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Efficient one-pot, two-step synthesis of (*E*)-cinnmaldehydes by dehydrogenation–oxidation of arylpropanes using DDQ under ultrasonic irradiation☆

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Abstract—A general, efficient and new approach to the synthesis of cinnamaldehydes with trans-selectivity has been accomplished starting from arylpropanes. One-pot, two-step dehydrogenation and oxidation of arylpropanes with excess DDQ in dioxane containing a few drops of acetic acid gave (*E*)-cinnmaldehydes under ultrasound irradiation.

1. Introduction

Cinnamaldehyde derivatives are common in nature[1] and they possess remarkable biological properties[2] such as antibacterial, antifungal, antitermitic, antioxidant and anti-cancer activities. Moreover, cinnamaldehydes are used to prevent darkening of skin[3] caused by UV rays of sun and also prevent hair-loss and promote hair growth.[4] Cinnamaldehydes are often used as starting materials for the synthesis of many bioactive compounds[5] including cytostatic[6] and anti-viral[7] drugs.

A number of reagents and processes are available for the preparation[8] of cinnmaldehydes including Wittig olefination reaction,[9] oxidation of arylpropene,[10] palladium cluster[11] or potassium dichromate[12] catalysed oxidation of allylic alcohols and most importantly, chain lengthening[13] of arylaldehydes (C_6–C_1 unit) by a C_2-unit. However, most of these methods mainly suffer from poor yield, harsh reaction conditions and contamination with small amounts of the undesirable *Z*-isomer.[14] Recently, some straightforward strategies have also been reported for the synthesis of cinnamaldehydes with trans-selectivity[15] and the most common approach is the Heck[16] reaction. Since the inception of the Heck reaction, a number of modifications[17] in the original protocols have been reported, however, problems such as side product formation, low yields and polymerization of acrolein incited chemists to look for alternatives. Direct oxidative[18] coupling of aromatic compounds with α,β-unsaturated aldehydes by palladium acetate/molybdovanadophosphoric acid/oxygen[19] system is a meticulous entry, however, expensive reagents and side product formation limit adoption of the protocol.

All these synthetic methods have also been exploited for introduction of α,β-unsaturated aldehyde moiety in the aromatic ring during the synthesis of various bioactive compounds[20] and natural products.[21] However, limitations such as harsh reaction conditions, heavy burden of protection–deprotection steps and lengthy protocols warrant alternative efficient and environmentally friendly procedures for the synthesis of (*E*)-cinnamaldehydes. The application of ultrasound irradiation[22] has emerged as a useful synthetic tool. In this paper, we report the DDQ-assisted one-pot, two-step dehydrogenation–oxidation of arylpropanes in dioxane, containing a few drops of acetic acid, into cinnamaldehydes with 100% (*E*)-selectivity under ultrasonic irradiation (Scheme 1).

2. Results and discussion

The methods for formation of cinnamaldehyde basically fall into three categories[8–19] (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) modification of an already existing C_6–C_3 unit. Among these three, use of a C_6–C_3 unit would ensure waste minimization through atom economy[23] as C_6–C_3 system in

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Keywords: Arylalkane; Cinnamaldehyde; DDQ; trans-Selectivity; Dehydrogenation–oxidation.
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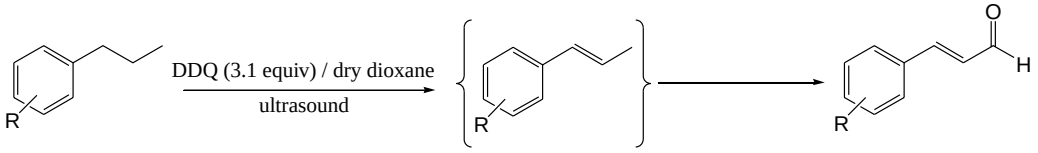


Where
R= OMe, OEt, –OCH_2O–, OH etc.

