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The Reaction of Some Halogenated Pyridine Thioethers and Sulphones with Carbon Disulphide

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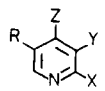
Abstract. Dithiocarboxylation of some halogenated pyridine sulphones with carbon disulphide and sodium hydride leads to the formation of thiomethyl derivatives via Smiles rearrangement of the inititially produced dianion, fragmentation and subsequent methylation. In one instance the pyridino[2,3-b]-1,4-dithiine **7** was obtained. The thioether **2d** was also converted into a thiomethyl derivative when subjected to the same reaction sequence.

In an attempt to prepare compounds in which a pyridine ring is fused to the *b* face of a 1,4-dithiine we have examined the reaction of some halogenated pyridine sulphones with carbon disulphide [1]. The required starting materials were prepared from the appropriate sulphanes which were accessible using a variety of literature methods. Thus treatment of **1a** (X = Cl) and **3a** (Z = Br) [2] with sodium methanethiolate (SMT) as described [3] gave the isomeric thioethers **1b** (X = SMe) and **2a** (Y = SMe), and **3b** (Z = SMe) respectively. Thioether **2a** was prepared in quantity from the diazonium tetrafluoroborate salt derived from **2b** (Y = NH_2) with SMT according to the published procedure [4]. In order to prepare a 4-halogenated-3-methylthio-pyridine we examined the reaction of **4c** (X = H, Y = SMe) with phosphoryl chloride.



1–3,5,6,8,9

1 R = Z = H, Y = Cl

2 R = Z = H, X = Cl

3 R = X = H, Y = Br

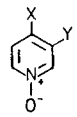
5 R = SMe, X = Cl, Y = Z = H

6 Y = SMe, R = X = H

8 Y = Z = Me, R = Br

9 X = I, R = Z = H

Oxide **4c**, whilst available from **4a** (X = H, Y = Cl) and SMT in DMF (100 – 120°), was best prepared from the oxide **4b** (X = H, Y = F) (0°, 96% crude yield). The use of **4b** for the synthesis of 3-alkylthiopyridine N-oxides is a superior method compared to other literature procedures [5 – 6]. For example **4d** (X = H, Y = SCH_2CO_2Me) can be obtained in 76% yield from the reaction of **4b** with the sodium salt of methyl thiogycolate (SMTG) at 100° in only 4 hours.



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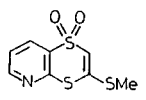
Treatment of **4c** with phosphoryl chloride gave a three component reaction mixture from which **2a**, **5** and **6a** (Z = Cl) were isolated after chromatography [7]. Thioether **6a** was further characterised as its morpholino derivative **6b** (Z = 4-morpholino) by reaction of the compound with morpholine at reflux.

Oxidation of **1b**, and **2a** with MCPBA gave sulphones **1c** (X = SO_2Me), and **2c** (Y = SO_2Me) whilst under the same reaction conditions **3b** gave a mixture of products due to competitive oxidation at both nitrogen and sulphur. The addition of further oxidant to the reaction mixture afforded the sulphone **4e** (X = SO_2Me, Y = Br) in 74% yield. No attempt was made to oxidise **6a** since this compound appeared unstable on storage.

Reaction of **1c** with carbon disulphide in the presence of sodium hydride followed by treatment of the reaction mixture with iodomethane gave only the thioether **1b**, whilst similar treatment of **2c** afforded both **2a** and **7** (major product). Whereas the bicyclic



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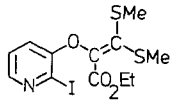

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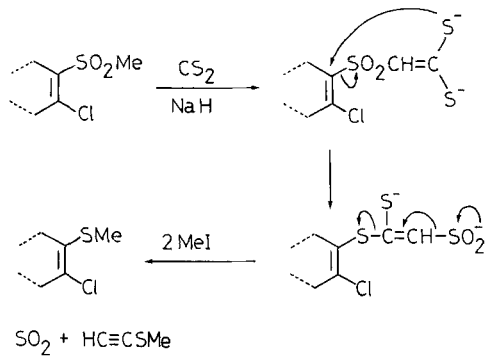
compound **7** was expected, we were surprised to find thioethers as products in these reactions, and a suggested mechanism for their formation involving Smiles rearrangement and subsequent fragmentation is shown in scheme 1. The fact that no bicyclic product



