

***N*-tosyl-nitropyrroles as dienophiles in polar cycloaddition reactions developed in protic ionic liquids.**

Claudia Della Rosa, Maria Kneeteman, Pedro Mancini*

Área Química Orgánica- Departamento de Química- Facultad de Ingeniería Química, Universidad Nacional del Litoral. Santiago del Estero 2829. (3000) Santa Fe, Argentina.
FAX: +54-342-4571162. *e-mail: pmancini@fiq.unl.edu.ar

Abstract. *N*-Tosyl-2-nitropyrrole and *N*-Tosyl-3-nitropyrrole reacts with poorly and activated dienes using protic ionic liquids as reaction media. They exhibit a dienophile character producing the corresponding indoles through a Diels-Alder process. In all cases the presence of protic ionic liquids as reaction media improve the yields respect to use of molecular solvent, while the temperature and the reaction time decrease.

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

Introduction

The Diels-Alder (D-A) 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. It provides the chemist with one of his best tool for the preparation of cyclic compounds having a six-membered ring. The process is in one step inter or intramolecular from a diene and dienophile bearing an almost unlimited number of variants. It is worth noting that these variants exist not only in the substitution of the reaction component but also in the electronic nature of these dienes and dienophiles.¹

Due to our interest in the cycloaddition chemistry of substituted aromatic heterocycles with electron-withdrawing groups, we have reported that *N*-tosyl-2- and 3-nitropyrroles react as electrophile in normal electron demand D-A reactions.²

These dienophiles were exposed to different dienes strongly, moderately and poorly activated under thermal conditions using molecular solvents as reaction media. In these reactions, the best results were obtained with chloroform as molecular solvent due to its potential character hydrogen bond donors (HBD) which could be influence the reactivity of the reaction systems.

In general, these cited polar cycloadditions are a domino process that is initialized by a D-A reaction to give the formally [4 + 2] cycloadduct followed for the subsequent concert irreversible elimination of nitrous acid, which is the factor responsible for the feasibility of the overall process.³ The participation of *N*-tosyl-nitropyrroles in cycloaddition reactions made possible a one spot simple indole synthesis.

In particular, for polar D-A reactions one of the most interesting aspects is its solvent dependence. Moreover, in recent years, this reaction has been subject of several studies in order to enhance the reactivity. For specific D-A reactions was demonstrated that the aqueous solutions have remarkable increase in reactivity and selectivity, and these results were discussed in terms of hydrophobic effects. Ionic liquids (ILs) with similar properties to water, such as being highly ordered media and good hydrogen bonding donor (HBD), have also been shown to have potential influence the outcome of polar D-A reactions. In general, it would be possible demonstrated that the ILs solvent effect in these reactions is in general determined by the solvent hydrogen bond donation ability.

Considering the results obtained in these thermal polar D-A reactions using molecular solvents as reaction media, the purpose of this work is to analyze the influence of room temperature ionic liquids (RTILs) in polar cycloaddition reactions in which the electrophiles are relatively poor. With this purpose, ammonium- and imidazolium-based ILs have been selected because the differences in their HBD acidity.

Results and Discussion

To explore the normal electron demand D-A dienophilicity of *N*-tosyl-nitropirroles **1a-b** we chose isoprene (**2**), 1-trimethylsilyloxy-1,3-butadiene (**3**), and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky diene) (**4**) as dienes (Figure 1).⁴ The selection of the dienes took into account the type of substitution present in their structures and the relative nucleophilicity.

To complete the reaction approach of aromatic carbocyclic and heterocyclic substituted with electron withdrawing groups as electrophiles in cycloaddition reactions, we have investigated protic ionic liquids (PILs) solvent effects in polar D-A reactions using ethylammonium nitrate (EAN), and 1-methylimidazolium tetrafluoroborate ([HMIM][BF₄]). Preparation of EAN and ([HMIM][BF₄]) followed the published methods.⁵

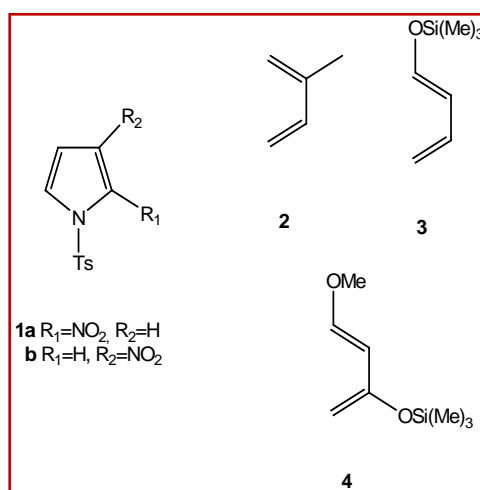


Figure 1

This approach allowed us compared in thermal cycloaddition reaction conditions not only the relative reactivity of these substrates also the regioselectivities when we change molecular solvents for PILs.

When **1a** was reacted with the less reactive **2** in a sealed ampoule at 60°C for 12 h using EAN as solvent, the reactions proceeded to produce a mixture of isomeric indoles **5a** and **5b** (1:1) as the principal products with reasonable yield (40%) and dihydroindoles **6a** and **6b** (1:1) (10%) (Figure 2). If the time of the reaction increased to 24 h we observe a 1:1 mixture of isomeric indoles **5a** and **5b** in 55% yield and traces of the isomeric dihydroindoles **6a** and **6b**.² Similar results were obtained when the reaction was developed in [HMIM][BF₄] although the yields were slightly lower (Table 1, Figure 2).

