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Room Temperature One-Pot Green Synthesis of Coumarin-3-carboxylic Acids in Water: A Practical Method for the Large-Scale Synthesis

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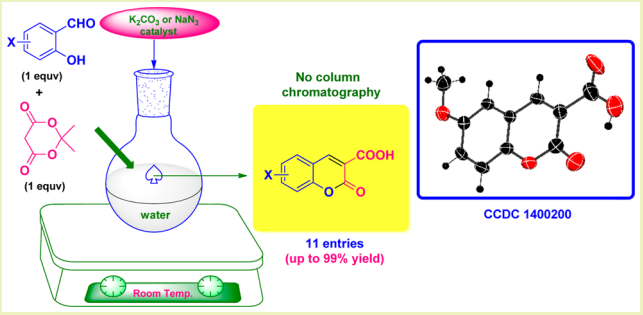
Supporting Information

ABSTRACT: A simple, facile, and convenient practical method for the room temperature one-pot synthesis of a series of potentially biologically active coumarin-3-carboxylic acids has been developed in water from the Knoevenagel condensation and intramolecular cyclization of diverse 2-hydroxybenzaldehydes with Meldrum's acid using either potassium carbonate or sodium azide as a commercially available, cheap, and eco-friendly catalyst. The salient features of the present protocol are mild reaction conditions, good to excellent yields, high atom-economy, environmentally benignity, easy isolation of products, without column chromatography, clean reaction profiles, and applicability toward large-scale synthesis.



KEYWORDS: *Coumarin-3-carboxylic acids, Potassium carbonate, Sodium azide, Water, Room-temperature, No column chromatography, Green chemistry*

INTRODUCTION

Coumarin (2-oxo-2*H*-1-benzopyran) heterocyclic moiety is well-regarded as a "privileged" structural motif both in numerous natural products[1,2] and synthetic organic compounds[3] of potential pharmacological activities including antibacterial,[4] antifungal,[3] anti-HIV,[6−9] antioxidant,[10−12] antimutagenic,[13] anticancer,[14−17] anti-inflammatory,[18,19] analgesic,[20] antibiotic,[21,22] anticoagulant,[23,24] antitumor,[25,26] tumor necrosis factor-α inhibitory,[27] serine protease inhibitory,[28] and steroid 5α-reductase inhibitory[29] activities. As a result, coumarins are very attractive targets for combinatorial library synthesis.[30] Coumarin derivatives find extensive uses as insecticides,[31] fragrances and perfumes,[32] agrochemicals,[33,34] and additives in foods and cosmetics.[35] In addition, such compounds are also found applications as fluorescence sensors,[36] optical brighteners,[37] fluorescent transthyretin folding sensors,[38] and molecular photonic devices.[39]

Coumarin-3-carboxylic acids or 3-carboxycoumarins (2-oxo-2*H*-chromene-3-carboxylic acids or 2-oxo-2*H*-1-benzopyran-3-carboxylic acids) represent a pronounced group of coumarin-heterocyclic compounds with a wide range of applications. Literature survey reveals that these compounds find applications as synthons of numerous natural and semisynthetic pharmacological agents like β-lactams,[40,41] isoureas,[42] and tetrahydropyridones.[43] Ester and amide derivatives of coumarin-3-carboxylic acid have been evaluated to possess efficient inhibitory activity against cancer cell invasion *in vitro* and tumor growth *in vivo*.[44] Certain metal complexes of such compounds have been reported to have several beneficial biological effects.[45,46] Apart from these applications, coumarin-3-carboxylic acids have been widely used as fluorescent probes[47] and triplet oxygen sensitizers.[48] Hence, chemists have been greatly motivated to explore useful synthetic strategies for such novel and promising targets for subsequent research and development.[49]

Among various available methods, Knoevenagel condensation is widely used for the synthesis of coumarin-3-carboxylic acids from the reaction between *ortho*-hydroxyaryl aldehydes with differently substituted malonates or cyanoacetates in the presence of a number of catalysts such as piperidine,[50,51] piperidinium acetate,[52] and ammonium acetate.[53,54] An exhaustive review on the synthesis of coumarin derivatives via Knoevenagel condensation has recently been recently reported.[55] However, use of Meldrum's acid as the β-dicarbonyl compound in the targeted Knoevenagel condensation has become the choice today because of several advantages in terms of yields, reaction times and purification of adducts. There are many reports so far on the condensation of *ortho*-hydroxyaryl carbonyls and Meldrum's acid involving the use of a variety of catalysts like ammonium acetate,[56] triethyl benzyl ammonium

