A Novel, Efficient, and Highly Selective O–Bn Bond Cleavage Reaction via a Rare K-Induced Electron Transfer Process

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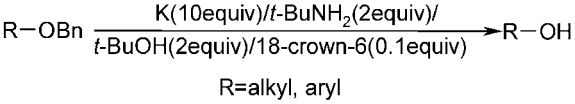
Abstract: A new, efficient and highly selective deprotective method of both benzyl and benzylidene groups for protection of monohydroxyl and dihydroxyl, respectively, has been developed by using the system K–*t*-BuNH$_2$–*t*-BuOH–18-crown-6. This method is valuable since it can not only selectively protect the TBDMS and THP groups and the ethylene ketal from cleavage, but also keep the separate or conjugated C=C bonds from reduction. A possible electron transfer reaction process was also suggested.

Key words: selective, benzyl, benzylidene, potassium, electron transfer

In the course of design and practical performance of organic synthesis, protection of the active monohydroxyl and 1,2-, 1,3- or 1,4-dihydroxyl with the benzyl and benzylidene groups, respectively, are the widely used strategies, because so many important organic compounds contain these oxygenated functions. In particular, the benzyl protective group exhibits more advantages. For example, formed benzyl ethers are stable to basic and acidic reaction conditions in most cases, and in some cases to the reduction and oxidation. To our knowledge, the efficient and general cleavage procedures for benzyl ethers are by use of catalyzed hydrogenolysis,[1] and in fewer cases the complicated Birch-like reduction[2] and two-stepped ozonization.[3] Some other procedures, such as those with Lewis acids[4] or through electrolysis,[5] are limited individual molecular structures. However, the generally applicable cleavage procedures listed above destroy the olefin, arene and ketone or aldehyde carbonyl functions. Thus these problems, to a large extent, limit the application of benzyl protective groups.

In our recent synthetic studies of natural products,[6] we have found that the system K (10 equiv)–*t*-BuNH$_2$ (2 equiv)–*t*-BuOH (2 equiv)–18-crown-6 (0.1 equiv) (or that without *t*-BuOH/18-crown-6) in THF solvent could effectively cleave benzyl ethers and benzylidene acetals within 1–6 hours in high yields (73–99%). This discovery encourages us to make a further extensive investigation and develop a new cleavage method of benzyl ethers and the benzylidene acetals. The advantages of this method over the previous generally used procedures is that it is effective in basic medium and thus did not destroy TBDMS or THP protective groups and ethylene ketal, which have been widely used in organic synthesis. It is quite different from catalyzed hydrogenolysis[1], Birch-like reduction[2] or ozonization,[3] it did not reduce either a separate or conjugated C=C bonds, active epoxy; and also the experimental conditions are mild and the procedure is simple.[7] Further investigation showed that absent or less equivalents of *t*-BuOH (0.5 equiv) and/or 18-crown-6 will delay the reaction time (2–10 h) and sometimes gave lower yield of the product. In addition, excess (10 equiv) of the potassium was essential and lower equivalents will slow the reaction. Furthermore, the metals Li or Na proved to be effective to this reaction, but the yields of the deprotection products were lower in some cases. Herein, we present our experiment results in detail.

The benzyl ether substrates (entries 2–4 and 6) were prepared by treatment of corresponding commercially available monoterpene alcohols with NaH–BnBr, and those (entries 9 and 10) from the corresponding *trans*,*trans*-spirodiol were prepared using the literature procedure.[8] All structures of both the substrates and products were determined using NMR (400 MHz) and mass spectroscopy. The benzyl ether cleavage experimentals with K–*t*-BuNH$_2$–*t*-BuOH–18-crown-6 were conducted in a standard procedure (Scheme 1).[7] And the results were listed in Table 1. So it was notable that all the benzyl deprotection reactions (entries 1–6, 9 and 10) completed well within 1–3 h and gave the corresponding alcohol products in high yields (92–99%). Particularly in entries 3–5, both isolated and conjugated C=C bonds were not attacked. More importantly in entry 6, the active epoxy still survived under this reaction condition. In the comparative experiments, the *t*-butyl-dimethyl-silyl ethers (entries 7–9) appeared inactive. Similarly, no reaction with the tetrahydropyrane ether (entry 10) was found.



Scheme 1

The benzylidene acetals we tested were prepared by treatment of the corresponding diol substrates with PhCH(OMe)$_2$,[9] among which the 1,3-diols (entries 2 and 3) were obtained in our reported procedure,[8] and the 1,4-diols (entries 4–6) obtained as the intermediates in the course of our synthesis of dihydroagarofuran sesquiterpenoids.[6] Therefore, the benzylidene acetal substrates were

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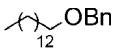
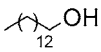
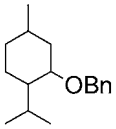
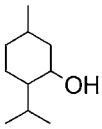
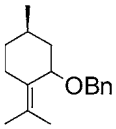
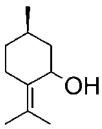
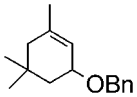
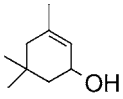
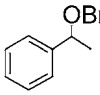
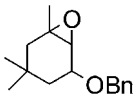
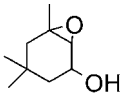
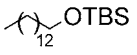
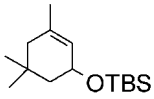
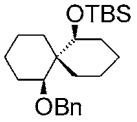
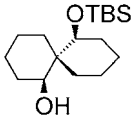
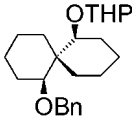
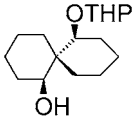
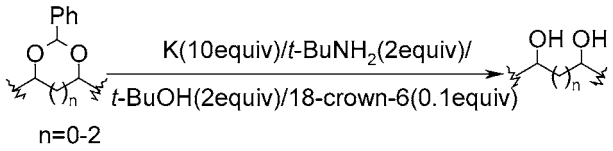
Table 1 The Cleavage of the Benzyl Ether[a]

Entry	Substrates	Time (h)	Products	Isolated yield (%)
1		2		98
2		1		99
3		3		94
4		3		90
5		2		93
6		3		90
7		10	–	[b]
8		10	–	[b]
9		1		96
10		1		92

[a] The results were obtained using the general procedure.[7]
[b] No reaction in 10 h.

