Articles

Reactions of 1-(α-Alkoxyalkyl)- and 1-(α-(Aryloxy)alkyl)benzotriazoles with the Grignard Reagents. A New and Versatile Method for the Preparation of Ethers

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Received April 10, 1989

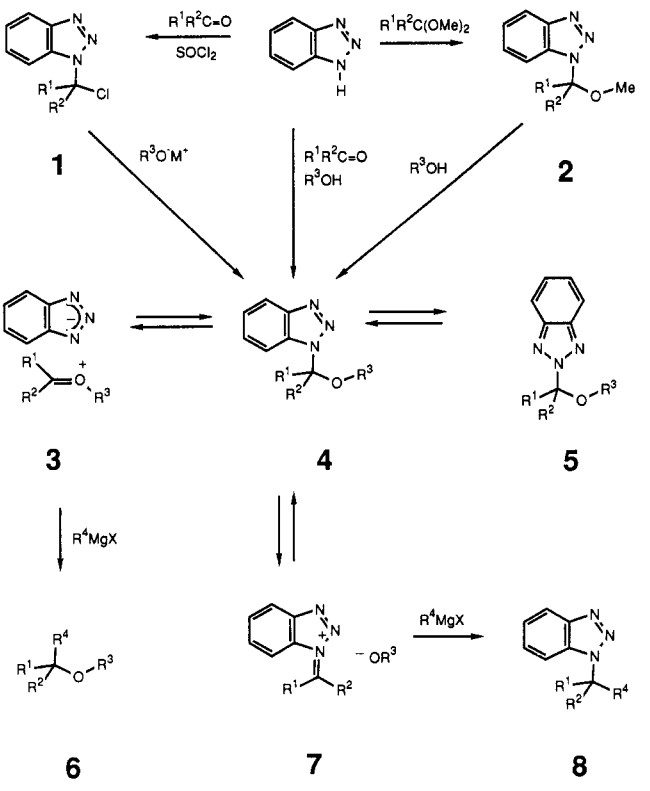
1-(α-Alkoxyalkyl)benzotriazoles deriving from aldehydes (other than formaldehyde), or from ketones, react with Grignard reagents at 110 °C to provide a high-yielding, general synthesis of dialkyl and alkyl aryl ethers. Under similar conditions, 1-(alkoxymethyl)- and 1-((aryloxy)methyl)benzotriazoles give, by a different cleavage pattern of the *N*–C–O grouping, 1-alkylbenzotriazoles and *N,N'*-dialkyl-*o*-phenylenediamines. The 1-(α-alkoxyalkyl)benzotriazoles are easily prepared: (a) by condensation of benzotriazole, an aldehyde, and an alcohol under water-removing conditions; (b) by condensation of a 1-(α-chloroalkyl)benzotriazole with a sodium or potassium alkoxide or aryloxide; and (c) by condensation of an acetal or of a ketal with benzotriazole. All the 1-(α-alkoxyalkyl)benzotriazoles and dialkyl or alkyl aryl ethers obtained were fully characterized by their ^1H and ^{13}C NMR spectra.

Introduction

Several general methods are known for the synthesis of ethers.[1,2] The majority of these methods are based on the formation of one of the C–O bonds. The most useful and general method for the preparation of structurally simple dialkyl ethers, the Williamson synthesis, has been recently extensively investigated and modified.[3–8] All these methods, however, suffer limitations; e.g., *tert*-butyl phenyl ether[9,10] can be obtained directly by reaction of bromobenzene with potassium *tert*-butoxide, but the yield is only 42–46%. Although *tert*-butyl aryl ethers can be obtained in high yield, by the addition of phenols to isobutylene,[11,12] no good synthetic method was previously available for the preparation of aryl alkyl ethers, such as aryl phenethyl ethers, where the alkyl group possesses a strong tendency toward elimination, and where addition of phenol to the olefin does not give the desired product.

Other methods for preparation of ethers based on modification of substituents on C-1 or C-2 of molecules where the C–O–C linkage already exists were also recently investigated and developed. These involve reduction of acetals with triethylsilane,[13,14] the substitution of one of the alkoxy groups in acetals[15–19] (or of two of the alkoxy groups in orthoesters[20,21]) with alkyl groups from organo-

Scheme I



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0022-3263/89/1954-6022$01.50/0

Table I. α-Benzotriazolylalkyl Alkyl and Aryl Ethers 4

no.	R^1	R^2	R^3	method of synthesis[a]	yield, %	mp, °C	molecular formula[b]
4a[28]	H	H	Me	A	40	*c*	$C_8H_9N_3O$
4b	H	H	t-Bu	A	83	*c*	$C_{11}H_{19}N_3O$
4c	H	H	$PhCH_2CH_2$	A	57	38	$C_{15}H_{15}N_3O$
4d[28]	H	H	Ph	A	87	64	$C_{13}H_{11}N_3O$
4e	H	H	$4\text{-}MeOC_6H_4$	B	86	96	$C_{14}H_{13}N_3O_2$
4f	i-Pr	H	i-Pr	C	97	64	$C_{13}H_{19}N_3O$
4g	i-Pr	H	cyclohexyl	C	96	61	$C_{16}H_{23}N_3O$
4h	i-Pr	H	Ph	B	60	77	$C_{16}H_{17}N_3O$
4i	i-Pr	H	2-naphthyl	B	20	108	$C_{20}H_{19}N_3O$
4j	Ph	H	i-Pr	C	65	67	$C_{16}H_{17}N_3O$
4k	$4\text{-}MeC_6H_4$	H	$Cl(CH_2)_3$	A	65	*c*	$C_{17}H_{18}N_3ClO$
4l	$R^1, R^2 = (CH_2)_5$		Pr	C	52	48	$C_{15}H_{21}N_3O$
4m	$R^1, R^2 = (CH_2)_5$		$PhCH_2$	C	80	92	$C_{19}H_{21}N_3O$
4n	Me	Me	Me	D	90	*c*	$C_{10}H_{13}N_3O$
4o	Me	Me	$CH_2(CH_2)_4CH_3$	A	88	*c*	$C_{15}H_{23}N_3O$
4p	Ac	H	Me	D	92	45	$C_{10}H_{11}N_3O_2$

[a] A: An individual method described in the experimental part. B: Reaction of 1-chloro-1-benzotriazolylalkane with the sodium salt of the appropriate phenol. C: Carbon tetrachloride solution of benzotriazole, aldehyde, and alcohol refluxed in a Soxhlet apparatus. D: Reaction of benzotriazole with the appropriate acetal; details in the experimental part. [b] Satisfactory analytical data (C, H, N) for ethers 4 were obtained (±0.3%, except of **4n** where the obtained percentage of N was 0.4% lower than that calculated). [c] Liquid.

metallic reagents or silanes,[22] the reactions of α-chloroalkyl[23,24] and β-chloroalkyl[25] ethers with organometallic compounds, and the reaction of α-chloro ethers with silanes.[26] These methods are mostly limited to preparation of one type of ethers, e.g., the method based on the hydrogenation of ketals in the presence of platinum cannot satisfactorily be used for acetals.[27] They are also usually limited to molecules possessing at least one simple alkyl group with a primary carbon atom adjacent to the oxygen bridge.

Benzotriazole reacts with aldehydes and alcohols under water-removing conditions to give α-(benzotriazolyl)alkyl alkyl ethers in high yields.[28] This report describes our application of these adducts as the starting materials for a versatile new synthesis of ethers by their reactions with Grignard reagents. We also demonstrate that novel benzotriazolylalkyl alkyl ethers can be obtained from ketones and used in our ether synthesis. This new method for the synthesis of dialkyl and of alkyl aryl ethers has many advantages in comparison to the previous routes.

Preparation of 1-(α-Alkoxyalkyl)- and 1-(α-(Aryloxy)alkyl)benzotriazoles. The previously reported reaction[28] of benzotriazole with aldehydes and alcohols leading to 1-(α-alkoxyalkyl)benzotriazoles **4** (R^1 = alkyl or aryl, R^2 = H) has been extended (Scheme I) to cyclohexanone, a reactive ketone,[29-32] which gives adducts **4** (R^1, $R^2 = (CH_2)_5$) under similar conditions. Although dialkyl ketones in general failed to undergo this reaction with benzotriazole and alcohols, adducts of type **2** deriving from other ketones can be obtained by a simple procedure from the corresponding ketone dimethyl ketals as was demonstrated by the acetone derivative ($R^1 = R^2$ = Me). Substitution of the methoxy group of **2** by any other desired alkoxy to give benzotriazolyl ethers **4** was easily accomplished by acid catalysis.

