Chemistry of Heterocyclic Compounds, Vol. 44, No. 11, 2008

REACTIONS OF 3-NITRO-1,2,4-TRIAZOLES WITH ALKYLATING AGENTS. 6*. ALKYLATION OF A NEUTRAL HETEROCYCLE BY ALCOHOLS IN ACID MEDIA*

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Reaction of 3-nitro-1,2,4-triazole and 5-methyl-3-nitro-1,2,4-triazole with secondary and tertiary alcohols in conc. H_2SO_4 takes place at the N(2) atom. Alkylation by 2-propanol occurs regioselectively to form the 1-isopropyl-3-nitro- and 1-isopropyl-3-methyl-5-nitro-1,2,4-triazoles. As a consequence of isomerization the alkylation using cyclohexyl or tert-butyl alcohols gives respectively a mixture of regioisomers substituted at atom N(1) (1-cyclohexyl-3-nitro- and 1-cyclohexyl-5-methyl-3-nitro-1,2,4-triazoles) and at atom N(2) (5-nitro-1-cyclohexyl- and 1-cyclohexyl-3-methyl-5-nitro-1,2,4-triazoles) and, in the second case, to 1-tert-butyl-3-nitro-1,2,4-triazole.

Keywords: 3-nitro-1,2,4-triazoles, alkylation, regioselectivity.

The physicochemical properties of N-substituted 3-nitro-5-R-1,2,4-triazoles are markedly affected by the positioning and type of substituent on the cyclic nitrogen atoms [2-5].

The development of directed methodology for the synthesis of N-substituted azoles and the search for conditions activating all three nitrogen atoms in the reactions of monofunctionalization of nitrotriazoles are important problems in basic and applied science. On the one hand it contributes to deciding one of the key challenges in the chemistry of heterocycles, (that of reaction selectivity) and, on the other, it allows users to achieve directivity i.e. the targeted regulation of the properties of nitrotriazoles by synthesis of a given isomer with the needed package of properties.

The N-monoalkylation of 3-nitro-5-R-1,2,4-triazoles in basic conditions at the pyrrole nitrogen atom and N–H form of the heterocycle at the pyridine nitrogen atom by alkyl halides and dialkyl sulfates occur with irregular selectivity [4-6]. Dependent on the type of reaction medium and alkylating agent there are principally formed the N(1)- or N(4)-isomers. In the presence of alkali a mixture of the N(1)- and N(2)-alkylnitrotriazole isomers [4] is formed with a predominance of the N(1)-isomer (fraction of the N(2)-isomer 18-34%). In neutral medium [5, 6] it is the N(4)-isomer (the corresponding N(1)-, N(2)-, and N(4)-methyl isomers being 1:12:230)-, with the ratio of N(2)- and N(4)-ethyl isomers being 1:2.5.

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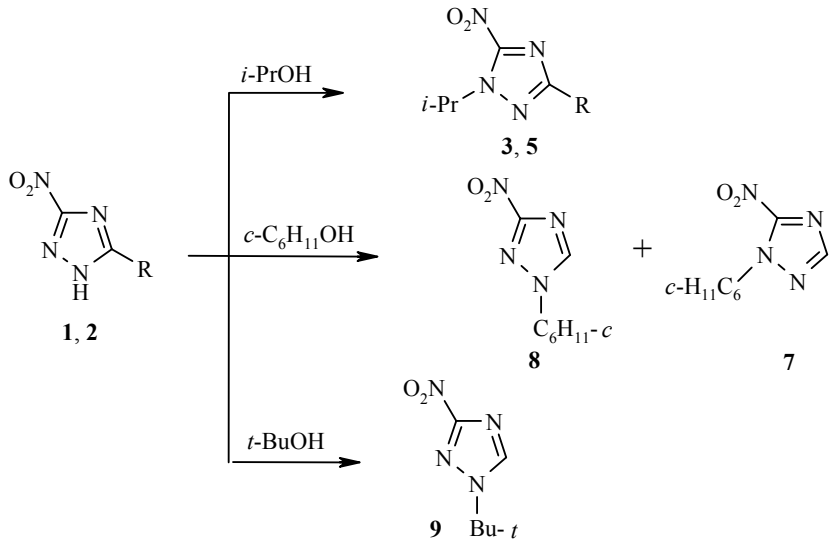
In continuing our work on the selectivity of alkylation of nitrotriazoles we have studied another type of reaction involving the pyridine nitrogen atoms of nitrotriazoles by alkylation in acidic media controlling selectivity of alkylation at the N(2) atom. The choice of alkylating agent determines the isomeric composition of the reaction products:



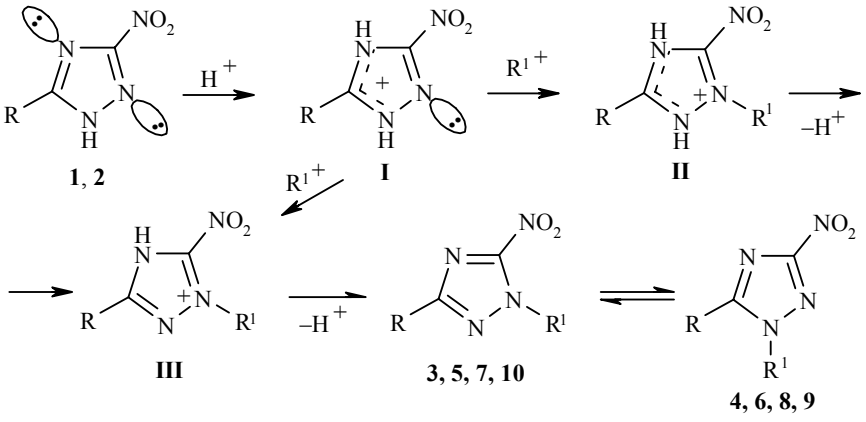
1, **3** R = H, **2**, **5** R = Me

With the high stability towards the action of mineral acids and the weakly basic properties of nitrotriazole rings in mind we have undertaken in this work the alkylation of 3-nitro-5-R-1,2,4-triazoles by alcohols in a medium of high acidity ensuring almost total protonation of the nitrotriazole ring hence excluding the possibility of alkylating of the triazoles both in the form of the nitrotriazolate anions [4] and as the free N–H acid [5, 6]. Sulfuric acid was used as such a medium in this reaction as it also plays a role as a universal solvent and an agent taking up water.

Alkylation of the nitrotriazoles was carried out using alcohols, the structure of which, to a certain extent, enables stabilization of the carbocations formed from them (isopropyl, cyclohexyl, *tert*-butyl).

As a result of carrying out the work it was found that the reaction of 3-nitro-1,2,4-triazole (**1**) and 5-methyl-3-nitro-1,2,4-triazole (**2**) with isopropyl alcohol successfully occurred over 1.5-3.0 h at room temperature in a conc. H_2SO_4 medium. The reaction products showed quite a high yield (Table 1) of only one of the three possible isomeric products, i.e. 1-isopropyl-5-nitro-1,2,4-triazole (**3**) and 1-isopropyl-3-methyl-5-nitro-1,2,4-triazole (**5**) respectively as shown by GLC data and by NMR and IR spectroscopy.

The regioselective course of this reaction in a high acidity medium can be represented by the following scheme:



1, 3, 4, 7–10 R = H; **2**, **5, 6** R = Me; **3–6** R^1 = *i*-Pr; **7, 8** R^1 = *c*-C_6H_{11}; **9, 10** R^1 = *t*-Bu

The protonation of the nitrotriazoles **1, 2** in a high acidity medium forms the 1H,4H-5-R-3-nitro-1,2,4-triazolium cation **1**. Only one reactive center (the N(2) atom) is available for attack by an electrophile, the N(1) and N(4) atoms being blocked by protons. The likelihood of attack at atoms N(1) and N(4) is also lowered due to localization of a significant positive charge on the ring carbon atom positioned between them. As a result of protonation and dehydration of the 2-propanol molecule in the conc. H_2SO_4 medium a carbocation ($C_3H_7^+$) is formed. This cation attacks the nitrotriazolium cation **I** at the N(2) electron pair available for coordination. Two schemes for obtaining the N(2)-substituted nitrotriazoles **3, 5** are possible. The first is of three stages *via* formation of the intermediate **II**. In the second stage the unstable intermediate **II** is stabilized by loss of a proton, apparently neighboring to the isopropyl substituent. In the last stage the N(2)-substituted nitrotriazolium salt **III**, protonated at atom N(4), is deprotonated to form the N(2)-substituted nitrotriazoles **3, 5**. The deprotonation is basically achieved through decreasing the acidity of the medium by dilution with water. The most likely second scheme is a simultaneous attack at position N(2) in the heterocycle by the $C_3H_7^+$ carbocation and deprotonation of the N(1) atom to the nitrotriazolium salt **I**. The nitrotriazolium salt **III** is then deprotonated as in the first scheme to the N(2)-substituted 1-isopropyl-3-R-5-nitro-1,2,4-triazoles **3, 5**.

