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Ionic liquids and microwave irradiation as synergistic combination for polar Diels–Alder reactions using properly substituted heterocycles as dienophiles. A DFT study related

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ABSTRACT

For the DA reactions between nitropyrrole derivatives and isoprene, the combination of microwave irradiation and protic ionic liquids, has a notable synergistic effect. DFT calculations suggest that a supplementary energy ranking in the IR region of 1.700–1400 cm^{-1} can favour the structural changes in the reactants to reach the TS.

Introduction

The Diels–Alder (DA) reaction is one of the most useful processes in preparative organic chemistry. Its potential in heterocyclic chemistry and natural product synthesis is very well known. The process is in one step inter or intramolecular from a diene and a dienophile bearing an almost unlimited number of variants. The DA reaction has remained as one powerful organic transformation in chemical synthesis, particularly in obtaining polycyclic rings.[1] This reaction underlies the synthesis of diverse carbo- and heterocycle compounds.[2]

An ionic liquid (IL) is a salt -substance composed exclusively of cations and anions-, and this fact differentiates them from simple ionic solutions, in which ions are dissolved in a molecular medium. They are also different from inorganic molten salts because their melting points are lower than 100 °C (most of them exist in liquid form at or near room temperature). The design and discovery of ionic liquids (ILs) displaying a melting point lower than 10 °C, mainly room temperature ionic liquids (RTILs), have been the subject of considerable research efforts over the past decade.

RTILs have attracted considerable attention because these are expected to be ideal solvents to provide novel reactions in green chemistry.[3,4] The interest in this class of molecules arises from their use as liquid media for a variety of chemical transformations specially DA reactions, as substitutes of organic molecular solvents.

RTILs exhibit a variety of desirable properties, such as negligible vapour pressure, which makes them interesting for various applications. In particular, the option of fine-tuning chemical and physical properties by an appropriate choice of cations and anions has stimulated much of the current excitement with respect to these compounds and has led to the term 'design solvents'. As a consequence, the characterization of the properties of different classes of ILs used as solvent for specific applications and for chemical reactions and catalysis, has been intensively investigated. [5]

In the last years we reported the electrophilic behaviour of different monocyclic five-membered nitroheteroaromatic compounds properly mono and disubstituted in their exposure to different dienes under thermal conditions, using molecular solvents and ionic liquids, respectively.[6] Moreover, we use as dienophile in this type of polar DA (P-DA) reactions a series of benzofused five-membered nitroheteroaromatic compounds, such as nitrotosylindoles, nitrobenzofuranes and nitrobenzothiophenes, properly substituted.

For P-DA reactions one of the most interesting aspects is its solvent dependence. Moreover, in recent years, these reactions have been subject of several studies in order to enhance the reactivity.

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For specific P-DA reactions it was demonstrated that the aqueous solutions have a remarkable increase in reactivity and selectivity, and these results were discussed in terms of hydrogen-bond (HB) formation. Protic ionic liquids (PILs) with similar properties to water, such as being highly ordered media and good hydrogen bonding donor, have also been shown to have potential influence on the outcome of P-DA reactions.

Considering that microwave irradiation (MW) has been used to enhance organic reactions, we have realized some experiences using a combination of microwave irradiation and PIL. We are supposing that MW has a major effect in a special range of energy activation barriers (ΔE). When the ΔE reaction is too low, the presence of microwave radiation is not especially important, and if the value is extremely high, this irradiation would not take effect.

The aim of the present work is twofold. The first purpose is to analyse the influence of PILs plus microwave irradiation in the polar cycloaddition reactions between 1-tosyl-2-nitropyrrole **1a** and 1-tosyl-3-nitropyrrole **1b**, respectively, with isoprene **4** in the presence of tetrafluoroborate of 1-methylimidazolio ([HMIM] [BF_4]), and development in a microwave reactor. Complementary we show a DFT study.

Results and discussion

The cited reactions were previously realized in thermal conditions using molecular solvents (benzene and chloroform) or PIL ([HMIM] [BF_4]).[6c] Usually DA transformations developed in molecular solvents require harsh conditions (high temperatures and pressures) and long reaction times.

