Preparation of Benzo[*c*][2,7]naphthyridines

Charles F. Nutaitis* and Stephen R. Marsh

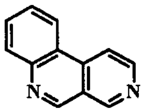
Department of Chemistry, Lafayette College,
Easton, PA 18042

Received February 17, 1992

A divergent synthesis of substituted benzo[*c*][2,7]naphthyridines **5a-h** is described, which features an intramolecular pyridyne cyclization step as the key reaction. The pyridyne precursors are conveniently prepared from the pyridinium hydrochloride **2** and the requisite anilines. Cyclization of the non-symmetric substrates **3e** and **3f** did not proceed with significant regioselectivity.

J. Heterocyclic Chem., **29**, 971 (1992).

Recently, several natural products have been isolated that contain as a subunit the benzo[*c*][2,7]naphthyridine ring system (**1**) [1]. These compounds have exhibited cytotoxic activity against L1210 and P388 murine leukemia cells, immunosupressant activity, antimicrobial activity against *E. coli* and *S. aureus*, and antifungal activity. A survey of the literature has revealed that little is known about the synthesis and chemistry of benzo[*c*][2,7]naphthyridine, the common feature of these biologically active substrates, and very few derivatives of the ring system have been previously prepared.

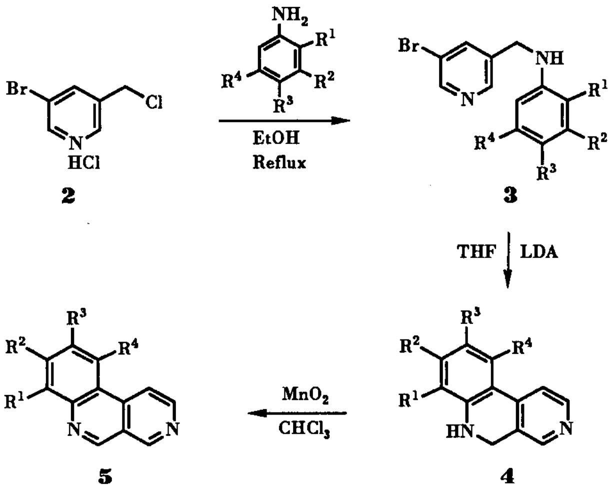


1

In 1976, Kessar and co-workers [2] reported a convenient seven step procedure for the preparation of **1**, which featured an intramolecular pyridyne cyclization as the key step. However, little experimental detail for the key reactions was provided and spectral data were not reported for the compounds. Recently, we have re-explored this procedure in order to determine optimum conditions for these reactions, and have developed several modifications/improvements for some of the more cumbersome steps. Furthermore, we have obtained the proton and carbon nmr spectral data for the final product and the intermediate compounds in the synthesis [3].

Although this sequence was reported 15 years ago, and appeared to have the potential to be a general synthesis of benzo[*c*][2,7]naphthyridines, it had been applied only to the parent compound. As compounds with this structural feature are now of biological interest, routes to a variety of analogs will undoubtedly be required. We report here the divergent synthesis of a variety of substituted benzo[*c*][2,7]naphthyridines utilizing our modified synthesis strategy (Scheme).

Scheme



a, $R^1 = R^2 = R^4 = H, R^3 = CH_3$
b, $R^1 = R^2 = R^4 = H, R^3 = OCH_3$
c, $R^1 = H, R^2 = R^3 = R^4 = OCH_3$
d, $R^1 = CH_3, R^2 = R^3 = R^4 = H$
e, $R^1 = R^3 = R^4 = H, R^3 = CH_3$
f, $R^1 = R^4 = H, R^2 = R^3 = OCH_3$
5g, $R^1 = R^2 = H, R^3 = R^4 = OCH_3$
5h, $R^1 = R^2 = R^3 = H, R^4 = CH_3$

Treatment of 5-bromo-3-chloromethylpyridinium hydrochloride (**2**), the common precursor to all of the benzo[*c*][2,7]naphthyridines prepared, with an appropriately substituted aniline afforded the cyclization precursors **3** in 48-75% yield. Cyclization of **3** with excess LDA followed by dehydrogenation with manganese dioxide gave the target naphthyridine compounds **5** in 50-69% yield for the two step conversion. We have found, by proton nmr, that the product of LDA cyclization is generally a mixture of **5** and the corresponding 5,6-dihydrobenzo[*c*][2,7]naphthyridine (**4**); separation prior to dehydrogenation is not necessary.

