Directed Metalation of Pyridinesulphonamides. Synthesis of Pyridine-fused Isothiazoles and 1,2-Oxathioles

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4-Lithio-*N*-*t*-butylpyridine-3-sulphonamide reacted with benzophenone and carbon dioxide respectively to give the corresponding intermediates which on appropriate treatment gave isothiazolo[5,4-*c*]pyridin-3-one 1,1-dioxides. Metalation of 2- and 4-(*N*,*N*-dialkylaminosulphonyl)pyridines with lithium diisopropylamide (LDA) gave anions which reacted with benzophenone to give carbinols which thermally cyclised to 1,2-oxathiolo[3,4-*b*]pyridine and 1,2-oxathiolo[4,3-*c*]pyridine respectively.

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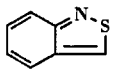
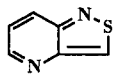
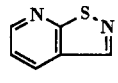
Pyridine rings fused to sulphur-containing heterocycles usually possess interesting pharmacological [1] and other bioactivities [2]. The precursors for such sulphur-fused pyridines are however not readily available. Some pyridine-fused sulphur-containing heterocycles previously synthesized include isothiazolo[3,4-*b*]pyridine **1** [1] and it's other analogues **2-5** [3].



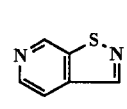
3,4-*b*
1



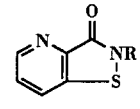
4,3-*b*
2



5,4-*b*
3



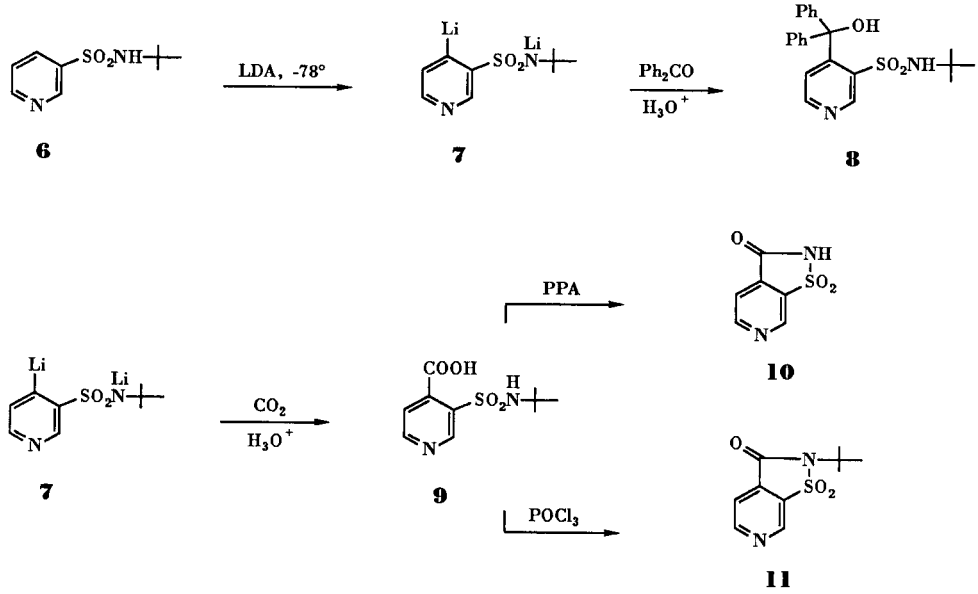
5,4-*c*
4



4,5-*b*
5

Sultones fused to benzene rings had been obained previously by either acid or thermal cyclisation of the corresponding carbinols [4]. Although yields are usually low, this method remains the only route of converting these types of carbinols to the sultones. As far as we are aware, pyridine-fused sultones have no parrallel in the pyridine literature.

Scheme 1



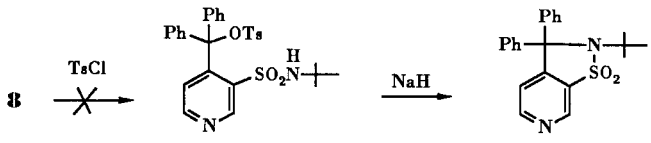
The removal of the initial difficulties accompanying metalation of π-deficient heterocycles in recent reports [5] coupled with our recent exposition [6] of the tertiary sulphonamide as an effective directing group in pyridine metalations make it expedient to explore and expand this route to obtaining diverse sulphur-containing pyridine systems. We therefore proposed the construction of new pyridine-fused sultones and sultams in continuation of our interest in synthesis of polycyclic heterocycles [7]. In this report we present some new sulphur-containing pyridine bicycles obtained *via ortho*-directed lithiation of pyridine-sulphonamides.

