A Green and Novel Method of Synthesizing 2,2'-Arylmethylene Bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) Catalyzed by *L*-Histidine in Ionic Liquid

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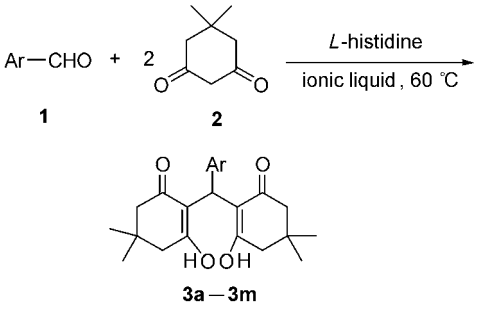
An efficient and green approach to the synthesis of 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) using *L*-histidine as the catalyst is described. In addition, room temperature ionic liquid 1-butyl-3-methylimidazonium tetrafluoroborate [bmim]BF_4 was used as green recyclable alternatives to volatile organic solvents for this condensation reaction. This green catalytic system can be recycled several times with no decreases in yields and reaction rates.

Keywords condensation reaction, ionic liquid, *L*-histidine, synthesis, xanthenedione

Introduction

Green chemistry movement began more than a decade ago. Specifically, the challenge in chemistry is to develop new products, processes and services that achieve the societal, economic and environmental benefits that are required now and tomorrow,[1] and the need for alternative solvents for reactions has been one of the major issues we have faced. Over the past few years the room temperature ionic liquids (ILs) which are low-melting-point (＜100 ℃) salts have received attention for their promise as alternative reaction media. Ionic liquids represent a new class of solvents with non-molecular, ionic character. In addition, ILs can exhibit certain desirable physical properties, such as high solvency, no effective vapor pressure, nonflammable, as well as ease of recovery and reuse, which make ILs a greener alternative to volatile organic solvents in a number of reactions.[2] Thus, the use of ionic liquids as solvents and/or catalysts for organic chemistry is an active and important area of current research.[3] Organo-catalysis also became a new research area in synthetic chemistry several years ago.[4] Developing cheap and recyclable organocatalysts that promote reactions in green solvent to expand the scope of organocatalysis becomes part of an environmentally benign approach to fine chemical synthesis, especially large scale reactions. In this paper, we report an environment-frindly direct condensation reactions between aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione(dimedone) catalyzed by *L*-histidine, which proceed well in the room temperature ionic liquid 1-butyl-3-methylimidazonium tetrafluoroborate to form the ring-opening derivatives of xanthenediones (Eq. 1).



(1)

Xanthenediones can be simply obtained by dehydration cyclization from their ring-opening derivatives **3**, which contain an inbuilt pyran ring in a number of natural products and occupy a prominent position in medicinal chemistry,[5] such as sauchinone and xanthaurine (Figure 1). Many reports describe the synthesis of xanthenediones or their ring-opening derivatives.[6-10] Conventional synthesis of these classes of compounds usually involves acid or base in order to catalyze the condensation of appropriate active methylene carbonyl compounds with aldehydes. However, most of these reported procedures have some disadvantages, such as low yields, excessive use of reagents and catalysts, use of toxic organic solvents, prolonged reaction times and so forth. So it is still necessary to develop novel and greener methods for the preparation of this class of compounds. We are lucky to see that the cheap and basic amino acid *L*-histidine is an efficient and reusable green catalyst for this condensation reaction in room temperature ionic liquid [bmim]BF_4.

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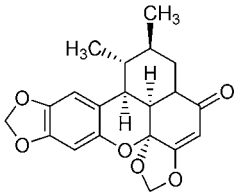
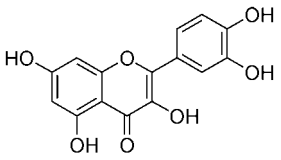


Sauchinone



Xanthaurine

Figure 1 Typical compounds containing an inbuilt pyran ring.

Results and discussion

In the initial stage of the experiment, we studied the synthesis of 2,2'-(furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3m**) as a model substrate with using various reaction conditions to achieve the best results for this condensation reaction (Eq. 1). Various temperatures have been studied in solution to determine their effect on the rate of the reaction. We also examined whether the presence of the catalyst plays a role in this reaction. The results are summarized in Table 1. According to our results, as the temperature increases, the reaction rate speeds up and the yield will reach the maximum. In addition, the existence of *L*-histidine can surely accelerate the reaction rate. The most satisfactory result was obtained at the temperature of 60 ℃ in the presence of the catalyst.

