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ORIGINAL PAPER

Highly efficient and chemoselective method for the thioacetalization of aldehydes and transthioacetalization of acetals and acylals catalyzed by H_2SO_4-silica under solvent-free conditions

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Abstract Chemoselective and efficient thioacetalization of a variety of aldehydes was achieved in excellent yields at room temperature using 1,2-ethanedithiol in the presence of catalytic amounts of H_2SO_4-silica. Thioacetals were also prepared by transthioacetalization of acylals and acetals under similar conditions.

Keywords Thioacetalization · Transthioacetalization · Aldehydes · Chemoselectivity · Solvent free · Acetal · Acylal

Introduction

Protection of carbonyl groups as thioacetals is quite often a necessary requirement in the synthesis of multiple functional organic molecules [1, 2]. This is because of their stability both in acidic and basic conditions. In general, these compounds are prepared by protic or Lewis acid catalyzed condensation of carbonyl compounds with thiols or dithiols [3–12]. Among many of the recently developed catalysts, solid supported catalysts such as $FeCl_3$-SiO_2 [13], $ZrCl_4$-SiO_2 [14], $SOCl_2$-SiO_2 [15], $Cu(OTf)_2$-SiO_2 [16], and glycerol [17] are of choice for this purpose because of easier handling, mildness of the reaction conditions, and simple workup procedures. However, literature survey shows that only a few of these methods are available for the chemoselective protection of aldehydes in the presence of ketones especially by using a heterogeneous catalyst. On the other hand, although some of these methods have convenient protocols with good to high yields, the majority of these methods have certain disadvantages such as long reaction times, reflux conditions, stoichiometric amount of catalyst, and the use of expensive and toxic catalysts. Consequently, it is necessary to develop alternative methods for the chemoselective thioacetalization of aldehydes.

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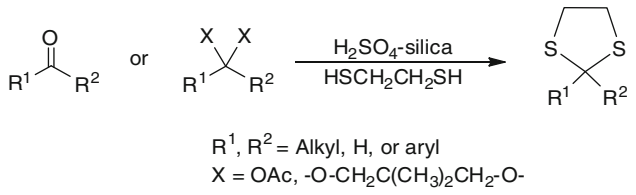
Results and discussion

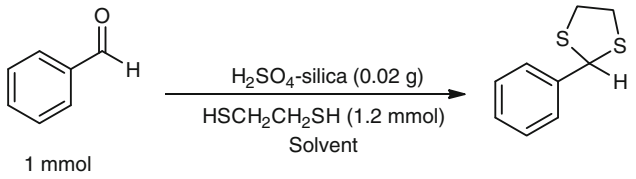
In the course of our studies on reactions under solvent-free conditions [18–20] and noting recent reports on the use of H_2SO_4-silica in various organic transformations [21–25], here we introduce a highly chemoselective, efficient, and fast method for the preparation of thioacetals in the presence of silica-supported sulfuric acid (H_2SO_4-silica). In this method thioacetalization of aldehydes and transthioacetalization of acylals and acetals have been investigated in the presence of 1,2-ethanedithiol and a catalytic amount of H_2SO_4-silica at ambient temperature under solvent-free conditions (Scheme 1). To the best of our knowledge, H_2SO_4-silica has not been used for thioacetalization or transthioacetalization.

To choose the most appropriate medium for the thioacetalization reaction, we examined the protection of benzaldehyde as the model compound with 1,2-ethanedithiol using H_2SO_4-silica in various solvents and under solvent-free conditions (Table 1). The solvents examined were ethyl acetate, dichloromethane, acetonitrile, and *n*-hexane. The reactions were carried out by stirring benzaldehyde with 0.02 g H_2SO_4-silica and 1.2 equiv. of 1,2-ethanedithiol at room temperature.



