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Acidic *N*-dealkylation in nitrotriazolium salts

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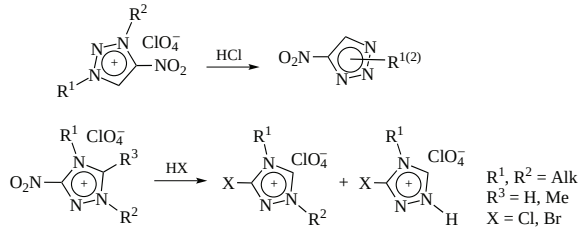
New selective synthesis of 1-alkyl-5-nitro-1,2,3-triazoles and 1-alkyl-4-nitro-1,2,3-triazoles has been developed, involving acid *N*-dealkylation of the relative 4-nitro-1,2,3- and 3-nitro-5-R-1,2,4-triazolium salts. The assortment of novel 1-alkyl-4(5)-nitro-1,2,3-triazoles has been thus essentially expanded. Treatment of relative 3-nitro-1,2,4-triazolium salts with HCl or HBr proceeds mostly as S_N^{ipso}-substitution of the nitro group.



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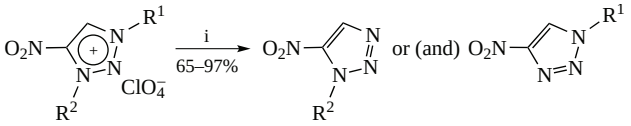
The promising ways of using 1,2,4- and 1,2,3-triazole derivatives in the drug synthesis are comprehensively reviewed.[1] Compounds based on 1,2,4- and 1,2,3-triazoles can be employed as ligands for the synthesis of coordination compounds,[2] components of energy-rich formulations, and in other industrial sectors concerned with the problems of fine organic synthesis.[3]

Reactions of ambident nucleophiles, in particular in heterocyclic chemistry, usually encounter problems regarding regiospecificity. The common methods for the alkylation of 1,2,4- and 1,2,3-triazoles generally afford mixtures of three regioisomers.[4] We have found by examining the chemical properties of *N*-alkyl-4-nitro-1,2,3-triazoles that the isomers are selectively quaternized in $Bu^tOH–HClO_4$ system. Among N^1-, N^2- and N^3-alkyl-4-nitro-1,2,3-triazoles, only N^3-substitution products are involved in the reaction to yield 1-*tert*-butyl-3-alkyl-4-nitro-1,2,3-triazolium salts.[5] The resulting salts can serve as convenient substrates bearing the *tert*-butyl protective group whose deprotection should give free N^3-alkylnitrotriazole. In this regard, the main idea of this study was to develop a targeted method for the synthesis of the desired isomer, including difficult-to-access N^3-derivatives of 4-nitro-1,2,3-triazole. *N*-Dealkylation of nitrotriazolium salts containing *tert*-butyl and other alkyl groups as protective groups was the method of choice. The reaction regularities, dependence on the structure of the azole heterocycle, the nature of the leaving alkyl group and its location in the ring were thoroughly investigated.

Our experiments revealed that the dealkylation of 4-nitro-1,2,3-triazolium salts took place smoothly in concentrated HCl and could proceed in three directions depending on the nature and location of the substituent.† The dealkylation of 1-*tert*-butyl-substituted nitrotriazolium salts **1a**–**e** bearing primary alkyl substituent on the N^3 atom resulted in selective elimination of this substituent linked to (N^1)-Bu^t group to afford N^3-alkyl-substituted triazoles **2a**–**e** (Scheme 1). Such de-*tert*-butylation of salts **1a**–**e** is not unpredictable because tertiary alkyl substituents are known to be labile enough.

