Synthesis Of 1-(Benzotriazol-1-yl)alkyldiphenylphosphine Oxides and Their Transformations to Novel Benzotriazol-1-yl-substituted Cyclopropanes

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Diphenylphosphinous anion reacted with chloromethylbenzotriazole to give (benzotriazol-1-yl)methyldiphenylphosphine oxide, which, after lithiation, was alkylated to give 1-(benzotriazol-1-yl)alkyldiphenylphosphine oxides in good yield. Treatment of 1-(benzotriazol-1-yl)alkyldiphenylphosphine oxides with *n*-butyllithium followed by condensation with epoxides, afforded benzotriazol-1-yl-substituted cyclopropanes, which underwent further lithiation and subsequent reaction with numerous electrophiles to provide a variety of novel benzotriazol-1-yl-substituted cyclopropane derivatives.

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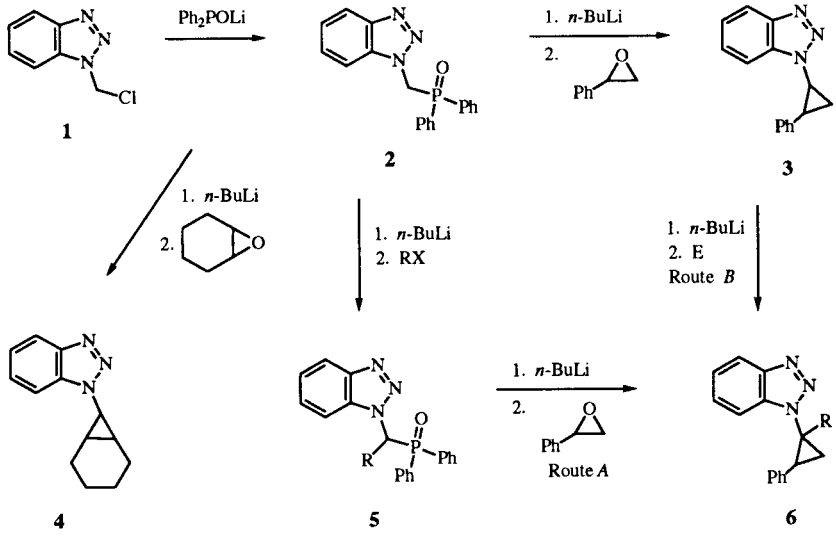
Benzotriazole derivatives are of wide interest due to their biological activity as herbicides, insecticides, and acaricides [1-3], their usefulness as precursors for many condensed heterocycles [4-5], and especially their versatility as efficient reagents for various synthetic transformations [6]. Although compounds of the type $BtCH_2Z$ (where Bt = benzotriazolyl, Z = OR, SR, NR, halogen) have been synthesized and intensively used in synthetic transformations [7], the phosphorous analogs have not previously been reported. The present paper describes a facile approach to 1-(benzotriazol-1-yl)alkyldiphenylphosphine oxides **2** and **5**.

Cyclopropane derivatives have received much attention due to their importance in theoretical, practical and bioorganic chemistry [8]. One of the most important preparative approaches to cyclopropane derivatives is *via* phosphonate/epoxide condensation as evidenced by the volume of literature on this subject [9-12]. However, most of these previous reports employed α-phosphono esters and ketones, and we have found no examples where this strategy has been used to prepare heterocycle substituted cyclopropanes. In this paper, we also report the preparation of a variety of benzotriazol-

Scheme 1



5	R	6	Route	E	R
a	Me	a	A	-	Me
b	$PhCH_2CH_2$	b	A	-	$PhCH_2CH_2$
c	*n*-Bu	c	B	*n*-BuI	*n*-Bu
d	Et	d	B	I_2	I
e	$PhCH_2$	e	B	*p*-MeC_6H_4CHO	*p*-MeC_6H_4CHOH
		f	B	PhSSPh	PhS

1-yl-substituted cyclopropanes **3** and **6** based on the condensation of the newly accessible compounds, 1-(benzotriazol-1-yl)alkyldiphenylphosphine oxides **2** and **5**, with epoxides.

Results and Discussion.