In an alternative route to **4**, 1-(α-chloroalkyl)benzotriazoles[33,34] **1** are treated with sodium alkoxides. This method is especially suitable for the preparation of benzotriazolyl derivatives of aromatic ethers (R^3 = aryl, Scheme I), which cannot be obtained directly by the condensation of phenols with benzotriazole and aldehydes. The new α-benzotriazolylalkyl ethers **4** are described in Table I.

Proton and Carbon-13 NMR Spectroscopy of α-Benzotriazolylalkyl Ethers. Isomerization of the Ethers. Although the preparation of α-benzotriazolylalkyl ethers **4** has been already reported,[28] their high-resolution ^1H and ^{13}C NMR spectra were not previously investigated. The spectral data are collected in Tables II and III. The deshielding influence of the alkoxy oxygen atom on the C(7) proton, shifting its resonance downfield, causes the benzotriazolyl proton resonances to display as an AMNX pattern, δ 8.08, 7.41, 7.53, 7.67 for H-4, H-5, H-6, and H-7, respectively, in **4d**. Higher coupling constants between protons 4,5 and 6,7 (8.0–8.3 Hz) indicate the higher bond order[35] between the corresponding carbon atoms compared to that between carbon atoms 5 and 6 ($J_{5,6}$ = 6.8–7.0 Hz). The meta and para coupling constants are almost equal ($J_{4,6} = J_{4,7}$ = 1.0 Hz) of 1-methylbenzotriazole.[36]

Carbon-13 NMR spectral data of ethers **4** are collected in Table III. Chemical shifts of the benzotriazolyl carbon resonances in **4** are similar to those reported for 1-methylbenzotriazole.[37] The strongest shift relative to 1-methylbenzotriazole was observed for the C-7a resonances (average Δδ: 1.3 ppm upfield) in accordance with the previous observations that the resonance of C-7a of benzotriazole system is most affected by the N-1 substituents.[38] On the other hand, in comparison with the ether, substitution of an α hydrogen atom by the benzotriazol-1-yl substituent has a dramatic influence on the ether carbon resonances; thus, resonances of aliphatic carbon atoms in

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Table II. ^{1}H NMR Spectral Data[a] of Benzotriazolyl Ethers 4

	benzotriazolyl[b]						
no.	4	5	6	7	R^1	R^2	R^3
4a	8.08 (8.2, 1.0, 0.8)	7.41 (8.1, 6.9, 0.9)	7.53 (8.3, 6.9, 1.0)	7.67 (8.3, 1.1, 1.0)	5.96 (1 H, s)	5.96 (1 H, s)	3.34 (3 H, s)
4b	8.06 (8.3, 1.0, 1.0)	7.38 (8.3, 7.0, 1.0)	7.50 (8.3, 7.0, 1.0)	7.72 (8.3, 1.0, 1.0)	6.06 (1 H, s)	6.06 (1 H, s)	1.20 (9 H, s)
4c	8.06 (8.0, 1.4, 0.9)	7.38 (8.1, 6.7, 1.4)	7.47 (8.2, 6.7, 1.4)	7.57 (8.2, 1.4, 0.9)	5.93 (1 H, s)	5.93 (1 H, s)	2.76 (2 H, t, 6.7), 3.69 (2 H, t, 6.8), 7.10 (5 H, m)
4d	8.05 (8.3, 1.0, 1.0)	7.37 (8.3, 6.8, 1.2)	7.49 (8.2, 6.8, 1.0)	7.65 (8.2, 1.2, 1.0)	6.54 (1 H, s)	6.54 (1 H, s)	7.00 (1 H, tt, 7.4, 1.1), 7.08 (2 H, m), 7.26 (2 H, m)
4e	8.06 (8.3, 1.0, 1.0)	7.39 (8.3, 6.8, 1.1)	7.49 (8.2, 6.8, 1.0)	7.62 (8.2, 1.2, 1.0)	6.46 (1 H, s)	6.46 (1 H, s)	3.71 (3 H, s), 6.76 (2 H, d, 9.2), 6.93 (2 H, d, 9.2)
4f	8.07 (8.2, 1.1, 1.0)	7.37 (8.2, 6.4, 1.1)	7.46 (8.0, 6.4, 1.1)	7.80 (8.0, 1.1, 1.0)	0.61 (3 H, d, 6.8), 0.92 (3 H, d, 6.3), 2.49 (1 H, m)	5.73 (1 H, d, 8.9)	1.19 (3 H, d, 6.7), 1.24 (3 H, d, 6.0), 3.53 (1 H, heptet, 6.1)
4g	8.07 (8.2, 1.1, 0.9)	7.37 (8.2, 7.0, 1.1)	7.45 (8.1, 7.0, 1.1)	7.81 (8.1, 1.1, 0.9)	0.60 (3 H, d, 6.8), 1.20 (3 H, d, 6.7), 2.50 (1 H, m)	5.77 (1 H, d, 8.9)	1.06 (1 H, m), 1.20 (3 H, m), 1.40 (3 H, m), 1.55 (1 H, m), 1.73 (1 H, m), 1.96 (1 H, m), 3.24 (1 H, m)
4h	8.02 (8.3, 1.1, 1.0)	7.32 (8.3, 7.0, 1.1)	7.43 (8.3, 7.0, 1.0)	7.81 (8.3, 1.1, 1.0)	0.74 (3 H, d, 6.8), 1.32 (3 H, d, 6.6), 2.79 (1 H, m)	6.43 (d, 8.9)	6.92 (1 H, t, 8.0), 6.95 (2 H, d, 8.0), 7.16 (2 H, t, 8.0)
4i	8.02 (8.3, 1.1, 1.0)	7.32 (8.3, 7.2, 1.0)	7.43 (7.9, 7.1, 1.1)	7.85 (7.9, 1.0, 1.0)	0.79 (3 H, d, 6.8), 1.36 (3 H, d, 6.6), 2.83 (1 H, m)	6.60 (d, 8.8)	7.19 (1 H, dd, 9.0, 2.6), 7.27 (1 H, m), 7.32 (1 H, m), 7.37 (1 H, dt, 1.3, 7.9), 7.61 (1 H, d, 8.0), 7.67 (2 H, d, 8.9)
4j	8.05 (8.2, 1.1, 1.0)	7.36[c]	7.42[c]	7.40[c]	7.32 (5 H, m)	7.30 (s)	1.00 (3 H, d, 6.2), 1.36 (3 H, d, 6.0), 3.79 (1 H, heptet, 6.1)
4k	8.06[c]	7.20–7.34[c]	7.20–7.34[c]	7.20–7.34[c]	2.33 (3 H, s), 7.16 (2 H, d, 8.4), 7.30 (2 H, d, 8.3)	7.10 (s)	2.05 (2 H, m), 3.50 (1 H, m), 3.61 (2 H, m), 3.89 (1 H, ddd, 5.0, 6.8, and 11.8)
4l	8.07 (8.2, 1.1, 1.0)	7.34 (8.2, 7.0, 1.1)	7.43 (8.3, 7.0, 1.1)	7.92 (8.3, 1.1, 1.0)	R^1,R^2: 1.77 (6 H, m) and 2.52 (2 H, m)	2.33 (2 H, m)	0.85 (3 H, t, 7.2), 1.50 (2 H, sextet, 6.7), 3.04 (2 H, t, 6.6)
4m	8.08[c]	7.33–7.42[c]	7.33–7.42[c]	7.86[c]	R^1,R^2: 1.80 (6 H, m) and 2.63 (2 H, m)	2.40 (2 H, m)	4.13 (2 H, s), 7.13–7.29 (5 H, m)
4n	8.09 (8.3, 1.2, 1.0)	7.48 (8.3, 7.0, 1.2)	7.90 (8.0, 7.0, 1.2)	7.39 (8.0, 1.2, 1.0)	2.01 (3 H, s)	2.01 (3 H, s)	3.09 (3 H, s)
4o	8.07 (8.3, 1.1, 1.0)	7.37 (8.3, 6.9, 1.1)	7.46 (8.3, 7.0, 1.1)	7.92 (8.3, 1.1, 1.0)	2.02 (3 H, s)	2.02 (3 H, s)	0.82 (3 H, t, 7.3), 1.17 (6 H, m), 1.48 (2 H, m), 3.15 (2 H, t, 6.8), 3.39 (3 H, s)
4p	8.11 (8.3, 1.1, 1.0)	7.39[c]	7.51[c]	7.53[c]	2.37 (3 H, s)	6.42 (1 H, s)	

[a] δ values are given in ppm from TMS, coupling constants (in parentheses) are in hertz. [b] An AMNX proton coupling pattern; in high-resolution spectra the signals are observed usually as ddd or dt (when $J_{4,6} = J_{4,7}$). [c] Shift of some resonances to the same field range made the coupling pattern difficult for interpretation.