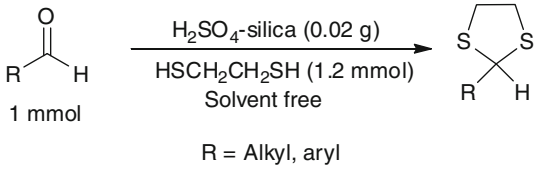
Scheme 1

Table 1 Thioacetalization of benzaldehyde catalyzed by H_2SO_4-silica under various solvent and solvent-free conditions



Entry	Solvent	Time	Yield/%[a]
1	Dichloromethane	16 h	20
2	Acetonitrile	14 min	100
3	Ethyl acetate	16 h	90
4	*n*-Hexane	16 h	10
5	No solvent	2 min	96

[a] Yields refer to isolated pure product



Scheme 2

As shown in Table 1, in comparison to conventional methods in solution, the yield of the reaction under solvent-free conditions is higher and the reaction time is shorter. It should be pointed out that in the absence of H_2SO_4-silica, the reaction did not proceed even after prolonged reaction times. In a typical procedure, the reaction of 1 mmol benzaldehyde with 1.2 mmol 1,2-ethanedithiol in the presence of 0.02 g H_2SO_4-silica at r.t. under solvent-free conditions afforded the desired dithioacetal in 96% yield. The versatility of the process has been proved with a wide range of aldehydes containing electron-withdrawing and electron-donating substituents (Scheme 2). The results of the thioacetalization of various aldehydes are shown in Table 2.

Various aldehydes gave dithioacetal derivatives in 74–98% yields after 2–17 min. The protections of hetero-aromatic and α,β-unsaturated aldehydes were also carried out under similar reaction conditions (Table 2, entries 11, 12, and 13).

This protocol was not effective for ketones as exemplified by entry 16 in Table 2. This result prompted us to explore the chemoselective protection of aldehydes in the presence of ketones. For example, when an equimolar mixture of benzaldehyde and acetophenone was allowed to react with 1,2-ethanedithiol in the presence of a catalytic amount of H_2SO_4-silica, only the dithioacetal derivative of benzaldehyde was obtained. The competition reactions are shown in Scheme 3.

Dithioacetals are quite stable toward a variety of reagents, including acidic ones, while acetals are not suitable for being handled in an acidic environment. Due to their stability, transthioacetalization of acetals and acylals to dithioacetals is a synthetically useful transformation and is usually carried out under the catalysis of a variety of Lewis acids such as $InCl_3$ [26], $MgBr_2$ [27], WCl_6 [28], $ZrCl_4$ [29], trichloroisocyanuric acid [30], SiO_2-$SOCl_2$ [31], and I_2 [32]. The results obtained in the case of thioacetalization prompted us to study the transthioacetalization of acetals and acylals using H_2SO_4-silica at room temperature. Accordingly, acetals and acylals were reacted with 1,2-ethaneditiol in the presence of 0.05 g H_2SO_4-silica (Scheme 4), and it was found that the thioacetals were obtained in high isolated yields (Table 3).

In conclusion, the present H_2SO_4-silica catalyzed procedure provides a highly efficient methodology for the chemoselective thioacetalization of aldehydes and transthioacetalization of acetals and acylals under solvent-free conditions. The significant advantages of this procedure are: (1) solvent-free conditions, (2) high yields, (3) fast reaction, (4) general applicability to a various aldehydes, acetals, and acylals, (5) operational simplicity, (6) chemoselectivity, and (7) H_2SO_4-silica is an inexpensive, easily available, and environmentally benign solid support acid. Thus, it offers a better and more practical alternative to the existing methodologies.

Experimental

Preparation of H_2SO_4-silica [25], acylals [25], and acetals [33] was carried out according to previously reported methods. Yields refer to isolated pure products. All the products were characterized by their ^{1}H NMR and IR spectra, and identified by comparison of their physical and spectral data with the well-known compounds [19, 34, 35]. All ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ relative to TMS (0.00 ppm). IR spectra were recorded on a Perkin-Elmer Spectrum RX I FT-IR spectrophotometer. Thin layer chromatography was performed on silica SIL G/UV 254 plates.

