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Open-air and solvent-free ester condensation catalyzed by sulfonic acids

Akira Sakakura [a], Yoshiki Koshikari [b], Kazuaki Ishihara [b,*]

[a] EcoTopia Science Institute, Nagoya University, Chikusa, Nagoya 464-8603, Japan
[b] Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

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ABSTRACT

Ester condensation is one among the most fundamental organic transformations, and more environmentally benign alternatives to current esterification processes are needed. Under solvent-free and drying agent-free conditions, catalytic amounts of sulfonic acids promote ester condensation between an equimolar mixture of carboxylic acids and alcohols. In particular, *p*-toluenesulfonic acid (TsOH) and 10-camphorsulfonic acid (CSA), which have appropriate acidities, efficiently catalyze the ester condensation of secondary alcohols without their decomposition. Since the present protocol does not require solvents under simple open-air conditions, a large amount of esters can be synthesized in a rather small apparatus.

Esterification is one of the most important reactions in organic synthesis.[1] Catalytic condensation between an equimolar mixture of carboxylic acids and alcohols is most desirable with regard to atom economy and E-factor.[2–4] Conventionally, the acid-catalyzed ester condensation is conducted under the azeotropic reflux conditions with the removal of water. For example, hafnium(IV) salts efficiently catalyze the ester condensation between an equimolar mixture of carboxylic acids and alcohols under the azeotropic reflux conditions in toluene.[3] However, catalytic activities of Hf(IV) salts significantly decrease when the reaction is conducted under the conditions without the removal of water due to the serious inactivation of the catalysts by water. Recently, we reported bulky diarylammonium pentafluorobenzenesulfonates as mild and selective ester condensation catalysts.[5] These bulky ammonium salts efficiently catalyze ester condensation under heating conditions even without the removal of water. The use of non-polar solvent such as heptane is critical for high reactivities.[6] In the course of our continuing study on ester condensation, we found that the reaction of some alcohols with carboxylic acids was efficiently promoted by sulfonic acids under open-air and solvent-free conditions.[7] We report here a very simple and practical method for ester condensation catalyzed by sulfonic acids.

We considered that the solvent effect might play a key role in ester condensation under conditions without the removal of water. First, the solvent effect was examined in sulfonic acid-catalyzed ester condensation (Fig. 1, graph A). 6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of 10-camphorsulfonic acid (CSA, 5 mol %) in several solvents (2 mL) at 80 °C without removal of the water produced. To reduce experimental errors, these reactions were performed in screw-capped vessels (∅ 16 mm × 100 mm). When the reaction was conducted in toluene, which is conventionally used as a solvent in Brønsted acid-catalyzed ester condensation, the reaction proceeded slowly and the corresponding ester was obtained in moderate yield (blue line). The water produced might decrease the catalytic activity of

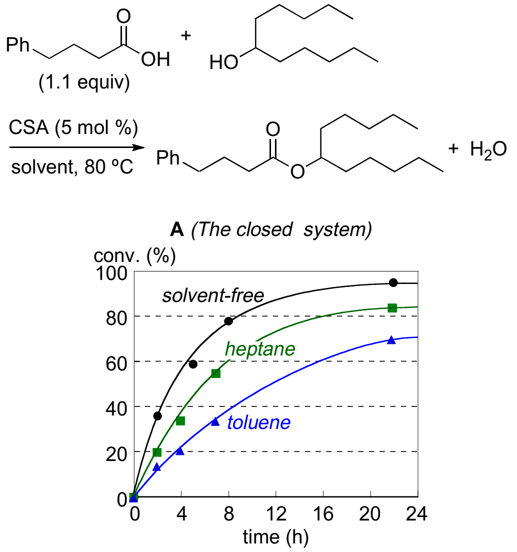

Figure 1. Solvent effect in CSA-catalyzed ester condensation. 6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of CSA (5 mol %) in solvent (2 mL) at 80 °C without the removal of water: black line, solvent-free; green line, heptane; blue line, toluene. Conversion yield was determined by ^{1}H NMR analysis.