Results and Discussion.

Tertiary sulphonamides such as 3-(*N,N*-dialkylaminosulphonyl)pyridine had been metalated in good yield [8,9]. Secondary sulphonamides had however not been metalated. Treatment of *N-t*-butylpyridine-3-sulphonamide **6** with three molar equivalents of lithium diisopropylamide at $-78°$ generated the 4-lithio compound **7** exclusively, similar to the earlier report of Marsais *et al.* [8] on the regioselective metalation of tertiary pyridine-3-sulphonamides.

Electrophiles used in this case were benzophenone and carbon dioxide giving carbinol **8** and acid **9** respectively, Scheme 1. It was anticipated that the tosylate **12** should give the desired isothiazolo[5,4-*c*]pyridine **13** smoothly, Scheme 2. Attempted tosylation of the carbinol was however unsuccessful. This may be due to the ease of decomposition of the tertiary arenesulphonate **12** as soon as formed [10].

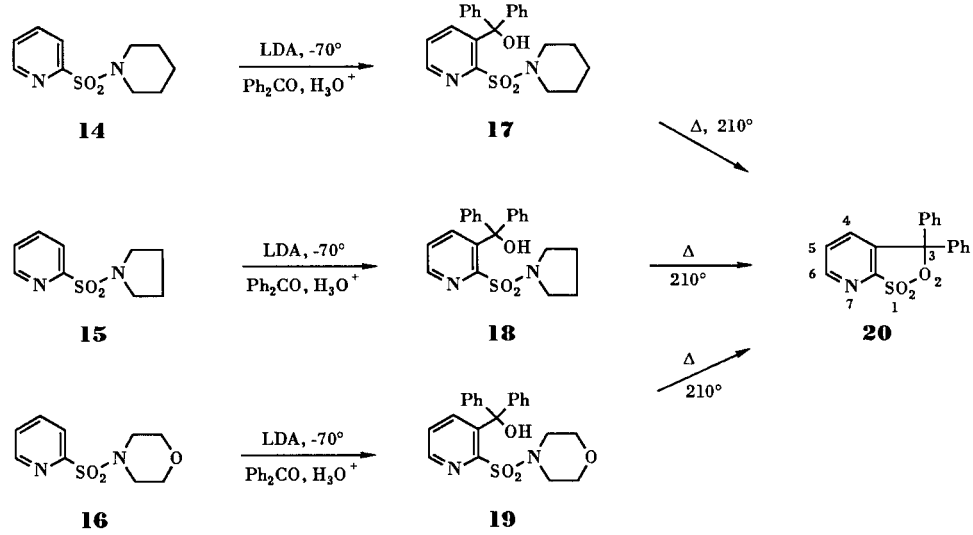
Scheme 2



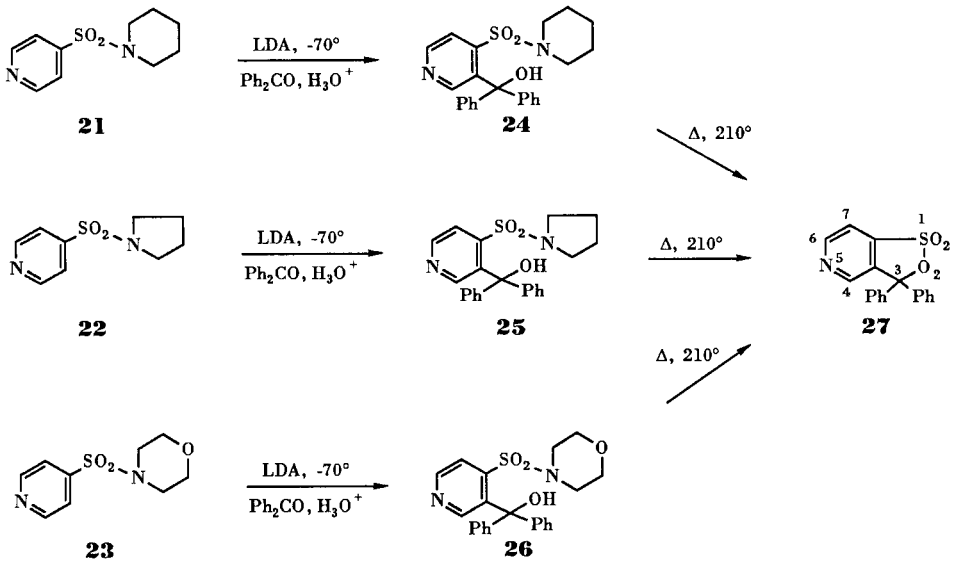
However, Lewis acid treatment of the acid **9** gave heterocycles. Polyphosphoric acid-mediated cyclisations were accompanied by a loss of the *N-t*-butyl group giving isothiazolo[5,4-*c*]pyridin-3-one 1,1-dioxide (**10**), whereas phosphorus oxychloride-mediated cyclisation left the equivalent group intact giving *N-t*-butylisothiazolo[5,4-*c*]pyridin-3-one 1,1-dioxide **11**.