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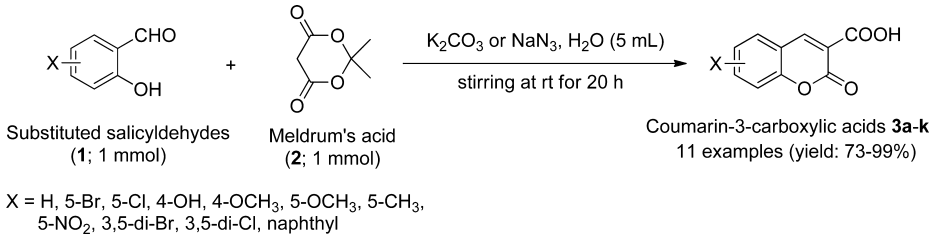
Scheme 1. One-Pot Synthesis of Coumarin-3-carboxylic Acids in Water at Room Temperature



chloride and potassium phosphate,[57] $SnCl_2$,[58] $FeCl_3$,[30] clays,[59] lithium salts,[60] silica sulfuric acid,[61] and $Yb(OTf)_3$/MW.[49] Although these protocols reported by others find certain merits of their own, still they suffer from a number of demerits such as harsh reaction conditions, low yields, tedious workup procedures, co-occurrence of several side reactions, use of toxic organic solvents and need of chromatography for purification of adducts. Therefore, a search for more general, clean, efficient, and high yielding routes for the large-scale synthesis of such useful synthones and pharmacologically potent coumarin-3-carboxylic acids remains a valid exercise in organic, medicinal and combinatorial chemistry and represents a field of research of current and growing interest.

As far as green chemistry practice is concerned in chemical enterprises, performing organic transformations in water medium is of prime importance because water is generally considered a "green solvent" for organic reactions, and a huge number of chemical reactions "in- or on-water" conditions are known.[62−66] Water is the solvent of choice not only from an environmental standpoint but also from an economic point of view because it is cheap, nonflammable, and abundantly available.[67−70] Water behaves differently from other commonly used organic solvents in terms of its unique and unusual physical properties, such as high surface tension, high dielectric constant, high specific heat, large cohesive energy density, and also chemical properties, particularly its amphoteric nature and the ability to form hydrogen bonds.[71,72] Moreover, hydrophobic interactions offered by water molecules with organic reactants sometimes facilitate certain organic processes.[73] Thus, the development of an energy-efficient one-pot protocol for a useful organic transformation under ambient conditions using simply water as a solvent medium is believed to be an advancement to the green chemistry practice.

In continuation of our efforts to develop green synthetic methodologies for organic transformations,[74−90] it has recently been explored in our laboratory that coumarin-3-carboxylic acids (**3**) can efficiently be synthesized via Knoevenagel condensation between substituted salicylaldehydes (**1**) and Meldrum's acid (**2**) in one-pot at room temperature using water as a solvent and commercially available potassium carbonate or sodium azide as an inexpensive and less-toxic catalyst (Scheme 1). The present method is not only cost-effective and environmentally benign but also experimentally safe and simple, easy to handle, clean, and efficient also for the large-scale synthesis eliminating the use of any toxic organic solvent and tedious operation of column chromatographic purification.

EXPERIMENTAL SECTION

General. Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using a KBr disc. ^1H and ^{13}C NMR spectra were obtained at 400 and 100 MHz respectively, using a Bruker DRX-400 spectrometer and DMSO-d_6 as the solvent. Mass spectra (TOF-MS) were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 microanalyzer instrument. X-ray data were collected on a Bruker single crystal X-ray difractometer (model: APEX 2). Melting point was recorded on a Chemiline CL-726 melting point apparatus and is uncorrected. Thin Layer Chromatography (TLC) was performed using silica gel 60 F_{254} (Merck) plates.

*General Procedure for the Synthesis of Coumarin-3-carboxylic Acids (**3**).* An oven-dried screw cap test tube was first charged with a magnetic stir bar, salicylaldehydes (**1**, 1.0 mmol), Meldrum's acid (**2**, 1.0 mmol; 144 mg), distilled water (5 mL), and K_2CO_3 (20 mol %; 28 mg). The whole mixture was then stirred vigorously at room temperature (24−26 °C) for 20 h to complete the conversion. Upon completion, the resulting solution was acidified with chilled acid−water, when solid mass precipitated out, filtered off, and thoroughly washed with water to obtain almost pure product of coumarin-3-carboxylic acids (**3**). For further purification, the products were crystallized from ethyl acetate. All the products (**3**) were also synthesized repeating the same reaction using sodium azide (50 mol %; 33 mg) as the catalyst in place of potassium carbonate. The structure of each purified product was confirmed by its analytical as well as spectral studies including FT-IR, ^1H NMR, ^{13}C NMR, and TOF-MS. For a few entries, 2D-NMR (^1H−^1H COSY, HMQC, and HMBC) spectral properties were also studied. In addition, single X-ray crystallographic studies for one entry, 6-methoxycoumarin-3-carboxylic acid (**3f**), was performed.

Characterization Data of All Compounds. *Coumarin-3-carboxylic Acid (**3a**).* White solid, mp: 189−191 °C. IR (KBr): ν_{max} = 3450, 3381, 3199, 3150, 3051, 3001, 1676, 1601, 1535, 1454, 1249, 1171, 1070, 878, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (1H, s, C_4—H), 7.83−7.78 (2H, m, Ar—H), 7.50 (2H, t, J = 8.4 and 7.6 Hz, Ar—H). ^1H NMR (400 MHz, DMSO-d_6): δ 8.74 (1H, s, C_4—H), 7.90 (1H, d, J = 7.6 Hz, Ar—H), 7.73 (1H, td, J = 7.6 and 1.2 Hz, Ar—H), 7.44 (1H, d, J = 8 Hz, Ar—H), 7.41 (1H, t, J = 7.2 Hz, Ar—H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.39 (C_3—COOH), 157.13 (C═O), 154.85 (C-8a), 148.75 (C-4), 134.70 (C-8), 130.59 (C-5), 125.25 (C-6), 118.74 (C-3), 118.37 (C-4a), 116.53 (C-7). 2D-NMR corrections are shown in the text. HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{10}H_6O_4Na$: 213.0164. Found: 213.0158. Anal. Calcd for $C_{10}H_6O_4$: C 63.16, H 3.18. Found: C 63.12, H 3.15.

