FULL PAPER

Benzylic functionalisation of phenyl all cis-2, 3, 5, 6 -tetrafluoro - cyclohexane provides access to new organo-fluorine building blocks

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Abstract: Selectively fluorinated hydrocarbons continue to attract attention for tuning pharmacokinetic properties in agrochemical and pharmaceutical discovery programmes. This study identifies benzylic bromination of phenyl all *cis*-2, 3, 5, 6–tetrafluoro-cyclohexane **2** as a key reaction for accessing building blocks containing the all *cis*-2, 3, 5, 6–tetrafluorocyclohexane ring system. These cyclohexanes are of interest as the fluorines are only on one face of the cyclohexane, and this imparts an unusual polar aspect, very different to an otherwise hydrophobic cyclohexane. Ritter type reactions of benzyl bromide **4** with DMF and acetonitrile generated the corresponding benzyl alcohol **6** and benzylacetamide **7** respectively. Benzylacetamide **7** was hydrolysed to benzyl amine **8** and *syn*-amino-alcohol **9**, and separately the phenyl ring was oxidatively cleaved to furnish carboxylic acid acetamide **10**, which after hydrolysis gave the tetrafluorocyclohexyl amino acid **11**. A transhalogenation of benzylbromide **4** with Ag(II)F gave benzyl fluoride **13**. Oxidative cleavage of the aryl ring then gave pentafluorocyclohexyl carboxylic acid **14**. This carboxylic acid was readily converted to amides **23**-**26** and the preferred conformations of these α-fluoroamides were explored by DFT, X-ray structure and ^{19}F-HOSEY-NMR analysis.

Introduction

We have recently introduced the concept of preparing cyclohexyl ring systems and placing single fluorine atoms on each carbon (Figure 1).[1-4] Although up to six fluorines are incorporated, their presence as -CHF- methylene carbons does not raise lipophilicity, instead it introduces polarity and has the useful effect of lowering Log P with increasing fluorination.[5] If the C-F bonds can be arranged to align in axial

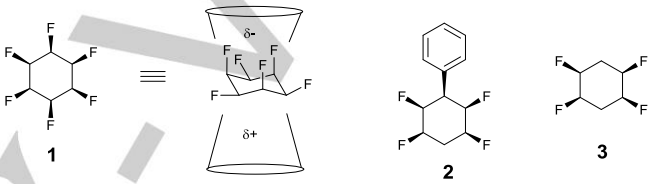

Figure 1. All cis-multifluorinated cyclohexanes are facially polarized motifs.

orientations, this further increases the molecular polarity and these all-*cis* multi-fluorocyclohexanes are among the most polar aliphatic rings known. The most dramatic example of this class of compound is all *cis*-1,2,3,4,5,6-hexafluorocyclohexane **1**,[6] which has a fluorine on all six carbons of the ring and with a stereochemistry where all of the fluorines are 'up'. This imparts a very high polarity (molecular dipole moment, μ = 6.2D) to this cyclohexane due to the three axial C-F bonds dictated by the chair conformation. The remaining three equatorial C-F bonds also lie above the plane of the cyclohexane, and this gives the fluorine face a negative electrostatic profile. It follows that the methylene hydrogens on the opposite face of the cyclohexane are positively polarized.[7] This compound is highly crystalline with a very high melting point (208 °C) for a fluorinated hydrocarbon. The facial polarity of cyclohexane **1** gives it the unique ability to coordinate alkali metal cations to the fluorine face and anions (eg Cl^-, $B_{12}F_{12}^{2-}$) to the hydrogen face.[8,9] Cyclohexane **1** is the prototypical example, however despite its intriguing properties it is not readily derivatised and is not an obvious starting point for introducing this ring system into higher molecular architectures. In that context we have focused on phenyl all *cis*-2, 3, 5, 6–tetrafluorocyclohexane **2**.[10,11] This compound can be prepared on a multi-gramme scale from biphenyl, and although it has only four fluorines, two of the C-F bonds align parallel in a diaxial orientation and they also impart significant polarity to the ring, which is evidenced by anisotropic effects in different NMR solvents.[2] This was observed too in our original synthesis[2] of all *cis*-1,2,4,5 tetrafluorocyclohexane **3** which is also a crystalline solid with a relatively high melting point (105 °C) and a large molecular dipole (μ = 4.1D). In the X-ray structure of **3** the molecules stack with fluorine to hydrogen contacts ordered by the electrostatic nature of the ring. Thus the facially polarized aspect

