



Indium tribromide-catalyzed chemoselective dithioacetalization of aldehydes in non-aqueous and aqueous media

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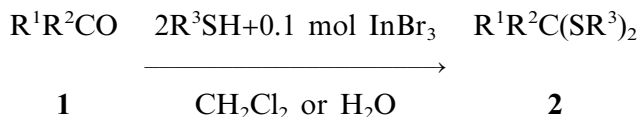
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Abstract

Indium tribromide efficiently catalyzes the chemoselective dithioacetalization of aldehydes in the presence of ketones in dichloromethane. The catalyst is also active in water, which can be reused, in the same pot, for several times without any decrease in the yield of reaction. © 2000 Published by Elsevier Science Ltd.

The preparation of dithioacetals involves the condensation of carbonyl compounds with thiols in the presence of a protic or a Lewis acid. Several Lewis acids catalysts, such as ZnCl_2 ,¹ LiBr ,² BF_3 -etherate,³ TiCl_4 ,⁴ SiCl_4 ,⁵ AlCl_3 ,⁶ TeCl_4 ,⁷ LaCl_3 ,⁸ etc., have been used for this purpose. Limitations associated with some of these methods include: presence of protic acids;^{1,3} excess of thiols;^{3,8} anhydrous conditions;^{1–8} stoichiometric amount of catalyst;^{1,4} formation of secondary products, such as hemithioacetals,³ and vinyl sulfides from enolizable carbonyl compounds;⁶ poor selectivity facing mixtures of aldehydes and ketones;⁶ and failure to react with aromatic and aliphatic ketones.²

We now report that InBr_3 effectively promotes the dithioacetalization of aliphatic and aromatic carbonyl compounds. Many of the limitations pointed above were overcome. Cyclic (1,3-dithiolanes) and acyclic (aromatic and aliphatic) dithioacetals (Table 1) have been prepared from ethanedithiol, benzenethiol and propanethiol and the corresponding carbonyl compound.



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Table 1
InBr₃-promoted dithioacetalization of carbonyl compounds

Entry	R ¹	R ²	R ³	Product	Yield (%)	Time (h)
1	C ₆ H ₅	H	-(CH ₂) ₂ -	2a	80 ^a	1.0
2	C ₆ H ₅	H	C ₆ H ₅	2b	70 ^a , 47 ^f , 38 ^g	2.0 ^a , 1.0 ^f , 3.0 ^g
3	C ₆ H ₅	H	C ₃ H ₇	2c	98 ^a	0.5
4	C ₄ H ₃ O ^h	H	-(CH ₂) ₂ -	2d	85 ^a	3.0
5	2,4,5-(CH ₃ O) ₃ -C ₆ H ₂	H	-(CH ₂) ₂ -	2e	70 ^a , 63 ^c	0.25 ^a , 3.0 ^c
6	2,4,5-(CH ₃ O) ₃ -C ₆ H ₂	H	C ₆ H ₅	2f	95 ^b , 98 ^c	1.0 ^b , 3.0 ^c
7	2,4,5-(CH ₃ O) ₃ -C ₆ H ₂	H	C ₃ H ₇	2g	96 ^b , 70 ^c	1.0 ^b , 3.0 ^c
8	2-CH ₃ O-C ₆ H ₄	H	C ₃ H ₇	2h	40 ^c	19.0
9	4-Cl-C ₆ H ₄	H	-(CH ₂) ₂ -	2i	98 ^b , 37 ^c , 20 ^d , 30 ^e	0.5 ^b , 20.0 ^c , 2.0 ^d , 2.0 ^e
10	C ₆ H ₅ CH=CH	H	C ₃ H ₇	2j	99 ^b , 68 ^c	1.0 ^b , 20.0 ^c
11	C ₂ H ₅	H	C ₃ H ₇	2k	99 ^b , 12 ^c	0.25 ^b , 18.0 ^c
12	C ₂ H ₅	H	C ₆ H ₅	2l	98 ^b	0.3
13	CH(CH ₃) ₂	H	-(CH ₂) ₂ -	2m	95 ^b	1.0
14	CH(CH ₃) ₂	H	C ₃ H ₇	2n	97 ^b , 14 ^c	0.25 ^b , 16.0 ^c
15	C(CH ₃) ₃	H	C ₃ H ₇	2o	99 ^b , 10 ^c	0.5 ^b , 18.0 ^c
16	-(CH ₂) ₅ -		-(CH ₂) ₂ -	2p	93 ^a , 50 ^c	1.0 ^a , 16.0 ^c
17	-(CH ₂) ₅ -		C ₆ H ₅	2q	57.3 ^a	16.0
18	-(CH ₂) ₅ -		C ₃ H ₇	2r	74 ^a , 14 ^c	16.0 ^a , 18.0 ^c
19	C ₆ H ₅	CH ₃	-(CH ₂) ₂ -	2s	88 ^a , N.R. ^c	2.0 ^b , 20.0 ^c
20	3,4,5-(CH ₃ O) ₃ -C ₆ H ₂	CH ₃	-(CH ₂) ₂ -	2t	73 ^a	0.25
21	C ₆ H ₅	CH ₃	C ₆ H ₅	2u	N.R. ^a	20.0
22	C ₆ H ₅	CH ₃	C ₃ H ₇	2v	Traces ^a	16.0
23	C ₃ H ₇	CH ₃	-(CH ₂) ₂ -	2w	90 ^b , N.R. ^c	1.2 ^b , 18 ^c
24	C ₂ H ₅	CH ₃	C ₆ H ₅	2x	N.R. ^a	16.0
25	C ₂ H ₅	CH ₃	C ₃ H ₇	2y	Traces ^a	3.0
26	CH ₃	CH ₃	C ₃ H ₇	2z	33 ^b	2.0

