Lithium Bromide-Catalyzed Highly Chemoselective and Efficient Dithioacetalization of α,β-Unsaturated and Aromatic Aldehydes under Solvent-Free Conditions

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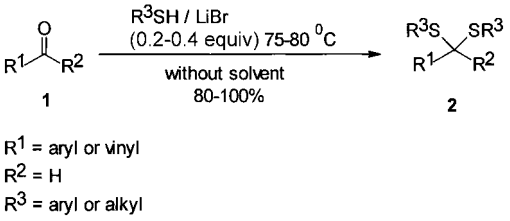
Abstract: Chemoselective dithioacetalization of aromatic- and α,β- unsaturated aldehydes in the presence of other structurally different aldehydes and ketones was achieved efficiently in the presence of catalytic amounts of LiBr under solvent-free conditions. Due to the neutral reaction conditions, this method is compatible with acid sensitive substrates.

Key words: dithioacetalization, thioacetals, lithium bromide, solvent-free conditions, 1,3-dithianes, 1,3-dithiolanes



Scheme

The protection of carbonyl groups as dithioacetals[1] (1,3-dithianes, 1,3-dithiolanes, or acyclic dithioacetals) is a frequently used synthetic technique for the preparation of many organic compounds including multifunctional complex molecules. This popularity of dithioacetals is due in part to their stability under usual acidic or basic conditions and also because of their behavior as masked acyl anions[2–4] or masked methylene functions.[5] In this regard, there have been continued improvements in the methods of preparation of dithioacetals. In general, these compounds are prepared by protic or Lewis acid-catalyzed condensation of carbonyl compounds with thiols.[1] Several types of Lewis acid catalysts were introduced previously for this purpose such as, $ZnCl_2$,[6] $LnCl_3$,[7] anhydrous $FeCl_3/SiO_2$,[8] $AlCl_3$,[9] $ZrCl_4/SiO_2$,[10] $TeCl_4$,[11] $SnCl_2{\cdot}2H_2O$,[12] $SiCl_4$,[13] $MgI_2{\cdot}Et_2O$,[14] etc.[1] Many of these methods require harsh reaction conditions, expensive reagents, or give poor selectivity when applied to a mixture of aldehydes or aldehydes and ketones. Another approach to this problem, i.e. dithioacetalization of aldehydes and ketones under neutral conditions has been reported very recently by means of 5 M ethereal solution of $LiClO_4$.[15] However, this method works much better with acetals than with the corresponding aldehydes and $LiClO_4$ is rather expensive. In this report we wish to introduce lithium bromide as an efficient catalyst for highly chemoselective dithioacetalizations of aromatic and α,β-unsaturated aldehydes in the presence of other, structurally different aldehydes and ketones under solvent-free conditions (Scheme).

The use of LiBr as chemical reagent has been reported previously for acylation of ferrocene,[16] transesterification of peptide esters and cleavage of resin-bound peptides,[17] and the Knoevenagel condensation of aldehydes with malononitrile in the solid state.[18] In this report, dithioacetalization of benzaldehyde with dithiols (1,2-ethanedithiol and 1,3-propanedithiol, 1.1 equiv) and monothiols (benzyl mercaptane, thiophenol, and cyclohexanethiol, 2.0–2.1 equiv) was achieved efficiently by heating their solvent-free mixture with the substrate and 0.25–0.4 equivalents of LiBr at 75–80 °C[19] (Table 1, **2a–e**). The efficiency of the method can be clearly visualized by the condensation of benzaldehyde with cyclohexanethiol in almost quantitative yield (Table 1, **2e**). Several types of substituted benzaldehydes with electron-donating and electron-withdrawing groups and 1-naphthaldehyde can be also protected in a similar manner (Table 1, **2f–k**). The present thioacetalization procedure is also applicable for cinnamaldehyde and citral (Table 1, **2l–p**). It was observed that under similar reaction conditions, saturated aldehydes (Table 1, entries 18, 19), aromatic and aliphatic ketones (Table 1, entries 20, 21), as well as acetals (Table 1, entry 2) remained intact even after several hours. It should be mentioned that this method is not suitable for dithioacetalization in solvents such as THF, CH_2Cl_2 and the substrates were re-isolated.

The selectivity of the present method is demonstrated by competition experiments using structurally differing carbonyl compounds. The results are shown in Table 2. Benzaldehyde and cinnamaldehyde both were cleanly thioacetalized quantitatively in the presence of acetophenone, butyraldehyde and cyclohexanone. As proposed for the ethereal $LiClO_4$ method,[15] we also believe that Li^+ under solvent-free conditions activates the carbonyl group for the initial addition of a thiol molecule. This is followed by the dehydration of the intermediate hemithioacetal, which is attacked by a second thiol moiety. Due to the neutrality of the reaction medium, this method is very useful for substrates with a high degree of acid sensitivity.

