## Zirconium Tetrachloride (ZrCl<sub>4</sub>) Catalyzed Highly Chemoselective and Efficient Acetalization of Carbonyl Compounds

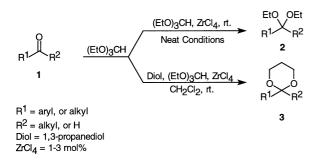
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**Abstract:** Zirconium tetrachloride (ZrCl<sub>4</sub>) is a highly efficient and chemoselective catalyst for the acetalization, and *in-situ* transacetalization of carbonyl compounds under mild reaction conditions.

**Key words:** acetals, zirconium tetrachloride, carbonyl compounds, 1,3-dioxanes, protection

Acetals are one of the most widely used and versatile protecting groups in organic synthesis. They find applications for instance in the protection of carbonyl, hydroxyl, and diol functions.<sup>1</sup> This versatility of acetals demands the development of new improved and mild acetalization procedures, specially based on Lewis acid catalysts.<sup>2</sup> In general, the formation of dialkyl acetals has been achieved with trialkyl orthoformate in the presence of Lewis or protic acid catalysts.<sup>1, 3</sup> A literature survey shows that a few methods are available for the preparation of diethyl acetals.<sup>1,4</sup> Thus it seems that convenient and general methods for this purpose are still being pursued. Now we wish to report that ZrCl<sub>4</sub> (1-3 mol%) efficiently and chemoselectively catalyzed acetalization and in-situ transacetalization of carbonyl compounds in the presence of (EtO)<sub>3</sub>CH at room temperature under solvent-free conditions or in solution (Scheme).



## Scheme

Various types of aromatic, aliphatic aldehydes and cinnamaldehyde were efficiently converted to the corresponding diethyl acetals in the presence of  $(EtO)_3CH$  (1.8-2 eq) and  $ZrCl_4$  (1mol%) under solvent-free conditions (Table 1, **2a-2f**). Under similar reaction conditions, aliphatic and aromatic ketones were converted to their corresponding diethyl acetals in low yields even after prolonged reaction times (Table 1, **2g-2h**). However, by this method, 4-phenylcyclohexanone as an example of cyclic aliphatic

 Table 1. Acetalization and *in-situ* Transacetalization of Carbonyl Compounds with (EtO)<sub>3</sub>CH and ZrCl<sub>4</sub> under Neat Conditions and in Solution

	duct R <sup>1</sup>	$R^2$	diol	Subst,/diol/	Time	Yield <sup>a)</sup>
				(EtO) <sub>3</sub> CH/ZrO	2 <b>1</b> 4 (n	nin)
	(%)					
2a	Ph	н	none	1:0:1.8:0.01	7	97 <sup>b)</sup>
2b	$4-(CH_3)C_6H_4$	Н	none	1:0:1.8:0.01	12	98 <sup>b)</sup>
2c	$4-(Cl)C_6H_4$	Н	none	1:0:1.8:0.01	25	93 <sup>b)</sup>
2d	$4-(NO_2)C_6H_4$	Н	none	1:0:2:0.01	120	78 <sup>b)</sup>
2e	PhCH=CH	Н	none	1:0:2:0.01	35	96 <sup>b)</sup>
2f		λH	none	1:0:2:0.01	2h	80 <sup>b,c)</sup>
2g	PhCH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub>	none	1:0:2.5:0.01	10h	52 <sup>b,c)</sup>
2h	Ph	CH <sub>3</sub>	none	1:0:2.5:0.02	7h	10 <sup>b,c)</sup>
		_				
2i	Ph-	www	none	1:0:2:0.01	45	52
	$\sim$					$(48)^{b-d)}$
3a	Ph	Н но	$\sim$	ОН 1:1.5:1:0.02	25	98
3a	Ph	Н	"	1:1.5:0:0.02	20h	0
3b	$4-(CH_3)C_6H_4$	Н	**	1:1.5:1:0.02	30	97
3c	$4-(Cl)C_6H_4$	Н	**	1:1.5:1:0.02	15	98
3d	$4-(NO_2)C_6H_4$	Н	"	1:2:1:0.03	60	98
3e	PhCH=CH	Н	**	1:1.5:1:0.01	10	95
3f	PhCH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub>	"	1:2:1:0.02	30	92
3g	Ph	$CH_3$	"	1:2:1:0.02	45	93
3h	Ph-		'n	1:1.5:1:0.01	20	90 <sup>e)</sup>
3i	[	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	"	1:2:1:0.01	50	80
3j	$\langle$		"	1:1.5:1:0.02	10	90

a) Isolated yields. b) Under neat conditions. c)Yields determined by GC and NMR. d) Yields in parenthesis refer to the corresponding ethyl vinyl ether. e)  $\sim 10\%$  of the corresponding ethyl vinyl ether was detected by GC and NMR spectroscopy.

ketones, was converted to the corresponding acetal with much higher reaction rate (Table 1, **2i**).

