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$SbCl_5$–wet acetonitrile: a new system for chemoselective *O*-desilylation

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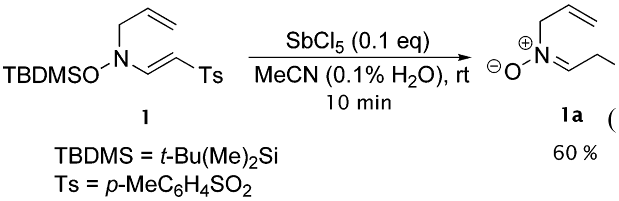
Abstract—A new efficient method for deprotection of TBDMS derivatives of phenols, primary alcohols, carboxylic acids and secondary amines, consisting of $SbCl_5$ and MeCN with 0.1% water (w/v), is reported. It effects inter alia desilylation of a $CH_2OTBDMS$ group in the presence of a ketal function.

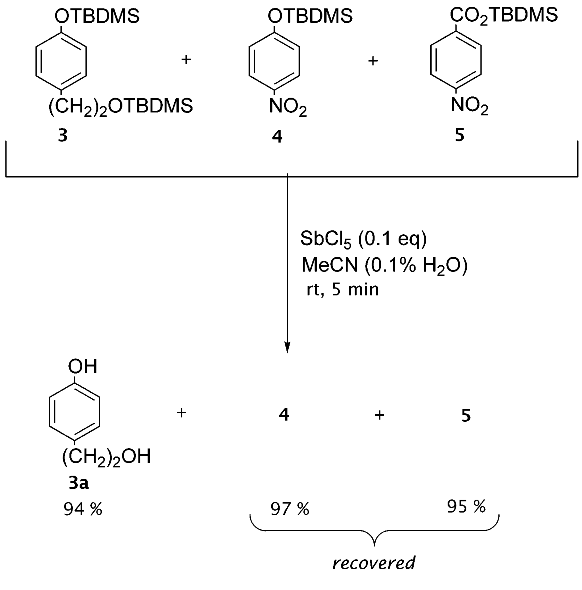
The application of silyl groups as protecting groups for O, N, S, etc., in synthesis is well known.[1] Since its introduction to organic chemistry by Corey,[2] one such group namely, the *t*-butyldimethylsilyl group (TBDMS) has occupied a privileged position. Its popularity, especially with respect to *O*-protection, is undoubtedly due to its enhanced stability in basic and mildly acidic conditions, compared with other common silicon-based analogues, and the mildness of conditions under which it can be removed. In connection with our current studies on the synthesis of heterocyclic compounds, an attempted desilylation of substance **1**, and other structurally related compounds,[3] with a variety of F^- ion sources in THF led to intractable mixtures. However, a solution of **1** in wet acetonitrile, 0.1% water (w/v), on treatment with a sub-stoichiometric quantity of $SbCl_5$ (0.1 equiv.) cleanly afforded the nitrone **1a** in good yield (Eq. (1)).



(1)

This observation led us to examine the scope of this reaction for the deprotection of other silylated compounds.[4] Our results (Table 1) show that the same system brings about an efficient deprotection of TBDMS derivatives of phenols, primary alcohols, carboxylic acids, and primary and secondary amines in good to excellent yields.[5]

The different rates of desilylation observed (Table 1; entries 1, 2, 3 and 4) prompted us to examine the existence if any, of substrate selectivity in a mixture consisting of different silyl ethers. With this end in view, an equimolar mixture (0.06 M) of **3**, **4** and **5** in wet acetonitrile (0.1% H_2O) was exposed, in a competitive reaction, to the action of $SbCl_5$ (0.1 equiv.) at rt and the following results were obtained (Eq. (2)).



(2)

