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An efficient, one-pot, synthesis of dithiocarbamates from the corresponding alcohols using Mitsunobu's reagent

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Abstract—A Mitsunobu-based protocol has been developed for the synthesis of dithiocarbamates from the corresponding alcohols using carbon disulfide and amines in good to excellent yields. This protocol is mild, chemoselective and efficient compared to other reported methods.

Organic dithiocarbamates have received much attention due to their interesting chemistry and wide utility. They have been used extensively as pharmaceuticals,[1] agrochemicals,[2] and intermediates in organic synthesis,[3] for the protection of amino groups in peptide synthesis,[4] as linkers in solid phase organic synthesis,[5] as radical precursors[6] and recently in the synthesis of ionic liquids.[7] These uses require their preparation by a convenient and safe methodology. The classical synthesis of dithiocarbamates involves the use of thiophosgene[8] and its substituted derivatives,[9] which are costly and toxic reagents. Moreover, their formation using CS_2 employs harsh reaction conditions such as the use of strong bases, high reaction temperatures and long reaction times.[10] Our group[11] has been engaged over several years on the development of new methodologies for the synthesis of carbamates and dithiocarbamates using cheap and safe reagents like CO_2 and CS_2, respectively. Recently, we reported[12] the synthesis of carbamates from the corresponding alcohols using Mitsunobu's reagent. Taking this last report as a guide, we report herein a chemoselective, highly efficient and mild synthesis of *N*-alkyl/aryl dithiocarbamates of primary, secondary and tertiary alcohols using Mitsunobu's reagent.

In our carbamate synthesis,[12] a reaction temperature of 90–100 °C was required. Due to the higher reactivity of CS_2 compared to CO_2 the reaction was tried at room temperature and the desired product was indeed obtained.

Thus, we carried out[13] the synthesis of dithiocarbamates by mild thiocarbamation of amines with carbon disulfide and an alcohol in the presence of Mitsunobu's reagent.

We assume that the unstable dithiocarbamic acid **1** generated from the amine and CS_2 reacts with the Mitsunobu zwitterion **2** formed from Ph_3P and diethyl azodicarboxylate, to furnish the stabilized zwitterionic species **3** which in turn undergoes S-alkylation giving rise to the formation of the dithiocarbamate ester as shown in Scheme 1.

Thus, aliphatic/aromatic amines (primary and secondary) were reacted with various alcohols (primary, secondary and tertiary) using Mitsunobu's reagent and carbon disulfide solution in dry dimethylsulfoxide (DMSO) at room temperature for 2–3 h, to afford dithiocarbamates in good to excellent yields (80–98%) as shown in Table 1. We examined several solvents such as *n*-heptane, *n*-hexane, DMSO, DMF and HMPA of which dry DMSO proved to be the most suitable. The overall reaction is shown in Scheme 2.

In conclusion, we have developed a convenient and efficient protocol for the one-pot, four component coupling of various aliphatic/aromatic amines with a variety of primary, secondary and tertiary alcohols via a Mitsunobu zwitterion. This highly chemoselective reaction

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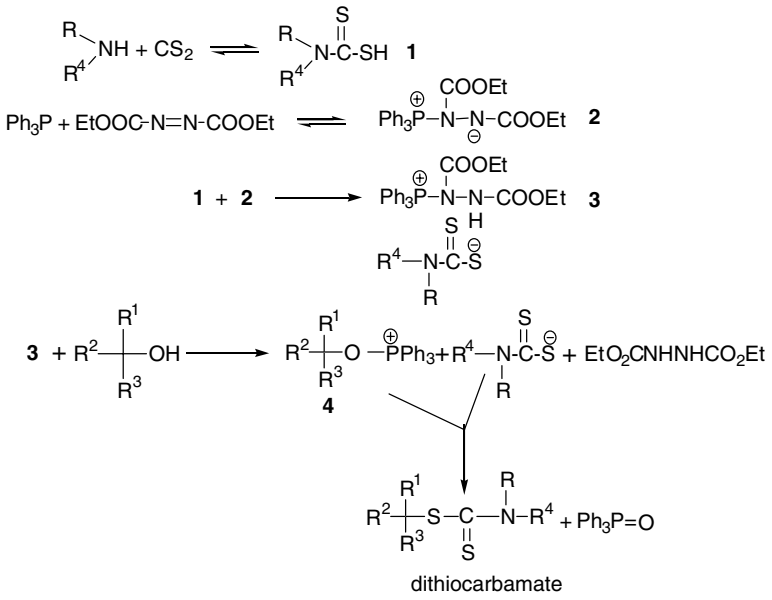
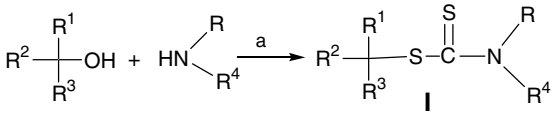


Scheme 1. Proposed mechanism of formation of the dithiocarbamates.

