An unusual cascade of S_N reactions of benzotetrazine 1,3-dioxide derivatives*

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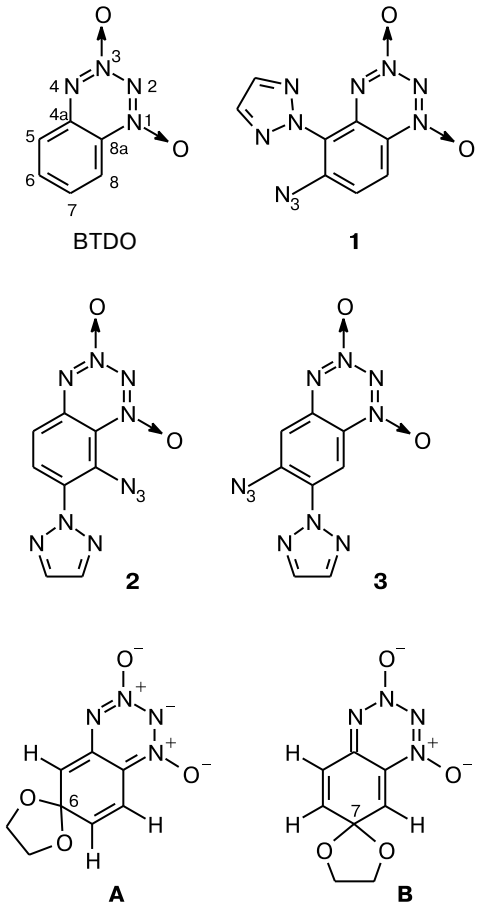
An unusual cascade of S_NAr reactions was discovered in the series of benzo-1,2,3,4-tetrazine 1,3-dioxides containing two adjacent nucleofuges X and Y in the benzene ring. First, the 1,2,3-triazole anion displaces the anion X^- from the more reactive site. Then the nucleophile X^- displaces the adjacent group Y. For instance, 1,2,3-triazole reacts with 6-azido-5-nitrobenzotetrazine 1,3-dioxide to give 5-azido-6-(1,2,3-triazol-2-yl)benzotetrazine 1,3-dioxide, with 8-azido-7-nitrobenzotetrazine 1,3-dioxide to give 7-azido-8-(1,2,3-triazol-2-yl)benzotetrazine 1,3-dioxide and 7-azido-8-(1,2,3-triazol-1-yl)benzotetrazine 1,3-dioxide, and with 7-bromo-6-(phenylthio)benzotetrazine 1,3-dioxide to give 7-phenylthio-6-(1,2,3-triazol-2-yl)benzotetrazine 1,3-dioxide.

Key words: 1,2,3,4-benzotetrazine 1,3-dioxides, 1,2,3-triazoles, S_NAr reactions; ^{1}H, ^{13}C, and ^{14}N NMR spectroscopy.

Earlier, we have reported on the synthesis of a number of benzotetrazine 1,3-dioxides (BTDO) annulated with tetraazapentalene fragments.[1—3] They were obtained by the thermolysis of BTDO with azido groups and 1,2,3-triazole fragments that are *ortho* to each other, the latter being in position 6 or 8. Our next goal was to synthesize azido-BTDO **1**, **2**, and **3** containing a triazole fragment in position 5 or 7 using nucleophilic substitution reactions as described previously.[1—3]

Earlier,[4] with reactions of mono- and dibromo-BTDO with the methoxide ion as examples, we have demonstrated that the nucleophilic substitution rates differ for different positions in the BTDO ring, decreasing in the order: 6 > 8 > 7 > 5. In most cases, this order is also true for reactions with other nucleophiles.[5] The substitution rate difference can be explained by the different thermodynamic stabilities of intermediate anionic σ-complexes. According to quantum-chemical calculations (B3LYP/6-31+G(d,p)) of the total energies of model isomeric anions **A** and **B**, isomer **A** is thermodynamically more stable than isomer **B** by 6.5 kcal mol^{-1}.

