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THE SYNTHESIS OF 5-SUBSTITUTED PYRROLO[4,3,2-de]ISOQUINOLINE DERIVATIVES[1]

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5-Substituted pyrrolo[4,3,2-de]isoquinolines, suitable intermediates for the synthesis of both 3,4-disubstituted indoles and Ergot alkaloids, were prepared from readily available 2-methyl-5-nitroisoquinolinium iodide.

Recently, pyrrolo[4,3,2-de]isoquinoline derivatives have attracted much attention due to their antihypertensive, hypoglycemic, and antidepressant activities.[2] In the previous paper,[3] we have developed two facile synthetic routes to 4-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline 1 from readily available 2-methyl-5-nitroisoquinolinium iodide 2 and described its successful conversion to 3,4-disubstituted indoles. Now, we wish to report the synthesis of the 5-substituted derivatives of 1, which would be suitable synthons for the synthesis of Ergot alkaloids.

Treatment of 2-methyl-5-nitroisoquinolinium iodide 2 with acetone in 0.2M aqueous NaOH at refluxing temperature for 4 h gave 1-acetonyl-1,2-dihydro-2-methyl-5-nitroisoquinoline 3 [NMR (δ): 2.01 (3H,s,CO-CH_3), 2.85 (2H,d,J=6.5 Hz,CH_2-CO), 3.03 (3H,s,N-CH_3), 4.94 (1H,d.t,J=6.5 and 1 Hz,C_1-H), 6.17 (1H,d,J=7 Hz,C_4-H), 6.33 (1H,d.d,J=7 and 1 Hz,C_3-H), 6.95 (1H,t,J=7.5 Hz,C_7-H), 7.16 and 7.86 (each 1H,d.d, J=7.5 and 2 Hz,C_6- and C_8-H); IR (film): 1712, 1593, 1358 cm^{-1}; MS m/e: 246 (M^+)]. Since this compound was found to be quite unstable, the residue obtained upon evaporation of the solvent in the above reaction was treated immediately with 1 mol equiv. of $NaBH_4$ in MeOH at room temperature to afford the compound 4, which was further acetylated to give a mixture of the diastereomers 5 [yield 82%, IR (film): 1740 cm^{-1}; MS m/e: 290 (M^+)]. When an excess of $NaBH_4$ was used for the reduction of 3 in the presence of acetic acid, the enamine part of 3 was further reduced to give a mixture of the diastereomers 6 [oil, IR (film): 3420-3270, 1530, 1350 cm^{-1}; MS

