An Efficient, One-Pot Synthesis of *S*-Alkyl Thiocarbamates from the Corresponding Thiols Using the Mitsunobu Reagent

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Abstract: A novel Mitsunobu-based protocol has been developed for the synthesis of variety of *S*-alkyl thiocarbamates from the corresponding thiols and amines using gaseous carbon dioxide, in good to excellent yields. This protocol is mild and efficient compared to other reported methods.

Key words: thiols, carbon dioxide, Mitsunobu reagent, thiocarbamates

S-Alkyl thiocarbamates (*S*-alkylthiourethanes) constitute an important and versatile class of compounds for a variety of industrial, synthetic and medicinal applications.[1] They have been extensively used as pharmaceuticals,[2] agrochemicals,[3] intermediates in organic synthesis,[4] for the protection of amino groups in peptide chemistry[5] and as linkers in combinatorial chemistry.[6] Despite the aforementioned reasons, these compounds are most noted for their use as commercial herbicides. Some of the potent herbicides such as Thiobencarb,[7] Orbencarb,[8] EPTC[9] and Molinate[10] are well-known examples. These compounds require preparation by convenient and safe methodologies.

Classical synthesis of *S*-alkyl thiocarbamates involves a two-step reaction using phosgene,[11] its derivatives[12] and carbon monoxide.[13] These methods are associated with several drawbacks, such as the use of costly, toxic and corrosive reagents. Many reports illustrate the intramolecular rearrangement of various derivatives to afford *S*-alkyl thiocarbamates, however, these rearrangements are extremely limited in starting substrates.[14] Transition-metal species containing elements such as palladium,[15] nickel[16] and rhodium[17] have also been employed to promote rearrangement and product formation. There are a variety of other methods, however, most require the preparation of complex starting materials.[18] Thus, most of these methods suffer from limitations such as long reaction times, use of expensive, strongly basic reagents, tedious work-up and low yields. Consequently, there is continuing interest in the development of new and convenient methods for the synthesis of *S*-alkyl thiocarbamates using mild reaction conditions.

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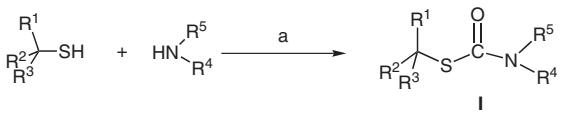
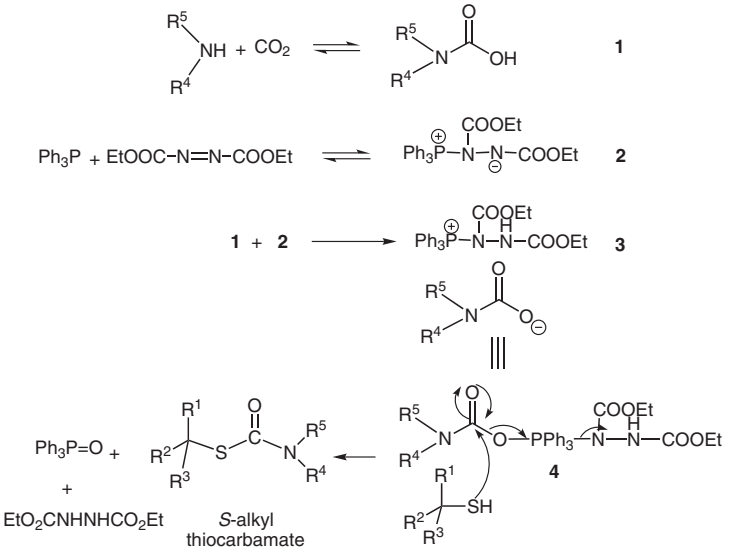
Our group[19] has been engaged over several years in the development of new and efficient protocols for the synthesis of carbamates, dithiocarbamates and dithiocarbonates (xanthates) using cheap and abundantly available reagents such as carbon dioxide and carbon disulfide. Recently, we reported[20] the synthesis of carbamates, dithiocarbamates, carbonates and *O*,*S*-dialkyl dithiocarbonates (xanthates) from the corresponding alcohols using the Mitsunobu reagent, diethyl azodicarboxylate (DEAD). Based on our recent work,[20] we report herein a chemoselective, highly efficient and mild synthesis of *S*-alkyl thiocarbamates of primary, secondary and tertiary thiols using the Mitsunobu reagent.

We carried out the synthesis of *S*-alkyl thiocarbamates by mild thiocarbamation of amines with gaseous carbon dioxide using a variety of primary secondary and tertiary thiols mediated by the Mitsunobu reagent at room temperature. We assume that the unstable carbamic acid **1**, generated from an amine with carbon dioxide, reacts with zwitterion **2**, formed from triphenylphosphine and DEAD, to furnish the unstable ionic species **3** which, in turn, would undergo a self rearrangement to form the more stabilized ionic species **4**. Nucleophilic attack of the sulfur atom from the corresponding thiol, followed by intramolecular electronic rearrangement leads to the formation of the thiocarbamate as shown in Scheme 1.



