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NEW METHOD FOR THE SYNTHESIS OF 1,2,3-TRIAZOLE 1-OXIDES

T. I. Godovikova, S. P. Golova, S. A. Vozchikova, E. L. Ignat'eva, M. V. Povorin, and L. I. Khmel'nitskii*

A general method is proposed for the synthesis of 1,2,3-triazole 1-oxides using 3,4-dinitro- or 4-amino-3-nitrofuroxanes.

1,2,3-Triazole 1-oxides and their derivatives, which possess several reaction sites, are starting materials for the synthesis of a whole series of products. These compounds also hold practical interest in industry and agriculture. Thus, 2-aryl-4-hydroxy-1,2,3-triazole 1-oxides and substituted 2-aryl-1,2,3-triazole 1-oxides containing a phosphorus atom hold promise as insecticides, fungicides, bactericides, nematocides, and acaricides [1, 2]. 2-(3-Phenyl-7-coumarinyl)-1,2,3-triazole 1-oxides with alkyl or aryl substituents at positions 4 and 5 have attracted interest as detergent [3] and fluorescent whitening agents [3].

Aminonitrotriazole oxides hold great interest for the synthesis of new compounds in this class, mainly due to the possibility of replacing the nitro group by the action of various nucleophiles. Furthermore, the 1,3-dipolar cycloaddition of olefins to the triazole oxide ring permits construction of other heterocyclic systems.

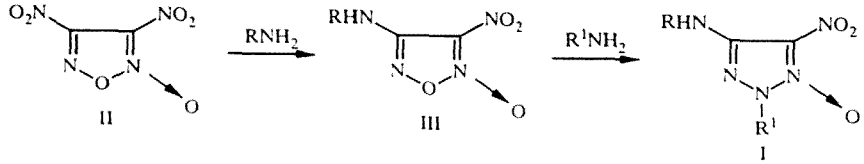
Analysis of the literature data devoted to the properties of 1,2,3-triazole 1-oxides [4] has indicated that the oxidative cyclization of hydrazone oximes of 1,2-dicarbonyl compounds, which is the most common method for the preparation of these compounds, is virtually unsuitable for the synthesis of aminonitro derivatives of 1,2,3-triazole 1-oxides due to the lack of availability of the starting reagents.

There is no information in the literature on preparation of nitrotriazoles by the oxidation of nitro-1,2,3-triazoles, which, by the way, are also not readily available compounds and, thus, only very few such compounds have been synthesized [5-8].

Only Begtrup [9, 10] and Vereshchagin [11] have studied the nitration of the corresponding triazole oxides. Substituted aminonitrotriazole 1-oxides were not obtained. Begtrup and Holm [9] described the reaction of unsubstituted 2-phenyltriazole 1-oxide with a mixture of concentrated nitric and sulfuric acids, which gave products of the nitration of the N-oxidotriazole and benzene rings depending on the reaction conditions. The analogous reaction in the case of 2-methyl-1,2,3-triazole 1-oxide under mild conditions at 20°C leads to a 1:3 mixture of the 4- and 5-nitro derivatives, while 4,5-dinitro-1,2,3-triazole 1-oxide was obtained at 100°C [10]. 5-Substituted 2-methyl-1,2,3-triazole 1-oxides are converted upon the action of a mixture of concentrated nitric and sulfuric acids into 4-nitro derivatives [10]. 4-Hydroxy-2-phenyl-1,2,3-triazole 1-oxide is nitrated by nitric acid only in the triazole ring [11].

In the present work, we describe a new general synthetic method for previously unreported substituted 4-amino-5-nitro-1,2,3-triazole 1-oxides (I) starting from 3,4-dinitrofuroxane (I) or 4-alkylamino-3-nitrofuroxanes (III).

Scheme 1



I, III a R = H, R^1 = CH_3; b R = R^1 = CH_3; c R = R^1 = C_2H_5; d R = $HOCH_2CH_2$, R^1 = CH_3; e R = $NCCH_2CH_2$, R^1 = CH_3; f R = H, R^1 = CH_2=$CHCH_2$

*Deceased.

