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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☆

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Abstract—The classical Knoevenagel–Doebner reaction is reinvestigated wherein the direct synthesis of substituted 4-vinylphenols instead of the expected 4-hydroxycinnamic acids is described. The condensation reaction is performed on 4-hydroxy substituted benzaldehydes and malonic acid with a mixture of acetic acid–piperidine as condensing agent under focused microwave irradiation. The occurrence of simultaneous condensation–double decarboxylation without the use of any decarboxylating agent is a new finding, the reaction being facilitated solely by the hydroxy substituent and microwave irradiation effect.

1. Introduction

4-Vinylphenols,[1] a class of functionalized styrenes, constitute one of the most extensively explored compounds due to their wide ranging applications in food and alcoholic beverages, flavouring substances[2] and as intermediates in the preparation of various bioactive molecules,[3] polymers and copolymers that are useful in coatings, electronic applications, ion exchange resins and photoresists,[4] etc. In addition, a number of biological activities such as antioxidant, antibacterial, antifungal, hypolipidemic and antimutagenic activities[5] have been attributed to these compounds. A burgeoning global demand coupled with the natural scarcity of FEMA GRAS[6] (Flavor Extract Manufacturer Association; Generally Regarded As Safe) approved 4-vinylguaiacol (3-methoxy-4-hydroxystyrene), 4-vinylphenol (4-hydroxystyrene), antimutagenic canolol[5d] (3,5-dimethoxy-4-hydroxystyrene) and other vinylphenols[7] or polymethoxylated styrenes[8] have provided an increased impetus towards their synthetic production. However, the development of a simple and efficient synthetic methodology for vinylphenols[9] has been a difficult proposition due to the susceptibility of the hydroxy function towards polymerization.[10] Consequently, a majority of the prevalent synthetic strategies comprise of protection–deprotection steps for vinylphenols as compared to styrenes.[11] Some of the precedents exemplifying this approach include Grignard addition to benzaldehyde,[9a] decarboxylation of *trans*-cinnamic acids at 240–260 °C in the presence of toxic quinoline and metal salts,[9b,c] catalytic dehydrogenation of ethylphenols[9d] or Wittig synthesis.[9e] For instance, Corson[12] et al. synthesized 4-vinylphenol in five steps starting from phenol.

Similarly, 4-vinylphenols[9a,13] were synthesized from hydroxybenzaldehydes adopting either Knoevenagel condensation–decarboxylation or Grignard addition–dehydration approach, however, only moderate yield of the product (29–34%) could be achieved despite prior protection of the hydroxyl group. A few recent reports[14] utilizing Suzuki cross coupling between aryl halides and 2,4,6-trivinylcyclotriboroxane-pyridine[15] provide styrenes in high yield, however, the reactions are delicate and require temperatures down to −78 °C. Styrenes have also been accessed through the coupling of arylboronic acids with vinyl bromide in the presence of palladium acetate,[16] however, the method is not compatible with the mild conditions required for hydroxy substituted styrenes.

In this context, a panacean approach for the synthesis of vinylphenols seems to be the transformation of commercially available 4-hydroxybenzaldehydes through Knoevenagel–Doebner[17] condensation into the corresponding

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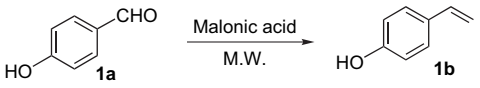
cinnamic acids in the first step, followed by decarboxylation[18] of the cinnamic acids to obtain the required 4-vinylphenols in the second step. There have been a number of reports for the preparation of cinnamic acids through this Knoevenagel–Doebner route including various green methodologies.[19] However, a majority of the decarboxylation protocols for cinnamic acid involve the use of toxic quinoline/metal salts,[18,20] which compromises their environmental sustainability besides involving tedious[18b] work up and formation of various side products.[18c] Although, some biotransformation[21] methods have been reported for decarboxylation of cinnamic acids, the difficulty in scaling up the protocol is a major impediment with these methods. The above contemporary concerns attracted our attention towards the development of a simple, efficient and environmentally[22] benign synthetic protocol for vinylphenols.[1e]

