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Potassium Fluoride–Barium Oxide Catalysis in an Easy and Efficient Synthesis of Methysticin from Piperonal under Microwave Irradiation[1]

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Abstract—Condensation of compounds containing active methylene group with aromatic aldehyde (piperonal) in the presence of BaO on KF without a solvent under microwave irradiation is an efficient synthetic approach to methysticin and derivatives of kavalactones (4-methoxy-6-styryl-pyran-2-ones).

Keywords: Solid basic catalyst, 4-methoxy-6-methylpyran-2-one, piperonal, microwave irradiation, natural kavalactones derivatives, methysticin

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INTRODUCTION

2-Pyranones have natural analogues [1–3] that are characterized by a wide range of biological (cytotoxic, antifungal, neurotoxic, and anxiolytic) activities [4–8]. The structure of triacetic lactone (4-hydroxy-2*H*-pyran-2-one) is a pattern of inhibition of the protease-type 1 virus of Sida (PRVIH-1) [9–10]. The best known representative of this class of compounds is kava-lactone that displays various important pharmaceutical properties (sedative, sleeping pills, local anesthetic, analgesic, anti-inflammatory, anticonvulsant, anti-malarial, and anti-TB) [11–14].

Main components of rhizome of kava (Piper methysticum piperacea) [10] are methysticin (1.2%) (2*R*)-2-[(*E*)-2-(1,3-benzodioxol-5-yl)ethenyl]-4-methoxy-2,3-dihydropyran-6-one, dihydromethysticin (0.5%), Kavain (1.8%), and Yangonin (1%) (see figure). Methysticin was reported as a neuroactive and potentially hepato-toxic metabolite [15]. It is an efficient drug for gout and cystitis as well as a remedy against fatigue and pain [16]. Inhibiting effect of unsaturated γ-lactones on the central nervous system [17] initiated the studies of synthesis of these bioactive compounds [18–22].

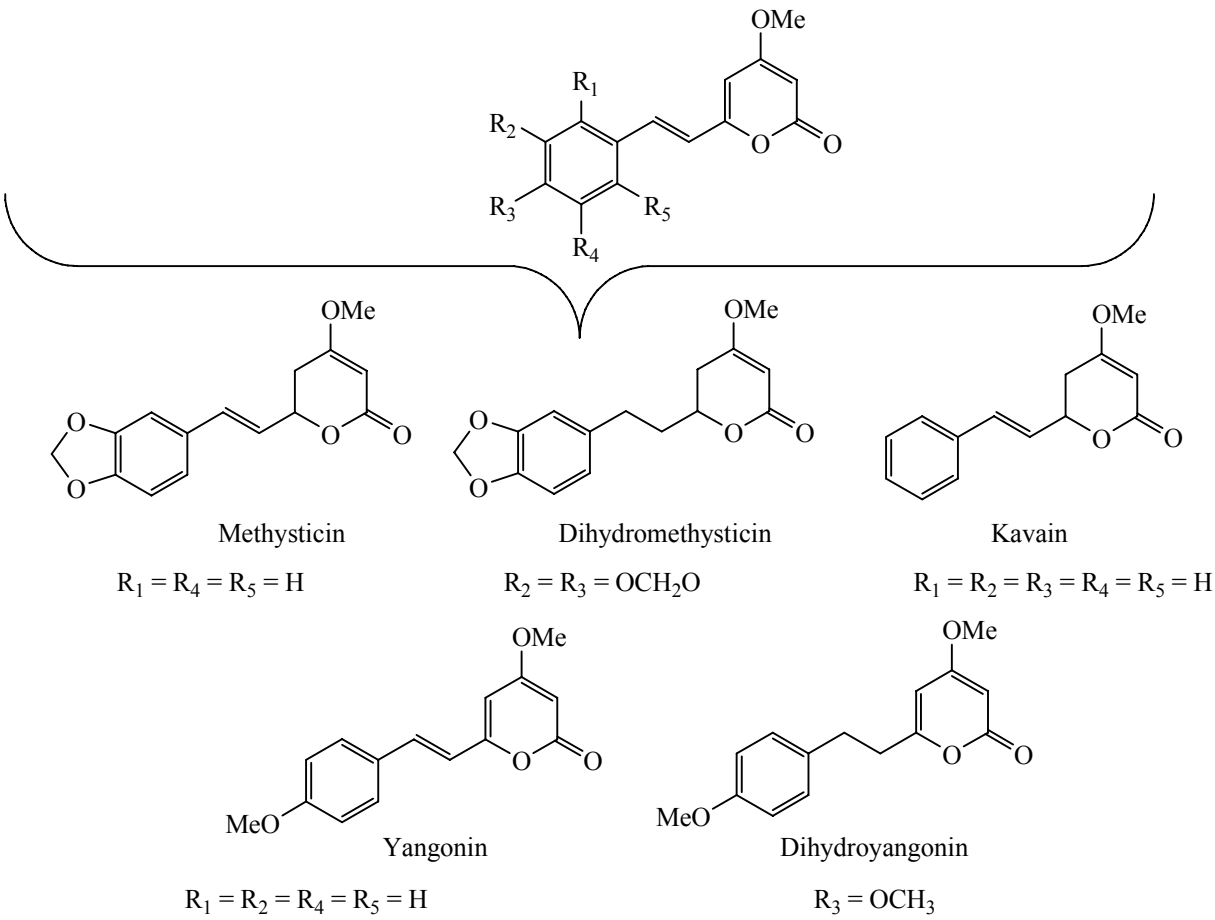
The current study is devoted to the synthesis of 6-{2-(benzo[*d*][1,3]dioxol-5-yl)ethenyl}-4-methoxy-2,3-dihydropyran-2-one (**IVa**) by condensation of aromatic aldehyde (piperonal) with 4-methoxy-6-methyl-2,3-dihydropyran-2-one (**III**) catalyzed by BaO–KF without a solvent under focused microwave irradiation (MWI) (Scheme 1).

