# Synthesis of 5-alkoxy-3-amino-7-nitro-1,2,4-benzotriazine 1-oxides from 1,3,5-trinitrobenzene

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1-Alkoxy-3,5-dinitrobenzenes were nitrated to give 1-alkoxy-2,3,5-trinitrobenzenes. The reaction of the latter with guanidine affords *N*-(2-alkoxy-4,6-dinitrophenyl)guanidines, which undergo cyclization under the action of KOH to form 5-alkoxy-3-amino-7-nitro-1,2,4-benzotriazine 1-oxides.

**Key words:** 5-alkoxy-3-amino-7-nitro-1,2,4-benzotriazine 1-oxides, 1,3,5-trinitrobenzene, 1-alkoxy-3,5-dinitrobenzenes, 1-alkoxy-2,3,5-trinitrobenzenes, nitration, guanidine, cyclization.

In the last few years, derivatives of 3-amino-1,2,4-benzotriazine 1-oxides have attracted attention because of their antitumor activity.[1]

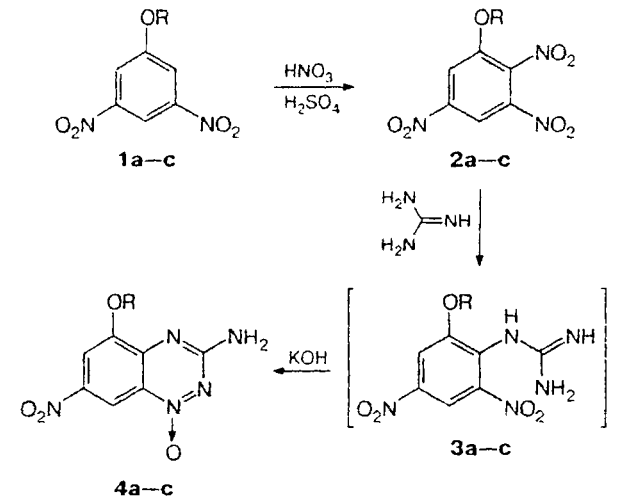
The compounds of this class are generally synthesized by heating 2-nitroanilines with cyanamide and subsequent cyclization at the nitro group (the Arndt method)[2–4] or by nucleophilic substitution of guanidine for the nitro group or the fluorine atom in 1,2-dinitrobenzenes or 1-fluoro-2-nitrobenzenes followed by cyclization with participation of the nitro group.[5]

In the present work, we propose a method for the synthesis of the previously unknown derivatives of 3-amino-1,2,4-benzotriazine 1-oxide from 1,3,5-trinitrobenzene. The latter can be easily prepared by oxidation of 2,4,6-trinitrotoluene into 2,4,6-trinitrobenzoic acid[6,7] followed by its decarboxylation.[6]

Earlier, it has been shown that the nitro group in 1,3,5-trinitrobenzene is smoothly replaced under the action of methanol[8] or polyfluorinated alcohols[9] in the presence of inorganic bases to give the corresponding 1-alkoxy-3,5-dinitrobenzenes (**1**).

Nitration of 3,5-dinitrobenzenes **1** with a mixture of conc. $HNO_3$ ($d$ = 1.5 g cm$^{-3}$) and conc. $H_2SO_4$ ($d$ = 1.84 g cm$^{-3}$) under mild conditions affords 1-alkoxy-2,3,5-trinitrobenzenes (**2a—c**) in quantitative yield. 2,3,5-Trinitroanisole **2a** has been obtained earlier,[10] but not characterized by $^1$H NMR spectroscopy. Trinitrobenzenes **2** react with guanidine base in boiling Pr$^i$OH to give the corresponding (2-alkoxy-4,6-dinitrophenyl)guanidines (**3a—c**), *i.e.*, the guanidyl fragment replaces only the 2-nitro group. When treated *in situ* with an equimolar amount of KOH, compounds **3a—c** undergo cyclization to form the corresponding 5-alkoxy-3-amino-7-nitro-1,2,4-benzotriazine 1-oxides (**4a—c**). The latter precipitate from the reaction mixture and need no additional purification (Scheme 1). The yield of *N*-oxides **4** reaches ~90%.