In the preceding work,[1] we have described the sequence of transformations **4** → **6** (Scheme 1). First, in a reaction of 6-bromo-5-nitro-BTDO **4** with 1,2,3-triazole in DMF in the presence of Na_2CO_3, the Br atom is replaced by the triazole fragment. Then the nitro group



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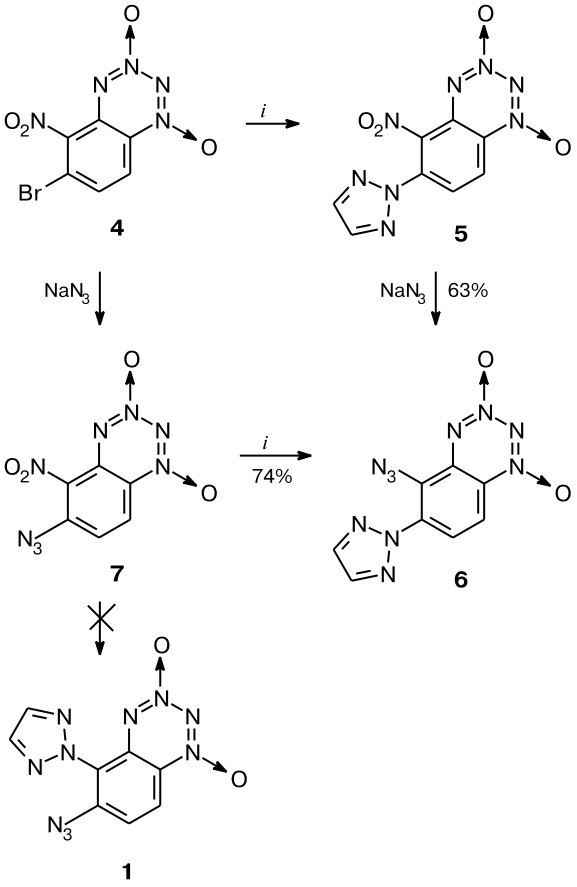
Scheme 1



Reagents and conditions: *i*, 1,2,3-triazole, Na_2CO_3, DMF, 20 °C, 2—3 h.

in BTDO **5** is replaced by the azido group *via* treatment with NaN_3 in DMF.

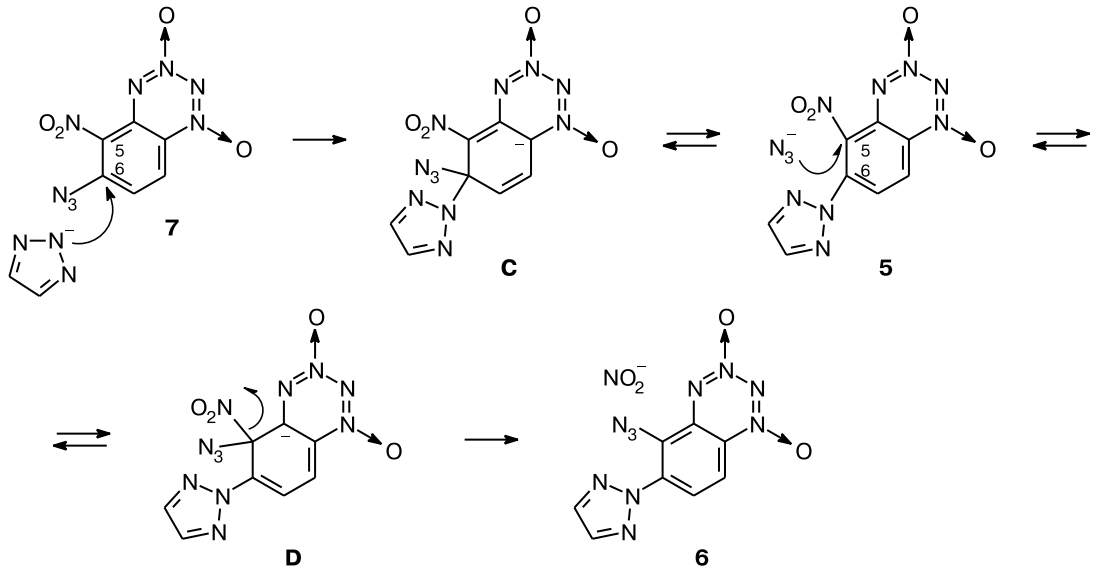
In an attempted synthesis of BTDO **1**, we changed the sequence of reactions. First, we obtained 6-azido-7-nitro-BTDO **7** from BTDO **4** and NaN_3 according to a known procedure.[6] Then BTDO **7** was treated with 1,2,3-triazole in DMF in the presence of Na_2CO_3 in the hope of directing the attack of the triazole at position 5. However, the substituents in product **6** (74% yield) were arranged inversely relative to the expected BTDO **1**. The structure of this product is identical with that obtained earlier[1] and hence is undoubted.

