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Synthesis and reactions of 1,10-phenanthroline-2(1*H*)-thione: a facile synthesis of 2,2′-thiobis-1,10-phenanthroline

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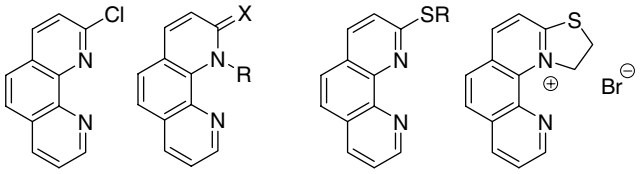
Abstract—Treatment of 2-chloro-1,10-phenanthroline with NaSH hydrate in DMF, Na_2S nonahydrate in DMF or thiourea in refluxing ethanol readily afforded 1,10-phenanthroline-2(1*H*)-thione. This thione undergoes reaction with 1,2-dibromoethane to yield a thiazole bromide salt. Upon heating the thione in diphenyl ether with 2-chloro-1,10-phenanthroline, the hydrochloride salt of 2,2′-thiobis-1,10-phenanthroline precipitated and could be converted into the corresponding free base on treatment with aqueous base. Heteroaryl substituted sulfides could be prepared by treatment of 2-chloro-1,10-phenanthroline with pyridine-2-thione or pyrimidine-1-thione with potassium carbonate in DMF.

Treatment of 2-chloro-1,10-phenanthroline (**1**) with NaSH hydrate in DMF,[1,2] Na_2S nonahydrate in DMF[3] or thiourea in refluxing ethanol[4] led to 1,10-phenantholine-2(1*H*)-thione (**2a**). The structure of **2a** as the thione, rather than the tautomeric thiol, was firmly established by ^{1}H NMR and ^{13}C NMR comparative data with related analogues. The gas phase and solvent dependent tautomeric equilibrium between pyridine-2-thione and 2-mercaptopyridine (thiol) has been reported using FTIR experiments and ab initio and density function theoretical computations.[5] In solvents such as heptane or dichloromethane, the thione tautomer is more stable in solution. The ^{1}H NMR spectrum of pyridine-2-thione in DMSO-d_6 exhibits the NH absorption at 13.25 ppm and the ^{13}C NMR C=S absorption at 177.7 ppm.[6] The C=S absorption in the ^{13}C NMR spectrum in $CDCl_3$ occurs at 176.4 ppm.[7] The ^{13}C NMR resonances for C–S in $CDCl_3$ for 2-methylthiopyridine[8] and analogue **3a**[9] are at 159.9 ppm and 161.2 ppm, respectively. The ^{1}H NMR spectrum of **2a** in $CDCl_3$ exhibits the NH peak at 12.35 ppm and the ^{13}C NMR thione carbon at 181.0 ppm. The *N*-methyl thione analogue **2b**[10] in $CDCl_3$ exhibits the ^{13}C NMR C=S resonance at 185.1 ppm. The comparative ^{13}C NMR chemical shifts in $CDCl_3$ for the C=S in pyridine-2-thione (176.4 ppm) and *N*-methylpyridine-2-thione (180.2 ppm) show an upfield shift of +3.8 ppm, respectively. A similar comparison of the ^{13}C NMR data for **2a** and **2b** shows an upfield shift of +4.1 ppm, respectively. These comparisons suggest that, at least in solution, the predominant tautomer is thione **2a**.

Thione **2a** on treatment with neat CH_3I readily underwent methylation in sulfur to afford the hydroiodide salt of **3a**, which on addition of aqueous base afforded **3a**. Compound **3a** could also be readily prepared by treatment of **1** with sodium methylthiolate in DMF at room temperature in DMF as solvent.[9]



1 **2a**, X = S, R = H; **b**, X = S, R = Me; **c**, X = O, R = Me **3a**, R = Me; **b**, R = $(CH_2)_3Br$ **4**

Upon heating **2a** with 1,3-dibromopropane at reflux, the S-alkylated product **3b** (as the hydrobromide salt) was formed which upon basification yielded the free base **3b**.[11] A similar reaction procedure using 1,2-dibromoethane led to thiazole salt **4** readily identifiable by the

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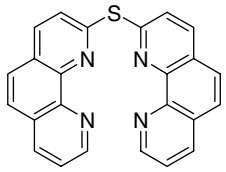
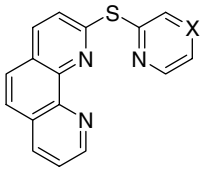
triplets at δ 6.40 and 4.02 ppm (DMSO-d_6) for the protons adjacent to the quaternary nitrogen and the sulfur, respectively.[12]

Of particular interest is the observation that upon heating a solution of equimolar amounts of **1** and **2a** in diphenyl ether (185–190 °C), the hydrochloride salt of 2,2′-thiobis-1,10-phenanthroline **5** precipitated and was easily isolated by filtration.[13] Treatment of this salt with aqueous KOH led to 2,2′-thiobis-1,10-phenanthroline **5**.[14] Compound **5** can also be readily obtained by treatment of **1** and **2** with K_2CO_3 in refluxing DMF. The thermal procedure is clearly superior to a previous preparation of **5** which required heating **1** and **2a** in KOH/DMA at reflux for 2.5 h.[2]



5



6a, X = CH
b, X = N

The structure of the product, previously formulated as the hydrochloride salt of **5**, formed on heating **1** under an atmosphere of H_2S gas for 10 h at 180 °C must be revised to **2a**.[15] The complete ^{1}H NMR spectrum, available in the Supplementary data of Ref. 15, exactly matches the spectrum of our preparations of **2a**.

