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REACTIONS OF 3-NITRO-1,2,4-TRIAZOLE DERIVATIVES WITH ALKYLATING AGENTS. 2.* ALKYLATION OF A NEUTRAL HETEROCYCLE BY DIMETHYL SULFATE

G. T. Sukhanov[1], G. V. Sakovich[1], A. G. Sukhanova[2], and A. Yu. Lukin[2]

The reaction of 3-nitro-1,2,4-triazole and 5-methyl-3-nitro-1,2,4-triazole with dimethyl sulfate leads to mixtures of N-mono- and N,N-dimethylnitrotriazolium compounds and products of the subsequent conversion of the latter, namely, N,N-dimethyl-1,2,4-triazol-5-ones.

Keywords: N-alkyl-3-nitro-1,2,4-triazole, N,N-dimethyl-1,2,4-triazol-5-one, alkylation, regioselectivity.

The presence of nitrogen atom of pyrrole and pyridine type in 3-nitro-1,2,4-triazoles permits two methods for the alkylation of these compounds in neutral and alkaline media. The strong nucleophilicity of the nitrogen atoms in the triazolate anion in the alkylation of the azoles in alkaline media permits us to carry out the reaction under extremely mild conditions, minimizing the formation of by-products of the hydrolysis of the alkyl halides and dialkyl sulfates, olefinization of alkyl halides, the formation of quaternary salts etc. [1-3]. The alkylation of the neutral heterocycle gives rise to the possibility of several side reactions. This method is rarely used and has not been studied extensively. On the other hand, an examination of this method of alkylation of 3-nitro-1,2,4-triazoles holds interest relative to the preparation of isomeric N-monoalkyl derivatives and the products of their quaternization, namely, N,N-dialkyl-3-nitro-1,2,4-triazolium salts.

The alkylation of 3-nitro-1,2,4-triazole by dialkyl sulfates and alkyl halides in the presence of alkali has been described in our previous work [1]. This reaction proceeds with low selectivity. The yield of the mixture of $N_{(1)}$- and $N_{(2)}$-isomers is 75-89%. The mass fraction of the $N_{(2)}$-isomer in the mixture is 14.6-33.8%.

In a continuation of a study of the alkylation of nitrotriazoles, we have found that 3-nitro-1,2,4-triazoles react vigorously with dimethyl sulfate (DMS) upon heating to give mixtures of N-monoalkyl- and N,N-dialkylnitrotriazole derivatives as well as the products of the subsequent transformations.

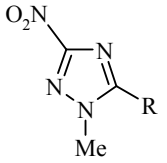
In this study, we examined 3-nitro-1,2,4-triazole (**1**) and 5-methyl-3-nitro-1,2,4-triazole (**2**). The reaction was carried out in the medium of the alkylating agent at temperatures not exceeding 80°C.

A special feature of the alkylation of 3-nitro-1,2,4-triazoles through the neutral molecule lies in the failure of the substituent to add at the site of the N–H proton but rather at the free azo group, i.e., formation of the N-derivative of less stable tautomer (the ratio of the 1-H and 4-H tautomers of 3-nitro-1,2,4-triazole is about

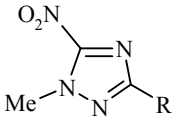
* For Communication 1, see [1].

[1] Institute of Problems of Chemical Energetic Technologies, Siberian Branch of the Russian Academy of Sciences, 659322 Biisk, Russia; e-mail: admin@ipcet.ru. [2] Federal Research and Production Center "Altai", 659322 Biisk, Russia; e-mail: post@frpc.secna.ru, lukin@mail.biysk.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1168-1173, August, 2005. Original article submitted August 1, 2003.

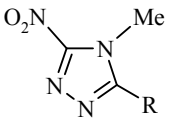
180:1) [4]. The reaction of triazole **1** with DMS gave 1-methyl-3-nitro-1,2,4 triazole (**3a**), 1-methyl-5-nitro-1,2,4-triazole (**4a**), 4-methyl-3-nitro-1,2,4-triazole (**5a**), and the 1,4-dimethyl-3-nitro-1,2,4-triazolium methylsulfate (**6a**), which was isolated from the reaction mixture as 1,4-dimethyl-3-nitro-1,2,4-triazolium perchlorate (**7a**) and 1,4-dimethyl-1,2,4-triazol-5-one (**8a**). We should note that 1,4-dimethyl-5-nitro-1,2,4-triazolium salt (**9a**), which is the precursor of triazolone **8a**, was not found in the reaction mixture.