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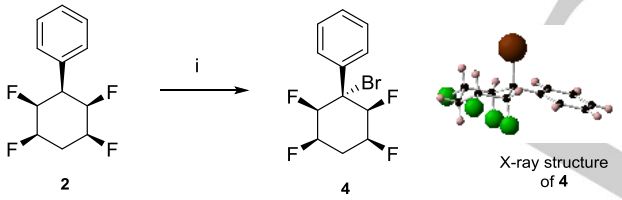
of the cyclohexane is retained in the all *cis*-1,2,4,5 tetrafluoro systems. Cyclohexane **3** is also unfuctionalised and not readily derivatised and therefore phenylcyclohexane **2** provides a much more attractive starting point for the synthesis of new building blocks and derivatives of this motif. We have already reported electrophilic aromatic substitutions of **2** (eg. nitration, halogenation), followed by a range of downstream transformations involving conversions to anilines, or cross coupling reactions of aryl halide derivatives.[12,13] The goal of this study was to explore direct functionalization at the benzylic (C1) position of **2** and in particular to exploit a straightforward benzylic bromination reaction to **4**. Transformations of **4** are explored in a variety of directions to generate a range of new and useful building blocks carrying partially fluorinated cyclohexanes. The results are discussed below.

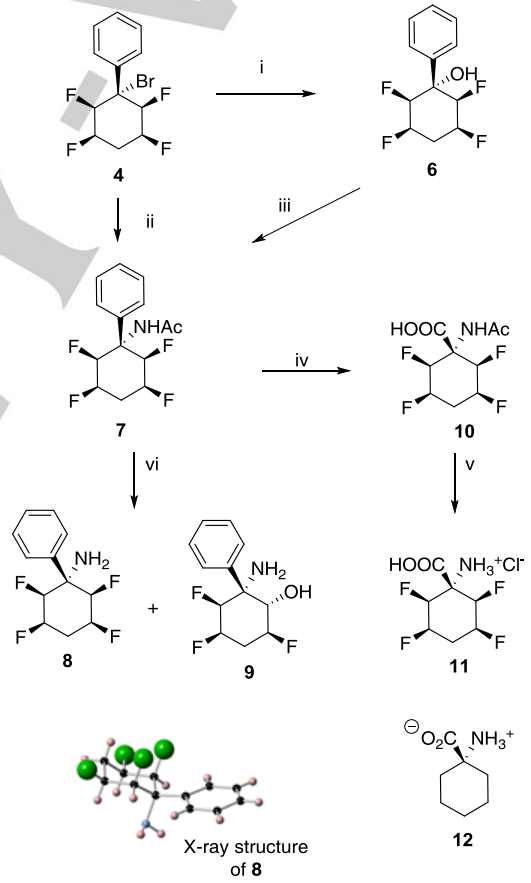
Results and Discussion

All *cis*-2, 3, 5, 6–tetrafluoro-cyclohexane **2** was prepared as previously described and was the starting point for the preparation of all compounds in this study.[10,11] Treatment of **2** with N-bromosuccinamide (NBS) in carbontetrachloride (CBr_4) (Scheme 1) resulted in an efficient conversion to a single isomer of benzylbromide **4**.[14] X-ray structure analysis indicated a retention of configuration with the bromine replacing hydrogen, and located on the opposite face of the cyclohexane ring to the indigenous fluorine atoms.



Scheme 1.: (i) NBS, CCl_4/ MeCN (10/1), 100 °C, 42 h (89%); and X-ray structure of **4**.

There was no indication of the presence of the *syn*-bromo isomer **5**, and presumably the outcome is dictated by a preference for the bromine to approach the intermediate benzylic radical *anti* to the fluorines. It was attractive to introduce an amine at the benzylic position of **2**, and to this end displacement of the bromide by azide in DMF was explored.[15] However this resulted in an efficient conversion only to tertiary alcohol **6** (Scheme 2). This outcome was unexpected, and after a series of control reactions it emerged that heating (90 °C) in DMF alone, without added sodium azide, was sufficient to mediate the conversion. The product alcohol suggested the presence of water in the reaction or perhaps that molecular oxygen was significant. Accordingly the DMF was rigorously dried over dehydrated molecular sieves and the solvolytic reaction was carried out under a positive pressure of argon. Again an efficient conversion of benzyl bromide **4** to tertiary alcohol **6** was apparent. When water (5%) was pro-actively added to the dried DMF, and heated at 90 °C, there was no conversion. In our assessment this reaction does not involve adventitious water, which actually inhibits the conversion. DMF appears to be the source of the alcoholic oxygen. The participation of DMF in substitution reactions, although not common, has been observed.[16] Perhaps the observation of Liu *et al.*,[16a] has the closest precedent in that an α-iodo ketone was converted to an α-hydroxy ketone in DMF, and it was concluded that DMF participates as the source of the alcohol oxygen. We have looked further at this reaction by VT ^{19}F-NMR in a sealed NMR tube (see SI for details). Consumption of **4** occurs relatively rapidly at 80 °C, to generate an unknown intermediate, which steadily converts to tertiary alcohol **6**. This intermediate could reasonably be an initial adduct in a reaction between **4** and DMF, consistent with the conclusion of *Liu et al*.[16a] Further investigation is required to secure the nature of this intermediate and a mechanism for this reaction.



