Journal Name RSCPublishing

COMMUNICATION

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

Cite this: DOI: 10.1039/x0xx00000x

Thomas C. Pijper,[†a] Jort Robertus,[†b] Wesley R. Browne[a,b] and Ben L. Feringa[a,b]*

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

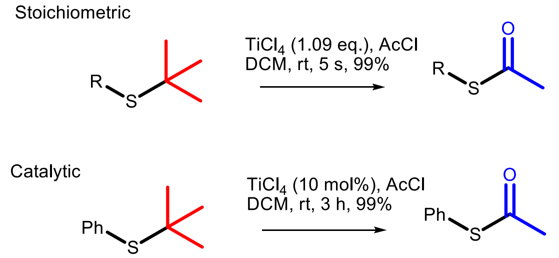
Abstract. We report a straightforward method for the rapid conversion of thio-ethers to thio-acetates using $TiCl_4$, in good to excellent yields. The reaction conditions tolerate a variety of functional groups, including halide, nitro, ether, thiophene and acetylene functionalities. A catalytic variant of this reaction is also described.

Introduction

Numerous nanoscale materials and devices[1] are based on self-assembled monolayers (SAMs) of thiols on gold substrates.[2] Thiols have proven to be versatile anchoring groups[3] for immobilising functional units for photoswitching,[4] molecular electronics,[5] control of surface wettability,[6] cell adhesion,[7] to name but a few examples. Although thiol chemistry is often used in SAM formation,[3] the introduction of a thiol group in a compound frequently presents synthetic challenges[8] because the R-S-H group can be deprotonated, is nucleophilic, and is prone to oxidation.[2] 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.[2] In particular acetyl protected thiol substituted arenes are convenient in their use as these can typically be cleaved *in situ* without requiring a exogenous base to form stable monolayers equivalent to those formed starting from free thiols.[9,10,11]

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.[12] 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 BBr_3.[13] The *t*-butyl thio-ether is beneficial as it is typically stable under both acidic[14] and basic conditions.[15] 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 BBr_3 followed by quenching with acetyl chloride at room temperature.[13]

Although S-*t*-butyl to S-acetyl exchange procedures have been reported (using BBr_3,[13] but also Br_2[8] or $AlCl_3$[16]), several important functionalities do not tolerate these conditions, examples being vinyl, TBDMSO, acetylene, aldehyde, and nitro functionalities.[8,13] 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 $TiCl_4$, as there have been several examples of $TiCl_4$/*n*-Bu_4NI-mediated deprotection of ethers (R-O-R).[17] Furthermore, $TiCl_4$ 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 $TiCl_4$-Lewis base (AcOEt, CH_3NO_2) complexes, are particularly encouraging.[18] Finally, $TiCl_4$ was used with great efficacy as a deprotection reagent in the hydrolysis of *t*-butyl esters in β-lactam chemistry, whereas the use of $AlCl_3$, BF_3, and $FeCl_3$ resulted in degradation of the starting material or poor yields.[19]



Scheme 1 Rapid and clean conversion of thiotertbutyl ethers to acetyl protected thiols with stoichiometric and catalytic $TiCl_4$.

Herein, we present a robust method for the conversion of *t*-butyl thio-ethers to thio-acetates using $TiCl_4$ instead of BBr_3. We have found that $TiCl_4$ is tolerant towards a wider variety of functional groups and performs consistently better than BBr_3, providing the desired thio-acetates in high yields and in shorter reaction times (Scheme 1).

