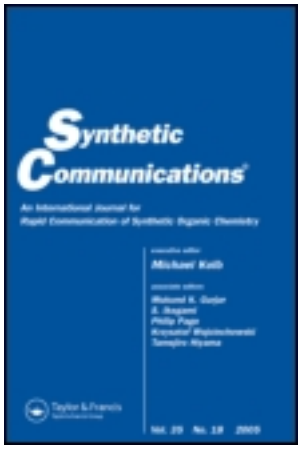


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient and Green Syntheses of 12-Aryl-2,3,4,12-tetrahydrobenzo[b]xanthene-1,6,11-triones in Water and Task-Specific Ionic Liquid

Jitender M. Khurana [a], Anshika Lumb [a], Ankita Chaudhary [a] & Bhaskara Nand [a]

[a] Department of Chemistry, University of Delhi, Delhi, India

Published online: 03 Jun 2013.

To cite this article: Jitender M. Khurana, Anshika Lumb, Ankita Chaudhary & Bhaskara Nand (2013): Efficient and Green Syntheses of 12-Aryl-2,3,4,12-tetrahydrobenzo[b]xanthene-1,6,11-triones in Water and Task-Specific Ionic Liquid, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:16, 2147-2154

To link to this article: http://dx.doi.org/10.1080/00397911.2012.688230

Synthetic Communications®, 43: 2147–2154, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.688230

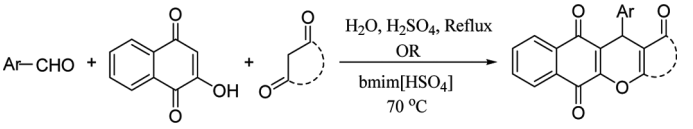
Taylor & Francis
Taylor & Francis Group

EFFICIENT AND GREEN SYNTHESES OF 12-ARYL-2,3,4,12-TETRAHYDROBENZO[*b*] XANTHENE-1,6,11-TRIONES IN WATER AND TASK-SPECIFIC IONIC LIQUID

Jitender M. Khurana, Anshika Lumb, Ankita Chaudhary, and Bhaskara Nand

Department of Chemistry, University of Delhi, Delhi, India

GRAPHICAL ABSTRACT



1a-x

Abstract *Facile and convenient one-pot cascade/tandem approaches for the syntheses of privileged medicinal scaffolds, 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-trione derivatives, have been reported under extremely mild reaction conditions using a catalytic amount of H_2SO_4 in water or in the presence of the acidic ionic liquid bmim[HSO_4], which could be recycled.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Aqueous media; benzoxanthenes; bmim[HSO_4],2-hydroxy-1,4-naphthoquinone; cyclic-1,3-dicarbonyl compounds

INTRODUCTION

The concept of privileged medicinal structures or scaffolds[1] has emerged as one of the guiding principles of the drug discovery process. These privileged scaffolds, such as substituted benzoxanthenes and naphthoquinones, commonly consist of a rigid heterocyclic system with well-defined orientation of appended functionalities for target recognition.[2] Benzoxanthenes show therapeutic and biological properties,[3] and they are used in photodynamic therapy,[4] polymer photoimaging systems,[5] and laser technologies.[6]

2-Hydroxy-1,4-napthoquinone (HNQ) is a principal natural dye in the leaves of henna, *Lawsonia inermis*. Today, semipermanent hairdyes containing henna as

Received March 14, 2012.

Address correspondence to Jitender M. Khurana, Department of Chemistry, University of Delhi, Delhi 110007, India. E-mail: jmkhurana1@yahoo.co.in

well as its pure dye ingredient HNQ are extensively used and have become increasingly popular because of their natural origin.[7] An array of naphthoquinone pigments (streptocarpone, α-dunnione, dunniol, and dunnione) have been isolated and characterized from *Streptocarpus dunni*.[8] Moreover, molecules containing naphthoquinone structure constitute an important class in organic chemistry because of their various biological activities, industrial applications, and potential as intermediates in the synthesis of heterocycles.[9]

The development of new and simple synthetic methods for xanthene containing a naphthoqinone framework is therefore an interesting challenge, and only few methods have been reported for the synthesis.[10–12] These methods have their own merits and demerits. An application of water as a green solvent for organic synthesis has received considerable attention.[13] Ionic liquids (ILs) also offer a unique environment because of their interesting properties such as chemical and thermal stability, nonvolatility, noncoordinating nature, good solvating capability, and ease of recycling.[14] Recently, task-specific acidic ionic liquids which can act as solvent and/or catalyst have been successfully used in different reactions.[15,16]

In continuation of our focus on the environmentally benign synthesis of diverse heterocyclic compounds of biological significance,[17] we disclose herein new and efficient protocols for the syntheses of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-triones.