*6-Bromocoumarin-3-carboxylic Acid (**3b**).* Creamy solid, mp: 193−195 °C. IR (KBr): ν_{max} = 3474, 3263, 3045, 2914, 1749, 1674, 1610, 1553, 1477, 1406, 1356, 1312, 1252, 1194, 1061, 1013, 878, 814, 758 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.67 (1H, s, C_4—H), 8.15 (1H, d, J = 2 Hz, Ar—H), 7.86 (1H, dd, J = 8.8 and 2.4 Hz, Ar—H), 7.40 (1H, d, J = 8.8 Hz, Ar—H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.14 (C_3—COOH), 156.52 (C═O), 153.91 (C-8a), 147.32 (C-4), 136.80 (C-7), 132.37 (C-5), 120.25 (C-6), 119.93 (C-3), 118.82 (C-8), 116.64 (C-4a). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{10}H_5BrO_4Na$: 290.9269. Found: 290.9261. Anal. Calcd for $C_{10}H_5BrO_4$: C 44.64, H 1.87. Found: C 44.66, H 1.84.

*6-Chlorocoumarin-3-carboxylic Acid (**3c**).* Pale yellow solid, mp: 122−123 °C. IR (KBr): ν_{max} = 3506, 3414, 3055, 1730, 1684, 1607, 1591, 1479, 1408, 1310, 1252, 1166, 1011, 868, 677 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.58 (1H, s, C_4—H), 7.99 (1H, d, J = 2.4 Hz, Ar—H), 7.71 (1H, dd, J = 8.8 and 2.4 Hz, Ar—H), 7.45 (1H, d, J = 8.8 Hz, Ar—H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.55 (C_3—

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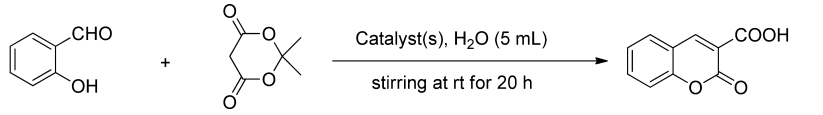
Table 1. Catalyst-Optimization for the Synthesis of 4-Unsubstituted Coumarin-3-carboxylic Acids in Water at Room Temperature



Salicyldehydes (**1**; 1 mmol) | Meldrum's acid (**2**; 1 mmol) | Coumarin-3-carboxylic acid **3a**

entry	catalyst (mol %; weight)	yield (%)[a,b]
1	no catalyst	0
2	cesium carbonate (20 mol %; 65 mg)	trace
3	sodium formate (20 mol %; 14 mg)	45
4	triethylamine (Et_3N; 20 mol %; 20 mg)	56
5	sodium azide (NaN_3; 20 mol %; 13 mg)	65
6	sodium azide (50 mol %; 33 mg)	99
7	potassium carbonate (10 mol %; 14 mg)	79
8	potassium carbonate (20 mol %; 28 mg)	92

[a]Experimental conditions: salicylaldehyde (**1**, 1.0 mmol) and Meldrum's acid (**2**, 1.0 mmol) in the presence or absence of different catalysts in 5 mL of distilled water at room temperature (24−26 °C). [b]Isolated yields.

COOH), 156.96 (C═O), 153.28 (C-8a), 146.11 (C-4), 133.60 (C-6), 129.15 (C-7), 128.78 (C-5), 121.57 (C-8), 119.94 (C-3), 118.49 (C-4a). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{10}H_5ClO_4Na$: 246.9774. Found: 246.9768. Anal. Calcd for $C_{10}H_5ClO_4$: C 53.48, H 2.24. Found: C 53.45, H 2.21.

*7-Hydroxycoumarin-3-carboxylic Acid (**3d**).* Dark yellow solid, mp: 260−262 °C. IR (KBr): ν_{max} = 3626, 3454, 3391, 3294, 3055, 1753, 1678, 1614, 1564, 1467, 1344, 1231, 1136, 1055, 1009, 910, 856, 754 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.09 (1H, br s, Ar—OH), 8.64 (1H, s, C_4—H), 7.70 (1H, d, J = 8.8 Hz, Ar—H), 6.81 (1H, dd, J = 8.8 and 2.4 Hz, Ar—H), 6.71 (1H, d, J = 2.0 Hz, Ar—H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.61 (C_3—COOH), 164.33 (C═O), 158.09 (C-7), 157.36 (C-8a), 149.82 (C-4), 132.40 (C-5), 114.42 (C-3), 112.78 (C-6), 111.00 (C-8), 102.18 (C-4a). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{10}H_6O_5Na$: 229.0113. Found: 229.0109. Anal. Calcd for $C_{10}H_6O_5$: C 58.26, H 2.93. Found: C 58.22, H 2.91.

