Synthesis of 2,3,4,6-Tetrasubstituted Pyridines as Precursors to Bicycles and Polycycles[†] Fathi A. Abu-Shanab^{*}

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Ammonium 1,1,3-tricyano-2-methylprop-2-enide **1a** and sodium 2-amino-1,1,3-tricyanoprop-2-enide **1b** are treated with H_2S in absolute ethanol to afford 3,4,6-trisubstituted pyridine-2(1*H*)-thione **3a,b**; their structures are confirmed by reaction with phenacyl bromide to give **4a,b**; also **3a,b** reacts with DMFDMA to give **6a,b**, and on treatment of **6a** with phenacyl bromide affords **8**; reaction of **4b** with DMFDMA gave **9** while methylation of **3a,b** by methyl iodide in ethanolic sodium hydroxide gives **10a,b**.

Interest in development of efficient synthetic approaches for the preparation of functionalized 3-cyano-2(1H)-pyridinethiones is related to their use as versatile precursors in the preparation of dyes, herbicides, bactericides and other biologically active compounds.^{1,3}

Generally, it is reported that 3-cyanopyridine-2(1*H*)thiones are prepared by the reaction of 2-cyanothioacetamide with arylmethylenemalononitriles,^{4,5} 1,3-diketones,^{6,7} β -enaminoketones,^{8,9} or bis(methylthio)methylene derivatives of malononitrile¹⁰ or 1,3-diketones.¹¹ Ammonium 1,1,3-tricyano-2-methylprop-2-enide **1a** and sodium 2-amino-1,1,3-tricyanoprop-2-enide **1b** are useful reagents for the preparation of heterocyclic compounds.¹²

We now report that the treatment of ammonium 1,1,3-tricyano-2-methylprop-2-enide 1a and sodium 2-amino-1,1,3-tricyanoprop-2-enide **1b**¹² with H₂S in ethanol afforded a trisubstituted pyridine-2(1H)-thione. The mass spectrum shows molecular ion peaks at m/z165 (C7H7N3S) and 166 (C6H6N4S) which indicates that only one molecule of H2S is added. Two modes of cyclisation may be envisaged, giving 4,5,6or 3,4,6-trisubstituted products, as outlined in Scheme 1. In practice only one isomer was isolated in each case, but their spectra did not enable unequivocal identification. In their ¹HNMR spectra, the signals for the ring protons were at δ ca. 5.9 but the chemical shifts for protons 3 and 5 of pyridin-2-ones are often very similar.¹



Scheme 1

Some illustrative reactions designed to confirm the structure, and also to demonstrate the potential usefulness of the products for further heterocyclic syntheses, are given in Scheme 2. Thus reaction of pyridines 2 or 3 with phenacyl bromide and potassium carbonate in ethanol gave a product that may be formulated as 4 or 5. IR spectra



show the disappearance of the cyano group, indicating that the cyano group is on the same side of the thione group and thus the products are the thieno[2,3-b]pyridine derivatives 4a,b.¹⁴ For further confirmation, the amino group was protected so that treatment of 2 or 3 with DMFDMA in boiling dioxane afforded pyridine-2(1H)-thione derivatives **6a**,**b** or **7a**,**b** which by IR show the absence of the amino group. Further reaction of pyridine-2(1H)-thione derivative 6a or 7a with phenacyl bromide and potassium carbonate in ethanol gave thieno[2,3-b]pyridine derivative 8^{14} the IR spectrum of which shows the disappearance of the cyano group and the appearance of an amino group (v 3346, 3175 cm⁻¹). This also indicates that the cyano group is on the same side of the thione group. Therefore the pyridine-2(1H)-thione obtained by the reaction of the salts 1a,b with H₂S is the 3,4,6-trisubstituted pyridine-2(1H)-thione 3. The tricyclic compound 9^{15} can also be obtained by the reaction of 4b with DMFDMA in boiling dioxane and its structure was confirmed by ¹HNMR which showed the disappearance of the amino groups and mass spectra which showed a molecular ion peak at m/z 349. Methylation of **3a**,**b** by methyl iodide in ethanolic sodium hydroxide afforded the corresponding thioethers 10a,b.

