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Efficient synthesis of *N*,*N*′-dialkyl-*N*″-dialkylaminocarbothioyl thioureas from cyclic secondary amines, CS_2, and *N*,*N*′-dialkyl carbodiimides in water

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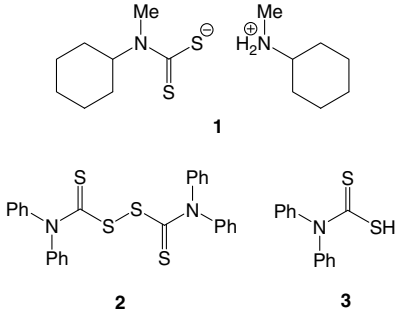
ABSTRACT

A mild, convenient, and practical one-pot procedure for direct synthesis of *N*,*N*′-dialkyl-*N*″-dialkylaminocarbothioyl thioureas is described via three-component reaction of cyclic secondary amines, CS_2, and *N*,*N*′-dialkyl carbodiimides in water at room temperature.

Acylureas and biurets are acyclic compounds with anticonvulsant activity. Replacement of one or both oxygen atoms of these compounds with sulfur results in the formation of thiobiurets and dithiobiurets. This modification increases the lipophilicity and possibly the biological activity of these compounds. The structural similarity of dithiobiuret to biurets has allowed researchers to test several analogues for their antifungal and insecticide activities.[1] Some dithiobiurets were synthesized as male insect chemosterilants.[2] Also these compounds are useful reagents or intermediates in the synthesis of heterocycles and polymers with biological properties.[3] Dithiobiurets are (*S*,*S*)-bidentate ligands and are used widely in coordination chemistry.[4,5] Several approaches for the synthesis of dithiobiurets have been described.[1–7]

It has been shown that the reaction of primary amines with CS_2 in Et_2O or THF leads to thioureas and/or isothiocyanates.[8] Also, using *N*-methylcyclohexylamine or diphenylamine as secondary amines, in Et_2O or pyridine, results in salt **1** or compound **2**, respectively. Compound **3** is readily oxidized to the disulfide **2** in the presence of oxygen[8] (Scheme 1).

Herein we report a three-component reaction between cyclic secondary amines **4** and CS_2 in the presence of *N*,*N*′-dialkyl carbodiimides **5** in water,[9,10] which leads to *N*,*N*′-dialkyl-*N*″-dialkylaminocarbothioyl thioureas **6** in excellent yields (Scheme 2). When these reactions were carried out in the presence of acyclic secondary amines (dibenzylamine, diethylamine, dimethylamine) and primary amines (benzylamine, *tert*-butylamine), a complex reaction mixture was obtained.



Scheme 1.

The reaction of **4**, CS_2, and **5** proceeded smoothly in H_2O, and was complete within 5 h. The ^1H NMR and ^{13}C NMR spectra of the reaction mixtures after work-up clearly indicated the formation of *N*,*N*′-dialkyl-*N*″-dialkylaminocarbothioyl thioureas **6a–6h** in 87–96% yields (Table 1).

The structures of compounds **6a–6h** were apparent from their mass spectra, which displayed, in each case, the molecular ion peak at the appropriate *m*/*z* value. The ^1H and ^{13}C NMR spectroscopic data, as well as the IR spectra, were in agreement with the proposed structures. For example, the ^1H NMR spectrum of **6a** showed characteristic multiplets for the methylene (δ = 1.05–2.00 and 3.83) and methine (δ = 4.27–4.34 and 4.93–4.99) protons, together with a doublet (δ = 6.03, ^3J = 7.5) for the NH group. The ^{13}C NMR

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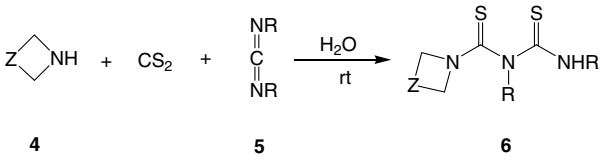
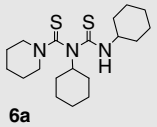
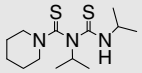
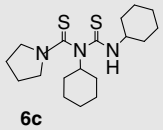
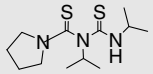
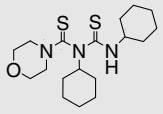
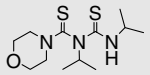
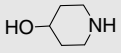
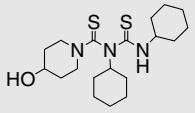
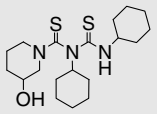


Scheme 2.

