Entirely Solvent-Free Procedure for the Synthesis of Distillable 1,3-Dithianes Using Lithium Tetrafluoroborate as a Reusable Catalyst

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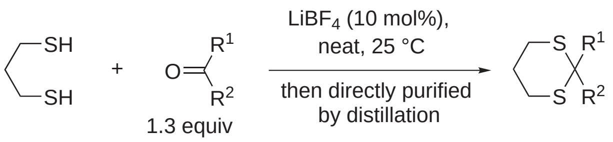
Abstract: Treatment of various types of aldehydes and ketones with 1,3-propanedithiol in the presence of a catalytic amount of lithium tetrafluoroborate at 25 °C under solvent-free conditions followed by direct purification by distillation of the resulting mixture affords the corresponding 1,3-dithianes in good to excellent yields. Chemoselective protection of keto aldehydes is also successfully achieved over the catalyst. The catalyst can be recovered and reused.

Key words: chemoselectivity, 1,3-dithiane, Lewis acids, lithium tetrafluoroborate, protecting groups

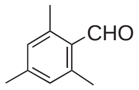
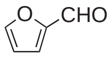
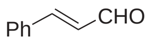
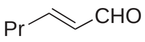
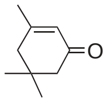
1,3-Dithianes have long been used as carbonyl protecting groups[1] and as masked acyl anions[2] or methylene functions[3] in organic synthesis.[4] They are generally prepared by protic[5] or Lewis acids,[6] or sometimes solid acids[7] catalyzed condensation of carbonyl compounds with 1,3-propanedithiol in various organic solvents. The solvent-free organic reactions are important not only for their simplicity, but also as green and sustainable procedures.[8] Moreover, in order to maximize these benefits, it is necessary to carry out product isolation, separation, and purification without using any organic solvent.[9] Lithium tetrafluoroborate ($LiBF_4$) has recently attracted attention as a mild and efficient Lewis acid catalyst due to its almost neutral property, ease of handling, and the thermal stability unlike lithium perchlorate.[10] In this paper we wish to disclose an entirely solvent-free procedure for the synthesis of distillable 1,3-dithianes from their corresponding carbonyl compounds and 1,3-propanedithiol catalyzed by $LiBF_4$ (Scheme 1).



Scheme 1

When a mixture of 1,3-propanedithiol, benzaldehyde (1.3 equiv), and a catalytic amount of $LiBF_4$ (10 mol%) was stirred at 25 °C for 1 h, 2-phenyl-1,3-dithiane was exothermically produced and isolated in 100% yield after direct distillation of the resulting almost odorless mixture (Table 1, entry 1).[11] The catalyst was quantitatively recovered in the distilling flask. Even with 2 mol% of $LiBF_4$, this thioacetalization proceeded quantitatively, but took longer to complete (entry 2). Substituted benzaldehydes possessing electron-donating and electron-withdrawing groups and acid-sensitive substrates like furfural[12] using the dithiol under such conditions provided the corre-

Table 1 $LiBF_4$-Catalyzed Formation of 1,3-Dithianes from Carbonyl Compounds under Solvent-Free Conditions[a]

Entry	$R^1R^2C=O$	Time (h)	Yield (%)[b]
1	C_6H_5CHO	1	100
2[c]	C_6H_5CHO	5	99
3	p-MeC_6H_4CHO	1	100
4	p-ClC_6H_4CHO	3	100
5	 CHO	3	100
6[d]	 O CHO	5	100
7	 Ph CHO	6	100[e]
8	 Pr CHO	5	85[f]
9	n-$C_7H_{15}CHO$	5	75
10	i-C_3H_7CHO	15	98
11	t-C_4H_9CHO	21	84
12	$(CH_2)_4C=O$	21	87
13	$(CH_2)_5C=O$	5	86
14	Bu(Me)C=O	21	74
15	 O	30	79
16	Ph(Me)C=O	24	74

[a] Reaction conditions: $R^1R^2C=O$ (6.5 mmol), 1,3-propanedithiol (5 mmol), $LiBF_4$ (0.5 mmol), 25 °C, unless otherwise noted.
[b] Isolated yields of pure products after distillation.
[c] $LiBF_4$ (0.1 mmol) was used.
[d] At 0 °C.
[e] Z/E = 0/100.
[f] Z/E = 11/89.