*7-Methoxycoumarin-3-carboxylic Acid (**3e**).* Pale yellow solid, mp: 192−194 °C. IR (KBr): ν_{max} = 3464, 3312, 3067, 2862, 1732, 1965, 1610, 1581, 1495, 1364, 1277, 1225, 1119, 1022, 852, 731 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.70 (1H, s, C_4—H), 7.81 (1H, d, J = 8.4 Hz, Ar—H), 7.01−7.00 (1H, m, Ar—H), 6.98 (1H, d, J = 2.0 Hz, Ar—H), 3.89 (3H, s, Ar—OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.05 (C_3—COOH), 164.56 (C═O), 157.65 (C-8a), 157.27 (C-7), 149.43 (C-4), 131.94 (C-5), 114.27 (C-3), 113.68 (C-8), 112.01 (C-4a), 100.66 (C-6), 56.63 (C_7—OCH_3). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{11}H_8O_5Na$: 243.0269. Found: 243.0261. Anal. Calcd for $C_{11}H_8O_5$: C 60.00, H 3.66. Found: C 59.96, H 3.64.

*6-Methoxycoumarin-3-carboxylic Acid (**3f**).* Pale yellow solid, mp: 198−200 °C. IR (KBr): ν_{max} = 3480, 3415, 3350, 3051, 2838, 1759, 1678, 1591, 1491, 1365, 1281, 1244, 1132, 1034, 968, 797, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.65 (1H, s, C_4—H), 7.35 (1H, d, J = 8.8 Hz, Ar—H), 7.29 (1H, d, J = 2.4 Hz, Ar—H), 7.27 (1H, d, J = 2.4 Hz, Ar—H), 3.79 (3H, s, Ar—OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.40 (C_3—COOH), 157.42 (C═O), 156.10 (C-6), 149.28 (C-8a), 148.50 (C-4), 122.43 (C-3), 118.89 (C-7), 118.75 (C-5), 117.63 (C-8), 112.17 (C-4a), 56.17 (C_6—OCH_3). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{11}H_8O_5Na$: 243.0269. Found: 243.0263. Anal. Calcd for $C_{11}H_8O_5$: C 60.00, H 3.66. Found: C 59.97, H 3.64.

*6-Methylcoumarin-3-carboxylic Acid (**3g**).* White solid, mp: 158−161 °C. IR (KBr): ν_{max} = 3526, 3396, 3024, 2904, 1722, 1695, 1593, 1581, 1487, 1358, 1272, 1115, 1033, 824, 728 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.60 (1H, s, C_4−H), 7.62 (1H, s, Ar−H), 7.50 (1H, d, J = 8.0 Hz, Ar—H), 7.28 (1H, d, J = 8.4 Hz, Ar—H), 2.34 (3H, s, Ar—CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.39 (C_3—COOH), 157.33 (C═O), 152.99 (C-8a), 148.56 (C-4), 135.57 (C-6), 134.53 (C-7), 129.97 (C-5), 118.59 (C-3), 118.05 (C-8), 116.26 (C-4a), 20.55 (C_6—CH_3). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{11}H_8O_4Na$: 227.0320. Found: 227.0314. Anal. Calcd for $C_{11}H_8O_4$: C 64.71, H 3.95. Found: C 64.68, H 3.97.

*6-Nitrocoumarin-3-carboxylic Acid (**3h**).* Yellow solid, mp: 232−234 °C. IR (KBr): ν_{max} = 3454, 3055, 2924, 1753, 1682, 1614, 1564, 1483, 1344, 1244, 1230, 1086, 1009, 856, 754, 655 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.88 (1H, d, J = 2.4 Hz, Ar−H), 8.79 (1H, s, C_4—H), 8.48 (1H, dd, J = 2.4, 2.8, and 9.0 Hz, Ar—H), 7.64 (1H, d, J = 9.2 Hz, Ar—H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.08 (C_3—COOH), 158.44 (C═O), 155.51 (C-8a), 146.40 (C-4), 144.03 (C-6), 128.43 (C-7), 126.15 (C-5), 122.05 (C-8), 118.94 (C-3), 118.05 (C-4a). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{10}H_5NO_6Na$: 258.0015. Found: 258.0011. Anal. Calcd for $C_{10}H_5NO_6$: C 51.08, H 2.14. Found: C 51.04, H 2.12.

*6,8-Dibromocoumarin-3-carboxylic Acid (**3i**).* Pale yellow solid, mp: 206−208 °C. IR (KBr): ν_{max} = 3490, 3178, 2926, 1765, 1745, 1614, 1604, 1571, 1391, 1371, 1167, 1086, 824, 722, 705 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.44 (1H, s, C_4—H), 8.16 (1H, d, J = 2.0 Hz, Ar—H), 8.12 (1H, d, J = 1.6 Hz, Ar−H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.10 (C_3—COOH), 150.00 (C═O), 144.82 (C-8a), 137.50 (C-4), 131.47 (C-7), 125.25 (C-5), 122.06 (C-6), 116.70 (C-3), 110.31 (C-8 and C-4a). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{10}H_4Br_2O_4Na$: 368.8374. Found: 368.8366. Anal. Calcd for $C_{10}H_4Br_2O_4$: C 34.52, H 1.16. Found: C 34.49, H 1.18.

