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N-tosyl-nitropyrroles as Dienophiles in Polar Cycloaddition Reactions Developed in Protic Ionic Liquids

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Abstract: *N*-tosyl-2-nitropirrole and *N*-tosyl-3-nitropirrole reacts with poorly and activated dienes using protic ionic liquids as reaction media. They exhibit a dienophilic 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 the use of molecular solvent, while the temperature and the reaction time decrease. A similar behavior was observed in disubstituted *N*-tosyl-pyrroles.

Key words: Nitropyrroles, indole, ionic liquid, Siels-Alder.

1. Introduction

The D-A (Diels-Alder) 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 reaction is an excellent 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 worth noting that exist these variants not only in the substitution of the reaction component but also in the electronic nature of these dienes and dienophiles [1-3].

Due to our interest in the cycloaddition chemistry of substituted aromatic heterocycles with electron-withdrawing groups, 2- and 3-nitropyrroles react as electrophiles in normal electron demand D-A reactions were reported in the paper [4].

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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 HBD (hydrogen bond donors) which could influence the reactivity of the reaction systems.

In general, these cited polar cycloadditions are a domino process initialized by a D-A reaction to give the formally [4π + 2π] cycloadduct, followed for the subsequent concert irreversible elimination of nitrous acid, which is the responsible factor for the feasibility of the overall process [5]. The participation of *N*-tosyl-nitropyrroles in cycloaddition reactions made possible a one step 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 it was demonstrated that

the aqueous solutions have a remarkable increase in reactivity and selectivity, and these results were discussed in terms of hydrophobic effects.

ILs (ionic liquids) with similar properties to water, such as being a highly ordered media and good HBD (hydrogen bonding donor), which have shown a potential influence in the outcome of polar D-A reactions.

The aim of the present work is twofold. Considering the results obtained in these thermal polar D-A reactions using molecular solvents as reaction media, the first purpose is to analyze the influence of RTILs (room temperature ionic liquids) in this type of polar cycloaddition reactions in which the dienophiles are relatively poor. With this purpose, ammonium- and imidazolium-based ILs have been selected because of its HBD acidity. In general, it would be possible demonstrated that the ILs solvent effect in these reactions is determined by the solvent hydrogen bond donation ability.

2. Computational Details

DFT calculations were carried out using the B3LYP exchange-correlation functional and the standard 6-31G* basis set [6, 7]. All calculations were carried out with the Gaussian 09 suite of programs [8].

The global electrophilicity index, ω, is given by the expression $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η [9]. Both quantities approached in terms of the one electron energies of the frontier molecular orbital HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital), ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively [10, 11]. Recently, Domingo et al. have introduced an empirical (relative) nucleophilicity index, *N*, based on the HOMO energies obtained within the Kohn-Sham scheme, and defined as $N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)}$ [12-14]. The nucleophilicity is referred to TCE (tetracyanoethylene), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us conveniently to handle a nucleophilicity scale of positive values. Local electrophilicity and nucleophilicity indices, ω_k and N_k, were evaluated using the following expressions: $\omega_k = \omega f_k^+$ and $N_k = N f_k^-$ where f_k^+ and f_k^- are the Fukui functions for a nucleophilic and electrophilic attacks, respectively [15].

3. Experimental Section

3.1 General Aspects

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

3.2 General Procedure

The temperature, the length of the reaction and the diene/dienophile ratio are specified in the Tables. 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. Completed the reaction time, 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.

4. Results and Discussion

To explore the normal electron demand D-A dienophilicity of *N*-tosyl-nitropirroles **1a-d** we choose isoprene (**2**), 1-trimethylsilyloxy-1,3-butadiene (**3**), and1-diethyl-amino-3-tert-butyldimethyl-silyloxy-1,3-butadiene (Rawal's diene) (**4**) as dienes (Fig. 1). The selection of the dienes took into account the type of substitution present in their structures and the relative nucleophilicity (Fig. 1).

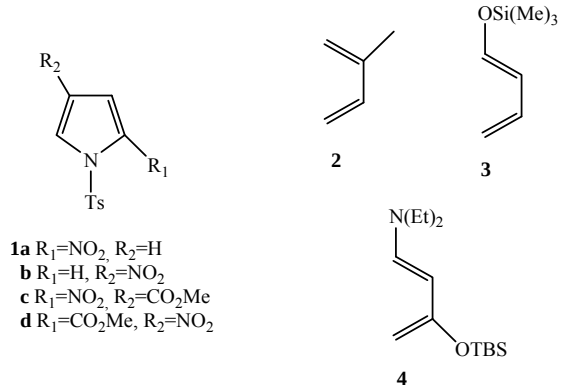

Fig. 1 Dienophiles and dienes.

