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Deprotection of benzyl and *p*-methoxybenzyl ethers by chlorosulfonyl isocyanate–sodium hydroxide

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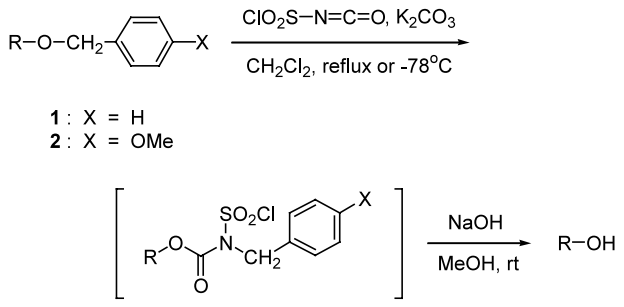
Abstract—CSI–NaOH procedure provided a new and mild methodology for the deprotection of benzyl and *p*-methoxybenzyl ethers without affecting the other functional groups under similar reaction conditions.

Deprotection of the benzyl group has been widely used in multi-step organic synthesis with a variety of reaction conditions, including catalytic hydrogenolysis,[1] Lewis acids such as $FeCl_3$,[2] $MgBr_2$[3] or $CrCl_2/LiI$[4] and lithium naphthalenide,[5] etc.[6] However, these procedures sometimes can be problematic with multifunctional substrates, such as unsaturated bonds during hydrogenolysis, an acid-labile moiety in Lewis acids, and a easily reducible functional groups in lithium naphthalenide. These facts prompt us to find a milder and more widely applicable method for debenzylation. Since we have developed the novel synthetic methods for *N*-protected allylic amines from allyl ether using chlorosulfonyl isocyanate (CSI)[7] and investigated its mechanism, we have found a novel technique for comparing directly the stability of carbocations in the solution phase and have established the stability order of the various carbocations under our reaction conditions.[8] Herein, we now report the extension of CSI under new reaction condition to the cleavage of various benzyl and *p*-methoxybenzyl protecting groups of alcohols and phenols in the presence of other functional groups (Scheme 1).



Scheme 1.

Our initial studies examined the deprotection of saturated benzyl ethers. The treatment of 2-phenylethyl benzyl ether (**1a**) with chlorosulfonyl isocyanate and Na_2CO_3 in methylene chloride under reflux and then with NaOH in methanol gave the corresponding alcohol in 82% yield in one pot.[9]

In the same way that other Lewis acids promote the debenzylation reaction, CSI should also lead to the activation of benzyl ether to form *N*-chlorosulfonyl-*N*-benzylcarbamate, which was easily cleaved by NaOH to form the alcohol (Scheme 1).

The formation of *N*-chlorosulfonyl-*N*-benzylcarbamate can be rationalized in terms of the abstraction of the alkoxy moiety by CSI to give the $ClSO_2–N^-–CO_2R$ species and a more stable benzyl carbocation. The nitrogen anion then attacks the benzyl carbocation to form *N*-chlorosulfonyl-*N*-benzylcarbamate. A wide range of structurally varied benzyl ethers has been subjected to cleavage with CSI to provide the corresponding alcohols. The results are shown in Table 1. Secondary alkyl benzyl ethers treated with the described reaction conditions produced consistently good yields of deprotected alcohols (entries 2 and 3). Treatment of benzyl ethers in the presence of a double bond with the same reaction conditions afforded the corresponding deprotected alcohols in good yields without affecting the double bond (entries 4–10).

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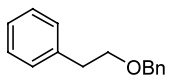
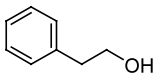
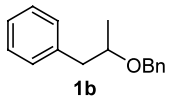
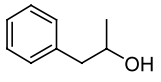
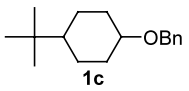
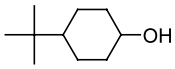
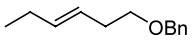
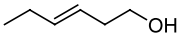
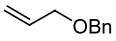
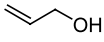
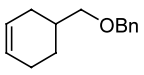
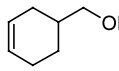
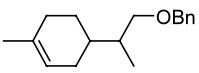
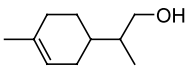
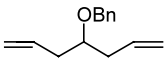
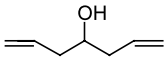
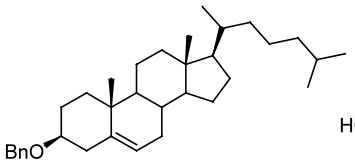
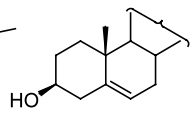
Table 1. Results of the deprotection of benzyl ethers

	Benzyl Ether	Alcohol	Yield (%)
1	 **1a**		82
2	 **1b**		88
3	 **1c**		83
4	 **1d**		86
5	 **1e**		69
6	 **1f**		75
7	 **1g**		82
8	 **1h**		83
9	 **1i**		84
10	 **1j**		74

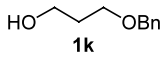
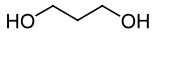
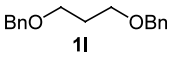
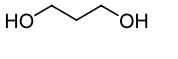
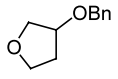
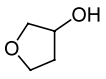
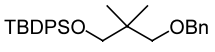
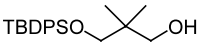
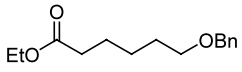
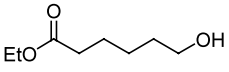
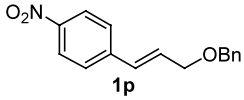
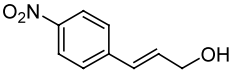
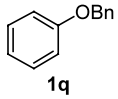
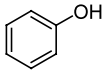
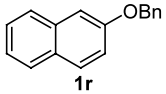
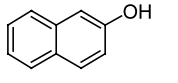
All the reactions were carried out under reflux conditions with CSI and at room temperature with NaOH. Isolated yield of pure material

