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Synthesis of 2,4-Diaminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines

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The heteroannelation reaction of 3-cyanopyridine-2(1*H*)-thiones with *N*-cyanochloroacetamidine leads consecutively to thieno[2,3-*b*]pyridines and 2,4-diaminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines.

Substituted pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines with different types of biological activity are obtained by multi-step syntheses.[1–3] The most common method of synthesis involves the preparation of substituted 3-amino-2-cyano(ethoxycarbonyl, carbamoyl)thieno[2,3-*b*]pyridines from 3-cyanopyridine-2(1*H*)-thiones and chloroacetonitrile (ethyl chloroacetate, chloroacetamide) followed by condensation with formamide, nitriles or diethyl oxalate.[4–7] The same compounds can be prepared in convenient yields by recyclisation of pyrido[3′,2′:4,5]thieno[3,2-*d*]oxazine-4-ones by amines or hydrazine.[8] However, 2,4-diamino-substituted compounds cannot be obtained by these methods.

We now report a new, simple method for the synthesis of 2,4-diamino[3′,2′:4,5]thieno[3,2,-*d*]pyrimidines from substituted 3-cyanopyridine-2(1*H*)-thiones[9] and *N*-cyanochloroacetamidine.[10]

Reaction of 3-cyanopyridine-2(1*H*)-thiones **1a–c** with *N*-cyanochloroacetamidine **2** in DMF in the presence of an equimolar amount of KOH/H_2O (10%) yields the products of regioselective *S*-alkylation, **3a–c** (Scheme 1, Table 1). *S*-

Table 1 Yields and characteristic data for **3**–**5**

Compound	R	M.p./ °C	Yield (%)	IR(KBr), ν/cm^{-1}	^{1}H NMR, δ/ppm[a]
3a	$R^1 = R^3 = Ph$ $R^2 = H$	204–205	48	3390, 3330, 3170 (NH_2); 2220 (3–CN); 2180 (amidine–CN)	4.38 (br. s, 2H ,CH_2) 7.98 (s, 1H, H-5) 8.70 (br. s, NH_2)
3b	$R^1 = 4\text{-}ClC_6H_4$ $R^2 = H$ $R^3 = 4\text{-}MeC_6H_4$	203–204	31	3390, 3320, 3150 (NH_2); 2215 (3–CN); 2190 (amidine-CN)	4.38 (br. s, 2H, CH_2) 7.95 (s, 1H, H-5) 8.69 (br. s, NH_2)
3c	$R^1 = 4\text{-}ClC_6H_4$ $R^2R^3 = (CH_2)_4$	206–207	46	3420, 3320, 3160 (NH_2); 2220 (3–CN); 2180 (amidine-CN)	4.23 (br. s, 2H, CH_2-amidine) 8.58 (br. s, NH_2)
4a	$R^1 = R^3 = Ph$ $R^2 = H$	242–244	88[b] 78[c]	3485, 3300, 3200 (NH_2); 2180, 2145 (CN)	6.26 and 6.28 (2s, 3-NH_2); 7.80 (s, 1H, H-5); 8.26 (2s, NH_2-amidine)
4b	$R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$, $R^3 = 4\text{-}MeC_6H_4$	244–247	80[b] 91[c]	3490, 3300, 3180 (NH_2); 2185, 2145 (CN)	6.30 and 6.33 (2s, 3-NH_2); 7.77 (s., 1H, H-5); 8.20 (2s., NH_2-amidine)
4c	$R^1 = 4\text{-}ClC_6H_4$ $R^2R^3 = (CH_2)_4$	264–265	86[b] 88[c]	3480, 3300, 3160 (NH_2); 2185, 2150 (CN)	5.96 and 5.98 (2s, 3-NH_2); 8.05 (2s, NH_2-amidine)
5a	$R^1 = R^3 = Ph$ $R^2 = H$	278–279[d]	64	3400 (br., NH_2)	5.53 (s, 2-NH_2) 7.03 (s, 4-NH_2) 7.85 (s, 1H, H-8)
5b	$R^1 = 4\text{-}ClC_6H_4$ $R^2 = H$ $R^3 = 4\text{-}MeC_6H_4$	276–277[d]	63	3400 (br., NH_2)	5.64 (s, 2-NH_2) 7.03 (s, 4-NH_2) 7.84 (s, 1H, H-8)
5c	$R^1 = 4\text{-}ClC_6H_4$ $R^2R^3 = (CH_2)_4$	271-272[d]	67	3400 (br., NH_2)	5.24 (s, 2-NH_2) 6.89 (s, 4-NH_2)

