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ORIGINAL PAPER

Highly efficient and selective methoxymethylation of alcohols and phenols catalyzed by reusable $ZrO(OTf)_2$ under solvent-free conditions

Majid Moghadam · Shahram Tangestaninejad · Valiollah Mirkhani · Iraj Mohammadpoor-Baltork · Mostafa Khajehzadeh

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Abstract Different primary, secondary, and tertiary alcohols were efficiently converted to their corresponding methoxymethyl ethers with formaldehyde dimethyl acetal in the presence of catalytic amounts of $ZrO(OTf)_2$ at room temperature. Phenols were also methoxymethylated by this catalytic system. Advantages of using this catalytic system are the short reaction times, easy catalyst preparation, high product yield, solvent-free conditions, applicability for both alcohols and phenols, and reusability of the catalyst.

Keywords Methoxymethylation · Alcohol · Phenol · Zirconyl triflate · Formaldehyde dimethyl acetal

Introduction

The protection of hydroxyl groups of alcohols and phenols has occupied a unique position in organic synthesis because of the fundamental importance of hydroxyl groups in multistep synthesis of polyfunctional molecules such as nucleosides, carbohydrates, steroids, and natural products [1]. Methoxymethylation of these functional groups is a commonly used protective process for alcohols and phenols in organic synthesis. These protecting groups provide a number of significant advantages such as ease of introduction and stability toward a wide variety of conditions including many organometallic, reducing, and oxidizing agents [2, 3]. Methoxymethyl (MOM) ethers are frequently prepared by the reaction of alcohols or phenols with formaldehyde dimethyl acetal (FDMA). The main disadvantage of FDMA is its low methoxymethylating power in the absence of a suitable catalyst. To solve this problem a number of catalysts such as LiBr/Tos-OH [4], P_2O_5 [5], *p*-toluenesulfonic acid [6], Nafion-H [7], TMSI [8], BF_3 [9], Envirocat [10], $[Sn(IV)(Br_8TPP)(OTf)_2]$ [11], expansive graphite [12], sulfated metal oxides [13], silica sulfuric acid [14], $Sc(OTf)_3$ [15], $Bi(OTf)_3$ [16], $ZrCl_4$ [17], $MoO_2(acac)_2$ [18], $H_3PMo_{12}O_{40}$ [19], anhydrous $FeCl_3$ dispersed on 3 Å molecular sieve [20], TiO_2/SO_4^{2-} [21], $H_3PW_{12}O_{40}$ [22], and $H_3PW_{12}O_{40}$ supported on silica and zirconia [23] have been reported. However, some of the reported methods suffer from one or more disadvantages such as harsh reaction conditions, high reaction temperature, long reaction times, high cost or toxicity of the reagents, inapplicability for phenolic OH, and tedious work-up. Consequently, introduction of efficient and selective methods for the preparation of methoxymethyl ethers using inexpensive, relatively non-toxic, easily handled, and environmentally friendly catalysts is of practical importance and is still in demand.

Zirconium(IV) salts have recently attracted much attention due to their low cost, high catalytic activity, easy availability, and low toxicity [24, 25]. A variety of Zr(IV) salts has been used for several organic transformations such as Friedel–Crafts reaction [26], Diels–Alder reaction [27], Michael reaction [28], acetalization of carbonyl compounds [29–31], conversion of nitriles to oxazolines and imidazolines [32, 33], and trimethylsilylation of alcohols and phenols [34].

Here, we report the highly efficient methoxymethylation of alcohols and phenols with FDMA catalyzed by reusable $ZrO(OTf)_2$ at room temperature (Scheme 1).

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Scheme 1

Results and discussion

The catalytic ability of different zirconium salts was investigated in the methoxymethylation of 4-chlorobenzyl alcohol. In this manner, 4-chlorobenzyl alcohol was reacted with FDMA in the presence of 2.5 mol% of $ZrCl_4$, $ZrOCl_2{\cdot}8H_2O$, and $ZrO(OTf)_2$. The results (Table 1) showed that $ZrO(OTf)_2$ is more efficient than the others and was therefore used as an efficient catalyst for methoxymethylation of alcohols and phenols with FDMA.