As expected, **3e** and **3f** afforded a mixture of regioisomers as a result of cyclization to either of the non-symmetric *ortho* carbons of the aniline ring. The dimethoxy products resulting from cyclization of **3f** were readily purified by flash chromatography and isolated in a 54/46 ratio in favor of 8,9-dimethoxybenzo[*c*][2,7]naphthyridine (**5f**). The regioisomers were readily identified by the proton nmr signals for the hydrogens in the carbocyclic ring. The protons at C-7 and C-10 of the 8,9-dimethoxy isomer appear as two singlets, while the 9,10-dimethoxy derivative exhibits two doublets for the C-7 and C-8 protons. While the regioisomers resulting from cyclization of **3e** could not be separated, the product ratio was determined by proton nmr, once again looking at the pattern for the carbocyclic hydrogens. The isomer 8-methylbenzo[*c*][2,7]naphthyridine (**5e**) featured a broad singlet for the C-7 proton while 10-methylbenzo[*c*][2,7]naphthyridine (**5h**) showed a triplet for the C-8 proton. Integration of these two signals as well as the signals for the corresponding methyl groups revealed a product ratio of 62/38 in favor of **5e**. In either instance, the major product is the one in which the substituents are directed away from the bay region of the ring system.

In summary, we have demonstrated that the method for the synthesis of benzo[*c*][2,7]naphthyridine originally reported by Kessar, and subsequently modified by us, can also be applied to the preparation of substituted benzo[*c*][2,7]naphthyridines through appropriate choice of the aniline starting material. This divergent approach makes available a variety of previously unknown benzo[*c*][2,7]naphthyridine analogs, compounds that should find wide applicability to natural products chemistry and medicinal chemistry. Studies are currently being conducted to further explore the scope and limitations of the procedure and its subsequent application to the synthesis of natural products and aza-polycyclic aromatic hydrocarbons.

EXPERIMENTAL

General Procedure for the Synthesis of 5-Bromo-3-anilinomethylpyridines **3a-f**. Synthesis of 5-Bromo-3-(2-methylanilino)methylpyridine (**3d**).

A solution of 5-bromo-3-chloromethylpyridinium hydrochloride (**2**) (0.396 g, 1.63 mmoles) and 2-methylaniline (0.90 g, 8.4 mmoles) in ethanol (15 ml) was magnetically stirred at reflux for 20 hours. The mixture was allowed to cool to 25°, then concentrated *in vacuo*. The resulting dark oil was suspended in water (50 ml) and basified to *p*H 11 with 10% aqueous sodium hydroxide. This mixture was extracted with methylene chloride (3 x 25 ml) and the combined extracts were dried with sodium sulfate, filtered, and adsorbed onto silica gel. Flash chromatography (3:1 hexane/ether) gave 5-bromo-3-(2-methylanilino)methylpyridine (**3d**, 0.340 g, 75%) as a tan solid, mp 96-98° (ether); ^{1}H nmr (deuteriochloroform): δ 8.58 (d, 1H), 8.54 (d, 1H), 7.84 (br s, 1H), 7.08 (t, 2H), 6.71 (t, 1H), 6.49 (d, 1H), 4.40 (s, 2H), 2.19 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 149.75, 147.0, 145.1, 137.5, 137.0, 130.3, 127.2, 122.2, 121.0, 117.95, 110.0, 45.2, 17.5.

Anal. Calcd. for $C_{13}H_{13}BrN_2$: C, 56.33; H, 4.73; N, 10.11; Br, 28.83. Found: C, 56.41; H, 4.73; N, 10.13; Br, 28.75.

5-Bromo-3-(4-methylanilino)methylpyridine (**3a**).