In conclusion, the striking selectivity and easy workup of the presented procedure can be utilized in the selective conversion of aromatic and α,β-unsaturated aldehydes to

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Table 1 Dithioacetalization of Aldehydes with LiBr Under Non-Solvent Conditions

Entry	Product	R^1	R^2	R^3	Subst./Thiol/LiBr Ratio	Time (min)	Yield (%)	mp (°C) or bp (°C)/Torr	
								found	reported
1	**2a**	Ph	H	$-(CH_2)_3-$	1:1.1:0.25	15	99	71–72	72[23]
2	**2a**	Ph	H	$-(CH_2)_3-$	1:1.1:0.3	120	30[a]	–	
3	**2b**	Ph	H	$-(CH_2)_2-$	1:1.1:0.3	15	93	166/20	145/1[20]
4	**2c**	Ph	H	Ph	1:2.1:0.3	20	90	51–52	51–52[15]
5	**2d**	Ph	H	$PhCH_2$	1:2.0:0.3	20	92	59–60	60–61[20]
6	**2e**	Ph	H	*c*-C_6H_{11}	1:2.1:0.4	20	99	202/1	200/1[20]
7	**2f**	4-MeC_6H_4	H	$-(CH_2)_3-$	1:1.1:0.25	15	94	91–92	91.5–92.5[21]
8	**2g**	3-MeC_6H_4	H	$-(CH_2)_3-$	1:1.1:0.25	30	94	65–66	66.5–67.0[21]
9	**2h**	3-ClC_6H_4	H	$-(CH_2)_3-$	1:1.1:0.25	20	90	62–63	62.5–63.5[23]
10	**2i**	4-ClC_6H_4	H	$-(CH_2)_3-$	1:1.1:0.25	20	97	85–86	85.5–86.5[23]
11	**2j**	4-$MeOC_6H_4$	H	$-(CH_2)_3-$	1:1.1:0.25	15	87	115–116	115–116[22]
12	**2k**	1-naphthyl	H	$-(CH_2)_3-$	1:1.1:0.4	35	80	144–145	145–146[23]
13	**2l**	PhCH=CH	H	Ph	1:2.1:0.3	20	89	63–63.5	64[15]
14	**2m**	PhCH=CH	H	$PhCH_2$	1:2.1:0.3	20	95	–[b]	–[15]
15	**2n**	PhCH=CH	H	$-(CH_2)_2-$	1:1.1:0.3	15	99	57–58	58–59[15]
16	**2o**	PhCH=CH	H	$-(CH_2)_3-$	1:1.1:0.4	20	95	62–63	63–64[11]
17	**2p**	(*E*/*Z*)-Me_2C=$CHCH_2CH_2C(Me)$=CH	H	$-(CH_2)_2-$	1:1.1:0.4	50	98	–[b]	–
18	**2q**	Me_2C=$CHCH_2CH_2CH(Me)CH_2$	H	$-(CH_2)_2-$	1:1.1:0.4	180	20[c]	–	
19	**2r**	Pr	H	$-(CH_2)_2-$	1:1.1:0.4	180	–[d]	–	–
20	**2s**	Ph	Me	$-(CH_2)_3-$	1:1.1:0.4	180	–[d]	–	–
21	**2t**	$PhCH_2CH_2$	Me	$-(CH_2)_3-$	1:1.1:0.4	180	–[d]	–	–

[a] Benzaldehyde dimethyl acetals were used.
[b] Oil, Structural assignment is based on spectroscopic data. **2p:** MS (20 eV): *m/z* (relative intensity) = 228 (M, 0.6), 200 (21.20), 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). **2m:** MS (20 eV): *m/z* (relative intensity) = 362 (0.1), 239 (41.9), 147 (29.9), 115 (100), 91 (84.6), 103 (1.0), 77 (2.5). ^{1}H NMR ($CDCl_3$/TMS): δ = 7.2 (m, 15 H), 6.2 (d, 1 H, *J* = 14 Hz), 5.9 (dd, 1 H, *J* = 14 Hz, 6.5 Hz), 4.6 (d, 1 H, 6.5 Hz), 3.6 (m, 4 H)
[c] GC yield.
[d] No reaction.

Table 2 Selective Dithioacetalization of Aromatic- and α,β-Unsaturated Aldehydes vs. Other Carbonyl Compounds with LiBr as Catalyst

Substrates	Subst. 1/Subst. 2/Thiol/LiBr Ratio	Time (min)	Product	Yield[a] (%)
PhCHO			**2b**	100
+	1:1:1.1:0.25	15		
$PhCOCH_3$			**2s**	0
PhCH=CHCHO			**2n**	100
+	1:1:1.1:0.25	15		
$PhCOCH_3$			**2s**	0
PhCHO			**2b**	100
+	1:1:1.1:0.25	15		
PrCHO			**2r**	0
PhCHO			**2b**	29
+	1:1:1.1:0.25	15		
PhCH=CHCHO			**2n**	71
PhCHO			**2b**	100
+	1:1:1.1:0.25	15		
cyclohexanone			–	0

[a] The yields were determined by GC and ^{1}H NMR spectroscopy.

their corresponding dithioacetals in the presence of other carbonyl moieties under very mild conditions.