To complete the reaction approach of aromatic carbocyclic and heterocyclic substituted with electron with-drawing groups as dienophiles in cycloaddition reactions, PILs solvent effects in polar D-A reactions using 1-methylimidazolium tetrafluoroborate ([HMIM][BF4]) and 1- methylimidazolium hexafluorphosphate ([HMIM][PF6]). Preparation of 1-methylimidazolium tetrafluoroborate ([HMIM][BF_4]) and 1-methylimidazolium hexafluorphosphate ([HMIM] [PF6]) followed the published methods [16].

This allowed us to compare in thermal cycloaddition reaction conditions not only the relative reactivity of these substrates also the regioselectivities when molecular solvents are changed for ILs.

When **1a** reacted with the less reactive isoprene **2** in a sealed ampoule at 60 ºC for 12 h using [HMIM][BF_4] as solvent, the reactions proceeded to produce a mixture of isomeric indoles **6a** and **6b** (1:1) as the principal products with reasonable yield (40%) and dihydroindoles **5a** and **5b** (1:1) (10%). If the time of the reaction increased to 24 h, a 1:1 mixture of isomeric indoles **6a** and **6b** in 55% yield and traces of the isomeric dihydroindoles **5a** and **5b** [2] were obtained. Similar results were observed when the reaction was developed in [HMIM][PF_6] (Table 1, Fig. 2).

The reactions of **1a** with 1-trimethylsilyloxy-1,3-butadiene using [HMIM][BF_4] or [HMIM][PF_6], respectively, as solvents in sealed ampoules at 60 ºC (12 and 24 h, respectively) offered in all cases a good yield in indole **9a** and **10a**.

The reaction of Rawal's diene (60 ºC, 12 and 24 h, respectively) with **1a** using the two IL´s cited in the before paragraph yielded **11a** in reasonable yield [2]. (Fig. 2, Table 2).

The reactions of **1c** with isoprene using the two IL´s proceeded to produce the mixture of isomeric cycloadducts **6c** and **6d** as the principal products and a mixture of double addition adducts **7a-d** and **8a-d**, in both cases, of regioisomeric mixtures (Fig. 2, Table 1).

Table 1 Thermal reactions of N-tosyl-nitropyrroles with isoprene.

Entry	Dienophile	Conditions[a]	Product	Product ratio	Yield[b] %
1	1a	HMIMBF_4 12h	5a,b; 6a,b	1:1; 5:5	50
2		HMIMBF_4 24h	5a,b; 6a,b	1:1; 5:5	55
3		HMIMPF_6 12h	5a,b; 6a,b	1:1; 5:5	52
4		HMIMPF_6 24h	5a,b; 6a,b	1:1; 5:5	50
5	1b	HMIMBF_4 12h	5a,b; 6a,b	5:5; 1:1	52
6		HMIMBF_4 24h	5a,b; 6a,b	5:5; 1:1	55
7		HMIMPF_6 12h	5a,b; 6a,b	5:5; 1:1	48
8		HMIMPF_6 24h	5a,b; 6a,b	5:5; 1:1	50
9	1c	HMIMBF_4 12h	6c, 6d, 7a-d, 8a-d	1:5; 1:3:1:2; 1:3:1:2	52
10		HMIMBF_4 24h	6c, 6d, 7a-d, 8a-d	1:5; 1:3:1:2; 1:3:1:2	55
11		HMIMPF_6 12h	6c, 6d, 7a-d, 8a-d	1:5; 1:3:1:2; 1:3:1:2	50
12		HMIMPF_6 24h	6c, 6d, 7a-d, 8a-d	1:5; 1:3:1:2; 1:3:1:2	55
13	1d	HMIMBF_4 12h	11a, 11b	5:1	52
14		HMIMBF_4 24h	11a, 11b	5:1	55
15		HMIMPF_6 12h	11a, 11b	5:1	55
16		HMIMPF_6 24h	11a, 11b	5:1	58

[a] 12 equiv of isoprene , reaction temperature 60 ºC.

[b] Based on consumed dienophile.

