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REACTION OF 3-NITRO-1,2,4-TRIAZOLE DERIVATIVES WITH ALKYLATING AGENTS. 1. ALKYLATION IN THE PRESENCE OF ALKALI

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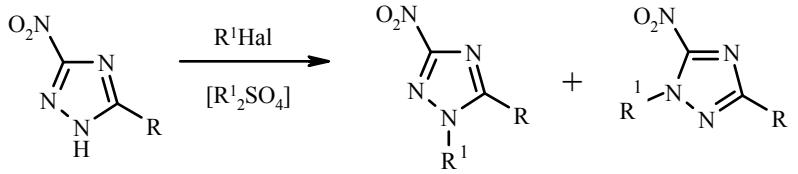
Alkylation of 3-nitro-1,2,4-triazole and 5-methyl-3-nitro-1,2,4-triazole with dialkyl sulfates or alkyl halides in the presence of alkali proceeds with a low selectivity for the alkylating agent with the formation of two regioisomers at the $N_{(1)}$ and $N_{(2)}$ atoms of the heterocycle. Depending on the reaction conditions the proportion of the $N_{(2)}$ isomer was 14.6-33.8%.

Keywords: 1-alkyl-3-nitro-1,2,4-triazoles, 1-alkyl-5-nitro-1,2,4-triazoles, 3-nitro-1,2,4-triazoles, alkylation, regioselectivity.

The selectivity of reactions is a general problem of heterocyclic chemistry. At the present time the selectivity of electrophilic substitution reactions in nitro derivatives of 1,2,4-triazoles has not been studied adequately. 3-Nitro-5-R-1,2,4-triazoles have three potential reaction centers, the $N_{(1)}$, $N_{(2)}$, and $N_{(4)}$ atoms, consequently on alkylation the formation of three isomers is theoretically possible. According to the data of [1, 2] alkylation of salts of 3-nitro-5-R-1,2,4-triazole derivatives with alkyl halides and dimethyl sulfate (DMS) proceeds regioselectively. The authors' opinion on the place of attack on the ring by an electrophilic reagent varied. On interacting 3-nitro-1,2,4-triazole (**1**) and 5-methyl-3-nitro-1,2,4-triazole (**2**) with DMS in acetone, alcohol, and mixtures of them with water in the presence of alkali only the $N_{(1)}$ isomer [1] was isolated, *viz.* 1-methyl-3-nitro-1,2,4-triazole (**3**) and 1,5-dimethyl-3-nitro-1,2,4-triazole (**4**), in 66 and 55% yield respectively. According to [2] alkylation of the sodium salt of triazole **1** in propanol also leads to one isomer, which however was erroneously assigned the structure of the corresponding 1-alkyl-2-nitro-1,3,4-triazole. However the selective course of the reaction in this and other cases seems less probable and this point requires defining more accurately.



1,2 **3a–7a** **3b–7b**

1, 3a,b, 5a,b-7a,b R = H; **2, 4 a,b** R = Me; **3 a,b, 4a**,**b** R^1 = Me; **5a,b** R^1 = Et; **6a,b** R^1 = Pr; **7a,b** R^1 = *i*-Pr

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On investigating the alkylation products of triazoles **1** and **2** more thoroughly by the method described in [1, 2], we established that the selectivity of methylation was not confirmed. It was found that on interacting salts of compounds **1** and 2 with dialkyl sulfates (DAS) and alkyl halides, in reality monoalkylation products were formed in all cases.

The reaction products, isolated in high yield (50-89%) and identified, were mixtures of two regioisomers (**3a-7a** and **3b-7b**). This was confirmed by data of GLC and ^{1}H NMR, IR, and UV spectroscopy (Tables 1-4).

The marked differences in dipole moment [3] and volatility of isomers **a** and **b** enabled us to use solvent extraction and distillation in vacuum for their separation (Table 2).

