewis Acid	Temp. (°C)	HP CO_2 (100 psi)	Time (h)	Outcome
H_2O	no	RT	no	170	hydantoin formed
PhMe	$TiCl_4$	RT	no	100	no product formed
PhMe	$TiCl_4$	100	no	100	no product formed
PhMe	no	RT	no	100	no product formed
PhMe	$TiCl_4$	100	yes	24	two products isolated
PhMe	$TiCl_4$	100	yes	24	two products isolated

Table 4 - The investigation of the synthesis of hydantoin **61**, using ammonium carbonate.

The Acher conditions resulted in the synthesis of a small amount of hydantoin (3 %) after an extended reaction time, however, it was not the desired hydantoin **61**, instead, it was unsubstituted hydantoin **65** (Figure **12**). The possible mechanism by which this hydantoin was formed will be discussed later. In attempt to take the reaction out of water, the reaction was attempted with toluene as solvent and titanium (IV) chloride. These conditions did not yield any product so the use of heat and omission of Lewis acid was attempted, in repeat procedures, but none of these changes resulted in the synthesis of hydantoin **61**. The use of high pressure CO_2 in an autoclave with similar conditions did lead to the synthesis of two compounds; one was the same unsubstituted hydantoin **65**, the other was (2-allylamino-2-naphthalen-2-ylpropionyl)urea **66** (Figure **12**). Both compounds were isolated in poor yield, but the reaction was repeatable.

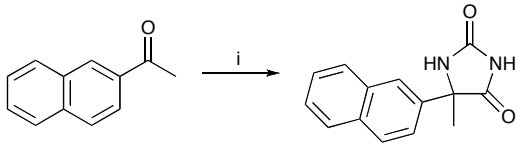


65 **66**

Figure 12 - The structures of **65** and **66**, isolated from the reactions described in Table **4**.

2.5.3 Confirmation of the Structures of 65 and 66

The melting point of hydantoin **65** (246 - 248 °C) matched literature values,[86] however, no NMR data existed in the literature. Therefore hydantoin **65** was synthesised using standard Bucherer-Bergs conditions from ketone **67** in high yield for characterisation purposes (Scheme **47**).



67 **65**

Scheme 47 - The synthesis of hydantoin **65** using standard Bucherer-Bergs reaction conditions. *Reagents and conditions:* (i) KCN (2 equiv.), $(NH_4)_2CO_3$ (4 equiv.), EtOH/H_2O, 60 °C, 24 h, 84 % yield.

Analysis of this compound proved that the hydantoin synthesised in the $(NH_4)_2CO_3$ reactions was the unsubstituted hydantoin **65**. The urea compound, **66** had not been reported in the literature, however, NMR spectroscopic analysis and mass spectrometry data indicate the structure of urea **66** was as shown. The structure of

66 was further analysed by HMBC (^{1}H NMR/^{15}N NMR) 2-D correlation analysis (Figure **13**).

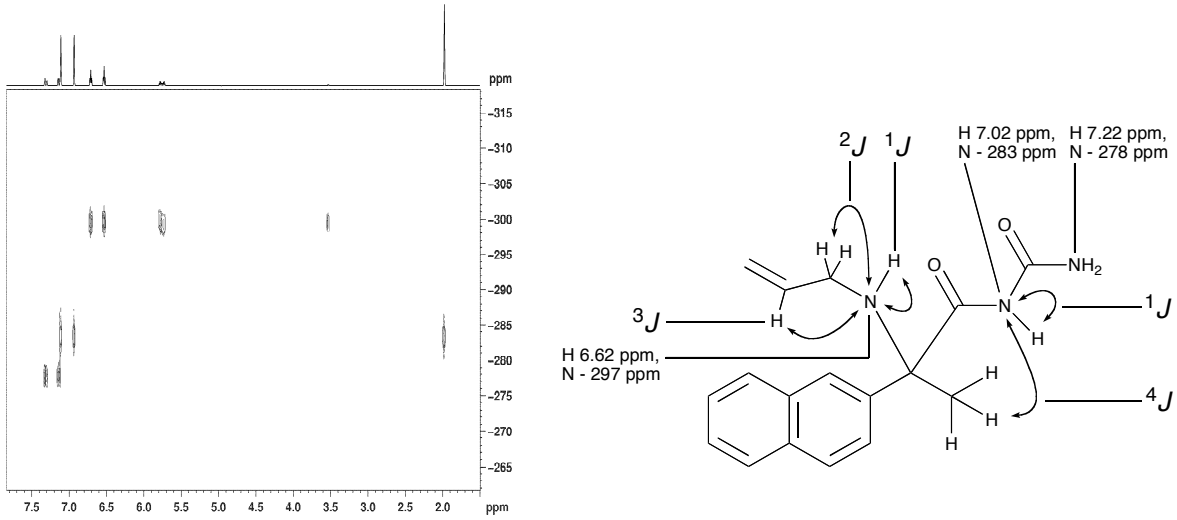


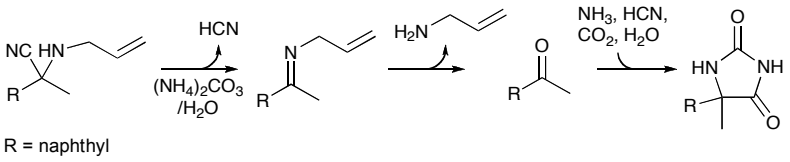
Figure 13 - 500 MHz, HMBC 2D correlation spectra between ^{1}H NMR and ^{15}N NMR of urea **66** and ^{15}N-^{1}H coupling and constants from HMBC analysis.

The cross peaks that appear between -300 and -295 ppm (^{15}N NMR) and 6.5-6.75 ppm (^{1}H NMR) represent a one bond coupling between the N and H of the *N*-allyl group; these peaks are coupled with the allyl peaks of the proton spectrum; ^{15}N-(-) 297 ppm with ^{1}H-3.6 ppm by a two bond distance; ^{15}N-(-)297 ppm with ^{1}H-5.7 ppm by a three bond distance. The chemical shift indicates that these peaks are not next to a carbonyl group, and are attached to the quaternary carbon atom. The peaks which appear between -285 and -280 ppm (^{15}N NMR) and 6.75-7.0 ppm (^{1}H NMR), represent a one bond coupling between the N and the H of the secondary amine (positioned between the two carbonyl groups), this nitrogen also couples with the methyl group (^{15}N-(-)283 ppm with ^{1}H-2.0 ppm by a four atom bond distance). The chemical shift of these peaks indicates that the N is part of an amide group (as expected). The final crosspeak, at -280 to -275 ppm (^{15}N NMR) and 7.0-7.5 ppm (^{1}H NMR) represent the coupling of the NH_2 (^{15}N-(-)278 ppm and ^{1}H-7.22, ^{1}J) which cannot couple with any other protons due to its isolation at the end of the urea fragment. Thorough characterisation of urea **66** has confirmed the structure to be the compound shown in Figure **12**.

2.5.4 Investigation of the Mechanism of Synthesis of 65 and 66

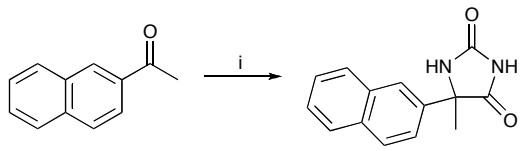
The hydantoin isolated from the water-based reaction probably results from degradation of the starting material. Experience of working with these compounds

has shown that they decompose back to starting materials when exposed to water. This decomposition would give a mixture of ketone, NH_3, HCN and CO_2 in the reaction solution, which, under mild conditions managed to transform a small amount of the ketone into the unsubstituted hydantoin **65** (Scheme **48**).



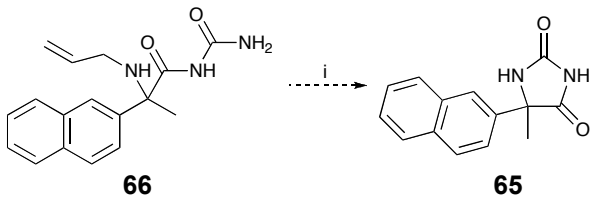
Scheme 48 - The proposed mechanism for the synthesis of hydantoin **65** using the Acher conditions.

The synthesis of hydantoin **65** in the Lewis acid-catalysed conditions was attempted from ketone **67** in order to prove that the ketone would transform to hydantoin in the conditions described. The substrate **67** was transformed to hydantoin in poor yield (5 %) when only 1 equivalent each of KCN and $(NH_3)_2CO_3$ was included (Scheme **49**). The low amount of reactants mirrors the conditions attempted earlier, and a similar yield of hydantoin **65** was synthesised. This result indicates that this mechanism is the most likely by which hydantoin **65** was synthesised in the high-pressure Lewis acid-catalysed reactions.



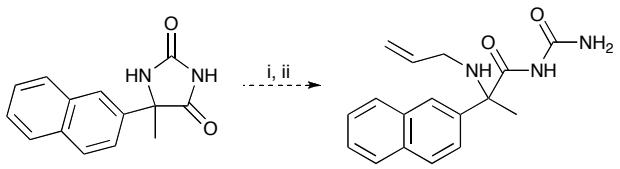
Scheme 49 - The synthesis of **65** from a ketone in the high pressure, Lewis acid-catalysed reaction conditions. *Reagents and conditions:* (i) KCN (1 equiv.), $(NH_4)_2CO_3$ (1 equiv.), CO_2 (g) (100 psi), $TiCl_4$, PhMe, 100 °C, 24 h, 5 % yield.

It was found that urea **66** would not cyclise under similar Lewis acid-catalysed conditions to hydantoin **65** (Scheme **50**), which demonstrates that urea **66** is not an intermediate in the synthesis of hydantoin **65**.



Scheme 50 - Attempted transformation of urea **66** to hydantoin **65** using similar conditions as noted previously. *Reagents and conditions:* (i) $(NH_4)_2CO_3$ (1.1 equiv.), $TiCl_4$, PhMe, CO_2 (g) (100 psi), 100 °C, 24 h, no reaction.

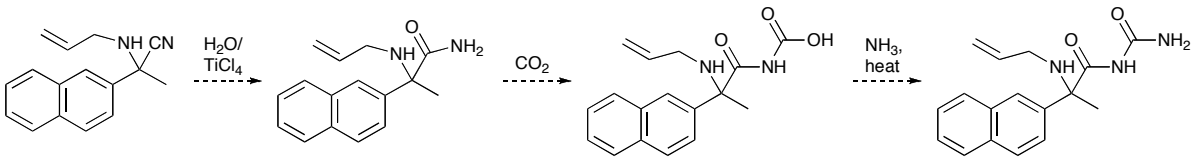
Investigation of the method of synthesis of urea **66** was attempted from hydantoin **65** and allylamine (Scheme **51**). This reaction was attempted twice but did not lead to the synthesis of urea **66**.



65 **66**

Scheme 51 - Attempted synthesis of urea **66** from hydantoin **65** in the conditions described. *Reagents and conditions:* (i) Allylamine (1.5 equiv.), $TiCl_4$, PhMe, CO_2 (g) (100 psi), 100 °C, 24 h, no reaction. (ii) Allylamine (1.5 equiv.), NH_4OH (30% v/v sol.) (1.5 equiv.), $TiCl_4$, PhMe, CO_2 (g) (100 psi), 100 °C, 24 h, no reaction.

It appears that the synthesis of urea **66** occurred independently from hydantoin **65**, which suggests that urea **66** may be formed by hydrolysis of the starting material (Scheme **52**). It was hypothesised that the nitrile may be hydrolysed to the terminal amide **68**. Further reaction with CO_2 could give acid **69**, which, under vigorous conditions may be transformed to the urea **66**. The conversion of an acid to a terminal amide through reaction with NH_3 seems unlikely but this reaction has been performed in good yield at elevated temperatures,[87] so it is possible that urea **66** may result from hydrolysis of α-aminonitrile **59** in the conditions described.



59 **68** **69** **66**

Scheme 52 - Proposed mechanism for the synthesis of urea **66** from α-aminonitrile **59** in the conditions described.

2.5.5 Super Critical CO_2 Reactions

The synthesis of hydantoins in supercritical CO_2 ($scCO_2$) was investigated. A super critical fluid exists at elevated temperatures and pressures as shown in the phase diagram (Figure **14**). At the triple point there are two distinct phases, but as temperature and pressure are increased, the phases become less distinct, until the super critical region is reached, where there is no distinction between the liquid or gas phase, and only the supercritical state exists.[88] A super critical fluid displays properties associated with both gases and liquids. The majority of recent work involving the use of $scCO_2$ as a reaction solvent has been focused on improving

green chemistry,[89,90] whereas the aim of this work was to use $scCO_2$ to achieve a greater saturation of the α-aminonitrile substrate in CO_2. It was proposed that this method would allow the formation of a hydantoin from an α-aminonitrile with greater ease.

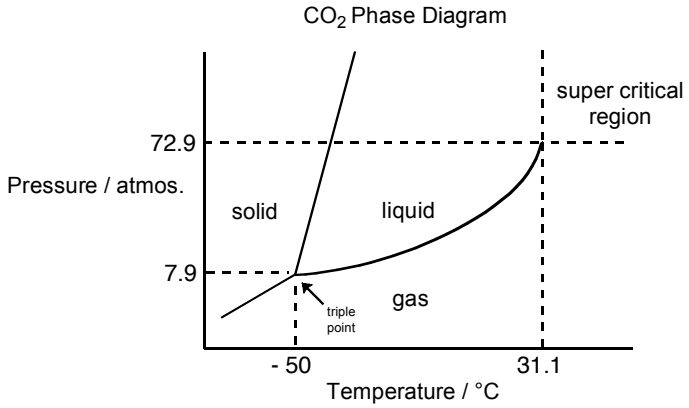
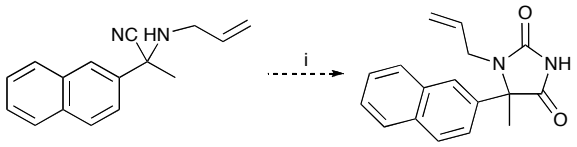


Figure 14 - Phase diagram of CO_2, showing the region where the fluid becomes super critical.[88]

The α-aminonitrile **59** was stirred in a mixture of toluene and $scCO_2$ for 72 h at 120 bar, 80 °C (Scheme **53**). This resulted in the synthesis of the unsubstituted hydantoin **65** in low yield, probably through the same mechanism as has been previously discussed. It was hoped that the increased concentration of CO_2 in the reaction would lead to the synthesis of the desired hydantoins. However, this has not been shown to be possible, and this result, coupled with others, shows that it may not be viable to synthesise hydantoins from *N*-substituted α-aminonitriles.



59 **61**

Scheme 53 - Attempted transformation of α-aminonitrile **59** to hydantoin **61** using $scCO_2$. *Reagents and conditions:* (i) PhMe, $scCO_2$ (120 bar), 80 °C, 72 h, no product.

2.6 Summary

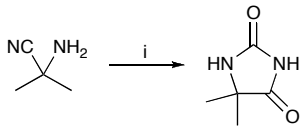
The stepwise development of reaction conditions for the Lewis acid-catalysed synthesis of hydantoins was attempted. The Lewis acid-catalysed synthesis of a range of *N*-substituted imines was achieved in good yields and the products were used to make a range of *N*-substituted α-aminonitriles in excellent yields. The transformation of α-aminonitriles to hydantoins was attempted using various conditions. It was found that bubbling CO_2 through the reaction solution did not result in the synthesis of hydantoins. The use of high pressure CO_2 also gave a similar result. The use of ammonium carbonate as the source of CO_2 did not lead to the synthesis of *N*-allyl hydantoin **61**, the desired product, but did lead to the isolation of unsubstituted hydantoin **65**. The mechanism by which this compound was synthesised was investigated and shown to result from degradation of the α-aminonitrile starting material. The synthesis of hydantoins in $scCO_2$ was also investigated and again unsubstituted hydantoin **65** was isolated, probably through the same mechanism. These results indicate that it may not be possible to synthesise hydantoins from *N*-substituted α-aminonitriles, therefore the investigation of the synthesis of hydantoins from α-aminonitriles with no *N*-substitutent will be investigated.

Results and Discussion (Part Two)

3 Results and Discussion (part two)

3.1 Investigation of the Bucherer Synthesis of Hydantoins from α-Aminonitriles

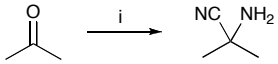
The work described above suggests that the synthesis of hydantoins from *N*-substituted α-aminonitriles does not readily occur, however, it is possible that hydantoins may be synthesised from α-aminonitriles that do not have an *N*-substituent. Bucherer has shown that the transformation of 2-amino-2-methyl propionitrile **70** to 5,5-dimethylimidazolidine-2,4-dione **71** occurs in high yield (Scheme **54**).[39]



70 **71**

Scheme 54 - Conditions reported by Bucherer for the synthesis of **71**.[39] *Reagents and conditions:* (i) H_2O (10 equiv.), CO_2 (g), 16 - 18 °C, 30 mins, 100 % yield.

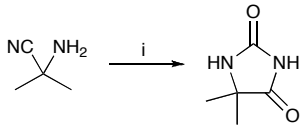
In an attempt to repeat this procedure, the α-aminonitrile **70** was synthesised from acetone (**72**) in excellent yield *via* a Strecker reaction (Scheme **55**). Due to the volatility of the product **70**, great care had to be taken to ensure no loss of material during removal of solvents and distillation.



72 **70**

Scheme 55 - The Strecker conditions used for the synthesis of α-aminonitrile **70**. *Reagents and conditions:* (i) **72** (1.2 equiv.), NH_4Cl (1 equiv.), KCN (1 equiv.), H_2O, RT, 16 h, 99 % yield.

In our hands Bucherer's conditions did not give the high yield reported, where only a 9 % yield (Scheme **56**) was noted compared to Bucherer's quantitative transformation (Scheme **54**). The Bucherer conditions were mirrored as closely as possible however, no exact details of the method of introduction of CO_2 were available, and the differences in yield may result from this.



70 **71**

Scheme 56 - The synthesis of hydantoin **71** using the Bucherer conditions. *Reagents and conditions:* (i) H_2O (10 equiv.), CO_2 (g), 16 - 18 °C, 15 h, 9 % yield.

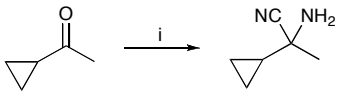
3.2 Optimisation of the Bucherer Conditions for the Synthesis of Hydantoins

As it was not clear how Bucherer was introducing CO_2 into the reaction we hypothesised that a solution of carbonic acid was being formed upon addition of CO_2 to water, and that the CO_2 reacts with the aminonitrile in the form of carbonic acid (CO_3H_2). Therefore optimisation of the Bucherer reaction conditions initially began by investigating the use of a solution of carbonic acid as solvent (Table **5**).

Conditions				Yield (%)
Solvent	**Extra CO_2**	**Heat (°C)**	**Time (h)**	
carbonic acid	CO_2 (g)	last 24 h, 60 °C	48	47
carbonic acid	CO_2 (s) for 48 h	4 °C	72	50
carbonic acid	CO_2 (s)	RT	17	41
carbonic acid	CO_2 (s)	6 h at 60 °C, then RT	18	42
carbonic acid	CO_2 (s)	100 °C	5	20

Table 5 - Conditions attempted in order to increase the yield of hydantoin **71**.

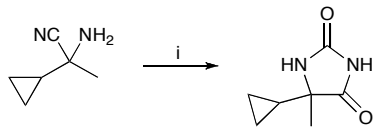
It was found that using a solution of carbonic acid required the addition of extra CO_2 (solid or gas) in order to drive the reactions to completion. Solid CO_2 addition directly into the reaction mixture was preferred, as it was believed this would give a higher concentration of carbonic acid in solution; this is confirmed by the shorter reaction times when using CO_2 (s). It was found that ambient temperatures were more suited to the reaction, as the starting material exhibited signs of degradation when reactions were heated, and cooling resulted in prolonged reaction times. On no occasion could the yield be increased above 50 %. To investigate whether the volatility of the starting material **70** was contributing to the low yields achieved, a less volatile α-aminonitrile, 2-amino-2-cyclopropylpropionitrile **74**, was synthesised from ketone **73** and used under the same reaction conditions (Scheme **57**).



73 **74**

Scheme 57 - Conditions used for the synthesis of α-aminonitrile **74**. *Reagents and conditions:* (i) NH_4Cl (1.06 equiv.), NH_4OH (1.06 equiv.), KCN (1.06 equiv.), H_2O, 4 °C → RT, 20 h, 88 % yield.

The α-aminonitrile **74** could be synthesised and isolated with ease, and was significantly less volatile than the acetone-derived **70**. This substrate was then used in the hydantoin-forming reaction (Scheme **58**).



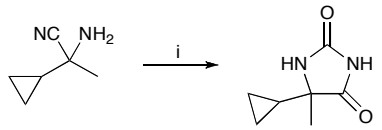
74 **75**

Scheme 58 - Conditions used for the synthesis of hydantoin **75**. *Reagents and conditions:* (i) H_2O, CO_2 (s), 12 h, RT, 50 % yield.

If volatility was responsible for the 50 % yield, the use of the new substrate should lead to an increase in the yield, however, this did not occur and the yield was again 50 %. The similar yields achieved from both reactions, involving different substrates, indicates that two equivalents of the α-aminonitrile may be required for the reaction to proceed. If the α-aminonitrile is unstable in water, hydrolysis would give an aqueous solution of the α-aminonitrile at equilibrium with the ketone, HCN and NH_3. The NH_3 may then act as a base in the reaction solution either by (1) preventing further α-aminonitrile hydrolysis (by raising the pH of reaction solution), or (2) by having an active role (as a proton shuttle) in the reaction. If NH_3 is acting as a proton shuttle, it can be hypothesised that for every molecule of α-aminonitrile **74** that is transformed to hydantoin **75**, one molecule of α-aminonitrile must degrade and release NH_3, which may then go on to play an active role in the protonation and deprotonation of reaction intermediates.

3.2.1 The Use of Various Additives in the Hydantoin-Forming Procedure

To investigate the role of the degradation products, a range of additives were included in the reaction conditions in order to determine if changes in either the concentration of base or pH of the reaction solution would increase the yield of the product. The following Scheme (**59**) and Table (**6**) detail the conditions, additives used and the yields attained for the investigation.



74 **75**

Scheme 59 - The development of new conditions, with the use of additives, for the synthesis of hydantoin **75**. *Reagents and conditions:* (i) H_2O, CO_2 (s), RT, other conditions see Table **6**.

Additive	Equivalents	Time (h)	Yield (%)
potassium cyanide	1	12	40 - 45[a]
	4	10	56
hydrogen cyanide	1	12	16
acetyl chloride	0.1	10	17
potassium cyanide and ammonia	2 and 4 (respectively)	6	68
ammonia	1	12	52
	2	9 - 10	62 - 64[b]
	2.5	10	62
	3	10	65 - 71[a]
	3.5	10	66
	4	8	64 - 70[a]
	5	10	66
	10	10	59

[a] Reaction performed in duplicate. [b] Reaction performed in triplicate.

Table 6 - Investigation of the effects of various additives in the hydantoin-forming reaction.

The use of excess potassium cyanide gave an increased yield of 56 %, whereas it was found that using a solution of hydrogen cyanide or acetyl chloride gave no improvement in yield. Conditions similar to those of the Bucherer-Bergs reaction resulted in a 68 % yield of product. The increased concentration of the α-aminonitrile breakdown products (KCN, NH_3) gave higher yields of hydantoin **75** as this would unbalance the proposed degradation equilibrium, favouring the formation of more α-aminonitrile. This in turn means more product is formed due to a higher proportion of the α-aminonitrile substrate in the reaction solution. The inclusion of acidic additives had a detrimental effect on the yield because the acidic conditions most likely promote the degradation of the α-aminonitrile, meaning less of the substrate is

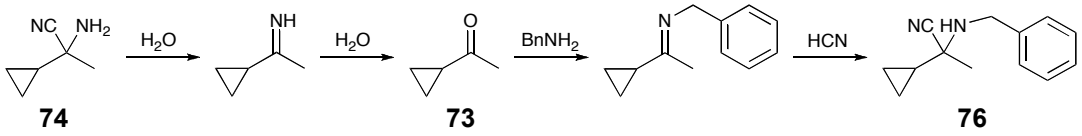
available for transformation to hydantoin. The use of ammonia as an additive was also investigated thoroughly, and though any excess ammonia did give yields above 50 %, it was found that 3 equivalents of ammonia was optimum. This investigation has shown that the yield of product achieved from the hydantoin-forming reaction is improved with the use of a base, therefore a more thorough investigation of various bases with pK_b similar to ammonia (~ 9.21)[91] was required (Table **7**).

Base	pK_b[a]	Equivalents	Time (h)	Yield (%)
benzylamine	9.33[91]	3	3	no product formed
trimethylamine	9.76[91]	3	6	70
		4	6	69
triethylamine	10.8[91]	1	5	44
		2	5	58
		3	5	61
		4	5	58
Hünig's base	11.0[91]	3	6	77
		4	6	75
DBU	~12[92]	1	12	26
		3	11	40
		4	11	34

[a] Measured in H_2O.

Table 7 - Investigation of the effects of various bases, with similar pK_b to ammonia, in the hydantoin-forming reaction.

The use of trimethylamine and Hünig's base gave improved yields for the transformation of α-aminonitriles to hydantoins, with 3 equivalents of Hünig's base giving the highest yields achieved so far. The increased nucleophilicity of the two amine bases compared to NH_3 accounts for the increase in yield, supporting the proton shuttle hypothesis made earlier. An interesting result involved the use of benzylamine, where the expected hydantoin was not formed, but a substituted α-aminonitrile, 2-*N*-(benzylamino)-2-cyclopropylpropionitrile **76** was isolated. The following Scheme (**60**) details the possible path by which the substituted compound **76** was synthesised.



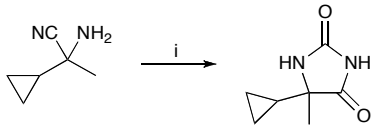
74 **73** **76**

Scheme 60 - Proposed mechanism for the synthesis of the substituted α-aminonitrile **76**, from the conditions described.

It is believed that the starting material is being hydrolysed back to the ketone and then forming the *N*-substituted α-aminonitrile **76** with the more nucleophilic primary amine. As was found in chapter 1, these α-aminonitriles will not react further to form a hydantoin. This result has led to some doubt about the mechanism of the reaction, and if stereochemistry could be maintained in the products. In order to investigate this mechanism further, enantiopure α-aminonitriles would have to be synthesised and reacted under the same conditions. It is probably clear that this mechanism is prevalent in all reactions involving non-tertiary amines, so future reactions would have to be performed with hindered, tertiary amine bases. Secondly, performing the reaction in another solvent may also prevent the hydrolysis of the starting material.

3.2.2 The Synthesis of Hydantoins in Organic Solvent

Next we investigated performing the reaction in organic solvents. We initially selected dichloromethane as it has been shown to be an effective solvent for the catalysed synthesis of α-aminonitriles (Scheme **61**).[93]



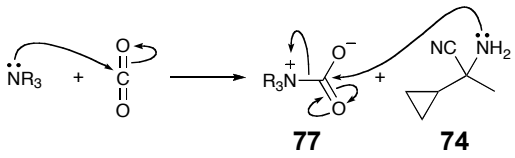
74 **75**

Scheme 61 - Investigation of the use of dichloromethane as solvent for the synthesis of hydantoin **75**. *Reagents and conditions:* (i) Hünig's base (0 or 3 equiv.), CH_2Cl_2, CO_2 (see Table **8**), RT.

CO_2 delivery	Hünig's Base	Time (h)	Yield (%)
solid - direct addition of dry-ice	3 eqiuv.	8	88
gas - from dry-ice sublimation	3 equiv.	12	90
gas - from lecture bottle	3 equiv.	12	85
gas - from dry-ice sublimation	-	20	no product formed

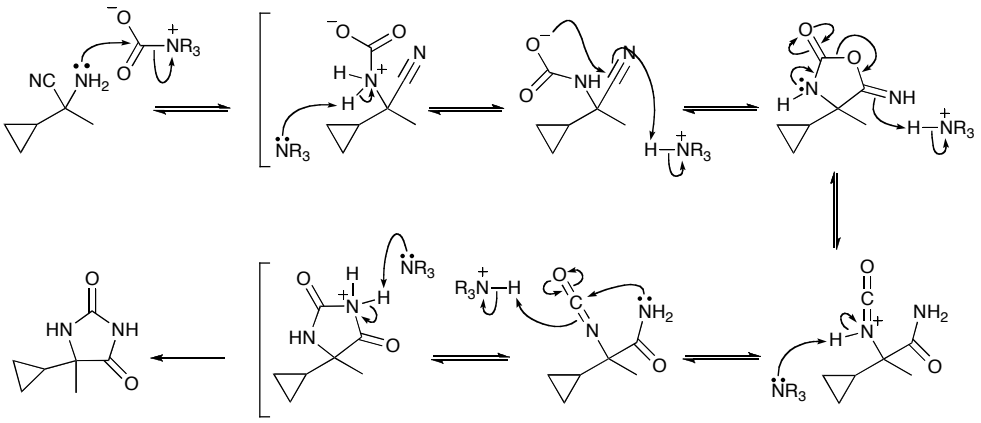
Table 8 - Investigation of the use of dichloromethane as solvent for the synthesis of hydantoin **75**.

The use of dichloromethane as reaction solvent resulted in an increased yield using the standard conditions developed so far (with dry-ice addition). In order to attempt the reaction under dry conditions (not possible with solid CO_2), the delivery of CO_2 was changed from solid to gas, where CO_2 (g) was sublimed from dry-ice, and passed through 4 Å molecular sieves prior to delivery to the reaction solution; the excess gas was then dissipated through a bubbler. This resulted in a slighter higher yield (90 %), but the reaction time had increased, as was expected. The reaction was repeated using CO_2 from a lecture bottle, as this is a dry source of the gas. It was found that under anhydrous conditions, an 85 % yield of product could be obtained. This indicates that an earlier assumption about carbonic acid being the reacting species is not true when using an organic solvent. In dichloromethane it can be argued that the initial addition of CO_2 may occur through the reactive species **77** (Scheme **62**) as the tertiary amine (base) could be more nucleophilic than the α-aminonitrile primary amine. This pattern of reactivity suggests that the tertiary amine would react with CO_2 first, followed by elimination from reactive species **77** through reaction with the α-aminonitrile **74**.



Scheme 62 - Proposed mechanism that may initiate the synthesis of hydantoins from α-aminonitriles using Hünig's base in dichloromethane.

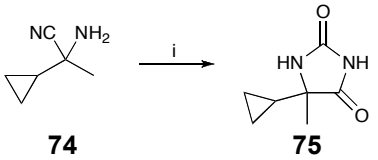
The same conditions were attempted in the absence of a base and it was found that no product was formed. These results show that the inclusion of base is essential when dichloromethane is used as solvent and suggests that hydantoins are formed in dichloromethane by the mechanism proposed below (Scheme **63**).



Scheme 63 - Proposed mechanism of hydantoin synthesis in dichloromethane with Hünig's base.

3.2.3 Investigation of the Scope of Bases that can be Employed in the Developed Methodology

The transformation of α-aminonitriles to hydantoins has been developed into a high-yielding process using dichloromethane as solvent, however, previous optimisation of the ideal base for the reaction was performed using water as solvent. Therefore, the effects of various tertiary amine bases were investigated, in order to determine the ideal base for use in the dichloromethane-solvated reaction. Currently the highest yield for the transformation (90 %, see pg. 56) involves using Hünig's base (3 equiv.) and dichloromethane at RT with 12 h of continuous CO_2 (g) addition. Consequently the following reactions were performed in the exact conditions for the same length of time (Scheme **64**, Table **9**).



74 **75**

Scheme 64 - Substrate and conditions employed to investigate the effects of various tertiary amine bases in the developed methodology with dichloromethane as solvent. *Reagents and conditions:* (i) base (3 equiv.), CO_2 (g), CH_2Cl_2, RT, 12 h.

Base	pK_b[a]	Yield (%)
pyridine	5.20[94]	no product formed
N-methylmorpholine	7.40[91]	no product formed
triallylamine	8.31[94]	no product formed
4-dimethylaminopyridine	9.20[95]	66 - 68
N,*N*-dimethylbutylamine	10.0[91]	25 - 34
N-methylpiperidine	10.1[91]	30 - 35
N,*N*-dimethylisopropylamine	10.3[91]	34 - 37
N-methyldibutylamine	10.5[91]	15 - 34
triethylamine	10.8[91]	75 - 91
tributylamine	10.9[91]	14 - 25
Hünig's base	11.0[91]	90 - 94
DBU	~ 12.0[92]	no product formed

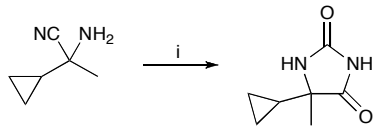
[a] Measured in H_2O.

Table 9 - Range of tertiary amine bases used and yields achieved in the developed methodology, with dichloromethane as solvent.

Each experiment was performed in duplicate. Initially a correlation between the yield and pK_b of the base was investigated, however, it can be seen from Table **9** that such a relationship does not exist. What can be gathered from the table is that amine bases with three small, acyclic groups attached to the nitrogen, with a pK_b of around 11 are optimal, with Hünig's base still the ideal choice. The low yielding results obtained with using cyclic tertiary amines, tributylamine, *N*-methyl dibutylamine, *N*,*N*-dimethylisopropylamine and *N*,*N*-dimethylbutylamine coupled with the impressive triethylamine and Hünig's base results support this hypothesis.

3.2.4 Investigation of the Optimal Solvent for the Transformation of α-Aminonitriles to Hydantoins

The transformation of α-aminonitriles to hydantoins has been shown to be effective in dichloromethane and water when Hünig's base has been included in the reaction conditions. In order to fully understand the effects of differing solvents in the developed methodology, a range of solvents was used under the optimum conditions developed so far (Scheme **65**, Table **10**).



74 **75**

Scheme 65 - Substrate and conditions employed to determine the optimum solvent for the developed methodology. *Reagents and conditions:* (i) Hünig's base (3 equiv.), CO_2 (g), RT, 12 h.

Solvent	Yield (%)
dichloromethane	90 - 94
ethyl acetate	62 - 80
ethanol	71 - 75
no solvent[a]	67 - 74
tetrahydrofuran	57 - 71
diethyl ether	65
acetonitrile	56
Hünig's base[b]	40 - 52
dimethylformamide	50
toluene	45
water	32

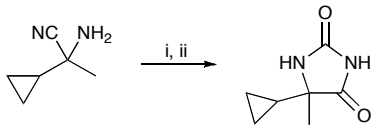
[a] Reaction performed in 3 equiv. of Hünig's base (1.5 mL). [b] Reaction performed in 5 mL of Hünig's base.

Table 10 - Range of solvents used, and yields achieved, in the developed methodology.

The investigation has shown that the ideal solvent for the transformation of α-aminonitriles to hydantoins is dichloromethane, though it can be noted that the transformation occurs in all solvents with ethyl acetate and ethanol also giving high yields. The yield attained for the water reaction (32 %), differs significantly from a similar result discussed earlier (see pg. 55, 77 %). Both of these reactions were performed under the same conditions except that this result involved using gaseous CO_2 and the earlier result involved direct dry-ice addition to the reaction solution. It is believed that the direct addition of dry-ice to the reaction solution produces a more concentrated carbonic acid solution, than bubbling gaseous CO_2 through the reaction solution. As discussed earlier, for the water-based reaction system, the aminonitrile probably reacts with carbonic acid in solution, therefore the reaction which has more CO_2 in solution would give the higher yield of product, as was observed.

3.2.5 Investigation of the Inclusion of a Lewis Acid in the Hydantoin Forming Reaction

The synthesis of hydantoin **75** was carried out with the inclusion of a Lewis acid catalyst, to investigate if this would increase the yield or decrease the reaction time. Gallium (III) triflate was identified in the literature as an effective, mild, non-hydrolysable catalyst for the synthesis of α-aminonitriles, which could be removed from the reaction with ease (Scheme **66**).[96]



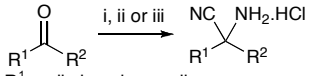
74 **75**

Scheme 66 - The use of Lewis acid catalysis in the optimum hydantoin-forming conditions. *Reagents and conditions:* (i) Ytterium triflate (0.2 equiv.), Hünig's base (3 equiv.), CO_2 (g), CH_2Cl_2, RT, 12 h, 39 % yield. (i) Gallium triflate (0.2 equiv.), Hünig's base (3 equiv.), CO_2 (g), CH_2Cl_2, RT, 12 h, 58 % yield.

The conditions attempted did not lead to an improvement in the yield or reaction time. The reactions did show that the starting materials had been consumed which indicates that perhaps the Lewis acids also catalysed the breakdown of aminonitrile **74**, to the corresponding ketone, which would have been removed during work-up.

3.3 Synthesis of a Range of α-Aminonitriles

In order to test the substrate range that could be applied to the developed methodology, a range of α-aminonitriles was synthesised. This was achieved with great difficulty, using existing variations of the Strecker reaction as described by Chinchon, O'Brien and Matier (Scheme **67**, Table **11**).[97-99]



R^1 = alkyl, aryl or cyclic
R^2 = alkyl or cyclic

Scheme 67 - General conditions used for the synthesis of a range of α-aminonitriles. *Reagents and conditions:* (i)[97] NH_4Cl (1.06 equiv.), NH_4OH (30 % v/v sol.) (1.06 equiv.), KCN (1.06 equiv.), H_2O, 4 °C → RT, 20 h, HCl (2 M sol., ether). (ii)[98] NH_4Cl (1.06 equiv.), NH_4OH (30 % v/v sol.) (1.06 equiv.), KCN (1.06 equiv.), H_2O/MeOH, 4 °C → RT, 20 h, HCl (2 M sol., ether); (iii)[99] NH_4Cl (2 equiv.), KCN (2 equiv.), DMSO/H_2O, RT, 20 h, HCl (2 M sol., ether).

R^1	R^2	Compound No.	Conditions[a]	Yield (%)
Me	Me	**78**	i	30
Et	Me	**79**	i	91
n-pentyl	Me	**80**	ii	82
n-Bu	*n*-Bu	**81**	ii	7
t-Bu	Me	**82**	i	23
cyclopropyl	Me	**83**	i	63
cyclohexyl	Me	**84**	ii	65
cyclopentyl		**85**	ii	77
cyclohexyl		**86**	ii	80
Ph	Me	**87**	iii	46
4-MePh	Me	**88**	iii	24
3-MeOPh	Me	**89**	iii	41
Ph	Et	**90**	iii	24

[a] See scheme **67**.

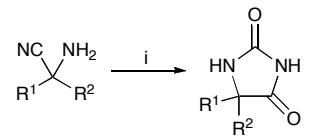
Table 11 - General conditions used for the synthesis of a range of α-aminonitriles.

Unlike earlier syntheses of α-aminonitriles, all of the above substrates were isolated as the hydrochloride salts as this was found to be the most efficient method of purification. The stability of the α-aminonitrile hydrochloride salts, as opposed to free α-aminonitriles, made characterisation and storage of the products more straightforward. Three different reaction conditions were employed to synthesise the range of α-aminonitriles. This was necessary as significant problems occurred when using less water-soluble ketones with water as solvent. Therefore, reactions were performed in water for small, water-soluble, alkyl ketones; in a water/methanol solution for large (bulky or strained) alkyl ketones or in a water/DMSO solution for aryl ketones. The results demonstrate that moderate to good yields could be attained for alkyl ketones, except for **78** (dimethyl), **82** (*t*-butyl/methyl) and **81** (*n*-butyl/*n*-butyl). The volatility of α-aminonitrile **78** led to the loss of some product during removal of the work-up solvent, resulting in a low yield. The low yields associated with the α-aminonitriles **82** (*t*-butyl/methyl) and **81** (*n*-butyl/*n*-butyl) are a combination of two problems; difficulty in converting the α-aminonitriles to

hydrochloride salts; and the steric bulk of the side chains of both ketones, which would hinder attack at the carbonyl carbon by a nucleophile. It was found that only very modest yields of aryl α-aminonitriles could be isolated using conditions i and ii however, the use of a water/DMSO solvent system did lead to the isolation of a range of aryl α-aminonitriles, though only in poor to moderate yield. The synthesis of aryl α-aminonitriles was improved by using the water/DMSO solvent system, however, the electrophilicity of the carbonyl group is reduced by having an aryl group adjacent, and this makes it harder for nucleophiles to react at that carbon center, resulting in low yields for this range of compounds. Further work in this area, by Matier and co-workers concurs with the yields achieved.[99]

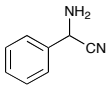
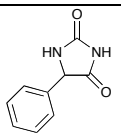
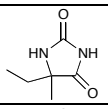
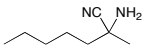
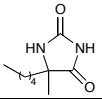
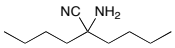
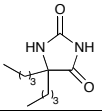
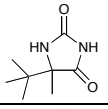
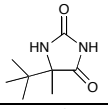
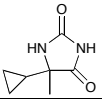
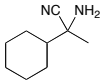
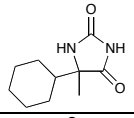
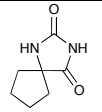
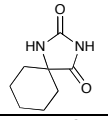
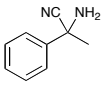
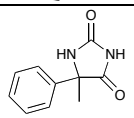
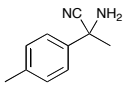
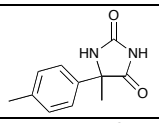
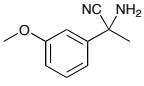
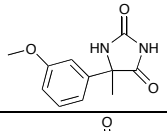
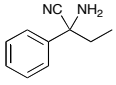
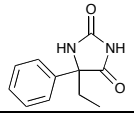
3.4 Investigation of Substrate Range for the α-Aminonitrile to Hydantoin Reaction

The substrate range of the developed methodology was investigated, using the optimum conditions identified. Each α-aminonitrile was either made or purchased as its hydrochloride salt, and was washed with base (1.0 M NaOH) and extracted with diethyl ether to generate the free amine prior to use in the reaction (Scheme **68**, Table **12**).



