DIRECT SYNTHESIS OF α-(BENZOTRIAZOL-1-YL)ALKYL ETHERS

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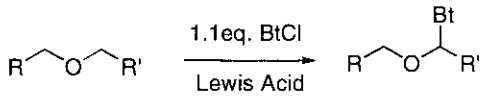
Abstract - α-(Benzotriazol-1-yl)alkyl ethers were prepared in synthetically useful yields by direct reaction of the corresponding ethers with *N*-chlorobenzotriazole in the presence of Lewis acids.

INTRODUCTION

N-Chlorobenzotriazole is a versatile synthetic reagent, widely used as a mild oxidant,[1a,1b] as a chlorinating agent,[2a,2b] for addition to olefins,[3a-3d] and in other transformations.[3e] *N*-Chlorobenzotriazole has also been shown to react with ethers to yield 5-40% of α-(benzotriazol-1-yl)alkyl ethers with yields reaching 65% when two equivalents of the reagent are used.[1a,4] Rees and Storr[3a] showed clearly that the reactions with olefins are ionic in character, proceeding by the initial addition of chloronium electrophile and then later addition of benzotriazole anion. They investigated the orientation of the addition showing it to be Markovnikoff type in character, and also found that the addition to both *cis*- and *trans*-butene is stereoselectively *trans*. They believed that the reactions of *N*-chlorobenzotriazole as an oxidant are radical in nature and showed that the balance between radical and ionic additions to olefins could be influenced by irradiation. However, neither the use of radical initiators nor UV light significantly improved the yields in substitution reactions of *N*-chlorobenzotriazole with ethers.[4]

RESULTS AND DISCUSSION

Under these circumstances it seemed of interest to investigate whether the presence of Lewis acids could improve the yields of such substitution reactions by binding to the 3-position of benzotriazole ring and increasing ionic character of the reagent. We now report that *N*-chlorobenzotriazole in the presence of Lewis acids provides 32-85% yields of synthetically versatile[5] α-(benzotriazol-1-yl)alkyl ethers (**2**).



1 32-85% **2**

R, R' = Alk, Aryl; Bt = benzotriazol-1-yl

For initial study of the reaction of *N*-chlorobenzotriazole with ethers we chose isochroman (**1c**) as a model substrate, and tested the effects of a number of Lewis acids at various reaction times and catalyst concentrations. The reaction was monitored by GC and the effect of the reaction conditions is summarized in Table 1. As shown in Table 1, $TiCl_4$ produced an optimum yield of compound (**2c**) (76%) when 20 mol% was used over 3 hours at room temperature. While polar solvents such as ethyl acetate (Entry 8) seemed to favor the formation of the product, moderately polar dichloromethane afforded no decomposition and thus better yields. The reaction time seems important, because the product is sensitive to the acidic reaction conditions and slowly decomposes. Other Lewis acids afforded significantly lower yields, while a protic acid yielded less than 10% of the desired product.

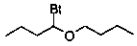
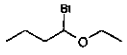
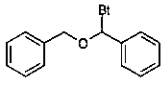
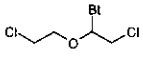
Table 1. Lewis Acid Promoted *N*-Chlorobenzotriazole conversion of Isochroman (**1c**) into (**2c**).

Entry	Lewis Acid	**2c**, Yield %		
		After 1 h	After 3 h	After 24 h
1	$B(OMe)_3/CH_2Cl_2$	9	27	40
2	$B(OMe)_3$/EtOAc	<2	12	37
3	9-BBN/CH_2Cl_2	12	36	46
4	AcOH	7	10	10
5	5 mol% $TiCl_4/CH_2Cl_2$	48	62	54
6	20 mol% $TiCl_4/CH_2Cl_2$	43	76	51
7	100 mol% $TiCl_4/CH_2Cl_2$	<2	25	<2
8	20 mol% $TiCl_4$/EtOAc	42	38	43
9	20 mol% $TiCl_4$/Toluene	17	29	21