The outcome of elimination of the substituent in 1,3-dialkylnitrotriazolium salts **1f**–**k** bearing N^1- and N^3-positioned unbranched primary alkyl groups seemed less predictable (these salts **1f**–**k** were obtained by the selective quaternization of 1-alkyl-4-nitro-1,2,3-triazoles[6]). In fact, reaction of salts **1f**–**k** with HCl proceeded as selective N^3-elimination to furnish 1-alkyl-substituted derivatives **3a**–**d**



1a–n **2a–f** (for **1a–e**,**n**) **3a–f** (for **1f–n**)

a	R^1 = Bu^t, R^2 = Et	**a** R^2 = Et	**a** R^1 = Me (from **1f**,**g**,**m**)
b	R^1 = Bu^t, R^2 = Pr	**b** R^2 = Pr	**b** R^1 = Et
c	R^1 = Bu^t, R^2 = Bu	**c** R^2 = Bu	**c** R^1 = Bu
d	R^1 = Bu^t, R^2 = $Pr^i(CH_2)_2$	**d** R^2 = $Pr^i(CH_2)_2$	**d** R^1 = $Pr^i(CH_2)_2$
e	R^1 = Bu^t, R^2 = 2-ethylhexyl	**e** R^2 = 2-ethylhexyl	**e** R^1 = Pr^i
f	R^1 = R^2 = Me	**f** R^2 = Me	**f** R^1 = Bn
g	R^1 = Me, R^2 = Et		
h	R^1 = R^2 = Et		
j	R^1 = Bu, R^2 = Me		
k	R^1 = $Pr^i(CH_2)_2$, R^2 = Me		
l	R^1 = Pr^i, R^2 = Et		
m	R^1 = Me, R^2 = Pr^i		
n	R^1 = Bn, R^2 = Me		

Scheme 1 *Reagents and conditions*: i, HCl, 100 °C, 5 h (for **1a**–**e**), 18 h (for **1f**–**k**), 32 h (for **1l**), 3.5 h (for **1m**), 8 h (for **1n**).

† *Dealkylation of 1,3-dialkyl-4-nitro-1,2,3-triazolium salts* **1a**–**n**. A solution of the corresponding salt **1a**–**m** (10 mmol) in 36% HCl (45 ml) was refluxed. The reaction time for each substrate is specified in Scheme 1. The reaction mixture was cooled to room temperature and extracted with dichloromethane (3 × 20 ml). The dichloromethane solutions were combined and washed with aqueous Na_2CO_3 and then with water until neutral pH. The solvent was removed under reduced pressure to furnish the corresponding 1-alkyl-5-nitro- (**2a**–**e**) or 1-alkyl-4-nitro-1,2,3-triazoles (**3a**–**e**). In case of salt **1n**, the obtained mixture of **2f** and **3f** was recrystallized from ethanol to furnish pure **3f**.

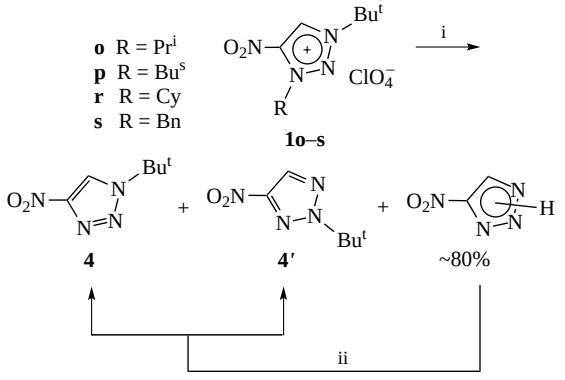
(see Scheme 1). Unlike *tert*-butyl group, N^1-positioned secondary isopropyl substituent was more stable. The dealkylation of salt **1l** eliminated the N^3-ethyl substituent and afforded triazole **3e**.

For the salts bearing the secondary N^3-positioned alkyl group combined with the primary N^1-alkyl substituent (salt **1m**), the dealkylation time shortened considerably (to 3.5 h). In case when the leaving group at position N^3 of the ring was the primary substituent (Me, Et), the reaction time increased by a factor of 4−9 (see Scheme 1). The processing of 1-benzyl-3-methyl-4-nitro-1,2,3-triazolium salt **1n** brought about N^1- and N^3-isomer mixture **3f**, **2f** in a ratio of 1.0 : 0.45.

