Microwave- and ultrasound-assisted semisynthesis of natural methoxylated propiophenones from isomeric mixture of phenylpropenes in minutes[1]

Bhupendra P. Joshi, Anuj Sharma, and Arun K. Sinha

Abstract: A rapid and practical semisynthesis of natural methoxylated propiophenones (**3a**–**3f**) is realized by reacting stereo- and regio-isomeric mixture of phenylpropenes (**1a**–**1f**) with a catalytic amount of palladium chloride – sodium formate in formic acid, methanol, and water (2:1:2) into single product phenylpropanes (**2a**–**2f**) followed by its oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in wet dioxane, containing a few drops of formic acid. Conventional, ultrasound, and microwave heating were compared through these studies.

Key words: focused microwave, ultrasound, phenylpropene, propiophenone, DDQ.

Résumé : On a mis au point une semi-synthèse rapide et pratique des propiophénones méthoxylées naturelles (**3a**–**3f**) en faisant réagir des mélanges stéréo- et régio-isomères de phénylpropènes (**1a**–**1f**) avec une quantité catalytique de chlorure de palladium – formiate de sodium dans l'acide formique, le méthanol et l'eau (2 : 1 : 2) qui conduisent à des phénylpropanes isolés sous la forme de produits uniques (**2a**–**2f**) qui ont été isolés par du 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) dans du dioxane humide contenant quelques gouttes d'acide formique. Dans toutes les études mentionnées ci-dessus, on a comparé les méthodes de chauffage traditionnelle, aux ultrasons et aux micro-ondes.

Mots clés : micro-onde focalisée, ultrason, phénylpropène, propiophénone, DDQ.

[Traduit par la Rédaction]

Introduction

Methoxylated propiophenones (1) are isolated from a large number of medicinally important plants and possess a wide range of biological (2–5) activities such as choleretic (2), antiplatelet activating factor (anti-PAF) (3), antifungal (4), and hypolipidemic (5) activities. In addition, methoxylated propiophenones are utilized as intermediates for the production of various bioactive molecules (6) and are also used as modifiers in flavour and perfumery formulations (7).

Various methods are reported for the preparation of propiophenones (C_6–C_3). These methods fundamentally fall under three categories: (*a*) combination of a C_6 unit with a C_3 unit, (*b*) combination of a C_6–C_1 unit with a C_2 unit, and (*c*) semisynthetic route from an already existing C_6–C_3 unit. The methods in category (*a*) include reactions of substituted benzene with phenyllithium – lithium propionate (8) and Zn-Cu–Pd$(PPh_3)_4$–CO (9). Similarly, Friedel–Crafts propionylation (6) of an aromatic ring with a Lewis acid (10) also falls under this category and remains a well-exploited method. Propionylation of a methoxylated aromatic ring, however, suffers from some degree of demethoxylation (11) with Lewis acids such as aluminium chloride (12). The methods in category (*b*) include the reaction of substituted benzaldehydes (13–15), benzonitrile (16), or benzoic acids (17, 18) with cyanohydrin – vinyl ether (13), chlorotrimethylsilane–KCN (14), Grignard (15), isobutylmagnesium bromide (16), thionyl chloride – $Cd(C_2H_5)_2$ (17), or propionic acid – iron(II) salt (18), respectively. Overall, all of the synthetic methods in categories (*a*) and (*b*) are limited by expensive starting material, maintenance of anhydrous conditions, and environmentally hostile reagents (19).

In this regard, the methods in category (*c*) hold a better semisynthetic approach (20, 21) than categories (*a*) and (*b*) because the former utilizes an already existing C_6–C_3 unit in the form of substituted phenylpropenes for the formation of methoxylated propiophenones. Hence, only slight modifications in the structure are desired, which may not require harsh conditions if a suitable choice of substrate and reagent is made.

Received 17 June 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 22 December 2005.

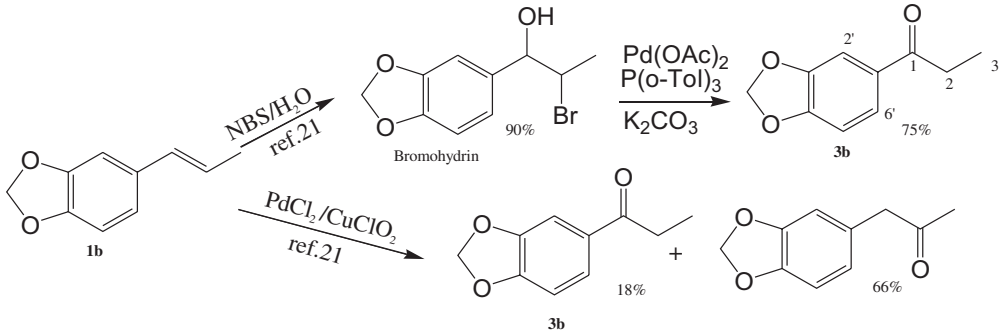
B.P. Joshi, A. Sharma, and A.K. Sinha.[2] Natural Plant Products Division, Institute of Himalayan Bioresource Technology, Palampur, HP 176061, India.

[1]IHBT communication No. 0307.

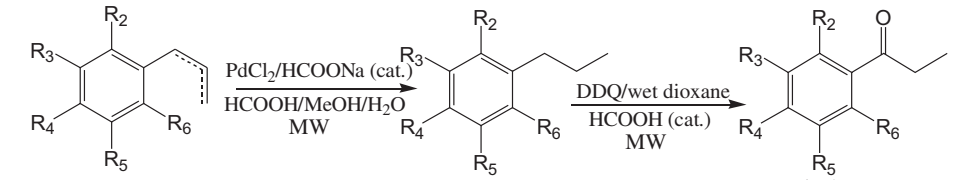
[2]Corresponding author (e-mail: aksinha08@rediffmail.com).

 doi: 10.1139/V05-185

Scheme 1.



Scheme 2.



