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Synthesis of Substituted 3-Pyridinecarbonitriles with Potential Biological Activity

C. Oliver Kappe** and **Thomas Kappe***

Institut für Organische Chemie, Karl-Franzens-Universität Graz, A-8010 Graz, Österreich

Summary. The synthesis of some 5-cyano-4-hydroxy-2-pyridone derivatives (**3a–c**) by condensation of 3-aminocrotononitrile (**1**) with substituted diethylmalonates (**2a–c**) is described. Reaction of **3a** with phosphorus oxychloride yields 4,6-dichloro-3-pyridinecarbonitrile (**7a**), which reacts with various nucleophiles to give substituted 3-pyridinecarbonitriles (**8–10**).

Keywords. 3-Pyridinecarbonitriles; 4-Hydroxy-6-oxo-1,6-dihydro-3-pyridinecarbonitriles; 4,6-Dichloro-3-pyridinecarbonitrile; 3-Aminocrotononitrile.

Synthese von substituierten 3-Pyridincarbonitrilen mit potentieller biologischer Wirkung

Zusammenfassung. Die Synthese einiger 5-Cyan-4-hydroxy-2-pyridon-Derivate (**3a—c**) durch Kondensation von 3-Aminocrotonsäurenitril (**1**) mit substituierten Malonestern (**2a—c**) wird beschrieben. Die Reaktion von **3a** mit Phosphoroxychlorid führt zu 4,6-Dichlor-3-pyridincarbonitril (**7a**), das bei der Reaktion mit verschiedenen Nucleophilen substituierte 3-Pyridincarbonitrile (**8—10**) liefert.

Introduction

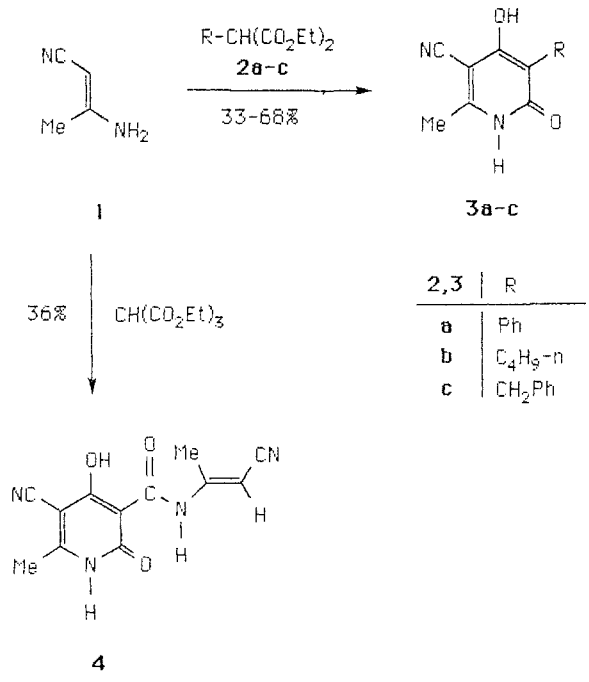
The synthesis of 4-hydroxy-2-pyridones *via* condensation of enamines or azomethines with malonic acid derivatives is well known and a literature survey was recently presented [2]. It has been shown that in many cases diethyl malonates can be used instead of the reactive bis-trichlorophenyl malonates or carbon suboxide. Since some halogenated pyridinecarbonitriles exhibit fungicidal activity [3–5] we herewith report on a new approach to 4,6-dihalogenated-3-pyridinecarbonitriles.

