A Rapid and Efficient Microwave-Assisted Synthesis of Substituted 3-Phenylpropionic Acids from Benzaldehydes in Minutes[1]

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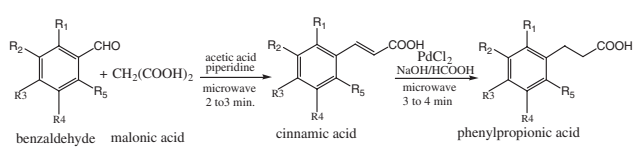
A convenient, inexpensive, and efficient synthesis of 3-phenylpropionic acids (**1a**–**1f**) by reacting benzaldehyde (**2a**–**2f**) and malonic acid in acetic acid and piperidine into cinnamic acid (**3a**–**3f**) in 77 to 89% followed by its reduction with $PdCl_2$ in the biphase of formic acid and aqueous sodium hydroxide is reported under microwave irradiation which utilizes short reaction time ranging 5 to 7 min to provide **1a**–**1f** in moderate to high yield (69–86%) depending upon methoxy, methylenedioxy, and hydroxy groups present at the phenyl ring.

3-phenylpropionic acids are important biologically active compounds and are generally found in nature[2] in traces. Moreover, 3-phenylpropionic acids are useful intermediates in the synthesis of a variety of organic compounds[3] including drugs such as anti-AIDS,[4] nonsteroidal, anti-inflammatory,[5] and antipsychotic[6] drugs. Various protocols are reported for the synthesis of 3-phenylpropionic acids e.g. reaction of cinnamaldehyde with $RuCl_3$/tri-cyclohexylphosphine[4] or trimethylsilylcyanide/Lewis base,[7] reaction of hydrocinnamaldehyde with sodium nitrite,[8] reaction of cinnamic acid with Iridium (I) catalyst[9] or biocatalyst,[10] hydrocarboxylation of styrene,[5,11] etc. However, the most common method to prepare 3-phenylpropionic acid remains two steps synthesis comprising the Knoevenagel–Doebner[12] condensation between aryl aldehyde and malonic acid in the presence of pyridine and piperidine to provide corresponding cinnamic acid in 6–18 h which is further hydrogenated into desired 3-phenylpropionic acid in 4–50 h.[6,13] But all of them are limited by drawbacks such as expensive reagents, longer reaction time, tedious work up involving column purification, low yields and lastly environmental pollution. Hence, there remains a scope for development of an efficient general method for the synthesis of phenylpropionic acids.

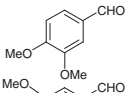
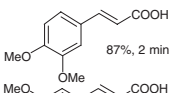
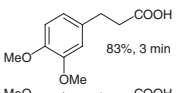
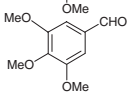
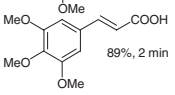
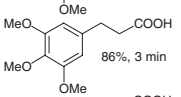
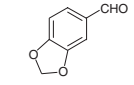
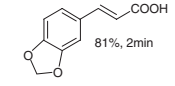
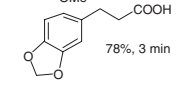
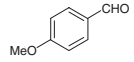
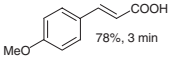
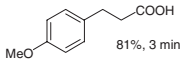
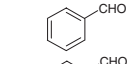
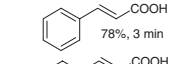
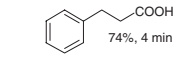
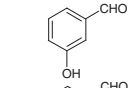
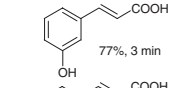
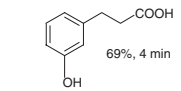
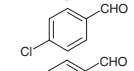
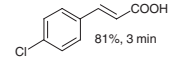
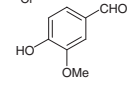
In recent past, microwave-assisted[14] synthesis of organic compounds has attracted a considerable amount of attention owing to several benefits such as shorter reaction time, reduction of the usual thermal degradation, better yield and most importantly, ecofriendly behaviour as compared to conventional heating.[12] As per our ongoing interest in microwave-assisted synthesis of organic molecules,[15] we decided to prepare 3-(3,4-dimethoxyphenyl)propionic acid (**1a**), a versatile antipsychotic drug[6] intermediate, by condensing 3,4-dimethoxybenzaldehyde (**2a**) with malonic acid in the presence of acetic acid and piperidine followed by reduction[16] of double bond of **3a** with formic acid, aqueous sodium hydroxide and $PdCl_2$ into **1a** in one pot, two steps under microwave irradiation intermittent for 5–7 min.[17] In selecting acetic acid and piperidine as a condensing agent under microwave irradiation, we thought that acetic acid would not allow evaporation of piperidine in open atmosphere during microwave irradiation besides inexpensive nature of acetic acid. Unfortunately, results revealed the presence of **3a** without expected hydrogenated product **1a**. The reason for the failure of hydrogenation step in one pot was assumed to be the presence of acetate ions which suppressed the dissociation of formic acid owing to common ion effect to ultimately effect generation of hydrogen gas. We, therefore, decided to replace acetic acid with formic acid in the condensation step which successfully provided **3a** as well as allowed hydrogenation to give **1a** in 37% yield with some unreacted **3a**. No further improvement in the yield of **1a** occurred even with a large excess of formic acid and sodium hydroxide. It is worthwhile to mention that progress of the reaction during hydrogenation was best monitored under UV spectroscopy wherein cinnamic acid **3a** provided four peaks at 217, 234, 294, and 318 nm while dihydrocinnamic acid **1a** provided only three peaks at 205, 228, and 279 nm. Recurrent low yield of **1a** prompted us to seek modifications in the above methodology and it was decided to retain with acetic acid-piperidine combination for condensation under microwave, though, removing them before hydrogenation step.[17] After condensation, mere addition of water to the acidic reaction mixture brought about the precipitation of product **3a** in 87% yield. However, a large excess of mineral acid is required to nullify the basicity of pyridine and piperidine in the Knoevenagel–Doebner reaction to bring about precipitation of cinnamic acid[6] or resin bound substrate are used to obtain cinnamic acid in solid state.[18] The filtered white solid (**3a**) was found pure enough for the next step on the basis of NMR and was charged in the same pot and hydrogenated with formic acid and aqueous sodium hydroxide in catalytic amount of $PdCl_2$ under microwave for 5–6 min to provide the **1a** in 77% yield. In attempts to increase the yield of the reaction further, a little amount of 2-propanol or *n*-butanol was added into reaction mixture which led to a significant increase in rate of reaction and the yield of **1a** upto 83% in 3 min[17] (Scheme 1). The hydrogenated product **1a** thus formed, was filtered hot which got solidified at room temperature. As a control experiment, the same reaction comprising condensation and hydrogenation was performed under conventional heating for 8 h and 14 h respectively which provided **3a** in 79% yield and **1a** in 76% yield. This observation demonstrated the advantage of microwave irradiation over conventional method for **3a** and **1a**. After success of **1a**, the method was successfully extended



