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Regioselective quaternization of *N*-alkyl-4-nitro-1,2,3-triazoles in Bu^{t}OH–HClO$_4$ system

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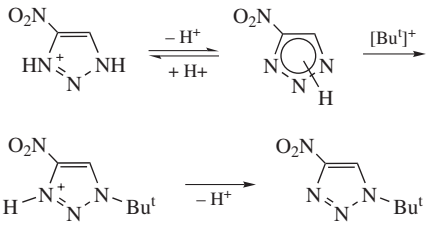
Quaternization of *N*-alkyl-4-nitro-1,2,3-triazoles in Bu^{t}OH–HClO$_4$ as a source of *tert*-butyl cation affords 1-*tert*-butyl-3-alkyl-4-nitro-1,2,3-triazolium perchlorates.

1,2,3-Triazole derivatives, including quaternary salts, are of great interest as pharmaceuticals,[1] high-energy materials,[2] ionic liquids,[3] ligands to produce metal complexes,[4] and as intermediates in the synthesis of the least obtainable 1-alkyl-5-nitro-1,2,3-triazoles.[5] A principal problem in the chemistry of polyatomic heterocycles is the selectivity of reactions. Significant advances have recently been made in the regioselectivity determination of N-monofunctionalization and in the synthesis of N-monosubstituted 4-nitro-1,2,3-triazoles.[4(a),5,6] Alkylation of 4-nitro-1,2,3-triazole proceeds, in most cases, non-selectively and affords mixtures of three hardly separable isomeric N1-, N2- and N3-substituted products.[4(a),6] The direction of the electrophilic attack on a nitrotriazolium substrate and the predominant formation of one or another isomer considerably depend on acidic and basic properties of an environment. Data on the exhaustive alkylation of isomeric N-substituted 4-nitro-1,2,3-triazoles are quite limited and have been described only by an example of the quaternization of 1-alkyl-4-nitro-1,2,3-triazoles.[5,7]

The aim of this work was to study quaternization of regioisomeric 1-alkyl-4-nitro (N1-isomer), 2-alkyl-4-nitro (N2-isomer), and 1-alkyl-5-nitro-1,2,3-triazoles (N3-isomer) in a new Bu^{t}OH–HClO$_4$ system. This system ensures the generation of a stable *tert*-butyl cation, which is capable of attacking *N*-alkyl-4-nitro-1,2,3-triazole molecules at nitrogen atoms available for coordination. Earlier,[5] we carried out a selective N-mono-*tert*-butylation of unsubstituted 4-nitro-1,2,3-triazole in Bu^{t}OH–H_2SO_4. In concentrated H_2SO_4, 4-nitro-1,2,3-triazole underwent protonation to afford the 1*H*,3*H*-4-nitro-1,2,3-triazolium cation wherein a single N2 atom available for the substituent introduction participates in positive charge distribution. In this respect, the electrophilic attack at this nitrogen atom is hindered, and the 1*H*,3*H*-4-nitro-1,2,3-triazolium cation is not alkylated. The *tert*-butyl cation thus attacks the neutral molecule of the 4-nitro-1,2,3-triazole giving 1-*tert*-butyl-4-nitro-1,2,3-triazole as the only product (Scheme 1).[5]

One can assume that both the similar mechanism based on the generation of the *tert*-butyl cation and the regioselective nature will also persist in quaternization processes of *N*-alkyl-4-nitro-1,2,3-triazoles in the Bu^{t}OH–HClO$_4$ system. The advantage of this system when used for quaternization is the one-stage formation of the corresponding perchlorates of disubstituted 4-nitro-1,2,3-triazoliums. The presence of the ClO_4^- anion preparatively facilitates their isolation and considerably increases the yield of the salts as compared to organo- and hydrophilic alkyl sulfates



Scheme 1

upon quaternization of 4-nitro-1,2,3-triazoles with dialkyl sulfates[7] and to hydrosulfates upon quaternization of 1,2,4-triazole derivatives with adamantanol in concentrated H_2SO_4.[8]

