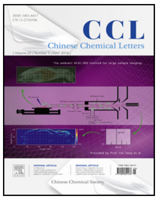
Chinese Chemical Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet



Original article

A new green approach for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-one derivatives using task specific acidic ionic liquid [NMP]H_2PO_4

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ARTICLE INFO

Article history:
Received 16 January 2014
Received in revised form 8 April 2014
Accepted 28 April 2014
Available online xxx

Keywords:
Benzo[a]xanthenes
Ionic liquids
Multicomponent reactions
Green synthesis

ABSTRACT

12-Aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-one derivatives were synthesized by a convenient and environmentally benign procedure involving multicomponent condensation reactions of substituted aromatic aldehydes with 2,7-dihydroxynaphthalene/2-naphthols/2,6-dihydroxynaphthlene and cyclic 1,3-dicarbonyl compounds in task specific acidic ionic liquid [NMP]H_2PO_4 at 80 °C. This protocol has proved to be efficient in terms of good yields, operational simplicity, easy workup, recyclability of reaction medium/catalyst, and short reaction time.

1. Introduction

The efficient and high-throughput synthesis of complex organic molecules with lower impact on the environment is one of the most important objectives in modern synthetic organic and green chemistry. There has been increasing concern for the development of new greener synthetic pathways which avoid the use of volatile organic solvents and replace them with non-flammable, non-volatile, non-toxic, and inexpensive green solvents [1–3]. In this context task specific ionic liquids have shown great promise as attractive alternatives to conventional solvents owing to their negligible vapour pressure, recyclability, solvophobic properties, and ability to promote association of reactants in their solvent cavity during the activation process [4]. However there are certain concerns over the use of ionic liquids as green solvents because large amounts of organic solvent and energy are used in the preparations of these ionic liquids [5]. Task specific acidic ionic liquid [NMP]H_2PO_4 can be considered environmentally benign, as it can be prepared in one step without the use of any organic solvent [6].

Multicomponent reactions (MCR) combined with the application of task specific ionic liquids (TSIL) are valuable tools for the environmentally friendly preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [7]. Tetrahydrobenzo[a]xanthene derivatives act as anti-microbial [8], anti-malarial [9], and cytotoxic agents [10]. Furthermore, some of these compounds have been used in photodynamic therapy [11], dyes [12], pH-sensitive fluorescent materials for visualization of biomolecules [13], and laser technology [14]. 12-Aryl-8,9,10,12-tetrahydrobenzo[a]xanthenes can be prepared by multicomponent condensation of 2-naphthols, aldehydes, and cyclic 1,3-dicarbonyl compounds in the presence of various acid catalysts [15]. Some of the reported methods have limitations such as longer reaction time, harsher reaction conditions, expensive catalysts, and generation of large amounts of side products. In view of our interest in the development of new syntheses of various heterocycles [16], we investigated the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives by one pot three-component condensation of naphthols, aldehydes, and cyclic 1,3-dicarbonyl compounds in task specific acidic ionic liquid [NMP]H_2PO_4.

2. Experimental

All chemicals were purchased from Sigma–Aldrich, Spectrochem and were used as received. F_{254} precoated aluminium plates with silica gel 60 from Merck were used to monitor reaction progress. IR (KBr) spectra were recorded on a Perkin Elmer FTIR spectrophotometer, and the values are expressed as ν_{max} cm^{-1}. The NMR (^1H and ^{13}C) spectra were recorded on a Jeol JNM ECX-400P at 400 MHz and 100 MHz, respectively. The chemical shift values are recorded on δ scale and the coupling constants (J) are in Hertz. Ionic

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http://dx.doi.org/10.1016/j.cclet.2014.05.014

liquid $[NMP]H_2PO_4$ was prepared according to the literature procedure [6].