R^1 = alkyl, aryl or cyclic
R^2 = H, alkyl or cyclic

Scheme 68 - The optimised conditions used for the synthesis of a range of hydantoins. *Reagents and conditions:* (i) Hünig's base (3 equiv.), CO_2 (g), CH_2Cl_2 (or EtOH), RT.

Starting Material	Compound No.	Time (h)	Product	Compound No.	Yield (%)
	**91**	17		**92**	73
	**78**	13		**71**	4
	**79**	16		**93**	14
	**80**	9		**94**	87
	**81**	14		**95**	47
	**82**	18		**96**	no product formed[a]
	**82**	17		**96**	55 - 62[b]
	**83**	12		**75**	90 - 94
	**84**	25		**97**	50
	**85**	21		**98**	30
	**86**	21		**99**	29
	**87**	20		**100**	88 - 90
	**88**	7		**101**	96
	**89**	24		**102**	60
	**90**	12		**103**	62

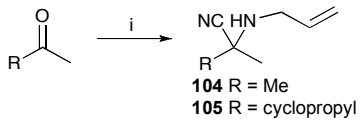
[a] Reaction performed in CH_2Cl_2. [b] Reaction performed in EtOH.

Table 12 - The optimised conditions used for the synthesis of a range of hydantoins.

Table **12** shows that the developed methodology can be applied to a range of substrates, where moderate to excellent yields can be achieved. It was pleasing to note that the reaction could be performed well using an aldehyde-derived α-aminonitrile (**91**); these types of substrates had not been attempted in any of the work previously described. The table shows that the reaction involving the dimethyl hydantoin **71** gave a poor yield. It is believed that the volatility of the starting material (34-36 °C, 4 mbar)[100] may be the primary reason for such a low yield. This effect is also notable in the synthesis of the butanone-derived hyantoin **93** (14 %), though the effects of the volatility of the starting materials are overcome when using α-aminonitriles with longer or larger alkyl groups. No product was formed when using *t*-butyl α-aminonitrile **82** in dichloromethane, however, it was noted while working with the α-aminonitrile that it was insoluble in all organic solvents except alcohols, so the reaction was attempted in ethanol and up to a 62 % yield of hydantoin **96** was noted. The low yields achieved for the spiro and cyclohexyl compounds (**97, 98** and **99**) suggest that there are unfavourable axial interactions in the strained substrates, which prevented a high yield of product; the extended reaction times also suggest this. Aryl α-aminonitriles also performed well in the developed methodology. The low yield of hydantoin **102** (3'-MeOPh/methyl) is probably a result of the electron-rich aromatic ring of the substrate, and the lower yield attained for hydantoin **103** (phenyl/ethyl) is a result of the incresed bulk of the ethyl group, as hydantoin **100** (phenyl/methyl) was synthesised in high yield.

3.5 Re-investigation of the Synthesis of *N*-Allyl Hydantoins

The synthesis of *N*-allyl hydantoins was re-investigated using the optimum conditions developed for the synthesis hydantoins with no *N*-substitutent. In order to establish if this transformation would occur, the α-aminonitriles **104** and **105** were synthesised using literature methods described by Exner and co-workers (Scheme **69**, Table **13**).[101]



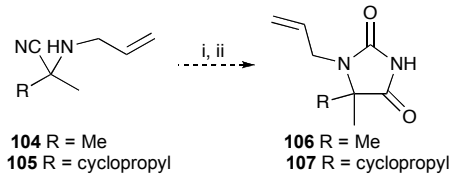
104 R = Me
105 R = cyclopropyl

Scheme 69 - Other conditions used for the synthesis of *N*-allyl α-aminonitriles.[101] *Reagents and conditions:* (i) Allylamine (40 % aq. v/v) (1 equiv.), HCN (sol.) (1 equiv.), RT, other conditions see Table **13**.

R	Compound No.	Time (h)	Yield (%)
Me	**104**	16	65
cyclopropyl	**105**	16	82

Table 13 - Other conditions used for the synthesis of a range of *N*-allyl α-aminonitriles.

Niether of these compounds were synthesised using Lewis acid-catalysed conditions (see chapter 1). However, the synthesis of both α-aminonitriles in the water-based reaction occurred in good yield and these substrates were used to investigate the synthesis of *N*-allyl hydantoins (Scheme **70**).



Scheme 70 - Conditions attempted for the synthesis of *N*-allyl hydantoins. *Reagents and conditions:* (i) **104** (1 equiv.), CO_2 (s), H_2O, RT, 16 h, no product. (ii) **105** (1 equiv.), Hünig's base (3 equiv.), CO_2 (g), CH_2Cl_2, RT, 12 h, no product.

This investigation was attempted prior to the identification of fully optimised reaction conditions (i.e. base, organic solvent) and the initial substrate was used in the water-based conditions, which included the addition of CO_2 (s) to the reaction solution. It was found that none of the expected hydantoin (**106**) was synthesised from these conditions. The investigation was also attempted with the optimised conditions and again none of the desired hydantoin (**107**) was synthesised. This shows that even though high-yielding conditions exist for the synthesis of hydantoins with no *N*-substitutent, the synthesis of *N*-allyl hydantoins in the same conditions is not possible, as was found in chapter 1.

3.6 Summary

The identification of a method for the synthesis of hydantoins from α-aminoitriles by Bucherer was attempted but the procedure could not be repeated in similar yield. This transformation was optimised by investigating the method of introduction of CO_2, the inclusion of various bases and by changing from a water-based to an organic-based reaction. The ideal conditions developed involved transforming α-aminonitrile **74** to hydantoin **75**, using dichloromethane as solvent and bubbling CO_2 (g) through the reaction solution at RT. The inclusion of 3 equivalents of Hünig's base was found to be essential for the transformation in organic solvents, which could be performed in excellent yield. It was found that the inclusion of a Lewis acid catalyst did not enhance the yield or decrease reaction time. A range of α-aminonitriles was synthesised and isolated using variations of the Strecker reaction in moderate to good yield. This range of α-aminonitriles was used in the optimised conditions to synthesise a range of hydantoins in good to excellent yield.

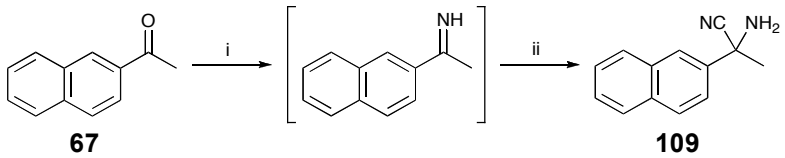
Results and Discussion (Part Three)

4 Results and Discussion (part three)

4.1 The Development of a One-Pot Synthesis of Hydantoins from Ketones

The development and optimisation of methodology for the synthesis of a range of hydantoins in organic solvent was successful, however, the synthesis of the α-aminonitrile starting materials was more challenging, resulting in poor yields over the two transformations. Therefore, a more direct method of synthesising hydantoins was sought, from ketone starting materials. This method would avoid isolation of the problematic α-aminonitrile intermediate, however, conditions for the transformation of ketones to α-aminonitriles in organic media are not known. Previously α-aminonitriles were synthesised in water-based conditions using salts as reagents, hence the development of the proposed one-pot conditions would involve identifying suitable reagents that will readily form α-aminonitriles from ketones in organic solvent.

Initial investigations would employ a solution of NH_3 in dioxane to effect the synthesis of the predictably unstable imine intermediate, followed by *in-situ* cyanation with a solution of HCN. Previous work has shown that pre-generating a solution of HCN is more suitable for the synthesis of α-aminonitriles than using TMSCN directly. As the reaction conditions will be developed in an organic solvent, the inclusion of a Lewis acid may catalyse the addition of NH_3 and HCN to the ketone, though prior work indicates that Lewis acids do not catalyse the transformation of α-aminonitriles to hydantoins. To develop this methodology, 2-acetylnaphthalene **67** was selected as the ketone substrate as it had proved impossible to synthesise the corresponding α-aminonitrile (**109**) using water-based reaction conditions (Scheme **71**, Table **14**).



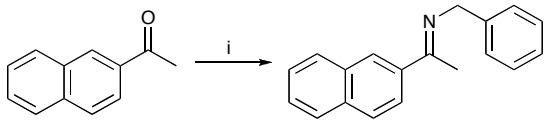
67 **109**

Scheme 71 - Proposed one-pot method of α-aminonitrile/hydantoin synthesis. *Reagents and conditions:* (i) Conditions see Table **14**. (ii) HCN (sol.) (1.5 equiv.), RT.

Catalyst	Conditions	Conversion to Imine	Cyanated
$ZnCl_2$	$ZnCl_2$ (0.1 eq.), NH_3 (2 eq.), RT, 45 h	no reaction	-
$Y(OTf)_3$	$Y(OTf)_3$ (0.1 eq.), NH_3 (2 eq.), RT, 40 h	no reaction	-
$Y(OTf)_3$	$Y(OTf)_3$ (2.0 eq.), NH_3 (2 eq.), RT, 24 h	no reaction	-
$Y(OTf)_3$	$Y(OTf)_3$ (0.5 eq.), NH_3 (2 eq.), RT, 40 h	no reaction	no reaction
$Ga(OTf)_3$	$Ga(OTf)_3$ (0.1 eq.), NH_3 (4 eq.), RT, 40 h	no reaction	no reaction

Table 14 - Conditions for the proposed one-pot method of α-aminonitrile/hydantoin synthesis.

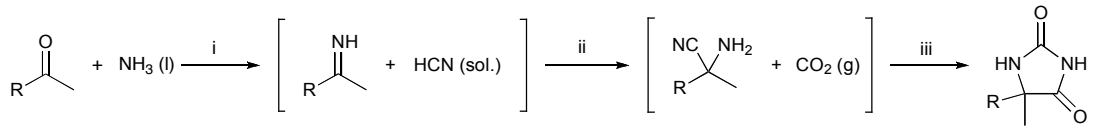
It can be noted from Table **14** that none of the conditions attempted led to the synthesis of an α-aminonitrile. Analysis of the reaction by ^1H NMR spectroscopy was not reliable, as removing solvents in the presence of the catalyst probably results in degradation of the imine intermediate. In order to test the one-pot procedure (ie solvent, Lewis acid) a similar reaction was performed using benzylamine, instead of a solution of ammonia in dioxane (Scheme **72**). This experiment would establish that the solvent and Lewis acid were compatible with the synthesis of imines and would demonstrate that the problem lay with the use of the ammonia solution.



67 **56**

Scheme 72 - Test reaction - imine synthesis. *Reagents and conditions:* (i) Benzylamine (1.5 equiv.), $Y(OTf)_3$ (0.2 equiv.), dioxane, RT, 48 h, 52 % yield.

The imine **56** was synthesised in similar yield as reported previously, which shows that the solvent and Lewis acid were not the problem in the one-pot synthesis, but it was indeed the use of the ammonia solution in dioxane. In order to deliver a higher concentration of ammonia to the reaction solution, further investigations would involve the use of liquid ammonia (Scheme **73**, Table **15**). The use of liquid ammonia would also allow the use of the favoured solvent, dichloromethane.



R = naphthyl

Scheme 73 - The development of one-pot conditions for the synthesis of hydantoins. *Reagents and conditions:* (i) NH_3 (l) (excess), Lewis acid (0.1 equiv. or stated), CH_2Cl_2, other conditions see Table **15**. (ii) HCN (sol.) (2 equiv. or stated), other conditions see Table **15**. (iii) Hünig's base (3 equiv.) or Polymer Supported (PS)-Hünig's base, CO_2 (g), RT.

Conditions[a]			**Yield (%)**
i	**ii**	**iii**	
$Ga(OTf)_3$, - 78 °C then RT, 8 h	RT, 16 h	8 h	18
$Ga(OTf)_3$, - 78 °C, 24 h then RT	RT, 24 h	3 h	27
$Ga(OTf)_3$, -78 °C, 24 h	- 78 °C, 24 h	6 h	5
$Ga(OTf)_3$, - 78 °C, 10 h then RT		10 h	9
$Ga(OTf)_3$, - 78 °C, 24 h	- 78 °C for 30 min, then RT, 24 h	6 h	53
$Ga(OTf)_3$, - 78 °C, 3 h	- 78 °C for 30 min, then RT, 20 h	5 h	47 - 50[b]
- 78 °C, 3 h	- 78 °C for 30 min, then RT, 20 h	5 h	no product formed
$Ga(OTf)_3$, - 78 °C, 3 h	HCN (1 equiv.), - 78 °C for 30 min, then RT, 20 h	6 h	27
$Ga(OTf)_3$, - 78 °C, 3 h	HCN (4 equiv.), - 78 °C for 30 min, then RT, 20 h	6 h	25
$Ga(OTf)_3$ (0.2 equiv.), - 78 °C, 3 h	- 78 °C for 30 min, then RT, 20 h	5 h	36
$TiCl_4$, - 78 °C, 3 h	- 78 °C for 30 min, then RT, 20 h	7 h	13
$Ga(OTf)_3$, - 78 °C, 3 h	- 78 °C for 30 min, then RT, 20 h	(PS)-Hünig's base (3 equiv.), 5 h	no product formed
$Ga(OTf)_3$, - 78 °C, 3 h	- 78 °C for 30 min, then RT, 20 h	(PS)-Hünig's base (excess), 5 h	no product formed

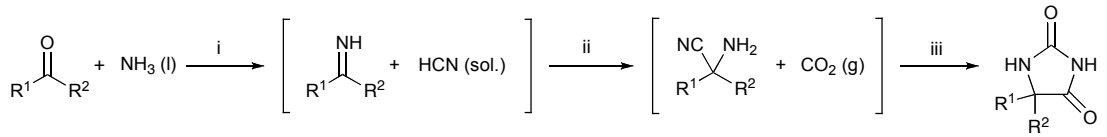
[a] See scheme **73**. [b] Reaction performed in duplicate.

Table 15 - The development of one-pot conditions for the synthesis of hydantoin **65**.

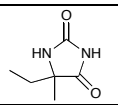
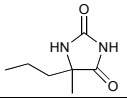
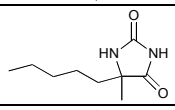
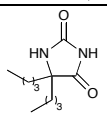
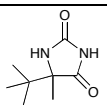
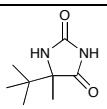
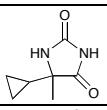
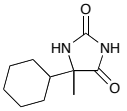
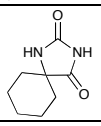
The use of a solution of liquid ammonia was successful, although the imine intermediate, predicably, could not be isolated nor analysed by either TLC or ^{1}H NMR spectroscopic analysis. The progress of the reaction could be monitored by the formation and consumption of the α-aminonitrile intermediate as it could be observed by both TLC analysis and ^{1}H NMR spectroscopy. After the stated time for α-aminonitrile formation, addition of Hünig's base and CO_2 (g) gave the desired hydantoin **65** in moderate yield. Subsequent entries in Table **15** detail other conditions attempted in an effort to increase the yield through changes in addition of reagents, temperature and reaction time. The highest yielding conditions developed to date involved maintaining the reaction at -78 °C for 3 h (with NH_3 (l) still present) for the addition of HCN, then allowing the reaction mixture to attain RT immediately after HCN addition. Attempting to use different concentrations of HCN (sol.) did not have a beneficial effect. It was also noted that the reaction did not occur when no Lewis acid was used and that increasing the concentration of Lewis acid or changing to titanium (IV) chloride did not increase the yield or change the rate of reaction. The volatility of the base and solvent in the reaction conditions was concerning, especially as the solvent level had to be monitored constantly. In an effort to allieviate these concerns the use of polymer-supported Hünig's base was investigated, however, this did not result in the synthesis of the desired hydantoin. The reaction was also performed with a water condensor to prohibit solvent loss, but this was found to be ineffective. This work represents the first example of a Lewis acid-catalysed modified Bucherer-Berg reaction. The ketone **67** has been shown to be a poor substrate for the synthesis of α-aminonitriles, thus the isolation of any hydantoin from this reaction was an improvement on the previously described step-wise conditions. Due to the choice of substrate, only a modest yield of product was noted in the optimum conditions, so the substrate-scope of the reaction was determined by applying a range of carbonyl compounds to the reaction conditions.

4.2 The Synthesis of a Range of Hydantoins Using the One-Pot Methodology

The optimum conditions for the synthesis of hydantoin **65** (naphthyl/methyl) (Table **73**), were used to synthesise a range of alkyl and aryl hydantoins (Scheme **74**, Tables **16** and **17**).



Scheme 74 - The synthesis of a range of hydantoins using the developed methodology. *Reagents and conditions:* (i) NH_3 (l) (excess), $Ga(OTf)_3$ (0.1 equiv.), CH_2Cl_2, - 78 °C, 3 h. (ii) HCN (sol.) (2 equiv.), - 78 °C to RT. (iii) Hünig's base (3 equiv.), CO_2 (g), RT.

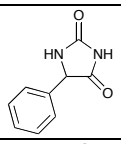
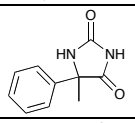
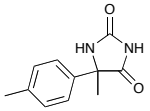
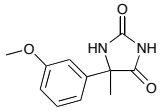
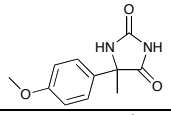
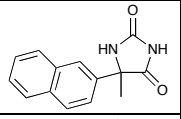
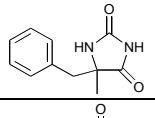
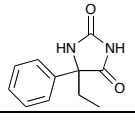
R^1	R^2	Conditions[a]			Product	Comp. No.	Yield (%)
		i	ii	iii			
Et	Me	CH_2Cl_2	20 h	14 h		**93**	25
n-propyl	Me	CH_2Cl_2	24 h	13 h		**110**	76
n-pentyl	Me	CH_2Cl_2	20 - 24 h	7 - 12 h		**94**	95 - 98[b]
n-Bu	*n*-Bu	CH_2Cl_2	20 h	14 h		**95**	71
t-Bu	Me	CH_2Cl_2	20 h	35 h		**96**	no product formed
t-Bu	Me	EtOH	24 h	17 h		**96**	25
cyclopropyl	Me	CH_2Cl_2	20 - 24 h	6 - 8 h		**75**	61 - 83[b]
cyclohexyl	Me	CH_2Cl_2	20 h	20 h		**97**	71
cyclohexyl		CH_2Cl_2	20 h	9 h		**99**	41

[a] See scheme **74**. [b] Reaction performed in duplicate.

Table 16 - The synthesis of a range of alkyl hydantoins using the developed one-pot methodology.

The synthesis of alkyl hydantoins generally occurred in good yield. The low yield achieved for hydantoin **93** (ethyl/methyl) is a result of the volatility of the α-aminonitrile intermediate. This was not a problem when using larger alkyl groups, as can be seen with the results for hydantoins **110** (*n*-propyl/methyl) and **94** (*n*-pentyl/methyl). The yield obtained for hydantoin **95** (*n*-butyl/*n*-butyl) was lower than expected, but can be attributed to the long alkyl chains, which may hinder

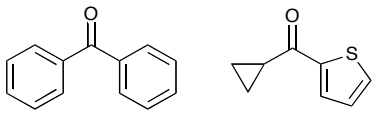
nucleophilic attack at the carbonyl and imine groups. The synthesis of hydantoin **96** (*t*-butyl/methyl) gave a similar result as was noted in chapter 2, where the reaction would not occur in dichloromethane but would occur when using an alcohol as solvent. The synthesis of hydantoin **96** (*t*-butyl/methyl) was the only one-pot reaction performed in a solvent other than dichloromethane, and although low yielding it was pleasing that the reaction worked for a difficult substrate in another solvent. The synthesis of hydantoins **75** (cyclopropyl/methyl) and **97** (cyclohexyl/methyl) occurred in good yield; however, the yield of the spiro-hydantoin **99** (cyclohexane) was low. This is probably due to axial interactions from the cyclohexyl group, which would hinder nucleophile attack. The same conditions were also used to synthesise a range of aryl hydantoins (Table **17**).

R^1	R^2	Conditions[a]			Product	Comp. No.	Yield (%)
		1	2	3			
Ph	H	CH_2Cl_2	20 h	17 h		**92**	82
Ph	Me	CH_2Cl_2	20 h	5 - 6 h		**100**	37 - 59[b]
4'-MePh	Me	CH_2Cl_2	20 h	6 h		**101**	32
3'-MeOPh	Me	CH_2Cl_2	20 h	7 h		**102**	39 - 41[b]
4'-MeOPh	Me	CH_2Cl_2	20 h	8 h		**111**	18
2-naphthyl	Me	CH_2Cl_2	20 h	5 h		**65**	47 - 50[b,c]
Bn	Me	CH_2Cl_2	20 h	11 h		**112**	99
Ph	Et	CH_2Cl_2	20 h	6 h		**103**	56

[a] See scheme **74**. [b] Reaction performed in duplicate. [c] Reactions discussed earlier.

Table 17 - The synthesis of a range of aryl hydantoins using the developed one-pot methodology.

The synthesis of a range of aryl hydantoins occurred in moderate to excellent yields. It was found that benzaldehyde performed well under the reaction conditions, which was advantageous as this was the first time a substrate other than a ketone had been used in the one-pot synthesis. The poor electrophilicity of ketones which have an α-aryl group is highlighted by some of the yields noted, where the hydantoins **65** (naphthyl/methyl), **102** (3'-MeOPh/methyl), **111** (4'-MeOPh/methyl) and **101** (4'-MePh/methyl) were all synthesised in medium to low yield. The similar results obtained for hydantoins **100** (phenyl/methyl) and **103** (phenyl/ethyl) suggest that either a methyl or ethyl group can be tolerated as the other substituent on the ketone. The most interesting result is that of hydantoin **112** (benzyl/methyl) where an excellent yield was achieved, showing that the position of the phenyl group can have a large effect on the outcome of the reaction. The ketones, benzophenone **113** and cyclopropyl-2-thienylketone **114** (Figure **15**) were also attempted under the reaction conditions, but did not lead to the synthesis of the desired hydantoins. It is believed that the poor electophilicity of these substrates resulted in no reaction occurring.

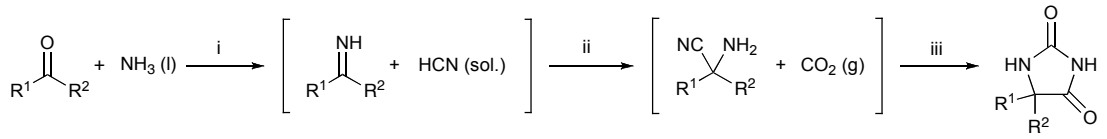


113 **114**

Figure 15 - Examples of ketones that would not form hydantoins in the developed methodology.

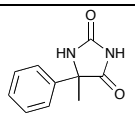
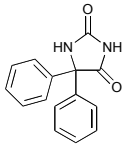
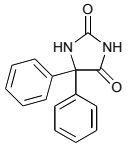
4.3 Investigation of the Use of TMSOTf as Lewis Acid in the One-Pot Methodology

Work carried out by Olah and co-workers has already shown that gallium (III) triflate was an effective catalyst for the synthesis of α-aminonitriles.[96] However, recent work by Olah and co-workers has shown that TMSOTf is a more effective catalyst for the synthesis of α-aminonitriles.[93] It was hoped that the use of this catalyst would lead to a higher yielding synthesis for certain substrates, which either did not perform well or did not react at all in the gallium (III) triflate reaction conditions (Scheme **75**, Table **18**).



R^1 = phenyl
R^2 = phenyl or Me

Scheme 75 - The synthesis of hydantoins using TMSOTf as catalyst in the one-pot methodology. *Reagents and conditions:* (i) NH_3 (l) (excess), TMSOTf (0.1 equiv. or stated), CH_2Cl_2, - 78 °C, 3 h. (ii) HCN (sol.) (2 equiv.), - 78 °C to RT. (iii) Hünig's base (3 equiv.), CO_2 (g), RT.

R^1	R^2	Conditions[a]			Product	Comp. No.	Yield (%)
		i	ii	iii			
Ph	Me	CH_2Cl_2	20 h	3 - 4 h		**100**	20 - 28 [b]
Ph	Ph	CH_2Cl_2	20 h	6 h		**115**	no product formed
Ph	Ph	CH_2Cl_2, TMSOTf (0.5 equiv.)	20 h	6 h		**115**	no product formed

[a] See scheme **75**. [b] Reaction performed in duplicate.

Table 18 - Conditions for the synthesis of hydantoins using TMSOTf as catalyst.

The use of TMSOTf did not lead to an increase in yield or rate of the reaction for the synthesis of hydantoin **100** (phenyl/methyl). The synthesis of hydantoin **115** (phenyl/phenyl) did not occur even when using a higher catalyst loading. It is unfortunate that this catalyst did not enhance the one-pot synthesis of hydantoins, however, it is believed that a more active catalyst would result in higher yields for difficult substrates.

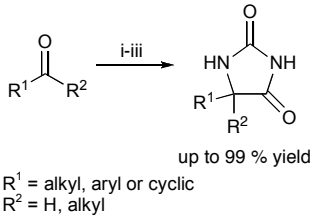
4.4 Summary

The one-pot synthesis of hydantoins was developed into a high-yielding process, where ketones were reacted with liquid ammonia at - 78 °C for 3 h in the presence of gallium (III) triflate, prior to the introduction of a solution of hydrogen cyanide. The reaction is allowed to attain RT and stirred for 20 h before Hünig's base and CO_2 (g) effect the final synthesis of the hydantoin. The process was found to be suitable for the synthesis of a range of alkyl and aryl hydantoins in moderate to excellent yields. Further efforts to increase the yield of the reaction (for difficult substrates) with the use of other catalysts have not been possible.

Results and Discussion (Part Four)

5 Results and Discussion (part four)

5.1 The Development of an Asymmetric One-Pot Synthesis of Hydantoins

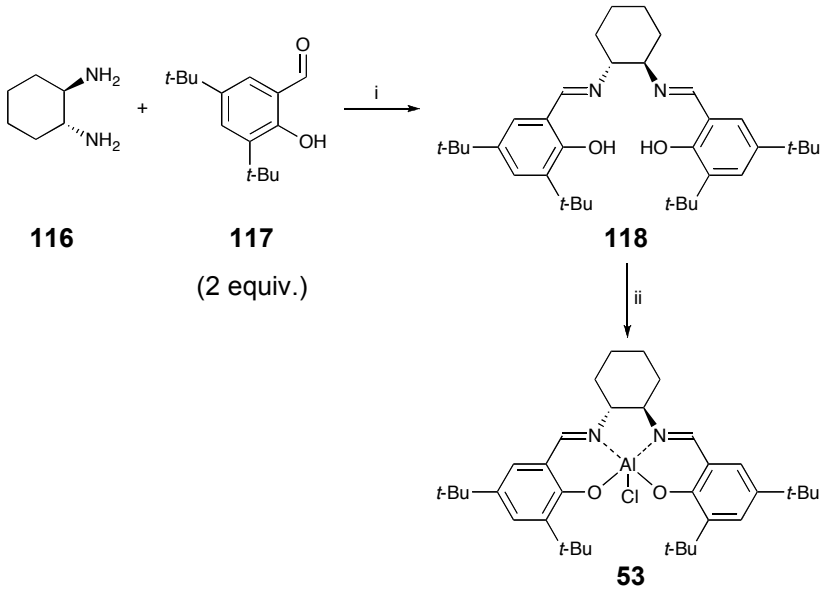


Scheme 76 - The conditions developed for the one-pot synthesis of hydantoins. *Reagents and conditions:* (i) NH_3 (l) (excess), $Ga(OTf)_3$ (0.1 equiv.), CH_2Cl_2, - 78 °C, 3 h. (ii) HCN (sol.) (2 equiv.). (iii) Hünig's base (3 equiv.), CO_2 (g), RT.

The one-pot conditions have been shown to be effective for the synthesis of a range of hydantoins in moderate to excellent yield with the use of Lewis acid catalysis (Scheme **76**). The next stage was to use a chiral Lewis acid catalyst to investigate the possibility of synthesising enantiomerically enriched hydantoins. The high yields noted for the synthesis of hydantoins **94** (*n*-pentyl/methyl) and **112** (benzyl/methyl) makes these substrates ideal for the proposed investigation, as they have been shown to react in the developed conditions with ease.

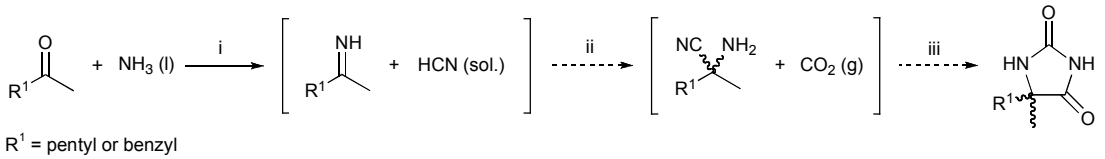
5.1.1 Investigation of Aluminium (Salen) Chloride as Catalyst

The first catalyst chosen was the aluminium salen chloride catalyst (**53**) used by Jacobsen for the synthesis of enantioenriched α-aminonitriles.[73] This catalyst had been shown to be effective for a range of nucleophile/electrophile reactions, and the work reported by Jacobsen has shown that this catalyst is suited for the enantioselective synthesis of α-aminonitriles from imines. The salen ligand **118** can be made with ease using literature procedures from 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde **117** and (*R*,*R*)-(-)-1,2-diaminocyclohexane **116**.[73] The salen ligand is reacted with diethylaluminium chloride to furnish catalyst **53** in excellent yield (Scheme **77**).



Scheme 77 - The synthesis of catalyst **53**.[73] *Reagents and conditions:* (i) EtOH, RT, 10 mins, 92 % yield. (ii) Et_2AlCl (1 equiv.), CH_2Cl_2, RT, 2 h, 92 % yield.

The catalyst **53** was used to attempt the synthesis of enantiomerically pure hydantoins from ketones (Scheme **78**, Table **19**).



R^1 = pentyl or benzyl

Scheme 78 - The attempted synthesis of enantioenriched hydantoins using chiral catalyst **53** in the one-pot methodology. *Reagents and conditions:* (i) NH_3 (l) (excess), Al (salen)Cl (0.05 equiv.), CH_2Cl_2, - 78 °C, 3 h. (ii) HCN (sol.) (2 equiv.). (iii) Hünig's base (3 equiv.), CO_2 (g), RT.

R^1	**R^2**	**Conditions**[a]		**Yield (%)**	**ee (%)**[c]
		ii	**iii**		
n-pentyl	Me	- 78 °C for 30 min, then RT, 20 h	13 - 19 h	69 - 98[b]	0 - 6
n-pentyl	Me	- 78 °C, 20 h	12 h	2	3
benzyl	Me	- 78 °C for 30 min, then RT, 20 h	14 h	56	not determined

[a] See scheme **78**. [b] Reaction performed in duplicate. [c] Determined by chiral HPLC analysis on a chiralpak AD column.

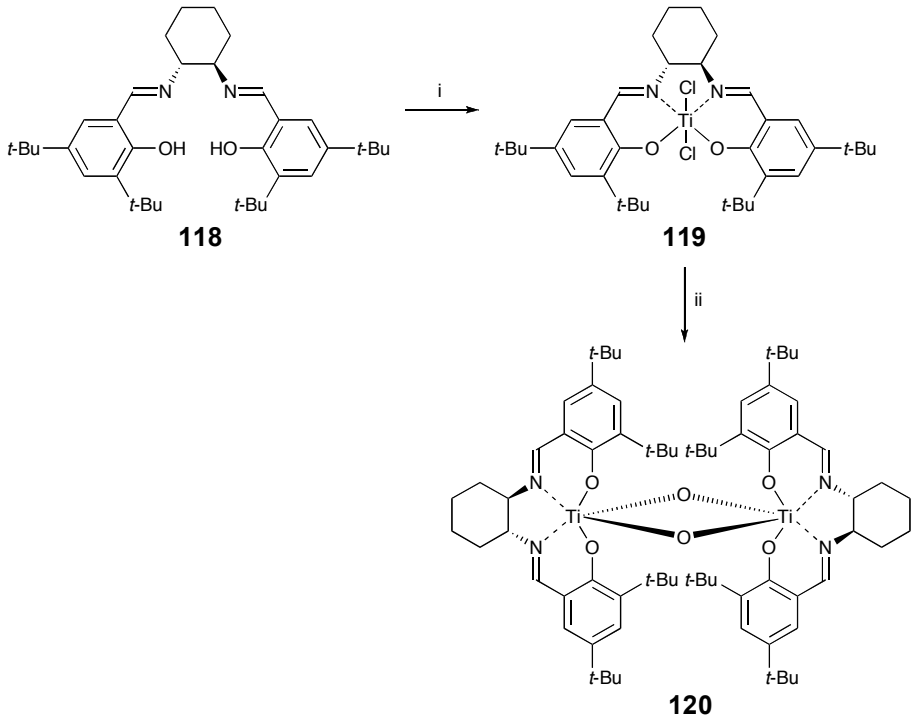
Table 19 - Conditions employed for the synthesis of enantiomerically enriched hydantoins using catalyst **53**.

The asymmetric synthesis of hydantoins did not readily occur using catalyst **53**. The reaction was initially attempted mirroring the exact conditions optimised in Table **16** and a similar yield was achieved for hydantoin **94** (*n*-pentyl/methyl), but the sample

was essentially racemic. The procedure was repeated and again, only racemic product was synthesised in inferior yield. The reason the yield was low was because the crude product had to purified by column chromatography, and it is believed that this resulted in loss of some material. It was hypothesised that the catalyst would be active at - 78 °C, where the background (uncatalysed) reaction, if present, would be suppressed. This procedure was attempted and only a 2 % yield of racemic product was achieved. In order to test if the substrate was the problem the reaction was attempted with hydantoin **112** (benzyl/methyl) as substrate. The hydantoin product **112** was synthesised in low yield, however, determination of the enantiomeric excess was not possible, as the two enantiomers could not be separated by chiral HPLC. It seems that this catalyst is not suited for the desired synthesis, therefore other asymmetric catalysts would have to be investigated.

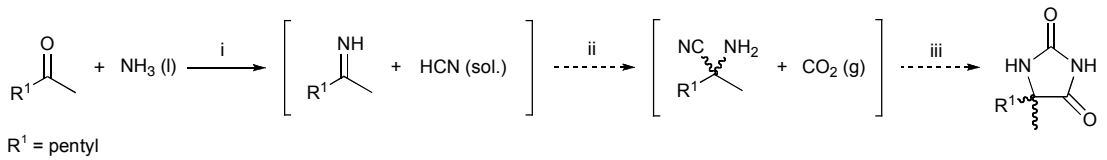
5.1.2 Investigation of Titanium (Salen) Dimer as Catalyst

The titanium (salen) dimer **120**, has been shown to promote the enantioselective synthesis of cyanohydrins from aldehydes in excellent yield and enantiomeric excess.[102] This catalyst was synthesised according to literature procedures from the salen ligand **118** (synthesised in Scheme **77**), over two steps (Scheme **79**).[102]



Scheme 79 - Synthesis of titanium (salen) dimer catalyst **120**.[102] *Reagents and conditions:* (i) $TiCl_4$ (1 equiv.), CH_2Cl_2, RT, 2 h, 38 % yield. (ii) H_2O (1 equiv.), Et_3N (1 equiv.), CH_2Cl_2, RT, 3 h, 36 % yield.

The synthesis of catalyst **120** proceeded smoothly, however, the yields quoted in the literature could not be reproduced. The catalyst was used in the developed methodology (Scheme **80**) to effect the asymmetric synthesis of hydantoins.

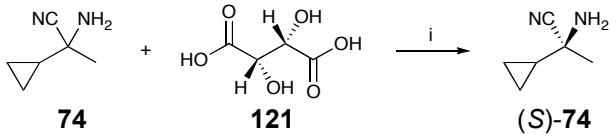


Scheme 80 - The attempted synthesis of enantioenriched hydantoins using aluminium (salen) dimer **120** as catalyst in the one-pot methodology. *Reagents and conditions:* (i) NH_3 (l) (excess), Al (salen) dimer (0.01 equiv.), CH_2Cl_2, - 78 °C, 3 h. (ii) HCN (sol.) (2 equiv.), - 78 °C to RT, 20 h. (iii) Hünig's base (3 equiv.), CO_2 (g), RT, 7 h, 9 % yield, 0 % ee.

The catalyst **120** was used in a lower concentration than the previous aluminium salen catalyst **53**, but in a higher concentration than was reported in the literature. It was shown that the product did form under the conditions but in poor yield and no enantiomeric excess was noted. This result was disappointing, however, other catalysts will be identified and used in this methodology with the hope of synthesising enantiomerically enriched hydantoins.

5.2 The Investigation of the Synthesis of Enantiomerically-Enriched α-Aminonitriles

The synthesis of hydantoins from α-aminonitriles has been fully optimised into high-yielding transformation for a range of substrates. Therefore, the next logical step was to investigate the synthesis of enantiomerically enriched α-aminonitriles, and use them in the developed methodology to determine whether optically enriched α-aminonitriles were transformed with stereochemical integrity intact. There are only two methods in the literature which detail the isolation of a single enantiomer of an α-aminonitrile that has no *N*-substitutuent; a resolution procedure by Los[103] and a diastereomeric separation using a chiral sulfoxide tether, reported by Fannelli.[104] The resolution of the two enantiomers of α-aminonitrile **74** using (L)-(+)-tartaric acid (**121**) was attempted first, using the procedure described by Los (Scheme **81**).

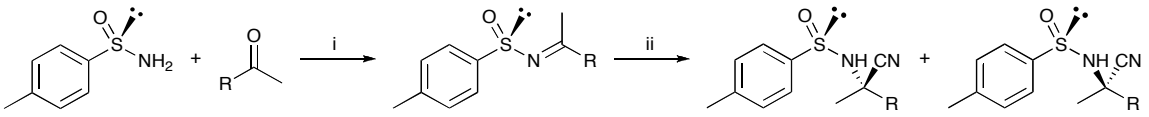


Scheme 81 - Conditions used for the resolution of **74**.[103] *Reagents and conditions:* (i) **74** (1.07 equiv.), H_2O, 0 °C, filter, suspend in H_2O, wash with 1.0 M NaOH, extract with Et_2O, concentrate *in vacuo*, repeat three times.

The resolution of α-aminonitrile **74** using (L)-(+)-tartaric acid did not lead to the isolation of a single enantiomer of the α-aminonitrile. It was found that only a very low return of enantiomerically enriched material could be recovered after each cycle of the resolution procedure. This procedure was repeated on a larger batch of α-aminonitrile **74** and again only a few milligrams of starting material were recovered after three cycles. This suggested that the starting material had degraded during the procedure so an alternative method was attempted.

5.2.1 The Investigation of the Synthesis of Enantiomerically-Enriched α-Aminonitriles, *via* Chiral Sulfonaminonitriles

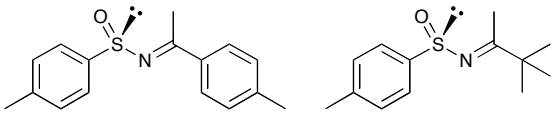
The second method, described by Fannelli and co-workers, involved synthesising a non-racemic *N*-sulfinimine **123** from (*S*)-(+)-*p*-toluenesulfinamide **122** and a ketone.[104] The sulfinimine **123** is cyanated with ethylaluminium cyanoisopropoxide to give a mixture of sulfinaminonitrile diastereoisomers, (*S*,*S*)-**124** and (*S*,*R*)-**124**, which can be separated by chromatography (Scheme **82**). Removal of the sulfinyl group by hydrolysis furnishes the desired enantiomerically enriched α-aminonitrile. It was anticipated that this procedure could be used to synthesise a range of enantiomerically pure α-aminonitriles, however, the conditions in the literature exist for the synthesis of only one derivative (from pinacolone) and further investigation of the removal of the *N*-sulfinyl group from other substrates would have to be explored.



122 R = *t*-Bu, tolyl. **123** (*S*,*S*)-**124** (*S*,*R*)-**124**

Scheme 82 - Conditions reported by Fannelli for the synthesis of enantiomerically pure aminonitriles.[104] *Reagents and conditions:* (i) ketone (5 equiv.), $Ti(OEt)_4$ (10 equiv.), CH_2Cl_2, reflux. (ii) EtAl(O-*i*-Pr)CN (1.5 equiv.), THF, -78 °C to RT.

The methodology reported by Fannelli and co-workers was used to synthesise two derivatives of the sulfinimine, (*S*)-(+)-*N*-α-methyl-(4'-methylbenzylidene)-(4'-methylphenyl) sulfinamide **125** and (*S*)-(+)-(1,2,2-trimethyl propylidene)-(4'-methylphenyl) sulfinamide **126** (Figure **16**, Table **20**). Both imines were synthesised in similar yield as was reported in the literature.[104]



125 **126**

Figure 16 - The sulfinimines **125** and **126**, synthesised using the Fannelli methodology.

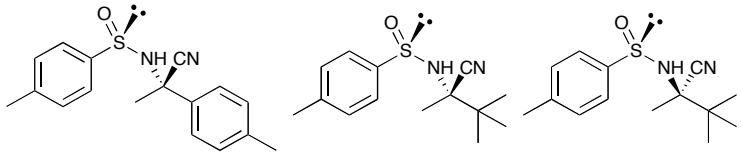
Compound	Time (h)	Yield (%)
125	16	65 - 80[a]
126	48	42

[a] Reaction performed in duplicate.

Table 20 - Examples of the synthesis of sulfinimines **125** and **126**.

5.2.2 The Cyanation of Chiral Sulfinimines

The imine **125** was cyanated as described (Scheme **82**), to give (2*S*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl) propionitrile (*S*,*S*)-**127** (Figure **17**, Table **21**), which was isolated as a single diastereoisomer. The same procedure was also used to isolate both (2*S*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl) propionitrile (*S*,*S*)-**128** and (*S*,*R*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl) propionitrile (*S*,*R*)-**128** (Figure **17**, Table **21**) as single diastereoisomers.



(*S*,*S*)-**127** (*S*,*S*)-**128** (*S*,*R*)-**128**

Figure 17 - The sulfinaminonitriles (*S*,*S*)-**127**, (*S*,*S*)-**128** and (*S*,*R*)-**128**, synthesised using the Fannelli methodology.