In both cases we observed a mixture of dihydrocycloadducts **2a** and **2b** regioisomers, joined to the corresponding aromatic cycloadducts **3a** and **3b** regioisomers (Fig. 1), with moderate yield. However when the PIL was the solvent the yield resulted was better and the aromatic cycloadducts improved (see Table 1).

In this study microwave irradiation has been used together with IL as the solvent, to explore if these polar cycloaddition reactions improved. These cycloadditions, where the electrophile is an aromatic heterocycle, were the first reaction type to be examined as a whole with microwave irradiation.

Then, with microwave irradiation (50 W, 30 min) and [HMIM] [BF_4] as reaction media, **1a** and **1b** react with isoprene **4** and yielded the mixture of isomeric dihydroindoles **2a** and **2b** and indoles **3a** and **3b** as the principal products. [6c] (global yield 95%) (Fig. 1).

Theoretical studies

In order to understand the synergistic effects of PILs and MW in P-DA reactions, the reaction between 1-mesyl-3-nitropyrrole **1c**, as a model of 1-tosyl-3-nitropyrrole **1b**, and isoprene **4**, in the absence and in the presence of [HMIM][BF_4] as a PIL, was theoretically studied. For this purpose only the *endo/para* approach mode of isoprene **4** with respect to the electron-withdrawing (EW) nitro group of **1c** was studied. Analysis of the gas-phase potential energy surfaces (PES) associated with this P-DA reaction indicates that the cycloaddition takes place through a one-step mechanism via a high asynchronous transition state (TS). Therefore, reagents, **1c**+**4**, one TS -**TS**- and the formal [4+2] cycloadduct (CA) **5**, were located and characterized. Relative gas-phase energies are summarized in Figure 2, while the total energies are given in Table S1 in Supplementary material.

Table 1
Thermal reactions of *N*-tosylpyrroles with isoprene

Entry	Dienophile	Conditions[a]	Products	Yield[b] (%)
1	**1a**	Benzene, 200 °C, 72 h	**2a**,**b**; **3a**,**b**	50
2		Cl_3CH, 150 °C, 72 h	**2a**,**b**; **3a**,**b**	48
3		[HMIM] [BF_4], 60 °C, 24 h	**2a**,**b**; **3a**,**b**	52
4		[HMIM] [BF_4], 50 W, 10 min	**2a**,**b**; **3a**,**b**	70
5		[HMIM] [BF_4], 50 W, 20 min	**2a**,**b**; **3a**,**b**	85
6		[HMIM] [BF_4], 50 W, 30 min	**2a**,**b**; **3a**,**b**	96
7	**1b**	Benzene, 200 °C, 72 h	**2a**,**b**; **3a**,**b**	50
8		Cl_3CH, 150 °C, 72 h	**2a**,**b**; **3a**,**b**	45
9		[HMIM] [BF_4], 60 °C, 24 h	**2a**,**b**; **3a**,**b**	50
10		[HMIM] [BF_4], 50 W, 10 min	**2a**,**b**; **3a**,**b**	65
11		[HMIM] [BF_4], 50 W, 20 min	**2a**,**b**; **3a**,**b**	80
12		[HMIM] [BF_4], 50 W, 30 min	**2a**,**b**; **3a**,**b**	95

[a] 12 Equiv of isoprene.
[b] Based on consumed dienophile.

In the gas-phase, the activation energy associated with the nucleophilic attack of the C4 carbon of isoprene **4** on the C2 carbon of 3-nitropyrrole **1c** via **TS** presents a high value, 21.4 kcal/mol; formation of the formal [4+2] CA **5** is exothermic by −23.9 kcal/mol. Although this P-DA reaction is thermodynamically favourable, the high activation energy associated with the process makes the cycloaddition reaction difficult.

