An expeditious and solvent-free approach to substituted bis-thioureas and bis-thiosemicarbazides

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An expeditious, high-yield and green approach to substituted bis-thioureas and bis-thiosemicarbazides by grinding the mixture of pyridine-2,6-dicarbonyl dichloride with ammonium thiocyanate and arylamines or aroyl hydrazines at room temperature under solvent-free condition *via* one-pot procedure is described.

Keywords: thioureas, thiosemicarbazides, solvent-free, grinding

The manufacture of fine chemicals for preparation of pharmaceuticals, agrochemicals and new materials is an ever expanding area of interest. Thioureas and thiosemicarbazides are of importance in medicinal chemistry[1] due to their biological activity,[2] such as against bacteria and microbial infection,[3] as fungicides, herbicides, rodenticides, phenoloxidase enzymatic inhibitors,[4] anti-HIV[5] and tuberculostatic[6] agents. Moreover, they are widely used in the preparation of corresponding semicarbazides,[7] metal complexes[8] and heterocyclic compounds.[9]

Besides this, the using of bis-thioureas and bis-thiosemicarbazides has emerged as a powerful method in analytical chemistry, for the identification of tantalum,[10] atomic absorption analysis,[11] emission spectral analysis,[12] extraction spectrophotometric analysis,[13] electrochemical analysis[14] and chromatographic analysis.[15] On the other hand, pyridine derivatives are also widely applied in medicine and agriculture, furthermore, pyridine is a good ligand. According to Lewis theory of acids and bases, the characteristic structure of pyridine and R–NH–CS–NH–R' which includes atom of N and S that have the strong capacity of complex and can form steady complex between regents and metal ions. In view of above, we report here the preparation of a new series of compounds bearing both pyridine and a R–NH–CS–NH–R' moiety.

Pyridine-2,6-dicarbonyl dichloride **1** was ground with ammonium thiocyanate in the presence of PEG-400 in a mortar at room temperature until the acid chloride **1** disappeared and pyridine-2,6-dicarbonyl diisothiocyanate **2** formed according to TLC analysis.

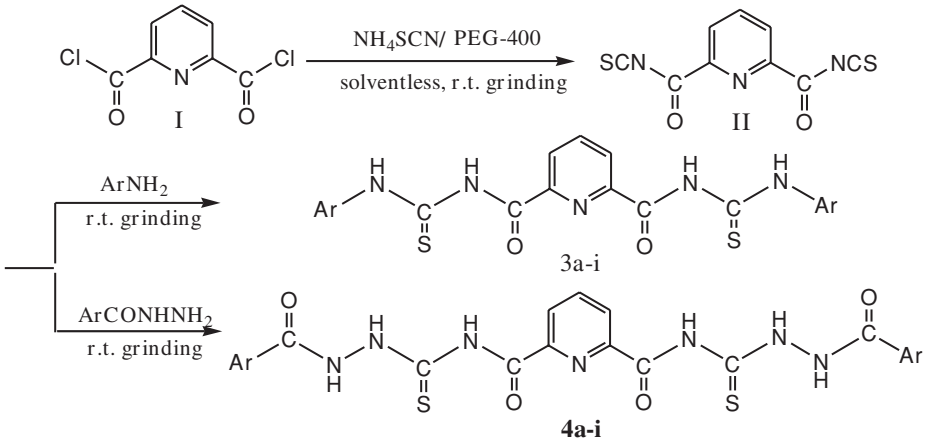
Compound **2** was ground *in situ* with an equivalent of arylamines or aroyl hydrazides until the significant colour changes were observed and the products (**3** or **4**) are formed (monitored by TLC). Compounds **3** and **4**, those were of acceptable purity for most purposes, were given in excellent yield only by washing the resulting solid using water. The overall reaction can be completed within 8 min in 86–99% yield (Scheme 1).

In conclusion, the title compounds can be expeditiously synthesised by one-pot procedure under solvent-free and phase transfer catalysis conditions in excellent yields. The features of easy handle and no need of any hazardous solvents make this protocol more suitable to combinatorial synthesis and industrial applications.

Experimental

Melting points were determined on XT-4 thermal apparatus and the thermometer was uncorrected. Microwave irradiation was carried out in a Galanz domestic microwave oven. ^{1}H NMR spectra were obtained on a Bruker Avanci-D2X 200MHz instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. IR spectra were recorded using KBr pellets on a Nicolet AVATAR 360 FT-IR. Elemental analyses were performed on Carlo-Erba 1106 Elemental Analysis instrument. The aroyl hydrazides[12] were prepared according to the literature method. Arylamines and PEG-400 were commercially available and used as received.