The formation of BTDO **6** can be explained as follows. In the first step, the triazole anion attacks BTDO **7** at the most reactive site 6 (Scheme 2), giving anionic complex **C**. Then the azide anion is eliminated to form BTDO **5**. However, the process goes on: the azide anion as a nucleophile attacks position 5 of BTDO **5** to give anionic intermediate **D** and finally, through elimination of the nitrite anion, BTDO **6**.

Thus, Scheme 1 is unsuitable for the synthesis of BTDO **1**. Nevertheless, the cascade of S_N reactions shown in Scheme 2 is of interest in itself. We found no references to similar cascades in the literature and wanted to know how far this process is of general character.

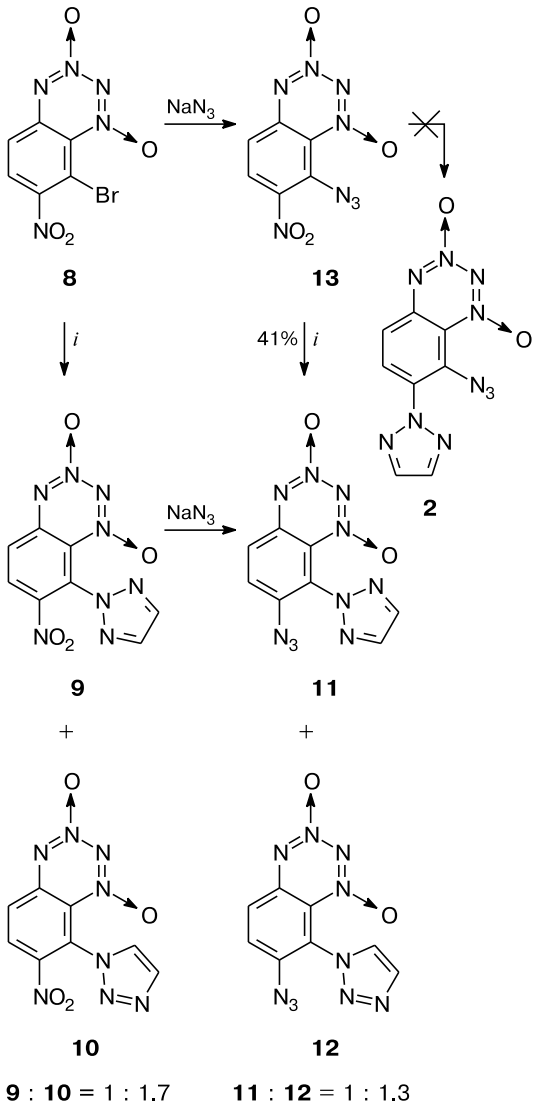
7,8-Disubstituted BTDO was used as an object of investigation (Scheme 3). Earlier,[3] we have demonstrated that 8-bromo-7-nitro-BTDO **8** reacts with triazole in acetone in the presence of Na_2CO_3 to give BTDO **9** and **10** *via* replacement of the Br atom in position 8 (Scheme 3). A subsequent reaction of BTDO **9** with NaN_3 in DMF results in replacement of the nitro group, yielding BTDO **11** (see Ref. 3). The inverted reaction sequence

Scheme 2



(first, BTDO **8** reacted with NaN_3[7] and then the resulting BTDO **13** reacted with the triazole anion) gave BTDO **11** and **12** in 18 and 23% yields, respectively; BTDO **2** was not obtained at all.