^a In anhydrous CH₂Cl₂, 1:1 molar ratio carbonyl compd:InBr₃.

^b In anhydrous CH₂Cl₂, 1:0.1 molar ratio.

^c In water, 1:0.1 molar ratio.

^d In water:tetrahydrofuran 1:1, v/v, 1:0.1 molar ratio.

^e In water:methanol 1:1, v/v, 1:0.1 molar ratio.

^f In water (100°C), 1:0.1 molar ratio.

^g In water (100°C), 1:1 molar ratio.

^h 2-Furaldehyde; N.R. = no reaction.

The reactions can be carried out in anhydrous (CH₂Cl₂) or aqueous media, with stoichiometric or catalytic amounts of InBr₃. When the chosen solvent is CH₂Cl₂, we have observed that no major change in the yields occurred when the reactions were carried out adding 2–3% of H₂O to the solvent.

The experiments in anhydrous CH₂Cl₂ lead quickly to the corresponding dithioacetals. Maximum reactivity was observed for 1,2-ethanedithiol, which reacts in stoichiometric amounts with every carbonyl functionality, including the less reactive aromatic (entries 19 and 20) and aliphatic (entries 16 and 23) ketones, to produce the corresponding 1,3-dithiolanes in good yields.

Chemoselectivity towards aldehydes, in non-aqueous media, was observed during the preparation of acyclic dithioacetals. Benzene and propanethiol, either failed to react or produced low

Table 2
InBr₃-promoted competitive dithioacetalization of carbonyl compounds

Entry	Substrates	Molar ratio (substr. 1/ substr. 2/thiol/InBr ₃)	Time (min)	Product(s)	Products molar ratio	Total yield (%)
1	C ₆ H ₅ CHO + (CH ₂) ₅ CO	1:1:2:0.1 ^a	120	2b	–	77
2	(CH ₃) ₃ CCHO + (CH ₂) ₅ CO	1:1:2:0.1 ^a	20	2o	–	85
3	C ₆ H ₅ CH=CHCHO + C ₆ H ₅ CHO	1:1:2:0.1 ^a	20	2j+2c	3:2	96
4	C ₆ H ₅ CHO + CH ₃ CH ₂ CHO	1:1:2:0.1 ^a	20	2c+2k	50:3	86
5	CH ₃ CH ₂ CHO + (CH ₃) ₃ CCHO	1:1:2:0.1 ^a	20	2k+2o	25:3	88
6	(CH ₃) ₂ CHCHO + CH ₃ CH ₂ CHO	1:1:2:0.1 ^a	15	2n+2k	7:4	85
7	C ₆ H ₅ CH=CHCHO + (CH ₃) ₂ CHCHO	1:1:2:0.1 ^a	20	2j+2n	40:33	95
8	C ₆ H ₅ CHO + (CH ₃) ₂ CHCHO	1:1:2:0.1 ^b	16	2c+2n	27:2	37
9	C ₆ H ₅ CHO + (CH ₂) ₅ CO	1:1:2:0.1 ^b	18	2c+2r	3:1	39
10	C ₆ H ₅ CH=CHCHO + C ₆ H ₅ CHO	1:1:2:0.1 ^b	18	2j+2c	10:4	63

^a In anhydrous CH₂Cl₂.

