Functionalization of 7-Azaindole

Hiroshige Kikuta and Yoshiki Ohshiro

Research Institute for Science and Technology, Kinki University
3-4-1, Kowakae, Higashi-Osaka, Osaka 577, Japan

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Abstract

Functionalization of 7-azaindole utilizing Reissert-Henze type reaction was studied. It was found that the direct halogenation, cyanation, and thiocyanation of 7-azaindole proceeded regioselectively. In chlorination of 7-azaindole, the regioselectivity was controlled by chlorination reagents as well as acylation reagents. These functional groups could be chemically modified to useful substituents.

Key words: Azaindole, Functionalization, Reissert-Henze reaction, Halogenation, Cyanation.

1 Introduction

7-Azaindole derivatives have been interested in biochemical and pharmaceutical studies, since they are aza analogues of indoles. Therefore, the functionalization of an azaindole ring is of great importance for development of novel materials.

In the case of π-sufficient pyrrole or indole, electrophilic substitution proceeds at 2- or 3-position, on the contrary, the π-deficient pyridine ring is attacked at 2-, 4-, and 6-positions by nucleophiles.

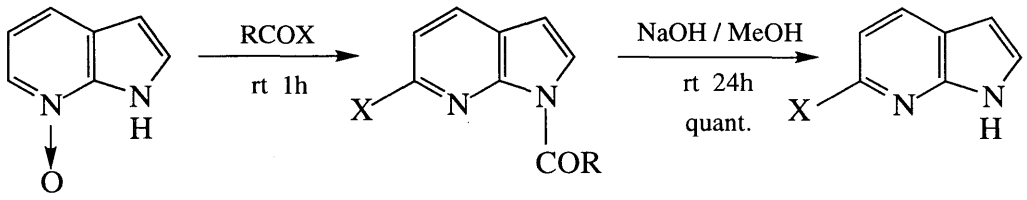
The chemical properties of azaindoles are depressed as compared with either pyridine ring or pyrrole ring since azaindole consists of the ring system having opposite π-electron densities. Reactivity of electrophilic substitution on the pyrrole ring of azaindoles is slightly low as compared with that of pyrrole and indole rings, whereas nucleophilic substitution of its pyridine ring is very difficult.[1]

In general, 6-substituted 7-azaindoles have been synthesized by the ring closure of pyridine derivatives possessing functional substituents,[2] and the procedure of direct functionalization at 6-position of 7-azaindole has rarely been known.[3] The only known method is chlorination of 7-azaindole at 4-position by the reaction of its *N*-oxide with $POCl_3$.[4]

The lack of convenient functionalization method of azaindoles caused to investigate regioselective functionalization of 7-azaindole by Reissert-Henze type reaction. In this paper, we wish to summarize the direct introduction method of halogeno, cyano, and thiocyanato groups to the pyridine nucleus of 7-azaindole.[5,6]

2 Regioselective Halogenation of 7-Azaindole

7-Azaindole *N*-oxide **1**[7] was treated with acid halides in anhydrous tetrahydrofuran to give 6-halo-7-azaindole derivatives **2a-c** in 57-66 % yields. Acyl groups on *N*-1 atom of **2** are readily removed by basic treatment to give **3** in quantitative yields.



1

2a : X = Cl, R = OMe
2b : X = Cl, R = Ph
2c : X = Br, R = Ph

3a : X = Cl
3b : X = Br

One of the important feature of the reaction is that the halogenation reaction are completely regioselective and no 4-halogenation was observed.