Scheme 1.

the substrate is retained in the product. Recently, we have reported[24] that arylpropane[25] effectively undergoes oxidation with DDQ[26] in wet dioxane leading to the formation of propiophenone while dehydrogenation of arylpropane with DDQ in anhydrous dioxane to form (*E*)-arylpropene[24] along with traces of (*E*)-cinnamaldehyde.[27] Hence, we decided to pursue both dehydrogenation and oxidation in one-pot for the formation of cinnamaldehydes. This would be achieved through the DDQ-assisted conversion of arylpropane directly into cinnamaldehyde via formation of intermediate (*E*)-arylpropene under ultrasound irradiation.

Thus, treatment of 3-(2,4,5-trimethoxyphenyl)propane[24] **1a** with 2 equiv of DDQ in dioxane for 6 h under ultrasonication provided (*E*)-2,4,5-trimethoxycinnamaldehyde[15c] **2a** in 48% yield along with some amount of starting **1a**. Subsequently, it was found that 3.1 equiv of DDQ was optimum for providing 73% yield of the product **2a** in 3.5 h under ultrasonication. Finally, conditions were optimized and we observed that addition of a catalytic amount of acetic acid (2–3 drops) increased the yield of **2a** up to 82% in 2 h. Acetic acid was found best among other homogeneous and heterogeneous acid catalysts (Table 1). After success of the above reactions for conversion of **1a** into **2a**, the same methodology was employed towards dehydrogenation–oxidation of other arylpropanes (**1b**–**1i**), which successfully provided the corresponding cinnmaldehydes (**2b**–**2i**) in moderate to good yield (Table 2). It is obvious from Table 2 that higher yields are obtained with the more electron rich aromatics and no cinnamaldehyde was formed in the case of unsubstituted phenylpropane **1j**. To make a comparative analysis, dehydrogenation and oxidation of **1a** with DDQ (3.1 equiv) in dioxane containing a few drops of acetic acid at room temperature (20 h) or reflux temperature (8 h) provided **2a** in 76% yield under conventional method. The results clearly showed that ultrasound activation afforded a better yield in a shorter reaction time compared to the classical method. We also found that small alterations in the reaction conditions such as changing the amount of DDQ and using hydrated or anhydrous conditions[24] provide a range of products as shown in Scheme 2.

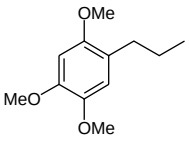
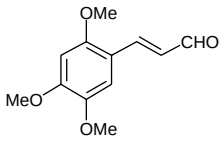
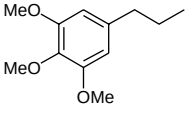
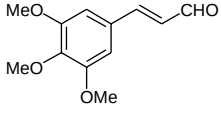
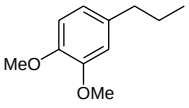
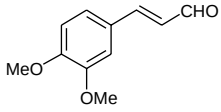
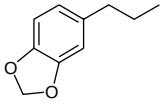
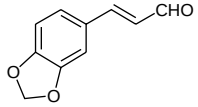
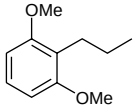
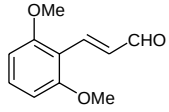
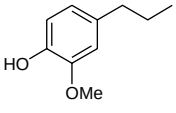
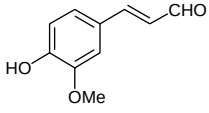
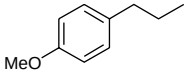
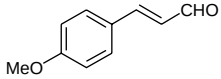
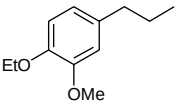
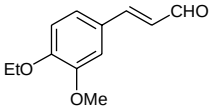
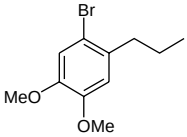
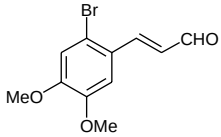
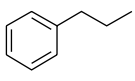
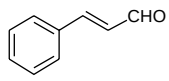
Table 1. Effect of catalyst on the yield of cinnamaldehyde (**1b**) under ultrasonic irradiation

