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ORIGINAL ARTICLE

Synthesis of 1,8-dioxo-octahydroxanthenes and bis(indolyl)methanes catalyzed by $[Et_3NH][H_2PO_4]$ as a cheap and mild acidic ionic liquid

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KEYWORDS

$[Et_3NH][H_2PO_4]$;
Bis(indolyl)methane;
1,8-Dioxo-octahydroxanthenes;
Ionic liquid

Abstract Triethyl ammonium dihydrogen phosphate was used as a cheap and mild acidic ionic liquid catalyst for synthesis of 1,8-dioxo-octahydroxanthenes and bis(indolyl)methanes. This methodology offers several advantages, such as good yields, short reaction times, simple procedure, and mild conditions.

1. Introduction

Ionic liquids (ILs) are very attractive and environmentally acceptable solvents because they have very low vapor pressure and are stable in a wide temperature range (Wasserscheid and Keim, 2000). Therefore, they can be used as environmentally benign solvents for a number of chemical processes, such as separations (Huddleston et al., 1998), reactions (Sheldon, 2001), homogeneous two-phase catalyses (Holbrey and Seddon, 1999), and extractions (Esser et al., 2004). The current emphasis on novel reaction media is motivated by the need for efficient methods for replacing of toxic or hazardous solvents and catalysts. The use of ionic liquids as novel reaction media may offer a convenient solution to both the solvent emission and the catalyst recycling problem (Gmouh et al., 2003). Another promising class of new media is molten salts which can be used instead of ionic liquids. Molten salts are generally thermally stable and chemically resistant.

Indole and xanthene derivatives are parent compounds generally of a large number of naturally occurring, as well as synthetic derivatives, and occupy a prominent position in medicinal chemistry. Many procedures are disclosed to synthesize bis-indolyl carbonyl compounds (Sonar et al., 2009; Kundu et al., 2010) and xanthenediones (Karthikeyana and Pandurangana, 2009; Dabiri et al., 2008). In spite of potential utility of these methods, many of them involve expensive reagents, strong acidic conditions, long reaction times, low yields, use of excess of reagents/catalysts, and use of toxic organic solvents. Therefore, to avoid these disadvantages, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time and simple work-up for the preparation of bis-indolyl methanes and xanthenediones under mild and practical conditions is of prime interest. The aim of this study is to utilize the $[Et_3NH][H_2PO_4]$ in molten state as

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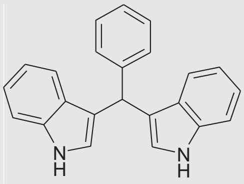
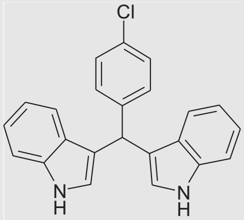
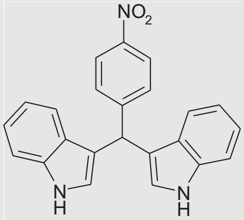
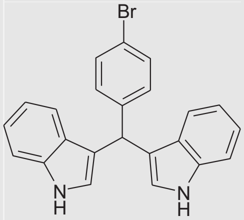
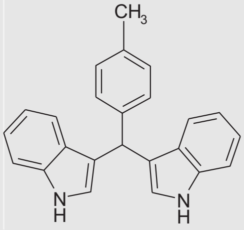
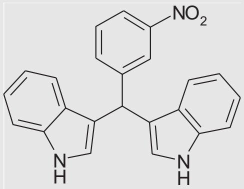
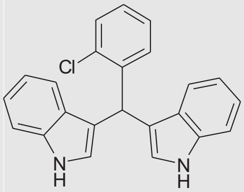
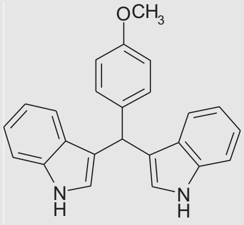
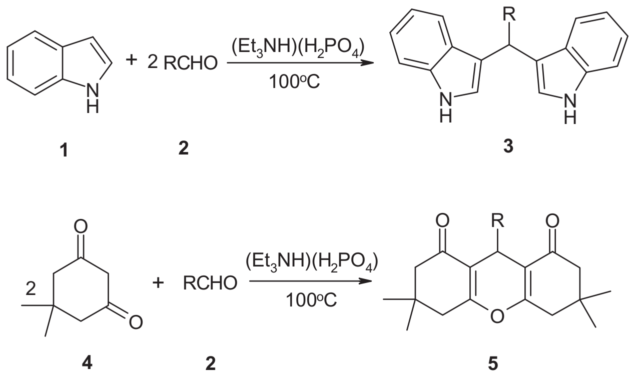
Table 1 Synthesis of bis(indolyl)methanes in molten $[Et_3NH][H_2PO_4]$.