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* Corresponding author. Tel.: +81 52 789 3331; fax: +81 52 789 3222.
E-mail address: ishihara@cc.nagoya-u.ac.jp (K. Ishihara).

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CSA in a relatively polar solvent such as toluene under these conditions without the removal of water. In contrast, the reaction proceeded more rapidly in heptane, a less polar solvent (green line). Interestingly, the reaction proceeded most rapidly under solvent-free conditions with little influence of water (black line). The finding that the reaction proceeded very well under solvent-free conditions without the removal of water is very important for the development of a practical ester condensation method. It is conceivable that the use of a sulfonic acid catalyst is the key to the success of the solvent-free ester condensation. In contrast to Lewis acids such as Hf(IV) salts, the affinity of sulfonic acids with water might be weak. Therefore, sulfonic acids were unlikely to be inactivated under the solvent-free conditions.

When CSA-catalyzed ester condensation was performed in a screw-capped vessel, the reaction did not proceed to completion, even though the reaction time was prolonged. It is conceivable that this result was due to hydrolysis of the product and/or the inactivation of CSA by the water produced. Therefore, we next performed ester condensation in an open-air vessel (∅ 16 mm × 100 mm) to remove water spontaneously. As a result, the reaction proceeded slightly more rapidly than in a screw-capped vessel, and was completed as expected (Fig. 2, graph B). The reactivity of ester condensation under solvent-free conditions in the open-air vessel was very high. In fact, the present ester condensation showed the same reactivity as that conducted under azeotropic reflux conditions in cyclohexane (bp 80.7 °C, bath temperature ∼115 °C) with the removal of water (Fig. 2, graph C). When the ester condensation in solvents is conducted under the open-air conditions, solvents would be evaporated, which causes some trouble in the reaction. These results showed that the present ester condensation has high potential as a practical method for the synthesis of esters.

Encouraged by these results, we next examined the catalytic activities of various sulfonic acids under the present reaction conditions. 6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of 5 mol % of concentrated sulfuric acid (H_2SO_4), *p*-toluenesulfonic acid (TsOH), methanesulfonic acid (MsOH), 2-propanesulfonic acid (*i*-$PrSO_3H$), and CSA in a screw-capped vessel (Table 1). The catalytic activities of the sulfonic acids depended on their pK_a values, and H_2SO_4 [pK_a (CD_3CO_2D) = 7.0][8] showed the highest reactivities among the catalysts examined (entry 1). However, the high acidity of H_2SO_4 resulted in the

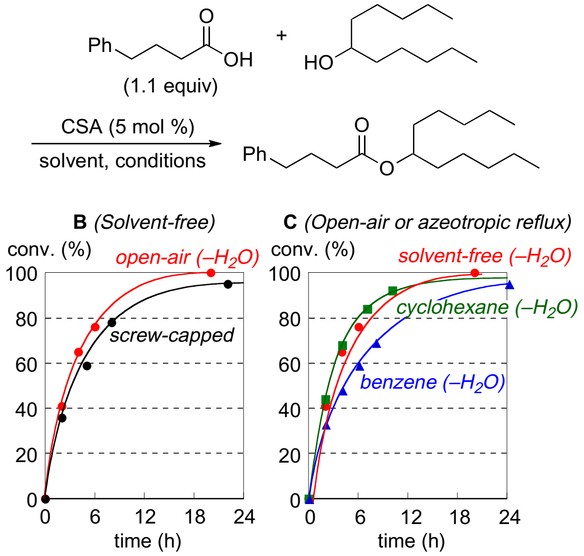
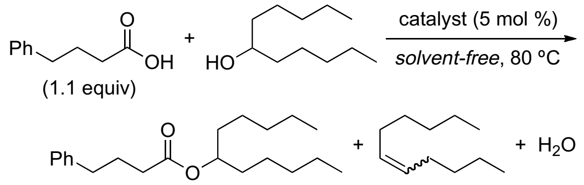


Figure 2. Effect of dehydration in CSA-catalyzed ester condensation. 6-Undecanol (2 mmol) was reacted with 4-phenylbutyric acid (1.1 equiv) in the presence of CSA (5 mol %) in solvent (2 mL) at 80 °C: red line, solvent-free conditions in an open-air vessel; black line, solvent-free conditions in a screw-capped vessel; green line, azeotropic reflux in cyclohexane (bp 80.7 °C) with the removal of water; blue line, azeotropic reflux in benzene (bp 80.1 °C) with the removal of water. The conversion yield was determined by ^{1}H NMR analysis.