Table 1
Reaction of cyclic secondary amines **4**, CS_2, and *N*,*N*′-dialkyl carbodiimides **5** in H_2O

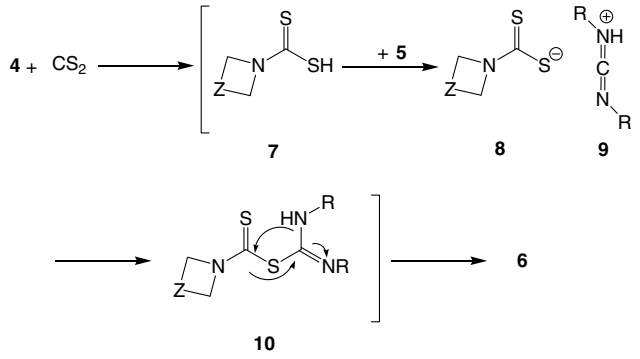
Entry	4	R in 5	6	Yield[a] (%)
a		Cyclohexyl	 **6a**	91
b		*i*-Pr	 **6b**	89
c		Cyclohexyl	 **6c**	92
d		*i*-Pr	 **6d**	95
e		Cyclohexyl	 **6e**	87
f		*i*-Pr	 **6f**	93
g		Cyclohexyl	 **6g**	95
h		Cyclohexyl	 **6h**	96

[a] Isolated yield.

spectrum of **6a** showed 11 distinct resonances (δ = 24.2–60.9) in the aliphatic region of the spectrum, together with two signals at δ = 179.0 and 183.4 ppm for the C=S groups.

A tentative mechanism for this transformation is proposed in Scheme 3. It is conceivable that the initial event is the formation of the SH-acidic intermediate **7** from **4** and CS_2 that can protonate **5** to afford **9**. Subsequent nucleophilic attack of the sulfur anion **8** on **9** results in **10**, which undergoes a well-documented rearrangement[11,12] to produce **6**.[13]

In conclusion, we have described a novel system that is effective for the synthesis of *N*,*N*′-dialkyl-*N*″-dialkylaminocarbothioyl thioureas in high yields at room temperature in water. The advantage



Scheme 3.

of the present procedure over existing methods is that the reaction is performed in aqueous media and under solvent-free conditions by simple mixing of the starting materials.