Utilizing the conditions optimized for isochroman (**1c**) (20 mol% $TiCl_4/CH_2Cl_2$, 3 hours), we prepared a number of α-(benzotriazol-1-yl)alkyl ethers (**2**) (Table 2) by the addition of *N*-chlorobenzotriazole (1 mmol) to dialkyl ethers (**1**) (1 mmol) in the presence of 9-BBN or $TiCl_4$ (0.25 mmol) at room temperature. The reaction time varied from 4 hours to 24 hours. The volatile starting ethers (**1a,b,d,e**) afforded pure

products after removal of unreacted ether on a rotary evaporator. In the cases of higher boiling ethers (**1c,g,h,I**) the products were isolated by column chromatography or filtration through a short silica gel plug. A small amount (less then 5% by GC) of the Bt[2] isomer was detected in some reactions. Strained 3,3-dimethyloxetane when reacted in the presence of $TiCl_4$ gave exclusively ring opening products; however, milder boron Lewis acids afforded a small amount of the desired product, which, although detected by GC/MS, decomposed upon purification. The reaction of *N*-chlorobenzotriazole with butyl ethyl ether (**1g**) afforded a 2:3 mixture of isomers (**2g**) in 85% yield. Benzyl ether (**1h**) yielded 37% of (**2h**) and 16% of benzaldehyde as a product of further hydrolysis of (**2h**). In contrast to these results, benzotriazole was introduced exclusively to a benzylic position of isochroman (**1c**) in 74% yield. While such a difference in the reactivity of the cyclic and acyclic benzylic position may perhaps be explained by the anomeric effect,[6,7] there is not enough data to draw any mechanistic conclusions.

Table 2. Reactions of *N*-Chlorobenzotriazole to Ethers.

	Starting Ether		Product	Lewis Acid	Yield (%)	No catalyst
1a	Diethyl ether	**2a**		$TiCl_4$ or 9-BBN*	60	5[1a]
1b	Dioxane	**2b**		$TiCl_4$	54	34[4]
1c	Isochroman	**2c**		$TiCl_4$	76	<5
1d	THP	**2d**		$TiCl_4$	41	<5
1e	THF	**2e**		$TiCl_4$ or 9-BBN*	82	35[1a]
1f	Di-*n*-butyl ether	**2f**		$TiCl_4$	77	<5
1g	*n*-Butyl ethyl ether	**2g**	 and its regioisomer	$TiCl_4$	85	<5
1h	Dibenzyl ether	**2h**		$TiCl_4$	42**	15
1i	Dichloroethyl ether	**2i**		$TiCl_4$	32	<5

Bt = Benzotriazol-1-yl; *Comparable yields were obtained for both Lewis acid; **Additional 16% of benzaldehyde (resulted from product hydrolysis) was isolated.

We found the following limitations to this method: (i), aryl alkyl ethers underwent chlorination of the aromatic ring in the *ortho* and *para* positions rather than forming the desired α-benzotriazolyl ethers. (ii), The reaction of *N*-chlorobenzotriazole with secondary alkyl ethers resulted in decomposition. (iii), 1-Alkoxymethylbenzotriazoles, although previously prepared in 15-16% yields from the corresponding alkylmethyl ethers,[4] were unstable under these reaction conditions. In the presence of Lewis acid we isolated small quantities of hydroxymethylbenzotriazole, perhaps as a decomposition product of 1-alkoxymethylbenzotriazoles. The use of a milder Lewis acid, such as $B(OMe)_3$, did not give any improvement.

In conclusion, we prepared a number of α-(benzotriazol-1-yl)alkyl ethers in 32-85% yields directly from reaction of the corresponding ethers and *N*-chlorobenzotriazole in the presence of Lewis acids.

EXPERIMENTAL

General. Melting points were determined with a MEL-TEMP capillary melting point apparatus. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard for ^1H (300 MHz) or solvent as internal standard for ^{13}C (75 MHz). Tetrahydrofuran (THF) was distilled under nitrogen immediately before use over sodium/benzophenone. Chloromethyltrimethylsilane was purchased from Gelest, Inc. Column chromatography was conducted with silica gel 230-400 mesh. All organometallic reactions were carried out under argon in oven-dried glassware. All other reagents were reagent grade and were used without purification.

