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Preparation of 1,2- and 1,4-Diols *via* Selective Cleavage of C-Benzotriazole Bonds in Reductive Lithiations of *N*-(α-Alkoxy-benzyl- and -allyl-)benzotriazoles

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Abstract: Selective cleavage of C-benzotriazole bonds in the presence of C-O bonds is reported for the reductive lithiation of *N*-(α-alkoxybenzyl)benzotriazoles and *N*-(α-alkoxyallyl)benzotriazoles in a one-step or two-step process. Trapping of the intermediates with carbonyl compounds gave unsymmetrically protected 1,2 or 1,4-diols in moderate yields. © 1998 Elsevier Science Ltd. All rights reserved.

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Transforming a C-X (X = heteroatom) bond into the corresponding carbanion is important for the preparation of functionalized organometallic reagents (Eq. 1).[1a,b] Many different heteroatoms (*e.g.* halides, S, P and O) have been utilized in these conversions; in particular, many kinds of C-O bond could be transformed into the corresponding carbanions.[2] However, similar transformations from C-N bonds into the carbanions have been more difficult; before our work the few known examples were restricted to the small heterocycles aziridines[3a] and azetidines.[3b] We recently demonstrated that in contrast to simple amino derivatives, allyl-,[5a,b] benzyl-[5a,6] and α-aminoalkyl-benzotriazoles[7] with benzotriazolyl (Bt) as a leaving group[4] could be converted into the corresponding carbanions *via* a C-benzotriazole bond (C-N) scission. We have now found that such C-benzotriazole bonds can be cleaved selectively in the presence of a geminal C-O bond.

$$\mathrm{C{-}X} \longrightarrow \mathrm{C}^{-} + \mathrm{X}^{-} \qquad \text{Eq. 1}$$

X = Br, Cl, S, P, O, N, Bt

When *N*-(α-ethoxybenzyl)benzotriazole (**1a**)[8] was treated with lithium/lithium bromide in the presence of cyclopentanone in THF at -78 °C for 2 h, unsymmetrically protected diol **4au** was isolated in 66% yield (Scheme 1, Table 1).[9] Interestingly, aromatic aldehydes, which usually show severe pinacol coupling problems under such Barbier-type conditions, can be used successfully as electrophiles in this new reaction to produce

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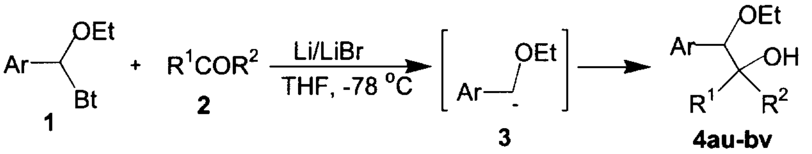
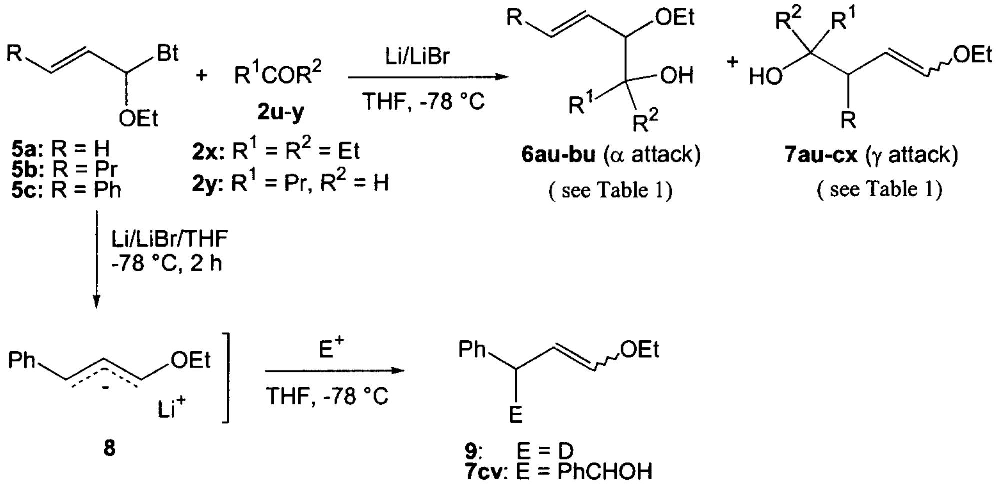
vicinal diols **4av,aw** in 54-57% yields, accompanied with about 10-15% pinacol coupling by-products. Treatment of *N*-(α-ethoxy-*p*-methylbenzyl)benzotriazole (**1b**)[8] with Li/LiBr and benzaldehyde gave **4bv** in 48% yield. Compounds **4av,aw,bv** were each formed as a diastereomeric mixture in about a 1:1 ratio. All of these results showed that good selectivity for the cleavage of C-Bt bonds in the pesence of C-O bonds could be obtained *via* carbanion **3**[10] under appropriate conditions.



