

Note

Chemoselective dithioacetalization of aldehydes using silica sulfuric acid as a reusable catalyst

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Silica sulfuric acid has been found to be an efficient and reusable catalyst for chemoselective dithioacetalization of aldehydes over ketones, in excellent yields.

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Thioacetals and acetals, due to their stability under both acidic and basic conditions are most commonly used protecting groups for aldehydes and ketones in a multistep synthesis of many natural products¹. In addition to the carbonyl protection, they behave as masked acylanions or masked methylene functions in carbon-carbon bond forming reactions^{2, 3}. Moreover, they are also important due to their easy conversion to parent hydrocarbon by reductive desulfurization method⁴.

Generally, dithioacetals are prepared by condensation of carbonyl compounds with dithiols under the catalysis of protic or Lewis acids^{5, 6}. In addition to the several reagents surveyed recently⁷, some new methods employing LiBr⁸, InCl₃⁹, LiBF₄¹⁰, NBS¹¹, trichloroisocyanuric acid¹², zirconiumsulphophenylphosphonate¹³, iodine on alumina¹⁴, phosphorous oxychloride on montmorillonite¹⁵, Bi(NO₃)₃¹⁶, NiCl₂¹⁷ and the triflates¹⁸ of Li, In and Sc have been developed to effect dithioacetalization of carbonyl compounds. Most of these recent methods are introduced to effect chemoselective protection of aldehydes in the presence of ketones. However, some of these methods use harsh reaction conditions, require inert atmosphere, involve expensive reagents,

need long reaction times or tedious work-up procedures. Consequently, a methodology for chemoselective dithioacetalization using an inexpensive and preferably a reusable catalyst under mild conditions is desirable.

Solid acid catalysts are becoming increasingly popular due to their ease of handling, mild reaction conditions and easy work-up procedures. Many acidic and basic solids are known to act as catalysts or promoters in liquid phase organic synthesis¹⁹. Silica sulfuric acid (SSA)²⁰ which can be prepared simply by reaction of chlorosulfonic acid with silica gel, has an immobilized sulfuric acid over silica gel and behaves as a Brönsted acid. Zolfigol *et al.*²¹⁻²³ have reported several of its applications in many oxidative transformations. It has also been used earlier in Biginelli reaction by Zolfigol²⁴, in chemoselective tetrahydropyranylation of alcohols over phenol by us²⁵ and recently it is used in one pot synthesis of β -acetamido ketones²⁶. In this communication we wish to report the use of SSA as a reusable solid acid catalyst to effect dithioacetalization of various aldehydes, ketones and chemoselective dithioacetalization of aldehydes over ketones (**Scheme I**).

Results and Discussion

As a case study, when a mixture of *p*-methoxybenzaldehyde **1b** (10 mmole) and 1, 2-ethanedithiol or 1, 3-propanedithiol (11 mmole) in acetonitrile (15 mL) was stirred at room temperature with a catalytic amount of SSA (0.2 g, 0.52 mmole), desired 1, 3-dithiolane or 1, 3-dithiane **2b** ($n = 1/2$) (**Table I**) were obtained in 93 and 98% yields, respectively. To optimize the reaction conditions, the reaction was performed with variable quantities of SSA and it was

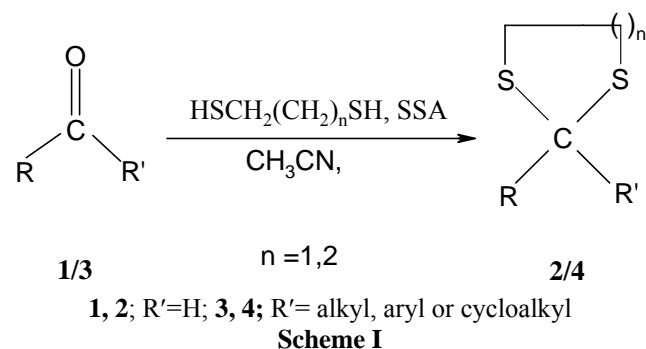
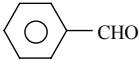
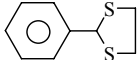

