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Mild Deprotection of *tert*-Butyl and *tert*-Amyl Ethers Leading either to Alcohols or to Trialkylsilyl Ethers

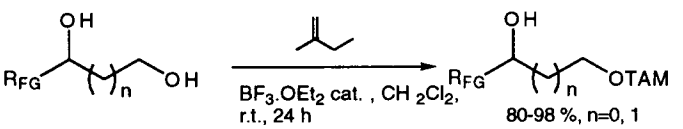
Xavier Franck, Bruno Figadère*, André Cavé

Laboratoire de Pharmacognosie, (CNRS, BIOCIS), Faculté de Pharmacie 92290 Châtenay-Malabry (France)

Abstract: *Tert-butyl and tert-amyl ethers afford the corresponding tert-butyldimethylsilyl ethers when treated by one equivalent of tert-butyldimethylsilyl triflate (TBDMSOTf), followed by one equivalent of 2,6-lutidine. However, treatment by a catalytic amount of TBDMSOTf without base, led to the corresponding free alcohols.*

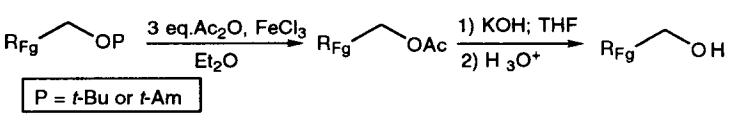
Functionalization of hydroxyl groups as alkyl ethers is a very attractive method for the protection of alcohols[1]. In the case of *tert*-butyl ethers, numerous reports in the literature have shown their synthetic use in different fields[1,2], since the products so obtained are stable under midly acidic, basic, and organometallic conditions. In a previous communication[3], we have demonstrated the advantages of *tert*-amylic ethers over the former ones : i) inexpensive starting material for their formation (2-methyl-1-butene), ii) use of stoichiometric quantities of 2-methyl-1-butene having a boiling point of + 31°C, iii) mild conditions for the preparation (use of catalytic amount of $BF_3.OEt_2$ or Amberlyst H15), iv) easy experimental conditions (work-up, and purification), and v) extremely good chemoselectivity toward primary hydroxyl groups (eq. 1).

equation 1



Tert-butyl ethers can be deprotected in several ways[1], but Alexakis[4] has found that using only three to five equivalents of acetic anhydride in the presence of a catalytic amount of iron tri-chloride in Et_2O, allowed to obtain the corresponding acetates in high yields, which upon saponification led to the free alcohols (eq. 2). We found that under the same conditions *tert*-amyl ethers can be also converted into their corresponding acetates[3] (eq. 2).

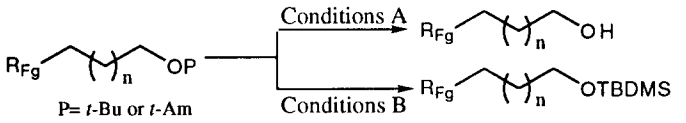
equation 2



In this letter we wish to report that *tert*-amyl and *tert*-butyl ethers, as well as *tert*-butyl esters, can be deprotected by trialkylsilyl triflates[5,6] to afford either the free alcohols and carboxylic acids or the

butyldimethylsilyl ethers from alcohols[1,7,8], but herein we propose a new access to these valuable compounds, starting with their corresponding *tert*-butyl or *tert*-amyl ethers (eq. 3 and table 1).

equation 3



When *tert*-amyl- or *tert*-butyl alkyl ethers are treated with 10 molar % of *tert*-butyldimethylsilyl triflate[9] (TBDMSOTf) in CH_2Cl_2 at room temperature under nitrogen (conditions A)[10], the corresponding alcohols are obtained in good to excellent yields (entries 1, 4, 5, 10). Whereas treatment of the same *tert*-amyl- or *tert*-butyl ethers by one equivalent of TBDMSOTf, followed by one equivalent of 2,6-lutidine (conditions B)[10], led to the corresponding silylated ethers in excellent yields (entries 2, 3, 6-9, 11, 12-14). Treatment of *tert*-butyl esters in conditions A led to the carboxylic acid in good yields[6] (entries 15 and 16). In order to obtain the silyl ethers, it is important to add the reagents in the order described above, since if the base is first added and then TBDMSOTf, no deprotection occurs, and silylation of free hydroxyl group arised, as already observed by Corey[8].

