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An efficient and reusable ionic liquid catalyst for the synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes under solvent-free conditions†

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In this work, it was found that acidic protic ionic liquid *N,N*-dimethylaminoethanol hydrosulfate ([DMEA][HSO₄]) was an efficient and reusable catalyst for the one-pot synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes under solvent-free conditions. This ionic liquid is very cheap, air and water stable, and can be easily recovered and reused for at least six cycles. The catalytic system described here is a green protocol since in the one-pot synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes, the yield of the target compounds is excellent, operation and work-up procedures are simple, and no volatile organic solvents have been used. It is suggested that the synergetic effect of the cation and the anion of this ionic liquid is the main reason for the high catalytic activity and high chemo-selectivity. Scale-up experiments also suggest that this catalytic system has potential in industrial application.

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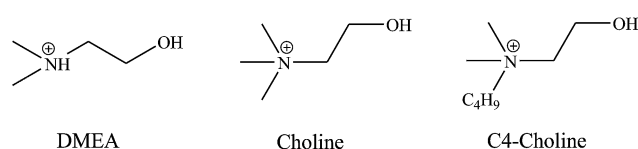
Introduction

The derivatives of benzoxanthenes have received great attention due to their antibacterial,¹ anti-inflammatory² and antiviral properties,³ and have been used in a wide range of applications in areas including photodynamic therapy for the treatment of tumor cells,⁴ laser technology,⁵ visualization of biomolecules,⁶ and others.⁷ Recently, various methodologies have been developed for the synthesis of benzoxanthenes, and the most frequently used procedure is through the reaction of 2-naphthol with various aldehydes in the presence of catalyst such as molecular iodine,⁸ amberlyst-15,⁹ wet cyanuric chloride,¹⁰ tungstophosphoric acid–zirconia composites,¹¹ WCl₆,¹² SO₃H-functionalized acidic ionic liquid,¹³ silica sulfuric acid,¹⁴ sulfonated polyethylene glycol¹⁵ and among others.^{16–20} Although this one-pot procedure makes various benzoxanthenes available, almost all of these catalytic systems suffered from one or more disadvantages such as low yield, long reaction time, tedious work-up procedure, use of special apparatus, excess reagents and expensive/un-reusable catalysts. Thus, the development of efficient, economical and environmentally benign methods for the preparation of benzoxanthenes is still in a great necessity.

It has been recognized that choline-based ionic liquids (ILs) are much more biocompatible than their traditional imidazolium-based companions, and they also benefit from wide resources and low preparation cost.^{21–24} Therefore, these ILs have received increasing attention in organic catalysis and synthesis in recent years.^{25–30} As our continuous work on the synthesis and utilization of choline-based ionic liquids in sustainable catalysis, the catalytic performances of a series of choline-based ionic liquids on the synthesis of benzoxanthenes were investigated in the present work. For the sake of easy understanding, the structures for the cations of typical choline-based ionic liquids are shown in Scheme 1. It was shown that the catalytic activity and chemical selectivity of the reaction between 2-naphthol and aldehydes were significantly influenced by the combination of cation and anion of the ionic liquids. The ionic liquid with acidic anion of hydrogen sulfate ([HSO₄]) and protic cation of *N,N*-dimethylaminoethanol ([DMEA]) was found to be an efficient and reusable catalyst for the one-pot preparation of a series of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes under solvent-free conditions. The reaction mechanism was suggested based on the successful detection of an intermediate and it was shown that cation and anion of the ionic liquid have synergetic effect on its catalytic performance.

