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RESEARCH LETTER

Silica supported orthophosphoric acid ($\text{H}_3\text{PO}_4 \cdot \text{SiO}_2$): a green, heterogeneous catalyst for solvent-free oxathioacetalization of aldehydes

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A silica supported orthophosphoric acid catalyst ($\text{H}_3\text{PO}_4 \cdot \text{SiO}_2$) was prepared by stirring silica gel (100–200 mesh) with orthophosphoric acid in chloroform at room temperature. The catalyst was characterized by scanning electron microscopy (SEM) and energy dispersion analytical X-ray (EDX). It demonstrated excellent activity, chemoselectivity, and recyclability for oxathioacetalization of aldehydes.

Keywords: $\text{H}_3\text{PO}_4 \cdot \text{SiO}_2$; oxathioacetalization; orthophosphoric acid; chemoselective; 1-3-oxathiolane

Introduction

The growing awareness of environmentally friendly approaches in organic synthesis has been influenced by the use of solid acids and chemical processes on solid surfaces. In general, heterogeneous catalysis is preferred over homogeneous catalysis in industrial processes as the extraction of the product and recovery of the catalyst are relatively easier (1–4). The development of non-metallic solid catalysts has drawn much attention in recent times due to their advantage of minimal product contamination from metal leaching. Apart from this, because of their ease of preparation, efficiency, and reusability, silica-supported catalysts as well as various acids impregnated on silica gel have gained considerable attention. So far various silica supported catalysts have been reported, e.g. $\text{SOCl}_2/\text{SiO}_2$ (5), $\text{CoBr}_2/\text{SiO}_2$ (6), $\text{ZrCl}_4/\text{SiO}_2$ (7), $\text{TaCl}_5/\text{SiO}_2$ (8), $\text{Cu}(\text{OTf})_2/\text{SiO}_2$ (9), $\text{HClO}_4/\text{SiO}_2$ (10), etc. The versatility and overall synthetic utility of such silica supported acid catalysts can be exemplified by their applications to various organic transformations such as stereoselective synthesis of thiochromans (11); acetylation of phenols, alcohols, and amines (12); glycosylation (13); synthesis of quinolines (14); etc. Fay et al. (15) used TEMPO supported on silica for Anelli oxidation of alcohols. Dias et al. (16) reported metal oxide supported on silica as an efficient catalyst for oxidation of methanol to formaldehyde. In one of the recent reports of esterification of carboxylic acids, Chakraborty et al. (17) used silica supported perchloric acid. However,

most of these catalysts have one or more drawbacks such as being difficult to prepare, sensitive to moisture, corrosive, etc. Also, silica supported metal catalysts such as $\text{CoBr}_2/\text{SiO}_2$, $\text{ZrCl}_4/\text{SiO}_2$, $\text{Cu}(\text{OTf})_2/\text{SiO}_2$, and $\text{AlCl}_3/\text{SiO}_2$ may lead to contamination of products with trace amounts of metal, which is one of the major problems in synthesis of pure active pharmaceutical ingredients (APIs) and industrially important compounds.

