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NATURAL ORGANIC ACIDS PROMOTED GREEN AND EXPEDITIOUS SYNTHESIS OF COUMARINS UNDER SOLVENT FREE CONDITION

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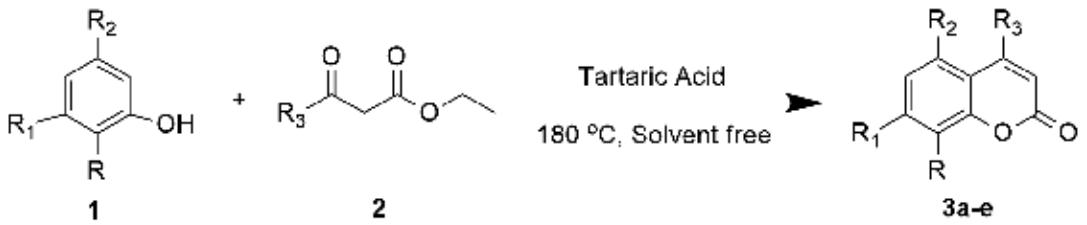
ABSTRACT Green and highly efficient synthesis of coumarins by Pechmann condensation, using naturally occurring acids under solvent free condition, is described. Various phenols efficiently condensed with ethyl acetoacetate under conventional as well as microwave irradiation conditions. Products are obtained in excellent yields.



KEYWORDS Coumarins, Green synthesis, Pechmann condensation, Tartaric acid

INTRODUCTION

Environmental pollution is a serious problem and there is worldwide growing concern over it. This fact has forced synthetic chemists to develop newer eco-friendly synthetic procedures which lead to the development of green chemistry concept. Green chemistry has gained momentum in the recent years and became a major scientific discipline[1–4] Use of toxic chemicals, especially solvents which are normally used in excess amount than reagents, by chemical and pharmaceutical industries is a major source of the environment pollution. The above problem may be solved by recycling the solvents which is economically as well as practically difficult. Another way to address this problem is the replacement of conventional organic solvents which are highly volatile, environmentally harmful, and/or biologically incompatible by environmentally benign solvents. Ionic liquids and fluorous solvents have been used with their limitations in organic syntheses. The use of water as benign solvent in organic synthesis has a limit due to the poor solubility of organic molecules in water.

Due to the toxicity of organic solvents and limitations of environmentally benign solvents, the most promising approach is to perform organic reactions under solvent-free conditions. In the recent years solvent-free reactions[5-9] have attracted considerable attention, not only for ecological and economical reasons, but also for simplicity of reaction conditions, high yields and short reaction times. Use of large amount of acid catalysts in organic reactions also generates toxic waste that is harmful to the environment. The use of naturally occurring, green and cheap acid catalyst under solvent free condition would be better solution to the environmental pollution which could change the traditional procedures into green ones, thus minimizing chemical waste further. Nature offers large number of

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organic acids (**Figure 1**) which are nontoxic, readily and cheaply available with tremendous potential as green catalyst in synthetic organic transformations. However, their synthetic potential as green catalysts in organic reactions has been ignored to a large extent except for a few scattered reports in the literature[10-14] even though these acids are biodegradable and renewable from nature.

As an ongoing program related to the development of a clean and eco-friendly acid catalyst, we have reported citric acid and several other naturally occurring organic acids as highly efficient and eco-friendly promoters for the Beckmann rearrangement,[15,16] synthesis of flavones[17] and 3,4-Dihydropyrimidin-2(1H)-ones/thiones[18] under solvent-free conditions. As a continuation of our interest in the development of clean and eco-friendly acid catalysts under solvent-free conditions, herein we wish to report the synthesis of coumarins via the Pechmann condensation promoted by naturally occurring organic acids. For this purpose, we selected several naturally occurring organic acids *viz*. citric, oxalic, tartaric, malic, succinic, malonic and fumaric acid (**Figure 1**) as green catalysts.

