

CYCLOADDITIONS OF α,β -UNSATURATED *N,N*-DIMETHYLHYDRAZONES. A DIELS-ALDER STRATEGY FOR THE BUILDING OF AZA-HETERO RINGS

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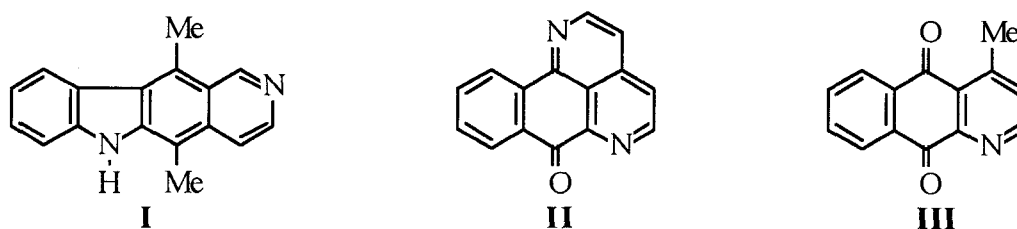
Abstract- The reactivity and the synthetic usefulness of α,β -unsaturated *N,N*-dimethylhydrazones in hetero Diels-Alder reactions are reviewed. Factors influencing the regiochemistry are discussed.

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I. INTRODUCTION

If we focus our attention on the structure of biologically active substances from synthetic or natural origin, we observe that many of them include an aza-heterocycle in a fused polycyclic framework. This fact is illustrated by compounds such as ellipticine (**I**), an antitumoral indole alkaloid,¹ sampangine (**II**), the parent derivative of a series of antifungal copyrine alkaloids² and cleistopholine (**III**), an azaanthraquinone with an antibiotic activity³ (Scheme 1).



Scheme 1

Considerable efforts have been devoted to develop efficient methods to synthesize these products and their analogues for biological evaluations. Among them hetero Diels-Alder reactions of 1-aza- and 2-aza-1,3-dienes with appropriate dienophiles were successfully exploited in the building of the aza-hetero ring part. For this purpose, the cycloaddition chemistry of azadienes was reviewed.⁴⁻⁸ In the field of 1-azadienes, the ability of α,β -unsaturated *N,N*-dimethylhydrazones to react readily with electron deficient dienophiles was extensively employed. The hetero Diels-Alder reactions afforded adducts which led to six-membered nitrogen structures. At our knowledge, no report was exclusively devoted to α,β -unsaturated *N,N*-dimethylhydrazones as dienes. In this paper, we wish to present an up to day review on this field.

II. REACTIVITY OF α,β -UNSATURATED *N,N*-DIMETHYLHYDRAZONES

Vinyl imines (1-aza-1,3-dienes) present a low reactivity towards electron-deficient dienophiles due to the normal electron-withdrawing effect of the nitrogen atom. So, to enhance the reactivity of such 1-azadienes, the substitution of N-1 by an electron-releasing substituent like a dimethylamino group has been envisaged in 1982 by Ghosez *et al.*⁹ (Scheme 2).

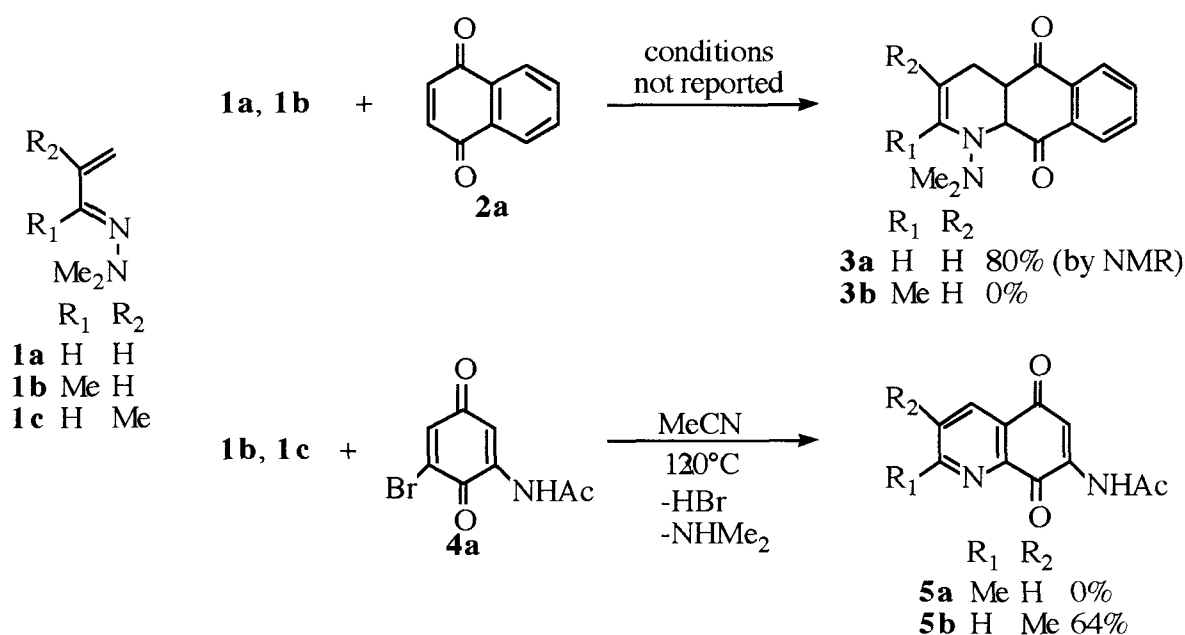


Scheme 2

Their experiments clearly demonstrate that α,β -unsaturated *N,N*-dimethylhydrazones behave as well defined electron-rich dienes in normal ($\text{HOMO}_{\text{DIENE}}$ controlled) Diels-Alder reactions with representative dienophiles. These results confirm that a tertiary amino group increases the nucleophilic character of the azadiene system and overcome the normal electron-deficient effect of N-1 atom by the virtue of the nitrogen lone pair interaction with the π -system.⁵ Since this pioneer work, cycloadditions have been developed with several α,β -unsaturated *N,N*-dimethylhydrazones substituted at C-2, C-3 or C-4. First, we plan to evaluate their reactivities towards dienophiles in relation with the nature and the position of substituents.

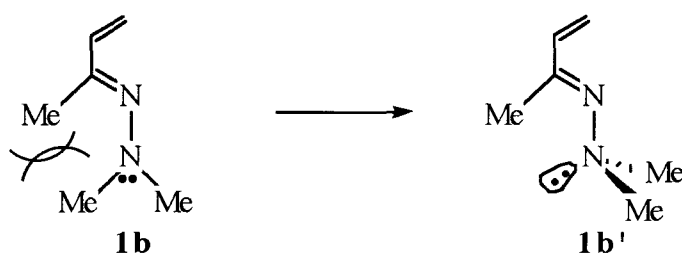
II.1. Substituent at C-2

The presence of a methyl group at C-2 prevents the Diels-Alder reaction of azadiene (**1b**) with naphthoquinone (**2a**)⁵ or benzoquinone (**4a**)¹⁰ (Scheme 3).



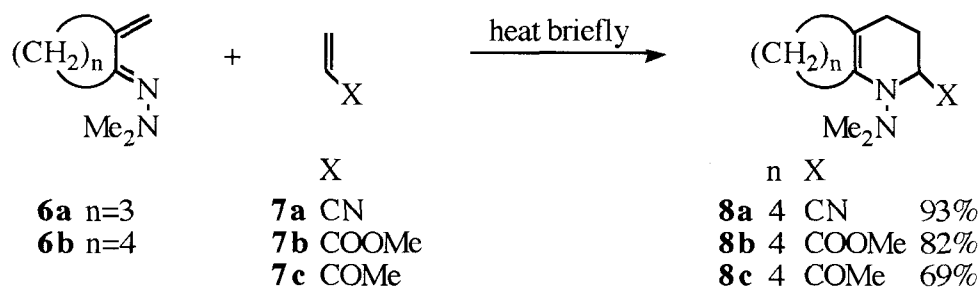
Scheme 3

Indeed, in this azadiene (**1b**) the steric hindrance between two methyl groups twists the lone pair out of the plane of the π electrons and prevents the azadiene system activation by conjugation^{5,10,11} (Scheme 4).



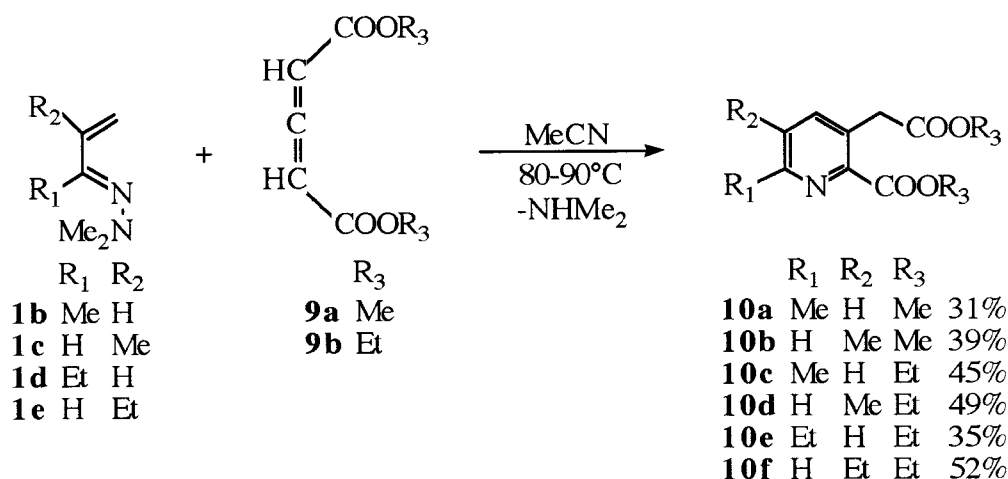
Scheme 4

Furthermore, the steric interaction due to the methyl substituent may also influence the equilibrium between *s-cis* and *s-trans* conformations of the diene. So, if only a fractional part of the favorable *s-cis* conformation is present, [4+2] cycloadditions would be unfavored. In addition, when the 1-azadiene has a fixed *s-cis* conformation (**6a-b**) high reactivities are observed with acrylate dienophiles¹² (Scheme 5).



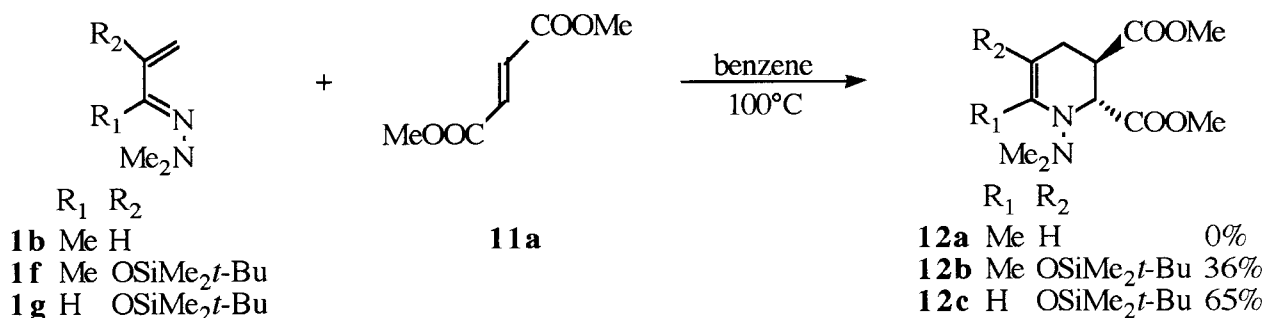
Scheme 5

Azadienes (**6a-b**) are also reactive towards dienophiles such as benzoquinone (n=3: 76%; n=4: 92%), *N*-phenylmaleimide (n=3: 97%; n=4: 98%) and benzylidenemalononitrile (n=3: 66%; n=4: 74%).¹² In the case of the allenyl dienophiles (**9a-b**) an alkyl substituent at C-2 induces a decrease in the cycloaddition yields^{13,14} (Scheme 6).



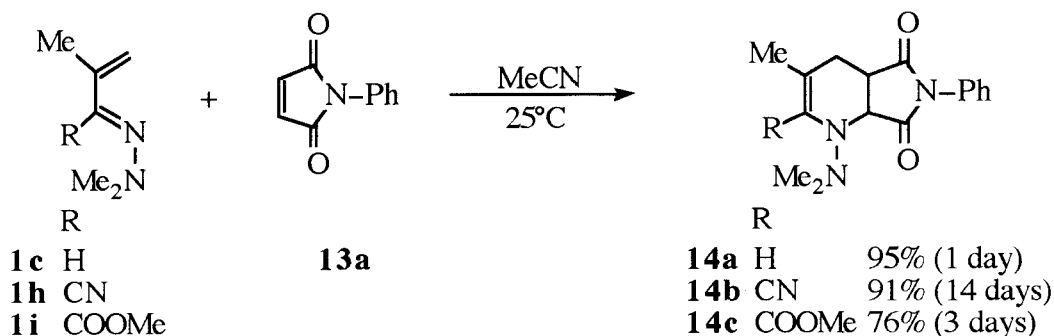
Scheme 6

The unfavorable steric effect of the methyl group at C-2 is partly compensated by the presence at C-3 of an electron-releasing substituent such as a silyloxy group which increases the electron density of the diene favoring cycloaddition⁵ (Scheme 7).



Scheme 7

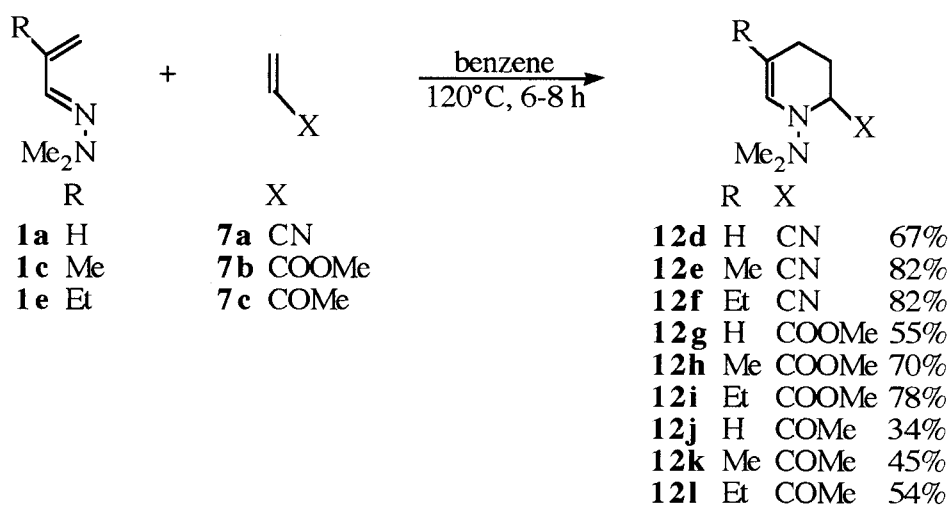
On the other hand, introduction of electron-withdrawing cyano and ester groups at C-2 (1h-i) reduces the electron density of the dienes and hence lowers their reactivity towards *N*-phenylmaleimide¹¹ (Scheme 8).



Scheme 8

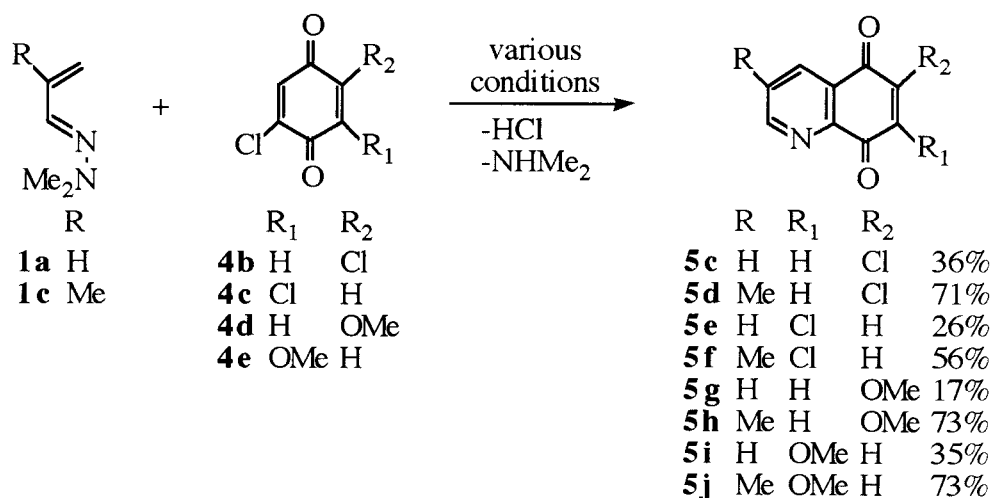
II.2. Substituent at C-3

The first 1-azadiene used by Ghosez bears a methyl substituent at C-3.⁹ It appears from several experimental results that the presence of an alkyl group at this position generally facilitates the Diels-Alder reactions. This fact is well illustrated by α -alkylacrolein dimethylhydrazones (1c, 1e) which react more readily under the same conditions and with higher yields than the acrolein derivative (1a)¹² (Scheme 9).