Table 1 Optimization of the condensation reaction

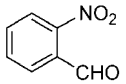
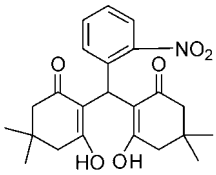
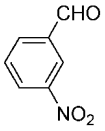
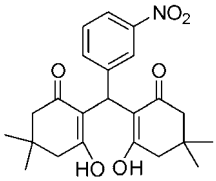
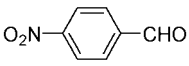
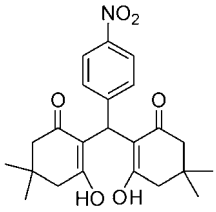
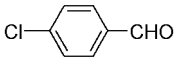
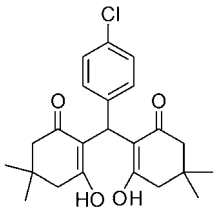
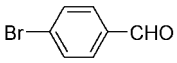
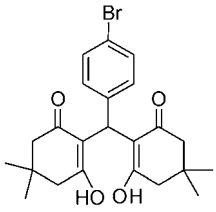
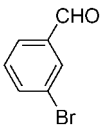
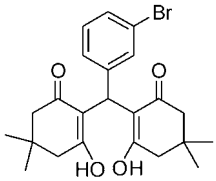
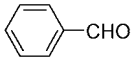
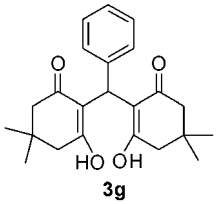
Entry	Temperature/℃	Catalyst	Time/min	Conversion[a]
1	30	20 mol%	40	60%
2	60	20 mol%	30	89%
3	80	20 mol%	30	90%
4	80	none	40	62%

[a] Conversions based on HPLC analysis.

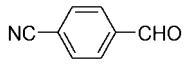
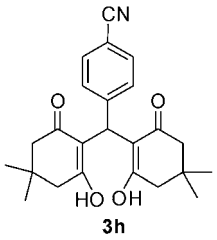
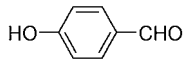
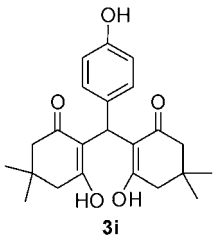
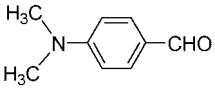
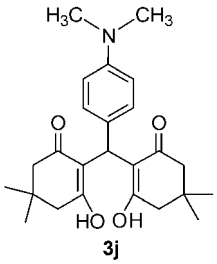
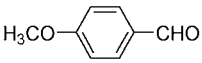
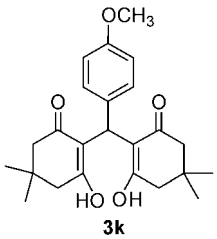
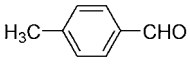
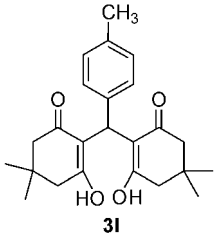
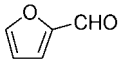
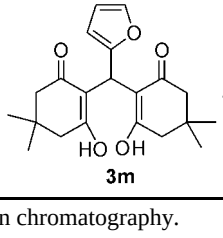
With our optimization of the reaction we have been able to achieve increases in both reaction rates and yields in a relatively shorter reaction time (30—45 min). The reaction was investigated using other aromatic aldehydes with dimedone under the optimized condition using 20 mol% of *L*-histidine in IL. The results are summarized in the Table 2.

The results in Table 2 show that aromatic aldehydes with both electron-donating and electron-withdrawing functionalities afforded high yields of the corresponding products, which reflects the wide applicability and usefulness of the method. What's more, this green catalytic system can be recovered and reused by dissolving the post-reaction mixture into dichloromethane and adding water. It was then possible to extract any unreacted substrates and the product *L*-histidine is not soluble in dichloromethane. So the organics were removed from the mixture of ionic liquid and water. The ionic liquid could be recovered by low-pressure rotary evaporation, which was reused by extracting with dichloromethane again (Table 3).

