HETEROCYCLES, Vol. 92, No. 9, 2016, pp. 1698 - 1705. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 27th May, 2016, Accepted, 28th June, 2016, Published online, 12th July, 2016
DOI: 10.3987/COM-16-13510

KH_2PO_4 PROMOTED PRACTICAL AND ENVIRONMENTALLY FRIENDLY PREPARATION OF COUMARIN-3-CARBOXYLIC ACIDS UNDER SOLVENT-FREE CONDITION

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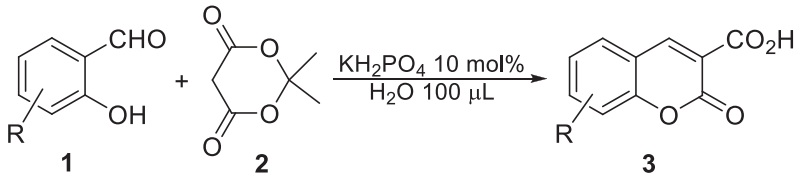
Abstract – An efficient and green protocol for synthesis of coumarin-3-carboxylic acids is developed in good to high yields via a Knoevenagel-intramolecular cyclization cascade reaction of Meldrum's acid with various *ortho*-hydroxyarylaldehydes. This reaction is catalyzed by a combination of KH_2PO_4 (10 mol%) and water (100 μL). Solvent-free, cheap and eco-friendly catalyst, clean reaction conditions, simple workup procedure and easy isolation are the best features in this process.

In recent years, the synthesis of coumarin-3-carboxylic acid and its derivatives has attracted considerable attention from organic and medicinal chemists due to coumarin-3-carboxylic acids are vital building blocks of various natural and semisynthetic pharmacological agents.[1] Searching for new and more convenient methods to accomplish their synthesis is significant and desirable.[2] Several routes have been reported in the literature for the synthesis of coumarin-3-carboxylic acid derivatives.[1c,3] The condensation of *ortho*-hydroxyarylaldehydes with Meldrum's acid is one of the simplest way.[4] Although this reaction can carry out under catalyst-free condition,[5] a series of developments and modifications has achieved utilizing ammonium acetate,[6] heteropolyacids,[7] benzyltriethylammonium chloride,[8] K_3PO_4,[9] $SnCl_2{\cdot}2H_2O$,[10] $FeCl_3$,[11] clays,[12] lithium salts,[13] $Yb(OTf)_3$,[2] silica sulfuric acid,[1c] K_2CO_3 or NaN_3,[4b] and acacic acid[14] as catalyst coupled with a variety of conditions such as solvent-free, heating, grinding, microwave irradiation and so on. Each of above-mentioned procedures has their own merits. However, the limited number of substrates, long reaction time, low yields, tedious workup procedures, co-occurrence of several side reactions, using large amount of organic solvents and need of chromatography for purification of adducts are problematic.[4b,14] Therefore, there is ample room for further development of milder reaction conditions, better yields and increased variation in the substituent

of both components.[4b]

Nowadays, environmental concerns have directly influenced the development of new methodologies.[11a,15] Solvent-free reaction is an important synthetic procedure from the view point of green and sustainable chemistry.[16] On the basis of our work[17] and the literature for the application of Meldrum's acid to synthesize useful organic molecules, we found that less water or a combination of KH_2PO_4 and water could smoothly promote the reaction of Meldrum's acid with aldehydes. Consequently, we decided to use a combination of KH_2PO_4 and water as efficient, green, and very cheap catalyst for the Knoevenagel condensation and intramolecular cyclization of 2-hydroxybenzaldehydes with Meldrum's acid under solvent-free condition to afford coumarin-3-carboxylic acids (Scheme 1).