As shown in Scheme 1, (benzotriazol-1-yl)methyldiphenylphosphine oxide (**2**) was easily prepared in 69% yield by lithiation of diphenylphosphine oxide with *n*-butyllithium at -78°, followed by treatment with chloromethylbenzotriazole (**1**). Derivative **2** underwent deprotonation with *n*-butyllithium at -78°. The anion formed was alkylated with methyl iodide, 2-phenylethyl bromide, *n*-butyl iodide, ethyl iodide and benzyl bromide to give the corresponding 1-(benzotriazol-1-yl)alkyldiphenylphosphine oxides **5a-e** in yields of 62-74% (Table 1). Compounds **2** and **5a-e** were all previously unknown and were characterized by their ^{1}H nmr spectra (Table 2) and CHN analyses (Table 1).

We next examined the reactions of these newly accessible compounds **2** and **5** with epoxides. Upon lithiation by *n*-butyllithium at -78°, (benzotriazol-1-yl)methyldiphenylphosphine oxide (**2**) reacted smoothly with styrene oxide. After refluxing for 2 hours, the desired cyclopropane derivative **3** was afforded in a yield of 74% (Scheme 1). Trisubstituted cyclopropanes **6a** and **6b** were similarly furnished when **5a** and **5b** were condensed with styrene oxide (*Route A*). Noteworthy is the fact that in these reactions steric effects were pronounced. In the case of **5a**, a longer refluxing period (6 hours) was required to give **6a** in 70% yield, compared with only 2 hours for the methylene derivative **2** and cyclopropane **6b** was obtained from **5b** in low yield (30%) even after refluxing for 24 hours.

By definition, condensation with a substituted epoxide results in a product containing two chiral centers, and such reactions might give mixtures of diastereomers. However, as for the analogous reactions reported [12-14], only one diastereomer was detected by ^{1}H nmr spectroscopy in the cases of **3**, **6a** and **6b**. NOE experiments determined that the phenyl and benzotriazolyl groups were positioned in a *trans* orientation.

We have also tested the reaction of compound **2** with a disubstituted epoxide, cyclohexene oxide. Similarly, 5-(benzotriazol-1-yl)bicyclo[4.1.0]heptane (**4**) was obtained readily in 73% yield.

Our previous work has demonstrated that benzotriazole can sufficiently stabilize an α-carbanion due to its electron-withdrawing ability [15]. Thus, a more general route to highly substituted and functionalized cyclopropanes **6** was provided from compound **3** *via* lithiation and subsequent reaction with electrophiles (*Route B*). Accordingly,

Table 1

Preparation of 1-(Benzotriazol-1-yl)alkyldiphenylphosphine Oxides **2**, **5a-e**

Compound	Yield (%)	Mp (°C)	Molecular Formula	Analysis Found C	Found H	Found N	Required C	Required H	Required N
2	69	125-126	$C_{19}H_{16}N_3OP$	68.24	4.83	12.48	68.46	4.84	12.61
5a	74	182-183	$C_{20}H_{18}N_3OP$	69.15	5.21	12.13	69.14	5.23	12.10
5b	64	152-153	$C_{27}H_{24}N_3OP$	74.06	5.59	9.60	74.13	5.53	9.61
5c	67	167-168	$C_{23}H_{24}N_3OP$	70.55	6.13	10.76	70.94	6.21	10.79
5d	64	193-194	$C_{21}H_{20}N_3OP$	69.51	5.57	11.51	69.80	5.58	11.63
5e	62	217-218	$C_{26}H_{22}N_3OP$	73.97	5.28	9.85	73.75	5.24	9.95

Table 2

^{1}H NMR Data of 1-(Benzotriazol-1-yl)alkyldiphenylphosphine Oxides **2**, **5a-e** (δ, ppm; J, Hz)

