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Note

Silica supported zinc chloride catalyzed acetylation of amines, alcohols and phenols

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Silica supported zinc chloride (SiO_2-$ZnCl_2$) has been prepared and found to efficiently catalyze the acetylation of amines, alcohols and phenols by stirring in acetonitrile at 80ºC under heterogeneous conditions. The catalyst can be separated from the reaction medium simply by filtration and re-used up to four times.

Keywords: Silica supported zinc chloride, acetylation, alcohols, phenols, amines, re-cyclable heterogeneous catalyst

In the area of green chemistry, the development of heterogeneous catalysts has played an important role, since they offer several advantages such as clean reaction conditions, easy separation of the catalyst from the reaction medium, greater selectivity and generally give higher yield of products and can be recycled for a number of times. The heterogeneous catalysts have been proven to offer similar levels of activity to their homogeneous counterparts. The majority of these novel heterogeneous catalysts are based primarily on silica, since silica displays many advantageous properties *i.e.* excellent stability (chemical as well as thermal), high surface area, good accessibility and in addition, organic groups can be robustly anchored to the surface, to provide catalytic centres.

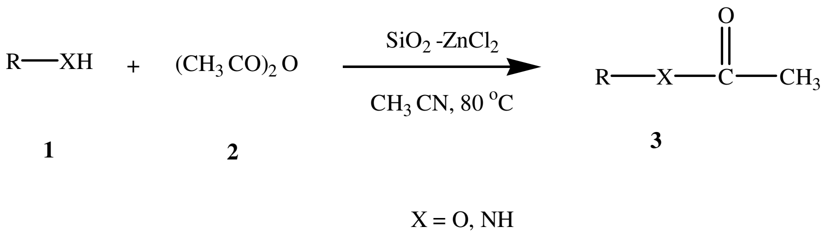
The acetylation of amines, alcohols and phenols is an important chemical reaction in organic synthesis[1]. Pyridine and 4-dialkylaminopyridines are the most commonly used basic catalysts[2]. Recent literature describes numerous catalysts which are either acidic or basic. Among the basic catalysts, Bu_3P (Ref. 3), $MgBr_2$-R_3N (Ref. 4) and an aminophosphine super base[5] are significant. Besides the basic catalysts, a number of acidic catalysts such as $Gd(OTf)_3$ immobilized in room-temperature ionic liquid[6], $HClO_4$-SiO_2 (Ref. 7), Ac_2O-Py/basic alumina (Ref. 8), $NiCl_2$ (Ref. 9), $RuCl_3$ (Ref. 10), Al_2O_3-MoO_3 (Ref. 11), $LiClO_4.2H_2O$ (Ref. 12), *N,N*-dichloro-4-methylbenzenesulphonimide[13], bis(cyclopentadienyl)zirconium dichloride[14], erbium (III) chloride[15], niobium pentachloride[16], $NaHSO_4.SiO_2$ (Ref. 17), tungstophosphoric acid supported over zirconium[18] and Sn (TPP)$(BF_4)_2$ (Ref. 19) have also been reported. Literature survey revealed that the application of inorganic solids especially zeolites have recently received considerable attention due to their unique physical and chemical properties. H-FER[20] has been reported for the acetylation of alcohols and phenols under solvent-free conditions. However, some of these acetylation methodologies suffer from one or more disadvantages such as stringent conditions, use of hazardous materials, use of expensive reagents/catalysts or in terms of lower yields leaving enough scope for the development of simple, efficient and milder methods.

Zinc chloride is widely used in organic synthesis as a lewis acid, but suffers from drawbacks such as its highly hygroscopic nature which often creates problems during work-up and thus making the process economically and environmentally undesirable. In an earlier communication, is reported the preparation of silica supported zinc chloride (SiO_2-$ZnCl_2$) and its applications for the synthesis of Biginelli compounds[21]. In this paper, is reported the use of SiO_2-$ZnCl_2$ for the acetylation of amines, alcohols and phenols by stirring in acetonitrile at 80ºC under heterogeneous conditions (**Scheme I**).

