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Reductive Cleavage of Benzyl Ethers with Lithium Naphthalenide. A Convenient Method for Debenzylation

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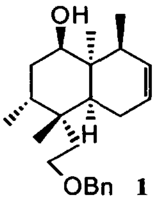
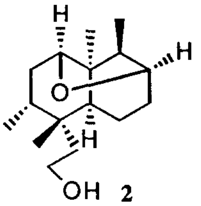
Abstract: An operationally simple, high-yielding and highly chemoselective procedure has been developed for the conversion of benzyl ethers to the corresponding alcohols, using lithium naphthalenide as the reagent. © 1997 Elsevier Science Ltd.

During the course of our synthetic studies on clerodanes,[1] it was necessary to remove the benzyl protecting group present in the advanced intermediate **1**. Several general methods have been well established for debenzylation,[2] including hydrogenolysis, acid induced cleavage and dissolving metal reduction.[3] Hydrogenolysis is obviously incompatible with the disubstituted double bond portion of the compound in question. On the other hand, treatment of **1** with an acid, such as ferric chloride,[4] gave exclusively the cyclization products **2** and **3** in various ratios. The reductive cleavage of **1** with lithium in ethylamine proved to be useful. However, the reaction was not reproducible. The desired diol **4** was obtained in 14-87% yield along with the over-reduced product **5** in 6-81% yield. As a result, a more reliable method was sought, and lithium naphthalenide was experimentally recognized as a superior reagent for the desired debenzylation. Thus, treatment of benzyl ether **1** with 6 equivalents of lithium naphthalenide, prepared *in situ* or as a stock solution, gave consistently the desired diol in high yield (>90%). The reaction, which was carried out in tetrahydrofuran, was rather rapid (~80 min) even at -25°C, and more importantly, not a trace of the over-reduced product **5** was observed.

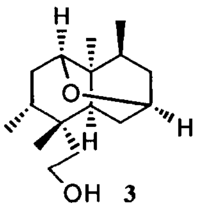
The effectiveness and generality of lithium naphthalenide as a reagent for reductive cleavage of benzyl ethers are evident from the results obtained for a large number of compounds possessing an array of diverse functionalities, including alcohol, carbon-carbon double bond, benzene ring and several other frequently used hydroxyl protecting groups, such as tetrahydropyranyl ether, silyl ether, and methoxymethyl ether. As indicated in Table 1, Entries 1-6, these functional groups are highly compatible with the conditions used for debenzylation. As expected, in the absence of active hydrogen, the amount of the reagent could be reduced to 3 equivalents. This was found to be the appropriate amount, in general, for the removal of the benzyl group. Table 1 also includes an example (Entry 7) in which the benzyloxy group is attached to an allylic carbon. The selective cleavage of the benzyl-oxygen linkage is difficult by any existing method. However, an 87% yield of the corresponding allylic alcohol was obtained, upon treatment of 6-benzyloxy-3,3-dimethylcyclohexene with lithium naphthalenide. A carbonyl-containing compound, 3β-benzyloxy-5-androsten-17-one, was also examined. Treatment of this ketonic benzyl ether with lithium naphthalenide resulted in the formation of a complex mixture containing only a small amount of the desired alcohol (Entry 8). The complication was apparently due to the susceptibility of ketone carbonyl to reduction, reductive coupling and addition reactions.[5] This problem was readily circumvented by the prior formation of the enolate ion[6] using lithium diisopropylamide followed by addition of lithium naphthalenide (Entry 9). In this way, an 82% yield of the desired alcohol was realized.