Results and Discussion

The synthesis of 5-substituted-4-hydroxy-2-methyl-6-oxo-1,6-dihydro-3-pyridinecarbonitriles **3a–c** was achieved by condensation of substituted diethyl malonates **2a–c** with 3-aminocrotononitrile (**1**). The unsubstituted 3-pyridinecarbonitrile **3** ($R = H$), the 5-benzyl- (**3c**), and 5-ethyl-derivatives had been

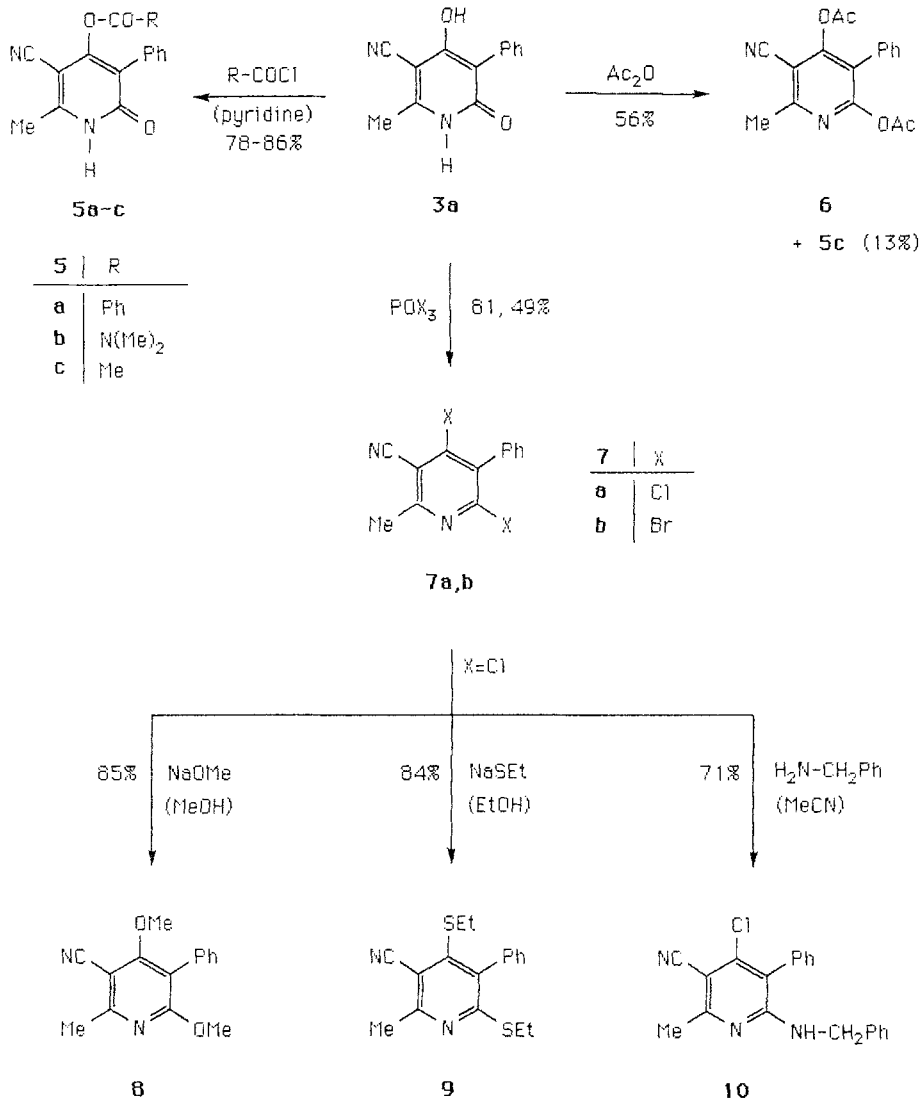
* Dedicated to Prof. Dr. J. Schurz, Graz, on the occasion of his 60th birthday

** See ref. [1]



prepared previously by reaction of (un)substituted bis-2,4,6-trichlorophenyl malonates with 3-aminocrotononitrile (**1**) [6, 7] (the reaction of 3-aminocrotononitrile with carbon suboxide does not yield **3** ($R = H$) but affords a linear condensation product [8]). Although the yields are considerable lower using diethyl malonates (33–68%) instead of active malonic esters (80–95%) this procedure represents a facile approach to 3-pyridinecarbonitriles **3**. If triethyl methanetricarboxylate was employed instead of malonic esters, the 2 : 1 condensation product **4** was the only isolated compound instead of the expected 5-carbethoxy-derivative.

