# NEW CYCLIZATION REACTIONS OF 3-DIALKYLAMINO-4-AMINO-PYRIDINES UNDER CONDITIONS OF NITRATION

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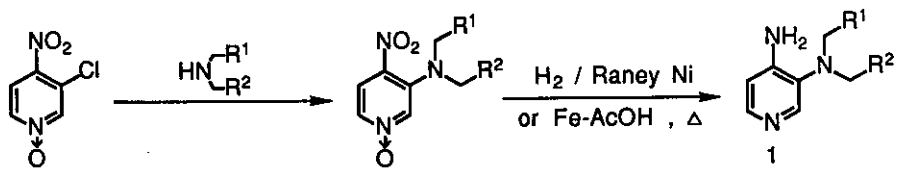
Abstract — Treatment of 3-dialkylamino-4-aminopyridines (**1**) with nitric and sulfuric acids affords imidazo-[4,5-*c*]pyridine derivatives (**2**, **3** and **4**) and 1,2,3-triazolo[4,5-*c*]pyridine 2-oxides (**5**) by cyclization reaction of the corresponding 4-nitroaminopyridines.

In the course of preparation of nitro derivatives of 3-dialkylamino-4-aminopyridines (**1**), we happened to find that treatment of **1** with nitric and sulfuric acids under the usual conditions for nitration brought about new types of cyclization to give imidazo[4,5-*c*]pyridines (**2**, **3** and **4**) and 1,2,3-triazolo[4,5-*c*]pyridine 2-oxides (**5**), the corresponding 4-nitroamino or simple nitro derivatives of **1** being not obtained at all.

3-Dialkylamino-4-aminopyridines (**1**) were prepared in good yields by treatment of 3-chloro-4-nitropyridine 1-oxide[1] with dialkylamines followed by the reduction of the resultant 3-dialkylamino-4-nitropyridine 1-oxides[2] in the presence of Raney nickel or with iron powder and acetic acid[3] (Scheme 1).

Treatment of 4-amino-3-piperidinopyridine (**1a**) with a mixture of fuming



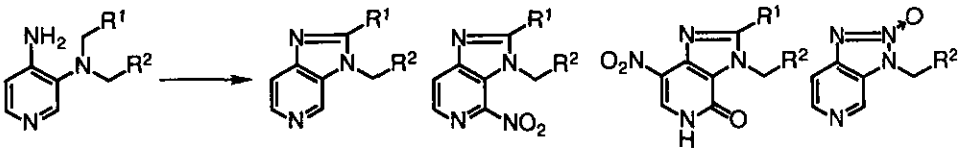

Scheme 1

nitric acid (d=1.50) and conc. sulfuric acid at 50-60°C for 3.5 h resulted in the formation of 5-nitro-1,2,3,4-tetrahydropyrido[1',2':1,2]imidazo[5,4-c]pyridine (**3a**) in a low yield of 12% accompanied by much resinification. A similar reaction of 4-amino-3-pyrrolidinopyridine (**1b**) gave 1,2,3-trihydropyrrolo[1',2':1,2]imidazo[5,4-c]pyridine (**2b**) and its 4-nitro derivative (**3b**) in 10 and 9% yields, respectively. From the reaction of 4-amino-3-morpholinopyridine (**1c**) at 120°C for 5 h, only morpholino-[3',4':2,3]imidazo[4,5-c]pyridine (**2c**) was obtained in 15% yield.

