Trends in Organic Chemistry
Vol. 17, 2014

Review

Pseudo-pericyclic reactions: Aromatic compound derivatives as electrophiles in polar Diels-Alder reactions. An experimental and theoretical study

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ABSTRACT

The Diels-Alder reaction is considered to be a pericyclic process. However, depending on the structure of the diene and the dienophile the nature of this reaction can change. In the recent years we have worked with aromatic nitro-substituted compounds as electrophiles in cycloaddition reactions with different dienes of diverse nucleophilicity. In this context, carbocyclic compounds such as nitronaphthalenes and heterocyclic compounds such as nitropyrroles, nitrofuranes, nitrothiophenes, nitroselenophenes, nitroindoles, nitrobenzofuranes, and nitrobenzothiophenes, in both cases mono and disubstituted, were used. The dienes used were Danishefky's diene, Rawal's diene, 1-trimethylsyliloxy-1,3-butadiene, and isoprene. The monosubstituted electrophiles whose aromatic character is higher, for e.g. nitronaphthalene and nitrothiophenes, follow a heterocyclic cycloaddition channel and present, in the reactions with the less nucleophilic dienes, a pyrrolyl derivative as principal product while the other electrophiles follow a normal cycloaddition channel. The solvent effect observed in these reactions was important. In thermal conditions we observed a substantial influence of ionic liquids (ILs) on reaction times and product yields comparing to molecular solvents. This fact persuades us to consider these processes as polar Diels-Alder reactions in which an electrophile reacts with a nucleophile. On the other hand when microwave irradiation was used, the best results were obtained in free solvent conditions. We confirm this approach using theoretical calculations based on Density Functional Theory (DFT).

KEYWORDS: Diels-Alder, polar, DFT, solvent effects, microwave irradiation

1. Introduction

1.1. Polar Diels-Alder reactions: Nitronaphthalenes as electrophiles - an overview

We will start with explaining some details related to the polar Diels-Alder (P-DA) reactions to introduce some of the general considerations covered in this review.

For many years the Diels-Alder (DA) reaction (Scheme 1) has remained as one of the most powerful transformation methods in chemical synthesis, particularly for obtaining polycyclic rings. With its potential to form carbon-carbon, carbon-heteroatom, and heteroatom-heteroatom bonds, the reaction underlies the synthesis of diverse carbon and heterocyclic compounds. It is a key step in the synthesis of many natural products and pharmaceutical compounds [1].

Its application not only leads to a strong increase in molecular complexity (molecular size, topology, stereochemistry, functionality, and appendages), but also can result in structures that lend themselves

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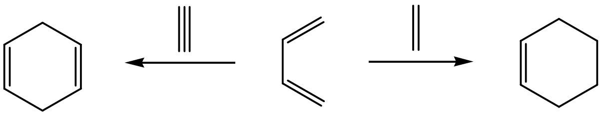


Scheme 1

to additional amplification of complexity by the use of other powerful synthetic reactions [2].

The one-step process could be an interaction between a diene (4π) and a dienophile (2π). This process can be inter or intramolecular bearing an almost unlimited number of variants. It is worth noting that these variants exist not only in the substitution of the reaction component but also in the electronic nature of these dienes and dienophiles.

Many versions of the DA reaction have been elaborated, including intramolecular [4π+2π] cycloadditions, hetero DA reactions, pressure-accelerated DA reactions, and Lewis acid accelerated DA reactions. Since the DA reaction is characterized by a negative volume of activation, the application of pressure facilitates the transformation of the reactants into the relatively more compact transition state, thereby lowering the activation energy of the process [3, 4]. More recently, it has been demonstrated that the use of microwave irradiation improves the yields in these reactions [5].

While the use of these aromatic 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. It was reported that several nitroheterocyclic compounds react with strong and poor dienes under different thermal conditions. It can be demonstrated that the transition state (TS) offers separation of charges, implying that the reaction constitute a polar cycloaddition with an asynchronous TS [6]. In general, these cited polar reactions where the dienophile is a nitroheterocycle compound, are domino processes initialized by a DA reaction to give the [4+2] cycloadduct that suffers the subsequent irreversible elimination of nitrous acid, which is the responsible factor for the feasibility of the overall process. In the last few years, the density functional theory (DFT) has been successful in explaining the reactivity and regioselectivity of cycloaddition reactions [7]. Current studies, based on DFT applied to DA reactions have shown that the classification of dienes and dienophiles in a unique scale of electrophilicity, is a powerful tool to predict the feasibility of the process and the type of mechanism involved.

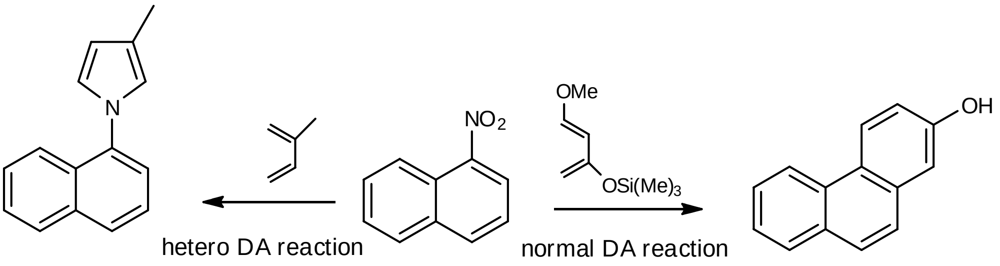
Due to the interest in the cycloaddition of substituted aromatic compounds with electron-withdrawing groups, we have reported several studies on the dienophilic character of various aromatic systems participating in DA reactions that were developed in molecular solvents such as benzene or toluene [8]. In these processes two ways of reaction are possibly observed depending on the aromatic character of the dienophile, the normal and hetero DA reaction, which takes place when some nitronaphthalenes act as the electrophiles [9]. This behavior is probably due to the aromatic character of these compounds (Scheme 2).

However, when the naphthalene has double substitution in one ring (for example: 1,3-dinitronaphtalene, 1,4-dinitronaphthalene, 1-ciano-4-nitronaphthalene etc.) and reacts with a diene, only the product that derives from the normal DA reaction is obtained. In the case of 1,5- and 1,8-dinitronaphthalenes the reaction behavior is very similar to that of 1-nitronaphthalene.

Taking into account the cited results, the aim of this review is to study the dienophilic behaviour of a series of aromatic heterocycles (mono and disubstituted with electron withdrawing groups such as nitro, acyl or carboxylate) in polar cycloaddition reactions when exposed to dienes with diverse nucleophilicity. Also, this allows to compare and discuss not only the relative reactivity of the substitution of the different aromatic rings but also the regioselectivities in the case of successful cycloaddition. Furthermore, the employment of appropriate dienophiles can lead to new routes for obtaining compounds with the potential to act as synthetic intermediates. The solvent effect (molecular solvents *vs* ionic liquids) on this type of cycloaddition processes is also analyzed. Heating of the reaction by microwave irradiation is also discussed. In addition, it is interesting to obtain information on the factors affecting reactivity, selectivity and the reaction mechanisms through theoretical calculations employing the DFT method.

1.2. Solvent effect on polar Diels-Alder reactions

Due to the aromaticity of the electrophiles, when molecular solvents such as benzene, toluene,



Scheme 2

chloroform etc. are employed, reactions require higher temperatures and longer reaction time. This situation may lead to undesirable side reactions. It is therefore useful to explore alternate working conditions. As the use of solvents in most of the cases is an essential part of the polar chemical process, it is of interest to study the use of non-conventional solvents and their influence on the reaction, and also consider their impact on the environment. It has been demonstrated that some DA reactions show a remarkable increase in reactivity and selectivity in aqueous solutions. This was discussed in the pioneering work of R. Breslow in terms of hydrophobic effects [10]. In this study the possibility of using ILs as substitutes for water was explored and the results showed that with neoteric solvents the reactions were faster than the ones developed with organic solvents.

The effect of the solvents on a chemical reaction can be considered at the theoretical level. For molecular solvents, computational methods that work with a continuous dielectric field (not considering the molecular structure of the solvent) can be used with good results; the nature of room temperature ionic liquids (RTILs) is very different from that of normal liquids, and hence the development of an appropriate computational model requires re-evaluation [11]. The ionic liquid (IL) is constituted by two oppositely charged ions with very different chemical nature. Their physico-chemical properties such as viscosity present values in a very different range than common molecular solvents. The dielectric constant values for RTILs, the key parameter in continuum solvent models, are not well established and different methods give different values, but each method gives values very similar to those of all the other RTILs investigated [12]. Recently evidenced calculations confirm that the DA reaction in the presence of imidazolium salts proceeds via concerted mechanisms similar to the uncatalyzed reaction [13]. The analysis of the computational results suggests that the coordination of the IL cation affects the geometry and electronic structure of the reacting species throughout the reaction pathway, leading to changes in reactivity and selectivity. They also demonstrate that the strong asynchronicity observed in ionic liquid media is due to the polarization effect of the cation.

