A Green Process Development for the Synthesis of Aliphatic Symmetrical *N, N'*-Disubstituted Thiourea Derivatives in Aqueous Medium

Asha D. Jangale, Priyanka P. Kumavat, Yogesh B. Wagh, Yogesh A. Tayade, Pramod P. Mahulikar,
Dipak S. Dalal*

**School of Chemical Sciences, North Maharashtra University, Jalgaon - 425 001 (M. S.), India*
Tel: +91-2572257432; Fax: +91-2572258406; *Email: dsdalal2007@gmail.com

Supplementary Data

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1. Experimental:

1.1 General Comments

Chemicals required for the synthesis were obtained from S D Fine chemicals, Spectrochem and used without further purification. Melting points were measured in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR Affinity-1 using KBr. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker ADVANCE II 300 MHz and Bruker ADVANCE II 400 MHz with TMS as an internal standard. Mass spectra were under ESI mode on WATERS, Q-TOF MICROMASS (LC-MS) mass spectrometer.

1.2 Synthesis of aliphatic thioureas

Typical experimental procedure for symmetrical thioureas derivatives

To a 50 mL round bottom flask equipped with a magnetic stirrer, add carbon disulphide (5 mmol) and amine (10 mmol) in ice cold condition followed by addition of water (5 mL). Cork the flask. The reaction mixture was stirred vigorously at room temperature. The progress of the reaction was checked by TLC (10% MeOH: chloroform or EtOAc: hexane). After completion of reaction, solid was obtained by removal of water under reduced pressure on rotary evaporator while in some cases (Entry 7, 9, 10, 11 and 14, 15) the reaction mixture solidified when the reaction on completion. The obtained solid product was recrystallized with ethanol or washing with mixture EtOAc: hexane.

Experimental procedure for a larger batch (Entry 3)

In a 250 mL two neck round bottom flask with reflux condenser attached in one of the neck with continue flow of cold water placed overhead stirrer, carbon disulphide (50 mmol) and 15 mL water was added. To this, isopropyl amine (100 mmol) was added over a period of 25-30 min by dropping funnel under cooling condition with constant stirring, white solid was obtained followed by addition of 35 mL of water. The reaction mixture was stirred vigorously at room temperature. The progress of reaction was monitored by TLC (10% MeOH: chloroform). After completion of the reaction (10 min), solid product of 1, 3-bis(isopropyl)thiourea was isolated by removing the water under reduced pressure with 97% yield.

2. Spectroscopic characterization data:

1,3-diethylthiourea (Entry 1)

White solid, 99%, mp 78 °C (lit.²⁶ 78 °C); IR $\nu_{\max}$ (KBr): 3228, 2972, 1550, 1246 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 5.813 (brs, 4H), 3.459 (brs, 2H), 1.244 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 180.71, 38.65, 13.78; MS (ESI): m/z 133 $[\text{M}+\text{H}]^+$.

1,3-dipropylthiourea (Entry 2)

White solid, 95%, mp 70 °C; IR $\nu_{\max}$ (KBr): 3230, 2960, 1521, 1230 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 6.049 (brs, 2H), 3.283 (brs, 4H), 1.458-1.581 (m, 4H), 0.853 (t, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 181.24, 45.98, 22.50, 11.24; MS (ESI): m/z 161 $[\text{M}+\text{H}]^+$.

1,3-diisopropylthiourea (Entry 3)

White solid, 97%, mp 140 °C (lit.²⁶ 142); IR $\nu_{\max}$ (KBr): 3221, 2970, 1517, 1244 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 5.754 (brs, 2H), 4.181 (brs, 2H), 1.194 (d, J = 6.3 Hz, 12H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 179.20, 45.85, 22.50; MS (ESI): m/z 161 $[\text{M}+\text{H}]^+$.

1,3-dibutylthiourea (Entry 4)

White solid, 96%, mp 63 °C (lit.²⁴ 62-65 °C); IR $\nu_{\max}$ (KBr): 3223, 2960, 1519, 1246 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 5.773 (brs, 2H), 3.412 (brs, 4H), 1.549-1.648 (m, 4H), 1.335-1.457 (m, 4H), 0.949 (t, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 181.11, 44.04, 30.96, 19.96, 13.64; MS (ESI): m/z 189 $[\text{M}+\text{H}]^+$.

1,3-di-tert-butylthiourea (Entry 5)

White solid, 93%, mp 132 °C (lit.²⁸ 129-131 °C); IR $\nu_{\max}$ (KBr): 3267, 2960, 1541, 1319, 1201 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 5.768 (brs, 2H), 1.478 (s, 18H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 180.09, 53.22, 29.61; MS (ESI): m/z 189 $[\text{M}+\text{H}]^+$.

