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An efficient protocol for the preparation of MOM ethers and their deprotection using zirconium(IV) chloride☆

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Abstract—An efficient protocol for the preparation of MOM ethers from alcohols and formaldehyde dimethyl acetal (DMFA) using $ZrCl_4$ (10 mol%) at room temperature under solvent free conditions has been developed. Similarly, the same Lewis acid, $ZrCl_4$ (50 mol%), in isopropanol at reflux was utilised for the deprotection of MOM ethers.

1. Introduction

Functional group protection and deprotection plays a prominent role in the synthesis of complex natural products,[1] while the selective removal of a protecting group is an important topic in synthetic chemistry. Alcohols are most commonly protected as ethers and esters, wherein alkyl and benzyl ethers are permanent protective groups (difficult to remove) while others, like THP, TBS, TPS and MEM/MOM ethers are acid labile (easier to remove). Of the acetal derived protecting groups for alcohols, such as THP and MOM/MEM, THP ethers generate diastereomers upon protection, while such problems do not arise with MOM and MEM groups. MOM ethers are commonly prepared by alkylation of the corresponding alkoxide anions with the highly carcinogenic MOMCl.[2,3] Alternatively, a variety of acidic reagents such as P_2O_5,[4] PTSA,[5] Nafion-H,[6] TMSI,[7] molybdenum(IV) acetyl acetonate,[8] $BF_3{\cdot}Et_2O$,[9] Envirocat,[10] sulfated zirconia,[11] expansive graphite,[12] $FeCl_3$ dispersed on 3 Å molecular sieves[13] and $Sc(OTf)_3$,[14] have been reported for the preparation of MOM ethers using formaldehyde dimethyl acetal (DMFA) and a new reagent, MOM-ON.[15] Similarly, several methods were reported earlier for the cleavage of MOM ethers, for example, using HCl,[16] BBr_3,[17] *p*-TsOH,[18] $ZnBr_2$,[19] $TiCl_4$,[19] Me_2BBr,[20a] $(i\text{-Pr})_2BBr$,[20b] CBr_4,[21] a clay catalyst,[22] $NaHSO_4{\cdot}SiO_2$,[23] and I_2/MeOH.[24] In view of the drawbacks associated with the known methods such as the need for stoichiometric amounts of expensive reagents, high temperatures, strong protic acid conditions, slow reactions and tedious workup procedures, there is a need to develop better reagents and conditions for the preparation and deprotection of MOM ethers. Our continued interest in the synthesis of new saccharides, natural products[25] from monosaccharides and synthetic methods,[25] prompted us to investigate a new procedure for MOM protection and deprotection. Herein, we report a simple and efficient $ZrCl_4$ (10 mol%) catalysed method for MOM protection (at room temperature under solvent free conditions) of alcohols in the presence of a variety of acid sensitive groups and on substrates such as carbohydrates, terpenes and others and the deprotection of MOM ethers in isopropanol at reflux (see Eq. 1).

$$\text{R-OH} \underset{\text{ZrCl}_4\text{ (50 mol\%), isopropanol, reflux}}{\overset{\text{ZrCl}_4\text{ (10 mol\%), DMFA, rt}}{\rightleftarrows}} \text{R-OMOM} \qquad (1)$$

2. Preparation of MOM ethers using $ZrCl_4$ (10 mol%)

Accordingly, the reaction of decanol **1** (Table 1, entry 1) with DMFA (2 equiv) and $ZrCl_4$ (10 mol%) at room temperature under solvent free conditions gave **1a**

Keywords: MOM ethers; Formaldehyde dimethyl acetal; Zirconium chloride.

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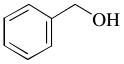
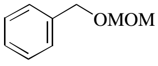
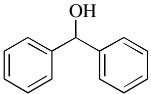
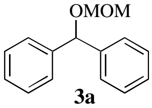
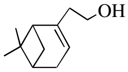
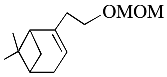
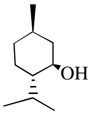
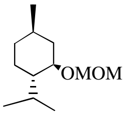
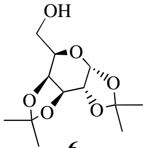
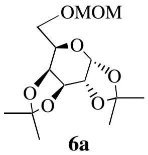
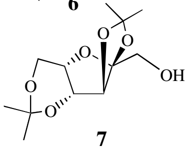
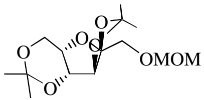
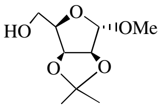
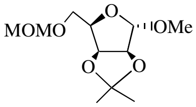
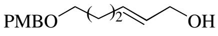
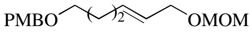
Table 1. $ZrCl_4$ (10mol%) catalysed preparation of MOM ethers

