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A convenient synthesis of functionalized *N*-(ethynyl)benzotriazoles

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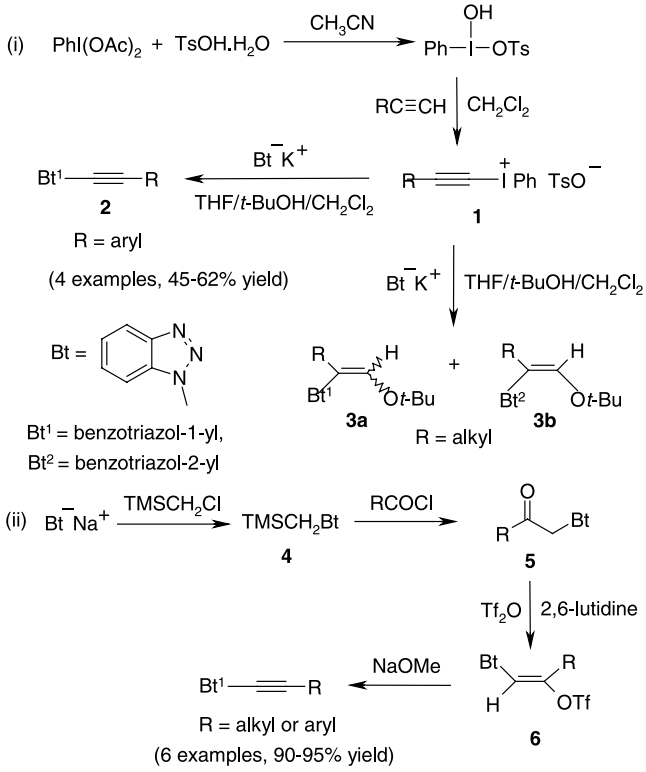
Abstract—1-(2,2-Dichlorovinyl)benzotriazole (**7**) was prepared by the reaction of 1-formylbenzotriazole with PPh_3/CCl_4. Lithiation–substitution of **7** with electrophiles gave a variety of functionalized *N*-(ethynyl)benzotriazoles **8a**–**h** in 32–84% yields.

1. Introduction

The carbon–carbon triple bond plays an important part in the preparation of compounds ranging from enediyne antitumor antibiotics to molecular electronics.[1] Acetylenes have been regarded as one of the key synthetic, structural, and functional tools of future chemistry[2] and *N*-(ethynyl)-benzotriazoles are versatile reagents for the synthesis of disubstituted acetylenes,[3a] esters,[3b] and carboxylic acids.[3c]

Previously reported methods for the direct introduction of a CC-triple bond on the nitrogen atom of 1*H*-benzotriazole involve (i) use of hypervalent iodine chemistry[4] in reactions of alkynylphenyliodonium tosylates with potassium benzotriazolate[5] or (ii) base treatment of benzotriazolyl enol triflates.[3b,c] The first method requires preparation of hypervalent iodonium salts **1**[4b] and is limited to the preparation of *N*-(arylethynyl)benzotriazoles **2**; attempted preparations of *N*-(alkylethynyl)benzotriazoles are reported to give mixtures of (*E*)- and (*Z*)-1-vinyl-1*H*-benzotriazoles **3a** and (*Z*)-2-vinyl-2*H*-benzotriazole **3b** as the main products.[5a] The second method proceeds through 1-(trimethylsilylmethyl)benzotriazole (**4**), *N*-acylbenzotriazoles **5** and benzotriazolyl enol triflates **6**, which on further treatment with base give *N*-(arylethynyl)- or *N*-(alkylethynyl)benzotriazoles (Scheme 1).[3c]



Scheme 1.

Corey and Fuchs introduced the well-known conversion of aldehydes to alkynes in 1972, and this method has been widely used in many synthetic protocols.[6] In a similar approach, we have devised a direct preparation of *N*-(ethynyl)benzotriazoles **8a**–**h** starting from commercially available 1-formylbenzotriazole. Treatment of 1-formylbenzotriazole with PPh_3/CCl_4 gave 1-(2,2-dichlorovinyl)-benzotriazole (**7**), which on subsequent lithiation–