The mixture of pyridine-2,6-dicarbonyl dichloride 1 (0.5 mmol), ammonium thiocyanate (1 mmol) and PEG-400 (0.02 mmol) was



3a-i Ar = C_6H_5, o-$NO_2C_6H_4$, m-$NO_2C_6H_4$, p-$NO_2C_6H_4$, p-$CH_3C_6H_4$, o-ClC_6H_4, p-ClC_6H_4, Á-$C_{10}H_7$, Â-$C_{10}H_7$

4a-i Ar = C_6H_5, m-$NO_2C_6H_4$, p-$NO_2C_6H_4$, o-$CH_3OC_6H_4$, p-$CH_3OC_6H_4$, o-ClC_6H_4, p-ClC_6H_4, o-IC_6H_4, p-IC_6H_4

Scheme 1

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ground in an agate mortar with a pestle for 4 min, until an orange solid was formed, and TLC indicated the disappearance of 1 and the formation of a new compound. Then arylamine or aroyl hydrazide (0.5 mmol) was added *in situ,* and the mixture was further ground for 4–6 min until a colour change was observed (monitored by TLC). Then the resulting solid was washed with water (3 × 10 ml) and the product was afforded as solid. The analytic sample was obtained by recrystallisation from DMF and EtOH.

3a: Yield 92% m.p. 208–209 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.31–7.85 (m, 10H, Ar–H), 8.31–8.53 (m, 3H, C_5H_3N), 11.97 (s, 2H, NH), 12.23 (s, 2H, NH); IR (KBr) ν 3240, 1694, 1158cm^{-1}; Anal. calcd for $C_{21}H_{17}N_5O_2S_2$: C 57.92, H 3.93, N 16.08; found: C 57.86, H 3.91, N 16.14.

3b: Yield 96% m.p. 224–225 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.45–7.99 (m, 8H, Ar–H), 8.36–8.45 (m, 3H, C_5H_3N), 12.09 (s, 2H, NH), 12.39 (s, 2H, NH); IR (KBr) ν 3358, 1707, 1164cm^{-1}; Anal. calcd for $C_{21}H_{15}N_7O_6S_2$: C 48.00, H 2.88, N 18.66; found: C 48.12, H 2.87, N 18.71.

3c: Yield 94% m.p. 225–227 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.48–7.97 (m, 8H, Ar–H), 8.39–8.47 (m, 3H, C_5H_3N), 12.14 (s, 2H, NH), 12.48 (s, 2H, NH); IR (KBr) ν 3364, 1706, 1161cm^{-1}; Anal. calcd for $C_{21}H_{15}N_7O_6S_2$: C 48.00, H 2.88, N 18.66; found: C 47.93, H 2.89, N 18.64.

3d: Yield 95% m.p. 221–222 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.43–7.96 (m, 8H, Ar–H), 8.34–8.48 (m, 3H, C_5H_3N), 12.12 (s, 2H, NH), 12.43 (s, 2H, NH); IR (KBr) ν 3336, 1694, 1164cm^{-1}; Anal. calcd for $C_{21}H_{15}N_7O_6S_2$: C 48.00, H 2.88, N 18.66; found: C 47.86, H 2.87, N 18.62.

3e: Yield 98% m.p. 214–215 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.34(s, 6H, CH_3), 7.28–7.86 (m, 8H, Ar–H), 8.32–8.44 (m, 3H, C_5H_3N), 12.03 (s, 2H, NH), 12.35 (s, 2H, NH); IR (KBr) ν 3330, 1690, 1164cm^{-1}; Anal. calcd for $C_{23}H_{21}N_5O_2S_2$: C 59.59, H 4.57, N 15.11; found: C 59.67, H 4.58, N 15.07.

3f: Yield 91% m.p. 205–206 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.31–7.87 (m, 8H, Ar–H), 8.35–8.43 (m, 3H, C_5H_3N), 12.04 (s, 2H, NH), 12.33 (s, 2H, NH); IR (KBr) ν 3340, 1686, 1154cm^{-1}; Anal. calcd for $C_{21}H_{15}N_5O_2S_2Cl_2$: C 50.01, H 3.00, N 13.88; found: C 50.04, H 2.97, N 13.86.

3g: Yield 96% m.p. 216–217 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.27–7.88 (m, 8H, Ar–H), 8.35–8.41 (m, 3H, C_5H_3N), 12.05 (s, 2H, NH), 12.34 (s, 2H, NH); IR (KBr) ν 3360, 1694, 1154cm^{-1}; Anal. calcd for $C_{21}H_{15}N_5O_2S_2Cl_2$: C 50.01, H 3.00, N 13.88; found: C 49.95, H 3.01, N 13.89.

3h: Yield 99% m.p. 234–235 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.29–8.01 (m, 14H, Ar–H), 8.44–8.58 (m, 3H, C_5H_3N), 12.07 (s, 2H, NH), 12.31 (s, 2H, NH); IR (KBr) ν 3360, 1696, 1154cm^{-1}; Anal. calcd for $C_{29}H_{21}N_5O_2S_2$: C 65.03, H 3.95, N 13.07; found: C 65.09, H 3.96, N 13.05.