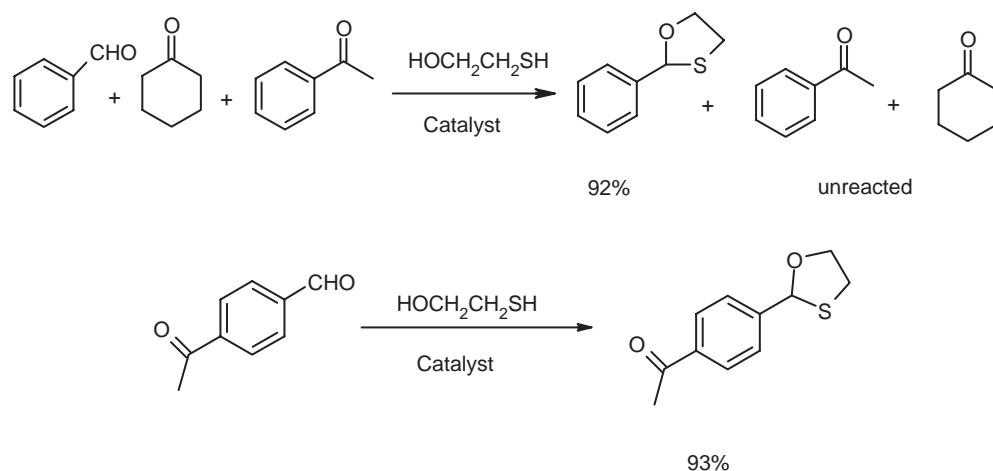
Today, organic synthesis has reached a remarkable level of competence, and even the most complex molecules are accessible. The prerequisites for this success are both the availability of a wide range of efficient synthetic methods and reagents. However, the complex synthetic intermediates and products contain, in general, a multiplicity of functional groups, most of which must be blocked and, at an appropriate point in the synthesis, liberated. In multistep synthesis of various industrially important polyfunctional organic molecules, the protection of carbonyl groups plays a key role. In this paper we report an easy-to-prepare, cost-effective, efficient, and reusable silica supported orthophosphoric acid catalyst for the protection of aldehydes as oxathioacetals.

Results and discussion

Catalyst synthesis and characterization

As a part of our program toward the development of environmentally benign protocols, herein we report a silica supported orthophosphoric acid catalyst for

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Scheme 1. Chemoselective oxathioacetalization of aldehyde (GC yields).

oxathioacetalization of aldehydes. Even though a similar kind of silica supported polyphosphoric acid catalyst has been reported earlier (18), the present catalyst has the advantage of chemoselectivity (Scheme 1) over the reported catalyst. We have also successfully characterized this silica supported catalyst with the help of scanning electron microscopy (SEM) and energy dispersion analytical X-ray (EDX).

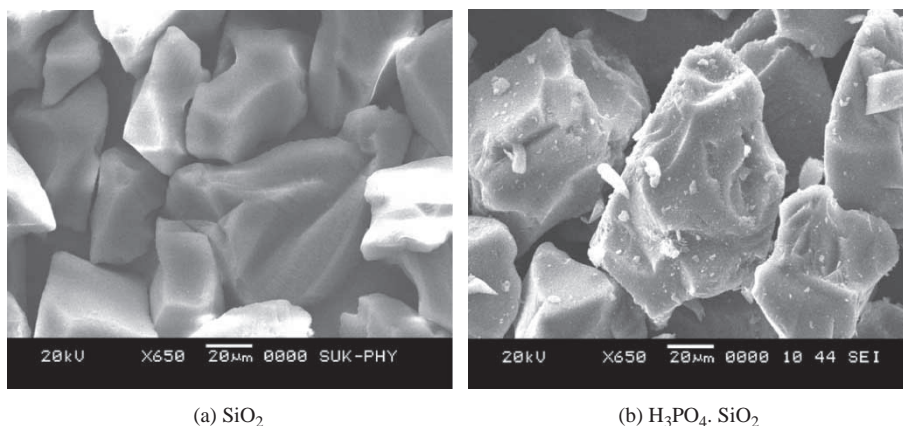
In a typical experiment, taking the reference of earlier reports (11,18,19) of preparation of silica supported catalysts, the orthophosphoric acid was added to a stirred suspension of silica gel in chloroform. After stirring for 2 h the white silica turned gray, indicating the formation of the catalyst. Then the chloroform was evaporated in vacuo, and the resultant powder was dried at 100°C to give a free-flowing material as catalyst.

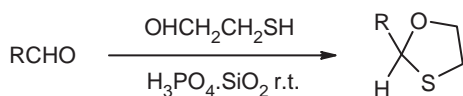
To study the surface morphology of the catalyst, the SEM monographs of the catalyst prepared were compared with that of the silica

gel used for its preparation. The SEM images of the catalyst (Figure 1) showed small buds on the surface. This change in surface morphology prompted us to go for EDX analysis of the catalyst. In EDX analysis (see supporting information) the characteristic peak at 2.013 keV for phosphorous confirmed the presence of phosphorous. The percentage mass content of phosphorous (15.83) perfectly matched the theoretically calculated value (15.82). This particular information revealed that the orthophosphoric acid had become supported on the silica.