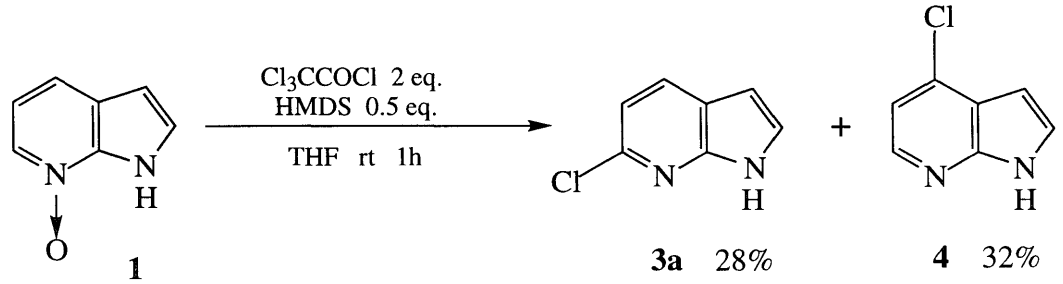
Though the present reaction proceeded without a base, the addition of an organic or inorganic base led to increase in the yield of the chlorinated product **2a**. Among the bases, 1,1,1,3,3,3-hexa-methyldisilazane (HMDS) was the most effective. Since unreacted pyridine *N*-oxide is often recovered as hydrogen halide salt in Reissert-Henze reactions, trapping of the generated acid is one of the important factors to result high yields. HMDS generates ammonia upon contact with hydrogen halide, while the other organic bases form ammonium salts which may act as proton donors.

$$\text{HMDS} + 2\,\text{HX} \longrightarrow 2\,\text{Me}_3\text{Si-X} + \text{NH}_3$$

Benzoyl chloride could be used instead of the chlorocarbonate to give 1-benzoyl analogue **2b**, where the chlorination reaction was effectively promoted by HMDS to obtain the high yield as compared with triethylamine. When benzoyl bromide was employed, 6-bromination successfully proceeded, and 1-benzoyl-6-bromo-7-azaindole (**2c**) was obtained according to a modified reaction procedure.[8]

When trichloroacetyl chloride was employed as an acid halide, both 6-chloro-7-azaindole and the 4-chloro- isomer were obtained in 28 % and 32 % yields, respectively.

Chlorination of pyridine itself is successfully carried out by the reaction of its *N*-oxide with $POCl_3$ or SO_2Cl_2,[9] but this reaction did not occur with acid halides, showing clear difference to that of 7-azaindole.

