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Brønsted acidic ionic liquid catalyzed tandem reaction of 4-hydroxy-1-methyl-2-quinolone with chalcone: regioselective synthesis of pyrano[3,2-*c*]quinolin-2-ones†

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A new methodology has been developed for the synthesis of pyrano [3,2-*c*]quinolin-2-one derivatives by the tandem cyclization of 4-hydroxy-1-methyl-2-quinolone with chalcones using a catalytic amount of task specific ionic liquid [1-methyl-3-(4-sulfobutyl)imidazolium-4-methylbenzenesulfonate] under solvent-free conditions. The developed protocol is applicable for the construction of pyrano [3,2-*c*]quinolin-2-ones from easily accessible chalcones having aryl and hetero aryl substituents. This reaction possibly proceeds through Michael addition followed by cyclization. The feasibility of the catalyst recycling is also demonstrated. This method produced only water as the byproduct and represents a green synthetic protocol.

The pyranoquinolinone moiety is found in many alkaloids which are generally seen in the plant family *Rutaceae* (Fig. 1). These derivatives exhibit a wide range of biological activities such as antibacterial, anticoagulant, antitumor, antihypertensive, antifungal, anti-algal, anti-inflammatory, and antimalarial activities.[1] In addition to these bioactivities, some of them show cancer cell growth inhibitory activity and have been found to be potential anti-cancer agents.[2] These are also useful intermediates for the construction of azo dyestuffs.[3] They are often used as synthetic precursors for the preparation of other natural products such as dimeric quinoline alkaloids and other polycyclic heterocycles.[4]

Several methodologies have been developed for the synthesis of pyranoquinolinone derivatives.[5] Most of the methodologies were developed *via* the reaction of 4-hydroxyquinolin-2-one with various 1,3-dielectrophiles like diethyl malonate,[5b] β-keto ester,[5c] α,β-unsaturated aldehyde,[5d] arylidenemalononitrile/arylidenecyanoacetate,[5e] *etc.* (Scheme 1). But most of these bear narrow substrates scope and are only applicable for the synthesis of pyrano[3,2-*c*]quinoline-2,5-dione type derivatives. In addition, these methodologies bear many drawbacks like requirement of high temperature, poor yield, use of toxic solvents, generation of significant amounts of waste materials, and special efforts for the preparation of the starting materials *etc.* As such, it is still desirable to develop an efficient and selective protocol for the diversified synthesis of pyrano[3,2-*c*] quinolin-2-one derivatives with broad substrate scopes under environmentally friendly reaction conditions.

α,β-Unsaturated ketones are easily accessible from readily available aldehydes and ketones by the condensation reaction. These are good Michael acceptor and have been used for the construction of biologically important scaffolds by exploring their bielectrophilic properties in cascade fashion.[6] During the studies on the construction of pyranocoumarin derivatives,[6d] we envisioned that pyrano[3,2-*c*]quinolin-2-one derivatives might be synthesized by the tandem reaction between 4-hydroxyquinolone and α,β-unsaturated ketones under suitable reaction conditions (Fig. 2).

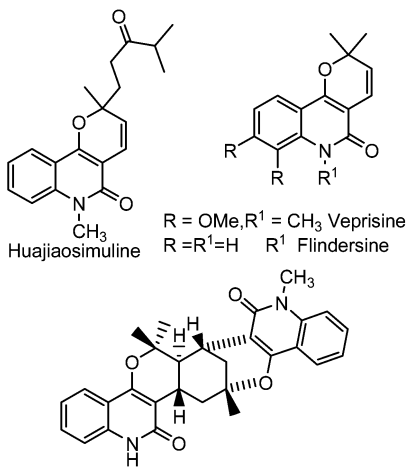

Fig. 1 Some alkaloids containing pyranoquinolinone moiety.

