REACTIVITY OF INDOLE AS AN ELECTROPHILE AND ITS APPLICATION FOR THE SYNTHESIS OF 2-PHENYLINDOLE AND 3-PHENYLINDOLE

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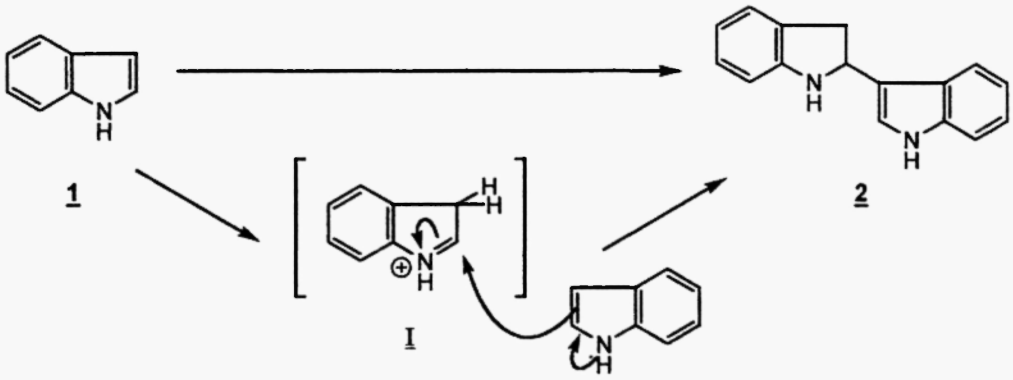
Abstract: Reactivity of *N*-acylindole 3a~c as an electrophile was studied and phenyl group was introduced at the 2 and 3-position of indole nucleus to afford phenylindoline derivatives 4a~c and 5a~c. which were derived to 2-phenylindole 8 and 3-phenyindole 9.

Indole is one of the most fascinating compounds and its chemistry had been studied for a century (1). Since the pyrrole part of indole nucleus is electron rich, nucleophilic reactivity of the 1~3 positions plays the major part of indole chemistry (1a). On the other hand, reactivity of indole as an electrophile has also been reported in polymerization of indole to give dimer *etc.* reported by Hodson and Smith (2) as shown in Scheme 1. The reaction mechanism could be realized by the key step that electron deficient 2-position of protonated cation I is attacked by electron rich 3-position of non-protonated 1. Here we report novel route to introduce pheny group at 2 and 3-position of *N*-acylindole.

We started our synthetic study on electron deficient indole (3) such as I type and chose *N*-acylindole 3a~c as the model compounds. Nucleophilic addition of benzene to electron deficient 3a~c–AlCl$_3$ complex II prepared in CH$_2$Cl$_2$ was easily achieved as summarized in Table 1. When *N*-acetylindole 3a was treated with 3~5 equiv. AlCl$_3$ in CH$_2$Cl$_2$ solution

Scheme 1.



containing 1.2 equiv. benzene at r.t., 3-phenylindoline derivative 5a (80%) and 2-phenylindole derivative 4a (8%) were obtained. In the case of *N*-trimethylacetylindole 3b, no 2-phenylindoline derivative 4b was produced in the reaction mixture. In the same reaction condition, *N*-benzoylindole 3c provided about 1 : 1 mixture of 4c (4) and 5c (5) in 82% yield. Thus we could readily introduce a phenyl group at the 2 and 3-position of *N*-acylindole 3a~c to give phenylindoline 4a~c and 5a~c in good yields.

2-phenylindole 8 and 3-phenylindole 9 are usually prepared by E. Fischer's indole synthesis (6), or other methods (7) starting from simple benzene derivative such as aniline. Recently, Yamanaka and Sakamoto (8) reported new route for the synthesis of 8 and 9 starting from protected indoles *via* its carbanion of 2 or 3-position, but no synthetic method of 8 and 9 utilizing electrophilic reactivity of indole nucleus has been reported.

A 1 : 1 mixture of 2 and 3-phenylindoline derivatives 4c and 5c was hydrolized with 6N HCl to give 2-phenylindoline 6 and 3-phenylindoline 7 in 89% yield. Separation of 6 and 7 was easily carried out by chromatography on silica gel PTLC plate (solvent: 10% EtOAc in hexane). Oxidation of 6 or 7 in dichloroethane with MnO_2 at 60 °C afforded 2-phenylindole 8 (9) and 3-phenylindole 9 (10) in 87% and 72% yield, respectively. Their m.p. and spectoscopic data were completely identical with reported data. Consequently, we could establish a novel and convenient synthetic route of 2-phenylindole 8 and 3-phenylindole 9 from indole.

