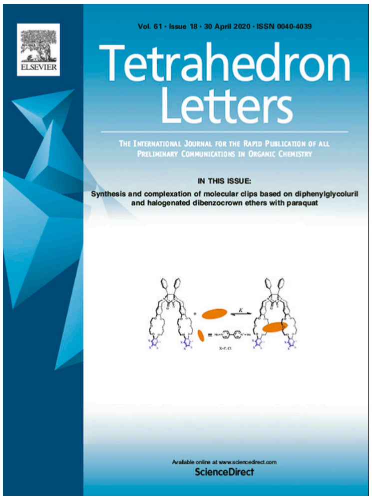

Silica gel-mediated catalyst-free and solvent-free Michael addition of 1,3-dicarbonyl compounds to highly toxic methyl vinyl ketone without volatilization

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Graphical Abstract

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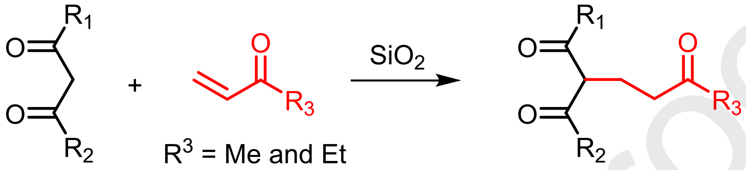

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Silica gel-mediated catalyst-free and solvent-free Michael addition of 1,3-dicarbonyl compounds to highly toxic methyl vinyl ketone without volatilization

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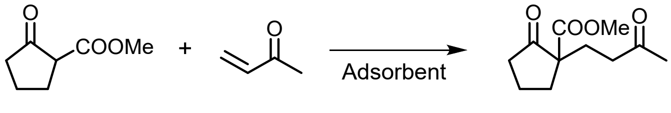
ABSTRACT

Silica gel-mediated Michael addition of 1,3-dicarbonyl compounds to methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) was carried out to give the corresponding adducts in quite excellent yields. The reactions could be carried out without any catalysts and solvents. In addition, highly toxic MVK and EVK could be employed without significant volatilization. Silica gel could be recycled five times without the decrease of the yields.

Great interest has been taken in solvent-free reactions in order to improve traditional methods from the economic and environmentally benign viewpoints since the procedure does not utilize harmful organic solvents [1, 2]. Convenient work-up and many faster reactions are attractive and valuable advantages. In relation to this methodology, silica gel and alumina-mediated reactions under organic solvent-free conditions have attracted much attention because of high selectivity, dramatic acceleration, and mild conditions [3, 4]. During the course of our investigations on the use of silica gel in chemical reactions [5-7], we have found that highly volatile compounds do not volatilize near and above their boiling points on heating in silica gel-mediated self-aldol reactions [8].

Michael addition is widely recognized as an efficient and important reaction to form carbon-carbon bonds in organic synthesis [9-13]. Generally, Michael addition was catalyzed by strong bases such as alkali metal alkoxides and hydroxides or some acids such as super acids, which remain environmentally harmful residues or afford undesirable side products [14-17]. Recently, considerable attention has been focused on the procedures under mild and environmentally friendly conditions. From these points of view, some methods using weakly acidic or basic solids have been devised [18-25]. However, frequently used methyl vinyl ketone (MVK) (**2a**) and ethyl vinyl ketone (EVK) (**2b**) are highly toxic and volatile compounds. MVK and EVK causes central nervous system depression, the edema of the lungs, and eye injury [26].

In this paper, we wish to report that silica gel-mediated catalyst-free and solvent-free Michael addition of 1,3-dicarbonyl compounds with highly toxic MVK and EVK proceeded with suppressing volatilization to give the corresponding adducts in quite excellent yields.



1a **2a** **3a**

Scheme 1. Michael addition mediated by adsorbent.

First, we examined Michael addition of methyl 2-oxocyclopentane-1-carboxylate (**1a**) with 3.0 equivalents of MVK **2a** at 70 °C for 8 h as a model reaction using some adsorbents (Scheme 1). The results are summarized in Table 1. The use of silica gel (Silica gel 60, 63-200 μm, spherical, Nacalai) as an adsorbent gave the adduct **3a** in the quite excellent yield (>99%) (entry 1). Even when a reflux condenser was not equipped, compound **3a** was obtained in 99% yield (entry 2). The use of the other silica gel gave almost the same results (entries 3-6). Crushed silica gel also led to the similar results although it is somewhat difficult to mix (entry 7). Michael addition mediated by sea sand yielded **3a** in the low yield (28%) (entry 8). Mixing was difficult in sea sand-mediated reactions owing to the formation of a large mass. Only 3% of **3a** was obtained without a reflux condenser, indicating that sea sand cannot adsorb a large amount of MVK (entry 9). Recently, Michael addition of 1,3-dicarbonyl compounds to nitroalkenes using quartz sand by a grinding method has been reported [27]. The reactions mediated by alumina, H-Mordenite, and Montmorillonite K10 resulted in the lower yields of **3a** together with the formation of complex mixture or polymeric material because of the more acidic nature of these solids (entries 10-12). The low yield (10%) of activated carbon would be attributed to the much weaker acidic nature of the adsorbent (entry 12). The reaction progressed in the absence of adsorbents to give **3a** in 12% yield (entry 14). Michael addition of **1a** in toluene hardly proceeded (entry 15). The

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rea

conditions and in toluene by the hydrogen-bonding activation with EtOH (entry 16) [28].