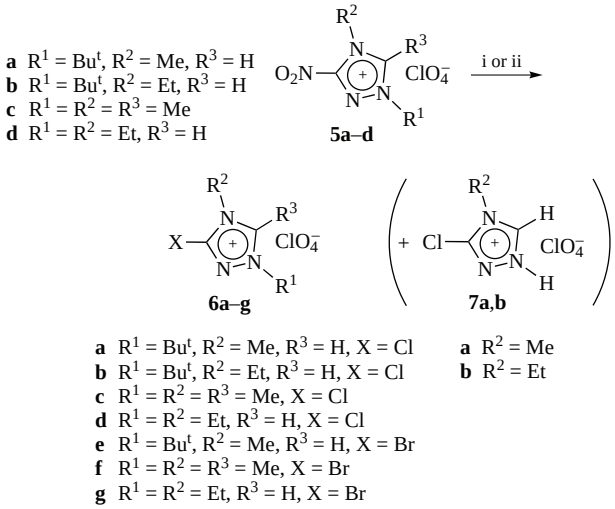
Thus, the dealkylation of the nitrotriazole salts containing primary, secondary alkyl and benzyl substituents at the N^1 position proceeded mostly at the N^3 position of the ring (salts **1f**–**n**). Apparently, the selective elimination of the N^3-alkyl groups can be explained by the higher electron deficiency at the N^3 atom neighbouring to the C atom bearing the nitro group. The peculiar feature of the dealkylation of nitrotriazolium salts with two branched N^1- and N^3-positioned alkyl substituents (as opposed to the case of salts **1a**–**e**,**l**,**m** with only one branched substituent) is that parallel *N*-mono-, *N*,*N*′-didealkylation and isomerization would take place.

Despite the presence of good leaving *tert*-butyl group at position N^1, the *N*-monodealkylation of 1-*tert*-butyl-3-alkyl-nitrotriazolium salts **1o-s** (where alkyl = Pr^i, Bu^s, Cy, Bn, Scheme 2) occurred largely at N^3 to produce triazole derivative **4**, with the full dealkylation having taken place to give *N*-unsubstituted nitrotriazole (78−79% yield). Due to the heterolysis of the exocyclic N–Bu^t bond, the triazoles may undergo migration of the alkyl substituent in a highly acidic medium. Therefore, isomeric 2-*tert*-butylnitrotriazole **4′** was also detected among the reaction products. In all cases, the ratio of **4**/**4′** was 1 : 1 while their total yield did not exceed 14%. It should be noted that similar **4**/**4′** mixture was previously obtained by H_2SO_4-catalyzed *tert*-butylation of nitrotriazole in benzene.[7]

3-Nitro-5-R-1,2,4-triazolium salts with another arrangement of nitrogen atoms in the heterocycle behaved differently



Scheme 2 *Reagents and conditions*: i, HCl, 100 °C, 5 h; ii, H_2SO_4, Bu^tOH, PhH (ref. 7).



Scheme 3 *Reagents and conditions*: i, HCl, 100 °C,10 h (for **5a**), 5 h (for **5b**), 6 h (for **5c**,**d**); ii, HBr, 120 °C, 10 h (for **5a**), 6 h (for **5c**,**d**).

compared to 1,2,3-triazolium analogues (Scheme 3). Salts **5a**–**d** (obtained by the quaternization of 1- and 4-alkyl-3-nitro-5-R-1,2,3-triazoles[8]) on treatment with HCl or HBr underwent mostly the S_N^{ipso}-substitution of the nitro group yielding 1,4-dialkyl-3-halogeno-1,2,4-triazolium salts **6a**–**g**. The tandem reaction was removal of the *tert*-butyl substituent to finally afford 1*H*-4-alkyl-3-chloro-1,2,4-triazolium salts **7a**,**b** (see Scheme 3).

3-Nitro-1,2,4-triazolium salts undergo S_N^{ipso}-substitution reactions quite easily. In 2.5 h, the conversion of salt **5a** was 86%, while after 5 h the nucleophilic substitution products **6a** and **7a** were formed. The longer processing facilitated complete de-*tert*-butylation of salt **6a** and its conversion into product **7a** (see Online Supplementary Materials, Figure S1).

Treatment of salt **5a** with concentrated HBr did not cause dealkylation and brought about only the corresponding bromodenitration derivative **6e**. Salts **5c**,**d** with linear alkyl groups underwent only replacement of the nitro group irrespective of the acid used (HCl or HBr) to furnish the corresponding chloro- or bromotriazoles **6c**,**d**,**f**,**g** in 91–99% yields.

