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Ionic Liquid Catalyzed One Pot Four Component Synthesis of Pyranopyrazoles

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ABSTRACT

The solvent used for this reaction is ionic liquid and there are ecologically friendly, safe, non-toxic, non-flammable, clean as well as readily available these compounds have various application in food industry as a safe preservative and antimicrobial agent. In the pyranopyrazole the pyrazole contains two nitrogen atom and these are adjacent to each other. The pyrazole rings are five membered and unsaturated with nitrogen atom adjacent to each other. The pyran and its derivative are the important part of natural products. These compounds are mainly synthesized using one pot, multicomponent processes. The advantage of multicomponent reaction is to synthesize active product easily within a short period of time. The condensation of aldehyde, active methylene compounds and hydrazine's leads to the formation of pyranopyrazoles. The development of new cheap and ecofriendly process by using these catalysts is possible. The reaction is focused on non-hazardous ionic liquid catalyzed synthesis. These are multicomponent reactions and sustainable development of chemical enterprise. In this reaction liquid acid catalyst used for the carry on the reaction to form the final product.

Keywords: Hydrazine hydrate, Ethyl acetoacetate, Malano nitrile, Concerted mechanism

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INTRODUCTION

Heterocyclic compound is class of ring compound; there are several derivative of pyranopyrazole. These are found in numerous natural product and synthetic compound with medicinal value. These have several applications in functional material and display a broad spectrum of biological and pharmacological activities such as fungicides, insecticides, herbicides, antibacterial, antimicrobial etc. Malaria is the one of serious disease and millions of population is infected by this disease [1-9]. These drugs have relieved human suffering from this disease. Pyranopyrazole have successful antimalarial activity.

In the recent year's ionic liquid have become powerful organic solvent due to their particular properties. These ionic liquid are readily recycled. The heterogenation of catalyst and reactant have important handling, separation and reuse procedures [10-16].

The heterocyclic compound is branch of organic chemistry and contains organic containing compound. The cyclic compound contains only carbon then they are known as carbocyclic compound. If one of the carbon atoms is replaced by hetero atom then these are known as heterocyclic compound. The most common heterocyclic compound contains N, S, O etc. The enormous number of heterocyclic compounds are aliphatic as well as aromatic. The aliphatic heterocyclic compounds amines, ester, amides and their property depends upon strain of ring. The larger rings are up to 5-7 and smaller rings up to 3-4. Aromatic heterocyclic compound contain benzene rings like properties as well as they obey Huckels rule [17-23].

Most of heterocyclic compounds are the building blocks of our genes like purine, pyrimidine ring structure. In chlorophyll and heme compound compounds are important class of heterocyclic compound. Heterocycles are present in most of the drug like vitamin, natural product, anti-inflammatory, anticancer, antimicrobial, antifungal, anti-viral, herbicides and insecticidal agents. Heterocyclic compound are structural unit of pharmaceutical and agrochemicals. These are also useful for synthesis of dyestuff, brightening agent, plastics and various reagents. These are also wide application in the polymer chemistry [24] and also useful for semiconductors, superconductors, photovoltaic cells, diodes etc.

Alkaloids are the major group of heterocyclic compound because they contains basic nitrogen compound. Alkaloids like indole and its derivative are more useful for the growth hormone; while quinoline is the antimalarial activities and triazole are the antifungal drug. Various natural amino acids are heterocycles and they contain many essential vitamins.

The wide application of heterocyclic compounds for the synthesis of pharmaceutical drugs. Various drugs are synthesized in the industrial sector.

Heterocyclic compounds are various types like pharmaceuticals, agrochemicals. These are used in the rocket propellants. Some of the heterocyclic compounds are rapidly reacts with electrophilic reagents and some of them react with nucleophilic reagents [25].

Heterocyclic compound are resist to reduction but easily oxidized. Many of the heterocyclic compounds have major biological significance. The indole and pyrrole have most application in pharmaceutical area. Furan rings is common in many naturally occurring in the terpenoids compounds. A number of simple pyridine is used in the treatment of muscular transmutation. These are also anticancer activities and other biological property [26].

The fusion of five and six membered rings shows useful property in pharmacologically active. The activity of the heterocyclic compound in biologically system is important for natural product. These have also rapid research area in medical chemistry.