Scheme 3

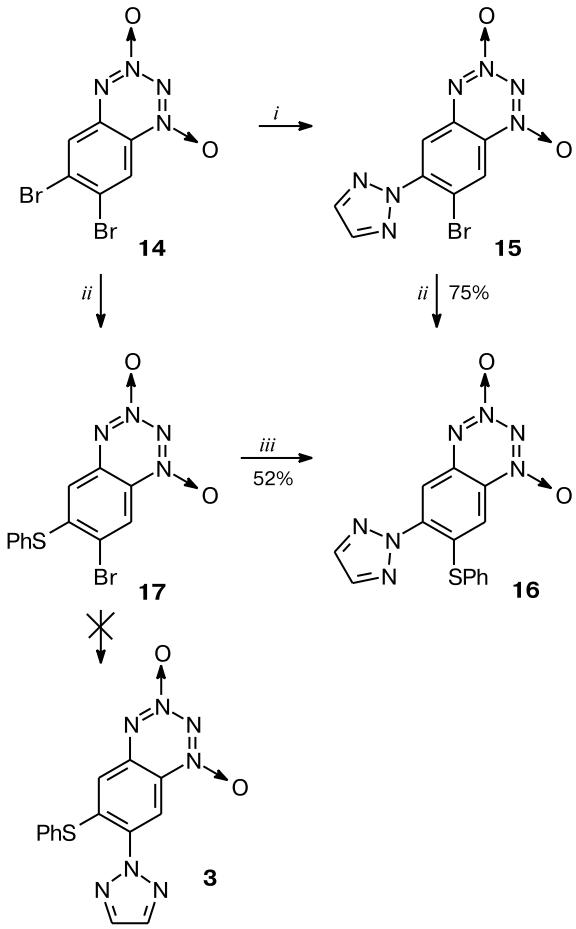


Reagents and conditions: *i*, 1,2,3-triazole, Na_2CO_3.

Another object of investigation was 6,7-disubstituted BTDO (Scheme 4). A reaction of dibromo-BTDO **14** with 1,2,3-triazole in DMF in the presence of KOH results in replacement of the Br(6) atom (see Ref. 2). When BTDO **15** was treated with benzenethiol in DMF in the presence of K_2CO_3, the Br(7) atom is replaced to give BTDO **16**.

In further experiments, the reaction sequence was changed. First, BTDO **14** was used in a reaction with

Scheme 4

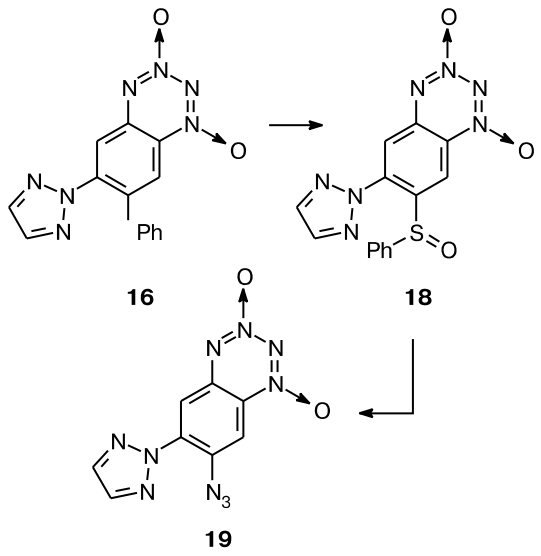


Reagents and conditions: *i*, 1,2,3-triazole, KOH, DMF, 20 °C, 15 min (see Ref. 2); *ii*, PhSH/K_2CO_3; *iii*, 1,2,3-triazole, KOH, DMSO, 20 °C, 12 h.