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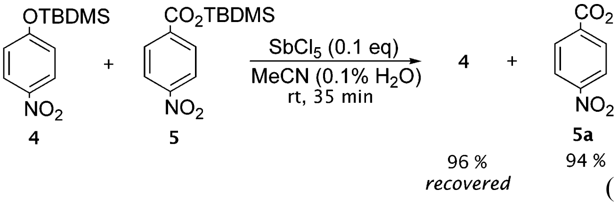
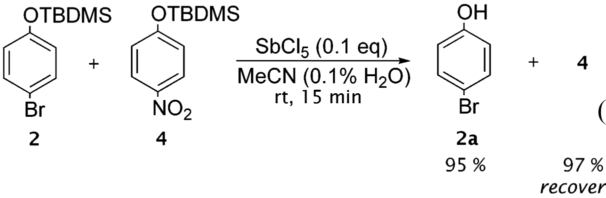
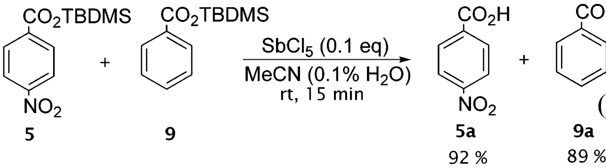
Thus, whilst no discrimination was observed in the cleavage between the phenolic and the alcoholic TBDMS groups in **3** (Eq. (2)), high chemoselectivity was noted for the *p*-nitro silyl ester **5** in the presence of the *p*-nitro silyl ether **4** (Eq. (3)). A similar rate difference noted for the TBDMS derivatives of *p*-bromo and *p*-nitro phenols, **2** and **4** respectively, was again reflected in the preferential conversion of **2** into **2a** (Eq. (4)). However, no such selectivity was observed between the silyl ester of benzoic acid **9** and its *p*-nitro derivative **5** (Eq. (5)).



(3)



(4)



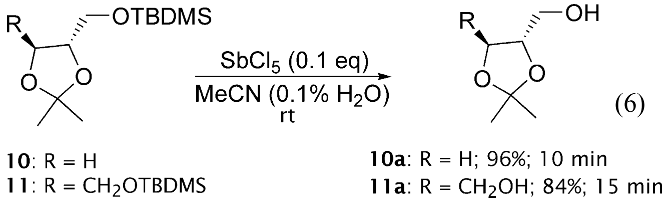
(5)

In experiments involving substances **10**, **11** and **12**, all of which contained both ketal and *O*-TBDMS groups, it is the latter that are selectively deprotected to provide the corresponding primary alcohols **10a**, **11a** and **12a** in excellent yields[6] (Eq. (6) and (7)).

Table 1. Silyl compounds deprotected by $SbCl_5$/MeCN (0.1% H_2O) at rt

Entry	Silyl compound *p*-R^1-C_6H_4-R^2	Product *p*-R^1-C_6H_4-R^2	Time	Yield (%)
1	**2** R^1=OTBDMS R^2=Br	**2a** R^1=OH R^2=Br	15 min	93
2	**3** R^1=OTBDMS R^2=$(CH_2)_2$OTBDMS	**3a** R^1=OH R^2=$(CH_2)_2$OH	10 min	92
3	**4** R^1=OTBDMS R^2=NO_2	**4a** R^1=OH R^2=NO_2	31 h	94
4	**5** R^1=CO_2TBDMS R^2=NO_2	**5a** R^1=CO_2H R^2=NO_2	40 min	85
5	**6** R^1=NHTBDMS R^2=CH_3	**6a** R^1=NH_2ae R^2=CH_3	5 min	62[a]
6	**7** R^1=CH_2NHTBDMS R^2=H	**7a** R^1=CH_2NH_2 R^2=H	5 min	72[a]
7	**8** $(CH_2)_5$NTBDMS	**8a** $(CH_2)_5$NH	5 min	75[a]

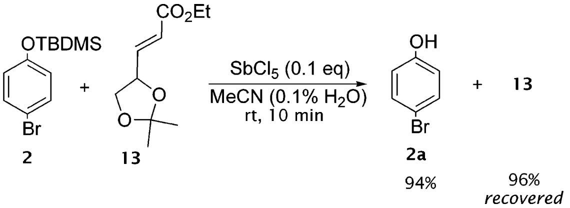
[a] Estimated by ^{1}H NMR.



(6)

(7)

A similar selectivity in favour of desilylation was also observed in a competition experiment involving the ketal-ester **13** and the phenolic OTBDMS ether **2** as shown in Eq. (8).



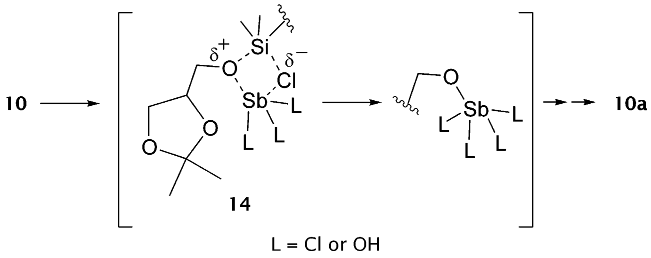
(8)

