A SIMPLE SYNTHESIS OF 2-METHOXYPYRIDINE-3-CARBONITRILES

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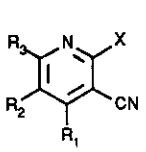
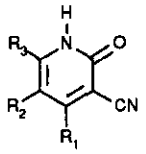
Abstract- The condensation of propanedinitrile with several enals or enones in a methanol-sodium methoxide system provides a one-step route to 2-methoxy-pyridine-3-carbonitriles. Together with these compounds substituted 2-aminobenzene-1,3-dicarbonitriles, were obtained as by-products.

2-Alkoxypyridine-3-carbonitriles (**3**) have been commonly synthesised either by nucleophilic displacement of halogen by alkoxide in 2-bromo- or 2-chloropyridine-3-carbonitriles (**1**)[1] or by *O*-alkylation of 1,2-dihydro-2-oxopyridine-3-carbonitriles (**2**).[2] Aryl-substituted 2-alkoxypyridine-3-carbonitriles (**3** with R_1, R_3= Aryl) can also be obtained by condensation of an aryl-substituted enone with propanedinitrile in an alcohol/sodium alkoxide system.[3] Our group has also studied this reaction.[4]



1 (X= Cl, Br)



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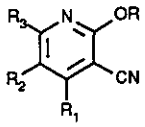
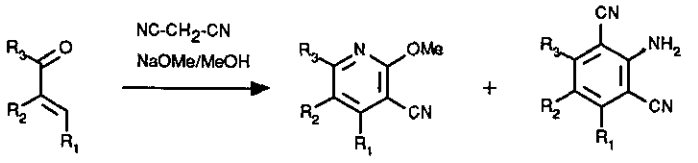


3

This latter method has been widely used for aryl-substituted enones but, to our knowledge, no examples of condensation of propanedinitrile with enals or alkyl-substituted enones leading to 2-alkoxypyridine-3-carbonitriles have hitherto been reported. In fact, Lora-Tamayo *et al.* reported a lack of reactivity of some α,β-unsaturated aldehydes and propanedinitrile in an alcohol-alkoxide system.[5]

RESULTS AND DISCUSSION

We have extended the reaction of aryl-substituted enones[3] with propanedinitrile to a wide range of carbonyl compounds which include enals and alkyl-substituted enones. 2-Methoxypyridine-3-carbonitriles (**5**) have always been obtained when the carbonyl compounds were treated with propanedinitrile in NaOMe/MeOH. All the pyridines prepared in this work are listed in Table 1. This investigation has shown that this procedure provides a single one-step route to substituted 2-methoxypyridine-3-carbonitriles from easily available materials. All the enals used **4a-e** gave the corresponding pyridines. We did not observe differences between the reactivity of enones and enals even as far as yields are concerned.



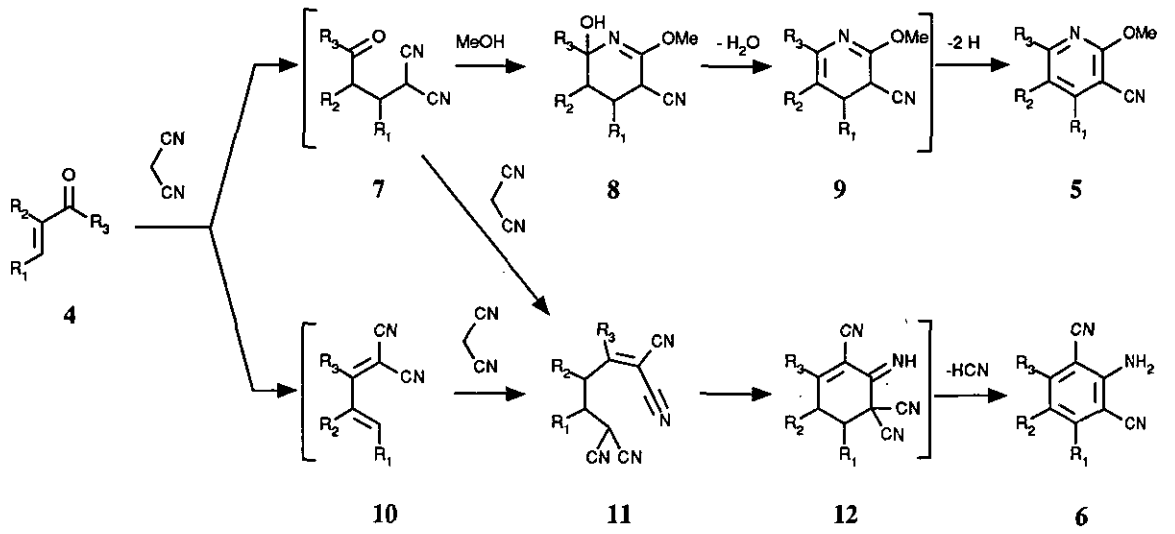
4 a-h **5 a-h** **6** (by-product)

Table 1.