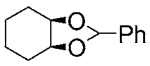
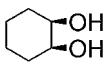
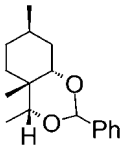
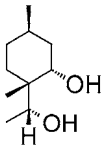
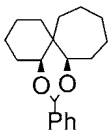
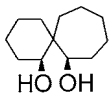
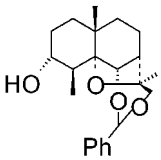
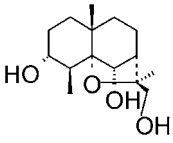
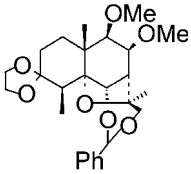
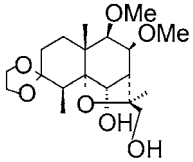
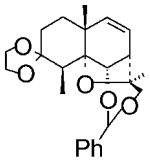
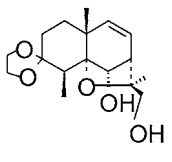
subjected to a general cleavage with K–*t*-$BuNH_2$–*t*-BuOH–18-crown-6 system (Scheme 2),[7] and the results are listed in Table 2. All the benzylidene 1,2-dioxacetal (entry 1), 1,3-dioxacetals (entries 2 and 3) and 1,4-dioxacetals (entries 4–6) were cleaved in yields of 73–96% within 2–6 h. Importantly, both the methyl ethers (entry 5) and the ethylene ketals (entries 5 and 6) were not destroyed in this reaction process, and also, the C=C bond (entry 6) still survived. In comparison with some established cleavage methods, the Pd-C–hydrazine–MeOH[10] or DIBAL-H[11] systems could not cleave the benzylidene 1,4-dioxacetals (entries 4–6), while I_2–MeOH[12] system gave the complex products.



Scheme 2

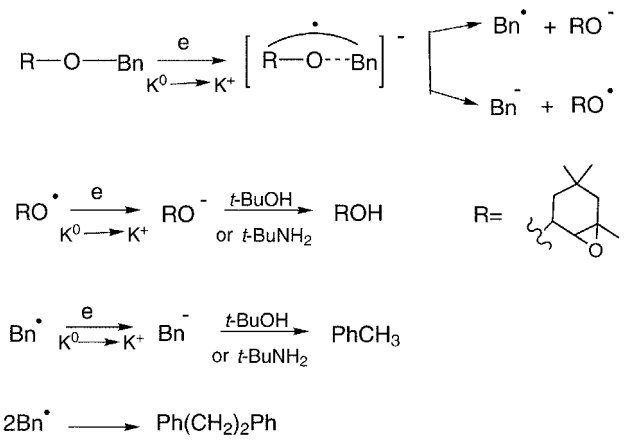
To investigate the reaction mechanism, the benzyl ether in Table 1, entry 6 was selected to repeat the cleavage experimental on a larger scale. As a result, a combination product, the 1,2-diphenylethane, of the benzyl was isolated in 5% yield. But we were not able to isolate the coupling product of the monoterpene moiety, or the cross coupling product of Bn with the monoterpene. On the basis of this and above facts and, in consideration of the literature result,[13] a possible reaction mechanism was deduced primarily as shown in Scheme 3. Firstly, The reaction process would involve the electron transfer from K to the ether, which would be promoted by the linking of K^+ with 18-crown-6.[14] This then activated the O-Bn bond and led it to cleave to form the anions RO^- (or Bn^-) and free radicals

Table 2 The Cleavage of the Benzylidene Acetal[a]

Entry	Substrate	Time (h)	Product	Isolated yield (%)
1		2		87
2		2		94
3		1		96
4		6		73
5		6		89
6		6		76

[a] The results were obtained using the general procedure.[7]

Bn•(or RO•). The following steps would be the proton transfer from *t*-BuOH or *t*-$BuNH_2$ to the anions RO^- (or Bn^-), the coupling of the radical Bn•, or the electron transfer from K to the radical RO• (or Bn•). This mechanism is uncommon, since the only reported K-induced electron transfer reaction involved two mixed bonds cleavages.[13] In conclusion, we have successfully developed a new and practical cleavage method of benzyl ether and benzylidene acetal. Further investigation on its application and a more detailed mechanism are still on going.



Scheme 3 The suggested mechanism of the *O*-Bn bond cleavage

Acknowledgement

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(7) One equiv of substrate dissolved in dried THF was sequentially added to two equiv of dry *t*-$BuNH_2$ and two equiv of *t*-BuOH and 10 equiv of potassium and 0.1 equiv of 18-crown-6. The mixture was stirred at r.t. for 1–6 h (the starting material disappeared, checked with TLC), workup as the general procedure to afford the corresponding alcohols in 73–99% yield.
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