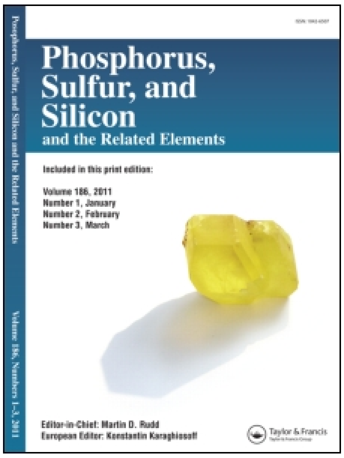

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A Mild and Chemoselective Catalyst for Thioacetalization Under Solvent Free Conditions

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A Mild and Chemoselective Catalyst for Thioacetalization Under Solvent Free Conditions

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Protection of a variety of carbonyl compounds as dithioacetals using P_2O_5/SiO_2 *(75%), as a mild and chemoselective catalyst, was achieved under solvent free conditions in very good yields.*

Keywords 1,3-dithiolane; dithioacetalization; diphosphorus pentoxide

Protection and deprotection of reactive functional groups are essential steps in the synthesis of natural products and polyfunctional compounds. Dithioacetalization is well-known as a reaction that protects carbonyl groups.[1] Dithioacetals are frequently used in the synthesis of natural products and organic compounds.[2] Their stability under acidic and basic conditions make them versatile carbonyl protecting groups.[3,4]

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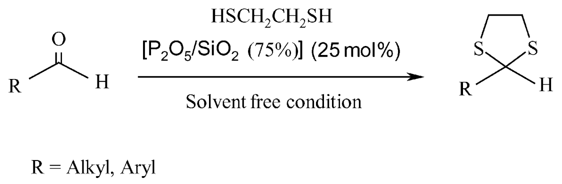
For this reason, the protection and deprotection of the carbonyl functional groups remain crucial challenges to the organic chemists. Experience shows that the critical parameters are generally the stability and the cleavage of the protecting group rather than its introduction. Therefore regeneration of the parent carbonyl groups from their masked form seems to be a useful synthetic process. There are several methods for the protection and the deprotection of dithioacetals.[5]

Literature survey shows that phosphorus pentoxide can be used as a dehydrating agent for the formation of anhydride from two molecules of an ordinary carboxylic acid, ketenimines from amides, vinyl ethers from acetals, nitriles from amides,[6] amides from oximes,[7] phenolic esters from carboxylic acids,[8] and sulfones from sulfonic acids.[9]

In continuation of our ongoing program to develop environmentally benign methods under solvent free conditions,[10] we wish to report an extremely convenient, mild, and highly chemoselective procedure for the conversion of aldehydes and ketones into 1,3-dithiolanes using a catalytic amount of P_2O_5/SiO_2 (75%) under solvent free conditions.

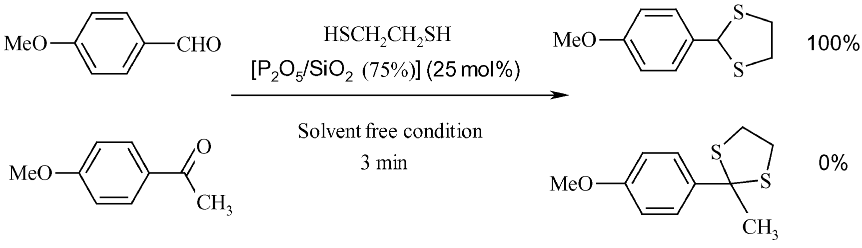
RESULTS AND DISCUSSION

The protection of a variety of aldehydes and ketones containing electron-withdrawing and electron-donating substituents, heteroaromatic and α, β-unsaturated aldehydes, and various ketones with 1,2-ethanedithiol in the presence of catalytic amount of P_2O_5/SiO_2(75%) was examined under solid-state conditions at room temperature (Scheme 1, Table I). In each case the corresponding dithioacetals were obtained in good to excellent yields in a short reaction time. The products were purified by column chromatography using silica gel and the purity of the products was determined by GC and TLC analysis.