On the other hand, the treatment of **1c** with **3** and **4** yielded **9b**, **10b** and **11b**, respectively [2] (Fig. 2, Table 2).

All the addition products showed extrusion of the nitro group as nitrous acid. In these reactions, only 1:1 adducts whose structure revealed site selectivity and regioselectivity were obtained. The nitro group orients the cycloaddition selectively towards the double bond to which it is directly attached.

Similarly, reactions of **1b** with isoprene yielded a mixture of isomeric cycloadducts **5a**, **5b**, **6a** and **6b**. On the other hand, the reactions with 3 and 4 offer the product **12a, 13a** and **14a**. Exposure of **1d** to **2** afforded indoles **11a** and **11b** (Fig. 3, Table 1).

The reactions of **1d** with **3** and **4** proceeded to produce **12b**, **13b** and **14b** respectively, with moderate to high yield and complete regioselectivity [2] (Fig. 3, Table 2).

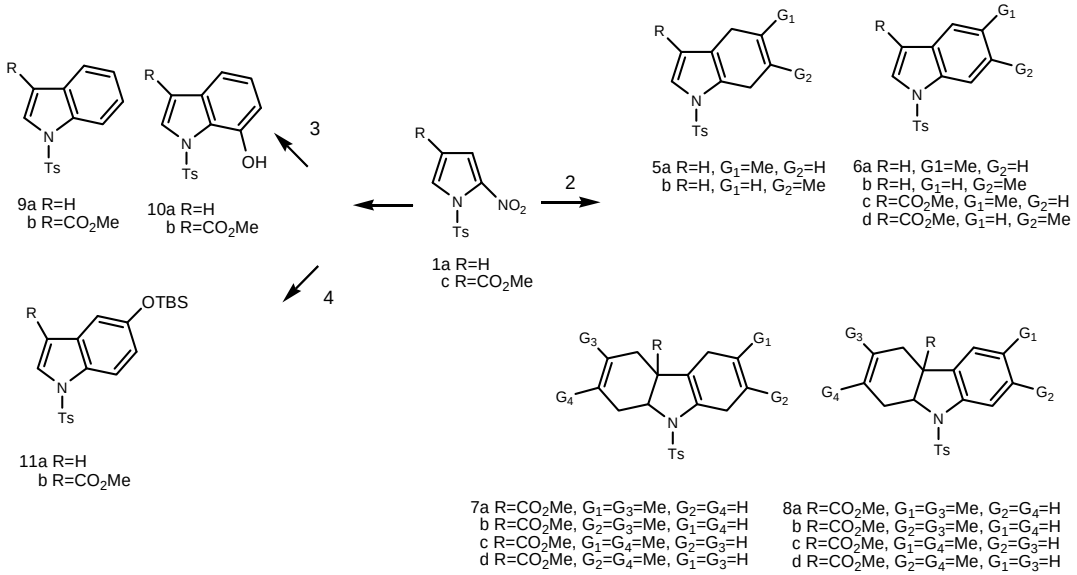

Fig. 2 Diels-Alder reactions of 1a and 1c with dienes 2, 3 and 4.

Table 2 Thermal reactions of N-tosyl-nitropyrroles with diene 3.

Entry	Dienophile	Conditions[a]	Prod.	Yield (%)[b]
1	1a	$HMIMBF_4$ 12h	11a	50
2		$HMIMBF_4$ 24h	11a	55
3		$HMIMPF_6$ 12h	11a	50
4		$HMIMPF_6$ 24h	11a	55
5	1b	$HMIMBF_4$12h	14a	52
6		$HMIMBF_4$ 24h	14a	55
7		$HMIMPF_6$ 12h	14a	50
8		$HMIMPF_6$ 24h	14a	55
9	1c	$HMIMBF_4$ 12h	11b	50
10		$HMIMBF_4$ 24h	11b	56
11		$HMIMPF_6$ 12h	11b	55
12		$HMIMPF_6$ 24h	11b	55
13	1d	$HMIMBF_4$ 12h	14b	56
14		$HMIMBF_4$ 24h	14b	52
15		$HMIMPF_6$ 12h	14b	50
16		$HMIMPF_6$ 24h	14b	55

[a] Diene/Dienophile ratio 3:1, reaction temperature 60 ºC.

[b] Based on consumed dienophile.

