A straightforward metal-free synthesis of 2-substituted thiazolines in air

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A straightforward metal-free synthesis of 2-substituted thiazolines in air†

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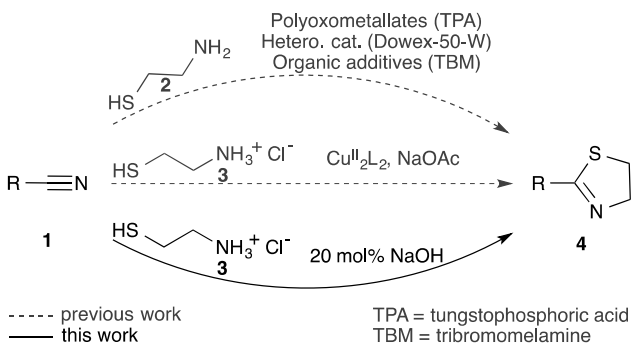
A base-catalysed procedure for the synthesis of 2-substituted thiazolines from nitriles and cysteamine hydrochloride under solvent-free conditions is presented. This straightforward approach allows high conversion for a broad range of nitriles and an easy isolation of the desired products.

2-Substituted thiazolines are important heterocyclic compounds present in a great number of natural products used in the food and pharmaceutical industries.[1] Currently, thiazoline-based compounds are used as antibiotics,[2] anticarcinogens,[3] anti-inflammatories[4] and antithrombotics.[5] Similarly to oxazolines, thiazolines are well-known ligands in metal-catalysed transformations, such as hydrosilylation,[6] allylic substitution,[7] Diels-Alder reaction,[8] cyclopropanation,[9] Henry reaction[10] and C-P bond[11] formation. Considering their broad applicability, finding a straightforward and inexpensive methodology to synthesise these compounds could be of great interest for the general synthetic community. During the last decades, several procedures leading to this end have been reported. These can be divided into two different approaches: cyclodehydration of thioamides[12] and condensation of carbonyl compounds[13] namely, *N*-acylbenzotriazoles[14] and nitriles with aminothiols. Among these possibilities, nitriles are inexpensive and readily available reagents, which explain their wider use as starting materials for this reaction. Different methodologies for the preparation of thiazolines have been reported to date and these are summarised in Scheme 1. The common approach requires an electrophile to activate the nitrile **1** towards the nucleophilic attack of cysteamine **2**. Procedures involving proton donor polyoxometallates, such as tungstophosphoric acid (TPA),[15] have also been developed, but rather harsh conditions were required in such protocols, *i.e.* high temperature (110 °C). Heterogeneous catalysts (for example, Dowex-50W-hydrogen ion exchange resins)[16] are also able to promote the reaction. Unfortunately, under these conditions, the scope remains narrow and only *para*-substituted benzonitriles can be used. Other types of electrophiles are used to activate nitriles such as tribromomelamine (TBM) which is able to generate Br^+ *in situ*.[17] However, a prior preparation of TBM is required using this approach. This involves bromination of the corresponding melamine in the presence of excess NaOH.

Metal catalysis has also been considered for this transformation. In 2012, Li and co-workers developed a methodology using a catalytic amount of a $Cu^{II}_2L_4$ (L = methacrylate) complex and cysteamine hydrochloride **3** instead of its neutral analogue **2**.[18] Unfortunately, a fairly high catalyst loading (8 mol%) and an excess of base (2 equiv. of NaOAc) were required, as well as the need for independent preparation of the $Cu^{II}_2L_4$ catalyst.

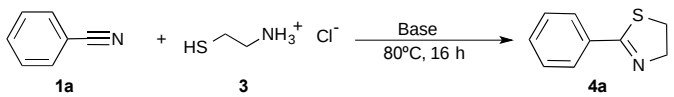


Scheme 1 Synthesis of 2-substituted thiazolines

In addition, an important drawback to all the aforementioned procedures exists in the purification step. Indeed, purification by column chromatography is necessary in order to obtain pure product. Despite the existence of these procedures (and maybe because of their existence), a more general and straightforward approach towards the synthesis of thiazolines **4** is highly desirable. Well-defined copper *N*-heterocyclic