The gas-phase geometry of **TS** is given in Figure 3. The lengths of C2–C4 and C3–C7 forming bonds at **TS** are 1.860 and 3.078 Å, respectively. These values suggest a two-stage one-step mechanism via a highly asynchronous TS.[7] While C2–C4 bond formation between the most nucleophilic centre of isoprene **4**, the C4 carbon, and one of the most electrophilic centre of 3-nitropyrrol **1c**, the C2 carbon, takes place in the first stage of the reaction, the second C3–C7 bond formation takes place at the second stage of the reaction, once the first C2–C4 bond is completely formed. The short C2–C4 distance indicates that the cycloaddition process is very advanced, in clear agreement with the high activation energies associated with **TS**.[8]

The polar nature of this DA reaction was evaluated analysing the charge transfer (CT) at **TS**. The natural charges were shared between the pyrrole derivative and the isoprene frameworks. At **TS**,

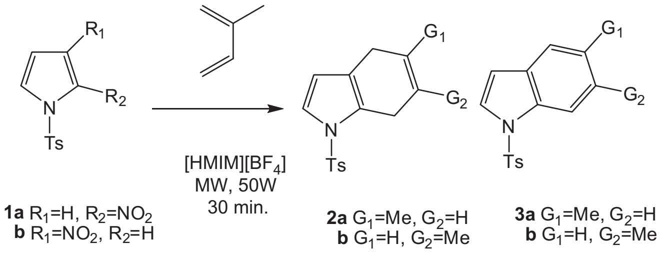

Figure 1. Reactivity of *N*-tosylnitropyrroles **1a** and **1b** with isoprene 4.

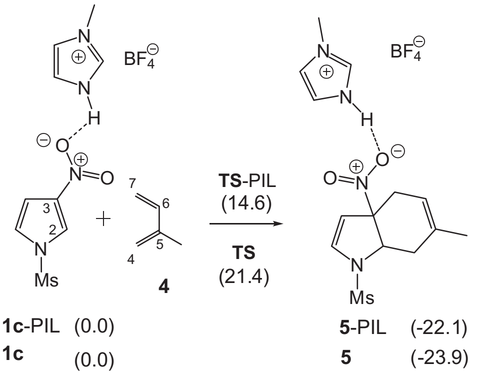

Figure 2. P-DA reaction between 1-mesyl-3-nitropyrrole **1c** and isoprene **4**. Relative energies, in kcal/mol, are given in parenthesis.

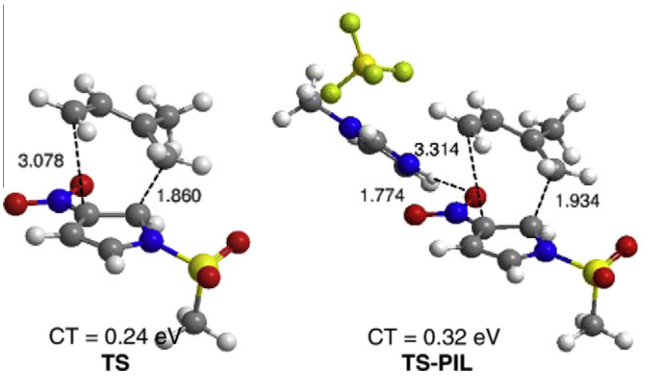

Figure 3. Transition structures associated with the P-DA reactions of **1c** and **1c**-PIL with **4**. Distances are given in angstroms.

the CT that flows from isoprene to nitropyrrole is 0.24 eV. This value points out the zwitterionic character of the TS.

The effects of the [HMIM][BF_4] PIL in the P-DA reaction between 1-mesyl-3-nitropyrrole **1c** and isoprene **4** were evaluated considering two computational approaches:[9] (i) the implicit effects of the PIL by forming a hydrogen bond (BH) between the acidic hydrogen of HMIM cation and one oxygen of the nitro group. The counter BF_4 anion was also included to minimize the positive charge present in the HMIM cation (see Fig. S1 in Supplementary material); and (ii) considering electrostatic interactions modelled by the polarizable continuum model (PCM) of Tomasi's group.[10] For PCM calculations, 1-heptanol was considered as solvent since it has a dielectric constant closer to [HMIM][BF4]; $\varepsilon = 11.3$. The energy results are summarized in Figure 2, while the total energies are given in Table S1 in Supplementary material.

Solvent effects of the PIL produce a larger stabilization of **TS**-PIL than reagents, due to the strong stabilization of the negative charge that is being located at the EW nitro group by the HB formation. Now, **TS**-PIL is located 14.6 kcal/mol above the separated reagents, **1c** plus **4**. Consequently, the PIL produces a large acceleration of the P-DA reaction to decrease the activation energy by 6.7 kcal/mol. In spite of this behaviour, the exothermic character of the cycloaddition, −22.1 kcal/mol, remains unmodified.