Our attention was then directed to the *ortho*-metalation of the tertiary sulphonamides: 2- and 4-(*N,N*-dialkylaminosulphonyl)pyridines [9]. Treatment of the sulphonamide homologues **14-16** or **21-23** with lithium diisopropylamide at $-78°$ gave the corresponding 3-pyridyl anions. Subsequent quenching with benzophenone gave the carbinols **17-19** and **24-26** respectively. Thermal heterocyclisation of the pyridine carbinols obtained required a modification of the Watanabe *et al.* [4] cyclisation protocol utilized in the homoaromatic series. Expectedly, each of the carbinols **17-19** on heating at 210° for 20 hours gave the same heterocycle: 3,3-diphenyl-1,2-oxathiolo[3,4-*b*]pyridine 1,1-dioxide **20** while carbinols **24-26** also gave the same end-product: 3,3-diphenyl-1,2-oxathiolo[4,3-*c*]pyridine 1,1-dioxide **27**.

Scheme 3



Scheme 4



EXPERIMENTAL

Experimental details are as in reference [11]. The nmr spectra were taken in deuterated chloroform solutions unless otherwise stated.

Pyridine-3-sulphonyl Chloride.

This compound was prepared *via* a modified literature [7] method. Commercial pyridine-3-sulphonic acid (14.5 g, 0.09 mole) and phosphorus pentachloride (20.0 g, 0.1 mole) mixture was stirred and refluxed at 110° for 3 hours. Distillation of excess phosphorus chloride left a residue to which was added dry toluene (50 ml) which was also removed *in vacuo*. The slightly fuming air sensitive sulphonyl chloride was immediately converted to the sulphonamide as outlined below; ^{1}H-nmr: δ 7.7 (1H, m) 8.4 (1H, d), 9.0 (1H, dd), 9.3 (1H, s).

N-t-Butylpyridine-3-sulphonamide (**6**).

Pyridine-3-sulphonyl chloride (32.2 g, 0.18 mole) in dry chloroform (100 ml) was added to *t*-butylamine (39.9 g, 0.54 mole) in chloroform (100 ml) at 0° and stirred for 30 minutes. Solid amine hydrochloride was filtered off from the reaction solution. The filtrate was washed with water and dried over magnesium sulphate. Solvents were removed off *in vacuo* to give a dark solid. Recrystallisation from ethyl acetate:hexane gave yellow plates (76%), mp 76-78°; ^{1}H-nmr δ 1.2 (9H, s), 5.9 (1H, NH), 7.4 (1H, dd), 8.2 (1H, d), 8.8 (1H, dd), 9.1 (1H, s); ir: 3300 (NH); 3090, 3050, 3000, 2960, 1690, 1350, 1170.

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.46; H, 6.54; N, 13.08. Found: C, 50.14; H, 6.88; N, 12.89.

1,1-Diphenyl-3-(*N-t*-butylsulphonyl)-4-pyridylmethanol (**8**).

n-Butyllithium 1.6*M* (0.0375 mole, 23.25 ml) was added to diisopropyl amine (3.7 g, 5.2 ml, 0.00375 mole) in diethyl ether (20 ml) at −30° and stirred for 1 hour at 0°. The resulting solution was cooled to −70°. *N-t*-Butylpyridine-3-sulphonamide (2.67 g, 0.0125 mole) in ether (30 ml) was added to the ether solution and stirred for 1.5 hours at −70°. Benzophenone (4.6 g, 0.025 mole) in ether (30 ml) was added to the deep red solution at −70° and stirred at that temperature for 3 hours. Water (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 50 ml). Combined organic extracts were dried over magnesium sulphate and concentrated under vacuum before recrystallisation from diethyl ether (80%), mp 180-182°; ^{1}H-nmr δ 1.2 (9H, s), 4.8 (1H, NH, exchangeable with deuterated water), 6.5 (1H, s, OH), 6.8 (1H, d), 7.3 (10H, m, 8.6 (1H, d), 9.4 (1H, s); ir: 3560 (-OH), 3290 (NH), 2980, 2870, 1580, 1340, 1160.

