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Solvent-assisted thiocarboxylation of amines and alcohols with carbon monoxide and sulfur under mild conditions

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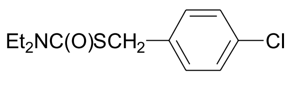
Abstract—DMSO or DMF as a solvent strongly accelerated the thiocarboxylation of amines and alcohols with carbon monoxide and sulfur. Under mild conditions (1 atm, 20 °C), this thiocarboxylation of amines assisted by DMSO with carbon monoxide and sulfur has been developed into a practical and convenient synthetic method for *S*-alkyl thiocarbamates in good to excellent yields, including EPTC, thiobencarb, orbencarb, and molinate (herbicides). DMF also showed the similar solvent effect. NMP slightly decreased the effect for the thiocarboxylation of amines, and the yield of *S*-alkyl thiocarbamate was lowered in DMAc. Surprisingly, no formation of *S*-alkyl thiocarbamate was observed at the use of the other solvents, such as THF, hexane, toluene, AcOEt, MeCN, MeOH, and H_2O. The present solvent-assisted thiocarboxylation with carbon monoxide and sulfur could be also applied to a new synthesis of *S*-alkyl *O*-alkyl carbonothioates from alcohols under mild conditions (1 atm, 20 °C) in DMF using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).

1. Introduction

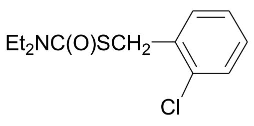
The development of useful and practical synthetic methods of *S*-alkyl thiocarbamates **1** is of importance, because a series of *S*-alkyl thiocarbamates is well known as useful herbicides, and these herbicides (e.g., EPTC (**1b**), thiobencarb (**1e**), orbencarb (**1f**), and molinate (**1m**)) have been produced in an industrial large-scale.[1–3]

$Pr_2NC(O)SEt$

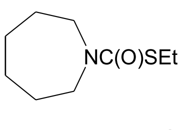
EPTC, **1b**



Thiobencarb, **1e**



Orbencarb, **1f**



Molinate, **1m**

Many methods for the synthesis of *S*-alkyl thiocarbamates **1** have been reported. Among them, the reaction of amines **2** with thiols and phosgene or with carbonyl sulfide, followed by alkylation with alkyl halides has been known as the general routes.[4–6] Indeed, *S*-alkyl thiocarbamate herbicides **1** are industrially produced two steps reaction, which includes the generation of carbonyl sulfide from carbon monoxide and sulfur under high temperature, and the reaction of carbonyl sulfide with amines **2** and alkyl halides.[2]

Direct thiocarboxylation of primary amines with carbon monoxide and sulfur to form urea derivatives was introduced by Monsanto group in 1961.[8–10] Furthermore, Grisley and Stephens developed *S*-alkyl thiocarbamate **1** synthesis from secondary amines, carbon monoxide, sulfur, and alkyl halides in similar manners.[11] However, these reactions require high temperature and pressurized carbon monoxide.

Our research group has found that selenium exhibits an excellent catalytic activity toward the thiocarboxylation of amines with carbon monoxide and sulfur in 1989. This selenium-catalyzed thiocarboxylation of amines **2** smoothly proceeded under mild conditions (1 atm, 30 °C) to give thiocarbamate salts **3**. Then, the alkylation of **3** by alkyl halides, led to the formation of *S*-alkyl thiocarbamates **1** in excellent yields.[12,13] Owing to the toxicity of elemental selenium, however, use of this preparative method was considerably limited for industrial production of herbicides.

Next, we also found a high-yield synthesis of *S*-alkyl thiocarbamate **1** by the reaction of carbamoyl lithiums, which were prepared in situ from lithium amides and carbon

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Keywords: *S*-Alkyl thiocarbamates; *S*-Alkyl *O*-alkyl carbonothioates; DMSO; DMF; Carbon monoxide; Sulfur; Thiocarboxylation.

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monoxide (1 atm) at low temperature (−78 °C), with elemental sulfur and alkyl halides, or disulfides.[14–16] However, this synthetic method may not be suitable for industrial production of *S*-alkyl thiocarbamate herbicide, because of the production cost of **1**.

Recently, we reported the thiocarboxylation of amines **2** with carbon monoxide and sulfur, assisted by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to provide *S*-alkyl thiocarbamates **1** in excellent yields in THF under mild conditions (1 atm, 20 °C).[17] But, this method also seemed to be not attractive for industrial production of *S*-alkyl thiocarbamate herbicides **1**, because of the price of DBU compared with inorganic bases, such as K_2CO_3. Furthermore, a more useful synthetic method for *S*-alkyl thiocarbamate herbicides **1** has been developed in 2004.[18] Under mild conditions (1 atm, 20 °C), in which the thiocarboxylation of amines **2** with carbon monoxide and sulfur was powerfully assisted by K_2CO_3 and DMSO as a solvent. However, still weak point of this procedure was the need of an excess amount of K_2CO_3 as a base.

