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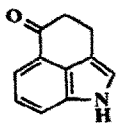
A FACILE BIOMIMETIC SYNTHESIS OF UHLE'S KETONE BY THE REGIOSELECTIVE FRIEDEL-CRAFTS CYCLIZATION OF INDOLE-3-YLPROPIONYL CHLORIDE

Katsunori Teranishi,[#] Syunzi Hayashi, Shin-ichi Nakatsuka [##*] and Toshio Goto[†]

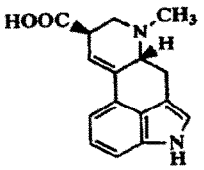
School of Agriculture, Nagoya University, Chikusa, Nagoya 464-01, Japan

Abstract : In the presence of a larg amount of oxocarbonium ion species generated from chloroacetyl chloride and aluminum chloride, 3-(1-trimethylacetylindol-3yl)-propionyl chloride reacts regioselectively to give a pivaloyl derivative of Uhle's ketone in excellent yield .

3,4-Dihydrobenz[*cd*]indole-5(*H*)-one (Uhle's ketone) (**1a**) , which was synthesized from 2-chloro-6-nitrotoluene through eight steps by Uhle in 1949,[1] is a key intermediate in the synthesis of pharmacologically active lysergic acid (**2**).[2] and this convenient chemical preparative methods have been extensively studied for many years.[3] Generally, for the synthesis of lysergic acid (**2**), indoline derivatives or 4-substituted indole derivatives are employed as starting materials.[4] While the direct cyclizations at the 4-position of indol-3-ylpropionic acid (**3a**) or its *N*-acetyl derivative **3b** have been studied, the cyclizations take place not at the desired 4-position but only at the undesired 2-position, because of its much more nucleophilic activity of 2-position than the 4-position.[5, 6] A notable exception is the formation of 1-acetyl-1,3,4,5-tetrahydro-5-oxo-benz[*cd*]indole-3-carboxylic acid from 3-indolesuccinic acid in two steps by Szmuszkovicz.[7] The unique inter and intramolecular cyclizations at the 4-position of indole nucleus, reported from our laboratory, is one of the most convenient and effective method for the preparation of precursor of indole alkaloids.[8]



1a



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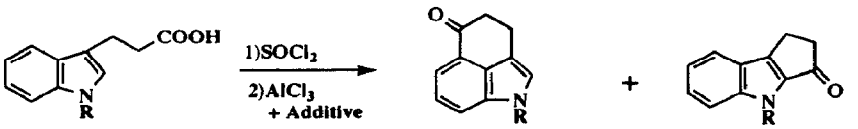
Increasing importance of synthesis of the pharmacologically active indole alkaloids prompted us to challenge new possibility to develop a simple and efficient method stating from easily available indole derivative for the synthesis of Uhle's ketone. In this communication, we would like to describe a highly regioselective cyclization synthesis of Uhle's ketone from indol-3-ylpropionic acid by using a novel Friedel-Crafts cyclization system.

Nagasaka and Ohki [9] reported Friedel-Crafts cyclizations of indol-3-ylpropionic acid (**3a**) and its *N*-acetyl derivative **3b**, however, they obtained cyclization products at the 2-position, **4a** or **4b**, as a sole product respectively. But, we assumed that nucleophilic activity of pyrrole ring of *N*-acyl derivatives should be decreased. Based on these results, a new possibility was considered that pivaloyl group might be convenient to inhibit the cyclization at the 2-position due to the electron acceptance from pyrrole ring and bulkiness to bloke the 2-position.



3a R = H
3b R = $COCH_3$
3c R = $COC(CH_3)_3$

1a R = H
1b R = $COCH_3$
1c R = $COC(CH_3)_3$

4a R = H
4b R = $COCH_3$
4c R = $COC(CH_3)_3$

Scheme 1. Friedel-Crafts cyclization of 3-indolepropionyl chloride derivatives.

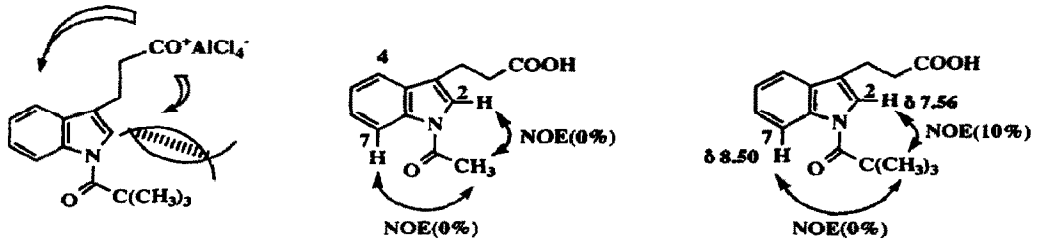
3-(1-Trimethylacetylindol-3-yl)-propionic acid (**3c**)[10] was prepared by trimethylacetylation of **3a** with *n*-butyl lithium (2.0 equiv.) and trimethylacetyl chloride (1.0 equiv.) in tetrahydrofuran at -78 °C in 91% yield. The results for the Friedel-Crafts reactions of the acid chlorides of **3b** and **3c** were shown in Table 1 (Entries 1, 2, 4 and 5).

