Synthesis of 2,3,4,6-Tetrasubstituted Pyridines as Precursors to Bicycles and Polycycles†

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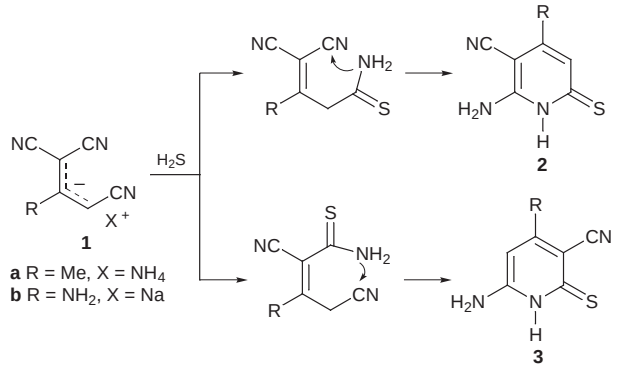
Ammonium 1,1,3-tricyano-2-methylprop-2-enide **1a** and sodium 2-amino-1,1,3-tricyanoprop-2-enide **1b** are treated with H_2S in absolute ethanol to afford 3,4,6-trisubstituted pyridine-2(1*H*)-thione **3a**,**b**; their structures are confirmed by reaction with phenacyl bromide to give **4a**,**b**; 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(1*H*)-pyridinethiones is related to their use as versatile precursors in the preparation of dyes, herbicides, bactericides and other biologically active compounds.[1,3]

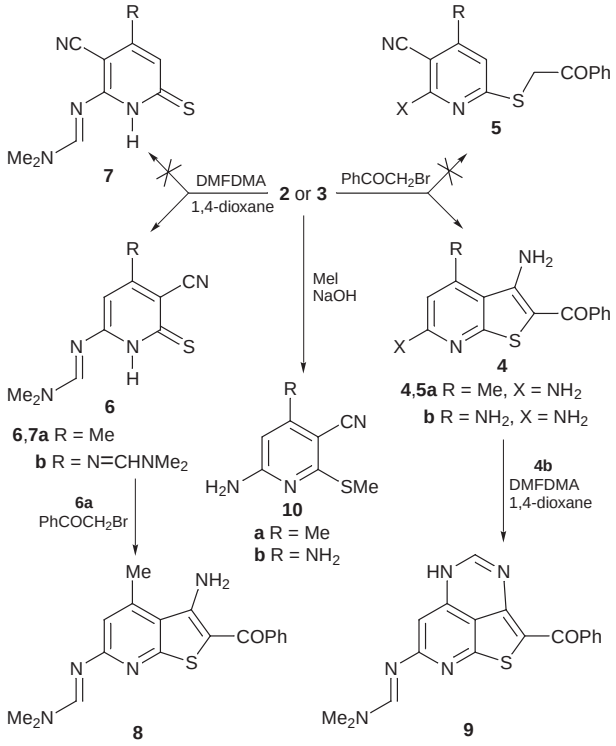
Generally, it is reported that 3-cyanopyridine-2(1*H*)-thiones are prepared by the reaction of 2-cyanothioacetamide with arylmethylenemalononitriles,[4,5] 1,3-diketones,[6,7] *β*-enaminoketones,[8,9] or bis(methylthio)-methylene derivatives of malononitrile[10] or 1,3-diketones.[11] Ammonium 1,1,3-tricyano-2-methylprop-2-enide **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 H_2S in ethanol afforded a trisubstituted pyridine-2(1*H*)-thione. The mass spectrum shows molecular ion peaks at *m/z* 165 ($C_7H_7N_3S$) and 166 ($C_6H_6N_4S$) which indicates that only one molecule of H_2S is added. Two modes of cyclisation may be envisaged, giving 4,5,6- or 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 ^{1}H NMR 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.[13]



