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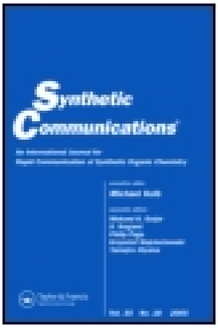

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Chemoselective Dithioacetalization and Oxathioacetalization of Carbonyl Compounds Using Alumina Sulfuric Acid as Catalyst

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Abstract: Carbonyl compounds have been successfully converted into their corresponding dithiolane, dithiane, and oxathiolane derivatives using a catalytic amount of alumina sulfuric acid (Al_2O_3–SO_3H) with excellent yields at room temperature in short reaction times under mild conditions. This simple method is a highly chemoselective procedure for protection of aldehydes in the presence of ketones, and the heterogeneous catalyst can be recovered and reused several times without any loss of its activity.

Keywords: 1,3-dithiane, 1,3-dithiolane, 1,3-oxathiolane, Alumina sulfuric acid, dithioacetalization, heterogeneous catalyst

INTRODUCTION

Organic synthesis involving heterogeneous and recyclable catalysts has been investigated worldwide, keeping in mind the stringent environment and economic regulations.[1] Homogeneous catalysts such as H_2SO_4, HF, HBr, HCl, CF_3COOH, and complexes of BF_3 are frequently used in organic synthesis.[2] However, processes involving conventional acids are inherently associated with problems such as high toxicity, catalyst waste, and corrosive and polluting reagents. In homogeneous reaction

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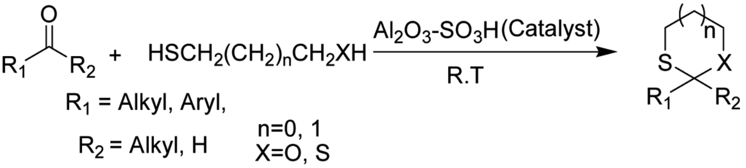
conditions, the catalyst is difficult to recover, reuse, and separate from the reaction mixture.[3] Replacement of these conventional acids by a solid heterogeneous catalyst is desirable to achieve effective catalyst handling, product purification, and decreased waste production.[3,4] The protection of carbonyl groups as dithioacetals is a common and popular practice in organic chemistry[5] as they are quite stable under basic or acidic conditions.[6] The dithioacetals in the form of 1,3-dithiolanes and 1,3-dithianes are also utilized as masked acyl anion[7–9] or masked methylene functions[10] in carbon–carbon bond-forming reactions and also protect the carbonyl groups against an attack by various reagents such as nucleophiles, oxidants, and hydride reducing agents. Dithioacetals are prepared by condensation of carbonyl compounds with thiols in the presence of Brønsted and Lewis acid catalysts such as $LiBF_4$,[11] $Bi(OTf)_3$,[12] SO_2,[13] $Sc(OTf)_3$[14] $InCl_3$,[15] $CoCl_2$,[16] $NiCl_2$,[17] $MoO_2(acac)_2$,[18] $Y(OTf)_3$,[19] *p*-toluenesulfonic acid,[20] LiBr,[21] and silica sulfuric acid.[22] Many of these methods require long reaction times,[11,12] reflux conditions,[12] the use of expensive reagents,[12] and stoichiometric amounts of catalyst.[13] Although some Lewis acid catalysts have been reported to show chemoselectivity, these catalysts are destroyed in the workup procedure and cannot be recovered and reused.[15,20] Some methods failed to protect deactivated aromatic substrates.[14] Therefore, there is still a need to develop a simple and efficient method for dithioacetalization of carbonyl groups and chemoselective protection of aldehydes in the presence of ketones using catalysts that could be superior to the existing ones with regards to toxicity, handling, and recyclability.

In continuation of our interest to develop application of heterogeneous catalysts in organic chemistry transformations,[23,24] herein we report an efficient method for the dithioacetalization and oxathioacetalization of carbonyl compounds as well as the chemoselective protection of various carbonyl compounds by employing Al_2O_3–SO_3H as catalyst (Scheme 1).

