

RSC Advances



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

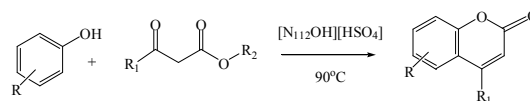
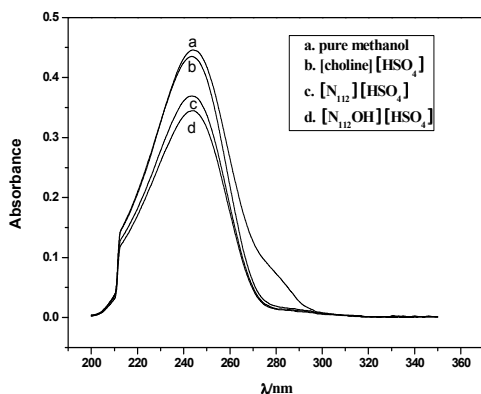
Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Graphic abstract

Cholinium ionic liquids as cheap and reusable catalysts for the synthesis of coumarins via Pechmann reaction under solvent-free condition

Yuehua Zhang, Anlian Zhu, Qianqian Li, Lingjun Li, Yang Zhao, Jianji Wang*

The influence of ionic liquid on the keto/enol tautomeric equilibria of ethyl acetoacetate



The ionic liquid [N₁₁₂OH][HSO₄] was found to be an efficient and reusable catalyst for the Pechmann reaction under solvent-free conditions. The Uv-vis studies suggested the increase of the acidity and the introduction of hydroxyl group to the cation benefit to the existence of keto tautomer of ethyl acetoacetate, which then lead to the excellent performance of [N₁₁₂OH][HSO₄].

Cholinium ionic liquids as cheap and reusable catalysts for the synthesis of coumarins via Pechmann reaction under solvent-free condition

Yuehua Zhang, Anlian Zhu, Qianqian Li, Lingjun Li, Yang Zhao, Jianji Wang*

School of Chemistry and Chemical Engineering, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Normal

University, Xinxiang, Henan 453007, P. R. China

Telephone: +86-0373-3325805; Fax: +86-0373-3329030

jwang@henannu.edu.cn

Abstract: A cheap cholinium ionic liquid N, N'-dimethylaminoethanol hydrosulfate ($[N_{112}OH][HSO_4]$) was found to be an efficient and reusable catalyst for the Pechmann condensation under solvent-free conditions. The coumarin products can be simply separated and the ionic liquid catalyst can be recycled and reused for at least six runs without noticeable decrease in the catalytic activity. The Uv-vis studies suggested the increase of the acidity and the introduction of hydroxyl group to the cation benefit to the existence of keto tautomer of ethyl acetoacetate, which then lead to the excellent performance of $[N_{112}OH][HSO_4]$.

Keywords: cholinium · ionic liquid · Pechmann reaction · coumarin · keto/enol tautomeric equilibrium.

1. Introduction

Coumarin is the core unit of a number of natural products and exhibits various biological activities such as antimicrobial,¹ antithrombotic,² anticancer,³ anti-HIV,⁴ antioxidant⁵ and central nervous system modulating activities.⁶ They have been widely used in pharmaceuticals, perfumes, agrochemicals, and cosmetics. The synthesis of coumarin derivatives has received great attention in the synthetic organic

and medicinal chemistry, and several routes including Pechmann,⁷ Perkin,⁸ Knoevenagel⁹, Reformatsky¹⁰, and Witting reactions¹¹ have been developed. Among these routes, Pechmann reaction is the most widely used method since it proceeds from simple and available starting materials of phenols and β -ketoesters. However, acidic catalysts have to be used such as concentrated H_2SO_4 ¹², P_2O_5 ¹³, trifluoroacetic acid¹⁴, TiCl_4 ¹⁵, $\text{HClO}_4/\text{SiO}_2$ ¹⁶, phosphotungstic acid¹⁷, Nafion resin¹⁸, Al-MCM-41¹⁹, superacidic sulfated zirconia²⁰, superacid-functionalized mesoporous nanocages²¹, nanostructure sulfated tin oxide²², zirconium phosphotungstate²³, SnCl_2 ²⁴, and sulfonic acid-functionalized ionic liquid^{25,26}. Most of these catalytic systems suffered from severe drawbacks such as the use of a large amount of catalyst, frequently long reaction time and low yields, sometimes high-cost for the preparation of catalyst and the difficulty or even impossibility in the catalyst reutilization. Therefore, it is still in great necessary to develop low-cost and highly efficient catalytic systems for the synthesis of coumarins with the possibility to reutilize the catalyst.

