SYNTHESIS OF 2-CYANAMINO-4,6-DIPHENYL-PYRIDINE-3-CARBONITRILE

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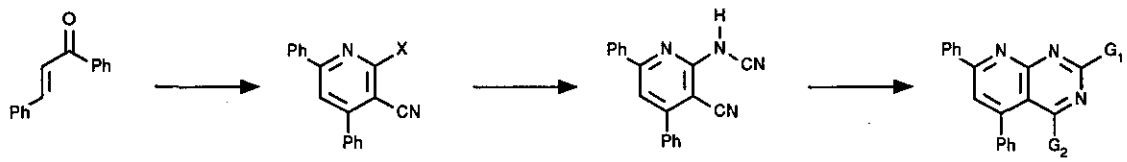
Abstract- The nucleophilic displacement of bromo, alkylthio and alkylsulphonyl groups from pyridine systems by cyanamide is studied in order to obtain a previously unreported 2-cyanaminopyridine-3-carbonitrile. A one-step synthesis of the same compound by cyclization in basic medium of the non-isolated Michael adduct of (*E*)-1,3-diphenylpropenone and propanedinitrile is also described.

Following the synthesis of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones from α,β-unsaturated esters previously reported,[1] our group has been engaged in the synthesis of pyrido[2,3-*d*]pyrimidines (**4**) from α,β-unsaturated ketones. Our strategy requires the synthesis of 2-cyanaminopyridine-3-carbonitrile (**3**) which, to the best of our knowledge, is not described in the literature.



1 **2** **3** **4**

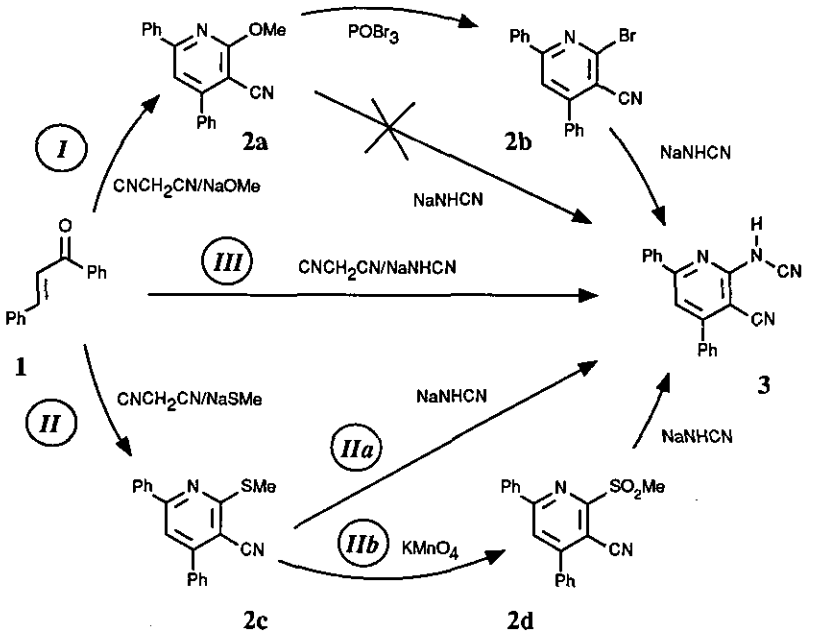
Scheme 1

In the first place, its synthesis can be pursued by nucleophilic displacement in a suitable pyridine substrate (**2**) (X must be an appropriate leaving group for S_NAr reactions).

Pyridine-3-carbonitriles that bear an alkoxy or amino group at position 2 (**2** with X= OR or X=NR_1R_2) can be prepared directly from **1** by treatment with propanedinitrile and sodium alkoxide[2] or an amine.[3] The mechanism for this reaction in the case of sodium alkoxide as a base is discussed in reference 4. This procedure, which has only been applied to sodium alkoxide or amines, opens a second route to **3**. Since the base used for catalysing the Michael addition of propanedinitrile to the enone (**1**) is involved in the cyclization of the Michael adduct thus becoming the substituent at C2 in the final product, it may be assumed that the treatment of **1** with propanedinitrile, using sodium cyanamide as the base, will lead to **3**.

RESULTS AND DISCUSSION

We have approached the synthesis of **3** by both procedures (Scheme 2): Nucleophilic displacement of X by cyanamide in **2** (*paths I* and *II*) and direct treatment of **1**, propanedinitrile and sodium cyanamide (*path III*).



Scheme 2

Table 1

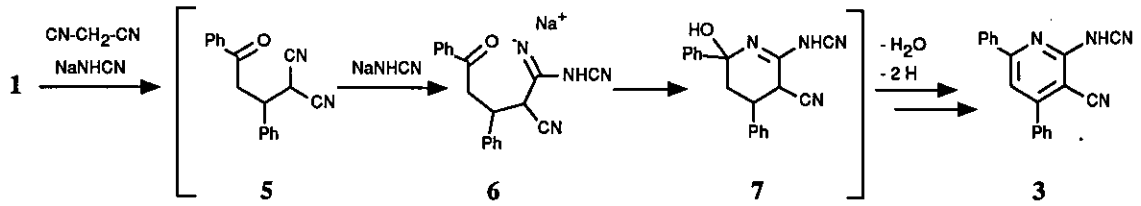
	YIELDS			
	first step	**second step**	**S_NAr of X by NaNHCN**	**Overall**
PATH I	58%[a]	85%	95%	47%
PATH IIa	40%	---	95%	38%
PATH IIb	40%	85%	95%	32%
PATH III	---	---	---	25%

a. Reported by Al-Arab.[2d]

In regard to *path I*, the synthesis of **2a** from **1** has been already reported by Meegan *et al.* and Al-Arab.[2] It is well-known that the methoxy substituent is a bad leaving group in a S_NAr reaction. In fact, **3** has not been obtained by treatment of **2a** with NaNHCN. On the contrary, under the same conditions, **2b** (available from **2a** in one step by treatment with phosphorous oxytribromide, pyridinium hydrobromide and phosphoric acid[5]) has yielded the new compound (**3**) in almost quantitative yield. It is interesting to point out that phosphorous oxytribromide, pyridinium hydrobromide and phosphoric acid have proved to be very useful reagents for converting 2-methoxypyridine-3-carbonitrile (**2a**) into 2-bromopyridine-3-carbonitrile (**2b**) in one step.

As for *path II*, **2c** was synthesised as **2a** by using NaSMe instead of NaOMe for the first time in this work. This method yields the final product in one step from enone (**1**). The synthesis of **2c** according to the procedure reported in the literature involves two steps.[6] Further oxidation with $KMnO_4$ in a solution of acetic acid/acetone gives **2d**. Both **2c** and **2d** yield 2-cyanaminopyridine-3-carbonitrile (**3**) by nucleophilic displacement of alkylthio and methylsulphonyl groups by cyanamide in almost quantitative yields. The S_NAr reaction in **2b**, **2c** and **2d** with sodium cyanamide is greatly enhanced by using dipolar non-hydrogen-bond donor solvents (dimethyl sulfoxide, *N,N*-dimethylacetamide or 1-methylpyrrolidin-2-one).

Finally, *path III*, which takes as a reference the synthesis of **2a** from enones and propanedinitrile, has led to **3** in only one step. These results can be rationalized by the mechanistic hypothesis depicted in Scheme 3. The reaction probably starts with a Michael addition of propanedinitrile to **1** yielding the open-chain adduct **5**. The addition of NaNHCN to a cyano group of **5** affords **6** which undergoes cyclization to give **7** followed by water elimination and dehydrogenation to yield **3**.



Scheme 3

In conclusion, the pyridine (**3**) can be obtained by three different pathways. The synthetic routes which involve the nucleophilic displacement of a leaving group by cyanamide as the last step give **3** with higher yields (see Table 1). The one-step process for obtaining **3** (*path III*) is the easiest one. Moreover, the cyclization of **5** catalysed by unusual bases (NaSMe and NaNHCN) described for the first time in this paper provides two new examples of formation of a pyridine ring from an enone in only one-step.

ACKNOWLEDGEMENTS

We thank Prof. M. Begtrup, Royal Danish School of Pharmacy, for very helpful discussions. We are grateful to the *Fundació J. Salañer* for a fellowship granted to one of us (A. V.-F.). We thank one of the referees for his constructive criticism and additional inclusion of some references.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus, and are uncorrected. The ir spectra were obtained in a Bomem Michelson-100 (FT-IR). The ^{1}H nmr spectra were recorded on a Bruker AC-80 spectrometer. The ^{13}C nmr spectra were recorded on a Varian XL-200/F-19 spectrometer. Chemical shifts are given in ppm (δ) and in the case of ^{1}H nmr signals are expressed as s(singlet), m(multiplet) or br(broad). Mass spectra were obtained on a Hewlett-Packard 5995 A and Hewlett-Packard 5998 A mass spectrometers. Microanalyses were performed on a Carlo-Erba CHNS-O/EA 1106 and a Carlo-Erba CHNS-O/EA 1108 carbon, hydrogen and nitrogen analyzers. Sodium cyanamide and sodium methanethiolate were obtained from Fluka. Phosphorous oxytribromide was obtained from Merck. Pyridinium hydrobromide was prepared using a previously reported procedure.[7]

2-Bromo-4,6-diphenylpyridine-3-carbonitrile: A mixture of 8.6 g (0.03 mol) of **2a**, 17.2 g (0.06 mol) of $POBr_3$, 0.05 g (0.3 mmol) of pyridinium hydrobromide and 0.03 g (0.3 mmol) of phosphoric acid in 60 ml of dioxane was refluxed for 48 h. After removal of the solvent *in vacuo*, 500 ml of water were added slowly. The mixture was basified to pH 8 with portions of solid Na_2CO_3 and extracted with dichloromethane (10 x 100 ml). After removal of the solvent and recrystallization from ethanol, 8.7 g (85%) of **2b** were obtained; mp 167-168 °C (lit.,[8] mp 164-166; **2b** was synthesised by another procedure in reference 8). Ir and ^1H nmr data are in agreement with the reported ones.[8]

