A SHORT STEP SYNTHESIS OF LESPEDAMINE[1]

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Abstract—— A convenient synthetic method for 1-hydroxy-, 1-methoxy-, and 1-acetoxy-2-oxindole was disclosed starting from methyl 2-nitrophenylacetate. A five-step synthesis of lespedamine was achieved utilizing this method.

In this report, we describe a practical synthetic method for 1-hydroxy-2-oxindole derivatives and a short step synthesis of lespedamine (1),[2,3] one of eight naturally occurring 1-methoxyindole derivatives.[4]

I. Syntheses of 1-Hydroxy-2-oxindole Derivatives

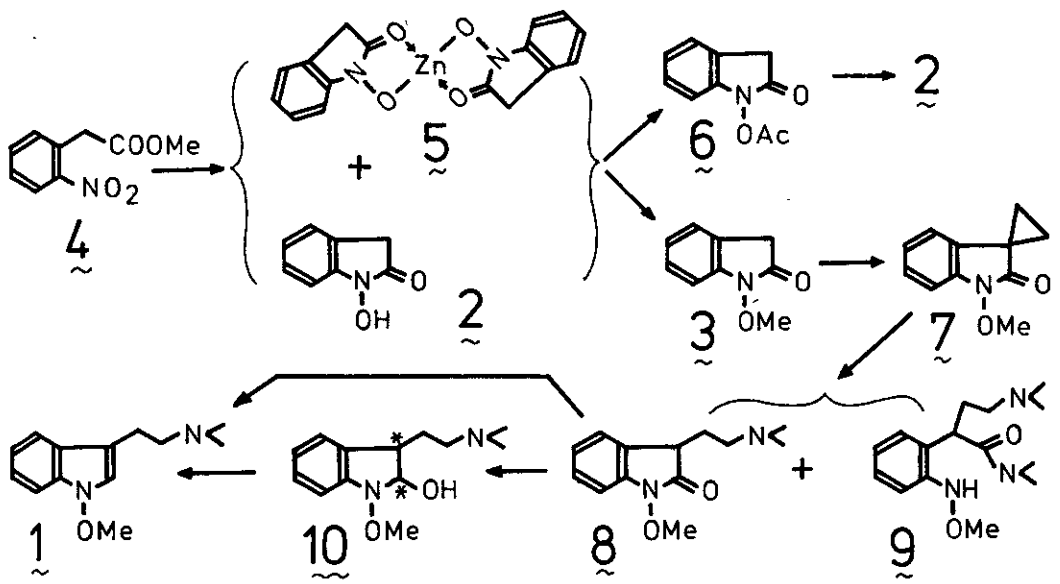
Various synthetic methods so far reported for 1-hydroxy- (2) and 1-methoxy-2-oxindole (3) are known to give unsatisfactory results.[5] However, we found that the readily available methyl 2-nitrophenylacetate (4) simply upon treatment with zinc (20 mol eq.) and ammonium chloride (3.8 mol eq.) in methanol for 3h afforded 2[6] in 48% yield. When an excess amount of reducing agents was used or a longer reaction time was adopted, the yield of 2 was decreased mainly due to its sensitivity toward reductive decomposition, resulting in the formation of 2-oxindole.

We have also found that a significant amount of 2 was lost by the formation of a complex[7] with zinc iron, which was rather insoluble in organic solvents. The structure of the complex was tentatively assigned to be 5 based mainly on its mass spectrum which showed the ratio of 2 and zinc iron to be 2 to 1.

Direct treatments of the reaction mixture, obtained by the reaction of 4 with zinc and ammonium chloride, with diazomethane and acetic anhydride and pyridine were found to give 1-methoxy- (3)[8] and 1-acetoxy-2-oxindole (6)[9] in 77% and 70% overall yields, respectively. Furthermore, hydrolysis of 6 with sodium carbonate afforded 2 in 94% yield.