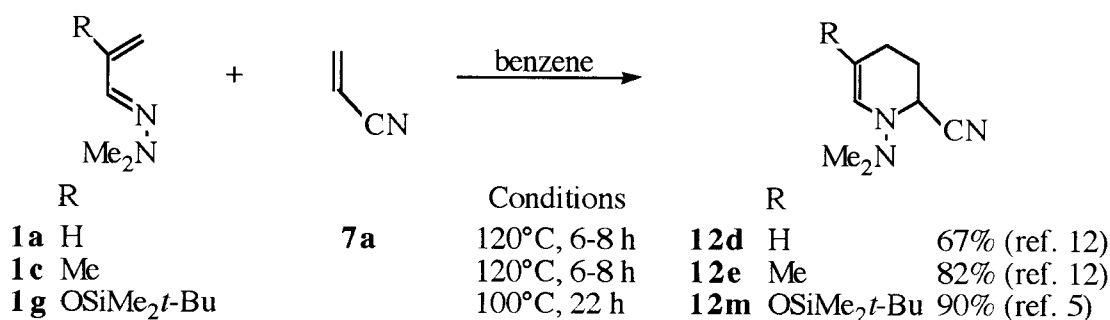
Scheme 9

Analogous results are observed with chloroquinones (**4b-e**) as dienophiles¹⁵ (Scheme 10). They can be explained by the complementary electronic effect of the alkyl groups on azadienes. With higher carbon condensed chains (propyl, isopropyl, butyl), mixtures of cycloadducts are obtained due to the 1-azadiene C3-C4 double bond isomerization in the experimental conditions.¹⁶



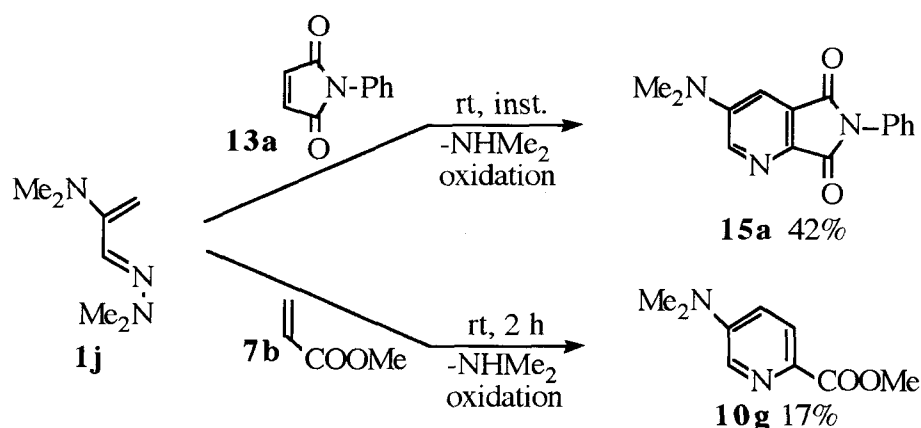
Scheme 10

High yields are also observed with the presence of electron-releasing substituents on azadienes^{5,12} (Scheme 11). Indeed, Ghosez *et al.* claimed in 1985 that azadiene (**1g**) was the most reactive that they used.⁵ Cycloadducts are also obtained with dimethyl maleate (65%), dimethyl fumarate (59%), methyl propiolate (50%) and benzoquinone (60%).⁵



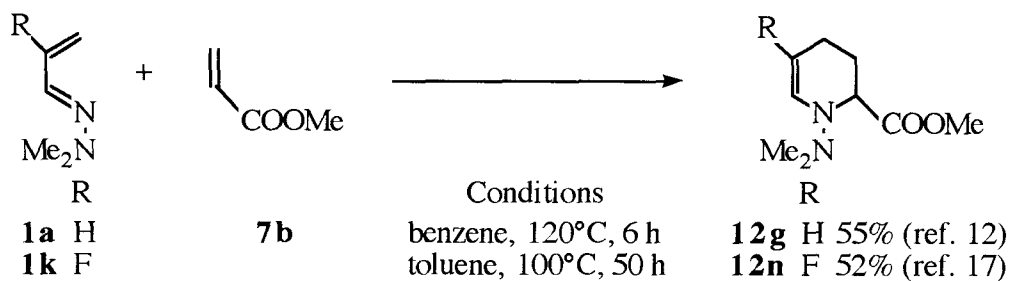
Scheme 11

With a trimethylsilyloxy substituent, the cycloadduct formed is an extremely unstable compound which completely polymerizes at room temperature.¹² In contrast, the presence of a dimethylamino group at C-3 increases the reactivity. Thus, azadiene (**1j**) reacts with *N*-phenylmaleimide even at -70°C in a dilute ether solution. At room temperature, the reaction takes place almost instantaneously with an exothermic effect. With methyl acrylate a slower reactivity is observed¹² (Scheme 12).



Scheme 12

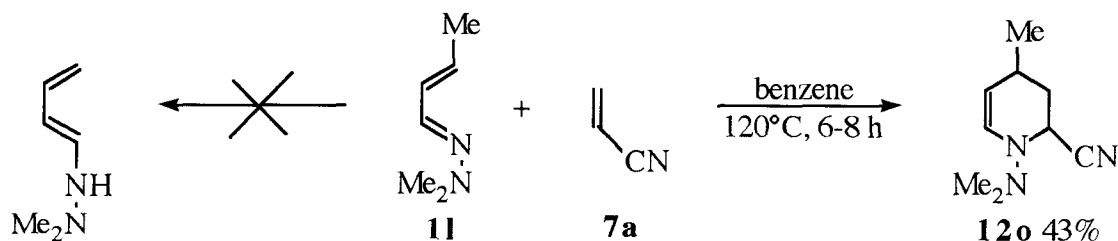
Substitution by a fluorine atom (a weak donor and strong σ -acceptor substituent) reduces only slightly the cycloaddition performances towards methyl acrylate¹⁷ (Scheme 13). As expected, the fluorinated diene (**1k**) reacts also under fairly mild conditions with dimethyl acetylenedicarboxylate (80°C , 50 h, 63%),¹⁷ benzoquinone (25°C , 50 h, 62%),¹⁷ naphthoquinone (25°C , 50 h, 57%),¹⁷ quinoline-5,8-dione (61°C , 72 h, 24%)¹⁸ and quinoline-2,5,8-trione (61°C , 72 h, 10%).¹⁸



Scheme 13

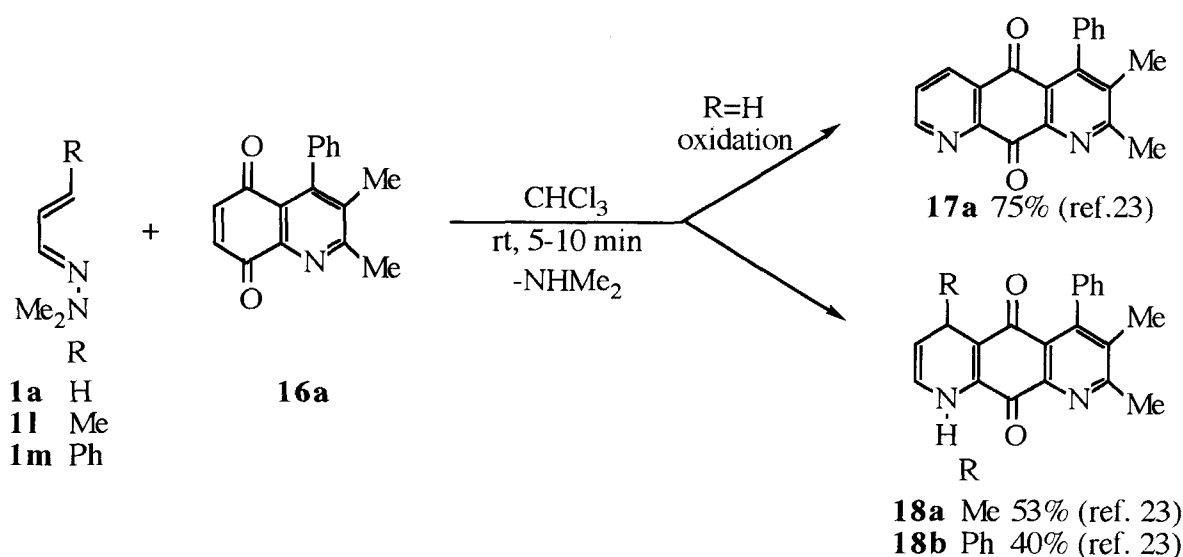
II.3 Substituent at C-4

It was believed that introduction of an alkyl substituent at C-4 might generate 1-azadienes suitable for a tautomeric rearrangement into dienamines which could undergo Diels-Alder reactions in this form. This hypothesis was checked by the reaction of crotonaldehyde dimethylhydrazone with acrylonitrile. The only isolated product was unambiguously the substituted tetrahydropyridine (**12o**)¹² (Scheme 14).



Scheme 14

This result casted some doubt on the dienamine path generally reported for a long time in the literature.¹² In fact, this opinion had been held from an early report where a failure in an attempted hetero Diels-Alder reaction was assigned to the tautomerism of the starting 1-azadiene.¹⁹ Nevertheless, a higher yield of cycloadduct (67%) is obtained in the same conditions with the unsubstituted azadiene (**1a**)¹² (Scheme 11). Towards quinones as dienophiles, a different behavior is frequently observed between unsubstituted and C-4 substituted 1-azadienes. With these latter, elimination of dimethylamine and isomerization of the primary cycloadduct are not always followed by an *in situ* oxidation into aromatic derivatives²⁰⁻²³ (Scheme 15).



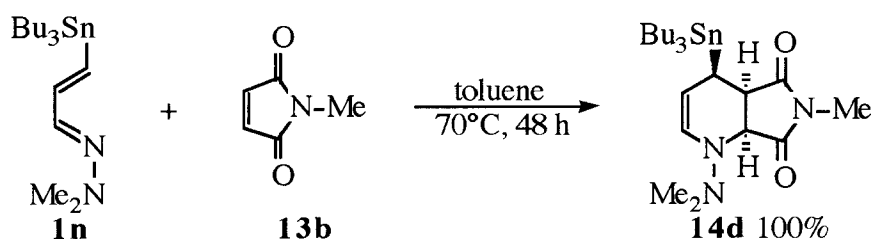
Scheme 15

The cycloadducts (**18a-b**) are respectively oxidized to the corresponding aromatic compounds by treatment with MnO_2 (1 day) or by exposure to air (5 days).²³ The more difficult aromatization of cycloadducts obtained from C-4 substituted 1-azadienes is ascribed, in the case of the methyl substituent, to its interaction with the nearest carbonyl in the planar aromatic structure. This situation does not exist in the dihydro derivative (**18a**).²⁰

Aryl substituents at C-4 induce a lowered reactivity to 1-azadienes. These latter do not react with benzoquinone,²⁴ and give moderate yields with naphthoquinone leading to a dihydro 1-azaanthraquinone derivative in 28% yield.²⁴ A limited success is also observed with different quinoline-5,8-diones^{23,25} and quinoline-2,5,8-triones.²⁰ Due to the same steric factors, cinnamoyl *N,N*-dimethylhydrazone (**1m**) gives the dihydro cycloadduct (**18b**) (Scheme 15).

Introduction of an electron-withdrawing group ($\text{R}=\text{COOMe}$) at C-4 generates an azadiene which reacts slowly with naphthoquinone at reflux of toluene affording the dihydro cycloadduct in 16 % yield.²⁶

Finally, the effect of a tributylstannyl substituent was recently evaluated. With *N*-methylmaleimide as a dienophile, a quantitative cycloaddition was observed²⁷ (Scheme 16).



Scheme 16

High yields of similar cycloadducts are also obtained with quinonic dienophiles in a toluene solution (1,4-benzoquinone, 25°C , 48 h, 50%; 1,4-naphthoquinone, 70°C , 48 h, 71%; juglone, 25°C , 16 h, 100%; methyljuglone, 70°C , 48 h, 60%). Its silyl analogue (SiEt_3) failed to react with simple dienophiles under analogous conditions.²⁷

In conclusion, it appears from the above experimental results that a substitution at C-3 by an electron-releasing group facilitates the cycloaddition reactions. In contrast, the presence of substituents at C-2 or C-4 reduces generally the reactivity of these 1-azadienes towards dienophiles. In the next part of this review, we will examine how the usefulness of α,β -unsaturated N,N -dimethylhydrazones has been well exploited in hetero Diels-Alder reactions.

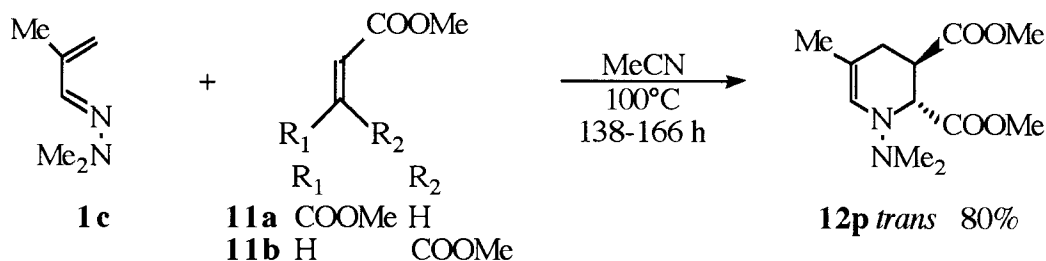
III. INTERMOLECULAR DIELS-ALDER REACTIONS

As partners of α,β -unsaturated N,N -dimethylhydrazones in intermolecular [4+2] cycloadditions, we consider successively non-quinonic and then quinonic dienophiles.

III.1 Non-quinonic dienophiles

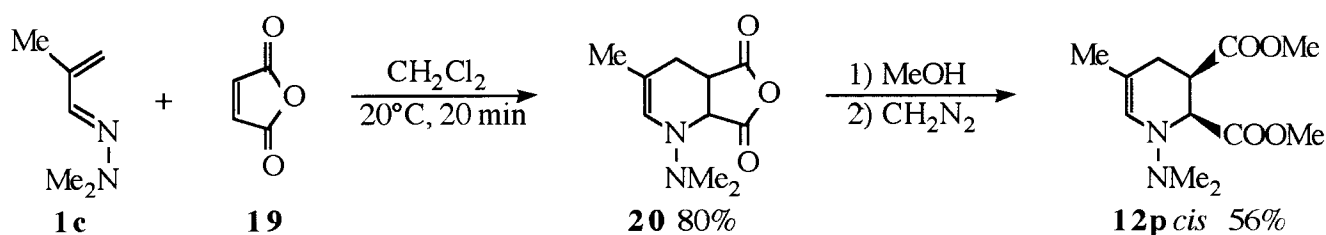
Symmetrical non-quinonic dienophiles

Electron-deficient dienophiles such as dimethyl maleate or dimethyl fumarate react with azadiene (**1c**) to give exclusively the *trans*-cycloadduct (**12p**). This result seems to be due to the isomerization of dimethylmaleate, in the harsh experimental conditions used, before its cycloaddition^{5,9} (Scheme 17).



Scheme 17

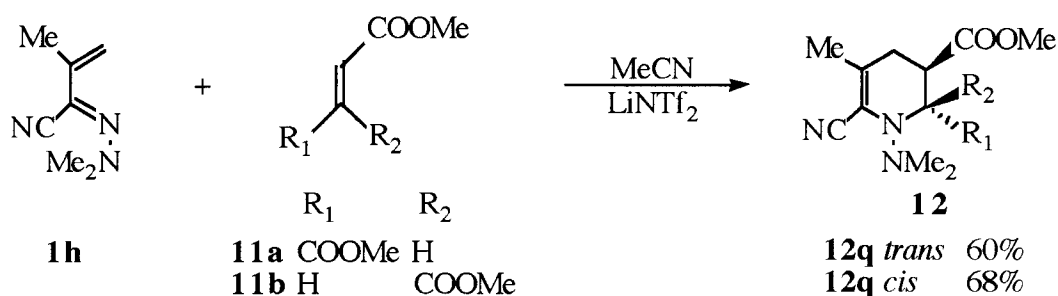
To obtain the *cis*-stereoisomer, these authors employed maleic anhydride. Then, the cycloaddition step was followed by methanolysis and esterification of the cycloadduct^{5,9} (Scheme 18).



Scheme 18

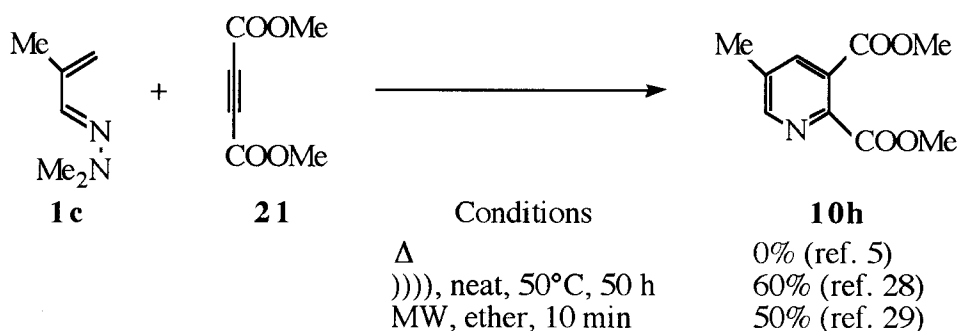
The synthetic usefulness of these cycloadditions lies on the possibility of dimethylamine removal by a reductive cleavage and reduction of the double bond by mean of Zn/AcOH to provide substituted piperidines.^{5,9}

In order to develop milder conditions than those used in Scheme 17, the reactions are performed under ultrasonic irradiation, salt effect or microwaves. Thus, sonication of a mixture of **1c** and **11a** or **11b** (probe, neat, 50°C , 49 h) give high yields of *trans* **12p** (99% and 95% respectively).²⁸ In contrast with sonicated experiments, stereospecific cycloadditions are obtained with **1h** in the presence of lithium trifluoromethanesulfonimide (LiNTf_2) in acetonitrile¹¹ (Scheme 19).



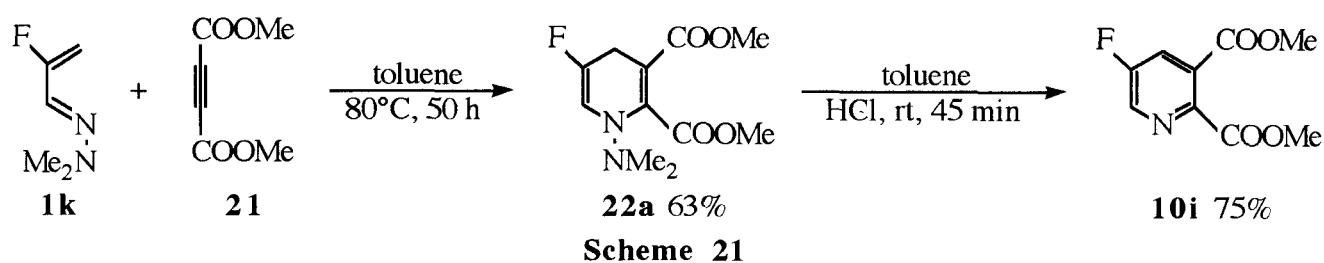
Scheme 19

Under heating, surprisingly azadiene (**1c**) does not react with dimethyl acetylenedicarboxylate (**21**) to give the corresponding cycloadduct.⁵ More recently, compound (**10h**) is obtained in good yields under an ultrasonic irradiation followed by air oxidation²⁸ or by microwaves treatment (MW) on a graphite support²⁹ (Scheme 20).

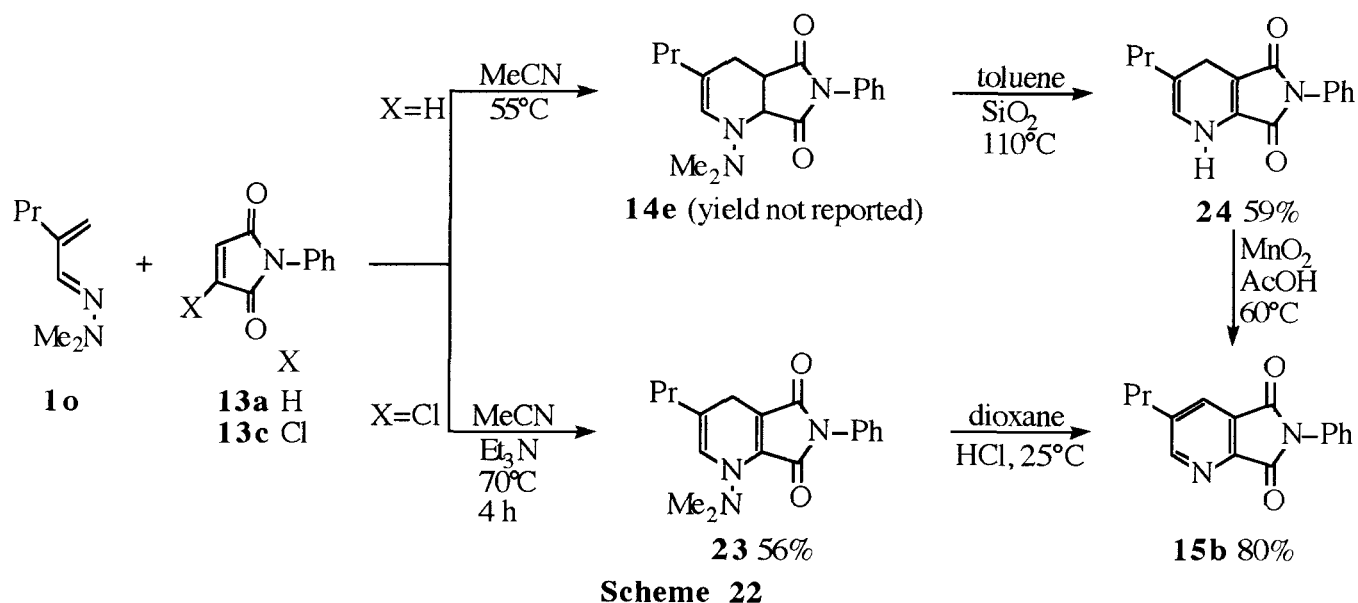


Scheme 20

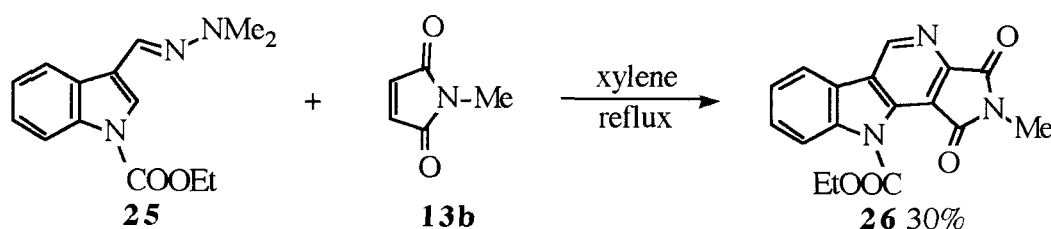
On the other hand, the fluorinated 1-azadiene (**1k**) reacts with **21** to afford a stable 1,4-dihydropyridine derivative which can be easily aromatized after an acidic treatment¹⁷ (Scheme 21).



