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N-Alkylation of 4-nitro-1,2,3-triazole revisited. Detection and characterization of the N3-ethylation product, 1-ethyl-5-nitro-1,2,3-triazole

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ABSTRACT

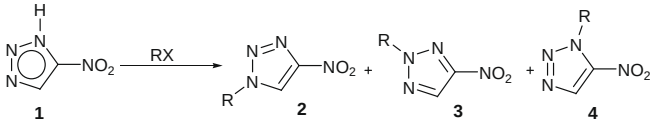
The products of the alkylation of sodium 4-nitro-1,2,3-triazolate with ethyl bromide were investigated using ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy. It was found that alkylation proceeds on the triazole nitrogen atoms giving a mixture of three isomeric *N*-ethyl-4-nitro-1,2,3-triazoles. The molar ratio of N1, N2, and N3-alkylation products was 4:8:1. The formation of a minor N3-isomer, namely 1-ethyl-5-nitro-1,2,3-triazole was confirmed by X-ray structural analysis of single crystals of its tetranuclear copper(II) complex obtained by reaction of copper(II) chloride dihydrate with a mixture of the N2 and N3-isomers.

4-Nitro-1,2,3-triazole **1** and its N-substituted derivatives are of interest as high-energy materials,[1] radiosensitizers in cancer radiation therapy,[2] precursors for the synthesis of medicines and other interesting compounds.[3] N-Substituted 4-nitro-1,2,3-triazoles are synthesized by simple procedures such as alkylation of triazole **1** or its salts with alkyl or aryl halides and dimethyl sulfate or cycloaddition of **1** to activated multiple bonds. Theoretically, in reactions with RX, three isomeric N-substituted 4-nitrotriazoles **2**–**4** could form (Scheme 1). However, in most cases only two isomers attributed to 1- and 2-substituted 4-nitrotriazoles **2** and **3** were isolated. N3-Alkylation products **4** (more precisely 1-substituted 5-nitro-1,2,3-triazoles) were not observed and this can be explained by steric factors and also the negative inductive effect of the nitro group, lowering the nucleophilicity of the neighboring nitrogen atom.[2b,3,4] At the same time, in a few cases, N-substituted 4-nitro-1,2,3-triazoles obtained using the above mentioned approach were assigned as 1- and 3-substituted 4-nitro-1,2,3-triazoles.[5]

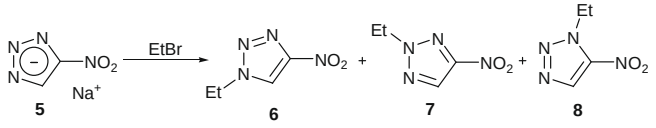
In particular, alkylation of sodium 4-nitro-1,2,3-triazolate **5** with ethyl bromide gave a mixture of 1-ethyl-4-nitro-1,2,3-triazole **6** and 2-ethyl-4-nitro-1,2,3-triazole **7** (molar ratio 40:60, total yield 85%).[4a] However, alkylation of **5** with ethyl iodide gave triazole **6** and 1-ethyl-5-nitro-1,2,3-triazole **8** in 57% and 21% yield, respectively.[5b] Obviously, such drastic apparent differences in selectivity during alkylation are actually due to the accuracy of the identification of the regioisomers, which were made based on ^{1}H NMR data only. Moreover, no physical or chemical characteristics of triazole **8** were reported.[5b]

In the present investigation, we found that the alkylation of sodium 4-nitro-1,2,3-triazolate **5** with ethyl bromide occured on all three triazole nitrogen atoms giving a mixture of isomeric *N*-ethyl-4-nitro-1,2,4-triazoles **6**-**8** (Scheme 2).[6]

The ratio of isomers **6**:**7**:**8**, determined from the intensities of the singlets of the protons on the endocyclic carbon atom in ^{1}H NMR spectra, was 4:8:1. Identification of isomers was achieved based on ^{1}H, ^{13}C, and ^{15}N NMR spectroscopic data (Table 1). The



Scheme 1.



Scheme 2.