While 4-amino-3-dimethylaminopyridine (**1d**) gave 3-methylimidazo[4,5-c]-pyridine (**2d**) again in a low yield of 10% after a vigorously exothermic and foaming reaction, 4-amino-3-diethylaminopyridine (**1e**) underwent mainly a different type of cyclization to give 3-ethyl-1,2,3-triazolo[4,5-c]pyridine 2-oxide (**5e**) in a good yield of 76% together with a small amount (8%) of an imidazopyridine, 3-ethyl-2-methyl-7-nitroimidazo[4,5-c]pyridin-4(5H)-one (**4e**). Similarly, the triazolopyridine 2-oxide (**5f**, 43%) and the 7-nitro-imidazopyridinone (**4f**, 13%) were formed in the reaction at room temperature of 4-amino-3-dipropylaminopyridine (**1f**). The reaction of 4-amino-3-(N-butyl-N-methylamino)pyridine (**1g**) gave 3-methyl-1,2,3-triazolo[4,5-c]-pyridine 2-oxide (**5g**, 18%) and 3-methyl-2-propylimidazo[4,5-c]pyridine (**2g**, 8%). The structures of these products were established by elemental analyses, $^1$H-nmr and mass spectroscopies, and those of **3a** and **5e** were further confirmed by X-ray analyses (Table).

