Indium Trifluoromethanesulfonate as a Mild and Chemoselective Catalyst for the Conversion of Carbonyl Compounds into 1,3-Oxathiolanes

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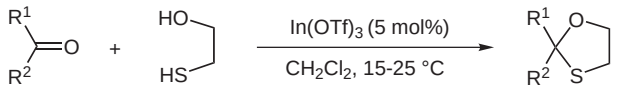
Abstract: An efficient method for the preparation of 1,3-oxathiolanes from aldehydes and ketones with 2-mercaptoethanol in the presence of a catalytic amount of indium trifluoromethanesulfonate is reported.

Key words: chemoselectivity, indium trifluoromethanesulfonate, Lewis acids, 1,3-oxathiolanes, protecting groups

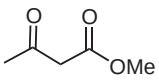
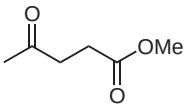
1,3-Oxathiolanes have long been used as carbonyl protective groups[1] and intermediates[2] in organic synthesis. Although a variety of methods for their formation are reported employing HCl,[3] $HClO_4$,[4] *p*-$MeC_6H_4SO_3H$,[5] $LiBF_4$,[6] $BF_3{\cdot}OEt_2$,[7] $BF_3{\cdot}OEt_2$–$CaCl_2$,[8] Bu_4NBr_3,[9] TMSCl–NaI,[2e] TMSOTf,[10] *i*-Pr_3SiOTf,[11] SO_2,[12] $ZnCl_2$–Na_2SO_4,[2e,13] $ZrCl_4$,[14] $[(dppb)Pt(\mu\text{-}OH)]_2(BF_4)_2$-$Mg(ClO_4)_2{\cdot}2H_2O$,[15] polystyryl diphenyl phosphonium iodide,[16] natural kaolinitic clay,[17] Amberlyst® 15[18] a large number of these methods employ rather harsh conditions or are inconvenient to use. Accordingly, there is still a need for more general pathways of 1,3-oxathiolanes synthesis. In this paper we wish to disclose an efficient method for preparing 1,3-oxathiolanes from aldehydes and ketones by reaction with 2-mercaptoethanol (1.5–2.0 equiv) using a catalytic amount of indium trifluoromethanesulfonate[19,20] (5 mol%) under mild reaction conditions (Scheme 1).



Scheme 1

Table summarizes some results and illustrates the efficiency of the present method.[21] Both activated and deactivated aromatic aldehydes including a sterically hindered one such as mesitaldehyde (entries 1–5), aliphatic aldehydes (entries 6 and 7), and cinnamaldehyde (entry 8) reacted rapidly with 2-mercaptoethanol (1.5 equiv) in dichloromethane as the solvent at 15 °C to afford the corresponding 1,3-oxathiolanes in good to excellent yields. The case of *p*-nitrobenzaldehyde (entry 4) is worth mentioning as this gives a high yield by our method, in contrast to a low yield (35%) of the product in an earlier

Table $In(OTf)_3$ Catalyzed Formation of 1,3-Oxathiolanes

Entry	Substrate	Conditions [°C/min (h)]	Yield (%)[a]
1[b]	PhCHO	15/1	82
2[b]	*p*-MeC_6H_4CHO	15/1	70
3[b]	*p*-ClC_6H_4CHO	15/5	75
4[b]	*p*-$NO_2C_6H_4CHO$	15/50	89
5[b]	2,4,6-$Me_3C_6H_2CHO$	15/1	72
6[b]	*n*-$C_7H_{15}CHO$	15/1	71
7[b]	*cyclo*-$C_6H_{11}CHO$	15/1	73
8[b]	(*E*)-PhCH=CHCHO	15/1	72[c]
9[d]	*n*-C_6H_{13}(Me)C=O	25/(6)	88
10[d]	*cyclo*-C_6H_{11}(Me)C=O	25/(5)	96
11[d]	$(PhCH_2)_2C$=O	25/(4.5)	81
12[d]	$(CH_2)_4C$=O	25/90	71
13[d]	$(CH_2)_5C$=O	15/30	84
14[d]	menthone	15/60	92[e]
15[d]	$(CH_2)_6C$=O	25/(3.5)	80
16[d]		25/60	82
17[d]		25/60	76
18[d]	PhMeC=O	25/(21)	79
19[d]	Ph(*i*-C_3H_7)C=O	25/(21.5)	71
20[d]	Ph_2C=O	25/(22)	71

[a] Isolated yields.
[b] $HO(CH_2)_2SH$ (1.5 equiv) was used.
[c] *E*/*Z* = 100/0.
[d] $HO(CH_2)_2SH$ (2.0 equiv) was used.
[e] As 46:54 mixture of diastereomers.