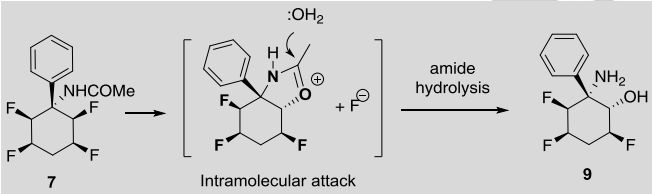
Scheme 2: (i) DMF, 90 °C, 16 h (82%); (ii) MeCN, H_2SO_4, 90 °C, 48 h, (68%); (iii) MeCN, H_2SO_4, 90 °C, 48 h, (72%); (iv) H_5IO_6, 5% $RuCl_3$, H_5IO_6, 5% $RuCl_3$, 90 °C, 42 h (61%); (v) 6N. HCl, 16 h, 100 °C (55%); (vi) 6N.HCl, 16 h, 100 °C, **8**(35%), **9**(15%).

A suitable crystal of product **6** demonstrated a retention of configuration with the hydroxyl group on the opposite face of the cyclohexane to the fluorines. This is consistent with an S_N1

process, and with the fluorines directing nucleophilic attack to the hydrogen face of the cyclohexane.

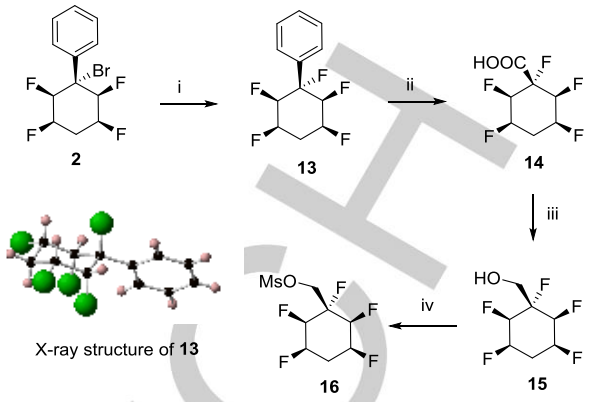
The Ritter reaction involving acetonitrile both as a solvent and as a nucleophile is widely described[17,18] and in the light of the observed solvolytic reaction between **4** and DMF, we decide to investigate a Ritter reaction with **6** as a means to introduce nitrogen. Accordingly when a solution of **4** in acetonitrile was heated under reflux with added sulfuric acid (2%), then an efficient reaction took place to generate acetamide **7** (68% yield), the anticipated Ritter product. Only a single isomer was apparent and X-ray crystallography confirmed both structure and stereochemistry, indicating substitution with a retention of configuration. Acetamide **7** could also be efficiently accessed directly from benzylbromide **4** under the same Ritter conditions (MeCN, H_2SO_4), suggestive of a common S_N1 reaction mode.

With acetamide **7** in hand, amide hydrolysis was explored with an objective to access free amine **8**. Thus acetamide **7** was heated in 6N.HCl under reflux, and this did generate amine **8**, but with amino alcohol **9** as a significant co-product, in a ratio of 3:2. The structure and stereochemistry of **8** of was confirmed by X-ray structure analysis. The relative stereochemistry of **9** was deduced by the magnitude of vicinal $^3J_{HF}$ and $^3J_{HH}$ coupling constants in the ^{19}F- & ^{1}H- NMR spectra, as well as ^{19}F-^{1}H-heteronuclear Overhauser (HOSEY) spectroscopy, which showed a strong and diagnostic through space correlation between the fluorine atom of carbon-2 and the hydrogen atom of carbon-6 of the cyclohexane ring consistent with a diaxial relationship (See SI for full details). The *syn* relationship between the amine and alcohol functionality in **9** is noteworthy and places limitations on a mechanistic rational. Although the mechanism is not clear the outcome is consistent with an intramolecular displacement of fluoride by the acetamide carbonyl, followed by hydrolysis[11] as illustrated in Scheme 3.



