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Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones catalyzed by biodegradable ionic liquid

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Abstract A biodegradable acyclic SO_3H-functionalized ionic liquid has been used as a novel catalyst for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones via one-pot multi-component condensation of β-naphthol, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds, under solvent-free conditions, to afford good to excellent yields ranging from 85 to 93 % within 30–60 min. After the reaction the products could be simply separated from the reaction mixture and the catalyst could be recycled and reused several times without noticeable reduction of catalytic activity.

Keywords Xanthene · Synthesis · Biodegradable ionic liquid · Solvent-free · Multi-component reaction

Introduction

Xanthenes and benzoxanthenes are important heterocyclic compounds because of their wide range of biological and pharmaceutical properties, for example antiviral and anti-inflammatory activity, and their efficacy in photodynamic therapy [1, 2]. Furthermore, some of these compounds have been used as dyes [3], as pH-sensitive fluorescent materials for visualization of bimolecules [4], and in laser technology [5]. Thus, their versatility has made xanthenes prime synthetic candidates thus accentuating the need to develop synthetic routes to xanthenes and benzoxanthenes. Reported methods for synthesis of tetrahydrobenzo[*a*]xanthene-11-ones involve three-component condensation of dimedone with an aromatic aldehyde and 2-naphthol in the presence of Lewis acids, Brønsted acids, or other organic

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compounds as catalysts [6–17]. However, the search for the new readily available and green catalysts is still being actively pursued.

With increasing public concern over degradation of the environment and over future resources, it became obvious that the solvents used in organic synthesis were high on the list of environmental pollutants. An important approach is to develop new processes involving the solvent-free conditions. In recent years, ionic liquids have attracted increasing attention because of their particular properties, for example negligible vapor pressure, wide liquid range, and high thermal stability, making them a greener alternative to volatile organic solvents. In addition, Brønsted acidic task-specific ionic liquids (TSILs) have a dual role (solvent and catalyst) in multi-component reactions [18, 19], affording higher yields and selectivity than traditional acid catalysts. Very recently, Luo and co-workers [20] used a magnetic nanoparticle-supported dual acidic ionic liquid to catalyze the one-pot synthesis of benzoxanthenes. In fact, use of Brønsted acidic TSILs as catalysts is a topic with ongoing activity, and the development and investigation of TSILs for multi-component reactions is, currently, extremely important.

In our previous work, novel, efficient, and eco-friendly SO_3H-functional halogen-free acidic TSILs were designed and their catalytic activity in multi-component reactions was investigated [21–23]. In continuation of our work in studying TSIL-catalyzed multi-component reactions, we now report here the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones in a biodegradable acidic ionic liquid.

Results and discussion

The biodegradable ionic liquid [DDPA][HSO_4], which combines a propane sulfonic acid group with an acyclic dimethyldodecylammonium cation, was prepared in accordance with our previous work. This catalyst is readily biodegradable; it can be biodegraded in the activated sludge process [21].

Initially in this study, β-naphthol, benzaldehyde, and dimedone were selected as model reactants to compare the catalytic performance of the TSILs. As shown in Table 1, almost no xanthenes could be detected in the absence of ionic liquids (entry 1), which indicated that the catalyst was necessary for this multi-component condensation reaction. All the prepared ionic liquids proved very active, generally leading to 65–93 % yield of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones in the presence of 3 % TSILs (entries 4, 7–9). In addition, the ionic liquid [DDPA][HSO_4] is biodegradable, which makes this procedure efficient and environmentally benign. Hence, [DDPA][HSO_4] should be the best catalyst for this condensation among these catalysts; the optimized reaction conditions are listed in Table 1 (entry 4).

Subsequently, the performance of [DDPA][HSO_4], after recycling, in the same model condensation reaction was investigated for economic and environmental reasons. After the reaction, the catalyst could be extracted from the mixture with water, washed with ethyl acetate, dried under vacuum, and reused in a subsequent

Table 1 Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones in the presence of different catalysts

Entry	Catalyst	Molar ratio (mol%)[a]	Time (min)	Yield (%)[b]
1	–	–	180	–
2	[DDPA][HSO_4]	1	60	80
3	[DDPA][HSO_4]	2	60	86
4	[DDPA][HSO_4]	3	60	91
5	[DDPA][HSO_4]	4	60	91
6	[DDPA][HSO_4]	5	60	92
7	[MIMPSA][HSO_4]	3	60	90
8	[PyPSA][HSO_4]	3	60	90
9	[BMIM][HSO_4]	3	60	65
10	*p*-Toluenesulfonic acid	3	60	79

1 mmol benzaldehyde, 1 mmol *β*-naphthol, 1.2 mmol dimedone

[a] Molar ratio of catalyst to benzaldehyde

[b] Isolated yields

reaction. The catalyst can be reused at least six times without appreciable decrease in yield, which ranged from 91 to 88 % (Table 2), or reaction rate.

