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SHORT COMMUNICATION

A simple route for the synthesis of symmetrical thiourea derivatives and amidinium cations by reaction between isocyanides, amines and carbon disulfide

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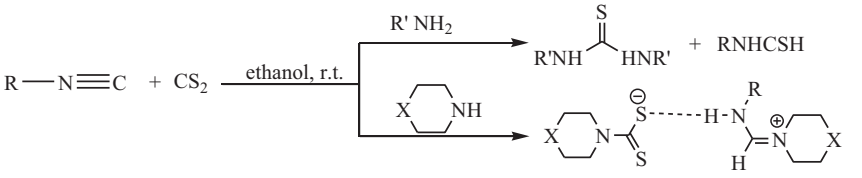
Reaction between primary amines and CS_2 promoted by alkyl isocyanides in ethanol as solvent provides a simple and efficient route for the synthesis of symmetrical thiourea derivatives. The reaction of secondary amines with carbon disulfide and alkyl isocyanides afforded new amidinium cations in good yields.



Keywords: thiourea; isocyanide; multi-component reaction; amidinium cations; carbon disulfide

1. Introduction

Thiourea derivatives are biologically active compounds existing as fungicides, herbicides (*1*) and antibacterial agents (*2*). They are also key intermediates in organocatalysis (*3a*) and references cited therein (*3b–f*). There are several routes for the synthesis of thioureas, which requires the use of hazardous and toxic reagents (*4*). For example, thioureas have been prepared by the reaction between primary and secondary amines and thiophosgene or isothiocyanates (*5*), which are hazardous compounds. Furthermore, the reaction of amines with carbon disulfide in the presence of mercury acetate and the reaction of unsubstituted thioureas with primary alkyl amines (*6*) have been utilized for the synthesize of thioureas. The reactions between carbon disulfide and amines have been reported utilizing a ZnO/Al_2O_3 composite as catalyst at high temperature (100°C) to afford thiourea derivatives (*7*). The reaction between carbon disulfide and primary amines was also reported in hot water to afford symmetrical thiourea derivatives in the absence of any catalyst (*8*).

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A similar reaction has been reported between carbon disulfide and primary or secondary amines in a boiling solution of sodium hydroxide in water to form di- and tri-substituted thioureas (*9*).

In continuation of our previous works on isocyanide-based multi-component reactions (*10–13*), we wish to report here the reaction between amines, carbon disulfide and alkyl isocyanides to form thiourea derivatives or amidinium salts.

2. Results and discussion

The reaction between cyclohexyl isocyanide **1a**, primary amine **2** and carbon disulfide (**3**) in ethanol, after 3 h stirring at room temperature, afforded thiourea derivatives **4** in high yields (Figure 1). To show the role of the isocyanide in the formation of thiourea derivatives from the reaction between amines and carbon disulfide, the reaction between aniline and CS_2 was conducted in the absence of isocyanide and only the salt $PhNHCSS^-$ $PhNH3^+$ was isolated in 80% yield after 12 h stirring at room temperature. As shown in Table 1, the reaction is compatible with aromatic and aliphatic amines. In all cases, the reaction was clean and complete after 3 h stirring at room temperature and the products were readily purified by evaporating the solvent and washing the precipitated solids with diethyl ether. All products in Table 1 are known compounds and their structures were proved by comparison of the melting points and IR and NMR data with the reported data (*7*).

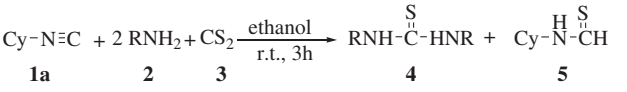
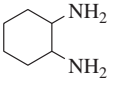
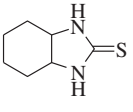
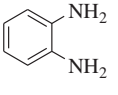
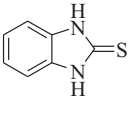
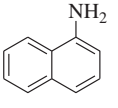
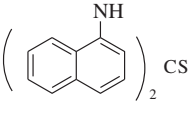


Figure 1. Synthesis of thiourea derivatives by reaction between primary amines and CS_2, promoted by cyclohexyl isocyanide.

Table 1. Preparation of thioureas from primary amines, CS_2 and isocyanide.

Entry	Amine **2**	Product **4**	Yield%*
1	$Ph-NH_2$	PhNHCSNHPh	94
2	4-$MeC_6H_4NH_2$	(4-$MeC_6H_4NH)_2CS$	95
3	4-$ClC_6H_4NH_2$	(4-$ClC_6H_4NH)_2CS$	97
4	$PhCH_2NH_2$	$(PhCH_2NH)_2CS$	90
5	$C_6H_{11}NH_2$	$(C_6H_{11}NH)_2CS$	95
6			93
7			92
8			90

*Isolated yields.

