Polar Diels-Alder Reactions Developed in a Protic Ionic Liquid: 3-Nitroindole as Dienophile. Theoretical Studies Using DFT Methods

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Abstract: *N*-Tosyl-3-nitroindole reacts with moderate and strong nucleophilic dienes in a polar Diels-Alder reaction using protic ionic liquid (PIL) [HMIM][BF$_4$] as reaction media. In the cases in which the diene has oxygenated substituents, the PIL favors the aromatization of the formal [4+2] cycloadducts. Although the presence of the PIL in the reactions of *N*-tosyl-3-nitroindole as electrophile shows a clear tendency to the aromatization of the [4+2] cycloadducts, we observed that the neoteric solvent did not increase the yields in relation to a molecular solvent. Part of this work is specifically concerned with theoretical studies using DFT reactivity indices. The global and local electrophilicity and nucleophilicity indices were calculated for *N*-tosyl-3-nitroindole, and the dienes used in this study. For the studied reactions, the regioselectivity involved in the polar Diels-Alder reaction is well predicted.

1. INTRODUCTION

The versatile Diels-Alder (DA) reaction is asset in the organic chemist's toolbox because it simultaneously sets ring(s), asymmetric centers, and functional groups [1]. It provides the chemist with one of his best tools for the preparation of cyclic compounds having a six-membered ring(s). Its potential in heterocyclic chemistry and natural products synthesis is very well known. This process is in one step inter or intramolecular from aspects 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 [2].

Due to our interest in the cycloaddition chemistry of substituted aromatic heterocycles with electron-withdrawing groups, we have reported that nitro-*N*-tosylpyrroles and nitrofurans react as electrophile in polar Diels-Alder (P-DA) reactions [3, 4]. These electrophilic heterocycles were exposed to different dienes with strong, moderate and poor nucleophilic activation under thermal conditions, using molecular solvents and ionic liquids (ILs) as reaction media. In general, these reactions are domino processes which are initialized by a P-DA reaction to give the formal [4+2] cycloadduct, which undergoes an irreversible elimination of nitrous acid; this elimination is the factor responsible for the feasibility of the overall process [5-9].

Accordingly, the purpose of the present work is to explore the behavior of *N*-tosyl-3-nitroindole (**1**) in P-DA reactions with different nucleophilic dienes in presence of a PIL, in order to analyze the influence of the solvent effects on the results. With this purpose, 1-methylimidazolium tetrafluoroborate ([HMIM][BF$_4$]) has been selected as PIL. The second purpose concerned with theoretical studies using DFT methods, was to obtain information about the factors affecting reactivity and selectivity [10].

