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Ionic Liquids in Polar Diels-Alder Reactions Using Carbocycles and Heterocycles as Dienophiles

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1. Introduction

The design and discovery of Ionic Liquids (ILs) displaying melting point lower than 100 °C, in particular Room Temperature Ionic Liquids (RTILs) have been the subject of considerable efforts over the past decade. In particular, RTILs attract considerable attention because they are expected ideal solvents that provide novel reactions fields in the green chemistry. (Hitchcock, et al, 1986; Welton, 1999)

The interest of this class of molecules arises in part from their use as liquid media for a variety of chemical transformations as a substituted for molecular solvents. Moreover it is possible think on ILs as reagents in chemical reactions. (Adam, et al, 2009)

ILs have generated a large amount of interest from the scientific and academic communities due to their surprising and unique properties and their potential use in areas as diverse as synthesis, biocatalysis, electrochemistry, etc. Thus, these classes of molecules are increasingly used in organic chemistry, material sciences and physical chemistry. (Wasserscheid & Keim, 2000; Welton, 2004)

ILs are salts -substances composed exclusively of cations and anions-. This fact differentiates them from simple ionic solutions, where ions are dissolved in a molecular medium. They are also distinct from inorganic molten salts because their melting points are lower than 100 °C (most of them exist in the liquid form at or near room temperature).

RTILs exhibits a variety of desirable properties, such as negligible vapour pressure, which make 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 "*designer solvents*". An alternative, complementary strategy to tailor properties is to mix two (or more) ionic liquids, including binary mixtures of ionic liquids and molecular solvent.

The majority of ILs belongs to the *N,N*-methyl-(alkyl)-imidazolium, alkyl-pyridinium or ammonium cations associated with a variety of anions such as X⁻, BF₄⁻, BPh₄⁻, PF₆⁻, NO₃⁻, CF₃SO₃⁻, NCS⁻, N(CN)₂⁻, TiO₄⁻, NTf₂⁻, AlCl₄⁻, etc. Recently a few amidinium-based ILs have been also reported. (Dechambenait, et al, 2010)

The many opportunities arising from all possible combination of cations and anions allows to tune with good precision the characteristics of ILs such as melting point, viscosity, hygroscopy, dielectric constant and microscopic molecular properties. (Rogers & Seddon, 2003; Forsyth, et al, 2004; Kulkarni, et al, 2007; Wilkes, 2002; Yamada, et al, 2007) Due to the large variety of ionic liquids, the imidazolium ILs constitute a large family of anion-cation couples considered as model system which have been the most intensively studied. Specifically, the imidazolium ILs formed by 1-alkyl-3-methyl imidazolium cations which different type of anions, exhibit nano scale structural organization in polar and non polar region for which the spatial distribution evolve with the alkyl chain length. This phenomenon results from the structural asymmetry of cation composed of a polar head group and a non polar alkyl side chain leading to a balance between domains constituted by the non polar alkyl chain interacting through van der Waals forces. The existence of the micro-phase segregation in polar/non polar domains provides new perspectives to elaborate high-performance materials or to consider new selective solvation abilities in imidazolium ILs with respect to non polar solutes and/or associating species. (Martins, et al, 2008; Mac Farlane & Seddon, 2007; Plechkova & Seddon, 2008; Weingärtner, 2008; Yamada, et al, 2007)

In base to their ionic nature, the structure of ILs incorporates different level of complexity. First and in order to maintain local electro neutrality, the high-charge density parts of cations and anions must create a three-dimensional network where the nearest neighbors of a given ion are of opposite sing. Second, the low-charge density residues that are often presents in the ions (generally as alkyl side chain) are segregated from the polar network, forming non polar domains. This nano-segregation/structuration between polar and non polar regions, first predicted by molecular dynamics simulation studies and later corroborated by diffraction techniques, implies the existence of differentiated and complex interactions not only in pure ionic liquid but also in their mixtures with molecular solvents or even other ionic liquids.

Various physical and chemical properties useful to understand the solubility of RTIL's have been studied, among which dielectric properties are crucially important. However, there are, at least, two problems in the study of dielectric properties. One concerns with experimental techniques and the other concerns with scientific aspects. Furthermore, there arises a basic question of how the permittivity derived assuming that the IL's are homogeneous is related to the interconnection polar to non polar domains predicted by computer simulation and evidenced by experiments. In addition, anomalous phase separation behavior was reported for binary system of RTILs with some organic compounds.

The specific properties of the RTILs mostly result from having both a very low vapour pressure gaseous phase and a liquid phase of significant polarity, high thermal conductivity offering wide electrochemical windows. ILs have high solvation ability for a wide variety of polar, non polar, organic and inorganic molecules as well as organometallic compounds. Moreover, the possibility of changing their properties allowing the selective solvation of solutes and thus control the mutual miscibility of particular organic compounds such as for instance alcohols and water. 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. (Mancini et al, 2008, 2004; Fortunato, et al, 2010). Nevertheless, many questions are still open and more fundamental studies remain to be done before achieving a better understanding of the physical properties of ILs at the molecular level. Experimental and theoretical research has been devoted to determine the

connection existing between the nanostructural organization in ILs or in its mixtures with molecular solvents, and the remarkable solvation and/or chemical properties.

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. 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 the dienes and dienophiles.

While a great effort has been dedicated to the development and use of aromatic compound in these reactions as diene, in general their use as dienophiles has been considered less probable, mainly because aromatic and heteroaromatic compounds have proved to be relatively unreactive as dienophiles. However, it exist a number of examples of five-membered aromatic heterocycles acting as dienophiles in DA reactions with normal electron demand. For example aromatic pentaheterocycles holding an electron withdrawing group in their structures at α - or β -position have shown to be good dienophiles in the interaction with different dienes at an elevated temperature. In that direction, in the 80's studies of aromatic heterocycles -furans, *N*-tosylpyrroles, and thiophenes- in cycloaddition reactions demonstrated the viability of these systems as dienophiles. (Wenkert, et al, 1988, Wenkert & Piettre, 1988)

While the use of these substrates as dienes in thermal and high-pressure DA reactions has been widely analyzed, the employment of such compounds as dienophile has received relatively little attention in the literature. Due to our interest in the cycloaddition chemistry of substituted aromatic heterocycles with electron withdrawing groups, we have reported that 2-and-3-nitrofurans, 2- and 3-nitrothiophenes, 2- and 3-nitro-*N*-tosylpyrroles and 2- and 3-nitroselenophenes react with strong and poor dienes under different thermal conditions. The participation of nitro-*N*-tosylpyrroles in cycloaddition reactions made possible a one spot simple indole synthesis. Further studies focused on the dienophilic character of indoles derivatives seemed to be appealing for the total synthesis of carbazol and *Aspidosperma* alkaloids. (Biolatto, et al, 2001). Moreover, we explored the synthesis of different dibenzofurans using nitrobenzofurans as dienophiles. (Della Rosa, et al, 2011) In addition, we have been realized studies on the dienophilic character in DA reactions of other aromatic systems such as nitronaphthalenes. (Paredes, et al, 2007)

In general, when these nitrodienophiles were exposed to a different dienes yielded the corresponding initial cycloadduct products, which normally suffer the thermal extrusion of the nitro group. Unexpected results were observed when using nitronaphthalenes with the less reactive dienes. Interestingly, when 1- and 2-nitronaphthalenes reacted with isoprene they produced the corresponding *N*-naphthylpyrrole. From the results obtained in all these processes, we can conclude that there are two competitive reactions that might take place on mononitronaphthalenes and related compound: the addition to the nitro group (hetero DA process) and the normal DA reaction on the C1-C2 bond, depending on the strength of the diene partner. This hetero DA behavior can be extended to the nitrothiophenes probably due to its high aromaticity in relation to the others aromatic heterocyclepentadienes. More recently, we have reported the findings on the dienophilic character of nitroquinolines and nitroisoquinolines, particularly 5- and 8-nitroquinolines. (Cancian et al, 2010). These dienophiles were exposed to different dienes under thermal conditions using molecular solvents as reaction media. In these last 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 DA 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. (Domingo, et al, 2008)

In particular, for polar DA 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 DA reactions were demonstrated that the aqueous solutions have remarkable increase in reactivity and selectivity, and these results were discussed in terms of hydrophobic effects. ILs with similar properties to water, such as being highly ordered media and good HBD ability have also been shown to have potential influence the outcome of polar DA reactions.

2. Main objectives

The aim of the present review is twofold. Considering the results obtained in the cited type of thermal polar DA reactions using molecular solvents as reaction media, the first purpose is to analyze the influence of Protic Ionic Liquids (PILs) in this class of polar cycloaddition reactions in which the dienophiles are relatively poor. With this purpose ammonium- and imidazolium-based PILs have been selected because the differences in their HBD acidity. The second purpose concerned with theoretically studies using the Density Functional Theory (DFT) methods. We try to obtain information about the factors affecting reactivity and selectivity. 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.

2.1 An overview

At first and with the purpose of comparison and reference, we show a compilation of the results corresponding to thermal cycloaddition reactions that using molecular solvent as reaction media. In each Figure we show the reaction conditions and the results by both thermal reactions in molecular solvents and the reactions development in PILs (described later). In the case of the reactions in PILs only we expressed the results with EAN because the results using

2.1.1 Nitroaromatic pentaheterocycles as dienophiles in thermal DA reactions using benzene as solvent

The study of dienophilic character of monosubstituted nitro-aromatic pentaheterocycles was carried out employing 2-nitrofurane **1a**, 2,5-dimethyl-3-nitrofurane **1b**, 1-tosyl-2-nitropyrrole **2a**, 1-tosyl-3-nitropyrrole **2b**, 2- and 3- nitrothiophene **3a**, **3b**, and 2- and 3-nitroselenophene **4a**, **4b**. In addition, isoprene **5**, 1-*N*-acetyl-*N*-propyl-1,3-butadiene **6**, 1-methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene) **7** and 1-diethyl-amino-3-*tert*-butyldimethyl-silyloxy-1,3-butadiene (Rawal's diene) **8** were selected as dienes, covering an attractive spectre of nucleophilic character (Figure 1).

When **1a** was heated with the less reactive isoprene **5** in a sealed ampoule at 150-200°C for 72 h using benzene as solvent, it showed its dienophilic character taking part in the DA cycloaddition reactions. The reactions proceeded to produce the mixture of isomeric benzofurans **10a** and **10b** as the principal products and dihydrobenzofurans **9a** and **9b** (global yield 62%) (Della Rosa, et al, 2005). (Figure 2) In the same manner, in the case of 1-tosyl-2-nitropyrrole **2a**, it reacted with isoprene furnishing dihydroindole isomers **11a,b** and

indole isomers **12a,b** as the principal products in moderate yield (50%). All addition products showed extrusion of the nitro group as nitrous acid. (Della Rosa, et al, 2007)

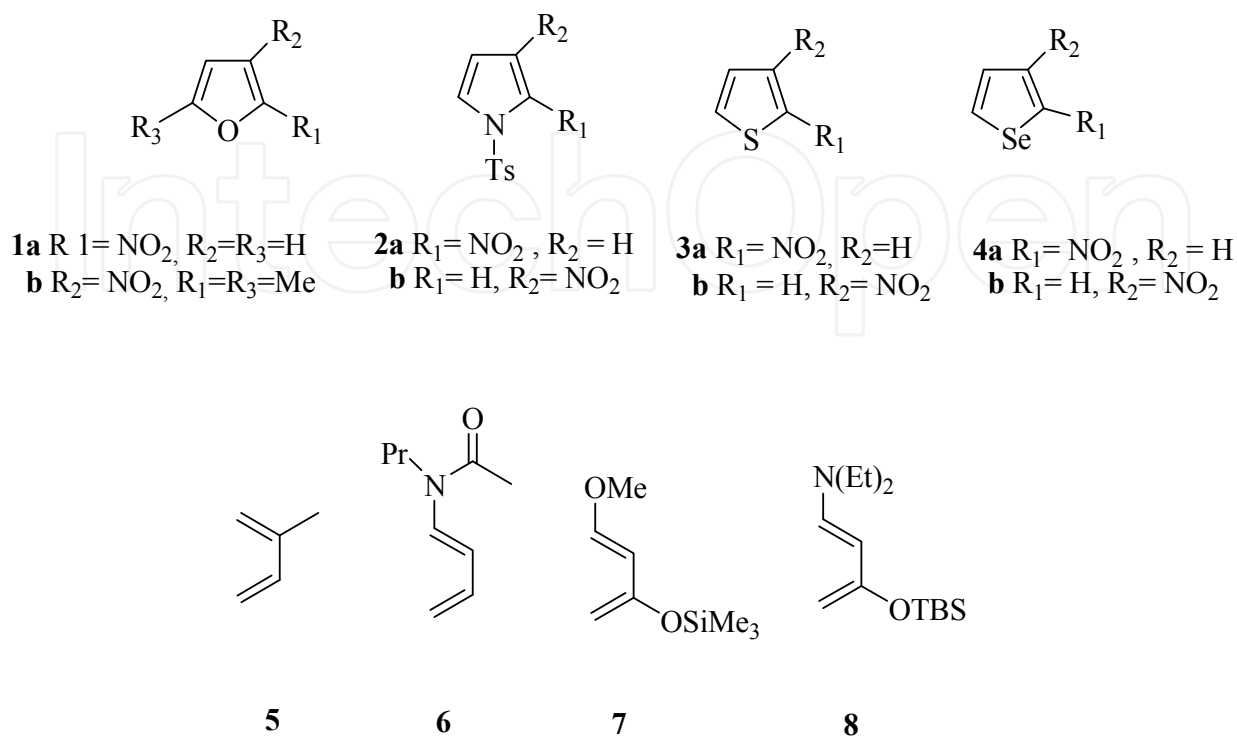


Fig. 1. Dienophiles and dienes used in the different experiences

In contrast with the above mentioned behavior, when 2-nitrothiophene **3a** was tested with **5**, it gave traces of pyrrolyl-thiophene **13** formed by a heterocycloaddition followed by thermal rearrangement. (Della Rosa, et al, 2004). This unexpected behavior was also found with nitronaphthalenes as dienophiles.

Quite unexpectedly, in the reaction of 2-nitroselenophene **4a** with the same diene, we obtained a mixture of aromatic cycloadducts **14a** and **14b** with moderate yields (55%). (Della Rosa, et al, 2007). No pyrrolyl-derivatives from hetero DA were detected.

Then, the dienophilicity of **1a**, **2a**, **3a** and **4a** was investigated in the reactions with 1-*N*-acetyl-*N*-propyl-1,3-butadiene **6**, Danishefsky's diene **7** and Rawal's diene **8**. The use of dienes **7** and **8** allowed analyze the influence of bulky substituents on the yields and regiochemistry of the cycloadditions under thermal conditions.