1,3-dioctylthiourea (Entry 6)

White solid, 98%, mp 53 °C (lit.²⁸ 53-55 °C); IR $\nu_{\max}$ (KBr): 3263, 2918, 1552, 1361 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} = 6.173 (brs, 2H), 3.417 (brs, 4H), 1.556-1.608 (m, 4H), 1.125-1.454 (m, 20H), 0.880 (t, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 181.32, 44.48, 31.75, 29.25, 29.16, 29.08, 26.93, 22.59, 14.03; MS (ESI): m/z 301 $[\text{M}+\text{H}]^+$.

1,3-didodecylthiourea (Entry 7)

White solid, 95%, mp 98 °C; IR ν_{max} (KBr): 3248, 3073, 2924, 1562, 1356 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} = 5.877 (brs, 2H), 3.399 (brs, 4H), 1.561-1.631 (m, 4H), 1.308 (t, J = 6.3 Hz, 36H), 0.881 (t, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 181.37, 44.42, 31.90, 29.64, 29.62, 29.57, 29.52, 29.33, 29.29, 29.03, 26.93, 22.67, 14.09; MS (ESI): m/z 413 $[\text{M}+\text{H}]^+$.

1,3-dicyclopropylthiourea (Entry 8)

White solid, 96%, mp 130 °C (lit.²⁷ 130-131 °C); IR ν_{max} (KBr): 3180, 3088, 2995, 1556, 1274 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 6.513 (brs, 2H), 2.711 (brs, 2H), 0.626-0.849 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 184.13, 25.38, 7.35; MS (ESI): m/z 157 $[\text{M}+\text{H}]^+$.

1,3-dicyclohexylthiourea (Entry 9)

White solid, 95%, mp 180 °C (lit.²⁸ 181 °C); IR ν_{max} (KBr): 3298, 2929, 1554, 1228 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 5.638 (brs, 2H), 3.854 (brs, 2H), 2.03 (d, 4H), 1.131-1.772 (m, 16H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 178.97, 52.82, 32.81, 25.36, 24.64; MS (ESI): m/z 241 $[\text{M}+\text{H}]^+$.

1,3-dibenzylthiourea (Entry 10)

White solid, 97%, mp 146 °C (lit.²⁸ 148 °C); IR ν_{max} (KBr): 3286, 3030, 2937, 1556, 1215 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 7.226-7.289 (m, 10H, Ar), 6.202 (brs, 2H), 4.607 (s, 4H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 181.99, 136.66, 128.86, 127.87, 127.47, 48.48; MS (ESI): m/z 257 $[\text{M}+\text{H}]^+$.

1,3-diphenethylthiourea (Entry 11)

White solid, 97%, mp 93 °C (lit.³¹ 90 °C); IR ν_{max} (KBr): 3201, 3028, 2931, 1560, 1284 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 7.138-7.288 (m, 10H, Ar), 5.872 (brs, 2H), 3.591 (brs, 4H), 2.821 (t, J = 6.7 Hz, 4H); ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 181.63, 138.32, 128.77, 128.74, 126.75, 45.39, 35.11; MS (ESI): m/z 285 $[\text{M}+\text{H}]^+$.

1,3-di((furan-2-yl)methyl)thiourea (Entry 12)

pale brown solid, 90%, mp 73 °C (lit.³¹ 68-73 °C); IR ν_{max} (KBr): 3261, 3064, 2918, 1564, 1267 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} = 7.330-7.332 (m, 2H), 6.525 (brs, 2H), 6.304-6.316 (m, 2H), 6.248-6.255 (m, 2H), 4.626 (d, J = 3.8 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 182.03, 150.22, 142.43, 110.59, 108.17, 41.52; MS (ESI): m/z 237 $[\text{M}+\text{H}]^+$.

1,3-di(2-(thiophen-2-yl)ethyl)thiourea (Entry 13)

White solid, 96%, mp 74 °C (lit.^{16a} 70-75 °C); IR $\nu_{\max}$ (KBr): 3312, 3049, 2938, 1551, 1329 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} = 7.143-7.158 (m, 2H), 6.921-6.942 (m, 2H) 6.821-6.831 (m, 2H), 5.997 (brs, H), 3.667 (d, J = 3.4 Hz, 4H), 3.072 (t, J = 5 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 181.93, 140.69, 127.24, 125.70, 124.25, 45.59, 29.42; MS (ESI): m/z 297 $[\text{M}+\text{H}]^+$.