1.3. High pressure conditions

Of the parameters that could be altered to achieve success in a synthetic method, high-pressure is an important factor in DA reactions. As the DA reaction is characterized by a negative volume of activation, high-pressure facilitates the transformation of the reactants into transition states, thereby lowering the activation energy of the process. Moreover the volume variation for the overall process is also negative, thus making it kinetically, as well as thermodynamically, favorable. At atmospheric pressure, some cycloadditions fail since they are reversible and reach a low equilibrium yield that cannot be improved by raising the temperature. Pressure, on the other hand, favors the forward reaction and disfavors the reverse, leading to higher yields [14]. The use of high-pressure conditions for preparative intermolecular DA reactions has been well studied [15], but no successful examples of high-pressure DA cycloadditions involving heteroatomic compounds as electrophiles have been reported. The first indication of the advantages of high-pressure conditions in DA reactions of aromatic compounds acting as dienophiles is the reaction between 1-nitronaphthale and Danishefsky's diene, which shows higher yields than the thermal reaction [16].

1.4. Microwave irradiation

The microwave-assisted controlled heating has become a powerful tool in organic synthesis, which is increasingly used to accelerate organic reactions and to get higher yields without by-products. In conventional synthesis involving one or more heat stages, developing the optimal reaction conditions for obtaining the desired product is often difficult and time consuming. Furthermore multi-stage heating of a reaction mixture is comparatively slow and energy inefficient, as first the heat energy is transferred from the heat source to the reaction vessel, and then the hot surface heats the content of the reaction vessel. Application of microwaves in organic reactions has become popular over the past few years. Often microwave-heating results in faster reactions, high yields and lower amount of side products. Microwave heating depends on the ability of the molecules present in the reaction mixture to absorb irradiation. In these conditions the reaction mixture undergoes dielectric heating by two ways: dipolar polarization and ionic conduction. In this way polar and ionic compounds can absorb microwave energy very efficiently and are heated up quickly. Indeed, a number of authors have described success in reactions that do not come about by conventional heating and even modifications of selectivity (chemio-, regio- and stereo-selectivity). The effect of microwave irradiation in organic synthesis is a combination of thermal effects, arising from the heating rate, superheating or ‘hot spots’ and the selective absorption of radiation by polar substances. However, the ‘specific microwave effect’ is still a controversial topic [17].

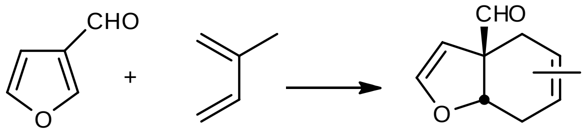
The use of microwave irradiation in this type of P-DA reactions presents advantages in relation with those developed in classical conditions although in general the products obtained are similar. In this way it is possible to obtain lower reaction times and better yields.

2. Pentaheterocycle derivatives as dienophiles

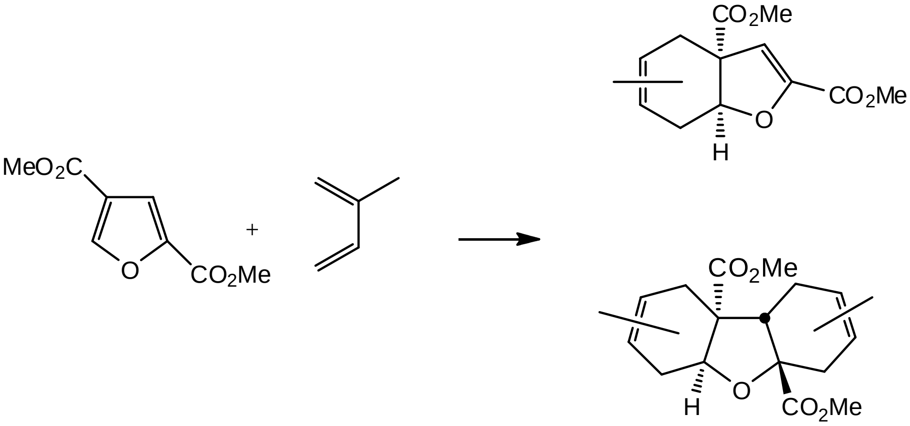
Heterocycles such as pyrrole, furan, thiophene and selenophene undergo DA reactions despite their stabilized 6π aromatic electronic configuration. In view of their electron-rich constitution and electron-donor properties, they have been mostly used as diene components in the cycloaddition processes. However, only a limited number of them act as dienophiles in DA reactions with normal electron demand (electronic transfer from the diene to the dienophile). In this context, several years ago E. Wenkert in a study [18, 19] of cycloaddition of five-membered aromatic heterocycles showed that β-acylfurans, acting as dienophiles, undergo the DA reaction whose products were useful for organic synthesis (Scheme 3).

Furthermore, as per this study the reaction of 1,3-butadiene with α-acylfuran, i.e. furfural, leads to a 2:1 adduct albeit in low yield. The 1:1 adduct was not observed in this reaction. Wenkert demonstrated that in contrast to the α-acylfurans, their β-isomers (β-furaldehyde and methyl β-furoate) are excellent dienophiles. The most efficient DA reaction was that of dimethyl 2,4-furandicarboxylate and isoprene (195 ºC, 72 h). It afforded a 1:1 mixture of bicycle isomers in good yield and 1:1 mixture of tricycle isomers (adduct 2:1) in moderate yield (Scheme 4) [18].

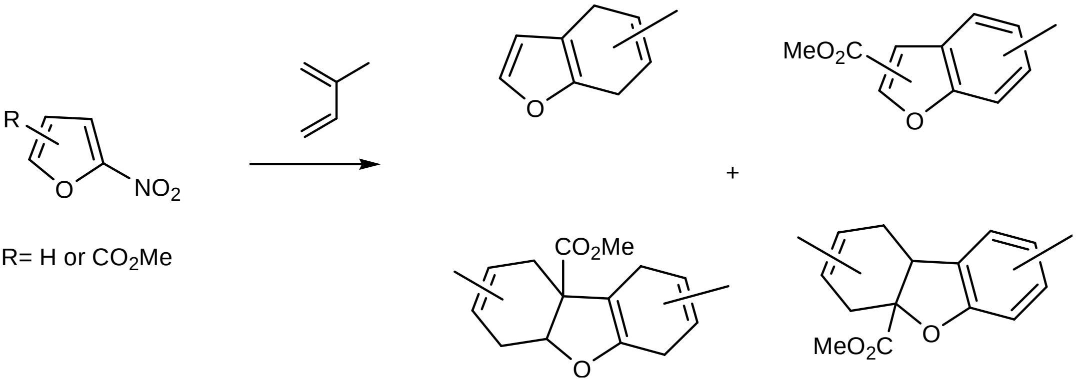
In an earlier work we studied the 2-nitrofuran derivatives in DA reactions under thermal conditions [20]. In contrast to 2-acylfurans, they act as efficient dienophiles when reacted as diene partners with isoprene, 1-*N*-acetyl-*N*-propyl-1,3-butadiene, 1-diethyl-amino-3-tert-butyldimethyl-siloxy-1,3-butadiene (Rawal’s diene) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky’s diene) in different reaction conditions using molecular solvents as reaction media. We tested the efficacy of 2-nitrofurans as dienophiles in DA reactions, using the following compounds: 2-nitrofuran, methyl 5-nitrofuran-3-carboxylate and methyl 5-nitrofuran-2-carboxylate. Treatment of 2-nitrofuran with isoprene gave a mixture of isomeric dihydrobenzofurans and isomeric benzofurans as principal products (with thermal extrusion of the nitro group in the form of nitrous acid from the initial DA adduct) (Scheme 5). Exposure of methyl 5-nitrofuran-3-carboxylate to isoprene yielded the mixture of isomeric benzofuranes as principal



