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Synthesis of Phenanthrenol Derivatives through Polar Diels-Alder Reactions Employing Nitronaphthalenes and (*E*)-1-(Trimethylsilyloxy)-1,3-butadiene. Theoretical Calculations

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Abstract: The cycloaddition reactions between dinitronaphthalenes and (*E*)-1-trimethylsilyloxy-1,3-butadiene produce nitrophenanthrenol derivatives as principal products. The primary adducts suffer the irreversible lost of nitrous acid and, consequently, the aromatization. In these reactions it is frequent to observe the presence of naphthalenyl-1*H*-pyrrole derivatives as a result of a hetero Diels-Alder process, which is competitive with the normal way. The global electrophilic character of the dienophile is responsible of these results. Other dienes (or dienophiles/electrophiles) with electron donor substitution in C-1 show a different behavior in which the hetero Diels-Alder products prevail. In the series explored only the substrate 1-cyano-4-nitronaphthalene produces the naphthalenyl-1*H*-pyrrole derivative as principal product, probably as a consequence of its charge distribution. A combination between stereoelectronic effects in the electrophile and the type of substitution joint to the nucleophilicity of the diene is responsible of the results and regioselectivity observed in these polar cycloaddition reactions. In all the cases studied the regioselectivity expected by theoretical calculations corresponds with the ones obtained experimentally.

Keywords: Phenanthrenols, Diels-Alder reaction, nitronaphthalenes, electrophiles, theoretical calculations.

INTRODUCTION

Phenanthrene derivatives are tricyclic aromatic compounds, probably biosynthesized by the oxidative coupling of the aromatic rings of stilbene precursors in higher plants [1]. They exhibit various biological activities such as anti-inflammatory, antiallergic, antimicrobial, cytotoxic, anti - platelet aggregation, phytotoxic, antifungal, spasmolytic, antifibrotic effects, and inhibitory effects on nitrous oxide production [2-10].

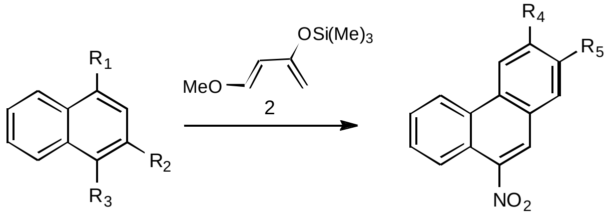
On the other hand, in the hierarchy of carbon-carbon bond constructions, the Diels-Alder (DA) reaction has attained a preminent position. If one chemical reaction had to be selected from the repertoire of synthetic organic chemists as the most useful and powerful way of synthetic construction, it was clear by 1970s that the DA reaction would be the logical choice [11, 12]. The DA cycloaddition has afforded numerous and unparalleled solutions to a diverse range of synthesis of natural products.

The process occurs in one inter or intramolecular step from a diene and a dienophile bearing an almost unlimited number of variants. It is noteworthy that these variants exist not only in the substitution of the reaction components but also in the electronic nature of these dienes and dienophiles.

Previous studies of aromatic heterocycles such as indoles, benzofurans, pyrroles, furans, and thiophenes in DA reactions demonstrate the viability of these systems as dienophiles [13]. Attention has been recently turned to the investigation of the dienophilicity of substituted naphthaalenes. While the use of these substrates as dienes in thermal and high-pressure DA reactions has been widely studied, the employment of such compounds as dienophiles has received relatively little attention in the literature [14, 15].

In the study developed with 1,3- and 1,4-dinitronaphthalene (**1a** and **1b**) and the Danishefsky diene (**2**) in benzene at 120 °C, 9-nitro-3- and -2-phenanthrenols **3a** and **3b** were obtained respectively in good yields (Scheme **1**) [16].

The reaction is a domino process that is initiated by a polar DA (P-DA); this reaction can be considered as



1a: R_1=NO_2; R_2=NO_2; R_3=H
1b: R_1=NO_2; R_2=H; R_3=NO_2

3a: R_4= OH; R_5=H
3b: R_4=H; R_5=OH

Scheme 1.