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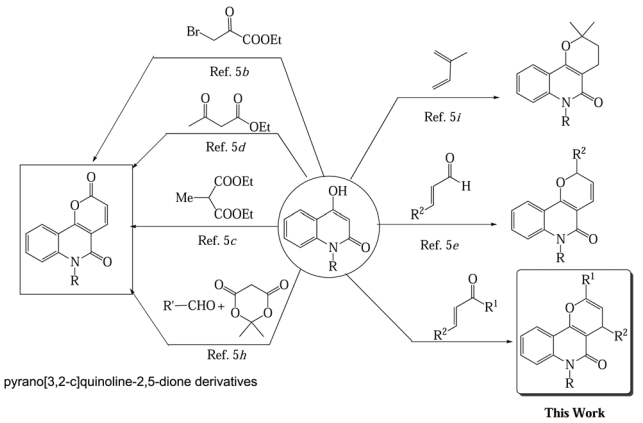
† Electronic supplementary information (ESI) available: Experimental procedure, *E*-factor calculations, crystallographic data (**3g**) and NMR spectra for all compounds. CCDC 964212. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra03221g



Scheme 1 Synthetic strategies for the pyranoquinolinones.

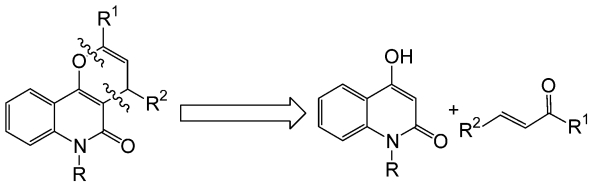
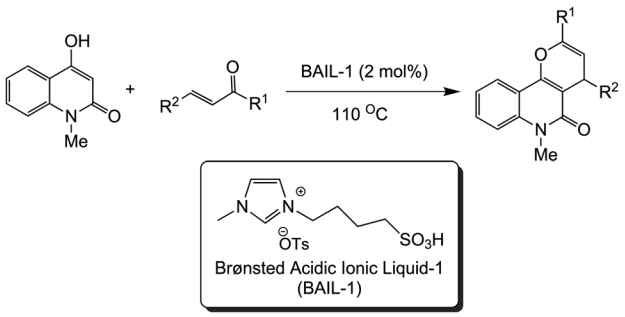


Fig. 2 Plan of our work.

Ideally, running a reaction in the absence of solvent presents the most environmentally friendly scenario, as a consequence significant interest has been focused on the development of new protocols with solvent minimization. On the other hand, catalytic applications of the ionic liquids have gained much interest due to their environmental compatibility, reusability, greater selectivity, operational simplicity, non-corrosiveness, and ease of isolation.[7] Combining the useful characteristics of solid acids and mineral acids, Brønsted acidic ionic liquids (BAILs) have been applied to replace traditional mineral liquid acids such as hydrochloric acid and sulfuric acid in chemical reactions. BAILs are more useful compare to the traditional ionic liquids as these combine strong acidity with the use of nonvolatile ionic liquids. After the report by Forbes and Davis, phosphonium- and imidazolium ion-based ionic liquids equipped with a pendant acidic sulfonic acid moiety have drawn considerable attention as a Brønsted acidic ionic liquid.[8] We are actively engaged with the catalytic application of ionic liquids and molten salts in various organic transformations[9] and our works also demonstrate that the imidazolium ion-based Brønsted acidic ionic liquid show remarkable catalytic activity in various syntheses.[10] Herein we report a new, significantly simplified, and environmentally friendly approach to the pyrano[3,2-*c*]quinolin-2-one derivatives having different aryl substituents on the pyran ring under solvent- and metal-free reaction conditions (Scheme 2).