2.1. *General procedure for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-one derivatives (**1a–1y**)*

A mixture of 2,7-dihydroxynaphthalene/2-naphthol/2,6-dihydroxynaphthalene (1.0 mmol), substituted aromatic aldehydes (1.0 mmol), dimedone/cyclohexane-1,3-dione (1.1 mmol) and task specific ionic liquid $[NMP]H_2PO_4$ (20 mol%) was placed in a 50 mL round-bottomed flask mounted over a magnetic stirrer. The reaction mixture was stirred at 80 °C for the appropriate time as mentioned in Table 3. The progress of the reaction was monitored by TLC using ethyl acetate: petroleum ether (20:80, v/v) as the eluent. After completion of the reaction as indicated by TLC, water (10 mL) was added to the reaction mixture. The precipitate formed was collected by vacuum filtration and washed with water. The product was recrystallized from ethanol to give the pure product (**1a**–**1y**) in high yield. The products were characterized by mp, IR, NMR and mass spectra.

2.1.1. *12-(4-Bromophenyl)-2-hydroxy-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**1a**) [15b]*

White solid; mp: 180–181 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H, OH), 7.77–7.74 (m, 2H, ArH), 7.40 (d, 2H, J = 6.9 Hz, ArH), 7.19 (d, 4H, J = 8.7 Hz, ArH), 6.98 (d, 1H, J = 8.7 Hz, ArH), 5.32 (s, 1H, ArCH), 2.67 and 2.56 (AB system, 2H, J = 17.7 Hz, CH_aH_b), 2.34 (d, 1H, J = 16.2 Hz, CH_aCO), 2.13 (d, 1H, J = 16.2 Hz, CH_bCO), 1.05 (s, 3H, CH_3), 0.86 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.92, 164.02, 156.52, 147.63, 144.00, 132.32, 131.00, 130.28, 129.01, 125.48, 119.26, 117.19, 114.74, 113.51, 112.75, 105.06, 50.04, 40.34, 33.79, 31.85, 28.78, 26.21; IR (KBr, cm^{-1}): ν_{max} 3328, 2959, 1626, 1597, 1380, 1225; MS (ESI) [M^+] calcd. for $C_{25}H_{21}BrO_3$: 448, found: 449 [M^++H], 451 [M^++H+2].

2.1.2. *12-(4-Bromophenyl)-2-hydroxy-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**1k**) [15f]*

White solid; mp: 234–236 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H, OH), 7.73–7.78 (m, 2H, ArH), 7.41 (d, 2H, J = 8.4 Hz, ArH), 7.13–7.21 (m, 4H, ArH), 6.95–6.99 (m, 1H, ArH), 5.35 (s, 1H, ArCH), 2.73–2.69 (m, 2H, CH_2), 2.37–2.26 (m, 2H, CH_2), 1.86–1.80 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.19, 165.90, 156.49, 147.65, 144.27, 132.33, 131.06, 130.32, 130.28, 128.99, 125.44, 119.28, 117.16, 114.70, 113.96, 113.46, 105.01, 36.36, 33.70, 26.90, 19.88; IR (KBr, cm^{-1}): ν_{max} 3326, 2944, 1626, 1597, 1379, 1231, 1197; MS (ESI) [M^+] calcd. for $C_{23}H_{17}BrO_3$: 421, found: 422 [M^++H], 424 [M^++H+2].

2.1.3. *12-(4-Bromophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**1p**) [15g]*

White solid; mp: 186–187 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, 1H, J = 8.3 Hz, ArH), 7.80–7.76 (m, 2H, ArH), 7.45–7.38 (m, 2H, ArH), 7.33–7.23 (m, 3H, ArH), 7.23–7.20 (m, 2H, ArH), 5.66 (s, 1H, ArCH), 2.60 and 2.50 (AB system, 2H, J = 17.60 Hz, CH_aH_b), 2.24 (d, 1H, J = 16.2 Hz, CH_aCO), 2.12 (d, 1H, J = 16.2 Hz, CH_bCO), 1.12 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.75, 164.0, 147.85, 143.7, 131.45, 131.22, 130.10, 129.12, 128.56, 127.20, 125.23, 123.48, 120.55, 117.25, 116.89, 113.52, 50.23, 41.23, 34.69, 32.87, 29.78, 26.98; IR (KBr, cm^{-1}): ν_{max} 2955, 1652, 1596, 1373, 1228, 1160; MS (ESI) [M^+] calcd. for $C_{25}H_{21}BrO_2$: 432, found: 433 [M^++H], 435 [M^++H+2].