(a) $R_2=R_4=R_5=OMe$; $R_3=R_6=H$ (b) $R_3=R_4=OCH_2O$; $R_2=R_5=R_6=H$ (c) $R_3=R_4=R_5=OMe$; $R_2=R_6=H$
(d) $R_3=R_4=OMe$; $R_2=R_5=R_6=H$ (e) $R_4=OMe$; $R_2=R_3=R_5=R_6=H$ (f) $R_3=OMe$; $R_4=OH$; $R_2=R_5=R_6=H$

Phenylpropenes are readily available natural phenylpropanoids (22)[3] whose structures and economical prices make them excellent precursors for the semisynthesis of a large number of products (23, 24) including propiophenones. Some methoxylated propiophenones (20, 21) (**3a** and **3b**) have already been synthesized from phenylpropenes utilizing either *N*-bromosuccinimide – H_2O – palladium acetate or $PdCl_2$–$CuCl$–O_2 (Scheme 1). However, the extension of these semisynthetic methods for a large-scale preparation of propiophenones is not viable due to a longer reaction time (20), the maintenance of anhydrous conditions, and the use of expensive reagents (21). In addition, phenylpropenes are usually available from natural sources as an isomeric (22) mixture, and their purification into a pure single isomer is tedious (25). Consequently, chemical modification of any isomer of phenylpropenes results in the formation of side products owing to the presence of its other two isomers (23).[4]

Against this backdrop, we report microwave- (26) and ultrasound-assisted (27) rapid and practical semisynthesis of methoxylated propiophenones (**3a**–**3f**) where toxic (28) *cis*-phenylpropenes with their stereo- and regio-isomeric mixtures (**1a**–**1f**) were first hydrogenated into a single product phenylpropane (**2a**–**2f**). This method thus eliminated the possibility of the formation of side products arising from the isomeric nature of phenylpropenes. These phenylpropanes (**2a**–**2f**) were then oxidized to provide bioactive propiophenones (**3a**–**3f**) (Scheme 2). The above microwave- and ultrasound-assisted reactions were also conducted under conventional conditions to compare all three methods viz. microwave, ultrasound, and conventional methods to establish the superiority of the microwave-assisted reactions.

Experimental

Melting points were determined with a Metler FP80 micromelting point apparatus and are uncorrected. Column chromatography was performed on silica gel (60–120 mesh size). ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-300 spectrometer. A CEM Discover® focused microwave (2450 MHz, 300 W) and a Sonics ultrasonicator (20 kHz, 750 W) were used for all the given reactions. GC and HR-ES-MS were determined using Shimadzu-2010 and Micromass Q-TOF Ultima spectrometers, respectively.

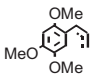
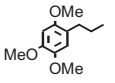
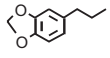
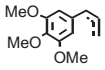
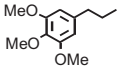
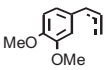
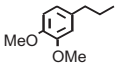
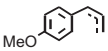
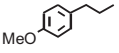
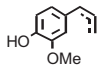
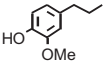
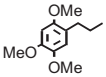
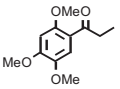
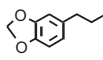
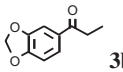
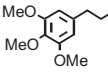
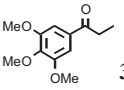
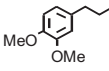
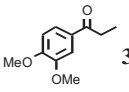
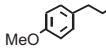
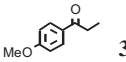
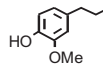
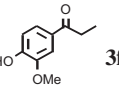
Representative experimental for conversion of stereo- and regio-isomeric mixtures of phenylpropenes (1a–1f) into phenylpropane (2a–2f)

A homogeneous mixture containing $PdCl_2$ (0.01 g) and sodium formate (0.01 g) was prepared by completely mixing both in a mortar. To this powdered mixture, the isomeric

[3] A large number of methoxylated phenylpropenes are found in high concentration (22) up to 90% in many essential oil-bearing plants, but generally exist as an isomeric mixture of three isomers namely trans (α), cis (β), and γ-isomers whose purification into a pure single isomer is tedious by column chromatography (25). On the other side, *cis*-phenylpropenes (e.g., *cis*-2,4,5-trimethoxyphenylpropene) are proven carcinogenic and toxic (26), which overall restrict the market potential of an essential oil rich in cis isomer, therefore, utilization of a stereo- and regio-isomeric mixture of phenylpropene (**1a**–**1f**) is an added benefit for phenylpropenes towards the formation of useful products including propiophenones (**3a**–**3f**).

[4] For example, the oxidation of *cis*- and (or) *trans*-phenylpropenes provides phenylaldehyde; however, contamination of γ-phenylpropene will lead to phenylacetaldehyde (23).

Table 1. Comparative analysis among microwave, ultrasound, and conventional reactions for the formation of phenylpropanes (**2a–2f**) and propiophenones (**3a–3f**) from phenylpropenes (**1a–1f**).

			Microwave[a]		Ultrasonic[b]		Conventional[c]	
S. No.	Substrate[d]	Product	Time (min)	Yield (%)	Time (min)	Yield (%)	Time[e] (min)	Yield (%)
1	 **1a**	 **2a**	10	94	60	84	300	79
2	 **1b**	 **2a**	10	89	60	81	300	76
3	 **1c**	 **2c**	10	93	60	84	300	78
4	 **1d**	 **2d**	10	94	60	86	300	77
5	 **1e**	 **2e**	10	92	60	82	300	79
6	 **1f**	 **2f**	10	96	60	89	300	84
7	 **2a**	 **3a**	16	69	20	64	480	59
8	 **2b**	 **3b**	16	73	20	70	480	64
9	 **2c**	 **3c**	16	71	20	65	480	58
10	 **2d**	 **3d**	16	81	20	78	480	70
11	 **2e**	 **3e**	16	66	20	61	480	58
12	 **2f**	 **3f**	16	56	20	53	480	47