benzenethiol in DMSO—K_2CO_3 and then the resulting BTDO **17** reacted with triazole in DMSO in the presence of KOH. It turned out that the triazole anion displaces from position 6 even such a poor leaving group as the benzenethiolate anion, although at an appreciably lower rate. The anion PhS^- in turn displaces the Br^- anion from position 7 to give BTDO **16**. The low yield of this product (52%) is due to the losses during its isolation. In any case, no other products of this reaction were detected by TLC in noticeable amounts.

For unambiguous determination of the structure of BTDO **16**, this insoluble compound was oxidized into well-soluble sulfoxide **18** (Scheme 5) identified from its ^1H and ^{13}C NMR spectra with the nuclear Overhauser effect (NOE) and selective polarization transfer (SPT) from protons. Moreover, BTDO **18** was transformed into azido derivative **19** by a reaction with NaN_3; compound **19** was identical with an authentic sample.[2] Note that the latter reaction follows a normal S_NAr reaction pathway:

Scheme 5



the azide ion attacks position 7, thus displacing the phenylsulfoxy group.

The mechanism of transformations **13** → **11** and **17** → **16** is similar to that shown in Scheme 2: the initial attack of the 1,2,3-triazole anion on BTDO displaces the corresponding anion (N_3^- or PhS^-) from the more reactive position and then this anion as a nucleophile displaces the adjacent group.

Experimental

^1H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13, 75.5, and 21.5 MHz, respectively). Chemical shifts were referenced to Me_4Si (^1H and ^{13}C) or $MeNO_2$ (^{14}N, an external standard, high-field chemical shifts are negative). IR spectra were recorded on a UR-20 instrument. Mass spectra were measured on a Varian MAT-311A instrument (EI, 70 eV). The course of the reactions was monitored by TLC on Silufol UV-254 plates. The compounds obtained in the present work were identified by comparing their IR and ^1H NMR spectra and melting points with those of the corresponding authentic samples.

Caution! The compounds obtained are sensitive to impact and friction and must be handled as with explosives.

Reaction of 6-azido-5-nitrobenzotetrazine 1,3-dioxide (7) with 1,2,3-triazole. 1,2,3-Triazole (33 mg, 0.48 mmol) and finely divided Na_2CO_3 (51 mg, 0.48 mmol) were added at 20 °C to a stirred solution of BTDO **7** (100 mg, 0.4 mmol) in DMF (2 mL). The reaction mixture was stirred for 2 h and poured into water. The precipitate was filtered off, washed with water, and purified by column chromatography on silica gel with benzene as an eluent. The yield of 5-azido-6-(triazol-2-yl)-benzotetrazine 1,3-dioxide (**6**) was 80 mg (74%). The product was identical with an authentic sample.[1]

Reaction of 8-azido-7-nitrobenzotetrazine 1,3-dioxide (13) with 1,2,3-triazole. 1,2,3-Triazole (67 mg, 0.97 mmol) and finely divided Na_2CO_3 (100 mg, 0.94 mmol) were added at 20 °C to a stirred solution of BTDO **13** (200 mg, 0.8 mmol) in DMF (2 mL). The reaction mixture was stirred for 1 h and poured into water. The precipitate was filtered off, washed with water, and dried *in vacuo*. After the extraction with AcOEt, the residue was identified as a nearly pure 7-azido-8-(triazol-1-yl)benzotetrazine 1,3-dioxide (**12**). The extract was concentrated and the residue was separated by column chromatography (silica gel, $CHCl_3$—AcOEt, 2 : 3) into 7-azido-8-(triazol-2-yl)-benzotetrazine 1,3-dioxide (**11**) (40 mg, 18%) and BTDO **12**. The total yield of BTDO **12** was 50 mg (23%). Compounds **11** and **12** were identical with the corresponding authentic samples.[3]