Scheme 1. The approach for the preparation of coumarin-3-carboxylic acids

During initial investigation, we conducted a model reaction between salicylaldehyde and Meldrum's acid in equimolecular amounts of 0.5 mmol by employing KH_2PO_4 (10 mol%) as catalyst at 80 °C for 6 h under solvent-free condition to afford target compound in 55% isolated yield (Table 1, entry 1). As we know, water could promote the condensation of Meldrum's acid and aldehydes avoiding the addition of any catalyst[18] and exhibits unique reactivity in the reaction of 2-hydroxybenzaldehydes with Meldrum's acid for the synthesis of coumarin-3-carboxylic acids.[4b,5,14] Thus, the effect of adding some water in this reaction was surveyed (Table 1, entries 2-4). After some experimentation, we were pleased to find that adding 100 μL water could considerably improve the yield (Table 1, entry 2). A control experiment without KH_2PO_4 was also examined in order to recognize the capability of the combined catalyst (Table 1, entry 5). The model reaction gave an unsatisfactory result, which supported the necessary of the combination of KH_2PO_4 and water. The reaction when repeated under similar conditions in the presence of other catalysts generating K^+ ions such as K_2HPO_4 and $KHSO_4$ was found to be sluggish and incomplete (Table 1, entries 6, 7). Thus, KH_2PO_4 and 100 μL water were chosen as the optimum catalytic system to extend the protocol. Then, the amount of KH_2PO_4 was tested (Table 1, entries 8, 9), the results showed 10 mol% was the best amount. The effect of the temperature on the reaction was also examined and reacted at 70 °C was a feasible option (Table 1, entry 11). Sequentially decreased the temperature would result in lower yield (Table 1, entry 12). Further, we examined the fate of varying the ratio of substrates. A better conversion of reactants to afford the desired product in 90% yield was observed when

employing 1.1 equiv. of Meldrum's acid (Table 1, entry 13). The effect of the reaction time was also surveyed and the time could decrease to 4 h (Table 1, entry 15). Continuously shorten the reaction time gave an inferior yield (Table 1, entry 16). So it is clear that the optimum conditions are salicylaldehyde and Meldrum's acid in a ratio of 1:1.1 and using 10 mol% KH_2PO_4 and 100 μL water as accelerant reacted at 70 °C for 4 h.

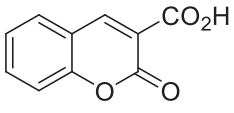
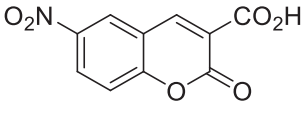
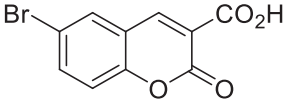
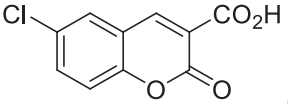
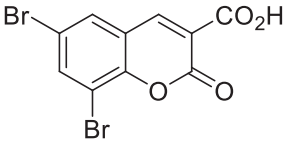
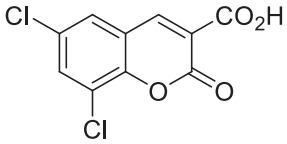
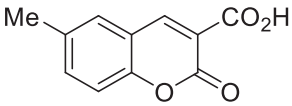
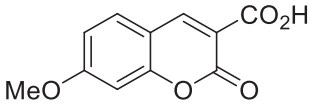
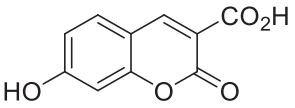
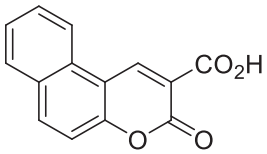
Table 1. The screening of reaction conditions

Entry[a]	Catalyst/mol%	Additive	Temp./°C	Time/h	Yield[b]/%
1	KH_2PO_4 (10)	--	80	6	55
2	KH_2PO_4 (10)	H_2O 100 μL	80	6	82
3	KH_2PO_4 (10)	H_2O 50 μL	80	6	79
4	KH_2PO_4 (10)	H_2O 200 μL	80	6	73
5	neat	H_2O 100 μL	80	6	62
6	K_2HPO_4 (10)	H_2O 100 μL	80	6	70
7	$KHSO_4$ (10)	H_2O 100 μL	80	6	52
8	KH_2PO_4 (15)	H_2O 100 μL	80	6	81
9	KH_2PO_4 (5)	H_2O 100 μL	80	6	73
10	KH_2PO_4 (10)	H_2O 100 μL	90	6	71
11	KH_2PO_4 (10)	H_2O 100 μL	70	6	84
12	KH_2PO_4 (10)	H_2O 100 μL	60	6	70
13[c]	KH_2PO_4 (10)	H_2O 100 μL	70	6	90
14[d]	KH_2PO_4 (10)	H_2O 100 μL	70	6	76
15[c]	KH_2PO_4 (10)	H_2O 100 μL	70	4	90
16[c]	KH_2PO_4 (10)	H_2O 100 μL	70	3	86

