An efficient one-pot synthesis of *bis*-1-(aroyl)-3-(aryl)thiourea

Razieh Mohebat* and Gholam Mohammadian

Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran

A three-component and one-pot reaction between 2,6-diaminopyridine or 1,2-diaminobenzene and ammonium thiocyanate with the subsequent addition of an aroyl chloride afforded the *bis*-1-(aroyl)-3-(aryl)thiourea in excellent yields. It was important to make the thiocyanate derivatives first and then to use those to prepare the thiourea derivatives.

Keywords: *bis*-1-(aroyl)-3-(aryl)thiourea, aroyl chlorides, ammonium thiocyanate, 2,6-diaminopyridine, 1,2-diaminobenzine, three-component reaction

Thiourea derivatives are widely used in many fields including the pharmaceutical industry because of their biological properties such as anticancer[1], antimicrobial[1–3], antibacterial[4], antifungal[5], antimalarial[6] and antituberculosis[7] activities. They have also been found to be organic inhibitors for corrosion because of the protonation of sulfur atoms that can occur in acidic solution[8,9]. Aroylthioureas are usually coordinated to a metal in a monodentate manner through the sulfur atom. However, they can also chelate to metal through S and O atoms, giving a six membered ring system[10]. The synthesis and application of monothioureas is progressing at considerable rate. Recently, the synthesis of their bis-thiourea analogues such as 1,2-bis[*N*′-(2,2-dimethylpropionyl) thioureido] cyclohexane, *N*-(2-methoxybenzoyl)-*N*′-(4-diphenylamine)thiourea, two bisthiourea compounds of 1,2-bis[*N*′-(2-methoxybenzoyl) thioureido]-4-nitrobenzene and 1,2-bis[*N*′-(2-methoxybenzoyl) thioureido]-4-chlorobenzene[11] has also received attention. As part of our current studies,[12] we report an efficient one-pot synthesis of the *bis*-1-(aroyl)-3-(aryl)thiourea, employing readily available starting materials.

Results and discussion

The reaction of diamine derivatives and ammonium thiocyanate in the presence of aroyl chlorides afforded the *bis*-1-(aroyl)-3-(aryl)thiourea in excellent yields. It is important to make the thiocyanate derivatives first and then to use them to prepare the thiourea derivatives (Schemes 1 and 2).

The structures of compounds **5a–f** and **6a–f** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data. For example, the ^{1}H NMR spectrum of **5a** showed two singlets (δ = 10.64 and 11.87 ppm) corresponding to the protons of the NH groups. These disappeared after the addition of a few drops of D_2O to the DMSO solution of **5a**. The aromatic protons resonated between 7.38 and 7.97 ppm.

The ^{13}C NMR spectrum of compound **5a** showed nine distinct signals, which was consistent with the proposed structure. The C=S group resonance in ^{13}C NMR spectra of **5a** appeared at 178.26 ppm. The mass spectrum of **5a** displayed the molecular ion peak at *m/z* = 435. The IR spectrum of compound 5a also supported the suggested structure. Strong absorption bands were observed at 3320 and 1664 cm^{-1} respectively for the NH and carbonyl group.

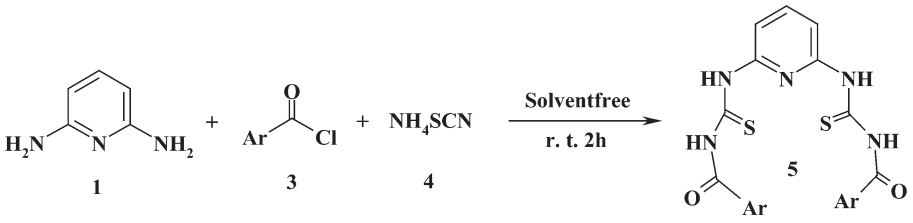
A tentative pathway for this transformation is proposed in Scheme 3.

It is conceivable that the reaction starts with formation of aroyl thiocyanate **7**, followed by addition of diamine derivatives to generate **5** or **6**.