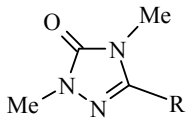
3a,b



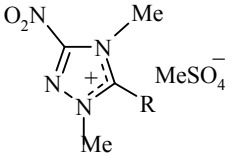
4a,b



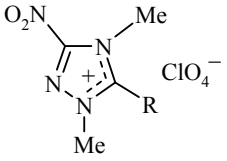
5a,b



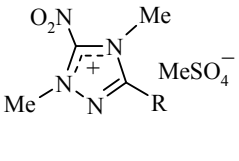
8a,b



6a,b



7a,b



9a,b

3–9 **a** R = H, **b** R = Me

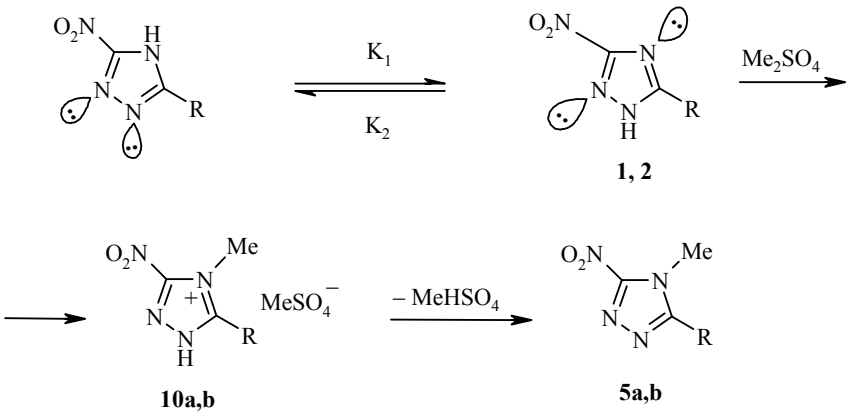
The reaction of triazole **2** with DMS gave 1,5-dimethyl-3-nitro-1,2,4-triazole (**3b**), 1,3-dimethyl-5-nitro-1,2,4-triazole (**4b**), 4,5-dimethyl-3-nitro-1,2,4-triazole (**5b**), and 1,4,5-trimethyl-3-nitro-1,2,4-triazolium methylsulfate (**6b**), which, as in the case of salt **6a**, was isolated as 1,4,5-trimethyl-3-nitro-1,2,4-triazolium perchlorate (**7b**). In this case, we did not detect 1,3,4-trimethyl-5-nitro-1,2,4-triazolium methylsulfate (**9b**), which is the precursor of triazolone **8b**.

On the basis of the signals of the protons at $C_{(5)}$ in the ^{1}H NMR spectra, triazole **5a** was identified as the 4H-isomer. Thus, the chemical shift of the proton at $C_{(5)}$ in 4-methyltriazole **5a** at 8.82 ppm is downfield relative to the ring protons in 1-methyltriazole **3a** at 8.75 ppm and in 2-methyltriazole **4a** at 8.15 ppm [1], while the singlet for the N–CH_3 group protons in triazole **5a** at 3.93 ppm is upfield relative to the signal of the analogous protons in 1-methyltriazole **3a** at 4.03 ppm and in 2-methyltriazole **4a** at 4.18 ppm [1]. A similar regularity in the ^{1}H NMR spectra of triazoles **3b-5b** permit us to identify triazole **5b** as the 4-isomer. The agreement of the physical constants, in particular, the melting points, of triazoles **5a**,**b** with the values given in earlier work [2, 5, 6] and comparative analysis of the ^{1}H NMR, IR, and UV spectra of these compounds and their analogs, **3a,b, 4a,b** [1, 4, 8] also support these assignments.