Cyclization reaction of ortho-substituted N,N-dialkylanilines are well

Table. Reaction of 1 with fuming $HNO_3$ and conc. $H_2SO_4$

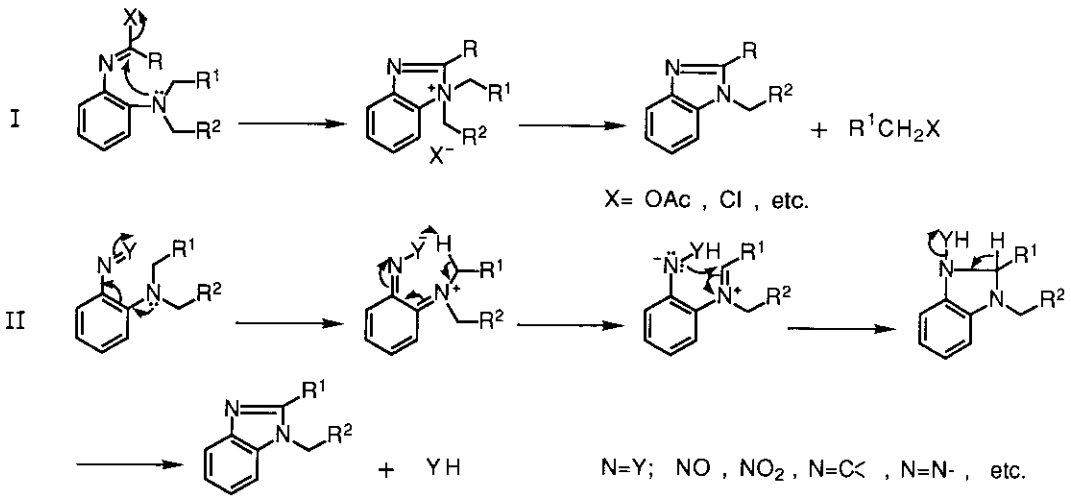


1 2 3 4 5

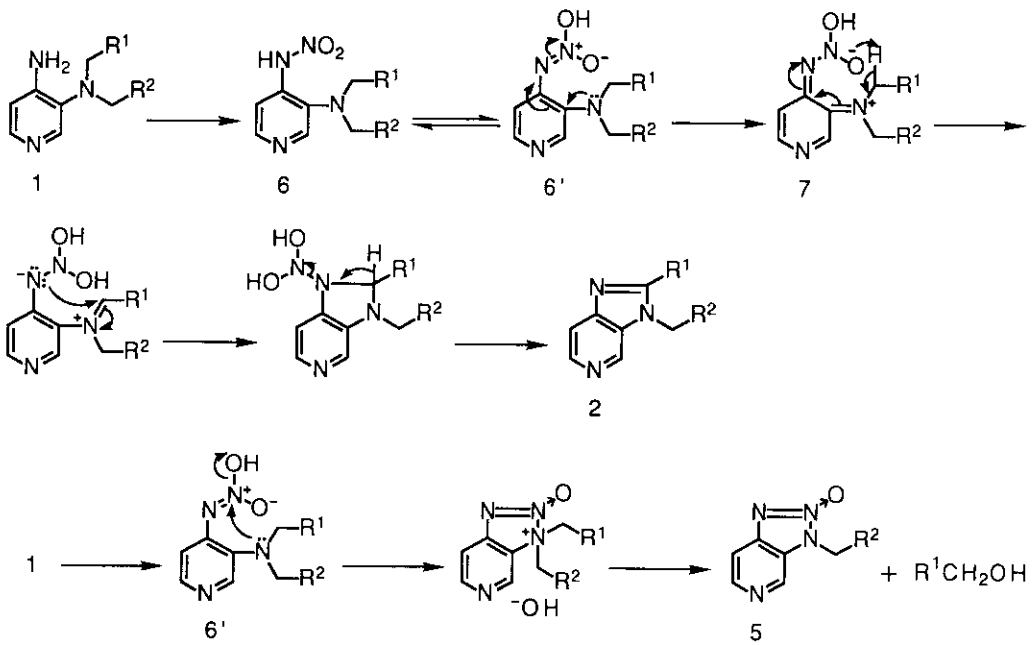
| | | Product (%) | | | |
|---|---|---|---|---|---|
| 1 | $R^1$, $R^2$ | 2 | 3 | 4 | 5 |
| a | $-(CH_2)_3-$ | - | 12 | - | - |
| b | $-(CH_2)_2-$ | 10 | 9 | - | - |
| c | $-CH_2OCH_2-$ | 15 | - | - | - |
| d | H, H | 10 | - | - | - |
| e | $CH_3$, $CH_3$ | - | - | 8 | 76 |
| f | $C_2H_5$, $C_2H_5$ | - | - | 13 | 43 |
| g | $C_3H_7$, H | 8 | - | - | 18 |

documented, and Meth-Cohn and Suschitzky have comprehensively reviewed this article in 1972.[4] Imidazole ring closure is most well known among these cyclizations, and can be divided broadly into two types shown in Scheme 2, apart from the details of the each reaction mechanism. Type I reaction is the ring closure between the ortho-substituent and the t-nitrogen, and type II involves the participation of the α-methylene group attached to the t-nitrogen through an o-quinoid intermediate.

Evidently from the structure, the formation of the imidazopyridine (**2**) belongs to the reaction of type II. Although there is no precedent for cyclization of o-nitroamino-N,N-dialkylanilines, it appears highly probable that a 4-nitroaminopyridine (**6**) is initially formed, and subsequently its isonitro tautomer (**6'**) is transformed into **2** through an o-quinoid intermediate (**7**) as shown in Scheme 3. Nitroimidazopyridines (**3a** and **3b**) and nitroimidazopyridinones (**4e** and **4f**) conceivably could arise from the




Scheme 2

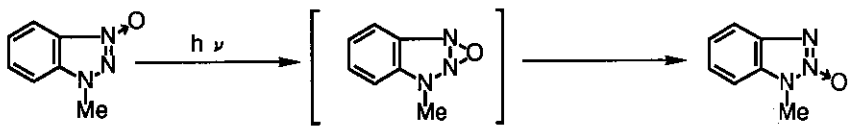



Scheme 3

corresponding imidazopyridines (**2a**, **2b**, **2e** and **2f**), though their details are not yet clear.

The formation of the triazolopyridine 2-oxides (**5e**, **5f** and **5g**) is apparently a cyclization of type I, and may be well rationalized by the course which involves the ring closure between the nitrogen of 3-dialkylamino group and the isonitro-nitrogen in **6'** as illustrated in Scheme 3.

The above-mentioned imidazopyridine formation is of little value as a synthetic means because of consistent poor yields. However, the formation of triazolopyridine 2-oxides is very significant from the viewpoint that, in spite of considerable amounts of papers on 1-oxides of 1,2,3-triazole ring system, there is no report on its 2-oxide except for that by Serve[5] who obtained 3-methylbenzotriazole 2-oxide upon irradiating 3-methylbenzotriazole 1-oxide. Further work on extending this reaction is in progress.

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