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A new synthetic approach to 7-hydroxynitidine

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ABSTRACT

Benzo[*c*]phenanthridine alkaloid, 7-hydroxynitidine, was synthesized from readily available 2-benzyloxy-6-bromo-3,4-dimethoxybenzaldehyde **5** and napthylamine **6** using reductive amination followed by radical cyclization in eight steps. This method is highly efficient and better way to synthesize fully aromatized benzo[*c*]phenanthridine compounds.

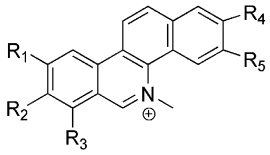
Benzo[*c*]phenanthridines are naturally occurring isoquinoline alkaloids with various biological activities.[1–3] Sanguinarine **1a** shows antibacterial[4] and antifungal[5] activities, while nitidine **1b** and fagaronine **1d** have been investigated as potential anti-tumor and antiviral agents.[6] Hence, more attention has been given to the development of a facile synthetic methodology of benzo[*c*]phenanthridines.[7–9] 7-Hydroxynitidine **1c** (see Fig. 1), a modified benzo[*c*]phenanthridine alkaloid, was shown to have strong cytotoxic activity against HeLa S3 cells.[10] The presence of the 7-hydroxy group enhances anti-tumor activity.

Nakanishi and Suzuki[10] attempted, unsuccessfully, to synthesize 6-bromo derivative, **5**, in various ways in order to make the synthesis of 7-hydroxynitidine easier. This Letter describes a simple and efficient synthetic way to synthesize the title compound (Scheme 1). NK109 was synthesized using the same strategy.[11]

The 2-(benzyloxy)-6-bromo-3,4-dimethoxybenzaldehyde **5**, required for the synthesis of 7-hydroxynitidine was obtained from the commercially available 5-bromo-2,3-dimethoxy benzaldehyde **2** in three steps and 41% yield as described in Scheme 2. Thus, aldehyde **2** undergoes Baeyer–Villiger oxidation by the treatment with performic acid and the resulting formate ester was hydrolyzed with aqueous KOH to give the corresponding phenol **3**.

Ortho formylation[12] of the latter to **4** followed by O-protection with benzyl bromide afforded aldehyde **5**. The aldehyde **5** and napthylamine **6**, which was synthesized from 2,3-dihydroxynapthalene,[13] were condensed in toluene to obtain the Schiff base simply by using microwave irradiation at 140 °C. The imine was reduced with dimethylamine borane[14] to obtain **7** (Scheme 3).

This reaction by using microwave irradiation gave a better yield[15] in shorter time with higher purity when compared to the classical reaction under reflux conditions (3 days, 25% yield). The subsequent radical cyclization using 2,2′-azobis(2-methylbutyronitrile) (AMBN) and tributyltin hydride gave **8**.[11] This radical cyclization led to good purity and fairly high yield[16] (55%) compared to the reported cyclization reaction through a benzyne intermediate which gave rise to many unknown side products and a very low yield[10] (5–10%). Compound **7** was purified by using Biotage SP4 purification system[17] followed by recrystallization from ethanol.



1a Sanguinarine : R_1 = H; R_2=R_3=R_4=R_5= -O-CH_2-O-
1b Nitidine : R_1 = R_2 = -OCH_3; R_3 = H; R_4=R_5= -O-CH_2-O-
1c 7- Hydroxynitidine : R_1 = R_2= -OCH_3; R_3 = -OH; R_4=R_5= -O-CH_2-O-
1d Fagaronine : R_1= R_2 = -OCH_3; R_3 =H; R_4 = -OH; R_5 = -OCH_3
1e NK109 : R_1=H; R_2= -OCH_3; R_3= -OH; R_4=R_5= -OCH_2O-

Figure 1. Structures of benzo[*c*]phenanthridine alkaloids.