Triazoles **7a**,**b** were identified as 1,4-dimethyl- and 1,4,5-trimethyl-3-nitro-1,2,4-triazolium salts using their ^{1}H NMR, ^{13}C NMR, and IR spectra. The IR spectra of triazolium salts **7a** and **7b** retain the nitro group bands characteristic for nitrotriazoles [7], namely, symmetrical antiphased vibrations at 1565 and 1587 cm^{-1} and synphased vibrations at 1340 and 1335 cm^{-1}. Intense bands are found for the perchlorate anion at 1085 and 1100 cm^{-1}. The ^{1}H NMR spectra of quaternary salt **7a** show a pair of singlets of equal intensity for the protons of the two methyl groups at 4.16 and 4.21 ppm and a signal for the ring C–H proton at 10.31 ppm. The ^{13}C NMR spectra of this compound feature methyl group carbon singlets at 37.09 and 40.22 ppm as well as signals for the C–H ring carbon at 147.17 ppm and the carbon attached to the nitro group at 150.99 ppm. The ^{1}H NMR spectrum of triazolium salt **7b** has three singlets of equal intensity (two singlets at 4.05 ppm and 4.15 ppm for the methyl group protons at $N_{(4)}$ and $N_{(1)}$) and singlet for the methyl group protons at $C_{(5)}$ at 2.89 ppm.

In examining the isomeric composition of the N-monoalkylation products, we should first note the virtual absence of the $N_{(1)}$-isomer (0.2-0.3%), low content of the $N_{(2)}$-isomer (6-8%),and rather high content of the $N_{(4)}$-isomer (46-65%). As a rule, the $N_{(1)}$- and $N_{(2)}$-isomers predominate in the alkylation of 3-nitro-1,2,4-triazoles [1-4], while the $N_{(4)}$-alkylated compounds are formed in only slight amounts (3%) when the dimethylacetal of DMF is used [6] and are not formed at all when nonselective alkylating agents such as diazomethane are used [2]. Hence, in our case, the 3-nitro-5-R-1,2,4-triazolate anion does not undergo alkylation but rather the N–H form of triazole **1** and **2**.

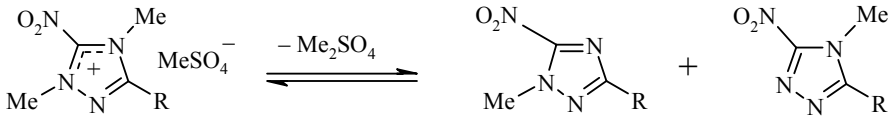
A special feature of the alkylation of the neutral heterocycle is that the reaction likely proceeds through formation of intermediate salts **10a**,**b** and the formation of the $N_{(4)}$-isomers may be represented in the following scheme. The electrophilic agent attacks triazoles **1** and **2** at the unshared electron pair of $N_{(4)}$, which is available for coordination, or at the π-bond of this atom with subsequent localization of the substituent at $N_{(4)}$ and formation of compounds protonated at $N_{(1)}$, namely, 1-H-4-methyl- or 1-H-4,5-dimethyl-3-nitro-1,2,4-triazolium salts **10a**,**b**. This proposal is in good accord with the result of the reaction of nitrotriazoles with the simplest electrophile, the proton [4]. The nitrotriazolium salts formed **10a**,**b** are unstable, lose a proton upon dilution of the reaction mixture by water, and are converted to the corresponding $N_{(4)}$-substituted triazoles **5a**,**b**.



a R = H, **b** R = Me, when R = H $K_1 : K_2 = 180 : 1$ [4]

The formation of the $N_{(2)}$-isomer is unexpected in this reaction. Since the predominant tautomer for 3-nitro-1,2,4-triazole derivatives is the 1-H isomer [4], we would have predicted a low probability for alkylation of triazoles **1** and **2** at $N_{(2)}$ due to the reduced nucleophilicity of this atom relative to $N_{(4)}$ related to the presence of a "pyrrolic" nitrogen atom adjacent to $N_{(2)}$. Nevertheless, rather significant amounts of the $N_{(2)}$-isomer (up to 8%) are detected in the products of the reaction of DMS with triazoles **1** and **2**.

In the absence of moisture, 1,4-dimethyl salts **9a** and **9b** are rather stable. Dissociation–recombination is a possible pathway for formation of the $N_{(2)}$-isomer.



R = H, Me

Another possible pathway for formation of the $N_{(2)}$-isomer is analogous to the scheme for formation of the $N_{(4)}$-isomer and involves attack of $N_{(2)}$ in triazoles **1** and **2** by the electrophilic agent.

N,N-Dimethyl-1,2,4-triazoles **8a**,**b** are formed from the corresponding azolium salts **9a**,**b** as a consequence of the great sensitivity of these compounds to the action of nucleophilic reagents due to delocalization of positive charge on the carbon atom at the nitro group.

