

A NOVEL ROUTE FOR SYNTHESIS OF CORYPALLINE

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ABSTRACT

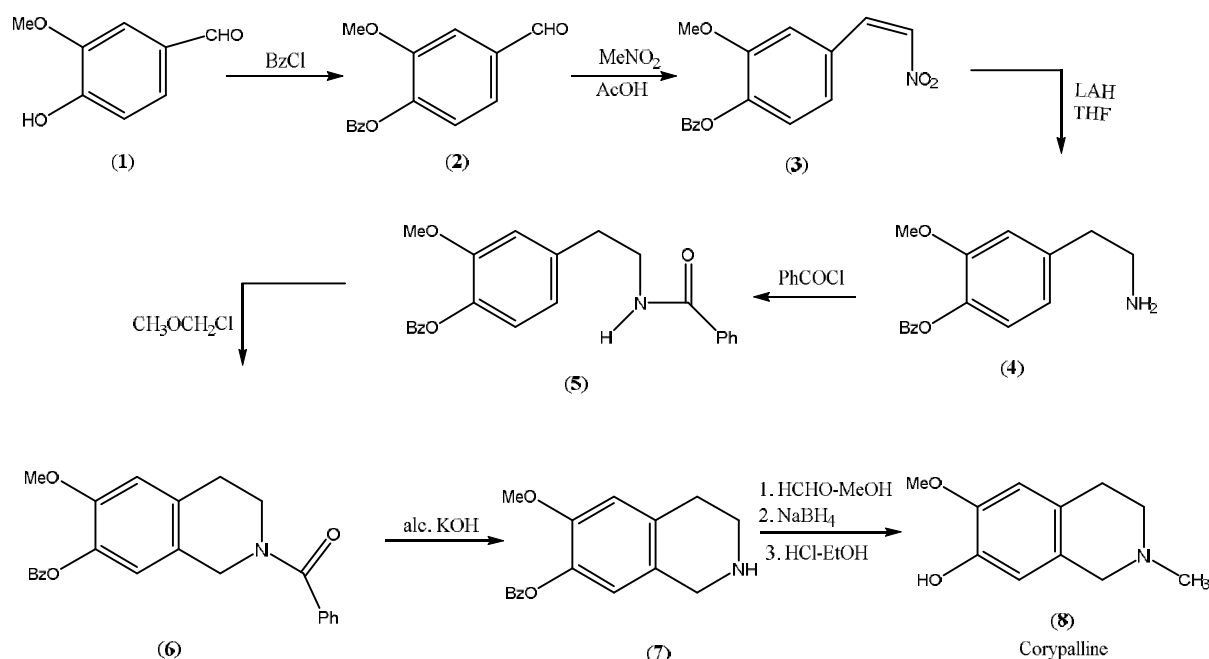
The present work describes a novel synthetic route for corypalline, using chloro methyl-methyl ether for cyclisation of N-benzoyl derivative of substituted β -phenethylamine followed by hydrolysis and N-methylation.

KEYWORDS: Corypalline, Chloromethyl-methyl Ether, cyclisation, N-methylation

The tetrahydroisoquinoline alkaloid Corypalline was isolated from *Corydalis Pallida* and *Corydalis aurea* by Manske. The structure (8) for this base was assigned on the basis of chemical and spectral evidences and further supported by its synthesis (MacLean and Snieckus, 1998). Bobbit *et al.* (1967) prepared corypalline (8) by the Pomeranz-Fritsch reaction of substituted N-benzylaminoacetaldehyde diethyl acetal. Brossi *et al.*, (1970) reported the synthesis of corypalline by partial demethylation of 3,4-dihydroisoquinoline derivative by treatment with conc. HBr followed by catalytic reduction of the imine methiodide intermediate. synthesized corypalline by a Pictet Spengler reaction of β -(4-benzyloxy-3-methoxy) phenethyl amine. Synthesized corypalline starting with the 3-isochromanone intermediate.

