Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4079–4083

Diels–Alder reaction in protic ionic liquids

Ewa Janus,[a] Izabela Goc-Maciejewska,[b] Marek Łożyński[b] and Juliusz Pernak[b,*]

[a]*Department of Organic Chemical Technology, Technical University of Szczecin, ul. Pułaski 10, 70-322 Szczecin, Poland*
[b]*Department of Chemical Technology, Poznań University of Technology, pl. Skłodowskiej-Curie 2, 60-965 Poznań, Poland*

Received 20 January 2006; revised 16 March 2006; accepted 28 March 2006
Available online 2 May 2006

Abstract—Protic imidazolium ionic liquids have been tested as reaction media in the Diels–Alder reaction between cyclopentadiene and two dienophiles (dimethyl maleate and methyl acrylate). Good conversions and *endo*/*exo* selectivities were achieved. The activation of the dienophile by hydrogen bonding with protic imidazolium ILs was demonstrated.

1. Introduction

The Diels–Alder reaction[1] is a powerful tool in organic synthesis and in the chemical industry. The use of two conjugated double bonds to form six-membered carbocycles in one concerted step is often used in the synthesis of natural products and bioactive molecules.[2] For many years, Diels–Alder reactions have attracted the interest of both experimental and theoretical chemists.[3–6] It is well established that the efficiency and selectivity of these reactions are influenced by the acidity of the medium. Therefore, the reaction has been investigated using water,[7] surfactants,[8] lithium amides[9] and low-melting temperature mixtures of bulk natural products.[10] The reaction is often non-selective, yielding a mixture of *endo*- and *exo*-stereoisomers.

Ionic liquids (ILs) have been used as solvents and as acid catalysts for Diels–Alder reactions. The first investigation on the reaction between cyclopentadiene and an alkyl acrylate in an IL was performed using ethylammonium nitrate and yielded a mixture of *endo* and *exo* products in the ratio 6.7:1.[11] More recently, a number of Diels–Alder cycloadditions were reported in aprotic, imidazolium ILs,[12–19] as well as a carbohydrate IL based on fructose.[20] Chloroaluminate ILs (with Al_2Cl_7 and Al_3Cl_{10} anions) were also used as both solvents and Lewis catalysts.[21,22] ILs have been employed to further increase the yield of *endo* products in the Diels–Alder reaction. In investigations on the effect of the cation structure of the imidazolium IL on the reaction of methyl acrylate and cyclopentadiene, it was demonstrated that the observed enhancements in yield and selectivity were due to an explicit hydrogen bond between the cation and the carbonyl group of the acrylate.[15]

Here we report the application of protic imidazolium ILs as both a solvent and a Brønsted catalyst for the Diels–Alder reaction. The reactions of cyclopentadiene with dienophiles (methyl acrylate and dimethyl maleate) were studied in protic room temperature ionic liquids (RTILs). The protic RTILs included 1-alkylimidazolium and 1-alkoxymethylimidazolium DL-lactates, L-lactates, salicylates, tetrafluoroborate and bis(trifluoromethylsulfonyl)imide [Tf_2N] (Table 1).

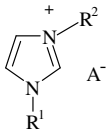
Diels–Alder cycloaddition (Scheme 1) proceeded readily at 25 °C. The products, as mixtures of *endo*- and *exo*-bicyclo[2.2.1]-hept-5-en-2-carboxylic acid methyl esters or *endo*- and *exo*-bicyclo[2.2.1]-hept-5-en-2,3-dicarboxylic acid dimethyl esters, were analyzed by GC. The estimated yields and ratios of *endo*/*exo* products are shown in Table 1.

