A New One-pot Synthesis of Thiocarbamates from Isocyanates and Disulfides in the Presence of Zn/AlCl$_3$ System

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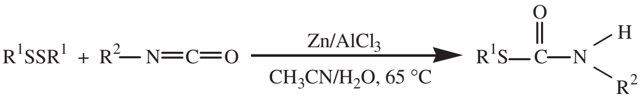
A novel method has been developed for the synthesis of *S*-alkyl(aryl) thiocarbamates. The route involves, first, the formation of zinc thiolates by reductive cleavage of disulfides in the presence of Zn/AlCl$_3$ system; then subsequent reaction of the thiolate anions with isocyanates gives the desired thiocarbamates in high to excellent yields.

Thiocarbamates, especially *S*-alkyl thiocarbamates, are an important class of compounds that have numerous biological effects ranging from fungicidal,[1,2] pesticidal,[3,4] anesthetic,[5] bactericidal,[6,7] and antiviral[8] activity; but, the most noted application of these compounds is their use as commercial herbicides[4,9] such as benthiocarb and orthobencarb.[10–13]

Classical methods for preparation of *S*-alkyl thiocarbamates illustrate the intramolecular rearrangement of various derivatives;[14] however, these rearrangements are extremely dependent upon starting substrates and the reaction conditions. They have also been prepared by acid catalysed hydration of alkyl and aryl thiocyanates; but, this method is limited to only N,N-unsubstituted thiocarbamates.[15] Several other methods have been reported for the preparation of this thiocarbamates; however, most require the preparation of complex starting materials and multistep approaches, among them: the reaction of alkyl chlorothioformate (RSCOCl, prepared from thiols and phosgene) with amines,[16] reaction of amines and thiols in the presence of carbon monoxide under $(PPh_3)_2NiBr_2$ and $(PPh_3)_2NiCl_2$ catalysts,[17] DBU-assisted carbonylation of amines with carbon monoxide and sulfur,[18] carbamoylation of thiols using carbamoyl imidazolium salts,[19] reaction of elemental sulfur with carbon monoxide and alkyl amines in the presence of a catalytic amount of selenium and subsequent addition of primary alkyl halides.[20] Condensation of thiols with isocyanates give the corresponding thiocarbamates.[21] Other groups[4,10] have prepared these compounds from condensation of gaseous carbonyl sulfide (COS) with a secondary amine in the presence of a base. N,N-Disubstituted *S*-alkyl thiocarbamates have also been prepared from salts of dithiocarbamic acid, which are prepared by the addition of secondary amines to carbon disulfide.[22] Recently, Wynne and co-workers[23] reported two approaches for the synthesis of *S*-alkyl thiocarbamates using trichloroacetyl chloride. Thiocarbamates have also been prepared from asymmetrical disulfides in two steps;[24] in the first step, disulfides were converted into the corresponding thiols, and finally the thiols reacted with isocyanates to afford thiocarbamates in good yields.

In connection with our ongoing work on Zn/AlCl$_3$ system, we now describe a new method for preparation of N-substituted-*S*-alkyl(aryl) thiocarbamates **3** which involves treatment of disulfides **1** and different isocyanates **2** promoted by cheap and reactive metallic zinc in the presence of AlCl$_3$ in CH_3CN–H_2O mixed solvent at 65 °C (Scheme 1).



1 **2** **3**

Scheme 1.

A series of symmetrical alkyl and aryl disulfides treated with various isocyanates in the presence of Zn/AlCl$_3$ system with a molar ratio of disulfide:AlCl$_3$:isocyanate = 0.5:1:1.5. The disappearance of zinc powder during the preliminary treatment of disulfides with Zn/AlCl$_3$ is attributed to the formation of zinc thiolate intermediate[25] which further undergoes nucleophilic attack to the isocyanate to afford the thiocarbamate in high to excellent yields.[26]

The results are summarized in Table 1. Reactions are very clean and thiocarbamates are obtained as a sole product during short times in high to excellent yields. The work-up of the reaction is accomplished by simple filtration and evaporation of the organic solvent (CH_3CN), and finally purification is involved.

In conclusion, this method is attractive since it offers some advantages over earlier reported protocols in that it avoids multistep procedures, and preparation of complex starting materials. Mild condition, short reaction time, and high isolated yields of the products are other advantages of this method.

Table 1. *N*-Substituted-*S*-alkyl (aryl) thiocarbamates **3a**–**3m**

Entry	R^1	R^2	Time /min	Product[a]	Yield /%[b]
1	Ph	Ph	40	**3a**[27]	90
2	p-MeC$_6$H$_4$	Ph	55	**3b**[27]	88
3	p-ClC$_6$H$_4$	Ph	35	**3c**[27]	93
4	CH_3	Ph	30	**3d**[18]	94
5	CH_3CH_2	Ph	35	**3e**[28]	92
6	CH_3	n-C$_4$H$_9$	45	**3f**[18]	91
7	CH_3CH_2	n-C$_4$H$_9$	45	**3g**[10]	90
8	$CH_3CH_2CH_2$	n-C$_4$H$_9$	25	**3h**[10]	92
9	n-C$_6$H$_{13}$	n-C$_4$H$_9$	50	**3i**[23]	89
10	CH_3CH_2	CH_3CH_2	40	**3j**[28]	91
11	$CH_3CH_2CH_2$	CH_3CH_2	30	**3k**[10]	93
12	n-C$_4$H$_9$	CH_3CH_2	25	**3l**[16]	95
13	$HOCH_2CH_2$	Ph	25	**3m**[29]	79

[a]References of the known compounds. [b]Isolated yields.

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26 General experimental procedure is as follows: A mixture of disulfide (0.5 mmol), zinc powder (2 mmol), anhydrous $AlCl_3$ (1 mmol), CH_3CN (10 mL), and H_2O (2.5 mL) were stirred at 65 °C for 1.5 h until the zinc powder disappeared; isocyanate (1.5 mmol) was then added at once to the solution and stirring was continued at that temperature for the specified time (Table 1). Progress of the reaction was monitored by TLC. After completion of the reaction, the solution was filtered and the solvent was evaporated in vacuo, and the residue was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The resulting crude product was purified by preparative TLC (silica, eluent, *n*-hexane:EtOAc = 4:1) to afford the desired thiocarbamate.

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