In conclusion, the reaction of diamine derivatives and ammonium thiocyanate in the presence of aroyl chlorides afforded the *bis*-1-(aroyl)-3-(aryl)thiourea in excellent yields. The present procedure has the advantage that the reaction is performed under neutral conditions and the starting material can be used without any activation or modification.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser at the analytical laboratory of Islamic Azad

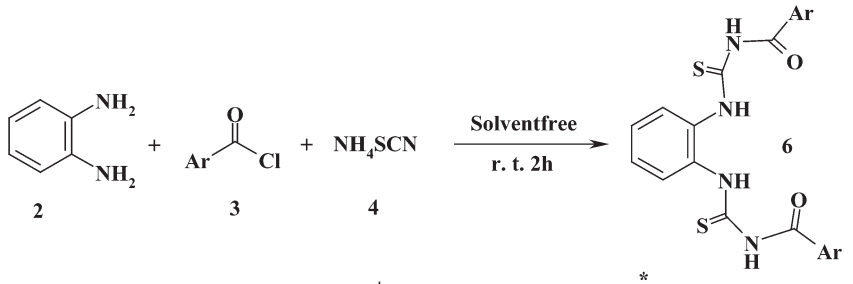


3, 5	Ar	%Yield*
a	phenyl	81
b	o-CH_3-phenyl	85
c	m-CH_3-phenyl	79
d	p-Cl-phenyl	82
e	p-Br-phenyl	81
f	m-NO_2-phenyl	80

* Isolated yields

Scheme 1 Condensation of 2,6-diaminopyridine and ammonium thiocyanate in the presence of aroyl chlorides.

* Correspondent. E-mail: rozitakalami@yahoo.com



3, 6	Ar	%Yield*
a	phenyl	80
b	o-CH_3-phenyl	85
c	m-CH_3-phenyl	78
d	p-Br-phenyl	77
e	m-NO_2-phenyl	72
f	p-NO_2-phenyl	74

* Isolated yields

Scheme 2 Condensation of 1,2-diaminobenzene and ammonium thiocyanate in the presence of aroyl chlorides.

University, Yazd branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation 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 solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

The aroyl chloride (2 mmol) was added to ammonium thiocyanate (0.15 g, 2 mmol) in a 50 mL flask at r.t. via a syringe. The reaction mixture was stirred in a water bath at about 60 °C for 5 min. Then, the diamine (1 mmol) was added at this temperature. The resulting mixture was stirred at r.t. for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, 30 mL distilled water was added over 5 min to the reaction mixture. The resulting precipitate was collected by filtration on a Buchner funnel. The crude product was recrystallised from hot ethanol to obtain the pure compound.

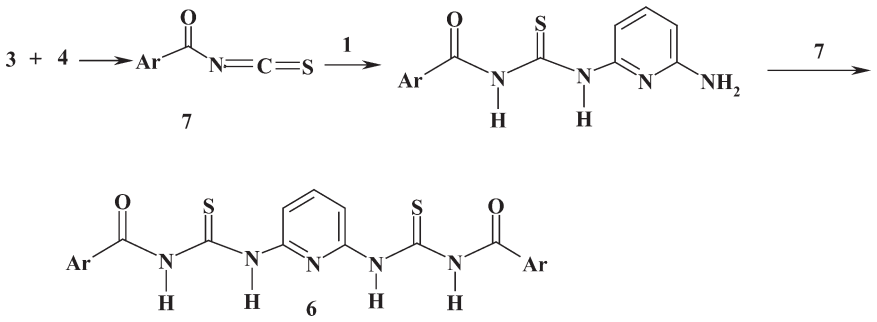
1-(Benzoyl)3-{6-[3-(benzoyl)thioureido]pyridine-2-yl}thiourea (**5a**): Yellow powder; m.p. 228–230 °C, IR (KBr) (ν_{max} cm^{-1}): 3320, 1664, 1623, 1530, 1447. Anal. Calcd for $C_{21}H_{17}N_5O_2S_2$: C, 57.91; H, 3.93; N, 16.08. Found: C, 57.75; H, 4.10; N, 16.20%. MS (*m/z*, %): 435 (5). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.38 (2H, d, ^3J = 6.9 Hz, 2CH), 7.46 (1H, t, ^3J = 6.9 Hz, CH), 7.54 (2H, t, ^3J = 8.0 Hz, 2CH of Ph), 7.64 (4H, t, ^3J = 8.0, 4CH of Ph), 7.97 (4H, d, ^3J = 8.0, 4CH of Ph), 10.64 and 11.87 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 113.24, 128.93, 129.47, 132.91, 134.70, 140.38 and 150.23 (7C aromatic), 171.05 (C=O), 178.26 (C=S) ppm.