2. RESULTS AND DISCUSSION

To explore reactivity of *N*-tosyl-3-nitroindole **1** in P-DA reactions we choose isoprene (**2**), 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky diene) (**3**) and 1-trimethylsilyloxy-1,3-butadiene (**4**) as dienes (Fig. **1**) [11]. The selection of dienes took into account the type of substitution present in their structures and the relative nucleophilicity. The *N*-tosyl-3-nitroindole **1** was prepared by nitration of indole, subsequent chromatographic separation and introduction of protecting group (tosyl).
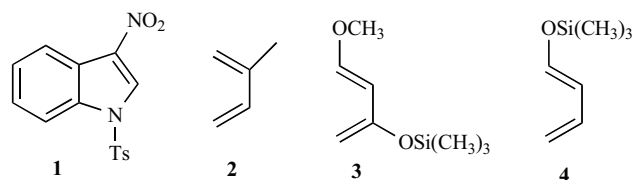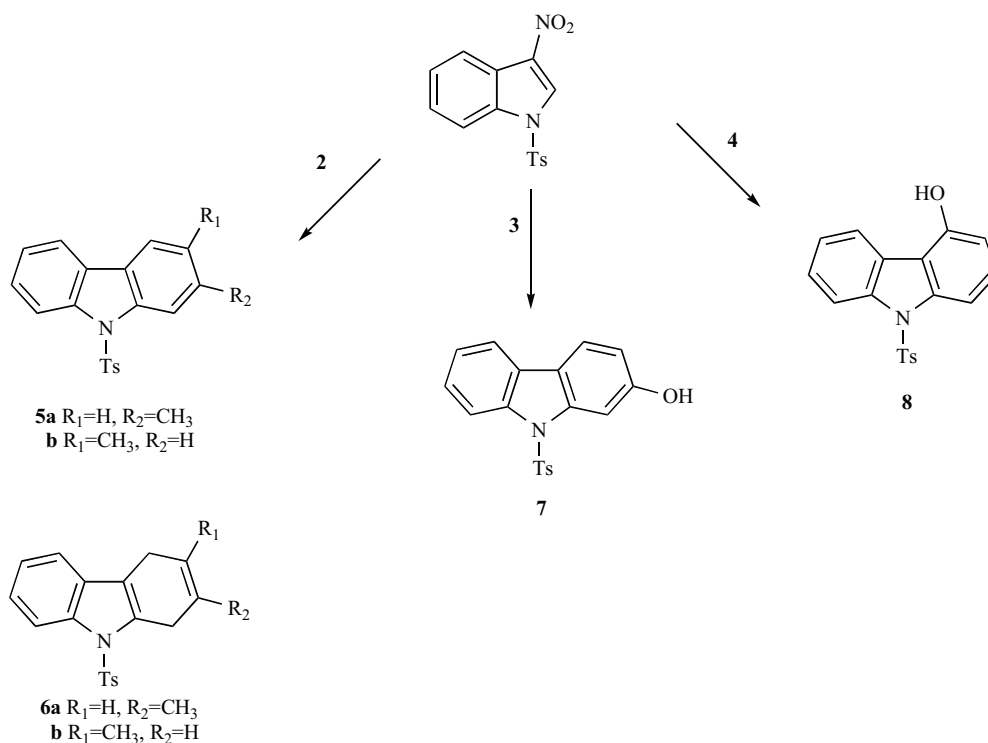

Fig. (1). Dienophile and dienes used in the different experiences.

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Fig. (2). Diels-Alder reactions of *N*-tosyl-3-nitroindole with dienes 2,3 and 4.

To complete the reaction approach of this aromatic heterocyclic substituted with an electron-withdrawing NO$_2$ group as dienophiles in P-DA reactions, we have investigated PIL solvent effects in this polar reaction using [HMIM][BF$_4$]. In general, it would be possible to demonstrate PIL solvent effect in these reactions determined by the solvent was HB donation ability. Preparation of [HMIM][BF$_4$] was followed the published methods [12]. This allowed us to compare in the thermal cycloaddition reaction, the conditions which are not only relative reactivity of this substrate but also the regioselectivities when we change molecular solvents by a PIL.

When *N*-tosyl-3-nitroindole **1** was reacted with the less reactive isoprene **2** in a sealed ampoule at 60ºC for 24 h using [HMIM][BF$_4$] as a solvent, the reactions proceeded to yield a mixture of isomeric carbazoles **5a** and **5b** (1:1) as the principal products with reasonable yield (40 %) and dihydrocarbazoles **6a** and **6b** (1:1) (10%) (Fig. **2**). If the time of the reaction increased to 48 h, we observe a 1:1 mixture of isomeric carbazoles **5a** and **5b** in 55% yield and traces of the isomeric dihydrocarbazoles **6a** and **6b** [6].

The reaction of Danishefsky´s diene **3** (60 ºC, 24 and 48 h), with **1** in the PIL yielded 2-hydroxycarbazole **7** in good yield. The product **7** obtained in these reactions resulted from the aromatization of the formal [4+2] cycloadducts 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 [6].