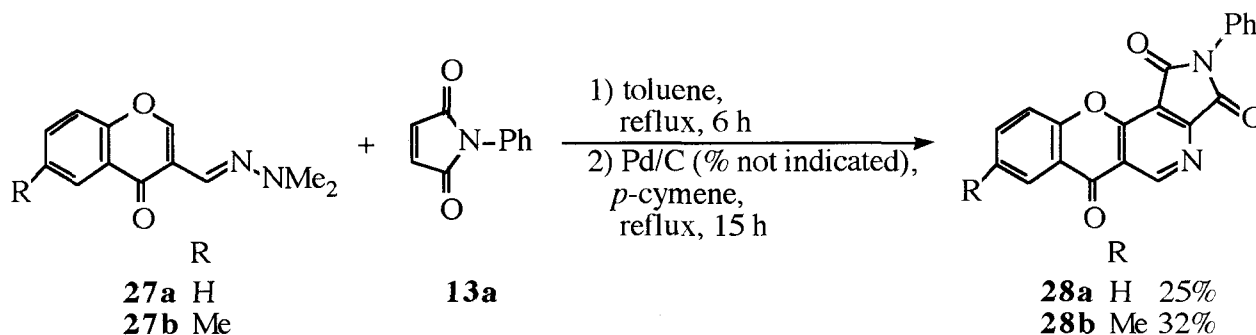
As previously shown, *N*-methyl- and *N*-phenylmaleimides react readily with various 1-azadienes^{11,12,27} (Schemes 8, 12, 16). In the case of these dienophiles comparative studies are undertaken with their 2-chloro derivatives.^{16,30,31} It appears from a lot of results, that the non-chlorinated ones afford the tetrahydro cycloadducts. Then, elimination of dimethylamine to give the dihydro derivatives is easily achieved by treatment with silica gel. In the case of 2-chloromaleimides, *N,N*-dimethylaminodihydro cycloadducts are directly obtained through hydrochloride elimination. Subsequent acidic treatment provides substituted pyridines. These compounds are also prepared by oxidation of the dihydro derivatives by means of manganese dioxide. These behaviors are illustrated in Scheme 22 for *N*-phenylmaleimides (**13a**) and (**13c**).



A carboline framework is built through a Diels-Alder reaction between indole-3-carbaldehyde *N,N*-dimethylhydrazone and *N*-methylmaleimide³² (Scheme 23). However, azadiene (**25**) does not react, under various conditions, with maleic anhydride, dimethyl acetylenedicarboxylate and naphthoquinone.



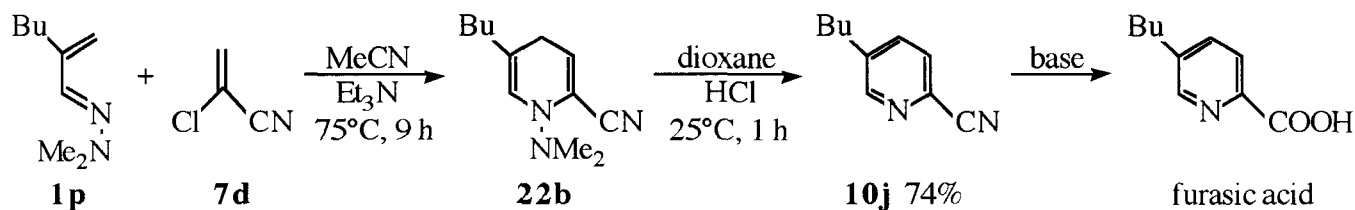
Formation of 2-azaxanthone proceeds similarly³³ (Scheme 24). In this [4+2] cycloaddition, the primary cycloadducts are stable enough to be isolated (respective yield : 64% and 58%) before their aromatization with palladised charcoal into **28a** or **28b**.



Scheme 24

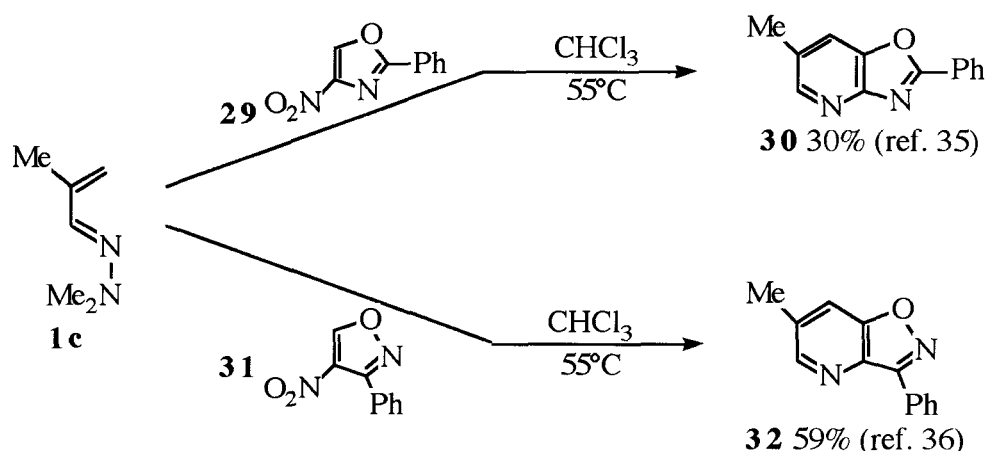
Unsymmetrical non-quinonic dienophiles

As it is shown in the first part of this review, cycloadditions of 1-azadienes with acrylate dienophiles (**7a-c**) generate always cycloadducts as the same single regioisomer (Schemes 5, 9, 11-14). Under ultrasonic conditions, an identical regiochemistry is observed in the cycloaddition of **1c** with **7a-c** (**7a**: neat, 50°C, 37 h, 47%; **7b**: neat, 50°C, 50 h, 35%; **7c**: neat, 50°C, 37 h, 60%).²⁸ Analogous results are obtained with **1c** and methyl crotonate or methyl propiolate (respective cycloadduct yields : 33% and 10%).⁵ Diels-Alder reactions of 2-chloroacrylonitrile with various C-3 or C-4 substituted 1-azadienes proceed with the same regiochemistry³⁴ (Scheme 25). The tetrahydro intermediate is not isolated due to a rapid elimination of hydrogen chloride. The dihydro derivative (**22b**) is also unstable. Elimination of dimethylamine to give the pyridine derivative (**10j**) is easily achieved in an acidic medium. Furasic acid is then obtained with a moderate yield (76%) after hydrolysis of **10j** with a base.



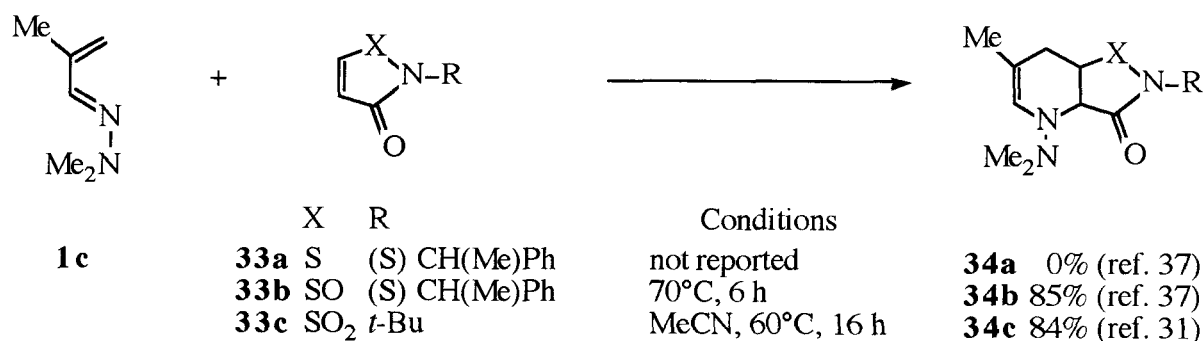
Scheme 25

In structures (**29**) and (**31**), the nitro electron-withdrawing substituent enables oxazole and isoxazole systems to participate as dienophiles in a normal [4+2] cycloaddition process with **1c**^{35,36} (Scheme 26). From labile intermediate cycloadducts, oxazolo- and isoxazolopyridine derivatives (**30**) and (**32**) are obtained with concomitant spontaneous loss of nitrous acid and dimethylamine. The regiochemistry of these cycloadditions is due to the control exerted by the nitro group.



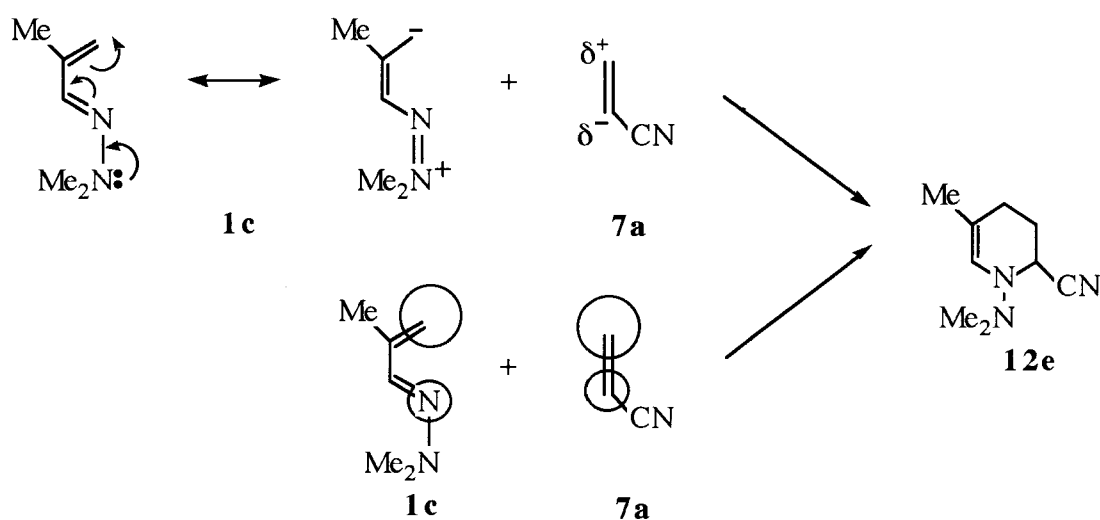
Scheme 26

Finally, various isothiazole structures are used as dienophiles with different 1-azadienes.^{31,37} The results are described in Scheme 27. The presence of a sulfinyl or sulfonyl group is necessary to activate sufficiently the carbon-carbon double bond. When the sulfinyl function is associated to a second chiral atom (**33b**), an excellent diastereoselectivity is obtained (**34b**, 98% d.e.). Cycloadducts incorporating the sulfonyl function are useful intermediates to access, after dimethylamine elimination and aromatization, to substituted azasaccharine derivatives. In all these cycloadditions the carbonyl group controls the regiochemistry whereas the sulfinyl or sulfonyl function activates the carbon-carbon double bond by an inductive effect.



Scheme 27

From all the above experiments, it appears that Diels-Alder reactions with the previous azadienes and unsymmetrical dienophiles are totally regioselective. The regiochemistry observed corresponds to the exclusive attack by C-4 of 1-azadiene on the β -position of acrylate dienophiles while N-1 adds to the α -position. This result is in agreement with the electronic resonance theory proposed by Thomson *et al.*³⁸ in order to explain the regiochemistry of many Diels-Alder reactions. Indeed, it is considered that the nucleophilic end of dienes adds to the poorer electronic site of dienophiles (Scheme 28).



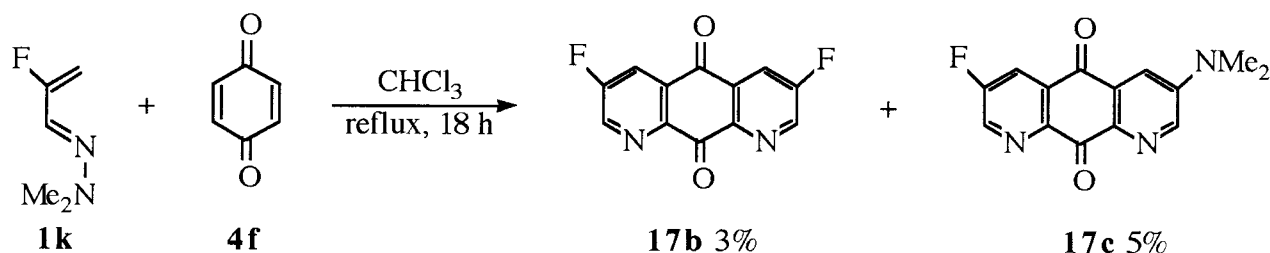
Scheme 28

Another explanation for this regiochemistry can be obtained by the use of the frontier molecular orbital theory.³⁹ Indeed, the formation of the major cycloadduct may result from the interaction between frontier orbitals with larger coefficients in the diene and dienophile.³⁹ Calculations are performed in some cases (**1c**, **11**, **7a**, **7b**, **7c**)⁴⁰⁻⁴³ by the semiempirical method PM3.⁴⁴ Thus, the larger values for HOMO coefficients of 1-azadienes are located at C-4 and for the LUMO of acrylate derivatives at the β -position. This method allows to determine the same favored regioisomer (Scheme 28). The more complex regiochemistry obtained with quinonic dienophiles will be discussed with this theory in the next part of this review.

III.2 Quinonic dienophiles

Symmetrical quinones

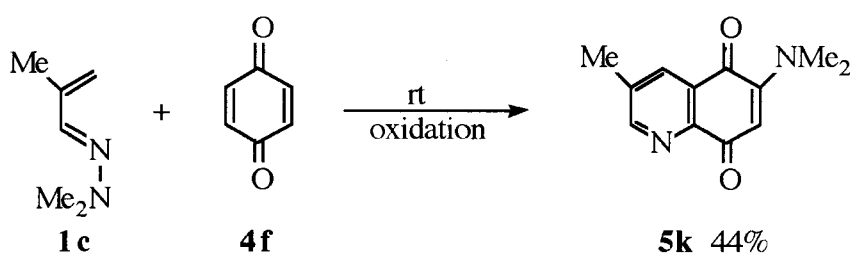
As it is shown from Part II, benzoquinone (**4f**) and naphthoquinone (**2a**) react readily with various azadienes. Due to its structure, quinone (**4f**) may give a double Diels-Alder reaction with dienes. The first literature report describing such cycloadditions is performed with the 3-fluorinated azadiene (**1k**).¹⁸ The aromatized bis-cycloadduct (**17b**) is obtained in low yield after air oxidation and concomitant loss of dimethylamine. Further nucleophilic substitution of the fluorine atom by dimethylamine affords compound (**17c**) (Scheme 29).



Scheme 29

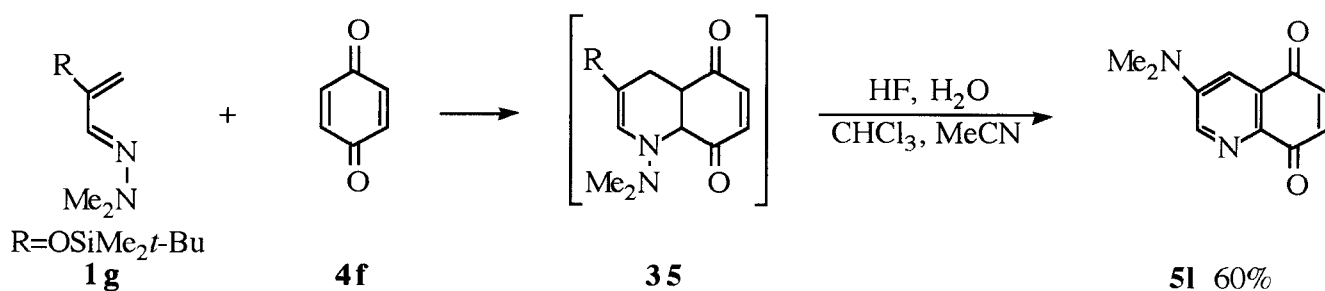
On the other hand, the aromatized mono-cycloadduct is obtained, at ambient temperature and without isolation of the primary cycloadduct, after treatment with silica gel and manganese dioxide (toluene, 25°C, 50 h, 62%).¹⁷

Starting with azadiene (**1c**) and quinone (**4f**), dimethylamine liberated from the primary cycloadduct adds to the quinonic carbon-carbon double bond and prevents the formation of a bis-cycloadduct⁴⁵ (Scheme 30). This regioselective nucleophilic addition of dimethylamine at C-6 of quinone (**5k**) is influenced by the ring nitrogen atom making the C-8 carbonyl more electron deficient than C-5 one. Attempts, not indicated, to avoid this addition remain unsuccessful.⁴⁵ An analogous result is described under ultrasonic conditions (MeCN, rt, 30 min, 50% yield in **5k**).²⁸ Recently, addition of a chloroformylpolystyrene scavenger resin provides a convenient and efficient method for complete suppression of a dimethylamine addition to the cycloadduct. Therefore, 3-methyl- and 3-ethylquinoline-5,8-diones are obtained, in 75 and 73% yields respectively, from benzoquinone and azadienes (**1c**) or (**1e**).⁴⁶



Scheme 30

On the other hand, the cycloaddition of azadiene (**1g**) to benzoquinone affords aminoquinone (**5l**). This latter result from a substitution of the silyloxy group by dimethylamine liberated from the tetrahydro cycloadduct (**35**) in the oxidation step⁵ (Scheme 31).