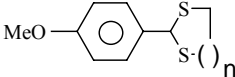
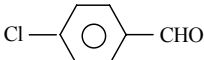
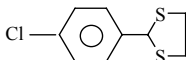
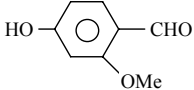
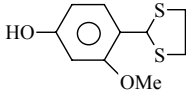
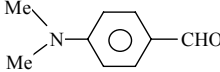
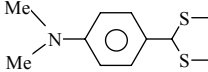
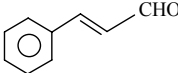
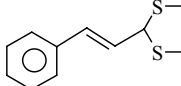
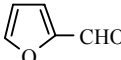
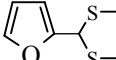
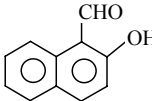
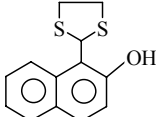
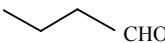
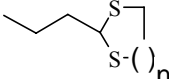
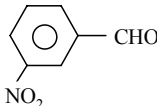
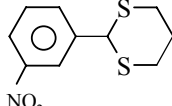
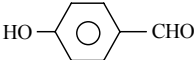
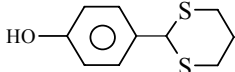


Table I — Dithioacetalization of aldehydes^a

Entry	Aldehyde 1	HSCH ₂ (CH ₂) _n SH	Time (min)	Product 2	Yield (%) ^{b, c}
a		n = 1	30		88
b		n = 1	20		93
		n = 2	25		98
c		n = 1	30		89
d		n = 1	30		91
e		n = 1	25		87
f		n = 1	30		92
g		n = 1	35		86
h		n = 1	30		91
i		n = 1	30		89
		n = 2	30		86
j		n = 2	30		89
k		n = 2	30		90

^a Yields refer to pure, isolated products.^b All the products gave satisfactory spectroscopic (IR, ¹H and ¹³C NMR) analysis.^c Reaction was carried out at room temperature.

noticed that 0.52 mmole of silica sulfuric acid is essential for the completion of reaction and the reaction proceeds equally well in various organic solvents, like CH₃CN, benzene, THF, etc. Under the optimized conditions, the reaction was then extended to the condensation of various aliphatic, aromatic, heterocyclic and unsaturated aldehydes with 1, 2-ethanedithiol or 1, 3-propanedithiol and the results are summarized in

Table I. The reaction proceeds smoothly with aldehydes bearing ring activating or deactivating groups, with acid sensitive substrate like furfural as well as with 2-hydroxynaphthaldehyde (entries **g**, **h**; **Table I**), however dithioacetalization of ketones under the same reaction conditions did not take place, rather, the use of excess silica sulfuric acid (1 mmole) and reflux condition became essential for dithioacetalization of ketones.

Thus, when a mixture of *p*-methoxyacetophenone **3g** (10 mmoles), 1, 2-ethanedithiol or 1, 3-propanedithiol (11 mmoles) in acetonitrile (15 mL) in presence of SSA (0.4 g, 1.04 mmole) was refluxed for 50 min, corresponding 1, 3-dithiolane or 1, 3-dithiane **4g** ($n = 1/2$) (**Table II**) were obtained in 87 and 86% yields, respectively. The reaction was also carried out with various aliphatic, cyclic, as well as aromatic ketones and the results are summarized in **Table II**.

Due to the appreciable difference in the reaction conditions employed for the protection of aldehydes and ketones it was proposed to check the usefulness of SSA for chemoselective dithioacetalization of aldehydes over ketones.

