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Synthesis of Thiocarbamates from Thiols and Isocyanates Under Catalyst- and Solvent-Free Conditions

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Summary. A simple and efficient procedure was developed for the synthesis of *S*-alkyl (aryl) thiocarbamates under solvent-free conditions without the use of a catalyst. The significant features of this protocol are (a) operational simplicity, (b) mild reaction conditions, (c) short reaction times, (d) solvent-free conditions, and (e) high product yields.

Keywords. Thiocarbamates; Thiols; Isocyanates; Solvent-free; Catalyst-free.

Introduction

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

S-Alkyl thiocarbamates have previously been prepared by reaction of carbamoyl chlorides with thiols in the presence of pyridine [14] or with alkali thiolates[15], or by reaction of alkyl chlorothioformate (*R*SCOCl) with amines [16]. They have also been prepared by acid catalyzed reaction of alcohols with alkyl and aryl thiocyanates [17]. Several other methods have been reported for the preparation of thiocarbamates; however, most require the preparation of complex starting materials and multistep approaches, among them: reaction of amines and thiols in the presence of carbon monoxide under $(PPh_3)_2NiBr_2$ and $(PPh_3)_2NiCl_2$ catalysts [18], *DBU*-assisted carbonylation of amines with carbon monoxide and sulfur [19], carbamoylation of thiols using carbamoyl imidazolium salts [20], reaction of elemental sulfur with carbon monoxide and alkyl amines in the presence of catalytic amount of selenium and subsequent addition of primary alkyl halides [21]. Other groups [2, 13] 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 isocyantes to afford thiocarbamates in good yields. In a recent report [25], we described a protocol for the synthesis of thiocarbamates from isocyanates and disulfides in the presence of the $Zn/AlCl_3$ system.

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Condensation of thiols with isocyanates under various catalytic (acidic or basic) conditions and solvents have been reported [26]. However, several disadvantages, such as long reaction times [26b, d, e], use of halogenated or harmful solvents [26a, b, e, f], low or high temperatures [26a, d, f], use of costly catalysts [26b, c], low to moderate yields [26b–d], *etc.* encountered in the reported methodologies necessitate the development of a more efficient and convenient method.

In practice, from an ecological point of view, the best solvent is without a doubt no solvent. There are of course many reactions that can already be carried out in the absence of solvent. Reports on solvent-free reactions have, however, become increasingly frequent and specialized over the past few years. Areas of growth include reactions between solids [27], between gases and solids [28], and on supported inorganic reagents [29], which in many cases are accelerated or even made possible through microwave irradiation [30]. There are also reactions in which at least one reactand is liquid under the conditions employed, which means that the solvent that would normally be used can simply be left out.

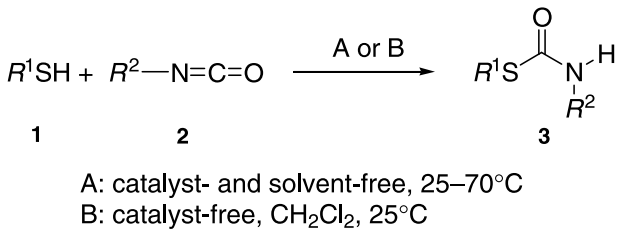
Although there are several examples for synthesis of thiocarbamates from isocyanates and thiols, to the best of our knowledege no study has been made under solvent- and catalyst-free conditions with a view to developing a practical methodology.

Results and Discussion

In continuation of our interest on solvent-free reactions [31], we wish to report herein a mild, clean, simple, and highly efficient uncatalyzed method for preparation of thiocarbamates from isocyanates and thiols under neat and solution conditions (Scheme 1).

The experimental procedure for the reaction is very simple: an equimolar amount of isocyanate was added to liquid or molten thiol at 25–70°C and was stirred at that temperature for 1–300 min as required to complete the reaction (monitored through TLC). The reaction was directly subjected to preparative TLC to furnish the pure product.

A series of aromatic thiols (containing electron-withdrawing and electron-releasing groups) as well as aliphatic thiols and different isocyanates were used (Table 1). The structures of all the products were established from their physical and spectral (IR, ^{1}H, and ^{13}C NMR) properties. The reaction of aromatic thiols and different isocyanates are in gen-



Scheme 1

Table 1. Synthesis of *S*-aryl (alkyl) thiocarbamates under catalyst-free conditions