Heterocyclic compound is class ring compound. There are several derivatives of pyranopyrazoles. There are formed in numerous natural products and synthetic compound with medicinal value. These have several applications in functional materials. These have display a broad spectrum of biological and pharmacological activities such as fungicides, insecticides, antibacterial and antimicrobial. Malaria is one of the most serious disease millions of population is infected by this disease these only have relived human suffering from this disease. These drugs have successful antimalarial activity.

In the organic chemistry, there are various uses of solvents. These solvents are very sensitive to the environmental due to their toxic nature affecting living bodies. To avoid such toxic solvents, the reactions can be conducted with the help of catalyst like ionic liquid or biocatalyst etc which are not harmful to environment [28-36].

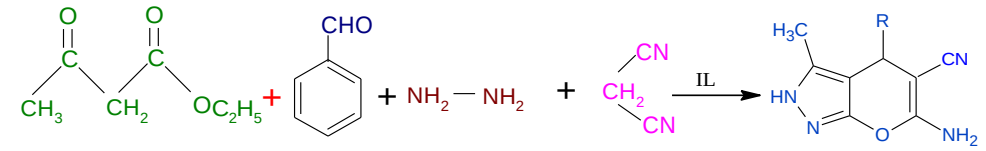
With the growing awareness in the society recyclable, ecofriendly and bio-based products are getting more preference. The traditional catalyst like H_2SO_4, HCl which are acidic catalyst or base catalyst like NaOH can be replaced with ecofriendly bio-catalyst like ionic liquid which serve as acidic as well as basic catalyst.

These bio-catalyst reactions can be carried with microwave and ultrasound. The main aim of green chemistry is to get higher yield, lower waste and avoid uses of solvents.

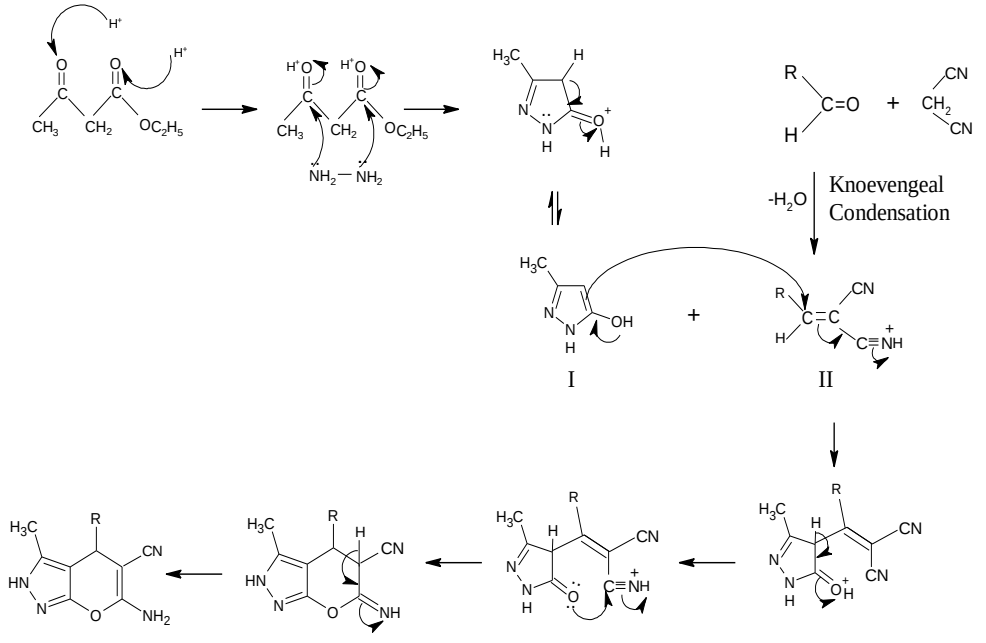
MATERIALS AND METHODS

To prepare the Pyranopyrazole, following methodology was employed. In a round bottom flask hydrazine hydrate, ethyl acetoacetate and malano nitrile are added along with ionic liquid [H-NMP][$MeSO_3$] as a catalyst. The flask was heated up to 75ºC with heater having magnetic stirrer for 80 min. The development of reaction was monitored over the TLC.

On completion of reaction time, the crude product was formed in the flask. The crude product is then separated by filtration. The residue of filtration then washed with distilled water. The washed material then dried at room temperature. The final product then re-crystalized by using ethanol.