4-Hydroxy-2-methyl-6-oxo-5-phenyl-1,6-dihydro-3-pyridinecarbonitrile (**3 a**) was easily acylated at the 4-hydroxy group using benzoylchloride and dimethylcarbamoylchloride in pyridine as acylation agents. If **3 a** was refluxed with acetic anhydride only small amounts of monoacetylated product (**5 c**) were isolated. The major product was the corresponding 4,6-diacetoxypyridine **6**. Reaction of **3 a** with phosphorus oxychloride or phosphorus oxybromide afforded 4,6-dichloro- or 4,6-dibromopyridines **7 a, b**. These compounds are related to substances with known fungicidal activity [4, 5] and are therefore considered as candidates for biological testing. Starting from dichloropyridine **7 a** several other substituted 3-pyridinecarbonitriles were obtained by exchange of one or both chlorine atoms with nucleophiles. If **7 a** is refluxed with sodium methoxide in methanol 4,6-dimethoxy-2-methyl-5-phenyl-3-pyridinecarbonitrile (**8**) was obtained in good yield. In a similar reaction—using ethanethiole as reagent—4,6-diethylthio-2-methyl-5-phenyl-3-pyridinecarbonitrile (**9**) was prepared. However, if **7 a** was reacted with benzylamine in acetonitrile only the monosubstituted product **10** was obtained. The position of the benzylamino group was determined from long range coupling constants and shift values of the C2 and C6 carbon atoms.



Thus the signal of the C2 carbon atom is splitted into a quadruplet ($\delta = 162.8$, $^2J = 6.5$ Hz) due to the adjacent methyl group. The signal from the C6 shows a 5 line splitting ($\delta = 157.2$, $J = 3$ Hz) which is due to a coupling with the hydrogen at the NH and methylene group of the benzylamino group in 6-position, as shown by deuterium exchange of the NH proton.

The second chlorine atom, however, could not be exchanged by nucleophiles (refluxing **10** in benzylamine or with sodium methoxide in methanol gave no reaction).

Acknowledgements

We thank Prof. H. Sterk for recording and the interpretation of the ^{13}C-NMR spectrum of **10**.

Experimental Part

The melting points were determined with a Gallenkamp Melting Point Apparatus Mod. MFB-595 and are uncorrected. IR-spectra were obtained on a Perkin-Elmer 298 Spectrophotometer using samples in potassium bromide disks. ^{1}H-NMR spectra were recorded on a Varian EM 360 (*TMS* as internal standard) in the solvents indicated, ^{13}C-NMR spectra on a Varian XL-200 in $CDCl_3$. Microanalyses were performed on a C,H,N-Automat Carlo Erba 1106.

4-Hydroxy-2-methyl-6-oxo-5-phenyl-1,6-dihydro-3-pyridinecarbonitrile (**3a**)

A solution of 3-aminocrotononitrile (**1**) (8.21 g, 0.10 mol) and diethyl phenylmalonate (**2a**) (26.0 g, 0.11 mol) in 20 ml of diphenylether is heated in an oil bath at 220°C. After the separation of product starts, the mixture is heated for an additional 30 min at 200°C. After cooling the mixture is digested with 20 ml of toluene and filtered. Yield: 15.4 g (68%), colorless prisms from dimethylformamide, dec. > 305°C. IR: 3250 m, 2225 s, 1645 s, 1605 s cm^{-1}. ^{1}H-NMR (*DMSO-d$_6$*): δ = 2.35 (s, *Me*), 7.38 (s, 5 aromat. H). $C_{13}H_{10}N_2O_2$ (226.2). Calcd. C 69.02, H 4.46, N 12.38; found C 69.21, H 4.45, N 12.23.

