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Highly Efficient and Chemoselective Acetalization of Carbonyl Compounds Catalyzed by New and Reusable Zirconyl Triflate, $ZrO(OTf)_2$

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ABSTRACT: *Various types of aromatic aldehydes were efficiently converted to their corresponding 1,3-dioxanes and 1,3-dioxolane with 1,3-propanediol and ethylene glycol, respectively, in the presence of catalytic amount of $ZrO(OTf)_2$ in acetonitrile at room temperature. The catalyst can be reused several times without loss of its catalytic activity. Very short reaction times, selective acetalization of aromatic aldehydes in the presence of aliphatic aldehydes and ketones, very mild reaction conditions, reusability of the catalyst, and easy workup are noteworthy advantages of this method.* Heteroatom Chem 20:131–135, 2009; DOI 10.1002/hc.20523

INTRODUCTION

Acetalization is one of the most widely used methods for protection of aldehydes and ketones in synthetic organic chemistry. Generally, these reactions are carried out by treatment of carbonyl compounds with the alcohols, diols, or the corresponding orthoformates in the presence of protic or Lewis acid catalysts. Several methods have been reported for this transformation [1–19]. However, many of the acid catalysts, which have been explored for this transformation, suffer from disadvantages such as toxicity, corrosiveness, and high cost of the catalyst, poor chemical selectivity, long reaction times, high temperature, and tedious workup procedure.

Zirconium(IV) salts have recently attracted much attention due to their low cost, high catalytic activity, easy availability, and low toxicity [20]. A variety of Zr(IV) salts have been used for several organic transformation such as the Friedel–Crafts reaction [21], Diels–Alder reaction [22], Michael reaction [23], acetalization of carbonyl compounds [24,25], conversion of nitriles to oxazolines and imidazolines [26,27], and some other reactions [28,29].

In this paper, we report a highly efficient and chemoselective acetalization of carbonyl compounds with 1,3-propanediol or ethylene glycol in the presence of catalytic amounts of $ZrO(OTf)_2$ in acetonitrile at room temperature (Scheme 1).

EXPERIMENTAL

Chemicals were purchased from Fluka and Merck. ^{1}H NMR spectra were recorded in $CDCl_3$ solvent on a Bruker AM 80 MHz or a Bruker AC 500 MHz

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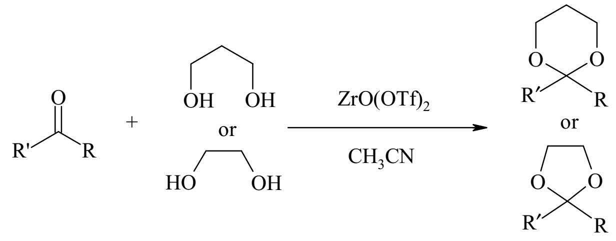

SCHEME 1

spectrometer using TMS as an internal standard. Infrared spectra (IR) were run on a Philips PU9716 or Shimadzu IR-435 spectrophotometer. All analyses were performed on a Shimadzu GC-16A instrument with a flame ionization detector using silicon DC-200 or Carbowax 20M columns. $ZrO(OTf)_2$ was prepared according to the reported procedure [30].

General Procedure for the Acetalization of Aldehydes or Ketones

To a solution of aldehyde or ketone (1 mmol) in CH_3CN (2 mL), 1,3-propanediol or ethylene glycol (3 mmol) and $ZrO(OTf)_2$ (4 mg, 0.01 mmol) were added and the mixture was stirred at room temperature. The reaction progress was monitored by GC. After completion of the reaction, cold aqueous solution of NaOH (5%, 15 mL, for neutralization of media to prevent the deprotection of product) was added and the mixture was extracted with Et_2O (3 × 10 mL). The organic solution was dried ($MgSO_4$). The filtrates were concentrated and chromatographed on a silica gel column to give the pure product.

RESULTS AND DISCUSSION

Acetalization of Carbonyl Compounds in the Presence of ZrO(OTf)₂

First, we investigated the ability of different zirconium salts such as $ZrCl_4$, $ZrOCl_2 \cdot 8H_2O$, and $ZrO(OTf)_2$ in the acetalization of 4-bromoenzaldehyde with 1,3-propanediol in CH_3CN as solvent at room temperature. As shown in Table 1, $ZrO(OTf)_2$ is superior in terms of reaction time and product yield. In comparison with acetonitrile, the reaction times were longer and the yields were lower when dichloromethane (75%, 30 min), chloroform (55%, 30 min), and *n*-hexane (15%, 30 min) were employed as solvents. Under the optimized conditions, various types of aromatic aldehydes were subjected to acetalization with 1,3-propanediol or ethylene glycol (3 mmol) in the presence of catalytic amount of $ZrO(OTf)_2$ (1 mol%) in dry CH_3CN at room temperature and the corresponding acetals were obtained in good to excellent yields (entries 1–13 in Table 2). Aliphatic aldehydes bearing aromatic ring in the α- or β-position are also protected with high yields (entries 14 and 15 in Table 2).

