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An Efficient and Green Synthesis of Flavones Using Natural Organic Acids as Promoter Under Solvent-free Condition

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Abstract: An efficient and eco-friendly synthesis of flavones, promoted by naturally occurring acids, *via* cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones using conventional and microwave heating under solvent-free condition is described.

Keywords: Flavones, naturally occurring acids, eco-friendly promoter, solvent-free synthesis.

INTRODUCTION

In recent years, demands for eco-friendly synthesis have been increased immensely due to the growing concerns regarding environmental pollution. Green chemistry is playing an important role in minimizing environmental pollution through elimination (or at least minimization) of waste, use of sustainable procedures, nontoxic chemicals, renewable materials and solvent-free reaction condition [1-4]. Chemical synthesis under solvent-free conditions has emerged as a powerful eco-friendly technique in recent years because it reduces the toxic waste by avoiding solvents. Solvent-free reactions are superior over reactions in solvents because their simplicity, high yields and short reaction times. Different types of acid catalysts are used in organic synthesis which generate toxic wastes that are harmful to the environment. The growing demand for clean and efficient chemical synthesis under solvent-free conditions, which when coupled with naturally occurring acids as green catalyst and microwave irradiation, provides a green approach required for both economical and environmental perspectives.

Naturally occurring organic acids can be used as green catalyst in organic reactions as they are nontoxic, readily and cheaply available in nature. There are few reports on the application of natural organic acids in the organic synthesis [5-7].

Recently, we have reported citric acid and several other naturally occurring organic acids as highly efficient and eco-friendly promoters for the Beckmann rearrangement under solvent-free conditions [8, 9]. This result provoked us to evaluate the potential of these naturally occurring organic acids in the synthesis of flavones by the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones. For this purpose, we selected seven naturally occurring organic acids *viz.* citric, oxalic, tartaric, malic, succinic, malonic and fumaric acid (Fig. 1) as green catalysts.

Flavonoids are present profusely in plants of the families Leguminosae, Compositae, and Moraceae (Fig. 2). They display a broad spectrum of biological activities [10] like, antibacterial [11], antioxidant and estrogen receptor modulator [12], and anti-inflammatory activity [13]. The thioflavanone derivatives have been used in the synthesis of biologically active compounds such as benzothiazepine and thiochroman-4-one [14]. One of the most commonly used methods for the synthesis of flavones is the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones. Many of these procedures use strong acids as a catalyst such as H_2SO_4 [15-16], HCl [17], HBr, or HI [18].

However, all the above reported methods suffer from certain drawbacks such as the use of toxic/costly solvents, expensive reagents, and production of considerable amount of byproducts, long reaction time and low yields. Herein, we report a simple and highly efficient synthesis of flavones by the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones using citric, oxalic, tartaric, malic, succinic, malonic and fumaric acid as green promoters under solvent-free condition by thermal and microwave irradiation.

RESULTS AND DISCUSSION

For screening of the catalysts, cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione **1a** was selected as a model reaction. Initially, **1a** (0.5 g) (Table **1**, entry 1) and citric acid (1.0 eq.), were heated either in an oil bath, preheated at 160 °C for 15 min or in microwave reactor for 5 min to yield flavone **2a** (92% and 94% respectively) (Table **1**, entry 1). The results with other organic acids indicate that all the acids act as an effective promoter to deliver flavones **2a** in good to excellent yields (Table **1**, entry 2-7). Microwave

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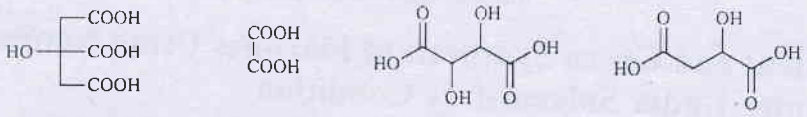
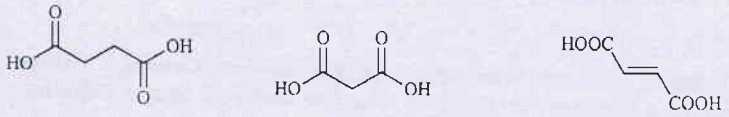


Citric Acid **Oxalic Acid** **Tartaric Acid** **Malic Acid**



Succinic Acid **Malonic Acid** **Fumaric Acid**

Fig. (1). Naturally occurring organic acids.

