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Diels–Alder reactions in pyridinium based ionic liquids

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Abstract—Diels–Alder reactions have been investigated in pyridinium based ionic liquids. These solvents are found to be more effective compared to the organic solvent studied, in enhancing the reaction rate and product yields. Recycled ionic liquids also gave excellent results.

1. Introduction

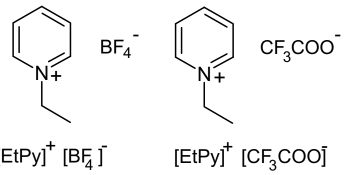
Diels–Alder reaction is one of the most important tools for carbon–carbon bond formation. It is a widely used reaction in organic synthesis,[1] and in the chemical industry.[2] It is well established that the reactivity and selectivity of Diels–Alder reactions are strongly influenced by the Lewis acidity of the medium. Therefore, the reaction has been investigated using water,[3] surfactants,[4] lithium amides,[5] alkylammonium nitrate,[6] borane–THF complex,[7] etc., and rate enhancement has been seen in different solvents and catalysts systems. Considering the practical importance and wide applications of Diels–Alder reaction in organic synthesis and chemical industry, lately an increased attention has been focused on the development of 'green' methods for the purpose of improving rate and selectivity of this reaction.

In recent years, ionic liquids have gained a lot of attention as green solvents in organic synthesis and other chemical processes. This is mainly due to their favorable inherent properties such as chemical and thermal stability, no measurable vapor pressure, nontoxicity, nonflammability, catalytic ability, high polarity, ease to recycle, etc.[8–10] As such, they have been investigated as reaction media in many organic and organometallic syntheses such as Heck reactions,[11] Friedel–Crafts reactions,[11] alkylation,[11] hydrogenation,[12] hydroformylation,[12] dimerization,[13] condensation,[14] acylative cleavage of cyclic and acyclic ethers,[15] and polymerization.[16] As highly ordered media with environmentally friendly properties, ionic liquids have the potential to influence the outcome of Diels–Alder reaction. There have been reports on the use of ionic liquids for Diels–Alder reactions.[17–24] However, all these studies have focused only on solvents derived from imidazole. Here we wish to report the first study on the application of pyridinium based ionic liquids as solvent for the Diels–Alder reaction.

2. Results and discussion

The utility of two ionic liquids (Scheme 1) namely, 1-ethyl-pyridinium tetrafluoroborate ($[EtPy]^+[BF_4]^-$) and 1-ethyl-pyridinium trifluoroacetate ($[EtPy]^+[CF_3COO]^-$) was investigated in reactions of isoprene (**1**) with acrylonitrile **2**, acrylic acid **3**, and methacrylic acid **4** (Scheme 2).

In a typical reaction,[25] the diene (**1**) and the dienophile (**2**, **3**, **4**) were added to the ionic liquid directly, and the mixture was stirred (400 rpm) at the desired reaction



Scheme 1. Pyridinium based ionic liquids studied.

Keywords: Ionic liquid; Diels–Alder reaction; 1-Ethyl-pyridinium tetrafluoroborate; 1-Ethyl-pyridinium trifluoroacetate.

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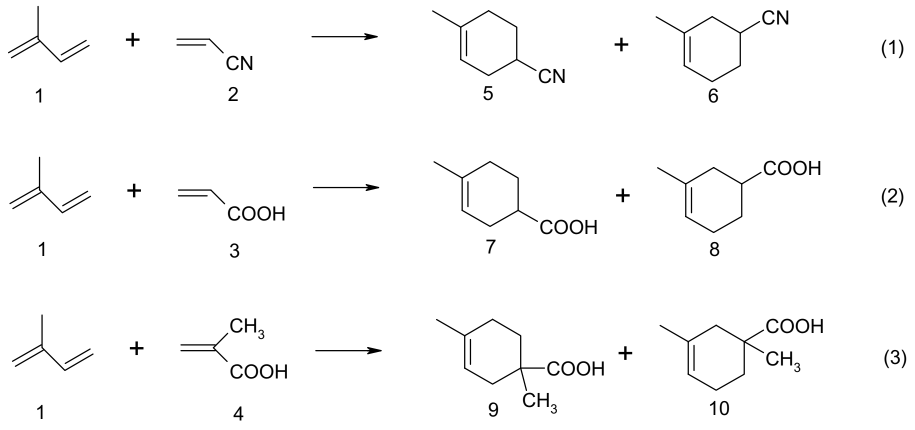


Scheme 2. Reactions of isoprene with different dienophiles.

temperature for the specified time period. The molar ratio of isoprene–dienophile–ionic liquid is 1.5:1:1. All reactions are heterogeneous in nature. At the end of the reaction, organic layer could be easily decanted from the ionic liquid, and any organic residues removed by extraction with ether. The purified ionic liquid could be reused without loss of activity. As shown in Scheme 2 (Eqs. 1–3), both '*para* like' (**5**, **7**, **9**) and '*meta* like' (**6**, **8**, **10**) products were obtained in each case. However, in all cases the major products are '*para* like'. Table 1 shows the results of reaction of isoprene with various dienophiles.