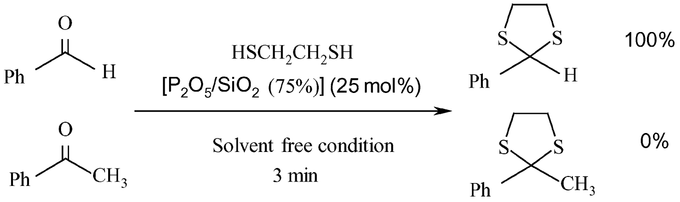


SCHEME 1

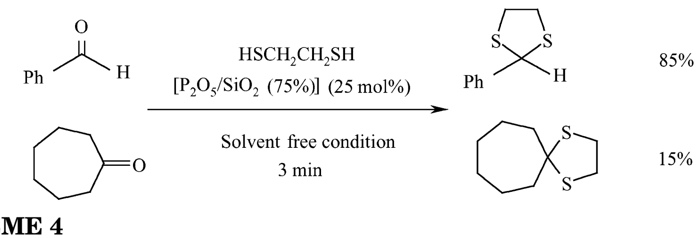
To evaluate the selectivity of the reagent we tried the chemoselectivity of this reagent. In representative examples, when an equimolar amount of *p*-methoxybenzaldehyde and *p*-methoxyacetophenone were treated with 1,2-ethanedithiol (an equimolar amount) and 25 mol% of this reagent, the *p*-methoxybenzaldehyde was converted to the corresponding 1,3-dithiolane in a 100% yield and *p*-methoxyacetophenon was intact (Scheme 2). In competition of benzaldehyde (in an equimolar amount) and acetophenone (in an equimolar amount) with 1,2-ethanedithiol (in an equimolar amount) in the presence of catalytic amount of reagent (25 mol%), benzaldehyde was converted to the corresponding 1,3-dithiolane in a 100% yield and acetophenon was intact (Scheme 3). In another experiment we treated an equimolar amount of benzaldehyde, cycloheptanone, and 1,2-ethanedithiol in the presence of 25 mol% of reagent under solvent free conditions, we observed that benzaldehyde reacted with 1,2-ethanedithiol in an 85% yield and cycloheptanone in an 15% yield (Scheme 4).



SCHEME 2



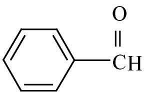
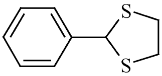
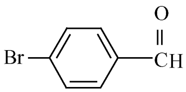
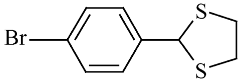
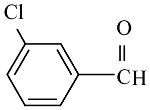
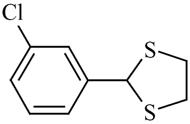
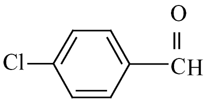
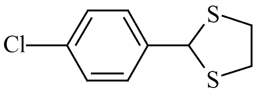
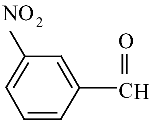
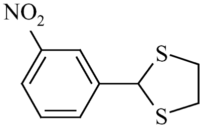
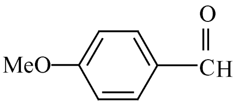
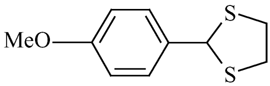
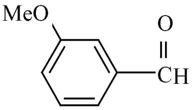
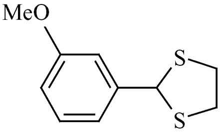
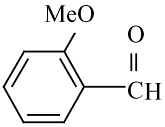
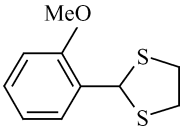
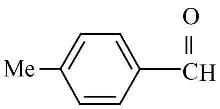
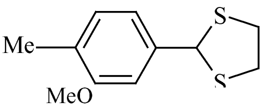
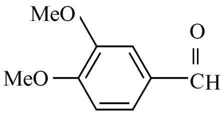
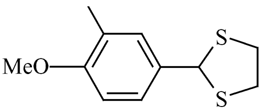
SCHEME 3