Compound	BtC*H*$_2$ or BtC*H*	Other Signals
2	5.59 (d, 2H, J = 6.3)	7.31-7.36 (m, 1H), 7.42-7.58 (m, 7H), 7.77-7.84 (m, 5H), 7.96 (d, 1H, J = 8.2)
5a	5.98-6.07 (m, 1H)	1.95 (dd, 3H, J = 13.3 and 7.6), 7.23-7.69 (m, 10H), 7.88-7.94 (m, 3H), 8.10 (d, 1H, J = 8.5)
5b	5.73-5.80 (m, 1H)	2.18-2.55 (m, 3H), 3.00-3.11 (m, 1H), 6.94-6.97 (m, 2H), 7.15-7.57 (m, 13H), 7.63-7.70 (m, 2H), 7.94 (d, 1H, J = 8.4), 8.05 (d, 1H, J = 8.4)
5c	5.79-5.86 (m, 1H)	0.70 (t, 3H, J = 7.1), 0.90-0.98 (m, 1H), 1.09-1.30 (m, 3H), 2.07-2.14 (m, 1H), 2.67-2.73 (m, 1H), 7.22-7.38 (m, 4H), 7.43-7.70 (m, 6H), 7.88-7.95 (m, 3H), 8.11 (d, 1H, J = 8.5)
5d	5.72-5.80 (m, 1H)	0.73 (t, 3H, J = 3.6), 2.10-2.25 (m, 1H), 2.60-2.80 (m, 1H), 7.20-7.40 (m, 4H), 7.41-7.57 (m, 4H), 7.65-7.72 (m, 2H), 7.88-7.93 (m, 3H), 8.12 (d, 1H, J = 8.3)
5e	5.97-6.04 (m, 1H)	3.46-3.53 (m, 1H), 3.80-3.91 (m, 1H), 6.73-6.76 (m, 2H), 6.99-7.03 (m, 3H), 7.23-7.30 (m, 3H), 7.33-7.57 (m, 5H), 7.69-7.76 (m, 2H), 7.85-7.96 (m, 3H), 8.05 (d, 1H, J = 7.1)

Table 3

Preparation of Benzotriazol-1-yl-substituted Cyclopropanes **3**, **4**, **6a-f**

Compound	Route	Yield (%)	Mp (°C)	Molecular Formula	Analysis Found C	Found H	Found N	Required C	Required H	Required N
3		74	86-87	$C_{15}H_{13}N_3$	76.82	5.60	18.05	76.56	5.57	17.87
4		73	92-93	$C_{13}H_{15}N_3$	73.13	7.16	19.71	73.20	7.09	19.71
6a	*A*	70	oil	$C_{16}H_{15}N_3$	77.42	6.18	16.89	77.08	6.06	16.85
6b	*A*	30	oil	$C_{23}H_{21}N_3$	81.38	6.19	12.26	81.37	6.24	12.39
6c	*B*	76	oil	$C_{19}H_{21}N_3$	78.32	7.41	14.32	78.32	7.26	14.42
6d	*B*	83	oil	$C_{15}H_{12}N_3I$	50.12	3.39	11.23	49.88	3.35	11.63
6e	*B*	54	261-262	$C_{23}H_{21}N_3O$	77.48	5.96	11.78	77.71	5.96	11.83
6f	*B*	43	100-101	$C_{21}H_{17}N_3S$	73.18	5.00	11.94	73.44	4.99	12.23

Table 4

^{1}H NMR Data of Benzotriazol-1-yl-substituted Cyclopropanes **3**, **4**, **6a-f** (δ, ppm; J, Hz)

