Waste-Free and Environment-Friendly Uncatalyzed Synthesis of Dithiocarbamates under Solvent-Free Conditions

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Abstract: A mild, convenient, and practical one-pot procedure for the direct synthesis of dithiocarbamates has been developed by condensation of amines, CS_2, and a Michael acceptor, under solvent-free conditions at room temperature in good to excellent yields.

Key words: amines, dithiocarbamates, solvent-free, carbon disulfide, waste-free

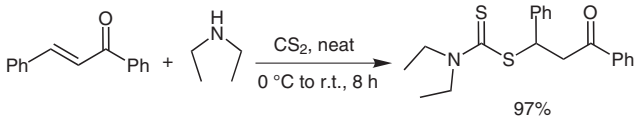
The development of solvent-free organic synthetic methods has become an important research area, since it preserves the environment and develops procedures that are both environmentally and economically feasible.[1] Among the most promising ways to reach this goal, solvent-free techniques hold a strategic position, since solvents are very often toxic, expensive, and problematic to use and to remove after the reaction. So it is the main reason for the development of such techniques, especially in the context of current green chemistry.[2]

Dithiocarbamates are ubiquitous in many biologically important compounds,[3] and have a variety of applications in agriculture[4] as pesticides, as well as in the rubber industries as vulcanization accelerators and antioxidants.[5] Because they have strong metal-binding capacity, they can act as inhibitors of enzymes and have a profound effect on biological systems, and are widely used in medicinal chemistry and cancer treatment.[6] The biological activities of dithiocarbamates are increased when they are in the form of heavy-metal salts as versatile classes of ligands with the ability to stabilize transition metals in a wide range of oxidation states and efficient ligands in surface science and nanomaterial chemistry.[7]

Therefore, the syntheses of biologically important thiocarbamates have received considerable attention, and there are few reports for the synthesis of dithiocarbamate derivatives in the literature. Among them, reaction of amine with costly and toxic reagents, such as thiophosgene and isothiocyanate, is reported as a general route.[8] A one-pot reaction of amines with carbonyl sulfide and Michael acceptor in organic solvent has also been developed.[9] However, many isothiocyanates are hazardous and tedious to prepare and display poor long-term stability and they are associated with formation of side products such as urethane in alcoholic medium. Furthermore, their reactions require toxic reagents and harmful organic solvents such as DMF and DMSO with limited substrate and moderate yields.

In continuation of our research interest for developing green organic chemistry by using water[10] as reaction medium or by performing organic transformations under solvent-free conditions,[11] recently, we have reported the use of water as reaction medium and activator to produce dithiocarbamate in efficient manner, from amine, CS_2, and enones.[10b] Although this methodology is very mild and novel, the yields are low and in a few cases organic solvent was used. We have decided to investigate an alternative synthesis of dithiocarbamates by performing the process in the absence of any organic solvent.

As a model reaction, chalcone was reacted with CS_2 and diethyl amine with different loading of starting materials. It was found that by simple mixing of chalcone (4 mmol), CS_2 (5 mmol) and diethyl amine (4.5 mmol), the corresponding dithiocarbamate was afforded in 97% yield (Scheme 1).



Scheme 1

To explore the scope of this new three-component coupling, we investigated different amines and Michael acceptor. This procedure is quite general, and a wide range of structurally varied amines such as primary, allylic, benzylic, hindered and unhindered secondary and tertiary alkyl primary amines were used in this protocol with excellent results. Generally, secondary amines such as pyrrolidine, piperidine, and diethylamine show higher yields compared with the primary amines. Primary amines such as benzylamine and *n*-butylamine, *sec*-butylamine and hindered amine such as *tert*-butylamine undergo efficient addition with Michael acceptors to give the correspondinding dithiocarbamate with excellent results. However, aromatic amines such as aniline did not participate in this reaction and give the corresponding products in very low yields (Table 1). With regard to Michael acceptors, the reactions proceeded smoothly with electron-

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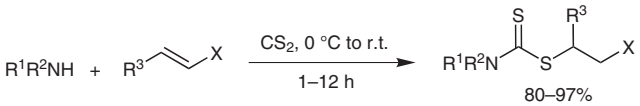
deficient olefins such as methyl vinyl ketone, chalcone, methyl acrylate, and acrylonitrile to afford the corresponding Michael adducts in good to excellent yields.

