

RESEARCH ARTICLE

Cycloaddition Reactions Assisted by Microwave Irradiation: Protic Ionic liquids vs Solvent-free Conditions

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Abstract: Background: The behavior of *N*-tosylnitroindoles acting as electrophilic dienophiles in polar Diels-Alder reactions joint to different dienes was analyzed. Reactions were developed under microwave irradiation using toluene or protic ionic liquids as solvents under solvent-free conditions. Good yields in short reaction times were observed. Solvent-free conditions and protic ionic liquids as solvents offered similar results. However, solvent-free conditions favor environmental sustainability. The processes between *N*-substituted nitroindoles and isoprene were selected for a theoretical study.

Method: The reactions between the different electrophile-nucleophile pairs were developed under two conditions: (A) reactants and solvents (PILs) were heated in a closed ampoule under conventional thermal conditions, 60°C-48h, except for those developed in toluene that react at 180°C-72h; (B) under the effect of MW irradiation in a MW apparatus at 180°C-0.5h. In both the cases, the solvents used were toluene and PILs. All calculations were carried out within the DFT framework using the Gaussian 09 suite of programs. For this purpose, the hybrid functional B3LYP was used together with the 6-31G(d) basis set.

Results: Experiments were carried out with P-DA process using microwave irradiation instead of conventional heating. Cycloaddition reactions of nitro substituted indoles with different dienes were particularly analyzed using this methodology in the presence of PILs as solvent and under solvent-free conditions. Good yields were obtained in short reaction times. The yields observed in this thermal reaction are lower than those obtained under MW irradiation. This can be explained considering the type of heating produced by MW irradiation. Nitro indoles substituted in the heterocyclic ring and in the benzene moiety were used to compare the behaviors. In both cases, yields and reactivity were similar. A theoretical analysis was performed using Density Functional Theory, which explained the experimental data.

Conclusion: The *N*-tosyl-nitroindoles explored in this work reacted as dienophilic electrophiles with dienes of different nucleophilicity. Reactions with different diene/dienophile pairs offered similar products under conventional heating or microwave irradiation. However, under the latter experimental condition, reaction times were significantly short with similar yields. Solvent-free conditions constitute a frequently used tool in microwave systems due to simpler manipulation, low cost, good product separation and for being environmentally friendly. Concerning the DFT study, the theoretically explored system shows that the TSs are unique and asynchronous. Theoretical calculations coincide with the experimental results. Under MW irradiation, in the presence of a PIL, the charge transfer is higher than solvent-free conditions.

Keywords: Cycloaddition, DFT, ionic liquids, microwave irradiation, nitroindoles, solvent effects, theoretical study.

1. INTRODUCTION

In organic synthesis, one of the most important reactions is the Diels-Alder (DA) cycloaddition reaction. With its property to form carbon-carbon, carbon-heteroatom, and heteroatom-heteroatom bonds, the reaction underlines the

preparation of diverse carbocyclic and heterocyclic compounds. For this reason, the reaction has been used as a key step in the synthesis of several natural products with biological properties [1]. Its application not only leads to a strong increase in molecular complexity but can also result in structures that lend themselves to additional amplification of complexity by the use of other powerful synthetic transformations [2, 3].

Due to our interest in the cycloaddition reactions of substituted aromatic heterocycles with electron-withdrawing

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groups, we have reported studies related to the electrophilic character of aromatic compounds with adequate substitution in their reactions with different dienes. In this process, the electrophiles react with the dienes through polar Diels-Alder (P-DA) reactions to obtain in one step the respective cycloadducts. In general, these cited reactions are domino processes initialized by a P-DA cycloaddition to yield the formal $[4\pi+2\pi]$ cycloadduct, which is followed by the concerted irreversible elimination of the nitro group as nitrous acid. This latter step is responsible for the feasibility of the overall process [4-14]. Considering the potential influence of the solvents and the specific effect, the reactions were opportunely developed under conventional thermal conditions and using toluene or protic ionic liquids (PILs) as reaction media. The experimental results showed that by employing neoteric solvents, the reactions were faster than those developed in traditional organic solvent [15, 16].

Microwave-assisted controlled heating has become a powerful tool in organic synthesis. This condition is being used to accelerate organic reactions, generally increasing the yield. The region of microwave (MW) irradiation is located between the infrared and radio waves. In the MW region, the electromagnetic energy affects the molecular rotation without changing the molecular structure [17, 18]. Using MW irradiation, the reaction mixture undergoes heating by a combination of thermal effect, dipolar polarization and ionic conduction. Then, the polar compound can absorb energy very efficiently [19]. This procedure has been successfully employed even observing selectivity modifications, although the MW effect is still a topic of discussion [20-22].

