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NUCLEOPHILIC SUBSTITUTION REACTION ON THE NITROGEN OF INDOLE NUCLEUS: A NOVEL SYNTHESIS OF 1-ARYLTRYPTAMINES[1]

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Abstract — 1-Hydroxytryptamine derivatives undergo nucleophilic substitution reaction on the indole nitrogen (*Na*) as a general reaction by the treatment with acid, providing a novel synthetic method for 1-aryltryptamines. Depending on the structures of nucleophiles, 5- and 7-substituted tryptamines can also be produced in addition to the 1-aryltryptamines.

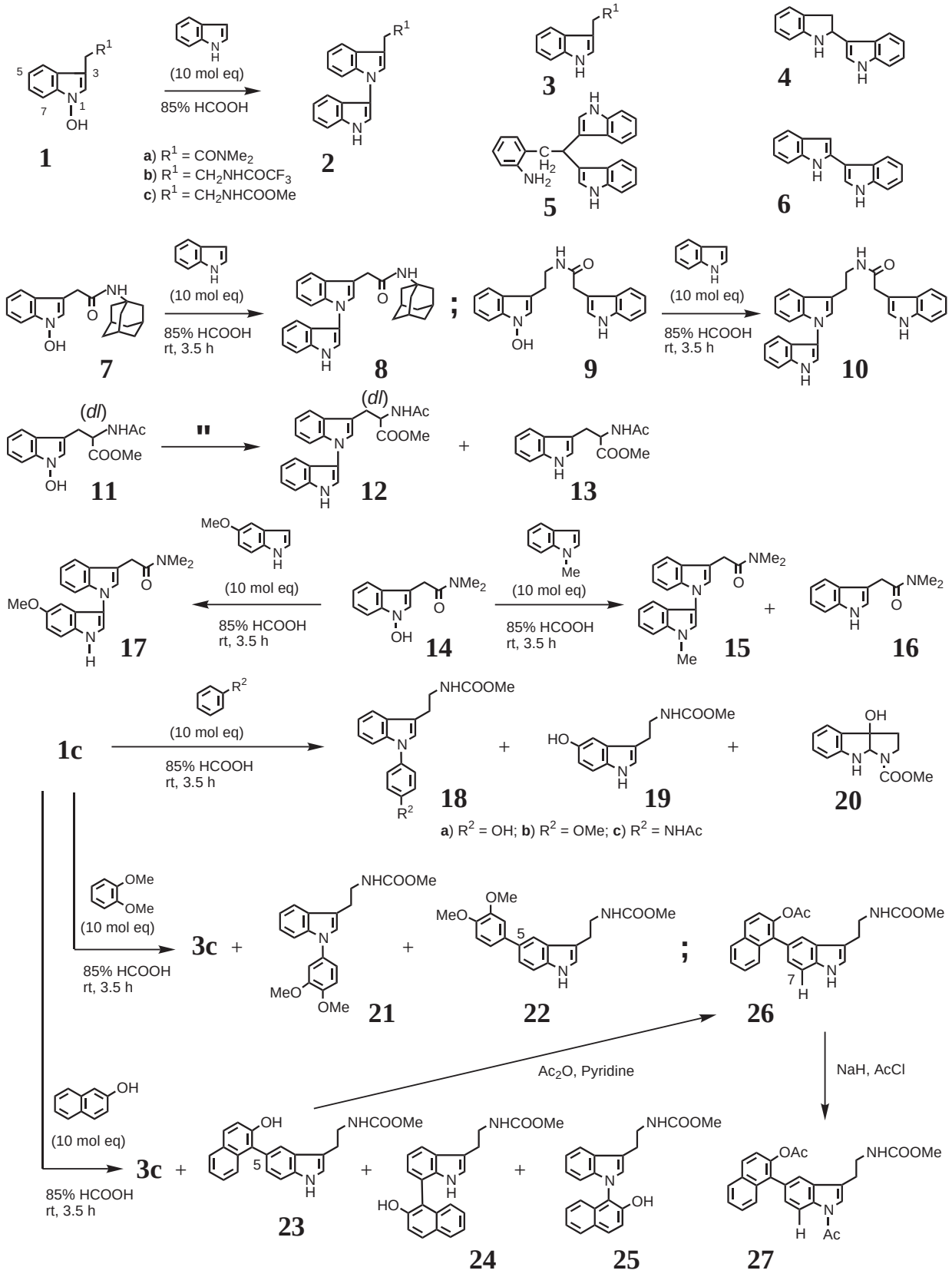
In this communication, we wish to report that the unprecedented nucleophilic substitution reaction on the indole nitrogen[2] (*Na*) is in fact a general reaction widely observed among the 1-hydroxytryptamine derivatives. We also describe that the formation of a C—C bond at the 5- or 7-position can be realized depending on the structures of nucleophiles.