RESULTS AND DISCUSSION

In the present study, we report "one-pot" syntheses of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthenes-1,6,11-triones (**1a–x**) by condensation of 2-hydroxy naphthalene-1,4-dione, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds catalyzed by sulfuric acid or the task-specific ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate (bmim[HSO_4]).

The reaction conditions were optimized by attempting the condensation of 4-nitrobenzaldehyde (1 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol), and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (1.2 mmol) in the presence or absence of acids such as HCl, H_2SO_4, HNO_3, and AcOH in various solvents such as water, acetonitrile, dimethylformanide (DMF), EtOH, tetrahydrofurane (THF), and bmim[HSO_4]. The standardization results are summarized in Table 1.

From Table 1 it is notable that 92% and 91% of 3,3-dimethyl-12-(4-nitrophenyl)-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-trione (**1a**) was obtained when the reaction was carried out in H_2O/H_2SO_4 under reflux (Table 1, entry 5) and bmim[HSO_4] at 70 °C (Table 1, entry 9) respectively. Increasing the amount of catalyst (H_2SO_4) did not affect the rate of reaction or yield while decreasing the amount of catalyst (H_2SO_4) decreases the rate of reaction and yields significantly. Hence, the reaction of 4-nitrobenzaldehyde, 2-hydroxy-1,4-naphthoquinone and dimedone (1.2 mmol) gives best and comparable results in water/H_2SO_4 (method A) and bmim[HSO_4] (method B). Therefore, we decided to pursue both protocols for the synthesis of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthenes-1,6,11-triones (Scheme 1).

Then, the generality of this protocol was applied to the synthesis of a variety of tetrahydrobenzo[*b*]xanthene-1,6,11-triones (Table 2, **1a–m**) using diversely subsituted aldehydes, 2-hydroxy-1,4-naphthpquinone, and dimedone. The scheme was

Table 1. Effect of different media and catalyst on the condensation of 4-nitrobenzaldehyde, 2-hydroxy-1,4-naphthoquinone, and dimedone (molar ratio 1:1:1.2)

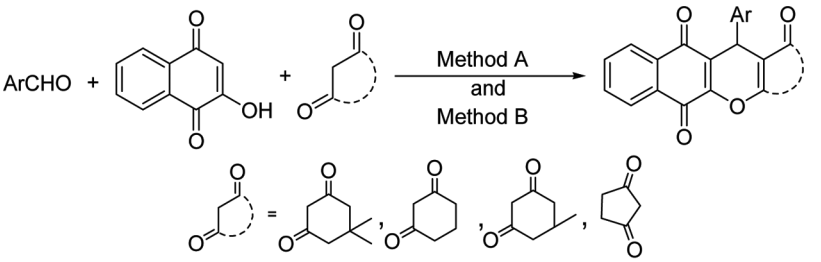
Entry	Reaction media	Temperature (°C)	Catalyst	Amount	Time	Yield (%)[a]
1	DMF	100	H_2SO_4	20	5.0 h	40
2	CH_3CN	80–85	H_2SO_4	20	5.0 h	45
3	THF	65–70	H_2SO_4	20	5.0 h	25
4	EtOH	70–80	H_2SO_4	20	2.0 h	78
5	H_2O	100	H_2SO_4	20	25 min	92
6	H_2O	100	CH_3COOH	20	5.0 h	—[b]
7	H_2O	100	HCl	20	5.0 h	—[b]
8	H_2O	100	HNO_3	20	5.0 h	—[c]
9	bmim[HSO_4] (1 mL)	70	—	—	30 min	91

