REGIOSELECTIVE SYNTHESIS OF 2-SUBSTITUTED 3-NITROPYRIDINES BY ONE-POT REACTION OF EITHER 4- OR 6-SUBSTITUTED 1-METHYL-3,5-DINITRO-2-PYRIDONES WITH KETONES AND AMMONIA

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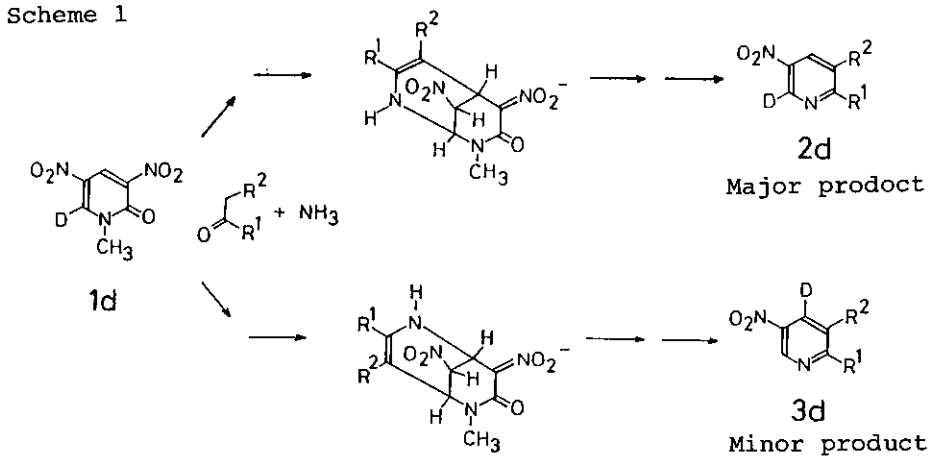
Abstract ---- Regioselective synthesis of 2-substituted 3-nitropyridines was achieved by one-pot reaction of either 4- or 6-substituted 1-methyl-3,5-dinitro-2-pyridones with ketones in the presence of ammonia. The selectivity is interpreted in terms of steric factor of substituent on the pyridone.

3-Nitropyridines (3-NPs) are versatile intermediates for dyes and medicinals, however they are hardly obtainable.[1] Recently we found a convenient synthesis of 3-NPs using a ring transformation of 1-methyl-3,5-dinitro-2-pyridone (**1**) with ketones and ammonia.[2] In the reaction of 6-deuterio derivative (**1d**) of **1**, two competitive paths were found which might involve two isomeric bicyclic intermediates (Scheme 1). Because the path in which ammonia attacks the C-6 carbon of **1d** was slightly predominant, we were prompted to perform selective syntheses of 2- (**2**) and 4-substituted (**3**) 3-

Scheme 1



NPs by ring transformation of 6-substituted (**4**) and 4-substituted 1-methyl-3,5-dinitro-2-pyridone (**5**), respectively. In this communication, we wish to report unexpected results of reactions of **4** and **5**.

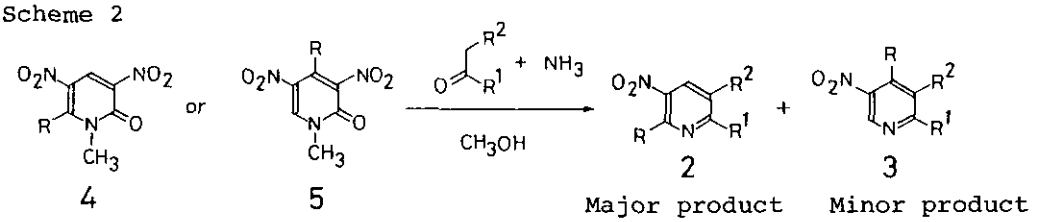
On treatment of not only **4** but also **5** with ketones (or their enamine derivatives) in the presence of ammonia, only one of two possible regioisomers, 2-substituted 3-NP (**2**), was selectively afforded. The other possible regioisomer (**3**) could not be detected at all in many cases (Scheme 2 and Table 1).[3] On the other hand, the regioselectivity of the reaction of 6-deuterio derivative (**1d**) had been very low (Table 1, entry 12).[2] The selectivity is obviously caused by the introduced substituents (**a**:methyl, **b**:4-pyridyl, **b'**:4-nitrophenyl, or **c**:methoxycarbonyl), regardless of their electronic character.

Another remarkable difference between **1** and the substituted pyridones (**4** or **5**) was found in a product selectivity. Thus, in the case of reaction with acetone or 3-pentanone, competitive formation of the 3-NPs with 4-nitroanilines (**6**) is expected as reported in previous papers[2,4] (Scheme 3). The substrates (**4**) and (**5**) selectively gave the 2-substituted 3-NP (**2**), while **1** had given the aniline (**6**) mainly (entries 13 and 25).[2]

Both the regio- and the product-selectivities were affected by structure of the substrates or the ketones. The 6-substituted substrate (**4**) or the ketones having α-methylene carbon gave **2** more selectively than the 4-substituted substrate (**5**) or the methyl ketones, respectively (Table 1). Both selectivities were generally higher as the yields of **2** were better.