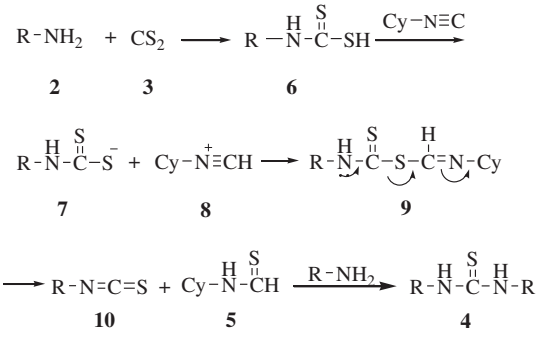


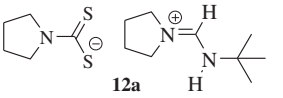
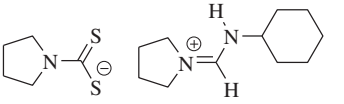
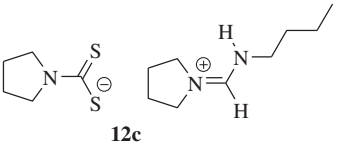
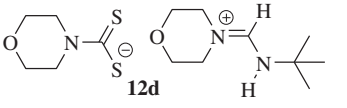
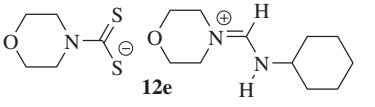
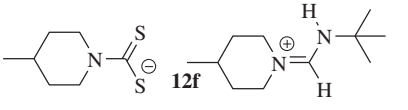
Figure 2. Suggested mechanism for the formation of compound **4** by the reaction of primary amine, isocyanide and CS_2.

A reasonable mechanism for the formation of thiourea from the reaction between isocyanide **1,** primary amine **2** and CS_2 is presented in Figure 2. The addition of amine to CS_2 leads to carbodithioic acid intermediate **6**, which protonates the alkyl isocyanide **1** to form nitrilium cation **8**. The addition of carbodithioate anion **7** to nitrilium cation **8** leads to intermediate **9** that converts to isothiocyanate **10** by loss of a molecule of CyNHCSH **5**. Addition of another molecule of amine to isothiocyanate **10** affords the product **4**.

To investigate the reaction between isocyanide, CS_2 and secondary amines, pyrrolidine was reacted with CS_2 and *t*-butyl isocyanide (Figure 3 and Table 2). After stirring the reaction mixture at room temperature for 3 h and removing the solvent at reduced pressure, a solid product was obtained. The ^{1}H NMR spectrum of this product exhibited the presence of the skeleton of one molecule of *t*-butyl isocyanide and two molecules of pyrrolidine. The elemental analysis also showed the presence of one molecule of CS_2 in the structure of the product. So, a four-component reaction has occurred between *t*-butyl isocyanide, pyrrolidine and CS_2. On the basis of the elemental analysis and IR and NMR spectral data, structure **12a** was considered for the product. The IR spectrum shows a strong peak at 1694 cm^{-1}, indicating the existence of iminium cation ($C{=}N^+$), which was further confirmed by ^{1}H NMR spectrum ($\delta = 8.38$ ppm, NC*H*=N$^+$) and ^{13}C NMR spectrum ($\delta = 151.4$ ppm, N*C*H=N$^+$). The ^{1}H NMR spectrum of **12a** exhibited a singlet at 1.36 ppm for *t*-butyl protons. A singlet that integrated for one hydrogen was observed at 8.38 ppm and a D_2O-exchangable signal was observed at 8.79 ppm. The ^{13}C NMR spectrum showed a signal at 209.7 ppm which is assigned to the NCS_2 carbon and a signal (CH) at 151.4 ppm which is attributed to N−CH−N carbon atom (on the basis of DEPT NMR data). This value is similar to $\delta = 149.4$ (*14*, *15*) in amidine carbocations and indicates significant stabilization of the cationic carbon. The ^{13}C NMR spectrum of **12a** showed signals related to the *t*-butyl group at 29.9 and 55.2 ppm. One of the pyrrolidine rings showed two signals at 53.4 and 25.0 ppm. The other pyrollidine ring that possesses a positively charged nitrogen showed three signals at 26.4, 51.9 and 47.5 ppm. This is attributed to the restricted rotation about the $C{=}N^+$ bond, desymmetrizing the methylene groups of the ring. The same behavior was observed for the two pyrrolidine rings in the ^{1}H NMR spectrum of compound **12a**, one ring showing two signals at 3.64 and 1.80 ppm for the four methylene groups and the positively charged ring showing four broad signals at 3.73, 3.38, 1.96 and 1.85 ppm for methylene groups of the ring.