**Scheme 1**




R = Me (**a**), $CH_2CF_3$ (**b**), $CH_2CF_2CF_2H$ (**c**)

Note that, unlike the case of *o*-dinitrobenzenes, in which the nitro group is replaced by guanidine in aprotic solvents such as *N*-methylpyrrolidone or THF,[5] we used isopropyl alcohol as a solvent. In the above aprotic solvents, our reaction mixture resinified sharply, which substantially decreased the yields of the target products.

Attention should be given to the fact that the 2-nitro group in compound **2** is especially easy to replace, despite the obvious steric hindrances to nucleophilic substitution. Previously,[11,12] it was reported that the rotation of the plane of the nitro group relative to the benzene plane, which is caused by the neighboring group, favors selective replacement of such a nitro group. According to the quantum-chemical calculations (the

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AM1 method, Chem3D Pro program, version 5.0) the 2-nitro group in 2,3,5-trinitroanisole (**2a**) is rotated through 54° to the benzene plane and thus can be replaced with high selectivity (*cf.*, the 3-nitro group is 39° rotated, while the 5-nitro group lies in the same plane as the benzene ring). Note that the AM1 calculations provide a good correlation with the known experimental data on the rotation of nitro groups in di- and polynitroarenes.

The structures of compounds **2** and **4** were determined using $^1$H NMR spectroscopy and elemental analysis. In addition, the structure of *N*-oxide **4a** was confirmed by mass spectrometry (EI). The mass spectra of compounds **4b,c** could not be recorded because of their low volatility; for this reason, their structures were determined by comparing their $^1$H NMR spectra with that of **4a** and confirmed by the data from elemental analysis.

## Experimental

NMR spectra were recorded on a Bruker AC-200 instrument with $Me_4Si$ as the internal standard. Melting points were measured on a Boetius hot stage. Solvents were purified according to the standard procedures.

**Nitration of dinitrobenzenes 1 (general procedure).** Dinitrobenzene **1** (1 g) was added to a mixture of 10 mL of $HNO_3$ ($d$ = 1.5 g cm$^{-3}$) and 10 mL of conc. $H_2SO_4$. The reaction mixture was stirred at 10—15 °C until the main reagent disappeared completely (~4.5—5 h, TLC), and the mixture was then poured into 150 g of ice. The precipitate that formed was filtered off, and the organic material was extracted from the aqueous layer with ethyl acetate (3×25 mL). The extract was washed with water to neutral reaction and dried over $MgSO_4$. The ethyl acetate was removed *in vacuo*, and the residue was combined with the isolated precipitate and crystallized from ethanol.

**1-Methoxy-2,3,5-trinitrobenzene (2a).** Yield 93%, m.p. 105—106 °C (*cf.* Ref. 10: m.p. 104 °C). $^1$H NMR (acetone-$d_6$), δ: 4.29 (s, 3 H, MeO); 8.60 (d, 1 H, H arom., $^4J$ = 2.3 Hz); 8.65 (d, 1 H, H arom., $^4J$ = 2.3 Hz).

**2,3,5-Trinitro-1-(2,2,2-trifluoroethoxy)benzene (2b).** Yield 90%, m.p. 61—63 °C (Pr$^i$OH). Found (%): C, 30.85; H, 1.32; N, 13.53. $C_8H_4F_3N_3O_7$. Calculated (%): C, 30.88; H, 1.30; N, 13.51. $^1$H NMR (acetone-$d_6$), δ: 5.32 (q, 2 H, $OCH_2$, $^3J_{HF}$ = 8.1 Hz); 8.79 (d, 1 H, H arom., $^4J$ = 2.4 Hz); 8.83 (d, 1 H, H arom., $^4J$ = 2.4 Hz).