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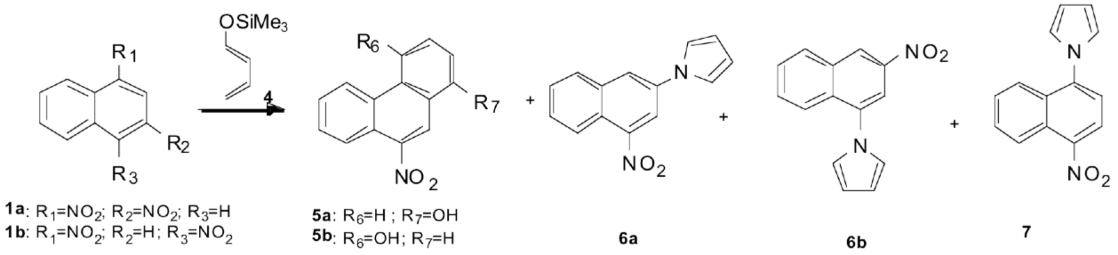

Scheme 2.

concerted cycloaddition [4π + 2π] with an asynchronous transition state [17]. The reaction between dinitronaphthalene, acting as the electrophilic component, and Danishefsky diene (**2**), acting as the nucleophilic one, gives a formally [4 + 2] cycloadduct. The subsequent elimination of nitrous acid yields the nitrophenanthrenol derivative.

With the aim to synthesize 1- and 4-substituted nitrophenanthrenols and taking into account a previous theoretical research (see theoretical calculations), we considered the possibility of using (*E*)-1-(trimethylsilyloxy)-1,3-butadiene (**4**) knowing that its nucleophilicity value is close to the Danishefsky diene (**2**) value and that the -OH function derives from the -$OSiMe_3$ group.

The dienophiles **1a** and **1b** were exposed to the diene **4** under thermal conditions using solvents as reaction media for demonstrating that the presence of this diene produces phenanthrenol derivatives as principal products in a similar way that the Danishefsky diene (**2**). Moreover, the obtained results were analyzed using theoretical calculations.

RESULTS AND DISCUSSION

The dinitronaphthalenes **1a,b** and the (*E*)-1-(trimethylsilyloxy)-1,3-butadiene (**4**) are shown in (Scheme **2**). The cited reactions were realized in thermal conditions using benzene as solvent [1].

At 120 °C the reaction of **1a** with **4** produced **5a** [18] resulting of the cycloaddition in C3-C4 bond position and the hetero DA product 1-(3-nitro-1-naphthalenyl)-1*H*-pyrrole (**6b**) in ca 6:1 ratio, in good yield (73%), and traces of 1-(1-nitro-3-naphthalenyl)-1*H*-pyrrole (**6a**) [16] (Table **1**, entry 1). On the other hand, the reaction of **1b** yielded the regioisomer 4-hydroxy-9-nitrophenanthrene (**5b**) and 1-(4-nitro-1-naphthalenyl)-1*H*-pyrrole (**7**) in a 6:1 ratio and good yield (72%) (Table **1**, entry 3). With respect to the last reaction we observed complete regioselectivity in the normal DA channel [18]. All these products are shown in (Scheme **2**).

Table 1. DA Reactions with (*E*)-1-(Trimethylsilyloxy)-1,3-butadiene (4)

Entry	Dienophile	Temperature	Product	Yield (%)
1	**1a**	120 °C	**5a, 6b, 6a**	62, 9, traces
2	**1a**	150° C	**5a**	71
3	**1b**	120 °C	**5b, 7**	61, 11
4	**1b**	150 °C	**5b**	72
5	**9**	120 °C	**10**	15
6	**9**	150 °C	**10**	17
7	**11**	120 °C	**12, 13**	48, 12
8	**11**	150 °C	**12**	52

When the reactions were developed at 150 °C during 72 h using benzene as solvent the global yields of the hydroxyphenanthrenes were higher due to the absence of the hetero [4 + 2] DA product (Table **1**, entries 2 and 4).

As it was said before, when the Danishefsky diene (**2**) was used in the DA reaction with **1a** and **1b** under the same conditions (120 °C and 72 h) only the hydroxyphenanthrene was observed as product (Scheme **1**) [16].

