Nickel Hydride Catalyzed Cleavage of Allyl Ethers Induced by Isomerization

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Abstract

This report discloses the deallylation of O- and N-allyl functional groups by using a combination of a Ni-H precatalyst and excess Brønsted acid. Key steps are the isomerization of the O- or N-allyl group through Ni-catalyzed double-bond migration followed by Brønsted acid induced O/N–C bond hydrolysis. A variety of functional groups are tolerated in this protocol, highlighting its synthetic value.

Key words nickel catalysis, deprotection, allylic ethers, isomerization, selectivity

The use of protecting groups undoubtedly permits the development of synthetic routes toward desired organic scaffolds. Depending on the requirements in a synthesis, numerous protecting groups for acidic functional groups can be used. The ideal protecting group is complementary to the requisite conditions in the relevant synthetic steps, such as a certain pH range or reagents, and it should not affect the overall desired reactivity. In turn, the protection and deprotection steps should be selective for the particular functionality. Owing to their ubiquitous nature and reactivity in target molecules and intermediates, the presence of hydroxy groups often requires the employment of protecting groups. To address the many needs, a wide range of acetel-, ether- and ester-based protecting groups for hydroxy functionality have been developed.

A particularly attractive O-protecting group is allyl, thanks to several factors such as its ease of installation, use of inexpensive and readily available reagents, and stability under various reaction conditions (Scheme 1). Beside the methods reported for the direct cleavage of allyl groups by using nucleophiles or oxidants, those using homogeneous metal catalysts stand out due to their mild reaction conditions and often high selectivity. This has been impressively demonstrated in several total syntheses of natural compounds. These reactions usually follow two main mechanisms. The first is based on the formation of a metal allyl intermediate by oxidative addition in the presence of a nucleophile or reducing agent. The underlying principle in other cases is an initial olefin isomerization (single-bond transposition) to an enol ether, followed by hydrolysis. Although the isomerization of allylic alcohols, ethers, and related substrates has been studied extensively, its application or suggested involvement in the deallylation is much less well investigated. Furthermore, the use of nonprecious metals in allyl deprotection methods is rare but clearly desirable.

![Scheme 1](image-url)

An important feature in deprotection chemistry is the concept of orthogonality, based on the selective removal of a protecting group through differential reactivity and stability. Recently, Yamada and co-workers reported an elegant method for orthogonal oxidative deprotection of p-methoxybenzyl ethers in the presence of a p-methoxybenzyl group, and vice-versa. In this context, the chemoselective removal of an allyl group in the presence of a benzyl protecting group is of interest.
During our investigations of nickel hydride/Brønsted acid catalyzed tandem reactions of allyl ethers for the generation of oxacyclic scaffolds, we observed an unexpected loss of an allyl group under the reaction conditions in some cases.\textsuperscript{10} A plausible explanation was an initial isomerization to form an alkenyl ether, as later proven by independent experiments, and subsequent acidic hydrolysis owing to the presence of water in the acid.

Having obtained this result and based on our interest in isomerization reactions\textsuperscript{11} and nickel catalysis,\textsuperscript{12} we envisaged developing a general catalytic process for O-deallylation of ethers. To investigate this further, we chose the O-deallylated phenol 1\textsubscript{a} as a substrate and the complex nickel hydride \([Ni(PMe_3)_4]_2[H][N(SO_2CF_3)_2]\) from our original study as a precatalyst, due to its structural simplicity (Table 1). The precatalyst can be synthesized in two steps from bis(cycloocta-1,5-dienyl)nickel(0), the appropriate ligand, and bistriflimidic acid on a gram scale, and can be stored under argon on the bench.\textsuperscript{13} In line with our previous investigations, partial isomerization to the corresponding enol ether occurred. This was followed by subsequent addition of a Brønsted acid in an attempt to obtain 2-methoxyphenol (2\textsubscript{a}). Initial experiments using catalytic amounts of diphenylphosphoric and triflic acid gave only a mixture of the starting material and its isomer (Table 1, entries 1 and 2). Increasing the amount of precatalyst and the use of a weaker acid gave only traces of 2\textsubscript{a} (entries 3 and 4). The use of triflic acid (10 mol\textpercent) with a prolonged reaction time led to formation of 2\textsubscript{a} in a moderate yield of 38\%(entry 5).