2. Results and discussion

We initially envisioned a two-step synthetic strategy involving condensation of hydroxybenzaldehydes and malonic acid followed by decarboxylation, both steps to be carried out under monomode microwave irradiation[22c] in an environmentally benign manner as compared to the existing conventional methodologies.[9] We had a successful precedent for the condensation of a number of methoxylated benzaldehydes and malonic acid (2 equiv) to the corresponding cinnamic acids using a mixture of piperidine–acetic acid[23] as condensing agent under domestic microwave oven. The use of acetic acid–piperidine[24] instead of the usual pyridine–piperidine[25] combination was found to be more effective and eco-friendly as the toxic pyridine–piperidine combination tends to vaporize easily under domestic microwave. We employed the same method[23] on 4-hydroxybenzaldehyde (**1a**) (Scheme 1, Table 1) under microwave irradiation (domestic, 960 W) for 3 min, and much to our surprise, instead of the expected 4-hydroxycinnamic acid,[26] an unexpected sweet smelling viscous liquid (37% yield) was obtained. The sweet smelling liquid was identified as vinylphenol (**1b**), which lead us to seek better optimization and mechanistic insights into the reaction. To this end, the method was attempted on

Table 1. Effect of different acid–base combinations on formation of **1b** from **1a** under microwave irradiation[a]

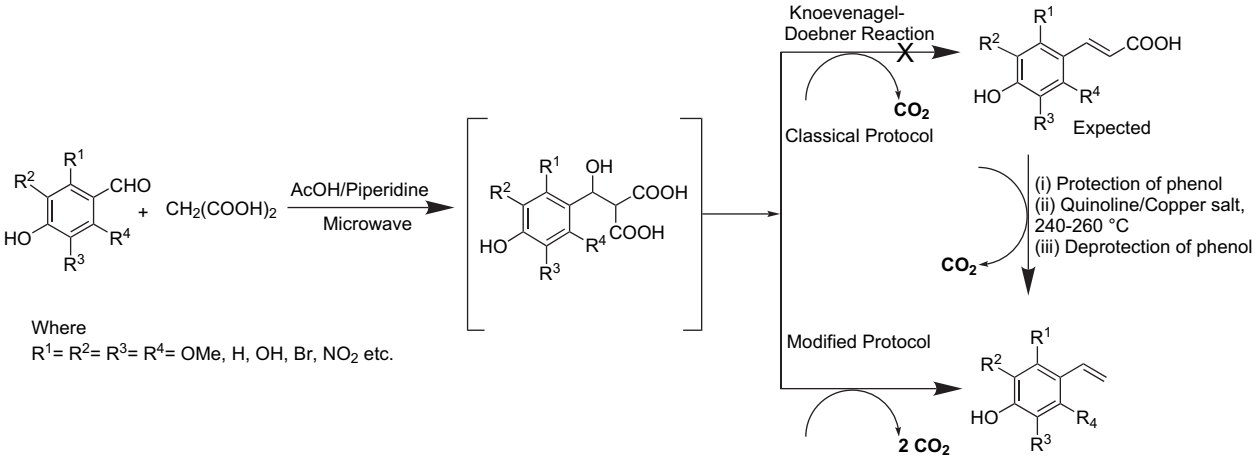


S. No.	Acid	Base	Yield (%)
1	AcOH	Piperidine	61
2	HCOOH	Piperidine	25
3	AcOH	Pyridine	39
4	AcOH	Triethylamine	31

[a] CEM Discover monomode microwave.

monomode[22c] microwave (150 W, 130 °C) and the yield of product **1b** increased up to 47% (Scheme 1). The low yield (37%) in the case of domestic microwave oven might be attributed to easy evaporation of the product vinylphenol, which gets subsided in monomode microwave due to open refluxing under condenser. It was also found that the optimum temperature for the above transformation was 130 °C, above which rapid evaporation of the product **1b** occurs and below which the yield of **1b** drops significantly and extended reaction times were observed. In our quest to further increase the yield of **1b**, the use of an excess of malonic acid[27] over the usual 2 equiv[17] was found to be an interesting option. Consequently, the 4-hydroxybenzaldehyde–malonic acid ratio was varied in our reaction mixture and 4 equiv of malonic acid was found to be optimum (yield of the product increased from 47 to 61%).