Entry	R	Product	Time (min)	Yield (%)
1	C_6H_5		10	97
2	$4\text{-Cl-}C_6H_4$		5	84
3	$4\text{-NO}_2\text{-}C_6H_4$		5	87
4	$4\text{-Br-}C_6H_4$		10	97
5	$4\text{-CH}_3\text{-}C_6H_4$		30	95
6	$3\text{-NO}_2\text{-}C_6H_4$		5	93
7	$2\text{-Cl-}C_6H_4$		5	96
8	$4\text{-OCH}_3\text{-}C_6H_4$		10	98



Scheme 1 [Et$_3$NH][H$_2$PO$_4$]-catalyzed synthesis of bis(indolyl)methanes and 1,8-dioxo-octahydroxanthenes.

a very efficient mild acidic ionic liquid catalyst for the synthesis of bis-indolyl methanes and 1,8-dioxo-octahydroxanthene derivatives (Scheme 1).

2. Materials and methods

All compounds are known and were identified by comparison of their spectral data and physical properties with those of the authentic samples. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer. All chemicals were purchased from Merck chemical company and used without further purification. [Et$_3$NH][H$_2$PO$_4$] was prepared according to a literature method (Wang et al., 2006).

2.1. General procedure for the preparation of bis(indolyl)methanes

A mixture of indole **1** (2 mmol), aldehyde **2** (1 mmol), and [Et$_3$NH][H$_2$PO$_4$] (0.4 g) was stirred at 100 °C for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in ethanol and poured into water. The resulting precipitate was filtered and purified by recrystallization from ethanol to afford the desired compound in pure form.

2.2. Spectral data for selected bis(indolyl)methanes

2.2.1. Bis(3-indolyl)phenylmethane (Table 1, entry 1)

^{1}H NMR (CDCl$_3$, 500 MHz): δ (ppm) 5.93 (s, 1H, CH), 6.67 (s, 2H), 7.05 (t, J = 7.3 Hz, 2H, arom), 7.21 (t, J = 7.3 Hz, 2H, arom), 7.25 (t, J = 7.2 Hz, 1H, arom), 7.29–7.33 (m, 2H, arom), 7.37–7.40 (m, 4H, arom), 7.43 (d, J = 7.9 Hz, 2H, arom), 7.88 (s, br, 2H, NH). ^{13}C NMR: δ (ppm) 40.6, 111.4, 119.7, 120.2, 120.4, 122.4, 124.1, 126.6, 127.5, 128.6, 129.2, 137.1, and 144.4.

2.2.2. Bis(3-indolyl)-(p-chlorophenyl)methane (Table 1, entry 2)

^{1}H NMR (CDCl$_3$, 500 MHz): δ (ppm) 5.09 (s, 1H, CH), 6.66 (s, 2H), 7.06 (t, J = 7.4 Hz, 2H, arom), 7.22 (t, J = 7.6 Hz, 2H, arom), 7.27–7.32 (m, 4H, arom), 7.40 (t, J = 7.7 Hz, 4H, arom), 7.92 (s, br, 2H, NH). ^{13}C NMR: δ (ppm) 40.1, 111.5, 119.6, 119.8, 120.3, 122.5, 124.0, 127.3, 128.8, 130.5, 132.2, 137.1, and 142.9.

2.2.3. Bis(3-indolyl)-p-nitrophenylmethane (Table 1, entry 3)

^{1}H NMR (CDCl$_3$, 500 MHz): δ (ppm) 5.92 (s, 1H, CH), 6.63 (s, 2H), 6.91 (t, J = 7.3 Hz, 2H, arom), 7.08 (t, J = 7.3 Hz, 2H, arom), 7.25 (d, J = 7.9 Hz, 2H, arom), 7.32 (d, J = 8.1 Hz, 2H, arom), 7.44 (d, J = 8.6 Hz, 2H, arom), 8.04 (d, J = 8.6 Hz, 2H, arom), 9.31 (s, br, 2H, NH). ^{13}C NMR: δ (ppm) 40.5, 111.8, 117.8, 119.4, 119.7, 122.1, 123.8, 124.4, 127.0, 129.9, 137.3, 146.7, and 152.8.