Table 1

Michael addition of **1a** mediated by some adsorbents.[a]

[a] Compound **1a** (2.0 mmol), MVK **2a** (6.0 mmol), adsorbent (6.0 g), 70 °C, 8 h.

[b] Isolated yields.

[c] Reflux condenser was not equipped.

[d] Silica gel 60 (63-200 µm, spherical, Nacalai) was used.

[e] Silica gel 60 (63-210 µm, spherical, Kanto) was used.

[f] Wakosil C-200 (64-210 µm, spherical, Wako) was used.

[g] Silica gel 60 (45-106 µm, spherical, Nacalai) was used.

[h] Wakosil C-300 (40-64 µm, spherical, Wako) was used.

[i] Silica gel 60 (63-200 µm, crushed, Nacalai) was used

[j] Sea sand C (40-80 mesh, Nakalai) was used.

[k] Alumina (activated, acidic, Brockmann I, 150 mesh, Aldrich) was used.

Entry	Adsorbent	Yield (%)[b]
1	Silica gel[d]	> 99
2[c]	Silica gel[d]	99
3	Silica gel[e]	95
4	Silica gel[f]	99
5	Silica gel[g]	97
6	Silica gel[h]	98
7	Silica gel[i]	> 99
8	Sea sand[j]	28
9[c]	Sea sand[j]	3
10	Alumina[k]	33[q]
11	H-Mordenite[l]	27[r]
12	Montmorillonite K10[m]	61[r]
13	Activated carbon[n]	10
14	–	12
15	–[o]	1
16	–[p]	25

[l] Hydrogen Mordenite (5-7 µm, Wako) was used.

[m] Montmorillonite K10 (surface area 220-270 m^2/g, Aldrich) was used.

[n] Activated carbon (Darco, 100 mesh, Aldrich) was used.

[o] Dry toluene (6.0 mL) was used as a solvent.

[p] Dry EtOH (6.0 mL) was used as a solvent.

[q] Complex mixture was obtained.

[r] Polymeric material was obtained.

Next, we tested the reactions of various 1,3-dicarbonyl compounds **1a-k** with MVK **2a** and EVK **2b**. The results are summarized in Table 2. Compounds **1a-k** reacted with 3.0 equivalents of MVK and EVK to give the corresponding adducts **3a-p** in quite excellent yields because of the weakly acidic nature of silica gel, respectively. One and a half equivalents of MVK were enough to complete the reactions of **1a** and **1b** at 70 °C (entries 1 and 2). It is interesting to note that compounds **1c** and **1d** possessing six-membered ring reacted considerably slower than **1a** and **1b** possessing five-membered ring probably due to the steric reason during the reaction although details are not clear at the present time (entries 1-4, 12, and 13). EVK reacted more slowly than MVK (entries 12-16). The reactions were sensitive to steric hindrance of 1,3-dicarbonyl compounds (entries 5 and 6, 9-11, 14 and 15). In spite of our extensive efforts, the other

. 1). The reactions at 120 °C resulted in exclusive polymerization.

Table 2

Michael addition of various Michael donors **1** with **2**.[a]

We examined the volatilization of MVK (bp 81 °C) and EVK (bp 103 °C) at 90 and 70 °C in the presence and absence of silica gel equipped with a reflux condenser (Liebig condenser) and a drying tube. The weight loss of MVK and EVK was determined by the electronic balance. The results are shown in Table 3. When silica gel was not employed, a large amount of MVK and a small amount of EVK were volatilized after the heating at 90 and 70 °C although polymeric material was formed in the case of EVK (entries 2, 4, 6, and 8). The reason for the larger weight loss of MVK at 70 °C than that of 90 °C will be attributed to the fact that a large amount of MVK attached at the joint between the flask and the condenser at 70 °C, while the reflux of MVK was observed inside the condenser and less amount of MVK attached at the joint at 90 °C (entries 2 and 4). On the other hand, the weight loss was not observed in the presence of silica gel although a small amount of complex mixture was obtained (entries 1, 3, 5, and 7).