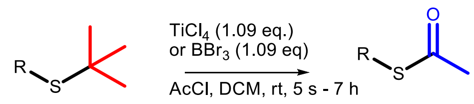
Results and discussion

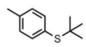
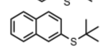
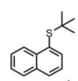
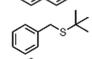
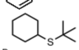
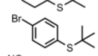
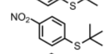
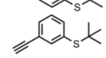
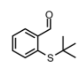
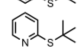
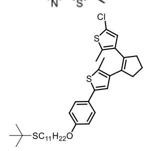
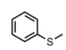
12 substrates were examined to explore the utility of $TiCl_4$ for the conversion of thio-ethers (**a**) to thio-acetates (**b**) (table 1). *t*-Butyl thio-ethers **1-6a** were converted to the corresponding thio-acetates **1-6b** in good to excellent isolated yields using $TiCl_4$ or BBr_3. However, whereas the reactions using BBr_3 were complete after 2.5 to 7 h, the use of $TiCl_4$ allowed for substantially shorter reaction times, in several cases providing the thio-acetate within a few seconds (**2a, 4a**, and **6a** as well as **8a** and **10a**). In addition, improved yields were observed for several substrates when $TiCl_4$ was used (**1a**, **3a**, and **5a**). Conversion of **7a-10a** using BBr_3 was found to result in decomposition only. In sharp contrast, **7a** and **8a** were converted to their corresponding thio-acetates in high yield when $TiCl_4$ 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 BBr_3 the *t*-butyl group was cleaved while with $TiCl_4$ the *t*-butyl group remained intact. In neither case, however, was thio-acetate **9b** obtained. For thio-ether **10a**, the $TiCl_4$-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 BBr_3 and $TiCl_4$. However, treatment of **12a** with $TiCl_4$ for 3 h resulted in the aromatic Friedel-Crafts acylation product.

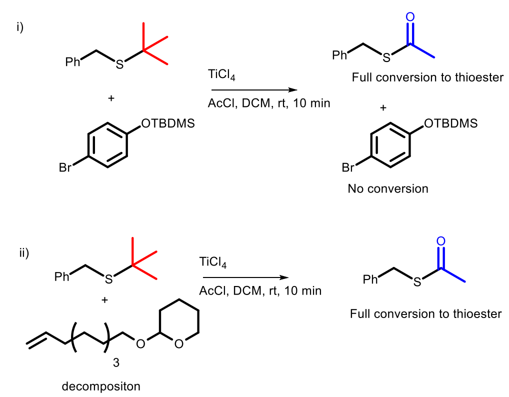
The stability of the OTBDMS protecting group, alkenes and THP ethers under reaction conditions was examined (Scheme 2). *p*-Br-phenyl TBDMS ether was found to be stable under reaction conditions (see ESI, Fig S2), however, both the THP and alkene of 2-(dec-9-en-1-yloxy)tetrahydro-2H-pyran were found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

Table 1. Thio-ether to thio-acetate exchange: comparison of BBr_3 and $TiCl_4$.



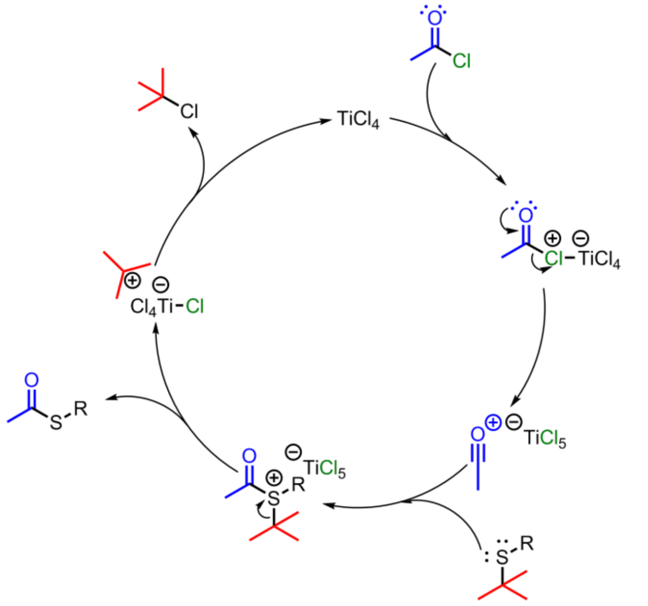
	Substrate	Reaction time BBr_3	Isolated yield	Reaction time $TiCl_4$	Isolated yield
1a		5 h	81%	<1 h	93%
2a		6 h	96%	5 s	94%
3a		5 h	76%	<1 h	88%
4a		7 h	>99%	5 s	>99%
5a		3 h	92%	1 h	>99%
6a		4 h	65%	5 s	89%
7a		-	dec.	<1 h	88%
8a		-	- [a]	5 s	83%
9a		-	dec.	-	dec.
10a		7 h	dec.	5 s	[b]
11a		n/a	n/a	2 h	87%
12a		7 h	no conv.	3 h	[c]

