Novel Synthesis of Pyridine-2(1*H*)-thiones: Reaction of Imino Esters with Cyanothioacetamide†

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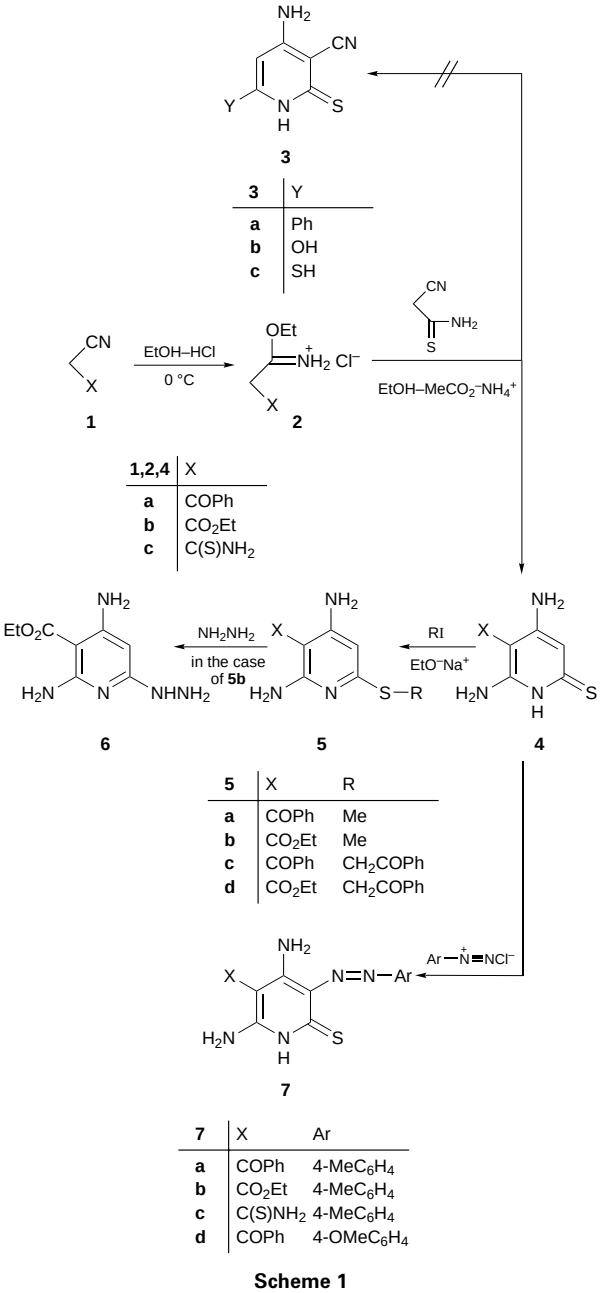
A novel synthesis of pyridine-2(1*H*)-thiones *via* the reaction of imino esters with cyanothioacetamide is reported and the synthetic potential of the method is demonstrated.

Imino esters are highly reactive compounds and are extensively utilized as reactants or reaction intermediates since their imino and ester functions are suitably situated to enable reactions with common bidentate reagents to form a variety of heterocyclic compounds.[1,2] Moreover, the active hydrogen atom on C-2 of these compounds can also take part in a variety of condensation and substitution reactions. As part of a medicinal chemistry program in our laboratories, the syntheses of several substituted pyridine-2(1*H*)-thiones were required. The importance of the synthesized compounds as intermediates for the synthesis of the biologically active deazafolic acid and deazapyrimidine nucleoside ring systems prompted our interest in the synthesis and chemistry of this class of compounds.[3–10] We now report the novel reaction of imino esters **2** with cyanothioacetamide.

It was found that treating the cyano compounds **1a–c** with hydrogen chloride in absolute ethanol at 0 °C gave the imino esters **2** in good yield. Compounds **2** reacted with cyanothioacetamide in refluxing ethanol containing ammonium acetate to yield 1:1 adducts, for which two possible structures, **3** and **4**, were considered. The structure of **4** was established and confirmed on the basis of elemental analysis and spectral data. The IR spectrum of compound **4a** showed the absence of a cyano group and the presence of a carbonyl group at 1650 cm^{-1}. The formation of **4** from the reaction of **2** with cyanothioacetamide is assumed to proceed *via* the initial Michael addition of the active methylene in **2** to the cyano group in cyanothioacetamide to yield intermediates, which cyclize *via* ethanol elimination to give the stable pyridine-2(1*H*)-thione derivatives **4**.