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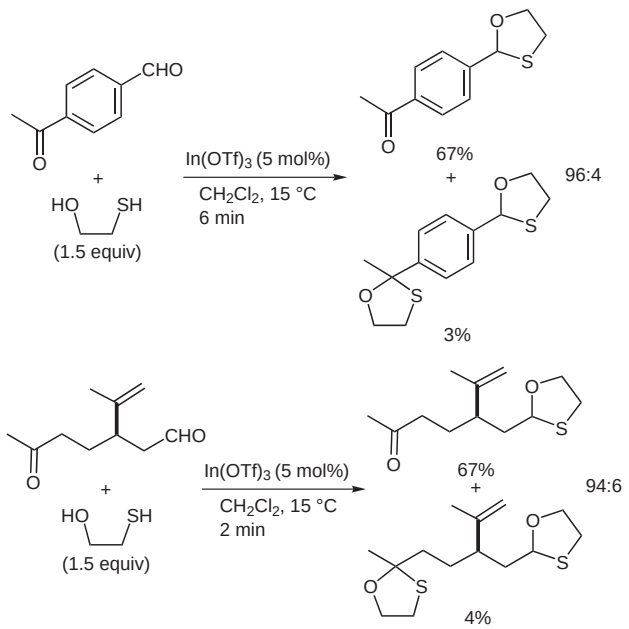
report.[4] Application of this method was then extended for the protection of different types of aliphatic (entries 9–11), cyclic (entries 12–15), and aromatic ketones (entries 18–20) including a γ-keto ester (entry 17) in the presence of 2-mercaptoethanol (2.0 equiv) at ambient temperatures.[22] The 1,3-oxathiolanes were formed in good yields, although the time required for the completion of the reaction was found to be longer compared to aldehydes. Interestingly, a β-keto ester (entry 16) was smoothly monothioacetalized in 82% yield under the above conditions without formation of a transesterification product, which was obtained in substantial amounts when the reaction was carried out by using natural kaolinitic clay.[17] It is important to point out that in contrast to the previous method which required stoichiometric amount of catalyst,[2e,7a,b,8,12,13a,16] in our method a catalytic amount of $In(OTf)_3$ is enough for the reaction to proceed smoothly. Moreover, neither using of dehydrating agent[2e,8,13a,15] nor the azeotropic removal of water[2a,c,d,3a,5a,d,12] is necessary in our procedure.

Because the conversion of aldehydes is faster than ketones as shown in Table, the chemoselective protection of aldehydes in the presence of ketone function could be achieved with the present method in good yields and with excellent chemoselectivities (Scheme 2).



Scheme 2

In conclusion, we have provided a facile and efficient method for the synthesis of 1,3-oxathiolanes of aldehydes and ketones catalyzed by indium trifluoromethanesulfonate as a mild Lewis acid catalyst.[23]

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(21) The experimental procedure for the reaction of cyclohexyl methyl ketone with 2-mercaptoethanol is representative. To a mixture of cyclohexyl methyl ketone (252 mg, 2.0 mmol) and $In(OTf)_3$ (56 mg, 0.1 mmol) in CH_2Cl_2 (5.5 mL) 2-mercaptoethanol (313 mg, 4.0 mmol) in CH_2Cl_2 (0.5 mL)

was added at 25 °C. After the reaction mixture was kept stirring at the same temperature for 5 h, it was quenched by adding sat. $NaHCO_3$. The resulting mixture was extracted three times with EtOAc. The combined extracts were dried over Na_2SO_4, and concentrated. Silica gel column chromatography (5% EtOAc–hexane) yielded 2-cyclohexyl-2-methyl-1,3-oxathiolane (359 mg, 96%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01–1.31 (m, 5 H), 1.51 (s, 3 H), 1.64–1.93 (m, 6 H), 2.94 (m, 1 H), 3.03 (m, 1 H), 4.08 (m, 1 H), 4.21 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 26.3, 26.4, 28.6, 28.7, 33.3, 49.5, 70.2, 98.9.

(22) By using $InBr_3$ (5 mol%), benzophenone was converted into 2,2-diphenyl-1,3-oxathiolane under similar reaction conditions in 40% yield. This result clearly shows the strong catalytic activity of $In(OTf)_3$ in comparison with $InBr_3$.

(23) Trifluoromethanesulfonic acid (TfOH) arising by hydrolysis of $In(OTf)_3$ is less effective than $In(OTf)_3$ in our reaction system. For example, benzophenone was treated with $HO(CH_2)_2SH$ and TfOH (15 mol%) at 25 °C for 22 h to afford the product in 50% yield.