Results and Discussion

Silica-supported zinc chloride[21] was prepared by refluxing $ZnCl_2$ (3 g) with activated K 100 silica gel (10 g) in sodium dried toluene for 10 hr. At this temperature, some of the $ZnCl_2$ may have reacted with the surface hydroxyl groups to create highly acidic species chemically bonded to the support. After separation of the catalyst by filtration under reduced pressure, it was dried at 110ºC for 12 hr and stored in a desiccator. It could be used for several months. The proposed structure of the catalyst in which $ZnCl_2$ may have reacted with the surface hydroxyl groups of the silica gel is shown in **Figure 1**.

The stability of the SiO_2-$ZnCl_2$ was determined by thermogravimetric analysis (TGA). The initial weight



Scheme I

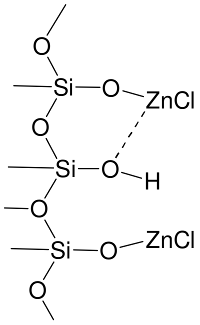


Figure 1 — Probable structure of covalently anchored silica supported zinc chloride

loss at 80°C followed by 95-150°C and 285- 310°C may be due to the loss of residual solvent and HCl, which may have formed during the reaction of $ZnCl_2$ with silica gel. Up to 310°C, there is no possibility of the loss of physisorbed and chemisorbed $ZnCl_2$ from the surface of silica gel. Therefore, it is safe to carry out the reaction at 80°C.

For optimizing the reaction conditions, the primary emphasis is laid on the selection of solvent for carrying out the reaction. Among various solvents tried (*n*-hexane, THF, toluene and acetonitrile), acetonitrile was found to be the best solvent in terms of reaction time and yield. Phenol was selected as the test substrate and the reaction with acetic anhydride (entry 3, **Table I**) was carried out under different set of conditions with respect to molar ratios of the substrate, catalyst and the reaction temperature (RT, 50, 80 and 100°C), to select the optimum reaction conditions. It was found that for 1 mmole of phenol and 1.2 mmole of acetic anhydride, 0.4 g (24 mol% of Zn) of SiO_2-$ZnCl_2$ and 10 mL of acetonitrile was required. 80°C was found to be the optimum reaction temperature.

To explore the generality and scope of SiO_2-$ZnCl_2$ for carrying out acetylations, different substrates were chosen including different phenols, alcohols and both aliphatic and aromatic amines. Excellent results were obtained (**Table I**). When benzyl alcohol (entry 1, **Table I**) was subjected to acetylation with SiO_2-$ZnCl_2$, 90% isolated yield of benzyl acetate was obtained in 3 hr. Similarly, amyl alcohol (entry 2, **Table I**) also undergoes acetylation efficiently and amyl acetate was obtained in 79% isolated yield in 4 hr. Similar studies have also been extended for the acetylation of 1-naphthol and 2-naphthol (entries 5 and 6, **Table I**) and it was found that 1-naphthol gave 1-acetoxynaphthalene in 80% isolated yield and 2-naphthol gave 2-acetoxynaphthalene in 83% isolated yield. The reagent SiO_2-$ZnCl_2$ was found to be highly selective in case of dihydroxybenzene. For example, in the case of resorcinol (entries 7 and 8, **Table I**), when 1.2 mmole of acetic anhydride was used, 1-acetoxy-3-hydroxybenzene was isolated in 80% yield in 4.5 hr. However, when 2.2 mmole of acetic anhydride was used, both 1-acetoxy-3-hydroxybenzene and 1,3-diacetoxybenzene were formed when stirred for 6.5 hr in acetonitrile at 80°C, though 1,3-diacetoxybenzene was the major product (70% isolated yield) and 1-acetoxy-3-hydroxybenzene was the minor product (18% isolated yield based on separation by column chromatography by elution with EtOAc : pet. ether). Similar methodology was also extended for both aliphatic and aromatic amines. Even aniline (entry 9, **Table I**) undergoes acetylation smoothly giving 95% isolated yield of acetanilide. All aromatic amines possessing both electro-donating (entries 10-13, **Table I**) and electron-withdrawing groups (entries 14-16, **Table I**) were efficiently acetylated with SiO_2-$ZnCl_2$. In addition to aromatic amines, aliphatic secondary amines (morpholine and piperidine) undergo acetylation efficiently (entries 17 and 18, **Table I**) under similar conditions. SiO_2-$ZnCl_2$ allows chemoselective acetylation of hydroxyl groups in the presence of other functional groups such as aldehyde and ketone. In the case of 4-hydroxybenzaldehyde (entry 19, **Table I**), 4-acetoxybenzaldehyde was isolated in 75% yield in 15 hr without affecting the -CHO group and 4-hydroxyacetophenone (entry 20, **Table I**) gave exclusively 4-acetoxyacetophenone in 75% isolated yield in 13 hr leaving behind keto group. The tolerance of different