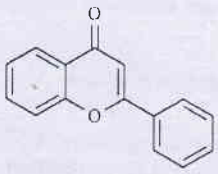


Fig. (2). Flavone backbone.

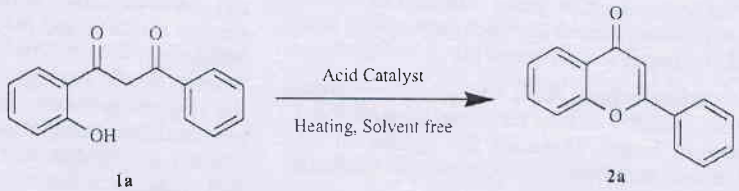
irradiation reduces time (5 min) and improves the yields as compared to conventional heating. In this screening study citric (Table **1**, entry 1), malonic (Table **1**, entry 4), oxalic (Table **1**, entry 5) and tartaric acid (Table **1**, entry 7) turned out to be better catalysts than fumaric (Table **1**, entry 2) and succinic acid (Table **1**, entry 6), whereas best results were obtained by using malic acid (Table **1**, entry 3).

Next, malic acid was used as a catalyst to test the scope and generality of the above methodology. While using less than one mole equivalent of the acid, yield of the product was reduced considerably with maximum recovery of starting material, even after continuing the reaction for longer time. This result suggests that one mole equivalent of malic acid is essential for the completion of the reaction. Then cyclodehydration of various 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones was tested under the above reaction condition. Results showed that the cyclodehydration of various 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones proceeded smoothly to completion within a short reaction time to give the corresponding flavones in good to excellent yields under both heating conditions (Table **2**, entry 1-14).

CONCLUSION

In conclusion, we have shown that the naturally occurring acids like citric, oxalic, tartaric, malic, succinic, malonic and fumaric acid can be used as an environment-friendly acid promoters in the synthesis of flavones *via* the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones under solvent-free condition. Malic acid showed superior

Table 1. Screening of catalysts in the synthesis of flavone 2a from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione 1a under solvent-free condition.[a]

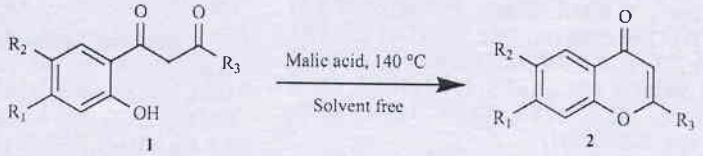


1a **2a**

Entry	Acid	Temp. (°C)[b]	Conventional Heating		Microwave Heating	
			Time (Min)	Yield[c] (%)	Time (Min)	Yield[c] (%)
1	Citric	160	15	92	5	94
2	Fumaric	290	30	60	5	85
3	Malic	140	10	94	5	96
4	Malonic	140	20	88	5	93
5	Oxalic	110	10	91	5	94
6	Succinic	190	30	65	5	81
7	Tartaric	180	20	89	5	92

[a]Reagents: 1a (0.5g), acid (1.0 eq.). [b]Heating was done in preheated oil bath or in microwave reactor. [c]Isolated yields.

Table 2. Malic acid promoted the synthesis of flavones from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione under solvent-free condition.[a]



1 2

Entry	R_1	R_2	R_3	Conventional Heating[b] (%) Yield[d,e]	Microwave Heating[c] (%) Yield[d,e]
1	H	H	Ph	94	96
2	H	H	*p*-$MeOC_6H_4$	94	96
3	H	H	*p*-FC_6H_4	87	90
4	H	H	*m*-$CF_3C_6H_4$	83	88
5	OMe	H	*m*-$CF_3C_6H_4$	88	91
6	OMe	H	Ph	89	92
7	OMe	H	*p*-$MeOC_6H_4$	89	94
8	H	OMe	Ph	94	92
9	H	OMe	*p*-$MeOC_6H_4$	94	95
10	OMe	H	*p*-FC_6H_4	94	94
11	H	F	Ph	86	95
12	H	Cl	Ph	96	92
13	H	H	Cyclohexyl	87	88
14	OMe	H	Cyclohexyl	86	89