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13. *Typical procedure for the synthesis of* **6**: Amine (2 mmol) was added slowly to a mixture of CS_2 (2 mmol) and *N*,*N*′-dialkyl carbodiimide (2 mmol) in 5 ml of water at rt. The reaction mixture was stirred for 5 h. After completion of the reaction, the resulting solid was filtered off, dried and analyzed by ^{1}H NMR, and ^{13}C NMR. In some cases, further purification was carried out by recrystallization from CH_3CN. Compound **6a**:White powder, mp 130–134 °C, 0.33 g, yield 91%. IR (KBr) (ν_{max}/cm^{-1}): 3330, 2905, 1511, 1473, 1433, 1384, 1350, 1314, 1228, 1131. MS (EI, 70 eV): *m*/*z* (%) = 367 (M$^+$, 6), 128 (60), 98 (100), 84 (46), 55 (78), 41 (62). Anal. Calcd for $C_{19}H_{33}N_3S_2$ (367.61): C, 62.08; H, 9.05; N, 11.43. Found: C, 61.97; H, 8.90; N, 11.25. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.05–1.22 (m, 4H, 2CH$_2$), 1.30–1.43 (m, 4H, 2CH$_2$), 1.56–1.77 (m, 14H, 7CH$_2$), 1.92–2.00 (m, 4H, 2CH$_2$), 3.83 (br, 4H, 2CH$_2$), 4.27–4.34 (m, 1H, CH), 4.93–4.99 (m, 1H, CH), 6.03 (d, ^3J = 7.5, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.2 (CH$_2$), 25.0 (2CH$_2$), 25.8 (CH$_2$), 25.9 (CH$_2$), 26.1 (2CH$_2$), 26.3 (2CH$_2$), 30.7 (2CH$_2$), 33.1 (2CH$_2$), 51.6 (2CH$_2$), 53.7 (CH), 60.9 (CH), 179.0 (C=S), 183.4 (C=S). Compound **6b**: Yellow powder, mp 166–170 °C, 0.25 g, yield 89%. IR (KBr) (ν_{max}/cm^{-1}): 3320, 2940, 1612, 1561, 1514, 1242. Anal. Calcd for $C_{13}H_{25}N_3S_2$ (287.48): C, 54.31; H, 8.78; N, 14.62. Found:C, 54.11; H, 8.52; N, 14.52. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.20 (d, ^3J = 6.5, 6H, 2CH$_3$), 1.34 (d, ^3J = 6.6, 6H, 2CH$_3$), 1.68 (br, 6H, 3CH$_2$), 4.08 (br, 4H, 2CH$_2$), 4.55–4.62 (m, 1H, 1CH), 5.35–5.40 (m, 1H, CH), 5.87 (d, ^3J = 6.5, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 20.2 (CH$_2$), 22.4 (2CH$_3$), 23.8 (2CH$_3$), 25.6 (2CH$_2$), 42.1 (2CH$_2$), 46.8 (CH), 52.7 (CH), 179.0 (C=S), 182.7 (C=S). Compound **6c**: White powder, mp 152–155 °C, 0.32 g, yield 92%. IR (KBr) (ν_{max}/cm^{-1}): 3330, 2905, 1514, 1475, 1435, 1314. Anal. Calcd for $C_{18}H_{31}N_3S_2$ (353.58): C, 61.14; H, 8.84; N, 11.88. Found: C, 61.09; H, 8.80; N, 11.79. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.04–1.25 (m, 4H, 2CH$_2$), 1.30–1.43 (m, 4H, 2CH$_2$), 1.56–1.62 (m, 4H, 2CH$_2$), 1.72–1.82 (m, 4H, 2CH$_2$), 1.88–1.90 (m, 2H, CH$_2$), 1.97 (br, 6H, 3CH$_2$), 3.46–3.56 (br, 2H, CH$_2$), 3.57–3.87 (br, 2H, CH$_2$), 4.31–4.37 (m, 1H, CH), 4.90–4.95 (m, 1H, CH), 5.85 (d, ^3J = 6.9, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.5 (2CH$_2$), 24.9 (2CH$_2$), 25.4 (CH$_2$), 25.5 (CH$_2$), 25.9 (3CH$_2$), 30.4 (2CH$_2$), 32.7 (2CH$_2$), 33.9 (CH$_2$), 53.0 (CH), 60.3 (CH), 178.4 (C=S), 181.6 (C=S). Compound **6d**: Yellow powder, mp 132–136 °C, 0.26 g, yield 95%. IR (KBr) (ν_{max}/cm^{-1}): 3305, 2940, 1516, 1439, 1384, 1311, 1283, 1248, 1210, 1162, 1122, 1077. Anal. Calcd for $C_{12}H_{23}N_3S_2$ (273.45): C, 52.71; H, 8.48; N, 15.37. Found: C, 52.67; H, 8.39; N, 15.30. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.17 (d, ^3J = 6.5, 6H, 2CH$_3$), 1.33 (d, ^3J = 6.7, 6H, 2CH$_3$), 1.98 (br, 4H, 2CH$_2$), 3.44–3.93 (br d, 4H, 2CH$_2$), 4.56–4.65 (m, 1H, CH), 5.26–5.34 (m, 1H, CH), 5.68 (d, ^3J = 6.5, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 20.6 (2CH$_3$), 22.5 (2CH$_3$), 22.6 (2CH$_2$), 46.6 (CH), 52.4 (2CH$_2$), 52.5 (CH), 178.6 (C=S), 181.0 (C=S). Compound **6e**: White powder, mp 147–150 °C, 0.32 g, yield 87%. IR (KBr) (ν_{max}/cm^{-1}): 3325, 2900, 1508, 1474, 1427, 1388, 1350, 1312, 1266, 1226, 1110. 1043. Anal. Calcd for $C_{18}H_{31}N_3OS_2$ (369.58): C, 58.50; H, 8.45; N, 11.37. Found: C, 58.41; H, 8.39; N, 11.28. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.05–