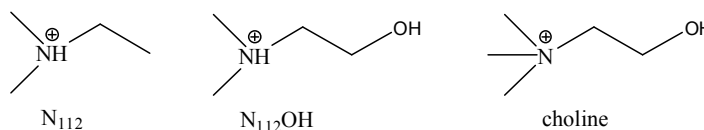
Due to the high biocompatibility, wide resource and low preparation cost, cholinium-based ionic liquids (CILs) have been widely used in electrochemistry²⁷, metal processing²⁸, ionothermal synthesis²⁹, and catalytic procedures³⁰⁻³³. As a continuous work on the utilization of CILs in green catalysis^{30, 32, 33}, the catalytic performance of a series of CILs on the synthesis of coumarins through the Pechmann reaction were investigated in this work. It was found that the existence of hydroxyl group on the cation and the enhancement in the acidity strength of the anions favored the catalytic activity for the Pechmann reaction, and the ionic liquid with acidic anion of hydrogen sulfate and protic cation of N,N-dimethylaminoethanol ($[\text{N}_{112}\text{OH}][\text{HSO}_4]$) was found to be an efficient and reusable catalyst for the synthesis of coumarins under solvent-free conditions. This catalytic system is cheap and affordable with the

advantages of easy experimental and work-up procedures and no use of toxic catalyst and solvents, and the catalyst can be recovered and reused at least six runs without significant activity decrease.

2. Experimental Section

2.1 Materials and methods

All chemicals of AR grade were commercially available and used without further purification. The synthesis methods for the ionic liquids were similar to the procedures reported in our previous work [30, 33]. According to the procedure described in literature [34], the deep eutectic mixtures of choline chloride and diacids were prepared at the molar ratio of 1:1 through simple mixing at 110°C under stirring for 2 hours. Melting points were determined on a XRC-1 Microscopic Melting Point Measurer without correction. ^1H NMR spectra were recorded on a Bruker AV-400 instrument at room temperature by using TMS as internal standard. For easy understanding, chemical structures for the cation of cholinium-based ionic liquids were shown in Scheme 1.



Scheme 1. The cation structure of cholinium-based ionic liquids

2.2 Typical procedures for the Pechmann reaction catalyzed by CILs

A mixture of phenol (2 mmol), ethyl acetoacetate (2.2 mmol) and ionic liquid (0.1 mmol) was added into a 10ml round-bottom flask and stirred at 90°C for the desired reaction time. After the reaction was completed as monitored by TLC, the reaction mixture was cooled to room temperature, and ice-cold water was added to the mixture to precipitate the product. The crude product was then recrystallized from ethanol to

give pure product. The ionic liquids contained in the filtrate can be reused for the next run after the evaporation of water.

2.3 UV-vis experiments

The UV-vis spectra were recorded using a TU-1900 UV-vis spectrometer to detect the keto/enol tautomeric equilibrium of ethyl acetoacetate (EAA). The concentration of EAA in methanol was kept at 5×10^{-4} mol/L, and the molar ratio of EAA to ionic liquid was kept at 1:0.05. The maximum absorbance of the enol tautomer of EAA is at 244nm.