Entry	R^1	R^2	Product	Solvent-free[a]		CH_2Cl_2[b]
				t/°C	Time/min (yield[c]/%)[d]	Time/min (yield[c]/%)
1	*Ph*	*cyhex*	*Ph*SCONH*cyhex*	25	1 (92) [17]	40 (98)
2	4-ClC_6H_4	*cyhex*	4-ClC_6H_4SCONH*cyhex*	55	8 (89) [17]	15 (81)
3	4-$CH_3C_6H_4$	*cyhex*	4-$CH_3C_6H_4$SCONH*cyhex*	45	4 (92) [17]	50 (96)
4	4-*Br*C_6H_4	*cyhex*	4-*Br*C_6H_4SCONH*cyhex*	70	6.5 (86) [16]	15 (91)
5	*n*-C_8H_{17}	*cyhex*	*n*-C_8H_{17}SCONH*cyhex*	25	300 (82) [17]	300 (75)
6	*n*-C_6H_{13}	*cyhex*	*n*-C_6H_{13}SCONH*cyhex*	25	270 (85) [17]	270 (71)
7	*Ph*	*Et*	*Ph*SCONH*Et*	25	90 (96) [32]	90 (91)
8	*Ph*	*n-Bu*	*Ph*SCONH*n-Bu*	25	90 (91) [32]	90 (86)
9	*Ph*	*Ph*	*Ph*SCONH*Ph*	45	35 (91) [25]	60 (74)
10	4-$CH_3C_6H_4$	*Ph*	4-$CH_3C_6H_4$SCONH*Ph*	45	50 (93) [25]	80 (81)
11	4-ClC_6H_4	*Ph*	4-ClC_6H_4SCONH*Ph*	55	30 (72) [25]	60 (88)
12	4-*Br*C_6H_4	*Ph*	4-*Br*C_6H_4SCONH*Ph*	70	32 (80) [25]	60 (80)

[a] All reaction were carried out using equimolar amounts of thiols and isocyanates without a solvent at 25–70°C
[b] All reaction were carried out using equimolar amounts of thiols and isocyanates (1 mmol) in 0.3 cm^3 CH_2Cl_2 at 25°C
[c] Isolated yield
[d] References for known compounds

eral fast (1–90 min) and clean, and thiocarbamates are obtained as the sole product in high to excellent yields. In the cases of aliphatic thiols (entries 5 and 6, Table 1) longer reaction times are required. In some cases, higher (>25°C) temperatures were needed to dissolve the solid thiols. The treatment of aromatic thiols with aliphatic (cyclohexyl) isocyanate (entries 1–4, Table 1) are much faster than those with aromatic (phenyl) isocyanate (entries 9–12, Table 1); this is due to the lower reactivity of phenyl isocyanate toward nucleophiles (thiols) compared to cyclohexyl isocyanate. The treatment of aromatic thiols containing an electron-releasing group, *e.g.*, 4-methylthiophenol, with isocyanates (entries 3 and 10, Table 1) gave higher yields than those bearing an electron-withdrawing group.

In order to compare the results with those obtained in solution, we studied the above reaction in a minimum amount (0.3 cm^3 per 1 mmol of substrate) of dichloromethane (CH_2Cl_2). As shown in the Table, there are appreciable differences, both in reaction times and/or isolated yields, between the results obtained in solution and those in neat conditions. Thus, by omitting the solvent, in addition to the ease of the work-up procedures, the reaction time was significantly reduced and thus, the need for solvent is avoided.

In conclusion, the present catalyst- and solvent-free procedure provides a powerful and versatile method for the preparation of *S*-aryl (alkyl) thiocarbamates. This method is endowed with several unique merits, namely, simplicity in operation, mild reaction conditions, avoiding hazardous organic solvents, toxic and expensive reagents, short reaction times, and high product yields. This environmentally benign process represents a suitable option to existing methods.

Experimental

All products were characterized by comparison of their spectral and physical data with those of known samples. IR spectra were obtained using an ABB FTLA 2000 instrument. NMR spectra were recorded on a Bruker AQS 300 Avance instrument at 300 MHz for ^1H and at 75 MHz for ^{13}C NMR in $CDCl_3$ solutions. Melting points and boiling points were determined by a Büchi B-540 melting point/boiling point capillary apparatus.

Typical Procedure Exemplified by the Preparation of S-4-Methylphenyl N-cyclohexylthiocarbamate ($C_{14}H_{19}NOS$) under Solvent-Free Conditions

Cyclohexyl isocyanate (1.0 mmol, 125 mg) was added to 124 mg molten (45°C) 4-methylthiophenol (1 mmol) and the whole mixture was stirred at 45°C (oil bath) for 4 min as indicated by TLC for a complete reaction. The reaction mixture was then allowed to cool at room temperature, followed by preparative TLC of the crude product over silica gel plate (EtO*Ac*:*n*-hexane = 1:4) to afford 229 mg of the pure thiocarbamate (92%) as colorless crystals, mp 125–126°C (Ref. [17] mp 125°C).

Typical Procedure Exemplified by the Preparation of S-4-Methylphenyl N-cyclohexylthiocarbamate in Dichloromethane

To 124 mg 4-methylthiophenol (1.0 mmol) dissolved in 0.3 cm^3 CH_2Cl_2 was added 125 mg cyclohexylisocyanate (1.0 mmol), and the mixture was stirred for 50 min at 25°C. After completion of the reaction (monitored by TLC), the solvent was evaporated *in vacuo* and the crude product was purified by preparative TLC (silica gel, eluent *Et*O*Ac*:*n*-hexane = 1:4) to obtain 239 mg (96%) of the pure thiocarbamate.

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