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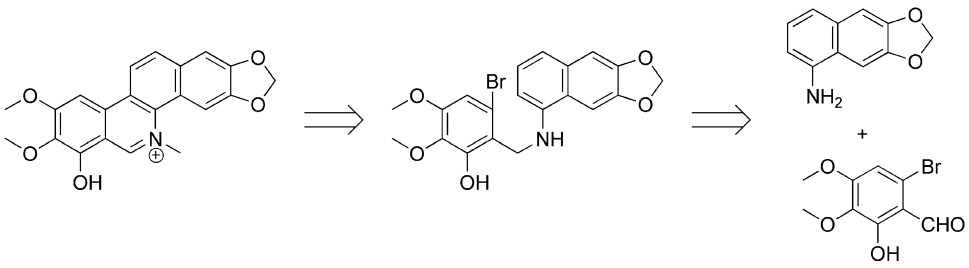
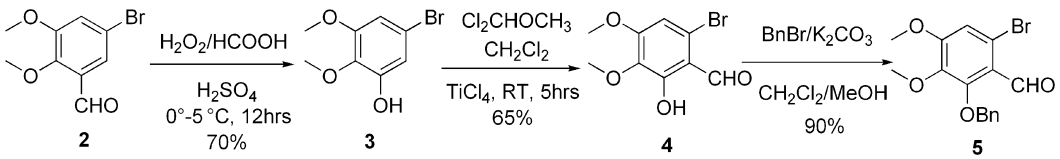
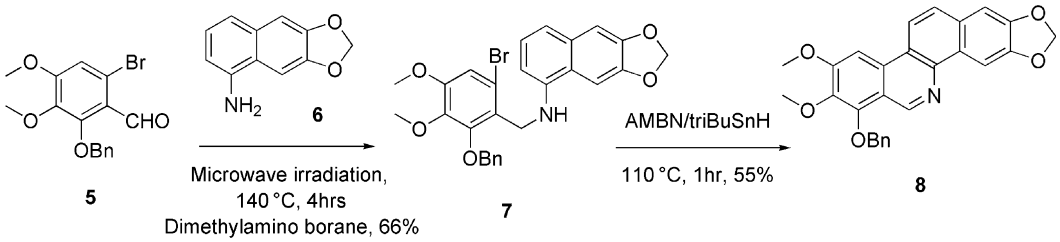


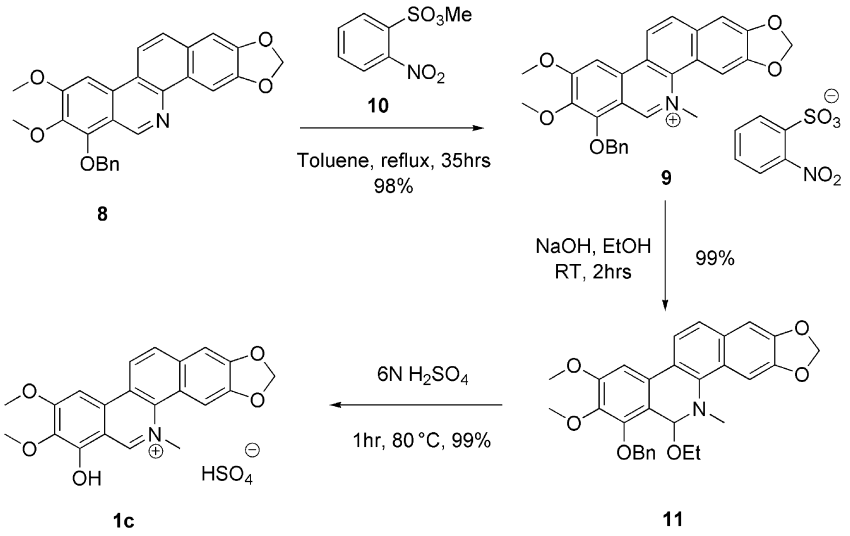
Scheme 1. Reterosynthesis of 7-hydroxynitidine.



Scheme 2. Synthesis of 6-bromoaldehyde unit.



Scheme 3. Microwave irradiation and radical cyclization to obtain cyclized product **8**.



Scheme 4. Synthesis of 7-hydroxynitidine.

With methyl *o*-nitrobenzenesulfonate **10**,[18] compound **8** was successfully methylated to benzo[*c*]phenanthridinium **9** (Scheme 4). Reagent **10** was easily prepared from *o*-nitrobenzenesulfonyl chloride and sodium methoxide in methanol. Since the resulting benzo[*c*]phenanthridinium *o*-nitrobenzensulfonate **9** is barely soluble in toluene, it was gradually precipitated and centrifuged after completion of the reaction.

Compound **9** was neutralized with sodium hydroxide in ethanol to remove the acid residue and gave the pseudobase **11**.[19] The deprotection of benzyl group of compound **11** was carried out by using 6 N H_2SO_4 at 80 °C to obtain 7-hydroxynitidine **1c** as hydrogen sulfate salt.

In summary, this synthetic pathway emphasizes the use of microwave irradiation for the formation of Schiff base and the radical cyclization for the easy synthesis of 7-hydroxynitidine. Thus, we have synthesized the benzo[*c*]phenanthridine alkaloid, 7-hydroxynitidine, in eight steps with an overall yield of 14.3%. This radical cyclization method is an efficient procedure for the

formation of benzo[*c*]phenanthridine framework and provides a facile access in multi-gram scale.

