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Dithiocarbamates as an efficient intermediate for the synthesis of 2-(alkylsul-fanyl)thiazoles in water

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Dithiocarbamates as an efficient intermediate for the synthesis of 2-(alkylsulfanyl)thiazoles	Leave this area blank for abstract info.
in water	
Azim Ziyaei Halimehjani, Leila Hasani, Ali Alaei, Mohammad	R. Saidi
$R \xrightarrow{O} Br + \frac{S}{H_2N} \xrightarrow{R'} \frac{H_2O}{reflux, 20 h} \xrightarrow{S} N$	$-S = \begin{bmatrix} 1. & I_2/CuO \\ ethanol, 8 & h, reflux \\ 2. & dithiocarbamate \\ reflux, 2 & h \end{bmatrix} \xrightarrow{O} \\ R \xrightarrow{O} \\ CH_3$



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### Dithiocarbamates as an efficient intermediate for the synthesis of 2-(alkylsulfanyl)thiazoles in water

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Accepted Available online ABSTRACT

A simple, green and high-yielding procedure for the synthesis of 4-substituted-2-(alkylsulfanyl)thiazoles from the reaction of dithiocarbamates and  $\alpha$ -halocarbonyl containing compounds in water is described. Also, a one-pot, two-step procedure for the synthesis of 2-(alkylsulfanyl)thiazoles from acetophenone and dithiocarbamates was developed.

Keywords: Dithiocarbamate 4-Substituted-2-(alkylsulfanyl)thiazole *a*-Halocarbonyl compounds Green chemistry Water

The thiazole motif is an important building block that is present in the structure of pharmacologically active substances and natural products.<sup>1</sup> Compounds containing thiazole rings have widespread biological applications as anti-inflammatory,<sup>2</sup> antitumural,<sup>3</sup> antiviral,<sup>4</sup> antifungal,<sup>5</sup> antipiron,<sup>6</sup> herbicidal,<sup>7</sup> and antimicrobial agents.<sup>8</sup> Many routes for the synthesis of thiazoles are reported in the literature.<sup>9</sup> Among them, the Hantzch thiazole synthesis,<sup>90</sup> dehydrative cyclization of  $\alpha$ -amidoketones using Lawesson's reagent,<sup>91,k</sup> reaction of thioureas with  $\alpha$ -haloketone derivatives<sup>9a-g,l,m</sup> and condensation of thioamides with epoxides<sup>9p,q,r</sup> are the most reported methods.

The synthesis of organic compounds using environmentally benign, mild, and simple procedures has received considerable attention. Among the different branches of green chemistry, reducing or eliminating the use of hazardous substances, or the generation of these materials, and performing reactions in green reaction medium have found widespread application. In this context, water is the preferred choice as a solvent because of its properties such as being environmentally safe, simple to handle, and low cost.<sup>10</sup> In addition, performing multi-step reactions in a one-pot procedure, without the separation of intermediates which reduces the final product yield, is in agreement with the goals of green chemistry. Keeping these goals in mind, herein, we report a simple one-pot procedure for the synthesis of 2-(alkylsulfanyl)thiazoles in water with high yields.

Recently, Rao and co-workers reported an efficient procedure for the synthesis of thiazoles and aminothiazoles from phenacylbromide and thioamide/thiourea in water using  $\beta$ - cyclodextrin (β-CD) as a catalyst. <sup>11</sup> We proposed that by using S-alkyldithiocarbamates instead of thioamides/thiourea, 2-(alkylsulfanyl)thiazoles could be obtained. For this purpose, alkyldithiocarbamates were synthesized via the one-pot, threecomponent reaction of aqueous ammonia, carbon disulfide, and alkyl halides as described in the literature.<sup>12</sup> The reaction of Sbenzyldithiocarbamate with phenacyl bromide was considered as a model reaction for optimization of the reaction conditions. We found that the best yield was obtained when equal amounts of dithiocarbamate and  $\alpha$ -bromoacetophenone were heated at reflux in water for 20 h without any catalyst. After quenching the reaction mixture with NaHCO<sub>3</sub>, the corresponding 4-phenyl-2benzylsulfanyl-thiazole was obtained by filtration or decanting. Also, we found that while  $\alpha$ -chloroacetophenone needed 2 days heating at reflux to reach completion,  $\alpha$ -bromoacetophenone needed only 20 h. Temperature screening revealed that the best yield was obtained at reflux.



