Heterogeneous Amine Catalyst Grafted on Amorphous Silica: An Effective Organocatalyst for Microwave-promoted Michael Reaction of 1,3-Dicarbonyl Compounds in Water

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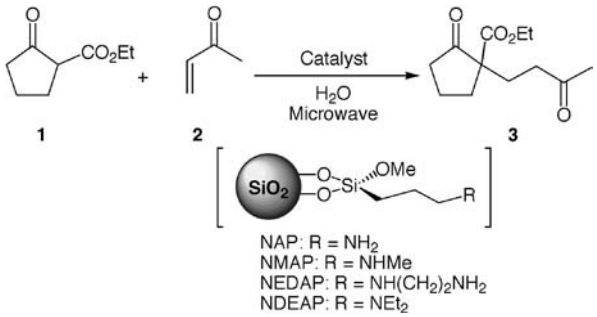
Michael addition of a 1,3-dicarbonyl compound to an α,β-unsaturated carbonyl compound was effectively catalyzed by heterogeneous *N*,*N*-diethylaminopropylated silica gel (NDEAP) in water under microwave heating. The reaction condition was mild, practical, and environmentally benign. The sustainable nature of the catalyst was exemplified by re-use up to 5 times.

Development of a sustainable and environmentally benign process is of prime interest in production of organic compounds,[1] in which a catalytic reaction in environmentally benign reaction media is desired for such purpose. A heterogeneous catalyst is better than a homogeneous catalyst due to its easy recovery and recycle-use. An organomolecular catalyst is superior to an organometallic catalyst, due to flexible design, availability independent of natural resource, and avoidance of pollution caused by use of heavy metal. One drawback of the organomolecular catalyst is its instability, which might be solved by supporting the organocatalytic moiety on solid surface such as silica gel.

From such standpoint, we recently disclosed 1,2- or 1,4-nucleophilic reactions of carbonyl compounds in environmentally friendly media such as an ionic liquid, super-critical carbon dioxide or water, employing propylamine grafted on silica gel.[2f] The reaction conditions were mild enough to apply to substrates having acid- or base-sensitive substituents.[2]

As a part of our ongoing program directed toward the development of green organic reactions, we investigated 1,4-addition of a 1,3-dicarbonyl compound to an α,β-unsaturated carbonyl compound in water[3] catalyzed by amine grafted on silica gel as a heterogeneous organomolecular catalyst. Water has many advantages from its ability to accelerate a bimolecular reaction due to high cohesive energy density and dielectric constant, safety based on non-flammability and non-toxicity, and economy.[4] Since the reaction is carried out in a tri-phasic system due to low solubility of organic substrates, we focused on internal heating by microwave irradiation,[5] in which water is advantageous due to relatively high loss factor (tan δ) for efficient heating.[5a] Although there are several attempts for Michael reaction employing a polymer-bound organomolecular catalyst,[6] there is no precedent to our knowledge of reaction catalyzed by a heterogeneous organomolecular catalyst grafted on silica gel, except 1,4-addition of nitroalkane.[7]

The optimum catalyst was examined at first employing the reaction of ethyl 2-oxocyclopentanecarboxylate (**1**) and 3-buten-2-one (**2**) (Scheme 1 and Table 1) in water under microwave heating by a multimode 500-W domestic oven. The temperature was ramped for 2 min from room temperature to 100 °C, which was monitored by a radiation thermometer. Without a catalyst, the reaction resulted in recovery of **1** (Table 1, Entry 1). Addition of silica gel also gave the same result (Table 1, Entry 2). Among



Scheme 1. Microwave-promoted Michael addition catalyzed by amine grafted on silica.

Table 1. Investigation of effective catalyst[a]

Entry	Catalyst	Amount (equiv.)	Yield/%[b]
1	—	—	17
2	Silica gel	—	11
3	NAP	0.1	55
4	NMAP	0.1	48
5	NEDAP	0.1	29
6	NDEAP	0.1	72
7	NDEAP	0.05	72
8	NDEAP	0.01	50

[a]The reaction was carried out with ethyl 2-oxocyclopentanecarboxylate (**1**) and 3-buten-2-one (**2**) (1.5 equiv.) and the catalyst (0.05 equiv.) in water under microwave (500-W) irradiation for 2 min. The temperature was ramped from room temperature to 100 °C, which was monitored by a radiation thermometer. After the reaction, the product was triturated with ethyl acetate. [b]Yields are for isolated pure products based on 2-oxocyclopentanecarboxylate (**1**).

heterogeneous amine catalysts investigated, *N*,*N*-diethylaminopropylated silica gel (NDEAP)[2f] provided the best result (Table 1, Entries 6 and 7).