^b In water.

yields with aromatic ($R^3 = C_6H_5$; entry 21; $R^3 = C_3H_7$; entry 22) and acyclic aliphatic ketones ($R^3 = C_6H_5$; entry 24; $R^3 = C_3H_7$; entries 25 and 26). A complete insight on the selectivity of the present method is demonstrated by competition experiments using structurally differing carbonyl compounds. An equimolar mixture of two carbonyl compounds was allowed to react with 2 molar equivalents of benzenethiol (or propanethiol). The results in Table 2 show that benzaldehyde (entry 1) and trimethylacetaldehyde (entry 2) were cleanly dithioacetalized in the presence of cyclohexanone. Competition between aliphatic aldehydes (entries 5 and 6) established the order of reactivity $(CH_3)_2CHCHO > CH_3CH_2CHO > (CH_3)_3CCHO$ when propanethiol is the reagent. Finally, it was demonstrated that cinnamaldehyde is preferentially dithioacetalized over benzaldehyde by benzenethiol (entry 3). The sum of these results demonstrates that the present procedure can be used in the selective conversion of aldehydes to the corresponding dithioacetals in the presence of ketones.

The action of a Lewis acid catalyst in dithioacetalization reactions in non-aqueous media has been ascribed to coordination of the carbonyl oxygen to the electron-acceptor site of the catalyst,⁸ thereby enhancing the electrophilicity of the carbonyl carbon. Also, the action of the Lewis acid as a water scavenger has been suggested as a factor; removal of water from the hemithioacetal leads to the dithioacetal final product and this, indeed, requires anhydrous conditions. Surprisingly, our results show that dithioacetalizations, intermediated by $InBr_3$, completely suppress the need for careful dehydration of solvents and starting materials, when carried out in CH_2Cl_2 solutions, and in fact proceed even in aqueous media, with catalytic amount of $InBr_3$. The scope of the method in water is not so wide as it is in CH_2Cl_2 . In fact, it proved to be efficient only for aromatic and α,β -unsaturated aldehydes where reasonable to good yields were obtained. There is no significant difference between reactivity of mono- and dithiols, since similar yields were obtained in both cases. Further, competition experiments revealed the impossibility of any carbonyl functionality be cleanly dithioacetalized in the presence of a second (Table 2, entries 8–10). We have attempted to improve the efficiency of this process by modifying some of the reaction conditions; nevertheless the use of excess of thiol, stoichiometric quantity of the catalyst, addition of a co-solvent to ensure solubility of reagents, and raise of reaction temperature did not show any significant improvement. Beside these restrictions, reasonable (Table 1, entries 5, 7 and 10) to good (entry 6) yields were obtained, suggesting some relevance for the methodology, particularly when consecutive experiments are needed. Table 3 describes the yields of ten consecutive dithioacetalization reaction, carried out in water, of 2,4,5-trimethoxy-benzaldehyde with benzenethiol to produce the dithioacetal **2f**. After the required time, the dithioacetal formed was extracted with dichloromethane, and fresh quantities of reagent and substrate were added to the aqueous phase. After ten runs, no appreciable decrease in the yield of reaction was observed ($\cong 3\%$), demonstrating that $InBr_3$ can, indeed, be reused as catalyst in dithioacetalization reactions in aqueous media.

Table 3
Consecutive dithioacetalization of 2,4,5-trimethoxy-benzaldehyde with benzenethiol

Run	1	2	3	4	5	6	7	8	9	10
Yield (%)	98	98	–	95	–	–	95	–	–	97

We conclude by pointing to the following advantages of the present methodology: high chemoselectivity towards aldehydes in non-aqueous media for acyclic dithioacetals; stoichiometric use of reagents; low concentration of catalyst; satisfactory yields and possibility to work under aqueous conditions with reutilization of the catalyst, especially with aromatic and α,β -unsaturated aldehydes.

Dithioacetalization of carbonyl compounds: general experimental procedure. (a) In CH_2Cl_2 : 1,2-Ethanedithiol (192 mg, 2.04 mmol) and anhydrous InBr_3 (71 mg, 0.20 mmol) were successively added to a stirred solution of the carbonyl compound (2.04 mmol, or 1.02 mmol for benzene and propane thiols) in CH_2Cl_2 (5 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred at 0°C for 5 minutes, warmed to room temperature for the required time (see Table 1), and then diluted with CH_2Cl_2 (20 mL). The organic phase was washed with a saturated solution of NaHCO_3 (20 mL), H_2O and dried (MgSO_4). After removal of volatiles, the product was purified by column chromatography. The purity of the product dithioacetals was checked by GC, and characterization involved NMR (^1H and ^{13}C) spectroscopy and mass spectrometry; in many cases spectral data were compared with reported values in the literature.^{9–15} The yields in Table 1 refer to isolated, analytically pure compounds.

(b) In water: Reagents and catalyst were added as above in oxygen-free water (5 mL) at room temperature and the mixture stirred for the required time (Table 1). 10 mL of NaOH (10%) was added and the dithioacetal extracted with CH_2Cl_2 (2×10 mL), dried (Na_2SO_4) and purified by column chromatography.

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