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Palladium on carbon–bromobenzene mediated esterification and transesterification

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ABSTRACT

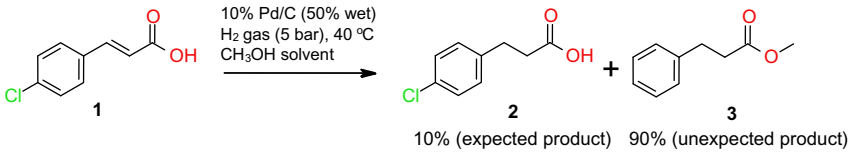
A series of carboxylic acids were converted into their corresponding esters using the Pd/C catalyzed hydrogenation conditions in the presence of catalytic bromobenzene in alcohols and the method could also be applicable for the transesterification of esters. Good to excellent yields were obtained for different aliphatic or aromatic starting materials. The success of this esterification relies on the in situ generation of hydrobromic acid (HBr) from bromobenzene which provides a mild and acidic reaction environment. The palladium catalyst exhibits a remarkable activity and is reusable for up-to three consecutive cycles.

Esterification of carboxylic acids and transesterification of esters have wide industrial applications. Esters are common in organic chemistry and biological materials, and often have a characteristic pleasant, fruity odor. This leads to their extensive use in the fragrance and flavor industries. Ester bonds are also found in many polymers, pharmaceutical, and agricultural compounds. Many useful and reliable esterifications of carboxylic acids and transesterifications of esters have been reported in the literature.[1–8] In the course of our research efforts, we found that Pd/C-catalyzed hydrogenation conditions in the presence of bromobenzene additive can accomplish simultaneous esterification and transesterification reactions in a highly efficient manner.

In an ongoing medicinal chemistry program, we wished to synthesize **2**, which we planned to prepare by hydrogenation of 4-chlorocinnamic acid **1** in the presence of 10% Pd/C (50% wet) using methanol as a solvent. To our surprise, only 10% of the desired 3-(4-chlorophenyl)-propanoic acid **2** was obtained. Instead, the reaction proceeded to produce 90% of methyl-3-phenylpropanoate **3** (Scheme 1). This finding encouraged us to study the influencing factors for the unprecedented esterification reaction.

The probable mechanism of this unprecedented esterification could be the result of the in situ generation of HCl from 4-chlorocinnamic acid **1** in the presence of palladium catalyst under hydrogen pressure, which provides a mild and an acidic reaction environment.

These results prompted us to explore further this unprecedented esterification reaction, and an optimization study was undertaken. First, we decided to employ bromobenzene as an external acid source to consider whether the esterification is accessible. Thus, phenylacetic acid **4** (0.0036 mol), bromobenzene (0.00018 mol), 10% Pd/C (0.01 g), and methanol (3 mL) were placed in an autoclave vessel. The autoclave was pressurized with 1–2 bar of nitrogen followed by 1–2 bar of hydrogen gas. The reaction



Scheme 1. Catalytic hydrogenation of alkene derivative **1**.

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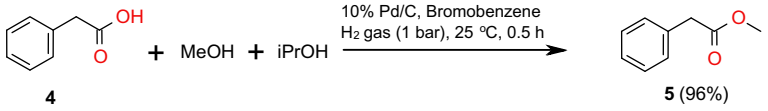
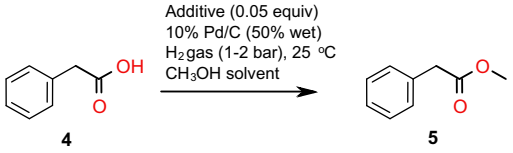


Scheme 2. Chemoselective esterification of acid **4** with a mixture of MeOH and *i*PrOH.

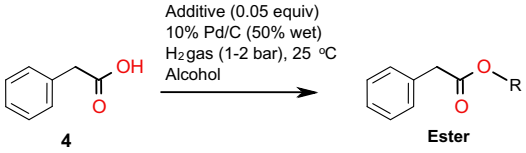
Table 1
Palladium-catalyzed esterification of phenylacetic acid under different reaction conditions[a]



Entry	Catalyst	Additive	Hydrogen Source	Isolated yield of **5** (%)
1	10% Pd/C (dry)	Bromobenzene	H_2 gas	98
2	10% Pd/C (50% wet)	Bromobenzene	H_2 gas	98
3	10% Pd/C (50% wet)	Chlorobenzene	H_2 gas	80
4	10% Pd/C (50% wet)	Bromobenzene	$HCOONH_4$	No reaction
5	10% Pd/C (50% wet)	Bromobenzene	—	No reaction
6	10% Pd/C (50% wet)	—	H_2 gas	No reaction
7	—	Bromobenzene	H_2 gas	No reaction
8	10% Pd/C (50% wet)	Bromobenzene + 0.5 equiv of *n*-$BuNH_2$	H_2 gas	No reaction

[a] Reaction conditions: phenylacetic acid (1.0 g, 0.00734 mol), bromobenzene (0.11 g, 0.000734 mol), chlorobenzene (0.08 g, 0.000734 mol), catalyst 10% Pd/C (0.1 g of 10% wt of **4**), methanol (3 mL), H_2 pressure (1–2 bar), temperature 25 °C, and time 2 h.