(a) R_2= R_3= OMe; R_1= R_2= R_5= H
(b) R_2= R_3= R_4= OMe; R_1= R_5= H
(c) R_2+ R_3= -OCH_2CH_2O-; R_1= R_2= R_5= H
(d) R_4= OMe; R_1= R_2 =R_3= R_5= H
(e) R_1= R_2=R_3=R_4= R_5= H
(f) R_2=OH; R_1=R_3=R_4= R_5= H

Scheme 1.

Table 1. Conversion of benzaldehyde derivatives into phenylpropionic acid via corresponding cinnamic acid

Run	Benzaldehyde (2)	Cinnamic acid (3)	Phenylpropionic acid (1)
a		 87%, 2 min	 83%, 3 min
b		 89%, 2 min	 86%, 3 min
c		 81%, 2min	 78%, 3 min
d		 78%, 3 min	 81%, 3 min
e		 78%, 3 min	 74%, 4 min
f		 77%, 3 min	 69%, 4 min
g		 81%, 3 min	No Reaction
h		No Reaction	—

for a variety of substituted phenylpropionic acids bearing methoxy, dimethoxy, trimethoxy, and hydroxy groups except for 3-chlorobenzaldehyde (**2g**) which did not provide the corresponding 3-(4-chlorophenyl)propionic acid though 3-(4-chlorophenyl)propenoic acid (**3g**) was obtained in good yield (81%). Similarly, 4-hydroxy-3-methoxybenzaldehyde (**2h**) did not provide either 4-hydroxy-3-methoxycinnamic acid or 4-hydroxy-3-methoxyphenylpropionic acid (Table 1). It is worthwhile to mention that precipitation of the solid during condensation as well as hydrogenation is an added advantage in our method, as reported methods for obtaining both cinnamic acid and phenylpropionic acid as solids are through resin bound solid phase synthesis.[18,19]

In conclusion, we have devised an efficient and rapid methodology for the preparation of substituted 3-phenylpropionic acids from benzaldehydes under microwave irradiation within 5–7 min which is a better yielding, economical and an environment friendly process.

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References and Notes

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17 General procedure for the preparation of substituted 3-phenylpropionic acids (**1a**–**1f**) from phenylaldehydes (**2a**–**2f**): A mixture of benzaldehyde (**2a**–**2h**) (0.005 mol), malonic acid (0.01 mol), piperidine (0.012 mol) and acetic acid (15 mL) were taken in a 100-mL Erlenmeyer flask and placed inside a Kenstar microwave oven (2450 MHz, 900 W) and irradiated for 2–3 min in parts. The mixture was poured in ice cold water and precipitated solid was filtered to afford cinnamic acid (**3a**–**3g**) in 77–89% yield which were found pure enough to be used in the next step without additional purification. For the next step, **3a**–**3g** (0.025 mol) was dissolved 2.5 M NaOH (45 mL or more till pH attained around 9–10), $PdCl_2$ (10–15 mg) and a few drops of 2-propanol (1–2 mL) followed by dropwise addition of HCOOH (10–15 mL or more) until the mixture becomes acidic (pH attained around 2–3) and then irradiation under microwave for 2–3 minutes. The reaction mixture was filterd while hot and filtrate upon standing at room temperature provided as a solid which after recrystallisation with mixture of ethyl acetate and hexane gave substituted phenylpropionic acid (**1a**–**1f**) in 69–86% yield whose mp and NMR spectra data was found similar to reported values.[2,6]
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