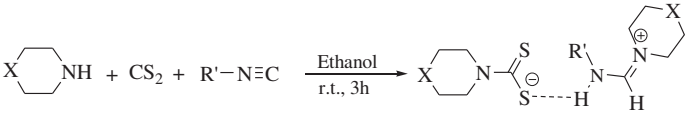
To investigate the scope of the reaction, different secondary amines were treated with CS_2 and cyclohexyl isocyanide or *t*-butyl isocyanide and related products were obtained in good yields (Table 2). It is noteworthy that the restricted rotations about CN bonds of NCHN moiety may also result in the presence of two rotational isomers. For example, the ^{1}H NMR spectrum of compound **12e** shows that it exists at solution as two rotamers (Figure 4).

Table 2. Amidinium cations from secondary amines, CS_2 and isocyanides.

Entry	Amine	R'	Product	Yield%*
1		*t*-Bu	 **12a**	95
2		Cy	 **12b**	90
3		n-Bu	 **12c**	90
4		*t*-Bu	 **12d**	75
5		Cy	 **12e**	71
6		*t*-Bu	 **12f**	80

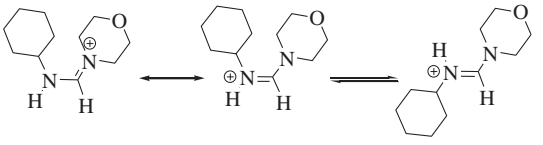
*Isolated yields.

A suggested mechanism for the formation of compound **12a** is presented in Figure 5. As shown in Figure 2, the treatment of amine, isocyanide and CS_2 leads to the formation of intermediate **13**, this cannot be converted to isothiocyanate intermediate in the case of secondary amines. Addition



12

Figure 3. Synthesis of amidinium cations by reaction between secondary amines, CS_2 and isocyanides.



12e Z-isomer E-isomer

Figure 4. Resonance forms and rotational isomers of compound **12e**.

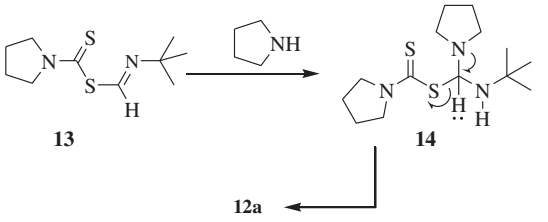


Figure 5. Suggested mechanism for the formation of compound **12** by the reaction of pyrrolidine, *t*-Butyl isocyanide and CS_2.

of another molecule of pyrrolidine to intermediate **13** affords compound **14**, which then ionizes to product **12a.**

3. Conclusions

In summary, we reported herein a simple and efficient route for the synthesis of thiourea derivatives by reaction between primary amines and CS_2 promoted by alkyl isocyanides. The reactions are conducted under neutral conditions and are clean and complete at room temperature after 3 h. The reaction of secondary amines with carbon disulfide and alkyl isocyanides afforded amidinium cations in good yields. In all the experiments, products were purified by simple washing with diethyl ether and were obtained in high yields.

4. Experimental section

4.1. *General*

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 or 75 MHz, respectively. ^{1}H and ^{13}C NMR spectra were obtained on solution in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

4.2. *General procedure for the preparation of compounds 4a–4j and 12a–12f*

Isocyanide (1 mmol) was added to a mixture of amine (2 mmol) and carbon disulfide (1 mmol) in ethanol (10 ml) and the mixture was stirred at room temperature for 3 h. Solvent was removed under reduced pressure and the solid residue was washed with diethyl ether (5 ml) to give the pure product. All products in Figure 1 are known compounds and their structures were proved by comparison of the melting points and IR and NMR data with the reported data. Compounds **12a**–**12f** are new and their structures were proved by IR and NMR spectroscopy and analytical data.

4.2.1. *12a*

White powder (0.29 g, 95%). mp: 161–163°C. FT-IR (KBr): ν_{max} (cm^{-1}) = 3190 (NH), 1693 ($C{=}N^+$). Anal. Calcd for $C_{14}H_{27}N_3S_2$ (301.2): C, 55.8; H, 9.0; N, 13.9; S, 21.3%. Found: C,

55.7; H, 9.1; N, 13.9; S, 21.2%. ^{1}H NMR (500 MHz; DMSO-d_6): $\delta = 1.36$ (s, 9H, *t*-butyl), 1.8 (m, 4H, 2 CH_2 of pyrrolidine), 1.85 and 1.96 (2 broad m, 4H, 2 CH_2 of positively charged pyrrolidine), 3.38 and 3.73 (2 broad m, 4H, 2NCH_2 of positively charged pyrrolidine), 3.66 (m, 4H, 2 CH_2 of pyrrolidine), 8.38 (s, 1H, CH), 8.79 (broad s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 25.0$ (2 CH_2), 26.4 (2 CH_2), 29.9 (3 CH_3 of *t*-butyl), 47.5 and 51.9 (2NCH_2 of positively charged pyrrolidine), 53.4 (2NCH_2 of pyrrolidine), 55.2 (*C* of *t*-butyl), 151.4 (N*CH*N), 209.7 (C=S).