The yield and selectivity of reactions in salicylates and lactates of 1-alkyl- and 1-alkoxymethylimidazolium were dependent upon the type of dienophile. For methyl acrylate, the yield of >90% was reached after 24 h and the resulting selectivity, expressed by the *endo*/*exo* ratio, ranged from 3.6 to 3.8. In contrast, for dimethyl maleate, a similar yield was not reached even after 48 h, with

Keywords: Diels–Alder reaction; Ionic liquids; Protic imidazolium salts.
* Corresponding author. Tel.: +48 6166 53681; fax: +48 6166 53649; e-mail addresses: juliusz.pernak@put.poznan.pl; ejanus@ps.pl

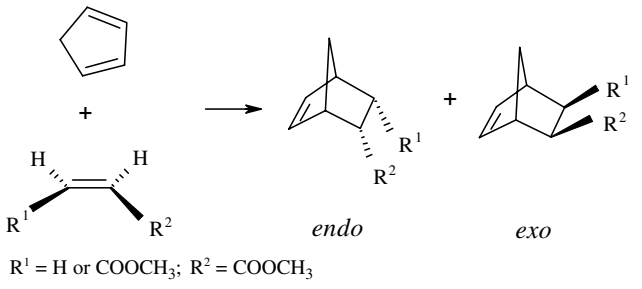
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.172

Table 1. Room temperature ionic liquids used in the Diels–Alder reaction



RTIL	R^1	R^2	Anion (A^-)	Methyl acrylate[a]		Dimethyl maleate[a]	
				Yield[b] (%)	Ratio *endo*/*exo*	Yield[c] (%)	Ratio *endo*/*exo*
1a	CH_3	H	DL-Lactate	95	3.9	97	3.7
1b	C_4H_9	H	DL-Lactate	90	3.8	96	3.5
1c	C_6H_{13}	H	DL-Lactate	91	3.8	96	3.4
1d1	$C_{10}H_{21}$	H	DL-Lactate	90	3.7	97	3.3
1d2	$C_{10}H_{21}$	H	L-Lactate	90	3.7	95	3.2
2a1	$CH_2OC_4H_9$	H	DL-Lactate	90	3.7	92	3.3
2a2	$CH_2OC_4H_9$	H	L-Lactate	90	3.7	92	3.4
2b	$CH_2OC_6H_{13}$	H	DL-Lactate	94	3.8	94	3.4
2c1	$CH_2OC_{10}H_{21}$	H	DL-Lactate	91	3.6	96	3.5
2c2	$CH_2OC_{10}H_{21}$	H	L-Lactate	91	3.7	95	3.3
3a	$CH_2OC_4H_9$	H	Salicylate	94	3.7	95	3.3
3b	$CH_2OC_6H_{13}$	H	Salicylate	93	3.7	93	3.3
3c	$CH_2OC_9H_{19}$	H	Salicylate	94	3.7	94	3.2
4	CH_3	H	BF_4	96	3.7	94[b]	3.9
5	CH_3	H	NTf_2	95	6.0	95[b]	5.2

[a] Diels–Alder reaction, cyclopentadiene/dienophile = 1.5 in 0.25 mL IL, temperature 25 °C.
[b] 24 h.
[c] 48 h.



Scheme 1. The reactions of cyclopentadiene with dienophiles.

the selectivity ranging from 3.2 to 3.7. The highest *endo*/*exo* ratio was obtained for ILs with an *N*-methyl group. Elongation of the alkyl substituent on the cation by the addition of methylene groups resulted in no significant alterations in the course of the reaction even though the viscosity of the ILs markedly increased. The type of anion employed was found to be significant. Important changes in the reaction course were observed for [Tf_2N], with a twofold higher selectivity recorded (*endo*/*exo* ratio = 5.2).

An increase in the temperature from 25 to 45 °C for methyl acrylate resulted in an increase in the yield of the reaction from 42 to as much as 78% after 2 h and from 61% to 85% after 4 h, with the selectivity preserved. An analogous relationship was obtained for the reaction with dimethyl maleate; in this case, the increase in the temperature from 25 to 45 °C augmented the yield of the process from 36% to 65% after 2 h and from 51% to 81% after 4 h reaction time (Fig. 1), paralleled by a decrease in selectivity from 3.3 to 2.9. In protic ILs, as in organic solvents, an increase in the temperature and extended duration of the reaction were accompanied by a decrease in selectivity towards the *endo* isomer and by an increase in the yield of the reaction. The reaction of cyclopentadiene with elevated concentrations of methyl acrylate and dimethyl maleate resulted in a higher efficiency of the process and in decreased selectivity. Moreover, protic ILs can be recycled and no alterations in the yield and selectivity of the process were observed after 10 reaction cycles.