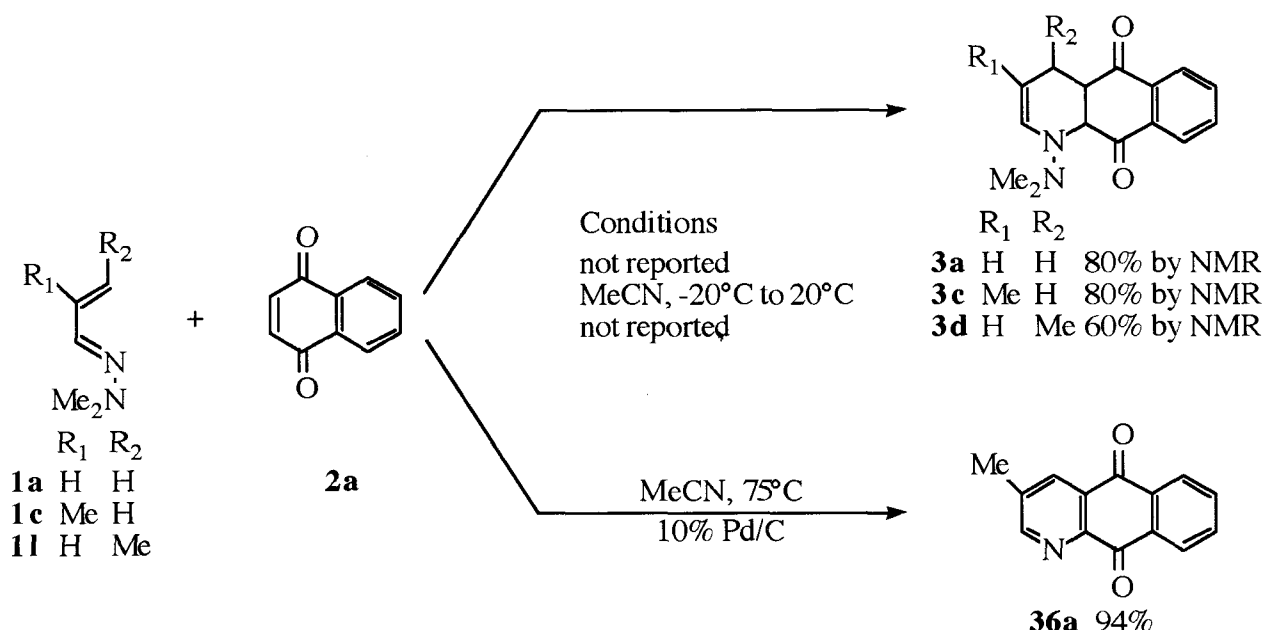


Scheme 31

Several stable *N,N*-dimethylaminotetrahydrocycloadducts, obtained under mild conditions, are isolated from benzoquinone and azadienes (**1c**, ether, 20°C, 2 weeks, 69%)¹², (**6a-b**, ether, 20°C, 24 h, 76% and 92% respectively)¹² and (**1n**, toluene, 25°C, 48 h, 50%).²⁷ In the case of **1n** all experiments carried out with 2-chloro- or 2-bromobenzoquinone afford directly aromatized products devoid of the C-4 stannyl and the N-1 dimethylamino groups. The silyl analogue of **1n** gives a similar reaction only with 2-bromobenzoquinone.²⁷ From these results, it appears that a halogen atom on the carbon-carbon double bond of benzoquinone activates the dienophile and facilitates the formation of aromatized cycloadducts.

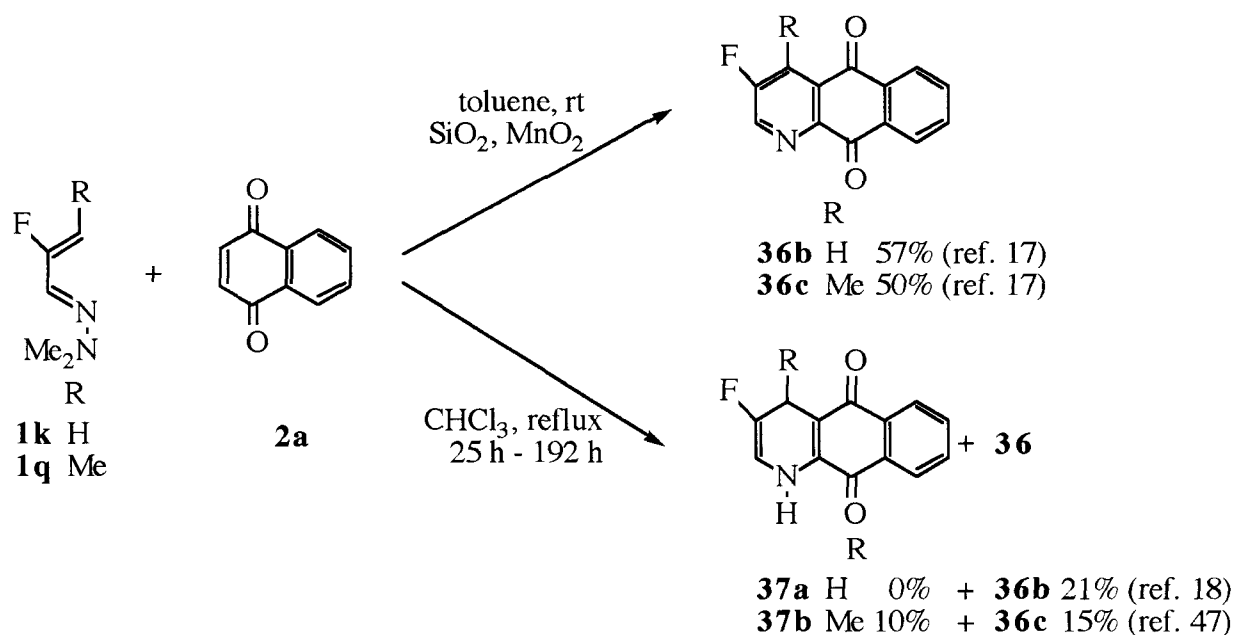
The behavior of 1,4-naphthoquinone in [4+2] cycloaddition reactions towards azadienes (**1a**), (**1c**), and (**1l**) was first reported by Ghosez *et al.*^{5,9} However, these authors did not isolate products from the cycloadditions of azadienes (**1a**), (**1c**) or (**1l**) and quinone (**2a**). The few stable primary adducts were observed by ¹H NMR spectroscopy (Scheme 32). More recently, the mild conditions used under ultrasonic irradiation allowed the isolation of the adduct (**3c**) (MeCN, rt, 30 min, 88%). The latter led to the

aromatized compound (**36a**) after elimination of dimethylamine and air oxidation (1 day, 92%).²⁸ Its formation is also directly observed at higher temperature^{5,9} (Scheme 32).



Scheme 32

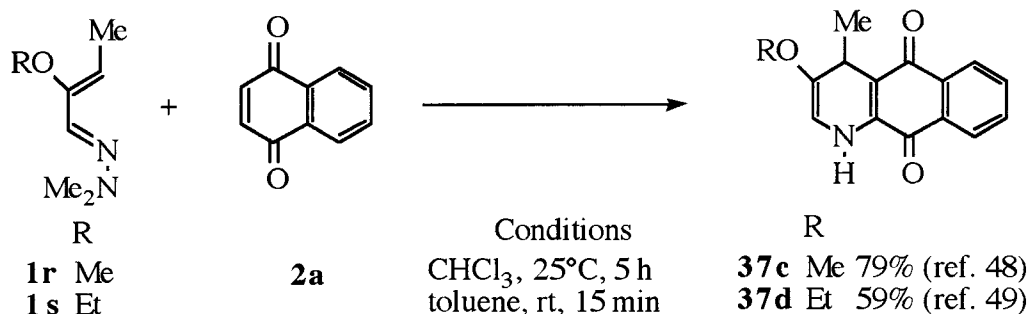
1,4-Naphthoquinone reacts also with the 3-fluorinated 1-azadienes (**1k**) and (**1q**) in the presence of silica gel and manganese dioxide to generate the directly aromatized cycloadducts (**36b**) and (**36c**) in moderate yields.¹⁷ Performing the reaction with **1k** at reflux of chloroform, without silica gel and manganese dioxide, affords **36b** in low yield¹⁸ while the use of **1q** gives the dihydro derivative (**37b**) admixed with **36c**⁴⁷ (Scheme 33).



Scheme 33

Similar 1,4-dihydro derivatives are obtained with other C-4 substituted 1-azadienes (**1r**, **1s**)^{48,49} (Scheme 34). Compounds (**37c**) and (**37d**) are further easily aromatized by treatment with MnO_2 at room

temperature with respective yields of 75 and 86%.^{48,49} A previous cycloaddition of **1r** and **2a** afforded the *N,N*-dimethylaminodihydro cycloadduct (CHCl_3 , 20°C, 2 h, 79%).⁵⁰



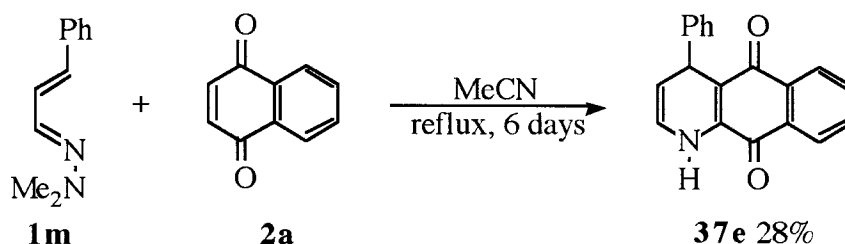
Scheme 34

When 1-azadiene is C-4 substituted by a tributylstannyl group (**1n**), naphthoquinone as well as benzoquinone afford a *N,N*-dimethylaminotetrahydro cycloadduct (toluene, 70°C, 48h, 71%).²⁷

The total synthesis of cleistopholine (**III**) is performed in a one pot synthesis *via* a [4+2] cycloaddition between 2-bromonaphthoquinone and azadiene (**1l**). *In situ* elimination of dimethylammonium bromide from the primary cycloadduct generates the directly aromatized product (xylene, reflux, 6 h, 52%). Similarly, methoxycleistopholine and homocleistopholine are obtained from appropriate C-4 substituted 1-azadienes (4-OMe, 12%; 4-Et, 14%).⁵¹⁻⁵³ The use of a chloroformylpolystyrene electrophilic resin as a dimethylamine scavenger is applied with various results to this previous synthesis.⁴⁶

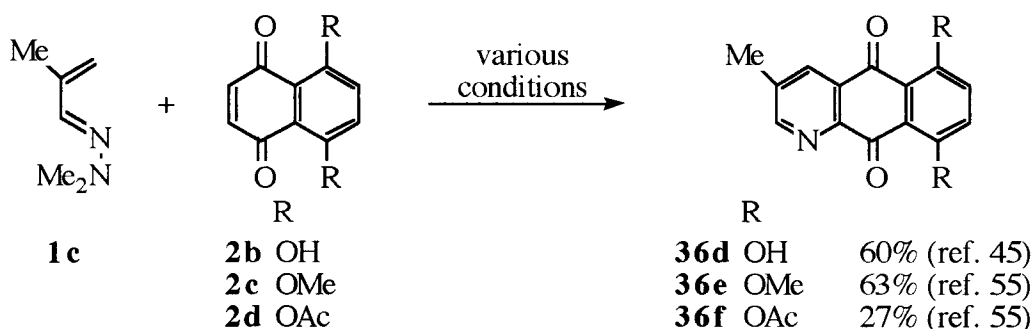
When 1-azadiene bears a methoxycarbonyl substituent at C-4, its reactivity towards naphthoquinone is low (16% yield in dihydro cycloadduct).²⁶ The use of 2-bromonaphthoquinone improves the yield of the reaction and affords directly the corresponding azaanthraquinone (toluene, NaHCO_3 , reflux/argon, 24 h, 53%).²⁶

In contrast with benzoquinone which does not react, a limited success is obtained in the reaction of naphthoquinone with cinnamoyl *N,N*-dimethylhydrazone (**1m**) (Scheme 35). The dihydroazaanthraquinone derivative (**37e**) arises from a Diels-Alder reaction followed by dimethylamine elimination and isomerization of the double bond.²⁴ *ortho* Substitution at the phenyl group of **1m** yields intractable mixtures of products.^{24,54}



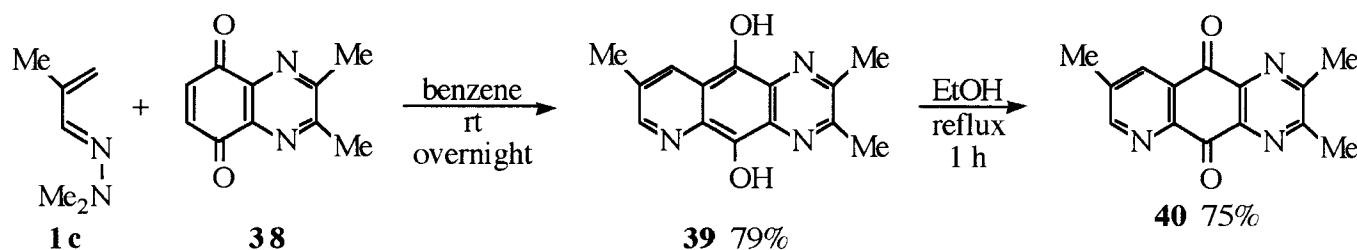
Scheme 35

Naphthazarine (**2b**) and its methyl or acetyl derivatives (**2c**) or (**2d**) undergo readily Diels-Alder reactions with azadiene (**1c**).^{45,55} Treatment of cycloadducts with Ag_2O ⁴⁵ or DDQ⁵⁵ affords azaanthraquinone derivatives which can be used as synthons in the building of heterocyclic analogues of anthraquinones (Scheme 36).



Scheme 36

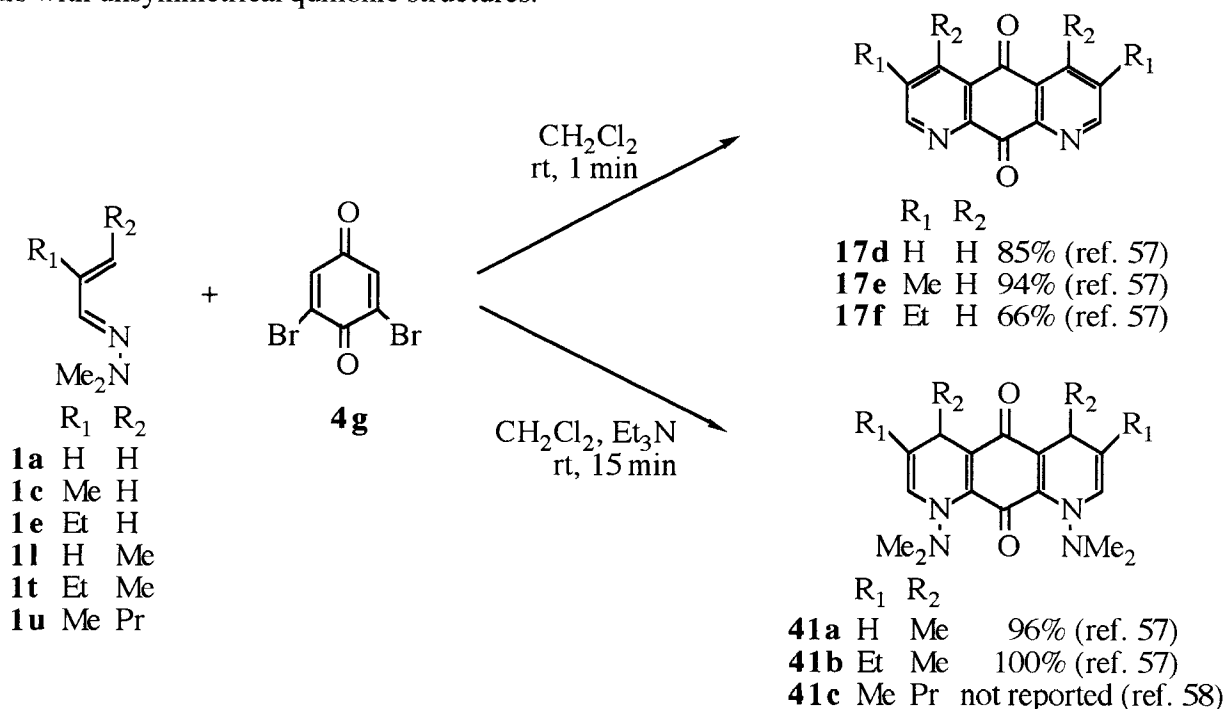
Finally, the reaction of 2,3-dimethylquinoxaline-5,8-dione with azadiene (**1c**) is successfully performed in benzene solution at room temperature^{45,56} (Scheme 37). The stable intermediate (**39**) proceeds from a tautomer of the initial 1:1 cycloadduct which eliminates dimethylamine. This result establishes that the elimination process precedes the oxidation step. Aromatization of **39** to **40** occurs in boiling ethanol.



Scheme 37

Unsymmetrical 1,4-quinones

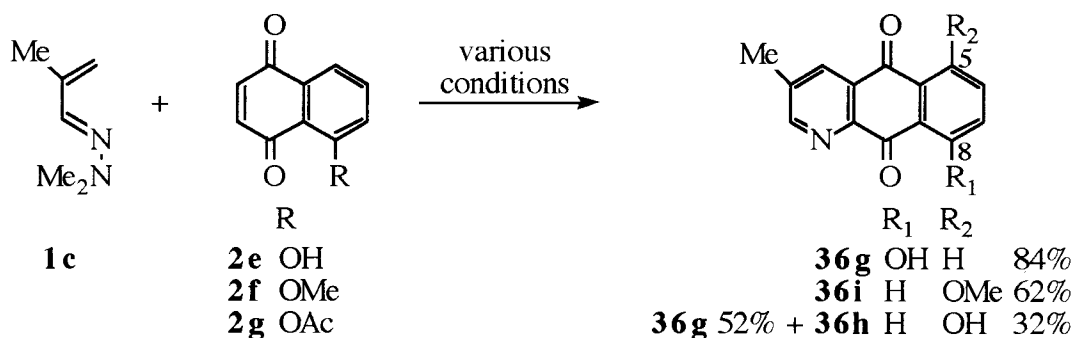
Among 1,4-quinones, the unsymmetrical benzoquinones used are halogenated ones. As shown from Part II, Diels-Alder reactions of bromoquinone (**4a**) and chloroquinones (**4b-e**) with azadienes (**1a**), (**1b**) and (**1c**) allow the exclusive formation of a single regioisomeric cycloadduct^{10,15} (Schemes 3, 10). Other examples of double cycloadditions^{57,58} are given in Scheme 38. The second Diels-Alder reaction occurs with unsymmetrical quinonic structures.



Scheme 38

In contrast with benzoquinone itself (Scheme 29), high yields of bis-cycloadducts are obtained from 2,6-dibromobenzoquinone. Indeed, the presence of a bromine atom activates the quinonic double bond and accelerates the Diels-Alder reactions. In the case of compounds (**17**), hydrogen bromide liberated from the oxidation step can be trapped with dimethylamine formed.⁵⁷ The absence of spontaneous aromatization of cycloadducts (**41**) is attributed, by authors, to the steric effect of C-4 alkyl substituents on azadienes (**11**, **1t**, **1u**), as previously observed. In all these examples a similar total regioselectivity is obtained. This orientation results from a nucleophilic attack by C-4 of 1-azadienes to the unsubstituted carbon atom of the quinonic double bond. Recently, these double hetero Diels-Alder reactions were reexamined.⁵⁹ Thus, treatment of 2-bromobenzoquinone with two equivalents of 1-azadiene (**1d**) afforded a mixture of the corresponding 1,5-diaza- and 1,8-diaza-9,10-anthraquinones in 18 and 35% yields respectively. In order to obtain dissymmetrically substituted derivatives of 1,8-diazaanthraquinones, a methodology to control the incorporation of two different 1-azadienes was successfully elaborated.

