$InCl_3 \cdot 4H_2O$-promoted green preparation of xanthenedione derivatives in ionic liquids

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Abstract: A green procedure for the synthesis of xanthenedione derivatives (**3**) through $InCl_3 \cdot 4H_2O$-promoted condensation of aldehydes (**1**) and 5,5-dimethyl-1,3-cyclohexanedione (**2**) in ionic liquids is described in this paper. This novel method has such advantages as operational simplicity and environmental benignancy together with enhanced atom utilization. Moreover, the reaction media and the catalyst can be recovered conveniently and reused effectively for at least six times.

Key words: ionic liquid, xanthenedione derivatives, indium trichloride, green synthesis.

Résumé : Dans ce travail, on décrit une méthode verte de synthèse de dérivés **3** de la xanthènedione par le biais d'une condensation, catalysée par le $InCl_3 \cdot 4H_2O$, des aldéhydes (**1**) avec la 5,5-diméthylcyclohexane-1,3-dione (**2**), dans des liquides ioniques. Cette nouvelle méthode allie la simplicité d'opération et un caractère bénin pour l'environnement avec une utilisation accrue des atomes. De plus, le milieu réactionnel ainsi que le catalyseur peuvent être facilement récupérés et réutilisés d'une façon efficace jusqu'à six fois.

Mots clés : liquide ionique, dérivés de la xanthènedione, trichlorure d'indium, synthèse verte.

[Traduit par la Rédaction]

Introduction

Xanthene derivatives have attracted considerable interest in recent years because of their promising activity as positive allosteric modulators of metabotropic (mGlu) receptors (1) and potent nonpeptidic inhibitors of recombinant human calpain I (2). They have been used as rigid carbon skeletons for the construction of new chiral bidentate phosphine ligands with potential applications in catalytic processes (3). In particular, xanthenediones constitute a structural unit in a number of natural products (4) and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring (5). Up to now, several methods have been developed for the preparation of xanthenediones. Among them, the conventional procedures involve acid- or base-catalyzed condensation of appropriate active methylene carbonyl compounds with aldehydes (6). However, these methods are plagued by the limitation of prolonged reaction times, poor yields, and side reactions of aldehydes. Recently, Singh et al. (7*a*) reported a new method for the preparation of xanthenediones through carbon transfer reactions of 1,3-oxazinanes and oxazolidines with carbon nucleophiles. It has also been reported that xanthenedione derivatives could be obtained through condensation of aldehydes and 5,5-dimethyl-1,3-cyclohexanedione in glycol under microwave irradiation (7*b*). Most recently, Jin et al. (7*c*) reported a novel and interesting procedure in which the above condensation process was realized in water in the presence of a dodecylbenzenesulphonic acid catalyst. However, due to their great importance, there still needs to be development of novel methods for the preparation of xanthenediones.

The development of environmentally friendly catalysts and solvents for organic chemistry is an area of considerable importance. From both economical and environmental points of view, the use of nonvolatile solvents is very promising. In the last few years, room-temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidaxolium cations, have been recognized as a possible environmentally benign alternative to chemically volatile solvents. They are nonvolatile, recyclable, nonexplosive, easy to handle, and thermally robust. In many cases, the products are weakly soluble in the ionic liquid phase so that the products can be easily separated by simple filtration or extraction with ether. Because of the great potential of RTILs as novel reaction media for catalytic processes, much attention has currently been focused on their applications as novel media for various kinds of organic reactions (8). As a continuation of our interest in the area of clean synthesis using ionic liquids as a green recyclable alternative to classical molecular solvents (9), we report here a very simple and green procedure for the preparation of xanthenediones (**3**, Scheme 1) through a $InCl_3 \cdot 4H_2O$-promoted cascade reaction between aldehydes (**1**) and 5,5-

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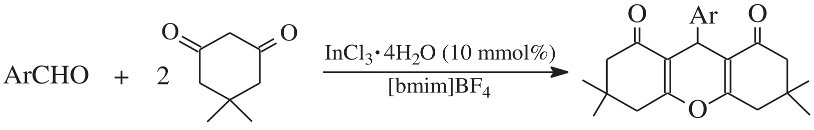
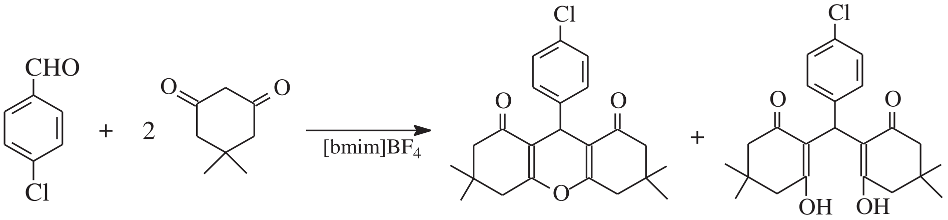
Scheme 1.



