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Synthesis of 6-Nitroderivatives of Oxazolo[3,2-a]-pyridines and Their Reactions with Nucleophiles

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Abstract: 5-Nitro-2-pyridone can be selectively N-phenacylated, and the resulting phenacylpyridones **I** undergo cyclization to 6-nitrooxazolo[3,2-a]pyridinium salts **II**. These salts **II** readily react with ammonia and aliphatic amines leading to the products of pyridine ring opening - previously unknown 1-amino-2-nitro-4-(oxazole-2-yl)butadienes-1,3. Reaction of salts **II** with water lead to hydrolytic cleavage of the oxazole fragment.

Keywords: 5-Nitro-2-pyridone, oxazolo[3,2-a]pyridine, butadiene, nitrodiene, aminodiene, oxazolyldiene.

Introduction

The aromatic oxazolo[3,2-a]pyridinium ring system, first prepared by Bradsher [1] and Kroehnke [2], has attracted recent attention due to its several modes of reaction with nucleophiles and the possibility of obtaining a wide variety of heterocyclic structures (oxazoles, pyridines, indolizines, various azolopyridines and azinopyridines) starting from this bicyclic system (for a review, see [3]). The key feature of the reactivity of the oxazolo[3,2-a]pyridinium cation is the possibility of cleavage of either the 5-membered ring (in reactions with alkali, hydrosulfide, ammonia and primary amines,

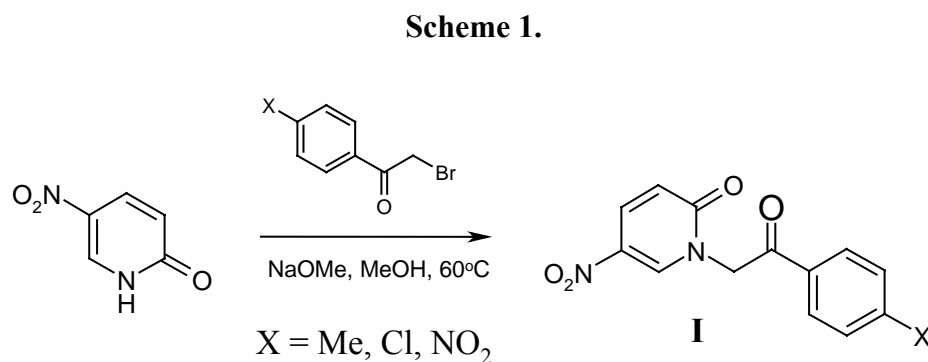
CH-acids) or the 6-membered ring (in reactions with secondary amines). One would expect that introduction of an electron withdrawing group into the 6-membered ring of this bicycle might dramatically increase its π -deficiency, causing predominant nucleophilic attack on the pyridine fragment.

In this communication we report our successful attempt to prepare 6-nitro derivatives of the oxazolo[3,2-a]pyridines and preliminary studies of their reactions with nucleophiles (hydrolysis, ammonolysis, and reactions with aliphatic amines).

Results and Discussion

Phenacylation of 5-nitro-2-pyridone

The standard route to oxazolo[3,2-a]pyridinium salts is the cyclization of N-phenacyl-2-pyridones, which in turn could be obtained either by hydrolysis of 2-halo-N-phenacylpyridinium salts or by phenacylation of 2-pyridones. Suitable precursors of 6-nitrooxazolo[3,2-a]pyridinium salts would therefore be N-phenacylated derivatives of readily available 5-nitro-2-pyridone or 5-nitro-2-halopyridines. Our attempts to perform phenacylation of 2-chloro-5-nitropyridine were unsuccessful. On the other hand, selective N-alkylation of the salts of 5-nitro-2-pyridone was reported in literature. We found that the sodium salt of 5-nitro-2-pyridone undergoes selective N-alkylation in reactions with phenacylbromides leading to phenacyl pyridones **I** (Scheme 1).