Nevertheless, the results of the diene **4** are related with those observed when (*E*)-1-methoxy-1,3-butadiene (**8**) [16], a diene with a similar nucleophilicity index, was used. In the last case a mixture of the hetero and normal DA products is observed. However with diene **4** the pyrrole derivative shows a lower percentage in the total yield, instead with the diene **8** the pyrrole derivative improves.

To continue exploring the dienophilicity of disubstituted naphthalenes, the 1-cyano-4-nitronaphthalene (**9**) was investigated**,** taking in account that when Danishefsky diene (**2**) reacts with this dienophile the phenanthrenol derivative is the only product got, and that the global electrophilicity index of this electrophile is close to the one of 1,3-dinitronaphthalene (**1a**) (Table **2**). In this case the results were not the ones expected. At 120 and 150 °C the reaction goes by the hetero DA channel and the product **10** is the only product observed, in a low yield. Phenanthrenol derivative is not observed. (Scheme **3**) (Table **1**, entries 5 and 6).

Knowing this behaviour, and in order to confirm the previous reactive tendency of (*E*)-1-(trimethylsilyloxy)-1,3-butadiene (**4**) as a intermediate nucleophilic diene between Danishefsky diene (**2**) and (*E*)-1-methoxy-1,3-butadiene (**8**)

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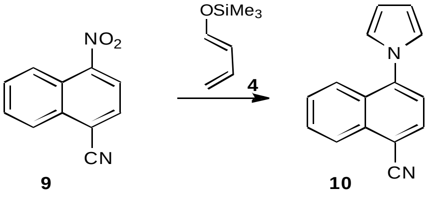
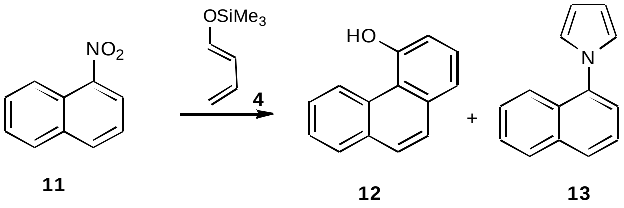
[1] General Procedure for the thermal reactions of nitronaphthalenes. The temperature, the length of the reaction, and the diene/dienophile ratio were dependent on the starting material and are indicated in (Table **1**). An ampulla, containing a solution of 1.0 mmol of the dienophile and the required amount of diene in 1 ml of dry benzene was cooled in liquid nitrogen, sealed (under nitrogen atmosphere), and then heated with stir in a bath. After the reaction time was completed, it was cooled once more in liquid nitrogen and opened. The solution was evaporated and the residue purified by column chromatography on silica gel or alumina using hexane / ethyl acetate mixtures as eluent.



Scheme 3.



Scheme 4.

(Table **2**), 1-nitronaphthalene (**11**) was used as dienophile (Scheme **4**) (Table **1**, entries 7 and 8).

The reactivity is proved again with both kind of products, the one **13** that derives from the hetero DA and phenanthrenol **12** deriving from the cycloadduct of the polar DA that involves the C1-C2 bond.

Theoretical calculations. The Density Functional Theory (DFT) was used in the present work to explain the behavior of the molecules involved in the DA reaction. It is a good complement that allows knowing electronic parameters of each dienophile and diene with the aim of getting some chemical properties that are interesting for this study.

The global electrophilicity index [19], ω, and the global nucleophilicity index [20], *N*, are introduced. An analysis of the global reactivity index indicates that in a polar DA reaction dienophiles will act as strong electrophiles, while the diene will act as a strong nucleophile.

The electronic chemical potential of dienophiles is lower than that of the diene. Therefore, it is expected that, along a polar DA reaction, the charge transfer (CT) will take place from the electron-rich diene to 1-nitronaphthalene derivatives.

Additionally, there are local reactivity indexes that are associated with site selectivity in a chemical reaction. They can be calculated from the Fukui function, local electrophilicity index [21] ω_k (for the dienophiles acting as electrophiles) and local nucleophilicity index [22] N_k (for the dienes acting as nucleophiles).

The static global properties of 1-nitronaphthalene derivatives and the dienes were calculated.

Taking into account the local counterpart, in a polar cycloaddition between asymmetrical reagents, the most favorable 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. (Table **3**) shows the local indexes of dienophiles and dienes.

In all the cases the regioselectivity expected by theoretical calculations corresponds with the ones obtained experimentally.

