Acid Catalyzed *tert*-Butylation and Tritylation of 4-Nitro-1,2,3-triazole: Selective Synthesis of 1-Methyl-5-nitro-1,2,3-triazole via 1-*tert*-Butyl-4-nitro-1,2,3-triazole

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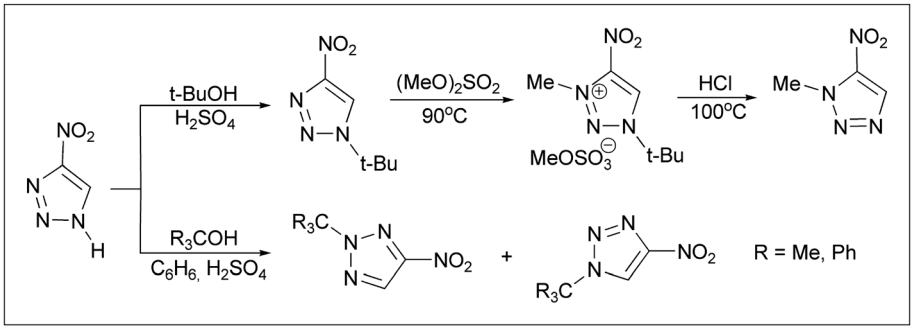

4-Nitro-1,2,3-triazole was found to react with *tert*-butanol in concentrated sulfuric acid to yield 1-*tert*-butyl-4-nitro-1,2,3-triazole as the only reaction product, whereas *tert*-butylation and tritylation of 4-nitro-1,2,3-triazole in presence of catalytic amount of sulfuric acid in benzene was found to provide mixtures of isomeric 1- and 2-alkyl-4-nitro-1,2,3-triazoles with predominance of N2-alkylated products. A new methodology for preparation of 1-alkyl-5-nitro-1,2,3-triazoles from 1-*tert*-butyl-4-nitro-1,2,3-triazole via exhaustive alkylation followed by removal of *tert*-butyl group from intermediate triazolium salts was demonstrated by the example of preparation of 1-methyl-5-nitro-1,2,3-triazole.

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INTRODUCTION

Nowadays N-alkylation of 4-nitro-1,2,3-triazole (**1**) is the most common and simple and, in many cases, the only synthetic pathway to N-substituted 4-nitro-1,2,3-triazoles, which are of interest as high-energetic materials and pharmaceuticals [1–3]. Previously, it has been shown that alkylation of triazole **1** under basic and neutral conditions is not regioselective and proceeds on all three nitrogen atoms of heteroring giving mixture of isomeric 1-*R*-4-nitro- (**2**), 2-*R*-4-nitro- (**3**), and 1-*R*-5-nitro-1,2,3-triazoles (**4**) [1,4]. In some cases 1,3-disubstituted 4-nitro-1,2,3-triazolium salts (**5**) are also observed in resulted mixture of products due to exhaustive alkylation of **2** or **4** [5] (Scheme 1).

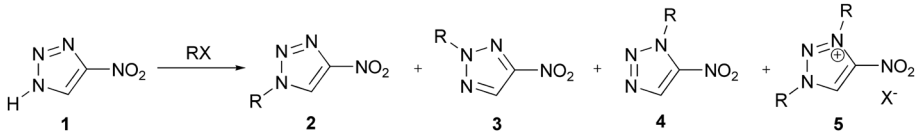
In general, derivatives **4** are less accessible in comparison with other N-substituted 4-nitro-1,2,3-triazoles. At the same time they are characterized with highest enthalpy of formation [6] and highest basicity [5] among isomers **2-4** and therefore they are most attractive as ligands for preparation of energetic metallocomplexes.

In the course of our investigations in the field of acid-catalyzed alkylation of azoles [7] we have studied alkylation of **1** with *tert*-butanol and triphenylmethanol. Moreover, we present new methodology for preparation of 1-alkyl-5-nitro-1,2,3-triazoles **4** by exhaustive alkylation of 1-*tert*-butyl-4-nitro-1,2,3-triazole (**6**) followed by de-*tert*-butylation of intermediate 1-*tert*-butyl-3-alkyl-4-nitro-1,2,3-triazolium salt.