Table 1. Reaction conditions and regioselectivities of Friedel-Crafts cyclization of acid chlorides prepared from **3b** and **3c**.[a]

Entry	Substrate	Additive (4.0 equiv)	Temp. (°C)	Time (h)	Yield of product (%)[b] **1b** or **1c**	**4b** or **4c**
1	**3b**	none	-10	3	0	43
2	**3b**	none	15	0.3	0	50
3	**3b**	propionyl chloride	15	36	21	15
4	**3c**	none	-10	3	35	26
5	**3c**	none	15	0.3	29	40
6	**3c**	propionyl chloride	15	6	70	6
7	**3c**	chloroacetyl chloride	15	1	78	5

[a] With 4.0 equiv.of $AlCl_3$ in CH_2ClCH_2Cl. [b] Isolated yield.

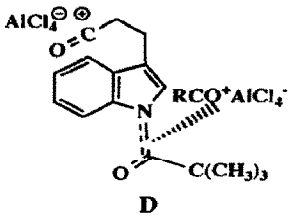
It was found that, by using pivaloyl function, **1c** was predominantly obtained in 35% yield (**1c** : **4c** = 1.35 : 1.00) as shown in Table 1 (Entry 4). Our hypothesis (illustrated in **A**) was supported by the characteristic chemical shift of aromatic H_7 of **3c** appeared at low field (8.50 ppm) in ^{1}H-NMR spectra. Moreover, NOE between methyl protons of acetyl group and H_2 of **3b** is not observed (**B** and **C**),



however, *tert* -butyl protons of pivaloyl group and H_2 of **3c** are close enough to give NOE (10%). After examining detailed reaction conditions, regioselective ratio was not improved even. It was postulated then that the 2-position of indole should be inactivated by addition of more strong electron acceptor. Based on the consideration, some attempts to cyclize at 4-position were tried to choose the suitable combination of Lewis acid. Then, in case of **3b** , by addition of propionyl chloride (4.0 equiv.), **1b** was obtained in 21% yield (Table 1, Entry 3). Additionally, high yield (78% yield) and regioselectivity (**1c** : **4 c** = 94 : 6)were attained, when oxocarbonium ion species as strong Lewis acid, generated in situ from chloroacetyl chloride and aluminum chloride, was employed for **3c** (Entry 7).

A typical procedure for these reactions is as follows ; treatment of **3c** (1.0 equiv.) with thionyl chloride (5.0 equiv.) at 25 °C for 10 min followed by complete evaporation of excess thionyl chloride in vacuo gave crude corresponding acid chloride. Thus, to a 1,2-dichloroethane solution of anhydrous aluminum chloride (4.0 equiv.) and chloroacetyl chloride (4.0 equiv.) was added a 1,2-dichloroethane solution of the acid chloride. Usual work up and isolation by silica gel column chromatography afforded **1c**[11] (78%) and **4c** (5%)[12]. Subsequent removal of the pivaloyl moiety of **1c** with catalytic sodium methoxide in methanol at 15 °C for 5 min gave Uhle's ketone (**1a**).

The present reaction is assumed to proceed *via* the intermediate **D**, which is consisted of acyl chloride-



aluminum chloride complex,'oxocarbonium ion'[13], and indole compound, and these oxocarbonium ions inactivate electrophilicaly the pyrrole ring of indole to give cyclization at 4-position. These bulky oxocarbonium ions block 2-position of indole, and 4-position carbon predominantly attacks to 3-indolepropionyl chloride-aluminum chloride complex.

In summary, this work has first demonstrated that regioselective Friedel-Crafts cyclization of 3-indolepropionyl chloride derivative is realized by using oxocarbonium ion species, easily prepared in situ from chloroacetyl chloride and aluminum chloride. Further studies to analyze the detailed mechanism of the interaction between the oxocarbonium ion and 3-indolepropionyl chloride-aluminum complex are now in progress.

References and Notes

Present address: #School of Bioresources, Mie University, Kamihama-chou, Tsu 514, Japan
##School of Agriculture, Gifu University, Yanagido, Gifu 501-11, Japan

† Deceased on August 29, 1990.

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10. **3c**: mp 126~127 °C, MS m/z 273 (M^+), ^{1}H-NMR ($CDCl_3$, 20 °C, 200 MHz), δ 1.49(9H, s), 2.78(2H, t, J= 7.3 Hz), 3.06(2H, t, J= 7.3 Hz), 7.28(1H, ddd, J= 7.0, 6.8, 1.0 Hz), 7.36(1H, ddd, J=7.8, 7.0, 1.5 Hz), 7.50(1H, dd, J= 6.8, 1.5 Hz), 7.56(1H, s), 8.50(1H, dd, J= 7.8, 1.0 Hz).
11. **1c**: mp 168~169 °C, MS m/z 255(M^+), ^{1}H-NMR ($CDCl_3$, 20 °C, 200 MHz), δ 1.52(9H, s), 2.89(2H, t, J= 7.1 Hz), 3.23(2H, t, J= 7.1 Hz), 7.44(1H, dd, J= 8.0, 7.9 Hz), 7.58(1H, s), 7.74(1H, dd, J=7.9, 0.8 Hz), 8.54(1H, dd, J= 8.0, 0.8 Hz).
12. **4c**: mp 132~133°C, MS m/z 255(M^+), ^{1}H-NMR ($CDCl_3$, 20 °C, 200 MHz), δ 1.45(9H, s), 3.06(4H, m), 7.28(1H, ddd, J= 8.0, 7.0, 1.0 Hz), 7.48(1H, ddd, J= 8.0, 7.0, 1.0 Hz), 7.68(1H dd, J= 7.0, 1.0 Hz), 7.72(1H, d, J= 8.0 Hz).
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