Computational details. All calculations were carried out with the Gaussian 09 suite of programs [23]. DFT calculations were carried out using the B3LYP exchange-correlation functional together with the 6-31G(d) basis set [24, 25].

The global electrophilicity index, ω, is given by the following simple expression: $\omega = (\mu^2/2\eta)$, in terms of the

Table 2. Global Electrophilicity Indexes.

Dienophile	ω	*N*	Diene	ω	*N*
1a	3.30	2.03	**2**	0.68	3.62
1b	3.63	2.11	**4**	0.75	3.59
9	3.33	2.19	**8**	0.81	3.56
11	2.49	2.65			

Table 3. Local Electrophilicity Indexes of Dienophiles and Local Nucleophilicity Indexes of Dienes.

		ω_k			N_k
1a	**C3**	0.15	**2**	**C1**	0.48
	C4	0.72		**C4**	1.37
1b	**C1**	0.37	**4**	**C1**	0.74
	C2	0.24		**C4**	0.97
9	**C1**	0.16	**8**	**C1**	0.67
	C2	0.30		**C4**	0.96

electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively [26]. Recently, Domingo *et al.* have introduced an empirical (relative) nucleophilicity index, ***N***, based on the HOMO energies obtained within the Kohn-Sham scheme [27] and defined as $N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)}$. The nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us conveniently to handle a nucleophilicity scale of positive values. Local electrophilicity and nucleophilicity indices, ω_k and N_k, were evaluated using the following expressions: $\omega_k = \omega f_k^+$ and $N_k = N f_k^-$ where f_k^+ and f_k^- are the Fukui functions for a nucleophilic and electrophilic attack, respectively [28].

CONCLUSION

It has been shown that it is possible to carry out the construction in a single step of products with phenanthrenol skeleton and the presence of hydroxyl group in 1 and 4 positions as a complement with the reactivity of the Danishefsky diene (**2**).

With the diene **4** the reactions of mono- and dinitronaphthalenes yield two types of products, the phenanthrenol derivatives as principal products and the *N*-naphthalenylpyrroles. It is important to understand that while working at higher temperatures (150 °C) the hetero DA product disappears. This behavior is similar to those of the Danishefsky diene (**2**).

As we expected, the introduction of a second nitro group in the substituted ring of 1-nitronaphthalene produces an extra activation in the nucleus.

To our knowledge the present work completes the formal study on the dienophilicity of nitronaphthalenes when they participate in DA reactions under standard conditions.

The results obtained may contribute to the comprehension of the general reactivity of naphthalenes and application of substituted aromatic hydrocarbons as electrophiles.

Furthermore, in this case DFT calculations are useful tools to predict the viability of the cycloaddition reactions through global electrophilicity and nucleophilicity indexes. Regioselectivity of the reactions is also well predicted by local indexes of diene and dienophile carbon atoms.

EXPERIMENTAL SECTION

General Aspects. ^{1}H and ^{13}C NMR spectra were recorded with the deuterated solvent as the lock and residual solvent as internal on 300 and 75 MHz, FT-spectrometers respectively, CG-MS analyses were performed in an instrument equipped with a PE-5-type column. IR spectra were recorded from NaCl cells.

Spectral data of compounds **5a**, **5b**, **6a**, **6b**, **9**, **10** and **11** is given below.

5a. ^{1}H NMR (CDCl$_3$) δ: 6.99 (dd, 1H, *J* = 8.3, 1.4 Hz), 7.56 (m, 2H), 7.73 (m, 2H), 8.16 (dd, 1H, *J* = 8.4, 1.3 Hz), 8.40 (s, 1H), 8.80 (dd, 1H, *J* = 8.5, 1.3 Hz). ^{13}C NMR (CDCl$_3$) δ: 110.5, 118.7, 121.3, 123.1, 124.8, 126.4, 126.8, 129.1, 129.7, 130.9, 131.8, 136.3, 149.2, 163.6. IR [cm^{-1}]: 3346, 1540, 1338.

