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A Green and Efficient Synthesis of 9-Aryl-3,4,5,6,7,9hexahydroxanthene-1,8-dione using a Task-Specific Ionic Liquid as Dual Catalyst and Solvent

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A green and efficient method for the preparation of 9-aryl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione has been developed using functionalized ionic liquids as a catalyst and a reaction medium. The nature of both the counter anion and cation influence the catalytic performance of the ionic liquids. The ionic liquid can be recycled and reused without apparently loss of activity.

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Due to environmental concerns, the development of environmentally friendly catalysts and solvents for organic reactions has received considerable attention in recent years. Recently, room-temperature ionic liquids (RTILs) have been recognized as a possible environmentally benign alternative to conventional volatile organic solvents, and they have been investigated extensively as solvents or catalysts for many important organic reactions because of their special properties such as their negligible vapour pressure, tunable polarity, high thermal stability, good solvating ability, ease of recyclability, and their potential to enhance reaction rates and selectivity.^[1,2] They have also been referred as 'designer solvents', as their properties can be altered by the fine tuning of parameters such as the choice of organic cation, inorganic anion, and alkyl chain attached to the organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent and catalyst for a specific chemistry task. Task-specific ionic liquids, which have a functional group in their framework, have been successfully employed as efficient catalysts or dual catalyst-solvent for a variety of reactions.[3-5]

Xanthene derivatives have attracted considerable attention owing to their biological activity, being potent non-petidic inhibitors of recombinant human calpain $I.^{[6]}$ In particular, xanthenedione derivatives constitute a structural unit in several natural products^[7] and they are valuable synthons because of the inherent reactivity of the inbuilt pyran ring.^[8] The conventional synthetic methods of xanthenedione derivatives were carried out in organic solvent. An improved reaction is the condensation of aromatic aldehydes with 5,5-dimethylcyclohexane-1,3-dione in water for 6 h using NH₂SO₃H and sodium dodecyl sulfate (SDS) as catalyst.^[9] It has also been reported that xanthenediones were prepared in glycol under microwave irradiation.^[10] Very recently, Fan et al. reported that the above condensation process could proceed in ionic liquid [bmim]BF₄ catalyzed by Lewis acids InCl₃^[11] and FeCl₃·6H₂O,^[12] respectively, in which the reaction times were between 4 and 10 h. However, some of

Table 1. The condensation reaction of 4-cholorobenzaldehyde and cyclohexane-1,3-dione in different ionic liquids

Reaction conditions: 1 mmol 4-chlorobenzaldehyde, 2 mmol cyclohexane-1,3-dione, 1 mL ionic liquid

Entry	RTIL	Temperature [°C]	Time [min]	Isolated yield [%]
1	[hmim]HSO4	80	30	83
2	[emim]HSO ₄	80	30	81
3	[bmim]HSO4	80	30	84
4	[bmim]H ₂ PO ₄	80	30	37
5	[bmim]Br	80	60	Trace
6	[bmim]BF ₄	80	60	Trace
7	[bmim]PF ₆	80	60	Trace
8	[bmim]HSO4	Room temp.	30	21
9	[bmim]HSO ₄	100	30	93

these methods have not been entirely satisfactory, with disadvantages such as relatively long reaction times, using a catalyst that cannot be recycled, and so on. Therefore, the development of simple, efficient, and environmentally benign methods for the synthesis of xanthenediones remains desirable.

As a continuation of our endeavor in green synthesis and using ionic liquids as a recyclable, eco-friendly reaction medium and catalyst, [13-15] herein we reported a simple and green procedure for the preparation of 9-aryl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione **3** using task-specific acidic ionic liquid as catalyst and reaction media.