[a]Reagents : 1 (0.5g), Malic acid (1.0 eq.). [b]10 min. in preheated oil bath. [c]5 min. in microwave reactor. [d]Isolated yields. [e]All the products were identified spectroscopically (IR, ^1H, ^{13}C NMR and LCMS)

reactivity under conventional as well as microwave irradiation conditions. Further, results indicated that microwave irradiation reduced reaction time and gave slightly higher yields against conventional heating. The operational simplicity, use of commercially available, biodegradable and renewable natural catalysts, solvent-free reaction condition, short reaction time, simple work up and high yields make these promoters a more convenient alternative to the reported catalysts. The application of this protocol to other synthetic reactions is under investigation.

EXPERIMENTAL SECTION

Reactions were performed in oven-dried glassware and were monitored by TLC silica gel plates (60 F254) which were visualized by UV and KMnO4 solution. All solvents and reagents were used as obtained from commercial source. Melting points (m. p., uncorrected) were determined in open capillary tubes using paraffin oil bath. All the microwave-assisted reactions were performed in Discover Lab Met microwave system (CEM Corporation, USA) at the specified temperature using the standard mode of operation. The 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones were prepared by standard methods and their purities were established before utilization by melting point. Standard ^1H NMR and ^{13}C NMR were recorded on a Varian Mercury spectrometer at 300 and 75 MHz respectively in $CDCl_3$ solution and with TMS as an internal standard. IR spectra were recorded on Perkin Elmer Model 1600 series FTIR instrument. Mass spectra were recorded on Agilent 1200SL-6100 LC/MS (ES-API) instrument. All the compounds synthesized have been previously reported, the physical and spectroscopic data are in agreement with reported values.

General Procedure

The mixture of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione **1a** (0.5 g) and malic acid (1.0 eq.) was heated either in an oil bath, preheated at 140 °C for 10 min or in a microwave reactor for 5 min. After the completion of reaction (TLC check), the reaction mixture was allowed to cool; at room temperature water (10 mL) and ethyl acetate (10 mL) were added. Reaction mixture was neutralized by addition of solid $NaHCO_3$. Organic layer was separated and the aqueous layer was extracted in ethyl acetate (2 × 10 mL). Combined organic extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane-ethylacetate solvent system to give the corresponding flavones in high yield.

2-Phenyl-chromen-4-one (Table **2**, entry 1): M.p. 96-97 °C (lit. [19] m.p. 96-97 °C); IR (KBr) $\bar{\upsilon}$: 1645, 1604, 1568, 1130, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.21 (d, J = 7.2 Hz, 1H), 7.91-7.88 (m, 2H), 7.70-7.65 (m, 1H), 7.55-7.46 (m, 4H), 7.39 (t, J = 7.8 Hz, 1H), 6.81 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.3, 163.3, 156.1, 133.7, 131.6, 131.5, 128.9, 126.1, 125.5, 125.1, 123.7, 117.9, 107.3; LCMS (ES-API) m/z: 223 $(M+H)^+$.

2-(4-Methoxy-phenyl)-chromen-4-one (Table **2**, entry 2): M.p. 157-158 °C (lit. [19] m.p. 157-158 °C); IR (KBr) $\bar{\upsilon}$: 1649, 1608, 1465, 1133, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.21 (dd, J = 8.1 & 2.1 Hz, 1H), 7.90-7.80 (m, 2H), 7.70-7.65 (m, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.03-6.99 (m, 2H), 6.80 (s, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.5, 163.5, 162.4, 156.1, 133.6, 127.9, 125.6, 125.1, 123.9, 123.7, 117.9, 114.4, 105.9, 55.4; LCMS (ES-API) m/z: 253 $(M+H)^+$.

