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Lithium Trifluoromethanesulfonate (LiOTf) as a Highly Efficient Catalyst for Chemoselective Dithioacetalization of Carbonyl Compounds under Neutral and Solvent-Free Conditions

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Abstract: Various types of carbonyl compound can be efficiently and chemoselectively converted to their corresponding dithioacetals in the presence of catalytic amounts of lithium triflate under solvent-free conditions. Due to the neutrality of the reaction medium, this method is especially useful for acid sensitive substrates. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Dithioacetals are among the most important and popular protective groups for carbonyl functions in organic synthesis.[1] In addition, they have been frequently used as precursors for acyl anions or masked methylene functions.[2] The preparation of dithioacetals has generally been achieved by the condensation of carbonyl compounds with a dithiol in the presence of protic acids, Lewis acids, or some supported and polymeric reagents.[1, 3] However, many of these methods for dithioacetalization require acidic and harsh reaction conditions, expensive reagents, or give poor selectivity when applied to a mixture of carbonyl compounds. Very recently, we have reported that lithium bromide (LiBr) under solvent-free conditions can be used as an efficient and neutral catalyst for highly chemoselective dithioacetalization of aromatic- and α,β-unsaturated aldehydes in the presence of other structurally different carbonyl compounds.[4] However, in the case of LiBr, ketones and saturated aldehydes remain intact even after prolonged reaction times, and LiBr is also a highly hygroscopic compound, which puts some restriction on its use. In continuation of our studies in this area, we wish to report that different types of carbonyl compounds under solvent-free conditions could be effectively thioacetalized in the presence of a catalytic amount of lithium triflate (Scheme, Table 1).[5] LiOTf has been shown previously to be a catalyst for the aminolysis of oxiranes[6] and glycosylation under neutral conditions.[7] In this report, dithioacetalization of benzaldehyde with 1,3-propanedithiol (1.1 eq) and monothiols (benzylmercaptan, thiophenol, and cyclohexanethiol, 2.1 eq) was achieved in the presence of LiOTf (5 mol%) under solvent-free conditions at 90 °C (Table 1, entries 1-4).

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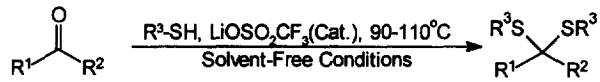


R^1 = Aryl, alkyl
R^2 = Alkyl or H
R^3 = Ph-, $PhCH_2$-, C_6H_{11}-, -$(CH_2)_3$-
Catalyst = 0.05-0.3 equivalent

Table 1. Dithioacetalization of Aldehydes with LiOTf under Solvent-Free Conditions.

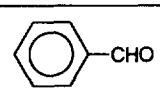
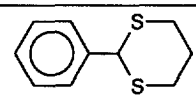
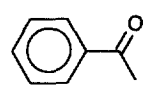
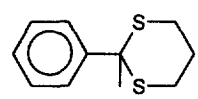
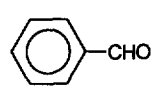
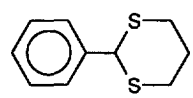
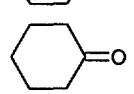
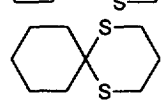
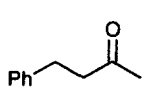
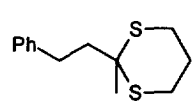
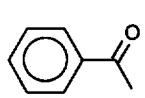
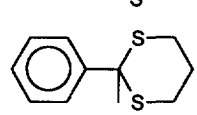
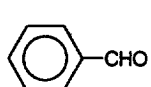
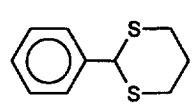
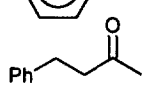
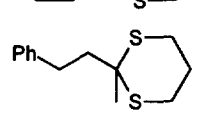
Entry	R^1	R^2	R^3	Subst./Thiol/ LiOTf Ratio	Time (min)	Yield[a, b] (%)
1	Ph	H	-$(CH_2)_3$-	1:1.1:0.05	5	99
2	Ph	H	Ph	1:2.1:0.05	70	90
3	Ph	H	$PhCH_2$	1:2.0:0.05	30	92
4	Ph	H	C_6H_{11}	1:2.1:0.05	50	99
5	4-MeC_6H_4	H	-$(CH_2)_3$-	1:1.1:0.05	5	98
6	4-ClC_6H_4	H	-$(CH_2)_3$-	1:1.1:0.05	10	96
7	4-$MeOC_6H_4$	H	-$(CH_2)_3$-	1:1.1:0.05	5	98
8	4-$O_2NC_6H_4$	H	-$(CH_2)_3$-	1:1.1:0.05	10	85
9	PhCH=CH-	H	-$(CH_2)_3$-	1:1.1:0.05	5	98
10	(*E/Z*)-Me_2C=CH$(CH_2)_2$C(Me)=CH	H	-$(CH_2)_2$-	1:1.1:0.05	50	97[c]
11	Me_2C=$CHCH_2CH_2CH(Me)CH_2$	H	-$(CH_2)_2$-	1:1.1:0.05	180	94[d,e]
12			-$(CH_2)_3$-	1:1.5:0.2	35	96
13	$PhCH_2CH_2$-	Me	-$(CH_2)_3$-	1:1.7:0.2	4.5h	95
14	Ph	Me	-$(CH_2)_3$-	1:1.7:0.3	19h	15[d]