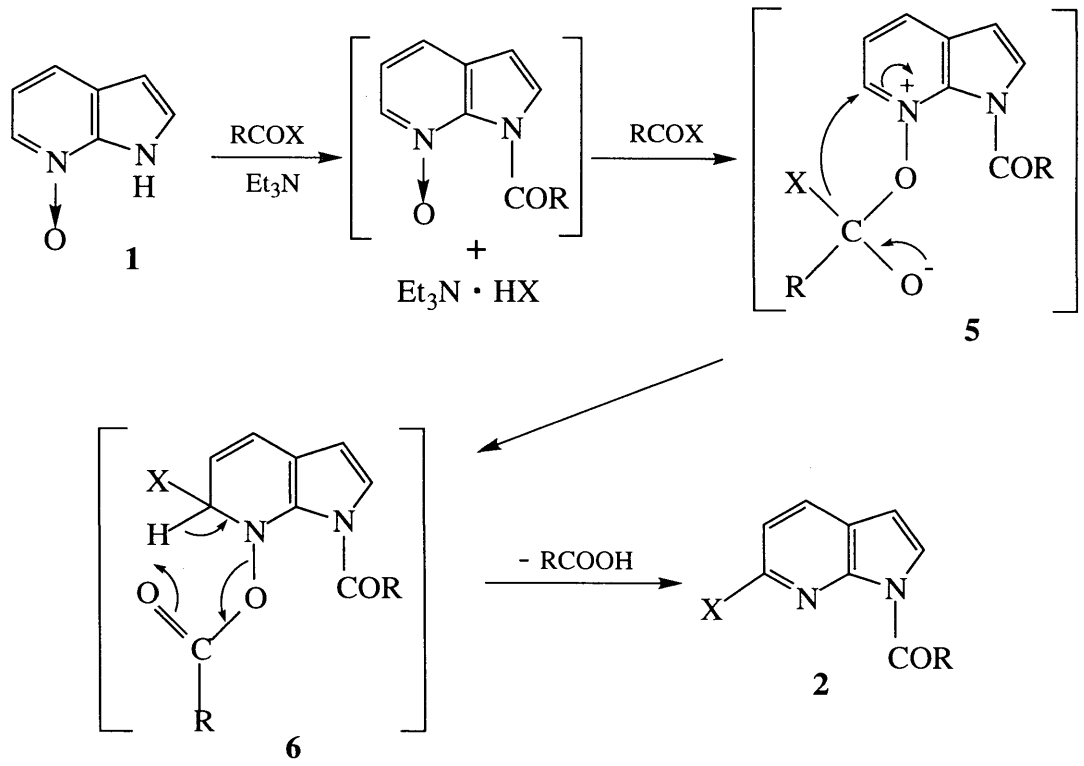


1

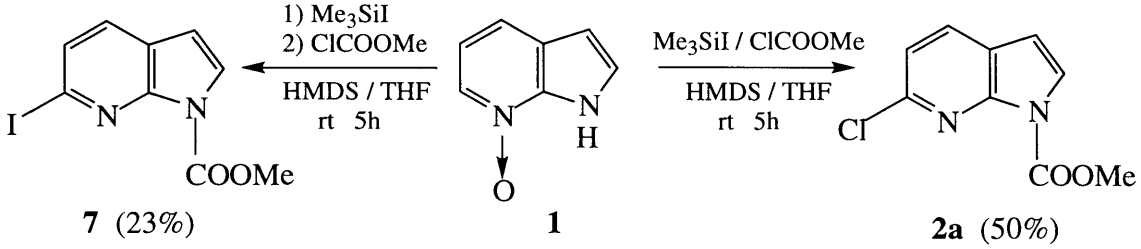
3a 28%

4 32%

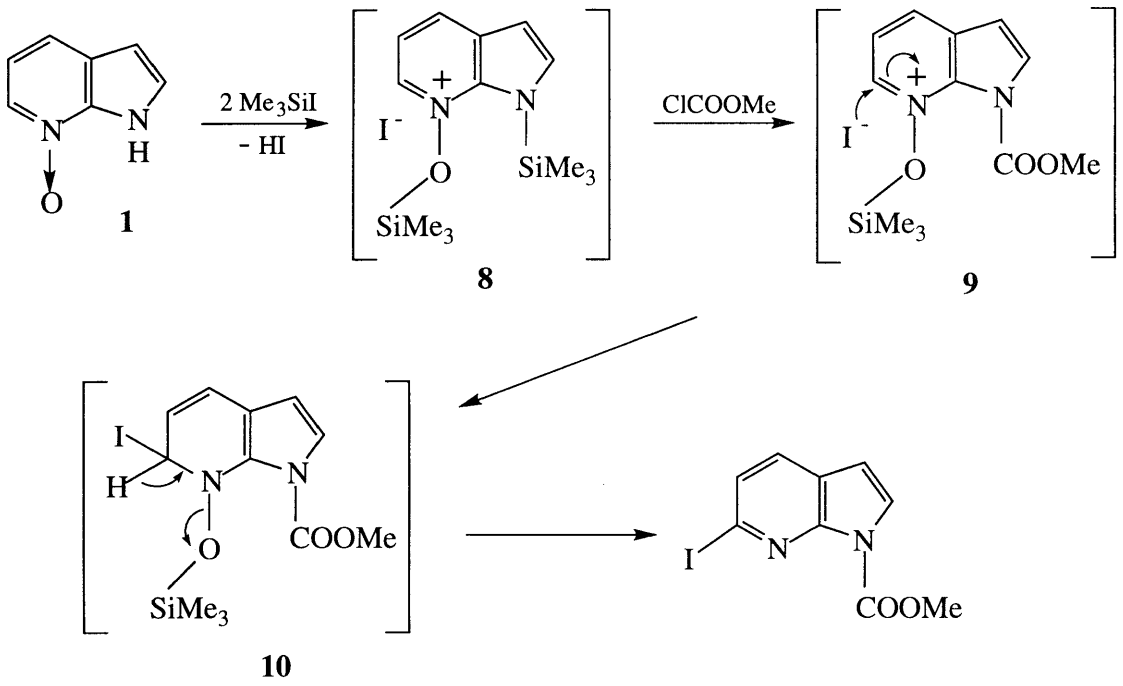
A plausible reaction path is assumed as follows. The pyridinium salt **5** was formed by acylation and addition with two moles of an acid halide. Intramolecular nucleophilic attack of the chloride ion to the 6-position of the intermediate **5** gave 1,2-dihydropyridine intermediate **6**. Intramolecular decarboxylation and successive aromatization occurred to afford the 6-halogenated product.



