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Obtaining 4-vinylphenols by decarboxylation of natural 4-hydroxycinnamic acids under microwave irradiation

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Abstract—4-Vinylphenols, useful compounds for industrial applications, were obtained by decarboxylation of 4-hydroxycinnamic acids under microwave irradiation in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base and basic aluminum oxide as solid support. The reactions were fast (15–30 min). The selective extraction of the final products with ethyl acetate avoids chromatographic purifications. The conversions are quantitative and the yields are satisfactory. Only the unstable 4-vinylcatechol was obtained in moderate yield. This procedure was successfully extended to a natural sample of ferulic acid extracted from wheat bran to get the corresponding 4-vinylguaiacol, a FEMA GRAS (Flavor and Extract Manufacturer's Association; General Regarded as Safe) approved flavoring agent.

1. Introduction

4-Vinylphenol derivatives such as 4-vinylphenol, 4-vinylcatechol, 4-vinylguaiacol, and 2,6-dimethoxy-4-vinylphenol are natural compounds widespread in the plant kingdom.[1] They have wide utility in industrial applications. For example, they are used as flavoring substances in perfumery, food, and beverage industries[2] being approved as FEMA GRAS (Flavor and Extract Manufacturer's Association; General Regarded as Safe);[3] they are the starting materials for the synthesis of bioactive compounds[4] and for the production of resins, elastomers, adhesives, coatings as well for electronic materials.[5] In addition, these compounds exhibit interesting biological activities. For example, 4-vinylphenol is an efficient antifungal agent against the pathogens of conifer trees;[6] 4-vinylcatechol acts as an inhibitor for the phenylalanine hydrolase and other pteridine-dependent monoxygenases;[7] 4-vinylguaiacol and 2,6-dimethoxy-4-vinylphenol (also named canolol or vinylsyringol) are potent antioxidant and antimutagenic compounds.[8]

The industrial demand of these compounds is not satisfied by the availability from the natural sources. As a result, a large number of chemical syntheses of 4-vinylphenols have been described. However, some procedures required expensive reagents and harsh conditions and the final products were isolated in low yields (30–40%). In addition, the protection-deprotection of the phenolic groups is often required to avoid the competitive reaction of polymerization. Recently, two new more efficient syntheses of these compounds by the Knoevenagel condensation[9] and Knoevenagel–Doebner reaction[10] from 4-hydroxybenzaldeydes and malonic acid were described. These procedures were achieved using milder conditions.

A more studied and tried procedure to synthesize 4-vinylphenols was the decarboxylation of cinnamic acids such as *p*-coumaric acid, ferulic acid, sinapic acid, and caffeic acid. These compounds are commercially available and they are present in food of vegetable origin. In particular, they are found in barley,[11] wheat bran,[12] sunflower seeds,[13] and in rapeseed meal.[8c] The decarboxylations were performed by a microbial or chemical pathway. *Saccaromyces cerevisiae*,[14] *Pseudomonas fluorescens*,[15] *Bacillus pumilis*,[16] and plant cell cultures[17] are some of the biocatalysts achieving the microbial decarboxylation; elevated temperatures, acids[18] or bases[19] are needed for the chemical procedures.

In the past few years, microwave-assisted chemical synthesis was a more and more used technique known for ecofriendly, rapid, and high yielding processes on laboratory-scale.[20] More recently, many efforts are being made to develop large reactors that will permit the extension of this technique to industrial applications.[21]

Keywords: Decarboxylation; 4-Hydroxycinnamic acids; 4-Vinylphenols; Microwave irradiation; Renewable sources; Agroindustrial wastes.
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Recently, Nomura et al. reported a base-catalyzed decarboxylation and amide-forming reaction of substituted cinnamic acids via microwave heating.[22] However, in these experimental conditions, the recovery was low (4–27%) and the yields of the 4-vinylphenols are moderate (30–63%).

In this paper, we describe new experimental conditions to perform in satisfactory yields the decarboxylation of cinnamic acids under microwave irradiation in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base, basic aluminum oxide as solid support, and hydroquinone as polymerization inhibitor. This procedure was successfully applied to a sample of ferulic acid extracted from wheat bran and converted in good yield to the corresponding useful and bioactive 4-vinylguaiacol.