a) Isolated yields. b) Reactions were performed at 90 °C for aldehydes, and at 110 °C for ketones. c) Oil, structural assignment is based on spectroscopic data. Ms (20eV): m/z (relative intensity) = 228 (M, 0.6), 200(21.2), 167 (8.1), 123 (12.0), 99 (53.4), 69 (100); ^{1}H NMR ($CDCl_3$/TMS): δ = 5.21-5.25 (m, 2H), 4.95 (m, 1H), 3.07-3.20 (m, 4H), 1.87-1.98 (m, 4H), 1.48-1.87 (m, 9H). d) GC yield. e) NMR yield

Various types of substituted benzaldehyde were also efficiently converted to the corresponding 1,3-dithianes in a similar manner (Table 1, entries 5-8). In contrast to our work with LiBr[4] under these conditions both saturated- and α,β-unsaturated aldehydes were protected in good to excellent yields (Table 1, entries 9-11). The efficient dithioacetalization of saturated cyclic and acyclic ketones such as cyclohexanone and benzyl acetone by the described method clearly shows the strong catalytic activity of LiOTf compared with LiBr [4] (Table 1 entries 12, 13). To the best of our knowledge the presented method is the first example of efficient dithioacetalization of aliphatic ketones under neutral reaction conditions.[8] However, under similar reaction conditions dithioacetalization of acetophenone was not successful and gave only 15% of the corresponding

dithiane after 19h at 110 °C. In order to show the selectivity of the described method we have performed several competitive dithioacetalization reactions, the results of which are shown in Table 2. Therefore, the described method shows clearly that LiOTf could be considered as a competitive substitute for the potentially explosive $LiClO_4$, [9] and highly hygroscopic LiBr.[4]

Table 2. Selective Dithioacetalization of Carbonyl Compounds with LiOTf under Solvent-Free Conditions.

Entry	Substrate	Product	Subst./Thiol/ LiOTf Ratio	Time (min)	Product ratio[a] (%)
1			1:1:1.1:0.05	5	100
					0
2			1:1:1.1:0.05	5	96
					4
3			1:1:1.7:0.2	4.5h	84
					4
4			1:1:1.1:0.05	5	98
					2

a) Product ratios based on NMR.

Due to the neutrality of the reaction medium in this method its application is useful for acid sensitive substrates. In addition, the catalytic nature of the system, easy work-up, high rate of reaction, and high chemoselectivity are worthy of mention as advantages of the method. Further investigations into potential new applications of LiOTf as a neutral Lewis acid in organic synthesis are ongoing in our laboratories.

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(5) *A typical procedure is as follows:* To a stirred mixture of the carbonyl compound (10 mmol) and dithiol (11-17 mmol) or monothiol (21 mmol), anhydrous LiOTf (0.5-3 mmol) was added. The mixture was heated at 90 °C (or 110 °C for ketones) while stirring was continued, and the progress of the reaction was followed by TLC. After completion of the reaction, $CHCl_3$ (100 mL) was added and the mixture was washed successively with 10% NaOH solution (2 × 25 mL), brine (15 mL), and water (15 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave almost pure product. Further purification was achieved by column chromatography on silica gel or recrystallization from an appropriate solvent to give the desired product(s) in good to excellent yield(s) (Table 1). Most of the products are known and gave satisfactory physical data compared with those of authentic samples.

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