The geometry of **TS**-PIL is given in Figure 3. The lengths of the C2–C4 and C3–C7 forming bond at the TS are 1.937 and 3.314 Å, respectively. Such as the gas-phase reaction, these values suggest a two-stage one-step mechanism through highly asynchronous TS. At **TS**-PIL, the distances between the nitro O9 oxygen and the acidic H10 hydrogen of HMIM, 1.774 Å, suggest a strong HB interaction. Note that at the **1c**-PIL complex this distance is 1.934 Å (see Fig. S1 in Supplementary material). Finally, the CT at the **TS**-s, which flows from **4** to **1c**-PIL, is 0.32 eV. This high value indicates the zwitterionic nature of the TS.

The large acceleration found in the presence of the PIL ionic pair can be understood as an increase of the polar character of the reaction as a consequence of the increased electrophilic character of the **1c**-PIL complex achieved by the HB formation, which favours the CT process.[7] Note that the HB formation increases the electrophilicity index[11] of **1c**, $\omega = 2.27$ eV, to 2.88 eV in **1c**-PIL.[9]

Recent electron localization function[12] (ELF) studies devoted to the bonding changes along P-DA reactions have pointed out that the main electronic changes on going from reagents to TSs are related to the reduction of C–C double-bond character in the diene and dienophile.[13] An analysis of the displacement vectors of the IR frequency vibrations in 1-mesyl-3-nitropyrrole **1c** and isoprene **4** shows the presence of stretching vibrations, 1.636 cm^{-1} at **1c** and 1.701 cm^{-1} at **4**, which show atomic movements similar to the electronic changes involved in the formation of the corresponding TSs. Note that the corresponding stretching vibration of **1c** decreases to 1.577 cm^{-1} in complex **1c**-PIL with formation of the HB with HMIM. A similar analysis at the corresponding TSs shows that these frequency vibrations have moved to 1.420 cm^{-1} at **TS** and 1.414 cm^{-1} at **TS**-PIL as a consequence of the reduction of the C2–C3 and C5–C4 double-bond character at the TSs.

This means that any additional energy comprised between 1.700 and 1400 cm^{-1} can favour stretching vibrations involving the π systems of 3-nitropyrrol **1c** and isoprene **4**, thus favouring the electronic changes needed to reach the TS geometry. Consequently, we suggest that the local activation energy provided by the MW could favour the corresponding structural changes, that together with the catalytic effects of the HB formation by the HMIM cation could synergistically favour the P-DA reactions.

Computational details

All calculations were carried out with the Gaussian09 suite of programmes.[14] DFT calculations were carried out using the B3LYP[15] exchange-correlation functionals together with the 6–31G(d) basis set.[16] Optimizations were carried out using the Berny analytical gradient optimization method.[17] The stationary points were characterized by frequency calculations in order to verify that TSs had one and only one imaginary frequency. The electronic structures of critical points were analysed by the natural bond orbital (NBO) method.[18] Solvent effects were considered at the same level of theory by geometry optimization of the gas-phase structures using a self-consistent reaction field (SCRF)[19] based on the polarizable continuum model (PCM) of Tomasi's group.[20] 1-Heptanol was considered as solvent since it has a dielectric constant closer to [HMIM][BF4]; $\varepsilon = 11.3$.

The global electrophilicity index,[21] ω, which measures the stabilization energy when the system acquires an additional electronic charge from the environment, is given by the following simple expression $\omega = (\mu^2/2\eta)$,[22] in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = (\varepsilon_L - \varepsilon_H)$, respectively.[23]

Conclusions

In this case we noted that the microwave more PILs constituted a synergic mixture with strong effects on the reaction yields.

On the other hand, a DFT study of the synergic effects of PILs and MW in the P-DA reaction between 1-mesyl-3-nitropyrrol **1c** and isoprene **4** suggests that while the HB formation between the acidic hydrogen atom of HMIM and one oxygen atom of the EW nitro group of **1c** accelerates markedly the reaction, any supplementary energy ranking in the IR region between 1.700 and 1400 cm^{-1} can favour the structural changes in pyrrole derivative **1c** and isoprene **4** demanded to reach the TS.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.071.

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