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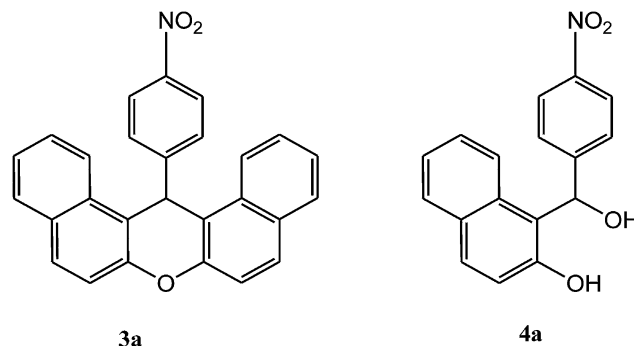
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ra06521b



Scheme 1 The structures for the cations of typical ionic liquids.

Results and discussion

In order to study the catalytic activity of choline-based ionic liquids with different combination of cation and anion on the condensation reactions, the reaction between *p*-nitrobenzaldehyde and 2-naphthol was initially selected as a model reaction, and the catalytic results were collected in Table 1. It was shown that when the ionic liquids with neutral anions, such as [choline][Cl] and [C₄-choline][Cl] (entries 1 and 2, Table 1), were used to promote this reaction at 100 °C, no products can be detected after 10 hours. When the ionic liquids with basic anions, such as [choline][Ac] and [DMEA][Ac] (entries 3 and 4, Table 1), were used as catalyst, the model reaction can proceed fluently at room temperature. After 10 hours, *p*-nitrobenzaldehyde could be completely used up as monitored by TLC, but 2-naphthol was still in the reaction mixtures. Then, the mixtures were recrystallized using 95% ethanol and a pure product (pale brown color) with the melting point of 210 °C was obtained. ¹H NMR detection suggested that only one 2-naphthol was reacted with *p*-nitrobenzaldehyde and **4a** (Scheme 2) was the sole product. It was noted that as the reaction temperature was increased up to 125 °C, another product was produced with melting point of 310 °C (entry 5, Table 1). ¹H NMR detection indicated that this is the target compound **3a** (Scheme 2), but its final isolated yield was only 70%. Interestingly, as ionic liquid with acidic anion such as [DMEA][HSO₄] or [choline][HSO₄] (entries 6 and 7, Table 1) was used as catalyst, the product was a mixture of **3a** and **4a** after 20 min reaction at 125 °C. Nevertheless, as the reaction time was extended to 1 hour, **4a** disappeared and turned to the target compound **3a**. It was clearly indicated that catalytic activity and chemical selectivity of [DMEA][HSO₄] for the reaction were higher than those of [choline][HSO₄] due to the stronger acidity of the former³⁰



Scheme 2 Chemical structures for target compound **3a** and intermediate **4a**.

compared with that of the latter. The above information suggests that in this multi-steps reactions, the first step is both acid and basic favorable, but the subsequent step is acid favorable.

The influence of the amount of [DMEA][HSO₄] catalyst on the reaction was also studied using the model reaction, and the results were included in Table 2. It can be seen that with increasing molar ratio of [DMEA][HSO₄] to substrates from 0.02 to 0.1, the yield for the target compound increased significantly, but further increase of the molar ratio did not have influence on the yield. Therefore, the molar ratio of the ionic liquid to substrates was kept at 0.1 : 1 for the further experiments.

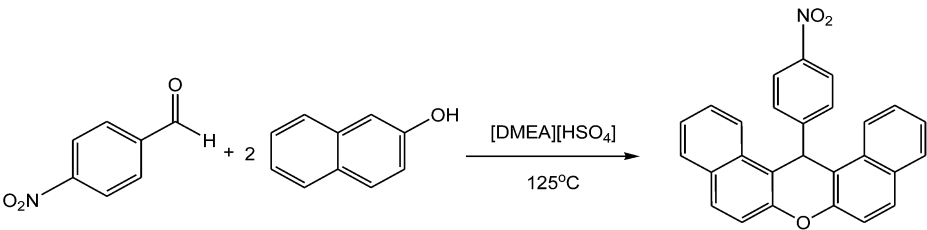
Using [DMEA][HSO₄] as catalyst, the reactions of 2-naphthol with different aldehydes were used to investigate the scope of the substrates, and the results were given in Table 3. It can be seen that the benzaldehydes and aromatic aldehydes with electron-withdrawing or weak electron-donating substituents such as -NO₂, -CH₃, -OH and halogens could react smoothly to

