NITROSATION OF 4-AMINO-1-PHENACYL-1,2,4-TRIAZOLIUM BROMIDES AND ω-(1,2,4-TRIAZOL-1-YL)ACETOPHENONES

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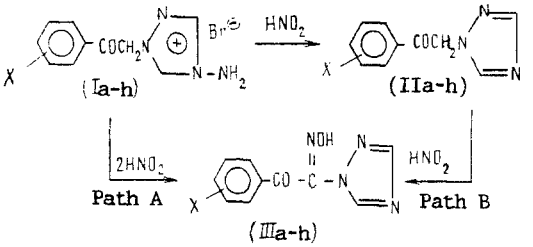
The reaction of 4-amino-1-phenacyl-1,2,4-triazolium bromides with an excess of nitrous acid leads to a mixture of the corresponding ω-(1,2,4-triazol-1-yl)-acetophenones and ω-hydroximino-ω-(1,2,4-triazol-1-yl)acetophenones. Products of the latter type are formed during nitrosation at the methylene group of both the intermediate ω-triazolylacetophenones, and the starting 4-amino-1-phenacyl-1,2,4-triazolium bromides. The role of Br^- as a catalyst is significant for both nitrosation paths. In the reaction of ω-(1,2,4-triazol-1-yl)acetophenones with HNO_2, SCN^- is a more active catalyst than Br^-. During the nitrosation of para-substituted 4-amino-1-phenacyl-1,2,4-triazolium bromides, the yield of ω-hydroximino-ω-(1,2,4-triazol-1-yl)acetophenones increases with increase in the acceptor properties of the aryl substituent, which is explained by the increase in the CH-acidity of the nitrosation substrates.

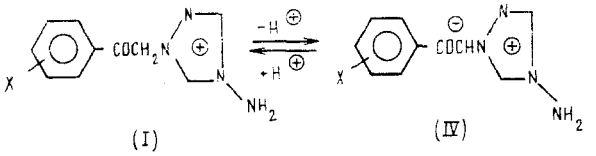
It was previously shown [1] that the preparation of ω-(1,2,4-triazol-1-yl)acetophenones (II) from 4-amino-1-phenacyl-1,2,4-triazolium bromides (I) according to Scheme 1 is complicated by the formation of ω-hydroximino-ω-(1,2,4-triazol-1-yl)acetophenones (III) as by-products:



(1)

X = H (a); 4-Cl (b); 2-Cl (c); 4-CH_3 (d); 4-Br (e); 2,4-Cl_2 (f); 2,4-Br_2 (g); 4-NO_2 (h).

It can be assumed that oximes (III) are formed from ketones (II) by the action of excess nitrous acid (path B) [2]. However our preliminary experiments [1] on the nitrosation of ketone (IIa) showed that its reactivity with respect to the nitrosating reagents is extremely low and insufficient for the formation of oxime (IIIa) by path B. Another reason for the formation of oximes (III) could be the attack of the NO^+ carrier initially at the methylene group of salt (I) in the form of an enol or ylide enolate (IV), followed by deamination of the nitrosation product [1].



(I) (IV)

To determine the paths of formation of hydroximino ketones (IIIa-h) from salts (Ia-h) (Scheme 1), we studied the reaction of salts (I) with two equivalents of HNO_2 and the reaction of ketones (II) with an equimolar amount of HNO_2. The reaction of ketones (II) with HNO_2 was studied both in the presence of an equimolar amount of the nitrosation catalysts – KBr or KSCN [3], and in their absence. The nitrosation of compounds (I) and (II) was carried

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TABLE 1. Conditions of Carrying Out the Nitrosation Reaction of Ketones (II) with Nitrous Acid at 20°C and Content of (III) in the Separated Mixture of (II) and (III)

Expt. No.	Ketone	Reaction time, h	Amount*			Content of oxime (III), %
			H_2SO_4	KBr	KSCN	
1	(IIa)	2	1,6			0
2		2	1,6	1,0		0
3		20	1,6			0
4		20	1,6	1,0		4
5		20	1,6		1,0	12
6		20	3,2			0
7		20	3,2	1,0		16
8	(IIb)	2	1,6			0
9		2	1,6	1,0		2
10		20	1,6			2
11		20	1,6	1,0		18
12		20	1,6		1,0	46
13		20	3,2			3
14		20	3,2	1,0		42
15	(IIc)	2	1,6			5
16		2	1,6	1,0		20
17		20	1,6			23
18		20	1,6	1,0		55
19		20	1,6		1,0	60
20		20	3,2			8
21		20	3,2	1,0		62
22	(IId)	20	1,6			0
23		20	1,6	1,0		6
24	(IIe)	20	1,6			2
25		20	1,6	1,0		17
26	(IIf)	2	1,6			5
27		2	1,6	1,0		26
28		20	1,6			20
29		20	1,6	1,0		58
30	(IIg)	20	1,6			9
31		20	1,6	1,0		36
32	(IIh)	20	1,6			5
33		20	1,6	1,0		41

*Molar excess with respect to ketones (II).