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TABLE 1. Physical Indices of Ia-If

Compound	Chemical formula	Found, % / Calculated, % C	H	N	mp, °C	PMR spectrum, δ, ppm in $COCl_3$	Yield, % method A (method B)
Ia	$C_3H_5N_5O_3$	22.52 22,64	3.22 3,17	44.08 4402	218...219 (decomp.)	3,95 (3H, s, CH_3), 5,35 (2H, br.s, NH_2)	30 (25)
Ib	$C_4H_7N_5O_3$	27.49 27,75	4.17 4,08	40.27 40,45	187 (decomp.)	3,07 (3H, d, CH_3NH), 3,93 (3H, s, CH_3) 5,87 (1H, br. s, NH)	48 (20)
Ic	$C_6H_{11}N_5O_3$	36.04 35,82	5.60 5,51	34.85 34,81	126 (decomp.)	1,35 (6H, m, $2CH_3$), 3,55 (2H, m, $\underline{CH_2}NH$), 4,30 (2H, q, $\underline{CH_2}N$), 5,80 (1H, br.s, NH)	28 (17)
Id*	$C_5H_9N_5O_4$	29.63 29,56	4.57 4,47	34.52 34,48	167...168	3,91 (2H, q, CH_2N), 3,77 (2H,m, CH_2O), 3,54 (3H, s, CH_3)	35
Ie	$C_6H_8N_6O_3$	34.05 33,96	3.98 3,80	39.89 39,61	168...170	3,93 (3H, s, CH_3), 3,77 (2H, q, $\underline{CH_2}NH$), 2,79 (2H, t, CH_2CN), 6,2 (1H, br.s, NH)	40
If	$C_5H_7N_5O_3$	32.74 32,43	3.96 3,81	38.01 37,83	151...152	5,27 (2H, br s NH_2), 4,88 (2H, d, CH_2N), 5,90 (1H, m, CH), 5,45 (2H, d, $\underline{CH_2}$=CH)	33

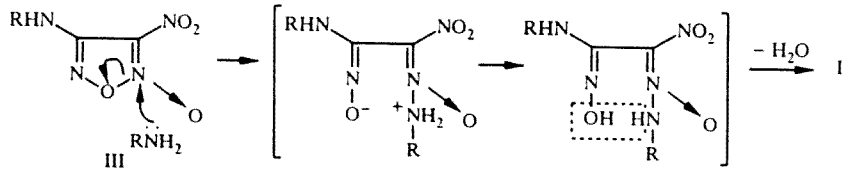
*PMR spectrum obtained in CD_3OD.

This safe and simple method is based on available starting reagents and involves only a few steps. We have already published a brief communication concerning the preparation of I [12].

As reported in our previous work [13, 14], dinitrofuroxane II readily reacts with nucleophilic reagents to give the corresponding substituted 3-nitrofuroxanes. We showed that the reaction of II and its derivatives, 4-alkylamino-3-nitrofuroxanes III with primary aliphatic amines gives 2-alkyl-4-alkylamino-5-nitro-1,2,3-triazole 1-oxides (I). Dinitrofuroxane may be used to obtain I without isolation of the intermediate aminonitrofuroxanes III. Thus, I may be prepared with nonidentical alkyl substituents using different alkylamines in the first and second steps. If ammonia is used as the nucleophile in the first step and alkylamines are used in the second, the reaction yields 4-amino-2-alkyl-5-nitro-1,2,3-triazole 1-oxides.

We propose that the furoxane ring is opened by the action of the primary amine, which attacks the nitrogen atom of the N-oxide fragment, and then cyclization occurs with loss of a water molecule to give the 1,2,3-triazole 1-oxide ring.

Scheme 2



This conversion of a noncondensed 3-nitrofuroxane ring to give a 5-nitro-1,2,3-triazole 1-oxide ring has not been reported.

We should note that recyclization of the furoxane ring to give the 1,2,3-triazole 1-oxide ring has been reported for benzofuroxanes by the action of the formylanilide [15-17] or acetylanilide anion [15].