7-Bromo-6-(phenylthio)benzotetrazine 1,3-dioxide (17). Benzenethiol (160 mg, 2.31 mmol) and finely divided K_2CO_3 (70 mg, 0.51 mmol) were added at 20 °C to a stirred solution of 6,7-dibromobenzotetrazine 1,3-dioxide **14** (161 mg, 0.5 mmol) in DMSO (6 mL). After 15 min, the reaction mixture was diluted with water. The precipitate that formed was filtered off, washed with MeOH and Et_2O, and dried. The yield of BTDO **17** was 172 mg (98%), m.p. 177—178 °C. Found (%): C, 41.36; H, 1.99; Br, 22.59; N, 15.73, S, 9.02. $C_{12}H_7BrN_4O_2S$. Calculated (%): C, 41.04; H, 2.01; Br, 22.75; N, 15.95; S, 9.13. IR (KBr, ν/cm^{-1}): 1275 m, 1368 s, 1435 s, 1515 s, 1578 m. ^1H NMR (DMSO-d_6), δ: 6.68 (s, 1 H, H(5)); 7.67 (m, 5 H, Ph); 8.54 (s, 1 H, H(8)). ^{13}C NMR (DMSO-d_6), δ: 117.8 (C(8)),122.3 (C(5)), 125.8 (C(8a)), 125.8 (*ipso*-C, Ph), 127.6 (C(7)), 130.8 (*m*-C, Ph), 131.1 (*p*-C, Ph), 135.2 (*o*-C, Ph), 142.4 (C(4a)), 154.3 (C(6)). ^{14}N NMR (DMSO-d_6), δ: −45 ($\Delta\nu_{1/2}$ = 200 Hz) (N(1), N(3)). MS, *m/z*: 350, 352 (1 : 1) $[M]^+$.

7-Phenylthio-6-(triazol-2-yl)benzotetrazine 1,3-dioxide (16). Benzenethiol (15 mg, 0.14 mmol) and finely divided K_2CO_3 (15 mg, 0.11 mmol) were added at 20 °C to a stirred solution of 7-bromo-6-(triazol-2-yl)benzotetrazine 1,3-dioxide (**15**) (31 mg, 0.1 mmol) in DMF (6 mL). After 20 h, the reaction mixture was diluted with water. The precipitate that formed was filtered off, washed with water, MeOH, and Et_2O, and dried. The yield of BTDO **16** was 25 mg (75%), m.p. 294 °C (from DMSO). Found (%): C, 49.59; H, 2.66; N, 28.71; S, 9.33. $C_{14}H_9N_7O_2S$. Calculated (%): C, 49.55; H, 2.67; N, 28.89; S, 9.45. IR (KBr, ν/cm^{-1}): 1365 s, 1420 s, 1459 s, 1480 m, 1510 m, 1650 m. ^1H NMR (DMSO-d_6), δ: 7.50 (s, 1 H, H(5)); 7.60 (m, 5 H, Ph); 8.80 (s, 1 H, H(8)); 8.87 (s, 2 H, triazole). ^{14}N NMR (DMSO-d_6), δ: −46 ($\Delta\nu_{1/2}$ = 300 Hz) (N(1), N(3)). MS, *m/z*: 339 $[M]^+$.

Reaction of 7-bromo-6-(phenylthio)benzotetrazine 1,3-dioxide (17) with 1,2,3-triazole. 1,2,3-Triazole (98 mg, 1.42 mmol) and finely divided KOH (80 mg, 1.42 mmol) were added at 20 °C to a stirred solution of BTDO **17** (500 mg, 1.24 mmol) in DMSO (10 mL). The reaction mixture was stirred for 12 h. The precipitate was filtered off, washed with MeOH and Et_2O, and dried to give nearly pure 7-phenylthio-6-(triazol-2-yl)benzotetrazine 1,3-dioxide (**16**) (250 mg, 52%), which was identical with the product obtained in the preceding entry.