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[†]This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research* (S), 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research* (M).

Experimental

Mps are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer as KBr disks. NMR spectra were recorded on a Bruker AC300 spectrometer at 200 MHz for solutions of CDCl₃ and [2H6]dimethyl sulfoxide with tetramethylsilane (TMS) as an internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometers using electron impact (EI). The salts, ammonium 1,1,3-tricyano-2-methyl-prop-2-enide **1a** and sodium 2-amino-1,1,3-tricyanoprop-2-enide **1b** were prepared according to literature methods.¹²

Reaction of 1a,b with H2S.-General Method. H2S was passed for 2h through a solution of salts 1a,b (0.01 mol) in absolute ethanol. Fine crystals separated and were recovered by filtration and purified by recrystallisation from the appropriate solvent.

6-Amino-3-cyano-4-methylpyridine-2(1H)-thione 3a. Crystallisation from ethanol, mp 260 °C (decomp.), yield 85%. IR: 3431, 3215 (NH₂), 2150 cm⁻¹ (CN), $\delta_{\rm H}$ (DMSO) 2.19 (s, 3H, CH₃), 5.95 (s, 1H, ring proton), 7.25 (br exchangeable, 2H, NH₂), 12.25 (br exch., 1H, NH). MS (EI): m/z 165 (M⁺, 100%) (Calc.: C, 50.9; H, 4.27; N, 25.45. Found: C, 50.77; H, 4.15; N, 25.34%).

4,6-Diamino-3-cyanopyridine-2(1H)-thione 3b. Crystallisation from ethanol, mp 310–312 °C, yield 65%. IR: 3346, 3215 (NH₂), 2155 cm⁻¹ (CN), $\delta_{\rm H}$ (DMSO) 5.29 (s, 1H, ring proton), 6.54 (br exch., 2H, NH₂), 6.69 (br exch., 2H, NH₂), 11.19 (s, exch., 1H, NH). MS (EI): m/z 166 (M⁺, 100%) (Calc.: C, 43.37; H, 3.64; N, 33.74. Found: C, 43.16; H, 3.42; N, 33.52%).

Preparation of Thieno[2,3-b]pyridines 4a,b and 8).-General Method. An equimolar mixture of pyridine-2(1H)-thione **3a**,**b** or **6a** (0.01 mol), phenacyl bromide (1.99 g, 0.01 mol) and potassium carbonate in absolute ethanol were refluxed for 2h. After cooling the mixture was diluted with water and the solid obtained recovered by filtration and purified by recrystallisation from the appropriate solvent.

3,6-Diamino-2-benzoyl-4-methylthieno[2,3-b]pyridine 4a. Crystallisation from ethanol, mp 280–282 °C, yield 2.4 g (86%). IR: ν_{max} 3460, 3325, 3160 (NH₂), 1630 (CO) cm⁻¹. $\delta_{\rm H}$ (DMSO) 2.61 (s, 1H, CH₃), 6.27 (s, 1H, ring proton), 6.84 (br exch., 2H, NH₂), 7.49-7.53 (m, 3H, Ar), 7.67–7.73 (m, 2H, Ar), 8.00 (br exch., 2H, NH₂). MS (EI): m/z 283 (M⁺, 70%) (Anal. Calc.: C, 63.59; H, 4.63; N, 14.84. Found: C, 63.28; H, 4.33; N, 14.57%).

3,5,6-Triamino-2-benzoylthieno[2,3-b]pyridine 4b. Crystallisation from ethanol, mp 240–242 °C, yield 2.3 g (82%). IR: v_{max} 3390, 3150 (NH₂), 1637 (CO) cm⁻¹. δ_{H} (DMSO) 5.66 (s, 1H, ring proton), 6.5 (br exch., 2H, NH₂), 6.45 (br exch., 1H, NH₂), 7.45–7.51 (m, 3H, Ar), 7.64–7.69 (m, 2H, Ar), 8.36 (br exch., 1H, NH₂). MS (EI): *m/z* 284 (M⁺, 30%) (Anal. Calc.: C, 59.14; H, 4.26; N, 19.72. Found: C, 58.86; H, 4.39; N, 19.50%).

