An Efficient Method for the Chemoselective Synthesis of *Germinal* Diacetates from Aromatic and Heteroaromatic Aldehydes Using Nano Silica Chloride

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Abstract

In this investigation, Nano silica chloride (nano SiO_2Cl) has been found to be efficient, chemoselective and recyclable catalyst for facile and simple synthesis of germinal diacetates from aromatic and heteroaromatic aldehydes in shorter reaction durations. The products were obtained in high to excellent yields. This work consistently has the advantages of excellent yields, short reaction time, mild condition and work-up procedures. This method might be useful in the future for the preparation of similar derivatives.

1. Introduction

Acylals (germinal diacetates) are one of the efficient protecting groups for carbonyl groups because they are stable to neutral and basic conditions [1]. Acylals are important precursors for the preparation of 1-acetoxydienes [2] and vinyl acetates [3a] in Diels-Alder reactions. Compounds bearing the acylal functionality are used as cross-linking reagents for cellulose in cotton [3b]. Several methods have been used for the synthesis of germinal diacetates from strong acids including sulfuric acid [4], methane sulfuric acid [5], sulfamic acid [6], Lewis acids such as lithium bromide [7],

aluminum chloride [8], anhydrous ferrous sulfate [9], PCl_3 [10], $FeCl_3$ [11], NBS [12], Nafion-H [13], sulfated zirconia [14], montmorillonite clay [15], expansive graphite [16], aluminum dodecatungstophosphate [17], Well-Dawson acid ($H_6P_2W_{18}O_{62}.24H_2O$) [18] zeolite HSZ-360 [19], $Cu(OTf)_2$ [20], $Sc(OTf)_3$ [21], $Bi(OTf)_3$ [22], $Zn(BF_4)_2$ [23], $Bi(NO_3)_3.5H_2O$ [24] and $ZrCl_4$ [25], P_2O_5/Al_2O_3 [26], dodecamolybdophoshporic acid [27], SO_4^{2-}/SnO_2 [28], bromodimethylsulfonium bromide [29], solid lithium perchlorate [30], [bmim]BF_4 [31], [Hmim]HSO_4 [32], zeolite Y [33], SO_3H-MIL-101 [34], propylphosphonic anhydride

(®T3P) [35] and transition metal compounds and complexes [36] which are also efficient for this conversion. However, many methodologies have drawbacks involve strongly acidic conditions, corrosive and expensive reagents, long reaction times, high temperature and high toxicity.

In continuation of our ongoing research for the development of simple and chemoselective method for the synthesis of various compounds [37-38]. Herein we wish to report a simple, economic and efficient method for the synthesis of acylals using nano silica chloride as the catalyst. Nano silica gel is one of the extensively used surface material supports for different chemical transformations in organic chemistry.

One such modified nano silica gel is nano silica chloride (nano SiO$_2$Cl) that our studies have shown that it was easily prepared by addition of thionyl chloride to nano silica gel. Preparation of nano silica chloride is simple, clean and without work-up procedure. Nano silica chloride is cheap and heterogeneous catalyst for the synthesis of acylals. It was prepared by the readily available material and can also be easily removed from the reaction mixture.

We wish to report that nano silica chloride is a highly efficient catalyst for the conversion of aromatic aldehydes to acylals (Scheme 1).
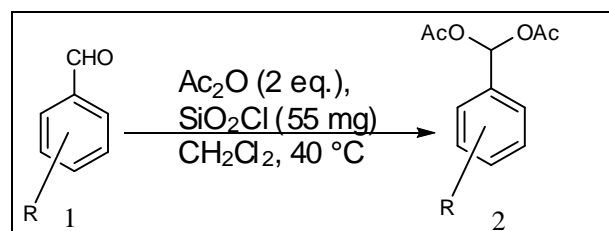
Scheme 1. Nano SiO$_2$Cl catalyzed synthesis of germinal diacetates.