Scheme 1

is obtained in the case of **1c** suggests that the ring nitrogen atom assists in charge dispersal during the rearrangement process and in stabilisation of the fragmented anion. When **4e** was treated with the reagent combination, no products could be isolated from the reaction mixture. Other pyridine sulphones could also be transformed to the corresponding methylthio derivatives by the above reagents. When **8a** (X = Br) [8 – 9] was treated with SMTG and the resulting thioether **8b** (X = SCH_2CO_2Me) (characterised as the free acid **8c** (X = SCH_2CO_2H) by saponification with aqueous ethanolic NaOH) oxidised with MCPBA the sulphone **8d** (X = $SO_2CH_2CO_2Me$) was obtained. Reaction of the latter with carbon disulphide, as described above, gave the thioether **8e** (X = SMe). Surprisingly halogenated pyridine thioethers were also converted into methylthio derivatives when subjected to the reaction sequence. Thus treatment of **2d** (Y = SCH_2CO_2Me) (prepared from **2b** as described for **2a** [4] and characterised as the amide **2e** (Y = SCH_2CONH_2) by treatment with ammonia in MeOH) with reagent combination gave **2a** as the only isolable reaction product. No ketene dithioacetals were detected in any of these reactions.

Smiles rearrangements in the pyridine field are well documented [10], and specific examples involving sulphides [11], sulphoxides [12] and sulphonamides [13] have been described. Activation by halogen atoms has also been reported [14], and similar reactions have been observed during the dithiocarboxylation of some sulphones in the benzene series [15].

The reaction of **2d** with carbon disulphide is in direct contrast to the behaviour of activated pyridine ethers with the reagent. For example when **9b** (Y = OCH_2CO_2Et) (prepared by the alkylation of **9a** (Y = OH) [16] using ethyl bromoacetate) is dithiocarboxylated, and the reaction quenched with iodomethane (2 equivalents), the ketene dithioacetal **10** is the sole reaction product.

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Experimental

Melting points were taken with an Electrothermal Melting Point Apparatus and are uncorrected, boiling points were measured by short path bulb-to-bulb distillation at reduced pressure (Kugelrohr). Infrared spectra were recorded using either a Perkin Elmer 137 or 1600 FT-IR instrument, and the spectra were recorded either as KBr discs (solids), or as thin films (liquids) or as melts (low melting solids) on NaCl. ^{1}H-n.m.r. spectra were recorded at either 60 or 90 MHz using Jeol PMX 60SI or FX 90Q instruments using tetramethylsilane as internal standard. Mass spectra were measured at 70 eV with an AEI MS 920S spectrometer. Chromatography was carried out on silica-gel using petrol/ether mixtures. All compounds gave satisfactory analytical data C, H, and N and, where appropriate, Br, Cl, I and S. All i.r. bands are reported in cm^{-1} and ^{1}H-n.m.r. peaks are given as δ values.

Preparation of Thioethers from Dihalogenated Pyridines **1a**, **3a** *and* **8a** *and from N-Oxide* **4b**
(General Procedure)

A solution of the dihalogenated pyridine (0.025 mole) in dry DMF (100 ml) was stirred under a nitrogen atmosphere, and solid SMT (added portionwise over 20 minutes) or SMTG (0.0275 mole) added. The reactions involving SMT were stirred at room temperature for one hour, whilst those involving SMTG were heated at 100 – 120 °C for four hours. The mixtures were then poured onto ice, the products extracted with ether, and the extracts purified by column chromatography. The separated products were then purified by short path bulb-to-bulb distillation. The ether **8b** was further purified by recrystallisation from ether/PE. The following products were thus obtained.

From **1a** and SMT *3-chloro-2-methylthio-pyridine* **1b** (81 %) b.p. 35 °C/0.1 mbar ([3] no b.p. recorded) and *2-chloro-3-methylthio-pyridine* **2a** (1.6 %) m.p. 29 – 31 °C (reported [4] m.p. 32 – 34 °C).

For **1b** ^{1}H-n.m.r.: 8.28 (1 H, dd), 7.49 (1 H, dd), 6.88 (1 H, dd), 2.56 (3 H, s); i.r.: 3046, 2926, 2854, 1566; MS m/z (%): 161 (36), 159 (100).

