Bronsted acid-type biosurfactant for heterocyclization: a green protocol for benzopyran synthesis

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General: All chemicals were commercially sourced from Sigma Aldrich and used without further purification. Melting points were determined on DBK programmable melting point apparatus and are uncorrected. Infrared spectra were measured with a Bruker FT-IR spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC (300 MHz for $^1$H NMR and 300 MHz for $^{13}$C NMR) spectrometer using CDCl$_3$ as solvent. Chemical shifts are expressed in $\delta$ parts per million (ppm) values with tetramethylsilane (TMS) as the internal reference and coupling constants are expressed in Hertz (Hz). Mass spectra were recorded on Shimadzu (QP 2010 GCMS). Equiptronics (Model EQ-664A) digital auto ranging conductivity meter was used for the measurement of critical micellar concentration. Optical micrograph was taken using ordinary light microscope (Leica DM 2000) under 100x magnifications.

Typical procedure for synthesis of 9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydroxanthen-1-one:
In a 25 mL round bottom flask, salicylaldehyde (1.1 mmol), 5,5-dimethyl 1,3-cyclohexanedione (2.2 mmol) were placed in lemon extract:water (6 mL, 1:1, v/v) and reaction mixture was stirred at 80°C temperature in preheated oil-bath till the completion of reaction as indicated by TLC (ethylacetate:hexane 4:6). The solid products was separated by simple filtration through a Buckner funnel, washed with cold water, and recrystalyzed from 96% ethanol (5 mL). The identity of the compound was ascertained on the basis of 1H NMR, 13C NMR, and FT-IR spectroscopy.

9-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-Dimethyl-2,3,4,9-tetrahydroxanthen-1-one (Table 3,Entry 1)

Yield: 85 %; mp 215–218 oC; 1H NMR (300 MHz, CDCl3): d 10.50(s, 1H, -OH), 7.08–7.16 (m, 1H, Ar-H), 6.93–7.01 (m, 3H, Ar-H), 4.65 (s, 1H, -CH), 2.54 (q, J=17.7, 20.0 Hz, 2H, -CH2), 2.35 (s, 2H, -CH2), 2.30 (s, 2H, -CH2), 1.93 (q, J=6.0, 16.4 Hz, 2H, -CH2), 1.14 (s, 3H, -CH3), 1.03 (s, 3H, -CH3), 1.00 (s, 6H, 2-CH3); 13C NMR (300 MHz, CDCl3): d 200.40, 196.13, 170.53, 168.78, 151.04, 127.98, 127.52, 124.53, 118.31, 115.78, 111.07, 96.20, 50.58, 49.93, 43.24, 41.60, 32.33, 31.02, 29.85, 29.43, 27.79, 27.21,26.42; IR (cm⁻¹): 3153, 2958, 1622, 1488, 1376, 1312, 1233, 1185, 1151, 1077, 1019, 762, 655, 582, 475; MS : 367 (M + 1), 389 (M + Na). Anal. calcd. for C23H26O4: C, 75.38; H, 7.15; O, 17.46. Found: C, 75.33; H, 7.15; HRMS m/z calcd. for C23H26O4: 366.0000, found 367.1918(M+H), 389.1737 (M+Na).

3-methoxy-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydroxanthen-1-one (Table 3,Entry 2)

Yield: 80 %; mp 224-227 oC; 1H NMR (300 MHz, CDCl3): d 10.50 (s, 1H, -OH), 7.08–7.21 (m, 1H, Ar-H), 6.93–7.01 (m, 3H, Ar-H), 4.65 (s, 1H, -CH), 2.54 (q, J=17.7, 20.0 Hz, 2H, -CH2), 2.35 (s, 2H, -CH2), 2.30 (s, 2H, -CH2), 1.93 (q, J=6.0, 16.4 Hz, 2H, -CH2), 3.88 (s, 1H, -OCH3) , 1.14(s, 3H, -CH3), 0.93 (s, 9H, 3CH3); 13C NMR (300 MHz, CDCl3): 200.40, 196.521, 170.554, 168.800, 147.081, 140.658, 125.203, 124.203, 119.760, 118.149, 110.887, 110.370, 56.058, 50.623, 49.930, 43.167, 41.533, 32.288, 30.887, 29.852, 29.051, 27.755 , 27.162, 26.421.
7-Bromo-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydroxanthen-1-one (Table 3, Entry 3)

