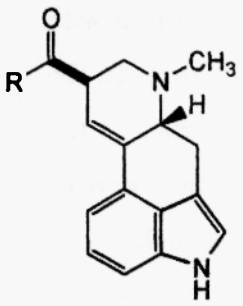
BIOMIMETIC INTRAMOLECURAR CYCLIZATION OF 1-TRIMETHYLACETYL -3- (3-METHANESULFONOXYBUTYL) INDOLE DERIVATIVE AT THE 4-POSITION OF INDOLE NUCLEUS

Nobumitsu Tajima, Yoshihiko Shinoda and Shin-ichi Nakatsuka*
United Graduate School of Agricultural Science, Gifu University,
1-1 Yanagido, Gifu 501-1193, Japan

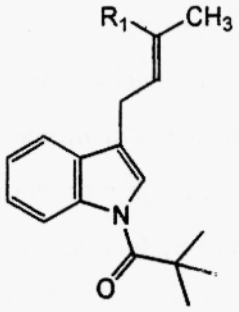
Abstract: 1-Trimethylacetyl indole derivative 4c was regioselectively cyclized in 54% yield at the 4-position of indole nucleus to afford dihydrobenz[c,d]indole 3b.

In the biosynthsis of ergot alkaloids 1 , a prenyl group is first introduced at 4-position of L-tryptophan (1). However, introduction of such substituent on the benzen ring part of indole nucleus is one of the most difficult problems in the chemical synthesis, because of its higher reactivity of the pyrrole ring part than the benzen ring part.

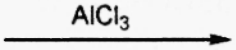
Schem1

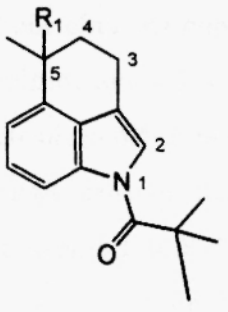


Ergot alkaloids (1)



2a R_1 = CH_3
2b R_1 = H





3a R_1 = CH_3 (70%)
3b R_1 = H (15%)

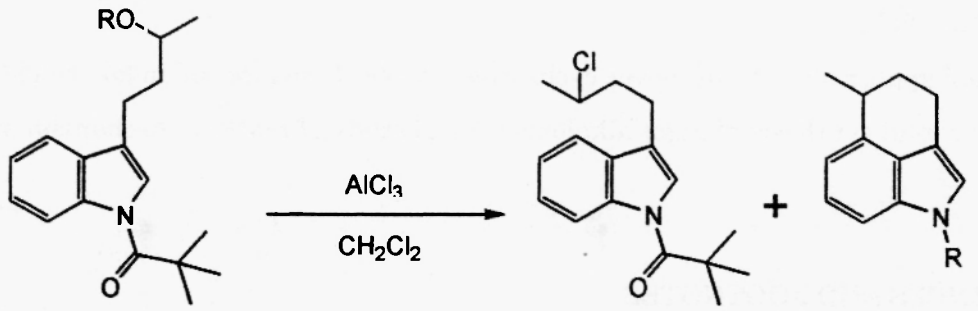
In our studies on synthesis of indole alkaloids, we have succeeded inter-, intramolecular cyclizations and direct introduction of a substituent at benzen ring part of simple indole derivatives (2). Now, we report much more efficient method of intramolecular cyclization for the synthesis of ergot alkaloids.

In the previous paper (2j), we reported novel AlCl3-catalyzed cycliztion of the tri-substituted olefin 2a to afford 5,5-dimethyl-dihydrobenz[c,d]indole derivative 3a in 70% yield. But cyclization yield of di-substituted 2b was only 15% to afford 5-methyl derivative 3b which contains the same carbon subsitiuents with ergot alkaloids (Schemel). Here we report an efficient cyclization starting from methanesulfonate 4c (3) toward our desired 3b (4).

An alcohol 4a was acetylated with Ac_2O/Pyr. to afford the corresponding acetate 4b in quantitative yield. Although 4a or 4b was treated with $AlCl_3$ in CH_2Cl_2 *etc.* in various conditions, each maximum yield of 3b was less than 30%. Therefore an methanesulfonate 4c was synthesized from 4a with MsCl/Pyr. in quantitative yield. $AlCl_3$ treatment of 4c in various reaction conditions were carried out and the results of typical case are shown in Table 1. When 2 equiv. $AlCl_3$ was used, no cyclization product 3b could be observed in the reaction mixture and the corresponding chloride 5 was obtained in 86% yield (entry 1). Maximum yield of 3b, 54% was obtained when large excess (19 equiv.) $AlCl_3$ was used in highly diluted CH_2Cl_2 solution at r.t. for 10 min (entry 4).