[a]Isolated yield (%) of **1a**.
[b]Sluggish and incomplete reactions.
[c]Number of products on TLC.

extended to another cyclic β-diketones viz. 5-methyl-cyclohexane-1,3-dione and cyclohexane-1,3-dione to give the corresponding novel tetrahydrobenzo[*b*]xanthene-1,6,11-triones in excellent yields (Table 2, **1n–v**). Reaction of aromatic aldehydes and 2-hydroxy-1,4-naphthoquinone with cyclopentane-1,3-dione also underwent successful condensation under similar conditions to afford novel dihydro-2*H*-4-oxa-cyclopenta[*b*]anthracene-1,5,10-trione derivatives (Table 2, **1w–x**).

The ionic liquid employed in method B could be recycled for three cycles before losing activity. A plausible mechanism for the formation of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-trione in the presence of acid catalyst is proposed in Scheme 2, which is confirmed by the initial condensation of 4-chlorobenzaldehyde and dimedone to form 2-[(4-chlorophenyl)methylene]-5,5-dimethylcyclohexane-1,3-dione[18] (**A**), which is then condensed with 2-hydroxy-1,4-naphthoquinone using H_2SO_4 in aqueous media and bmim[HSO_4] to give desired product **1c**.

The electronic absorption spectra of 2×10^{-5} M solutions of 1a–x in $CHCl_3$ were measured (Table 3**)**. The longest wavelength maximum absorption (λ_{max}) of all the compounds was located between 335 and 341 nm. The color of the compounds varied from yellow to orange.



Method A= H_2O, H_2SO_4, Reflux
Method B= bmim[HSO_4], 70°C

Scheme 1. Synthesis of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-triones.

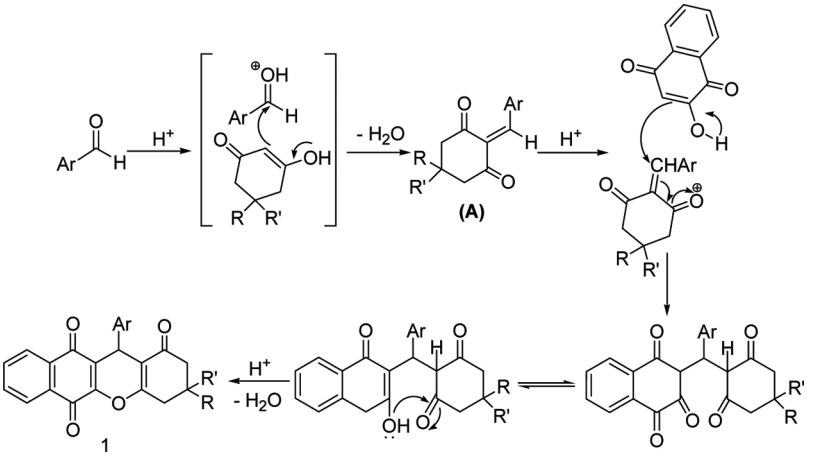
Table 2. Synthesis of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-trione derivatives by condensation of aldehydes, 2-hydroxy-1,4-naphthoquinone, and cyclic 1,3-dicarbonyl compounds