[a] The reactions were carried out with salicylaldehyde and Meldrum's acid in equimolecular amounts of 0.5 mmol. [b] Isolated yield. [c] Meldrum's acid 0.55 mmol. [d] Salicylaldehyde 0.55 mmol.

With the optimized reaction conditions in hand, we decided to explore the condensation of Meldrum's acid with various structurally diverse salicylaldehydes. The results are summarized in Table 2. A variety of functional groups in the examined substituted salicylaldehydes were well tolerated to give good yields. As we can see, the presence of weakly electron-withdrawing or electron-donating substituent on the ring of salicylaldehydes had similar influences on the procedure to furnish the desired products. These substrates were transformed into the corresponding products in a lower yield than that of salicylaldehyde (Table 2, entries 3, 4, 7, 8). Introduction of strongly electron-withdrawing group on the benzene ring favored to the yield of the reaction. Particularly, when employing 5-nitrosalicylaldehyde or 3,5-dibromosalicylaldehyde as substrate a higher yield than that of salicylaldehyde was obtained (Table 2, entries 2, 5). Surprisingly, hydroxyl group at the 4-position of salicylaldehyde gave the desired product in good yield (Table 2, entry 9). Unfortunately, naphthyl-based salicylaldehyde had a low reactivity in this reaction (Table 2, entry 10). Only 30% yield was obtained, even utilizing 30 mol% KH_2PO_4 as catalyst reacted at 90 °C for 8 h.

Table 2. Substrate scope for the synthesis of **3**

Entry[a]	Product	Temp./°C	Yield[b]/%	Mp/°C
1	 **3a**	70	90	188-190 (188-190[14])
2	 **3b**	95	94	231-233 (232-234[4b])
3	 **3c**	95	80	201-203 (194-196[14])
4	 **3d**	95	75	158-160 (122-123[4b])
5	 **3e**	85	92	217-219 (206-208[4b])
6	 **3f**	85	90	201-203 (199-202[4b])
7	 **3g**	70	79	164-166 (167-168[14])
8	 **3h**	70	81	194-196 (193-195[14])
9	 **3i**	85	92	268-270 (260-262[4b])
10[c]	 **3j**	90	30	235-237 (216-218[14])

[a] The reactions were carried out with salicylaldehyde/Meldrum's acid (0.5 mmol/0.55 mmol) under solvent-free condition. [b] Isolated yield. [c] Reacted with 30 mol% KH_2PO_4 at 90 °C for 8 h.

The plausible mechanism for this reaction is illustrated in Figure 1. Based on the above observations and the literature survey, we suggest that adding water can accelerate the dissociation of Meldrum's acid to generate the nucleophilic species, due to water has high dielectric constant.[18] On the other hand, the hydrogen ion, which is donated by the KH_2PO_4 can not only activate the carbonyl group of salicyldehyde but also help the dehydration to form the Knoevenagel condensation adduct.[5c,10,19] In the next step, the geometrically favored phenolic group within Knoevenagel reaction product undergoes ring-closure reaction through an intramolecularly nucleophilic attack onto the carbonyl carbon of Medlrum's acidic to

give the intermediate with the elimination of an acetone molecule. Finally, proton transfer gives coumarin-3-carboxylic acid.