RESULTS AND DISCUSSION

We found that **1** reacts with *tert*-butanol in concentrated sulfuric acid to yield 1-*tert*-butyl-4-nitro-1,2,3-triazole (**6**) as the only reaction product. The isolated yield of **6** was 71%. It should be noted that this reaction is a new example of selective alkylation of azoles with alcohols in acidic medium. Previously regioselectivity was also observed under alkylation of 5-*R*-tetrazoles and some 1,2,4-triazoles in analogous conditions [7,8].

Scheme 1



Parent 1,2,3-triazole was found to react with isopropanol in concentrated sulfuric acid giving only 1-isopropyl-1,2,3-triazole as reaction product [9]. The regioselective course of alkylation of 1,2,3-triazoles in concentrated sulfuric acid can be clarified in the view of specificity of high acidic medium and thermodynamic control of alkylation process. In acidic medium triazole **1** being weak base (pK_{BH+} = −6.80 [10]) undergoes protonation giving 1*H*,3*H*-4-nitro-1,2,3-triazolium cation. The calculated ratio between concentrations of free triazole **1** and above mentioned cation comes to ∼1 : 1200 in 96% sulfuric acid (H_o= −9.88). Electrophilic attack at endocyclic nitrogen atoms, which are involved in distributing positive charge is unlikely to occur due to electrostatic reasons [9]. Probably, *tert*-butyl cation generated from *tert*-butanol attacks neutral molecules of **1** providing 1-*tert*-butyl-3*H*-4-nitro-1,2,3-triazolium cation which is converted after deprotonation into triazole **6** (Scheme 2).

Formation of 1-*tert*-butyl-3*H*-4-nitro-1,2,3-triazolium cation is preferred due to thermodynamic factors. Quantum-chemical calculations of the relative energies shows that 1-*tert*-butyl-3*H*-4-nitro-1,2,3-triazolium cation is most stable among cations formed by protonation of isomeric *N*-*tert*-butyl-4-nitro-1,2,3-triazoles (Table 1). Moreover, due to heterolysis of the exocyclic N—CMe_3 bond these triazoles can undergo migration of alkyl substituent in media of high acidity, similarly to *N*-*tert*-butyltetrazoles [11].

Proposed mechanism of N1-alkylation is also confirmed by results of *tert*-butylation and tritylation of **1** in presence of catalytic amount of sulfuric acid in benzene. Under these conditions mixtures of isomeric 1- and 2-alkyl-4-nitro-1,2,3-triazoles **6**-**9** were obtained (Scheme 3). The ratio of isomers **6**:**7** and **9**:**8**, determined from the intensities of the singlets of the protons on the endocyclic carbon atom in ^{1}H-NMR spectra, was 1:9 and 1:8, correspondingly. Observed drastic change in regioselectivity of alkylation can be explained with essential lowering of acidity of reaction medium. Since under described conditions *N*-alkyltriazoles exist in neutral form and there is no possibility of mutual interconversions isomer ratio is determined by kinetic control [5].

Taking into account selectivity of quaternisation of 1-alkyl-4-nitro-1,2,3-triazoles with dialkyl sulfates [12] and possibility of de-*tert*-butylation of azolium salts [13] we investigated tandem methylation and de-*tert*-butylation reactions of **6** to elaborate new selective route to 1-alkyl-5-nitro-1,2,3-triazoles from available triazole **6**. Previously such methodology was successfully used for selective preparation of 1,5-disubstituted tetrazoles [14], including binuclear ones [15], from 5-substituted tetrazoles via 2-*tert*-butyl derivatives and 1,3,5-trisubstituted tetrazolium salts. Triazole **6** was found to react with excess of dimethyl sulfate giving 1-*tert*-butyl-3-methyl-4-nitro-1,2,3-triazolium salt **10** which was isolated as perchlorate **11** with 72% yield. De-*tert*-butylation of **10** was achieved under refluxing with hydrochloric acid, and target 1-methyl-5-nitro-1,2,3-triazole (**12**) was obtained with 51% overall yield (Scheme 4).

Structural assignments of synthesized *N*-trityl- and *N*-*tert*-butyl-4(5)-nitro-1,2,3-triazoles were made based on the analysis of their ^{1}H- and ^{13}C-NMR spectra in comparison with those of *N*-ethyl-4(5)-nitro-1,2,3-triazoles [4].