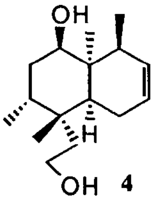
1



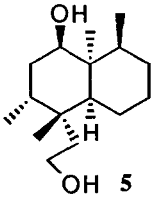
2



3



4

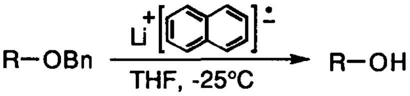


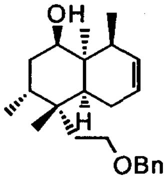
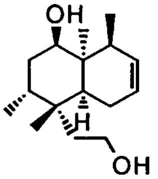
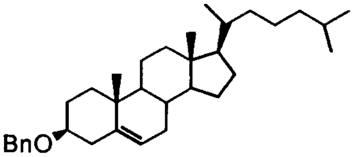
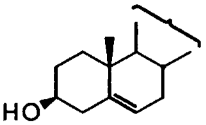
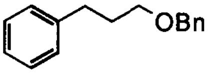
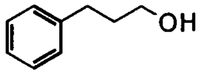
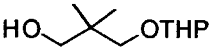
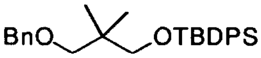
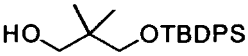
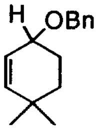
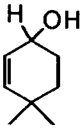
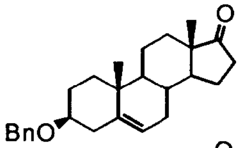
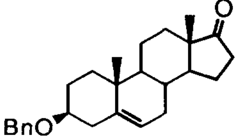
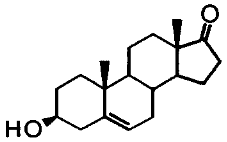
5

As described above, lithium naphthalenide presents itself as a mild, highly effective reagent for the conversion of benzyl ethers to the corresponding alcohols. In addition to high yields and good chemoselectivity, the application of this reagent has the great advantage of operational simplicity as demonstrated by the following typical experiment.

To a solution of naphthalene (0.35 g, 2.8 mmol) in THF (12 mL), were added lithium metal (15 mg, 2.1 mmol) in small pieces. The reaction mixture was stirred at room temperature under an argon atmosphere until lithium metal was completely dissolved (~3 h).[9] The resulting dark green solution of lithium naphthalenide was then cooled to -25°C, followed by addition of a solution of 1-benzyloxy-3-phenylpropane (157 mg, 0.69 mmol) in THF (4 mL) dropwise over 5 min. The resulting mixture was stirred at -25°C for 70 min. Saturated aqueous ammonium chloride (3 mL) and water (3 mL) were then added. The resulting solution was extracted with ether (3 x 15 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was then purified by flash chromatography on silica gel. Elution with ethyl acetate in *n*-hexane (5-10%) gave 3-phenylpropan-1-ol (80 mg, 85% yield).[10]

Table 1. Reductive Debenzylation with Lithium Naphthalenide (LN)



Entry	Substrate	Time (min)	LN (eq)	Product	% Yield[a]
1		80	6		94
2		60	3.2		85
3		70	3.1		85
4		70	3.3		91
5		75	3.2		73
6	BnO–(CH$_2$)$_{10}$–OMOM	55	3	HO–(CH$_2$)$_{10}$–OMOM	98
7		70	3.5		87
8		65	6	complex mixture	
9		60	8[b]		82

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[a] Yields are for isolated, chromatographically pure products. [b] The starting material was treated with 1.5 eq of lithium diisopropylamide at -25°C for 50 min prior to the addition of LN.

Acknowledgment: We are grateful to the Natural Sciences and Engineering Research Council of Canada, the University of Alberta and National Tsing Hua University for financial support.

References and Notes

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6. For previous examples of using the enolate as a protecting group, see references 1, 7 and 8.
7. Coates, R.M.; Shaw, J.E. *J. Org. Chem.* **1970**, *92*, 5657-5664.
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9. Alternatively, a stock solution of lithium naphthalenide prepared in the same manner could be conveniently used. The stock solution was found to retain virtually the same reactivity after storage in a fridge at *ca.* -4°C under argon atmosphere for more than a month.
10. While the present work was in progress, Azzena *et al.* reported the reduction of several phthalans using 5 equivalents of lithium in the presence of a catalytic amount (3 mol %) of naphthalene.[11]
11. Azzena, U.; Demartis, S.; Melloni, G. *J. Org. Chem.* **1996**, *61*, 4913-4919.

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