Scheme 3



Scheme 4

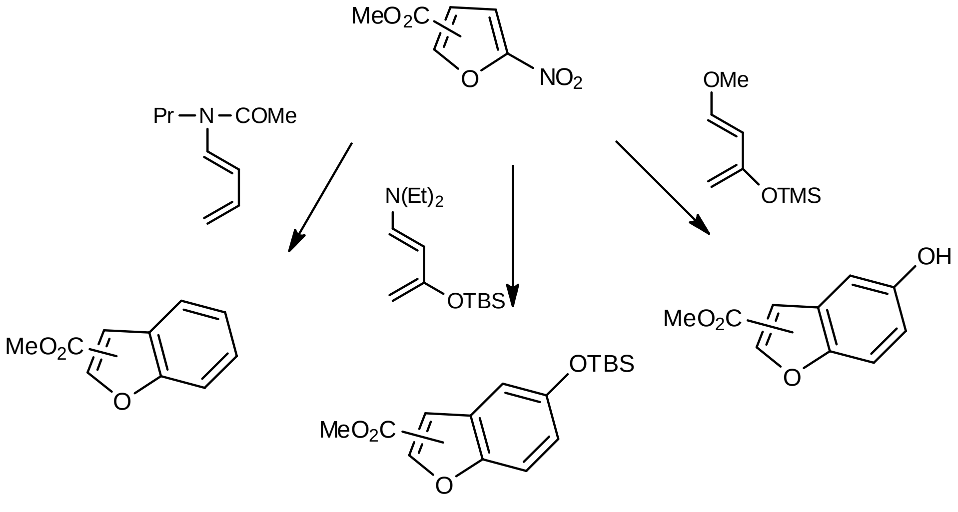


Scheme 5

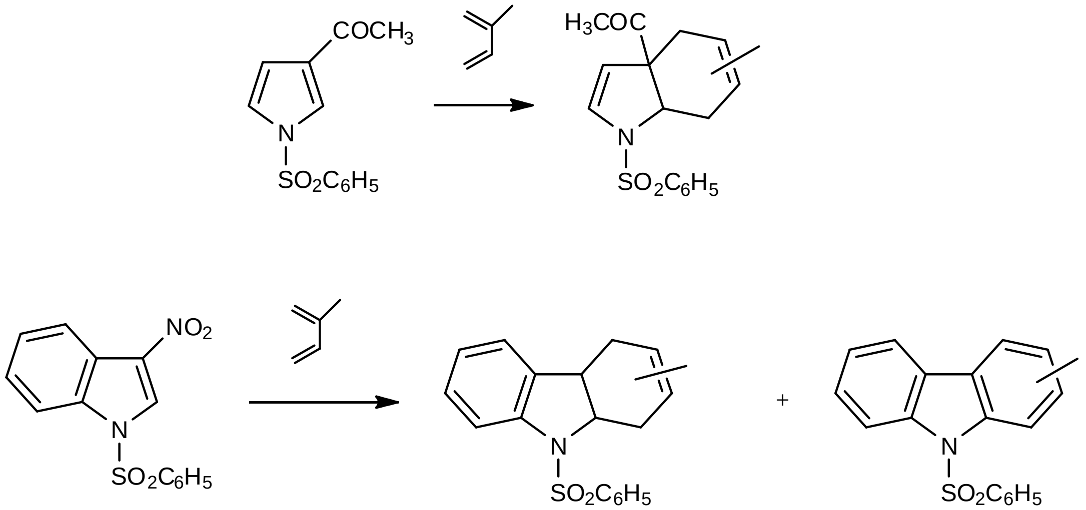
products with good yield, and a mixture of double addition adducts in low yield. On the other hand, reactions of methyl 5-nitrofuran-2-carboxylate with isoprene gave a mixture of aromatic cycloadducts of simple addition with moderate yields. In general, the yield increases with the temperature in every experiment. It should be noted that isolation of the primary nitroadduct has not been achieved under these conditions.

Our previous research [20] showed that the reaction of 2-nitrofuran with 1-*N*-acetyl-*N*-propyl-1,3-butadiene afforded the benzofuran after losing *N*-acetyl-*N*-propylamino and nitro groups. In the reactions with Rawal's and Danishefsky's diene, aromatic cycloadducts were also obtained [20] in moderate to high yield and with complete regioselectivity (Scheme 6). When one of the dienes namely 1-*N*-acetyl-*N*-propyl-1,3-butadiene, 1-diethyl-amino-3-tert-butyldimethyl-siloxy-1,3-butadiene (Rawal's diene) or 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) was allowed to react with one of the dienophiles namely methyl 5-nitrofuran-3-carboxylate or methyl 5-nitrofuran-2-carboxylate, aromatic cycloadducts were obtained. These reactions proceed by stereo-selective addition of the diene to the nitro-substituted double bond of the furan. All addition products showed extrusion of the nitro group in the form of nitrous acid. It is noteworthy that only 1:1 adducts whose structure reveals site and regioselectivity were obtained [19].

The reactivity showed by furans β-substituted with electron-withdrawing groups can be explained by taking into account the fact that the exposure of 2,5-dimethyl-3-nitrofuran to isoprene at higher temperatures yield the isomeric cycloadducts (with thermal extrusion of nitrous acid accompanying the DA reaction). E. Wenkert reported that the reaction



Scheme 6



Scheme 7

of 3-acetyl-1-(phenylsulfonyl)pyrrole with isoprene (195 ºC, 72 h) produces a 1:1 mixture of isomeric dihydroindoles in moderate yield (Scheme 7) [19].

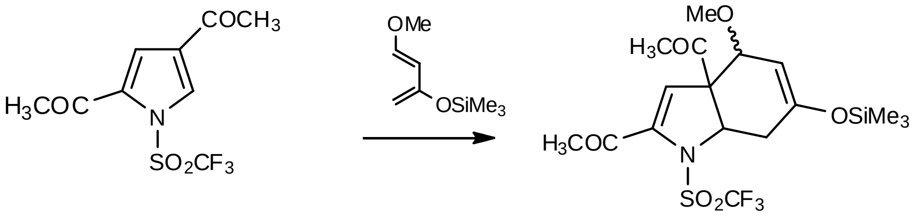
When 1-(phenylsulfonyl)-3-nitroindole was chosen as dienophile, it proved to be more reactive and its interaction with isoprene (175 ºC, 48 h) gave moderate yields of the four products (two methyl-dihydrocarbazol derivatives and two methylcarbazol derivatives) shown in Scheme 7 in the ratio 6(2-methyl-N-benzenesulfonyldihydrocarbazol):2(3-methyl-N-benzenesulfonyldihydrocarbazol) and 3(2-methyl-N-bezenesulfonylcarbazol):1(3-methyl-N-benzenesulfonylcarbazol).

S. Piettre *et al.* reported [21] that 1-triflylpyrroles bearing acetyl group at positions 2, or 3, and 4, are efficient dienophiles in normal electron demand DA reactions activated by high pressures and Lewis acids (Scheme 8). Activation by Lewis acid catalysis and high pressure allows pyrrole derivatives to react with electron-rich dienes in normal electron demand [4+2] cycloadditions, provided that the aromatic ring is substituted by at least two electron-withdrawing groups. The dienophilic behaviour of the heterocycle is expressed through the involvement of either the aromatic carbon-carbon double bond in an all-carbon process or the carbonyl moiety of the substituent in a heterocycloaddition reaction. In this regard, the nature of heterocyclic substituents is shown to have a dramatic influence on the reactivity and chemoselectivity of the cycloaddition [21].

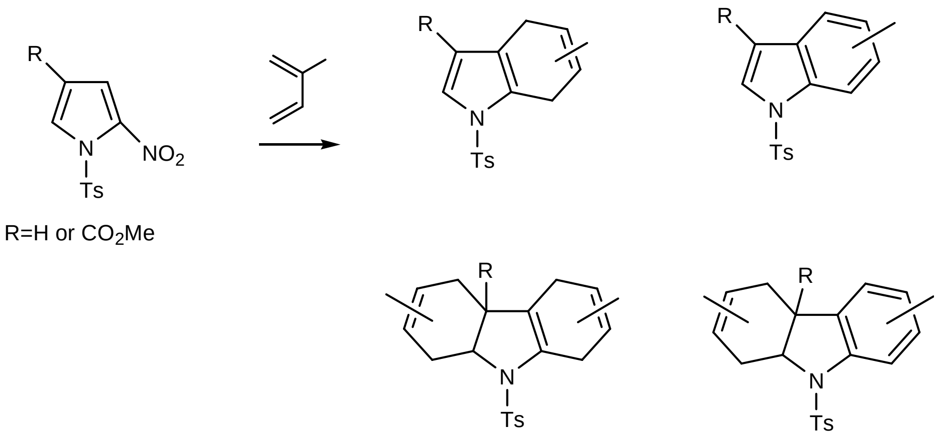
We reported in a previous study that *N*-tosyl-nitropyrroles react at high temperatures with poor and strongly activated dienes [22]. They exhibit an electrophilic character producing the corresponding indoles through a classical DA process. A similar behavior was observed with disubstituted *N*-tosyl-pyrroles as well. The study was carried out using 1-tosyl-2-nitropyrrole, 1-tosyl-3-nitropyrrole, methyl 5-nitro-1-tosylpyrrole-3-carboxylate and methyl 4-nitro-1-tosylpyrrole-2-carboxylate. The diene components were isoprene, 1-*N*-acetyl-*N*-propylamino-1,3-butadiene and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene). When *N*-tosylnitropyrroles were allowed to react with the dienes mentioned above under different reaction conditions employing benzene as the reaction media, the DA cycloadditions were successful. When 1-tosyl-2-nitropyrrole was heated with less reactive isoprene, it gave a mixture of isomeric dihydroindoles (with thermal extrusion of nitrous acid accompanying the DA reaction) and indoles as principal products. Reactions of methyl 5-nitro-1-tosylpyrrole-3-carboxylate with isoprene proceeded to produce the mixture of isomeric indoles in moderate yield and a mixture of double addition adducts in low yield (Scheme 9).