The cyclization of 4c was carried out as follows: powdered $AlCl_3$ was added to a CH_2Cl_2 solution (104 mg 4c in 40 ml CH_2Cl_2) at r.t. and stirred for 10 min. The reaction mixture was washed with sat. potassium sodium tartrate solution and extracted with CH_2Cl_2 (3 times) . After evapolation of the combined and dried extract with Na_2SO_4, the mixture was purified with PTLC (10% EtOAc in Hexane) to give cyclized product 3b (41mg, 54%).

When the chloride 5 was treated with large excess $AlCl_3$ under the same condition with entry 4, 3b was obtained in 55% yield. Therefore, cyclization of 4c may proceed through the chloride 5. No cyclization products at the 2-position of indole nucleus were obserbed in the reaction mixture. Reaction mechanism producing 3b was realised that nucleophilic pyrrole part (1, 2 and 3-positions) of 4c was deactivated by formation of $AlCl_3$ – complex such as I or II, and relatively electron rich 4-position was attacked by Friedel-Crafts type cationic site on the side chain at 3-position of indole nucleus to afford 5-methyl-3,4-dihydro(1*H*)benz[c,d]indole 3b. Hydrolysis of 3b with 1N-NaOH in MeOH afforded 6 (5) in



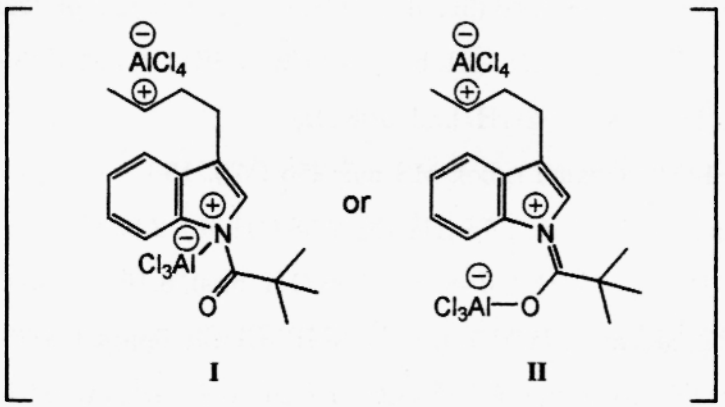
4a R = H
4b R = $COCH_3$
4c R = SO_2CH_3

5

3b R = $COC(CH_3)_3$
6 R = H

Table 1. $AlCl_3$ catalized cyclization of **4c** in various reaction conditions

					products (Yield)	
entry	$AlCl_3$ (eq.)	solvent (times)	condition	time (min.)	**5**	**3b**
1	2	100	r.t.	30	86%	-
2	5	100	r.t.	40	-	26%
3	5	400	r.t.	5	75%	-
4	19	400	r.t	10	-	54%



I II

quantitative yield.

Further application of our novel cyclization at the 4-position of indole nucleus to the biomimetic total synthesis of ergot alkaloids (1) and study of reaction mechanism are now in progress.

REFERENCES AND FOOTNOTES

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(3) 4c; ^{1}H-NMR ($CDCl_3$) δppm 1.46 (3H, d, J=6 Hz), 1.52 (9H, s), 2.06 (2H, m), 2.86 (2H, m), 3.05 (3H, s), 4.91 (1H, m), 7.28 (1H, br.t, J=8 Hz), 7.36 (1H, br.t, J=8 Hz), 7.50 (1H, br.d, J=8 Hz), 7.66 (1H, br.s), 8.53(1H, br.d, J=8 Hz).

(4) 3b; m.p. 144~145°C (sealed tube); MS m/z 255 (M^+), 156. ^{1}H-NMR ($CDCl_3$) δppm 1.38 (3H, d, J=7 Hz), 1.51 (9H, s), 1.76 (1H, m), 2.08 (1H, m), 2.82 (2H, m), 3.07 (1H, m), 7.10 (1H, br.d, J=8 Hz), 7.29 (1H, t, J=8 Hz), 7.36 (1H, br.s), 8.18 (1H, br.d, J=8 Hz).

(5) 6; m.p. 63-64°C; MS m/z 171(M^+), 156. ^{1}H-NMR ($CDCl_3$) δppm 1.40 (3H, d, J=7 Hz), 1.78 (1H, m), 2.10 (1H, m), 2.88 (2H, m), 3.10 (1H, m), 6.85 (1H, m), 6.92 (1H, m), 7.14-7.17 (2H, m), 7.83 (1H. br.s).

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