a) Forms multiple products. b) Full conversion to an unidentified product with an R_f = 0.19 on SiO_2. c) The Friedel-Crafts acylation product *p*-$CH_3(C{=}O)C_6H_4SCH_3$ was isolated in 94 % yield.[22] Dec. = decomposition of the starting material.



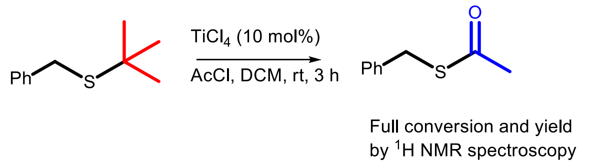
Scheme 2 Stability of (i) the OTBDMS protecting group and (ii) terminal alkenes, THP ethers under reaction conditions

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),[23] 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-ylium 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).



Scheme 3. Proposed cycle for the conversion of thio-ethers to thio-acetates using $TiCl_4$ as a catalyst.

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.



Scheme 4 Thio-ether to thio-acetate conversion as catalysed by $TiCl_4$.

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.[8] 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

[a] Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 4, 9747 Groningen, The Netherlands, b.l.feringa@rug.nl.
[b] Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 Groningen, The Netherlands Address here.
† Funding from the Ministry of Education, Culture and Science (Gravity program 024.001.035, WRB, BLF), the European Research Council (Advanced Investigator grant no. 227897) and Netherlands organization for Fundamental Research on Materials (FOM, TCP) are acknowledged for financial support.
Electronic Supplementary Information (ESI) available: Experimental procedures, characterization and spectroscopic data. See DOI: 10.1039/c000000x/