Scheme 1 Proposed mechanism of the formation of *S*-alkylthiocarbamates

Thus, various primary and secondary amines were reacted with a range of primary, secondary and teriary thiols using the DEAD/CO_2 system to afford the thiocarbamates in very good to excellent yields (80–99%) at room temperature in two to four hours (Table 1). We examined many solvents such as dimethyl sulfoxide, *N*,*N*-dimethylformamide, benzene, acetonitrile, dichloromethane, hexane, heptane, methanol, chloroform and acetone, and found that anhydrous dimethyl sulfoxide proved to be the most suitable solvent for carrying out this transformation. The overall reaction is shown in Scheme 2.



Scheme 2 *Reagents and conditions*: (a) DMSO (anhyd), DEAD, Ph_3P, CO_2, r.t., 2–4 h.

Table 1 Conversion of Thiols into *S*-Alkyl Thiocarbamates of General Formula **I**[a]

Entry	R^1	R^2	R^3	R^4	R^5	Time (h)	Isolated yield (%)
1	Ph	H	H	*n*-Pr	*n*-Pr	3	96
2	4-$MeOC_6H_4$	H	H	Et	Et	3	99
3	4-ClC_6H_4	H	H	-$(CH_2)_4$-		3	98
4	*n*-C_5H_{11}	H	H	*n*-Bu	H	2.5	99
5	*n*-C_7H_{15}	H	H	Et	Et	3	99
6	*i*-C_5H_{11}	H	H	-$(CH_2)_5$-		3	94
7	Ph	Me	H	-$(CH_2)_2O(CH_2)_2$-		3.5	96
9	*n*-Bu	*n*-Bu	H	4-$MeOC_6H_4$	H	3.5	85
10	*n*-Bu	*n*-Bu	*n*-Bu	*n*-C_8H_{17}	H	4	80
11	*n*-C_6H_{13}	H	H	Bn	H	3	94
12	*n*-C_7H_{15}	Me	H	*n*-$C_{12}H_{23}$	H	3	85
13	*n*-C_8H_{17}	H	H	$PhCH_2CH_2$	H	2.5	96
14	*n*-C_7H_{15}	H	H	*n*-Bu	*n*-Bu	2.5	98
15	*n*-C_5H_{11}	Me	H	*c*-C_6H_{11}	H	4	90
16	(2-$C_{10}H_7$)OCH_2CH_2	H	H	*n*-C_8H_{17}	H	3	86
17	(2-$C_{10}H_7$)$OCH_2CH_2CH_2$	H	H	*n*-$C_{12}H_{23}$	H	2	92
18	*n*-C_6H_{13}	Me	Me	Bn	H	4	93
19	*n*-$C_{10}H_{21}$	H	H	*c*-C_6H_{11}	H	3	99

[a] All products were characterized by IR, NMR and mass spectral data.

In conclusion, we have developed a convenient and efficient protocol for one-pot, three-component coupling of a range of amines with primary, secondary and tertiary thiols via a combination of DEAD and CO_2. This reaction generates the corresponding *S*-alkyl thiocarbonates in excellent yields (80–99%) at room temperature. Furthermore, this method exhibits substrate versatility, mild reaction conditions and experimental convenience. This synthetic protocol is believed to offer a more general method for the formation of C–S and C–N bonds essential to numerous organic syntheses.

Chemicals were procured from Merck, Aldrich and Fluka chemical companies. Reactions were carried out under an atmosphere of N_2. IR spectra were recorded on Bomem MB-104–FTIR spectrophotometer, and NMR spectra were obtained on an AC-300F instrument [^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz)], using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded using a Bruker Esquire 3000 spectrometer.

General Procedure

Amine (7.56 mmol) was taken in anhydrous DMSO (25 mL) and gaseous CO_2 was bubbled through at r.t. for 30 min. To this, a mixture of Ph_3P (7.56 mmol) and DEAD (7.56 mmol) was added slowly in 2–3 small portions. The corresponding thiol (7.56 mmol) was then added at r.t. with constant stirring and the reaction was allowed to continue until completion (Table 1; reaction monitored by TLC). The reaction mixture was then poured into distilled H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was separated and dried over anhydrous $NaSO_4$ and then concentrated to afford the desired *S*-alkylated thiocarbamate.

***S*-Benzyl *N*,*N*-Dipropylthiocarbamate (Entry 1)**

Oil.

IR (neat): 2965, 1650, 1405, 1220, 1125 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7 Hz, 6 H), 1.60 (q, *J* = 7 Hz, 4 H), 3.22 (br s, 2 H), 3.32 (br s, 2 H), 4.15 (s, 2 H), 7.22–7.36 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 21.6, 34.7, 49.3, 127.0, 128.5, 128.9, 138.3, 167.2.

MS (EI, 70 eV): *m*/*z* (%) = 251 (50), 128 (100), 92 (21), 91 (97), 86 (51).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{14}H_{21}NOS$: 251.1344; found: 251.1328.

***S*-(4-Methoxybenzyl) *N*,*N*-Diethylthiocarbamate (Entry 2)**

Oil.

IR (neat): 2975, 1650, 1515, 1405, 1250, 1115 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7 Hz, 6 H), 3.37 (br s, 4 H), 3.78 (s, 3 H), 4.11 (s, 2 H), 6.83 (d, *J* = 8 Hz, 2 H), 7.27 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 34.0, 41.9, 55.2, 113.9, 130.0, 130.2, 158.6, 166.8.

MS (EI, 70 eV): *m*/*z* (%) = 253 (98), 121(100), 100 (60), 72 (29).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{13}H_{19}NO_2S$: 253.1137; found: 253.1141.

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