Table III. ^{13}C NMR Spectral Data[a] of Benzotriazolyl Ethers 4

	benzotriazolyl									
no.	4	5	6	7	3a	7a	O–C–N	R^1	R^2	R^3
4a	120.0	124.3	127.9	109.8	146.4	132.7	78.4			56.8
4b	119.6	123.9	127.3	110.3	146.2	132.6	71.9			27.6, 76.0
4c	119.7	124.1	127.7	109.8	146.2	132.5	77.0			35.5, 69.9, 126.1, 128.1, 128.5, 137.8
4d	120.0	124.4	128.1	109.8	146.3	132.7	74.9			116.3, 123.0, 129.7, 156.2
4e	119.6	124.4	128.1	109.9	146.1	132.7	76.1			55.5, 114.7, 118.1, 150.0, 155.6
4f	119.9	124.0	127.1	111.8	146.7	131.5	94.0	17.7, 18.9, 33.2		20.9, 22.6, 70.5
4g	119.9	124.0	127.0	111.8	146.8	131.5	93.8	17.8, 19.1, 33.3		23.6, 23.7, 25.5, 30.8, 32.6, 76.0
4h	120.0	124.2	127.6	111.4	146.6	131.1	93.2	17.6, 18.8, 33.5		116.1, 122.8, 129.7, 156.4
4i	120.1	124.3	127.5	111.4	146.7	131.3	93.1	17.7, 18.9, 33.6		109.9, 118.3, 124.5, 126.6, 127.2, 127.7, 129.7, 129.8, 134.0, 154.2
4j	119.7	124.0	127.2	111.7	146.9	131.1	87.4	125.9, 128.4, 128.8, 136.8		21.0, 22.5, 70.7
4k	119.9	124.2	127.5	111.5	146.9	131.0	89.7	21.1, 125.7, 129.3, 133.0, 139.0		32.1, 41.3, 65.7
4l	119.8	123.8	126.8	113.0	146.7	131.8	93.2	R^1, R^2: 22.4, 25.4, 34.8		10.7, 22.9, 63.3
4m	119.7	124.0	126.9	112.9	146.5	131.7	93.5	R^1, R^2: 22.2, 25.1, 34.6		64.0, 127.8, 128.2, 128.2, 139.0
4n	119.7	124.2	127.4	112.7	146.6	131.8	92.8	26.2	26.2	50.5
4o	119.8	123.9	127.0	112.8	146.8	131.8	92.2	26.6	26.6	14.0, 22.5, 25.7, 29.5, 31.5, 63.0
4p	120.2	124.6	128.3	110.8	146.6	131.6	91.6	26.3, 198.7		57.4

[a] δ values are given in ppm from TMS.

4n are shifted +19.9, +4.5, and −4.7 ppm (Cα, Cβ, and methoxy group, respectively) in comparison with 2-methoxypropane.[39]

Proton and carbon-13 NMR spectra of the majority of the benzotriazolyl ethers **4** obtained revealed the presence of only the 1-benzotriazolyl isomers. In a few instances (ketone derivatives), the 2-benzotriazolyl isomers **5** were also observed in the crude products by additional signals of lower intensity in the ^{13}C spectrum, e.g., of 1-(benzotriazol-1-yl)-1-propoxycyclohexane **41**, **51** at δ 10.2, 22.5, 25.0, 25.9, 34.9, 64.6, 95.7, 118.6, 126.4, and 143.9. The last three resonances were assigned to the C(4,7), C(5,6), and C(3a,7a) of the benzotriazol-2-yl carbon atoms, respectively, and do not differ much from the corresponding values reported for 2-methylbenzotriazole:[37] 117.5, 125.9, and 144.3 ppm. From the integration of the triplet in the proton NMR spectrum at δ 3.65, originating from the CH_2O group of the 2-benzotriazolyl isomer, the amount of the 2-isomer was estimated as 15%. As another exam-

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Table IV. Dialkyl and Alkyl Aryl Ethers 6

no.	R^1	R^2	R^3	R^4	method of synthesis[a]	yield, %	bp, °C (mmHg)	molecular[b] formula
6a	i-Pr	H	i-Pr	Me	S	75	112 (760)	$C_8H_{18}O$
6b	i-Pr	H	i-Pr	Et	S	76	128 (760)	$C_9H_{20}O$
6c	i-Pr	H	i-Pr	cyclohexyl	R	40	38 (0.04)	$C_{13}H_{26}O$
6d	i-Pr	H	i-Pr	$PhCH_2$	R	95	*c*	$C_{14}H_{22}O$
6e	i-Pr	H	i-Pr	Ph	R	73	36 (0.05)	$C_{13}H_{20}O$
6f	i-Pr	H	cyclohexyl	$PhCH_2$	R	95	*c*	$C_{17}H_{26}O$
6g	i-Pr	H	Ph	Me	R	86	*c*	$C_{11}H_{16}O$
6h	i-Pr	H	2-naphthyl	Me	R	45	*c*	$C_{15}H_{18}O$
6i	Ph	H	i-Pr	$PhCH_2$	R	85	70 (0.04)	$C_{17}H_{20}O$
6j	Ph	H	i-Pr	Ph	R	80	*c*	$C_{16}H_{18}O$
6k	4-MeC_6H_4	H	$Cl(CH_2)_3$	Ph	R	25	*c*	$C_{17}H_{16}ClO$
6l	$(CH_2)_5$		Pr	$PhCH_2$	R	93	*c*	$C_{16}H_{24}O$
6m	$(CH_2)_5$		$PhCH_2$	$PhCH_2$	R	68	*c*	$C_{20}H_{24}O$
6n	Me	Me	Me	Et	S	60	79 (760)[d]	$C_6H_{14}O$[e]
6o	Me	Me	Me	$PhCH_2$	I	73	46 (0.2)	$C_{11}H_{16}O$
6p	Me	Me	hexyl	$PhCH_2$	I	96	*c*	$C_{16}H_{26}O$

[a] R: Regular method applying toluene as the solvent. S: Special method for volatile ethers with use of diphenylmethane as the solvent. I: Individual method described in the Experimental Section. [b] Satisfactory analytical data (C, H) for ether 6 (±0.3%) were obtained except of **6n**. [c] Purified by column chromatography (silica gel, toluene). [d] Lit.[44] bp 83–84 °C (760 mm). [e] Volatile substance; HRMS found *m/e* 101.0957, calcd for M − 1 101.0966.

ple, the proton NMR spectrum of an analytically pure sample of 1-benzotriazolyl-1-(benzyloxy)cyclohexane (**4m**) revealed two benzyl methylene singlets at 4.13 and 4.26 in the intensity ratio 4.4:1, indicating the presence of 18% of the benzotriazol-2-yl isomer.

Isomerization of **4** to **5** was observed only in the cases of the ethers derived from ketones (R^1 and R^2 = alkyl). The higher stability of the intermediate cation **3** evidently lowers the interconversion barrier, similarly to the behavior found in *N,N*-bis(1-benzotriazolylmethyl)arylamines.[40] Steric hindrance around the benzotriazolyl N–C bond destabilizes molecules of **4** relative to **5**, again as previously observed for *N*-(benzotriazolylmethyl)alkylamines.[41,42]

Grignard Reactions on 1-(α-Alkoxyalkyl)- and 1-(α-(Aryloxy)alkyl)benzotriazoles. The procedures developed for the preparation of amines by Grignard reactions on *N*-(α-benzotriazolylalkyl)arylamines[43] are not directly applicable for the preparation of ethers. α-Benzotriazolylalkyl ethers are more stable and less reactive than the corresponding amino compounds. Hence higher temperatures are required for the present Grignard reactions, and the preferred method uses toluene as the reaction medium. However, problems arise here with separation of the ether product when this has a boiling point similar to that of toluene. Because of the large excess of solvent toluene in relation to the prepared ether, a good separation and high-recovery yield of the ether require that the boiling point of the ether be above 200 °C. For the synthesis of more volatile ethers, the higher boiling hydrocarbon, diphenylmethane, was used successfully as a solvent. The ethers obtained are recorded in Table IV.