When an equimolar mixture (10 mmoles each) of benzaldehyde and acetophenone was stirred with 1, 2-ethanedithiol (11 mmoles) in acetonitrile (15 mL) at room temperature in the presence of SSA (0.2 g,

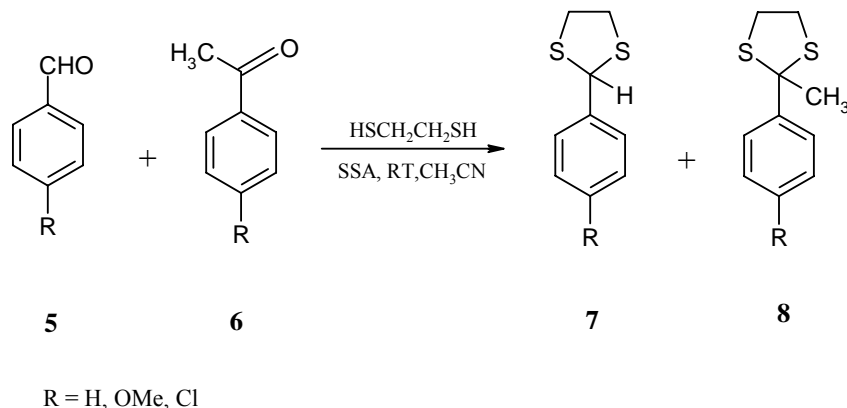
Table II — Dithioacetalization of ketones^a

Entry	Ketone 3	HSCH ₂ (CH ₂) _n SH	Time (min)	Product 4	Yield (%) ^{b,c}
a		$n = 1$	40		90
b		$n = 1$	45		85
c		$n = 1$	30		88
d		$n = 1$	40		91
e		$n = 1$	30		91
f		$n = 1$	45		93
g		$n = 1$ $n = 2$	50 50		87 86
h		$n = 2$	50		89
i		$n = 2$	4h		81

^a Yields refer to pure, isolated products.

^b All the products gave satisfactory spectroscopic (IR, ¹H and ¹³C NMR) analysis.

^c Reaction was carried out at reflux temperature.



Scheme II

0.52 mmole), benzaldehyde was converted into corresponding 1, 3-dithiolane in 26 min while acetophenone remained unreacted (Scheme II) as confirmed by GC analysis. This chemoselectivity was further confirmed by performing the reaction with the mixtures of (i) *p*-chlorobenzaldehyde and *p*-chloroacetophenone and (ii) *p*-methoxybenzaldehyde and *p*-methoxyacetophenone with 1, 2-ethanedithiol and the results are summarized in Table III. The results clearly reveal that under the reaction conditions employed only aldehyde gets converted into corresponding dithiolane while ketone remains unaffected.

Reusability is one of the interesting features of solid acid catalysts. To check the reusability of SSA, after the first reaction between *p*-methoxybenzaldehyde and 1, 2-ethanedithiol in the presence of SSA was completed, the catalyst was filtered, washed with CH₃CN, CH₂Cl₂, dried and reused in same molar proportion for the next run. It was found that the catalyst can be recycled for atleast six times to yield dithioacetal in almost comparable yields, as for the freshly prepared catalyst.

In summary, SSA can be effectively employed as a reusable solid acid catalyst for chemoselective dithioacetalization of aldehydes over ketones in excellent yields at room temperature.

Experimental Section

Silica sulfuric acid was prepared according to the reported procedure²⁰.

Dithioacetalization of an aldehyde. To a well stirred solution of an aldehyde **1a-k** (10 mmole) in acetonitrile (15 mL) was added 1, 2-ethanedithiol or 1, 3-propanedithiol (11 mmole) and SSA (0.2 g, 0.52 mmole). The stirring was continued till completion of

Table III — Chemoselective dithioacetalization of aldehydes over ketones*

Entry	Substrate (5 & 6) R	Time (min)	Yield (%)	
			7	8
a	H	26	91	0
b	Cl	30	93	0
c	OMe	20	95	0

* (i) Yields refer to GC analysis: Column = SE 30 5%, length = 2 meters, Injector temp = 270°C, oven temp = 240°C.

(ii) Reaction conditions: aldehyde, 1, 2-ethanedithiol (10 mmole each), SSA (0.52 mmole), CH₃CN (15 mL), RT.

the reaction (TLC). The reaction mixture was filtered and the catalyst was washed with acetonitrile (3×10 mL). The combined filtrate was concentrated *in vacuo* and the residue was filtered through a short column of silica gel to obtain respective 1, 3-dithiolanes or 1, 3-dithianes **2a-k**.