RESULTS AND DISCUSSION

Basic solid catalysts are widely used in synthesis due to their high selectivity, environment friendliness and some other advantageous properties. KF is an efficient base applied in organic chemistry [23–26] and its activity can be intensified by coding it on inorganic oxides (BaO, CaO, MgO, Al_2O_3) [27]. In such case the system becomes hyperbasic and can deprotonate carbonic acids. The basic system BaO–KF can be used without an organic solvent. In our studies we used efficiently the approach in synthesis of kavalactones promoted by MWI.

Synthesis of 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**I**) was based on the method presented earlier [28–30]. The reaction of two equivalents of β-ketoester in the presence of Na_2CO_3 (Scheme 2) led to DHA (**I**) (yield 80%). The product was also available commercially.

[1] The text was submitted by the authors in English.

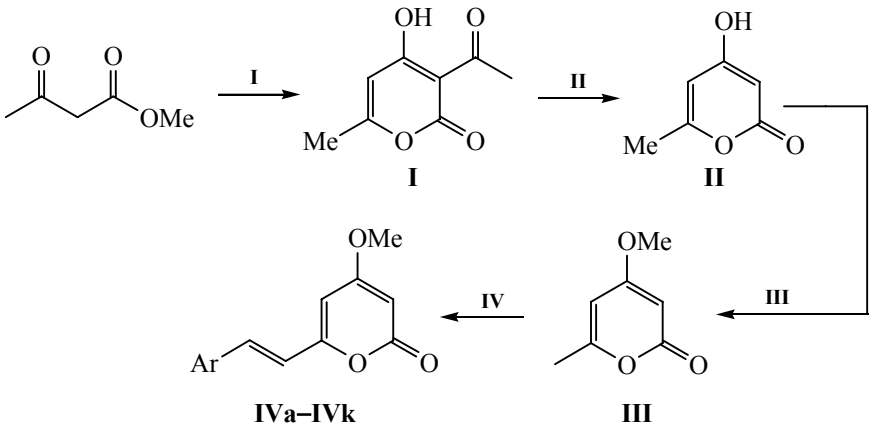


Lactones isolated from Piper methysticin.

Triacetic acid lactone [TAL] **II** was prepared by removal of the acetyl group (position 3) from dehydroacetic acid by heating in sulfuric acid (90%) [31–34] (Scheme 3) and identified by TLC, UV-Vis, IR, ^{1}H and ^{13}C NMR, and MS.