Upon screening of additional Brønsted acids, we found that a stoichiometric amount of p-toluenesulfonic acid monohydrate (TsOH$\cdot$H$_2$O) gave complete conversion into the phenol (isolated yield 73\%) within 30 minutes (Table 1, entry 6). TsOH$\cdot$H$_2$O is an attractive option owing to its bench stability, its ease of handling, and its straightforward removal through aqueous workup, after which the product 2\textsubscript{a} was determined to be spectroscopically pure without the need for column chromatographic purification. This reaction was also demonstrated at 5 mmol scale (entry 6). A control experiment with TsOH$\cdot$H$_2$O in the absence of the catalyst led to complete recovery of unreacted 1\textsubscript{a} (entry 7). The precatalyst loading could be decreased to 0.5 mol\textpercent without any loss in activity (entry 8). Unfortunately, longer reaction times were deemed necessary to achieve complete conversion when 0.5 equiv of TsOH$\cdot$H$_2$O were used (entry 9), and only traces of product were detected when using 1 mol\textpercent of acid (entry 10). In addition, we examined whether a catalytic amount of acid could be used in the presence of water to promote the hydrolysis, but we found this not to be the case (entry 11). Addition of all components at the onset of the reaction resulted in 1:1 mixture of 1\textsubscript{a} and 2\textsubscript{a} (entry 12). Furthermore, the use of slightly weaker camphorsulfonic acid (CSA) required longer reaction times for complete conversion (entry 13).

Therefore, a system consisting of 1 mol\textpercent of Ni-H and 1 equivalent of TsOH$\cdot$H$_2$O was chosen for further study of the transformation. With an operationally simple and straightforward protocol in hand, we proceeded to evaluate its generality through deprotection of a variety of substituted O-deallylated compounds, starting with aryl allyl ethers 1\textsubscript{b}–\textsubscript{p} (Scheme 2). First, the influence of substituents in the 3- and 4-positions of the phenyl ring was evaluated. Compounds containing electron-donating groups performed much better under the catalytic conditions than those with electron-withdrawing substituents. Ethers 1\textsubscript{c}, 1\textsubscript{g}, 1\textsubscript{h}, 1\textsubscript{l}, and 1\textsubscript{n} were smoothly deallylated to the corresponding phenols in yields of 68–95\%. Note that no column chromatographic purification was necessary to obtain phenols 2\textsubscript{c} and 2\textsubscript{g} in adequate purity (>95\%). The boronate ester 1\textsubscript{d} was converted in a satisfactory 73\% yield, albeit with a longer reaction time of 20 hours. The trifluoromethanesulfonyl ether 1\textsubscript{f} underwent deallylation to give 2\textsubscript{f} in 34\% yield. Upon testing the halide-substituted ethers 1\textsubscript{b}, 1\textsubscript{m}, and 1\textsubscript{o}, we obtained the corresponding phenols in low to moderate yields of 56,

![Table 1 Optimization of the Reaction Conditions for the Ni-Catalyzed Deallylation\textsuperscript{\textdagger}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni-H (mol\textpercent)</th>
<th>Acid (mol\textpercent)</th>
<th>Time (h)</th>
<th>Yield\textsuperscript{\textdagger\textdagger} (%)</th>
<th>of 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>(PhO)$_2$P(O)OH (8)</td>
<td>1</td>
<td>-\textsuperscript{\textdagger}</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>MeSO$_2$H (8)</td>
<td>1</td>
<td>-\textsuperscript{\textdagger}</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>(PhO)$_2$P(O)OH (120)</td>
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<td>traces</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>(PhO)$_2$P(O)OH (200)</td>
<td>0.5</td>
<td>traces</td>
<td>5</td>
</tr>
<tr>
<td>5\textsuperscript{\textdagger}</td>
<td>2</td>
<td>F$_3$SO$_3$H (10)</td>
<td>15</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>TsOH$\cdot$H$_2$O (100)</td>
<td>0.5</td>
<td>73 (79)\textsuperscript{\textdagger}</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>TsOH$\cdot$H$_2$O (100)</td>
<td>1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
<td>TsOH$\cdot$H$_2$O (100)</td>
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<td>84</td>
<td>9</td>
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<tr>
<td>9</td>
<td>0.5</td>
<td>TsOH$\cdot$H$_2$O (50)</td>
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<td>75</td>
<td>10</td>
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<tr>
<td>10</td>
<td>1</td>
<td>TsOH$\cdot$H$_2$O (1)</td>
<td>1</td>
<td>traces</td>
<td>11</td>
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<tr>
<td>11\textsuperscript{\textdagger}</td>
<td>0.5</td>
<td>TsOH$\cdot$H$_2$O (10)</td>
<td>5</td>
<td>traces</td>
<td>12\textsuperscript{\textdagger}</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>CSA (100)</td>
<td>5</td>
<td>1 (11)\textsuperscript{\textdagger}</td>
<td>13</td>
</tr>
</tbody>
</table>