The proposal that the carbocation $C_3H_7^+$ attacks carbocation **I** seems unusual at first glance. However, such a scheme explains the regioselectivity of the alkylation. Possible the course of this reaction and the regioselectivity are due to the properties of the reaction medium and the reagents chosen. The isopropyl carbocation is a powerful electrophilic agent since its central carbon atom has a marked positive charge +0.432 [7].

The nitrotriazoles **1** and **2** are weak bases with several reaction centers of different basicity. In the conditions of carrying out this reaction (96% H_2SO_4, H_o = -9.9) the nitrotriazoles are virtually totally protonated at the most basic N(4) atom [1] to form a nitrotriazolium 1H,4H-5-R-cation. However, protonation at one nitrogen atom does not fully suppress the nucleophilic properties of the whole compound due to the presence of an unshared electron pair on atom N(2) and, evidently, at N(2) of the protonated nitrotriazole ring quite a negative π charge is preserved for attack by a powerful electrophile at this position of the heterocycle. Hence the alkylation products of the nitrotriazoles are formed in quite high yields (Table 1).

The possibility of alkylation of the nitrotriazoles by the scheme reported above is confirmed by the results of work presented previously by P. N. Gaponik in [8-10] regarding a detailed study of the selective alkylation by alcohols of close tetrazole analogs of the nitrotriazoles. In particular, in [10] a scheme of attack by a tetrazolium alkylcarbocation fully substantiated by a kinetic study was presented by V. A. Ostrovskii from the Saint Petersburg Technological Institute for the example of alkylation of 5-phenyltetrazole by *tert*-butyl alcohol.

With regard to the absence of isomerization of the 1-isopropyl-3-R-5-nitro-1,2,4-triazoles **3, 5** in sulfuric acid medium over 3 h it was concluded from special experiments that the alkylation of the N-unsubstituted nitrotriazoles by isopropyl alcohol occurs specifically at position N(2) in the heterocycle.

TABLE 1. Reaction Conditions and Yields of the Nitrotriazoles **3, 5, 7-9**

Starting reagents		Reaction time, h	Reaction product	bp, °C*	Yield, %
Azole	Alcohol				
1	*2*-PrOH	1.5	**3**	90–92	60.7
1	*2*-PrOH	3	**3**	90–92	66.7
2	*2*-PrOH	2	**5**	98–100	43.3
1	*c*-$C_6H_{11}OH$	2	**7** + **8***[2]	—	45.4
1	*t*-BuOH	3	**9**	—*[3]	80.0

* 12-15 mm Hg.

*[2] Ratio of nitrotriazoles **7, 8** = 0.8:1.0.

*[3] Mp 95-97ºC.

In addition, the nature of the attacking carbocation and the reaction conditions to a marked extent fix the reaction products which, in turn, depend on the possibility of isomerization. Upon prolonged holding of the reaction mixtures or individual 1-isopropyl-3-R-5-nitro-1,2,4-triazoles **3, 5** in conc. H_2SO_4 a partial isomerization occurs to give the isomeric 1-isopropyl-3-nitro-5-R-1,2,4-triazoles **4, 6**.

Reaction of the nitrotriazole **1** with cyclohexyl alcohol occurs to give a mixture of the regioisomers at atoms N(1) and N(2). The mixture of 1-cyclohexyl-5-nitro- (**7**) and 1-cyclohexyl-3-nitro- (**8**) 1,2,4-triazole isomer products formed are difficult to separate and the isomer ratio was determined using ^{1}H NMR spectroscopy.

The most likely explanation for formation of a mixture of isomeric cyclohexyl nitrotriazoles **7** and **8** is an increase in the tendency in the acid media towards isomerization of the 1-cyclohexyl-5-nitro-1,2,4-triazole to the corresponding 1-cyclohexyl-3-nitro-1,2,4-triazole by comparison with the isomerization of the 1-isopropyl-5-nitro-3-R-1,2,4-triazole analogs **3, 5** to the 1-isopropyl-3-nitro-5-R-1,2,4-triazoles **4, 6**.