TABLE 2. pK_a Values of Salts (I) and Content of Hydroximino Ketones (III) in a Mixture of (II) and (III), Formed during Nitrosation of (I)*

Salt	pK_a	Reaction time, h	Content of oxime (III),** %
(Ia)	11,2	2	5(0)
		20	26(4)
(Ib)	10,8	2	10(2)
		20	33(18)
(Ic)	8,8	2	30(20)
		20	66(55)
(Id)	11,6	20	8(6)
(Ie)	10,8	20	33(17)
(If)	8,9	20	71(58)
(Ig)	8,7	20	91(36)
(Ih)	8,9	20	44(41)

*The molar excess of H_2SO_4 with respect to salts (I) was 1.6 in all experiments.
**In brackets – the corresponding values for the nitrosation reaction of ketones (II).

out under homogeneous conditions. Thus, the overall yield of ketones (II) and oximes (III) in the mixture of products separated was higher than 85%.

The content of oximes (IIIa-h) in the nitrosation products and the reaction conditions are given in Tables 1 and 2, which show that with the identical reaction time and excess of H_2SO_4, the content of oximes in the nitrosation products increases in the following order (II) < (II) + KBr < (I). The data obtained confirm a catalytic action of Br^- on the nitro-

sation of (II), which probably consists in the formation of NOBr in the reaction mixture – an effective carrier for NO^+ [3]. A still higher rate of nitrosation is observed in the presence of KSCN (see Table 1, expts. 3-5, 10-12, 17-19), which is in agreement with the previously observed series of influence of catalyst anions on the rate of nitrosation of β-diketones [4], and also of amines and of other heteroatomic substrates [3]. The catalytic action of Br^- intensifies when the excess H_2SO_4 is increased (see Table 1, expts. 4, 7, 11, 14, 18, 21), which may be due to the increase in the concentration of NOBr in the reaction mixture occurring on decrease in pH.

This supposition is in agreement with the fact that according to the data in Table 1 (expts. 3 and 6, 10, and 13, 17 and 20), the use of a large amount of H_2SO_4 in the nitrosation of ketones (IIa-c) without the addition of KBr does not lead to an increase in the content of the corresponding oximes (IIIa-c) in the products of these reactions. Comparison of the percent content of oximes (III) in the products of the nitrosation reactions of salts (I) and ketones (II) + KBr (see Table 2) shows that under the conditions studied the formation of hydroximino ketones (III) from (I) may proceed by two routes, differing in the sequence of the attack by the nitrosating reagent on the methylene and the amino groups in the starting salts (I) (scheme (1), paths A and B).

To clarify the influence of substituents in the aromatic ring on the occurrence of the nitrosation reaction of (I), we determined the values of pK_a of salts (Ia-h) in water (see Table 2). As expected, these values for para-substituted salts (Ia, b, d, e, h) correlate well with the corresponding σ_π Hammet constants [5], $r = -0.984$.

It can be seen from Table 2 that the reactivity of the methylene group in the para-substituted salts (Ib, d, e, h) increases with decrease in pK_a of salts (I). The reactivity of the ortho-substituted salts (Ic, f, g) does not correlate with their acidity. Thus, salts (Ic, f, g) containing Br or Cl in the ortho position of the phenyl ring, are nitrosated at the methylene group more rapidly than salt (Ih) closest to them with respect to acidity.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra (with uncoupling from protons) were recorded on a "Bruker AC-80" spectrometer with a working frequency of 80 (^1H) and 20.15 MHz (^{13}C), using $(CD_3)_2SO$ as a solvent, TMS as internal standard, at the sensor temperature of 25-30°C. The electronic absorption spectra were recorded in the 230-500 nm region on a "Specord M40" spectrophotometer, using quartz cuvettes (ℓ = 1.0 cm). The pH values of the aqueous solutions were monitored by means of an EV-74 pH-meter, calibrated with respect to buffer solutions at pH 9.18 and 12.4.