2. Results and discussion

Our initial experiments have been designed to investigate better conditions to achieve the decarboxylation of *p*-coumaric acid **1** chosen as model substrate (Scheme 1). We worked under microwave irradiation following the recommended safe method for a domestic microwave oven.[20] Then, the cinnamic acid was dissolved in methanol; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), hydroquinone, and silica or aluminum oxide as solid supports were added. After the complete evaporation of the solvent, the mixture was heated in the microwave oven for 20–30 min. We choose the DBU as base because it is known that the diazabicycloalkenes are efficient bases for the decarboxylation of acid unsaturated fatty acids.[23] Moreover, DBU has a pK_a=12[24] and it was reported that the decarboxylation of cinnamic acids proceeded in better yields with bases having higher basicity (pK_a>7).[22]

The conversions were quantitative but the highest yield of the 4-vinylphenol **2** was obtained using basic aluminum oxide in place of silica as solid support (Table 1, compare entry 1 with entry 2). The selective extraction of **2** from the reaction mixture was achieved using ethyl acetate as solvent. In absence of a polymerization inhibitor such as hydroquinone, the dimeric species **3** depicted in Figure 1 was isolated as a secondary product (yield: 8%).

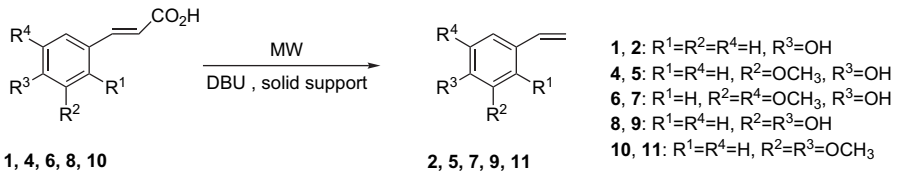
After these initial investigations, we extended the procedure to ferulic acid **4**, sinapic acid **6**, and caffeic acid **8** to obtain corresponding 4-vinylguaiacol **5**, 2,6-dimethoxy-4-vinylphenol **7**, and 4-vinylcatechol **9**. The yields of **5** and **7** are satisfactory (70 and 84%, see Table 1, entries 3, 4); in contrast, the yield of purified **9** is lower (35%, Table 1, entry 5) probably because of its chemical instability due to the *o*-diphenolic function and its tendency to polymerize.[26] The recovery of the final products is in all cases satisfactory.

The decarboxylation took place only in the presence of a *p*-hydroxyl group. In fact, in the same experimental conditions, the 2′,3′-dimethoxylated cinnamic acid **10** did not react and the corresponding decarboxylated product **11** was not isolated (Table 1, entry 6). These results are accounted by the mechanism reported in the Scheme 2.[22,25] Cinnamic acids having a hydroxyl group at the *para* position such as **1**, **4**, **6**, and **8** were deprotonated by the DBU to get the intermediates **12** and **13**; the quinone methide **13** undergoes a rapid decarboxylation and easily rearomatize to yield the corresponding 4-vinilphenols **2**, **5**, **7**, and **9** (Scheme 2).

As part of a program devoted to the utilization of renewable natural sources such as the agroindustrial wastes to get fine-chemicals and bioactive compounds,[27] we applied these procedures to a sample of crude ferulic acid extracted from wheat bran. Ferulic acid is a constitutive phenolic acid of the bran, which is covalently bound to the arabinoxylane backbone of the polysaccharide fraction that constitutes the plant cell wall of the wheat bran. The recovery of the ferulic acid needs a chemical or enzymatic hydrolysis of the plant cell wall.[28] Here, the hydrolysis was performed using an enzymatic mixture composed of Cytolase M102® and Termamyl® 120L, which exhibited a large ferulic acid release from wheat bran.[29] This amount was about 30% of the covalently bound ferulic acid on the plant cell walls of the bran. The release of ferulic acid from wheat bran was accompanied with a huge release of carbohydrates as a consequence of the hydrolytic reaction. Treatment with the Amberlite IRA95 resin resulted in a concentrated ethanolic extract of ferulic acid in which the content of reducing carbohydrates was reduced to 28% of those originally occurring in the crude extract. The alcoholic phase obtained from the resin washing gave a ferulic acid recovery of 80%. After evaporation under reduced pressure of the alcoholic solvent and extractions with ethyl acetate, we obtained crude ferulic acid. After addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), hydroquinone, and aluminum oxide, this sample was decarboxylated in a microwave oven as previously described. The yield of the corresponding 4-vinylguaiacol **5** was comparable to those obtained using commercial ferulic acid (Table 1, entry 3).