Sulfuric acid supported on alumina as inorganic solid compound was prepared according to silica sulfuric acid.[25,26] Alumina sulfuric acid as a



Scheme 1. Dithioacetalization and oxathioacetalization of carbonyl compounds using alumina sulfuric acid as catalyst.

heterogeneous solid Brønsted acid catalyst is safe, easy to handle, environmentally benign, and presents fewer disposal problems.

RESULTS AND DISCUSSION

To choose optimal conditions, first we tried to prepare 2-phenyl-1,3-dithiane in the reaction of 1,3-propanedithiol (1.05 mmol) with benzaldehyde (1 mmol) in the presence of a different amount of alumina sulfuric acid in different solvents (2 mL) (Table 1).

As can be seen from Table 1, the best results were obtained using 50 mg of catalyst. Among these solvents acetonitrile was the solvent of choice in terms of time and product yield (Table 1). Thus, we prepared a range of dithiolane, dithiane, and oxathiolane derivatives under the optimized reaction conditions: aldehydes or ketones (1 eq); 1,3-propandithiol, 1,2-ethanedithiol, or 2-mercaptoethanol (1.05 eq); and acetonitrile (as solvent, 2 mL) in the presence of alumina sulfuric acid (50 mg) (Table 2). Interestingly, the experimental procedure for these reactions is very simple and does not need the use of dry solvents or inert atmospheres. A catalytic amount of heterogeneous Al_2O_3–SO_3H as catalyst is sufficient to obtain the desired compounds in excellent yields (Scheme 1).

As shown in Table 2, several different aliphatic or aromatic aldehydes with both electron-withdrawing and donating substituents produced corresponding cyclic dithioacetal without the formation of any side products, in high to excellent yields and short reaction times at room

Table 1. Conversion of benzaldehyde (1 mmol) to 2-phenyl-1,3-dithiane using 1,3-propanedithiol (1.05 mmol) in the presence of different amounts of solid alumina sulfuric acid as catalyst under a variety of solvents (2 mL) at room temperature

Entry	Solvent	Catalyst (mmol)	Time	GC yield (%)
1	Diethyl ether	0.1	2 h	100
2	Dichloromethane	0.1	19.5 h	100
3	Ethylacetate	0.1	13.5 h	100
4	Chloroform	0.1	15.5 h	100
5	Acetonitrile	0.2	3.7 min	100
6	Acetonitrile	0.1	5 min	100
7	Acetonitrile	0.05	6 min	100
8	Acetonitrile	0.02	20 min	98
9	Acetonitrile	0.01	1 h	96
10	Acetonitrile	0	20 h	—

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Table 2. Conversion of aldehydes and ketones to the corresponding 1,3-dithiane, 1,3-dithiolane, and 1,3-oxathiolane using $HXCH_2(CH_2)_nCH_2SH$ in the presence of alumina sulfuric acid as catalyst in acetonitrile as solvent at room temperature

Entry	Aldehyde and ketone	X, n	Time (min)/ GC yield (%)	Yield (%)[a]	X, n	Time (min)/ GC yield (%)	Yield (%)[a]
1	Benzaldehyde	X = S, n = 12	6/100	93–98[b]	X = S, n = 0	8/100	96
2	4-Methylbenzaldehyde	X = S, n = 1	10/100	97	X = S, n = 0	7/100	98
3	2,5-Dimethoxybenzaldehyde	X = S, n = 1	3/100	95	X = S, n = 0	4/100	94
4	4-Methoxybenzaldehyde	X = S, n = 1	6/100	97	X = S, n = 0	10/100	96
5	4-(N,N-Dimethylamino) benzaldehyde	X = S, n = 1	7/100	93	X = S, n = 0	8/100	91
6	4-Nitrobenzaldehyde	X = S, n = 1	75/100	98	X = S, n = 0	75/100	98
7	3-Nitrobenzaldehyde	X = S, n = 1	65/100	97	X = S, n = 0	60/100	97
8	4-Chlorobenzaldehyde	X = S, n = 1	14/100	96	X = S, n = 0	10/100	96
9	4-Flourobenzaldehyde	X = S, n = 1	9/100	94	X = S, n = 0	7/100	93
10	2-Chloro benzaldehyde	X = S, n = 1	9/100	96	X = S, n = 0	17/100	94
11	3-Fluouro benzaldehyde	X = S, n = 1	9/100	95	X = S, n = 0	13/100	92
12	Cinnamaldehyde	X = S, n = 1	10/100	95	X = S, n = 0	15/100	97
13	Butyraldehyde	X = S, n = 1	30/100	88	X = S, n = 0	30/100	87