Table 2 Results of the synthesis of **3** with *L*-histidine in IL

Entry	Aldehyde	Product	Time/min	Yield[a]/%
1		 **3a**	30	93
2		 **3b**	30	91
3		 **3c**	30	90
4		 **3d**	40	90
5		 **3e**	40	88
6		 **3f**	40	86
7		 **3g**	45	85

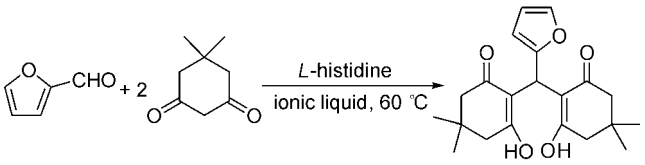
Continued

Entry	Aldehyde	Product	Time/ min	Yield[a]/ %
8		 **3h**	30	89
9		 **3i**	45	91
10		 **3j**	45	88
11		 **3k**	45	85
12		 **3l**	45	88
13		 **3m**	40	86

[a] Isolated yields after column chromatography.

In conclusion, we have described a procedure for the preparation of 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) catalyzed by organocatalyst *L*-histidine in ionic liquid. The method has many practical advantages (high yields, green solvent, moderate temperature, easy recycling of the catalytic system), which may contribute to the environmental benign process.

Table 3 Recycling experiments with the catalytic system[a]



Run	1	2	3
Time/min	40	40	40
Yield[b]/%	86	84	85

[a] Reactions performed with furfural (1.0 mmol), dimedone (2.0 mmol), and *L*-lysine (20 mol%) in IL (2 mL) and stirred for 40 min at 60 ℃; [b] Isolated yields after column chromatography.

Experimental

General description of the experimental techniques

Melting points were recorded on an electrothermal digital microscopical melting point apparatus and uncorrected. The process of reactions was monitored by TLC on silica. ^{1}H NMR and ^{13}C NMR spectra were recorded with TMS as internal standard using a Bruker AMX-500 MHz spectrometer at 500 and 125 MHz, respectively. IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. Low-resolution MS analyses were measured on a Bruke Esquire 3000 spectrometer using ESI (electrospray ionization) technique.

Typical experimental procedure

In a typical experiment, add aldehyde **1** (1 mmol), dimedone **2** (2 mmol) and *L*-histidine (20 mol%) to a 15 mL round-bottom flask equipped with efficient magnetic stirrer. Then 2 mL of IL [bmim]BF_4 is added to the flask. The reaction is kept at 60 ℃, which is monitored using thin-layer chromatography (TLC), and stirring is continued until the end. When the reaction was completed, add water (5 mL) to the reaction mixture which was then poured into a separatory funnel and extract with CH_2Cl_2 (5 mL×3). The organic layer was separated and concentrated, then the residue was purified by column chromatography eluting with petroleum/ethyl acetate or ethyl acetate/dichloromethane to give the pure product.

The physical and spectra data of all the compounds (Entry 1—13)

2,2'-((2-Nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3a**): Yellow solid, m.p. 172—174 ℃, R_f=0.56 [*V*(EtOAc)∶*V*(Petroleum), 1∶1]; IR (KBr) *v*: 3422, 2958, 2872, 1721, 1596, 1524, 1384, 1065, 788 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz), *δ*: 1.02 (s, 6H, 2×CH_3), 1.10 (s, 6H, 2×CH_3), 2.21—2.51 (m, 8H, 4×CH_2), 6.04 (s, 1H, CH), 7.24 (d, *J*=7.9 Hz, 1H, ArH), 7.32 (t, *J*=7.6 Hz, 1H, ArH), 7.45—7.49 (m, 1H,

ArH), 7.54 (q, J=1.2 Hz, 1H, ArH), 11.6 (br, s, 2H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 191.0, 189.6, 149.9, 132.3, 131.6, 129.8, 127.4, 124.5, 114.8, 47.0, 46.5, 32.1, 30.2, 28.7, 28.4; MS (ESI) *m*/*z*: 414.2 ($[M+H]^+$), 412.2 ($[M-H]^-$).

