ACS Sustainable Chemistry & Engineering

Research Article

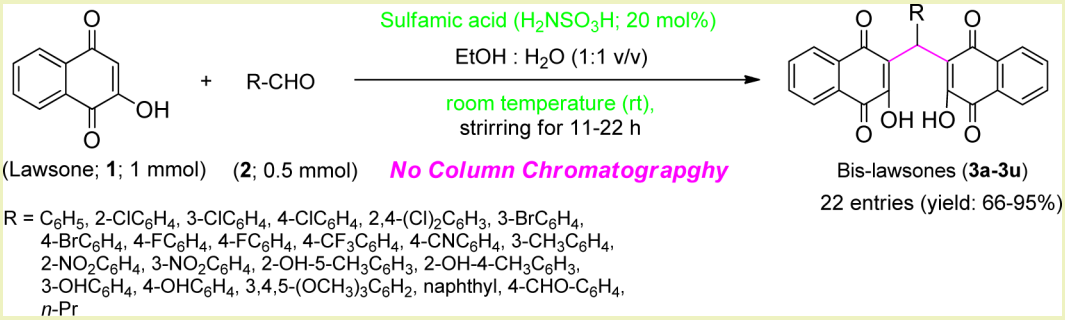
pubs.acs.org/journal/ascecg

Sulfamic Acid-Catalyzed One-Pot Room Temperature Synthesis of Biologically Relevant Bis-Lawsone Derivatives

Goutam Brahmachari*

Laboratory of Natural Products & Organic Synthesis, Department of Chemistry, Visva-Bharati (a Central University), Santiniketan, 731235 West Bengal, India

Supporting Information



ABSTRACT: A simple and energy-efficient green protocol for the synthesis of a series of biologically interesting functionalized bis-lawsone [i.e., 3,3′-(aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione)] scaffolds has been developed in the presence of sulfamic acid as an eco-friendly organocatalyst via one-pot pseudomulticomponent reaction at room temperature. The salient features of the present protocol are mild reaction conditions, good to excellent yields, operational simplicity, energy-efficiency, high atom-economy, eco-friendliness, easy isolation of products and no column chromatographic separation.

KEYWORDS: *Bis-lawsones, Functionalized 3,3′-(aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) scaffolds, Sulfamic acid, Aqueous ethanol, Room-temperature, No column chromatography, Green and sustainable chemistry*

INTRODUCTION

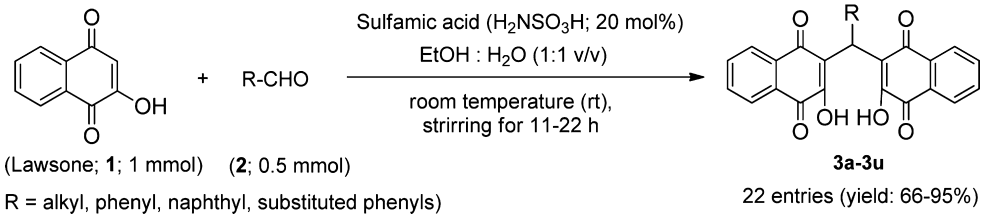
Lawsone (2-hydroxy-1,4-naphthoquinone) is a major chemical constituent of the medicinal plant, *Lawsonia inermis* Linn. (Synonyms: *L. alba*, *L. spinosa*; also known as *Henna* or *Mhendi*. Family: Lythraceae), different parts of which have been traditionally used all over the world as cosmetics (hair dye, body paint and tattoo dye) and herbal remedies in treating various ailments.[1−7] Pharmacological studies with *L. inermis* extracts during the last two decades have indicated strong nootropic, CNS depressing, antimicrobial, antioxidant, wound healing, anti-inflammatory, antipyretic, analgesic, hepatoprotective, tuberculostatic, diuretic, hypoglycemic and antiparasitic actions[8−24] of the plant. It has also been revealed that lawsone is primarily responsible for most the pharmaceutical and coloring properties of the plant. Lawsone has been evaluated to possess a wide range of biological and pharmacological activities such as antioxidant,[25] antibacterial,[26] antifungal,[27] cytotoxic,[28] trypsin inhibitor,[29] anticoagulant,[30] advanced glycated end products (AGEs) formation inhibitor,[31] antiacute pancreatitis[32] and many more.[24] The interesting structural pattern of lawsone coupled with its so-called multifaceted pharmacological potential have motivated the chemists to explore this useful scaffold in certain chemical processes, particularly in synthesizing ligands for metal complexations[33,34] and also few of its derivatives having a number of biological activities[35,36] as reported so far.

However, available reports on the novel scaffold developments with lawsone are still very limited, and hence a systematic effort has been taken to develop a simple, efficient and eco-friendly protocol for the synthesis of a series of 3,3′-(aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) scaffolds from lawsone with a view that the synthetic bis-lawsone derivatives would exhibit certain promising biological activities, as these molecules bear the lawsone moiety as a substructure. In fact, hydroxynapthalene[37,38] and arylmethylene[39,40] derivatives have already been proven to be effective antimicrobial, herbicidal and antioxidant compounds, respectively. A literature survey revealed that there is an earlier report on the synthesis of such kind of compounds using lithium chloride as catalyst under reflux conditions.[41] When the present method was developed, another report on the synthesis of 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) using lipase as a biocatalyst under heating condition has just been reported.[42] However, these methods suffer from certain limitations such as the use of environmentally hazardous or expensive catalyst, high reaction temperature or long reaction time, and most notably the scope of both the methods are very much limited. Hence, the development of a simple, efficient,

Received: April 19, 2015
Revised: July 7, 2015
Published: July 23, 2015

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

Scheme 1. Synthesis of Functionalized Bis-Lawsone Derivatives (i.e., 3,3′-(Aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) Scaffolds) (3)



high-yielding, environmentally benign and energy-efficient protocol for the one-pot synthesis of such biologically relevant diverse hydroxynapthalene and arylmethylene scaffolds is of great interest.

As part of our continuing efforts to develop green synthetic methodologies for useful organic transformations,[43−58] herein I wish to report a convenient, clean and highly efficient protocol for the one-pot synthesis of functionalized bis-lawsones, i.e., 3,3′-(aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) derivatives **3** from the reaction of lawsone (i.e., 2-hydroxynaphthalene-1,4-dione; **1**; 2 equiv) and aldehydes (**2**; 1 equiv) in aqueous ethanol at room temperature using commercially available sulfamic acid as an inexpensive and environmentally benign organo-catalyst (Scheme 1).

Sulfamic acid (NH_2SO_3H), a commercially available, inexpensive and nontoxic eco-friendly substance, finds useful applications as an organo-catalyst in many organic transformations of considerable interests.[59] The striking advantage of using sulfamic acid as an organo-catalyst is its amphoteric nature, possessing both amine and sulfonic acid moiety, the amino group could catalyze the reaction via electrophilic imine formation and the sulfonic acid group might stabilize the charge generated on the nitrogen.[60−66] This successful prehistory of sulfamic acid as a commercially available low-cost and environmentally benign organo-catalyst with intrinsic zwitterionic property encouraged the investigation of its further applications in some other carbon−carbon bond forming reactions. In this paper, I wish to extend the synthetic applicability of this unique organo-catalyst in the one-pot synthesis of bis-lawsone derivatives (**3**) via a puesdo-multicomponent reaction (MCR). Implementation of several transformations in a single manipulation in a MCR strategy offers a handful of advantages, particularly a facile automation, operational simplicity, reduction in the number of workup steps, thereby minimizing the extraction and purification processes as well as waste generation, and savings of energy and manpower. All these issues are directly linked with the goals of "green and sustainable chemistry".[67−75] In addition, designing for room temperature conditions coupled with other green aspects is also an area of current choice in synthetic organic chemistry.[76]

EXPERIMENTAL SECTION

General. Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using KBr disc. ^{1}H and ^{13}C NMR spectra were obtained at 500 and 400 MHz and 125 and 100 MHz, respectively, using Bruker DRX-500 Bruker DRX-400 spectrometers 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. Melting point was recorded on a Chemiline CL-725 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 3,3′-(Aryl/alkylmethylene)bis(2-hydroxynaphthalene-1,4-dione) Scaffolds (Bis-lawsones 3). An oven-dried screw cap test tube was charged with a magnetic stir bar, aldehyde (**2**; 0.5 mmol), 2-hydroxynaphthalene-1,4-dione (**1**; 1 mmol), sulfamic acid (20 mol %), EtOH:H_2O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature for appropriate range of time as indicated in Table 2. The progress of the reaction was monitored by TLC. Upon completion of reaction, a solid mass precipitated out which was filtered off followed by washing with aqueous ethanol to obtain crude product of bis-lawsone **3** purified just by recrystallization from hot ethanol without carrying out column chromatographic purification. The structure of each purified bis-lawsone [3,3′-(aryl/alkylmethylene)bis(2-hydroxynaphthalene-1,4-dione)] scaffolds was confirmed by analytical as well as spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR and TOF-MS.

