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The synthesis and structures of deuterium-labeled 5-substituted 1*H*-tetrazoles†

Hong Zhao*

The synthesis and crystal structures of deuterium-labeled 5-substituted 1*H*-tetrazoles, 5-[$^2H_5$]phenyl-1*H*-tetrazole (I), 5-[$^2H_7$]tolyl-1*H*-tetrazole (II), and 5-[$^2H_7$]benzyl-1*H*-tetrazole (III) are reported. All syntheses were carried out using simple, facile steps and the products were obtained in high yields.

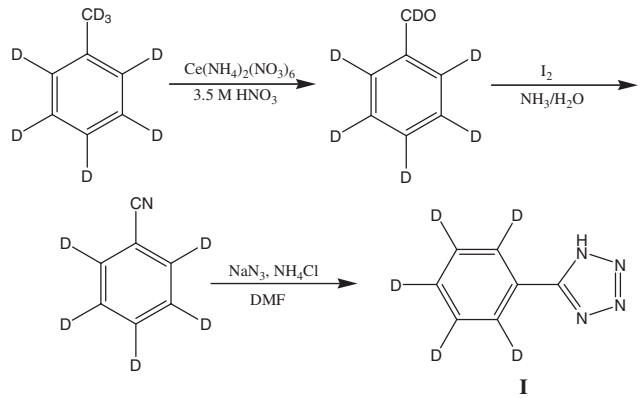
Keywords: deuterium labeling; 5-substituted 1*H*-tetrazoles; crystal structures

Introduction

In 2001, Demko and Sharpless[1–4] and Himo *et al.*[5,6] reported a safe, convenient, and environmentally friendly procedure for the synthesis of a variety of 5-substituted 1*H*-tetrazoles in water. The 1*H*-tetrazoles are prepared by addition of azide to nitriles in water with Zn salts as Lewis acid catalysts. The role of Zn in this reaction is unclear.[7–10] Since then our group has used other Lewis acids and solvents and tried different methods (e.g. hydrothermal conditions) in an attempt to find more convenient methods for the synthesis of 5-substituted 1*H*-tetrazoles. The tetrazole group acts as a metabolically stable surrogate for a carboxylic acid group in medicinal chemistry[11] and as a ligand in coordination chemistry.[8] Because of the variety of applications for tetrazoles in many fields of science, research into tetrazoles is expanding rapidly. To our knowledge, however, studies on deuterium-labeled 5-substituted 1*H*-tetrazoles are rare, which is surprising since such materials can potentially mimic the useful properties found in both organic and inorganic compounds. In this context and as part of an ongoing program in our laboratory to explore the medicinal and physical properties of tetrazole coordination compounds, we report the synthesis of three deuterium-labeled 5-substituted 1*H*-tetrazoles.

Results and discussion

Although the synthesis of many 5-substituted-1*H*-tetrazoles has been reported, the preparations of 5-[$^2H_5$]phenyl-1*H*-tetrazole (**I**), 5-[$^2H_7$]tolyl-1*H*-tetrazole (**II**), and 5-[$^2H_7$]benzyl-1*H*-tetrazole (**III**) have not been described previously. The synthesis of 5-[$^2H_5$]phenyl-1*H*-tetrazole (**I**) is shown in Scheme 1. [$^2H_8$]Toluene was treated with cerium (IV) ammonium nitrate to yield [$^2H_6$]benzaldehyde.[12] Then reaction with iodine in aqueous ammonia gave [$^2H_5$]benzonitrile.[13] Reaction with NaN_3 and NH_4Cl in *N*,*N*-dimethylformamide (DMF) yielded 5-[$^2H_5$]phenyl-1*H*-tetrazole (**I**).[14] The structure of **I** was confirmed by a single-crystal X-ray diffraction study. As shown in Figure 1, the phenyl and tetrazole rings exist in the same plan with a dihedral angle of 1.92 (0.28)°.



Scheme 1.