The optimized conditions obtained for methoxymethylation of 4-chlorobenzyl alcohol were alcohol, FMDA, and catalyst in a molar ratio of 40:7:1. Under the same conditions a wide variety of primary, secondary, and tertiary alcohols were subjected to methoxymethylation with FDMA in the presence of catalytic amounts of $ZrO(OTf)_2$ at room temperature. The results which are summarized in Table 2 showed that all primary, secondary, and tertiary alcohols including aromatic, aliphatic, and cyclic ones were completely converted efficiently to their corresponding methoxymethyl ethers in 5–20 min. In the case of aromatic alcohols, the nature of substituents has no significant effect on the methoxymethylation yield. No dehydration product was observed in the case of tertiary alcohols.

The actual mechanism of these reactions is not truly clear, but due to the strong interaction between Zr and oxygen it seems that first an oxonium ion **1** is formed via activation of FDMA by $ZrO(OTf)_2$. The alcohol attacks **1** to give **2** which in turn converts to the methoxymethylated product **3** and releases the catalyst for the next catalytic cycle (Scheme 2).

Table 1 Investigation of the catalytic activity of different zirconium salts in the methoxymethylation of 4-chlorobenzyl alcohol with FDMA

Catalyst	Catalyst amount (mg, mol%)	Time (min)	Yield (%)
$ZrO(OTf)_2$	10 (2.5)	10	100
$ZrCl_4$	5 (2.5)	10	45
$ZrOCl_2$	8 (2.5)	10	0

This catalyst was successfully applied for methoxymethylation of phenols with FDMA and the corresponding ethers were obtained in excellent yields. As with alcohols the reactions were completed for all phenols in 10–15 min (Table 3).

In order to check the chemoselectivity of the present method, a set of competitive reactions was conducted between primary or secondary and tertiary alcohols or phenols (Table 4). The results indicated that the present protocol is potentially applicable for the chemoselective conversion of primary and secondary or tertiary alcohols to their MOM ethers in the presence of phenols and alcohols.

In order to show the effectiveness of the presented method in the methoxymethylation of hydroxyl compounds, the results obtained in the methoxymethylation of benzyl alcohol catalyzed by $ZrO(OTf)_2$ were compared with some of those reported in the literature (Table 5). The results showed that our method is superior in terms of catalyst amount, reaction time, or product yield.

The reusability of the catalyst was monitored in the multiple methoxymethylation of 4-chlorobenzyl alcohol. After each consecutive run, the solvent was evaporated and the catalyst was filtered off and washed with Et_2O and CH_2Cl_2 successively and used in the next run, using fresh alcohol and FDMA. The results showed that after reusing the catalyst for four runs no significant loss of its activity was observed.

In conclusion, we showed that different primary, secondary, and tertiary alcohols as well as phenols could be efficiently converted to their corresponding methoxymethyl ethers (MOM ethers) with formaldehyde dimethyl acetal (FDMA) in the presence of catalytic amounts of $ZrO(OTf)_2$ at room temperature. The advantages of using this catalytic system are the short reaction times, easy preparation of catalyst, high product yield, solvent-free conditions, applicability for both alcohols and phenols, and reusability of the catalyst.

Experimental

All materials were purchased from Merck. All products were identified by comparison of their physical and spectral data with those of authentic samples. ^1H NMR spectra were recorded in a $CDCl_3$ solution on a Bruker-AC 500 MHz spectrometer. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. Melting points were determined using a Stuart Scientific SMP2 apparatus. $ZrO(OTf)_2$ was prepared and characterized according to our previously reported procedure [34].

Table 2 Protection of alcohols with FDMA catalyzed by $ZrO(OTf)_2$ at room temperature