Table 1 The catalytic activity of different choline-based ionic liquids on the synthesis of 14-(4-nitrophenyl)-14H-dibenzo[a,j]xanthene

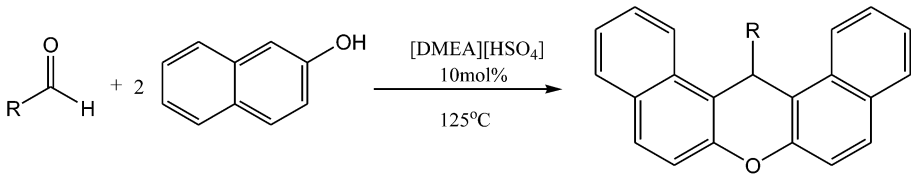
Entry	IL ^a	Reaction temperature (°C)	Reaction time	Product (yield)
1	[Choline][Cl]	rt/125	10 h	—
2	[C ₄ -choline][Cl]	rt/125	10 h	—
3	[Choline][Ac]	rt	10 h	4a (90%)
4	[DMEA][Ac]	rt	10 h	4a (92%)
5	[DMEA][Ac]	125	2 h	3a (70%)
6	[Choline][HSO ₄]	125	20 min, 1 h	3a + 4a (15% + 45%), 3a (85%)
7	[DMEA][HSO ₄]	125	20 min, 1 h	3a + 4a (30% + 50%), 3a (99%)

^a The molar ratio of ionic liquid to substrates was kept at 0.1.

Table 2 The influence of the IL amount on the catalytic performance



Entry	Molar ratio (IL : aldehyde)	Reaction time	Isolated yield (%)
1	0.02 : 1	1 h	80
2	0.05 : 1	1 h	90
3	0.1 : 1	1 h	99
4	0.5 : 1	1 h	99
5	2 : 1	40 min	99
6	5 : 1	40 min	99

Table 3 Preparation of 14-aryl-14H-dibenzo[a,j]xanthenes catalyzed by [DMEA][HSO₄] under solvent free conditions^a


Entry	R	Time	Product	Isolated yield (%)	Mp (°C)	Lit. mp (°C)
1	4-NO ₂ C ₆ H ₄	1 h	3a	99	310–312	311–312 (ref. 13)
2	C ₆ H ₅	1 h	3b	90	178	181 (ref. 20)
3	3-NO ₂ C ₆ H ₄	1 h	3c	98	233–234	235–237 (ref. 20)
4	4-OHC ₆ H ₄	4 h	3d	74	140–142	140 (ref. 14)
5	4-CH ₃ C ₆ H ₄	1 h	3e	90	228	227–228 (ref. 13)
6	4-ClC ₆ H ₄	1 h	3f	92	300–301	300–302 (ref. 20)
7	4-BrC ₆ H ₄	1 h	3g	95	298	295–297 (ref. 12)
8	4-FC ₆ H ₄	5 min	3h	90	250–252	238–240 (ref. 13), 265–267 (ref. 20)
9	4-CH ₃ OC ₆ H ₄	3 h	3i	65	206	203–205 (ref. 12)
10	4-(OH)C ₆ H ₃ -3-(OCH ₃)	4 h	3j	45	198–201	—
11	4-CHOC ₆ H ₄	1 h	3k	91	328	—

^a The sixth run of the recovered ionic liquid.

