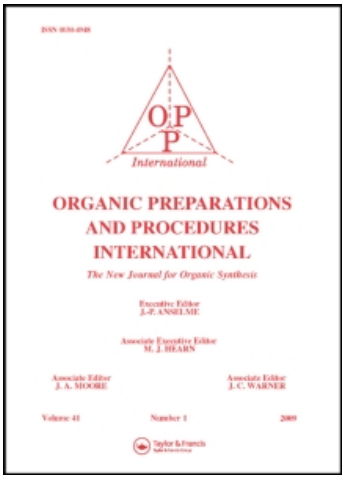

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PREPARATION OF BENZO[c-2,7]NAPHTHYRIDINE

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PREPARATION OF BENZO[c-2,7]NAPHTHYRIDINE

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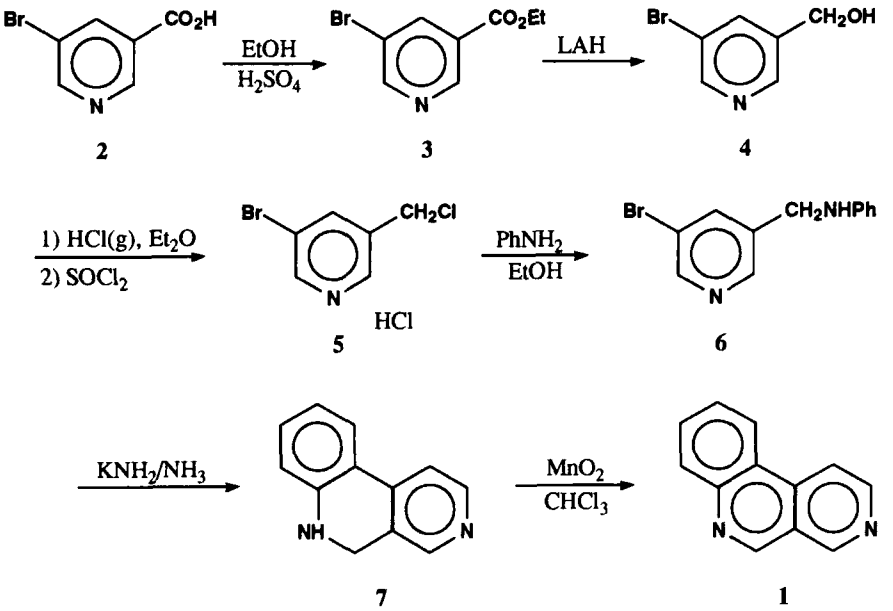
Recently, the benzo[c-2,7]naphthyridine ring system (**1**) has been identified in a number of natural products.[1] In connection with projects aimed at the total synthesis of some of these compounds, we required a convenient preparation of **1**. A seven-step route to **1**, illustrated in the Scheme, has been described.[2] However, little or no experimental or spectroscopic details were included for several of the products and intermediates. As interest in this compound is likely to increase as a result of the discovery of biologically active natural products containing this ring system,[1] we felt a reexamination of the previously reported synthesis strategy was important. We now describe, in both experimental and spectroscopic detail, each of the reactions utilized in the preparation of benzo[c-2,7]naphthyridine from the starting material 5-bromonicotinic acid. Also presented are several modifications of the original reported procedure which we feel render the synthesis more attractive.