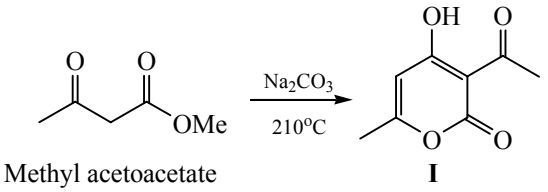
The method of methylation of the hydroxyl group developed by Smith [35] was used in the synthesis of the compound **III**. Refluxing of TAL **II** with dimethyl sulfate in the presence of K_2CO_3 (Scheme 4) gave the product **III** (yield 79 %).

Scheme 1.



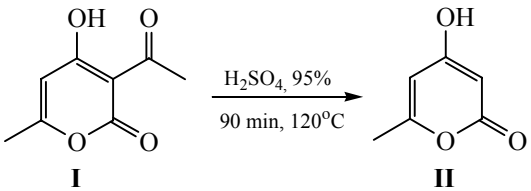
Na_2CO_3 (**I**), deacetylation (**II**), methylation (**III**), carbonyl compounds (**IV**).

Scheme 2.



Methyl acetoacetate **I**

Scheme 3.



I **II**

Contrary to the earlier methods of synthesis [35–38] that had been based on the corresponding reactions in solutions, our approach to 4-methoxy-6-styryl-2*H*-pyran-2-ones (**IVa–IVk**) was the coupling between the reagents under basic heterogenic catalysis (BaO–KF) and MWI (Scheme 5).

EXPERIMENTAL

MWI was carried out with a commercial microwave oven (Whirlpool WMC10007AW) at 2450 MHz with resonance cavity TEo13, joined to a MW generator MES 73-800. Progress of the reactions was monitored by TLC on commercial silica gel plates. Melting points were determined with a Kofler apparatus. IR spectra were recorded as KBr discs on JASCO FTIR-4100 spectrophotometer. UV-Vis spectra were recorded on a UV-Force of T60U spectrophotometer. NMR spectra were recorded on an Avance III 400 Brüker spectrometer at 293 K at 400 MHz with a solvent as an internal reference. High resolution mass spectra were recorded on an Orbitrap instrument using electrospray ionization (ESI).

Preparation of BaO–KF. BaO was added to a solution of KF dissolved in 100 mL of distilled water (molar ratio 3 : 1). The mixture was stirred for 24 h at room temperature. The suspension was washed twice with distilled water, centrifuged, washed with methanol, and re-centrifuged. The residue was dried for 24 h in vacuum and finely ground to produce a clear beige color powder.

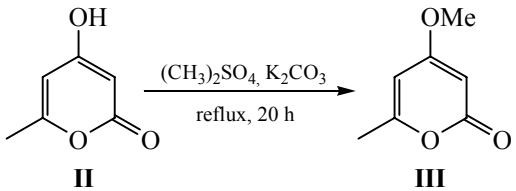
Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one [DHA] (I). 50 mL of methyl acetoacetate and 2 g of Na_2CO_3 were heated to 200°C for 8 h. In the course of the process 12.5 mL of distillate were collected at 72°C (methanol) while color of the reaction mixture turned dark brown. The resulting dehydroacetic acid was distilled under reduced pressure (140°C and 12 mmHg) and recrystallized from ethyl acetate.

4-Hyroxy-6-methyl-2*H*-pyran-2-one [TAL] (II). Dehydroacetic acid **I** (0.15 mol, 25.2 g) was dissolved in 50 mL of H_2SO_4 (95%). The mixture was heated at 120°C for 90 min. The reaction flask was rapidly cooled down and its content poured into ice-cold water. The solid residue was collected by filtration, washed with water and recrystallized from water.

4-Methoxy-6-methyl-2*H*-pyran-2-one (III). A 200 mL flask was loaded by 4-hydroxy-6-methyl-2*H*-pyran-2-one (20 mmol, 2.52 g), dimethyl sulfate (20 mmol, 2.52 g), K_2CO_3 (8 g), and butan-2-one (40 mL) and stirred at 90°C. Upon cooling down the reaction mixture was filtered and the solvent evaporated under reduced pressure in a rotary evaporator. The residue was refluxed for 20 h. The product was recrystallized from petroleum ether.

