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The First Synthesis of 1,2,3,4-Tetrazine-1,3-di-*N*-oxides

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The first synthesis of benzo-1,2,3,4-tetrazine-1,3-di-*N*-oxides has been accomplished by an intramolecular reaction between a *tert*-butylazoxy group and groups capable of generating the diazonio-oxide cation.

The first 1,2,3,4-tetrazine was reported in 1988 and, as predicted, it proved to be unstable.[1]

The transformation of tetrazines into their *N*-oxides should considerably alter their properties. We propose that benzo-1,2,3,4-tetrazine-1,3-dioxide **1** should be more stable than the parent benzo-1,2,3,4-tetrazine. Moreover it should be more stable than mono-*N*-oxides and di-*N*-oxides with other arrangements of oxygen atoms. There are two reasons for such stability. The first is the absence of ring–chain tautomerization for molecule **1**, the second is that electrocyclic extrusion of the stable nitrogen molecule from this compound is impossible.

We planned to carry out the synthesis of benzo-1,2,3,4-tetrazine-1,3-di-*N*-oxides (BTDO) by an intramolecular reaction between the *tert*-butyl-*NNO*-azoxy group† and the diazonio-oxide cation (Scheme 1).

The method of generating such a cation described previously[2] could be applied in this case owing to the instability of *tert*-butylazoxy compounds in strong acids. We have developed two new methods which allow us to obtain BTDO from structures **A** and **B**. These structures contain fragments capable

† For the first time we have shown the ability of the *tert*-butyl group in this fragment to be substituted by electrophilic reagents when synthesising 1-aryl-2-nitrodiazene 1-oxides *via* nitration of 1-aryl-2-*tert*-butyldiazene 1-oxides (see future publications).

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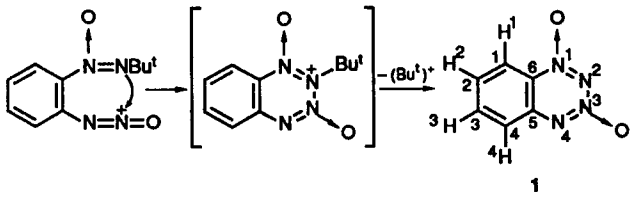
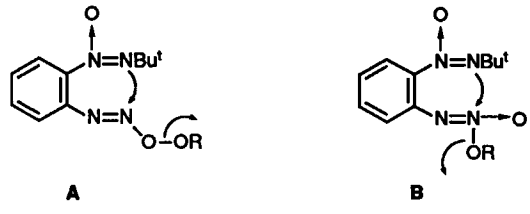


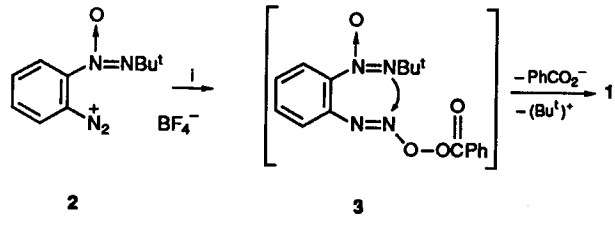
Scheme 1

of either generating the diazonio-oxide cation or reacting in a similar way to this cation.

The first method involves the treatment of diazonium salt **2** with a peracid in the presence of a base. The original method[3]



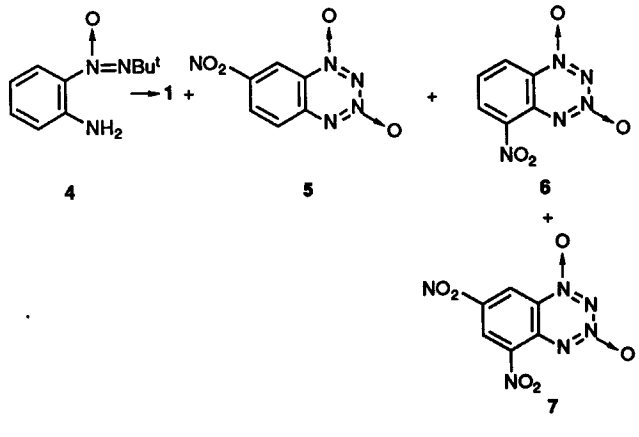
suggested that the reaction be carried out at − 30 °C in dry acetonitrile using pyridine as a base, *m*-chloroperbenzoic acid (MCPBA) being used as the peracid. The improved method allows us to carry out the reaction with perbenzoic acid at 0 °C in aqueous acetonitrile using sodium acetate as a base (Scheme 2).



Scheme 2 *Reagents and conditions*: i, PBA, $MeCO_2Na$, $MeCN–H_2O$, 0 °C, 15 min (**1**, m.p. 170–172 °C, 70% after column chromatography)

We assume that azoperoxy compound **3** appears at the first stage of the reaction and that splitting-off of the *tert*-butyl cation occurs after cyclization.