General Procedure for α-(Benzotriazol-1-yl)alkyl Ether Preparation. Ether (2 mmol) was dissolved in CH_2Cl_2 (0.5 mL), and $TiCl_4$ (0.4 mmol, 1 M solution in CH_2Cl_2) was added under a flow of nitrogen. A solution of *N*-chlorobenzotriazole (346 mg, 2.25 mmol) in CH_2Cl_2 (1.5 mL) was added to the reaction mixture which was stirred at rt. The resulting solution was diluted with 10 mL of ether, quenched with 0.5 M NaOH (30 mL), washed with water and extracted with ether (3 x 20 mL). The combined extracts were washed with water (1 x 10 mL) and then dried with Na_2SO_4. Pure product was obtained by evaporating the solvent. In some cases it was further purified by silica gel column chromatography.

1-(1-Ethoxyethyl)-1*H*-1,2,3-benzotriazole[1a] **(2a)**: oil, ^1H NMR δ 1.14 (t, 3H, J = 6.9 Hz), 1.87 (d, 3H, J = 6.2 Hz), 3.15-3.35 (m, 1H), 3.45-3.60 (m, 1H), 6.27 (q, 1H, J = 6.1 Hz), 7.39 (t, 1H, J = 7.8 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 8.2 Hz), 8.08 (d, 1H, J = 8.4 Hz); ^{13}C NMR δ 14.7, 21.2, 64.3, 87.0, 111.2, 120.1, 124.1, 127.4, 131.7, 146.8.

1-(1,4-Dioxan-2-yl)-1*H*-1,2,3-benzotriazole[4] (**2b**): oil, ^{1}H NMR δ 3.78-3.92 (m, 4H), 4.16 (dd, 1H, J = 3.0 Hz, 12.4 Hz), 4.46 (dd, 1H, J = 7.2 Hz, 11.8 Hz), 6.02 (dd, 1H, J = 3.0 Hz, 7.2 Hz), 7.32 (t, 1H, J = 7.4 Hz), 7.44 (t, 1H, J = 7.4 Hz), 7.68 (d, 1H, J = 8.3 Hz), 8.01 (d, 1H, J = 8.3 Hz); ^{13}C NMR δ 65.4, 65.9, 67.3, 81.9, 110.5, 120.0, 124.3, 127.8, 132.5, 146.0; Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.41. Found: C, 58.41; H, 5.39.

1-(3,4-Dihydro-1*H*-isochroman-1-yl)-1*H*-1,2,3-benzotriazole (**2c**): mp 71.3-72.1 CH_2Cl_2; ^{1}H NMR δ 2.98- 3.19 (m, 2H), 4.04 (t, 2H, J = 5.5 Hz), 6.88 (d, 1H, J = 7.6 Hz), 7.00-7.10 (m, 1H), 7.10-7.20 (m, 1H), 7.20-7.35 (m, 4H), 7.40 (s, 1H), 8.01-8.05 (m, 1H); ^{13}C NMR δ 27.4, 61.6, 83.0, 110.5, 119.6, 123.7, 126.5, 126.6, 127.3, 128.7, 129.8, 132.3, 134.4, 146.0; HRMS 252.1133 (M^+ 252.1137).

1-(Tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-benzotriazole (**2d**): oil, ^{1}H NMR δ 1.95-2.10 (m, 3H), 2.35-2.50 (m, 2H), 2.75-2.95 (m, 1H), 3.95-4.10 (m, 1H), 4.10-4.20 (m, 1H), 6.27 (d, 1H, J = 7.9 Hz), 7.60 (t, 1H, J = 7.6 Hz), 7.72 (t, 1H, J = 8.0 Hz), 7.98 (d, 1H, J = 8.4 Hz), 8.30 (d, 1H, J = 8.2 Hz). ^{13}C NMR δ 21.5, 24.8, 29.2, 66.8, 85.6, 111.0, 119.8, 124.1, 127.4, 132.3, 146.3.