From the mixture of high-melting triazoles **3** and **4** (by method A), isomers **3b** and **4b** were isolated by extraction with hexane. From the residues triazole isomers **3a** and **4a** respectively were isolated by crystallization from alcohols.

TABLE 1. Alkylation Products of Salts of Triazoles **1** and **2** with Alkyl Sulfates and Alkyl Halides

Exp No.	Initial triazole	Alkylating Agent	Alkali	Temperature, °C	Reaction time, h	Compounds (mixtures)	% by weight (GLC)		Yield of isomers **a** + **b**, %
							Isomer **a**	Isomer **b**	
1	**1**	DMS	NaOH	20-25	72	**3a** + **3b**	70.8	29.2	76.2
2	**1**	DMS	LiOH	75-78	3	**3a** + **3b**	72.5	27.5	84.2
3	**1**	MeI	LiOH	20-25	200	**3a** + **3b**	78.8	21.2	75.0
4	**1**	DES*	LiOH	20-25	24	**5a** + **5b**	68.2	31.8	88.1
5	**1**	$MeCH_2I$	LiOH	20-25	200	**5a** + **5b**	79.9	20.1	76.8
6	**1**	$MeCH_2Br$	LiOH	15-18	700	**5a** + **5b**	66.7	33.3	50.1
7	**1**	$MeCH_2Br$	LiOH	75-78	7	**5a** + **5b**	71.2	28.8	85.8
8	**1**	$MeCH_2Br$	NaOH	75-78	7	**5a** + **5b**	78.3	21.7	82.5
9	**1**	$Me(CH_2)_2Br$	NaOH	75-78	20	**6a** + **6b**	82.2	17.8	89.4
10	**1**	Me_2CHBr	NaOH	72-78	20	**7a** + **7b**	74.8	25.2	79.4
11	**2**	DMS	LiOH	20-25	24	**4a** + **4b**	66.2	33.8	84.5
12	**2**	MeI	LiOH	20-25	200	**4a** + **4b**	75.3	24.7	78.2

* Diethyl sulfate.

TABLE 2. Properties of the Isomeric Alkyl-substituted Triazoles **3a,b-7a,b**

Compound	Separation method	mp, °C	mp, °C [lit.]	Bp., °C (mm Hg)	Yield, %
3a	A	65-66	64-65 [4]		51.2
3b		81-82	79-80 [4]		19.1
4a	A	90-91	89-90 [1]		45.6
4b		57-58	55-56 [1]		20.4
5a	B	32-33	—	125-130 (1)	50.0
5b		29-30	—	62-65 (0.5)	31.0
6a	B		—	140-142 (1)	72.1
6b			—	74-75 (1)	11.5
7a	C	52-53	—	92-95	63.1
7b			—	(12-15)	14.7

TABLE 3. Influence of the Nature of the Alkaline Agent on the Total Yield and Ratio in the Mixture of Triazoles **5a** and **5b***

	K_2CO_3	Na_2CO_3	KOH	NaOH	LiOH	NH_4OH	TMA·OH*[2]
Total yield of mixture **5a**+**5b**, %	74.8	69.9	74.5	71.3	69.3	73.0	88.7
Content in mixture (GLC), %							
5a	83.5	83.7	82.2	82.5	82.0	85.4	83.2
5b	16.5	16.3	17.8	17.5	18.0	14.6	16.8

* Solvent was water, alkylating agent ethyl bromide.
*[2] TMA·OH is tetramethylammonium hydroxide.

