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Silica gel catalyzed highly selective C–S bond formation via Michael addition of thiols to α,β-unsaturated ketones under solvent-free conditions

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Abstract

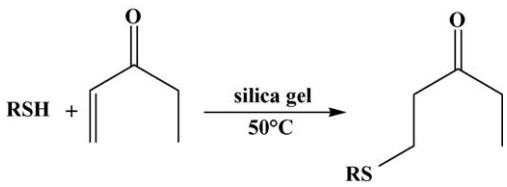
Silica gel, as a heterogeneous catalyst has been applied for the highly selective C–S bond formation versus C–N and C–O ones via Michael addition of thiols to α,β-unsaturated ketones under solvent-free conditions at 50 °C. The catalyst has been separated easily and reused in five runs without observable loss of its catalytic activity.

Keywords: Silica gel; Thiols; Michael addition; Solvent-free; Heterogenenous catalyst; Thioether

1. Introduction

In the recent years, preparation of organic materials using organic or inorganic heterogeneous catalysts or media without employing any organic solvents has been of extreme interest [1]. Among solids, silica gel has been effectively utilized in organic synthesis as a simply available, cheap heterogenenous medium and also mild acid catalyst, which is easily separable from the reaction products [2].

Sulfur-containing compounds are found in a quite number of natural products and are also of particular importance regarding pharmaceutically active substances [3]. Clearly, the 1,4-conjugate addition of thiols to α,β-unsaturated carbonyl compounds is a transformation of seemingly fundamental simplicity and constitutes a key reaction in the synthesis of biologically active organo-sulfur compounds [4]. Michael addition reactions generally require the activation of starting materials under acidic or basic conditions [5]. This led to development of catalytic methods especially using Lewis acid catalysts such as $InBr_3$ [6], $Bi(NO_3)_3$ [7], $Bi(OTf)_3$ [8], $InCl_3$ [9] and $Cu(BF_4)_2$ [10]. However, it has long been known that thiols act as transition metal catalyst poisons due to their strong coordinating and adsorptive properties and often rendered the catalytic reactions totally ineffective [11]. Recently, the use of ionic liquids such as $[Bmim]PF_6/H_2O$ [12], and molten tetrabutylammonium bromide [13], have been successfully used as convenient solvents and also efficient catalysts for this goal. However, most of the conventional ionic liquids are expensive and anxiety regarding the toxicity of some of them limited their employments as the reaction media [13]. More recently, we have described a useful method for conjugate addition of thiols to enones using tungstophosphoric acid ($H_3PW_{12}O_{40}$) as the efficient catalyst [14], and Michael addition of indoles and pyrrole to α,β-unsaturated electron-deficient compounds catalyzed by aluminium dodecyl sulfate trihydrate $[Al(DS)_3]\cdot 3H_2O$ in water [15]. Herein, we wish to report that one of the most abundant material; silica gel has been used as a recycable, very efficient and a highly selective catalyst for C–S bond formation by conjugate addition of thiols to α,β-unsaturated ketones (Michael addition) under solvent-free conditions (Scheme 1).



Scheme 1.

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Table 1
Michael addition of thiols to electron deficient olefins in the presence of silica gel under solvent-free conditions