\textsuperscript{\textdagger} Reaction conditions: 1\textsubscript{a} (0.25 mmol), \([Ni(PMe_3)_4]_2[H][N(SO_2CF_3)_2]\), Brønsted acid, THF (0.16 M), 30 min, RT with Ni-H, then 60 °C for the indicated time with acid.
\textsuperscript{\textdagger} Isolated yield.
\textsuperscript{\textdagger\textdagger} Mixture of olefin isomers (unreacted 1\textsubscript{a} along with enol ethers).
\textsuperscript{\textdagger} 30 min at RT with Ni-H then 15 h at RT with F$_3$SO$_3$H.
\textsuperscript{\textdagger\textdagger} Yield at 5 mmol scale.
\textsuperscript{\textdagger} 1\textsubscript{a} was recovered.
\textsuperscript{\textdagger} With H$_2$O (1 equiv).
\textsuperscript{\textdagger\textdagger} All reaction components were added at the start.
\textsuperscript{\textdagger\textdagger} Ratio 1\textsubscript{a}/2\textsubscript{a} determined by $^1$H NMR analysis.
18, and 37%, respectively. A competing dehalogenation was not observed; low yields are therefore attributable to lower reactivity in both steps. Note that the isomerization to an enol ether was more closely investigated in our previous work; although it was never complete (usually 50%), it did not impact the overall yield if both reactions were successful.

Although the aldehyde 1e displayed poor reactivity and gave 2e in only 17% yield, its protected derivative 1f underwent deallylation to give a 52% yield of 2f. The allyl group could be successfully removed from the monoprotected hydroquinone 1f. A selective allyl deprotection was observed in the presence of a tert-butyl(diphenyl)silyl group by using a weaker acid (CSA); however, the reaction was slow, and only a 33% yield of 2k was obtained.

In the presence of an oxazole motif, deallylation to the phenol 2p occurred in 62% yield; an additional equivalent of TsOH·H2O was used in this case. In contrast to other substrates with electron-withdrawing groups, the 2-acetyl-substituted ether 1q was converted into the product in good yield (87%). Moreover, it was found that a sulfone functionality, which is often found in biologically active compounds, can be present in the molecule, as 2r was obtained in 41% yield.

Primary, secondary and tertiary allylic alcohol ethers 3 also underwent facile C–O bond cleavage (Scheme 3). The homobenzyl alcohol 4a, citronellol (4b), (–)-menthol (4c), and α-terpinol (4d) were obtained from the corresponding allylic ethers in appreciable yields (82–95%). Note that the allyl protecting group was removed selectively in the presence of a benzyl group in the case of 4e. Moreover, the protected cholesterol derivative 3f gave cholesterol (4f) without any racemization in 84% yield. The internal double bonds in substrates 3b, 4d, and 4f did not isomerize during the transformation. It is noteworthy that, apart from 4e, all aliphatic compounds were obtained in high yields without the need for chromatographic purification.

In addition, we also examined the feasibility of deallylation of amides, which has received less attention in the literature despite its potential in, for example, the synthesis of immobilized DNA oligomers, where allyl groups are used to protect the nucleotide bases. Employing our O-deallylation method, the deprotection of N-allylated benzamide 5 was possible and gave the corresponding product 6 in 48% yield (Scheme 4). To the best of our knowledge, there are no previous reports on the deallylation of amides by employing a nickel catalyst.

In summary, we have developed a rapid and straightforward protocol for a nickel hydride catalyzed, Brønsted acid promoted deprotection of allyl ethers. The transformation occurs through an initial nickel-catalyzed isomerization of the terminal double bond to the enol ether, which, in turn, is hydrolytically cleaved by the Brønsted acid. The deprotection of the allyl ether moiety occurs chemoselectively in the presence of internal double bonds and other protecting groups, such as the widely used benzyl group. The low catalyst loading along with the generality of the substrate
References and Notes