From the perspective of kinetic control, a strong influence on the quaternization process is exerted by the basicity of reagents. As per quantum chemical calculations, the basicity of regioisomeric *N*-alkyl-4-nitro-1,2,3-triazoles rises in the series N2-(**1b**–**6b**) < < N1-(**5c**,**6c**) < N3-(**1a**–**6a**). The calculated pK_{BH^+} value of the N3-isomer is 4 units higher than that of the N1-isomer.[6(a)] The basicity effect of isomeric *N*-alkyl-4-nitro-1,2,3-triazoles on the selectivity of chemical reactions was earlier exemplified by the selective comlexation process wherein only the most basic N3-isomers are involved. Mixtures of isomeric *N*1-, *N*2- and *N*3-ethyl-4-nitro-1,2,3-triazoles (N3-isomer fraction is below 8%) were treated with copper(II) salts to furnish a crystalline complex only with the N3-isomer.[4] The basicity effect was found upon quaternizing isomeric *N*-alkyl-4-nitro-1,2,3-triazoles of the series of lower primary (**1a**,**b** R = Me, **2a**,**b** R = Et, **3a**,**b** R = Pr), secondary (**5a**–**c** R = Pr^i, **6a**–**c** R = Bu^s), and cyclic (**4a**,**b** R = = cyclohexyl) alkyls in the Bu^{t}OH–HClO$_4$ system. Irrespective of the substituent type, only the N3-isomers, **1a**–**6a**, participate in the reaction, even despite their low fraction in mixtures **1a**,**b**, **2a**,**b**, **3a**,**b**, and **4a**,**b** (Scheme 2, Table 1).†

† *N*-alkyl-4-nitro-1,2,3-triazoles were synthesized by the known procedures.[4(a),6(b)]

*Synthesis of 1-*tert*-butyl-3-alkyl-4-nitro-1,2,3-triazolium salts* **7**–**12**. A solution of the corresponding mixture of nitrotriazoles **1a**,**b**, **2a**,**b**, **3a**,**b**, **4a**,**b**, **5a**–**c**, or **6a**–**c** (25 mmol) and *tert*-butyl alcohol (25 mmol) in concentrated perchloric acid (72%, 4 ml) was stirred for 3 h and then dissolved in water (5 ml). The precipitated product was filtered off, washed with water, and dried to give the corresponding 1-*tert*-butyl-3-alkyl-4-nitro-1,2,3-triazolium salts **7**–**12**, yields were calculated per portions of N3-isomers **1b**–**6b** in starting mixtures (see Table 1).

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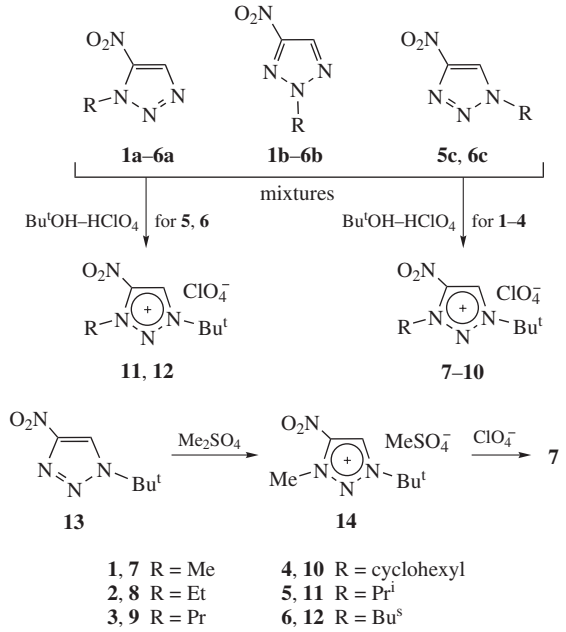
Table 1 Quaternization of *N*-alkyl-4-nitro-1,2,3-triazoles in a Bu^tOH–$HClO_4$ system.