The lower reactivity of the 1-(α-alkoxyalkyl)benzotriazoles (**4**), in comparison with their amine analogues, supports the general reaction mechanism postulated for these types of compounds with nucleophiles. Ionization to the benzotriazole anion and cation **3** (or its nitrogen analogue) is followed by reaction of **3** with nucleophiles like Grignard reagents or hydride ion donors to give neutral molecules. The lower reactivity of α-(benzotriazolyl)alkyl ethers in relation to α-(benzotriazolyl)alkylamines reflects the lower stability of cations **3** (stabilized by the oxygen atom) than their analogues stabilized by a nitrogen atom.

These reactions proceed smoothly for α-(benzotriazolyl)alkyl ethers derived from aldehydes other than formaldehyde and ketones, when R^3 is an alkyl group (Scheme I). However, when similar reaction conditions were applied to benzotriazolyl ethers **4** derived from formaldehyde (R^1 = R^2 = H), none of the expected ether products **6** were detected in the reaction mixtures. Reaction of benzotriazolylmethyl phenyl ether (**4d**) with benzylmagnesium chloride gave 1-phenethylbenzotriazole (**8**, R^4 = $PhCH_2$) as the main product. The spectra of several other crude products also indicated the presence of the respective 1-alkylbenzotriazoles of **8**.

Cleavage of the carbon–nitrogen bond in the molecule of **4** to form ion pair **3** is evidently not the only possibility: ion pair **7**, formed by the cleavage of the carbon–oxygen bond, can be of comparable or even higher stability. This is apparently the case when there is no alkyl group R^1 and R^2 to stabilize cation **3**. Further, an aryl group as R^3 can stabilize the negative charge lowering the energy of ion pair **7**.

Cation **7** as an intermediate assists the assignment of the structures of other products formed from benzotriazolyl ethers **4** and Grignard reagents (Scheme II). The Grignard can add to cation **7** (to give **8**) or alternatively reduce **7** to simpler alkylbenzotriazole **9**, as, e.g., in the reaction of benzotriazolylmethyl phenyl ether with ethylmagnesium iodide to give 1-methylbenzotriazole and 1-propylbenzotriazole in a ratio of 2.4:1.

A more complex route leads from **7** to substituted *o*-phenylenediamines **13** (Scheme II). To our knowledge, this is the first report of benzotriazole ring opening upon treatment with a Grignard reagent. Traces of **13** were detected in many of the ethers **6** obtained, as contaminants which cause coloration after exposure to air and light. Their structures were recognized after pure *N*-benzyl-*N'*-phenethyl-*o*-phenylenediamine **13**, R^4 = $PhCH_2$) was separated from the reaction of benzotriazolylmethyl phenethyl ether with benzylmagnesium chloride.

The positive charge in **7** is delocalized, rendering positive the 3-position nitrogen. Attack of the Grignard molecule at the 3-nitrogen leads to betaine **10** with an additional stabilization from cyclized structure **11**. Further Grignard attack on **10** then leads to **12**, which on hydrolysis gives

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(42) Katritzky, A. R.; Yannakopoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673.
(43) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 805.
(44) Winstein, S.; Ingraham, L. L. *J. Am. Chem. Soc.* **1952**, *74*, 1160.

Table V. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of Ethers 6

no.	R^1	R^2	R^3	R^4
6a	0.86 (3 H, d, 6.8), 0.90 (3 H, d, 6.8), 1.64 (1 H, heptet, 6.8)	3.15 (1 H, quintet, 6.1), 3.60 (1 H, heptet, 6.1)	1.11 (3 H, d, 6.1), 1.13 (3 H, d, 6.1)	1.05 (3 H, d, 6.1)
6b	0.87 (3 H, 6.8), 0.89 (3 H, d, 6.8), 1.78 (1 H, m)	2.97 (1 H, ddd, 4.5, 5.3, and 7.0)	1.13 (3 H, d, 6.1), 1.14 (3 H, d, 6.2), 3.58 (1 H, heptet, 6.1)	0.90 (3 H, t, 7.4), 1.41 (2 H, m)
6c	0.90 (3 H, d, 6.9), 0.92 (3 H, d, 7.5), 1.43 (1 H, m)	2.79 (1 H, t, 5.5)	1.13 (6 H, d, 6.1), 3.60 (1 H, heptet, 6.1)	1.00–1.30 (5 H, m), 1.55–1.90 (6 H, m)
6d	0.93 (3 H, d, 6.8), 0.95 (3 H, d, 6.8), 1.72 (1 H, m)	3.26 (1 H, dt, 4.7 and 7.5)	0.85 (3 H, d, 6.1), 1.07 (3 H, d, 6.2), 3.38 (1 H, heptet, 6.1)	2.65 (1 H, dd, 7.6 and 13.7), 2.73 (1 H, dd, 4.8 and 13.6), 7.22 (5 H, m)
6e	1.02 (3 H, d, 6.8), 1.30 (3 H, d, 6.7), 2.14 (1 H, octet, 6.7)	4.24 (1 H, d, 7.3)	1.34 (3 H, d, 6.1), 1.43 (3 H, d, 6.1), 3.72 (1 H, heptet, 6.1)	7.58 (5 H, m)
6f	0.94 (3 H, d, 6.8), 0.95 (3 H, d, 6.8), 1.72 (1 H, m)	3.33 (1 H, dt, 7.3 and 4.8)	1.10 (4 H, m), 1.43 (1 H, m), 1.56 (2 H, m), 1.69 (2 H, m), 1.72 (1 H, m), 3.04 (1 H, m)	2.66 (1 H, dd, 13.7 and 7.5), 2.73 (1 H, dd, 13.7 and 4.9), 7.23 (5 H, m)
6g	0.95 (3 H, d, 6.8), 0.98 (3 H, d, 6.8), 1.92 (1 H, octet, 6.8)	4.11 (1 H, quintet, 6.1)	6.87 (2 H, d, 8.0), 6.89 (1 H, t, 7.3), 7.24 (2 H, dd, 9.0 and 7.0)	1.21 (3 H, d, 6.2)
6h	1.00 (3 H, d, 6.8), 1.03 (3 H, d, 6.8), 1.99 (1 H, m)	4.29 (1 H, quintet, 6.1)	7.13 (1 H, dd, 2.5 and 9.6), 7.13 (1 H, d, 2.7), 7.30 (1 H, ddd, 1.2, 6.9, and 8.1), 7.41 (1 H, ddd, 1.3, 6.8, and 8.2), 7.72 (3 H, m)	1.30 (3 H, d, 6.2)
6i	7.10–7.40 (5 H, m)	4.50 (1 H, dd, 5.7 and 7.6)	0.98 (3 H, d, 6.0), 1.05 (3 H, d, 6.2), 3.42 (1 H, heptet)	2.86 (1 H, dd, 5.6 and 13.5), 3.04 (1 H, dd, 7.7 and 13.5), 7.10–7.40 (5 H, m)
6j	7.20–7.40 (5 H, m)	5.48 (1 H, s)	1.21 (6 H, d, 6.1), 3.66 (1 H, heptet, 6.1)	7.20–7.40 (5 H, m)
6k	2.30 (3 H, s), 7.10 (2 H, d, 8.1), 7.21 (2 H, d, 8.1)	5.30 (1 H, s)	2.04 (2 H, m), 3.55 (2 H, t, 5.9), 3.67 (2 H, t, 6.5)	7.24 (1 H, m), 7.30 (4 H, m)
6l	R^1R^2: 1.21 (4 H, m), 1.50 (6 H, m)		0.97 (3 H, t, 7.3), 1.64 (2 H, m), 3.39 (2 H, t, 6.8)	2.74 (2 H, s), 7.16 (5 H, m)
6m	R^1R^2: 1.10–1.70 (8 H, m), 1.81 (2 H, m)		4.57 (2 H, s), 7.16–7.43 (5 H, m)	2.88 (2 H, s), 5.16–7.43 (5 H, m)
6n	1.13 (3 H, s)	1.13 (3 H, s)	3.17 (3 H, s)	0.87 (3 H, t, 7.3), 1.49 (2 H, q, 7.3)
6o	1.10 (3 H, s)	1.10 (3 H, s)	3.23 (3 H, s)	2.73 (2 H, s), 7.20 (5 H, m)
6p	1.12 (3 H, s)	1.12 (3 H, s)	0.90 (3 H, t, 7.2), 1.30 (6 H, m), 1.55 (2 H, m), 3.40 (2 H, t, 6.6)	2.77 (2 H, s), 7.21 (5 H, m)