5b. ^{1}H NMR (CDCl$_3$) δ: 4.80 (br s, 1H), 7.13 (d, 1H, *J* = 8.2, 1.3 Hz), 7.28 (m, 2H), 7.68-7.75 (m, 3H), 8.13 (s, 1H), 8.50 (d, 1H, *J* = 8.2, 1.1 Hz). ^{13}C NMR (CDCl$_3$) δ: 111.2, 118.4, 121.5, 122.8, 124.8, 126.4, 126.7, 129.6, 132.2, 140.1, 148.5, 165.4. IR [cm^{-1}]: 3350, 1534, 1356.

6a. ^{1}H NMR (CDCl$_3$) δ: 6.45 (t, 2H, *J*= 2.1 Hz), 7.08 (t, 2H, *J*= 2.1 Hz), 7.63-7.97 (m, 3H), 8.15 (dd, 1H, *J*= 7.1, 2.9 Hz), 8.23 (d, 1H, *J*= 2.2 Hz), 8.83 (d, 1H, *J*=2.3 Hz). ^{13}C NMR (CDCl$_3$) δ: 110.2, 116.7, 121.1, 121.4, 126.4, 130.2, 130.5, 133.1, 133.8, 140.3, 146.0. IR [cm^{-1}]: 1534, 1353.

6b. ^{1}H NMR (CDCl$_3$) δ: 6.44 (t, 2H, *J* = 2.1 Hz), 7.12 (t, 2H, *J* = 2.1 Hz), 7.65-7.98 (m, 3H), 8.19 (dd, 1H, *J* = 7.0, 2.8 Hz), 8.29 (d, 1H, J=8.3 Hz), 8.85 (d, 1H, *J* = 2.3 Hz). ^{13}C NMR (CDCl$_3$) δ: 110.2, 116.6, 121.0, 121.4, 126.4, 128.6, 130.2, 130.5, 132.2, 132.8, 139.5, 145.9. IR [cm^{-1}]: 1532, 1355.

9. ^{1}H NMR (CDCl$_3$) δ: 6.46 (t, 2H, *J* = 2.1 Hz), 7.04 (t, 2H, *J* = 2.1 Hz), 7.50 (d, 1H, *J* = 8.2 Hz), 7.66 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.78 (ddd, 1H, *J* = 8.5, 7.0, 1.5 Hz), 7.99 (dd, 1H, *J* = 8.3, 1.5 Hz), 8.33 (d, 1H, *J* = 8.2 Hz), 8.36 (dd, 1H, *J* = 8.5, 1.3 Hz). ^{13}C NMR (CDCl$_3$) δ: 110.3, 121.2, 123.0, 123.3, 123.6, 124.2, 126.2, 128.1, 129.8, 130.1, 143.2. IR [cm^{-1}]: 2225.

10. ^{1}H NMR (CDCl$_3$) δ: 6.27 (t, 2H, *J*= 2.1 Hz), 7.01 (t, 2H, *J*= 2.1 Hz), 7.50 (d, 1H, *J*=8.2 Hz), 7.65 (ddd, 1H, *J*=8.3, 7.0, 1.3 Hz), 7.77 (ddd, 1H, *J*=8.5, 7.0, 1.5 Hz), 7.95 (dd, 1H, *J*=8.3, 1.5Hz), 8.25 (d, 1H, *J*=8.2 Hz), 8.64 (dd, 1H, *J*=8.5, 1.3Hz). ^{13}C NMR (CDCl$_3$) δ: 108.5, 111.8, 117.4, 120.6, 121.0 121.6, 122.6, 124.3, 125.3, 128.0, 128.6, 128.8, 132.3, 133.5, 141.5. IR [cm^{-1}]: 2222 cm $^{-1}$.

11. ^{1}H NMR (CDCl$_3$) δ: 7.83 (t, 2H, *J* = 2.2 Hz), 8.18 (d, 1H, *J* = 8.1 Hz), 8.27 (d, 1H, *J* = 8.1 Hz), 8.31 (d, 1H); 8.42 (d, 1H, *J* = 8.2 Hz), 8.48 (m, 2H), 8.52 (s, 1H), 9.64 (br s, 1H). ^{13}C NMR (CDCl$_3$) δ: 110.3, 120.5, 121.7, 125.7, 127.8, 128.1, 131.2, 134.4, 136.3. IR [cm^{-1}]: 3614, 3054, 1601, 1450, 1093.

CONFLICT OF INTEREST

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

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