1-(2-Methylbenzoyl)3-{6-[3-(2-methylbenzoyl)thioureido]pyridine-2-yl}thiourea (**5b**): Yellow powder; m.p. 207–209 °C, IR (KBr) (ν_{max} cm^{-1}): 3240, 1681, 1619, 1560, 1440. Anal. Calcd for $C_{23}H_{21}N_5O_2S_2$: C, 59.59; H, 4.57; N, 15.11. Found: C, 59.41; H, 4.40; N, 15.30%. MS (*m/z*, %): 463 (7). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.38 (6H, s, 2CH_3), 7.30 (2H, d, ^3J = 6.8 Hz, 2CH), 7.38 (1H, t, ^3J = 6.8 Hz, CH), 7.42 (2H, t, ^3J = 7.5 Hz, 2CH), 7.52 (2H, d, ^3J = 7.5 Hz, 2CH), 7.82 (2H, d, ^3J = 7.5 Hz, 2CH), 8.02 (2H, t, ^3J = 7.5 Hz, 2CH), 10.75 and 11.79 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 19.98 (CH_3), 113.58, 126.00, 128.72, 131.13, 131.59, 134.25, 136.69, 140,50 and 150.31 (9C aromatic), 171.19 (C=O), 178.48 (C=S) ppm.

1-(3-Methylbenzoyl)3-{6-[3-(3-methylbenzoyl)thioureido]pyridine-2-yl}thiourea (**5c**): Yellow powder; m.p. 197–199 °C, IR (KBr) (ν_{max} cm^{-1}): 3390, 1673, 1619, 1518, 1448. Anal. Calcd for $C_{23}H_{21}N_5O_2S_2$: C, 59.59; H, 4.57; N, 15.11. Found: C, 59.41; H, 4.40; N, 15.30%. MS (*m/z*, %): 463 (3). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.37 (6H, s, 2CH_3), 7.40 (2H, d, ^3J = 6.4 Hz, 2CH), 7.46 (1H, t, ^3J = 6.4 Hz, CH), 7.65 (2H, d, ^3J = 7.6 Hz, 2CH), 7.82 (2H, s, CH), 7.87 (2H, d, ^3J = 7.6 Hz, 2CH), 8.01 (2H, t, ^3J = 7.6 Hz, 2CH), 10.75 and 11.76 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 21.28 (CH_3), 113.44, 126.40, 128.81, 129.06, 129.67, 134.34, 138.31, 140.49 and 150.29 (9C aromatic), 168.94 (C=O), 178.57 (C=S) ppm.

1-(4-Chlorobenzoyl)3-{6-[3-(4-chlorobenzoyl)thioureido]pyridine-2-yl}thiourea (**5d**): Yellow powder; m.p. 244–246 °C, IR (KBr) (ν_{max} cm^{-1}): 3327, 1670, 1626, 1580, 1442. Anal. Calcd for $C_{21}H_{15}Cl_2N_5O_2S_2$: C, 50.00; H, 3.00; N, 13.88. Found: C, 50.11; H, 2.94; N, 13.73%. MS (*m/z*, %): 503 (5). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.38 (2H, d, ^3J = 6.4 Hz, 2CH), 7.46 (1H, t, ^3J = 6.4 Hz, CH), 7.79 (4H, d, ^3J = 8.0 Hz, 4CH), 7.90 (4H, d, ^3J = 8.0 Hz, 4CH), 10.54 and 11.90 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 113.11, 128.80, 129.55, 133.28, 136.12, 140.32 and 150.18 (7C aromatic), 169.18 (C=O), 180.05 (C=S) ppm.

1-(4-Bromobenzoyl)3-{6-[3-(4-bromobenzoyl)thioureido]pyridine-2-yl}thiourea (**5e**): Yellow powder; m.p. 253–255 °C, IR (KBr) (ν_{max} cm^{-1}): 3315, 1672, 1620, 1585, 1448. Anal. Calcd for $C_{21}H_{15}Br_2N_5O_2S_2$: C, 42.51; H, 2.55; N, 11.80. Found: C, 42.41; H, 2.70; N, 11.95%. MS (*m/z*, %): 593 (6). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.32 (2H,



Scheme 3 Suggested pathway for formation of compound **6**.

d, ^3J = 6.5 Hz, 2CH), 7.41 (1H, t, ^3J = 6.5 Hz, CH), 7.71 (4H, d, ^3J = 8.4 Hz, 4CH), 7.92 (4H, d, ^3J = 8.4 Hz, 4CH), 10.63 and 11.98 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 113.19, 127.23, 130.95, 132.38, 135.88, 140.34 and 150.10 (7C aromatic), 169.04 (C=O), 179.78 (C=S) ppm.

