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Mild Ti-mediated transformation of t-butyl thio-ethers into thio-acetates

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Abstract. We report a straightforward method for the rapid conversion of thio-ethers to thio-acetates using TiCl₄, in good to excellent yields. The reaction conditions tolerate a variety of functional groups, including halide, nitro, ether, thiophene and acetylene functionalities. A catalytic variant of this reaction is also described.

Introduction

Numerous nanoscale materials and devices are based on self-assembled monolayers (SAMs) of thiols on gold substrates. Thiols have proven to be versatile anchoring groups for immobilising functional units for photoswitching, molecular electronics, control of surface wettability, cell adhesion, to name but a few examples. Although thiol chemistry is often used in SAM formation, the introduction of a thiol group in a compound frequently presents synthetic challenges because the R-S-H group can be deprotonated, is nucleophilic, and is prone to oxidation. Hence, protected thiols such as thio-acetates are frequently used. Indeed, acetyl and trityl protected thiols can be deprotected readily in situ during self-assembly on gold surfaces. In particular acetyl protected thiol substituted arenes are convenient in their use as these can typically be cleaved in situ without requiring an exogenous base to form stable monolayers equivalent to those formed starting from free thiols.

However, the thio-acetate group is often not stable under aqueous reaction conditions, while the thio-trityl group is not stable under various other reaction conditions, such as those employed in Suzuki-Miyaura cross-coupling reactions. These drawbacks can be overcome through a method developed by Stuhr-Hansen in which the thiol is initially protected by a t-butyl protecting group and later exchanged for the desired acetyl protecting group by treatment with BBr₅. The t-butyl thio-ether is beneficial as it is typically stable under both acidic and basic conditions. Furthermore, t-butyl thio-ethers can be synthesised with relative ease, either from the free thiol using t-butyl chloride or t-butanol, or from halides (R-X) using t-butyl thiol. Once the synthetic steps incompatible with the thio-acetate have been performed, exchange of the protecting groups can be achieved by deprotection of the t-butyl thio-ether by BBr₅ followed by quenching with acetyl chloride at room temperature.

Although S-t-butyl to S-acetyl exchange procedures have been reported (using BBr₅, but also Br₂ or AlCl₃), several important functionalities do not tolerate these conditions, examples being vinyl, TBDMSO, acetylene, aldehyde, and nitro functionalities. This prompted us to identify more versatile Lewis acids, with which the exchange reaction can be performed under mild conditions while tolerating a wider variety of functionalities. One such candidate is TiCl₄, as there have been several examples of TiCl₄/n-Bu₄NI-mediated deprotection of ethers (R-O-R). Furthermore, TiCl₄ has been used in the deprotection of silyl ether protected alcohols. The results of Tanabe and co-workers, who successfully deprotected aryl and aliphatic TBDMS-ethers in excellent yields (91-99%) using TiCl₄-Lewis base (AcOEt, CH₂NO₂) complexes, are particularly encouraging. Finally, TiCl₄ was used with great efficacy as a deprotection reagent in the hydrolysis of t-butyl esters in β-lactam chemistry, whereas the use of AlCl₃, BF₃, and FeCl₃ resulted in degradation of the starting material or poor yields.

NOTES

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COMMUNICATION
Herein, we present a robust method for the conversion of tert-butyl thioethers to thioacetates using TiCl₄ instead of BBr₃. We have found that TiCl₄ is tolerant towards a wider variety of functional groups and performs consistently better than BBr₃, providing the desired thioacetates in high yields and in shorter reaction times (Scheme 1).

Results and discussion

12 substrates were examined to explore the utility of TiCl₄ for the conversion of thioethers (a) to thioacetates (b) (Table 1). tert-Butyl thioethers 1-6a were converted to the corresponding thioacetates 1-6b in good to excellent isolated yields using TiCl₄ or BBr₃. However, whereas the reactions using BBr₃ were complete after 2.5 to 7 h, the use of TiCl₄ allowed for substantially shorter reaction times, in several cases providing the thioacetate within a few seconds (2a, 4a, and 6a as well as 8a and 10a). In addition, improved yields were observed for several substrates when TiCl₄ was used (1a, 3a, and 5a). Conversion of 7a-10a using BBr₃ was found to result in decomposition only. In sharp contrast, 7a and 8a were converted to their corresponding thioacetates in high yield when TiCl₄ was used.

Aldehyde and pyrid-2-yl functionalized thioethers were examined to explore functional group limitations. Treatment of aldehyde 9a under these reaction conditions still resulted in decomposition. Analysis of the product revealed that with BBr₃ the tert-butyl group was cleaved while with TiCl₄ the tert-butyl group remained intact. In neither case, however, was thioacetate 9b obtained. For thio-ether 10a, the TiCl₄-mediated reaction did not provide the desired product either with full conversion to an unidentified compound instead.²⁰,²¹ It was also attempted to use the above reaction conditions for the conversion of a methyl thio-ether group to the corresponding thio-acetate group. The methyl thio-ether group of 12a was found to be stable to both BBr₃ and TiCl₄. However, treatment of 12a with TiCl₄ for 3 h resulted in the aromatic Friedel-Crafts acylation product.