Substitution of other functional groups to pyridine ring of 7-azaindole was also attempted. Since silicon has a strong affinity toward oxygen, iodination of 7-azaindole was performed with trimethylsilyl iodide. Two different procedures gave rise to different products. When trimethylsilyl iodide was added to a solution of 7-azaindole *N*-oxide and HMDS in tetrahydrofuran prior to addition of methyl chloroformate, 6-iodo-1-methoxycarbonyl-7-azaindole (**7**) was obtained in 23 % yield. On the other hand, a solution of trimethylsilyl iodide and methyl chloroformate in tetrahydrofuran was added dropwise to a solution of the *N*-oxide and HMDS in tetrahydrofuran to afford only the chlorinated product **2a**. Reissert-Henze iodination reaction has not been reported even for pyridine itself.[10]



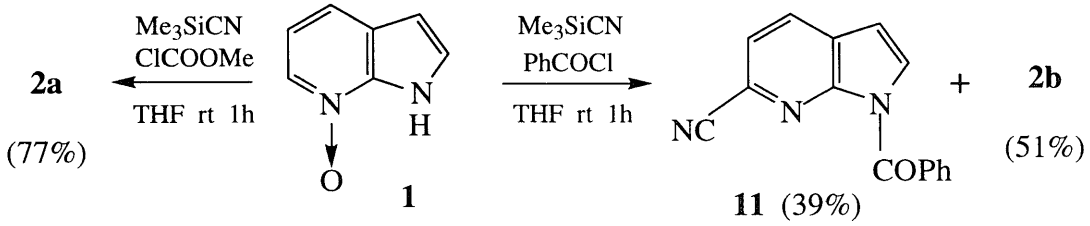
A presumable mechanism of the iodination is as follows. Two molecules of trimethylsilyl iodide reacted with 7-azaindole *N*-oxide to give the siloxypyridinium salt **8**, which was confirmed by PMR spectroscopy. Methoxycarbonylation of *N*-1 by methyl chloroformate caused addition of iodide ion onto the 6-position. Furthermore, silanol was eliminated from 1,2-dihydropyridine intermediate **10** to give the product.



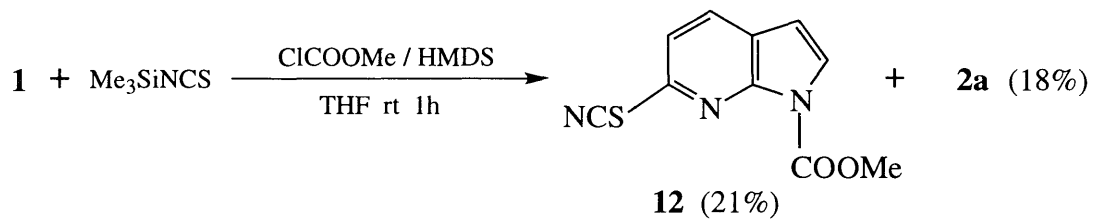
3 Cyanation and Thiocyanation of 7-Azaindole

Pyridine *N*-oxide can be derived to 2- or 4-cyanopyridine by the reaction with trimethylsilyl cyanide[11] or diethyl phosphorocyanidate[12] and by alkylation[13] or acylation[14] and subsequent treatment with aqueous alkali cyanide. However, no reaction was observed when 7-azaindole *N*-oxide was heated with trimethylsilyl cyanide in refluxing tetrahydrofuran.