Yield: 92%; mp 248-251°C; 1H NMR (300 MHz, CDCl₃): δ 10.15 (s, 1H, -OH), 7.21–7.24 (dd, J=1.9, 6.8 Hz, 1H, Ar-H), 7.08 (s, 1H, Ar-H), 6.87 (d, J=8.7 Hz, 1H, Ar-H), 5.02 (s, 1H, -CH-), 2.28–2.59 (m, 6H, 3-CH₂), 1.95 (s, 2H, -CH₂), 1.33 (s, 3H, -CH₃), 0.99–1.05 (m, 9H, 3-CH₃); ¹³C NMR (300 MHz, CDCl₃ + DMSO): δ 195.65, 164.33, 148.79, 130.56, 129.10, 127.74, 116.93, 115.41, 110.34, 50.27, 40.65, 40.33, 40.05, 39.78, 39.22, 38.94, 38.66, 31.35, 31.27, 28.93, 27.56, 26.30; IR (cm⁻¹): 3103, 2963, 1618, 1475, 1374, 1302, 1231, 1178, 1075, 1037, 884, 817, 657, 590, 478; MS: 445 (M⁺+1), 447 (M⁺+2). Anal. calcd. for C₂₃H₂₅BrO₄: C, 62.03; H, 5.66; Br, 17.94; O, 14.37. Found: C, 62.03; H, 5.65. HRMS m/z calcd. for C₂₃H₂₅BrO₄: 445.0000, found 445.1003 (M⁺).

7-Chloro-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydroxanthen-1-one (Table 3, Entry 5)

Yield: 91%; mp 232–234°C; ¹H NMR (300 MHz, CDCl₃): δ 10.50 (s, 1H, -OH), 7.09 (dd, J=2.2, 2.6 Hz, 1H, Ar-H), 6.91–6.97 (m, 2H, Ar-H), 4.61 (s, 1H, -CH), 2.62 (q, J=17.3, 18.5 Hz, 2H, -CH₂), 2.37 (d, J=4.9 Hz, 2H, -CH₂), 2.30 (s, 2H, -CH₂), 1.96 (s, 2H, -CH₂), 1.14 (s, 3H, -CH₃), 1.00–1.05 (m, 9H, 3-CH₃); IR (cm⁻¹): 3102, 2965, 2710, 1624, 1571, 1476, 1374, 1301, 1233, 1179, 1077, 1038, 1015, 879, 819, 657, 618, 591, 549, 469; MS: 401 (M⁺+1), 403 (M⁺+2). Anal. calcd. for C₂₃H₂₅ClO₄: C, 68.91; H, 6.29; Cl, 8.84; O, 15.96. Found: C, 68.89; H, 6.24. HRMS m/z calcd. for C₂₃H₂₅ClO₄: 400.0000, found 401.1529 (M+H), 423.1328 (M+Na).

5-Bromo-7-chloro-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydroxanthen-1-one (Table 3, Entry 6)

Yield: 90%; mp 241-243°C; ¹H NMR (300 MHz, CDCl₃): δ 10.34 (s, 1H, -OH), 7.36 (d, J=2.2 Hz, 1H, Ar-H), 6.90 (d, J=2.0 Hz, 1H, Ar-H), 4.60 (s, 1H, -CH), 2.62 (q, J=17.7,18.5 Hz, 2H, -CH₂), 2.38 (d, J=4.5 Hz, 2H, -CH₂), 2.31 (s, 2H, -CH₂), 1.97 (s, 2H, -CH₂), 1.16 (s, 3H, -CH₃), 1.00–1.05 (m, 9H, 3-CH₃); ¹³C NMR (300 MHz, CDCl₃): δ 196.47, 195.10, 163.43, 144.77, 128.68, 127.79, 127.41,
126.35, 112.78, 109.93, 108.78, 94.79, 49.58, 49.03, 39.81, 30.77, 28.24, 26.92, 26.03, 25.64, 25.17; IR (cm$^{-1}$): 3184, 2940, 1647, 1599, 1452, 1375, 1313, 1257, 1207, 1183, 1150, 1017, 887, 855, 803, 722, 587, 475; MS: 479 (M$^+$), 481 (M+2). Anal. calcd. for C$_{23}$H$_{24}$BrClO$_4$: C, 57.58%; H, 5.04%; Br, 16.65%; Cl, 7.39%; O, 13.34. Found: C, 57.57%; H, 5.04%; HRMS m/z calcd. for C$_{23}$H$_{23}$ClBrO$_4$: 478.0000, found 479.0618 (M + H), 481.0602 (M + 2) 501.0421 (M + Na), 503.0415 (M + Na + 2).