Reaction

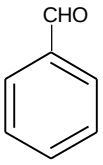
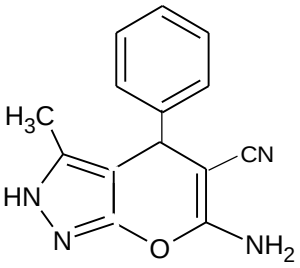
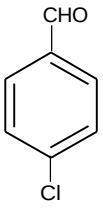
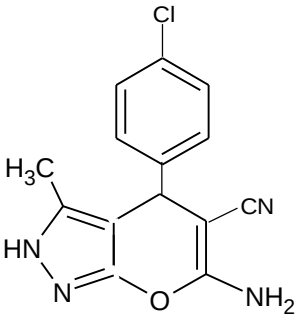
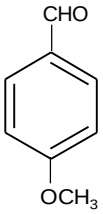
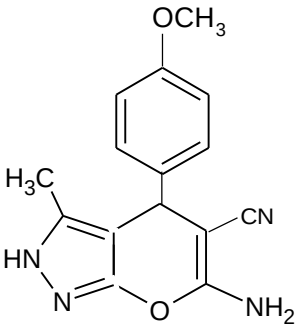
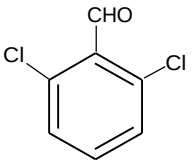
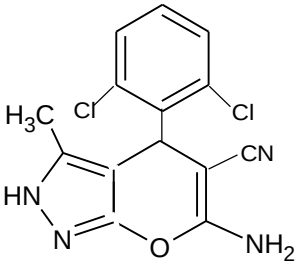
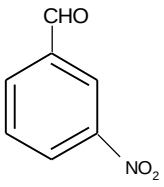
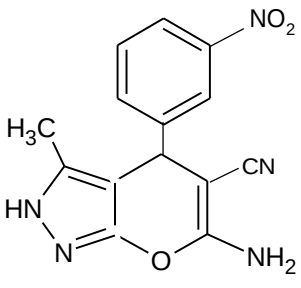


Mechanism

RESULTS AND DISCUSSION

The mixing of equimolar amount of hydrazine hydrate, ethyl acetoacetate, malano nitrile and ionic liquid produces final product pyranopyrazole. We use different aldehyde give different percentage of product. There is presence of one tatomer indicated by using ^{1}H NMR and ^{13}CNMR spectrums. IR indicates involvement of cyano functional group. The reaction is not possible in water. The synthesis of biologically active heterocyclic compound by using ionic liquid [H-NMP][$MeSO_3$]. In one pot four components utilizes hydrazine hydrate, ethyl acetoacetate, malano nitrile and ionic liquid used as a catalyst. All the products were confirmed by using spectral characterization.

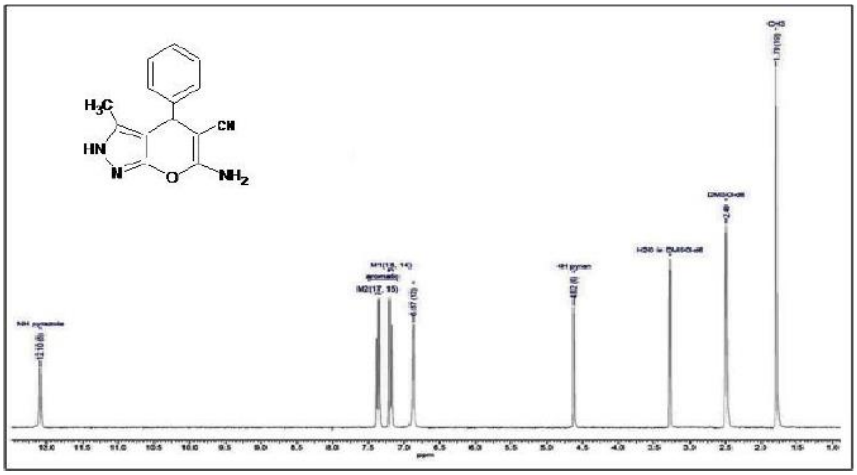
Synthesis of pyranopyrazoles

Entry	Aldehyde	Product	Time in min.	Yield (%)
1			90	60
2			70	75
3			70	75
4			80	70
5			80	70