2. Experimental procedure
2.1. Chemicals and apparatus

Chemical reagents in high purity were purchased from the Merck Chemical Company. All materials were commercial reagent grade. NMR spectra (^{1}H-NMR and ^{13}C-NMR) were recorded with a Bruker DRX-250 spectrometer at 250 and 63 MHz respectively and reported as parts per million (ppm) downfield from tetramethylsilane as internal standard. FT-IR spectra were obtained with potassium bromide pellets in the range 400-4000 cm^{-1} with a Perkin-Elmer 550 spectrometer. The purity determination of the substrates and reaction monitoring were accomplished by thin layer chromatography (TLC) on silica gel polygram SILG/UV 254 plates. Scanning electron microscope (SEM) was performed with a PHILIP XL-30, operated at 30 KV. Transmission electron microscopy (TEM) was performed with Zeiss-EM10C-80 KV, operated at 80 KV.

2.2. Preparation of nano silica chloride:
Nano SiO$_2$Cl powder was prepared according to the procedure reported [37-38]. To an oven-dried (120 °C) nano silica gel (5 g) in a round bottomed flask (250 ml) equipped with a condenser and a drying tube, was added thionyl chloride (toxic and should be used with caution) (100 ml) and refluxed for one week. The excess thionyl chloride was distilled off. The resulting white-grayish powder was flame-dried and stored in a tightly capped bottle.

2.3. Typical Experimental Procedure:
To a solution of aldehyde (1 mmol) and freshly distilled acetic anhydride (2 mmol) in CH$_2$Cl$_2$ (5 ml), SiO$_2$Cl (55mg) was added at 40 °C. The reaction mixture was magnetically stirred for a specified period (Table 3). The progress of the reaction was monitored by GC or TLC. After complete conversion of the starting material, the catalyst was filtered and saturated NaHCO$_3$ (5 ml) was added to

solution. The product was extracted with diethyl ether (2×15 ml) and the etherates were dried over Na_2SO_4. The solvent was evaporated to give the corresponding 1,1-diacetate. Products were characterized according to their data of ^{1}H and ^{13}C NMR and IR. The representative spectral (^{1}H and ^{13}C NMR and IR) data 1,1-diacetates 2a–o are given below.

PhCH(OAc)₂ (2a) IR (KBr disk): 1758 (**C-O**), 1220 (**O-C**OMe); ^{1}H NMR (250 MHz, CDCl₃): δ 2.16 (s, 6H), 7.31-7.44 (m, 5H), 7.60 (s, 1H); ^{13}C NMR (63 MHz, CDCl₃): δ 178, 135.9, 130.16, 128.31, 120.2, 80.9, 22.14.

3-NO₂(C₆H₄)CH(OAc)₂ (2b) IR (KBr disk): 3099 (**C-H**(OAc)₂), 1781 (**C-O**), 1225 (**O-C**OMe); ^{1}H NMR (250 MHz, CDCl₃): δ 2.2 (s, 6H), 7.61 (t, J = 7.5 Hz, 1H), 7.75 (s, 1H), 7.85 (d, J = 7 Hz, 1H), 8.27 (d, J = 7 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR (63 MHz, CDCl₃): δ 148.1, 145.1, 130.2, 127.8, 123.4, 122.8, 111.9, 101.7, 25.8.

4-Br(C₆H₄)CH(OAc)₂ (2g) IR (KBr disk): 3100 (**C-H**(OAc)₂), 1743 (**C-O**), 1230 (**O-C**OMe); ^{1}H NMR (250 MHz, CDCl₃): δ 2.10 (s, 6H), 7.41 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.59 (s, 1H); ^{13}C NMR (63 MHz, CDCl₃): δ 168.4, 134.3, 131.0, 128.0, 123.8, 88.9, 20.6.

4-Me(C₆H₄)CH(OAc)₂ (2h): IR (KBr disk): 3090 (**C-H**(OAc)₂), 1765 (**C-O**), 1228 (**O-C**OMe); ^{1}H NMR (250 MHz, CDCl₃): δ 2.22 (s, 6H), 2.45 (s, 3H), 7.24 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 7.79 (s, 1H); ^{13}C NMR (63 MHz, CDCl₃): δ 175.9, 139.9, 134.6, 130.3, 128.2, 89.9, 24.5, 22.9.