Table 1 One-Pot Synthesis of Dithiocarbamates Under Solvent-Free Conditions[13]



X = COOMe, COPh, COMe, $CONH_2$, CN

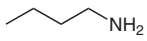
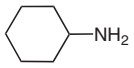
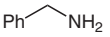
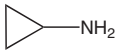
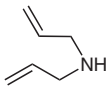
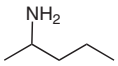
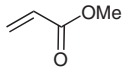
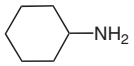
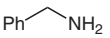
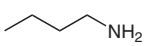
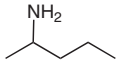
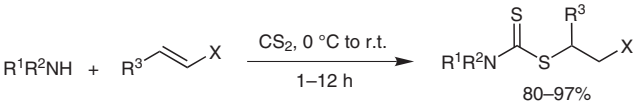
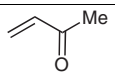
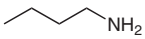
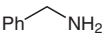
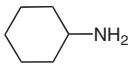
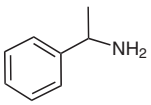
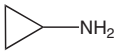
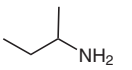
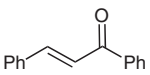
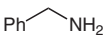
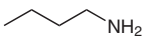
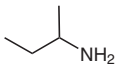
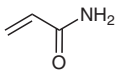
Entry	Michael acceptor	Amine (R^1R^2NH)	Yield (%)
1			97
2			90
3			97
4			84
5			90
6			80
7			84
8			90
9			80
10			84
11			97
12			94
13			97
14			82
15			85
16			92
17			88
18			78

Table 1 One-Pot Synthesis of Dithiocarbamates Under Solvent-Free Conditions[13] (continued)



X = COOMe, COPh, COMe, $CONH_2$, CN

Entry	Michael acceptor	Amine (R^1R^2NH)	Yield (%)
19			90
20			82
21			92
22			82
23			76
24			76
25			94
26			84
27			92
28			96
29			92
30			92
21			80
32			84
33			80
34			90
35			84
36			82
37		$PhNH_2$	12

Generally, the reaction is experimentally simple and proceeding well under solvent-free conditions without using a catalyst at room temperature and generating virtually no byproducts. This methodology is compatible with various α,β-unsaturated ketones, esters, nitriles, amides, and different substituted amines under mild reaction conditions. Equally important is the wide scope, high selectivity, and nearly quantitative yields of this transformation, which lead to significant structural diversity in the products, that is not possible with the older procedures.

In summary, we have described a novel system that is quite effective and entirely green procedure for the synthesis of dithiocarbamates at room temperature. The mild reaction conditions, enhanced reaction rates, clean reaction profiles, operational and experimental simplicity, and with options of further transformations of the resulting dithiocarbamates into synthetically interesting biologically active compounds, this synthetic methodology is ideally suited for automated applications in organic synthesis.

General Procedure for the One-Pot Reaction of Amines, CS_2, and Michael Acceptor Under Solvent-Free Conditions

Amine (4.5 mmol) was added slowly to the mixture of CS_2 (5 mmol) and the Michael acceptor (4 mmol) into a test tube in an ice bath[12] and the reaction mixture was stirred at 0 °C for 30 min. Then, the mixture was warmed to r.t. and stirred for another 1–12 h. After completion of the reaction, the excess of CS_2 and amine was removed under reduced pressure to give the dithiocarbamates in the almost pure form. The crude product was analyzed by ^{1}H NMR and ^{13}C NMR. In some cases, further purification was carried out by recrystallization or short-column chromatography on silica gel (EtOAc–PE). All compounds were characterized on the basis of NMR spectroscopic data (in the case of primary amines, the ^{1}H NMR spectra shows mixture of *E*- and *Z*-isomers).

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(12) The reaction was very exothermic and should be controlled by slow addition of amine and maintaining the temperature by using an ice bath.

(13) **Selected Spectroscopic Data**

Table 1, Entry 1: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92–0.96 (6 H, m), 2.53 (2 H, t, *J* = 6.7 Hz), 3.12 (2 H, t, *J* = 6.2 Hz), 3.42 (2 H, q, *J* = 6.7 Hz), 3.67 (2 H, t, *J* = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.4, 11.7, 18.2, 32.0, 47.2, 49.9, 118.6, 192.7.

Table 1, Entry 2: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30–1.51 (6 H, m), 2.74 (2 H, t, *J* = 6.2 Hz), 3.39 (2 H, t, *J* = 6.3 Hz), 3.75 (2 H, m), 4.12 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 25.9, 32.2, 51.9, 53.4, 54.2, 118.7, 193.0. Anal. Calcd (%) for $C_9H_{14}N_2S_2$: C, 50.43; H, 6.58; N, 13.07. Found: C, 50.80; N, 12.92; H, 6.62.

Table 1, Entry 3: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72–1.92 (4 H, m), 2.66 (2 H, t, *J* = 6.5 Hz), 3.29 (2 H, t, *J* = 6.5 Hz), 3.43 (2 H, t, *J* = 6.7 Hz), 3.64 (2 H, t, *J* = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.6, 24.5, 26.2, 31.6, 51.1, 53.9, 55.5, 118.7, 190.0. Anal. Calcd for $C_8H_{12}N_2S_2$: C, 47.97; H, 6.04; N, 13.98. Found: C, 48.30; H, 5.82, N, 13.69.

Table 1, Entry 7: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.82 (2 H, t, *J* = 6.2 Hz), 3.46 (2 H, t, *J* = 6.3 Hz), 4.88 (2 H, s), 7.26–7.39 (5 H, m), 8.02 (1 H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.9, 31.4, 51.5, 119.0, 128.3, 128.8, 129.7, 136.5, 196.0.