4	R_1	R_2	R_3	Product	Yield (%)
a	Me	H	H	**5a**	15
b	Ph	H	H	**5b**	25
c	2-thienyl	H	H	**5c**	30
d	H	Me	H	**5d**	10
e	H	Ph	H	**5e**	20
f	H	H	Me	**5f**	15
g	H	H	Ph	**5g**	35
h	H	H	2-thienyl	**5h**	30

The experimental conditions that led to **5b** in the yield depicted in Table 1 were found using the Simplex method. Simplex optimization is a steepest ascent method which can be used for moving towards an optimum.[6] These experimental conditions correspond to the boiling temperature of the sodium methoxide/methanol system (65 °C) and a molar ratio of carbonyl compound to propanedinitrile of 1 : 0.8. The best yield of **5b** is only slightly superior to the ones observed in the neighborhood of the optimum. The yield does not show significant variations in temperatures near to 65 °C and molar ratios of carbonyl compound to propanedinitrile near to 1 : 1. For instance, the yield varies from 18 to 25% in a range of temperatures from 50 °C to 65 °C and in a range of molar ratios of carbonyl compound to propanedinitrile from 1 : 0.7 to 1 : 1.45. The optimum experimental conditions obtained for **5b** have been extended to the other carbonyl compounds and the yields are depicted in Table 1.

It is worth pointing out that by-products (**6**) were formed in all reactions carried out. The structure of **6** has been established as a substituted 2-amino-benzene-1,3-dicarbonitrile by spectroscopic methods. A bibliographic search has revealed **6** as the first 2-aminobenzene-1,3- dicarbonitriles derived from enones or enals and propanedinitrile. As the formation of a benzene ring from propanedinitrile and an enone or enal appeared to be unusual, we have confirmed the structure of these compounds by X-ray analysis.[7]



Scheme 1

The formation of **5** probably starts with a Michael addition of propanedinitrile to **4** yielding **7** which undergoes cyclization to give **8**. This compound leads to **5** by water elimination followed by spontaneous dehydrogenation (Scheme 1). On the other hand, the formation of **6** starts with a Michael addition followed by a Knoevenagel condensation (or *vice versa*) of two mol of propanedinitrile with **4** to yield **11**. This product undergoes an intramolecular Thorpe cyclization to give **12** and HCN elimination to afford **6** (Scheme 1). The formation of **6** requires two mol of propanedinitrile whereas **5** requires only one.[8]

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 ^1H nmr and ^{13}C nmr spectra were recorded on a Bruker AC-80 spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane or sodium trimethylsilylpropionate-d_4 respectively as internal standards. Chemical shifts are given in ppm (δ) and in the case of ^1H nmr signals are expressed as s(singlet), d(doublet), 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. "Preparative column chromatography" refers to Flash chromatography using 230-400 mesh silica gel (Macherey- Nagel Reagent). Uv spectra were recorded in a Perkin-Elmer Lambda 2 instrument. Carbonyl compounds (**4a**), (**4b**), (**4d**) and (**4f**) were obtained from Fluka. The remaining carbonyl compounds (**4c**),[9] (**4e**),[10] (**4g**)[11] and (**4h**)[12] were prepared following known procedures.

2-Methoxypyridine-3-carbonitriles (5a-h) (General Procedure). Propanedinitrile (5.3 g, 0.08 mol)in 70 ml of MeOH was added to a freshly prepared NaOMe solution at 5°C [2.3 g (0.1 mol) of sodium in 70 ml of MeOH]. After stirring for 5 min, 0.1 mol of the corresponding **4a-h** in 150 ml of MeOH was added dropwise (2 h). The mixture was refluxed for 90 min and the solvent was removed *in vacuo*. The resulting oil was dissolved in 250 ml of water and extracted with 10 x 50 ml of CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent was removed. The desired product **5a-h** was purified by preparative column chromatography with a mixture of CH_2Cl_2 and hexane (1 : 1) as the eluent. The second product of lower Rf was the corresponding **6a-h**.