Spectral data of synthesized compounds

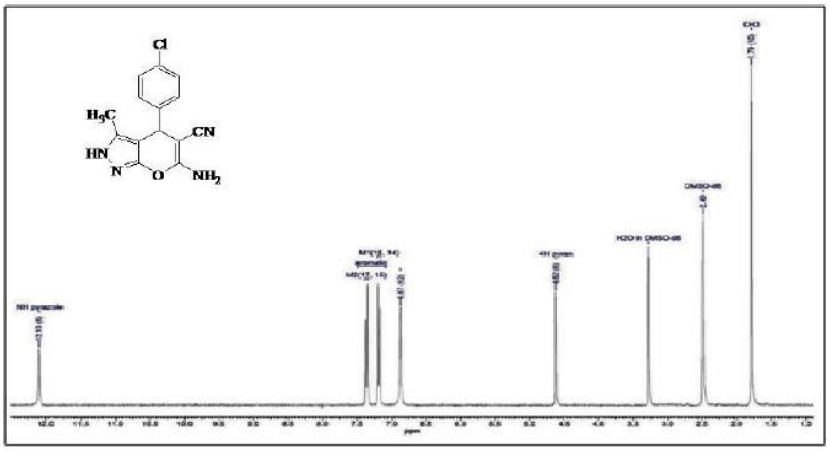
1) 6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

White powder, m.p. 244-246ºC; IR (KBr): υ=3371, 3248, 2192, 1613, 1445 cm^{-1}; ^1H NMR (300, $CDCl_3$): δ = 1.79 (s, 3H), 4.85 (s, 1H), 6.91 (bs, 2H), 7.18–7.35 (m, 5H), 12.13 (bs, 1H); MS (ESI): *m/z*=252 (M^+).



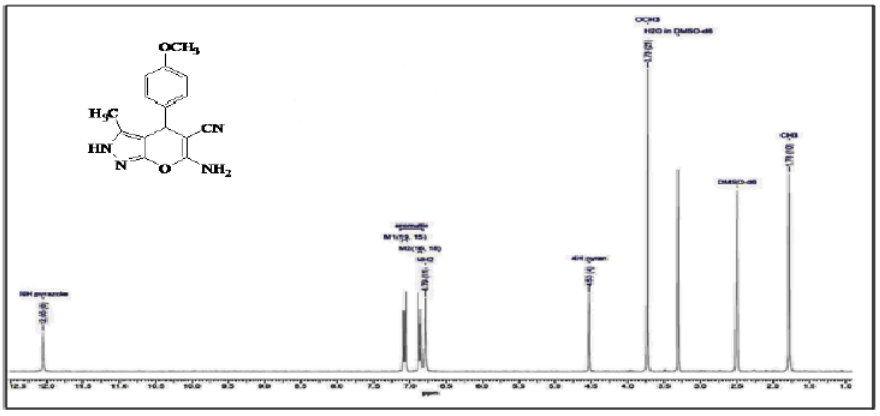
2) 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

IR(KBr): υ=3368, 3312, 3176, 2192, 1648, 1600 cm^{-1}; ^1H NMR (300, $CDCl_3$): δ=1.79 (s, 3H), 4.62 (s, 1H), 6.87 (bs, 2H), 7.19 (d, 2H, *J*=8.4 Hz), 7.36 (d, 2H, *J*=8.2 Hz), 12.10 (bs, 1H); MS (ESI): *m/z*=286 (M^+).



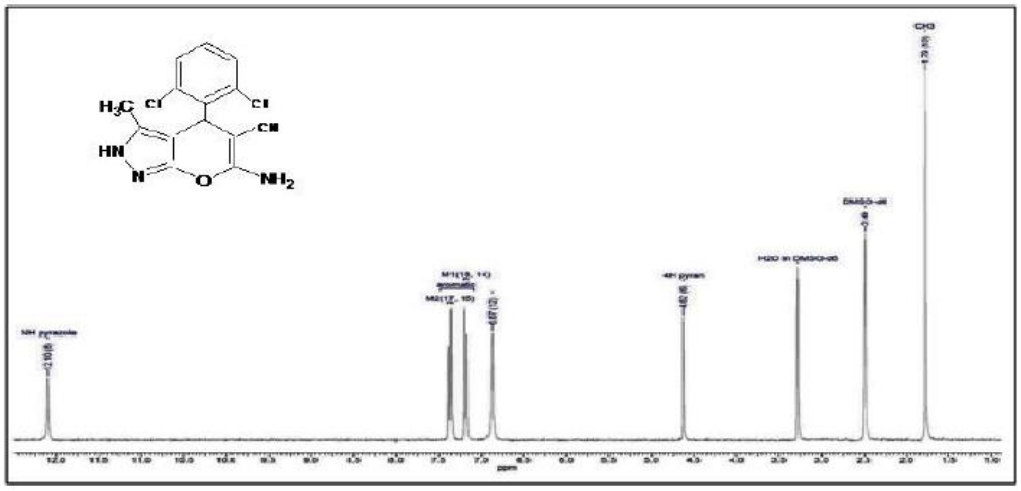
3) 6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

