Nucleophilic Substitution of Benzotriazolylalkyl Chlorides with Grignard Reagents: A Direct Route to Benzotriazoloalkyl(hetero)aromatic Compounds

Alan R. Katritzky,* Ashraf A. A. Abdel-Fattah, Dmytro O. Tymoshenko, Sergei A. Belyakov

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611–7200, USA
Fax +1(352)3929199; E-mail: KATRITZKY@chem.ufl.edu

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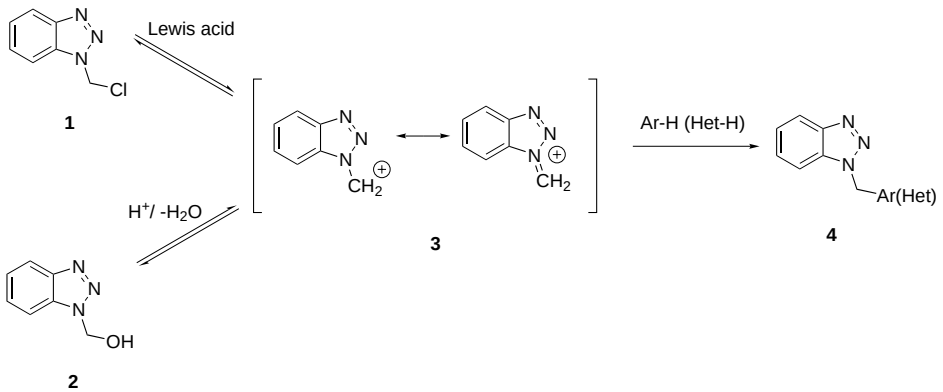
Abstract: Benzotriazolylalkyl chlorides **5** react with (hetero)aromatic Grignard reagents generated from the corresponding halogen derivatives to afford benzotriazoloalkyl(hetero)aromatic compounds **8a–k** and **10a–c** in good yields.

Key words: benzotriazolylalkyl chlorides, Grignard reagents, synthesis, benzotriazoloalkyl(hetero)aromatics

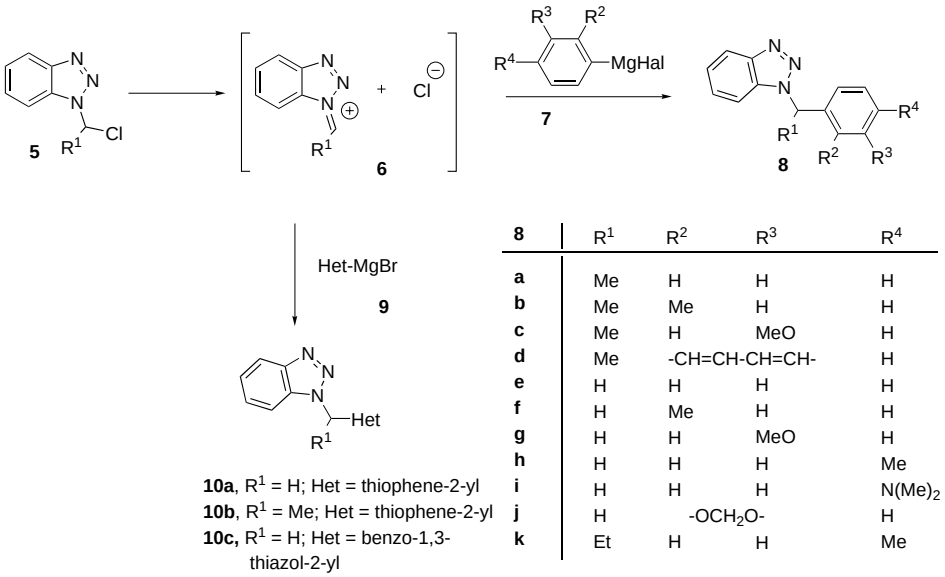
Many synthetically useful *N*-substituted benzotriazoles are of type Bt-C-X, where X is halogen,[1,2] amino-nitrogen,[3,4] amido-nitrogen,[5] oxygen[6] or sulfur.[7] Such adducts can react further either by Bt–C bond scission to form alkyleneonium cations or by C–X bond scission to give alkylenebenzotriazolium intermediates **3** (Scheme 1). Species **3** are normally generated from α-haloalkylbenzotriazoles (*cf.* **1**)[8] in the presence of Lewis acids or alternatively from *N*-(α-hydroxyalkyl)benzotriazoles (*cf.* **2**)[9] with Brønsted acids. However, these methods for the generation of the benzotriazolyl-stabilized cation **3** have some limitations. Even with electron-rich (hetero)aromatic systems[9,10] some product **4** yields were moderate. Acidic catalysts can dehydrohalogenate *N*-(α-haloalkyl)benzotriazoles derived from aldehydes containing an α-hydrogen.[11] The much greater leaving ability of chloride, as compared to the benzotriazolyl anion,[12] suggested that reactions of *N*-(α-haloalkyl)benzotriazoles with organometallic carbanionic species (Scheme 2) should lead to benzotriazolyl-C-(hetero)aromatics **8**,**10** via normal nucleophilic substitution as previously demonstrated for many nucleophiles.[13]