Entry	Starting material	Product	Time (h)	Yield (%)
1	$CH_3(CH_2)_8CH_2OH$ **1**	$CH_3(CH_2)_8CH_2OMOM$ **1a**	4	96
2	 **2**	 **2a**	1	97
3	 **3**	 **3a**	2	96
4	 **4**	 **4a**	6.5	97
5	 **5**	 **5a**	7	94
6	 **6**	 **6a**	5	93
7	 **7**	 **7a**	6.5	94
8	 **8**	 **8a**	5	93
9	$TPSOCH_2(CH_2)_2CH_2OH$ **9**	$TPSOCH_2(CH_2)_2CH_2OMOM$ **9a**	3.5	98
10	 **10**	 **10a**	5	95
11	$CH_3(CH_2)_8CH_2OTBDMS$ **11**	$CH_3(CH_2)_8CH_2OMOM$ **11a**	6	96
12	$CH_3(CH_2)_8CH_2OTHP$ **12**	$CH_3(CH_2)_8CH_2OMOM$ **12a**	5	97

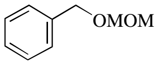
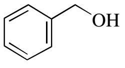
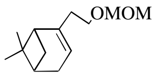
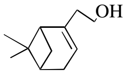
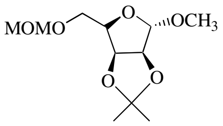
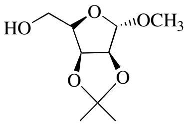
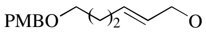
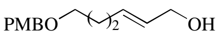
(96%) in 4h. However, benzylic alcohols **2** and **3** (Table 1, entries 2 and 3) gave the respective products **2a** (97%) and **3a** (96%) more quickly (1 and 2h). Similarly, nopol **4** and menthol **5** (Table 1, entries 4 and 5) underwent smooth reaction to give **4a** (97%) and **5a** (94%), respectively, wherein formation of **5a** took longer (7h). In a further study, the sugar substrates **6**, **7** and **8**[26] containing acid sensitive isopropylidene groups as well as an anomeric methoxy group (**8**) were unaffected under the above reaction conditions and gave **6a** (93%), **7a** (94%) and **8a** (93%), respectively.

Having established the reaction conditions for MOM protection on a variety of substrates, the study was then extended to other alcohols with acid sensitive protecting groups. Thus, alcohols **9** and **10** (Table 1, entries 9 and 10) with TPS and PMB groups, respectively, underwent facile MOM protection to give the MOM ethers **9a** (98%) and **10a** (95%) as indicated in Table 1. However, substrates **11**[27] and **12**[28] with TBS and THP ether groups on reaction with DMFA and $ZrCl_4$ (10mol%) underwent a one-pot deprotection and conversion to give the MOM ethers **11a** (96%) and **12a** (97%), respectively. This study thus infers that TPS, PMB and acetonide groups survive the reaction conditions along with substrates such as sugars/terpenes, while TBS and THP are not compatible and were converted into MOM ethers in one pot.

3. Deprotection of (MOM) ethers using $ZrCl_4$ (50mol%)

MOM ether **2a** when treated with 20mol% $ZrCl_4$ in isopropanol at room temperature, gave **2** (Table 2, entry 1)

Table 2. ZrCl$_4$ (50 mol%) catalysed deprotection of MOM ethers

Entry	Starting material	Product	Time (h)	Yield (%)
1	 **2a**	 **2**	1	97
2	$CH_3(CH_2)_8CH_2OMOM$ **1a**	$CH_3(CH_2)_8CH_2OH$ **1**	4	97
3	 **4a**	 **4**	4	93
4	 **8a**	 **8**	5	93
5	$TPSOCH_2(CH_2)_2CH_2OMOM$ **9a**	$TPSOCH_2(CH_2)_2CH_2OH$ **9**	3.5	97
6	 **10a**	 **10**	4.5	94

in 92% yield in 24 h, while at reflux, the reaction was complete in 11 h to give **2** in 90% yield. However, with 50 mol% ZrCl$_4$, the reaction with **2a** was complete in 1 h and gave **2** in 97% yield. Further, the reaction of **1a** (Table 2, entry 2) with 50 mol% ZrCl$_4$ in isopropanol at reflux gave **1** (97%) in 4 h. A similar study on **4a** and **8a** (Table 2, entries 3 and 4) resulted in **4** (93%) and **8** (93%), while, substrates **9a** and **10a** containing TPS and PMB groups, respectively, gave **9** (97%), and **10** (94%), wherein the TPS and PMB groups were found to be intact.