Table 1

Comparison of the catalytic activities of sulfonic acids for ester condensation between 6-undecanol and 4-phenylbutyric acid[a]



Entry	Catalyst	pK_a[b]	Conv.[c] (%)	
			2 h	22 h
1	H_2SO_4	7.0	60	93 (7)[d]
2	TsOH	8.5	45	97 (0)[d]
3	MsOH	8.6	45	97 (0)[d]
4	CSA	9.0	36	95 (0)[d]
5	*i*-$PrSO_3H$	9.6	22	93 (0)[d]

[a] The reaction was conducted in the presence of a sulfonic acid (5 mol %) under solvent-free conditions at 80 °C in a screw-capped vessel.

[b] pK_a values were measured in CD_3CO_2D.

[c] Determined by ^{1}H NMR analysis.

[d] Conversion yield of 5-undecene is shown in brackets.

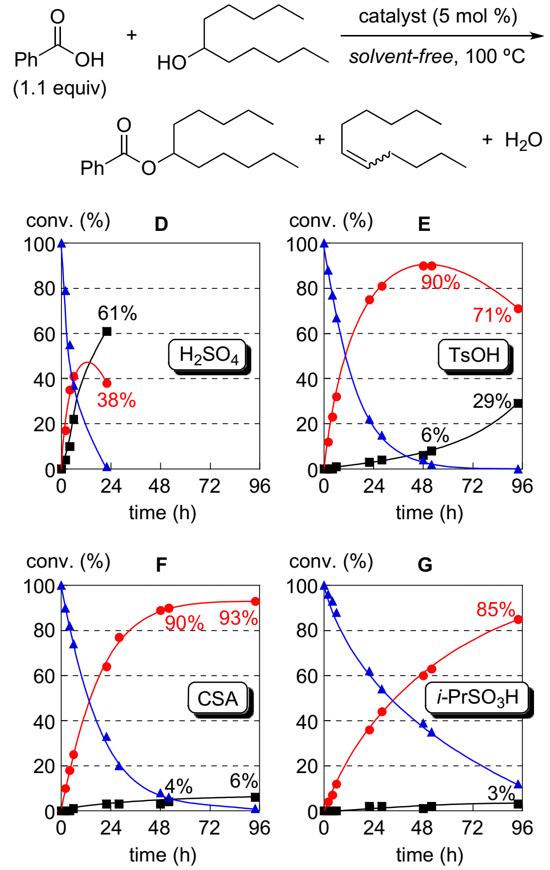


Figure 3. Ester condensation with benzoic acid catalyzed by sulfonic acid. 6-Undecanol (2 mmol) was reacted with benzoic acid (1.1 equiv) in the presence of sulfonic acid (5 mol %) under solvent-free conditions at 100 °C in a screw-capped vessel. The proportions of 6-undecanol (blue line), 6-undecyl benzoate (red line) and 5-undecene (black line) over time were evaluated by ^{1}H NMR analysis.

production of 5-undecene as a byproduct (7%), and the yield of the desired ester decreased (93%). In contrast to the results with H_2SO_4, other sulfonic acids such as TsOH [pK_a (CD_3CO_2D) = 8.5], MsOH [pK_a (CD_3CO_2D) = 8.6], CSA [pK_a (CD_3CO_2D) = 9.0], and *i*-$PrSO_3H$ [pK_a (CD_3CO_2D) = 9.6] did not cause the production of 5-undecene, and gave the ester in good yields (93–97%). In general, sterically hindered secondary alcohols are easily dehydrated to give alkenes under acidic conditions. However, the results described above showed that sulfonic acids with appropriate acidities successfully promoted the ester condensation of secondary alcohols without the production of alkenes.