Similarly, the reactions of 1-tosyl-3-nitropyrrole with isoprene [22] yielded a mixture of isomeric indoles and dihydroindoles. On the other hand, the treatment of methyl 4-nitro-1-tosylpyrrole-2-carboxylate with isoprene afforded a mixture of isomeric indoles. These reactions proceed by the selective addition of the diene to the nitro-substituted double bond of the pyrrolyl ring (Scheme 10).

The cycloaddition of 1-*N*-acetyl-*N*-propylamino-1,3-butadiene with 1-tosyl-2-nitropyrrole and 1-tosyl-3-nitropyrrole [22] yielded only 1-tosyl-indol in moderate to high yield. The results of this type of DA reactions indicate a possible sequential



Scheme 8



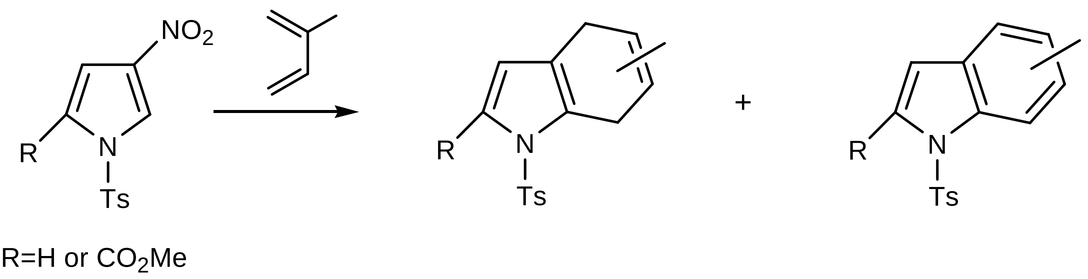
Scheme 9

pathway where the ease of thermal extrusion of nitrous acid accompanying the DA reaction would lead to the formation of substituted-*N*-tosyl-dihydroindoles adduct, which would undergo thermal aromatization by losing the *N*-acetyl-*N*-alkylamino substituent (Scheme 11).

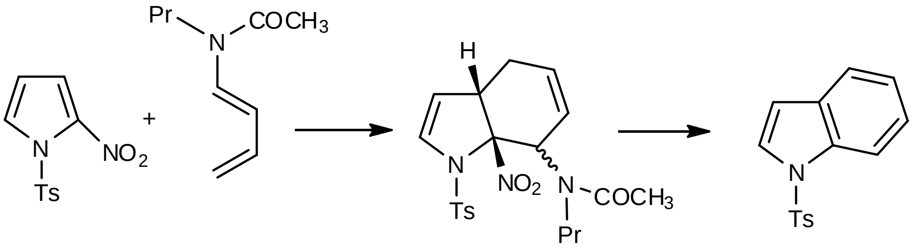
Similarly, in the reactions with Danishefsky's diene [22], hidroxy-indole cycloadduct was obtained in high yield and with complete regioselectivity, which is controlled by the nitro and methoxy groups. These products result from the expected aromatization of the nitro-adducts promoted by the loss of the nitro and methoxyl groups in the form of nitrous acid and methanol, respectively (Scheme 12).

A very strong electron-acceptor group such as a nitro group induces a similar reactivity at 2- and 3-positions in the pyrrole ring [22]. The ease of thermal extrusion of nitrous acid accompanying the DA reaction of 2- and 3-nitropyrroles and the further aromatization make this reaction a simple method for the preparation of indole, a useful intermediate in the synthesis of some alkaloids such as serotonine, trytamine and gramine [22].

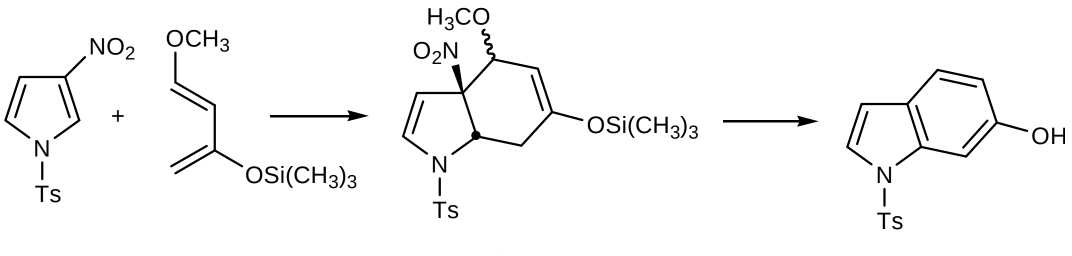
In analogy with their behaviour as diene, thiophene proved to be a poor dienophile [23]. 2-thiophenecarboxaldehyde remained unchanged on being heated with 12 equivalent of isoprene at 195 ºC for 72 h using benzene as reaction media, while 3-thiophenecarboxaldehyde underwent cycloaddition with less than 6% yield. However, substituted thiophenes can act as dienophiles in normal electron demand DA reactions, when



Scheme 10



Scheme 11



Scheme 12

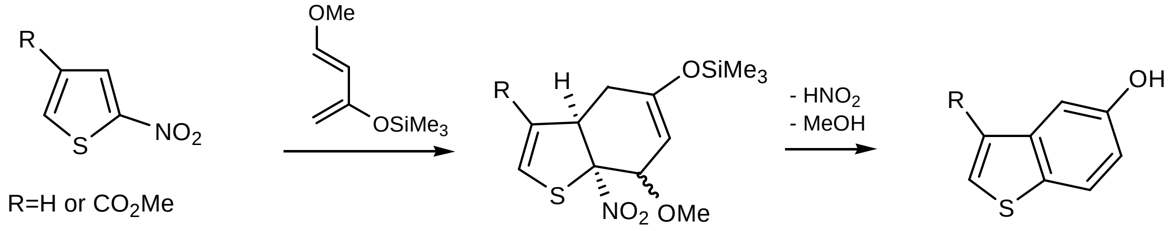
the nitro group is one of the substituents. Cycloaddition with Danishefsky’s diene provides the benzothiophene derivatives with stereoselectivity. The 2-substituted substrates were the most dienophilic ones. The reaction with isoprene leads mainly to the corresponding (pyrrol-1-yl) thiophenes [23]. Because of the high stability of thiophenes, the study was carried out employing the disubstituted substrate 5-nitro-thiophene-3-carboxylic acid methyl ester as dienophile. The Danishefsky’s diene and isoprene were chosen as diene partners. They reacted for 72 h at 120 ºC in benzene as solvent affording, in moderate yield, the hydroxyl-benzothiophene that derives from regioselective cycloaddition with the nitro-substituted double bond and a further aromatization by the loss of nitrous acid and methanol. Similar treatment at 180 ºC for 72 h yielded a comparable amount of product. These results indicate that a properly substituted thiophene functions as a normal dienophile with a highly activated diene (Scheme 13).

When 5-nitro-thiophene-3-carboxylic acid methyl ester was heated with less reactive isoprene [23], it gave pyrrolyl-thiophene as the principal product formed by heterocycloaddition followed by thermal rearrangement (Scheme 14).

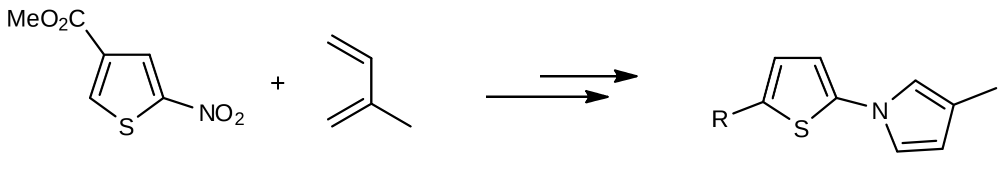
When thiophenes were 3-nitro substituted [23], their DA reactivity dropped dramatically. Reactions of 4-nitro-thiophene-2-carboxylic acid methyl ester with Danishefsky’s diene under conditions similar to those employed with α-nitro substituted substrates (120 ºC, 72 h; 180 ºC, 72 h), failed to give any product. Nevertheless, with isoprene, reactions led to the formation of pyrrolyl-thiophene (72 h at 150 ºC and at 180 ºC, in both cases with low yield). 3-nitrothiophene did not undergo cycloaddition (120 ºC and 150 ºC for 72 h) with Danishefsky’s diene but traces of pyrrolyl-thiophene were obtained in the interaction with isoprene (150 ºC, 72 h). According to the normal hetero DA mechanism, a second electron-withdrawing group placed on thiophene nucleus in 2- and 3-nitrothiophenes appears to have caused an increase in pyrrole yields.