As data show, the reaction rate and yields of Diels–Alder reaction are dependent on the solvent. An initial study of reactions carried out in CH_2Cl_2 as solvent gave low product yields (entries 1, 7, 13), indicating the need for a polar medium for the reaction. These observations and results of our earlier studies,[27,28] prompted us to investigate this reaction in pyridinium based ionic liquids. The ionic liquids were prepared following a method reported earlier in the literature.[29] A comparison of the results with literature data of reactions using borane–THF complex (entries 8, 14), improved yields were obtained using ionic liquids in relatively short reaction period. Also, much better yields were obtained using our reaction protocol, compared to the other ionic liquids for the same system reported in the literature (entry 2). When $[EtPy]^+[BF_4]^-$ was used as solvent medium the reaction occurred slowly, but at a relatively faster rate than seen in CH_2Cl_2. The same reactions when carried out in $[EtPy]^+[CF_3COO]^-$, occurred rapidly with much higher product yields. Interestingly though, as the reaction is continued beyond 2 h there is a decrease in '*para*/*meta* like' product ratio, while overall yield of the combined products increased. This was true in case of all reactions irrespective of the ionic liquid used. Figure 1 shows the effect of various solvents on the rate of reac-

Table 1. Diels–Alder reactions of isoprene **1** with dienophiles at 20 °C

Entry	Solvent	Dienophile	Time (h)	Yield[a] (%)	Selectivity[a] ('*para* like':'*meta* like')
1	CH_2Cl_2	Acrylonitrile, **2**	72	12	64:36
2[c]	Phosphonium tosylates	Acrylonitrile, **2**	24	38	69:31[b]
3	$[EtPy]^+[CF_3COO]^-$	Acrylonitrile, **2**	2 (24)	90 (97)	89:11[b] (75:25)
4	$[EtPy]^+[CF_3COO]^-$	Acrylonitrile, **2**	72	99	75:25
5	$[EtPy]^+[BF_4]^-$	Acrylonitrile, **2**	2 (24)	42 (64)	84:16[b] (66:34)
6	$[EtPy]^+[BF_4]^-$	Acrylonitrile, **2**	72	83	58:42
7	CH_2Cl_2	Acrylic acid, **3**	72	27	70:30
8[d]	Borane–THF + CH_2Cl_2	Acrylic acid, **3**	30	75	—
9	$[EtPy]^+[CF_3COO]^-$	Acrylic acid, **3**	2 (24)	97 (98)	95:5[b] (85:15)
10	$[EtPy]^+[CF_3COO]^-$	Acrylic acid, **3**	72	98	80:20
11	$[EtPy]^+[BF_4]^-$	Acrylic acid, **3**	2 (24)	32 (50)	82:18[b] (65:35)
12	$[EtPy]^+[BF_4]^-$	Acrylic acid, **3**	72	55	62:38
13	CH_2Cl_2	Methacrylic acid, **4**	72	5	58:42
14[e]	Borane–THF + CH_2Cl_2	Methacrylic acid, **4**	68	66	—
15	$[EtPy]^+[CF_3COO]^-$	Methacrylic acid, **4**	2 (24)	55 (64)	62:38 (54:46)
16	$[EtPy]^+[CF_3COO]^-$	Methacrylic acid, **4**	72	67	1:1[b]
17	$[EtPy]^+[BF_4]^-$	Methacrylic acid, **4**	24	18	66:34
18	$[EtPy]^+[BF_4]^-$	Methacrylic acid, **4**	72	22	55:45[b]

[a] Determined by GC.

[b] Ratio determined by ^1H NMR.

[c] Ref. 26, 80 °C.

[d] Ref. 7, 0 °C.

[e] Ref. 7.