carbene (NHC) complexes are well-known to be active catalysts in a plethora of reactions such as click-chemistry,[19] the borylation of alkynes,[20] the synthesis of phenols[21] and many others.[22] While testing two of our well-defined copper *N*-heterocyclic carbene complexes[23, 24] in this transformation, using benzonitrile **1a** and cysteamine hydrochloride **3** as model substrates, we found that the base alone is capable of promoting this reaction (Table 1).[25] All bases tested gave excellent results (Table 1). Amongst these, NaOH was selected for further investigation as it is inexpensive. When the amount of NaOH is decrease to 5 mol% (Table 1, entry 4), a slight decrease in conversion is observed (91%). Finally, the time parameter and the amount of **3** were investigated. After 2 hours and using only 0.75 mmol of **3**, quantitative conversion was observed using 20 mol% of NaOH (Table 1, entry 5). When the time is further decreased to 1 hour (Table 1, entry 6), a modest decrease in conversion is detected (94%). In order to eliminate the possibility of metal contaminants in the NaOH actually catalysing the reaction, a test using semiconductor grade NaOH was performed. Gratifyingly, full conversion was obtained reinforcing the role of NaOH as the sole promoter of the reaction (see supporting information).

Table 1 Optimisation of the reaction conditions for the synthesis of 2-phenyl-4,5-dihydrothiazole[a]

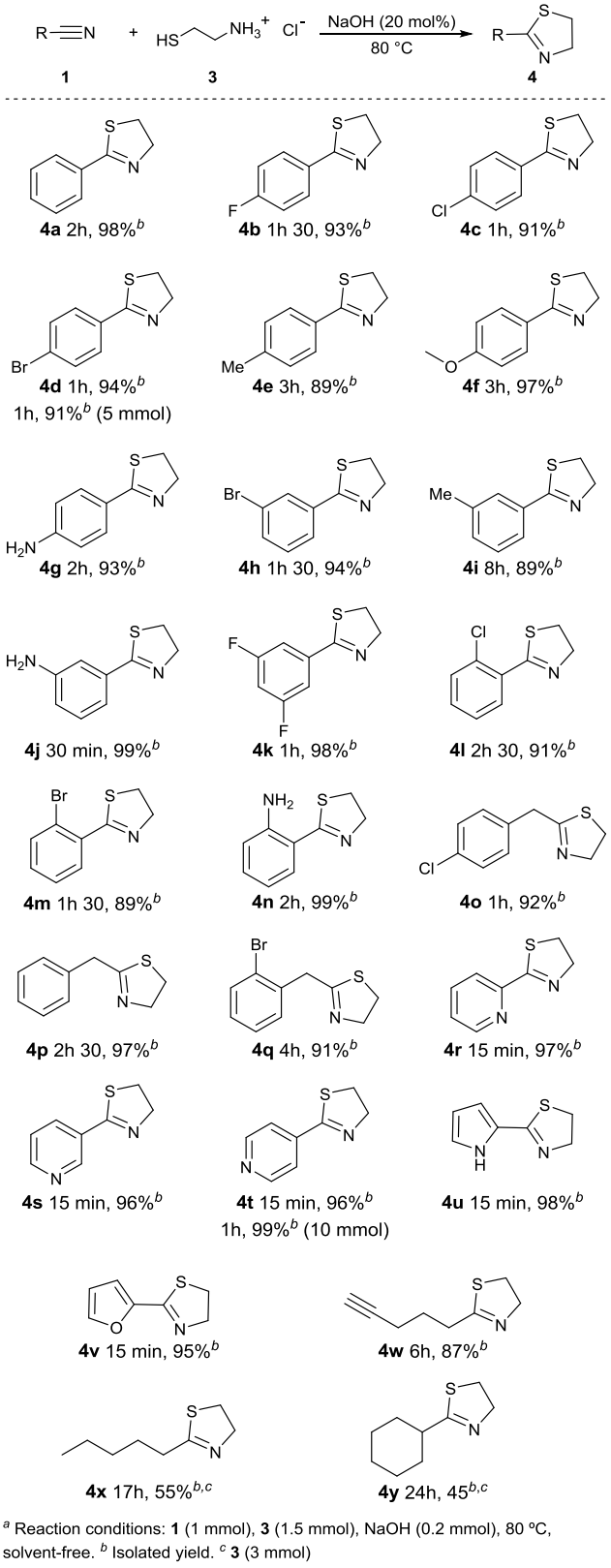


1a 3 4a

Entry	Base	Loading (mol%)	Time (h)	Conversion (%)[b]
1	CsOH	10	16	> 99
2	KOH	10	16	> 99
3	NaOH	10	16	> 99
4	NaOH	5	16	91
5[c]	**NaOH**	**20**	**2**	**> 99 (98)**[d]
6[c]	NaOH	20	1	94

[a] Reaction conditions: **1a** (0.5 mmol), **3** (1 mmol), base (5-20 mol%), 80 °C, 16 h. [b] Determined by GC, based on benzonitrile. [c] 0.75 mmol of **3**. [d] isolated yield.