Chart I

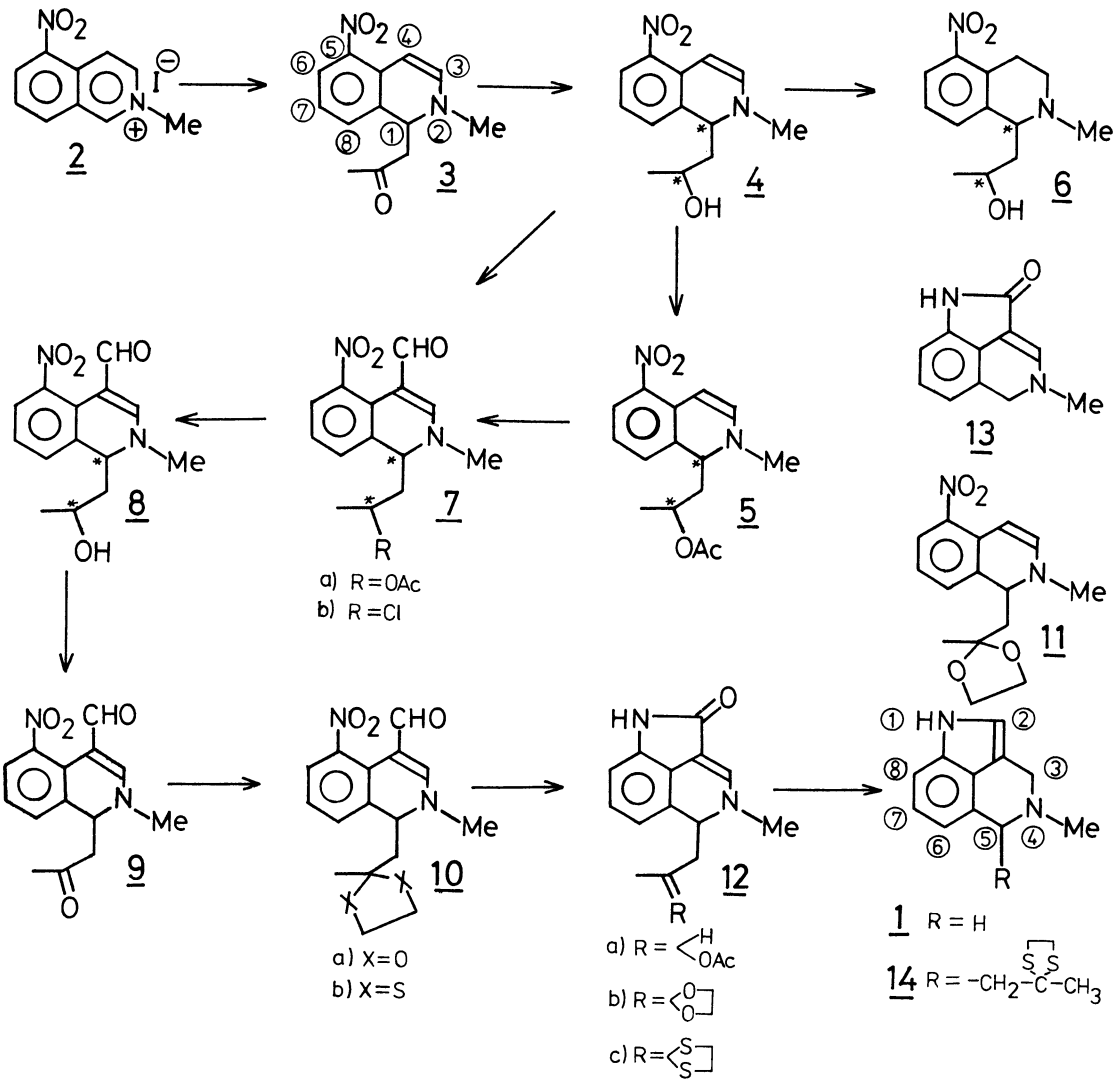
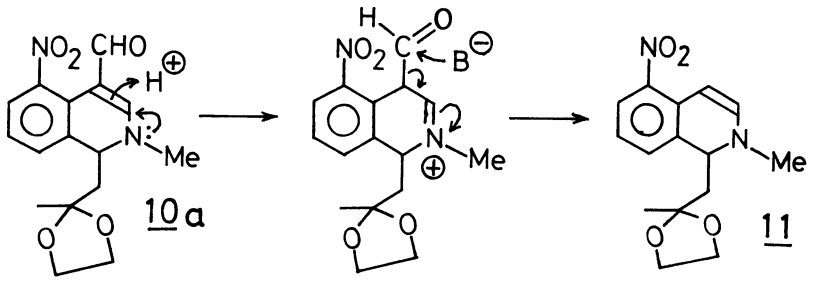


Chart II



m/e: 250 (M^+)] in a quantitative yield.

Vilsmeier reaction of 4 or 5 then afforded 4-formyl derivatives, 7b or 7a with the respective overall yields of 57% or 39% from 2. Aqueous alkaline hydrolysis of 7a gave 8 in a quantitative yield and the subsequent oxidation with DMSO-DCC-CF_3COOH[4] gave 9 [mp 169-170°, NMR (δ): 2.07 (3H,s,CO-CH_3), 2.87 (2H,d,J=5.5 Hz, CH_2-CO), 3.32 (3H,s,N-CH_3), 5.09 (1H,t,J=5.5 Hz,C_1-H), 7.24 (1H,s,C_3-H), 7.10-7.40 (2H,m), 7.58 (1H,d.d,J=6 and 3 Hz), 9.04 (1H,s,CHO); IR (KBr): 1710, 1653, 1605, 1518, 1359 cm^{-1}; MS m/e: 274 (M^+)] in 91 % yield. The attempts to prepare 9 directly from 3 resulted in failure under various Vilsmeier reaction conditions.

In examining the way for protection of the carbonyl group of 9, somewhat unexpected result was obtained. Thus, in an attempt for the acetalization using p-toluenesulfonic acid and ethylene glycol in benzene under reflux, the efficient deformylation of 9 occurred to give 11. Lowering the reaction temperature to 25° still resulted in the formation of 11 together with 9 and 10a in 5%, 13%, and 25% yields, respectively. Even under the conditions using much weaker acids such as adipic or fumaric acid, formation of 11 was observed. The mechanism of the reaction seems to be explained as illustrated in Chart II.

