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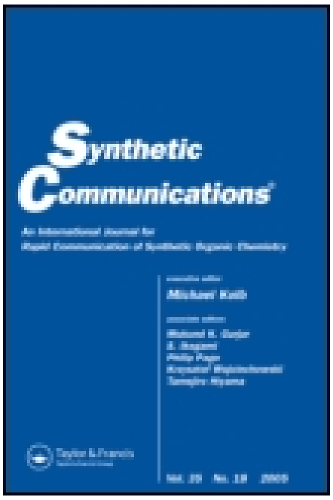

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INDIUM(III) CHLORIDE CATALYZED EFFICIENT CONVERSION OF CARBONYL COMPOUNDS TO 1,3-DITHIOACETALS

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INDIUM(III) CHLORIDE CATALYZED EFFICIENT CONVERSION OF CARBONYL COMPOUNDS TO 1,3-DITHIOACETALS

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ABSTRACT

Several aldehydes and ketones were efficiently converted into their corresponding dithioacetals and 1,3-dithianes in high yields using catalytic amount of indium(III) chloride in dichloromethane.

Acetals and thioacetals are the most commonly used protecting groups for aldehydes and ketones in multi-step synthesis of many natural products. Among various acetals, dithioacetals and 1,3-dithianes are versatile because of their use as nucleophilic acylating agents in carbon–carbon bond forming reactions.

As a result, several methods have been reported for the preparation of thioacetals from aldehydes and thiols using protic as well as Lewis acids as catalysts. In addition lithium salts have also been used for this transformation. However, many of these procedures are often accompanied by the use of stoichiometric amount of catalysts, moisture sensitive reagents, longer

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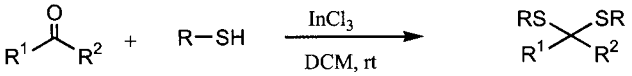
reaction times and low yields of products in case of aliphatic aldehydes. Even though, zinc triflate and trialkylsilyl triflates are found to be effective, there are still some limitations regarding selectivity and incompatibility with other functional groups. In recent years, $InCl_3$ has received considerable attention as a mild Lewis acid in various transformations such as Mukaiyama aldol reactions, Diels-Alder reactions, Mannich reactions, Prins type cyclizations and Michael reactions in both aqueous and non-aqueous medium. Unlike traditional Lewis acids, $InCl_3$ is stable and recoverable in water. These unique properties inherent to $InCl_3$ prompted us to explore this catalyst for dithioacetalization of carbonyl compounds.

In this report, we wish to introduce $InCl_3$ as a new and efficient catalyst for thioacetalization of aldehydes and ketones with thiols under mild conditions. The reaction of benzaldehyde with ethane 1,2-dithiol in the presence of 10 mol% $InCl_3$ in dichloromethane gave 1,3-dithiane derivative in 90% yield. Similarly, several aromatic, aliphatic, α,β-unsaturated and heterocyclic aldehydes were efficiently converted into the corresponding dithioacetals in the presence of indium(III) chloride. However, aliphatic and aromatic ketones took longer reaction times to achieve comparable yields with those of their aldehyde analogues. The reactions proceeded smoothly at ambient temperature to afford dithioacetals in high yields.



R= CH_3CH_2, $CH_2CH_2CH_2SH$ or CH_2CH_2SH

The cyclic ketones like cyclohexanone, cyclopentanone, tetralone and 4-phenyl cyclohexanone reacted with dithiol and monothiol to give the corresponding dithioacetals in high yields. Acid sensitive substrate like furfural is also protected as dithioacetal in good yield without the formation of any side products. Acyclic ketones like benzophenone, acetophenone, 3-pentanone, and 2-hexanone were also converted into dithioacetals in good yields. The tolerance of various functional groups under the present reaction conditions have been examined by reacting the substrates bearing OBn, OPh, OMe, methylenedioxy, cyano, olefinic groups and the reaction conditions are compatible with these functional groups. When ethane 1,2-dithiol was replaced with propane 1,3-dithiol gave the corresponding 1,3-dithiane derivatives in good yields.

In conclusion, $InCl_3$ is found to be an highly efficient and recoverable catalyst for the conversion of carbonyl compounds into dithioacetals under mild reaction conditions. The procedure offers several advantages including mild reaction conditions, high yields of products, catalytic amount of the reagent, regeneration of the catalyst, cleaner reactions, simple experimental and product isolation procedure which makes it a useful and attractive procedure for this transformation.