Further, to study the behavior of five-membered aromatic heterocycles in cycloaddition reactions, it is of interest to investigate the DA reactions of substituted selenophenes in the presence of different dienes. The selenophene derivatives used as electrophiles [24] were: 2-nitroselenophene, 3-nitroselenophene, 2-acetyl-5-nitroselenophene, and 2-acetyl-4-nitroselenophene. Isoprene, and 1-diethylamino-3-*tert*-butyldimethyl-silyloxy-1,3-butadiene (Rawal’s diene) were chosen as the diene component.

The reactions of nitrobenzoselenophenes [24] with isoprene proceeded to produce the mixture of isomeric benzoselenophene cycloadducts in moderate yield. This reaction sequence constitutes a simple way to produce benzoselenophenes. On the



Scheme 13



Scheme 14

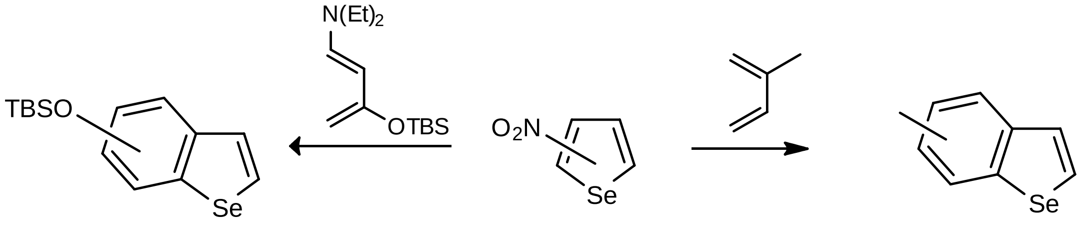
other hand, when Rawal's diene reacted with the nitroselenophenes, the reaction afforded the isomeric derivatives which retain the silyloxy group, in moderate yield. The fact that the *tert*-butyldimethyl-silyloxy group is retained in the product clearly shows the difference in reactivity with respect to Danishefsky's diene whose trimethylsilyloxy group is converted into hydroxyl group during the process. This difference is probably due to the presence of the *t*-butyl group (Scheme 15).

Exposure of disubstituted selenophenes to isoprene gave the mixture of isomeric benzoselenophenes in moderate yield [24]. In a similar way the reactions of these selenophene derivatives with Rawal's diene produce the corresponding benzoselenophenes in high yield and with complete regioselectivity. In this case as well, the products retained the *tert*-butyldimethyl-silyloxy group (Scheme 16). The results observed with these electrophiles are more consistent with previously published reactions of nitrofurans and nitropyrroles with different dienes than those observed with nitrothiophenes, probably due to the high aromatic character that sulfur derivatives present [24].

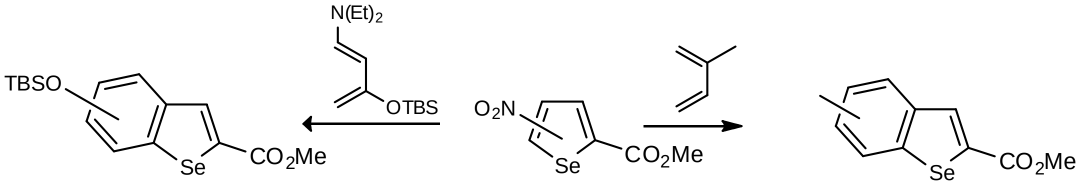
3. Benzopentaheterocycle derivatives as dienophiles

Benzoheterocycles such as indoles, benzofurans and benzothiophenes, all substituted with electron withdrawing groups located in the heterocycle ring, were used as electrophiles in P-DA reactions using different reaction conditions [25]. The DA electrophiles used were: 1-tosyl-3-acetylindole, *N*,*N*-diethyl-1-tosyl-3-indoleglyoxylamide, and 1-tosyl-3-nitroindole, with different dienes: isoprene, 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene, and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) under thermal and/or high-pressure conditions. Compared to the acylated indoles, the nitroderivatives proved to be better electrophiles. In general, the use of Danishefsky's diene led to high-yielding reactions under milder conditions. Likewise, high-pressure conditions proved to be better for producing high yield of products. The advantage of high-pressure over thermal conditions is the ability of the former to generate highly functionalized adducts in better yields, which are otherwise very difficult or impossible to obtain. On the other hand, the thermal reactions needed longer reactions times, higher temperatures and a higher diene:dienophile ratio, to get acceptable yields. The use of thermal or high-pressure conditions led to different regio- and/or stereo-selectivity in cycloadducts, allowing the control of the regio- or stereo-isomer produced (Scheme 17).

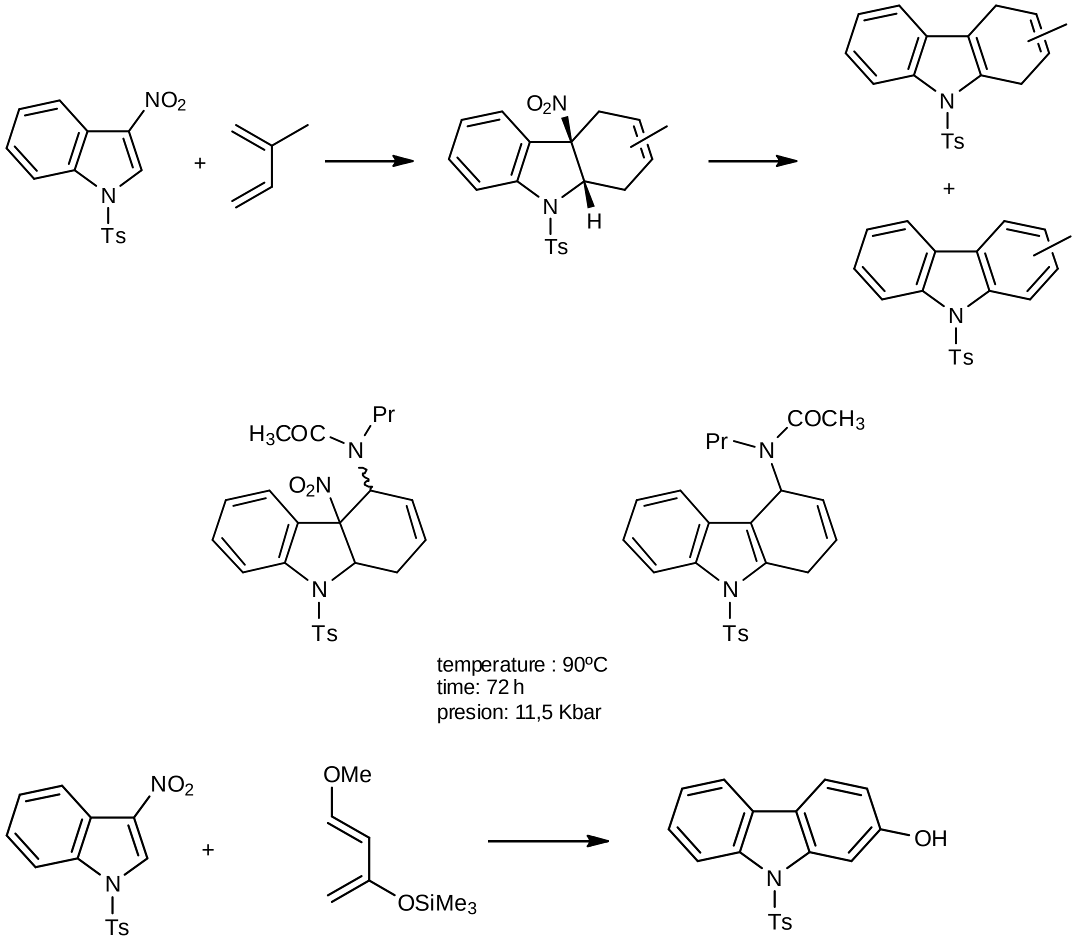
2- and 3-nitrobenzofurans were studied [25] in P-DA reactions with normal electron demand using



