Eco-friendly and Highly Chemoselective 1,3-Oxathio- and 1,3-Dithioacetalization of Aldehydes Using Ionic Liquids

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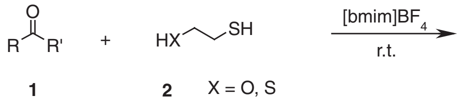
(Received March 25, 2003; CL-030256)

Room temperature ionic liquids have been employed for the first time as novel and recyclable reaction media for the chemoselective conversion of aldehydes into their corresponding 1,3-oxathio- and dithioacetal derivatives in excellent yields under mild and neutral conditions. A wide range of functional and protecting groups such as TBDMS, PMB, THP, MOM, benzyl, propargyl ethers, acetonides, carbamates and esters are survived under these reaction conditions. The recovered activated ionic liquids can be recycled for four to five subsequent runs with consistency in activity.

Protective groups play an important role in multi-step synthesis of complex natural products; hence there are always demands for selective reagents.[1] 1,3-Doxolane group is the most widely used carbonyl protecting groups in the course of total synthesis of biologically active molecules.[2] Since the introduction of 1,3-dithianes as nucleophilic acylating agents by Corey and Seebach,[3] dithioacetals have become widely used tools for carbon–carbon bond formation. Consequently, varoius methods have been developed for the preparation of thioacetals from carbonyl compounds.[4–8] Acid catalysts such as protic acids,[5] Lewis acids,[6] solid acids[7] and metal triflates[8] are employed to promote the reaction. Despite their potential utility in the protection of simple carbonyl compounds, many of these methods have limitations when applied to complex molecules containing acid-sensitive functionalities and acid labile protecting groups.

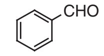
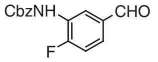
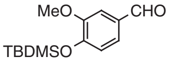
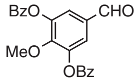
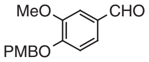
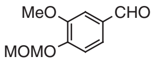
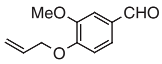
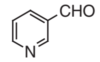
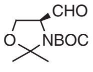
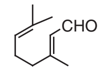
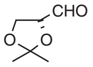
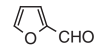
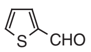
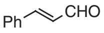
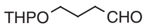
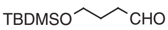
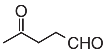
In recent times, ionic liquids have emerged as a set of green solvents with unique properties such as good solvating ability, tunable polarity, wide liquid range, high thermal stability, negligible vapor pressure and ease of recycle.[9] They are referred to as 'designer solvents' as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain attached to an organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering to the needs of any particular process. The use of room temperature ionic liquids has made significant advancement in the development of clean chemical processes in organic synthesis targeted to avoid or at least minimize the use of toxic or waste generating reagents or solvents.[10]

In view of the emerging importance of ionic liquids as green solvents, we wish to report the use of ionic liquids as novel and recyclable reaction media for the conversion of aldehydes to 1,3-dithio- and oxathioacetals under mild and neutral conditions (Scheme 1). Accordingly, treatment of benzaldehyde with 2-mercaptoethanol in 1-butyl-3-methylimidazolium tetraflouroborate ([bmim]BF_4) ionic liquid for 2.5 h afforded the corresponding 1,3-oxathiolane derivative in 92% yield. A variety of aromatic and aliphatic aldehydes were rapidly converted into their corresponding 1,3-oxathio- and 1,3-dithiolane derivatives in excellent yields by using this procedure without the need of any acid catalyst. The reactions proceeded readily at room temperature with high chemoselectivity. The reaction conditions are mild enough not to induce isomerization of C–C multiple bonds during thioacetalization of aldehydes bearing allylic and propargylic systems and are selective enough to the protection of aldehyde functionality in the presence of other acid sensitive protecting groups. These results encouraged us to extend this process for the preparation of dithioacetals from aldehydes and ethanethiol. Interestingly, thioethanol was also smoothly reacted with aldehydes to produce the corresponding dithioacetals in excellent yields (Table 1). This method is highly chemoselective to protect aldehydes as thioacetals in the presence of ketones in multi-functional compounds. The ketones such as acetophenone, benzophenone, 3-pentanone and 2-heptanone did not react with thiols under these reaction conditions. The chemoselectivity of the present method was further illustrated by using ketoaldehyde (Entry 17). It should be noted that the aldehydes bearing α-stereogenic centers gave thioacetals with complete retention of the original configuration (Entries 9 and 11). When compared to Lewis acid-promoted thioacetylization procedures, enhanced reaction rates, improved yields especially with α, β-unsaturated aldehydes and high functional group compatibility are obtained by ionic liquids. Another advantage of the use of ionic liquids is that these ionic liquids can be easily recovered after completion of the reaction and can be reused in subsequent reactions. Since the products were partially soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the ionic liquid was thoroughly washed with ether and activated at 80 °C under reduced pressure and recycled in four to five subsequent runs without any loss of activity. The products obtained were of the same purity as in the first run and no decrease in yields was observed in runs carried out using recovered ionic liquid after activation. For instance, treatment of benzaldehyde with 2-mercaptoethanol in [bmim]BF_4 ionic liquid afforded 92%, 91%, 89%, 90%, and 89% yields over five cycles. However, in the absence of ionic liquids, the reaction did not proceed in conventional solvents even after long reaction times (15–20 h). In these reactions, the activity of ionic liquid was strongly influenced by the nature of anion. The reactivity of various aldehydes with ethanethiol



Scheme 1.