Application of catalyst for oxathioacetalization

There are various reports (19–22) on protection of carbonyl compounds by acetalization, thioacetalization, oxathioacetalization, and dithioacetalization. However, the oxathioacetalization has advantages like stability in acidic conditions and easy removal. Aoyama et al. (18) used PPA.SiO₂ for oxathioacetalization of aldehydes and ketones. In one of the recent

(a) SiO₂(b) H₃PO₄.SiO₂Figure 1. SEM images of (a) SiO₂, (b) H₃PO₄.SiO₂.



Scheme 2. Oxathioacetalization of aldehyde.

reports Kumar et al. (23) used nanosized nickel particles for selective protection of carbonyl compounds. In their report of oxathioacetalization of carbonyl compounds, Liang et al. (24) used a novel organo catalyst. Recently, Konwar et al. (25) demonstrated the application of tin (IV) hydrogen phosphate nanodiscs for oxathioacetalization of aldehydes.

Further, to test the utility of the catalyst in organic transformations, we decided to use the catalyst for oxathioacetalization of aldehydes (Scheme 2). Taking benzaldehyde as the model substrate, we investigated the reaction in various solvents as indicated in Table 1. The reaction proceeded with good yields in chloroform. An attempt to further improve the method and yield prompted us to try solvent-free conditions, and to our delight the reaction went smoothly under solvent-free conditions. To explore the efficiency of the silica supported orthophosphoric acid catalyst and to optimize the reaction conditions, a set of reactions were carried out under different catalytic conditions taking benzaldehyde as the model substrate. It was found that there was no reaction without the catalyst or in the presence of silica even after stirring at room temperature for 20 h. We studied the reaction using 50, 25, and 20 mg of catalyst per mmol of substrate and found that the reaction proceeded smoothly with good yields in the presence of 25 mg of catalyst per mmol. There was no any substantial effect on yields even after use of 50 mg of catalyst.

Table 1. Optimization of reaction conditions.

No	Solvent	Catalyst	Yield ^a
1	Ethyl acetate	H3PO4. SiO2, 50 mg	21
2	[bmim]BF4	H3PO4. SiO2, 50 mg	56
3	[bmim]PF6	H3PO4. SiO2, 50 mg	61
4	THF	H3PO4. SiO2, 50 mg	20
5	Acetonitrile	H3PO4. SiO2, 50 mg	80
6	Chloroform	H3PO4. SiO2, 50 mg	82(78)
7	–	H3PO4. SiO2, 50 mg	92(86)
8	–	H3PO4. SiO2, 100	90(81)
9	–	H3PO4. SiO2, 40 mg	89(80)
10	–	SiO2	0
11	–	No catalyst	0

^a% GC yields; % isolated yields are in parenthesis; reactions were carried out at r.t. with 2 mmol of benzaldehyde; [bmim]BF4, butyl methyl imidazolium tetrafluoroborate and [bmim]PF6, butyl methyl imidazolium hexafluorophosphate.

It was found that a number of aromatic and aliphatic aldehydes underwent the reaction smoothly under solvent-free conditions at room temperature with good to excellent yields (Table 2). The reactions were completed in 30–70 min with excellent yields. The reaction for the aldehydes (*c*) and (*o*) proceeded fast in comparison with other substrates. The aldehydes with electron-deficient substituents (entry *b*) gave poor yields while on the contrary aldehydes with electron-rich substituents (entry *c*) gave good yields. Even a bulky molecule like aldehyde (*p*), which is an intermediate used in synthesis of the antiobesity drug fluvastatin, underwent the reaction with a good yield.