Product	Time (h)	Mix. of dr's (*SS*/*SR*)[a]	Method of Separation	Yield (%)
(*S*,*S*)-**127**	21	67/33	prep. TLC	27
(*S*,*S*)-**128**	24	55/45	column chromatography	41
(*S*,*R*)-**128**				53

[a] As judged by ^{1}H NMR spectroscopy.

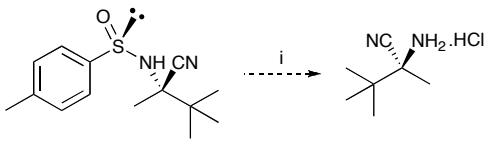
Table 21 - The products and yields achieved for the synthesis of enantiomerically pure sulfinaminonitriles.

The isolated yield of sulfinaminonitrile (*S*,*S*)-**127** was less than was reported in the literature (60 %). This is because the reaction performed was not as selective for

one diasteroisomer as was reported in the literature (83/17). The other diastereoisomer was not isolated in high yield. The synthesis and isolation of sulfinaminonitriles (*S*,*S*)-**128** and (*S*,*R*)-**128** was achieved in similar yield, however, the selectivity of the reaction as reported in the literature could not be repeated. The mixture of diastereoisomers could be separated with ease by column chromatography.

5.2.3 Investigation of the Removal of the *N*-Sulfinyl Group

The removal of the sulfinyl group was investigated initially using sulfinaminonitrile (*S*,*S*)-**128** as this procedure had been reported in the literature. The conditions described by Fannelli and co-workers involved hydrolysing (*S*,*S*)-**128** with 6 M HCl to give the enatiomerically-enriched (*S*)-**82** (Scheme **83**).

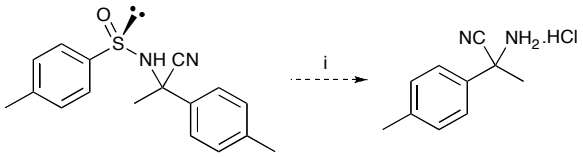


(*S*,*S*)-**128** (*S*)-**82**

Scheme 83 - Conditions for the hydrolysis of sulfinaminonitrile (*S*,*S*)-**128**. *Reagents and conditions:* (i) 6 M HCl, reflux, 16 h, product not isolated.

The procedure was attempted and after 16 h, TLC analysis indicated that the starting material had been consumed. However, following the procedure exactly did not lead to the isolation of α-aminonitrile (*S*)-**82**; a mixture of the α-aminonitrile and sulfinic acid was isolated. Attempts to remove the sulfinic acid by (1) washing with excess ether (as in the literature) or (2) acidifying a solution of the crude reaction product in water and extracting the sulfinic acid with organic solvent were unsuccessful.

The removal of the *N*-sulfinyl group from racemic sulfinaminonitrile **127** was also investigated (Scheme **84**, Table **22**) as the development of this methodology could lead to a general method for the synthesis of a range of enantiomerically pure α-aminonitriles.



(±)-**127** (±)-**88**

Scheme 84 - Conditions used for the hydrolysis of sulfinaminonitrile (±)-**127**. *Reagents and conditions:* (i) Conditions see Table **22**.

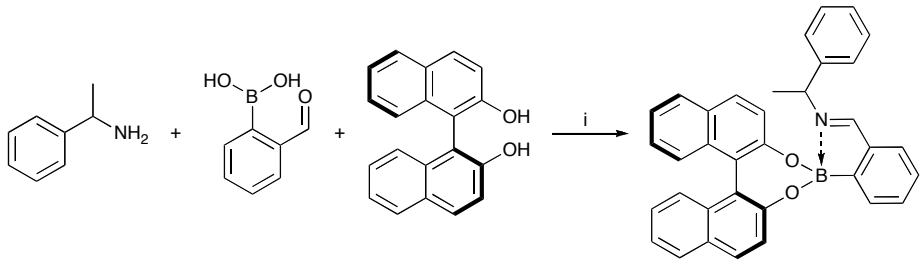
Conditions	Work-Up	Outcome
TFA, RT, 2 h	vac., suspend in CH_2Cl_2 and wash with sodium bicarbonate, then vac.	crude mixture of products
6 M HCl, reflux, 4 h	extract with Et_2O and conc. aq. phase	crude mixture of products
2 M HCl, reflux, 4 h	extract with Et_2O and conc. aq. phase	crude mixture of products
0.1 M HCl/MeOH (1/1), RT, 20 h	vac., suspend in water, extract with EtOAc, conc. aq. phase	isolated sulfinic acid and crude mixture of products
0.1 M HCl/MeOH (1/1), RT, 26 h	vac., suspend in water, extract with EtOAc, conc. aq. phase	isolated sulfinic acid and crude mixture of products
0.1 M HCl/THF (1/1), RT, 20 h	vac., suspend in water, extract with CH_2Cl_2, conc. aq. phase	isolated sulfinic acid and crude mixture of products

Table 22 - The investigation of the removal of the *N*-sulfinyl group from racemic sulfinaminonitrile **127**.

None of the conditions attempted led to the isolation of α-aminonitile hydrochloride salt **88**. The use of highly acidic conditions led to the isolation of a crude mixture of products, which included the amino acid (formed by hydrolysis of the nitirile group), so milder conditions were sought. The use of 0.1 M HCl had to be performed with an organic co-solvent to overcome solubility issues and the use of methanol would also capture any acid produced from the conditions, in the form of an ester. In each of the attempted conditions only the sulfinic acid could be isolated from the water phase and a crude mixture of products from the organic phase, which included the ester when using methanol and the acid when using tetrahydrofuran. It was hoped that this investigation would result in an easy method for the synthesis of a range of enantiomerically pure α-aminonitriles however, the ideal conditions for the cleavage of the *N*-sulfinyl group were not identified.

5.3 Investigation of the Analysis of the Enantiomeric Purity of α-Aminonitriles

A method reported by Bull and co-workers has shown that the enantiomeric purity of range of tertiary amines could be analysed by a simple and easy to use ^{1}H NMR derivatisation technique.[105] A racemic or enantiopure amine, for example (±)-α-methylbenzylamine (**129**), is reacted with 2-formylphenylboronic acid **130** and (*S*)-BINOL **131** to form a diol-imino-boronate complex (for example **132**) in $CDCl_3$ (Scheme **85**). In solution, diol-imino-boronate **132** forms two distinct diastereoisomeric complexes with each enantiomer of the amine, and the different amounts of each diastereoisomer can be analysed by ^{1}H NMR spectroscopy to give a measure of the enantiopurity of the amine. This procedure was used to analyse the enantiomeric purity of (±)-α-methylbenzylamine **129** (from the literature) and racemic α-aminonitrile **74**.



(±)-**129** **130** (*S*)-**131** **132**

Scheme 85 - Analysis of the enantiomeric purity of tertiary amine (±)-**129,** by Bull's method.[105] *Reagents and conditions:* (i) (±)-**129** (1 equiv.), **130** (1 equiv.), (*S*)-**131** (1.1 equiv.), 4 Å mol. sieves, $CDCl_3$, 5 min.

Analysis of tertiary amine (±)-**129** by the Bull method did reveal that a racemic mixture of the amine **129** (45/55, 3 sets of peaks) was present (Figure **18**).

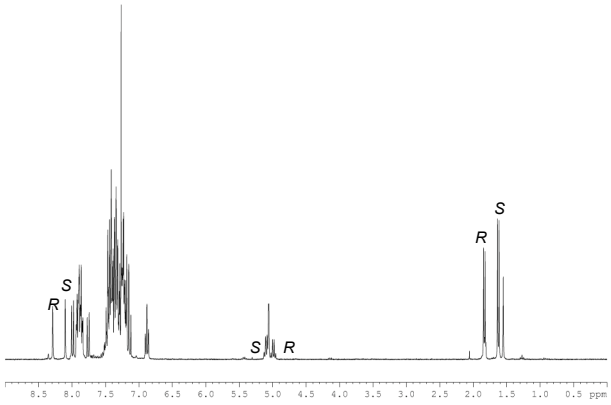
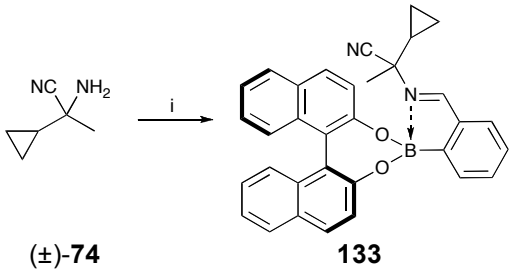


Figure 18 - Partial 300 MHz, ^{1}H NMR spectrum ($CDCl_3$) showing the analysis of the enantiomeric excess of tertiary amine (±)-**129**, by the Bull method.[105]

The α-aminonitrile (±)-**74**, was also subjected to the same method and analysis of the ^{1}H NMR spectrum suggested that diol (*S*)-**131** had not reacted to form the diol-imino-boronate complex **133** (Scheme **86**, Figure **19**).



Scheme 86 - Analysis of the enantiomeric purity of α-aminonitrile (±)-**74**, by Bull's method. *Reagents and conditions:* (±)-**74** (1 equiv.), **130** (1 equiv.), (*S*)-**131** (1.1 equiv.), 4 Å mol. sieves, $CDCl_3$, 5 min and 12 h.

The broad singlet at δ = 5.18 ppm corresponds to the hydroxyl groups of the unreacted diol (*S*)-**131**. The sample was left to stand for 12 h and was analysed again by ^{1}H NMR spectroscopy, but again diol (*S*)-**131** had not reacted, so no determination of the enantiomeric excess was possible. There are two theories why the complex was not forming; (1) the α-aminonitrile is too bulky for diol (*S*)-**131** to form the complex, or (2) donation from the nitrogen lone pair to boron may stabilise the complex; with the α-aminonitrile complex **133** this stabilisation is reduced, hence no complex forms.

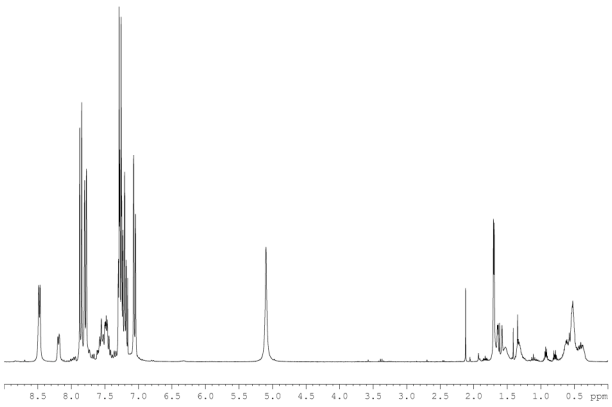


Figure 19 - Partial 300 MHz, ^{1}H NMR spectrum ($CDCl_3$) showing the analysis of the enantiomeric excess of α-aminonitrile (±)-**74**, by the Bull method.

Another method to test if diol (*S*)-**131** was reacting to form the diastereomeric complex was to first react α-aminonitrile (±)-**74** with aldehyde **130**. With the titration of increasing amounts of diol (*S*)-**131** to the solution, the formation of complex **133** could be monitored. The following ^{1}H NMR cascade diagram demonstrates the real-time addition of increasing amounts of diol (*S*)-**131**, from 0 to 1.3 equivalents (Figure **20**).

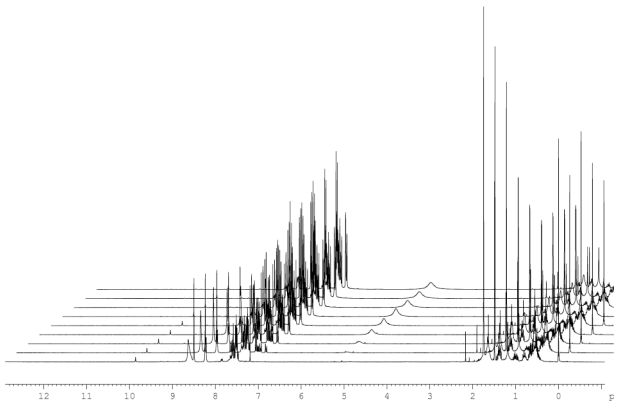
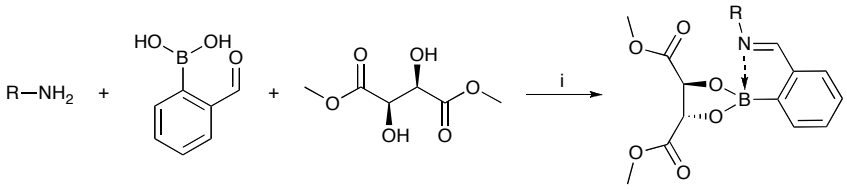


Figure 20 - 300 MHz, ^{1}H NMR spectra ($CDCl_3$) exhibited as a cascade diagram, demonstrating the addition of increasing amounts of diol (*S*)-**131** to the imino-boronate complex.

The cascade diagram demonstrates that the addition of increasing amounts of diol (*S*)-**131** to the reaction solution had no effect and did not lead to the formation of the desired complex **133**. The broad peak (δ = ~ 5.0 ppm) shows where the hydroxyl peaks of unreacted diol (*S*)-**131** are located in each spectrum. As the amount of diol (*S*)-**131** increases, the size of these peaks also increase, demonstrating that none of the desired complex was being formed. Therefore no determination of enantiomeric excess could be achieved. It is also apparent that α-aminonitrile (±)-**74** is not the

most suited substrate for this analysis, due to the mutiplets associated with the cyclopropyl group.

Further work by Bull has shown that his methodology could be used with a range of chiral diols.[106] Therefore, a smaller diol than BINOL **131**, (+)-dimethyl-(L)-tartrate **134** was identified and it was expected that the use of this diol may result in the formation of the diol-imino-boronate complex. This method was used to analyse the enantiomeric purity of α-aminonitrile (±)-**82** and tertiary amine (±)-**129** (Scheme **87**).



Scheme 87 - Analysis of the enantiomeric purity of amines using tartrate (+)-(L)-**134** as diol. *Reagents and conditions:* (i) (±)-**82** or (±)-**129** (1 equiv.), **130** (1 equiv.), **134** (1.1 equiv.), 4 Å mol. sieves, $CDCl_3$, 5 min.

The following spectrum illustrates the results for the analysis of the enantiomeric purity of tertiary amine (±)-**129** by the new method (Figure **21**). The enantiomeric excess could be determined by the splitting of three separate peaks relating to the two diastereoisomers of the diol-imino-boronate complex.

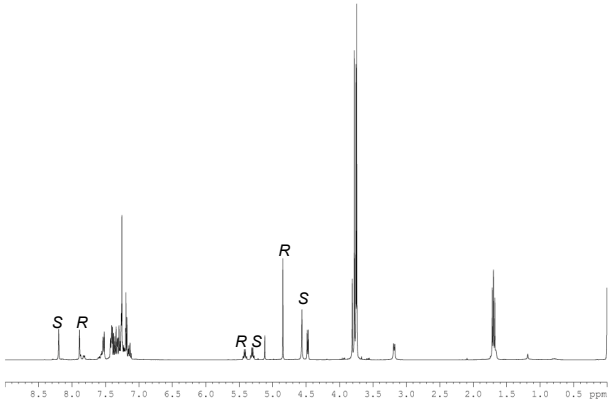


Figure 21 - Partial 300 MHz, ^1H NMR spectrum ($CDCl_3$) showing the analysis of the enantiomeric excess of tertiary amine (±)-**129**, using tartrate (+)-(L)-**134** as diol.

The method was applied to α-aminonitrile (±)-**82**, as it was hoped that the ^1H NMR singlets associated with the *t*-butyl and methyl functionality would make analysis of the diastereomeric ratio easier. However, the spectrum demonstrates that the diol-imino-boronate complex did not form, as the peak at δ = ~3.75 ppm represents

unreacted diol (+)-(L)-**134**, and the cluster of peaks at δ = ~1.0 ppm suggest that α-aminonitrile (±)-**82** may even be degrading in solution (Figure **22**).

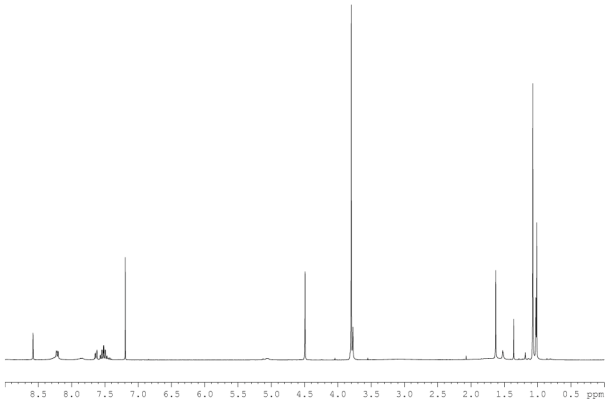


Figure 22 - Partial 300 MHz, ^{1}H NMR spectrum ($CDCl_3$) showing the analysis of the enantiomeric excess of α-aminonitrile (±)-**82**, using tartrate (+)-(L)-**134** as diol.

A titration experiment was also performed for α-aminonitrile (±)-**82**, where increasing amounts of tartrate (+)-(L)-**134** was titrated into the solution so that the formation of the diol-imino-boronate complex could be monitored. The addition of increasing amounts of tartrate (+)-(L)-**134** to the reaction solution had no effect and did not lead to the formation of the desired complex (Figure **23**).

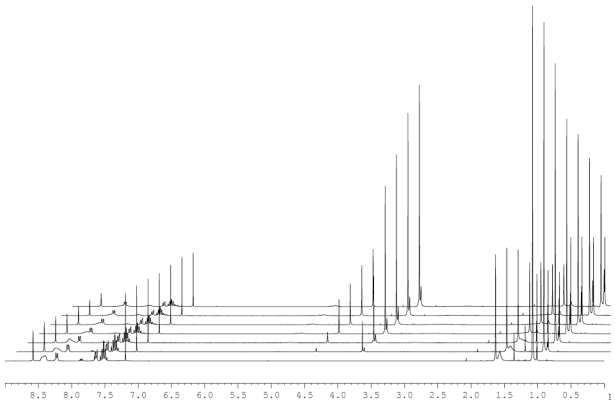


Figure 23 - 300 MHz, ^{1}H NMR spectra ($CDCl_3$) exhibited as a cascade diagram, demonstrating the addition of increasing amounts of tartrate (+)-(L)-**134** to the imino-complex.

These results suggest that the analysis of the enantiomeric excess of a range of α-aminonitriles is not possible using this method.

5.4 Summary

The chiral Lewis acid-catalysed one-pot synthesis of hydantoins from ketones was investigated, however, a suitable catalyst for the production of enantiomerically-enriched hydantoins has not been identified.

The synthesis of a range of enantiomerically pure α-aminonitriles was investigated but an easy, reliable method was not identified. The investigation of a method to analyse the enantiomeric purity of a range of α-aminonitriles was investigated. However, it transpired that this was not a viable method for the analysis of the enantiomeric purity of α-aminonitriles.

5.5 Conclusions

The overall aim of the project, to develop an asymmetric variation of the Bucherer-Bergs reaction, was not achieved. However, suitable conditions for the one-pot Lewis acid-catalysed synthesis of hydantoins from ketones were developed into a high-yielding process. Attempts to convert this procedure into an asymmetric transformation, with the use of a chiral Lewis acid catalyst, were not successful.

These conditions were developed in a step-wise fashion, where the transformation of α-aminonitriles to hydantoins was optimised into a high-yielding process that was found to be suitable for the synthesis of a range of hydantoins in excellent yield. It was established that *N*-substituted α-aminonitriles did not form hydantoins in any of the conditions attempted. The one-pot Lewis acid-catalysed synthesis of hydantoins from ketones and aldehydes was attempted in similar conditions (as the α-aminonitrile to hydantoin transformation) and was optimised into a high-yielding process, which was also suitable for the synthesis of a range of hydantoins in excellent yield.

In order to investigate if enantiomeric purity could be maintained in the developed conditions, the synthesis of a range of enantiomerically pure α-aminonitriles was investigated, but an easy, reliable method was not identified. The investigation of a method to analyse the enantiomeric purity of a range of α-aminonitriles was investigated however, it transpired that this was not a viable method for the analysis of the enantiomeric purity of α-aminonitriles.

Experimental Section

6 Experimental Section

6.1 General

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300.1 MHz) instrument, Varian Gemini 2000 (300.0 MHz) instrument, Bruker Avance II 400 (400.1 MHz) instrument or Bruker Avance 500 (499.9 MHz) instrument, using deuteriochloroform (or other indicated solvent) as reference and internal deuterium lock. The chemical shift data for each signal are given as δ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ_{TMS} = 0.00 ppm. The multiplicity of each signal is indicated by: s (singlet); br s (broad singlet); d (doublet); t (triplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); ddt (doublet of doublet of triplets); q (quartet): sp (septet) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz.

^{13}C NMR spectra were recorded on a Bruker Avance 300 (75.5 MHz) instrument, Bruker Avance II 400 (100.6 MHz) instrument or Bruker Avance 500 (125.7 MHz) instrument using the PENDANT sequence and internal deuterium lock or on a Varian Gemini 2000 (75.5 MHz) instrument using proton decoupling and internal deuterium lock. The chemical shift data for each signal are given as δ in units of ppm relative to TMS where δ_{TMS} = 0.00 ppm.

IR spectra were recorded on a Perkin-Elmer Paragon Series 1000 FTIR spectrometer as thin films between sodium chloride discs or as potassium bromide discs as indicated. Absorption maxima are reported in wavenumbers (cm^{-1}). Intensities of the maxima are quoted as strong (s), medium (m) or weak (w).

Melting points were determined using a Gallenkamp MF-370 melting point apparatus and are uncorrected.

Optical rotations were measured using an Optical Activity AA-1000 automatic polarimeter or a Bellingham+Stanley Ltd. ADP220 instrument, in cells with a path length of 2 dm or 1 dm. The concentration (c) is expressed in g/100 mL (equivalent to g/0.1 dm^3). Specific rotations are denoted $[\alpha]_D^T$ and are given in implied units of 10^{-1} deg cm^2g^{-1}, where T is temperature in °C.

Chiral HPLC analysis was performed on a Varian Pro-Star HPLC instrument, using a normal-phase Chiralpack AD column at 254 nm, eluting with either a 95/5 or 90/10 mixture of hexane/2-propanol. Where appropriate, t_r = 1 mL/min.

Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm ICN Biomedicals GmbH 60 F_{254} silica gel plates. Visualisation was by absorption of UV light, or thermal development after dipping in either an aqueous solution of potassium permanganate, potassium carbonate and sodium hydroxide; an ethanolic solution of phosphomolybdic acid (PMA) or a solution of ninhydrin in butan-2-ol.

Flash column chromatography was carried out on silica gel (Apollo Scientific Ltd. 40-63 micron) or on activated aluminium oxide (Acros, 50-200 micron, neutral) as indicated, under a positive pressure of compressed air.

Preparative thin layer chromatography was carried out on silica gel 60 F_{254} plates (1 mm) with 4 mm concentrating zone (Merck). Products were recovered by suspending the recovered silica in a methanol/dichloromethane solution (1/10); stirring the suspension for 15 mins, filtering, drying over $MgSO_4$, prior to concentration *in vacuo*.

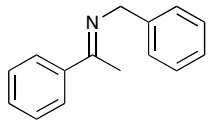
Hydrogen cyanide solutions were prepared as follows, toluene (or indicated solvent) (2 mL) and trimethylsilylcyanide (1.5 equiv. or as indicated) were combined and cooled to 5 °C. Methanol was added (1.5 equiv. or same as TMSCN) and the solution was stirred for 2 h prior to addition to the reaction vessel.

Carbonic acid solutions were prepared as follows, CO_2 (s) (10.0 g) in H_2O (100 mL, pH 7.0), leave until no more gas evolves, (pH 4.5).

Dry dichloromethane was distilled from calcium hydride in a recycling still. Diethyl ether was distilled from sodium in a recycling still using benzophenone ketyl as an indicator. Toluene was distilled from sodium in a recycling still. Dichloromethane, tetrahydrofuran, and toluene were also dried by passage through two columns of alumina using an MBRAUN (SPS-800) solvent purification system. Anhydrous *N,N*-dimethylformamide was purchased from Aldrich UK and dried by distillation from 4 Å molecular sieves onto 4 Å molecular sieves under an atmosphere of nitrogen. Chemicals were purchased from Acros UK, Aldrich UK, Avocado UK, Fisher UK or Fluka UK. All reagents and solvents were purified and dried, where necessary, by standard techniques.[107] Where appropriate and if not stated otherwise, all non-aqueous reactions were performed under an inert atmosphere of nitrogen or argon, using a vacuum manifold with the gas passed through 4 Å molecular sieves and self-indicating silica gel. *In vacuo* refers to the use of a rotary evaporator attached to a diaphragm pump. Hexane refers to a mixture of hexanes and petroleum ether to

the fraction boiling between 40 - 60 ºC. Room temperature (RT) refers to the temperature of approximately 25 °C.

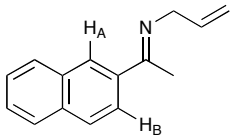
N-Benzyl(1-phenylethylidene)amine 54



54

To a mixture of acetophenone (2.92 mL, 25.0 mmol, 1 equiv.), titanium (IV) chloride (1.0 M sol. in toluene) (0.50 mL, 0.50 mmol, 0.02 equiv.) and 4 Å molecular sieves (3 g) in toluene (25 mL) was added benzylamine (4.10 mL, 37.5 mmol, 1.5 equiv.) under an inert atmosphere. The reaction mixture was stirred for 20 h at RT, after which time ^{1}H NMR spectroscopic analysis indicated a 65 % conversion of starting materials to products. The reaction mixture was filtered through Celite,® washed with toluene and the solvent was removed *in vacuo* to give a crude oil. Cooling of this oil overnight resulted in the precipitation of a solid, which was isolated by filtration and crystallised from hexanes to give *N*-benzyl(1-phenylethylidene)amine **54** (2.73 g, 52 % yield) as a yellow solid. mp 41 - 43 °C (*from hexanes*, lit.,[108] 43 - 44 °C); *E*/*Z* 17/1 (by ^{1}H NMR); δ_H (300 MHz; $CDCl_3$), 7.93-7.87 (2H, m, aromatic C*H* × 2), 7.50-7.25 (8H, m, aromatic C*H* × 8), 4.78 (2H, s, NCH_2Ph), 2.37 (3H, s, CH_3); δ_C (75.5 MHz; $CDCl_3$), 166.0, 141.1, 140.6, 129.6, 128.4, 128.5 (2C), 127.7 (2C), 126.8 (2C), 126.6 (2C), 55.7, 15.9; *m/z* (ES^+) 210 ($[M+H]^+$, 100 %). These data are in agreement with the literature values.[108,109]

N-Allyl(1-naphthalen-2-ylethylidene)amine 55



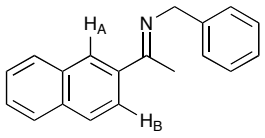
55

To a mixture of 2-acetylnaphthalene (2.38 g, 14.0 mmol, 1 equiv.), 4 Å molecular sieves (3 g) and titanium (IV) chloride (1.0 M in toluene) (0.28 mL, 0.28 mmol, 0.02 equiv.) in toluene (15 mL) was added allylamine (1.58 mL, 21.0 mmol, 1.5 equiv.) under an inert atmosphere. The reaction mixture was stirred for 3 h at RT, after which time ^{1}H NMR spectroscopic analysis indicated a 94 % conversion of starting materials to products. The reaction mixture was filtered through Celite,® washed with toluene and the solvent was removed *in vacuo*. The crude material was crystallised from hexanes to give *N*-allyl(1-naphthalen-2-ylethylidene)amine **55** (2.41 g, 82 % yield) as a colourless crystalline solid. mp 41 - 43 °C (*from hexanes*);

E/*Z* 20/1 (by ^{1}H NMR); δ_H (300 MHz; $CDCl_3$), 8.11 (1H, br s, aromatic CH_A), 8.01 (1H, dd, *J* 1.8, 8.5, aromatic CH_B), 7.87-7.73 (3H, m, aromatic C*H* × 3), 7.47-7.37 (2H, m, aromatic C*H* × 2), 6.09 (1H, ddt, *J* 5.5, 10.3, 17.2, NCH_2CHCH_2), 5.22 (1H, dddd [apparent dq], *J* 1.7, 1.7, 1.7, 17.2, $NCH_2CHCH_AH_B$), 5.11 (1H, dddd [apparent dq], *J* 1.7, 1.7, 1.7, 10.3, $NCH_2CHCH_AH_B$), 4.18 (2H, d, *J* 5.5, NCH_2CHCH_2), 2.30 (3H, s, CH_3); δ_C (75.5 MHz; $CDCl_3$), 166.1, 138.4, 136.1, 134.1, 133.0, 128.8, 127.9, 127.6, 126.7, 126.6, 126.2, 124.3, 115.3, 54.8, 15.6; *m/z* (ES^+) 210 ($[M+H]^+$, 100 %); 232 ($[M+Na]^+$, 50 %). These data are in agreement with the literature values.[76]

Repeat Synthesis - 2-Acetylnaphthalene (17.0 g, 100 mmol, 1 equiv.), 20 h, 90 % conversion. *N*-Allyl-(1-naphthalen-2-ylethylidene) amine **55** (18.2 g, 87 % yield) as a yellow crystalline solid. The data obtained are in agreement with other syntheses of this compound.

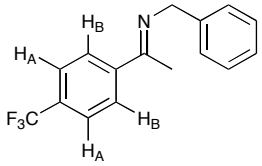
N-Benzyl(1-naphthalen-2-ylethylidene)amine 56



56

To a mixture of 2-acetylnaphthalene (2.38 g, 14.0 mmol, 1 equiv.), 4 Å molecular sieves (3 g) and titanium (IV) chloride (1.0 M in toluene) (0.28 mL, 0.28 mmol, 0.02 equiv.) in toluene (15 mL) was added benzylamine (1.50 mL, 14.0 mmol, 1 equiv.) under an inert atmosphere. The reaction mixture was stirred for 22 h at RT, after which time ^{1}H NMR spectroscopic analysis indicated a 65 % conversion of starting materials to products. The reaction mixture was filtered through Celite,® washed with toluene and the solvent was removed *in vacuo*. The crude was crystallised from hexanes to give *N*-benzyl(1-naphthalen-2-ylethylidene)amine **56** (2.18 g, 60 % yield) as a colourless solid. mp 107 - 108 °C (*from hexanes,* lit.,[109] 108 - 110 °C); *E*/*Z* 20/1 (by ^{1}H NMR); δ_H (300 MHz; $CDCl_3$), 8.24 (1H, br s, aromatic CH_A), 8.18 (1H, dd, *J* 1.8, 8.7, aromatic CH_B), 7.96-7.81 (3H, m, aromatic C*H* × 3), 7.57-7.22 (7H, m, aromatic C*H* × 7), 4.82 (2H, s, NCH_2Ph), 2.47 (3H, s, CH_3); δ_C (75.5 MHz; $CDCl_3$), 165.9, 140.6, 138.3, 134.1, 133.1, 128.8, 128.5 (2C), 127.9, 127.8, 127.7, 126.8, 126.7, 126.6, 126.2, 124.4, 123.9, 55.9, 15.8; *m/z* (ES^+) 260 ($[M+H]^+$, 100 %), 282 ($[M+Na]^+$, 20 %). These data are in agreement with the literature values.[109]

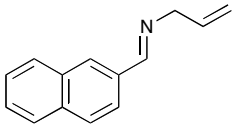
N-Benzyl[1-(4'-trifluoromethyl)phenylethylidene]amine 57



57

To a mixture of 4'-trifluoromethylacetophenone (2.63 g, 14.0 mmol, 1 equiv.), 4 Å molecular sieves (3 g) and titanium (IV) chloride (1.0 M in toluene) (0.28 mL, 0.28 mmol, 0.02 equiv.) in toluene (15 mL) was added benzylamine (1.50 mL, 14.0 mmol, 1 equiv.) under an inert atmosphere. The reaction mixture was stirred for 20 h at RT, after which time ^{1}H NMR spectroscopic analysis indicated a 99 % conversion of starting materials to products. The reaction mixture was filtered through Celite,® washed with toluene and concentrated *in vacuo* to give *N*-benzyl(1-[4'-trifluoromethylphenyl]ethylidene)amine **57** (3.19 g, 82 % yield) as a clear oil. *E*/*Z* 20/1 (by ^{1}H NMR); δ_H (300 MHz; $CDCl_3$), 7.91-7.85 (2H, m, aromatic CH_A × 2), 7.58-7.52 (2H, m, aromatic CH_B × 2), 7.38-7.13 (5H, m, aromatic C*H* × 5), 4.67 (2H, s, NCH_2Ph), 2.27 (3H, s, CH_3); *m/z* (ES^+) 278 ($[M+H]^+$, 100 %), 300 ($[M+Na]^+$, 70 %). These data are in agreement with the literature values.[76]

N-(Allyl)naphthalen-2-ylmethyleneamine 58

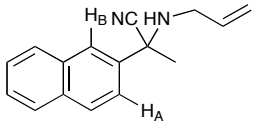


58

To a mixture of 2-naphthaldehyde (3.12 g, 20.0 mmol, 1 equiv.), 4 Å molecular sieves (3 g) and ethanol (0.60 mL, 10 mmol, 0.5 equiv.) in toluene (20 mL) was added allylamine (2.25 mL, 30.0 mmol, 1.5 equiv.) under an inert atmosphere. The reaction mixture was stirred for 16 h at RT, after which time ^{1}H NMR spectroscopic analysis indicated that the reaction was complete. The reaction mixture was filtered under a constant flush of nitrogen and concentrated *in vacuo*. The crude material was crystallised from hexanes to give *N*-(allyl)naphthalen-2-ylmethyleneamine **58** (2.28 g, 58 % yield) as a colourless solid. mp 49 - 51 °C (*from hexanes*, lit.,[110] 51 °C); δ_H (300 MHz; $CDCl_3$), 8.49 (1H, s, N=C*H*), 8.14-8.04 (2H, m, aromatic C*H* × 2), 7.99-7.85 (3H, m, aromatic C*H* × 3), 7.62-7.50 (2H, m, aromatic C*H* × 2), 5.86 (1H, ddt, *J* 5.5, 10.2, 17.2, NCH_2CHCH_2), 5.33 (1H, dddd [apparent dq], *J* 1.6, 1.6,

1.6, 17.2, $NCH_2CHCH_AH_B$), 5.24 (1H, dddd, *J* 1.6, 1.6, 1.6, 10.2, $NCH_2CHCH_AH_B$), 4.37 (2H, m, NCH_2CHCH_2); δ_C (75.5 MHz; $CDCl_3$), 162.1, 136.0, 134.8, 133.9, 133.1, 130.0, 128.6, 128.5, 127.9, 127.2, 126.5, 123.9, 116.2, 63.7; *m/z* (ES^+) 196 ($[M+H]^+$, 100 %), 218 ($[M+Na]^+$, 20 %). These data are in agreement with the literature values.[110]

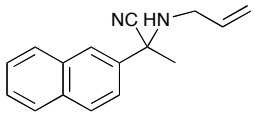
2-Allylamino-2-naphthalen-2-ylpropionitrile 59



59

A solution of *N*-allyl(1-naphthalen-2-ylethylidene)amine **55** (0.21 g, 1.00 mmol, 1 equiv.) in dichloromethane (2 mL) was cooled to 5 °C prior to the addition of hydrogen cyanide solution (1.5 equiv. in PhMe, 2 mL) under an inert atmosphere. The reaction mixture was stirred for 10 h at 5 °C, after which time ^{1}H NMR spectroscopic analysis indicated complete conversion of starting materials to products. The solvents were removed *in vacuo*; the crude material was suspended in diethyl ether and left to cool at 0 °C overnight. Filtration followed by concentration *in vacuo* gave 2-allylamino-2-naphthalen-2-ylpropionitrile **59** (0.22 g, 93 % yield) as a clear oil. R_f 0.6 (40/60 ethyl acetate/petroleum ether); δ_H (400.1 MHz; $CDCl_3$), 8.05 (1H, d, *J* 1.8, aromatic CH_B), 7.85-7.75 (3H, m, aromatic C*H* × 3), 7.61 (1H, dd, *J* 1.8, 8.7, aromatic CH_A), 7.48-7.42 (2H, m, aromatic C*H* × 2), 5.84 (1H, dddd, *J* 5.2, 6.5, 10.2, 17.2, NCH_2CHCH_2), 5.20 (1H, dddd [apparent dq], *J* 1.6, 1.6, 1.6, 17.2, $NCH_2CHCH_AH_B$), 5.05 (1H, dddd [apparent dq], *J* 1.6, 1.6, 1.6, 10.2, $NCH_2CHCH_AH_B$), 3.33 (1H, dd, *J* 6.5, 13.5, $NCH_AH_BCHCH_2$), 2.98 (1H, dd, *J* 5.2, 13.5, $HNCH_AH_BCHCH_2$), 1.77 (3H, s, CH_3), 1.65 (1H, br s, N*H*); δ_C (75.5 MHz; $CDCl_3$), 137.0, 135.3, 133.3, 133.0, 129.0, 128.3, 127.6, 126.7, 126.6, 125.1, 122.7, 121.4, 116.7, 60.4, 48.0, 31.1; *m/z* (Cl^+) 237 ($[M+H]^+$, 20 %), 209 ($[M-HCN]^+$, 100 %). These data are in agreement with the literature values.[76]

2-Allylamino-2-naphthalen-2-ylpropionitrile 59

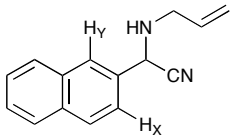


59

A solution of *N*-allyl(1-naphthalen-2-ylethylidene)amine **55** (1.30 g, 6.22 mmol, 1 equiv.) and titanium (IV) chloride (1.0 M in toluene) (0.12 mL, 0.12 mmol, 0.02 equiv.) in toluene (40 mL) was cooled to 5 °C prior to the addition of hydrogen cyanide solution (1.5 equiv. in PhMe, 2 mL) under an inert atmosphere. The solution was allowed to stir for 24 h at 5 °C, after which time ^{1}H NMR spectroscopic analysis indicated an 81 % conversion of starting materials to products. The solvents were removed *in vacuo*; the crude was suspended in diethyl ether and left to cool at 0 °C overnight. The sample was filtered and the solvent was removed *in vacuo* to give 2-allylamino-2-naphthalen-2-ylpropionitrile **59** (1.16 g, 79 % yield) as a brown oil. Attempts to remove the colour impurity were unsuccessful. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - *N*-Allyl(1-naphthalen-2-ylethylidene)amine **55** (5.00 g, 24.0 mmol, 1 equiv.), 40 h, 96 % conversion; 2-allylamino-2-naphthalen-2-yl propionitrile **59** (5.02 g, 88 % yield) as a brown oil. The data obtained are in agreement with other syntheses of this compound.

1-*N*-(Allylamino)-1-naphthalen-2-ylacetonitrile 60

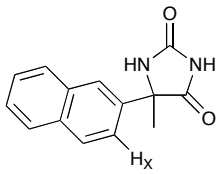


60

To a solution of *N*-(allyl)naphthalen-2-ylmethyleneamine **58** (1.50 g, 7.69 mmol, 1 equiv.) and titanium (IV) chloride (1.0 M in toluene) (0.15 mL, 0.15 mmol, 0.02 equiv.) in toluene (25 mL) was added a solution of hydrogen cyanide (1.5 equiv. in PhMe, 2 mL) under an inert atmosphere. The solution was allowed to stir for 16 h at 5 °C, after which time ^{1}H NMR spectroscopic analysis indicated a 95 % conversion of starting materials to products. The solvents were removed *in vacuo*; the crude material was suspended in diethyl ether and left to cool at 0 °C overnight. Filtration and concentration *in vacuo* gave 1-*N*-(allylamino)-1-naphthalen-

2-ylacetonitrile **60** (1.53 g, 90 % yield) as a brown oil. R_f 0.5 (40/60 ethyl acetate/petroleum ether); ν_{max} (thin film)/cm^{-1} 3323 (m), 3058 (m), 2840 (m), 2225 (w), 1644 (m), 1601 (m), 1508 (m), 1455 (m), 1418 (w), 1362 (w), 925 (s), 858 (s), 819 (s), 750 (s); δ_H (400.1 MHz; $CDCl_3$), 7.87 (1H, br s, aromatic CH_Y), 7.84-7.76 (3H, m, aromatic C*H* × 3), 7.53 (1H, dd, *J* 1.8, 8.5, aromatic CH_X), 7.49-7.44 (2H, m, aromatic C*H* × 2), 5.86 (1H, dddd, *J* 5.5, 6.5, 10.2, 17.2, NCH_2CHCH_2), 5.28 (1H, dddd [apparent dq], *J* 1.5, 1.5, 1.5, 17.2, $NCH_2CHCH_AH_B$), 5.16 (1H, dddd [apparent dq], *J* 1.5, 1.5, 1.5, 10.2, $NCH_2CHCH_AH_B$), 4.91 (1H, s, C*H*), 3.48 (1H, dddd [apparent ddt], *J* 1.5, 1.5, 5.5, 13.7, $NCH_AH_BCHCH_2$), 3.40 (1H, dddd [apparent ddt], *J* 1.5, 1.5, 6.5, 13.7, $NCH_AH_BCHCH_2$), 1.88 (1H, br s, N*H*); δ_C (75.5 MHz; $CDCl_3$), 134.8, 133.4, 133.1, 132.1, 129.0, 128.2, 127.8, 126.9, 126.8, 126.5, 124.8, 118.8, 118.0, 53.7, 50.0; HRMS *m/z* (ES$^+$) [found (M+H)$^+$ 233.1229, $C_{15}H_{15}N_2$ requires M$^+$ 223.1231]; *m/z* (ES$^+$) 223 ([M+H]$^+$, 100 %); 196 ([M-CN]$^+$, 60 %), 182 ([$C_{12}H_9N_2^+$], 40 %).