*6,8-Dichloromocoumarin-3-carboxylic Acid (**3j**).* Pale yellow solid, mp: 199−202 °C. IR (KBr): ν_{max} = 3481, 3055, 2957, 1762, 1653, 1607, 1553, 1450, 1265, 1090, 887, 696, 634 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.68 (1H, s, C_4—H), 8.02 (1H, d, J = 2.0 Hz, Ar—H), 8.00 (1H, d, J = 2.0 Hz, Ar—H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.85 (C_3—COOH), 155.51 (C═O), 149.33 (C-8a), 147.16 (C-4), 133.26 (C-7), 128.69 (C-6), 128.49 (C-5), 121.14 (C-8), 120.82 (C-3), 120.67 (C-4a). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{10}H_4Cl_2O_4Na$: 280.9384. Found: 280.9377. Anal. Calcd for $C_{10}H_4Cl_2O_4$: C 46.37, H 1.56. Found: C 46.33, H 1.54.

*3-Oxo-3H-benzo[f]chromene-2-carboxylic Acid (**3k**).* Pale orange solid, mp: 194−196 °C. IR (KBr): ν_{max} = 3440, 3086, 2945, 1744, 1693, 1618, 1582, 1478, 1394, 1223, 1041, 814, 755, 640 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.28 (1H, s, C_4—H), 8.51 (1H, d, J = 8.4 Hz, Ar—H), 8.25 (1H, dd, J = 8.4 and 2.8 Hz, Ar—H), 8.03 (1H, d, J = 8.0 Hz, Ar—H), 7.72 (1H, d, J = 6.8 Hz, Ar—H), 7.64−7.59 (1H, m, Ar—H), 7.54 (1H, dd, J = 8.4 and 2.8 Hz, Ar—H);. ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.74 (C_3—COOH), 155.34 (C═O), 143.93 (C-10a), 138.81 (C-4), 136.17 (C-9), 130.15 (C-4a), 129.68 (C-8a), 126.80 (C-8), 124.63 (C-6), 122.57 (C-7), 119.01 (C-3), 117.67 (C-5a), 116.79 (C-5), 112.42 (C-10). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{14}H_8O_4Na$: 263.0320. Found (TOF-MS):

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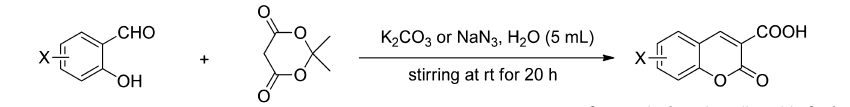
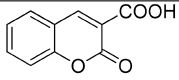
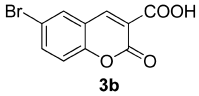
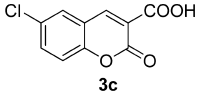
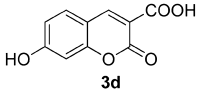
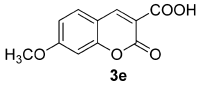
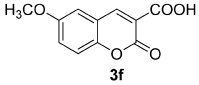
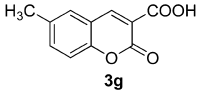
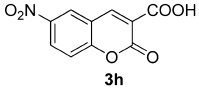
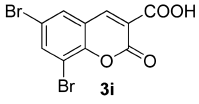
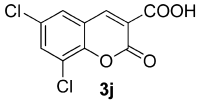
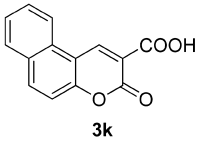
Table 2. Synthesis of Coumarin-3-carboxylic Acids in Water at Room Temperature



Substituted salicyldehydes (**1**; 1 mmol) | Meldrum's acid (**2**; 1 mmol) | Coumarin-3-carboxylic acids **3a-k**

Entry	Salicylaldehyde (**1**)	Coumarin-3-carboxylic acid (**3**)	%Yield[a,b]		Melting point (°C)	
			K_2CO_3 (20 mol%)	NaN_3 (50 mol%)	Found	Reported [Lit.]
1	Salicylaldehyde	 **3a**	92	99	189-191	188-189[58]
2	5-Bromosalicyldehyde	 **3b**	93	99	193-195	192-196[62-66]
3	5-Chlorosalicyldehyde	 **3c**	92	99	122-123	120[62-66]
4	4-Hydroxysalicyldehyde	 **3d**	91	97	260-262	259-260[58]
5	4-Methoxysalicyldehyde	 **3e**	92	96	192-194	193-194[58]
6	5-Methoxysalicyldehyde	 **3f**	93	96	198-200	-
7	5-Methylsalicyldehyde	 **3g**	89	92	158-161	-
8	5-Nitrosalicyldehyde	 **3h**	73	78	232-234	233-234[58]
9	3,5-Dibromosalicyldehyde	 **3i**	90	94	206-208	-
10	3,5-Dichlorosalicyldehyde	 **3j**	92	95	199-202	-
11	3-Hydroxy-2-naphthaldehyde	 **3k**	86	92	194-196	195-196[58]

[a]Experimental conditions: salicyladehydes (**1**, 1.0 mmol), Meldrum's acid (**2**, 1.0 mmol) and K_2CO_3 (20 mol %) or NaN_3 (50 mol %) as the catalyst in 5 mL of distilled water at room temperature (24−26 °C). [b]Isolated yields.

