Microwave-promoted Synthesis of Methoxylated Benzaldehydes from Natural *cis*-Phenylpropenes Using $NaIO_4/OsO_4$ (cat.)[1]

Arun K. Sinha,* Bhupendra P. Joshi, and Ruchi Acharya
Natural Plant Products Division, Institute of Himalayan Bioresource Technology, Palampur (H.P.)-176061, India

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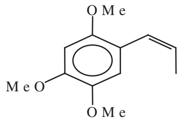
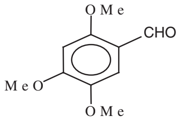
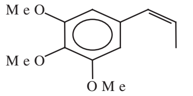
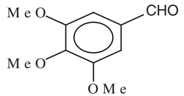
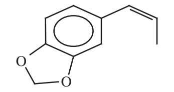
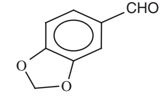
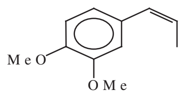
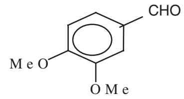
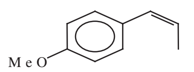
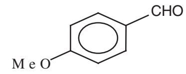
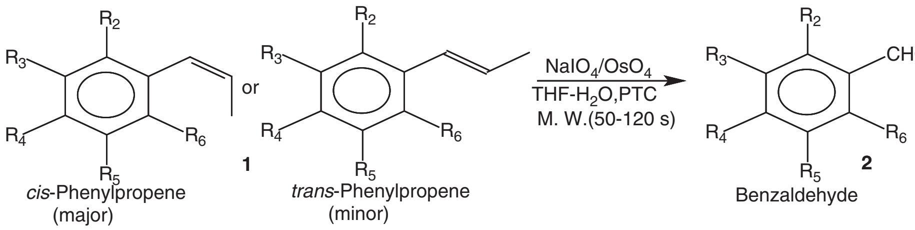
Microwave-promoted rapid oxidation of toxic natural *cis*-phenylpropenes (**1a**–**1e**) into high valued methoxylated benzaldehydes (**2a**–**2e**) was achieved within 2 min in high yield (71–84%) by reacting with sodium metaperiodate in the presence of catalytic amount of osmium tetraoxide (co-oxidant) and benzyltriethylammonium chloride (PTC).

A large number of naturally occurring methoxylated benzaldehydes[2] contribute significantly to the taste and flavour of many foods, drinks, perfumery[3] and also used for the synthesis of many bioactive compounds.[4] There are synthetic methods[5] reported for the preparation of these important benzaldehydes including oxidation of phenylpropenes.[6] However, most of the reported methods are associated with drawbacks such as low yields, long reaction time, maintenance of temperature, expensive reagents and overall environmentally hazardous reaction conditions. In this context, new emerging microwave technique[7] coupled with potassium permanganate ($KMnO_4$)[8] is proven to be high yielding oxidant as well as free from most of the above drawbacks, however, $KMnO_4$ in our hands converted β-asarone[9] (**1a**), a natural toxic *cis*-phenylpropene,[10] into asaronaldehyde (**2a**) in only 37% yield. In addition, $KMnO_4$ generated excessive fumes inside the microwave oven which once resulted in a spark.[11] Similarly, manganese dioxide/sulphanilic acid[6,9] coupled in microwave provided **2a** in 21% yield only and most of the starting **1a** remained unreacted. All this finally prompted us to search for an alternative oxidant. Herein, we report a facile oxidative conversion of an abundantly available toxic methoxylated *cis*-phenylpropenes or a mixture of *cis*- and *trans*-phenylpropenes (**1**) into methoxylated benzaldehydes (**2**) in aqueous[12] media using sodium metaperiodate ($NaIO_4$)[13] as an oxidant in the presence of osmium tetraoxide (OsO_4) and benzyltriethylammonium chloride under microwave irradiation (Scheme 1).