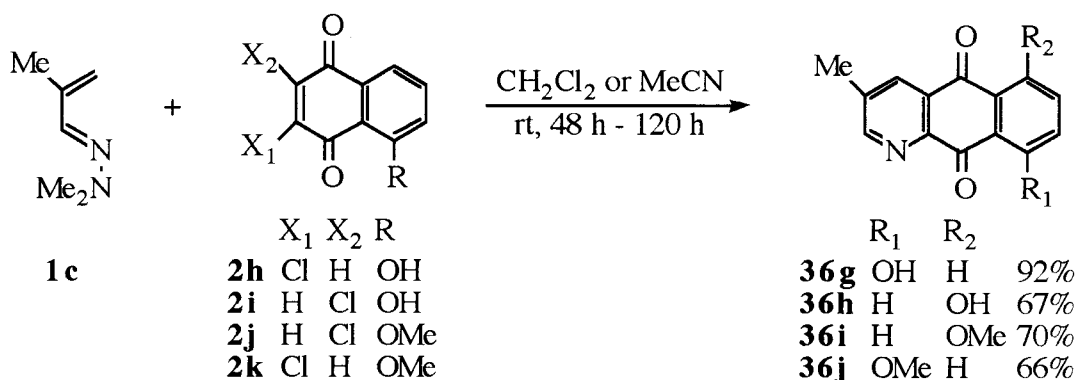
Juglone (**2e**) and its methyl or acetyl derivative (**2f**) or (**2g**) are attractive unsymmetrical quinonic dienophiles for Diels-Alder reactions. Their first cycloadditions towards an azadiene were performed by Potts *et al.*^{45,56} (Scheme 39).



Scheme 39

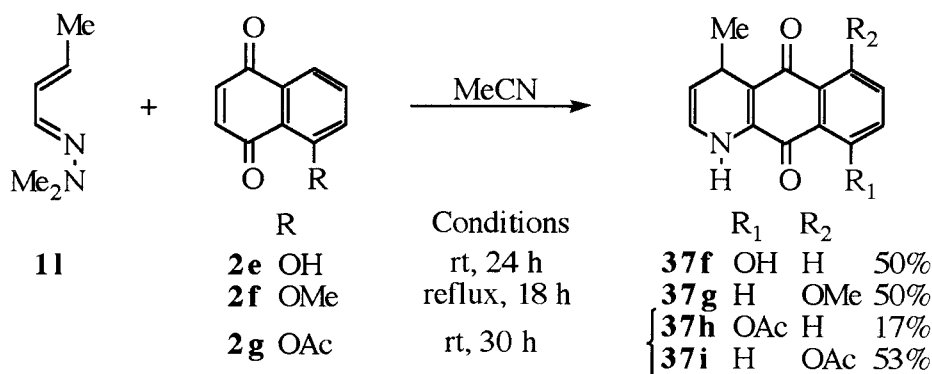
It appears from Scheme 39 that the cycloadditions of **1c** with juglone (**2e**) or methyljuglone (**2f**) are totally regioselective. Structural assignment for **36g** agrees with the well known electron-withdrawing effect exerted by the 5-hydroxy group on the adjacent carbonyl making C-2 electron deficient.⁶⁰ The opposite regiochemistry observed with **2f** is attributed to the electron-donating influence of the 5-methoxy substituent making C-3 more electron deficient. Starting with acetyljuglone (**2g**), in the same experimental conditions, no acetate derivatives are detected. But, a mixture of 5- and 8-hydroxylated regioisomers (**36h** and **36g**) is identified. Formation of these products results from the removal of the acetyl group by dimethylamine eliminated from the primary cycloadduct both before and after the cycloaddition step.

In order to obtain selectively these different regioisomers, a control of the regiochemistry is reached by the use of 2-chloro- or 3-chloro-5-substituted naphthoquinone¹⁵ (Scheme 40). Indeed, the halogen atom exerts a stronger regiochemical control than other existing constraints. This methodology which was employed with 2-azadienes,⁶¹ was not previously evaluated in the case of 1-azadienes. Juglone and methyljuglone with inversed electronic effects induce the same regiochemistry when they are substituted by a bromine or a chlorine atom at the same position. Like for bromobenzoquinone, the electron-rich end (C-4) of 1-azadiene adds to the unsubstituted carbon atom of the quinonic double bond.



Scheme 40

The behavior of azadiene (**11**) towards unsymmetrical quinones was first examined in our group⁶² (Scheme 41). Juglone (**2e**) and methyljuglone (**2f**) gave respectively a single dihydro cycloadduct according to the expected regioselectivity. Using acetyljuglone (**2g**) as a dienophile, and to avoid a further deacetylation by the liberated dimethylamine, we performed the cycloaddition reaction in the presence of acetic anhydride. The reaction was only highly regioselective. The 5-acetoxy group induces a similar but weaker orientational effect than the 5-methoxy one.

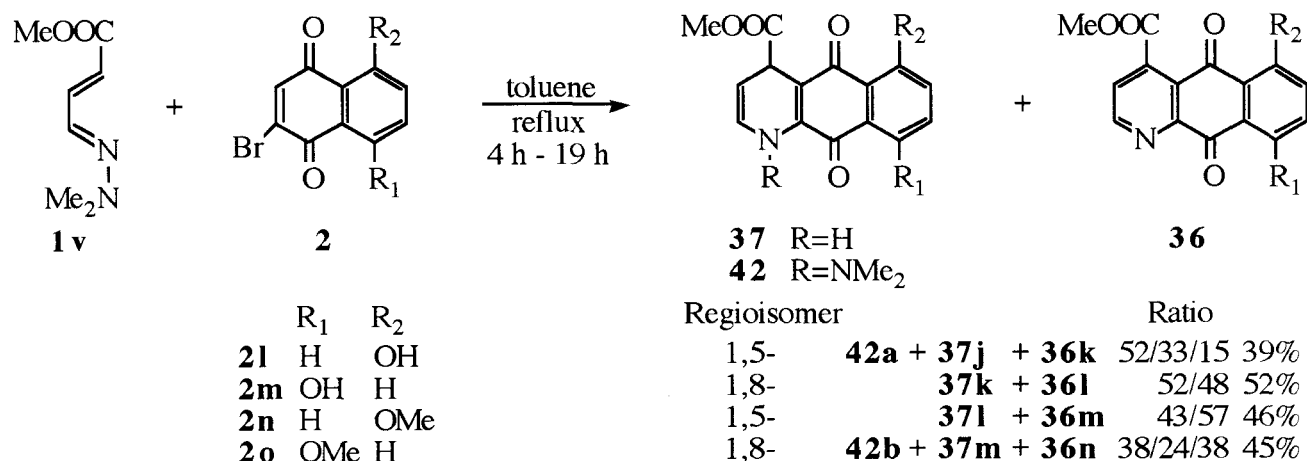


Scheme 41

Further oxidation of **37f** and **37g** with activated manganese dioxide afforded the corresponding azaanthraquinones. Moreover, azadiene (**11**) is less reactive towards juglone and its derivatives than **1c**. This lower reactivity is explained by the lack of the C-3 activating substituent. In order to improve the yields, the non-conventional ultrasound and high pressure conditions were envisaged.⁶³ Thus, ultrasonic irradiation, carried out under similar experimental conditions than the conventional one, increases the reaction rate of **11** towards juglone (silent reaction, 24 h, 48%; ;), 6 h, 52%). But, an enhancement in the dimethylamine addition on the starting quinone is observed. The use of high pressure (10 kbars, 6 h) leads to a similar yield (48%) while only traces of aminoquinones are formed.

We also studied the behaviour of 1-azadiene (**1v**) towards juglone and its methyl derivative. This C-4 substituted azadiene by an electron-withdrawing group reacts slowly, at reflux of toluene, to give the 1,4- dihydro derivatives in low yield (9%) and without any selectivity.²⁶ So, we turned out our attention to the use of bromojuglones. Under the same experimental conditions, a mixture of dihydro (**37**, **42**) and aromatized (**36**) cycloadducts is obtained with an increased yield (Scheme 42). Formation of the dihydro derivatives (**37**) is probably due to the N-N bond cleavage in compounds (**42**) by hydrogen bromide

liberated from the primary adducts. Carrying out the reaction in the presence of two equivalents of sodium hydrogencarbonate, at reflux of xylene, give directly the aromatized compounds (**36**).

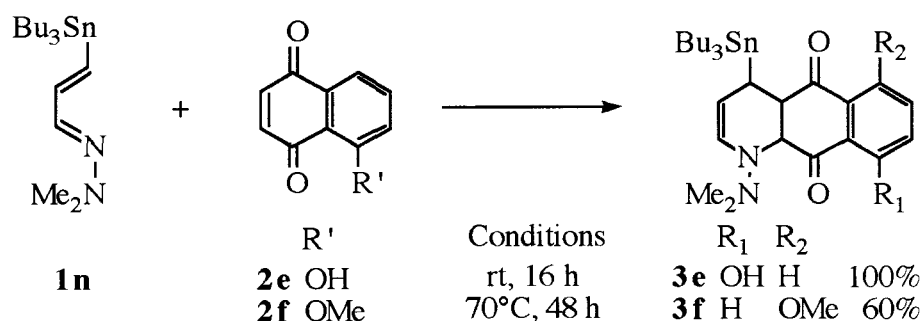


Scheme 42

Under the reaction conditions, a nucleophilic addition of dimethylamine occurs on the starting quinones. The structure elucidation of these aminoquinones is confirmed by a study on the oxidative addition of dimethylamine to bromojuglones and bromomethyljuglones at various temperatures.⁶⁴

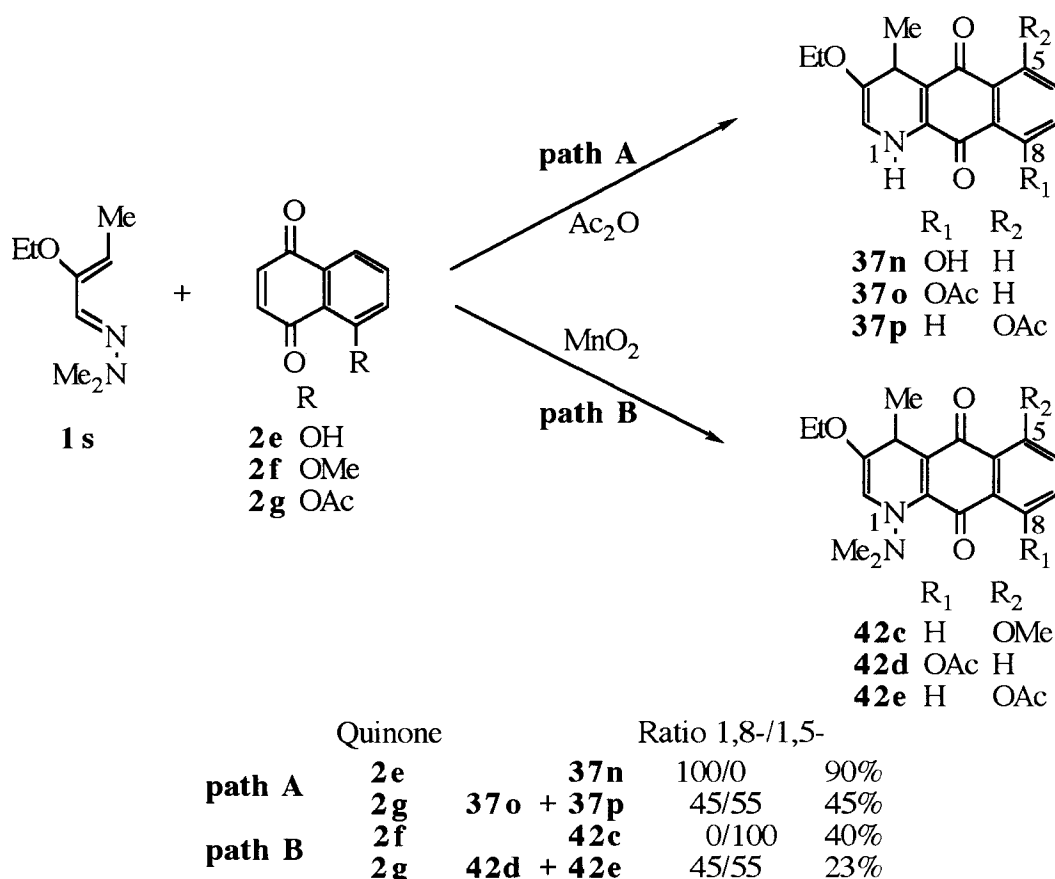
Concerning the regiochemistry of the cycloadditions, the 1,5-regioisomers are obtained from 2-bromoquinones (**2l**, **2n**) while the 1,8-regioisomers are formed from 3-bromoquinones (**2m**, **2o**). So, the regioselectivity is independent of the nature of the C-5 substituent (OH, OMe) but, it is due to the position of the bromine atom on the carbon-carbon double bond of the corresponding naphthoquinone.

Stable tetrahydro derivatives are formed with a tributylstannyl group at C-4 of 1-azadiene²⁷ (Scheme 43). The cycloaddition is quantitative with juglone and the expected regiochemistry is observed. Experiments carried out with 2-chloro or 2-bromoquinones provide aromatized products lacking the stannyl group.



Scheme 43

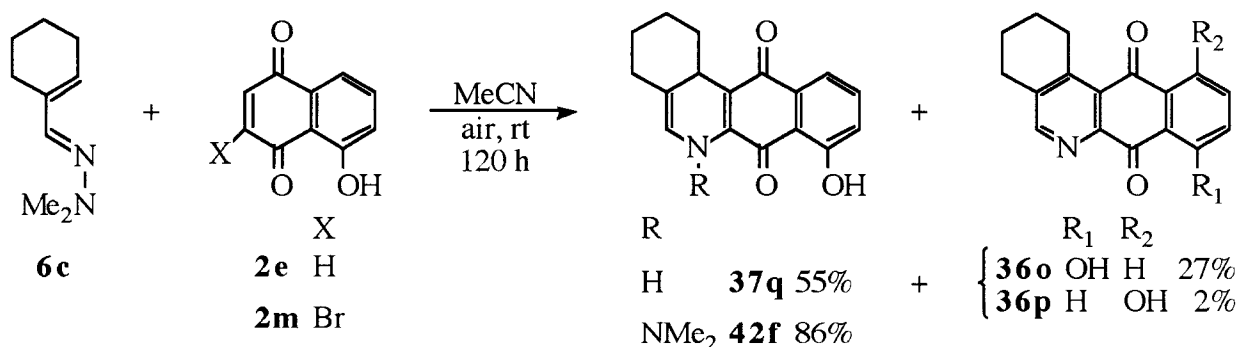
The first example of cycloaddition with a disubstituted diene in the juglone series was realized in our group with azadiene (**1s**).^{49,65} We found that the latter reacts faster than **1l** and gave higher yields (Scheme 44). In path A, the cycloadditions were carried out in the presence of acetic anhydride to avoid a nucleophilic attack of the liberated amine on the starting quinones while in path B, addition of MnO₂ led to the stable *N,N*-dimethylamino derivatives (**42**). With **2e** and **2f** the cycloadditions are totally regioselective. The regiochemistry follows the expected directing effects of the 5-hydroxy and 5-methoxy groups. In contrast, acetyljuglone gives a poor regioselectivity.



Scheme 44

Oxidation of compounds (**37**) is easily performed with activated manganese dioxide. In the case of the *N,N*-dimethylamino derivatives (**42**), the aromatization by SiO_2 treatment is accompanied with a nucleophilic displacement of the ethoxy group by dimethylamine.⁴⁹

The cycloaddition between juglone and azadiene (**6c**) provides hexahydrobenzo[*b*]phenanthridine (**37q**) in 55% yield along with tetrahydrobenzo[*b*]phenanthridines (**36o**) and (**36p**)^{66,67} (Scheme 45). In the presence of oxygen, quinones (**37q**) and (**36o**) are formed in 18 and 47% yields respectively. The high regiocontrol observed in these cycloadditions is ascribed to the well polarized azadiene (**6c**). Indeed, FMO calculations indicate that the C-4 primary orbital possesses a larger HOMO coefficient than the N-1 atom. On the other hand, these authors explain the absence of reactivity of benzaldehyde *N,N*-dimethylhydrazone towards naphthoquinones by the low polarization and energy of its HOMO. Starting with 3-bromojuglone and in the presence of sodium hydrogencarbonate to avoid by-products formation, the reaction proceeds cleanly providing the stable compound (**42f**) in 86% yield. Heating **42f** in the presence of hydrogen chloride affords the aromatized derivative (**36o**) (78%).



Scheme 45

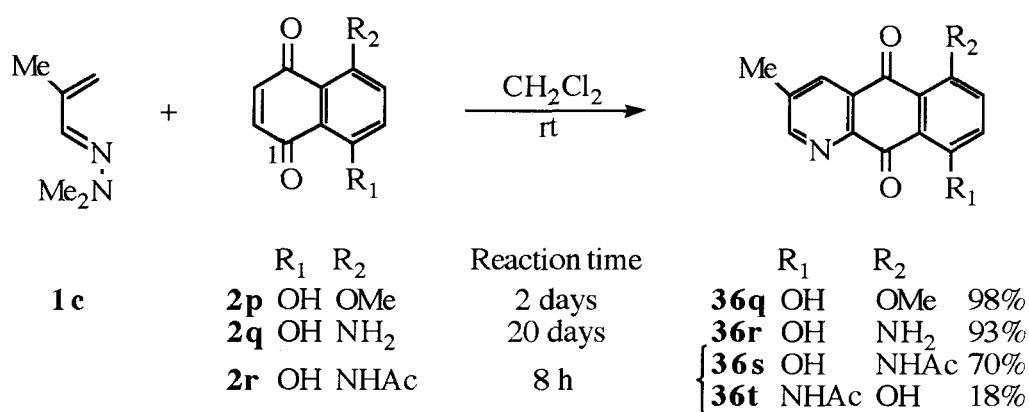
In all the above experiments, the regiochemistry observed in the cycloadditions of juglone and its methyl or acetyl derivatives with different 1-azadienes agrees with the opposite electronic effects of the 5-hydroxy group on one hand and the 5-methoxy or 5-acetoxy substituent on the other hand. In the case of halogenated quinones, the addition of the nucleophilic end (C-4) of azadienes to the unsubstituted carbon atom of dienophiles is independent from the nature of the 5-substituent. In fact, the regiochemical control results from the blocking effect of the halogen atom in the initial step of the cycloaddition. In search for a better understanding of the behavior of halogenated quinones in cycloaddition reactions, the FMO theory was applied. As shown in Part II, larger values for HOMO coefficients for some 1-azadienes are located at C-4 (Scheme 28). Calculations give similar results for azadienes (**1s**) (C-4: 0.4085; N-1: 0.306)⁴², (**1v**) (C-4: 0.392; N-1: 0.268) and (**6c**) (C-4: 0.3593; N-1: 0.1962).⁶⁶ Values for the LUMO coefficients of quinonic dienophiles are reported in Table 1. They are calculated by the semiempirical PM3 method⁴³ except for methyljuglone and its derivatives where the AM1 method is used.⁶⁸

Table 1. LUMO orbital coefficients for quinonic dienophiles

Quinone	C-2	C-3
Juglone	0.357	0.335
Methyljuglone	0.320	0.330
Acetyljuglone	0.284	0.295
2-Bromojuglone	0.374	0.363
3-Bromojuglone	0.386	0.351
2-Bromomethyljuglone	0.340	0.358
3-Bromomethyljuglone	0.353	0.356
2-Bromoacetyljuglone	0.315	0.336
3-Bromoacetyljuglone	0.326	0.327

For juglone, the larger values are located at C-2 while those of methyl and acetyljuglone are situated at C-3. Therefore, the major regioisomers may result from the interaction between the C-4 end of azadienes and C-2 carbon of juglone or C-3 of methyl and acetyljuglone. This predicted inversion of the regiochemistry is effectively confirmed by experiments. For 2-bromo- and 3-bromojuglones, the larger coefficients are always located at C-2 while they are situated at C-3 for bromomethyl- and bromoacetyljuglones. These results do not agree with the inversed regioselectivities experimentally observed for bromojuglones and bromomethyljuglones cycloadditions (Schemes 40, 42). These calculations remain insufficient to explain the exact nature of the orientational effect of the halogen atom. More accurate methods, such as *ab initio* calculations, would be envisaged.