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References and notes

1. Simanek, V. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 26, pp 185–240.
2. Mackay, S. P. et al. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1997; Vol. 67, pp 345–389.
3. Ishikawa, T.; Ishii, H. *Heterocycles* **1999**, *50*, 627–639.
4. Hwang, J. K.; Baek, N. I.; Park, J. H. *Int. J. Antimicrob. Agents* **2004**, *23*, 377–381.
5. Eun, J. P.; Koh, G. Y. *Biochem. Biophys. Res. Commun.* **2004**, *317*, 618–624.
6. Li, D.; Zhao, B.; Sim, S. P.; Li, T. K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 521–528.
7. Le, T. N.; Gang, S. G.; Cho, W.-J. *Tetrahedron Lett.* **2004**, *45*, 2763–2766.
8. Geen, G. R.; Mann, I. S.; Mullane, M. V. *Tetrahedron* **1998**, *54*, 9875–9894.
9. Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768–2772.
10. Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1*, 985–988.
11. Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235–4239.
12. Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* **1963**, *96*, 308–313.
13. (a) Stermitz, F. R.; Gillespie, J. P.; Amoros, L. G.; Romero, R.; Stermitz, T. A. *J. Med. Chem.* **1975**, *18*, 708–713; (b) Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett.* **1976**, *41*, 3361–3364.
14. Billman, J. H.; McDowell, J. W. *J. Org. Chem.* **1961**, *26*, 1437–1440.
15. Compounds **5** (500 mg, 1.42 mmol) and **6** (399 mg, 2.14 mmol) were dissolved in toluene and subjected to microwave irradiation for 4 h at 140 °C. After the amination was over, the solution was transferred to a single neck flask, dimethylamine borane (102 mg) and acetic acid (1 mL) were added at 20 °C slowly. The reaction was stirred at room temperature for 1 h. The reaction mixture was quenched with 1 N HCl and stirred for 30 min and neutralized with 5 N NaOH. The organic layer was separated and aqueous phase was reextracted with toluene (2×50 mL). The organic layers were combined, washed with water, dried (Na_2SO_4) and concentrated in vacuum. The crude product was purified by using Biotage SP4 purification system[17] followed by recrystallization from ethanol to give **7** (590 mg, 66%) as a white solid. Mp: 136–138 °C. ^{1}H NMR ($CDCl_3$) δ: 3.91 (s, 3H), 3.93 (s, 3H), 4.46 (s, 2H), 5.13 (s, 2H), 6.01 (s, 2H), 6.78 (d, 1H), 6.9 (s, 1H), 7.1 (d, 1H), 7.2 (d, 2H), 7.29–7.38 (m, 5H), 7.383–7.88, (m, 2H); MS (*m*/*z*) 522(M^+), 524 (M^+ (Br isotope)).
16. A solution of **7** (406 mg, 0.78 mmol) in toluene (87 mL) was heated to 110 °C. A solution of Bu_3SnH (0.840 mL, 3.1 mmol) and AMBN (600 mg, 3.1 mmol) in toluene (87 ml) was added to the reaction mixture. After 1 h, the mixture was cooled to room temperature, MnO_2 (0.5 g, 5.5 mmol) was added, and the resulting solution was stirred for 1 h. After oxidation was complete, the reaction mixture was filtered through a thin Celite bed and the filtrate was concentrated in vacuum to obtain thick oil. The product **8** (190 mg, 55.6%) was obtained as a colourless solid by precipitation using diethyl ether at 10–15 °C. Mp: 174–175 °C. ^{1}H NMR (DMSO-d_6) δ: 4.0 (s, 3H), 4.1 (s, 3H), 5.3 (s, 2H), 6.1 (s, 2H), 7.2 (s, 1H), 7.28–7.4 (m, 2H), 7.40–7.44 (m, 2H), 7.6 (m, 1H), 7.7 (m, 1H), 8.24 (d, 1H), 8.7 (s, 1H), 9.6 (s, 1H). MS *m*/*z* 440 (M+1).
17. http://www.biotage.com/DynPage.aspx?id=22017.
18. Kiprianov, A. I.; Tolmachev, A. I. *Zh. Obshch. Khim.* **1959**, *29*, 2868–2874; *Chem. Abstr.* **1960**, *54*, 12126.
19. (a) Simanek, V.; Preininger, V. *Heterocycles* **1977**, *6*, 475–497; (b) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1–82.