Scheme 3: Putative mechanism for the formation of *syn*-aminoalcohol **9**.

Oxidative treatment (H_5IO_6, 5% $RuCl_3$) of acetamide **7** under the biphasic conditions originally described by Sharpless,[19] resulted in a relatively efficient conversion of the aryl ring of **7** to a carboxylic acid to generate protected amino acid **10**. Hydrolytic cleavage of the acetamide with 6N.HCl then gave the free amino acid **11**, this time without any accompanying hydroxydefluorination side product, as was previously observed in the conversion of **7** to **9**. This offers an entirely novel amino acid carrying the all *cis*-2,3,5,6-tetrafluorocyclohexyl ring system, and an analogue of the well described cyclohexylamino acid **12** which has found relatively wide application as a non-proteinogenic amino acid in peptide mimetic and biochemistry studies.[20].



Scheme 4: Preparation of carboxylic acid **14**, and its progression to reduced derivatives. (i) Ag(II)F, $(C_2H_5)_2O$, 35°C, 20 h (82%); (ii) H_5IO_6, 5% $RuCl_3$, 90 °C, 42 h (74%); (iii) BH_3.THF, THF, 16 h, 50 °C (55%); (iv) MsCl, Et_3N, DCM, 0 °C, 0.5 h, then RT, 18 h (63 %).

A particularly efficient reaction in this study involved the transhalogenation of benzyl bromide **4** to benzyl fluoride **13** (Scheme 4). This was accomplished using Ag(II)F in refluxing diethyl ether.[21] The structure and stereochemistry of **13** was once again confirmed by X-ray structure analysis and indicates substitution with retention of configuration. Aryl oxidation (H_5IO_6, 5% $RuCl_3$)[19] was then achieved to generate the pentafluorocyclohexyl carboxylic acid **14**. It is noteworthy that direct oxidation of phenyl all *cis*-2, 3, 5, 6 –tetrafluoro-cyclohexane **2** by this method is unsuccessful, as the presence of the benzylic α-hydrogen, leads to HF elimination and then decomposition.[22] However with **13**, the fluorine atom at C1 operates as a blocking group to HF elimination and carboxylic acid **14** is stable and relatively easy to isolate. This carboxylic acid could be reduced with BH_3.THF to generate the corresponding alcohol **15**.[23] Alcohol **15** proved difficult to secure as it was found to sublime under reduced pressure (rotary evaporation) and was generally volatile at atmospheric pressure, hence it was converted to the corresponding mesylate **16** as a useful storage compound, and one ready for further transformations to introduce the pentafluorocyclohexyl motif into higher molecular architectures.

α-Fluoroamide conformation.

Carboxylic acid **14** offers an unusual and potentially attractive building block for bioactives research, and in this context it became of interest to explore amides derived from **14**. With the fluorine at C1 of the cyclohexane ring, this will necessarily generate an α-fluoroamide, a class of compounds that are already recognised to have a particularly preferred conformation.[24,25] As a general rule such amides adopt a *trans*-planar conformation, such that the C-F and N-H bonds are co-planar and *syn*-parallel, and the C-F bond orientates co-planar and *anti*-parallel to the amide C=O bond as illustrated in Figure 2. Previous studies on α-fluoroacetamides such as **16** have calculated up to an 8 kcal mol^{-1} preference for this conformation on an energy profile, rotating around the (O)C-C(F) bond.[24] The arrangement is favoured to minimize oxygen/fluorine repulsion and maximize CF…H(N) electrostatic attraction, and with an overall dipolar relaxation between the amide and C-F dipoles. Such conformations can be disrupted however by intra and inter molecular hydrogen bonds.[26]

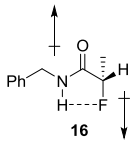


Figure 2: The preferred conformation of α-fluoroamide **16**.[18]