SCHEME 4

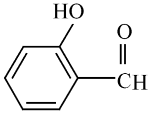
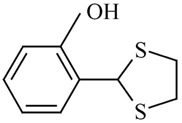
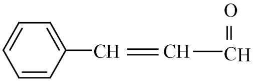
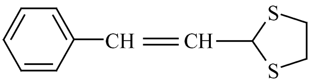
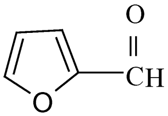
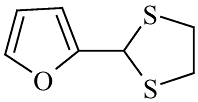
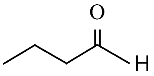
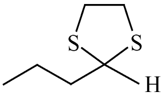
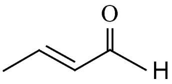
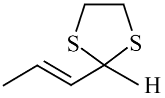
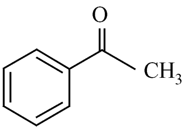
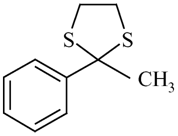
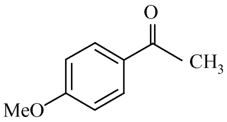
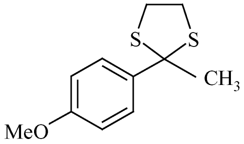
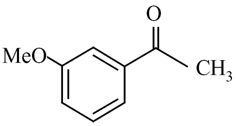
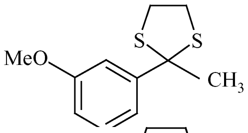
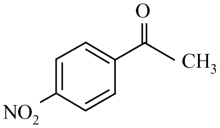
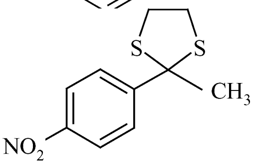
In order to show the merit of the present work in comparison with recently reported articles, we compared our results with other

TABLE I Dithioacetalization of Aldehydes and Ketones in the Presence of P_2O_5/SiO_2 (75%) Under Solvent Free Conditions at R.T.[a,b]

Entry	Substrate	Product	Time (Min)	Yield (%)	m.p. (°C)
1			3	87	Oil[5a,5c]
2			3	88	76
3			3	90	Oil
4			3	88	61-63
5			3	86[c]	66–67
6			3	90	63–64 (60–62)[5a]
7			3	88	Oil
8			3	85	Oil
9			3	91	60–61 (56–58)[5a]
10			3	83	66–68 (62–65)[5c]

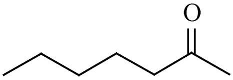
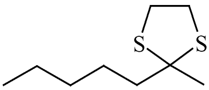
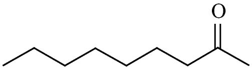
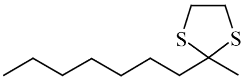
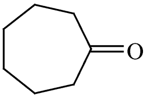
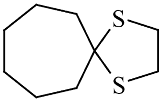
(Continued on next page)

TABLE I Dithioacetalization of Aldehydes and Ketones in the Presence of P_2O_5/SiO_2 (75%) Under Solvent-Free Conditions at R.T.[a,b] *(Continued)*

Entry	Substrate	Product	Time (Min)	Yield (%)	m.p. (°C)
11			3	82	49–51
12			3	85	60–62 (58–59)[5c]
13			3	90	Oil[5a]
14			1	80	Oil
15			1	82	Oil[15]
16			6	48	Oil[15,5c]
17			6	40	Oil
18			6	45	Oil
19			6	42[c]	56–57

(Continued on next page)

TABLE I Dithioacetalization of Aldehydes and Ketones in the Presence of P_2O_5/SiO_2 (75%) Under Solvent-Free Conditions at R.T.[a,b] *(Continued)*

Entry	Substrate	Product	Time (Min)	Yield (%)	m.p. (°C)
20			4	86	Oil
21			4	85	Oil
22			4	88	53–54

[a] The yields refer to the isolated products after purification.

[b] All of the products were characterized from their spectral (IR, ^{1}H-NMR,TLC, and GC).