In conclusion, mild and efficient protocols for the preparation of MOM ethers using ZrCl$_4$ (10 mol%)[29] and deprotection of MOM ethers with ZrCl$_4$ (50 mol%)[30] have been established. The study also demonstrated that acid sensitive groups and substrates such as sugars and terpenes are unaffected by the present reagent system. THP and TBS ethers were converted in one pot into MOM ethers taking advantage of their vulnerability to ZrCl$_4$. Thus the above reaction conditions are simple, efficient and high yielding both for the protection and deprotection of MOM ethers and might find use in carbohydrate and other chemistry.

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29. General experimental procedure for the protection of MOM ethers: To a solution of alcohol (1 mmol) in DMFA (2 mmol), $\mathrm{ZrCl_4}$ (0.1 mmol) was added and stirred at room temperature until the starting material completely disappeared (TLC analysis). The reaction mixture was treated with EtOAc (20 mL), washed with water (15 mL), brine (15 mL), dried ($\mathrm{Na_2SO_4}$) and evaporated under reduced pressure to give the MOM ethers, which were characterised by ^{1}H NMR, IR and mass spectroscopy. Spectral data: **7a**: $[\alpha]_D$ −23.33 (*c* 1.50, $\mathrm{CHCl_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$, 400 MHz): δ 1.35 (s, 3H, $\mathrm{CH_3}$), 1.40 (s, 3H, $\mathrm{CH_3}$), 1.45 (s, 3H, $\mathrm{CH_3}$), 1.50 (s, 3H, $\mathrm{CH_3}$), 3.35 (s, 3H, –$\mathrm{OCH_3}$), 3.70 (d, 1H, *J* = 2.2 Hz, H-6), 3.80 (d, 1H, *J* = 2.2 Hz, H-6′), 3.90–4.05 (m, 3H, H-3, H-4, H-5), 4.25 (d, 1H, *J* = 2.28 Hz, H-5′), 4.40 (s, 1H, H-2), 4.64 (d, 1H, *J* = 6.09 Hz, $\mathrm{H_a}$), 4.68 (d, 1H, *J* = 6.09 Hz, $\mathrm{H_b}$); FABMS (*m*/*z*): 303 ($\mathrm{M^+}$−1) (8), 289, 215, 85, 44; IR (neat): 2914, 1612, 1464, 1248, 1174, 1096 cm^{-1}; **10a**: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 1.65 (q, 2H, *J* = 7.5 Hz, $\mathrm{CH_2}$), 2.15 (q, 2H, *J* = 7.96 Hz, $\mathrm{CH_2}$), 3.30 (s, 3H, –$\mathrm{OCH_3}$), 3.40 (t, 2H, *J* = 6.42 Hz, $\mathrm{CH_2}$), 3.80 (s, 3H, –$\mathrm{OCH_3}$), 3.95 (d, 2H, *J* = 4.91 Hz, $\mathrm{CH_2}$), 4.40 (s, 2H, $\mathrm{CH_2}$), 4.60 (s, 2H, $\mathrm{CH_2}$), 5.50–5.70 (m, 2H, olefinic), 6.80 (d, 2H, *J* = 8.68 Hz, Ar–H), 7.20 (d, 2H, *J* = 8.68 Hz, Ar–H); EIMS: 280 ($\mathrm{M^+}$), 236, 205, 156, 107, 91; IR (neat): 2985, 2954, 1617, 1513, 1337, 1214, 1075 cm^{-1}.
30. General experimental procedure for the deprotection of MOM ethers: A mixture of MOM ether (1 mmol) and $\mathrm{ZrCl_4}$ (0.5 mmol) in dry isopropanol (4 mL) was heated at reflux. After the completion of reaction (TLC analysis), it was cooled to room temperature, the solvent was removed under reduced pressure and the residue was treated with EtOAc (10 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried ($\mathrm{Na_2SO_4}$) and evaporated under reduced pressure to give the products. Spectral data for **10**: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 1.65 (q, 2H, *J* = 7.0 Hz, $\mathrm{CH_2}$), 2.15 (q, 2H, *J* = 7.5 Hz, $\mathrm{CH_2}$), 3.40 (t, 2H, *J* = 5.5 Hz, $\mathrm{CH_2}$), 3.80 (s, 3H, –$\mathrm{OCH_3}$), 3.95 (d, 2H, *J* = 8.6 Hz, 1H), 4.40 (s, 2H, $\mathrm{CH_2}$), 5.50–5.70 (m, 2H, olefinic), 6.80 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.20 (d, 2H, *J* = 8.7 Hz, Ar–H); EIMS: 250 ($\mathrm{M^+}$), 204, 156, 107, 91; IR (neat): 2976, 2947, 1622, 1517, 1341, 1221, 1081 cm^{-1}.