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Table 3. 2D-NMR Behavior of Coumarin-3-carboxylic Acid (3a)

carbon	^{1}H (ppm/δ) (DMSO-d_6)	^{13}C (ppm/δ) (DMSO-d_6)	DEPT-135	^{1}H−^{1}H COSY-45	^{1}H−^{13}C HMQC	^{1}H−^{13}C HMBC
2		157.13	C			
3		118.74	C			
4	8.74	148.75	CH		δ 8.74 (H-4) vs δ 148.75 (C-4)	δ 8.74 (H-4) vs δ 157.13 (C-3), 130.59 (C-5), 154.85 (C-8a), 164.39 (COOH)
4a		118.37	C			
5	7.90 (1H, d, J = 7.6 Hz)	130.59	CH	H-5 (δ 7.90) vs H-6 (δ 7.41)	δ 7.90 (H-5) vs δ 130.59 (C-5)	δ 7.90 (H-5) vs δ 148.75 (C-4), 134.70 (C-8), 154.85 (C-8a)
6	7.41 (1H, t, J = 7.2 Hz)	125.25	CH	H-6 (δ 7.41) vs H-5 (δ 7.90) and H-7 (δ 7.44)	δ 7.41 (H-6) vs δ 125.25 (C-6)	δ 7.41 (H-6) vs δ 118.37 (C-4a), 116.53 (C-7), 154.85 (C-8a)
7	7.44 (1H, d, J = 8 Hz)	116.53	CH	H-7 (δ 7.44) vs H-6 (δ 7.41) and H-8 (δ 7.73)	δ 7.44 (H-7) vs δ 116.53 (C-7)	δ 7.44 (H-7) vs δ 118.37 (C-4a), 125.25 (C-6)
8	7.73 (1H, td, J = 7.6 and 1.2 Hz)	134.70	CH	H-8 (δ 7.73) vs H-7 (δ 7.44)	δ 7.73 (H-8) vs δ 134.70 (C-8)	δ 7.73 (H-8) vs δ 130.59 (C-5)
8a		154.85	C			
C_3−COOH	did not appear	164.39	C			

Table 4. 2D-NMR Behavior of 7-Methoxycoumarin-3-carboxylic Acid (3e)

carbon	^{1}H (ppm/δ) (DMSO-d_6)	^{13}C (ppm/δ) (DMSO-d_6)	DEPT-135	^{1}H−^{1}H COSY-45	^{1}H−^{13}C HMQC	^{1}H−^{13}C HMBC
2		164.56	C			
3		114.27	C			
4	8.70	149.43	CH		δ 8.70 (H-4) vs δ 149.43 (C-4)	δ 8.70 (H-4) vs δ 131.94 (C-5), 157.65 (C-8a)
4a		112.01	C			
5	7.81 (1H, d, J = 8.4 Hz)	131.94	CH	H-5 (δ 7.81) vs H-6 (δ 7.01−7.00)	δ 7.81 (H-5) vs δ 131.94 (C-5)	δ 7.81 (H-5) vs δ 164.56 (C-2), 149.43 (C-4), 157.27 (C-7), 157.65 (C-8a), 165.05 (COOH)
6	7.01−7.00 (1H, m)	100.66	CH	H-6 (δ 7.01−7.00) vs H-5 (δ 7.81)	δ 7.01−7.00 (H-6) vs δ 100.66 (C-6)	δ 7.01−7.00 (H-6) vs δ 113.68 (C-8)
7		157.27	C			
8	6.98 (1H, d, J = 2.0 Hz)	113.68	CH		δ 6.98 (H-8) vs δ 113.68 (C-8)	δ 6.98 (H-8) vs δ 164.56 (C-3), 112.01(C-4a), 100.66 (C-6), 157.27 (C-7)
8a		157.65	C			
C_3−COOH	did not appear	165.05	C			
C_7−OCH_3	3.89 (3H, s)	56.63	CH_3		δ 3.89 (OCH_3) vs δ 56.63 (OCH_3)	δ 3.89 (C_7−OCH_3) vs δ 165.05 (C_3−COOH)

263.0312 $[M + Na]^+$. Anal. Calcd for $C_{14}H_8O_4$: C 70.00, H 3.36. Found: C 69.97, H 3.34.