[c] We did not observe any reduction of the nitro groups.

reagents such as NBS,[11] $NiCl_2$,[12] In(OTf)$_3$[5a], $InCl_3$,[13] $CoCl_2$,[14] $SOCl_2$-SiO_2,[15] $LiClO_4$,[5c] and P_2O_5/SiO_2 (Table II). The results show that the reaction yields are compatible with the reported ones and this reagent (P_2O_5/SiO_2) is superior to other reagents in view of the lowest reaction time and green chemistry view.

In conclusion, we have described a mild, efficient, and chemoselective method for the preparation of dithioacetals from carbonyl compounds and 1,2-ethane dithiol in the presence of P_2O_5/SiO_2(75%) at r.t. in high yields and short reaction times. The use of an inexpensive, relatively nontoxic, and green catalyst are advantages of this method. Further investigation on the new application of silica sulfuric acid is ongoing in our laboratories.

EXPERIMENTAL SECTION

Products were characterized by comparison with authentic samples (IR, ^{1}H NMR spectrum, CHN analysis, melting point),[5,15] All m.p.s were taken on a Gallenkamp melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 250 NMR spectrometer operating at 250 MHz. The spectra were measured in CCl_4 and $CDCl_3$ relative to TMS (0.00 ppm). IR spectra were recorded on a Shimadzu 435 IR spectrophotometer. Spectra of solids were performed using KBr pellets.

TABLE II Comparison of Dithioacetalization of Some Carbonyl Compounds Under Different Conditions

		Yield% (min) [hr]							
Entry	Substrate	NBS[a] 15 mol%	$NiCl_2$[b] 10 mol%	$In(OTf)_3$[c] 10 mol%	$InCl_3$[d] 30 mol%	$CoCl_2$[e] 5 mol%	$SOCl_2$-SiO_2[f] 0.2 g	$LiClO_4$[g] 5 equiv.	P_2O_5/SiO_2 25 mol%
1	Benzaldehyde	80 (40)	96 [2.75]	89 (8)	—	89 [2.5]	—	77 (15)	87 (3)
2	4-methoxybenzaldehyde	75 (30)	90 [0.75]	96 (6)	92 (15)	93 [2]	98 [5]	81 (15)	90 (3)
3	4-chlorobenzaldehyde	80 (30)	—	—	—	—	99 [5]	—	88 (3)
4	Furfural	90 (30)	—	87 (8)	—	—	95 [5]	—	90 (3)
5	Cinnamaldehyde	—	—	90 (8)	—	—	—	—	85 (3)

[a] Reaction was carried out at r.t. in CH_2Cl_2.

[b] Reaction was carried out at r.t. in CH_2Cl_2/MeOH.

[c] Reaction was carried out at r.t. in CH_2Cl_2.

[d] Reaction was carried out at r.t. in CH_2Cl_2.

[e] Reaction was carried out at r.t. in CH_3CN.

[f] Reaction was carried out at 20°C in benzene.

[g] Reaction was carried out at r.t. in diethylether.

Preparation of P_2O_5/SiO_2(75%)

Silica gel 60 (2.5 g) and dried P_2O_5 (7.5 g) were mixed for 10 min in a sealed round-bottomed flask. This reagent was stored in a sealed flask for later using.

General Procedure

In a mortar a mixture of carbonyl compounds (1 mmol), 1,2-ethane dithiol (0.11 mL, 1.3 mmol), and P_2O_5/SiO_2(75%) (0.05 g, 25 mol %) was ground with a pestle for the time specified in Table I. The progress of the reaction was followed by TLC/GC. The product was isolated by adding ether (2 × 15 mL), and the solid was removed by filtration through a sintered glass funnel and the solvent was evaporated by rotary evaporator. The crude product was purified through a short column of silica gel (hexane: EtOAc, 80:20) to obtain a pure product.

4-bromophenyl-1,3-dithiolane. ^{1}H NMR ($CDCl_3$), δ ppm 7.50 (2 H, d, J = 5.00 Hz), 7.20 (2 H, d, J = 5.00 Hz), 5.55 (1 H, s), 3.47–3.39 (2 H, m), 3.34–3.28 (2 H, m).