Exposure of **1a**, **2a** and **4a** to dienamide at 120 °C for 72 h led to benzofuran **15**, tosylindole **18** and benzoselenophene **23**, with moderate yield (58%, 53%, and 48%, respectively) (Figure 3). The results of this type of DA reactions indicate a possible sequential pathway where the ease of thermal extrusion of nitrous acid accompanying the DA reaction would lead to the 4-substituted-dihydro adduct, which would undergo thermal aromatization by losing the *N*-acetyl-*N*-alkylamino substituent. On the other hand, when 2-nitrothiophene reacted with **6**, it generated only pyrrolyl-thiophene **21**. To confirm this result the reaction was performed using 2-nitrothiophene and 1-methoxy-1,3-butadiene, thus obtaining pyrrole derivative **21**. With this dienophile, the reaction way was determined by the nucleophilicity of diene as a consequence of the similar energy between the processes, normal DA and hetero DA. (Della Rosa, et al, 2007, 2004, 2007)

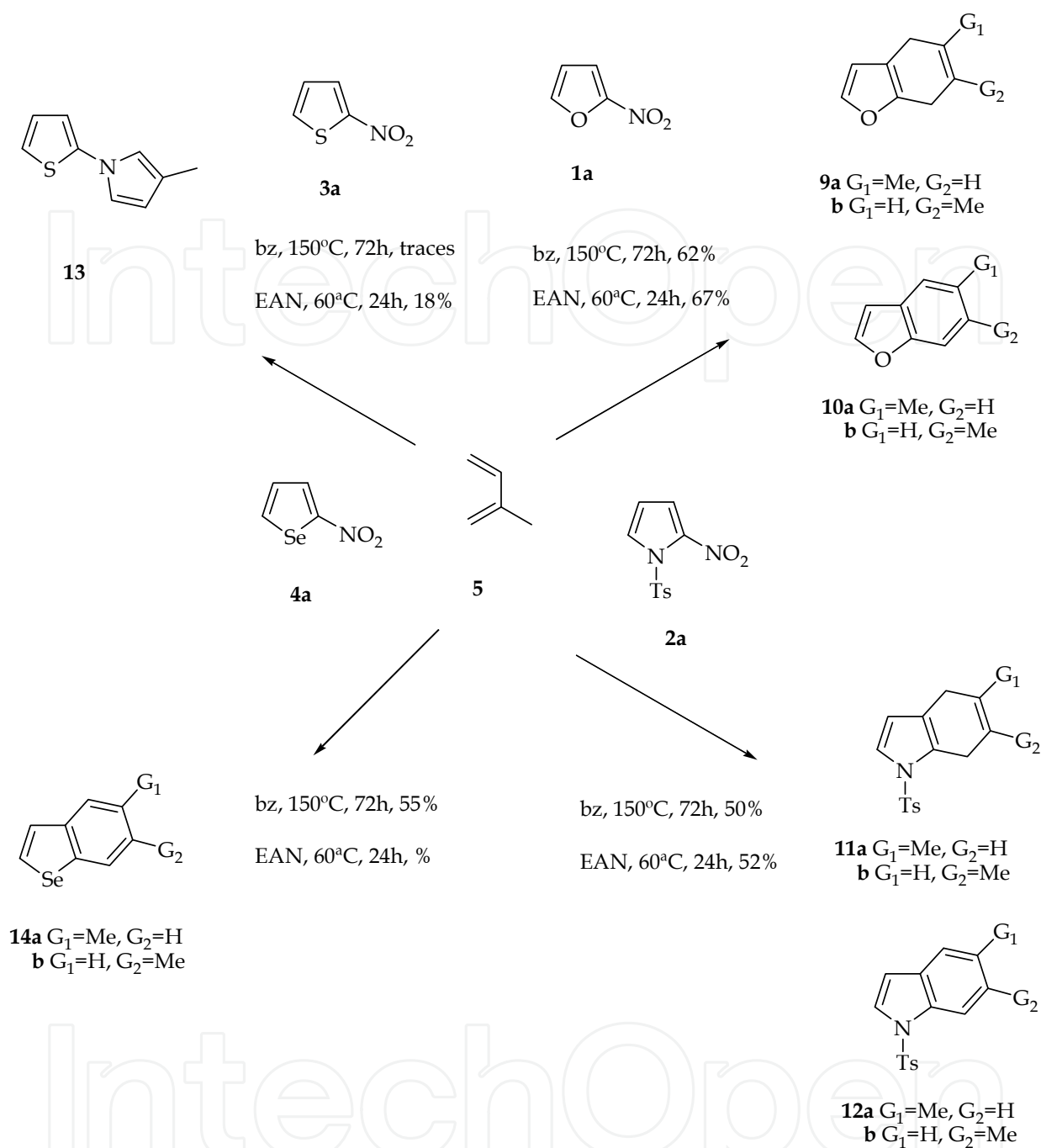


Fig. 2. Diels-Alder reactions of aromatic 2- nitroheterocycles with isoprene

The reaction of Danishefsky's diene with **1a** yielded benzofuran **16**. Similarly, in the reaction of **2a** and **3a** with diene **7** all they provided normal DA products **19** and **22** (Figure 4), respectively. The products in the reactions with diene **7** 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. (Della Rosa, et al, 2005, 2007)

The reactions of **1a**, **2a**, **4a** with Rawal's diene afforded benzofuran **17** with very good yield, tosylindole **20**, and benzoselenophene **24** (82%, 50%, and 50%, respectively), (Figure 5). (Della Rosa, et al, 2007, 2005)

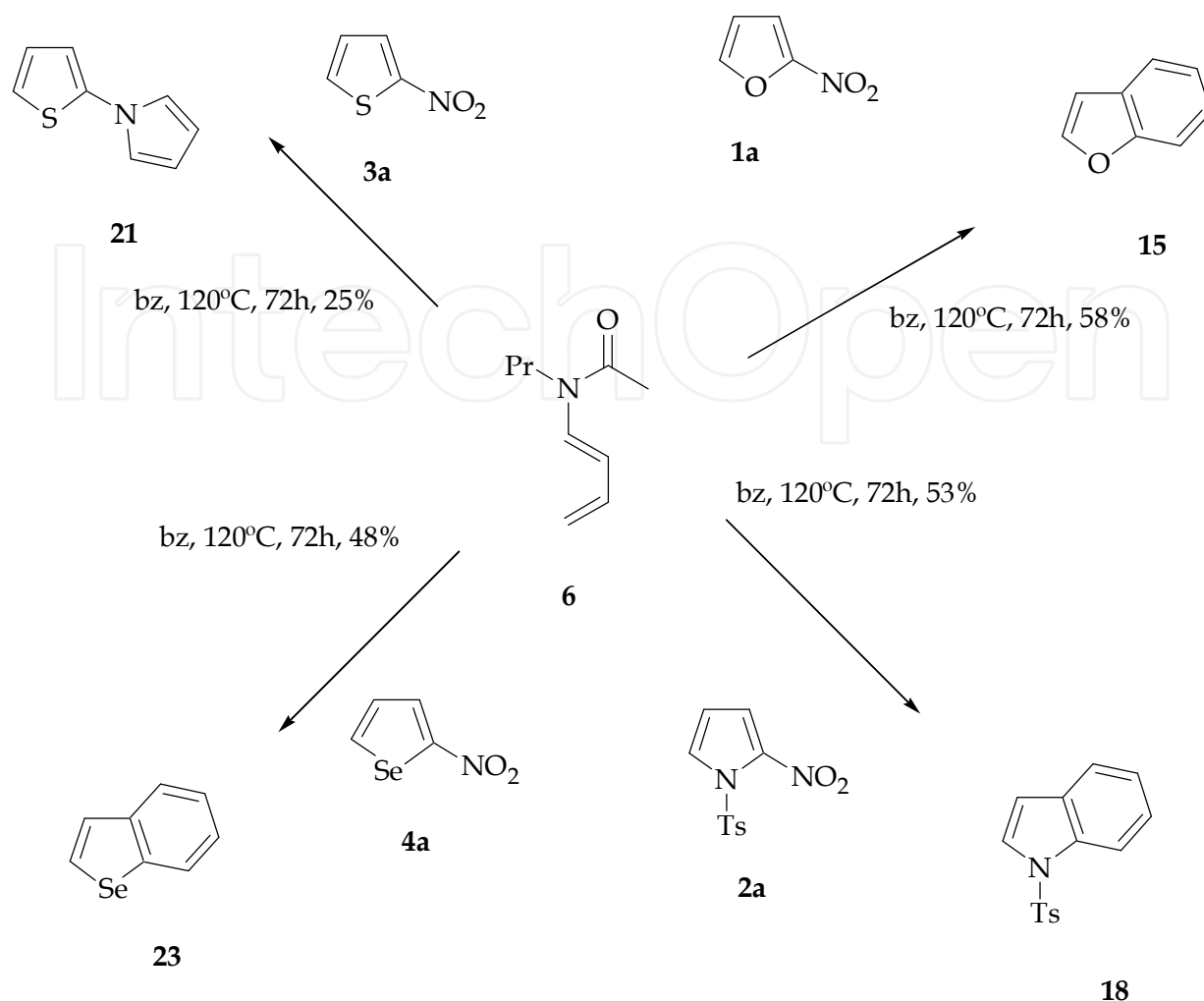


Fig. 3. Diels-Alder reactions of aromatic 2- nitroheterocycles with 1-*N*-acetyl-*N*-propyl-1,3-butadiene.

When 1-tosyl-3-nitropyrrrole **2b** and 3-nitroselenophene **4b** were tested with isoprene as diene under thermal conditions, the reactions afforded a mixture of regioisomeric cycloadducts previously informed: **11 a,b**; **12 a,b** and **14 a,b**, respectively (Figure 6). In the same direction and due to the impossibility of obtaining 3-nitrofuran, when 2,5-dimethyl-3-nitrofuran **1b** was exposed to **5**, the DA reaction at 150°C and 200°C proceeded to furnish the mixture of regioisomers **25a** and **25b** (Figure 6). (Della Rosa, et al, 2007)

Exposure of 1-tosyl-3-nitropyrrrole **2b** to dienes **6** and **7** yielded 1-tosyl-indole **18** and 1-tosyl-1-indole-6-ol **26**, respectively with moderate to high yield (Table 1). The selenophene derivative **4b** reacted with diene **8** yielding **28**. At the same time, mononitrated substrate **3b** with diene **6** afforded the pyrrolyl derivative **27'** and **3b** did not undergo cycloaddition with diene **7**. Probably this behavior is a consequence of the special reactivity of this substrate connected with its aromaticity. (See the results with 1-nitronaphthalene)

2.1.2 Disubstituted nitroaromatic pentaheterocycles as dienophiles

Complementary, the behavior of aromatic pentaheterocycles disubstituted with electron withdrawing groups, a nitro group being one of the substituents, was studied. The influence of the disubstitution was first considered for the substrates indicated below.

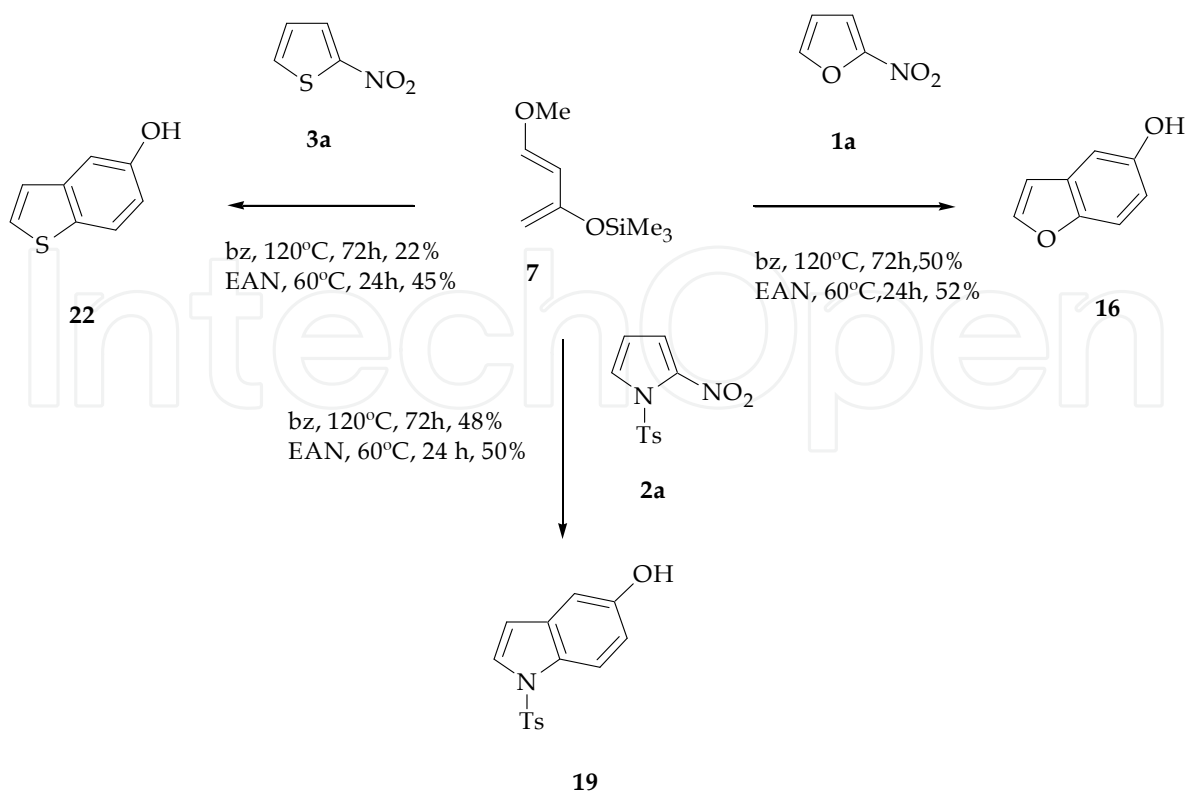


Fig. 4. Diels-Alder reactions of aromatic 2- nitroheterocycles with Danishefsky's diene.

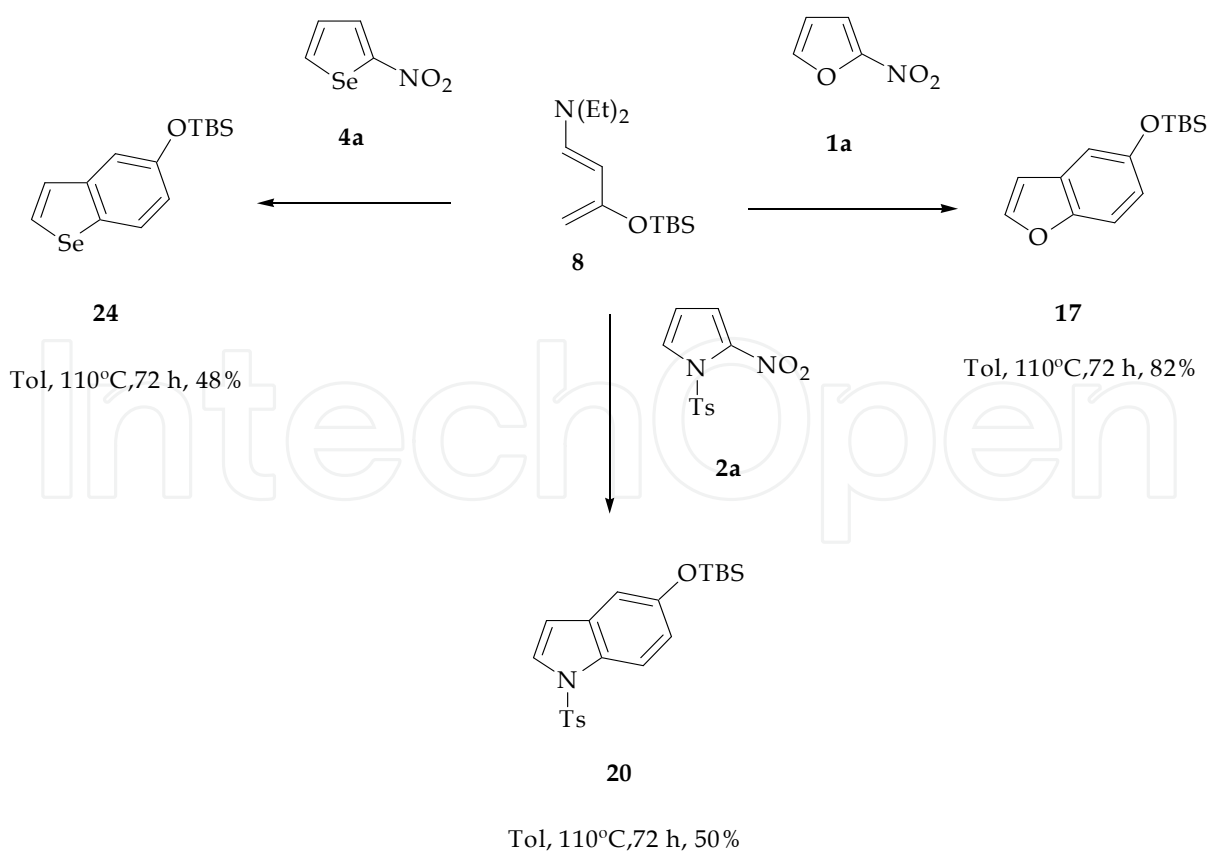


Fig. 5. Diels-Alder reactions of aromatic 2- nitroheterocycles with Rawal's diene.