Characterization Data of Bis-lawsones ***3****. 3,3′-(Phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) (****3a****).* Yellow solid. Yield: 92%. mp: 198−200 °C. IR (KBr) ν_{max}/cm^{-1}: 3632, 3607, 3373, 3063, 2907, 1657, 1647, 1597, 1520, 1458, 1381, 1367, 1163, 953, 874, 735, 719, 656, 644, 631, 555. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 6.03 (1H, s, −C*H*), 7.12 (1H, t, J = 7.2 and 6.8 Hz, Ar*H*), 7.19 (1H, d, J = 8 Hz, Ar*H*), 7.24 (3H, t, J = 7.2 and 6.8 Hz, Ar*H*), 7.77 (2H, td, J = 8.4, 7.2, and 1.6 Hz, Ar*H*), 7.82 (2H, td, J = 7.2 and 1.2 Hz, Ar*H*), 7.93 (2H, dd, J = 7.2 and 1.2 Hz, Ar*H*), 7.99 (2H, dd, J = 7.6 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 38.08, 123.53 (2C), 125.86 (2C), 125.99 (2C), 126.46 (2C), 128.02 (2C), 128.56 (2C), 130.27 (2C), 132.61 (2C), 133.50 (2C), 135.07 (2C), 141.26, 156.76 (2C), 181.65 (2C), 183.97 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{16}O_6Na$: 459.0845. Found: 459.0849. Elemental analysis Calcd (%) for $C_{27}H_{16}O_6$: C, 74.31; H, 3.70. Found: C, 74.35; H, 3.72.

*3,3′-((2-Chlorophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (****3b****).* Yellow solid. Yield: 88%. mp: 216−218 °C. IR (KBr) ν_{max}/cm^{-1}: 3587, 3406, 3173, 2982, 1657, 1647, 1582, 1460, 1352, 1323, 1248, 1148, 1028, 953, 885, 810, 712. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 6.11 (1H, s, −C*H*), 7.21−7.19 (2H, m, Ar*H*), 7.35 (2H, d, J = 6.8 Hz, Ar*H*), 7.78 (2H, t, J = 7.6 and 7.2 Hz, Ar*H*), 7.83 (2H, t, J = 7.6 and 7.2 Hz, Ar*H*), 7.94 (2H, d, J = 7.2 Hz, Ar*H*), 8.00 (2H, d, J = 7.2 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 36.73, 122.47 (2C), 126.07 (2C), 126.50 (2C), 126.96, 127.93, 128.97, 130.25 (2C), 130.90, 132.43 (2C), 133.20, 133.61 (2C), 135.17 (2C), 138.78, 156.76 (2C), 181.42 (2C), 183.64 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{15}ClO_6Na$: 493.0455. Found: 493.0457. Elemental analysis Calcd (%) for $C_{27}H_{15}ClO_6$: C, 68.87; H, 3.21. Found: C, 68.89; H, 3.23.

*3,3′-((3-Chlorophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (****3c****).* Yellow solid. Yield: 93%. mp: 210−212 °C. IR (KBr) ν_{max}/cm^{-1}: 3614, 3568, 3419, 3065, 1653, 1601, 1582, 1238, 1209, 1007, 989, 868, 735, 650. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 5.98 (1H, s, −C*H*), 7.20−7.17 (1H, m, Ar*H*), 7.26−7.21 (2H, m, Ar*H*), 7.31 (1H, s, Ar*H*), 7.77 (2H, td, J = 7.6, 7.2. 2, and 1.2 Hz, Ar*H*), 7.82 (2H, td, J = 7.6, 7.2, and 1.2 Hz, Ar*H*), 7.93 (2H, dd, J = 7.2 and 0.8 Hz, Ar*H*), 7.99 (2H, dd, J = 7.2, 1.2, and 0.8 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.91, 122.76, 125.95 (2C), 126.02 (2C), 126.46 (2C), 127.42, 128.33, 129.76 (2C), 130.35 (2C),

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

132.57 (2C), 132.80, 133.52 (2C), 135.05 (2C), 144.08, 156.83, 181.57 (2C), 183.88 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{15}ClO_6Na$: 493.0455. Found: 493.0459. Elemental analysis Calcd (%) for $C_{27}H_{15}ClO_6$: C, 68.87; H, 3.21. Found: C, 68.86; H, 3.24.

*3,3′-((4-Chlorophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3d**).* Yellow solid. Yield: 89%. mp: 195−196 °C. IR (KBr) ν_{max}/cm^{-1}: 3650, 3075, 2895, 3408, 1665, 1640, 1593, 1465, 1379, 1339, 1301, 1160, 1040, 935, 825, 725. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 6.06 (1H, s, −C*H*), 7.27−7.22 (4H, m, Ar*H*), 7.77 (2H, t, J = 7.6 and 7.2 Hz, Ar*H*), 7.81 (2H, t, J = 7.2 and 6.8 Hz, Ar*H*), 7.94 (2H, d, J = 7.2 Hz, Ar*H*), 7.98 (2H, d, J = 7.2 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.00, 122.98 (2C), 125.95 (2C), 126.42 (2C), 127.92 (2C), 130.30 (2C), 130.44 (2C), 132.72 (2C), 133.37 (2C), 134.97 (2C), 140.57 (2C), 157.92 (2C), 181.92 (2C), 183.73 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{15}ClO_6Na$: 493.0455. Found: 493.0458. Elemental analysis Calcd (%) for $C_{27}H_{15}ClO_6$: C, 68.87; H, 3.21. Found: C, 68.86; H, 3.22.

*3,3′-((2,4-Dichlorophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3e**).* Yellow solid. Yield: 85%. mp: 200−202 °C. IR (KBr) ν_{max}/cm^{-1}: 3590, 3448, 3060, 2907, 1653, 1593, 1576, 1472, 1462, 1373, 1231, 1150, 1094, 1030, 827, 677. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 6.05 (1H, s, −C*H*), 7.25 (1H, dd, J = 8 and 1.6 Hz, Ar*H*), 7.38 (1H, d, J = 8.4 Hz, Ar*H*), 7.49 (1H, d, J = 1.6 Hz, Ar*H*), 7.78 (2H, t, J = 8 and 7.2 Hz, Ar*H*), 7.83 (2H, t, J = 8.4 and 7.6 Hz, Ar*H*), 7.94 (2H, d, J = 7.6 Hz, Ar*H*), 8.00 (2H, d, J = 7.6 Hz Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 36.32, 121.93 (2C), 126.09 (2C), 126.50 (2C), 127.04, 128.32, 130.28 (2C), 131.54, 132.31, 132.38 (2C), 133.64 (2C), 133.98, 135.17 (2C), 138.17, 156.90 (2C), 181.34 (2C), 183.62 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{14}Cl_2O_6Na$: 527.0065. Found: 527.0068. Elemental analysis Calcd (%) for $C_{27}H_{14}Cl_2O_6$: C, 64.18; H, 2.79. Found: C, 64.16; H, 2.81.

*3,3′-((3-Bromophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3f**).* Yellow solid. Yield: 85%. mp: 219−220 °C. IR (KBr) ν_{max}/cm^{-1}: 3610, 3590, 3418, 3067, 1661, 1651, 1583, 1574, 1466, 1367, 1279, 1269, 1151, 1030, 980, 960, 885, 773. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 5.98 (1H, s, −C*H*), 7.17 (1H, t, J = 8.0 and 7.6 Hz, Ar*H*), 7.27 (1H, d, J = 7.2 Hz, Ar*H*), 7.32 (1H, d, J = 7.6 Hz, Ar*H*), 7.44 (1H, s, Ar*H*), 7.78 (2H, t, J = 7.6 and 7.2 Hz, Ar*H*), 7.82 (2H, t, J = 8.0 and 7.2 Hz, Ar*H*), 7.93 (2H, d, J = 7.2 Hz, Ar*H*), 7.99 (2H, d, J = 7.2 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.85, 121.54, 122.73 (2C), 126.02 (2C), 126.46 (2C), 127.81, 128.84, 130.11, 130.35 (2C), 131.09, 132.57 (2C), 133.51 (2C), 135.05 (2C), 144.37, 156.91 (2C), 181.58 (2C), 183.85 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{15}BrO_6Na$: 536.9950. Found: 536.9955. Elemental analysis Calcd (%) for $C_{27}H_{15}O_6Br$: C, 62.93; H, 2.93. Found: C, 62.96; H, 2.92.

