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CONTROLLED SYNTHESIS OF ELECTRON DEFICIENT NITRO-1*H*-BENZOTRIAZOLES

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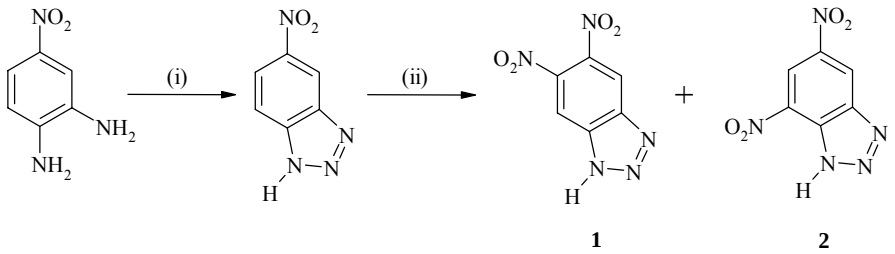
Abstract – Nitro-1*H*-benzotriazole derivatives containing electron withdrawing substitutents in the *ortho* and *meta* positions to the nitro group have been synthesized by the simple and direct nitration of the parent 1*H*-benzotriazoles. The route of nitration and assignment of isomerism in these compounds is proposed based upon high level density functional theory (DFT) calculations.

Substituted nitroaromatic derivatives containing strongly electron withdrawing groups are important reagents used throughout organic syntheses. [1-3] The withdrawing groups can impart useful properties and hence reactivity upon the aromatic ring and substituents thereon, or themselves may be modified to provide important synthetic intermediates such as aromatic amines. [1-3] The synthesis of nitroaromatic derivatives containing *ortho* and *para* directed withdrawing groups is generally difficult to achieve, through the strong *meta* directing influence of the electron deficient groups. [4] Consequently, new simple routes to the preparation of these important compounds are desirable. As part of our current studies in benzotriazole chemistry we required the use of electron deficient nitro-1*H*-benzotriazoles, preferably containing withdrawing groups in the *ortho* position to the nitro, as key building blocks towards other

important molecules containing the benzotriazole motif. A review of the literature revealed that few precedents had been set for the synthesis of this type of compound. The 4,6-dinitro-1*H*-benzotriazole derivative was prepared by Nietzke and Hagenbach as early as 1897 [5] and 5,6-dinitro-1*H*-benzotriazole by Coburn in 1973. [6] The 5-trifluoromethyl-7-nitro-1*H*-benzotriazole and 7-nitro-1*H*-benzotriazole-5-carboxylic acid have been reported previously, [7,8] although neither the 5-trifluoromethyl-6-nitro nor the 6-nitro-5-carboxylic acid isomers were obtained. In each of these cases the nitrobenzotriazoles were obtained through ring closure of the corresponding diamine in high yield. Unfortunately, the preparation of the necessary diamine precursors is tedious, requiring a lengthy protection, nitration, deprotection and reduction strategy. [5-8] Furthermore, the need for five steps in the synthesis results in a large reduction in overall yield and at best recoveries of the benzotriazoles are moderate. [5-8] The 4-nitro-5-chloro-1*H*-benzotriazole has been reported, however the synthetic route to this compound was not described. [9] The 4,6-dinitro-1*H*-benzotriazole was also obtained by Altmann *et al.* [10] during studies of tetraazapentalenes through decomposition of nitrotriazolobenzotriazoles. As the routes to these molecules are also complex we were interested in obtaining a simpler alternative for the controlled synthesis of the substituted nitro-1*H*-benzotriazoles in high yields.