We have recently demonstrated that the combination of MW radiation and the use of a protic ionic liquid (PIL) as solvent (1-methylimidazolium tetrafluoroborate) improves the yield of the reaction between 2-nitro-*N*-tosylpyrrole and isoprene in shorter reaction times [23].

Considering the influence of MW irradiation to improve organic reactions, we carried out several experiments with the P-DA process using this methodology instead of conventional heating. The aim of this work is to study the cycloaddition reactions of nitro substituted indoles with dienes of different nucleophilicity using MW irradiation in two experimental situations, in the presence of PILs as solvent and under solvent-free conditions. This latter one could be especially important due to its low impact on the environment. In this study, we employed nitro substituted indoles in the heterocyclic ring and in the benzene moiety to compare reactivities. Besides, the behavior of the cycloaddition reactions between nitroindoles and different dienes is discussed in a theoretical way using Density Functional Theory (DFT). For this purpose, we selected the reactions between *N*-mesyl-nitroindoles and isoprene as an example of this type of processes because it is the simplest computational system to work with.

2. MATERIALS AND METHOD

The reactions between the different electrophile-nucleophile pairs were developed under two conditions: (A) the reactants and solvents (PILs) were heated in a closed ampoule, under conventional thermal conditions, 60°C-48h except for those developed in toluene that react at 180°-72h;

and (B) under the effect of MW irradiation, in a MW apparatus, at 180°C-0.5h. In both cases, the solvents used were toluene and PILs. In both cases, the PILs used were 1-methylimidazolium tetrafluoroborate [HMIM][BF₄], 1-methylimidazolium hexafluorophosphate [HMIM][PF₆] and ethylammonium nitrate [NEA]. The same reactions were simultaneously developed under MW irradiation under solvent-free conditions. The diene/dienophile relation was 12:1 when isoprene was the diene and 3:1 for the other dienes employed. The yields of reaction were measured in relation to the dienophile consumption. The preparation of [HMIM][BF₄], [HMIM][PF₆] and [NEA] was carried out following published methods [24, 25].

2.1. Computational Details

All calculations were carried out within the DFT framework using the Gaussian 09 suite of programs [26]. For this purpose, the hybrid functional B3LYP was used together with the 6-31G(d) basis set [27, 28]. Optimizations were carried out using the Bery analytical gradient optimization method [29]. The frequency calculations were performed in order to validate the optimized structures. In this sense, reactants and cycloadduct (CA) structures were verified by the absence of negative frequencies, and the transition states (TSs) by the presence of only one imaginary frequency. The electronic structures of critical points were analyzed by the natural bond orbital (NBO) method [30, 31]. Solvent effects were considered at the same level of theory by the geometry optimization of the system structures based on the supermolecular approach.