1.21 (m, 4H, $2CH_2$), 1.29–1.42 (m, 4H, $2CH_2$), 1.56–1.69 (m, 4H, $2CH_2$), 1.69–1.77 (m, 4H, $2CH_2$), 1.87–1.90 (br, 2H, CH_2), 1.97–2.00 (br, 2H, CH_2), 3.65–3.75 (m, 4H, $2CH_2$), 3.88 (br, 4H, $2CH_2$), 4.26–4.33 (m, 1H, CH), 4.91–4.98 (m, 1H, CH), 5.92 (d, ^3J = 7.5, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.5 ($2CH_2$), 25.3 (CH_2), 25.4 (CH_2), 25.8 ($2CH_2$), 30.2 ($2CH_2$), 32.7 ($2CH_2$), 50.1 ($2CH_2$), 53.2 (CH), 60.5 (CH), 65.9 ($2CH_2$), 178.9 (C=S), 184.2 (C=S). Compound **6f**: White powder, mp 123–127 °C, 0.27 g, yield 93%. IR (KBr) (ν_{max}/cm^{-1}): 3315, 2945, 2830, 1514, 1456, 1427, 1383, 1313, 1263, 1220, 1117. Anal. Calcd for $C_{12}H_{23}N_3OS_2$ (289.45): C, 49.79; H, 8.01; N, 14.52. Found: C, 49.70; H, 7.96; N, 14.49. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.15 (d, ^3J = 6.5, 6H, $2CH_3$), 1.29 (d, ^3J = 6.7, 6H, $2CH_3$), 3.67 (t, ^3J = 4.9, 4H, $2CH_2$), 3.84 (br, 4H, $2CH_2$), 4.51–4.55 (m, 1H, CH), 5.27–5.33 (m, 1H, CH), 5.72 (d, ^3J = 7.0, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 20.2 ($2CH_3$), 22.5 ($2CH_3$), 46.9 (CH), 50.0 ($2CH_2$), 52.7 (CH), 65.9 ($2CH_2$), 179.2 (C=S), 183.8 (C=S). Compound **6g**: Pale yellow powder, mp 59–61 °C, 0.36 g, yield 95%. IR (KBr) (ν_{max}/cm^{-1}): 3335, 2905, 1504, 1477, 1437, 1377, 1338, 1258, 1216, 727. Anal. Calcd for $C_{19}H_{33}N_3OS_2$ (383.61): C, 59.49; H, 8.67; N, 10.95. Found: C, 59.21; H, 8.49; N, 10.79. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.01–1.14 (m, 4H, $2CH_2$), 1.25–1.32 (m, 4H, $2CH_2$), 1.50–1.71 (m, 10H, $5CH_2$), 1.82–1.89 (m, 6H, $3CH_2$), 2.30 (br, 1H, OH), 3.78 (br, 2H, 2CH), 3.98 (br, 3H, 3CH), 4.20 (br, 1H, CH), 4.85 (br, 1H, CH), 5.95 (d, ^3J = 7.1, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.5 ($2CH_2$), 25.2 (CH_2), 25.4 (CH_2), 25.9 ($3CH_2$), 30.2 (CH_2), 32.6 ($2CH_2$), 32.3 ($2CH_2$), 46.6 ($2CH_2$), 53.3 (CH), 60.6 (CH), 64.7 (CH), 178.5 (C=S), 183.1 (C=S). Compound **6h**: Pale brown powder, mp 115–120 °C, 0.37 g, yield 96%. IR (KBr) (ν_{max}/cm^{-1}): 3340, 2905, 1521, 1472, 1328, 1270, 1214, 1128. Anal. Calcd for $C_{19}H_{33}N_3OS_2$ (383.61): C, 59.49; H, 8.67; N, 10.95. Found: C, 59.20; H, 8.51; N, 10.80. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.03–1.14 (m, 6H, $3CH_2$),1.15–1.22 (m, 2H, CH_2), 1.23–1.36 (m, 6H, $3CH_2$), 1.62–1.81 (m, 4H, $2CH_2$), 1.83–1.93 (m, 2H, CH_2), 1.94–1.99 (m, 4H, $2CH_2$), 2.97 (br, 1H, OH), 3.39–3.99 (br, 4H, $2CH_2$), 4.00 (br, 1H, CH), 4.23–4.25 (br, 1H, CH), 4.85–4.89 (br, 1H, CH), 6.17 (d, ^3J = 6.9, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.6 ($2CH_2$), 25.3 ($2CH_2$), 25.4 ($2CH_2$), 25.8 (CH_2), 25.9 ($2CH_2$), 29.5 (CH_2), 29.9 (CH_2), 30.3 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 49.1 (CH), 56.2 (CH), 60.7 (CH), 178.2 (C=S), 184.4 (C=S).