Scheme 15



Scheme 16



temperature : 90ºC
time: 72 h
presion: 11,5 Kbar

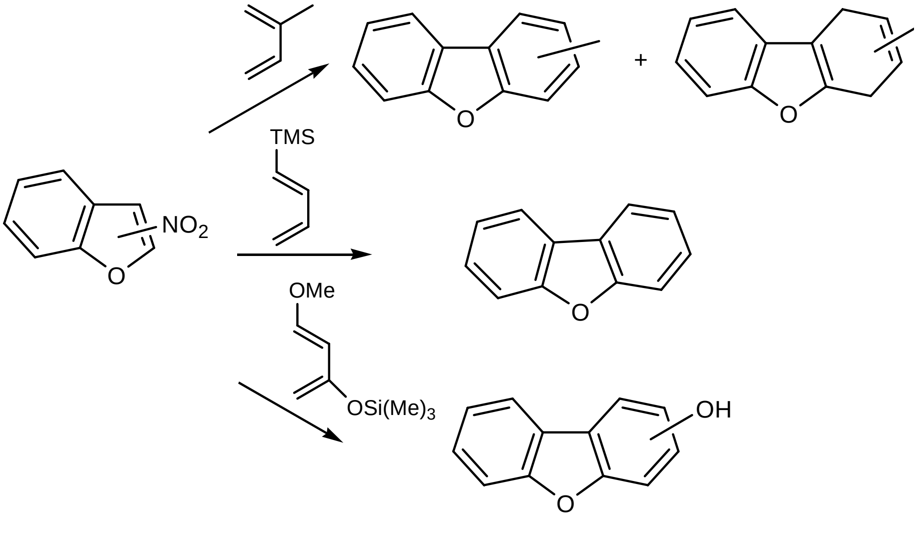
Scheme 17

several structurally different dienes. When these electrophiles were allowed to react with isoprene, 1-trimethylsilyloxy-1,3-butadiene and the Danishefsky's diene, under different thermal reaction conditions, their dienophilic character is observed (Scheme 18) [25]. A very strong electron-acceptor group such as the nitro group is responsible for the dienophilic character of these heterocyclic compounds. The nitro group induces similar reactivity at 2- and 3-positions. Since this substituent is easily extruded under thermal conditions, this reaction sequence becomes a simple method for the preparation of several families of organic compounds with heteroatomic ring. Dibenzofuranes are also important heteroatomic compounds that display a wide variety of biological activities [26].

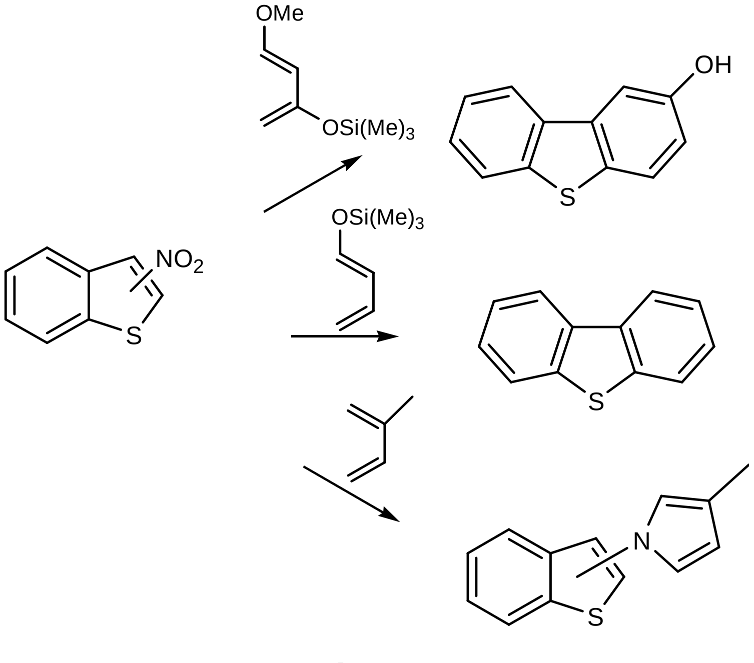
The reaction between 2- and 3-nitrobenzothiophenes and the dienes, isoprene, 1-trimethylsilyloxy-1,3-butadiene, and Danishefsky's diene [27], to produce dibenzothiophenes allows one to conclude that both the nitroheterocycles act as electrophiles. In the cases of the two dienes with higher nucleophilicity the observed product is the one that derives from normal cycloaddition. However, when isoprene (the less nucleophilic diene) is used, the product is the one that corresponds to the hetero DA way. All these reactions were developed in anhydrous benzene, under microwave irradiation with molecular solvents or in free solvent conditions.

These reactions are considered as polar cycloaddition reactions and the yields obtained were reasonable (Scheme 19) [27].

On working under microwave irradiation, it was observed [27] that in all cases where nitrated nitroindoles (2- and 3-) are involved, the nitro group is responsible for orientation and selectivity. All the processes showed nitro extrusion in the form of



Scheme 18



Scheme 19

nitrous acid. In the case of nitrobenzothiophene this behavior was observed only with 1-trimethylsilyloxy-1,3-butadiene. When the other dienes were employed, hetero cycloaddition was achieved, specially using nitrobenzene. This behavior of the different diene/dienophile pairs was the same as that observed when the reaction was carried out with conventional heating in benzene as solvent, but with the use of microwave irradiation, the reaction times decrease significantly. It is important to note that microwave irradiation in solvent-free conditions yielded the best results. This type of experiment is important due to the possible reduction in toxicity and cost; moreover it is a very simple method. The use of microwave irradiation in this type of P-DA reactions presents advantages in relation with those developed in classic conditions although in general the products obtained are similar.

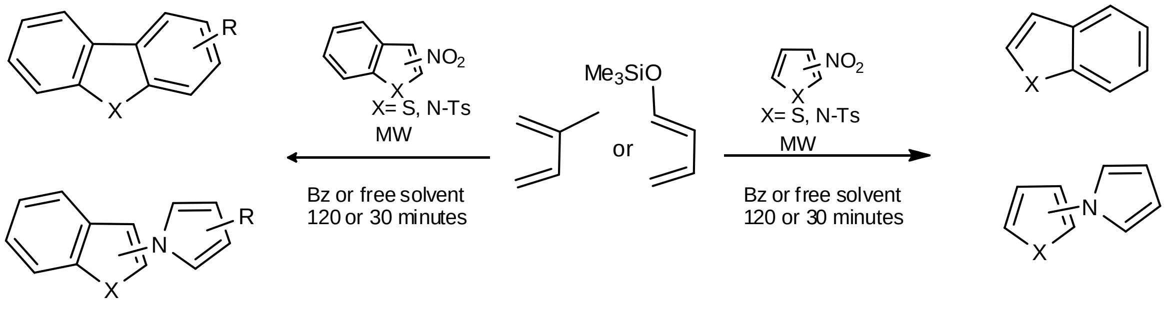
In this context it is possible to have lower reaction times and better yields (Scheme 20).

4. P-DA reactions in ionic liquids

An IL is a salt-substance exclusively composed of cations and anions. This fact differentiates them from simple ionic solutions, in which ions are dissolved in the molecular medium. They are also different from inorganic molten salts because their melting points are lower than 100 ºC. Room temperature ionic liquids (RTILs) have been the subject of considerable research efforts. RTILs have attracted considerable attention because they are expected to be ideal solvents that could aid in novel reactions in green chemistry [28]. The interest in this class of molecules arises from the fact that they could be used as liquid media for a variety of chemical transformations, especially for DA reactions, as a substitute of molecular solvents. RTILs exhibit a variety of desirable properties which make them of interest in various applications. In particular, the possibility 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 "design solvents". As a consequence, the characterization of the properties of different classes of ILs used as solvent for specific applications in chemical reactions and catalysis has been intensively investigated [29].

The behavior of different heterocyclic compounds as electrophiles in P-DA reactions in the presence of ILs was explored [30] in order to analyze the solvent effects. *N*-Tosyl-2-nitropyrrole and *N*-tosyl-3-nitropyrrole were allowed to react with different dienes using Polar Ionic Liquids (PILs) as solvent. They exhibit an electrophilic character producing the corresponding indoles through a DA process. The PILs used were ethylammoniun nitrate (EAN) and 1-methylimidazolium tetrafluoroborate [HMIM][BF_4]. These results can be compared with those obtained in normal thermal conditions. In all cases the presence of PILs as reaction media improves the yields with respect to the use of molecular solvents, while the temperature and reaction time decrease. EAN is a better solvent than [HMIM][BF_4] [30]. For the DA reactions between nitropyrrole derivatives and isoprene, the combination of microwave irradiation and PILs has a notable synergistic effect.

When 2-nitrofuran was allowed to react with the less nucleophilic isoprene in a sealed ampoule at 60 ºC for 24 h using EAN as the solvent, the reactions produced a mixture of isomeric benzofurans (1:1) as the primary products in moderate yield, and dihydrobenzofurans derivatives (1:1) in lower yield [30]. When the reaction time reached 24 h we observed a 1:1 mixture of isomeric benzofurans with better yield, and only traces of the isomeric dihydrobenzofurans. Similar results were observed [30] when the reaction was conducted in [HMIM][BF_4] although the yields were slightly lower. At the same time, the reactions of 2-nitrofuran with 1-trimethylsilyloxy-1,3-butadiene using EAN, [HMIM][BF_4], and [BMIM][BF_4] as solvents, in a sealed ampoule at 60 ºC (12 and 24 h) afforded benzofuran in good yield in all the cases. The best yield was obtained with EAN as solvent and a reaction time of 24 h. On the other hand [HMIM][BF_4] is a better solvent than [BMIM][BF_4], probably due to its HBD (Hydrogen Bond Donor) character. Finally, the reaction of Danishefsky's diene with



Scheme 20

2-nitrobenzofuran (60 ºC, 12 and 24 h) using the three PIL's cited above produced 1-tosyl-5-hydroxyibenzofuran in reasonable yield with EAN as solvent. The product obtained in the reactions with Danishefsky's diene resulted from the aromatization of the nitro-adducts promoted by the loss of the nitro and methoxyl groups in the form of nitrous acid and methanol, respectively. The intermediate that suffered nitrous acid extrusion and retained the methoxy group was not detected in any of the cases. Similar results were observed [30] when the electrophile was 3-nitrofurane.

