Hydrogen-Bond-Promoted C–C Bond-Forming Reaction: Catalyst-Free Michael Addition Reactions in Ethanol

Seiji Shirakawa,* Shoichi Shimizu

Department of Applied Molecular Chemistry and High Technology Research Center, College of Industrial Technology, Nihon University, Narashino, Chiba, 275-8575, Japan
Fax +81(47)4742579; E-mail: s5siraka@cit.nihon-u.ac.jp

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Abstract: A practical protocol for catalyst-free Michael addition reactions in ethanol was developed. The reaction was promoted efficiently in alcohol without any additives, and the importance of hydrogen-bonding activation was suggested.

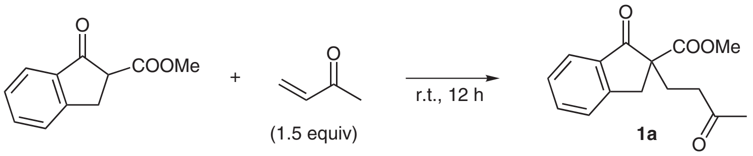
Key words: alcohols, green chemistry, Michael additions, solvent effects, enols

Reducing the use of hazardous solvents and reagents is one of the most important challenges in the effort to minimize pollution and risks associated with the production of chemicals. Accordingly, the use of water as a reaction medium alternative to toxic organic solvents has received considerable attention in organic synthesis.[1] However, because of the low solubility of many organic substrates in water, additives such as surfactants are often needed to promote reactions in water.

On the other hand, ethanol is an attractive reaction solvent due to availability, low toxicity, and the fact that many organic substrates are soluble in ethanol. In addition, reactions in alcohol may offer different reactivity and selectivity compared with other organic solvents, due to the effect of hydrogen-bonding interactions.[2] Recently, Rawal et al. reported hydrogen-bond-promoted hetero-Diels–Alder reactions of ketones in alcohol without any acid or base catalyst.[3,4] In their study, dramatic solvent effects on the reaction rate were observed, and the importance of hydrogen-bonding activation of ketones by alcohol to promote the reaction was mentioned.

In this context, our group is interested in the development of environmentally benign catalyst-free organic reactions in ethanol. This report documents catalyst-free Michael addition reactions of active methylene compounds with various Michael acceptors in ethanol.[5,6] In the present study, interesting solvent effects were observed and the reaction was promoted efficiently only in alcohol, a hydrogen-bonding solvent.

Table 1 Solvent Effect of Michael Addition Reaction



Entry	Solvent	Yield (%)[a]
1	Benzene	7
2	$CHCl_3$	4
3	MeCN	2
4	THF	9
5	THF–H_2O (9:1)	34
6	H_2O	39
7	EtOH	99
8	1-PrOH	99
9	diethylene glycol	99

[a] Determined by GC.

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As a starting point for the investigation, our group tested solvent effects in the Michael addition reaction of 1-oxo-indan-2-carboxylic acid methyl ester to methyl vinyl ketone (Table 1 and Figure 1). The reactions in benzene and chloroform proceeded very slowly and produced the product only in 7% and 4% yields, respectively (entries 1 and 2). Also, aprotic polar solvents such as acetonitrile and THF were employed for the reaction and gave poor results (entries 3 and 4). On the other hand, the ethanol solvent promoted the reaction smoothly and produced the Michael adduct **1a** in quantitative yield after 12 hours (entry 7). Other alcohols also promoted the reaction efficiently (entries 8 and 9). It is noteworthy that reactions in aqueous media also moderately promoted the reaction, and obtained the product in 34–39% yields (entries 5 and 6).[7,8] These results suggested the hydrogen-bonding activation of the substrate by the solvent was important for efficient promotion of the reaction.[9]

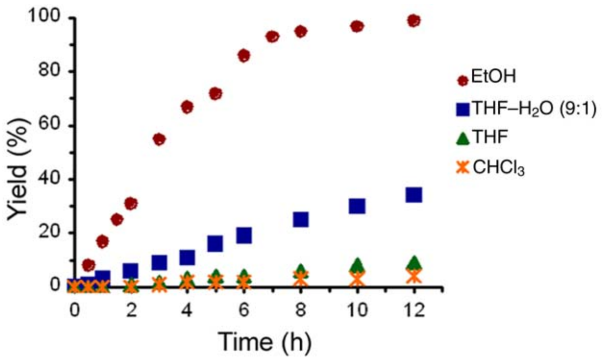
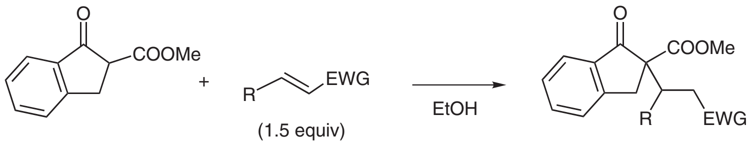