For **2a** ^{1}H-n.m.r.: 8.14 (1 H, dd), 7.46 (1 H, dd), 7.21 (1 H,

dd), 2.52 (3H, s); i.r.: 3053, 2920, 1550; MS m/z (%): 161 (34), 159 (100).

From **3a** and SMT *3-bromo-4-methylthio-pyridine* **3b** (88%) b.p. 90°C/0.6mbar (reported [17] b.p. 150°C/18mm); ^{1}H-n.m.r.: 8.52 (1H, s), 8.39 (1H, d), 7.15 (1H, d), 2.50 (3H, s); i.r.: 3032, 2921, 1560; MS m/z (%): 205 (100), 203 (98).

From **8a** and SMTG *(5-bromo-3,4-dimethyl-pyrid-2-ylsulphanyl)-acetic acid methyl ester* **8b** (83%) m.p. 59.5–60.5°C; ^{1}H-n.m.r.: 8.32 (1H, s), 3.95 (2H, s), 3.75 (3H, s), 2.36 (3H, s), 2.29 (3H, s); i.r.: 2940, 1730, 1160; MS m/z (%): 291 (20), 289 (20). The free acid **8c** (see text) was obtained as pale yellow crystals (66%) m.p. 138–139°C (from aqueous MeOH), ^{1}H-n.m.r.: 11.20 (1H, broad s, exch.), 8.37 (1H, s), 3.77 (3H, s), 2.44 (3H, s), 2.34 (3H, s); i.r.: 2800, 1710 (broad); MS m/z (%): 277 (18), 275 (13).

The N-oxides **4c** and **4d** were prepared essentially as described above from **4b** and SMT or SMTG, in the case **4c** the reaction was carried out by the portionwise addition of the thiolate with ice cooling (reaction time about 10 minutes), and in the case of **4d** the reaction was performed at 100°C (reaction time 4 hours).

3-Methylthio-pyridine-N-oxide (**4c**) was a colourless hygroscopic solid (75% purified yield) m.p. 80–81°C (from EtOAc/ether) (reported m.p. 76°C [5] and 52–54°C [6]), ^{1}H-n.m.r.: 8.04 (2H, complex), 7.17 (2H, complex), 2.51 (3H, s); i.r.: 3067, 1546, 1257; MS m/z (%): 141 (100).

(1-Oxy-pyrid-3-ylsulphanyl)-acetic acid methyl ester (**4d**) was obtained as colourless crystals (76%) m.p. 79–81°C (from EtOAc), ^{1}H-n.m.r.: 8.23 (1H, complex), 8.10 (1H, complex), 7.24 (1H, complex), 3.76 (3H, s), 3.70 (2H, complex); i.r.: 1750, 1235, 1160; MS m/z (%): 199 (100).

2-Chloro-3-methylthio-pyridine (**2a**) *and (2-Chloro-pyrid-3-ylsulphanyl)-acetic acid methyl ester* (**2d**)

The reaction was carried out exactly as described [4] using **2b** (10.0g). The crude reaction mixture was concentrated, partitioned between water and ether, and the dried concentrated ethereal extracts purified by column chromatography. Concentration of the major product fractions followed by vacuum distillation gave pure **2a** (33%) which rapidly crystallised on cooling. The substance was identical in all respects (i.r., and ^{1}H-n.m.r. and t.l.c.) to the product obtained from **1a** and SMT (see above).

Substitution of SMT in the above reaction with SMTG gave **2d** as a colourless oil (66%) which rapidly solidified on cooling m.p. 34–36°C, ^{1}H-n.m.r.: 8.23 (1H, dd), 7.73 (1H, dd), 7.22 (1H, dd), 3.74 (3H, s), 3.72 (2H, s); i.r.: 1730, 1560, 1269, 1214; MS m/z (%): 219 (19), 217 (53). The amide **2e** (see text) was obtained as a colourless crystalline solid (86%) m.p. 186–188°C (from MeOH), ^{1}H-n.m.r.: 8.18 (1H, dd), 7.9–7.1 (4H, complex becoming 7.82 (1H, dd) and 7.42 (1H, dd) on exch.), 3.76 (2H, s); i.r.: 3300, 3148, 1682, 1552; MS m/z (%): 204 (4), 202 (12).