2,6-Cl₂(C₆H₃)CH(OAc)₂ (2k): IR (KBr disk): 3081 (**C-H**(OAc)₂), 1771 (**C-O**), 1257 (**O-C**OMe); ^{1}H NMR (250 MHz, CDCl₃): δ 2.07 (s, 6H), 7.05 (t, 1H), 7.31 (d, J=7.24 Hz, 2H), 8.82 (s, 1H); ^{13}C NMR (63 MHz, CDCl₃): δ 168.86, 139.62, 133.22, 131.01, 129.37, 85.66, 21.1.

Acetylbenzaldehyde (4o): IR (KBr disk): 3080 (**C-H**(OAc)₂), 1770 (**C-O**), 1731 (**C=O**), 1251 (**O-C**OMe); ^{1}H NMR (250 MHz, CDCl₃): δ 2.10 (s, 6H), 2.55 (s, 3H), 7.60-7.87 (m, 5H); ^{13}C NMR (63 MHz, CDCl₃): δ 197.34, 168.55, 139.88, 137.90, 128.46, 126.84, 88.86, 24.61, 20.70.

3. Results and discussion

To initiate our study, a much more simple and effective catalytic route for the synthesis of germinal diacetates under aerobic conditions is described. 55 mg of amorphous silicon dioxide, nano silicon dioxide (55 mg), amorphous silica chloride (55 mg) and nano silica chloride (55 mg), catalyzed synthesis of germinal diacetates. In order to show the applicability and efficiency of this method, our results have been compared with some of the same catalysts on the synthesis of germinal diacetates. As you can see in Table 1, nano silica chloride is superior to the other catalysts (table 1, entry 4).

Table 1. Comparison of results for the synthesis of (4-chlorophenyl)methylene diacetate catalyzed by some of the silicon catalysts at the same conditions.

Entry	Catalyst	Time (min)	Yield (%)
1	SiO_2	120	75
2	Nano SiO_2	40	89
3	SiO_2Cl	55	87
4	Nano SiO_2Cl	15	95

To find the reaction media, the reaction of 4-chlorobenzaldehyde (**1f**) with acetic anhydride was performed in different solvents. Among the CH_2Cl_2, CH_3CN, CH_3OH, EtOAc and n-hexane, dichloromethane showed higher yield. Therefore, dichloromethane was used as solvent. Then, the amount of catalyst was optimized in the same reaction. As can be seen, the highest yield was obtained in the presence of 55 mg SiO_2Cl at 40 °C (table 2, entry 3). The amount of acetic anhydride

was also optimized and the best result was obtained with 2:1 M ratio of acetic anhydride to aldehyde.

Table 2. Optimization studies using acetic anhydride and 4-chlorobenzaldehyde (1f).

$$\text{1f} \xrightarrow[\text{CH}_2\text{Cl}_2,\ 40\ ^\circ\text{C}]{\text{Ac}_2\text{O} + \text{SiO}_2\text{Cl} (55\ \text{mg})} \text{2f}$$
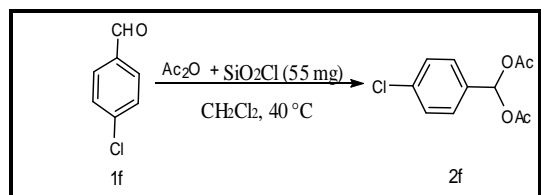
Entry	SiO$_2$Cl (mg)	Temp. (°C)	Time (min)	Yield^a (%)
1	35	40	65	71
2	45	40	30	85
3	55	40	15	95
4	55	r.t.	65	71
5	55	30	55	79
6	55	35	30	89

^{a}Reaction performed with aldehyde 1f (1 mmol), acetic anhydride (2 mmol), product 2f determinated by GC.

Thus, the best condition for the reaction was the use of nano silica chloride (55 mg), acetic anhydride (2 mmol), and aldehyde (1 mmol) in dry CH$_2$Cl$_2$ (5 ml) at 40 °C under air atmosphere (scheme 1). These results prompted us to investigate the scope and the generality of this new protocol for various aromatic and heteroaromatic aldehydes under optimized conditions (Table 3).

