

# Nitroquinolines as dienophiles in polar Diels-Alder reactions. Influences of molecular solvents and ionic liquids

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## Abstract

5- and 8-nitroquinolines are studied as dienophiles in polar thermal Diels-Alder reactions with normal electron demand using several and structural different dienes, and chloroform as solvent media. A very strong electron-acceptor group, such as nitro group, push the dienophilic character of these heterocyclic compounds and owing to this substituent is easily extruded under thermal conditions. When the cited dienophiles were reacted with isoprene, 1-trimethylsilyloxy-1,3-butadiene and de Danishesky diene, under different reaction conditions they showed their dienophilic character taking part in a normal demand DA cycloaddition reactions. These cycloaddition reactions were analyzed in presence of ionic liquids (IL's). In this sense was used ethyl ammonium nitrate (NEA) as protic IL's and another composed by 1-butyl-3-methyl-imidazolium [bmim] as the cation and tetrafluoroborate as the anion [BMIM] [BF<sub>4</sub>]. The presence of IL's improved the yields and the reaction conditions are softer.

## Introduction

The Diels-Alder (D-A) 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.<sup>1</sup> 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 these dienes and dienophiles.

While a great effort has been dedicated to the development and use of aromatic compound as diene in this reaction, 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 limited number of examples of five-membered aromatic heterocycles acting as dienophiles in D-A reactions with normal electron demand. For example aromatic heterocyclopentadienes holding an electron withdrawing group in their structures at  $\beta$ -position have shown to be good dienophiles in the interaction with isoprene at an elevated temperatura. In that direction, in the 1980's studies of aromatic heterocycles - furans, *N*-tosylpyrroles, and tiophenes- in cycloaddition reactions demonstrated the viability of these systems as dienophiles.<sup>2</sup> Further studies focused on the dienophilic character of indoles derivatives since their adducts seemed to be appealing for the total synthesis of carbazol and *Aspidosperma* alkaloids.<sup>3,4</sup>

Due to our interest in the cycloaddition chemistry of substituted aromatic heterocycles with electron withdrawing groups, we have reported that 2-nitrofurane, 2-nitrothiophene, 2-nitro-*N*-tosylpyrrole and 2-nitroselenophene react with strong and poor dienes under different conditions. The participation of nitro-*N*-tosylpyrroles in cycloaddition reactions made possible a one spot simple indole synthesis.<sup>5</sup>

In addition, we have realized studies on the dienophilic character in D-A reactions of other aromatic systems such as nitronaphthalenes. While the use of these substrates as dienes in thermal and high-pressure D-A reactions has been widely analyzed, the employment of such compounds as dienophile has received relatively little attention in the literatura. In the last direction we have shown the dienophilic behaviour of naphthalenes properly mono and disubstituted with electron withdrawing groups -nitro, cyano, acetyl, and chloro-. In general, when these dienophiles were exposed to a different dienes yielded the corresponding initial cycloadducts products which normally suffer the thermal extrusion of the nitro group. Unexpected results were observed when using nitronaphthalenes with less reactivities dienes. Interestingly, when 1- and 2-nitronaphthalenes reacted with isoprene they produced the corresponding *N*-naphthylpyrroles. From the results obtained in all these reactions, we can conclude that there are two competitive reactions that might take place on mononitronaphthalenes: the addition to the nitro group

(hetero D-A process) and the normal D-A reaction on the C1-C2 bond, depending on the strength of the diene partner. This behaviour can be extended to the nitrothiophenes probable due its high aromaticity in relation to the others aromatic heterocyclopentadienes.<sup>6-8</sup>

Herein we report our findings on the dienophilic character of nitroquinolines. These dienophile was exposed to a different dienes under thermal conditions using molecular solvents and ionic liquids, respectively as reaction media. This allowed us compared not only the relative reactivity of this substrate also the regioselectivities in the cases of successful cycloaddition. Moreover, we try to complete the reactivity scheme of carbocyclic and heterocyclic aromatic compounds containing two condense nucleous and nitro group as substituent.

## Results and discussion

To explore the normal electron demand D-A dienophilicity of nitroquinolines **1a-d** we choose isoprene (**2**), 1-trimethylsilyloxy-1,3-butadiene (**3**), 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky diene) (**4**), and 1-*N,N*-diethylamino-3-tert-butylidimethylsilyloxy-1,3-butadiene (Rawal diene) (**5**) as diene (Figure 1). The selected dienes present different order of nucleophilicity. The selection of the dienes taken into account the type of substitution present in their structures and the relative nucleophilicity. The reactions were development in thermal conditions using two types of solvents, molecular solvents and ionic liquids.

