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# Molten Salt as a Green Reaction Medium: Efficient and Chemoselective Dithioacetalization and Oxathioacetalization of Aldehydes Mediated by Molten Tetrabutylammonium Bromide

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Tetrabutylammonium bromide in the molten state has been demonstrated to be a very efficient catalyst and reaction medium for the highly chemoselective dithioacetalization and oxathioacetalization of aldehydes. The tetrabutylammonium bromide is recycled for subsequent reactions.

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The protection of a carbonyl group is often required in a multi-step organic synthesis to avoid nucleophilic attack at the carbonyl centre. Among various carbonyl protecting groups, dithioacetals and oxathioacetals are preferred for many substrates because of their inherent stability under both acidic and basic conditions.<sup>[1]</sup> On the other hand, both dithioacetals<sup>[2a,b]</sup> and oxathioacetals<sup>[2c,d]</sup> have been used successfully as acyl anion equivalents in C-C bond forming reactions. In addition, dithioacetals are also used as intermediates in the conversion of a carbonyl group into a hydrocarbon derivative.<sup>[3]</sup> Thus, synthesis of these compounds is of much importance. In a classical procedure, dithioacetals are prepared by the reaction of a carbonyl compound with a dithiol in the presence of a strong protic acid such as HCl<sup>[4]</sup> or a Lewis acid like BF<sub>3</sub> · OEt<sub>2</sub>.<sup>[5]</sup> However, these procedures using strong acids may not be safe for acid-sensitive groups. Thus, several other, relatively mild, catalysts such as Nafion-H,<sup>[6]</sup> AlCl<sub>3</sub>,<sup>[7]</sup> TiCl<sub>4</sub>,<sup>[8]</sup> LiBF<sub>4</sub>,<sup>[9]</sup> magnesium and zinc triflates,<sup>[10]</sup> Sc(OTf)<sub>3</sub>,<sup>[11]</sup> Cu(OTf)<sub>2</sub>–SiO<sub>2</sub>,<sup>[12]</sup> ZrCl<sub>4</sub>–SiO<sub>2</sub>,<sup>[13]</sup> TaCl<sub>3</sub>–SiO<sub>2</sub>,<sup>[14]</sup> InCl<sub>3</sub>,<sup>[15]</sup> Amberlyst,<sup>[16]</sup> I<sub>2</sub>,<sup>[17]</sup> NiCl<sub>2</sub>,<sup>[18]</sup> and TMSOTf<sup>[19]</sup> have been employed in a variety of organic solvents and also under solvent-free conditions. On the other hand, several procedures using HCl,<sup>[20]</sup> HClO<sub>4</sub>,<sup>[21]</sup> p-TsOH,<sup>[22]</sup> BF<sub>3</sub>-OEt<sub>2</sub>,<sup>[23]</sup> Bu<sub>4</sub>NBr<sub>3</sub>,<sup>[24]</sup> ZrCl<sub>4</sub>,<sup>[25]</sup> ZnCl<sub>2</sub>-Na<sub>2</sub>SO<sub>4</sub>,<sup>[26]</sup> TMSOTf,<sup>[27]</sup> and Amberlyst<sup>[28]</sup> as catalyst have been reported for oxathioacetalization. But most of these metal halides and triflates are highly expensive, some are toxic, and the solvents like chlorinated hydrocarbons used in these processes are not ecologically friendly. Hence, a procedure using an efficient, inexpensive, and non-toxic catalyst is considered to be of much practical utility.

As a part of our program to develop efficient and green synthetic procedures,<sup>[29]</sup> we have discovered that a cheap,



## Scheme 1.

commercially available, non-toxic inorganic salt, tetrabutylammonium bromide, can be used in the molten state as a catalyst as well as reaction medium for the dithioacetalization and oxathioacetalization of aldehydes (Scheme 1).

The experimental procedure is very simple. A mixture of the aldehyde and ethane/propane dithiol (or 2-mercaptoethanol) was added to molten tetrabutylammonium bromide (mp 102–103°C), and the reaction mixture was stirred at 90– 100°C until completion of the reaction (TLC). The product dithioacetal or oxathioacetal was isolated by direct distillation under reduced pressure from the reaction mixture. The products are of high purity and are identified by their IR, and <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data. The tetrabutylammonium bromide remaining in the reaction flask was washed with hexane (2 × 0.5 mL), dried under vacuum, and recycled for subsequent uses without any loss of efficiency.