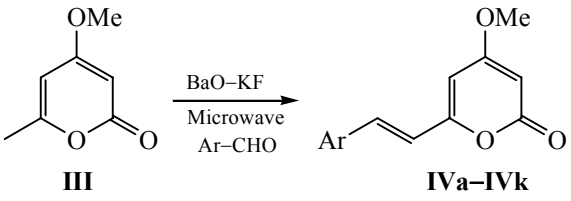
Synthesis of 4-methoxy-6-Styryl-2*H*-pyran-2-ones *(general procedure)*. Product **III** (5 mmol, 0.7 g) and KF–BaO (3 g) were added to the aromatic aldehyde (50 mmol) in minimum amount of methylene chloride. The solvent was evaporated at room temperature under reduced pressure and the process was activated by MWI in a microwave oven at 60 W for 5 min. The product was acidified with HCl, 20% (2 mmol). The residue was dissolved in 10 mL of CH_2Cl_2 and filtered off. The organic phase was washed

Scheme 4.



II **III**

Scheme 5.



III **IVa–IVk**

with saturated NaCl solution and dried over $MgSO_4$. The solid product was recrystallized from ethanol (0.5 g).

3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one [DHA] (I). White solid recrystallized from ethyl acetate, yield 80%, mp 108–110°C ([27]). IR spectrum, ν, cm^{-1}: 1710 ($\nu_{C=O}$, cycle), 1610 ($\nu_{C=O}$), 1570 ($\nu_{C=C}$), 1186 (ν_{OCO}). TLC (pentane : ethyl acetate = 80 : 20). UV-Vis (EtOH), λ, nm (log ε): 303 (3.23), 228 (3.27). ^1H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 2.66 s (3H, CH_3), 5.92 s (CH). ^{13}C NMR spectrum, δ, ppm: 20.71, 29.97, 99.94, 101.19, 161.17, 169.40, 181.24, 205.25. MS, *m/z*, %: 169 [M^+, 100]. $C_8H_8O_4$. *M* 168.15 g/mol.

4-Hyroxy-6-methyl-2*H*-pyran-2-one [TAL] (II). White solid recrystallized from water, yield 85%, mp 186–188°C ([27]). IR spectrum, ν, cm^{-1}: 3320 (ν_{OH}), 1721 ($\nu_{C=O}$), 1626 ($\nu_{C=C}$), 1540, 1303, 1250 (ν_{COC}), 870, 813. TLC (pentane : ethyl acetate = 80 : 20). UV-Vis (EtOH), λ, nm (log ε): 390 (3.38), 278 (3.45), 215 (3.30). ^1H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 5.21 s (H^3), 5.95 s (H^5). ^{13}C NMR spectrum, δ, ppm: 19.58, 88.30, 100.32, 163.42, 164.07, 170.70. MS, *m/z*, %: 126 [M^+, 33]. $C_6H_6O_3$. *M* 126.12 g/mol.

4-Methoxy-6-methyl-2*H*-pyran-2-one (III). Yellow solid recrystallized from ether, yield 79%, mp 86°C ([39]). IR spectrum, ν, cm^{-1}: 1731, 1718 ($\nu_{C=O}$), 1646 ($\nu_{C=C}$), 1462, 1401, 1145 (ν_{COC}), 940, 542. TLC (pentane : ethyl acetate = 80 : 20). ^1H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 3.79 s (3H, CH_3O), 5.40 d (H^3), 5.77 d (H^5). ^{13}C NMR spectrum, δ, ppm: 19.74, 55.73, 87.27, 100.28, 161.88, 164.98, 171.24. MS, *m/z*, %: 140 [M^+, 53], 132 (8.6), 125 (47), 113 (8), 112 (100), 69 (36), 59 (25), 53 (30), 43 (45). $C_7H_8O_3$. *M* 140.15 g/mol.