The nitration of commercially available 1*H*-benzotriazole using H_2SO_4/KNO_3 at 60 °C has been reported by us previously [11] and affords the 4-nitro-1*H*-benzotriazole in good yield (66%). [12,13] However, there are no reports for the synthesis of strongly deactivated nitro-1*H*-benzotriazoles by direct nitration. The controlled preparation of 5,6- and 5,7-dinitro-1*H*-benzotriazole and also the 5,6,7-trinitro-1*H*-benzotriazole derivatives by direct nitration of 5-nitro-1*H*-benzotriazole and 1*H*-benzotriazole are thus presented. Also reported is the controlled preparation of the 5,6- and 5,7-trifluoromethyl-nitro-1*H*-benzotriazoles, the 7-nitro-5-carboxylic acid and the 6-chloro-7-nitro-1*H*-benzotriazole derivatives through nitration of the corresponding parent benzotriazoles. Additionally, the route of nitration of benzotriazole is proposed based on high level density functional theory (DFT) calculations, which show that previous assignments of the isomerisation of the dinitro-1*H*-benzotriazole compounds may be inaccurate.



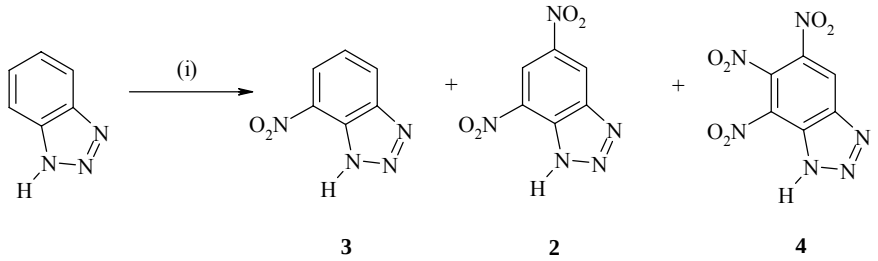
1 **2**

Scheme 1 *(i) AcOH, $NaNO_2$ (ii) H_2SO_4/HNO_3 115 ˚C, 12 h*

The 5,6- and 5,7-dinitro derivatives were obtained from 5-nitro-1*H*-benzotriazole, which is prepared in

high yield by ring closure of commercially available 4-nitro-1,2-phenylenediamine using nitrous acid. [14] Nitration of 5-nitro-1*H*-benzotriazole with H_2SO_4/HNO_3 at 115 ˚C for 12 h (*Scheme 1)* gave the 5,6-dinitro-1*H*-benzotriazole (**1**) (67 %) and the 5,7-dinitro-1*H*-benzotriazole (**2**) (30 %) (*Table 1*). Purification of the isomers was achieved by first pouring the reaction mixture over ice to precipitate (**1**) in a pure form. Extraction of the remaining liquors yielded isomer (**2**).

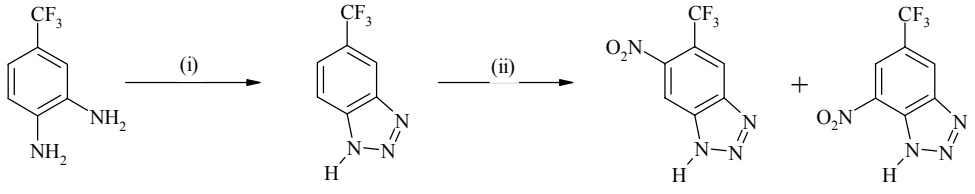
Extended nitration of 1*H*-benzotriazole with H_2SO_4/HNO_3 at 120 ˚C for 48 h (*Scheme 2*) afforded three products, assigned as 5,7-dinitro-1*H*-benzotriazole (63 %) (**2**), 7-nitro-1*H*-benzotriazole (8 %) (**3**) and the previously unreported 5,6,7-trinitro-1*H*-benzotriazole (12 %) (**4**) (*Table 1*). Purification of the three isomers was simple. Pouring the reaction mixture over ice precipitated **2** in a pure form. Extraction of the remaining mother liquors and column chromatography gave pure fractions containing compounds (**2**), (**3**) and (**4**) in acceptable yields.