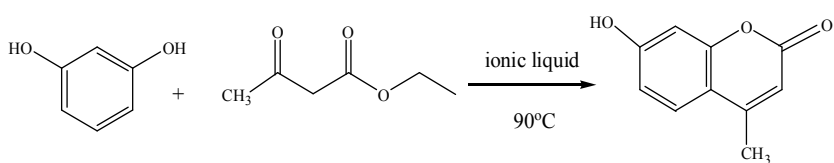
3. Results and discussion

3.1 The catalytic activity of different ionic liquids on the Pechmann reaction

The reaction between resorcinol and EAA was selected as a model system to study the catalytic activity of different ionic liquids on the Pechmann reaction, and the results are collected in Table 1. It was found that the ionic liquids with cholinium cation and weak acidic anions have no significant catalytic activity on the Pechmann reaction (entries 1-3, Table 1), while the ionic liquids with strong acidic anion of $[\text{HSO}_4]^-$ showed moderate catalytic activity and 50% isolated yield could be obtained for the target compound in 12 hours (entry 4, Table 1). This suggests that acidity of the ionic liquids is essential for the Pechmann reaction. Then the catalytic activities of several acidic deep eutectic mixtures based on choline chloride on the Pechmann reaction were also studied (entries 5-7, Table 1). Compared with $[\text{choline}][\text{HSO}_4]$, $[\text{N}_{112}\text{OH}][\text{HSO}_4]$ has stronger acidity³³, thus showing excellent catalytic activity for the Pechmann reaction, and 87% isolated yield has been observed for the target compound within 1.5 hours (entry 8, Table 1). However, the ionic liquids $[\text{N}_{112}\text{OH}][\text{H}_2\text{PO}_4]$ and $[\text{N}_{112}\text{OH}]\text{Cl}$ showed no catalytic activity (entries 9-10, Table 1) although they have the same cation with $[\text{N}_{112}\text{OH}][\text{HSO}_4]$. This is because their

acidity is weaker than the ionic liquid composed with HSO_4^- anion as suggested by their Hammett acidity functions.³³ On the other hand, the ionic liquid composed of $[\text{HSO}_4^-]$ anion and N,N-dimethylethylamine cation ($[\text{N}_{112}][\text{HSO}_4^-]$) can only get 50% isolated yield after 4 hours of reaction (entry 11, Table 1). These results suggest that besides the acidity of the anion, hydroxyl group on the cation of the ionic liquid is also important for the catalysis of this reaction.

Table 1. The catalytic activity of different ionic liquids on the Pechmann reaction.



entry ^{a,b}	Ionic liquid	Reaction time (h)	Isolated yield (%)
1	[choline][Ac]	10	—
2	[choline]Cl	10	—
3	[choline][H ₂ PO ₄]	12	—
4	[choline][HSO ₄]	12	50
5	[choline]Cl/oxalic acid	12	43
6	[choline]Cl/malonic acid	12	40
7	[choline]Cl/succinic acid	12	10
8	[N ₁₁₂ OH][HSO ₄]	2	87
9	[N ₁₁₂ OH][H ₂ PO ₄]	12	—
10	[N ₁₁₂ OH]Cl	10	—
11	[N ₁₁₂][HSO ₄]	4	50

^a The molar ratio of resorcinol to ethyl acetoacetate to ionic liquid was 1:1.1:1, and the reaction was conducted at 90°C.

3.2 The influences of the catalyst amount and reaction temperature on the catalytic activity of ionic liquids

The influence of the catalyst amount on the catalytic activity of $[\text{N}_{112}\text{OH}][\text{HSO}_4^-]$ on the Pechmann reaction was studied and the results were given in Table 2. It was

interesting to find that the catalytic activity of the ionic liquid increased with the decrease of the molar ratio of ionic liquid to resorcinol from 1.5 to 0.05 (entries 1-5, Table 2), while the further decrease in the amount of ionic liquid from 0.05 to 0.02 led to the decrease of the catalytic activity (entry 6, Table 2). This suggests that the optimal molar ratio of ionic liquid to resorcinol should be at 0.05. Then the influence of the temperature on the reaction was studied by using the optimized catalyst amount. It was shown that the decrease in temperature reduced the catalytic activity (entries 6-8, Table 2). However, when the temperature was increased to 120°C, the enhancement in catalytic activity accompanied by the decrease in selectivity (detected by TLC), and only 90% isolated yield was found for the target compound (entry 9, Table 2).

Table 2. The influence of catalyst amount and temperature on the model reaction.

Entry	Molar ratio (ionic liquid: resorcinol)	Reaction temperature(°C)	Reaction time(h)	Isolated yield(%)
1	1.5:1	90	2	86
2	1:1	90	2	87
3	0.5:1	90	3.5	94
4	0.2:1	90	3.5	98
5	0.05:1	90	3	99
6	0.02:1	90	3.5	90
7	0.05:1	60	5.5	75
8	0.05:1	25	5.5	—
9	0.05:1	120	2	90

3.3 The effect of ionic liquid on the keto/enol tautomeric equilibria of EAA and the plausible reaction mechanism for the Pechmann reaction