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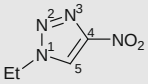
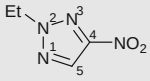
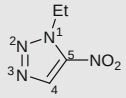
Table 1
^{1}H (500.13 MHz), ^{13}C (125.76 MHz), and ^{15}N (50.69 MHz) chemical shifts of *N*-ethyl-4-nitro-1,2,3-triazoles in DMSO-d_6

Atom or group	δ (ppm)		
	Compound **6**	Compound **7**	Compound **8**
			
CH_3	1.46 (*J* 7.3); 15.3	1.47 (*J* 7.3); 14.5	1.47 (*J* 7.0); 14.9
CH_2	4.46 (*J* 7.3); 46.8	4.54 (*J* 7.3); 52.0	4.70 (*J* 7.0); 47.3
$C_{endocyclic}$–H	9.29; 125.0	8.60; 131.8	8.64; 133.5
$C_{endocyclic}$–NO_2	153.5	153.4	144.4
N-1	−121.7	−44.2	−134.5
N-2	−18.8	−117.9	−9.1
N-3	−37.7[a]	−56.9	−31.5[a]
NO_2		−25.9	

[a] Signal was not assigned unambiguously.

least volatile isomer isolated as a solid was assigned as 1-substituted 4-nitro-1,2,3-triazole **6** since the signal due to the proton of the endocyclic carbon atom in l-mono- and 1,4-disubstituted 1,2,3-triazoles occurs at lower field compared to the corresponding signal in the 2- and 2,4-isomers.[7] Attempts to separate the remaining isomers by fraction distillation were unsuccessful due to the similarity in their boiling points. The NMR spectra of the resulting mixture clearly showed the presence of two isomeric *N*-ethyl-4-nitro-1,2,3-triazoles (molar ratio of isomers **7** and **8** was 9:1). In the ^{1}H and ^{13}C NMR spectra, the CH_3 and $C_{endocyclic}$–H groups had nearly identical chemical shifts, but different chemical shifts of the CH_2 and $C_{endocyclic}$–NO_2 groups. Such differences are due to displacement of the ethyl group from N-2 to the neighboring N-3 position. They are in good agreement with electron density-based ^{1}H and ^{13}C NMR structural correlation for *N*-methylene shifts in *N*-alkylazoles which allows clear distinctions between *N*-alkyl substituents located on azole nitrogen atoms, =N–N(CH_2R)–N= versus =N–N(CH_2R)–CH=.[8] Taking into account the low sensitivity of ^{15}N nuclei, ^{15}N NMR spectra were analyzed using the 2D HMBC technique.[9] In the ^{1}H–15N HMBC NMR spectra, we also observed two series of signals. The major isomer, assigned as **7**, showed signals which were close to those of 2-(2,4-dinitrophenyl)-4-nitro-1,2,3-triazole.[4b] The remaining signals were assigned to isomer **8**. Unfortunately, not all the nitrogen atoms of **8** appeared as signals in the ^{1}H–15N 2D NMR spectra. For this reason, the signals due to the NO_2 group and the N-3 atom were not distinguished. The same problem also occurred during the ^{15}N NMR study of triazole **6**.

Formation of triazole **8** was also confirmed by X-ray structural analysis of single crystals of its tetranuclear copper(II) complex, $Cu_4OCl_6L_4$ which was formed under prolonged (~1 month) action of copper(II) chloride dihydrate with the above-mentioned mixture of N2- and N3-isomers.[10] Interestingly, in spite of the large excess of the N2-isomer **7**, only the pure crystalline complex of N3-isomer **8** was isolated. This can be explained by a significant difference in complexing ability (or basicity) of the isomers due to electronic and steric factors. Experimental and theoretical studies on the basicity of *N*-methyl-1,2,3-triazoles in the gas phase, in solution and in the solid state showed that 1-substituted 4(5)-*R*-1,2,3-triazoles have a higher basicity in comparison with 2-substituted examples.[11] Previously, we successfully used similar differences for the separation of isomeric N-monosubstituted tetrazoles.[12] In this case, treatment of an isomeric mixture of 1- and 2-monosubstituted tetrazoles with copper(II) chloride in ethanol led to the precipitation of the complex CuL_2Cl_2, where L = 1-monosubstituted tetrazole.

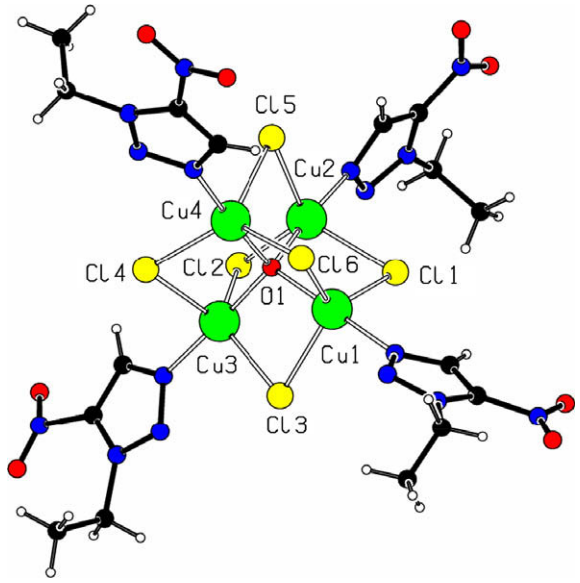


Figure 1. The structure of the tetranuclear copper(II) complex with 1-ethyl-5-nitro-1,2,3-triazole **8**.