3 **2** **4**

Scheme 2 *Nitration of Benzotriazole (i) 120 ˚C, 48 h*

The trifluoromethyl nitro derivatives were obtained directly from 5-trifluoromethyl-1*H*-benzotriazole. Ring closure of the commercially available 4-trifluoromethyl-1,2-phenylenediamine with sodium nitrite in acetic acid and concentrated HCl afforded the triazole derivative (**5**) in quantitative yield. Nitration using H_2SO_4 and HNO_3 at 90 ˚C for 2 h gave the 5-trifluormethyl-6-nitro-1*H*-benzotriazole (**6**) and 5-trifluoromethyl-7-nitro-1*H*-benzotriazole (**7**) derivatives as a mixture in 41 % and 25 % yields respectively by ^{1}H NMR spectroscopy (*Scheme 3*, *Table 1*). Purification of the crude product by wet flash chromatography afforded both compounds in yields of 22 % and 17 % overall.

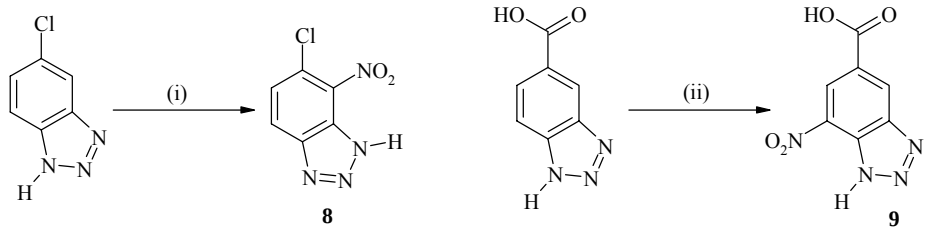


5 **6** **7**

Scheme 3 *(i) AcOH, $NaNO_2$ (ii) H_2SO_4/HNO_3 90 ˚C, 2 h*

Regioselective nitration of the commercially available 5-chloro-1*H*-benzotriazole using H_2SO_4 and HNO_3

at 60 ˚C for 1 h gave the 6-chloro-7-nitro-1*H*-benzotriazole (**8**) exclusively in 83 % yield. Selective nitration of the readily available 1*H*-benzotriazole-5-carboxylic acid was also achieved, in this case using H_2SO_4 and HNO_3 at 90 ˚C for 2 h to give the 7-nitro-5-carboxylic acid derivative (**9**) as the only product in 48 % yield (*Scheme 4*, *Table 1).*



Scheme 4 *(i) H_2SO_4/HNO_3 60 ˚C, 1 h (ii) H_2SO_4/HNO_3 90 ˚C, 2 h*

Somewhat unexpectedly, nitration of both 5-nitro-1*H*-benzotriazole and 1*H*-benzotriazole yielded a product of identical structure by ^{1}H NMR, ^{13}C NMR and Raman spectroscopy. As tautomerism of the triazole proton is possible to give both 5,7-dinitro-1*H*-benzotriazole and 4,6-dinitro-1*H*-benzotriazole (*Figure 1*) the fact that only one isomer was isolated suggests that one form is thermodynamically more stable than the other.

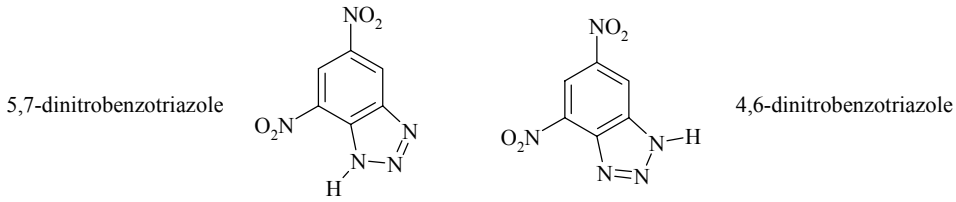


Figure 1 *Possible structures of **2** (isomerism can also extend to N2 in the triazole ring although this isomer was not seen)*