In order to discern the specific role of microwave, compound **1a** and malonic acid were reacted in the presence of acetic acid and piperidine under conventional heating at reflux temperature for 5–6 h. The method provided cinnamic acid (68%) as the major product along with a small amount of **1b** (12% yield). This result emphatically proved the role of microwave in effectively bringing about condensation–decarboxylation within minutes, without the use of any decarboxylating agent at all (Scheme 1). It is well recognized that microwave hastens the approach of ground state (GS) towards the transition summit in case of polar reactions.[22b,h] The foregoing effect is rather pronounced

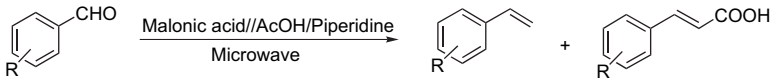


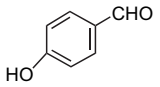
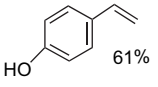
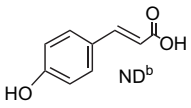
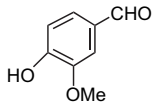
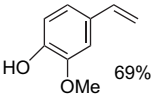
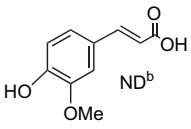
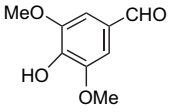
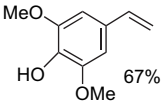
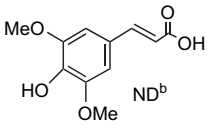
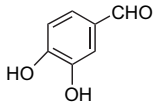
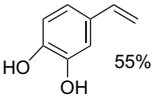
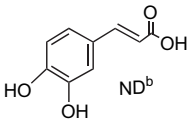
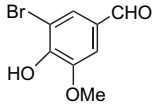
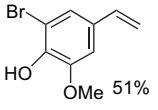
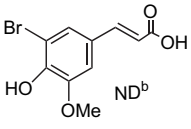
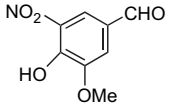
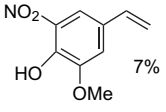
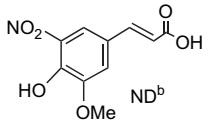
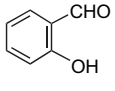
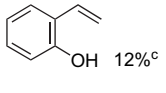
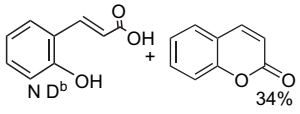
Scheme 1.

in the case when the transition state (TS) occurs later along the reaction coordinates.[22b] Presumably, such a microwave effect facilitates the simultaneous condensation–decarboxylation observed in our case, especially in view of the fact that decarboxylation generally requires high activation energy thus rendering the corresponding TS to occur later along the reaction coordinates. On the other hand, the lower yield of **1b** under conventional heating might be ascribed to the concomitant polymerization reactions as well as to the slow rate of heat transfer. Interestingly, the use of pyridine–piperidine combination also provided comparable yields, but it affected the quality of product **1b** due to degeneration of aroma. It is pertinent to mention here that the classical Knoevenagel–Doebner reaction has been widely used for the synthesis of a variety of cinnamic acid derivatives from benzaldehydes[9a] including hydroxybenzaldehydes[26] and malonic acid in the presence of pyridine–piperidine. In this context, the developed Knoevenagel–Doebner–Sinha protocol[1e] discloses, for the first time, an observation of a simultaneous condensation–double decarboxylation effect leading to the formation of **1b** from 4-hydroxybenzaldehyde and malonic acid. Our above premise of simultaneous condensation–decarboxylation was proved when treatment of 4-hydroxycinnamic acid with acetic acid and piperidine under microwave-irradiation did not yield **1b**.