3. EXPERIMENTAL

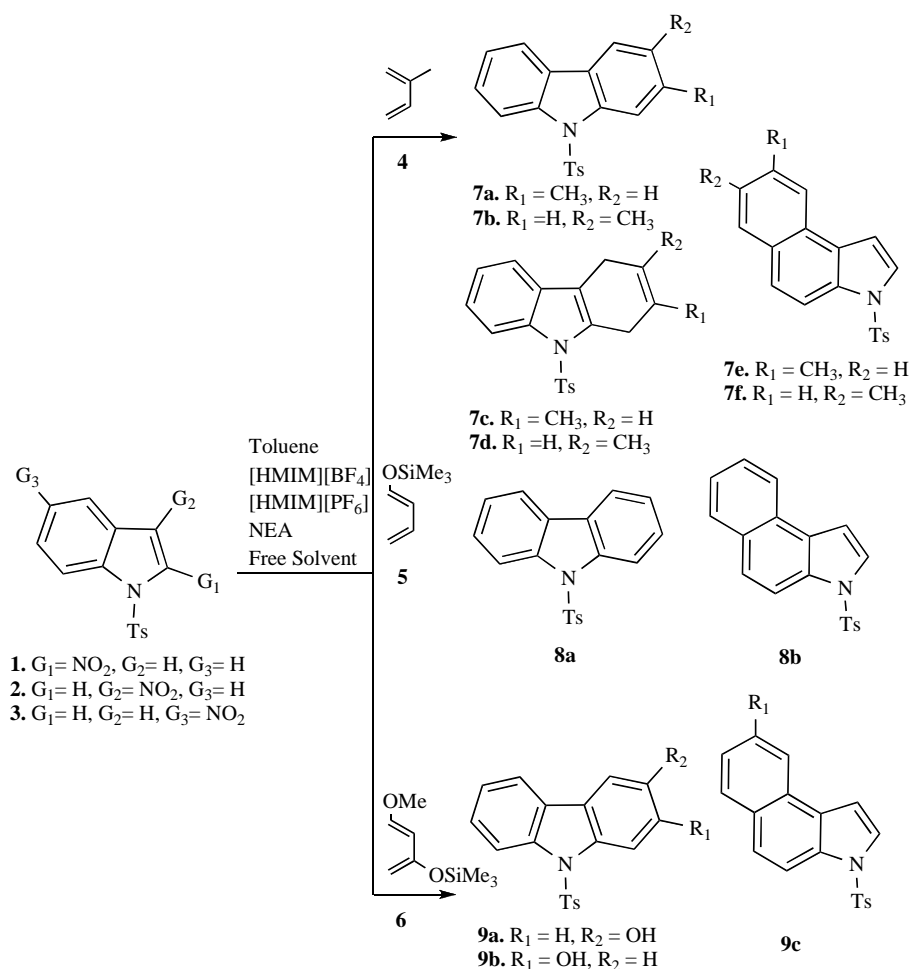
¹H and ¹³C NMR spectra were recorded in CDCl₃ on 300 MHz FT spectrometers, using TMS as the internal standard. GC-MS analyses were performed in an instrument equipped with a PE-5-type column. IR spectra were recorded from NaCl cells as CCl₄ solutions. Silica gel of 70-230 mesh was used for chromatography. The following reagents were prepared according to the reported methods: **1**, **2** [32, 33]. Other reagents: **3**, **4**, **5**, and **6** were obtained from commercial sources and were used as received or purified as required by standard methods. Products **7a**, **7b**, **7c**, **7d**, **8a** and **9b** were previously reported [34, 35].

3.1. **7e** (8-methyl-3-tosyl-3H-benzo[e]indole) and **7f** (7-methyl-3-tosyl-3H-benzo[e]indole)

IR [cm⁻¹]: 3053, 1625, 1374, 1179 NMR ¹H (300 MHz, CDCl₃) δ: 2.35 (s, 3H), 2.47 (s, 3H), 6.30 (br s, 1H), 6.92 (t, 1H), 7.19 (d, 1H), 7.38 (t, 1H), 7.44 (d, 2H), 7.60 (d, 1H), 7.78 (d, 2H), 8.00 (m, 2H). NMR ¹³C (75 MHz) δ: 21.2, 21.6, 105.0, 111.8, 118.7, 119.3, 123.8, 126.5, 127.2, 128.9, 130.3, 130.8, 132.6, 134.9, 135.6, 136.5, 136.8, 139.2. HRMS (C₂₀H₁₇O₂NS) m/z 335.0979 (Theoretical 335.0985).

3.2. **8b** (3-tosyl-3H-benzo[e]indole)

IR [cm⁻¹]: 3045, 1462, 1365, 1175. NMR ¹H (300 MHz, CDCl₃) δ: 2.35 (s, 3H), 6.33 (d, 1H), 7.46 (d, 2H), 7.60 (d, 1H), 7.70 (m, 2H), 7.87 (d, 2H), 8.02 (m, 2H), 8.12 (m, 1H), 8.45 (d, 1H). NMR ¹³C (75 MHz) δ: 21.3, 103.0, 112.1, 117.2, 119.3, 122.3, 127.8, 128, 128.6, 128.9, 129.2, 129.7,



Scheme 1. Diels-Alder reaction of *N*-tosyl-nitroindoles with different dienes under several reaction conditions.

130.6, 134.6, 135.2, 136, 139.3. HRMS (C₁₉H₁₅O₂NS) *m/z* 321.0822 (Theoretical 321.0828).

