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A concise synthesis of nornitidine via nickel- or palladium-catalyzed annulation

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Abstract—A concise method to synthesize benzo[*c*]phenanthridine alkaloid, nornitidine, was developed utilizing nickel- or palladium-catalyzed iminoannulation of an internal alkyne. The advantages of this strategy included readily available starting materials, inexpensive reagents, short reaction steps, and good yields.

1. Introduction

The fully aromatized benzo[*c*]phenanthridine alkaloids, such as nitidine and fagaronine (Fig. 1), are an important group of naturally occurring alkaloids with a broad range of pharmacological activities, including anti-tumor and anti-viral activities.[1] Nitidine and other benzo[*c*]phenanthridine alkaloid analogues exhibit potent anti-tumor activity by the inhibition of DNA topoisomerase I,[2] and are considered as potential anti-tumor drugs. However, these compounds can only be isolated in very small amounts. For example, nitidine could be isolated in a yield of 0.003–0.07% from *Zanthoxylum* and *Fagara* varieties.[3] For these reasons, synthetic chemists have devoted enormous efforts to establish concise and versatile methods for the preparation of benzo[*c*]phenanthridine alkaloids and their analogues.[4] Many of the previously reported benzophenanthridine synthetic processes have shown some disadvantages such as numerous steps, low yields or poor generality. Thus, a convenient synthesis is needed for the synthesis of these compounds as well as their analogues. In this paper we report a concise synthesis of nornitidine, which is a synthetic precursor to nitidine.[5]

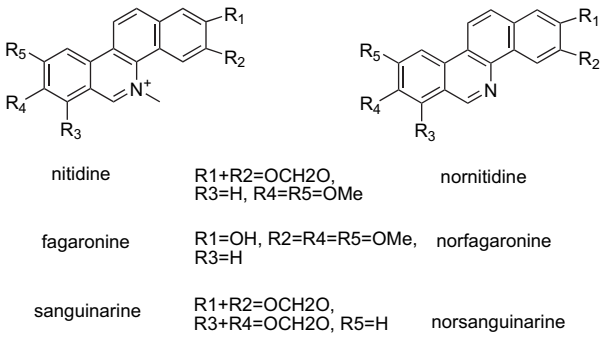
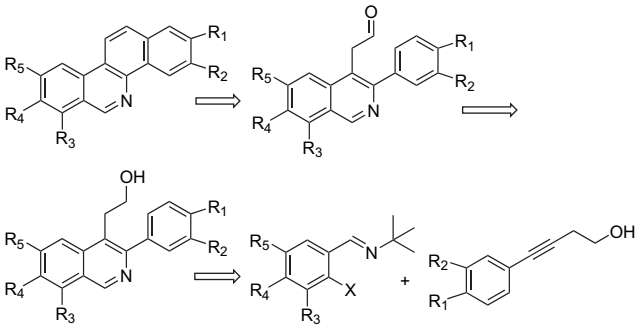


Figure 1. Structures of some benzo[*c*]phenanthridine alkaloids.

Retrosynthetic analysis indicated that the application of Larock's[6] or Cheng's[7] methodology could afford isoquinolines, which could be further transformed to benzo[*c*]phenanthridine alkaloids (Scheme 1). In this paper we report a new synthetic approach to nornitidine by nickel- and palladium-catalyzed annulation reactions. The advantages of our method include easy access to starting materials, short reaction steps, good yields and one-step reaction to construct all carbon atoms of the alkaloid.



Scheme 1. Retrosynthesis of benzo[*c*]phenanthridine alkaloids.

Keywords: Benzo[*c*]phenanthridine; Isoquinolines; Nitidine; Palladium; Nickel; Catalysis.
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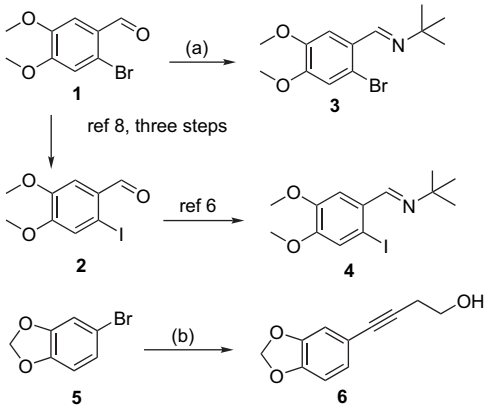
2. Results and discussion

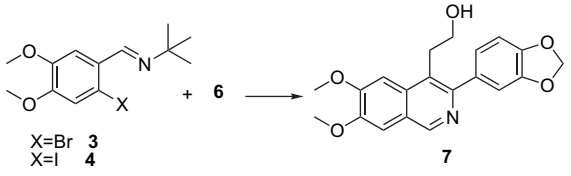
First, 2-bromobenzaldimine **3**, 2-iodobenzaldimine **4**, and alkyne **6** were prepared as outlined in Scheme 2. 2-Bromobenzaldimine **3** was prepared in a 96% yield, by treatment of the aldehyde **1** with *tert*-butylamine.[6] 2-Iodobenzaldimine **4** was synthesized from the aldehyde **2**,[6] which was prepared from **1** in three steps.[8] The internal alkyne **6** was prepared via Sonogashira reaction[9] from the commercially available bromide **5** in 80% yield.



Scheme 2. Reagents and conditions: (a) *tert*-butylamine, 96%; (b) $Pd(PPh_3)_2Cl_2$, CuI, 3-butyn-1-ol, DIPA, 80%.

Then, the annulation of 2-bromobenzaldimine **3** and 2-iodobenzaldimine **4** with the alkyne **6** was investigated (Table 1). We first chose $Pd(OAc)_2$ as the catalyst[6] and bromide **3** and iodide **4** as the substrates to synthesize iosquinoline **7**. Bromide **3** did not react with alkyne **6** (entry 1), while iodide **4** reacted with alkyne **6** to give compound **7** in a poor yield (entry 2). Optimization of this reaction, using a variety of ligands such as PPh_3, tri-*o*-tolylphosphin, *rac*-BINAP, did not improve the yield. Cyclization of bromide **3** and alkyne **6** by $NiBr_2$(dppe)/Zn[7] afforded isoquinoline **7** in a good yield, while annulation of iodide **4** and alkyne **6** gave a moderate yield. Since bromide **1** was more conveniently available than iodide **2** (Scheme 2), synthesis of isoquinoline **7** from 2-bromobenzaldimine **3** appeared to be more appealing both synthetically and economically. The NOESY spectrum of compound **7**, shown in Figure 2, indicated the correlation between H_1 and H_2. Therefore, H_3 could be assigned, which

Table 1. Catalytic annulation of bromide **3** and iodide **4** with alkyne **6**



Entry	Imine	Method[a]	Yield[b] (%)
1[b]	**3**	$Pd(OAc)_2$	—
2	**4**	$Pd(OAc)_2$	38
3	**3**	$NiBr_2$(dppe)/Zn	73
4	**4**	$NiBr_2$(dppe)/Zn	58

[a] Isolated yields.
[b] No reaction occurred.

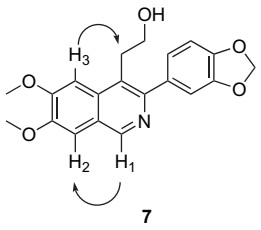
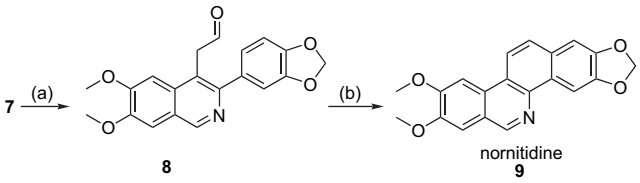


Figure 2. NOESY spectrum of isoquinoline **7**.

showed the correlation with the methylene. As expected, the regioselectivity of the annulation reaction was correct.

Subsequently, oxidation of **7** was investigated. While oxidation of compound **7** with PCC or Dess–Martin reagent gave a low yield, Swern oxidation[10] of isoquinoline **7** proceeded smoothly to afford aldehyde **8**, which was then cyclized under acidic conditions[11] to afford nornitidine **9** in a good yield, as illustrated in Scheme 3.



Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, 77%; (b) AcOH, 40% HBr, 78%.

3. Conclusion

We have developed a concise synthetic method to prepare nornitidine via nickel- or palladium-catalyzed annulation in three linear steps in a good yield, using readily available starting materials and inexpensive reagents. This efficient process should allow for easy synthesis of a variety of benzo[*c*]phenanthridine alkaloids and their analogues.

4. Experimental

4.1. General

^1H, ^{13}C NMR, and NOESY spectra were recorded on Bruker DRX-500. Chemical shifts (δ, ppm) were reported for signal center, and coupling constant *J* was reported in units of hertz. High-resolution mass spectra were recorded on Finnigan MAT-95 mass spectrometer. Elemental analyses were performed on Elementar Vario EL *III*. Column chromatography was performed on 200–300 mesh silica gel. All reagents were used directly as obtained commercially, unless otherwise noted.

4.1.1. *N*-(2-Bromo-4,5-dimethoxybenzylidene)-*tert*-butylamine (3). A mixture of 2-bromo-4,5-dimethoxybenzaldehyde **1** (4.00 g, 16.3 mmol) and *tert*-butylamine (25 mL) was stirred under a nitrogen atmosphere at room temperature for 20 h. The excessive *tert*-butylamine was removed under reduced pressure, and the resulting mixture was dissolved in dichloromethane, dried (Na_2SO_4), and filtered. Removal of

the solvent afforded 4.7 g of imine **3** as a pale yellow solid (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.33 (s, 9H), 3.92 (s, 3H), 3.97 (s, 3H), 7.02 (s, 1H), 7.60 (s, 1H), 8.54 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=29.5, 55.6, 55.8, 57.2, 109.6, 114.5, 116.2, 127.6, 148.3, 150.9, 153.7. MS (EI): *m*/*z*=299, 301.

4.1.2. 4-(3,4-Methylenedioxyphenyl)-3-butyn-1-ol (6). A mixture of $Pd(PPh_3)_2Cl_2$ (0.71 g, 1.00 mmol), CuI (0.19 g, 1.00 mmol), bromide **5** (6.8 g, 33.8 mmol), and 3-butyn-1-ol (2.6 g, 37.2 mmol) in degassed DIPA (20 mL) was refluxed for 4 h under nitrogen atmosphere. After cooling, the reaction mixture was filtered, and the filtrate was concentrated to give a residue, which was purified by silica gel chromatography (ethyl acetate/petroleum ether = 3:1) to afford 5.1 g of compound **6** (80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.66 (t, *J*=6.3 Hz, 2H), 3.79 (t, *J*=6.3 Hz, 2H), 5.96 (s, 2H), 6.73 (d, *J*=7.8 Hz, 1H), 6.86 (d, *J*=1.5 Hz, 1H), 6.93 (dd, *J*=1.5 Hz, *J*=7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=23.3, 60.6, 81.5, 84.7, 100.9, 107.9, 111.3, 116.4, 125.7, 146.9, 147.1. MS (EI): *m*/*z*=190. HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}O_3$ [M^+]: 190.0630; found: 190.0632.

4.1.3. 6,7-Dimethoxy-4-(2-hydroxy-ethyl)-3-(3,4-methylenedioxyphenyl)-isoquinoline (7).

4.1.3.1. Palladium-catalyzed annulation. To a mixture of dry DMF (34 mL), $Pd(OAc)_2$ (100 mg, 0.44 mmol), Na_2CO_3 (980 mg, 9.2 mmol), and alkyne **6** (2.6 g, 13.6 mmol) under nitrogen atmosphere was added imine **4** (3.2 g, 9.2 mmol). The contents were heated in an oil bath at 100 °C for 8 h. The reaction mixture was cooled, diluted with chloroform (90 mL), which was washed with water (400 mL). The organic layer was concentrated and the residue was purified by silica gel chromatography (acetone/dichloromethane = 1:4) to afford 1.2 g of pure compound **7** (38% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.32 (t, *J*=7 Hz, 2H), 3.86 (t, *J*=7 Hz, 2H), 4.05 (s, 3H), 4.07 (s, 3H), 6.01 (s, 2H), 6.89 (d, *J*=8 Hz, 1H), 6.96 (dd, *J*=8 Hz, *J*=1.2 Hz, 1H), 6.99 (d, *J*=1.2 Hz, 1H), 7.23 (s, 1H), 7.37 (s, 1H), 8.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=32.1, 56.0, 56.1, 62.4, 101.0, 102.3, 105.8, 108.0, 110.0, 122.9, 123.8, 123.9, 132.4, 135.2, 147.0, 147.4, 147.7, 149.9, 151.4, 153.3. MS (EI): *m*/*z*=353. HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}NO_5$ [M^+]: 353.1263; found: 353.1276. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.51; H, 5.72; N, 4.04.