3-Amino-6-(N,N-dimethylformimdyl)-4-methylthieno[2,3-b]pyridine 8. Crystallisation from ethanol, mp 167–169 °C, yield 2.7 g (80%). IR: v_{max} 3346, 3175 (NH₂), 1632 (CO) cm⁻¹. δ_{H} (DMSO) 2.64 (s, 1H, CH₃), 3.05 (s, 3H, NCH₃), 3.18 (s, 3H, NCH₃), 6.3 (s, 1H, ring proton), 6.5 (br exch., 2H, NH₂), 7.48-7.55 (m, 3H, Ar), 7.67-7.73 (m, 2H, Ar), 8.4 (s, 1H, enamine proton). MS (EI): m/z 338 (M+, 30%) (Anal. Calc.: C, 63.88; H, 5.37; N, 16.57. Found: C, 63.67; H, 5.42; N, 16.65%).

Preparation of Pyridine-2(1H)-thiones 6a,b.-Pyridine-2(1H)thione 3a,b (0.01 mol) and DMFDMA in dry dioxane were refluxed for 2 h. The solvent was then evaporated and the resulting solid collected by filtration and recrystallised from ethanol.

3-Cyano-6-(N,N-dimethylformimdyl)-4-methylpyridine-2(1H)-thione 6a. Mp 186–188 °C, yield 1.7 g (76%). IR: v_{max} 2150 cm⁻¹ (CN), δ_H(DMSO) 2.26 (s, 3H, CH₃), 3.04 (s, 3H, NCH₃), 3.16 (s, 3H, NCH₃), 6.42 (s, 1H, ring proton) 8.32 (s, 1H, enamine proton), 12.69 (br exch., 1H, NH). MS (EI): m/z 220 (M⁺, 100%) (Anal. Calc.: C, 54.53; H, 5.50; N, 25.45. Found: C, 54.66; H, 5.34; N, 25.26%).

 $\label{eq:second} 3-Cyano-4, 6-bis (N, N-dimethyl formindyl) pyridine-2 (1H)-thione~~ \mathbf{6b}.$ Mp 160–162 °C, yield 2.2 g (80%). IR: ν_{max} 2160 cm⁻¹ (CN), $\delta_{\rm H}$ (DMSO) 3.005 (s, 3H, NCH₃), 3.013 (s, 3H, NCH₃), 3.102 (s, 3H, NCH₃), 3.131 (s, 3H, NCH₃) 6.273 (s, 1H, ring proton), 8.184 (s,

1H, enamine proton), 8.677 (s, 1H, enamine proton). MS (EI): m/z 276 (M⁺, 100%) (Anal. Calc.: C, 52.15; H, 5.84; N, 30.43. Found: C, 51.92; H, 6.00; N, 30.56%).

Preparation of Compound 9.—Equimolar amounts of thieno[2,3-b]pyridine 4b (0.3 g, 0.001 mol) and DMFDMA (0.26 ml, 0.002 mol) in dry dioxane were refluxed for 2 h. The resultant solid was recovered by filtration and recrystallised from dioxane, mp 165–167 °C, yield 3 g (85%). $\delta_{\rm H}$ (DMSO) 3.08 (s, 3H, CH₃), 3.11 (s, 3H, CH₃), 5.45 (s, 1H, ring proton), 7.46-7.55 (m, 3H, Ar), 7.74 (m, 2H, Ar), 8.36 (s, 1H, CH), 8.55 (s 1H, CH), 8.65 (br exch., 1H,

pyridine-2(1H)-thione 10a,b.—Pyridine-2(1H)-thione 3a,b (0.01 mol) was dissolved in ethanol (25 ml)-sodium hydroxide (10%, 10 ml) and treated with methyl iodide [2 ml(excess)] dropwise with stirring at room temperature. The reaction mixture was left stirring at room temperature for 2 h and the resultant solid recrystallised from ethanol as colourless crystals.