Elucidation of the precise structure of this derivative using 2D NMR techniques such as NOESY NMR, HETCOR NMR and HMQC NMR was attempted. Unfortunately an exact structural assignment from the information available was not possible. The presence of intramolecular hydrogen bonding has been reported previously in the solid state crystal structure of the closely related 7-nitro-1*H*-indazole. [15] We therefore propose that in this case tautomerism of the triazole is also highly likely to occur to give the most stable isomer as determined by formation of a stabilized six membered ring through an intramolecular hydrogen bond between the 7-nitro group and triazole system. In order to determine the most stable isomer, Density Functional Theory (using the B3LYP functional in conjunction with the 6-31G(d) basis set) calculations were used in an attempt to model which isomer was more

thermodynamically stable. The minimum energies of each isomer were determined and found to be -804.8515 Hartree for 4,6-dinitro-1*H*-benzotrizole and -804.8647 Hartree for 5,7-dinitro-1*H*-benzotriazole. This corresponds to a significant energy difference of 34.7 kJ mol^{-1} in favor of the 5,7-dinitro-1*H*-benzotriazole isomer and led us to conclude that this was the most thermodynamically stable conformation adopted. Thus the isomer produced was assigned as being exclusively the 5,7 and not 4,6 as previously reported. [6,10]

Table 1 *Product distributions for the nitration of selected 1H-benzotriazoles*

Benzotriazoles	**Nitration Conditions**	**Product(s)**	**Isolated Yield (%)**
5-Nitro	H_2SO_4/HNO_3, 115 ˚C, 12 h	(**1**) (**2**)	67 30
1*H*-Benzotriazole	H_2SO_4/HNO_3, 120 ˚C, 48 h	(**2**) (**3**) (**4**)	63 8 12
5-Trifluoromethyl	H_2SO_4/HNO_3, 90 ˚C, 2 h	(**6**) (**7**)	22 17
5-Chloro	H_2SO_4/HNO_3, 60 ˚C, 1 h	(**8**)	83
5-Carboxylic acid	H_2SO_4/HNO_3, 90 ˚C, 2 h	(**9**)	48

This also led to the question of the assignment of the mononitrated form of benzotriazole. Initially we had assigned the product as being the 4-isomer as reported previously. [11-13] However, in view of the products formed on the extended nitration of benzotriazole the heats of formation of the 4-isomer versus the 7-isomer were calculated. The DFT results obtained fit with the experimental observations in that 7-nitrobenzotriazole is 34.4 kJ mol^{-1} more stable than 4-nitrobenzotriazole. Thus we propose that the route for extended nitration of benzotriazole is nitration at the 7-position followed by the 5-position and finally the 6-position.

Mononitration of the 5-chloro-1*H*-benzotriazole and 1*H*-benzotriazole-5-carboxylic acid was completely regioselective to afford only one isomer of the nitrated benzotriazoles. Through extended nitration at higher temperatures it is expected that additional substitution should be observed. The structural assignment and route of nitration was based upon the DFT information obtained for the dinitrobenzotriazoles. The *ortho* substitution of the nitro group to the chlorine is expected through the directing influence of the halogen. In this case we believe that nitration at the 4-position on the benzene

ring is favoured compared to the 6-position. This would allow tautomerism of the triazole proton to give the 6-chloro-7-nitro-1*H*-benzotriazole, which would be preferred through formation of the stabilized intramolecular hydrogen bond between the nitro group and triazole ring system. The selective formation of the 7-nitro-1*H*-benzotriazole-5-carboxylic acid (**9**) was rationalised based upon the *meta* directing influence of the carboxylic acid. In this case nitration at the 7-position would also facilitate further stabilisation through intramolecular hydrogen bonding of the nitro group and triazole ring.