In our initial research, 4-chlorobenzaldehyde was selected as a representative reactant in order to optimize the reaction conditions. As shown in Table 1, the reaction proceeded efficiently in acidic ionic liquids [hmim]HSO₄, [emim]HSO₄, and [bmim]HSO₄ (entries 1–3). However, only moderate yields of **3e** could be obtained when [bmim]H₂PO₄ was employed (entry 4). Attempts to perform the reaction in [bmim]Br, [bmim]BF₄,

Table 2. Studies on the reuse of [bmim]HSO₄ for the preparation of 3e

 Table 3.
 Synthesis of 9-aryl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)dione in acidic ionic liquid [bmim]HSO4

Round	1	2	3	4	5
Yield [%]	93	91	92	90	88

and [bmim]PF₆ (entries 5-7) led only to recovery of unreacted starting material even at prolonged reaction time. These results suggested that the Brønsted acidic ionic liquids play the dual role of acidic catalyst and solvent. The catalytic activity of the ionic liquids to the condensation reaction was dependent very much upon the Brønsted acidity of the counter anion. The catalytic performance of the ionic liquids with hydrogen sulfate counter anion was much better than that of the other employed ionic liquids under the same reaction conditions. Probably, this is due to the high Brønsted acidity of the hydrogen sulfate counter anion. According to the literature, the Hammett function (H_0) of [bmim]HSO₄ and [bmim]H₂PO₄ is 0.73 and 2.55, respectively.^[16] The catalytic performance of [emim]HSO₄, [bmim]HSO4, and [hmim]HSO4 were similar, indicating that the low impact of the cation on the catalytic activity. [bmim]HSO₄ was chosen for further study in this work. The Lewis acidic ionic liquids, especially those based upon chloroaluminate anions, are sensitive to moisture and unstable in water. However, the Brønsted acidic ionic liquids with hydrogen sulfate as counter anion are insensitive to moisture and stable in water, so they were easily prepared and application without special operation conditions.

Effects of reaction temperature on the yields of the products were also studied by processing the condensation reaction at room temperature, 80°C, and 100°C (entries 3, 8, 9, respectively). The results shown that the higher the reaction temperature, the more efficiently the reaction could proceed.

Since the recovery and reuse of catalyst and solvent are highly preferable for a green process, we next investigated the reusability and recycling of the ionic liquid. After completion of the reaction, water was added into the reaction mixture, and the solid was collected by filtration to give the product. The filtrate containing [bmim]HSO₄ was concentrated under reduced pressure to recover the ionic liquid. The recycled [bmim]HSO₄ was reused in the model reaction of **1c** and **2**. The catalytic activity of [bmim]HSO₄ did not show any significant decrease even after five runs. The results were shown in Table 2. The results also indicated that the acidic liquid employed was stable at the reaction temperature.

A variety of substituted aromatic aldehydes were subjected to the condensation reaction to study the substituted effects on the reactivity of them. The results are summarized in Table 3. For most of the substrates, the reaction was complete at 25–40 min with high yields, whether the substrates bore electron-donating or -withdrawing groups. However, when the aromatic aldehydes with a bigger *ortho*-substituent, such as 2-nitrobenzaldehyde and 2,4-dinitrobenzaldehyde, were used the reaction could not take place owing to the stereo effect.

In conclusion, the present synthetic method offers a simple, efficient, and green synthesis of 9-aryl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione. The method offers marked improvements with regard to operational simplicity, reaction time, general applicability, high yields of products, and greenness of the procedure, avoiding hazardous organic solvents and toxic catalysts, so it provides a practical alternative to the existing procedures. The application studies of the task-specific ionic liquids for other reactions are in progress.



Entry	Ar	Time [min]	mp [°C] (lit.)	Yield [%]
3 a	C ₆ H ₅	35	274–275 (270–271) ^[17]	85.3
3b	4-CH ₃ OC ₆ H ₄	25	204-206 (201-202)[17]	92.3
3c	2-ClC ₆ H ₄	25	248-249 (250-251) ^[17]	93.6
3d	3-NO ₂ C ₆ H ₄	40	286-287 (286-288)[17]	90.1
3e	4-ClC ₆ H ₄	30	283-284 (289-291) ^[17]	93.3
3f	$4-BrC_6H_4$	30	284-285 (285-286) ^[17]	93.3
3g	4-HO-3-CH ₃ OC ₆ H ₃	25	242-243 (245-246) ^[17]	92.2
3h	4-HOC ₆ H ₄	25	258-260	91.1
3i	4-CH ₃ C ₆ H ₄	25	250-252	88.2
3j	3,4-(OCH ₂ O)C ₆ H ₃	40	238-239	84.6