5-n-Butyl-4-hydroxy-2-methyl-6-oxo-1,6-dihydro-3-pyridinecarbonitrile (**3b**)

A mixture of **1** (8.21 g, 0.10 mol) and diethyl butylmalonate (**2b**) (32.4 g, 0.15 mol) is heated at 220°C for 30 min. After cooling the precipitated crude material is digested with diethyl ether and filtered. Yield: 7.4 g (36%), m.p. 255°C (from 1-propanol). IR: 3250 m, 2950 w, 2860 w, 2235 m, 1635 s cm^{-1}. ^{1}H-NMR (*DMSO-d$_6$*): δ = 0.75–1.61 (m, 7 alipathic H), 2.22–2.39 (m, CH_2), 2.42 (s, *Me*). $C_{11}H_{14}N_2O_2$ (206.2). Calcd. C 64.06, H 6.84, N 13.58; found C 64.32, H 6.97, N 13.75.

5-Benzyl-4-hydroxy-2-methyl-6-oxo-1,6-dihydro-3-pyridinecarbonitrile (**3c**)

From **1** (8.21 g, 0.10 mol) and diethyl benzylmalonate (**2c**) (26.8 g, 0.12 mol) using the method as described for **3b**. Yield 7.9 g (33%), m.p. 279–281°C (from ethanol), lit. m.p. 280–281°C [6].

5-[N-2-(1-Cyano-1-propenyl)-carbamoyl]-4-hydroxy-2-methyl-6-oxo-1,6-dihydro-3-pyridinecarbonitrile (**4**)

A mixture of **1** (8.21 g, 0.10 mol) and triethyl methanetricarboxylate (16.24 g, 0.07 mol) is heated at 200°C for about 5 min. After cooling the crude material is digested with 20 ml of diethyl ether and filtered. Yield: 6.5 g (36%), dec. > 230°C (from ethanol). IR: 3040 m, 2920 w, 2240 m, 2220 m, 1630 s cm^{-1}. ^{1}H-NMR (*DMSO-d$_6$*): δ = 2.25 (2 s, 2 *Me*), 6.21 (s, olefinic proton). $C_{12}H_{10}N_4O_3$ (258.8). Calcd. C 55.81, H 3.88, N 21.30; found C 55.93, H 3.94, N 21.41.

4-Benzoyloxy-2-methyl-6-oxo-5-phenyl-1,6-dihydro-3-pyridinecarbonitrile (**5a**)

A suspension of the hydroxypyridine **3a** (6.78 g, 0.03 mol) and benzoylchloride (4.63 g, 0.033 mol) in 20 ml of pyridine is stirred for 12 h at room temperature. The mixture is diluted with 200 ml of ice-water and the resulting precipitate collected by filtration. Yield: 8.5 g (86%), m.p. 108–110°C (from dioxane). IR: 3050 m, 2230 m, 1750 s, 1650 s cm^{-1}. ^{1}H-NMR (*DMSO-d$_6$*): δ = 2.55 (s, *Me*), 6.85–8.08 (m, 5 aromat. H), 7.29 (s, 5 aromat. H). $C_{20}H_{14}N_2O_3$ (330.3). Calcd. C 72.72, H 4.27, N 8.48; found: C 72.56, H 4.23, N 8.23.

4-(N,N-Dimethylcarbamoyloxy)-2-methyl-6-oxo-5-phenyl-1,6-dihydro-3-pyridinecarbonitrile (**5b**)

A suspension of **3a** (4.52 g, 0.02 mol) and dimethylcarbamoylchloride (2.36 g, 0.022 mol) in 10 ml of pyridine is stirred for 12 h at room temperature. The resulting solution is poured into 200 ml of ice-

water and the precipitated solid collected by filtration. Yield: 4.6 g (78%), m.p. 224–226°C (from ethanol). IR: 2 880 m, 2 230 m, 1 740 s, 1 645 s cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 2.46$ (s, *Me*), 2.82 (s, 2 *Me*), 7.33 (s, 5 aromat. H). $C_{16}H_{15}N_3O_3$ (297.3). Calcd. C 64.64, H 5.06, N 14.14; found C 64.76, H 5.20, N 13.97.