3-chlorophenyl-1,3-dithiolane. ^{1}H NMR ($CDCl_3$), δ ppm 7.58 (1 H, s), 7.43–7.37 (1 H, m), 7.28–7.21 (2 H, d, J = 7.58 Hz), 5.62 (1 H, s), 3.56–3.48 (2 H, m), 3.42–3.36 (2 H, m).

4-chlorophenyl-1,3-dithiolane. ^{1}H NMR ($CDCl_3$), δ ppm 7.70 (2 H, d, J = 6.55 Hz), 7.25 (2 H, d, J = 6.55 Hz), 5.60 (1 H, s), 3.51–3.41 (2 H, m), 3.36–3.29 (2 H, m).

3-nitrophenyl-1,3-dithiolane. ^{1}H NMR ($CDCl_3$), δ ppm 8.44 (1 H, s), 8.16 (1 H, d, J = 7.0 Hz), 7.87 (1 H, d, J = 7.73 Hz), 7.52 (1 H, t, J = 7.46 Hz), 5.71 (1 H, s), 3.59–3.54 (2 H, m), 3.48–3.43 (2 H, m).

3-methoxyphenyl-1,3-dithiolane. ^{1}H NMR ($CDCl_3$), δ ppm 7.28 (1 H, t, J = 7.56 Hz), 7.16 (2 H, s), 6.85 (1 H, d, J = 7.57 Hz), 5.67 (1 H, s), 3.85 (3 H, s), 3.52–3.51 (2 H, m), 3.37–3.36 (2 H, m).

2-methoxyphenyl-1,3-dithiolane. ^{1}H NMR ($CDCl_3$), δ ppm 7.78 (1 H, d, J = 7.66 Hz), 7.29–7.26 (1 H, m), 6.99 (1 H,t, J = 7.50 Hz), 6.89 (1 H, d, J = 8.19 Hz), 6.10 (1 H, s), 3.90 (3 H, s), 3.49–3.45 (2 H, m), 3.38–3.35 (2 H, m).

2-hydroxyphenyl-1,3-dithiolane. ^{1}H NMR ($CDCl_3$), δ ppm 7.34 (1 H, d, J = 7.00 Hz), 7.26 (1 H, t, J = 8.02 Hz), 6.93–6.88 (2 H, m), 6.77(OH, s), 5.85 (1 H, s), 3.62–3.56 (2 H, m), 3.45–3.38 (2 H, m).

2-methyl-2-(4-methoxyphenyl)-1,3-dithiolane. ^{1}H NMR (CDCl3), δ ppm 7.72 (2 H, d, J = 8.81 Hz), 6.88 (2 H, d, J = 8.81 Hz), 3.80 (3 H, s), 3.51–3.48 (2 H, m), 3.42–3.39 (2 H, m), 2.20 (3 H, s).

2-methyl-2-(3-methoxypheny)-1,3-dithiolane. ^{1}H NMR (CDCl3), δ ppm 7.40–7.37 (2 H, m), 7.28 (1 H, t, J = 7.93 Hz), 6.82 (1 H, d, J = 8.09 Hz), 3.86 (3 H, s), 3.52–3.48 (2 H, m), 3.44–3.38 (2 H, m), 2.20 (3 H, s).

2-methyl-2-(4-nitropheny)-1,3-dithiolane. ^{1}H NMR (CDCl3), δ ppm 8.19 (2 H, d, J = 8.88 Hz), 7.96 (2 H, d, J = 8.86 Hz), 3.58–3.51 (2 H, m), 3.43–3.37 (2 H, m), 2.25 (3 H, s).

2-methyl-2pentyl-1,3-dithiolane. ^{1}H NMR (CDCl3), δ ppm 3.40–3.30 (4 H, m), 1.96–1.93 (2 H, m), 1.77 (3 H, s), 1.56–1.51 (2 H, m), 1.39–1.28 (4 H, m), 0.92 (3 H, t, J = 6.82 Hz).

1,4-dithia-spiro[4.6]undecane. 1H NMR (CDCl3), δ ppm 3.30 (4 H, m), 2.24–2.19 (4 H, m), 1.64–1.62 (8 H, m).

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