Bearing in mind the sensitivity of the reaction of N(2)-substituted nitrotriazoles to N(1)-substituted nitrotriazoles upon exchange of one alkylating agent for another (especially isopropyl for cyclohexyl alcohols) a significant dependence of the isomerization process for the carbocation on the nature of the attacking nitrotriazole substrates can be proposed. However, the appearance of a sharp change in the nature and products of the reaction on going to the *tert*-butyl alcohol was unexpected since, in the reaction of nitrotriazole **1** with *tert*-butyl alcohol in conc. H_2SO_4 medium, the only product is 1-*tert*-butyl-3-nitro-1,2,4-triazole (**9**). The isomeric 1-*tert*-butyl-5-nitro-1,2,4-triazole (**10**) was only found in the reaction mixture in trace amounts in the initial period of the reaction.

TABLE 2. Spectroscopic Characteristics of the Nitrotriazoles **3-9**

Compound	IR spectrum, ν_{NO2}, cm^{-1}	UV spectrum, λ_{max}, nm	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{13}S NMR spectrum, δ, ppm
3	1558, 1330	266, 218	1.48 (6H, d, *J* = 6.6, $(CH_3)_2$); 5.30 (1H, m, $\underline{CH}(CH_3)_2$); 8.20 (1H, s, =CH)	21.77 ($C\underline{C}H_3)_2$); 54.18 ($\underline{C}H(CH_3)_2$); 148.07 (CH–); 151.77 (C–NO_2)
4	1555, 1305	257, 222	1.50 (6H, d, *J* = 6.7, $(CH_3)_2$; 4.76 (1H, m, $CH(CH_3)_2$); 8.67 (1H, s, =CH)	21.82 ($C\underline{C}H_3)_2$); 53.69 ($\underline{C}H(CH_3)_2$); 144.99 ($\underline{C}H$–); 161.94 (C–NO_2)
5	1562, 1340	282, 227	1.45 (6H, d, $CH(CH_3)_2$); 5.22 (1H, m, $C\underline{H}(CH_3)_2$); 2.34 (3H, s, CCH_3)	11.43 ($CH(\underline{C}H_3)_2$); 21.46 ($CH(\underline{C}H_3)_2$); 51.35 ($\underline{C}H(CH_3)_2$); 154.08 ($\underline{C}_\kappa$–CH_3); 160.88 (C–NO_2)
6	1558, 1320	266, 218	1.47 (6H, d, $CH(CH_3)_2$); 4.31 (1H, m, $C\underline{H}(CH_3)_2$); 2.58 (3H, s, C–CH_3)	13.78 ($CH(CH_3)_2$); 21.77 ($CH(\underline{C}H_3)_2$); 53.75 ($\underline{C}H(CH_3)_2$); 151.29 (C–NO_2); 157.64 (CCH_3)
7	1552, 1325	—	1.76-2.33 (10H, m, $(CH_2)_5$); 4.90 (1H, m, CH); 8.20 (1H, s, =CH)	60.74 (CH_{cycle}); 149.00 $(CH)_\kappa$; 161.65 (C–NO_2)
8	1550, 1305	—	1.65-1.75 (10H, m, $(CH_2)_5$); 4.88 (1H, m, CH); 8.99 (1H, s, =CH)	62.94 (CH_{cycle}); 144.73 $(CH)_\kappa$; 151.80 (C–NO_2)
9	1555, 1307	257, 220	1.6 (9H, s, $C(CH_3)_3$); 8.95 (1H, s, CH)	28.58 ($C(\underline{C}H_3)_3$); 61.01 ($\underline{C}(CH_3)_3$); 144.13 ($\underline{C}H)_{cycle}$; 161.82 (C–NO_2)

Assignment of the nitrotriazoles **3, 5, 7** (Table 2) as the N(2)-substituted compounds was made on the basis of the high sensitivity of the chemical shifts of atoms C-3 in the NMR spectra towards the position of an alkyl substituent on the cyclic nitrogen atoms in N(1)- or N(2)-substituted 3-nitro-1,2,4-triazoles.