9-(2-Hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 7)

Yield: 87%; mp 240-243°C; $^1$H NMR (300 MHz, CDCl$_3$): d 10.00 (s, 1H, -OH), 6.80–7.14 (m, 4H, Ar-H), 4.84 (s, 1H, -CH), 1.60–2.40 (m, 12H, 6-CH$_2$); IR (cm$^{-1}$): 2951, 2538, 1830, 1641, 1553, 1485, 1421, 1372, 1235, 1192, 1142, 1071, 993, 924, 850, 773, 564, 493; MS: 311 (M+1). Anal. calcd. for C$_{19}$H$_{18}$O$_4$: C, 73.53%; H, 5.85%; O, 20.62. Found: C, 73.52%; H, 5.84%; HRMS m/z calcd. for C$_{19}$H$_{18}$O$_4$: 310.0000, found 311.1295 (M + H), 333.1081 (M + Na).

7-Bromo-9-(2-hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 9)

Yield: 88%; mp 238-240°C; 1H NMR (300 MHz): d 10.75 (s, 1H, -OH), 7.25 (d, J=3.0 Hz, 1H, Ar-H), 7.09 (d, J=2.2 Hz, 1H, Ar-H), 6.89 (dd, J=5.2, 6.0 Hz, 1H, Ar-H), 4.57 (s, 1H, -CH), 1.76–2.85 (m, 12H, 6-CH$_2$); $^{13}$C NMR (300 MHz, CDCl$_3$): 202.18, 193.99, 167.43, 166.15, 148.45, 129.74, 129.28, 128.61, 126.86, 116.51, 116.10, 115.09, 47.57, 35.57, 35.02, 33.26, 26.02, 22.80, 18.95; IR (cm$^{-1}$): 3105, 2955, 1596, 1477, 1374, 1279, 1233, 1186, 1144, 1070, 981, 819, 763, 620, 530, 470; MS: 389 (M$^+$) 391 (M + 2); Anal. calcd. for C$_{19}$H$_{17}$BrO$_4$: C, 58.63%; H, 4.40%; Br, 20.53%; O, 20.34; found: C, 58.63%; H, 4.39%; HRMS m/z calcd. for C$_{19}$H$_{17}$BrO$_4$: 389.0000, found 391.0551 (M + 2).

7-Chloro-9-(2-hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 11)

Yield: 94%; mp 242-244°C; $^1$H NMR (500MHz, CDCl$_3$): d 10.76 (s, 1H, -OH), 7.09 (d, J=6.3 Hz, 1H, Ar-H), 6.91–6.96 (m, 2H, Ar-H), 4.57 (s, 1H, -CH), 1.77–2.81 (m, 12H, 6-CH$_2$); $^{13}$C NMR (300MHz, CDCl$_3$+DMSO-d$_6$): 201.86, 193.94, 167.23, 165.96, 147.56, 127.13, 126.76, 125.61, 124.53,
5-Bromo-7-chloro-9-(2-hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 12)

Yield: 91%; mp 238–240 °C; \( ^1 \)H NMR (300 MHz, CDCl\(_3\)): \( \delta 10.44 \) (s, 1H, -OH), 7.30 (d, \( J=2.6 \) Hz, 1H, Ar-H), 6.95 (d, \( J=1.7 \) Hz, 1H, Ar-H), 5.04 (s, 1H, -CH), 1.93–2.12 (m, 4H, 2-CH\(_2\)), 2.25–2.51 (m, 8H, 4CH\(_2\)); \( ^{13} \)CNMR (300 MHz, CDCl\(_3\)): 195.44, 163.90, 145.45, 129.31, 128.72, 127.93, 110.62, 109.50, 50.29, 40.33, 40.05, 39.77, 39.50, 39.2, 38.94, 38.76, 31.45, 31.3, 28.97, 27.56, 26.69, 26.20, 25.75 29; IR (cm\(^{-1}\)): 49, 2887, 2526, 1651, 1560, 1452, 1363, 1279, 1245, 1185, 1133, 1063, 1007, 857, 765, 707, 538, 500, 438; MS: 423 (M\(^{+}\)), 425 (M+2) Anal. calcd. for C\(_{19}\)H\(_{16}\)BrClO\(_4\): C, 53.86; H, 3.81; Br, 18.86; Cl, 8.37; O, 15.11, found: C, 53.85; H, 3.81.

5-methoxy-2,3-Dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)-cyclopenta[b]chromen-1(9H)-one (Table 3, Entry 14)

Yield: 84%; mp 257-260 °C; \( ^1 \)H NMR (300 MHz DMSO): 2.29~2.36 (m, 6H, 3CH₂), 2.72~2.74 (m, 2H, CH₂), 3.82 (s, 3H, CH₃O), 4.58 (s, 1H, CH), 6.58~6.60 (m, 1H, ArH), 6.92 (dd, \( J = 8.0 \) Hz, \( J = 1.2 \) Hz, 1H, ArH), 6.99~7.03 (m, 1H, ArH), 11.80 (b, 1H, OH); IR (cm\(^{-1}\)): 3438, 3024, 2971, 2939, 1682, 1637, 1579, 1480, 1445, 1380, 1322, 1273, 1255, 1237, 1170, 1125, 1076, 825, 788, 739, 716.