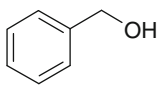
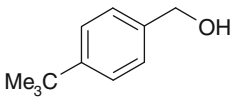
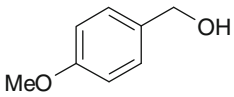
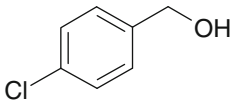
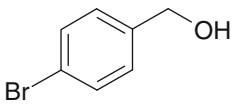
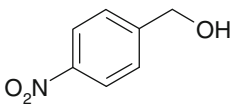
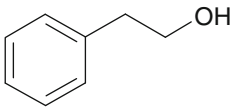
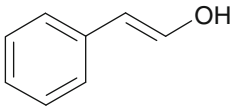
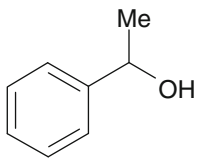
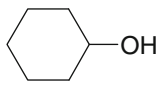
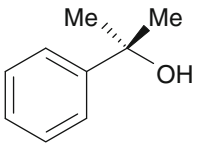
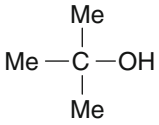
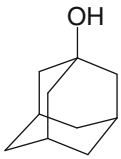
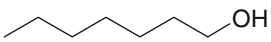
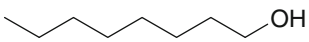
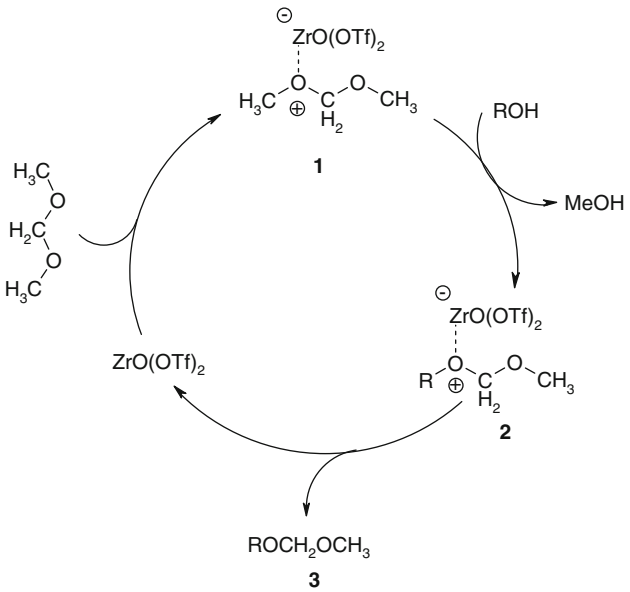
Entry	ROH	ROMOM	Time (min)	Yield (%)[a]	Ref.
1		**3a**	10	97	[35]
2		**3b**	5	96	–
3		**3c**	5	96	[14]
4		**3d**	15	97	–
5		**3e**	15	98	[14]
6		**3f**	10	95	[35]
7		**3g**	5	96	[35]
8		**3h**	5	95	[36]
9		**3i**	15	97	[14]
10		**3j**	5	94	[12]

Table 2 continued

Entry	ROH	ROMOM	Time (min)	Yield (%)[a]	Ref.
11		**3k**	15	97	[14]
12		**3l**	10	93	[36]
13		**3m**	20	95	[14]
14		**3n**	10	94	[12]
15		**3o**	10	93	[35]

[a] Isolated yields



Scheme 2

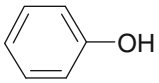
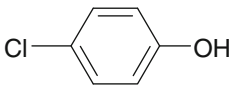
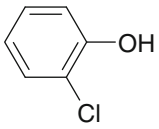
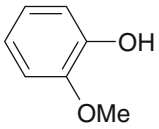
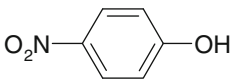
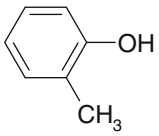
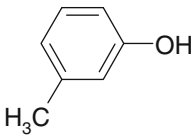
General procedure for the methoxymethylation of alcohols and phenols at room temperature

To a solution of alcohol or phenol (1 mmol) in FDMA (7 mmol), 0.01 g $ZrO(OTf)_2$ (2.5 mol%) was added and the mixture was stirred at room temperature for the appropriate time according to Table 2. The progress of the reaction was monitored by TLC (eluent cyclohexane/ethyl acetate, 4:1). After completion of the reaction, the excess FDMA was evaporated and 10 cm^3 Et_2O was added and the catalyst was filtered. The filtrate was evaporated and the crude product was purified by column chromatography on silica gel (eluent cyclohexane/ethyl acetate, 4:1) to afford the pure product.

Catalyst reusability

The reusability experiments were carried out as follows: 0.03 g $ZrO(OTf)_2$ (2.5 mol%) was added to a solution of benzyl alcohol (3 mmol) in FDMA (21 mmol) and the

Table 3 Protection of phenols with FDMA catalyzed by $ZrO(OTf)_2$ at room temperature

Entry	ArOH	ArOMOM	Time (min)	Yield (%)[a]	Ref.
1		**3p**	10	96	[36]
2		**3q**	10	97	[37]
3		**3r**	15	95	[37]
4		**3s**	15	94	[36]
5		**3t**	10	96	[36]
6		**3u**	15	96	[37]
7		**3v**	10	97	[37]

[a] Isolated yield

mixture was stirred at room temperature for 10 min. After the reaction was completed, the excess FDMA was evaporated and 30 cm^3 Et_2O was added. The catalyst was filtered, dried at 50 °C, and used in the subsequent run.

