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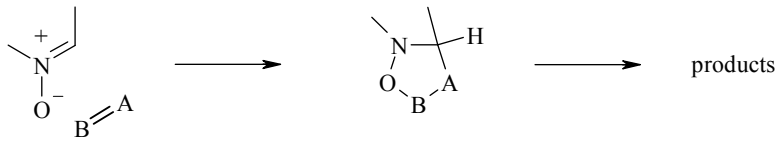
A CONVENIENT ROUTE TO CYANO DERIVATIVES OF BENZONAPHTHYRIDINES

A smooth synthesis of benzo[*c*][1,5]naphtyridine-6-carbonitrile and benzo[*h*][1,6]-naphthyridine-5-carbonitrile, starting from benzonaphthyridine N-oxides, is achieved by treatment with trimethylsilane carbonitrile (Me_3SiCN) in CH_2Cl_2 at 0–5°C. The resulting nitriles are then hydrolyzed to corresponding acids by boiling in aqueous alkali.

Keywords: benzonaphthyridine N-oxides, carbonitriles, carboxylic acids, cyanation.

A number of rearrangements starting with N-oxides may be used as convenient methods for the introduction of substituents into aza-aromatic systems [1–4].

Most of these reactions involve addition of an A=B fragment to an equivalent of nitrone function to give the structure **1** (possibly *via* 1,3-dipolar addition path) followed by N–O bond cleavage and rearrangement of the products thus formed.



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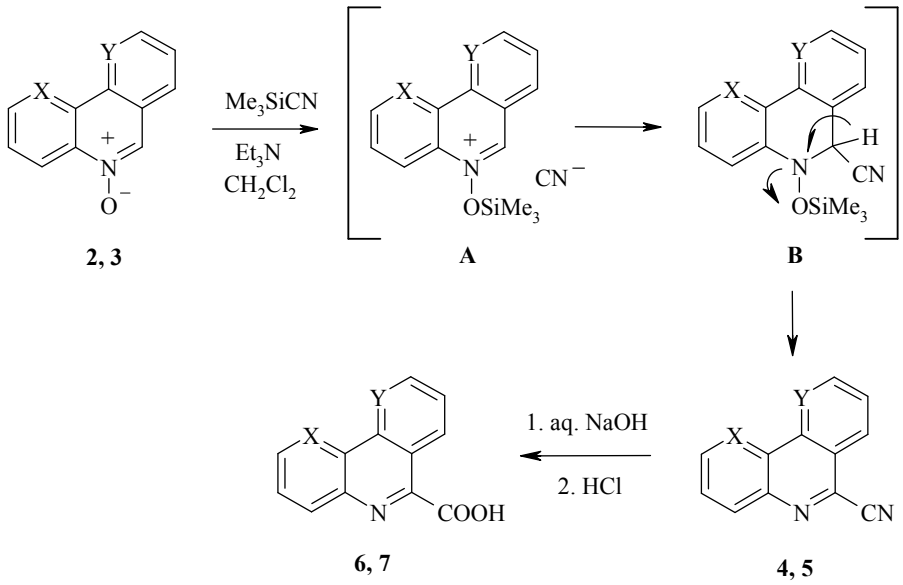
The application of benzonaphthyridine N-oxides **2** and **3** for this purpose has been only rarely described. It was found that the reactions of benzonaphthyridine N-oxides with phenyl isocyanate lead to anilinobenzonaphthyridine [5]. Moreover, it has also been reported that benzonaphthyridine N-oxides with chloromethyl-, phenyl-, and 4-tolylsulfone, chloro- and bromomethane-sulfomorpholide, and neopentyl chloromethanesulfonate undergo vicarious nucleophylic substitution of hydrogen, which offers another attractive methodology for the introduction of substituents into benzonaphthyridine rings [6, 7].

In this paper, the cyanation of benzo[*c*][1,5]- and benzo[*h*][1,6]-naphthyridines at C(6) and C(5), respectively, is reported, starting with the corresponding benzonaphthyridine 5- and -6-oxides. The resulting nitriles were then hydrolyzed to the corresponding acids.

In recent years, synthetic methods for the formation of C–C bonds using silanes have been studied extensively [8–11]. Fundamental work by Vorbrüggen on the cyanation of N-oxides of 6-membered heterocycles using Me_3SiCN has opened new perspectives for the synthesis of cyano derivatives [12].