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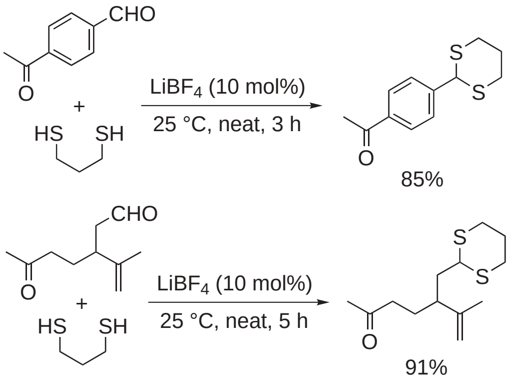
sponding 1,3-dithianes in excellent yields (entries 3–6). Futhermore, α,β-unsaturated and aliphatic aldehydes were cleanly and efficiently dithioacetalized at ambient temperatures in good yields (entries 7–11). Interestingly, sterically-hindered aldehydes such as mesitaldehyde and pivalaldehyde were also applicable (entries 5 and 11). Similarly, lithium tetrafluoroborate catalyzed the protection of different types of cyclic (entries 12 and 13), aliphatic (entry 14), α,β-unsaturated (entry 15), and aromatic ketones (entry 16) to afford the corresponding 1,3-dithianes in good yields,[13] although the time required for the completion of the reaction was found to be longer compared to aldehydes. It is noteworthy that the double bond at the 2,3-position of isophorone remained unaffected under the conditions (entry 15).[14]

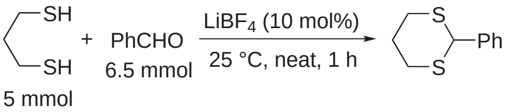
Because the conversion of aldehydes is faster than ketones, as shown in Table 1, the present method can be used for the chemoselective protection of aldehydes in the presence of ketone function.[15] For example, when 4-acetylbenzaldehyde was allowed to react with the dithiol under the usual conditions, only the aldehyde group reacted and the corresponding 1,3-dithiane was selectively obtained in 85% yield. GC analysis of the crude product showed the absence of any other by-products. Furthermore, the thioacetalization of 3-isopropenyl-6-oxoheptanal also exhibited splendid selectivity towards the formyl group (Scheme 2).



Scheme 2

Another advantage of this $LiBF_4$-catalyzed 1,3-dithiane synthesis is that the catalyst can be easily recovered quantitatively and reused. The activity of the recovered catalyst did not decrease even after the fourth use (Table 2).

Table 2 Recovery and Reuse of $LiBF_4$



Run	1	2	3	4
Yield (%)	100	98	97	98
Recovery of catalyst (%)	quant	quant	quant	quant

A typical procedure is as follows (Table 1, entry 1): To a mixture of benzaldehyde (690 mg, 6.5 mmol) and $LiBF_4$ (46.9 mg, 0.5 mmol) 1,3-propanedithiol (541 mg, 5.0 mmol) was added dropwise with stirring over ten minutes at 25 °C under N_2. After the reaction mixture was stirred at the same temperature for one hour (completion of the reaction was checked by GC), it was directly distillated by using a Kügelrohr apparatus at 0.5 mmHg with an oven temperature of 170–200 °C to give 2-phenyl-1,3-dithiane (982 mg, 100%) as a white solid. $LiBF_4$ remained in the distilling flask as a white solid (47.9 mg, 102%) and was used directly for the next reaction without any purification.

In conclusion, we have demonstrated the use of lithium tetrafluoroborate for the synthesis of 1,3-dithianes of a variety of carbonyl compounds under solvent-free conditions where the catalyst could be readily recovered and reused.[16,17] Moreover, the relatively slow reaction rate of ketones allows for the chemoselective protection of aldehydes in the presence of ketones. Works on other reactions catalyzed by $LiBF_4$ and related compounds are currently underway in our laboratory.

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(11) $LiBF_4$ was the best catalyst among the lithium salts tested under identical conditions: LiOTf (41%), LiCl (4%), $LiClO_4$ (36%), LiBr (16%), LiI (39%).

(12) For a review, see: Gandini, A. *Adv. Polym. Sci.* **1977**, *25*, 47.

(13) It is important to note that ketones were efficiently thioacetalized in our method, whereas $LiBF_4$/MeCN has been an ineffective reaction system, and the substrates remained intact after prolonged reaction times.[6f]

(14) For example, see: Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.

(15) Only a few methods are known in the literature for the chemoselective protection of aldehydes in the presence of ketones: ref. 6c and references cited therein.

(16) As far as we know, the present system is the first example for the synthesis of 1,3-dithianes under entirely solvent-free conditions, although our procedure is applicable for only distillable such compounds. Though 1,3-dithiane synthesis under solvent-free conditions has been reported in some cases, unfortunately, all of these used organic solvents in the work-up processes: (a) ref. 6d,e. (b) ref. 6i. (c) ref. 7b. (d) Laskar, D. D.; Prajapati, D.; Sandhu, J. S. *J. Chem. Res., Synop.* **2001**, 313. (e) Firouzabadi, H.; Iranpoor, N.; Kohmareh, G. *Synth. Commun.* **2003**, *33*, 167.

(17) 1,2-Ethanedithiol worked equally well under the same reaction conditions. For example, treatment of benzaldehyde (6.5 mmol) with 1,2-ethanedithiol (5 mmol) in the presence of $LiBF_4$ (0.5 mmol) at 25 °C for 1 h afforded 2-phenyl-1,3-dithiolane in 99% yield.