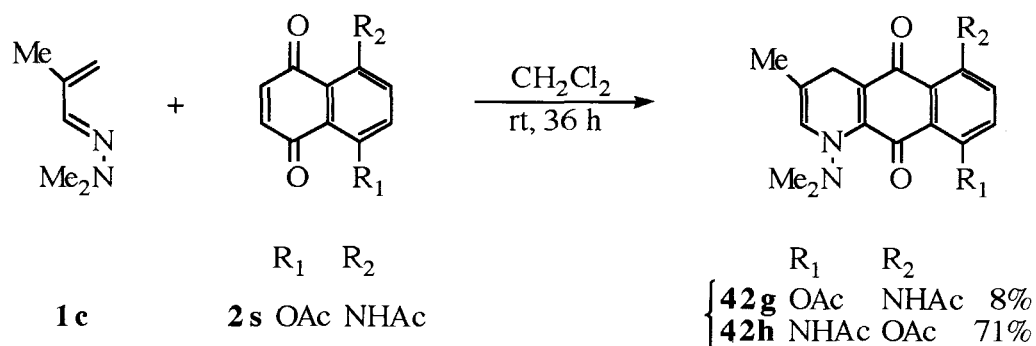
The cycloaddition reactions with 5,8-disubstituted naphthoquinones (**2p-s**) undergo regioselectivities directed by the electronic effect of R₁ or R₂.⁵⁵ In the case of **2p-r** the aromatized cycloadducts are directly obtained (Scheme 46).



Scheme 46

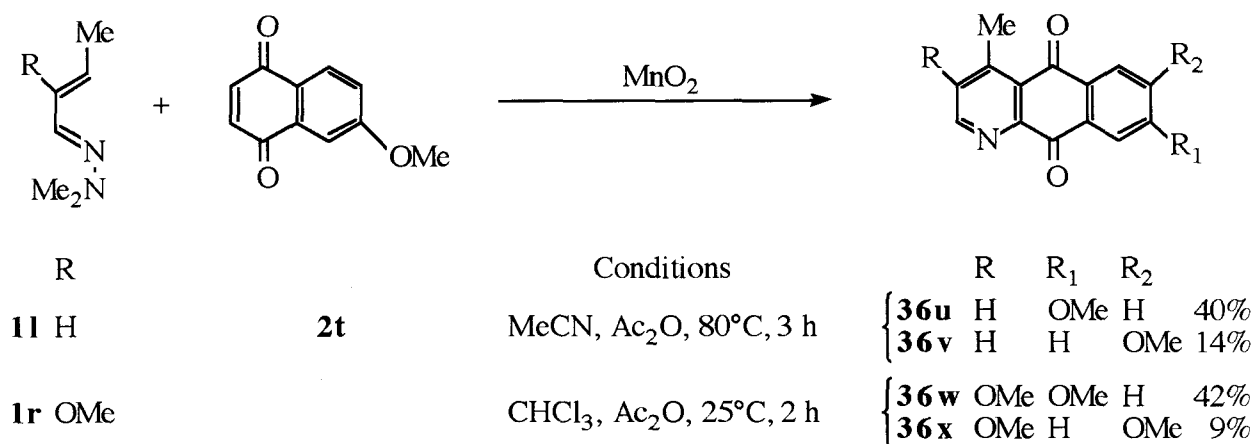
The complementary electronic effects of 5-hydroxy and 8-methoxy groups explain the total regioselectivity observed with **2p**. In **2q**, the intramolecular hydrogen bonding of the *peri*-OH group is stronger than the *peri*-NH one.⁶⁹ This feature is in agreement with the formation of the regioisomer (**36r**). The regioselectivity observed in the cycloaddition of **2r** can be interpreted in terms of a competition between the activation of CO-1 and CO-4 by OH and NHAc groups.

With quinone (**2s**), a mixture of dihydro cycloadducts is obtained. The regioselectivity is attributed to the larger electronic effect due to a hydrogen bonding which exists between the NHAc group and the C-4 carbonyl (Scheme 47).



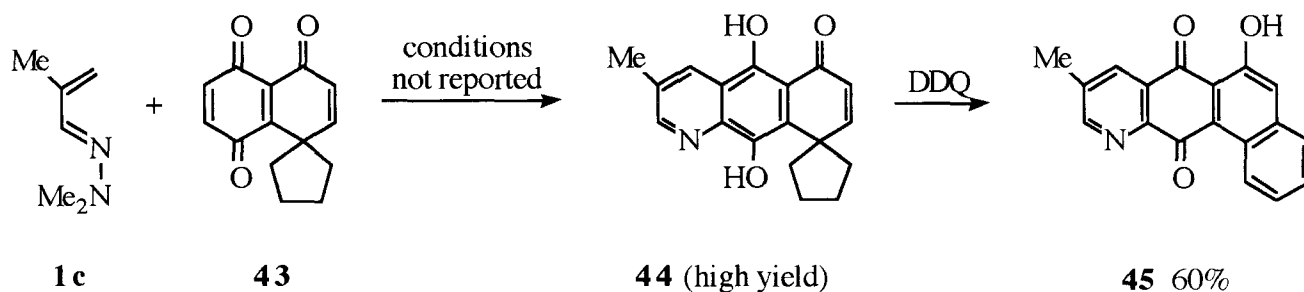
Scheme 47

A series of intermediates of the total synthesis of the aromatic eupomatidines alkaloids was obtained from the hetero Diels-Alder reactions of azadienes (**1l**) or (**1r**) and 6-methoxy-1,4-naphthoquinone⁴⁸ (Scheme 48). The unseparable mixture of dihydro derivatives was oxidized with MnO_2 to give azaanthraquinones (**36u-x**). The favored regiochemistry observed corresponds to the electron-donating effect of the 6-methoxy group.⁷⁰ As expected, the reactions of 2-bromo and 3-bromo derivatives of **2t** with azadiene (**1r**) proceed regioselectively and give **36x** and **36w** in 32 and 53% yields respectively. These compounds are useful synthons to obtain the corresponding eupomatidines.



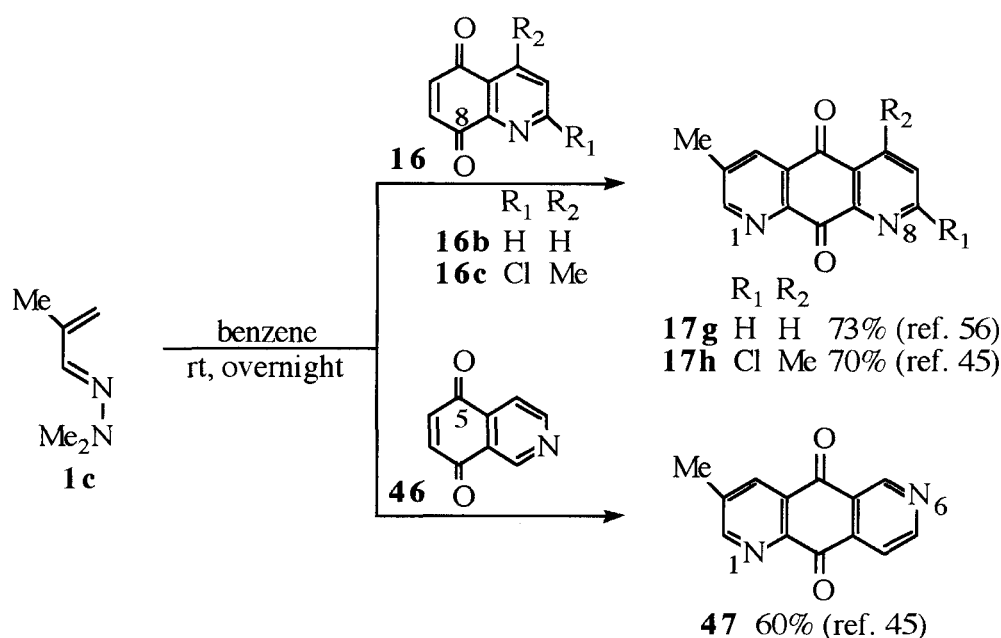
Scheme 48

An efficient method to synthesize the benz[*a*]azaanthraquinone (**45**) through the cycloaddition of **43** with azadiene (**1c**) affords the intermediate (**44**).⁷¹ Its structure elucidation is based on the HOMO-LUMO interactions of quinone (**43**) with azadiene (**1c**) by using the semiempirical AM1 method. Its oxidation with DDQ into quinone (**45**) proceeds probably *via* a dienone-phenol rearrangement⁷¹ (Scheme 49).



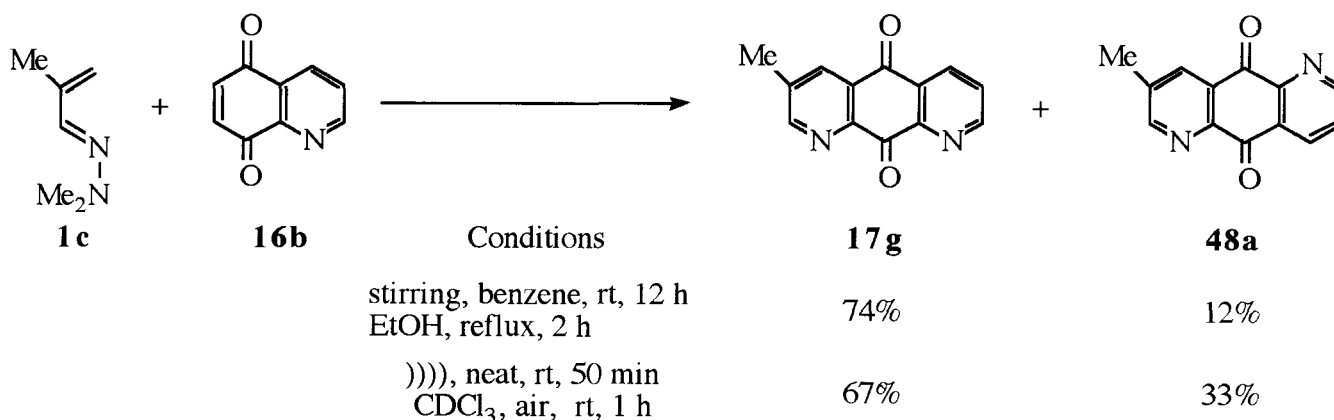
Scheme 49

The diazaanthraquinone framework is present in numerous biologically active alkaloids. Therefore, construction of this ring system through Diels-Alder reactions of quinoline or isoquinonoline diones with 1-azadienes was largely explored. In their first experiment with azadiene (**1c**), Potts *et al.*^{45,56} did not isolate the primary cycloadducts. The latter were directly air oxidized in boiling ethanol to afford the corresponding 1,8- or 1,6-diazaanthraquinones (**17g-h**) or (**47**) (Scheme 50). The regiochemistry observed is consistent with the control exerted by the ring nitrogen atom relative to the carbonyl groups. Indeed, the electron-withdrawing effect of the nitrogen atom makes the C-8 carbonyl of quinoline-5,8-diones (**16b-c**) and the C-5 one of isoquinoline-5,8-dione (**46**) more electron deficient directing the nucleophilic C-4 end of azadiene (**1c**) to attack C-6 or C-7 carbons of these dienophiles.



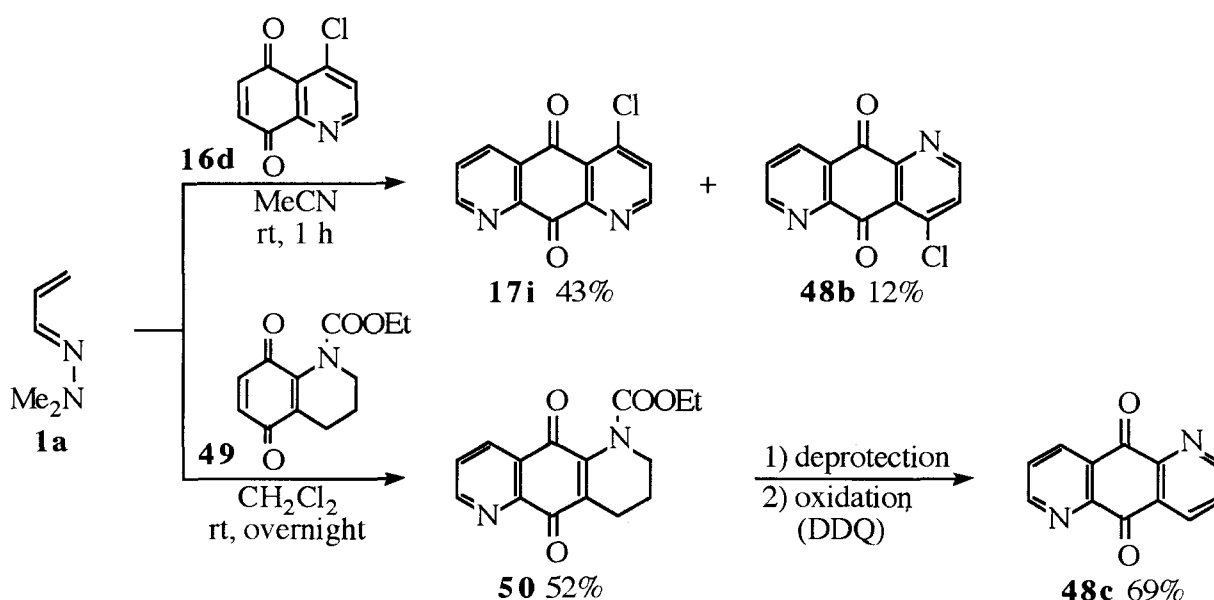
Scheme 50

A regioselectivity was also observed with the unsubstituted quinoline-5,8-dione (**16b**) and azadienes (**1k**)¹⁸ or (**1g**).⁷² However, by modifying the cycloaddition conditions between **1c** and **16b**, the reported regioselectivity dropped to give 12% of the 1,5-regioisomer (**48a**).⁷² More recently, this reaction was reexamined under thermal and ultrasonic conditions. Under sonication an increase of kinetic and yield of the reaction was observed, but with a slight loss of regioselectivity²⁸ (Scheme 51).



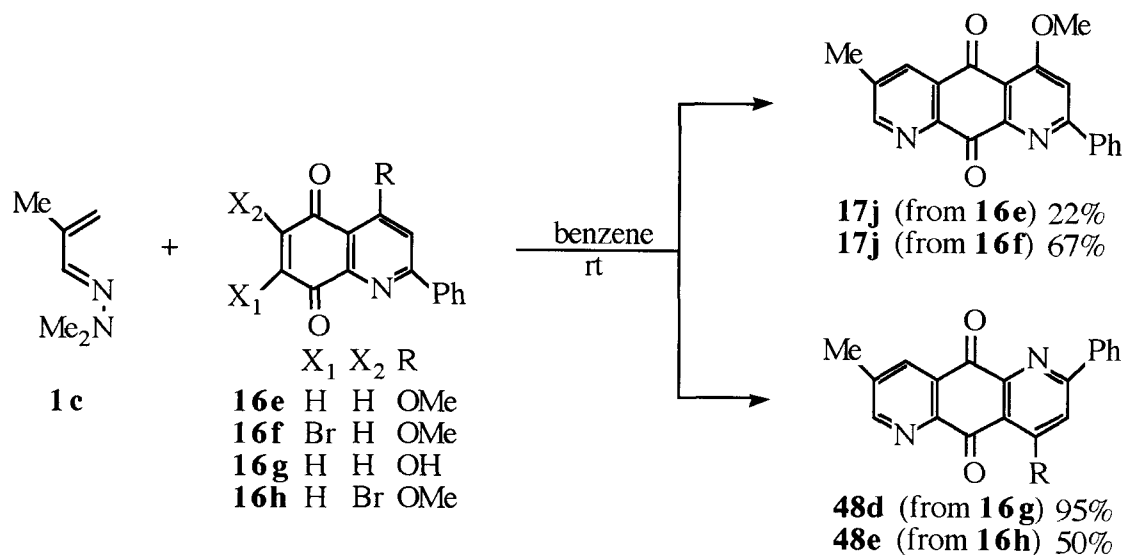
Scheme 51

In search for a method to obtain regioselectively the 1,5-regioisomer, introduction at C-4 of quinoline-5,8-dione of a substituent having a stronger and an opposite regiochemical control than the ring nitrogen atom was envisaged. Thus, dienophiles (**16d**) and (**49**) possessing respectively a chlorine or an ethoxycarbonyl group were expected to have the C-5 carbonyl more electron deficient⁷³ (Scheme 52). The cycloaddition between **1a** and **16d** gives the 1,8-regioisomer (**17i**) as the main product. Therefore, the chlorine atom has no significant effect on the regioselectivity. In contrast, a strong electron-withdrawing substituent like the ethoxycarbonyl group produces a reverse in the selectivity of the reaction. Thus, tetrahydroquinoline-5,8-dione (**49**) is a valuable precursor to synthesize 1,5-diazaanthraquinone (**48c**).