Treatment of *cis*-isomer[14] (**1a**) with a mixture of $NaIO_4$, OsO_4 (co-oxidant) and benzyltriethylammonium chloride in a 4:1 mixture of water and THF under microwave irradiation[7] gave 2,4,5-trimethoxybenzaldehyde (**2a**) in 82% yield in 50 s. Similarly, α-asarone (*trans*-isomer, procured from Sigma) upon oxidation produced **2a** in 84% yield which clearly confirmed that *cis* or *trans* geometry of phenylpropene does not effect the yield of the oxidized product.[14] As an extention to this method, crude *Acorus calamus* oil[15] rich in *cis*- and *trans*-asarone is also directly oxidized under microwave to provide **2a** in 76% yield in 1 min while conventional method provides 57% yield of **2a** in 6 h. It is worthwhile to mention that the direct utilization of crude calamus oil for its high value added product **2a** is a huge economical gain for *A. calamus* oil obtained from tetraploid and hexaploid strains.[9,16] Moreover, high price of co-oxidant OsO_4 did not become restrain in our process as 0.001 mole of OsO_4 per mole of phenylpropene was effective in oxidizing phenylpropenes in optimum yield. Finally, the above combina-

Table 1. Conversion of Phenylpropenes (1) into Benzaldehydes (2)

Entry	Phenylpropene (1)	Benzaldehyde (2)	Microwave irradiation Time (s)	Microwave irradiation Yield (%)
a)			50	82
b)			60	79
c)			90	78
d)			90	79
e)			120	71



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

Scheme 1.

tion of oxidants[13] was employed successfully on a series of other toxic[10] methoxylated *cis*-phenylpropenes (**1b**–**1e**) towards formation of respective methoxylated benzaldehydes (**2b**–**2e**) in high yield[17] as summarized in Table 1.

In conclusion, we report a mild, ecofriendly, rapid and efficient process for the preparation of high valued methoxylated benzaldehydes from toxic *cis*-phenylpropenes using NaIO$_4$/OsO$_4$ under microwave irradiation in aqueous[12] condition. Moreover, this process is capable of converting crude calamus oil containing 85% of toxic β-asarone along with 3% α-asarone into useful asaronaldehyde[3] in 76% yield which makes this process attractive for industrial use.

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9 Phenylpropenes[2,3] exist in three isomeric forms namely *trans* (α), *cis* (β) and allyl (γ) isomers where *cis*-phenylpropenes (e.g. β-asarone) are recently found carcinogenic and toxic[9] which prompted us to utilize *cis*-phenylpropenes or a mixture of *cis*- and *trans*-isomers as a cheaper and economical starting material. Among three isomers, *cis*-phenylpropene is generally present in high concentration e.g., β-asarone (*cis*-2,4,5-trimethoxyphenylpropene) is present upto 90% in tetraploid and hexaploid strains (distributed extensively in India, Pakistan, Japan and China) restricts the market potential of *A. calamus* oil.

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14 General procedure for microwave-promoted oxidation of methoxylated *cis*-phenylpropenes (**1a**–**1e**) into phenylaldehyde (**2a**–**2e**): A mixture of *cis*-phenylpropene (0.015 mol), OsO$_4$ (0.004 g, 0.015 mmol), NaIO$_4$ (11.75 g, 0.055 mol) and benzyltriethylammonium chloride (0.08–0.1 g) were dissolved in H$_2$O- THF (10 mL, 4:1) and irradiated for 40 s to 2 min (Table 1) under microwave oven (2450 MHz, 900 Watts, Kenstar, India). The mixture was filtered and washed with dichloromethane. Evaporation of the solvent under reduced pressure gave a crude product, which was purified on silica gel column with hexane–ethyl acetate, 9:1 to 4:1 to afford **2a**–**2e**.

15 The hydrodistillation of rhizomes of *Acorus calamus* gave yellowish oil in 1.7% yield (w/w) with a presence of 3% of α-asarone and 85% β-asarone (**1a**) (by GC) and used directly for oxidation. A mixture of crude calamus oil (9.00 g), OsO$_4$ (0.08 to 0.002 g), NaIO$_4$ (50 to 55 g) and benzyltriethylammonium chloride (0.15 g) were dissolved in H$_2$O–THF (50–60 mL, 4:1) and irradiated for 1 min in parts which provided **2a** in 76% yield (based upon percentage of α- and β-asarone present in crude calamus oil).

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17 The yield of liquid anisaldehyde (**2e**) is found lesser than other solid phenylaldehydes (**2a**–**2d**) because of volatility of **2e** during microwave irradiation reaction.[14]

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