Kauffmann and Fischer[3] have reported that ethyl 5-bromonicotinate (**3**) may be reduced to alcohol 4 with lithium aluminum hydride (LAH) in 66% yield, but the required workup is quite tedious and cumbersome. We have effected this same transformation in 43% yield with sodium borohydride in ethanol. Despite the lower yield for the latter reaction, the ease of workup should make it a viable alternative for this reduction. The original procedure[3] for the conversion of **4** to **5** requires precipitation of the hydrochloride salt with benzene. We have found that the product can also be obtained by addition of diethyl ether, thus eliminating the use of a carcinogenic solvent. No experimental details were reported for the transformation of **5** to **6** nor for the purification of the product. The original report by Kessar and coworkers[2] simply states "aniline in ethanol". The results of our studies (Table) show that the highest yield was obtained when **5** was refluxed in ethanol for 17 hrs

TABLE. Preparation of 3-(N-Phenylamino)methyl-5-bromopyridine (**6**)

Aniline/Hydrochloride	Temp. (°C)	Reaction Time	Yield (%)[a]
3/1	25	14 hrs	40
5/1	25	2 weeks	52
10/1	25	24 hrs	48
2/1	reflux	8 hrs	33
5/1	reflux	17 hrs	73

a) Isolated yield after flash chromatography.

with a five molar excess of aniline. Similarly, no experimental details were reported for the cyclization of **6** to **7** nor for the purification of the product. The original report by Kessar and coworkers[2] simply states "KNH_2 in liquid ammonia followed by stirring with manganese dioxide in chloroform". We have found that the cyclization of **6** can also be effected with the less cumbersome procedure of LDA in THF, to afford a mixture of **7** and **1**, which need not be purified before aromatization with manganese dioxide. The presence of 5,6-dihydrobenzo[c-2,7]naphthyridine (**7**) in the crude cyclization product was indicated by the proton NMR (δ 4.4 H-5) and IR (3354 cm^{-1} N-H) spectra. The yield of this two-step conversion is 38%, resulting in an 8% overall yield for the synthesis of benzo[c-2,7]naphthyridine (**1**) from 5-bromonicotinic acid (**2**).

EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware (120°). LDA was purchased as a 2.0 M solution in heptane-THF-ethylbenzene from Aldrich. Tetrahydrofuran was distilled from sodium-benzophenone. Thin layer chromatography was performed on pre-coated (0.25 mm) silica gel 60 F_{254} plastic sheets; the plates were visualized with 254 nm ultraviolet light. Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected. All proton and carbon NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard on a Bruker ACE300 FT-NMR spectrometer. All IR spectra were recorded as solutions in ether on a Perkin Elmer 1600 FT-IR spectrophotometer.

Ethyl 5-Bromonicotinate (3).- A solution of 5-bromonicotinic acid (5.15 g, 25.5 mmol) in a mixture of ethanol (100 mL) and conc. sulfuric acid (1 mL) was magnetically stirred at reflux under nitrogen for 18 hrs. The ethanol was removed *in vacuo* and the resulting white residue was dissolved in water (50 mL). The aqueous solution was basified to pH 8 with saturated aqueous sodium bicarbonate and extracted with ether (3 x 50 mL). The combined extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford ethyl 5-bromonicotinate (5.0 g, 85%) cleanly as a pale yellow oil that solidified upon refrigeration, mp. 38-40°, lit.[4] mp. 42°. ^{1}H NMR: δ 9.13 (d, 1H), 8.85 (d, 1H), 8.44 (dd, 1H), 4.42 (q, 2H), 1.44 (t, 3H). ^{13}C NMR: δ 163.8, 154.2, 148.7, 139.25, 127.5, 120.4, 61.7, 14.1. IR: 1732 cm^{-1} (C=O).

5-Bromo-3-hydroxymethylpyridine (4).- To a magnetically stirred solution of ethyl 5-bromonicotinate (6.50 g, 28.3 mmol) in 95% ethanol (150 mL) at 25° was added over 30 min sodium borohydride pellets (10 g, 0.26 mol). The resulting mixture was magnetically stirred at 25° for three days, after which water was added (100 mL). The ethanol was removed *in vacuo* and the aqueous phase was extracted with methylene chloride (3 x 100 mL). The combined extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford an oil. Flash chromatography (ether) gave 5-bromo-3-hydroxymethylpyridine[3] (2.26 g, 43%) as a yellow oil. ^{1}H NMR: δ 8.57 (d, 1H), 8.47 (d, 1H), 7.90 (br s, 1H), 4.75 (s, 2H). ^{13}C NMR: δ 149.1, 145.75, 138.7, 137.5, 120.8, 61.2. IR: 3262 cm^{-1} (O-H).