**Scheme 1.** Catalyst-free synthesis of 2-alkylsulfanylthiazoles in water.

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#### Tetrahedron

#### Table 1. Synthesis of 2-(alkylsulfanyl)thiazoles in water

 $\begin{array}{c} O \\ R^{1} \\ \hline \\ R^{1} \\ \hline \\ R^{1} \\ = Ph, X = Br \\ \textbf{1b} R^{1} = Me, X = Cl \end{array} \xrightarrow{R^{2}} \begin{array}{c} H_{2}O \\ \hline \\ R^{2} \\ \hline \\ reflux, 20 h \\ \hline \\ reflux, 20 h \\ \hline \\ R^{1} \\ \hline \\ R^{1} \\ \hline \\ \\ R^{2} \\ \hline \\ R^{2} \\ \\ R^{2} \\ \hline \\ R^{2} \\ \\ R^$ 



<sup>a</sup>Isolated yield. <sup>b</sup>Reaction conditions: dithiocarbamate (5 mmol),  $\alpha$ -halocarbonyl (5 mmol), water (15 mL), reflux, 20 h.

After optimization of the reaction conditions, the generality of these conditions was examined using various Salkyldithiocarbamates and  $\alpha$ -halocarbonyl compounds (Table 1). 2-All dithiocarbamates gave high yields of (alkylsulfanyl)thiazoles using α-bromoacetophenone or αchloroacetone. The structures of the products were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and CHN analysis. The <sup>1</sup>H-NMR spectrum showed a singlet peak around 6.7-7.4 ppm which was related to the C-5 hydrogen of the thiazole ring. The <sup>13</sup>C NMR spectra clearly confirmed the product structure; the chemical shift for C-2 of the thiazole ring was assigned to approximately 165 ppm, while the C-4 and C-5 of the thiazole ring appeared around 155 ppm and 112 ppm, respectively.

After the successful synthesis of 2-(alkylsulfanyl)thiazoles, we expanded our investigation for the synthesis of these compounds *via* a one-pot, two-step procedure starting from acetophenone. For this purpose, acetophenone was initially converted to the phenacyl iodide using CuO/I<sub>2</sub> in ethanol at reflux, followed by the addition of *S*-alkyldithiocarbamates and further heating at reflux for 2 h. We observed that high yields were obtained using this protocol (Scheme 2). The second step of this reaction was complete in 2 h which confirmed that the reaction rate had been increased by increasing the leaving-group ability of the halogen.



**Scheme 2.** One-pot, two-step procedure for the synthesis of 2-alkylsulfanylthiazoles from acetophenone.

A proposed mechanism for this reaction is given in Scheme 3. It is conceivable that the initial event is nucleophilic substitution of the halide by the thiocarbonyl sulfur atom of dithiocarbamate 2 to afford intermediate A. Intramolecular addition of the nitrogen to the carbonyl group furnishes intermediate B, which then undergoes dehydration to afford the corresponding product 3.



Scheme 3. Proposed mechanism for the synthesis of thiazoles 3

In conclusion, an efficient, environmentally benign and high yielding procedure for the synthesis of 2-(alkylsulfanyl)thiazoles from the reaction of dithiocarbamates and  $\alpha$ -halocarbonyl compounds in water is described. Also, a one-pot two-step procedure for the synthesis of 2-(alkylsulfanyl)thiazoles from acetophenone and dithiocarbamates was developed. The reactivity of phenacyl halides in this protocol was assigned in order of phenacyl iodide>phenacyl bromide>phenacyl chloride.

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#### **Supplementary Material**

Supplementary data associated with this article can be found, in the online version, at ....