			Method A		Method B			
Entry	Ar	Cyclic-1,3-dicarbonyl compounds	Time (min)	Yield (%)	Time (min)	Yield (%)	Mp (°C) obs.	Mp (°C) lit.
1a	4-$O_2NC_6H_4$	5,5-Dimethyl-cyclohexane-1,3-dione	25	92	30	91	256–258	—
1b	3-$O_2NC_6H_4$	5,5-Dimethyl-cyclohexane-1,3-dione	25	92	30	89	236–238	—
1c	4-ClC_6H_4	5,5-Dimethyl-cyclohexane-1,3-dione	30	90	25	89	275–278	282–284[12]
1d	4-$CH_3OC_6H_4$	5,5-Dimethyl-cyclohexane-1,3-dione	40	88	30	88	268–270	—
1e	C_6H_5	5,5-Dimethyl-cyclohexane-1,3-dione	25	90	30	89	260–262	263–265[12]
1f	4-$CH_3C_6H_4$	5,5-Dimethyl-cyclohexane-1,3-dione	35	89	25	90	178–180	—
1g	2-ClC_6H_4	5,5-Dimethyl-cyclohexane-1,3-dione	25	88	25	91	242–244	—
1h	3-ClC_6H_4	5,5-Dimethyl-cyclohexane-1,3-dione	35	90	30	86	210–212	—
1i	2,4-ClC_6H_3	5,5-Dimethyl-cyclohexane-1,3-dione	25	90	25	88	256–258	—
1j	2-Naphthyl	5,5-Dimethyl-cyclohexane-1,3-dione	20	89	30	85	268–270	—
1k	4-OH C_6H_4	5,5-Dimethyl-cyclohexane-1,3-dione	45	85	30	87	198–200	—
1l	3-OH C_6H_4	5,5-Dimethyl-cyclohexane-1,3-dione	40	88	25	88	194–196	—
1m	Thien-2-yl	5,5-Dimethyl-cyclohexane-1,3-dione	30	90	25	87	178–180	—
1n	4- $O_2NC_6H_4$	Cyclohexane-1,3-dione	15	94	25	91	218–220	—
1o	4-ClC_6H_4	Cyclohexane-1,3-dione	20	90	30	92	188–190	—
1p	4-$CH_3OC_6H_4$	Cyclohexane-1,3-dione	40	89	30	89	190–192	—
1q	C_6H_5	Cyclohexane-1,3-dione	30	91	30	88	220–222	—
1r	4-$CH_3C_6H_4$	Cyclohexane-1,3-dione	35	85	30	87	260–262	—
1s	2,4-ClC_6H_3	Cyclohexane-1,3-dione	25	91	30	86	252–254	—
1t	Thien-2-yl	Cyclohexane-1,3-dione	30	92	25	89	212–214	—
1u	4-$O_2NC_6H_4$	5-Methyl-cyclohexane-1,3-dione	20	90	30	88	180–184	—
1v	4-$CH_3OC_6H_4$	5-Methyl-cyclohexane-1,3-dione	35	89	30	90	182–184	—
1w	4-$O_2NC_6H_4$	Cyclopentane-1,3-dione	40	88	25	91	198–200	—
1x	4-$CH_3OC_6H_4$	Cyclopentane-1,3-dione	35	90	25	91	256–258	—

Notes. Method A: H_2SO_4, water, reflux.
Method B: bmim[HSO_4], 70 °C.

EXPERIMENTAL

All the chemicals used were purchased from Sigma-Aldrich and used as received. Silica gel 60 F_{254} (precoated aluminium plates) from Merck was used to monitor reaction progress. Melting points were determined on a Tropical Labequip



Scheme 2. Proposed pathway for the synthesis of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-triones.

apparatus and are uncorrected. Infrared (IR) (KBr) spectra were recorded on Perkin-Elmer Fourier transform (FT–IR) spectrophotometer, and the values are expressed as ν_{max} cm^{-1}. Absorbance measurements were made using an Analytikjena Specord 250 spectrophotometer. Mass spectral data were recorded on a

Table 3. UV/visible data for compounds **1** in $CHCl_3$

Compound	λ_{max} (nm)	ε (10^4 L mol^{-1} cm^{-1})
1a	343	6.00
1b	336	7.50
1c	335	5.50
1d	336	3.30
1e	338	5.80
1f	337	3.50
1g	333	5.00
1h	338	5.50
1i	333	5.50
1j	339	6.00
1k	340	3.50
1l	338	6.50
1m	338	4.00
1n	343	4.50
1o	336	7.50
1p	338	3.50
1q	335	6.00
1r	338	6.00
1s	336	4.00
1t	339	6.50
1u	338	5.50
1v	340	5.00
1w	340	5.00
1x	339	5.50

Jeol-AccuTOF mass spectrometer having a direct analysis in real time (DART) source. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 MHz, using tetramethylsilane (TMS) as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (*J*) are in hertz (Hz). Ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate bmim[HSO_4] was synthesized according to a reported procedure.[19]

General Procedure for the Synthesis of 12-Aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-triones (1a–x)

Method A. In a 50-mL round-bottom flask, aldehyde (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol), 5,5-dimethylcyclohexane-1,3-dione or 5-methyl-cyclohexane-1,3-dione or cyclohexane-1,3-dione or cyclopentane-1,3-dione (1.2 mmol), H_2SO_4 (0.20 mmol), and 10 mL water were taken. The reaction mixture was refluxed for appropriate time as mentioned in Table 2, Method A. The progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate–petroleum ether (30:70, v/v) as eluent. After completion, the reaction mixture was filtered and the crude product was purified on silica gel (100–200 mesh) column chromatography to yield pure 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-trione derivatives.