[a]CEM monomode synthesizer at temp. 110–120 °C, power 150–250 W.
[b]Sonics with pulse length 9 s, 75% duty, pause after every 10 min.
[c]At reflux temp.
[d]Dotted lines over the phenylpropenes represent an isomeric mixture of cis, trans, and allyl isomers.
[e]The mentioned reaction period required for maximum yield.

mixture of substituted phenylpropene **1a–1f** (2.9 mmol) and an 8–10 mL reagent mixture of HCOOH–MeOH–H_2O (2:1:2) was added. The mixture was then either irradiated using a focused monomode microwave system (in a round bottom flask fitted with a reflux condenser at 110–120 °C, power 150–250 W) for 10 min, or ultrasonicated (power 560 W) for 60 min, or refluxed for 300 min using the conventional method. After completion of the reaction, the catalyst[5] was removed by filtration and the filtrate was evaporated. The residue was partitioned between ethyl acetate (70 mL) and water (15 mL), and the ethyl acetate layer was washed with water (2 × 10 mL), $NaHCO_3$ (10%), brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated, and the obtained residue was purified by column chromatography (hexane – ethyl acetate, 9:1) to afford phenylpropane **2a–2f** in 89%–96% yield (Table 1).

1-(2′,4′,5′-Trimethoxyphenyl)propane (2a) (23)

Liquid. ^{1}H NMR ($CDCl_3$) δ: 6.81 (1H, s, H-6′), 6.32 (1H, s, H-3′), 3.84, 3.82, 3.78 (each 3H, s, three -OCH_3),

[5]After reaction, palladium chloride was filtered and was reused for the hydrogenation reaction, and was found to be active even after three cycles of reuse with a mere 5% loss in the activity.

2.42 (2H, t, J = 7.7 Hz, H-1), 1.64 (2H, m, H-2), 0.93 (3H, t, J= 7.2 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 151.4 (C-2′), 147.4 (C-4′), 142.7 (C-5′), 122.7 (C-1′), 114.3 (C-6′), 98.0 (C-3′), 56.5, 56.2, 55.0 (2′-OCH_3, 4′-OCH_3, 5′-OCH_3), 31.6 (C-1), 23.3 (C-2), 13.7 (C-3).

1-(3′,4′-Dioxymethylenephenyl)propane (2b) (29a)

Liquid. ^{1}H NMR ($CDCl_3$) δ: 6.79 (3H, m, H-2′, H-5′, H-6′), 5.94 (2H, s, -OCH_2O-), 2.56 (2H, t, J = 7.8 Hz, H-1), 1.66 (2H, m, H-2), 0.99 (3H, t, J = 7.3 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 147.5 (C-3′), 145.4 (C-4′), 136.5 (C-1′), 121.4 (C-6′), 108.9 (C-5′), 107.9 (C-2′), 100.6 (-OCH_2O-), 37.5 (C-1), 24.8 (C-2), 13.6 (C-3).

1-(3′,4′,5′-Trimethoxyphenyl)propane (2c)

Liquid. ^{1}H NMR ($CDCl_3$) δ: 6.46 (2H, s, H-2′, H-6′), 3.89 (9H, s, three -OCH_3), 2.55 (2H, t, J = 7.8 Hz, H-1), 1.66 (2H, m, H-2), 0.96 (3H, t, J = 7.2 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 151.2 (C-3′, C-5′), 140.5 (C-1′), 136.8 (C-4′), 107.2 (C-2′, C-6′), 60.9 (4′-OCH_3), 56.7 (3′-OCH_3, 5′-OCH_3), 31.3 (C-1), 23.9 (C-2), 13.4 (C-3). HR-EI-MS (positive) m/z: 211.2826. Anal. calcd. for $C_{12}H_{19}O_3$: 211.2821.

1-(3′,4′-Dimethoxyphenyl)propane (2d) (29b)

Liquid. ^{1}H NMR ($CDCl_3$) δ: 6.76 (3H, m, H-2′, H-5′, H-6′), 3.82, 3.79 (each 3H, s, two OCH_3), 2.50 (2H, t, J = 7.7 Hz, H-1), 1.61 (2H, m, H-2), 0.92 (3H, t, J = 7.2 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 148.8 (C-3′), 147.1 (C-4′), 135.3 (C-1′), 120.2 (C-6′), 112.7 (C-5′), 111.6 (C-2′), 55.7 (3′-OCH_3), 55.6 (4′-OCH_3), 37.6 (C-1), 24.6 (C-2), 13.7 (C-3).

1-(4′-Methoxyphenyl)propane (2e)

Liquid. ^{1}H NMR ($CDCl_3$) δ: 7.29 (2H, d, J = 8.07 Hz, H-2′, H-6′), 7.03 (2H, d, J = 8.07 Hz, H-3′, H-5′), 3.98 (3H, OCH_3), 2.71 (2H, t, J = 7.6 Hz, H-1), 1.77 (2H, m, H-2), 1.06 (3H, t, J = 7.1 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 157.9 (C-4′), 134.7 (C-1′), 129.7 (C-2′, C-6′), 114.1 (C-3′, C-5′), 55.1 (4′-OCH_3), 37.2 (C-1), 24.7 (C-2), 13.8 (C-3). HR-EI-MS (positive) m/z: 151.2298. Anal. calcd. for $C_{10}H_{16}O$: 151.2294.

1-(4′-Hydroxy-3′-methoxyphenyl)propane (2f) (29c)

Liquid. ^{1}H NMR ($CDCl_3$) δ: 6.80 (2H, m, H-2′, H-6′), 6.62 (1H, d, J = 8.3 Hz, H-5′), 6.01 (1H, s, -OH), 3.91 (3H, s, -OCH_3), 2.48 (2H, t, J = 7.9 Hz, H-1), 1.58 (2H, m, H-2), 0.96 (3H, t, J = 7.3 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 146.5 (C-3′), 143.7 (C-4′), 134.6 (C-1′), 121.4 (C-6′), 114.4 (C-5′), 111.4 (C-2′), 55.8 (-OCH_3), 37.7 (C-1), 24.9 (C-2), 13.8 (C-3).

