SILICA-PCl$_5$: A NOVEL HETEROGENOUS CATALYST FOR SIMPLE AND EFFICIENT CHEMOSELECTIVE PROTECTION OF CARBONYL COMPOUNDS

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Abstract –A simple, efficient and environmentally benign procedure has been developed for chemoselective protection of carbonyl compounds using the newly developed heterogeneous catalyst: Silica-PCl$_5$. A variety of aldehydes and ketones were efficiently converted to the corresponding acyclic and cyclic dithioacetals by using catalytic amounts of Silica-PCl$_5$ in CH_2Cl_2 under very mild conditions.

Keywords- Silica-PCl$_5$, Thioacetalization, carbonyl compounds, dithianes, dithiolanes

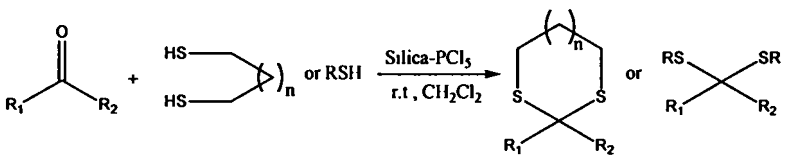
Introduction- Protection of carbonyl compounds as thioacetals is an important synthetic strategy and is frequently used in the synthesis of multifunctional organic molecules.[1] Thioacetals are quite stable towards different reagents under various reaction conditions.[2] In addition to the carbonyl protection, they behave as masked acyl anions or masked methylene functions in carbon-carbon bond forming reactions.[3, 4] Generally, thioacetals are prepared by condensation of carbonyl compounds with thiols or dithiols under the catalysis of protic or Lewis acids hence, the catalyst used also plays an important role in dictating the efficiency of the process. Various catalyst reported are HCl,[5a] WCl$_6$,[5b] LiBr,[5c] LiOTf,[5d] I$_2$,[5e] AlCl$_3$[5f] trichloroisocyanuric acid,[5g] LaCl$_3$,[5h] CuBr,[5i] ZnCl$_2$,[5j].

The use of heterogeneous catalysts is becoming very popular as it has many advantages: reduced pollution, reusability, high selectivity, low cost, and simplicity in process and in handling. Recently supported catalyst such as anhydrous SOCl$_2$-SiO$_2$,[6a] FeCl$_3$/SiO$_2$,[6b] Cu(OTf)$_2$-SiO$_2$,[6c] Nafion-H catalyst,[6d] Amberlyst-15,[6e] modified clay such as Ce-Mont,[6f] Heteropoly acids[6g] and Natural Kaolinitic Clay[6h] have been reported for efficient thioacetalisation. Still some of these methods suffer from limitations such as long reaction time and reflux temperatures, non selectivity when applied to a mixture of aldehydes and ketones, inert atmospheric reaction conditions, incompatible with other functional groups and high cost. Therefore, the search for a better reagent/method had continued with an aim to develop a mild, clean, simple, selective and inexpensive procedure, having functional group compatibility.

In continuation to our interest in developing novel reagents and methods for organosulfur transformations,[7] we now report a new heterogenous catalyst: Silica-PCl$_5$[8] for a very simple and efficient protection of carbonyl compounds.

Silica-PCl_5 can be prepared conveniently from silica and PCl_5 which is inexpensive and easily available. In the present investigation the protection of various aldehydes and ketones with different protecting agent was investigated (Scheme 1). The reaction was found to occur cleanly under mild condition. Through a simple work-up thioacetals were obtained in excellent yield and purity.

Result and discussion- Silica-PCl_5 is a safe, stable, easily handled and reusable solid acid catalyst. Protection of several aromatic, heterocyclic and aliphatic aldehydehydes and ketones was carried out by simple stirring of the carbonyl compound with appropriate protecting agent in CH_2Cl_2 and catalytic amount of Silica-PCl_5 at room temperature (Table 1). The reaction was complete within 10-30 minutes to afford the products in excellent yields and purity. The applicability of this catalyst to various protecting agents was studied. Commonly used protecting agents such Ethane and propane dithiols and thiols of different chain lengths (Entry 4 and 5) were investigated and the catalyst was found to be useful. An array of substrates with different functional groups was also studied. Several functional groups such as ether, halogen, nitro, olefin, hydroxyl, amino groups remained intact (Entry 6, 9, 13, 17, 21 and 29). The reaction proceeds smoothly with aldehydes bearing ring activating or deactivating groups. Aliphatic ketones were also converted to the corresponding dithioketals in excellent isolated yields (Table 1: Entry 25 and 28). However, aromatic ketones required prolonged reaction time even in excess amount of catalyst.