4-Acetoxy-2-methyl-6-oxo-5-phenyl-1,6-dihydro-3-pyridinecarbonitrile (**5c**)

Hydroxypyridine **3a** (1.13 g, 0.005 mol) and 10 ml of acetic anhydride are refluxed for 30 min. The resulting solution is allowed to stand at 0°C for 6 h. The separated crystals are filtered and recrystallized from ethanol. Yield 0.18 g (13%) colorless needles, m.p. 252–255°C. IR: 3 000 w, 2 840 m, 2 220 m, 1 785 s, 1 640 s cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): $\delta = 2.10$ (s, *Me*), 2.51 (s, *Me*), 7.39 (s, 5 aromat. H). $C_{15}H_{12}N_2O_3$ (268.3). Calcd. C 67.16, H 4.51, N 10.44; found C 67.41, H 4.65, N 10.42.

4,6-Diacetoxy-2-methyl-5-phenyl-3-pyridinecarbonitrile (**6**)

The mother liquor from the reaction above is poured into 100 ml of ice-water and stirred at 10°C until crystallization of the product occurs. The crude product is filtered and recrystallized from chloroform-petroleum ether. Yield: 0.87 g (56%), dec. > 101°C. IR: 2 230 m, 1 790 s, 1 775 s, 1 605 m, 1 595 m, 1 540 m cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.02 (s, *Me*), 2.08 (s, *Me*), 2.79 (s, *Me*), 7.15–7.56 (s, 5 aromat. H). $C_{17}H_{14}N_2O_4$ (310.3). Calcd. C 65.80, H 4.55, N 9.03; found C 66.17, H 4.70, N 8.98.

4,6-Dichloro-2-methyl-5-phenyl-3-pyridinecarbonitrile (**7a**)

Compound **3a** (22.6 g, 0.1 mol) and 50 ml of phosphorusoxychloride are refluxed for 2 h. After cooling the solution is poured into 500 ml of ice-water and is allowed to stand at 0°C for 12 h. The resulting precipitate is filtered. Yield: 21.3 g (81%), m.p. 130°C (from methanol). IR: 2 240 m, 1 600 w, 1 565 s cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 2.80$ (s, *Me*), 7.02–7.51 (m, 5 aromat. H). $C_{13}H_8Cl_2N_2$ (263.1). Calcd. C 59.34, H 3.06, Cl 26.95, N 10.65; found C 59.00, H 3.04, Cl 26.71, N 10.52.

4,6-Dibromo-2-methyl-5-phenyl-3-pyridinecarbonitrile (**7b**)

Compound **3a** (6.78 g, 0.03 mol) and phosphorusoxybromide (22.9 g, 0.08 mol) are heated in an oil bath to 160°C for 1 h. After cooling the resulting residue is treated with 400 ml of ice-water and is allowed to stand for 12 h at 0°C. The precipitated solid is filtered. Yield 5.1 g (49%), m.p. 145°C (from 1-propanol). IR: 2 240 m, 1 605 w, 1 550 s cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 2.86$ (s, *Me*), 7.08–7.62 (m, 5 aromat. H). $C_{13}H_8Br_2N_2$ (352.0). Calcd. C 44.36, H 2.29, N 7.96; found C 44.70, H 2.12, N 8.01.

4,6-Dimethoxy-2-methyl-5-phenyl-3-pyridinecarbonitrile (**8**)

Dichloropyridine **7a** (13.15 g, 0.05 mol) is added to a solution of sodium (5.75 g, 0.25 mol) in 100 ml of methanol and the resulting mixture is refluxed for 1 h. After cooling the solution is poured into 500 ml of ice-water and the precipitated product filtered. Yield: 10.8 g (85%) colorless needles, m.p. 97°C (from ethanol). IR: 3 000 w, 2 960 w, 2 225 m, 1 590–1 540 s cm^{-1}. ^{1}H-NMR ($CDCl_3$): $\delta = 2.63$ (s, *Me*), 3.58 (s, O*Me*), 3.86 (O*Me*), 7.24 (s, 5 aromat. H). $C_{15}H_{14}N_2O_2$ (254.3). Calcd. C 70.86, H 5.51, N 11.02; found C 70.83, H 5.62, N 10.94.