Experimental

Materials and Instruments

Melting points were recorded on an electrothermal apparatus and are uncorrected. ¹H (400 MHz) and ¹³C NMR (100 MHz) spectra were determined with a Bruker AVANCE 400 spectrometer (CDCl₃) using TMS as internal standard. IR spectra were measured with a BIO-RAD FTS3000 spectrometer. Mass spectra were measured with a VG7070E spectrograph. Element analyses were preformed on Perkin-Elmer 2400CHN instrument. 1-n-Butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄), 1-hexyl-3-methylimidazolium hydrogen sulfate ([hmim]HSO₄), 1-ethyl-3-methylimidazolium hydrogen sulfate ([emim]HSO₄), 1-n-butyl-3-methylimidazolium hydrogen sulfate ([bmim]HSO₄), 1-n-butyl-3-methylimidazolium dihydrogen phosphate ([bmim]H2PO4), 1-n-butyl-3-methylimidazolium bromide ([bmim]Br), and 1-n-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) were prepared according to the literature.[18,19]

General Procedure for the Preparation of Xanthenediones

A mixture of 1.0 mmol aromatic aldehydes 1, 2.0 mmol cyclohexane-1,3-dione 2, and 1 mL [bmim]HSO₄ were stirred at 100°C for a specified time (shown in Table 3) to complete the reaction (monitored by TLC). After completion, water was added into the reaction mixture and the resulting solid products were filtered off to afford the primary product. The pure desired product, 9-aryl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione **3a**–**3j**, was obtained by further recrystallization with 80% ethanol. The results are summarized in Table 3. All the known products **3a**–**3g** were fully characterized by IR and ¹H NMR spectroscopy, and melting points, which were consistent with the literature data. The new compounds **3h**–**3j** were identified by IR and ¹H NMR spectroscopy, mass spectrometry, and elemental analysis.

3h: $\delta_{\rm H}$ (CDCl₃, 400 MHz) 1.995–2.063 (m, 4H, CH₂), 2.342–2.398 (m, 4H, CH₂), 2.592–2.704 (m, 4H, CH₂), 4.844 (s, 1H, CH), 7.124–7.160 (m, 1H, OH), 7.246 (d, *J* 7.6, ArH), 7.324 (d, *J* 7.6, 2H, ArH). $\nu_{\rm max}$ (KBr)/cm⁻¹ 3360, 2950, 1671, 1654, 1620, 1520, 1361, 1205, 1176, 1135, 956. *m/z* [%] 293 (M⁺ – 17, 100),

276 (14), 216 (99), 77 (38), 55 (26). (Calc. for C₁₉H₁₈O₄: C 73.5, H 5.8. Found C 73.4, H 5.8.)

3i: $\delta_{\rm H}$ (CDCl₃, 400 MHz) 1.995–2.056 (m, 4H, CH₂), 2.28 (s, 3H, CH₃), 2.335–2.391 (m, 4H, CH₂), 2.583–2.660 (m, 4H, CH₂), 4.803 (s, 1H, CH), 7.054 (d, *J* 8.0, 2H, ArH), 7.214 (d, *J* 8.0, 2H, ArH). $\nu_{\rm max}$ (KBr)/cm⁻¹ 2954, 1658, 1619, 1510, 1423, 1361, 1200, 1176, 1124, 956. *m*/*z* [%] 308 (M⁺, 12), 307(48), 292 (68), 216 (100), 55 (20). (Calc. for C₂₀H₂₀O₃: C 77.9, H 6.5. Found C 77.9, H 6.5.)

3*j*: $\delta_{\rm H}$ (CDCl₃, 400 MHz) 1.961–2.064 (m, 4H, CH₂), 2.343–2.411 (m, 4H, CH₂), 2.581–2.689 (m, 4H, CH₂), 4.757 (s, 1H, CH), 5.896 (s, 1H, OCH₂O), 6.676–6.820 (m, 3H, ArH). $\nu_{\rm max}$ (KBr)/cm⁻¹ 2956, 1672, 1655, 1620, 1504, 1486, 1440, 1384, 1361, 1246, 1200, 1178, 1136, 1037, 956, 927. *m/z* [%] 338 (M⁺, 93), 321 (18), 308 (13), 282 (30), 252 (10), 217 (100), 55 (29). (Calc. for C₂₀H₁₈O₅: C 71.0, H 5.3. Found C 71.0, H 5.3.)

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