We have disclosed that when 1-hydroxyindoles[3] (**1a**–**c**) are allowed to react with indole in 85% HCOOH, 1-(indol-3-yl)indoles (**2a**–**c**) are produced in good to excellent yields together with **3a-c**, **4**, **5**, and **6** (Scheme 1). To extend the scope of this new type reaction in indole chemistry, we prepared novel 1-hydroxytryptamines (**7**, **9**, and **11**). In 85% HCOOH, these compounds underwent the expected reaction with indole (10 mol eq) rapidly at room temperature in every case. Consequently, **8**, **10**, and **12** were produced as major products in 72, 52, and 60% yields, respectively.

Based on these results, we next tried to change nucleophile's structure to see its effect on the nucleophilic substitution reactions. First, 1-methylindole was employed to react with **14** in 85% HCOOH to give **15** and **16** in 64 and 8% yields, respectively. The reaction of 5-methoxyindole with **14** afforded **17** in 58% yield. In cases where nucleophilicity of nucleophiles becomes poorer, the yield of the substitution product on the nitrogen (*Na*) decreases, instead many by-products are formed. Thus, the reaction of **1c** with phenol led to the formation of **18a** in 20% yield together with 5-hydroxy-*Nb*-methoxycarbonyltryptamine[4] (**19**) and 3a-hydroxy-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole[5] (**20**) in 11 and 5% yields, respectively. Anisole reacted with **1c** to provide **18b** in 15% yield, while the main product was **3c** (26%). When **1c** was reacted with acetanilide, **18c**, **19**, **20**, and **3c** were obtained in 3, 12, 3, and 9% yields, respectively. Structural correlation between **18a** and **18b** were carried out by reacting **18a** with ethereal diazomethane affording **18b** in quantitative yield.

When veratrole is employed as a nucleophile in the reaction with **1c**, interesting results are observed. In addition to the expected products (**21**, 10%) and (**3c**, 13%), *Nb*-methoxycarbonyl-5-(3,4-dimethoxy-

