A Facile Synthesis of the 1,3-Dithiolo[4,5-*b*]pyridine Ring System *via* Pyridylthiocyanates

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2-Chloro-3-thiocyanatopyridine reacted with thioacetic acid and thiobenzoic acid to yield 2-acetylimino-1,3-dithiolo[4,5-*b*]pyridine and 2-benzoylimino-1,3-dithiolo[4,5-*b*]pyridine respectively. 2,5,6-Trihalo-3-thiocyanatopyridine under the same conditions gave only the corresponding 3-*S*-acetyl-3-thio or 3-*S*-benzoyl-3-thiopyridine.

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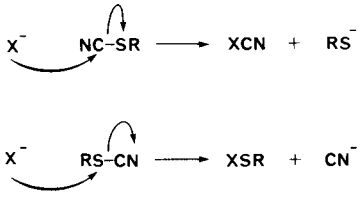
Nucleophilic displacement reactions on thiocyanates, RS≡CN may take place either on the cyanide carbon or on the sulphur atom (Scheme 1) [2]. The selectivity often follows the hard soft acids and bases (HSAB) principle [3].

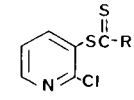
Scheme 1



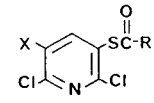
Organic thiocyanates also resemble cyanides in undergoing addition reactions at the C≡N bond, the orientation being controlled by the polarity of the thiocyanato group:

$\delta+\ \delta-$
S-C≡N [4]. The difference in behaviour of alkyl (R) and aryl (Ar) thiocyanates is also often due to the relative stabilities of the RS^-, CN^- and ArS^- anions. The reaction of phenylthiocyanates with thiobenzoic acid for example, yielded solely the corresponding thioester whilst alkylthiocyanates gave primarily *N*-acyldithiocarbamates [5]. The formation of *N*-acyldithiocarbamates from the reaction of thioacids with thiocyanates has been used [6] to distinguish thiocyanates from the corresponding isothiocyanates which under the same conditions give *N*-acylamine and carbon disulphide [7]. We wish to report here facile formation of ring-cyclised product from the reaction of pyridylthiocyanates with thioacids.

Igarashi and Honma reported the formation of 3,4,6-tri-*O*-acetyl-2-*S*-(*N*-acetylthiocarbamoyl)-2-thio-α-D-glucopyranoside from the reaction of 3,4,6-tri-*O*-acetyl-2-deoxy-2-thiocyanato-α-D-glucopyranoside with thioacetic acid [8]. In conjunction with other work, we found that when 2-chloro-3-thiocyanatopyridine was reacted with thioacetic acid under the same conditions of Igarashi and Honma [8], the adduct 2-chloro-3-*S*-(*N*-acetylthiocarbamoyl)-3-thiopyridine **1** was not isolated, but cyclisation took place to afford in good yield, 2-acetylimino-1,3-dithiolo[4,5-*b*]pyridine **2**. The structure of **2** was assigned based on the following data. The nmr spectrum showed a singlet at δ 2.45 (3H) for the acetyl methyl and 7.35 (1H, dd, J = 4 and 8 Hz), 7.95 (1H, dd, J = 1.1 and 7.2 Hz) as well as 8.15 (1H, dd, J = 1 and 4 Hz) for the pyridine nucleus protons. The primary electron-impact mass spectral fragmentation showed a loss of $\cdot COCH_2$ from the molecular ion followed by HCN to give fragments consistent with structures such as **3** and **4** respectively. The infrared absorption of the carbonyl function in 2-acetylimino-1,3-dithiolo[4,5-*b*]pyridine **2** was not at the "normal" amide region but was shifted to 1640 cm^{-1}. Similar shifts of the carbonyl absorption are also seen in the imide tautomer, 2-(chloroacetylimino)-benzothiazoline **5** and the "fixed" imide, 3-methyl-2-(chloroacetylimino)benzothiozoline **6** when compared with the amide tautomer 2-(chloroacetylamino)benzothiazole **7** [9].



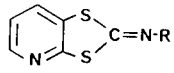
1 R=NHCOCH$_3$



9 R=CH$_3$ X=Br

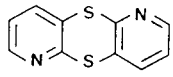
10 R=φ X=Cl

The reaction of 2-chloro-3-thiocyanatopyridine with thiobenzoic acid similarly yielded 2-benzoylimino-1,3-dithiolo[4,5-*b*]pyridine **8** in good yield. This reaction thus affords a novel and facile route to 1,3-dithiolo[4,5-*b*]pyridine ring system. Previous synthesis [10] of this ring system employed a rather circuitous route with less readily available starting materials.