2-(4-Fluoro-phenyl)-chromen-4-one (Table **2**, entry 3): M.p. 148-150 °C (lit. [20] m.p. 134-135 °C); IR (KBr) $\bar{\upsilon}$: 1663, 1608, 1574, 1467, 1234, 1134, 869, 806, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.24 (d, J = 7. 2 Hz, 1H), 7.94 (m, 2H), 7.72 (m, 1H), 7.58 (d, J = 7.1 Hz, 1H), 7. 47 (t, J = 7. 1 Hz, 1H), 7.23 (m, 2H), 6.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.1, 162.6, 156.0, 134.2, 128.1, 127.1, 126.0, 125.5, 123.9, 118.5, 117.0, 116.6, 107.1; LCMS (ES-API) m/z: 241 $(M+H)^+$.

2-(3-Trifluoromethyl-phenyl)-chromen-4-one (Table **2**, entry 4): M.p. 146-147 °C (lit. [21] m.p. 146-147 °C); IR (KBr) $\bar{\upsilon}$: 1664, 1610, 1582, 1571, 1439, 376, 1293, 879, 802, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.22 (2H, m), 8.09 (d, J = 7.8 Hz, 1H), 7.82-7.60 (m, 4H), 7.45 (t, J = 7. 5 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.1, 161.5, 156.1, 134.0, 132.5, 131.8, 129.6, 129.3, 128.0, 125.6, 125.4, 123.7, 123.0, 118.1, 108.2; LCMS (ES-API) m/z: 291 $(M+H)^+$.

7-Methoxy-2-(3-trifluoromethyl-phenyl)-chromen-4-one (Table **2**, entry 5): M.p. 166-167 °C (lit. [21] m.p. 142-143 °C); IR (KBr) $\bar{\upsilon}$: 1737, 1639, 1577, 1487, 1467, 1163, 1133, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.17 (s, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 8.1 Hz, 1H), 7.55 (m, 2H), 7.30 (m, 1H), 6.84 (s, 1H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.9, 161.2, 157.2, 150.9, 132.7, 129.6, 129.2, 127.9, 127.8, 124.5, 124.1, 123.0, 122.5, 119.5, 107.5, 104.8, 55.9; LCMS (ES-API) m/z: 321 $(M+H)^+$.

7-Methoxy-2-phenyl-chromen-4-one (Table **2**, entry 6): M.p. 109-110 °C (lit. [22] m.p. 105-106 °C); IR (KBr) $\bar{\upsilon}$: 1647, 1626, 1606, 1450, 1163, 908, 767 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, J = 8.7 Hz, 1H), 7.88 (m, 2H), 7.51 (m, 3H), 6.95 (m, 2H), 6.77 (s, 1H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 177.7, 164.1, 162.9, 157.8, 131.6, 131.4, 128.9, 126.9, 126.0, 117.6, 114.9, 107.3, 100.3, 55.8; LCMS (ES-API) m/z: 253 $(M+H)^+$.

7-Methoxy-2-(4-methoxy-phenyl)-chromen-4-one (Table **2**, entry 7): M.p. 194-195 °C (lit. [20] m.p. 180.5 °C); IR (KBr) $\bar{\upsilon}$: 1629, 1593, 1516, 1379, 1260, 1186, 977, 862 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 6.95-6.86 (m, 4H), 6.60 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.6, 163.9, 162.8, 162.1, 157.7, 127.6, 126.7, 123.8, 117.6, 114.2, 114.0, 105.9, 100.2, 55.7, 55.3; LCMS (ES-API) m/z: 283 $(M+H)^+$.

6-Methoxy-2-phenyl-chromen-4-one (Table **2**, entry 8): M.p. 160-161 °C (lit. [22] m.p. 165-167 °C); IR (KBr) $\bar{\upsilon}$: 1641, 1618, 1488, 1361, 1255, 1030, 846, 658 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.91-7.88 (m, 2H), 7.57 (d, J = 2.7 Hz, 1H), 7.51-7.46 (m, 4H), 7.28 (dd, J = 6.7 & J = 3.5 Hz, 1H), 6.79 (s, 1H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.2, 163.0, 156.9, 150.8, 131.7, 131.4, 128.8, 126.1, 124.4, 123.6, 119.4, 106.7, 104.7, 55.8; LCMS (ES-API) m/z: 253 $(M+H)^+$.