*3,3′-((4-Bromophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3g**).* Yellow solid. Yield: 87%. mp: 195−197 °C. IR (KBr) ν_{max}/cm^{-1}: 3657, 3597, 3393, 3142, 3128, 3053, 2976, 1663, 1474, 1360, 1284, 1165, 1032, 962, 904, 893, 814, 743. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 5.95 (1H, s, −C*H*), 7.22 (2H, d, J = 8.4 Hz, Ar*H*), 7.38 (2H, d, J = 8.4 Hz, Ar*H*), 7.78 (2H, td, J = 7.6 and 1.2 Hz, Ar*H*), 7.82 (2H, td, J = 7.6 and 1.6 Hz, Ar*H*), 7.93 (2H, dd, J = 7.6 and 0.8 Hz, Ar*H*), 7.99 (2H, dd, J = 7.6 and 1.2 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.72, 118.95, 123.04 (2C), 126.05 (2C), 126.50 (2C), 130.34 (2C), 130.85 (2C), 130.94 (2C), 132.62 (2C), 133.57 (2C), 135.12 (2C), 141.03, 156.88 (2C), 181.64 (2C), 183.92 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{15}BrO_6Na$: 536.9950. Found: 536.9952. Elemental analysis Calcd (%) for $C_{27}H_{15}O_6Br$: C, 62.93; H, 2.93. Found: C, 62.94; H, 2.93.

*3,3′-((2-Fluorophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3h**).* Bright yellow solid. Yield: 85%. mp: 225−227 °C. IR (KBr) ν_{max}/cm^{-1}: 3632, 3404, 3281, 3168, 3050, 1655, 1585, 1491, 1478, 1362, 1279, 1221, 1018, 959, 810, 741. ^1H NMR (500 MHz, DMSO-d_6): δ/ppm 6.08 (1H, s, −C*H*), 7.00−7.07 (2H, m, Ar*H*), 7.18−7.22 (1H, m, Ar*H*), 7.25 (1H, t, J = 8 and 7.5 Hz, Ar*H*), 7.77 (2H, td, J = 7, 7.5, and 1 Hz, Ar*H*), 7.82 (2H, td, J = 7.5 and 1 Hz, Ar*H*), 7.92 (2H, d, J = 7 Hz, Ar*H*), 7.98 (2H, d, J = 7 Hz, Ar*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm 32.05, 114.23, 114.40, 121.99, 123.76, 125.73 (2C), 126.15 (2C), 127.67, 127.74, 127.85, 129.88, 130.31, 132.11 (2C), 133.28 (2C), 134.83 (2C), 156.34, 159.60, 161.53, 181.10 (2C), 183.37 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{15}FO_6Na$: 477.0750. Found: 477.0747. Elemental analysis Calcd (%) for $C_{27}H_{15}FO_6$: C, 71.37; H, 3.33. Found: C, 71.31; H, 3.37.

*3,3′-((4-Fluorophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3i**).* Yellow solid. Yield: 84%. mp: 177−178 °C. IR (KBr) ν_{max}/cm^{-1}: 3666, 3593, 3571, 3508, 3414, 3335, 3061, 1659, 1593, 1583, 1495, 1354, 1238, 1227, 1032, 959, 829. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 5.98 (1H, s, −C*H*), 7.01 (2H, t, J = 8.8 Hz, Ar*H*), 7.27 (2H, td, J = 6.8 and 2.4 Hz, Ar*H*), 7.78 (2H, td, J = 7.6 and 1.2 Hz, Ar*H*), 7.82 (2H, td, J = 7.6 and 1.6 Hz, Ar*H*), 7.93 (2H, dd, J = 7.6 and 0.8 Hz, Ar*H*), 7.99 (2H, dd, J = 7.6 and 0.8 Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.44, 114.49, 114.71, 123.39 (2C), 125.98 (2C), 126.44 (2C), 130.29, 130.35 (2C), 132.60 (2C), 133.50 (2C), 135.06 (2C), 137.35, 156.84 (2C), 159.69, 162.08, 181.68 (2C), 183.91 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{15}FO_6Na$: 477.0750. Found: 477.0752. Elemental analysis Calcd (%) for $C_{27}H_{15}FO_6$: C, 71.37; H, 3.33. Found: C, 71.35; H, 3.31.

*3,3′-((4-(Trifluoromethyl)phenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3j**).* Yellow solid. Yield: 86%. mp: 191−193 °C. IR (KBr) ν_{max}/cm^{-1}: 3599, 3583, 3402, 3044, 2908, 1659, 1643, 1582, 1479, 1356, 1225, 1138, 1122, 1036, 712. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 6.07 (s, 1H, −C*H*), 7.47 (2H, d, J = 8 Hz, Ar*H*), 7.51 (2H, d, J = 8.0 Hz, Ar*H*), 7.79 (2H, t, J = 8.0 and 7.2 Hz, Ar*H*), 7.83 (2H, t, J = 6.8 Hz, Ar*H*), 7.93 (2H, d, J = 7.2 Hz, Ar*H*), 7.99 (2H, d, J = 6.8 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.85, 122.60 (2C), 124.87 (2C), 126.03 (2C), 126.47 (2C), 129.18, 129.22 (2C), 130.36 (2C), 132.59 (2C), 133.54 (2C), 135.08 (2C), 146.60 (2C), 157.28 (2C), 181.64 (2C), 183.80 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{15}F_3O_6Na$: 527.0718. Found: 527.0720 $[M + Na]^+$. Elemental analysis Calcd (%) for $C_{28}H_{15}F_3O_6$: C, 66.67; H, 3.00. Found: C, 66.69; H, 3.05.

*4-(Bis(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-benzonitrile (**3k**).* Yellow solid. Yield: 90%. mp: 150−152 °C. IR (KBr) ν_{max}/cm^{-1}: 3670, 3627, 3363, 3069, 2937, 2228, 1661, 1582, 1462, 1442, 1371, 1358, 1331, 1236, 1153, 1034, 978, 879, 795, 623. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 6.04 (1H, s, −C*H*), 7.46 (2H, d, J = 8 Hz, Ar*H*), 7.67 (2H, d, J = 8 Hz, Ar*H*), 7.78 (2H, t, J = 8 and 7.6 Hz, Ar*H*), 7.82 (2H, t, J = 9.6 and 6.8 Hz, Ar*H*), 7.92 (2H, d, J = 7.2 Hz, Ar*H*), 7.99 (2H, d, J = 7.2 Hz, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 38.21, 108.57, 119.64, 122.32 (2C), 126.05 (2C), 126.47 (2C), 129.60 (2C), 130.34 (2C), 131.93 (2C), 132.54 (2C), 133.56 (2C), 135.09 (2C), 147.84, 157.14 (2C), 181.54 (2C), 183.78 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{15}NO_6Na$: 484.0797. Found: 484.0799. Elemental analysis Calcd (%) for $C_{27}H_{16}O_7$: C, 72.88; H, 3.28; N, 3.04. Found: C, 72.87; H, 3.27; N, 3.02.

*3,3′-(m-Tolylmethylene)bis(2-hydroxynaphthalene-1,4-dione) (**3l**).* Yellow solid. Yield: 94%. mp: 210−212 °C. IR (KBr) ν_{max}/cm^{-1}: 3588, 3492, 3429, 3344, 3275, 3045, 1653, 1589, 1478, 1379, 1335, 1273, 1217, 1034, 970, 908, 812, 793. ^1H NMR (500 MHz, DMSO-d_6): δ/ppm 2.21 (3H, s, Ar−CH_3), 5.97 (1H, s, −C*H*), 6.92 (1H, d, J = 7 Hz, Ar*H*), 7.01 (2H, t, J = 7.5 Hz, Ar*H*), 7.07 (1H, t, J = 7.5 Hz, Ar*H*), 7.77 (2H, td, J = 7.5 and 1.5 Hz), 7.81 (2H, td, J = 7.5 and 1.5 Hz), 7.91 (2H, dd, J = 7.5 and 1 Hz), 7.98 (2H, dd, J = 7.5 and 1 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm 21.20, 37.59, 123.23 (2C), 125.42, 125.64 (2C), 126.12 (2C), 126.27, 127.57, 128.71, 129.96 (2C), 132.29 (2C), 133.16 (2C), 134.72 (2C), 136.48 (2C), 140.85, 156.43, 181.32 (2C), 183.61 (2C). HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{28}H_{18}O_6Na$: 473.1001. Found: 473.0968. Elemental analysis Calcd (%) for $C_{28}H_{18}O_6$: C, 74.66; H, 4.03. Found: C, 74.63; H, 4.01.

*3,3′-((2-Nitrophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3m**).* Yellow solid. Yield: 91%. mp: 192−193 °C. IR (KBr) ν_{max}/cm^{-1}: 3663, 3585, 3352, 3065, 2395, 1666, 1595, 1578, 1519, 1510, 1458, 1377, 1265, 1148, 1032, 960, 795, 743, 714, 696, 619. ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 6.42 (1H, s, −C*H*), 7.43 (1H,

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

m, ArH), 7.56 (2H, d, J = 2.8 Hz, ArH), 7.79 (2H, t, J = 8 and 7.2 Hz, ArH), 7.84 (2H, t, J = 7.6 and 6.4 Hz, ArH), 7.89 (1H, d, J = 8 Hz, ArH), 7.93 (2H, d, J = 7.2 Hz, ArH), 7.99 (2H, d, J = 6.4 Hz ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 34.93, 122.19 (2C), 124.39, 126.11 (2C), 126.52 (2C), 127.66, 130.27 (2C), 131.71, 132.31 (2C), 133.09, 133.68 (2C), 135.21 (2C), 135.50, 149.36, 156.91 (2C), 181.35 (2C), 183.65 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{15}NO_8Na$: 504.0695. Found: 504.0696. Elemental analysis Calcd (%) for $C_{27}H_{15}NO_8$: C, 67.36; H, 3.14; N, 2.91. Found: C, 67.35; H, 3.17; N, 2.93.