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65

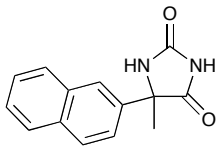


65

A solution of 2-allylamino-2-naphthalen-2-ylpropionitrile **59** (1.00 g, 4.23 mmol, 1 equiv.) and ammonium carbonate (0.45 g, 4.65 mmol, 1.1 equiv) in water (5 mL) was stirred at RT and after 80 h, another reaction equivalent of ammonium carbonate was added. After 170 h the solvents were removed *in vacuo* and the crude was purified by silica gel column chromatography [eluting with 5/95 ethyl acetate/petroleum ether (1.2 L), 30/70 (800 mL), 45/55 (1.2 L)] to give 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (27.0 mg, 3 % yield) as a colourless solid. R_f 0.2 (50/50 ethyl acetate/petroleum ether); mp 246 - 248 °C (*from ethanol*, lit.,[86] 247 - 248 °C); ν_{max} (KBr disc)/cm^{-1} 3450 (s), 3210 (m), 1773 (m), 1719 (m), 1638 (m), 1400 (w), 638 (w); δ_H (300 MHz; D^6-DMSO), 10.80 (1H, br s, N*H*), 8.71 (1H, s, N*H*), 8.00-7.88 (4H, m, aromatic C*H* × 4), 7.59 (1H, dd, *J* 2.0, 8.6, aromatic CH_X), 7.56-7.49 (2H, m, aromatic C*H* × 2), 1.75 (3H, s, CH_3); δ_C (75.5 MHz; D^6-DMSO), 177.3, 156.7, 137.7, 132.9, 132.6, 128.6, 128.5, 127.8, 126.9, 126.8, 124.5, 124.0, 64.5, 25.1; HRMS *m/z* (CI$^+$) [found (M+H)$^+$ 241.0975, $C_{14}H_{13}N_2O_2$ requires M$^+$

241.0977]; *m/z* (CI$^+$) 241 ([M+H]$^+$, 100 %), 113 ([$C_4H_5N_2O_2$]$^+$, 70 %); Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7 Found: C, 69.8; H, 4.8; N, 11.6. These data are in agreement with the literature values.[86]

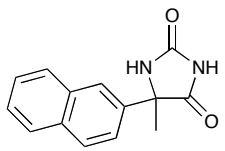
5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



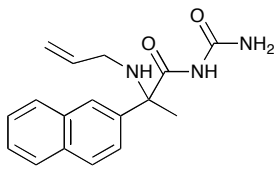
65

A solution of 2-acetylnaphthalene (5.11 g, 30.0 mmol, 1 equiv.), potassium cyanide (3.91 g, 60.0 mmol, 2 equiv.) and ammonium carbonate (11.5 g, 120 mmol, 4 equiv.) in ethanol/water (1/1, 70 mL) was stirred at 60 °C for 24 h, after which time TLC analysis indicated that the reaction was complete. The reaction solution was concentrated *in vacuo* to a volume of 30 mL, and the organics were extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo.* The crude material was purified by silica gel column chromatography [eluting with 35/65 ethyl acetate/petroleum ether (1.0 L), ethyl acetate (500 mL)] and recrystallised from ethanol to give 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (6.02 g, 84 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65 and (2-allylamino-2-naphthalen-2-yl propionyl)urea 66



65



66

A solution of 2-allylamino-2-naphthalen-2-ylpropionitrile **59** (1.00 g, 4.23 mmol, 1 equiv.), ammonium carbonate (0.45 g, 4.65 mmol, 1.1 equiv) and titanium (IV) chloride (1.0 M in toluene) (0.28 mL, 0.28 mmol, 62.0 × 10^{-3} equiv.) in toluene (15 mL) was heated to 100 °C, under CO_2 (g) at a pressure of 100 psi. After 24 h the solvents were removed *in vacuo* and the crude was purified by silica gel column chromatography [eluting with 5/95 ethyl acetate/petroleum ether (1.2 L), 30/70 (800 mL), 45/55 (1.2 L), 70/30 (800 mL)] to give 5-methyl-5-naphthalen-2-yl

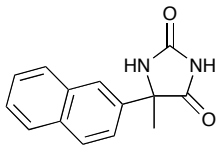
imidazolidine-2,4-dione **65** (91.0 mg, 9 % yield) as a colourless solid and *(2-allylamino-2-naphthalen-2-ylpropionyl)urea* **66** (122 mg, 10 % yield) as a yellow solid.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione **65** - the data obtained are in agreement with other syntheses of this compound.

(2-Allylamino-2-naphthalen-2-ylpropionyl)urea **66** - R_f 0.1 (50/50 ethyl acetate/ petroleum ether); mp 120 - 130 °C; ν_{max} (KBr disc)/cm^{-1} 3352 (s), 3010 (s), 2968 (s), 1700 (s), 1635 (s), 1556 (s), 1442 (s), 1351 (s), 1273 (s), 1130 (s), 857 (s), 817 (s), 749 (s); δ_H (499.9 MHz; $CDCl_3$), 7.95-7.81 (4H, m, aromatic C*H* × 4), 7.55-7.46 (3H, m, aromatic C*H* × 3), 7.25-7.15 (2H, m, CONH_2), 7.02 (1H, br s, CON*H*CO), 6.62 (1H, t, *J* 5.7, N*H*CH_2CHCH_2), 5.75 (1H, dddd, *J* 5.0, 5.0, 10.3, 17.2, $NHCH_2CHCH_2$), 5.11 (1H, dd, *J* 1.5, 17.2, $NHCH_2CHCH_AH_B$), 5.00 (1H, dd, *J* 1.5, 10.3, $NHCH_2CHCH_AH_B$), 3.53 (2H, dd [apparent t], *J* 5.0, 5.0, $NHCH_2CHCH_2$), 1.97 (3H, s, CH_3); δ_C (75.5 MHz; $CDCl_3$), 177.1, 157.6, 140.1, 135.7, 133.5, 133.0, 129.0, 128.6, 127.9, 126.8, 126.7, 124.8, 124.2, 115.7, 62.8, 42.9, 25.8; HRMS *m/z* (ES^+) [found $(M+Na)^+$ 320.1368, $C_{17}H_{19}N_3O_2Na$ requires M^+ 320.1375]; *m/z* (ES^+) 320 ($[M+Na]^+$, 100 %); Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.7; H, 6.4; N, 14.1; Found: C, 68.5; H, 6.6; N, 13.9.

Repeat Synthesis - 2-Allylamino-2-naphthalen-2-ylpropionitrile **59** (1.35 g, 5.71 mmol, 1 equiv.), 24 h, 5-methyl-5-naphthalen-2-ylimidazolidine-2,4-dione **65** (39.0 mg, 3 % yield) as a colourless solid and *(2-allylamino-2-naphthalen-2-yl propionyl)urea* **66** (37.0 mg, 2 % yield) as a yellow solid. The data obtained for both compounds are in agreement with other syntheses of these compounds.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65

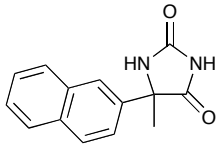


65

A mixture of 2-acetylnaphthalene (1.00 g, 5.88 mmol, 1 equiv.), potassium cyanide (0.38 g, 5.88 mmol, 1 equiv.), ammonium carbonate (0.57 g, 5.88 mmol, 1 equiv.) and titanium (IV) chloride (1.0 M in toluene) (0.24 mL, 0.24 mmol, 0.04 equiv.) in toluene (20 mL) was prepared under an inert atmosphere. The mixture was stirred

for 24 h at 100 °C, under CO_2 (g) at a pressure of 100 psi. The reaction vessel was washed with methanol (20 mL) and the solvents were removed *in vacuo*. The resulting paste was suspended in water and extracted with ethyl acetate (3 × 30 mL). The extracts were combined, dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The crude was purified by silica gel column chromatography [eluting with 10/90 ethyl acetate/petroleum ether (250 mL), 20/80 (250 mL), ethyl acetate (500 mL)] to give 5-methyl-5-naphthalen-2-ylimidazolidine-2,4-dione **65** (66.0 mg, 5 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



65

A solution of 2-allylamino-2-naphthalen-2-ylpropionitrile **59** (1.00 g, 4.22 mmol, 1 equiv.) in toluene (10 mL) was stirred in supercritical CO_2 (120 bar) at 80 °C, for 72 h. The solvent was removed *in vacuo* and the crude was purified by silica gel column chromatography [eluting with 5/95 ethyl acetate/petroleum ether (300 mL), 30/70 (500 mL), 40/60 (300 mL), ethyl acetate (400 mL)] to give 5-methyl-5-naphthalen-2-ylimidazolidine-2,4-dione **65** (63.0 mg, 6 % yield) as a colourless solid. The data obtained are in agreement with other synthesis of this compound.

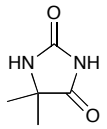
2-Amino-2-methylpropionitrile 70

70

A solution of acetone (8.10 mL, 111 mmol, 1.2 equiv.), ammonium chloride (4.92 g, 92.2 mmol, 1 equiv.) and potassium cyanide (6.00 g, 92.2 mmol, 1 equiv.) in water (100 mL) was stirred for 16 h at RT, after which time TLC analysis indicated that a new product had been formed. The organic components were extracted with diethyl ether (4 × 50 mL) and combined, washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated carefully *in vacuo*. The crude material was distilled (600 mbar, 30 °C) to give 2-amino-2-methylpropionitrile **70** (7.69 g, 99 % yield) as a colourless oil. R_f 0.5 (50/50 ethyl acetate/petroleum ether); δ_H (300 MHz;

$CDCl_3$), 1.89 (2H, br s, NH_2), 1.49 (6H, s, CH_3 × 2); δ_C (100.6 MHz; $CDCl_3$), 125.2, 46.0, 29.2 (2C). These data are in agreement with the literature values.[111]

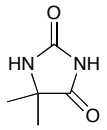
5,5-Dimethylimidazolidine-2,4-dione 71



71

A solution of 2-amino-2-methylpropionitrile **70** (2.00 g, 23.8 mmol, 1 equiv.) in water (2.10 mL) was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution for 15 h, until TLC analysis indicated that the starting material had been consumed. The solvent was removed *in vacuo* and the resulting colourless solid was purified by silica gel column chromatography [eluting with 60/40 ethyl acetate/petroleum ether (1.0 L), ethyl acetate (1.0 L)] followed by crystallisation from ethanol gave 5,5-dimethyl imidazolidine-2,4-dione **71** (0.28 g, 9 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 167 - 168 °C (*from ethanol*, lit.,[112] 170 - 174 °C); ν_{max} (KBr disc)/cm^{-1} 3222 (s), 1770 (s), 1708 (s), 1442 (s), 1290 (m), 799 (s), 769 (s); δ_H (300 MHz; D^6-DMSO), 10.59 (1H, s, N*H*), 7.96 (1H, s, N*H*), 1.23 (6H, s, CH_3 × 2); δ_C (100.6 MHz; D^6-DMSO), 179.1, 155.9, 58.8, 24.5 (2C); *m/z* (ES^-) 127 ([M-H]$^-$, 100 %); Anal. Calcd. for $C_5H_8N_2O_2$: C, 46.9; H, 6.3; N, 21.9; Found: C, 47.1; H, 6.5; N, 22.2. These data are in agreement with the literature values.[112]

5,5-Dimethylimidazolidine-2,4-dione 71

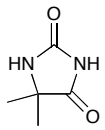


71

A solution of 2-amino-2-methylpropionitrile **70** (1.00 g, 11.9 mmol, 1 equiv.) in carbonic acid solution (1.10 mL) was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution for 24 h. The reaction solution was heated to 60 °C for 24 h, after which time, TLC analysis indicated that the starting material had been consumed. The solvent was removed *in vacuo* and the resulting paste was suspended in water (10 mL). The organic components were extracted with ethyl acetate (3 × 20 mL) and

combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. No further purification was necessary to give 5,5-dimethyl imidazolidine-2,4-dione **71** (0.72 g, 47 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

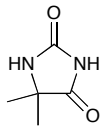
5,5-Dimethylimidazolidine-2,4-dione 71



71

A solution of 2-amino-2-methylpropionitrile **70** (0.84 g, 9.96 mmol, 1 equiv.) in carbonic acid solution (1.80 mL) was stirred at 4 °C for 48 h, after which time, CO_2 (s) (approx. 0.50 g every 30 mins) was added to the reaction mixture. After a further 24 h, TLC analysis indicated that the starting material had been consumed. The organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5,5-dimethylimidazolidine-2,4-dione **71** (0.63 g, 50 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

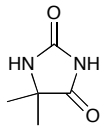
5,5-Dimethylimidazolidine-2,4-dione 71



71

A solution of 2-amino-2-methylpropionitrile **70** (1.00 g, 11.9 mmol, 1 equiv.) in carbonic acid solution (2.10 mL) was stirred at RT with the addition of CO_2 (s) (approx. 0.50 g every 30 mins) to the reaction mixture. After 17 h, TLC analysis indicated that the starting material had been consumed. The organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5,5-dimethylimidazolidine-2,4-dione **71** (0.62 g, 41 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

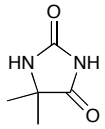
5,5-Dimethylimidazolidine-2,4-dione 71



71

A solution of 2-amino-2-methylpropionitrile **70** (1.00 g, 11.9 mmol, 1 equiv.) in carbonic acid solution (2.10 mL) was stirred for 6 h at 60 °C with the addition of CO_2 (s) (approx. 0.50 g every 30 mins). The reaction solution was stirred for a further 12 h at RT after which time TLC analysis indicated that the starting material had been consumed. The organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5,5-dimethyl imidazolidine-2,4-dione **71** (0.64 g, 42 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

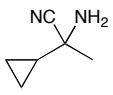
5,5-Dimethylimidazolidine-2,4-dione 71



71

A solution of 2-amino-2-methylpropionitrile **70** (1.00 g, 11.9 mmol, 1 equiv.) in carbonic acid solution (2.10 mL), was stirred at 100 °C with the addition of CO_2 (s) (approx. 0.50 g every 30 mins). After 5 h, TLC analysis indicated that the starting material had been consumed. The organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5,5-dimethylimidazolidine-2,4-dione **71** (0.31 g, 20 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

2-Amino-2-cyclopropylpropionitrile 74

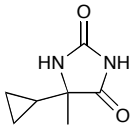


74

A solution of ammonium chloride (1.70 g, 31.8 mmol, 1.06 equiv.), cyclopropyl methylketone (3.00 mL, 30.0 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v

sol. in H_2O) (3.80 mL, 31.8 mmol, 1.06 equiv.) in water (15 mL) was cooled to 4 °C and potassium cyanide (2.07 g, 31.8 mmol, 1.06 equiv.) was added portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The organic components were extracted with dichloromethane (3 × 30 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated carefully *in vacuo*. The crude material was distilled (0.5 mbar, RT) to give 2-amino-2-cyclopropylpropionitrile **74** (2.89 g, 88 % yield) as a colourless oil. R_f 0.6 (50/50 ethyl acetate/petroleum ether); δ_H (300 MHz; $CDCl_3$), 1.94 (2H, br s, N*H*$_2$), 1.57 (3H, s, C*H*$_3$), 1.17-0.98 (1H, m, cyclopropyl C*H*), 0.66-0.50 (4H, m, cyclopropyl C*H*$_2$ × 2); δ_C (100.6 MHz; $CDCl_3$), 120.7, 50.7, 26.1, 18.7, 0.08, 0.00; *m/z* (ES^+) 84 ($[M\text{-}CN]^+$, 100 %). These data are in agreement with literature values.[97]

5-Methyl-5-cyclopropylimidazolidine-2,4-dione 75

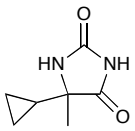


75

A solution of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.) in water (1.80 mL) was stirred at RT with the addition of CO_2 (s) (approx. 0.50 g every 30 mins) to the reaction mixture. After 12 h, TLC analysis indicated that the starting material had been consumed. The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropylimidazolidine-2,4-dione **75** (0.35 g, 50 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 145 - 146 °C (*from ethyl acetate*, lit.,[113] 147 - 148 °C); ν_{max} (KBr disc)/cm^{-1} 3420 (s), 3240 (s), 3010 (m), 1775 (s), 1720 (s), 1429 (m), 1265 (w), 1113 (w), 792 (w), 771 (w), 760 (w); δ_H (300 MHz; D^6-DMSO), 10.39 (1H, br s, N*H*), 7.58 (1H, s, N*H*), 1.18 (3H, s, C*H*$_3$), 0.99-0.88 (1H, m, cyclopropyl C*H*), 0.34-0.14 (3H, m, cyclopropyl C*H*$_2$ and C*H*H), 0.04-(-)0.06 (1H, m, cyclopropyl CH*H*); δ_C (75.5 MHz; D^6-DMSO), 178.8, 156.9, 61.3, 23.4, 17.4, 0.61, 0.00; HRMS *m/z* (ES^+) [found $(M+Na)^+$ 177.0642, $C_7H_{10}N_2O_2Na$ requires M^+ 177.0640]; *m/z* (ES^+) 177 ($[M+Na]^+$, 100 %); (ES^-) 153 ($[M\text{-}H]^-$, 100 %); Anal. Calcd.

for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.5; N, 18.2; Found: C, 54.1; H, 6.7; N, 18.1. These data are in agreement with the literature values.[113,114]

General Conditions for the Inclusion of Various Additives for the Synthesis of 5-Methyl-5-Cyclopropylimidazolidine-2,4-dione 75



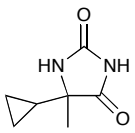
75

A solution of 2-amino-2-cyclopropylpropionitrile **74** (1 equiv.) and additive(s) (X equiv., see Table **23**) in water (5 mL) was stirred at RT with the addition of CO_2 (s) (approx. 0.50 g every 30 mins) to the reaction mixture. After time (X h, see Table **23**), TLC analysis indicated that the starting material had been consumed. The organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropylimidazolidine-2,4-dione **75** (X g, X % yield, see Table **23**). The data obtained for each product are in agreement with other syntheses of this compound.

Additive	Equiv.	Reaction Time (h)	Wt. of Product (g)	Yield (%)
KCN	1	12	0.56	40
	1	12	0.63	45
	4	10	0.79	56
HCN (sol.)	1	12	0.22	16
acetyl chloride	0.1	10	0.24	17
KCN and NH_3	2 and 4	6	0.68	68
NH_3	1	12	0.36	52
	2	10	0.45	64
	2	10	0.44	63
	2	9	0.44	62
	2.5	10	0.44	62
	3	10	0.49	71
	3	10	0.45	65
	3.5	10	0.46	66
	4	8	0.49	70
	4	8	0.45	64
	5	10	0.46	66
	10	10	0.41	59
trimethylamine	3	6	0.49	70
	4	6	0.48	69
triethylamine	1	5	0.31	44
	2	5	0.41	58
	3	5	0.43	61
	4	5	0.41	58
DBU	1	12	0.18	26
	3	11	0.28	40
	4	11	0.24	34
Hünig's base	3	6	0.54	77
	4	6	0.52	75

Table 23 - Experimental conditions for the inclusion of various additives in the hydantoin-forming reaction.

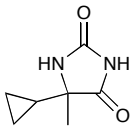
5-Methyl-5-cyclopropylimidazolidine-2,4-dione 75



75

A solution of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.) and Hünig's base (2.37 mL, 13.6 mmol, 3 equiv.) in dichloromethane (5 mL) was stirred at RT with the addition of CO_2 (s) (approx. 0.50 g every 30 mins) to the reaction mixture. After 8 h, TLC analysis indicated that the starting material had been consumed. The organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with 0.1 M HCl (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropylimidazolidine-2,4-dione **75** (0.62 g, 88 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

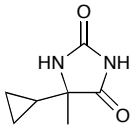
5-Methyl-5-cyclopropylimidazolidine-2,4-dione 75



75

A solution of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.) and Hünig's base (2.37 mL, 13.6 mmol, 3 equiv.) in dichloromethane (5 mL) was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution until TLC analysis indicated that the starting material had been consumed. After 12 h, the organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with 0.1 M HCl (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropylimidazolidine-2,4-dione **75** (0.63 g, 90 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

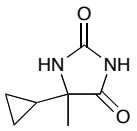
5-Methyl-5-cyclopropylimidazolidine-2,4-dione 75



75

A solution of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.) and Hünig's base (2.37 mL, 13.6 mmol, 3 equiv.) in dichloromethane (5 mL) was stirred at RT and CO_2 (g) (from a lecture bottle) was bubbled through the reaction solution until TLC analysis indicated that the starting material had been consumed. After 12 h the organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with 0.1 M HCl (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropylimidazolidine-2,4-dione **75** (0.59 g, 85 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

General conditions for the inclusion of various bases for the synthesis of 5-methyl-5-cyclopropylimidazolidine-2,4-dione 75 in dichloromethane



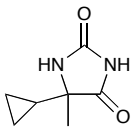
75

A solution of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.) and base (3 equiv., see Table **24**) in dichloromethane (5 mL) was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution. After 12 h, the solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropyl imidazolidine-2,4-dione **75** (X g, X % yield, see Table **24**). The data obtained for each product are in agreement with other syntheses of this compound.

Base	Wt. of Product (g)	Yield (%)
DMAP	0.48	68
	0.46	66
N,*N*-dimethylbutylamine	0.24	34
	0.18	25
N-methylpiperidine	0.25	35
	0.21	30
N,*N*-dimethylisopropylamine	0.26	37
	0.24	34
N-methyldibutylamine	0.24	34
	0.10	15
triethylamine	0.64	91
	0.53	75
tributylamine	0.18	25
	97.0×10^{-3}	14
Hünig's base	0.66	94
	0.63	90

Table 24 - Experimental conditions for the inclusion of various bases in the hydantoin-forming reaction.

General Conditions for the Inclusion of Various Solvents for the Synthesis of 5-Methyl-5-Cyclopropylimidazolidine-2,4-dione 75



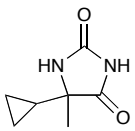
75

A solution of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.) and Hünig's base (2.37 mL, 13.6 mmol, 3 equiv.) in solvent (5 mL, see Table **25**), was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution. After 12 h, the solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropylimidazolidine-2,4-dione **75** (X g, X % yield, see Table **25**).

Solvent	Wt. of Product (g)	Yield (%)
dichloromethane	see Table **24**	see Table **24**
ethyl acetate	0.56	80
	0.43	62
ethanol	0.52	75
	0.50	71
no solvent	0.52	74
	0.47	67
tetrahydrofuran	0.50	71
	0.40	57
diethyl ether	0.45	65
acetonitrile	0.39	56
Hünig's base	0.37	52
	0.28	40
dimethylformamide	0.35	50
toluene	0.31	45
water	0.22	32

Table 25 - Experimental conditions for the inclusion of various solvents in the hydantoin-forming reaction.

5-Methyl-5-cyclopropylimidazolidine-2,4-dione 75

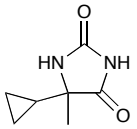


75

A mixture of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.), ytterium (III) triflate (0.49 g, 0.91 mmol, 0.2 equiv.) and Hünig's base (2.37 mL,

13.6 mmol, 3 equiv.) in dichloromethane (5 mL), was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution. After 12 h, the solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropyl imidazolidine-2,4-dione **75** (0.27 g, 39 % yield). The data obtained are in agreement with other syntheses of this compound.

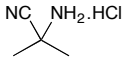
5-Methyl-5-cyclopropylimidazolidine-2,4-dione 75



75

A mixture of 2-amino-2-cyclopropylpropionitrile **74** (0.50 g, 4.54 mmol, 1 equiv.), gallium (III) triflate (0.47 g, 0.91 mmol, 0.2 equiv.) and Hünig's base (2.37 mL, 13.6 mmol, 3 equiv.) in dichloromethane (5 mL), was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution. After 12 h, the solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-cyclopropyl imidazolidine-2,4-dione **75** (0.41 g, 58 % yield). The data obtained are in agreement with other syntheses of this compound.

2-Amino-2-methylpropionitrile hydrochloride salt 78

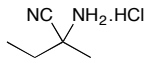


78

A solution of ammonium chloride (2.44 g, 45.6 mmol, 1.06 equiv.), acetone (3.20 mL, 43.0 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (6.70 mL, 45.6 mmol, 1.06 equiv.) in water (20 mL) was cooled to 4 °C and potassium cyanide (2.97 g, 45.6 mmol, 1.06 equiv.) was added, portion wise over a

period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The organic components were extracted with diethyl ether (3 × 30 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (20 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and crystallisation from water gave 2-amino-2-methylpropionitrile hydrochloride salt **78** (1.60 g, 30 % yield) as colourless crystals. mp 148 - 149 °C (*from water*, lit.,[115] 144 - 146 °C); δ_H (400.1 MHz; D_2O), 1.70 (6H, s, C*H*$_3$ × 2); δ_C (100.6 MHz; D_2O), 118.5, 47.1, 24.5 (2C); HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 85.0759, $C_4H_9N_2$ requires M^+ 85.0760]; *m/z* (ES^+) 85 ($[M\text{-}Cl]^+$, 100 %). These data are in agreement with the literature values.[115]

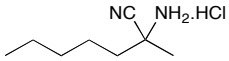
2-Amino-2-methylbutyronitrile hydrochloride salt 79



79

A solution of ammonium chloride (1.13 g, 21.2 mmol, 1.06 equiv.), 2-butanone (1.80 mL, 20.0 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (2.80 mL, 21.2 mmol, 1.06 equiv.) in water (20 mL) was cooled to 4 °C and potassium cyanide (1.38 g, 21.2 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The organic components were extracted with diethyl ether (3 × 30 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (10 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and crystallisation from water gave 2-amino-2-methylbutyronitrile hydrochloride salt **79** (2.43 g, 91 % yield) as colourless crystals. mp 120 °C dec. (*from water*, lit.,[116] 110 °C dec.); δ_H (400.1 MHz; D_2O), 2.03-1.85 (2H, m, C*H*$_2$CH$_3$), 1.65 (3H, s, C*H*$_3$), 1.04 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C (100.6 MHz; D_2O), 117.7, 51.8, 31.0, 22.2, 7.80; *m/z* (ES^+) 99 ($[M\text{-}Cl]^+$, 100 %), 72 ($[C_4H_{10}N]^+$, 35 %). These data are in agreement with the literature values.[116]

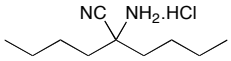
2-Amino-2-methylheptanonitrile hydrochloride salt 80



80

A solution of ammonium chloride (1.24 g, 23.2 mmol, 1.06 equiv.), 2-heptanone (3.10 mL, 21.9 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (3.10 mL, 23.2 mmol, 1.06 equiv.) in water/methanol (3/2, 25 mL) was cooled to 4 °C and potassium cyanide (1.47 g, 23.2 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The reaction solution was concentrated *in vacuo* to a volume of 10 mL and the organic components were extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated carefully *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (11 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and recrystallised from water to give *2-amino-2-methylheptanonitrile hydrochloride salt* **80** (3.16 g, 82 % yield) as colourless crystals. mp 116 - 118 °C (*from water*); δ_H (300 MHz; D_2O), 1.98-1.81 (2H, m, C*H*$_2$), 1.67 (3H, s, C*H*$_3$), 1.52-1.38 (2H, m, C*H*$_2$), 1.33-1.18 (4H, m, C*H*$_2$ × 2), 0.78 (3H, t, *J* 7.1, $(CH_2)_4CH_3$); δ_C (75.5 MHz; D_2O), 118.3, 51.5, 37.7, 30.7, 23.5, 23.1, 21.9, 13.4; HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 141.1385, $C_8H_{17}N_2$ requires M^+ 141.1386]; *m/z* (ES^+) 141 ($[M\text{-}Cl]^+$, 100 %).

2-Amino-2-*n*-butylhexanonitrile hydrochloride salt 81

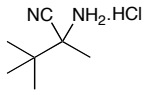


81

A solution of ammonium chloride (1.13 g, 21.2 mmol, 1.06 equiv.), 5-nonanone (3.50 mL, 20.0 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (2.80 mL, 21.2 mmol, 1.06 equiv.) in water/methanol (1/1, 20 mL) was cooled to 4 °C and potassium cyanide (1.34 g, 21.2 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The reaction solution was concentrated under reduced pressure to a volume of 10 mL and the organic components were extracted with dichloromethane (3 × 20 mL). The

extracts were combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (10 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and crystallised from water to give *2-amino-2-n-butylhexanonitrile hydrochloride salt* **81** (0.29 g, 7 % yield) as colourless crystals. mp 118 - 120 °C (*from water*); δ_H (300 MHz; D_2O), 2.00-1.83 (4H, m, CH_2 × 2), 1.45-1.24 (8H, m, CH_2 × 4), 0.81 (6H, t, *J* 7.3, CH_3 × 2); δ_C (75.5 MHz; D_2O), 117.5, 55.0, 35.3 (2C), 25.2 (2C), 21.5 (2C), 12.8 (2C); HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 169.1699, $C_{10}H_{21}N_2$ requires M^+ 169.1699]; *m/z* (ES^+) 169 ($[M\text{-}Cl]^+$, 100 %), 142 ($[C_9H_{20}N]^+$, 30 %).

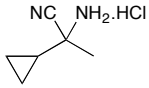
2-Amino-2,3,3-trimethylbutyronitrile hydrochloride salt 82



82

A solution of ammonium chloride (1.42 g, 26.5 mmol, 1.06 equiv.), 2,2-dimethyl-3-butanone (3.10 mL, 25.0 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (3.50 mL, 26.5 mmol, 1.06 equiv.) in water (20 mL) was cooled to 4 °C and potassium cyanide (1.73 g, 26.5 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The organic components were extracted with diethyl ether (3 × 20 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent was removed carefully *in vacuo*. The crude material was suspended in 2-butanol (5 mL) and a solution of HCl (2.0 M in diethyl ether) (12 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and recrystallised from water to give 2-amino-2,3,3-trimethylbutyronitrile hydrochloride salt **82** (0.93 g, 23 % yield) as colourless crystals. mp 158 - 159 °C (*from water*, lit.,[117] 154 - 155 °C); δ_H (300 MHz; D_2O), 1.68 (3H, s, CH_3), 1.08 (9H, s, CH_3 × 3); δ_C (75.5 MHz; D_2O), 118.1, 59.5, 36.9, 24.3 (3C), 19.7; HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 127.1230, $C_7H_{15}N_2$ requires M^+ 127.1230]; *m/z* (ES^+) 451 ($[3 \times M\text{-}Cl]^+$, 10 %), 253 ($[2 \times M\text{-}HCl_2]^+$, 10 %), 127 ($[M\text{-}Cl]^+$, 100 %), 100 ($[C_6H_{14}N]^+$, 15 %). These data are in agreement with the literature values.[117]

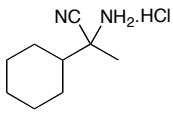
2-Amino-2-cyclopropylpropionitrile hydrochloride salt 83



83

A solution of ammonium chloride (2.05 g, 38.4 mmol, 1.06 equiv.), cyclopropyl methylketone (3.60 mL, 36.2 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (5.20 mL, 38.4 mmol, 1.06 equiv.) in water (20 mL) was cooled to 4 °C and potassium cyanide (2.50 g, 38.4 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The organic components were extracted with dichloromethane (3 × 20 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (18 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and recrystallised from water to give *2-amino-2-cyclopropylpropionitrile hydrochloride salt* **83** (3.31 g, 63 % yield) as colourless crystals. mp 110 - 111 °C (*from water*); δ_H (300 MHz; D_2O), 1.70 (3H, s, C*H*$_3$), 1.35-1.28 (1H, m, cyclopropyl C*H*), 0.79-0.57 (4H, m, cyclopropyl C*H*$_2$ × 2); δ_C (75.5 MHz; D_2O), 113.7, 52.0, 20.5, 14.3, 0.30, 0.00; HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 111.0919, $C_6H_{11}N_2$ requires M^+ 111.0917]; *m/z* (ES^+) 111 ($[M\text{-}Cl]^+$, 70 %), 94 ($[C_6H_8N]^+$, 100 %), 84 ($[C_5H_{10}N]^+$, 30 %).

2-Amino-2-cyclohexylpropionitrile hydrochloride salt 84

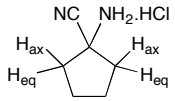


84

A solution of ammonium chloride (0.85 g, 15.9 mmol, 1.06 equiv.), cyclohexylmethyl ketone (2.10 mL, 15.0 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (2.10 mL, 15.9 mmol, 1.06 equiv.) in water/methanol (1/1, 20 mL) was cooled to 4 °C and potassium cyanide (1.04 g, 15.9 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The reaction solution was concentrated under reduced pressure to a volume of 10 mL and the organic components were extracted with diethyl ether (3 × 20 mL). The

extracts were combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (8 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and recrystallised from water to give *2-amino-2-cyclohexylpropionitrile hydrochloride salt* **84** (1.84 g, 65 % yield) as colourless rhombic crystals. mp 142 - 144 °C (*from water*); δ_H (400.1 MHz; D_2O), 1.84-1.72 (5H, m, cyclohexyl C*H* × 5), 1.64 (3H, s, CH_3), 1.63-1.55 (1H, m, cyclohexyl C*H*), 1.23-0.99 (5H, m, cyclohexyl C*H* × 5); δ_C (75.5 MHz; D_2O), 117.5, 55.1, 43.9, 27.0, 26.4, 25.0 (2C), 24.9, 20.8; HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 153.1384, $C_9H_{17}N_2$ requires M^+ 153.1386]; *m/z* (ES^+) 153 ($[M\text{-}Cl]^+$, 100 %), 126 ($[C_8H_{16}N]^+$, 40 %).

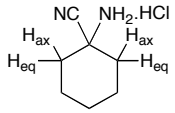
1-Aminocyclopentanecarbonitrile hydrochloride salt 85



85

A solution of ammonium chloride (1.68 g, 31.5 mmol, 1.06 equiv.), cyclopentanone (2.60 mL, 29.7 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (4.20 mL, 31.5 mmol, 1.06 equiv.) in water/methanol (1/1, 20 mL) was cooled to 4 °C and potassium cyanide (2.02 g, 31.5 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The reaction solution was concentrated under reduced pressure to a volume of 10 mL and the organic components were extracted with diethyl ether (3 × 20 mL). The extracts were combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (15 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and recrystallised from water to give 1-aminocyclopentanecarbonitrile hydrochloride salt **85** (3.35 g, 77 % yield) as a colourless solid. mp 128 - 130 °C (*from water*, lit.,[118] 129 °C); δ_H (400.1 MHz; D_2O), 2.32-2.23 (2H, m, cyclopentane CH_{eq} × 2), 1.98-1.88 (2H, m, cyclopentane CH_{ax} × 2), 1.75-1.65 (4H, m, cyclopentane CH_2 × 2); δ_C (100.6 MHz; D_2O), 118.9, 54.8, 37.2 (2C), 23.3 (2C); *m/z* (ES^+) 111 ($[M\text{-}Cl]^+$, 100 %), 94 ($[C_6H_8N]^+$, 40 %), 84 ($[C_5H_{10}N]^+$, 20 %). These data are in agreement with the literature values.[118]

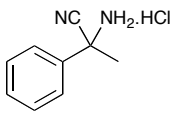
1-Aminocyclohexanecarbonitrile hydrochloride salt 86



86

A solution of ammonium chloride (1.44 g, 27.0 mmol, 1.06 equiv.), cyclohexanone (2.60 mL, 25.5 mmol, 1 equiv.) and ammonium hydroxide (30 % v/v sol. in H_2O) (3.60 mL, 27.0 mmol, 1.06 equiv.) in water/methanol (1/1, 20 mL) was cooled to 4 °C and potassium cyanide (1.76 g, 27.0 mmol, 1.06 equiv.) was added, portion wise over a period of 10 min. The reaction solution was stirred for 20 h at RT, after which time TLC analysis indicated that a new product had been formed. The reaction solution was concentrated under reduced pressure to a volume of 10 mL and the organic components were extracted with diethyl ether (3 × 20 mL). The extracts were combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (13 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and recrystallised from water to give 1-aminocyclohexanecarbonitrile hydrochloride salt **86** (3.27 g, 80 % yield) as colourless crystals. mp 190 - 192 °C (*from water*, lit.,[118] 190 °C); δ_H (400.1 MHz; D_2O), 2.26-2.15 (2H, m, cyclohexane C*H*$_{eq}$ × 2), 1.88-1.76 (2H, m, cyclohexane C*H*$_{ax}$ × 2), 1.72-1.60 (3H, m, cyclohexane C*H* × 3), 1.57-1.41 (2H, m, cyclohexane C*H*$_2$), 1.21-1.06 (1H, m, cyclohexane C*H*); δ_C (75.5 MHz; D_2O), 117.4, 52.6, 33.5 (2C), 23.1, 22.0 (2C); HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 125.1074, $C_7H_{13}N_2$ requires M^+ 125.1073]; *m/z* (ES^+) 125 ($[M\text{-}Cl]^+$, 100 %), 108 ($[C_7H_{10}N]^+$, 50 %), 98 ($[C_6H_{12}N]^+$, 20 %). These data are in agreement with the literature values.[118]

2-Amino-2-phenylpropionitrile hydrochloride salt 87

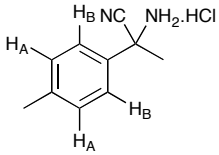


87

A slurry of potassium cyanide (1.63 g, 25.0 mmol, 2 equiv.) and ammonium chloride (1.34 g, 25.0 mmol, 2 equiv.) in dimethyl sulfoxide/water (6/1, 20 mL) was stirred and a solution of acetophenone (1.46 mL, 12.5 mmol, 1 equiv.) in dimethyl sulfoxide (2 mL) was added and allowed to stir for 20 h at RT, after which time TLC analysis indicated that a new compound had been formed. The mixture was suspended in

water (20 mL); the organic components were extracted with diethyl ether (3 × 30 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solution was concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (6 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration, and recrystallised from water to give 2-amino-2-phenylpropionitrile hydrochloride salt **87** (1.03 g, 46 % yield) as colourless crystals. mp 116 - 118 °C (*from water*); δ_H (300 MHz; D_2O), 7.62-7.55 (2H, m, aromatic C*H* × 2), 7.52-7.44 (3H, m, aromatic C*H* × 3), 2.10 (3H, s, CH_3); δ_C (75.5 MHz; D_2O), 133.3, 131.2, 130.1 (2C), 125.6 (2C), 118.1, 53.8, 25.4; HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 147.0917, $C_9H_{11}N_2$ requires M^+ 147.0917]; *m/z* (ES^+) 147 ($[M\text{-}Cl]^+$, 20 %), 130 ($[C_9H_8N]^+$, 100 %). This is a known compound, however, no experimental data using modern analytical techniques could be located.

2-Amino-2-(4'-methylphenyl)propionitrile hydrochloride salt 88

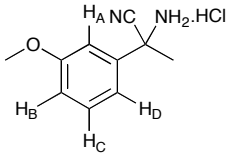


88

A slurry of potassium cyanide (1.46 g, 22.4 mmol, 2 equiv.) and ammonium chloride (1.20 g, 22.4 mmol, 2 equiv.) in dimethyl sulfoxide/water (6/1, 20 mL) was stirred and a solution of 4'-methylacetophenone (1.50 mL, 11.2 mmol, 1 equiv.) in dimethyl sulfoxide (2 mL) was added and allowed to stir for 20 h at RT, after which time TLC analysis indicated a new compound had been formed. The mixture was suspended in water (20 mL); the organic components were extracted with diethyl ether (3 × 20 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solution was concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (6 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration, and recrystallised from water to give 2-amino-2-(4'-methylphenyl)propionitrile hydrochloride salt **88** (0.51 g, 24 % yield) as colourless crystals. mp 105 - 106 °C (*from water*); δ_H (400.1 MHz; D_2O), 7.46 (2H, d, *J* 8.5, aromatic CH_B × 2), 7.29 (2H, d, *J* 8.5, aromatic CH_A × 2), 2.28 (3H, s, PhCH_3), 2.05 (3H, s, CH_3); δ_C (75.5 MHz; D_2O), 141.5, 130.2 (2C), 130.0, 125.2 (2C), 117.8, 53.2, 24.9, 20.2; HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$

161.1075, $C_{10}H_{13}N_2$ requires M^+ 161.1073]; *m/z* (ES^+) 161 ([M-Cl]$^+$, 10 %), 144 ([$C_{10}H_{10}N$]$^+$, 100 %), 134 ([$C_9H_{12}N$]$^+$, 60 %).

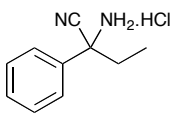
2-Amino-2-(3'-methoxyphenyl)propionitrile hydrochloride salt 89



89

A slurry of potassium cyanide (1.73 g, 26.6 mmol, 2 equiv.) and ammonium chloride (1.42 g, 26.6 mmol, 2 equiv.) in dimethyl sulfoxide/water (6/1, 20 mL) was stirred and a solution of 3'-methoxyacetophenone (1.80 mL, 13.3 mmol, 1 equiv.) in dimethyl sulfoxide (2 mL) was added and allowed to stir for 20 h at RT, after which time TLC analysis indicated a new compound had been formed. The mixture was suspended in water (20 mL); the organic components were extracted with diethyl ether (3 × 20 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solution was concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (7 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration, crystallised from water and washed with ethyl acetate to give *2-amino-2-(3'-methoxyphenyl) propionitrile hydrochloride salt* **89** (1.15 g, 41 % yield) as a colourless solid. mp 120 °C dec. (*from water*); δ_H (300 MHz; D_2O), 7.41 (1H, dd [apparent t], *J* 8.1, 8.1, aromatic C*H*$_C$), 7.17 (1H, dd, *J* 2.1, 8.1, aromatic C*H*$_D$), 7.12 (1H, dd [apparent t], *J* 2.1, 2.1, aromatic C*H*$_A$), 7.05 (1H, dd, *J* 2.1, 8.1, aromatic C*H*$_B$), 3.77 (3H, s, OC*H*$_3$), 2.05 (3H, s, C*H*$_3$); δ_C (75.5 MHz; D_2O), 159.7, 134.8, 131.1, 117.8, 117.6, 116.0, 111.3, 55.6, 53.2, 25.2; HRMS *m/z* (ES^+) [found (M-Cl)$^+$ 177.1023, $C_{10}H_{13}N_2O$ requires M^+ 177.1022]; *m/z* (ES^+) 177 ([M-Cl]$^+$, 20 %), 160 ([$C_{10}H_{10}NO$]$^+$, 100 %), 134 ([$C_9H_{12}NO$]$^+$, 35 %).