Method B. A mixture of aldehyde (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol), and cyclic-1,3-dicarbonyl (1.2 mmol) was placed in a 50-mL, round-bottomed flask and 1 mL bmim[HSO_4] was added. The mixture was heated at 70 °C. After completion of the reaction as monitored by TLC, water (~5–7 mL) was added to the mixture. The product was filtered at the pump and purified through column chromatography (silica gel 100–200 mesh) to yield pure products **1a–x**.

After separation of the product by filtration, the filtrate containing the ionic liquid was rinsed with ether and further vacuumed to dryness at 100 °C to eliminate any trapped moisture. It afforded bmim[HSO_4], which was reused directly for the next run. Marginal loss in the yield of the products were observed in first three runs (90%, 88%, and 86%), while in fourth and fifth runs the yields were quite poor.

The spectral data of the synthesized compounds have been provided in the Supplementary Information, available online.

CONCLUSION

In conclusion, we have reported efficient syntheses of 12-aryl-2,3,4,12-tetrahydrobenzo[*b*]xanthene-1,6,11-trione derivatives via an acid-catalyzed condensation reaction in aqueous media as well as with the task-specific ionic liquid bmim[HSO_4].

ACKNOWLEDGMENTS

A. L. thanks the University of Delhi for the award of a university teaching assistantship. A. C. and B. N. thank the Council for Scientific and Industrial Reserch, New Delhi, for the grant of a junior/senior research fellowship.

