SmI₂/Water/Amine Mediates Cleavage of Allyl Ether Protected Alcohols: Application in Carbohydrate Synthesis and Mechanistic Considerations
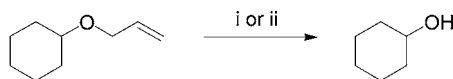
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ABSTRACT

i. SmI₂/H₂O/Et₃N, rt, 2 h, > 99 %
ii. SmI₂/H₂O/*i*-PrNH₂, rt, 1 min, > 99 %

SmI₂/H₂O/amine provides selective cleavage of unsubstituted allyl ethers in good to excellent yields. This method is therefore useful in deprotection of alcohols and carbohydrates.

The protection and deprotection of alcohols is a central topic in organic synthesis, in particular in carbohydrate synthesis. A valuable protecting group is the allyl group, due to the high stability of allyl ethers under a wide range of reaction conditions.[1] It is therefore not surprising that a large number of deallylation methods have been developed. The conventional methods of deprotection combine a transition-metal-catalyzed isomerization (Pd, Rh, or Ir) of the double bond to the enol ether and subsequent hydrolysis of the latter to furnish the corresponding alcohol.[2]

Recently, some one-step procedures for the cleavage of allyl ethers, e.g., PdCl₂/CuCl/O₂,[3] PdCl₂,[4] SmCl₃,[5]

NaI/Me₃SiCl,[6] Pd(PPh₃)₄ with NaBH₄[7] or Bu₃SnH[8] as reducing agent, and NiCl₂(dppp)/DIBALH[9] have been reported.

The single electron-transfer agent SmI₂ has received much interest for its reducing properties both in selective reductions and reductive couplings.[10]

Previously, we have shown that the combination of amine and water in the SmI₂/water/amine reagent mixture mediates fast reductions of ketones, α,β-unsaturated esters, alkyl and aryl halides, and conjugated alkenes.[11] We now report on the use of the SmI₂/water/amine reagent system, rendering

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a simple method for the selective cleavage of allyl ethers. The cleavage reaction is clean and proceeds in almost quantitative yield at room temperature.

During our course of exploring the SmI$_2$/water/amine-mediated intramolecular coupling reactions with aryl bromides, we observed that unsubstituted allyl ethers as substrates were cleaved rather than converted into their expected coupling products.[12]

After 5 min at ambient temperature, allyloxybenzene was converted to the corresponding phenol using a mixture of SmI$_2$, water, and triethylamine (Scheme 1).[13] Extended

Scheme 1. Cleavage of Allyloxybenzene Using SmI$_2$/H$_2$O/Amine[a]
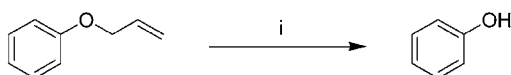
[a] Key: (i) SmI$_2$/H$_2$O/Et$_3$N, rt, 5 min, >90%.

reaction times with excess SmI$_2$ also produced a second product, 3-cyclohexene-1-ol.[14]

The aliphatic analogue, allyloxycyclohexane, was also converted to the corresponding alcohol although the reaction was considerably slower (Scheme 2). Using a primary amine

Scheme 2. Cleavage of Allyloxycyclohexane Using SmI$_2$/H$_2$O/Amine[a]
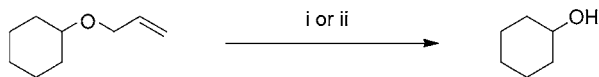
[a] Key: (i) SmI$_2$/H$_2$O,Et$_3$N, rt, 2 h, >99%; (ii) SmI$_2$/H$_2$O/i-OPrNH$_2$, rt, 1 min, >99%.

as base, e.g., isopropylamine, instead of triethylamine accelerated the deprotection step remarkably (approximately 75−100 times).[15]

Several different primary and secondary aliphatic allylic alcohols were synthesized and subjected to the SmI$_2$/water/isopropylamine reaction conditions in order to explore the versatility of this method (Table 1, entries 1−6). All these

substrates were rapidly and cleanly deprotected. To investigate the scope of the SmI$_2$/water/amine system for the deallylation of carbohydrates, some different protected derivatives bearing one or more allyl groups were employed (entries 7−12).