TABLE 4. Spectral Characteristics of Triazoles **3-7**

Com-pound	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm	^1H NMR spectrum (DMSO-d_6), δ, ppm. (*J*, Hz)
3a	1546, 1310 1555, 1313 [6]	255 255 [5]	4.03 (3H, s, N–CH_3); 8.75 (1H, s, =CH) 4.02 (3H, s, N–CH_3); 8.22 (1H, s, =CH) [4]
3b	1556, 1338 1555, 1320 [7]	265 270 [5]	4.18 (3H, s, N–CH_3); 8.15 (1H, s, =CH) 4.08 (3H, s, N–CH_3); 8.04 (1H, s, =CH) [4]
4a	1540, 1312	266 262.5 [5]	2.50 (3H, s, C–CH_3); 3.91 (3H, s, N–CH_3)
4b	1562, 1346	280 279 [5]	2.32 (3H, s, C–CH_3); 4.10 (3H, s, N–CH_3)
5a	1550, 1305	257	1.47 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 4.39 (2H, q, *J* =6.0, $\underline{CH_2}CH_3$); 8.78 (1H, s, =CH)
5b	1558, 1336	266	1.47 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$); 4.61 (2H, q, *J* =6.2, $\underline{CH_2}CH_3$); 8.12 (1H, s, =CH)
6a	1550, 1305	255	0.87 (3H, t, *J* = 7.4, $CH_2\underline{CH_3}$); 1.85 (2H, m, $=CH_2$); 4.29 (2H, t, N–CH_2–); 8.78 (1H, s, =CH)
6b	1560, 1335	267	0.90 (3H, t, *J* = 7.7, $CH_2\underline{CH_3}$); 1.90 (2H, m, $=CH_2$); 4.52 (2H, t, N–CH_2–); 8.13 (1H, s, =CH)
7a	1555, 1305	257	1.50 (6H, d, *J* = 6.7, $CH(\underline{CH_3})_2$); 4.76 (1H, m, $CH(CH_3)_2$); 8.67 (1H, s, =CH)
7b	1558, 1330	266	1.48 (6H, d, *J* = 6.6, $CH(\underline{CH_3})_2$); 5.30 (1H, m, $CH(CH_3)_2$); 8.20 (1H, s, =CH)

The mixture of liquid and low-melting 1-ethyl-3-nitro-1,2,4-triazole (**5a**) and 1-ethyl-5-nitro-1,2,4-triazole (**5b**), and also 3-nitro-1-propyl-1,2,4-triazole (**6a**) and 5-nitro-1-propyl-1,2,4-triazole (**6b**) were separated (method B) by vacuum distillation. Finally, from the mixture of 1-isopropyl-3-nitro-1,2,4-triazole (**7a**) and 1-isopropyl-5-nitro-1,2,4-triazole (**7b**) the latter was isolated by vacuum distillation, and triazole **7a** was isolated by crystallization of the still residue from ethanol (method C).

The correctness of the assignments made were confirmed by the agreement of the melting points (Table 2) of the isomeric triazoles **3a,b 4a,b** isolated from the mixture with the melting points of these triazoles given in [1,4].

When alkylating triazoles **1** and **2** with alkyl halides and dialkyl sulfates, the ratio of isomeric triazoles **a** and **b** depends on the reaction conditions.

The solvent proved to have a significant influence on reaction selectivity. Carrying out the reaction in water leads to the formation of a product with a larger proportion of the polar isomer **a** (Table 3). An increase in the polarity of the reaction medium by increasing the reactant concentrations to double that given in the general procedure increases the proportion of this isomer further by 3-3.5%. In all cases water in comparison with

ethanol levels the effect of the nature of the counter ion on the selectivity of alkylation (Table 3). The proportion of isomer **b** depends significantly on the nature of the alkylating agent and the reaction temperature (Table 1).

The structures of the isomeric 1-alkyltriazoles obtained were confirmed by analysis of their spectral data. In the ^{1}H NMR spectra a singlet was recorded for the proton of the ring carbon atom at 8.12-8.78 ppm and the protons of the alkyl groups were recorded (Table 4). In the spectra of all the 1-alkyl-3-nitro-1,2,4-triazoles (**3a**, **5a-7a**) the signal for the proton at $C_{(5)}$ is found at lower field (δ 8.67-8.78 ppm), but the signals for the CH_3 (CH_2, CH) group protons at position 1 were found at higher field than the signals of the same protons in the spectra of the isomeric 1-alkyl-5-nitro-1,3,4-triazoles **3b**, **5b-7b**.