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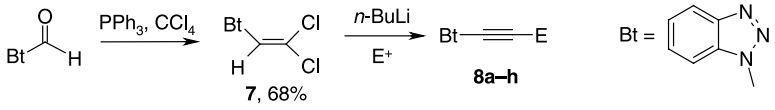
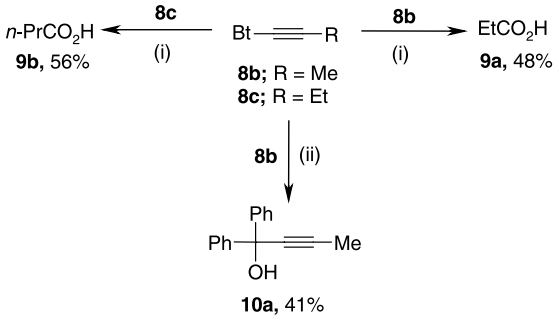
Table 1. Preparation of *N*-(ethynyl)benzotriazoles **8a–h**



Entry	Electrophile (E^+)	E	Product (% yield)[a]
1	MeOH	H	**8a** (73)
2	MeI	Me	**8b** (84)
3	EtI	Et	**8c** (58)
4	Me_3SiCl	Me_3Si	**8d** (82)
5	Ph_2CO	$Ph_2C(OH)$	**8e** (84)
6	Me_2CO	$Me_2C(OH)$	**8f** (71)
7	PhCHO	PhCH(OH)	**8g** (32)
8	*trans*-Chalcone	PhCH=CHC(OH)Ph	**8h** (43)

[a] Isolated yield.



(i) (a) *p*-TSA in CH_3CN, reflux, (b) TBAF in THF, reflux; (ii) Lithium naphthalenide in THF, Ph_2CO, -78 °C.

Scheme 2.

substitution with a range of electrophiles gave *N*-(ethynyl)benzotriazoles **8a–h**.

2. Results and discussion

Reaction of 1-formylbenzotriazole with PPh_3 and CCl_4 under Corey–Fuchs conditions[6] gave 1-(2,2-dichlorovinyl)-benzotriazole (**7**) in 68% yield as a crystalline solid. The ^1H NMR spectrum of **7** showed the vinylic proton at 7.69 ppm as a singlet, and the ^{13}C NMR spectrum showed the disappearance of the carbonyl signal at 159.7 ppm and the appearance of additional signals at 125.1 and 121.5 ppm due to the vinylic moiety. Subsequent treatment of **7** with 2 equiv of *n*-BuLi at −78 °C in THF for 1 h and reaction with a variety of electrophiles gave the corresponding *N*-(ethynyl)benzotriazoles **8a–h** in good yields (Table 1).

1-(2,2-Dichlorovinyl)benzotriazole (**7**) and *N*-(ethynyl)-benzotriazoles **8a–h**, except **8b**, are novel compounds and were characterized by their ^1H and ^{13}C NMR spectra and elemental analysis. As expected, the ^1H NMR spectra of *N*-(ethynyl)benzotriazoles **8a–h** revealed the disappearance of the vinylic proton at 7.69 ppm and appearance of additional signals from the newly attached substituent. In the ^{13}C NMR spectra, the signals from vinylic carbons at 121.5 and 125.1 ppm were replaced by new signals corresponding to the acetylenic carbons. The signals from benzotriazolyl moiety in all of the benzotriazolylacetylenes **8a–h** experienced a negligible change in the chemical shift values from those in the ^1H and ^{13}C NMR spectra of the precursor 1-(2,2-dichlorovinyl)benzotriazole (**7**).

Treatment of **8b**,**c** with *p*-toluenesulfonic acid followed by hydrolysis using TBAF gave carboxylic acids **9a**,**b** in 48 and 56% yields, respectively. Also, reaction of **8b** with benzophenone in presence of lithium naphthalenide furnished propargyl alcohol **10a** in 41% yield (Scheme 2).

In summary, a general method has been introduced for a short synthesis of functionalized *N*-(ethynyl)benzotriazoles starting from commercially available 1-formylbenzotriazole in overall two steps. It has also been shown that functionalized *N*-(ethynyl)benzotriazoles can be used to prepare carboxylic acids and propargyl alcohols.

3. Experimental

3.1. General

Melting points are uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ (with TMS for ^1H and chloroform-*d* for ^{13}C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument. THF was distilled from sodium/benzophenone prior to use. All of the reactions were carried out under N_2. Column chromatography was performed on silica gel 200–425 mesh.

1-Formylbenzotriazole was prepared according to the published procedure.[7]

3.1.1. Procedure for the preparation of 1-(2,2-dichlorovinyl)-1*H*-1,2,3-benzotriazole (7). 1-Formylbenzotriazole (1.0 g, 6.80 mmol) and PPh_3 (5.35 g, 20.4 mmol) were dissolved in THF (70 mL). Carbon tetrachloride (7 mL, 68 mmol) was added slowly at 60 °C and the mixture was heated under reflux for 6 h. After stirring for an additional hour, the mixture was diluted with ethyl acetate. Aqueous work-up with satd $NaHCO_3$ and purification by flash column chromatography on silica gel using hexanes–EtOAc (9.5/0.5) as eluent afforded **7** (1.0 g, 68%).

3.1.1.1. 1-(2,2-Dichlorovinyl)-1*H*-1,2,3-benzotriazole (7). Yellow microcrystals (from hexanes); mp 88–90 °C; yield, 68%; ^{1}H NMR δ 7.43–7.48 (m, 1H), 7.53–7.62 (m, 2H), 7.69 (s, 1H), 8.12 (d, J=8.4 Hz, 1H); ^{13}C NMR δ 110.1, 120.4, 121.5, 124.7, 125.1, 128.6, 132.2, 145.2. Anal. Calcd for $C_8H_5Cl_2N_3$: C, 44.89; H, 2.35; N, 19.63. Found: C, 45.09; H, 2.25; N, 19.28.

3.1.2. General procedure for the preparation of benzotriazolylacetylenes 8a–h by lithiation–electrophilic substitution of 7. To a solution of **7** (0.22 g, 1 mmol) in dry THF (20 mL) at −78 °C, was added *n*-BuLi (1.33 mL, 2.1 mmol, 1.6 M). The mixture was stirred at −78 °C for 1 h and an appropriate electrophile (1.0 mmol) was added. The reaction mixture was allowed to warm to 25 °C and quenched by adding water. Aqueous work-up and purification by flash column chromatography on silica gel using hexanes–EtOAc (9/1) as eluent afforded **8a**–**h**.

3.1.2.1. 1-Ethynyl-1*H*-1,2,3-benzotriazole (8a). Yellow prisms (from hexanes); mp 71–72 °C; yield, 73%; ^{1}H NMR δ 3.86 (s, 1H), 7.44–7.49 (m, 1H), 7.61–7.69 (m, 2H), 8.11 (d, J=8.4 Hz, 1H); ^{13}C NMR δ 68.6, 69.4, 109.9, 120.5, 125.4, 129.6, 134.2, 143.6. Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.35. Found: C, 66.76; H, 3.39; N, 29.67.

3.1.2.2. 1-(1-Propynyl)-1*H*-1,2,3-benzotriazole (8b).[3b] Colorless oil; yield, 84%; ^{1}H NMR δ 2.22 (s, 3H), 7.38–7.43 (m, 1H), 7.54–7.64 (m, 2H), 8.06 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 3.4, 66.7, 76.2, 109.8, 120.0, 124.8, 128.8, 134.1, 143.5.

3.1.2.3. 1-(1-Butynyl)-1*H*-1,2,3-benzotriazole (8c). White microcrystals (from hexanes); mp 44 °C; yield, 58%; ^{1}H NMR δ 1.35 (t, J=7.5 Hz, 3H), 2.61 (q, J=7.5 Hz, 2H), 7.41–7.46 (m, 1H), 7.57–7.68 (m, 2H), 8.09 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 12.4, 13.5, 67.3, 81.7, 110.0, 120.3, 125.0, 129.0, 134.3, 143.7. Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30. Found: C, 70.48; H, 5.65.

3.1.2.4. 1-[2-(Trimethylsilyl)ethynyl]-1*H*-1,2,3-benzotriazole (8d). Yellow oil; yield 82%; ^{1}H NMR δ 0.48 (s, 9H), 7.50–7.62 (m, 1H), 7.68–7.86 (m, 2H), 8.21 (d, J=8.4 Hz, 1H); ^{13}C NMR (major peaks) δ −0.4, 83.6, 87.3, 110.0, 120.3, 125.2, 129.3, 134.0, 143.5. HRMS calcd for $C_{11}H_{14}N_3Si$ $[M+H]^+$216.0952, found: 216.0956.

3.1.2.5. 3-(1*H*-1,2,3-Benzotriazol-1-yl)-1,1-diphenyl-2-propyn-1-ol (8e). White needles (from EtOAc/hexanes); mp 125–126 °C; yield, 84%; ^{1}H NMR δ 3.72 (s, 1H), 7.30–7.39 (m, 7H), 7.42–7.58 (m, 2H), 7.69–7.71 (m, 4H), 8.02 (d, J=8.1 Hz, 1H); ^{13}C NMR δ 74.0, 74.8, 82.9, 109.9, 120.3, 125.3, 126.0, 128.0, 128.4, 129.4, 134.2, 143.5, 144.0. Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.29; H, 4.69; N, 12.82.