In order to expand the scope of this system, the present procedure was scaled up 20-fold for the addition of compound **1a** to MVK. The reactions proceeded without any difficulty to give **3a** in 92% yield.

The recycle experiments of Michael addition of **1a** with MVK were carried out. The recovered silica gel was washed with EtOAc and dried at 120 °C under reduced pressure (20 Torr) (1 Torr = 133.322 Pa) for 3 h. Silica gel could be reused five times without significant decrease of the yields (Table 4).

A plausible mechanism for the formation of **3** is shown in Scheme 2. The keto form **1** of the 1,3-dicarbonyl compounds is in equilibrium with the enol form **4**. Compound **4** would attack the Michael acceptor **2** to give **3** *via* the enol form **5**. The function of silica gel is probably to shift the equilibrium to the enol form **4** by the coordination of the weakly acidic hydrogen atom of silica gel to the oxygen atom of the keto form **1**. In addition, the attack of the enol from **4** to **2** would be accelerated by the coordination of the hydrogen atom of silica gel to the oxygen atom of **2**. Thus, hydrogen bonding between surface hydroxy groups of silica gel and substrates would play an important role.

In conclusion, we devised the silica gel-mediated Michael addition of 1,3-dicarbonyl compounds with MVK and EVK. The reactions proceeded without any catalysts and solvents. The products were obtained in quite excellent yields. We could carry out Michael addition with preventing the discharge of highly toxic MVK and EVK compared to neat reactions. The products could be separated only by filtration. Furthermore, silica gel could be recycled without the significant decrease of the yields.

Acknowledgments

We thank Center for Coordination of Research Facilities, Institute for Research Promotion, Niigata University for NMR measurements and high-resolution mass analysis. K. T. thanks the Research Promotion Grant (NDU Grants N-20009) from Nippon Dental University. T. R. thanks the University Cadi Ayyad and specially the Faculty Polydisciplinaire of Safi for the financial support to the LACM laboratory.

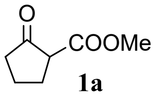
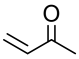
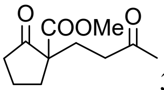
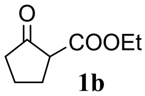
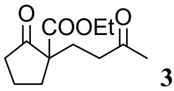
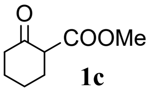
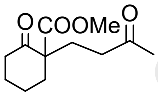
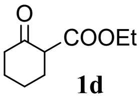
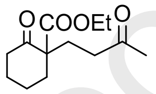
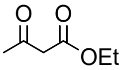
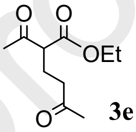
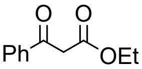
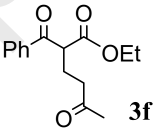
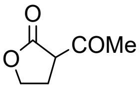
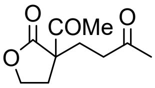
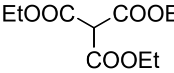
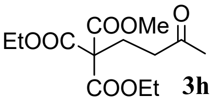
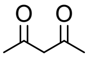
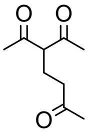
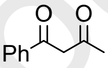
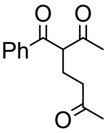
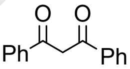
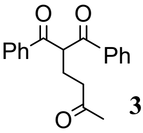
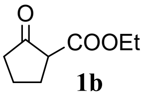
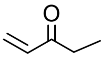
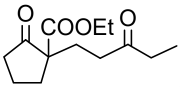
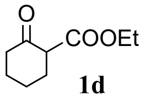
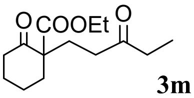
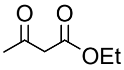
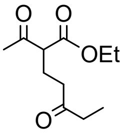
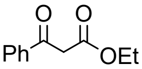
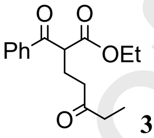
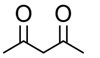
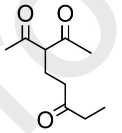
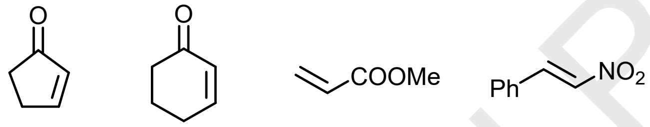
Entry	Donor	Acceptor	Temp (°C)	Time (h)	Product	Yield (%)[b]
1	 **1a**	 **2a**	70	8	 **3a**	> 99 (94)[c] (86)[d]
2	 **1b**	**2a**	70	8	 **3b**	> 99 (95)[c]
3	 **1c**	**2a**	90	24	 **3c**	92
4	 **1d**	**2a**	90	24	 **3d**	96
5	 **1e**	**2a**	90	8	 **3e**	> 99
6	 **1f**	**2a**	90	16	 **3f**	99
7	 **1g**	**2a**	90	20	 **3g**	> 99
8	 **1h**	**2a**	90	24	 **3h**	92
9	 **1i**	**2a**	90	24	 **3i**	98
10	 **1j**	**2a**	90	32	 **3j**	> 99
11	 **1k**	**2a**	90	48	 **3k**	> 99
12	 **1b**	 **2b**	70	24	 **3l**	99

