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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[1]

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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 *SN*2 mechanism on the indole nitrogen is proposed.

In this communication,[1] we wish to report a formation of 1-(indol-3-yl)indoles (**2a**–**c**) upon reaction of 1-hydroxyindoles[2] (**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_2O to the reaction mixture, the whole was extracted with 5% MeOH-$CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, 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%.

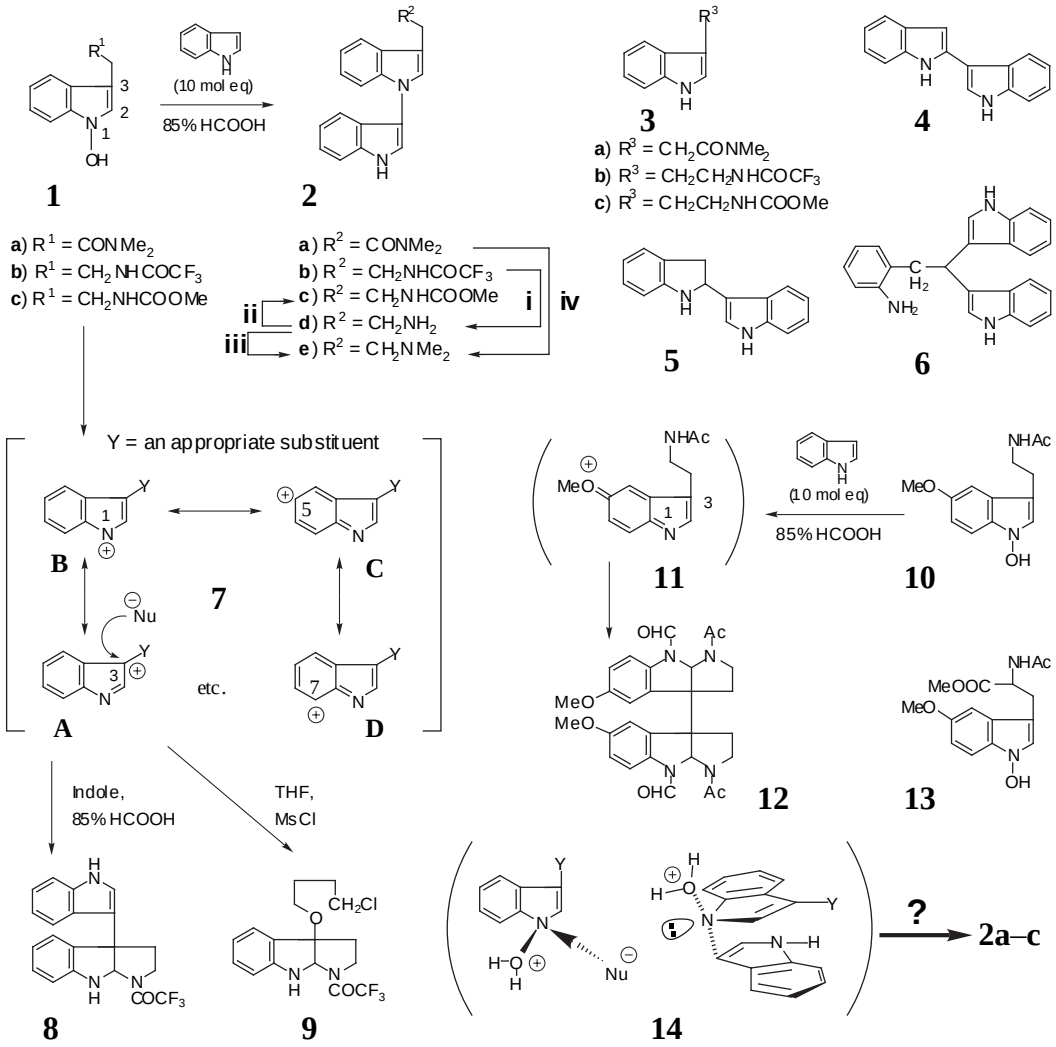
Under similar reaction conditions, **1b** provided **2b** and **3b** in 55 and 9% yields, respectively, while **1c** afforded **2c** and **3c** in the respective yields of 47 and 9%. In both reactions, concomitant formations of **4**, **5**, and **6** were observed as well.

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. $NaHCO_3$ provided tryptamine (**2d**) in 99% yield. Methoxycarbonylation of **2d** with methyl chloroformate in the presence of Et_3N afforded 99% yield of **2c**, which was identical with the sample obtained from **1c**. Dimethylation of **2d** with HCHO and $NaBH_3CN$ 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 $LiAlH_4$ 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?

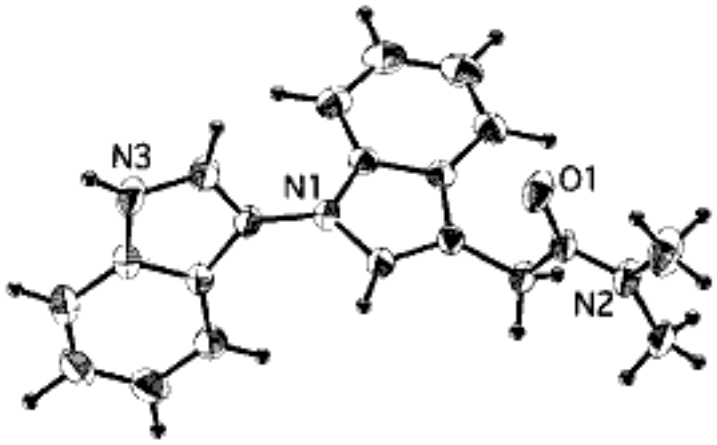
Scheme 1



i) $NaHCO_3$, H_2O, MeOH, 60°C, 8 h; ii) ClCOOMe, Et_3N, MeOH, rt, 30 min; iii) HCHO, AcOH, $NaBH_3CN$, rt, 3 h; iv) $LiAlH_4$, THF, reflux, 1 h.

Figure 1

ORTEP Drawing of **2a** (R = 0.038)



We could consider the reaction proceeds by the *SN*1 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

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[5] or MsCl in THF[6] resulting in **8**[5] and **9**,[6] respectively. The other possibility for the formations of **8** and **9** is the *SN*2' 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[8] (**13**) lies above the plane of indole deviated by about 15°.[9] 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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