Pd-C/ammonium formate: a selective catalyst for the hydrogenation of chalcones to dihydrochalcones

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Pd-C/ammonium formate is a highly efficient catalyst for the selective hydrogenation of chalcones to dihydrochalcones (DHCs). The reaction proceeds under mild conditions and the Pd-C catalyst is recovered without loss of activity.

Keywords: dihydrochalcones, α,β-unsaturated carbonyl compounds, Pd-C/ammonium formate catalyst, and hydrogen transfer hydrogenation reaction

Dihydrochalcones (DHCs), an important class of flavonoids, exhibit antibacterial, antifungal,[1a] anticancer[1b] and antioxidant[1c] properties, and selected derivatives are used as sweeteners.[1d] They are also key synthetic intermediates towards the preparation of flavenes[1e], anthocyanin-type dyes[1f] and homoisoflavonoids.[1g] DHCs are synthesised through a Claisen–Schmidt condensation[2] followed by reduction of the intermediate chalcone, or through the alkaline reduction of the corresponding flavanone.[3]

Recently reported alternative routes for the synthesis of DHCs include the palladium mediated coupling of iodobenzenes and the enol form of acetophenone,[4] and the Friedel–Craft acylation of phenols and acids.[1g] Although substantially improved, these novel procedures still have some shortcomings such as long reaction times and low yields. For the reduction of chalcones, different catalytic systems including $(Ph_3P)_3RhCl$–EtSiH–Bz,[5a,b] $NaBH_4$–py,[5c] $NaBH_4$–$NiCl_2$–dioxane–MeOH,[5d] $NiCl_2.6H_2O$–$NaBH_4$–MeOH–H_2O,[5e] $SiCl_4$–NaI–MeCN,[5f] $Na_2S_2O_4$–$NaHCO_3$–aq.$C_2H_4Cl_2$,[5g] and Pd–C/H_2[6] have been reported. The latter system is most commonly used; however, the solubility of molecular hydrogen in solvent is a limiting factor resulting in long reaction times and low yields. Such problems can be overcome by increasing the interfacial area among the gas, liquid and solid phases[7] or by using supercritical carbon dioxide ($scCO_2$)[8] as solvent. Although these remedies improve the solubility problem, such systems are not easy to handle. Thus, there remains a need for mild and rapid methods for this selective reduction both in basic laboratory manipulations as well as manufacturing processes.[9] Our interest in flavonoids chemistry[10] prompted us to investigate novel procedures for the synthesis of DHCs.

In a typical procedure, chalcones (1.0 mmol) were dissolved in 2 ml saturated ammonium formate ($HCOONH_4$) in MeOH/THF (1 : 0.1 v/v), followed by addition of Pd–C catalyst (10–15 mg, 10 wt.%) and stirred at room temperature for different times (Scheme 1). Product formation was monitored by TLC and Pd–C catalyst was collected by filtration upon completion of the reaction, and reused several times without loss of activity. The products remained in the filtrate and were isolated in good yield (see Experimental).

These reactions are more efficient (>50% reduction in the reaction time) using saturated $HCOONH_4$ solution as hydrogen source.[11] In this study we explored the use of this catalytic system for the selective reduction of α,β-unsaturated ketones (chalcones). However, chromones, flavones, isoflavones and ynones were not reduced under these conditions. This could be due to the aromatic character of the double and triple bonds combined with steric hindrance. In this system, the Pd–C catalyst is highly active and selective for the hydrogen transfer-hydrogenation reaction from $HCOONH_4$ to the carbon-carbon double and triple bonds. Since it is known the Pd–C catalyses the decomposition of formate, our data suggest that the hydrogen transfer to the reactant is much faster than the hydrogen evolution. Hence, the reaction rate increases with increasing concentration of formate, while the added THF assures the solubility of the substrate. On the other hand, no products were obtained using Pd–C or ammonium formate alone, even after prolonged reaction times of 48 h.

In conclusion, we have developed a selective and highly efficient hydrogenation method for the preparation of dihydrochalcones. The catalyst can easily be recovered and reused many times without loss of activity.