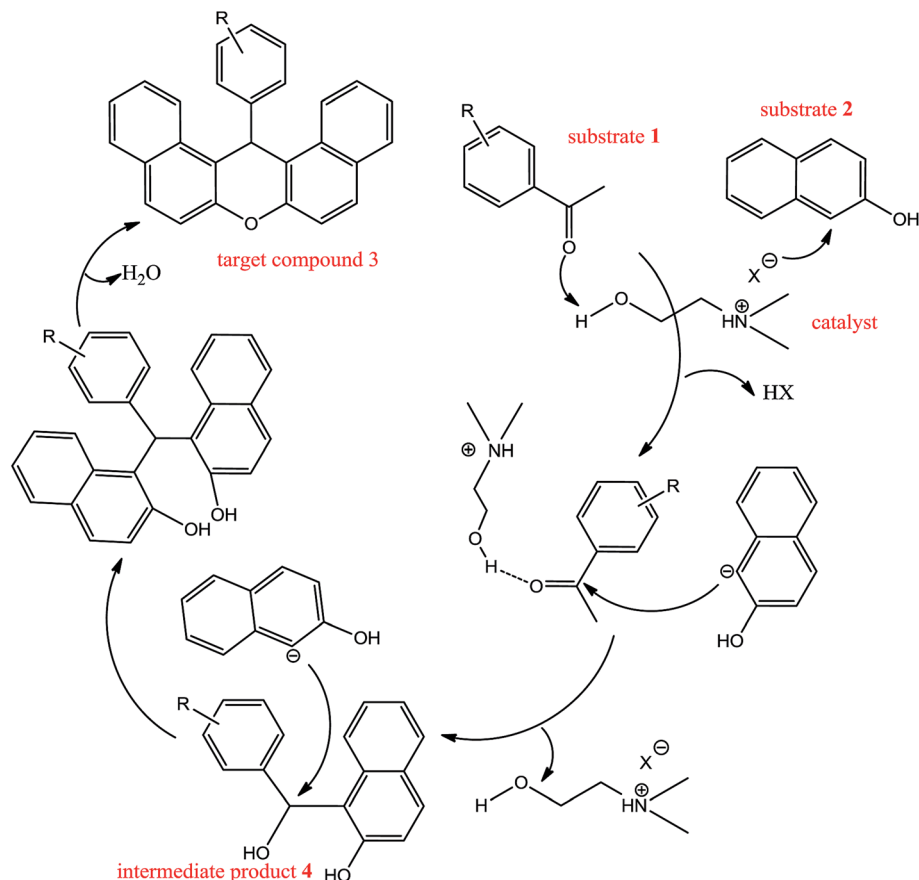
afford the corresponding products with good to excellent isolated yields (entries 1–8), while the benzaldehydes with strong electron-donating groups such as –OCH₃ showed low reactivity and could only get moderate isolated yields with the prolonged reaction time (entries 9 and 10). However, it is interesting to note that when 1,4-phthalaldehyde was used as the substrate, only one aldehyde group was reacted with 2-naphthol, and another aldehyde group was kept intact (entry 11).

The scale up effect of this catalytic system has also been investigated using the model reaction. The results showed that when the reaction scale was increased to 10 mmol, the target compound can still give almost quantitative isolated yields in 1

hour. When the reaction was completed, the target compound can be precipitated and the ionic liquid can be recovered by addition of 1 ml of water and then filtrated. It was found that the amount of IL leaching into the product was negligible. The IL could be recovered after drying of its aqueous solution, and

Table 4 The reusability of [DMEA][HSO₄] in the model reaction

Runs	1	2	3	4	5	6
Yield (%)	99	98	97	96	98	97



Scheme 3 Proposed reaction mechanism for [DMEA][HSO₄] catalyzed synthesis of 14-aryl-14H-dibenzo[a,j]xanthenes.

then directly used for the next run. No significant activity decrease was observed after six runs (Table 4), which suggests that this ionic liquid catalyst is recyclable and reusable.

According to the above discussion, the cation and the anion of this ionic liquid have synergetic effect on its catalytic performance, and a plausible reaction mechanism is proposed as illustrated in Scheme 3. The findings that the first step is both acid and basic favorable but the subsequent steps are acid favorable may provide some important information for the further catalyst design of the reactions mentioned.