Thiocarbonohydrazide (Entry 14)

White solid, 98%, mp 168 °C; IR $\nu_{\max}$ (KBr): 3323, 3261, 1517, 960 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} = 4.820 (brs, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 182.64; MS (ESI): m/z 105 $[\text{M}-\text{H}]^+$.

1,5-diphenylthiocarbonohydrazide (Entry 15)

Green Solid, 90%, mp 155 °C; IR $\nu_{\max}$ (KBr): 3267, 3163, 1550, 1492, 1249 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} = 7.408-7.438 (m, 2H), 7.291-7.393 (m, 4H), 7.265-7.193 (m, 4H), 6.757 (brs, 2H), 4.628 (brs, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 183.19, 148.13, 129.20, 121.56, 114.13; MS (ESI): m/z 257 $[\text{M}-\text{H}]^+$.

3. Selected copies of IR, ^1H , ^{13}C NMR and Mass Spectra:

IR spectrum of 1,3-diethylthiourea (Entry 1)

Mass spectrum of 1,3-diethylthiourea (Entry 1)

¹H NMR spectrum of 1,3-diethylthiourea (Entry 1)

¹³C NMR spectrum of 1,3-diethylthiourea (Entry 1)

IR spectrum of 1,3-dipropylthiourea (Entry 2)

Mass spectrum of 1,3-dipropylthiourea (Entry 2)

^1H NMR spectrum of 1,3-dipropylthiourea (Entry 2)

^{13}C NMR spectrum of 1,3-dipropylthiourea (Entry 2)

IR spectrum of 1,3-diisopropylthiourea (Entry 3)

Mass spectrum of 1,3-diisopropylthiourea (Entry 3)

^1H NMR spectrum of 1,3-diisopropylthiourea (Entry 3)

^{13}C NMR spectrum of 1,3-diisopropylthiourea (Entry 3)

IR spectrum of 1,3-dibutylthiourea (Entry 4)

Mass spectrum of 1,3-dibutylthiourea (Entry 4)

^1H NMR spectrum of 1,3-dibutylthiourea (Entry 4)

^{13}C NMR spectrum of 1,3-dibutylthiourea (Entry 4)

IR spectrum of 1,3-dioctylthiourea (Entry 6)

Mass spectrum of 1,3-dioctylthiourea (Entry 6)

¹H NMR spectrum of 1,3-dioctylthiourea (Entry 6)

¹³C NMR spectrum of 1,3-dioctylthiourea (Entry 6)

IR spectrum of 1,3-didodecylthiourea (Entry 7)

Mass spectrum of 1,3-didodecylthiourea (Entry 7)

¹H NMR spectrum of 1,3-didodecylthiourea (Entry 7)

¹³C NMR spectrum of 1,3-didodecylthiourea (Entry 7)

IR spectrum of 1,3-dicyclohexylthiourea (Entry 9)

Mass spectrum of 1,3-dicyclohexylthiourea (Entry 9)

^1H NMR spectrum of 1,3-dicyclohexylthiourea (Entry 9)

^{13}C NMR spectrum of 1,3-dicyclohexylthiourea (Entry 9)

IR spectrum of 1,3-dibenzylthiourea (Entry 10)

Mass spectrum of 1,3-dibenzylthiourea (Entry 10)

¹H NMR spectrum of 1,3-dibenzylthiourea (Entry 10)

¹³C NMR spectrum of 1,3-dibenzylthiourea (Entry 10)

IR spectrum of 1,3-diphenethylthiourea (Entry 11)

Mass spectrum of 1,3-diphenethylthiourea (Entry 11)

¹H NMR spectrum of 1,3-diphenethylthiourea (Entry 11)

¹³C NMR spectrum of 1,3-diphenethylthiourea (Entry 11)

IR spectrum of 1,3-di((furan-2-yl)methyl)thiourea (Entry 12)

Mass spectrum of 1,3-di((furan-2-yl)methyl)thiourea (Entry 12)

¹H NMR spectrum of 1,3-di((furan-2-yl)methyl)thiourea (Entry 12)

¹³C NMR spectrum of 1,3-di((furan-2-yl)methyl)thiourea (Entry 12)

IR spectrum of 1,3-di(2-(thiophen-2-yl)ethyl)thiourea (Entry 13)

Mass spectrum of 1,3-di(2-(thiophen-2-yl)ethyl)thiourea (Entry 13)

¹H NMR spectrum of 1,3-di(2-(thiophen-2-yl)ethyl)thiourea (Entry 13)

¹³C NMR spectrum of 1,3-di(2-(thiophen-2-yl)ethyl)thiourea (Entry 13)