A Convenient Synthesis of 2-Aminopyridine-3-carbonitriles

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The 5- and/or 6-alkyl substituted derivatives of 2-aminopyridine-3-carbonitrile were synthesized *via* dienamine intermediates (3) produced by the addition-elimination reaction of various enamines to methoxymethylene malondinitrile. The reaction can be carried out without the isolation of the dienamine intermediates.

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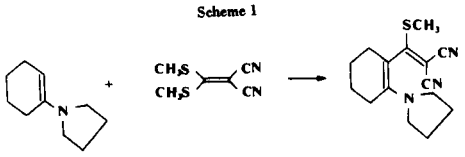
Substituted 2-aminopyridines have been synthesized in a variety of ways (1a-f). Recent biological interest (2) in the 2-aminopyridines prompted us to explore a convenient synthesis of these compounds.

Though the chemical literature abounds with examples of the Michael addition reaction of enamines to α,β-unsaturated carbonyl compounds (3), there appears to be few reports of similar reaction to a Michael acceptor such as an α,β-unsaturated nitrile bearing a heteroatom (N, O or S) at the β-position. A reaction of keten-mercaptal and an enamine has been patented (4).

Scheme 1



The reaction of pyrrolidine enamine (**1e**; R^1, R^2 = -$(CH_2)_4$-) of cyclohexanone with methoxymethylene malondinitrile (**2**) at room temperature for half an hour gave a good yield of pale yellow prisms subsequently identified as 2-(2-pyrrolidino-cyclohexenyl)ethylene-1,1-dicarbonitrile (**3e**; R^1, R^2 = -$(CH_2)_4$-) by spectral data and elemental analysis. The dienamine (**3e**) can be quantitatively converted to 2-amino-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**4e**; R^1, R^2 = -$(CH_2)_4$-) (**1e**) on treatment with ammonia in tetrahydrofuran solution at an ambient or slightly high temperature.

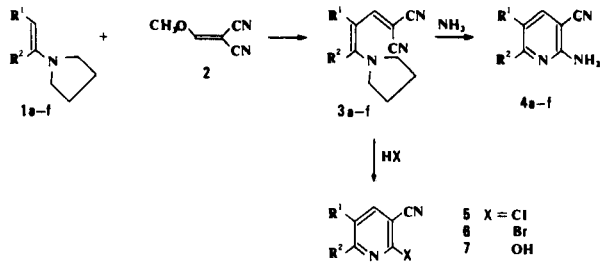
The reaction can take place *in situ* without the isolation of the intermediate (**3**).

By analogy, one would expect the syntheses of the 5- and/or 6-alkyl substituted derivatives of 2-aminopyridine-3-carbonitrile (**4**) from the enamines of cyclic or acyclic ketones or aldehydes. Thus, treatment of various enamines with methoxy-methylene malondinitrile (**2**) followed by ammonia gave 2-aminopyridine derivatives. The results of the reactions are compiled in Table I. No attempt was made to maximize the conversion of **1** to **4** with the exception of the case of **4e**.

The short reaction time, simple procedure, and good yield of the reaction make it a valuable method for preparing 2-aminopyridine derivatives (5).

There are indications in the literature that conjugated enamines or conjugated enol ethers analogous to the dienamine (**3**) undergo acid catalyzed cyclization (6). Treatment of **3e** with hydrogen chloride or hydrogen bromide gives rise to the expected 2-chloro (**5**) (7) and 2-bromo derivative (**6**) of 5,6,7,8-tetrahydroquinoline-3-carbonitrile, respectively. It was found that **3e** can be converted to the corresponding 2-hydroxytetrahydroquinoline (**7**) (8) by refluxing in 2*N* hydrochloric acid.