Table 1. Conversion of alcohols into dithiocarbamates of general formula **I**

Entry	R^1	R^2	R^3	R	R^4	Time (h)	Yields (%)
1	Benzyl	H	H	*n*-Butyl	H	2.5	94
2	2-Phenethyl	H	H	*n*-Hexyl	H	2	97
3	2-Phenethyl	H	H	*n*-Propyl	*n*-Propyl	2.5	86
4	*n*-Propyl	H	H	*n*-Octyl	H	2	96
5	*i*-Amyl	H	H	Cyclohexyl	H	2.5	85
6	*n*-Butyl	H	H	*n*-Butyl	H	2	90
7	2-Naphthyloxyethyl	H	H	$R\&R^4$ = morpholinyl		2.5	85
8	2-Naphthyloxyethyl	H	H	$R\&R^4$ = pyrrolidinyl		2.5	83
9	*n*-Butyl	*n*-Butyl	H	*n*-Octyl	H	2.5	84
10	*n*-Butyl	*n*-Butyl	*n*-Butyl	*n*-Dodecyl	H	2.5	81
11	*n*-Hexyl	H	H	Phenyl	H	3	80
12	*n*-Heptyl	H	H	Benzyl	H	2.5	83
13	*n*-Octyl	H	H	3-Methoxybenzyl	H	2.5	89
14	*n*-Heptyl	H	H	*n*-Dodecyl	H	2	98
15	*n*-Pentyl	Methyl	H	Cyclohexyl	H	2.5	90
16	2-Naphthyloxyethyl	H	H	*n*-C_4H_9	H	2.5	86
17	3-(2-Naphthyloxy)prop-1-yl	H	H	*n*-Octyl	H	2	95

All the products were characterized by IR, NMR and mass spectral data.



Scheme 2. Reagents and conditions: (a) dry DMSO, DEAD/Ph_3P, CS_2, rt.

generates the corresponding dithiocarbamates in high yields without direct N-alkylation. Furthermore, this method exhibits substrate versatility, mild reaction conditions and experimental convenience. This synthetic protocol developed in our laboratory is believed to offer a more general method for the formation of C–S bonds, essential in numerous organic syntheses.

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13. Typical experimental procedure: 2-phenylethyl *n*-butyl dithiocarbamate: *n*-Butylamine (0.83 ml, 9 mmol) and CS_2 (4 ml, in excess) were dissolved in dry DMSO (35 ml). To the reaction mixture, triphenylphosphine (2.2 g, 9 mmol) was added and then diethyl azodicarboxylate (1.33 ml, 9 mmol) was added slowly in 2–3 small portions. Next, 2-phenylethyl alcohol (1 ml, 9 mmol) was added. The reaction mixture was stirred until completion (2.5 h) as checked by TLC. The reaction mixture was then poured into distilled water (50 ml) and extracted with ethyl acetate thrice. The organic layer was separated and dried over anhydrous sodium sulfate and then concentrated to obtain 2-phenylethyl *n*-butyl dithiocarbamate (1.94 g, 94%), mp: 70 °C, IR (KBr, cm^{-1}): 649 (C–S), 1086 (C=S), 1467 (Ar), 2884 (CH), 2927 (CH), 3398 (NH). ^1H NMR ($CDCl_3$): $\delta = 0.89$–0.96 (t, 3H, $J = 7.1$ Hz, CH_3), 1.28–1.34 (m, 2H, CH_2CH_3), 1.54–1.57 (m, 2H, $CH_2CH_2CH_3$), 2.0 (br, H, N*H*), 2.63–2.65 (m, 2H, CH_2NH), 3.18–3.20 (t, 2H, $PhCH_2CH_2$), 3.23–3.25 (t, 2H, $J = 6.3$ Hz, $PhCH_2$), 7.08–7.21 (m, 5H, Ar-H) ppm; Mass: *m*/*e* 253 (95%). Analysis: $C_{13}H_{19}NS_2$, calcd: C, 61.61; H, 7.56; N, 5.53; found: C, 61.89; H, 7.42; N, 5.39.