



The reaction of acetal-type protective groups in combination with TMSOTf and 2,2'-bipyridyl; mild and chemoselective deprotection and direct conversion to other protective groups

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ARTICLE INFO

Article history:

Received 21 January 2011

Received in revised form 16 February 2011

Accepted 17 February 2011

Available online 23 February 2011

Keywords:

Deprotection
Chemoselective
MOM-type ether
2,2'-Bipyridyl acetal

ABSTRACT

A mild and chemoselective deprotection method of various acetal-type protective groups, such as MOM, MEM, BOM, and SEM ethers, has been developed. The combination of TMSOTf and 2,2'-bipyridyl was very effective for the deprotection, and the reaction proceeded via the formation of pyridinium intermediates, which were hydrolyzed to the corresponding alcohols in good to high yields. The features of this method are mild (almost neutral) reaction conditions and the tolerability of acid-sensitive functional groups. This method is also applicable for the direct conversion of MOM ether to BOM or SEM ether using the appropriate alcohols instead of H₂O.

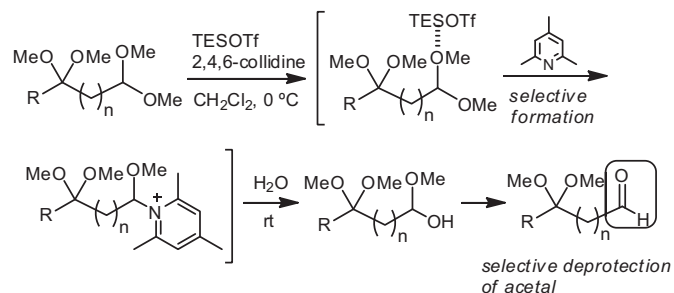
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1. Introduction

The protection of functional groups is fundamental in organic syntheses, especially when constructing complex molecules. A number of protective groups have been developed to date since appropriate choice of them is the key for the success of total synthesis. Deprotection is also important and must be conducted under mild reaction conditions in order to avoid any side reactions with sensitive functional groups as well as racemization or epimerization of stereo center because the protective groups are often cleaved at late stage in the synthesis.¹ Many protective groups for the hydroxy group have been developed,² and the acetal-type protective groups are one of the most popular groups and recognized as very useful. Acetal is known to be stable not only under strongly basic to neutral conditions but also to the strong nucleophiles including organometallic and hydride reducing reagents. Various acetal-type protective groups, such as the methoxymethyl (MOM), tetrahydropyranyl (THP), and methoxyethoxymethyl (MEM) ethers, are widely used in organic syntheses. In addition, these groups can be used as directing groups by their chelating ability. The deprotection of these acetal-type protective groups is generally performed under mildly acidic conditions. However, rather strongly acidic conditions are sometimes required to cleave them depending on the substrates and undesirable side reactions of other functional groups occur due

to the acidity of the reagents. Therefore, a milder deprotection method is necessary and has been desired.

We have recently developed a novel chemoselective deprotection of dimethylacetals using triethylsilyl triflate (TESOTf)/2,4,6-collidine that allows the ketals to remain intact (Scheme 1).³ The reaction conditions are mild and the reaction proceeded via the selective formation of the collidinium intermediates, which are susceptible to hydrolysis to give the hemiacetal. The chemoselectivity toward the acetals arises from the selective coordination of TESOTf to the less hindered acetal oxygen. Many acid-labile functional groups, such as trityl ether and TBS ether are tolerable in this reaction.

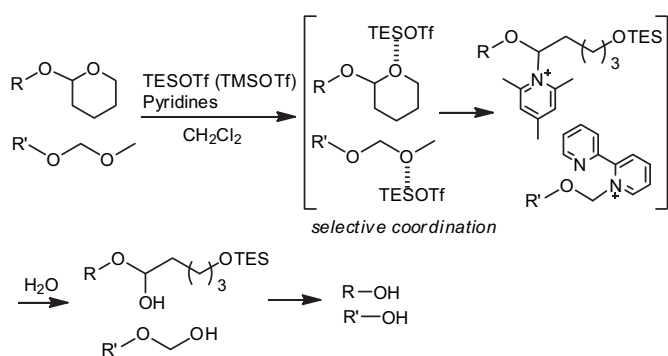


Scheme 1. Chemoselective deprotection of acetal in the presence of a ketal.

As an extension of this method, we developed the mild deprotection of THP ethers in combination with TESOTf/2,4,6-collidine⁴

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as well as the MOM ethers in combination with TMSOTf (or TESOTf)/2,2'-bipyridyl.⁵ In these reactions, we rationalized that the silyl triflate also selectively coordinated to the less hindered oxygen to form the pyridinium salt by attack of the pyridine derivative. Sequential hydrolysis led to the deprotected alcohol via the hemiacetal (Scheme 2).



Scheme 2. Mild deprotection of the THP and MOM ethers.

We were next interested in the deprotection of other acetal-type protective groups, i.e., MEM, benzylloxymethyl (BOM) and trimethylsilylethoxymethyl (SEM) ethers, which have more bulky substituents than the THP and MOM ethers.

In this paper, we report the mild and efficient deprotection of acetal-type protective groups, such as the MEM, BOM and SEM ethers including the MOM ether, and the investigation of the reaction mechanism in detail. Further application to the direct conversion of MOM ethers to other protective groups is also described.

