An Efficient and Chemoselective Method for Synthesis of 1,3-Oxathiolanes from Aldehydes and their Deprotection Catalyzed by $V(HSO_4)_3$

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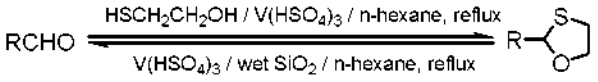
The carbonyl group plays a predominant role in organic synthesis due to its electrophilic nature. One of the major common problems during many multi-step syntheses in organic, medicinal, carbohydrate and drug design chemistry is how to protect the carbonyl group from nucleophilic attack until its electrophilic properties could be utilized. Therefore, the protection and deprotcetion of carbonyl groups remain an area of interest in synthetic organic chemistry. Among the carbonyl protecting groups, 1,3-oxathiolanes are important class of compounds that are more stable than corresponding O,O-acetals under acidic conditions and compared with S,S-acetals are more easily deprotected.[1] In addition, 1,3-oxathiolanes can be utilized as acylation equivalents in C-C bond formation.[2] Moreover, the chiral 1,3-oxathiolanes are valuable synthons for enantioselective synthesis of α-hydroxyaldehydees.[3] Different types of reagents have been used for the promotion of oxathioacetalization of carbonyl compounds with 2-maercaptoethanol which of them HCl,[4] $HClO_4$,[5] *p*-TsOH,[6] TMSOTf,[7] BF_3·OEt_2,[8] I_2,[9] $TaCl_5/SiO_2$,[10] $ZrCl_4$,[11] PPA/SiO_2,[12] NBS,[13] $LiBF_4$,[14] $MoO_2(acac)_2$,[15] $Y(OTf)_3$,[16] Amberlyst®-15,[17] $Fe(CF_3CO_2)_3$ and $Fe(CF_3SO_2)_3$,[18] novel catalyst {H-$(C_{10}H_5SO_3H)$-$CH_2]_n$-$C_{10}H_6SO_3H$},[19] $H_3PW_{12}O_{40}/SiO_2$,[20] $Sn(HPO_4)_2$·H_2O,[21] $Pr(OTf)_3$,[22] Me_2S/Br_2[23] and [bmim]BF_4[24] are examples. Although some of these methods afford good to high yields of the corresponding 1,3-oxathiolanes, the majority suffer from one or more of the following disadvantages: low yields, long reaction times, harsh reaction conditions, use of expensive, not readily available or moisture sensitive reagents, tedious work-up, poor chemoselectivity and the use of stoichiometric amounts of the catalyst. Therefore, introduction of new methods and catalysts for the preparation of 1,3-oxathiolnes is still in demand.

Recently we have reported the preparation of vanadium hydrogen sulfate, and its application in the chemoselective trimethylsilylation and acetylation of alcohols.[25,26] In continuation of these studies, herein, we report the applicability of this reagent in the promotion of the oxathioacetalyzation of aldehydes with 2-mercaptoethanol. All reactions were performed in *n*-hexane at reflux temperature under completely heterogeneous reaction conditions in relatively short reaction times in excellent yields (Table 1, Scheme 1).



Scheme 1

As shown in Table 1, different types of aromatic aldehydes, including different substituents such as Cl, Br, Me and NO_2 are converted to their corresponding 1,3-oxathiolanes in good to high yields (Table 1, entries 1-9). This method is also very useful for the oxathioacetalyzation of aliphatic aldehydes (Table 1, entries 10-12). Acid and heat sensitive furfural afforded the desired product under the same reaction conditions (Table 1, entry 13). Ketones are so stable under the same reaction conditions, that the starting material was recovered unchanged after 30 min (Table 1, entries 14, 15). This indicates that the present method is applicable for the chemoselective protection of aldehydes in the presence of ketones. This is examplified by the competitive of 4-chlorobenzaldehyde in the presence of phenylacetone (Table 1, entry 16).