N-(α-Haloalkyl)benzotriazoles **5** were readily obtained according to the procedure reported earlier.[1] We find that the nature of the metal in the organometallic reagent determines the course of the reaction. Thus, *N*-chloromethylbenzotriazole with the strongly basic lithio-thiophene and -benzo[*b*]thiophene gave deep blue reaction mixtures (characteristic of α-benzotriazolyl anions) and formed complex product mixtures (perhaps via carbene species) with no detectible benzotriazoloalkyl(hetero)aromatics. The simultaneous activation of α-CH in **8**,**10** by both the benzotriazole ring and the (hetero)aromatic ring will facilitate deprotonation, as illustrated by syntheses of triarylcyclopropanes,[14] diarylacetylenes,[15] alkenes and dienes[16] and substituted heteroaromatics,[17] recently elaborated by our group. The less reactive analogous organozinc, organocerium and silyl derivatives of benzo[*b*]thiophene caused neither deprotonation nor any other reaction.

However, the reactions of *N*-(α-haloalkyl)benzotriazoles **5** with Grignard reagents (Scheme 2), freshly prepared from the corresponding aryl halide and Mg turnings, in anhydrous THF led to the desired benzotriazoloalkyl aromatic compounds **8a–k** in good yields. Significantly, this methodology could be extended to the benzotriazoloalkyl(hetero)aromatics **8a–d**, **k** derived from aldehydes other than formaldehyde. In particular, this sequence allowed the syntheses of benzotriazole-substituted compounds **8a–d** (R^1 = Me) and **8k** (R^1 = Et), de-



Scheme 1



8	R^1	R^2	R^3	R^4
a	Me	H	H	H
b	Me	Me	H	H
c	Me	H	MeO	H
d	Me	-CH=CH-CH=CH-		H
e	H	H	H	H
f	H	Me	H	H
g	H	H	MeO	H
h	H	H	H	Me
i	H	H	H	$N(Me)_2$
j	H	-OCH_2O-		H
k	Et	H	H	Me

Scheme 2

rived from aldehydes other then formaldehyde, and acid sensitive **8j**, which are difficult to obtain using the methods described earlier.[8,9] Our attempted reaction of 1-(1-chloro-2-methylpropyl)-1*H*-1,2,3-benzotriazole (**5**, R^1 = *i*-Pr) with phenyl and *o*-tolylmagnesium bromide afforded 1-(2-methylprop-1-enyl)-1*H*-1,2,3-benzotriazole in 60% and 63% yields, respectively, because of the competing dehydrochlorination reaction, which was already reported for *N*-(α-haloalkyl)benzotriazoles derived from aldehydes containing an α-hydrogen.[11] Although 1-(1-chloro-2,2-dimethylpropyl)-1*H*-1,2,3-benzotriazole **5** (R^1 = *t*-Bu) was stable to dehydrochlorination, the nucleophilic substitution with phenyl, *o*-tolyl and methylmagnesium bromide did not occur, perhaps because of steric hindrance of the electrophile.

