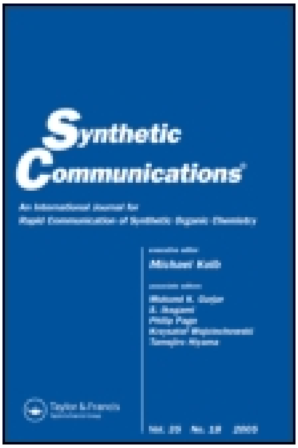

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Zinc Chloride as an Efficient Catalyst for Chemoselective Dimethyl Acetalization

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Abstract: Commercially available anhydrous zinc chloride has been found to be a highly efficient catalyst for dimethyl acetalization in high yields by treatment of aldehydes and ketones with trimethyl orthoformate in methanol-cyclohexane at reflux temperature.

Keywords: Carbonyl compound, chemoselectivity, dimethyl acetalization, trimethyl orthoformate, zinc chloride

INTRODUCTION

Selective protection of carbonyl groups as acetals is essential step in modern organic chemistry as it is often necessary to carry out a reaction on a multifunctional substrate without affecting carbonyl groups.[1] Acetals are one of the most useful carbonyl protecting groups because of their stability under both neutral and basic media. In addition, acetals can be converted to a variety of other functional groups.[2] A variety of reagents have been developed for the dimethyl acetalization of carbonyl compounds, which include mainly protic acids and Lewis acids.[3] However, many of these methods are associated with expensive and toxic reagents, strongly acidic conditions, stoichiometric amounts of catalysts, and incompatibility with other functional groups. Moreover, many of the

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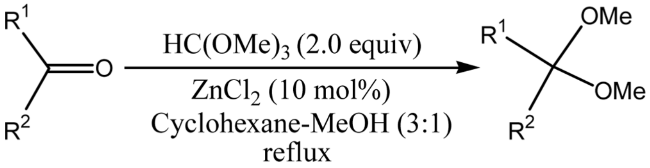


Scheme 1. R^1 = alkyl/aryl; R^2 = H/alkyl.

procedures are practical for aldehydes only. Efficient methods for the dimethyl acetalization are very limited. Hence, a practical and more efficient alternative for dimethyl acetalization using an inexpensive and environment friendly reagent is still of interest.

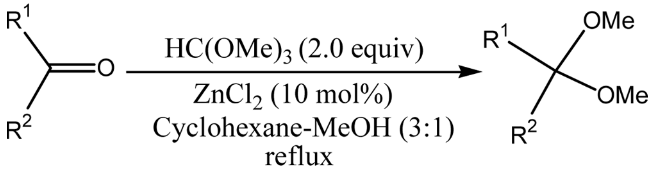
Zinc chloride, a very inexpensive and easily available Lewis acid catalyst, has been widely used in organic synthesis,[4] but it has not been studied as a catalyst for the synthesis of dimethyl acetals from the parent aldehydes and ketones. As a part of our ongoing studies to test the effectiveness of various inexpensive Lewis acid catalysts in organic synthesis,[5] we decided to investigate the zinc chloride–catalyzed dimethyl acetalization of carbonyl compounds (Scheme 1).

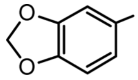
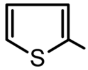
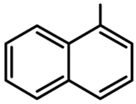
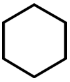
RESULTS AND DISCUSSION

Initially to optimize the reaction conditions, we tried to convert benzaldehyde to its dimethyl acetal in various reaction conditions. The best result was obtained when the reaction was carried out by stirring the carbonyl compounds and trimethyl orthoformate (2.0 equiv) in a mixture of anhydrous methanol and cyclohexane (1:3, 0.5 mL per mmol of substrate) in the presence of a catalytic amount of a anhydrous $ZnCl_2$ (10 mol%) at reflux temperature. When the reaction was attempted using the catalyst in cyclohexane only (no methanol), significant acetal formation was not observed. We examined the dimethyl acetalization of a wide range of simple aldehydes and ketones. The results are summarized in Table 1.