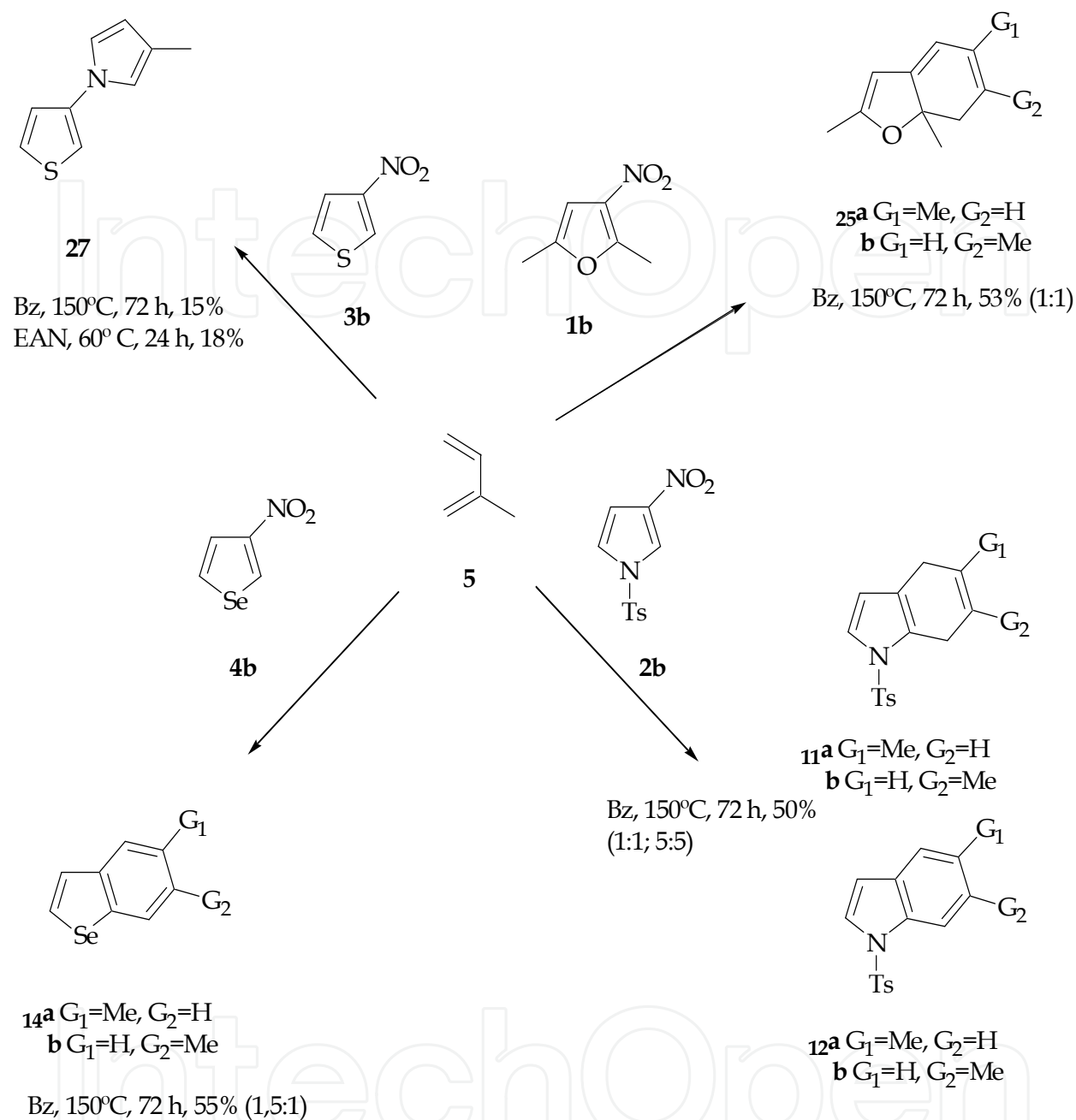


Fig. 6. Diels-Alder reactions of aromatic 3-nitroheterocycles with isoprene

The DA behavior of methyl 5-nitrofuran-3-carboxylate **29a** with isoprene was studied under similar conditions than before (Figure 8).³⁰ These reactions yielded the mixture of isomeric cycloadducts **30a** and **30b**, as principal products (60%) and a mixture of double addition adducts **31a-d** (10%) and **32a-d** (10%), in both cases as regioisomer mixtures. When 1-*N*-acetyl-*N*-propyl-1,3-butadiene (**6**) reacted with **29a**, it afforded benzofuran **33**. Meanwhile, exposure of **29a** to **7** and **8** yielded benzofurans **34** and **35**, respectively. In these reactions, only 1:1 adducts whose structure revealed site selectivity and regioselectivity were obtained.

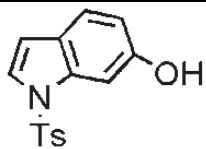
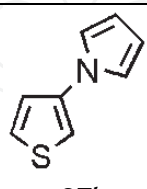
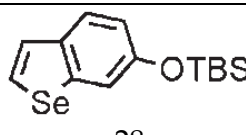
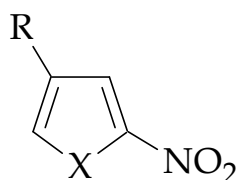
Entry	Dienophile	Diene	Solvent, T, Time	Product	Yield
1	2b	6	Bz, 150° C, 72 h	18	55
2	2b	7 ^c	Bz, 150° C, 72 h	 26	48
3	2b	7	EAN, 60° C, 24 h	26	50
4	3b	6	Bz, 150° C, 72 h	 27'	20
5	4b	8	Bz, 150° C, 72 h	 28	54

Table 1. Diels-Alder reactions of aromatic 3-nitroheterocycles with dienes 6-8



- 29 a** X= O, R= CO₂CH₃
b X= N-Ts, R= CO₂CH₃
c X= S, R= CO₂CH₃

Fig. 7. Dienophiles nitroaromatic pentaheterocycles disubstituted

On the other hand, the treatment of methyl 5-nitro-1-tosyl-pyrrole-3-carboxylate **29b** with **5** afforded a mixture of isomeric indoles **36a** and **36b**, as the principal products (45%) and a mixture of double addition adducts **37a-d** and **38a-d** (global 15%), in both cases as regioisomeric mixtures (Figure 9). (Della Rosa, et al, 2007)

Exposure of **29b** to diene **6** produced indole **39**, with moderate yield (48%) and with loss of nitro group and N-acetyl-N-alkylamino substituents. The cycloaddition between diene **7** and **29b** proceeded to produce indole **40** (52%). (Figure 9) (Della Rosa, et al, 2007)

When methyl 5-nitrothiophene-3-carboxylate **29c** was heated with less reactive isoprene, it gave pyrrolyl-thiophene **42** as the principal product formed (32%) by a hetero DA followed by thermal rearrangement (Figure 9). (Della Rosa, et al, 2004). We assumed cycloaddition of the diene to the heterodienophilic fragment of the nitro group forming the oxazine *N*-oxide (Paredes, et al, 2007; Della Rosa, et al, 2004). According to the normal hetero DA mechanism, a second electron-withdrawing group placed on thiophene nucleus in **29c** caused an

increase in pyrrole yields. Therefore, this behavior would confirm the preference of these substrates for the hetero DA process, as a consequence of a minor reaction energy requirement.

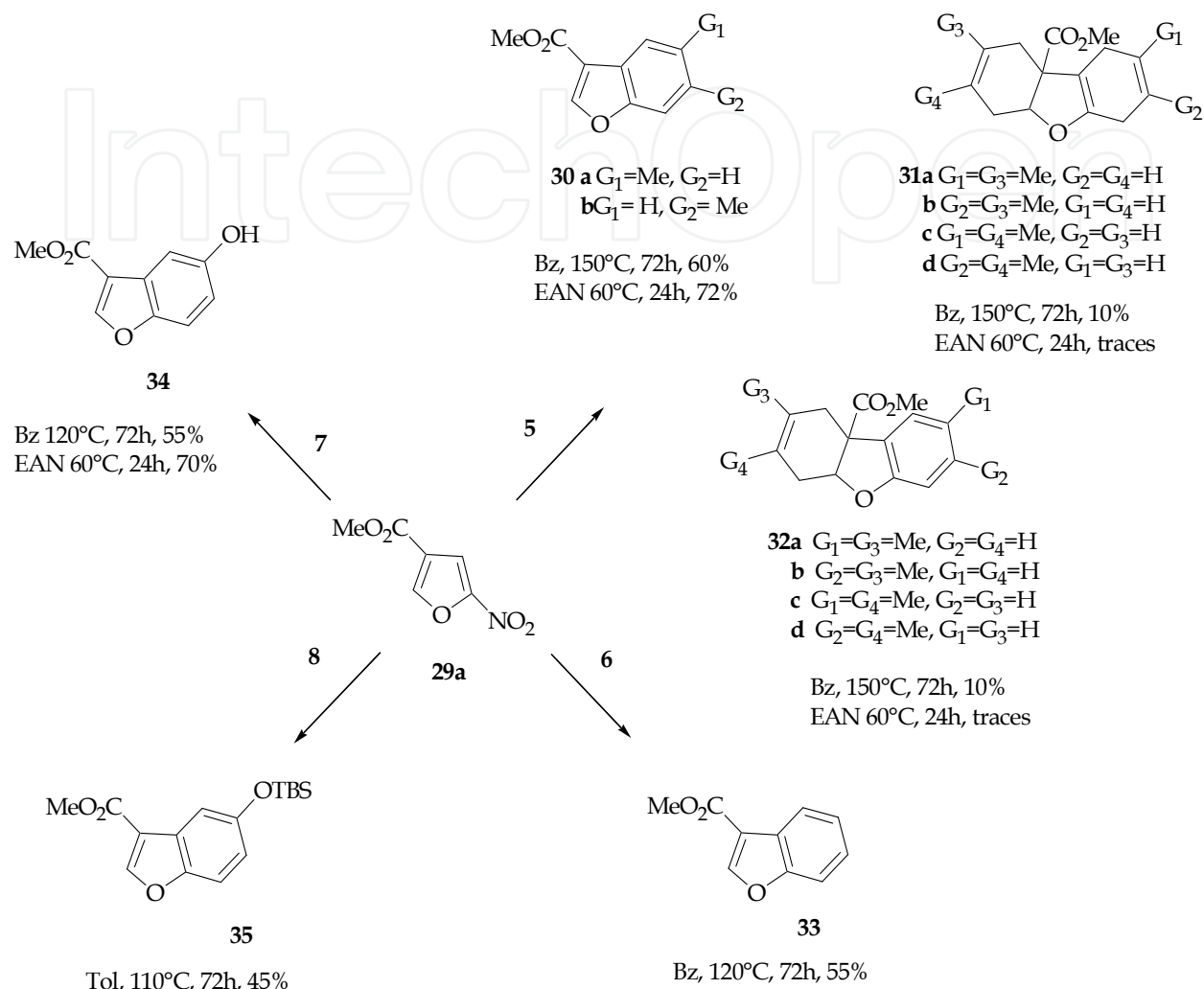


Fig. 8. Diels-Alder reactions of methyl 5-nitrofuran-3-carboxylate with different dienes

The products of normal cycloaddition to the C4-C5 bond of thiophene **41a** and **41b** were isolated as well although in minor proportion. In all cases, the reactive double bond of thiophene nucleus was the nitrated one. In any case the bis-adduct from double cycloaddition of diene was detected. When the diene 1-*N*-acetyl-*N*-propyl-1,3-butadiene was used the loss of the substituents was observed in the resultant pyrrolyl-thiophene **43** (Figure 10). With a highly activated diene such as Danishefsky's diene react with **29c** (like **29a** and **29b**) afforded **44** (Figure 9). With Danishefsky's diene, **29a**, **29b** and **29c** gave the nitro-adducts. These cycloadducts suffer aromatization providing the corresponding methyl 5-hydroxybenzofuran-3-carboxylate, methyl 5-hydroxybenzothiophene-3-carboxylate and methyl 5-hydroxy-1-tosylindole-3-carboxylate, respectively. In these reactions, only 1:1 adducts were obtained. The products structure revealed site selectivity and regioselectivity. This behavior could be ascribed to the stronger electron-withdrawing effect of the nitro group.

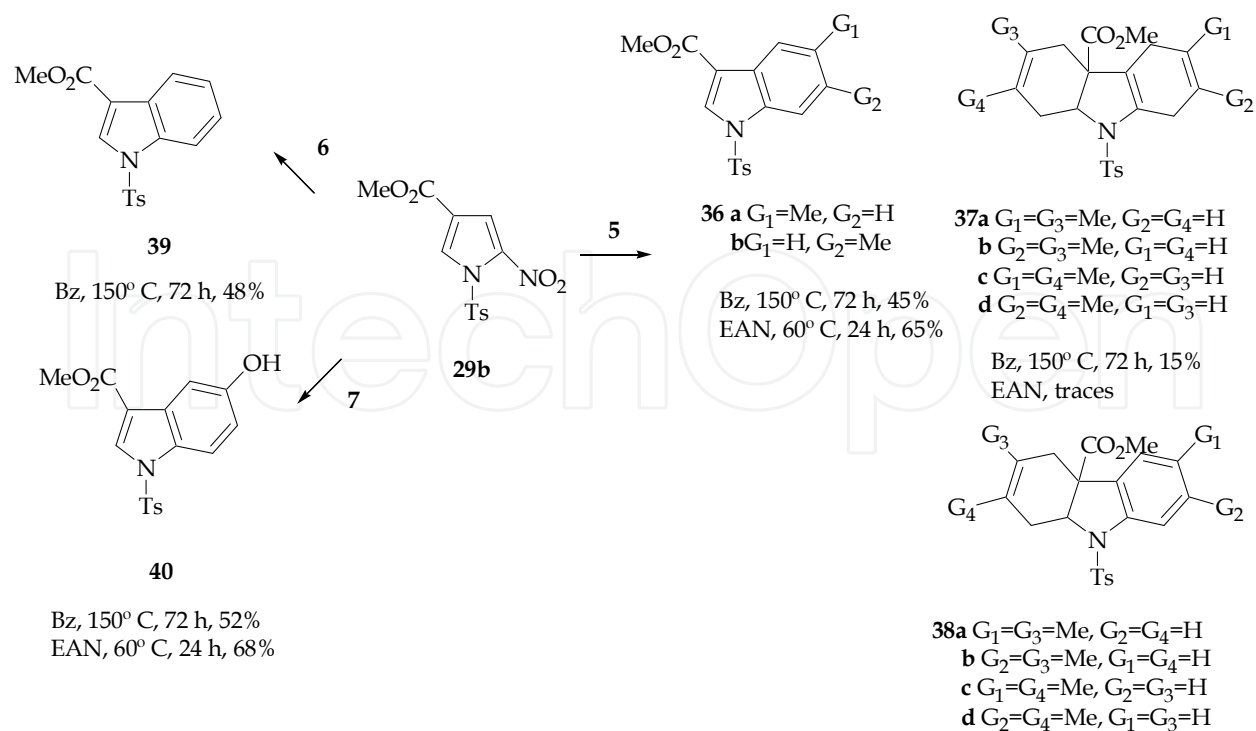


Fig. 9. Diels-Alder reactions of methyl 5-nitro-1-tosylpyrrole-3-carboxylate with diverse dienes