The nitrosation reactions were carried out at 20°C in 0.05 M solutions of salts (I) or ketones (II) in a mixture (1:1 by volume) of distilled water and acetonitrile (c.p.). To a solution containing 1.25 mole of substrate (I) (or (II)), 2.0 mmoles of H_2SO_4 (the excess of acid is necessary to improve the reproducibility of the experiments) and, if necessary, 1.25 mmoles of a catalyst – KBr or KSCN, 2.50 (1.25 for ketones (II)) mmoles of $NaNO_2$ was added and the mixture was stirred until completely dissolved. The solution was then thermostated during the reaction. At the end of the reaction, the mixture was neutralized with an ammonia solution, extracted with chloroform (3 × 20 ml), the organic layer was separated and dried over Na_2SO_4. After distillation of the solvent, the residue was analyzed by means of ^1H NMR spectroscopy. The relative content of compounds (II) and (III) was determined from the ratio of the integral intensities of the H^5 signals of the triazole ring of these compounds. The accuracy of the integration was 3-5%.

The pK_a values of salts (I) in water (doubly distilled) was determined spectrophotometrically from the ratio of the absorption band intensities ($\pi \rightarrow \pi^*$) of salts (I) and ylides (IV) observed at various values of pH in a region of 8-12 pH units. The spectra of the solutions of salts (I) and ylides (IV) are stable with time, but at pH > 13, the virtual disappearance of the absorption bands of the ylides (IV) was observed, indicating their decomposition under these conditions.

4-Amino-1-(2,4-dichlorophenacyl)-1,2,4-triazolium N-Ylide (IVf). A 5 ml portion of concentrated NH_4OH solution was added to 0.1 mole of a pulverized salt (If). The mixture was stirred for 20 min, filtered, the precipitate was washed with concentrated NH_4OH solu-

tion, and dried in vacuo. Yield, 95%, mp 138°C (dec). Spectrum (δ, ppm, DMSO-d_6): 6.28 s (1H, COCH), 7.0 s (2H, NH_2), 7.1-7.7 m (3H, ArH), 8.86 s (1H, 3-CH of the triazole ring) and 10.90 s (1H, 5-CH of the triazole ring). ^{13}C NMR spectrum (δ, ppm, DMSO-d_6): 94.6 (HC^-N^+); 126.8; 128.9; 131.2 (CH groups of $C_6H_3Cl_2$); 125.7; 131.7; 132.2; 132.6; 140.9; 141.4.

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gem-DINITRO COMPOUNDS IN ORGANIC SYNTHESIS.

2. SYNTHESIS OF 4-NITROPYRAZOLES FROM DINITROMETHANE AND ITS DERIVATIVES

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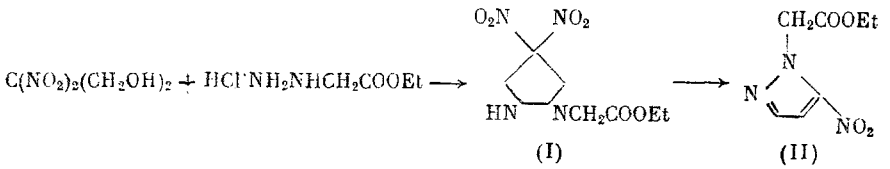
A series of 4-nitropyrazoles was synthesized from dinitromethane and other gem-dinitro derivatives. New cyclization reactions of aliphatic azines with dinitromethane and an intramolecular cyclization of dinitroacetazines have been discovered, with which 4-nitropyrazoles substituted at the 3- and 5-positions of the pyrazole ring can be obtained in one stage.

Simple paths of synthesis of functionalized gem-dinitro compounds from acetoacetic ester [1] make it possible to treat them as useful bifunctional synthones for the preparation of biologically active nitroheterocyclic compounds. Compared with direct nitration of the ring [2, 3], this approach is more promising, for example, in the synthesis of 4-nitropyrazoles with functional groups at the 3- and 5-positions, which are labile toward nitrating mixtures, among which structures with neuroleptic and antibacterial activity were found [4].

A single example only of this reaction has been described in the literature (an intramolecular Mannich condensation), for which it was noted that in the case of an unsubstituted hydrazine, pyrazole with a free NH bond is not formed [5].



(I) (II)

According to the data in [6], during the reaction of hydrazine with dinitroethanol under the Mannich reaction conditions betaine (III) is formed. We showed that this compound reacts with formaldehyde, giving dinitrohydrazinopropanol (IV) [1], which cannot be converted into unsubstituted 4-nitropyrazole.

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