The present work describes a novel synthetic route for Corypalline using chloromethyl-methyl ether for cyclisation of N-benzoyl derivative of substituted β -phenethyl amine followed by hydrolysis and N-methylation.

Vanillin (1) on benzylation with benzyl chloride gave the O-benzyl vanillin (2) which on treatment with nitromethane gave 4-benzyloxy-3-methoxy- ω -nitro styrene (3). Lithium aluminium hydride reduction of substituted ω -nitrostyrene gave corresponding β -phenethylamine (4) which on benzylation with benzoyl chloride gave N-benzoyl derivative (5). This (5) was treated with chloromethylmethyl ether to give N-benzoyl-1,2,3,4-tetrahydroisoquinoline derivative (6) which on hydrolysis followed by N-methylation and debenylation gave Corypalline (8).

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EXPERIMENTAL

(I) Synthesis of O-benzyl vanillin: (2)-A mixture of vanillin(1) (7.6 g), anh. potassium carbonate (5.0 g), benzyl chloride (4 mL), sodium iodide (0.4 g) and ethanol (130 mL) was stirred and refluxed for 6 h. After cooling, the solvent was distilled out in vacuo and resulting oil poured into alkaline ice cold water (250 mL). The solid product was crushed under water, filtered and dried (Na_2SO_4). Recrystallisation from aq. ethanol gave O-benzyl vanillin (2).(9.6 g; 79.34%), m.p. 64-65^oC.

(Found C,74.2, H,5.96, O-19.8, $\text{C}_{15}\text{H}_{14}\text{O}_3$ requires C 74.5; H 5.78; O 19.9%)

(II) Synthesis of 4-benzyloxy-3-methoxy- ω -nitrostyrene: (3)- A mixture of O-benzylvanillin (2) (9 g), ammonium acetate (3 g), nitromethane (15mL) and glacial acetic acid (25mL) was refluxed for 1.5 h. The crystals of the product which deposited on cooling were filtered, dried and recrystallised from ethanol to give the styrene (3) as yellow needles (8.47 g; 80%) m.p. 120-122^oC (lit⁶,m.p. 121-123^oC).

(Found C:67.42; H: 5.25; N:4.90; $\text{C}_{16}\text{H}_{15}\text{NO}_4$ requires C:67.36; H:5.26; N:4.91%)

(III) Synthesis of 4-benzyloxy-3-methoxy- β -phenethylamine: (4)- To a stirred suspension of lithium aluminium hydride (5.36 g) in tetrahydrofuran was added the styrene (3)(8 g), in portions, with ice bath cooling. The mixture was refluxed at 100^oC for 4 h, cooled, excess hydride was decomposed by addition of water and mixture was extracted with methylene dichloride. The extract was washed with 2N aq. sodium hydroxide, washed with water, dried (Na_2SO_4) and solvent removed to give the amine as oil (5.62 g, 78%). The hydrochloride had m.p. 171-172^oC.

(IV) Synthesis of N-benzoyl-2-(4'-benzyloxy-3'-methoxy phenyl) ethyl amine:(5)-To a stirred mixture of 2-(4'-benzyloxy-3'-methoxy phenyl) ethyl amine (5.5 g) in benzene (45mL) and 4N NaOH(90mL) was added about 11mL of benzoyl chloride in small portions of 0.5 mL each with cooling in water. The stirring was continued for 2.5h at room temperature. The benzene layer was then separated, washed with 1N HCl, water, dried (Na_2SO_4) and the solvent removed under reduced pressure to give (5)(5.8 g; 75%) m.p. 133^oC.

IR(KBr):3320 cm^{-1} (NH); 1630 cm^{-1} (C=O).

(Found C:76.72; H:6.21; N:3.59; $\text{C}_{23}\text{H}_{23}\text{NO}_3$ requires C:76.45; H:6.37; N:3.88%)

(V) Preparation of monochloromethyl ether: In a round bottomed flask fitted with a stopper carrying a reflux condenser and a glass tube reaching nearly to the bottom of the flask were placed 35 g (1.09 mole) of methyl alcohol and 90 g of technical formalin containing 25.2 g (0.84 mole) of formaldehyde.