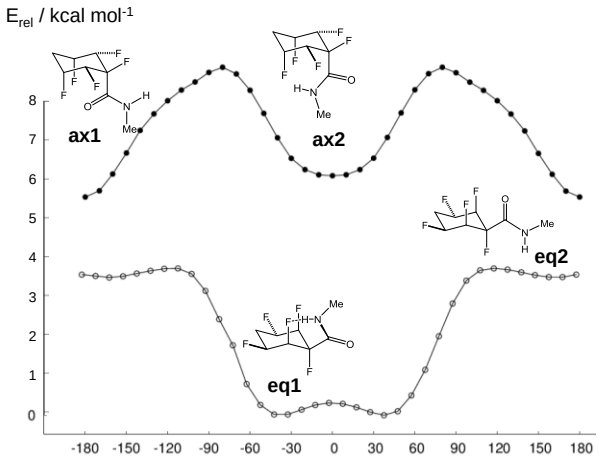


Figure 3: Rotational profiles about the C(F)-C(=O) bond in model methylamide **17** for the target conformations (B3LYP/6-311+G** level), energies are in kcal mol^{-1} relative to the most stable conformer (**eq1**).

	Conformer of α-fluoroamide **17**			
Property	**ax1**	**ax2**	**eq1**	**eq2**
ΔE_{rel} [kcal mol^{-1}] gas phase	5.6	6.1	0.0	3.5
(ΔE_{rel} [kcal mol^{-1}] in water) [a]	(0.3)	(0.9)	(0.0)	(0.6)
$\theta_{F\text{-}C\text{-}C=O}$ calc [°]	179.9	-1.7	37.6	163.7
X-ray	*161.1*[b]	*n.a.*	*5.8*[c]	*n.a.*
nearest $d_{F\ldots H(N)}$ [Å] [d]	2.084	2.141	1.991	2.112
μ [D]	4.9	7.2	2.1	6.4

Table 1: Computed properties of **17** (energies ΔE_{rel} relative to **eq1**, dipole moments *μ*, selected angles and distances) at the B3LYP/6-311+G** level (gas phase values, unless otherwise noted).

Amides of carboxylic acid **14** may adopt the classical conformation as discussed above, however it was of interest to assess how the amide group may orient the tertiary fluorine attached to the conformationally biased (chair) cyclohexane, carrying four additional configurationally defined fluorines. To gain an insight into the possible conformational preferences of such amides a DFT study was carried out at the outset, to act as a frame of reference for experimental (X-ray, NMR) structure analysis.

DFT theory study on α-fluoroamide 17 conformation

Methylamide **17** was selected as a model system for DFT (B3LYP/6-311+G**).[27-29] Modelling of the core structure (amide + cyclohexyl ring) used coordinates from the X-ray structures of benzylamides (*vide infra*), where the *N*-benzyl groups were replaced by *N*-methyl. Two conformational scenarios were explored and compared. These had the carboxamide group of **17** either in an axial (**ax**) or an equatorial (**eq**) conformation. After initial optimisation to find the minima in each case a rotational energy profile was calculated considering rotation only around the (F)C-C(O) bond, keeping that dihedral angle frozen at values in steps of 10° and minimizing the rest of the molecule. Full rotational energy profiles were constructed from relaxed scans of the F-C-C=O dihedral angles (θ). The resulting profiles are displayed in Figure 3.

From these profiles, higher-lying minima were apparent, and these were subject to full geometry optimisations, affording conformers **ax2** and **eq2**. Relative energies and salient geometrical parameters of all minima are collected in Table 1. While **ax1** and **ax2** are essentially C_s-symmetric with dihedral angles θ of 180 ° and 0 °, respectively, **eq1** and **eq2** are lacking such planes of symmetry and come in enantiomeric pairs, although they are separated by very low energy barriers, as illustrated in the lower profile in Figure 3.

As might be anticipated, there is a preference for the bulkier carboxamide to be placed in an equatorial rather than an axial orientation. This preference is rather pronounced in the gas phase, as the computed energy difference between **eq1** and **ax1** is 5.5 kcal mol^{-1}. However, there are significant variations in the dipole moments between the minima (see μ values in Table 1). Thus, the equilibrium is anticipated to be sensitive to the polarity of the environment. To probe the extent of this sensitivity, the relaxed scan and subsequent optimisations were repeated using a simple solvent model, namely the polarizable conductor variant of the polarizable continuum model (CPCM), employing the parameters of water and the default options in Gaussian 09.[30,31] The outcome is illustrated in Figure 4.