6-{2-(Benzo[*d*][1,3]dioxol-5-yl)ethenyl}-4-methoxy-2*H*-pyran-2-one (IVa) synthesized from piperonal (5 mmol, 0.75 g), MW power 60 W, time 6 min. The yellow solid product was recrystallized from methanol, yield 93%, mp 238°C. IR spectrum, ν, cm^{-1}: 3076, 1720 ($\nu_{C=O}$), 1634 ($\nu_{C=C}$), 1608, 1553, 1496, 1450, 1412, 1258, 962, 924, 810, 684. ^1H NMR spectrum, δ, ppm: 3.80 s (3H, OCH_3), 5.46 d (H^3), 5.89 d (H^5), 5.97 s (2H, OCH_2O), 6.42 d (H^7), 6.81 d (H^2_{arom}), 6.99 d (H^6_{arom}), 7.41 d (H^8). ^{13}C NMR spectrum, δ, ppm: 55.86, 88.50, 100.68, 101.44, 105.91, 108.63, 116.82, 123.52, 129.15, 133.62, 148.30, 148.90, 158.80, 164.04, 171. MS *m/z*, %: 274 (42), 273 (100), 272 [M^+, 58], 201 (16), 190 (20), 197 (12), 195 (14), 185 (10), 183 (15), 181 (13), 179 (19), 165 (8), 148 (14), 77 (19), 69 (22), 57 (24), 43 (15). $C_{15}H_{12}O_5$. *M* 272.16 g/mol.

6-(4-Chlorostyryl)-4-methoxy-2*H*-pyran-2-one (IVb) synthesized from parachlorobenzaldehyde (5 mmol, 0.7 g), MW power 40 W, time 7 min. The yellow solid product was recrystallized from methanol, yield 82%, mp 144°C ([40]). IR spectrum, ν, cm^{-1}: 1720 ($\nu_{C=O}$), 1648, 1554, 1256. ^1H NMR spectrum, δ, ppm: 3.83 s (3H), 5.50 d, 5.95 d, 6.55 d, 7.32–7.48 m (5H), ^{13}C NMR spectrum, δ, ppm: 55.91, 89.06, 101.73, 119.18, 128.51, 129.10, 133.74, 134.37, 135.22, 158.26, 163.89, 170.9. MS *m/z*, %: 262 [M^+]. $C_{14}H_{11}ClO_3$. *M* 262.04 g/mol.

6-(4-Methoxystyryl)-4-methoxy-2*H*-pyran-2-one (IVc) synthesized from paramethoxybenzaldehyde (5 mmol, 0.675 g), MW power 40W, time 10 min. The yellow solid product was recrystallized from methanol, yield 86%, mp 157°C ([41]). IR spectrum, ν, cm^{-1}: 2840 [ν(CH, OCH_3)], 1728 ($\nu_{C=O}$), 1645, 1607, 1576, 1512, 1456, 1251, 1158, 1003, 833, 676. ^1H NMR spectrum, δ, ppm: 3.83 s (3H, OCH_3), 3.85 s (3H, OCH_3), 5.49 d (H^3), 5.89 d (H^5), 6.46 d (H^7), 6.72 d (2H, H_{arom}), 7.44–7.49 m (3H, H_{arom}). ^{13}C NMR spectrum, δ, ppm: 55.30, 55.88, 88.35, 100.41, 114.36, 116.40, 127.89, 129.9, 135.37, 159.12, 160.77, 164.15, 171.22. MS *m/z*, %: 259 (6), 258 [M^+, 20], 254 (45), 253 (100), 226 (9), 225 (26), 211 (12), 198 (12), 187 (45), 184 (34), 183 (45), 169 (5), 158 (10), 115 (11), 89 (5), 77 (8), 69 (7). $C_{15}H_{14}O_4$. *M* 228.28 g/mol.

6-[2-(3,4-Dimethoxyphenyl)ethenyl]-4-methoxy-2*H*-pyran-2-one (IVd) synthesized from 3,4-dimethoxybenzaldehyde (5 mmol, 0.8 g), MW power 40 W, time 10 min. The yellow solid product was recrystallized from methanol, yield 79%, mp 162–163°C. IR spectrum, ν, cm^{-1}: 2848 [ν(CH, OCH_3)], 1718 ($\nu_{C=O}$), 1551, 1412, 1251, 1053, 843, 687. ^1H NMR spectrum, δ, ppm: 3.79 s (3H, OCH_3-C_4), 3.88 s (3H, OCH_3-C_{12}), 3.90 s (3H, OCH_3-C_{11}), 5.44 d (H^3), 5.88 d (H^5), 6.43 d (H^7), 6.84 d (H^{13}), 7.00 d (H^{10}), 7.05 d (H^{14}), 7.42 d (H^8). ^{13}C NMR spectrum, δ, ppm: 55.80, 55.90, 88.40, 100.50, 109.30, 111.20, 116.50, 121.6, 128.2, 135.60, 149.2, 150.4, 158.90, 164.1, 171.2. MS, *m/z*, %: 288 [M^+]. $C_{16}H_{16}O_5$. *M* 288.29 g/mol.