Scheme II

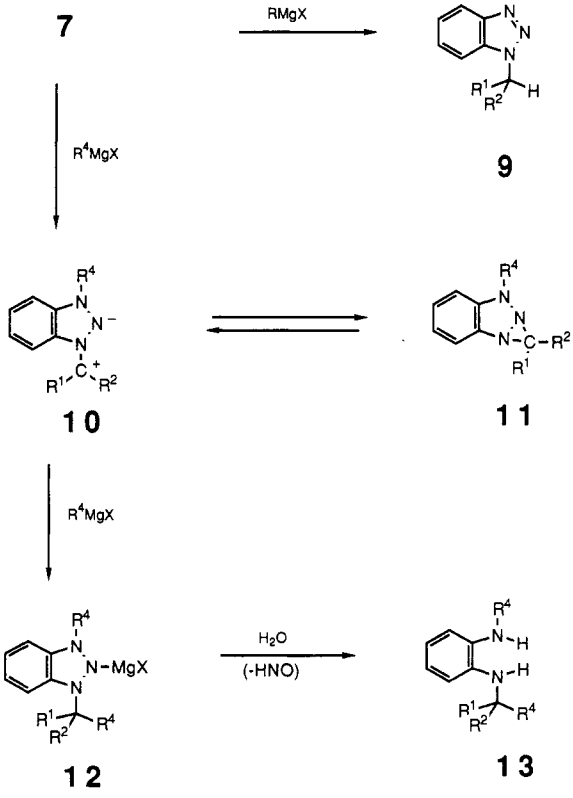
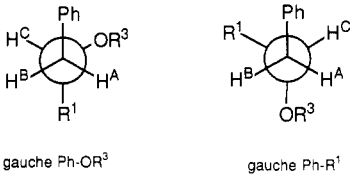


Chart I



the *o*-phenylenediamine **13** and nitrous oxide.

Spectral Characterization of Ethers 6. Surprisingly, most of the ethers now described are new compounds; this is, for example, the first report of the synthesis of a variety of β-phenylalkyl ethers. They have been fully characterized by proton (Table V) and carbon-13 (Table VI) NMR spectra. The benzyl methylene protons of **6f**, which resonate at slightly different fields, 2.66 and 2.73 ppm, possess quite different coupling constants to the neighboring carbon proton (7.5 and 4.9 Hz, respectively), indicating different dihedral angles between them (a preferential conformation). The same difference between the coupling constants of the benzylmethylene protons H^A and H^B to H^C observed in the spectrum of **6d** (R^3: cyclohexyl switched to isopropyl) and a smaller difference in the case of **6i** (R^1: isopropyl switched to phenyl) indicates that, in the preferred conformation, gauche interaction between the benzyl Ph and R^1 is found rather than gauche interaction between the Ph and the alkoxy group OR^3 (Chart I).

Comparison of the ^{13}C NMR spectra of ethers **6** allows observation of long-range substituent effects via a C–O–C linkage in sterically hindered molecules. Thus, comparison of the chemical shift of the secondary isopropoxy carbon of **6b** (δ 70.0) with the analogous carbon of **6a** (δ 69.4) (a hydrogen atom of the methyl group was substituted by another methyl) gives a value for the δ effect of +0.6 ppm, contrary to the reported data[45] for a series of simpler methyl alkyl ethers (−0.5 to −0.9 ppm), indicating additional steric interactions.

Scope and Limitations of the New Method for Preparation of Ethers. The new method now presented for the preparation of ethers seems to have few limitations. Although diaryl ethers cannot be obtained, many types of dialkyl ethers and of alkyl aryl ethers can be synthesized

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Table VI. ^{13}C NMR Chemicals Shifts (ppm) of Ethers 6

no.	R^1	C(1)	R^3	R^4
6a	17.3, 18.0, 33.5	77.8	22.4, 23.1, 69.4	18.8
6b	18.0, 18.6, 30.6	83.2	22.90, 22.93, 70.0	9.6, 23.3
6c	17.9, 20.7, 30.1	86.3	22.9, 22.9, 72.0	26.5, 26.7, 26.8, 28.8, 31.0, 41.0
6d	17.8, 18.6, 31.3	83.4	22.5, 22.6, 70.5	38.2, 125.7, 127.9, 129.4, 140.0
6e	19.0, 19.2, 34.9	84.9	21.1, 23.4, 68.8	127.0, 127.3, 127.8, 142.7
6f	18.0, 18.6, 31.2	83.3	24.4, 24.5, 25.8, 32.9, 33.0, 76.8	38.2, 125.7, 128.0, 129.6, 140.2
6g	17.7, 18.5, 33.0	78.3	115.9, 120.3, 129.4, 158.4	16.0
6h	17.8, 18.5, 33.0	78.4	108.3, 119.8, 123.4, 126.2, 126.6, 127.6, 128.8, 129.4, 134.6, 156.2	15.9
6i	127.3, 128.1, 129.6, 143.2	80.7	21.1, 23.3, 69.3	45.5, 126.0, 126.7, 127.9, 138.9
6j	127.0, 127.2, 128.3, 142.9	80.4	22.2, 69.0	127.0, 127.2, 128.3, 142.9
6k	21.0, 126.7, 129.0, 137.0, 139.1	83.6	32.9, 42.0, 65.4	126.8, 128.3, 127.3, 142.3
6l	R^1, R^2: 21.8, 25.7, 34.1	75.2	11.0, 23.6, 61.6	43.4, 125.9, 127.8, 130.4, 138.2
6m	R^1, R^2: 21.9, 25.7, 34.1	76.3	62.3, 127.0, 127.3, 128.3, 139.8	43.7, 126.0, 127.9, 130.5, 138.0
6n	R^1, R^2: 24.3	74.6	48.9	8.05, 32.0
6o	R^1, R^2: 24.5	75.1	49.1	46.0, 125.9, 127.7, 130.3, 138.2
6p	R^1, R^2: 25.1	74.8	14.0, 22.6, 26.0, 30.5, 31.7, 61.3	47.0, 125.9, 127.7, 130.5, 138.6

in high yield. No restriction has been found in relation to substituents R^1, R^2, R^3, and R^4 in the product ethers **6**, which therefore can possess primary, secondary, or tertiary alkyl groups, except that R^1 and R^2 cannot both be protons. Such simple ethers ($R^1 = R^2 = H$) can, however, easily be prepared by classical methods. Formation of new alkyl groups during the process, by the substitution of the benzotriazolyl group by an alkyl or aryl from the Grignard reagent, brings considerable versatility to this ether synthesis. The method is especially suitable for the preparation of ethers possessing bulky secondary or tertiary alkyl groups with a strong tendency toward elimination.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on a Varian VXR-300 instrument as solutions in $CDCl_3$ with tetramethylsilane as internal standard for ^1H and ^{13}C. Elemental analyses were determined by the Atlantic Microlab, Norcross, GA or in the Department of Chemistry under the supervision of Dr. R. W. King. Solvents for the Grignard reactions (ether, toluene, benzene) were dried by reflux under argon with sodium benzophenone and distilled immediately prior to use.

One-Pot Method for the Preparation of 1-(Chloromethyl)benzotriazole (1) from Benzotriazole and Aqueous Formaldehyde. A mixture of benzotriazole (11.91 g, 100 mmol), 37% formaldehyde (9.0 mL, 120 mmol), and toluene (250 mL) was stirred and heated to reflux under a Dean–Stark water trap. When the water level in the trap was established at about 8 mL (approximate time 45 min), the mixture was slightly cooled (to stop reflux), the water trap was replaced by a reflux condenser with a hydrogen chloride trap, and thionyl chloride (22 mL, 300 mmol) was added dropwise over 30 min. The mixture was refluxed for 2 h. After cooling, excess thionyl chloride and part of the toluene (150 mL of distillate) were distilled off. The remaining solution of 1-(chloromethyl)benzotriazole in toluene was used directly for the preparation of ethers. Vacuum evaporation of a small sample of this solution gave 1-(chloromethyl)benzotriazole[46] with purity above 90% (according to ^1H NMR).