TABLE 1 Acetalization of 4-Bromobenzaldehyde with 1,3-Propanediol and in the Presence of Zirconium Salts at Room Temperature[a]

	Yield (%)[b]			
Entry	*ZrCl₄*	*ZrOCl₂*	*ZrO(OTf)₂*	*Time (min)*
1	0	0	89	1
2	0	0	93	2
3	0	10	94	3
4	0	26	100	4

[a] Reaction conditions: aldehyde (1 mmol), diol (3 mmol), catalyst (1 ml%), and CH_3CN (2 mL).
[b] GC yield.

However, aliphatic aldehydes without aromatic rings, cinammaldehyde, and ketones were less reactive under these conditions and the corresponding acetals were obtained in very low yields (entries 16–20 in Table 2). On the basis of the obtained results, it seems that this protocol can be used for the selective acetalization of aromatic aldehydes in the presence of aliphatic aldehydes (without aromatic ring) and ketones. In this respect, we found that in the reaction of an equimolar mixture of 4-bromobenzaldehyde with 1,3-propanediol in the presence of acetophenone or heptanal, 4-bromobenzaldehyde was converted to 2-(4-bromophenyl)-1,3-dioxane with high degree of chemoselectivity and acetophenone and heptanal remained intact in the reaction mixture (Scheme 2). As there are only a few reports on the selective acetalization of aromatic aldehydes in the presence of aliphatic aldehydes or ketones, therefore, the present acetalization method catalyzed by $ZrO(OTf)_2$ can be considered as a useful practical achievement in protection reactions. Blank experiments showed that under similar reaction conditions and in the absence of $ZrO(OTf)_2$, no acetal was observed in the reaction mixture.

Catalyst Reusability

The recovery and reusability of the catalyst was investigated in the acetalization of 4-bromobenzaldehyde with 1,3-propanediol. After each reaction, the solvent was evaporated, Et_2O (10 mL) was added and filtered. The recovered catalyst was washed with Et_2O (10 mL) and used in another acetalization reaction. The results showed the catalyst can be used for five consecutive times without any decrease in its catalytic activity.

TABLE 2 Acetalization of Carbonyl Compounds with 1,3-Propanediol and Ethylene Glycol Catalyzed by $ZrO(OTf)_2^a$

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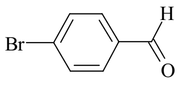
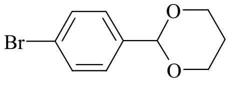
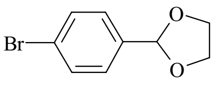
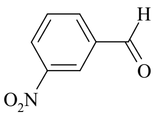
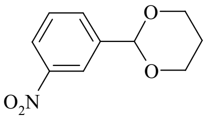
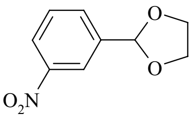
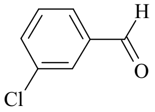
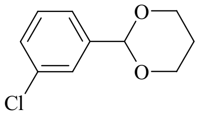
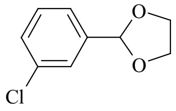
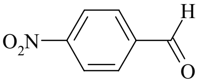
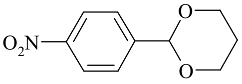
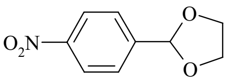
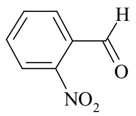
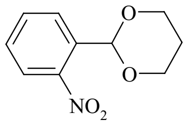
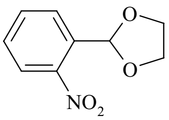
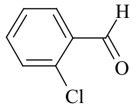
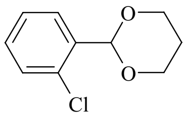
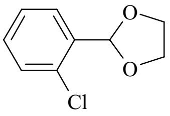
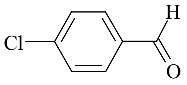
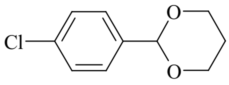
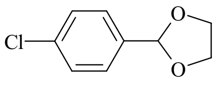
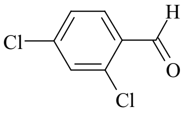
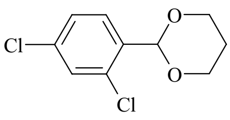
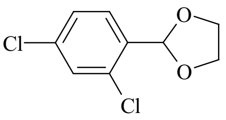
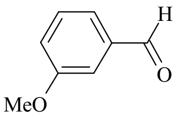
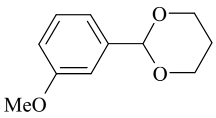
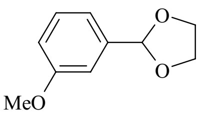
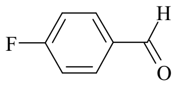
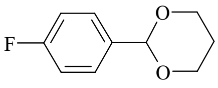
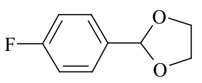
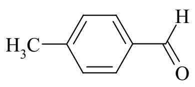
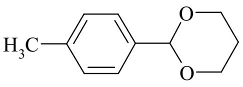
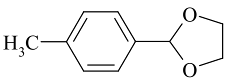
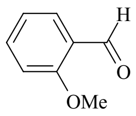
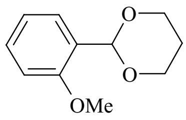
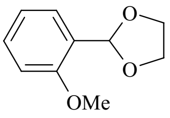
1			4	100		6	100
2			2	96		4	100
3			2	95		2	81
4			3	94		3	100
5			2	90		5	89
6			3	89		3	92
7			1	86		2	80
8			2	85		2	81
9			1	80		3	60
10			1	75		5	81
11			1	69		2	58
12			3	63		1	73