General procedure for the preparation of methoxylated propiophenones 3a–3f from the oxidation of phenylpropanes 2a–2f with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)

A mixture of substituted phenylpropane **2a–2f** (2.4 mmol), DDQ (4.8–5.24 mmol), and HCOOH (1 to 2 drops) in wet dioxane (30 mL, water–dioxane 1:9) was irradiated using focused microwave irradiation (in a round bottom flask fitted with a reflux condenser at 110–120 °C, power 150–250 W) for 25 min, or ultrasonicated (power 560 W) for 20 min, or refluxed for 240 min under conventional method. The precipitated hydroquinone ($DDQH_2$) was filtered, and the red-coloured filtrate was evaporated and subsequently chromatographed on silica gel (hexane – ethyl acetate, 7:3) to provide methoxylated propiophenone **3a–3f** in 56%–81% yield (Table 1).

1-(2′,4′,5′-Trimethoxyphenyl)propan-1-one (3a)

White solid; mp 108 to 109 °C (lit. value (6*b*) mp 108–110 °C). ^{1}H NMR ($CDCl_3$) δ: 7.45 (1H, s, H-6′), 6.77 (1H, s, H-3′), 3.96, 3.93–3.89 (each 3H, s, three OCH_3), 2.99 (2H, q, J = 6.9 Hz, H-2), 1.18 (3H, t, J = 6.9 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 201.1 (C-1), 155.5 (C-2′), 153.9 (C-4′), 143.3 (C-5′), 118.9 (C-1′), 112.6 (C-6′), 96.7 (C-3′), 56.1 (4′-OCH_3, 5′-OCH_3), 55.9 (2′-OCH_3), 36.9 (C-2), 8.4 (C-3).

1-(3′,4′-Dioxymethylenephenyl)propan-1-one (3b)

White solid; mp 35 to 36 °C (lit. value (30*a*) mp 38 to 39 °C). ^{1}H NMR ($CDCl_3$) δ: 7.60 (1H, d, J = 8.1 Hz, H-6′), 7.50 (1H, s, H-2′), 6.86 (1H, d, J = 8.1 Hz, H-5′), 6.34 (2H, s, -OCH_2O-), 2.91 (2H, q, J = 6.9 Hz, H-2), 1.25 (3H, t, J = 6.9 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 199.1 (C-1), 151.8 (C-4′), 148.2 (C-3′), 132.1 (C-1′), 122.4 (C-6′), 110.1 (C-2′), 109.7 (C-5′), 100.5 (-OCH_2O-), 31.4 (C-2), 8.6 (C-3).

1-(3′,4′,5′-Trimethoxyphenyl)propan-1-one (3c)

White solid; mp 52 to 53 °C (lit. value (17) mp 51.5–52.5 °C). ^{1}H NMR ($CDCl_3$) δ: 7.23 (2H, s, H-2′, H-6′), 3.90 (9H, s, three OCH_3), 2.95 (2H, q, J = 7.2 Hz, H-2), 1.22 (3H, t, J = 7.2 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 199.5 (C-1), 153.1 (C-3′, C-5′), 141.4 (C-4′), 137.6 (C-1′), 105.4 (C-2′, C-6′), 60.8 (4′-OCH_3), 56.3 (3′-OCH_3, 5′-OCH_3), 31.8 (C-2), 8.4 (C-3).

1-(3′,4′-Dimethoxyphenyl)propan-1-one (3d)

White solid; mp 59 to 60 °C (lit. value (30*b*) mp 59 to 60 °C). ^{1}H NMR ($CDCl_3$) δ: 7.62 (1H, d, J = 8.0 Hz, H-6′), 7.56 (1H, s, H-2′), 6.88 (1H, d, J = 8.0 Hz, H-5′), 3.96 (6H, s, two OCH_3), 2.97 (2H, q, J = 7.2 Hz, H-2), 1.23 (3H, t, J = 7.2 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 200.0 (C-1), 153.4 (C-4′), 149.3 (C-3′), 130.5 (C-1′), 122.9 (C-6′), 110.4 (C-2′), 110.3 (C-5′), 56.5 (3′-OCH_3, 4′-OCH_3), 31.7 (C-2), 9.0 (C-3).

1-(4′-Methoxyphenyl)propan-1-one (3e) (30c)

Liquid. ^{1}H NMR ($CDCl_3$) δ: 7.58 (2H, d, J = 8.05 Hz, H-2′, H-6′), 6.85 (2H, d, J = 8.05 Hz, H-3′, H-5′), 3.90 (3H, s, OCH_3), 2.93 (2H, q, J = 7.2 Hz, H-2), 1.18 (3H, t, J = 7.2 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 199.2 (C-1), 163.2 (C-4′), 130.4 (C-1′), 129.9 (C-2′, C-6′), 113.5 (C-3′, C-5′), 55.3 (4′-OCH_3), 31.2 (C-2), 8.2 (C-3).

1-(4′-Hydroxy-3′-methoxyphenyl)propan-1-one (3f)

White solid; mp 61 to 62 °C (lit. value (2) mp 63 °C). ^{1}H NMR ($CDCl_3$) δ: 7.58 (2H, m, H-2′, H-6′), 6.95 (1H, d, J = 8.4 Hz, H-5′), 6.08 (1H, s, Ar-OH), 3.92 (3H, s, three OCH_3), 2.96 (2H, q, J = 6.9 Hz, H-2), 1.23 (3H, t, J = 6.9 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ: 199.7 (C-1), 151.3 (C-3′), 147.8 (C-4′), 130.9 (C-1′), 123.7 (C-6′), 112.1 (C-5′), 111.9 (C-2′), 55.2 (OCH_3), 31.7 (C-2), 8.4 (C-3).