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Experimental

All chalcones were synthesised following reported procedures and characterised by their spectral properties.[2] Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 621 spectrophotometer. ^{1}H NMR in $CDCl_3$ were recorded on a Bruker Avone DPX-300 (300 MHz) using TMS as an internal standard and mass spectra on a JEOL-D-300 spectrometer at 70eV and high resolution mass spectra (HR MS) on a Micromass Model ZAB-1F.

General procedure for the selective hydrogenation of chalcones

Substrate (1.0 mmol) was added to 2 ml of a saturated solution of $HCOONH_4$ (prepared by stirring 40–50 mg of $HCOONH_4$ in MeOH/THF, 2: 1 v/v) followed by the addition of Pd–C (10–15 mg, 10 wt.%) and stirred for the time given in Table 1 under argon.

CAUTION: Pd–C reacts violently with MeOH in the presence of air.

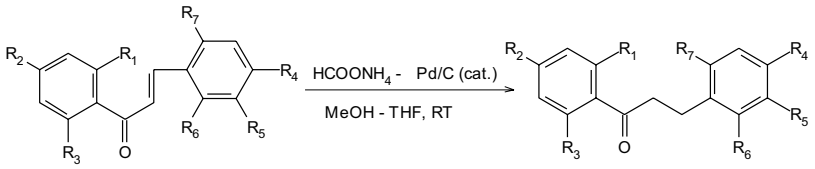
After collecting the Pd–C catalyst on a 0.2 μm nylon filter and washing with THF, drying for 1 h at 120°C (recovery 80–85%), the catalyst can be reused without loss of activity. The products remained in the filtrate and were isolated in good yield by evaporating the solvent *in vacuo*, or by dispersing the residue with water, extracting with ether, drying over anhydrous Na_2SO_4 and purifying by silica gel column chromatography in hexane-ethyl acetate. The products were characterised by comparing their spectral properties with those of authentic samples (wherever applicable).

1-(2-Hydroxyphenyl)-3-phenyl-propan-1-one (**2a**): Oily; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3452(OH), 1631(C=O), 1225, 1160, 984; ^{1}H NMR (δ): 12.3 (s, 1H, *OH*), 7.79 (dd, 1H, *J* = 8.11, 1.3 Hz), 7.37–7.20 (m, 5H), 7.52 (dt, 1H, *J* = 9.2, 1.6 Hz), 6.98 (dd, 1H, *J* = 8.1, 1.3 Hz), 6.69 (dt, 1H, *J* = 9.2, 1.6 Hz), 3.37 (t, 2H, *C–3H*, *J* = 7.6 Hz), 3.11 (t, 2H, *C–2H*, *J* = 7.63 Hz); EIMS (70eV) *m/z*: $M^{+\cdot}$ 226(60), 207(30), 131(15), 121(100), 91(35); HRMS calculated for $C_{15}H_{14}O_2$, 226.0994, found 226.0998.

1-(2-Hydroxyphenyl)-3-(4-N, N-dimethylaminophenyl)-propan-1-one (**2b**): M.p. 68–69°C (Lit. 69–71°C and 62°C).[12e]

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-bromophenyl)-propan-1-one (**2c**): M.p. 106–108°C; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3448(OH), 1624 (C=O), 1215, 1160, 1134, 969; ^{1}H NMR(δ): 12.35 (s, 1H, *OH*), 7.45–7.15 (m, 4H), 6.10 (d, 1H, *J* = 1.2 Hz), 5.92 (d, 1H, *J* = 1.2 Hz), 3.82 and 3.84 (2 x s, 6H, *2xOMe*), 3.34 (t, 2H, *C–3H*, *J* = 7.8 Hz), 3.09 (t, 2H, *C–2H*, *J* = 7.8 Hz); EIMS(70eV) *m/z*: $M^{+\cdot}$ 365(80); HRMS calculated for $C_{17}H_{18}O_4$, 286.1205, found 286.1202.