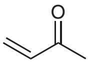
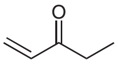
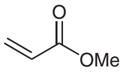
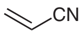
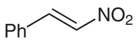
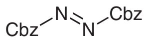
Figure 1 Reaction rate of Michael addition in different solvents

After these interesting observations, the substrate generality of catalyst-free Michael addition reactions in alcohol was investigated. Initially, the generality of Michael acceptors was examined (Table 2). Michael addition reactions using vinyl ketones proceeded smoothly at ambient temperature and produced the Michael adducts **1a** and **1b** in good yields (entries 1 and 2). Also, when vinyl compounds containing another electron-withdrawing group (EWG) were used as the acceptor, the corresponding products **1c**–**e** were obtained in moderate to good yields (entries 3–5). Furthermore, when the present reaction system was applied to the C–N bond-forming reaction by using azodicarboxylate as a Michael acceptor, the desired amination product **1f** was obtained in excellent yield (entry 6).[10]

Table 2 Michael Addition Reactions of β-Ketoester with Various Michael Acceptors in Alcohol



1

Entry	Michael acceptor	Conditions[a]	Yield (%)[b]
1		r.t., 12 h	99 (**1a**)[c]
2		r.t., 24 h	72 (**1b**)
3[d,e]		90 °C, 24 h	71 (**1c**)
4[d,e]		70 °C, 48 h	52 (**1d**)
5[d,f]		90 °C, 24 h	80 (**1e**)[g]
6		r.t., 2 h	99 (**1f**)[h]

[a] Reaction was carried out in a screw-capped flask heated at given temperature.

[b] Isolated yield.

[c] Determined by GC.

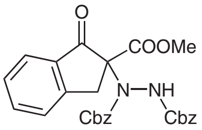
[d] Reaction in MeOH.

[e] Michael acceptor (5 equiv).

[f] Michael acceptor (3 equiv).

[g] Diastereomeric ratio ca. 1:1.

[h] Product **1f**:



Next, substrate generality with respect to the Michael donor was examined, and a variety of active methylene compounds were subjected to Michael addition reactions of methyl vinyl ketone (Table 3). When substrates containing 1,3-dicarbonyls, sulfonyl-, cyano-, and nitro-groups were employed as Michael donors the desired Michael addition products **2a**–**g** were obtained in moderate to good yields. In the case of benzoylacetonitrile as a Michael donor, the bis-alkylated product **2e** was selectively obtained (entry 5).

The present catalyst-free Michael addition reactions in ethanol were easily practicable on a larger scale; the reaction of 1-oxoindan-2-carboxylic acid methyl ester and methyl vinyl ketone (1.2 equiv) was carried out on a 10 mmol scale (Scheme 1). After reaction for 24 hours at ambient temperature, the reaction mixture was evaporated to remove the ethanol and excess methyl vinyl ketone, and dried in vacuo to obtain the desired product **1a** in quantitative yield. It is noteworthy that the present method was very simple and that the Michael addition product was easily obtained without tedious workup procedures.

The utility and applicability of the present reaction system was extended to hydroxymethylation using aqueous formaldehyde (Scheme 2).[11] The reaction of 1-oxoindan-2-carboxylic acid methyl ester with aqueous formaldehyde in ethanol occured cleanly and afforded the desired hydroxymethylation product **3** in quantitative yield.

The proposed hydrogen-bonding interactions of ethanol with the Michael donor and acceptor are shown in Scheme 3. The hydrogen in ethanol may interact with carbonyl oxygen of the vinyl ketone via a hydrogen bond, that is, it may work as a Brønsted acid. Also, the oxygen in ethanol may coordinate with the hydrogen in enol, and as a result, function as a Brønsted base. This dual activation mode[12,13] by ethanol may be important in promoting Michael addition reactions efficiently under catalyst-free conditions.

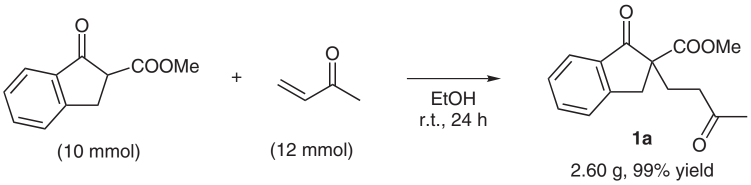
In summary, our group has developed catalyst-free Michael addition reactions in ethanol. It is noteworthy that the present reactions proceeded without the addition of any acid or base catalyst, and that a variety of Michael adducts were obtained. This remarkably simple and environmentally benign reaction system offers a practical C–C bond-forming method.

