# 2-Amino-3-substituted 1,6-Naphthyridines

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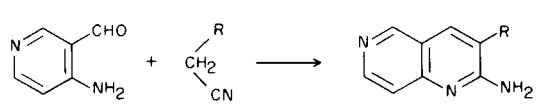
A new versatile method for the synthesis of 2-amino-3-substituted 1,6-naphthyridines has been achieved through an application of the Friedländer method. Derivatives containing alkyl, aryl, heteroaryl, nitrile, carboxamide, and carboxylic acid substituents in the 3-position were directly prepared from 4-aminonicotinaldehyde.

The direct synthesis of naphthyridine systems substituted in only one of the fused pyridine rings is difficult (1). The only approach from aminopyridines which is applicable to most of the systems is the Skraup. Only one step is required but it lacks versatility with respect to the substituents which may be introduced. The alternative general approach is from *o*-disubstituted pyridines. Many 1,8-naphthyridines were directly prepared from 2-aminonicotinaldehyde, but the latter required a multistep synthesis (2). This approach has not been reported for 1,6-naphthyridines and was investigated in the present paper for 2-amino-3-substituted derivatives (III).

4-Aminonicotinaldehyde (I), the required intermediate for the synthesis of III, was prepared in a 10% overall yield on a large scale in six steps from the commercially available 3-picoline 1-oxide by modification of the methods of Armarego (3) and Wibberley (4). A direct sodium metaperiodate oxidation of 4-aminonicotinic hydrazide, rather than its isopropylidene derivative, consistently afforded the aldehyde in 50% yield, in contrast to the 26% yield reported for the latter literature method (3), which was carried out on a smaller scale. No special storage conditions were required for I. The disadvantages so frequently quoted for the Friedländer synthesis (5), namely difficulty of bulk synthesis and storage of the *o*-amino aromatic carbonyl compound were not apparent in this work.




I II III

Condensation of substituted acetonitriles (II) with I in boiling alcohol with a base catalyst has proved to be a versatile method for the synthesis of III as shown in Table I. Three base catalysts were tried with each cyanomethylene compound. Piperidine (Procedure A) was successful only with those most readily forming carbanions, namely cyanoacetamide, *N*-monosubstituted cyanoacetamides, malononitrile, cyanoacetic acid and the most strongly activated arylacetonitriles. Sodium hydroxide (Procedure B) was necessary for all the remaining arylacetonitriles and the related 1-cyclohexenylacetonitrile. Acetonitrile and two other alkyl cyanides required sodium methoxide (Procedure C). Yields were greater than 50%, except in the case of butyronitrile. No product was isolated with methoxyacetonitrile.

The experimental data indicates that the rate of reaction is related to the activity of the methylene group of the substituted acetonitrile. Thus it appears that the addition of the anion of the methylene group to the aldehyde precedes the addition of primary amine to nitrile. This is contrary to the observations of other authors (5a,b) as to the mechanism of the Friedländer synthesis of quinoline.

The synthesis of 2-amino-1,6-naphthyridine has been previously reported (6). A Chichibabin reaction on the parent naphthyridine gave a product with identical melting point and spectra to the product obtained by the Friedländer method. This proof of structure is worthy of note in view of the controversy over the amination product of 1,5-naphthyridine (7). Only one other 2-amino-1,6-naphthyridine is reported in the literature and the authors were unable to confirm its structure (8).

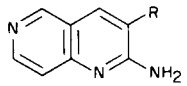
The nmr characteristics of the ring protons of III are particularly useful for structural determinations. Most were soluble in deuteriodimethylsulfoxide solutions in which the spectral patterns of the $H_5$, $H_7$, and $H_8$ protons are grossly similar to each other. The chemical shifts are in the range $\delta$ 9.04-8.80 for the 5 proton, $\delta$ 8.54-8.42 for the 7 proton and $\delta$ 7.48-7.36 for the 8 proton. The inductive character of the 3-substituent has a far greater effect at the *o*-position, thus the 4 proton is in the range $\delta$ 8.70-7.90. Also, in this solvent the coupling constant was identical for all compounds examined ($J_{7,8}$ 6 Hz).

## EXPERIMENTAL

Infrared spectra were recorded as potassium bromide pellets

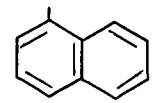
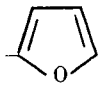
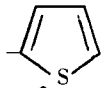
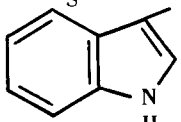
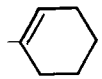
TABLE I

