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Yttrium triflate as an efficient and useful catalyst for chemoselective protection of carbonyl compounds

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This paper is dedicated to my mentor Prof. Niels H. Andersen, Department of Chemistry, University of Washington, for his valuable guidance and constant encouragement

Abstract—Carbonyl compounds have been successfully converted into their corresponding oxathiolane, dithiolane, and dithiane derivatives with 2-mercaptoethanol, 1,2-ethanedithiol, and 1,3-propanedithiol using catalytic amount of yttrium triflate. In addition, by using this catalyst, high chemoselective protection of carbonyl compounds has been achieved.

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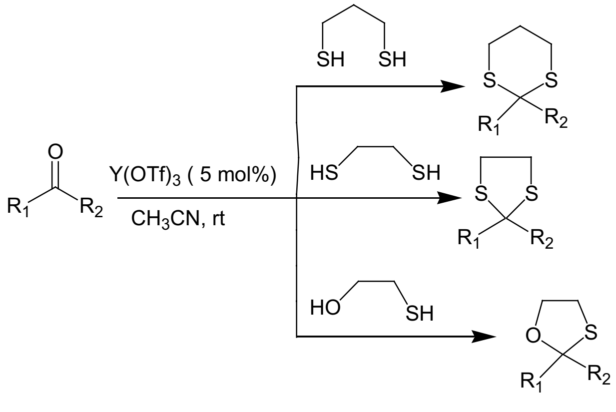
The protection of carbonyl compounds plays an important role during multistep syntheses in organic, medicinal, carbohydrate, and drug design chemistry. Among carbonyl protecting groups, 1,3-diothiolanes, 1,3-oxathiolanes, and 1,3-dithianes are important as they are quite stable under both mildly acidic and basic conditions.[1] In addition, these are also utilized as masked acyl anions[2] or masked methylene functions[3] in carbon–carbon bond forming reactions. Several methods for preparation of thioacetals, dithiolanes, or dithianes derivatives from carbonyl compounds such as PTSA[4] in refluxing benzene (removing the water as an azeotrope with benzene), BF_3–OEt_2,[5] $ZnCl_2$,[6] SO_2,[7] TMSCl–NaI,[8] TMSOTf,[9] $AlCl_3$,[10] $TiCl_4$,[11] $Cu(OTf)_2$–SiO_2,[12] $SOCl_2$–SiO_2,[13] $ZrCl_4$–SiO_2,[14] $NiCl_2$,[15] $Bi(NO_3)_3$,[16] $Bi(OTf)_3$,[17] LiBr,[18] $LiBF_4$,[19] $InCl_3$,[20] molecular I_2,[21] 5 M $LiClO_4$[22] have been reported. Although some of these methods are carried out under mild reaction conditions, most of them require drastic conditions,[7,13] reflux temperature,[4,17] long reaction times, expensive, not readily available reagents,[17] they need to be prepared and tedious work-up procedure.[10,11] Interestingly, only a few methods are known for chemoselective protection of aldehydes[12,13,15,18–22] in the presence of ketones. So simple, efficient, and chemoselective methods are still desirable.

Recently, there has been growing considerable interest in the use of lanthanide triflates in organic synthesis[23] as they are water tolerable and reusable. The reagent $Y(OTf)_3$ is commercially available and can be used for preparation of oxathiolanes, dithiolanes, and dithianes from carbonyl compounds. Like lanthanide triflates, $Y(OTf)_3$ is also water tolerable, reusable, and chemoselective reagent for protection of carbonyl compounds. Interestingly, the experimental procedure for these reactions is very simple and does not need the use of dry solvents or inert atmospheres. A catalytic amount of yttrium triflate (5 mol %) is sufficient to obtain the desired compounds in excellent yields (Scheme 1). Thus,



Scheme 1.

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Table 1. $Y(OTf)_3$ catalyzed protection of carbonyl compounds as dithianes, dithiolanes, or oxathiolanes at room temperature