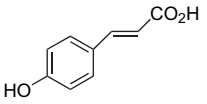
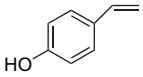
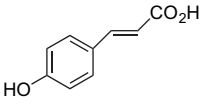
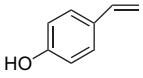
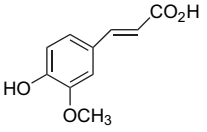
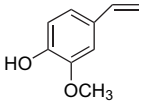
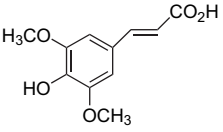
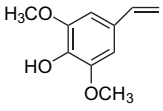
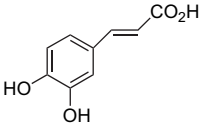
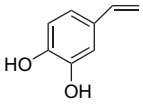
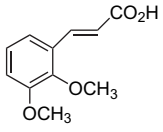
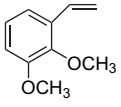
3. Conclusions

In conclusion, a simple and satisfactory procedure for the preparation of useful and bioactive 4-vinylphenols under microwave irradiation has been developed; it has also been successfully applied to a sample of ferulic acid extracted from a natural source (wheat bran). This work represents an interesting example of the use of renewable natural sources to obtain fine-chemicals and bioactive compounds.

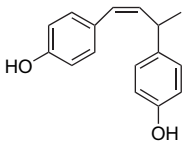


Scheme 1. Microwave irradiation of cinnamic acids **1**, **4**, **6**, **8** and **10**.

Table 1. Experimental data of the reactions depicted in Scheme 1[a]

Entry	Cinnamic acid	Solid support	Time reaction (min)	4-Vinylphenol	Conversion (%)	Recovery[b] (%)	Yield (%)
1	 **1**	Silica	20	 **2**	>98	60	20
2	 **1**	Basic aluminum oxide	20	 **2**	95	85	85
3	 **4**	Basic aluminum oxide	30	 **5**	>98	70	70
4	 **6**	Basic aluminum oxide	15	 **7**	>98	84	84
5	 **8**	Basic aluminum oxide	15	 **9**	60	75	35
6	 **10**	Basic aluminum oxide	30	 **11**	—	>98	—

[a] Conditions: SiO_2 or Al_2O_3 (1 g), DBU (6 mmol), hydroquinone (0.1 mmol), MW irradiation (650 MW).
[b] After extraction with ethyl acetate.



3

Figure 1. 4-Vinylphenol dimer **3**.