The P-DA reactions between 2- and 3-nitrobenzothiophenes derivatives and different dienes such as 2-methyl-1,3-butadiene and 1-trimethylsilyloxy-1,3- butadiene were studied [30] using PILs as reaction media. The PILs used were EAN and [HMIM][BF_4]. The reactions of both nitrobenzothiophenes with isoprene using EAN or [HMIM][BF_4], as solvents in a sealed ampoule at 60 ºC (12 and 24 h) afforded in all the cases the corresponding pyrrolyl derivative. The best yield was obtained with EAN as solvent and a reaction time of 24 h. On the other hand the reaction of Danishefsky's diene (60 ºC, 12 and 24 h) with these electrophiles in the two PIL's cited yielded the dibenzothiophenes. In this case as well, EAN is the best solvent.

To explore the reactivity of *N*-tosyl-3-nitroindole in P-DA reactions in the presence of PILs isoprene, 1-trimethylsilyloxy-1,3-butadiene, and Danishefsky's diene were chosen as dienes [30]. The selection of dienes depends on the type of substitution present in its structures and the relative nucleophilicity [31]. When *N*-tosyl-3-nitroindole was allowed to react with less reactive isoprene in the presence of [HMIM][BF_4] as solvent, the reaction proceeded to yield a mixture of isomeric carbazoles as the primary products in moderate yield and the dihydrocarbazoles in low yield (see Scheme 17). If the reaction time is increased, the yield in carbazoles improves and the dihydrocarbazoles appear only in traces. The reaction of *N*-tosyl-3-nitroindole with Danishefsky's diene using the cited PIL yielded 2-hydroxylcarbazole in good yield (see Scheme 17). It is necessary to take into account that when the reaction of the tosylnitroindole with Danishefsky's diene was carried out in the presence of a molecular solvent, the [4+2] cycloadduct with retention of nitro and methoxy groups (the *cis* stereochemistry was preferred in conditions of low temperature) was observed, along with the corresponding carbazole. However, when the PIL is used, only the aromatic hydroxycarbazole was isolated. This indicates than PIL as reaction media can favor the subsequent elimination reactions.

To confirm the previous results, the reaction of tosylnitroindole with 1-trimethylsilyloxy-1,3-butadiene, a diene with a nucleophilicity that is intermediate between isoprene and Danishefsky's diene, was probed [30]. In this case the PIL [HMIM][BF_4] was used and resultant product was 4-hydroxycarbazole which was obtained in good yield. When benzene is used as solvent, the reaction yields the same product. In all the cases the presence of ILs as reaction media, compared with molecular solvents, improves the product yields while the temperature and reaction time decrease, and the type of products does not change.

5. Theoretical calculations

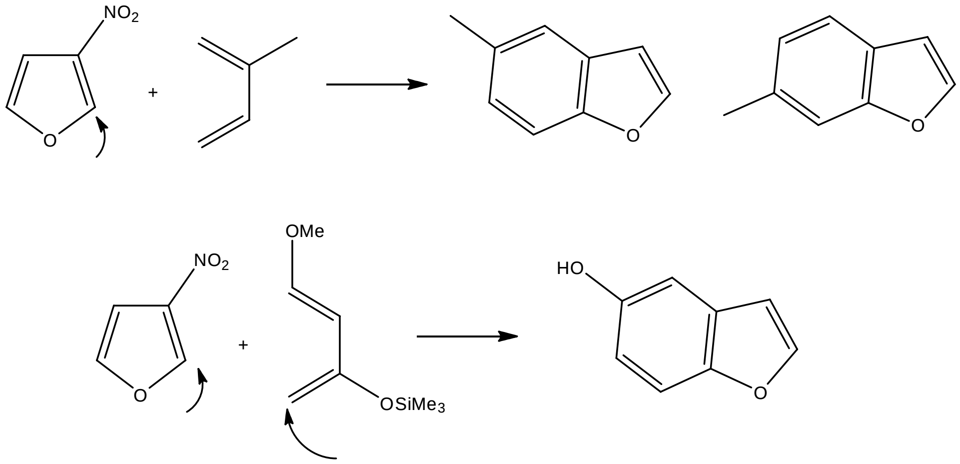
Theoretical studies using DFT calculations are a useful tool to understand and predict the reactivity of this type of heterocyclic aromatic molecules involved in DA reactions. It was demonstrated that the reactivity indices are powerful tools for establishing the polar character of such reactions. Static global properties of dienes and dienophiles namely μ, η, ω, and N have been calculated in [7]. For normal demand DA reactions, the electronic chemical potential of dienophiles is always lower than that of the dienes. Therefore, it is expected that in a P-DA reaction, the charge transfer (CT) will take place from the electron-rich dienes to the nitro-substituted dienophiles. The electrophilicity ω (0.92-2.82 eV) of dienophiles allows one to classify them as strong electrophiles on the electrophilicity scale. On the other hand, they present low nucleophilicity N values and hence are classified also as a moderate nucleophile on the nucleophilicity scale. The electrophilicity ω of dienes is 0.94 eV (isoprene), 0.73 eV (1-trimethylsilyloxy-1,3-butadiene), 0.68 eV (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) and 0.71 eV (1-diethyl-amino-3-tert-butyldimethyl-silyloxy-1,3). It classifies them as marginal electrophiles in the electrophilicity scale. On the other hand, the nucleophilicity N of these species is 2.94 eV (isoprene), 3.67 eV (1-trimethylsilyloxy-1,3-butadiene), 3.77 eV (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) and 3.73 eV (1-diethyl-amino-3-tert-butyldimethyl-silyloxy-1,3). Therefore, while isoprene is a moderate nucleophile, the other dienes are strong nucleophiles. As expected, the presence of one or two strong electron-releasing substituents in the diene system increases the nucleophilicity of 1-trimethylsilyloxy-1,3-butadiene and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene. An analysis of the global reactivity indices indicates that in a polar DA reaction, nitro-substituted dienophiles will act as strong electrophiles, while dienes 1-trimethylsilyloxy-1,3-butadiene and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene will act as strong nucleophiles. The $\Delta\omega$ value between the dienophile and the diene determines how polar a DA reaction is. Electron withdrawing groups activate the heterocycle molecules to act as dienophiles and increase the polar character of DA cycloadition.

Taking into account the local characteristics in a polar cycloaddition between asymmetrical reagents, we consider that the most favourable two-center interaction will take place between the more electrophilic center, characterized by the highest value of the local electrophilicity index ω_k at the electrophile, and the more nucleophilic center, characterized by the highest value of the local nucleophilicity index N_k at the nucleophile. The local electrophilicity ω_k indices for nitro-substituted dienophiles, and nucleophilicity N_k indices for dienes have been evaluated [30, 31].

For pentaheterocycles and their benzofusionated derivatives, substituted in postion 2, the most-electrophilic centre is C3, while for the ones substituted in position 3, it is C2. As expected, a change in the position of the nitro group causes a change in the local reactivity of the system. When nitronaphtalene is analized, we found that the ones substituted in position 2 activate C1 for the nucleophilic attack while the 1-substituted derivative activates C2 or C3 depending on the nature of the substitution [5, 25, 30, 31].

For isoprene, the most-nucleophilic center corresponds with the C1, whereas for the rest of the dienes the most-nucleophilic center corresponds with the C4. Consequently, a change in regioselectivity is expected among isoprene and the other dienes. It is also important to consider the ΔN_k values of each one, because for isoprene and 1-trimethylsilyloxy-1,3-butadiene the difference between C1 and C4 is small ($\Delta N_k \approx 0.3$ eV) and a mixture of both isomers are expected to be formed as a result of the Diels-Alder reaction. On the other hand, for Danishefsky's and Rawal's dienes ΔN_k is greater than 0.8 eV; consequently the cycloaddition is considered to be enantioselective (Scheme 21).

Solvent effects of ILs in these Diels-Alder reactions were estimated [31] based on the formation of a hydrogen-bonded complex between the nitro oxygen



Scheme 21

atoms of dienophiles and the most acidic hydrogen atom of the solvent. Formation of a non-classical hydrogen bond between dienophiles and chloroform increases the electrophilcity ω of the dienes over the original value by 0.5 eV approximately. A more drastic effect is found in the dienophile-IL complexes where the electrophilcity ω increases in the range from 4 to 5 eV. The more acidic IL EAN produces the highest increase in electrophilicity. Although these values have to be carefully considered according to the simplicity of the model, they indicate that the use of ILs as solvents will accelerate P-DA reactions. This is a consequence of the increase of the reaction's polar character achieved by an increase of the electrophilcity of dienophiles.