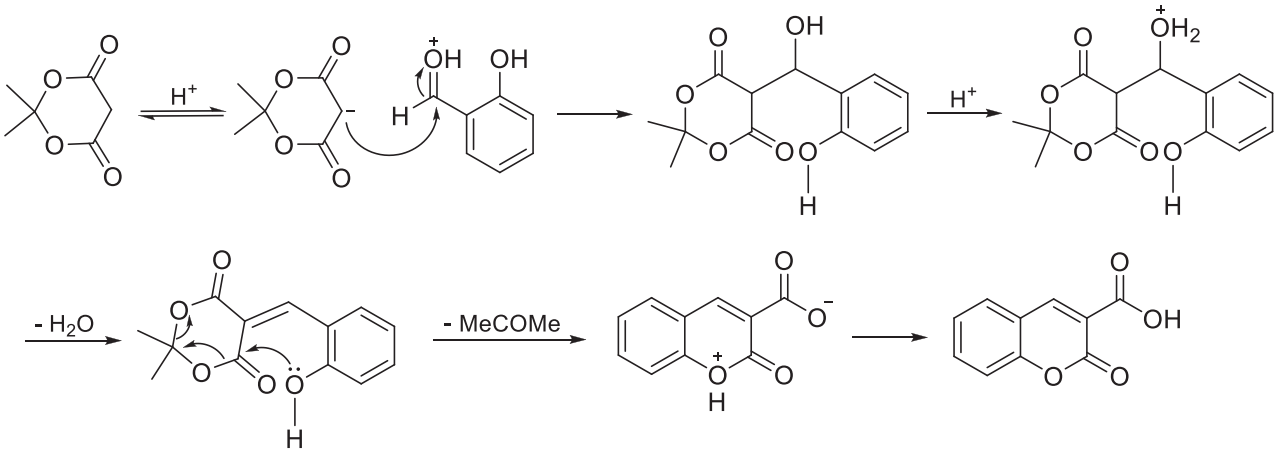


Figure 1. Plausible mechanistic pathway for the synthesis of coumarin-3-carboxylic acid

In summary, we have documented a practical route to synthesize coumarin-3-carboxylic acids in good to high yields using a combination of KH_2PO_4 and water as the accelerant. This nontoxic, and readily available catalytic system efficiently promotes the Knoevenagel condensation and intramolecular cyclization of various 2-hydroxybenzaldehydes with Meldrum's acid. Using of inexpensive and safe catalyst and solvent-free condition display both economic and environmental advantages.

EXPERIMENTAL

Melting points were determined on Beijing Tech X-5 Melting point detector and were uncorrected. The IR spectra were measured with a Bruker Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz. The chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) in Hertz. Unless otherwise stated, all reagents were obtained from commercial sources and were used without further purification.

Typical procedure for the synthesis of 3. A mixture of Meldrum's acid (0.55 mmol) and salicylaldehydes (0.5 mmol) was added in a 10 mL Schlenk tube, then KH_2PO_4 (0.05 mmol) and 100 μL water were added. The reaction mixture was stirred at the indicated temperature in Table 2 for 4 h. After completion of reaction, 3 mL 30% aqueous EtOH was added to the mixture and vigorously stirred for a moment. The precipitate was separated by filtration and washed with aqueous EtOH without further purification to afford the desired products. But the crude product needed to be recrystallized from EtOH to give the corresponding adduct when employing 2-hydroxynaphthyl-1-aldehyde as the starting material.

Coumarin-3-carboxylic acid (3a): White solid; IR (KBr) v: 3062, 2944, 2793, 1748, 1685, 1608, 1567, 1425, 1380, 1216, 1039, 828, 765 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.40-7.46 (m, 2H), 7.72-7.76

(m, 1H), 7.91 (d, J = 8 Hz, 1H), 8.76 (s, 1H), 13.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.09, 117.95, 118.32, 124.78, 130.15, 134.24, 148.32, 154.44, 156.65, 163.93.

6-Nitrocoumarin-3-carboxylic acid (3b): Yellow solid; IR (KBr) v: 3650, 3298, 3074, 1750, 1621, 1531, 1350, 1239, 1212, 805, 751 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.63 (d, J = 8 Hz, 1H), 8.47 (dd, J = 4, 8 Hz, 1H), 8.84 (s, 1H), 8.90 (d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 117.62, 118.42, 121.08, 125.78, 128.09, 143.58, 146.38, 155.51, 157.93, 163.59.