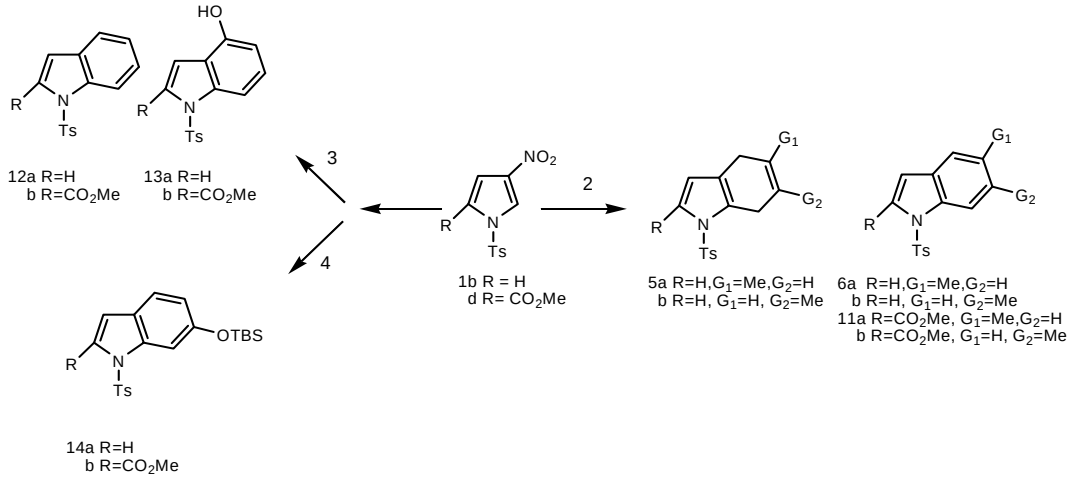

Fig. 3 Diels-Alder reactions of 1b and 1d with dienes 2, 3 and 4.

In all cases the presence of ILs as reaction media improve the yields respect to the use of molecular solvent, while the temperature and reaction time decrease [17].

Reactivity indices as electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (*N*), defined within the conceptual DFT, are powerful tools for establishing the polar character of Diels-Alder reactions [18].

Table 3 Thermal reactions of *N*-tosyl-nitropyrroles with diene 4.

Entry	Dienop-hile	Conditions[a]	Prod.	Yield (%)[b]
1	1a	$HMIMBF_4$ 12 h	9a,10a	50
2		$HMIMBF_4$ 24 h	9a,10a	55
3		$HMIMPF_6$ 12 h	9a,10a	52
4		$HMIMPF_6$ 24 h	9a,10a	55
5	1b	$HMIMBF_4$ 12 h	12a,13a	50
6		$HMIMBF_4$ 24 h	12a,13a	55
7		$HMIMPF_6$ 12 h	12a,13a	50
8		$HMIMPF_6$ 24 h	12a,13a	50
9	1c	$HMIMBF_4$ 12 h	9b,10b	51
10		$HMIMBF_4$ 24 h	9b,10b	55
11		$HMIMPF_6$ 12 h	9b,10b	57
12		$HMIMPF_6$ 24 h	9b,10b	50
13	1d	$HMIMBF_4$ 12 h	12b,13b	52
14		$HMIMBF_4$ 24 h	12b,13b	54
15		$HMIMPF_6$ 12 h	12b,13b	55
16		$HMIMPF_6$ 24 h	12b,13b	58

[a] Diene/Dienophile ratio 3:1, reaction temperature 60 ºC
[b] Based on consumed dienophile.

The static global properties of *N*-tosyl- nitropirroles **1a-d**, and the butadienes **2-4**, namely, are shown in Table **4.**

The electronic chemical potential of nitropirroles, between -4.80 and -4.54 eV, are lower than the ones obtained for butadienes **2-4**, μ range from -3.30 to -2.27 eV. Therefore, it is expected that along a polar DA reaction, the charge transference (CT) will take place from the electron-rich dienes to nitropirroles.

The electrophilicity, ω, of nitropirroles, from 2.14 to 2.48 eV, allows the classification of this species as a strong electrophile within the electrophilicity scale, and as moderate nucleophile within the nucleophilicity scale (*N* between 1.99 and 2.21 eV) [19, 20].

The electrophilicities of butadienes are 0.94 eV (2), 0.73 eV (3) and 0.51 eV (4), which classifies them as marginal electrophiles within the electrophilicity

Table 4 Electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (N), in eV, of nitripirroles 1a-d, and butadienes 2-4.