Anal. Calcd. for $C_{22}H_{24}N_2O_3S$: C, 66.66; H, 6.06; N, 7.07. Found: C, 66.28; H, 6.30; N, 6.92.

3-(*N-t*-Butylsulphonyl)pyridine-4-carboxylic Acid (**9**).

Carbon dioxide was added to the same anion generated as in **8** above. After stirring for 3 hours at −70°, the solution was initially extracted with dichloromethane (2 x 50 ml) before acidifying to *p*H 2. Dichloromethane extracts of the acid solution was dried over magnesium sulphate. Evaporation of the solvent left a residue which was recrystallised from diethyl ether giving white needles (80%), mp 207-208°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.1 (9H, s), 6.6 (1H, NH), 7.4 (1H, OH), 7.6 (1H, d), 8.8 (1H, d), 9.1 (1H, s); ir: 3300, 1750, 1580, 1350, 1170 cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.43; N, 10.85. Found: C, 46.47; H, 5.23; N, 10.47.

Isothiazolo[5,4-*c*]pyridin-3-one 1,1-Dioxide (**10**).

3-(*N-t*-Butylsulphonyl)pyridine-4-carboxylic acid (**9**) (0.3 g) and polyphosphoric acid (15 g) were heated together at 110° with stirring for 20 minutes. The resulting thick syrup was poured into ice and vigorously stirred. The solid that separated was filtered and rinsed with water, dried and recrystallised to give off white microcrystals; ^{1}H-nmr (trifluoroacetic acid-d): δ 7.0 (1H, m), 8.2 (1H, d), 9.0 (1H, d), 9.3 (1H, s).

Anal. Calcd. for $C_6H_4N_2O_3S$: C, 39.13; H, 2.19; N, 15.21. Found: C, 39.04; H, 2.04; N, 15.44.

N-t-Butylisothiazolo[5,4-*c*]pyridin-3-one 1,1-Dioxide (**11**).

The acid **9** was added to phosphorus oxychloride (6 ml) and was heated at 110° for 3 hours. The reaction mixture was poured onto crushed ice, when a brown solid separated. The solid was thoroughly washed with water at the pump and recrystallised to leave light brown plates; ^{1}H-nmr (deuterioacetone): δ 1.4 (9H, s), 7.8 (1H, d), 8.9 (1H, d), 9.1 (1H, s); ir: 2950, 2880, 1680, 1580, 1340, 1146 cm^{-1}; ms: (m/e) 240, 225 (100%), 185, 167, 77, 57, 41, 29.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66. Found: C, 50.31; H, 5.20; 11.34.

(*N,N*-Dialkylaminosulphonyl)pyridine-2-sulphonamides **14-16**.

These compounds were prepared as reported earlier [9] from pyridine-2-sulphonyl chloride and the corresponding amine.

Metalation of Pyridinesulphonamides and Reaction with Benzophenone.

These reactions were carried out as reported for compound **8**.

Diphenyl-2-(piperidinosulphonyl)-3-pyridylmethanol (**17**).

Using 2-(piperidinosulphonyl)pyridine (**14**) as the substrate, a white solid was obtained on purification from diethyl ether (90%), mp 182-183° (lit [9] mp 182°); ^{1}H-nmr: δ 1.6 (6H, m), 3.0 (4H, m), 6.6 (1H, s), 7.4 (12H, m), 8.5 (1H, d); ir: 3400 (OH), 1600, 1570, 1375, 1160.

Anal. Calcd. for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.60; H, 6.04; N, 6.93.

Diphenyl 2-(pyrrolidinosulphonyl)-3-pyridylmethanol (**18**).

Using 2-(pyrrolidinosulphonyl)pyridine (**15**) as the substrate, a white solid was obtained on recrystallisation from diethyl ether (70%), mp 163-164°; ^{1}H-nmr: δ 1.9 (4H, m), 3.1 (4H, m), 6.8 (1H, s), 7.4 (12H, m), 8.5 (1H, d).

Anal. Calcd. for $C_{22}H_{22}N_2O_3S$: C, 67.00; H, 5.58; N, 7.11. Found: C, 66.92; H, 5.50; N, 7.08.

