International Journal of Engineering Science Invention (IJESI)
ISSN (Online): 2319-6734, ISSN (Print): 2319-6726
www.ijesi.org ||Volume 09 Issue 5 Series III || May 2020 || PP 30-31

A Novel Route for Synthesis of (±) Discretine

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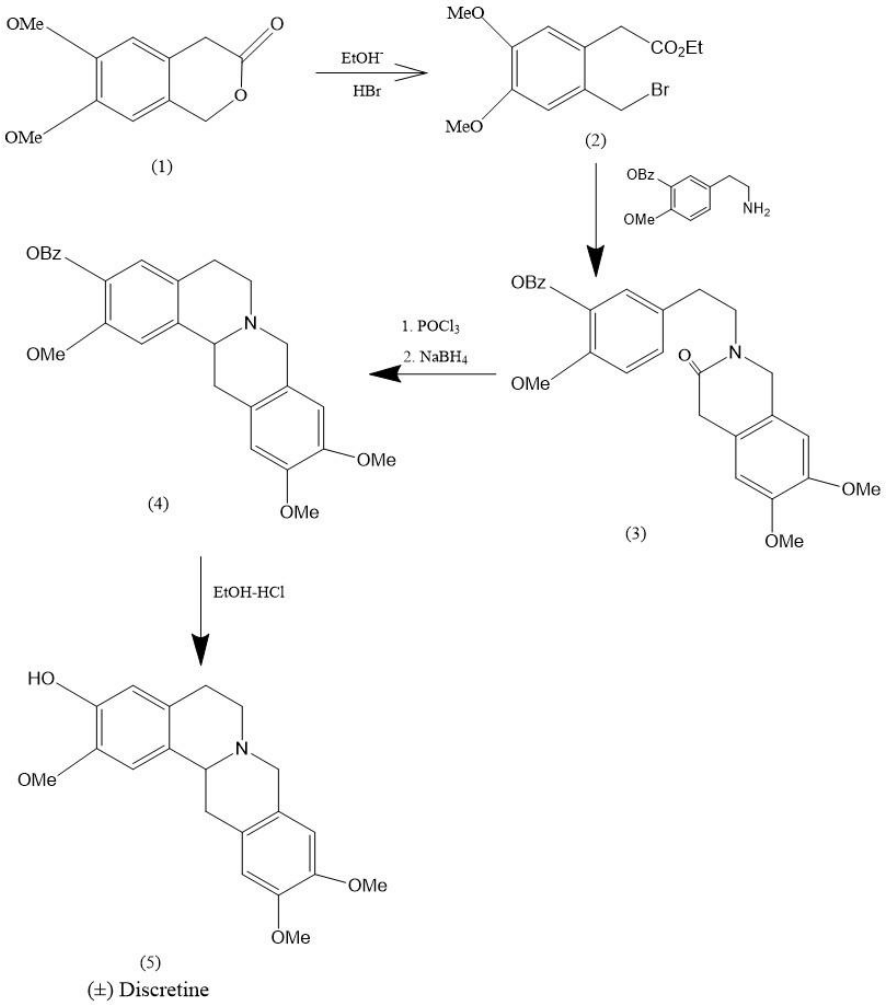
ABSTRACT
A new convenient total synthesis of (±) Discretine is achieved. Condensation of bromoester with substituted phenyl ethyl amine gave the lactam which on phosphoryl chloride cyclization followed by Sodium Borohydride reduction gave O-benzyl discretine. Debenzylation of O-benzyl discretine by reflux with Ethanol-HCl mixture gave (±) Discretine.
KEYWORDS: *(±)Discretine, Bromoester,Phosphoryl Chloride.*

The structure of (±) Discretine , a phenolic berbine alkaloid, was established on the basis of the Permanganate oxidation of O-ethyl discretine[1,2]. It was further confirmed by an unambiguous synthesis. Kametani et al[3] reported a nine step route for the synthesis of (±) Discretine(5) starting from 3-benzoyloxy-4-methoxy-β-phenethylamine. R.S. Mali and co-workers[4] reported synthesis of (±) Discretine via the formation of hydroxyl amide.

Here a new synthesis of (±) Discretine is reported. Bromoester is prepared starting from the easily accessible 6,7,-dimethoxy-3- isochromanone[5]. The bromoester on condensation with the 3-benzyloxy-4-methoxy-β-phenylethylamine gave the lactam, which on phosphoryl chloride cyclization followed by Sodium borohydride reduction gave O-benzyl Discretine. O-benzyl Discretine on debenzylation gave (±) Discretine.