The cleavage of allyl groups from carbohydrate derivatives turned out to be more delicate than for the less functionalized alcohols. A major drawback is the reduction of ester groups, but benzyl, benzylidene, and silyl ether groups (not shown) withstand the reaction conditions (entries 7−11). Furthermore, the thioethyl group, valuable for consecutive glycosylation, does not interfere with the SmI$_2$ mixture (entries 9 and 10). An unexpected result is the resistance of the anomeric allyl group. Different allyl glycosides tested (e.g., entry 11) remained unchanged after elongated reaction times (>1 d). It is even possible to remove primary and secondary allyl ethers without destroying the anomeric allyl group (entry 12). An advantage of this new method is the simple removal of multiple allyl groups in one step (entry 12), which can be difficult to accomplish by standard methods.

Since it is known that the relative rate of isomerization versus the rate of cleavage depends on the promoting system, the effect of alkyl substitution at different carbons of the allyl group was also investigated (Table 2).[16] Slow cleavage (5 h) was observed with an α-methylated allyl group (entry 1), while no deprotection occurred with substrates bearing a branching (entry 2) or elongating (entry 3) methyl substituent directly on the double bond. Thus, the alkyl substituent stabilizes the allyl group to an extent that reductive cleavage cannot proceed. The corresponding allylamine (entry 4) or sulfide (entry 5) proved to be completely inert to the reaction conditions.

Initially, we anticipated that the SmI$_2$/water/amine mixture promoted the isomerization of the allyl ether to the corresponding enol ether, followed by hydrolysis of the latter either directly or during acidic workup. However, a vinyl ether, i.e., an isomerized allyl ether, stayed unchanged after treatment with SmI$_2$/water/amine (entry 6). Obviously, the SmI$_2$/water/amine system mediates direct cleavage of the allyl ether. Furthermore, the carbon connected to the oxygen bridge, originating from the alcohol, is left unchanged. Consequently, a chiral allyl ether, prepared from an enantiomeric pure alcohol, gave no racemisation at the stereogenic carbon (entry 7).

Details about the byproducts formed in the reaction were necessary in order to clarify the reaction pathway. Unfortunately, we were unable to detect any traces or remains of the allyl group in the reactions summarized in Tables 1 and 2.

Assuming that an allyl radical is the intermediate that is formed first, there are several possibilities to continue. The

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(13) SmI$_2$ is commercially available but it is also easily prepared in good yields and at low cost from powder of samarium and iodine in THF in an ultrasonic bath (see the Supporting Information).

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Table 1. Deallylation of Various Alcohols Using $SmI_2/H_2O/i\text{-PrNH}_2$

entry	substrate	product	time (min)	conversion % (isolated yield %)[a]
1			1	> 99
2			2	> 99 (88)
3			5	> 99 (87)
4	C_8H_{17}–O–	$C_8H_{18}OH$	3	> 99
5			1	> 99 (93)
6			1	> 99
7			2 d	(80)
8			15	> 99 (95)
9			5	> 99 (95)
10			10	> 99 (89)
11		no reaction (N.R.)	1 d	N/A
12			2 h	(81)[b]

[a] Isolated yields are based on a 100 mg scale of substrate (1 equiv) using SmI_2 in THF (5 equiv/allyl group), $i\text{-PrNH}_2$ (20 equiv), and H_2O (15 equiv) as reagents. [b] The product allyl mannoside was isolated as a tetraacetate in order to simplify the workup.

