Synthesis of 3-Methoxyolivacine and Olivacine by Friedel–Crafts Reaction of Indole-2,3-dicarboxylic Anhydride with 2,4,6-Trimethoxypyridine

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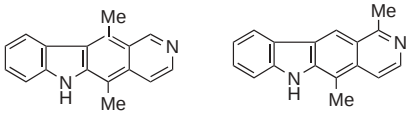
Abstract: 1-Benzylindole-2,3-dicarboxylic anhydride (**1**) was reacted with 2,4,6-trimethoxypyridine in the presence of titanium(IV) chloride to give 3-(2,4,6-trimethoxynicotinoyl)indole-2-carboxylic acid (**2**) as the sole product in high yield, which could be converted to olivacine.

Keywords: indole, Friedel–Crafts reaction, Heck reaction, demethylation, olivacine

Olivacine is a member of the pyrido[4,3-*b*]carbazole alkaloid family and possesses potent antitumor activity.[1] Pyrido[4,3-*b*]carbazole alkaloids, ellipticine[2] and olivacine (Figure 1), are intercalating compounds and have high DNA binding ability, which is responsible in part for their pharmacological properties.[3] Many methods to synthesize olivacine have been developed including cyclization of substituted carbazole derivatives,[4] intramolecular cyclization of indole 2,3-quinodimethane[5] or pyridine 3,4-quinodimethane,[6] and intermolecular cyclization of pyridine 3,4-quinodimethane.[7] Gribble reported an excellent synthetic method of olivacine by the reaction of 2-lithioindole and pyridine-3,4-dicarboxylic anhydride.[8] Recently, some synthesized olivacine derivatives also have been found to have high antitumor activity.[9]

We showed a novel synthesis of ellipticine by a reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**) with 3-bromo-4-lithiopyridine, but an application of this method to the synthesis of olivacine by this method is difficult because introduction of the 1-methyl group of olivacine is not easy.[10]



ellipticine olivacine

Figure 1

Recently, we have reported that reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**) with anisoles gave 3-benzoylindole-2-carboxylic acids, but 1-benzenesulfonylindole-2,3-dicarboxylic anhydride with anisoles afforded 2-benzoylindole-3-carboxylic acids as the sole product, respectively.[11] In this paper we report a simple and useful synthesis of 3-methoxyolivacine and olivacine by regioselective Friedel–Crafts reaction of **1** with 2,4,6-trimethoxypyridine.

1-Benzylindole-2,3-dicarboxylic anhydride (**1**)[12,15] reacted with 2,4,6-trimethoxypyridine (2 equiv) in the presence of titanium(IV) chloride (3 equiv) in dichloromethane to provide the corresponding 3-acylindole-2-carboxylic acid (**2**) in 97% yield, which was converted to ketone **3** by treatment with copper chromite in quinoline (180 °C) in 94% yield. The mixture of **3** with 47% hydrobromic acid in acetic acid was warmed at 50 °C to provide **4** in 94% yield as the sole product. Treatment of 1-hydroxy compound **4** with triflic anhydride (Tf_2O) in the presence of triethylamine gave triflate **5** (Scheme 1).

The triflate **5** could be converted to methyl derivative **6** by reaction with MeMgBr[13] in the presence of $NiCl_2$ (dppe)$_2$ in 79% yield. Selective demethylation of the 4-methoxy group of **6** by treatment with boron tribromide was performed to provide 4-hydroxy compound **7** in 99% yield, which was changed by diborane reduction, followed by treatment with Tf_2O in the presence of triethylamine to benzyl derivative **8**. Benzyl derivative **8** was reacted with (1-ethoxyvinyl)tributyltin in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] in refluxing toluene, then 10% hydrochloric acid in tetrahydrofuran to give 6-benzyl-3-methoxyolivacine (**9**) in 84% yield (Scheme 2).

Debenzylation of **9** was performed by treatment with 47% hydrobromic acid at 80 °C to provide 3-methoxyolivacine (**10**), which was treated with hot 47% hydrobromic acid in acetic acid gave 3-hydroxyolivacine (**11**) in 92% yield. Hydrogenation of the triflate, which was prepared by treatment with Tf_2O and triethylamine (50%), with ammonium formate in the presence of $Pd(PPh_3)_4$ in hot methanol afforded olivacine[14] in 67% yield (Scheme 3).