Then, thiocarboxylation of alcohols **5** with carbon monoxide and sulfur to give *S*-alkyl carbonothioates **4** was also established by us, using base such as DBU[19–21] and triethylamine,[22,23] and selenium-catalyst.[24] However, these thiocarboxylation reactions from alcohols **5** proceeded under high temperature and pressurized carbon monoxide using an autoclave.

Therefore, in our strategy, we explored a new practical synthetic method to the *S*-alkyl thiocarbamates **1** including herbicides under mild conditions (1 atm, 20 °C) without using additional base, and useful route of *S*-alkyl *O*-alkyl carbonothioates (**4**) under similar mild conditions.

2. Results and discussion

Our trial employing DMSO or DMF as a solvent, which is cheap and commercially available, led to a successful thiocarboxylation of dipropylamine (**2a**) with carbon monoxide and sulfur without other base. Dipropylamine (**2a**) smoothly reacted with carbon monoxide (1 atm) and sulfur (1.0 equiv) at 20 °C for 5 h in DMSO solvent. Then, color of solution was changed from reddish black to green, the resulting thiocarbamate salt (**3a**) in DMSO solution was esterified by methyl iodide (1.2 equiv) under an ambient pressure at 20 °C for 1 h. Finally, *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) was obtained in 88% yield (Eq. 1) (Table 1, entry 1).

$$\underset{\mathbf{2a}}{2\,\mathrm{Pr_2NH}} + \mathrm{CO} + \mathrm{S} \xrightarrow[5\ \mathrm{h}]{\mathrm{DMSO}} \underset{\mathbf{3a}}{[\mathrm{Pr_2NH_2}]^+\,[\mathrm{Pr_2NC(O)S}]^-}$$

$$\text{1 atm, 20 °C}$$

$$\xrightarrow[1\ \mathrm{h}]{\mathrm{MeI}} \underset{\mathbf{1a},\ 88\%}{\mathrm{Pr_2NC(O)SMe}} \qquad (1)$$

To examine the influence of solvent on this thiocarboxylation of dipropylamine (**2a**) with carbon monoxide and sulfur, various solvents were screened (Table 1). When DMF was employed as a solvent for this thiocarboxylation, DMF also showed the similar solvent effect to afford *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) in good yields (82%) (entry 2). NMP used as solvent somewhat weakly accelerated the carboxylation of **2a** to give *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) in moderate yield (67%) (entry 3). In DMAc, the yield of **1a** was lowered (entry 4). In contrast, we surprisingly observed that the use of other solvents (THF, hexane, toluene, AcOEt, MeCN, MeOH, and H_2O) resulted in no formation of the desired **1a** at all (entries 5–11). Therefore, we believe that solvents are a predominant factor for reactivity of the present thiocarboxylation of amines with carbon monoxide and sulfur.

Table 1. Influence of solvent on the synthesis of *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**)

Entry	Solvent	Isolated yield[a]
1	DMSO	88
2	DMF	82
3	NMP	67
4	DMAc	30
5	THF	0
6	Hexane	0
7	Toluene	0
8	AcOEt	0
9	MeCN	0
10	MeOH	0
11	H_2O	0

[a] Reaction conditions: dipropylamine (2.74 mL, 20 mmol), sulfur (321 mg, 10 mmol), methyl iodide (0.75 mL, 12 mmol), solvent (20 mL), CO (1 atm), 20 °C, 5 h for carbonylation and 1 h for alkylation.

To demonstrate the efficiency and scope of the present method, a variety of *S*-alkyl thiocarbamates **1a–o** were synthesized from the corresponding amines **2a–j** and alkyl halides (Eq. 2, Table 2). Under 1 atm of carbon monoxide at 20 °C for 5 h in DMSO, ammonium salts of thiocarbamates **3a–j** were formed from amines **2a–j** with carbon monoxide and sulfur, followed by quenching by alkyl halides to afford the corresponding *S*-alkyl thiocarbamates **1a–o** in good to excellent yields.

$$\underset{\mathbf{2a\text{-}j}}{\mathrm{R^1R^2NH}} + \mathrm{CO} + \mathrm{S} \xrightarrow[\text{1 atm, 20 °C, 5 h}]{\mathrm{DMSO}} \underset{\mathbf{3a\text{-}j}}{[\mathrm{R^1R^2NH_2}]^+,\ [\mathrm{R^1R^2NC(O)S}]^-}$$

$$\xrightarrow[\text{20 °C, 1 h}]{\mathrm{R^3X}} \underset{\mathbf{1a\text{-}o}}{\mathrm{R^1R^2NC(O)SR^3}} \qquad (2)$$

Secondary amines **2a–c**, **2e–h** were suitable for this thiocarboxylation to provide *S*-alkyl thiocarbamates **1a–g**, **1i–m** in good to excellent yields under mild conditions (1 atm, 20 °C) (entries 1–8 and 10–14). Even in 10 times large scale, *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) was obtained in excellent yield (91%) for longer reaction time (entry 2). Furthermore, the chlorination of *S*-alkyl *N*,*N*-dialkylthiocarbamates **1** from secondary amines was successfully performed using sulfuryl chloride, to afford the corresponding carbamoyl chlorides in good yields (Eq. 3).[17]