The synthesis of 5-[$^2H_7$]tolyl-1*H*-tetrazole (**II**) is shown in Scheme 2. The procedure used for **II** is similar to that for **I**, using 1,4-[$^2H_{10}$]xylene instead of [$^2H_8$]toluene. The crystal structure of **II** (Figure 2) shows that the phenyl and tetrazole rings exist in the same plan with a dihedral angle of 2.90 (0.19)° similar to **I**.

Finally, the synthesis of 5-[$^2H_7$]benzyl-1*H*-tetrazole (**III**) is shown in Scheme 3. [$^2H_8$]Toluene was treated with N-Bromosuccinimide in CCl_4 to yield [$^2H_7$]benzyl bromide. Reaction with NaCN then gave 2-[$^2H_7$]phenylacetonitrile, which was

†*CCDC: 668483–668485 contain the supplementary crystallographic data (excluding structure factor) for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).*

Ordered Matter Science Research Center, Southeast University, Nanjing 211189, People's Republic of China

**Correspondence to: Hong Zhao, Ordered Matter Science Research Center, Southeast University, Nanjing 211189, People's Republic of China.*
E-mail: zhaohong@seu.edu.cn

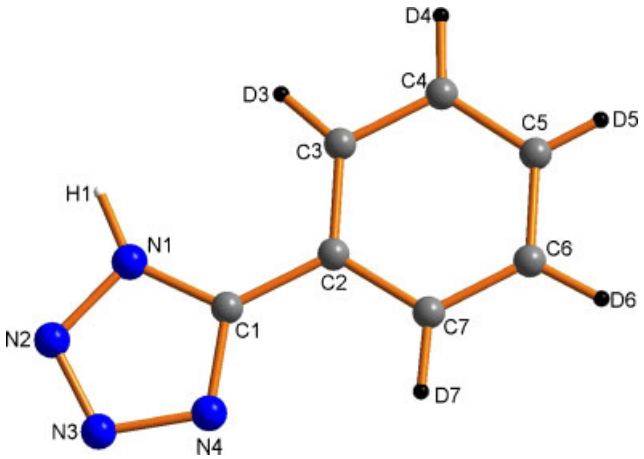
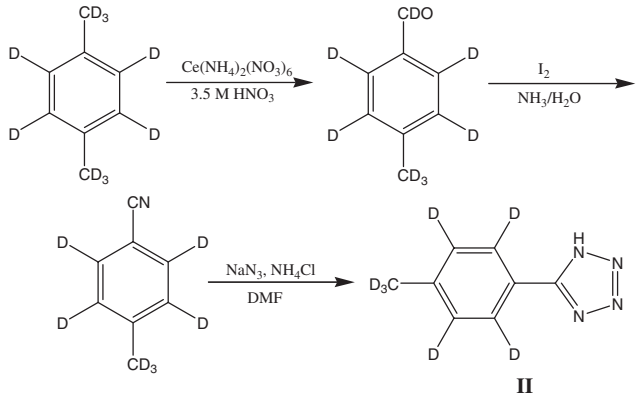


Figure 1. The crystal structure of **I**. This figure is available in color online at www.interscience.wiley.com/journal/jlcr.



Scheme 2.