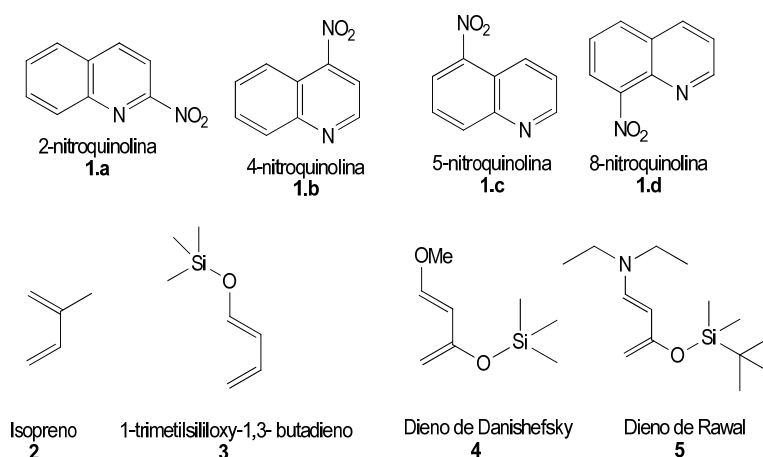


Figure 1

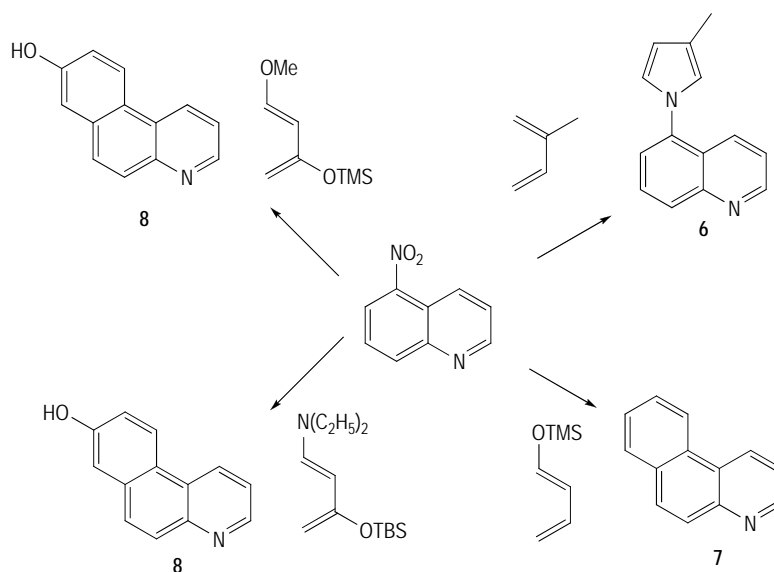
### Reactions in molecular solvents

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. We have used different times of reaction.

Because 2-nitroquinoline **1a** and 4-nitroquinoline **1b** were no reactive in all the experiences development in this reaction conditions, the study started by testing the reactivity of 5-nitroquinoline **1c** and 8-nitroquinoline **1d**, with the above mentioned dienes.

When 5- and 8-nitroquinolines were reacted with the cited dienes under different reaction conditions, they showed their dienophilic carácter taking part in the D-A cycloaddition reactions.

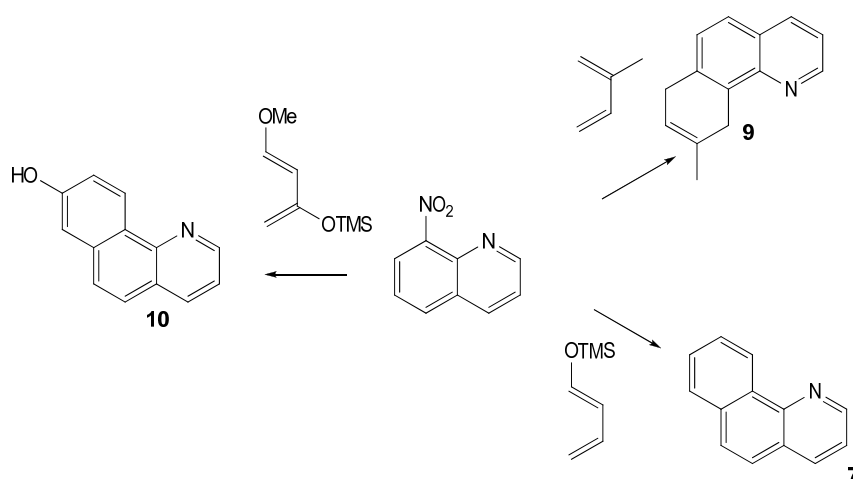
When **1c** was heated with the less reactive isoprene it gave as principal product the 5-(3-methyl-1*H*-pyrrolii)-quinoline **6** throughout the participation of the nitro group in a hetero D-A process followed by a thermal rearrangement -hetero D-A channel-. In a similar way that in the reaction of isoprene with 1-nitronaphthalene we observed only one regioisomer.<sup>6</sup>