Preparation of Benzotriazolylmethyl Methyl Ether (4a). To a stirred solution of 1-(chloromethyl)benzotriazole (100 mmol) in toluene (200 mL) was added dropwise a solution of sodium methoxide (100 mmol) in methanol (25 mL), and the reaction mixture was then refluxed for 1 h (formation of a white precipitate of NaCl was observed). The reaction mixture was poured into ice water, washed with 10% sodium hydroxide (100 mL) followed by water, and dried overnight over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product (23.0 g) was obtained. According to the NMR spectrum, it was a mixture of benzotriazolylmethyl methyl ether (**4a**) and dibenzotriazol-1-ylmethane[47] in a molar ratio of 1:1. Dibenzotriazol-1-ylmethane was removed from the mixture by trituration with toluene, cooling in the refrigerator overnight, and filtering off the precipitate. Evaporation of the solvent (rotary vacuum evaporator) gave oily benzotriazolylmethyl methyl ether of purity above 95% (according to ^1H NMR analysis). The analytical sample was prepared by column chromatography (silica gel, methylene chloride).

Preparation of Benzotriazolylmethyl *tert*-Butyl Ether (4b). Potassium *tert*-butoxide solution in *tert*-butyl alcohol was prepared by reaction of potassium metal (3.91 g, 100 mmol) with dry (molecular sieves) *tert*-butyl alcohol (47.15 mL, 500 mmol) at reflux temperature under argon. This solution was added dropwise to a toluene solution of 100 mmol of 1-(chloromethyl)benzotriazole (prepared according to the above procedure) and stirred under argon at room temperature. The obtained mixture was heated to reflux for 4 h and poured into ice–water (200 g), and the organic layer was separated. The toluene solution was washed with ice-cold 10% sodium hydroxide (100 mL) followed by water and dried over anhydrous potassium carbonate. The toluene and excessive *tert*-butyl alcohol were evaporated to give crude benzotriazol-1-ylmethyl *tert*-butyl ether. The analytical sample was obtained by column chromatography of the crude material (silica gel, methylene chloride).

Preparation of Benzotriazolylmethyl Phenethyl Ether (4c). Sodium hydride (2.64 g, 110 mmol) was added to a stirred solution of 1-(chloromethyl)benzotriazole (100 mmol, prepared according to the above procedure) and phenethyl alcohol (11.94 mL, 100 mmol) in dry toluene (200 mL). The mixture was stirred and refluxed under argon for 6 h. After being cooled to room temperature, the reaction mixture was poured into water (200 mL), and the organic layer was separated. The toluene solution was washed twice with ice-cold 10% sodium hydroxide (2 × 100 mL) followed by water (200 mL). The solution was dried over anhydrous potassium carbonate (5 g), and the solvent was evaporated (rotary vacuum evaporator) to give crude benzotriazol-1-ylmethyl phenethyl ether of purity above 90% (^1H NMR). The analytical sample was prepared by column chromatography (silica gel, chloroform). The product was characterized in Tables I–III.

Preparation of Benzotriazolylmethyl Phenyl Ether (4d) by a One-Pot Method. Formaldehyde (37%; 100 mL, 1.3 mol) was added dropwise over 1 h to a stirred benzotriazole (119.13 g, 1 mol) suspension in benzene (1 L). The mixture was stirred then at 20 °C for 1 h, followed by reflux under a Dean–Stark trap until no more water was carried over (2 h) to give white suspension of 1-(hydroxymethyl)benzotriazole. The water trap was removed, and a tubing connected to a hydrogen chloride trap was fitted on the reflux condenser top. To the stirred and refluxed suspension of the 1-(hydroxymethyl)benzotriazole was added thionyl chloride (140 mL, 2 mol) dropwise over 1 h, and the obtained solution was refluxed for an additional 1 h. Toluene (500 mL) was added, and the excess of thionyl chloride was distilled off with benzene and toluene until the distillate temperature reached 110 °C.

(46) Burckhalter, J. H.; Stephens, V. C.; Hall, L. A. R. *J. Am. Chem. Soc.* **1952**, *74*, 3868.

(47) Gaylord, N. G.; Naughton, J. M. *J. Org. Chem.* **1957**, *22*, 1022.

Methanolic sodium phenoxide [from sodium (23 g, 1 mol), phenol (94 g, 1 mol), and methanol (500 mL)] was added dropwise to the stirred solution of the 1-(chloromethyl)benzotriazole; sodium chloride precipitated. The reaction mixture was refluxed for 2 h, cooled to 20 °C, poured into water, and extracted with toluene (300 mL). The organic layer was washed with 10% sodium hydroxide (200 mL) followed by water (200 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated (rotary vacuum evaporator) to give benzotriazol-1-ylmethyl phenyl ether (196.1 g, 87%) of purity above 90% (according to NMR). The analytical sample was prepared by column chromatography (silica gel, methylene chloride).

General Method B for the Synthesis of α-Benzotriazolylalkyl Aryl Ethers (4). To methanolic sodium methoxide [from sodium (4.60 g, 200 mmol) and methanol (50 mL)] were added phenol (200 mmol) and toluene (150 mL). By use of a rotary vacuum evaporator, part of the solvent was evaporated to give 100 mL of sodium phenoxide suspension in toluene. 1-(α-Chloroalkyl)benzotriazole **3** (200 mmol) in toluene (100 mL) was added to this suspension of sodium phenoxide. The mixture was stirred and heated under reflux for 4 h and then poured into ice–water (200 g). The organic layer was separated, washed with 10% sodium hydroxide followed by water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the α-benzotriazolylalkyl aryl ether satisfactory for further reactions (purity above 90%). An analytical sample was prepared by column chromatography using silica gel and methylene chloride as an eluent.

General Method C for the Synthesis of α-Benzotriazolylalkyl Alkyl Ethers (4). Benzotriazole (23.82 g, 200 mmol), the appropriate aldehyde or cyclohexanone (250 mmol), the alcohol (250 mmol), and sulfuric acid (0.5 mL) in carbon tetrachloride (200 mL) were magnetically stirred and refluxed for 4 h in a Soxhlet apparatus with its extraction thimble filled with granular calcium chloride (33 g, 300 mmol). The solution was poured then into ice–water (300 mL), and the organic layer was separated, washed with 10% sodium carbonate followed by water, and dried over anhydrous sodium sulfate. Evaporation of the solvent by means of a rotary vacuum evaporator gave the crude α-benzotriazolylalkyl alkyl ether, satisfactory for further reactions (purity above 90%). Analytical samples were prepared by column chromatography using silica gel and methylene chloride as an eluent.

Preparation of Chloro Ether (4k). Benzotriazole (23.8 g, 200 mmol), *p*-tolualdehyde (24.0 g, 200 mmol), 3-chloropropanol (23.6 g, 250 mmol), thionyl chloride (0.01 mol), and methylene chloride (100 mL) were placed in an Erlenmeyer flask. Molecular sieves (100 g, dried for 24 h at 250 °C) were added. The capped reagent mixture was left at room temperature and occasionally shaken. Progress of the reaction was monitored by NMR and TLC. After 2 days (when reaction was complete), the crude mixture was poured into ice water, and the organic layer was separated, washed with 10% sodium carbonate (to remove benzotriazole) and water, and dried over anhydrous sodium sulfate, and the solvent was evaporated to give the crude product as a mixture with *p*-tolualdehyde. The aldehyde was removed by extraction with hexanes (3 × 50 mL) to leave almost pure **4k** (41.0 g, 65%). An analytical sample was prepared by column chromatography using silica gel and methylene chloride as an eluent.