6-Methoxy-2-(4-methoxy-phenyl)-chromen-4-one (Table **2**, entry 9): M.p. 195-196 (lit. [19] m.p. 194-195 °C); IR (KBr) $\bar{\upsilon}$: 1647, 1607, 1584, 1454, 1268, 1196, 1014, 817, 558 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 3.0 Hz, 1H), 7.27 (m, 1H), 7.01 (d, J = 9.0 Hz, 2H), 6.73 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.2, 163.1, 162.3, 156.8, 150.9, 127.8, 124.4, 124.1, 123.5, 119.3, 114.4, 105.4, 104.8, 55.9, 55.4; LCMS (ES-API) m/z: 283 $(M+H)^+$.

7-Methoxy-2-(4-fluoro-phenyl)-chromen-4-one (Table **2**, entry 10): M.p. 172-173 °C (lit. [20] m.p. 172-173 °C); IR (KBr) $\bar{\upsilon}$: 1660, 1631, 1608, 1577, 1456, 1419, 1514, 1294, 1163, 1022, 923, 841, 781 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.90 (m, 2H), 7.89 (m, 1H), 7.15 (t, J = 8.7 Hz, 2H), 6.64 (s, 1H), 6.48-6.41 (m, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.8, 165.9, 165.3, 130.1, 129.9, 128.9, 128.9, 116.0, 115.7, 112.4, 110.0, 108.0, 101.3, 55.6; $C_{16}H_{11}FO_3$; LCMS (ES-API) m/z: 271 $(M+H)^+$.

6-Fluoro-2-phenyl-chromen-4-one (lit. [23]) (Table **2**, entry 11): M.p. 128-129 °C; IR (KBr) $\bar{\upsilon}$: 1660, 1624, 1570, 1359, 1176, 835, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.93-7.85 (m, 3H), 7.61-7.50 (m, 4H), 7.46-7.39 (m, 1H), 6.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.5, 163.1, 152.3, 131.7, 131.3, 129.0, 126.2, 122.0, 121.7, 120.2, 120.0, 110.7, 106.7; LCMS (ES-API) m/z: 241 $(M+H)^+$.

6-Chloro-2-phenyl-chromen-4-one (Table **2**, entry 12): M.p. 183-184 °C (lit. [24] m.p. 185-186 °C); IR (KBr) $\bar{\upsilon}$: 1651, 1601, 1567, 1457, 1438, 1307, 1132, 908, 682 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, J = 2.3 Hz, 1H), 7.90-7.88 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.50 (m, 4H), 6.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.1, 163.7, 154.4, 133.0, 131.8, 131.2, 131.1, 129.1, 126.3, 125.1, 124.7, 119.7, 107.3; LCMS (ES-API) m/z: 257 $(M+H)^+$.

2-Cyclohexyl-chromen-4-one (Table **2**, entry 13): M.p. 127-129 °C (lit. [22] colorless oil); IR (KBr) $\bar{\upsilon}$: 1736, 1676, 1606, 1580, 1469, 1024, 844, 758, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (m, 1H), 7.64 (m, 1H), 7.39 (m, 2H), 6.17 (s, 1H), 2.52 (m, 1H), 2.11-1.20 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.6, 173.4, 156.4, 133.3, 125.5, 124.7, 123.7, 117.7, 107.8, 42.7, 30.3, 25.7, 25.6; LCMS (ES-API) m/z: 229 $(M+H)^+$.

7-methoxy-2-Cyclohexyl-chromen-4-one (lit. [25]) (Table **2**, entry 14): M.p. 152-154 °C; IR (KBr) $\bar{\upsilon}$: 1641, 1606, 1572, 1502, 1442, 1384, 1238, 1026, 923, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, J = 8.7 Hz, 1H), 6.95-6.83 (m, 2H), 6.09 (s, 1H), 3.88 (s, 3H), 2.47 (m, 1H), 1.86 (m, 5H), 1.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.9,

172.7, 163.7, 158.0, 126.7, 117.5, 113.9, 107.5, 99.9, 55.6, 42.5, 30.3, 25.7, 25.6; LCMS (ES-API) m/z: 259 $(M+H)^+$.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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