Coumarin and its derivatives are structural subunits present in many complex natural products and have shown array of biological activities, such as antitumor,[19] anti-HIV (NNRTI),[20] antioxidation,[21] tumor necrosis factor-a (TNF-a) inhibition,[22] antimicrobial activity,[23] serine protease inhibition[24] and anticancer activity.[25] The Pechmann reaction is one of the simplest and direct methods for the synthesis of coumarins,[26] utilizing various catalysts, such as concentrated sulfuric acid,[27] and trifluoroacetic acid.[28]

However, the above reported methods suffer from certain drawbacks such as use of toxic solvents, expensive reagents, production of considerable amount of byproducts, long reaction time and low yields. Therefore, the development of simple, inexpensive, highly efficient yet eco-friendly catalysts for acid catalyzed organic transformations is worthwhile. We report herein a simple and highly efficient protocol for synthesis of coumarins by Pechmann condensation reaction using citric acid, oxalic acid, tartaric acid, malic acid, succinic acid, malonic acid and fumaric acid as green promoters under solvent free conditions by thermal and microwave irradiation.

RESULTS AND DISCUSSION

For screening purpose, initially reaction between phloroglucinol **1a** and ethyl acetoacetate **2** was selected as model reaction. All the acids gave coumarin **3a** in good to excellent yields (**Scheme 1**, **Table 1**). Yields and reaction times were found to be analogous under conventional and microwave irradiation. Tartaric acid (**Table 1, entry 7**) was found to be the best catalyst for this reaction in terms of yields. Next, we studied the effect of amount of catalyst on reaction time and yield. Result showed that one mole equivalent of tartaric acid is required for the completion of the reaction. With less than one mole equivalent of the acid, yield of the product was reduced considerably with maximum recovery of starting material, even after continuing reaction for longer time. In order to check generality and scope and of the above methodology, various phenols and β- keto esters were subjected to Pechmann condensation under the above reaction condition (**Scheme-2**). Results shown in **Table 2** indicated that reactions proceed smoothly and give corresponding coumarins (**3a-e)** in good to excellent yields (**Table 2**). Reactions are faster under microwave irradiation and deliver slightly more yields of corresponding coumarins as compared to conventional heating.

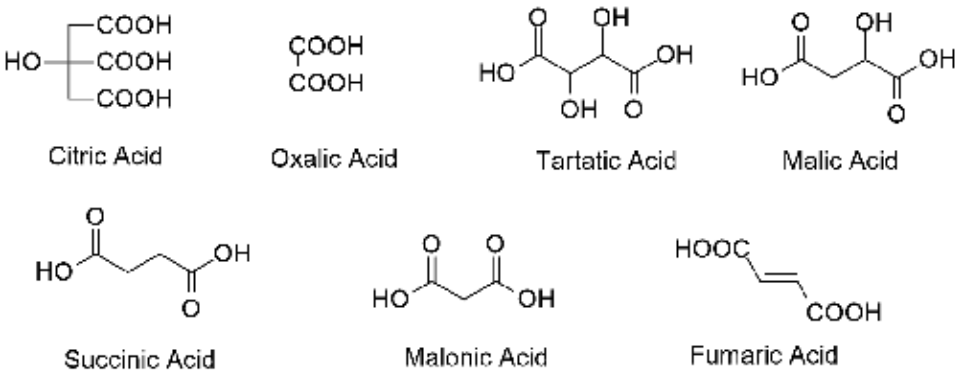
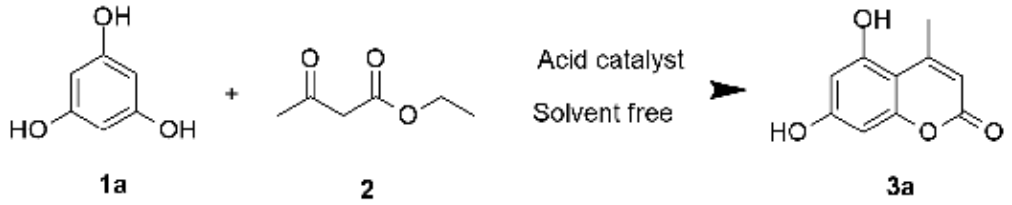