Multi-component condensation of other substituted benzaldehydes, *β*-naphthol, and cyclic 1,3-dicarbonyl compounds under solvent-free conditions in the presence of [DDPA][HSO_4] was then accomplished under the above optimized reaction conditions; the results are presented in Table 3.

As is apparent from Table 3, the procedure enabled effective preparation of the required products, 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones **4**. All aromatic aldehydes with either electron-withdrawing or electron-donating groups, for example nitro, or methoxy groups, gave reasonable to good yields ranging from 85 to 93 % within 30–60 min. Both dimedone and 1,3-cyclohexanedione gave good results. However, aromatic aldehydes with electron-withdrawing groups are less active than those with electron-donating groups. The benzoxanthenes were characterized by the use of ^1H NMR spectral data and comparison of their physical properties with literature values.

Table 2 Reuse of the ionic liquid [DDPA][HSO_4]

Entry	Run	Isolated yield (%)
1	Fresh	91
2	1	91
3	2	90
4	3	91
5	4	89
6	5	89
7	6	88

1 mmol benzaldehyde, 1 mmol *β*-naphthol, 1.2 mmol dimedone, 0.03 mmol catalyst, 90 °C, 60 min

Table 3 Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones catalyzed by [DDPA][HSO_4]

Entry	R_1	R_2	Time (min)	mp (°C) [Ref.]	Yield (%)[a]
1	C_6H_5	CH_3	60	148–150 [8]	91
2	*m*-ClC_6H_4	CH_3	60	173–175 [17]	92
3	*p*-ClC_6H_4	CH_3	45	178–180 [8]	90
4	2,4-ClC_6H_3	CH_3	30	178–180 [8]	91
5	*p*-BrC_6H_4	CH_3	60	184–186 [17]	89
6	*p*-HOC_6H_4	CH_3	60	220–222 [8]	87
7	*o*-$NO_2C_6H_4$	CH_3	60	222–224 [8]	85
8	*m*-$NO_2C_6H_4$	CH_3	45	166–167 [8]	91
9	*p*-$NO_2C_6H_4$	CH_3	30	176–178 [8]	93
10	*p*-$CH_3C_6H_4$	CH_3	60	175–176 [8]	86
11	*p*-$CH_3OC_6H_4$	CH_3	60	202–204 [8]	85
12	C_6H_5	H	60	185–187 [20]	87
13	*p*-ClC_6H_4	H	45	202–204 [20]	85
14	*m*-$NO_2C_6H_4$	H	60	228–230 [20]	90
15	*p*-$CH_3C_6H_4$	H	60	201–203 [20]	88
16	*p*-$CH_3OC_6H_4$	H	60	179–181 [20]	85

1 mmol benzaldehyde, 1 mmol *β*-naphthol, 1.2 mmol cyclic 1,3-dicarbonyl compounds, 0.03 mmol catalyst, 90 °C

[a] Isolated yields

The results obtained with *β*-naphthol, benzaldehyde, and dimedone under the optimized conditions were compared with those obtained by use of other catalysts reported in recent years for this reaction, the data listed in Table 4 show that the biodegradable ionic liquid [DDPA][HSO_4] was relatively a good catalyst for synthesis of tetrahydrobenzo[*a*]xanthene-11-ones.

Table 4 Comparison of our results with those for previously reported methods

Entry	Catalyst	Reaction conditions	Time	Yield (%) [Ref.]
1	$InCl_3$	Neat/120 °C	30 min	84 [8]
2	$NaHSO_4 \cdot SiO_2$	CH_2Cl_2/reflux	4 h	87 [9]
3	$Sr(OTf)_2$	CH_2Cl_2/80 °C	5 h	85 [10]
4	Proline triflate	H_2O/80 °C	2.5 h	88 [12]
5	*p*-Toluenesulfonic acid	[bmim]BF_4/80 °C	3 h	90 [13]
6	Caro's acid–SiO_2	Neat/80 °C	30 min	90 [14]
7	TCT	Neat/80 °C	30 min	93 [15]
8	CAN	DCM-EtOH/us/26 °C	2 h	85 [16]
9	Trityl chloride	Neat/110 °C	50 min	89 [17]
10	AIL@MNP	Neat/90 °C	45 min	89 [20]
11	[DDPA][HSO_4]	Neat/90 °C	60 min	91 (This work)

Conclusions

In summary, it was demonstrated that a readily available, economical, task-specific ionic liquid could be used as a recyclable catalyst for the condensation of benzaldehydes, β-naphthol, and cyclic 1,3-dicarbonyl compounds in the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones under solvent-free conditions. The merit of this methodology is that it is simple, highly efficient, and environmentally benign.