A wide range of structurally diverse aldehydes, including aromatic, aliphatic, and heterocyclic ones, underwent dithioacetalization and oxathioacetalization by this procedure to provide the corresponding dithiolanes or oxathiolanes. The results are summarized in Table 1.<sup>[30–34]</sup> A variety of substitutuents such as Cl, NO<sub>2</sub>, OMe, OAc, and *O*-allyl on the aromatic ring of the aldehydes are compatible with this reagent. The conjugated aldehydes (entries 11, 12) are converted into the corresponding dithioacetals without any damage to the double bond. The clean thioacetalization of

Table 1. Dithioacetalization and oxathioacetylization of aldehydes catalyzed by molten tetrabutylammonium bromide

Entry	R	Dithiol/mercaptol	Time [h]	Product	Yield [%] <sup>A</sup>	Ref.
1	PhCHO	HS(CH <sub>2</sub> ) <sub>2</sub> SH	7	PhCH <sup>S</sup>	84	[18]
2	PhCHO	HS(CH <sub>2</sub> ) <sub>3</sub> SH	7.5		88	[18]
3	p-ClC <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>3</sub> SH	7.2	<i>p</i> -CIC <sub>6</sub> H₄CH <sup>S</sup> S−S	83	[31]
4	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>2</sub> OH	7.3	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H₄CH < O S	81	[32]
5	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>2</sub> SH	7.5	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sup>S</sup> S	90	[18]
6	p-OMeC <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>2</sub> OH	8	<i>p</i> -OMeC <sub>6</sub> H₄CH <sup><o< sup="">S</o<></sup>	76	[32]
7	p-OMeC <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>3</sub> SH	7.8	<i>p</i> -OMeC <sub>6</sub> H₄CH <s── S──</s── 	78	[18]
8	<i>p</i> -OAcC <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>2</sub> OH	8	<i>p</i> -OAcC <sub>6</sub> H₄CH <sup>O</sup> _S_	74	[33]
9	<i>p</i> -CH <sub>2</sub> =CHCH <sub>2</sub> OC <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>2</sub> SH	8	CH <s CH<s< td=""><td>80</td><td>[30]</td></s<></s 	80	[30]
10	СНО	HS(CH <sub>2</sub> ) <sub>2</sub> SH	8.2	CH <s 0 0</s 	78	[30]
11	Ph	HS(CH <sub>2</sub> ) <sub>2</sub> OH	6.5	Ph CH S	90	[32]
12	CHO	HS(CH <sub>2</sub> ) <sub>2</sub> SH	6.8	CH S	91	[34]
13	Сно	HS(CH <sub>2</sub> ) <sub>2</sub> SH	8	CH <s CH<s< td=""><td>78</td><td>[34]</td></s<></s 	78	[34]
14	СНО	HS(CH <sub>2</sub> ) <sub>2</sub> SH	8.2	CH <s S</s 	75	
15	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> CHO	HS(CH <sub>2</sub> ) <sub>2</sub> SH	3.7	$CH_3(CH_2)_8CH < S $	91	[18]
16	PhCHO + PhCOCH <sub>3</sub>	HS(CH <sub>2</sub> ) <sub>2</sub> SH	12	PhCH <s< td=""><td>81</td><td>[18]</td></s<>	81	[18]
17	decanol + cyclohexanone	HS(CH <sub>2</sub> ) <sub>2</sub> SH	14	$CH_3(CH_2)_8CH < S $	79	[18]
18	<i>p</i> -MeCOC <sub>6</sub> H <sub>4</sub> CHO	HS(CH <sub>2</sub> ) <sub>2</sub> SH	8	CH <s COCH3</s 	76	[15]

<sup>A</sup> Yields refer to pure isolated products characterized by spectroscopic data (IR and <sup>1</sup>H and <sup>13</sup>C NMR).

acid-sensitive molecules [furfural (entry 13) and thiophene-2-carboxaldehyde (entry 14)] shows the advantage of this semi-neutral reaction medium. It has been found that ketones remained completely inert under the reaction conditions, making this procedure chemoselective for aldehydes. Thus, when an equimolar mixture of benzaldehyde and acetophenone was subjected to thioacetalization under this procedure, the benzaldehyde was converted into the corresponding 1,3ditholane derivative, leaving acetophenone intact (entry 16). This selective reaction of aldehydes over ketones was also observed for a mixture of decanal and cyclohexanone (entry 17) and 4-acetylbenzaldehyde (entry 18).