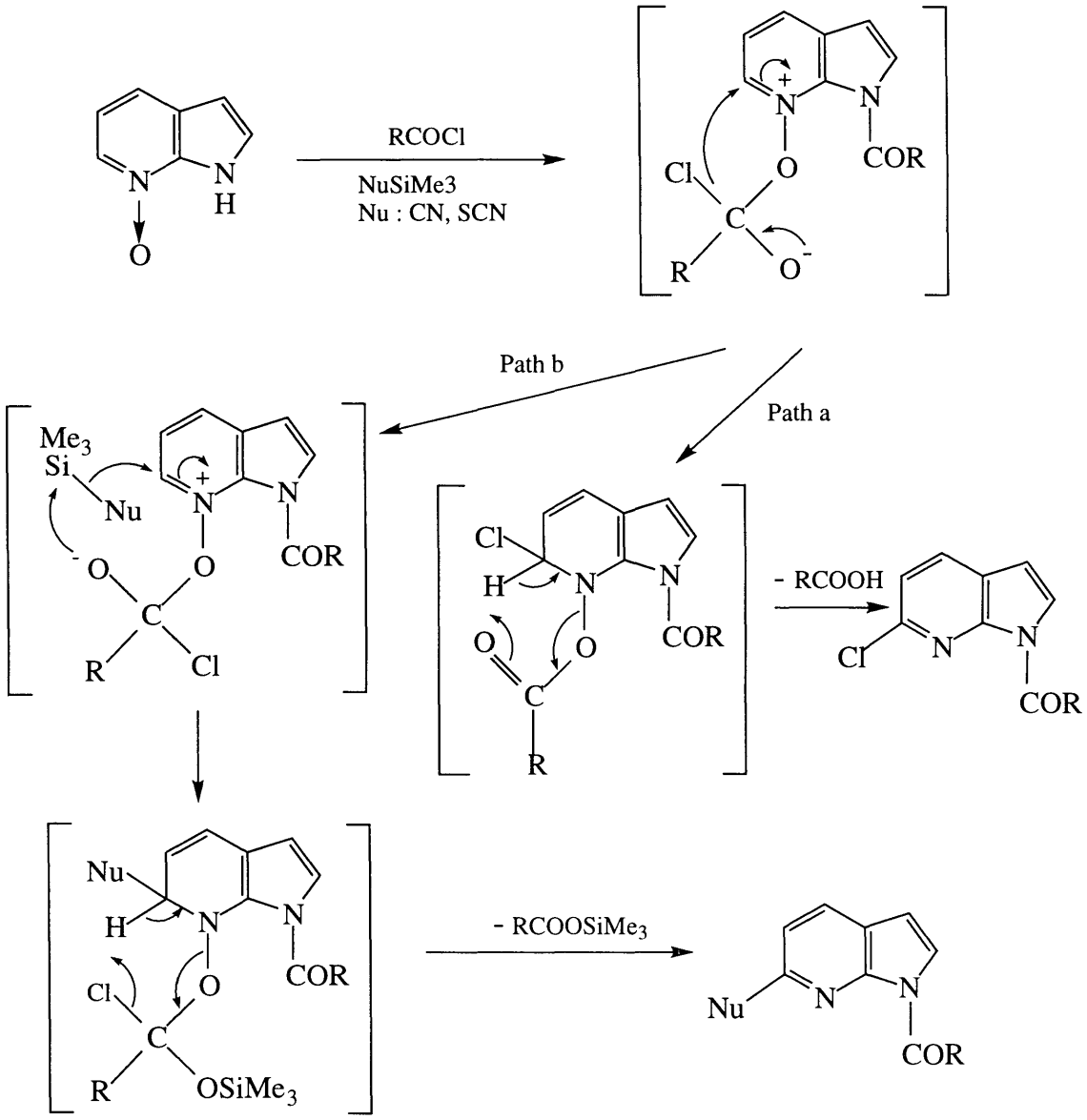
Addition of benzoyl chloride accelerated the substitution by cyanide ion and the reaction gave considerable amount of 1-benzoyl-6-cyano-7-azaindole **11** accompanied with the formation of the chlorinated derivative **2b**. The substitution occurred selectively at 6-position similarly to halogenation. Interestingly, in the case of using methyl chloroformate as the acylating agent, cyanation was not observed, and 1-methoxycarbonyl-6-chloro-7-azaindole (**2a**) was isolated only.



As the silyl cyanide proceeds a cyanation, another silyl derivative such as trimethylsilyl isothiocyanate was allowed to react with 7-azaindole *N*-oxide in a similar manner, and 1-methoxycarbonyl-6-thiocyanato-7-azaindole (**12**) was obtained. No isothiocyanato derivative was isolated in the reaction. Preparation of thiocyanato- or isothiocyanatopyridine by direct substitution has never been known.[15]



The possible reaction path of the cyanation and thiocyanation of 7-azaindole is given below. As both products were accompanied by chlorinated compounds, paths a and b are considered to be competitive in this reaction. The path a is the intramolecular chlorination as mentioned above. In the path b, the oxygen anion of the pyridinium salt attacks the silicon reagent, and the generated nucleophile attacks at the 6-position. In the last step, the products were given by elimination of silyl ester and aromatization.



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