It is necessary to take into account that if the reaction with the Danishefsky diene **3** was developed in the presence of a molecular solvent – benzene - we observe the presence of the [4+2] cycloadduct with retention of nitro and methoxy groups (the *cis* stereochemistry was preferred in this condition) joint to a percentage of the corresponding carbazole. However, when the PIL was used, only the aromatic hydroxycarbazole was isolated. Since the reaction conditions were soft in the last case. It indicates that PIL as reaction media can favor the subsequent elimination reactions.

A DFT study for the P-DA reaction of 1-nitronaphthalene with Danishefsky diene **3** showed that (i) the transition state associated with the concerted elimination of nitrous acid is located above the transition state associated with the P-DA reaction, and (ii) in spite of the endergonic character of the P-DA reaction, the irreversible character of the elimination reaction is responsible for the feasibility of the overall process [13]. Changes in the nature of dienophile and inclusion of a PIL solvent can change these behaviors, allowing for an explanation of the unlike results for the reaction between **1** and diene **3** in PIL, and the molecular solvent benzene.

To confirm the previous results we have realized the reaction of **1** with 1-trimethylsilyloxy-1,3-butadiene **4** where nucleophilicity is observed intermediate between **2** and **3**, in benzene (90 ºC, 48 h) or in [HMIM][BF$_4$] (60 ºC, 24 and 48 h, respectively), as solvents in seals ampoule. In both cases, the observed product was 4-hydroxycarbazole **8** (entry 5 and 6 Table **1**). In benzene, the yield was ca 70 % [14, 15].

In general, although the presence of a PIL in the reactions of the electrophilic *N*-tosyl-3-nitroindole **1** changes the observed products with respect to a molecular solvent, showing a clear tendency to the aromatization of the [4+2] cycloadducts, we noted that this neoteric solvent did not improve the yields in relation to a molecular solvent. It is necessary to consider that in similar reactions, using nitrofurans or nitro-

Table 1. Diels-Alder Reactions of 1 with Diverse Dienes in [HMIM][BF$_4$].

Entry	Diene	Conditions	Product	Yield[a]
1	**2**, 12 equiv	60ºC, 24h	**5a,b; 6a,b**	50
2		60ºC, 48h	**5a,b; 6a,b**	55
3	**3**, 2 equiv	60ºC, 24h	**7**	72
4		60ºC, 48h	**7**	75
5	**4**, 3 equiv	60ªC, 24h	**8**	65
6		60ªC, 48h	**8**	70

[a] Based on consumed dienophile

Table 2. Electronic Chemical Potential (μ), Chemical Hardness (η), Global Electrophilicity (ω), and Global Nucleophilicity (N), in eV, of *N*-tosyl-3-nitroindole 1, and butadienes 2-4.

Molecule (diene or dienophile)	μ	η	ω	N
1-[HMIM][BF$_4$]	-0.18	0.12	3.48	2.64
1	-4.37	4.24	2.25	2.63
2	-3.30	5.77	0.94	2.94
3	-2.69	5.31	0.68	3.77
4	-2.79	5.33	0.73	3.67

tosylpyrroles as dienophiles with the same dienes, the presence of a PIL as reaction media improves the yields with respect to the use of a molecular solvent, while the temperature and reaction time decrease. Probably, these results would be ascribed to the better electrophilicity of *N*-tosyl-3-nitroindole **1**. In this direction, the reactions of *N*-tosylnitropyrroles with these dienes developed in molecular solvents need 120ºC to produce a reasonable yield. Then, when the activation energy is lower the PIL effect is not determined in the yield.

3. THEORETICAL STUDIES

Studies carried out in DA reactions have shown that the reactivity indices defined within the conceptual DFT are powerful tools for establishing the polar character of such reactions [16]. The static global properties of *N*-tosyl-3-nitroindole **1**, and the butadienes **2**, **3** and **4**, namely electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (*N*), are shown in Table **2**.