The reaction of 1,3-cyclopentadiene with dimethyl maleate was used as a computational model to explore the effect of protic IL catalysis. Simple PM3 semi-empirical analysis suggested that a hydrogen bond-catalyzed process, passing through a maleate imidazolium complex, was more feasible than a non-catalyzed reaction. In fact, we found that the chemical shift of the H–N3 proton of **4** was much more shielded in an equimolar complex with maleate (1.60 ppm upfield) than was the H–C2 proton (0.02 ppm). Thus, imidazolium H–N3 hydrogen bonded complexes of maleate to the diene in *exo* and *endo* modes. Although both theory and experiment suggested that a stepwise diradical mechanism was a few kilocalories per mole higher in energy terms than the concerted pathway,[23–26] we arbitrarily assumed the latter conventional view for the catalyzed Diels–Alder reaction and also in the protic IL environment.

Predictably, the energetics for the *endo* and *exo* reaction products were noticeably different. Stereospecific imidazolium-catalyzed cycloadditions were predicted to be exothermic by 19.1 and 15.5 kcal/mol for the *exo* and *endo* isomers, respectively (*exo* isomer is thermodynamically preferred for steric reasons).

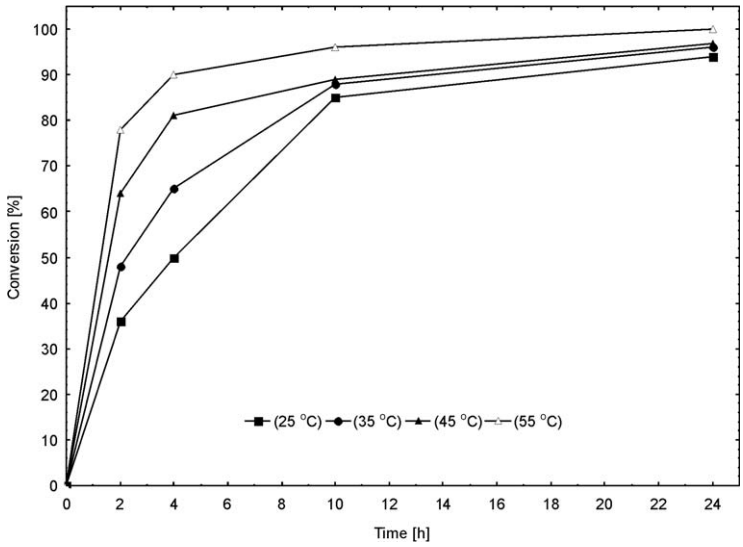


Figure 1. The conversion percentages as a function of time and temperature for **3a** (cyclopentadiene/dimethyl maleate ratio = 1.5).

Figure 2 shows both uncatalyzed and imidazolium catalyzed *endo* and *exo* transition state (TS) structures. The catalyzed TS *endo* complex manifested a structure that was 2.2 kcal/mol more stable than that for the