Table 1. Conversion of aldehydes to thioacetals[a] in ionic liquids

Entry	Aldehyde	Thiol	[bmim]BF$_4$		[bmim]PF$_6$	
			Time/h	Yield/%[b]	Time/h	Yield/%[b]
1		$HSCH_2CH_2OH$	2.5	92	3.5	87
2		$HSCH_2CH_2OH$	3.0	89	4.0	85
3		CH_3CH_2SH	2.0	85	3.5	80
4		$HSCH_2CH_2OH$	3.0	90	4.0	85
5		$HSCH_2CH_2SH$	2.5	91	3.5	87
6		$HSCH_2CH_2OH$	4.0	90	5.0	85
7		CH_3CH_2SH	3.5	85	6.5	82
8		$HSCH_2CH_2OH$	5.0	80	7.0	75
9		CH_3CH_2SH	3.5	78	5.5	70
10		$HSCH_2CH_2OH$	3.5	89	5.0	85
11		$HSCH_2CH_2OH$	4.0	85	5.0	78
12		$HSCH_2CH_2OH$	3.5	90	4.5	85
13		CH_3CH_2SH	3.0	91	5.0	87
14		CH_3CH_2SH	2.0	93	3.0	90
15		$HSCH_2CH_2OH$	3.5	85	5.5	81
16		$HSCH_2CH_2SH$	3.5	89	5.0	85
17		$HSCH_2CH_2SH$	4.0	87[c]	6.0	82[c]

[a] All the products were characterized by ^1H NMR, IR and mass spectroscopy.

[b] Yield refers to isolated pure products after column chromatography.

[c] Monoprotection of aldehyde was obtained.

was studied in hydrophilic [bmim]BF$_4$ and hydrophobic [bmim]PF$_6$ ionic liquids and the results are presented in the Table. Among these ionic liquids, [bmim]BF$_4$ was found to be superior in terms of yields and reaction rates. As evidenced from the Table, the acid sensitive protecting groups such as THP, TBDMS, TBDPS, PMB, MOM ethers, acetonide and carbamates are compatible in ionic liquids. In addition, this method is very useful for the protection of α,β-unsaturated aldehydes as thioacetals without the formation of 1,4-adducts, which are generally formed under strongly acidic conditions (Entries 10 and 14). Thus, the present method is mild enough to tolerate a wide range of functional groups present in the substrate.

In summary, the paper describes a novel method for the chemoselective conversion of aldehydes to dithioacetals using ionic liquids as recyclable reaction media that operates under neutral conditions thereby leaving acid- and base-labile protecting groups intact. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green strategy for the preparation of 1,3-oxathio- and dithioacetals.

BVS and GK thank CSIR, New Delhi, for the award of fellowships.

References and Notes

1 a) T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Willey, New York (1991), p 178. b) P. J. Kocienski, in "Protecting Groups," Thieme, Stuttgart (1994), p 156.

2 B. Smith, S. M. Condon, and J. A. McCauley, *Acc. Chem. Res.*, **31**, 35 (1998).

3 a) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed.*, **4**, 1075 (1965). b) E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966).

4 a) L. F. Tietze, B. Weigand, and C. Wulff, *Synthesis*, **2000**, 69. b) H. Firouzabadi, N. Iranpoor, and B. Karimi, *Synthesis*, **1999**, 58.

5 a) P. C. B. Page, J. C. Prodger, and D. Westwood, *Tetrahedron*, **49**, 10355 (1993). b) C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953).

6 a) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954). b) V. Kumar and S. Dev, *Tetrahedron Lett.*, **24**, 1289 (1983). c) B. Karimi and H. Seridj, *Synlett*, **2000**, 805.

7 a) G. A. Olah, S. C. Narang, D. Meider, and G. F. Salem, *Synthesis*, **1981**, 282. b) P. Kumar, R. S. Reddy, A. P. Singh, and B. Pandey, *Synthesis*, **1993**, 67. c) J. Tateiwa, H. Horiuchi, and S. Uemura, *J. Org. Chem.*, **60**, 4039 (1995).

8 a) E. J. Corey and K. Shimoji, *Tetrahedron Lett.*, **24**, 169 (1983). b) R. V. Anand, P. Saravanan, and V. K. Singh, *Synlett*, **1999**, 415. c) A. Kamal and G. Chouhan, *Tetrahedron Lett.*, **43**, 1347 (2002).

9 a) T. Welton, *Chem. Rev.*, **99**, 2071 (1999). b) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, **39**, 3772 (2000).

10 R. Sheldon, *Chem. Commun.*, **2001**, 2399.

11 Experimental procedure: A mixture of aldehyde (1 mmol), ethanedithiol or 2-mercaptoethanol (1.5 mmol) or ethanethiol (2.5 mmol), in [bmim]BF$_4$ or [bmim]PF$_6$ (2 mL) was stirred at 27 °C for an appropriate time (Table). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate: n-hexane (1:9) to afford pure thioacetal. The rest of the viscous ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs.