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## COMMUNICATION

Easy access to thiazolines and thiazines *via* tandem *S*-alkylation-cyclodeamination of thioamides/haloamines†

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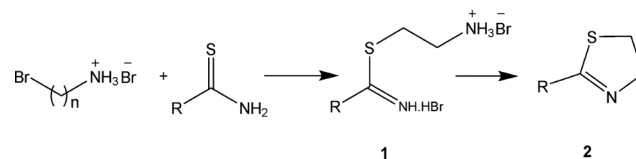
This is the first report of a facile synthesis of thiazolines and thiazines from a self-catalyzed, water assisted tandem *S*-alkylation-cyclodeamination reaction of thioamides/haloamines. The reaction is clean and efficient with simple product work-up, and is applicable to a variety of substrates.

Thiazolines and thiazines are of considerable interest because of their biological and industrial importance.<sup>1</sup> They exhibit a wide range of pharmacological activities such as antidiabetic, anticancer, anti-HIV, antitumor, antidepressive, bioluminescence *etc.*<sup>1–6</sup> Several methods exist for the preparation of thiazolines and thiazines.<sup>7</sup> Current methods of their synthesis rely on condensation of  $\beta$ -amino thiols<sup>8</sup> or  $\beta$ -amino alcohols<sup>9</sup> with nitriles, carboxylic acids and esters.<sup>10–11</sup> In the case of amino alcohols, for introducing sulfur a sulfuring agent has to be used. The other exploitable synthetic procedures are the cyclisation of *N*-( $\omega$ -hydroxy) thioamides<sup>12,13</sup> and acylamino thiols,<sup>14</sup> and thionation of oxazolines.<sup>15</sup> Despite these procedures, there continues to be a demand for improved methods for their preparation in terms of mild reaction conditions, cleaner reactions, and simple isolation of the product.

Thioamides are well known to react with alkyl halides to yield imidothiolic ester *via* *S*-alkylation. Considering this reaction we reasoned that the reaction of 2-halo-ethylamine with primary thioamides may result in the formation of thiazolines *via* *S*-alkylation, and subsequent cyclodeamination of *S*-alkylated product. Nevertheless, due to the potential side reactions such as transamidation, and self-condensation of susceptible haloamines; this is not generally considered a very favorable route for the preparation of thiazoline, hence it has never been extensively explored.

Haloamines are commercially available or alternatively can also be prepared conveniently from amino alcohols which are

accessible in a great variety. To explore the possibility of thiazoline formation from thioamides and haloamines, we attempted the reaction in various solvents by reacting equimolar amounts of 2-bromoethylamine hydrobromide salt, thiobenzamide and triethylamine. Triethylamine was added to make the amine free. As expected, 2-Phenyl-4, 5-dihydro-[1, 3]-thiazole, was formed along with benzonitrile, benzamide, polymeric amine and unreacted thiobenzamide. The reaction profile (Scheme 1) suggested that, since in the first step (*i.e.* *S*-alkylation) the amine moiety is not involved, formation of **1** was also feasible with protonated 2-bromoethylamine. Hence, to further improve the reaction, we attempted it without triethylamine. In solvents like chloroform, ethyl acetate, toluene, benzene, and tetrahydrofuran no reaction occurred, mainly due to the insolubility of the salt in these solvents. In polar solvents like acetonitrile, ethanol and methanol though, the reactants were soluble but, even after allowing the reaction for long time at reflux, significant product formation was not achieved. In methanol, a somewhat better conversion into the desired product (10%) was obtained. A more polar solvent than methanol that we could envisage was water.