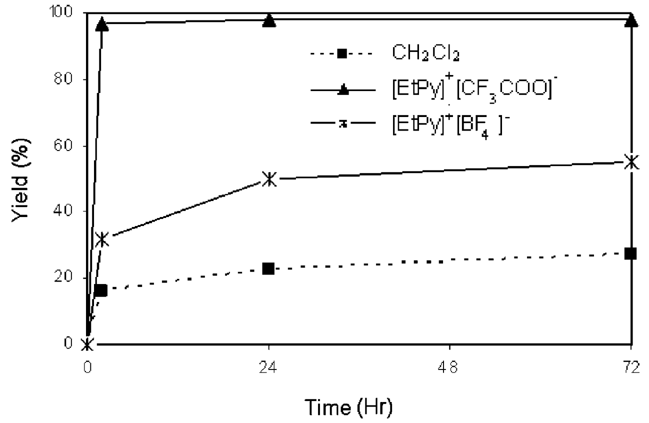


Figure 1. Diels–Alder reactions of isoprene with acrylic acid in different solvents at 20 °C.

tion between isoprene and acrylic acid at 20 °C. In each solvent initially the reaction occurs rapidly and there is only little change with prolonged time period. Ionic liquid $[EtPy]^+[BF_4]^-$ has an effect in enhancing the rate of reaction. However, $[EtPy]^+[CF_3COO]^-$ seems to be ideal and has the greatest effect on increasing the reaction rate.

The varied effect on the rate could be attributed to the difference in coordination of cation and anion in these two solvents. As Lewis acids, ionic liquids form complex with the substituents (such as –C(O)R and –CN) on dienophiles. A complexed dienophile is then more reactive toward diene. The complexation accentuates both the energy and orbital distortion effects of the substituents and, therefore, enhances both the selectivity and reactivity of dienophiles. In other words, the interaction between dienophile and ionic liquid increases the coefficient of C-2 in lowest unoccupied molecular orbital (LUMO) of dienophile and make it more efficient to react with C-1 in highest occupied molecular orbital (HOMO) of isoprene as shown in Scheme 3. Hence, there is a change in the ratio of '*para* like' to '*meta* like' products.

Similarly, due to its inductive effect the methyl group makes the methacrylic acid relatively less electrophilic than acrylic acid. As a result overall yields are lower than those seen in the case of reaction with acrylic acid. We further investigated the effect of temperature on Diels–Alder reaction in ionic liquid $[EtPy]^+[CF_3COO]^-$. These reactions were also carried out at 0 and 45 °C. Results are shown in Table 2. With a decrease in temperature to 0 °C, the selectivity increased slightly, but the overall yield decreased. On the other hand at 45 °C the rate of reaction was accelerated, while selectivity dropped significantly. It is also important to note that at 0 and 20 °C, the reactions mixtures were in two phases and on increasing the reaction temperature to 45 °C gave a homogenous mixture.

Finally, we investigated the reusability and efficiency of ionic liquid $[EtPy]^+[CF_3COO]^-$. After the first reaction the ionic liquid was separated from the organic layer. Any leftover organic material was extracted with ethyl ether and the ionic liquid dried at 65 °C under vacuum. Successive runs were performed with the recovered ionic liquid $[EtPy]^+[CF_3COO]^-$ for reaction between isoprene and acrylonitrile (Scheme 2, Eq. 1), at 20 °C for 24 h. As results in Table 3 show, the ionic liquid could be recovered quantitatively and without loss of activity. This is evident from the fact that the overall product yield of the Diels–Alder reaction is not affected even after six runs with the recovered ionic liquid.

Table 2. Diels–Alder reactions in $[EtPy]^+[CF_3COO]^-$ at 0 and 45 °C

Entry	Dienophile	Time (h)	Temp (°C)	Yield[a] (%)	Selectivity [b] to main product (%)
1	Acrylic acid	2 (24)	0	91 (98)	98 (90)
2	Acrylic acid	2 (24)	45	98 (98)	74 (56)
3	Acrylonitrile	2 (24)	0	81 (94)	98 (84)
4	Acrylonitrile	2 (24)	45	98 (98)	67 (50)
5	Methacrylic acid	2 (24)	0	40 (61)	72 (60)
6	Methacrylic acid	2 (24)	45	62 (69)	50 (50)

[a] Determined by GC.

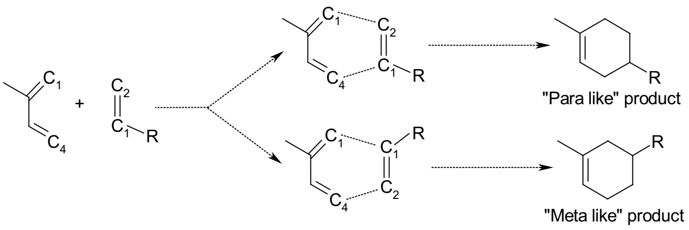
[b] Determined by ^1H NMR.