Since our interests in molecules related to **5** deal with DNA metal-binding ligands, the reactions of two heterocyclic thiones with 2-chloro-1,10-phenanthroline (**1**) were also studied. Treatment of **1** with pyridine-2-thione or pyrimidine-1-thione in DMF in the presence of K_2CO_3 readily afforded **6a**[16] or **6b**,[17] respectively.

Acknowledgement

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References and notes

1. 2-Chloro-1,10-phenanthroline (**1**) (1 M equiv) and NaSH hydrate (3 M equiv) in DMF (dark green solution) were kept at 120 °C for 3 h. The cooled mixture was quenched into water, treated with dilute acetic acid and the yellow thione **2a** (90%) was collected by filtration, mp 214–217 °C; lit.[2] mp 221–222 °C. ^{1}H NMR ($CDCl_3$) δ 12.35 (br s), 8.95 (m, 1H), 8.22 (m, 1H), 7.65 (m, 5H); ^{1}H NMR (DMSO-d_6) δ 12.25 (br s), 9.07 (dd, $J = 1.5$, 4.3 Hz, 1H), 8.55 (dd, $J = 1.4$, 8.2 Hz, 1H), 8.07 (d, $J = 9.1$ Hz, 1H), 7.90 (m, 2H), 7.83 (m, 1H), 7.55 (d, $J = 9.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 181.0, 149.8, 136.0, 135.9, 135.1, 134.4, 134.1, 128.4, 124.8, 123.8, 123.1, 121.1.
2. Hunziker, M.; Hauser, U. *Heterocycles* **1982**, *19*, 2131. The rather drastic treatment of **1** with KSH in ethanol in a Teflon cup at 140 °C for 24 h led to **2a**.
3. 2-Chloro-1,10-phenanthroline (**1**) (1 M equiv) and Na_2S nonahydrate in DMF (green solution) were stirred at 60 °C for 4 h. The mixture was quenched into water, aq acetic acid was added to afford a yellow solid which was collected by filtration to yield product **2a** (85 mg, 90%), quite pure as evidenced by ^{1}H NMR analysis. The product was further purified by gravity column chromatography over silica gel using CH_2Cl_2/MeOH (99:1) as the eluent. The fractions were allowed to evaporate to afford beautiful yellow needles of **2a** (55 mg, 56%).
4. 2-Chloro-1,10-phenanthroline (**1**) (1 M equiv) and thiourea (3 M equiv) were refluxed in ethanol for 24 h. The resultant solid was collected by filtration, dissolved in dichloromethane to remove a trace of insoluble substances and concentrated to yield **2a** (37%).
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9. A mixture of **1** and $NaSCH_3$ (3 M excess) was stirred at room temperature for 20 h, quenched into water and the sulfide was collected by filtration (80%), mp 52–54 °C; ^{1}H NMR ($CDCl_3$) δ 9.17 (dd, $J = 1.8$, 4.4 Hz, 1H); 8.23 (dd, $J = 1.8$, 8.2 Hz, 1H), 8.01 (d, $J = 8.5$ Hz, 1H), 7.73 (m, 2H), 7.69 (dd, $J = 4.3$, 8.0 Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 1H), 2.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 161.2, 150.3, 146.0, 145.4, 136.2, 135.7, 129.2, 126.5, 125.9, 125.1, 122.9, 122.0, 13.6.
10. Unpublished observations. Prepared by treatment of **3c** with Lawesson's reagent in THF.
11. Thione **2a** was heated with excess 1,3-dibromopropane (120 °C, 1 h). The hydrobromide salt was collected by filtration (80%). ^{1}H NMR (DMSO-d_6) δ 9.37 (dd, $J = 1.5$, 5.3 Hz, 1H), 9.26 (d, $J = 8.2$ Hz, 1H), 8.51 (d, $J = 8.6$ Hz, 1H), 8.30 (m, 1H), 8.28 (d, $J = 8.8$ Hz, 1H), 8.22 (d, $J = 8.8$ Hz, 1H), 7.90 (d, $J = 8.6$ Hz, 1H), 3.74 (m, 4H), 2.30 (quintet, $J = 6.8$ Hz, 2H). Treatment of this salt with water and aqueous KOH followed by extraction with dichloromethane and evaporation led to **3b** (49%). ^{1}H NMR (DMSO-d_6) δ 9.18 (dd, $J = 1.6$, 4.5 Hz, 1H), 8.67 (d, $J = 7.5$ Hz, 1H), 8.37 (d, $J = 6.5$ Hz, 1H), 8.00 (m, 2H), 7.90 (m, 1H), 7.72 (d, $J = 8.5$ Hz, 1H), 3.76 (t, $J = 6.8$ Hz, 2H), 3.59 (t, $J = 6.8$ Hz, 2H), 2.36 (quintet, $J = 6.8$ Hz, 2H).
12. A mixture of **2a** and 1,2-dibromoethane was heated at reflux (6 h), the product was collected and recrystallized from water; mp >300 °C. ^{1}H NMR (DMSO-d_6) δ 9.26 (dd, $J = 1.4$, 4.0 Hz, 1H), 9.03 (d, $J = 8.5$ Hz, 1H), 8.75 (dd, $J = 1.5$, 8.0 Hz, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.31 (m, 2H), 8.01 (dd, $J = 4.5$, 8.5 Hz, 1H), 6.40 (t, $J = 8.7$ Hz, 2H), 4.02 (t, $J = 8.7$ Hz, 2H).
13. A small flask containing equimolar amounts of **1** and **2a** in diphenyl ether was heated in an oil bath held at 185–190 °C for 4.5 h. The resultant yellow solid was collected by filtration and washed thoroughly with ether. ^{1}H NMR (DMSO-d_6) HCl salt δ 9.2 (dd, $J = 1.5$, 5.0 Hz, 2H), 9.0 (d, 8.0 Hz, $J = 8.5$ Hz, 2H), 8.61 (d, $J = 8.5$ Hz, 2H), 8.19 (m, 4H), 8.13 (m, 4H).