The synthesis of I proceeds in methylene chloride with a 1:4 mole ratio of II and the amine. Substitution of the nitro group at $C_{(4)}$ occurs at from −30 to −20°C and the product III is not isolated from the reaction mixture. The action of alkylamine at room temperature converts III into a 1,2,3-triazole 1-oxide derivative.

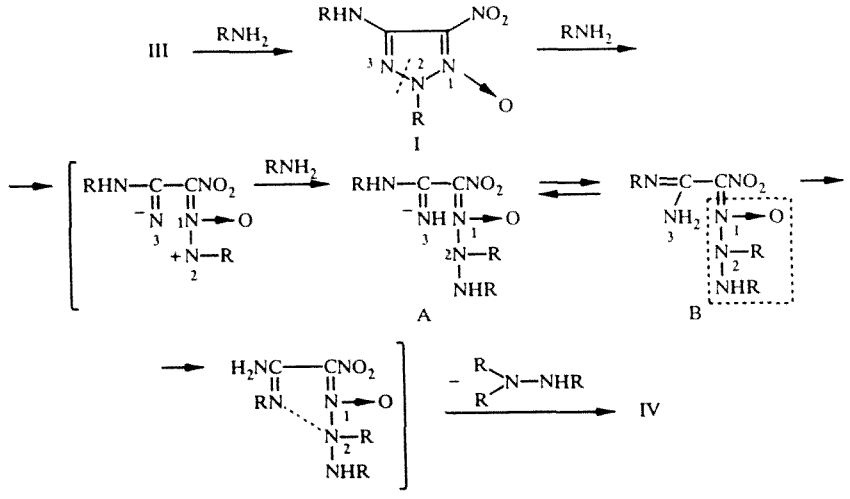
4-Amino-5-nitrofurazane (IV) was isolated as a side-product in all the experiments. We showed that IV is the product of the conversion of I. For example, the action of excess ethylamine on 5-nitro-2-ethyl-4-ethylamino-1,2,3-triazole 1-oxide Ic leads to aminonitrofurazane IV in quantitative yield.

These experimental data and the finding of a triethylhydrazine in the reaction mixture (detected by gas—liquid chromatography) indicate the following scheme for formation of IV in the reaction of furoxanes III with primary aliphatic amines.

The action of the amine leads to cleavage of the $N_{(2)}—N_{(3)}$ bond as the weakest bond (indicated by x-ray diffraction structural analysis data [12]) and formation of amidine A, which may convert to tautomeric form B [19]. An unstable N-oxidotriazane system is found in form B (shown by a dashed line in Scheme 3), in which the $N_{(1)}—N_{(2)}$ bond is destabilized due to nonbonding orbital interactions between the unshared electron pair on the oxygen atom and antibonding orbital of the highly polarized $N_{(1)}—N_{(2)}$ bond, leading to heterolytic cleavage of the $N_{(1)}—N_{(2)}$ bond. Then, $N_{(2)}$, which loses an electron pair in this step, replenishes this deficit from the bond of the carbon atom with the imine group nitrogen (=N—R) with loss of a trisubstituted hydrazine and recombination of the residual fragment to give a furazane ring. These transformations occur synchronously including a series of anchimeric effects facilitating cleavage and cyclization.

Recyclization of a 1,2,3-triazole 1-oxide ring to give a furazane ring has not been reported.

Scheme 3



All the newly synthesized compounds were characterized by NMR, IR, and mass spectral data. All the mass spectra show molecular ion peaks. The predominant fragmentation pathway involves initial loss of NO_2 from the molecular ion followed by loss of the corresponding neutral diazoalkane molecule. This fragmentation pathway is an important general feature of all the triazole N-oxides studied and, thus, the set of corresponding peaks may be used for identification of this compound type. The structure of the substituted 5-nitro-1,2,3-triazole 1-oxide has also been demonstrated by x-ray diffraction structural analysis for Ia [12].