1 **2** **3**

Scheme 2.



1a **2** **3a** **4a**

Table 1. Reaction condition screening for the condensation of **1a** and **2** in the ionic liquid.[a]

				Isolated yield (%)	
Entry	Amount of $InCl_3·4H_2O$ (mmol)	Reaction temp. (°C)	Reaction time (h)	**3a**	**4a**
1	0	r.t.	1.5	5	20
2	0	50	1.5	10	30
3	0	50	3	15	35
4	0	70	3	18	42
5	0	100	3	20	55
6	0	120	5	23	69
7	0.10	50	3	55	10
8	0.10	70	3	75	5
9	0.10	70	5	83	0
10	0.10	80	5	95	0

[a]Reaction conditions: 1 mL solvent, 0.5 mmol **1a**, and 1 mmol **2**.

dimethyl-1,3-cyclohexanedione (**2**) in ionic liquid 1-butyl-3-methylimidazolium tetra-fluoroborate ([bmim][BF_4]).

Results and discussion

The mixture of 5,5-dimethyl-1,3-cyclohexanedione (**2**) and 4-chlorobenzaldehyde (**1a**) in [bmim][BF_4] was prepared and stirred at room temperature. After 0.5 h, some solid was observed and TLC analysis gave a positive result for the formation of a new compound together with the remaining aldehyde **1a**. To have a complete conversion, stirring of the mixture was continued for 1 h. To our surprise, another compound was formed as indicated by the TLC analysis. At this stage, the reaction was quenched by the addition of 5 mL H_2O to the mixture. Then, the solid compound was collected and separated through column chromatography. Subsequent analysis in terms of physical and spectral data (IR, ^{1}H NMR, and MS) showed that these two compounds were 9-(4 chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-exahydro-1*H*-xanthene-1,8(2*H*)-dione (**3a**) and bis(5,5-dimethyl-3-hydroxy-1-oxa-2-cyclohexen-2-yl)-4′-chlorophenylmethane (**4a**). Their yields were found to be 5% and 20%, respectively. In addition, it should be noted that the compound formed first in this process was **4a**. The reaction process is shown in Scheme 2.

To obtain **3a** alone, rather than the mixture of **3a** and **4a**, with more increased yield, the reaction mixture of **1a** and **2** was then stirred at different elevated reaction temperatures and (or) over a prolonged reaction time. The results obtained are shown in Table 1. It can be seen that with increased reaction temperature and (or) prolonged reaction time, although **3a** could be obtained in higher yields, the yields of **4a** were also increased to some extent. Thus, it seems impossible to get **3a** alone just by adjusting such factors as temperature and reaction time. Considering the fact that $InCl_3·4H_2O$, as an efficient Lewis acid catalyst, has been successfully used in promoting many kinds of organic reactions (10), especially in several condensation processes, we then added a catalytic amount of $InCl_3·4H_2O$ into the reaction mixture with the hope of obtaining an improved result in terms of both yield and selectivity of **3a**. To our delight, $InCl_3·4H_2O$ showed high efficiency for this process by affording **3a** not only in high yield, but also with excellent selectivity (entries 7–10, Table 1).

Based on the above results, this process was then extended to other structurally varied aldehydes to investigate its scope and generality. The results are listed in Table 2. It

Table 2. Preparation of xanthenediones promoted by $InCl_3{\cdot}4H_2O$ in [bmim][BF_4] at 80 °C.

Entry	Ar	Time (h)	Products	Yield (%)	mp (Lit. value) (ref.)
1	p-ClC_6H_4	5	**3a**	95	237–239 (230 to 231) (7*b*)
2	p-$CH_3C_6H_4$	4	**3b**	90	210–212 (218–220) (7*b*)
3	p-$NO_2C_6H_4$	5	**3c**	86	222–224 (222–224) (7*b*)
4	C_6H_5	4	**3d**	87	199–201 (198–200) (7*b*)
5	o-ClC_6H_4	10	**3e**	83	225–227 (228 to 229) (7*b*)
6	p-$CH_3OC_6H_4$	5	**3f**	87	241–243 (227–228) (10)
7	p-FC_6H_4	4	**3g**	90	224–226 (225–227) (10)
8	o-BrC_6H_4	10	**3h**	76	226–228
9	p-BrC_6H_4	4	**3i**	93	234–236
10	m-$NO_2C_6H_4$	4	**3j**	92	145–147

Table 3. Reusability of [bmim][BF_4] and the catalyst.[a]

Round	Ionic liquid recovered (%)	Isolated yield of **3a** (%)
1	98	95
2	99	98
3	98	93
4	99	91
5	98	88
6	97	87

[a]Reaction conditions: reaction temp. 80 °C, reaction time 5 h.