6-Amino-3-cyano-4-methyl-2-methylthiopyridine-2(1H)-thione 10a. Mp 218–220 °C, yield 1.43 g (80%). IR: ν_{max} 3340, 3310 (NH₂), 2165 cm⁻¹ (CN), δ_{H} (DMSO) 2.22 (s, 3H, CH₃), 2.5 (s, 3H, CH₃), 6.1 (s, 1H, ring proton), 6.97 (br exch., 2H, NH₂). MS (EI): m/z 179 (M⁺, 100%) (Anal. Calc.: C, 53.62; H, 5.07; N, 23.46. Found: C, 53.77; H, 5.17; N, 23.28%).

4,6-Diamino-3-cyano-2-methylthiopyridine-2(1H)-thione 10b. Mp 153–155 °C, yield 1.4 g (77%). IR: v_{max} 3430, 3320, 3205 (NH₂), 2150 (CN), 1618, 1573 (C=N, C=C) cm⁻¹, $\delta_{\rm H}$ (DMSO) 2.45 (s, 3H, SCH₃), 3.46 (br exch., 2H, NH₂), 5.46 (s, 1H, ring proton), 6.23 (br exch., 1H, NH₂). MS (EI): m/z 180 (M⁺, 100%) (Anal. Calc.: C, 46.65; H, 4.48; N, 31.11. Found: C, 46.44; H, 4.60; N, 30.96%).

Received, 17th August 1998; Accepted, 29th March 1999 Paper E/8/06439C

References

- V. P. Litvino, L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov and A. Senning, *Sulfur Rep.*, 1992, 13, 155. A. M. Shestopalov, V. K. Promomenkov, Yu. A. Sharanin, L
- A. Rodinovskaya and S. Yu. Sharanin, Zh. Org. Khim., 1984, 20, 1517.
- A. M. Shestopalov, V. K. Promomenkov, Yu. A. Sharanin and 3 A. M. Shestopalov, Enaminocarbonyl Compounds in Synthesis of 3-cyano-2(1H)-pyridinethiones, in Itogi Nauki i Techniki, Ser. Organicheskaya Khimiya, ed. Kabachnie, VINITI, Moscow, 1989, vol. 17, pp. 72–156 and references therein.
 G. E. Elgemeier, M. M. Sallam, M. S. Sherif and M. H.
- Elnagdi, Heterocycles, 1985, 23, 3107.
- F. M. A. Galil, M. M. Sallam, M. S. Sherif and M. H. Elnagdi, 5 Liebigs Ann. Chem., 1986, 1639.
- 6
- U. Schmidt and H. Kubitzek, *Chem. Ber.*, 1960, **93**, 1559. H. Vieweg, S. Leistner and G. Wagner, *Pharmazie*, 1986, 41. 7
- F. A. Abu-Shanab, A. D. Redhouse, J. R. Thompson and B. J. 8 Wakefield, Synthesis, 1995, 557.
- F. A. Abu-Shanab, F. A. Ali and B. J. Wakefield, Synthesis, 9 1995, 923.
- D. Briel, S. Dumke, G. Wagner and B. Olk, J. Chem. Res., 10 1991, (S) 178; (M) 1841.
- F. A. Abu-Shanab, M. H. Elnagdi, F. A. Ali and B. J. 11 Wakefield, J. Chem. Soc., Perkin Trans. 1, 1994, 1449.
- A. W. Erian, Chem. Rev., 1993, 93, 1991 and references 12 therein.
- D. H. Williams and I. Fleming, Spectroscopic Methods in Organic Chemistry, McGraw-Hill, London, 4th edn., 1987. 13
- 14 K. Gewald, Chimia, 1980, 34, 101 and references therein.
- H. Sliwa, D. Blondeau and R. Rydzkowsk, J. Heterocycl. 15 Chem., 1983, 20, 1613.