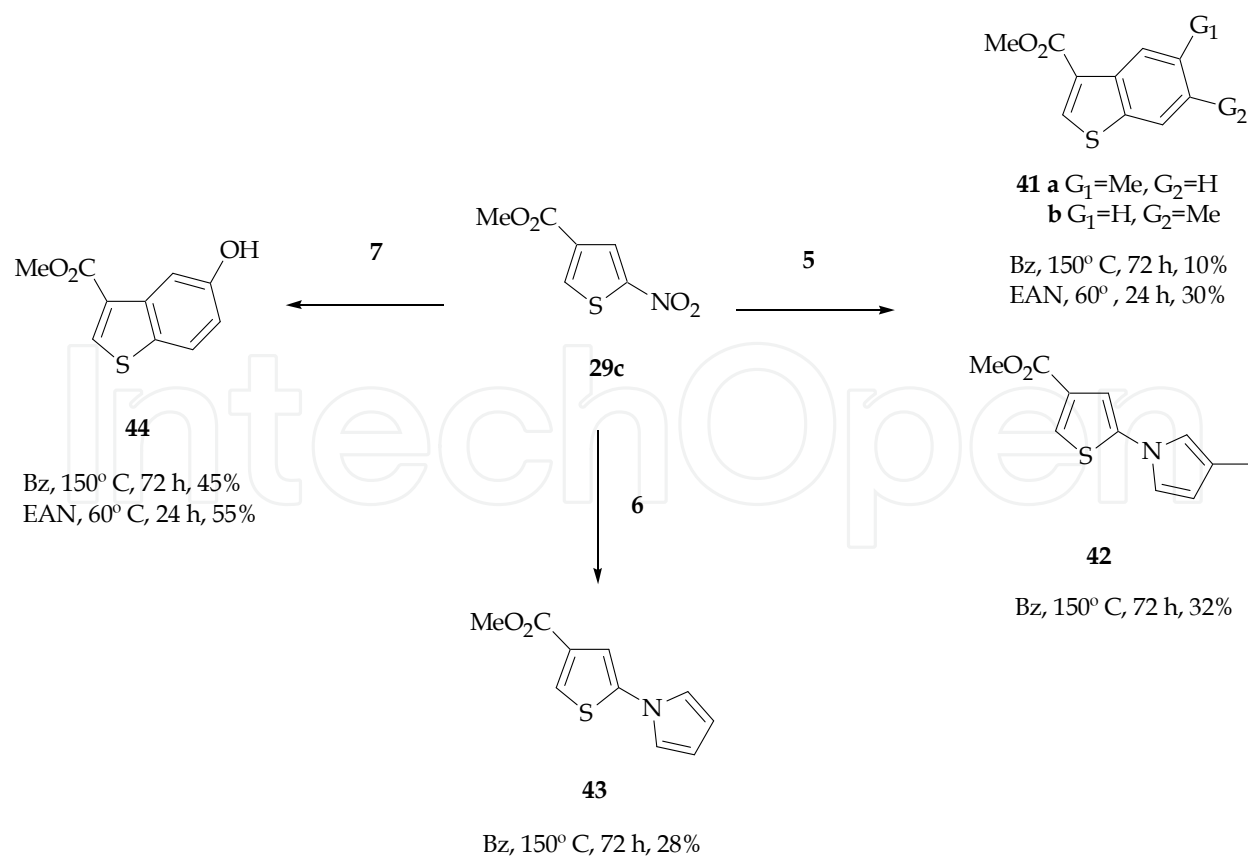


Fig. 10. Diels-Alder reactions of methyl 5-nitrothiophene-3-carboxylate with different dienes.

In the Figure 11 we show others dienophiles pentaheterocycles aromatic disubstituted. In the case of methyl 5-nitrofuran-2-carboxylate (**45a**), the thermal reaction with isoprene gave a mixture of aromatic cycloadducts of simple addition **47a** and **47b** with moderate yields (Figure 12). (Della Rosa, et al, 2005) The reactivity and regioselectivity of methyl 5-nitrofuran-3-carboxylate, which were higher than those methyl 5-nitro-2-carboxylate compounds is in consonance with the different behavior informed for β -acylfurans and their α -acyl isomers. (Wenkert, et al, 1988)

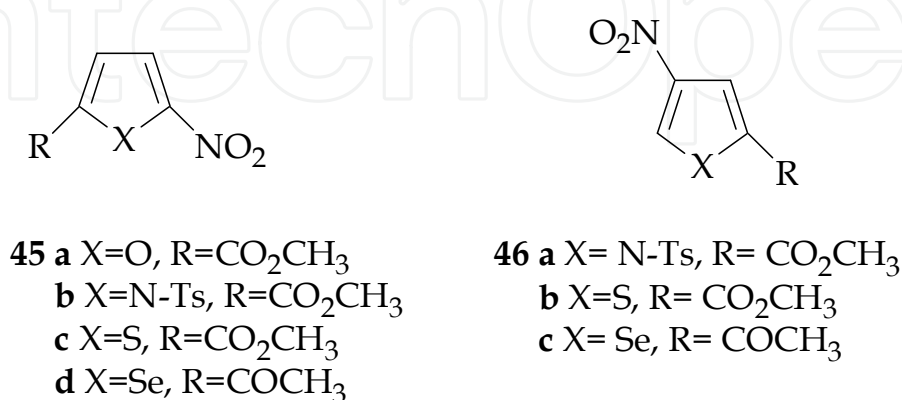


Fig. 11. Dienophiles nitroaromatic pentaheterocycles disubstituted

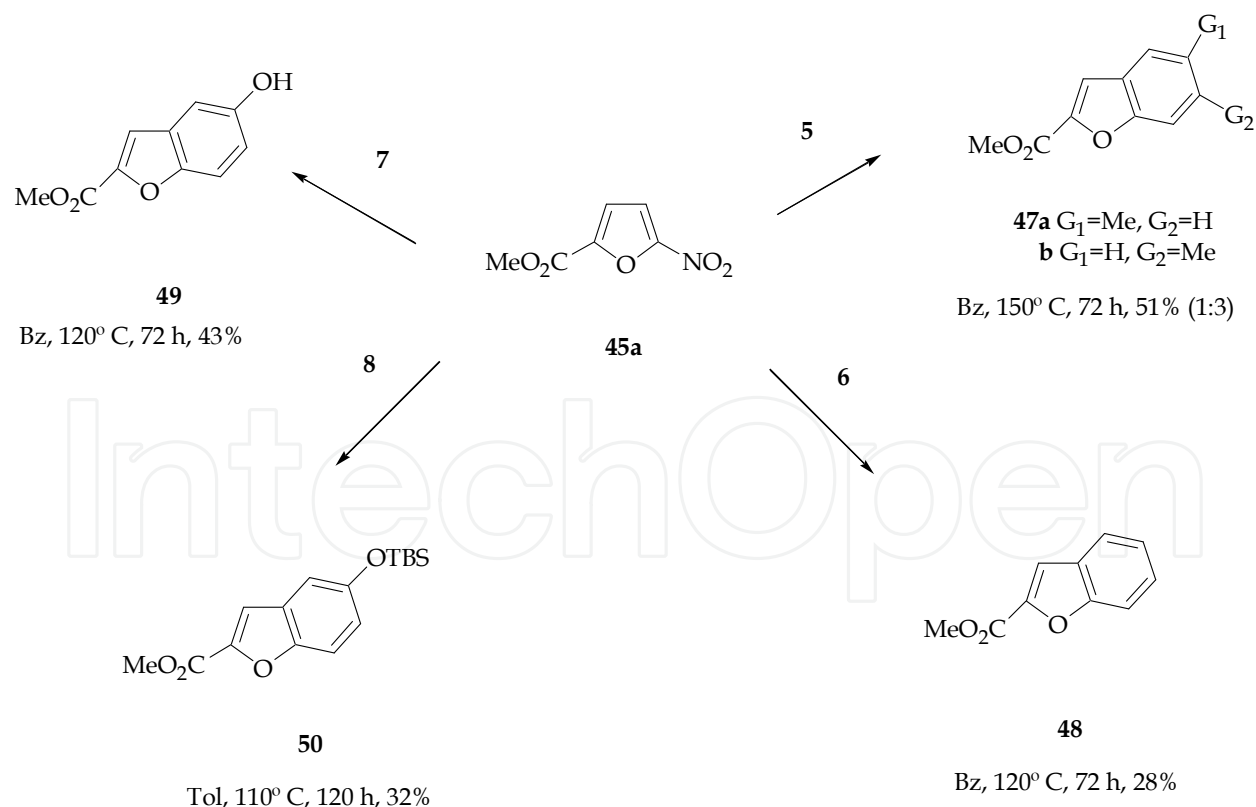


Fig. 12. Diels-Alder reactions of methyl 5-nitrofuran-2-carboxylate with diverse dienes

Treatment of **45a** with dienes **6**, **7**, and **8** yielded benzofused compounds **48**, **49** and **50**, respectively (Figure 12). On the other hands, the reactions of **45b** with dienes **5**, **6** and **7**

yielded a mixture of dihydrotosylindoles **51a**, **51b**, and the indoles derivatives **53** and **54a**. (Figure 13)

Again, these reactions proceeded by the selective addition of the diene to the nitro-substituted double bond of the dienophile (Della Rosa, et al, 2007, 2007)

The reactive behavior of 4-nitro-2-carboxylate compounds was also studied under similar conditions. Reactions of nitropyrrole **46a** with isoprene proceeded to produce the regioisomer mixtures of the dihydroindoles **51a,b** and the indoles **52a,b**. The reactions of **46a** with the dienes **6** and **7** afforded with the reasonable yield the tosyl indole derivatives **53** and **54b** (Figure 13).

After 72 h at 150 °C, the reaction of methyl 5-nitrothiophene-2-carboxylate (**45c**) with isoprene afforded pyrrolyl-thiophene **55**. This dienophile yielded the pyrrolyl-thiophene **56** when reacted with diene **6**, and in the reactions with diene **7** afforded the benzothiophene derivative **57**, in both cases with good yield. (Figure 14)

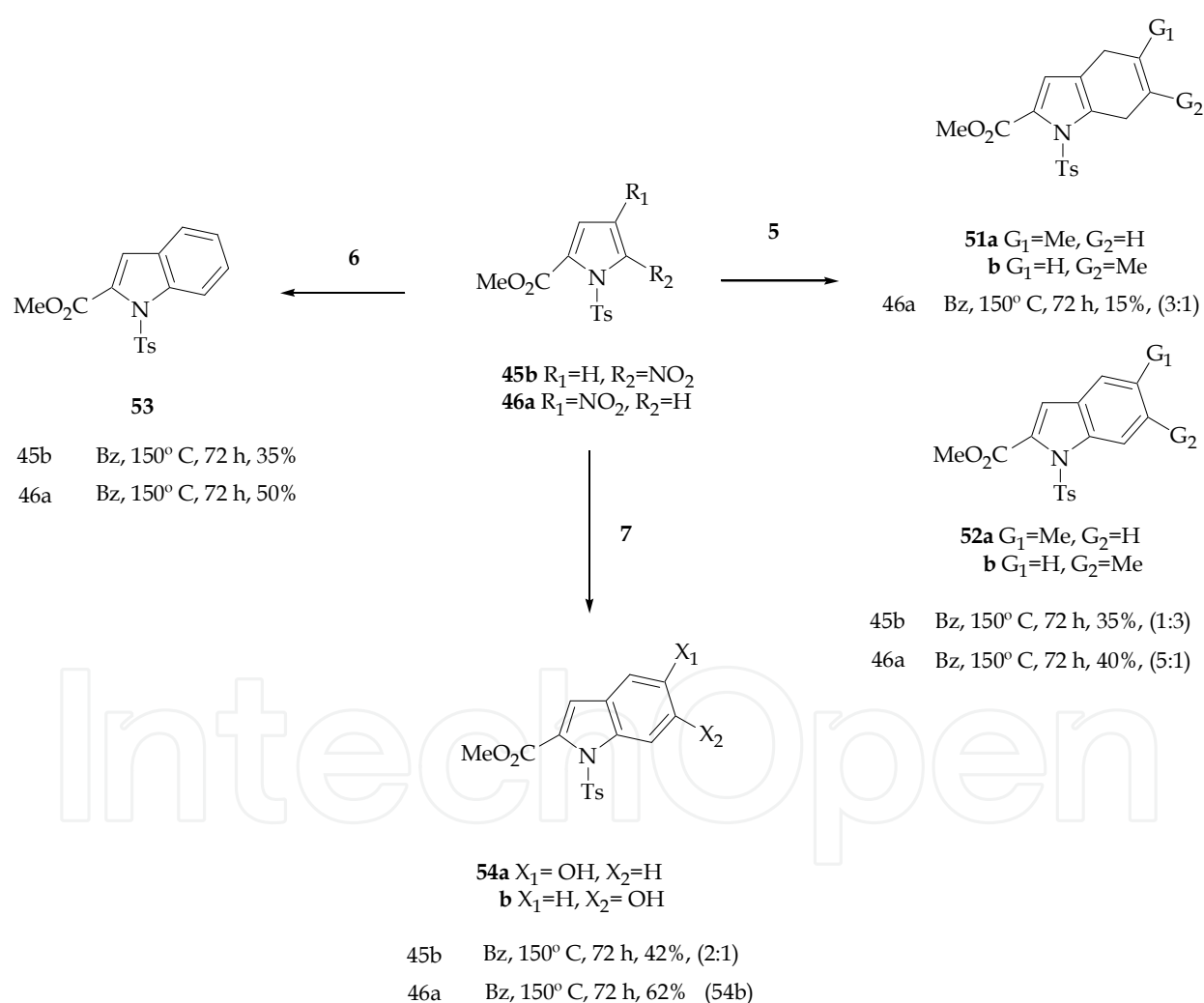


Fig. 13. Thermal reactions of disubstituted pyrroles with dienes **5**, **6** and **7**

2.1.3 Nitroindoles as dienophiles

When 1-tosyl-3-nitroindole **58** was reacted with Danishefsky's diene under thermal conditions (120 °C, 72 h) the reaction surprisingly afforded 37% of a mixture of

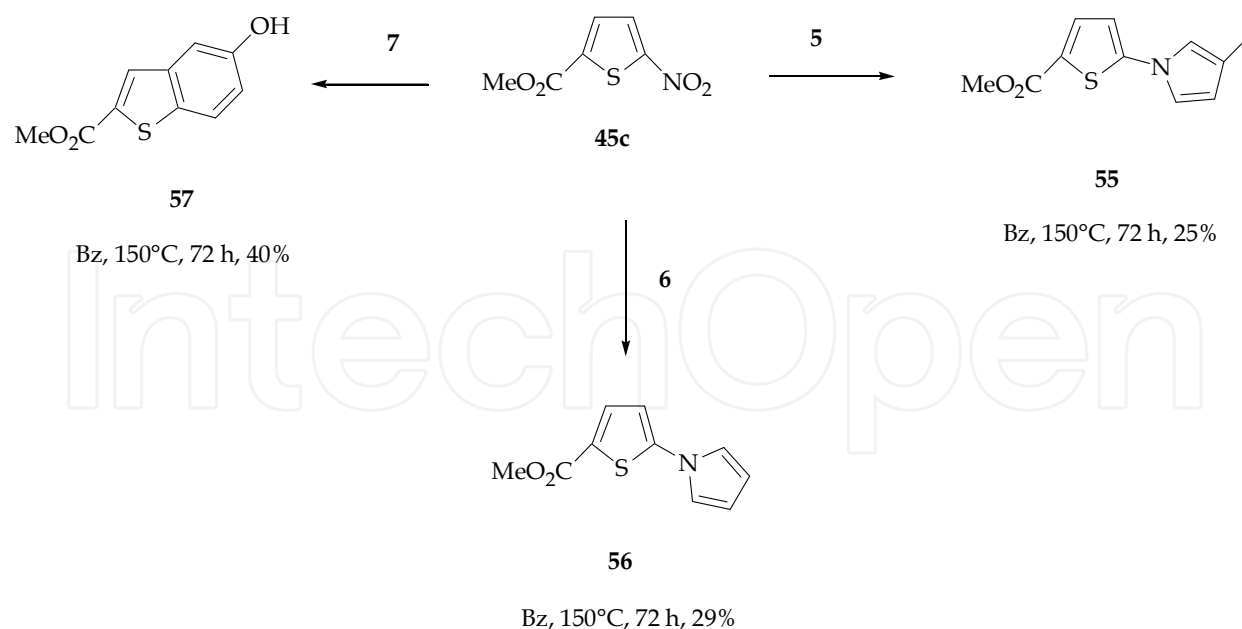


Fig. 14. Thermal reaction of methyl 5-nitrothiophene-2-carboxylate **45c** with dienes **5**, **6** and **7**

diastereoisomeric cycloadducts **60** and **61** in a 30:1 ratio after hydrolysis, with 48% of hydroxycarbazole **59** (Figure 15). When the reaction temperature was lowered to 70°C the isomeric ratio change to ca. 1:1 (64% yield), with only 11% to hydroxycarbazole **59**. This result demonstrated that the isomer **61** is more likely to suffer thermal aromatization because of the *trans* arrangement of its nitro and methoxy substituents. The intermediate that suffered nitrous acid extrusion and retained the methoxy group was not detected in either case. (Biolatto, et al, 2001)