Similarly in the spectrum of compound **4a** the signal of the 5-CH_3 protons was at 2.5 ppm, and in the spectrum of the isomeric 5-methyltriazole **4b** the protons of the 3-CH_3 group resonate at higher field (δ 2.32 ppm).

Two absorption maxima were observed in the UV spectra of triazoles **3-7**. The short wave maximum in the derivatives of 3-(5)-nitro-1,2,4-triazoles **a**(**b**) had low sensitivity towards the nature of the substituent, while in the long wave region the absorption maximum of the nitrotriazole derivatives depends on the position of the nitro group [5]. In the spectra of isomers **3a-7a** a characteristic displacement is observed for the absorption maximum by 9-14 nm into the short wave region [5] compared with isomers **3b-7b** (Table 4).

The IR spectra were also fairly informative. In them were present the absorption bands of the nitro group, most characteristic in frequency for derivatives of 3-nitro-1,2,4-triazoles [6, 7], localized in fairly narrow spectral ranges, the symmetrical antiphase stretching vibration at 1540-1562 and the synphase at 1305-1346 cm^{-1} (Table 4). Both bands for isomers **a** were displaced compared with isomers **b** towards lower frequencies, and the synphase vibrations were displaced to a greater extent (by 25-34 cm^{-1}).

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AM 400 (400 MHz) spectrometer in DMSO-d_6, internal standard was DMSO-d_6. The IR spectra were taken on a Perkin-Elmer instrument in KBr disks, and the UV spectra on a Specord instrument and an M-80 spectrophotometer. 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) packed with SE-30 siloxane elastomer, carrier gas was nitrogen (40 ml/min), thermostat temperature 220°C, detector temperature 220°C. Melting points were determined on a Boetius small scale hot stage with a RNMK-05 viewing device.

Preparation of Reactants. Dialkyl sulfates were washed with 3% sodium carbonate solution, then with distilled water, dried, and distilled in vacuum (≥99.9%) main substance, acid calculated on sulfur ≤0.1%). Triazoles **1** and **2** were recrystallized twice from water and had mp 214 and 197°C respectively (210 and 194°C [7]). Alkyl halides were obtained by the procedures of [8]. The remaining reactants and solvents of chemically pure grade were used without further purification.

Preparation of Triazoles 3-7 (General Procedure). A 0.25 M alcoholic (aqueous) solution of lithium (sodium) hydroxide (36 ml) and dialkyl sulfate (0.1 mol) or alkyl halide* (0.08-0.15 mol) were added to a suspension of triazole **1** or **2** (0.1 mol) in ethanol or water (30 ml). In water the reaction time was 8 h, temperature 75-78°C (Table 1). The precipitated inorganic salt was filtered off, the solvent removed in vacuum from the filtrate, and the residue was treated with methylene chloride. The solution obtained was washed sequentially with 3% aqueous sodium carbonate solution, and with water, dried over anhydrous magnesium sulfate, and the solvent distilled in vacuum. The ratio of isomers was determined before and after separation of the mixture (Table 2). Isomers **3b** and **4b** were isolated from the mixture by extraction with hexane and were

* At a reaction temperature of 75°C C_2H_5Br was added evenly during the synthesis.

recrystallized from aqueous isopropyl alcohol (method A). Triazoles **3a** and **4a** were isolated from the residue by recrystallization from 2-propanol or ethanol. The mixture of compounds **5a,b** and **6a,b** was fractionated in vacuum (method B). Isomer **7b** was distilled in vacuum from the mixture of triazoles **7a,b**. Triazoles **5a** and **7a** were additionally recrystallized from ethanol and **5b** from hexane. The characteristics of the products are given in Tables 1-3.

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