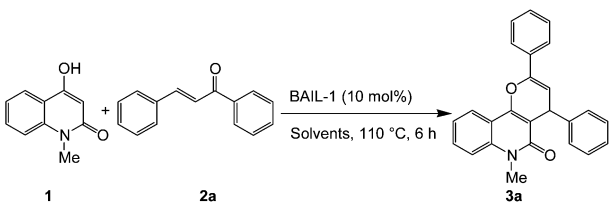
To find out the suitable reaction conditions, we commenced our study by choosing the reaction of 4-hydroxy-1-methyl-2-quinolone with 1, 3-diphenyl-propenone as the model reaction employing 10 mol% 1-methyl-3-(4-sulfobutyl)imidazolium-4-methylbenzenesulfonate (BAIL-1) as the catalyst. Initially the



Scheme 2 Synthesis of pyranoquinolinones catalyzed by Brønsted acidic ionic liquid.

reaction was carried out in various organic solvents such as DMSO, DMF, PEG, toluene, 1,4-dioxane, DCE, methanol, ethanol *etc.* as well as in aqueous medium. The results are summarized in Table 1. Either no formation or trace amount of the desired product was observed in DMSO, DMF, H_2O, dioxane, DCE, toluene (Table 1, entries 1–3, 7–9). In case of ethanol, methanol and PEG, the desired product was obtained in 27%, 24%, 15% yields respectively (Table 1, entries 4–6). The targeted product was obtained with maximum yield (82%) under solvent-free conditions at 110 °C for 6 h (Table 1, entry 10). These results indicate the detrimental effect of the solvents for this transformation. Next the effects of reaction time and temperature on the reaction were also investigated. The yield of the reaction did not improve by increasing the reaction time from 6 h to 8 h (Table 2, entry 5) and the best operating reaction temperature was found to be 110 °C (Table 2, entry 3). Increasing the temperature was not beneficial (Table 2, entry 4) while decreasing the reaction temperature decreased the yield of the reaction (Table 2, entries 2 & 3). No significant amount of

Table 1 Screening of the solvents effects[a]



Entry	Catalyst (10 mol%)	Solvents	Yields[b] (%)
1	BAIL-1	DMSO	2
2	BAIL-1	DMF	0
3	BAIL-1	H_2O[c]	0
4	BAIL-1	EtOH[c]	27
5	BAIL-1	MeOH[c]	24
6	BAIL-1	PEG	15
7	BAIL-1	Dioxane[c]	0
8	BAIL-1	DCE[c]	0
9	BAIL-1	Toluene	5
10	BAIL-1	Neat	82

[a] Reaction conditions: mixture of **1** (0.5 mmol) and **2a** (0.5 mmol) was heated at 110 °C for 6 h. [b] Isolated yield. [c] Under reflux.

Table 2 Effect of temperature on the reaction[a]

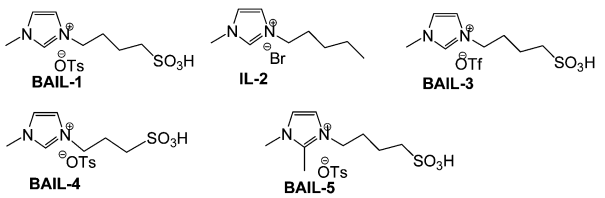
Entry	Temp. (°C)	Time	Yields[b] (%)
1	RT	24	Trace
2	80	6	51
3	100	6	75
4	110	6	82
5	110	8	82
6	120	6	83

[a] Reaction conditions: mixture of **1** (0.5 mmol), **2a** (0.5 mmol) and BAIL-1 (10 mol%). [b] Isolated yield.

the desired product was formed when the reaction was carried out at room temperature (Table 2, entry 1).