Scheme 2



EXPERIMENTAL

Melting points were determined in open glass capillaries on a Büchi apparatus and are uncorrected. Nmr spectra were recorded

Table I

Compounds	R^1	R^2	Over-all Yield, %	Uv λ max (Methanol):	nm (log ε)
4a	$(CH_3)_2CH$	H	51	246 (4.11),	332 (3.73)
4b	CH_3	C_2H_5	67	247 (4.07),	329 (3.88)
4c	C_2H_5	n-C_3H_7	50	248 (4.08),	329 (3.88)
4d	-$(CH_2)_3$-		37	251 (4.03),	335 (3.88)
4e	-$(CH_2)_4$-		91	248 (4.04),	332 (3.88)
4f	-$(CH_2)_5$-		41	251 (4.06),	331 (3.89)

on a Varian HA-60 spectrometer and chemical shifts are expressed in δ units, ppm downfield from TMS as the internal standard. Ir spectra were obtained in potassium bromide discs using a JASCO IRA-2 spectrometer. Uv absorption spectra were obtained with Cary 14CM-50 or Cary 118C spectrophotometers. Mass spectra were recorded on a JEOL JMS-OISG at 75 ev using a direct inlet system. The relative intensity of the molecular ion is indicated in parenthesis as a percent of the base peak.

2-(2-Pyrrolidino-cyclohexenyl)ethylene-1,1-dicarbonitrile (**3e**).

A solution of pyrrolidine enamine (1.51 g., 10 mmoles) of cyclohexanone in THF (5 ml.) was added dropwise to a solution of **2** (1.08 g., 10 mmoles) in THF (10 ml.) below -20° under argon atmosphere. The mixture was stirred until room temperature was reached and held there for half an hour. Concentration of the mixture *in vacuo* gave a crystalline residue. Chromatography on alumina (Merck, activity II-III) (fractions eluted with methylene chloride-*n*-hexane 1:1 mixture) and recrystallization from methanol gave **3e** (80%), m.p. 144-146° dec., as pale yellow prisms; ir: 2180, 1573, 1500 and 1318 cm^{-1}; nmr (deuteriochloroform): 1.63 (4H, m), 1.96 (4H, m), 3.63 (4H, m), 7.00 (1H, s); ms: M^+ = 227 (40), 186 (15), 161 (base peak), and 133 (20) m/e.

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 10.48. Found: C, 74.00; H, 7.52; N, 18.46.

2-Amino-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**4e**).

Ammonium hydroxide (28%, 4 ml.) was added dropwise to a solution of **3e** (1.14 g., 5 mmoles) in THF (20 ml.) with the temperature kept below 0°. The mixture was heated under reflux (40-50°) for 2 hours. The solvent was stripped off to give a solid residue, which was dissolved in ethyl acetate (50 ml.). The ethyl acetate solution was extracted with 1*N* hydrochloric acid (20 ml. x 3). The combined aqueous extracts were basified with saturated aqueous sodium bicarbonate and extracted with methylene chloride (50 ml. x 2). The methylene chloride extracts were washed with brine, dried over sodium sulfate, and evaporated to give **4e** (0.82 g., 94%). Recrystallization from methanol gave prisms melting at 195-197° (Lit. (1e), m.p. 195°).

General Procedure for **4** from **1** (*in situ* Method).

A solution of an enamine (10 mmoles) in dry THF (5 ml.) was added dropwise to a solution of **2** (10 mmoles) in dry THF (10 ml.) as in the preceding manner. The temperature was raised to room temperature and held there for an additional half an hour. Once again the mixture was cooled to -20° and ammonium hydroxide (28%, 5 ml.) was added to it. The reaction mixture was heated to reflux for 2 hours, and conventional work-up described above gave **4a-f**.

2-Amino-5-isopropylpyridine-3-carbonitrile (**4a**).

This compound had m.p. 113-114° (from cyclohexane); ir: 3450, 3350, 2220, 1665, 1643 and 767 cm^{-1}; nmr (deuteriochloroform): 1.21 (6H, d, J = 7), 2.86 (1H, heptet, J = 7), 7.56 (1H, d, J = 2.5), 8.15 (1H, d, J = 2.5); ms: M^+ = 161 (32); 146 (base peak), 129 (4) and 119 (5) m/e.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.06. Found: C, 67.10; H, 6.86; N, 26.06.

2-Amino-6-ethyl-5-methylpyridine-3-carbonitrile (**4b**).