4.1.3.2. Nickel-catalyzed annulation. A flask containing $NiBr_2$(dppe) (62 mg, 0.1 mmol), zinc powder (260 mg, 4.0 mmol), and 2-bromobenzaldimine **3** (0.60 g, 2.0 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled acetonitrile containing alkyne **6** (0.50 g, 2.6 mmol) was added to the system and the reaction mixture was stirred at reflux for 2 h. The reaction mixture was cooled, filtered, and evaporated to give a residue, which was purified by silica gel chromatography (acetone/dichloromethane = 1:4) to afford 0.51 g of pure compound **7** (73% yield). When 2-iodobenzaldimine **4** was used in place of bromide **3**, 0.40 g of compound **7** was obtained (58% yield).

4.1.4. 6,7-Dimethoxy-4-(2-oxo-ethyl)-3-(3,4-methylenedioxyphenyl)-isoquinoline (8). To a cooled (−60 °C) solution of oxalyl chloride (0.21 mL, 2.2 mmol) in 7.0 mL of CH_2Cl_2 was added dropwise a solution of DMSO (0.32 mL, 4.4 mmol) in 3 mL of CH_2Cl_2, and the mixture was stirred for 15 min. Then a solution of compound **7** (0.40 g, 1.1 mmol) in 30 mL of CH_2Cl_2 was added dropwise, and the stirring was continued for 30 min. Then DIPEA (2.8 mL, 17 mmol) was added slowly. After stirring for 15 min, the mixture was allowed to reach room temperature, and quenched with water (25 mL). The organic phase was separated, dried (Na_2SO_4), and evaporated to afford a residue, which was purified by silica gel chromatography (acetone/chloroform = 1:15) to give 0.31 g of pure **8** (77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.02 (s, 3H), 4.05 (s, 3H), 4.12 (s, 2H), 6.02 (s, 2H), 6.82–6.87 (m, 2H), 6.92–6.93 (m, 2H), 7.28 (s, 1H), 9.07 (s, 1H), 9.78 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=45.0, 56.0, 101.1, 101.8, 106.0, 108.1, 110.0, 117.9, 123.1, 123.7, 132.5, 134.7, 147.4, 147.7, 149.0, 150.2, 152.4, 153.7, 199.0. MS (EI): *m*/*z*=351. HRMS (EI): *m*/*z* calcd for $C_{20}H_{17}O_5$ [M^+]: 351.1107; found: 351.1201.

4.1.5. Nornitidine (9). To a mixture of aldehyde **8** (0.13 g, 0.37 mmol) and acetic acid (3.0 mL), was added 40% hydrobromic acid (1.0 mL), and stirred at room temperature for 30 min. To the mixture was added 10% NaOH solution (30 mL), and it was extracted with CH_2Cl_2 (80 mL). The organic phase was dried and evaporated to give a residue, which was purified by silica gel chromatography (acetone/chloroform = 1:100) to give 96 mg of nornitidine (78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.10 (s, 3H), 4.17 (s, 3H), 6.13 (s, 2H), 7.28 (s, 1H), 7.41 (s, 1H), 7.84 (d, *J*=9 Hz, 1H), 7.91 (s, 1H), 8.30 (d, *J*=9 Hz, 1H), 8.73 (s, 1H), 9.26 (s, 1H). MS (EI): *m*/*z*=333. HRMS (EI): *m*/*z* calcd for $C_{20}H_{15}NO_4$ [M^+]: 333.1001; found: 333.1010.

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