Under the optimized reaction conditions, a wide range of aromatic aldehydes bearing electron donating and electron withdrawing groups were reacted with acetic anhydride in the presence of SiO$_2$Cl at 40 °C and the corresponding 1,1-diacetates were obtained in high to excellent yields (62–95%) in 7–155 min. The electronic properties of the substituents on the aromatic aldehydes have a significant influence on the reaction time and yield.

Table 3. Nano Silica chloride catalyzed formation of acylals from aldehydes using Ac$_2$O.

| Entry	ArCHO	Product	Time (min)	Yield^{a,b} (%)
a	PhCHO	Ph(OAc)$_2$	15	95
b	3-O$_2$N-C$_6$H$_4$CHO	3-O$_2$N-C$_6$H$_4$CH(OAc)$_2$	10	88
c	4-O$_2$N-C$_6$H$_4$CHO	4-O$_2$N-C$_6$H$_4$CH(OAc)$_2$	10	92
d	4-F$_3$C-C$_6$H$_4$CHO	4-F$_3$C-C$_6$H$_4$CH(OAc)$_2$	7	91
e	4-F-C$_6$H$_4$CHO	4-F-C$_6$H$_4$CH(OAc)$_2$	15	88
f	4-Cl-C$_6$H$_4$CHO	4-Cl-C$_6$H$_4$CH(OAc)$_2$	15	95
g	4-Br-C$_6$H$_4$CHO	4-Br-C$_6$H$_4$CH(OAc)$_2$	15	92
h	4-H$_3$C-C$_6$H$_4$CHO	4-H$_3$C-C$_6$H$_4$CH(OAc)$_2$	22	89
i	4-H$_3$CO-C$_6$H$_4$CHO	4-H$_3$CO-C$_6$H$_4$CH(OAc)$_2$	55	75
j	4-Me$_2$N-C$_6$H$_4$CHO	4-Me$_2$N-C$_6$H$_4$CH(OAc)$_2$	155	62
k	2,6-Cl$_2$-C$_6$H$_3$CHO	2,6-Cl$_2$-C$_6$H$_3$CH(OAc)$_2$	10	95
l	2-furyl-CHO	2-furyl-CH(OAc)$_2$	50	80
m	2-thienyl-CHO	2-thienyl-CH(OAc)$_2$	50	75
n	4-HO-C$_6$H$_4$CHO	4-AcO-C$_6$H$_4$CH(OAc)$_2$	65	78
o	4-acetyl-C$_6$H$_4$CHO	4-acetyl-C$_6$H$_4$CH(OAc)$_2$	45	92

^{a} All of the products were characterized by comparison of their spectral and physical data with those of authentic samples. ^{b} Isolated yields.

Benzaldehyde and the aldehydes bearing electron withdrawing groups such as nitro, fluoro, chloro and bromo, afforded the corresponding products in excellent yields (Table 3, entries a–g).

By contrast, aldehydes containing electron donating groups such as 4-methoxy and 4-methyl groups gave the corresponding 1,1-diacetates in lower yield and longer reaction times (Table 3, entries h and i). This is attributed to the reduced electrophilicity of the aldehyde group as a result of the electron-rich nature of the phenyl ring to which the aldehyde is attached. The product yield for reaction of 4-(dimethylamino)benzaldehyde with Ac$_2$O was 62% after 155 min (Table 3, entry j). When, a heteroaromatic aldehyde such as furfural and 2-thenaldehyde was used, good yields of the corresponding 1,1-diacetate was produced after 50 min (Table 3 entries l and m).

In order to show the chemoselectivity of the method, we have performed two competitive reactions as shown in Scheme 2. These results indicate that the presented protocol is potentially applicable for the chemoselective protection of aldehydes in the presence of ketone functionalities in multifunctional compounds. As shown in Scheme 2a, when a 1:1 mixture of benzaldehyde and Cyclohexanone was allowed to react with acetic anhydride in the presence of SiO$_2$Cl for 15 min, benzaldehyde diacetate was isolated in about 95% yield and unreacted Cyclohexanone was isolated in 100% yield. Furthermore, when 4-acetylbenzaldehyde was allowed to react with acetic anhydride under the usual conditions, only the aldehyde group reacted (Scheme 2b).

