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A facile zirconium(IV) chloride catalysed selective deprotection of *t*-butyldimethylsilyl (TBDMS) ethers☆

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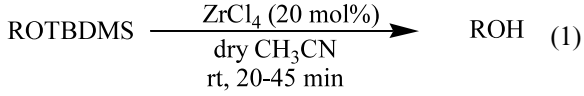
Abstract—A simple and efficient protocol for the selective deprotection of *t*-butyldimethylsilyl (TBDMS) ethers using 20 mol% $ZrCl_4$ in 20–45 min and in high yields, is reported, wherein it is demonstrated that acid and base sensitive groups and allylic and benzylic groups are unaffected.

Successful total syntheses of complex natural products depend not only on the correct strategy, but also on the correct choice of protecting groups,[1] the ease of their introduction, their stability towards a variety of reagents and finally their removal without effecting other functional groups present in the molecule. Since the selective protection and deprotection of functional groups is always very important in achieving a total synthesis, several protecting groups of different nature are available. Ever since the discovery of the *t*-butyldimethylsilyl (TBDMS) group by Corey et al.,[2] the TBDMS group has occupied a prominent place in synthetic chemistry and aided in the development of other related trialkylsilyl reagents as efficient protecting groups. The TBDMS group is one of the most versatile protecting groups due to its ease of introduction and ease of removal by TBAF,[2] as a result of its high fluoride ion affinity. A vast array[3] of acidic, basic, reducing, oxidizing and fluoride-based reagents were developed for the removal of the TBDMS group. In spite of these, there is still a need to develop new reagents in order to selectively remove TBDMS that function catalytically, and without effecting any acid or base sensitive groups. In continuation of our studies on the protection and deprotection[4] of alcoholic functional groups by use of Lewis acids, herein, we report a simple and facile zirconium(IV) chloride (20 mol%) catalyzed deprotection of TBDMS ethers (Eq. (1)).



(1)

A variety of TBDMS ethers were prepared from substrates comprising aliphatic, terpenoidal and sugar alcohols, in addition to diols possessing other different protecting groups. Initially, TBDMS ether **1** was subjected to desilylation with 20 mol% of $ZrCl_4$ in CH_3CN at room temperature for 20 min to give **1a** in 93% yield. A similar study on terpenoidal ether **2** resulted in **2a** in 20 min (87%). Extension of the same study to substrates **3** and **4** containing TBDMS protected secondary alcohols gave the desilylated products **3a** (89%) albeit in 2 h, and **4a** (95%) in 40 min, respectively.

The study was then extended to the sugar substrates **5** and **6** possessing 1,3-dioxolane protecting groups. Initially, reaction of **5** with 20 mol% $ZrCl_4$ at room temperature gave the expected product, along with the acetonide cleaved product. However, treatment of **5** with $ZrCl_4$ at 0°C gave **5a** in 83% yield in 45 min, while similar desilylation of **6** at 0°C gave **6a** (80%) in 45 min.

In a further study, desilylation of TBDMS ethers was attempted on substrates containing both acid and base sensitive protecting groups. Thus, ethers **7**, **8** and **9** possessing the acid sensitive groups THP, MEM and MDPM, gave the expected products **7a** (87%), **8a** (76%) and **9a** (81%), respectively, in which the THP, MEM and MDPM groups remained unaffected during the desilylation. A similar study with **10** and **11** which possess the base sensitive acetate and benzoate groups gave the respective alcohols **10a** (92%) and **11a** (95%) in 30 min.

Keywords: TBDMS ethers; zirconium(IV) chloride; desilylation; protecting groups.

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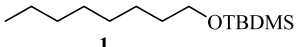
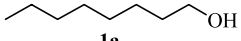
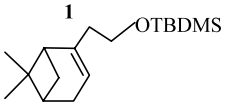
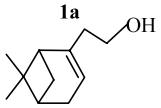
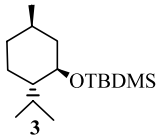
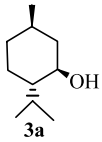
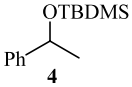
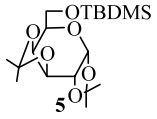
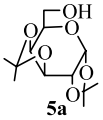
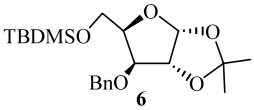
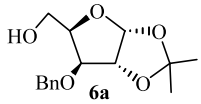
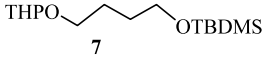
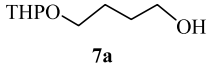
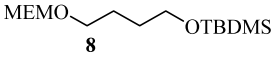
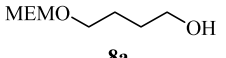
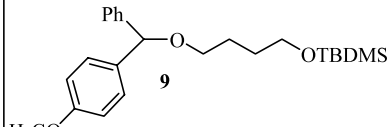
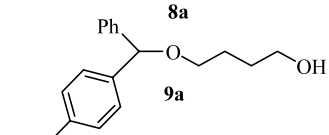
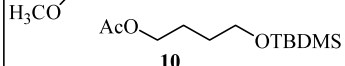
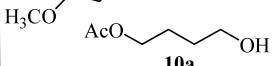
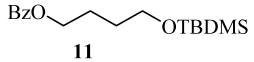
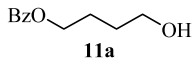
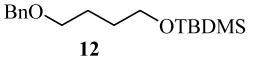
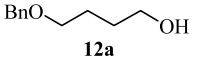
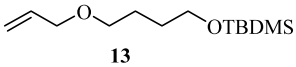
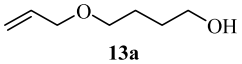
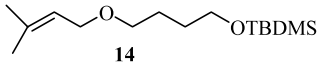
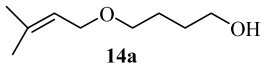
In addition, TBDMS ethers **12**, **13** and **14**, possessing benzylic, allylic and acid sensitive prenyl protecting groups, when treated with $ZrCl_4$ at room temperature in CH_3CN, gave the expected products **12a** (95%), **13a** (94%) and **14a** (88%), respectively.