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra was determined on a 400 MHz Bruker spectrometer in DMSO-d_6 as a solvent. Melting points were determined with Heating Table Boetius with viewing device PHMK 05. 4-Nitro-1,2,3-triazole was prepared according to the literature procedure [16]. Quantum-chemical calculations of relative energies of isomeric molecules and cations were carried out with the aid of the Gaussian-03 set of programs [17] within the framework of DFT theory (B3LYP functional) [18] as described in [5].

1-*tert*-Butyl-4-nitro-1*H*-1,2,3-triazole (6). *Tert*-butanol (2 g, 27.5 mmol) was added dropwise with stirring to a solution of 4-nitro-1,2,3-triazole (2.85 g, 25 mmol) in 96% sulfuric acid (18 mL). The mixture was further stirred at room temperature for 3 h. Then the reaction mixture was poured into ice (∼100 g), extracted with dichloromethane (4 × 25 mL). Combined extracts were washed by aqueous solution of sodium

Scheme 2

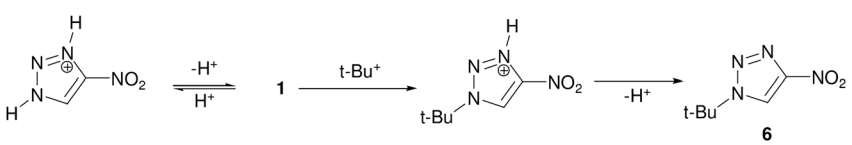
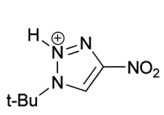
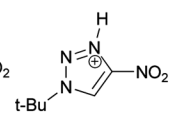
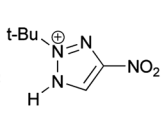
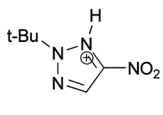
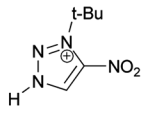
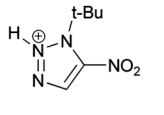


Table 1

Calculated relative energies of isolated cations of protonated *N-tert*-butyl-4(5)-nitro-1,2,3-triazoles at 0 K (ΔE_o) and their Gibbs free energies ($\Delta G^o_{298,H2O}$) in aqueous solution.

Cation						
ΔE_o (kJ/mol)	0.0	−38.3	−8.4	−3.5	−11.0	30.5
$\Delta G^o_{298,H2O}$ (kJ/mol)	0.0	−15.2	−6.1	19.1	14.8	57.2

carbonate and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Treatment of residue with diethyl ether afforded **6** (3.04 g, 71%). Colorless crystals, mp 68–70°C (from ethanol).

^{1}H-NMR: δ 9.43 (s, 9H, *t*-Bu), 1.65 (s, 1H, CH); ^{13}C-NMR δ: 153.5, 123.3, 62.3, 29.4; *Anal*. Calcd. for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.92%. Found: C, 42.55; H, 5.63; N, 32.49%.

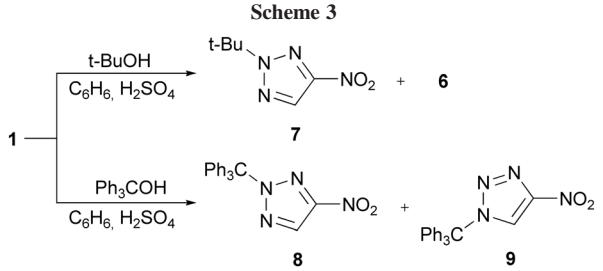
2-tert-Butyl-4-nitro-2H-1,2,3-triazole (7). Mixture of 4-nitro-1,2,3-triazole (1.15 g, 10 mmol), *tert*-butanol (0,81 g, 11 mmol), benzene (25 mL) and 96% sulfuric acid (2–3 drops) was heating under boiling with Dean-Stark apparatus for 1.5 h. Then the reaction mixture was evaporated under reduced pressure. Obtained solid residue containing mixture of **6** and **7** (molar ratio 1:9) was recrystallized from water-isopropanol (10:1) giving pure **7** (1.2 g, 70%). Colorless crystals, mp 35–38°C.