6-Bromocoumarin-3-carboxylic acid (3c): Creamy solid; IR (KBr) v: 3644, 3045, 1755, 1678, 1608, 1561, 1373, 1243, 1209, 1028, 804 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.40 (d, J = 8 Hz, 1H), 7.85 (dd, J = 4, 8 Hz, 1H), 8.16 (d, J = 4 Hz, 1H), 8.69 (s, 1H), 13.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.17, 118.38, 119.58, 119.84, 131.93, 136.30, 146.80, 153.47, 156.04, 163.72.

6-Chlorocoumarin-3-carboxylic acid (3d): Pale yellow solid; IR (KBr) v: 3637, 3104, 3045, 1755, 1687, 1614, 1561, 1478, 1367, 1243, 1216, 1032, 962, 811 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.47 (d, J = 8 Hz, 1H), 7.74 (dd, J = 4, 8 Hz, 1H), 8.03 (d, J = 4 Hz, 1H), 8.70 (s, 1H), 13.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 118.12, 119.32, 119.54, 128.38, 128.93, 133.56, 146.93, 153.06, 156.07, 163.71.

6,8-Dibromocoumarin-3-carboxylic acid (3e): Yellow solid; IR (KBr) v: 3650, 3066, 2889, 1768, 1689, 1605, 1524, 1443, 1359, 1252, 1216, 974, 793, 691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.16 (dd, J = 4, 16 Hz, 2H), 8.67 (s, 1H), 13.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 109.98, 116.17, 120.11, 120.77, 131.57, 138.10, 146.68, 150.33, 155.18, 163.36.

6,8-Dichlorocoumarin-3-carboxylic acid (3f): Creamy solid; IR (KBr) v: 3664, 3071, 1779, 1695, 1562, 1452, 1254, 1017, 952 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.02, (dd, J = 2, 8 Hz, 2H), 8.71 (s, 1H), 13.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 120.14, 120.37, 120.69, 128.06, 128.24, 132.84, 146.79, 148.90, 155.02, 163.39.

6-Methylcoumarin-3-carboxylic acid (3g): White solid; IR (KBr) v: 3650, 3074, 3030, 1743, 1667, 1614, 1567, 1373, 1220, 1039, 804 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.37 (s, 3H), 7.32 (d, J = 8 Hz, 1H), 7.53 (dd, J = 4, 8 Hz, 1H), 7.67 (s, 1H), 8.65 (s, 1H), 13.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.14, 115.85, 117.65, 118.19, 129.56, 134.08, 135.15, 148.17, 152.57, 156.86, 163.99.

7-Methoxycoumarin-3-carboxylic acid (3h): Pale yellow solid; IR (KBr) v: 3051, 2950, 1743, 1695, 1614, 1501, 1427, 1380, 1262, 1216, 1115, 1015, 804 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.90 (s, 3H), 6.99 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 1H), 8.71 (s, 1H), 13.00 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 56.19, 100.22, 111.56, 113.23, 113.75, 131.50, 149.03, 156.84, 157.18, 164.09, 164.61.

7-Hydroxycoumarin-3-carboxylic acid (3i): Yellow solid; IR (KBr) v: 3626, 3454, 3068, 1753, 1676, 1612, 1560, 1403, 1341, 1231, 1135, 1056, 910, 856 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.75 (d, J = 4 Hz, 1H), 6.84 (dd, J = 4, 8 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 101.76, 110.58, 112.42, 113.97, 131.98, 149.37, 156.95, 157.56, 163.89, 164.18.

3-Oxo-3*H*-benzo[*f*]chromene-2-carboxylic acid (3j): Pale green solid; IR (KBr) *v*: 3017, 1744, 1671, 1600, 1568, 1393, 1344, 1210, 796 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.54 (d, J = 8 Hz, 1H), 7.62 (t, J = 8 Hz, 1H), 7.73 (t, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 8.26 (d, J = 8 Hz, 1H), 8.52, (d, J = 8 Hz, 1H), 9.30 (s, 1H), 13.36 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 111.97, 116.36, 117.04, 122.17, 126.32, 128.89, 128.91, 129.71, 135.74, 143.60, 154.94, 156.71, 164.23.

ACKNOWLEDGEMENTS

We are grateful for financial support from the National Natural Science Foundation of China (21403100) and Liaoning Province, the Doctoral Scientific Research Foundation (20141100).

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