Thus, in conclusion, $ZrCl_4$ in CH_3CN provides a mild and efficient catalytic (20 mol%) system for the highly selective removal of the TBDMS protecting group. The study also demonstrated that both acid and base sensitive groups and allylic and benzylic groups were unaffected. Further, it was shown that substrates such as sugars and terpenes are also unaffected by the present reagent system. Thus, $ZrCl_4$ (20 mol%) in CH_3CN with simple reaction conditions, shorter reaction times, high selectivity for the TBDMS group and high yields should find use in synthetic chemistry as a new and efficient reagent for the desilylation of TBDMS ethers.

Typical experimental procedure for deprotection: A solution of TBDMS ether (1.0 mmol) in CH_3CN (10 mL) was treated with $ZrCl_4$ (0.2 mmol) and stirred at room temperature for 20–45 min. The reaction mixture was evaporated and purified by column chromatography (60–120 mesh silica gel, EtOAc–petroleum ether) to furnish the desilylated products in 76–95% yields.

S.No.	STARTING MATERIAL	PRODUCT	TIME (min)	YIELD (%)
1	 **1**	 **1a**	20	93
2	 **2**	 **2a**	20	87
3	 **3**	 **3a**	120	89
4	 **4**	 **4a**	40	95
5	 **5**	 **5a**	45	83
6	 **6**	 **6a**	45	80
7	 **7**	 **7a**	30	87
8	 **8**	 **8a**	30	76
9	 **9**	 **9a**	20	81
10	 **10**	 **10a**	30	92
11	 **11**	 **11a**	30	95
12	 **12**	 **12a**	30	95
13	 **13**	 **13a**	30	94
14	 **14**	 **14a**	60	88

Spectral data for selected compounds:

Compound ***8***: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.73 (d, $J=5.92$ Hz, 1H), 4.68 (s, 1H), 3.69–3.62 (m, 4H), 3.58–3.41 (m, 4H), 3.39 (s, 3H), 1.60–1.30 (m, 4H) 0.92 (s, 9H) 0.05 (s, 6H); EIMS (m/z): 292 (M^+); IR (neat): 2934, 2886, 1513, 1253, 1105, 1036 cm^{-1}.
Compound ***10***: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.04–3.93 (t, $J=5.9$ Hz, 2H), 3.65–3.62 (t, $J=5.6$ Hz, 2H), 2.1 (s, 3H), 1.69–1.32 (m, 4H), 0.92 (s, 9H), 0.04 (s, 6H); EIMS (m/z): 246 (M^+), 218 (8), 100 (80), 68 (58); IR (neat): 2910, 1750, 1560, 1260, 1039 cm^{-1}.
Compound ***14***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.34–5.29 (t, $J=6.6$ Hz, 1H), 3.9 (d, $J=4.8$ Hz, 2H), 3.41–3.39 (t, $J=5.4$ Hz, 2H), 3.32 (t, $J=5.6$ Hz, 2H), 1.72 (s, 3H), 1.68 (s, 3H), 1.61–1.32 (m, 4H) 0.94 (s, 9H), 0.05 (s, 6H); EIMS (m/z): 272 (M^+); IR (neat): 2937, 2858, 2359, 1512, 1180, 1037 cm^{-1}.
Compound ***8a***: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.68 (d, $J=5.61$ Hz, 1H), 4.64 (s, 1H), 3.66–3.61 (t, $J=5.8$ Hz, 2H), 3.56–3.44 (m, 6H), 3.41 (s, 3H), 1.64–1.32 (m, 4H); EIMS (m/z): 178 (M^+); IR (neat): 3469, 2926, 1521, 1471 cm^{-1}.
Compound ***10a***: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.14–4.06 (t, $J=5.9$ Hz, 2H), 3.63–3.59 (t, $J=5.9$ Hz, 2H), 2.1 (s, 3H), 1.68–1.34 (m, 4H); EIMS (m/z): 132 (M^+), 121, 91; IR (neat): 3482, 2910, 1750, 1560, 1260 cm^{-1}.
Compound ***14a***: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.38–5.32 (t, $J=6.6$ Hz, 1H), 3.96 (d, $J=4.8$ Hz, 2H), 3.62 (t, $J=6.4$ Hz, 2H), 3.36–3.39 (t, $J=6.4$ Hz, 2H), 1.71 (s, 3H), 1.66 (s, 3H), 1.62–1.34 (m, 4H); EIMS (m/z): 158 (M^+), 141, 83, 69; IR (neat): 3506, 2942, 2861, 1523 cm^{-1}.

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