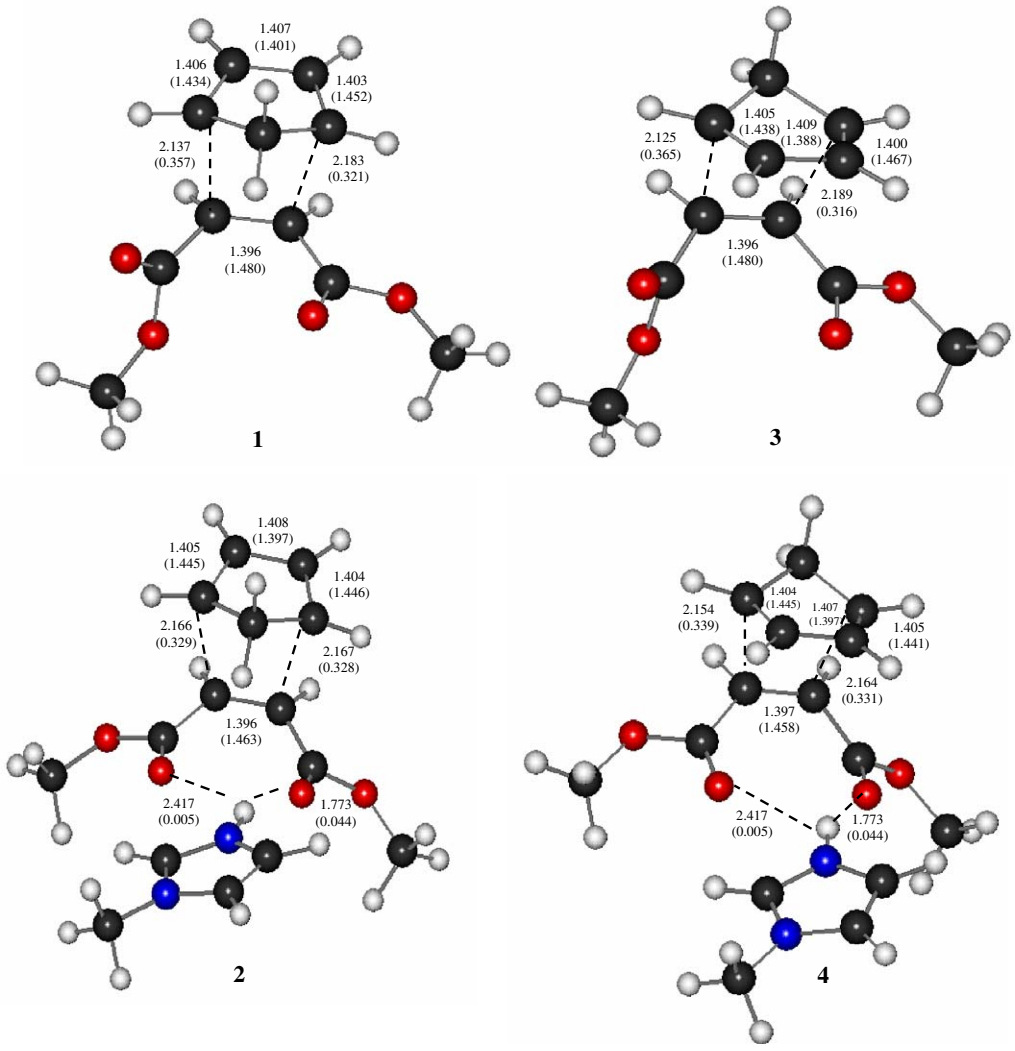


Figure 2. Model transition states used in calculations for the purpose of computational efficiency **1** and **2** for *exo* isomers and **3**, **4** for *endo* isomers. The bond lengths and bond orders (values in parentheses) are presented.

uncatalyzed *endo* reaction. The energy difference between the *exo* and *endo* TSs was only −0.4 kcal/mol, and poorly reflected the preferential formation of the *endo* isomer, in accordance with experiment.