The effect of various ionic liquids were also studied which are summarized in Table 3. The acidic ionic liquid BAIL-1 afforded the maximum yield (Table 3, entry 1). Neutral ionic liquid (IL-2) was totally ineffective for this transformation (Table 3, entry 2) and the BAIL-3 also produced the desired products with comparable yields (Table 3, entry 3). The yields of the reaction decreased when the chain length of the ionic liquid (BAIL-4) was decreased (Table 3, entry 4).[11] The methyl group at the C-2 position of the imidazolium ring (BAIL-5) decreased the yield of the reaction (Table 3, entry 5). This results suggest that C_2–H of imidazolium ring plays a significant role to catalyze the reaction probably through the formation of H-bonding.[7f] However lower yield was obtained by employing 10 mol% *p*-TsOH as the catalyst while AcOH was not effective at all (Table 3, entries 6 & 7). The catalyst loading was also optimized. 2 mol% acidic ionic liquid is the optimum amount as further decreasing the catalyst loading decreased the yield while the significant increment of the yield was not observed with 5 mol% and 10 mol% (Table 3, entries 8–10). Lewis acids such as $Cu(OTf)_2$, $Zn(OTf)_2$, $In(OTf)_3$, $La(OTf)_3$ were not so effective and afforded 30 to 40% yields. Thus the optimal yield (81%) was obtained when the reaction was carried out employing 2 mol% BAIL-1 at 110 °C under solvent-free conditions for 6 h.

Table 3 Effect of various ionic liquids and catalyst loading[a]

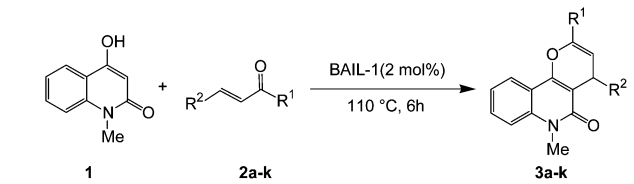


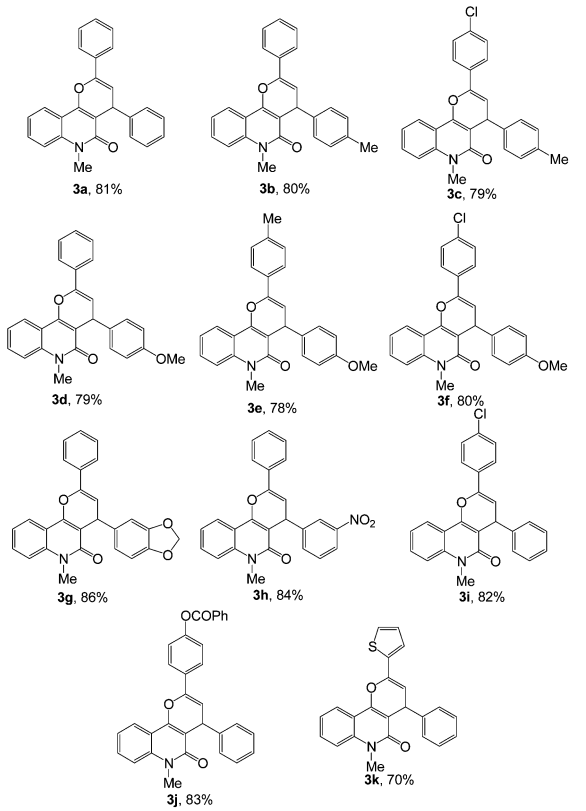
Entry	Catalyst	mol%	Yield[b] (%)
1	BAIL-1	10	82
2	IL-2	10	—
3	BAIL-3	10	80
4	BAIL-4	10	69
5	BAIL-5	10	57
6	*p*-TsOH	10	40
7	AcOH	10	—
8	BAIL-1	5	82
9	BAIL-1	2	81
10	BAIL-1	1	70

[a] Reaction conditions: **1** (0.5 mmol) and **2a** (0.5 mmol) was heated at 110 °C for 6 h. [b] Isolated yield.