Mixture	Ratio of isomers	Product	Yield (%)	Mp/°C
1a,**b**	1:9	**7**	79	209–210
2a,**b**	1:9	**8**	78	211–212
3a,**b**	1:8	**9**	85	167–168
4a,**b**	1:9	**10**	77	175–176
5a–c	15:47:1	**11**	81	181–182
6a–c	10:23:1	**12**	72	151–152



Scheme 2

In the case of thermodynamically controlled reactions, the ratio of the isomers being formed in the quaternization reaction of the triazole ring is to be defined by their relative stabilities.[7] Based on the quantum-chemical calculations of the relative energies of the isomeric *N*,*N*′-dialkyl-*C*-nitro-1,2,3-triazole cations[7], the formation of the most thermodynamically stable 1,3-disubstitution products is possible only when the N1- and N3-isomers are involved.

In concentrated $HClO_4$, the *N*1- and *N*3-alkyl-4-nitro-1,2,3-triazoles undergo protonation to form cations of 1-R-3*H*- (**k1**) and 1*H*-3-R-4-nitro-1,2,3-triazoliums (**k2**) of the imidazolium type.[9] It is unlikely that the electrophile attack on endocyclic nitrogen atoms participating in the positive charge distribution is caused by electrostatic factors.[10] Probably, the *tert*-butyl cation being generated from *tert*-butyl alcohol attacks the neutral molecule of triazoles **1a–6a**. The quaternization of N3-isomers **1a–6a** in the Bu^tOH–$HClO_4$ system was found to proceed selectively at the N1 nitrogen atom to form thermodynamically stable 1,3-disubstituted 1-*tert*-butyl-3-R-4-nitro-1,2,3-triazolium salts **7–12** (Scheme 2). The reaction proceeds smoothly at room temperature within 3 h.† The hydrophobicity of the *tert*-butyl group of salts **7–12** contributes to their precipitation from the reaction mixtures in good yields (Table 1).

The quaternization products of the N1-isomers when used either individually or in mixtures with other regioisomers were not detected. This is attributable to the steric hindrance in introducing the bulky *tert*-butyl substituent on the N3 nitrogen atom. 2-Substituted *tert*-butyl-4-nitro-1,2,3-triazoles were also not detected. This indicates that cations **k1** and **k2** do not participate in the quaternization reaction because, in this case, the attack by the *tert*-butyl cation must occur on the single N2 nitrogen atom available for coordination.

The synthesized compounds were characterized by ^1H and ^{13}C NMR, IR spectroscopy, mass spectra, and elemental analysis.

The independent synthesis of salt **7** *via* quaternization of 1-*tert*-butyl-4-nitro-1,2,3-triazole **13** with dimethyl sulfate[5] (Scheme 2) and the results of our study into the molecular and crystal structure of salt **11** by X-ray structural analysis allowed us to reliably determine the regioselectivity of the *tert*-butyl cation attack on 1-alkyl-5-nitro-1,2,3-triazoles **1a–6a** at the N1 nitrogen atom and prove the structure of obtained nitrotriazolium salts as being 1,3-disubstituted (Figure 1).‡

In conclusion, the Bu^tOH–$HClO_4$ system is shown to be effective for the regioselective introduction of the lipophilic and easily removable *tert*-butyl group into molecules of N-substituted 4-nitro-1,2,3-triazoles and for the synthesis of 1,3-disubstituted 4-nitro-1,2,3-triazolium salts, which are gaining increasing interest in the chemistry of energy-rich materials and ionic liquids. Of the