Dithioacetalization of ketone. To a well stirred solution of a ketones **3a-i** (10 mmole) and 1, 2-ethanedithiol or 1, 3-propanedithiol (11 mmole) in acetonitrile (15 mL) was added SSA (0.4 g, 1.04 mmole) and the reaction mixture was refluxed with stirring till completion of the reaction (TLC). The work-up as described earlier furnished respective dithiolanes or dithianes **4a-i**.

4-Methoxyphenyl-1, 3-dithiolane 2b: m.p. 60°C; IR (neat): 3018, 2930, 1609, 1585, 1509, 1216, 1034, 756 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 3.33 (2H, m, -CH₂), 3.51 (2H, m, -CH₂), 3.79 (3H, s, -OCH₃), 5.64 (1H, s, -CH), 6.85 (2H, d, ArH), 7.45 (2H, d, *J* = 8 Hz, ArH); ¹³C NMR (50.32 MHz, CDCl₃): δ 40.3 (CH₂), 55.3 (-OCH₃), 56.1 (CH), 113.8 (=CH), 129.2 (=CH), 131.9 (quat. C), 159.3 (quat. C).

4-Dimethylaminophenyl-1, 3-dithiolane 2e: m.p. 105°C; IR (neat): 3005, 2926, 1611, 1520, 1480,

1355, 1215, 1145 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 2.93 (6H, s,), 3.35 (2H, m), 3.48 (2H, m), 5.65 (1H, s), 6.66 (2H, d, J = 8 Hz, ArH), 7.25 (2H, d, J = 8 Hz); ^{13}C NMR (50.32 MHz, CDCl_3): δ 39.91(CH_2 ,) 40.31 (CH_3), 56.46 (CH), 112.12 (=CH), 126.57 (quat. C), 128.59 (=CH), 150.20 (quat. C).

2-(2-Phenylethenyl)-1, 3-dithiolane 2f: m.p. 56-57°C (CHCl_3 - pet. ether) (lit.^{18b} m.p. 57-59°C); IR (neat): 3082, 3059, 2972, 2860, 1642, 1600, 1577, 1496, 1447, 1272, 1216 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 3.28-3.41 (4H, m), 5.24 (1H, d, J = 10 Hz), 6.22 (1H, dd, J = 15 Hz and 10Hz), 6.53 (1H, d, J = 15 Hz), 7.29-7.37 (5H, m, ArH); ^{13}C NMR (50.32 MHz, CDCl_3): δ 39.43 (CH_2), 54.32 (CH), 126.44 (=CH), 127.6 (=CH), 128.32 (=CH), 129.93 (=CH), 135.92 (quat. C).

2-Methyl-2-phenyl-1, 3-dithiolane 4e: viscous liquid; IR (neat): 2979, 1596, 1489, 1373, 1276, 1062, 1035 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 2.14 (3H, s), 3.38-3.44 (4H, m), 7.73-7.79 (4H, m, ArH); ^{13}C NMR (50.32 MHz, CDCl_3): δ 34(CH_3), 40(CH_2), 69(quat.C), 127.40 (=CH), 128 (=CH), 146 (quat. C).

2-Methyl-2-(4-methoxyphenyl)-1, 3-dithiolane 4g: viscous liquid; IR (neat): 2965, 1686, 1590, 1488, 1396, 1260, 1093, 1059 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 2.17 (3H, s), 3.85 (3H, s), 3.41-3.50 (4H, m), 6.88 (2H, d, J = 8 Hz, ArH), 7.70 (2H, d, J = 8 Hz, ArH); ^{13}C NMR (50.32 MHz, CDCl_3): δ 33.26 (CH_3), 39.26 (CH_2), 54.50 (OCH_3), 67.33 (quat.C), 112.43 (=CH), 127.40 (=CH), 136.84 (quat.C), 157.7 (quat.C).