The S_N^{ipso}-substitution of the nitro group under the action of the halogen one in the *N*,*N*-disubstituted nitrotriazolium salts has not been studied so far. However, we previously noticed a clearly pronounced tendency of *N*-alkyl-substituted 3-nitro-1,2,4-triazoles to undergo a nucleophilic attack by O- and N-nucleophiles.[9] Pevzner and Kofman investigated the nucleophilic substitution reaction for 3-nitro-1,2,4-triazoles and 1-substituted 5-nitro-1,2,4-triazoles, including those activated by two electron-acceptor groups (NO_2, NH_2, Cl or Br).[10]

The structures of the resultant compounds were proved by spectral data and elemental analysis. The structures of salts **7a** and **6b** were unambiguously validated by X-ray diffraction study (Figure 1).‡

‡ *Crystal data for* **7a**. $C_3H_5N_3Cl^+ClO_4^-$, M = 218.00, monoclinic, space group $P2_1/c$, at 298 K: a = 6.6703(4), b = 10.3931(6) and c = 11.5536(10) Å, β = 101.781(4)°, V = 1244.57(16) Å^3, Z = 4, d_{calc} = 1.847 g cm^{-3}, μ(MoKα) = 0.807 mm^{-1}. Total of 7170 reflections were measured (θ < 30°) and 2305 independent reflections (R_{int} = 0.0298) were used for further refinement. The refinement converged to wR_2 = 0.0946 and GOF = 1.032 for all independent reflections [R_1 = 0.0341 for 1520 $I > 2\sigma(I)$].

Crystal data for **6b**. $C_8H_{15}N_3Cl^+ClO_4^-$, M = 288.13, rhombic crystals, space group $Pna2_1$, a = 18.7211(11), b = 9.1117(6) and c = 7.8930(5) Å, V = 1346.40(15) Å^3, Z = 4, d_{calc} = 1.421 g cm^{-3}, μ(MoKα) = 0.489 mm^{-1}. 10159 reflections were measured with $\theta \leqslant 25.7°$, 2478 independent, R 0.0589 [for 1677 reflections with $I > 2\sigma(I)$], and wR_2 0.1870 (for all I). The ethyl group is disordered in a ratio of 0.54(4) : 0.46(4) [rotation around the N(4)–C(10) bond]. The anion is also disordered in a ratio of 0.496(14) : 0.504(14) [rotation at the fixed Cl(2) atom].

The structure was solved by direct methods and refined by full-matrix least-squares method against all F^2 in anisotropic approximation using the SHELXT-2014 and SHELXL-2018 set of programs.[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 2085627 (**7a**) and 2086116 (**6b**) contain 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.

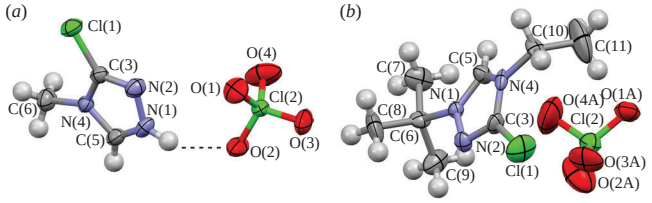


Figure 1 General view of salts (*a*) **7a** and (*b*) **6b** (atoms are represented as thermal ellipsoids at a 30% probability level).

To sum up, we have developed a synthesis of difficult-to-access 1-alkyl-5-nitro-1,2,3-triazoles based on selective mono-dealkylation of available 1,3-dialkyl-4-nitro-1,2,3-triazolium salts in acidic media. Refluxing the 4-nitro-1,2,3-triazolium salts in concentrated HCl resulted in their dealkylation, and furnished N^1- or N^3-isomers or mixtures of *N*-mono- and *N*,*N'*-dealkylation products, depending on the nature of the leaving substituent and its location in the azole ring. In cases of 3-nitro-1,2,4-triazolium salts, chiefly S_N^{ipso}-substitution occurred under the same conditions to afford the products of replacement of the nitro group with the halogen one.

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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.2022.03.020.

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