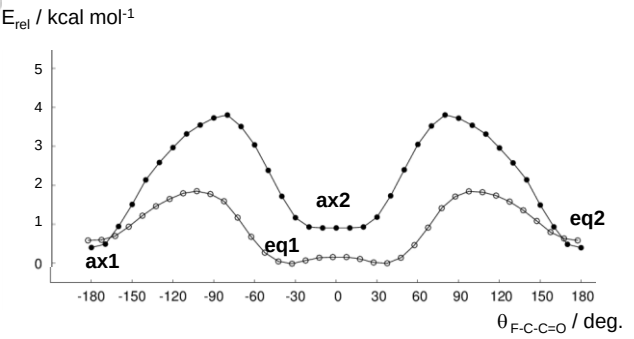


Figure 4: Rotational energy profiles around the C(F)-C(=O) bond in a methylamide **17** in a continuum, modelling water (CPCM/B3LYP/6-311+G** level). Energies are given in kcal mol^{-1} relative to the most stable conformer (**eq1**).

The resulting profiles are now much closer in energy (Figure 4), indicating that this CPCM model is more realistic for interpreting this class of amide conformation in the bulk relative to that in the gas phase (see Table 1). The conformer **eq1** emerges from this DFT study to be lowest in energy, whereas **eq2** conforms more to the classical α-fluoroamide conformation (Figure 2). However the data suggest that in a polar environment the relative energies of

all of the minima are within 1 kcal mol^{-1} of each other. To explore this conformational bias further, X-ray structure and solution NMR analysis were investigated.

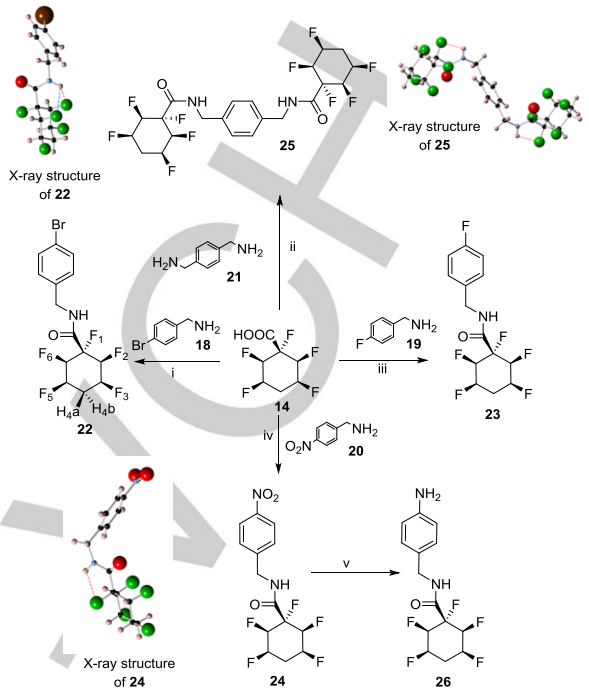
X-ray structures of benzylamides of carboxylic acid 14.

For this structural study carboxylic acid **14** was coupled to the three benzylamines **18-20** which are distinguished by their *para*-aryl substitution, as well as *bis*-benzylamine **21**. These reactions all proved straightforward and the corresponding amide products **22**, **23**, **24** and **25** were obtained in good yields as illustrated in Scheme 5, indicating that carboxylic acid **14** is a good coupling partner despite being sterically demanding and carrying an electronegative fluorine adjacent to the carboxylic acid moiety. In addition the *para*-nitrobenzyl amide **24** was successfully reduced to the corresponding aniline **26** using stannous chloride, conditions which did not affect the amide or the tetrafluorocyclohexane ring system.[32]

From the collection of amide products, **22**, **24** and **25** generated suitable crystals for X-ray structure analysis, where there are four structurally characterised amide bonds. Two of these, both in the *bis*-amide **25**, adopt the **ax1** structure. This structure also conforms to the classical conformation of an α-fluoroamide (Figure 2). In the **ax1** structure the amide oxygen is directed towards the two axial fluorines on the cyclohexane ring, but none the less this is an energy minimum by DFT and it is experimentally observed here. Amide (*p*Br) **22** adopts the **eq1** structure, which is the lowest energy DFT derived structure in the gas phase and *iso*-energetic with the **ax1** structure in the solvent (H_2O) continuum model determined by DFT. In this case, the structure shows that the amide NH makes an extremely short NH...C-F contact (2.09 Å) to one of the diaxial C-F bonded fluorines. This very short distance for an intramolecular H...F contact suggests a stabilizing electrostatic interaction.[33] Finally the experimental conformation in amide **24** (*p*NO_2) is most closely defined by the **eq1** structure (F-C-C-O dihedral angle of 123 °C). Thus both the DFT and X-ray structure analysis suggest two closely isoelectronic conformations for this class of α-fluoroamides, defined as **ax1** and **eq1**.