Table 2. Catalytic transfer hydrogenation of 2,4,5-trimethoxyphenylpropene (**1a**) into 2,4,5-trimethoxyphenylpropane (**2a**) using $PdCl_2$ as catalyst.

	Catalytic transfer hydrogenating agents			
Entry	Reagents and solvents	Catalyst	CEM Discover microwave irradiation[a] time (min)	Yield[b] (%)
1	HCOOH (excess)	$PdCl_2$	80	20
2	HCOOH (excess) – NaOH (10%)	$PdCl_2$	65	15
3	HCOOH (excess) – isopropanol	$PdCl_2$	50	35
4	HCOOH (excess) – ethylene glycol	$PdCl_2$	50	38
5	HCOOH (excess) – methanol	$PdCl_2$	50	54
6	HCOOH (excess) – MeOH – water (2:1:2)	$PdCl_2$	40	82
7	HCOOH (excess) – MeOH – water (2:1:2) (HCOONa, cat.)	$PdCl_2$	9	94
8	HCOOH (excess) – MeOH – water (2:1:2) (HCOOK, cat.)	$PdCl_2$	9	94
9	HCOOH (excess) – MeOH – water (2:1:2) ($HCOONH_4$, cat.)	$PdCl_2$	9	93
10	HCOOH (excess) – MeOH – water (2:1:2) (HCOONa, cat.)	Pd/C	30	25
11	HCOOH (excess) – MeOH – water (2:1:2) (HCOONa, cat.)	$PdCl_2$	15[c]	67
12	HCOOH (excess) – MeOH – water (2:1:2) (HCOONa, cat.)	$PdCl_2$	6[c]	79

[a]CEM monomode Discover synthesizer at temp. 110–120 °C, power 150–250 W.
[b]Yields based on GC (Shimadzu).
[c]The reaction was performed using a domestic microwave oven at power 300 and 900 W (entries 11 and 12, respectively) resulting in either unreacted starting material (entry 11) or evaporation of the product (entry 12).

Results and discussion

In recent years, there has been a tremendous shift in the use of microwave (26) and ultrasound (27) irradiation in organic reactions owing to the shorter reaction time, higher yields, operational simplicity, and most importantly, the fact that it is a more eco-friendly process compared with conventional heating. As per our ongoing interest in semisynthesis of phenylpropanoids, we decided to prepare 2,4,5-trimethoxypropiophenone (**3a**), a hypolipidemic (5) active compound, from abundantly available toxic (28) 2,4,5-trimethoxyphenylpropene (**1a**) through catalytic transfer hydrogenation (31) (CTH) of **1a** in the first step to form 2,4,5-trimethoxyphenylpropane (**2a**), which would then be oxidized by addition of the suitable oxidant in the next step to form **3a**. For catalytic transfer hydrogenation, a stereo- and regioisomeric mixture of phenylpropene **1a** was treated with $PdCl_2$ in formic acid (98%) as a hydrogen transferring agent for 80 min under focused monomode (32) microwave (CEM Discover® synthesizer); but only 20% of product **2a** formed (Table 2, entry 1), the rest being a number of side products. Similarly, a combination of HCOOH and NaOH (33) did not improve the yield of the product (Table 2, entry 2). The addition of isopropanol (34) or high boiling ethylene glycol (31*a*, 35) to formic acid also did not improve the yield of product **2a** (Table 2, entries 3 and 4). Later on, hydrogenating a mixture comprising $PdCl_2$–HCOOH in methanol was found suitable, and **2a** was obtained up to 54% yield (Table 2, entry 5). Prompted by reports on water–methanol assisted yield enhancement of products (36), we decided to utilize a combination of methanol and water as solvents in this reaction. After a lot of experimentation, a 2:1:2 mixture of HCOOH–MeOH–H_2O in catalytic amounts of $PdCl_2$ for 40 min under microwave proved to give the optimum results, and provided an 82% yield of **2a** (Table 2, entry 6). Later on, we realized that the addition of a catalytic amount of either sodium formate, potassium formate, or ammonium formate,[6] along with this hydrogenating system, was important in increasing the yield of the product (**2a**) up to 94% with a drastic reduction in reaction time up to 9 min under focused monomode (32) microwave (Table 2, entries 7–9). For comparison, the same reaction performed in a domestic microwave oven provided the product (**2a**) in 79% yield and the loss in yield may be due to the easy evaporation of the product in the domestic microwave oven (Table 2, entries 11 and 12).

In the next step, comprising oxidation of phenylpropane **2a** into **3a**, several common oxidizing reagents (37) such as pyridinium chlorochromate and potassium permanganate were tried, but none of the oxidants was found to be effective and a number of side products were obtained with little or no product **3a**. Use of excess potassium permanganate – copper sulphate (10 mol equiv. of reactant **2a**) under ultrasound and microwave irradiation (38) was also unfruitful. Similarly, under various conditions, chromium(IV) oxide (37*b*, 39) also failed to convert **2a** into **3a**, although a yellow-colored solid was obtained; NMR studies revealed it to be 2-propyl-5-methoxy-1,4-benzoquinone (40). The reason for the failure of all the above general oxidants (37–39) was believed to be due to the substituent effect of methoxy groups present at the 2, 4, and 5 positions of phenylpropane, while oxidation of unsubstituted phenylpropane into propiophenones is well-reported with potassium permanganate (38*c*).

Later on, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (41) was found to be an appropriate oxidant for successfully converting **2a** into **3a**. Initially, **2a** was reacted with 1.25–

[6]Ammonium formate itself is a well-known hydrogen-transferring agent for reduction of various functional groups (31, 32) including carbon–carbon double bonds; however, a large excess of ammonium formate (10 equiv.) and its sublimation on the walls of the vessels somewhat limit its use.