Scheme 1

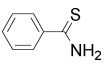
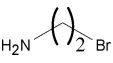
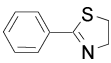
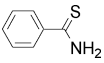
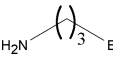
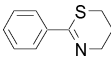
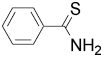
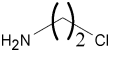
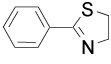
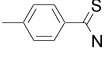
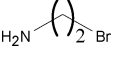
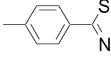
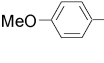
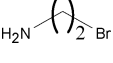
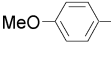
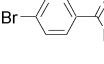
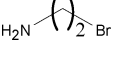
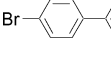
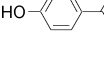
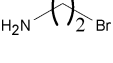
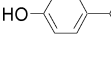
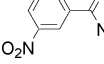
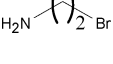
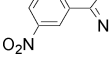
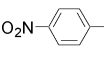
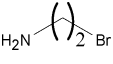
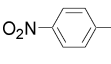
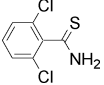
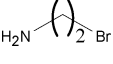
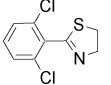
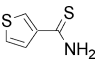
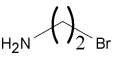
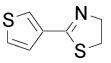
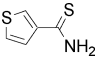
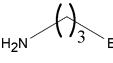
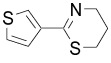
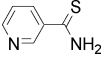
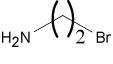
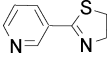
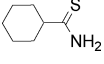
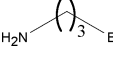
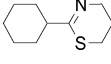
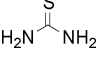
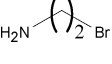
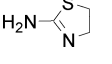
The use of water as a medium for organic synthesis is one of the latest challenges in organic synthesis. Water is non-toxic, safe and cost effective. In view of the potential advantages of replacing organic solvents with water, many reactions are being discovered that can be accomplished in water and the progress here has been dramatic.<sup>16</sup> Additionally, water facilitates ion separation through solvation which often results in altered behavior of reactants in an aqueous environment. There is no report available for the preparation of thiazolines in water hence, considering all these points we were curious to know whether this reaction would occur in water.

To investigate a water compatible thioamide-haloamine reaction we conducted the reaction in water. However, when water

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† Electronic supplementary information (ESI) available: General details, experimental procedures, characterisation data, and copies of <sup>1</sup>H, <sup>13</sup>C NMR and mass spectra for selected compounds. See DOI: 10.1039/c1gc15285h

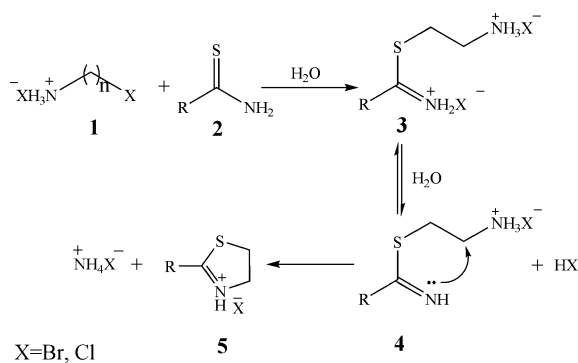
**Table 1** Formation of thiazolines and thiazines from thioamides and haloamines

$\text{R}-\text{C}(=\text{S})\text{NH}_2 + \text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{X} \xrightarrow{\text{H}_2\text{O}} \text{R}-\text{C}(\text{S})\text{N}(\text{CH}_2)_n$						
Entry no.	Thioamide	Amine-HBr/HCl	Product <sup>a</sup>	Yield (%) <sup>b</sup>	Time	mp (°C)
1.				91	3 h	Oil <sup>17a</sup>
2.				90	2.5 h	44–45 <sup>17a</sup>
3.				79	5 h	Oil <sup>17a</sup>
4.				83	3 h	41–42 <sup>17a</sup>
5.				89	2 h	43–44 <sup>17b</sup>
6.				87	2.5 h	90–92 <sup>17c</sup>
7.				90	2.5 h	198–199 <sup>17c</sup>
8.				96	4 h	135–137 <sup>17b</sup>
9.				87	25 min	150–152 <sup>17b</sup>
10.				86	30 min	71–72 <sup>17d</sup>
11.				81	2 h	Oil
12.				86	2 h	oil
13.				92	15 min	111–113 <sup>17b</sup>
14.				91	2 h	Oil
15.				88	2.5 h	80–82 <sup>17e</sup>

<sup>a</sup> All the products gave satisfactory spectral data. <sup>b</sup> Yield refers to isolated products.

was used as the solvent thiobenzamide remained insoluble, and after a prolonged reaction it converted to benzamide with a modest formation of thiazoline. Previously, while working with haloamines we had noticed that hydrated salts of these amines behave very similar to ionic liquids in terms of their solubilizing capability. Hence, the reaction was investigated once again by taking a very limited amount of water.