1-(Tetrahydro-2-furanyl)-1*H*-1,2,3-benzotriazole[1a] (**2e**): oil, ^{1}H NMR δ 2.10-2.30 (m, 1H), 2.30-2.60 (m, 2H), 3.05-3.20 (m, 1H), 3.95-4.15 (m, 2H), 6.50 (d, 1H, J = 6.8 Hz), 7.37 (t, 1H, J = 7.7 Hz), 7.49 (t, 1H, J = 7.9 Hz), 7.71 (d, 1H, J = 8.2 Hz), 8.05 (d, 1H, J = 8.2 Hz); ^{13}C NMR δ 24.3, 30.7, 69.2, 87.8, 110.4, 119.8, 124.0, 127.4, 132.8, 146.4.

1-(1-Butoxybutyl)-1*H*-1,2,3-benzotriazole (**2f**): oil, ^{1}H NMR δ 0.81 (t, 3H, J = 7.4 Hz), 0.93 (t, 3H, J = 7.4 Hz), 1.20-1.40 (m, 3H), 1.40-1.60 (m, 3H), 2.05-2.20 (m, 1H), 2.20-2.35 (m, 1H), 3.15-3.25 (m, 1H), 3.40-3.55 (m, 1H), 6.05 (t, 1H, J = 6.8 Hz), 7.38 (t, 1H, J = 8.0 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.79 (d, 1H, J = 8.2 Hz), 8.08 (d, 1H, J = 8.2 Hz); ^{13}C NMR δ 13.4, 13.6, 18.2, 19.1, 31.2, 36.6, 68.8, 90.8, 111.3, 119.9, 124.1, 127.2, 131.2, 146.7. Anal. Calcd for $C_{14}H_{21}N_3O$: N, 16.99. Found: N, 17.00.

1-(1-Ethoxybutyl)-1*H*-1,2,3-benzotriazole (**2g**): oil, ^{1}H NMR δ 0.93 (t, 3H, J = 7.4 Hz), 1.14 (t, 3H, J = 7.1 Hz), 1.20-1.35 (m, 1H), 1.35-1.55 (m, 1H), 2.05-2.20 (m, 1H), 2.20-2.40 (m, 1H), 3.25-3.40 (m, 1H), 3.45-3.60 (m, 1H), 6.08 (t, 1H, J = 6.8 Hz), 7.38 (t, 1H, J = 7.9 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.79 (d, 1H, J = 8.1 Hz), 8.08 (d, 1H, J = 8.2 Hz). ^{13}C NMR δ 13.4, 14.7, 18.1, 36.7, 64.5, 90.6, 111.2, 120.0, 124.1, 127.3, 131.2, 146.7. Anal. Calcd for $C_{12}H_{17}N_3O$: N, 19.17. Found: N, 19.38.

1-[(Benzyloxy)(phenyl)methyl]-1*H*-1,2,3-benzotriazole (**2h**): oil, ^{1}H NMR δ 4.57 (s, 2H), 7.20-7.45 (m, 14H), 8.05-8.10 (m, 1H); ^{13}C NMR δ 70.7, 88.3, 111.6, 119.8, 124.2, 125.9, 126.5, 127.4, 128.0, 128.1, 128.4, 128.5, 128.9, 131.1, 136.0, 146.9; HRMS (M^+ +1, 316.1449), 316.1450; Anal. Calcd for $C_{20}H_{17}N_3O$: N, 13.33. Found: N, 13.69.

1-[2-Chloro-1-(2-chloroethoxy)ethyl]-1*H*-1,2,3-benzotriazole (**2i**): oil, ^{1}H NMR δ 3.54-3.64 (m, 3H), 3.75-3.89 (m, 1H), 4.01-4.17 (m, 2H), 6.23 (t, 1H, J = 6.1 Hz), 7.36 (t, 1H, J = 7.3 Hz), 7.45 (t, 1H, J = 7.3 Hz), 7.65 (d, 1H, J = 8.3 Hz), 8.03 (d, 1H, J = 8.3 Hz); ^{13}C NMR δ 41.9, 43.3, 69.6, 89.4, 110.5, 111.6, 120.4, 124.7, 128.3, 131.5, 146.6; HRMS 260.0383 (M^+ 260.0357).

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