6-[2-(3,4,5-Trimethoxyphenyl)ethenyl]-4-methoxy-2*H*-pyran-2-one (IVe) synthesized from 3,4,5-trimethoxybenzaldehyde (5 mmol, 0.975 g), MW power 40 W, time 10 min. The yellow solid product was recrystallized from ethyl acetate, yield 90%, mp 201°C. IR spectrum, ν, cm^{-1}: 2838 [ν(CH, OCH_3)],

1704 ($\nu_{C=O}$), 1640, 1580, 1548, 1507, 1449, 1403, 1250, 1146, 990, 837, 812. ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H, OCH_3), 3.88 s (3H, OCH_3), 3.90 s (6H, OCH_3), 5.49 d (H^3); 5.95 d (H^5), 6.49 d (H^7), 6.76 s (2H, $H^{2,6}{}_{arom}$), 7.43 d (H^8). MS *m/z*, %: 318 [M^+, 63.9], 333 (2.9), 275 (9.5), 259 (8.6), 247 (5.3), 243 (6.8), 198 (6.8), 181 (3.8), 149 (27.1), 123 (11.3), 121 (9.6), 112 (14.7), 69 (100), 65 (47.1). $C_{17}H_{18}O_6$. *M* 318.32 g/mol.

6-(4-Bromostyryl)-4-methoxy-2*H*-pyran-2-one (IVf) synthesized from parabromobenzaldehyde (5 mmol, 0.925 g), MW power 60 W, time 8 min. The white solid product was recrystallized from methanol, yield 76%, mp155°C. IR spectrum, ν, cm^{-1}: 1727 ($\nu_{C=O}$), 1644, 1559, 1250, 1155. ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H), 5.50 d, 5.95 d, 6.56 d, 7.35 d (2H), 7.42 d, 7.50 d (2H). ^{13}C NMR spectrum, δ, ppm: 56.04, 89.15, 101.9, 119.4, 123.7, 129, 132, 139.8, 134.6, 158.4, 164, 171.5. MS *m/z*, %: 306 [M^+]. $C_{14}H_{11}BrO_3$. *M* 305.98 g/mol.

6-(4-Fluorostyryl)-4-methoxy-2*H*-pyran-2-one (IVg) synthesized from parafluorobenzaldehyde (5 mmol, 0.625 g), MW power 60 W, time 10 min. The white solid product was recrystallized from methanol, yield 82%, mp 137°C. IR spectrum, ν, cm^{-1}: 1724, 1566, 1245, 1163. ^{1}H NMR spectrum, δ, ppm: 3.80 s (3H), 5.55 d, 5.92 d, 6.43 d, 7.09 t (2H), 7.42–7.52 m (3H). ^{13}C NMR spectrum, δ, ppm: 55.7, 88.1, 101.6, 116.0, 118.5, 129.3, 131.6, 134.9, 159.1, 162.8, 164.2, 172. MS, *m/z*, %: 246 [M^+]. $C_{14}H_{11}FO_3$. *M* 246.069 g/mol.

6-(4-Nitrostyryl)-4-methoxy-2*H*-pyran-2-one (IVh) synthesized from paranitrobenzaldehyde (5 mmol, 0.75 g), MW power 60 W, time 8 min. The orange solid was recrystallized from methanol, yield 78%, mp 212°C ([40]). IR spectrum, ν, cm^{-1}: 3077, 1690, 1606, 1587, 1549, 1510, 1444, 1333, 1250, 1150, 949, 806. ^{1}H NMR spectrum, δ, ppm: 3.84 s (3H, OCH_3), 5.54 d (H^3), 6.03 d (H^5), 6.70 d (H^7), 7.51 d (H^8), 7.62 d (2H, H^{10}), 8.23 d (2H, H^{11}). ^{13}C NMR spectrum, δ, ppm: 55.1, 89.9, 103.3, 122.6, 124.2, 127.9, 132.9, 141.4,147.8, 157.3, 163.4, 170.6. MS, *m/z*, %: 273 [M^+]. $C_{14}H_{11}NO_5$. *M* 273.06 g/mol.

