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## NUCLEOPHILIC SUBSTITUTION REACTION ON THE NITROGEN OF INDOLE NUCLEUS :FORMATION OF 1-(INDOL-3-YL)INDOLES UPON REACTION OF 1-HYDROXYINDOLES WITH INDOLE IN FORMIC ACID<sup>1</sup>

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Abstract — 1-(Indol-3-yl)indoles are obtained in excellent to good yields by the reaction of 1-hydroxyindoles with indole in 85% formic acid. Their structures are determined by X-Ray crystallographic analysis and chemical correlations. The unprecidented SN2 mechanism on the indole nitrogen is proposed.

In this communication, <sup>1</sup> we wish to report a formation of 1-(indol-3-yl)indoles (2a-c) upon reaction of 1-hydroxyindoles<sup>2</sup> (1a-c) with indole in 85% HCOOH (Scheme 1).

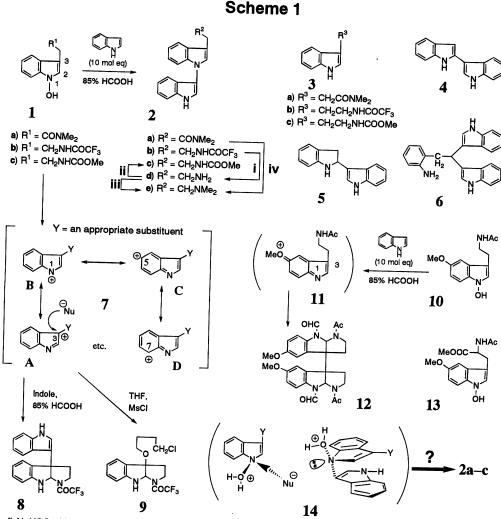
A typical procedure is as follows: 85% aqueous HCOOH was added to a mixture of N,N-dimethyl-1-hydroxyindole-3-acetamide (1a) and indole (10 mol eq), and stirring was continued at room temperature for 2 h. After addition of H<sub>2</sub>O to the reaction mixture, the whole was extracted with 5% MeOH-CHCl<sub>3</sub>. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil which was column-chromatographed to give 2a and 3a in 84 and 8% yields, respectively. From the reaction mixture, 4,3 5, 4 and 6,4 products originated from an excess amount of indole, were also isolated in the respective yields of 1, 11, and 37%.

Under similar reaction conditions, 1b provided 2b and 3b in 55 and 9% yields, respectively, while 1c afforded 2c and 3c in the respective yields of 47 and 9%. In both reactions, concomitant formations of 4, 5, and 6 were observed as well.

Chemical correlations among 1-(indol-3-yl)indoles (2a-c) were readily attained by the following sequence of reactions. Thus, hydrolysis of 2b with sat. aq. NaHCO<sub>3</sub> provided tryptamine (2d) in 99% yield. Methoxycarbonylation of 2d with methyl chloroformate in the presence of Et<sub>3</sub>N afforded 99% yield of 2c, which was identical with the sample obtained from 1c. Dimethylation of 2d with HCHO and NaBH<sub>3</sub>CN smoothly proceeded to give 92% yield of dimethyltryptamine (2e), which was identical with the sample prepared in 76% yield by the reduction of 2a with LiAlH<sub>4</sub> in THF.

Compound (2a) was suitable prisms for X-Ray single crystallographic analysis. The results shown in Figure 1 clearly show the presence of a covalent bond connecting the N-1 of indole to the C-3 of the other indole molecule. Based on this fact, chemically correlated structures of 2b-e were also determined unequivocally.

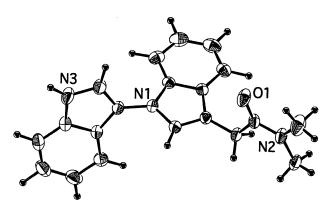
Now that the structures of 2a-e are established, how can we explain the substitution mechanism for the 1-hydroxy group of 1a-c by a nucleophile, indole?



i) NaHCO $_3$ , H $_2$ O, MeOH, 60°C, 8 h; ii) CICOOMe, Et $_3$ N, MeOH, rt, 30 min; iii) HCHO, AcOH, NaBH $_3$ CN, rt, 3 h; iv) LiAlH $_4$ , THF, reflux, 1 h.

We could consider the reaction proceeds by the SN1 mechanism. Thus, the reaction begins with a protonation of 1-hydroxy oxygen atom converting it to a good leaving group. Liberation of water leaves an indolyl cation (7) which is a resonance hybrid consisted of resonance structures, A, B, C, D, and others. The contribution of B is generally considered to be poor because positive charge is placed on the electron negative nitrogen, while

Figure 1
ORTEP Drawing of 2a (R = 0.038)



the contributions of C, D, and others are less important due to the lack of aromaticity of benzene part. The resonance structure (A) would therefore be the most responsible for the reaction with nucleophiles. In accord with this view, we have already succeeded in trapping A in the reaction of 1b with either indole in 85% HCOOH<sup>5</sup> or MsCl in THF<sup>6</sup> resulting in  $8^5$  and 9,  $6^6$  respectively. The other possibility for the formations of 8 and 9 is the SN2' mechanism. An attempt to stabilize the resonance structure B was made by introducing a methoxy group at the 5-position with an expectation to increase the yield of the corresponding 1-(indol-3-yl)indole through a cation (11). The employed substrate (10), however, did not provide the expected product at all in the reaction with indole in 85% HCOOH, instead  $12^7$  was generated in 26% yield.

On the other hand, we have already shown based on X-Ray single crystallographic analysis that the 1-hydroxy oxygen on the N-1 of tryptophan derivative<sup>8</sup> (13) lies above the plane of indole deviated by about  $15^{\circ}$ . This result suggests that the indole nitrogen in 1-hydroxyindoles is no longer exactly  $sp^2$  hybridized. Upon protonation of 1-hydroxy oxygen of 1a-c, the nitrogen might become more  $sp^3$  like hybridized. When water departs from it, a nucleophile (indole) could approach from the back side of the leaving group in a transition state (14), resulting in the formations of 2a-c. Although such  $Sn^2$  reaction on the N-1 of indole nucleus has not been proposed in indole chemistry, this concerted mechanism seems to be attractive because it can easily explain why the concomitant formation of 8 was not observed at all. We might have found the first example of the  $Sn^2$  reaction on the indole nitrogen, 10 though the possibility of the reaction of B with indole is not excluded yet.

Further extentions of this novel reaction to other nucleophiles and 1-hydroxyindoles are in progress.

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