3,3′-((3-Nitrophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) ***(3n)***. Yellow solid. Yield: 95%. mp: 136−138 °C. IR (KBr) ν_{max}/cm^{-1}: 3699, 3676, 3582, 3045, 2980, 2959, 1655, 1622, 1585, 1478, 1410, 1340, 1122, 1026, 912, 837, 731, 650. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 6.08 (1H, s, −CH), 7.52 (1H, t, J = 8 Hz, ArH), 7.77 (2H, td, J = 6.0, 2.4, 0.8, ArH), 7.83 (3H, td, J = 7.6, 2.4, 1.2, 0.8 Hz ArH), 7.93 (2H, d, J = 7.2 Hz, ArH), 8.00 (2H, dd, J = 6.8 and 1.2 Hz, ArH), 8.03 (1H, dd, J = 7.6 and 1.6 Hz, ArH), 8.09 (1H, br s, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 38.00, 121.16, 122.38 (2C), 123.24, 126.07 (2C), 126.48 (2C), 129.42, 130.35 (2C), 132.54 (2C), 133.57 (2C), 135.10 (2C), 135.63, 144.03, 148.01, 157.03 (2C), 181.55 (2C), 183.84 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{15}NO_8Na$: 504.0695. Found: 504.0694. Elemental analysis Calcd (%) for $C_{27}H_{15}NO_8$: C, 67.36; H, 3.14; N, 2.91. Found: C, 67.38; H, 3.13; N, 2.92.

3,3′-((3-Hydroxyphenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) ***(3o)***. Yellow solid. Yield: 91%. mp: 205−207 °C. IR (KBr) ν_{max}/cm^{-1}: 3672, 3661, 3425, 3069, 2937, 1661, 1583, 1462, 1443, 1371, 1331, 1236, 1153, 1034, 978, 879, 795. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 5.97 (1H, s, −CH), 6.54 (1H, d, J = 6.4 Hz, ArH), 6.65 (1H, br s, ArH), 6.68 (1H, d, J = 7.6 Hz, ArH), 6.99 (2H, t, J = 6.8 Hz, ArH), 7.77 (2H, d, J = 7.6 Hz, ArH), 7.82 (2H, t, J = 8 Hz, ArH), 7.94 (2H, d, J = 6.8 Hz, ArH), 7.99 (2H, d, J = 6.8 Hz, ArH), 9.04 (1H, br s, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.82, 112.95, 115.48, 119.46, 123.62 (2C), 125.99 (2C), 126.48 (2C), 128.91, 130.23 (2C), 132.61 (2C), 133.51 (2C), 135.09 (2C), 142.59, 156.80 (2C), 157.23, 181.70 (2C), 183.94 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{16}O_7Na$: 475.0794. Found: 475.0796. Elemental analysis Calcd (%) for $C_{27}H_{16}O_7$: C, 71.68; H, 3.56. Found: C, 71.69; H, 3.55.

3,3′-((4-Hydroxyphenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) ***(3p)***. Yellow solid. Yield: 87%. mp: 213-215 °C. IR (KBr) ν_{max}/cm^{-1}: 3656, 3644, 3506, 3069, 2949, 1651, 1639, 1589, 1572, 1504, 1350, 1337, 1231, 1109, 1032, 959, 912, 773, 752, 687, 646. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 5.59 (1H, s, −CH), 7.03 (2H, d, J = 8.4 Hz, ArH), 7.60 (2H, d, J = 8.4 Hz, ArH), 7.77 (2H, td, J = 7.2 and 0.8 Hz, ArH), 7.82 (2H, td, J = 7.2, 1.2, and 0.8 Hz, ArH), 7.92 (2H, dd, J = 8.0 and 0.8 Hz, ArH), 7.98 (2H, dd, J = 7.2 and 0.8 Hz, ArH), 9.11 (1H, br s, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 37.42, 114.91 (2C), 124.16 (2C), 125.95 (2C), 126.42 (2C), 129.56 (2C), 130.24 (2C), 131.11, 132.62 (2C), 133.48 (2C), 135.05 (2C), 155.64, 156.50 (2C), 181.73 (2C), 184.06 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{16}O_7Na$: 475.0794. Found: 475.0796. Elemental analysis Calcd (%) for $C_{27}H_{16}O_7$: C, 71.68; H, 3.56. Found: C, 71.67; H, 3.58.

3,3′-((2-Hydroxy-5-methylphenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) ***(3q)***. Yellow solid. Yield: 89%. mp: 238−239 °C. IR (KBr) ν_{max}/cm^{-1}: 3655, 3625, 3010, 2955, 1675, 1645, 1625, 1575, 1355, 1275, 1220, 1115, 1025, 971, 945, 828, 741. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 2.19 (3H, s, −CH$_3$), 5.71 (1H, s, −CH), 6.92 (1H, br s, ArH), 7.05 (1H, d, J = 8.4 Hz, ArH), 7.12 (1H, d, J = 8.4 Hz, ArH), 7.77 (1H, t, J = 8.0 and 7.2 Hz, ArH), 7.80−7.83 (3H, m, ArH), 7.86−7.89 (1H, m, ArH), 7.94 (1H, d, J = 7.2 Hz ArH), 8.03−8.06 (2H, m, ArH), 11.41 (1H, br s, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 20.71, 37.56, 116.70, 126.13, 126.19 (2C), 126.37 (2C), 129.23, 129.44, 130.36, 130.68, 131.61, 131.95, 133.75, 134.25, 135.02, 135.14, 135.19 (2C), 147.25 (2C), 151.85, 156.19, 178.33, 181.67, 183.27 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{28}H_{18}O_7Na$: 489.0950. Found: 489.0956. Elemental analysis Calcd (%) for $C_{28}H_{18}O_7$: C, 72.10; H, 3.89. Found: C, 72.13; H, 3.87.

3,3′-((3-Hydroxy-4-methoxyphenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) ***(3r)***. Brownish yellow solid. Yield: 76%. mp: 171−173 °C. IR (KBr) ν_{max}/cm^{-1}: 3612, 3520, 3345, 3184, 3072, 2916, 2843, 1647, 1583, 1514, 1450, 1385, 1277, 1124, 1040, 974, 876, 731. ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm 3.69 (3H, s, Ar−OCH$_3$), 5.88 (1H, s, −CH), 6.15 (1H, s, ArH), 6.61 (1H, dd, J = 8, 2, and 1.5 Hz, ArH), 6.67 (1H, d, J = 2 Hz, ArH), 6.73 (1H, d, J = 8.5 Hz, ArH), 7.73−7.82 (4H, m, ArH), 7.91 (1H, d, J = 7.5 Hz, ArH), 7.97 (1H, d, J = 7. Hz, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm 37.14, 55.66, 111.08 (2C), 123.67, 125.47 (2C), 125.62, 126.00 (2C), 126.11, 129.85, 130.62, 131.94, 132.26, 133.16, 133.27, 133.32 (2C), 134.52 (2C), 134.73, 145.83, 156.09, 181.33 (2C), 183.68 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{28}H_{18}O_8Na$: 505.0899. Found: 505.0891. Elemental analysis Calcd (%) for $C_{28}H_{18}O_8$: C, 69.71; H, 3.76. Found: C, 69.68; H, 3.78.

3,3′-((3,4,5-Trimethoxyphenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) ***(3s)***. Yellow solid. Yield: 89%. mp: 201−203 °C. IR (KBr) ν_{max}/cm^{-1}: 3682, 3661, 3339, 3096, 2926, 2835, 1663, 1593, 1576, 1501, 1439, 1358, 1285, 1124, 1018, 999, 987, 910, 795, 732, 662, 631, 590, 548. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 3.62 (3H, s, −OCH$_3$), 3.64 (6H, s, −OCH$_3$), 5.95 (1H, s, −CH), 6.54 (2H, s, ArH), 7.79 (2H, t, J = 7.2 and 6.8 Hz, ArH), 7.82 (2H, t, J = 7.2 Hz, ArH), 7.94 (2H, d, J = 7.6 Hz, ArH), 7.98 (2H, d, J = 6.8 Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 38.26, 56.25 (2C), 60.32, 106.35 (2C), 123.49 (2C), 125.98 (2C), 126.46 (2C), 130.30 (2C), 132.62 (2C), 133.48 (2C), 135.05 (2C), 136.07, 136.90, 152.66 (2C), 156.73 (2C), 181.68 (2C), 184.02 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{30}H_{22}O_9Na$: 549.1162. Found: 549.1168. Elemental analysis Calcd (%) for $C_{30}H_{22}O_9$: C, 68.44; H, 4.21. Found: C, 68.48; H, 4.19.

