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Sulfuric acid catalyzed addition of β-dicarbonyl compounds to alcohols under conventional heating and microwave-assisted conditions

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ABSTRACT

The highly efficient direct addition of β-dicarbonyl compounds to secondary alcohols has been achieved using one of the cheapest acids, H_2SO_4, as the catalyst. For a series of β-dicarbonyl compounds and various secondary alcohols, the addition reactions all complete in 5 min with high yields both under the conventional heating condition and under the microwave heating condition. The comparison of the results obtained from the microwave heating condition with those obtained from the conventional heating condition shows that no obvious specific or nonthermal microwave effects exist in the microwave-assisted addition reactions.

The carbon–carbon bond formation is the most fundamental strategy for the construction of molecular framework and thus undisputedly is one of the central themes in modern organic chemistry.[1] In recent years, the direct addition of β-dicarbonyl compounds to alcohols affording the alkylated β-dicarbonyl compounds has attracted much interest due to the green features. In comparison with the traditional synthetic procedures, the preparation of halides or related species is unnecessary and the usage of stoichiometric bases can be avoided, and only H_2O is generated as a side product.[2] Since the pioneering work of Baba and co-workers etc. in 2006 using $InCl_3$ as the effective catalyst,[3] various Lewis acidic metal catalysts, such as $InBr_3$,[4] $FeCl_3$,[5] $Bi(OTf)_3$,[6] and $Ln(OTf)_3$ (Ln = La, Yb, Sc, Hf)[7] etc. have been discovered to be effective in catalyzing the direct addition of β-dicarbonyl compounds to allylic and benzylic alcohols. Recently, we reported a perchloric ruthenium complex as the effective catalyst for the addition of β-diketones to secondary alcohols,[8] but further detailed mechanistic investigations illustrate that an equivalent of perchloric acid generated from the fast and irreversible reaction of the ruthenium complex and β-diketone is the true catalyst for the addition. Our results alert that the investigators have to be prudent to elucidate that the true catalytic species in a metal catalyzed catalytic reaction is the metal complex or the proton produced by the reaction of the metal with the substrate.

Molecular iodine[9] and various Brønsted acids, such as dodecylbenzenesulfonic acid,[10] *p*-toluenesulfonic acid,[11] phosphotungstic acid,[12] H-montmorillonite,[13] and triflic acid[14] have also been reported to be effective in catalyzing the addition of β-diketones to benzylic alcohols. Very recently, we demonstrated that perchloric acid can be used as the effective catalyst for the addition, and proved that the mechanism of the Brønsted acid catalyzing addition is an S_{N1} mechanism.[15] As a further extension, we successfully prepared the silica gel supported TfOH and applied it as an efficient and recoverable heterogeneous catalyst for the addition.[16] Whereas prominent progress has been made in the direct addition of β-dicarbonyl compounds to secondary alcohols, exceedingly long reaction time (several hours to dozens of hours) is needed in all the catalytic reactions under the conventional heating conditions and the enhancement of the reactivity of the catalytic reactions is still challenging. Herein, we report the highly efficient addition of β-dicarbonyl compounds to secondary alcohols using sulfuric acid (H_2SO_4) as the catalyst, which can be completed in 5 min.

In the former studies, H_2SO_4 has been reported ineffective in catalyzing the addition of acetylacetone to 2-phenylethanol with toluene as the solvent.[15] But in the reaction of 1,3-diphenylpropane-1,3-dione (**1a**) and 1-phenylethanol (**2a**), we surprisingly found H_2SO_4 was a highly effective catalyst in 1,2-dichloroethane (DCE) and the reaction completed in 5 min under reflux with 67% yield (Table 1, entry 1). Encouraged by this exciting result, we screened various solvents for the reactions of **1a** and **2a** in the presence of 5 mol % H_2SO_4 and found that the reactions in THF, dioxane, EtOAc, heptane, CH_2Cl_2, $CHCl_3$, and toluene afforded no or trace amount of the product (Table 1, entries 2–8). But when CH_3NO_2 was used as the solvent, the reaction of **1a** and **2a** catalyzed by

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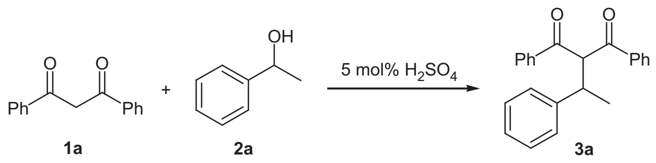
Table 1
Reactions of **1a** and **2a** using H_2SO_4 as the catalyst under various conditions[a]