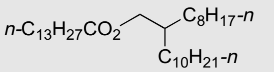
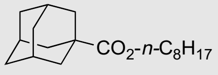
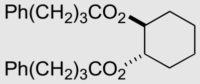
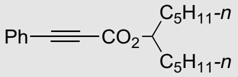
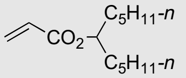
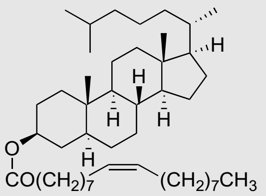
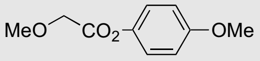
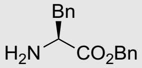
Next, we examined the catalytic activities of sulfonic acids in ester condensation between 6-undecanol and benzoic acid (Fig. 3). The reaction was conducted at 100 °C, since the reactivity of benzoic acid was rather low. This high reaction temperature caused the generation of an increased amount of 5-undecene. Especially, the reaction catalyzed by H_2SO_4 produced a significant amount of 5-undecene, and the yield of the desired ester was poor (graph D). Lower catalyst loading (1 mol % of H_2SO_4) did not suppress the generation of 5-undecene, and merely decreased the reactivity (ester: 63% yield, 5-undecene: 20% yield for 47-h reaction). In contrast, TsOH and CSA efficiently promoted the ester condensation with little production of 5-undecene, and a 50-h reaction gave the desired ester in 90% yield (graphs E and F). In the ester condensation catalyzed by TsOH, however, a prolonged reaction time caused the generation of a significant amount of 5-undecene (graph E). The catalytic activity of *i*-$PrSO_3H$ was much lower than those of TsOH and CSA, due to its lower acidity.

To explore the generality and scope of the present ester condensation catalyzed by sulfonic acids, the reaction was examined with an equimolar mixture of various alcohols and carboxylic acids under solvent-free conditions in an open-air vessel (Table 2). The ester condensation of primary alcohols proceeded very well even with sterically hindered carboxylic acids such as 1-adamantanecarboxylic acid, and the corresponding esters were obtained in excellent yields (entries 1–6). The present protocol could be easily

Table 2

Ester condensation under solvent-free conditions[a]

$$R^1CO_2H \ + \ R^2OH \xrightarrow[\text{open-air, solvent-free}\\ \text{heat}]{\text{catalyst (5 mol \%)}} R^1CO_2R^2$$

Entry	Product ($R^1CO_2R^2$)	Catalyst	Conditions (°C, h)	Isolated yield (%)
1[b]		H_2SO_4	60, 39	97
2[b]		CSA	60, 39	92
3[b,c]		CSA	60, 24	97 (97)[d]
4[e]		H_2SO_4	80, 3	93
5[e]		TsOH	80, 3	95
6[e]		CSA	80, 3	92
7[e]		H_2SO_4	80, 22	89 (93:7)[f]
8[e]		TsOH	80, 22	95
9[e]		CSA	80, 22	95
10		H_2SO_4	80, 19	78 (12)[g]
11		TsOH	80, 29	95
12		CSA	80, 29	90
13[e]		H_2SO_4	80, 48	81
14[e]		TsOH	80, 48	87
15[e]		CSA	80, 48	91
16[h]		TsOH	60, 35	98
17		H_2SO_4	80, 20	34
18		TsOH	80, 26	39
19		CSA	80, 26	35
20[i]		CSA	60, 36	89 (>99)[j]

[a] Unless otherwise noted, a mixture of alcohol (2 mmol) and carboxylic acid (2 mmol) was heated with sulfonic acid (5 mol %) in an open-air vessel (∅ 16 mm × 100 mm).

[b] The reaction was conducted with sulfonic acid (1 mol %).

[c] The reaction of alcohol (100 mmol) and carboxylic acid (100 mmol) was conducted in a 100-mL round-bottomed flask.

[d] The purity of the product is shown in brackets.

[e] The reaction was conducted with 1.1 equiv of carboxylic acid.

[f] The ratio of *trans* isomer:*cis* isomer is shown in brackets.