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



Scheme 2

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(1*H*)-thione derivatives **6a**,**b** or **7a**,**b** which by IR show the absence of the amino group. Further reaction of pyridine-2(1*H*)-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 (*ν* 3346, 3175 cm^{-1}). This also indicates that the cyano group is on the same side of the thione group. Therefore the pyridine-2(1*H*)-thione obtained by the reaction of the salts **1a**,**b** with H_2S is the 3,4,6-trisubstituted pyridine-2(1*H*)-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 ^{1}H NMR 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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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 $CDCl_3$ and [$^2H_6$]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-methylprop-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* H_2S.—*General Method*. H_2S was passed for 2 h 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 (NH_2), 2150 cm^{-1} (CN), δ_H(DMSO) 2.19 (s, 3H, CH_3), 5.95 (s, 1H, ring proton), 7.25 (br exchangeable, 2H, NH_2), 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 (NH_2), 2155 cm^{-1} (CN), δ_H(DMSO) 5.29 (s, 1H, ring proton), 6.54 (br exch., 2H, NH_2), 6.69 (br exch., 2H, NH_2), 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(1*H*)-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 2 h. 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 (NH_2), 1630 (CO) cm^{-1}. δ_H(DMSO) 2.61 (s, 1H, CH_3), 6.27 (s, 1H, ring proton), 6.84 (br exch., 2H, NH_2), 7.49–7.53 (m, 3H, Ar), 7.67–7.73 (m, 2H, Ar), 8.00 (br exch., 2H, NH_2). 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: ν_{max} 3390, 3150 (NH_2), 1637 (CO) cm^{-1}. δ_H(DMSO) 5.66 (s, 1H, ring proton), 6.5 (br exch., 2H, NH_2), 6.45 (br exch., 1H, NH_2), 7.45–7.51 (m, 3H, Ar), 7.64–7.69 (m, 2H, Ar), 8.36 (br exch., 1H, NH_2). 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: ν_{max} 3346, 3175 (NH_2), 1632 (CO) cm^{-1}. δ_H(DMSO) 2.64 (s, 1H, CH_3), 3.05 (s, 3H, NCH_3), 3.18 (s, 3H, NCH_3), 6.3 (s, 1H, ring proton), 6.5 (br exch., 2H, NH_2), 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(1*H*)-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: ν_{max} 2150 cm^{-1} (CN), δ_H(DMSO) 2.26 (s, 3H, CH_3), 3.04 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 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%).

3-*Cyano*-4,6-*bis*(N,N-*dimethylformimdyl*)*pyridine*-2(1H)-*thione* **6b**. Mp 160–162 °C, yield 2.2 g (80%). IR: ν_{max} 2160 cm^{-1} (CN), δ_H(DMSO) 3.005 (s, 3H, NCH_3), 3.013 (s, 3H, NCH_3), 3.102 (s, 3H, NCH_3), 3.131 (s, 3H, NCH_3) 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%). δ_H(DMSO) 3.08 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 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, NH). MS (EI): *m/z* 349 (M^+, 60%) (Anal. Calc.: C, 61.87; H, 4.33; N, 20.06. Found: C, 61.69; H, 4.25; N, 21.88%).

Preparation of 4-*Substituted* 6-*Amino*-3-*cyano*-2-*methylthiopyridine*-2(1H)-*thione* **10a**,**b**.—Pyridine-2(1*H*)-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 (NH_2), 2165 cm^{-1} (CN), δ_H(DMSO) 2.22 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 6.1 (s, 1H, ring proton), 6.97 (br exch., 2H, NH_2). 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: ν_{max} 3430, 3320, 3205 (NH_2), 2150 (CN), 1618, 1573 (C=N, C=C) cm^{-1}, δ_H(DMSO) 2.45 (s, 3H, SCH_3), 3.46 (br exch., 2H, NH_2), 5.46 (s, 1H, ring proton), 6.23 (br exch., 1H, NH_2). 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%).

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