In conclusion, we have developed regio controlled routes to several isomers of nitro-1*H*-benzotriazole containing additional electron withdrawing groups in the *ortho* and *meta* positions to the nitro group. Nitration of commercially available 1*H*-benzotriazoles or easily prepared 1*H*-benzotriazoles was simple, resulting in products that were easily purified. DFT calculations showed the structure of 5,7-dinitro-1*H*-benzotriazole to be more thermodynamically stable than the 4,6-dinitro-1*H*-benzotriazole and thus helps to explain the formation of only one isomer by nitration of different starting materials. The route for extended nitration of benzotriazole was also examined and rationalized with the aid of DFT calculations to give further control over synthesis of the desired isomer. The nitration routes and structural assignments of the 5-chloro-1*H*-benzotriazole and 1*H*-benzotriazole-5-carboxylic acid were also rationalised, based upon the DFT observations for the dinitrobenzotriazoles. In both cases it is proposed that structural isomerism is controlled through preferred formation of a stabilized 6-membered ring, through intramolecular hydrogen bonding of the 7-nitro group and triazole system. We are currently investigating the use of these molecules towards the synthesis of more complex systems containing the benzotriazole framework.

EXPERIMENTAL SECTION

^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.62 MHz) spectra were recorded with the solvent peak (^{1}H NMR Acetone, $\delta = 2.05$ or DMSO, $\delta = 2.50$), (^{13}C NMR Acetone, $\delta = 29.9$ or DMSO, $\delta = 39.9$) as a reference. High resolution EI and FAB MS were recorded on a JEOL AX505 spectrometer in methanol and nitrobenzyl alcohol/glycerol matrices. The GAUSSIAN 98W [16] program running on a Windows NT workstation was used to perform the DFT calculations. The B3LYP method - Becke's 3-parameter hybrid functional [17] combined with the LYP correlation functional of Lee, Yang and Parr [18] was used in conjunction with the 6-31G(d) basis set for geometry optimization.

5,6-Dinitro-1*H*-benzotriazole (1) 5-Nitro-1*H*-benzotriazole (5.000 g, 30 mmol) was dissolved in concd sulfuric acid (60 mL) and cooled to 0 °C in an ice bath. Nitric acid (70 %, 60 mL) was added dropwise to

the cooled solution over a period of 20 min. Stirring was continued for another 15 min at 0 °C and then at 115 °C overnight. The solution was cooled to rt and poured over ice to precipitate a pale yellow solid and leave a clear yellow solution. The solid was collected by filtration and washed with water until neutral to afford **1** (4.149 g, 67 %), mp 136-137 °C. *Rf* (DCM/MeOH 9:1) 0.26. ^{1}H NMR (DMSO-d_6) δ 9.02 (s, 2H). *m/z* (FAB) 210.02695 [$C_6H_4N_5O_4$ $(M + H)^+$ < 3 ppm]. *Anal*. Calcd for $C_6H_3N_5O_4.H_2O$ [lit.,[6]]: C, 31.57; H, 2.19; N, 30.70. Found: C, 31.66; H, 2.33; N, 29.89.

5,7-Dinitro-1*H*-benzotriazole (2) (from 5-nitro-1*H*-benzotriazole) The clear yellow solution obtained after precipitation of **1** was neutralized with sodium bicarbonate and extracted with ethyl acetate (50 mL) and sodium chloride (4 × 20 mL) to afford a yellow organic layer that was dried over sodium sulfate. Removal of the solvent *in vacuo* gave **2** (1.688 g, 30 %) as a pale yellow solid, mp 196-197 °C. R_f (DCM/MeOH 9:1) 0.45. ^{1}H NMR (DMSO-d_6) δ 9.02 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (Acetone-d_6) δ 119.5 (CH), 123.5 (CH), 130.5 (CN), 133.7 (CN), 144.59 (CNO_2), 147.6 (CNO_2). *m/z* (FAB) 210.02633 [$C_6H_4N_5O_4$ $(M + H)^+$ < 4.2 ppm].