6-[2-(2-Furyl)ethenyl]-4-methoxy-2*H*-pyran-2-one (IVi) synthesized from furfural (5 mmol, 0.475 g), MW power 40 W, time 12 min. The yellow solid product was recrystallized from MeOH, yield 89%, mp 180°C ([42]). IR spectrum, ν, cm^{-1}: 3179, 1700 ($\nu_{C=O}$), 1634, 1562, 1544, 1450, 1149, 1010, 946, 778. ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H, OCH_3), 5.46 d (H^3), 5.92 d (H^5), 6.44–6.54 m (2H, H_{furyl}), 6.47 d (H^7), 7.26 d (H^8), 7.41–7.47 m (H_{furyl}). ^{13}C NMR spectrum, δ, ppm: 55.86 (OCH_3), 88.69 (C_3), 101.23 (C_5), 112.30 ($C^3{}_{furanyl}$),113.33 ($C^4{}_{furanyl}$), 116.59 (C^7) 122, 59 (C^8), 143.96 ($C^5{}_{furanyl}$), 151.64 ($C^2{}_{furanyl}$), 158.46 (C^6), 163.88 (C^2), 171.33 (C^4). $C_{12}H_{10}O_4$. *M* 218.21 g/mol.

6-[2-(2-Thienyl)ethenyl]-4-methoxy-2*H*-pyran-2-one (IVj) synthesized from thiophene-2 carboxaldehyde (5 mmol, 0.55 g), MW power 60 W, time 9 min. The yellow solid product was recrystallized from methanol, yield 82%, mp 183°C. IR spectrum, ν, cm^{-1}: 3074, 1724 ($\nu_{C=O}$), 1634 ($\nu_{C=C}$), 1604, 1452, 1406, 1152, 1000, 958, 832. ^{1}H NMR spectrum, δ, ppm: 3.82 s (3H, OCH_3), 5.47 d (H^3), 5.90 d (H^5), 6.37 d (H^7), 7.04 d ($H^4{}_{arom}$), 7.18 d ($H^3{}_{arom}$), 7.32 d (H^5), 7.61 d (H^8). ^{13}C NMR spectrum, δ, ppm: 55.88, 88.67, 100.93, 117.7, 27.16, 128.12, 128.55, 129.53, 140.62, 158.29, 163.81, 171.4. MS, *m/z*, %: 234 [M^+, 98]. $C_{12}H_{10}O_3S$. *M* 234.27 g/mol.

4-Methoxy-6-styryl-2*H*-pyran-2-one (IVk) synthesized from benzaldehyde (5 mmol, 0.525 g), MW power 40 W, time 9 min. The yellow solid product was recrystallized from methanol, yield 88%, mp 136°C [43]. IR spectrum, ν, cm^{-1}: 3076, 1722 ($\nu_{C=O}$), 1639, 1549, 1446, 1251, 1154, 1006, 831, 686. ^{1}H NMR spectrum, δ, ppm: 3.56 s (3H, OCH_3), 5.51 d (H^3), 5.96 d (H^5), 6.61 d (H^7), 7.31–7.41 m ($3H_{arom}$), 7.47–7.51 d ($2H_{arom}$), 7.50 d (H^8). ^{13}C NMR spectrum, δ: 55.83, 88.76, 101.23, 118.60, 127.25, 128.87, 129.33, 135.22, 135.77, 158.54, 163.98, 171.21. MS, *m/z*, %: 229 (17), 228 [M^+, 98], 211 (6), 210 (7), 200 (16), 199 (67), 198 (24), 183 (19), 182 (68), 168 (14), 167 (20), 157 (10), 141 (10), 115 (20). $C_{14}H_{12}O_3$. *M* 228.25 g/mol.

CONCLUSIONS

The general method of synthesis of methysticin from piper methisticum and dehydroacetic acid (DHA) based on the Knoevenagel reaction under basic heterogeneous conditions without a solvent initiated by microwave irradiation is developed. The method involves KF–BaO catalysis which is highly efficient and makes the process much more rapid than classical methods.

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