*Scheme 1*

In the other hand the reactions between **1c** and 1-trimethylsilyloxy-1,3-butadiene at 120-140 °C, 72 h yielded the normal addition product **7** with complete aromatization due to the loss of the nitro and trimethylsilyloxy groups (Scheme 1). In the same way, in the thermal reactions of **1c** with the Danishesfky diene at 120-150 °C, 96 h, aromatic cycloadduct **8** was obtained with very good yield and complete regioselectivity (Scheme 1). Then was explored the reaction between **1c** and Rawal diene, 120 °C, 96 h; observing the same product **8** that in the cycloaddition using the diene (**5**) although with higher yield (Scheme 1). In the last three processes we observed normal D-A sequence followed of the expected aromatization of the initial nitro adduct promoted by the loss of nitro and the metoxyl and dimethylamine groups, respectively. The presence of the nitro group, enhance the cycloaddition by favouring aromatization, thus preventing the retrocycloaddition. The isolation of the intermediate cycloadduct was never achieved under these conditions. These reactions could be considered a domino process that is initialized by a polar D-A reaction, and the latter concerted elimination of nitrous acid from the [4+2] cycloadduct yields the corresponding aromatic heterocyclic products.

In turn the reactions of 8-nitroquinoline **1d** with the dienes (**2**), (**3**), and (**4**) yielded in all cases the normal addition products (Scheme 2)



*Scheme 2*

The reaction between 8-nitroquinoline **1d** with isoprene shown as principal product el dihydro derivative 7,10-dihydro-9-methyl-benzo[f]quinoline **9** joint to traces of its regioisomer (Scheme 2). 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 1-trimethylsilyloxy-1,3-butadiene as diene yielded the aromatic cycloaddition product **7** with a high yield that in the reaction using 5-nitroquinoline. The reaction of **1.d** and de Danishefsky diene yielded the aromatic heterotricyclic product **10** with very high yield and complete regioselectivity (Scheme 2). All the cycloaddition reactions using **1.d** proceed via the normal D-A reaction channel. Excepting for the reaction between **1.c** and isoprene, all the reactions of **1.c** and **1.d** with the dienes used in this work follow a mechanistic sequence similar to those proposed for the reaction between 1-nitronaphthalene and the Danishefsky diene.<sup>9</sup>

### *Reactions in ionic liquids*

Many papers refer to the D-A 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 D-A reactions between two purely hydrocarbon reactants, such as cyclopentadiene dimerization.<sup>10</sup> Actually, Diels–Alder 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.<sup>11</sup>

Ionic Liquids (IL's), 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 Diels–Alder reactions.<sup>12</sup> 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. Subsequently, Welton *et al.* have investigated the influence of IL's based on the 1-butyl-3-methylimidazolium cation, [bmim]<sup>+</sup> in D-A reactions. The *endo* : *exo* ratio and associated acceleration observed in the D-A cycloaddition of cyclopentadiene with methyl acrylate was attributed to the ability of the IL to hydrogen bond to the dienophile (methyl acrylate).

Taken into account the above considerations, it was explored the cycloaddition reactions between 5-nitro and 8-nitroquinolines with the dienes (1-trimethylsilyloxy-1,3-butadiene and Danishefsky diene), respectively, in presence of NEA and [BMIM][BF<sub>4</sub>]. With both IL's the reaction systems improved the yields (approximately 20%) and the reaction time and temperature were considerably smaller (24 h and 60°C). In all reaction systems, NEA made possible major yields than [BMIM][BF<sub>4</sub>]. The cycloaddition products were the same that those obtained using chloroform as reaction media.

### Conclusions

When 5- and 8-nitroquinolines were reacted with the above mentioned dienes under different reaction conditions they showed their dienophilic character taking part in a normal demand D-A cycloaddition reactions. A very strong electron-acceptor group, such as a nitro group, induces a similar reactivity at 5- and 8-positions in quinoline ring. The ease of thermal extrusion of nitrous acid accompanying the D-A reaction of 5- and 8-nitroquinolines followed by the further aromatization makes this reaction sequence a simple, economical and efficient method of precursors of natural products, which display a wide variety of biological activities. The employ of IL's as solvents in these reactions accelerate the reactions due to the hydrogen bonding interactions between the neoteric solvent and the dienophile.

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