Measurements of Reaction Rates in Michael Addition Reaction (Table 1 and Figure 1)

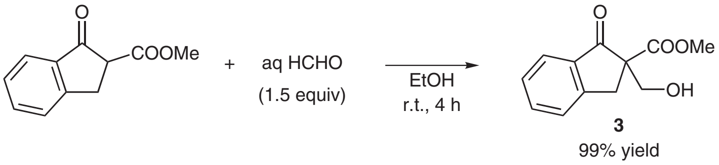
Methyl vinyl ketone (0.75 mmol) was added to a stirring solution of 1-oxoindan-2-carboxylic acid methyl ester (0.50 mmol) and diphenyl ether (0.50 mmol) as an internal standard in solvent (1.0 mL) at r.t. At appropriate intervals, the reaction solution (20 μL) was transferred to a microtube containing Et_2O (0.50 mL) as diluent, and then subjected to a GC analysis to determine the yield of product.

General Experimental Procedure for Michael Addition Reactions in EtOH (Tables 2 and 3)

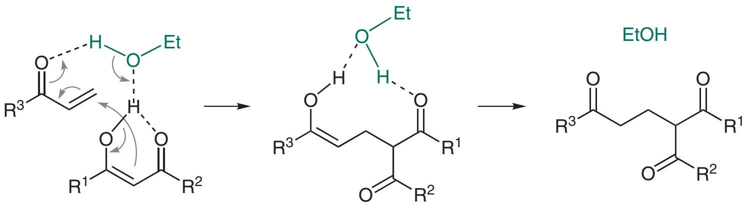
Michael acceptor (1.5–5.0 equiv) was added to a stirring solution of Michael donor (0.50 mmol) in EtOH (1.0 mL),[14] and the reaction mixture was stirred in given conditions. After the evaporation of EtOH, the resulting crude product was purified by flash chromatography (neutral silica gel), and yielded a Michael addition product.



Scheme 1 Larger-scale synthesis

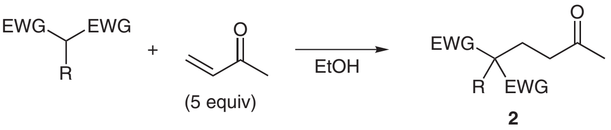


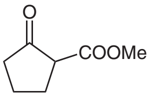
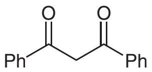
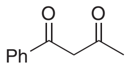
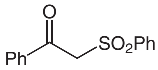
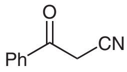
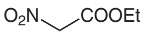
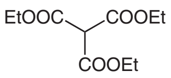
Scheme 2 Hydroxymethylation with aqueous formaldehyde



Scheme 3 Proposed hydrogen-bonding activation mode

Table 3 Michael Addition Reactions of Various Michael Donors with Methyl Vinyl Ketone in Alcohol



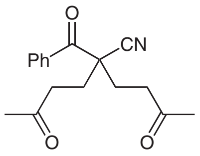
Entry	Michael donor	Conditions[a]	Yield (%)[b]
1[c]		70 °C, 48 h	90 (**2a**)
2		90 °C, 24 h	81 (**2b**)
3		90 °C, 24 h	82 (**2c**)
4		90 °C, 24 h	83 (**2d**)
5		70 °C, 48 h	85 (**2e**)[d]
6		90 °C, 48 h	52 (**2f**)
7		90 °C, 24 h	70 (**2g**)

[a] Reaction was carried out in a screw-capped flask heated at given temperature.

[b] Isolated yield.

[c] Reaction in MeOH.

[d] Product was dialkylated product **2e**:



Larger-Scale Synthesis (Scheme 1)

Methyl vinyl ketone (12 mmol) was added to a stirring solution of 1-oxoindan-2-carboxylic acid methyl ester (10 mmol) in EtOH (20 mL), and the reaction mixture was stirred for 24 h at r.t. The reaction mixture was evaporated to remove EtOH and excess methyl vinyl ketone, and dried in vacuo to obtain Michael adduct **1a** as a white solid.

Compound **1a**:[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 7.7 Hz, 1 H), 7.64 (dt, J = 1.1, 7.5 Hz, 1 H), 7.48 (d, J = 7.7 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 1 H), 3.70 (s, 3 H), 3.68 (d, J = 17.3 Hz, 1 H), 3.05 (d, J = 17.3 Hz, 1 H), 2.48–2.68 (m, 2 H), 2.18–2.28 (m, 2 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5, 202.3, 171.6, 152.5, 135.6, 135.0, 128.0, 126.4, 124.9, 59.1, 52.8, 38.8, 37.8, 30.0, 28.6 ppm. IR: 2953, 1743, 1713, 1607, 1434, 1277, 1251, 1210, 1195, 1176, 756 cm^{-1}. MS (EI): m/z = 260 [M$^+$], 228, 190, 157, 130.

Acknowledgment

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