2-Amino-3-substituted 1,6-Naphthyridines



| R | M.p., °C (a) | Procedure | Reaction Time (hr.) | Yield % | Formula | Analyses Calcd. C | H | N | Found C | H | N | Chemical Shift (δ) of ring protons (j) $H_4$ | $H_5$ | $H_7$ | $H_8$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $-CONH_2$ | 294-295 dec. (b) | A | 1 | 87 | $C_9H_8N_4O$ | 57.47 | 4.40 | 29.77 | 57.30 | 4.40 | 30.07 | 8.70 | 9.00 | 8.54 | 7.38 |
| $-CONHCH_3$ | 264-266 (b) | A | 2 | 80 | $C_{10}H_{10}N_4O$ | 59.41 | 4.95 | 27.72 | 59.29 | 4.86 | 27.72 | 8.53 | 8.93 | 8.44 | 7.45 |
| $-CONHCH_2CH_3$ | 210.5-212.5 | A | 2 | 65 | $C_{11}H_{12}N_4O$ | 61.11 | 5.69 | 25.90 | 61.24 | 5.82 | 26.11 | 8.63 | 9.04 | 8.54 | 7.40 |
| $-CONHCH_2CH_2N(C_2H_5)_2$ | 124.5-126 (c) | A | 24 | 57 | $C_{15}H_{21}N_5O$ | 62.72 | 7.32 | 24.39 | 62.35 | 7.34 | 24.68 | 8.54 | 9.00 | 8.52 | 7.37 |
| $-CONHCH_2CH_2N$ O | 181-183 | A | 24 | 75 | $C_{15}H_{19}N_5O_2$ | 59.80 | 6.31 | 23.26 | 60.03 | 6.27 | 23.05 | 8.54 | 9.00 | 8.51 | 7.38 |
| $-CN$ | >360 (b) | A | 0.25 | 90 | $C_9H_6N_4$ | 63.53 | 3.55 | 32.91 | 63.22 | 3.54 | 32.69 | 9.17 (k) | 9.61 | 8.92 | 8.25 |
| $-COOH$ | 340-345 dec. (d,e) | A | 2 | 52 | $C_9H_7N_3O_2$ | ---- | --- | ---- | ---- | --- | ---- | 8.97 (l) | 8.90 | 8.32 | 7.60 |
| $-C_6H_4-NO_2$ | 267-270 (f) | A | 12 | 84 | $C_{14}H_{10}N_4O_2$ | 63.16 | 3.76 | 21.05 | 63.35 | 4.00 | 20.79 | 8.07 | 8.96 | 8.45 | 7.48 |
| $-C_6H_4-N$ | 188-190 | A | 24 | 63 | $C_{13}H_{10}N_4$ | 70.27 | 4.50 | 25.23 | 69.99 | 4.38 | 25.12 | 8.04 | 8.97 | 8.46 | 7.40 |
| $-C_6H_5$ | 214.5-217 | B | 2 | 68 | $C_{14}H_{11}N_3$ | 76.02 | 4.98 | 19.00 | 75.86 | 4.93 | 18.82 | 7.94 | 8.92 | 8.42 | 7.38 |
| $-C_6H_4-Br$ | 195-197 | B | 2 | 86 | $C_{14}H_{10}BrN_3$ | 56.02 | 3.33 | 14.00 | 55.96 | 3.21 | 13.86 | 7.94 | 8.92 | 8.42 | 7.36 |
| $-C_6H_4-Cl$ | 206-208 | B | 1 | 70 | $C_{14}H_{10}ClN_3$ | 65.88 | 3.92 | 16.47 | 65.83 | 3.74 | 16.41 | 7.97 | 8.96 | 8.42 | 7.37 |
| $-C_6H_4-F$ | 232-234 | B | 2 | 67 | $C_{14}H_{10}FN_3$ | 70.29 | 4.18 | 17.57 | 70.21 | 4.21 | 17.42 | 7.98 | 8.95 | 8.45 | 7.42 |
| $-C_6H_4-CH_3$ | 179-181 | B | 1 | 80 | $C_{15}H_{13}N_3$ | 76.60 | 5.53 | 17.87 | 76.64 | 5.64 | 17.73 | 7.90 | 8.95 | 8.42 | 7.38 |
| $-C_6H_4-C_6H_5$ | 271-274 (g) | B | 0.5 | 87 | $C_{20}H_{15}N_3$ | 80.81 | 5.05 | 14.14 | 80.59 | 5.20 | 13.99 | 8.50 (k) | 9.52 | 8.89 | 8.32 |

TABLE I (continued)