Thereafter, a lot of changes were made in the devised protocol. For instance, other acid–base combinations were investigated, however, optimum results were obtained only with the piperidine–acetic acid combination (Table 1). Our efforts to generalize this method with various other substituted benzaldehydes led us to some more surprises (Table 2). It was found that 4-hydroxy substitution is a mandatory condition for the synthesis of the corresponding vinylphenols in a single step. Interestingly, 5-nitrovanillin (entry 6) gave the corresponding vinylphenol in only 7% yield along with the unreacted nitrovanillin and various side products. Further, 2-hydroxybenzaldehyde (entry 7) provided coumarin (34%) as the major product along with a small amount of

Table 2. Microwave[a] induced conversion of substituted benzaldehydes (**a**) into styrenes (**b**) and cinnamic acids (**c**)



Entry	Benzaldehydes (**a**)	Time (min)	Styrene (**b**)	Cinnamic acid (**c**)	Ref.
1		5	 61%	 ND[b]	20b,21
2		5	 69%	 ND[b]	20b,21
3		7	 67%	 ND[b]	5c,8
4		8	 55%	 ND[b]	20b
5		8	 51%	 ND[b]	14b,29
6		20	 7%	 ND[b]	21,29
7		8	 12%[c]	 34%	20b,23

(*continued*)

Table 2. (*continued*)

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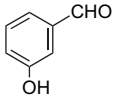
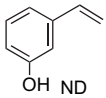
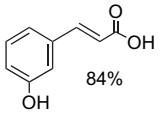
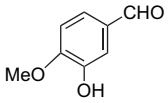
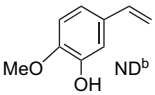
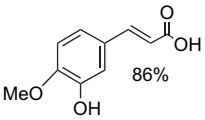
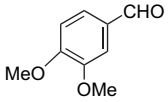
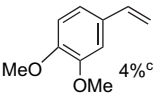
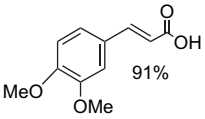
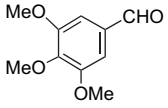
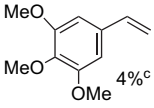
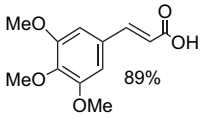
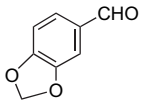
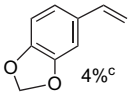
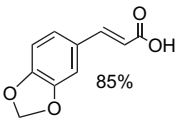
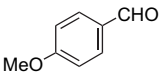
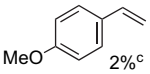
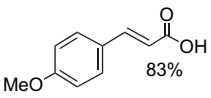
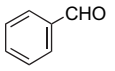
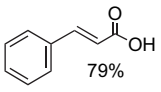
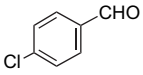
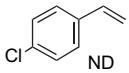
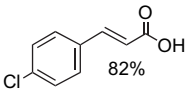
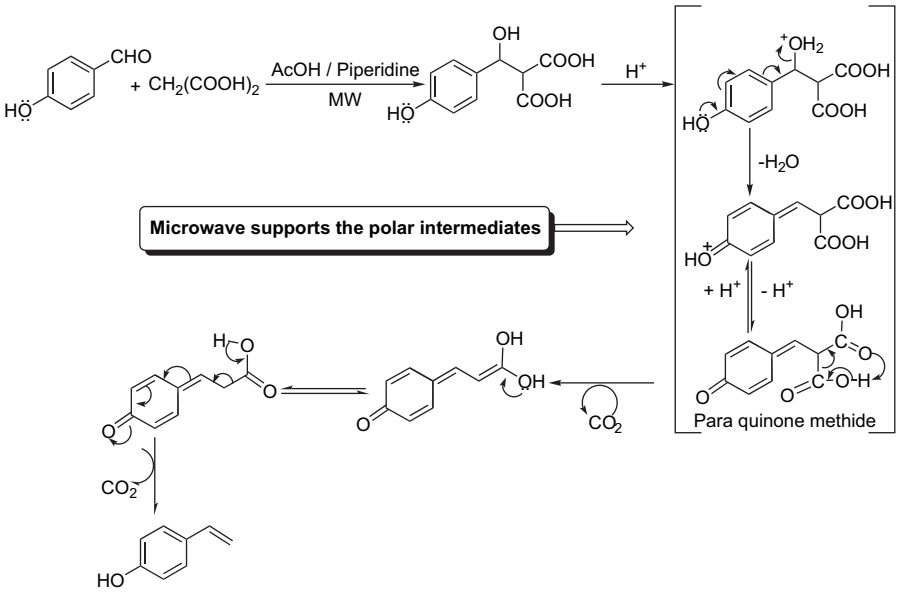
8		20	 ND	 84%	20b
9		20	 ND[b]	 86%	20b
10		8	 4%[c]	 91%	8,20b,23
11		8	 4%[c]	 89%	8b,23,29
12		8	 4%[c]	 85%	3e,29
13		8	 2%[c]	 83%	16,23
14		15	 ND	 79%	3b
15		15	 ND	 82%	21