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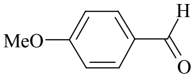
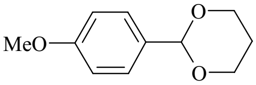
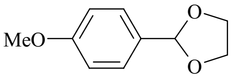
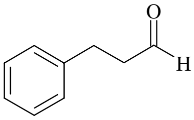
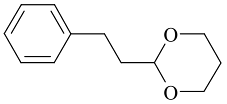
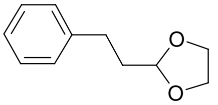
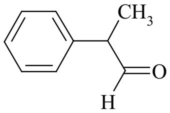
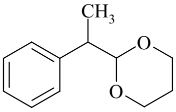
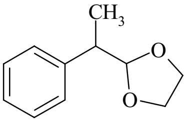
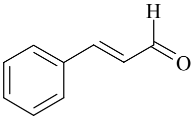
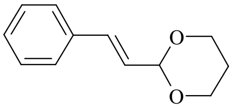
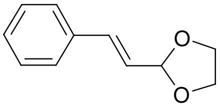
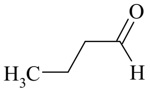
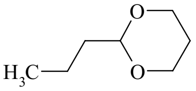
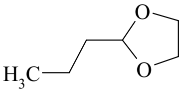
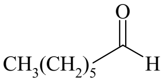
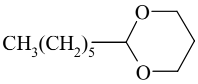
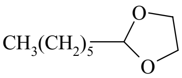
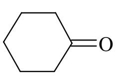
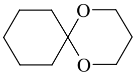
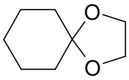
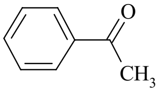
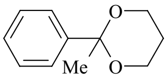
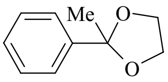
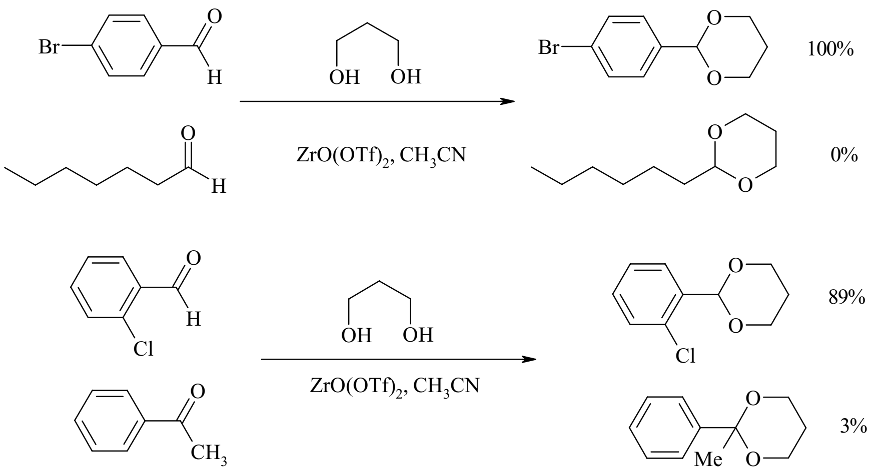
13			2	63		2	65
14			4	100		2	97
15			4	88		4	91
16			2	8		1	57
17			3	16		2	20
18			3	10		4	12
19			2	27		4	31
20			4	10		1	12

[a] Reaction conditions: carbonyl compound (1 mmol), diol (3 mmol), $ZrO(OTf)_2$ (1 ml%), and CH_3CN (2 mL).
[b] GC yields.



SCHEME 2

CONCLUSION

In conclusion, an efficient method has been developed for the selective acetalization of aromatic aldehydes in the presence of aliphatic aldehydes and ketones in the presence of catalytic amounts of $ZrO(OTf)_2$. Very short reaction times, easy workup, very mild reaction conditions, and high to excellent yields make this method a useful addition to the existing methodologies for the acetalization of carbonyl compounds.

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