After getting the optimized reaction conditions, various chalcones were reacted with the 4-hydroxy-1-methyl-2-quinolone to prove the general applicability of this methodology. The results are summarized in Table 4. In the most cases the desired products were obtained with good yields (**3a–k**). The chalcones bearing electron donating substituents like –Me, –OMe (**3b–f**) and electron withdrawing substituents such as –Cl, $-NO_2$ (**3h, 3i**) reacted well to afford the corresponding pyranoquinolinone derivatives. The acid sensitive group containing chalcones (**3g, 3j**) were unaffected under the present reaction conditions which signify the mildness of the reaction conditions. The hetero aryl substituted α,β-unsaturated ketone also produced the

Table 4 Substrate scopes[a,b]





[a] Reaction conditions: mixture of **1** (0.5 mmol) and **2** (0.5 mmol) was heated at 110 °C for 6 h in presence of 2 mol% BAIL-1. [b] All are isolated yields and obtained as a racemic mixture.

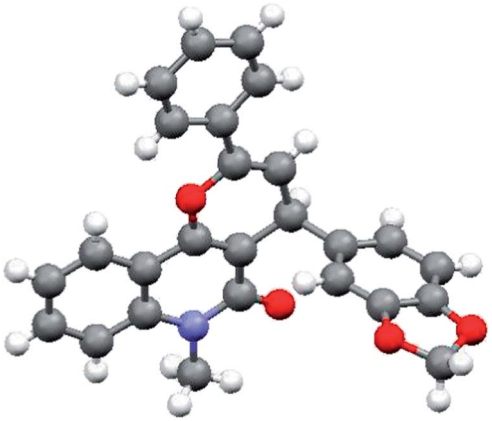
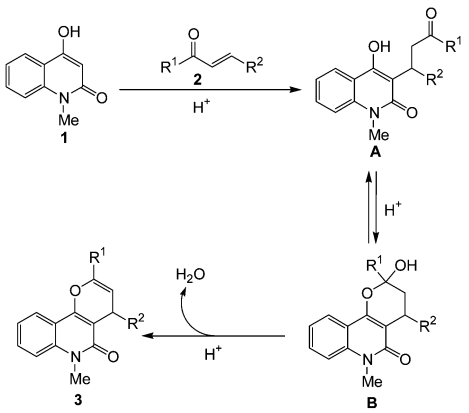


Fig. 3 The single crystal XRD structure of compound **3g**.



Scheme 3 Probable mechanism.

corresponding pyranoquinolinone (**3k**) derivative having three different heterocycles in moderate yield. However, the α,β-unsaturated aldehydes (cinnamaldehyde and crotonaldehyde) produced a mixture of unidentified product under the present reaction conditions. All the prepared compounds have been characterized by spectral and analytical data. Finally the single-crystal X-ray analysis[12] of **3g** was performed to confirm the substituent pattern on pyran moiety of pyranoquinolinone (Fig. 3). It is interesting to note that two aryl substituents on pyran moiety are orthogonal to each other.

Next, we turn our attention towards the recovery and reusability of the catalyst. For this purpose, we have chosen the reaction of 4-hydroxy-1-methyl-2-quinolone (**1**) with 1, 3-diphenyl-propenone (**2a**) in presence of 2 mol% acidic ionic liquid at 110 °C as the model reaction. After completion of the reaction water was added to the reaction mixture. The reaction mixture was then filtered off and the ionic liquid was recovered by evaporating the water. Pure product was obtained by recrystallizing the residue from hot ethanol. The recovered ionic liquid was reused for a subsequent fresh batch of the reaction after reactivation. The catalytic activity was found to be retained up to a fifth cycle (Table 5). This newly developed protocol also bears low *E*-factor[13] of 0.29 and 0.30 in the cases of synthesizing **3a** and **3f** respectively (see ESI†).

The probable mechanism of the reaction is outlined in Scheme 3. First step of this tandem reaction is either electrophilic substitution or the Michael addition of 4-hydroxy-1-methyl-2-quinolone to the α,β-unsaturated ketone and the adduct **A** is formed. The intermediate **A** on intramolecular cyclization afforded the intermediate **B** which finally afforded the pyranoquinolinone on subsequent removal of water. The acidic ionic liquid activates the unsaturated ketone through protonation of the carbonyl group and increased the electrophilic character at the β-carbon which promote the Michael adduct formation. In addition the acidic ionic liquid also helps to facilitate the intramolecular cyclization step by the protonation of carbonyl group of intermediate **A**.