Table 4. Reaction of **1c** and **2** in different solvents.[a]

				Isolated yield (%)	
Entry	Solvent	Reaction temp. (°C)	Reaction time (h)	**3c**	**4c**
1	Ethanol	Reflux	5	29	31
2	Methanol	Reflux	5	24	23
3	Toluene	80	5	25	27
4	Ethyl acetate	Reflux	5	59	Traces
5	[bmim][BF_4]	80	5	86	0

[a]Reaction conditions: 1 mL solvent, 0.5 mmol **1c**, and 1 mmol **2**.

is shown that under the similar fashion, a wide range of aldehydes underwent smooth condensation with 5,5-dimethyl-1,3-cyclohexanedione (**2**) to give xanthenedione derivatives in high yields. One feature of the present procedure is that aldehydes both with electron-withdrawing groups and with electron-donating groups afforded the corresponding product in good yields, and para- and meta-substituted substrates reacted almost equally well. However, aldehydes bearing an ortho group turned out to be reluctant to undergo the condensation reaction probably because of steric hindrance. Thus, longer reaction time is required for these substrates to get the corresponding products in high yields (entries 5 and 8, Table 2).

Our attention was then directed toward the possibility of recycling the reaction media since the recovery and reuse of catalyst and solvent are highly preferable for a greener process. At completion, water was added into the reaction mixture, and the solid was collected by filtration to give the product. The filtrate containing [bmim][BF_4] and the dissolved In(III) was concentrated under reduced pressure to recover the ionic liquid and the catalyst. Then, their reusability was investigated by using **1a** and **2** again as the model substrates. It has been observed that even in the sixth round, the corresponding product could still be obtained with fairly good yield by using the ionic liquid and the catalyst recovered from the fifth (Table 3, entry 6).

For the sake of comparison with [bmim][BF_4], several conventional organic solvents including methanol, ethanol, toluene, and ethyl acetate, were also used in this catalytic process with **1c** (*p*-nitrobenzaldehyde) and **2** as model substrates. The results are summarized in Table 4.

It has been shown that of the five solvents used, [bmim][BF_4] gave the best result in terms of both yield and selectivity. In fact, only when [bmim][BF_4] was used as the reaction medium, can **3c** be obtained with a high yield (86%, Table 4, entry 5). On the other hand, when toluene, methanol, ethanol, or ethyl acetate was used, not only was the reaction incomplete after being stirred at reflux or at 80 °C for 5 h, but a mixture of **3c** and **4c** was also obtained with much lower yields (Table 4, entries 1–4). Actually, **3c** is in the solid state when the reaction is complete and therefore can be obtained through simple filtration because of its poor solubility in [bmim][BF_4]. On the contrary, when toluene, methanol, ethanol, or ethyl acetate was used, the product was dissolved in the solution. Therefore, with toluene or ethyl acetate as solvent, the product has to be obtained through tedious experimental operations, such as washing with water, drying over anhydrous sodium sulfate, concentrating under vacuum, and subsequent separation on column chromatography. When ethanol or methanol was used, the separation procedure turned out to be even more complicated. First, the solvent had to be removed and the residue was redissolved in another solvent immiscible with water. Then the solution was washed with water, dried, concentrated, and finally separated on column. Considering all of these differences, it may be safe to say that using [bmim][BF_4] in place of conventional organic solvents as the reaction medium actually results in a much enhanced reactivity, and avoids the disadvantages such as tedious operational procedure and potential experimental pollution in relation to the organic solvents.

It has been reported that another green solvent, water, has also been used as reaction medium for this procedure (11). However, due to the poor solubility of substrates in water, a phase-transfer catalyst (quaternary ammonium salt) and a strong acid catalyst (such as TsOH) have to be used to facilitate the cyclodehydration reaction. Even so, xanthenedione derivatives **3** (Scheme 2) can only be obtained from para-substituted aromatic aldehydes through a much longer reaction period. In the case of ortho- and meta-substituted aromatic aldehydes, non-cyclodehydrated products **4** (Scheme 2) instead of **3** were obtained. In contrast, the substrates are well-dissolved in the [bmim][BF_4]/In^{3+} system, no phase-transfer catalyst is needed, and the reaction time is much shorter in our situation. Moreover, aromatic aldehydes with ortho- or meta-substituents can react smoothly with **2** to produce xanthenedione derivates **3** in good yields (Table 2, entries 5 and 10). In another case, microwave irradiation technique has also been successfully used in the condensation of aldehydes with 5,5-dimethyl-1,3-cyclohexanedione to give xanthenedione (7*b*). However, its potential use for larger scale preparation may be rather limited compared to the method presented in this paper.