7-Bromo-2,3-dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)cyclopenta[b]chromen-1(9H)-one (Table 3, Entry 15)

Yield: 86%; mp 280-282°C; \( ^1 \)H NMR (300 MHz DMSO): 2.26~2.43 (m, 6H, 3CH₂), 2.56~3.34 (m, 2H, CH₂), 5.01 (s, 1H, CH), 7.01~7.24 (m, 2H, ArH), 7.27 (d, \( J = 8.4 \) Hz, 1H, ArH), 10.60 (b, 1H, OH); IR (cm\(^{-1}\)): 3505, 2932, 2910, 1699, 1653, 1585, 1474, 1383, 1276, 1259, 1240, 1198, 1160, 1126, 1071, 1018, 818, 707, 659.
7-nitro-2,3-Dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)cyclopenta[b]chromen-1(9H)-one

(Table 3, Entry 16)
Yield: 89 %; mp 265-268°C; ¹H NMR (300 MHz DMSO ): 2.34~2.41 (m, 6H, 3CH₂), 2.74~2.76 (m, 2H, CH₂), 4.72(s, 1H, CH), 7.41 (d, J = 8.8 Hz, 1H, ArH), 7.87 (d, J =2.4Hz, 1H, ArH), 8.11 (dd, J=8.8 Hz, J= 2.4 Hz, 1H, ArH), 12.06 (b, 1H, OH). IR (cm⁻¹): 3512, 2943, 2926, 1698, 1656, 1581, 1528, 1481, 1458, 1379, 1277, 1253, 1168, 1134, 1020, 929, 912, 840, 805, 748, 666.

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7-Chloro-2,3-dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)cyclopenta[b]chromen-1(9H)-one

(Table 3, Entry 17)
Yield: 90 %; mp 271-273°C; ¹H NMR (300 MHz DMSO): 2.33~2.38 (m, 6H, 3CH₂), 2.71~2.73 (m, 2H, CH₂), 4.60(s, 1H, CH), 7.01 (dd, J = 2.4 Hz, J = 1.2 Hz, 1H, ArH), 7.18 (d, J = 8.8 Hz, 1H, ArH), 7.27~7.30 (m, 1H, ArH), 12.00 (b, 1H, OH); IR (cm⁻¹): 3508, 2935, 2914, 1699, 1654, 1583, 1477, 1409, 1384, 1277, 1259, 1240, 1162, 1126, 1018, 819, 677.

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7,8-h-pent-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (3h) (Table 4, Entry 1)
Yield: 95 % mp 235-237 °C. ¹H NMR (300 MHz, CDCl₃) δ = 10.70 (s, 1H, OH), 7.78 (d, 1H, ArH), 7.73 (d, 2H, ArH), 7.48 (t, 1H, ArH), 7.39 (t, 1H, ArH), 7.27 (d, 1H, ArH), 5.27 (s, 1H, CH), 2.68 (ABq, J = 17.6 Hz, 1H, CH₂), 2.57 (ABq, J = 17.6 Hz, 1H, CH₂), 1.96 (ABq, J = 16.4 Hz, 1H, CH₂), 1.83 (ABq, J = 16.4 Hz, 1H, CH₂), 2.36-2.41 (m, 4H, 4CH₂), 1.17 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 0.95 (s, 3H, CH₃), 0.72 (s, 3H, CH₃) ppm;¹³C NMR (300 MHz, CDCl₃) δ = 201.11, 196.85, 170.22, 169.09, 148.89, 131.26, 130.96, 158.54, 128.50, 126.71, 124.64, 122.87, 117.68, 116.59, 116.14, 111.08, 50.71, 49.98, 43.18, 41.37, 32.42, 30.62, 29.92, 29.33, 27.10, 26.37, 25.38 ppm; IR (KBr): 3182, 2941, 2862, 1643, 1593, 1464, 1373, 1315, 1261, 1235, 1061, 1026, 888, 813 cm⁻¹.
Determination of Critical micellar concentration (CMC) of lemon extract by conductivity method

To maintain better lemon extract:water composition i.e above CMC for this protocol, we employed electrical conductivity method to determine the critical micelle concentration (CMC) of reaction medium. The conductivity experiments were carried using Equiptronics (Model EQ-664 A) digital auto ranging conductivity meter. Different composition of solutions of Lemon extract was prepared in deionized water having specific conductance 7.0 \( \mu \text{s cm}^{-1} \). A step-by step dilution method was adopted for the measurements of specific conductance of the various compositions to avoid dilution error. The conductance was plotted as a function of percentage composition of lemon extract:water (v/v) and the inflection point gives the value (40 %) of CMC which is indicated in the figure.