The reactions in molten tetrabutylammonium bromide (TBAB) are, in general, very clean and high yielding. When a mixture of aldehyde and ethane dithiol (or 2-mercaptoethanol) was refluxed in THF in the absence of TBAB, no reaction was observed; in addition, no conversion occurred when solid TBAB in refluxing THF was used. Presumably, molten tetrabutylammonium bromide acts as a ready source of the bromide ion, which is hydrogen-bonding to –SH and increasing the nucleophilicity of the S atom. This makes the thiolate anion a better nucleophile and leads to more efficient thioacetalization.

In conclusion, the present procedure using molten tetrabutylammonium bromide as a reaction medium provides an efficient method for the dithioacetalization and oxathioacetalization of aldehydes. The significant improvements offered by this methodology are as follows: (a) simple operation, (b) almost neutral (pH 6-7) reaction medium, (c) requirement of no additional catalyst and conventional organic solvent, (d) excellent chemoselectivity of aldehyde over ketone. (e) recyclability of TBAB and cost efficiency (no consumption of catalyst or organic solvent during the reaction, isolation of the product by direct distillation which avoids the need for chromatography, and no generation of waste), and (f) environmentally friendly reaction condition, which avoids toxic catalysts and hazardous organic solvents. Moreover, this work demonstrates the potential of molten tetrabutylammonium bromide as a catalyst as well as a reaction medium, and broadens the scope for further useful applications in green synthesis.

#### Experimental

## General

NMR spectra were recorded on a Bruker DPX 300 instrument at 300 MHz for <sup>1</sup>H and at 75 MHz for <sup>13</sup>C. IR spectra were measured on an FT 8300 Shimadzu spectrometer. Melting points were determined on a glass disk with an electrical bath (Reichert, Austria), and are uncorrected. Elemental analyses were done on a Perkin–Elmer autoAnalyzer 2400 II. Tetrabutylammonium bromide (Lancaster, UK) was used as provided. All aldehydes, dithiols, and 2-mercaptoethanol were distilled before reaction.

#### *Representative Procedure for Dithioacetalization of Benzaldehyde (Entry 1)*

A mixture of benzaldehyde (318 mg, 3.0 mmol) and ethane-1,2-dithiol (376 mg, 4.0 mmol) was added to molten (mp  $102-103^{\circ}$ C) tetrabutylammonium bromide (290 mg, 30 mol %), and the homogenous mixture was stirred at 90–100°C for 7 h (monitored by TLC). The product was then distilled from the reaction mixture under reduced pressure as a colourless liquid (460 mg, 84%) whose spectroscopic data (IR and <sup>1</sup>H and <sup>13</sup>C NMR) are in good agreement with those reported.<sup>[18]</sup>

This procedure was followed for the dithioacetalization and oxathioacetalization of the aldehydes and ketones listed in Table 1. All the products except one (entry 14) are known compounds, and are easily identified by comparison of their spectroscopic data with those reported (these data are provided as Accessory Material). The characterization data for the new dithioacetal (entry 14) are provided below.

#### 2-Thiophenyl-1,3-dithiolane (Entry 14)

This dithioacetal was obtained as a pale yellow liquid (Found: C 44.5, H 4.2.  $C_7H_8S_3$  requires C 44.6, H 4.3%).  $\nu_{max}/cm^{-1}$  2920, 1412, 1269.  $\delta_H$  (CDCl<sub>3</sub>) 3.01–3.52 (m, 4H), 5.94 (s, 1H), 6.94–6.96 (m, 1H), 7.07–7.11 (m, 1H), 7.22–7.28 (m, 1H).  $\delta_C$  (CDCl<sub>3</sub>) 39.9 (2C), 50.7, 125.5, 125.6, 126.5, 146.9.

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## **Accessory Material**

IR and <sup>1</sup>H and <sup>13</sup>C NMR data for entries 1–15 and 18 (listed in Table 1) are available from the author or, until June 2009, the *Australian Journal of Chemistry*.

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