3.3. 9a (9-tosyl-3-hidroxy-9H-carbazole)

IR [cm⁻¹]: 3218, 1632, 1378, 1165. NMR 1H (300 MHz, CDCl₃) δ: 2.32 (s, 3H), 7.08 (d, 1H), 7.25 (m, 1H), 7.38 (m, 1H), 7.45 (d, 2H), 7.52 (d, 1H), 7.68 (s, 1H), 7.92 (d, 2H), 8.01 (m, 1H) 8.55 (d, 1H). NMR 13C (75 MHz) δ: 21.6, 104.2, 107, 112.6, 112.9, 114.2, 120.6, 122.5, 125, 125.6, 127.8, 129.9, 132.3, 135.4, 136.3 139.4, 153.2. HRMS (C₁₉H₁₅O₃NS) *m/z* 321.0771 (Theoretical 321.0778).

3.4. 9c (3-tosyl-8-hidroxy-3H-benzo[e]indole)

IR [cm⁻¹]: 3198, 1375, 1172. NMR 1H (300 MHz, CDCl₃) δ: 2.35 (s, 3H), 5.36 (s br, 1H), 6.39 (d, 1H), 7.22 (d, 1H), 7.38 (s, 1H), 7.48 (d, 2H), 7.66 (d, 1H), 7.92 (d, 2H), 8.05 (m, 3H). NMR 13C (75 MHz) δ: 21.2, 102.8, 109.2, 111.6, 117.6, 118.4, 118.9, 123, 128.2, 128.6, 128.9, 129.8, 131.3, 134, 135.4, 136.2, 139, 155.3. HRMS (C₁₉H₁₅O₃NS) *m/z* 321.0771 (Theoretical 321.0778).

4. RESULTS AND DISCUSSIONS

To explore the normal electron demand P-DA reaction, the electrophilicity of 2-nitro-*N*-tosylindole (1), 3-nitro-*N*-

tosylindole (2) and 5-nitro-*N*-tosylindole (3), we selected isoprene (4), 1-trimethylsilyloxy-1,3-butadiene (5), and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky diene) (6) as dienes (Scheme 1). The dienes were selected taking into account the type of substitution present in their structures and their relative nucleophilicity. The nitroindoles were prepared by the nitration of indole, following the conventional form, subsequent chromatographic separation and introduction of the protecting group (tosyl). 5-Nitro-*N*-tosylindole was a commercial one. The yields observed in these thermal reactions were lower than those developed under MW irradiation. These results can be explained considering the type of heating produced by MW irradiation.

Reactions 1 and 2 with 4 under MW irradiation using the three PILs respectively as reaction media offered in each case the mixture (1:1) of the isomeric carbazoles (7a and 7b) with reasonable yield (ca 60%, Table 1). The same products were obtained under solvent-free conditions. Under MW irradiation we do not observe the presence of dihydrocarbazoles, which is frequent under normal thermal conditions (7c and 7d).

When electrophiles 1 and 2 reacted with 5 using MW irradiation and PILs as solvent or under solvent-free conditions the only product was *N*-tosylcarbazole (8a). All reactions show a good yield (ca. 75%, Table 2).

Table 1. Reaction conditions of isoprene with *N*-tosyl-nitroindoles.

Reaction	Dienophile	Condition	Solvent	Product	η (%)	
1	2-nitro- <i>N</i> -tosylindole	A	Toluene	7a,7b	36	
				7c,7d	8	
2			[HMIM][BF ₄]	7a,7b	37	
				7c,7d	trace	
3			[HMIM][PF ₆]	7a,7b	36	
				7c,7d	8	
4			NEA	7a,7b	54	
				7c,7d	trace	
5			B	Toluene	7a,7b	50
6				Solvent-Free	7a,7b	62
7	[HMIM][BF ₄]	7a,7b		60		
8	[HMIM][PF ₆]	7a,7b		58		
9	NEA	7a,7b		63		
10	3-nitro- <i>N</i> -tosylindole	A	Toluene	7a,7b	32	
				7c,7d	8	
11			[HMIM][BF ₄]	7a,7b	38	
				7c,7d	6	
12			[HMIM][PF ₆]	7a,7b	36	
				7c,7d	7	
13			NEA	7a,7b	40	
				7c,7d	6	
14			B	Toluene	7a,7b	53
15				Solvent-Free	7a,7b	63
16	[HMIM][BF ₄]	7a,7b		60		
17	[HMIM][PF ₆]	7a,7b		60		
18	NEA	7a,7b		62		
19	5-nitro- <i>N</i> -tosylindole	A	Toluene	7e,7f	29	
			[HMIM][BF ₄]	7e,7f	46	
[HMIM][PF ₆]			7e,7f	46		
NEA			7e,7f	47		
23		B	Toluene	7e,7f	51	
			Solvent-Free	7e,7f	58	
			[HMIM][BF ₄]	7e,7f	62	
			[HMIM][PF ₆]	7e,7f	60	
			NEA	7e,7f	63	
20						
21						
22						
24						
25						
26						
27						

Table 2. Reaction conditions of 1-trimethylsilyloxy-1,3-butadiene *N*-tosyl-nitroindoles.