14. The HCl salt was treated with aqueous KOH and crystallized from acetonitrile; mp 280–283 °C; lit.[2] mp 277–278 °C. ^{1}H NMR ($CDCl_3$) free base δ 9.23 (dd, $J = 1.8$, 4.0 Hz, 2H), 8.25 (dd, $J = 1.8$, 8.1 Hz, 2H), 8.16 (d, $J = 8.4$ Hz, 2H), 8.01 (d, $J = 8.4$ Hz, 2H), 7.78 (m, 4H), 7.65 (dd, $J = 4.3$, 8.1 Hz, 2H). ^{1}H NMR (DMSO-d_6) δ 9.12 (m, 2H), 8.52 (m, 4H), 8.17 (d, $J = 8.4$ Hz, 2H), 8.03 (br s, 4H), 7.80 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 156.8, 150.1, 145.5, 144.6, 137.5, 136.2, 128.8, 126.9, 126.7, 126.2, 124.6, 123.5.
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16. Equimolar amounts of pyridine-2 thione, **1** and K_2CO_3in DMF were refluxed for 4 h. The DMF was removed under reduced pressure and the residue quenched into water. The product was extracted with dichloromethane and the residue was treated with ether and placed in the freezer to afford **6a** as orange-brown crystals. On dissolving in acetonitrile, addition of silica gel and removal of the gel by filtration followed by removal of the acetonitrile, a pale yellow solid was obtained which readily crystallized from acetonitrile, mp 114–116 °C. ^{1}H NMR (DMSO-d_6) δ 9.0 (dd, $J = 2.0$, 4.5 Hz, 1H), 8.58 (d, $J = 4.5$ Hz, 1H), 8.50 (dd, $J = 1.5$, 8.0 Hz, 1H), 8.44 (d, $J = 8.5$ Hz, 1H), 8.00 (m, 2H), 7.86 (m, 2H), 7.79 (dd, $J = 4.0$, 8.0 Hz, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.40 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 157.3, 156.0, 150.5, 150.4, 145.8, 144.9, 138.1, 137.6, 136.5, 129.1, 127.0, 126.9, 126.5, 126.2, 124.7, 123.8, 122.8.
17. As in Ref. 16 using pyrimidine-2-thione, the mixture was quenched into water and product **6b** was collected by filtration. On solution in acetonitrile, addition of silica gel and removal of the gel by filtration, followed by removal of the solvent, a yellow solid was obtained, mp 198–200 °C. ^{1}H NMR (DMSO-d_6) δ 9.10 (dd, $J = 1.8$, 4.2 Hz, 1H), 8.70 (d, $J = 4.8$ Hz, 2H), 8.54 (d, $J = 8.4$ Hz, 1H), 8.51 (dd, $J = 1.8$, 8.0 Hz, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 8.00 (m, 2H), 7.80 (dd, 4.3, 8.1 Hz, 1H), 7.35 (t, $J = 4.8$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 158.3, 153.8, 150.1, 145.5, 144.8, 137.2, 136.3, 128.7, 128.2, 127.5, 127.4, 126.2, 124.6, 123.5, 118.6.