Following the methodology for cyanation of 2-unsubstituted 1H-imidazole 3-oxides [11], the solutions of benzo[*c*][1,5]naphthyridine 5-oxide (**2**) and benzo[*h*][1,6]naphthyridine 6-oxide (**3**) in dry CH_2Cl_2 in the presence of Et_3N were treated with Me_3SiCN. The temperature of the mixture was kept at 0–5°C, and the progress of the reaction was followed by TLC. After 2 h in the case of compound **2** and 6 h in the case of compound **3**, the starting material was consumed. After chromatographic workup, benzo[*c*][1,5]naphthyridine-6-carbonitrile (**4**) and benzo[*h*][1,6]naphthyridine-5-carbonitrile (**5**) were obtained in good yields.



2, **4**, **6** X = N, Y= CH; **3**, **5**, **7** X = CH, Y = N

The reaction mechanism for the formation of compounds **4** and **5** is analogous to that proposed for the cyanation of azine N-oxides [11, 12]: silylation of the N-oxide leads to the benzonaphthyridinium ion **A** which adds a cyanide ion to give the intermediate **B** which, in turn, eliminates Me_3SiOH.

The resulting nitriles **4** and **5** were then hydrolyzed to the corresponding acids **6** and **7** by boiling with diluted sodium hydroxide and treatment of the resulting salt with diluted hydrochloric acid.

These results illustrate the interesting smooth conversion of benzo[*c*][1,5]-naphthyridine 5-oxide and benzo[*h*][1,6]naphthyridine 6-oxide into the corresponding benzonaphthyridine carbonitriles, which readily lead to benzonaphthyridine carboxylic acids. The described method is highly recommended for the preparation of benzonaphthyridine derivatives of the type **4**–**7**. For further extension of these procedures and completion of the series of compounds obtained previously in our laboratory [5–7, 13–17] the conversion of compounds **6** and **7** into functional derivatives of benzonaphthyridine carboxylic acids will be investigated.

EXPERIMENTAL

IR spectra were recorded on a Nexus Nicolet FTIR spectrometer in KBr. ^{1}H NMR spectra were recorded on a Bruker Avance III WB spectrometer at 400 MHz in $CDCl_3$, using TMS as the internal standard. Electron impact mass spectra were recorded on a AMD-604 instrument at 70 eV. Elemental analysis was performed on Perkin-Elmer 2400 CHN elemental analyzer. Melting points were determined on Boëtius apparatus.

Synthesis and properties of the N-oxides **2** and **3** have been described previously [18]. Me_3SiCN is a commercial reagent (Aldrich) distilled prior to use and stored in refrigator.

Cyanation of benzonaphthyridine N-oxides (General procedure). To the solution of compound **2** or **3** (392 mg, 2 mmol) in dry CH_2Cl_2 (10 ml) freshly activated molecular sieves (4 Å, 200 mg) were added. The mixture was stirred in a 50 ml flask closed with septum at room temperature for 1 h and then placed in a water/ice cooling bath. Subsequently, a solution of Me_3SiCN (398 mg, 0.52 ml, 4 mmol) and Et_3N (303 mg, 0.42 ml, 3 mmol) in CH_2Cl_2 (3 ml) was slowly added through the septum using a syringe. The stirring was continued for 2 h (compound **2**) or 6 h (compound **3**) at 0–5°C. Then the brown mixture was diluted with CH_2Cl_2 (20 ml) and extracted with H_2O (4 × 30 ml), the organic layer was dried ($MgSO_4$) and the solvent evaporated. The crude products were purified by column chromatography using dichloromethane as eluent, followed by recrystallization from benzene.

Benzo[*c*][1,5]naphthyridine-6-carbonitrile (4) (300 mg, 73%); mp 154–155°C. IR spectrum, ν, cm^{-1}: 2215 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.92 (1H, dd, *J* = 7.8, *J* = 1.7, H-10); 8.77–8.71 (2H, m, H-2,4); 8.51 (1H, dd, *J* = 8.4, *J* = 1.25, H-7); 7.95 (1H, dd, *J* = 8.4, *J* = 6.9, H-8); 7.85 (1H, dd, *J* = 8.3, *J* = 4.15, H-3); 7.70 (1H, dd, *J* = 7.8, *J* = 6.9, H-9). Mass spectrum, *m/z* (I_{rel}, %): 205 $[M]^+$ (100), 178 $[M–HCN]^+$ (15). Found, %: C 76.20; H 3.45; N 20.35. $C_{13}H_7N_3$. Calculated, %: C 76.09; H 3.43; N 20.47.