Reaction	Dienophile	Condition	Solvent	Product	η (%)
1	2-nitro- <i>N</i> -tosylindole	A	Toluene	8a	39
2			[HMIM][BF ₄]	8a	62
3			[HMIM][PF ₆]	8a	61
4			NEA	8a	71
5		B	Toluene	8a	61
6			Solvent-Free	8a	73
7			[HMIM][BF ₄]	8a	76
8			[HMIM][PF ₆]	8a	73
9			NEA	8a	76
10	3-nitro- <i>N</i> -tosylindole	A	Toluene	8a	40
11			[HMIM][BF ₄]	8a	62
12			[HMIM][PF ₆]	8a	60
13			NEA	8a	60
14		B	Toluene	8a	61
15			Solvent-Free	8a	72
16			[HMIM][BF ₄]	8a	76
17			[HMIM][PF ₆]	8a	73
18			NEA	8a	77
19	5-nitro- <i>N</i> -tosylindole	A	Toluene	8b	33
20			[HMIM][BF ₄]	8b	36
21			[HMIM][PF ₆]	8b	33
22			NEA	8b	37
23		B	Toluene	8b	62
24			Solvent-Free	8b	70
25			[HMIM][BF ₄]	8b	72
26			[HMIM][PF ₆]	8b	68
27			NEA	8b	75

The reactions of **1** and **2** with **6** under the conditions indicated above offer isomeric hydroxylated *N*-tosylcarbazoles (**9a** and **9b**), respectively, with good yield (ca. 75 %, Table 3). The reactions are regioselective as a consequence of the diene substitution combined with its nucleophilicity. Under both reaction conditions, the results were similar.

When **3** reacted with **4** under MW irradiation in the presence of a PIL or under solvent-free conditions, in all cases it offers the isomeric mixture (1:1) of benzo[e]indoles (**7e** and **7f**) with reasonable yield (ca. 60%). On the other hand, the reactions of **3** with **5** under all the mentioned reaction conditions produced the benzo[e]indole (**8b**) with good yield (ca. 70%). Finally, the reactions of **3** with **6** yielded in regioselective

form the hydroxylic benzo[e]indole (**9c**) with good yield (ca. 75%). Once again, the regioselectivity observed is a consequence of the diene employed.

In all cases studied the nitro group is responsible for the orientation.

As in conventional heating, under MW irradiation all PILs produced similar yields in the reactions between the electrophiles (**1-3**) with the different dienes. These yields are comparable with those observed under solvent-free conditions and lightly higher than those obtained employing a molecular solvent such as toluene. In general, it would be possible to demonstrate that the effect of the PIL under MW irradiation is due to various causes (*e.g.*: hydrogen bonding

Table 3. Reaction conditions of Danishefsky diene with *N*-tosyl-nitroindoles.

Reaction	Dienophile	Condition	Solvent	Product	η (%)
1	2-nitro- <i>N</i> -tosylindole	A	Toluene	9a	30
2			[HMIM][BF ₄]	9a	75
3			[HMIM][PF ₆]	9a	72
4			NEA	9a	75
5		B	Toluene	9a	60
6			Solvent-Free	9a	72
7			[HMIM][BF ₄]	9a	77
8			[HMIM][PF ₆]	9a	74
9			NEA	9a	76
10			3-nitro- <i>N</i> -tosylindole	A	Toluene
11	[HMIM][BF ₄]	9b			72
12	[HMIM][PF ₆]	9b			70
13	NEA	9b			75
14	B	Toluene		9b	62
15		Solvent-Free		9b	72
16		[HMIM][BF ₄]		9b	75
17		[HMIM][PF ₆]		9b	74
18		NEA		9b	77
19		5-nitro- <i>N</i> -tosylindole		A	Toluene
20	[HMIM][BF ₄]		9c		56
21	[HMIM][PF ₆]		9c		55
22	NEA		9c		55
23	B		Toluene	9c	65
24			Solvent-Free	9c	72
25			[HMIM][BF ₄]	9c	76
26			[HMIM][PF ₆]	9c	70
27			NEA	9c	76