2 R=$COCH_3$

8 R=$CO\phi$



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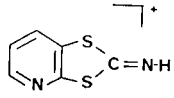
The reactions of thioacids with 2,6-dichloro-3-thiocyanato-5-bromopyridine or 2,5,6-trichloro-3-thiocyanatopyridine did not yield the ring cyclised products, however. Only the corresponding thioesters, 2,6-dichloro-5-bromo-3-*S*-acetyl-3-thiopyridine **9** and 2,5,6-trichloro-3-*S*-benzoyl-3-thiopyridine **10** were obtained. The additional halogens on the pyridine ring apparently enhanced the leaving group capability of the mercaptopyridine anion and favored its displacement over the displacement of the cyanide anion, CN^-. The reaction of 2-chloro-3-thiocyanatopyridine with sodium ethanethiolate on the other hand gave only 1,4-dithiino[2,3-*b*:5,6-*b'*]dipyridine **11** in 83% yield. 1,4-Dithiino[2,3-*b*:5,6-*b'*]dipyridine **11** presumably was formed *via* head to tail dimerisation of 2-chloro-3-thiopyridine anion [11].



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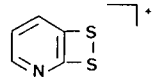

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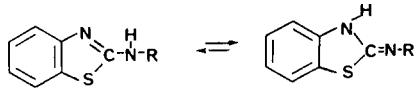
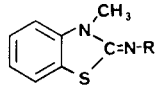


7 R=$COCH_2Cl$ 5 R=$COCH_2Cl$



6 R=$COCH_2Cl$

EXPERIMENTAL

Melting points were obtained in open capillary tubes in a Thomas-Hoover melting point apparatus and are reported uncorrected. The ^1H nmr spectra were recorded on a Perkin Elmer R32 spectrometer. Chemical shifts were measured as value from internal tetramethylsilane reference. The ^{13}C nmr spectrum was recorded on a Bruker WP60 spectrometer using DMSO-d_6 as both solvent and internal reference.

2-Chloro-3-thiocyanatopyridine, 2,6-dichloro-3-thiocyanato-5-bromopyridine and 2,5,6- trichloro-3-thiocyanatopyridine were prepared according to previously published methods [12].

Reaction of 2-Chloro-3-thiocyanatopyridine with Thioacetic Acid.

2-Chloro-3-thiocyanatopyridine, (1 g, 0.0059 mole) was dissolved in 25 ml dry benzene. To this solution, thioacetic acid, (2 g, 0.026 mole) was added and the reaction mixture was refluxed under dry nitrogen atmosphere for 6 hours. The reaction mixture was a homogenous solution at the start of the reaction. After refluxing for ½ hour, some precipitate appeared but partially redissolved on further heating. After 6 hours, the reaction mixture was cooled and filtered. The tlc analysis of the clear filtrate showed that all reactants had been consumed and a single product was indicated. The clear filtrate was evaporated to dryness and recrystallised from petroleum ether (bp 60-80) to yield 1.1 g (89%) of 2-acetylimino-1,3-dithiolo[4,5-*b*]pyridine **2**, mp 141-142°; ^1H nmr (deuteriochloroform): δ 8.15 (dd, 1H, J = 1 and 4 Hz), 7.95 (dd, 1H, J = 1.1 and 7.2 Hz), 7.35 (dd, 1H, J = 4 and 8 Hz), 2.45 (s, 3H); ms: (m/e) 210 (M^+, 61), 195 (22), 168 (100), 141 (5.2), 109 (8.8), 82 (22.7); ^{13}C nmr (DMSO-d_6): ppm 27.1, 113.4, 122.4, 130.6, 132.0, 135.1, 148.9, 180.4.

Anal. Calcd. for $C_8H_6N_2OS_2$: C, 45.7; H, 2.86; N, 13.33. Found: C, 46.0; H, 2.9; N, 13.5.

Reaction of 2-Chloro-3-thiocyanatopyridine with Thiobenzoic Acid.

2-Chloro-3-thiocyanatopyridine (1 g, 0.0059 mole) was dissolved in 25 ml dry benzene. To this solution, thiobenzoic acid, (3.6 g, 0.026 mole) was added and the reaction mixture was refluxed under dry nitrogen for 6 hours. Excess reagent was evaporated *in vacuo* to leave 1.8 g of residue. Column chromatography (silica gel, elution with chloroform) afforded 1.52 g (95%) of pure 2-benzoylimino-1,3-dithiolo[4,5-*b*]pyridine **8**. Recrystallisation from chloroform gave slightly yellowish crystals, mp 172°; ^1H nmr (deuteriochloroform): δ 8.55 (dd, 1H, J = 1.2 and 3.8 Hz), 8.37 (dd, 1H, J = 2 and 6 Hz), 7.92 (dd, 1H, J = 4.2 and 7.2 Hz), 7.3-7.6 (5H); ms: (m/e) 272 (M^+, 2.8), 167 (0.1) 141 (0.6), 114 (0.1), 109 (5.3), 105 (100), 82 (2.2).