A study of the effect of the reaction conditions on the product yields showed that the reagent ratio and reaction time are significant factors.

A significant amount of unreacted starting components (up to 60%) remains after a relatively short reaction time (15-20 min) and the use of a 10-25% molar excess of triazoles **1** and **2**. The predominant reaction products are N-monomethyltriazoles **3a,b–5a,b** (15-30%), while the yields of N,N-dimethyl derivatives **7a**,**b** and triazolones **8a**,**b** are only 2-3%. The triazolones, as a rule, are obtained in only trace amounts.

Increasing the reaction time to 2.0-2.5 h leads to virtually quantitative conversion of DMS. The ratio of the N-monomethyl and N,N-dimethyl derivatives and the triazolones is markedly altered. The total yield of monomethyl derivatives **3a,b–5a,b** rises to 53-73% and the yield of triazolones **7a**,**b** rises to 3-6%. The relatively ready formation of N,N-dimethyl-3-nitro-1,2,4-triazolium salts **6a**,**b** isolated as salts **7a**,**b** in 12 and 8% yield, respectively, is unusual in this reaction despite the less than equivalent amount of alkylating agent and the presence of the electron-withdrawing nitro group in heterocycles **1** and **2**.

When the excess of DMS is increased to two- or three-fold and the reaction time is extended to 2-3 h, starting triazoles **1** and **2** are no longer found in the reaction mixture. The mass yield of the N-monoalkylation products **3a,b–5a,b** is significantly reduced to 15-24% and $N_{(1)}$-methyl isomers **3a**,**b** are lacking and $N_{(4)}$-methyl isomers **5a** and **7a** may also completely disappear. The yield of the N,N-dimethylnitrotriazoles is increased to 45-60% and 1,4-dimethylation products **7a**,**b** predominate in these products. The fraction of triazolones **8a**,**b** is 5-7%. The synthesis of 1,4-dialkyl- and 1,4,5-trialkyl-3-nitro-1,2,4-triazolium salts will be described in a subsequent communication.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on a Bruker AM-400 spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 with DMSO as the internal standard. The IR spectra were taken on a Perkin Elmer spectrometer for KBr pellets. The UV spectra were taken on a Specord spectrometer. The gas chromatographic analysis of the reaction products was carried out using an internal standard method on a Chrom-5 chromatograph with a flame ionization detector using a glass column (l = 200 mm, d = 3 mm) packed with SE-30 siloxane elastomer. The flow rate of the nitrogen gas carrier was 40 ml/min. The thermostat temperature was 180°C. The temperature of the injector and detector was 220°C. Melting points were found on a Boetius block with an RNMK-05 observation device.

Preparation of Components and Reagents. N-Methyl-1,2,4-triazoles and triazolones (**3a-5a, 8a, 3b-5b, 8b**) prepared by reported procedures [2, 6, 9] were used as standards for studying the ^1H NMR spectra and in gas–liquid chromatography. In order to remove impurities, a sample of dimethyl sulfate was washed with 3% aq. sodium carbonate and then distilled water, dried, and distilled in vacuum (purity ≥99.9%, the amount of acid calculated relative to sulfuric acid was ≤0.1%). Triazoles **1** and **2** were recrystallized twice from water and then from methanol; mp 214°C for **1** (210°C [5]) and mp 197°C for **2** (194°C [5]).

Reaction of 3-Nitro-1,2,4-triazole (1) with DMS. A suspension of **1** (22.8 g, 0.2 mol) and DMS (22.4 g, 0.178 mol) was stirred at 78-80°C for 2.5 h, cooled to 30°C, and extracted with CH_2Cl_2. The following compounds were detected in the extract by ^1H NMR spectroscopy and gas–liquid chromatography using authentic samples as references: DMS in 7.2%, **3a** in 1.9% yield, **4a** in 38.6% yield, **5a** in 52.5% yield, and **8a** in trace yield. The total yield of the mixture after distilling off CH_2Cl_2 in vacuum was 2.8 g. The residue of the reaction mixture was stirred with water (100 ml) and extracted with CH_2Cl_2. ^1H NMR spectroscopy and gas-liquid chromatography indicated that the extract contained **4a** in 2.85% yield, **5a** in 90.75% yield, and **8a** in 6.40% yield. The total yield of the reaction mixture after distilling off CH_2Cl_2 was 9.9 g.