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References

- (a) Greene T W & Wuts P G M, *Protective Groups in Organic Synthesis*; 2ndedn, (Wiley, New York), **1999**, p 329. (b) Kocienski P J, *Protecting Groups*, (Thieme, Stuttgart), **1994**, p. 156. (c) Eliel E L & Morris-Natsche S, *J Am Chem Soc*, 106, **1984**, 2937. (b) Utimoto K, Nakamura A & Matsubara S, *J Am Chem Soc*, 112, **1990**, 8189. (c) Corey E J & Seebach D, *Angew Chem Int Ed Engl* 4, **1965**, 1075. (d) Corey E J & Seebach D, *J Org Chem* 31, **1966**, 4097. (e) Asokan C V, Shukla J, Syam Kumar U K, Ila H & Junjappa H, *Indian J Chem*, 40 B, **2001**, 937. (f) Suresh J R, Syam Kumar U K, Ila H & Junjappa H, *Tetrahedron*, 57, **2001**, 781.
- (a) Eliel E L & Morris-Natsche S, *J Am Chem Soc*, 106, **1984**, 2943. (b) Seebach D, *Synthesis*, **1969**, 17. (c) Bulmanpage P C, Van Niel M B & Podger J, *Tetrahedron*, 45, **1989**, 7643. (d) Grobel B J & Seebach D, *Synthesis*, **1977**, 357. (e) Mohanta P K, Peruncheralathan S, Ila H & Junjappa H, *J Org Chem*, 66, **2001**, 1503.
- Olsen R K & Curries J O, *Chemistry of thiol group*, Part-2, edited by S Patai, (Wiley; New York), **1974**, p 519.
- Ong B S & Chan T H, *Synth Commun*, 7, **1977**, 283.
- Kumar V & Dev S, *Tetrahedron Lett*, 24, **1983**, 1289.
- Banerjee A K, Laya Mimo M S & Vera Vegas W, *J Russ Chem Rev*, 69, **2000**, 947.
- Firouzabadi H, Iranpoor M & Karimi B, *Synthesis*, **1999**, 58.
- Ranu B C, Das A & Samanta S, *Synlett*, **2002**, 727.
- Yadav J S, Subba Reddy B V & Pandey S K, *Synlett*, **2001**, 238.
- Kamal A & Chouhan G, *Synlett*, **2002**, 474.
- Firouzabadi H, Iranpoor N & Hazarkhani H, *Synlett*, **2001**, 1641.
- Carini M, Epifano F, Marcotullio M C & Rosati O, *Synlett*, **2001**, 1182.
- Deka N & Sarma J, *Chem Lett*, **2001**, 794.
- Jin T S, Sun Xu, Ma Y R & Li T S, *Synth Commun*, 31, **2001**, 1669.
- Srivastava N, Dasgupta S K & Banik B K, *Tetrahedron Lett*, 44, **2003**, 1191.
- Khan A T, Mondal E, Sahu P R & Islam S, *Tetrahedron Lett*, 44, **2003**, 919.
- (a) Firouzabadi H, Karimi B & Eslami S, *Tetrahedron Lett*, 40, **1999**, 4055. (b) Sengodagounder M & Srinivasarao A B, *Tetrahedron*, 58, **2002**, 7897. (c) Kamal A & Chouhan G, *Tetrahedron Lett*, 44, **2003**, 3337.
- (a) Hattori H, *Chem Rev*, 95, **1995**, 537. (b) Corma A, *Chem Rev*, 95, **1995**, 559.
- Zolfigol M A, *Tetrahedron*, 57, **2001**, 9509.
- Zolfigol M A & Madrakian E, *Molecules*, 7, **2002**, 734.
- Zolfigol M A, Mirjalili B F & Bamoniri A, *Molecules*, 7, **2002**, 751 and references cited therein.
- Zolfigol M A, Shirin F, Choghamarani A G & Baltork I M, *Green Chem*, 4, **2002**, 562.
- Zolfigol M A, Salehi P, Dabiri M & Fard M A, *Tetrahedron Lett*, 44, **2003**, 2889.
- Pore D M, Desai U V, Mane R B & Wadgaonkar P P, *Synth Commun*, 34, **2004**, 1.
- Khodaei M M, Khosropour A R & Fattahpour P, *Tetrahedron Lett*, 46, **2005**, 2105.