2.1.4. *12-(4-Bromophenyl)-3-hydroxy-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**1u**) [15e]*

White solid; mp: 208–209 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 1H, OH), 7.82 (d, 1H, J = 9.5 Hz, ArH), 7.67 (d, 1H, J = 9.5 Hz, ArH), 7.37–7.33 (m, 3H, ArH), 7.20 (d, 2H, J = 8.04 Hz, ArH), 7.13–7.10 (m, 1H, ArH), 7.05–7.02 (m, 1H, ArH), 5.48 (s, 1H, ArCH), 2.64 and 2.53 (AB system, 2H, J = 17.45 Hz, CH_aH_b), 2.30 (d, 1H, J = 16.2 Hz, CH_aCO), 2.10 (d, 1H, J = 16.2 Hz, CH_bCO), 1.03 (s, 3H, CH_3), 0.85 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.96, 164.10, 154.70, 145.01, 144.43, 132.70, 131.02, 130.66, 130.30, 127.48, 124.78, 124.51, 119.40, 119.23, 117.30, 116.73, 112.53, 110.01, 50.08, 33.78, 31.90, 28.73, 28.60, 26.50, 26.20; IR (KBr, cm^{-1}): ν_{max} 3340, 2950, 1614, 1547, 1379, 1220; MS (ESI) [M^+] calcd. for $C_{25}H_{21}BrO_3$: 448, found: 449 [M^++H], 451 [M^++H+2].

Table 1
Effect of solvent and temperature on the reaction of 2,7-dihydroxynaphthlaene, 4-bromobenzaldehyde and dimedone.

No.	Solvent	Temp (°C)	Time (min)[a]	Yield (%)[a]	Standard deviation (SD)[c]
1	Ethanol	80	82	44[b]	1.414
2	Water	80	58	67[b]	2.828
3	DMF	80	41	81.5	2.121
4	Methanol	80	73	62[b]	1.414
5	THF	80	70	65.5[b]	3.535
6	Acetonitrile	80	60	72[b]	4.242
7	–	80	14	90	1.414
8	–	60	22	85	2.828
9	–	100	14	86.5	0.070

[a] Results were averaged for two measurements to minimize random errors.
[b] Mixture of two products.
[c] S.D. for yield measurement.

3. Results and discussion

We present herein an efficient and environmentally benign protocol for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives by one pot condensation of 2-naphthols, aldehydes and cyclic 1,3-dicarbonyl compounds using task specific acidic ionic liquid $[NMP]H_2PO_4$ at 80 °C. The most suitable reaction conditions for the proposed reaction were achieved by investigating the model reaction of 4-bromobenzaldehyde (1.0 mmol), 2,7-dihydroxynaphthalene (1.0 mmol), and dimedone (1.1 mmol) under different reaction conditions as shown in Table 1. The best result was obtained when the reaction was carried at 80 °C in the absence of any solvent using 20 mol% of task specific ionic liquid $NMP[H_2PO_4]$. The reaction was complete in 14 min and yielded 90% of 12-(4-bromophenyl)-2-hydroxy-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one (**1a**) after a simple workup (Table 1, entry 7). Reactions attempted in solvents such as ethanol, water, DMF, methanol, THF and acetonitrile in the presence of ionic liquid $[NMP]H_2PO_4$ (20 mol%) as the catalyst required longer reaction time and resulted in inferior yields of the product **1a** (Table 1, entries 1–6). Reactions repeated at 60 °C required longer times while reactions attempted at 100 °C required the same reaction times (Table 1, entries 8 and 9). Thus, ionic liquid $[NMP]H_2PO_4$ with dual roles of solvent and catalyst was found to be most suitable for this three-component reaction for the synthesis of benzo[*a*]xanthene derivatives.