[a] CEM Discover monomode microwave.
[b] Not detected.
[c] Yield of the product based on ^{1}H NMR spectra.

vinylphenol (12%). Presumably, coumarin might have formed by the ring closure of the hydroxy carboxylic acid intermediate. On the other hand, its 3-hydroxy counterpart (entry 8) did not form vinylphenol even when the irradiation time was increased to 20 min and 3-hydroxycinnamic acid was formed as the major product. In all other cases (entries 7–15), cinnamic acids were obtained and styrenes were formed in traces (Table 2). Ironically, the hitherto problematic hydroxy functional group[9,12,13] proved to be important. The above method successfully provided commercially important FEMA GRAS approved vinylphenols (entries 1 and 2) and anti-mitotic canolol (entry 3, Table 2) in a single step in a cost effective manner thus obviating the need for the prevalent multistep protocols.[9,12,13] It may be mentioned here that the developed protocol allowed us to further synthesize important acetoxylated[9g,h] or methoxylated[8] styrenes by acetylation or alkylation of the corresponding vinylphenols under microwave[22c] within minutes.

We envisage a rather new mechanistic pathway for the peculiar simultaneous condensation–double decarboxylation observed in our case. The selectivity for 4-hydroxy substituted benzaldehydes may be due to the assistance provided by *para* hydroxy group towards dehydration of benzylic hydroxy group in acidic medium[28] with the subsequent formation of a *para*-quinone methide. The *para*-quinone methide then eliminates a molecule of carbon dioxide. Finally, hydrogen transfer followed by release of second molecule of carbon dioxide ensures the formation of styrene as shown in Scheme 2.

The facile progress of the reaction under microwave might be ascribed to the fact that all the intermediates proposed in the mechanism are more polar than the starting material. Consequently, microwave stabilizes the more polar transition states to a greater extent than the ground state.[22b] Further investigations regarding the elucidation of precise mechanism are currently under progress.



Scheme 2.

3. Conclusion

In conclusion, we disclose a new protocol wherein the age-old Knoevenagel–Doebner method is modified to give commercially important vinylphenols in a single step from 4-hydroxybenzaldehydes and malonic acid under microwave via simultaneous condensation–double decarboxylation. The developed method eliminates the need for toxic decarboxylating agents like quinoline and metal salts. Operational simplicity, utilization of commonly used inexpensive reagents, rapid conversion and good yield of the product make the developed protocol a useful alternative to the prevalent multistep methods for the synthesis of vinylphenols.

4. Experimental section

4.1. General procedure

All benzaldehydes were obtained from commercial sources. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. Kenstar microwave oven (2450 MHz, 960 W) and CEM Discover™ focused microwave (2450 MHz, 300 W) were used wherever mentioned. GC–MS was determined using Shimadzu-2010 spectrometer.

4.2. Synthesis of 4-vinylphenols under microwave irradiation

A mixture of benzaldehyde (**1a–15a**) (0.0164 mol), malonic acid (0.0656 mol), piperidine (0.0656 mol) and acetic acid (10–12 mL) was taken in a 100 mL round-bottomed flask. The flask was shaken well and irradiated under focused monomode microwave system fitted with reflux condenser for 5–20 min (150 W, 130 °C). The cooled mixture was poured into ice-cold water (20 mL) and extracted with ethyl acetate (3×20 mL). The organic layer was washed with saturated sodium chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure to obtain a viscous liquid, which was purified on silica gel column using a mixture of hexane and ethyl acetate (9:1 to 6:4) to provide vinylphenols along with cinnamic acids (Table 2) whose spectra matched with those reported.[8,20,26,29]

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Supplementary data

Spectral data of some representative 4-vinylphenols. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.11.023.

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