Communications to the Editor

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A TOTAL AND PRACTICAL SYNTHESIS OF ERGOT ALKALOID, (±)-AURANTIOCLAVINE[1)]

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The first synthesis of (±)-aurantioclavine by a convenient and practical five-step synthetic method, involving a new intra-molecular cyclization of nitro-olefin, is achieved starting from 3-formylindole with a 31% overall yield without using any protective groups.

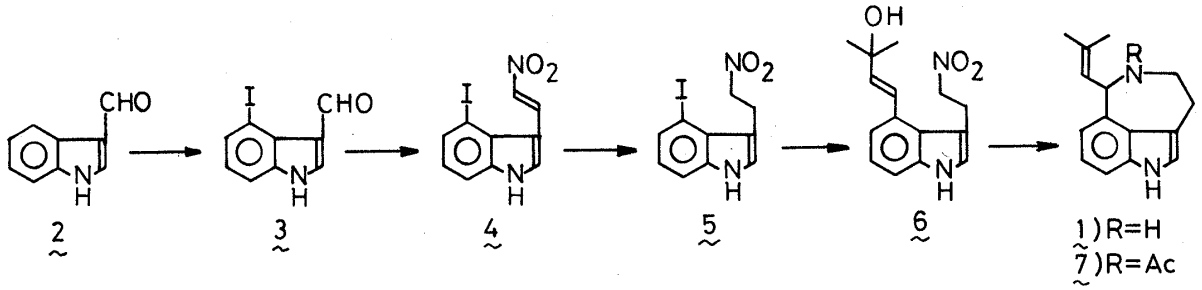
KEYWORDS ———— ergot alkaloid: (±)-aurantioclavine; short step synthesis; intra-molecular cyclization; olefin amination; nitro-olefin

In this paper, we wish to describe the first and the most effective synthesis of ergot alkaloid, (±)-aurantioclavine (1), isolated by A.G. Kozlovskii et al.[2)] in 1981 from mold Penicillium aurantio-virens. A new acid catalyzed intra-molecular amination method of olefin is also reported.

Aldol condensation reaction of 3-formyl-4-iodoindole (3), prepared in 72% yield from 3-formylindole[3)] (2), with nitromethane by the action of ammonium acetate yielded 4-iodo-3-(2-nitrovinyl)indole[4a)] (4) in 96% yield. Reduction of 4 with sodium borohydride in 2-propanol and chloroform in the presence of silica gel[5)] afforded 4-iodo-3-(2-nitroethyl)indole[4b)] (5) in 84% yield. Improved Heck reaction of 5 with 2-methyl-3-buten-2-ol in N,N-dimethylformamide in the presence of tetra-n-butylammonium bromide[6)] and a catalytic amount of palladium acetate at 120°C for 0.5 h produced 4-(3-hydroxy-3-methyl-1-buten-1-yl)-3-(2-nitroethyl)indole[4c)] (6) in 80% yield.

Next, we have developed a new reductive cyclization method of nitro-olefin under acidic reaction conditions.[7)] Thus, treatment of 6 with amalgamated zinc in refluxing methanolic 2N-hydrochloric acid furnished (±)-aurantioclavine[4d)] (1) in 67% yield. It should be noted that only with amalgamated zinc were we able to achieve this new intra-molecular reductive amino-cyclization.[8)] Acetylation of 1 with acetic anhydride and pyridine gave a 71% yield of (±)-N-acetylaurantioclavine (7).[4e)] The proton nuclear magnetic resonance spectrum of 1 was identical with that of the natural product, aurantioclavine, reported in the literature.[2a)]

In conclusion, (±)-aurantioclavine (1) was prepared from 3-formylindole (2) in the simplest five steps with an overall yield of 31%, without using any protective groups. This method should prove valuable in the synthesis of clavicipitic acid.[9)] Attempts to produce various related derivatives in large quantities and their biological evaluations are currently in progress.



REFERENCES AND NOTES

1) This paper is part XXVI of a series entitled "The Chemistry of Indoles". Part XXV: M. Somei, H. Sato, N. Komura, and C. Kaneko, Heterocycles, in press.

2) a) A.G. Kozlovskii, T.F. Soloveva, V.G. Sakharovskii, and V.M. Adanin, Dokl. Akad. Nauk SSSR, 260, 230 (1981); b) V.G. Sakharovskii, A.V. Aripovskii, M.B. Baru, and A.G. Kozlovskii, Khim. Prir. Soedin., 1983, 656.

3) M. Somei and F. Yamada, Chem. Pharm. Bull., 32, 5064 (1984).