5-Bromo-3-chloromethylpyridinium Hydrochloride (5).- To a solution of 5-bromo-3-hydroxymethylpyridine (3.95 g, 21.0 mmol) in diethyl ether (30 mL) at 25° was bubbled hydrogen chloride until precipitation was complete. The resulting white solid was collected by vacuum filtration and then carefully dissolved (initial reaction is vigorous) in thionyl chloride (25 mL). The solution was heated at reflux for 1.5 hr and then allowed to cool to 25°. Dropwise addition of diethyl ether (50 mL) precipitated a white solid which was collected by vacuum filtration, washed with diethyl ether (50 mL) and dried *in vacuo* to afford 5-bromo-3-chloromethylpyridinium hydrochloride (3.04 g) as an off white solid. The filtrate was refrigerated to yield a second crop (1.11 g, Total Yield: 4.15 g, 81%), mp. 137-140°, lit.[3] mp. 136-138°.

3-(N-Phenylamino)methyl-5-bromopyridine (6).- A solution of 5-bromo-3-chloromethylpyridinium hydrochloride (102 mg, 0.42 mmol) and aniline (209 mg, 2.25 mmol) in ethanol (10 mL) was magnetically stirred at reflux under nitrogen for 17 hr. The ethanol was removed *in vacuo* and the resulting oil was suspended in water (15 mL) and adjusted to pH 11 with 10% sodium hydroxide. The aqueous mixture was extracted with methylene chloride (3 x 20 mL) and the combined extracts were dried with sodium sulfate, filtered, and adsorbed onto silica gel. Flash chromatography (2:1 hexane/ether) gave 3-(N-phenylamino)methyl-5-bromopyridine[2] (80 mg, 73%) as a light orange oil. ^{1}H NMR: δ 8.56 (br s, 1H), 8.52 (br s, 1H), 7.84 (br s, 1H), 7.18 (t, 2H), 6.75 (t, 1H), 6.59 (d, 2H), 4.34 (d, 2H), 4.16 (br, 1H). ^{13}C NMR: δ 149.7, 147.2, 147.0, 137.5, 137.0, 129.3, 120.9, 118.3, 112.9, 45.2. IR: 3354 cm^{-1} (N-H).

Benzo[c-2,7]naphthyridine (1).- To a magnetically stirred solution of 3-(N-phenylamino)methyl-5-

bromopyridine (1.15 g, 4.37 mmol) in dry THF (25 mL) at -78° under nitrogen was added over 10 min via syringe LDA (2.0 M, 8.8 mL, 17.6 mmol). The resulting dark solution was allowed to warm to 25° and stirred for 24 hr. The mixture was poured into water (75 mL) and extracted with methylene chloride (3 x 50 mL). The combined extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The resulting dark oil was dissolved in chloroform (25 mL), manganese dioxide (1.91 g, 21.9 mmol) was added and the resulting mixture was magnetically stirred at 25° under nitrogen for 21 hr. The reaction was adsorbed directly onto silica gel and flash chromatography (ether) gave benzo[c-2,7]naphthyridine (0.30 g, 38%) as a light tan solid, mp. 138-140°, lit.[5] mp. 140-142°. ^{1}H NMR: δ 9.41 (s, 1H), 9.38 (s, 1H), 8.94 (dd, 1H), 8.53 (br d, 1H), 8.34 (d, 1H), 8.23 (d, 1H), 7.87 (td, 1H), 7.75 (td, 1H). ^{13}C NMR: δ 152.2, 152.0, 149.0, 145.7, 137.2, 130.9, 130.4, 127.7, 122.7, 121.95, 121.2, 115.2.

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