Compound	Signals
3	1.66-1.73 (m, 1H), 1.99-2.06 (m, 1H), 2.63-2.70 (m, 1H), 3.79-3.84 (m, 1H), 7.17-7.41 (m, 7H), 7.52 (dd, 1H, J = 8.2 and 0.9), 7.96 (dd, 1H, J = 8.3 and 0.9)
4	1.24-1.44 (m, 4H), 1.80-1.90 (m, 2H), 1.96-2.13 (m, 4H), 3.40 (t, 1H, J = 3.1), 7.31 (t, 1H, J = 8.3), 7.44 (t, 1H, J = 8.3), 7.56 (dd, 1H, J = 8.3 and 0.9), 7.99 (dd, 1H, J = 8.3 and 0.9)
6a	1.43 (s, 3H), 1.69 (dd, 1H, J = 7.4 and 6.2), 2.02 (dd, 1H, J = 9.9 and 6.2), 2.96 (dd, 1H, J = 9.9 and 7.4), 7.29-7.49 (m, 6H), 7.52-7.58 (m, 1H), 7.77 (dd, 1H, J = 8.4 and 1.0), 8.10 (dd, 1H, J = 8.4 and 1.0)
6b	1.73 (t, 1H, J = 7.4), 1.87-1.95 (m, 1H), 1.99-2.10 (m, 2H), 2.39-2.44 (m, 2H), 2.98 (dd, 1H, J = 9.7 and 7.4), 6.74-6.77 (m, 2H), 7.05-7.13 (m, 3H), 7.31-7.59 (m, 7H), 7.78 (dd, 1H, J = 8.3 and 0.9), 8.13 (dd, 1H, J = 8.3 and 0.9)
6c	0.62 (t, 3H, J = 7.0), 0.93-1.19 (m, 4H), 1.41-1.51 (m, 1H), 1.70-1.85 (m, 2H), 1.99-2.06 (m, 1H), 2.89 (dd, 1H, J = 9.8 and 7.4), 7.27-7.57 (m, 7H), 7.77 (d, 1H, J = 8.3), 8.10 (d, 1H, J = 8.3)
6d	2.24 (t, 1H, J = 7.5), 2.67 (dd, 1H, J = 10.3 and 7.5), 2.79 (dd, 1H, J = 10.3 and 7.5), 7.40-7.57 (m, 6H), 7.65 (t, 1H, J = 8.3), 7.82 (d, 1H, J = 8.3), 8.12 (d, 1H, J = 8.3)
6e	1.82 (dd, 1H, J = 9.5 and 7.4), 2.10 (s, 3H), 2.40 (dd, 1H, J = 9.5 and 7.4), 3.12 (t, 1H, J = 7.4), 4.46 (d, 1H, J = 3.5), 5.78 (d, 1H, J = 3.5), 5.94 (d, 2H, J = 7.7), 6.66 (d, 2H, J = 7.7), 7.35 (t, 1H, J = 8.1), 7.43-7.53 (m, 6H), 7.68-7.75 (m, 1H), 7.98 (d, 1H, J = 8.1)
6f	2.32 (dd, 1H, J = 8.8 and 6.6), 2.59 (dd, 1H, J = 8.8 and 6.6), 3.24 (t, 1H, J = 8.8), 6.95-6.97 (m, 2H), 7.08-7.19 (m, 3H), 7.39-7.56 (m, 7H), 7.70 (d, 1H, J = 8.3), 8.10 (d, 1H, J = 8.3)

Table 5

^{13}C NMR Data of Benzotriazol-1-yl-substituted Cyclopropanes **3**, **4**, **6a-f** (δ, ppm)

Compound	Benzotriazole C_{3a}	C_{7a}	C_5	C_6	C_4	C_7	other signals
3	145.9	134.1	126.8	124.0	120.0	109.6	15.0, 24.3, 37.2, 126.3, 127.4, 128.7, 138.7
4	145.5	133.7	126.8	123.5	119.5	109.6	18.4, 20.9, 21.8, 38.8
6a	146.1	132.7	127.0	123.8	120.1	109.8	17.1, 19.0, 29.2, 40.9, 127.2, 128.5, 128.9, 135.8
6b	146.1	133.2	125.8	123.9	120.3	110.0	16.3, 29.6, 32.0, 34.7, 45.1, 127.2, 127.4, 128.0, 128.1, 128.6, 128.9, 135.5, 140.6
6c	146.1	133.2	127.0	123.8	120.3	110.1	13.6, 16.3, 22.1, 27.9, 29.7, 32.2, 45.4, 127.3, 128.5, 128.9, 135.9
6d	146.3	132.4	128.0	124.8	120.5	110.8	16.8, 24.1, 32.2, 128.1, 128.1, 128.5, 137.2
6e	144.7	134.4	126.8	123.5	118.9	112.2	15.4, 20.5, 30.6, 50.6, 72.8, 125.6, 127.2, 127.7, 128.5, 129.1, 135.6, 135.6, 136.0
6f	146.0	132.6	127.4	124.1	120.0	110.6	21.1, 33.5, 50.2, 127.5, 128.0, 128.2, 128.6, 129.1, 131.4, 132.2, 134.3

compound **3** was treated with *n*-butyllithium, followed by *n*-butyl iodide, iodine, *para*-tolualdehyde, and diphenyl disulfide respectively to furnish the expected products **6c-f** (Scheme 1) (Table 3).

