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Indium(III) chloride as an efficient, convenient catalyst for thioacetalization and its chemoselectivity

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Abstract—An efficient method for the preparation of 1,3-dithiolanes from aldehydes and ketones with 1,2-ethanedithiol in the presence of a catalytic amount of anhydrous indium(III) chloride is reported. A mild and highly chemoselective thioacetalization of carbonyl compounds using indium(III) chloride as the catalyst is also described. The desired products were obtained in 71-95% yield. © 2000 Elsevier Science Ltd. All rights reserved.

Since the introduction of 1,3-dithianes as nucleophilic acylating reagents by Corey and Seebach,¹ dithioacetals have become widely used tools for the formation of C-C bonds. In addition, the stability exhibited by 1,3dithiolanes under acidic or basic conditions has led to their synthetic utility as carbonyl protecting groups² and as intermediates in the conversion of a carbonyl function to a hydrocarbon derivative.³ For their preparation from carbonyl compounds, acid catalysts such as concentrated HCl, ZnCl₂ or BF₃·Et₂O have invariably been used.² Numerous other methods that are reported for this conversion include the use of a Nafion-H⁴ catalyst, titanium tetrachloride,5 magnesium or zinc triflates,⁶ and anhydrous lanthanum chloride.⁷ Yet, despite their importance and necessity in synthesis, chemoselectivity between aldehydes and ketones has only been reported with catalysts like silica gel treated with thionyl chloride,⁸ an Amberlyst-15 catalyst⁹ and ceric ammonium nitrate.¹⁰ So far in the literature, no Lewis acid has been reported to show chemoselectivity for the carbonyl compound. In view of the recent surge in activity on the use of indium(III) chloride as a mild Lewis acid catalyst for various organic transformations.¹¹ we wish to report a new and efficient synthesis of 1.3-dithiolanes, as well as the chemoselective protection of various carbonyl compounds using indium(III) chloride as the catalyst.

When a solution of *p*-methoxybenzaldehyde, 1.1 equivalents of 1,2-ethanedithiol and 0.3 equivalents of anhydrous indium(III) chloride in dry dichloromethane was stirred at 25°C under an argon atmosphere for 15 min, thioacetal **1** was produced¹² and isolated in 92% yield after extractive workup and chromatography on silica gel. The reaction is clean and the workup procedure is very simple.

Encouraged by this result, we carried out further investigations on *p*-nitrobenzaldehyde and *p*-hydroxybenzaldehyde which were also converted to the corresponding 1,3-dithiolanes 2 and 3 in very good yields (see Table 1) $^{13-16}$ using indium(III) chloride as the catalyst. Enolizable ketones like ethyl acetoacetate under the same reaction conditions with indium(III) chloride as the catalyst for 5 hours were converted to the corresponding thioacetal, e.g. 4, in 74% yield. With our continuing interest in the synthesis¹⁷ of oxa-polycyclic compounds, even an oxa-bridged compound was converted into the corresponding 1,3-dithiolane derivative 5 in good yield. Alicyclic ketones like 2-carbethoxy-2-methylcyclohexanone, ethyl 2-(2-oxocyclohexane)acetate; α,β -unsaturated ketones like benzylidene tetralone and (E)-4-phenyl-3-buten-2-one in the presence of 1,2-ethanedithiol with indium(III) chloride as a catalyst were converted to the corresponding dithiolanes 6-9 in good yields, respectively.

We observed that the reaction with aldehydes takes place rapidly in the presence of indium(III) chloride when compared to the rate with ketones (see Table 1). The difference in reactivity of the indium(III) chloride catalyst towards aldehydes and ketones gave us impetus to study chemoselective reactions.

Keywords: aldehydes; ketones; indium(III) chloride; 1,2-ethanedithiol; 1,3-dithiolanes.

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Towards this objective, we carried out initial experiments with equimolar mixtures of an aldehyde and a ketone (Scheme 1). When an equimolar (1.5 mmol) mixture of p-hydroxybenzaldehyde and acetophenone was allowed to react with 1.5 mmol of 1,2-ethanedithiol and a catalytic amount of indium(III) chloride in dry methanol at ambient temperature, a high yield (93%) of **3** was obtained and the unchanged acetophenone was recovered. A similar result was obtained when the experiment was performed on a mixture of p-hydroxy-

Table 1. Preparation of 1,3-dithiolanes¹³ using anhydrous indium(III) chloride

Substrate	product	Time	Yield ^a %
1	CS-OMe	15 min	92 ⁸
2	\sim NO ₂	20 min	79 ¹⁴
3 ^b	Сунон	10 min	95 ⁸
4		5 h	74 ¹⁵
5	MeOOC COOMe	28 h	73
6	S CH ₃ COOEt	20 h	85
7	S S COOEt	20 h	85
8	S H Ph	5 h	71
9	S H ₃ C	3.5 h	83 ¹⁶

^a Yields (unoptimized) refer to isolated and chromatographically pure compounds.

^b Dry methanol was used as solvent.



Scheme 1.





benzaldehyde ethyl 3-(2-oxocyclohexane)and propionate. Further, we studied thioacetalization of the keto-aldehydes 12^{18} (Scheme 2) which also exhibited splendid selectivity towards the formyl group. When 4-acetylbenzaldehyde (12a)reacted with 1.2ethanedithiol under the usual conditions, only the aldehyde group reacted and afforded the corresponding product 13a in 87% yield. Repetition of this reaction with 12b furnished the dithiolane 13b in 89% yield. There was no evidence that the ketonic carbonyl group reacted to any measurable extent.

In summary, mild conditions coupled with an exceedingly simple protocol for the protection of aldehydes or ketones as dithiolanes using indium(III) chloride as a catalyst is reported. Furthermore, the relatively slow reaction rate of ketones allows for chemoselective protection of aldehydes in the presence of ketones, making this is an important tool in synthetic organic chemistry. The notable advantages of this method are its chemoselectivity and the requirement for minimum amounts of catalyst.

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- 12. Typical experimental procedure: To a freshly distilled dichloromethane (dried over phosphorous pentoxide) solution of the appropriate carbonyl compound (1 mmol) and 1,2-ethanedithiol (1.1 mmol) was added anhydrous indium(III) chloride (0.3 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature followed by TLC until the starting material disappeared. The reaction mixture was quenched with a brine solution and repeatedly extracted using diethyl ether. The combined organic layer was dried over anhydrous MgSO₄ and the solvent was purified by silica gel column chromatography to furnish the 1,3-dithiolanes in good yields.
- 13. All new compounds gave satisfactory spectral data in accordance to their proposed structures.

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