Table 2
Esterification of phenyl acetic acid with various alcohols[a]



Entry	Alcohol	Time (h)	Product (R)	Yield[b] (%)
1	CH_3OH	0.5	$C_6H_5CH_2COOCH_3$	95
2	C_2H_5OH	1.0	$C_6H_5CH_2COOC_2H_5$	91
3	*n*-C_4H_9OH	2.0	$C_6H_5CH_2COOC_4H_9$	84
4	*n*-$C_8H_{17}OH$	2.0	$C_6H_5CH_2COOC_8H_{17}$	80
5	$C_6H_5CH_2OH$	2.0	$C_6H_5CH_2COOCH_2C_6H_5$	75
6	$(CH_3)_2CHOH$	15	$C_6H_5CH_2COOCH(CH_3)_2$	64
7	$(CH_3)_3COH$	48	$C_6H_5CH_2COOC(CH_3)_3$	No reaction
8	C_6H_5OH	48	$C_6H_5CH_2COOC_6H5$	No reaction

[a] Reaction conditions: acid (1.0 equiv), bromobenzene (0.1 equiv), catalyst 10% Pd/C (50% wet) (0.2 g), methanol (3 mL), 5–6 bar H_2 pressure, temperature 55–60 °C, and time 4–8 h.
[b] Isolated yields.

mixtures were then warmed to 25 °C temperature and stirred for 1 h at 300 rpm. The methyl phenyl acetic acid ester **5** could be isolated in 98% yield (Scheme 2).

A series of combinations of reagents were screened, and the results are presented in Table 1. Esterification reaction proceeded smoothly when halo benzenes were used in the presence of catalytic amount of palladium under 1–2 bar of hydrogen pressure (entries 1–3). During attempts to conduct the reaction with palladium and bromobenzene in the absence of hydrogen gas (entry 5), no esterification occurred and starting material was recovered almost quantitatively by column chromatography. Furthermore, in the absence of either bromobenzene or palladium no product formation **5** was observed (entries 6 & 7).

From entries 1 and 2, it is clear that esterification progressed by the in situ generation of HBr from bromobenzene. In support of this hypothesis, the addition of 0.5 equiv of *n*-butylamine to the reaction mixture did not render **5**, which should neutralize the liberated HBr acid, inhibits the esterification reaction (Table 1, entry 8). This observation indicates that a Brønsted acid is involved in the mechanism. Alternatively a reaction sample of entry 1 was withdrawn for gas chromatography–mass spectral analysis (GC–MS) after 1 h. Two peaks corresponding to masses 78 and 150 were observed, which corresponds to the structure of benzene and methyl phenyl acetate (Table 2, entry 1), GC–MS traces indicated that bromobenzene converted completely to benzene.

The probable mechanism for the unprecedented esterification of the aryl/aliphatic acids with alcohols could be the oxidative insertion of Pd(0) into the Ar–X bond to produce an aryl palladium halide under the present reaction conditions. This aryl palladium species in contact with hydrogen gas leads to generation of anhydrous HBr acid, Pd(0), and benzene as the by-products. Proton transfer from the generated HBr to carbonyl oxygen increases the electrophilicity of carbonyl carbon of acid followed by the Fischer esterification with alcohol (Fig. 1).

We proceeded to examine the substrate scope of the reaction of model acid **4** with different alcohols (methanol, ethanol, 1-butanol, 1-octanol, benzyl alcohol, isopropanol, *t*-butanol, and phenol) with bromobenzene as an additive to determine the scope of this procedure. The results are given in Table 2.

The results obtained in the esterification of model acid **4** under the optimized reaction conditions were, in general, good to excellent. Thus, when alcohols were used (entries 1–6)[9] we obtained the corresponding esters in excellent yields. However, when more hindered hydroxyl groups (secondary or tertiary or phenol, entries 6–8) were studied, poor results or no products were observed.

The rate of esterification becomes much slower when methanol is replaced with a more sterically hindered alcohol, such as isopropanol. Thus, when we treated phenylacetic acid **4** with a mixture of MeOH and *i*PrOH in the presence of catalytic amounts of