Entry	Solvent	Temp. (°C)	**1a**:**2a**	Yield[b] (%)
1	DCE	Reflux	3:1	67
2	THF	Reflux	3:1	0
3	Dioxane	101	3:1	0
4	EtOAc	Reflux	3:1	2
5	Heptane	Reflux	3:1	11
6	CH_2Cl_2	Reflux	3:1	21
7	$CHCl_3$	Reflux	3:1	24
8	Toluene	101	3:1	28
9	CH_3NO_2	101	3:1	98
10	CH_3NO_2	85	3:1	76
11[c]	CH_3NO_2	70	3:1	44
12	CH_3NO_2	101	2:1	81
13	CH_3NO_2	101	1:1	74
14[d]	CH_3NO_2	101	1:2	61
15[e]	CH_3NO_2	101 (MW)	3:1	95

[a] Reaction conditions: H_2SO_4 (0.05 mmol), **2a** (1.0 mmol), solvent (2 mL), 5 min, unless noted.

[b] Isolated yields based on **2a**.

[c] Reaction time: 20 min.

[d] Compound **1a** (1.0 mmol) was used and the isolated yield was based on **1a**.

[e] The conventional heating condition was changed to MW condition.

5 mol % H_2SO_4 gave out exceptionally high yield of 98% after 5 min under 101 °C (Table 1, entry 9). In former reports of the addition of β-dicarbonyl compounds to alcohols using Brønsted acids as the catalysts, CH_3NO_2 was also proved to be the best solvent,[14,16] probably due to the strong polarity stabilizing the cation intermediates. If the reaction temperature was decreased to 85 °C or 70 °C, the yields concomitantly reduced to 76% or 44% (Table 1, entries 10 and 11). Moreover, if the ratio of **1a** to **2a** was changed from 3:1 to 2:1, 1:1, or 1:2, the reaction yields were affected negatively (Table 1, entries 12–14), which was mainly caused by the etherification of the alcohol as a side reaction.

Since the first example in 1986,[17] microwave irradiation (MW) has matured into a highly useful technique in organic synthesis to promote numerous organic reactions.[18] Compared with the conventional thermal heating method, controlled microwave heating approach often elicits a dramatic increase of the reaction rate and yields. However, the exact reasons for the enhancement of the reaction rate and yields are still ambiguous and ongoing debate remains in the scientific community until now. In particular, some reports declared that non-thermal microwave effects exist and attributed the remarkable increase of the reaction rate and yields to the selective interactions of the electromagnetic field with specific substrate molecules, reagents, or catalysts.[19] On the other hand, recent investigations using accurate on-line reaction temperature measurements demonstrate that the specific microwave effects on the standard synthetic organic reactions in solvents probably do not exist, and the observed enhancements are the result of purely thermal effects induced by the rapid heating and high bulk reaction temperatures through microwave heating.[20] The ongoing argument about the intrinsic reason (thermal or non-thermo effect) promoting the reaction rate and yields in MW-assisted reactions triggered our interest to compare the reaction results under conventional heating condition with those under MW condition for the addition of β-dicarbonyl compounds to alcohols.[21] Then, the reactions of **1a** and **2a** in CH_3NO_2 were carried out under MW condition with 5 mol % H_2SO_4 as the catalyst, and 95% yield was obtained (Table 1, entry 15). During the reaction course, the reaction mixture was kept under 101 °C (refluxing) in the open vessel, which assured that the reaction under MW condition possessed the same reaction temperature to the conventional heating condition. For the addition of β-dicarbonyl compounds to alcohols, no obvious specific or non-thermo effects can be derived from the result of microwave-assisted reaction in comparison with that under the conventional heating condition (Table 1, entries 15 and 9).

Subsequently, the addition of various β-dicarbonyl compounds to a series of alcohols was examined in CH_3NO_2, using 5 mol % H_2SO_4 as the catalyst. As indicated in Table 2, the reactions were all carried out under 101 °C both under the conventional heating[22] and MW conditions,[23] and all the reactions completed in 5 min. When β-diketone **1a** reacted with the benzylic alcohol **2b** and **2c** bearing a fluoride or a chloride group, excellent 97% and 95% yields were obtained, illustrating that the electron-withdrawing substitution on the aromatic ring has no obvious effect on the reactivity under current reaction conditions (Table 2, entries 2 and 3). By contrast, the reaction of **1a** with 4-methoxy-1-phenylethanol bearing an electron-donating methoxyl group afforded very low yield both under conventional heating and MW conditions, mainly due to the decomposition of the methoxy substituted phenylethanol under strong acidity. As 1-(2-naphthyl)ethanol **2d** and benzhydrol **2e** were applied as the substrates in the reactions with **1a**, the products **3d** and **3e** were generated smoothly in good to excellent yields both under conventional heating and MW conditions (Table 2, entries 4 and 5). For the reaction of **1a** with the propargylic alcohol **2f**, good yields were observed both under the conventional heating and MW conditions (Table 2, entry 6).