4,6-Diethylthio-2-methyl-5-phenyl-3-pyridinecarbonitrile (**9**)

To a solution of dichloropyridine **7a** (5.26 g, 0.02 mol) in 50 ml of ethanol, sodium hydroxide (1.6 g, 0.04 mol) and ethanethiol (3.72 g, 0.06 mol) are added. The mixture is stirred for 12 h and then poured into 500 ml of ice-water. The resulting oil is allowed to crystallize and is recrystallized from methanol. Yield: 5.3 g (84%) colorless crystals, m.p. 88–90°C (from methanol). IR: 2 960 w, 2 920 w, 2 220 m,

1 600 w, 1 530 s, 1 505 s cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 1.03 (t, J = 7.2 Hz, *Me*), 1.22 (t, J = 7.2 Hz, *Me*), 2.70 (s, *Me*), 2.72 (q, J = 7.2 Hz, SCH_2), 3.08 (q, J = 7.2 Hz, SCH_2), 7.05–7.59 (m, 5 aromat. H). $C_{17}H_{18}N_2S_2$ (314.5). Calcd. C 64.93, H 5.77, N 8.91; found C 65.02, H 5.69, N 8.96.

6-Benzylamino-4-chloro-2-methyl-5-phenyl-3-pyridinecarbonitrile (**10**)

A solution of dichloropyridine **7a** (7.89 g, 0.03 mol) and benzylamine (7.49 g, 0.07 mol) in 20 ml of acetonitrile is refluxed for 1 h. The reaction mixture is poured into 200 ml of water and the separated solid is collected by filtration. Yield: 7.1 g (71%), m.p. 150–152°C (from 1-propanol). IR: 3 425 s, 3 080–3 040 w, 2 930 w, 2 220 s, 1 605 s, 1 555 s cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 2.63 (s, *Me*), 4.60 (d, J = 5.6 Hz, CH_2), 4.95 (d, J = 5.6 Hz, NH), 7.05–7.62 (m, 5 aromat. H), 7.22 (s, 5 aromat. H). ^{13}C-NMR ($CDCl_3$): δ = 24.1 (CH_3), 45.2 (CH_2), 97.8 (C-3), 116.4 (CN), 118.0 (C-5), 127.1–131.9, 133.5, 138.2 (aromat. C), 143.2 (C-4), 157.2 (C-6), 162.8 (C-2). $C_{20}H_{16}ClN_3$ (333.8). Calcd. C 71.96, H 4.83, N 12.59; found C 72.29, H 4.86, N 12.61.

References

[1] Undergraduate research work (1984)
[2] Kappe T., Ajili S., Stadlbauer W. (1988) J. Heterocycl. Chem. **25**: 463
[3] Krämer W. (1983) Fungicides and Bactericides. In: Büchel K. H. (ed.) Chemistry of Pesticides. Wiley, New York, p. 310
[4] Mohr G., Niethammer K., Lust S., Schneider G. (E. Merck AG) Ger. Offenl. 1.182.896 (Cl. A 01n), Dec. 3, 1964, Appl. Apr. 2, 1963; (1965) Chem. Abstr. **62**: 4012h
[5] Noeroske R. L., Tobol H. K. (Dow Chemical Co.) United States Patent 3.578.434 (Cl. 71–77, A 01cn), May 11, 1971, Appl. July 23, 1968; (1971) Chem. Abstr. **75**: 19194m
[6] Kappe T., Chirazi A., Stelzel H. P., Ziegler E. (1972) Monatsh. Chem. **103**: 586
[7] Soliman F. S. G., Kappe T. (1977) Pharmazie **32**: 278
[8] Ziegler E., Hradetzky F. (1964) Monatsh. Chem. **95**: 1247

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