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A facile synthesis of benzo[*c*]phenanthridine alkaloids: oxynitidine and oxysanguinarine using lithiated toluamide–benzonitrile cycloaddition

Thanh Nguyen Le, Seong Gyoung Gang and Won-Jea Cho*

College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Yong-Bong dong, Buk-gu, Kwangju 500-757, South Korea

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Abstract—Benzo[*c*]phenanthridine alkaloids oxynitidine and oxysanguinarine were synthesized from easily available starting benzonitrile **5** and toluamide **6** using toluamide–benzonitrile cycloaddition reaction in six steps. This method is so highly efficient that it could be a more useful way for preparing fully aromatized benzo[*c*]phenanthridine compounds.

Benzo[*c*]phenanthridine alkaloids, including nitidine and sanguinarine, have been attractive to synthetic organic chemists and biochemists over the last two decades since such compounds have shown interesting biological properties.[1–4] To date, previously reported benzophenanthridine synthetic studies have involved multi-step sequences as well as having a lack of generality for synthesizing substituted target compounds.[5,6] Not only for studying the structure–activity relationships of these molecules, but also for the total synthesis of alkaloids facile syntheses of these compounds are needed (Fig. 1).

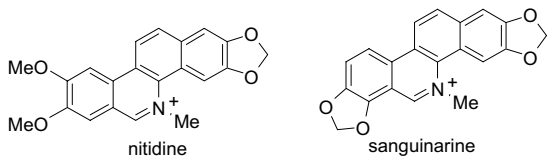

Figure 1. Structure of nitidine and sanguinarine.

We recently reported the synthesis of 3-arylisoquinoline derivatives including biological evaluation.[7] The synthetic strategy involved in the cycloaddition reaction of *N*-methyl-*o*-toluamide with benzonitrile to afford 3-arylisoquinolines.[8,9] We believe that the above 3-arylisoquinoline synthetic approach could be applied to the total synthesis of benzo[*c*]phenanthridine alkaloids. Our strategy is based on the formation of 3-arylisoquinoline, which could be transformed to benzo[*c*]phenanthridine alkaloids via intramolecular enamide ring formation reactions. The advantages of this methodology include easy access to the starting materials and a one pot procedure for constructing all carbon atoms for alkaloids. Similar methodologies such as imine–toluamide condensation,[10,11] cyclization of phenyl ethyl isocyanate,[12] homophthalic ester[13]—and homophthalic anhydride[14]—imine condensation have also been reported. However, limited application to diverse substituted pattern on aromatic rings of benzo[*c*]phenanthridine is a barrier for broadening the utility of this method. Retrosynthetic consideration of benzo[*c*]phenanthridine indicates that the coupling of benzonitrile with *o*-toluamide might afford 3-arylisoquinoline, which could be converted to an aldehyde. The C ring of benzo[*c*]phenanthridine could be constructed by an intramolecular ring cyclization method as outlined in Scheme 1.

The starting bromide **1** was treated with CuCN in DMF[15] to give benzonitrile **2** in 66% yield. The acetal group of **2** was removed by 5% HCl to afford aldehyde

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* Corresponding author. Tel.: +82-62-530-2933; fax: +82-62-530-2911; e-mail: wjcho@jnu.ac.kr

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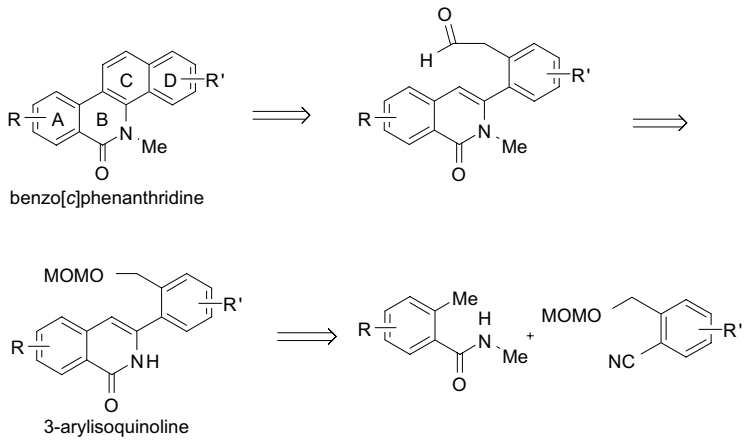
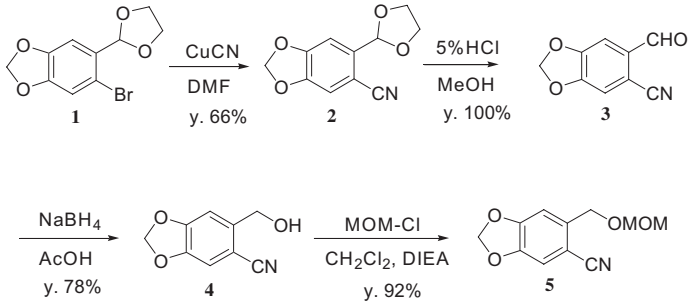