It is worth pointing out that many functional groups are tolerated : e.g. methyl- and allyl ethers, lactone, bromine, trimethylsilylalkynyl derivatives, isolated double bonds (entries 7, 9, 8, 14, 11, respectively). Indeed, in the case of (*Z*)-1-*tert*-amyloxy-3-octene, we did not observe, neither by gpc nor by NMR, any isomerization of the double bond (entry 11). Furthermore, 1-bromo-2-*tert*-butyloxy-hexane when treated in conditions B gave rise to the expected silyl ether in quantitative yield, without any formation of the oxirane which could be formed by deplacement of the bromine atom (entry 13).

We postulate that the reaction occurs through a catalytic pathway depicted on scheme 1. The first step involves formation of an oxonium intermediate, followed by an elimination leading to the corresponding trialkylsilyl ether and triflic acid which is responsible for the cleavage of this silyl ether, affording the free alcohol and regenerating the catalyst. After work-up the free alcohol is obtained, but if a base is added instead (and TBDMSOTf used in stoichiometric amount) the formation of the silylated ether is observed as expected. In fact, if the *tert*-amyl ether is directly treated by 10 mol % of triflic acid, the corresponding free alcohol is obtained in only 34 % yield (eq. 4). Whereas, the trialkylsilyl ether treated by one equivalent of triflic acid gave rise to the expected alcohol in 67 % yield (eq. 5).

equation 4

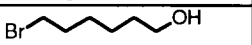
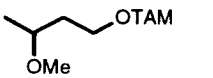
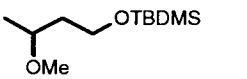
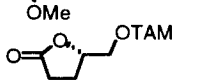
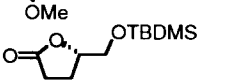
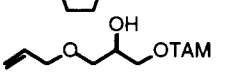
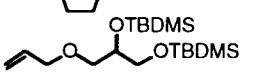
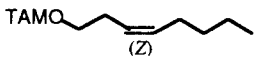
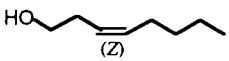
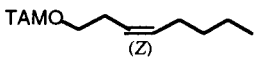
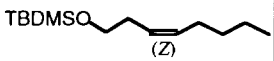
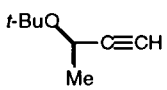
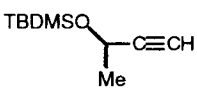
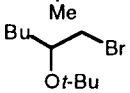
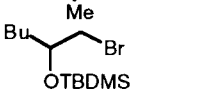
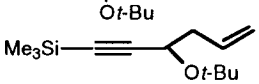
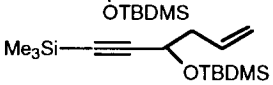
$$Br(CH_2)_6OTAM \xrightarrow[CH_2Cl_2,\ 24\ h,\ r.t.]{10\%\ TfOH} Br(CH_2)_6OH \quad 34\ \%$$

equation 5

$$C_8H_{17}OTBDMS \xrightarrow[CH_2Cl_2,\ 24\ h,\ r.t.]{1\ eq.\ TfOH} C_8H_{17}OH \quad 67\ \%$$

This process is related to the mechanism proposed for the deprotection of *tert*-butyl alkyl ethers by trimethylsilyl iodide[11] (TMSI). However, the use of TBDMSOTf presents several advantages over its counter part TMSI : i) the procedure is catalytic, ii) absence of traces of iodine responsible of side reactions, iii) possible preparation of the protected alcohol as a silyl ether when the conditions B are applied.