The dimethylpyridones (**4a**) and (**5a**) were more reactive than **1** in the pyri-

Scheme 2



Scheme 3

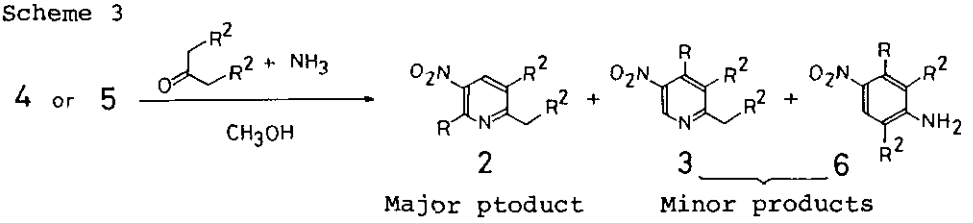


Table 1. Reaction of Substituted 1-Methyl-3,5-dinitro-2-pyridones

entry	Substrate[a]	Reagent[b]	Temp. θ / °C	Yields of Products/% 2	3	6	Selectivity[c]/% Regio-	Product-
			Ketones having α-Methylene Carbon					
1	**4a**	**A**	70	88	0	-	100	-
2	**4a**	**B**	70	54	0	0	100	100
3	**4b'**	**A'**	70	78	0	-	100	-
4	**4c**	**A'**	70	90	0	-	100	-
5	**4c**	**B**	100	46	0	4.2	100	92
6	**5a**	**A**	70	90	0	-	100	-
7	**5a**	**B**	70	32	0	0	100	100
8	**5b**	**A'**	70	81	0	-	100	-
9	**5b**	**B**	100	62	0	0	100	100
10	**5c**	**A'**	100	27	0	-	100	-
11	**5c**	**B**	100	4.9	0	9.5	100	34
12[d]	**1d**	**A**	70	48	35	-	58	-
13[d]	**1**	**B**	70	34		47	-	42
			Methyl Ketones					
14	**4a**	**C'**	20	74	0	-	100	-
15	**4a**	**D**	70	59	0	2.5	100	96
16	**4b'**	**C'**	100	34	0	-	100	-
17	**4c**	**C'**	70	68	7.4	-	90	-
18	**4c**	**D**	100	54	1.2	10.7	98	82
19	**5a**	**C'**	20	68	0	-	100	-
20	**5a**	**D**	70	40	0	1.4	100	96
21	**5b**	**C'**	100	29	14	-	67	-
22	**5b**	**D**	100	20	4.0	0	83	100
23	**5c**	**C'**	100	6.0	20	-	23	-
24	**5c**	**D**	100	1.3	1.1	4.1	54	37
25[d]	**1**	**D**	70	17		34	-	25

a) The subscripts **a**, **b**, **b'**, and **c** denote the substituents at the pyridone carbons as methyl, 4-pyridyl, 4-nitrophenyl, and methoxycarbonyl groups, respectively.

b) **A**=Cyclohexanone, **A'**=α-Morpholinocyclohexene, **B**=3-Pentanone, **C'**=α-Morpholinostyrene, **D**=Acetone.

c) The regio- and the product-selectivities are given by **2**/**2**+**3** and **2**+**3**/**2**+**3**+**6**, respectively.

d) The data are quoted from the reference 2.

dine formation. Thus these substrates reacted with α-morpholinostyrene even at room temperature, while **1** gave no ring transformed products under the same conditions. On the other hand, 1,4,6-trimethyl-3,5-dinitro-2-pyridone (**7**) did not react with these reagents at all.

Most of these experimental facts can be rationalized very well by a following simple assumption: Steric effect of the substituents on the pyridone ring is one of the main factors which determine the reaction courses to give **2**, **3**, or **6**. This is consistent with the fact that the main effect of the substituents is not electronic. Since bulkiness of these nucleophiles is evaluated as following; a nucleophile derived from ketone having α-methylene carbon > that from methyl ketone >> ammonia, the assumption leads to a prediction that the ketonic nucleophiles hardly attack the electrophilic pyridone carbon bearing any substituents. Consequently, the sterically hindered pyridone carbon is preferentially attacked by the smallest nucleophile, ammonia, to give the 2-substituted 3-nitropyridines (**2**) selectively. The reaction courses from **4** or **5** to the anilines (**6**) or the 4-substituted 3-NPs (**3**) must involve the sterically unfavorable process. Inertness of the substrate (**7**) can also be interpreted in terms of the steric factor. Such a selectivity should be more efficient as the ketonic nucleophile becomes more bulky, interpreting the difference of the selectivity between methyl and "methylene" ketones.

In conclusion, the present reaction is a unique method for synthesis of 2-substituted 3-nitropyridines (**2**). Procedure of the reaction is similar with one reported in the previous paper.[2]

REFERENCES

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2. Y. Tohda, M. Eiraku, T. Nakagawa, Y. Usami, M. Ariga, T. Kawashima, K. Tani, H. Watanabe, and Y. Mori, Bull. Chem. Soc. Jpn., 1990, **63**, 2820.
3. Structures of **2** and **3** were easily identified by chemical shifts and coupling patterns of protons of the 3-nitropyridine ring. Chemical shifts of protons at the C-4 position of **2** were found δ values between 8.0 and 8.2 and those at the C-2 position of **3** were between 9.0 and 9.3.
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