According to the well accepted reaction mechanism for the acid catalyzed Pechmann reaction, the increased polarization of C=O bond of β -ketoesters would benefit to its reactivity. When it comes to EAA, the polarization change of C=O will affect its keto/enol tautomeric equilibrium. Therefore, we studied the effect of several

ionic liquids with $[\text{HSO}_4]$ anion on the keto/enol tautomeric equilibrium of EAA in methanol and the results are illustrated in Fig 1. It can be seen that when the selected ionic liquids were added to the methanol solution of EAA, absorbance of the enol decreased in the sequence of $[\text{choline}][\text{HSO}_4] > [\text{N}_{112}][\text{HSO}_4] > [\text{N}_{112}\text{OH}][\text{HSO}_4]$. This suggests that the addition of ionic liquid will increase the keto content in the tautomeric equilibrium and ionic liquid $[\text{N}_{112}\text{OH}][\text{HSO}_4]$, which has stronger acidity than $[\text{choline}][\text{HSO}_4]$ and a hydroxyl group on the cation, is the most favorable for the existence of keto. Therefore, a plausible reaction mechanism was proposed and illustrated in Fig. 2. It is suggested that the hydroxyl group on the cation of $[\text{N}_{112}\text{OH}][\text{HSO}_4]$ acts as a hydrogen bond donor to polarize the carbonyl group of EAA and increase keto content of EAA. This makes the carbonyl group more susceptible to the subsequent nucleophilic attacks by resorcinol.

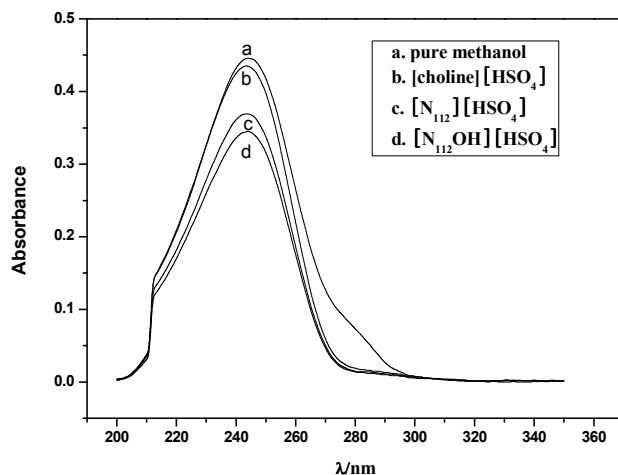


Fig. 1. The influence of ionic liquids on the keto/enol tautomeric equilibria of EAA.

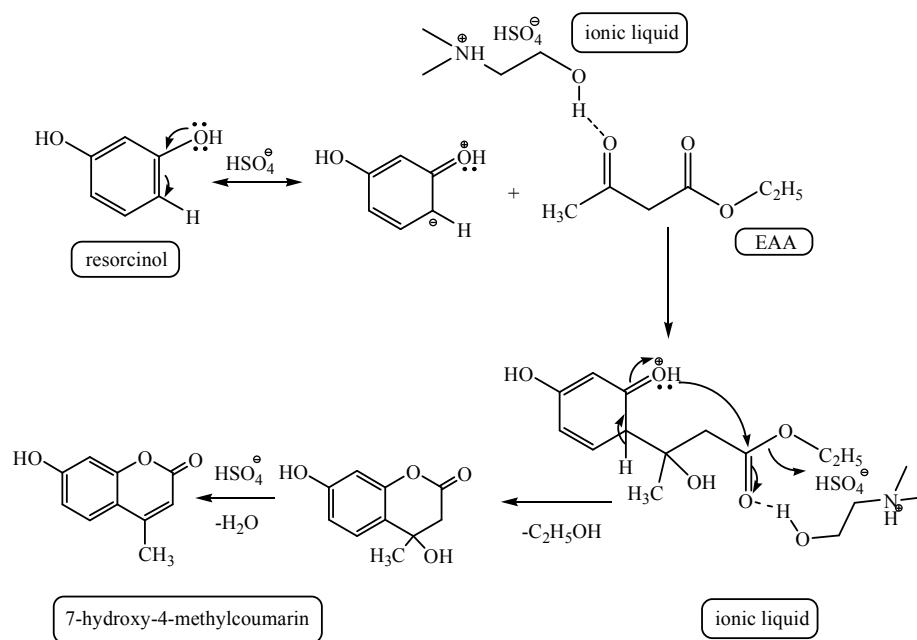


Fig. 2. The plausible reaction mechanism.

