The *tert*-butyl-*NNO*-azoxy group in the synthesis of 1,2,4-benzotriazin-3(4*H*)-one 1-oxides

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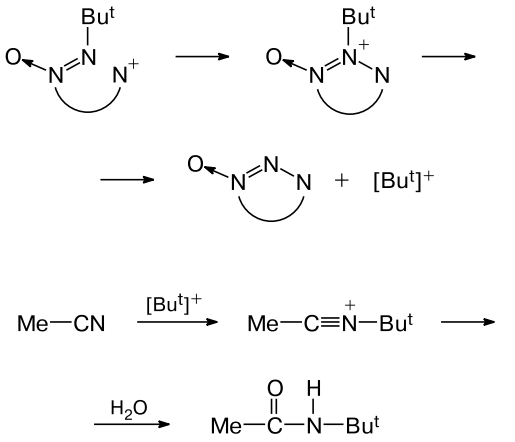
Treatment of 2-(*tert*-butyl-*NNO*-azoxy)anilines with phosgene at 20 °C was proposed as a novel route to 1,2,4-benzotriazin-3(4*H*)-one 1-oxides. This method involves a new reaction, *viz.*, an intramolecular interaction of the *tert*-butyl-*NNO*-azoxy group with a C-electrophile (leading to the formation of the N(2)—C(3) bond of the triazine ring) followed by elimination of the *tert*-butyl group. Complete assignment of the signals in the ^{1}H and ^{13}C NMR spectra of the compounds obtained was performed.

Key words: 1,2,4-benzotriazin-3(4*H*)-one 1-oxides, *tert*-butyl-*NNO*-azoxy group, phosgene, cyclization, ^{13}C NMR spectroscopy, novel synthetic methods.

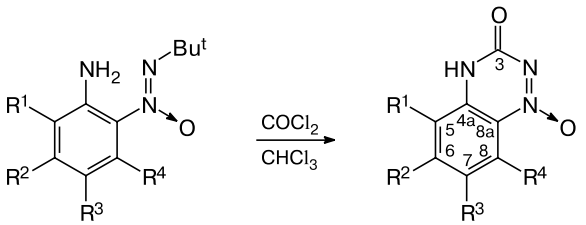
Earlier, we have proposed a method for introduction of a diazene oxide fragment into six-membered cyclic systems through the use of the *tert*-butyl-*NNO*-azoxy group.[1] This process can be schematically represented as an intramolecular interaction of the terminal N atom of the *tert*-butyl-*NNO*-azoxy group with an electrophile followed by elimination of the *tert*-butyl cation. When MeCN is used as a solvent, the *tert*-butyl group interacts with the latter to give, upon treatment with water, *N*-*tert*-butylacetamide.



Earlier, we employed in this reaction only N-electrophiles (namely, diazonium and oxodiazonium tetrafluoroborates) and obtained benzo-1,2,3,4-tetrazine 1-oxides and 1,3-dioxides.[1] Here we studied for the first time intramolecular interactions of the *tert*-butyl-*NNO*-azoxy group with C-electrophiles.

Synthesis of 1,2,4-benzotriazin-3(4*H*)-one 1-oxides. We found that treatment of 2-(*tert*-butyl-*NNO*-azoxy)anilines **1a**—**e** with phosgene in $CHCl_3$ at 20 °C gives 1,2,4-benzotriazin-3(4*H*)-one 1-oxides **2a**—**e** in high yields (Scheme 1).

Scheme 1



1a—e **2a—e**

Compound	R^1	R^2	R^3	R^4	Yield of **2** (%)
a	H	H	H	H	92
b	H	H	Br	H	90
c	Br	H	Br	H	85
d	H	H	H	Br	75
e	H	Br	Br	H	80

Up to now, compounds of this class have been obtained under rather drastic conditions by reactions of *ortho*-nitroanilines with phosgene followed by ammonolysis and cyclization in a boiling aqueous alkali.[2,3] Derivatives of these compounds exhibit a broad spectrum of biological activity. They are receptors of benzodiazepine ligands[4,5] and show antimalarial,[6] insecticidal, and acaricidal activities.[7]