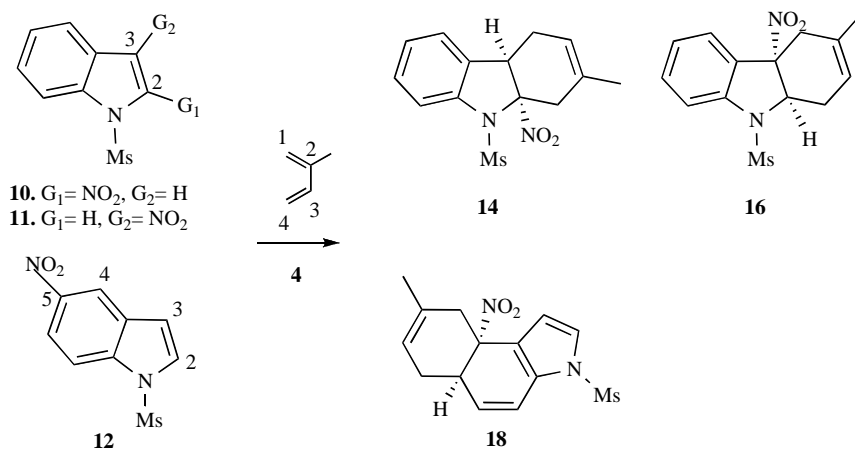
ability, ionic pair character, polarity, molecule vibration, etc.) [36, 37].

4.1. Theoretical Studies

In order to understand the effects of PILs and solvent-free conditions under MW irradiation in P-DA processes, the reactions between 2-nitro-*N*-mesylindole (**10**), 3-nitro-*N*-mesylindole (**11**), and 5-nitro-*N*-mesylindole (**12**) with **4**, as models in the absence and in the presence of [HMIM][BF₄] as a PIL were theoretically studied. For this purpose, in all cases the reactions were analyzed until the formation of the DA product (cycloadduct) result of the endo/para approach mode of **4** with respect to the electron-withdrawing (EW) nitro group was analyzed (Scheme 2).

Analysis of the potential energy surfaces (PES) associated with this process indicates that the cycloaddition takes place through a one-step mechanism *via* a high asynchronous TS. Therefore, reagents, one TS and the formal [4+2] CA were located and characterized.

The effects of the [HMIM][BF₄] in this P-DA reactions were evaluated employing the supermolecular approach, particularly considering the implicit effects of the PIL by forming a hydrogen bond (HB) between the acidic hydrogen of [HMIM]⁺ cation and the oxygen of the nitro group. The counter [BF₄]⁻ anion was also included to minimize the positive charge present in the [HMIM]⁺ cation. The results of relative energy are summarized in Table 4.



Scheme 2. Diels-Alder reactions of *N*-mesyl-nitroindoles with isoprene.

Table 4. Activation energies and enthalpies of reaction of Diels-Alder reactions of *N*-mesyl-nitroindoles with isoprene in the presence and absence of [HMIM][BF₄] as PIL.

Molecule	$\Delta E(\text{kcal/mol})$	
	Gas-Phase	[HMIM][BF ₄]
2-nitro- <i>N</i> -mesylindole	-	-
Isoprene	-	-
TS	18.09	13.53
CA	-29.67	-28.46
3-nitro- <i>N</i> -mesylindole	-	-
Isoprene	-	-
TS	17.37	12.49
CA	-25.94	-22.34
5-nitro- <i>N</i> -mesylindole	-	-
Isoprene	-	-
TS	29.8	26.11
CA	-5.34	-4.36

In the gas-phase, the activation energy associated with the nucleophilic attack of the C₁ carbon of **4** on the C₃ carbon of **10** via TS (**13a**) presents a value of 18.09 kcal/mol and the formation of the CA (**14**) is exothermic by -29.67 kcal/mol. When the effect of the PIL is considered (**13b**), the activation energy value decreases to 13.53 kcal/mol and the formation of the CA value changes to -28.46 kcal/mol. In the case of the reaction between **11** and **4**, the nucleophilic attack of the C₁ of the diene on the C₂ carbon of dienophile via TS (**15a**) presents an activation energy value of 17.37 kcal/mol and the formation of the CA (**16**) is exothermic by -25.94 kcal/mol. When the effect of the PIL is considered (**15b**), the activation energy value decreases to 12.49 kcal/mol and the formation of the CA value changes to -22.34 kcal/mol. On the other hand, in the reaction between **12** and **4** the activation energy associated with the nucleophilic attack of the C₁ of the diene on the C₄ carbon of dienophile via TS (**17a**) pre-