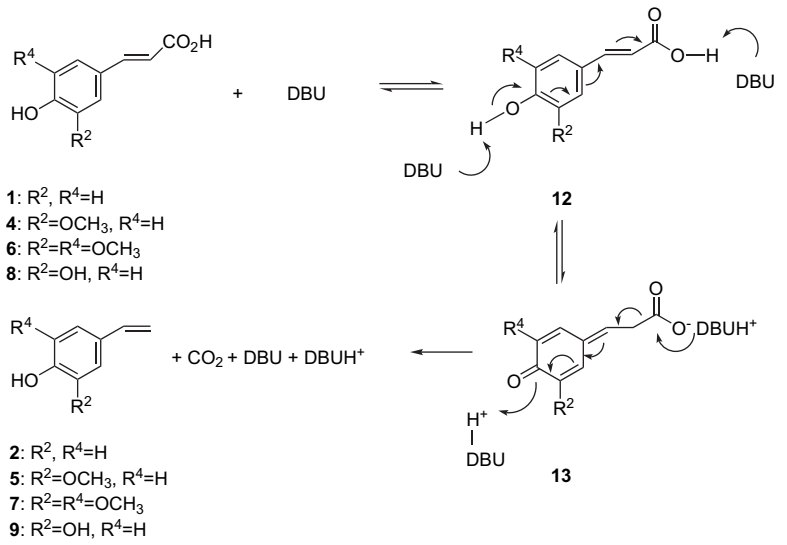
4. Experimental

4.1. Materials and instruments

Cinnamic acids **1**, **4**, **6**, **8**, and **10** were purchased from Aldrich and used as received. Solvents (Carlo Erba) were of the highest commercially available quality and were used without further purification. Silica and basic aluminum oxide are commercially available (Merck). Thin layer chromatography was carried out using Merck platen Kieselgel 60 F254. NMR spectra were recorded on a Bruker (200 MHz) spectrometer and are reported in δ values. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV and a CP-SIL 8 CB-MS column (25 m×0.25 mm and 0.25 mm film thickness). GC analysis were performed using an isothermal temperature profile of 60 °C for 5 min, followed by a 10 °C/min temperature gradient to 250 °C for 10 min. The injector temperature was 280 °C. Melting points were determined on a Buchi SMP apparatus.

4.2. Decarboxylation of 4-vinylphenols: general procedure

Cinnamic acid (1 mmol) was taken in a 20 mL round flask and solubilized in methanol (2 mL). Then, DBU (6 mmol), hydroquinone (0.1 mmol), and silica or allumine oxide (2 g) were added. The solvent was completely evaporated under reduced pressure. The mixture was heated in microwave oven at 650 W. For each 10 min, the reactions were



Scheme 2. Mechanism of base-catalyzed decarboxylation of cinnamic acids **1**, **4**, **6** and **8**.

monitored by thin layer chromatography and by gas-mass chromatography. When the substrate disappeared, the mixture was cooled at room temperature and neutralized by 1 M HCl. Then, it was extracted with ethyl acetate (3×10 mL). The organic layer was washed with saturated sodium chloride and dried over sodium sulfate. Products were identified by comparing spectroscopic data (^{1}H and ^{13}C NMR) and GC–MS spectra with those reported in the literature.[8a,22,26,30]

4.3. Extraction of ferulic acid from wheat bran and preparation of the sample for the decarboxylation reaction

Wheat bran (40 g), purchased from Molino Grassi S.p.A. (Fraore, Parma, Italy), was suspended in 0.28 L of water weighed in a 0.5 L Duran bottle and then subjected to a thermal treatment at 121 °C for 20 min. The suspension was added with 1% (w/w) Cytolase M102® (DSM, Heerlen, The Netherlands) and 0.1% (w/w) Termamyl® 120L (Sigma–Aldrich, Milan, Italy) and the enzymatic hydrolysis was carried out incubating at 30 °C for 20 h. Ferulic acid was selectively recovered from the crude enzymatic hydrolyzate after separating the polysaccharide suspension, filtering it on paper by employing an Amberlite IRA 95 resin. The resin was activated with 1 N HCl and then was washed with distilled water. The enzymatic hydrolyzate was added with the activated resin 6% (w/v) and stirred at 50 rpm for 3–4 h. The hydrolyzate was then removed and the resin 25% (w/v) was treated with ethanol additioned with 4% (v/v) HCl for 1 h at room temperature to mobilize sorbed ferulic acid. The alcoholic ferulic acid rich extract thus obtained was neutralized by using 2 N NaOH and then concentrated by evaporation of the solvent under reduced pressure. These extracts contain a ferulic acid concentration of 2.34 g/L, which corresponded to a ferulic acid recovery of 80%. Before the decarboxylation reaction, these extracts have been worked up as it follows: after removal of the alcoholic solvent by evaporation under reduced pressure, three extractions with ethyl acetate and a washing with a saturated solution of NaCl were achieved. After drying over dry Na_2SO_4, the ethyl acetate was removed by evaporation and the sample was decarboxylated as previously described.