Methylnitrotriazole 5a was isolated from this mixture by recrystallization from 2-propanol and water; mp 122-124°C (118-120°C [6]). IR spectrum, ν_{NO_2}, cm^{-1}: 1565, 1330. UV spectrum, λ_{max}, nm: 261, 218. ^1H NMR spectrum, δ, ppm: 3.93 (3H, s, N–CH_3); 8.82 (1H, s, C–H). ^{13}C NMR spectrum, δ, ppm: 34.40 (N–$\underline{C}H_3$), 148.37 ($\underline{C}$–H), 154.49 ($\underline{C}$–NO_2). IR spectrum, ν_{NO_2}, cm^{-1}: 1550, 1335 [7]. UV spectrum, λ_{max}, nm: 260, 225 [4]. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.9 (3H, s, N–CH_3), 8.8 (1H, s, C–H) [6].

The reaction mixture was extracted twice with CH_2Cl_2 and then heated to 75-80°C. Ammonium perchlorate (3.2 g) was added to the residue, the mixture was cooled to 20°C, and the precipitate was filtered off to give 5.2 g (12.2%) of compound **7a**, mp 175-177°C (water). IR spectrum, ν, cm^{-1}: 1565 (NO_2), 1340 (NO_2), 1085 (ClO_4). UV spectrum, λ_{max}, nm: 230. ^1H NMR spectrum, δ, ppm: 4.16 (3H, s, N–CH_3); 4.21 (3H, s, N–CH_3); 10.31 (1H, s, C–H). ^{13}C NMR spectrum, δ, ppm: 37.09 (N–$\underline{C}H_3$), 40.22 (N–$\underline{C}H_3$), 147.17 ($\underline{C}$–H), 150.99 ($\underline{C}$–NO_2).

Reaction of 5-Methyl-3-nitro-1,2,4-triazole (2) with DMS. A suspension of 3-nitro-1,2,4-triazole (25.6 g, 0.2 mol) and DMS (23.2 g, 0.184 mol) was stirred at 75-80°C for 2 h and then cooled to 30°C. The mixture was extracted with methylene chloride. ^1H NMR spectroscopy and gas-liquid chromatography with reference standards indicated the presence of DMS in 22% yield, **4b** in 55% yield, **5b** in 24% yield, and **8b** in trace yield. The total yield of the mixture after distilling off CH_2Cl_2 in vacuum was 3.3 g. The residue was stirred with water (60 ml) and extracted with CH_2Cl_2. ^1H NMR spectroscopy and gas-liquid chromatography with reference standards indicated the presence of DMS in 1.6% yield, **3b** in 0.4% yield, **4b** in 2.4% yield, **5b** in 91.7% yield, and **8b** in 8.1% yield. The total yield of the mixture after distilling off CH_2Cl_2 in vacuum was 17.5 g.

Dimethylnitrotriazole 5b was obtained from this mixture by recrystallization from 2-propanol and then from water; mp 75-76°C. IR spectrum, ν_{NO_2}, cm^{-1}: 1520, 1328. UV spectrum, λ_{max}, nm: 275, 210. ^1H NMR spectrum, δ, ppm: 2.50 (3H, s, C–CH_3); 3.83 (3H, s, N–CH_3). ^{13}C NMR spectrum, δ, ppm: 10.84 (C–$\underline{C}H_3$), 33.15 (N–$\underline{C}H_3$), 154.61 ($\underline{C}$–NO_2), 155.78 ($\underline{C}$–H). The residue of the reaction mixture was extracted twice with CH_2Cl_2 and then heated to 75-80°C. Then, ammonium perchlorate (3.6 g) was added. The mixture was cooled to 20°C and filtered to give 3.6 g (7.6%) **7b**; mp 194-195°C (water). IR spectrum, ν, cm^{-1}: 1587 (NO_2), 1100 (ClO_4). UV spectrum, λ_{max}, nm: 238. ^1H NMR spectrum, δ, ppm: 2.89 (3H, s, C–CH_3); 4.05 (3H, s, N–CH_3); 4.15 (3H, s, N–CH_3). ^{13}C NMR spectrum, δ, ppm: 10.38 (C–$\underline{C}H_3$), 35.67 (N–$\underline{C}H_3$), 38.93 (N–$\underline{C}H_3$), 150.38 ($\underline{C}$–NO_2), 156.18 ($\underline{C}$–CH_3).

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