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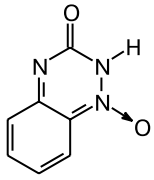
Discussion of plausible mechanisms of the reaction. The sequence of steps in the transformation of azoxyaniline **1a** into benzotriazinone **2a** can be represented as follows. The initially formed carbamoyl chloride **3** releases HCl to give isocyanate **5** (Scheme 2, pathway *a*). According to quantum-chemical calculations, this "open" isomer is thermodynamically more stable than the cyclic isomer **6** (the difference between the total energies of their molecules is 13.8 kcal mol^{-1}, HF/6-31G(dp)). However, the reaction mixture could contain small amounts of compound **6**. Hydrogen chloride evolved during the reaction could protonate the latter to give salt **4**, which decomposes into benzotriazinone **2a** and *tert*-butyl chloride. The formation of the latter was confirmed by ^{1}H NMR spectroscopic data for the reaction **1c** → **2c** in the presence of CH_2I_2 as an external standard. The corresponding amounts of *tert*-butyl chloride were detected with both a deficiency (0.5 equiv.) and an excess of phosgene (5 equiv.).

To verify this mechanism, we carried out a series of reactions of compounds **1a,c** with phosgene in the presence of bases (triethylamine, pyridine, or aqueous 10% Na_2CO_3) for detection of isocyanate **5**. Both equivalent and deficient amounts of phosgene were used. In all cases, the reaction mixtures contained only the starting and final compounds **1a,c** and **2a,c**, respectively (^{1}H NMR data). Isocyanate **5** was not detected; therefore, the reaction mechanism involving its formation seems to be unlikely.

An alternative sequence of steps involves a direct transformation of carbamoyl chloride **3** into salt **4** *via* an attack of the terminal N atom of the azoxy group on the C atom of the carbamoyl chloride (Scheme 2, pathway *b*) followed by decomposition of salt **4** to benzotriazinone **2a**.

It is assumed that both pathways *a* and *b* lead to intermediate salt **4**, which eliminates the *tert*-butyl cation rather than a proton even in the presence of a base. The preferred leaving of the *tert*-butyl group can be explained by the higher thermodynamic stability of structure **2a** compared to the quinonoid structure **6**. We performed calculations of the total energies of model compounds: 4*H*-isomer **2a** and hypothetical 2*H*-isomer **7** (HF/6-31G(dp)). Indeed, the isomers differ greatly in thermodynamic stability (by 14.2 kcal mol^{-1}).



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NMR studies of 1,2,4-benzotriazin-3(4*H*)-one 1-oxides. The compounds obtained were examined by NMR spectroscopy. The signals in their ^{1}H and ^{13}C NMR spectra were comprehensively assigned by the HMBC and HSQC techniques. The results obtained are summarized in Tables 1 and 2.

Scheme 2

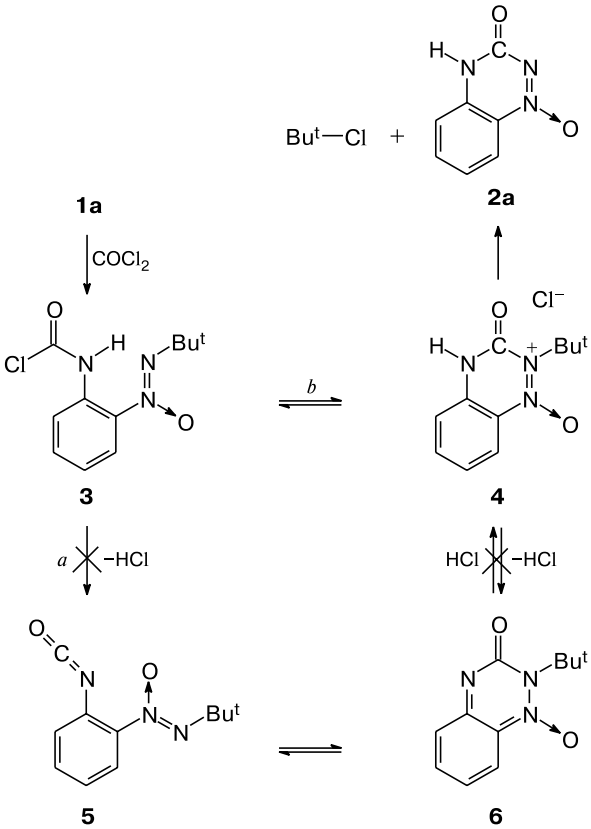

Table 1. ^{1}H NMR spectra of compounds **2a**—**e** (DMSO-d_6, δ, *J*/Hz)