2-Amino-2-phenylbutyronitrile hydrochloride salt 90



90

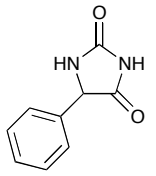
A slurry of potassium cyanide (1.46 g, 22.4 mmol, 2 equiv.) and ammonium chloride (1.20 g, 22.4 mmol, 2 equiv.) in dimethyl sulfoxide/water (4/1, 20 mL) was stirred

and a solution of propiophenone (1.50 mL, 11.2 mmol, 1 equiv.) in dimethyl sulfoxide (2 mL) was added and allowed to stir for 24 h at RT, after which time TLC analysis indicated a new compound had been formed. The mixture was suspended in water (20 mL); the organic components were extracted with diethyl ether (3 × 20 mL) and combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solution was concentrated *in vacuo* to a volume of 10 mL. A solution of HCl (2.0 M in diethyl ether) (6 mL) was added and the salt was allowed to precipitate at 0 °C. The precipitate was isolated by filtration and recrystallised from water to give 2-amino-2-phenylbutyronitrile hydrochloride salt **90** (0.52 g, 24 % yield) as colourless crystals. mp 124 - 126 °C (*from water*, lit.,[32] 118 - 119 °C); δ_H (400.1 MHz; D_2O), 7.57-7.44 (5H, m, aromatic C*H* × 5), 2.32 (2H, q, *J* 7.4, CH_2CH$_3$), 0.90 (3H, t, *J* 7.4, CH$_2$CH_3); δ_C (75.5 MHz; D_2O), 134.1, 133.3, 132.3 (2C), 128.2 (2C), 119.2, 61.7, 34.7, 10.6; HRMS *m/z* (ES^+) [found $(M\text{-}Cl)^+$ 161.1072, $C_{10}H_{13}N_2$ requires M^+ 161.1073]; *m/z* (ES^+) 553 ($[3 \times M\text{-}Cl]^+$, 5 %), 481 ($[3 \times M\text{-}HCl_2]^+$, 10 %), 321 ($[2 \times M\text{-}HCl_2]^+$, 40 %), 161 $([M\text{-}Cl)]^+$, 90 %), 134 ($[C_9H_{12}N]^+$, 100 %). These data are in agreement with the literature values.[32]

General Conditions for the Synthesis of Racemic Hydantoins from Aminonitriles

The aminonitrile hydrochloride salt was suspended in 1.0 M NaOH (sol.) (10 mL) and the free amine was extracted with diethyl ether (3 × 10 mL), washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated carefully *in vacuo*. A solution of aminonitrile (1 equiv.) and Hünig's base (3 equiv.) in dichloromethane (5 mL) was stirred at RT and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the reaction solution until TLC analysis indicated that the starting material had been consumed. The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting hydantoins were purified either by concentration under reduced pressure or silica gel column chromatography as indicated; followed by crystallisation.

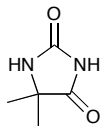
5-Phenylimidazolidine-2,4-dione 92



92

2-Phenylglycinonitrile (0.20 g, 1.52 mmol, 1 equiv.); addition of CO_2: 17 h. Purification by crystallisation from ethanol gave 5-phenylimidazolidine-2,4-dione **92** (0.20 g, 73 % yield) as a colourless solid. R_f 0.6 (ethyl acetate); mp 176 - 178 °C (*from ethanol*, lit.,[119] 179 °C); δ_H (300 MHz; D^6-DMSO), 10.79 (1H, br s, N*H*), 8.39 (1H, br s, N*H*), 7.43-7.30 (5H, m, aromatic C*H* × 5), 5.15 (1H, s, C*H*); δ_C (125.7 MHz; D^6-DMSO), 174.8, 158.1, 136.6, 129.1 (2C), 128.7, 127.2 (2C), 61.6; *m/z* (ES^+) 199 ($[M+Na]^+$, 10 %); (ES^-) 175 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[119,120]

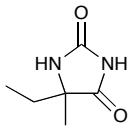
5,5-Dimethylimidazolidine-2,4-dione 71



71

2-Amino-2-methylpropionitrile (0.45 g, 5.36 mmol, 1 equiv.); addition of CO_2: 13 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5,5-dimethylimidazolidine-2,4-dione **71** (0.02 g, 4 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-ethylimidazolidine-2,4-dione 93

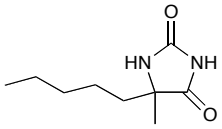


93

2-Amino-2-methylbutyronitrile (0.32 g, 3.26 mmol, 1 equiv.); addition of CO_2: 16 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-ethylimidazolidine-2,4-dione **93** (0.07 g, 14 % yield) as a colourless solid. R_f 0.4 (ethyl acetate); mp 134 - 136 °C (*from ethanol*, lit.,[121] 141 °C); δ_H (300 MHz; D^6-DMSO), 10.53 (1H, s, N*H*), 7.86 (1H, s, N*H*), 1.67-1.42

(2H, m, CH_2CH$_3$), 1.21 (3H, s, CH_3), 0.75 (3H, t, *J* 7.4, CH$_2$CH_3); δ_C (100.6 MHz; D^6-DMSO), 178.5, 156.4, 62.4, 30.1, 23.2, 7.7; *m/z* (ES$^+$) 165 ([M+Na]$^+$, 100 %); (ES$^-$) 141 ([M-H]$^-$, 100 %). These data are in agreement with the literature values.[121]

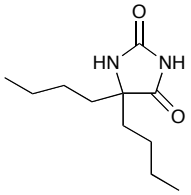
5-Methyl-5-*n*-pentylimidazolidine-2,4-dione 94



94

2-Amino-2-methylheptanonitrile (0.50 g, 5.00 mmol, 1 equiv.); addition of CO_2: 9 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-*n*-pentylimidazolidine-2,4-dione **94** (0.57 g, 87 % yield) as a colourless solid. R_f 0.6 (ethyl acetate); mp 97 - 98 °C (*from ethanol*, lit.,[122] 101 °C); ν_{max} (KBr disc)/cm^{-1} 3241 (s), 2923 (s), 2859 (s), 1785 (s), 1707 (s), 1468 (s), 1433 (s), 1290 (m), 1241 (m), 1193 (m), 814 (m), 776 (s), 649 (m); δ_H (400.1 MHz; D^6-DMSO), 10.53 (1H, br s, N*H*), 7.87 (1H, br s, N*H*), 1.60-1.41 (2H, m, CH_2), 1.32-1.15 (8H, m, C*H* × 5 and CH_3), 1.10-0.99 (1H, m, C*H*), 0.83 (3H, t, *J* 7.0, (CH$_2$)$_4$CH_3); δ_C (75.5 MHz; D^6-DMSO), 181.7, 159.4, 65.1, 40.2, 34.1, 26.8, 25.7, 25.0, 16.9; HRMS *m/z* (ES$^+$) [found (M+NH$_4$)$^+$ 202.1551, $C_9H_{20}N_3O_2$ requires M$^+$ 202.1550]; *m/z* (ES$^+$) 207 ([M+Na]$^+$, 100 %); (ES$^-$) 183 ([M-H]$^-$, 100 %). These data are in agreement with the literature values.[48,122]

5,5-Di-*n*-butylimidazolidine-2,4-dione 95

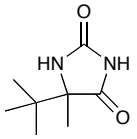


95

2-Amino-2-*n*-butylhexanonitrile (0.21 g, 1.23 mmol, 1 equiv.); addition of CO_2: 14 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5,5-di-*n*-butylimidazolidine-2,4-dione **95** (0.12 g, 47 % yield) as a colourless solid. R_f 0.6 (ethyl acetate); mp 156 - 158 °C (*from ethanol*, lit.,[123] 159 - 161 °C); δ_H (400.1 MHz; D^6-DMSO), 10.52 (1H, br s, N*H*), 7.78 (1H, s, N*H*), 1.60-1.42 (4H, m, CH_2 × 2), 1.28-1.16 (6H, m, CH_2 × 3), 1.08-0.96 (2H, m, CH_2), 0.83 (6H, t, *J* 7.2, CH_3 × 2); δ_C (100.6 MHz; D^6-DMSO), 178.0, 156.8, 65.5, 36.2 (2C),

25.0 (2C), 22.1 (2C), 13.8 (2C); HRMS *m/z* (Cl^+) [found $(M+H)^+$ 213.1597, $C_{11}H_{21}N_2O_2$ requires M^+ 213.1603]; *m/z* (ES^+) 235 ($[M+Na]^+$, 100); (ES^-) 211 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[123]

5-Methyl-5-*t*-butylimidazolidine-2,4-dione 96

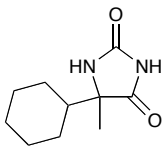


96

2-Amino-2,3,3-trimethylbutyronitrile (0.20 g, 1.59 mmol, 1 equiv.), ethanol (5 mL) as reaction solvent; addition of CO_2: 17 h. Purification by concentration under reduced pressure followed by crystallisation from ethyl acetate gave 5-methyl-5-*t*-butyl imidazolidine-2,4-dione **96** (0.17 g, 62 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 219 - 220 °C (*from ethyl acetate*, lit.,[124] 218 - 219 °C); δ_H (400.1 MHz; D^6-DMSO), 10.59 (1H, br s, N*H*), 8.04 (1H, br s, N*H*), 1.30 (3H, s, CH_3), 0.99 (9H, s, CH_3 × 3); δ_C (75.5 MHz; D^6-DMSO), 178.1, 156.7, 66.7, 36.1, 24.5 (3C), 18.8; *m/z* (ES^+) 193 ($[M+Na]^+$, 100 %); (ES^-) 169 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[47,124]

Repeat Synthesis - 2-Amino-2,3,3-trimethylbutyronitrile (0.25 g, 1.98 mmol, 1 equiv.); addition of CO_2: 17 h. Yield 55 %, 0.18 g, colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-cyclohexylimidazolidine-2,4-dione 97

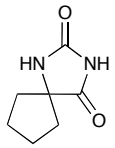


97

2-Amino-2-cyclohexylpropionitrile (0.44 g, 2.90 mmol, 1 equiv.); addition of CO_2: 25 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-cyclohexylimidazolidine-2,4-dione **97** (0.29 g, 50 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 210 - 211 °C (*from ethanol*, lit.,[125] 210 - 211 °C); δ_H (400.1 MHz; D^6-DMSO), 10.54 (1H, br s, N*H*), 7.88 (1H, br s, N*H*), 1.78-1.55 (4H, m, CH_2 × 2), 1.51-1.35 (2H, m, CH_2), 1.24-0.87 (8H, m, cyclohexyl C*H* × 5 and CH_3); δ_C (100.6 MHz; D^6-DMSO), 178.6, 156.7, 64.8,

43.2, 26.3, 25.7, 25.6, 25.5, 25.4, 21.2; *m/z* (ES^+) 219 ($[M+Na]^+$, 100 %); (ES^-) 195 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[125]

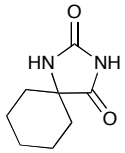
1,3-Diazaspiro[4.4]nonane-2,4-dione 98



98

1-Aminocyclopentanecarbonitrile (0.50 g, 4.54 mmol, 1 equiv.); addition of CO_2: 21 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 1,3-diazaspiro[4.4]nonane-2,4-dione **98** (0.21 g, 30 % yield) as a colourless solid. R_f 0.4 (ethyl acetate); mp 203 - 204 °C (*from ethanol*, lit.,[126] 204 - 205 °C); δ_H (300 MHz; D^6-DMSO), 10.57 (1H, br s, N*H*), 8.16 (1H, br s, N*H*), 1.98-1.80 (2H, m, cyclopentyl C*H* × 2), 1.78-1.59 (6H, m, cyclopentyl C*H* × 6); δ_C (100.6 MHz; D^6-DMSO), 179.3, 156.2, 68.2, 37.1 (2C), 24.6 (2C); *m/z* (ES^+) 177 ($[M+Na]^+$, 100 %); (ES^-) 153 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[126,127]

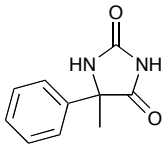
1,3-Diazaspiro[4.5]decane-2,4-dione 99



99

1-Aminocyclohexanecarbonitrile (0.50 g, 4.03 mmol, 1 equiv.); addition of CO_2: 21 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 1,3-diazaspiro[4.5]decane-2,4-dione **99** (0.19 g, 29 % yield) as a colourless solid. R_f 0.4 (ethyl acetate); mp 216 - 217 °C (*from ethanol*, lit.,[128] 217 °C); δ_H (400.1 MHz; D^6-DMSO), 10.59 (1H, br s, N*H*), 8.45 (1H, br s, N*H*), 1.76-1.48 (9H, m, cyclohexyl C*H* × 9), 1.38-1.24 (1H, m, cyclohexyl C*H*); δ_C (100.6 MHz; D^6-DMSO), 178.5, 156.3, 62.0, 33.2 (2C), 24.4, 20.8 (2C); *m/z* (ES^+) 191 ($[M+Na]^+$, 100 %); (ES^-) 167 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[128,129]

5-Methyl-5-phenylimidazolidine-2,4-dione 100

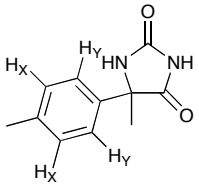


100

2-Amino-2-phenylpropionitrile (0.41 g, 2.84 mmol, 1 equiv.); addition of CO_2: 20 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] followed by crystallisation from ethanol gave 5-methyl-5-phenylimidazolidine-2,4-dione **100** (0.49 g, 90 % yield) as a colourless solid. R_f 0.5 (10/90 methanol/ethyl acetate); mp 196 - 198 °C (*from ethanol*, lit.,[122] 194 - 195 °C); δ_H (400.1 MHz; D^6-DMSO), 10.82 (1H, br s, N*H*), 8.67 (1H, br s, N*H*), 7.55-7.51 (2H, m, aromatic C*H* × 2), 7.48-7.43 (2H, m, aromatic C*H* × 2), 7.41-7.36 (1H, m, aromatic C*H*), 1.71 (3H, s, CH_3); δ_C (100.6 MHz; D^6-DMSO), 176.9, 156.2, 139.9, 128.4 (2C), 127.8, 125.3 (2C), 63.9, 24.9; *m/z* (ES^+) 213 ($[M+Na]^+$, 100 %); (ES^-) 189 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[114,122]

Repeat Synthesis - 2-Amino-2-phenylpropionitrile (0.50 g, 3.42 mmol, 1 equiv.); addition of CO_2: 19 h. Yield 88 %, 0.57 g, colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-(4'-methylphenyl)imidazolidine-2,4-dione 101

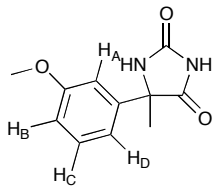


101

2-Amino-2-(4'-methylphenyl)propionitrile (0.17 g, 1.08 mmol, 1 equiv.); addition of CO_2: 7 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] followed by crystallisation from ethanol gave 5-methyl-5-(4'-methylphenyl)imidazolidine-2,4-dione **101** (0.21 g, 96 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 202 - 203 °C (*from ethanol*, lit.,[126] 204 °C); δ_H (400.1 MHz; D^6-DMSO), 10.78 (1H, br s, N*H*), 8.63 (1H, br s, N*H*), 7.40 (2H, d, *J* 8.3, aromatic CH_Y × 2), 7.26 (2H, d, *J* 8.3, aromatic CH_X × 2), 2.35 (3H, s, PhCH_3), 1.68 (3H, s, CH_3); δ_C (75.5 MHz; D^6-DMSO), 177.5, 156.6,

137.4 (2C), 129.3 (2C), 125.6 (2C), 64.1, 25.2, 20.7; *m/z* (ES^+) 227 ($[M+Na]^+$, 100 %); (ES^-) 203 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[126,130]

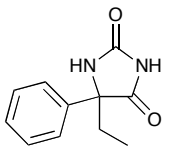
5-Methyl-5-(3'-methoxyphenyl)imidazolidine-2,4-dione 103



103

2-Amino-2-(3'-methoxyphenyl)propionitrile (0.31 g, 1.77 mmol, 1 equiv.); addition of CO_2: 24 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] followed by crystallisation from ethanol gave *5-methyl-5-(3'-methoxyphenyl)imidazolidine-2,4-dione* **103** (0.23 g, 60 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 100 - 102 °C (*from ethanol*); ν_{max} (KBr disc)/cm^{-1} 3256 (m), 3020 (w), 1773 (s), 1720 (s), 1599 (m), 1492 (w), 1426 (m), 1263 (m), 795 (w), 773 (w), 715 (w); δ_H (400.1 MHz; D^6-DMSO), 10.76 (1H, br s, N*H*), 8.60 (1H, br s, N*H*), 7.30 (1H, dd [apparent t], *J* 8.0, 8.0, aromatic CH_C), 7.04 (1H, ddd, *J* 0.8, 2.2, 8.0, aromatic CH_D), 6.99 (1H, dd [apparent t], *J* 2.2, 2.2, aromatic CH_A), 6.89 (1H, ddd, *J* 0.8, 2.2, 8.0, aromatic CH_B), 3.75 (3H, s, OCH_3), 1.62 (3H, s, CH_3); δ_C (75.5 MHz; D^6-DMSO), 177.1, 159.6, 156.5, 141.9, 130.0, 117.9, 113.2, 111.8, 64.2, 55.5, 25.5; HRMS *m/z* (CI^+) [found $(M+H)^+$ 221.0919, $C_{11}H_{13}N_2O_3$ requires M^+ 221.0926]; *m/z* (CI^+) 221 ($[M+H]^+$, 100 %); Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7 Found: C, 60.1; H, 5.3; N, 12.6.

5-Ethyl-5-phenylimidazolidine-2,4-dione 103

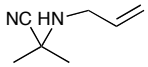


103

2-Amino-2-phenylbutyronitrile (0.34 g, 2.10 mmol, 1 equiv.); addition of CO_2: 12 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] followed by crystallisation from ethanol gave 5-ethyl-5-phenylimidazolidine-2,4-dione **103** (0.26 g, 62 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 199 - 200 °C (*from ethanol*, lit.,[32] 199 °C);

δ_H (400.1 MHz; D^6-DMSO), 10.80 (1H, br s, N*H*), 8.71 (1H, br s, N*H*), 7.59-7.54 (2H, m, aromatic C*H* × 2), 7.49-7.43 (2H, m, aromatic C*H* × 2), 7.41-7.36 (1H, m, aromatic C*H*), 2.18-2.08 (1H, m, $CH_AH_BCH_3$), 2.01-1.90 (1H, m, $CH_AH_BCH_3$), 0.87 (3H, t, *J* 7.3, CH_2CH_3); δ_C (100.6 MHz; D^6-DMSO), 176.2, 156.6, 139.0, 128.4 (2C), 127.7, 125.3 (2C), 68.0, 31.1, 8.0; HRMS *m/z* (ES^+) [found $(M+Na)^+$ 227.0797, $C_{11}H_{12}N_2O_2Na$ requires M^+ 227.0796]; *m/z* (ES^-) 203 ($[M-H]^-$, 100 %); *m/z* (ES^+) 227 ($[M+Na]^+$, 100 %). These data are in agreement with the literature values.[32]

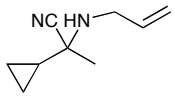
2-*N*-Allylamino-2-methylpropionitrile 104



104

To an aqueous solution of allylamine (40 %, v/v) (6.45 mL, 34.4 mmol, 1 equiv.) was added acetone (2.53 mL, 34.4 mmol, 1 equiv.) over a period of 30 mins. After stirring for 1 h at RT, a solution of hydrogen cyanide (1.5 equiv. in H_2O, 2 mL) was added. The solution was stirred for 16 h and salt (5 g) was added to separate out the layers. Any remaining organic components were extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered, and concentrated carefully *in vacuo*. No further purification was necessary to give 2-*N*-allylamino-2-methylpropionitrile **104** (2.72 g, 65 % yield) as a brown oil. R_f 0.4 (50/50 ethyl acetate/petroleum ether); ν_{max} (thin film)/cm^{-1} 3321 (m), 3082 (w), 2987 (m), 2940 (m), 2221 (w), 1697 (w), 1645 (w), 1466 (m), 1213 (m); δ_H (300 MHz; $CDCl_3$), 5.78 (1H, dddd [apparent ddt], *J* 5.9, 5.9, 10.2, 17.2, NCH_2CHCH_2), 5.12 (1H, dddd, *J* 1.6, 1.6, 1.6, 17.2, $NCH_2CHCH_AH_B$), 5.00 (1H, dddd, *J* 1.6, 1.6, 1.6, 10.2, $NCH_2CHCH_AH_B$), 3.23 (2H, d, *J* 5.9, NCH_2CHCH_2), 1.34 (6H, s, CH_3 × 2), 1.22 (1H, br s, N*H*); δ_C (75.5 MHz; $CDCl_3$), 135.8, 123.0, 117.2, 51.7, 48.1, 27.7 (2C); *m/z* (ES^+) 125 ($[M+H]^+$, 50 %). This compound is not novel however, no experimental data using modern analytical techniques could be located.

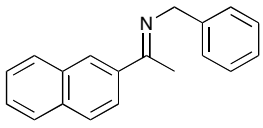
2-*N*-Allylamino-2-cyclopropylpropionitrile 105



105

To an aqueous solution of allylamine (40 %, v/v) (2.23 mL, 11.9 mmol, 1 equiv.) was added cyclopropylmethylketone (1.18 mL, 11.9 mmol, 1 equiv.) over a period of 30 mins. After stirring for 1 h at RT, a solution of hydrogen cyanide (1.5 equiv. in H_2O, 2 mL) was added. The solution was stirred for 5 h and then salt (5 g) was added to separate out the layers. Any remaining organic components were extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. No further purification was necessary to give *2-N-allylamino-2-cyclopropylpropionitrile* **105** (1.46 g, 82 % yield) as a brown oil. R_f 0.6 (50/50 ethyl acetate/petroleum ether); ν_{max} (thin film)/cm^{-1} 3321 (m), 3083 (m), 3010 (m), 2987 (m), 2938 (m), 2222 (w), 1691 (w), 1645 (m), 1462 (m), 1163 (s), 921 (s); δ_H (300 MHz; $CDCl_3$), 5.87 (1H, dddd [apparent ddt], *J* 5.9, 5.9, 10.2, 17.2, NCH_2CHCH_2), 5.20 (1H, dddd [apparent dq], *J* 1.5, 1.5, 1.5, 17.2, $NCH_2CHCH_AH_B$), 5.08 (1H, dddd [apparent dq], *J* 1.5, 1.5, 1.5 10.2, $NCH_2CHCH_AH_B$), 3.41 (1H, dddd [apparent dt], *J* 1.5, 1.5, 5.9, 13.2, $NCH_AH_BCHCH_2$), 3.27 (1H, dddd [apparent dt], *J* 1.5, 1.5, 5.9, 13.2, $NCH_AH_BCHCH_2$), 1.57-1.40 (5H, m, CH_3, N*H* and cyclopropyl C*H*), 1.01-0.91 (1H, m, cyclopropyl C*H*H), 0.62-0.38 (3H, m, cyclopropyl CH_2 and cyclopropyl CH*H*); δ_C (75.5 MHz; $CDCl_3$), 134.6, 118.6, 115.8, 57.9, 46.9, 25.3, 18.4, 2.2, 0.0; HRMS *m/z* (CI^+) [found $(M+H)^+$ 151.1232, $C_9H_{13}N_2$ requires M^+ 151.1230]; *m/z* (ES^-) 203 ($[M-H]^-$, 100 %); *m/z* (CI^+) 151 ($[M+H]^+$, 20 %), 124 ($[C_8H_{14}N]^+$, 80 %).

N-Benzyl(1-naphthalen-2-ylethylidene)amine 56

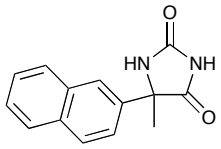


56

To a mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.), 4 Å molecular sieves (2 g) and ytterium (III) triflate (0.32 g, 0.59 mmol, 0.2 equiv.) in dioxane (10 mL) was added benzylamine (0.48 mL, 4.41 mmol, 1.5 equiv.) under an inert atmosphere. The reaction mixture was stirred for 48 h at RT, after which time ^1H NMR spectroscopic analysis indicated a 90 % conversion of starting materials to

products. The reaction mixture was filtered through Celite,® washed with dioxane and concentrated *in vacuo*. The crude material was crystallised from hexanes to give *N*-benzyl(1-naphthalen-2-ylethylidene)amine **56** (0.39 g, 52 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

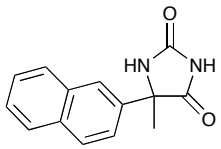
5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. The reaction vessel was allowed to attain RT and was stirred for 8 h, after which a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added and the mixture was stirred for a further 16 h. Hünig's base (1.53 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (6 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (0.13 g, 18 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65

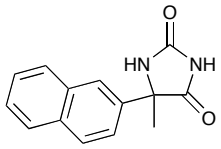


65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and

approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. After 24 h the reaction mixture was allowed to attain RT, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added and the mixture was stirred for a further 24 h. Hünig's base (1.53 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (3 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-ylimidazolidine-2,4-dione **65** (0.19 g, 27 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65

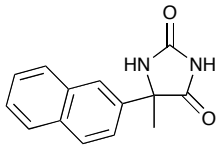


65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. After 24 h a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added and the mixture was stirred for a further 24 h at -78 °C. The reaction mixture was allowed to attain RT; Hünig's base (1.53 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (6 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 ml), ethyl acetate (300 ml)] gave 5-methyl-5-naphthalen-2-ylimidazolidine-2,4-dione **65**

(34.4 mg, 5 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

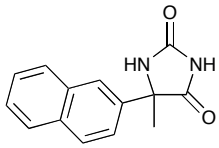
5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. A solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added and after 10 h the reaction mixture was allowed to attain RT. Hünig's base (1.53 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (10 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (60.0 mg, 9 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65

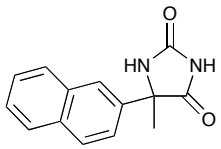


65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 24 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 24 h. Hünig's base (1.53 mL, 8.82 mmol,

3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (6 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (0.37 g, 53 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



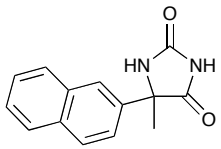
65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (1.53 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (5 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (0.33 g, 47 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - Aminonitrile formation time: 20 h; hydantoin formation time: 5 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl

acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (0.35 g, 50 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

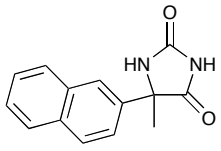
5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (1 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (1.53 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (6 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (0.19 g, 27 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65

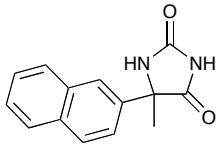


65

A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen

cyanide (4 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (1.53 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (6 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (0.18 g, 25 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

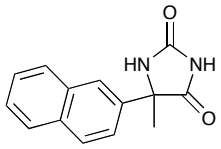
5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



65

A mixture of 2-acetylnaphthalene (0.25 g, 1.47 mmol, 1 equiv.) and gallium (III) triflate (0.15 g, 0.29 mmol, 0.2 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, in 2 mL) was added. The reaction vessel was allowed to attain RT, and the mixture was stirred for 20 h. Hünig's base (0.79 mL, 4.41 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (5 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-yl imidazolidine-2,4-dione **65** (0.13 g, 36 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-naphthalen-2-ylimidazolidine-2,4-dione 65



65

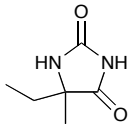
A mixture of 2-acetylnaphthalene (0.50 g, 2.94 mmol, 1 equiv.) and titanium (IV) chloride (1.0 M in dichloromethane) (0.29 mL, 0.29 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared, and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, in 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (1.54 mL, 8.82 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (7 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-naphthalen-2-ylimidazolidine-2,4-dione **65** (90.0 mg, 13 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

General Conditions for the Racemic Synthesis of Hydantoins from Ketones and Aldehydes

A mixture of ketone (1 equiv.) and gallium (III) triflate (0.1 equiv.) in dichloromethane (or ethanol) (5 mL) was prepared and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for approximately 20 h. Hünig's base (3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until TLC analysis indicated the reaction was complete. The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic

components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting hydantoins were purified either by concentration under reduced pressure or silica gel column chromatography; followed by crystallisation.

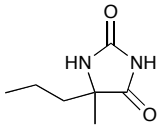
5-Methyl-5-ethylimidazolidine-2,4-dione 93



93

2-Butanone (0.27 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 14 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-ethyl imidazolidine-2,4-dione **93** (0.11 g, 25 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

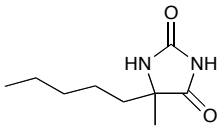
5-Methyl-5-*n*-propylimidazolidine-2,4-dione 110



110

2-Pentanone (0.32 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 24 h; hydantoin formation time: 13 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-*n*-propyl imidazolidine-2,4-dione **110** (0.36 g, 76 % yield) as a colourless solid. R_f 0.4 (ethyl acetate); mp 120 - 121 °C (*from ethanol*, lit.,[126] 123 - 124 °C); δ_H (400.1 MHz; D^6-DMSO), 10.58 (1H, s, N*H*), 7.88 (1H, s, N*H*), 1.59-1.40 (2H, m, CH_2CH_2CH_3), 1.34-1.01 (5H, m, CH_2CH_2CH_3 and CH_3), 0.84 (3H, t, *J* 7.3, CH_2CH_2CH_3); δ_C (100.6 MHz; D^6-DMSO), 178.6, 156.3, 62.0, 23.6, 16.4 (2C), 13.8; *m/z* (ES^+) 179 ($[M+Na]^+$, 30 %). These data are in agreement with the literature values.[48,126]

5-Methyl-5-*n*-pentylimidazolidine-2,4-dione 94

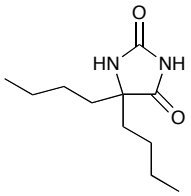


94

2-Heptanone (0.57 mL, 5.00 mmol, 1 equiv.); aminonitrile formation time: 24 h; hydantoin formation time: 7 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-*n*-pentylimidazolidine-2,4-dione **94** (0.90 g, 98 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - Aminonitrile formation time: 20 h; hydantoin formation time: 12 h. 5-Methyl-5-*n*-pentylimidazolidine-2,4-dione **94** (0.87 g, 95 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

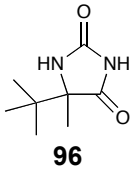
5,5-Di-*n*-butylimidazolidine-2,4-dione 95



95

5-Nonanone (0.52 mL, 3.00 mmol, 1 equiv.), aminonitrile formation time: 20 h; hydantoin formation time: 14 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5,5-di-*n*-butylimidazolidine-2,4-dione **95** (0.46 g, 71 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-*t*-butylimidazolidine-2,4-dione 96

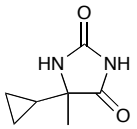


96

2,2-Dimethyl-3-butanone (0.37 mL, 3.00 mmol, 1 equiv.), ethanol (5 mL) as reaction solvent; aminonitrile formation time: 24 h; hydantoin formation time: 17 h. Purification by concentration under reduced pressure followed by crystallisation from ethyl acetate gave 5-methyl-5-*t*-butylimidazolidine-2,4-dione **96** (0.13 g, 25 % yield)

as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-cyclopropylimidazolidine-2,4-dione 75

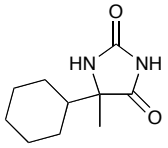


75

Cyclopropylmethylketone (0.59 mL, 5.94 mmol, 1 equiv.); aminonitrile formation time: 24 h; hydantoin formation time: 6 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-cyclopropylimidazolidine-2,4-dione **75** (0.76 g, 83 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - Aminonitrile formation time: 20 h; hydantoin formation time: 8 h. 5-Methyl-5-cyclopropylimidazolidine-2,4-dione **75** (0.55 g, 61 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

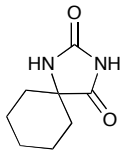
5-Methyl-5-cyclohexylimidazolidine-2,4-dione 97



97

Cyclohexylmethylketone (0.41 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 20 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 5-methyl-5-cyclohexyl imidazolidine-2,4-dione **97** (0.42 g, 71 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

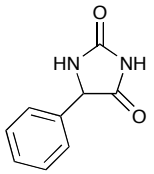
1,3-Diazaspiro[4.5]decane-2,4-dione 99



99

Cyclohexanone (0.31 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 9 h. Purification by concentration under reduced pressure followed by crystallisation from ethanol gave 1,3-diazaspiro[4.5]decane-2,4-dione **99** (0.21 g, 41 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

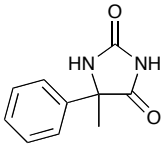
5-Phenylimidazolidine-2,4-dione 92



92

Benzaldehyde (0.41 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 17 h. Purification by crystallisation from ethanol gave 5-phenylimidazolidine-2,4-dione **92** (0.43 g, 82 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-phenylimidazolidine-2,4-dione 100

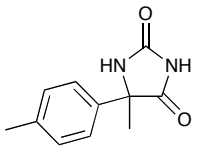


100

Acetophenone (0.35 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 5 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-phenylimidazolidine-2,4-dione **100** (0.34 g, 59 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - Aminonitrile formation time: 20 h; hydantoin formation time: 6 h. 5-Methyl-5-phenylimidazolidine-2,4-dione **100** (0.20 g, 37 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

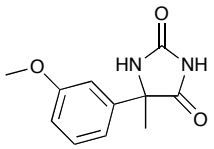
5-Methyl-5-(4'-methylphenyl)imidazolidine-2,4-dione 101



101

4'-Methylacetophenone (0.40 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 6 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-(4'-methylphenyl)imidazolidine-2,4-dione **101** (0.14 g, 32 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-(3'-methoxyphenyl)imidazolidine-2,4-dione 102

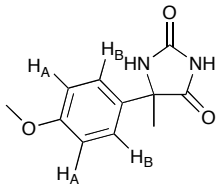


102

3'-Methoxyacetophenone (0.46 mL, 3.33 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 7 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave *5-methyl-5-(3'-methoxyphenyl)imidazolidine-2,4-dione* **102** (0.30 g, 41 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - Aminonitrile formation time: 20 h; hydantoin formation time: 7 h. *5-Methyl-5-(3'-methoxyphenyl)imidazolidine-2,4-dione* **102** (0.29 g, 39 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

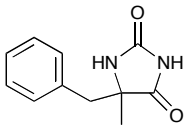
5-Methyl-5-(4'-methoxyphenyl)imidazolidine-2,4-dione 111



111

4'-Methoxyacetophenone (0.45 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 8 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] followed by crystallisation from ethanol gave 5-methyl-5-(4'-methoxyphenyl)imidazolidine-2,4-dione **111** (0.12 g, 18 % yield) as a colourless solid. R_f 0.4 (ethyl acetate); mp 206 - 208 °C (*from ethanol*, lit.,[131] 210 - 212 °C); δ_H (400.1 MHz; D^6-DMSO), 10.75 (1H, br s, N*H*), 8.54 (1H, br s, N*H*), 7.35 (2H, dd, *J* 1.9, 6.8, aromatic CH_B × 2), 6.93 (2H, dd, *J* 1.9, 6.8, aromatic CH_A × 2), 3.73 (3H, s, OCH_3), 1.60 (3H, s, CH_3); δ_C (100.6 MHz; D^6-DMSO), 177.2, 158.8, 156.2, 131.8, 126.5 (2C), 113.7 (2C), 63.4, 55.1, 24.9; *m/z* (ES^+) 243 ($[M+Na]^+$, 100 %); *m/z* (ES^-) 219 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[131,132]

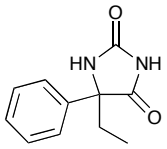
5-Methyl-5-benzylimidazolidine-2,4-dione 112



112

Benzylmethylketone (0.40 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 11 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] followed by crystallisation from ethanol gave 5-methyl-5-benzyl imidazolidine-2,4-dione **112** (0.60 g, 99 % yield) as a colourless solid. R_f 0.5 (ethyl acetate); mp 226 - 227 °C (*from ethanol*, lit.,[133] 227 - 228 °C); δ_H (400.1 MHz; D^6-DMSO), 10.28 (1H, br s, N*H*), 7.96 (1H, br s, N*H*), 7.28-7.20 (3H, m, aromatic C*H* × 3), 7.15-7.11 (2H, m, aromatic C*H* × 2), 2.92 (1H, d, *J* 13.6, CH_AH$_B$Ph), 2.73 (1H, d, *J* 13.6, CH$_A$$H_B$Ph), 1.34 (3H, s, C$H_3$); δ_C (100.6 MHz; D^6-DMSO), 177.6, 155.8, 135.4, 130.0 (2C), 127.9 (2C), 126.7, 63.1, 42.8, 24.0; *m/z* (ES^+) 227 ($[M+Na]^+$, 100 %); *m/z* (ES^-) 203 ($[M-H]^-$, 100 %). These data are in agreement with the literature values.[114,133]

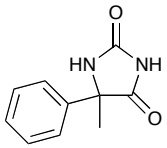
5-Ethyl-5-phenylimidazolidine-2,4-dione 103



103

Propiophenone (0.66 mL, 5.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 6 h. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-ethyl-5-phenylimidazolidine-2,4-dione **103** (0.37 g, 56 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-phenylimidazolidine-2,4-dione 100



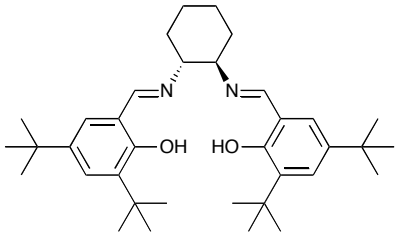
100

A mixture of acetophenone (0.35 mL, 3.00 mmol, 1 equiv.) and trimethylsilyl trifluoromethanesulfonate (54.0 µL, 0.30 mmol, 0.1 equiv.) in dichloromethane (5 mL) was prepared and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (1.59 mL, 9.00 mmol, 3 equiv.) was added and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (3 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined. The combined fractions were washed with 0.1 M HCl (10 ml), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-phenylimidazolidine-2,4-dione **100** (0.16 g, 28 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - Aminonitrile formation time: 20 h; hydantoin formation time: 4 h. Purification by concentration under reduced pressure gave 5-methyl-5-phenyl

imidazolidine-2,4-dione **100** (0.11 g, 20 % yield) as a colourless solid. The data obtained are in agreement with other syntheses of this compound.