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-fluorophenyl)-propan-1-one (**2d**): M.p. 90–92°C; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3450 (OH), 1625



1a–l **2a–l**

Entry	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield,% (reaction time, h)	Entry	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield,% (reaction time, h)
a	OH	H	H	H	H	H	H	99(0.55)	f	OH	OMe	OMe	NO_2	H	H	H	97(0.65)[b]
b	OH	H	H	NMe_2	H	H	H	98(0.50)	g	OH	OMe	OMe	OMe	H	H	H	98(0.65)
c	OH	OMe	OMe	Br	H	H	H	98(0.55)[a]	h	OH	OMe	OMe	H	OMe	OMe	H	96(0.50)
d	OH	OMe	OMe	F	H	H	H	99(0.60)	i	H	H	H	H	H	H	H	96(0.70)
e	OH	H	H	OH	H	H	H	86(16)	j	OH	H	H	OMe	H	H	H	96(0.60)
k	OH	OMe	H	OMe	H	H	H	98(0.66)	l	H	H	H	NO_2	H	H	H	96(1.0)[b]

[a]Br debrominated in product **2c**.[11] The F-analog **2d** was stable.
[b]The NO_2 group is converted to NH_2 in the product.

(C=O), 1213,1163, 1144, 979; ^{1}H NMR(δ): 12.35 (s, 1H, *OH*), 7.45–7.15 (m, 4H), 6.10 (d, 1H, *J* = 1.2 Hz), 5.92 (d, 1H, *J* = 1.2 Hz), 3.82 and 3.84 (2xs, 6H, *2xOMe*), 3.34 (t, 2H, *C–3H*, *J* = 7.8 Hz), 3.09 (t, 2H, *C–2H*, *J* = 7.8 Hz); EIMS(70eV) *m/z*: $M^{+\cdot}$ 304(85); HRMS calculated for $C_{15}H_{17}FO_4$, 304.1111, found 304.1111.

1-(2-Hydroxyphenyl)-3-(4-hydroxyphenyl)-propan-1-one (**2e**): M.p. 105–107°C (Lit. 106–107°C).[12c]

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-aminophenyl)-propan-1-one, (**2f**): Oily; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3620 (NH_2), 3443 (OH), 1630 (C=O), 1388, 1245, 1135, 884; ^{1}H NMR(δ): 12.6 (s, 1H, *OH*), 6.98 (dd, 2H, *J* = 8.3, 1.2 Hz), 6.63 (dd, 2H, *J* = 8.3, 1.2 Hz), 6.12 (d, 1H, *J* = 1.4 Hz), 5.96(d, 1H, *J* = 1.4 Hz), 4.42 (brs, 2H, *NH_2*), 3.83 and 3.8 (2xs, 6H, *2xOMe*), 2.83 (t, 2H, *C–3H*, *J* = 7.5 Hz), 2.66 (t, 2H, *C–2H*, *J* = 7.5 Hz); EIMS(70eV) *m/z*: $M^{+\cdot}$ 299(35), 286(25), 178(55), 134(43), 106(100), 84(35); HRMS calculated for $C_{17}H_{19}NO_4$, 301.1314, found 301.1315.

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-propan-1-one, (**2g**): M.p. 110–113°C (Lit. 110–112°C).[12e]

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(2,5-dimethoxyphenyl)-propan-1-one, (**2h**): M.p. 108–110°C; IR ($CHCl_3$, ν_{max}, cm^{-1}): 3442 (OH), 1632 (C=O), 1385, 1244, 1136, 887; ^{1}H NMR(δ): 12.6 (s, 1H, *OH*), 6.78 (m, 2H), 6.71 (d, 1H, *J* = 1.02 Hz), 6.06 (d, 1H, *J* = 1.2 Hz), 5.94 (d, 1H, *J* = 1.2 Hz), 3.78, 3.76, 3.67 and 3.66 (4xs, 12H, *4xOMe*), 3.28 (t, 2H, *C–3H*, *J* = 7.6 Hz), 2.96 (t, 2H, *C–2H*, *J* = 7.6 Hz); EIMS(70eV) *m/z*: $M^{+\cdot}$ 346(55); HRMS calculated for $C_{19}H_{22}O_6$, 346.1416, found 346.1416.

1,3-diphenylpropan-1-one (**2i**): oily (Lit.).[12b]

1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-propan-1-one, (**2j**): M.p. 51–52°C (Lit. 51–54°C).[12f]

1-(2-Hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)-propan-1-one, (**2k**): Oily (Lit. oil).[12d]

1-phenyl-3-(4-aminophenyl)-propan-1-one (**2l**): oily (Lit.).[12b]

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