When the β-diketone benzoylacetone **1b** was employed in the reactions with secondary alcohols **2a**, **2b**, **2d**, and **2e**, high yields (83–97%) of the corresponding products were obtained both under conventional heating and MW conditions, and no obvious difference was observed between the two reaction conditions for all substrates (Table 2, entries 7–10). Furthermore, when the diketone **1a** with two phenyl substitutes was changed to acetylacetone **1c**, the nucleophilicity of the enol form of the diketone decreases because the methyl group is less electron rich compared with phenyl group in the diketones. But the reaction of **1c** with **2d** and **2e** also afforded **3k** and **3l** in excellent yields both under the conventional heating and MW conditions (Table 2, entries 11 and 12). When the allylic alcohol **2g** was used to react with **1c**, the reaction proceeded smoothly and similar results were observed both under the conventional heating and MW conditions (Table 2, entry 13). At last, with the hope to expand the substrate scope, β-keto esters **1d** and **1e** with relatively low reactivities were applied as the nucleophiles to react with benzhydrol **2e**, and the products **3n** and **3o** were obtained successfully in 95% and 93% yields under the conventional heating and MW conditions, respectively (Table 2, entries 14 and 15). It is noteworthy that the addition of **1a** to the secondary alkyl alcohols such as 2-octanol did not proceed both under the conventional heating and MW conditions, due to the instability of the alkyl cation intermediate.

In summary, we have demonstrated that H_2SO_4, one of the cheapest Brønsted acids, is a highly efficient catalyst for the direct addition of β-dicarbonyl compounds to secondary alcohols both under conventional heating condition and under MW condition. For various β-dicarbonyl compounds and a series of secondary alcohols, the addition reactions afford high yields in most cases only after 5 min. To date, H_2SO_4 is the most effective catalyst for the addition of β-dicarbonyl compounds to alcohols and possesses the potential for the application in industry. Moreover, the reactions under conventional heating condition or under MW condition afford similar results and no obvious specific or nonthermal microwave effects have been observed in the addition reactions.

Table 2
Addition reactions of β-dicarbonyl compounds to alcohols catalyzed by H_2SO_4 under conventional heating and MW conditions