Synthesis of 2-Chloro-3-methylthio-pyridine (**2a**), *2-Chloro-5-methylthio-pyridine* (**5**) *and 4-Chloro-3-methylthio-pyridine* (**6a**)

The N-oxide **4c** (3.6g) was added in small portions to ice cold phosphorus oxychloride (15ml). A vigorous reaction took place and HCl gas was evolved. The resulting brown mixture was then heated under reflux for one hour, cooled and the mixture poured onto ice. The resulting solution was cautiously treated with dilute aqueous sodium hydroxide solution and the mixture extracted with ether (×3). The dried concentrated extracts were chromatographed to afford **5** as a colourless oil. Further purification by vacuum distillation gave pure **5** (11%) as a low melting solid m.p. 28°C (reported [18] b.p. 56–58°C/0.05), ^{1}H-n.m.r.: 8.25 (1H, d), 7.53 (1H, dd), 7.23 (1H, d), 2.50 (3H, s); i.r.: 2921, 1547; MS m/z (%): 161 (35), 159 (100).

The next compound eluted was **2a** (14%) identical in all respects to an authentic sample (i.r., t.l.c., m.p., m.m.p.). Finally increasing the polarity of the eluant gave the 4-chloro-3-methylthio-pyridine (**6a**) as a pale yellow oil. Purification by short path bulb-to-bulb distillation afforded pure **6a** as a colourless mobile oil (18%) b.p. 60°C/0.2mbar; ^{1}H-n.m.r.: 8.33 (1H, s), 8.24 (1H, d), 7.24 (1H, d), 2.56 (3H, s); i.r.: 3033, 2989, 2922, 1542.

N-(3-Methylthio-pyrid-4-yl)-morpholine (**6b**)

A mixture of **6a** (600mg) and morpholine (5ml) was heated under reflux for six hours. The solvents were removed at reduced pressure and the residue partitioned between water and ether. The dried ethereal extracts were concentrated and the resulting syrup purified by column chromatography and then by vacuum distillation (b.p. 135°C/0.1mbar). The product crystallised immediately on cooling to yield pure **6b** as colourless crystals (95%) m.p. 79–80°C, ^{1}H-n.m.r.: 8.30 (2H, complex), 6.81 (1H, d), 3.86 (4H, complex), 3.21 (4H, complex), 2.51 (3H, s); i.r.: 2964, 2921, 2862, 2849, 1570; MS m/z (%): 210 (100).

Synthesis of 3-chloro-2-methylsulphonyl-pyridine (**1c**), *2-chloro-3-methylsulphonyl-pyridine* (**2c**), *(5-bromo-3,4-dimethyl-pyrid-2-ylsulphonyl)-acetic acid methyl ester* (**8d**) *and 3-bromo-4-methylsulphonyl-pyridine N-oxide* (**4e**)

A solution of the appropriate thioether **1b**, **2a**, **3b** or **8b** (2.0g) in dichloromethane was treated with 2.1 equivalents of 3-chloroperoxybenzoic acid (3.1 equivalents in the case of **3b**) as described in [19] and the products isolated in the usual manner.

From **1b**, **1c** (67%) m.p. 98–99°C (from EtOAc), (reported [3] 98–99°C), ^{1}H-n.m.r.: 8.53 (1H, dd), 7.92 (1H, dd), 7.50 (1H, dd), 3.41 (3H, s); i.r.: 3062, 1559, 1399, 1297, 1148; MS m/z (%): 191 (6).

From **2a**, **2c** (62%) m.p. 121–123°C (from EtOH), (reported [4] m.p. 106–108°C), ^{1}H-n.m.r.: 8.65 (1H, dd), 8.48 (1H, dd), 7.51 (1H, dd), 3.34 (3H, s); i.r.: 3073, 3058, 3029, 1560, 1392, 1310, 1157; MS m/z (%): 193 (21), 191 (66).