The sum of the Mulliken atomic charges in the TSs of the atoms of cyclopentadiene and the maleate fragment showed that the electrons were shifted from the diene to the dienophile (0.148 and 0.156 for *exo* and *endo*, respectively, but 0.201 and 0.200 for the protic IL catalyzed reaction). Selected bond orders (BOs) were used to appraise the extent of reaction at the TS. We observed that the BOs for the formation of bonds and for the diene and dienophile fragments of the TS spanned a reliable range (Fig. 2). The distances and BO trends suggested that the catalyst augmented dienophile acceptor properties only slightly. For non-catalyzed and catalyzed TSs, the distance sums of C3–C6 and C5–C7 bond formation were essentially the same but the sum of the BOs was greater for the non-catalyzed TS for both *endo* and *exo* structures. This was ascribed to the more product-like character of the TS in the non-catalyzed reaction. Examination of the geometries of the TSs and their BOs evidently indicated a concerted reaction, although involving an asynchronous mechanism. The imidazolium-catalyzed process was much more synchronous: the BO differences for the formation of carbon–carbon bonds were 0.001 and 0.008 for *exo* and *endo*, respectively, while the differences amounted to 0.036 and 0.049 for the non-catalyzed process. Moreover, the sum of the active orders for the non-catalyzed reaction was close to 6.45 but was only 6.41 for the imidazolium-catalyzed reaction and it did not depend on the *exo*/*endo* stereoselectivity.

In conclusion, we have reported on the use of protic, imidazolium-based ILs as reaction media and as Brønsted catalysts for Diels–Alder reactions. In comparison to conventional organic solvents, fast conversion with good *endo*/*exo* selectivities was observed. On the grounds of the semi-empirical computational model, we have found that hydrogen bonding of protic imidazolium ILs to the dienophile provides a rationale for the catalysis observed.

2. Experimental and computational methods

Preparation of 1-alkyl- and 1-alkoxymethylimidazolium salts followed the published method.[27] The densities of the obtained RTILs ranged from 1.1231 to 0.9861 g/mL for lactates **1**–**2** and from 1.1396 to 1.0578 g/mL for salicylates **3**, and they were thermally stable up to 185–244 °C.[28] Gas phase PM3 semi-empirical calculations employing HyperChem (Hypercube) software were used to model structures of reagents, transition states (TS) and products. The bond order (BO) calculations were performed with MOPAC2002 software (Fujitsu Ltd).

1-Methylimidazolium tetrafluoroborate **4**: 1-Methylimidazole (8.21 g, 100 mmol) was placed in a round-bottomed flask equipped with a stirring bar and tetrafluoroboric acid (8.78 g, 100 mmol, 48% solution in water) was added in portions with stirring. The mixture was stirred at room temperature for 3 h and then concentrated on a rotary evaporator. The product was washed with ethyl acetate (2×20 mL) and dried under a vacuum (2–3 Torr) for 8 h at 70 °C (90% yield). ^{1}H NMR (CD_3CN) 3.79 (s, 3H), 7.27 (s, 2H), 8.18 (s, 1H), 12.24 (s, N^+–H). ^{13}C NMR (CD_3CN) 35.4, 122.9, 123.7 and 137.2. Elemental analysis: calcd for $C_4H_7BF_4N_2$; C 28.28, H 4.15, N 16.49. Found: C 28.56, H 4.48, N 15.25.

1-Methylimidazolium bis(trifluoromethylsulfonyl)imide **5**: 1-Methylimidazolium chloride (3.56 g, 30 mmol) was dissolved in 30 mL of distilled water and $LiNTf_2$ (8.61 g, 30 mmol) was added. The reaction mixture was stirred at room temperature for 10 min. After separation of the phases, the organic phase was washed with 2×20 mL distilled water until chloride ions were no longer detected ($AgNO_3$). The liquid obtained was dried at 70 °C in a vacuum (98% yield). ^{1}H NMR (DMSO-d_6) 3.89 (s, 3H), 7.66 (s, 2H), 9.03 (s, 1H), 12.17 (s, wide, N^+–H). ^{13}C NMR (DMSO-d_6) 35.4, 119.7, 123.0, 135.8 and anion 125.9 (q, $-CF_3$, $J = 321$ Hz). Elemental analysis: calcd for $C_6H_7F_6N_3O_4S_2$; C 19.84, H 1.94, N 11.57. Found: C 20.06, H 2.28, N 11.29.

1-Methylimidazolium chloride (mp = 75 °C) was prepared by saturating a chloroform solution of 1-methylimidazole at 15 °C with HCl.