The formation of the tetranuclear copper(II) complex is caused by slow hydrolysis of copper(II) chloride leading to a cluster of high thermodynamic stability. Single-crystal X-ray analysis[13] showed that in the complex, the central oxygen atom is tetrahedral coordinated to four copper atoms, each of which is connected to three other copper atoms via chlorine atoms. The copper atoms exist in a distorted trigonal-bipyramidal environment, with the N3 triazole atom and the central oxygen atom in axial positions. Three chlorine atoms lie in the equatorial plane (Fig. 1). Tetranuclear complexes of copper(II) with the composition $Cu_4OX_6L_4$ (X is Cl or Br, and L is halogen or N-, O- or P-donor ligands) have been the subject of numerous investigations, mainly because of their unusual magnetic properties, which are caused by the existence of two different exchange interaction channels, Cu–O–Cu and Cu–X–Cu, and which depend on the nature of the ligand L.[14] Among azoles, similar complexes have been described for imidazoles,[15] pyrazoles,[16] and tetrazoles.[17] The tetranuclear copper(II) complex reported here containing a 1,2,3-triazole derivative is the first synthesized and structurally characterized complex of vicinal nitrotriazoles.

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6. Ethyl bromide (21.8 g, 0.2 mol) was added with stirring to a suspension of salt **5** (13.6 g, 0.1 mol) in ethanol (115 mL) at 40 °C. The reaction mixture was heated gradually to 80 °C and stirred for 10 h at this temperature. After cooling to room temperature, the resulting precipitate was filtered off and the filtrate was evaporated under vacuum. The residue was dissolved in dichloromethane. The resulting solution was washed with 3% aqueous sodium bicarbonate solution, water, and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum giving a crude mixture of triazoles **6–8** (12.4 g, 87%). Vacuum distillation afforded a mixture of isomers **7** and **8** (bp 112–118 °C/18–20 mm Hg, 6.9 g, 49%). Triazole **6** (5.1 g, 36%) was isolated by recrystallization of the distillation residue from ethanol. Mp 78.5–79 °C.
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9. Typical acquisition conditions for the ^{1}H-^{15}N HMBC experiments were as follows: relaxation delay 1.5 s, 256 *F*1 increments, 2048 *F*2 points, sweep width 9.0 ppm for ^{1}H and 400 ppm for ^{15}N, ^{n}J (N,H) = 8 Hz. The ^{15}N NMR signals were referenced against $MeNO_2$ (0 ppm) as internal standard.
10. A solution of copper(II) chloride dihydrate (190 mg, 1.1 mmol) in ethanol (1 mL) was added to a mixture of triazoles **7** and **8** (1.5 g, 10.5 mmol, molar ratio of isomers 9:1) obtained by vacuum distillation. The mixture was heated at 70–80 °C for 1 h and kept at room temperature for ~1 month to give brown crystals of the complex $Cu_4OCl_6L_4$, where L = 1-ethyl-5-nitro-1,2,3-triazole **8** (49 mg, 0.05 mmol). Decomposition temperature = 214 °C (10 °C/min, nitrogen atmosphere).
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13. X-ray data were collected on a Nicolet R3 m diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at room temperature. The structure was solved by direct methods (SIR2004[18]) and refined by the full matrix least square technique against F^2 (SHELXL 97[19]). *Crystal data*: $C_{16}H_{24}Cl_6Cu_4N_{16}O_9$, M = 1051.37, triclinic, space group $P\bar{1}$, a = 12.037(2) Å, b = 12.133(2) Å, c = 14.868(3) Å, α = 107.78(2)°, β = 111.03(2)°, γ = 91.89(2)°, V = 1905.0(6) Å^3, Z = 2, D_c = 1.833 g cm^{-3}, μ(Mo Kα) = 2.687 mm^{-1}, crystal dimensions 0.32 × 0.24 × 0.12 mm. The intensities were corrected for absorption (ψ-scans), 9381 were measured, 8377 were symmetry independent (R_{int} = 0.0473). $R1$ = 0.0598 for 5368 reflections with $I > 2\sigma(I)$, $wR2$ = 0.1775 for all data. CCDC reference number 703180.
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