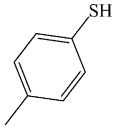
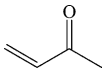
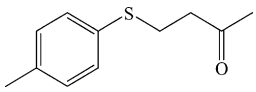
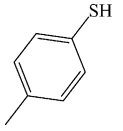
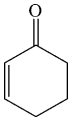
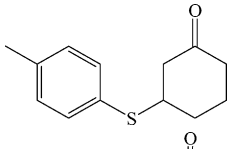
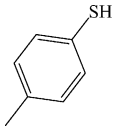
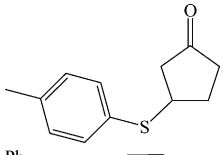
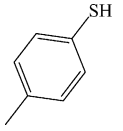
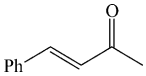
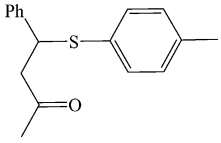
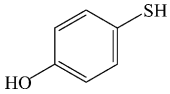
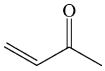
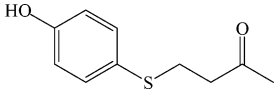
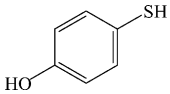
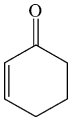
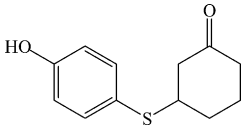
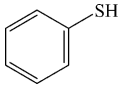
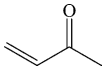
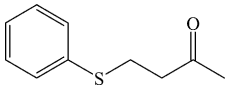
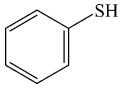
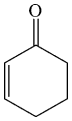
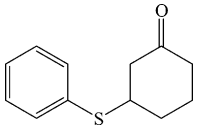
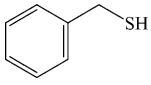
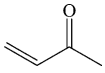
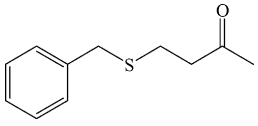
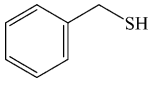
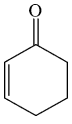
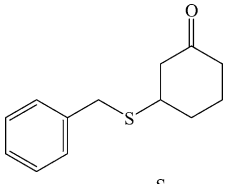
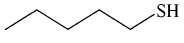
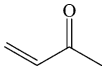
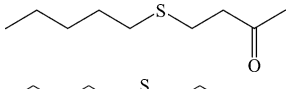
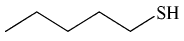
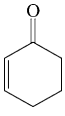
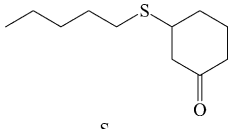
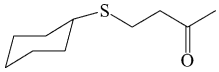
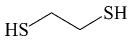
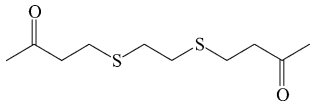
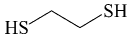
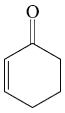
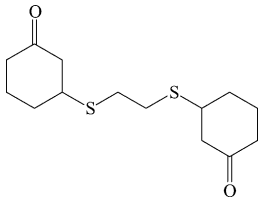
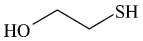
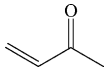
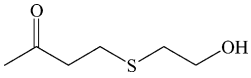
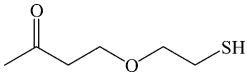
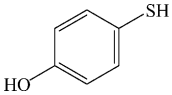
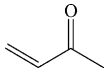
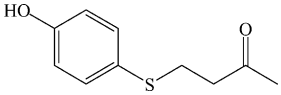
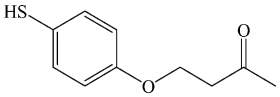
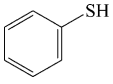
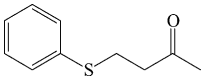
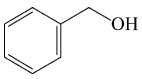
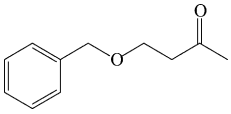
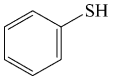
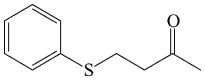
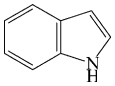
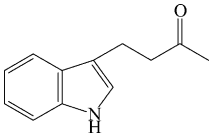
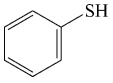
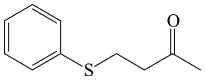
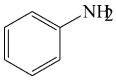
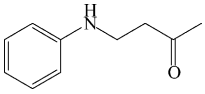
Entry	Thiol	Enone	Product[a]	Time (min)/yield (%)	Reference
1				2/96	[16]
2				10/95	[13]
3				10/93	[6]
4				90/90	[6]
5				2/95	–
6				7/93	–
7				5/94	[16]
8				10/95	[16]
9				20/90	[17]
10				50/75	[13]
11				60/95	[14]
12				90/63	[14]
13				60/80	–
14				90/70	–

Table 1 (*Continued*)

Entry	Thiol	Enone	Product[a]	Time (min)/yield (%)	Reference
15[b]				25/85	–
16[b]				35/80	–

[a] All products were identified by spectroscopic techniques and comparison with known samples [14].
[b] Isolated yield after column chromatography. The molar ratio of α,β-unsaturated carbonyl:dithiol is 2.1:1.