With the optimised conditions in hand, the scope of the reaction was investigated on a range of nitrile derivatives (Figure 1).



[a] Reaction conditions: **1** (1 mmol), **3** (1.5 mmol), NaOH (0.2 mmol), 80 ºC, solvent-free. [b] Isolated yield. [c] **3** (3 mmol)

Fig. 1 Formation of 2-substituted thiazolines from nitriles and cysteamine hydrochloride[a]

For all substrates, the reaction proceeds with quantitative conversion and excellent isolated yield. Both electron withdrawing (EWG) and electron donating (EDG) groups are tolerated. However, an effect of the nature of the substitution was observed on the reaction time. In the case of *para*-substituted benzonitriles bearing EWG (**4b**-**4d**), the reaction proceeds with a shorter reaction time compared to substrates bearing EDG (**4e**-**4g**). Regarding the position on the aryl ring, as expected, *ortho*-substituted benzonitriles (**4l**-**4n**) reacts more slowly than the corresponding *meta*- (**4h**-**4j**) and *para*-substituted (**4b**-**4d**) derivatives. When the steric hindrance is higher, as for 2,6-dimethylbenzonitrile, no conversion was observed. The synthesis of benzyl thiazolines has been achieved in excellent yields (**4o**-**4q**). As previously noted, the substitution does not affect the conversion but only the reaction time, with *ortho*-substituted benzyl nitriles reacting more slowly than 2-phenylacetonitrile and the *para*-substituted analogue. Heteroaromatic nitriles show great reactivity, reaching full conversion to the desired product after *15 minutes!* The outcome of the reaction is independent of the size of the ring, the position and the nature of the heteroatom, making this a general procedure leading to polyheterocyclic compounds (**4r**-**4v**). Interestingly, a simple extraction using water and ethyl acetate was sufficient to purify and remove excess of **3**, eliminating any need for column chromatography. When aliphatic nitriles are used, moderate to good yields are obtained (**4w**-**4y**).

In order to control the progress of the reaction and to identify intermediates, *in situ* IR measurements were performed, using a ReactIR system (see supporting information). However, no signals of a possible stable intermediate were identified. It is possible that the base initiates the HCl scavenging process, liberating the cysteamine that acts as a nucleophile towards the nitrile. As the reaction goes on, the generated ammonia becomes the HCl scavenger forming NH_4Cl and closing the catalytic cycle. Unfortunately, the synthesis of oxazolines was not possible under these conditions. However, efforts to investigate the mechanism and possibly expand the scope to these interesting structures are the subject of future studies.

Conclusions

In conclusion, a straightforward procedure for the conversion of nitriles and cysteamine hydrochloride to 2-substituted thiazolines is reported. The reaction is promoted by a catalytic amount of NaOH under solvent-free conditions. A broad variety of aromatic, benzyl, heteroaryl and aliphatic nitriles can be converted into the desired product. This simple synthetic protocol is rendered even more attractive as product isolation can be performed using a simple extraction technique.

Experimental

General procedure for the preparation of 2-subtituted thiazolines: In air, a vial was charged with the nitrile (1 mmol), cysteamine hydrochloride (1.5 mmol) and NaOH (0.2 mmol). The reaction was stirred at 80 °C for the appropriate time. The crude product was dissolved in ethyl acetate (2 mL) and water (10 mL) was added. The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and dried under vacuum to yield the desired product.

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Notes and references

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† Electronic supplementary information (ESI) available: Optimisation details and full characterisation data. See DOI: 10.1039/x0xx00000x

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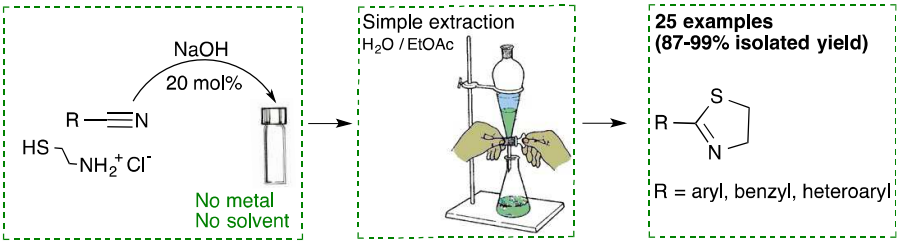
25 A precedent using a weak base (*e.g.*, NaOAc) has been reported, although a very low yield was obtained (15%); for more details, see ref.18.



A range of 2-substituted 4,5-dihydrothiazoles was easily synthesised from the reaction of nitriles with cysteamine in the presence of a catalytic amount of NaOH