RESULTS AND DISCUSSION

Herein, a straightforward energy-efficient and high yielding protocol for the one-pot synthesis of a series of biologically relevant 4-unsubstituted coumarin-3-carboxylic acids (**3a**−**3k**) in water at room temperature under the catalysis of potassium carbonate or sodium azide is reported (Scheme 1). First, a series of trial reactions using salicylaldehyde (**1**; 1.0 mmol) and Meldrum's acid (**2**; 1.0 mmol) in the absence or presence of different base catalysts (easily available, cheap and less-toxic) in water were performed at room temperature to obtain the best yield of the desired product, coumarin-3-carboxylic acid (2-oxo-2*H*-chromene-3-carboxylic acid; **3a**). It appeared that both K_2CO_3 (20 mol %) and NaN_3 (50 mol %) in water at room temperature provide the best result affording **3a** with the yields of 92% and 99%, respectively at 20 h (Table 1, entries 6 and 8). Compound **3a** was characterized by its physical and spectral properties.[58] The overall results are summarized in Table 1.

After optimizing the reaction conditions, the reaction of 5-bromosalicylaldehyde with Meldrum's acid was carried out under the same reaction conditions using both the optimized catalysts, and the product, 6-bromocoumarin-3-carboxylic acid (**3b**), was obtained in 93% yield with K_2CO_3 and 99% yield with NaN_3 within 20 h (Table 2, entry 2). To check the generality as well as the effectiveness of this newly developed protocol, a number of salicylaldehydes having substituents, such as hydroxy, methoxy, nitro, halogens, etc. were reacted with Meldrum's acid under identical reaction conditions using both the catalysts separately, and all of them underwent the reaction smoothly affording the coumarin-3-carboxylic acids (**3c**−**3k**) (Table 2, entries 3−11) in good to excellent yields (73−99%) in water at room temperature. The overall results are summarized in Table 2.

All the products were isolated pure just by washing with water followed by recrystallization from ethyl acetate; no tedious chromatographic purification was required. The isolated products were fully characterized on the basis of their analytical data and detailed spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR, and TOF-MS. All the known compounds had physical and spectroscopic data identical to those reported in literature.[58,62−66] In addition, detailed 2D-NMR (^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC and ^{1}H−^{13}C HMBC) behavior for compounds **3a**, **3e**, and **3j** were also studied to elicit such correlative interactions among the homo and heteronuclei for the first time. 1D- and 2D-NMR values and the respective

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Table 5. 2D-NMR Behavior of 6,8-Dichloromocoumarin-3-carboxylic Acid (3j)

carbon	^{1}H (ppm/δ) (DMSO-d_6)	^{13}C (ppm/δ) (DMSO-d_6)	DEPT-135	^{1}H–^{1}H COSY-45	^{1}H–^{13}C HMQC	^{1}H–^{13}C HMBC
2		155.51	C			
3		120.82	C			
4	8.68	147.16	CH		δ 8.68 (H-4) vs δ 147.16 (C-4)	δ 8.68 (H-4) vs δ 155.51 (C-2), 120.67 (C-4a), 128.49 (C-5), 149.33 (C-8a), 163.85 (COOH)
4a		120.67	C			
5	8.00 (1H, d, J = 2.0 Hz)	128.49	CH		δ 8.00 (H-5) vs δ 128.49 (C-5)	δ 8.00 (H-5) vs δ 149.33 (C-8a), 147.16 (C-4)
6		128.69,	C			
7	8.02 (1H, d, J = 2.0 Hz)	133.26	CH		δ 8.02 (H-7) vs δ 133.26 (C-7)	δ 8.02 (H-7) vs δ 128.48 (C-5)
8		121.14	C			
8a		149.33	C			
C_3–COOH	did not appear	163.85	C			

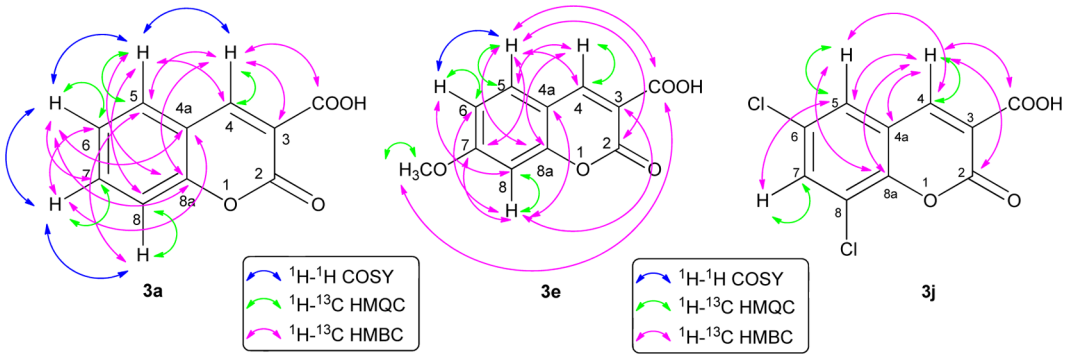

Figure 1. ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC interactions for **3a**, **3b**, and **3j** (COSY, correlation spectroscopy; HMQC, heteronuclear multiple quantum coherence; HMBC, heteronuclear multiple bond correlation).

correlations for the compounds are tabulated in Tables 3–5, and the interactions are depicted in Figure 1.