Scheme 1

Table 1: Thioacetalisation of Carbonyl Compounds and with Silica-PCl_5

Entry	Substrate	Reagent	Product	Time (min)	Yield(%)[a]
1.	Benzaldehyde	$HS(CH_2)_2SH$	**1a**	15	91
2.		$HS(CH_2)_3SH$	**1b**	20	93
3.		C_2H_5SH	**1c**	15	88
4.		C_4H_9SH	**1d**	20	95[c]
5.		$C_6H_{13}SH$	**1e**	25	93[c]
6.	*p*-Methoxy benzaldehyde	$HS(CH_2)_2SH$	**2a**	12	92
7.		$HS(CH_2)_3SH$	**2b**	14	89
8.	Acetophenone	$HS(CH_2)_2SH$	**3a**	10	92
9.	*p*-Chloro benzaldehyde	$HS(CH_2)_2SH$	**4a**	15	94
10.	*p*-Chloro acetophenone	$HS(CH_2)_2SH$	**5a**	18	93
11.		$HS(CH_2)_3SH$	**5b**	20	89
12.	Benzophenone	$HS(CH_2)_2SH$	**6a**	30	85
13.	*p*-Nitrobenzaldehyde	$HS(CH_2)_2SH$	**7a**	18	88
14.		$HS(CH_2)_3SH$	**7b**	22	87
15.		C_2H_5SH	**7c**	25	93
16.	Camphor	$HS(CH_2)_2SH$	**8a**	24[b]	92[c]
17.	Cinamaldehyde	$HS(CH_2)_2SH$	**9a**	15	93
18.	N, N dimethylamino benzaldehyde	$HS(CH_2)_2SH$	**10a**	25	85
19.	Butyraldehyde	$HS(CH_2)_2SH$	**11a**	25	88
20.		$HS(CH_2)_3SH$	**11b**	25	89
21.	Salcilaldehyde	$HS(CH_2)_3SH$	**12b**	30	90
22.	3, 4, 5-Trimethoxy benzaldehyde	$HS(CH_2)_3SH$	**13b**	18	92
23.	1-Naphthaldehyde	$HS(CH_2)_2SH$	**14a**	20	85
24.		$HS(CH_2)_3SH$	**14b**	20	84
25.	Cyclohexanone	$HS(CH_2)_2SH$	**15a**	20	88
26.		$HS(CH_2)_3SH$	**15b**	25	84
27.		C_2H_5SH	**15c**	20	86
28.	2-Butanone	$HS(CH_2)_2SH$	**16a**	35	84
29.	2-Amino-5-chloro benzophenone	$HS(CH_2)_2SH$	**17a**	30	97[c]
30.	Furfuraldehyde	$HS(CH_2)_2SH$	**18a**	30	86
31.	2, 3-Dichlorobenzaldehyde	$HS(CH_2)_2SH$	**19a**	25	92

[a] Isolated Yield, Products were characterized by IR, NMR and Mass spectra.

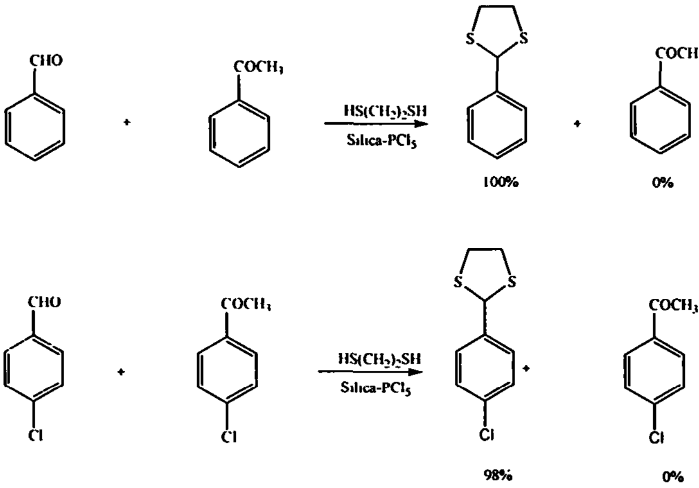
[b] Time in hours

[c] Conversion by GLC

The presented results indicates that aliphatic and aromatic aldehydes were protected more quickly than aromatic and hindered ketones.

It was realized that the methodology could be applied for chemoselective protection of aldehyde in presence of a ketone due to their reactivity difference. To study this, when an equimolar mixture of benzaldehyde and acetophenone (1 mmol) was treated with 1, 2-ethanedithiol (1.0 mmol) in CH_2Cl_2 at room temperature in the presence of Silica-PCl_5, benzaldehyde was converted into corresponding 1, 3-dithiolane in 30 minutes while acetophenone remained unreacted. This chemoselectivity was further convincingly demonstrated by performing the reaction with mixture of p-chlorobenzaldehyde and p-chloroacetophenone (Scheme 2). Under the reaction condition employed only aldehyde were converted into corresponding dithiolane while ketone remains unaffected.