Compounds **4** bearing latent functional substituents were found to be useful for the synthesis of pyridine derivatives. Thus, compounds **4** reacted with methyl iodide and phenacyl bromide in sodium ethoxide to afford the corresponding *S*-substituted derivatives **5**. When compound **5b** was treated with hydrazine, the 2-hydrazino derivative **6** was obtained. Compounds **4** were also coupled with aryldiazonium chlorides in ethanol containing sodium acetate to yield the corresponding hydrazones **7**. The structures of **7** were established on basis of their elemental analysis and spectral data.



Scheme 1

Experimental

All melting points are uncorrected. The IR spectra were obtained (KBr disk) on a Perkin Elmer/1650 FT-IR instrument. ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University. Compounds **2a**,**b** were prepared following the literature procedures.[11]

β-Imino-β-ethoxythioacetamide Hydrochloride **2c**.—Hydrogen chloride gas was passed through a mixture of cyanothioacetamide (0.1 mol) and absolute ethanol (0.1 mol) in dry 1,4-dioxane for 3 h at 0 °C. The resultant precipitate was isolated by filtration and recrystallized from 1,4-dioxane–ethanol (2:1) to give **2c**, mp 154 °C, yield 96%; ν_{max} (KBr)/cm^{-1} 3590–3124 (NH_2, NH).

5-Substituted 4,6-Diaminopyridine-2(1H)-thiones **4**. *General Procedure.*—A mixture of cyanothioacetamide (0.1 mol) and compounds **2a–c** (0.1 mol) was treated with sodium acetate (0.15 mol)

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and dry ethanol (100 ml) and then heated for 12 h. The solution was then poured into iced water and the resultant precipitate was collected and recrystallized from the appropriate solvent. **4a**: mp 190 °C, yield 67%; ν_{max} (KBr)/cm^{-1} 3637–3443, 3302 (NH_2), 1650 (CO); δ_H [$(CD_3)_2SO$] 6.18 (brs, 2 H, NH_2), 6.83 (s, 1 H, CH), 7.22–7.58 (m, 5 H, Ph), 7.62 (brs, 2 H, NH_2), 13.86 (brs, 1 H, NH); *m/z* 245 (M^+) (Found: C, 60.0; H, 4.8; N, 17.6. $C_{12}H_{11}N_5SO$ requires C, 58.8; H, 4.5; N, 17.1%). **4b**: mp >300 °C, yield 53%; ν_{max} (KBr)/cm^{-1} 3400–3132 (NH_2, NH), 1747 (CO); *m/z* 213 (M^+) (Found: C, 45.6; H, 5.0; N, 19.9. $C_8H_{11}N_3SO_2$ requires C, 45.1; H, 5.2; N, 19.7%). **4c**: mp >300 °C, yield 53%; ν_{max} (KBr)/cm^{-1} 3404–3200 (NH_2, NH); *m/z* 200 (M^+) (Found: C, 35.8; H, 4.3; N, 28.5. $C_6H_8N_4S_2$ requires C, 36.0; H, 4.0; N, 28.0%).

5-*Substituted* 4,6-*Diamino*-2-*methylsulfanylpyridines* **5a,b**. *General Procedure.*—To a solution of sodium ethoxide [prepared by dissolving sodium metal (0.01 mol) in anhydrous ethanol (10 ml)], the equivalent amounts of **4a**,**b** dissolved in 6 ml DMF were added. The reaction mixture was refluxed for 15 min, cooled, and then methyl iodide (0.012 mol) was added. The solution was stirred for 1 h at room temperature and allowed to stand overnight. The product was isolated by neutralizing the reaction mixture with dil. HCl and recrystallizing from the appropriate solvent. **5a**: mp 165 °C, yield 62%; ν_{max} (KBr)/cm^{-1} 3227, 3112 (NH_2), 1707 (CO); *m/z* 259 (M^+) (Found: C, 60.5; H, 4.8; N, 16.0. $C_{13}H_{13}N_3SO$ requires C, 60.2; H, 5.0; N, 16.2%). **5b**: mp >300 °C, yield 79%; ν_{max} (KBr)/cm^{-1} 3350–3186 (NH_2), 1750–1730 (CO); *m/z* 227 (M^+) (Found: C, 47.8; H, 5.4; N, 18.4. $C_9H_{13}N_3SO_2$ requires C, 47.5; H, 5.7; N, 18.4%).