Table 3. Recovery and reuse of $[EtPy]^+[CF_3COO]^-$ in reaction of isoprene and acrylonitrile at 20 °C

Recycling #	Recovered ionic liquid yield (wt%)[a]	Overall product Yield (%)[b]
1	96	97
2	97	97
3	95	95
4	96	96
5	97	94
6	96	92

[a] Isolated yield.

[b] GC yield.



Scheme 3. The mechanism of Diels–Alder reactions.

3. Conclusion

Our study has shown for the first time that pyridinium based ionic liquids can be used effectively as solvent in the Diels–Alder reaction. The ionic liquid $[EtPy]^+$-$[CF_3COO]^-$ is found to be an excellent reaction solvent with significantly increased rate for this reaction compared to organic solvent. Applications of this solvent for number of other reactions are under investigation in our laboratory.

References and notes

1. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Reactions and Synthesis (Part B)*, 4th ed.; Plenum: New York, Chapter 6.
2. Griffiths, G. J.; Previdoli, F. E. *J. Org. Chem.* **1993**, *58*, 6129.
3. Rideout, D. C.; Breslow, R. J. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
4. Diego-Castro, M. J.; Haailes, H. C. *Tetrahedron Lett.* **1998**, *39*, 2211.
5. Handy, S. T.; Grieco, P. A.; Mineur, C.; Ghosez, L. *Synlett* **1995**, 565.
6. Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1995**, *30*, 1785.
7. Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254.
8. Zhao, H.; Malhotra, S. V. *Aldrichim. Acta* **2002**, *35*(3), 75.
9. Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157.
10. Malhotra, S. V.; Zhao, H. *Phys. Chem. Liq.* **2004**, *42*(2), 215.
11. Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083.
12. Chauvin, Y.; Oliver-Bourbigon, H. *ChemTech* **1995** (September), 26–30.
13. Ellis, B.; Kein, W.; Wasserscheid, P. *Chem. Commun.* **1999**, 337.
14. Davis, J. H., Jr.; Forrester, K. J. *Tetrahedron Lett.* **1999**, *40*(9), 1621.
15. Green, L.; Hemeon, I.; Singer, R. D. *Tetrahedron Lett.* **2000**, *41*, 1343.
16. Carmichael, A. J.; Haddleton, D. M.; Bon, S. A. F.; Seddon, K. R. *Chem. Commun.* **2000**, *14*, 1237.
17. Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785.
18. Howarth, J.; Hanlon, K.; Fayne, D.; Mc Cormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097.
19. Song, C. E.; Roh, E. J.; Lee, S. G.; Shim, W. H.; Chol, J. H. *Chem. Commun.* **2001**, 1122.
20. Ludley, P.; Karodia, N. *Tetrahedron Lett.* **2001**, *42*, 2011.
21. Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.
22. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23.
23. Lee, C. W. *Tetrahedron Lett.* **1999**, *40*, 2461.
24. Zulfiqar, F.; Kitazume, T. *Green Chem.* **2000**, *2*, 137.
25. Representative reaction procedure: General experimental procedure: Isoprene (4.09 g, 60 mmol) was added slowly to a mixture of **2** (1.64 g, 40 mmol) and ionic liquid $[EtPy]^+[CF_3COO]^-$ (8 mL, 46 mmol) under argon at room temperature. The biphasic reaction mixture was allowed to stir (400 rpm) at room temperature for the desired time period. After the reaction was over, the mixture was diluted with 3 mL water and 3 mL petroleum ether, and shaken vigorously. The organic layer was separated from ionic liquid. Any leftover organic material was extracted with ethyl ether and the ionic liquid was dried at 65 °C under vacuum to remove moisture, and then reused. The combined organic extracts were washed with saturated sodium bicarbonate (5 mL) followed by water (5 mL), and finally brine (5 mL). Drying over Na_2SO_4 and evaporation under reduced pressure yielded the product, which was further purified by flash column chromatography (acetone/petroleum ether 1:25) to give the purified material. The product was analyzed by gas chromatograph and the ratio of isomers confirmed by ^1H NMR (500 Hz, in $CDCl_3$).
26. Ludley, P.; Karodia, N. *Tetrahedron Lett.* **2001**, *42*, 2011.
27. Zhao, H.; Malhotra, S. V. *Biotechnol. Lett.* **2002**, *24*, 1257.
28. Zhao, H.; Luo, R. G.; Malhotra, S. V. *Biotechnol. Prog.* **2003**, *19*(3), 1016.
29. Zhao, H.; Malhotra, S. V.; Luo, R. G. *Phys. Chem. Liq.* **2003**, *41*(5), 487.