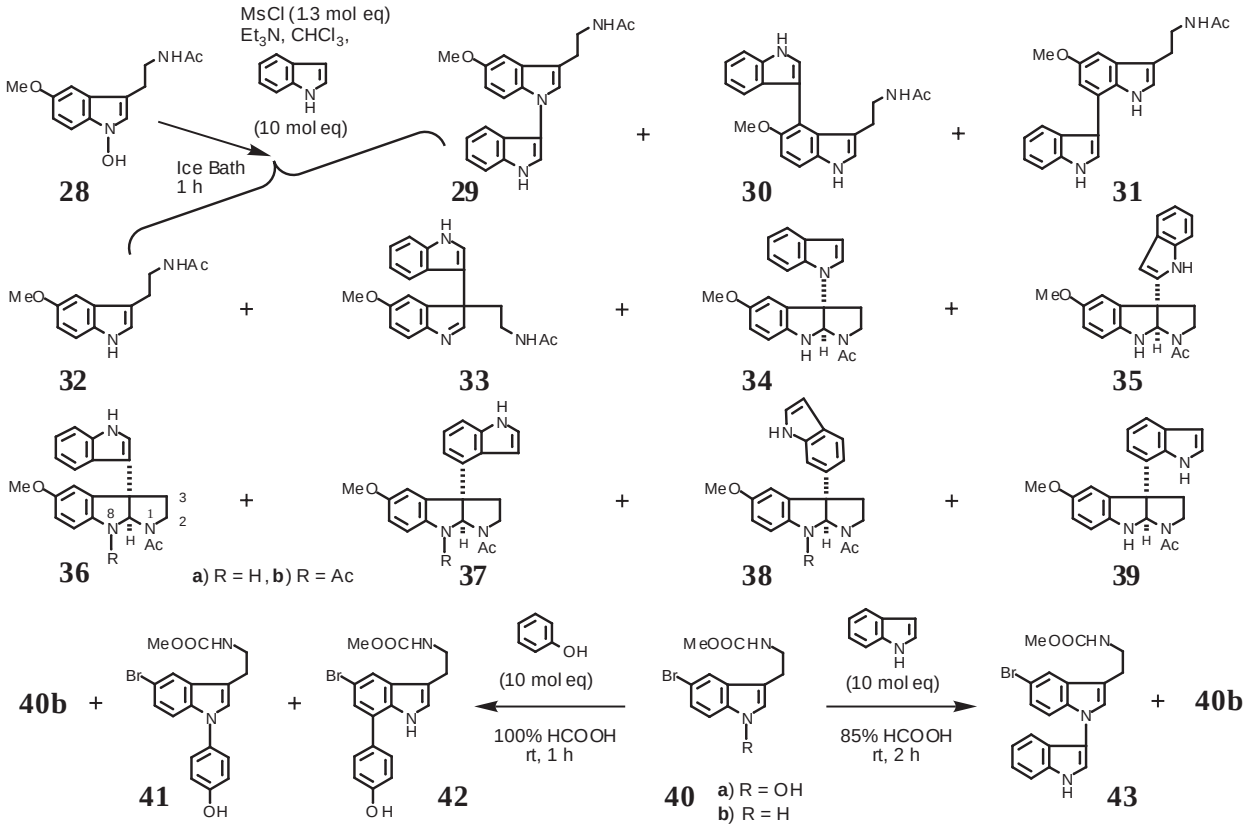
Scheme 1


(10 mol eq)
85% HCOOH
a) R1 = CONMe2
b) R1 = CH2NHCOCF3
c) R1 = CH2NHCOOMe
1
2
3
4
5
6
7
8
9
10
rt, 3.5 h
(dl)
11
12
13
17
14
15
16
1c
18
19
20
a) R2 = OH; b) R2 = OMe; c) R2 = NHAc
3c
21
22
26
Ac2O, Pyridine
NaH, AcCl
23
24
25
27

phenyl)tryptamine (**22**) was isolated in 9% yield. This type of reaction forming a C—C bond on the indole nucleus became a major one in the reaction of 2-naphthol with **1c**, producing **23**, **3c**, **24**, and **25** in 16, 13, 5, and 4% yields, respectively.

The structure of **23** was determined according to our usual methodology. First, **23** was converted to **26** in 77% yield by the reaction with Ac_2O-pyridine. Subsequent treatment of **26** with NaH, followed by the reaction with AcCl produced **27** in 19% yield together with unreacted **26** (39%). Comparison of ^{1}H-NMR spectra of **26** and **27** clearly showed an anisotropy effect on the C-7 proton (d, J = 8 Hz) by *ca.* 0.8 ppm by the newly introduced *Na*-acetyl group.

Scheme 2



We next turned our attention to evaluate the substituent effect of benzene part on the present nucleophilic substitution reactions on indole nitrogen. The reaction of 1-hydroxymelatonin (**28**) with 85% HCOOH has been found to give folicanthine type dimer.[6] Therefore, **28** was treated with mesyl chloride[7] and Et_3N in the presence of indole (10 mol eq). To our surprise, more than ten products were formed as shown in Scheme 2. Separation of **36a**, **37a**, and **38a** was quite difficult because of their close Rf values. Therefore, a mixture fraction involving them was acetylated with Ac_2O-pyridine to afford the corresponding 8-acetyl compounds (**36b**), (**37b**), and (**38b**), which were easily separated by column chromatography. Assuming the acetylation process proceeded in quantitative yield, yields of **36a**, **37a**, and **38a** were estimated. Structures of all products were determined unequivocally based on their spectral data and the above mentioned anisotropy effects observed between *Na*-acetyl derivatives and the

corresponding *Na*-H compounds. As a result, the substitution product (**29**) on the nitrogen was isolated only in 7% yield, while **30**, **31**, **32**, **33**, **34**, **35**, **36**, **37**, **38**, and **39** were produced in 12, 7, 7, 0.4, 1, 4, 5, 2, 2, and 4% yields, respectively. It is interesting to note that various types of C—C bond formation can be realized at the almost all possible positions between the nucleophile and the substrate nuclei.

In the reaction of *Nb*-methoxycarbonyl-5-bromo-1-hydroxytryptamine (**40a**) with phenol in 100% HCOOH at room temperature, **41**, **42**, and **40b** were produced in 37, 6, and 11% yields, respectively. Under similar reaction conditions, the reaction of **40a** with indole led to the formations of **43** and **40b** in 43 and 19% yields, respectively, together with unreacted starting material (**40a**, 24%).

In summary, we have proved that nucleophilic substitution reactions actually occur on the indole nitrogen (*Na*) when 1-hydroxytryptamines are allowed to react with nucleophiles under acidic conditions. This means that a novel and simple synthetic method for 1-aryltryptamines[8] is discovered. Their yields change dramatically depending on structures of both 1-hydroxytryptamines and nucleophiles. Some nucleophiles are found to be introduced into the benzene part of indole nucleus. Further investigations on this novel reaction are in progress.

REFERENCES AND NOTES

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