2.3. General procedure for the preparation of 1,8-dioxo-octahydroxanthenes

A mixture of 5,5-dimethyl-1,3-cyclohexanedione **4** (2 mmol), aldehyde **2** (1 mmol), and [Et$_3$NH][H$_2$PO$_4$] (0.4 g) was stirred at 100 °C for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in ethanol and poured into water. The resulting precipitate was filtered and purified by recrystallization from ethanol to afford the desired compound in pure form.

2.4. Spectral data for selected 1,8-dioxo-octahydroxanthenes

2.4.1. 3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2H-xanthene-1,8(5H, 9H)-dione (Table 2, entry 1)

^{1}H NMR (CDCl$_3$, 500 MHz): δ (ppm) 1.03 (s, 6H), 1.14 (s, 6H), 2.33–2.51 (m, 8H, 4CH$_2$), 4.79 (s, 1H, CH), 7.13 (d, J = 7.8 Hz, 2H, arom), 7.20 (t, J = 7.2 Hz, 1H, arom), 7.28–7.31 (m, 2H, arom). ^{13}C NMR: δ (ppm) 27.1, 29.0, 31.5, 31.8, 40.5, 51.0, 115.6, 126.1, 127.7, 128.2, 142.0, 163.2, and 196.1.

2.4.2. 9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2H-xanthene-1,8(5H, 9H)-dione (Table 2, entry 2)

^{1}H NMR (CDCl$_3$, 500 MHz): δ (ppm) 0.99 (s, 6H, 2CH3), 1.10 (s, 6H, 2CH3), 2.25–2.50 (m, 8H, 4CH$_2$), 4.66 (s, 1H), 7.26–7.43 (m, 4H, arom). ^{13}C NMR: δ (ppm) 27.3, 29.2, 31.5, 32.2, 40.9, 50.7, 115.3, 128.2, 129.8, 132.0, 143.8, 162.4, and 196.3.

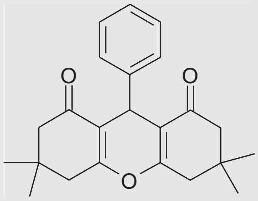
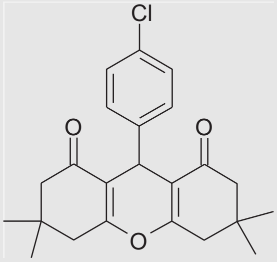
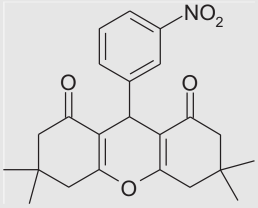
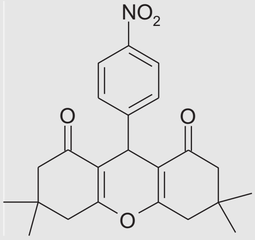
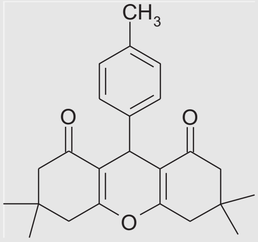
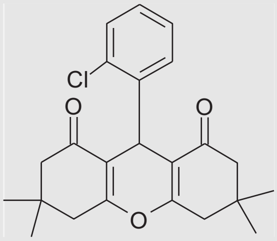
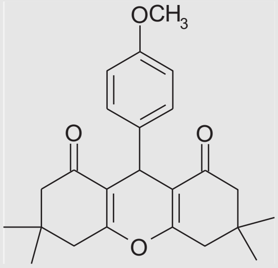
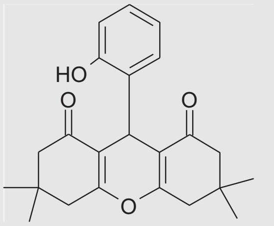
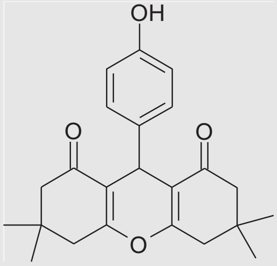
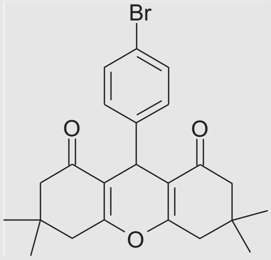
3. Results and discussion

We first studied a reaction between benzaldehyde (1 mmol) and indole (2 mmol) by screening the reaction conditions. In order to determine the optimum conditions, we examined the influence of the reaction temperature, the reaction time, and the amounts of (Et$_3$NH)(H$_2$PO$_4$). The best result was obtained with 0.4 g of [Et$_3$NH][H$_2$PO$_4$] at 100 °C.