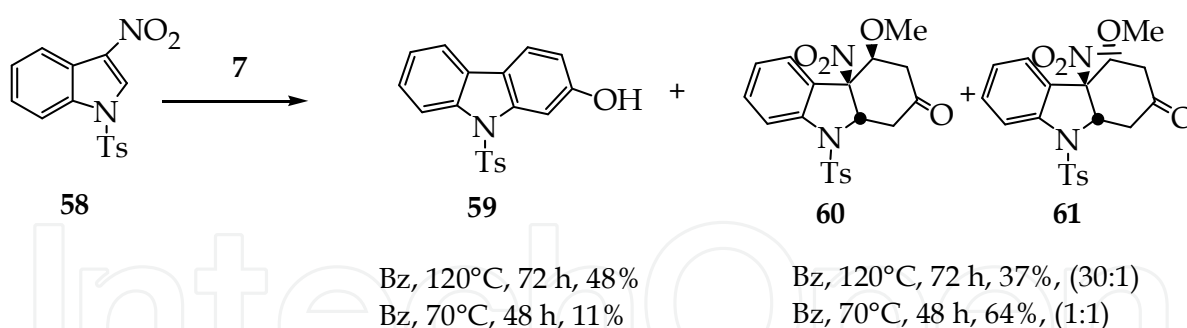


Fig. 15. Thermal reaction of 1-tosyl-3-nitroindol with Danishefsky's diene

2.1.4 Nitrobenzofurans as dienophiles

To explore the normal electron demand DA dienophilicity of nitrobenzofurans **62a-b** we choose 1-trimethylsilyloxy-1,3-butadiene (**63**), as diene (Figure 16).

The thermal reactions of **62a** with isoprene (150 °C, 72 h) afforded the mixture of aromatic regioisomeric cycloadducts **64a** as principal products and dihydridibenzofurans **65a** and **65b** with reasonable yield (Figure 17). On the other hand, reactions of **62a** with 1-trimethylsilyloxy-1,3-butadiene (120-140°C, 72 h) yielded dibenzofuran **66** with loss of trimethylsilyloxy and nitro groups. The yield is good. In the same way, in the thermal reaction of **62a** with the Danishefsky's diene aromatic cycloadduct **67a** was obtained with very good yield and complete regioselectivity (Figure 17). (Della Rosa, et al, 2011)

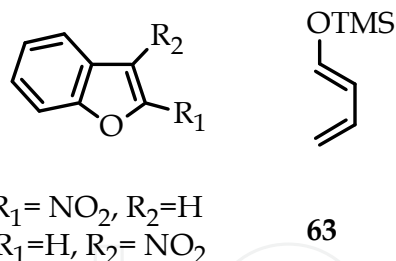


Fig. 16. 2- and 3- nitrobenzofurans, and 1-trimethylsilyloxy-1,3butadiene

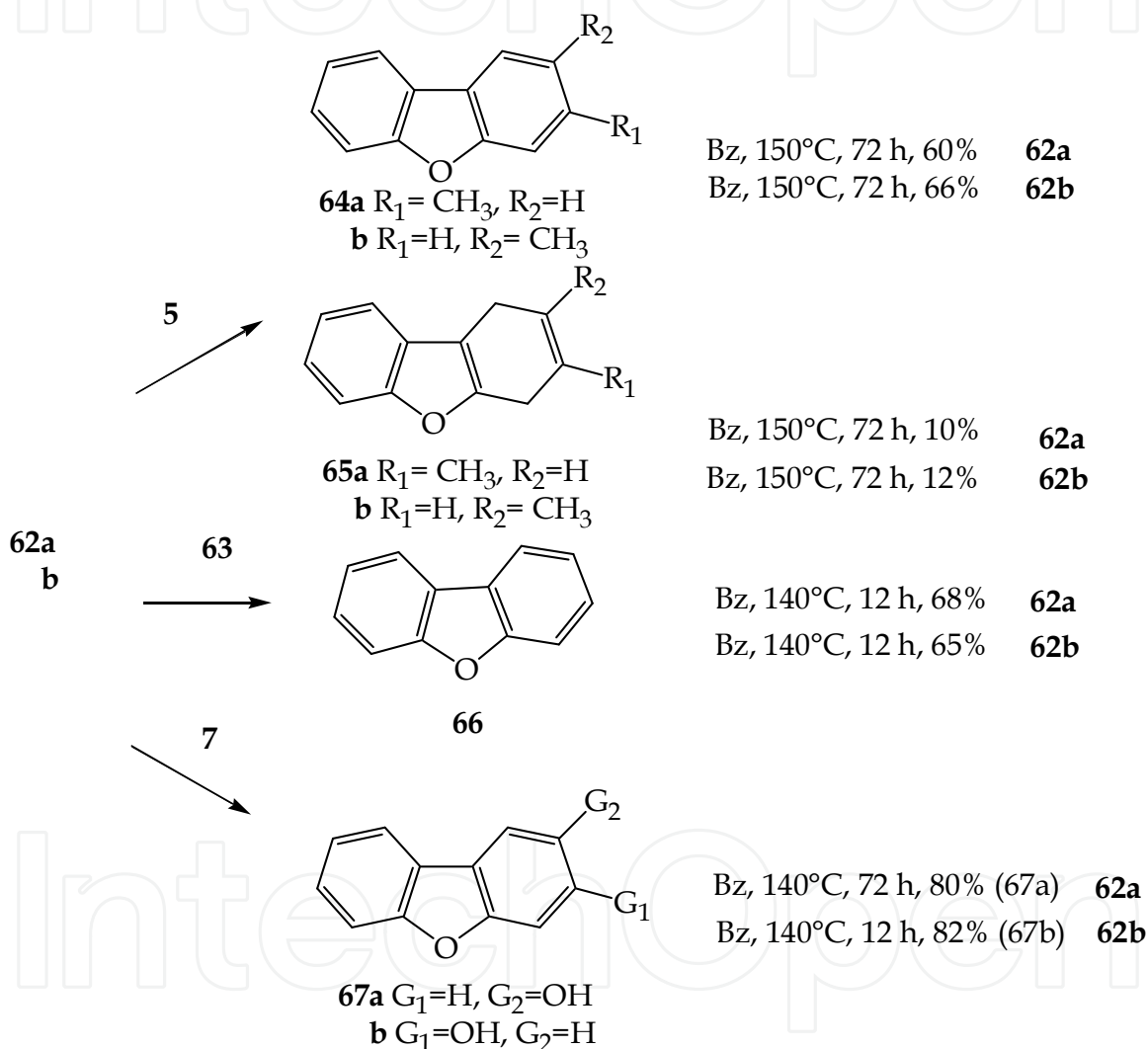


Fig. 17. Thermal reactions of 2- and 3-nitrofurans with different dienes

Then, we analyzed the reactivity of 3-nitrobenzofuran **62b** with the dienes **5**, **63** and **7**. This allowed us to compare not only the relative reactivity of the 2- and 3-substitution of the aromatic ring but also the regioselectivities in the reactions with dienes properly substituted. When **62b** reacted with isoprene (150 °C, 72 h) we observed the same mixture of regioisomeric products **64a**, **64b**, **65a** and **65b** obtained in the reaction with the substrate **62a**. The yield of these reactions was reasonable. The reaction of **62b** with the diene **5** (120-140 °C, 72 h) offer the dibenzofuran **66** in a similar yield that before. On the other hand, the thermal

reaction of **62b** with the Danishefsky's diene yielded the aromatic cycloadducts **67b** with high yield and complete regioselectivity, which is controlled by the nitro and methoxy groups. (Figure 17)

2.1.5 Nitronaphthalenes as dienophiles

To explore the normal electron-demand DA dienophilicity of 1-nitronaphthalenes (**1-NN**) **68**, 2-nitronaphthalene (**2-NN**) **69**, 1,3-dinitronaphthalene (**1,3-DNN**) **70**, 1,4-dinitronaphthalene (**1,4-DNN**) **71**, 1,5-dinitronaphthalene (**1,5-DNN**) **72** and 1,8-dinitronaphthalene (**1,8-DNN**) **73**, the dienes **5**, **6**, **7** and 1-methoxy-1,3-butadiene **74** were selected.

We started the study by testing the reactivity of 1-nitronaphthalene with Danishefsky's diene since it is one of the strongest dienes and is appropriate to test these aromatic substrates. Thus, when **68** and **7** were heated in sealed ampoule (150 °C, 72 h) using benzene as solvent, 62% of 2-hydroxy-phenanthrene **75** was regioselectively produced. (Figure 18)

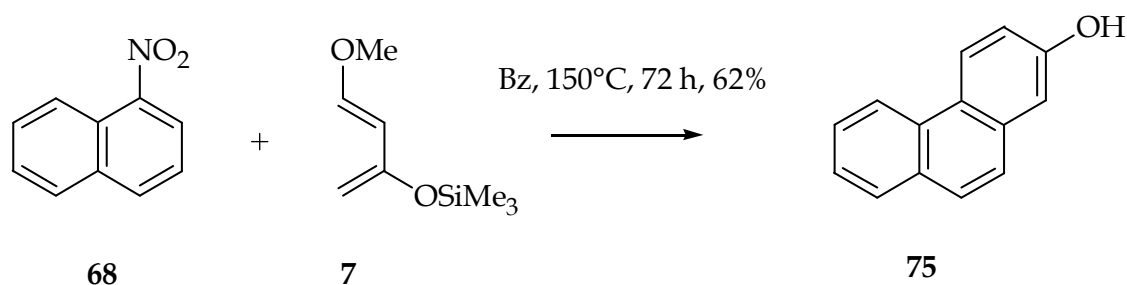


Fig. 18. Diels- Alder reaction of 1-nitronaphthalene with Danishefsky's diene

In an analogous fashion to **68**, 2-nitronaphthalene **69** reacted with diene **7** to give 45% of hydroxyphenanthrene **76**. The regioselectivity of these reactions was controlled by both the nitro group of the dienophile and the methoxyl group of Danishefsky's diene.

In the case of 1,4-dinitronaphthalene, due to the enhanced reactivity of this dienophile, the DA reaction with **7** proceeded to furnish 75% of the single regioisomer 2-hydroxy-9-nitrophenanthrene **77**. On the other hand, the reaction of 1,3-dinitronaphthalene with the same diene produced the two isomers 2-hydroxy-10-nitrophenanthrene and 3-hydroxy-9-nitrophenanthrene resulting from the cycloaddition to C1-C2 and C3-C4 bonds (1:4,6 ratio, respectively), with a total yield of 88%. The reactions of 1,5-dinitronaphthalene and 1,8-dinitronaphthalene yielded in both cases the corresponding phenanthrenes derivative. With **72** the yield is similar to mononitronaphthalenes. In the case of **73**, the low yields obtained could be explained by steric effects derived from the proximity of the nitro groups, which caused considerable overcrowding in the molecule. (Paredes, et al, 2007)

Unexpected results were observed when using nitronaphthalenes with less reactive dienes such as **5** and **6**. Interestingly, when **68** and **69** reacted with these dienes, they produced *N*-(1-naphthyl)-3-methylpyrrole **78** and *N*-(2-naphthyl)-3-methylpyrrole **79** with yields according to the electron-donor properties of the diene. Moreover, when the dinitronaphthalenes reacted with these dienes they generated a mixture of *N*-naphthylpyrroles and phenanthrenes with different yield ratios. In the case of 1,3-dinitronaphthalene, a clear tendency towards the DA cycloaddition to the C3-C4 bond was observed with these dienes. With isoprene, 1,3-dinitronaphthalene gave the corresponding 2-methyl-10-nitro-phenanthrene **80**, together with traces of [3-methyl-1-(1-nitronaphthalen-3-

yl)-pyrrole] **81a** and [3-methyl-1-(2-nitronaphthalen-4-yl)-pyrrole] **81b**. The reactions with **6** yielded 3-methyl-9-nitrophenantrene **82** and traces of corresponding *N*-naphthylpyrroles **83a** and **83b**.

2.1.6 Nitroquinolines as dienophiles

Considering that with benzene or toluene -molecular solvent frequently used in this type of process- were observed solubility problem we decided employ chloroform as reaction media. This molecular solvent has potential HBD character which could be influence the reactivity of the reaction systems. The reaction temperature was in the range 120-150 °C, and we used different times of reaction.

Because 2-nitroquinoline and 4-nitroquinoline were no reactive in all the experiences development in this reaction conditions, the study started by testing the reactivity of 5-nitroquinoline **84** and 8-nitroquinoline **85**, with the dienes **5,7, 8** and 1-trimethylsilyloxy-1,3-butadiene **63**. When **84** was heated with the less reactive isoprene **5** it gave as principal product the 5-(3-methyl-1*H*-pyrrolil)-quinoline **86**, through the participation of the nitro group in a hetero DA process followed by a thermal rearrangement -hetero DA pathway-. (Cancian, et al, 2010)

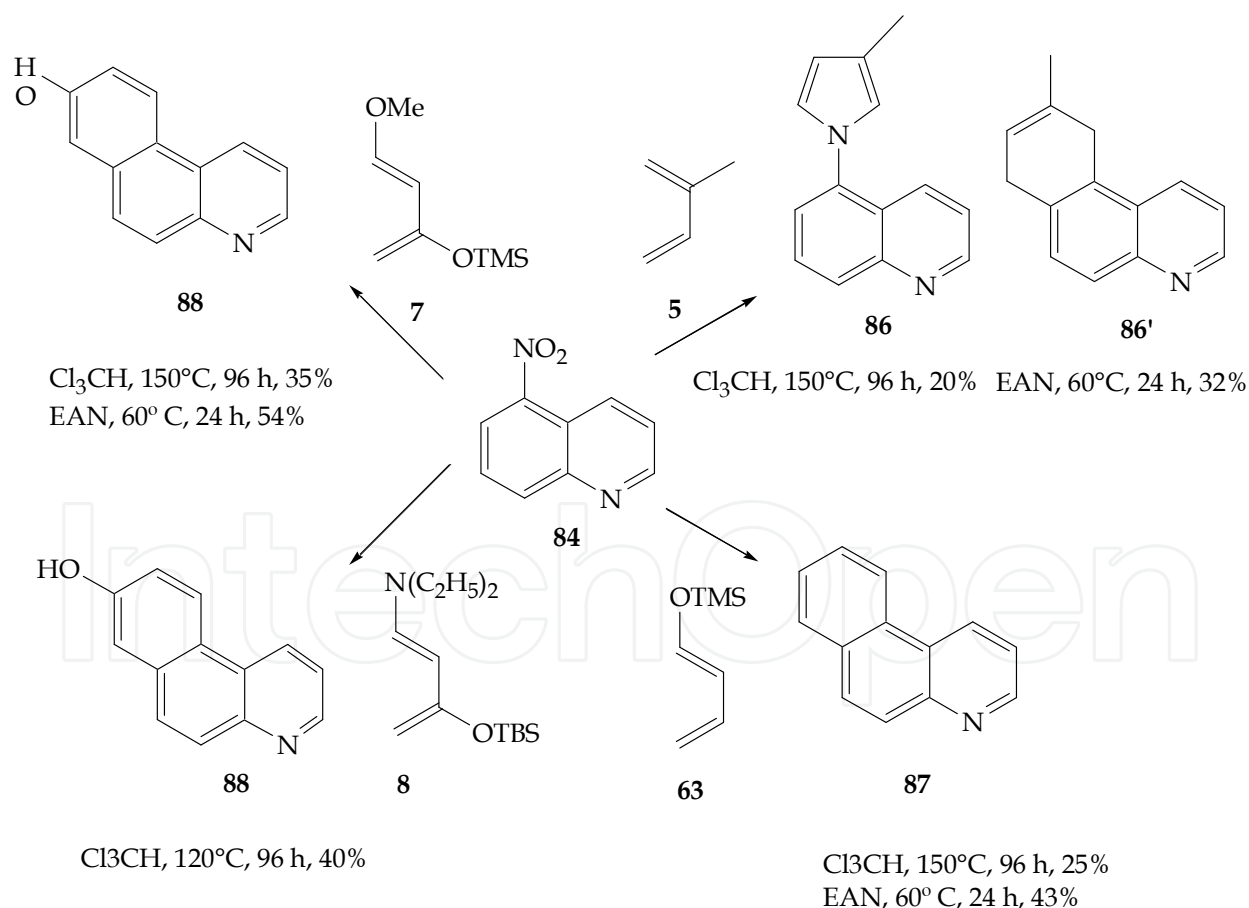


Fig. 19. Thermal reactions of 5-nitroquinoline and different dienes

In the other hand the reactions between **84** and **63** (120-140 °C, 96 h) yielded the normal addition product **87** with complete aromatization due to the loss of the nitro and

trimethylsilyloxy groups. In the same way, in the thermal reactions of **84** with the diene **7** (120-140°C, 96 h), aromatic cycloadduct **88** was obtained with very good yield and complete regioselectivity. Then was explored the reaction between **84** and **8** observing the same product that in the cycloaddition using the diene **7** although with higher yield. (Figure 19) In turn the reactions of **85** with the dienes **5**, **7**, and **63**, yielded in all cases the normal addition products (Figure 20).