White solid, m.p. 210-212 ºC; IR (KBr): υ=3372, 3320, 3192, 2200, 1644, 1592 cm^{-1}; ^1H NMR (300, $CDCl_3$): δ=1.78 (s, 3H), 3.73 (s, 3H), 4.53 (s, 1H), 6.79 (bs, 2H), 6.87 (d, 2H, *J*=8.8 Hz), 7.07 (d, 2H, *J*=8.8 Hz), 12.05 (bs, 1H); MS (ESI): *m/z*=175 (M^+).



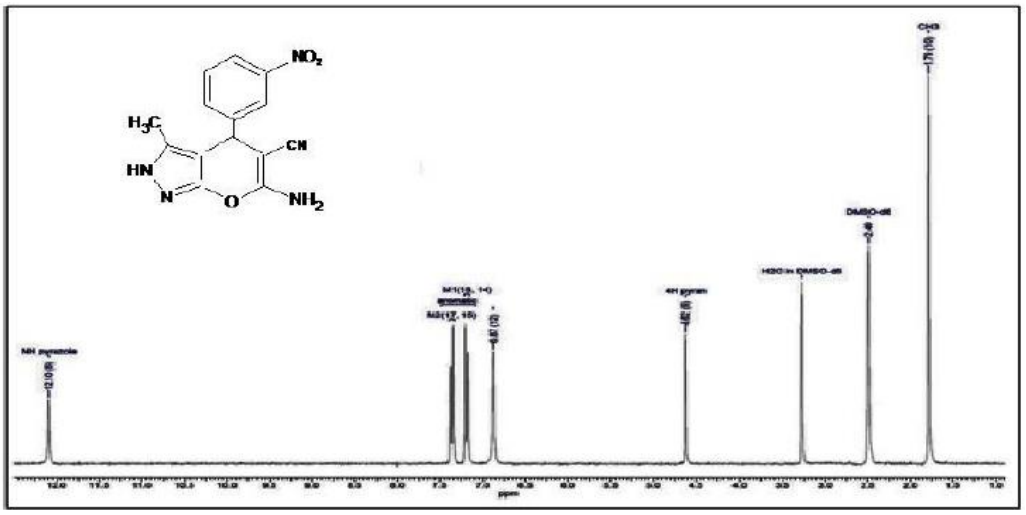
4) 6-Amino-4-(2,4-dichlorophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

White solid, m.p. 196-198ºC; IR (KBr): υ=3422, 3240, 2190, 1610, 1424, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.82 (s, 3H), 4.80 (s, 1H), 7.05 (bs, 2H), 7.18 (d, J=8.4 Hz, 1H), 7.33 (d, J=8.4 Hz, 1H), 7.86 (s, 1H), 12.18 (bs, 1H); MS (ESI): *m/z*=307 (M^+).



5) 6-Amino-3-methyl-4-(3-nitro-phenyl)-2,4, dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile

Brown solid, m.p. 214-216ºC; IR (KBr): υ=3385, 3278, 2189, 1622, 1456 cm^{-1}; ^1H NMR (300, $CDCl_3$): δ=1.83 (s, 3H), 4.98 (s, 1H), 6.95 (bs, 2H), 7.84 (s, 1H), 7.78 (d, *J* =8.4 Hz, 1H), 7.42-7.45 (m, 2H), 12.16 (bs, 1H); MS (ESI): *m/z* = 297 (M^+).



CONCLUSION

It is concluded that, the synthesis of pyranopyrazole through one pot four components method in the presence of ionic liquid as a biocatalyst. The reaction followed is eco-friendly as ethanol is used as an organic solvent and ionic liquid used as a biocatalyst to conduct the reaction. The advantages of this kind of reactions are clean, short time, high yielding and easily purificable. Moreover the reaction procedure is very simple and easy to workup. Hence it can be used for large scale production of pyranopyrazole in eco-friendly manner.

