

Ionic Liquids and Microwave irradiation as synergistic combination for Polar Diels-Alder Reactions using properly substituted Heterocycles as Dienophiles.

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Abstract. For the DA reactions between nitropyrroles derivatives and isoprene, the combination of microwave irradiation and protic ionic liquids, has a notable synergistic effect

Keywords: Nitropyrroles, Indole, Ionic Liquid, Diels-Alder, Microwave

Introduction

The Diels-Alder (DA) reaction is one of the most useful processes in preparative organic chemistry. Its potential in heterocyclic chemistry and natural products 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 been remained as one powerful organic transformation in chemical synthesis, particularly in the formation of 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 vapor 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, have been intensively investigated.⁵

In the last years we reported the electrophilic behavior of different monocyclic five-membered nitroheteroaromatic compounds properly mono and disubstituted in their exposure to different dienes under thermal conditions, using as solvent molecular ones and ionic liquids, respectively.⁶ Moreover, we use as dienophile in this type of polar DA (P-DA) reactions a serie of benzofused five-membered nitroheteroaromatic compounds, such as nitrosylindoles, 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. 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 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 purpose of this work is to analyze 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 **2** in presence of tetrafluoroborate of 1-methylimidazolium ([HMIM] [BF₄]), and development in a microwave reactor.

Results and Discussion

The cited reactions were previously realized in thermal conditions using molecular solvents (benzene and chloroform) or PIL ([HMIM] [BF₄]).^{6c,7} 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 the dihydrocycloadducts **3a** and **3b** regioisomers, joined to the corresponding aromatic cycloadducts **4a** and **4b** regioisomers (Figure 1), with moderate yield. However when the PIL was the solvent the yield resulted better and the aromatic cycloadducts improve (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.⁷ 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] [BF₄] as reaction media, **1a** and **1b** react with isoprene **2** yielded the mixture of isomeric dihydroindoles **3a** and **3b** and indoles **4a** and **4b** as the principal products.^{6c} (global yield 95%) (Figure 1)

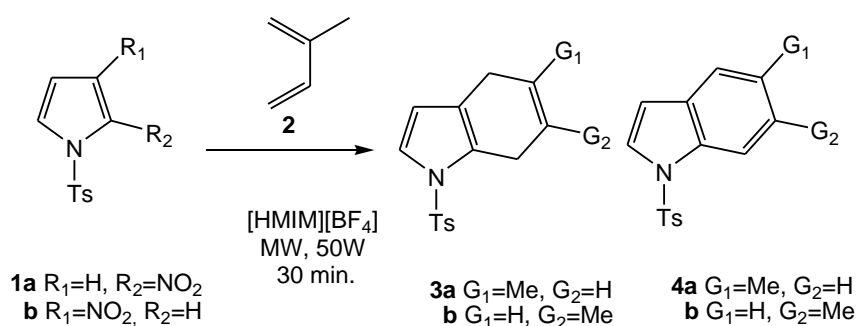


Figure 1. Reactivity of *N*-tosylnitropyrroles **1a** and **1b** with isoprene **2**

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 ₃ CH, 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], 50W, 10 min	2a,b; 3a,b	70
5		[HMIM] [BF ₄], 50W, 20 min	2a,b; 3a,b	85
6		[HMIM] [BF ₄], 50W, 30 min	2a,b; 3a,b	96
7	1b	Benzene, 200°C, 72 h	2a,b; 3a,b	50
8		Cl ₃ CH, 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], 50W, 10 min	2a,b; 3a,b	65
11		[HMIM] [BF ₄], 50W, 20 min	2a,b; 3a,b	80
12		[HMIM] [BF ₄], 50W, 30 min	2a,b; 3a,b	95

[a] 12 equiv of isoprene

[b] Based on consumed dienophile

Conclusions

It has been demonstrated that *N*-tosyl-nitropyrroles reacts efficiently with isoprene as diene in normal electron demand D-A reactions, with the nitro group inducing side selectivity.

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

Acknowledgments

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7. *Thermal reactions*. The temperature, the length of the reaction and the diene/dienophile ratio are given in Table 1. An ampoule containing 1.0 mmol of the dienophile and the

required amount of diene in 1 ml of ionic liquid was cooled in liquid nitrogen, sealed and then heated with stir in a bath. After the reaction time was completed, it was cooled once more in liquid nitrogen and opened. After separation of the phases, the organic phase was evaporated and the residue purified by column chromatography in silica gel or alumina using hexane/ethyl acetate mixtures as eluent.

Reactions under microwave irradiation. Microwave irradiation was performed in a Anton Paar microwave reactor in standard closed vessels.

^1H and ^{13}C NMR spectra were recorded in CDCl_3 on 300 and 75 MHz FT-spectrometers, respectively, using TMS as the internal standard; GC-MS analyses were performed in an instrument equipped with a PE-5-type column. IR spectra were recorded from NaCl cells.