Table 2 Thioacetalization of aldehydes in the presence of 0.02 g H_2SO_4-silica

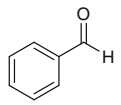
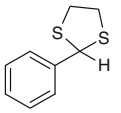
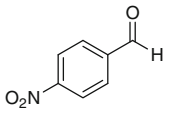
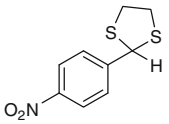
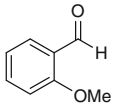
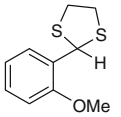
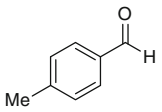
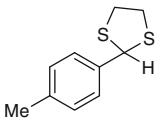
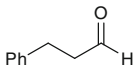
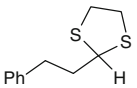
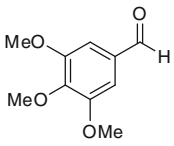
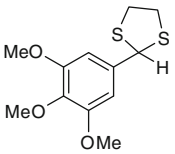
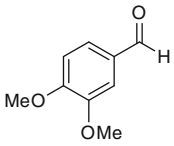
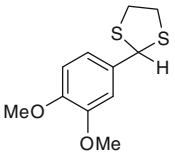
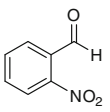
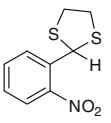
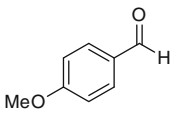
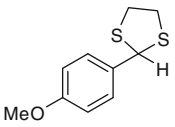
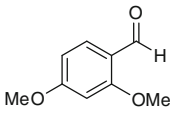
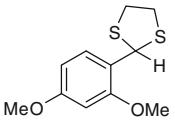
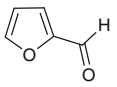
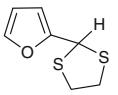
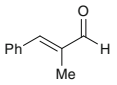
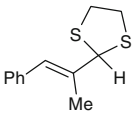
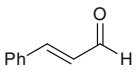
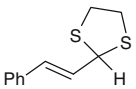
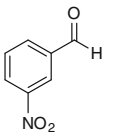
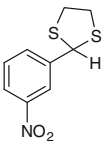
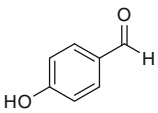
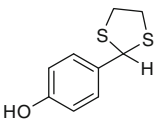
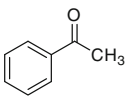
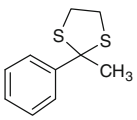
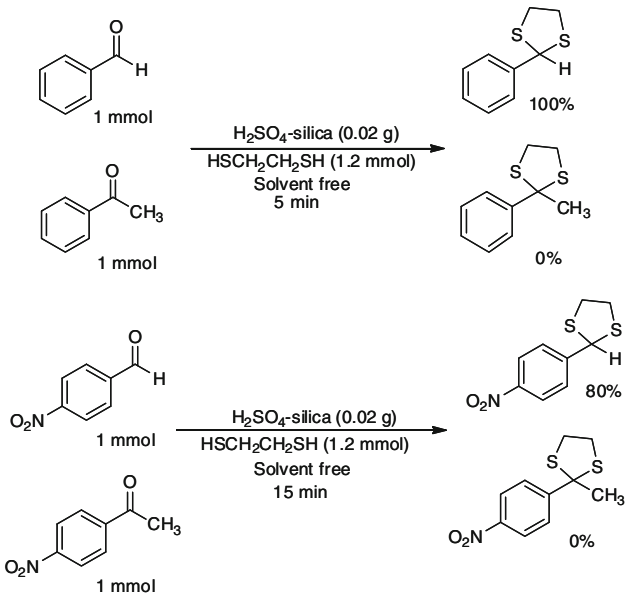
Entry	Substrate	Product	Time/min	Yield/%
1			3	96
2			14	74
3			5	94
4			6	94
5			2	98
6			5	98
7			8	98
8			10	89