2-Methoxy-4-methylpyridine-3-carbonitrile (**5a**); yield: 2.2 g (15%), mp 87-88 °C; ir(film): 2223 (C≡N), 1572

and 1590 (C=C and C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ= 2.51 (s, 3H, Me), 4.04 (s, 3H, MeO), 6.84 (d, $^3J_{HH}$= 5.3 Hz, 1H, H-C5), 8.18 (d, $^3J_{HH}$= 5.3 Hz, 1H, H-C6) ppm; ^{13}C nmr ($CDCl_3$): δ= 19.6 (Me), 53.9 (MeO), 96.8 (C3), 113.9 (CN), 117.9 (C5), 149.6 (C6), 154.2 (C4), 164.2 (C2) ppm; ms (70 eV): *m/z* (%): 148 (48.9) [M^+], 147 (100), 119 (50.5), 118 (54.4), 93 (22.8), 92 (15.1), 91 (42.0), 78 (15.9), 64 (17.9), 63 (18.1); uv λ_{max} (MeOH): 228, 290 nm. *Anal.* Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.77; H, 5.39; N, 19.21.

2-Methoxy-4-phenylpyridine-3-carbonitrile (**5b**); yield: 5.3 g (25%), mp 110-111 °C (lit.,[13] 110-111); ir and ^1H nmr data are in agreement with the reported ones.[13]

2-Methoxy-4-(2-thienyl)pyridine-3-carbonitrile (**5c**); yield: 6.5 g (30%), mp 104-106 °C; ir (KBr): 2220 (C≡N), 1581, 1548 and 1522 (C=C and C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ= 4.07 (s, 3H, MeO), 7.11 (d, $^3J_{HH}$= 5.5 Hz, 1H, H-C5), 7.11-7.22 (m, 1H, 2-thienyl), 7.49-7.57 (m, 1H, 2-thienyl), 7.89-7.95 (m, 1H, 2-thienyl), 8.24 (d, $^3J_{HH}$= 5.5 Hz, 1H, H-C6) ppm; ^{13}C nmr ($CDCl_3$): δ= 54.3 (MeO), 92.4 (C3), 115.3 (CN), 115.7 (C5), 128.5, 129.2, 129.4 and 137.0 (2-thienyl), 147.2 (C4), 150.2 (C6), 165.7 (C2) ppm; ms (70 eV): *m/z* (%): 216 (79.9) [M^+], 215 (100), 188 (14.8), 187 (15.2), 186 (10.6), 185 (16.1), 160 (9.5), 159 (11.3); uv λ_{max} (MeOH): 231, 307 nm. *Anal.* Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95; S, 14.84. Found: C, 61.17; H, 3.71; N, 13.09; S, 14.90.

2-Methoxy-5-methylpyridine-3-carbonitrile (**5d**); yield: 1.5 g (10%), mp 72-73 °C; ir ($CHCl_3$ film): 2224 (C≡N), 1574 and 1488 (C=C and C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ= 2.31 (s, 3H, Me), 4.01 (s, 3H, MeO), 7.69 (d, $^4J_{HH}$= 2.2 Hz, 1H, H-C4), 8.16 (d,$^4J_{HH}$= 2.2 Hz, 1H, H-C6) ppm; ^{13}C nmr ($CDCl_3$): δ= 16.4 (Me), 53.8 (MeO), 95.5 (C3), 114.7 (CN), 125.6 (C5), 142.7 (C4), 150.7 (C6), 162.0 (C2) ppm; ms (70 eV): *m/z* (%): 148 (97.6) [M^+], 147 (100), 120 (11.9), 119 (88.1), 118 (85.7), 93 (56.0), 92 (30.4), 91 (44.0), 78 (42.3), 76 (17.9), 65 (23.2), 64 (30.1), 63 (22.0); uv λ_{max} (MeOH): 227, 299 nm. *Anal.* Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.01; H, 5.45; N, 18.80.

2-Methoxy-5-phenylpyridine-3-carbonitrile (**5e**); yield: 4.2 g (20%), mp 111-112 °C (lit.,[14] 114.5).

2-Methoxy-6-methylpyridine-3-carbonitrile (**5f**); yield: 2.2 g (15%), mp 82-83 °C (lit.,[15] 81.5); ir, ^1H nmr and ms data are in agreement with the reported ones.[16]

2-Methoxy-6-phenylpyridine-3-carbonitrile (**5g**); yield: 7.35 g (35%), mp 115-116 °C (lit.,[2d] 169-171); ir and ^{1}H nmr data are in agreement with the reported ones.[2d]

2-Methoxy-6-(2-thienyl)pyridine-3-carbonitrile (**5h**); yield: 6.5 g (30%), mp 114-116 °C; ir (KBr): 2217 (C≡N), 1585, 1566, 1528 and 1516 (C=C and C=N) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ= 4.06 (s, 3H, MeO), 7.05-7.66 (m, 3H, 2-thienyl), 7.20 (d, $^3J_{HH}$= 7.9 Hz, 1H, H-C5), 7.75 (d, $^3J_{HH}$= 7.9 Hz, 1H, H-C4) ppm; ^{13}C nmr ($CDCl_3$): δ= 54.2 (MeO), 93.6 (C3), 110.8 (C5), 115.4 (CN), 129.8, 128.3 and 126.9 (2-thienyl), 143.0 (C4), 153.8 (C6), 163.5 (C2) ppm; ms (70 eV): *m/z* (%): 216 (100) [M$^+$], 215 (42.5), 187 (51.6), 186 (22.5), 185 (20.0), 161 (23.1), 160 (14.8), 159 (18.2); uv λ_{max} (MeOH): 268, 338 nm. *Anal.* Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95; S, 14.84. Found: C, 61.10; H, 3.71; N, 12.95; S, 14.53.

2-Aminobenzene-1,3-dicarbonitriles (6a-e). These compounds were obtained as by-products in the synthesis of **5a-h**. They were separated from the crude mixture by preparative column chromatography (*cfr.* general procedure).

2-Amino-4-methylbenzene-1,3-dicarbonitrile (**6a**); yield: <5%, mp 158-159 °C (lit.,[17] 158-159); ir and ^{1}H nmr data are in agreement with the reported ones.[17]

2-Amino-4-phenylbenzene-1,3-dicarbonitrile (**6b**); yield: <5%, mp 149-150 °C; ir ($CHCl_3$ film): 3430, 3344 and 3237 (N-H), 2213 (C≡N), 1638 (N-H), 1576, 1553, 1466 and 1450 (C=C), 758 and 700 (Ph) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ= 6.04 (br, 2H, NH_2), 6.74 (d, $^3J_{HH}$= 8.1 Hz, 1H, H-C5), 7.45 (s, 5H, Ph), 7.60 (d, $^3J_{HH}$= 8.1 Hz, 1H, H-C6) ppm; ^{13}C nmr (DMSO-d_6): δ= 94.9 and 95.4 (C3, C1), 115.6 and 116.2 (CN), 117.4 (C5), 128.2, 128.5, 129.1 and 137.5 (Ph), 137.6 (C6), 150.4 (C4), 152.9 (C2) ppm; ms (70 eV): *m/z* (%): 219 (100) [M$^+$], 218 (8.9), 192 (5.9), 191 (7.5), 165 (5.6), 164 (9.3); uv λ_{max} (MeOH): 227, 225, 357 nm. *Anal.* Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.81; H, 4.12; N,19.33.

2-Amino-4-(2-thienyl)benzene-1,3-dicarbonitrile (**6c**); yield: <5%, mp 168-170 °C; ir (KBr): 3468, 3361 and 3238 (N-H), 2215 (C≡N), 1635 (N-H), 1582, 1563, 1523 and 1474 (C=C) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ= 6.86 (br, 2H, NH_2), 6.96 (d, $^3J_{HH}$= 8.2 Hz, 1H, H-C5), 7.24-7.91 (m, 3H, 2-thienyl), 7.83 (d, $^3J_{HH}$= 8.2 Hz, 1H, H-C6) ppm; ^{13}C nmr (DMSO-d_6): δ= 93.5 and 94.7 (C3, C1), 115.9 and 116.1 (CN), 116.8 (C5), 128.2, 128.7,

129.3 and 138.2 (2-thienyl), 137.8 (C6), 142.0 (C4), 153.3 (C2) ppm; ms (70 eV): *m/z* (%): 225 (100) [M^+], 198 (8.9), 197 (5.6), 171 (2.6); uv λ_{max} (MeOH): 247, 313, 367 nm.

2-Amino-5-methylbenzene-1,3-dicarbonitrile (**6d**); yield: <5%, mp 178-179 °C (lit.,[18] 179); ir, ^{1}H nmr, ^{13}C nmr and ms data are in agreement with the reported ones.

2-Amino-5-phenylbenzene-1,3-dicarbonitrile (6e); yield: <5%, mp 233-234 °C; ir (KBr): 3401, 3350 and 3249 (N-H), 2221 (C≡N), 1667 (N-H), 1586, 1551 and 1480 (C=C), 771 and 699 (Ph) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ= 6.77 (br, 2H, NH_2), 7.39-7.77 (m, 5H, Ph), 8.15 (s, 2H, H-C4 + H-C6) ppm; ^{13}C nmr (DMSO-d_6): δ= 97.0 ppm (C1 + C3), 116.1 (CN), 125.7, 127.3, 128.7 and 136.6 (Ph), 128.4 (C5), 136.0 (C4), 151.0 (C2 + C6) ppm; ms (70 eV): *m/z* (%): 219 (100) [M^+], 218 (9.0), 192 (5.9), 191 (7.9), 165 (6.1), 164 (11.2); uv λ_{max} (MeOH): 217, 236, 281, 367 nm. *Anal.* Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.76; H, 4.36; N,18.87.

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