Tetrahedron Letters, Vol.31, No.4, pp 567-568, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

New Synthetic 'Tricks'. Trimethylsilyl Triflate Mediated Cleavage of Hindered Silyl Ethers

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Summary.- An alternative, mild procedure for the cleavage of t*-butyldimethylsilyl and triphenylsilyl ethers to alcohols is shown, which is based on an exchange reaction with trimethylsilyl triflate below 0 °C.* t*-Butyldiphenylsilyl groups are not removed under these conditions.*

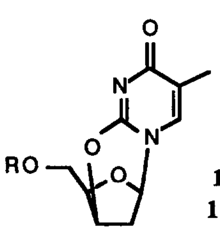
The *tert*-butyldimethylsilyl group (Bu^tMe_2Si, TBDMS) has become the most outstanding member of a very useful set of silicon-based protective groups for alcohols.[1] The corresponding silyl ethers may be cleaved by several reagents among which $Bu_4N^+F^- \cdot nH_2O$ (in THF at r.t.) is frequently used. However, even this almost perfect deprotection method has some limitations, due to the basicity of the 'naked' fluoride ion, which may promote transacylations in O-acyl-protected sugars and polyols[2] and other undesired reactions.[1]

In connection with a work aimed at synthesizing novel nucleosides[3] we required alternative procedures to deprotect Bu^tMe_2Si ethers. On the basis of the known fact that Me_3SiI cleaves dialkyl ethers to afford alkyl iodide(s),[4] we envisaged the possibility of exchange reactions between silyl ethers and trimethylsilyl triflate (Me_3SiOTf, TMSOTf) such as the following example, in which the poor nucleophilicity of triflate anion would preclude the formation of alkyl triflate from the intermediate oxonium ion:

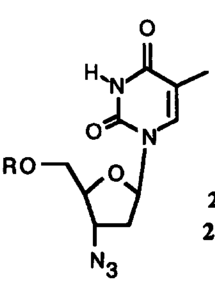
$$\mathrm{Bu^tMe_2Si\text{-}O\text{-}\mathbf{R}} + \mathrm{Me_3SiOTf} \rightleftharpoons [\ \mathrm{Bu^tMe_2Si\text{-}\underset{Me_3Si}{O^+}\text{-}\mathbf{R}}\ \underset{TfO^-}{]} \rightleftharpoons \mathrm{Me_3Si\text{-}O\text{-}\mathbf{R}} + \mathrm{Bu^tMe_2SiOTf}$$

If by steric and/or electronic reasons these equilibria were shifted to the right, addition of either water or methanol would readily cleave the much more prone-to-hydrolysis trimethylsilyl ethers ($Me_3Si\text{-}O\text{-}\mathbf{R}$). We wish to report here our results regarding this point.

Treatment of 0.5 mmol of compounds **1a**-**5a** with Me_3SiOTf (1.0-2.5 mmol depending on the case; see the Table in the next page), in 3-5 ml of *cold* anh. CH_2Cl_2 under argon, *for a few minutes,* followed by addition of neutral alumina (grade I) to the reaction flask and filtration of the mixture through a small pad of alumina with CH_2Cl_2/MeOH 98:2 or 90:10 as eluents, afforded deprotected nucleosides **1**-**3**, glucose derivative **4**, and cholesterol (**5**), respectively, in almost quantitative yields.[5]

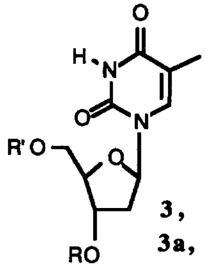


1, R = H
1a, R = Bu^tMe_2Si

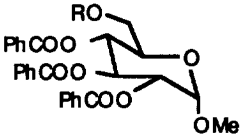


2, R = H
2a, R = Bu^tMe_2Si

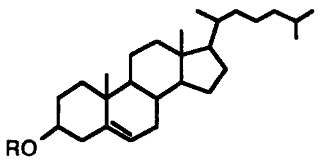
Analogously, but below 0 °C to avoid byproducts, the triphenylsilyl groups (Ph_3Si, TPS) of **4b** and **5b** can be readily removed, as shown in the Table.[5] No transacylation is observed in the **4a** and **4b** cases.



3, $R=R'=H$
3a, $R=R'=Bu^tMe_2Si$
3b, $R=Bu^tMe_2Si$, $R'=Bu^tPh_2Si$
3c, $R=H$, $R'=Bu^tPh_2Si$



4, $R = H$
4a, $R = Bu^tMe_2Si$
4b, $R = Ph_3Si$



5, $R = H$
5a, $R = Bu^tMe_2Si$
5b, $R = Ph_3Si$

The simplicity of the procedure is worth noting; moreover, it takes less than 1 h, including the workup, and the reaction is fast even at -78 °C. We think that other moderately hindered R_3Si protective groups may also be amenable to this cleavage method. On the other hand, the corresponding Bu^tPh_2Si (TBDPS) ethers are much less reactive since under our conditions even secondary Bu^tMe_2SiOR may be cleaved without touching primary Bu^tPh_2SiOR (see **3b**→**3c**).[6] Attempts to remove Bu^tPh_2Si, warming up to r.t., caused partial decomposition of the samples.[7]

Table. Cleavage of Silyl Ethers to Alcohols

substrate	Me_3SiOTf (no. equiv)	time (min)	temp. (°C)	product	yield[a] (%)
1a	3	5	0	**1**	98
2a	3	5	0	**2**	86-92
3a	5	5	0	**3**	95
3a	5	30	-78	**3**	90-95
4a	3	5	0	**4**	97
5a	2	10	0	**5**	95
4b	3	30	-10	**4**	90
5b	3	30	-20	**5**	96
3b	3	15	-20	**3c**	86

[a] Yield of isolated product; 97-100% crude yields (^1H NMR) in all cases.

Acknowledgments.

We thank the CIRIT (Generalitat de Catalunya, Barcelona) and CICYT (Ministerio de Educación y Ciencia, Madrid) for financial support during 1986-87 and for 1988-90 (Grant PB86-0137), respectively. A fellowship to V. B. (1988-91) from the Ministerio de Educación y Ciencia is also deeply acknowledged.

References and footnotes

1. For recent reviews, see: 'Silylating Agents'; Fluka Chemie; Buchs, 1988. Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817. Also see: Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19, and references therein.
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4. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. Review: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.
5. The substrates studied here are not significantly deprotected by column chromatography (alumina, $CH_2Cl_2/MeOH$), i.e. without previous addition of TMSOTf. By identical treatment of **1a** with 3 equiv. of TfOH, it is only observed a partial deprotection.
6. Prakash et al. (ref. 1) have just reported that pyridinium *p*-toluenesulphonate in EtOH at r.t. also removes selectively TBDMS groups in the presence of TBDPS ones. Looking for similar facts in the literature, in a paper on the cleavage of MOM ethers by trimethylsilyl bromide (Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515) it is incidentally mentioned that the TBDPS ethers were stable whereas the TBDMS ones were partially stable.
7. Si-C cleavages seem to take place. Exchange experiments between TMSOTf and $PhCH_2CH_2OSiR_3$ (where SiR_3 = TMS, TBDMS, TPS, or TBDPS) have been monitored by 200-MHz ^1H NMR and will be reported elsewhere.

(Received in UK 13 November 1989)