Table 5 Reuse of BAIL for the synthesis of pyranoquinolinones[a]

Entry	Use	Yield[b] (%)
1	1st	81
2	2nd	81
3	3rd	80
4	4th	78
5	5th	77

[a] Reaction conditions: **1** (0.5 mmol) and **2a** (0.5 mmol) was heated at 110 °C for 6 h in presence of 2 mol% BAIL-1. [b] Isolated yield.

Conclusions

In summary, we have successfully developed an efficient and regioselective methodology for the synthesis of pyrano[3,2-*c*]quinolin-2-one derivatives by the coupling of 4-hydroxy-1-methyl-2-quinolone with chalcones catalyzed by Brønsted acidic ionic liquid (BAIL-1). This tandem reaction possibly proceeds through the Michael addition followed by annulation reaction and only water is produced as the byproduct. A library of pyranoquinolinone derivatives having variety of aryl and hetero aryl substituents on the pyran moiety have been synthesized employing this atom efficient methodology. Clean reaction, ease of product isolation/purification, easily accessible reactants, metal and solvent-free and environmentally friendly reaction conditions are the notable advantages of the present methodology and these features makes this procedure to be a green synthetic protocol. We believe that our present methodology will open up a new route for the synthesis of bioactive pyrano[3,2-*c*]quinolin-2-one derivatives.

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Notes and references

1 (*a*) H. M. F. Madkour, M. R. Mahmoud, A. M. Sakr and M. M. Habasy, *Sci. Pharm.*, 2001, **69**, 33; (*b*) R. Raghunathan, S. Sainath and M. Raghunathan, *Bioorg.*

Med. Chem., 2009, **17**, 660; (*c*) C. Jolivet, C. Rivalle and E. Bisagni, *Heterocycles*, 1996, **43**, 995; (*d*) M. Sugimori, A. Ejima, S. Ohsuki, K. Uoto, I. Mitsui, K. Matsumoto, Y. Kawato and H. Terasawa, *J. Med. Chem.*, 1994, **37**, 3033; (*e*) M. Anniyappan, D. Muralidhran and P. T. Perumal, *Tetrahedron Lett.*, 2003, **44**, 3653; (*f*) C. L. Cantrell, K. K. Schrader, L. K. Mamonov, G. T. Sitpaeva, T. S. Kustova, C. Dunbar and D. E. Wedge, *J. Agric. Food Chem.*, 2005, **53**, 7741; (*g*) I. S. Chen, I. W. Tsai, C. M. Teng, J. J. Chen, Y. L. Chang, F. N. Ko, M. C. Lu and J. M. Pezzuto, *Phytochemistry*, 1997, **46**, 525; (*h*) J. J. Chen, P. H. Chen, C. H. Liao, S. Y. Huang and I. S. Chen, *J. Nat. Prod.*, 2007, **70**, 1444; (*i*) F. Hanawa, N. Fokialakis and A. L. Skaltsounis, *Planta Med.*, 2004, **70**, 531; (*j*) C. Ito, M. Itoigawa, A. Furukawa, T. Hirano, T. Murata, N. Kaneda, Y. Hisada, K. Okuda and H. Furukawa, *J. Nat. Prod.*, 2004, **67**, 1800.

2 I. S. Chen, S. J. Wu, I. L. Tsai, T. S. Wu, J. M. Pezzuto, M. C. Lu, H. Chai, N. Suh and C. M. Teng, *J. Nat. Prod.*, 1994, **57**, 1206.