^{1}H-NMR: δ 8.71 (s, 1H, CH), 1.65 (s, 9H, *t*-Bu); ^{13}C-NMR δ: 152.4, 130.9, 65.6, 28.5; *Anal*. Calcd. for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.92%. Found: C, 42.42; H, 5.83; N, 32.89%.

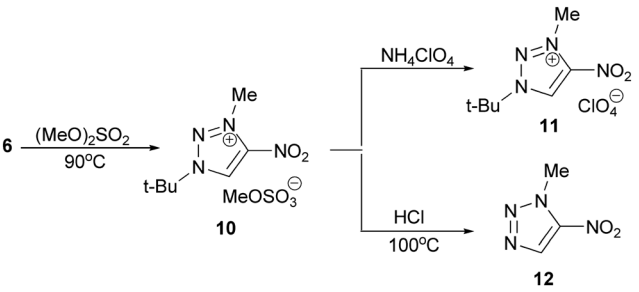
Mixture of 2-trityl-4-nitro-2H-1,2,3-triazole (8) and 1-trityl-4-nitro-1H-1,2,3-triazole (9). Mixture of 4-nitro-1,2,3-triazole (1.15 g, 10 mmol), triphenylmethanol (2.86 g, 11 mmol), benzene (25 mL) and 96% sulfuric acid (2–3 drops) was heating under boiling with Dean-Stark apparatus for 3 h. Then the reaction mixture was evaporated reduced pressure, and solid residue was washed with diethyl ether, water and dried under reduced pressure. Mixture of **8** and **9** (molar ratio 8:1) was obtained as white amorphous solid (2.85 g, 75%).

^{1}H-NMR: δ 8.84 (s, 1H, CH of isomer **8**); 8.81 (s, 1H, CH of isomer **9**), 7.01–7.46 (m, 5H, Ph); ^{13}C-NMR δ: 152.6, 147.7, 140.8, 140.5, 131.3, 129.7,129.5, 128.5, 128.3, 127.8, 127.7, 127.4, 126.5, 84.1. *Anal*. Calcd. for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72%. Found: C, 70.60; H, 4.40; N, 15.68%.

Scheme 3



Scheme 4



3-tert-Butyl-1-methyl-5-nitro-3H-1,2,3-triazolium perchlorate (11). Mixture of **6** (2.55 g, 15 mmol) and dimethyl sulphate (4.3 mL, 45 mmol) was heated at 90–95° for 0.5 h. Then saturated aqueous solution of ammonium perchlorate (1.76 g, 15 mmol) was added to the solution. The resulting precipitate was filtered off, washed with water and dried *in vacuo* to give **11** (3.07 g, 72%). Colorless crystals, mp 208–210°C (decomp.).

^{1}H-NMR: δ 10.31 (s, 1H, CH), 4.56 (s, 3H, Me); 1.75 (s, 9H, *t*-Bu). ^{13}C-NMR δ: 145.5, 128.5, 69.2, 42.3, 28.6. *Anal*. Calcd. for $C_7H_{13}ClN_4O_6$: C, 29.54; H, 4.60; N, 19.68%. Found: C, 29.78; H, 4.24; N, 19.50%.

1-Methyl-5-nitro-1*H*-1,2,3-triazole (12). Mixture of **6** (2.55 g, 15 mmol) and dimethyl sulphate (4.3 mL, 45 mmol) was heated at 90–95° for 0.5 h. Then hydrochloric acid (36%, 45 mL) was added and the mixture was stirred for 10–15 min. Excess of dimethyl sulphate was separated off. The aqueous solution containing salt **10** was heated under reflux for 10 h. Then the reaction mixture was extracted with dichloromethane (4 × 25 mL). Combined extracts were washed by aqueous solution of sodium carbonate and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give **12** (0.98 g, 51%). Colorless crystals, mp 70–71°C (from ethanol).

^{1}H-NMR: δ 8.63 (s, 1H, CH), 4.32 (s, 3H, Me). ^{13}C-NMR δ: 144.9, 132.9, 38.8. *Anal*. Calcd. for $C_3H_4N_4O_2$: C, 28.13; H, 3.15; N, 43.74%. Found: C, 28.38; H, 3.10; N, 44.01%.

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