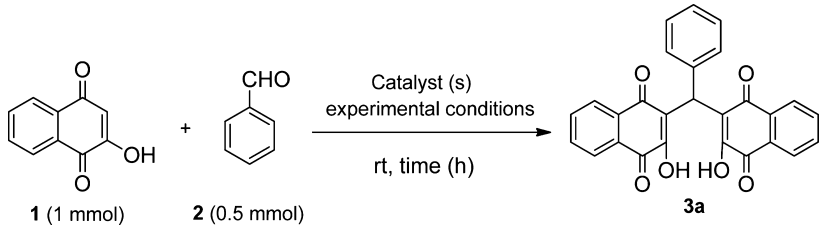
3,3′-(Naphthalen-2-ylmethylene)bis(2-hydroxynaphthalene-1,4-dione) ***(3t)***. Orange yellow solid. Yield: 90%. mp: 248−250 °C. IR (KBr) ν_{max}/cm^{-1}: 3638, 3421, 3339, 3053, 1651, 1587, 1521, 1462, 1375, 1269, 1030, 970, 910, 815, 735. ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm 6.16 (1H, s, −CH), 7.38−7.42 (2H, m, ArH), 7.46 (1H, dd, J = 8.5 and 1.5 Hz, ArH), 7.46 (1H, dd, J = 8.5 and 1.5 Hz, ArH), 7.69 (1H, s, ArH), 7.73 (1H, d, J = 9 Hz, ArH), 7.76−7.83 (6H, m, ArH), 7.92 (2H, dd, J = 7.5, 1.5, and 1 Hz, ArH), 8.00 (2H, dd, J = 7.5 and 1 Hz, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm 38.02, 123.00 (2C), 125.12, 125.55 (2C), 125.68 (2C), 126.14 (2C), 126.88, 127.37, 127.56, 127.83, 130.02 (2C), 131.72, 132.31 (2C), 133.12, 133.18 (2C), 134.74 (2C), 138.76 (2C), 156.57, 181.34 (2C), 183.66 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{31}H_{18}O_6Na$: 509.1001. Found: 509.1000. Elemental analysis Calcd (%) for $C_{31}H_{18}O_6$: C, 76.54; H, 3.73. Found: C, 76.48; H, 3.71.

3,3′-(Butane-1,1-diyl)bis(2-hydroxynaphthalene-1,4-dione) ***(3u)***. Yellow solid. Yield: 66%. mp: 136−138 °C. IR (KBr) ν_{max}/cm^{-1}: 3660, 3623, 3044, 2953, 2866, 1651, 1587, 1572, 1533, 1456, 1352, 1267, 1225, 1161, 1101, 1020, 854, 741, 638, 574. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 0.89 (3H, t, −CH$_3$), 1.32−1.26 (2H, m, −CH$_2$), 2.14−2.09 (2H, m, −CH$_2$), 4.62 (1H, t, J = 8 and 7.6 Hz, −CH), 7.75 (2H, td, J = 7.6 and 0.8 Hz, ArH), 7.81 (2H, td, J = 8 and 6.8 Hz, ArH), 7.94 (4H, d, J = 8.4 Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 14.55, 21.90, 32.94, 33.74, 124.87 (2C), 125.86 (2C), 126.42 (2C), 130.03 (2C), 132.62 (2C), 133.40 (2C), 135.02 (2C), 156.13 (2C), 157.23, 181.70 (2C), 184.37 (2C). HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{24}H_{18}O_6Na$: 425.1001. Found: 425.1009. Elemental analysis Calcd (%) for $C_{24}H_{18}O_6$: C, 71.64; H, 4.51. Found: C, 71.66; H, 4.52.

3,3′,3″,3‴-(1,4-Phenylenebis(methanetriyl))tetrakis(2-hydroxynaphthalene-1,4-dione) ***(3v)***. Yellow solid. Yield: 86%. mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3623, 3475, 3356, 3065, 2978, 1657, 1587, 1482, 1373, 1279, 1032, 974, 901, 796, 727. ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm 5.99 (2H, s, −CH), 7.05 (4H, s, ArH), 7.75 (4H, td, J = 7.5 and 1 Hz, ArH), 7.80 (4H, td, J = 7.5, 7, and 1 Hz, ArH), 7.92 (4H, d, J = 7.5 Hz, ArH), 7.96 (4H, dd, J = 7.5 and 0.5 Hz, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm 37.37 (2C), 123.36 (4C), 125.64 (4C), 126.15 (4C), 127.55 (4C), 129.90 (4C), 132.22 (4C), 133.17

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

Table 1. Optimization of Reaction Conditions in the Synthesis of 3,3′-(Phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) Derivative 3a



entry	catalyst (mol %)	solvent	time (h)	yield (%)[a,b]
1	no catalyst	no solvent	24	trace
2	no catalyst	EtOH:H_2O (1:1 v/v)	24	trace
3	$ZrOCl_2$, $8H_2O$ (10 mol %)	EtOH:H_2O (1:1 v/v)	24	52
4	CAN (20 mol %)	EtOH:H_2O (1:1 v/v)	24	58
5	urea (20 mol %)	EtOH:H_2O (1:1 v/v)	24	15
6	HCOONa (20 mol %)	EtOH:H_2O (1:1 v/v)	24	26
7	$CuCl_2$, $2H_2O$ (20 mol %)	EtOH:H_2O (1:1 v/v)	24	46
8	L-proline (20 mol %)	EtOH:H_2O (1:1 v/v)	24	68
9	TBATB (20 mol %)	EtOH:H_2O (1:1 v/v)	24	42
10	I_2 (20 mol %)	EtOH:H_2O (1:1 v/v)	24	61
11	sulfamic acid (10 mol %)	EtOH:H_2O (1:1 v/v)	24	79
12	sulfamic acid (15 mol %)	EtOH:H_2O (1:1 v/v)	24	85
13	sulfamic acid (20 mol %)	EtOH:H_2O (1:1 v/v)	16	92
14	sulfamic acid (20 mol %)	EtOH	24	45
15	sulfamic acid (20 mol %)	EtOH (1:2 v/v)	24	62
16	sulfamic acid (20 mol %)	H_2O	24	trace
17	sulfamic acid (20 mol %)	no solvent	24	trace

[a]Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol) and benzaldehyde (0.5 mmol) in the presence or absence of catalyst in neat/4 mL of water/ethanol/ethanol−water at room temperature. [b]Isolated yields.

(4C), 134.74 (4C), 137.52 (2C), 156.41 (4C), 181.44 (4C), 183.77 (4C). HRMS (ESI-TOF) *m/z* $[M + Na]^+$ Calcd for $C_{48}H_{26}O_{12}Na$: 817.1322. Found: 817.1307. Elemental analysis Calcd (%) for $C_{48}H_{26}O_{12}$: C, 72.54; H, 3.30. Found: C, 72.51; H, 3.28.

RESULTS AND DISCUSSION

To optimize the reaction conditions, a series of trial reactions with lawsone (**1**; 1 mmol) and benzaldehyde (**2**; 0.5 mmol) were first conducted in the absence or presence of a number of catalysts including sulfamic acid under neat conditions or using water, ethanol and/or ethanol−water (1:1 v/v) as the solvent at room temperature (Table 1). From these preliminary experiments, 20 mol % of sulfamic acid in aqueous ethanol (1:1 v/v) at room temperature came out as the optimized conditions for the reaction in terms of yield and time (Table 1, entry 13) for the desired product, 3,3′-(phenylmethylene)bis(2-hydroxynaphthalene-1,4-dione) (**3a**), which was characterized by its physical and spectral properties.

Under the optimized conditions, the reaction of 2-chlorobenzaldehyde with lawsone (**1**) was then carried out, and it furnished the product 3,3′-((2-chlorophenyl)methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3b**) in 88% yield within 16 h (Table 2, entry 2). To check the generality as well as the effectiveness of this newly developed protocol, a number of aromatic aldehydes having both electron-donating and electron-withdrawing substituents such as bromo, chloro, fluoro, trifluoromethyl, cyano, hydroxy, methoxy, methyl, nitro etc. were reacted with lawsone using identical reaction conditions; all of them underwent the reaction smoothly affording the corresponding 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) (**3c**−**3t**) (Table 2, entries 3−20) in good yields ranging from 76 to 95% at room temperature. Besides, butaraldehyde, an aliphatic aldehyde was also found to undergo the reaction at room temperature leading to the formation of 3,3′-(butane-1,1-diyl)bis(2-hydroxynaphthalene-1,4-dione) (**3u**) with moderate yield of 66%. The results are summarized in Table 2.

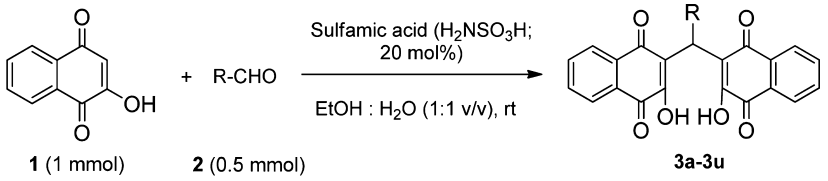
To our delight, this reaction protocol was also successfully applied for the synthesis of tetrakis-lawsone scaffold for the first time. One such entry, 3,3′,3″,3‴-(1,4-phenylenebis-(methanetriyl))tetrakis(2-hydroxynaphthalene-1,4-dione) **3v**, from the reaction between lawsone and terephthaldehyde, was achieved following this protocol with good yield of 86% (Scheme 2).