In principle these reactions could be yet another example[7] of a simple protic acid catalysed process (i.e. HCl generated in situ from $SbCl_5$ and the water present in MeCN) (Eq. (9)).

$$SbCl_5 + H_2O \rightleftharpoons SbCl_4(OH) + HCl \qquad (9)$$

That water is clearly implicated in these reactions is supported by the observation that they became progressively slower as the water content in the acetonitrile was reduced by successive distillations from CaH_2 and P_2O_5. In spite of similar readings by a pH meter[8] for both a solution of $SbCl_5$ (6×10^{-3} M) in MeCN containing 0.1% water and a 0.265 M solution of HCl in the same solvent system, the OTBDMS *cleavage in* **10** *with aq. HCl occurred non-selectively (Eq. (6)).* A similar result was observed for the competition process shown in Eq. (2). Instead only glycerol, in the former, and *a mixture of varying proportions* of **3a**, **4a** *and* **5a**, in the latter, were obtained. On the basis of these observations the following mechanism involving an Sb(V) intermediate of type **14** for the *O*-desilylation[9] of **10** is suggested (the precise number of OH groups attached to Sb(V) remains undetermined) (Scheme 1).

In conclusion, $SbCl_5$, in sub-stoichiometric quantity, in moist acetonitrile, is introduced as an efficient and mild system for the deprotection of TBDMS derivatives of amines, phenols, primary alcohols and aryl carboxylic acids in good to excellent yields. High selectivity for OTBDMS cleavage is noted in the presence of a ketal group. A similar discrimination was observed for aryl



Scheme 1. Proposed activation of **10** for the selective *O*-desilylation.

silyl carboxylates and aryl silyl ethers providing the latter carries a *p*-nitro substituent. The method was also found to be useful for the clean *O*-deprotection of *N*-silyloxy-*N*-allyl-*N*-vinyl enamines, a class of compounds which led to an array of products with conventional F$^-$ ion based desilylating reagents.

Acknowledgements

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2. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
3. Gomes, M. J. S.; Sharma, L.; Prabhakar, S.; Lobo, A. M.; Glória, P. M. C. *Chem. Commun.* **2002**, 746–747.
4. All silylated substances in Table 1 are known compounds and were prepared from the corresponding commercially available precursors by the method of Corey.[2]
5. These results were presented at the 5th National Meeting of Organic Chemistry and 1st Portuguese–Japanese Chemical Symposium, held in Aveiro, Portugal (July 2003).
6. *Typical experimental procedure*: To a stirred solution of commercial (Aldrich) 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidine-D-ribonic acid **12** (25 mg, 0.06 M, 1 equiv.) in acetonitrile [1.4 ml, 0.1% water (w/v)] was added (0.213 ml, 0.1 equiv.) of $SbCl_5$ (freshly distilled; 0.039 M in MeCN), under an atmosphere of nitrogen at room temperature. On completion of the reaction (10 min., TLC control; AcOEt) the product **12a** was isolated by evaporating the solvent under reduced pressure and purifying the resulting residue by PTLC. 2,3-*O*-Isopropylidene-D-ribonic γ-lactone **12a** was obtained in 85% yield as a colourless solid; mp 136–138°C (lit., 135–139°C); this possessed spectral data identical with those of the starting material. See: Beilstein, F. K. *Beilstein Handbuch der Organischen Chemie*, 19, IV, Springer: Berlin, 1972; pp. 5144.
7. For desilylation, by HI generated in situ from I_2/MeOH, by HCl from $TMSCl/H_2O$, and by HBr from *n*-Bu_4N^+ Br_3^-/MeOH, see, respectively: (a) Lipshutz, B. H.; Keith, J. *Tetrahedron Lett.* **1998**, *39*, 2495–2498; (b) Grieco P. A.; Markworth, C. J. *Tetrahedron Lett.* **1999**, *40*, 665–666; (c) Gopinath, R.; Patel B. K. *Org. Lett.* **2000**, *26*, 4177–4180.
8. Readings obtained using a Schott pH meter with a Schott Gerate N 65 electrode: for the Sb(V) system, −1.13; for a HCl solution (0.265 M) in the same solvent system, −1.12.
9. The considerable rate difference observed for the TBDMS ethers of *p*-bromophenol (15 min) and *p*-nitrophenol (31 h) is consistent with the suggested mechanism. Ease of prior coordination of the Sb(V) species with the oxygen lone-pair for the cleavage to occur becomes less favoured when an EWG group such as NO_2 is present at the *para* position.