We study the comprehensive effect of temperature and amount of acidic ionic liquid $[NMP]H_2PO_4$ on the yield of **1a** using factorial analysis. Factorial analysis was carried out by considering two experimental factors with three levels, *i.e.* temperature (with levels 60 °C, 80 °C, 100 °C) and amount of ionic liquid (with levels 10 mol%, 20 mol%, 30 mol%). The model reaction for the synthesis of **1a** was performed under different conditions as obtained by fully designed factorial array for these factors (Table 2).

The factorial analysis was performed using Minitab 17 software, and the results of factorial analysis are shown in Fig. 1. From Fig. 1

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Table 2
Full designed factorial array for the study of temperature and amount of catalyst over yield of **1a**.

Run	Temp (°C)	Amount of catalyst (mol%)	Yield (%) of **1a**
1	80	20	90
2	100	10	79
3	60	10	72
4	80	10	77
5	60	30	79
6	60	20	85
7	100	30	83
8	100	20	86
9	80	30	88

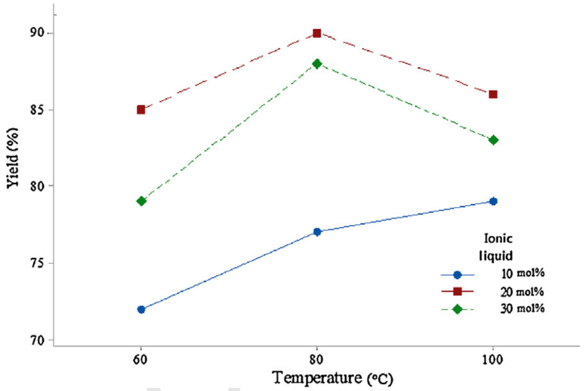

Fig. 1. Results of factorial analysis for the effect temperature and amount of ionic liquid over yield of **1a**.

it can be concluded that the combination of two experimental parameters, *i.e.*, temperature of 80 °C and ionic liquid NMP[H_2PO_4] (20 mol%), gave the best yield of compound **1a** (90%). Thus, the three-component reaction of 4-bromobenzaldehyde (1.0 mmol), 2,7-dihydroxynaphthalene (1.0 mmol), and dimedone (1.1 mmol) in the presence of NMP[H_2PO_4] (20 mol%) at 80 °C was chosen as the most suitable set reaction conditions for this reaction, as these gave the product in the highest yield (90%) in the shortest reaction time.

Subsequently, reactions of variously substituted aromatic aldehydes with 2,7-dihydroxynaphthalene and dimedone were carried out under these most suitable reaction conditions. The reactions proceeded smoothly for different aromatic aldehydes to afford the corresponding 12-aryl-2-hydroxy-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives in high yields (**1b**–**1j**, Table 3). The protocol was further extended by exploring the cyclocondensation of aromatic aldehydes and 2,7-dihydroxynaphthalene with cyclohexane-1,3-dione. The reaction of 4-bromobenzaldehyde (1.0 mmol), 2,7-dihydroxynaphthalene (1.0 mmol), and cyclohexane-1,3-dione (1.1 mmol) in the presence of ionic liquid [NMP]H_2PO_4 (20 mol%) at 80 °C yielded 88% of 12-(4-bromophenyl)-2-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (**1k**) after 20 min. Other substituted benzaldehyde derivatives also underwent successful condensation, giving excellent yields of corresponding 12-aryl-2-hydroxy-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives (**1l**–**1o**, Table 3).

The scope of the three-component reaction was further investigated with other naphthols. It was observed that 2-naphthol (1.0 mmol) also underwent reactions with dimedone (1.1 mmol) and substituted aromatic aldehydes (1.0 mmol) in the presence of [NMP]H_2PO_4 (20 mol%) at 80 °C giving high yields of corresponding 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives in good yield (**1p**–**1t**, Table 3). Similarly, reaction of 2,6-dihydroxynaphthalene (1.0 mmol) with dimedone (1.1 mmol) and various aromatic aldehydes (1.0 mmol) under the above optimized reaction conditions proceeded smoothly to afford the corresponding 12-aryl-3-hydroxy-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones derivatives in high yields (**1u**–**1y**, Table 3). However, no xanthene derivatives were obtained when the reactions were attempted with sesamol, 1-naphthol, 1,5-dihydroxynaphthalene and 1,6-dihydroxynaphthalene. Also all our efforts to achieve bis-condensation of 2,6- and 2,7-dihydroxynaphthalenes using two molar equivalents of aldehyde and active methylene compounds have also been unsuccessful under these conditions. The generalized reaction scheme is shown in Scheme 1.