REFERENCES

[1] S. Narayan, M. Fokin, H. Kolb, K. Sharpless, *Angew. Chem. Int. Ed*., **2005**, 44, 3275.
[2] J.H. Clark, *Acc. Chem. Res*., **2002**, 35, 791.
[3] I.V. Kozhevnikov, *Chem. Rev*., **1998**, 98: 171.
[4] I.V. Kozhevnikov, E. Derouane, Wiley: NY, USA, **2002**.
[5] G.P. Romanelli, D. Bennardi, D.M. Ruiz, G. Baronetti, H.J. Thomas, J.C. Autino, *Tetrahedron. Lett*., **2004**, 45, 8935.
[6] A. Sharanin Yu, L.G. Sharanina, V.V. Puzanova, *Zh. Org. Khim*., **1983**, 19, 2609.
[7] G. Vasuki, K. Kumaravel, *Tetrahedron Lett*., **2008**, 49, 5636.
[8] E.A.A. Hafez, M.H. Elnagdi, A.G.A. Elagamey, F.M.A.A. Ei-Taweel, *Heterocycles*., **1987**, 26, 03-907.
[9] D. Armetso, W.H. Horspool, N. Martin, A. Ramos, C. Seaone, *J. Org. Chem*., **1989**, 54, 3069- 3072.
[10] I. Kanizsai, S. Gyónfalvi, Z. Szadonyi, R. Sillanpaa, F. Fülöp, *Green Chem*., **2007**, 9, 357.
[11] H. Junek, H. Aigner, *Chem. Ber*., **1973**, 106, 914-921.
[12] H.H. Otto, *Arch. Pharm*., 307, 444-447.
[13] D. Tejedor, F. Garcia-Tellado, *Chem. Soc. Rev*., **2007**, 36, 484.
[14] I. Ugi, *Pure Appl. Chem*., **2001**, 73, 187.
[15] F. Lie'by-Muller, C. Simon, T. Constantieux, J. Rodriguez, *Comb. Sci*., **2006**, 25, 432.
[16] C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem*., **2004**, 4957.
[17] M. Pirrung, K. Das Sarma, *Tetrahedron*., **2005**, 61, 11456.
[18] N. Evdokimov, A. Kireev, A. Yakovenko, M. Antipin, I. Magedov, A. Kornienko, *J. Org. Chem*., **2007**, 72, 3443.
[19] L. Weber, *Drug Discovery Today.*, 2002, 7, 143.

[20] C. Hulme, V. Gore, *Curr. Med. Chem*., **2001**, 10, 51.
[21] C. Herrerias, X. Yao, Z. Li, C. Li, *Chem. Rev*., **2007**, 107, 2546.
[22] V. Bonifacio, *Org. Chem. High*., **2005**.
[23] J. Kljin, J. Engberts, *Nature*., **2005**, 435, 746.
[24] M. Pirrung, K. Das Sarma, *J. Am. Chem. Soc*., **2004**, 126, 444.
[25] H. Junek, H. Aigner, *Chem. Ber*., **1973**, 106, 914.
[26] H. Wamhoff, E. Kroth, K. Strauch, *Synthesis*., **1993**, 11, 1129
[27] H. Hailes, *Org. Process. Res. Dev*., **2007**, 11, 114.
[28] J. Holbrey, K. Seddon, *Chem. J. Soc. Dalton Trans*., **1999**, 2133.
[29] T. Welton, *Chem. Rev*., **1999**, *99*:2071.
[30] M. Earle, P. McCormac, K. Seddon, *Green Chem*., **1999**, 1, 23.
[31] M. Reetz, W. Iesenhöfer, G. Franciò, W. Leitner, *Chem. Commun*., **2002**, 992.
[32] Y. Gu, C. Ogawa, S. Kobayashi, *Org. Lett*., **2007**, 9, 175.
[33] H. Olivier-Bourbigou, L. Magna, *Mol. Catal. J. A: Chem*., **2002**, 182.
[34] R. Noyori, *Chem. Rev*., **1999**, 99: 353.
[35] J. Chen, K. Spear, J. Huddleston, R. Rogers, *Green Chem*., **2005**, 7, 64.
[36] I. Horv´ath, *Acc. Chem. Res*., **1998**, 31, 641.