All the products were isolated pure just by washing with aqueous ethanol followed by recrystallization from hot ethanol; no tedious chromatographic purification was needed. The isolated products were fully characterized on the basis of analytical data and detailed spectral studies including FT-IR, ^1H NMR, ^{13}C NMR and TOF-MS.

I herein propose a mechanism in Scheme 3 for the formation of 3,3′-(aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) (**3**) under the optimized reaction conditions where sulfamic acid acts as a Lewis acid catalyst. It is supposed that initially there occurs a Knoevenagel-type condensation reaction between sulphamic acid-activated aldehyde (**1**) and one molecule of 2-hydroxynaphthalene-1,4-dione (**2**) resulting *in situ* formation of intermediate **5**, which then reacts with another molecule of **2** under the influence of the Lewis acidic catalyst to generate the species **6**, followed by its tautomerization to furnish the desired product **3**.

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

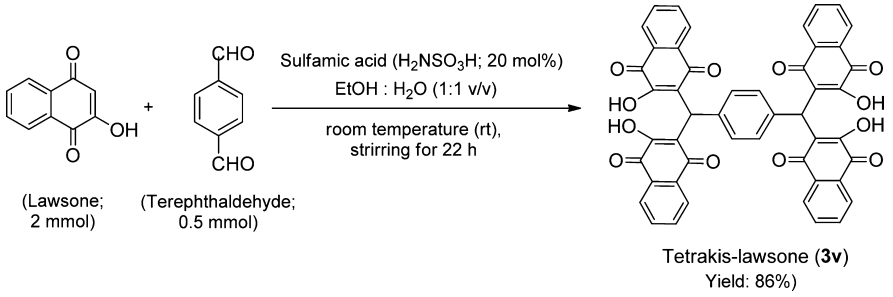
Table 2. Synthesis of 3,3′-(Aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) (3)



entry	product	substituent (R)	time (h)	yield (%)[a,b]
1	**3a**	C_6H_5	16	92
2	**3b**	2-ClC_6H_4	16	88
3	**3c**	3-ClC_6H_4	18	93
4	**3d**	4-ClC_6H_4	19	89
5	**3e**	2,4-$(Cl)_2C_6H_3$	20	85
6	**3f**	3-BrC_6H_4	19	85
7	**3g**	4-BrC_6H_4	18	87
8	**3h**	2-FC_6H_4	21	85
9	**3i**	4-FC_6H_4	20	84
10	**3j**	4-$CF_3C_6H_4$	21	86
11	**3k**	4-CNC_6H_4	19	90
12	**3l**	3-$CH_3C_6H_4$	20	94
13	**3m**	2-$NO_2C_6H_4$	20	91
14	**3n**	3-$NO_2C_6H_4$	11	95
15	**3o**	3-OHC_6H_4	19	91
16	**3p**	4-OHC_6H_4	20	87
17	**3q**	2-OH-5-$CH_3C_6H_3$	21	89
18	**3r**	3-OH-4-$OCH_3C_6H_3$	22	76
19	**3s**	3,4,5-$(OCH_3)_3C_6H_2$	21	89
20	**3t**	2-naphthyl	20	90
21	**3u**	$CH_3CH_2CH_2$	21	66

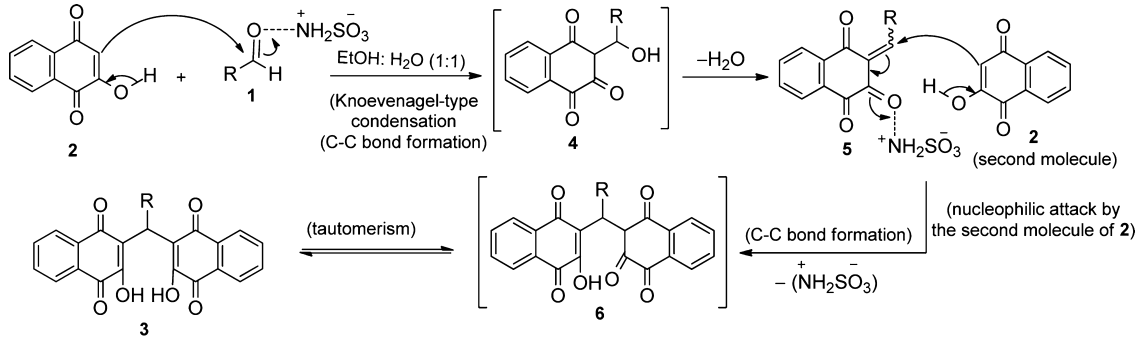
[a]Reaction conditions: 2-hydroxynaphthalene-1,4-dione (**1**, 1 mmol), aldehyde (**2**, 0.5 mmol), and 20 mol % sulfamic acid as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

Scheme 2. Synthesis of Tetrakis-Lawsone Derivative (3v) from the Reaction between Lawsone and Terephthaldehyde[a]



[a]Reaction conditions: lawsone (2 mmol), terephthaldehyde (0.5 mmol) and 20 mol % sulfamic acid as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature.

Scheme 3. Proposed Mechanism for the Synthesis of Bis-Lawsone 3



DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

CONCLUSION

In conclusion, a simple, energy-efficient, and conveniently practical method for easy access to a series of biologically interesting functionalized bis-lawsone scaffolds [i.e., 3,3′-(aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) derivatives] has been developed in the presence of sulfamic acid as an eco-friendly organo-catalyst via one-pot pseudomulticomponent reaction of commercially available aldehydes and lawsone in aqueous ethanol at room temperature. Mild reaction conditions, excellent yields, operational simplicity, absence of tedious separation procedures, clean reaction profiles, energy-efficiency and high atom-economy, as well as the use of inexpensive and environmentally benign catalyst are the key advantages of the present method.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b00325.

Materials and apparatus, general experimental procedure, spectral data and respective scanned spectra (^{1}H- and ^{13}C NMR) of all the synthesized compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*G. Brahmachari. E-mail: brahmg2001@yahoo.co.in; brahmg2001@gmail.com. Tel./Fax: 91-3463-261526.

Notes

The author declares no competing financial interest.

ACKNOWLEDGMENTS

This paper is dedicated to Dr. Rajender S. Varma on the occasion of his 65th birthday. Financial assistance from Council of Scientific and Industrial Research [Grant No. 02(0110)/12/EMR-II], New Delhi is gratefully acknowledged. The author is also thankful to the Bose Institute, Kolkata and IICB, Kolkata for spectral measurements.

REFERENCES

(1) Chaudhary, G.; Goyal, S.; Poonia, P. *Lawsonia inermis* Linnaeus: A phytopharmacological review. *Int. J. Pharm. Sci. Drug Res.* **2010**, *2*, 91−98.

(2) Sastri, B. N. *The wealth of India: Raw materials*, 6th ed.; CSIR: New Delhi, 1962; Vol. (L-M), pp 47−50.

(3) Ashnagar, A.; Shiri, A. Isolation and characterization of 2-hydroxy-1,4-naphthoquinone (lawsone) from the powdered leaves of henna plant marketed in Ahwaz city of Iran. *Int. J. ChemTech Res.* **2011**, *3*, 1941−1944.

(4) Chopra, R. N.; Nayer, S. L.; Chopra, I. C. *Glossary of India medicinal plants*; CSIR Publications: New Delhi, 1956; p 151.

(5) Reddy, K. R. Folk medicine from Chittoor district Andhra Pradesh, India used in the treatment of jaundice. *Pharm. Biol.* **1988**, *26*, 137−140.

(6) Mahkam, M.; Nabati, M.; Kafshboran, H. R. Isolation, identification and characterization of lawsone from henna leaves powder with soxhlet technique. *Iran. Chem. Commun.* **2014**, *2*, 34−38.

(7) Pratibha, G.; Korwar, G. R. Estimation of lawsone in henna (*Lawsonia inermis*). *J. Med. Aromat. Plant Sci.* **1999**, *21*, 658−660.

(8) Nayak, B. S.; Isitor, G.; Davis, E. M.; Pillai, G. K. *Phytother. Res.* **2007**, *21*, 827−831.

(9) White, J. M.; Kullavanijaya, P.; Duangdeeden, I.; Zazzeroni, R.; Gilmour, N. J.; Basketter, D. A.; Mc Fadden, J. P. *Clin. Exp. Allergy* **2006**, *36*, 1289−1293.

(10) Khan, M. S.; Khan, Z. H. Ab initio and semiempirical study of structure and electronic spectra of hydroxy substituted naphthoquinones. *Spectrochim. Acta, Part A* **2005**, *61*, 777−790.