3.4 The synthesis of coumarins via Pechmann reaction catalyzed by $[\text{N}_{112}\text{OH}][\text{HSO}_4]$

The reactivity of other phenols with β -keto esters using $[\text{N}_{112}\text{OH}][\text{HSO}_4]$ as catalyst was also investigated and the results were collected in Table 3. It can be seen that dihydric phenol and trihydric phenol can react with EAA smoothly, giving target compound almost quantitative yields (entries 1, 6-7, Table 3), and their corresponding reactions with methyl acetoacetate (MAA) can also arrive at excellent isolated yield (entries 8-10, Table 3). However, the introduce of weak electro-donating group such as methyl group led to the decrease of catalytic activity (entries 4-5, Table 3), and the reactivity of monohydric phenol with electro-withdrawing groups such as $-\text{NH}_2$ and $\text{CH}_3\text{O}-$ are also lowered compared with dihydric phenol and trihydric phenol (entries 2-3, Table 3). The reaction between resorcinol and other keto ester such as ethyl 2-methylacetoacetate (EMAA) can also give moderate yield under the same catalytic

conditions (entry 12), but its reaction with methyl 4-methoxyacetoacetate (MMOAA) only proceed with low yield.

Table 3. The synthesis of coumarins derivatives.

Entry	Phenols	β -keto ester	Reaction temperature (°C)	Reaction time (h)	Isolated yield (%)
1 ^a		EAA	90	3	99
2 ^a		EAA	90	7	70
3 ^a		EAA	90	8	50
4 ^a		EAA	90	24	63
5 ^b		EAA	90	6	95
6 ^b		EAA	90	6	98
7 ^b		EAA	120	7	99
8 ^a		MAA	90	6	90
9 ^a		MAA	90	6	92

10 ^b		MAA	120	6	85
11		EMAA	90	8	65
12		MMOAA	90	8	20

^a The molar ratio of ionic liquid to phenol was 0.05:1; ^b The molar ratio of ionic liquid to phenol was 0.5:1.

3.5 The reusability of [N₁₁₂OH][HSO₄] catalyst in Pechmann reaction

After the reaction was completed, the recovered ionic liquid catalyst [N₁₁₂OH][HSO₄] from the filtrate was concentrated by rotary evaporation, dried under vacuum at 50°C and then utilized for the next run of Pechmann reaction between resorcinol and EAA. It was found from Fig. 3 that there was no significant activity decrease after six runs for the model reaction.

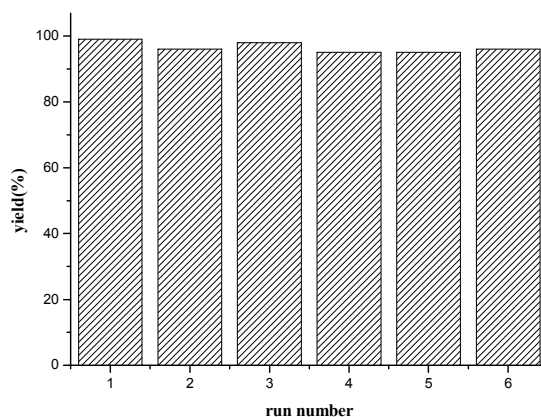


Fig. 3. The reutilization of [N₁₁₂OH][HSO₄].

4. Conclusions

In summary, the catalytic activities of a series of cholinium-based ionic liquids on the Pechmann reaction were investigated, and a cheap and reusable ionic liquid,

[N₁₁₂OH][HSO₄], was found to be an highly efficient catalyst for the Pechmann condensation reaction under solvent-free condition. The excellent catalytic performance of [N₁₁₂OH][HSO₄] on the Pechmann reaction was suggested to come from the hydrogen bond activation effect of the cation and the acidity of the anion. This catalytic methodology benefits from several green aspects such as no use of toxic catalysts and solvents, ease of preparation, recovery and reutilization of the catalyst, simple experimental procedure and high chemoselectivity. Further work about the utilization of this class of ionic liquids to catalyze other organic transformations is in progress in our laboratory.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21373079, 21003039).