Table I — SiO_2-$ZnCl_2$ catalyzed acetylation[a] of amines, alcohols and phenols with acetic anhydride by stirring in acetonitrile at 80°C

Entry	Substrate	Time (hr)	Yield[b] (%)	m.p./b.p. (Lit./Obs.)
1[c]	Benzyl alcohol	3	90	Liq./206 (b.p.) (Ref. 22)
2[c]	Amyl alcohol	4	79	Liq./36 (b.p.) (Ref. 22)
3[c]	Phenol	3.5	83	Liq./196 (b.p.) (Ref. 22)
4[c]	4-Chlorophenol	4	83	Liq./260 (b.p.) (Ref. 23)
5[c]	1-Naphthol	6	80	44-46/46 (Ref. 24)
6[d]	2-Naphthol	6.5	83	69-70/69 (Ref. 24)
7[d]	Resorcinol	6.5	70	Liq./27 (b.p.) (Ref. 24)
8[d]	Resorcinol	4.5	80	Liq./139(b.p.) (Ref. 24)
9[c]	Aniline	2.5	95	113-114/114 (Ref. 25)
10[c]	*o*-Anisidine	3	87	89-91/91 (Ref. 25)
11[c]	*p*-Anisidine	2.5	92	130-132/130 (Ref. 25)
12[c]	*m*-Toluidine	3	83	66-68/68 (Ref. 25)
13[c]	*p*-Toluidine	3	87	154-156/156 (Ref. 25)
14[c]	*o*-Nitroaniline	4.5	79	94-96/95-96 (Ref. 25)
15[c]	*m*-Nitroaniline	3.5	85	155-157/155 (Ref. 25)
16[c]	*p*-Nitroaniline	3	87	214-216/216 (Ref. 25)
17[c]	Morpholine	4.5	80	Liq./13-14 (Ref. 25)
18[c]	Piperidine	4	81	Liq./226-27 (b.p.) (Ref. 25)
19[d,e]	*p*- *p*- Hydroxybenzaldehyde	15	75	158-159/158-160 (Ref. 26)
20[d]	*p*-Hydroxyacetophenone	13	75	53-54/52-54 (Ref. 27)

[a] All the products were characterized by ^1H NMR, IR and mass spectral data and comparison with authentic samples.
[b] Isolated yields of the purified products.
[c] Products were purified by passing through a column of silica gel and elution with EtOAc: pet. ether (1:9).
[d] Products were purified by crystallization from ethyl acetate and petroleum ether.
[e] The reaction was carried out at 100°C.

functional groups towards these reaction conditions illustrates the flexibility and generality of SiO_2-$ZnCl_2$.

In the context of "Green Chemistry" those reagents that can be re-cycled and used for infinite number of times are preferred. The reagent SiO_2-$ZnCl_2$ was also studied for re-cyclability and it was found that in case of entry 3, SiO_2-$ZnCl_2$ can be re-cycled up to 4th use (**Figure 2**). There is a slight loss of activity after every use, which may be due to some microscopic changes in the structure of the catalyst. However, the amount of zinc for the fresh and catalyst after 4th use remained same (determined by atomic absorption spectrophotometer (AAS)).