Anal. Calcd. for $C_{13}H_8N_2OS_2$: C, 57.36; H, 2.94; N, 10.29. Found: C, 57.6; H, 2.8; N, 10.3.

Reaction of 2,6-Dichloro-3-thiocyanato-5-bromopyridine with Thioacetic Acid.

2,6-Dichloro-3-thiocyanato-5-bromopyridine, (0.9 g, 0.003 mole) was refluxed with thioacetic acid, (0.6 g, 0.007 mole) in 13 ml dry benzene for 6 hours under dry nitrogen atmosphere. After 6 hours, the residue was taken into diethyl ether, dried (magnesium sulfate), filtered and concentrated. Recrystallisation from petroleum ether (bp 60-80°) followed by vacuum sublimation (100°/0.3 mm Hg) afforded 0.5 g (56%) of 2,6-dichloro-5-bromo-3-*S*-acetyl-3-thiopyridine **9**, mp 78.5-79°; ms: (m/e) 305 (0.2), 303 (2.6), 301 (5.7), 299 (M^+, 3.3), 263 (5.1), 261 (31.7), 259 (55.6), 257 (40), 225 (2.4), 223 (7.3), 221 (5.3), 181 (2.7), 179 (13), 177 (19.2), 144 (1.9), 142 (4.8), base peak at m/e 42.

Anal. Calcd. for $C_7H_4BrCl_2NOS$: C, 27.91; H, 1.33; N, 4.65. Found: C, 27.9; H, 1.2; N, 4.9.

Reaction of 2,5,6-Trichloro-6-thiocyanatopyridine with Thiobenzoic Acid.

2,5,6-Trichloro-3-thiocyanatopyridine (0.4 g, 0.0017 mole) was refluxed with thiobenzoic acid, (0.4 g, 0.003 mole) in 15 ml of dry benzene for 6 hours under a dry nitrogen atmosphere. Excess thiobenzoic acid and the solvent were evaporated *in vacuo* to give 0.5 g of residue which was

chromatographed on a 600 cm (50 mm diameter) silica gel column. Elution with chloroform separated the product from other impurities which stayed on the top of the column. Evaporation of the effluent followed by recrystallisation from chloroform afforded 0.36 g (57%) of 2,5,6-trichloro-3-*S*-benzoyl-3-thiopyridine **10**, mp 133°; ^{1}H nmr (deuteriochloroform): δ 8.0 (s, 1H), 7.4-7.7 (multiplet, 5H); ms: (m/e) 321 (0.1), 319 (0.3), 317 (M^+, 0.2), 286 (0.1), 284 (0.3), 282 (0.5), 216 (2.4), 214 (6.5), 212 (6.2), 181 (1.4), 179 (6.1), 177 (8.7), 172 (1.2), 170 (3.8), 168 (4.0), 155 (0.5), 153 (2.1), 151 (3.2), 144 (1.4), 142 (3.2), 118 (2.1), 116 (5.5), 105 (100), 107 (19.6).

Anal. Calcd. for $C_{12}H_6C_{13}NOS$: C, 45.21; H, 1.88; N, 4.40. Found: C, 45.2; H, 1.7; N, 4.2.

Reaction of 2-Chloro-3-thiocyanatopyridine with Sodium Ethanethiolate.

To a solution of (0.6 g, 0.0035 mole) 2-chloro-3-thiocyanatopyridine dissolved in dry THF, (1.5 g, 0.025 mole) solid sodium ethanethiolate was added. The reaction mixture was then heated to reflux under dry nitrogen atmosphere for 6 hours. The solvent was evaporated *in vacuo* and the residue recrystallised from aqueous methanol to give 0.57 g (73%) of 1,4-dithiino[2,3-*b*:5,6-*b'*]dipyridine **11**, mp 181°, lit [11] mp 179-181°; ^{1}H nmr (deuteriochloroform): δ 8.45 (dd, 2H, J = 2 and 4 Hz), 7.75 (dd, 2H, J = 2 and 8 Hz), 7.20 (dd, 2H, J = 4.5 and 8 Hz).

Anal. Calcd. for $C_{10}H_6N_2S_2$: C, 55.1; H, 2.75; N, 12.83. Found: C, 55.2; H, 2.5; N, 13.0.

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