5,7-Dinitro-1*H*-benzotriazole (2) (from 1*H*-benzotriazole) 1*H*-Benzotriazole (5.000 g, 42 mmol) was dissolved in concd sulfuric acid (60 mL) and cooled to 0 °C in an ice bath. Nitric acid (70 %, 60 mL) was added dropwise to the cooled solution over a period of 20 min. Stirring was continued for a further 15 min at 0 °C and then at 120 °C for 48 h. The solution was cooled to rt and poured over ice to precipitate a white solid and leave a clear yellow solution. The solid was collected by filtration and washed with water until neutral to afford **2** (4.060 g, 46 %), mp 196-197 °C. R_f (DCM/MeOH 9:1) 0.45. ^{1}H NMR (DMSO-d_6) δ 9.02 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (Acetone-d_6) δ 119.5 (CH), 123.5 (CH), 130.5 (CN), 133.7 (CN), 144.59 (CNO_2) 147.6 (CNO_2). *m/z* (EI) 209.01850 [$C_6H_3N_5O_4$ $(M)^+$ < 0.2 ppm]. *Anal*. Calcd for $C_6H_3N_5O_4$: C, 34.28; H, 1.43; N, 33.33. Found: C, 34.59; H, 1.55; N, 33.00.

7-Nitro-1*H*-benzotriazole (3) and 5,6,7-Trinitro-1*H*-benzotriazole (4) The clear yellow solution obtained after precipitation of **2** was neutralized with sodium bicarbonate and extracted with ethyl acetate (50 mL) and sodium chloride (4 × 20 mL) to afford a yellow organic layer that was dried over sodium sulfate. Removal of the solvent *in vacuo* gave a straw coloured solid containing **2**, **3** and **4**. Column chromatography in hexane, eluting with ethyl acetate (0-100 %) and then MeOH (0-30 %) gave the pure title compounds in yields of 17 %, 12 % and 8 % respectively. **3** mp 220 °C (decomp). R_f (DCM/MeOH 9:1) 0.61. ^{1}H NMR (DMSO-d_6) δ 7.63 (dd, 1H, J = 7.96, 8.08 Hz), 8.46 (d, 1H, J = 7.84 Hz), 8.58 (d, 1H, J = 8.20 Hz). (**4**) mp 210 °C (decomp). R_f (DCM/MeOH 9:1) 0.1. ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1H) *m/z*

(EI) 209.01850 [$C_6H_3N_5O_4$ $(M - NO_2)^+$ < 2.7 ppm].

5-Trifluoromethyl-1*H*-benzotriazole (5) To a solution of 4-trifluoromethyl-1,2-phenylenediamine (1.056 g, 6 mmol) in acetic acid (12 mL) at 0 ˚C was added concd HCl (0.6 mL) resulting in the precipitation of the white hydrochloride salt. A solution of $NaNO_2$ (0.46 g, 6.6 mmol) in water (5 mL) was added dropwise to the suspension over 20 min to afford a clear dark solution. Stirring was continued at 0 ˚C for a further 10 min and then at 25 ˚C for 15 min to afford a clear orange solution. The solution was extracted into ethyl acetate (20 mL) with sodium chloride (3 × 10 mL) and then dried quickly over sodium sulfate. Removal of the solvent *in vacuo* gave an acidic residue that was co-evaporated with toluene under reduced pressure to afford **5** (1.122 g, 100 %) as a tan powder, mp 132 °C. ^{1}H NMR (DMSO-d_6) δ 7.75 (1H, d, *J* = 7.2 Hz, ArH), 8.09 (1H, br s, ArH), 8.44 (1H, br s, ArH) 16.41 (1H, br s, NH). *m/z* (EI) 187.03517 [$C_7H_4N_3F_3$ $(M)^+$ < 3.0 ppm].