Conclusions

In this work, we found that ionic liquid [DMEA][HSO₄] is an efficient and environmentally friendly catalyst for the one-pot synthesis of a series of 14-aryl-14H-dibenzo[a,j]xanthenes under solvent-free conditions. This catalytic system benefits from easy operation and work-up procedure, wide substrates tolerance and high chemical selectivity. In addition, the catalyst is cheap, feasible, and can be easily recovered and reused for at least six runs without significant activity decrease. It is suggested that the synergetic effect of the cation and anion of the ionic liquid plays a predominant role in the catalytic activity and chemoselectivity. This finding would be constructive for the rational design of novel catalysts for this type of reactions.

Experimental

Synthesis and characterization of the ionic liquids

N,N'-Dimethylaminoethanol (DMEA) and 1-chlorobutane were obtained from Beijing Chem. Reagent Co. and distilled at reduced pressure before use. Choline chloride was also obtained from Beijing Chem. Reagent Co. Sulfuric acid (H₂SO₄) and acetic acid were purchased from Shanghai Reagent Co., and strong basic ion exchange resin (Ambersep 900 OH) was purchased from Alfa Aesar. 2-Naphthol, benzaldehyde and substituted benzaldehydes were purchased from Aladdin Reagent Co. All of the commercially available reagents were AR grade and used as received unless indicated otherwise. The ionic liquids [DMEA][HSO₄] and *N,N'*-dimethylaminoethanol acetate ([DMEA][Ac]) were synthesized by simple neutralization of *N,N'*-dimethylaminoethanol with corresponding acids such as sulfuric acid or acetate acid in an equal molar ratio. Choline hydrogen sulfate ([choline][HSO₄]) and choline acetate ([choline][Ac]) were prepared by neutralization of corresponding acid with choline hydroxide which was obtained by the ion-exchange of choline chloride using strong basic anion exchange resin. *N,N*-Dimethyl-*N*-butylaminoethanol chloride ([C₄-choline][Cl]) was prepared by quaternary amination of *N,N'*-dimethylaminoethanol with chlorobutane. ¹H-NMR spectra were recorded on a BRUKER AV-400 instrument at room

temperature using TMS as internal standard. Melting points were determined by a XRC-1 Microscopic Melting Point Measurer (Sichuan University Instrument Factory) without correction.

Typical procedures for the preparation of 14*H*-dibenzo[*a,j*]-xanthene derivatives

To a mixture of benzaldehyde (0.5 mmol) and 2-naphthol (1 mmol), a certain amount of choline-based ionic liquid was added as catalyst, and the reaction was monitored by TLC method. After the reaction was completed, the mixtures were cooled to room temperature and washed with water to get the crude product. The pure product can be obtained from the recrystallization using 95% ethanol, and the collected aqueous solution was concentrated by evaporation to regenerate the ionic liquid.