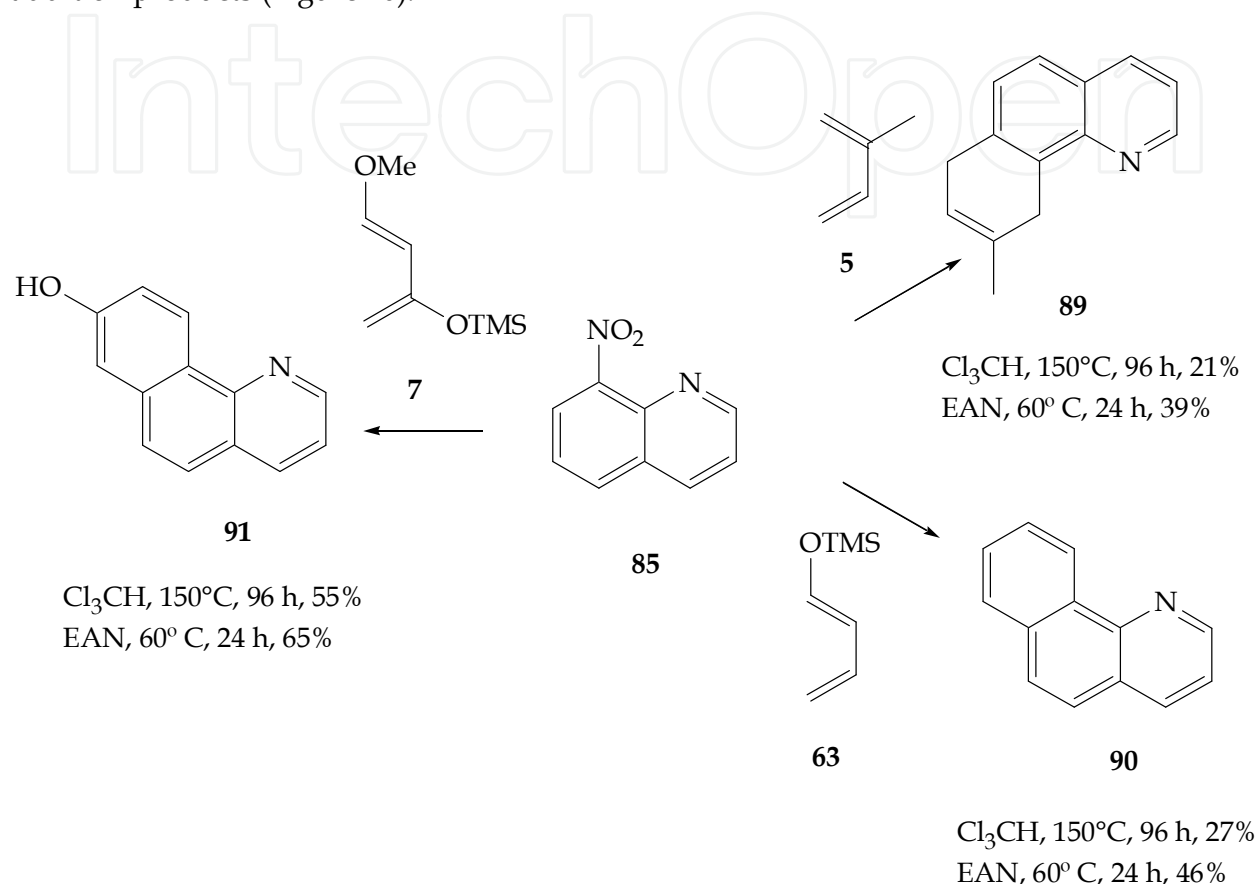


Fig. 20. Thermal reactions of 8-nitroquinoline and different dienes

The reaction between **85** with **5** shown as principal product el dihydro derivative 7,10-dihydro-9-methyl-benzo[f]quinoline **89**, joint to traces of its regioisomer. In this case the normal addition process observed could be attributed to the near position and consequent interaction of the nitro group and the heteroatom. The employ of **63** as diene yielded the aromatic cycloaddition product **90** with a hight yield that in the reaction using **84**. The reaction of **85** and diene **7** yielded the aromatic heterotricyclic product **91** with very high yield and complete regioselectivity. (Figure 20)

2.2 Ionic liquids as solvent in polar DA reactions

Many reports refer to the DA cycloaddition as a typical example of a reaction that is indifferent towards the choice of the solvent. This is only strictly true for the very special case of DA reactions between two purely hydrocarbon reactants, such as cyclopentadiene dimerization. Actually, DA reactions proceed at an appreciable rate only when either the diene or the dienophile are activated by an electron donating or electron withdrawing group, normally characterized by the presence of a heteroatom that can therefore efficiently

interact with the solvent. The influence of the solvent on these latter reactions has been extensively investigated, in particular after Breslow and Rideout in 1980 evidenced the dramatic accelerating effect exerted by water. (Rideout, & Breslow, 1980)

PILs, with their peculiar properties such as high polarizability/dipolarity, good hydrogen bond donor ability, etc., were straight away considered to have the potential to influence the outcome of DA reactions. The first investigation on the reaction between cyclopentadiene and alkyl acrylates in an IL was performed using ethylammonium nitrate which, surprisingly, gave a mixture of *endo* and *exo* products in a ratio of 6,7 : 1 (Jaeger & Tucker, 1989). Subsequently, Welton have investigated the influence of ILs based on the 1-butyl-3-methylimidazolium cation, [BMIM]⁺ in DA reactions. The *endo* : *exo* ratio and associated acceleration observed in the DA cycloaddition of cyclopentadiene with methyl acrylate was attributed to the ability of the IL to hydrogen bond to the dienophile (methyl acrylate).

In that direction and to complete the reaction approach of aromatic carbocyclic and heterocyclic substituted with electron with-drawing groups as dienophiles in cycloaddition reactions, we have investigated PILs solvent effects in polar DA reactions using ethylammonium nitrate (EAN), 1-methylimidazolium tetrafluoroborate ([HMIM][BF₄]), and 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF₄]). The dienophiles studied were 2-nitrofuran, 1-tosyl-2-nitropyrrole, 1-tosyl-3-nitropyrrole, 2-nitrothiophene, 3-nitrothiophene, methyl-5-nitrofuran-3-carboxylate, methyl 5-nitro-1-tosylindole-3-carboxylate, methyl-5-nitrothiophene-3-carboxylate, 1-nitronaphthalene, 2-nitronaphthalene, 1,3-dinitronaphthalene, 1,4-dinitronaphthalene, and 5- and 8-nitroquinolines. These dienophiles were exposed to different dienes with variable nucleophilicity. This 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 ILs.

2.2.1 2-nitrofuran (1.a) as dienophile

When **1a** was reacted with the less reactive isoprene **5** in a sealed ampoule at 60°C for 24 h using EAN as solvent, the reactions proceeded to produce a mixture of isomeric benzofurans **10a** and **10b** (1:1) as the principal products with reasonable yield (40%) and dihydrobenzofurans **9a** and **9b** (1:1) (10%). (Figure 2). If the time of the reaction increased to 24 h we observe a 1:1 mixture of isomeric benzofurans **10a** and **10b** in 55% yield and traces of the isomeric dihydrobenzofurans **9a** and **9b**. Similar results were observed when the reaction was development in [HMIM][BF₄] although the yields were slightly lower.

The reactions of **1a** with 1-trimethylsilyloxy-1,3-butadiene using EAN, [HMIM][BF₄], and [BMIM][BF₄], respectively as solvents, in seals ampoule at 60°C (12 and 24 h, respectively) offered in all cases good yield in benzofuran. The best yield (ca. 60%) was obtained with EAN as solvent working 24 h. On the other hand [HMIM][BF₄] is a better solvent than [BMIM][BF₄], probable due to its character HBD.

The reaction of Danishefsky's diene (60°C, 12 and 24 h, respectively) with **1a** using the three ILs cited in the before paragraph yielded 5-hydroxybenzofuran **16** in reasonable yield (Figure 4). Similarly to the reactions with isoprene and 1-trimethylsilyloxy-1,3-butadiene, the best yield was observed with EAN (ca. 65%). The product obtained in the reactions with diene **7** 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.

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

2.2.2 2-and 3-nitro-1-tosylpyrrole (2a and 2b)

In the reactions of **2a** and **2b** with diene **7** in EAN and [HMIM][BF₄] (60°C, 24 h), all they provided normal DA products **19** (Figure 4) and its isomer 1-tosyl-6-hydroxyindole **26**, respectively, with moderate yield (ca 50%). The products in the reactions with diene **7** resulted from the aromatization of the nitro-adducts promoted by the loss of the nitro and methoxyl groups as nitrous acid and methanol, respectively. Again, the intermediate that suffered nitrous acid extrusion and retained the methoxy group was not detected in any case. In these reactions the regioselectivity was controlled by the nitro and the methoxy group of the diene.

2.2.3 2-and 3-nitrothiophenes (3a and 3b) as dienophile

When 2-nitrothiophene **3a** was tested with isoprene using EAN, and [HMIM][BF₄], respectively as solvent (60°C, 12, 24 and 48 h), afforded pyrrolyl-thiophene **13** formed by an heterocycloaddition followed by thermal rearrangement, in relatively low yield (ca de 13, 18 and 25%, depending on the temperature) (Figure 2). The yields using EAN were lightly better. This behavior was also found with molecular solvents and probably is due to the aromatic character of the thiophene ring. Similar results were obtained when we use the dienophile **3b** (Figure 6). In this case the observed product was **27** and the yields were lightly lower than when the dienophile was **3a**.

On the other hand, the reactions of **3a** with diene **7** using both IL's, provided the normal DA product **22** (Figure 4) with moderate yield (ca de 45%) (60°C, 24h). This result is compatible with those corresponding to the use of molecular solvent. Only the yields are better in presence of ILs.

2.2.4 Disubstituted nitroaromatic heterocyclepentadienes as dienophiles

In this case the behavior of aromatic heterocyclepentadienes disubstituted with electron withdrawing groups (a nitro group being one of the substituents) as dienophile in the presence of IL's (EAN and [HMIM][BF₄]) was studied. With this purpose we choose the following dienophiles: methyl 5-nitrofurano-3-carboxylate **29a**, methyl 5-nitro-1-tosylindole-3-carboxylate **29b**, and methyl 5-nitrothiophene-3-carboxylate **29c**.

The reaction of methyl 5-nitrofurano-3-carboxylate **29a** with isoprene was studied in presence of both PILs at 60°C, 24 h (Figure 8). These reactions yielded a mixture of isomeric cycloadducts **30a** and **30b**, as principal products (72%) and traces of double addition adducts **31a-d** and **32a-d** in both cases as regioisomer mixtures. Meanwhile, exposure of **29a** to diene **7** yielded benzofurans **34** (70%). In this last reaction, only 1:1 adducts whose structure revealed site selectivity and regioselectivity were obtained. In all cases the presence of EAN produce lightly better yields than the use of [HMIM][BF₄].

The treatment of methyl 5-nitro-1-tosylpyrrole-3-carboxylate **29b** with **5** in both PILs afforded a mixture of isomeric indoles **36a** and **36b**, as the principal products (65%) and traces of a mixture of double addition adducts **37a-d** and **38a-d**, in both cases as regioisomeric mixtures (Figure 9). The cycloaddition between diene **7** and **29b** proceeded to produce indole **40** (Figure 10) with good yield (68%). Once again EAN is better solvent.

When methyl 5-nitrothiophene-3-carboxylate **29c** was heated with less reactive isoprene in both PIL's at 60 °C, 24 h, it gave a mixture 1:1 of methyl 5-methylbenzothiophene-3-

carboxylate and methyl 6-methylbenzothiophene-3-carboxylate (30%). In this condition we observe differences respect to the reactions in molecular solvents where the process is hetero DA. When a highly activated diene, such as Danishefsky's diene, react with **29c** (like **29a** and **29b**) in the presence of PILs yielded **44** (Figure 10) (55%). Once again EAN is a better reaction media.

2.2.5 Nitronaphthalenes as dienophiles

To explore the normal electron-demand DA dienophilicity of nitronaphthalenes in presence both PILs (EAN and [HMIM][BF₄]) we selected 1-nitronaphthalene **68**, 2-nitronaphthalene **69**, 1,3-dinitronaphthalene **70**, and 1,4-dinitronaphthalene **71**.

When **68** and **7** were heated in a sealed ampoule (60°C, 24 h) using EAN or [HMIM][BF₄] as solvent, 65% of 2-hydroxy-phenanthrene **75** was regioselectively produced. In a similar way 2-nitronaphthalene **69** reacted in the same conditions to give 43% of 3-hydroxyphenanthrene. The regioselectivity of both reactions was controlled by both the nitro group of the dienophile and the methoxyl group of Danishefsky's diene.

On the other hand, when 1-nitronaphthalenes reacted with isoprene in the presence of the cited PILs (60°C, 24 h), it produced a mixture of *N*-naphthyl-2-methylpyrrole (30%) and 2-methylphenanthrene (12%). Similar result was obtained using 2-nitronaphthalene as dienophile although the yields were lightly lower. It is interesting cite that the presence of PILs modify the products obtained in these reactions. With molecular solvents we observed only the hetero DA product, meanwhile using IL's appear in the mixture the normal DA product.

Moreover, when the dinitronaphthalenes **70** and **71** reacted with isoprene (60°C, 24 h) in the presence of EAN or [HMIM][BF₄], they generated a mixture of phenanthrenes and *N*-naphthylpyrroles with different yield ratios and a moderate predominance of the normal DA product. In the case of 1,3-dinitronaphthalene **70**, newly a clear tendency towards the DA cycloaddition to the C3-C4 bond was observed. In the reactions with isoprene, 1,3-dinitronaphthalene gave the corresponding 2-metil-10-nitro-phenanthrene (32%), together with [3-methyl-1-(1-nitronaphthalen-3-yl)-pyrrole] and [3-methyl-1-(2-nitronaphthalen-4-yl)-pyrrole]. On the other hand, the reactions of 1,4-dinitronaphthalene with isoprene afforded 2-methyl-9-nitrophenanthrene (27%) and 3-methyl-1-(4'-nitronaphthalene-1'-yl)-pyrrole.