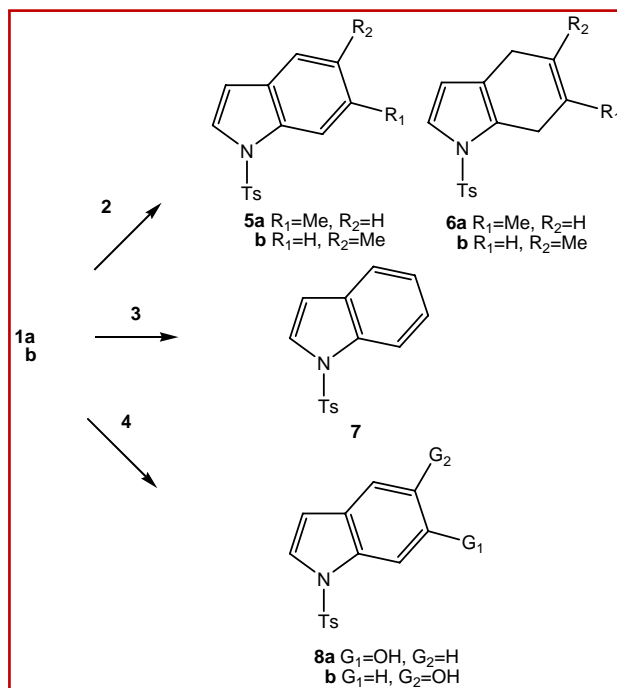


Figure 2

Table 1. Diels-Alder reactions of **1a** with diverse dienes

Entry	Diene	Conditions. ^a	Product	Yield ^b
1	2, 12 eq	EAN 12h	5a,b; 6a,b	50
		EAN 24 h	5a,b; 6a,b	55
2	3, 3 equiv	HMIM 12h	5a,b; 6a,b	45
		HMIM 24 h	5a,b; 6a,b	50
3	3, 3 equiv	EAN 12h	7	50
		EAN 24 h	7	60
4	4, 2 equiv	HMIM 12h	7	52
		HMIM 24h	7	55
5	4, 2 equiv	EAN 12h	8b	60
		EAN 24 h	8b	65
6	4, 2 equiv	HMIM 12h	8b	52
		HMIM 24 h	8b	55

[a] Reaction temperature 60°C, . [b] Based on consumed dienophile

The reactions of **1a** with **3** using EAN or [HMIM][BF₄], respectively, in seals ampoule at 60°C (12 and 24 h, respectively) offered in all cases good yield in indole. The best yield (ca. 60%) was obtained with EAN as the solvent (24 h).

The reaction of diene **4** (60°C, 12 and 24 h, respectively) with **1a** using the two IL's cited before yielded 1-tosyl-5-hydroxyindole **8b** in reasonable yield.² Similarly to the reactions with dienes **2** and **3**, the best yield was observed with EAN (ca. 65%).

The product obtained in the reactions with diene **4** resulted from the aromatization of the nitro-adducts promoted by the loss of the nitro and methoxyl groups as nitrous acid and methanol, respectively. The intermediate that suffered nitrous acid extrusion and retained the methoxy group was not detected in any case.

Similarly, reactions of **1b** with diene **2** yielded a mixture of isomeric cycloadducts **5a**, **5b**, **6a** and **6b**. In turn the reactions with **3** offer the product **7**. In the reactions with diene **4** cycloadduct **8a** was obtained with complete regioselectivity (Figure 2, Table 2).

Table 2. Diels-Alder reactions of **1b** with different dienes

Entry	Diene	Conditions. ^a	Product	Yield ^b
1	2, 12 eq	EAN 12h	5a,b ; 6a,b	52
		EAN 24 h	5a,b ; 6a,b	55
2		HMIM 12h	5a,b ; 6a,b	48
		HMIM 24 h	5a,b ; 6a,b	50
3	3, 3 equiv	EAN 12h	7	50
		EAN 24 h	7	65
4		HMIM 12h	7	50
		HMIM 24h	7	50
5	4, 2 equiv	EAN 12h	8a	62
		EAN 24 h	8a	65
6		HMIM 12h	8a	50
		HMIM 24 h	8a	55

a] Reaction temperature 60°C, . [b] Based on consumed dienophile

In all cases the presence of ILs as reaction media improve the yields respect to use of molecular solvent, while the temperature and reaction time decrease.

Conclusions

It has been demonstrated that *N*-tosyl-nitropyrroles reacts efficiently with the above-mentioned dienes in polar normal electron demand D-A reactions, with the nitro group inducing side selectivity. In all cases the presence of PILs as reaction media improve the yields respect to the use of molecular solvent, while the temperature and the reaction time decrease. EAN is a better solvent than [HMIM][BF₄].

Acknowledgments

This research was supported by Argentine Agency of Science and Technology (ANCyT)-PICT 2008 N° 1214 and by CAI+D 2009 -12/Q271 at Universidad Nacional del Litoral, Santa Fe, Argentina.

References and notes

- For general review, see: (a) W. Carruthers in *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, UK, **1990**; (b) F. Fringelli, A. Taticchi in *The Diels-Alder Reaction*, J. Wiley & Sons, Chichester, UK, **2002**; (c) E.J. Corey, *Angew. Chem. Int. Ed.*, **41**, 1650-1667, **2002**.
- C. Della Rosa, M.N. Kneeteman, P.M.E. Mancini, *Tetrahedron Lett.*, **48**, 1535-1538, **2007**.
- L.R. Domingo, M.J. Aurell, M. Kneeteman, P.M.E. Mancini. *J. Molecular Structure: THEOCHEM*, **853**, 68-76, **2008**.
- General Procedure. The temperature, the length of the reaction and the diene/dienophile ratio is 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.
- E. Janus, I. Goc-Maciejewska, M. Lozynski, J. Pernak. *Tetrahedron Lett.* **47**, 4079-4083, **2006**.