All of the benzotriazol-1-yl-substituted cyclopropanes **3**, **4** and **6a-f** were previously unknown and their structures were confirmed by ^{1}H and ^{13}C nmr and by CHN analysis data (Tables 4 and 5).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^{1}H, ^{13}C and NOE nmr spectra were recorded on a Varian VXR 300 spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer in this department. Tetrahydrofuran was dried by distillation over the sodium ketyl of benzophenone. All reactions were carried out

under a dry argon atmosphere. Flash column chromatography was carried out on silica gel (EM Merck 60, 230-400 mesh).

(Benzotriazol-1-yl)methyldiphenylphosphine Oxide (**2**).

To a solution of diphenylphosphine oxide (25.0 g, 0.12 mole) in dry tetrahydrofuran (100 ml) was added *n*-butyllithium (66 ml, 0.13 mole, 2 *M* in hexanes) under argon at -78° and the mixture stirred for 1.5 hours at the same temperature. A solution of chloromethylbenzotriazole (**1**) (20 g, 0.12 mole) in dry tetrahydrofuran (250 ml) was slowly added. The mixture was allowed to warm to room temperature overnight. After quenching with water (150 ml) and extraction with diethyl ether (3 x 70 ml), the combined organic layer was dried (magnesium sulfate). The solvent was then evaporated and the residue purified by column chromatography with diethyl ether to give **2** as a white solid.

General Procedure for the Lithiation of **2** and Subsequent Reaction with Electrophiles to Produce 1-(Benzotriazol-1-yl)alkyldiphenylphosphine Oxides **5a-e**.

To a solution of **2** (3.33 g, 10 mmoles) in dry tetrahydrofuran (60 ml) under argon at -78° was added *n*-butyllithium (5.5 ml, 11 mmoles, 2 *M* in hexanes). The mixture was stirred at -78° for 1.5 hours, and a solution of the corresponding alkyl halide (10 mmoles) in dry tetrahydrofuran (10 ml) was added. The mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into water (40 ml), and the aqueous layer extracted with ether (3 x 30 ml). The combined organic layer was dried (magnesium sulfate), and the solvent removed under reduced pressure to afford the crude product, which was purified by column chromatography using ether (see Table 1).

General Procedure for the Condensation of 1-(Benzotriazol-1-yl)alkyldiphenylphosphine Oxides with Epoxides to Produce Benzotriazol-1-yl-substituted Cyclopropanes **3**, **4** and **6a-b** (*Route A*).

To a solution of **2**, **5a** or **5b** (3 mmoles) in dry tetrahydrofuran (50 ml) under argon at -78° was added *n*-butyllithium (1.5 ml, 3.3 mmoles, 2 *M* in hexanes). The mixture was stirred at -78° for 1.5 hours, and a solution of styrene oxide (for the preparation of **3**, **6a** and **6b**) or cyclohexene oxide (for the preparation of **4**) (3 mmoles) in dry tetrahydrofuran (10 ml) was added. The mixture was allowed to warm to room temperature overnight, then refluxed for several hours (2 hours for **3**, 6 hours for **4**, 6 hours for **6a**, 24 hours for **6b**). The mixture was poured into water (30 ml), and the aqueous layer extraced with ether (3 x 15 ml). The combined organic layer was dried (magnesium sulfate) and the solvent evaporated to give the crude product, which was purified by column chromatography using ether (see Table 4).

General Procedure for the Lithiation of **3** and Subsequent Reaction with Electrophiles to Produce Benzotriazol-1-yl-substituted Cyclopropanes **6c-f** (*Route B*).

To a solution of **3** (2.4 g, 10 mmoles) in dry tetrahydrofuran (100 ml) under argon at -78° was added *n*-butyllithium (5.5 ml, 11 mmoles, 2 *M* in hexanes). The mixture was stirred at -78° for 1.5 hours, and a solution of the corresponding electrophile (10 mmoles) in dry tetrahydrofuran (10 ml) was added. The mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into water (30 ml) (in the case of **6d**, a 10% aqueous sodium bisulfite solution was used instead of water), and the aqueous layer extracted with ether (3 x 30 ml). The combined organic layer was dried (magnesium sulfate) and the solvent removed under pressure to afford the crude product, which was purified by column chromatography (eluent: ether for **6c**, **6e**; chloroform:hexanes = 1:1 for **6d**, **6f**) (Table 3).

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