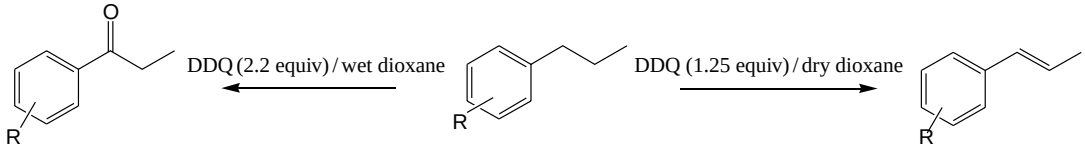
Support	Reaction time (in hours)	Product yield (%)
Acetic acid	2	82
Silica gel	2	78
Alumina (acidic)	2	76
Hydrochloric acid	2	42

3. Conclusion

In conclusion, we have realised a convenient synthetic approach towards the preparation of a number of *(E)*-cinnmaldehydes (**2a**–**2i**) via dehydrogenation–oxidation

Table 2. DDQ assisted dehydrogenation–oxidation of arylpropanes (**1**) into cinnamaldehydes (**2**)

S. no.	Substrate (**1**)	Product (**2**)	Yield (%)
a			82
b			79
c			78
d			76
e			72
f			32
g			72
h			72
i			74
j			0



Scheme 2.

of available arylpropanes (**1a–1i**) with DDQ utilizing ultrasound irradiation. The merits of the protocol lie in one-pot, two-steps methodology, economical substrate, atom economy and consequent waste minimization, ultrasound irradiation and 100% (*E*)-selectivity. The method may be useful in natural product synthesis due to mild nature of the protocol.

4. Experimental

4.1. General methods

All melting points were determined with a Metler FP80 micromelting point apparatus. IR spectra were recorded on a Perkin-Elmer spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were taken on a Bruker AM-300 spectrometer, using TMS as internal reference standard in $CDCl_3$. HRMS spectra were determined using a Micromass Q-TOF Ultima spectrometer. Sonication (20 kHz, 400 W; pulse length:10 s; 75% duty) was used for all the given reactions. Commercial reagents and solvents were of analytical grade and were purified by standard procedures prior to use. Column chromatographic separations have been carried out on neutral alumina (Qualigens India).

4.2. General procedure for ultrasound-assisted dehydrogenation–oxidation of arylpropanes (1a–1i) into cinnamaldehydes (2a–2i)

To a solution of **1a–1i** (0.017 mol) in dry dioxane (100 mL), a catalytic amount of acetic acid (2–4 drops) and DDQ (0.053 mol) was added. The reaction mixture was sonicated for 2 h or till disappearance of starting material on TLC plate. After completion of the reaction, the precipitated solid $DDQH_2$ was removed by filtration and the filtrate was evaporated. The residue was taken in ethyl acetate (70 mL) and was washed with water (2×10 mL), 2% sodium bicarbonate (2×5 mL), brine (2×10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated to afford a crude yellow liquid, which was chromatographed on neutral alumina using hexane–ethyl acetate mixture with increasing proportion of ethyl acetate up to 40% to provide **2a–2i** whose spectral data agreed well with the reported values.[1a–d,2b,8e,15b–c,19,24]

4.2.1. (*E*)-2,4,5-Trimethoxycinnamaldehyde[1c,15c,31] (2a). Yellow solid; 3.09 g (82% yield); mp 139–140 °C (lit.[15c,31] 140–141 °C).

4.2.2. (*E*)-3,4,5-Trimethoxycinnamaldehyde[1a,31] (2b). Yellow solid; 2.98 g (79% yield); mp 110 °C (lit.[31] 109–111 °C).

4.2.3. (*E*)-3,4-Dimethoxycinnamaldehyde[2b,8e] (2c). Yellow solid; 2.54 g (78% yield); mp 81–82 °C (lit.[8e] mp 83–84 °C).

4.2.4. (*E*)-3,4-Methylenedioxycinnamaldehyde[9,31] (2d). Yellow solid; 2.27 g (76% yield); mp 78 °C (lit.[9] mp 77–79 °C, lit.[31] mp 83–84 °C).