1.5 equiv. of DDQ in the presence of various organic solvents such as methanol, ethanol, THF, and dioxane. Dioxane along with 3 to 4 mL of water (42), considered most suitable, provided **3a** only up to 47% along with 11% of α-asarone (23).[7] An increased amount of DDQ, varying from 2 to 2.2 equiv., provided a little more improvement in the yield (58%) of **3a**, but no more improvement in the yield resulted from a further addition of DDQ. Interestingly, the addition of a few drops of HCOOH (98%) in this reaction mixture increased the yield of propiophenone **3a** up to 69% (Scheme 2) within 16 min under focused microwave irradiation.

After choosing DDQ as the reagent, we decided to carry out both hydrogenation of **1a** into **2a** and oxidation of **2a** into **3a** in one pot. One-pot synthesis has recently attracted interest, providing a simple and efficient entry to compounds by amalgamating two or more operations into a single step. Hence, after performing hydrogenation of **1a** into **2a** for 10 min, DDQ was added in the same reaction pot and irradiated under microwave irradiation intermittently for 20 min. We had thought that HCOOH, besides acting as hydrogen source, would not interfere in the DDQ-assisted oxidation of phenylpropane **2a** into propiophenone **3a** in the same pot, as the importance of an acidic (42) medium in DDQ-assisted oxidation is well-understood. Unfortunately, the conversion of **2a** into **3a** resulted in a poor yield (up to 22%). This implied that oxidation could not occur completely in one pot probably owing to the presence of $PdCl_2$, which would keep on reacting with formic acid to release hydrogen, thus hampering the abstraction of the benzylic proton of **2a** with DDQ for the formation of **3a**. Hence, we decided to remove $PdCl_2$ by mere filtration in the first step before the addition of the oxidant (DDQ) in the same pot. Although product **3a** was formed in this case, the yield was still no higher than 34% and there was no further increase in the yield by either lengthening the reaction period or changing the amount of DDQ. This implied that the hydrogenating solvent mixture must have interfered in the oxidation of **2a** into **3a**, which is otherwise performed effectively in dioxane in the two-step methodology. Finally, all this prompted us to change the one-pot two-step methodology, and retain the two-step methodology by performing the hydrogenation in methanol and oxidation in a dioxane medium.

After the success of these reactions for the conversion of **1a** into **2a** followed by the oxidation of **2a** into **3a**, the same methodology was employed for the oxidation of other natural methoxylated phenylpropenes **1b**–**1f**, which successfully provided the corresponding propiophenones **3b**–**3f** in moderate yields (56%–81%). To make a comparative analysis, these reactions (hydrogenation and oxidation) were performed under ultrasonication as well as refluxed under conventional heating and the results are shown in Table 1. The results clearly show that microwave activation afforded better yields of **3a**–**3f** with shorter reaction time than those obtained under other classical or sonication methods. Moreover, the reactions using microwave are more environment friendly than conventional heating in terms of a reduced reaction time and the use of less solvent for the reaction.

Conclusion

In conclusion, we have realized a microwave and ultrasound-assisted rapid and mild semi-synthetic approach towards preparation of a number of natural bioactive methoxylated propiophenones (**3a**–**3f**) from abundantly available stereo- and regio-isomeric mixtures of phenylpropenes (**1a**–**1f**) via phenylpropanes (**2a**–**2f**). Moreover, such a comparative analysis among microwave, ultrasound, and conventional methodologies, to the best of our belief, is disclosed for the first time. Overall, this is an environment friendly process with none of the steps requiring maintenance of anhydrous conditions or hazardous chemicals. The intermediates (**2a**–**2f**) may have general utilities in the convenient synthesis of many other phenylpropanoids (26*d*, 27*c*).

Acknowledgments

AS and BP are indebted to the Council for Scientific and Industrial Research (CSIR), Delhi for the award of a Senior Research Fellowship (SRF). The authors gratefully acknowledge the Director of the Institute of Himalayan Bioresource Technology, Palampur, for his kind cooperation and encouragement.

References

1. (*a*) J. Mėndez. Phytochemistry, **19**, 1557 (1980); (*b*) M.G.A. Hassan. Phytochemistry, **25**, 2417 (1986); (*c*) J.B. Harborne and H. Baxter. *In* Phytochemical dictionary: A handbook of bioactive compounds from plants. Taylor & Francis Ltd., Washington, D.C. 1993; (*d*) B.V. de O. Santos and M.C. de O. Chaves. Biochem. Syst. Ecol. **25**, 539 (1999); (*e*) J. Hu and X. Feng. Planta Med. **66**, 662 (2000); (*f*) V.A. Facundo and S.M. Morais. Biochem. Syst. Ecol. **31**, 111 (2003).
2. O.P. Suri, R.S. Bindra, N.K. Satti, and R.K. Khajuria. Indian J. Chem. Sect. B, **26B**, 587 (1987).
3. C. Lariucci, L.I.B. Homar, P.H. Ferri, and L.S. Santos. Anais Assoc. Bras. Quim. **44**, 22 (1995).
4. A.Z. Susana, N.L. Silvia, D.P. Germán, L.F. Ricardo, B.S. Carina, M.F. Lorena, A.G. Fernando, M.R. Ana, and D.E. Ricardo. J. Nat. Prod. **62**, 1353 (1999).
5. (*a*) A. Cruz, L. Gardu, M. Salazar, E. Martínez, H.A. Jiménez-Vázquez, F. Diaz, G. Chamorro, and J. Tamariz. Arzneim. Forsch. Drug Res. **51**, 535 (2001); (*b*) Z. Chilmonczyk, D. Siluk, R. Kaliszan, B. Łozowicka, J. Popławski, and S. Filipek. Pure Appl. Chem. **73**, 1445 (2001).
6. (*a*) C.W. Perry. US Patent 3 769 350, 30 October 1973; (*b*) T. Högberg, S. Bengtsson, T. de Paulis, L. Johansson, P. Ström, H. Hall, and S.O. Ögren. J. Med. Chem. **33**, 1155 (1990); (*c*) D. Francisco, C. Leticia, F. Rosa, T. Joaquin, L. Fernando, C. German, and M. Heber. Org. Prep. Proced. Int. **23**, 133 (1991); (*d*) A. Cruz, L. Garduño, M. Salazar, E. Martínez, F. Díaz, G. Chamorro, and J. Tamariz. Med. Chem. Res. **10**, 587 (2001).
7. A. Steffen. *In* Perfume and flavor chemicals: Aroma chemicals. Vols. I and II. Allured Publishing Corporation, Carol Stream, Ill. 1994.