From **8b**, **8d** (88%) m.p. 82.5–83°C (from ether and PE); ^{1}H-nmr: 8.47 (1H, s), 4.58 (2H, s), 3.75 (3H, s), 2.70 (3H, s), 2.49 (3H, s); i.r.: 3000, 2950, 2910, 1745, 1310, 1115; MS m/z (%): 321 (0.3), 244 (99), 242 (100).

From **3b**, **4e** (74%) m.p. 219–222°C (sample washed once with hot ethanol and then acetone); ^{1}H-n.m.r.: 8.86 (1H, d), 8.42 (1H, dd), 7.90 (1H, d), 3.40 (3H, s); i.r.: 3112, 3062, 2998, 2908, 1590, 1510, 1331, 1297, 1242, 1146, 1040; MS m/z (%): 253 (43), 251 (41).

Attempted dithiocarboxylation of **1c**, **2c**, **4e** *and* **8d**. *Synthesis of 3-methylthio-pyridino[2,3-b]-1,4-dithiine 1,1-dioxide* (**7**) *and 5-bromo-3,4-dimethyl-2-methylthio-pyridine* (**8e**)

A solution of the sulphone **1c**, **2c**, **4e** or **8d** (1.0g) in dry DMSO (20ml) was stirred under a nitrogen atmosphere and

carbon disulphide (0.6 g) added. The temperature was maintained at 25 °C and the solution treated with sodium hydride (0.29 g) added in small portions. After stirring for about 30 minutes the solution was heated to 55 – 65 °C and kept at this temperature for one hour. The mixture was then cooled, iodomethane (0.84 g) added, stirred for a further hour and finally poured into ice water. The aqueous mixture was extracted several times with ethyl acetate and the combined, dried extracts concentrated and purified by column chromatography.

From **1c** the thioether **1b** (12 %), identical in all respects (as above) to an authentic sample, was the only product obtained.

From **2c** two products were obtained i.e. the thioether **2a** (2 %) and the bicycle **7** (23 %) m.p. 109.5 – 111.5 °C (from EtOAc and PE), ^{1}H-n.m.r.: 8.70 (1 H, dd), 8.36 (1 H, dd), 7.52 (1 H, dd), 6.66 (1 H, s), 2.60 (3 H, s); i.r.: 3056, 1560, 1404, 1283, 1248, 1233, 1070, 1040; MS m/z (%): 245 (100).

From **8d, 8e** (44 %) m.p. 34 – 35 °C, ^{1}H-n.m.r.: 8.37 (1 H, s), 2.52 (3 H, s), 2.36 (3 H, s), 2.26 (3 H, s); i.r.: 2980, 2915, 1550; MS m/z (%): 233 (78) 231 (80) was obtained.

2-Iodo-pyrid-3-yloxy-acetic acid ethyl ester (**9b**)

The pyridinol **9a** (8.8 g) was alkylated in the usual manner with anhydrous potassium carbonate (20 g), potassium iodide (0.5 g) and ethyl bromoacetate (7.2 g) in dry acetone (200 ml) (room temperature six hours). The crude product was recrystallised from PE to afford pure **9b** (74 %) m.p. 43 – 44 °C as a white powder. ^{1}H-n.m.r.: 8.06 (1 H, dd), 7.23 (1 H, dd), 6.97 (1 H, dd), 4.71 (2 H, s), 4.27 (2 H, q), 1.13 (3 H, t); i.r.: 1750, 1730, 1408, 1215, 1195; MS m/z (%): 307 (33).

Dithiocarboxylation of (**2d**) *and* (**9b**), *synthesis of bis-methylthiomethylene-(2-iodo-pyrid-3-yloxy)-acetic acid ethyl ester* (**10**)

A solution of **2d** or **9b** (1.0 g) was treated with carbon disulphide as described above except that in these cases the reaction mixture was quenched with two equivalents of iodomethane. From **2d**, the thioether **2a** (27 %), identical in all respects to an authentic sample, was obtained. From **9b**, **10** (37 %) m.p. 62 – 63 °C (from PE), ^{1}H-n.m.r.: 8.09 (1 H, dd), 7.18 (1 H, dd), 6.90 (1 H, dd), 4.15 (2 H, q), 2.50 and 2.49 (6 H, 2s), 1.13 (3 H, t); i.r.: 3050, 2970, 2900, 1680, 1280; MS m/z (%): 411 (38), 284 (100) was obtained.

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