Experimental

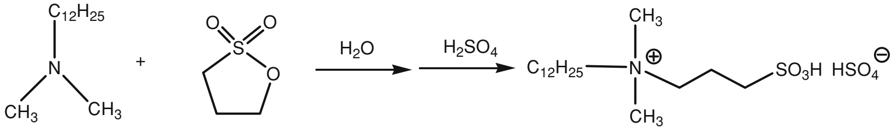
Melting points were determined on an X-6 melting point apparatus with microscope. ^{1}H NMR spectra were recorded on a Bruker DRX300 (300 or 500 MHz) spectrometer and ^{13}C NMR spectra on Bruker DRX300 (75.5 MHz) spectrometer. Mass spectra were obtained with an automated Finnigan Trace Ultra-Trace DSQ GC/MS spectrometer. All chemicals (AR grade) were commercially available and used directly without further purification.

Synthesis of SO_3H-functional acidic ionic liquid [DDPA][HSO_4]

The biodegradable SO_3H-functionalized ionic liquid [DDPA][HSO_4] was synthesized in accordance with our previous methods [21]. The pyridine, imidazole-based SO_3H-functionalized ionic liquids used for comparison were obtained in accordance with reported methods [24, 25]. Structural analysis of TSILs was performed by use of ^{1}H NMR, ^{13}C NMR, and MS data (Scheme 1).

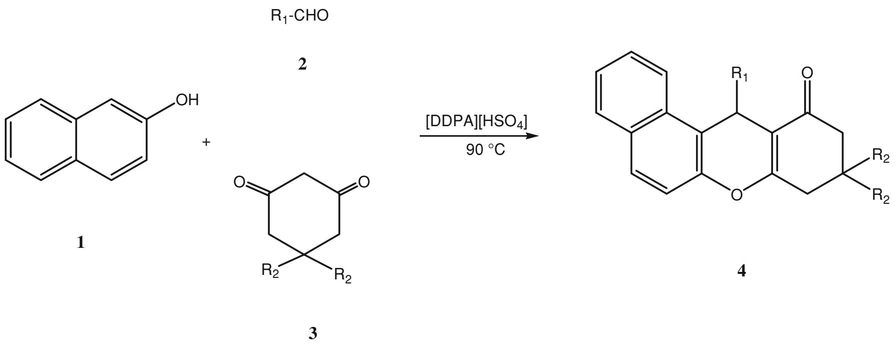
Selected spectral data for SO_3H-functionalized [DDPA][HSO_4]:

3-(N,N-dimethyldodecylammonium)propanesulfonic acid hydrogen sulfate [DDPA][HSO_4]. ^{1}H NMR (300 MHz, D_2O): δ0.53 (t, 3H, $J = 6.62$ Hz, $-CH_3$), 0.95–1.02 (m, 18H, $-(CH_2)_9-$), 1.42 (m, 2H, $-C-CH_2-C-N$), 1.83–1.87 (m, 2H, $-C-CH_2-C-SO_3$), 2.60 (t, 2H, $J = 6.91$ Hz, $-CH_2-SO_3$), 2.77 (s, 6H, $N-CH_3$), 2.98 (t, $J = 7.95$ Hz, 2H, $-C-CH_2-N$), 3.14 (t, $J = 8.25$ Hz, 2H, $-CH_2-C-C-SO_3$). Ansl. Calcd. For CHNOS: C, 47.09; H, 9.07; N, 3.23; Found: C, 46.82; H, 9.08; N, 3.09. MS (*m/z*): 432.18 ($M^{+} - 1$).



[DDPA][HSO_4]

Scheme 1 Synthesis and structure of the acidic functional ionic liquid [DDPA][HSO_4]



Scheme 2 Synthesis of tetrahydrobenzo[*a*]xanthene-11-ones catalyzed by [DDPA][HSO_4]

General procedure for synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones

In a typical experiment, [DDPA][HSO_4] (0.3 mmol) was added, with stirring, to *β*-naphthol (1 mmol) **1**, aldehyde (1 mmol) **2**, and a cyclic 1,3-dicarbonyl compound (1.2 mmol) **3** in a round-bottomed flask. The mixture was then stirred for a specific time at 90 °C (Scheme 2). On completion (monitored by TLC), 5 mL water was added and the precipitated crude product was collected by filtration and recrystallized from ethanol (95 %) to afford pure 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one **4**. The ionic liquid contained in the filtrate was then washed with ethyl acetate and used for subsequent cycles after drying under vacuum. The products were identified by IR and ^{1}H NMR, and comparison of their physical data (m.p.) with those reported in the literature.