radical can either dimerize, polymerize, or be quenched directly by receiving another electron and a proton to yield propene, which we cannot detect. Therefore, a substituted allyl ether with a pentyl group on the allylic carbon was prepared and subjected to SmI_2/water/$i\text{-PrNH}_2$ to elucidate the remainder of the allyl group after the cleavage reaction (Scheme 3). After workup, only *n*-decanol and octene, but no traces of any reduced or dimerized octane, were observed. Interestingly, besides 1-octene, a mixture of *cis*- and *trans*-2-octene was detected by GC−MS, which shows a 1,3-isomerization to some extent.[11d]
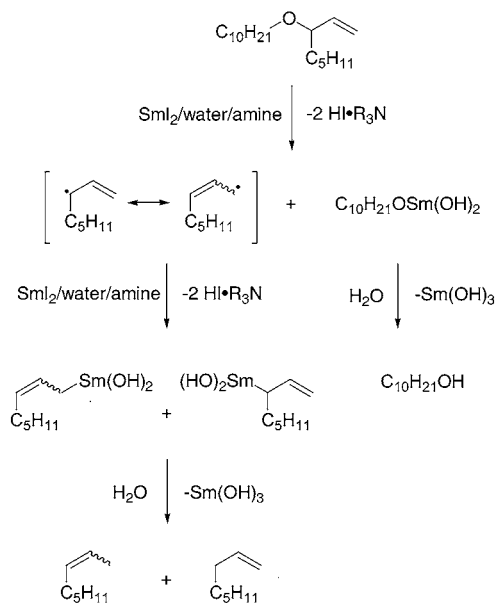
Based on this result, we suggest the following mechanism for the SmI_2/water/amine-mediated cleavage of allyl ethers (Scheme 3). Samarium(II) is oxidized to Sm(III), while the electron is received by the carbon−oxygen bond, which is then cleaved. The alkoxide anion becomes an additional ligand to Sm(III). This strong Lewis acid readily attracts two hydroxides from the water. The two released iodides (I⁻) and the two remaining protons precipitate as a quarternary iodine salt ($R_3N\times HI$). An additional water molecule is needed to regenerate the unprotected alcohol and insoluble $Sm(OH)_3$. The unpaired electron of the resonance stabilized allyl radical reacts immediately with another set of SmI_2/water/amine to give the alkene, $Sm(OH)_3$ and $R_3N\times HI$. The

Table 2. Exploring the Scope of the Cleavage Reaction Using $SmI_2/H_2O/i\text{-PrNH}_2$

entry	compound	conditions	product
1	Ph–O–	5 h, Et_3N	Ph−OH >90 %
2	Ph–O–	20 h, $i\text{-PrNH}_2$	N.R.
3	Ph–O–	20 h, $i\text{-PrNH}_2$	N.R.
4	Ph–N(H)–	20 h, $i\text{-PrNH}_2$	N.R.
5	Ph–S–	20 h, $i\text{-PrNH}_2$	N.R.
6	Ph–O–	20 h, $i\text{-PrNH}_2$	N.R.
7	H_3C–CH(Ph)–O– (R)	1 min, $i\text{-PrNH}_2$	H_3C–CH(OH)–Ph (R) >80%Yd

order and details of the electron and the proton transfers may be more complicated.

entry	compound	time	product
1	(allyloxy compound with C_5H_{11})	1 min	1- and 2-octene
2	(bis-allyloxymethyl benzene)	< 1 h	2-methylphenol (OH)
3	(benzyl allyl ether)	< 1 h	toluene
4	(pyridyl-CH₂-O-allyl)	1 min	2-methylpyridine

Kinetic experiments showed that the reaction between the allyl ether allyloxy cyclohexane and SmI₂/water/amine proceeds with first-order kinetics in both SmI₂ and amine and zero order in water. Although the reaction order in water is zero, the reaction still requires 2.5−3 equiv of water/SmI₂ for completion. No more than 3 equiv of water per SmI₂ should be used since excess water appeared to retard the reaction, most likely due to unwanted breakdown of SmI₂. The reaction order of zero in water is not surprising since the water molecules are already coordinated to samarium in the initial state according to UV/vis studies.[11c] Furthermore, we observed no kinetic isotope effect, i.e., k_{H2O}/k_{D2O} = 1.0.

In addition, for substrates containing a good radical stabilizing group, e.g., benzylic, to the allyloxy group, an unexpected deoxygenation reaction was observed (Table 3). First the allyl group is cleaved, followed by the deoxygenation reaction.

In summary, it has been demonstrated that the SmI₂/water/ amine reagent system is an attractive alternative to other deallylation methods, exhibiting unique reactivity. The deallylation reactions occurred with high yields and chemoselectivity. However, the presence of ketones, esters (in particular α,β-unsaturated esters) or conjugated dienes precludes selective deallylation as reduction of these functional groups is instantaneous under these conditions.

Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.