Experimental Section

Silica gel (K 100, 0.63-0.200 mm) was purchased from Merck (Germany), anhydrous zinc chloride was purchased from Merck and fused prior to use. Melting points were determined on Tempo melting point apparatus and are uncorrected. ^1H NMR spectra was obtained on Bruker DPX-200 NMR spectrometer (200 MHz) in $CDCl_3$ using tetramethylsilane as an internal standard. The IR spectra were recorded using KBr disc on Perkin-Elmer FTIR spectrophotometer (model no. Spectrum RX 1). Mass spectral data was recorded on Jeol JMS D-300 mass spectrometer at 70 eV. Thermal analysis was carried out on DTG- 60 Shimadzu thermal analyzer and the amount of zinc was determined on double beam atomic absorption spectrophotometer GBC 932 AB (manufactured in Australia). The catalyst was stirred in dil. HCl for 10 hr and the resulting filtrate was subjected to atomic absorption spectrophotometric analysis. The progress of the reactions were monitored by TLC.

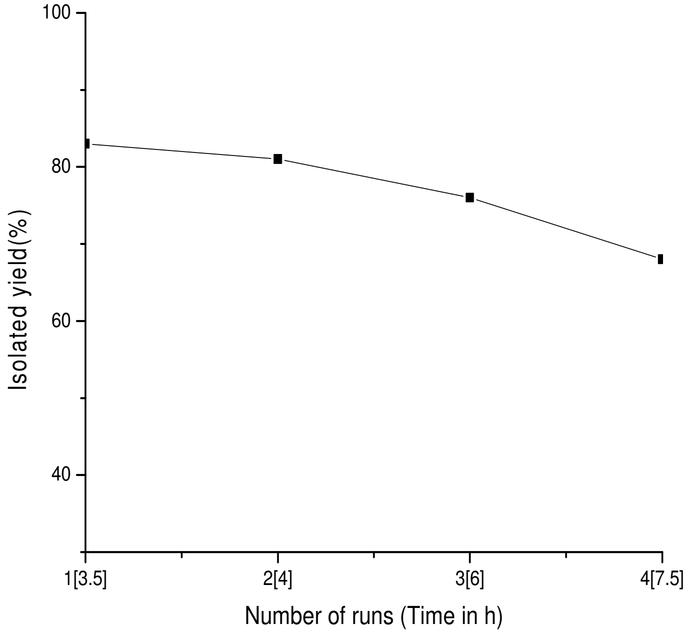


Figure 2

Preparation of activated silica

Silica gel (10 g) was added to a round-bottomed flask (250 mL) containing a 1:1 mixture of conc. HCl and distilled water (100 mL). The reaction mixture was refluxed in an oil-bath for 24 hr. On cooling, silica gel was filtered off and washed with excess distilled water until the washings were neutral. It was dried in an oven at 110ºC for 15 hr.

General procedure for the preparation of silica-supported zinc chloride

To a mixture of anhydrous zinc chloride (3 g) and activated silica (10 g, K 100) in a round-bottomed flask (100 mL), sodium dried toluene (60 mL) was added and the reaction mixture was refluxed for 12 hr. SiO_2-$ZnCl_2$ was obtained as a free flowing powder after filtration under reduced pressure and drying at 110ºC for 12 hr. It was stored in a desiccator and could be used for several months without loss of activity.

General procedure for the acetylation of amines, alcohols and phenols

To a mixture of amine, alcohol or phenol (1 mmol), acetic anhydride (1.2 mmol) and SiO_2-$ZnCl_2$ (0.4 g, 24 mol% of Zn), acetonitrile (10 mL) was added in a round-bottomed flask (50 mL). The reaction mixture was stirred at 80ºC in an oil-bath for the appropriate time (**Table I**). After completion of the reaction (monitored by TLC), the reaction mixture was filtered off. The product was obtained after removal of the solvent under reduced pressure and extraction with methylene chloride. The combined methylene chloride extracts were washed with water and dried over anhydrous sodium sulfate. Finally, the products were purified by recrystallization or by passing through a column of silica gel and elution with ethyl acetate and petroleum ether.

The structures of the products were confirmed by ^{1}H NMR, IR and mass spectral data and comparison with authentic samples available commercially or prepared according to the literature methods.

Conclusion

In conclusion, a mild and economic method has been developed for the acetylation of amines, alcohols and phenols with acetic anhydride in the presence of SiO_2-$ZnCl_2$. The catalyst can be re-cycled up to 4th use without much loss of activity. Thus, this method can be used as an alternative to other existing methodologies.

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