Zirconium Tetrachloride ($ZrCl_4$) Catalyzed Highly Chemoselective and Efficient Transthioacetalization of Acetals

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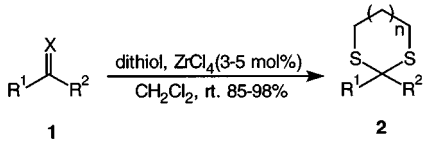
Abstract: Zirconium tetrachloride ($ZrCl_4$) is an efficient catalyst for the highly chemoselective transthioacetalization of acetals under mild reaction conditions.

Key words: acetals, thioacetals, zirconium tetrachloride, transthioacetalization, protection

The protection of carbonyl groups as acetals or dithioacetals is often an unavoidable process during multistep organic syntheses.[1] In addition, the widespread applications of 1,3-dithianes as nucleophilic acyl anion precursors,[2] and as masked methylene functions[3] demand an intense search for new improved and chemoselective synthetic methods for their preparation. Although thioacetals, generally, have been prepared by protic and solid acids,[1, 4] supported reagent systems,[5] and Lewis acid[6] catalyzed condensation of carbonyl compounds with thiols,[1] transthioacetalization of acetals also has gained attention as the method of choice for this purpose.[7] To the best of our knowledge there is no report on the selective transdithioacetalization of open chain acetals in the presence of cyclic acetals. Here, we wish to report that in the presence of $ZrCl_4$ (3-5 mol%) and a dithiol (1.1-1.5 eq) in CH_2Cl_2 several types of dialkyl acetals could be efficiently and rapidly converted to the corresponding dithioacetals at room temperature (Scheme, Table 1).



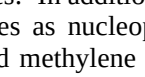
1 2

R^1, R^2 = aryl, alkyl, or H
X = $(OMe)_2$, $(OEt)_2$, $-OCH_2CH_2O-$, $-O(CH_2)_3O-$
n = 0, 1

Scheme

As shown in Table 1, dialkyl acetals derived from various types of substituted aromatic aldehydes and cinnamaldehyde were cleanly and rapidly converted to the corresponding 1,3-dithianes and 1,3-dithiolanes at room temperature in excellent yields (entries 1-5). Dialkyl acetals of cyclic and open chain aliphatic ketones as well as aromatic ketones were efficiently thioacetalized at room temperature, giving the corresponding dithioacetals in the presence of $ZrCl_4$ (5 mol%) (Table 1, entries 6-9). However, under similar reaction conditions, cyclic acetals (1,3-dioxolanes and 1,3-dioxanes) were relatively less reactive than the corresponding dialkyl acetals and gave the corresponding dithioacetals only after prolonged reaction times (Table 1, entries 10-12). In order to establish the applicability of the method for the selective transthioacetalization of dialkyl vs. cyclic acetals, several competitive reactions were designed (Table 2). we have observed that acyclic acetals derived from benzaldehyde, acetophenone, and 4-phenylcyclohexanone in the presence of various types of cyclic acetals were converted to their corresponding dithioacetals and ketals with high chemoselectivity (Table 3, entries 1-5). To the best of our knowledge this is the first example of efficient chemoselective transthioacetalization of dialkyl ketals in the presence of cyclic acetals (Table 2, entries 2,3).

Table 1. Transthioacetalization of Acetals with $ZrCl_4$

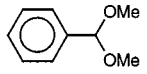
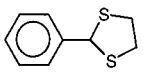
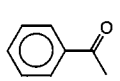
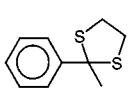
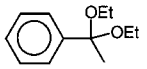
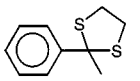
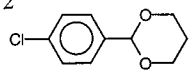
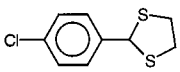
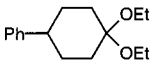
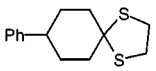
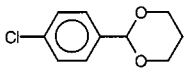
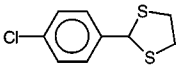
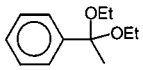
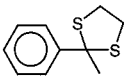
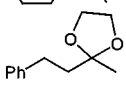
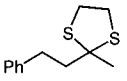
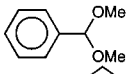
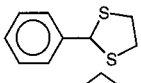
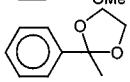
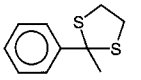
Entry	R^1	R^2	X	n	subst./thiol/ $ZrCl_4$	Time (min)	Yield[a] (%)
1	Ph	H	$(OMe)_2$	3	1:1.1:0.03	2	98
2	Ph	H	$(OMe)_2$	2	1:1.1:0.03	2	95
3	*p*-MeC_6H_4	H	$(OEt)_2$	3	1:1.1:0.03	2	93
4	*p*-ClC_6H_4	H	$(OEt)_2$	3	1:1.1:0.03	2	98
5	PhCH=CH	H	$(OEt)_2$	2	1:1.1:0.04	3	94
6	Ph	Me	$(OEt)_2$	3	1:1.5:0.05	10	96
7	*p*-ClC_6H_4	Me	$(OEt)_2$	3	1:1.5:0.05	15	92
8			$(OEt)_2$	2	1:1.5:0.05	5	98
9	$PhCH_2CH_2$	Me	$(OEt)_2$	3	1:1.5:0.05	5	91
10	*p*-ClC_6H_4	H	$O(CH_2)_3O$	3	1:1.1:0.03	24h	90
11	Ph	Me	$O(CH_2)_2O$	3	1:2:0.1	20h	89
12	*p*-MeC_6H_4	H	$O(CH_2)_2O$	3	1:1.1:0.03	24h	85

a) Isolated yields.

In conclusion, high rates of the reactions, mild reaction conditions, high chemoselectivity, easy work-up, and high yields of the desired products are worthy to be mentioned for the presented method.

General procedure for transthioacetalization of acetals. To a solution of O,O-acetal **1** (5 mmol) and dithiol (5.5-7.5 mmol) in dry CH_2Cl_2 (25 mL), $ZrCl_4$ (0.15-0.25 mmol) was added and the mixture was stirred at room temperature. After the reaction was completed (TLC or GC), the reaction was quenched with an aqueous solution

Table 2. Selective Transthioacetalizations with $ZrCl_4$

entry	substrate	subst. 1/subst. 2/thiol /$ZrCl_4$	product	time (min)	yield[a] (%)
					100
1		1:1:1.1:0.03		5	0
2		1:1:1.5:0.05		10	85
					15
3		1:1:1.5:0.05		5	88
					12
4		1:1:1.5:0.05		10	92
					8
5		1:1:1.1:0.05		5	85
					10[b]

a) Yields based on GC and NMR. b) Small amount (≈ 5-7%) of acetophenone was formed based on GC and NMR.

of NaOH (10%, 25 mL), and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was separated and washed with water (2 × 15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave almost pure dithioacetal **2**. Further purification was achieved by column chromatography on silica gel using petroleum ether as eluent to give the desired product(s) in good to excellent yields (Table 1).

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