These results were further extended by treatment of **5** with heterocyclic Grignard reagents under the same conditions to yield heteroaromatics **10a–c** (Scheme 2). Compounds **10a,b** were obtained smoothly with no dehydrochlorination products being detected for **10b**, although it is derived from an aldehyde with an α-hydrogen. Compound **10b** was prone to isomerization and was isolated, according to ^{1}H and ^{13}C NMR, as a mixture of 1- and 2-benzotriazolyl derivatives in a 5:1 ratio. The generation of Grignard type heterocyclic carbanions with strongly basic species (transmetalation of lithiated benzothiaphene, benzothiazole and indole was performed with $MgBr_2{\cdot}Et_2O$ or by treatment with EtMgBr or *i*-PrMgCl) did not afford benzotriazoloalkyl heteroaromatics, probably because of deprotonation. The utility of less nucleophilic magnesium diisopropylamide gave compound **10c** in low yield, which could be explained by the instability of thiazole derived anions.[18]

In conclusion, we have described a general method for the synthesis of compounds of types **8** and **10** which are valuable intermediates for benzannulation reactions[19] and for the introduction of complex C-linked substituents into aromatic and heteroaromatic ring systems.[13]

Mps were measured with a Kofler hot stage apparatus without correction. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini (300 MHz) spectrometer in $CDCl_3$ with TMS as the internal standard. Elemental analyses were performed using a Carlo Erba 1106 elemental analyzer.

1-Aryl(heteryl)alkylbenzotriazoles 8a–k and 10a,b; General Procedure

To a solution of arylmagnesium bromide **7** for **8a–k** (4 mmol), or 2-thienylmagnesium bromide (**9**) for **10a,b**, in Et_2O (50 mL) (freshly prepared from aryl bromide or 2-thienyl bromide and Mg turnings) was added dropwise a solution of 1-chloroalkylbenzotriazole (4 mmol) in THF under N_2. The solution was heated under reflux for 3 h. The mixture was cooled to r.t. and poured into ice/H_2O (100 mL). HOAc (5 mL) was added, and the whole was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with 20% aq $NaHCO_3$ (2 x 40 mL) and then H_2O, until the aqueous layer remained at pH = 7. The ethereal solution was dried ($MgSO_4$) and evaporated in vacuo to give the crude product as an oil, which was subjected to column chromatography (silica gel, CH_2Cl_2/hexanes, 4:1) to give the products **8a–k** or **10a,b**.

1-(1-Phenylethyl)-1*H*-1,2,3-benzotriazole (8a)

Prism-shaped crystals; mp 59–60 °C; yield: 0.57 g (64%).

^{1}H NMR: δ = 8.1 (d, 1H, *J* = 4.2 Hz), 7.36–7.19 (m, 8H), 6.08 (q, 1H, *J* = 7.1 Hz), 2.22 (d, 3H, *J* = 3.2 Hz).

^{13}C NMR: δ = 146.2, 140.1, 132.7, 128.9, 128.3, 128.1, 126.3, 123.8, 119.9, 110.1, 59.0, 21.1.

$C_{14}H_{13}N_3$	calcd	C	75.31	H	5.87	N	18.82
(223.28)	found		75.17		5.87		18.99

1-[1-(2-Methylphenyl)ethyl]-1*H*-1,2,3-benzotriazole (8b)
Prism-shaped crystals; mp 83–85 °C; yield: 0.64 g (68%).