In conclusion, we have found a novel procedure for the preparation of xanthenedione derivatives. The main advantages of this procedure include high yields, simple experimental procedure, and ease of recovering and reusing of the catalyst and the reaction media. Therefore, the present method is expected to serve as an alternative process for the preparation of xanthenedione derivatives.

Experimental

Melting points were measured by a Kofler micromelting point apparatus and the results were uncorrected. IR spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC 400 spectrometer as $CDCl_3$ solutions. Chemical shifts (δ) are expressed in ppm downfield from the internal standard tetramethylsilane, and coupling constants (*J*) are given in Hz. Elemental analyses were performed on an EA-1110 instrument.

The ionic liquid [bmim][BF_4] was prepared and purified according to literature procedure (12). Other reagents were of reagent grade and were used without further purification.

General procedure for the preparation of xanthenedione derivatives

Aldehyde (**1**, 1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**2**, 2 mmol), and $InCl_3 \cdot 4H_2O$ (0.1 mmol) were added to a 10 mL round-bottomed flask containing 1 mL [bmim][BF_4]. Then the mixture was stirred at 80 °C for a certain period of time (shown in Table 2) to complete the reaction (monitored by TLC). At completion, water was added into the reaction mixture and the solid was collected by suction and rinsed with cold ethanol to give the product **3**. All the products were fully characterized by IR, ^1H NMR, and elemental analysis. The aqueous solution of ionic liquid together with the catalyst was concentrated under reduced pressure to recover the ionic liquid and catalyst for subsequent use.

*9-(4′-Flurophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3g)*

Colorless needles, mp 224~226 (lit. value (10) mp 225~227). ν: IR (KBr, cm^{-1}) ν: 3030, 2950, 2878, 1685, 1660, 1627, 1467, 1357, 1203. ^1H NMR ($CDCl_3$) δ: 1.04 (s, 6H, 2 × CH_3), 1.11 (s, 6H, 2 × CH_3), 2.14~2.46 (m, 8H, 4 × CH_2), 4.77 (s, 1H, CH), 7.31(d, *J* = 8.4 Hz, 2H, ArH), 7.65 (d, *J* = 8.4 Hz, 2H, ArH). Anal. calcd. for $C_{23}H_{25}FO_3$: C 74.98, H 6.84; found: C 74.88, H 6.75.

*9-(2′-Bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3h)*

Colorless needles, mp 226~228. IR (KBr, cm^{-1}) ν: 2959, 2871, 1679, 1666, 1627, 1469, 1357, 1203. ^1H NMR ($CDCl_3$) δ: 1.04 (s, 6H, 2 × CH_3), 1.11 (s, 6H, 2 CH_3), 2.14~2.46 (m, 8H, 4 CH_2), 5.04 (s, 1H, CH), 6.98 (t, *J* = 8.0 Hz, 1H, ArH), 7.21 (t, *J* = 4.0 Hz, 1H, ArH), 7.45 (m, 1H, ArH), 7.47 (d,d, *J* = 8.0, 0.9 Hz, 1H, ArH). Anal. calcd. for $C_{23}H_{25}BrO_3$: C 64.39, H 5.87; found: C 64.25, H 5.77.

*9-(4′-Bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3i)*

Colorless needles, mp 234~236. IR (KBr, cm^{-1}) ν: 2953, 2878, 1679, 1662, 1625, 1487, 1470, 1362. ^1H NMR ($CDCl_3$) δ: 1.00 (s, 6H, 2 × CH_3), 1.12 (s, 6H, 2 × CH_3), 2.16~2.48 (m, 8H, 4 × CH_2), 4.72 (s, 1H, CH), 7.18 (d, *J* = 8.4 Hz, 2H, ArH), 7.35 (d, *J* = 8.4 Hz, 2H, ArH). Anal. calcd. for $C_{23}H_{25}BrO_3$: C 64.39, H 5.87; found: C 64.30, H 5.82.

*9-(3′-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3j)*

Colorless crystals, mp 145~147. IR (KBr, cm^{-1}) ν: 2958, 1677, 1655, 1622, 1525, 1475, 1363, 1202. ^1H NMR ($CDCl_3$) δ: 1.02 (s, 6H, 2 × CH_3), 1.14 (s, 6H, 2 × CH_3), 2.17~2.53 (m, 8H, 4 CH_2), 4.86 (s, 1H, CH), 7.43 (t, *J* = 8.0 Hz, 1H, ArH), 7.84 (d, *J* = 7.6 Hz, 1H, ArH), 7.99~8.04 (m, 2H, ArH). Anal. calcd. for $C_{23}H_{25}NO_5$: C 69.86, H 6.37, N 3.54; found: C 69.66, H 6.29, N 3.51.

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