3 Y. Bansho, S. Surzuki and I. Saito, *Kogyo Kagaku Zasshi*, 1960, **63**, 1390.

4 (*a*) B. T. Ngadjui, J. F. Ayafor, A. E. N. Bilon, B. L. Sondengam, J. D. Connolly and D. S. Rycroft, *Tetrahedron*, 1992, **48**, 8711; (*b*) M. F. Grundon, *Tetrahedron*, 1978, **34**, 143; (*c*) S. A. Barr, C. F. Neville, M. F. Grundon, D. R. Boyd, J. F. Malone and T. A. Evans, *J. Chem. Soc., Perkin Trans. 1*, 1995, 445.

5 (*a*) T. Kamikawa, Y. Hanaoka, S. Fujie, K. Saito, Y. Yamagiwa, K. Fukuhara and I. Kubo, *Bioorg. Med. Chem. Lett.*, 1996, **4**, 1317; (*b*) V. V. Mulwad and V. Suryanarayan, *Indian J. Heterocycl. Chem.*, 1996, **5**, 281; (*c*) T. Kappe, *Il Farmaco*, 1999, **54**, 309; (*d*) N. V. Kumar and S. P. Rajendran, *Heterocycl. Commun.*, 2004, **10**, 289; (*e*) Y. R. Lee, H.-I. Kweon, W. S. Koh, K. R. Min, Y. Kim and S. H. Lee, *Synthesis*, 2001, 1851; *Chem Abstr*, 2002, **136**, 53920; (*f*) N. Dodia and A. Shah, *Heterocycl. Commun.*, 2001, **7**, 289; (*g*) K. C. Majumdar and P. P. Mukhopadhyay, *Synthesis*, 2003, 97; (*h*) K. Rad-Moghadam, S. C. Azimi and E. Abbaspour-Gilandeh, *Tetrahedron Lett.*, 2013, **54**, 4633; (*i*) D. Thangavel, S. Ravindran, G. R. Moonsamy and M. S. Palathurai, *J. Chem. Res.*, 2007, **2**, 124; (*j*) V. Nair, A. U. Vinod, R. Ramesh, R. S. Menon, L. Varma, S. Mathew and A. Chiaroni, *Heterocycles*, 2002, **58**, 147; (*k*) E. Galariniotou, V. Fragos, A. Makri, K. E. Litinas and D. N. Nicolaides, *Tetrahedron*, 2007, **63**, 8298; (*l*) A. Klásek, K. Kořistek, P. Sedmera and P. Halada, *Heterocycles*, 2003, **60**, 799; (*m*) C. O. Kappe and T. Kappe, *J. Heterocycl. Chem.*, 1989, **26**, 1555.

6 (*a*) Y. Liu, J. Zhu, J. Qian, B. Jiang and Z. Xu, *J. Org. Chem.*, 2011, **76**, 9096; (*b*) A. Sarkar, S. R. Roy and A. K. Chakraborti, *Chem. Commun.*, 2011, **47**, 4538; (*c*) M. Rahman, A. Majee and A. Hajra, *J. Chem. Res.*, 2009, 178; (*d*) A. K. Bagdi, A. Majee and A. Hajra, *Tetrahedron Lett.*, 2013, **54**, 3892; (*e*) K. Monir, A. K. Bagdi, S. Mishra, A. Majee and A. Hajra, *Adv. Synth. Catal.*, 2014, **365**, 1105; (*f*) K. Revathy and A. Lalitha, *RSC Adv.*, 2014, **4**, 279; (*g*) V. K. Rao, R. Tiwari, B. S. Chhikara, A. N. Shirazi, K. Parang and A. Kumar, *RSC Adv.*, 2013, **3**, 15396; (*h*) B. C. Ranu and S. S. Dey, *Tetrahedron*, 2004, **60**, 4183.