Diphenyl-2-(morpholinosulphonyl)-3-pyridylmethanol (**19**).

Using 2-(morpholinosulphonyl)pyridine (**16**) as the substrate, a white solid was obtained on recrystallisation from diethyl ether (69%), mp 159-160°; ^{1}H-nmr: δ 3.4 (4H, m), 3.65 (4H, m), 6.5 (1H, s), 7.25 (12H, m), 8.5 (1H, d).

Anal. Calcd. for $C_{22}H_{22}N_2O_4S$: C, 64.39; H, 5.36; N, 6.83. Found: C, 64.46; H, 5.26; N, 6.56.

Diphenyl-4-(piperidinosulphonyl)-3-pyridylmethanol (**24**).

Using 4-(piperidinosulphonyl)pyridine (**21**) as the substrate, a white solid was obtained on recrystallisation from diethyl ether (80%), mp 135-136°; ^{1}H-nmr: δ 1.6 (6H, m), 3.1 (4H, m), 6.6 (1H, s), 7.7 (1H, d), 8.2 (1H, s), 8.7 (1H, d).

Anal. Calcd. for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.42; H, 5.90; N, 6.78.

Diphenyl-4-(pyrrolidinosulphonyl)-3-pyridylmethanol (**25**).

Using 4-(pyrrolidinosulphonyl)pyridine (**22**) as the substrate, a white solid was obtained (65%), mp 126-127°; ^{1}H-nmr: δ 1.8 (4H, m), 3.1 (4H, m), 6.6 (1H, OH), 7.3 (1H, m), 7.8 (1H, d), 8.15 (1H, s), 8.65 (1H, d).

Anal. Calcd. for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found: C, 66.93; H, 5.32; N, 7.07.

Diphenyl-4-(morpholinosulphonyl)-3-pyridylmethanol (**26**).

Using 4-(morpholinosulphonyl)pyridine (**23**) as the substrate, a white solid was obtained on recrystallisation from diethyl ether (78%), mp 158-159°; ^{1}H-nmr: δ 3.0 (4H, m), 3.6 (4H, m), 6.35 (1H, s), 7.3 (10H, m), 7.65 (1H, d), 8.2 (1H, s), 8.70 (1H, d).

Anal. Calcd. for $C_{22}H_{22}N_2O_4S$: C, 64.39; H, 5.36; N, 6.83. Found: C, 64.33; H, 5.11; N, 6.85.

3,3-Diphenyl-1,2-oxathiolo[3,4-*b*]pyridine 1,1-Dioxide (**20**).

Each of the diphenyl-(*N,N*-dialkylaminosulphonyl)-3-pyridylmethanols **17-19** (1.3 g) was heated at 210° for 20 hours under argon. It was allowed to cool and the residue was extracted into methanol. The methanol was distilled off and the residue dissolved in dichloromethane (50 ml), washed with water (3 x 40 ml) and dried over sodium sulphate. The solvent was removed *in vacuo* to leave a brown solid. Flash chromatography with diethyl ether:hexane 2:1 gave pale yellow crystals (45%), mp 141-143°; ^{1}H-nmr: δ 7.3 (12H, m), 8.4 (1H, d); ir: 3000, 2940, 2880, 1580, 1450, 1350, 1170 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}NO_3S$: C, 66.86; H, 4.05; N, 4.33. Found: C, 66.81; H, 4.14; N, 4.53.

3,3-Diphenyl-1,2-oxathiolo[4,3-*c*]pyridine 1,1-Dioxide (**27**).

Each of the diphenyl-(4-*N,N*-dialkylaminosulphonyl)-3-pyridyl)-methanols **24-26** (1.0 g) was heated at 210° for 20 hours under a slow stream of argon. The reaction mixture was allowed to cool and the residue was extracted into methanol. Solvent was distilled off and the residue taken up in dichloromethane (50 ml). The solution was washed with water (3 x 40 ml) and dried over sodium sulphate before solvents were stripped off *in vacuo* to leave a brown solid. Recrystallisation of the solid from diethyl ether gave pale yellow prisms (45%), mp 80-81°; ^{1}H-nmr: δ 7.0 (11H, m), 8.40 (1H, d), 8.65 (1H, s); ir: 2900, 1600, 1340, 1160 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}NO_3S$: C, 66.86; H, 4.05; N, 4.33. Found: C, 66.83; H, 3.94; N, 4.50.

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