^{1}H NMR: δ = 8.06 (d, 1H, *J* = 4.1 Hz), 7.37–7.11 (m, 8H), 6.26 (q, 1H, *J* = 7.1 Hz), 2.35 (s, 3H), 2.15 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR: δ = 146.2, 137.7, 135.3, 132.3, 130.9, 128.2, 126.9, 126.6, 125.9, 123.8, 119.8, 110.0, 56.1, 20.4, 19.0.

$C_{15}H_{15}N_3$	calcd	C	75.90	H	6.37	N	17.71
(237.3)	found		75.86		6.36		17.81

1-[1-(3-Methoxyphenyl)ethyl]-1*H*-1,2,3-benzotriazole (8c)
Light-yellow oil; yield: 0.57 g (56%).

^{1}H NMR: δ = 8.08 (d, 1H, *J* = 6.6 Hz), 7.41–7.25 (m, 4H), 6.92–6.84 (m, 3H), 6.04 (q, 1H, *J* = 5.8 Hz), 3.82 (s, 3H), 2.20 (d, 3H, *J* = 7.1 Hz).

^{13}C NMR: δ = 160.0, 141.7, 129.9, 127.6, 127.0, 123.8, 119.9, 118.5, 114.2, 113.3, 112.2, 110.1, 59.0, 55.2, 21.0.

$C_{15}H_{15}N_3O$	calcd	C	71.11	H	5.97	N	16.60
(253.3)	found		71.07		6.37		16.59

1-[1-(1-Naphthyl)ethyl]-1*H*-1,2,3-benzotriazole (8d)
Plate-shaped crystals; mp 111–113 °C; yield: 0.72 g (66%).

^{1}H NMR: δ = 8.15 (d, 1H, *J* = 7.5 Hz), 8.04 (d, 1H, *J* = 7.7 Hz), 7.89–7.83 (m, 2H), 7.51–7.41 (m, 4H), 7.26–7.21 (m, 2H), 7.10–7.07 (m, 1H), 6.88 (q, 1H, *J* = 6.9 Hz), 2.30 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR: δ = 146.1, 134.8, 133.5, 132.1, 130.2, 128.8, 128.0, 126.6, 125.6, 124.9, 124.3, 123.6, 123.5, 121.9, 119.4, 109.9, 55.5, 20.3.

$C_{18}H_{15}N_3$	calcd	C	79.10	H	5.53	N	15.37
(273.13)	found		78.70		5.68		15.47

1-Benzyl-1*H*-1,2,3-benzotriazole (8e)
Prism-shaped crystals; mp 115–117 °C (Lit.[8] 114–115 °C); yield: 0.59 g (71%).

^{1}H NMR: δ = 8.08 (d, 1H, *J* = 8.0 Hz), 7.44–7.27 (m, 8H), 5.85 (s, 2H).

^{13}C NMR: δ = 146.2, 134.7, 132.7, 128.9, 128.3, 127.4, 127.3, 123.8, 119.9, 109.6, 52.1.

1-(2-Methylbenzyl)-1*H*-1,2,3-benzotriazole (8f)
Prism-shaped crystals; mp 87–89 °C (Lit.[20] 87 °C); yield: 0.60 g (67%).

^{1} H NMR: δ = 8.11 (d, 1H, *J* = 7.2 Hz), 7.42–7.17 (m, 6H), 7.08 (d, 1H, *J* = 7.4 Hz), 5.88 (s, 2H), 2.38 (s, 3H).

^{13}C NMR: δ = 146.2, 136.5, 132.9, 132.5, 130.9, 128.6, 128.5, 127.3, 126.4, 123.8, 120.0, 109.8, 50.7, 19.2.

$C_{14}H_{13}N_3$	calcd	C	75.31	H	5.87	N	18.82
(223.28)	found		75.21		5.96		19.07

1-(3-Methoxybenzyl)-1*H*-1,2,3-benzotriazole (8g)
Prism-shaped crystals; mp 52–54 °C; yield:0.58 g (60%).