Acknowledgements

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References

- H. Wang, L. Lu, S. Y. Zhu, Y. Li and W. Cai, *Curr. Microbiol.*, 2006, **52**, 1–5.
- K. Chibale, M. Visser, D. V. Schalkwyk, P. J. Smith, A. Saravanamuthu and A. H. Fairlamb, *Tetrahedron*, 2003, **59**, 2289–2296.
- J. M. Jamison, K. Krabill, A. Hatwalkar, E. Jamison and C. Tsai, *Cell Biol. Int. Rep.*, 1990, **14**, 1075–1084.
- R. M. Ion, A. Planner, K. Wiktorowicz and D. Frackowiak, *Acta Biochim. Pol.*, 1998, **45**, 833–845.
- E. Klimtchuk, M. A. J. Rodgers and D. C. Neckers, *J. Phys. Chem.*, 1992, **96**, 9817–9820.
- C. G. Knight and T. Stephens, *Biochem. J.*, 1989, **258**, 683–687.
- A. Kumar, S. Sharma, R. A. Maurya and J. Sarkar, *J. Comb. Chem.*, 2010, **12**, 20–24.
- (a) B. Das, B. Ravikanth, R. Ramu, K. Laxminarayana and B. V. Rao, *J. Mol. Catal. A: Chem.*, 2006, **255**, 74–77; (b) M. A. Pasha and P. J. Vaderapura, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 621–623.
- S. Ko and C. F. Yao, *Tetrahedron Lett.*, 2006, **47**, 8827–8829.
- M. A. Bigdeli, M. M. Heravi and G. H. Mahdavinia, *Catal. Commun.*, 2007, **8**, 1595–1598.
- T. S. Rivera, A. Sosa, G. P. Romanelli, M. N. Blanco and L. R. Pizzio, *Appl. Catal., A*, 2012, **443**, 207–213.
- M. A. Zolfigol, A. R. Moosavi-Zare, P. Arghavani-Hadi, A. Zare, V. Khakyzadeh and G. Darvishi, *RSC Adv.*, 2012, **2**, 3618–3620.
- K. Gong, D. Fang, H. L. Wang, X. L. Zhou and Z. L. Liu, *Dyes Pigm.*, 2009, **80**, 30–33.
- H. R. Shaterian, M. Ghashang and A. Hassankhani, *Dyes Pigm.*, 2008, **76**, 564–568.
- D. Prasad and M. Nath, *Catal. Sci. Technol.*, 2012, **2**, 93–96.
- A. R. Khosropour, M. M. Khodaei and H. Moghannian, *Synlett*, 2005, 955–958.
- J. Li, W. Tang, L. Lu and W. Su, *Tetrahedron Lett.*, 2008, **49**, 7117–7120.
- F. Shirini and N. G. Khaligh, *Dyes Pigm.*, 2012, **95**, 789–794.
- N. G. Khaligh, *Catal. Sci. Technol.*, 2012, **2**, 2211–2215.
- S. Kantevari, M. V. Chary, A. P. R. Das, S. V. N. Vuppapapati and N. Lingaiah, *Catal. Commun.*, 2008, **9**, 1575–1578.
- M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez and J. C. Palacios, *Angew. Chem., Int. Ed.*, 2006, **45**, 3904–3908.
- P. Nockemann, B. Thijs, K. Driesen, C. R. Janssen, H. K. L. Van Meervelt, S. B. Kirchner and K. Binnemans, *J. Phys. Chem. B*, 2007, **111**, 5254–5263.
- J. Pernak, A. Syguda, I. Mirska, A. Pernak, J. Nawrot, A. Pradzynska, S. T. Griffin and R. D. Rogers, *Chem.-Eur. J.*, 2007, **13**, 6817–6827.
- M. Francisco, A. van den Bruinhorst and M. C. Kroon, *Angew. Chem., Int. Ed.*, 2013, **52**, 3074–3085.
- A. L. Zhu, T. Jiang, B. X. Han, J. C. Zhang, Y. Xie and X. M. Ma, *Green Chem.*, 2007, **9**, 169–172.
- A. P. Abbott, T. J. Bell, S. Handa and B. Stoddart, *Green Chem.*, 2006, **8**, 784–786.
- S. Sunitha, S. Kanjilal, P. S. Reddy and R. B. N. Prasad, *Tetrahedron Lett.*, 2007, **48**, 6962–6965.
- A. L. Zhu, L. J. Li, J. J. Wang and K. L. Zhuo, *Green Chem.*, 2011, **13**, 1244–1250.
- A. L. Zhu, R. X. Liu, L. J. Li, L. Y. Li, L. Wang and J. J. Wang, *Catal. Today*, 2013, **200**, 17–23.
- A. L. Zhu, Q. Q. Li, L. J. Li and J. J. Wang, *Catal. Lett.*, 2013, **143**, 463–468.