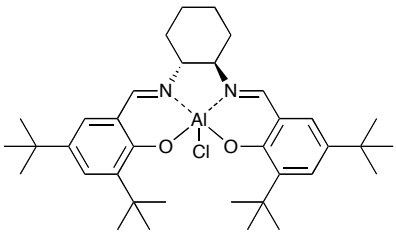
(*R*,*R*)-*N*,*N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine 118



118

A solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (3.90 g, 16.6 mmol, 2 equiv.) and (*R*,*R*)-(-)-1,2-diaminocyclohexane (0.95 g, 8.32 mmol, 1 equiv.) in ethanol (15 mL) was heated under reflux for 10 mins, until a precipitate formed. ^{1}H NMR analysis indicated complete transformation of starting material to product. The precipitate was isolated by filtration and washed with cold ethanol (30 mL). The crude material was dried *in vacuo* prior to crystallisation from hexanes, which gave (*R*,*R*)-*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine **118** (4.13 g, 92 % yield) as a yellow solid. $[\alpha]_D^{20}$ - 350.5 (*c* 1.0, CH_2Cl_2, lit.,[134] $[\alpha]_D^{20}$ - 309, *c* 1.0, CH_2Cl_2); mp 202 - 203 °C (*from hexanes*, lit.,[134] 202 - 203 °C); ν_{max} (KBr disc)/cm^{-1} 3422 (s), 2963 (s), 2863 (m), 2360 (w), 1630 (s), 1437 (m), 1390 (w), 1361 (m), 1270 (m), 1174 (m), 879 (m), 827 (w), 772 (m); δ_H (400.1 MHz; $CDCl_3$), 8.32 (2H, s, N=C*H* × 2), 7.33 (2H, d, *J* 2.5, aromatic C*H* × 2), 7.01 (2H, d, *J* 2.5, aromatic C*H* × 2), 3.39-3.30 (2H, m, O*H* × 2), 2.02-1.85 (4H, m, cyclohexyl CH_2 × 2), 1.83-1.70 (2H, m, C=NC*H* × 2), 1.60-1.38 (22H, m, CH_3 × 6 and cyclohexyl CH_2 × 2), 1.31-1.21 (18H, s, CH_3 × 6); δ_C (75.5 MHz; $CDCl_3$), 165.9 (2C), 158.0 (2C), 139.9 (2C), 136.4 (2C), 126.8 (2C), 126.1 (2C), 117.8 (2C), 72.4, (2C), 35.0 (2C), 34.1 (2C), 33.3 (2C), 31.4 (6C), 29.5 (6C), 24.4 (2C); *m/z* (ES$^+$) 548 ([M+H]$^+$, 100 %). These data are in agreement with the literature values.[134]

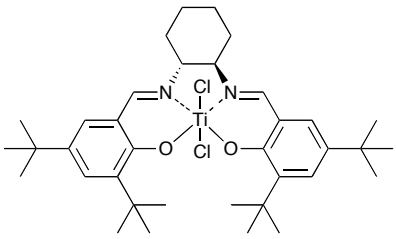
Aluminium (III) (salen) chloride 53



53

To a solution of (*R*,*R*)-*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (0.50 g, 0.92 mmol, 1 equiv.) in dichloromethane (15 mL) was slowly added diethylaluminium chloride (1.8 M solution in toluene) (0.51 mL, 0.92 mmol, 1 equiv.) at RT, and the solution was stirred for 2 h. The solvents were removed *in vacuo*, the resulting residue was washed with hexanes and dried *in vacuo* to give aluminium (III) (salen) chloride **53** (0.51 g, 92 % yield) as a pale solid. mp 300 °C dec. (lit.,[73] 350 °C dec.); $[\alpha]_D^{20}$ - 704.8 (*c* 1.0, CH_2Cl_2); δ_H (400.1 MHz; C_6D_6), 7.98-7.94 (2H, m, N=C*H* × 2), 7.86 (1H, br s, aromatic C*H*), 7.69 (1H, br s, aromatic C*H*), 7.22 (2H, m, aromatic CH × 2), 3.71-3.60 (2H, m, NC*H* × 2), 2.06-1.97 (18H, m, CH_3 × 3), 1.57-1.42 (22H, m, CH_3 × 3 and cyclohexyl CH_2 × 2), 0.94-0.47 (4H, m, cyclohexyl CH_2 × 2); *m/z* (LSIMS$^+$) 571 ([M-Cl]$^+$, 100 %). These data are in agreement with the literature values.[73]

Titanium (IV) (salen) dichloride 119

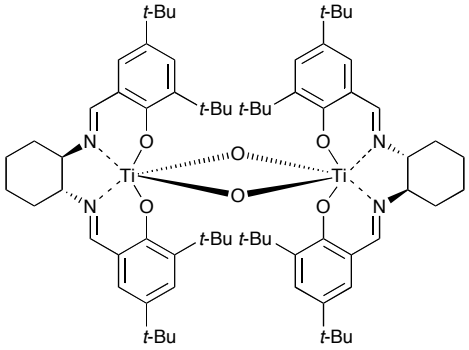


119

To a solution of (*R*,*R*)-*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (0.50 g, 0.92 mmol, 1 equiv.) in dichloromethane (5 mL) was added titanium (IV) chloride (1.0 M solution in toluene) (0.92 mL, 0.92 mmol, 1 equiv.) at RT, and the solution was stirred for 2 h. The solvents were removed *in vacuo*, the resulting residue was washed with diethyl ether (50 ml), diethyl ether/petroleum ether (1/1, 50 ml) and dried *in vacuo*. The crude was crystallised from chloroform to give titanium (IV) (salen) dichloride **119** (0.23 g, 38 % yield) as a brown solid. mp 310 °C dec. (*from dichloromethane*, lit.,[102] 330 °C dec.); δ_H (400.1 MHz; $CDCl_3$), 8.33 (2H,

s, N=C*H* × 2), 7.62 (2H, d, *J* 2.4, aromatic C*H* × 2), 7.36 (2H, d, *J* 2.4, aromatic C*H* × 2), 4.10-4.05 (2H, m, NC*H* × 2), 2.67-2.57 (2H, m, cyclohexyl C*H* × 2), 2.17-2.05 (2H, m, cyclohexyl C*H* × 2), 1.66-1.43 (22H, m, cyclohexyl C*H* × 4 and CH_3 × 3), 1.36 (18H, s, CH_3 × 3); δ_C (100.6 MHz; $CDCl_3$), 160.5 (2C), 159.7 (2C), 144.6 (2C), 136.8 (2C), 131.2 (2C), 130.1 (2C), 125.7 (2C), 67.8 (2C), 35.6 (2C), 34.5 (2C), 31.4 (6C), 29.9 (6C), 28.5 (2C), 24.1 (2C). These data are in agreement with the literature values.[102]

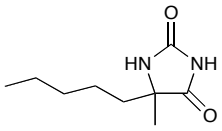
Titanium (IV) (salen) dimer 120



120

To a solution of titanium (IV) (salen) dichloride (0.15 g, 0.23 mmol, 1 equiv.) and triethylamine (30.0 µL, 0.23 mmol, 1 equiv.) in dichloromethane (5 mL) at RT was added water (4.00 µL, 0.73 mmol, 1 equiv.) and the solution was stirred for 3 h. The resulting yellow solution was washed with water (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give titanium (IV) (salen) dimer **120** (100 mg, 35 % yield) as a yellow solid. mp 250 °C dec. (lit.,[102] 315 °C dec.); $[\alpha]_D^{20}$ - 330.4 (*c* 0.0125, $CHCl_3$, lit.,[102] - 267, *c* 0.0125); δ_H (400.1 MHz; D^6-DMSO), 7.87 (2H, m, N=C*H* × 2), 7.81 (2H, m, N=C*H* × 2), 7.32 (2H, d, *J* 2.5, aromatic C*H* × 2), 7.22 (2H, d, *J* 2.5, aromatic C*H* × 2), 6.99 (2H, d, *J* 2.5, aromatic C*H* × 2), 6.94 (2H, d, *J* 2.5, aromatic C*H* × 2), 3.67-3.58 (2H, m, NC*H* × 2), 3.35-3.24 (2H, m, NC*H* × 2), 2.17-2.08 (2H, m, cyclohexyl C*H* × 2), 1.53-1.37 (9H, s, CH_3 × 3), 1.26-1.01 (53H, m, CH_3 × 15 and cyclohexyl CH_2 × 4), 0.94-0.70 (22H, m, CH_3 × 6 and cyclohexyl CH_2 × 2); *m/z* (LSIMS$^+$) 1216 ($[M]^+$, 20 %), 1200 ($[M\text{-}O]^+$, 100 %), 1184 ($[M\text{-}O_2]^+$, 20 %). These data are in agreement with the literature values.[102]

5-Methyl-5-*n*-pentylimidazolidine-2,4-dione 94

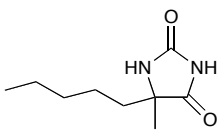


94

A mixture of 2-heptanone (0.70 mL, 5.00 mmol, 1 equiv.) and aluminium (III) (salen) chloride (0.15 g, 0.25 mmol, 0.05 equiv.) in dichloromethane (5 mL) was prepared and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (2.61 mL, 15.0 mmol, 3 equiv.) was added to the reaction mixture and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (11 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. No further purification was necessary to give 5-methyl-5-*n*-pentyl imidazolidine-2,4-dione **94** (0.88 g, 96 % yield) as a colourless solid. Chiral HPLC analysis indicates 6 % ee, 95/5 hexane/2-propanol, [t_r = 13.8 (minor), 17.3 (major)]. The data obtained are in agreement with other syntheses of this compound.

Repeat Synthesis - 2-Heptanone (0.42 mL, 3.00 mmol, 1 equiv.); aminonitrile formation time: 20 h; hydantoin formation time: 19 h. 5-Methyl-5-*n*-pentyl imidazolidine-2,4-dione **94** (0.38 g, 69 % yield) as a colourless solid. Chiral HPLC analysis indicates 0 % ee, 90/10 hexane/2-propanol, (t_r = 7.0, 7.8). The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-*n*-pentylimidazolidine-2,4-dione 94

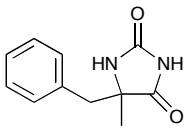


94

A mixture of 2-heptanone (0.40 mL, 2.83 mmol, 1 equiv.) and aluminium (III) (salen) choride (86.0 mg, 0.14 mmol, 0.05 equiv.) in dichloromethane (5 mL) was prepared

and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. A solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added and the mixture was stirred for a further 20 h at -78 °C. The reaction mixture was allowed to attain RT and Hünig's base (1.48 mL, 8.49 mmol, 3 equiv.) was added to the reaction mixture and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (12 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-methyl-5-*n*-pentylimidazolidine-2,4-dione **94** (8.00 mg, 2 % yield) as a colourless solid. Chiral HPLC analysis indicates 3 % ee, 90/10 hexane/2-propanol, [t_r = 7.2 (major), 8.1 (minor)]. The data obtained are in agreement with other syntheses of this compound.

5-Methyl-5-benzylimidazolidine-2,4-dione 112

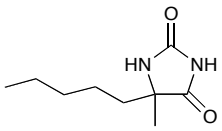


112

A mixture of benzylmethylketone (0.42 mL, 3.00 mmol, 1 equiv.) and aluminium (III) (salen) chloride (91.0 mg, 0.15 mmol, 0.05 equiv.) in dichloromethane (5 mL) was prepared and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (1.59 mL, 9.00 mmol, 3 equiv.) was added to the reaction mixture and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (14 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [eluting with 20/80 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL)] gave 5-

methyl-5-benzylimidazolidine-2,4-dione **112** (0.34 g, 56 % yield) as a colourless solid. No accurate determination of ee was possible. The data obtained are in agreement with other syntheses of this compound.

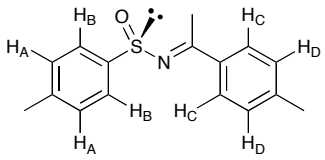
5-Methyl-5-*n*-pentylimidazolidine-2,4-dione 94



94

A mixture of 2-heptanone (0.43 mL, 3.00 mmol, 1 equiv.) and titanium (salen) dimer (37.0 mg, 0.03 mmol, 0.01 equiv.) in dichloromethane (5 mL) was prepared and approximately 10 mL of liquid ammonia was condensed into the reaction mixture at -78 °C. This temperature was maintained for 3 h after which, a solution of hydrogen cyanide (2 equiv. in CH_2Cl_2, 2 mL) was added. The reaction vessel was allowed to attain RT and the mixture was stirred for 20 h. Hünig's base (1.59 mL, 9.00 mmol, 3 equiv.) was added to the reaction mixture and CO_2 (g) (sublimed from dry ice and passed through 4 Å molecular sieves) was bubbled through the mixture until the reaction was complete (7 h). The solvent was removed *in vacuo* and the resulting paste was suspended in water (5 mL). The organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with 0.1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by concentration under reduced pressure gave 5-methyl-5-*n*-pentyl imidazolidine-2,4-dione **94** (50.0 mg, 9 % yield) as a colourless solid. Chiral HPLC analysis indicates 0 % ee, 95/5 hexane/2-propanol, (t_r = 13.5, 16.9). The data obtained are in agreement with other syntheses of this compound.

(*S*)-(+)-*N*-α-Methyl-(4-methylbenzylidene)-(4'-methylphenyl) sulfinamide 125



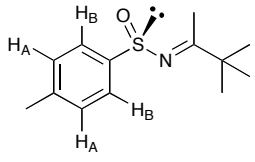
125

A solution of (*S*)-(+)-*p*-toluenesulfonamide (0.31 g, 2.00 mmol, 1 equiv.) and 4'-methylacetophenone (1.34 mL, 10.0 mmol, 5 equiv.) in dichloromethane (10 mL) was prepared under an inert atmosphere. Titanium (IV) ethoxide (4.20 mL,

20.0 mmol, 10 equiv.) was added, and the reaction solution was stirred under reflux for 16 h, after which time TLC analysis indicated that the starting materials had been consumed. The reaction solution was cooled to 0 °C and water (10 mL) was added. The suspension was filtered through Celite® and the organic components were extracted with dichloromethane (3 × 20 mL). The extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography [eluting with 15/85 ethyl acetate/petroleum ether (800 mL), 35/65 (600 mL)] followed by crystallisation from diethyl ether to give (*S*)-(+)-*N*-α-methyl-(4-methylbenzylidene)-(4'-methylphenyl) sulfinamide **125** (0.43 g, 80 % yield) as colourless needles. R_f 0.3 (60/40 ethyl acetate/petroleum ether); mp 102 - 104 °C (*from diethyl ether*, lit.,[104] 102 - 104 °C); $[\alpha]_D^{20}$ + 115.2 (*c* 1.2, $CHCl_3$, lit.,[104] $[\alpha]_D^{20}$ + 117, *c* 1.2, $CHCl_3$); δ_H (300 MHz; $CDCl_3$), 7.73 (2H, d, *J* 8.0, aromatic CH_C × 2), 7.65 (2H, d, *J* 8.0, aromatic CH_B × 2), 7.25 (2H, d, *J* 8.0, aromatic CH_A × 2), 7.13 (2H, d, *J* 8.0, aromatic CH_D × 2), 2.69 (3H, s, CH_3), 2.33 (3H, s, PhCH_3), 2.31 (3H, s, PhCH_3); δ_C (75.5 MHz; $CDCl_3$), 174.0, 143.5, 142.6, 141.8, 135.4, 129.8 (2C), 129.2 (2C), 127.6 (2C), 125.3 (2C), 21.5 (2C), 20.0; *m/z* (ES^+) 294 ($[M+Na]^+$, 100 %). These figures are in agreement with the literature values.[104]

Repeat Synthesis - (*S*)-(+)-*p*-Toluenesulfonamide (0.62 g, 4.00 mmol, 1 equiv.); yield 65 %, 0.72 g, colourless needles. The data obtained are in agreement with the literature values.[104]

(*S*)-(+)-(1,2,2-Trimethylpropylidene)-(4'-methylphenyl) sulfinamide 126

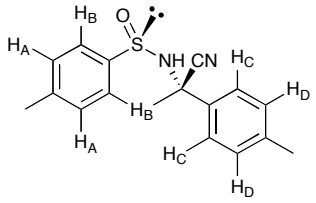


126

A solution of (*S*)-(+)-*p*-toluenesulfonamide (0.62 g, 4.00 mmol, 1 equiv.) and 2,2-dimethyl-3-butanone (2.49 mL, 20.0 mmol, 5 equiv.) in dichloromethane (25 mL) was prepared under an inert atmosphere. Titanium (IV) ethoxide (8.40 mL, 40.0 mmol, 10 equiv.) was added, and the reaction solution was stirred and heated under reflux for 48 h, after which time TLC analysis indicated that the starting materials had been consumed. The reaction solution was cooled to 0 °C and water

(20 mL) was added. The suspension was filtered through Celite® and the organic components were extracted with dichloromethane (3 × 30 mL). The extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The resulting oil was purified by silica gel column chromatography [eluting with 20/80 ethyl acetate/petroleum ether (600 mL), 50/50 (500 mL)] to give (*S*)-(+)-(1,2,2-trimethylpropylidene)-(4'-methylphenyl) sulfinamide **126** (0.40 g, 42 % yield) as a colourless oil. R_f 0.7 (60/40 ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ + 36.1 (*c* 1.2, $CHCl_3$, lit.,[104] $[\alpha]_D^{20}$ + 29.9, *c* 1.2, $CHCl_3$); δ_H (400.1 MHz; $CDCl_3$), 7.58 (2H, d, *J* 8.1, aromatic CH_B × 2), 7.23 (2H, d, *J* 8.1, aromatic CH_A × 2), 2.34 (3H, s, PhCH_3), 2.26 (3H, s, PhCH_3), 1.08 (9H, s, CH_3 × 3); δ_C (100.6 MHz; $CDCl_3$), 188.0, 143.6, 141.6, 129.7 (2C), 125.3 (2C) 42.6, 27.4 (3C), 21.5, 18.6; *m/z* (ES^+) 260 ($[M+Na]^+$, 100 %). These data are in agreement with the literature values.[104]

(2*S*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile 127

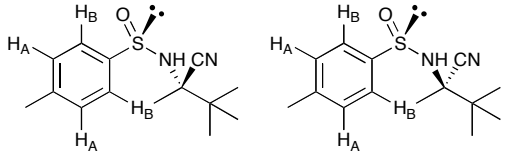


127

A solution of (*S*)-(+)-*N*-α-methyl-(4-methylbenzylidene)-(4'-methylphenyl) sulfinamide (0.27 g, 1.00 mmol, 1 equiv.) in tetrahydrofuran (15 mL) was prepared under an inert atmosphere and cooled to -78 °C. In a separate flask, under an inert atmosphere, a solution of diethylaluminium cyanide (1.0 M in toluene) (1.50 mL, 1.50 mmol, 1.5 equiv.) in tetrahydrofuran (5 mL) was cooled to -78 °C and *iso*-propyl alcohol (0.08 mL, 1.00 mmol, 1 equiv.) was added. The solution was allowed to attain RT, stirred for 30 min, and added to the primary reaction vessel at -78 °C. The reaction solution was allowed to attain RT and stirred for 21 h, after which time TLC analysis indicated the starting materials had been consumed. The solution was cooled to -78 °C and quenched with saturated aqueous solution of NH_4Cl (5 mL). The suspension was filtered through Celite;® the organic components were extracted with ethyl acetate (3 × 20 mL) and combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography [eluting with 15/85 ethyl acetate/petroleum

ether (500 mL), 20/80 (500 mL), 25/75 (500 mL)] to give a mixture of diastereoisomers (*SS*/*SR*, 67/33) (0.27 g, 91 % yield). The diastereoisomers were separated by preparative TLC (diethyl ether/dichloromethane, 5/95) to give (2*S*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile **127** (80.0 mg, 27 % yield) as a colourless oil. R_f 0.5 (60/40 ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ + 64.2 (*c* 1.0, $CHCl_3$, lit.,[104] $[\alpha]_D^{20}$ + 62.1, *c* 1.0, $CHCl_3$); δ_H (300 MHz; $CDCl_3$), 7.57 (2H, d, *J* 8.3, aromatic CH_B × 2), 7.48 (2H, d, *J* 8.3, aromatic CH_A × 2), 7.26 (2H, d, *J* 8.3, aromatic CH_D × 2), 7.21-7.16 (2H, m, aromatic CH_C × 2), 4.48 (1H, s, N*H*), 2.35 (3H, s, PhCH_3), 2.30 (3H, s, PhCH_3), 2.02 (3H, s, CH_3); δ_C (75.5 MHz; $CDCl_3$), 142.0, 141.9, 139.6, 135.5, 129.8 (4C), 125.8 (2C), 125.1 (2C), 121.0, 57.2, 29.4, 21.4, 21.1; *m/z* (CI^+) 299 ($[M+H]^+$, 30 %), 272 ($[M-CN]^+$, 100 %). These data are in agreement with the literature values.[104]

(2*S*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile 128 and (*S*,*R*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile 128



(*S*,*S*)-**128** (*S*,*R*)-**128**

A solution of (*S*)-(+)-(1,2,2-trimethylpropylidene)-(4'-methylphenyl) sulfinamide (0.48 g, 1.00 mmol, 1 equiv.) in tetrahydrofuran (30 mL) was prepared under an inert atmosphere, and cooled to -78 °C. In a separate flask, under an inert atmosphere, a solution of diethylaluminium cyanide (1.0 M in toluene) (3.00 mL, 3.00 mmol, 1.5 equiv.) in tetrahydrofuran (5 mL) was cooled to -78 °C and *iso*-propyl alcohol (0.18 mL, 2.40 mmol, 1.2 equiv.) was added. The solution was allowed to attain RT, stirred for 30 min, and added to the primary reaction vessel at -78 °C. The reaction solution was allowed to attain RT and stirred for 24 h, after which time TLC analysis indicated the starting materials had been consumed. The solution was cooled to -78 °C and quenched with saturated aqueous solution of NH_4Cl (5 mL). The suspension was filtered through Celite;® the organic components were extracted with ethyl acetate (3 × 10 mL) and combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography [eluting with 15/85 ethyl acetate/petroleum ether

(500 mL), 20/80 (700 mL)] to give (2*S*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile **128** (0.22 g, 41 % yield) as a colourless solid and (*S*,*R*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile **128** (0.28 g, 53 % yield) as a colourless solid.

(2*S*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile **128** - R_f 0.5 (60/40 ethyl acetate/petroleum ether); mp 131 - 132 °C (*from dichloromethane*, lit.,[104] 135 - 136 °C); $[\alpha]_D^{20}$ + 191.1 (*c* 1.0, $CHCl_3$, lit.,[104] $[\alpha]_D^{20}$ + 185, *c* 1.0, $CHCl_3$); δ_H (400.1 MHz; $CDCl_3$), 7.72 (2H, d, *J* 8.0, aromatic CH_B × 2), 7.26 (2H, d, *J* 8.0, aromatic CH_A × 2), 4.19 (1H, s, N*H*), 2.36 (3H, s, PhCH_3), 1.78 (3H, s, CH_3), 1.04 (9H, s, CH_3 × 3); δ_C (100.6 MHz; $CDCl_3$), 142.0, 141.9, 129.8 (2C), 125.3 (2C), 121.0, 60.1, 38.4, 24.7 (3C), 21.4, 19.5; *m/z* (ES^+) 551 ([2 × M+Na]$^+$, 60 %), 287 ([M+Na]$^+$, 100 %). These data are in agreement with the literature values.[104]

(*S*,*R*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl)propionitrile **128** - R_f 0.4 (60/40 ethyl acetate/petroleum ether); mp 117 - 118 °C (*from dichloromethane*); $[\alpha]_D^{20}$ + 91.8 (*c* 1.0, $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3411 (s), 3100 (s), 3010 (s), 2900 (s), 1700 (m), 1653 (m), 1635 (m), 1457 (m), 1160 (m), 1126 (m), 1036 (m), 1009 (m), 814 (w), 686 (w); δ_H (400.1 MHz; $CDCl_3$), 7.54 (2H, d, *J* 8.2, aromatic CH_B × 2), 7.26 (2H, d, *J* 8.2, aromatic CH_A × 2), 4.00 (1H, s, N*H*), 2.36 (3H, s, PhCH_3), 1.77 (3H, s, CH_3), 1.06 (9H, s, CH_3 × 3); δ_C (100.6 MHz; $CDCl_3$), 142.2, 142.0, 129.9 (2C), 125.3 (2C), 120.3, 63.2, 38.4, 25.0 (3C), 22.7, 21.4; *m/z* (ES^+) 287 ([M+Na]$^+$, 100 %).

General Procedures for Chiral Derivatisation of Amines; for Analysis of Enantiomeric Excess by ^{1}H NMR

Method 1

A solution of an amine (1 equiv.), a chiral diol (1.1 equiv.,) and 2-formylphenyl boronic acid (1 equiv.) was prepared under an inert atmosphere in $CDCl_3$ (2 mL) and stirred for 5 mins. An aliquot was acquired and analysed by ^{1}H NMR spectroscopy to determine the enantiomeric excess of a range of amines.

(*S*)-BINOL

(±)-2-Amino-2-cyclopropylpropionitrile (0.02 g, 0.18 mmol, 1 equiv.), (*S*)-BINOL (0.06 g, 0.02 mmol, 1.1 equiv.). No determination of enantiomeric excess was possible.

(±)-α-Methylbenzylamine (0.03 g, 0.25 mmol, 1 equiv.), (*S*)-BINOL (0.08 g, 0.27 mmol, 1.1 equiv.). ^{1}H NMR spectroscopic analysis determined that the amine is 55/45 mixture of enantiomers.

L-(+)-Dimethyl tartrate

(±)-2-Amino-2-cyclopropylpropionitrile (0.02 g, 0.18 mmol, 1 equiv.), L-(+)-dimethyl tartrate (0.04 g, 0.20 mmol, 1.1 equiv.). No determination of enantiomeric excess was possible.

(±)-2-Amino-2,3,3-trimethylbutyronitrile (0.03 g, 0.24 mmol, 1 equiv.), L-(+)-dimethyl tartrate (0.05 g, 0.26 mmol, 1.1 equiv.). No determination of enantiomeric excess was possible.

(±)-α-Methylbenzylamine (0.03 g, 0.25 mmol, 1 equiv.), L-(+)-dimethyl tartrate (0.05 g, 0.27 mmol, 1.1 equiv.). ^{1}H NMR spectroscopic analysis determined that the amine is 55/45 mixture of enantiomers.

Method 2

A solution of an amine (1 equiv.) and 2-formylphenylboronic acid (1 equiv.) was prepared in an NMR tube, under an inert atmosphere in $CDCl_3$ (2 mL). Increasing amounts of a chiral diol (up to 1.1 equiv.) was titrated into the solution and the sample was analysed by ^{1}H NMR spectroscopy (after every addition) to show the formation of the imino-complex with increasing amounts of diol.

(*S*)-BINOL

(±)-2-Amino-2-cyclopropylpropionitrile (5.00 mg, 0.05 mmol, 1 equiv.), (*S*)-BINOL (up to 1.1 equiv.). No determination of enantiomeric excess was possible.

(±)-α-Methylbenzylamine (5.00 mg, 0.04 mmol, 1 equiv.), (*S*)-BINOL (up to 1.1 equiv.). ^{1}H NMR spectroscopic analysis determined that the amine is 55/45 mixture of enantiomers.

L-(+)-Dimethyl tartrate

(±)-2-Amino-2-cyclopropylpropionitrile (5.00 mg, 0.04 mmol, 1 equiv.), L-(+)-dimethyl tartrate (up to 1.1 equiv.). No determination of enantiomeric excess was possible.

(±)-2-Amino-2,3,3-trimethylbutyronitrile (5.00 mg, 0.04 mmol, 1 equiv.), L-(+)-dimethyl tartrate (up to 1.1 equiv.). No determination of enantiomeric excess was possible.

(±)-α-Methylbenzylamine (5.00 mg, 0.04 mmol, 1 equiv.), L-(+)-dimethyl tartrate (up to 1.1 equiv.). ^{1}H NMR spectroscopic analysis determined that the amine is 55/45 mixture of enantiomers.

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7 References

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Appendices

1-*N*-(allylamino)-1-naphthalen-2-yl acetonitrile **60**

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Current Data Parameters
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EXPNO                           10
PROCNO                           1

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PULPROG                      zg30
TD                          65536
SOLVENT                     CDCl3
NS                              8
DS                              2
SWH                      5597.015 Hz
FIDRES                   0.085404 Hz
AQ                       5.8545995 sec
RG                            322
DW                         89.333 usec
DE                          6.00 usec
TE                          300.0 K
D1                     1.00000000 sec
TD0                             1

======== CHANNEL f1 ========
NUC1                           1H
P1                          12.00 usec
PL1                         -2.00 dB
SFO1                   400.1324008 MHz

F2 - Processing parameters
SI                          32768
SF                     400.1300399 MHz
WDW                            EM
SSB                             0
LB                           0.30 Hz
GB                              0
PC                           1.00
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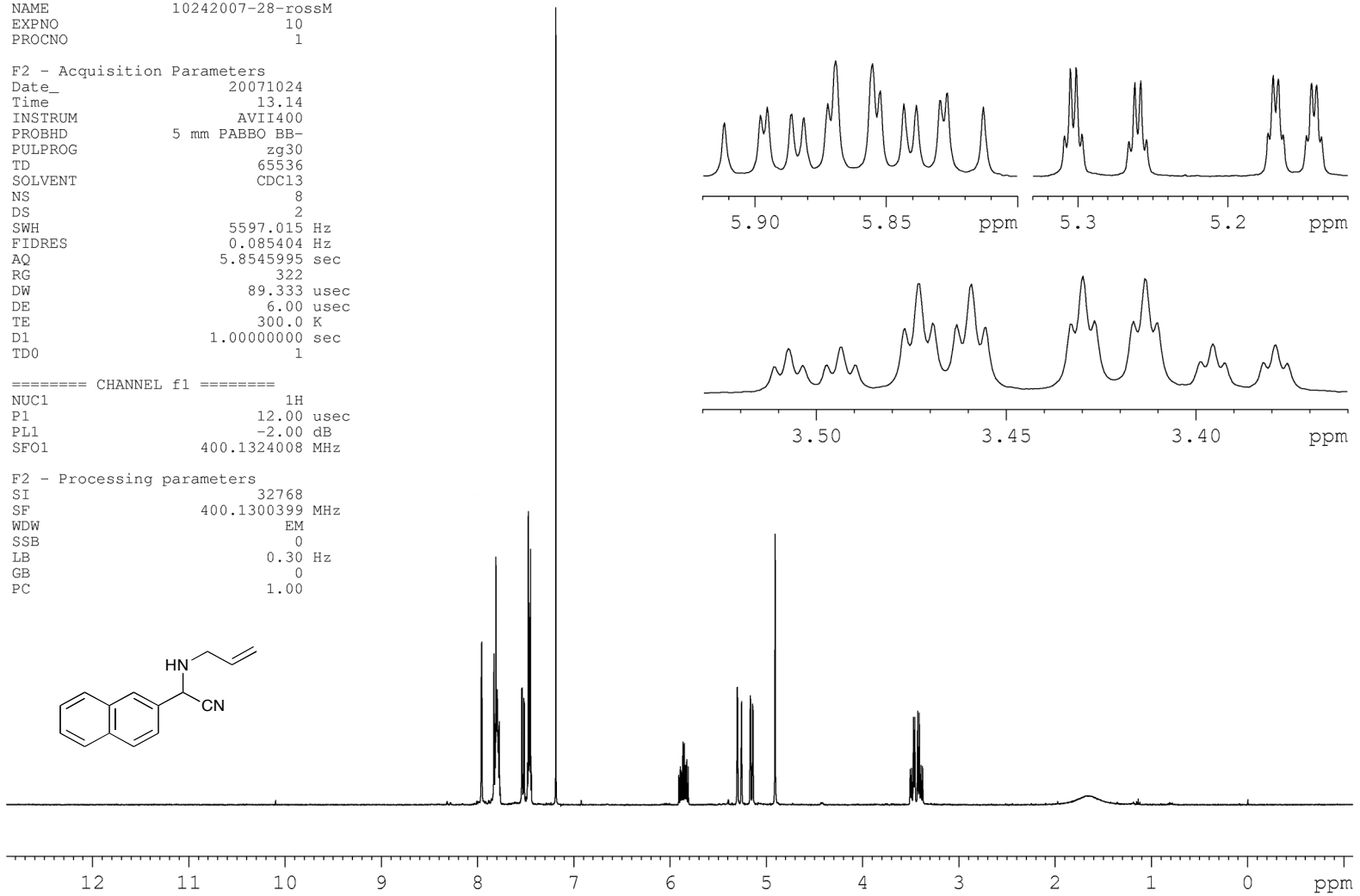
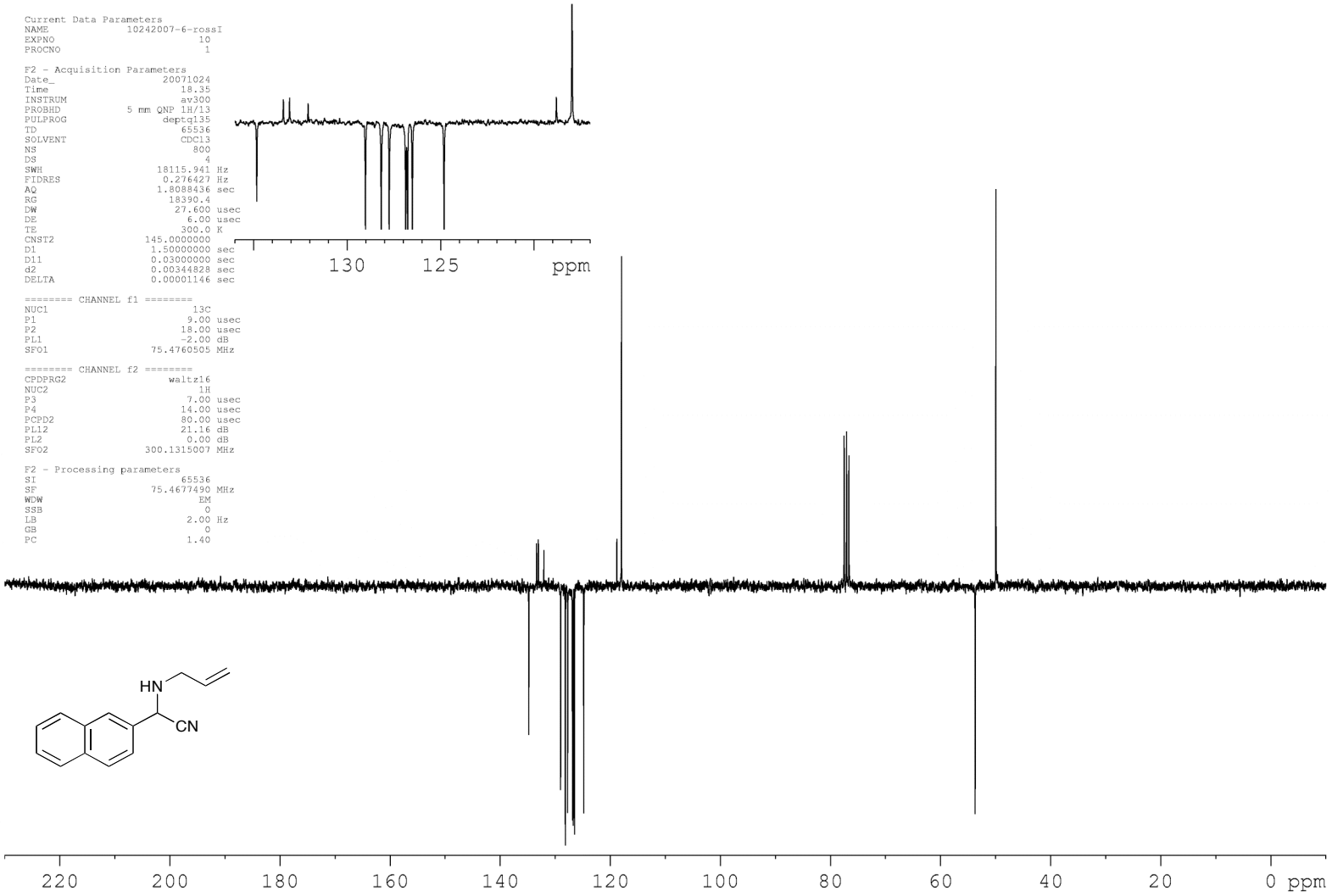
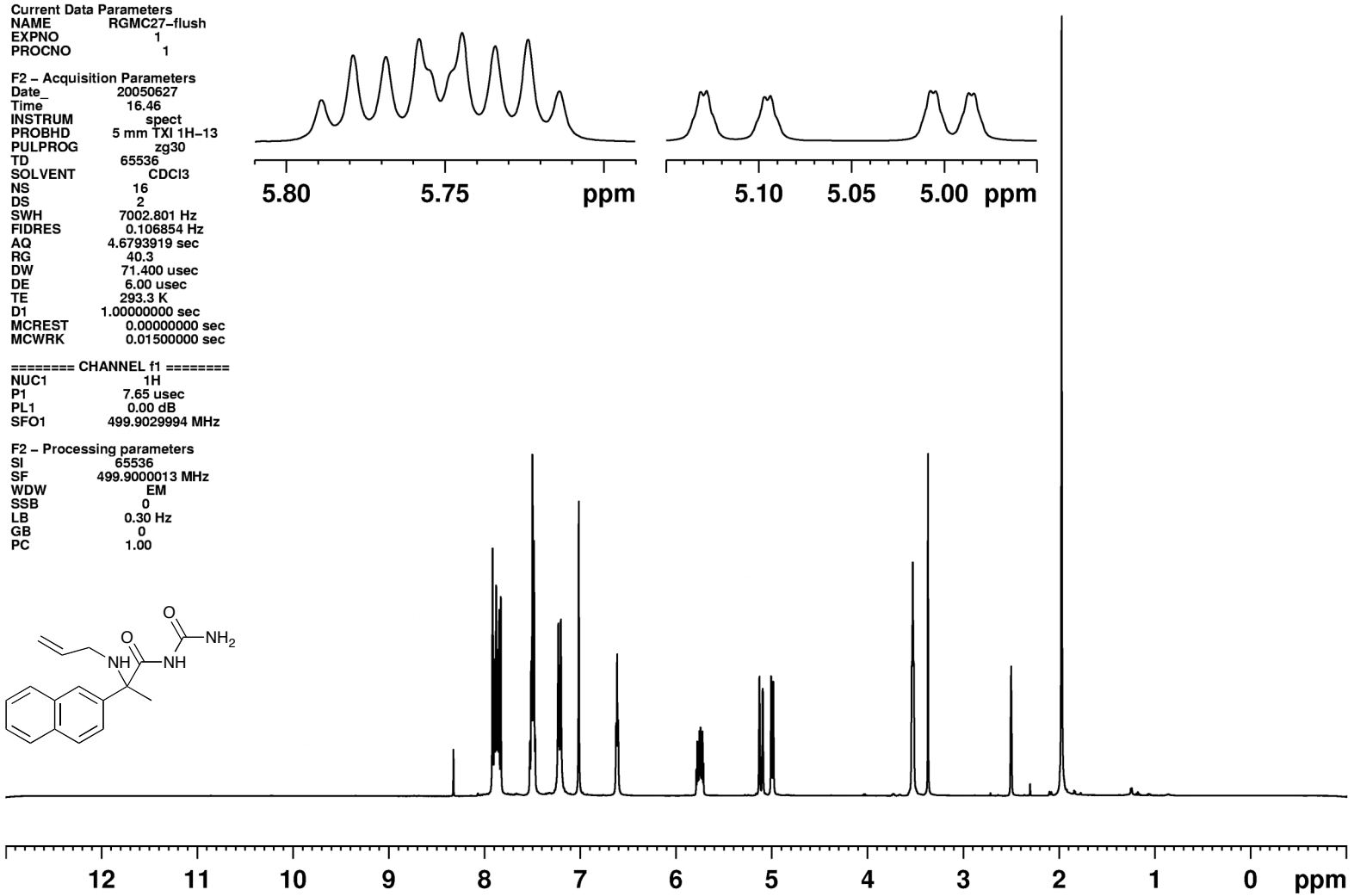


1-*N*-(allylamino)-1-naphthalen-2-yl acetonitrile **60**



(2-allylamino-2-naphthalen-2-yl propionyl) urea **66**



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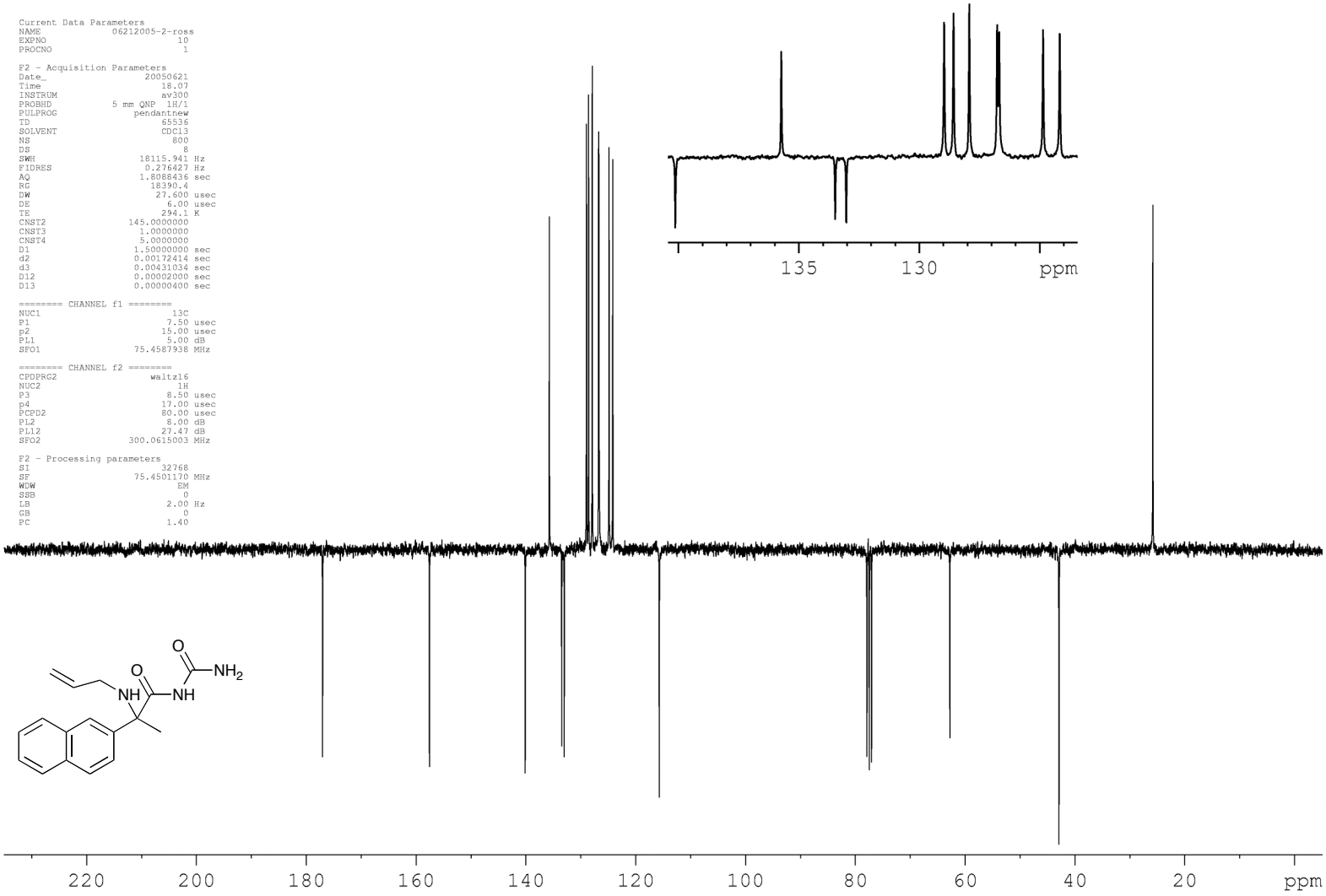
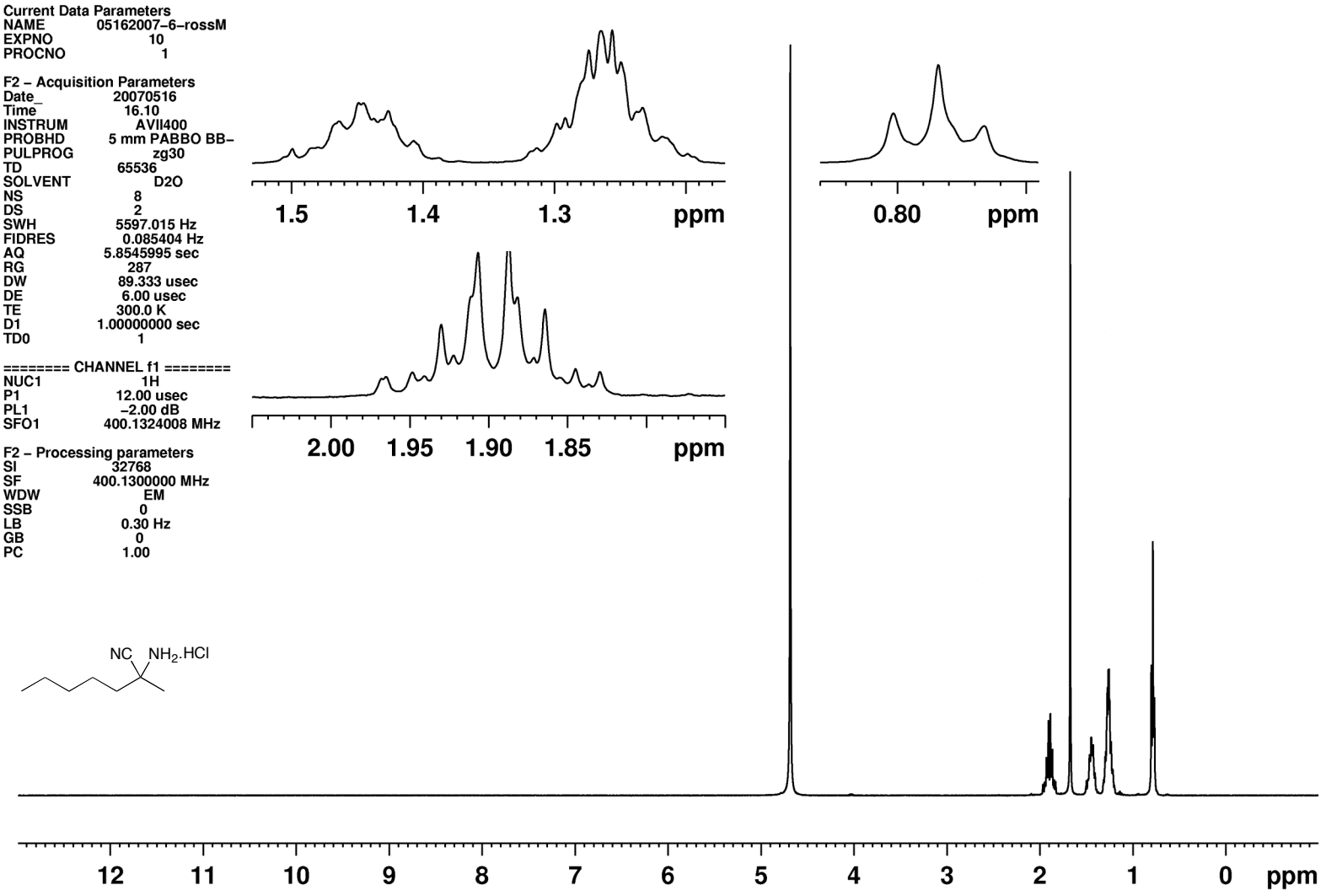