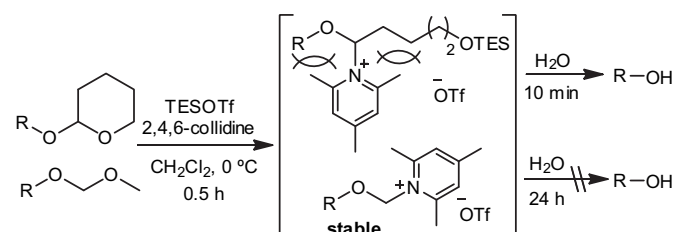
2. Results and discussion

2.1. Deprotection of MOM ethers

The deprotection of the MOM ether is usually performed under acidic conditions using protic acids,⁶ Lewis acids,⁷ Lewis acid-thiol,⁸ boron halides,⁹ and other reagents¹⁰ in protic or aprotic media. However, some methods cause undesirable side reactions of other functional groups due to the acidity of the reagents. Therefore, a few methods for the deprotection of the MOM ether with acid-labile functional groups have been reported,¹¹ but they require a high reaction temperature or limit the generality of the substrates.

We first attempted our deprotection method of the THP ether (TESOTf and 2,4,6-collidine) to the deprotection of the MOM ether, but only the stable collidinium salt was obtained even after a 24 h-treatment with H₂O (Scheme 3).

These results are attributed to the steric hindrance around the acetal carbons. The structures of the pyridines may play an



Scheme 3. The reaction of the THP and MOM ethers with TESOTf and 2,4,6-collidine.

important role in the formation of the pyridinium salt intermediates and hydrolysis. We then investigated the effect of the pyridines using *n*-decylmethoxymethyl ether (**1a**) with TMSOTf (Table 1).¹² The reaction of 2,6-lutidine and **1a** followed by H₂O treatment gave a trace amount of the deprotected alcohol (**2a**) and the corresponding lutidinium salt as the major product (entry 2). The more bulky 2,6-di-*tert*-butylpyridine and 2,6-dichloropyridine afforded a trace amount of **2a**, while the starting material **1a** and byproduct¹³ were mainly obtained (entries 3 and 4). The deprotection effectively proceeded to give the corresponding alcohol (**2a**) in 77% yield when 2-chloropyridine was used (entry 5). Surprisingly, the results of the deprotection with the similar 2-substituted pyridine, 2-phenylpyridine, and 2,2'-bipyridyl, were quite different. The reaction with 2,2'-bipyridyl was completed within 6 h and **2a** was obtained in 85%, but 2-phenylpyridine gave **2a** in 75% yield even after 72 h (entries 6 and 7). 4,4-Bipyridyl formed the corresponding pyridinium salt at rt but successive hydrolysis did not occur (entry 8).

Table 1
Effect of pyridines^a

Entry	Pyridines	Time [h]	Yield [%]
1	2,4,6-Collidine	24	Trace ^b
2	2,6-Lutidine	24	Trace ^b
3	2,6-Di- <i>tert</i> -butylpyridine	24	Trace ^b
4	2,6-Dichloropyridine	24	3
5	2-Chloropyridine	24	77
6	2-Phenylpyridine	72	75
7	2,2'-Bipyridyl	6	83
8	4,4'-Bipyridyl	24	Trace ^{b,c}

^a Reaction conditions: **1a** (1.0 equiv), TMSOTf (2.0 equiv) and the pyridine (3.0 equiv) in CH₂Cl₂ (0.2 M) were stirred at 0 °C for 0.5 h, then H₂O and Et₂O were added and stirred at rt.

^b Formation of the pyridinium salt was detected by TLC analysis.

^c Pyridinium salt was formed at rt for 1 h.

We employed the combination of TMSOTf (or TESOTf) and 2,2'-bipyridyl as the optimized conditions and next examined the deprotection of diverse MOM ethers (Table 2).

MOM-protected aliphatic primary, secondary, and tertiary alcohols were easily deprotected under the stated conditions and the corresponding alcohols were obtained in high yields (Table 2, entries 1–6). The use of both TMSOTf and TESOTf gave almost similar results in these cases. However, in the case of the MOM ether of the allyl alcohol **1d**, TMSOTf was more effective (entries 7 and 8). Other hydroxy protecting groups, such as the acetyl, benzoyl, and benzyl groups, were tolerated under the stated conditions (entries 9–14). It is noteworthy that the selective deprotection of the MOM ether could be achieved in the presence of acid-sensitive TBS ether, trityl ether and *tert*-butyl ester (entries 15–19), while the reaction of the MOM ether containing a *tert*-butyl ester resulted in a slight decrease of the yield (74%).¹⁴ These results indicated that the reaction conditions are nearly neutral. Some conventional deprotection methods under acidic conditions are known to cause undesirable side reactions with acid-sensitive functionalities due to their acidity.^{7c,d,15} The presence of a methyl ester, halogen, and amide did not affect the reaction although the additional TMSOTf and 2,2'-bipyridyl were necessary in the case of the amide (entries 20–23). The aromatic MOM ether, interestingly, is less reactive under the stated conditions (entries 24 and 25) and no pyridinium intermediate was formed at all for the combination of TESOTf and

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