Preparation of 2-(Benzotriazol-1-yl)-2-methoxypropane (4n). Sulfuric acid (0.27 mL, 5 mmol) was added to a stirred mixture of benzotriazole (11.91 g, 100 mmol), 2,2-dimethoxypropane (12.30 mL, 100 mmol), and methylene chloride (100 mL). After the mixture turned into a clear solution (about 40 min), it was poured into ice–water (200 g), and the organic layer was separated. The methylene chloride solution was washed with 10% sodium carbonate (100 mL) followed by water and dried over anhydrous sodium sulfate (10 g). The solvent was evaporated (rotary vacuum evaporator) to give 2-(benzotriazol-1-yl)-2-methoxy propane (**4n**) as colorless oil of purity (according to ^{1}H NMR) above 90%. The analytical sample was obtained by column chromatography (silica gel, methylene chloride) of the crude material. According to ^{1}H and ^{13}C NMR analyses, the analytical sample (after chromatography) appeared to contain also the 2-benzotriazolyl isomer (**5n**): ^{1}H NMR δ 2.08 (6 H, s), 3.12 (3 H, s), 7.43 (2 H, m), 7.96 (2 H, m); ^{13}C NMR δ 26.1, 50.8, 95.2, 118.4, 126.4, and 144.1. Attempted crystallization of the product from ether at −10 °C gave colorless needles which were separated from the mother liquor but soon melted at room temperature. NMR spectra of the obtained sample revealed that it was isomerically pure **4n**.

Preparation of 2-(Benzotriazol-1-yl)-2-(hexyloxy)propane (4o). A solution of 2-(benzotriazol-1-yl)-2-methoxypropane (19.1 g, 100 mmol), hexyl alcohol (10.2 g, 100 mmol), and *p*-toluenesulfonic acid (200 mg, 1 mmol) in 50 mL of methylene chloride was stirred at room temperature for 1 h, and then the solvent was evaporated using a vacuum rotary evaporator (at about 60 °C) to give 29.1 g of crude **4o** with purity above 80% (yield 88%). The analytical sample was prepared by column chromatography using silica gel and a mixture of methylene chloride and hexanes (1:1) as an eluent.

Preparation of 1-(Benzotriazol-1-yl)-1-methoxypropan-2-one (4p). A mixture of benzotriazole (11.91 g, 100 mmol), pyruvic aldehyde dimethyl acetal (14.2 g, 120 mmol), and 4 drops of concentrated hydrochloric acid was stirred and refluxed for 30 min. After cooling, the reflux condenser was replaced with a distillation one, and then less than the stoichiometric amount of methyl alcohol (about 2.5 mL) was distilled off. The condenser was replaced again with a reflux one, and heating at reflux was continued for the next 30 min. The reaction mixture was poured into ice–water, chloroform (100 mL) was added, and after shaking, the organic layer was separated, washed with 10% sodium carbonate (100 mL) followed by water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product (18.9 g, 95%). The crystalline analytical sample was prepared by trituration of a small sample of crude **4p** with ether and storage of the ethereal solution at −5 °C overnight.

General Method R for the Synthesis of Nonvolatile Ethers 6. α-Benzotriazolylalkyl alkyl or aryl ether **4** (50 mmol) in toluene (120 mL) in a three-necked, round-bottom flask of 250 mL equipped with a distillation condenser, a dropping funnel, a magnetic stirrer, and a heating mantle was stirred and heated, and when the solvent started to distil, a solution of Grignard reagent [from magnesium turnings (3.65 g, 150 mmol) and the appropriate alkyl or aryl halide (120 mmol)] was added dropwise. The rate of addition was balanced with the rate of distillation, keeping the same quantity level of the mixture in the flask. After the addition was finished, the distillation was continued until the distillate reached 100 °C. The distillation condenser was then replaced by a reflux one, and stirring and refluxing was continued for 3 h. The whole was then poured into ice–water (200 g) and neutralized with acetic acid. The organic layer was separated, washed with water followed by 10% sodium hydroxide (100 mL), and again water, and then dried over anhydrous sodium sulfate. The solvent was evaporated using a rotary vacuum evaporator. The obtained crude ether was purified by vacuum distillation or column chromatography (silica gel and hexane as an eluent). The obtained ethers are collected in Table IV.

General Procedure S for Volatile Ethers 6. To the stirred Grignard reagent [prepared from alkyl halide (300 mmol), magnesium turnings (9.7 g, 400 mmol), iodine (2.5 g, 10 mmol) in dry ether (250 mL)] placed in a three-necked, round-bottom flask equipped with a distillation condenser, a thermometer, a dropping funnel, and an efficient mechanical stirrer was added a solution of benzotriazolyl ether **4** (100 mmol) in dry diphenylmethane (200 mL). Stirring and distillation were carried out until the mixture in the flask reached 150 °C. The mixture was then poured into ice water (300 g) and neutralized carefully with glacial acetic acid. The organic layer was separated, washed with 10% sodium carbonate (100 mL) followed by water and dried over anhydrous sodium sulfate. The diphenylmethane solution was combined with the distillate, and careful column distillation was carried out to give the pure ether.

Preparation of 2-Methoxy-2-methyl-1-phenylpropane (6o). To a solution of benzotriazolyl ether **4n** (19.12 g, 100 mmol) in dry benzene (150 mL) stirred in a three-necked, round-bottom flask equipped with a distillation condenser, a thermometer, a dropping funnel, a mechanical stirrer and a heating mantel was added portionwise an ethereal solution of the benzyl Grignard reagent prepared from benzyl chloride (35 mL, 300 mmol), magnesium turnings (9.7 g, 400 mmol), and iodine (2.5 g, 10 mmol) in dry ether (250 mL). The heating was carried on until the

distillate temperature reached 80 °C. The reaction mixture was poured into ice water (100 g) and neutralized with acetic acid. The organic layer was separated and washed with water followed by 10% sodium carbonate (100 mL) and again water, and the solution was dried over anhydrous sodium sulfate. After evaporating off the solvent with a vacuum rotary evaporator, the crude product (purity about 90% according to ^{1}H NMR) was obtained. Vacuum column distillation (0.2 mmHg) gave pure **6o** (data in Tables IV–VI).

Procedure for Preparation of 6p. The reaction was carried out in a three-necked, round-bottom flask equipped with a reflux condenser, a magnetic stirrer, a heating mantel, and a dropping funnel. A Grignard reagent was prepared from benzyl chloride (11.5 mL, 100 mmol), magnesium turnings (3.0 g, 125 mmol), and iodine (0.5 g, 2 mmol) in dry ether (100 mL). To the stirred solution was added dropwise an ethereal solution of benzotriazolyl ether **4o** (5.23 g, 20 mmol). The reaction mixture was then heated at reflux for 24 h. Progress of the reaction was monitored by NMR (after workup of a small sample taken from the reaction mixture). After the reaction was accomplished (24 h), the mixture was poured into ice–water (100 g) and neutralized with acetic acid. The organic layer was separated, washed with water followed by 10% sodium carbonate (50 mL) and again water. The solution was dried over anhydrous sodium sulfate, and the solvent was evaporated to give crude ether **6p** with yield of about 95% (only bibenzyl was formed as a side product). An analytical sample was prepared by column chromatography using silica gel and methylene chloride/hexanes (1:1) as an eluent.

Reaction of Benzotriazolylmethyl Methyl Ether (4a) with Benzylmagnesium Chloride. To a solution of **4a** (4.90 g, 30 mmol) in dry toluene (200 mL) was added a solution of benzylmagnesium chloride obtained from magnesium turnings (8.75 g, 360 mmol) and benzyl chloride (34.5 mL, 300 mmol) in dry ether (200 mL). The resulting mixture was heated at reflux (about 50 °C) for 24 h. The mixture was poured into ice–water (300 g) and neutralized with acetic acid, and the organic layer was separated. The solution was washed with water, followed by 10% sodium carbonate (200 mL) and again water, and then dried over anhydrous sodium sulfate (50 g). The solvent was evaporated (rotary vacuum evaporator) to give a crude mixture (19.4 g), consisting (according to ^{1}H and ^{13}C NMR; together with a little bibenzyl and benzyl alcohol) of 1-phenethylbenzotriazole (**8a**, $R^1 = R^2 = H$, $R^4 = PhCH_2$), *N*-benzyl-*N'*-phenethyl-*o*-phenylenediamine (**13a**, $R^1 = R^2 = H$, $R^4 = PhCH_2$), and 1-methylbenzotriazole as the main products (total yield above 80%) in a ratio of 2:5:3.