EXPERIMENTAL

General procedure: A mixture of carbonyl compound (5 mmol) dithiol (5 mmol) or monothiol (10 mmol) and $InCl_3$ (0.5 mmol) in dichloromethane (15 ml) was stirred at room temperature for an appropriate time (table). After completion of the reaction as indicated by TLC, the reaction mixture

Table. $InCl_3$ Catalyzed Formation of Dithioacetals and 1,3-Dithianes[a]

Entry	Carbonyl Compound	Thiol	Reaction Time (h)	Yield[b] (%)
a	C_6H_5CHO	$HSCH_2CH_2SH$	2.5	90
b	$4\text{-}MeC_6H_4CHO$	CH_3CH_2SH	2.0	88
c	$3,4\text{-}Cl_2C_6H_3CHO$	$HSCH_2CH_2SH$	3.5	81
d	$3,4\text{-}(EtO)_2C_6H_3CHO$	$HSCH_2CH_2SH$	2.5	87
e	$3\text{-}PhOC_6H_4CHO$	CH_3CH_2SH	3.0	75
f	$3\text{-}NO_2C_6H_4CHO$	$HSCH_2CH_2SH$	6.0	70
g	$PhCH{=}CHCHO$	$HSCH_2CH_2SH$	3.5	85
h	Piperonal	$HSCH_2CH_2CH_2SH$	4.0	89
i	1-Naphthaldehyde	$HSCH_2CH_2SH$	5.0	80
j	2-Furfuraldehyde	CH_3CH_2SH	2.5	90
k	Thiophene-2-carboxaldehyde	$HSCH_2CH_2SH$	2.0	92
l	3-Phenylpropanal	$HSCH_2CH_2SH$	3.5	83
m	*n*-Hexanal	$HSCH_2CH_2CH_2SH$	4.0	85
n	Cyclohexanone	CH_3CH_2SH	5.0	80
o	3-Pentanone	CH_3CH_2SH	6.5	75
p	2-Hexanone	$HSCH_2CH_2SH$	7.0	70
q	Tetralone	$HSCH_2CH_2SH$	4.5	82
r	Acetophenone	$HSCH_2CH_2SH$	5.5	85
s	4-Phenylcyclohexanone	$HSCH_2CH_2CH_2SH$	5.0	80

[a] All products were characterized by ^1H NMR, IR and mass spectra.
[b] Isolated yields after purification.

was diluted with water (10 ml) and extracted twice with dichloromethane (2×10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1 : 9) to give pure dithioacetal.

Representative spectroscopic data for compounds: **a:** ^{1}H NMR (200 MHz; $CDCl_3$): δ 3.50 (s, 4H); 5.75 (s, 1H); 7.25–7.40 (m, 5H). EIMS: *m/z*: 182 M^+, 165, 154, 136, 122, 91, 77. IR (KBr) ν: 2965, 2855, 1446, 1374, 1246, 1189, 1130, 1050, 976, 822. **b:** ^{1}H NMR (200 MHz; $CDCl_3$): δ 1.25 (t, 6H, $J = 6.8$ Hz); 2.35 (s, 3H); 2.55 (m, 4H); 4.90 (s, 1H); 7.15 (d, 2H, $J = 7.8$ Hz); 7.35 (d, 2H, $J = 7.8$ Hz). EIMS: *m/z*: 226 M^+, 165, 136, 104, 91, 69, 55, 43. IR (KBr) ν: 2968, 2870, 1510, 1375, 1264, 1183, 1153, 1110, 1049, 974, 830. **m:** ^{1}H NMR (200 MHz; $CDCl_3$): δ 1.05 (t, 3H, $J = 7.0$ Hz); 1.15 (m, 8H); 2.70 (m, 2H); 4.50 (m, 4H); 4.60 (t, 1H, $J = 7.0$ Hz). FAB Mass: *m/z*: 190 M^+, 119, 73. IR (KBr) ν: 2929, 1588, 1424, 1379, 1271, 1180, 907, 730. **n:** ^{1}H NMR (200 MHz; $CDCl_3$): δ 1.15 (t, 6H, $J = 6.8$ Hz); 1.45 (m, 2H); 1.65 (m, 4H); 1.85 (t, 4H, $J = 6.8$ Hz); 2.60 (q, 4H, $J = 6.8$ Hz). EIMS: *m/z*: 204 M^+, 175, 143, 81, 75, 43. IR (KBr) ν: 2965, 2855, 1446, 1374, 1264, 1189, 1130, 1050, 1008, 976, 883, 822. **o:** ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, 6H, $J = 6.8$ Hz); 1.20 (t, 6H, $J = 6.8$ Hz); 1.65 (q, 4H, $J = 6.8$ Hz); 2.60 (q, 4H, $J = 6.8$ Hz). EIMS: *m/z*: 192 M^+, 163, 131, 102, 69, 55, 43. IR (KBr) ν: 2969, 2872, 1455, 1375, 1322, 1260, 1160, 1132, 1069, 1048, 976, 922, 863. **r:** ^{1}H NMR (200 MHz; $CDCl_3$): δ 2.15 (s, 3H); 3.35 (s, 4H); 7.35–7.45 (m, 5H). FAB Mass: *m/z*: 196 M^+, 181, 136, 121, 103, 91, 77. IR (KBr) ν: 2924, 1440, 1274, 1059, 845, 765, 699.

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