I. EXPERIMENTAL

I. **Synthesis of Ethyl-2-bromomethyl-4,5-dimethoxy phenyl acetate(2):**
The lactone(1) (6.3g) was added to a stirred solution of hydrogen bromide (300mL) in absolute ethanol (300mL) at 5^0C. The solid formed gets dissolved as the stirring was continued and the mixture was allowed to reach room temperature. After 24h at room temperature, the excess reagent and solvent were distilled at 5mm and 20^0C to leave an oil(2) (7.65g; 86%)
IR(max) 1707cm^{-1}
(Found C: 49.1; H: 5.45; Br: 25.28; $C_{13}H_{17}O_4Br$ requires C: 49.2; H: 5.36; Br: 25.2%)

II. **Synthesis of 2(3'-benzyloxy-4'-methoxy-β-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro 3 (2H) isoquinolone(3):**
The bromoester(2) (4.0g) dissolved in dioxan (25mL) containing potassium carbonate (1g) and potassium iodide (0.5g) was condensed with the amine (2.65g) dissolved in dioxan (30mL), by refluxing at 100^0C for 74h. The mixture was cooled and solvent distilled in vacuo. The residue left was diluted with water and mixture extracted with chloroform. The chloroform extract was washed with 3N hydrochloric acid, with water and dried (Na_2SO_4). Removal of the solvent left a gummy syrup(3) which could not be crystallised.
IR (CHCl3): 1640 (six membered lactam), 1600, 1460 cm^{-1}
(Found: C: 71.73; H: 6.68; O: 17.72; $C_{27}H_{29}NO_5$ requires C: 72.48; H: 6.4; O: 17.89%)

III. **Synthesis of 3-benzyloxy-2,10,11-trimethoxy berbine(4):**
Freshly distilled phosphoryl chloride (4mL) was added to a solution of lactam(3) (2.5g) in xylene (10mL). The mixture was refluxed for 1.5h. The residue left after evaporation of the excess reagent and solvent was treated with cold water and solution extracted with chloroform. Removal of solvent in vacuo gave a residue which was dissolved in methanol (20mL) and treated with Sodium borohydride (1.75g) and mixture refluxed for 1h. Evaporation of the solvent, dilution with water, extraction with ether, followed by removal of ether gave a residue which was recrystallised from chloroform, Pet. Ether to give O-benzyl discretine(4) (1.82g; 75.51%) m.p. 154^0C.
IR(nujol): 1610, 2740, 2770 cm^{-1}
NMR($CDCl_3$):δ 2.4-3.75 (m, 9H, methylene and methine protons and C_8-H), 3.88, 3.9, 3.91 (S, 3H each, 3xOMe), 5.16 (S, 2H, Ph-CH_2-O-), 6.58-6.80 (m, 4H, Ar-H) 7.25-7.55 (bs, 5H, -Ph)
MS m/e: 431 (M^+)
(Found: C: 74.6; H: 7.0; $C_{27}H_{29}NO_4$ requires C: 75.2; H: 6.7%)

IV. **Synthesis of 3-hydroxy-2,10,11-trimethoxy berbine; (±) Discretine(5):**
O-Benzyldiscretine(4) (1.5g) was dissolved in ethnol (6mL) and conc. HCl (15mL) was added to it and refluxed for 4h. The reaction mixture was neutralised with saturated sodium bicarbonate followed by extraction with ether (2x30mL). The organic extract was dried (Na_2SO_4) and evaporated to give a solid which was recrystallised from methanol to give (±) Discretine. m.p. 181^0C.
IR($CHCl_3$)- 2750, 2840, 2920, 3550 cm^{-1}
NMR($CDCl_3$-$DMSOd_6$): δ 2.4-3.8 (m, 9H, methylene and methine protons and C_8-H) 3.83, 3.84, 3.87 (s, 3H each, 3X-OMe) 6.4-6.9 (m, 4H, Ar-H)
MS m/e: 341 (M^+); 164
(Found: C: 66.2; H: 6.8; $C_{20}H_{23}NO_4.H_2O$ requires C: 66.8; H: 7.0%)

ACKNOWLEDGEMENT-The author is extremely thankful to Prof. K.P.Tiwari, Department of Chemistry, University of Allahabad for his valuable guidance.

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