Typical procedure for the Diels–Alder reaction in protic IL: 0.25 mL of IL, cyclohexanone (10 μL) as an internal chromatographic standard, dimethyl maleate or methyl acrylate (1 mmol) and freshly cracked cold cyclopentadiene (1.5 mmol) were added into a 4 mL vial containing a small stirring bar. The reaction was conducted at 25 °C. The progress of the reaction was monitored by GC analysis over 48 h. The yield of products and *endo*/*exo* ratios were calculated based on the GC analysis.

Acknowledgement

We are grateful for the financial support received from the Polish Committee for Scientific Research, Grant No. 3 T09B 053 29.

References and notes

1. Diels, O.; Alder, K. *Liebigs Ann.* **1928**, *460*, 95–122.
2. Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321–352.
3. Robertson, A.; Philip, D.; Spencer, N. *Tetrahedron* **1999**, *55*, 11365–11384.
4. Manka, J. T.; Douglass, A. G.; Kaszynski, P.; Friedli, A. C. *J. Org. Chem.* **2000**, *65*, 5202–5206.
5. Rulisek, L.; Sebek, P.; Havlas, Z.; Hrabal, R.; Capek, P.; Svatos, A. *J. Org. Chem.* **2005**, *70*, 6295–6302.
6. Hirao, H.; Ohwada, T. *J. Phys. Chem. A* **2005**, *109*, 816–824.

7. Rideout, D. C.; Breslow, R. J. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.
8. Diego-Castro, M. J.; Hailes, H. C. *Tetrahedron Lett.* **1998**, *39*, 2211–2214.
9. Handy, S. T.; Grieco, P. A.; Mineur, C.; Ghosez, L. *Synlett* **1995**, 565–567.
10. Imperato, G.; Eibler, E.; Niedermaier, J.; König, B. *Chem. Commun.* **2005**, 1170–1172.
11. Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785–1788.
12. Fisher, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793–796.
13. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23–25.
14. Ludley, P.; Karodia, N. *Tetrahedron Lett.* **2001**, *42*, 2011–2014.
15. Aggarwal, A.; Lancaster, N. L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002**, *4*, 517–520.
16. Dzyuba, S. V.; Bartsch, R. A. *Tetrahedron Lett.* **2002**, *43*, 4657–4659.
17. Abbott, A. A.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24–26.
18. Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465–6468.
19. Handy, S. T.; Okello, M. *Tetrahedron Lett.* **2003**, *44*, 8399–8402.
20. Xiao, Y.; Malhotra, S. V. *Tetrahedron Lett.* **2004**, *45*, 8339–8342.
21. Lee, W. *Tetrahedron Lett.* **1999**, *40*, 2461–2464.
22. Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2004**, *69*, 1419–1420.
23. Bradley, A. Z.; Kociolek, M. G.; Johnson, R. P. *J. Org. Chem.* **2000**, *65*, 7134–7138.
24. Firestone, R. A. *Tetrahedron* **1996**, *52*, 14459–14468.
25. Horn, B. A.; Herek, J. L.; Zewail, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 8755–8756.
26. Sakai, S. *J. Phys. Chem. A* **2000**, *104*, 922–927.
27. Pernak, J.; Goc, I. *Polish J. Chem.* **2003**, *77*, 975–984.
28. Density ($g\,mL^{-1}$): **1a** 1.1231, **1b** 1.0595, **1c** 1.0374, **1d1** 0.9793, **1d2** 0.9879, **2a1** 1.0640, **2a2** 1.0695, **2b** 1.02552, **2c1** 0.9861, **2c2** 0.9910, **3a** 1.1396, **3b** 1.0956, **3c** 1.0578; temperature onset of decomposition (°C): **1a** 196.5, **1b** 244.5, **1c** 226, **1d1** 206.5, **1d2** 199, **2a1** 188, **2a2** 186.5, **2b** 211, **2c1** 207.5, **2c2** 202, **3a** 199.5, **3b** 212, **3c** 205.