sents a value of 29.80 kcal/mol and the formation of the CA (**18**) is exothermic by -5.34 kcal/mol. Once again, under the effect of the PIL (**17b**), the activation energy value decreases to 26.11 kcal/mol and the formation of the CA value changes to -4.36 kcal/mol. In this sense, the P-DA reactions involving 2- and 3- nitro-*N*-mesylindoles are thermodynamically more favorable and the activation energies lower in relation to the reaction that involves 5-nitro-*N*-mesylindole. This is expected because in the latter case, the reaction involves the loss of the benzene aromaticity. Besides, the activation energies decrease when PILs are used making the process more favorable. As expected, the presence of the nitro group in the heterocyclic moiety is more favorable than when it is in the benzene moiety.

The gas-phase geometry of the TS and TS-PIL of every reaction is given in Fig. (1). The lengths of C₃-C₁ and C₂-C₄

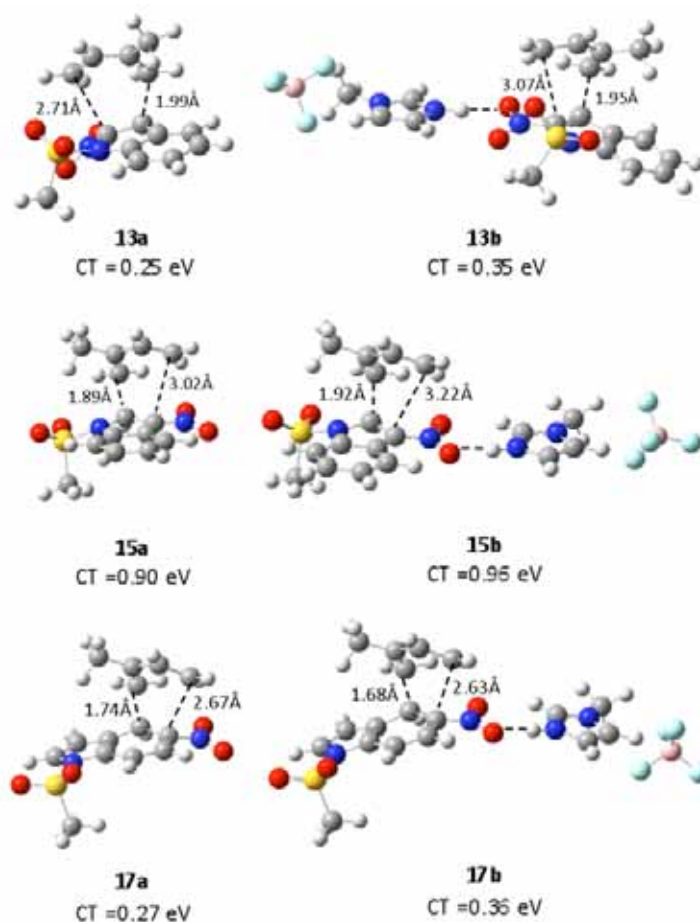


Fig. (1). Transition states of Diels-Alder reactions of *N*-mesyl-nitrolindoles with isoprene in the presence and absence of [HMIM][BF₄] as PIL.

forming bonds at TS are 1.99 and 2.71 Å ($\Delta r = 0.72$ Å), respectively in the reaction between **10** and **4**. When the effect of the PIL is considered, this values changes to 1.95 and 3.07 Å ($\Delta r = 1.12$ Å), respectively. The lengths of C₂-C₁ and C₃-C₄ forming bonds at TS are 1.89 and 3.02 Å ($\Delta r = 1.13$ Å), respectively in the reaction between **11** and **4**. When the effect of the PIL is considered, this values changes to 1.92 and 3.22 Å ($\Delta r = 1.30$ Å), respectively. The lengths of C₄-C₁ and C₅-C₄ forming bonds at TS are 1.74 and 2.67 Å ($\Delta r = 0.93$ Å), respectively in the reaction between **12** and **4**. When the effect of the PIL is considered, these values change to 1.68 and 2.63 Å ($\Delta r = 0.95$ Å), respectively. These values suggest a mechanism with highly asynchronous TS. The bond formation between the most nucleophilic center of the diene and the most electrophilic center of dienophile takes place in the first stage of the reaction, and the second bond formation takes place at the second stage of the reaction. The effect of the PIL increases the asynchronism of the reactions considering the changes in the values of Δr .