Aromatic aldehydes with variety of substitutions such as Cl (entry 3), NO_2 (entry 5), OMe (entries 4, 6, and 7), and methylenedioxy (entry 8) underwent smooth transformation to corresponding acetals in excellent yields. The acid-sensitive heterocyclic substrate such as 2-thiophenecarboxaldehyde was efficiently protected as dimethyl acetal without accompanying self-condensation or ring cleavage (entry 9). Cinnamaldehyde was also acetalized without concomitant double-bond isomerization (entry 11). Acetalization of hydroxybenzaldehyde under Lewis acid–catalyzed conditions is a very difficult process and is usually accompanied with low yields of the products. Nevertheless, this methodology worked

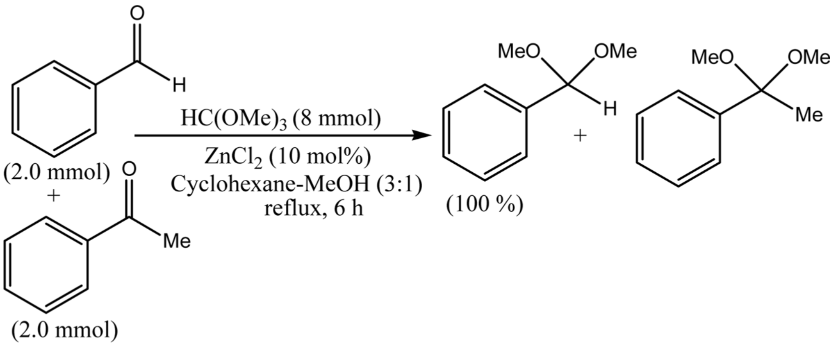
Table 1. Dimethyl acetalization of carbonyl compounds



Entry	R^1	R^2	Time (h)	Yield (%)[a]
1	Ph	H	6	88
2	*p*-MeC_6H_4	H	7	92
3	*p*-ClC_6H_4	H	5	90
4	*p*-(MeO)-C_6H_4	H	10	84
5	*p*-$NO_2C_6H_4$	H	5	94
6	4-(OH)-3-(OMe)-C_6H_3	H	14	72
7	4-(OMe)-3-(OMe)-C_6H_3	H	12	78
8		H	11	81
9		H	8	78
10		H	10	84
11	PhCH=CH (t)	H	9	88
12	CH_3-$(CH_2)_6$-	H	8	89
13	CH_3-$(CH_2)_8$-	H	9	85
14	$(CH_3)_2CH$–CH_2	Me	8	86
15			5	79
16			6	88
17	Ph	Me	24	20

[a] Yields refer to isolated pure products fully characterized by spectral and analytical data.

very well on hydroxybenzaldehyde and gave desired protected product in high yields (entry 6). Aliphatic aldehydes worked equally well (entries 12 and 13). Saturated aliphatic and cyclic ketones afforded excellent results



Scheme 2. Chemoselective acetalization of aldehydes.

(entries 14–16). However, the reaction of aromatic ketone such as acetophenone produced only low yields (~20%) of the corresponding acetal under similar reaction conditions after 24 h.

To evaluate the chemoselectivity of this method, we also investigated competitive reactions for acetalization of benzaldehyde in the presence of acetophenone under the reaction conditions. Employing this catalytic system, the highly selective conversion of benzaldehyde in the presence of acetophenone was observed (Scheme 2). This observation indicates that aldehydes are more reactive than aromatic ketones. This may be due to higher electrophilicity of aldehydes in comparison to aromatic ketones. Thus, this methodology will be useful for chemoselective acetalization of aldehydes in the presence of aromatic ketones.

CONCLUSION

In conclusion, the work presented here demonstrates a straightforward and mild procedure for the efficient and chemoselective method for the dimethyl acetalization of aldehydes and ketones catalyzed by zinc chloride. The reaction possesses the following synthetic features: (a) mild conditions, (b) simple operation, (c) good yields, (d) nontoxic and cheap metal catalyst, and (e) excellent chemoselectivity. The easy formation of dimethyl acetals using inexpensive catalyst under mild reaction conditions makes the present methodology a practical alternative.

EXPERIMENTAL

In a typical experimental procedure, a mixture of 4-methylbenzaldehyde (240 mg, 2 mmol, 236 μL) and trimethyl orthoformate (425 mg, 4 mmol, 438 μL) was stirred in the presence of a catalytic amount of $ZnCl_2$ (27 mg, 10 mol%) at reflux temperature in anhydrous methanol–cyclohexane mixture (1:3, 1 mL) for 7 h as required for completion (monitored by thin-layer chromatography, TLC). After completion of the reaction, the solvent was evaporated, and the reaction mixture was filtered through a plug of silica gel eluted by Et_2O (20 mL) and evaporated. Analytically pure 4-(dimethoxy)methylbenzene was obtained by a rapid silica-gel chromatography using *n*-hexane–EtOAc (20:1) as a colorless oil (92%, 306 mg) whose identity was established by comparison of its spectroscopic data (IR, ^1H NMR) with those reported.[3k]

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