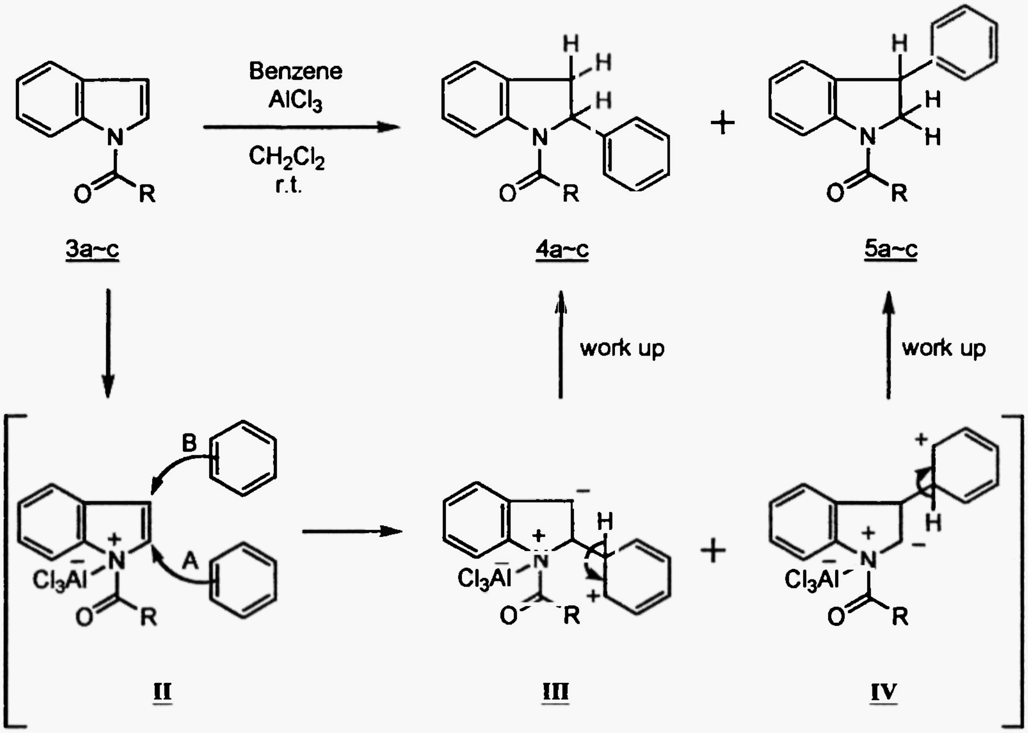
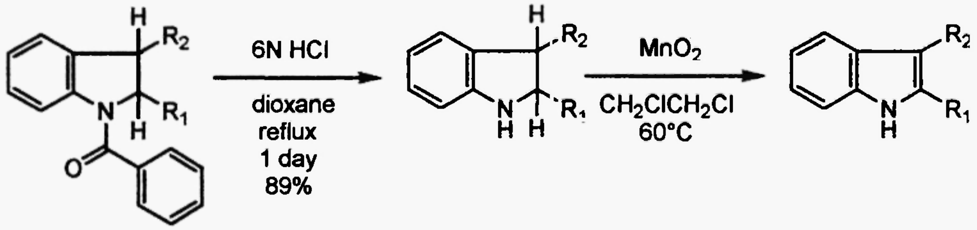


Table 1. Electrophile addition of 3a~c

Starting Materials 3	Products 4	5
3a: R = CH_3	4a (8%)	5a (80%)
3b: R = $C(CH_3)_3$	4b (0%)	5b (81%)
3c: R = C_6H_5	4c (39%)	5c (43%)



4c: $R_1 = C_6H_5$, $R_2 = H$
5c: $R_1 = H$, $R_2 = C_6H_5$

6: $R_1 = C_6H_5$, $R_2 = H$
7: $R_1 = H$, $R_2 = C_6H_5$

8: $R_1 = C_6H_5$, $R_2 = H$ (87%)
9: $R_1 = H$, $R_2 = C_6H_5$ (72%)

REFERENS AND FOOTNOTES

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(4) 4c; MS m/z 299 (M^+), 105. ^{1}H-nmr ($CDCl_3$) δppm 2.98 (1H, d.d., J=2 & 16 Hz), 3.74 (1H, d.d., J=10 & 16 Hz), 5.44 (1H, br.s), 6.99~7.08 (3H, m), 7.17~7.43(10H,m), 8.26 (1H, extremely br.s).

(5) 5c; MS m/z 299 (M^+), 105. ^{1}H-nmr ($CDCl_3$) δppm 4.01 (1H, br.s), 4.45 (1H, br.s), 4.56(1H, br.t, J=9 Hz), 7.01 (2H,m), 7.18~7.20 (3H,m), 7.26 (1H,m), 7.32 (2H,m), 7.41~7.46 (2H, m), 8.27 (1H, extremely br.s).

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(9) 8; m.p. 189~190°C (lit.,[7a] 188~189°C), MS m/z 193 (M^+). ^{1}H-nmr ($CDCl_3$) δppm 6.83 (1H, br.s), 7.13 (1H, br.t, J=8 Hz), 7.20 (1H, br.t, J=8 Hz), 7.34 (1H, br.t, J=8Hz), 7.44~7.50 (3H, m), 7.63 (1H, br.d, J=8 Hz), 7.68 (2H, m), 8.36 (1H, br.s).

(10) 9; m.p. 86.5~87°C (lit.,[6b] 88~89°C), MS m/z 193 (M^+). ^{1}H-nmr ($CDCl_3$) δppm 7.20 (1H, br.t, J=8Hz), 7.26 (1H, br.t, J=8 Hz), 7.29 (1H, br.t, J=8 Hz), 7.38 (1H, d, J=3Hz), 7.43~7.47 (3H, m), 7.68 (2H, br.d, J=8 Hz), 7.95 (1H, br.d, J=8 Hz), 8.25 (1H, br.s).

Received on October 30, 1999