References

1. S.V. Laxmi, B.S. Kuarm, B. Rajitha, *Med. Chem. Res.*, 2013, **22**, 768.
2. A.K. Mitra, A. De, N. Karchaudhuri, S.K. Misra, A.K. Mukhopadhyay, *J. Indian Chem. Soc.*, 1998, **75**, 666.
3. C. J. Wang, Y. J. Hsieh, C.Y. Chu, Y.L. Lin, T.H. Tseng, *Cancer Lett.*, 2002, **183**, 163.
4. I. Kostova, *Curr. HIV Res.*, 2006, **4**, 347.
5. C. Xiao, X.Y. Luo, D.J. Li, H. Lu, Z.Q. Liu, Z.G. Song, Y.H. Jin, *Eur. J. Med. Chem.* 2012, **53**, 159.
6. M. Noeldner, H. Hauer, S.S. Chatterjee, *Drugs Future*, 1996, **21**, 779.
7. H. von Pechmann, C. Duisberg, *Chem. Ber.*, 1984, **17**, 929.
8. J. R. Johnson, *Org. React.*, 1942, **1**, 210.
9. G. Jones, *Org. React.*, 1967, **15**, 204.
10. R. L. Shriner, *Org. React.*, 1942, **1**, 1.
11. I. Yavari, R. Hekmat-Shoar, A. Zonouzi, *Tetrahedron Lett.*, 1998, **39**, 2391.
12. E.C. Horning, *Organic Synthesis*, vol. 3, Wiley, New York, 1955, p. 281.
13. F.W. Canter, F.H. Curd, A. Robertson, *J. Chem. Soc.*, 1931, 1245.

14. L.L. Woods, J. Sapp, *J. Org. Chem.*, 1962, **27**, 3703.
15. H. Valizadeha, A. Shockravi, *Tetrahedron Lett.*, 2005, **46**, 3501.
16. M. Maheswara, V. Siddaiah, G.L.V. Damu, Y.K. Rao, C. V. Rao, *J. Mol. Catal. A: Chem.*, 2006, **255**, 49.
17. R.S. Keri, K.M. Hosamani, H.R.S. Reddy, *Catal. Lett.*, 2009, **131**, 321.
18. R. Hinze, M.C. Laufer, W.F. Hoelderich, W. Bonrath, T. Netscher, *Catal. Today*, 2009, **140**, 105.
19. S. Sudha, K. Venkatachalam, S. Vishnu Priya, J. Herbert Mabel, M. Palanichamy, V. Murugesan, *J. Mol. Catal. A: Chem.*, 2008, **291**, 22.
20. G.D. Yadav, N.P. Ajgaonkar, A. Varma, *J. Catal.*, 2012, **292**, 99.
21. P. Kalita, B. Sathyaseelan, A. Mano, S.M. Javaid Zaidi, M.A. Chari, A. Vinu, *Chem. Eur. J.*, 2010, **16**, 2843.
22. A. I. Ahmed, S. A. El-Hakam, A.S. Khder, W.S.A. El-Yazeed, *J. Mol. Catal. A: Chem.*, 2013, **366**, 99.
23. S. Ghodke, U. Chudasama, *Appl. Catal. A: Gen.*, 2013, **453**, 219.
24. K.K. Upadhyay, R.K. Mishra, A. Kumar, *Catal. Lett.*, 2008, **121**, 118.
25. S. Das, A. Majee, Al. Hajra, *Green Chem. Lett. Rev.*, 2011, **4**, 349.
26. N.G. Khaligh, *Catal. Sci. Technol.*, 2012, **2**, 1633.
27. C.A. Nkuku, R.J. LeSuer, *J. Phys. Chem. B*, 2007, **111**, 13271.
28. A.P. Abbott, G. Frisch, J. Hartley, K. S. Ryder, *Green Chem.*, 2011, **13**, 471.
29. E. R.Cooper, C.D. Andrews, P.S. Wheatley, P.B. Webb, P. Wormald, R.E. Morris, *Nature*, 2004, **430**, 1012.
30. A.L. Zhu, R.X. Liu, L.J. Li, L.Y. Li, L.Wang, J.J. Wang, *Catal.Today*, 2013, **200**, 17.
31. A.P. Abbott, T.J. Bell, S. Handa, B. Stoddart, *Green Chem.*, 2005, **7**, 705.
32. A.L. Zhu, L.J. Li, J.J. Wang, K.L. Zhuo, *Green Chem.*, 2011, **13**, 1244.
33. A.L. Zhu, Q.Q. Li, L.J. Li, J.J. Wang, *Catal. Lett.*, 2013, **143**, 463.
34. A.P. Aboott, D. Boothby, G. Capper, D.L. Davies, R.K. Rasheed, *J. Am. Chem. Soc.*, 2004, **126**, 9142.