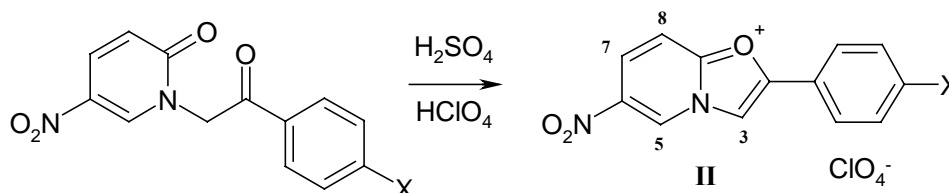
The reaction is complete after 10-12 hours, and the yields vary from 40% ($X=\text{NO}_2$) up to 80% ($X=\text{Cl}$). The alkylation is easily monitored by TLC (since the R_f values of the products **I** lay in-between the values of the reactants), and there were no signs of formation of alternative O-alkylated products (for spectral differences between N- and O-phenacylated isomers of 2-hydroxypyridine see [4]). The compounds **I** have been characterized by $^1\text{H-NMR}$ spectra (Table I) and MS; in the mass-spectra of the pyridones **I** the expected molecular ions were observed.

Table 1. $^1\text{H-NMR}$ spectra of pyridones **I**

X in Ar	Chemical shift, ppm					J, Hz	
	H ₆	H ₄	H ₃	-CH ₂ -	H _{Ar}	J ₄₆	J ₃₄
4-Me	9.17	8.16	6.50	5.60	7.95-7.93 7.37-7.35	3.2	9.4
4-NO ₂	9,22	8,24	6,59	5,74	8.45-8.40 8,32-8,27	2.8	10.1
4-Cl	9.20	8.19	6.52	5.73	8.18-8.15 7.65-7.62	3.1	9.7

Synthesis of 2-aryl-6-nitrooxazolo[3,2-a]pyridinium perchlorates.

The usual technique of cyclodehydration of N-phenacylpyridones to oxazolopyridinium salts (dissolving a compound in concentrated sulfuric acid, diluting with water, and precipitating the product with perchloric acid) was not appropriate for the case of nitropyridones **I**. The most successful procedure required complete avoidance of water. This was achieved by pouring the reaction mixture of pyridone **I** in sulfuric acid (containing few drops of HClO₄) into anhydrous diethyl ether. The precipitate formed corresponds to pure perchlorate **II** (Scheme 2).

Scheme 2.

The $^1\text{H-NMR}$ spectra (Table 2) clearly confirm the bicyclic structure of compounds **II** – the initial singlet of the CH₂-group disappears, and a new singlet corresponding to the H₃ proton of the oxazole ring appears at 9.1 ppm. The most downfield signal at 10.3 ppm corresponds to the H₅ proton, located ortho to the nitro group and the pyridinium heteroatom.

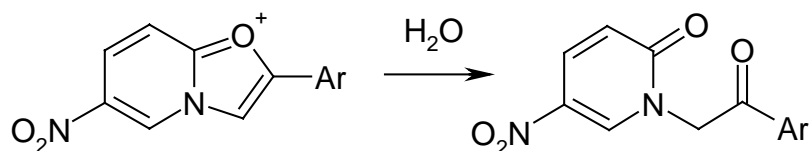
Table 2. $^1\text{H-NMR}$ spectra of the salts **II**

X in Ar	Chemical shift, ppm.					J, Hz	
	H ₅ (d)	H ₇ (dd)	H ₈ (d)	H ₃ (s)	H _{Ar} (m)	J ₅₇	J ₇₈
CH ₃	10.28	9.03	8.43	9.11	7.82-7.80; 7.35-7.32	1.3	9.3
NO ₂	10.35	9.06	8.51	9.18	8.47-8.42; 8.36-8.31	1.6	10.0
Cl	10.31	9.04	8.46	9.13	8.12-8.08; 7.87-7.82	1.3	9.8

Reaction of the salts **II** with nucleophiles.

As we found had found earlier [5], oxazolo[3,2-a]pyridinium salts unsubstituted at the pyridine fragment react with NaOH, NaSH and NH₃ leading to the products of oxazole ring cleavage / transformation, namely to N-phenacylpyridones, N-phenacylpyridinethiones, and imidazo[1,2-a]-pyridines, respectively. In the case of the 6-nitroderivatives **II** all these reactions occur abnormally. Reaction of the salts **II** with water rapidly resulted in starting N-phenacylpyridones **I** (Scheme 3).