Table 2
Silica gel used for selective Michael addition reaction of different nucleophiles to methyl vinyl ketone[a]

Entry	Substrate(s)	Enone	Products	Time (min)	Yields
1[b,c]				90	92
					0
2[d]				2	95
					0
3[b]				10	100
					0
4[d]				10	100
					0
5[b]				10	70
					30

[a] The reaction was carried out under solvent-free conditions using silica gel (0.1 g), nucleophiles (1 mmol) and methyl vinyl ketone (1.1 mmol) at 50 °C.
[b] GC yields.
[c] ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 2.18 (s, 3H), 2.68–2.78 (m, 6H), 3.7 (t, J = 5.87 Hz, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 24.56, 30.08, 35.03, 42.82, 60.31, 207; ^{1}H NMR.
[d] ^{1}H NMR yields.

2. Results and discussion

For optimization of the reaction conditions, condensation of methyl vinyl ketone with 4-methylthiophenol was studied as a model reaction under neat conditions in the absence of silica gel at the temperature range from 50 to 90 °C. It was found that the temperature change did not affect the yield of the adduct and the desired product was formed in only 40% yield (GC) after 1 h. Increase of the reaction time did not also affect the yield of the product. Then, similar reaction was studied in the presence of silica gel. We have observed that the reaction between methyl vinyl ketone (1.1 mmol) and 4-methylthiophenol (1 mmol) and silica gel (0.1 g) was completed after 2 min at 50 °C under solvent-free conditions to afford the Michael adduct in 96% isolated yield.

Then we applied similar reaction condition for the reaction of structurally diverse α,β-unsaturated cyclic and acyclic ketones with different thiols in order to show the general applicability of the method. All the reactions proceeded well within 2–90 min and the desired Michael adducts were isolated in 70–96% yields (Table 1, entries 1–14).

Michael adducts carrying two sulfur heteroatoms in the β-position of carbonyl groups is scant in the literature [14]. Therefore, the reaction of α,β-unsaturated ketones with dithiols were also studied. For this aim, addition of ethane dithiol with methyl vinyl ketone and cyclohexenone were studied. The reactions proceeded smoothly and the desired products were obtained in 80–85% yields within 25–35 min (Table 1, entries 15 and 16). These compounds are potential precursors for the synthesis of macrocyclic or polymeric sulfur-containing compounds.

The spent silica gel was easily recycled after simple filtration, washing with acetone and drying at 100 °C. This regenerated catalyst has been used for the addition of 4-methylthiophenol to methyl vinyl ketone for five runs without observable loss of its catalytic activity. We have also proceeded similar reaction on a larger scale in order to show the catalyst is also active at semi large-scale operation. For this purpose 4-methylthiophenol (5 mmol, 0.72 g) was reacted with methyl vinyl ketone (5.1 mmol, 0.357 g) in the presence of silica gel (0.5 g). The reaction proceeded very fast in less than 2 min to produce the corresponding Michael adduct in 90% isolated yield.

Chemoselectivity of the methods is important, especially when the method is applied for the synthesis of multifunctional complex target molecules. To study this important goal, the chemoselectivity of the method has been studied. For this purpose, the addition of nucleophiles such as indoles, amines and alcohols to methyl vinyl ketone in the presence of different thiols was examined under similar reaction conditions as described in the previous section. As it is indicated in Table 2, the reactions proceeded with high chemoselectivity in favor of C–S bond formation and the desired thioethers were formed in high yields.