4.2.5. (*E*)-2,6-Dimethoxycinnamaldehyde[1b] (2e). Yellow solid; 2.35 g (72% yield); mp 78 °C (lit.[1b] mp 77–78 °C).

4.2.6. (*E*)-4-Hydroxy-3-methoxycinnamaldehyde[1d,31] (2f). Yellow solid; 0.97 g (32% yield); mp 83–84 °C (lit.[31] mp 84 °C).

4.2.7. (*E*)-4-Methoxycinnamaldehyde[15b,19,31] (2g). Light yellow solid; 1.98 g (72% yield); mp 58 °C (lit.[15b,31] mp 58–59 °C).

4.2.8. (*E*)-4-Ethoxy-3-methoxycinnamaldehyde (2h). Yellow solid; 2.52 g (72% yield); mp 78–80 °C; IR (KBr) 1670 cm^{-1} (conjugated carbonyl); ^{1}H NMR ($CDCl_3$): δ 9.59 (1H, d, J=7.8 Hz, H-3′), 7.36 (1H, d, J=15.8 Hz, H-1′), 7.07 (1H, d, J=8.1 Hz, H-6), 7.00 (1H, s, H-2), 6.83 (1H, d, J=8.1 Hz, H-5), 6.56 (1H, dd, J=15.8, 7.8 Hz, H-2′), 4.11 (2H, q, J=6.9 Hz, 4-OCH_2), 3.83 (3H, s, 3-OCH_3), 1.44 (3H, t, J=6.9 Hz, 4-CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 193.6 (C-3′), 152.9 (C-1′), 151.4 (C-4), 149.5 (C-3), 126.8 (C-2′), 126.6 (C-1), 123.4 (C-6), 112.1 (C-5), 110.2 (C-2), 64.4 (4-OCH_2), 56.0 (3-OCH_3), 14.6 (4-CH_3); HRMS (M+Na) *m/z*: 229.2335 (Calcd for $C_{12}H_{14}O_3Na$: 229.2321).

4.2.9. (*E*)-2-Bromo-4,5-dimethoxycinnamaldehyde (2i). Yellow solid; 3.41 g (74% yield); mp 136–138 °C; IR (KBr) 1671 cm^{-1} (conjugated carbonyl); ^{1}H NMR ($CDCl_3$): δ 9.66 (1H, d, J=7.8 Hz, H-3′), 7.75 (1H, d, J=15.8 Hz, H-1′), 7.19 (1H, s, H-3), 7.02 (1H, s, H-6), 6.53 (1H, dd, J=15.8, 7.8 Hz, H-2′), 3.84 (3H, s, 4-OCH_3), 3.82 (3H, s, 5-OCH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 193.4 (C-3′), 152.1 (C-1′), 150.5 (C-5), 148.8 (C-4), 128.6 (C-1), 125.8 (C-2′), 118.0 (C-3), 115.7 (C-6), 109.3 (C-2), 56.3 (4-OCH_3), 56.1 (5-OCH_3); HRMS (M+Na) *m/z*: 294.1006 (Calcd for $C_{11}H_{11}O_3BrNa$: 294.1012).

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25. The arylpropane derivatives are prepared either by catalytic reduction[28] of abundantly available isomeric mixture of arylpropenes (α,β and γ-isomers) or hydrogenolysis[29] of arylpropanol.
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27. To our best knowledge, formation of (*E*)-cinnamaldehyde is detected for the first time as a side product[24] along with expected (*E*)-arylpropene during dehydrogenation of arylpropane with 1.25 equiv of DDQ–SiO_2 in anhydrous dioxane under ultrasonication. It is presumed that formation of cinnamaldehyde could be due to the presence of atmospheric oxygen/moisture in the reaction mixture during sonication, which would form highly reactive peroxy radicals[30] to further oxidize (*E*)-arylpropene into (*E*)-cinnamaldehyde.
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