Table 2 Continued

Entry	Donor	Acceptor	Temp (°C)	Time (h)	Product	Yield (%)^{b}
13	 **1d**	**2b**	90	64	 **3m**	> 99
14	 **1e**	**2b**	90	36	 **3n**	> 99
15	 **1f**	**2b**	90	64	 **3o**	> 99
16	 **1i**	**2b**	90	72	 **3p**	92

[a] Compound **1** (2.0 mmol), acceptor **2** (6.0 mmol), Silica gel 60 (63-200 μm, spherical, Nacalai, 6.0 g).
[b] Isolated yields.
[c] Compound **1** (2.0 mmol), MVK **2a** (3.0 mmol), Silica gel 60 (63-200 μm, spherical, Nacalai, 3.8 g), 70 °C, 24 h.
[d] Compound **1** (2.0 mmol), MVK **2a** (3.0 mmol), Silica gel 60 (63-200 μm, spherical, Nacalai, 3.8 g), 90 °C, 8 h.



2c **2d** **2e** **2f**

Fig. 1. Structure of some Michael acceptors.

Table 3

Entry	Acceptor	Temp (°C)	Silica gel^{c}	Weight loss (wt%)
1^{a}	MVK	90	+	0^{d}
2^{a}	MVK	90	−	60
3^{a}	MVK	70	+	0^{e}
4^{a}	MVK	70	−	90
5^{b}	EVK	90	+	0^{f}
6^{b}	EVK	90	−	15^{g}
7^{b}	EVK	70	+	0^{h}
8^{b}	EVK	70	−	8^{i}

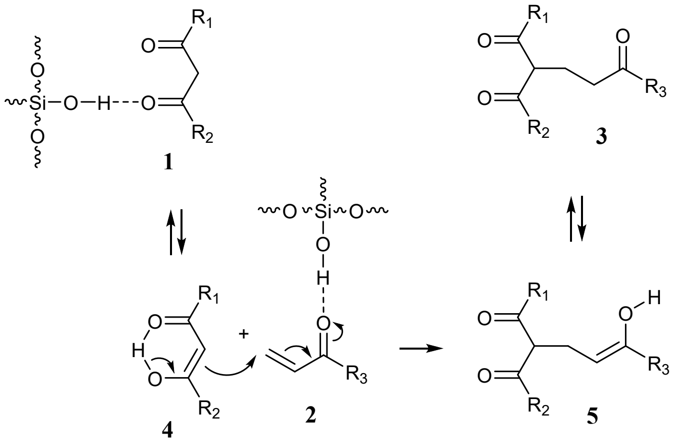
Effect of silica gel for the heating of MVK **2a** and EVK **2b**.

[a] MVK **2a** (3.0 mmol), Silica gel 60 (60-200 μm, spherical, Nacalai, 2.3 g), 8 h.
[b] EVK **2b** (3.0 mmol), Silica gel 60 (60-200 μm, spherical, Nacalai, 2.3 g), 8 h.
[c] + (Silica gel was used), − (silica gel was not used).
[d] Complex mixture was obtained in 8 wt%.
[e] Complex mixture was obtained in 3 wt%.
[f] Complex mixture was obtained in 20 wt%.
[g] Polymeric material was obtained in 77 wt%.
[h] Complex mixture was obtained in 14 wt%.
[i] Polymeric material was obtained in 14 wt%.

Table 4
Recycle experiments for the reaction mediated by silica gel.[a]

	1st	2nd	3rd	4th	5th
Yields (%)^{b}	94	96	99	97	98

[a] Compound **1a** (2.0 mmol), MVK **2a** (3.0 mmol), Silica gel 60 (63-200 μm, spherical, Nacalai, 3.8 g), 70 °C, 24 h.
[b] Isolated yields.



Scheme 2. Mechanism for the formation of **3**.

Supplementary data

S
in the online version.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical Abstract

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* Silica gel-mediated Michael addition was developed.

* Highly toxic methyl vinyl ketone can be used without volatilization.

* Reactions proceeded under catalyst-free and solvent-free conditions.

* Michael adducts can be obtained in quite excellent yields.

* Products can be separated by filtration.

Silica gel-mediated catalyst-free and solvent-free Michael addition of 1,3-dicarbonyl compounds to highly toxic methyl vinyl ketone without volatilization

Kiyoshi Tanemura, Taoufik Rohand

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