3I: Yield 97% m.p. 241–242 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.28–7.96 (m, 14H, Ar–H), 8.47–8.59 (m, 3H, C_5H_3N), 12.06 (s, 2H, NH), 12.48 (s, 2H, NH); IR (KBr) ν 3360, 1694, 1154cm^{-1}; Anal. calcd for $C_{29}H_{21}N_5O_2S_2$: C 65.03, H 3.95, N 13.07; found: C 64.94, H 3.93, N 13.04.

4a: Yield 87% m.p. 184–186 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.26–7.98 (m, 10H, Ar–H), 8.37–8.51 (m, 3H, C_5H_3N), 11.21 (s, 2H, NH), 12.38 (s, 4H, NH); IR (KBr) ν 3236, 3124, 1688, 1657, 1174cm^{-1}; Anal. calcd for $C_{23}H_{19}N_7O_4S_2$: C 52.97, H 3.67, N 18.80; found: C 53.02, H 3.66, N 18.76.

4b: Yield 87% m.p. 246–247 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.35–8.11 (m, 8H, Ar–H), 8.41–8.49 (m, 3H, C_5H_3N), 11.33 (s, 2H, NH), 12.41 (s, 4H, NH); IR (KBr) ν 3360, 3163, 1690, 1674, 1172cm^{-1}; Anal. calcd for $C_{23}H_{17}N_9O_8S_2$: C 45.17, H 2.80, N 20.61; found: C 45.05, H 2.81, N 20.67.

4c: Yield 91% m.p. 232–234 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.38–8.14 (m, 8H, Ar–H), 8.43–8.50 (m, 3H, C_5H_3N), 11.32 (s, 2H, NH), 12.43 (s, 4H, NH); IR (KBr) ν 3204, 3104, 1682, 1648, 1170cm^{-1}; Anal. calcd for $C_{23}H_{17}N_9O_8S_2$: C 45.17, H 2.80, N 20.61; found: C 45.25, H 2.79, N 20.64.

4d: Yield 86% m.p. 201–202 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.83(s, 6H, CH_3), 7.04–7.89 (m, 8H, Ar–H), 8.36–8.46 (m, 3H, C_5H_3N), 11.12 (s, 2H, NH), 12.25 (s, 4H, NH); IR (KBr) ν 3288, 3248, 1688, 1658, 1172cm^{-1}; Anal. calcd for $C_{25}H_{23}N_7O_6S_2$: C 51.63, H 3.99, N 16.86; found: C 51.58, H 3.97, N 16.89.

4e: Yield 92% m.p. 193–194 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.85(s, 6H, CH_3), 7.07–7.95 (m, 8H, Ar–H), 8.35–8.47 (m, 3H, C_5H_3N), 11.10 (s, 2H, NH), 12.26 (s, 4H, NH); IR (KBr) ν 3256, 3072, 1688, 1666, 1174cm^{-1}; Anal. calcd for $C_{25}H_{23}N_7O_6S_2$: C 51.63, H 3.99, N 16.86; found: C 51.71, H 4.00, N 16.87.

4f: Yield 97% m.p. 229–230 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.27–8.01 (m, 8H, Ar–H), 8.35–8.48 (m, 3H, C_5H_3N), 11.19 (s, 2H, NH), 12.35 (s, 4H, NH); IR (KBr) ν 3226, 3184, 1695, 1678, 1189cm^{-1}; Anal. calcd for $C_{23}H_{17}N_7O_4S_2Cl_2$: C 46.79, H 2.90, N 16.61; found: C 46.73, H 2.89, N 16.62.

4g: Yield 88% m.p. 204–205 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.28–8.02 (m, 8H, Ar–H), 8.36–8.46 (m, 3H, C_5H_3N), 11.17 (s, 2H, NH), 12.36 (s, 4H, NH); IR (KBr) ν 3228, 3188, 1680, 1663, 1172cm^{-1}; Anal. calcd for $C_{23}H_{17}N_7O_4S_2Cl_2$: C 46.79, H 2.90, N 16.61; found: C 46.86, H 2.89, N 16.64.

4h: Yield 90% m.p. 214–216 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.26–8.03 (m, 8H, Ar–H), 8.35–8.48 (m, 3H, C_5H_3N), 11.19 (s, 2H, NH), 12.33 (s, 4H, NH); IR (KBr) ν 3248, 3116, 1688, 1673, 1170cm^{-1}; Anal. calcd for $C_{23}H_{17}N_7O_4S_2I_2$: C 35.72, H 2.22, N 12.68; found: C 35.68, H 2.24, N 12.71.

4I: Yield 94% m.p. 218–219 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.28–8.03 (m, 8H, Ar–H), 8.36–8.47 (m, 3H, C_5H_3N), 11.18 (s, 2H, NH), 12.34 (s, 4H, NH); IR (KBr) ν 3248, 3216, 1688, 1653, 1172cm^{-1}; Anal. calcd for $C_{23}H_{17}N_7O_4S_2I_2$: C 35.72, H 2.22, N 12.68; found: C 35.63, H 2.21, N 12.66.

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