In Table 3, entries 2–6 [6–8,12,13], we have also shown the merit of this operationally simple and cheap catalytic protocol for Michael addition of thiophenol to cyclohexenone in comparison with the other catalysts or media used for this purpose.

Table 3
Comparison of the reaction of thiophenol with cyclohexenone catalyzed by silica gel under solvent-free conditions with the other methods used for this reaction

Entry	Catalyst	Time (min)	Yield (%)
1	Silica gel [solvent-free]	10	95
2	$InBr_3$ [CH_2Cl_2] [6]	24 h	80
3	$Bi(NO_3)_3$ [CH_2Cl_2] [7]	240	65
4	$Bi(OTf)_3$ [CH_3CN] [8]	90	72
5	Molten Bu_4NBr [ionic liquid] [13]	30	92
6	[Bmim]PF_6/H_2O [Ionic liquid] [12]	10	95

3. Conclusions

We have introduced a new catalytic activity of silica gel that catalyzes highly selective C–S bond formation via Michael addition of thiols to α,β-unsaturated ketones under solvent-free conditions. The yields of the adducts are high and the work up of the reaction mixture is simple and not time-consuming. The spent catalyst can be easily separated from the reaction mixture, which after washing with acetone and drying at 100 °C can be reused without noticeable change in its catalytic activity.

4. Experimental

4.1. General procedure for the Michael addition of thiols to α,β-unsaturated carbonyl compounds

Silica gel [0.1 g (60, 70–230 mesh) dried at 100 °C under vacuum for 24 h], thiol (1 mmol) and α,β-unsaturated carbonyl compound (1.1 mmol) were mixed and stirred at 50 °C for the appropriate reaction time (Table 1, entries 1–14). The progress of the reaction was monitored by TLC and GC. After completion of the reaction, acetone (10 mL) was added to the mixture and filtered. Evaporation of the solvent afforded the desired product in high purity (Table 1, entries 1–9 and 11). For the adducts (Table 1, entries 10 and 12–14), after removal of silica gel, the mixture was washed with an aqueous solution of NaOH (10%, 10 mL) and extracted with EtOAc or CH_2Cl_2 (2× 10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum on a rotary evaporator to afford the desired product in high purity. Further purification was performed by column chromatography eluted with petroleum ether/EtOAc (2/1). Structural assignments of the products are based on their ^1H NMR, ^{13}C NMR, MS spectra and elemental analysis.

4.2. General procedure for the Michael addition of 1,2-ethanedithiol to α,β-unsaturated carbonyl compounds

Silica gel [0.1 g (60, 70–230 mesh) dried at 100 °C under vacuum for 24 h], 1,2-ethanedithiol (1 mmol) and α,β-unsaturated carbonyl (2.1 mmol) were mixed together and stirred at 50 °C for the appropriate reaction time (Table 1, entries 15 and 16). After completion of the reaction, acetone (10 mL) was added and the mixture was filtrated. Evaporation of the solvent resulted the crude product which was purified by column chromatography

eluted with petroleum ether/EtOAc (2/1). Structural assignments of the products are based on their ^{1}H NMR, ^{13}C NMR, MS spectra and elemental analysis.

4.3. Spectral data of some isolated Michael adducts

Table 1, entry 1: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 2.13 (s, 3H), 2.32 (s, 3H), 2.75 (t, J = 8.7 Hz, 2H), 3.11 (t, J = 8.4 Hz, 2H), 7.12 (d, J = 10.2 Hz, 2H), 7.23 (d, J = 10.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 21, 28.2, 30.07, 43.2, 129.78, 130.45, 136.6, 207; MS (*m/e*) = 194 $[M]^+$; Anal. Calcd for ($C_{11}H_{14}OS$): C, 68.00; H, 7.26. Found: C, 68.03; H, 7.27.