After optimizing the conditions, we next examined the generality of these conditions to other substrates using several aromatic aldehydes. The results are summarized in Table 1. The results showed that the reaction proceeds very efficiently in all cases.

Encouraged by these results, we used same conditions for the synthesis of 1,8-dioxo-octahydroxanthenes (Scheme 1). We optimized amount of [Et$_3$NH][H$_2$PO$_4$] for condensation reaction of 5,5-dimethyl-1,3-cyclohexanedione **4** and benzalde-

Table 2 Synthesis of 1,8-dioxo-octahydroxanthenes in molten [Et_3NH][H_2PO_4].

Entry	R	Product	Time (min)	Yield (%)
1	C_6H_5		5	96
2	4-Cl-C_6H_4		20	95
3	3-NO_2-C_6H_4		5	86
4	4-NO_2-C_6H_4		5	86
5	4-CH_3-C_6H_4		30	84
6	2-Cl-C_6H_4		5	95
7	4-OCH_3-C_6H_4		15	86
8	2-OH-C_6H_4		10	90
9	4-OH-C_6H_4		10	92
10	4-Br-C_6H_4		5	94

hyde at 100 °C. The best result was obtained with a 0.4 g of [Et_3NH][H_2PO_4].

To investigate the versatility of the catalyst, the reaction of 5,5-dimethyl-1,3-cyclohexanedione **4** was carried out with various aromatic aldehydes in molten [Et_3NH][H_2PO_4] at 100 °C, which also afforded 1,8-dioxo-octahydroxanthene derivatives **5** in good to excellent yields. The results are given in Table 2.

Here also the aromatic aldehydes containing both electron-donating and electron withdrawing groups afforded the products with high yields. Work-up procedure was so simple and including addition of water at the end of the reaction, filtration, and finally recrystallizing the products from ethanol.

Comparison of the time, and yield of our method for the synthesis of bis(indolyl)methanes and 1,8-dioxo-octahydroxanthenes with the literature are indicated in Tables 3 and 4. As it is evident from the results, [Et_3NH][H_2PO_4] was found to be effective catalyst for the synthesis of bis(indolyl)methanes and 1,8-dioxo-octahydroxanthenes.

Table 3 Comparison of [Et_3NH][H_2PO_4]-catalyzed reaction of benzaldehyde and indole with literature results.

Entry	Catalyst	Solvent	Time (min)	Yield (%)	Refs.
1	$ZrOCl_2 \cdot 8H_2O$	Solvent-free	40	84	Firouzabadi et al. (2006)
2	$Al(HSO_4)_3$	EtOH	60	92	Srinivasa et al. (2008)
3	Bu_4NBr_3	EtOH	150	72	Kundu et al. (2010)
4	[Et_3NH][H_2PO_4]	[Et_3NH][H_2PO_4]	10	97	–

Table 4 Comparison of [Et_3NH][H_2PO_4]-catalyzed reaction of benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione with literature results.

Entry	Catalyst	Solvent	Time (min)	Yield (%)	Refs.
1	[bmim]HSO_4	[bmim]HSO_4	25	92	Ma et al. (2008)
2	[TMPSA]HSO_4	H_2O	60	94	Fang et al. (2009)
3	Silica-sulfuric	Solvent-free	60	97	Seyyedhamzeh et al. (2008)
4	[Et_3NH][H_2PO_4]	[Et_3NH][H_2PO_4]	5	96	–

4. Conclusion

In summary, a mild Brønsted-acidic task-specific ionic liquid such as [Et_3NH][H_2PO_4] was found to be efficient catalyst for synthesis of 1,8-dioxo-octahydroxanthenes and bis(indolyl)methanes. The merit of this methodology is that it is simple, mild, and efficient and the used ionic liquid is cheaper than conventional ionic liquids. Therefore, we believe that the work reported here would have potential application in green chemistry.

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