This compound was analogously prepared in 55% yield after purification by flash chromatography (3:1 hexane/ether), mp 56-58° (hexane/ether); ^{1}H nmr (deuteriochloroform): δ 8.48 (br s, 1H), 8.43 (br s, 1H), 7.76 (br s, 1H), 6.90 (d, 2H), 6.42 (d, 2H), 4.23 (s, 2H), 3.94 (br, 1H), 2.15 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 149.6, 147.0, 144.9, 137.5, 137.2, 129.8, 127.5, 120.9, 113.1, 45.5, 20.3.

Anal. Calcd. for $C_{13}H_{13}BrN_2$: C, 56.33; H, 4.73; N, 10.11; Br, 28.83. Found: C, 56.41; H, 4.74; N, 10.05; Br, 28.77.

5-Bromo-3-(4-methoxyanilino)methylpyridine (**3b**).

This compound was analogously prepared in 63% yield after purification by flash chromatography (methylene chloride), mp 64-66° (hexane/ether); ^{1}H nmr (deuteriochloroform): δ 8.57 (d, 1H), 8.52 (d, 1H), 7.85 (br s, 1H), 6.77 (d, 2H), 6.57 (d, 2H), 4.30 (s, 2H), 3.90 (br, 1H), 3.73 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 152.6, 149.65, 147.1, 141.3, 137.5, 137.2, 120.9, 114.9, 114.2, 55.7, 46.1.

Anal. Calcd. for $C_{13}H_{13}BrN_2O$: C, 53.26; H, 4.47; N, 9.55; Br, 27.26. Found: C, 53.39; H, 4.51; N, 9.49; Br, 27.34.

5-Bromo-3-(3,4,5-trimethoxyanilino)methylpyridine (**3c**).

This compound was analogously prepared in 49% yield after purification by flash chromatography (7:1 methylene chloride/ethyl acetate), oil; ^{1}H nmr (deuteriochloroform): δ 8.60 (br s, 1H), 8.55 (br s, 1H), 7.88 (br s, 1H), 5.85 (s, 2H), 4.34 (s, 2H), 4.01 (br, 1H), 3.78 (s, 6H), 3.76 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 154.0, 149.9, 147.1, 144.0, 137.6, 136.8, 130.8, 121.0, 90.7, 61.1, 55.95, 45.7.

Anal. Calcd. for $C_{15}H_{17}BrN_2O_3$: C, 51.01; H, 4.85; N, 7.93. Found: C, 51.00; H, 5.06; N, 7.79.

5-Bromo-3-(3-methylanilino)methylpyridine (**3e**).

This compound was analogously prepared in 55% yield after purification by flash chromatography (2:1 hexane/ether), mp 36-38° (hexane/ether); ^{1}H nmr (deuteriochloroform): δ 8.55 (d, 1H), 8.50 (d, 1H), 7.82 (br t, 1H), 7.05 (t, 1H), 6.57 (d, 1H), 6.42-6.38 (m, 2H), 4.30 (d, 2H), 4.12 (br, 1H), 2.25 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 149.6, 147.2, 146.9, 139.1, 137.4, 137.1, 129.2, 120.9, 119.1, 113.6, 109.9, 45.1, 21.5.

Anal. Calcd. for $C_{13}H_{13}BrN_2$: C, 56.33; H, 4.73; N, 10.11; Br, 28.83. Found: C, 56.05; H, 4.69; N, 10.09; Br, 29.05.

5-Bromo-3-(3,4-dimethoxyanilino)methylpyridine (**3f**).

This compound was analogously prepared in 48% yield after purification by flash chromatography (12:1 methylene chloride/ethyl acetate), mp 86-88° (ether/methylene chloride); ^{1}H nmr (deuteriochloroform): δ 8.58 (br s, 1H), 8.53 (br s, 1H), 7.87 (br s, 1H), 6.72 (d, 1H), 6.26 (d, 1H), 6.11 (dd, 1H), 4.31 (s, 2H), 3.93 (br, 1H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 150.0, 149.7, 147.05, 142.1, 142.0, 137.6, 137.1, 120.9, 113.0, 103.6, 99.2, 56.55, 55.7, 46.0.

Anal. Calcd. for $C_{14}H_{15}BrN_2O_2$: C, 52.03; H, 4.68; N, 8.67; Br, 24.73. Found: C, 52.10; H, 4.69; N, 8.61; Br, 24.74.