[7] DDQ is a well-known dehydrogenating agent used to provide carbon–carbon double bonds in anhydrous (41) conditions and also used as an oxidizing agent to provide benzylic ketones in aqueous (45) conditions. However, formation of dehydrogenated product, α-asarone (11%), during oxidation of **2a** with DDQ and dioxane in wet conditions is a surprise finding.

8. R. Levine, M.J. Karten, and W.M. Kadunce. J. Org. Chem. **40**, 1770 (1975).
9. Y. Tamaru, H. Ochiai, Y. Yamada, and Z. Yoshida. Tetrahedron Lett. **24**, 3869 (1983).
10. (*a*) S.R. Stauffer, C.J. Coletta, R. Tedesco, G. Nishiguchi, K. Carlson, J. Sun, B.S. Katzenellenbogen, and J.A. Katzenellenbogen. J. Med. Chem. **43**, 4934 (2000); (*b*) P. Salehi, M.K. Mohammad, A.Z. Mohammad, and S. Sara. Bull. Chem. Soc. Jpn. **76**, 1863 (2003).
11. (*a*) R.H. Prager and Y.T. Tan. Tetrahedron Lett. **8**, 3661 (1967); (*b*) T. Horie, H. Tominaga, Y. Kawamura, T. Hada, N. Ueda, Y. Amano, and S. Yamamoto. J. Med. Chem. **34**, 2169 (1991).
12. B.H. Lipshutz, P. Mollard, S.S. Pfeiffer, and W. Chrisman. J. Am. Chem. Soc. **124**, 14282 (2002).
13. M. Makosza and T. Goetzen. Org. Prep. Proced. Int. **5**, 203 (1973).
14. M.L. Edwards, D.M. Stemerick, and P.S. Sunkara. J. Med. Chem. **33**, 1948 (1990).
15. J.S. Henk, J.M.V. Frank, A.F. Jim, and B.P.A.W. Joannes. J. Nat. Prod. **61**, 1110 (1998).
16. H.L. Haller and P.S. Schaffer. J. Am. Chem. Soc. **61**, 2175 (1939).
17. C.D. Gutsche and F.A. Hoyer. J. Am. Chem. Soc. **72**, 4285 (1950).
18. C. Granito and H.P. Schultz. J. Org. Chem. **28**, 879 (1963).
19. (*a*) H. Nakamura, Y. Kashiwara, and K. Arata. Bull. Chem. Soc. Jpn. **76**, 1071 (2003); (*b*) R. Sigrid, L.R. Christophe, R. Nicolas, and J. Dubac. Tetrahedron Lett. **44**, 2037 (2003).
20. V. Lander and P. Schreier. Flavour Fragrance, J. **6**, 21 (1991).
21. J. Tsuji, H. Nagashima, and K. Sato. Tetrahedron Lett. **23**, 3085 (1982).
22. K. Bauer, D. Garbe, and H. Surburg. *In* Common fragrance and flavor materials: Preparation, properties and uses. 4th ed. Wiley-VCH Verlag GmbH, Weinheim, Germany. 2001.
23. A. Patra and A.K. Mitra. J. Nat. Prod. **44**, 668 (1981).
24. P.Z. Bezoukian. *In* Perfumery and flavoring synthetics. Allured Publishing Corp. Wheaton, Ill. 1986.
25. B.D. Gates and J.S. Swenton. Tetrahedron Lett. **33**, 2127 (1992).
26. (*a*) M. Larhed and A. Hallberg. Drug Discovery Today, **6**, 406 (2001); (*b*) N.E. Leadbeater and H.M. Torenius. J. Org. Chem. **67**, 3145 (2002); (*c*) A.K. Sinha, B.P. Joshi, and R. Acharya. Chem. Lett. **32**, 780 (2003); (*d*) A.K. Sinha, B.P. Joshi, and R. Dogra. US Patent 6 544 390, 8 April 2003; (*e*) A. Sharma, B.P. Joshi, and A.K. Sinha. Bull. Chem. Soc. Jpn. **77**, 2231 (2004); (*f*) N. Kaval, W. Dehaen, P. Mátyus, and E. Van der Eycken. Green Chem. **6**, 125 (2004); (*g*) V. Pathania, A. Sharma, and A.K. Sinha. Helv. Chim. Acta, **88**, 811 (2005).
27. (*a*) S.R. Soudagar and S.D. Samant. Ultrason. Sonochem. **2**, S15 (1995); (*b*) L.H. Thompson and L.K. Doraiswamy. Ind. Eng. Chem. Res. **38**, 1215 (1999); (*c*) B.P. Joshi, A. Sharma, and A.K. Sinha. Tetrahedron, **61**, 3075 (2005).
28. S.C. Kim, A. Liem, B.C. Stewart, and J.A. Miller. Carcinogensis, **20**, 1303 (1999).
29. (*a*) M.T. Bogert and G. Powell. J. Am. Chem. Soc. **53**, 2747 (1931); (*b*) W.J. Horton and E.G. Paul. J. Am. Chem. Soc. **79**, 2264 (1957); (*c*) M. Ogata, M. Hoshi, S. Urano, and T. Endo. Chem. Pharm. Bull. **48**, 1467 (2000).
30. (*a*) I. Hirao. J. Pharm. Soc. Jpn. **73**, 1224 (1954); (*b*) C.W. Perry, M.V. Kalnins, and K.H. Deitcher. J. Org. Chem. **37**, 4371 (1972); (*c*) C.R. Noller and R. Adams. J. Am. Chem. Soc. **46**, 1889 (1924).
31. (*a*) K.J. Barakat, B.K. Banik, D.R. Wagle, M.S. Manhas, and A.K. Bose. J. Org. Chem. **64**, 5746 (1999); (*b*) Z. Paryzek, H. Koenig, and B. Tabaczka. Synthesis, **13**, 2023 (2003).
32. B.L. Hayes. *In* Microwaves: Chemistry at the speed of light. CEM Publishing, Matthews, N.C. 2002.
33. A. Sharma, B.P. Joshi, and A.K. Sinha. Chem. Lett. **32**, 1186 (2003).
34. S.U. Sonavane and R.V. Jayaram. Synlett, **1**, 146 (2004).
35. H.S.P. Rao and S. Jothilingam. J. Org. Chem. **68**, 5392 (2003).
36. (*a*) J.M. Khurana and P. Sharma. Bull. Chem. Soc. Jpn. **77**, 549 (2004); (*b*) S. Bhar and S. Guha. Tetrahedron Lett. **45**, 3775 (2004).
37. (*a*) R. Rathore, N. Saxena, and S. Chandrasekaran. Synth. Commun. **16**, 1493 (1986); (*b*) J. Muzart. Tetrahedron Lett. **27**, 3139 (1986).
38. (*a*) M. Mačiarova, Š. Toma, and A. Heribanová. Tetrahedron, **56**, 8561 (2000); (*b*) A. Shaabani, and D.G. Lee. Tetrahedron Lett. **42**, 5833 (2001); (*c*) A. Shaabani, A. Bazgir, F. Teimouri, and D.G. Lee. Tetrahedron Lett. **43**, 5165 (2002).
39. R. Rangarajan and E.J. Eisenbraun. J. Org. Chem. **50**, 2435 (1985).
40. A.A.L. Gunatilaka, J.M. Berger, R. Evans, J.S. Miller, J.H. Wisse, K.M. Neddermann, I. Bursuker, and D.G.I. Kingston. J. Nat. Prod. **64**, 2 (2001).
41. (*a*) P.P. Fu and R.G. Harvey. Chem. Rev. **78**, 317 (1978); (*b*) D. Walker and J.D. Hiebert. Chem. Rev. **67**, 153 (1967); (*c*) A.G. Gonzalez, Z.E. Aguiar, J.G. Luis, and A.G. Ravelo. J. Nat. Prod. **52**, 1231 (1989); (*d*) F.D. Ramdayal, D.J. Kiemle, and R.T. Lalonde. J. Org. Chem. **64**, 4607 (1999).
42. A.G. Gonzalez, Z.E. Aguiar, J.G. Luis, and A.G. Ravelo. J. Nat. Prod. **52**, 1231 (1989).