Figure 1: Naturally occurring organic acids

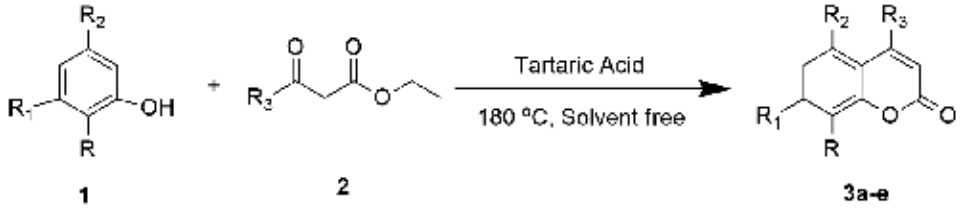


Scheme 1

Table 1: **Screening of catalysts in Pechmann coumarin synthesis under solvent free condition**[a]

Entry	Acid	Temp. (°C)[b]	Conventional heating %Yield[c]	Microwave heating %Yield[c]
1	Citric	160	82	84
2	Fumaric	290	72	78
3	Malic	140	83	88
4	Malonic	140	90	92
5	Oxalic	110	84	85
6	Succinic	190	65	71
7	Tartaric	180	94	97

[a] Reagents: **1a** (0.5g), **2** (1.0 eq.), acid (1.0 eq.).
[b] 5 min. in preheated oil bath, 3 min. in microwave reactor.
[c] Isolated yields.



Scheme 2

Table 2: Reaction scheme and characterization data for synthesized compounds[a]

Entry	Compd.	R	R_1	R_2	R_3	Conventional heating[b] (%) Yield[c]	Microwave heating[b] (%)Yield[c]	Observed M.P. (°C)	Reported M.P. (°C)
1	**3a**	H	OH	OH	Me	94	97	282- 284	289-292[29]
2	**3b**	H	OH	H	Me	88	92	184-185	185-187[29]
3	**3c**	H	OMe	H	Me	90	94	162-164	166-169[29]
4	**3d**	OH	OH	H	Me	84	89	236-238	240-244[29]
5	**3e**	H	OH	OH	Ph	93	95	212- 214	208-210[30]

[a] Reagents: **1a** (0.5g), **2** (1.0 eq.), acid (1.0 eq.),
[b] 5 min. in preheated oil bath, 3 min. in microwave reactor.
[c] Isolated yields.

EXPERIMENTAL SECTION

All reagents were used as obtained from commercial source. All melting points were determined in open capillary tubes using paraffin oil bath and are uncorrected. All the microwave-assisted reactions were performed in Discover LabMet microwave system (CEM corporation, USA) at the specified temperature using the standard mode of operation. Infra red (IR) spectra were recorded on Perkin Elmer Model 1600 series Fourier Transform (FT) instrument. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 and 75 MHz respectively in DMSO/$CDCl_3$ solution and tetramethylsilane (TMS) as internal reference (δ scale). All the compounds synthesized are previously reported, physical and spectroscopic data is in agreement with reported values.

General procedure for Synthesis of Coumarins 3

A mixture of phenol (**1**, 0.5 g), β-keto ester (**2**, 1.0 eq.) and tartaric acid (1.0 eq.) was heated either in an oil bath, preheated at 180 °C for 5 min or in microwave reactor for 3 min. After completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature and water (10 mL) was added. The solid obtained on stirring was filtered and washed with water. Crude product was purified by recrystalization using aqueous ethanol.