2,2'-((3-Nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3b**): Red-brown oil, R_f=0.31 [*V*(EtOAc)∶*V*(Petroleum), 1∶1]; IR (KBr) *v*: 2959, 2870, 1725, 1594, 1529, 1471, 1447, 1377, 1347, 1253, 1074, 803, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.25 (d, J=4.0 Hz, 6H), 1.44 (d, J=7.6 Hz, 6H), 2.32—2.52 (m, 8H), 5.55 (s, 1H), 7.42 (q, J=6.2 Hz, 2H), 8.01 (d, J=1.3 Hz, 2H), 11.86 (s, 1H, OH).

2,2'-((4-Nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3c**): Yellow solid, m.p. 169—171 ℃; R_f=0.23 [*V*(EtOAc)∶*V*(Petroleum), 1∶4]; IR (KBr) *v*: 3435, 2958, 1594, 1513, 1468, 1451, 1375, 1345, 1252, 1167, 1154, 1044, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.94 (broad signal, OH), 8.12 (d, J=8.4 Hz, 2H), 7.25 (d, J=7.8 Hz, 2H), 5.56 (s, 1H), 2.31—2.46 (m, 8H), 1.11 (s, 6H), 1.06 (s, 6H); MS (ESI) *m*/*z*: 414.2 ($[M+H]^+$), 412.2 ($[M-H]^-$).

2,2'-((4-Chlorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3d**): White solid, m.p. 139—141℃; R_f=0.46 [*V*(EtOAc)∶*V*(Petroleum), 1∶4]; IR (KBr) *v*: 3435, 2958, 2872, 1595, 1490, 1468, 1374, 1304, 1253, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.86 (s, 1H, OH), 7.22 (d, J=8.6 Hz, 2H), 7.01 (d, J=8.4 Hz, 2H), 5.47 (s, 1H), 2.29—2.48 (m, 8H), 1.21 (s, 6H), 1.10 (s, 6H).

2,2'-((4-Bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3e**): Yellow solid, m.p. 172—174 ℃; R_f=0.45 [*V*(EtOAc)∶*V*(Petroleum), 1∶5]; IR (KBr) *v*: 3420, 2958, 1594, 1486, 1468, 1450, 1373, 1304, 1265, 1167, 898, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.86 (s, 1H, OH), 7.37 (d, J=8.6 Hz, 2H), 6.95 (d, J=8.0 Hz, 2H), 5.45 (s, 1H), 2.33—2.44 (m, 8H), 1.21 (s, 6H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 190.9, 189.6, 137.5, 131.5, 128.8, 119.9, 115.5, 47.3, 46.7, 32.7, 31.7, 29.8, 27.7; MS (ESI) *m*/*z*: 448.8 ($[M+H]^+$).

2,2'-((3-Bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3f**): Pink solid, m.p. 184—186 ℃; R_f=0.50 [*V*(EtOAc)∶*V*(Petroleum), 1∶4]; IR (KBr) *v*: 3447, 2955, 2869, 1597, 1471, 1419, 1377, 788, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.88 (broad signal, OH), 7.29 (t, J=7.8 Hz, 1H), 7.23 (s, 1H), 7.13 (t, J=7.8 Hz, 1H), 7.01 (d, J=7.8 Hz, 1H), 5.49 (s, 1H), 2.29—2.48 (m, 8H), 1.22 (s, 6H), 1.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 190.9, 189.7, 141.0, 130.4, 129.9, 129.2, 125.7, 122.7, 115.3, 47.3, 46.7, 32.9, 31.7, 29.8, 27.6; MS (ESI) *m*/*z*: 447.2 ($[M+H]^+$), 446.8 ($[M-H]^-$).

2,2'-(Phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3g**): White solid, m.p. 190—192 ℃; R_f=0.50 [*V*(EtOAc)∶*V*(Petroleum), 1∶4]; IR (KBr) *v*: 3450, 2962, 2872, 1594, 1492, 1448, 1375, 1302, 1251, 1164, 845, 777, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.89 (s, 1H, OH), 7.26 (q, J=7.6 Hz, 2H), 7.17 (d, J=7.0 Hz, 1H), 7.09 (d, J=8.1 Hz, 2H), 5.54 (s, 1H), 2.29—2.48 (m, 8H), 1.23 (s, 6H), 1.10 (s, 6H).