Potential energy surface (PES) analysis associated with P-DA reaction indicates that the cycloaddition takes place through a one-step mechanism via a highly asynchronous TS. Therefore, reagents 1-mesyl-3-nitropyrrole and isoprene, the TS, and the formal [4+2] cycloadduct (CA), were located and characterized through theoretical calculations [5]. In the gas-phase, the activation energy associated with the nucleophilic attack of the C4 carbon of isoprene on the C2 carbon of 1-mesyl-3-nitropyrrole via TS presents a high value, 21.4 kcal/mol; formation of the formal [4+2] CA is exothermic by –23.9 kcal/mol. Although this P-DA reaction is thermodynamically favorable, the high activation energy associated with the process makes the cycloaddition reaction difficult. The lengths of the bonds formed at TS are 1.860 and 3.078 Å. These values suggest a two-stage one-step mechanism via highly asynchronous TS. While the formation of the bond between the most nucleophilic centre of isoprene and one of the most electrophilic centres of 1-mesyl-3-nitropyrrole takes place in the first stage of the reaction, the second bond formation takes place at the second stage of the reaction, once the first bond is completely formed. The short distance indicates that the cycloaddition process is very advanced, in clear agreement with the high activation energies associated with TS.

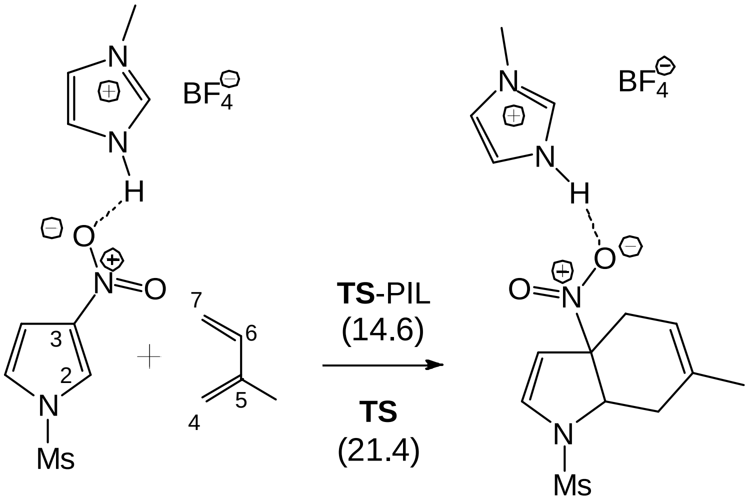
The polar nature of this DA reaction was evaluated by analyzing [31] the charge transfer at TS. The electronic charges were shared between the pyrrole derivative and the isoprene frameworks. At TS, the CT that flows from isoprene to nitropyrrole is 0.24 eV. This value points to the zwitterionic character of the TS.

The effects of [HMIM][BF_4] PIL in the P-DA reaction between 1-mesyl-3-nitropyrrole and isoprene were evaluated [31] by considering two computational approaches: (i) the implicit effects of PIL when forming a hydrogen bond (BH) between the acidic hydrogen of HMIM cation and one oxygen of the nitro group. The counter BF_4 anion was also included to minimize the positive charge present in the HMIM cation; and (ii) the electrostatic interactions modelled by the polarizable continuum model (PCM) of Tomasi's group. For PCM calculations, 1-heptanol was considered as the solvent since it has a dielectric constant that is closer to [HMIM][BF_4]; ε = 11.3.

Solvent effects of PIL lead to a larger stabilization of the transition state in polar ionic liquid (TS-PIL) than in the reagents, which is due to the strong stabilization of the negative charge that is located at the electron-withdrawing nitro group, by the HB (Hydrogen Bond) formation (Scheme 22).

TS-PIL is located 14.6 kcal/mol over the separated reagents 1-mesyl-3-nitropyrrole plus isoprene. Consequently, the PIL brings about a substantial acceleration of the P-DA reaction thus decreasing the activation energy by 6.7 kcal/mol. In spite of this behavior, the exothermic character of the cycloaddition, 22.1 kcal/mol, remains unchanged. At TS-PIL, the distances between the nitro oxygen and the acidic hydrogen of HMIM, 1.774 Å, suggest a strong HB interaction (Note that at the 1-mesyl-3-nitropyrrole-PIL complex this distance is 1.934 Å). Finally, the CT at the TSs is 0.32 eV. This high value is indicative of the zwitterionic nature of the TS. The large acceleration found in the presence of the PIL ionic pair can be attributed to the increase of the polar character of the reaction as a consequence of the increased electrophilic character of the 1-mesyl-3-nitropyrrole-PIL complex achieved by the HB formation, which favours the CT process. The HB formation increases the electrophilicity index of 1-mesyl-3-nitropyrrole, ω = 2.27 eV, to 2.88 eV on using 1-mesyl-3-nitropyrrole-PIL as reaction media.

An analysis of the displacement vectors of the IR frequency vibrations in reactants shows the presence of stretching vibrations, 1.636 cm^{-1} at 1-mesyl-3-nitropyrrole and 1.701 cm^{-1} at isoprene, indicating



Scheme 22

atomic movements similar to the electronic changes involved in the formation of the corresponding TSs. Note that the corresponding stretching vibration of 1-mesyl-3-nitropyrrole decreases to 1.577 cm^{-1} in the complex 1-mesyl-3-nitropyrrole-PIL with the formation of the HB whit [HMIM]$^{+}$ cation. A similar analysis of the corresponding TSs shows that these frequency vibrations have moved to 1.420 cm^{-1} at TS and 1.414 cm^{-1} at TS-PIL as a consequence of the reduction of the double-bond character at the TSs. This means that any additional energy value between 1.700 and 1400 cm^{-1} can favour stretching vibrations involving the p systems of 3-nitropyrrol and isoprene, thus favouring the electronic changes needed to reach the TS geometry. Consequently, we suggest that the local activation energy provided by the MW could favor the corresponding structural changes, which together with the catalytic effects of HB formation by the HMIM cation could synergistically favour the P-DA reactions. Furthermore, one of the most interesting aspects of this reaction is its pronounced solvent dependence, which has been the subject of several studies in recent years, in order to enhance reactivity and, therefore, reduce by by-products formation.

5.1. Computational details

All calculations were carried out with the Gaussian09 suite of programmes [8, 30, 31]. DFT calculations were carried out using the B3LYP exchange-correlation functionals together with the 6–31G(d) basis set. Optimizations were carried out using the Berny analytical gradient optimization method. The stationary points were characterized by frequency calculations in order to verify that TSs had one and only one imaginary frequency. The electronic structures of critical points were analyzed by the natural bond orbital (NBO) method. Solvent effects were considered by geometry optimization of the gas-phase structures using a self-consistent reaction field (SCRF) based on the polarizable continuum model (PCM) of Tomasi's group.

6. Conclusion

Aromatic compound derivatives can act as electrophiles in cycloaddition processes with dienes of different nucleophilicity. In the normal DA way the primary cycloadducts are converted to aromatic products as a consequence of the loss of the substituents, nitro group in particular, during the process. Alternatively, depending on the electrophile aromatic character and the diene nucleophilicity, it is possible to observe a hetero DA process. These transformations constitute a simple, economical and efficient one-step procedure to synthesize aromatic carbo- or hetero-cycle compounds with potential biological activity.

The considered reactions represent a special type of pericyclic processes in which the transition state is an asynchronous one with charge separation. For this reason these reactions are considered P-DA transformations, and we term them "pseudo-pericyclic reactions”. In particular, for these processes the solvent dependence is one of the most interesting aspects. To compare the behaviour of these reactions, molecular solvents and ionic liquids were explored. In general, the presence of PILs as reaction media improves the reaction yields with respect to the molecular solvents while the temperature and the reaction time decrease. A positive influence of heating with microwave irradiation in the development of the process was also observed. In particular, the combination of microwave irradiation with a PIL as reaction media could produce a synergetic effect on the transformation. This means that any additional energy value between 1.700 and 1.400 cm^{-1} can favor stretching vibrations involving the π system of the electrophile and nucleophile favouring the electronic changes needed to reach the transition state energy.

Theoretical calculations prove to be useful in explaining the behavior of the molecules studied in DA reactions. Their electrophilic and nucleophilic character is explained with energy distribution within the molecular orbitals. As observed, the polar condition of the reactions increased with the charge separation, which is affected by PIL and microwave irradiation. By studying some mechanism pathways of these polar cycloadditons we can derive the molecular structure of the asynchronous form of TS, thereby confirming the polarity of these cycloadditions.

CONFLICT OF INTEREST STATEMENT

The authors have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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