5-Trifluoromethyl-6-nitro-1*H*-benzotriazole (6) Compound (**5**) (0.940 g, 5 mmol) was dissolved in sulfuric acid (10 mL) and cooled to 0 ˚C in an ice bath. Nitric acid (70 %, 10 mL) was added dropwise to the cooled solution over a period of 20 min. Stirring was continued for a further 15 min at 0 °C and then at 90 °C for 2 h. The solution was cooled to rt and poured over ice to precipitate a pale yellow solid and leave a clear yellow solution. The solid was collected by filtration and washed with water until neutral. The remaining filtrate was neutralized with sodium bicarbonate and extracted into ethyl acetate (20 mL) with sodium chloride solution (3 × 10 mL). The organic layer was dried over sodium sulfate and solvent removed to afford a pale yellow powder. The solids were combined to afford a mixture of **6** and **7** in 66 % yield overall. Column chromatography, eluting with ethyl acetate (0-100 %) in hexane and then methanol (20 %) in dichloromethane afforded pure **6** as a white powder (0.255 g, 22 %), mp 151-152 °C. ^{1}H NMR (DMSO-d_6) δ 8.74 (1H, s, ArH), 8.91 (1H, s, ArH). *m/z* (EI) 232.02054 [$C_7H_3N_4O_2F_3$ $(M)^+$ < 1.2 ppm]. *Anal*. Calcd for $C_7H_3N_4O_2F_3$: C, 36.20; H, 1.29; N, 24.13. Found: C, 37.33; H, 1.58; N, 22.51.

5-Trifluoromethyl-7-nitro-1*H*-benzotriazole (7) As per the procedure for **6** to afford **7** as a white powder (0.197 g, 17 %), mp 164 °C. ^{1}H NMR (DMSO-d_6) δ 8.64 (1H, s, ArH), 9.15 (1H, s, ArH). *m/z* (EI) 232.02030 [$C_7H_3N_4O_2F_3$ $(M)^+$ < 2.2 ppm]. *Anal*. Calcd for $C_7H_3N_4O_2F_3$: C, 36.20; H, 1.29; N, 24.13. Found: C, 36.30; H, 1.57; N, 22.52.

6-Chloro-7-nitro-1*H*-benzotriazole (8) 5-Chloro-1*H*-benzotriazole (3.080 g, 20 mmol) was dissolved in concd sulfuric acid (40 mL) and cooled to 0 °C on an ice bath. Nitric acid (70 %, 40 mL) was added

dropwise to the cooled solution over a period of 20 min. Stirring was continued for 1 h at 0 °C and then at 60 °C for an additional 1 h. The solution was cooled to rt and poured over ice to precipitate a white solid. The solid was collected by filtration and washed with water until neutral to afford **8** (3.303 g, 83 %), mp 163 °C (decomp). ^{1}H NMR (DMSO-d_6) δ 7.75 (1H, d, *J* = 8.8 Hz, ArH), 8.38 (1H, br s, ArH). *m/z* (EI) 197.99383 [$C_6H_3N_4O_2{}^{35}Cl$ $(M)^+$ < 3.2 ppm] and 199.99345 [$C_6H_3N_4O_2{}^{37}Cl$ $(M)^+$ < 9.7 ppm].

7-Nitro-1*H*-benzotriazole-5-carboxylic acid (9) 1*H*-Benzotriazole-5-carboxylic acid (1.000 g, 6 mmol) was dissolved in concd sulfuric acid (20 mL) and cooled to 0 °C on an ice bath. Nitric acid (70 %, 20 mL) was added dropwise to the cooled solution over a period of 20 min. Stirring was continued for another 15 min at 0 °C and then at 90 °C for 2 h. The solution was cooled to rt and poured over ice to precipitate a white solid. The solid was collected by filtration and washed with water to afford **9** (0.599 g, 48 %), mp 310 °C (decomp). ^{1}H NMR (DMSO-d_6) δ 8.77 (1H, s, ArH), 9.01 (1H, s, ArH), 13.75 (1H, br s, OH), 16.90 (1H, s, NH). *m/z* (EI) 208.02288 [$C_7H_4N_4O_4$ $(M)^+$ < 1.8 ppm].

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