	μ	η	ω	N
1a	-4.61	4.60	2.31	2.21
1b	-4.54	4.80	2.14	2.18
1c	-4.80	4,64	2.48	1.99
1d	-4.66	4.94	2.20	2.00
2	-3.30	5.77	0.94	2.94
3	-2.79	5.33	0.73	3.67
4	-2.27	5.07	0.51	4.32

scale. On the other hand, the nucleophilicities *N* of these species are 2.94 eV (**2**), 3.67 eV (**3)** and 4.32 eV (**4**). Therefore, while isoprene **2** is a moderate nucleophile, butadienes **3** and **4** are strong nucleophiles. As expected, presence of one or two strong electron-releasing substituents in the diene system increases the nucleophilicity of **3** and **4**. An analysis of the global reactivity indexes indicates that in a polar D-A reaction, nitropirroles will act as a strong electrophile, while dienes **3** and **4** will act as a strong nucleophile.

In a polar cycloaddition between asymmetrical reagents, the most favourable two-center interaction will take place between the more electrophilic center, characterized by the highest value of the local electrophilicity index ω_k at the electrophile (diene), and the more nucleophilic center, characterized by the highest value of the local nucleophilicity index N_k at the nucleophile (dienophile) [21, 22]. The local electrophilicity ω_k indexes for nitropirroles **1a-d**, and nucleophilicity N_k, indexes for butadienes **2-4** are presented in Table **5**.

For 1-nitropirrole **1a**, the most electrophilic centres are C2 and C4, while for 2-nitropirrole **1b** is the C1. This shows that a change in the position of the nitro group in pirrole, as it is expected, causes a change in the local reactivity of the pirrole system. In the same way, for the disubstituted pirrole **1c** the highest value of local electrophilicity appears in C2 and for **1d** in C4.

About dienes, the most nucleophilic center for isoprene is the C1 carbon, N_{C1} = 1.11 eV, whereas for the dienes **3** and **4** the most nucleophilic center corresponds to the C4 carbon. Consequently, a change in regioselectivity is expected for isoprene **2** and dienes **3** and **4**.

Finally, solvent effects of ILs in these Diels-Alder reactions were estimated by formation of a hydrogen-bonded complex between the nitro oxygen atoms of pirroles **1a-d**, and the most acidic hydrogen atom of the solvent [23]. The global electrophilicity (ω) of the corresponding hydrogen-bonded complexes are shown in Table **6**.

Solvent effect is found in the nitropirroles-IL complexes where the electrophilcity increases in the range from 4 to 5.50 eV. Although these values have to be carefully considered because of the simplicity of the models, they indicate that in these ILs the polar Diels-Alder reactions of nitropirroles will be accelerated as a consequence of an increase of the polar character of the reactions, achieved by an increase in the electrophilcity of the dienophile.

Table 5 Local electrophilicity (ω_k, in eV) of nitripirroles 1a-d, and local nucleophilicity (N_k, in eV) of butadienes 2-4.

		ω_k			N_k
1a	C1	0.12			
	C2	0.19	2	C1	1.11
	C3	0.02		C4	0.80
	C4	0.23			
1b	C1	0.12			
	C2	0.04	3	C1	0.80
	C3	0.00		C4	0.97
	C4	0.02			
1c	C1	0.06			
	C2	0.33	4	C1	0.41
	C3	0.01		C4	1.19
	C4	0.21			
1d	C1	0.00			
	C2	0.07			
	C3	0.05			
	C4	0.42			

Table 6 Global electrophilicity (ω), in eV, of nitripirroles 1a-d, in HMIM.

	HMIM
1a	6.93
1b	6.75
1c	7.26
1d	6.87

5. Conclusions

It has been demonstrated that mono and disubstituted *N*-tosyl-pyrroles, reacts efficiently with the above mentioned dienes polar D-A reactions. The nitro group induces 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.

DFT calculations of the electrophilicity and nucleophilicity indexes agree with the experimental results and they are good reactivity and regioselectivity predictors in these types of reactions.

Analysis of the global DFT reactivity indexes accounts for the polar nature of these D-A reactions. Formation of a HB between one oxygen atom of the nitro group present in *N*-tosyl-pirroles **1a-d** and the acidic hydrogen of [HMIM][BF_4]/[PF_6] remarkably increases the electrophilicity of the corresponding HB complex. Consequently, the P-DA reaction should be favored through a more polar process.

Acknowledgments

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