This compound had m.p. 153-155° (from cyclohexane-isopropanol); ir: 3425, 3180, 2220, 1650, 1475 and 776 cm^{-1}; nmr (deuteriochloroform): 1.20 (3H, t), 2.67 (2H, q, J = 7), 2.17 (3H, s), 7.40 (1H, s); ms: M^+ = 161 (100), 160 (80), 146 (14), 133 (23) and 106 (14) m/e.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.06. Found: C, 66.92; H, 6.91; N, 26.19.

2-Amino-5-ethyl-6-propylpyridine-3-carbonitrile (**4c**).

This compound had m.p. 111-115° (from cyclohexane); ir: 3440, 3160, 2190, 1640, 1593 and 1475 cm^{-1}; nmr (deuteriochloroform): 0.98 (3H, t, J = 7), 1.17 (3H, t, J = 7), 1.70 (2H, m), 2.58 (4H, m), 7.44 (1H, s); ms: M^+ = 189 (22), 174 (36), 161 (base peak), and 146 (20) m/e.

Anal. Calcd. for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.72; H, 7.97; N, 22.31.

2-Amino-6,7-dihydro-5(*H*),1-pyrindine-3-carbonitrile (**4d**).

This compound had m.p. 219° (from ethanol); ir: 3420, 3150, 2210, 1655 and 763 cm^{-1}; nmr (DMSO-d_6): 1.99 (2H, m, J = 7), 2.78 (4H, br. t, J = 7), 7.60 (1H, s); ms: M^+ = 159 (100), 158 (99), 131 (12) and 104 (10) m/e.

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.86; H, 5.65; N, 26.43.

2-Amino-6,7,8,9-tetrahydro-5-cyclohepta[*b*]pyridine-3-carbonitrile (**4f**).

This compound had m.p. 204-206° (from methanol); ir: 3420, 3170, 2220, 1655, 1475, 1200 and 776 cm^{-1}; nmr (DMSO-d_6): 1.68 (6H, br. s), 2.71 (4H, br. t, J = 10), 7.52 (1H, s); ms: M^+ = 187 (100), 186 (44), 173 (32), 158 (47), 145 (20) and 132 (17) m/e.

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.49; H, 7.06; N, 22.68.

2-Chloro-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**5**).

A solution of **3e** (2.27 g., 10 mmoles) in 2-propanol (20 ml.) was saturated with hydrogen chloride with the temperature kept below 0°. The mixture was refluxed for 2 hours. The reaction mixture was re-cooled, basified by dropwise addition of saturated aqueous sodium bicarbonate, and extracted with methylene chloride. The methylene chloride extracts were dried over sodium sulfate and evaporated, leaving a solid (1.78 g., 92%). Recrystallization from cyclohexane-isopropanol mixture gave leaflets, m.p. 136-136.5° (Lit. (9), m.p. 134-135°).

2-Bromo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**6**).

A solution of **3e** (2.27 g., 10 mmoles) in 2-propanol (20 ml.) was treated with hydrogen bromide as described for the chloride (**5**). Concentration of the methylene chloride extracts gave **6** (2.19 g., 87%) as a crystalline mass. An analytical sample was recrystallized from cyclohexane to give leaflets melting at 161-161.5°; ir: 2245, 1583, 1420, 1388, 1021 and 943 cm^{-1}; nmr (deuteriochloroform): 1.87 (4H, m), 2.87 (4H, m), 7.61 (1H, s); M^+ = 236 (100), 220 (9), 208 (24) and 164 (14) m/e.

Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.65; H, 3.83; N, 11.82. Found: C, 50.93; H, 3.76; N, 11.82.

2-Hydroxy-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**7**).

Two g. of **3e** was suspended in 2*N* hydrochloric acid (5 ml.). After refluxing for 2 hours, the mixture was cooled and basified with saturated aqueous sodium bicarbonate. The resultant precipitates were filtered and washed with water. Dried product weighed 1.30 g. (78%). Recrystallization from acetic acid gave prisms melting at 245-248° (Lit. (10), m.p. 248-249°).

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