This article has been cited by:

1. V. Ragaini, C. Pirola, S. Borrelli, C. Ferrari, I. Longo. 2012. Simultaneous ultrasound and microwave new reactor: Detailed description and energetic considerations. *Ultrasonics Sonochemistry* **19**:4, 872-876. [CrossRef]
2. Cheol Hyeong Park, Ki Hyun Kim, Il Kyun Lee, Seung Young Lee, Sang Un Choi, Jei Hyun Lee, Kang Ro Lee. 2011. Phenolic constituents of Acorus gramineus. *Archives of Pharmacal Research* **34**:8, 1289-1296. [CrossRef]
3. Rajendra P. Tanpure, Amanda R. Harkrider, Tracy E. Strecker, Ernest Hamel, Mary Lynn Trawick, Kevin G. Pinney. 2009. Application of the McMurry coupling reaction in the synthesis of tri- and tetra-arylethylene analogues as potential cancer chemotherapeutic agents. *Bioorganic & Medicinal Chemistry* **17**:19, 6993-7001. [CrossRef]
4. H.R. Memarian, A. Saffar-Teluri. 2007. Microwave-assisted and light-induced catalytic ring opening of α-epoxyketones using DDQ. *Journal of Molecular Catalysis A: Chemical* **274**:1-2, 224-230. [CrossRef]
5. Vinod Kumar, Abhishek Sharma, Meenakshi Sharma, Upendra K. Sharma, Arun K. Sinha. 2007. DDQ catalyzed benzylic acetoxylation of arylalkanes: a case of exquisitely controlled oxidation under sonochemical activation. *Tetrahedron* **63**:39, 9718-9723. [CrossRef]
6. Arun K. Sinha, Anuj Sharma, Anand Swaroop, Vinod Kumar. 2007. An efficient chemoselective strategy for the preparation of (E)-cinnamic esters from cinnamaldehydes using heterogeneous catalyst and DDQ. *Tetrahedron* **63**:4, 1000-1007. [CrossRef]
7. Arun K. Sinha, Anuj Sharma, Bhupendra P. Joshi. 2007. One-pot two-step synthesis of 4-vinylphenols from 4-hydroxy substituted benzaldehydes under microwave irradiation: a new perspective on the classical Knoevenagel–Doebner reaction. *Tetrahedron* **63**:4, 960-965. [CrossRef]
8. Bhupendra P. Joshi, Anuj Sharma, Arun K. Sinha. 2006. Microwave- and Ultrasound-Assisted Semisynthesis of Natural Methoxylated Propiophenones from Isomeric Mixture of Phenylpropenes in Minutes. *ChemInform* **37**:25. . [CrossRef]
9. Bhupendra P. Joshi, Anuj Sharma, Arun K. Sinha. 2006. Efficient one-pot, two-step synthesis of (E)-cinnmaldehydes by dehydrogenation–oxidation of arylpropanes using DDQ under ultrasonic irradiation. *Tetrahedron* **62**:11, 2590-2593. [CrossRef]