**2,3,5-Trinitro-1-(2,2,3,3-tetrafluoropropoxy)benzene (2c).** Yield 92%, m.p. 64—67 °C (Pr$^i$OH). Found (%): C, 31.53; H, 1.50; N, 12.24. $C_9H_5F_4N_3O_7$. Calculated (%): C, 31.50; H, 1.47; N, 12.25. $^1$H NMR (acetone-$d_6$), δ: 5.22 (tt, 2 H, $OCH_2$, $^3J_{HF}$ = 12.7 Hz, $^4J_{HF}$ = 1.4 Hz); 6.44 (tt, 1 H, $CF_2H$, $^2J_{HF}$ = 52.3 Hz, $^3J_{HF}$ = 4.7 Hz); 8.77 (d, 1 H, H arom., $^4J$ = 2.4 Hz); 8.83 (d, 1 H, H arom., $^4J$ = 2.4 Hz).

**Synthesis of 5-alkoxy-3-amino-7-nitro-1,2,4-benzotriazine 1-oxides (4a—c) (general procedure).** A mixture of guanidine hydrochloride (2 mmol) and MeONa (2 mmol) in 5 mL of Pr$^i$OH was refluxed for 30 min. The sodium chloride that formed was filtered off, and the filtrate was added to a solution of trinitrobenzene **2** (1 mmol) in 30 mL of Pr$^i$OH. The reaction mixture was refluxed for 2 h and, after addition of KOH (1 mmol), for an additional 15 min. On cooling, crystals of *N*-oxide were formed. The crystals were filtered off, washed with Pr$^i$OH, and dried *in vacuo*.

***N*-Oxide 4a.** Yield 92%, m.p. 320 °C (decomp., Pr$^i$OH). Found (%): C, 40.58; H, 2.99; N, 29.56. $C_8H_7N_5O_4$. Calculated (%): C, 40.51; H, 2.97; N, 29.53. $^1$H NMR (DMSO-$d_6$), δ: 3.71 (s, 3 H, MeO); 7.18 (br.s, 2 H, $NH_2$); 7.21 (d, 1 H, H arom., $^4J$ = 3.0 Hz); 8.44 (d, 1 H, H arom., $^4J$ = 3.0 Hz). MS (EI, 70 eV), $m/z$ ($I_{rel}$ (%)): 237 $[M]^+$ (76), 223 (39), 219 (34), 181 (59), 105 (100).

***N*-Oxide 4b.** Yield 90%, m.p. 300 °C (decomp., Pr$^i$OH). Found (%): C, 35.41; H, 1.94; N, 22.97. $C_9H_6F_3N_5O_4$. Calculated (%): C, 35.42; H, 1.98; N, 22.95. $^1$H NMR (DMSO-$d_6$), δ: 4.19 (q, 2 H, $OCH_2$, $^3J_{HF}$ = 8.1 Hz); 7.35 (br.s, 2 H, $NH_2$); 7.47 (d, 1 H, H arom., $^4J$ = 2.4 Hz); 8.50 (d, 1 H, H arom., $^4J$ = 2.4 Hz).

***N*-Oxide 4c.** Yield 87%, m.p. 263—265 °C (Pr$^i$OH). Found (%): C, 35.64; H, 2.11; N, 20.79. $C_{10}H_7F_4N_5O_4$. Calculated (%): C, 35.62; H, 2.09; N, 20.77. $^1$H NMR (DMSO-$d_6$), δ: 4.61 (tt, 2 H, $OCH_2$, $^3J_{HF}$ = 12.7 Hz, $^4J_{HF}$ = 1.4 Hz); 6.51 (tt, 1 H, $CF_2H$, $^2J_{HF}$ = 52.3 Hz, $^3J_{HF}$ = 5.3 Hz); 7.38 (br.s, 2 H, $NH_2$); 7.67 (d, 1 H, H arom., $^4J$ = 2.6 Hz); 8.63 (d, 1 H, H arom., $^4J$ = 2.6 Hz).

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