The stability of the OTBDMS protecting group, alkenes and THP ethers under reaction conditions was examined (Scheme 2). p-Br-phenyl TBDMS ether was found to be stable under reaction conditions (see ESI, Fig S2), however, both the THP and alkene of 2-(dec-9-en-1-yl)oxy)tetrahydro-2H-pyran were found to react also. It should be noted, however, that more complex structures such as 11a are stable under reaction conditions (vide infra).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction time TiCl₄</th>
<th>Isolated yield</th>
<th>Reaction time TiCl₄</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>5 h</td>
<td>81%</td>
<td>≤1 h</td>
<td>93%</td>
</tr>
<tr>
<td>2a</td>
<td>6 h</td>
<td>96%</td>
<td>5 s</td>
<td>94%</td>
</tr>
<tr>
<td>3a</td>
<td>5 h</td>
<td>76%</td>
<td>≤1 h</td>
<td>88%</td>
</tr>
<tr>
<td>4a</td>
<td>7 h</td>
<td>&gt;99%</td>
<td>5 s</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>5a</td>
<td>3 h</td>
<td>92%</td>
<td>1 h</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>6a</td>
<td>4 h</td>
<td>65%</td>
<td>5 s</td>
<td>89%</td>
</tr>
<tr>
<td>7a</td>
<td>-</td>
<td>dec.</td>
<td>≤1 h</td>
<td>88%</td>
</tr>
<tr>
<td>8a</td>
<td>-</td>
<td>-</td>
<td>5 s</td>
<td>83%</td>
</tr>
<tr>
<td>9a</td>
<td>-</td>
<td>dec.</td>
<td>-</td>
<td>dec.</td>
</tr>
<tr>
<td>10a</td>
<td>7 h</td>
<td>dec.</td>
<td>5 s</td>
<td>b</td>
</tr>
<tr>
<td>11a</td>
<td>n/a</td>
<td>n/a</td>
<td>2 h</td>
<td>87%</td>
</tr>
<tr>
<td>12a</td>
<td>7 h</td>
<td>no conv.</td>
<td>3 h</td>
<td>c</td>
</tr>
</tbody>
</table>

a) Forms multiple products. b) Full conversion to an unidentified product with an Rf = 0.19 on SiO₂. c) The Friedel-Crafts acylation product p-CH₃(C=O)C₆H₄SCH₃ was isolated in 94 % yield.²² Dec. = decomposition of the starting material.
A possible mechanism by which the reaction may proceed is that addition of TiCl$_4$ to acetyl chloride results in the formation of the acylium ion (Scheme 3), as is supported by the Friedel-Crafts acylation product obtained with compound 12a. The acylium ion undergoes nucleophilic attack from the sulphur of the thio-ether. Expulsion of the 2-methylpropan-2-ylum carbocation subsequently results in product formation. Conversion of the anionic Ti species is achieved by dissociation of a chloride and the subsequent capture of the chloride ion by the carbocation resulting in the formation of 2-chloro-2-methylpropane and TiCl$_4$, thus completing the catalytic cycle for the exchange of the t-Bu thio-ether to the thio-acetate. In $d_2$-dichloromethane, the formation of iso-2-chloro-2-methylpropane was observed, whereas the formation of isobutene was not, which supports the proposed pathway (see SOI).

The reaction mechanism proposed furthermore implies that TiCl$_4$ might be used catalytically. Indeed, it was found that treatment of 4a with a catalytic amount of TiCl$_4$ (10 mol%) resulted in full conversion to the thio-acetate in 3 h with isolated yields of ca. 86 % (Scheme 4). These results therefore support the proposed mechanism and further establish the potential of TiCl$_4$ to mediate the S-t-Bu to S-acetyl exchange reaction. The conversion from 4a to 4b under stoichiometric was conditions completed within 5 s, whereas under catalytic conditions the reaction was finished within 3 h. It should be noted that under these catalytic conditions the catalytic reaction still proceeds faster with TiCl$_4$ then when a stoichiometric quantity of BBr$_3$ is used.

In summary, the method reported herein provides a versatile, mild and selective method compared to existing thio-ether to thio-acetate exchange methods. The use of TiCl$_4$ is more atom economic then the use of BBr$_3$ given that the former can be employed catalytically. Furthermore, conditions using TiCl$_4$ for the exchange tolerate a wider range of functional groups than BBr$_3$-mediated methods, including acetylene groups, which is in contrast to conditions using Br$_2$ that provide only moderate conversion to the thio-acetate. The exchange of the t-butyl protecting group for a thio-acetate group in aliphatic thio-ether 11a provides 11b in high yield (Table 1), even though 11a contains a dithienyl ethene photochromic switching unit. The high reaction rate at room temperature implies that the exchange reaction is also able to proceed at low temperature. Indeed, the reaction was found to proceed with full conversion of 4a to 4b within 30 min at -78 °C, whereby. Performing the exchange at low temperature opens opportunities to avoid undesirable side-reactions of sensitive substituents.

Conclusions

In conclusion, the conversion from thio-ether to thio-acetate using TiCl$_4$ represents a highly versatile and fast method for a wide range of applications, not least those involving the synthesis of SAM forming thiols.

Notes and references

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REFERENCES

(20) This compound is currently thought to be an adduct 10a-TiCl4, as although its 1H-NMR spectrum similar to that of 10a, its retention on SiO2; TLC plates is significantly different from that of 10a.