7 (*a*) D. A. Kotadia and S. S. Soni, *J. Mol. Catal. A: Chem.*, 2012, **353**, 44; (*b*) D. Fang, X.-L. Zhou, Z.-W. Ye and Z.-L. Liu, *Ind. Eng. Chem. Res.*, 2006, **45**, 7982; (*c*) Y. Leng, J. Wang, D. Zhu, X. Ren, H. Ge and L. Shen, *Angew. Chem., Int. Ed.*, 2009, **48**, 168; (*d*) A. Sarkar, S. R. Roy, N. Parikh and A. K. Chakraborti, *J. Org. Chem.*, 2011, **76**, 7132; (*e*) B. C. Ranu and S. Banerjee, *Org. Lett.*, 2005, **7**, 3049; (*f*) A. K. Chakraborti and S. Raha Roy, *J. Am. Chem. Soc.*, 2009, **131**, 6902; (*g*) A. K. Chakraborti, S. R. Roy, D. Kumar and P. Chopra, *Green Chem.*, 2008, **10**, 1111; (*h*) W. Liu, S. Gao, C. Feng, X. Zang, X. Zhou, J. Ma and C. Wang, *Chin. J. Org. Chem.*, 2012, **32**, 962; (*i*) P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH Verlag, 2008; (*j*) N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123; (*k*) P. Hallett and T. Welton, *Chem. Rev.*, 2011, **111**, 3508; (*l*) T. L. Greaves and C. J. Drummond, *Chem. Rev.*, 2008, **108**, 206.

8 (*a*) A. C. Cole, J. L. Jensen, I. Ntai, K. L. T. Tran, K. J. Weaver, D. C. Forbes and J. H. Davis, *J. Am. Chem. Soc.*, 2002, **124**, 5962; (*b*) L. Myles, R. G. Gore, N. Gathergood and S. J. Connon, *Green Chem.*, 2013, **15**, 2740; (*c*) A. K. Ressmann, P. Gaertner and K. Bica, *Green Chem.*, 2011, **13**, 1442; (*d*) X. Liu, H. Ma, Y. Wu, C. Wang, M. Yang, P. Yana and U. Welz-Biermann, *Green Chem.*, 2011, **13**, 697.

9 (*a*) D. Kundu, A. K. Bagdi, A. Majee and A. Hajra, *Synlett*, 2011, 1165; (*b*) M. Rahman, A. K. Bagdi, D. Kundu, A. Majee and A. Hajra, *J. Heterocycl. Chem.*, 2012, **49**, 1224; (*c*) M. Rahman, A. Roy, M. Ghosh, S. Mitra, A. Majee and A. Hajra, *RSC Adv.*, 2014, **4**, 6116.

10 (*a*) S. Das, M. Rahman, D. Kundu, A. Majee and A. Hajra, *Can. J. Chem.*, 2010, **88**, 150; (*b*) S. Das, A. Majee and A. Hajra, *Green Chem. Lett. Rev.*, 2011, **4**, 349; (*c*) D. Kundu, A. Majee and A. Hajra, *Green Chem. Lett. Rev.*, 2011, **4**, 205; (*d*) S. Santra, A. Majee and A. Hajra, *Tetrahedron Lett.*, 2011, **52**, 3825; (*e*) M. Rahman, A. Sarkar, M. Ghosh, A. Majee and A. Hajra, *Tetrahedron Lett.*, 2014, **55**, 235.

11 (*a*) K. Asano and S. Matsubara, *Org. Lett.*, 2009, **11**, 1757; (*b*) A. Sarkar, S. R. Roy, D. Kumar, C. Madaan, S. Rudrawar and A. K. Chakraborti, *Org. Biomol. Chem.*, 2012, **10**, 281.

12 ESI.†

13 (*a*) R. A. Sheldon, *Chem. Commun.*, 2008, 3352; (*b*) A. Kamal, V. Srinivasulu, B. N. Seshadri, N. Markandeya, A. Alarifi and N. Shankaraiah, *Green Chem.*, 2012, **14**, 2513.