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14	Heptanaldehyde	X = S, n = 1	40/100	93	X = S, n = 0	45/100	94
15	Cyclohexanone	X = S, n = 1	120/100	82	X = S, n = 1	25/100	95[c]
16	Cyclohexanone	X = S, n = 0	40/100	98[c]	—	—	—
17	Benzyl methyl ketone	X = S, n = 1	18 h/100	95[c]	X = S, n = 0	14 h/100	98[c]
18	Isobutyl methyl ketone	X = S, n = 1	20 h/100	86[c]	X = S, n = 0	22 h/100	89[c]
19	Cyclopentanone	—	—	—	X = S, n = 0	30 h/100	96[c]
20	Acetophenone	X = S, n = 1	45 h/95	85[c]	X = S, n = 0	53 h/95	87[c]
21	Benzaldehyde	X = O, n = 0	7/100	91	—	—	—
22	4-Methylbenzaldehyde	X = O, n = 0	6/100	92	—	—	—
23	4-Nitrobenzaldehyde	X = O, n = 0	8/100	92	—	—	—
24	3-Chlorobenzaldehyde oxime	X = S, n = 1	20 h/20	12	—	—	—
25	Acetophenone oxime	X = S, n = 1	20 h/20	10	—	—	—
26	4-Methylacetophenone oxime	X = S, n = 1	20 h/20	8	—	—	—
27	Cyclohexanone oxime	X = S, n = 1	20 h/10	7	—	—	—

[a] Yields refer to the pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of MP, IR, ^{13}C NMR, and ^{1}H NMR spectra with authentic samples.[11–22]

[b] Isolated yield after five cycles with reused catalyst.

[c] The reaction was performed under reflux conditions in acetonitrile as solvent.

temperature (Table 2, entries 1–14). In addition, this catalyst is able to protect carbonyl compounds using 2-mercaptoethanol and produce corresponding 1,3-oxathiolanes in excellent yields under ambient conditions (Table 2, entries 21–23).

The reaction of cyclohexanone with 1,3-propanedithiol was completed after 120 min at room temperature (Table 2, entry 15); to decrease reaction time, we performed this reaction at 80 °C in an oil bath (Table 2, entry 15, time = 25 min). In continuation of this work, we performed dithioacetalization reactions with aromatic and aliphatic ketones under reflux conditions (Table 2, entries 15–20). Transthioacetalization of benzaldehyde and acetophenone oximes, in the reaction conditions (rt, 0.05 g catalyst, and acetonitrile as solvent) did not give the desired product (Table 2, entries 24–27). It is noteworthy that aromatic or acyclic aliphatic ketones did not undergo the reaction at room temperature. This result prompted us to explore the chemoselective protection of aldehydes in the presence of ketones. For instance, when an equimolar mixture of aldehyde and ketone was allowed to react with dithiol in the presence of a catalytic amount of Al_2O_3–SO_3H, only the 1,3-dithiane derivative of the corresponding aldehyde was obtained, whereas ketone was recovered quantitatively (Table 3, entries 1–3). Thus, the catalyst can promote dithioacetalization and oxathiaoacetalaization in a rapid, mild, and selective manner.

The reusability of the catalysts is one of the most important benefits. Thus, the recovery and reusability of Al_2O_3–SO_3H were investigated. In a typical experiment, after the reaction was completed, in the workup stage, solution was filtrated and the catalyst was isolated from the reaction mixture. The purified catalyst was achieved by washing the solid residue catalyst with dichloromethane and followed by drying in an oven at 100 °C for 30 min. In every experiment, more than 98% of the catalyst was easily recovered from the reaction mixture. Catalytic activity of the recovered catalyst was tested at least five times and showed activity the same as alumina sulfuric acid that was used for the first time (Table 2, entry 1).