^{1}H NMR: δ = 8.09 (d, 1H, *J* = 8.2 Hz), 7.43–7.36 (m, 3H), 7.27 (t, 1H, *J* = 7.9 Hz), 6.86 (m, 3H), 5.83 (s, 2 H), 3.76 (s, 3H).

^{13}C NMR: δ = 160.0, 146.2, 136.2, 132.7, 130.0, 127.3, 123.8, 119.9, 119.7, 113.8, 113.2, 109.7, 55.2, 52.1.

$C_{14}H_{13}N_3O$	calcd	C	70.26	H	5.48	N	17.57
(239.11)	found		70.19		5.55		17.75

1-(4-Methylbenzyl)-1*H*-1,2,3-benzotriazole (8h)
Prism-shaped crystals; mp 107–109 °C (Lit.[20] 108–109 °C); yield: 0.63 g (70%).

^{1}H NMR: δ = 8.07 (d, 1H, *J* = 8.0 Hz), 7.40–7.33 (m, 3H), 7.19 (d, 2 H, *J* = 8.0 Hz), 7.13 (d, 2 H, *J* = 8.2 Hz), 5.81 (s, 2 H), 2.32 (s, 3 H).

^{13}C NMR: δ = 146.1, 138.3, 132.4, 131.7, 129.6, 127.6, 127.3, 123.8, 120.0, 109.8, 52.1, 21.1.

$C_{14}H_{13}N_3$	calcd	C	75.31	H	5.87	N	18.82
(223.28)	found		75.15		5.85		19.03

4-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-*N*,*N*-dimethylaniline (8i)
Prism-shaped crystals; mp 166–168 °C (Lit.[21] 167–168.5 °C); yield: 0.66 g (65%).

^{1}H NMR: δ = 8.05 (d, 1H, *J* = 7.9 Hz), 7.39–7.29 (m, 3H), 7.21 (d, 2H, *J* = 8.0 Hz), 6.68 (s, 1H), 6.67 (d, 1H, *J* = 7.9 Hz), 5.74 (s, 2H), 2.93 (s, 6H).

^{13}C NMR: δ = 150.4, 146.3, 132.7, 128.9, 127.0, 123.6, 122.0, 119.8, 112.4, 110.0, 52.2, 40.3.

$C_{15}H_{16}N_4$	calcd	N	22.21				
(223.28)	found		22.06				

1-(1,3-Benzodioxol-4-ylmethyl)-1*H*-1,2,3-benzotriazole (8j)
Prism-shaped crystals; mp 128–130 °C; yield: 0.71 g (70%).

^{1}H NMR: δ = 8.09–8.05 (m, 1H), 7.41–7.34 (m, 3H), 6.83–6.75 (m, 3H), 5.94 (s, 2H), 5.75 (s, 2H).

^{13}C NMR: δ = 148.2, 147.8, 146.3, 132.6, 128.4, 127.3, 123.9, 121.3, 120.0, 109.7, 108.4, 108.1, 101.3, 52.1.

$C_{14}H_{11}N_3O_2$	calcd	C	66.39	H	4.39	N	16.60
(253.26)	found		66.44		4.46		16.67

1-[1-(4-Methylphenyl)propyl]-1*H*-1,2,3-benzotriazole (8k)
Plates; mp 47–49 °C: yield: 0.58 g (57%).

^{1}H NMR: δ = 8.04 (d, 1H, *J* = 8.0 Hz), 7.37–7.28 (m, 3H), 7.25 (d, 2H, *J* = 7.7 Hz), 7.11 (d, 2H, *J* = 7.6 Hz), 5.67 (t, 1H, *J* = 7.2 Hz), 2.81–2.72 (m, 1H), 2.55–2.46 (m, 1H), 2.28 (s, 3H), 0.95 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR: δ = 146.19, 138.0, 136.1, 132.7, 129.4, 126.9, 126.7, 123.7, 119.9, 109.9, 65.2, 27.9, 21.0, 11.3.