All yields refer to isolated products unless otherwise stated. The products were purified by column chromatography and the purity determination of the products were accomplished by GC on a Shimadzu model GC-8A instrument or by TLC on Silica gel polygram SIL G/UV254 plates. Mass spectra were run on a Shimadzu GC MS-QP 1000EX at 20 eV. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. The NMR spectra were recorded on a Hitachi R-2413 60 MHz or Bruker Avance DPX 250 MHz spectrometer.

Dithioacetalization of Aldehydes; General Procedure

To a stirred mixture of the carbonyl compound **1** (10 mmol) and dithiol (11 mmol) or monothiol (20–21 mmol) was added anhyd LiBr (2.5–4.0 mmol). The mixture was heated to 75–80 °C and the progress of the reaction was followed by TLC. After completion of the reaction (15–50 min.), CH_2Cl_2 (100 mL) was added and the mixture was washed successively with 10% NaOH solution (2 × 25 mL), brine (15 mL), and H_2O (15 mL). The organic layer was separated and dried (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 appropriate solvent to give the desired product(s) in good to excellent yield(s) (Table 1).

Selective Dithioacetalization of Benzaldehyde vs. Acetophenone with 1,2-Ethanedithiol; Typical Procedure

To a stirred mixture of benzaldehyde (530 mg, 5 mmol), acetophenone (601 mg, 5 mmol) and 1,2-ethanedithiol (518 mg, 5.5 mmol) was added anhyd LiBr (130 mg, 1.5 mmol). The mixture was heated to 75–80 °C in 15 min, CH_2Cl_2 (70 mL) was added and the mixture was washed successively with 10% NaOH solution (2 × 15 mL), brine (10 mL), and water (10 mL). The organic layer was separated and dried (Na_2SO_4) and concentrated under reduced pressure. The NMR spectrum of the mixture was similar to the NMR spectrum of a 1:1 authentic mixture of 2-phenyl-1,3-dithiolane and acetophenone.

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References

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991.
(2) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl*. **1965**, *4*, 1075, 1077; *Angew. Chem.* **1965**, *77*, 1134, 1135.
(3) Seebach, D. *Angew. Chem., Int. Ed. Engl*. **1969**, *8*, 639; *Angew. Chem*. **1969**, *81*, 690.
(4) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357.
(5) Pettit, G. R.; Van Tamelen, E. E. *Org. React*. **1962**, *12*, 356.
(6) Truce, W. E.; Roberts, F. E. *J. Org. Chem.* **1963**, *28*, 961.
(7) Galaschelli, L.; Vidari, G. *Tetrahedron Lett*. **1990**, *31*, 581; Hauptmann, H.; Moura Campos, M. *J. Am. Chem. Soc*. **1950**, *72*, 1405;
Seebach, D. Kolb, M. *Chem. Ind. (London)* **1974**, 687.
(8) Patney, H. K. *Tetrahedron Lett*. **1991**, *32*, 2259.
(9) Ong, B. S. *Tetrahedron Lett.* **1980**, *21*, 4225.
(10) Patney, H. K.; Margan, S. *Tetrahedron Lett*. **1996**, *37,* 4621.
(11) Tani, H.; Masumoto, K.; Inamasu, T. *Tetrahedron Lett*. **1991**, *32*, 2039.
(12) Das, N. B.; Nayak, A.; Sharma, R. P. *J. Chem. Res. (Synop)* **1993**, 242.
(13) Ku, B.; Oh, D. Y. *Synth. Commun.* **1989**, *19*, 433.
(14) Chowdhury, P. K. *J. Chem. Res. (Synop)* **1993**, 124.
(15) Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1994**, *52*, 4665.
(16) Pushin, A. N.; Tkachenko, S. E.; Martynov, I. V. *Dokl. Akad. Nauk SSR,* **1988**, *299*, 154; *Chem. Abstr*. **1989**, *110*, 115052.
(17) Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta.* **1991**, *74*, 1102.
(18) Prajapati, D.; Lekhok, K. C.; Sandhu, J. S.; Ghosh, A. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 959.
(19) For a review on the solid state reactions see: Toda, F. *Synlett* **1993**, 303.
(20) Kakimoto, M.; Seri, T.; Imai, Y. *Synthesis* **1987**, 164.
(21) Semmelhack, M. F.; Hall, H. T.; Farina, R.; Yoshifuji, M.; Clarck, G.; Bargar, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 3535.
(22) Golding, B. T.; Ioannou, P. V.; Eckhard, I. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 774.
(23) Kruse, C. G.; Wijsman, A.; Van der Gen, A. *J. Org. Chem.* **1979**, 44, 1847.

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