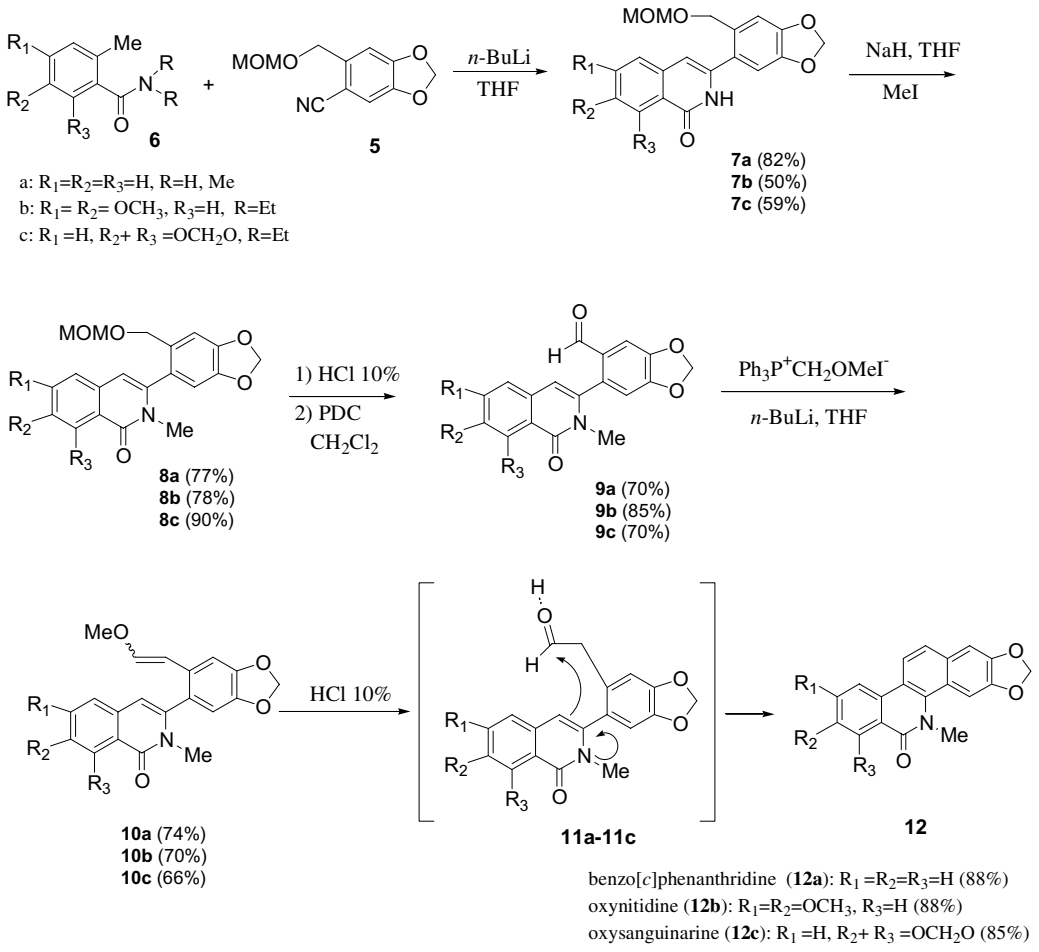
Scheme 1. Retrosythesis of benzo[*c*]phenanthridines.



Scheme 2. Synthesis of benzonitrile **5**.

