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p-Toluenesulfonic acid mediated hydroarylation of cinnamic acids with anisoles and phenols under metal and solvent-free conditions

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Abstract—Hydroarylation of cinnamic acids with anisoles and phenols mediated by *p*-toluenesulfonic acid (*p*-TSA) under metal and solvent-free conditions gave 3-(4-methoxyphenyl)-3-phenylpropanoic acids and dihydrocoumarins, respectively, in high yields and excellent selectivity.

Coumarin derivatives exist widely in Nature, especially in plants, and show a wide range of biological activities[1] such as anti-inflammatory, anti-oxidative, anti-aging and anti-cancer.[2] For example, tannin-containing plant extracts possessing the 4-aryldihydrocoumarin unit have been used for the treatment of infections and diseases for centuries in China and Japan.[3] Studies have established that phenolic dihydrocinnamic acids are antioxidants, which prevent chronic diseases such as coronary heart disease and colorectal cancer. The beneficial effects of phenolic antioxidants on health have been attributed to their antioxidant capacity, particularly their ability to protect low-density lipoproteins from oxidative attack.[4]

The preparation of dihydrocoumarins has been accomplished in many ways: (i) the hydroarylation[5] of cinnamic acids with phenols in strong acidic media;[6] (ii) the catalytic hydrogenation of coumarins;[7] (iii) Lewis acid mediated reaction of highly activated phenols with acrylonitrile;[8] (iv) reaction of chromium Fisher carbene complexes with ketal acetals.[9] However, many of these methods suffer from disadvantages such as lack of substrate generality and the use of a large excess of expensive trifluoroacetic acid,[6a] and the concerns regarding the use of transition metals.[6a,b,d] For instance, hydroarylation is substrate specific and occurs only with electron-rich phenols and cinnamic acids.[6] In this Letter, we report that *p*-toluenesulfonic acid (*p*-TSA) has been found to effect hydroarylation of a variety of phenols and anisoles onto cinnamic acids under metal and solvent-free conditions (Tables 1 and 2).

When a mixture of cinnamic acid **1** and phenol **2** ($R' = H$) was heated in the presence of a stoichiometric amount of *p*-toluenesulfonic acid at 130 °C, the corresponding dihydrocoumarin **3** was obtained in 99% yield (Scheme 1)[10] instead of linear ester **4** ($R' = H$). However, under identical conditions, cinnamic acid was smoothly esterified with 4-nitrophenol **2** ($R' = NO_2$) to furnish the ester **4** ($R' = NO_2$) in 98% yield.

Surprised by this result, we carried out several experiments to optimize systematically the reaction conditions for this transformation. The hydroarylation reaction failed when carried out in organic solvents (CH_2Cl_2, $CHCl_3$, C_6H_6, toluene and DMF, even at reflux temperatures) as well as when using other acid catalysts (camphorsulfonic acid or acetic acid). After several experiments, *p*-toluenesulfonic acid, phenol and cinnamic acid, in equimolar amounts with heating at 125 °C for 3 h were found to be the optimum conditions, which gave the dihydrocoumarin in 99% yield. Lowering the quantity of *p*-TSA resulted in the formation of **3** in reduced yield. As can be seen from Table 1, several phenols with a variety of substituents such as Me, Cl and ^{t}Bu underwent esterification with substituted cinnamic acids followed by their intramolecular hydroarylation to afford the corresponding dihydrocoumarins **3a**–**j** in

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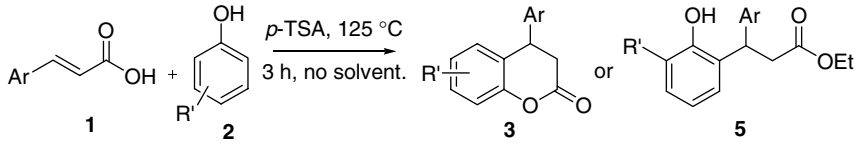
Table 1. *p*-Toluenesulfonic acid mediated hydroarylation of cinnamic acids with phenols[a]