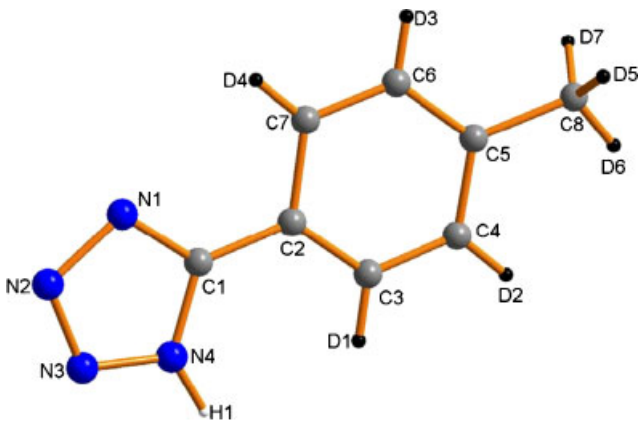
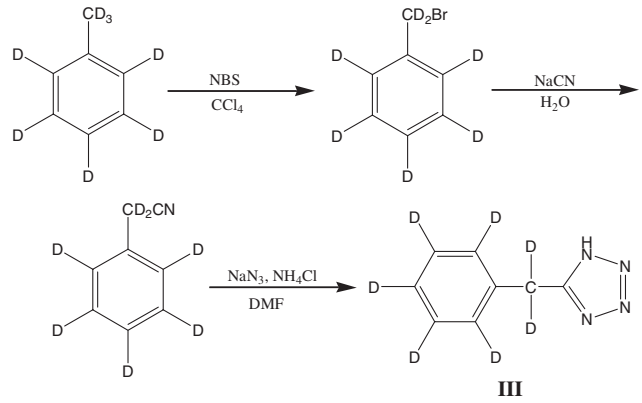


Figure 2. The crystal structure of **II**. This figure is available in color online at www.interscience.wiley.com/journal/jlcr.

heated under reflux with NaN_3 and NH_4Cl in water to generate 5-[$^2H_7$]benzyl-1*H*-tetrazole (**III**). The crystal structure of III (Figure 3) shows that the dihedral angle between the phenyl and tetrazole rings is 71.82 (0.11)° as a result of the additional methylene connection.



Scheme 3.

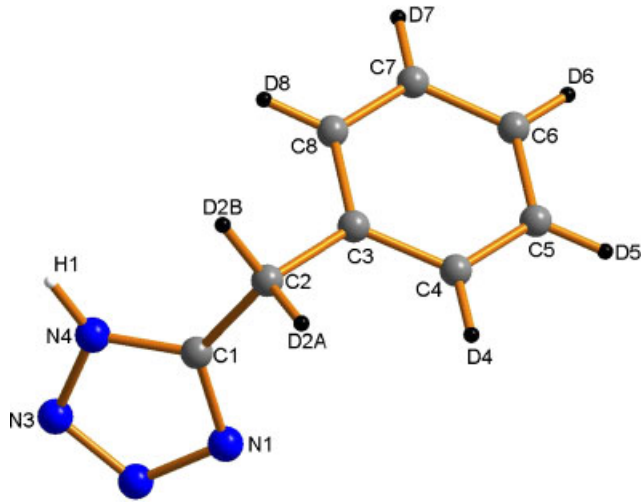


Figure 3. The crystal structure of **III**. This figure is available in color online at www.interscience.wiley.com/journal/jlcr.

In conclusion, three per-deutereated tetrazoles have been successfully synthesized and characterized and their solid state structures determined. This work will provide an insight into the application of tetrazoles as high-energy materials with potential uses in nuclear chemistry and medicine.

Experimental

General

[$^2H_8$]Toluene and 1,4-[$^2H_{10}$]xylene were obtained from Sigma-Aldrich Chemicals. All other reagents were also commercially available. ^1H, ^{13}C NMR spectra were acquired on a Bruker 300 MHz spectrometer. Elemental analyses for carbon, hydrogen, and nitrogen were performed on a Perkin-Elmer 240C elemental analyzer. IR spectra were obtained with KBr pellets in the 4000–400 cm^{-1} region, using a VECTOR22 spectrophotometer. Electrospray ionization-mass spectrometry analysis was carried out on an LCQ ADVANTAG MAX mass spectrometer. The crystal structures were determined by Rigacu SCX mini diffractionmeter. Melting points were measured with XT-4 thermometer.