Compound	H(5)	H(6)	H(7)	H(8)	NH
2a	7.35 (d, *J* = 7.4)	7.80 (t, *J* = 7.4)	7.32 (dt, *J* = 8.1, *J* = 1.5)	8.10 (d, *J* = 8.1)	12.6
2b	7.28 (d, *J* = 8.8)	7.95 (dd, *J* = 8.8, *J* = 2.2)	—	8.22 (d, *J* = 2.2)	12.7
2c	8.39 (d, *J* = 2.2)	—	8.30 (d, *J* = 2.2)	—	12.5
2d	7.32 (d, *J* = 8.7)	7.71 (dd, *J* = 8.8, *J* = 8.7)	7.45 (d, *J* = 8.8)	—	12.6
2e	7.63 (s)	—	—	8.36 (s)	12.7

Table 2. ^{13}C NMR spectra of compounds **2a**—**c,e** (DMSO-d_6, δ)

Compound	C(3)	C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)
2a	152.9	136.6	116.3	136.4	123.8	120.9	129.3
2b	152.6	136.0	118.5	139.0	114.9	123.0	130.0
2c	155.3	136.5	115.8	141.0	131.7	122.7	130.3
2e	152.5	136.4	120.5	132.5	117.6	125.1	129.2

The low-field signal for the C(3) atom, which is characteristic of carbonyl carbon, unambiguously indicates the attachment of the acidic proton to the N rather than O atom.

The position of the H atom in the triazine ring of compound **2a** was confirmed by a NOE-diff spectrum showing a single response from H(5) atom to the NH proton.

The characteristic feature of compounds **2** is a signal for the *N*-oxide nitrogen atom in the ^{14}N NMR spectrum at δ −37 to −41.

In conclusion, we proposed a novel method for the synthesis of 1,2,4-benzotriazin-3(4*H*)-one 1-oxides. The key step of the method is an intramolecular interaction of the terminal N atom of the *tert*-butyl-*NNO*-azoxy group with a C-electrophile followed by elimination of the *tert*-butyl group.

Experimental

IR spectra were recorded on a Specord M-80 spectrometer. Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-300 (300.13 and 75.5 MHz, respectively) and Bruker-DRX-500 spectrometers (500.13 and 125.5 MHz, respectively). The course of the reactions was monitored by TLC (Silufol UV-254). Azoxyanilines **1a—e** were prepared as described earlier.[8,9]

Synthesis of 1,2,4-benzotriazin-3(4*H*)-one 1-oxides 2a—e from *ortho*-azoxyanilines 1a—e and phosgene (general procedure). A flow of phosgene was slowly passed through a stirred solution of azoxyaniline **1** (1 mmol) in $CHCl_3$ (5 mL) until the starting reagent was completely consumed (15—20 min, TLC). The precipitate of the product was filtered off, washed with a small amount of $CHCl_3$, and dried in air.

1,2,4-Benzotriazin-3(4*H*)-one 1-oxide (2a). The yield was 150 mg, yellow crystals, m.p. 242—245 °C (*cf.* Refs 2, 3: m.p. 244—246 °C). IR (KBr), ν/cm^{-1}: 1670 (C=O); 3430 (NH). MS, *m/z*: 163 $[M]^+$. ^{14}N NMR (DMSO-d_6), δ: −37 ($\Delta\nu_{1/2}$ = 190 Hz, N→O).