A sample of the crude mixture (3.0 g) was subjected to column chromatography (silica gel, methylene chloride) to give pure **13a** (0.53 g), **8a** (0.22 g), and **9a** (0.36 g), in the order of the elution. **13a**: ^{1}H NMR δ 2.97 (2 H, t, J = 7.1 Hz), 3.38 (2 H, t, J = 7.1 Hz), 3.90 (2 H, b), 4.27 (2 H, s), 6.78 (4 H, m), 7.30 (10 H, m); ^{13}C NMR δ 35.5, 45.8, 48.8, 112.7, 119.8, 126.4, 127.3, 127.9, 128.6, 128.8, 136.4, 136.8, 139.0, 139.3. The compound was characterized as its picrate, yellow prisms, mp 165 °C. Anal. Calcd for $C_{27}H_{25}N_5O_7$: C, 61.01; H, 4.74; N, 13.18. Found: C, 60.74; H, 4.76; N, 13.04.

8a: ^{1}H NMR δ 3.28 (2 H, t, J = 7.6 Hz), 4.82 (2 H, t, J = 7.1 Hz), 7.2 (8 H, m), 8.00 (1 H, d, J = 7.6 Hz); ^{13}C NMR δ 36.2, 49.6, 109.1, 119.8, 123.7, 126.9, 127.1, 127.4, 128.4, 128.7, 137.2, 141.0. The product was characterized as its picrate, dark orange grains, mp 116 °C. Anal. Calcd for $C_{20}H_{16}N_6O_7$: C, 53.10; H, 3.56; N, 18.50. Found: C, 53.08; H, 3.53; N, 18.54.

Reaction of Benzotriazol-1-ylmethyl Methyl Ether (4a) with Methylmagnesium Chloride. A solution of benzotriazolylmethyl methyl ether (**4a**, 8.2 g, 50 mmol) in dry toluene (100 mL) was poured portionwise into a solution of the Grignard reagent prepared from methyl iodide (30 mL, 0.6 mol), iodine (1.25 g, 5 mmol), and magnesium turnings (19.5 g, 0.8 mol) in dry ether (300 mL). The mixture was stirred and heated, and distillation was carried on until its temperature reached 105 °C. The distillation condenser was replaced with a reflux one, and the heating at reflux was continued for 12 h. No starting material was left after that time (according to NMR). The mixture was then poured into ice-cold water (100 mL) and neutralized with acetic acid. The organic layer was separated, washed with water followed by 10% sodium carbonate and again water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude product mixture consisting mainly of 1-ethylbenzotriazole[48] (**8b**, $R^1 = R^2 = H$, $R^4 = CH_3$) and 1-methylbenzotriazole in a molar ratio of 5:7. Column chromatography (silica gel, chloroform) afforded an analytical sample of 1-ethylbenzotriazole (**8b**): ^{1}H NMR δ 1.59 (t, 3 H, J = 7.8 Hz), 4.65 (q, 2 H, J = 7.8 Hz), 7.30–7.54 (m, 3 H), 8.03 (d, 1 H, J = 8.3 Hz); ^{13}C NMR δ 14.6, 42.9, 109.1, 119.6, 123.5, 126.8, 132.3, 145.8. The product was characterized as the picrate: orange grains; mp 110–112 °C. Anal. Calcd for $C_{14}H_{12}N_6O_7$: C, 44.69; H, 3.21; N, 22.33. Found: C, 44.71; H, 3.16; N, 22.46.

Reaction of Benzotriazolylmethyl Phenethyl Ether (4c) with Benzylmagnesium Chloride. A solution of benzylmagnesium chloride, prepared from magnesium turnings (4.86 g, 200 mmol) and benzyl chloride (17.26 mL, 150 mmol) in dry ether (150 mL), was added to a solution of benzotriazol-1-ylmethyl phenethyl ether (**4c**, 6.32 g, 25 mmol) in dry toluene (200 mL). The mixture was heated, and the ether was distilled off until the temperature of the distillate reached 105 °C. The remaining solution was heated at reflux for 3 h. The reaction mixture was poured into ice–water (200 g) and neutralized with acetic acid. The organic layer was separated, washed with water, followed by 10% sodium hydroxide and again water. The solution was dried over anhydrous sodium sulfate, and the solvent was evaporated (rotary vacuum evaporator). The ^{1}H NMR spectra revealed that the crude product is a complex mixture. Column chromatography (silica gel, toluene) of a sample of the mixture (1.0 g) gave a fraction of pure *N*-benzyl-*N'*-phenethyl-*o*-phenylenediamine (**13a**, 70 mg) characterized above.

Reaction of Benzotriazolylmethyl Phenyl Ether (4d) with Ethylmagnesium Iodide. A solution of ethylmagnesium iodide prepared from magnesium turnings (7.72 g, 0.4 mol) and ethyl iodide (24 mL, 0.3 mol) in dry ether (150 mL) was added to a solution of benzotriazol-1-ylmethyl phenyl ether (**4d**, 22.52 g, 100 mmol) in dry benzene (250 mL). The ether and a part of the benzene were distilled off until the distillate temperature reached 80 °C. The remaining solution was refluxed for 3 h. The reaction mixture was poured into ice water (200 g) and neutralized with acetic acid, and the organic layer was separated. The benzene solution was washed with water followed by 10% sodium carbonate and again water. The solution was dried over anhydrous sodium sulfate, and the solvent was evaporated to give the crude product (20.75 g). According to ^{1}H NMR spectroscopy, the mixture consisted mainly of methylbenzotriazole and propylbenzotriazole in a ratio of 2.4:1. Column chromatography (silica gel, chloroform) gave, as the first fraction, 1-propylbenzotriazole[49] (**8c**, $R^1 = R^2 = H$, $R^4 = Et$) as a colorless liquid: ^{1}H NMR δ 0.97 (3 H, t, J = 7.3 Hz), 2.05 (2 H, hextet, J = 7.3 Hz), 4.61 (2 H, t, J = 7.1 Hz), 7.36 (2 H, m), 7.50 (1 H, m), 8.06 (1 H, d, J = 8.2 Hz); ^{13}C NMR δ 11.3, 23.1, 49.7, 109.3, 120.0, 123.7, 127.1, 133.3, 147.7; HRMS calcd for $C_9H_{11}N_3$ 161.0952 (M^+), found 161.0948.

Registry No. 1 ($R_1 = R_2 = H$), 54187-96-1; 1 (R_1 = *i*-Pr, $R_2 = H$), 111098-59-0; **4a**, 71878-80-3; **4b**, 123622-03-7; **4c**, 123622-04-8; **4d**, 111198-02-8; **4e**, 123622-05-9; **4f**, 111507-93-8; **4g**, 111507-97-2; **4h**, 123622-06-0; **4i**, 123622-07-1; **4j**, 123622-08-2; **4k**, 123622-09-3; **4l**, 123622-10-6; **4m**, 123622-11-7; **4n**, 123622-12-8; **4o**, 123622-13-9; **4p**, 123622-14-0; **5n**, 123622-25-3; **6a**, 90951-62-5; **6b**, 123622-15-1; **6c**, 123622-16-2; **6d**, 123622-17-3; **6e**, 123622-18-4; **6f**, 123622-19-5; **6g**, 62338-26-5; **6h**, 123622-20-8; **6i**, 33598-42-4; **6j**, 5670-79-1; **6k**, 123622-21-9; **6l**, 123622-22-0; **6m**, 123622-23-1; **6n**, 994-05-8; **6o**, 69278-45-1; **6p**, 123622-24-2; **8a**, 63777-68-4; **8b**, 16584-05-7; **8b**·picrate, 123622-28-6; **8c**, 16584-02-4; **9a**, 13351-73-0; **13a**, 123622-26-4; **13a**·picrate, 123622-27-5; benzotriazole, 95-14-7; dibenzotriazol-1-ylmethane, 88064-00-0; benzeneethanol, 60-12-8; sodium phenoxide, 139-02-6; 4-methoxyphenol, 150-76-5; phenol, 108-95-2; 2-naphthol, 135-19-3; isobutyraldehyde, 78-84-2; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; 2-propanol, 67-63-0; cyclohexanol, 108-93-0; 1-propanol, 71-23-8; benzyl alcohol, 100-51-6; 4-tolualdehyde, 104-87-0; 3-chloro-1-propanol, 627-30-5; 2,2-dimethoxypropane, 77-76-9; hexyl alcohol, 111-27-3; pyruvic aldehyde dimethyl acetal, 6342-56-9.

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