4.4. Spectroscopica data

4.4.1. 4-Vinylphenol (2). Yield: 85%, solid; mp 70–72 °C (lit.[26] 72–73.5 °C); δ_H (200 MHz, $CDCl_3$) 5.04 (1H, s, O*H*), 5.11 (1H, dd, *J*=0.9 and 11.0 Hz, =CH_2), 5.57 (1H, dd, *J*=0.9 and 17.6 Hz, =CH_2), 6.63 (1H, dd, *J*=10.9 and 17.6 Hz, =C*H*), 6.70–6.79 (2H, d, *J*=8.5 Hz, Ar–*H*), 7.26–7.30 (2H, d, *J*=8.5 Hz, Ar–*H*); δ_C (200 MHz, $CDCl_3$) 111.5, 115.3, 127.5, 130.6, 136.1, 155.3; *m*/*z* 121 (M^++1).

4.4.2. 4-Vinylphenol dimer (3). Yield: 8%, oil; δ_H (200 MHz, $CDCl_3$) 1.33 (3H, d, *J*=7.0 Hz, CH_3), 3.47 (1H, m, ArC*H*CH$_3$), 6.10 (1H, d, *J*=6.4 Hz, =C*H*), 6.22 (1H, d, *J*=6.4 Hz, =C*H*); δ_C (200 MHz, $CDCl_3$) 18.6, 37.0, 115.8, 115.9, 126.2, 127.5, 132.1, 134.5, 154.2, 159.2; *m*/*z* 240 (M^+).[30]

4.4.3. 4-Vinylguaiacol (5). Yield: 70%, oil;[22] δ_H (200 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 5.11 (1H, dd, *J*=0.9 and 10.8 Hz, =CH_2), 5.57 (1H, s, O*H*), 5.68 (1H, dd, *J*=0.9 and 17.6 Hz, =CH_2), 6.60 (1H, dd, *J*=10.8 and 17.6 Hz, =C*H*), 6.78 (1H, d, *J*=8.2 Hz, Ar–*H*), 6.86 (1H, dd, *J*=2.0 and 8.2 Hz, Ar–*H*), 7.03 (1H, d, *J*=2 Hz, Ar–*H*); δ_C (200 MHz, $CDCl_3$) 56.0, 108.4, 111.6, 114.7, 119.8, 130.4, 136.6, 145.8, 147.1; *m*/*z* 151 (M^++1).

4.4.4. 2,6-Dimethoxy-4-vinylphenol (7). Yield: 84%, oil; δ_H (200 MHz, $CDCl_3$) 3.89 (3H, s, OCH_3), 5.10 (1H, dd, *J*=0.9 and 11.0 Hz, =CH_2), 5.51 (1H, s, O*H*), 5.63 (1H, dd, *J*=0.9 and 17.4 Hz, =CH_2); 6.52–6.67 (1H, dd, *J*=10.8 and 17.6 Hz,=C*H*), 6.63(2H, s, Ar–*H*), δ_C (200 MHz, $CDCl_3$) 56.3, 103.0, 111.8, 129.2, 134.8, 136.8, 147.0; *m*/*z* 180 (M^+).[8a]

4.4.5. 4-Vinylcatechol (9). Yield: 35%, solid; mp 51–53 °C (lit.[22] 50–53 °C); δ_H (200 MHz, $CDCl_3$) 4.92 (1H, dd, *J*=1.2 and 10.9 Hz, =CH_2), 5.41 (1H, dd, *J*=1.2 and 17.5 Hz,

=CH_2), 6.46 (1H, dd, J=10.9 and 17.5 Hz, =C*H*), 6.65–6.71 (2H, m, Ar–*H*), 6.81 (1H, d, J=1.2 Hz, Ar–*H*); δ_C (200 MHz, $CDCl_3$) 110.7, 112.7, 115.7, 118.7, 129.0, 137.0, 145.5, 145.8; *m/z* 136 (M^++1).

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