4,6-Diphenyl-2-methylthiopyridine-3-carbonitrile: To a solution of 75.0 g (0.36 mol) of **1** and 23.76 g (0.36 mol) of propanedinitrile in 1.9 l of ethanol, were added 25.33 g (0.36 mol) of sodium methanethiolate. The mixture was stirred at room temperature for 7 h. The separated solid was filtered, washed and recrystallized from ethanol to give 43.5 g (40%) of **2c**; mp 158.5-159.5 °C (lit.,[6] mp 156-158; **2c** was synthesised by another procedure in reference 6). Ir, ^1H nmr and ms data are in agreement with the reported ones.[6]

4,6-Diphenyl-2-methylsulphonylpyridine-3-carbonitrile: To a solution of 2.0 g (6.6 mmol) of **2c** in 6 ml of acetic acid and 60 ml of acetone, 2.09 g (13.2 mmol) of $KMnO_4$ were added. The mixture was stirred at room temperature for 12 h. A second portion of 2.09 g (13.2 mmol) of $KMnO_4$ was added and the mixture was stirred for another 12 h. A saturated aqueous solution of Na_2SO_3 was added until the mixture became colourless. It was poured into 850 ml of water. The solid was filtered, washed and recrystallized from ethanol to yield 1.88 g (85%) of **2d**; mp 209-210 °C; ir (KBr): 2220 (C≡N), 1590, 1570, 1145 (S=O), 760, 750, 710 and 700 cm^{-1}; ^1H nmr ($CDCl_3$): δ= 3.52 (s, 3H, $MeSO_2$), 7.50-8.15 (m, 11H, Ph + Ph + H-C5) ppm; ^{13}C nmr ($CDCl_3$): δ= 40.1 ($MeSO_2$), 102.8 (C3), 112.8 (CN), 123.0 (C5), 127.6-135.7 (Ph), 157.4, 158.8 and 161.2 (C4, C6 and C2) ppm; ms (70 eV): *m/z* (%): 334 (100) [M^+], 333 (46.2), 273 (12.0), 272 (58.5), 271 (16.0), 270 (27.8), 269 (20.0), 255 (46.0), 228 (15.0), 77 (23.0). Anal. Calcd for $C_{19}H_{14}N_2O_2S$: C, 68.25; H, 4.22; N, 8.38; S, 9.59. Found: C, 68.56; H, 4.28; N, 8.54; S, 9.64.

2-Cyanamino-4,6-diphenylpyridine-3-carbonitrile:

From 2-Bromo-4,6-diphenylpyridine-3-carbonitrile: A solution of 1.0 g (3 mmol) of **2b** and 0.38 g (6 mmol) of NaNHCN in 15 ml of DMSO was heated at 140 °C for 3 h. The mixture was poured into 400 ml of water

and acidified to pH 1-2 with 2M HCl. The solid was filtered, washed and dried to give 0.84 g (95%) of **3**; ir (KBr): 3212 and 3057 (weak) (N-H), 2252 (N-*C*≡*N*), 2219 (C-*C*≡*N*), 1587, 1537, 1503, 1481, 755 and 692 cm^{-1}; ^1H nmr (acetone-d_6): δ= 3.0 (br, 1H, NH-CN, exchangeable with D_2O), 7.51-8.37 (m, 11H, Ph + Ph + H-C5) ppm; ^{13}C nmr (DMSO-d_6): δ= 91.8 (C3), 110.3 (N-*CN*), 114.7 (C5), 115.0 (C-*CN*), 127.5-135.9 (Ph), 154.4 (C4), 156.1 and 157.7 (C2, C6) ppm; ms (70 eV): *m/z* (%): 296 (100) [M^+], 295 (40.7), 269 (15.6), 255 (7.4), 242 (2.2), 228 (3.3), 227 (8.0). The sample can be recrystallized from a mixture of CCl_4 : hexane; mp 220-222 °C. Anal. Calcd for $C_{19}H_{12}N_4$: C, 77.01; H, 4.08; N, 18.91. Found: C, 77.11; H, 4.07; N, 18.71.

From 4,6-diphenyl-2-methylthiopyridine-3-carbonitrile: **3** was prepared in the same manner with the same reagents using 0.91 g (3 mmol) of **2c** (Yield 95%).

From 4,6-diphenyl-2-methylsulphonylpyridine-3-carbonitrile: (**3**) was prepared in the same manner with the same reagents using 1.0 g (3 mmol) of **2d** (Yield 95%).

From (E)-1,3-diphenylpropenone: To a mixture of 3.16 g (4.8 mmol) of propanedinitrile and 6.14 g (9.6 mmol) of sodium cyanamide in 10 ml of dioxane, a solution of 10.0 g (4.8 mmol) of **1** in 25 ml of dioxane was added at room temperature and dropwise. The mixture is refluxed for 90 m. After removal of the solvent *in vacuo*, 100 ml of dichloromethane were added. The solid was filtered and dissolved in 100 ml of water. The aqueous layer is acidified to pH 1-2 with 2M HCl. After filtering the solid, washing with water and drying, 3.54 g (25%) of **3** were obtained.

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Received, 21st September, 1992