7-Bromo-1,2,4-benzotriazin-3(4*H*)-one 1-oxide (2b). The yield was 220 mg, lemon yellow crystals, m.p. 249—253 °C. Found (%): C, 34.98; H, 1.55; Br, 29.58; N, 17.71. $C_7H_4BrN_3O_2$. Calculated (%): C, 34.74; H, 1.67; Br, 33.01; N, 17.36. IR (KBr), ν/cm^{-1}: 1650 (C=O); 3440 (NH). MS, *m/z* (integral intensity ratio): 241, 243 (1 : 1) $[M]^+$. ^{14}N NMR (DMSO-d_6), δ: −40 ($\Delta\nu_{1/2}$ = 240 Hz, N→O).

5,7-Dibromo-1,2,4-benzotriazin-3(4*H*)-one 1-oxide (2c). The yield was 270 mg, yellow crystals, m.p. 255—258 °C. Found (%): C, 25.99; H, 0.98; Br, 50.11; N, 13.24. $C_7H_3Br_2N_3O_2$. Calculated (%): C, 26.20; H, 0.94; Br, 49.80; N, 13.09. IR (KBr), ν/cm^{-1}: 1700 (C=O); 3380 (NH). MS, *m/z* (integral intensity ratio): 319, 321, 323 (1 : 2 : 1) $[M]^+$. ^{14}N NMR (DMSO-d_6), δ: −43 ($\Delta\nu_{1/2}$ = 270 Hz, N→O).

8-Bromo-1,2,4-benzotriazin-3(4*H*)-one 1-oxide (2d). The yield was 180 mg, brown crystals, m.p. 215—220 °C (decomp.). Found (%): C, 35.02; H, 1.69; Br, 29.61; N, 17.03. $C_7H_4BrN_3O_2$. Calculated (%): C, 34.74; H, 1.67; Br, 33.01; N, 17.36. IR (KBr), ν/cm^{-1}: 1660 (C=O); 3420 (NH). MS, *m/z* (integral intensity ratio): 241, 243 (1 : 1) $[M]^+$. ^{14}N NMR (DMSO-d_6), δ: −41 ($\Delta\nu_{1/2}$ = 250 Hz, N→O).

6,7-Dibromo-1,2,4-benzotriazin-3(4*H*)-one 1-oxide (2e). The yield was 260 mg, yellow-orange crystals, m.p. 232—235 °C. Found (%): C, 25.81; H, 1.09; Br, 50.08; N, 12.86. $C_7H_3Br_2N_3O_2$. Calculated (%): C, 26.20; H, 0.94; Br, 49.80; N, 13.09. IR (KBr), ν/cm^{-1}: 1670 (C=O); 3400 (NH). MS, *m/z* (integral intensity ratio): 319, 321, 323 (1 : 2 : 1) $[M]^+$. ^{14}N NMR (DMSO-d_6), δ: −41 ($\Delta\nu_{1/2}$ = 260 Hz, N→O).

NMR study of the reaction of 2,4-dibromo-6-(*tert*-butyl-*NNO*-azoxy)aniline 1c with phosgene. ***A.*** A 0.5 *M* solution of phosgene (1 mL, 0.5 mmol) in CCl_4 was added to a stirred solution of azoxyaniline **1c** (350 mg, 1 mmol) in CCl_4 (5 mL) containing CH_2I_2 (270 mg, 1 mmol). The reaction mixture was stirred for 15 min and decanted. The precipitate was compound **2c** (160 mg, 0.5 mmol) identical with that obtained earlier. To an aliquot of the solution, DMSO-d_6 was added and the reaction mixture was examined by ^{1}H NMR spectroscopy (CCl_4/DMSO-d_6, δ, *J*/Hz). The spectrum showed, apart from the signal at δ 4.02 (CH_2I_2), signals due to compound **1c** (0.5 equiv.) at δ 1.45 (s, 9 H, 3 CH_3), 6.57 (br.s, 2 H, NH_2), 7.68 (s, 1 H), and 7.98 (s, 1 H) and to *tert*-butyl chloride (0.5 equiv.) at δ 1.62 (s, 9 H, 3 CH_3).

B. An analogous reaction was carried out with an excess of phosgene (5 equiv.). After separation of compound **2c**, the solution contained *tert*-butyl chloride (1 equiv.).

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