Solution state ^{19}F HOESY NMR studies.

Compounds **22**, **24** and **25** were all investigated by ^{19}F-HOESY NMR[34] in $CDCl_3$ to explore preferred solution state conformations relative to their solid state structures. Through space contacts to the amide N-H proton were anticipated to be particularly diagnostic in differentiating the minimum energy conformations **ax1**/**ax2**/**eq1**/**eq2** that emerged from the DFT study. Through space correlations between the amide N-H and the F1 fluorine would support conformations **ax 1/eq2**, and correlations between the amide N-H and the F2/F6 fluorines would support conformation **eq1**, and correlations between the amide N-H and the F3/F5 fluorines would support conformation **ax2**.



Scheme 5: (i) EDCI, HOBt, N-Methylmorpholine (NMM), DMF, rt, 18 h (87%); (ii) EDCI, HOBt, NMM, DMF, rt, 18 h (70%); (iii) EDCI, HOBt, NMM, DMF, rt, 18 h (57%); (iv) EDCI, HOBt, NMM, DMF, rt, 18 h (82%); (v) $SnCl_2.2H_2O$, EtOH, 90 °C, 18 h (65%).

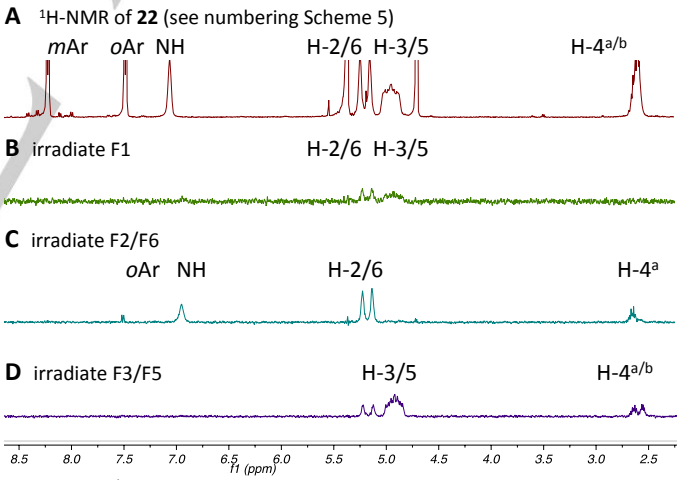
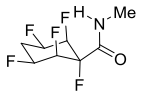


Figure 5: A) ^{1}H NMR Spectrum of **22** in $CDCl_3$ with selective proton assignments. **B-D**) 1D selective ^{1}H, ^{19}F-HOESY: **B**) Irradiation of F1. **C**) Irradiation of F2/F6. **D**) Irradiation of F3/F5. The data is consistent with the **eq1** conformation (Fig 3).

In the event all three compounds displayed very similar ^{19}F-HOESY NMR spectra indicating strong correlations between the N-H proton and the proximate diaxial F2/F6 fluorines, suggesting the dominance of conformer **eq1** in chloroform. By way of example the ^{19}F-HOESY NMR spectra for amide **22** are collated in Figure 5. The diagnostic spectrum in shown in Figure 5(C) where there is a clear perturbation of the NH proton on irradiating fluorines F2/F6. No other fluorine irradiations significantly perturb the amide resonance. A very much weaker correlation was

detectable between F1 and the N-H (Figure 5B) proton, offering only partial support for conformer **ax1** in solution. No through space correlations from NH to F3/F5 were obvious offering no support for conformer **ax2**. This solution state study suggests **eq1** as the dominant conformer in chloroform for all three compounds explored. The ^{19}F-HOESY NMR spectra for amides **24** and **25**, with a very similar outcome, are shown more fully in the SI section. The amides of carboxylic acid **14** do not appear to adopt the equatorial α-fluoroamide structure (**eq2**) in solution, where the C-F bond lies coplanar and *syn*-parallel to the amide N-H in what should be a favourable arrangement (Figure 2). However such an arrangement aligns the amide dipole with the two diaxial C-F bonds (F2/F6) raising the molecular dipole (Table 1). For **eq1**, the preferred conformation in solution, the bulky carboxamide group lies equatorial, and the N-H hydrogen and is able to pick up very short, and presumably stabilizing F…H interactions with either of the two axial fluorines (F2/F6), and this emerges as a preferred arrangement. The observation of the **ax1** conformer in the X-ray structure for **25** suggests however that conformers **eq1** and **ax1** are close in energy in the solid state. It seems reasonable that a polar crystal environment will impart a similar electrostatic stabilization as a polar solvent such as water (see continuum modelling in water, Table 1), where the DFT study indicates that these conformers are *iso*-energetic. In that case, the precise conformation that crystallizes may well be determined by additional intermolecular interactions (packing forces). In the less polar organic solvent the situation is expected to be in between the scenarios of Figure 3 (gas phase) and Figure 4 (polar environment);



conformer **1eq**
Figure 3

Figure 6: The preferred conformation (**eq1**) of amide **17**.

in this case **eq1** would be the lowest conformer, not quite as dominant as in the gas phase (Figure 3), but lower enough in energy to be essentially exclusively populated as indicated by NMR.