Table 1, Entry 10: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (3 H, t, *J* = 7.3 Hz), 1.07 (3 H, d, *J* = 6.4 Hz), 1.41–1.51 (4 H, m), 2.65 (2 H, t, *J* = 6.6 Hz), 3.35 (2 H, *J* = 6.7 Hz), 4.37–4.38 (1 H, m), 7.73 (1 H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.8, 18.5, 19.4, 29.7, 31.1, 55.1, 55.2, 119.1, 194.3.

Table 1, Entry 11: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93–0.99 (6 H, m), 2.47 (2 H, t, *J* = 6.4 Hz), 3.20 (2 H, t, *J* = 6.5 Hz), 3.44 (3 H, s), 3.45 (2 H, q, *J* = 6.9 Hz), 3.70 (2 H, q, *J* = 6.9 Hz). ^{13}C NMR (125 MHz; $CDCl_3$): δ = 11.7, 12.9, 31.7, 33.9, 46.9, 49.6, 51.6, 171.9, 194.4.

Table 1, Entry 12: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41–1.47 (6 H, m), 2.53 (2 H, t, *J* = 6.4 Hz), 3.42–4.01 (9 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5, 25.8, 31.8, 34.0, 44.3, 51.5, 51.8, 52.9, 172.1, 194.5. Anal. Calcd (%) for $C_{10}H_{17}NO_2S_2$: C, 48.55; N, 5.66; H, 6.93. Found: C, 48.70; N, 5.79; H, 6.95.

Table 1, Entry 13: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.76–1.86 (4 H, m), 2.57 (2 H, t, *J* = 6.7 Hz), 3.28–3.46 (7 H, m), 3.64–3.66 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5, 26.3, 31.2, 34.1, 50.8, 51.8, 55.2, 172.3, 191.7.

Table 1, Entry 15: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.82 (2 H, t, *J* = 6.7 Hz), 3.52 (2 H, t, *J* = 6.7 Hz), 3.67 (3 H, s), 4.90 (2 H, s), 7.33–7.35 (5 H, m), 7.90 (1 H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.3, 34.6, 51.4, 52.3, 128.3, 128.6, 129.3, 135.7, 172.8, 197.7.

Table 1, Entry 17: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3 H, t, *J* = 7.2 Hz), 1.19 (3 H, d, *J* = 5.3 Hz), 1.51–1.61 (2 H, m), 2.74 (2 H, t, *J* = 6.8 Hz), 3.44 (2 H, t, *J* = 6.8 Hz), 3.66 (3 H, s), 4.52 (1 H, m), 7.38 (1 H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.6, 20.9, 29.1, 30.9, 34.2, 52.1, 54.7, 54.8, 172.8, 196.0.

Table 1, Entry 19: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01–1.06 (6 H, m), 1.94 (3 H, s), 2.72 (2 H, t, *J* = 6.6 Hz), 3.23 (2 H, t, *J* = 6.6 Hz), 3.52 (2 H, q, *J* = 7.1 Hz), 3.79 (2 H, q, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.8, 12.7, 30.1, 30.6, 43.3, 46.9, 49.6, 195.2, 206.9.

Table 1, Entry 21: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38–1.76 (7 H, m), 2.53 (2 H, t, *J* = 6.1 Hz), 3.01–3.44 (6 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.8, 25.9, 29.9, 43.1, 50.7, 55.1, 191.7, 206.3. Anal. Calcd (%) for $C_9H_{15}NOS_2$: C, 49.73; H, 6.96; N, 6.44. Found: C, 49.53; H, 6.82; N, 6.61.

Table 1, Entry 25: ^{1}H NMR (500 MHz, $CDCl_3$–CCl_4): δ = 1.58 (3 H, d, *J* = 6.8 Hz), 2.14 (3 H, s), 2.89 (2 H, t, *J* = 6.1 Hz), 3.40 (2 H, t, *J* = 6.1 Hz), 5.81 (1 H, q, *J* = 6.8 Hz), 7.26–7.35 (5 H, m), 8.18 (1 H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 29.0, 30.4, 43.3, 56.4, 127.0, 128.2, 129.3, 141.7, 196.8, 207.6.

Table 1, Entry 28: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26–1.31 (6 H, m), 3.68–4.21 (6 H, m), 5.76 (1 H, dd, *J* = 4.1, 10.2 Hz), 7.24–7.69 (8 H, m), 8.00–8.01 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.9, 128.5, 128.7, 129.1, 129.6, 134.1, 137.6, 140.8, 190.8, 197.4.

Table 1, Entry 30: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.93–2.05 (4 H, m), 3.58–4.02 (6 H, m), 5.83 (1 H, dd, *J* = 4.1, 9.8 Hz), 7.27–7.56 (8 H, m), 8.00 (2 H, d, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6, 26.5, 51.0, 54.6, 55.3, 128.0, 128.6, 128.8, 129.0, 129.4, 133.6, 137.0, 140.0, 191.5, 197.4.