Inspection of the SEM and TEM images of a sample catalyst from this reaction indicates the involvement of silica chloride nanoparticles with a size distribution of 15–35 nm (Figs. 1 and 2). After the reaction, nano silica chloride can be easily separated (by centrifuge and filtration) and reused without decrease in its activity.
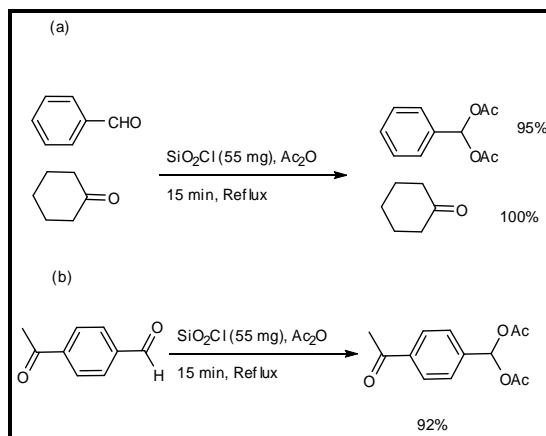
Scheme 2. (a and b) Competitive reactions of aldehydes and ketones using Ac$_2$O in the presence of SiO$_2$Cl. The percentage of the products in the reaction mixture was determined by GC-analysis.

For example, the reaction of Ac$_2$O with 4-chlorobenzaldehyde afforded the corresponding 1,1-diacetates in 95%, 95%, and 90% isolated yield over three cycles. When we carried out the reaction in CH$_2$Cl$_2$, the reaction proceeded very slowly to give moderate yields.
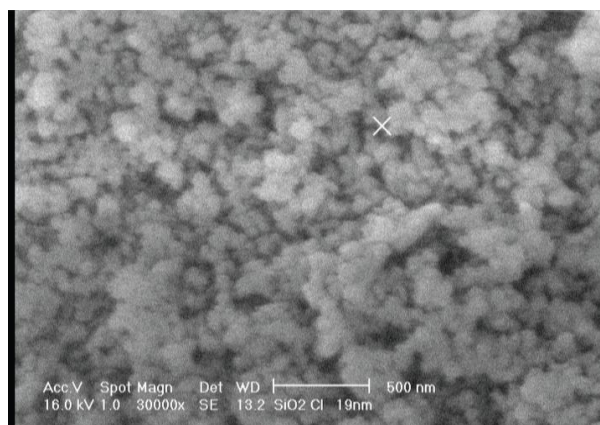

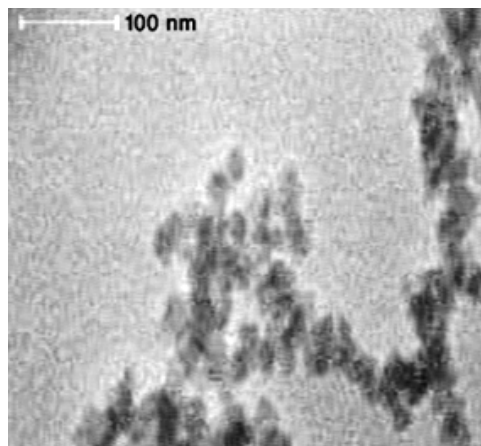**Fig. 1.** SEM image of silica chloride nano particle.

Fig. 2. TEM image of silica chloride nano particle.

4. Conclusion

In conclusion, nano SiO_2Cl has been found to be a novel, highly efficient, low cost catalyst for germinal diacetates formations from aromatic and heteroaromatic aldehydes. Operational simplicity, exceptionally fast, low cost of the catalyst used, high yields, excellent chemoselectivity, applicability to large scale reactions are the key features of this methodology.

Acknowledgment

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