EXPERIMENTAL

The IR spectra were taken on a Specord spectrometer for KBr pellets. The ^1H, ^{13}C, and ^{14}N NMR spectra were obtained on a Bruker AM-300 spectrometer at 300, 75.5, and 21.67 MHz, respectively, with TMS as the internal standard. The melting points were determined on a Boetius block with heating rate 4°C/min at the melting point. Silica gel L 100/160μ was used for column chromatography. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using CH_2Cl_2 as the eluent with detection in UV light at 254 nm and development of the spots using 1% ethanolic diphenylamine. Gas – liquid chromatography was carried out on an LKhM-8 MD chromatograph with a flame-ionization detector and 300×0.4-cm stainless steel column packed with 10% Carbowax 20μ, 3% Na_3PO_4, and 0.5% NaOH on Celite 545 (52-60 mesh). The nitrogen gas carrier flow rate was 30 ml/min. The injector temperature was 250°C. The temperature of the thermostat at the sample inlet was +50°C. The temperature programming was carried out at 6°C/min up to 220°C. The retention time of authentic triethylhydrazine was 2.8 min. The samples for analysis were dissolved in ether since the triethylhydrazine peak exits along with the peak for CH_2Cl_2.

A compound with retention time 2.8 min exited first in the chromatography of the products of the reaction of Ic with ethylamine in ether, which corresponds to triethylamine.

The elemental analysis for C, H, N was carried out on a Perkin-Elmer C,H,N analyzer. The yields and major physical indices of Ia-If are given in Table 1.

The syntheses of starting 3,4-dinitrofuroxane (II) and 4-amino- and 4-alkylamino-3-nitrofuroxanes (III) were described in our previous work [14].

Synthesis of Ia-If (general method). A. From dinitrofuroxane II. A solution of the corresponding amine in dry CH_2Cl_2 was added dropwise with stirring to a solution of 2 g (11.4 mmoles) II in 150 ml dry CH_2Cl_2 at from −30 to −20°C. Ammonia, methylamine, and ethylamine were initially passed into dry CH_2Cl_2 over 30 min at 18-20°C. The reaction course was monitored by thin-layer chromatography. The amine solution was added until only traces of the starting material remained in the reaction mixture. The temperature was then raised to 18-20°C. The flask contents were filtered. A fresh solution of the amine in dry methylene chloride was readded at the same temperature until a clear spot for product I appeared in the chromatogram. At the end of the reaction, the mixture was washed with 50 ml cold water and dried over $MgSO_4$. Most of the solvent was distilled off in vacuum. The residue was subjected to chromatography on a silica gel column. Elution with CH_2Cl_2 first gave furoxane derivatives III and then triazole oxide I.

B. From alkylaminonitrofuroxane III. A solution of alkylamine in dry CH_2Cl_2 was added with stirring to a solution of III in dry CH_2Cl_2 at 18-20°C. At the end of the reaction, as indicated by thin-layer chromatography, the reaction mixture was treated as above in procedure A.

The IR spectra of Ia-If contain strong bands at 1620-1640 (C=N) and 1510-1520, 1320-1340, and 820-830 cm^{-1} (NO_2).

Product Ia. ^{13}C NMR spectrum in DMSO: 39.5 (CH_3), 123.8 (C—NO_2, $\Delta\nu_{1/2}$ 13 Hz), 144.7 (C—NH_2, $\Delta\nu_{1/2}$ 5 Hz). ^{14}N NMR spectrum in DMSO: −83.9 (N→O, $\Delta\nu_{1/2}$ 120 Hz), −30.42 (NO_2, $\Delta\nu_{1/2}$ 37 Hz).

Product Ib. ^{14}N NMR spectrum in DMSO: −85 (N→O, $\Delta\nu_{1/2}$ 300 Hz), −30.73 (NO_2, $\Delta\nu_{1/2}$ 25 Hz).

Reaction of Ic with Ethylamine. A freshly prepared solution of ethylamine in 50 ml dry CH_2Cl_2 was added with stirring to a solution of 0.12 g (.6 mmole) Ic in 100 ml dry CH_2Cl_2 at 18-20°C. The reaction mixture was maintained for 48 h at room temperature. The solvent was then removed in vacuum. Column chromatography of the residue using CH_2Cl_2 as the eluent gave 0.075 g (~98%) IV, mp 123-124°C (122.5-123.0°C [19]). A mixed sample with authentic IV did not give a depressed melting point. The IR spectrum of IV was identical to that given by Solodyuk et al. [19].

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