Table 1, entry 4: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 2.15 (s, 3H), 2.34 (s, 3H), 2.8–3.1 (dd, J = 2.75 Hz, J = 9.25, 2H), 4.6 (t, J = 9.25, 1H), 7.1–7.6 (m, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 21, 30.71, 48.45, 49.85, 128, 128.2, 129.05, 129.25, 129.4, 133.3, 137.45, 139.2, 141.55, 205.91; MS (*m/e*) = 270 $[M]^+$; Anal. Calcd for ($Cl_7H_{18}OS$): C, 75.51; H, 6.71. Found: C, 75.48; H, 6.74.

Table 1, entry 5: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 2.14 (s, 3H), 2.7 (t, J = 7.3 Hz, 2H), 3.04 (t, J = 7.35 Hz, 2H), 5.6 (b, 1H), 6.8 (d, J = 6.9 Hz, 2H), 7.28 (d, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 28.2, 30.07, 43.2, 117.47, 132.6, 133, 156, 207; MS (*m/e*) = 196 $[M]^+$; Anal. Calcd for ($C_{10}H_{12}O_2S$): C, 61.20; H, 6.16. Found: C, 61.23; H, 6.17.

Table 1, entry 6: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 2 (m, 2H), 2.1 (m, 2H), 2.2 (t, J = 6.5 Hz, 2H), 2.5 (d, J = 8.5 Hz, 2H), 2.6 (m, 1H), 5.6 (b, 1H), 6.8 (d, J = 8.25 Hz, 2H), 7.28 (d, J = 8.25 Hz, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 29.3, 36.78, 43.86, 45.18, 117.47, 132.6, 133, 156, 207; MS (*m/e*) = 222 $[M]^+$; Anal. Calcd for ($C_{12}H_{14}O_2S$): C, 64.83; H, 6.35. Found: C, 64.80; H, 6.37.

Table 1, entry 13: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 1.30 (m, 6H), 1.63 (m, 1H), 1.77 (m, 2H), 2 (m, 2H), 2.17–2.18 (m, 2H), 2.73–2.75 (dd + m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 24.10, 26.10, 30.74, 34.34, 44.08, 207.25; MS (*m/e*) = 186 $[M]^+$; Anal. Calcd for ($C_{10}H_{18}OS$): C, 64.47; H, 9.74. Found: C, 64.48; H, 9.74.

Table 1, entry 14: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 1.28–1.35 (m, 5H), 1.63–1.74 (m, 5H), 1.92 (m, 2H), 2.11–2.15 (m, 2H), 2.31–2.41 (m, 3H), 2.64–2.71 (m, 2H), 3.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 25.61, 26.28, 33.11, 34.51, 41.38, 42.36, 49.00, 209.11; MS (*m/e*) = 212 $[M]^+$; Anal. Calcd for ($C_{12}H_{20}OS$): C, 67.88; H, 9.49. Found: C, 67.86; H, 9.48.

Table 1, entry 15: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 2.18 (s, 6H), 2.70–2.76 (m, 12H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 26.01, 30.45, 32.63, 43.97, 207; MS (*m/e*) = 234 $[M]^+$; Anal. Calcd for ($C_{10}H_{18}O_2S_2$): C, 51.25; H, 7.74. Found: C, 51.19; H, 7.72.

Table 1, entry 16: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 1.70–1.74 (m, 4H); 2.13–2.16 (m, 4H), 2.32–2.42 (m, 6H), 2.65–2.7 (m, 2H), 2.76 (m, 4H), 3.10–3.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 24.25, 30.91, 31.74, 41.09, 42.68, 48.27, 208.53; MS (*m/e*) = 286 $[M]^+$; Anal. Calcd for ($C_{14}H_{22}O_2S_2$): C, 58.70; H, 7.74. Found: C, 58.64; H, 7.73.

Table 2, entry 1: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 2.18 (s, 3H), 2.68–2.78 (m, 6H), 3.7 (t, J = 5.87 Hz, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 24.56, 30.08, 35.03, 42.82, 60.31, 207; MS (*m/e*) = 148 $[M]^+$; Anal. Calcd for ($C_6H_{12}O_2S$): C, 48.62; H, 8.16. Found: C, 48.64; H, 8.2.

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