(1) (a) M, Irie, *Chem. Rev.*, 2000, **100**, 1685; (b) H. Tian and S. Wang, *Chem. Commun.*, 2007, 781.
(2) J. C. Love, L. A. Estroff, J. K. Kriebel, R. G. Nuzzo and G. M. Whitesides, *Chem. Rev.*, 2005, **105**, 1103.
(3) J. C. Love, D. B. Wolfe, R. Haasch, M. L. Chabinyc, K. E. Paul, G. M. Whitesides and R. G. Nuzzo, *J. Am. Chem. Soc.*, 2003, **125**, 2597.
(4) N. Katsonis, M. Lubomska, M. M. Pollard, B. L. Feringa, and P. Rudolf, *Prog. Surf. Sci.*, 2007, **82**, 407.
(5) (a) N. Katsonis, T. Kudernac, M. Walko, S. J. van der Molen, B. J. van Wees and B. L. Feringa, *Adv. Mater.*, 2006, **18**, 139; (b) A. J. Kronemeijer, H. B. Akkerman, T. Kudernac, B. J. van Wees, B. L. Feringa, P. W. M. Blom and B. de Boer, *Adv. Mater.*, 2008, **20**, 1467; (c) S. J. van der Molen, J. Liao, T. Kudernac, J. S. Agustsson, L. Bernard, M. Calame, B. J. van Wees, B. L. Feringa and C. Schönenberger, *Nano Lett.*, 2009, **9**, 76; (d) T. Arramel, T. C. Pijper, T. Kudernac, N. Katsonis, M. van der Maas, B. L. Feringa, B. J. van Wees, *J. Appl. Phys.*, 2012, **111**, 083716; (e) T. Arramel, T. C. Pijper, T. Kudernac, N. Katsonis, M. van der Maas, B. L. Feringa and B. J. van Wees, *Nanoscale*, 2013, **5**, 9277; (f) E. H. van Dijk, D. J. T. Myles, M. H. van der Veen and J. C. Hummelen, *Org. Lett.*, 2006, **8**, 2333.
(6) K. Y. Chen, O. Ivashenko, G. T. Carroll, J. Robertus, J. C. M. Kistemaker, G. London, W. R. Browne, P. Rudolf, B. L. Feringa, *J. Am. Chem. Soc.*, 2014, **136**, 3219.
(7) J. Robertus, W. R. Browne and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 354.
(8) A. Blaszczyk, M. Elbing and M. Mayor, *Org. Biol. Chem.*, 2004, **2**, 2722.
(9) S. R. Wasserman, H. Biebuyck, G. M. Whitesides, *J. Mater. Res.*, 1989, **4**, 886.
(10) M. Jevric, S. L. Broman and M. B. Nielsen, *J. Org. Chem.*, 2013, **78**, 4348.
(11) J. M. Tour, L.-R. Jones II, D. L. Pearson, J. J. S. Lamba, T. P. Burgin, G. M. Whitesides, D. L. Allara, A. N. Parikh and S. V. Atre, *J. Am. Chem. Soc.*, 1995, **117**, 9529.
(12) T. Itoh and T. Mase, *J. Org. Chem.*, **2006**, *71*, 2203.
(13) (a) N. Stuhr-Hansen, *Synth. Commun.*, 2003, **33**, 641; (b) N. Stuhr-Hansen, J. Kryger-Sørensen, K. Moth-Poulsen, J. B. Christensen, T. Bjørnholm and M. B. Nielsen, *Tetrahedron*, 2005, **61**, 12288; (c) V. Kaliginedi, P. Moreno-García, H. Valkenier, W. Hong, V. M. García-Suárez, P. Buiter, J. L. H. Otten, J. C. Hummelen and C. J.; Lambert Wandlowski, T., *J. Am. Chem. Soc.*, 2012, **134**, 5262; (d) H. Valkenier, C. M. Guédon, T. Markussen, K. S. Thygesen, S. J.; van der Molen and J. C. Hummelen, *Phys. Chem. Chem. Phys.*, 2014, **16**, 653; (e) T. C. Pijper, T. Kudernac, W. R. Browne and B. L. Feringa, *J. Phys. Chem. C*, 2013, **117**, 17623.
(14) N. Weibel, A. Blaszczyk, C. von Hänisch, M. Mayor, I. Pobelov, T. Wandlowski, F. Chen and N. Tao, *Eur. J. Org. Chem.*, 2008, 136.
(15) W. R. Browne, J. J. D. de Jong, T. Kudernac, M. Walko, L. N. Lucas, K. Uchida, J. H. van Esch and B. L. Feringa, *Chem. Eur. J.*, 2005, **11**, 6430.
(16) I. A. Aliev, G. A. Kalabin and N. Ghelis, *Sulfur Lett.*, 1991, **12**, 123.
(17) T. Tsuritani, H. Shinokubo and K. Oshima, *Tetrahedron Lett.*, 1999, **40**, 8121.
(18) A. Iida, H. Okazaki, T. Misaki, M. Sunagawa, A. Sasaki and Y. Tanabe, *J. Org. Chem.*, 2006, **71**, 5380.
(19) M. Valencic, T. van der Does, E. de Vroom, *Tetrahedron Lett.*, 1998, **39**, 1625.
(20) This compound is currently thought to be an adduct **10a**-$TiCl_x$, as although its ^{1}H-NMR spectrum similar to that of **10a**, its retention on SiO_2 TLC plates is significantly different from that of **10a**.
(21) K. Hensen, R. Mayr-Stein, B. Spangenberg, M. Bolte and S. Rühl, *Z. Naturforsch. B Chem. Sci.*, 2000, **55**, 248.
(22) (a) R. A. Cutler, R. J. Stenger and C. M. Suter, *J. Am, Chem. Soc.*, 1952, **74**, 5475; (b) J. Ruan, X. Li, O. Saidi and J. Xiao, *J. Am, Chem. Soc.*, 2008, **130**, 2424.
(23) H. P. Treffers and L. P. Hammett, *J. Am. Chem. Soc.*, 1937, **59**, 1708.