1-(3-Nitrobenzoyl)3-{6-[3-(3-nitrobenzoyl)thioureido]pyridine-2-yl} thiourea (**5f**): Yellow powder; m.p. 210–212 °C, IR (KBr) (ν_{max} cm^{-1}): 3355, 1670, 1609, 1523, 1447, 1345. Anal. Calcd for $C_{21}H_{15}N_7O_6S_2$: C, 48.00; H, 2.88; N, 18.66. Found: C, 48.18; H, 3.02; N, 18.89%. MS (*m/z*, %): 525 (5). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.44 (2H, d, ^3J = 6.4 Hz, 2CH), 7.53 (1H, t, ^3J = 6.4 Hz, CH), 7.93 (1H, t, ^3J = 6.4 Hz, CH), 8.34 (2H, d, ^3J = 7.8 Hz, 2CH), 8.40 (2H, t, ^3J = 8.0 Hz, CH)), 8.76 (2H, s, 2CH), 10.99 and 12.20 (4H, 2s, 4NH) ppm. ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 112.22, 126.92, 127.86, 130.47, 130.57, 134.81, 140,67, 147.76 and 148.03 (9C aromatic), 168.75 (C=O), 178.22 (C=S) ppm.

1-(Benzoyl)3-{2-[3-(benzoyl)thioureido]phenyl}thiourea (**6a**): White powder; m.p. 222–224 °C, IR (KBr) (ν_{max} cm^{-1}): 3200, 1669, 1594, 1509, 1483. Anal. Calcd for $C_{22}H_{18}N_4O_2S_2$: C, 60.81; H, 4.18; N, 12.89. Found: C, 60.96; H, 4.30; N, 12.65%. MS (*m/z*, %): 434 (7). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.34 (2H, dd, ^3J = 7.2 Hz and ^4J = 2.6 Hz, 2CH), 7.42 (2H, dd, ^3J = 7.2 Hz and ^4J = 2.6 Hz, 2CH), 7.51 (4H, t, ^3J = 7.4 Hz, 4CH of Ph), 7.66 (2H, t, ^3J = 7.2, 2CH of Ph), 8.01 (4H, d, ^3J = 7.4, 4CH of Ph), 10.12 and 11.74 (4H, 2s, 4NH) ppm. ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 107.36, 125.75, 128.35, 128.66, 131.99, 133.14 and 134.13 (7C aromatic), 168.31 (C=O), 180.43 (C=S) ppm.

1-(2-Methylbenzoyl)3-{2-[3-(2-Methylbenzoyl)thioureido]phenyl} thiourea (**6b**): White powder; m.p.195–197 °C, IR (KBr) (ν_{max} cm^{-1}): 3215, 1666, 1599, 1509, 1474. Anal. Calcd for $C_{24}H_{22}N_4O_2S_2$: C, 62.32; H, 4.79; N, 12.11. Found: C, 62.50; H, 4.90; N, 12.25%. MS (*m/z*, %): 462 (11). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.32 (6H, s, $2CH_3$), 7.29 (2H, dd, ^3J = 6.8 Hz and ^4J = 2.5 Hz, 2CH), 7.44 (2H, t, ^3J = 7.4 Hz, 2CH), 7.51 (2H, dd, ^3J = 6.8 Hz and ^4J = 2.5 Hz, 2CH), 7.59 (2H, d, ^3J = 7.6 Hz, 2CH), 7.71 (2H, t, ^3J = 7.4 Hz, 2CH), 7.94 (2H, d, ^3J = 7.6 Hz, 2CH), 9.75 and 11.84 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): 19.64 (CH_3), 107.03, 125.16, 126.05, 128.57, 130.63, 131.04, 131.73, 134.39 and 136.42 (9C aromatic), 168.25 (C=O), 178.83 (C=S) ppm.