5,7-Dihydroxy-4-methyl-chromen-2-one (3a)

IR (KBr): 3392, 2912, 2352, 1705, 1648, 1600, 1459, 1366, 1292, 1152, 853, 713 cm^{-1};

^{1}H NMR (DMSO, 300 MHz) δ: 10.42 (bs, 2H, OH), 6.27 (s, 1H, ArH), 6.19 (s, 1H, ArH), 5.85 (s, 1H, C=CH), 2.38 (s, 3H, C-CH_3);

^{13}C NMR (DMSO, 75 MHz) δ: 161.0, 160.1, 157.9, 156.5, 154.9, 110.8, 102.1, 99.1, 94.5, 23.4.

7-Hydroxy-4-methyl-chromen-2-one (3b)

IR (KBr): 3135, 1601, 1390, 1273, 1068, 846 cm^{-1};

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.90 (bs, 1H, OH), 7.44 (d, *J* = 8.5 Hz, 1H, ArH), 6.82 (m, 2H, ArH), 6.05 (s, 1C=CH), 2.38 (s, 3H, C-CH_3);

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 161.2, 160.8, 154.7, 152.7, 125.3, 112.7, 112.0, 110.2, 102.5, 18.2.

7-Methoxy-4-methyl-chromen-2-one (3c)

IR (KBr): 3027, 1763, 1563, 1374, 1155, 1026, 809, 795 cm^{-1};

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.49 (d, *J* = 8.9 Hz, 1H, ArH), 6.86 (dd, *J* = 2.4 and 8.9 Hz, 1H, ArH), 6.79 (d, *J* = 2.5 Hz, 1H, ArH), 6.12 (s, 1H, C=CH), 3.87 (s, 3H, OCH_3), 2.39 (s, 3H, C-CH_3);

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 162.6, 161.2, 155.2, 152.5, 125.5, 113.5, 112.1, 111.8, 100.7, 55.6, 18.6.

7,8-Dihydroxy-4-methyl-chromen-2-one (3d)

IR (KBr): 3312, 2928, 1702, 1651, 1641, 1580, 1452, 1366, 1062, 1020, 762, 713 cm^{-1};

^{1}H NMR (DMSO, 300 MHz) δ: 9.97 (bs, 1H, OH), 9.35 (bs, 1H, OH), 7.04 (d, *J* = 8.4 Hz, 1H, ArH), 6.78 (d, *J* = 8.4 Hz, 1H,ArH), 6.08 (s, 1H, C=CH), 2.39 (s, 3H, C-CH_3);

^{13}C NMR (DMSO, 75 MHz) δ: 160.2, 153.9, 149.4, 143.3, 132.2, 115.5, 112.8, 112.1, 110.9, 18.2.

5,7-Dihydroxy-4-phenyl-chromen-2-one (3e)

IR (KBr): 3376, 2928, 1660, 1606, 1542, 1452, 1369, 765, 712 cm^{-1};

^{1}H NMR (DMSO, 300 MHz) δ: 10.38 (bs, 1H, OH), 10.16 (bs, 1H, OH), 7.31-7.39 (m, 5H, ArH), 6.28 (d, *J* = 2.4 Hz, 1H, ArH), 6.17 (d, *J* = 2.4 Hz, 1H, ArH), 5.75 (s, 1H, C=CH);

^{13}C NMR (DMSO, 75 MHz) δ: 161.6, 159.8, 157.0, 156.7, 155.9, 139.5, 127.7, 127.3, 127.2, 110.1, 100.5, 99.1, 94.6.

CONCLUSION

In conclusion, we found that the naturally occurring acids like citric acid, oxalic acid, tartaric acid, malic acid, succinic acid, malonic acid and fumaric acid can be used as environment-friendly acid promoters in Pechmann condensation reaction for synthesis of coumarins under solvent free condition. 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 promoter, solvent free reaction condition, short reaction time, easy work up and high yields makes this protocol a more convenient alternative to the reported methods. Further studies are in progress to expand the scope of this protocol in other reactions.

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