The polar nature of the DA reactions was evaluated analyzing the charge transfer (CT) at TSs. The natural charges were shared between the indole derivatives and the isoprene frameworks. At TS, the CT that flows from isoprene to the dienophile is 0.25 eV, 0.90 eV and 0.27 eV in the reactions of **10**, **11** and **12**, respectively. When PIL is considered, the CT values increase to 0.35 eV, 0.96 eV and 0.36 eV, respec-

tively. These values point out the zwitterionic character of the TSs.

The large acceleration found, in terms of reaction times 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 HB formation, which favors the CT process [38]. This leads to lower activation energies values and high asynchronous reactions.

Electron localization function (ELF) [39-42] studies devoted to the bonding changes along P-DA reactions have suggested that the main electronic changes from reagents to TSs are related to the reduction of the C-C double-bond character in the diene and dienophile [43, 44]. An analysis of the displacement vectors of the IR frequency vibrations of the reactive systems shows the presence of stretching vibrations with atomic movements similar to the electronic changes involved in the formation of the corresponding TSs.

The stretching vibrations of **13a** and **13b** are 1393 cm⁻¹ and 1390 cm⁻¹ respectively. In the case of **15a**, the stretching vibrations are 1404 cm⁻¹ and 1401 cm⁻¹ for **15b**. Similarly, the stretching vibrations of **17a** are 1383 cm⁻¹ and 1380 cm⁻¹ for **17b**. This means that any additional energy comprised between 1700 and 1400 cm⁻¹ can favor the process by favoring the electronic changes needed to reach the TS geometry. Consequently, a decrease in the reaction time is experimen-

tally observed. Note that the stretching vibration values between TS and TS-PIL are similar within systems, which means that the MW effects should be similar in both cases. This is in agreement with the experimental results of similar yields and reaction times.

CONCLUSION

The *N*-tosyl-nitroindoles explored in this work react as dienophilic electrophiles with dienes of different nucleophilicity under a normal cycloaddition process. The reactions analyzed occur with normal electron demand and all of them show polar nature. The presence of the nitro substituent induces the electrophilic behavior in the ring in which it is present. This group is responsible for the reaction orientation and the selectivity observed. However, the reactions with different diene/dienophile pairs offer similar products when developed under conventional heating or with microwave irradiation. Under the latter experimental condition, significantly short reaction times with similar yields (48/72h vs 0.5h) are observed.

Solvent-free conditions constitute a frequently used tool in microwave systems since they accredit simpler manipulations, have low cost, guarantee good product separation, and are environmentally friendly.

In relation to the DFT study, the theoretically explored system shows that the TSs are unique and asynchronous. Moreover, the theoretical calculations are in agreement with the experimental results. We can note that under MW irradiation, in the presence of a PIL, the charge transfer is higher in relation with free solvent conditions. This is translated into a more polar reaction and a decrease of the activation energy. However, based on ELF, we can consider that the effect of MW is practically the same when we use a PIL or solvent-free conditions due to the similar stretching vibrations observed in both cases. Then, the MW effect appears to be independent of the use of a solvent. Moreover, the reactions under MW irradiation are better than those developed under thermal conditions.

LIST OF ABBREVIATIONS

[HMIM][BF ₄]	=	Methyl imidazolium tetrafluoro borate
[HMIM][PF ₆]	=	Methyl imidazolium hexafluoro phosphate
¹³ C NMR	=	Carbon-13 magnetic resonance spectroscopy
¹ H NMR	=	Proton magnetic resonance spectroscopy
CA	=	Cycloadduct
CT	=	Charge transfer
DA	=	Diels-Alder
DFT	=	Density functional theory
ELF	=	Electron localization function
EW	=	Electron withdrawing
HB	=	Hydrogen bond
IR	=	Infrared

MW	=	Microwave
NEA	=	Ethyl ammonium nitrate
P-DA	=	Polar Diels-Alder
PES	=	Potential energy surfaces
PIL	=	Protic ionic liquid
PILs	=	Protic ionic liquids
TS	=	Transition state
TSs	=	Transition states

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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