1-(3-Methylbenzoyl)3-{2-[3-(3-Methylbenzoyl)thioureido]phenyl} thiourea (**6c**): White powder; m.p.179–181 °C, IR (KBr) (ν_{max} cm^{-1}): 3265, 1645, 1594, 1525, 1474. Anal. Calcd for $C_{24}H_{22}N_4O_2S_2$: C, 62.32; H, 4.79; N, 12.11. Found: C, 62.50; H, 4.90; N, 12.25%. MS (*m/z*, %): 462 (5). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.35 (6H, s, $2CH_3$), 7.32 (2H, dd, ^3J = 7.0 Hz and ^4J = 2.6 Hz, 2CH), 7.57 (2H, dd, ^3J = 7.0 Hz and ^4J = 2.6 Hz, 2CH), 7.64 (2H, t, ^3J = 7.5 Hz, 2CH), 7.70 (2H, d, ^3J = 7.5 Hz, 2CH), 7.82 (2H, d, ^3J = 7.5 Hz, 2CH), 7.94 (2H, d, ^3J = 7.5 Hz, 2CH), 9.77 and 11.73 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 19.31 (CH_3), 105.62, 125.71, 126.20, 127.98, 130.49, 130.90, 135.37, 135.55 and 136.45 (9C aromatic), 168.29 (C=O), 177.96 (C=S) ppm.

1-(4-Bromobenzoyl)3-{2-[3-(4-Bromobenzoyl)thioureido]phenyl} thiourea (**6d**): White powder; m.p. 245–247 °C, IR (KBr) (ν_{max} cm^{-1}): 3256, 1670, 1605, 1520, 1442. Anal. Calcd for $C_{22}H_{16}Br_2N_4O_2S_2$: C, 44.61; H, 2.72; N, 9.46. Found: C, 44.74; H, 2.60; N, 9.35%. MS (*m/z*, %): 592 (7). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.36 (2H, dd, ^3J = 7.0 Hz and ^4J = 2.8 Hz, 2CH), 7.55 (2H, dd, ^3J = 7.0 Hz and ^4J = 2.8 Hz, 2CH), 7.74 (4H, d, ^3J = 8.0 Hz, 4CH), 8.02 (4H, d, ^3J = 8.0 Hz, 4CH), 10.22 and 11.75 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 107.32, 125.17, 127.78, 130.28, 131,68, 132.11, 135.67 and 135.88 (7C aromatic), 168.31 (C=O), 180.43 (C=S) ppm.

1-(3-Nitrobenzoyl)3-{2-[3-(3-Nitrobenzoyl)thioureido]phenyl} thiourea (**6e**): White powder; m.p. 203–205 °C, IR (KBr) (ν_{max} cm^{-1}): 3230, 1671, 1612, 1522, 1471, 1346. Anal. Calcd for $C_{22}H_{16}N_6O_6S_2$: C, 50.38; H, 3.07; N, 16.02. Found: C, 50.23; H, 3.20; N, 15.95%. MS (*m/z*, %): 524 (3). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.33 (2H, dd, ^3J = 6.9 Hz and ^4J = 2.6 Hz, 2CH), 7.57 (2H, dd, ^3J = 6.9 Hz and ^4J = 2.6 Hz, 2CH), 7.85 (2H, d, ^3J = 8.0 Hz, 2CH), 8.29 (2H, t, ^3J = 8.0 Hz, 2CH), 8.37 (2H, d, ^3J = 8.0 Hz, 2CH), 8.84 (2H, s, 2CH), 10.37 and 12.10 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 108.20, 123.64, 125.85, 127.37, 130.18, 131.17, 134.25, 134.99 and 147.59 (9C aromatic), 167.38 (C=O), 181.49 (C=S) ppm.

1-(4-Nitrobenzoyl)3-{2-[3-(4-Nitrobenzoyl)thioureido]phenyl}thiourea (**6f**): White powder; m.p. 211–213 °C, IR (KBr) (ν_{max} cm^{-1}): 3255, 1664, 1602, 1526, 1341. Anal. Calcd for $C_{22}H_{16}N_6O_6S_2$: C, 50.38; H, 3.07; N, 16.02. Found: C, 50.23; H, 3.20; N, 15.95%. MS (*m/z*, %): 524 (5). ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.32 (2H, dd, ^3J = 7.0 Hz and ^4J = 2.5 Hz, 2CH), 7.67 (2H, dd, ^3J = 6.9 Hz and ^4J = 2.5 Hz, 2CH), 8.08 (4H, d, ^3J = 8.7 Hz, 4CH), 8.36 (4H, d, ^3J = 8.8 Hz, 4CH), 10.28 and 12.11 (4H, 2s, 4NH) ppm.^{13}C NMR (125.8 MHz, d_6-DMSO): δ 108.04, 123.37, 125.88, 130.20, 133.36, 140.20 and 149.82 (7C aromatic), 166.84 (C=O), 180.10 (C=S) ppm.

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