Taking into account the mildness of the catalyst, we decided to study the chemoselectivity. For that we took equimolar amounts (2 mmole each) of cyclohexanone, acetophenone, benzaldehyde, and mercaptoethanol and stirred the reaction mixture at room temperature with the catalyst (50 mg). After 2 h of reaction, only aldehyde underwent the reaction and (from GC analysis) the ketones remained unreacted (Scheme 1). This kind of selectivity is not found even with the silica supported polyphosphoric acid (PPA.SiO₂) (18), making it clear that H₃PO₄.SiO₂ is milder than this catalyst. In the case of 4-acetyl benzaldehyde the chemoselective oxathioacetalization (93% conversion) of aldehyde was observed. We have compared this catalyst with some recently reported catalysts. The present catalyst is simple owing to its easy preparation and workup procedures and good yields under solvent-free conditions (Table 3).

Reusability of the catalyst

To test the reusability of the catalyst, benzaldehyde was treated with mercaptoethanol in the presence of the catalyst. After completion of the reaction (TLC), ethyl acetate was added and filtered to get the solid catalyst. This, after vacuum drying at 80°C, was reused for the reaction. The catalyst was reused without any substantial loss of catalytic activity for four consecutive cycles (Table 4).

Experimental

Silica gel (100–200 mesh, Aldrich), orthophosphoric acid (85% aqueous, Aldrich), chloroform (AR grade, Runa chemicals, India), and ethyl acetate (AR grade, Runa chemicals, India) were used as received. The mercaptoethanol (caution: avoid inhalation and contact with skin) and dihydropyran were purchased from Aldrich and were used as received. The aldehydes were either purchased from Aldrich or prepared in the lab and were used as is. The progress

Table 2. Oxathioacetalization of aldehydes.

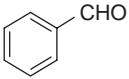
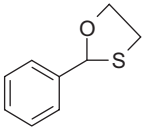
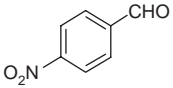
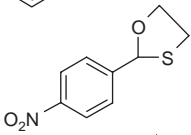
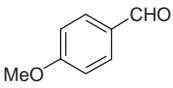
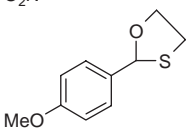
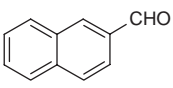
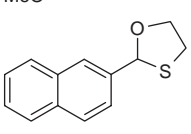
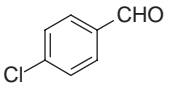
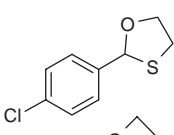
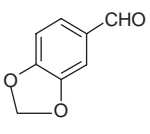
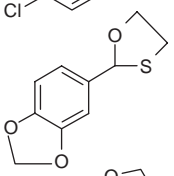
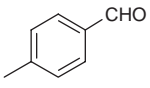
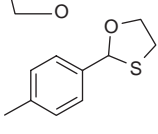
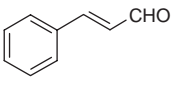
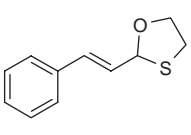
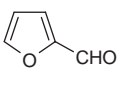
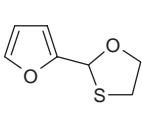
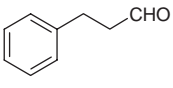
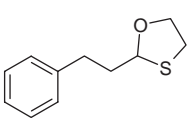
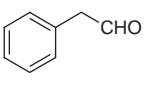
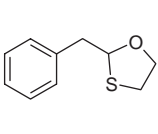
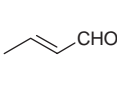
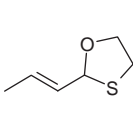
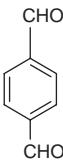
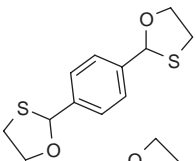
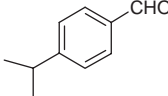
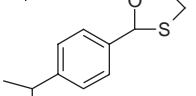
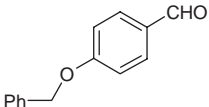
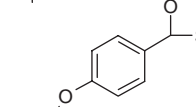
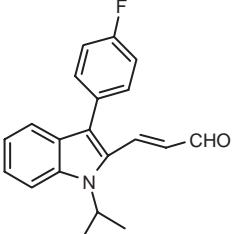
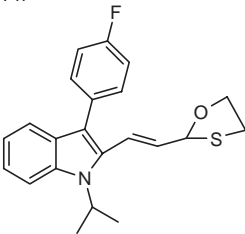
No.	Substrate	Time (min)	Product	Yield (%) ^a	Ref.
<i>a</i>		70		86	(26)
<i>b</i>		60		78	(26)
<i>c</i>		25		93	(19)
<i>d</i>		70		88	(25)
<i>e</i>		60		85	(19)
<i>f</i>		40		90	(26)
<i>g</i>		45		92	(27)
<i>h</i>		30		91	(19)
<i>i</i>		40		93	(29)
<i>j</i>		30		89	(28)
<i>k</i>		30		92	(19)
<i>l</i>		40		90	(28)