*Preparation and analysis of (**I**)*

To [$^2H_8$]toluene (2.5 g, 25 mmol) in 3.5 M HNO_3 (50 mL) was added $Ce(NH_4)_2(NO_3)_2$ (54.8 g 100 mmol) in 3.5 M HNO_3 (200 mL). After 2.5 h at 80 °C, the solution was cooled to room temperature, extracted with chloroform (3 × 50 mL), and the combined organic layers were washed with water until pH ≈ 7. The orange extract was dried ($MgSO_4$) and the solvent removed under vacuum. The resulting red residue was distilled to give [$^2H_6$]benzaldehyde (2.6 g, 91%). Iodine (12.57 g, 49.5 mmol) was added to a stirring solution of [$^2H_6$]benzaldehyde (4.56 g, 40 mmol) in aqueous ammonia (350 mL of a 28% solution) and tetrahydrofuran (45 mL) at room temperature. The dark solution became colorless after being stirred for 1 h, an indication that the reaction was complete. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ (50 mL of 20% solution) and then extracted with chloroform (3 × 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and the solvent removed under vacuum to give [$^2H_5$]benzonitrile (4.01 g, 90%), which was used without purification. A mixture of [$^2H_5$]benzonitrile (2.16 g, 20 mmol), NaN_3 (1.43 g, 22 mmol), and NH_4Cl (1.177 g, 22 mmol) in DMF (15 mL) was heated at 120°C for 20 h then cooled and the solvent removed under vacuum. The residue was poured into water (20 mL) to give the crude product. 5-[$^2H_5$]Phenyl-1*H*-tetrazole (**I**) was obtained (2.85 g, 94.7%) after recrystallization from ethanol (95%). m.p.: 222–225°C. Anal. calcd. for $C_7HD_5N_4$: [%] C, 55.61; H, 7.33; N, 37.06; Found: [%] C, 55.42; H, 7.93; N, 36.65; IR (KBr, cm^{-1}): 3447.5(br, w), 3016.4(m), 2918.5(w), 2707.8(m), 2617.8(m), 2483.1(w), 1870.8(br, w), 1584.4(s), 1550.0(s), 1401.9(m), 1330.4(s), 1138.9(s), 1105.2(s), 1083.9(m), 1052..6(s), 984.7(s), 773.8(w), 543.6(s), 445.4(s); δ_C (300 MHz; $CDCl_3$) 123.7 (C-5), 126.4 (C-3 and C-7), 128.6(C-4 and C-6), 130.7 (C-2), 155.9 (Ar-C-1); *m/z* (-ve ion electrospray) $[M-H]^-$ $C_7D_5N_4$ required 150.09, found 150.22.

*Preparation and analysis of (**II**)*

To 1,4-[$^2H_{10}$] xylene (2.34 g, 20 mmol) in 3.5 M HNO_3 (50 mL) was added dropwise $Ce(NH_4)_2(NO_3)_2$ (44.23 g, 80 mmol) in 3.5 M HNO_3 (100 mL). After 1.5 h at 80°C, workup and purification as described for [$^2H_6$]benzaldehyde gave 4-[$^2H_5$]methylbenzaldehyde, which was treated by the same procedure as [$^2H_6$]benzaldehyde to yield 4-[$^2H_7$]methylbenzonitrile. The nitrile was then reacted with NaN_3 and NH_4Cl in DMF to give 5-[$^2H_7$]tolyl-1*H*-tetrazole (**II**) (2.1 g, 64.2% based on [$^2H_5$]1,4-xylene). m.p.: 109–112°C. Anal. calcd. for $C_8HD_7N_4$: [%] C, 57.46; H, 9.03; N, 33.51; Found: [%] C, 57.20; H, 9.33; N, 33.47; IR (KBr, cm^{-1}): 3447.4(br, w), 3023.4(w), 2933.4(w), 2830(w), 2739.2(m), 2592.2(m), 2512.7(m), 1889.5(br, w), 1591.1(s), 1563.3(m), 1405.6(s), 1363.9(s), 1255.6(w), 1189.8(w), 1136.5(s), 1084.2(m), 1056.1(s), 983.9(s), 655.6(s), 442.1(s); δ_C (300 MHz; $CDCl_3$) 19.16(Ar-CD_3), 120.7 (C-2), 126.3 (C-3 and C-7), 129.3(C-4 and C-6), 141.8 (C-5), 155.5 (Ar-C-1); *m/z* (-ve ion electrospray) $[M-H]^-$ $C_8D_7N_4$ required 166.23, found 166.22.