A rapid stream of hydrogen chloride was run in to the mixture which was cooled with running water. In about 1.5 h a layer of monochloromethyl ether started appearing. The stream of hydrogen chloride was continued for 0.5 h longer until the solution was saturated. The layer of monochloromethyl ether was then separated. The water layer was saturated with CaCl_2 and more ether separated. This was added to the main portion which was then dried over CaCl_2 and fractionally distilled (b.p. 56^oC)

(VI) Synthesis of N-benzoyl-7-benzyloxy-6 methoxy-1,2,3,4-tetrahydro isoquinoline:(6)-A mixture of monochloromethyl ether (3 g) in glacial acetic acid (25mL) was treated with N-benzoyl-2-(4'-benzyloxy-3'-methoxyphenyl) ethyl amine (5.5 g) at about 18^oc for eighteen hour. The excess solvent and reagent were removed under reduced pressure. The residue was washed with 25% NH_3 solution, extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and the solvent removed to afford (6)(4.08 g; 72%) m.p. 108^oC (MeOH-ether)

IR(KBr): 1650 cm^{-1} (C=O)

(Found C: 76.92; H: 6.18; N: 3.72; $\text{C}_{24}\text{H}_{23}\text{NO}_3$ requires C: 72.21; H: 6.16; N: 3.75%)

(VII)Synthesis of 7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline:(7)-N-benzoyl-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6) (4.0 g) was refluxed with 30% methanolic KOH (60mL) for thirty minute, cooled and was made acidic with the addition of conc. HCl drop by drop. The acid separated was filtered off and the filtrate was then made alkaline with NaOH solution, cooled and extracted with ether. After extraction, the ether was evaporated under reduced pressure to give (7)(2.30g; 80%) m.p. 130^oC.

IR(CHCl_3): 3269 cm^{-1} (NH)

(Found C:75.48, H: 6.92; N: 5.00; $\text{C}_{17}\text{H}_{19}\text{O}_2\text{N}$ requires C:75.81; H: 7.11; N: 5.20%)

The hydrochloride salt recrystallised from methyl alcohol-ether gave colourless scales m.p. 218^oC.

(VIII) Synthesis of 7-hydroxy-6-methoxy-2-methyl-1,2,3,4-terahydro isoquinoline: (8)-

To a solution of 7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (7) (2.0 g) in 180mL of methyl alcohol, was added 37% formaline (4.5 mL) and the reaction mixture was stirred for 45 minutes. To this was added sodium borohydride (21 g) within 15 min. The stirring was continued for 45 min. and then the mixture was acidified with 10% HCl solution. After removal of solvent in vacuo, the residue left was basified with ammonia and extracted with benzene, dried over Na₂SO₄ and evaporated. The solid left was taken in ethanol (50 mL) and 12N HCl (50mL) mixture and refluxed for 3h. Neutralisation with aq. NaOH and extraction with chloroform, followed by distillation off the solvent in vacuo left a residue which was recrystallised from benzene to give corypalline (8)(1 g; 70%) m.p. 166⁰C (lit¹; 164-165⁰C)

NMR (CDCl₃+DMSO-d₆): 2.36 (3H, N-Me), 2.51-2.84 (4H, m, -CH₂-CH₂), 3.40 (2H, s, C₁-H), 3.0 (3H, s, OMe), 4.37 (1H, broad signal, -OH, exchangeable with D₂O), 6.53 (1H, s, C₈-H), 6.66 (1H, s, C₅-H) ppm

MS m/e: 193 (M⁺), 177, 150 and 135

Found C: 68.38, H: 7.90; N: 7.80; C₁₁H₁₅NO₂ requires C: 69.56; H: 7.77; N: 7.25%

ACKNOWLEDGEMENT

Author is extremely thankful to Professor K. P. Tiwari, Department of Chemistry, University of Allahabad, for his valuable guidance.

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