An examination on the effect of the solvent is compiled in Table 2. In THF or xylene, a large amount of substrate **1** was recovered (Table 2, Entry 2 or 4), though the reaction proceeded

Table 2. Effect of solvent[a]

Entry	Solvent	Yield/%
1	—	33
2	THF	2
3	PEG	0
4	Xylene	7
5	H_2O	72

[a]The reaction was carried out in the same manner as in Table 1.

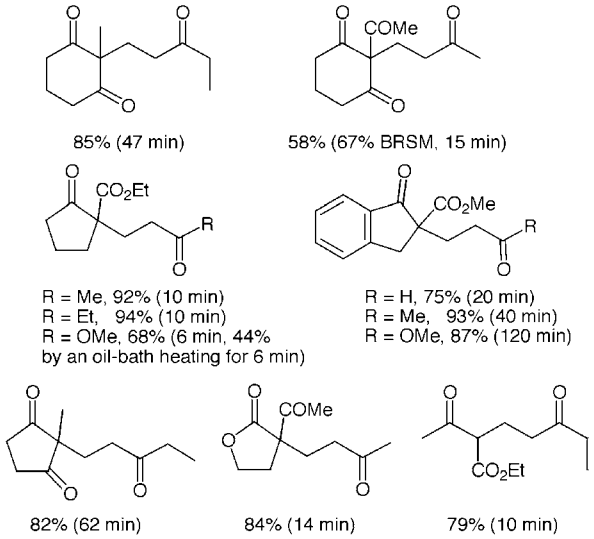


Figure 1. Michael additions with various Michael donors and acceptors catalyzed by 0.1 equiv. of NDEAP.

without solvent (Table 2, Entry 1). The reaction in polyethyleneglycol (PEG) having higher tan δ than that of water, resulted in decomposition and did not recover **1** probably due to overheating (Table 2, Entry 3). Among solvents investigated, water was the best medium for the present reaction (Table 2, Entry 5).

The optimized reaction condition (Table 1, Entry 7) was applied to a variety of Michael donors. Different from the preliminary experiments in Tables 1 and 2, the power of microwave irradiation was reduced to 100-W in order to prevent overheating. The reaction temperature was ramped to 80 °C quickly and maintained at the temperature until termination of the reaction. Actually, the yield was improved from 72 (Table 1, Entries 6 and 7) to 92% (Table 3, Entry 1). Satisfactory Michael additions with a variety of cyclic and acyclic 1,3-dicarbonyl compounds are compiled in Figure 1. Microwave heating is superior to conventional heating in an oil bath as shown in the reaction with methyl acrylate (Figure 1).

After the reaction, the product was triturated with ethyl acetate and the suspension of NDEAP in water could be easily recycled at least four times as shown in Table 3. A certain amount of decrease (Table 3, Entry 4) of the catalytic activity was retrieved after washing the NDEAP with dilute aqueous sodium carbonate (Table 3, Entry 5). The end-capped NDEAP as trimethylsiloxide showed similar reactivity and recyclability as non-end-capped NDEAP.

Table 3. Recycle use of NDEAP[a]

Entry	Recycle	Yield/%
1	0	92
2	1	78
3	2	74
4	3	51
5[b]	4	76

[a]The reaction was carried out in a similar manner as in Table 1 except NDEAP loading (0.1 equiv.) under microwave irradiation at 100-W for 10 min, when the temperature was ramped from room temperature to 70 °C. [b]NDEAP was washed with Na_2CO_3.

In summary, we have developed a new protocol for Michael addition of 1,3-dicarbonyl compounds catalyzed by a clean catalyst (NDEAP) in a clean medium (water) under clean activation (microwave heating).[8] The catalyst was effectively recycled. The present reaction is mild, practical, environmentally benign, and sustainable, which would be useful for large-scale preparation.