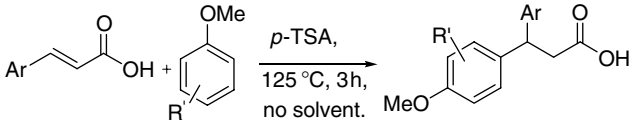


1 2 3 5

Entry	Ar	R′	Yield[b] (%) of	
			3	**5**[c]
a	Ph	H	99	—
b	Ph	2-Me	95	—
c	Ph	3-Me	97	—
d	Ph	4-Me	99	—
e	Ph	4-Cl	89	—
f	Ph	4-Bu′	89	—
g	Ph	1-Naphthol	93	—
h	4-ClC_6H_4	H	87	—
i	4-ClC_6H_4	4-Me	94	—
j	4-$MeOC_6H_4$	H	89	—
k	Ph	2-Br	—	92
l	Ph	2-Cl	—	87[11]
m	Ph	2-Ome	—	79
n	Ph	2-CO_2Me	—	93

[a] Reaction conditions: cinnamic acid (5 mmol), phenol (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 °C, 3 h.
[b] Isolated yield after column chromatographic purification.
[c] Workup reaction mixture was quenched with ethyl acetate followed by the addition of water.

Table 2. *p*-Toluenesulfonic acid mediated hydroarylation of cinnamic acids with anisoles[a]



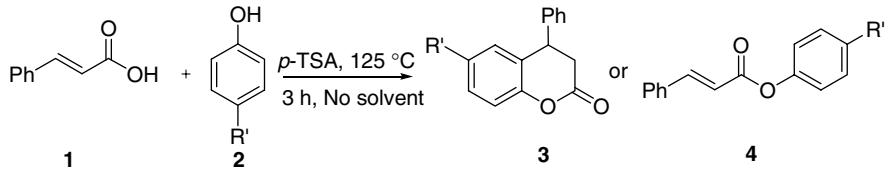
1 6 7a-j

Entry	Ar	R′	Yield[b] (%)
a	Ph	H	95[c]
b	Ph	2-Br	87[11]
c	Ph	3-Br	88
d	Ph	2-Cl	75
e	Ph	2-Me	91
f	Ph	3-Me	93
g	Ph	4-Me	95[d]
h	H	3-OMe	71
i	4-ClC_6H_4	H	82
j	4-$MeOC_6H_4$	H	65

[a] Reaction conditions: cinnamic acid (5 mmol), anisole (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 °C, 3 h.
[b] Isolated yield after column chromatographic purification; also ~5% of the corresponding demethylated phenolic compounds were formed.
[c] (*ortho:para* = 1:1).
[d] Only *ortho* product was formed.

good to excellent yields. In the case of phenolic substrates with *ortho* substituents such as Cl, Br, OMe and CO_2Me, the dihydrocoumarins formed initially were labile, possibly due to neighbouring group participation by the heteroatom, and underwent hydrolysis on treatment with water and ethyl acetate to give the corresponding acids along with a small amount of esters. However, if the reaction mixture was quenched with ethyl acetate,[12] followed by the addition of water, the corresponding phenolic esters **5k**–**n** were formed, due to transesterification, in excellent yields (entries k–n, Table 1).

In contrast, when anisole was subjected to hydroarylation with cinnamic acid under the same reaction conditions, the corresponding 3-(4-methoxyphenyl)-3-phenylpropanoic acid **7a** (*o*/*p* = 1:1) was obtained in 95% yield. Subsequently, several anisoles with substituents such as Br, Cl and OMe underwent hydroarylation successfully with cinnamic acids to produce the corresponding carboxylic acids **7a**–**j** in excellent yields, the results of which are presented in Table 2. Exclusive *para*-selectivity was observed for all the substrates studied (except **1a**), in accordance with the Friedel–Crafts alkylation mechanism.[13] However, if the *para* position was



1 2 3 4

R'	Yield (%) 3	4
H	99	-
NO_2	-	98

Scheme 1. *p*-Toluenesulfonic acid mediated reaction of cinnamic acid with phenols.

blocked, alkylation occurred at the *ortho* position (Table 2, entry g). Other less activated substrates such as toluene failed to undergo hydroarylation. Acetanilide underwent complete hydrolysis producing aniline. Treatment of chalcone with anisole in the presence of *p*-TSA yielded a mixture of products that was difficult to separate.

