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New synthesis of linear furoquinoline alkaloids

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Abstract—A new synthetic method for the synthesis of the linear furoquinoline alkaloids, dictamnine, γ-fagarine, evolitrine and pteliene from 3-oxiranylquinoline using dimethylsulfonium methylide is described.

1. Introduction

The furoquinoline alkaloids of dictamnine type (**1**–**4**) are derivatives of the furo[2,3-*b*] quinoline system, which occurs widely in Rutaceae plant species.[1] These compounds have several pharmacological properties such as antimicrobial,[2] antiviral,[3] mutagenic[4] and cytotoxic[5] activities. Several methods have been reported for the synthesis of furoquinoline alkaloids (Fig. 1).[6–16]

A common feature of the reported syntheses of the furoquinoline alkaloids is that the quinoline ring is built along with an appropriate carbon chain at the 3-position, which is then modified into the furan ring. This is necessary because incorporation of a carbon chain later at the 3-position of the quinoline ring through an electrophilic aromatic substitution is difficult. For example, it has been reported that introduction of a formyl group at the 3-position of 2,4-dimethoxyquinolines by a Vilsmeier–Haack reaction gave a complex reaction mixture. Narasimhan and co-workers[14b,17,18] overcame this problem by introducing a formyl group at the 3-position using an aromatic lithiation reaction. 3-Formylquinolines can be converted into 3-quinolinylacetaldehydes by reaction with Wittig ylides. These 3-quinolinylacetaldehydes were then cyclized if an oxygen substituent was present at the C-2 position of the quinoline ring, to furoquinoline alkaloids by reaction with polyphosphoric acid. Herein we report an improved synthetic methodology for the construction of furoquinoline alkaloids from 3-formylquinolines in good yields requiring fewer steps than those reported earlier.

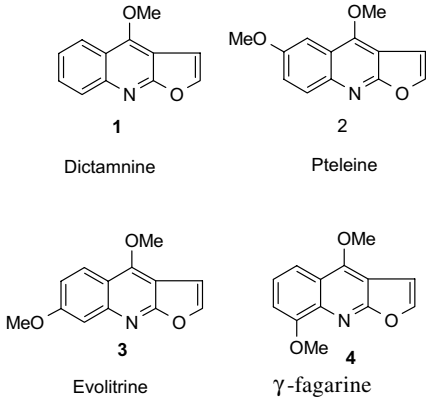

Figure 1. Structures of furoquinoline alkaloids.

In our strategy, 3-formylquinolines were synthesized from 2,4-dimethoxy quinolines (**5a**–**d**). The second step was conversion of the 3-formylquinolines into the corresponding 3-oxiranylquinolines, and finally inducing acid catalyzed intramolecular cyclization to yield the desired furoquinoline alkaloids. We synthesized the 3-formylquinolines by reaction between 2,4-dimethoxyquinolines and *n*-butyllithium and then dimethylformamide. This gave the corresponding 3-formylquinolines (**6a**–**d**) in good yields (48–60%). The 3-formylquinolines were treated with dimethylsulfonium methylide[19] to afford the corresponding 3-oxiranylquinolines. This reaction gave various products depending on the substituents on the aromatic ring. For example, **6a** gave both 3-oxiranylquinoline **7a** and dictamnine **1**, which were separated, in 34% and 10% yields, respectively, by column

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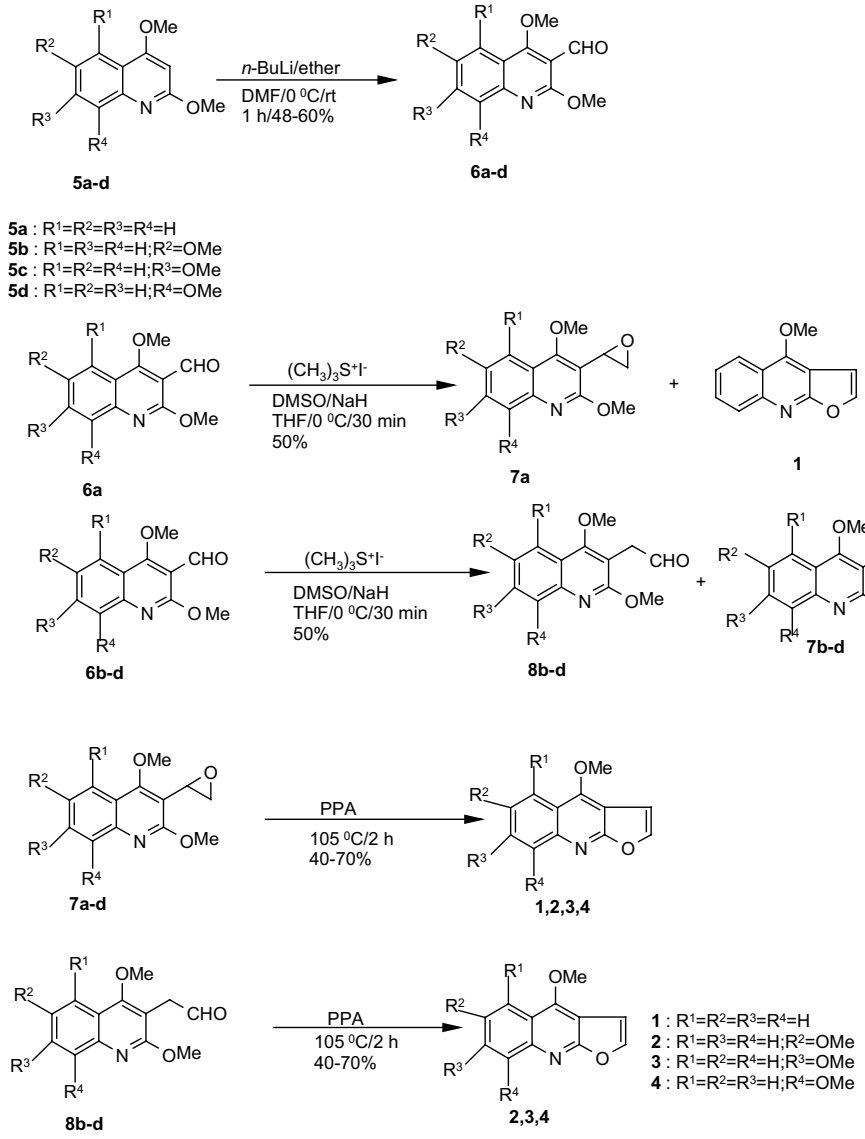