Benzo[*h*][1,6]naphthyridine-5-carbonitrile (5) (307 mg, 75%); mp 165–166°C (mp 163–164.5°C [19]). IR spectrum, ν, cm^{-1}: 2231 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.27 (1H, dd, *J* = 4.4, *J* = 1.8, H-2); 9.19 (1H, dd, *J* = 8.1, *J* = 1.65, H-10); 8.71 (1H, dd, *J* = 8.25, *J* = 1.8, H-4); 8.29 (1H, dd, *J* = 8.4, *J* = 1.8, H-7); 7.98–7.89 (2H, m, H-8,9); 7.79 (1H, dd, *J* = 8.25, *J* = 4.4, H-3). Mass spectrum, *m/z* (I_{rel}, %): 205 $[M]^+$ (100), 178 $[M–HCN]^+$ (12). Found, %: C 75.98; H 3.40; N 20.23. $C_{13}H_7N_3$. Calculated, %: C 76.09; H 3.43; N 20.47.

Hydrolysis of benzonaphthyridine carbonitriles (General procedure). Compound **4** or **5** (300 mg, 1.5 mmol) was stirred and heated at 100°C in aqueous sodium hydroxide (6 ml, conc. 20%) for 6 h. After cooling to room temperature, the precipitated salt was filtered off, the aqueous phase was washed with ethyl ether and then acidified with diluted hydrochloric acid (conc. HCl–water, 1:1) to pH ~4. The precipitated pale yellow crystals were separated and recrystallized from benzene.

Benzo[*c*][1,5]naphthyridine-6-carboxylic acid (6) (237 mg, 72%); mp 191–192°C. IR spectrum, ν, cm^{-1}: 3000 (O–H), 1690 (C=O), 1264 (C–O), 920 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.50 (1H, s, COOH); 9.05 (1H, dd, *J* = 4.45, *J* = 1.8, H-2); 8.60 (1H, dd, *J* = 7.9, *J* = 1.8, H-10); 8.43 (1H, dd, *J* = 8.45, *J* = 1.3, H-7); 8.30 (1H, dd, *J* = 8.35, *J* = 1.8, H-4); 7.82 (1H, dd, *J* = 8.45, *J* = 6.9, H-8); 7.72 (1H, dd, *J* = 4.45, *J* = 8.35, H-3); 7.58 (1H, dd, *J* = 7.9, *J* = 6.9, H-9). Mass spectrum, *m/z* (I_{rel}, %): 224 $[M]^+$ (100), 179 $[M–COOH]^+$ (15). Found, %: C 69.46; H 3.42; N 12.37. $C_{13}H_8N_2O_2$. Calculated, %: C 69.64; H 3.60; N 12.49.

Benzo[*h*][1,6]naphthyridine-5-carboxylic acid (7) (229 mg, 70%); mp 185–187°C. IR spectrum, ν, cm^{-1}: 2890 (O–H), 1680 (C=O), 1307, 1263 (C–O), 940 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.31 (1H, s, COOH); 9.69 (1H, dd, *J* = 8.25, *J* = 1.35, H-10); 9.12 (1H, dd, *J* = 4.75, *J* = 1.75, H-2); 8.69 (1H, dd, *J* = 8.1, *J* = 1.4,

H-7); 8.47 (1H, dd, J = 8.45, J = 1.75, H-4); 8.01 (1H, dd, J = 8.25, J = 6.9, H-9); 7.69 (1H, dd, J = 4.75, J = 8.45, H-3); 7.54 (1H, dd, J = 6.9, J = 8.1, H-8). Mass spectrum, m/z (I_{rel}, %): 224 $[M]^+$ (100), 179 $[M–COOH]^+$ (17). Found, %: C 69.37; H 3.48; N 12.35. $C_{13}H_8N_2O_2$. Calculated, %: C 69.64; H 3.60; N 12.49.

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Received December 14, *2010*