The electronic chemical potential of *N*-tosyl-3-nitroindole **1**, μ = -4.37eV, is lower than that of dienes **2**, **3** and **4**, μ range from –3.30 to –2.69 eV. Therefore, it is expected that along a P-DA reaction, the CT will take place from these electron-rich dienes to *N*-tosyl-3-nitroindole **1**.

The electrophilicity ω of *N*-tosyl-3-nitroindole **1**, is 2.25 eV, which allows its classification as a strong electrophile within the electrophilicity scale [17]. On the other hand, its nucleophilicity *N* index, 2.63 eV, allows its classification as a moderate nucleophile within the nucleophilicity scale [18].

The electrophilicities ω of dienes are 0.94 eV (**2**), is 0.73 eV (**4**) and 0.68 eV (**3**), being classified then as marginal electrophiles within the electrophilicity scale. On the other hand, the nucleophilicities *N* of these species are 2.94 eV (**2**), 3.77 eV (**3**) and 3.67 eV (**4**). Therefore, while diene **2**, is classified as poor nucleophile, dienes **3** and **4** are classified as strong and moderate nucleophiles. As expected, the 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 indices indicates that in a P-DA reaction, *N*-tosyl-3-nitroindole **1** will act as a strong electrophile, while dienes **4** and **3** will act as strong nucleophiles.

Solvent effects of the PIL in these P-DA reactions were estimated by implicit formation of a BH between one oxygen atom of the nitro group of *N*-tosyl-3-nitroindole **1** and the most acidic hydrogen atom of the PIL solvent, the H-N hydrogen of HMIM$^+$ cation [19]. The BF$_4^-$ anion was included over the plain of the counteraction. The global electrophilicity of the corresponding **1**-[HMIM][BF$_4$] complex is ω = 3.48 eV (see Table **2**). Note that this high value decreases to 2.98 eV when implicit solvent effects are considered [20]. Consequently, HB formation on the **1**-[HMIM][BF$_4$] complex considerably increases the electrophillcity of **1**, allowing for an acceleration of the reaction *via* a more polar process. However, as the subsequent elimination reaction can be the rate-determining of the reaction, PIL effects of these P-DA reactions can not be evidenced in the overall process.

In a polar cycloaddition between asymmetrical reagents, the most favorable two-center interaction will take place more between the electrophilic center, characterized by the highest value of the local electrophilicity index [21] ω_k at the

Table 3. Local Electrophilicity (ω_k, in eV) of *N*-tosyl-3-nitroindole 1 and the HB Complex 1-[HMIM][BF$_4$], and Local Nucleophilicity (N_k, in eV) of butadienes 2-4.

Dienophile	Atom	ω_k	Diene	Atom	N_k
1	C$_1$	0.48	**2**	C$_1$	1.11
	C$_2$	0.07		C$_4$	0.80
1-[HMIM][BF$_4$]	C$_1$	0.75	**3**	C$_1$	0.56
	C$_2$	0.04		C$_4$	1.47
			4	C$_1$	0.80
				C$_4$	0.97

electrophile, and the more nucleophilic center, characterized by the highest value of the local nucleophilicity index [22] N_k at the nucleophile [23]. The local electrophilicity ω_k indices for *N*-tosyl-3-nitroindole, and nucleophilicity N_k, indices for butadienes **2**, **3**, and **4** are presented in Table **3**.

For *N*-tosyl-3-nitroindole, the most electrophilic centre is C2 carbon, $\omega_{C2} = 0.48$ eV. Thus, presence of a strong electron-withdrawing NO$_2$ group at C3, electrophilically activates the C2 position of the indole system. For 2-methylbutadiene **2**, the most nucleophilic center corresponds with the C1 carbon, $N_{C1} = 1.11$ eV whereas for the dienes **3** and **4** the most nucleophilic center corresponds with the C4 carbon; $N_{C4} = 1.47$ eV (**3**) and $N_{C4} = 0.97$ eV (**4**). Consequently, a change in regioselectivity is expected for 2-methylbutadiene **2** with respect to dienes **3** and **4**.