*Preparation and analysis of (**III**)*

To [$^2H_8$]toluene (20 g, 200 mmol) in CCl_4 (350 mL) was added NBS (35.6 g, 200 mmol) and benzoyl peroxide (0.2 g). The mixture was heated at 90°C for 2 h then cooled and filtered. The filtrate was concentrated to 40 mL and [$^2H_7$]benzyl bromide (29.4 g, 82.5%) collected by filtration and dried. A mixture of [$^2H_7$]benzyl bromide (17.68 g, 100 mmol), NaCN (7.35 g, 150 mmol), and tetrabutylammonium bromide (0.4 g) in water (30 mL) was then heated under reflux at 120°C for 8 h, 2-[$^2H_7$]phenylacetonitrile (10.1 g, 80.1%) was collected from the dark solution by steam distillation. 5-[$^2H_7$]benzyl-1*H*-tetrazole (**III**) was obtained following the method described for **II**. The crystals that formed were collected by filtration and recrystallized from 95% ethanol in 91.3% yield. m.p.: 256–258°C. Anal. calcd. for $C_8HD_7N_4$: [%] C, 57.46; H, 9.03; N, 33.51; Found: [%] C, 57.12; H, 9.24; N, 33.64; IR (KBr, cm^{-1}): 2950.3(br, m), 2861.4(m), 2775.9(m), 2701.7(m), 2596.5(m), 2271.8(m), 1801.2(br, w), 1530.0(s), 1427.6(s), 1380.7(m), 1365.5(w), 1340.8(w), 1251.8(s), 1241.3(s), 1167.6(w), 1109.0(m), 1075.6(s), 1057.6(s), 1039.1(w), 999.8(s), 900.9 (s), 820.9(m), 577.1(m), 538.0(s), 423.2(s); δ_C (300 MHz; $CDCl_3$) 28.87 (Ar-CD_2), 134.9 (C-3), 128.2 (C-4 and C-8), 127.9 (C-5 and C-7), 126.6 (C-6), 155.8 (C-1); *m/z* (-ve ion electrospray) $[M-H]^-$ $C_8D_7N_4$ required 166.23, found 166.29.

X-ray crystallography

Data collection: *CrystalClear* (Rigaku, 2005); cell refinement: *CrystalClear* (Rigaku, 2005); data reduction: *CrystalClear* (Rigaku, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: Bruker *SHELXTL* (Sheldrick, 1999); Software used to prepare material for publication: Bruker *SHELXTL* (Sheldrick, 1999).

Crystal data for 1

$M_r = 151.19$; orthorhombic; *Ama2*; $a = 9.81(2)$, $b = 15.26(4)$, $c = 4.544(10)$Å; $V = 680(3)$Å^3; $Z = 4$; $D_{calcd} = 1.476$ Mg.m^{-3}; $R_1 = 0.0552$; $wR_2 = 0.1281$; $T = 293$ K; $\mu = 0.096$ mm^{-1}; $S = 1.127$.

Crystal data for 2

$M_r = 167.23$; orthorhombic; *Pbcm*; $a = 4.5376(9)$, $b = 17.715(4)$, $c = 9.771(2)$Å; $V = 785.4(3)$Å^3; $Z = 4$; $D_{calcd} = 1.414$ Mg.m^{-3}; $R_1 = 0.0769$; $wR_2 = 0.1555$; $T = 293$ K; $\mu = 0.089$ mm^{-1}; $S = 1.096$.

Crystal data for 3

$M_r = 167.23$; monoclinic; $P2_1/c$; $a = 8.620(13)$, $b = 9.906(14)$, $c = 9.500(13)$Å; $\beta = 91.49(3)$; $V = 811(2)$Å^3; $Z = 4$; $D_{calcd} = 1.370$ Mg.m^{-3}; $R_1 = 0.0497$; $wR_2 = 0.1223$; $T = 293$ K; $\mu = 0.087$ mm^{-1}; $S = 0.994$.

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