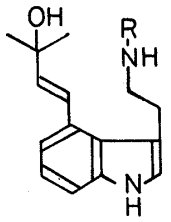
4) All melting points are uncorrected. All compounds afforded acceptable combustion data. IR spectra were recorded in KBr pellets and absorption bands are shown in cm^{-1}. ^1H-NMR spectra were taken in deuterated-chloroform (d-C), -methanol (d-M), or -pyridine (d-P). Chemical shifts are reported in ppm (δ) from TMS. a) mp 250-255°C (dec.). IR: 3230, 1598. NMR (d-P): 6.83 (1H, dd, J=8.0 and 7.2 Hz), 7.42 (1H, dd, J=8.0 and 1.0 Hz), 7.67 (1H, dd, J=7.2 and 1.0 Hz), 7.75 (1H, s), 8.07 (1H, d, J=13.2 Hz), 9.65 (1H, d, J=13.2 Hz). MS m/e: 314; b) mp 96.5-97.5°C. IR: 3320, 1604, 1539, 1375. NMR (d-C): 3.63 (2H, t, J=6.8 Hz), 4.67 (2H, t, J=6.8 Hz), 6.74 (1H, dd, J=8.0 and 7.2 Hz), 6.96 (1H, d, J=2.5 Hz), 7.21 (1H, dd, J=8.0 and 1.2 Hz), 7.47 (1H, dd, J=7.2 and 1.2 Hz), 8.04 (1H, br s). MS m/e: 316; c) mp 106-107°C. IR: 3447, 3305, 3227, 1611, 1562, 1537, 1370, 1344. NMR (d-C): 1.45 (6H, s), 1.91 (1H, br s), 3.51 (2H, t, J=7.5 Hz), 4.55 (2H, t, J=7.5 Hz), 6.16 (1H, d, J=15.2 Hz), 6.74-7.24 (4H, m), 7.16 (1H, d, J=15.2 Hz), 8.06 (1H, br s, NH). MS m/e: 274. This compound is also accessible starting from 4-formylindole: M. Somei, F. Yamada, Y. Karasawa, and C. Kaneko, Chem. Lett., 1981, 615; d) mp 194-196°C. IR: 3290, 2915, 1612, 1569. NMR (10% d-M in d-C): 1.82 (6H, s), 2.82-3.68 (4H, m), 4.82 (1H, d, J=9.2 Hz), 5.39 (1H, br d, J=9.2 Hz), 6.58-7.23 (4H, m). MS m/e: 226; e) mp 235-236°C. IR: 3200, 1664, 1593. NMR (10% d-M in d-C): 1.70 (3H, br s), 1.80 (3H, br s), 2.18 (3H, s), 2.64-4.54 (4H, m), 5.27 (1H, br d, J=7.5 Hz), 5.80 (1H, br d, J=7.5 Hz), 6.57-7.28 (4H, m). MS m/e: 268.

5) A.K. Sinhababu and R.T. Borchardt, Tetrahedron Lett., 24, 227 (1983).

6) T. Jeffery, J. Chem. Soc., Chem. Commun., 1984, 1287. The first application of Heck reaction for 4-substituted indole synthesis: M. Somei and M. Tsuchiya, Chem. Pharm. Bull., 29, 3145 (1981).

7) Application of this new reaction to other natural product synthesis will be reported elsewhere. Review for amination of olefins: M.B. Gase, A. Lattes, and J. J. Perie, Tetrahedron, 39, 703 (1983); D. Barton and W.D. Ollis, "Comprehensive Organic Chemistry," Vol. 2, Pergamon Press, New York (1979); S. Patai, "The Chemistry of the Amino Group," Interscience, New York (1968).

8) We have failed in obtaining aurantioclavine by using such reagent systems as $SnCl_2$/HCl/MeOH, $TiCl_3$/MeOH, Fe/AcOH, and Zn/AcOH. Furthermore, using the resulted amine (i) and its acetyl- and tosyl-derivatives, (ii) and (iii), intra-molecular cyclization was examined under various reaction conditions, including metal catalyzed amination of olefins, but all attempts ended in failure. We believe that this new cyclization occurred at the hydroxylamine stage because the corresponding unstable hydroxylamine derivative of 1 was isolated when the reaction was stopped in a short reaction time.



i)R=H
ii)R=Ac
iii)R=Ts

9) A.P. Kozikowski and M.N. Greco, Heterocycles, 19, 2269 (1982); H. Muratake, T. Takahashi, and M. Natsume, Heterocycles, 20, 1963 (1983).

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