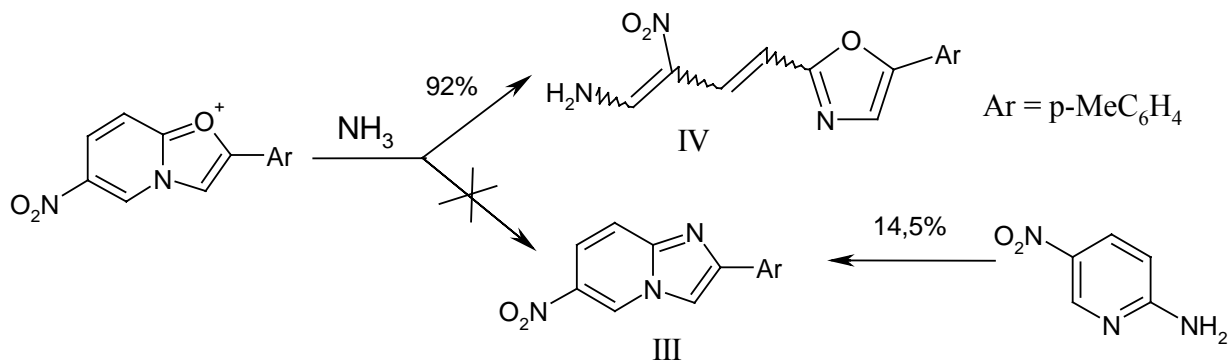
Scheme 3.



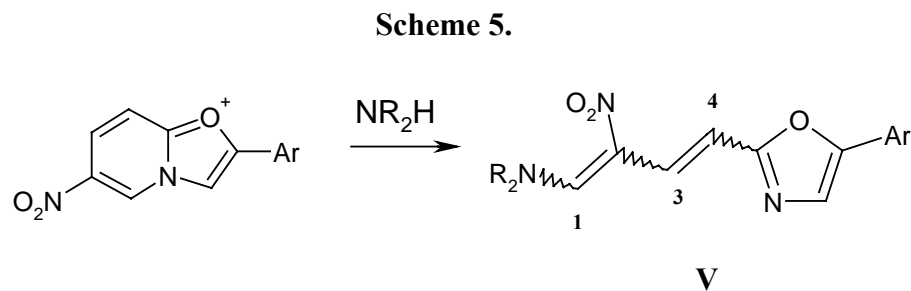
Reaction of the salts **II** with sodium hydrosulfide led to a complex mixture of products. Several attempts to optimize the reaction conditions were unsuccessful. We suppose that the main reason of abnormal behavior of the 6-nitro derivatives **II** (in contrast to the parent oxazolopyridines) may be due either by the cleavage of more reactive nitropyridine fragment (leading to a probably unstable diene) or even by the reduction of nitro group by hydrosulfide ion.

In the reactions with ammonia and primary amines oxazolopyridinium salts could be readily transformed to imidazopyridines and their salts [1, 5]. However, the product formed in the reaction of the 6-nitrooxazolo[3,2-a]pyridinium salt with anhydrous ammonia (in DMF) was not the expected 6-nitroimidazo[1,2-a]pyridine **III** (independently prepared as a reference compound), but rather the diene **IV**. Mass-spectra indicated that the molecular formula corresponded to that of an adduct. In the NMR spectrum of the product the signals of butadiene system were observed together with the peak of amino group, thus confirming the proposed butadiene structure **IV** (Scheme 4).

Scheme 4.



Use of primary and secondary amines in the reaction with the salts **II** led to formation of analogous aminobutadienes **V** (Scheme 5):



The NMR spectra of the obtained dienes (Table 3) were very similar to that of product **IV**. No conclusions could be made regarding the exact configuration of the obtained dienes based only on the NMR data (including various 2D NMR techniques examined) due to the small magnitude of the coupling constants.

Table 3. $^1\text{H-NMR}$ spectra of dienes **III,V**.