(11) Satoh, T.; Tsuji, T.; Matsuda, H.; Sudoh, S. DFT calculations and IR studies on 2-hydroxy-1,4-naphthoquinone and its 3-substituted derivatives. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 321−323.

(12) Syamsudin, I.; Winarno, H. The effects of Inai (*Lawsonia inermis*) leave extract on blood sugar level: An experimental study. *Res. J. Pharmacol.* **2008**, *2*, 20−23.

(13) Arayne, M. S.; Sultana, N.; Mirza, A. Z.; Zuberi, M. H.; Siddiqui, F. A. *In vitro* hypoglycemic activity of methanolic extract of some indigenous plants. *Pak. J. Pharm. Sci.* **2007**, *20*, 268−273.

(14) Mikhaeil, B. R.; Badria, F. A.; Maatooq, G. T.; Amer, M. M. A. Antioxidant and immunomodulatory constituents of henna leaves. *Z. Naturforsch., C: J. Biosci.* **2004**, *59*, 468−476.

(15) Dikshit, V.; Dikshit, J.; Saraf, M.; Thakur, V.; Sainis, K. Immunomodulatory activity of naphthoquinone fraction of *Lawsonia inermis* Linn. *Phytomed.* **2000**, *7*, 102−103.

(16) Ahmed, S.; Rahman, A.; Alam, A.; Saleem, M.; Athar, M.; Sultana, S. Evaluation of the efficacy of *Lawsonia alba* in the alleviation of carbontetrachloride induced oxidative stress. *J. Ethnopharmacol.* **2000**, *69*, 157−164.

(17) Anand, K. K.; Singh, B.; Chand, D.; Chandan, B. K. An evaluation of *Lawsonia alba* extract as hepatoprotective agent. *Planta Med.* **1992**, *58*, 22−25.

(18) Bhandarkar, M.; Khan, A. Protective effect of *Lawsonia alba* Lam. against carbontetrachloride induced hepatic damage in albino rats. *Indian J. Exp. Biol.* **2003**, *41*, 85−87.

(19) Hemalatha, K.; Natraj, H. N.; Kiran, A. S. Hepatoprotective activity of leaves of *Lawsonia alba*. *Indian J. Nat. Prod.* **2004**, *20*, 14−17.

(20) Latha, P. G.; Suja, S. R.; Shyamal, S.; Rajasekharan, S. Some hepatoprotective garden plants. *Nat. Prod. Rad.* **2005**, *4*, 278−279.

(21) Dasgupta, T.; Rao, A. R.; Yadava, P. K. Modulatory effect of henna leaf (*Lawsonia inermis*) on drug metabolizing phase I and phase II enzymes, antioxidant enzymes, lipid peroxidation and chemically induced skin and forestomach papillomagenesis in mice. *Mol. Cell. Biochem.* **2003**, *245*, 11−22.

(22) Endrini, S.; Rahmat, A.; Ismail, P.; Taufiq-Yap, Y. H. Comparing of the cytotoxicity properties and mechanism of *Lawsonia inermis* and *Strobilanthes crispus* extract against several cancer cell lines. *J. Med. Sci.* **2007**, *7*, 1098−1102.

(23) Prakash, D.; Suri, S.; Upadhyay, G.; Singh, B. N. Total phenol, antioxidant and free radical scavenging activities of some medicinal plants. *Int. J. Food Sci. Nutr.* **2007**, *58*, 18−28.

(24) Singh, D. K.; Luqman, S.; Mathur, A. K. *Lawsonia inermis* L. − A commercially important primaeval dying and medicinal plant with diverse pharmacological activity: A review. *Ind. Crops Prod.* **2015**, *65*, 269−286.

(25) Omar, M. A. Effects of 2-hydroxy-1,4-napthoquinone, a natural dye of henna, on aldehyde oxidase activity in guinea pigs. *J. Med. Sci.* **2005**, *5*, 163−168.

(26) Dama, L. B.; Poul, B. N.; Jadhav, B. V. Antimicrobial activity of napthoquinonic compounds. *J. Ecotoxicol. Environ. Monitor.* **1999**, *8*, 213−215.

(27) Dixit, S. N.; Srivastava, H. S.; Tripathi, R. D. Lawsone, the antifungal antibiotic from the leaves of *Lawsonia inermis* and some aspects of its mode of action. *Indian Phytopathol.* **1980**, *31*, 131−133.

(28) Wang, D.; Sauriasari, R.; Takemura, Y.; Tsutsui, K.; Masuoka, N.; Sano, K.; Horita, M.; Wang, B. L.; Ogino, K. Cytotoxicity of lawsone and cytoprotective activity of antioxidants in catalase mutant *Escherichia coli*. *Toxicology* **2007**, *235*, 103−111.

(29) Yogisha, S.; Samiulla, D. S.; Prashanth, D.; Padmaja, R.; Amit, A. Trypsin inhibitory activity of *Lawsonia inermis*. *Fitoterapia* **2002**, *73*, 690−691.

