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journal or publication title	Heterocycles
volume	55
number	3
page range	457-460
year	2001-03-01
URL	http://hdl.handle.net/2297/4366

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 ACID¹

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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 unprecedented *S_N2* 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-hydroxyindoles² (**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 H₂O to the reaction mixture, the whole was extracted with 5% MeOH-CHCl₃. The extract was washed with brine, dried over Na₂SO₄, 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. NaHCO₃ provided tryptamine (**2d**) in 99% yield. Methoxycarbonylation of **2d** with methyl chloroformate in the presence of Et₃N afforded 99% yield of **2c**, which was identical with the sample obtained from **1c**. Dimethylation of **2d** with HCHO and NaBH₃CN 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 LiAlH₄ 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

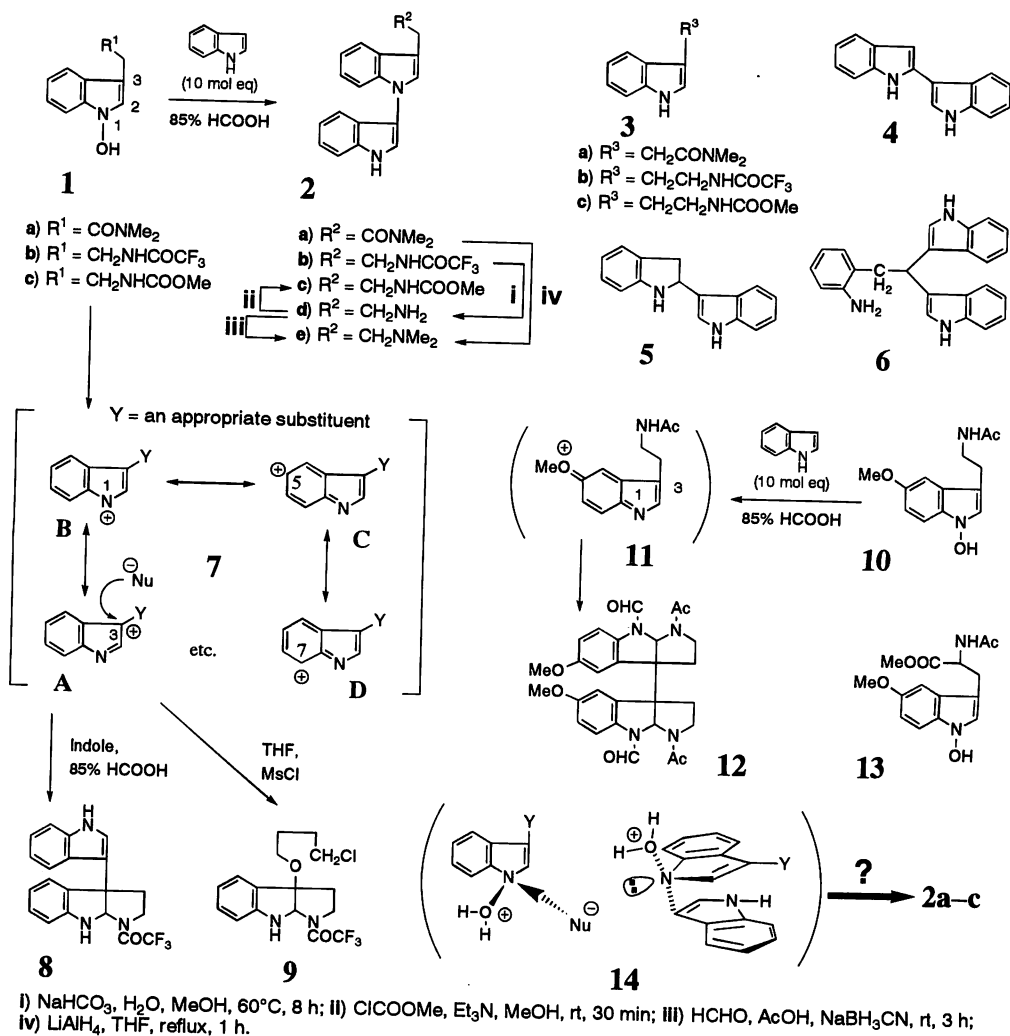
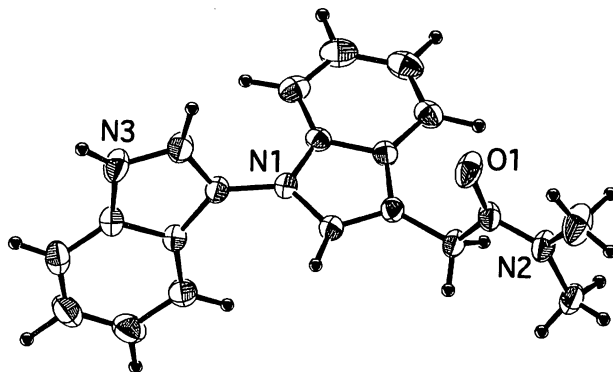


Figure 1

ORTEP Drawing of 2a (R = 0.038)



We could consider the reaction proceeds by the S_N1 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% HCOOH⁵ or MsCl in THF⁶ resulting in **8**⁵ and **9**,⁶ respectively. The other possibility for the formations of **8** and **9** is the *S_N2'* 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 derivative⁸ (**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 *S_N2* 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 *S_N2* reaction on the indole nitrogen,¹⁰ though the possibility of the reaction of **B** with indole is not excluded yet.

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

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Received, 30th November, 2000