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References and Notes

1 P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, **1998**.

2 a) K. Isobe, T. Hoshi, T. Suzuki, H. Hagiwara, *Mol. Diversity* **2005**, *9*, 317. b) H. Hagiwara, J. Hamaya, T. Hoshi, C. Yokoyama, *Tetrahedron Lett.* **2005**, *46*, 393. c) M. Fukushima, S. Endou, T. Hoshi, T. Suzuki, H. Hagiwara, *Tetrahedron Lett.* **2005**, *46*, 3287. d) H. Hagiwara, A. Koseki, K. Isobe, K. Shimizu, T. Hoshi, T. Suzuki, *Synlett* **2004**, 2188. e) K. Shimizu, H. Suzuki, T. Kodama, H. Hagiwara, Y. Kitayama, *Stud. Surf. Sci. Catal.* **2003**, *145*, 145. f) J. Hamaya, T. Suzuki, T. Hoshi, K. Shimizu, Y. Kitayama, H. Hagiwara, *Synlett* **2003**, 873. g) K. Shimizu, E. Hayashi, T. Inokuchi, T. Kodama, H. Hagiwara, Y. Kitayama, *Tetrahedron Lett.* **2002**, *43*, 9073. h) H. Hagiwara, S. Tsuji, T. Okabe, T. Hoshi, T. Suzuki, H. Suzuki, K. Shimizu, Y. Kitayama, *Green Chem.* **2002**, *4*, 461. i) K. Shimizu, H. Suzuki, E. Hayashi, T. Kodama, Y. Tsuchiya, H. Hagiwara, Y. Kitayama, *Chem. Commun.* **2002**, 1068.

3 a) E. Keller, B. L. Feringa, *Tetrahedron Lett.* **1996**, *37*, 1879. b) H. Kotsuki, K. Arimura, *Tetrahedron Lett.* **1997**, *38*, 7583. c) Y. Mori, K. Kakumoto, K. Manabe, S. Kobayashi, *Tetrahedron Lett.* **2000**, *41*, 3107.

4 a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095. b) E. K. Wilson, *Chem. Eng. News* **2005**, No. 30, 49. c) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751. d) S. Ribe, P. Wipf, *Chem. Commun.* **2001**, 299, and earlier references cited in these references. e) G. W. V. Cave, C. L. Raston, J. L. Scott, *Chem. Commun.* **2001**, 2159. f) *Blackie Academic and Professional*, ed. by P. A. Grieco, London, **1998**.

5 a) C. O. Kappe, *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. b) R. A. Abramovitch, *Org. Prep. Proced. Int.* **1991**, *23*, 685.

6 a) P. Hodge, E. Khoshdel, J. Waterhouse, *J. Chem. Soc., Perkin Trans. 1* **1983**, 2205. b) M. Inagaki, J. Hiratake, Y. Yamamoto, J. Oda, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121. c) R. Alvarez, M. A. Hourdin, C. Cave, J. d'Angelo, P. Chaminade, *Tetrahedron Lett.* **1999**, *40*, 7091. d) D. Bensa, T. Constantieux, J. Rodriguez, *Synthesis* **2004**, 923.

7 R. Ballini, G. Bosica, D. Livi, A. Palmieri, R. Maggi, G. Sartori, *Tetrahedron Lett.* **2003**, *44*, 2271.

8 Typical experimental procedure in practical scale: A commercial microwave oven was modified to install magnetic stirring unit at the bottom and a pipe vertically through the top to insert a glass condenser. A stirred suspension of ethyl 2-cyclopentanecarboxylate (**1**) (3.124 g, 20 mmol), 3-buten-2-one (**2**) (1.65 mL, 30 mmol), and NDEAP (766 mg, 1 mmol) in water (20 mL) was irradiated 100-W microwave for 2 min with vigorous stirring. The reaction temperature was ramped from room temperature to 70 °C and maintained at the temperature, which was monitored by a radiation thermometer. After being cooled to room temperature, the product was triturated with ethyl acetate. Evaporation of the solvent followed by Kugelrohr distillation (120 °C, 1.0 mmHg) and column chromatography (eluent: ethyl acetate:hexane = 1:1) of the forerun provided product **3** (3.596 g, 79%, 92% BRSM) along with recovered starting material **1** (437 mg, 14%).

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