Scheme 52

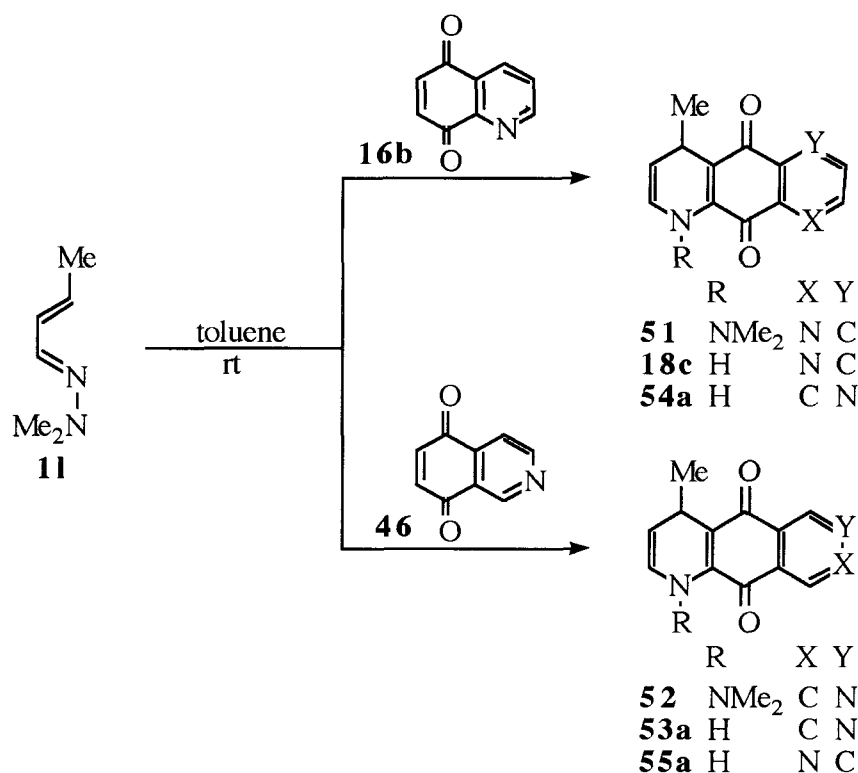
Another method to access to this kind of regioisomer is to use the regio directing effect of halogen atom at the dienophilic double bond. Effectively, an inversion of the regioselectivity is observed between 6-bromo- and 7-bromoquinones (**16f**) and (**16h**)⁷⁴ (Scheme 53). It appears from this Scheme that quinones (**16e**) and (**16f**) react with **1c** to give the cycloadduct (**17j**) as a single product. The low yield obtained from **16e** corresponds to a competitive reverse Diels-Alder reaction in the aromatization step. With **16g** and **16h**, an inversed regioselectivity is observed comparatively to the previous one. This result is due to the directing effect of the 4-hydroxyl group (similar to that of juglone) or to the 6-bromine atom. Therefore, the 4-hydroxyl group provides another method for the synthesis of 1,5-diazaanthraquinone ring system. Moreover, the brominated dienophiles react faster than others (respective reaction time for **16f** : 15 min; **16h** : 30 min; **16e** and **16g** : 3 h).



Scheme 53

The cycloadditions of azadiene (**11**) to quinoline-5,8-dione and isoquinoline-5,8-dione are studied under thermal and ultrasonic conditions⁶³ (Scheme 54). Under the experimental conditions reported, the stable

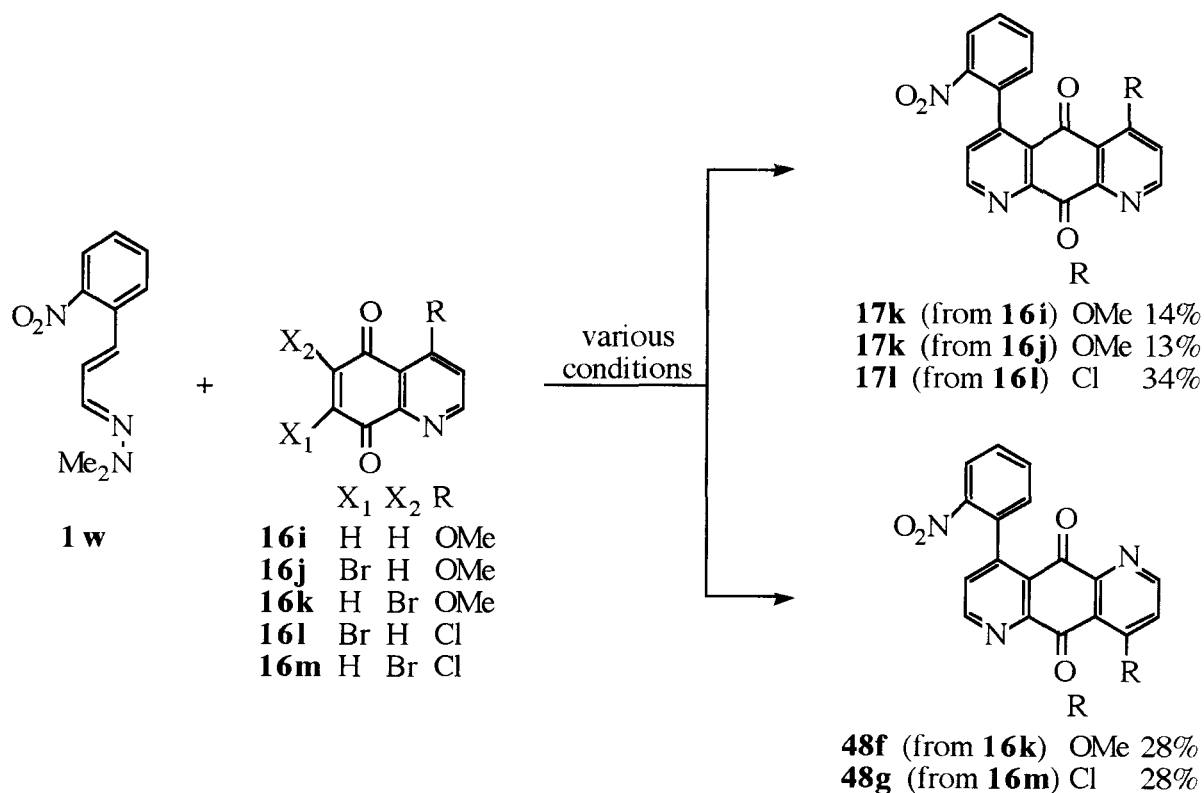
dihydro-*N,N*-dimethylamino derivatives (**51**) and (**52**) are isolated from quinones (**16b**) or (**46**). Starting with **16b**, sonication leads to an overall yield lowered by 10% than in the silent reaction, due to the absence of the *N,N*-dimethylamino derivative. In contrast, quinone (**46**) yields always to a mixture of the same three products (**52**), (**53a**) and (**55a**). Under stirring (6 h), no traces of cycloadducts are observed. But, after a longer time, a higher overall yield with a larger amount of *N,N*-dimethylamino compound (**52**) is obtained. The regioselectivity of the cycloaddition is slightly affected by ultrasound.



Quinone	Conditions	Ratio
16b	stirring, 6 h	18c + 54a 80/20 35%
16b	))))), 6 h	51 + 18c + 54a 22/62/16 45%
46	stirring, 48 h	52 + 53a + 55a 51/34/15 65%
46	))))), 6 h	52 + 53a + 55a 38/38/24 48%

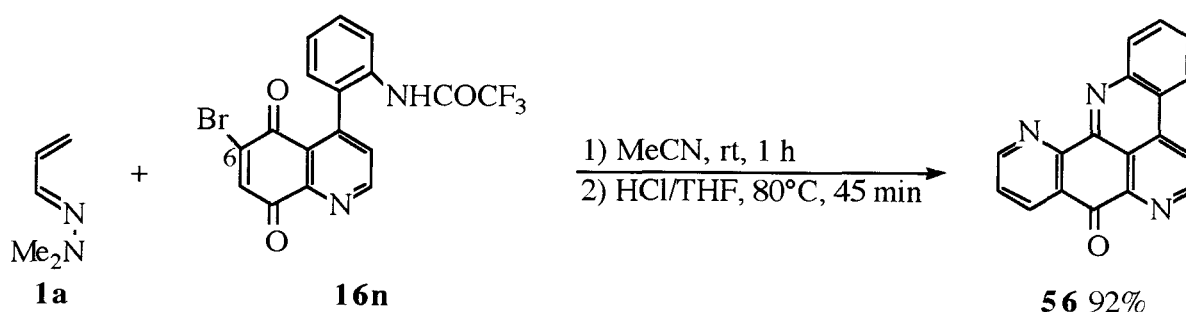
Scheme 54

A limited success is observed in the cycloaddition reaction of the C-4 aryl substituted azadiene (**1w**) and quinoline-5,8-dione (**16i**). Under standard conditions, oxidation of the dihydro cycloadduct affords only 6% of the aromatized derivative (**17k**).²⁵ Due to the interest of this intermediate in the synthesis of biologically active pentacyclic alkaloids (meridine, cystodamine) various experimental conditions are attempted^{75,76} (Scheme 55). To improve the yield, the cycloaddition is carried out in the presence of acetic anhydride and silica gel at reflux of various solvents. Addition of Lewis acid is also effective. Using haloquinones (**16j-m**), better yields are obtained. With 2-bromoquinones (**16j**) and (**16l**), large amounts of dihydro derivatives (respective yields 14% and 21%) are also formed. After reduction of the nitro group, compounds (**17**) and (**48**) are annelated to the corresponding pentacyclic structures.



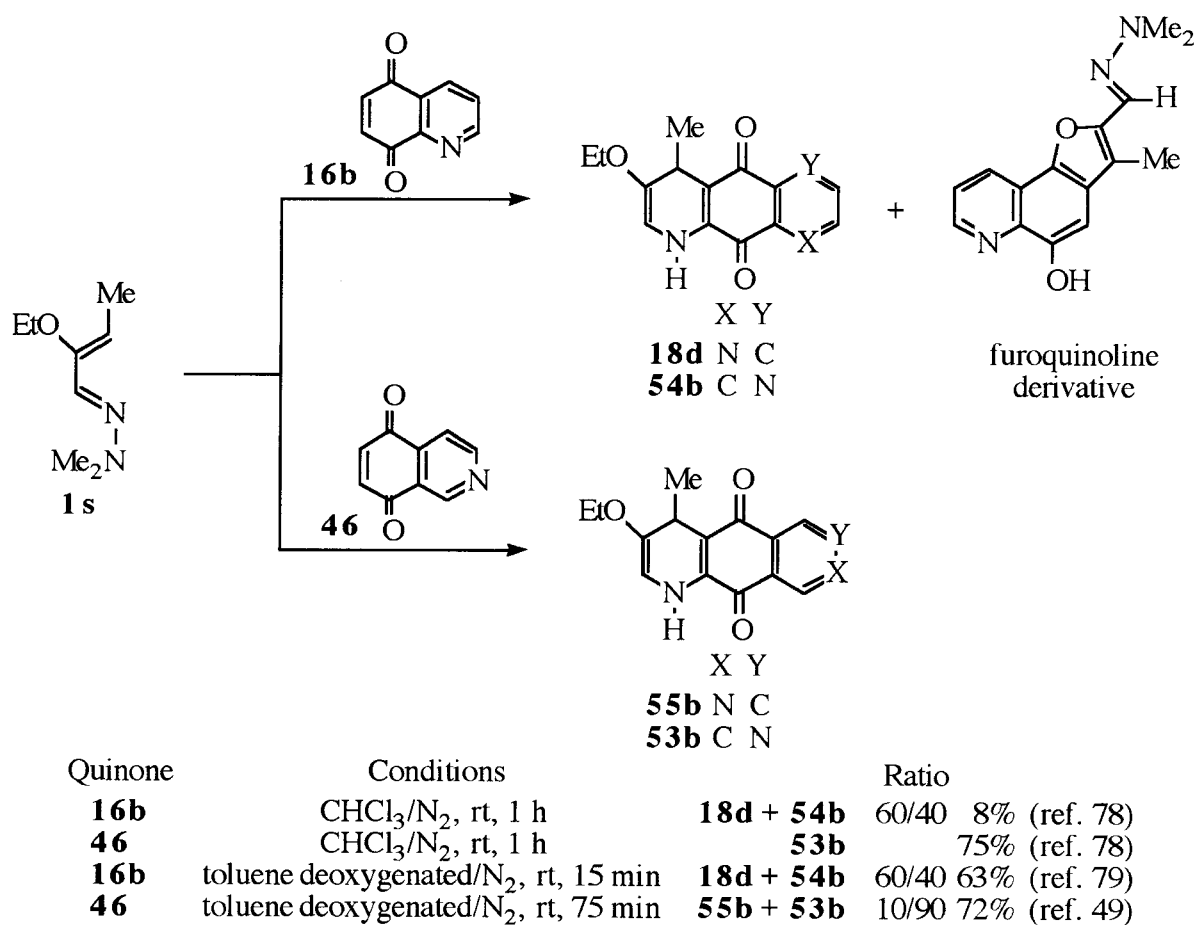
Scheme 55

An alternative route to obtain this kind of compound was successfully established by the cycloaddition reaction between the unsubstituted azadiene (**1a**) and 6-bromoquinoline-5,8-dione (**16n**). The cycloadduct intermediate was directly annelated, without characterization, by acidic treatment into isoascididemin (**56**)^{77a} (Scheme 56). An analogous strategy was recently applied to the synthesis of regioisomeric amphimedine derivatives.^{77b}



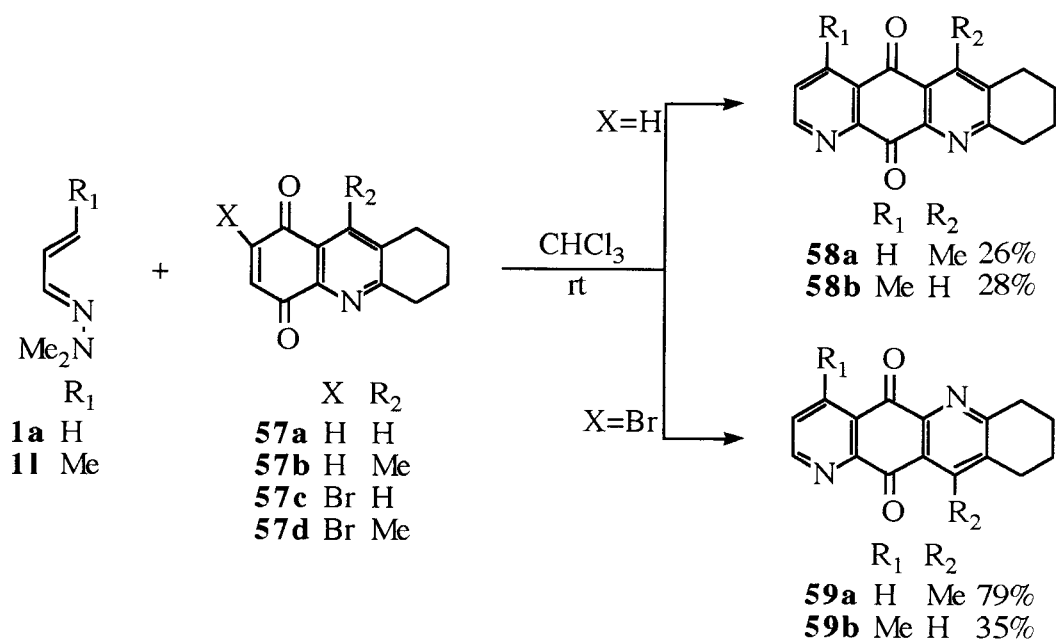
Scheme 56

The cycloaddition between the disubstituted azadiene (**1s**) and quinoline-5,8-dione (**16b**) is very sensitive to acidic medium and oxygen^{49,78,79} (Scheme 57). In an usual medium, only low yields of cycloadducts (**18d**) and (**54b**) are formed admixed with a furoquinoline derivative. The latter, isolated as the major product, results from an acid catalysed [3+2] process. In a neutral medium and in the absence of oxygen, the expected regioisomeric dihydrodiazanthraquinones are formed in large amounts. In contrast with the behavior of **16b**, isoquinoline-5,8-dione (**46**) gives chemo- and regioselectively the dihydrodiazanthraquinone (**53b**) according to the [4+2] process. The regioselectivities observed in these Diels-Alder reactions are explained by the directing effect of the nitrogen ring atom. All these products are easily aromatized after oxidation with MnO₂.



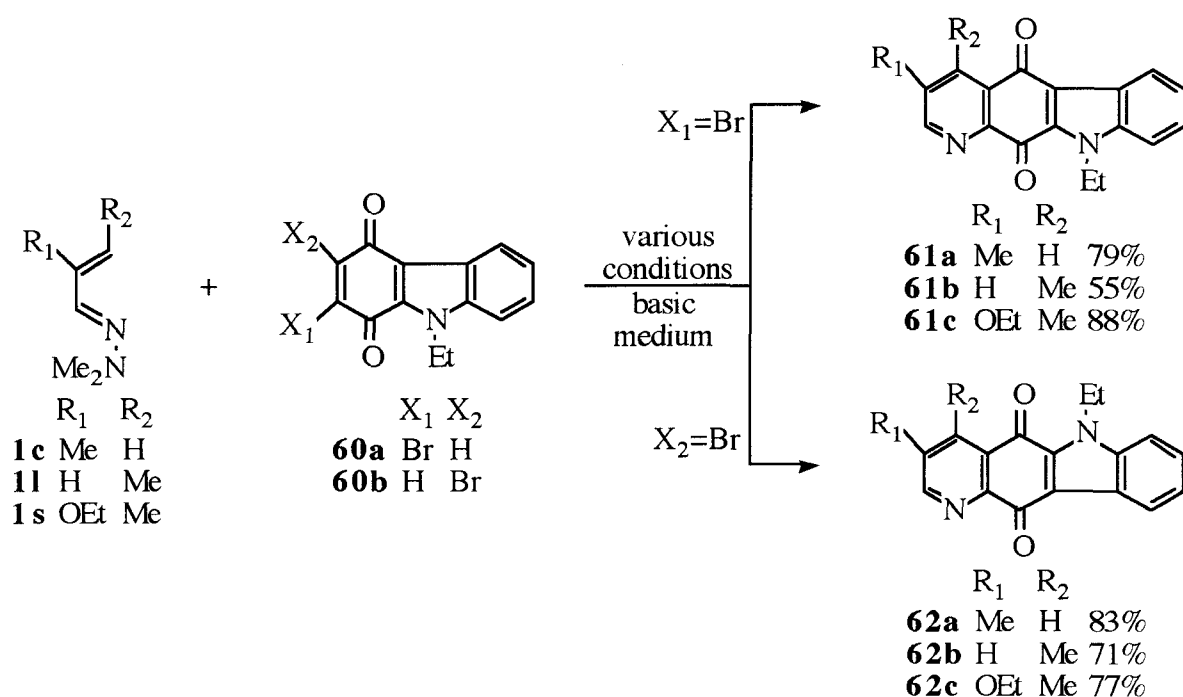
Scheme 57

Similar reactivity and regioselectivity are observed for 6,7,8,9-tetrahydroacridine-1,4-diones (**57**)^{80,81} (Scheme 58). Cycloadditions between **1a** or **11** and **57a-b** present a marked preference for the pyridoacridine derivatives (**58a-b**). Therefore, to obtain regioselectively the opposite regioisomers (**59a-b**) a bromine atom at C-2 of dienophiles is required. With the C-4 substituted azadiene (**11**) an oxidation step is necessary to obtain aromatized cycloadducts.