Next, we examined the deprotection of benzyl ethers in the presence of other functional groups as shown in Table 2. 3-Benzyloxypropanol (**1k**) was treated with CSI–NaOH to give the corresponding alcohol in 87% yield in one pot. Benzyl ethers in the presence of cyclic ether, silyl ether, ester or nitro group also produced the corresponding deprotected alcohols in moderate yields without affecting these functional groups (entries 3–6). Unfortunately, in the case of entries 7 and 8, the aromatic benzyl ethers gave poor yields in deprotection under our reaction condition.

The *p*-methoxybenzyl (PMB) group is one of the most useful groups for alcohol protection, and there are various methods for selectively removing the PMB group which include Lewis acid-catalyzed cleavage ($TMSCl–SnCl_2$–anisole,[10] Me_2BBr,[11] $BF_3{\cdot}OEt_2$–$NaCNBH_3$,[12] $AlCl_3$–EtSH,[13] $CeCl_3$–NaI),[14] oxidation (2,3-dichloro-5,6-dicyanobenzoquinone,[15] ceric ammonium nitrate[16]), trifluoroacetic acid,[17] and clay-supported ammonium nitrate-irradiation.[18] Many of these procedures sometimes have one or more problems, for example, use of a heavy metal, a side reaction, low yield, or the cost of the reagent. Especially, DDQ is inclined to overoxidize allylic *p*-methoxybenzyl ether to an unsaturated ketone.[19] These problems led us to find a mild and efficient methodology for cleavage of PMB ethers.

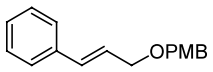
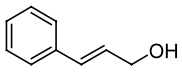
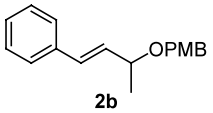
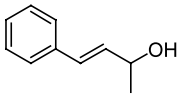
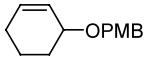
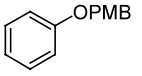
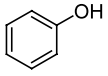
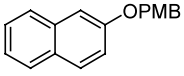
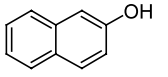
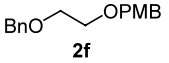
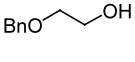
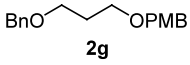
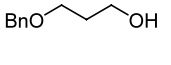
We examined the cleavage of *p*-methoxybenzyl protected alcohols and phenols in the presence of a double bond under the CSI–NaOH reaction conditions used in the deprotection of benzyl ethers. The results of deprotection of PMB ethers using CSI–NaOH are summarized in Table 3. In the case of cleavage of PMB-protected allyl alcohols, the similar results were obtained at lower temperature (–78°C) than the case of benzyl protected alcohols (entries 1–3). However, entries 4 and 5 reveal that the yield was highly increased and the reaction occurred rapidly in the case of cleavage of PMB-protected phenols compared to the case of benzyl protected phenols. Also, we tried to find appropriate reaction conditions for the selective cleavage of benzyl- and *p*-methoxybenzyl-protected alcohols.

Table 2. Results of the deprotection of benzyl ethers

	Benzyl Ether	Alcohol	Yield (%)
1[a]	 **1k**		87
2[b]	 **1l**		70
3	 **1m**		63
4	 **1n**		72
5	 **1o**		60
6	 **1p**		58
7	 **1q**		33
8	 **1r**		16

All the reactions were carried out under reflux conditions with CSI and at room temperature with NaOH. Isolated yield of pure material. [a] 7.5eq. of CSI, 11eq. of Na_2CO_3 and 15eq. of NaOH. [b] 3.0eq. of CSI, 4.5eq. of Na_2CO_3 and 10eq. of NaOH.

Table 3. Results of the deprotection of *p*-methoxybenzyl ethers

	PMB Ether	Alcohol	Yield (%)
1	 **2a**		85
2	 **2b**		86
3	 **2c**		86
4	 **2d**		80
5	 **2e**		72
6[a]	 **2f**		85
7[a]	 **2g**		88

All reactions were carried out at –78°C with CSI and at room temperature with NaOH. Isolated yield of pure material. [a] 3.0eq. of CSI, 4.5eq. of Na_2CO_3.

Entries 6 and 7 showed that the *p*-methoxybenzyl group was cleaved selectively without affecting the benzyl group at −78°C. This phenomenon is quite different from the result of debenzylation by catalytic hydrogenolysis.[1f]

In conclusion, we have developed a new and mild methodology for the deprotection of benzyl and *p*-methoxybenzyl without affecting the other functional groups using CSI–NaOH reaction conditions. The use of the CSI–NaOH procedure for cleavage of benzyl and *p*-methoxybenzyl ethers, both or selectively, in the presence of other various functional groups is in progress.

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9. **General procedure for the deprotection of benzyl ether by CSI–NaOH**. A suspension of Na_2CO_3 (22.5 mmol) in anhydrous CH_2Cl_2 (40 mL) was added CSI (15 mmol), and benzyl ether (10 mmol) was added under N_2. The reaction mixture was stirred under reflux for 20 h and cooled to 0°C. MeOH (40 mL) and NaOH (50 mmol) were added and stirred at rt for 1 h. The reaction mixture was concentrated and dissolved in H_2O. The solution was neutralized with 1N HCl and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc) or distillation to afford the alcohol.
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