Finally, analysis of the local electrophilicity ω_k in the **1**-[HMIM][BF$_4$] complex asserts that the HB formation at the NO$_2$ group activates more electrophilically at the C1 position of the indole system (see Table **3**).

COMPUTATIONAL DETAILS

DFT calculations were carried out using the B3LYP [24] exchange-correlation functionals, together with the standard 6-31G* basis set [25]. All calculations were carried out with the Gaussian 03 suite of programs [26].

The global electrophilicity index [27], ω, is given by the following simple expression. $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively [28]. Recently, Domingo *et al.* have introduced an empirical (relative) nucleophilicity index, N [29], based on the HOMO energies obtained within the Kohn-Sham scheme [30], and defined as $N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)}$. The nucleophilicity is referred to tetracyanoethylene (TCE), 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 to handle a conveniently nucleophilicity scale of positive values. Local electrophilicity [21] and nucleophilicity [22] 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 [31].

4. CONCLUSIONS

It has been demonstrated that *N*-tosyl-3-nitroindole **1** reacts efficiently in presence of [HMIM][BF$_4$] as PIL with the above-mentioned dienes of increased nucleophilicity in P-DA reactions, with the 3-nitro group inducing C2-site selectivity. In all studied cases, the presence of [HMIM][BF$_4$] as reaction media produces a complete aromatization of the initial [4+2] cycloadduct, when oxygenated dienes **3** and **4** are used. The reaction with diene **4** was also developed in a molecular solvent, obtaining the same product than that using PIL. Using diene **3** in benzene, the initial [4+2] cycloadduct is observed. This PIL did not improve the yields. Previously, we noted that when N-tosyl-nitropyrroles are the electrophiles, the influence of the PIL increases the reaction yields. This situation is not observed with the N-tosyl-nitroindole as the dienophile probably as a consequence of its better reactivity.

Analysis of the global DFT reactivity indices accounts for the polar nature of these DA reactions. Formation of an HB between one oxygen atom of the nitro group present in *N*-tosyl-nitroindole **1** and the acidic hydrogen of [HMIM][BF$_4$] remarkably increases the electrophilicity of the corresponding HB complex. Consequently, the P-DA reaction should be favored through a more polar process. On the other hand, analysis of the local electrophilicity in N-tosyl-nitroindole **1** and the local nucleophilicity in dienes **2**, **3** and **4** accounts for the regioselectivity experimentally observed. Changes in regioselectivity are mainly due to changes in C1 or C4 local nucleophilic activation in this diene systems as a consequence of the unlike electron-releasing substitution.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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[11] 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.

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[14] General Aspects. ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ on 300 and 75 MHz FT-spectrometers, respectively, using TMS as the internal standard; CG-MS analyses were performed in an instrument equipped with a PE-5-type column. IR spectra were recorded from NaCl cells. Melting points were observed on a Winkle-Zeiss Gottingen microhot stage. The silica gel and neutral alumina used for chromatography were 70-230 mesh.

[15] Spectral data: Compound **8**: IR 3200, 1378, 1173 cm^{-1}. NMR (CDCl$_3$) δ: 2.37 (s, 3H); 6.75 (dd, 1H, J=8.1Hz, 2.3Hz); 7.30 (m, 2H); 7.60 (m, 2 H); 7.66 (d, 2H, J= 8.0 Hz); 7.84 (d, 2H, J= 8.0 Hz); 8.14 (dd, 1H, J=7.5Hz, J=1.2Hz); 8.89 (dd, 1H, J=7.8Hz, J=1.5Hz).^{13}C NMR (CDCl$_3$) δ: 21.6; 108.5; 109.9; 118.7; 121.5; 127.2; 130.2; 131.2; 133.5; 134.6; 135.4; 136.0; 145.8. HRMS m/z 337.3935 (Calcd C$_{19}$H$_{15}$O$_3$NS 337.3927).

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