$C_{16}H_{17}N_3$	calcd	C	76.46	H	6.82	N	16.72
(251.33)	found		76.66		7.12		16.82

1-(Thien-2-ylmethyl)-1*H*-1,2,3-benzotriazole (10a)
Prism-shaped crystals; mp 101–103 °C (Lit.[22] 103–104 °C); yield:0.59 g (69%).

^{1}H NMR: δ = 8.06 (d, 1H, *J* = 8.4 Hz), 7.47–7.35 (m, 3H), 7.25 (s, 1H), 7.11 (d, 1H, *J* = 3.1 Hz), 6.98–6.96 (m, 1H), 6.0 (s, 2H).

^{13}C NMR: δ = 146.2, 136.6, 132.6, 127.4, 127.1, 126.4, 123.9, 119.8, 109.5, 46.8.

$C_{11}H_9N_3S$	calcd	C	61.37	H	4.22		
(215.28)	found		61.80		4.41		

1-[1-(Thien-2-yl)ethyl]-1*H*-1,2,3-benzotriazole (10b) and its 2*H*-Isomer
Prism-shaped crystals; mp 65–67 °C; yield:0.62 g (68%).

^{1}H NMR: δ = 8.08 (d, *J* = 8.0 Hz, 1H), 7.44–7.32 (m, 3H), 7.29–7.25 (m, 1H), 7.06 (s, 1H), 6.99–6.95 (m, 1H), 6.44 (q, *J* = 6.9 Hz, 1H), 6.26 [(q, *J* = 6.9 Hz)], 2.22 (d, *J* = 7.2 Hz, 3H) [2.15 (d, *J* = 7.2 Hz)].

^{13}C NMR: δ = 146.5, 142.9, 131.8, 127.1 [127.0], 126.9 [126.3], 125.7, 125.5, 123.9 [120.1], 120.0, 110.2, 54.8 [55.1], 21.5 [20.7].

$C_{12}H_{11}N_3S$	calcd	N	18.32				
(229.31)	found		18.30				

1-(1,3-Benzothiazol-2-ylmethyl)-1*H*-1,2,3-benzotriazole (10c)
Under N_2, diisopropylamine (0.404 g, 4 mmol) was added to a mixture of 1.0 M dibutylmagnesium in heptane (2 mL, 2 mmol) and anhyd THF (5 mL). The mixture was stirred at r.t. for 5 h. Benzothiazole (0.54 g, 4 mmol) was added to the mixture, and stirring was continued at r.t. for 3 h. *N*-Chloromethylbenzotriazole (0.67 g, 4 mmol) in anhyd THF (10 mL) was added, and the mixture was stirred at r.t. for 12 h. and then at boiling temperature for 4 h. The mixture was cooled to r.t., poured into an ice/H_2O mixture (100 mL) and treated with HOAc (5 mL); the whole was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with 20% aq $NaHCO_3$ (2 x 40 mL) and then H_2O, until the aqueous layer remained at pH = 7. The ethereal solution was dried anhyd ($MgSO_4$) and evaporated in vacuo to give the crude product as an oil, which was subjected to column chromatography (silica gel, CH_2Cl_2/hexanes, 3:2) to give the product **10c** (0.16 g, 15%) as prism-shaped crystals; mp 122–123 °C.

^{1}H NMR: δ = 8.13–8.06 (m, 2H), 7.83–7.81 (d, 1H, *J* = 8.0 Hz), 7.64–7.52 (m, 1H), 7.50–7.47 (m, 2H), 7.44–7.30 (m, 2H), 6.29 (s, 2H).

^{13}C NMR: δ = 164.0, 152.7, 146.2, 135.5, 132.8, 128.0, 126.5, 125.8, 124.3, 123.4, 121.8, 120.1, 109.6, 50.1.

$C_{14}H_{10}N_4S$	calcd	C	63.13	H	3.79	N	21.04
(266.33)	found		63.09		3.77		20.95

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