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

(30) Rao, V. R.; Kumar, R. A.; Rao, T. V. P. Synthesis and anticoagulant activity of some new phenoxazines from lawsone. *Indian J. Chem.* **1993**, *32B*, 903−904.
(31) Sultana, N.; Choudhary, M. I.; Khan, A. J. Protein glycation inhibitory activities of *Lawsonia inermis* and its active principles. *Enzyme Inhib. Med. Chem.* **2009**, *24*, 257−61.
(32) Biradar, S.; Veeresh, B. Protective effect of lawsone on L-arginine induced acute pancreatitis in rats. *Indian J. Exp. Biol.* **2013**, *51*, 256−261.
(33) Kavitha Rani, P. R.; Fernandez, A.; George, A.; Remadevi, V. K.; Sudarsanakumar, M. R.; Laila, S. P.; Arif, M. Synthesis, spectral characterization, molecular structure and pharmacological studies of N′-(1,4-naphtho-quinone-2yl)isonicotinohydrazide. *Spectrochim. Acta, Part A* **2015**, *135*, 1156−116.
(34) Neves, A. P.; Barbosa, C. C.; Greco, S. J.; Vargas, M. D.; Visentin, L. C.; Pinheiro, C. B.; Mangrich, A. S.; Barbosa, J. P.; da Costa, G. L. Novel aminonaphthoquinone mannich bases derived from lawsone and their copper(II) complexes: Synthesis, characterization and antibacterial activity. *J. Braz. Chem. Soc.* **2009**, *20*, 712−727.
(35) Elavarasan, S.; Gopalakrishnan, M. Synthesis, structural analysis, theoretical studies of some lawsone derivatives. *Spectrochim. Acta, Part A* **2014**, *133*, 1−6.
(36) Hueso-Falcón, I.; Amesty, A.; Martín, P.; López-Rodríguez, M.; Fernández-Pérez, L.; Estévez-Braun, A. Indium catalyzed solvent-free multicomponent synthesis of cytotoxic dibenzo[*a*,*h*]anthracenes from aldehydes, 2-hydroxy-1,4-naphthoquinone, and 2-naphthol. *Tetrahedron* **2014**, *70*, 8480−8487.
(37) Gonec, T.; Kos, J.; Zadrazilova, I.; Pesko, M.; Keltosova, S.; Tengler, J.; Bobal, P.; Kollar, P.; Cizek, A.; Kralova, K.; Jampilek, J. Antimycobacterial and herbicidal activity of ring-substituted 1-hydroxynaphthalene-2-carboxanilides. *Bioorg. Med. Chem.* **2013**, *21*, 6531−6541.
(38) Ayhan-Kılcıgil, G.; Gürkan, S.; Coban, T.; Ozdamar, E. D.; Can-Eke, B. Synthesis and evaluation of antioxidant properties of novel 2-[2-(4-chlorophenyl) benzimidazole-1-yl]-*N*-(2-arylmethylene amino) acetamides and 2-[2-(4-chlorophenyl) benzimidazole-1-yl]-*N*-(4-oxo-2-aryl-thiazolidine-3-yl) acetamides-I. *Chem. Biol. Drug Des.* **2012**, *79*, 869−877.
(39) Saadeh, H. A.; Mosleh, I. M.; El-Abadelah, M. M. New synthesis and antiparasitic activity of model 5-aryl-1-methyl-4-nitroimidazoles. *Molecules* **2009**, *14*, 2758−2767.
(40) Yang, X.; Zhang, P.; Zhou, Y.; Wang, J.; Liu, H. Synthesis and antioxidant activities of novel 4,4′-arylmethylene-bis(1*H*-pyrazole-5-ol)s from lignin. *Chin. J. Chem.* **2012**, *30*, 670−674.
(41) Tisseh, Z. N.; Bazgir, A. An efficient, clean synthesis of 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) derivatives. *Dyes Pigm.* **2009**, *83*, 258−261.
(42) Wang, H.; Wang, Z.; Wang, C.; Yang, F.; Zhang, H.; Yue, H.; Wang, L. Lipase catalyzed synthesis of 3,3′-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione). *RSC Adv.* **2014**, *4*, 35686−35689.
(43) Brahmachari, G.; Laskar, S. A very simple and highly efficient procedure for *N*-formylation of primary and secondary amines at room temperature under solvent- free conditions. *Tetrahedron Lett.* **2010**, *51*, 2319−2322.
(44) Brahmachari, G.; Laskar, S.; Sarkar, S. Metal acetate/metal oxide in acetic acid: An efficient reagent for the chemoselective *N*-acetylation of amines. *J. Chem. Res., Synop.* **2010**, *34*, 288−295.
(45) Brahmachari, G.; Das, S. Bismuth nitrate-catalyzed multicomponent reaction for efficient and one-pot synthesis of densely functionalized piperidine scaffolds at room temperature. *Tetrahedron Lett.* **2012**, *53*, 1479−1484.
(46) Brahmachari, G.; Banerjee, B. A comparison between catalyst-free and $ZrOCl_2 \cdot 8H_2O$-catalyzed Strecker reactions for the rapid and solvent-free one-pot synthesis of racemic α-aminonitrile derivatives. *Asian J. Org. Chem.* **2012**, *1*, 251−258.
(47) Brahmachari, G.; Das, S. One-pot synthesis of 3-[(*N*-alkylanilino) (aryl)methyl] indoles *via* a transition metal assisted three-component condensation at room temperature. *J. Heterocyclic Chem.* **2014**, *51*, E140−E145.
(48) Brahmachari, G.; Das, S. Sodium formate-catalyzed one-pot synthesis of benzopyranopyrimidines and 4-thio-substituted 4*H*-chromenes via multicomponent reaction at room temperature. *J. Heterocyclic Chem.* **2015**, *52*, 653−659.
(49) Brahmachari, G.; Das, S. A simple and straightforward method for one-pot synthesis of 2,4,5-triarylimidazoles using titanium dioxide as an eco-friendly and recyclable catalyst under solvent-free conditions. *Indian J. Chem.* **2013**, *52B*, 387−393.
(50) Brahmachari, G.; Banerjee, B. Facile synthesis of symmetrical bis(benzhydryl)ethers using *p*-toluenesulfonyl chloride under solvent free conditions. *Org. Med. Chem. Lett.* **2013**, *3*, 1.
(51) Brahmachari, G.; Laskar, S.; Barik, P. Magnetically separable $MnFe_2O_4$ nano-material: An efficient and reusable heterogeneous catalyst for the synthesis of 2-substituted benzimidazoles and the extended synthesis of quinoxalines at room temperature. *RSC Adv.* **2013**, *3*, 14245−14253.
(52) Brahmachari, G.; Laskar, S.; Banerjee, B. Eco-friendly, one-pot multicomponent synthesis of pyran annulated heterocyclic scaffolds at room temperature using ammonium or sodium formate as non-toxic catalyst. *J. Heterocyclic Chem.* **2014**, *51*, E303−E308.
(53) Brahmachari, G.; Banerjee, B. Facile and one-pot access to diverse and densely functionalized 2-amino-3-cyano-4*H*-pyrans and pyran-annulated heterocyclic scaffolds via an eco-friendly multicomponent reaction at room temperature using urea as a novel organo-catalyst. *ACS Sustainable Chem. Eng.* **2014**, *2*, 411−422.
(54) Brahmachari, G.; Das, S. L-Proline catalyzed multicomponent one-pot synthesis of *gem*-diheteroarylmethane derivatives using facile grinding operation under solvent-free conditions at room temperature. *RSC Adv.* **2014**, *4*, 7380−7388.
(55) Brahmachari, G.; Laskar, S. Nano-Mgo-catalyzed one-pot synthesis of phosphonate ester functionalized 2-amino-3-cyano-4*H*-chromene scaffolds at room temperature. *Phosphorus, Sulfur Silicon Relat. Elem.* **2014**, *189*, 873−888.
(56) Brahmachari, G.; Banerjee, B. Facile and one-pot access of 3,3-bis(indol-3-yl)indolin-2-ones and 2,2-bis(indol-3-yl)acenaphthylen-1(2*H*)-one derivatives via an eco-friendly pseudo-multicomponent reaction at room temperature using sulfamic acid as an organocatalyst. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2802−2812.
(57) Brahmachari, G.; Banerjee, B. Ammonium chloride catalysed one-pot multicomponent synthesis of 1,8-dioxo-octahydroxanthenes and *N*-aryl-1,8-dioxodecahydroacridines under solvent free conditions. *J. Chem. Res.* **2014**, *38*, 745−750.
(58) Brahmachari, G.; Banerjee, B. Cerric ammonium nitrate (CAN): an efficient and eco-friendly catalyst for the one-pot synthesis of alkyl/aryl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methanes at room temperature. *RSC Adv.* **2015**, *5*, 39263−39269.
(59) Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. Application of Sulfamic acid in organic synthesis-A short review. *Curr. Org. Chem.* **2009**, *13*, 1002−1014.
(60) Harbison, G. S.; Kye, Y.-S.; Penner, G. H.; Grandin, M.; Monette, M. ^{14}N quadrupolar, ^{14}N and ^{15}N chemical shift, and ^{14}N-^{1}H dipolar tensors of sulfamic acid. *J. Phys. Chem. B* **2002**, *106*, 10285−10291.
(61) Montes D'Oca, M. G.; Soares, R. M.; de Moura, R. R.; de Freitas Granjão, V. Sulfamic acid: An efficient acid catalyst for esterification of FFA. *Fuel* **2012**, *97*, 884−886.
(62) Rostami, A.; Ahmad-Jangi, F. Sulfamic acid: An efficient, cost-effective and green catalyst for crossed-aldol condensation of ketones with aromatic aldehydes under solvent-free. *Chin. Chem. Lett.* **2011**, *22*, 1029−1032.
(63) Li, J.; Qiu, J.; Li, H.; Zhang, G. An efficient, three-component one-pot preparation of 1,4-dihydropyridines containing novel substituted pyrazole under sulfamic acid catalysis. *Chin. J. Chem.* **2011**, *29*, 511−514.
(64) Luo, H.-T.; Kang, Y.-R.; Nie, H.-Y.; Yang, L.-M. Sulfamic acid as a cost effective and recyclable catalyst for β-amino carbonyl compounds synthesis. *J. Chin. Chem. Soc.* **2009**, *56*, 186−195.
(65) Heravi, M. M.; Ranjbar, L.; Derikvand, F.; Alimadadi, B. Three component one-pot synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066

under solvent-free conditions in the presence of sulfamic acid as a green and reusable catalyst. *Mol. Diversity* **2008**, *12*, 191−196.
(66) An, L.-T.; Zou, J.-P.; Zhang, L.-L.; Zhang, Y. Sulfamic acid-catalyzed Michael addition of indoles and pyrrole to electron-deficient nitroolefins under solvent-free condition. *Tetrahedron Lett.* **2007**, *48*, 4297−4300.
(67) Verma, A. K.; Kotla, S. K. R.; Choudhary, D.; Patel, M.; Tiwari, R. K. Silver-catalyzed tandem synthesis of naphthyridines and thienopyridines via three-component reaction. *J. Org. Chem.* **2013**, *78*, 4386−4401.
(68) Singh, M. S.; Chowdhury, S. Recent developments in solvent-free multicomponent reactions: A perfect synergy for eco-compatible organic synthesis. *RSC Adv.* **2012**, *2*, 4547−4592.
(69) Mukhopadhyay, C.; Tapaswi, P. K.; Drew, M. G. B. Room temperature synthesis of tri-, tetrasubstituted imidazoles and bisanalogues by mercaptopropylsilica (MPS) in aqueous methanol: Application to the synthesis of the drug trifenagrel. *Tetrahedron Lett.* **2010**, *51*, 3944−3950.
(70) Kumaravel, K.; Vasuki, G. Multi-component reactions in water. *Curr. Org. Chem.* **2009**, *13*, 1820−1841.
(71) Brauch, S.; Gabriel, L.; Westermann, B. Seven-component reactions by sequential chemoselective Ugi-Mumm/Ugi-Smiles reactions. *Chem. Commun.* **2010**, *46*, 3387−3389.
(72) Khurana, J. M.; Chaudhary, A.; Lumb, A.; Nand, B. An expedient four-component domino protocol for the synthesis of novel benzo[*a*]phenazine annulated heterocycles and their photophysical studies. *Green Chem.* **2012**, *14*, 2321−2327.
(73) Prasad, D.; Nath, M. Three-component domino reaction in PPG: An easy access to 4-thiazolidinone derivatives. *J. Heterocyclic Chem.* **2012**, *49*, 628−633.
(74) Trost, B. M. The atom economy. A search for synthetic efficiency. *Science* **1991**, *254*, 1471−1477.
(75) Sheldon, R. A. Atom efficiency and catalysis in organic synthesis. *Pure Appl. Chem.* **2000**, *72*, 1233−1246.
(76) Brahmachari, G. *Room temperature organic synthesis*, 1st ed.; Elsevier: Amsterdam, The Netherlands, 2014.

DOI: 10.1021/acssuschemeng.5b00325
ACS Sustainable Chem. Eng. 2015, 3, 2058−2066