1a: Ar = Ph **1b**: Ar = *p*-$CH_3C_6H_4$ (see Table 1)
2u: $R^1 = R^2 = -(CH_2)_4-$ **2v**: R^1 = Ph, R^2 = H **2w**: R^1 = *p*-$CH_3C_6H_4$, R^2 = H

Scheme 1

In a similar manner, the C-Bt bond in *N*-(α-ethoxyallyl)benzotriazoles (**5a-c**)[8] could be cleaved selectively under the same Barbier-type conditions (Scheme 2). The reactions of *N*-(α-ethoxyallyl)benzotriazole (**5a**) and ketones or aliphatic aldehydes displayed mainly α-attack to form vicinal diols **6au,ax,ay** in 50-67% yields; γ-attack product could be detected in the crude reaction mixture by ^{1}H NMR and 25% of compound **7au** was isolated alongside 50% of **6au**. The selectivities for α/γ attack were between 2 and 4:1. By contrast, aromatic aldehydes **2v** and **2w** as electrophiles gave predominantly the γ-attack products **7av** (61%, *cis* only) and **7aw** (45%, *cis*:*trans* = 4:1).



Scheme 2

Table 1. The Preparation of Unsymmetrically Protected Diols **4**, **6** and **7**

Substrates				Products						
No.	Ar/R	R^1	R^2	**4 or 6**	yield (%)	ratio[a]	7	yield (%)	*cis*:*trans*	**6**:**7**[b]
1a/2u	Ph	$-(CH_2)_4-$		**4au**	66	-				
1a/2v	Ph	Ph	H	**4av**	54	1:1				
1a/2w	Ph	*p*-Tol	H	**4aw**	57	1:1				
1b/2v	*p*-Tol	Ph	H	**4bv**	48	1:1				
5a/2u	H	$-(CH_2)_4-$		**6au**	50	-	**7au**	25	11:1	2 : 1
5a/2x	H	Et	Et	**6ax**	61	-	-[c]			4:1
5a/2y	H	Pr	H	**6ay**	67	1:1	-[c]			4:1
5a/2v	H	Ph	H	-[d]			**7av**	62	> 98:2	-[d]
5a/2w	H	*p*-Tol	H	-[d]			**7aw**	45	4:1	-[d]
5b/2u	Pr	$-(CH_2)_4-$		**6bu**	42	-[e]	**7bu**	20	10:1	2:1
5b/2v	Pr	Ph	H	-[d]			**7bv**	56	10:1[f]	-[d]
5c/2u	Ph	$-(CH_2)_4-$		-[d]			**7cu**		1:2	-[d]
5c/2v	Ph	Ph	H	-[d]			**7cv**	65[g]	1:2[f]	-[d]
5c/2w	Ph	*p*-Tol	H	-[d]			**7cw**	58	1:2[f]	-[d]
5c/2x	Ph	Et	Et	-[d]			**7cx**	60	1:2	-[d]

[a] Diastereoisomer ratio. [b] Regioselectivity of α/γ attack by ^1H NMR of the crude products. [c] Compounds **7** were detected by NMR but not isolated. [d] Compounds **7** predominant from NMR of the crude products, and no corresponding compounds **6** were isolated. [e] *Trans* only. [f] Diastereoisomers in a ratio of 1:1 were formed. [g] The yield was 58% when the reaction was carried out in the two-step procedure.

γ-Propyl substituted allylbenzotriazole **5b** affords both α- and γ-attack products **6bu** (42 %, *trans* only) and **7bu** (20 %, *cis*:*trans* = 10:1, Table 1) when a ketone was the electrophile. When an aromatic aldehyde was the electrophile, only γ-attack product **7bv** (*cis*:*trans* = 10:1) was detected. However γ-attack 1,4-diols **7cu**,**cv**,**cw**,**cx**, (*trans*:*cis* $\cong$ 2:1, about 1:1 diastereomers) were obtained from the reaction of γ-phenyl substituted allylbenzotriazole **5c** with both aliphatic or aromatic carbonyl electrophiles (Scheme 2, Table 1).

The above reactions can also be carried out as a two-step process. Thus, *N*-(α-ethoxy-γ-phenylallyl)benzotriazole (**5c**) was treated with Li/LiBr in THF at -78 °C for 2 h to form the allylmetal intermediate **8**,[10] which was then trapped by D_2O or benzaldehyde to give γ-attack products **9** and **7cv** in 70% and 58% yields, respectively (Scheme 2).

In summary, we developed a reductive lithiation of *N*-(α-ethoxy-benzyl- or -allyl-)benzotriazoles and demonstrated selective C-benzotriazole (C-N type) bond scission to provide a potentially useful alternative route for the preparation of α-alkoxy carbanions.[2] However, the α:γ and *cis*:*trans* selectivities are strongly dependant on the substrates used and require further investigation.

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9. **Representative Experimental Procedures for the Reactions of Compounds 1 or 5 with Carbonyl Compounds**: Lithium (0.57 g, 25 mmol, 30% dispersion in mineral oil) was washed twice with THF under argon. THF (10 mL) was added and the lithium suspension was treated with 1,2-dibromoethane (2 mmol) and then cooled to -78 °C. A solution of *N*-(α-ethoxybenzyl)benzotriazole (**1a**, 5 mmol) and cyclopentanone (10 mmol) in THF (20 mL) was added dropwise into the lithium over 1 h (typically, a dark-green color will develop during this time) and kept another 2-4 h before being quenched with water (15 mL) at the same temperature. After ether extraction, the crude product was purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes = 1/10) to give **4au** in 66% yield. All of the 1,2- and 1,4-diols prepared gave satisfactory ^1H and ^{13}C NMR spectra, and novel products gave satisfactory microanalyses or HRMS.
10. The generation of α-alkoxy carbanions of type $RO\text{-}C^-$ has been recently surveyed, see Guijarro, A.; Yus, M. *Tetrahedron Lett.* **1996**, *37*, 5593-5596.