Table 2 continued

Entry	Substrate	Product	Time/min	Yield/%
9			4	97
10			2	97
11			17	98
12			9	96
13			4	95
14			16	76
15			5	94
16			10	5

The yields refer to isolated pure products

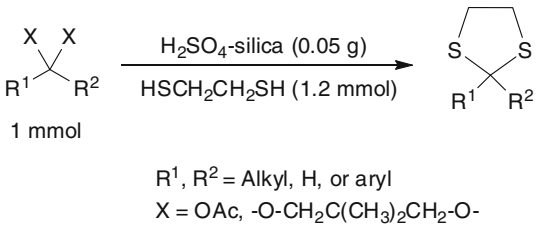
The products were characterized from their spectral data (IR and ^{1}H NMR) and comparison with authentic samples



Scheme 3

Preparation of H_2SO_4-silica

In a mortar 2 g silica gel (0.063–0.2 mm) and 1 g H_2SO_4 (98%, 10 mmol) were ground with a pestle, and the residue was heated at 100 °C for 12 h to furnish 2.95 g H_2SO_4-silica as a free-flowing powder (2.95 mg = 0.01 mmol of H_2SO_4).



Scheme 4

General procedure for the thioacetalization of aldehydes, acetals, and acylals by H_2SO_4-silica

A mixture of aldehyde or acetal (acylal) (2 mmol), 1,2-ethanedithiol (2.4 mmol), and 0.02–0.05 g H_2SO_4-silica in a mortar was ground with a pestle for the time specified in Table 2. The progress of the reaction was monitored by TLC using ethyl acetate/cyclohexane 15:85 as eluent. After completion of the reaction, the mixture was washed with CH_2Cl_2 (4 × 10 cm^3) and filtered. Evaporation of the solvent under reduced pressure gave the almost pure thioacetal. Further purification was done by preparative

Table 3 Transthioacetalization of acetals and acylals in the presence of 0.05 g H_2SO_4-silica

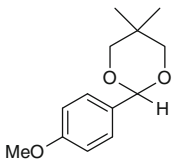
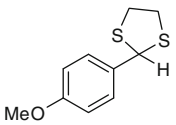
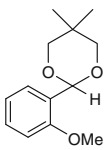
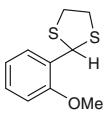
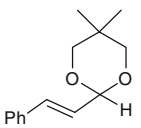
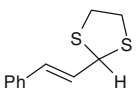
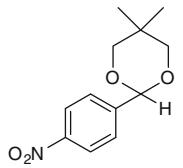
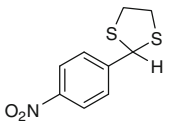
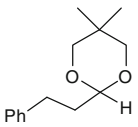
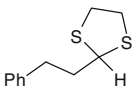
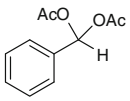
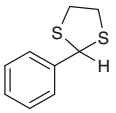
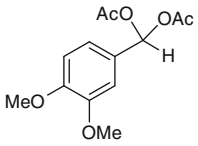
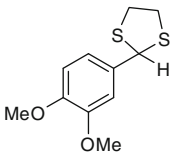
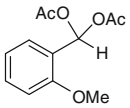
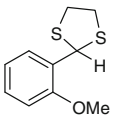
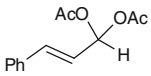
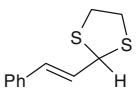
Entry	Substrate	Product	Time/min	Yield/%[a]
1			5	94
2			7	92
3			5	97

Table 3 continued

Entry	Substrate	Product	Time/min	Yield/%[a]
4			15	80
5			4	98
6			9	90
7			2	96
8			6	91
9			8	97

The yields refer to isolated pure products

[a] The products were characterized from their spectral data (IR and ^{1}H NMR) and comparison with authentic samples

thin-layer chromatography (eluent ethyl acetate/cyclohexane 9:1).

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