Scheme 1. Synthesis of furoquinoline alkaloids.

chromatography. Complete conversion of the oxiranylquinoline to dictamnine did not occur (Scheme 1).

The reaction of 3-formylquinolines (**6b**–**d**) with the sulfonium ylide gave 3-oxiranylquinolines (**7b**–**d**) and quinolinylacetaldehydes (**8b**–**d**) in 43–55% and 42–57% yields, respectively. This suggests that the 3-oxiranylquinoline undergoes a 1,2-hydride shift to give 3-quinolinylacetaldehydes. However, the mechanism is not well understood. Finally, the 3-oxiranylquinolines and the 3-quinolinylacetaldehydes were separately cyclized in polyphosphoric acid (PPA) to obtain the corresponding furoquinolines in 30–80% yields.

The synthesis of 3-formylquinolines is well known.[14b]

2. Typical reaction: 2,4-dimethoxy-3-oxiranylquinoline 7a

To a well-stirred solution of trimethylsulfonium iodide (4.5 g, 22 mmol), NaH (528 mg, 22 mmol) and DMSO (15 mL) in dry THF (15 mL) was added **6a** (3.1 g, 15 mmol) at 0 °C and the reaction mixture was allowed to stir for 25 min at rt with monitoring by TLC. After the reaction was complete the reaction mixture was poured in ice-cold water (250 mL) and extracted with chloroform (5 × 10 mL). The combined extracts were washed with water and sodium thiosulfate solution and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was purified by chromatography over silica gel using benzene as eluent to afford firstly the 3-oxiranylderivative **7a** as solid (1 g, 34%), mp 95 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (m, 1H), 2.90 (m, 1H), 3.95 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 5.05 (m, 1H), 7.32 (m, 1H), 7.38 (m, 1H), 7.56 (m, 1H), 7.74 (m, 1H).

Further elution with benzene gave dictamnine **1** (310 mg, 10%), which was identical with an authentic sample. Mp130 °C (lit. mp 131 °C),[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28 (s, 3H), 6.95 (d, J = 2.7 Hz, 1H), 7.39 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.53 (d, J = 2.7 Hz,

1H), 7.64 (ddd, $J = 8.3$, 6.8, 1.7 Hz, 1H), 8.00 (dd, $J = 8.6$, 1.5 Hz, 1H), 8.19 (dd, $J = 8.3$, 1.7 Hz, 1H).

3. 2,4,6-Trimethoxyquinolinyl-3-acetaldehyde 8b

Yield 42%, mp 111 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61 (d, $J = 3$ Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 7.12 (d, $J = 1.5$ Hz, 1H), 7.18 (dd, $J = 8$, 1.5 Hz, 1H), 7.48 (d, $J = 8$ Hz, 1H), 9.72 (t, $J = 3$ Hz, 1H, CHO).

4. Furoquinoline alkaloids

3-Oxiranylquinolines (**7a–d)** and quinolinylacetaldehydes (**8b–d**) (1.3 mmol) were separately heated with polyphosphoric acid at 125–130 °C for 2 h. The reaction mixture was poured onto crushed ice (10 g), neutralized with aqueous sodium bicarbonate and extracted with ether (5×10 mL). The combined organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent furnished a residue, which was purified by chromatography over silica gel using benzene as eluent to afford furoquinoline alkaloids.[21,22] Dictamnine **1** was obtained in 70% yield using the above procedure.

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