2-amino-2-methyl heptanonitrile hydrochloride salt **80**



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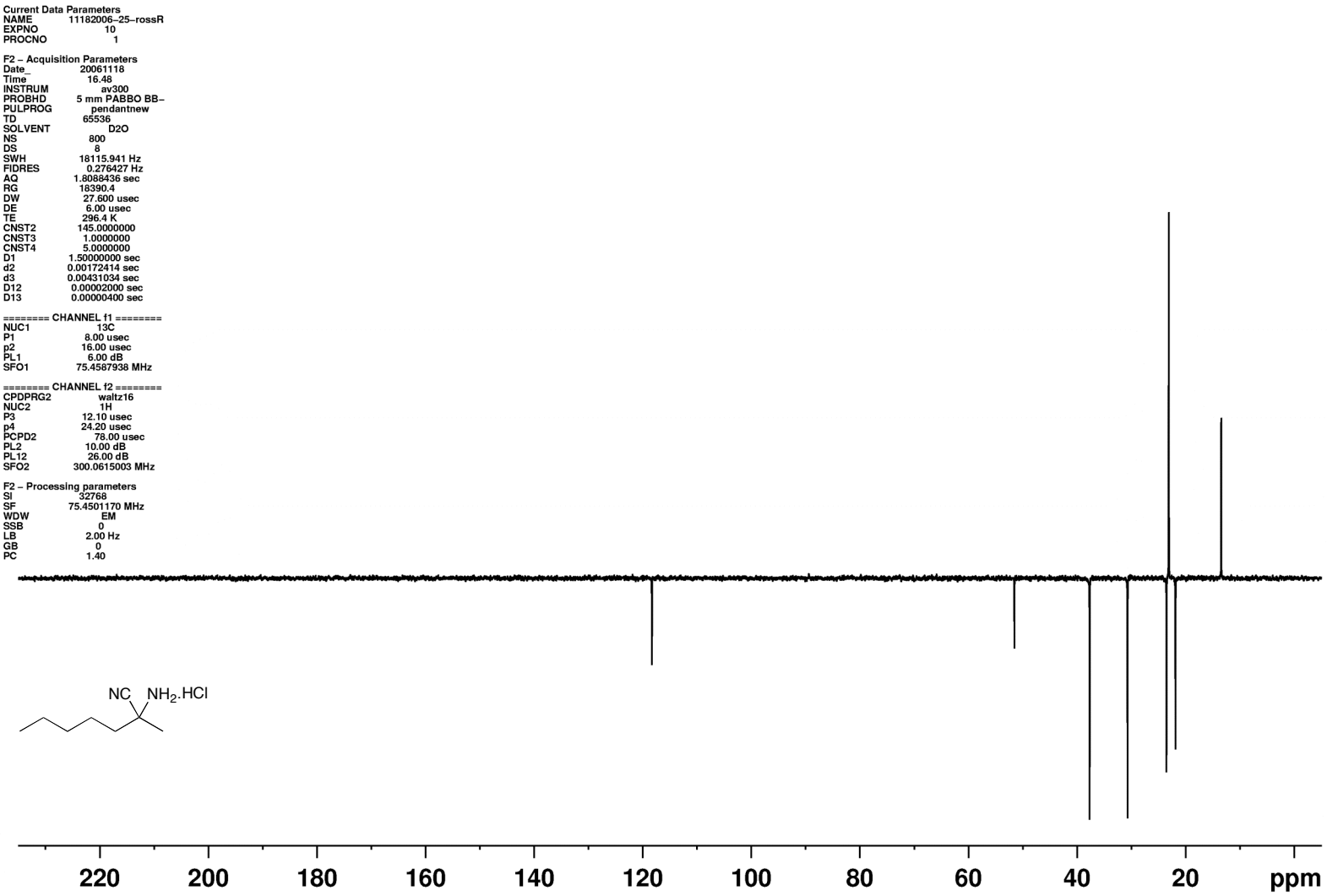
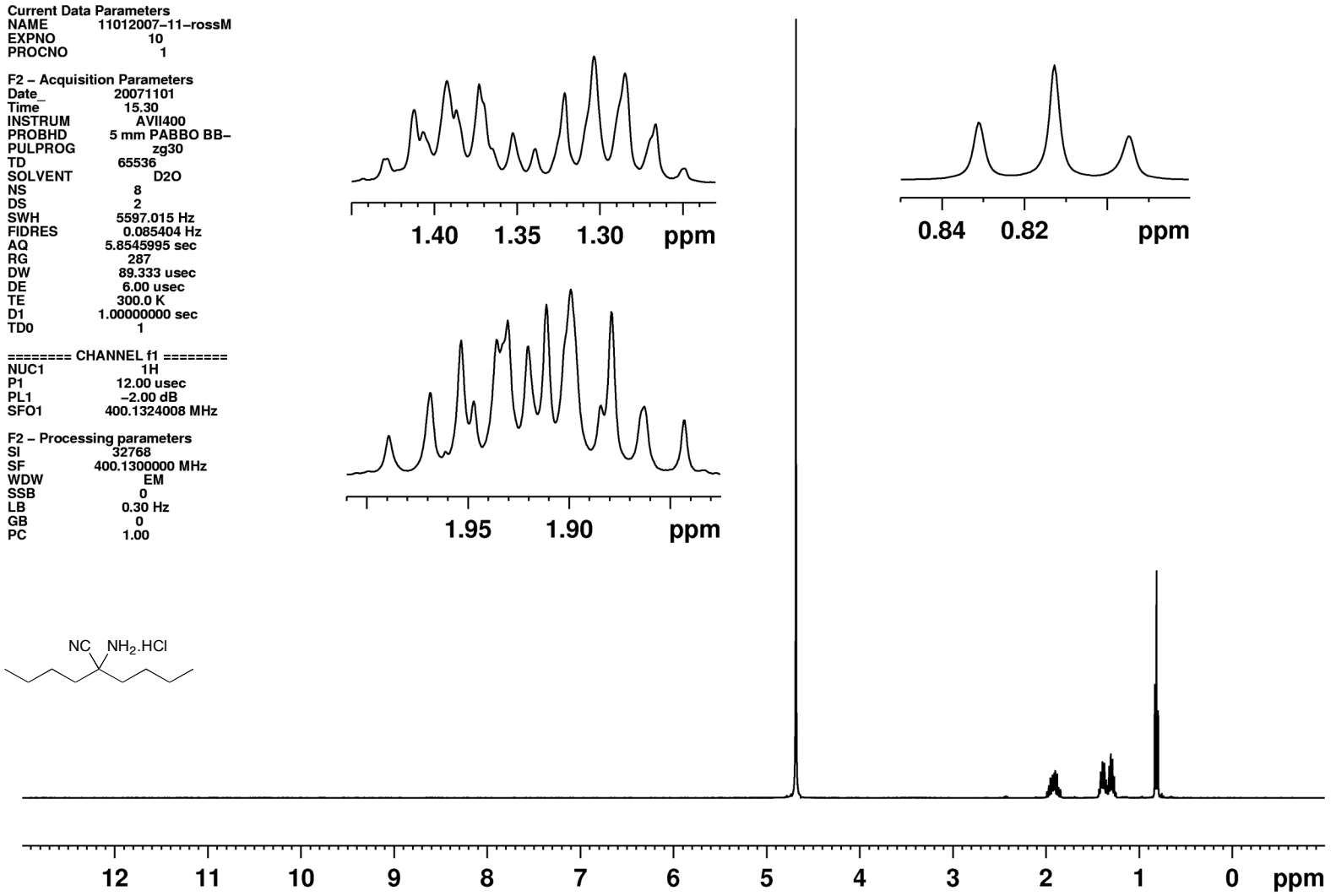


2-amino-2-*n*-butyl hexanonitrile hydrochloride salt **81**



2-amino-2-*n*-butyl hexanonitrile hydrochloride salt **81**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PROCNO                            1

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PULPROG                   deptq135
TD                           65536
SOLVENT                        D2O
NS                             800
DS                               4
SWH                      24038.461 Hz
FIDRES                    0.366798 Hz
AQ                        1.3631988 sec
RG                             203
DW                           20.800 usec
DE                            6.00 usec
TE                           300.0 K
CNST2                  145.0000000
D1                       2.00000000 sec
D11                      0.03000000 sec
d2                       0.00344828 sec
DELTA                    0.00001082 sec

======== CHANNEL f1 ========
NUC1                            13C
P1                             8.50 usec
P2                            17.00 usec
PL1                           -2.00 dB
SFO1                  100.6238364 MHz

======== CHANNEL f2 ========
CPDPRG2                     waltz16
NUC2                            1H
P3                            12.00 usec
P4                            24.00 usec
PCPD2                         85.00 usec
PL12                          15.00 dB
PL2                           -2.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                             32768
SF                    100.6127690 MHz
WDW                               EM
SSB                                0
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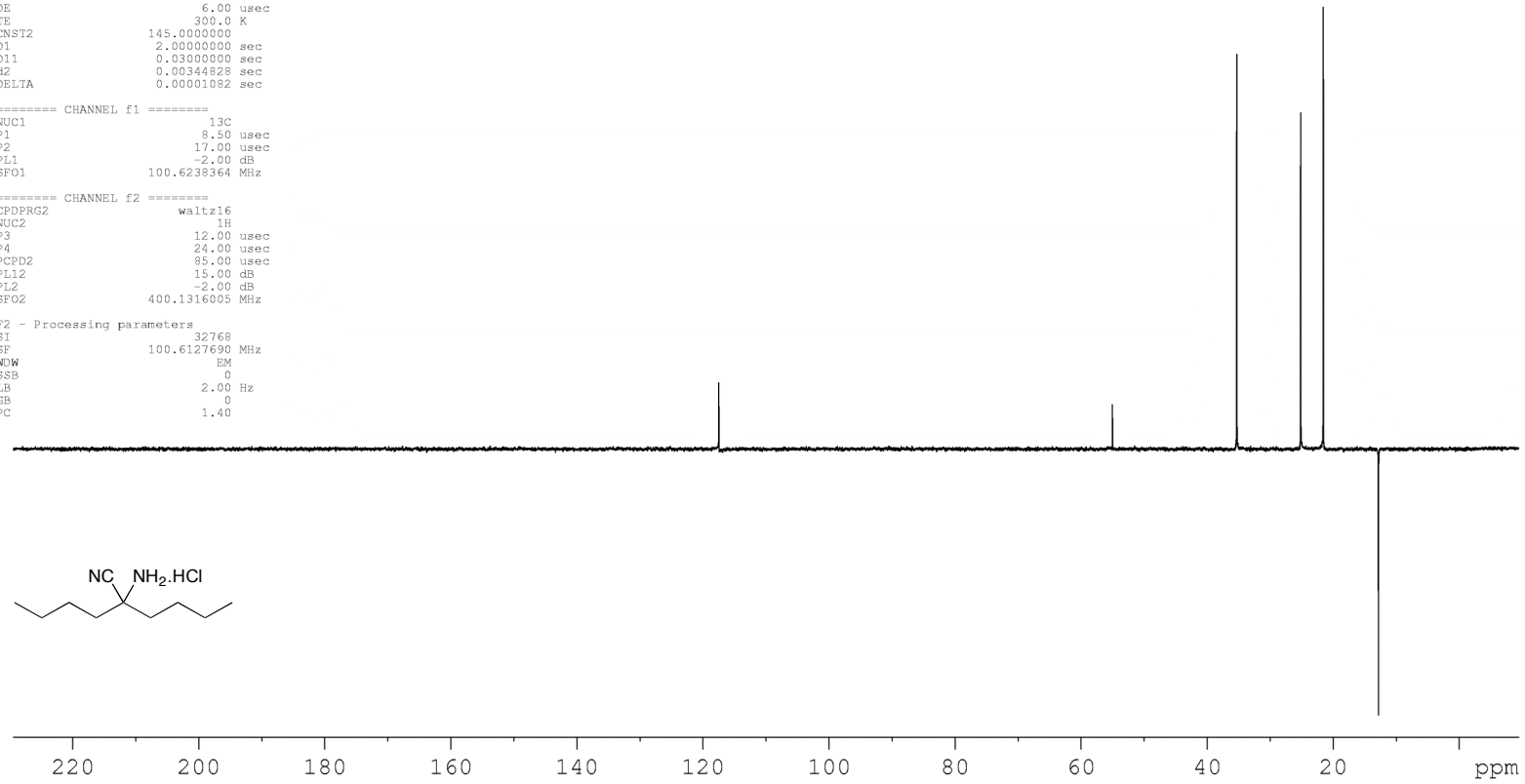
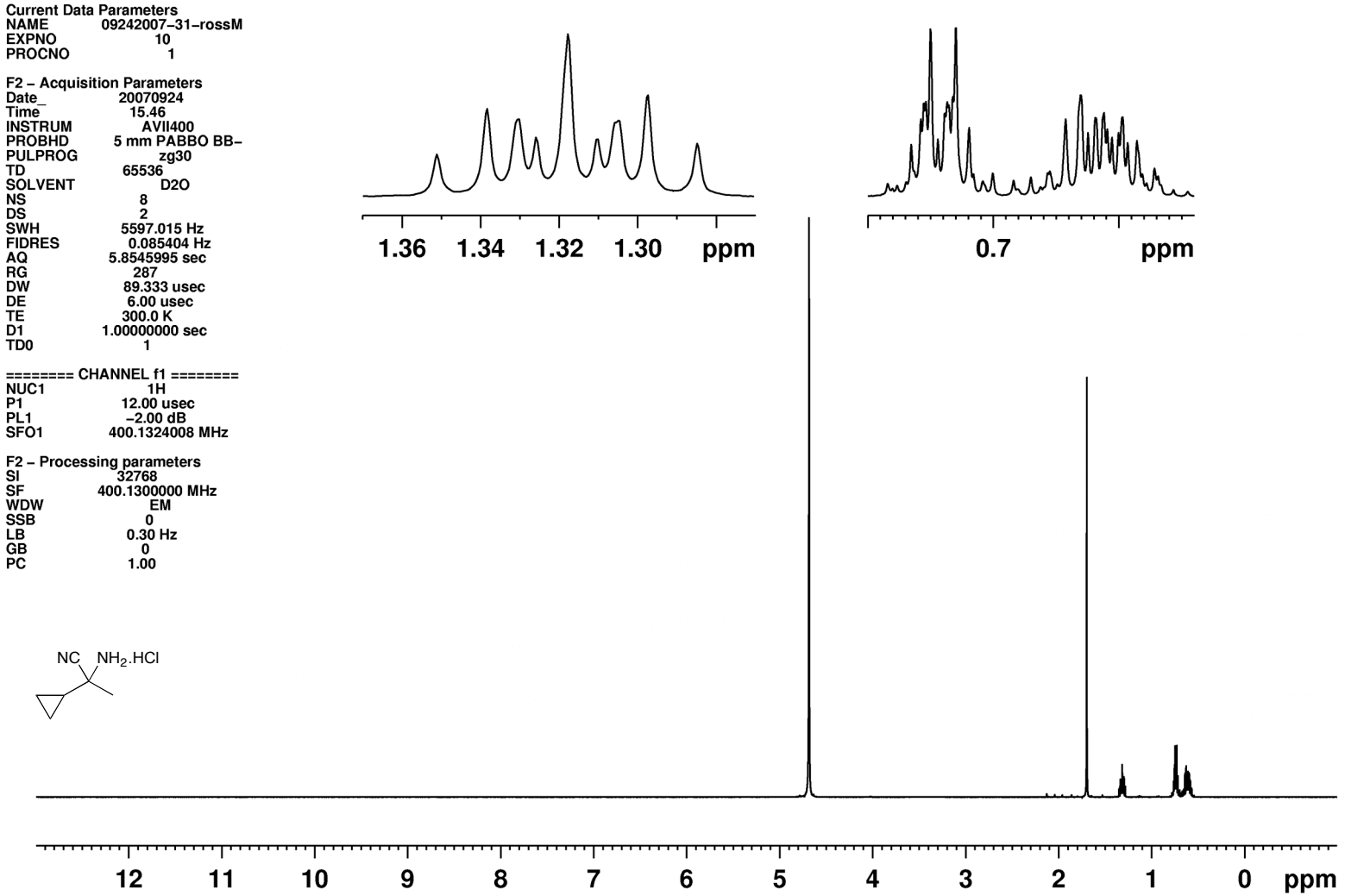


2-amino-2-cyclopropyl propionitrile hydrochloride salt **83**



2-amino-2-cyclopropyl propionitrile hydrochloride salt **83**

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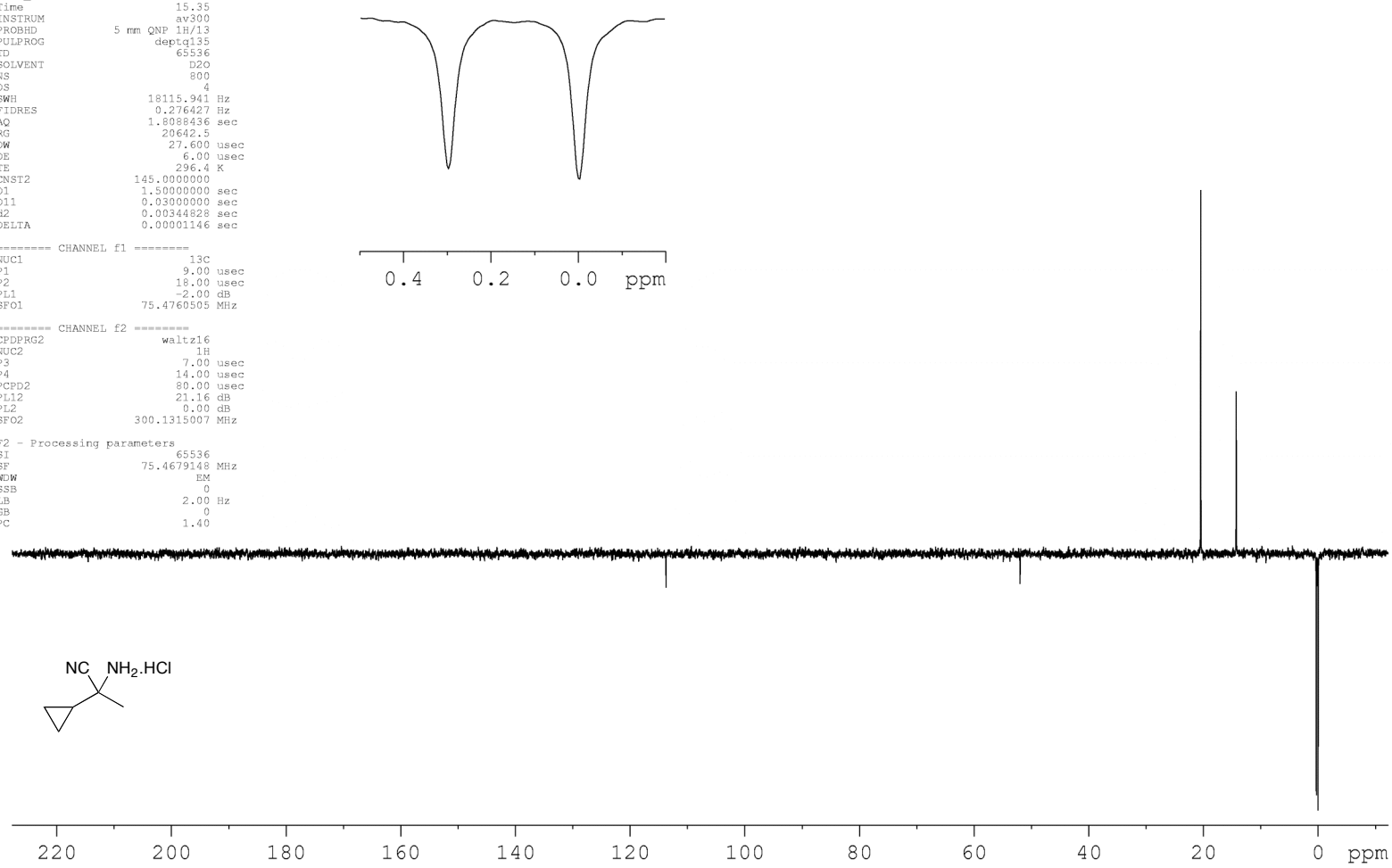

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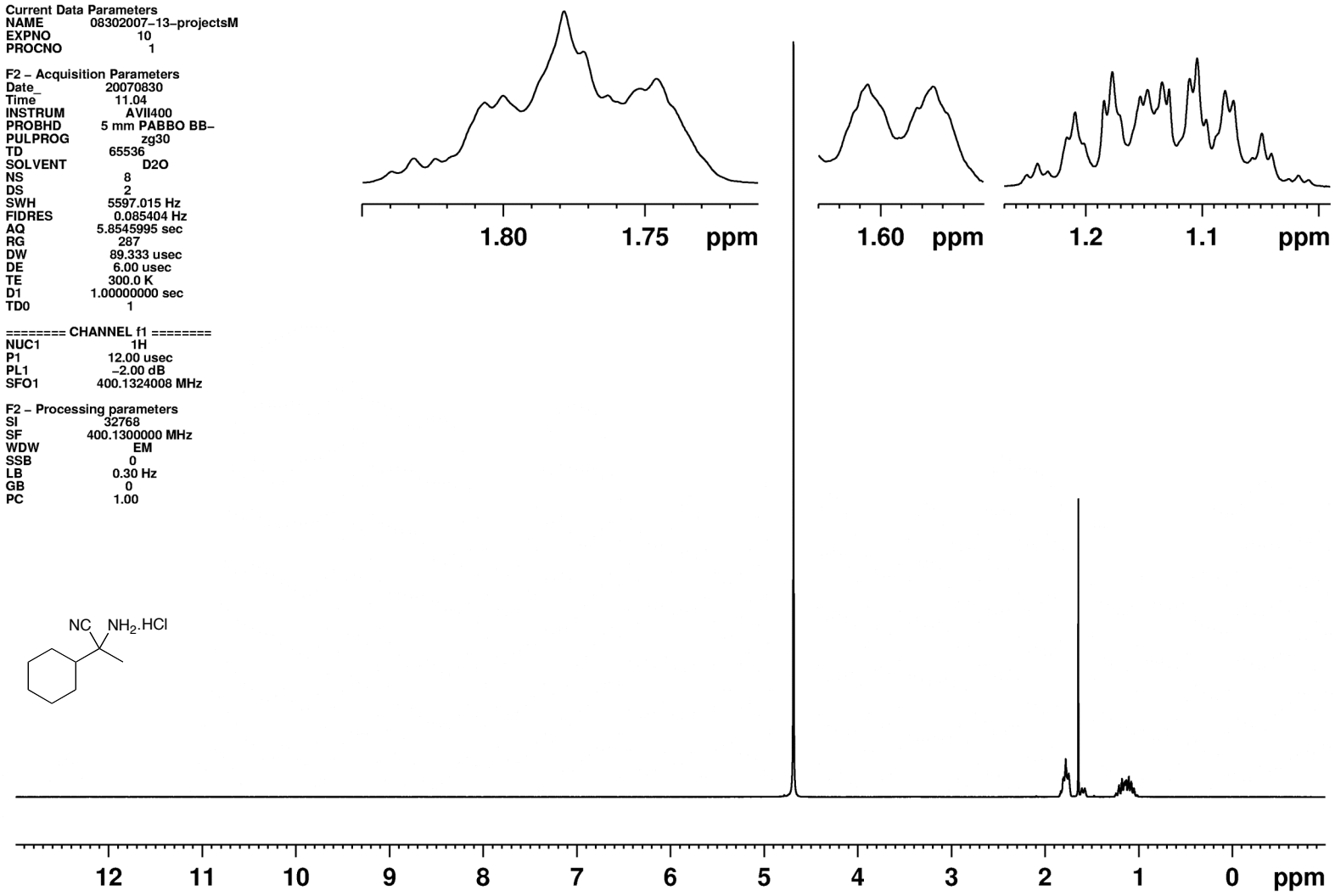

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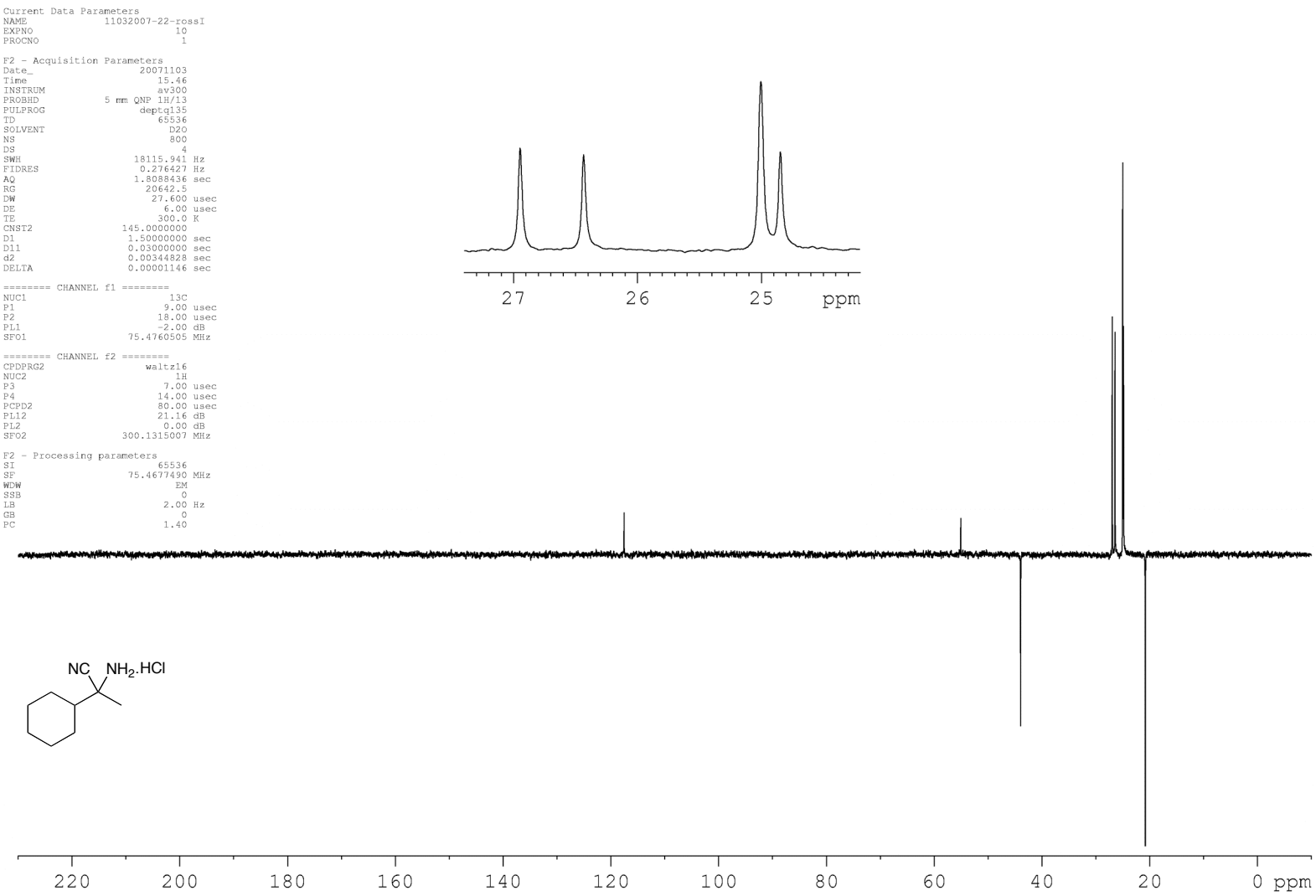
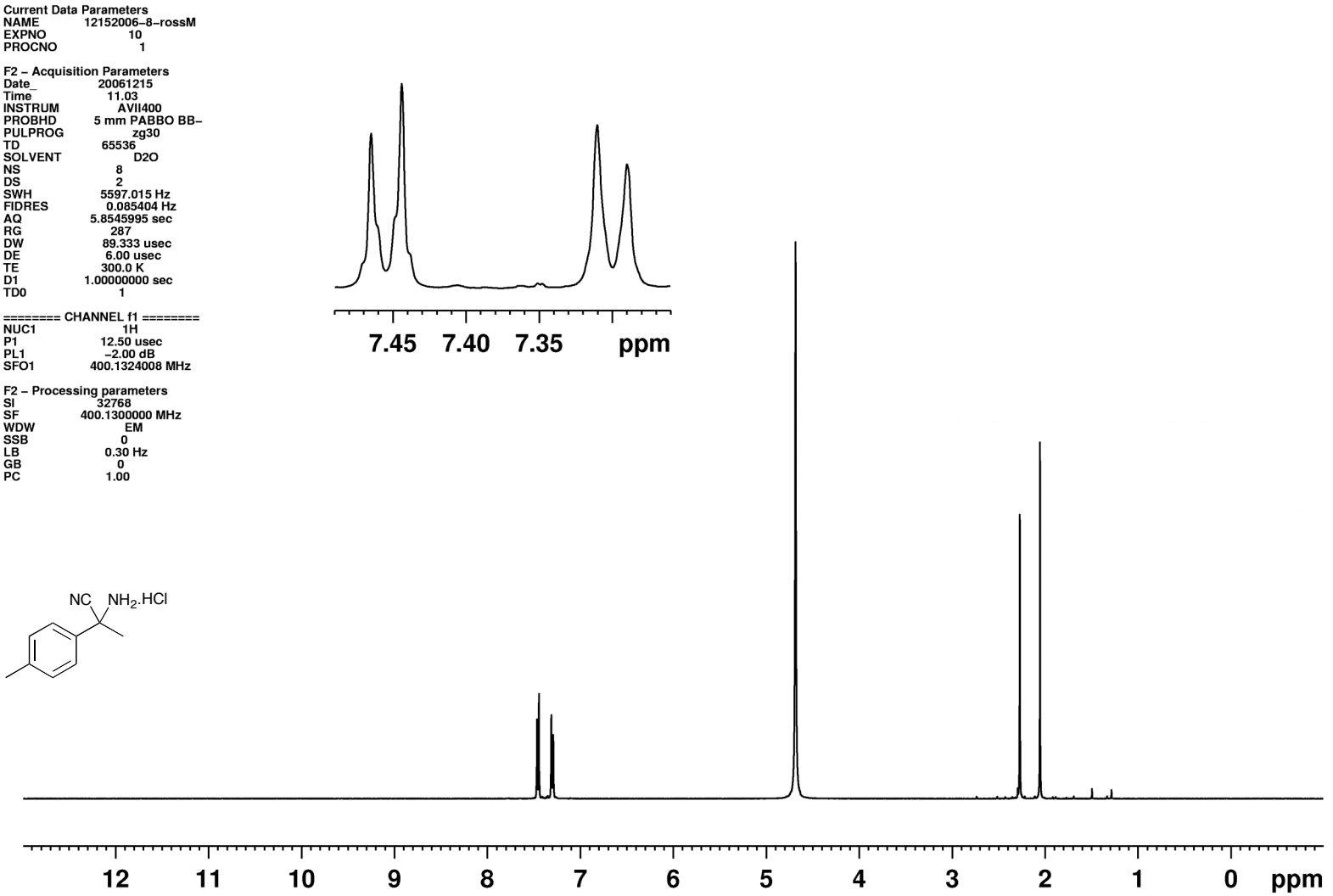


2-amino-2-(4'-methylphenyl) propionitrile hydrochloride salt **88**



2-amino-2-(4'-methylphenyl) propionitrile hydrochloride salt **88**

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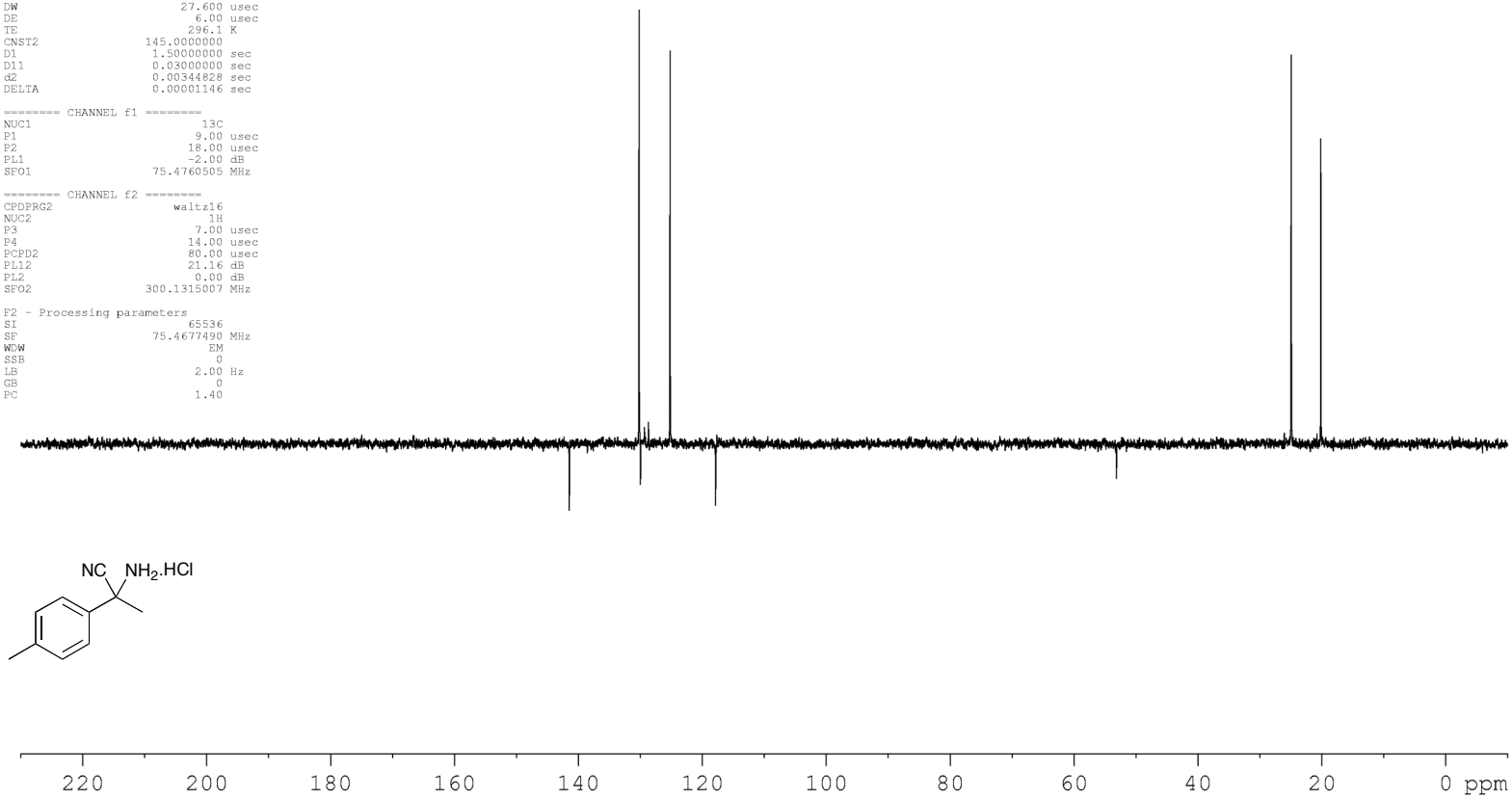

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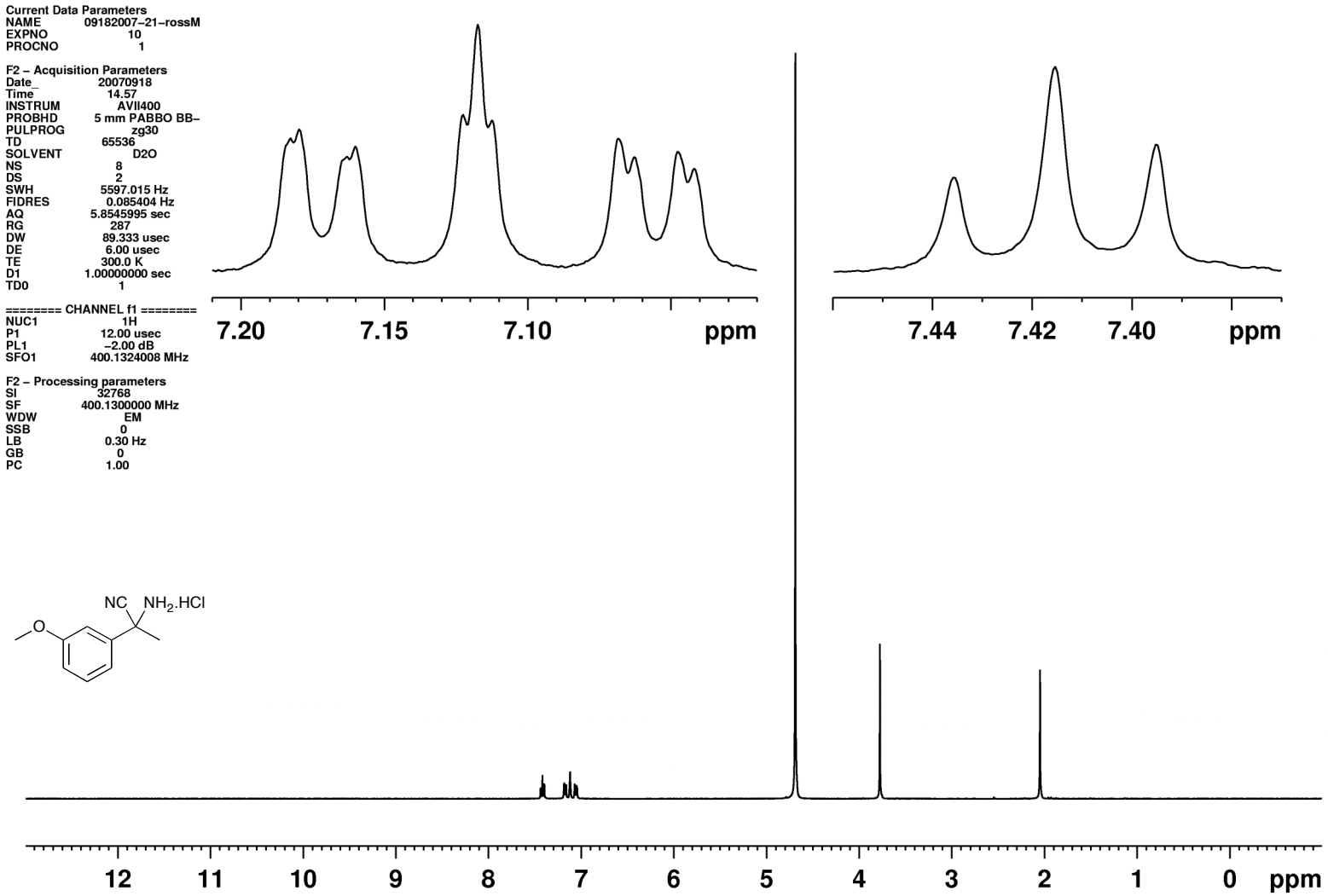

