Phosphorofluoridic Acid-catalyzed Condensation Reaction of Carboxylic Acids with 1-Arylalkyl Alcohols Leading to Esters under Solvent-free Conditions

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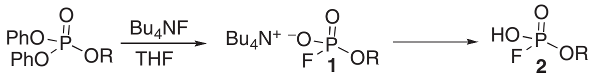
Phosphorofluoridic acid with an L-menthyl group catalyzed condensation reaction between carboxylic acids and 1-arylalkyl alcohols under solvent-free conditions to give esters in moderate to high yields. Results using aliphatic acids are shown.

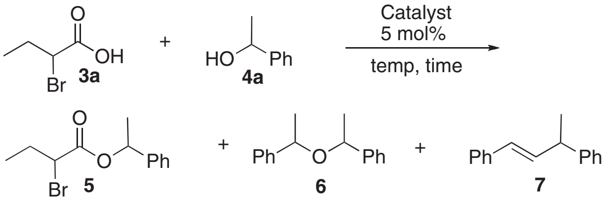
Condensation reactions between carboxylic acids and alcohols leading to esters are some of the most fundamental chemical processes.[1] Recently, attention has been focused on these reactions using acid-sensitive substrates mediated by nonmetal Brønsted acid catalysts. For example, ammonium[2] and phosphonium[3] salts of sulfonic acids have been developed to achieve these reactions. In these cases, it is not necessary to remove water, which is a coproduct of condensation reactions, from the reaction vessels. However, the reaction has to be performed in organic solvents. From an environmental perspective, it would be more preferable if the reactions could be carried out under solvent-free conditions. Instead of organic solvents, ionic liquids have been used as a reaction media under microwave-irradiation.[4] Alternatively, ammonium tribromide has been used to mediate the condensation reaction, but large excess amounts of alcohols were used.[5] Very recently, Ishihara et al. reported that sulfuric, toluenesulfonic, and camphorsulfonic acid-catalyzed condensation reaction under open air effectively gave the corresponding esters.[6] Nevertheless, even these systems do not always mediate the esterification with high efficiency. For example, the use of alcohols, such as 1-arylethyl alcohols, which readily undergo acid-catalyzed dehydration, results in the formation of esters in only low yields.[7] The acid catalysts that have been developed to date mainly have sulfonic acid moieties. In contrast, less attention has been paid to those with phosphoric acid moieties. This may partly be due to their lower acidities compared to those of sulfonic acids. The introduction of electron-withdrawing groups at the phosphorus atom might be expected to provide stronger acids. Furthermore, the introduction of hydrophobic sites to the oxygen atoms of phosphoric acids makes it possible to remove water from the reactive centers while maintaining high catalytic activities. While phosphorofluoridic acids with various alkyl substituents have been described,[8] to the best of our knowledge there has been no report on their application as acid catalysts, most likely due to their complicated syntheses.

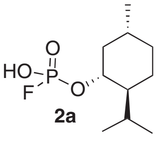
Very recently, we found that fluoridative hydrolysis of *O*,*O*-diaryl phosphoric acid esters gave phosphorofluoridic acid salts **1**,[9] which can be converted to the corresponding acids **2** (Scheme 1). We report herein the first example of a phosphorofluoridic acid-catalyzed condensation reaction of carboxylic acids and 1-arylalkyl alcohols leading to esters under solvent-free conditions.



Scheme 1.

Table 1. Acid-catalyzed condensation between **3a** and **4a**[a]



Entry	Catalyst	Temp /°C	Time /h	Yield /% 5	6	7
1	None	80	29	24	0	0
2	H_2SO_4	80	1	0	0	60
3	TsOH	80	2	40	0	27
4	PhOP(O)(OH)$_2$	80	22.5	51	0	0
5	PhP(O)(OH)$_2$	80	26	77	42	0
6	PhP(O)(OH)$_2$	100	6	38	27	0
7	PhP(O)H(OH)	80	22	54	30	0
8	 **2a**	80	21	51	37	0
9		100	3	57	13	0
10		100	5.5	75	35	3
11		100	22.5	76	44	1

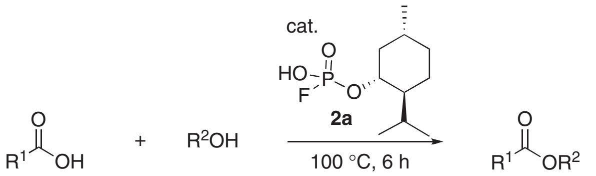
[a]The reaction mixture of **3a** (2 mmol) and **4a** (3 mmol) was heated with stirring in the presence of a catalyst (0.1 mmol).