On the other hand, dithioacetalization of 9 using 1,2-ethanedithiol and BF_3-etherate at room temperature lead to the formation of 10b [oil, NMR (δ): 1.68 (3H, s,CH_3), 2.44 (2H,d,J=5 Hz,CH-C$\underline{H}_2$), 3.26 (3H,s,N-CH_3), 3.32 (4H,s,S-$(CH_2)_2$-S), 4.72 (1H,t,J=5 Hz,C_1-H), 7.05 (1H,t,J=8 and 7 Hz,C_7-H), 7.10 (1H,s,C_3-H), 7.30 (1H,d.d, J=8 and 1.5 Hz), 7.50 (1H,d.d,J=7 and 1.5 Hz), 8.92 (1H,s,CHO); IR (KBr): 1650, 1597, 1357 cm^{-1}; MS m/e: 350 (M^+)] in a satisfactory yield (83%).

Refluxing of 7a, 10a, or 10b in triethylphosphite afforded 12a [oil, IR (film): 3650-3000, 1734, 1658 cm^{-1}; MS m/e: 286 (M^+)], 12b [mp 224-226°, MS m/e: 286 (M^+); IR (KBr): 3106-2876, 1656, 1592 cm^{-1}; NMR (δ): 1.30 (3H,s,CH_3), 2.26 (2H,d,J=5 Hz,C$\underline{H}_2$-CH), 3.19 (3H,s,N-CH_3), 4.00 (4H,br.s,O-$(CH_2)_2$-O), 4.76 (1H,t,J=5 Hz,C_5-H), 6.60 and 6.71 (each 1H,d,J=8 Hz,C_6- and C_8-H), 6.98 (1H,t,J=8 Hz,C_7-H), 7.30 (1H,s,C_3-H)], or 12c [mp 216-217°, MS m/e: 318 (M^+); IR (KBr): 3136-2906, 1654, 1598 cm^{-1}; NMR (δ): 1.73 (3H,s,CH_3), 2.51 (2H,d,J=5 Hz,C$\underline{H}_2$-CH), 3.30 (3H,s, N-CH_3), 3.33 (4H,s,S-$(CH_2)_2$-S), 4.86 (1H,t,J=5 Hz,C_5-H), 6.68 and 6.81 (each 1H,d, J=9 Hz,C_6- and C_8-H), 7.01 (1H,t,J=9 Hz,C_7-H), 7.31 (1H,s,C_3-H), 8.25 (1H,br.s,NH)] in the respective yields of 61%, 71%, and 50%. It is noteworthy that the compounds 12a-12c prepared in this study were stable, while the compound 13 having no

substituent at the 5-position was quite unstable.[3]

Reduction of 12c with $LiAlH_4$ in THF under reflux gave 14 [oil, IR (KBr): 3406, 1608, 1443 cm^{-1}; MS m/e: 304.166, Calcd. for $C_{16}H_{20}N_2S_2$: 304.163; NMR (δ): 1.96 (3H,s,CH_3), 2.18 (1H,d.d,J=15 and 5 Hz,H_a-CH_b-CH), 2.28 (3H,s,N-CH_3), 2.65 (1H,d.d, J=15 and 7.5 Hz,H_b-CH_a-CH), 3.30 (4H,s,S-$(CH_2)_2$-S), 3.77 and 4.41 (each 1H,d,J=16 Hz,AB pattern,C_3-H_2), 4.05 (1H,d.d,J=5 and 7.5 Hz,C_5-H), 6.77 (1H,br.s,C_2-H), 6.84 (1H,t,J=4 Hz,C_7-H), 7.10 (2H,d,J=4 Hz,C_6- and C_8-H), 7.97 (1H,br.s,NH)] in 9% overall yield from 10b.

Further conversion of 14 and the related compounds to Ergot alkaloids is currently in progress.

References and Notes

All NMR spectra were recorded in $CDCl_3$.

1) This report is part VIII of a series entitled "The Chemistry of Indoles." Part VII: M.Somei, F,Yamada, and C.Kaneko, Chemistry Lett., 1249 (1978).

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