5-*Substituted* 4,6-*Diamino*-2-*phenacylsulfanylpyridines* **5c**,**d**. *General Procedure.*—To a solution of sodium ethoxide (0.01 mol), the equivalent amounts of **4a**,**b** and phenacyl bromide were added. The mixture was then heated for 3 h and the product isolated by neutralization of the reaction mixture with dil. HCl and recrystallization from ethanol. **5c**: mp 175 °C, yield 70%; ν_{max} (KBr)/cm^{-1} 3650, 3334 (NH_2), 1706, 1633 (2CO); δ_H [$(CD_3)_2SO$] 4.49 (s, 2 H, CH_2), 6.77 (brs, 2 H, NH_2), 6.92 (s, 1 H, CH), 7.18–7.76 (m, 10 H, 2Ph), 7.89 (brs, 2 H, NH_2); *m/z* 363 (M^+) (Found: C, 66.5; H, 4.5; N, 11.9. $C_{20}H_{17}N_3SO_2$ requires C, 66.1; H, 4.7; N, 11.6%). **5d**: mp 221 °C, yield 56%; ν_{max} (KBr)/cm^{-1} 3327 (NH_2), 1795–1647 (2 CO); *m/z* 331 (M^+) (Found: C, 57.7; H, 5.4; N, 12.8. $C_{16}H_{17}N_3SO_3$ requires C, 58.0; H, 5.1; N, 12.7%).

Ethyl 4,6-*Diamino*-2-*hydrazinopyridine*-5-*carboxylate* **6**.—An equivalent mixture of **5b** and hydrazine hydrate (0.01 mol) was stirred in ethanol (20 ml) for 1 h. The product that separated on cooling was filtered and recrystallized from DMF–EtOH. **6**: mp >300 °C, yield 54%; ν_{max} (KBr)/cm^{-1} 3748, 3450–3175 (NH_2, NH), 1735–1688 (CO); *m/z* 211 (M^+) (Found: C, 45.0; H, 5.8; N, 33.5. $C_8H_{13}N_5O_2$ requires C, 45.5; H, 6.2; N, 33.17%.

5-*Substituted* 3-*Arylazo*-4,6-*diaminopyridine*-2(1H)-*thiones* **7a–d**. *General Procedure.*—A solution of compounds **4** (0.01 mol) in ethanol containing sodium acetate (2.0 g) was cooled to 0 °C and then treated gradually with a cold solution of aryldiazonium chloride [prepared from arylamine (0.01 mol) and the appropriate quantities of HCl and $NaNO_2$]. The solid product formed was collected and recrystallized from the appropriate solvent. **7a**: mp 210 °C, yield 80%; ν_{max} (KBr)/cm^{-1} 3443, 3304, 3198 (NH_2, NH), 1640–1620 (CO); δ_H [$(CD_3)_2SO$] 2.52 (s, 3 H, CH_3), 7.13 (brs, 2 H, NH_2), 7.20–7.50 (m, 9 H, Ph and C_6H_4), 7.97 (brs, 2 H, NH_2), 9.60 (brs, 1 H, NH); *m/z* 363 (Found: C, 62.3; H, 4.5; N, 19.0. $C_{19}H_{17}N_5SO$ requires C, 62.8; H, 4.7; N, 19.3%). **7b**: mp 280 °C, yield 75%; ν_{max} (KBr)/cm^{-1} 3550–3367 (NH_2, NH), 1677–1614 (CO); *m/z* 331 (M^+) (Found: C, 54.8; H, 4.98; N, 21.4. $C_{15}H_{17}N_5SO_2$ requires C, 54.4; H, 5.14; N, 21.15%). **7c**: mp >300 °C, yield 86%; ν_{max} (KBr)/cm^{-1} 3400–3122 (NH_2, NH); *m/z* 318 (M^+) (Found: C, 49.2; H, 4.6; N, 27.0. $C_{13}H_{14}N_6S_2$ requires C, 49.0; H, 4.4; N, 26.4%). **7d**: mp 222 °C, yield 67%; ν_{max} (KBr)/cm^{-1} 3450, 3368–3275 (NH_2, NH), 1680–1619 (CO); δ_H [$(CD_3)_2SO$] 3.88 (s, 3 H, OCH_3), 7.06 (brs, 2 H, NH_2), 7.11–7.55 (M, 9 H, Ph and C_6H_4), 7.78 (brs, 2 H, NH_2), 9.99 (brs, 1 H, NH); *m/z* 379 (M^+) (Found: C, 59.8; H, 4.7; N, 18.3. $C_{19}H_{17}N_5SO_2$ requires C, 60.2; H, 4.5; N, 18.5%).

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