EAN was a better reaction media in all cases discussed. The preference for the normal DA products in the presence of PILs respect to the use of molecular solvent, probably is due to the increase of the electrophilicity of the dinenophile as a consequence of HBD interactions

2.2.6 5-and 8-nitroquinolines as dienophiles

It was explored the cycloaddition reactions between 5-nitro and 8-nitroquinolines with the dienes 1-trimethylsilyloxy-1,3-butadiene and Danishefsky's diene, respectively, in presence of EAN and [HMIM][BF₄]. With both PIL's the reaction systems improved the yields (approximately 20%) and the reaction time and temperature were considerably smaller (60°C, 24 h) than similar reactions development in molecular solvents. In all reaction systems, EAN make possible major yields than [HMIM][BF₄]. The cycloaddition products were the same than those obtained using chloroform as reaction media, except for the reaction of **84** whit **5** in which the observed product was consequence of normal DA process (8-Methyl-7,10-dihydro-benzo[h]quinoline) **86**. (Cancian, et al, 2010)

2.3 Theoretical studies

In the last years the DFT has been successful in explaining the reactivity and regioselectivity of cycloaddition reactions. In this direction there are several parameters which can be used as global or local reactivity descriptors. For instance, the chemical hardness (η) describes the resistance of the chemical potential to a change in the number of electrons. The electronic chemical potential (μ) it is usually associated with the charge-transfer ability of the system in its ground state geometry. Both quantities can be approximated in terms of the energies of the HOMO and LUMO frontier molecular orbitals (Eqs. 1 and 2) (Domingo, et al, 2002; Domingo & Aurell, 2002)

$$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO}) \quad (1)$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2} \quad (2)$$

The global electrophilicity index (ω), introduced by Parr (Parr, et al, 1999) is a useful descriptor of the reactivity that allows a quantitative classification of the global electrophilicity character of a molecule within a unique scale. Current studies based on the DFT and applied to DA reactions, have shown this classification of the diene/dienophile pair is a powerful tool to predict the feasibility of the process and the type of mechanism involved. This index defined as Eq. 3

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

Useful information about polarity of de DA processes may be obtained from the difference in the global electrophilicity power of the reactants. This difference has been proposed as a measure of the polar character of the reaction. On the other hand, local reactivity indexes are associated with site selectivity in a chemical reaction. These descriptors should reflect the sites in a molecule where the reactivity pattern stated by the global quantities should take place. For instance, an important local reactivity parameter was introduced by Parr *et al.*, and it was defined as the Fukui function (Domingo, et al, 2002)

Eq. (4) provides a simple and direct formalism to obtain the Fukui function from an approach based on a relationship with the FMO's. The condensed Fukui function for electrophilic (nucleophilic) attack involves the HOMO (LUMO) FMO coefficients (c) and the atomic overlap matrix elements (S).

$$f_k^a = \sum_{\mu \in k} |c_{\mu a}|^2 + \sum_{v \neq \mu} c_{\mu a} c_{va} S_{\mu v} \quad (4)$$

This scheme has been corroborated for several reactions that are well documented.

Eq. (5) has been introduced to analyze at which atomic site of a molecule the maximum electrophilicity power will be developed.

$$\omega_k = \omega f_k^+ \quad (5)$$

Furthermore, the first approaches toward a quantitative description of nucleophilicity, in the form of a regional reactivity index, have also been reported. Eq (6) has been developed by

Domingo (Domingo, et al, 2008) with the purpose of identifying the most nucleophilic site of a molecule and assessing the activation/deactivation caused by different substituents on the electrophilic aromatic substitution reactions of aromatic compounds.

$$N_k = Nf_k^- \quad (6)$$

$$N = (\epsilon_{HOMO, Nu} - \epsilon_{HOMO, TCE}) \quad (7)$$

Where $\epsilon_{HOMO, TCE}$ is the HOMO energy of tetracyanoethylene (TCE) taken as a reference molecule because it exhibits the lowest HOMO energy in a large series of molecules previously considered in the framework of polar DA cycloadditions). N is the global nucleophilicity index and N_k is its local counterpart. This nucleophilicity index has been useful to explain the nucleophilic reactivity of some molecules towards electrophiles in cycloaddition as well as substitution reactions. (Domingo, et al, 2008)

Normally the polarity of the normal electron demand DA process has been studied by means of global electrophilicity index difference between reactants and the regioselectivity of the normal electron demand DA reaction using the local electrophilicity index for dienophiles (electrophiles in the reaction) and the local nucleophilicity index for dienes (nucleophiles in the reaction).

In the direction cited before we show different theoretical studies related to the polar DA reactions described experimentally, in which the dienophiles are aromatic heterocycles or carbocycles. In some cases, the mechanism of these reactions, specially respect to regio-, site- and stereochemistry were analyzed in detail.

2.3.1 Five-membered heterocycles: General

In Table 2 we present a classification of the dienophiles and dienes in decreasing order of the electrophilicity power (ω). We can assume that high nucleophilicity and high electrophilicity corresponds to opposite extremes of this scale. (Della Rosa, et al, 2011; Brasca, et al, 2009). In the table we also included some global properties such as the chemical potential and the chemical hardness. A good electrophile is characterized by a high value of μ and a low value of η .

In order to verify the validity of this scale we carried out the corresponding thermal DA reactions of some dienophiles with dienes of different nucleophilicity such as isoprene and Danishefsky's diene.

- The substitution of one hydrogen atom in all the dienophiles by one of the most powerful electron-withdrawing groups (nitro group) produces an increment in the electrophilicity character and therefore an increase in the reaction rate is expected. The 2-nitro-substituted heterocycles show high electrophilicity power respect to the 3-nitro-substituted ones. Experimentally we obtained higher yields when the nitro group is place in the 2-position of the thiophene's ring than when it is in the 3-position. So these last results support the tendency observed in the tables.
- The dienophiles substituted by two different electron-withdrawing groups (methyl carboxylate and nitro groups) show the highest values in electrophilicity power, indicating that these disubstitutions are suitable in order to increment the reactivity of the dienophiles. Moreover, the yields corresponding to the DA reactions of the disubstituted heterocycles with the dienes showed an increase respect of that corresponding to the monosubstituted heterocycles.

I. Dienes

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Isoprene	-0.1209	0.1962	1.01
Danishefsky's diene	-0.0945	0.1851	0.66

II. Dienophiles

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Methyl 5-nitrofuran-3-carboxylate	-0.1897	0.1814	2.70
2-Nitrofuran	-0.1810	0.1775	2.51
3-Nitrofuran	-0.1767	0.1808	2.35
Furan	-0.1024	0.2441	0.58

a. Furan and derivatives.

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Methyl 5-nitrothiophene-3-carboxylate	-0.1922	0.1767	2.84
2-Nitrothiophene	-0.1845	0.1738	2.66
3-nitrothiophene	-0.1794	0.1821	2.40
Thiophene	-0.1545	0.1566	2.07

b. Thiophene and derivatives.

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
1-Tosyl-methyl 5-nitropyrrole-3-carboxylate	-0.1734	0.1776	2.30
1-Tosyl-2-nitropyrrole	-0.1655	0.1739	2.14
1-Tosyl-3-nitropyrrole	-0.1668	0.1765	2.14
1-Tosylpyrrole	-0.1348	0.1752	1.41

c. 1-Tosyl-pyrrole and derivatives.

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Methyl 5-nitroselenophene-3-carboxylate	-0.1899	0.1717	2.85
2-Nitroselenophene	-0.1829	0.1695	2.68
3-Nitroselenophene	-0.1776	0.1803	2.38
Selenophene	-0.1220	0.2195	0.92

d. Selenophene and derivatives.

Table 2. Global properties for some common reagents participating in Diels-Alder reactions

On the other hand, the differences in the global electrophilicity power between the dienophile/diene pair ($\Delta\omega$) are higher for the Danishefsky's diene than for isoprene. Therefore, we can expect a high reactivity and a high regioselectivity for the pair dienophile/Danishefsky's diene. This fact is also consistent with the experimental researches in both molecular solvent and IL's.

2.3.2 2-and 3-nitrobenzofurans as dienophiles

When 2-nitrobenzofuran (**2-NBF**) and 3-nitrobenzofuran (**3-NBF**) were reacted with isoprene, 1-trimethylsilyloxy-1,3-butadiene and de Danishefsky's diene, under different reaction conditions they showed their dienophilic character taking part in a normal demand polar DA cycloaddition reactions. These reactions could be considered a domino process that is initialized by a polar DA reaction, and the latter concerted elimination of nitrous acid from the [4+2] cycloadduct yields the corresponding dibenzofurans. (Della Rosa, et al, 2011) The electrophilicity of isoprene falls in the range of moderate electrophiles within of the electrophilicity scale proposed by Domingo *et al.* When electron-donating substituents, -OCH₃ and -OSi(CH₃)₃, are incorporated into the structure of butadiene, a decrease in the electrophilicity power is observed. Therefore, the electrophilicity of Danishefsky's diene falls in the range of marginal electrophiles, good nucleophiles, within of the electrophilicity scale. This behavior indicates that the nucleophilic activation in Danishefsky's diene is greater than in isoprene, in clear agreement with the high nucleophilicity index of the diene. 1-trimethylsilyloxy-1,3-butadiene have a intermediate behavior.

As consequence of the high electrophilic character of these substituted dienophiles and the high nucleophilic character of the dienes, it is expected that these DA reactions proceed with polar character. The polarity of the process is assessed comparing the electrophilicity index of the diene/dienophile interacting pairs, that is $\Delta\omega$. Evidently, the differences in the global electrophilicity power ($\Delta\omega$ are higher for the Danishefsky's diene than 1-trimethylsilyloxy-1,3-butadiene and isoprene. Therefore, a high reactivity and high regioselectivity are expected for the pair dienophile/Danishefsky's diene.

Finally, the flux of the electron-density in these polar cycloaddition reactions is also supported by means of a DFT analysis based on the electronic chemical potentials of the reagents. The electronic chemical potentials of the substituted heterocyclic dienophiles (nearly -5 eV), are higher than those of the dienes (nearly -3 eV), thereby suggesting that the net charge transfer will take place from these electron-rich dienes towards the aromatic dienophiles. (Table 3 and 4)

Compound	ω (eV)
2-NBF	3.3275
3-NBF	3.0002

Table 3. Global electrophilicity indexes for dienophiles

Dienophile	Site	ω_k (eV)
2-NBF	2	0.1571
	3	0.5359
3-NBF	2	0.7263
	3	0.0482

Table 4. Local electrophilicity indexes for dienophiles

According to the global electrophilicity index ω shown, the dienes will act as nucleophiles and the dienophiles as electrophiles. To study the regioselectivity we used the local

electrophilicity and nucleophilicity indexes for dienophiles and dienes respectively. The sites of study were C2 and C3 in **2-NBF** and **3-NBF** and C1 and C4 in the dienes. The more favourable adducts are the ones where the most electrophilic and nucleophilic sites interact first. In the reactions in which it is possible discussed the regioselectivity the experimental data agree with the computational results. (Della Rosa, et al, 2011)

The 2-nitrosubstituted benzofuran show higher electrophilicity power than the 3-nitrosubstituted benzofuran probably due to the proximity of the nitro group with the heteroatom

2.3.3 Nitrofurans as dienophiles: Theoretical mechanistic approach

Specifically the reactions of 2-nitrofurans, methyl 5-nitro-3-furancarboxylate, and methyl 5-nitrofurans-2-carboxylate, respectively, and Danishefsky's diene were studied using the hardness, the polarizability and the electrophilicity of the corresponding DA primary adducts as global reactivity indexes. The experimentally observed products for these DA reactions using different conditions were indicated in the Figure 21, and related experiments. It has been demonstrated that both the hardness as well as the electrophilicity power of adducts are appropriate descriptors for predicting the major product of the reactions at least in the cases study here. (Brasca, et al, 2011)

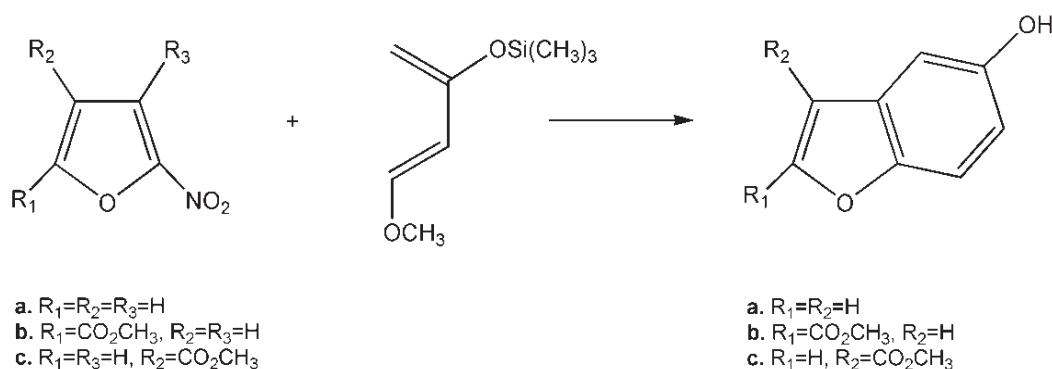


Fig. 21. Reactions of 2-nitrofuranes with Danishefsky's diene

For each reaction four pathways, which lead to the regioisomers **I**, **I'**, **II** and **II'** are feasible (Figure 22). Clearly, depending on the orientation of the nitro and methoxy groups, two stereoisomers can be obtained in each pathway (i.e. *endo* and *exo* adducts).

The regioisomer that have the higher value of η and the lower values of ZPE, α and ω , should correspond to the major product.ⁱ The calculated hardness and electrophilicity power correctly predict the regioisomers **I.a-I.c** as the main adducts of the DA reactions. However, the calculated total energies and polarizabilities show a random behaviour. Therefore, neither of these two parameters can predict the predominant regioisomer of the DA reactions in a correct way.

The results obtained in gas phase revealed the same tendency as in molecular solvent and in ILs. The chemical hardness and the electrophilicity power are useful parameters to predict which regioisomers will lead to the main product of the DA reactions.

We can conclude that the predominant regioisomeric adduct of the reactions between furan derivatives and Danishefsky's diene has always the less electrophilicity and high hardness values. Therefore, the regioselectivity experimentally observed can be confirmed by this approach.