Thus the signals for the C-3 atom bound with the nitro group in the 2-mono- and 2,5-disubstituted nitrotriazoles **3, 5, 7** lie in the narrow range 151.29-151.80 ppm. The signals for the N(1)-substituted nitrotriazoles **4, 6, 8** in the same conditions are shifted by 9.59-10.14 ppm to low field (160.88-161.94 ppm).

Comparison of the physicochemical and spectroscopic characteristics for the N(1)-substituted nitrotriazoles **4, 6, 8** with compounds **3, 5, 7** indicate that the latter materials are, in fact, 5-nitrotriazoles.

Compound **9** is identified as the N(1)-isomer on the basis that the singlet for the ring proton at 8.95 ppm is found at characteristically low field for N(1)-alkyl-substituted nitrotriazoles [4, 11] relative to the N(2)-alkyl-substituted isomers (including isomer **10** at 8.08 ppm). In addition, comparison of the chemical shift of the cyclic C-3 atom with the nitro group in the ^{13}C NMR spectrum of nitrotriazole **9** (161.82 ppm) with the chemical shifts of the corresponding atoms of the N(1)-substituted nitrotriazoles **4, 6, 8** (160.88-161.94 ppm) and nitrotriazoles **3, 5, 7** (151.29-151.80 ppm) indicates that compounds **9** is an N(1)-substituted nitrotriazole.

The IR spectra of the 5-nitrotriazoles **3, 5, 7** showed absorption bands typical of a nitro group [12, 13], the asymmetric stretching bands being at 1562-1552 and symmetric streching bands at 1340-1325 cm^{-1}. A characteristic low field shift of the absorption bands of the N(1)-isomers **4, 6, 8, 9** was seen compared with those of the isomers **3, 5, 7** [4, 12, 13].

The UV spectra of the nitrotriazoles **3, 5, 7** and **4, 6, 8, 9** show two absorption maxima. The short wave maximum showed little sensitivity to the nature and position of the substituent. In the long wavelength region the absorption maximum value for the alkyl nitrotriazoles depends on the position of the nitro group [14] and for the 5-nitro isomers **3, 5, 7** it is found at longer wavelength than for the N(1)-isomers **4, 6, 8, 9**. In the N(1)-isomers **4, 6, 8, 9** a characteristic shift of the absorption maximum of 9-16 nm to shorter wavelength is seen when compared with the isomers **3, 5, 7** (Table 2).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were taken on a Bruker AM-400 (400 and 100 MHz respectively) for a solution in DMSO-d_6 with DMSO as internal standard. IR spectra were recorded on a Perkin-Elmer instrument for KBr tablets and UV spectra on a Specord instrument. Gas chromatographic analysis of the reaction products was carried out by the internal standard method on a CHROM-5 chromatograph with a flame ionization detector, glass column (l = 200 mm, d = 3 mm) with an SE-30 siloxane packing, gas carrier nitrogen (40 ml/min), thermostat temperature 180ºC, evaporator 220ºC, and detector 220ºC. Melting points were determined on a mini Boetius heating block with a PHMK-05 viewing attachment.

Preparation of Components and Reagents. Triazoles **1, 2** were recrystallized twice from water and then from methanol, mp 214 and 197ºC [5] (mp 210 and 194ºC [13]).

The N-alkyl-1,2,4-triazoles **3-6** reference samples were obtained by a known method [4] and were identified by ^{1}H NMR and GLC. The properties of **3, 4** agreed with the literature: 1-isopropyl-5-methyl-3-nitro-1,2,4-triazole (**6**) mp 42-43ºC, 1-isopropyl-3-methyl-5-nitro-1,2,4-triazole (**5**), bp 98-100ºC (12 mm Hg). The ^{1}H and ^{13}C NMR and IR spectroscopic characteristics are given in Table 2.

Preparation of Nitrotriazoles 3, 5, 7-9 (General Method). The alcohol (0.28 mol) was added dropwise over 10 min with stirring to a solution of the nitrotriazole **1** or **2** (0.25 mol) in conc. H_2SO_4 (180 ml) holding the temperature 20-25ºC. The reaction mixture was stirred for the time indicated in Table 1, poured into iced water (1 kg), and extracted with methylene chloride (3×250 ml). The combined extract was washed with a 3-5% solution of sodium carbonate (100 ml) to neutral pH, and dried over anhydrous $MgSO_4$ (Tables 1 and 2).

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