3, which was then reduced with $NaBH_4$ followed by MOM protection to provide the desired benzonitrile **5** in good yield as shown in Scheme 2. When benzyl or *p*-methoxybenzyl was introduced on to the hydroxyl group, the desired coupling reaction did not occur. Toluamides **6a**–**c**[16] were synthesized from the corresponding substituted benzoic acids by treatment of oxalyl chloride followed by methylamine or diethylamine in good yield. In a model study, unsubstituted starting material, *N*-methyl-*o*-toluamide **6a** was used for cycloaddition. The deprotonation of **6a** with 2 equiv *n*-BuLi gave dianion, which was treated with MOM protected benzonitrile **5** to afford the 3-arylisoquinoline-1(2*H*)-one **7a** in 82% yield. Compound **7a** was then reacted with MeI in the presence of 60% NaH to give N-methylated compounds **8a** without giving an O-methylated one. Deprotection of **8a** with 10% HCl followed by oxidation with PDC to afford aldehyde **9a**, which were then treated with Ph_3PCH_2OMe/*n*-BuLi to give the olefins **10a** as an *E*/*Z* (1:1.5) mixture. Hydrolysis of **10a** with 10% HCl produced the desired benzo[*c*]phenanthridine compound **12a** in 88% yield. In this reaction we assumed that hydrolysis produced the aldehyde **11a** and the consecutive intramolecular enamide–aldehyde cyclization occurred under an acidic condition as shown in Scheme 3.[17] After ring formation, dehydration would easily occur thus producing a fully aromatized ring system of benzo[*c*]phenanthridine. For the preparation of oxynitidine **12b**, the readily available *N*-methyl toluamide was condensed with **5** as before. However, the desired cycloaddition product **7b** was not obtained due to it having a weak solubility in organic solvents (DMSO, THF, dioxane, etc.,). Therefore, we modified the *N*-methyl toluamides to *N*,*N*-diethyl toluamides **6b**, **c**, which are soluble in THF and as expected, the cycloaddition reaction proceeded to furnish the desired products **7b**,**c**. The consecutive N-methylation, deprotection with 10% HCl, oxidation with PDC and Wittig reaction followed by hydrolysis afforded the desired natural benzo[*c*]phenanthridine alkaloids[18]; oxynitidine **12b** and oxysanguinarine **12c** in a 20.5% and 20.7% overall yield, respectively. Herein, we have also accomplished the formal synthesis of nitidine and sanguinarine because the process to these alkaloids from the corresponding oxynitidine and oxysanguinarine were already established.[5]

Thus we have synthesized the benzo[*c*]phenanthridine alkaloids in six steps from benzonitrile **5** and toluamide **6**. This cycloaddition method could be added an advanced alternative procedure for a construction of benzo[*c*]phenanthridine framework and provide the facile access to diverse analogues of it in multi-gram scale, which are necessary to study structure–activity relationships for the development of new chemotherapeutic agents.



Scheme 3. Synthesis of benzo[*c*]phenanthridine alkaloids.

Acknowledgements

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18. All synthesized compounds were fully characterized by spectroscopy. Selected data for key compounds: Compound **7b**; mp: 151.0–154.2 °C. IR (cm^{-1}): 3400 (NH), 1657 (CO). ^1H NMR (300 MHz, $CDCl_3$): δ: 9.62 (s, 1H), 7.78 (s, 1H), 6.97 (s, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 6.44 (s, 1H), 6.06 (s, 2H), 4.80 (s, 2H), 4.46 (s, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.44 (s, 3H). EIMS m/z (%) 399 (M^+, 17), 354 (20), 336 (100). Compound **7c**; mp: 151–153 °C. IR (cm^{-1}): 3400 (NH), 1665 (CO) ^1H NMR (300 MHz, $CDCl_3$) δ: 9.38 (s, 1 H), 7.18 (d, $J = 8.2$ Hz, 1H), 7.04 (d, $J = 8.2$ Hz, 1H), 6.94 (s, 1H), 6.93 (s, 1H), 6.39 (s, 1H), 6.04 (s, 2H), 4.77 (s, 2H), 4.45 (s, 2H), 3.51 (s, 3H). EIMS m/z (%) 383 (M, 17), 338 (20), 320 (100), 292 (27). Compound **12b** (oxynitidine); mp: 284–285 °C (lit.[10] mp: 280–283 °C, lit.[19] mp: 284–285 °C). IR (cm^{-1}): 1642 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, $J = 9.0$ Hz, 1H), 7.91 (s, 1H), 7.63 (s, 1H), 7.58 (s, 1H), 7.57 (d, $J = 8.8$ Hz, 1H), 7.17 (s, 1H), 6.10 (s, 2H), 4.10 (s, 3H), 4.04 (s, 3H), 3.97 (s, 3H). EIMS m/z (%) 363 (M^+, 100). Compound **12c** (oxysanguinarine); mp: 360–362 °C (lit.[20] mp: 366–368 °C). IR (cm^{-1}): 1652 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, $J = 8.6$ Hz, 1H), 7.18 (d, $J = 9.6$ Hz, 1H), 7.53 (s, 1H), 7.52 (d, $J = 8.6$ Hz, 1H), 7.18 (d, $J = 9.6$ Hz, 1H), 7.16 (s, 1H), 6.20 (s, 2H), 6.09 (s, 2H), 3.90 (s, 3H). EIMS m/z (%) 347 (M^+, 100).
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