Very recently, it has been reported that  $Sc(OTf)_3$  and  $Sc(NTf)_3$  are effective catalysts for the acetalization and *in-situ* transacetalization of carbonyl compounds.<sup>3e</sup> We have also observed that  $ZrCl_4$  (1-3 mol%) in the presence of (EtO)<sub>3</sub>CH (1 eq) and 1,3-propanediol (1-2 eq) efficiently catalyzed *in-situ* acetal exchange reactions of various types of carbonyl compounds to give their corresponding 1,3-dioxanes in good to excellent yields in dry CH<sub>2</sub>Cl<sub>2</sub> at room temperature (Scheme). 1,3-Dioxanation of a variety of substituted benzaldehydes and cinnamaldehyde was

time yield<sup>a)</sup> entry substrate subst1/subst2/thiol or diol product /ZrCL (min) (%) сно 95 1:1:1.5:0.02<sup>b)</sup> 1 15 5 92 1:1:1.5:0.02<sup>b)</sup> 2 15 Pł 8 100 1:1:0:0.01<sup>c)</sup> 3 7 0 OE 60 1:1:1.5:0.02<sup>b)</sup> 4 10 40 97 1:1:1.5:0.02<sup>b)</sup> 5 10 0 100 1:1:1.5:0.02<sup>b)</sup> 10 6 0

 Table 2. Selective Acetalization and in-situ Transacetalization with

 ZrCl<sub>4</sub>

a) Yields based on GC and NMR. b) 1 equiv. of  $(EtO)_3CH$  was used and the reactions were performed in dry  $CH_2Cl_2$ . c) 1.8 equiv. of  $(EtO)_3CH$  was used and the reaction was performed under solvent-free conditions.

carried out efficiently in the presence of  $(EtO)_3CH$  (1 eq), 1,3-propanediol (1.5-2 eq) and  $ZrCl_4$  (2-3 mol%) in excellent yields (Table 1, **3a-3e**). Aromatic and aliphatic open chain ketones as well as cyclic ketones were also converted to the corresponding 1,3-dioxanes under similar reaction conditions in good to excellent yields (Table 1, **3f-3j**). In order to show the ability of the presented methods for chemoselective acetalization of carbonyl compounds, we have performed several competitive acetalization reactions, whose results are demonstrated in Table 2. Benzaldehyde undergoes acetalization and transacetalization in the presence of acetophenone, benzyl acetone and cyclohexanone respectively (Table 2, entries 1-4). On the other hand, cyclohexanone as a model for cyclic ketones is converted to the corresponding 1,3-dioxane with absolute chemoselectivity in the presence of benzylacetone and acetophenone, respectively (Table 2, entries 5-6).

In conclusion, mild reaction conditions, versatile and good chemoselectivity, easy workup, and high yields of the desired products are worthy to be mentioned as the characteristics of the described methods.

General Procedure for the preparation of diethyl acetals. To a mixture of carbonyl compound **1** (5 mmol) and  $(EtO)_3CH$  (10-12.5 mmol),  $ZrCl_4$  (0.05-0.1 mmol) was added, and the resulting solution was stirred at room temperature. After completion of the reaction (TLC or GC), a cold aqueous solution of NaOH (10%, 25 mL) was added and the mixture was extracted with  $CH_2Cl_2$  (3 × 40 mL). The organic extracts were washed with water (2 ×15 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent under reduced pressure gave almost pure product(s). Further purification was proceeded by vacuum distillation to afford pure diethyl acetals **2** in good to excellent yields (Table 1).

General procedure for the preparation of 1,3-dioxanes via in-situ transacetalization; To a solution of carbonyl compound 1 (5 mmol), 1,3-propanediol (7.5-10 mmol), and (EtO)<sub>3</sub>CH (5 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL), ZrCl<sub>4</sub> (0.05-0.15 mmol) was added and the resulting solution was stirred at room temperature. After completion of the reaction (TLC or GC), the reaction was quenched with a cold aqueous solution of NaOH (10%, 25 mL) and the organic layer was separated and the residue was extracted with  $CH_2Cl_2$  (3 × 40 mL). The organic extracts were combined together and washed with water  $(3 \times 35 \text{ mL})$ , and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent under reduced pressure gave almost pure 1,3-dioxane 3. Further purification was achieved by vacuum distillation or recrystallization from the appropriate solvent to give pure product(s) in good to excellent yields (Table 1).

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