[g] The yield of alkenes is shown in brackets.

[h] The reaction was conducted with octane (1 mL).

[i] The reaction was conducted with 2 equiv of benzyl alcohol.

[j] The optical purity of the product is shown in brackets.

applied to a large-scale process. The ester condensation of an equimolar mixture of 2-octyldodecanol and myristic acid catalyzed by CSA (1 mol %) gave the corresponding ester in 97% yield, just after simple extraction with the minimal use of organic solvents (entry 3).[9]

Esters derived from secondary alcohols were also obtained in good yields (entries 7–16), although the reactivities of secondary alcohols were lower than those of primary alcohols. Ester condensation of *trans*-1,2-cyclohexanediol gave the corresponding diester in high yields (entries 7–9), while Lewis acidic metal salts, such as $HfCl_4(THF)_2$, were not suitable for use with these diols due to tight chelation with metal ions.[3c] The reactions catalyzed by TsOH and CSA gave particularly excellent results (entries 8 and 9), although the use of H_2SO_4 led to isomerization of the product (*trans*:*cis* = 93:7) (entry 7). When the reaction of 6-undecanol with 3-phenylpropionic acid was conducted with a catalytic amount of H_2SO_4, a significant amount of 5-undecene was generated (12%) and the yield of the desired ester was decreased (78%) (entry 10). In contrast, neither TsOH nor CSA promoted the generation of 5-undecene and the ester was obtained in good yields (entries 11 and 12). Ester condensation of acrylic acid was also successfully conducted without promoting undesired conjugate addition (entries 13–15). When substrates and/or products were solid, they were effectively dissolved by the addition of a small amount of octane. For example, the reaction of β-cholestanol (solid, 2 mmol) with oleic acid proceeded well in the presence of octane (1 mL), and gave the corresponding ester (solid) in 98% yield (entry 16). Tertiary alcohols are generally much less reactive than secondary alcohols and decompose much more easily to give alkenes under acidic conditions. In fact, the reaction of 2-methyl-4-phenyl-2-butanol with 4-phenylbutyric acid resulted in the generation of alkenes in ca. 85% yields under the present reaction conditions.

In contrast to the ester condensation of aliphatic alcohols, the reaction of 4-methoxyphenol with methoxyacetic acid gave poor results (entries 17–19), while bulky ammonium salt-catalyzed esterification gave the corresponding ester in 99% yield.[5] It is conceivable that the hydrophilic nature of sulfonic acids promoted hydrolysis of the product to decrease its yield without the removal water.[10] Amino acid esters could be prepared through the present ester condensation by using 1 equiv of an additional sulfonic acid. When L-phenylalanine and benzyl alcohol (2 equiv) were reacted with CSA (1.05 equiv), the corresponding benzyl ester was obtained in good yield and with complete retention of its chiral center (entry 20).

In conclusion, we have demonstrated that 1–5 mol % of sulfonic acids could efficiently catalyze the ester condensation of alcohols with carboxylic acids (1.0–1.1 equiv) under open-air and solvent-free conditions. This is a highly practical and atom-economical esterification method, since it does not require any solvent as well as additional equipment or additional amounts of materials and energy for dehydration. Through the present protocols, a large amount of esters can be synthesized in a rather small apparatus. For example, 49 g of 2-octyldodecyl palmitate was synthesized in a 100-mL round-bottomed flask (Table 2, entry 3).

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Supplementary data

Analytical data for new compounds, and ^1H and ^{13}C NMR data of all products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.058.

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9. *Experimental procedure*: A 100-mL round-bottomed flask was charged with 2-octyl-1-dodecanol (100 mmol), myristic acid (100 mmol) and CSA (1 mmol). The mixture was stirred at 60 °C for 24 h, and then the reaction mixture was quenched by the addition of $NaHCO_3$ (1 mmol) and water (30 mL). After the mixture was stirred for 5 min, the resulting aqueous mixture was extracted with hexane (10 + 20 mL), and the organic layer was concentrated in vacuo to give the product (49.3 g, 97% yield, 97% purity).
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