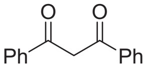
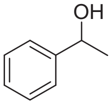
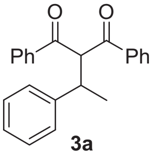
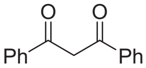
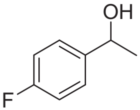
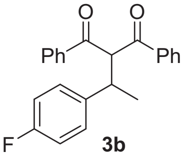
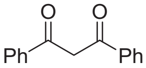
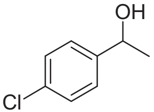
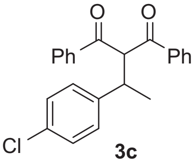
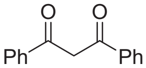
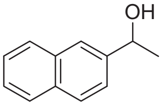
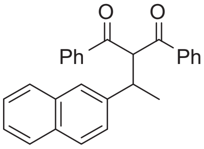
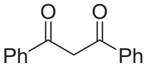
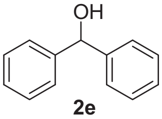
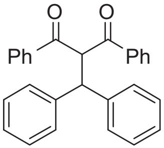
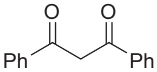
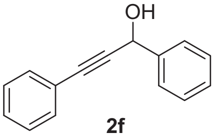
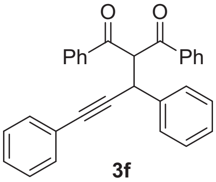
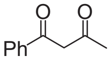
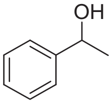
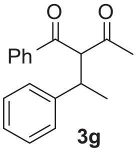
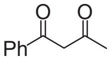
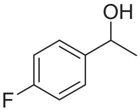
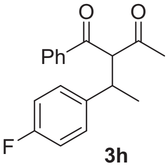
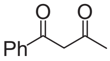
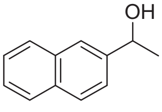
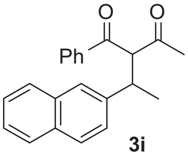
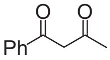
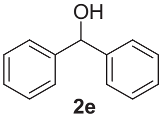
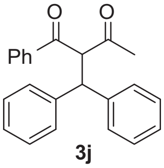
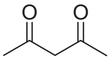
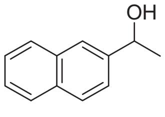
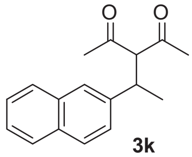
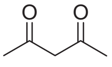
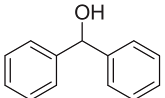
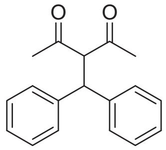
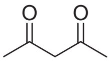
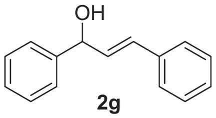
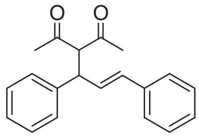
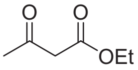
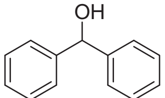
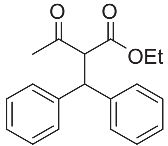
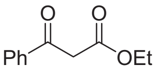
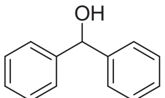
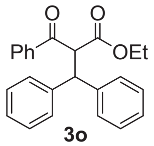
Entry	β-Dicarbonyl compound	Alcohol	Product	Yield[a] (%)	Yield[b] (%)
1	 1a	 2a	 3a	98	95
2	 1a	 2b	 3b	93	97
3	 1a	 2c	 3c	90	95
4	 1a	 2d	 3d	97	92
5	 1a	 2e	 3e	82	83
6	 1a	 2f	 3f	86	85
7	 1b	 2a	 3g	88	83
8	 1b	 2b	 3h	92	91
9	 1b	 2d	 3i	97	92
10	 1b	 2e	 3j	90	86

Table 2 (*continued*)

Entry	β-Dicarbonyl compound	Alcohol	Product	Yield[a] (%)	Yield[b] (%)
11	 **1c**	 **2d**	 **3k**	98	92
12	 **1c**	 **2e**	 **3l**	91	80
13	 **1c**	 **2g**	 **3m**	87	94
14	 **1d**	 **2e**	 **3n**	95	90
15	 **1e**	 **2e**	 **3o**	93	87

[a] Reaction conditions: H_2SO_4 (0.05 mmol), alcohol (1.0 mmol), β-dicarbonyl compound (3.0 mmol), CH_3NO_2 (2 mL), 101 °C, 5 min, isolated yield based on alcohol.

[b] Reaction conditions: H_2SO_4 (0.05 mmol), alcohol (1.0 mmol), β-dicarbonyl compound (3.0 mmol), CH_3NO_2 (2 mL), 101 °C, MW for 5 min, isolated yield based on alcohol.

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Supplementary data

Supplementary data (list of compounds along with their yield, analytical data, and copies of ^{1}H NMR and ^{13}C NMR spectra are included) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.104.

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22. *Typical procedure A for the reaction of β-dicarbonyl compound with alcohol catalyzed by H_2SO_4 under conventional heating condition:* β-Dicarbonyl compound (3.0 mmol) and alcohol (1.0 mmol) were combined in 2 mL of nitromethane, and H_2SO_4 (2.7 μL, 0.05 mmol) was added. The mixture was stirred under 101 °C in oil bath for 5 min. Then Na_2CO_3 (10 mg) was added to the reaction mixture to quench the reaction and the solvent was removed under reduced pressure, and the residue was flash column chromatographed over silica gel to afford the product.
23. *Typical procedure B for the microwave-assisted addition of β-dicarbonyl compounds to alcohols catalyzed by H_2SO_4:* β-Dicarbonyl compound (3.0 mmol) and alcohol (1.0 mmol) were combined in 2 mL of nitromethane, and H_2SO_4 (2.7 μL, 0.05 mmol) was added, and the resulting mixture was stirred under 101 °C with the microwave irradiation (650 W, 70%) for 5 min. Then Na_2CO_3 (10 mg) was added to the reaction mixture to quench the reaction and the solvent of the reaction mixture was removed under reduced pressure and the residue was passed through the flash column chromatography on silica gel to afford the product.