The second method of generating BTDO involves the treatment of 2-*tert*-butyl-*NNO*-azoxyaniline **4** with an excess of N_2O_5 in an organic solvent at 20 °C (Scheme 3). 5-Nitro-,



Scheme 3 (**5**, m.p. 166–168 °C; **6**, m.p. 193–195 °C; **7**, m.p. 209–211 °C)

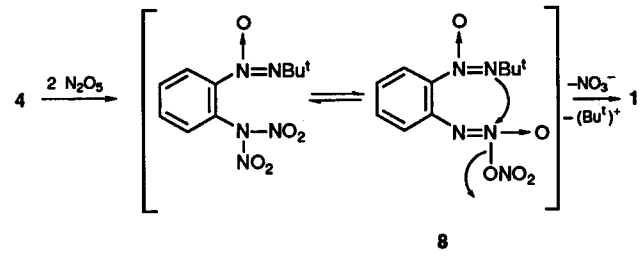
Table 1 Synthesis of BTDOs **1**, **5**, **6** and **7** *via* nitration

Starting compound	Nitrating reagent	Reaction conditions	Product yield[a] (%) 1	5	6	7
4	N_2O_5 (3.5 mol)	$MeNO_2$, − 20→0 °C, 0.5 h	65	9	4	5
	N_2O_5 (3.5 mol)	CH_2Cl_2, − 20→0 °C 0.5 h	6	7	10	28
1	$HNO_3–H_2SO_4$ (1:3, 4 mol)	24 °C, 2 h	–	61	30	–
	HNO_3–20% oleum (1:5, 10 mol)	80°C, 2 h	–	–	–	90

[a] Yield determined by HPLC after work-up of the reaction mixture.

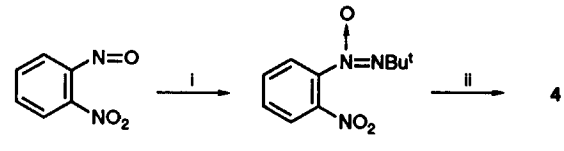
7-nitro- and 5,7-dinitro-benzotetrazine 1,3-dioxides are also formed in this reaction along with compound **1**‡

It was shown by a separate experiment that under the reaction conditions compound **1** was not converted into compounds **5**, **6** and **7**. Therefore nitration of the benzene ring preceded the cyclization and the product ratio depends upon the solvent temperature and the rate of addition of the reagents (Table 1). We propose that BTDO **1** is formed *via* the intermediate σ-form of dinitroamine **8** and its subsequent cyclization (Scheme 4).



Scheme 4

The parent aniline **4** was obtained from *o*-nitronitrosobenzene in 77% yield as shown in Scheme 5.



Scheme 5 *Reagents and conditions*: i, Br_2NBu^t, CH_2Cl_2, room temp., 2 h; ii, $SnCl_2·2H_2O$, EtOH–EtOAc, 30 °C, 4 h

‡ All novel compounds isolated were fully characterized by IR, ^1H, ^{13}C and ^{14}N NMR, MS and microanalysis. Full details of the X-ray crystallographic data and NMR investigations will be published elsewhere.

Spectral data for **1** in [$^2H_6$]acetone: ^1H NMR (300 MHz, standard $SiMe_4$) δ 7.91 (H^2, $^3J_{H\text{-}1}$ 8.6, $^3J_{H\text{-}3}$ 7.1, ^4J 1.2 Hz), 7.92 (H^4, ^3J 8.5 Hz), 8.18 (H^3, ^4J 1.3 Hz), 8.35 (H^1, ^5J 0.6 Hz); ^{13}C NMR (75.43 MHz, standard $SiMe_4$) δ 119.89 (C^1, ^1J 173.54, ^2J 1.9, ^3J 7.8, ^4J − 1.3), 125.22 (C^4, ^1J 170.78, ^2J 1.49, ^3J 7.6, ^4J − 1.3 Hz), 128.95 (C^6, ^2J 2.6, $^3J_{H\text{-}2}$ 10.5, $^3J_{H\text{-}3}$ 6.7, ^4J 1.5 Hz), 132.32 (C^2, ^1J 168.77, $^2J_{H\text{-}1}$ − 0.27, $^2J_{H\text{-}3}$ 1.18, ^3J 8.7 Hz), 139.20 (C^3, ^1J 165.54, $^2J_{H\text{-}2}$ 1.66, $^2J_{H\text{-}4}$ 0.47, ^3J 8.7 Hz), 144.68 (C^5, $^3J_{H\text{-}1}$ 5.0, $^3J_{H\text{-}3}$ 10.2, ^2J 1.5 Hz); ^{14}N NMR (21.69 MHz, standard $MeNO_2$) δ − 22 ± 10 (N^2, $\Delta\nu_{1/2}$ > 400 Hz), − 40.4 (N^1, $\Delta\nu_{1/2}$ 22 Hz), − 48.0 (N^3, $\Delta\nu_{1/2}$ 33 Hz), − 85 ± 10 (N^4, $\Delta\nu_{1/2}$ > 400 Hz); ^{15}N NMR (30.42 MHz, standard CH_3NO_2) δ − 23.89 (N^2), − 40.99 (N^1) − 48.73 (N^3), − 81.94 (N^4); MS, *m/z* 165 (30%, M^+), 120 (11%, $M^+ - N_2O$), 90 ($M^+ - N_2O$, − NO), 76 ($M^+ - 2N_2O$); IR (KBr) ν/cm^{-1} 1402, 1497 [N(O)NN(O)N].

BTDO, as expected, appear to be stable compounds which melt without decomposition. BTDO **1** is stable in both aqueous bases and strong acids. Nitration with HNO_3–H_2SO_4 results in mono-nitrated BTDOs **5** and **6**. When nitrated with HNO_3–oleum BTDO **1** gave product **7** in good yield (Table 1).

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