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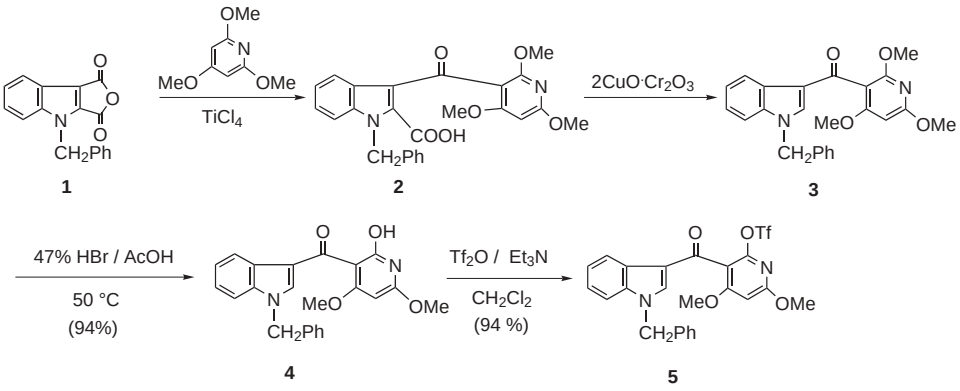
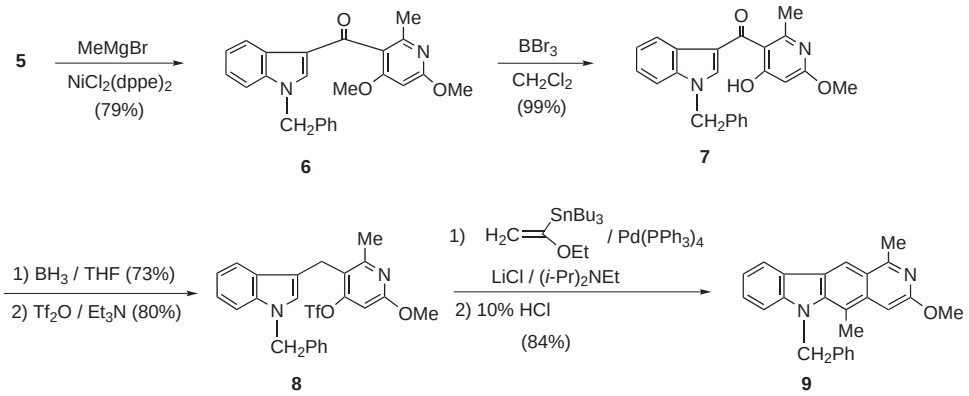
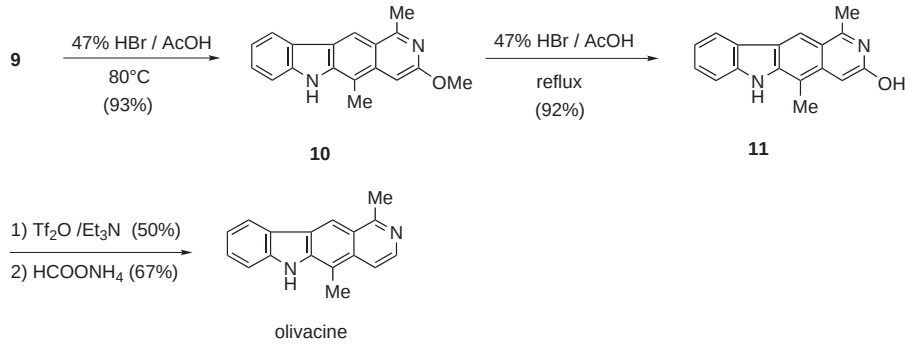


Scheme 1



Scheme 2



Scheme 3

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(14) Olivacine: mp >300 °C (MeOH) (lit.[5n] 318–326 °C). IR (nujol): ν = 3267 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ = 158.0, 142.7, 144.2, 133.9, 132.8, 128.2, 126.0, 122.4, 121.6, 121.0, 119.7, 116.6, 116.2, 111.9, 111.2, 20.8, 12.3. ^1H NMR (270 MHz, $CDCl_3$): δ = 2.82 (3 H, s, 5-CH_3), 3.03 (3 H, s, 1-CH_3), 7.21–7.26 (1 H, m, aromatic proton), 7.47–7.55 (2 H, m, aromatic protons), 7.79 (1 H, d, *J* = 6.0 Hz, H-4), 8.25 (1 H, d, *J* = 6.0 Hz, H-3), 8.35 (1 H, d, *J* = 7.5 Hz, H-10), 8.89 (1 H, s, H-11), 11.20 (1 H, br s, NH). HRMS: *m/z* [M^+] calcd for $C_{17}H_{14}N_2$: 246.1157. Found: 246.1138.
(15) **Reaction of Anhydride (1) with 2,4,6-Trimethoxypyridine: 1-Benzyl-3-(2,4,6-trimethoxynicotinoyl)-indole-2-carboxylic Acid (2).**
To a solution of 1-benzylindole-2,3-dicarboxylic anhydride (**1**, 1.90 g, 7 mmol) and 2,4,6-trimethoxypyridine (2.40 g, 14 mmol) in CH_2Cl_2 (28 mL) was added titanium(IV) chloride (21 mL of a 1 M CH_2Cl_2 solution, 21 mmol) and the mixture was stirred for 18 h at r.t. To this reaction mixture H_2O was added and then the mixture was extracted with CH_2Cl_2. The combined extracts were washed with H_2O and dried over Na_2SO_4, then concentrated under reduced pressure to give a solid, which was purified by column chromatography (*n*-hexane–EtOAc) to afford 1-benzyl-3-(2,4,6-trimethoxynicotinoyl) indole-2-carboxylic acid (**2**, 3.02 g, 97%).
Analytical data of compound **2**: mp 170–172 °C (*n*-hexane–EtOAc). IR (nujol): 1722, 1593 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.65 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 4.01 (3 H, s, OCH_3), 6.02 (1 H, s, H-5′), 6.09 (2 H, s, CH_2Ph), 7.08–7.34 (8 H, m, aromatics), 7.46 (1 H, d, *J* = 8.0 Hz, H-4). Anal. Calcd for $C_{25}H_{22}N_2O_6$: C, 67.26; H, 4.95; N, 6.27. Found: C, 67.19; H, 5.01; N, 6.34.