| R | M.p., °C (a) | Procedure | Reaction Time (hr.) | Yield % | Formula | Analyses Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N | Chemical Shift (δ) of ring protons (j) $H_4$ | $H_5$ | $H_7$ | $H_8$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  | 219-221 | B | 3 | 57 | $C_{18}H_{13}N_3$ | 79.70 | 4.80 | 15.50 | 79.93 | 4.92 | 15.35 | 8.01 | 8.95 | 8.46 | 7.42 |
|  | 183-184 dec. | B | 3 | 78 | $C_{12}H_9N_3O$ | 68.25 | 4.27 | 19.91 | 68.25 | 4.17 | 19.64 | 8.43 | 9.03 | 8.47 | 7.38 |
|  | 163-165 (b) | B | 3 | 78 | $C_{12}H_9N_3S$ | 63.44 | 3.96 | 18.50 | 63.48 | 3.86 | 18.40 | 8.15 | 9.00 | 8.46 | 7.39 |
|  | 276-278 (b) | B | 4 | 58 | $C_{16}H_{12}N_4$ | 73.85 | 4.62 | 21.54 | 74.24 | 4.50 | 21.34 | 8.16 | 9.02 | 8.48 | 7.45 |
|  | 235-237 | B | 4 | 59 | $C_{14}H_{15}N_3$ | 74.67 | 6.67 | 18.67 | 75.08 | 6.64 | 18.49 | 7.73 (l) | 8.67 | 8.18 | 7.52 |
| H | 238-239 dec. (h) | C | 2 | 53 | $C_8H_7N_3$ | ---- | --- | ---- | ---- | --- | ---- | 8.07 | 8.80 | 8.45 | 7.35 |
| $-CH_3$ | 265-267 (i) | C | 2 | 55 | $C_9H_9N_3$ | 67.92 | 5.66 | 26.42 | 67.91 | 5.65 | 26.36 | 7.84 (l) | 8.68 | 8.20 | 7.56 |
| $-CH_2CH_3$ | 223-224 (i) | C | 2 | 25 | $C_{10}H_{11}N_3$ | 69.36 | 6.36 | 24.28 | 69.13 | 6.32 | 24.07 | 7.85 (l) | 8.69 | 8.20 | 7.56 |

(a) Recrystallized from benzene unless otherwise noted. (b) Recrystallized from ethanol. (c) Recrystallized from ligroin (b.p. 60-90°). (d) Reprecipitation. (e) Acid did not give correct analysis but gave an ethyl ester with satisfactory analysis figures. (f) Recrystallized from butanol. (g) Recrystallized from benzene-ligroin (b.p. 60-90°). (h) Lit. (6) m.p. 239-240°. (i) Recrystallized from water. (j) Deuteriodimethylsulfoxide solutions with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard. (k) Trifluoroacetic acid solution. (l) Deuteriosulfuric acid solution.

on a Unicam SP 200G spectrometer. Nmr spectra were obtained with a Varian T-60 spectrometer with DSS as the internal standard. Melting points were determined on a Gallenkamp block and are uncorrected. Elemental analysis were determined by Dr. Strauss, Oxford, England.

Cyanomethylene Compounds (II).

Most of the starting materials used in this work were obtained from commercial sources. *N*-Methyl-, *N*-ethyl-, *N*-(2-diethylaminoethyl)- and *N*-(2-morpholinoethyl)cyanoacetamides were prepared by the method of Osdene *et al.* (9).

4-Aminonicotinaldehyde (I).

A mixture of 25 g. of 4-aminonicotinic acid hydrazide (3,4), 409 ml. of water and 81 ml. of ammonia (d. 0.90) were slowly added with vigorous stirring to a cooled solution of 45 g. of sodium metaperiodate in 620 ml. of water and 409 ml. of ammonia (d. 0.90). The reaction was allowed to proceed for 20 minutes, then stopped by the addition of 46.5 g. of barium acetate in 195 ml. of water and the resulting precipitate filtered off. The filtrate was adjusted to *p*H 7.0-8.0 and saturated with sodium chloride, then extracted several times with chloroform and dried (sodium sulfate). Evaporation under reduced pressure and one crystallization from benzene-ligroin (b.p. 60-90°) yielded 10 g. (50%) of 4-aminonicotinaldehyde, m.p. 110-112° (lit. (3) m.p. 113-114°).

2-Amino-3-substituted 1,6-naphthyridines (III).

Procedure A.

A mixture of 0.366 g. (0.003 mole) of 4-aminonicotinaldehyde, the appropriate cyanomethylene derivative (0.006 mole) and 0.075 g. (0.00075 mole) of piperidine in 5 ml. of absolute ethanol were heated under reflux on a steam bath. The naphthyridines were obtained in the recorded yield by direct filtration or on evaporation, trituration with a suitable solvent and filtration. The products were purified by crystallization from the recorded solvent (see Table I).

Procedure B.

The conditions and work-up is as described for Procedure A, except that 0.4 ml. (0.001 mole) of 10% aqueous sodium hydroxide was used instead of piperidine.

Procedure C.

A mixture of 0.366 g. (0.003 mole) of 4-aminonicotinaldehyde, 5 ml. of the appropriate alkyl cyanide and 0.324 g. (0.006 mole) of sodium methoxide in 0.2 ml. of methanol were heated under reflux. The reaction mixture was cooled and the product which separated was collected by filtration and washed with water to yield the naphthyridine in the recorded yield. The products were purified by crystallization from the stated solvent (see Table I).

The procedures, reaction times, yields, and melting points of all the title compounds (III) are listed in Table I. The infrared spectra show bands at 3480-3260 (NH free), 3220-3100 (NH bonded) and 1670-1615 (NH bending) $cm^{-1}$.

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