7-Phenylsulfoxy-6-(triazol-2-yl)benzotetrazine 1,3-dioxide (18). 4-Ethoxycarbonylperoxybenzoic acid (0.3 mmol) was added to a stirred suspension of BTDO **16** (100 mg, 0.3 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at 20 °C for 1.5 h. The precipitate of 4-ethoxycarbonylbenzoic acid was filtered off and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the residue was washed with Et_2O and dried to give nearly pure BTDO **18** (58 mg, 54%). The ethereal rinse solution was concentrated and purified by column chromato-

graphy (silica gel, $CHCl_3$), which gave an additional crop (31 mg) of BTDO **18**. The total yield of BTDO **18** was 84%, m.p. 254—256 °C. Found (%): C, 47.48; H, 2.57; N, 27.33; S, 8.90. $C_{14}H_9N_7O_3S$. Calculated (%): C, 47.32; H, 2.55; N, 27.59; S, 9.02. IR (KBr, ν/cm^{-1}): 1160 s, 1217 m, 1275 m, 1370 s, 1405 m, 1433 s, 1455 m, 1490 m, 1515 s, 1585 m, 1618 w. ^{1}H NMR (acetone-d_6), δ: 7.42 (m, 3 H, Ph); 7.70 (m, 2 H, Ph); 8.26 (s, 2 H, triazole); 8.44 (s, 1 H, H(5)); 9.30 (s, 1 H, H(8)). ^{13}C NMR (DMSO-d_6), δ: 114.2 (C(5)); 118.5 (C(8)); 126.9 (*o*-C, Ph); 127.3 (br.s, C(8a), ^2J = 3.2 Hz); 129.4 (*m*-C, Ph); 131.8 (*p*-C, Ph); 139.0 (triazole); 141.2 (C(6), ^3J = 8.4 Hz); 141.8 (C(7), ^2J = 4.2 Hz); 144.8 (*ipso*-C, Ph); 145.5 (C(4a), ^3J = 5.9 Hz). For signal assignments, the SPT and NOE techniques were used. ^{14}N NMR (acetone-d_6), δ: –42 ($\Delta\nu_{1/2}$ = 60 Hz), –45 ($\Delta\nu_{1/2}$ = 80 Hz) (N(1), N(3)). MS, *m/z*: 355 $[M]^+$.

7-Azido-6-(triazol-2-yl)benzotetrazine 1,3-dioxide (19). Finely divided NaN_3 (10 mg, 0.15 mmol) was added at 20 °C to a stirred solution of BTDO **18** (36 mg, 0.1 mmol) in DMF (5 mL). After 40 min, the reaction mixture was diluted with water and the product was extracted with AcOEt. The extract was concentrated *in vacuo*. The residue was washed with water and purified by column chromatography (silica gel, $CHCl_3$) to give BTDO **19** (14 mg, 51%). The product was identical with an authentic sample.[2]

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References

1. A. Yu. Tyurin, A. M. Churakov, Yu. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 186 [*Russ. Chem. Bull, Int. Ed.*, 2008, **57**, 193].
2. O. Yu. Smirnov, A. M. Churakov, Yu. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 2140 [*Russ. Chem. Bull, Int. Ed.*, 2008, **57**, 2180].
3. A. Yu. Tyurin, A. M. Churakov, Yu. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 186 [*Russ. Chem. Bull, Int. Ed.*, 2008, **58**, 193].
4. O. Yu. Smirnov, A. M. Churakov, A. Yu. Tyurin, Yu. A. Strelenko, S. L. Ioffe, V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1701 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 1849].
5. A. M. Churakov, V. A. Tartakovsky, *Chem. Rev.*, 2004, **104**, 2601.
6. O. Yu. Smirnov, A. Yu. Tyurin, A. M. Churakov, Yu. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 133 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 137].
7. A. Yu. Tyurin, O. Yu. Smirnov, A. M. Churakov, Yu. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 341 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 351].

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