Conclusions

Although fluorine incorporation into organic molecules is often thought to increase lipophilicity, it is increasingly being articulated that partial fluorination of aliphatic residues generate substituents that lower rather than raise Log P values.[35] This is attractive for medicinal chemistry research. Partially fluorinated cyclohexanes are particularly noteworthy in this context because the aligned diaxial C-F bonds maximize the polarity of these cyclohexanes and very significant Log P reductions are observed relative to the cyclohexane itself.[5] In this paper we have shown that benzylic bromination of phenyl all-*cis*-2, 3, 5, 6 –tetrafluorocyclohexane **2** can efficiently generate benzyl bromide **4**, and that **4** becomes a substrate for further elaboration by halogen displacement to prepare new building blocks for the introduction of the all *cis*-2, 3, 5, 6 –tetrafluorocyclohexane motif for bioactives research. In this context tertiary alcohol **6**, tertiary amine **8** and cyclohexyl amino acid **11** derivatives were prepared, as well as the pentafluorocyclohexane carboxylic acid **14**. This carboxylic acid was readily coupled with amines to prepare a range of α-fluoroamides. Conformational analysis indicated that the preferred solution conformation **eq1** (in chloroform) was stabilized by an amide NH…F-C(axial) interaction. It will be interesting to see how this polarized cyclohexane will interact, in co-crystallisation studies, with the surface of proteins if high affinity ligands containing the motif are developed from such building blocks.

Experimental Section

Experimental Details are presented in SI.

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Keywords: Organofluorine • all *cis*-2,3,5,6-tetrafluorocyclohexane • fluorinated building blocks • Ritter reaction• conformational analysis

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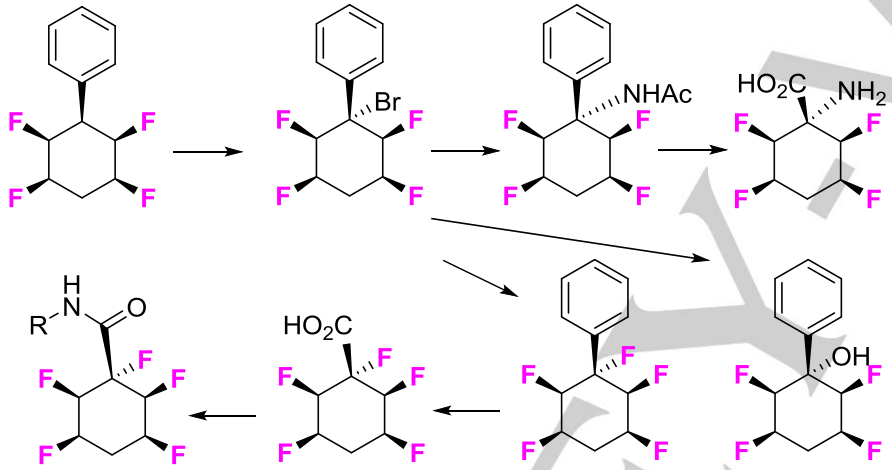

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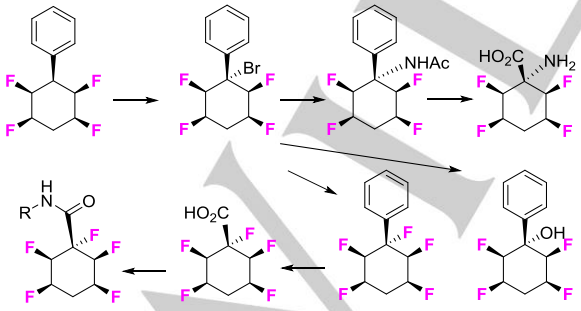

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Benzylic functionalisation of phenyl all cis-2, 3, 5, 6 –tetrafluoro - cyclohexane provides access to new organo-fluorine building blocks