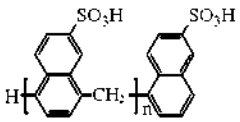
In order to show the efficiency of this method, Table 2 compares the results obtained from the oxathioacetalization of

Table 1. Oxathioacetalyzation of aldehydes and deprotection of 1,3-oxathiolanes.[a,b]

Entry	Substrate	Protection		Deprotection	
		Tmie (min)	Yield (%)	Time (min)	Yield (%)
1	PhCHO	15	95	60	90
2	2-MeC_6H_4CHO	15	87	90	85
3	4-MeC_6H_4CHO	15	90	75	87
4	2-ClC_6H_4CHO	10	92	30	90
5	3-ClC_6H_4CHO	10	90	30	92
6	4-ClC_6H_4CHO	7	95	25	95
7	2-BrC_6H_4CHO	15	92	15	92
8	2-$NO_2C_6H_4CHO$	7	90	70	50
9	3-$NO_2C_6H_4CHO$	15	95	60	90
10	$PhCH_2CH_2CHO$	10	92	90	92
11	PhCH(Me)CHO	12	95	65	90
12	$MeCH_2CH_2CH_2CHO$	10	92	45	85
13		20	90	40	90
14	$PhCH_2COCH_3$	30	0	-	-
15	$PhCOCH_3$	60	0	-	-
16	$PHCH_2COCH_3$ + 4-ClC_6H_4CHO	15	0[c] + 100[c]	-	-

[a]Products were characterized by comparison with authentic samples and IR and NMR spectroscopy. [b]Isolated yields. [c]Conversion.

Table 2. Comparison of the efficiency of $V(HSO_4)_3$ with other reported catalysts in the oxathioacetalyzation of benzaldehyde.

Entry	Reagent	Catalyst load	Time (min)	Yield (%)	Ref.
1	PPA/SiO_2	0.5 g	30	99	12
2	$MoO_2(acac)_2$	22 mg	240	86	15
3	Amberlyst®-15	220 mg	60	84	17
4	 (Novel catalyst)	60 mg	25	96	19
5	$Sn(HPO_4)_2{\cdot}H_2O$	5 mol%	30	96	21
6	$[bmim]BF_4$	2 mL	150	92	24
7	$V(HSO_4)_3$	3 mol%	15	95	Present method

benzaldehyde by our method with some of those reported in the literature.

Our investigations clarified that the deprotection of 1,3-oxathiolanes can also be easily catalyzed in the presence of a mixture of $V(HSO_4)_3$ and wet SiO_2 (Table 1, Scheme 1). The reaction is efficient and the corresponding aldehydes are separated in high yields.

In conclusion, in this study, we have developed a mild, efficient and chemoselective method for oxathioacetalization of aldehydes, in the presence of ketones, and their deprotection. The significant advantages of this methodology are mild and heterogeneous reaction conditions, relatively short reaction times, high yields of the products, selectivity and easy work-up. We are exploring further applications of $V(HSO_4)_3$ for the other types of functional group transformations in our laboratory.

Experimental

Oxathioacetalyzation of 4-chlorobenzaldehyde as a typical procedure. A mixture of 4-chlorobenzaldehyde (1 mmol), 2-mercaptoethanol (1.2 mmol) and $V(HSO_4)_3$ (0.03 mmol) in *n*-hexane (3 mL) was stirred at reflux temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the filtrate was washed with *n*-hexane (5 mL). The organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) and water (10 mL) and dried over $MgSO_4$. Eevaporation of the solvent followed by column chromatography on silica gel gave 2-[4'-chlorophenyl]-1,3-oxathiolane in 95% yield. IR (neat)1598, 1496, 1414, 1209, 1091, 1015 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 3.10-3.23 (m, 2H), 3.82-3.92 (m, 1H), 4.41-4.54 (m, 1H), 5.94 (s, 1H), 7.30 (d, 2H), 7.44 (d, 2H). Anal. Calcd for C_9H_9ClOS: C, 53.86; H, 4.52; S, 15.98%. Found: C, 53.63; H, 4.59; S, 15.77%.

Deprotection of 2-[4'-chlorophenyl]-1,3-oxathiolane as a typical procedure. A mixture of the substrate (1 mmol), $V(HSO_4)_3$ (0.5 mmol) and wet SiO_2 [(SiO_2/ H_2O: 50% *w*/*w*), 0.1 g] in *n*-hexane (3 mL) was stirred and heated at reflux. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the solid residue was washed with *n*-hexane (5 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 5 mL) and water (10 mL) and dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel afforded 4-chlorobenzaldehyde in 95% yield.

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