R_2N	R'	<i>Chem. shifts, ppm.</i>							<i>J, Hz</i>	
		H_1	H_3 , d	H_4 , d	H_{oxazol} , s	H_{Ar} , m	$\text{H}_{\text{R}'}$, s	H_{R}	J_{34}	
Morpholine	CH_3	8.63 (s)	6.76	6.51	7.71	7.60-7.58 7.31-7.29	2.35	3.52 3.39 3.32	12.0	
Pyrrolidine	Cl	8.81 (s)	6.82	6.51	7.80	7.71-7.67 7.56-7.52		3.73 2.92 1.73	12.2	
NH_2	CH_3	8.95 (m)	6.94	6.03	7.46	7.56-7.53 7.23-7.21	2.38	9.22 (NH_2)	13.3	
t-BuNH	CH_3	9.71 (d) 13.7Hz	7.13	6.08	7.27	7.53-7.51 7.23-7.21	2.38	1.47(tBu) 10.13(NH)	14.0	
n-PrNH	CH_3	9.31 (d) 13.81 Hz	7.05	6.11	7.28	7.53-7.51 7.23-7.21	2.38	9.86 (NH)	12.6	

Conclusions

As we have demonstrated, insertion of the 6-nitro group into the pyridine ring of the oxazolo[3,2-a]-pyridinium ring system dramatically changes its reactivity: first, the oxazole fragment of this bicycle becomes hydrolytically unstable and second, an unusual selectivity is observed in reactions with ammonia and primary amines, leading to previously unknown aminodienes and not imidazopyridines.

Acknowledgments

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Experimental

General

¹H- and ¹³C-NMR spectra were obtained using a Bruker AC 400 NMR spectrometer and were recorded at 360 MHz. All reagents and chemicals were obtained from Acros or Merck and were used as received unless otherwise noted.

Typical procedure for the preparation of *N*-phenacyl-5-nitro-2-pyridones (**I**).

To a solution of sodium hydroxide (35 mmol) in methanol (250 mL) 5-nitro-2-pyridone (30 mmol) was added under vigorous stirring. After 10-15 min. of stirring, phenacylbromide (30 mmol) was added to the reaction mixture. The mixture was refluxed for 1.5-2 hours. Reaction monitoring was carried out by TLC (Merck "SilufoI", CHCl₃-CCl₄-EtOAc=1:1:2); R_f of *N*-phenacyl-2-pyridones =0.45-0.49). Usually after cooling the reaction mixture was allowed to stand overnight at room temperature. The precipitate (light-yellow needles) was filtered off, washed once with methanol and twice with water and dried. Yields 40-78%; for the NMR data of compounds **I** see Table 1.

Typical procedure for the preparation of 2-Aryl-6-nitrooxazolo[3,2-*a*]pyridinium perchlorates (**II**)

The *N*-Phenacyl-2-pyridone (**I**, 10 mmol) was dissolved in concentrated sulfuric acid (10 mL) and kept for 20-25 hours. Then 71% perchloric acid (2.5 mL, 25 mmol) was carefully added to the mixture and after stirring 10-15 min. the solution was poured into vigorously stirred diethyl ether (500 mL). After decanting the oily residue was mixed again with a fresh portion of ether (500 mL); this procedure should be repeated until a pure white powder formed. The precipitate was filtered, washed with ether and dried in vacuum over P₂O₅. Yields 95-98%; for the NMR data of compounds **II** see Table 2.

Typical procedure for the reaction of 2-aryl-6-nitrooxazolo[3,2-*a*]pyridinium perchlorates (**II**) with aliphatic amines.

The oxazolo[3,2-*a*]pyridinium perchlorate (1 mmol) was added to a solution of the desired amine (1 mL) in of anhydrous acetonitrile (20 mL) at 60°C with good stirring (for secondary amines) or in an ultrasonic bath (for primary amines). These solutions were kept for 10 hours and then poured into cold water (40-50 mL). After an appropriate period (ranging from three hours for primary amines to up to two days for secondary amines) the aminooxazolybutadiene precipitated as the needles of yellow or

orange-yellow color. Crystals were separated, washed with water and dried. Yields 55-74% (primary amines) and 48-51% (secondary amines). For the NMR data of the compounds **V** see Table 3.

Reaction of 2-(4-methylphenyl)-6-nitrooxazolo[3,2-a]pyridinium perchlorate with ammonia.

2-(4-Methylphenyl)-6-nitrooxazolo[3,2-a]pyridinium perchlorate (0.2 mmol) was dissolved in anhydrous distilled DMF (2 mL) and mixed with a solution (1 mL) prepared by saturation of DMF with gaseous ammonia (kept under 0°C). The reaction mixture immediately turned to deep red color. This mixture was kept for 3 min. and then poured into cold water. The product precipitated as a yellow powder, which was separated, washed with water and dried. Yield 93%; for the NMR data see Table 3.

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