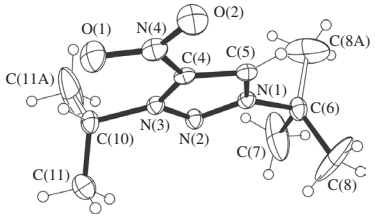


Figure 1 General view of **11** (30% thermal ellipsoid) with ClO_4^- and minor part of the cation omitted for clarity. Atoms C(8A) and C(11A) are situated in crystallographically dependent part of the crystal cell. Selected bond lengths (Å) and angles (°): O(1)–N(4) 1.228(7), O(2)–N(4) 1.215(8), N(4)–C(4) 1.449(7), N(1)–N(2) 1.319(6), N(2)–N(3) 1.318(6), N(3)–C(4) 1.343(6), C(4)–C(5) 1.360(7), N(1)–C(5) 1.344(6); O(1)–N(4)–O(2) 125.3(5), O(1)–N(4)–C(4) 118.2(5), O(2)–N(4)–C(4) 116.5(5), N(3)–C(4)–C(5) 108.2(4), C(4)–C(5)–N(1) 103.7(4), N(1)–N(2)–N(3) 105.5(4), N(2)–N(3)–C(4) 109.9(4).

Caution! 1-*tert*-Butyl-3-alkyl-4-nitro-1,2,3-triazolium salts are energetic materials with shock and friction sensitivities. Therefore, proper safety precautions (safety glass, face shield, grounded equipment and shoes, Kevlar gloves, and ear plugs) should be employed while synthesizing and handling the compounds described.

1-tert-*Butyl-3-ethyl-4-nitro-1,2,3-triazolium perchlorate* **8**: colourless crystals. ^1H NMR, δ: 10.37 (s, 1H, $HC_{endocyclic}$), 4.97 (q, 2H, CH_2Me, *J* 7.3 Hz), 1.75 (s, 9H, CMe_3), 1.61 (t, 3H, CH_2Me, *J* 7.3 Hz). ^{13}C NMR, δ: 145.47 (C–NO_2), 128.95 (CH), 69.17 (CMe_3), 51.76 (CH_2), 28.64 (CMe_3), 13.52 (Me). FTIR (ν/cm^{-1}): 3126, 3102, 2997, 2949, 2025, 1580, 1543, 1475, 1438, 1379, 1353, 1328, 1294, 1192, 1167, 1088, 1030, 878, 840, 803, 747, 706, 689, 625, 585. Found (%): C, 32.14; H, 5.12; N, 18.75. Calc. for $C_8H_{15}ClN_4O_6$ (%): C, 32.17; H, 5.06; N, 18.76.

Structures and numbering of isomeric *N*-alkyl-4-nitro-1,2,3-triazoles, preparation of components and reagents as well as characteristics of compounds **7–12** can be found in Online Supplementary Materials.

‡ *Crystallographic data*. Crystals of **11** ($C_9H_{17}N_4O_2ClO_4$, *M* = 319.60) are orthorhombic, space group *Pnma*, at 200 K: *a* = 12.138(5), *b* = 7.629(3) and *c* = 16.382(7) Å, *V* = 1517.0(11) $Å^3$, *Z* = 4, d_{calc} = 1.369 g cm^{-3}, μ(MoKα) = 0.281 mm^{-1}. Intensities of 13 802 reflections were measured with a Bruker Kappa Apex II CCD diffractometer [λ(MoKα) = 0.71073 Å, φ,ω-scans of narrow (0.5°) frames], and 1447 independent reflections (R_{int} = 0.075) were used in further refinement. The final values of the refined parameters were R_1 = 0.0746, wR_2 = 0.2136 based on reflections with $I > 2\sigma(I)$; R_1 = 0.1037, wR_2 = 0.2419 based on all reflections. The structure was solved by direct methods and refined by full-matrix least-squares method against all F^2 in anisotropic approximation using the SHELX-97 programs set.[11] The hydrogen atom positions were calculated with the riding model. Absorption corrections were applied using the empirical multiscan method with the SADABS program.[12]

CCDC 956775 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.

isomeric *N*1-, *N*2- and *N*3-alkyl-4-nitro-1,2,3-triazoles, only the N3-isomers participate in the reaction of quaternization to form the most thermodynamically stable 1-*tert*-butyl-3-alkyl-4-nitro-1,2,3-triazolium salts. On the whole, the $Bu^tOH–HClO_4$ system is promising for selective alkylation of nitrogen-containing heterocycles.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.09.011.

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