4.2.2. ***12b***

White powder (0.29 g, 90%). mp: 189–191°C; FT-IR (KBr): ν_{max} (cm^{-1}) = 3197 (NH), 1681 (C=N^+). Anal. Calcd for $C_{16}H_{29}N_3S_2$ (327.2): C, 58.7; H, 8.9; N, 12.8; S, 19.6%. Found: C, 58.7; H, 9.0; N, 12.8; S, 19.4%. ^{1}H NMR (500 MHz; DMSO-d_6): $\delta = 1.08$, 1.22, 1.24, 1.38, 1.41, 1.57 and 1.86 (6m, 10H, 5 CH_2 of cyclohexyl), 1.75 (m, 4H, 2 CH_2 of pyrrolidine), 1.79 and 1.94 (2 broad m, 4H, 2 CH_2 of positively charged pyrrolidine), 3.38 (m, 3H, CH of cyclohexyl and CH_2 of positively charged pyrrolidine), 3.65 (m, 6H, 3 CH_2), 8.46 (m, 1H, CH), 8.95 (broad s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 25.0$, 25.3, 26.4, 33.5, 47.3, 51.7, 53.4, 57.0, 153.2 (N*CH*N), 209.6 (C=S).

4.2.3. ***12c***

White powder (0.27 g, 90%). mp 108–110°C. FT-IR (KBr): ν_{max} (cm^{-1}) = 3184 (NH), 1690 (C=N^+). ^{1}H NMR (300 MHz; DMSO-d_6): $\delta = 0.9$ (*t*, 3H, CH_3 of *n*-Bu), 1.31 (sextet, 2H, CH_2 of *n*-Bu), 1.59 (quintet, 2H, CH_2 of *n*-Bu), 1.85–3.68 (m, 8H, 4 CH_2 of pyrrolidine rings), 3.42–3.68 (2m, 8H, 4 CH_2 of pyrrolidine rings), 8.60 (m, 1H, CH), 9.24 (broad s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 14.2$, 19.6, 32.6 and 53.4 (carbons of *n*-Butyl), 25.0, 26.3, 46.7, 47.3 and 51.7 (2 pyrrolidine rings), 154.3 (N*CH*N), 209 (C=S).

4.2.4. ***12d***

White powder (0.25 g, 75%). mp: 161–163°C. FT-IR (KBr): ν_{max} (cm^{-1}) = 3192 (NH), 1689 (C=N^+). ^{1}H NMR (500 MHz; DMSO-d_6): $\delta = 1.34$ (s, 9H, *t*-butyl), 3.33 and 4.29 (2t, $j = 5.2$ Hz, 8H, 4 CH_2 of morpholine), 3.69, 3.79 and 3.10 (broad signals, 4 CH_2 of positively charged morpholine), 8.12 (s, 1H, CH), 9.29 (broad s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 29.7$ and 55.5 (carbons of *t*-Butyl), 50.2 and 66.7 (4 CH_2 of morpholine), 43.8, 45.7, 64.5 and 66.1 (4 CH_2 of positively charged morpholine), 152.9 (NCHN), 214.6 (C=S).

4.2.5. ***12e***

White powder (0.25 g, 71%). mp: 204–209°C. FT-IR (KBr): ν_{max} (cm^{-1}) = 3426 (NH), 1691 (C=N^+). ^{1}H NMR (500 MHz; DMSO-d_6): $\delta = 1.09$–2.36 (6m, 10H, 5 CH_2 of cyclohexyl), 3.36 and 4.20 (broad signals, 8 CH_2 of morpholine rings and CH of cyclohexyl), 7.83 and 8.14 (2s, 1H, CH of two isomers), 9.4 and 9.54 (2 broad s, 1H, NH of two isomers).

4.2.6. ***12f***

White powder (0.29 g, 80%). mp 155–157°C; FT-IR (KBr): ν_{max} (cm^{-1}) = 3150 (NH), 1680 (C=N^+). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.86$ (d, $J = 7$ Hz, 6H, 2 CH_3), 1.11 (m, 2H, 2

CH), 1.33 (s, 9H, *t*-Bu), 1.67, 2.49, 3.20, 3.91, 4.35 (broad signals, 8 CH_2 of piperidine rings, 7.72 (s, 1H, NC*H*N), 7.97 (broad s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.2$, 21.3, 29.7, 30.1, 30.8, 32.8, 33.4, 34.0, 34.3, 46.5, 50.7, 52.5, 53.1, 56.0, 150.0 (NCHN), 212.6 (C=S).

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