The recyclability of ionic liquid [NMP]H_2PO_4 was also investigated, as it is an important aspect of green chemistry. After completion of the reaction for synthesis of **1a**, the reaction mixture was cooled to room temperature and water (5 mL) was added. The

Table 3
Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives (**1a**–**1u**).

No.	Ar	R^1	R^2	R^3	Product	Yield (%)	Time (min)	Mp (°C)	Lit. Mp (°C)
1	4-BrC_6H_4	OH	H	CH_3	**1a**	89	15	180 –181	182 [15b]
2	4-FC_6H_4	OH	H	CH_3	**1b**	91	20	184–185	186 [15b]
3	4-$NO_2C_6H_4$	OH	H	CH_3	**1c**	88	15	176–178	178 [15g]
4	4-CH_3O C_6H_4	OH	H	CH_3	**1d**	85	20	202–204	205 [15b]
5	3,4$(CH_3O)_2C_6H_3$	OH	H	CH_3	**1e**	90	30	256 –258	258 [15g]
6	4-$CH_3C_6H_4$	OH	H	CH_3	**If**	85	20	173–175	176 [15g]
7	3-$NO_2C_6H_4$	OH	H	CH_3	**1g**	87	15	>300 (decom)	>300(decom) [15g]
8	C_6H_5	OH	H	CH_3	**1h**	90	25	152–153	153 [15g]
9	4-ClC_6H_4	OH	H	CH_3	**1i**	92	20	180–182	181 [15g]
10	2-Naphthyl	OH	H	CH_3	**1j**	84	20	231–233	233 [15f]
11	4-BrC_6H_4	OH	H	H	**1k**	88	20	234–236	237 [15f]
12	2-Naphthyl	OH	H	H	**1l**	83	35	286–288 (decom)	288 (decom) [15g]
13	4-$CH_3C_6H_4$	OH	H	H	**1m**	91	25	286–288 (decom)	288 (decom) [15g]
14	4-$(CH_3)_2CHC_6H_4$	OH	H	H	**1n**	86	30	258–260	258 [15g]
15	C_6H_5	OH	H	H	**1o**	93	40	202–205	203 [15b]
16	4-BrC_6H_4	H	H	CH_3	**1p**	84	40	186–187	187 [15g]
17	4-CH_3O C_6H_4	H	H	CH_3	**1q**	83	35	202–203	204 [15h]
18	4-$NO_2C_6H_4$	H	H	CH_3	**1r**	86	45	178–180	180 [15h]
19	4-$CH_3C_6H_4$	H	H	CH_3	**1s**	88	30	176–178	177 [15b]
20	4-ClC_6H_4	H	H	CH_3	**1t**	87	40	180–182	183 [15b]
21	4-BrC_6H_4	H	OH	CH_3	**1u**	85	45	208–209	208 [15e]
22	4-$CH_3OC_6H_4$	H	OH	CH_3	**1v**	84	35	237–239	238 [15e]
23	4-ClC_6H_4	H	OH	CH_3	**1w**	83	40	250–251	250 [15e]
24	4-$CH_3C_6H_4$	H	OH	CH_3	**1y**	87	35	245–247	246 [15e]