General Pyridyne Cyclization Procedure for the Preparation of Substituted Benzo[*c*][2,7]naphthyridines **5a-h**. Synthesis of 7-Methylbenzo[*c*][2,7]naphthyridine (**5d**).

To a magnetically stirred solution of 5-bromo-3-(2-methylanilino)methylpyridine (**3d**) (0.210 g, 0.758 mmole) in dry THF (10 ml) at −78° under a nitrogen atmosphere was added *via* syringe LDA (2 *M*, 1.5 ml, 3 mmoles) over 3 minutes. The resulting solution was allowed to warm to 25° and stirred at 25° for 20 hours. The dark mixture was diluted with saturated aqueous sodium chloride (25 ml) and extracted with methylene chloride (3 x 50 ml). The combined extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to a dark oil. The oil was dissolved in chloroform (10 ml), manganese dioxide (0.34 g, 3.9 mmoles) was added, and the resulting suspension was magnetically stirred at 25° under a nitrogen atmosphere for 24 hours. The reaction mixture was adsorbed directly onto silica gel, and flash chromatography (ether) gave 7-methylbenzo[*c*][2,7]naphthyridine (**5d**, 0.080 g, 53%) as a light tan solid; mp 179-181° (hexane/methylene chloride); ^{1}H nmr (deuteriochloroform): δ 9.43 (s, 1H), 9.42 (s, 1H), 8.93 (d, 1H), 8.42 (d, 1H), 8.37 (d, 1H), 7.74 (d, 1H), 7.63 (t, 1H), 2.90 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 152.2, 150.6, 148.65, 144.4, 138.2, 137.5, 131.65, 127.3, 121.8, 121.0, 120.5, 115.4, 18.5.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.21; H, 5.25; N, 14.33.

9-Methylbenzo[*c*][2,7]naphthyridine (**5a**).

This compound was analogously prepared in 56% yield after purification by flash chromatography (ether), mp 187-189° (hexane/methylene chloride); ^{1}H nmr (deuteriochloroform): δ 9.37 (s, 1H), 9.31 (s, 1H), 8.90 (d, 1H), 8.30 (d, 1H), 8.29 (br s, 1H), 8.11 (d, 1H), 7.68 (dd, 1H), 2.64 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 152.1, 151.1, 148.7, 144.0, 137.8, 136.9, 132.6, 130.0, 122.2, 121.8, 121.3, 115.2, 21.8.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.13; H, 5.22; N, 14.39.

9-Methoxybenzo[*c*][2,7]naphthyridine (**5b**).

This compound was analogously prepared in 69% yield after purification by flash chromatography (ether), mp 144-146°; ^{1}H nmr (deuteriochloroform): δ 9.41 (s, 1H), 9.27 (s, 1H), 8.93 (d, 1H), 8.30 (d, 1H), 8.16 (d, 1H), 7.85 (d, 1H), 7.50 (dd, 1H), 4.04 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 158.9, 152.3, 149.5, 148.5, 141.1, 136.7, 131.8, 121.4, 120.9, 115.3, 103.3, 55.75.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.22. Found: C, 74.19; H, 4.96; N, 13.37.

8,9,10-Trimethoxybenzo[*c*][2,7]naphthyridine (**5c**).

This compound was analogously prepared in 57% yield after purification by flash chromatography (ethyl acetate), mp 121-122° (hexane/ether); ^{1}H nmr (deuteriochloroform): δ 9.35 (s, 1H), 9.26 (s, 1H), 9.04 (d, 1H), 8.87 (d, 1H), 7.52 (s, 1H), 4.11 (s, 3H), 4.07 (s, 3H), 4.05 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 155.7, 152.1, 152.0, 151.8, 149.0, 143.9, 142.8, 136.5, 120.95, 118.9, 110.8, 107.1, 61.2, 60.55, 56.1.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.67; H, 5.20; N, 10.41.

8-Methylbenzo[*c*][2,7]naphthyridine (**5e**) and 10-Methylbenzo[*c*][2,7]naphthyridine (**5h**).