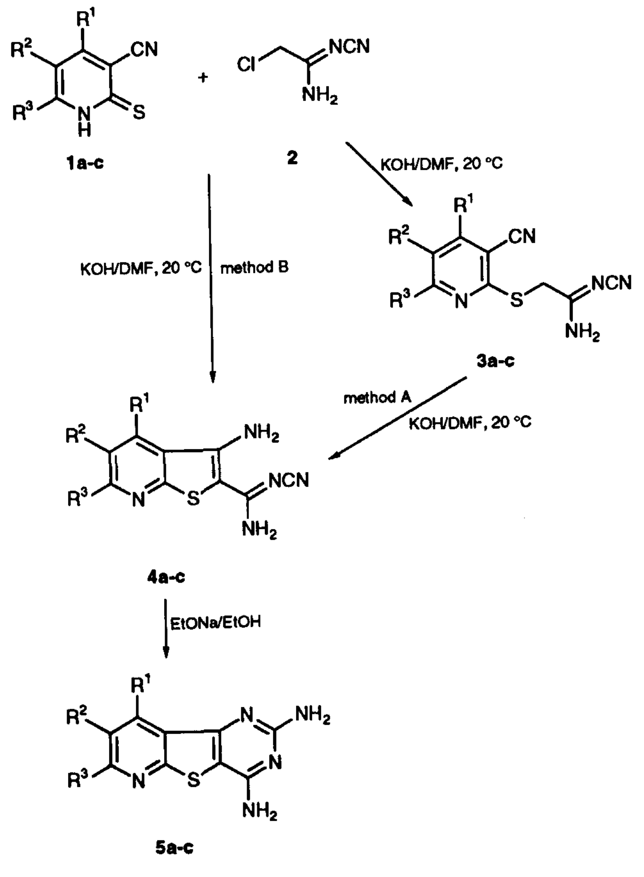
[a] 250 MHz, $(CD_3)_2SO$. [b] Method A. [c] Method B. [d] At *ca.* 260 °C the substance sublimes.

substituted 3-cyanopyridines **3a–c** smoothly give, by Thorpe-type cyclisation, substituted 3-aminothieno[2,3-*b*]pyridines **4a–c** (method A). In a typical experiment, a solution of **3** in DMF was treated at room temperature with KOH/H_2O (10%) (2 mol. equiv.). The reaction mixture was kept at room temperature for 30 min and then decomposed with water. The same compounds **4a–c** can be prepared by a one-step synthesis from **1a–c** and **2** in DMF on treatment with an excess of base (method B, Scheme 1, Table 1).

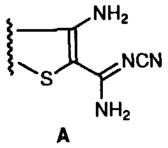
Substituted thieno[2,3-*b*]pyridines were found to be convenient reagents for the synthesis of 2,4-diaminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines **5a–c**. Hence, on treating a solution of **4** in EtOH with sodium ethoxide (3 mol. equiv.) and boiling the reaction mixture for 6 h crystals of **5** were precipitated from solution (Scheme 1, Table 1).

The structures of compounds **3**–**5** were confirmed by elemental analysis data and IR and ^{1}H NMR spectroscopy.

IR-spectroscopy appeared to be the most informative method for the structural determination of compounds **3**–**5**. Compounds **3** have two absorption bands due to nitrile groups (Table 1). Based on the spectra of previously-described 2-alkylthio-3-cyanopyridines,[8] the high-frequency absorption band at 2215–2220 cm^{-1} was assigned to the 3-cyano group and, therefore, the low-frequency band at 2180–2190 cm^{-1} to the $N{-}C{\equiv}N$ group. On closure of the thiophene ring, an absorption band due to the 3-cyano group (2220 cm^{-1}) disappears and an absorption band due to the $N{-}C{\equiv}N$ group appears as two bands at 2180–2185 cm^{-1} and 2145–2150 cm^{-1} (Table 1). An analogous doubling of the absorption band was sometimes observed in alkyl- and arylcyanoamidines.[10] Such doubling of the $N{-}C{\equiv}N$ absorption band may probably be accounted for by the existence of compound **4** as a sort of mixture of geometrical isomers or tautomers, *e.g.* in the fragment **A**.



Scheme 1



A

A detailed investigation of the structure of compounds **4** will be the subject of subsequent research.

The signals due to amino groups in the ^1H NMR spectra are also characteristic. The amino group in compound **3** appears as a clear singlet at 8.7 ppm. In 3-aminothieno[2,3-*b*]pyridines **4** the signals due to the amino groups appear at 6.3 (3-NH_2) and 8.2 (amidine–NH_2) ppm. Upon closure of the pyrimidine ring the signals due to the NH_2 groups shift in a strong field and appear at 5.5–5.6 (2-NH_2) and *ca.* 7.0 (4-NH_2) ppm.†

The regioselectivity of formation of compounds **5** is governed by a sequence of nucleophilic substitution reactions (S_N2), Thorpe-type cyclisation and intramolecular interaction of NH_2 and CN groups.

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† Assignments of amino group resonances were achieved based on the chemical shifts of model compounds: 3-amino-2-benzoyl(cyano)-thieno[2,3-*b*]pyridines and 4-aminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines.[5]