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Selective Acidic Cleavage of Ketals in the Presence of tert-Butyldimethylsilyl Ethers

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SELECTIVE ACIDIC CLEAVAGE OF KETALS IN THE PRESENCE OF TERT.-BUTYLDIMETHYLSILYL ETHERS

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Abstract:
Dilute methanolic HCl in anhydrous THF ($<0.5\%$ CH_3OH, ca. 10^{-2} molar H^+) cleaves acetals and ketals, whereas *t*-butyldimethylsilyl ethers where recovered unchanged even at elevated temperatures.

Keywords: selective cleavage of ketals in the presence of TBDMS ethers

Introduction:
Silyl ethers and ketals (including acetals, e.g. THP ether, MOM ether) are some of the most useful protecting groups in organic chemistry. Whereas the selective cleavage of silyl ethers beside ketals is achieved by the use of fluorid ions[1], the solvolysis of ketals beside silyl ethers is less trivial.
Triflouracetic acid in THF/H_2O is commonly used to hydrolyse acetals[2], but it usually also cleaves TBDMS ethers, although some selectivity could be observed in a few cases[3]. Anhydrous $MgBr_2$[4], $MgBr_2$ plus thiols[5], $(CH_3)_2AlCl$[6], several boron halides[7] and thiostannanes[8] were reported to cleave ketals selectively, tolerating TBDMS ethers.

The author wants to present a more convenient method towards this target, combining the benefits of using cheap reagents, clean reactions and easy workup.

Results:
During attempts towards a synthesis of *(+)-nodusmicin*[9] an interesting solvent dependence of the rate of solvolysis of TBDMS ethers was found. Whereas the TBDMS ether of **1** was cleaved in a solution of 0.06 M $HCl_{(gasous)}$ in THF/CH_3OH (50% CH_3OH), it was stable against 0.12 M $HCl_{(gasous)}$ in THF/CH_3OH (4% CH_3OH) (see table).

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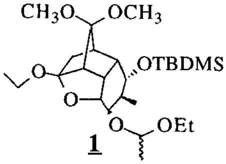
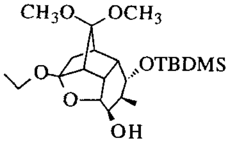
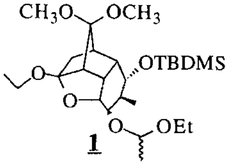
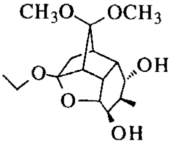
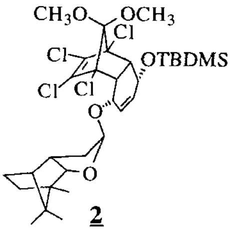
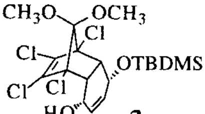
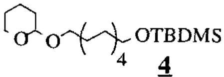
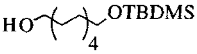
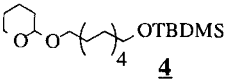
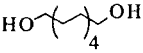
Table

substrate	$[H^+]$ (mmol/l)	% CH_3OH (v/v)	T (°C)	t (h)	product	yield (%)
 **1**	115	4	25	16		95
 **1**	60	50	25	16		98
 **2**	9.3	0.3	63	31	 **3**	86
 **4**	13	0.4	67	4		90
 **4**	5.9	50	0	2		90

This selective solvolysis was successfully applied to cleave the relative acid stable 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl[10] protecting group (MBF group, Noe's lactol; exo isomer). **2**[11] is converted to the silyl ether **3**[9] (86%) by heating to 63°C with anhydrous methanolic HCl ($[H^+]$ = 0.009 M, 0.3% CH_3OH) in THF for 30^h.

Aqueous H_2SO_4 in acetone or HCl in CH_3OH did cleave both protecting groups of **2** unselectively.

To examine the applicability of these conditions decan-1,10-diol was converted to **4**[6] via monosilylation[12] and THP ether formation[13].

The THP group of 4 is selectively hydrolysed with 0.06 molar HCl in THF plus CH_3OH (0.4% methanol) within 2 hours at 45°C. The primary TBDMS ether is stable to this acidic conditions for 20 hours at reflux, but is cleaved with 0.06 molar HCl in THF plus CH_3OH (50% methanol) even faster than the THP ether within 2 hours at 0°C.

The over all reaction is a reversible transfer of the ketal type protecting group to methanol, explaining the necessity to use at least a few equivalents of CH_3OH. A very large excess of methanol results in a loss of selectivity. These results may reflect that cleavage of silyl ethers seem to need assistance by a nucleophile[14], whereas ketals can be cleaved (to oxonium ions) without a nucleophile present.

General Procedure:

To a solution of the starting material in dry THF the calculated amount of methanolic HCl is added. The mixture is stirred at the temperature indicated in the table, during which time the reaction is followed by TLC for the disappearance of starting material[15]. After cooling the reaction is quenched by addition of a saturated aqueous solution of $NaHCO_3$. Extraction with ethyl acetate, washing the combined organic layers with brine and drying with Na_2SO_4 leads to isolation of the product.

Conclusions:

Methanolic HCl in anhydrous THF has been found to cleave THP ethers, 1-ethoxyethyl ethers, and MBF ethers. Primary, secondary and allylic TBDMS ethers are stable under these conditions. This observation may be of use in the field of differentiating between multiple protected hydroxy groups, a common problem in organic synthesis.

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(15) This reaction is a transketalisation and leads to an equilibrium. A small amount (<5%) of starting material remains in the mixture.

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