These compounds were analogously prepared as an inseparable mixture in 50% yield after purification by flash chromatography (ether): ^{1}H nmr (deuteriochloroform): δ 9.43 (s), 9.39 (s), 9.37 (s), 8.93 (m), 8.65 (d), 8.44 (d), 8.32 (d), 8.15 (br d), 8.03 (br s), 7.76 (t), 7.58 (br d), 3.14 (s), 2.64 (s); ^{13}C nmr (deuteriochloroform): δ 152.5, 152.23, 152.17, 152.15, 148.9, 148.7, 147.4, 145.95, 141.6, 138.3, 136.7, 131.7, 130.0, 129.9, 129.5, 129.4, 122.6, 119.7, 119.4, 115.15, 26.1, 21.8.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.11; H, 5.25; N, 14.28.

8,9-Dimethoxybenzo[*c*][2,7]naphthyridine (**5f**) and 9,10-Dimethoxybenzo[*c*][2,7]naphthyridine (**5g**).

These compounds were analogously prepared in 37% and 31% yield, respectively after separation by flash chromatography (ethyl acetate). Compound **5f** was an oil; ^{1}H nmr (deuteriochloroform): δ 9.36 (s, 1H), 9.25 (s, 1H), 8.85 (d, 1H), 8.18 (d, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 4.12 (s, 3H), 4.09 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 152.5, 152.4, 150.0, 149.9, 148.0, 142.3, 136.3, 120.7, 116.1, 114.7, 110.1, 101.8, 56.2, 56.1.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.93; H, 5.12; N, 11.79.

Compound **5g** was an oil; ^{1}H nmr (deuteriochloroform): δ 9.36 (s, 1H), 9.20 (s, 1H), 9.17 (d, 1H), 8.92 (d, 1H), 8.02 (d, 1H), 7.56 (d, 1H), 4.07 (s, 3H), 4.05 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 151.85, 151.55, 150.5, 149.25, 146.65, 141.3, 136.5, 126.5, 121.75, 120.0, 116.8, 116.25, 60.05, 56.5.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.04; H, 5.07; N, 11.52.

Acknowledgement.

These studies were supported by the Committee on Advanced Study and Research of Lafayette College.

REFERENCES AND NOTES

[1a] F. S. de Guzman and F. J. Schmitz, *Tetrahedron Letters*, **30**, 1069 (1989); [b] J. Kobayashi, J. Cheng, H. Nakamura, Y. Ohizumi, Y. Hirata, T. Sasaki, T. Ohta and S. Nozoe, *Tetrahedron Letters*, **29**, 1177 (1988); [c] F. J. Schmitz, S. K. Agarwal, S. P. Gunasekera, P. G. Schmidt and J. N. Shoolery, *J. Am. Chem. Soc.*, **105**, 4835 (1983); [d] J. Kobayashi, J. Cheng, M. R. Walchli, H. Nakamura, Y. Hirata, T. Sasaki, Y. Ohizumi, *J. Org. Chem.*, **53**, 1800 (1988); [e] G. A. Charyulu, T. C. McKee and C. M. Ireland, *Tetrahedron Letters*, **30**, 4201 (1989); [f] A. Rudi, Y. Benayahu, I. Goldbergt and Y. Kashman, *Tetrahedron Leters*, **29**, 6655 (1988); [g] A. R. Carroll, N. M. Cooray, A. Poiner and P. J. Scheuer, *J. Org. Chem.*, **54**, 4231 (1989); [h] N. M. Cooray, P. J. Scheuer, L. Parkanyi and J. Clardy, *J. Org. Chem.*, **53**, 4619 (1988); [i] G. P. Gunawardana, S. Kohmoto and N. S. Burres, *Tetrahedron Letters*, **30**, 4359 (1989); [j] G. P. Gunawardana, S. Kohmoto, S. P. Gunasekera, O. J. McConnell and F. E. Koehn, *J. Am. Chem. Soc.*, **110**, 4856 (1988); [k] T. F. Molinski and C. M. Ireland, *J. Org. Chem.*, **54**, 4256 (1989).

[2] S. V. Kessar, Y. P. Gupta, P. S. Pahwa and P. Singh, *Tetrahedron Letters*, 3207 (1976).

[3] C. F. Nutaitis and M. W. Ledeboer, *Org. Prep. Proc. Int.*, in press.