It was also possible to develop a single unit crystal of the new compound, 6-methoxycoumarin-3-carboxylic acid (**3f**) (Table 2, entry 6), and its single crystal X-ray analysis (CCDC 1400200; unit cell parameters: a 3.8044(3), b 10.8022(8), c 11.6217(9), P21) is documented in this present communication (Figure 2).[91]

Herein is a plausible mechanism for the base-catalyzed formation of coumarin-3-carboxyic acid entity (Scheme 2). The conjugate base (**2a**) of Meldrum's acid (**2**) generated in the basic reaction medium takes part in a nucleophilic attack at the electron-deficient carbonyl carbon of salicylaldehyde **1** leading to the Knoevenagel intermediate **6** via the intermediate species **4** and **5**. In the next step, the geometrically favored phenolic group within **6** undergoes ring-closure reaction through a nucleophilic attack onto the carbonyl carbon of Medlrum's acidic part of the intermediate yielding coumarin-3-carboxylate **7** with the elimination of an acetone molecule. Acidification of the salt **7** affords the free coumarin-3-carboxylic acid **3** (Scheme 2). Interestingly, azide ion does not act as a nucleophile in this reaction in spite of its use in a 0.5 equivalency.

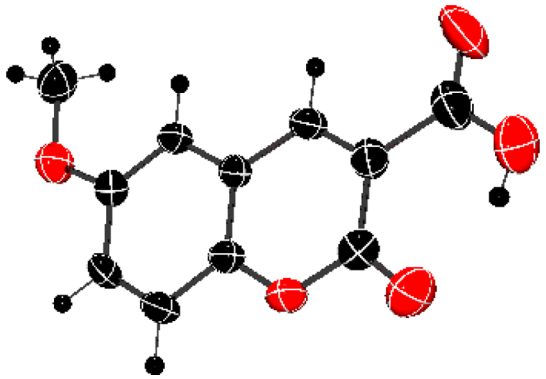

Figure 2. ORTEP diagram of 6-methoxycoumarin-3-carboxylic acid (**3f**) (CCDC 1400200).

The feasibility of the present method was also examined for a somewhat scaled-up (on the gram scale) experiment with salicylaldehyde (1.22 g; 10 mmol) and Meldrum's acid (1.44 g; 10 mmol) in two different set-ups involving the use of K_2CO_3 (280 mg; 20 mol %) in one and NaN_3 (330 mg; 50 mol %) in another as the catalysts at room temperature in water; the reaction was found to proceed smoothly affording the desired product, coumarin-3-carboxylic acid (**3a**, a commercially available fine chemical), respectively in 88% (1.67 g) and 98% (1.86 g) yields, almost similarly in all respects with 1 mmol scale entry (Table 2, entry 1). This experiment demonstrated the efficiency of the catalyst(s) for large-scale production as well.

CONCLUSION

In conclusion, a simple, facile, energy-efficient, and conveniently practical method has been developed for easy access to coumarin-3-caboxylic acids from the one-pot reaction between salicyladehydes and Meldrum's acid in water using either potassium carbonate or sodium azide as catalyst at room temperature. Mild reaction conditions, good to excellent yields,

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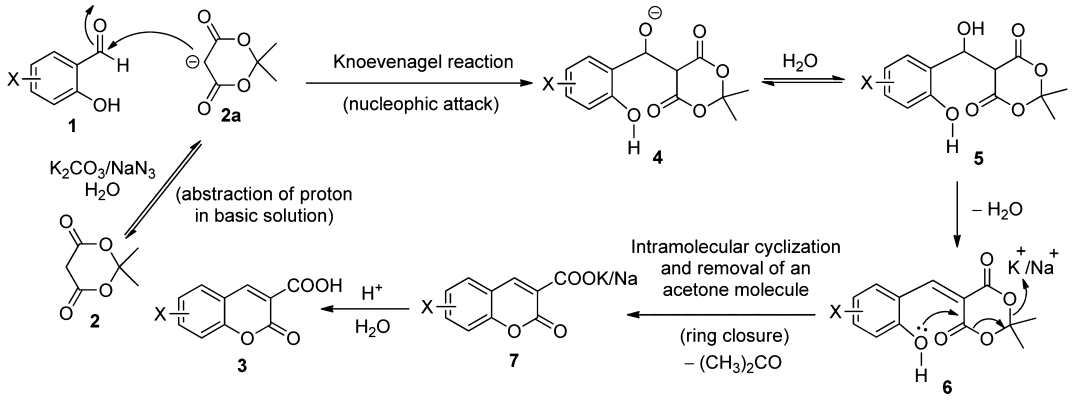
Scheme 2. Proposed Mechanism for the Base-Catalyzed One-Pot Synthesis of Coumarin-3-carboxylic Acids in Water



operational simplicity, avoidance of organic solvent, use of water as reaction medium, absence of tedious separation procedures, clean reaction profiles, and energy-efficiency as well as the use of inexpensive and environmentally benign catalysts are the key advantages of the present method. Keeping in mind that the synthetic importance of such biologically relevant coumarin scaffolds directly relate to medicinal chemistry, the present water-mediated methodology with mild reaction conditions and operational simplicity offers the possibility of its use with cost-effective and environmentally friendlier ways for large-scale industrial syntheses as well.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b00826.

Materials and apparatus, general experimental procedure, spectral data and respective scanned spectra (^{1}H and ^{13}C NMR) of all the synthesized compounds. This material is available free of charge (PDF).

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Notes

The authors declare no competing financial interest.

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