

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

Alan R. Katritzky,* Michael V. Voronkov, Alfredo Pastor, and Douglas Tatham

Department of Chemistry, Center for Heterocyclic Compounds, University of Florida, Gainesville, Florida 32611-7200, USA

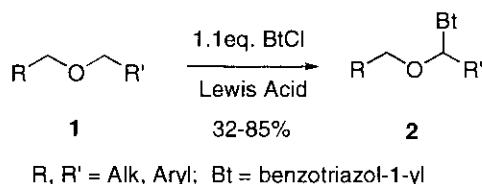
Abstract - α -(Benzotriazol-1-yl)alkyl ethers were prepared in synthetically useful yields by direct reaction of the corresponding ethers with *N*-chlorobenzotriazole in the presence of Lewis acids.

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 versatile⁵ α -(benzotriazol-1-yl)alkyl ethers (2).



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, TiCl₄ 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.






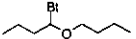
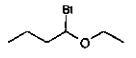
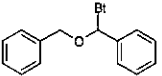
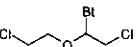
Table 1. Lewis Acid Promoted *N*-Chlorobenzotriazole conversion of Isochroman (**1c**) into (**2c**).

Entry	Lewis Acid	2c, Yield %		
		After 1 h	After 3 h	After 24 h
1	B(OMe) ₃ /CH ₂ Cl ₂	9	27	40
2	B(OMe) ₃ /EtOAc	<2	12	37
3	9-BBN/CH ₂ Cl ₂	12	36	46
4	AcOH	7	10	10
5	5 mol% TiCl ₄ /CH ₂ Cl ₂	48	62	54
6	20 mol% TiCl ₄ /CH ₂ Cl ₂	43	76	51
7	100 mol% TiCl ₄ /CH ₂ Cl 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% TiCl₄/CH₂Cl₂, 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 TiCl₄ (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 than 5% by GC) of the Bt² isomer was detected in some reactions. Strained 3,3-dimethyloxetane when reacted in the presence of TiCl₄ 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- <i>n</i> -butyl ether	2f 	TiCl ₄	77	<5
1g <i>n</i> -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-Alkoxyethylbenzotriazoles, 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-alkoxyethylbenzotriazoles. 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 CDCl₃ with tetramethylsilane as internal standard for ¹H (300 MHz) or solvent as internal standard for ¹³C (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 CH₂Cl₂ (0.5 mL), and TiCl₄ (0.4 mmol, 1 M solution in CH₂Cl₂) was added under a flow of nitrogen. A solution of *N*-chlorobenzotriazole (346 mg, 2.25 mmol) in CH₂Cl₂ (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 Na₂SO₄. 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); ¹³C 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-benzotriazole⁴ (**2b**): oil, ¹H 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); ¹³C 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 C₁₀H₁₁N₃O₂: 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 CH₂Cl₂; ¹H 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); ¹³C 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, ¹H 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). ¹³C 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, ¹H 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); ¹³C 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, ¹H 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); ¹³C 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 C₁₄H₂₁N₃O: N, 16.99. Found: N, 17.00.

1-(1-Ethoxybutyl)-1*H*-1,2,3-benzotriazole (**2g**): oil, ¹H 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). ¹³C 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 C₁₂H₁₇N₃O: N, 19.17. Found: N, 19.38.

1-[(Benzyloxy)(phenyl)methyl]-1*H*-1,2,3-benzotriazole (**2h**): oil, ^1H 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 $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}$: N, 13.33. Found: N, 13.69.

1-[2-Chloro-1-(2-chloroethoxy)ethyl]-1*H*-1,2,3-benzotriazole (**2i**): oil, ^1H 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).

ACKNOWLEDGMENT

A. P. is grateful to the Ministerio de Educación y Cultura of Spain for the concession of a fellowship and its financial support.

REFERENCES

1. (a) C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 1969, 1474; (b) W. D. Kingsbury and C. R. Johnson, *J. Chem. Soc., Chem. Commun.*, 1969, 365.
2. (a) P. M. Bowyer, D. H. Iles and A. Ledwith, *J. Chem. Soc.*, 1971, 2775; (b) M. Cinquini and S. Colonna, *Synthesis*, 1972, 259.
3. (a) C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 1969, 1478; (b) S. J. Barker and R. C. Storr, *J. Chem. Soc., Perkin Trans. I*, 1990, 485; (c) P. A. Wender and C. B. Cooper, *Tetrahedron*, 1986, **42**, 2985; (d) G. Garcia-Muñoz, R. Madroñero, M. C. Saldaña, M. Stud and M. Rico, *J. Heterocycl. Chem.*, 1971, **8**, 1031; (e) A. R. Katritzky, A. V. Ignatchenko, X. Lan, H. Lang and C. V. Stevens, *Tetrahedron*, 1994, **50**, 6005.
4. P. M. Pojer, *Aust. J. Chem.*, 1979, **32**, 2787.
5. A. R. Katritzky, X. Lan, J. Z. Yang, and O. V. Denisko, *Chem. Review*, 1998, **98**, 409.
6. V. Malatesta and K. U. Ingold, *J. Am. Chem. Soc.*, 1981, **103**, 609.
7. A. L. Beckwith and C. J. Easton, *J. Am. Chem. Soc.*, 1981, **103**, 615.

Received, 14th April, 1999