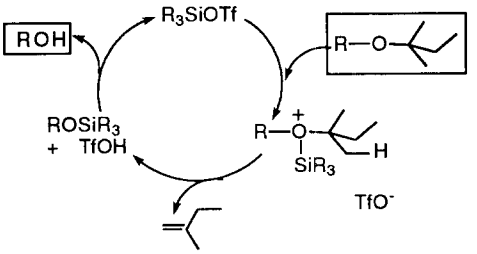
table 1

entry	substrate	Conditions	product	yield[a]
1		A		82
2		B		98
3	$C_{16}H_{34}OTAM$	B	$C_{16}H_{34}OTBDMS$	99
4	$C_{16}H_{34}OTAM$	A	$C_{16}H_{34}OH$	96[b]
5	$C_{16}H_{34}OTAM$	A	$C_{16}H_{34}OH$	52[c]
6	$C_8H_{17}OTAM$	B	$C_8H_{17}OTBDMS$	89
7		B		96
8		B		76[d]
9		B		82[e]
10		A		46[c]
11		B		79[f]
12		B		89
13		B		99
14		B		80
15	$Br\text{-}(CH_2)_{10}\text{-}COOt\text{-}Bu$	A	$Br\text{-}(CH_2)_{10}\text{-}COOH$	91
16	$Ph\text{—}CH\text{=}CH\text{—}COOt\text{-}Bu$	A	$Ph\text{—}CH\text{=}CH\text{—}COOH$	85

a) isolated yields (%); spectroscopic data of the products so obtained are in accord with the structures; b) 20% of TBDMSOTf was used; c) remainder of the mass balance is starting material; d) 1.5 eq. of 2,6 lutidine was used; e) 2.2 eq. of TBDMSOTf and 2,6-lutidine were used; f) measured by NMR (with 21% of starting material)

In conclusion we found that *tert*-butyl or *tert*-amyl alkyl ethers can give rise to silyl ethers in neutral conditions, or to the free alcohols in very mild conditions.

Scheme 1



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6 Carboxylic acid *tert*-butyl esters have been deprotected into their corresponding trimethylsilyl esters or free acids by treatment with TMSOTf and Et_3N in boiling dioxan, see : Borgulya J., Bernauer K., *Synthesis*, **1980**, 545-547.

7 Corey E. J., Venkateswarlu A., *J. Am. Chem. Soc.*, **1972**, *94*, 6190-6191.

8 Corey E. J., Cho H., Rücker C. Hua D. H., *Tetrahedron Lett.*, **1981**, *22*, 3455-3458.

9 In some cases, 20 % of TBDMSOTf are used in order to accelerate and improve the yield of the reaction (see table 1, entries 4 and 5).

10 Conditions **A** : To a solution of 6-bromo-1-*tert*-amyloxy-hexane[12] (0.271 g, 1.08 mmol.) in dichloromethane (1 mL) at room temperature is added dropwise 10 molar % of TBDMSOTf[13] (0.025 mL, 0.108 mmol.) and the resulting solution is stirred for 24 hours. Saturated $NaHCO_3$ (1 mL) is then added and the solution extracted with AcOEt. Combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure. The crude product is purified by flash-chromatography (cyclohexane/AcOEt 8/2) to afford 0.160 g (82 %) of the desired 6-bromo-hexanol. Conditions **B** : To a solution of 6-bromo-1-*tert*-amyloxy-hexane[12] (0.242 g, 0.96 mmol.) in dichloromethane (1 mL) at room temperature is added dropwise 1.1 equivalent of TBDMSOTf (0.243 mL, 1.06 mmol.) and the resulting solution is stirred for 2 hours before cooling at 0°C and adding 1.1 equivalent of 2,6-lutidine (0.123 mL, 1.06 mmol.). The resulting solution is stirred for two more hours at 0°C and saturated $NaHCO_3$ (1 mL) is added. The solution is extracted with AcOEt, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash-chromatography (cyclohexane/AcOEt 95/5) to afford 0.279 g (98 %) of the desired 6-bromo-1-*tert*-butyldimethylsilyloxy-hexane.

11 Jung M. E., Lyster M. A., *J. Org. Chem.*, **1977**, *42*, 3761-3764.

12 *Tert*-amyl ethers have been prepared as described in ref. 3.

13 It is worth to note that trimethylsilyl triflate can be used in place of TBDMSOTf when the free alcohol is desired; for example

$$C_8H_{17}OTAM \xrightarrow[CH_2Cl_2,\ r.t.]{10\ \%\ TMSOTf} C_8H_{17}OH \quad (85\ \%)$$

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