Table 2 (Continued)

No.	Substrate	Time (min)	Product	Yield (%) ^a	Ref.
m		35		89	—
n		45		86	—
o		20		94	—
p		65		88	—

^aIsolated yields.

of the reaction was monitored by TLC (Silica gel 60 F₂₅₄). Mass spectra were obtained using GC/MS Shimadzu QP-2010 (EI, 70eV). The samples for SEM were prepared in an auto fine sputter coater with a gold target. The SEM-EDX characterization was performed on a JEOL JSM-6360 scanning electron microscope equipped with a JEOL EX-54175JMU energy dispersive X-ray high vacuum germanium detector (E = 20 kV, W-filament). Samples were analyzed from 15 mm working distance, with a resolution of 12 nm. The content of phosphorous was also measured by EDX. IR spectra were recorded on a Perkin Elmer Spectrometer. The ¹H NMR and ¹³C NMR were recorded on a JEOL 300 MHz/ Bruker 300 MHz Avance II spectrometer in CDCl₃.

Preparation of silica supported orthophosphoric acid catalyst

Orthophosphoric acid (3.5 gm) was added to a suspension of SiO₂ (5 g) in chloroform (30 mL) and stirred at room temperature for 2 h. The mixture was concentrated and heated at 100°C to get free-flowing powder.

Oxathioacetalization of aldehydes

A stirred mixture of aldehyde (2 mmol) and 2-mercaptoethanol (2.4 mmol, 0.17 mL) was treated with the catalyst (50 mg) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate and the

Table 3. Comparison of some recent results with present protocol.

Catalyst	Solvent	Catalyst quantity	Time (min)	Yield (%) ^a	Ref.
SiO ₂ .H ₃ PO ₄	—	50 mg	60	78	—
SiO ₂ .HClO ₄	—	40 mg	30	65	(10)
SiO ₂ .HBF ₄	—	20 mg	25	78	(18)
SiO ₂ .PPA	C ₂ H ₂ Cl ₂	1 g	30	82	(22)
Sn(HPO ₄) ₂ .H ₂ O	CH ₂ Cl ₂	5 mole%	50	88	(25)

^aIsolated yields based on reaction of 4-Nitro benzaldehyde (2 mmol) and mercaptoethanol (2.4 mmol).

Table 4. Reusability of the catalyst.

Run	Conversion (%) ^a
1	92
2	88
3	84
4	82

^aGC yields for oxathioacetalization of benzaldehyde.

catalyst was filtered off. The organic layer was washed with bicarbonate solution, then with water, and dried over anhydrous sodium sulfate. Then the filtrate was concentrated and purified by silica gel column chromatography.

Conclusions

A simple and recyclable silica supported orthophosphoric acid catalyst has been prepared, characterized, and used to devise a mild and efficient protocol for chemoselective oxathioacetalization of aldehydes. The yields are excellent with chemoselective reaction of the aldehydes. The catalyst can be called green because of its ease of preparation, mildness, easy workup procedure (filtration), and stability in air. Apart from this, the solvent-free reaction conditions and applicability to a wide spectrum of aldehydes are other advantages of the present protocol.

Acknowledgements

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