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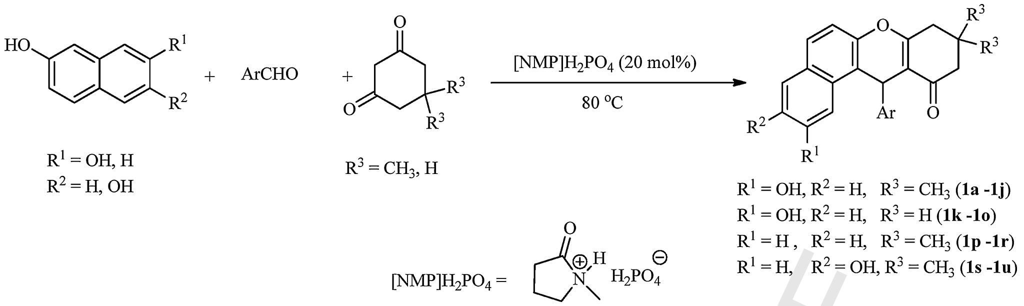
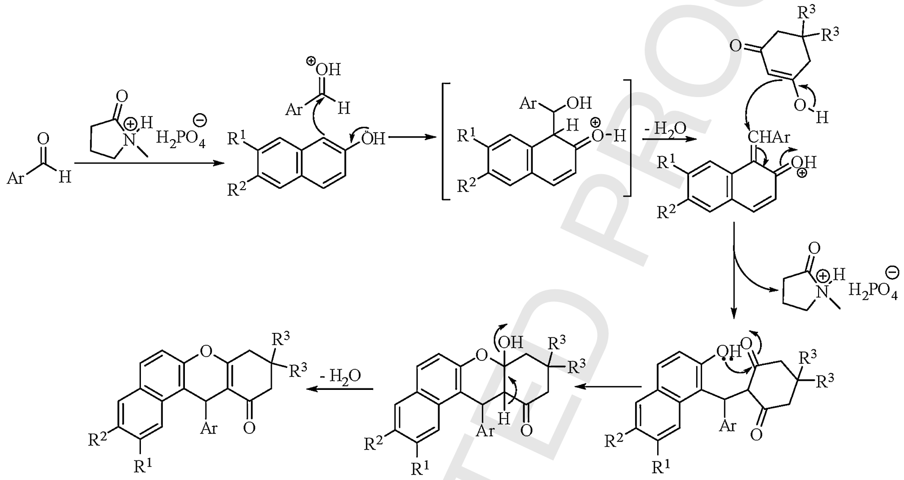


Scheme 1. Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives in ionic liquid $[NMP]H_2PO_4$.



Scheme 2. Plausible reaction mechanism for synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene derivatives in task specific ionic liquid $[NMP]H_2PO_4$ at 80 °C.

ionic liquid dissolved in water, and the solution was filtered to isolate the product. The ionic liquid was recovered by evaporating the water containing the ionic liquid, and the remaining viscous liquid was washed with CH_2Cl_2 (5 mL) and dried under reduced pressure. The recovered ionic liquid was tested to study its catalytic activity in the subsequent runs. No appreciable loss in the yield of **1a** was observed after four cycles, as **1a** was obtained in 89%, 88%, 85%, and 81% yield after the first, second, third and fourth cycle, respectively. However, yield of 1a was reduced to 74% in the fifth cycle.

The plausible reaction mechanism is given in Scheme 2. The reaction proceeds through the *in situ* formation of *ortho*-quinone methide intermediate by the nucleophilic addition of 2-naphthol derivative to aldehyde in the presence of $[NMP]H_2PO_4$ which is further attacked by cyclic 1,3-dicarbonyl compound followed by cyclization and elimination of water to yield the 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene derivatives.

4. Conclusion

In conclusion, we have reported a new and improved protocol for the eco-friendly one pot synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives by three-component reaction of aromatic aldehydes, 2,7-dihydroxynaphthalene/2-naphthol/2,6-dihydroxynaphthalene and dimedone/cyclohexan-1,3-dione in task specific acidic ionic liquid $[NMP]H_2PO_4$ at 80 °C. This protocol offers advantages in terms of operational simplicity, solvent free reaction, easy work up, short reaction times, and recyclability of reaction medium/catalyst.

Acknowledgments

HS thank UGC, New Delhi, India for the grant of Junior and Senior Research Fellowship, SK thank UGC, New Delhi, India for the grant of Junior Research Fellowship.

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