II. Synthesis of Lespedamine

The reaction of 3 with ethylene dibromide in the presence of sodium hydride afforded spiro compound (7)[10] in 90% yield. Subsequent treatment of 7 with aq. dimethylamine (50 mol eq.) and its hydrochloride (9 mol eq.) in N,N-dimethylformamide produced the desired 3-(2-N,N-dimethylaminoethyl)-1-methoxy-2-oxindole (8)[11] in 54% yield, together with 10% yield of a phenylhydroxylamine derivative (9).[12] The reduction of 8 with lithium aluminum hydride ($LiAlH_4$) in ether was found to produce 3-(2-N,N-dimethylaminoethyl)-2-hydroxy-1-methoxy-2,3-dihydroindole (10)[13] in 62% yield as a mixture of diastereoisomers. The compound (10) was unstable and instantaneously changed by treatment with aq. hydrochloric acid to lespedamine[14] (1) in 95% yield. On the basis of the above results, the final step was improved as follows. Thus, after reduction of 8 with $LiAlH_4$, the reaction mixture was treated briefly with aq. hydrochloric acid. By this modification, lespedamine (1) was prepared in 64% yield directly from 8. Thus, the total synthesis[3] of 1 was achieved in five steps with 24% overall yield from 4. The spectral data of synthetic material and melting point of its picrate were identical with those of lespedamine.[2] In conclusion, building blocks such as 2, 3, and 6 for 1-hydroxyindole derivatives have now become readily available from 4 in excellent yields. Investigation of their reactions and preparation of other naturally occurring 1-methoxyindole derivatives are currently in progress.



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6. mp 200.5-202.0°C (lit.[5] mp 199-200°C). IR (KBr): 1675, 1617 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.35 (1H, br s), 3.43 (2H, s), 6.65-7.41 (4H, m).
7. mp > 300°C. IR (KBr): 1630, 1605 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 3.28 (4H, s), 6.62-7.38 (8H, m). High MS m/z: Calcd for $C_{16}H_{12}N_2O_4Zn$: 360.0087 and 362.0057. Found: 360.0109 and 361.9963.
8. mp 84.5-86.0°C (lit.[5] mp 84-86°C). IR (KBr): 1712, 1617 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (2H, s), 3.95 (3H, s), 6.65-7.42 (4H, m). MS m/z: 163 (M^+), 132.
9. mp 97-99°C. IR (KBr): 1807, 1727 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.55 (2H, s), 6.50-7.35 (4H, m). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 63.00; H, 4.72; N, 7.04.
10. Oil. IR (film): 1723, 1619 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.17-1.54 (2H, m), 1.54-1.87 (2H, m), 3.92 (3H, s), 6.41-7.21 (4H, m). High MS m/z: Calcd for $C_{11}H_{11}NO_2$: 189.0789. Found: 189.0795
11. Oil. IR (film): 1727, 1616 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.69-2.50 (4H, A_2B_2, m), 2.06 (6H, s), 3.32 (1H, t, J=5.6 Hz), 3.86 (3H, s), 6.57-7.29 (4H, m). High MS m/z: Calcd for $C_{13}H_{18}N_2O_2$: 234.1367. Found: 234.1375.
12. Oil. IR (film): 3480, 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67-2.57 (4H, m), 2.32 (6H, s), 2.73 (3H, s), 2.86 (3H, s), 3.66 (3H, s), 3.90 (1H, dd, J=8.8 and 5.2 Hz), 6.50-7.30 (4H, m), 6.93 (1H, br s). High MS m/z: Calcd for $C_{15}H_{25}N_3O_2$: 279.1944. Found: 279.1937.
13. Oil. IR (film): 3340, 1612, 1596, 1475, 1463 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.84-2.75 (5H, m), 2.25 (6H, s), 3.82 (3H, s), 4.60 and 4.92 (total 1H, each d, J=8 Hz), 5.83 (1H, br s), 6.44-7.15 (4H, m). High MS m/z: Calcd for $C_{13}H_{20}N_2O_2$: 236.1523. Found: 236.1539.
14. Spectra of IR and ^{1}H-NMR were identical with those of lespedamine. Charts of IR and ^{1}H-NMR spectra of lespedamine are reported in the ref. 2. Oil. IR ($CHCl_3$): 1459 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 2.19 (6H, s), 2.32-2.96 (4H, m), 3.92 (3H, s), 6.62-7.45 (5H, m). MS m/z: 218 (M^+), 187 (M^+-OMe). Picrate: mp 161-163°C (lit.[2] mp 160-162°C).

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