4-tert-Butyl-1-(methoxymethoxy)methylbenzene (**3b**, $C_{13}H_{20}O_2$)
Oil; IR (KBr): $\bar{\nu} = 2{,}900$, 1,365, 1,090, 1,030, 755, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.18$ (s, 3H, OCH_3), 1.34 (s, 9H, $C(CH_3)_3$), 4.60 (s, 2H, OCH_2O), 4.76 (s, 2H, $ArCH_2$), 7.31 (d, $J = 8.16$ Hz, 2H, Ar), 7.40 (d, $J = 8.20$ Hz, 2H, Ar) ppm.

4-Chloro-1-(methoxymethoxy)methylbenzene (**3d**, $C_9H_{11}O_2Cl$)
Mp 70–72 °C; IR (KBr): $\bar{\nu} = 2{,}900$, 1,315, 1,285, 1,100, 845, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.16$ (s, 3H, OCH_3), 4.54 (s, 2H, OCH_2O), 4.74 (s, 2H, $ArCH_2$),

Table 4 Selective methoxymethylation of alcohols and phenols catalyzed by $ZrO(OTf)_2$

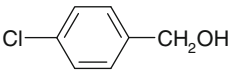
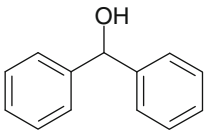
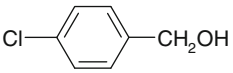
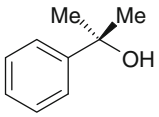
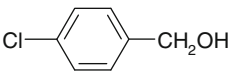
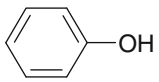
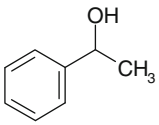
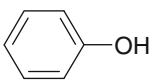
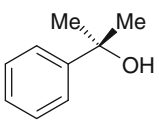
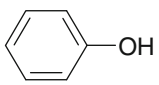
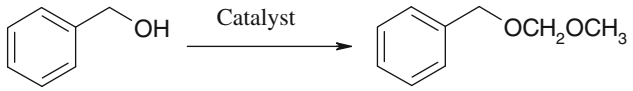
Row	ROH	Time (min)	Yield (%)
1		15	97
		15	0
2		15	97
		15	0
3		15	97
		15	0
4		15	97
		15	0
5		15	97
		15	0

Table 5 Comparison of the results obtained for the methoxymethylation of benzyl alcohol catalyzed by $ZrO(OTf)_2$ with those obtained by using other catalysts



Entry	Catalyst	Catalyst (mol%)	Temperature	Time (h)	Yield (%)	Ref.
1	$ZrO(OTf)_2$	2.5	RT	0.16	96	–
2	Expansive graphite	20 mg	Reflux	6	91	[12]
3	Sulfated metal oxides	50 mg	RT	3	91	[13]
4	Silica sulfuric acid	200 mg	Reflux	1.5	85	[14]
5	$Sc(OTf)_3$	5	Reflux	3	98	[15]
6	$Bi(OTf)_3$	5	Reflux	1	95	[16]
7	$ZrCl_4$	10	RT	1	97	[17]
8	$MoO_2(acac)_2$	2	Reflux	4	85	[18]
9	$H_3PMo_{12}O_{40}$	5	Reflux	3	90	[19]
10	Anhydrous $FeCl_3$ dispersed on 3 Å molecular sieves	90	RT	1	90	[20]
11	TiO_2/SO_4^{2-}	20	Reflux	6	92	[21]
12	$H_3PW_{12}O_{40}$	0.4	RT	3	91	[22]
13	$H_3PW_{12}O_{40}$ on silica	0.4	RT	1	94	[23]
14	$H_3PW_{12}O_{40}$ on zirconia	0.4	RT	2.5	84	[23]

RT room temperature

7.30 (d, $J = 7.44$ Hz, 2H, Ar), 7.35 (d, $J = 6.42$ Hz, 2H, Ar) ppm.

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