3.1.2.6. 4-(1*H*-1,2,3-Benzotriazol-1-yl)-2-methyl-3-butyn-2-ol (8f). Light yellow oil; yield, 71%; ^{1}H NMR δ 1.75 (s, 3H), 1.76 (s, 3H), 2.90 (s, 1H), 7.42–7.46 (m, 1H), 7.47–7.65 (m, 2H), 8.09 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 31.3, 65.6, 69.7, 84.4, 110.0, 120.5, 125.3, 129.4, 134.2, 143.8. Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.38; H, 5.53; N, 20.63.

3.1.2.7. 3-(1*H*-1,2,3-Benzotriazol-1-yl)-1-phenyl-2-propyn-1-ol (8g). Light yellow oil; yield, 32%; ^{1}H NMR δ 3.61 (s, 1H), 5.91 (s, 1H), 7.35–7.44 (m, 4H), 7.53–7.66 (m, 4H), 8.05 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 64.6, 73.2, 80.2, 110.0, 120.4, 125.4, 126.6, 128.7, 128.8, 129.5, 134.1, 139.5, 143.6. Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45. Found: C, 72.21; H, 5.03.

3.1.2.8. (*E*)-5-(1*H*-1,2,3-Benzotriazol-1-yl)-1,3-diphenyl-1-penten-4-yn-3-ol (8h). White microcrystals (from hexanes); mp 138–140 °C; yield, 43%; ^{1}H NMR δ 3.34 (br s, 1H), 6.52 (d, J=15.8 Hz, 1H), 7.07 (d, J=15.8 Hz, 1H), 7.23–7.45 (m, 9H), 7.50–7.62 (m, 2H), 7.77–7.80 (m, 2H), 8.10 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 73.3, 74.3, 81.3, 110.0, 120.5, 125.4, 125.7, 127.0, 128.2, 128.4, 128.6, 128.6, 129.6, 130.0, 131.8, 134.3, 135.7, 142.5, 143.8. HRMS calcd for $C_{23}H_{17}N_3ONa$ $[M+Na]^+$372.1264, found: 374.1272.

3.1.3. General procedure for the preparation of carboxylic acids 9a,b. To a solution of **8b**,**c** (1 mmol) in acetonitrile (10 mL) was added *p*-toluenesulfonic acid monohydrate (0.20 g, 1 mmol) at room temperature. The reaction mixture was stirred under reflux for 8 h. The resulting mixture was concentrated in vacuo to dryness and the residue was treated with TBAF (1.2 mL, 1.2 mmol, 1 M) in THF (10 mL) under reflux for 10 h. The reaction mixture was diluted with diethyl ether and washed with 1 N HCl. Evaporation of the solvent gave a residue, which was purified by flash column chromatography on silica gel using hexanes–EtOAc (9/1) as eluent to give **9a**,**b**.

3.1.3.1. Propionic acid (9a).[8] Colorless oil; yield, 48%; ^{1}H NMR δ 1.16 (t, J=7.6 Hz, 3H), 2.39 (q, J=7.6 Hz, 2H), 10.9 (br s, 1H); ^{13}C NMR δ 8.8, 27.4, 181.0.

3.1.3.2. *n*-Butyric acid (9b)[9] Colorless oil; yield, 56%; ^{1}H NMR δ 0.98 (t, J=7.4 Hz, 3H), 1.61–1.73 (m, 2H), 2.34 (t, J=7.3 Hz, 2H), 11.0 (br s, 1H); ^{13}C NMR δ 13.6, 18.1, 35.9, 180.2.

3.1.4. Procedure for the preparation of propargyl alcohol 10a. A mixture of lithium powder (0.070 g, 10 mmol) and naphthalene (1.28 g, 10 mmol) in THF (20 mL) was stirred at 25 °C until a dark green color appeared. The suspension of lithium naphthalenide thus formed was cooled to −78 °C and **8b** (0.35 g, 2.1 mmol) was added. The reaction mixture was stirred at −78 °C for

2 h before adding benzophenone (0.36 g, 2.1 mmol). The mixture was allowed to warm to 25 °C and stirred overnight. Aqueous work up followed by flash column chromatography on silica gel using hexanes–EtOAc (9/1) as eluent gave **10a**.

3.1.4.1. 1,1-Diphenyl-2-butyn-1-ol (10a)[10] Colorless oil; yield, 41%; ^{1}H NMR δ 1.93 (s, 3H), 2.81 (s, 1H), 7.19–7.32 (m, 6H), 7.57–7.60 (m, 4H); ^{13}C NMR δ 3.8, 74.4, 82.1, 83.6, 126.0, 126.8, 127.4, 128.1, 128.2, 128.3, 128.5, 129.3, 129.5, 145.4.

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