For this, 2-bromoethylamine hydrobromide was dissolved in a small quantity of water (40–50 µl per mmol) at 60–70 °C and thiobenzamide was added to it. After few minutes the reaction mixture become homogeneous which was then allowed to progress at the same temperature and monitored by TLC and GC-MS. We expected that initially we may get **3**, and with the help of a base, **3** could be cyclised to **5** (Scheme 2). But,



Scheme 2

analysis of the reaction after two hours revealed unexpectedly, to our delight, a direct formation of 2-phenyl-[1,3]-thiazoline **5**. When the same reaction was carried out with free amino halide only a 40% conversion into the desired product was observed.

The formation of **5** from thioamides and protonated amino-halide in the presence of water was rationalized as follows: first an imidothiolium species **3** is formed *via* *S*-alkylation. Imine nitrogen of imidothiolic ester being mildly basic is not able to hold the proton strongly in the presence of water and undergoes reversible protonation. The free iminium nitrogen is attacking the electrophilic carbon attached to the ammonium ion, leading to clean formation of thiazoline **5**. Additionally, the presence of water is also suppressing the dehydration of thioamide. Further, employment of protonated aminohalide is inhibiting the undesired side reactions such as transamidation and self-condensation leaving *S*-alkylation and subsequent cyclisation the only available reaction path way.

With a suitable reaction system in hand, we then set to examine the scope of this transformation. Our results are compiled in Table 1. Diverse thioamides bearing different functional groups were reacted with bromoethylamine and bromopropylamine. The reaction of bromopropylamine with thioamides yielded 2-substituted thiazines in a similar fashion. To study the *S*-alkylation with halides in water; simple alkyl halides such as butyl iodide, butyl bromide and butyl chloride were treated with thiobenzamide. The order of reaction was found to be I = Br > Cl. When 2-chloroethylamine was reacted with thiobenzamide, as per our anticipation a slow reaction occurred and formation of corresponding nitrile and amide was also noticed.

Thionicotinamide reacted with bromoethyl amine at a slightly higher temperature 95–100 °C under almost solventless conditions (experimental procedure 2, ESI†). Although the desired reaction occurred at higher temperature, it took a shorter reaction time (15 min) to reach completion (entry 12). Thioamides having electron withdrawing groups and sterically hindered thioamides exhibited a similar tendency (entry 9, 10). With aliphatic and unsubstituted or electronically rich thioamides, application of higher temperature led to significant dehydration of thioamides producing nitrile as a side product. Reaction of thiourea with 2-bromoethylamine hydrobromide resulted in the formation of 2-amino thiazoline (entry 15).

## Conclusions

In conclusion, the first water assisted green synthesis of thiazolines and thiazines from thioamides and ω-haloamines has been reported. A clean and efficient reaction, simple isolation of the product and wide application to a variety of substrates renders this method practical.

## Experimental

Typical experimental procedure for 2-phenyl-4,5-dihydro-[1,3]-thiazole: 250 μl of water was added to 2-bromoethylamine hydrobromide salt (5.5 mmol) and mixed thoroughly. To this thiobenzamide (5 mmol) was added and the reaction mixture was heated at 60–70 °C for three hours. Contents were cooled and neutralized with cold 5% sodium carbonate solution. Yellow oil gets separated which was extracted with ethyl acetate.<sup>18</sup> Solvent removal under vacuum yielded 2-phenyl-4,5-dihydro-[1,3]-thiazole as a yellow oil. If required the compound can be further purified by column chromatography. Data for **1**; **2-Phenyl-4,5-dihydro-[1,3]-thiazole**: Yellow oil, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.9–7.8 (m, 2H), 7.4–7.3 (m, 3H), 4.45 (t, 2H, *J* = 8.4 Hz), 3.40 (t, 2H, *J* = 8.0 Hz); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 167.69, 132.87, 130.68, 128.06, 127.97, 64.85, 33.82; EIMS: *m/z* 163 [M<sup>+</sup>], 117, 104, 77, 60.

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