REFERENCES

1. (a) Evans, B. E.; Rittle, K. E.; Bock, G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. G.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. Methods for drug discovery: Development of potent, selective, orally effective cholecystokinin antagonists. *J. Med. Chem.* **1988**, *31*, 2235–2246; (b) Patchett, A. A.; Nargund, R. P. Privileged structures: An update. *Ann. Rep. Med. Chem.* **2000**, *35*, 289–298.
2. Poupaert, J.; Carato, P.; Colacino, E. 2(3*H*)-Benzoxazolone and bioisosters as ''privileged scaffold'' in the design of pharmacological probes. *Curr. Med. Chem.* **2005**, *12*, 877–885.
3. (a) Chatterjee, S.; Iqbal, M.; Kauer, J. C.; Mallamo, J. P.; Senadhi, S.; Mallaya, S.; Bozyczko-Coyne, D.; Siman, R. Xanthene-derived potent nonpeptidic inhibitors of recombinant human calpain I. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1619–1622; (b) Naya, A.; Ishikawa, M.; Matsuda, K.; Ohwaki, K.; Saeki, T.; Noguchi, K.; Ohtake, N. Structure–activity relationships of xanthene carboxamides, novel CCR1 receptors antagonists. *Bioorg. Med. Chem.* **2003**, *11*, 875–884.
4. Saint-Ruf, G.; Hieu, H. T.; Poupelin, J. P. The effect of dibenzoxanthenes on the paralyzing action of zoxazolamine. *Naturwissenschaften* **1975**, *62*, 584–585.
5. Monroe, B. M.; Weed, G. C. Photoinitiators for free-radical-initiated photoimaging systems. *Chem. Rev.* **1993**, *93*, 435–448.
6. Green, G. R.; Evans, J. M.; Vong, A. K.; Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, 1995; vol. 5, p. 469.
7. Siddiqui, B. S.; Kardar, M. N.; Ali, T.; Khan, S. Two new and a known compound from *Lawsonia inermis*. *Helv. Chim. Acta* **2003**, *86*, 2164–2169.
8. Perez, A. L.; Lamoureux, G.; Sanchez-Kopper, A. Efficient syntheses of streptocarpone and (±)-α-dunnione. *Tetrahedron Lett.* **2007**, *48*, 3735.
9. Thomson, R. H. In *Naturally Occurring Quinones*, 4th ed.; Chapman & Hall: London, 1997.
10. Yuling, L.; Baixiang, D.; Xiaoping, X.; Daqing, S.; Shunjun, J. A green and efficient synthesis of 13-aryl-5,7,12,14-tetrahydrodibenzo[*b,i*]xanthene-5,7,12,14(*13H*)-tetraone derivatives in ionic liquid. *Chin. J. Chem.* **2009**, *27*, 1563–1568.
11. Tisseh, Z. N.; Azimi, S. C.; Mirzaei, P.; Bazgir, A. The efficient synthesis of aryl-5*H*-dibenzo[*b,i*]xanthene-5,7,12,14(*13H*)-tetraone leuco-dye derivatives. *Dyes Pigm.* **2008**, *79*, 273–275.
12. (a) Dabiri, M.; Tisseh, Z. N.; Bazgir, A. An efficient three-component synthesis of benzoxanthenes in water. *J. Heterocycl. Chem.* **2010**, *47*, 1062–1065; (b) Shaterian, H. R.; Ranjbar, M.; Azizi, R. Synthesis of benzoxanthene derivatives using Brønsted acidic ionic liquids (BAILs), 2-pyrrolidonium hydrogen sulfate and (4-sulfobutyl)tris(4-sulfophenyl) phosphonium hydrogen sulfate. *J. Mol. Liq.* **2011**, *162*, 95–99.
13. (a) Lindstrom, U. M. Stereoselective organic reactions in water. *Chem. Rev.* **2002**, *102*, 2751; (b) Li, C. J.; Chen, L. Organic chemistry in water. *Chem. Soc. Rev.* **2006**, *35*, 68–82.
14. Welton, T. Room-temperature ionic liquids: Solvents for synthesis and catalysis. *Chem. Rev.* **1999**, *99*, 2071–2084.
15. Wasserschield, P.; Keim, W. Ionic liquids—New ''solutions'' for transition metal catalysis. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789.
16. Gupta, N.; Sonu, Kad, G. L.; Singh, J. Acidic ionic liquid [bmim]HSO_4: An efficient catalyst for acetalization and thioacetalization of carbonyl compounds and their subsequent deprotection. *Catal. Commun.* **2007**, *8*, 1323–1328.
17. (a) Khurana, J. M.; Lumb, A.; Pandey, A.; Magoo, D. Green approaches for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones in aqueous media and microwave

irradiation in solventless condition. *Synth. Commun.* **2012**, *42*, 1796–1803; (b) Khurana, J. M.; Nand, B.; Kumar, S. Rapid synthesis of polyfunctionalized pyrano[*2,3-c*]pyrazoles via multicomponent condensation in room-temperature ionic liquids. *Synth. Commun.* **2011**, *41*, 405–410; (c) Khurana, J. M.; Magoo, D. *p*TSA-catalyzed one-pot synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*] xanthen-11-ones in ionic liquid and neat conditions. *Tetrahedron Lett.* **2009**, *50*, 4777–4780; (d) Khurana, J. M.; Nand, B.; Saluja, P. DBU: A highly efficient catalyst for one-pot synthesis of substituted 3,4-dihydropyrano[*3,2-c*]chromenes, dihydropyrano[*4,3-b*]pyranes, 2-amino-4*H*-benzo[*h*]chromenes, and 2-amino-4*H* benzo[*g*]chromenes in aqueous medium. *Tetrahedron* **2010**, *66*, 5637–5641.

18. Dandia, A.; Arya, K.; Khaturia, S.; Jain, A. K. Microwave-induced preparation of biologically important benzothiazolo[2,3-*b*]quinazolines, and comparison with ultrasonic and classical heating. *Monatsh. Chem.* **2010**, *141*, 979–985.
19. Wang, W.; Shao, L.; Cheng, W.; Yang, J.; He, M. Brønsted acidic ionic liquids as novel catalysts for Prins reaction. *Catal. Commun.* **2008**, *9*, 337–341.