4-(Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)methyl)benzonitrile (**3h**): Pale-yellow solid, m.p. 164—166 ℃; R_f=0.56 [*V*(EtOAc)∶*V*(Petroleum), 1∶4]; IR (KBr) *v*: 3484, 2964, 2887, 2225, 1594, 1501, 1447, 1375, 1306, 1253, 1120, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.86 (broad signal, OH), 7.56 (d, J=8.3 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 5.52 (s, 1H), 2.31—2.46 (m, 8H), 1.22 (s, 6H), 1.11 (s, 6H).

2,2'-((4-Hydroxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3i**): Red solid, m.p. 188—190 ℃; R_f=0.40 [*V*(EtOAc)∶*V*(Petroleum), 1∶1]; IR (KBr) *v*: 3392, 2959, 2929, 1730, 1691, 1594, 1512, 1448, 1375, 1255, 1169, 1071, 834 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.10 (s, 6H), 1.19 (s, 6H), 2.30—2.43 (m, 8H), 5.47 (s, 1H), 6.71 (d, J=8.4 Hz, 2H), 6.93 (d, J=8.0 Hz, 2H), 11.90 (s, 1H, OH); MS (ESI) *m*/*z*: 383.0 ($[M-H]^-$).

2,2'-((4-(Dimethylamino)phenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3j**): Yellow solid, m.p. 181—183 ℃; R_f = 0.68 [*V*(EtOAc)∶*V*(Petroleum), 1∶1]; IR (KBr) *v*: 3410, 2960, 2877, 1601, 1522, 1449, 1372, 1312, 1258, 1165, 1065, 912, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.96 (s, 6H, 2×CH_3), 1.10 (s, 6H, 2×CH_3), 2.29—2.42 (m, 8H, 4×CH_2), 2.90 (s, 6H, 2×CH_3), 5.47 (s, 1H, CH), 6.67 (d, J=8.2 Hz, 2H, ArH), 6.95 (d, J=8.4 Hz, 2H, ArH), 11.95 (s, 1H, OH); MS (ESI) *m*/*z*: 412.3 ($[M+H]^+$).

2,2'-((4-Methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3k**): White solid, m.p. 142—144 ℃; R_f=0.43 [*V*(EtOAc)∶*V*(Petroleum), 1∶4]; IR (KBr) *v*: 3452, 2959, 1593, 1509, 1467, 1452, 1417, 1375, 1305, 1248, 1179, 1034, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.91 (s, 1H, OH), 6.99 (d, J=8.4 Hz, 2H), 6.81 (d, J=8.7 Hz, 2H), 5.48 (s, 1H), 3.77 (s, 3H), 2.29—2.47 (m, 8H), 1.22 (s, 3H), 1.09 (s, 3H).

2,2'-(*p*-Tolylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3l**): Yellow solid, m.p. 126—128 ℃; R_f = 0.52 [*V*(EtOAc)∶*V*(Petroleum), 1∶4]; IR (KBr) *v*: 2958, 2871, 1714, 1596, 1511, 1450, 1372, 1305, 1041, 813 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.90 (broad signal, OH), 7.07 (d, J=8.0 Hz, 2H), 6.97 (d, J=7.8 Hz, 2H), 5.50 (s, 1H), 2.29—2.47 (m, 11H), 1.22 (s, 6H), 1.09 (s, 6H).

2,2'-(Furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3m**): Pale-yellow solid, m.p. 207—209 ℃; R_f=0.48 [*V*(EtOAc)∶*V*(Petroleum), 1∶1]; IR (KBr) *v*: 3435, 2958, 2930, 1740, 1715, 1641, 1603, 1385, 1242, 1044, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.86 (s, 3H, CH_3), 1.17 (d, J=1.0 Hz, 9H, 3×CH_3), 2.22 (d, J=16 Hz, 4H), 2.28 (d, J=3.1 Hz, 1H), 2.56 (d, J=3.1 Hz, 1H), 2.62 (q, J=1.1 Hz, 2H), 4.67 (s, CH, 1H), 6.17 (d, J=3.2 Hz, 1H), 6.33 (q, J=1.8 Hz, 1H), 7.40 (d, J=1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 199.5, 198.9, 193.4, 177.9, 148.9, 143.1, 111.6,

110.3, 110.2, 101.8, 52.9, 51.4, 50.4, 48.4, 37.6, 34.5, 30.9, 30.7, 29.0, 28.6, 26.5; MS (ESI) *m*/*z*: 359.2 ($[M+H]^+$, 357.1 ($[M-H]^-$.

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