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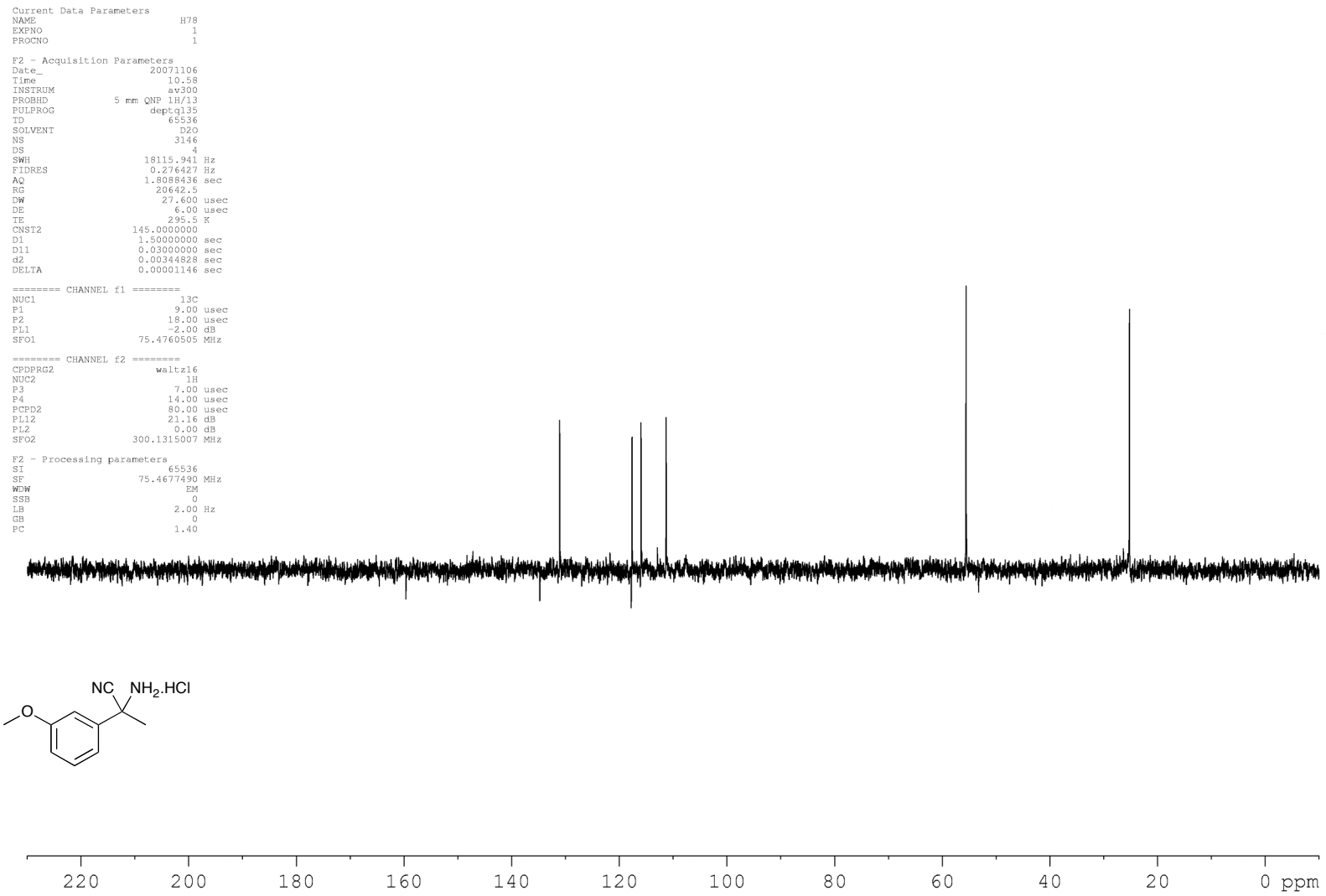

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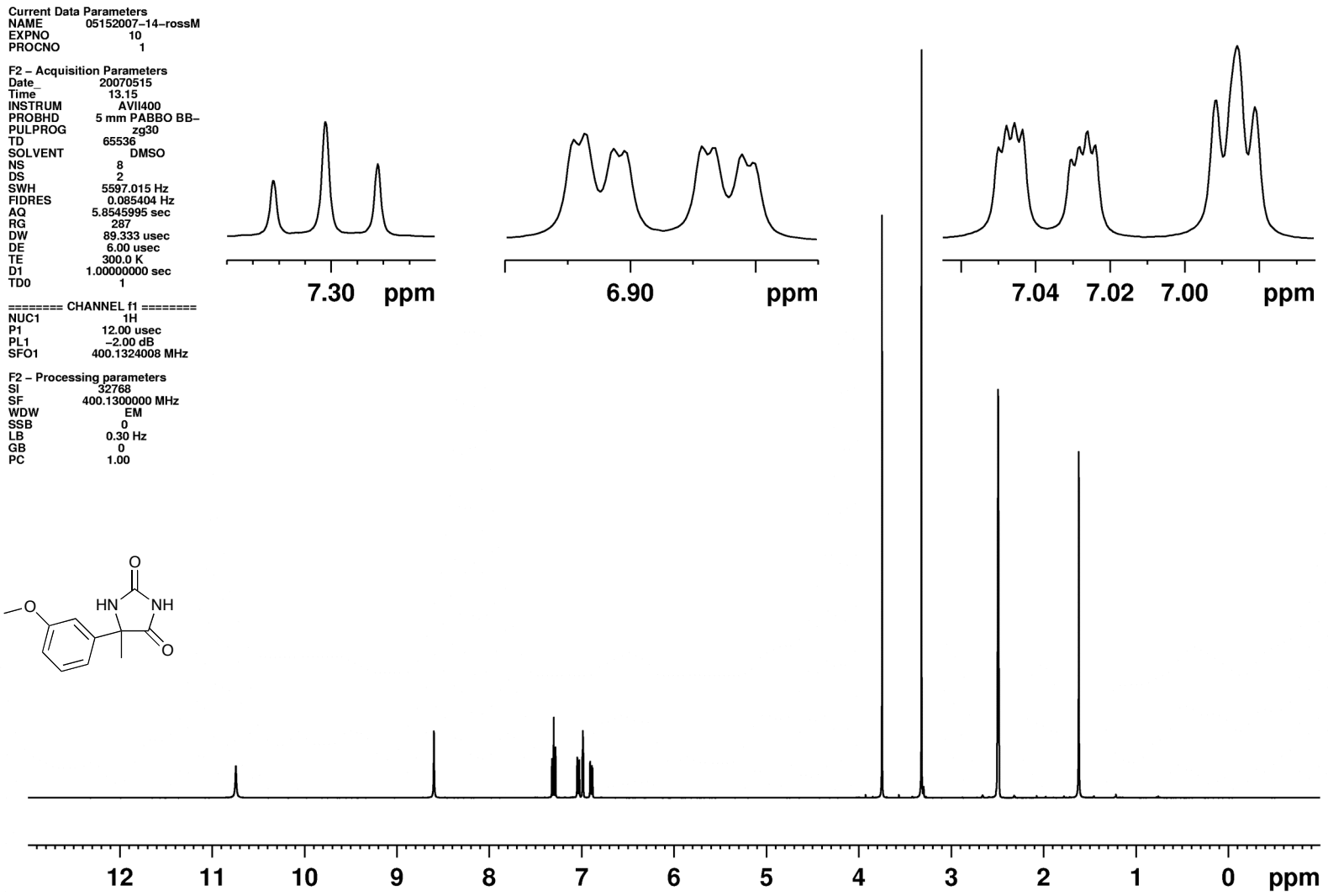
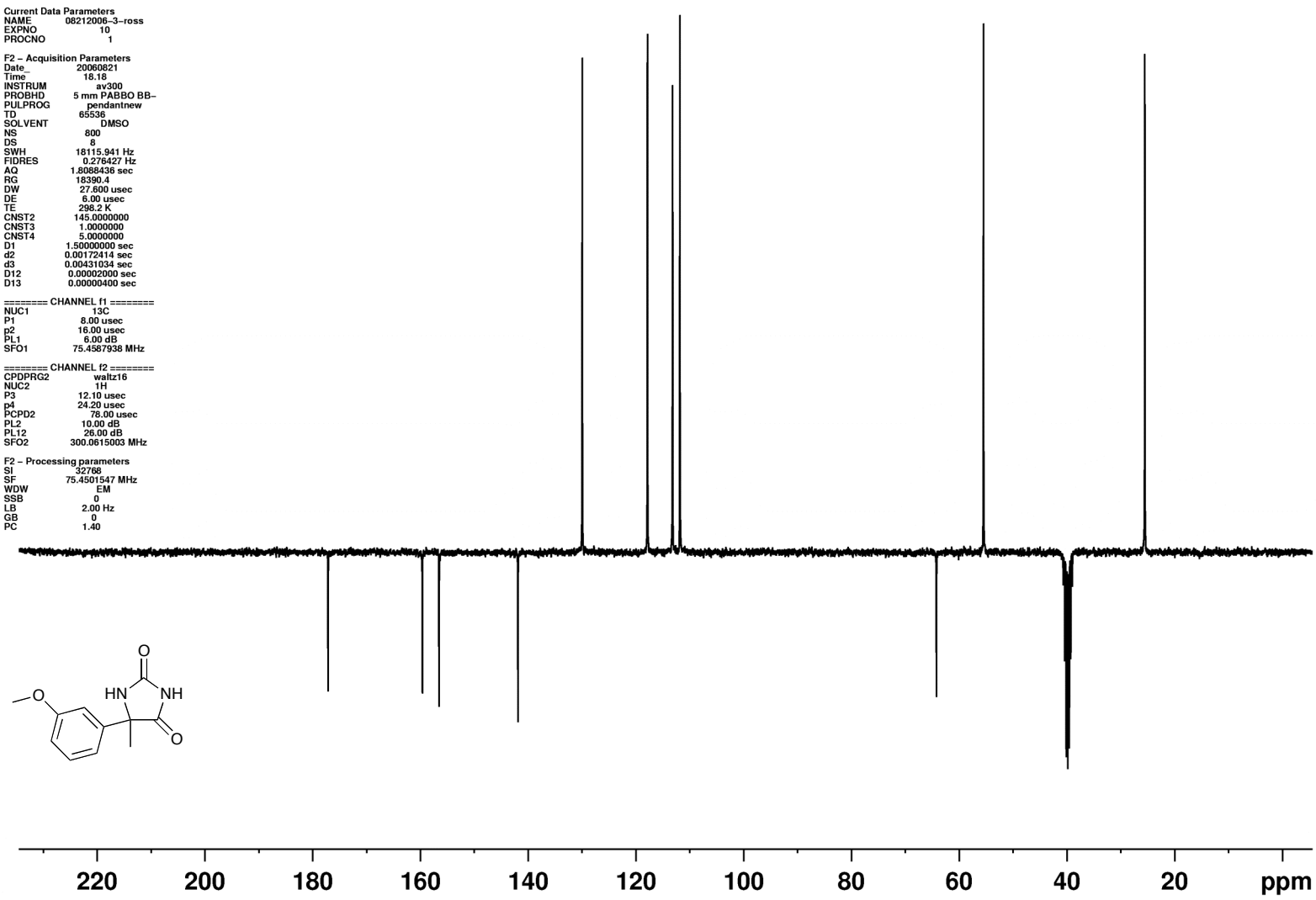
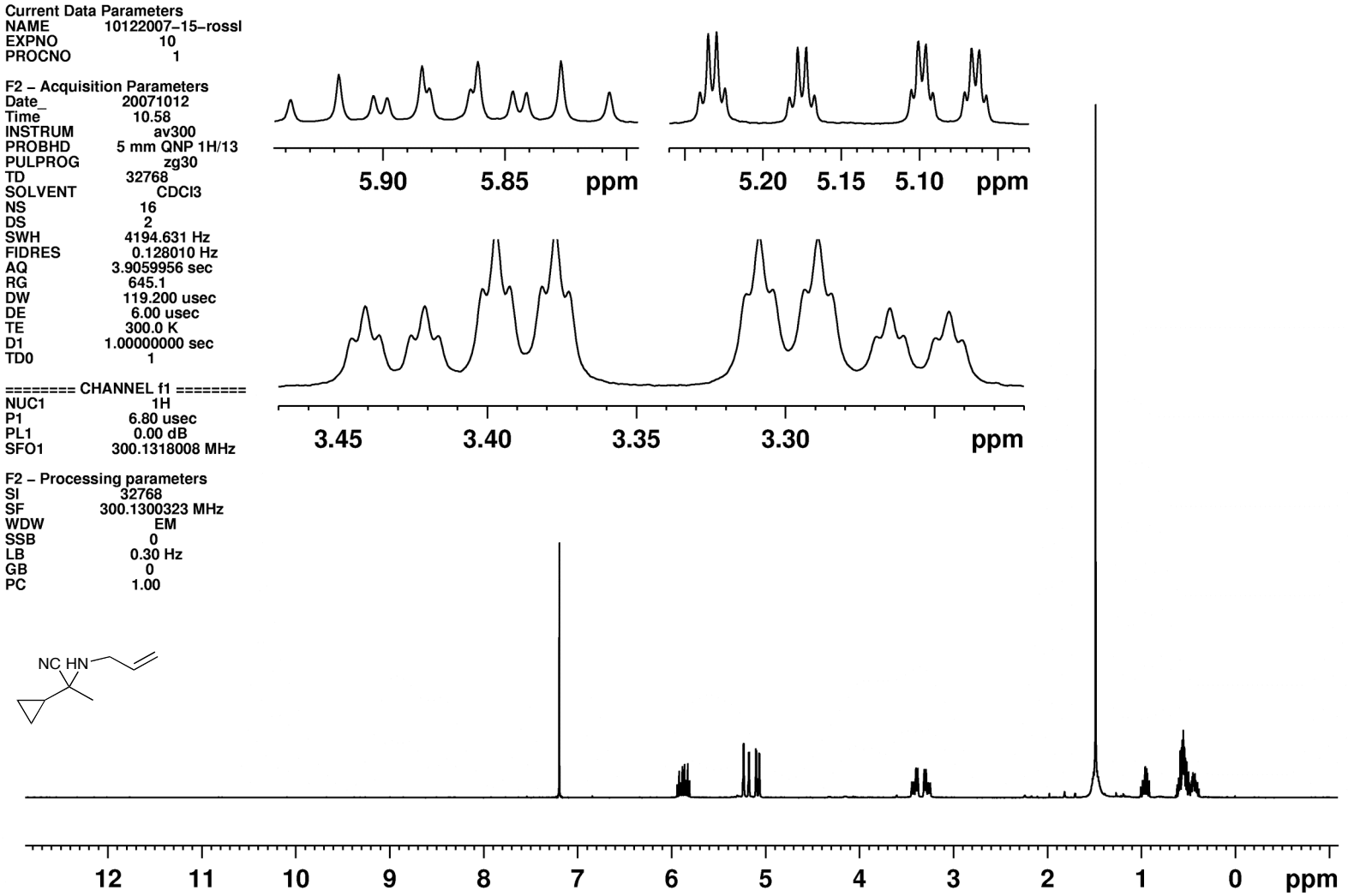


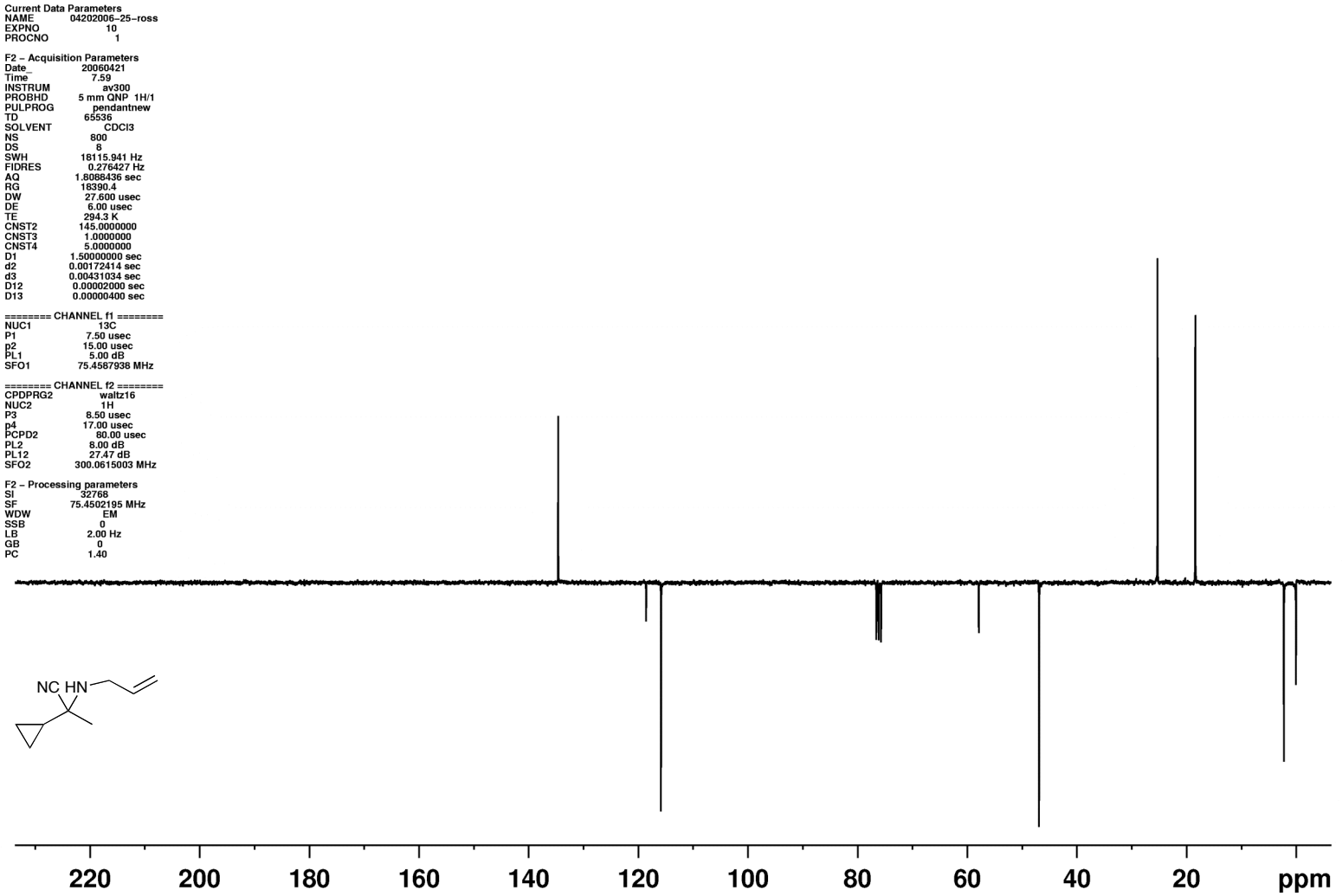
5-methyl-5-(3’-methoxylphenyl) imidazolidine-2,4-dione **103**



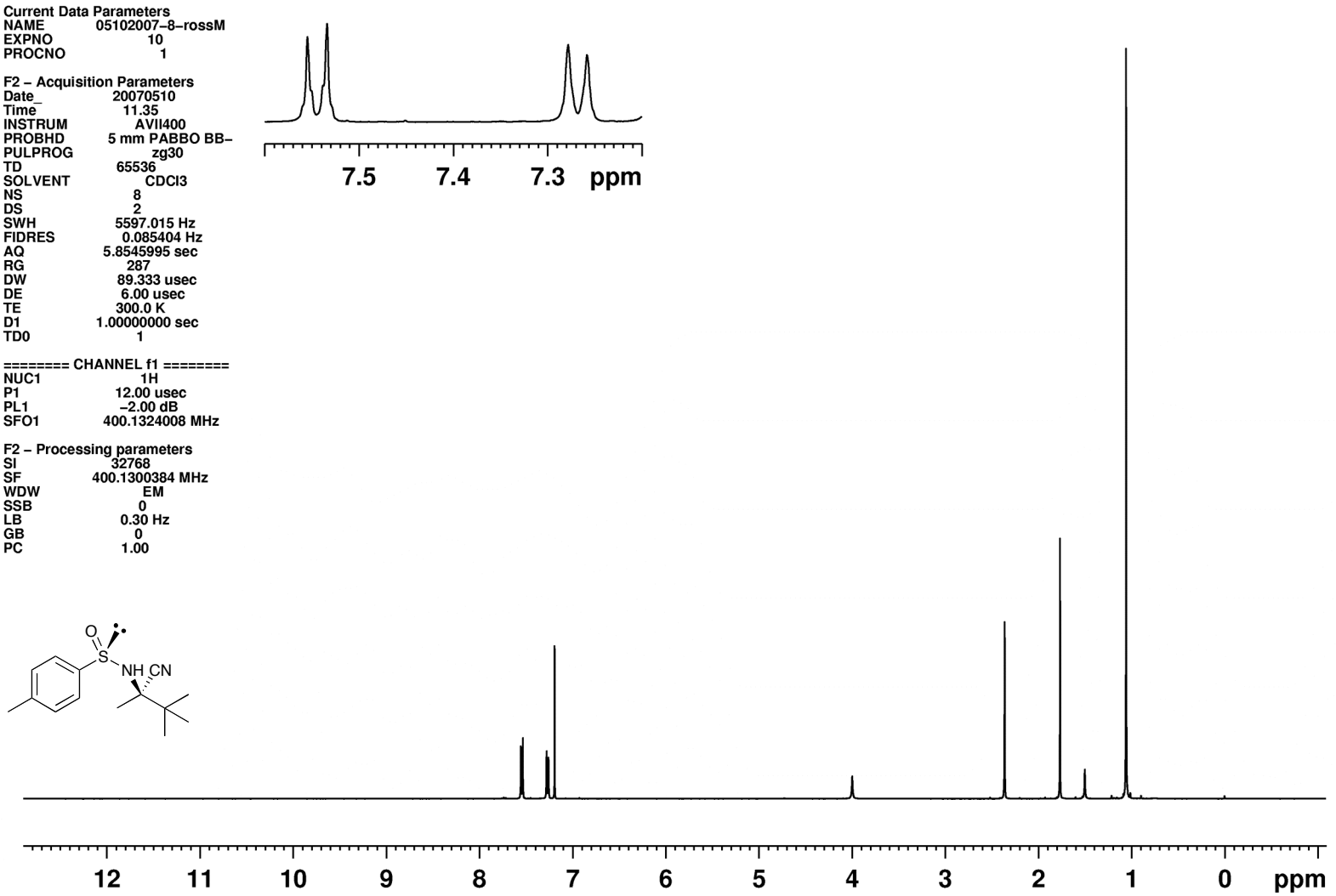
2-*N*-allylamino-2-cyclopropyl propionitrile **105**



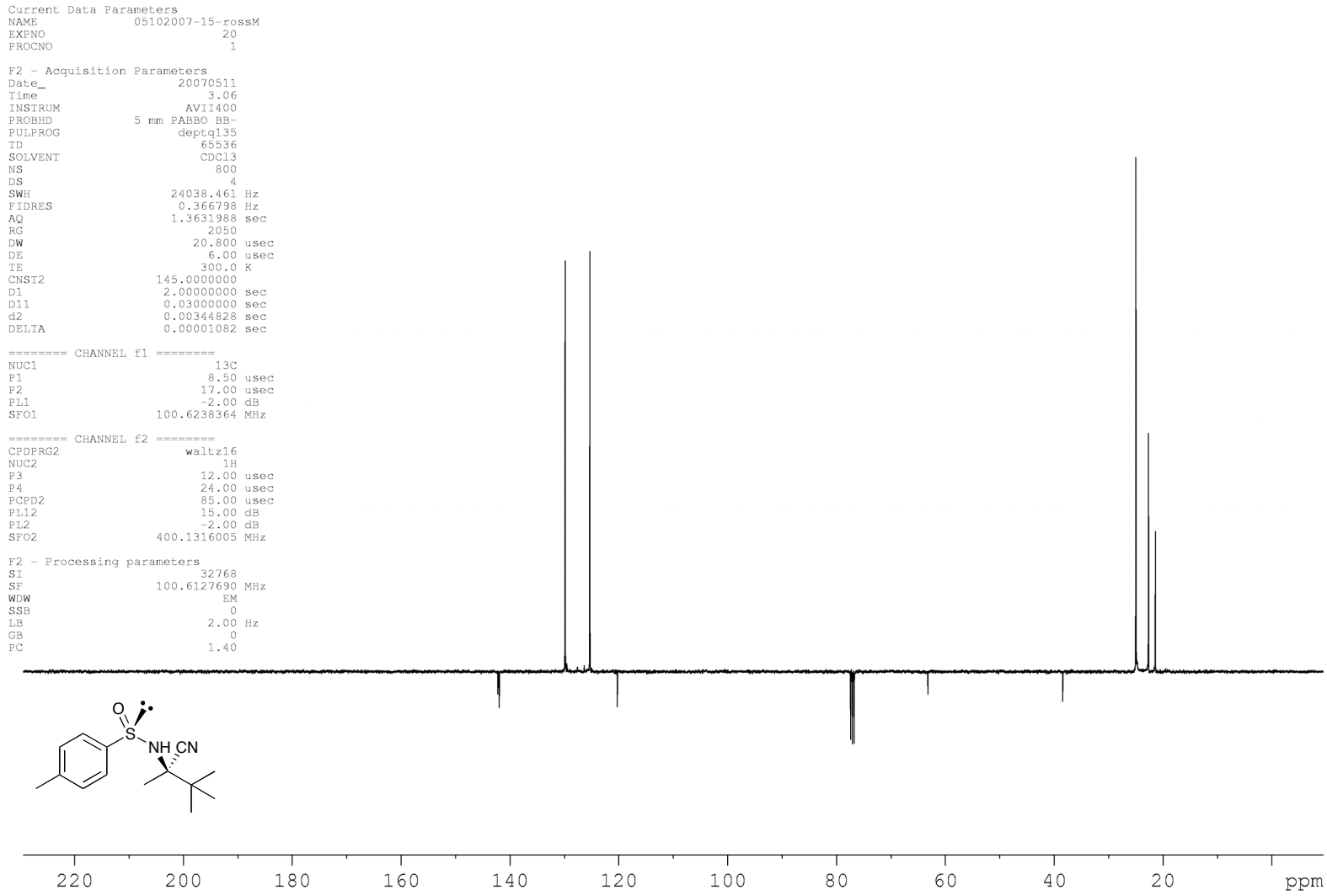
2-*N*-allylamino-2-cyclopropyl propionitrile **105**



(*S*,*R*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl) propionitrile **128**



(*S*,*R*)-(+)-[(*S*)-*N*-(4'-methylphenyl)sulfinyl]-2-amino-2-(4'-methylphenyl) propionitrile **128**



Publications

Facile one-pot synthesis of 5-substituted hydantoins†

Ross G. Murray,[a] David M. Whitehead,[b] Franck Le Strat[b] and Stuart J. Conway*[a]

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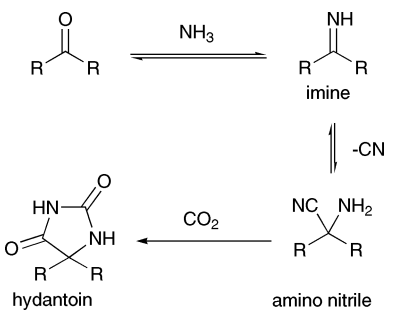
5-Substituted and 5,5-disubstituted hydantoins are synthesised from the corresponding aldehydes or ketones, using a one-pot, gallium(III) triflate-catalysed procedure that is compatible with a range of substrates and solvents.

The hydantoin scaffold is an important structural component that is present in a number of natural products[1–5] and pharmacologically important compounds.[1,6–12] More recently, hydantoin-derived guanine oxidation products have emerged as markers of oxidative cell damage. These hydantoins are significant DNA lesions that are targeted by repair enzymes and may be implicated in cancer, aging and neurological disorders.[13–17] Synthetically, hydantoins are important precursors to amino acids, *via* either acid-, base- or enzyme-catalysed hydrolysis. The Bucherer–Bergs reaction (Scheme 1) is the most commonly used method for the synthesis of hydantoins.[18] This multicomponent reaction commences from an aldehyde or a ketone and their ready availability makes the Bucherer–Bergs reaction an attractive method for the synthesis of hydantoins. However, the use of water and ethanol as solvents gives rise to solubility problems with a number of substrates, and the inclusion of ammonium carbonate can lead to problems with sublimation, causing the reaction to often be conducted within a sealed tube or acid digestion bomb. Other methods of furnishing hydantoins include the treatment of α-amino amides with triphosgene,[19] the reaction of amino acids with acetic anhydride and ammonium thiocyanate (to give the thiohydantoin),[20] combination of carbodiimides and α,β-unsaturated carboxylic acids, and the treatment of nitriles with organometallic reagents followed by potassium cyanide and ammonium carbonate.[21,22] Both microwave[23] and solid phase[24,25] technologies have been employed in the synthesis of hydantoins. There are also more esoteric syntheses of hydantoins that involve complex rearrangements.[1,26,27]



Scheme 1 Intermediates in the proposed mechanism of the Bucherer–Bergs reaction.[30,31]

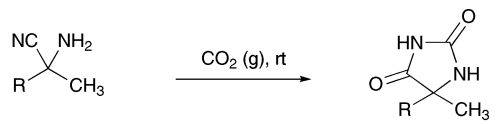
We have investigated a Lewis acid-catalysed variation of the Bucherer–Bergs reaction, which is compatible with a range of organic solvents and that commences from simple aldehyde or ketone starting materials. Lewis acid catalysis engenders the possibility of chiral catalysis and ultimately an enantioselective reaction. Herein, we report the development of a one-pot, Lewis acid-catalysed, hydantoin synthesis that is compatible with a range of substrates and organic solvents.

The mechanism of the Bucherer–Bergs reaction (Scheme 1) mirrors that of the Strecker synthesis until the formation of the amino nitrile. At this point, the Strecker synthesis is complete, whereas in the Bucherer–Bergs reactions, the amino nitrile goes on to react with carbon dioxide. As enantioselective Lewis acid-catalysed Strecker reactions are well documented,[28,29] our initial investigations focused on the conversion of amino nitriles to hydantoins by treatment with carbon dioxide.

Literature from 1934 details one example of the conversion of 2-amino-2-methylpropionitrile to 5,5-dimethylhydantoin by treatment with carbon dioxide in water.[32] In our hands, this reaction only proceeded in 9% yield, although this could be improved to 50% yield by conducting the reaction in a preformed solution of aqueous carbonic acid (Table 1).

To determine whether the volatility of amino nitrile **1** contributed to the poor yield, the reaction was repeated using the less volatile **2**. This reaction gave a yield of 50%, prompting us to consider whether two equivalents of the aminonitrile are required for the reaction to proceed. It was postulated that the amino

Table 1 Initial optimisation for the conversion of amino nitriles to hydantoins



1 R = CH_3
2 R = cyclopropyl

3 R = CH_3
4 R = cyclopropyl

Entry	R	Solvent	Time	Yield
1	CH_3	Water	15 h	9%
2	CH_3	Carbonic acid solution	24 h	50%
3	Cyclopropyl	Carbonic acid solution	12 h	50%
4	Cyclopropyl	Water & Hünig's base (3 eq)	6 h	77%
5	Cyclopropyl	CH_2Cl_2 & Hünig's base (3 eq)	12 h	90–94%

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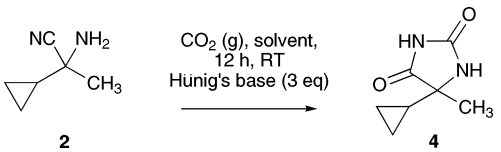
[b]*Sanofi-aventis, Department of Isotope Chemistry and Metabolite Synthesis, Alnwick Research Centre, Willowburn Avenue, Alnwick, Northumberland, U.K. NE66 2JH*

† Electronic supplementary information (ESI) available: Experimental procedures and analytical data, ^{1}H and ^{13}C NMR spectra, and optimisation of the one-pot reaction. See DOI: 10.1039/b719675j

Table 2 Screening for the optimum solvent



2 4

Entry	Solvent	Yield
1	Dichloromethane	90–94% ($n = 2$)
2	Ethyl acetate	61–80% ($n = 2$)
3	Ethanol	71–75% ($n = 2$)
4	Diethyl ether	65%
5	Toluene	45%
6	Water	32–75%[a]

[a] Adding solid CO_2 gave 75% yield, bubbling $CO_{2(g)}$ gave 32% yield.

nitrile was hydrolysing to give the ketone, hydrogen cyanide and ammonia. The ammonia might then act as a base, either preventing further amino nitrile hydrolysis, or playing a role in the reaction itself. To investigate whether the addition of a base would improve the yield of hydantoin **4**, the reaction was repeated in the presence of Hünig's base (3 equivalents) and a yield of 77% was obtained. At this stage our working hypothesis was that the carbon dioxide was dissolving in the water to form carbonic acid and this was reacting with the amino nitrile. We were thus gratified to find that, when dichloromethane was employed as the solvent, **2** was converted to the corresponding hydantoin (**4**) in excellent (90–94%) yield. This high yield was maintained when strictly anhydrous conditions were employed. Failure to include Hünig's base resulted in no product formation, indicating that the base plays a vital role in the reaction when organic solvent is used.

Using dichloromethane as the solvent, a range of bases was investigated. Both Hünig's base and triethylamine promoted the formation of **4** in excellent yield. Pyridine and DBU failed to promote hydantoin formation of **4**, indicating that those bases with a pK_b of approximately 11 are optimal. However, pK_b is not the only factor that affects the reaction, as the use of tributylamine ($pK_b = 10.9$) only afforded a 14–25% yield of the hydantoin **4**.

Having established that either triethylamine or Hünig's base would effectively promote hydantoin formation, a range of reaction solvents were investigated, but none was superior to dichloromethane (Table 2). The reaction proceeded in good yield when ethyl acetate, ethanol and diethyl ether were used as solvents. Moderate yields were obtained when toluene and water were used.

A range of amino nitriles (**1**, **2**, **5–10**) was then chosen so as to investigate the scope of the reaction. The amino nitriles were synthesised as shown in Table 3. Problems with solubility were encountered during the synthesis of the aromatic amino nitriles, hence DMSO or methanol was used as a co-solvent. The isolation of pure amino nitriles proved a challenge and we eventually found it convenient to purify the amino nitriles by crystallisation as their hydrochloride salts.

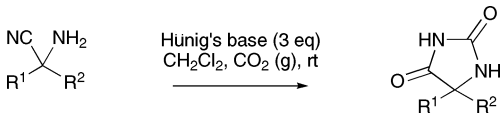
The amino nitrile salts were converted to the free amino nitriles, and these were transformed to hydantoins using the conditions described in Table 4. It can be seen that both aliphatic and aromatic methyl ketones can be converted to the corresponding hydantoins in good yield.

Table 3 The synthesis of amino nitriles

Amino nitrile	R^1	R^2	Reaction time	Yield
1[a]	CH_3	CH_3	20 h	30%
5[b]	C_5H_{11}	CH_3	20 h	82%
6[c]	^{t}Bu	CH_3	20 h	23%
2[c]	Cyclopropyl	CH_3	20 h	62%[e]/88%[f]
7[d]	Ph	CH_3	20 h	46%
8[d]	3-MeOPh	CH_3	40 h	41%
9[d]	Ph	C_2H_5	24 h	24%
10[c]	C_4H_9	C_4H_9	20 h	7%

[a] Conditions used: KCN, NH_4Cl, H_2O, rt.[33] [b] Conditions used: KCN, NH_4Cl, NH_4OH, H_2O, MeOH, 4 °C → rt.[34] [c] Conditions used: KCN, NH_4Cl, NH_4OH, H_2O, 4 °C → rt.[34] [d] Conditions used: KCN, NH_4Cl, DMSO, H_2O, rt.[35] [e] Isolated as HCl salt. [f] Isolated as the free amino nitrile.

Table 4 Scope of the amino nitrile to hydantoin reaction



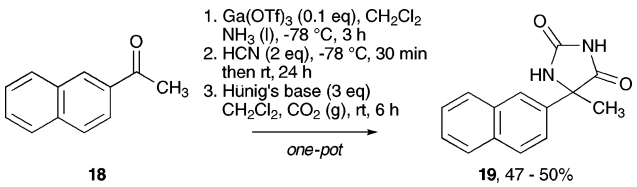
Hydantoin	R^1	R^2	Reaction time[a]	Yield
11	Ph	H	17 h	73%
12	C_5H_{11}	CH_3	9 h	87%
13[b]	^{t}Bu	CH_3	18 h	0%
13[b]	^{t}Bu	CH_3	17 h	62%
4	Cyclopropyl	CH_3	12 h	94%
14	Ph	CH_3	20 h	90%
15	3-MeOPh	CH_3	24 h	60%
16	Ph	C_2H_5	12 h	62%
17	C_4H_9	C_4H_9	14 h	47%

[a] Time of exposure to CO_2. [b] Ethanol was used as the solvent as pinacolone-derived amino nitrile is insoluble in dichloromethane.

The reaction times vary as each reaction was continued until no starting material was present by TLC analysis. In the case of **13**, successful reaction was only observed when using ethanol as a solvent, due to the insolubility of **6** (free amine) in dichloromethane. Both the steric and electronic nature of the amino nitrile affect the reaction, as lower yields were observed when **8** and **9** were subjected to the reaction conditions. In contrast, **7** was converted into the corresponding hydantoin in excellent yield (90%). It proved impossible to isolate 2-amino-2-phenylacetonitrile using the above conditions, however, commercially obtained material was used to evaluate the conversion of this amino nitrile to the corresponding hydantoin (**11**). Both *N*-allyl and *N*-benzyl substituted aminonitriles, derived from cyclopropyl methyl ketone and the corresponding primary amine, were submitted to our optimised conditions. In neither case was any hydantoin formed. This seems to indicate that *N*-substitution interferes with the formation of a hydantoin.

Although the above conversion of amino nitriles to hydantoins is useful, it is limited by the difficulty associated with the isolation and purification of the amino nitriles. It was therefore desirable to develop a one-pot synthesis of hydantoins from ketones or aldehydes. The formation of imines from aldehydes and amines is

often spontaneous. However, the formation of imines from amines and the less electrophilic ketones often requires the presence of a Brønsted or Lewis acid catalyst. The formation of an amino nitrile from an imine may also require the presence of a Brønsted or Lewis acid. In addition, it is possible that the addition of a Lewis acid may assist in the conversion of the amino nitrile to hydantoin, by interaction with carbon dioxide. Olah and co-workers have recently shown that a range of *N*-substituted amino nitriles can be formed from the corresponding amine, ketone and TMSCN using gallium(III) triflate as a Lewis acid catalyst.[36] We have extended these conditions to use ammonia, giving the free amino nitriles, which were then transformed *in situ* to the hydantoin. Optimisation studies (Scheme 2 and see ESI†) were conducted on 2-acetonaphthalene (**18**), as it had proved impossible to isolate a pure sample of the corresponding amino nitrile for use in the reaction described above.



Scheme 2 The optimised conditions for the conversion of 2-acetonaphthalene to its corresponding hydantoin.

The optimum conditions were found to involve the addition of liquid ammonia at −78 °C followed by stirring at this temperature for 3 h with gallium(III) triflate. The hydrogen cyanide solution in dichloromethane was added at −78 °C and the reaction solution allowed to warm to room temperature with stirring over 24 h, resulting in the evaporation of most of the liquid ammonia and leaving the dichloromethane solvent present. Hünig's base was added and the carbon dioxide bubbled through the reaction solution. When the gallium(III) triflate was excluded from the reaction solution no product was isolated, indicating that Lewis acid catalysis is required for either the formation of the imine or formation of both the imine and the amino nitrile. Although these conditions only gave modest yields (~50%), they were applied to a range of ketones in order to investigate the scope of the reaction. It can be seen from Fig. 1 (dark bars) that the conversion of aldehydes and ketones to the corresponding hydantoins was achieved in modest to excellent yield (25–98%). Benzaldehyde, heptan-2-one and cyclopropylmethyl ketone all underwent the transformation in excellent yield. Ketone-derived hydantoins with aromatic substituents were formed in more modest yields, presumably due to the less electrophilic nature of the ketone. The extended chain **17** was also formed in good yield. The yields for the two-pot reaction (Fig. 1, light bars) are obtained by combining the yields from Table 3 and Table 4. In all cases it can be seen that the yields of the one-pot reaction are equal to or higher than those of the two-pot reaction, demonstrating the advantages of the one-pot approach. It should be noted that the one- and two-pot procedures cannot be directly compared, as gallium(III) triflate is used in the one-pot procedure, but not the two-pot procedure and hence two different reactions are being considered. All compounds isolated displayed analytical and spectroscopic data consistent with the assigned structure.†

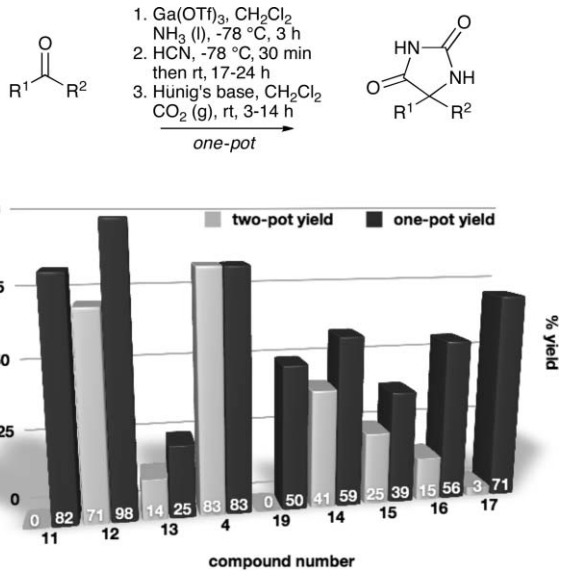


Fig. 1 Comparison of yields in the one- and two-pot conversions of ketones and aldehydes to hydantoins. **11**: R^1 = Ph, R^2 = H; **12**: R^1 = C_5H_{11}, R^2 = Me; **13**: R^1 = ^{t}Bu, R^2 = Me (EtOH is solvent); **4**: cyclopropyl, R^2 = Me; **19**: R^1 = naphthyl, R^2 = Me; **14**: R^1 = Ph, R^2 = Me; **15**: R^1 = 3-MeOPh, R^2 = Me; **16**: R^1 = Ph, R^2 = Et; **17**: R^1 = C_4H_9, R^2 = C_4H_9.

The methodology described herein represents a significant advance over the existing Bucherer–Bergs reaction for the synthesis of hydantoins. In the first instance we developed conditions for the synthesis of hydantoins from amino nitriles. Although one example of this transformation existed in the early literature,[31] we have demonstrated that the solvent can be changed from water to a range of organic solvents and discovered that the inclusion of Hünig's base or triethylamine is required for the reaction to progress in good yield. Despite these advances, however, we have found that the synthesis and purification of unsubstituted amino nitriles can be challenging, mainly resulting from the difficulty of isolating the amino nitriles or their salts. In order to address this problem, we have developed a one-pot, gallium(III) triflate-catalysed synthesis of hydantoins. Our methodology has a number of advantages over the existing Bucherer–Bergs reaction. Firstly, the use of organic, rather than aqueous, solvents makes the reaction applicable to a wide range of substrates. Secondly, the lower temperature at which the reaction is conducted avoids complications related to the volatility of the ammonium carbonate. In addition, it is operationally simple to carry out the one-pot reaction on both aldehydes and ketones.

In summary, we have synthesised a range of 5-substituted and 5,5-disubstituted hydantoins from the corresponding aldehydes and ketones in a one-pot procedure. We have demonstrated clearly that gallium(III) triflate catalysis is required for this reaction to progress.

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