Mechanistically, in the case of phenols, formation of phenolic esters followed by intramolecular Friedel–Crafts type cyclization leads to dihydrocoumarin derivatives **3**.[5a] This observation was supported by the fact that when (*E*)-phenyl cinnamate was subjected to hydroarylation under the same reaction conditions, dihydrocoumarin **3** was obtained. In the case of anisoles, protonation of cinnamic acids leads to a highly electrophilic benzylic carbon such that Friedel–Crafts type alkylation with electron-rich anisole took place producing 3-(4-methoxyphenyl)-3-phenylpropanoic acids **7a**–**j**.

In conclusion, we have developed a convenient, practical and metal and solvent-free process for hydroarylation of cinnamic acids with phenols and anisoles mediated by *p*-toluenesulfonic acid affording dihydrocoumarins **3**, esters **5** and 3-(4-methoxyphenyl)-3-phenylpropanoic acids **7a**–**j**, respectively, in good to high yields. High regioselectivity, easy handling, broad substrate scope and the use of cheap *p*-toluenesulfonic acid as acid mediator are some of the advantages of this methodology.

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10. *Typical experimental procedure:* To a 25 mL round-bottomed flask equipped with a reflux condenser, were charged phenol or anisole (5.5 mmol), cinnamic acid (5 mmol), and *p*-toluenesulfonic acid (5 mmol). The reaction mixture was heated to 125 °C for 3 h. After completion (monitored by TLC), the reaction mixture was cooled and quenched with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel (230–400 mesh) using ethyl acetate and petroleum ether as eluent.
11. *Spectal data for representative compounds. Ethyl 3-(3-chloro-2-hydroxyphenyl)-3-phenylpropanoate* (**5l**): Yield 87%, ^{1}H NMR (200 MHz) δ 1.12 (t, $J = 7.1$ Hz, 3H),

3.05 (dd, $J = 8.1$, 4.1 Hz, 2H), 4.06 (t, $J = 7.1$, 2H), 4.90 (t, $J = 8.1$ Hz, 1H), 5.89 (s, 1H), 6.80 (t, $J = 7.8$ Hz, 1H), 7.06 (dd, $J = 1.5$, 7.8, 1H), 7.15–7.28 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.08, 39.51, 40.95, 60.45, 120.49, 120.80, 126.57, 126.86, 127.18, 127.86, 128.40, 131.46, 142.39, 149.03, 171.80. Anal. Calcd for $C_{17}H_{17}ClO_3$: C, 67.00; H, 5.62%. Found: C, 67.11; H, 5.55%. *3-(3-Bromo-4-methoxyphenyl)-3-phenylpropanoic acid* (**7b**): Yield 87%, ^{1}H NMR (200 MHz) δ 3.03 (d, $J = 7.8$ Hz, 2H), 3.87 (s, 3H), 4.43 (t, $J = 7.8$ Hz, 1H), 6.79 (d, $J = 8.5$ Hz, 1H), 7.12 (dd, $J = 2.1$, 8.5 Hz, 1H), 7.17–7.32 (m, 5H), 7.38 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.14, 45.23, 55.87, 111.49, 111.75, 126.56, 127.21, 127.31, 128.49, 132.18, 136.70, 142.64, 154.25, 177.59; Anal. Calcd for $C_{16}H_{15}BrO_3$: C, 57.33; H, 4.51%. Found: C, 57.21; H, 4.66%.

12. Ethyl acetate (50 mL) was added to the hot reaction mass (~80 °C) and the reaction mixture was stirred for 10 min followed by the addition of water (50 mL).
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