To show the merit of the present work in comparison with reported results in the literature, we observed that the alumina-supported catalyst was much more effective than other catalysts derived from transition metals and related elements.[16–19,22]

CONCLUSION

In conclusion, we demonstrated that alumina sulfuric acid is a new, efficient, mild, and heterogeneous catalyst for dithioacetalization and

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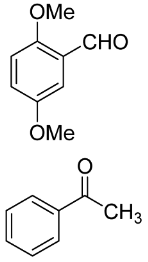
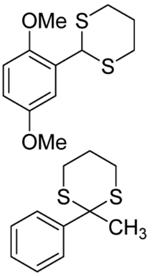
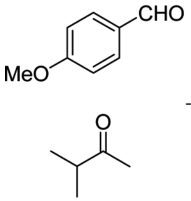
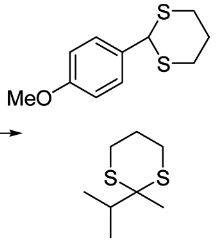
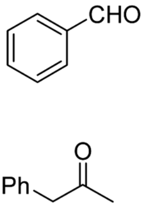
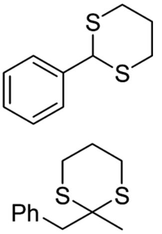
Table 3 Selective dithioacetalization of different aldehydes and ketones

Entry	Aldehyde and ketone	Products	Time (min)	Yield (%)[a,b]
1			3	100 0
2			10	100 0
3			6	100 0

[a] GC yield using n-octane as internal standard.

[b] The molar ratio of substrate 1/substrate 2/1,3-propanedithiol/catalyst was chosen 1/1/1.05/0.05 (g).

oxathioacetalization of various aldehydes and ketones at room temperature. This simple and efficient method is a highly chemoselective procedure for protection of aldehydes in the presence of ketones. Alumina sulfuric acid can be recovered from reaction mixtures and reused at there reaction conditions.

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EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. Alumina sulfuric acid was prepared according to the reported procedure.[25] All yields refer to isolated products after purification. The products were characterized by comparison with those of the authentic samples of the spectroscopy data (IR, ^{1}H NMR, ^{13}C NMR spectra). The NMR spectra were recorded on a Bruker Avance DEX 300-MHz instrument in $CDCl_3$ relative to TMS (0.00 ppm). IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Thin-layer chromatography (TLC) was performed on silica-gel polygram SIL G/UV 254 plates.

General Procedure for the Dithioacetalization and Oxathioacetalization of Carbonyl Compounds

The carbonyl compound (1 mmol), 1,2-ethanedithiol, 1,3-propanedithiol (1.05 mmol) or 2-mercaptoethanol (1.05 mmol), and Al_2O_3–SO_3H as catalyst (50 mg, 0.15 mmol of H^+)[26] were combined together in acetonitrile (2 mL). The reaction mixture was stirred at room temperature. Completion of the reaction was indicated by TLC or gas chromatography (GC). After completion of the reaction, acetonitrile was evaporated from the reaction mixture. The reaction mixture was combined with dichloromethane and filtered. The catalyst washed with dichloromethane and then dried; the recovered catalyst can be used again. The organic layer was extracted with 10% sodium hydroxide solution (10 ml) followed by a water (10 ml) and brine solution (5 ml). The organic layer was dried with anhydrous sodium sulfate and filtered, the solvent was evaporated under reduced pressure, and the pure product was obtained. All the desired pure product(s) were characterized by comparison of their physical data with those of the known the dithioacetals and oxothioacetals.[11–22] The spectral data of 2-phenyl-1,3-dithiane (Table 2, entry 1) is given here: mp = 68–70°C (lit.[21] 71–72); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.92$–1.96 (m, 1H), 2.15–2.17 (m, 1H), 2.88–3.10 (m, 4H), 5.17 (s, 1H), 7.29–7.48 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.73$, 31.01 (2C), 50.00, 127.49 (2C), 128.22, 128.64 (2C), 139.54 ppm; IR (KBr, cm^{-1}): 3063, 3022, 2929, 2894, 1685, 1598, 1487, 1445, 1429, 1276, 1240, 1158, 1071, 845, 698.

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