Selected data for benzoxanthene:

9,9-dimethyl-12-phenyl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-one (*product 4a,* $C_{25}H_{22}O_2$). White solid; m.p. 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 3H, CH3), 0.95 (s, 3H, CH3), 2.26 (d, $J = 16.2$ Hz, 1H, CH2), 2.33 (d, $J = 16.2$ Hz, 1H, CH2), 2.52 (s, 2H, CH2), 5.62 (s, 1H, CH), 6.81–7.70 (m, 11H, Ar-H).

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References

1. J.M. Jamison, K. Krabill, A. Hatwalkar, Cell Biol. Int. Rep. **14**, 1075 (1990)
2. K. Chibale, M. Visser, D.V. Schalkwyk, P.J. Smith, A. Saravanamuthu, A.H. Fairlamb, Tetrahedron **59**, 2289 (2003)
3. B.B. Bhowmik, P. Ganguly, Spectrochim. Acta A **61**, 1997 (2005)
4. C.G. Knight, T. Stephens, Biochem. J. **258**, 683 (1989)
5. M. Ahmad, T.A. King, B.H. Cha, J. Lee, J. Phys. D Appl. Phys. **35**, 1473 (2002)
6. C.S. Sundar, K.U.M. Rao, N.B. Reddy, M.V.N. Reddy, S.S. Prasad, C.S. Reddy, Catal. Sci. Technol. (2012). doi:10.1039/c2cy20041d

7. A. Kumar, S. Sharma, R.A. Maurya, J. Sarkar, J. Comb. Chem. **12**, 20 (2010)
8. G.C. Nandi, S. Samai, R. Kumar, M.S. Singh, Tetrahedron **65**, 7129 (2009)
9. B. Das, K. Laxminarayana, M. Krishnaiah, Y. Srinivas, Synlett **20**, 3107 (2007)
10. J.J. Li, W.Y. Tang, L.M. Lu, W.K. Su, Tetrahedron Lett. **49**, 7117 (2008)
11. R.Z. Wang, L.F. Zhang, Z.S. Cui, Synth. Commun. **39**, 2101 (2009)
12. J.J. Li, L.M. Lu, W.K. Su, Tetrahedron Lett. **51**, 2434 (2010)
13. J.M. Khurana, D. Magoo, Tetrahedron Lett. **50**, 4777 (2009)
14. N. Karimi, H.A. Oskooie, M.M. Heravi, L. Tahershamsi, Synth. Commun. **41**, 307 (2011)
15. Z.H. Zhang, P. Zhanz, S.H. Yang, H.J. Wang, J. Deng, J. Chem. Sci. **122**, 427 (2010)
16. S. Sudha, M.A. Pasha, Ultrason. Sonochem. **19**, 994 (2012)
17. A. Khazaei, M.A. Zolfigol, A.R. Moosavi-Zare, A. Zare, M. Khojasteh, Z. Asgari, V. Khakyzadeh, A. Khalafi-Nezhad, Catal. Commun. **20**, 54 (2012)
18. C.B. Yue, T.F. Yi, C.B. Zhu, G. Liu, J. Ind. Eng. Chem. **15**, 653 (2009)
19. W. Chen, H. Yin, Y. Zhang, Z. Lu, A. Wang, Y. Shen, T. Jiang, L. Yu, J. Ind. Eng. Chem. **16**, 800 (2010)
20. Q. Zhang, H. Su, J. Luo, Y. Wei, Green Chem. **14**, 201 (2012)
21. D. Fang, S.T. Cao, Z.H. Fei, Z.L. Liu, Chin. J. Energ. Mater. **17**, 404 (2009)
22. D. Fang, C.M. Jiao, H.B. Zhang, J. Ind. Eng. Chem. **16**, 233 (2010)
23. D. Fang, J.M. Yang, C.M. Jiao, Catal. Sci. Technol. **1**, 243 (2011)
24. A.C. Cole, J.L. Jensen, I. Ntai, K.L.T. Tran, K.J. Weaver, D.C. Forbes Jr, J.H. Davis, J. Am. Chem. Soc. **124**, 5962 (2002)
25. J. Shen, H. Wang, H. Lium, Y. Sun, Z. Liu, J. Mol. Catal. A: Chem. **280**, 24 (2007)