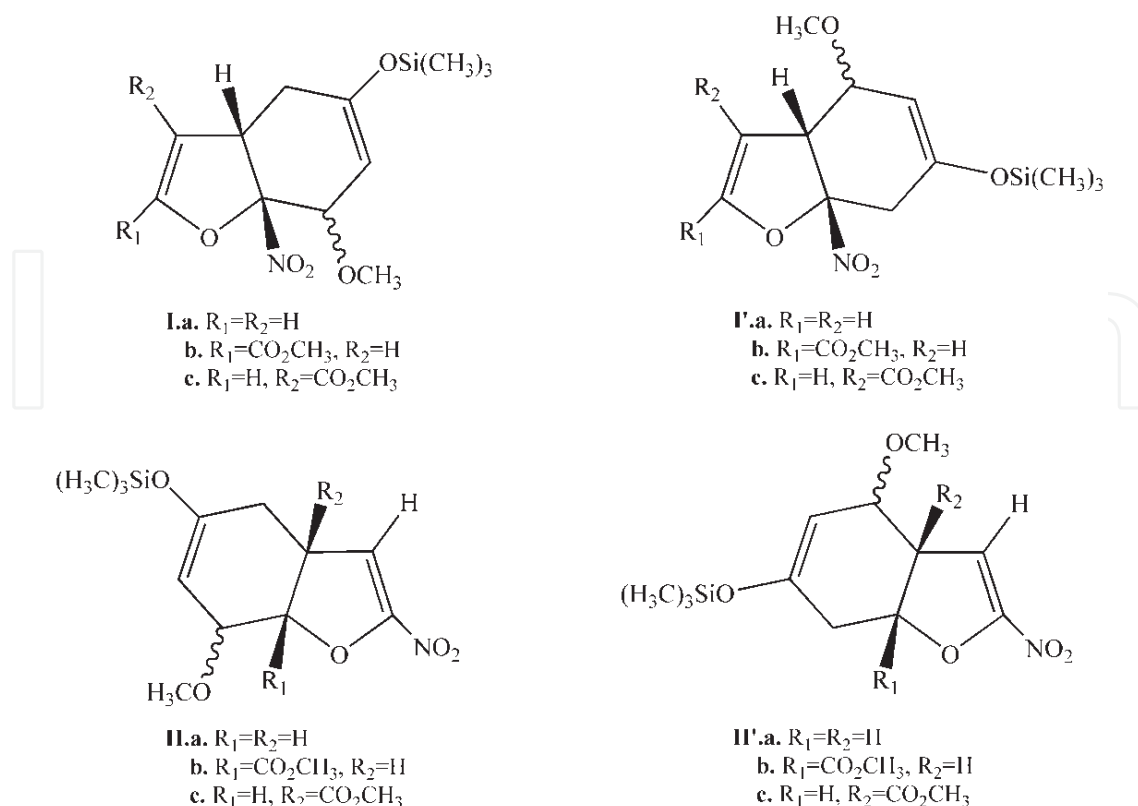


Fig. 22. Possible regioisomeric Diels-Alder adducts

The obtained energies show that the *Endo* isomer is more stable than the *Exo* one. Moreover, the more stable *Endo* isomer has lower electrophilicity value than the *Exo* isomer in all cases. Regarding the hardness, we found that only in the presence of solvent the maximum hardness principle is obeyed.

The investigation by DFT theory, including solvent effects (molecular solvents and ILs), shows that these cycloadditions proceed by a concerted but asynchronous reaction mechanism. The lowest activation energies for concerted reactions are obtained. However, the stepwise additions have significantly lower activation energy lead to substantially less stable products. Moreover, the primary cycloadducts could never be isolated but were converted into 5-hydroxybenzofurans by subsequent extrusion of nitrous acid, hydrolysis of the silyl enoether, and elimination of methanol. Elimination of nitrous acid is calculated to have lower overall barriers than cycloaddition reactions and is strongly exothermic, thus explaining the preferred reaction pathway.

2.3.4 Nitronaphthalenes as dienophiles

The reactions of naphthalenes properly mono- and disubstituted with an electron-withdrawing and a series of dienes in thermal conditions, were evaluated with the frontier molecular orbitals (FMO) theory which provide qualitative information about the feasibility of these DA reactions. Besides, the global electrophilicity index (ω) is employed to estimate the electrophilic character of the dienophiles used in the cycloaddition reactions.

Taking into account that the reactivity of a DA reaction depends on the HOMO-LUMO energy separation of the reactants, and that in a normal electron demand DA reaction the strongest interaction takes place between the HOMO of the diene and the LUMO of the

dienophile, we compared the corresponding energies of the reacting partners in order to explain the experimental tendency observed. (Table 5).

Molecule	FMO Energy
1,4-DNN	-3.3223
1,3-DNN	-3.1313
1,5-DNN	-3.1022
1,8-DNN	-2.7392
Danishefsky's diene	-5.0883

Table 5. Calculated LUMO energies for the dinitronaphthalenes and calculated HOMO energy for Danishefsky's diene

When the FMO of the reacting pairs are closer in energies, the interaction is higher. Therefore, we expected higher reactivities for **1,4-DNN** and **1,3-DNN**, which is consistent with the experimental results

Since all the reactions involving **1,3-DNN** produce only one product in appreciable amounts, we selected this dienophile to explain the difference in reactivity towards the different dienes. Thus, the FMO energies of the reactants were evaluated and calculations of the electrophilicity index were performed. Table 6 shows how Danishefsky's diene leads to the minimum HOMO-LUMO energy difference compared to the other dienes, so that an increase in the reactivity of the system is to be expected. This effect is revealed by an increase in the yield of the DA reaction. (Paredes, et al, 2007; Domingo, et al, 2008)

Molecule	Energy	μ	η	ω
1,3-DNN	-3.1313	-5.11	3.97	3.30
Isoprene	-5.9563	-3.29	5.34	1.01
1-(N-acetyl-N-propylamine)-1,3-Butadiene	-5.3250	-2.99	4.67	0.96
1-Methoxy-1,3-butadiene	-5.3032	-2.83	4.95	0.81
Danishefsky's diene	-5.0883	-2.57	5.03	0.66

Table 6. Global properties values and global electrophilicity scale for reagents of DA reaction. The calculated LUMO energy for **1,3-DNN** and the calculated HOMO energies for the dienes are also shown.

It has been demonstrated a good correlation between the difference in the global electrophilicity of the diene/dienophile interacting pair ($\Delta\omega$) and the feasibility of the cycloaddition.

2.3.5 Study of the domino reaction of 1-nitronaphthalene with the Danishefsky's diene: Theoretical mechanistic approach

The reaction of 1-nitronaphthalene with the Danishefsky's diene to give 3-hydroxyphenantrene has been theoretically studied using DFT methods. This reaction is a domino process that is initialized by a polar DA reaction between the par dienophile/diene to give the formally [2 + 4] cycloadduct. The subsequent concerted elimination of nitrous

acid from the primary adduct yields the precursor of the phenatrene derivative. Analysis of the global reactivity indexes as well as the thermodynamic data for this domino process indicates that while the large electrophilic character of 1-nitronaphthalene together with the large nucleophilic character of Danishefsky's diene are responsible for the participation of these reagents in a polar DA reaction. The DA reaction has a two-step non-intermediate mechanism characterized by the nucleophilic attack of the non-substituted methylene of the diene to the electrophilically activated C2 position of 1-nitronaphthalene. The subsequent ring closure affords the primary cycloadduct. The latter concerted elimination of nitrous acid yielded the precursor of the tricyclic aromatic final product. Spite of the large activation free energy associated with the DA reaction and the endergonic in the primary adduct, the irreversible extrusion of nitrous acid makes feasible thermodynamically the domino reaction. (Domingo, et al, 2008)

2.3.6 Nitroquinolines as dienophiles

Although the global electrophilicity for the 5-nitroquinoline indicated a lightly major reactivity than the 8-nitro isomer (Figure 23). This result does not agree with the experimental data. In this respect it is possible think that the attack of the dienophile to the "para" position would be a reversible process meanwhile the attack to the "orto" position to the nitro group evolves in form irreversible to the cycloaddition product. The major reactivity of the 8-nitro derivative could be occur due to the presence of electroelectronic factors more favourable, which are produced during the nucleophilic attack of the diene, for instance a better stabilization of the negative charge in the nitro group. These effects were does not considered in the reagents. (Cancian, et al, 2010)

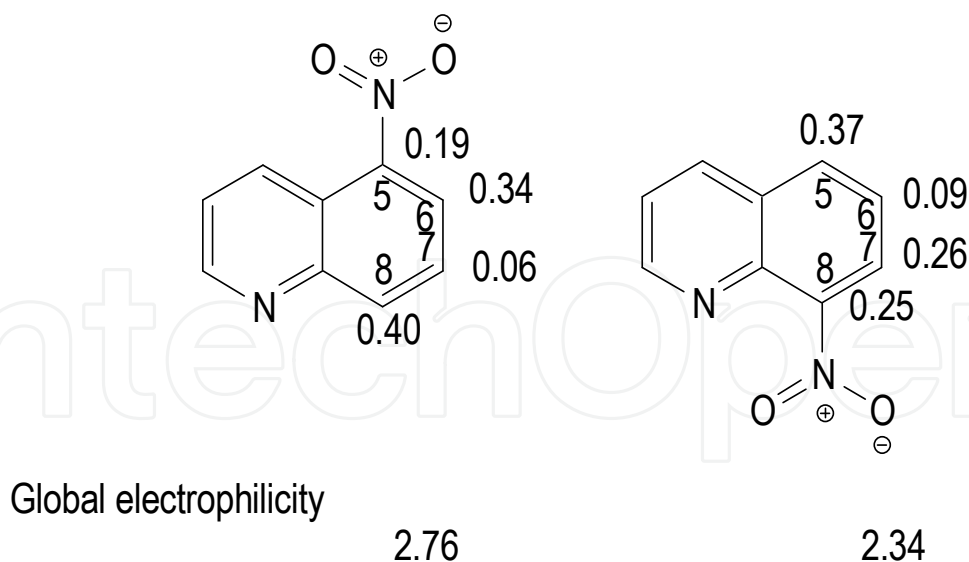


Fig. 23. Global and local electrophilic indexes for 5- and 8-nitroquinolines

Using the 8-nitroquinoline we showed specifically the interactions models with the lowest energy between the dienophile and the solvents (chloroform, EAN and HMIM) (Figure 24). For these structures were calculated the global electrophilicity and nucleophilicity values (Table 7).

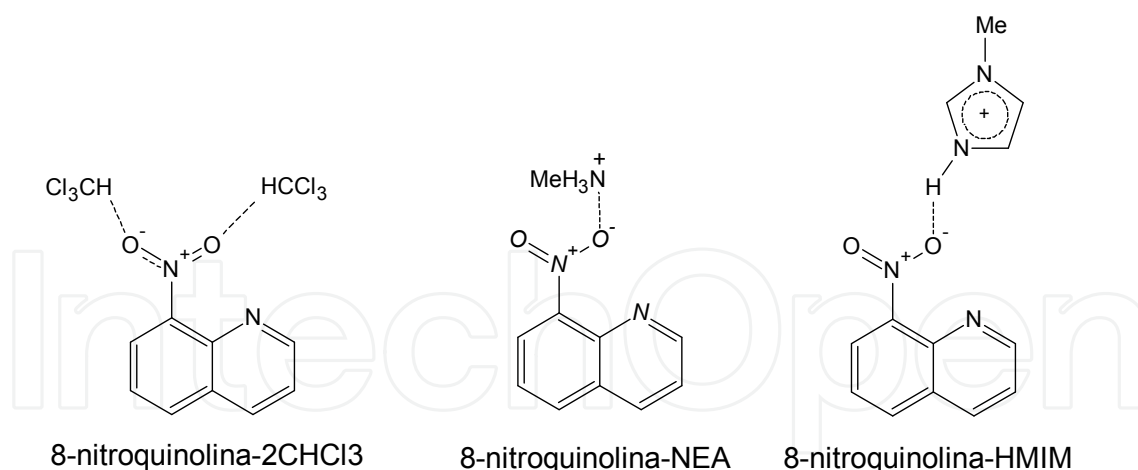


Fig. 24. Theoretical models for the interaction between 8-nitroquinoline and solvent molecules

	HOMO	LUMO	μ	η	ω	N
8-nitroquinolina	-0,2497	-0,0945	-0,1721	0,1553	2,59	2,32
8-nitroquinolina-2CHCl₃	-0,2677	-0,1060	-0,1868	0,1617	2,94	1,84
8-nitroquinolina-HMIM	-0,3615	-0,2242	-0,2929	0,1373	8,50	-0,72
8-nitroquinolina-NEA	-0,3482	-0,2044	-0,2763	0,1438	7,22	-0,35
Dieno Danishefsky	-0,1705	0,0125	-0,0790	0,1830	0,46	4,48

Table 7. Global electrophilicity and nucleophilicity indexes

3. Conclusions

It was possible demonstrate the influence of the solvent in these particular type of DA reactions. A series of aromatic carbocyclic and heterocyclic substituted by electron withdrawing groups can act as dienophiles in polar cycloaddition reactions joint to a different dienes in the presence of PILs. However, DA reactions proceed at an appreciable rate only when either the diene or the dienophile are activated by an electron donating or electron withdrawing group, normally characterized by the presence of a heteroatom that can therefore efficiently interact with the solvent. ILs, with their peculiar properties such as high polarizability/dipolarity, good hydrogen bond donor ability, were straight away considered to have the potential to influence the outcome of these DA reactions, accelerating them.

In general, the products of the reactions development in PILs are similar to those in molecular solvents. However, the presence of PILs improved the reaction rate probably due to the hydrogen bonding interactions between the neoteric solvent and the dienophile. Only in a few cases we can note differences in the product distribution. For the reactions in which are possible to observe a competition between normal and hetero DA process, the PILs favor the normal pathway because they improve the electrophilicity of the dienophiles.

The DFT analysis of the global properties of the interacting pair diene/dienophile illustrates the normal electron demand character of these DA reactions. It is possible to show that the local indexes provide useful clues about the regiodirector effects, particularly of the nitro group. The presence of a solvent (molecular or neoteric) as the reaction media does not

impart a prominent influence on the relative reactive sites. In few cases among those studied we can note that the relative reactive sites are affected by the solvent and the basis set (e.g. methyl 5-nitrofuran-2-carboxylate).

The site-, regio-, and stereochemistry of some of these DA reactions has been investigated by the density functional theory, including solvent effects. Generally, these cycloadditions proceed by a concerted but asynchronous reaction mechanism. The *endo* stereochemistry is in most case preferred.

In general, the normal DA reaction mechanism is a domino process that is initialized by the polar reaction between the diene and the dienophile to give the primary cycloadduct. These DA reactions have a two-step non-intermediate mechanism characterized by the nucleophilic attack on the non-substituted methylene of the diene to the electrophilically activated position of the dienophile. The subsequent ring-closure affords the primary cycloadduct. This behavior makes the reaction to be regioselective. The latter concerted elimination of the nitrous acid from the primary cycloadduct yields the precursor of the final aromatic product. Spite of the large activation free energy associated with the DA reaction and the endergonic character of formation of the primary cycloadduct, the irreversible extrusion of the nitrous acid make feasible thermodynamically the domino reaction.

DFT calculations of the electrophilicity and nucleophilicity indexes in general agree with the experimental results and they are a good reactivity and regioselectivity predictors in this type of polar cycloaddition reactions

The presence of a PILs in the reaction media improves significantly the electrophilic character of the dienophile. However, the differences between the experimental results using PILs or molecular solvents are not so bigger how the calculated electrophilic values indicated.

With the present results in mint, in a second step would be desirable development others DA reactions using new dienes with a strong projection in organic synthesis.

4. Acknowledgement

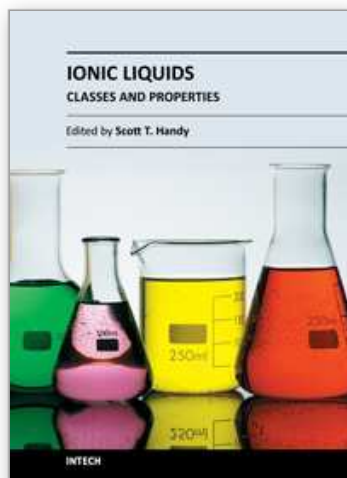
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Ionic Liquids - Classes and Properties

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Room temperature ionic liquids (RTILs) are an interesting and valuable family of compounds. Although they are all salts, their components can vary considerably, including imidazolium, pyridinium, ammonium, phosphonium, thiazolium, and triazolium cations. In general, these cations have been combined with weakly coordinating anions. Common examples include tetrafluoroborate, hexafluorophosphate, triflate, triflimide, and dicyanamide. The list of possible anionic components continues to grow at a rapid rate. Besides exploring new anionic and cation components, another active and important area of research is the determination and prediction of their physical properties, particularly since their unusual and tunable properties are so often mentioned as being one of the key advantages of RTILs over conventional solvents. Despite impressive progress, much work remains before the true power of RTILs as designer solvents (i.e. predictable selection of a particular RTIL for any given application) can be effectively harnessed.

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