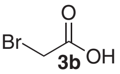
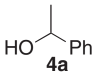
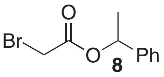
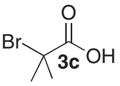
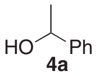
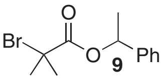
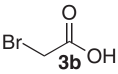
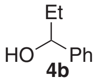
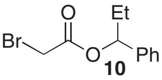
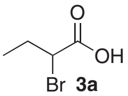
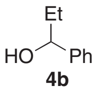
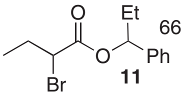
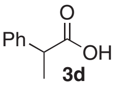
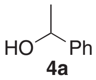
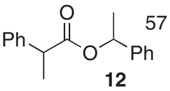
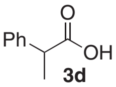
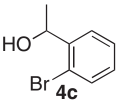
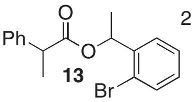
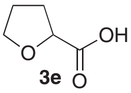
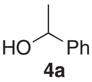
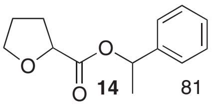
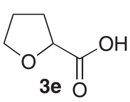
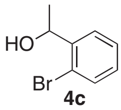
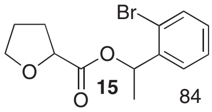
Initially, to clarify the catalytic ability of phosphorofluoridic acids **2**, the reaction between 2-bromobutanoic acid (**3a**) and 1-phenylethyl alcohol (**4a**) was carried out in the presence of a variety of acids under solvent-free conditions (Table 1). The reaction in the presence of H_2SO_4 catalyst was complete within 1 h, but mainly gave alkene **7**,[10] which may be formed via two molecules of styrene derived from the dehydration of **4a** (Entry 2). The *p*-toluenesulfonic acid-catalyzed condensation reaction gave the desired product **5** to some extent, but also produced some inseparable impurities (Entry 3). Phosphoric acid analogues were then used to catalyze the reaction (Entries 4–7). The reaction for more than 20 h gave **5** in yields of more than 50%, but the reaction at a higher temperature and for a shorter reaction time gave **5** in a reduced yield (Entry 6).

The catalytic activity of phosphorofluoridic acid **2a** for the esterification was then examined. The reaction at 80 °C for 21 h gave **5** in 51% yield, and that at 100 °C for 5.5 h gave **5** in 75% yield, although ether **6** was also formed as a by-product.

Various combinations of acids **3** and 1-arylethyl alcohols **4** were subjected to an acid **2a**-catalyzed condensation reaction (Table 2). In most cases, acid **2a** catalyzed the condensation re-

Table 2. Acid **2a**-catalyzed esterification of **3** with **4a**[a]

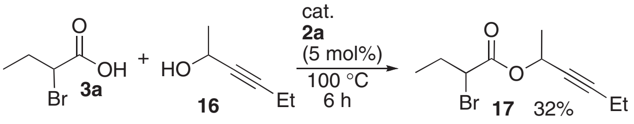


Entry	3	4	Product	Yield/%
1	 **3b**	 **4a**	 **8**	81
2	 **3c**	 **4a**	 **9**	57
3	 **3b**	 **4b**	 **10**	82
4	 **3a**	 **4b**	 **11**	66
5	 **3d**	 **4a**	 **12**	57
6	 **3d**	 **4c**	 **13**	24
7	 **3e**	 **4a**	 **14**	81
8	 **3e**	 **4c**	 **15**	84

[a]Acid **3** (2 mmol) was reacted with alcohol **4** (3 mmol) in the presence of **2a** (0.1 mmol).

action of **3** and **4** with high efficiency. In the reaction of **3d** with **4c**, the ester **13** was obtained in only 24%, but the starting materials **3d** and **4c** were recovered in around 70% (Entry 6). For the reaction leading to diastereomers, two diastereomers were formed in a nearly equal ratio (Entries 4–8). 2-Bromoacetic acid (**3b**), and 2-bromo-2-methylpropanoic acid (**3c**) reacted with **4a** to give the corresponding esters **8** and **9** in good to high yields (Entries 1 and 2). As alcohols, 1-phenyl-1-propanol (**4b**) also participated in the esterification, although a small amount of ether derived from the dehydration of **4b** was formed (Entries 3 and 4). 2-Tetrahydrofurancarbxylic acid (**3e**) was also used to give the corresponding esters in high yields (Entries 7 and 8). In the latter case, the bromine atom at the ortho position in **4c** did not influence the efficiency of the reaction.

Finally, 2-propynyl alcohol (**16**), which is also susceptible to dehydration under acidic conditions,[11] was used as an alcohol (Scheme 2). The condensation reaction of **3a** and **16** under identical conditions took place to give the corresponding ester **17**, albeit in moderate yield, along with the recovery of **3a** (68%).



Scheme 2.

In summary, the catalytic activity of **2a** in the condensation reaction between acids and 1-arylalkyl alcohols was demonstrated for the first time. The results obtained with a range of aliphatic acids were shown. To further improve the efficiency of the reaction and to apply this method to asymmetric reactions, studies on the modification of the alkyl substituents on an oxygen atom attached to the phosphorus atom are underway.[12]

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References and Notes

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