Entry	Substrate	Reagent	Time (min)	Yield[a] (%)
1	Benzaldehyde	$HSCH_2CH_2CH_2SH$	45	89
2	4-Methoxybenzaldehyde	$HSCH_2CH_2CH_2SH$	25	93/86[b]
3	4-Chlorobenzaldehyde	$HSCH_2CH_2CH_2SH$	28	90
4	4-Nitrobenzaldehyde	$HSCH_2CH_2CH_2SH$	83	84
5	Furfural	$HSCH_2CH_2CH_2SH$	32	91
6	3-Methoxy-4-benzyloxybenzaldehyde	$HSCH_2CH_2CH_2SH$	50	88
7	Cinnamaldehyde	$HSCH_2CH_2CH_2SH$	45	87
8	2-Naphthaldehyde	$HSCH_2CH_2CH_2SH$	120	83
9	Thiophene 2-carboxaldehyde	$HSCH_2CH_2CH_2SH$	36	91
10	4-Hydroxybenzaldehyde	$HSCH_2CH_2CH_2SH$	240	88
11	α-Tetralone	$HSCH_2CH_2CH_2SH$	300	82
12	Cyclohexanone	$HSCH_2CH_2CH_2SH$	360	87
13	Cyclopentanone	$HSCH_2CH_2CH_2SH$	340	83
14	1-Hexanal	$HSCH_2CH_2CH_2SH$	75	79
15	2-Heptanone	$HSCH_2CH_2CH_2SH$	140	83[c]
16	Acetophenone	$HSCH_2CH_2CH_2SH$	120	91[c]
17	4-Methoxyacetophenone	$HSCH_2CH_2CH_2SH$	85	92[c]
18	4-Chloroacetophenone	$HSCH_2CH_2CH_2SH$	90	89[c]
19	Benzaldehyde	$HSCH_2CH_2SH$	90	92
20	4-Methoxybenzaldehyde	$HSCH_2CH_2SH$	45	93
21	4-Bromobenzaldehyde	$HSCH_2CH_2SH$	55	89/85[b]
22	Cyclohexanone	$HSCH_2CH_2SH$	390	81
23	Benzaldehyde	$HSCH_2CH_2OH$	110	79
24	4-Methoxybenzaldehyde	$HSCH_2CH_2OH$	120	81
25	1-Hexanal	$HSCH_2CH_2OH$	340	79
26	Cinnamaldehyde	$HSCH_2CH_2OH$	115	71

[a] Yields refer to pure isolated products, characterized by IR, ^1H NMR, and MS.

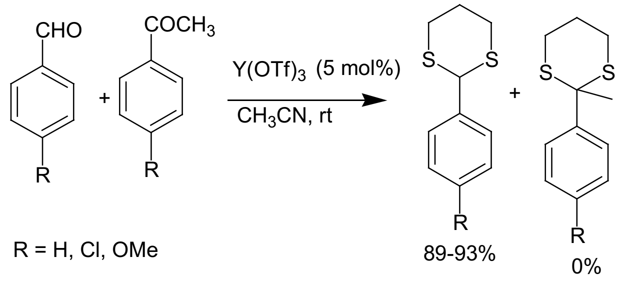
[b] Isolated yields with reused catalyst.

[c] Refluxed in acetonitrile.

various aromatic, aliphatic, and heterocyclic aldehydes undergo the protection reactions using 1,3-propanedithiol, 1,2-ethanedithiol, or 2-mercaptoethanol in the presence of catalytic amount of $Y(OTf)_3$ in acetonitrile at room temperature to give the corresponding 1,3-dithianes, 1,3-dithiolanes, or 1,3-oxathilanes in good to excellent yields.[24] The results of these studies are summarized in Table 1.

It is noteworthy that aromatic or acyclic aliphatic ketones did not undergo the reaction at room temperature. This result prompted me to explore the chemoselective protection of aldehydes in the presence of ketones. For instance, when an equimolar mixture of aldehyde and ketone was allowed to react with 1,3-propanedithiol in the presence of catalytic amount of $Y(OTf)_3$ only the 1,3-dithiane derivative of corresponding aldehyde was obtained, ketone was recovered quantitatively (Scheme 2). However, ketones are converted to the corresponding dithianes derivatives at reflux temperature in excellent yields.

In conclusion, I have developed a simple and efficient method for chemoselective protection of carbonyl compounds as dithianes, dithiolanes, and oxathiolanes using catalytic amount of yttrium triflate. Further, the catalyst can be readily recovered and reused thus making this procedure more environmentally acceptable. The method has great advantage compared with conventional Lewis acid-mediated reactions in dry organic solvents, because tedious procedures to remove water from the solvents, substrates, and catalyst are not necessary.



Scheme 2.

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24. A typical procedure: To a stirred mixture of 4-methoxybenzaldehyde (680 mg, 5 mmol) and 1,3-propanedithiol (648 mg, 6 mmol) in acetonitrile (25 mL) was added $Y(OTf)_3$ (135 mg, 5 mol%) at room temperature. The reaction mixture was stirred at room temperature for 25 min, diluted with ethyl acetate (100 mL), washed with water (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (15% ethyl acetate in hexane) to afford pure 2-(4-methoxy)phenyl-1,3-dithiane (93%). ^1H NMR (500 MHz, $CDCl_3$) δ 1.86–1.98 (m, 1H), 2.10–2.18 (m, 1H), 2.85–2.95 (m, 2H), 2.98–3.10 (m, 2H), 3.79 (s, 3H), 5.13 (s, 1H), 6.86 (d, $J = 8.5$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 2H). The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which could be reused for the next thioacetalyzation reaction, without losing any significant activity (Table 1, entries 2 and 21).