Reusability is one of the additional attractive features of Silica-PCl_5. The reaction of benzaldehyde and 1, 2-ethanditithiol was studied to investigate the reusability. It was found that the catalyst can be recycled for at least four times to yield thioacetal in almost comparable yields, as for the freshly prepared catalyst.



Scheme 2

Conclusion- In summary, a novel reusable heterogeneous acid catalyst Silica-PCl_5 has been developed for a very mild clean, efficient, and selective protection of carbonyl compounds. The interesting feature of this protocol is the simple reaction and facile isolation of the pure product without any extensive work-up. The acid catalyst remains bound to the silica and can be removed by simple filtration. No undesirable side product formation was observed under reaction. In addition, the use of this solid acid catalyst has resulted in evading the unwanted and hazardous waste that is produced during conventional homogeneous processes. The other applications of the newly developed reagent are being investigated and will be reported in due course of time.

Experimental-*General procedure:* 1 mmol of carbonyl compound was taken in dichloromethane (2 ml) and 1 mmol of dithiol or 2 mmol of thiol as applicable was added. To this 0.30 g of Silica-PCl_5 was added and reaction mixture was stirred for a specified time (Table 1). Silica was filtered off and removal of the solvent afforded thioacetals. In case of amino compounds contents were washed with sodium bicarbonate solution prior to solvent removal. Liquid products were purified further by distillation and solids by recrystallisation from appropriate solvents. The catalyst was regenerated by heating the used catalyst at 100 °C for two hours.

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8. *Preparation of Silica-PCl_5*: 15 g. of dry silica was mixed with 10 g of PCl_5. To this 50 ml. of dry dichloromethane was added drop wise and the mixture was stirred at room temperature for one hour. Solvent was evaporated and the Contents were heated at 70 °C for three hours with stirring. HCl evolved was removed with a slow stream of Nitrogen. Contents were then washed with 100 ml. of dichloromethane, filtered under vacuum and dried at 100 °C for three hours. The free flowing white Silica-PCl_5 thus obtained was stored in a tightly caped bottle. IR spectra of both silica and Silica-PCl_5 were found to be similar and both showed strong adsorption at 1098 cm^{-1} and 800 cm^{-1}. Acid-Base titration of the reagent gave a total acid content of 54 mg KOH/g of Silica-PCl_5.

Spectral Data for the selected compounds:

4-Nitrobenzaldehyde diethyldithioacetal 7c. Light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3+CCl_4$): δ 1.24 (t, 6H, J=7.34Hz), 2.48-2.68 (m, 4H), 4.98 (s, 1H), 7.65 (d, 2H, 8.58Hz), 8.22 (d, 2H, J=8.58Hz); ^{13}C NMR (101.6 MHz, $CDCl_3+CCl_4$); δ 14.08, 26.23, 51.58, 123.74, 128.53, 147.12, 148.12. Anal. Calcd. For $C_{11}H_{15}O_2NS_2$: C 51.33; H 5.87; S 24.92. Found: C, 51.27; H, 5.98; S, 24.80.

2-(3, 4, 5-Trimethoxyphenyl)-1, 3-dithiane 13b. White Solid; mp 86-87°C; ^{1}H NMR (400 MHz, $CDCl_3+CCl_4$): δ 1.78-2.32 (m, 2H), 2.81-3.17 (m, 4H), 3.81-3.87 (m, 3H), 3.89 (s, 6H), 5.08 (s, 1H), 6.67 (s, 2H); ^{13}C NMR (101.6 MHz, $CDCl_3+CCl_4$); δ 25.6, 32.32, 51.90, 56.14, 60.78, 104.76, 134.82, 137.84, 153.32; Mass (m/z): 286 (M^+). Anal. Calcd. For $C_{13}H_{18}O_3S_2$: C 54.52; H 6.33; S 22.39. Found C 54.67; H 6.47; S 22.49.

2-(2, 3-Dichlorophenyl)-1, 3-dithiolane 19a. White solid; mp 58-60°C; ^{1}H NMR (400 MHz, $CDCl_3+CCl_4$): δ 3.37-3.46 (m, 4H), 6.08 (s, 1H), 7.24 (t, J=8Hz, 1H), 7.40 (dd, J=8Hz, J=2Hz, 1H), 7.78 (dd, J=8Hz, J=2Hz, 1H); ^{13}C NMR (101.6 MHz, $CDCl_3+CCl_4$); δ 38.00, 54.05, 127.92, 128.62, 128.90, 134.51, 134.89, 141.02; Mass (m/z): 250 (M^+). Anal. Calcd. For $C_9H_8Cl_2S_2$: C 43.03; H 3.21; Cl 28.23, S 25.53. Found C 43.10; H 3.34; Cl 27.94; S 25.60.

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