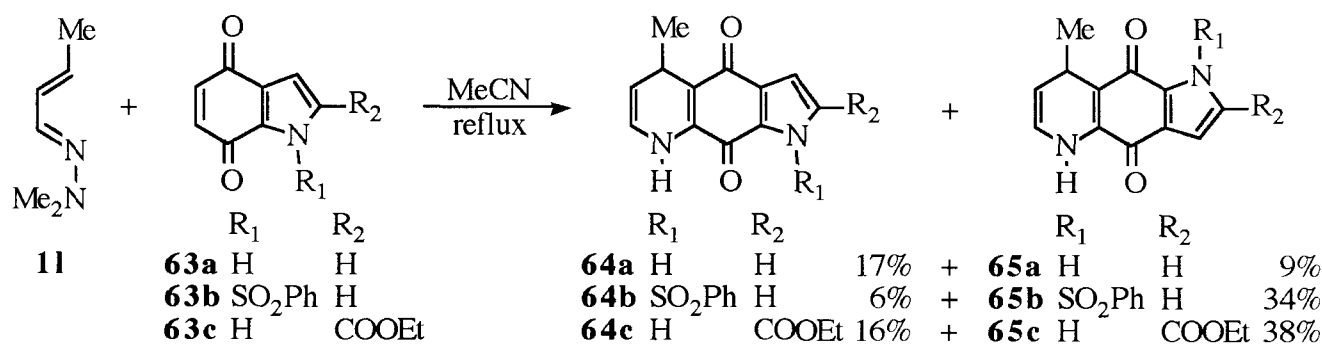
Scheme 58

Among the properties of carbazole-1,4-diones, recently reviewed,⁸² their usefulness in hetero Diels-Alder reactions towards 1-azadienes was evaluated. Thus, cycloadditions between azadienes (**1c**) or (**1l**) and *N*-ethylcarbazole-1,4-dione afforded mixtures of the corresponding regioisomeric pyridocarbazolequinones (yields % of **61a/62a**: 75/6; **61b/62b**: 52/25). Only **61c** was obtained alone in 85% yield from **1s**. To obtain regiospecific cycloadditions, the regiocontrol of the bromine atom was applied⁴² (Scheme 59). Formation of the major regioisomer with the non brominated dienophile agree with the FMO theory since the larger orbital coefficients are located at C-3 for *N*-ethylcarbazolequinone (C-2: 0.3113; C-3: 0.3490). In the case of the brominated quinones (**60a-b**), calculations by the PM3 method fail to explain the inversion of the regiochemistry observed due to the location of the larger coefficients at the same C-3 atom.



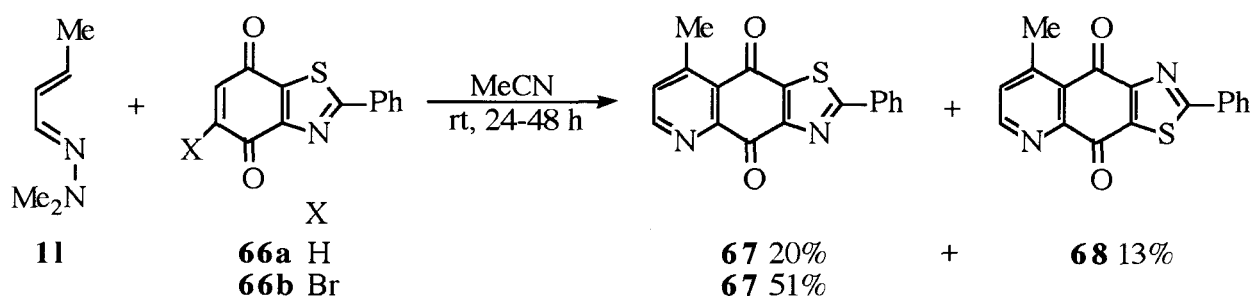
Scheme 59

The cycloadditions of indoloquinones (**63a-c**) with azadiene (**1l**) afford mixtures of the regioisomeric dihydropyridoindoloquinones⁸³ (Scheme 60). With the unsubstituted quinone (**63a**), the regioisomer (**64a**) is favored, in agreement with the electronic effect of the nitrogen ring atom. The presence of electron-withdrawing substituents reversed the regiochemistry. So, cycloadducts (**65b-c**) are obtained from **63b-c**. These results agree with the FMO theory.



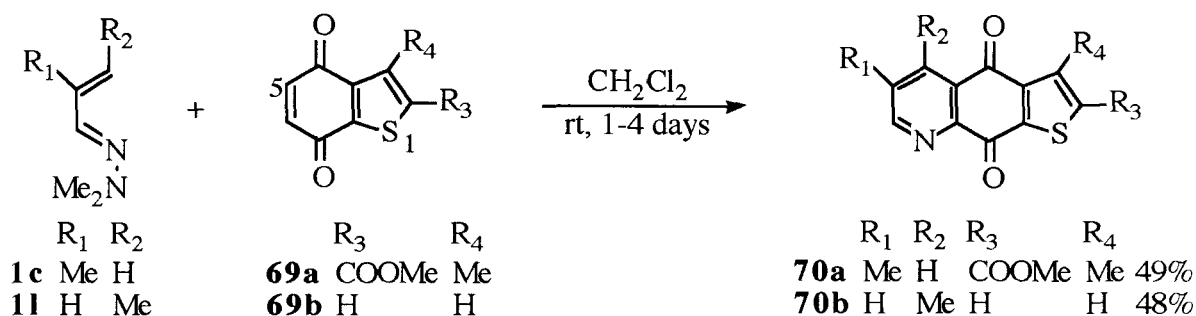
Scheme 60

The synthesis of a kuanoniamine A analogue involves hetero Diels-Alder reaction of azadiene (**11**) with 4,7-dioxo-2-phenylbenzothiazoles (**66a-b**) followed by dehydrogenation. Reaction with **66a** produces the regioisomeric thiazoloquinolinediones (**67**) and (**68**). A competitive addition reaction of dimethylamine occurs (29%). Running the reaction under microwave conditions increases the yield. Starting from **66b**, only the expected aromatized cycloadduct (**67**) is obtained in 51%⁸⁴ (Scheme 61).



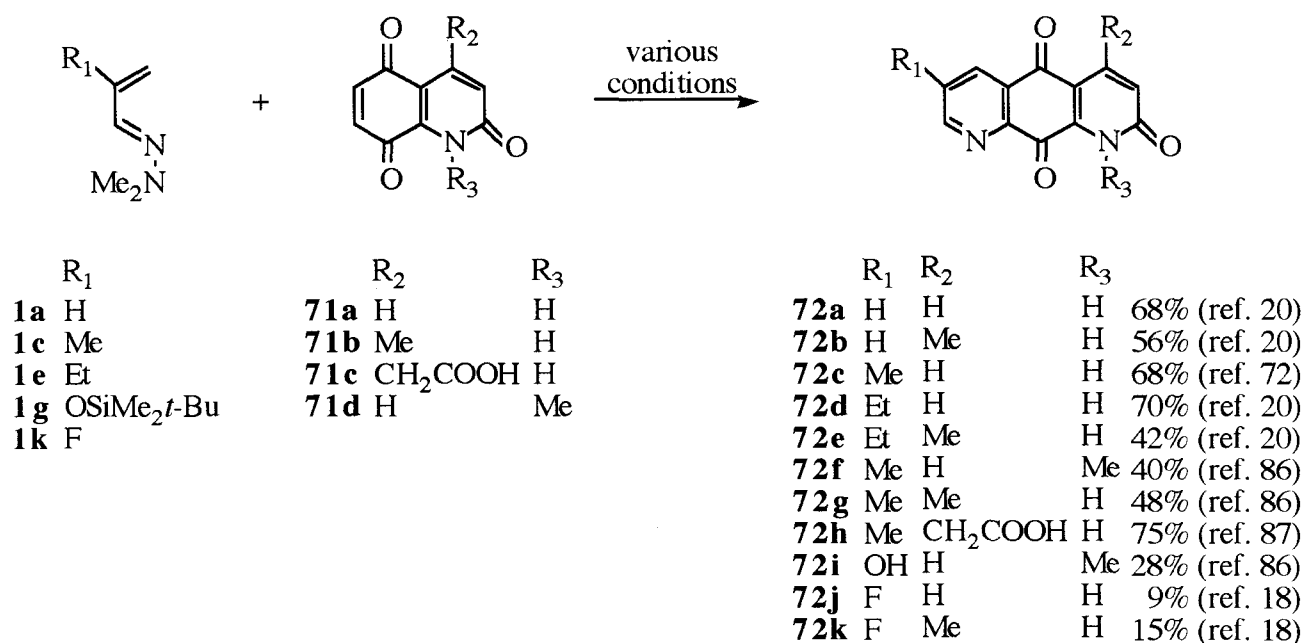
Scheme 61

Two thienoquinolinequinones (**70a-b**) are prepared through cycloadditions of **1c** or **11** with **69a-b**, followed by air oxidation.⁸⁵ The corresponding regiochemistry is established on the basis of HOMO-LUMO interactions. The larger orbital coefficient values are located at C-4 for azadienes (**1c**) and (**11**) and at C-5 for quinones (**69a-b**). The calculations indicate that compounds (**70a-b**) would be the favored regioisomers (Scheme 62). It seems that the regiocontrol of sulfur atom is similar to the nitrogen one in indoloquinone (**63c**).



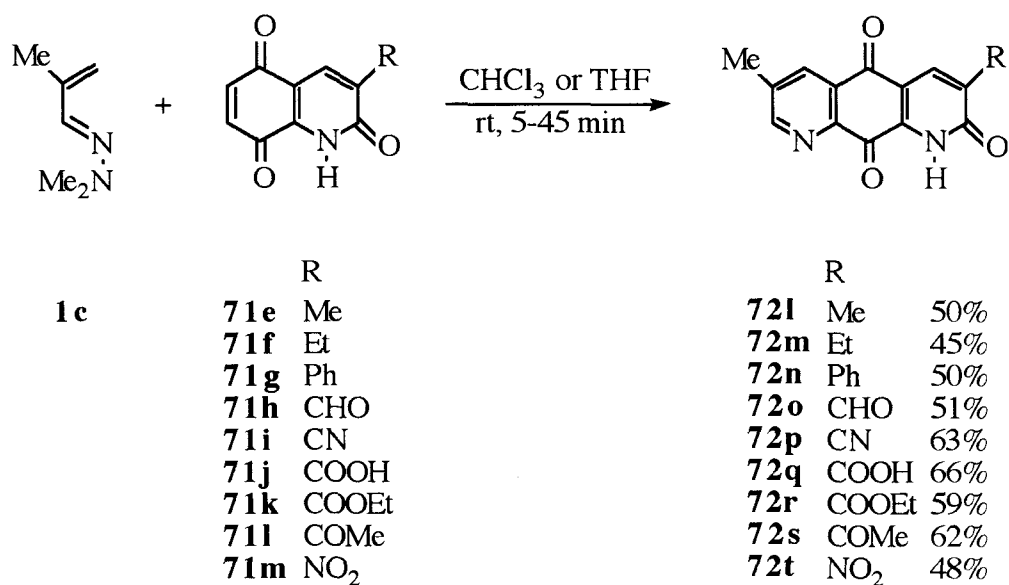
Scheme 62

During the course toward the synthesis of diazaquinomycin A analogues, a hetero Diels-Alder methodology based on reactions between quinoline-2,5,8-triones and 1-azadienes is developed. The results obtained are dependent on the substitution pattern of dienes. Thus, unsubstituted and C-3 substituted azadienes afford directly aromatized cycloadducts^{18,20,72,86,87} (Scheme 63). All reactions are completely regioselective, except in the case of the less polarized azadiene (**1a**) which provides few amounts of 1,5-cycloadducts (respectively 13 and 14% yields).²⁰ The favored regiochemistry could be explained through the combined effects of the C-2 carbonyl group and the amide nitrogen atom. The low yield obtained with the fluorinated azadiene (**1k**) is due to the competitive formation as major products of a furoquinoline derivative in a [3+2] process (21%) or a dimethylamino cycloadduct formed by a nucleophilic substitution of the fluorine atom (23%).¹⁸



Scheme 63

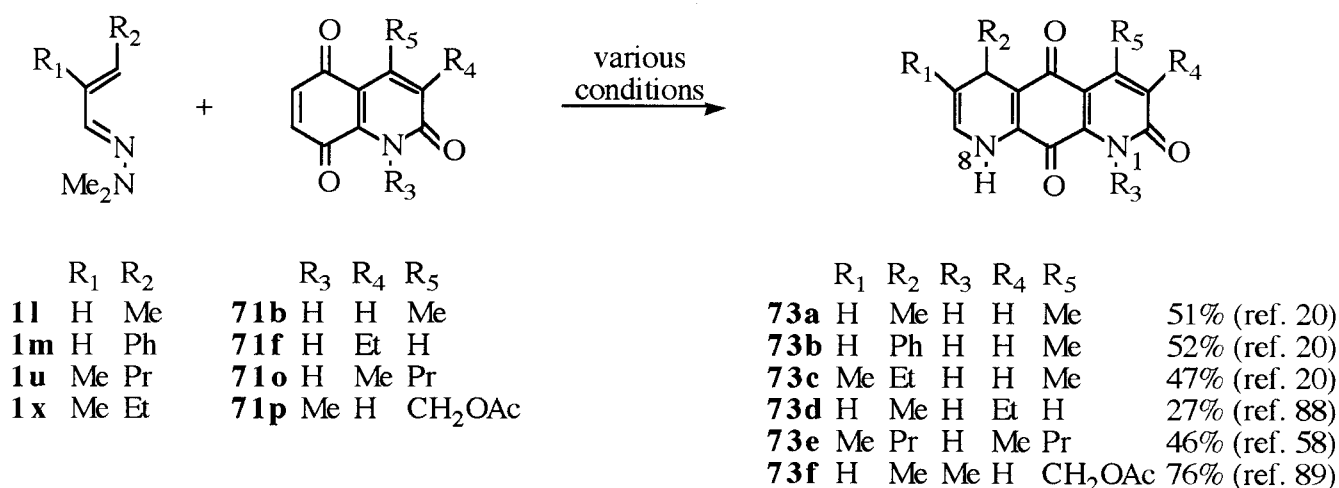
In contrast, reactions between C-3 substituted quinoline-2,5,8-triones (**71e-l**) and azadiene (**1c**) give only aromatic cycloadducts with no trace of dimethylamine addition on the starting quinone⁸⁸ (Scheme 64). Together with the expected **72t**, formation of a small amount (10%) of a furoquinoline derivative, in a [3+2] process is observed.



Scheme 64

On the other hand, treatment of C-4 substituted azadienes with various quinoline-2,5,8-triones gave 1,8-dihydro derivatives as major products^{20,58,88,89} (Scheme 65). Appreciable amounts of aromatized cycloadducts are also obtained in addition with **73d** and **73e** (respectively 18% and 24%). In many cases,

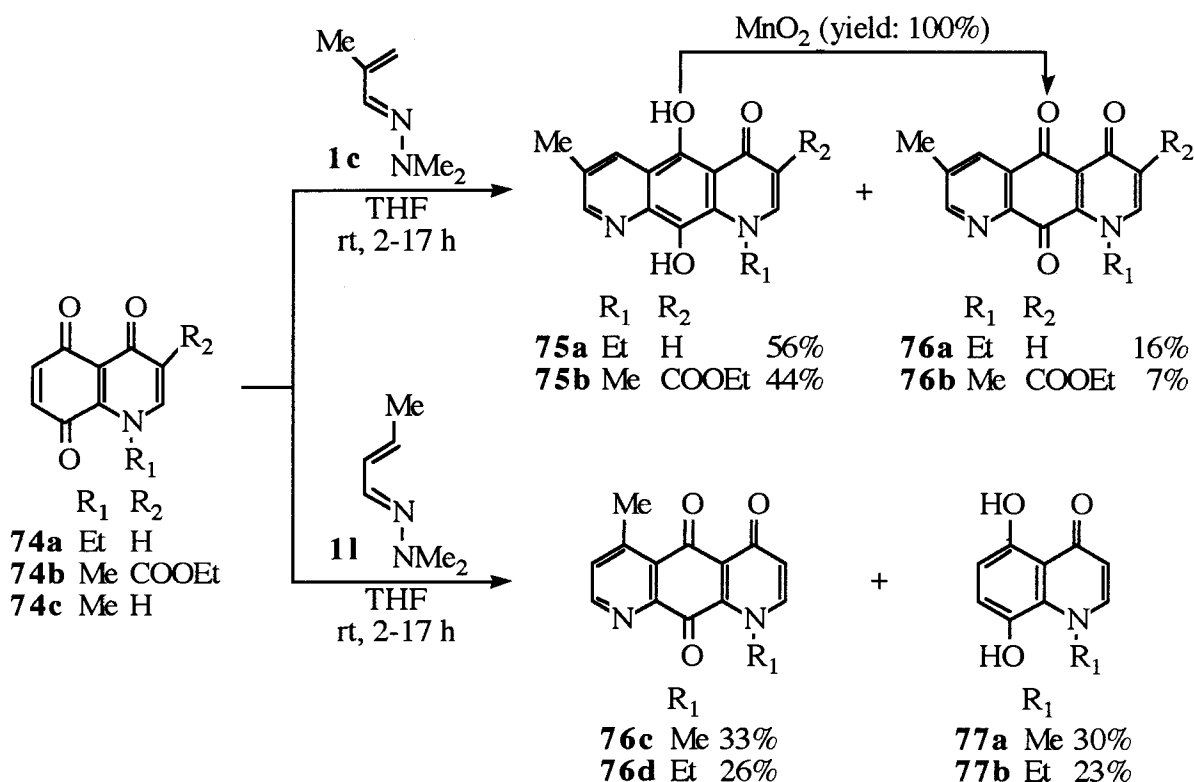
substantial quantities of dimethylaminoquinones are isolated. All cycloadditions are completely regioselective in favor of the 1,8-regioisomers, except in the case of **73f** where the 1,5-cycloadduct is obtained in 11% yield. As shown with other cycloadditions, ultrasound conditions increase the reaction rate and yield between **1m** and quinoline-2,5,8-trione (**71b**).²⁸ To avoid or diminish the competitive addition of dimethylamine on the starting quinone, silica gel or resin is used as scavenger. So, instead to add silica gel to the reaction mixture,⁹⁰ the corresponding quinolinetrione is adsorbed on this support prior to react with the azadiene. Under these conditions, aminoquinones by-products are diminished or suppressed and cycloadduct yields arise to 80-90% levels in most cases.²¹ Similar evolution is observed with a chloroformylpolystyrene resin.⁴⁶



Scheme 65

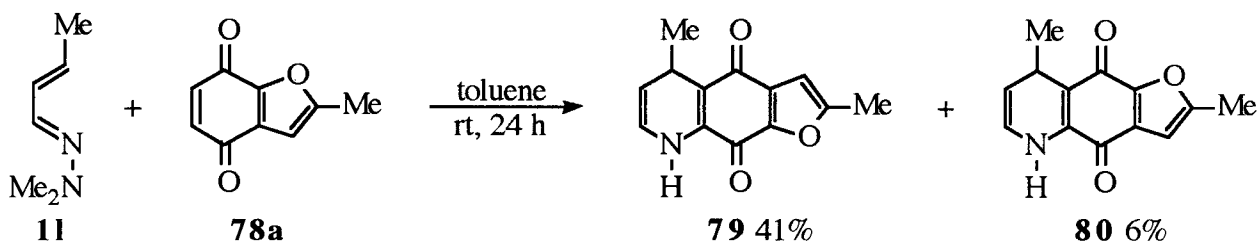
Heterocyclization of various 4-aryl-3,4-dihydro-2,5,8-1*H*-quinoline-2,5,8-triones⁹¹ and 3,4-dihydro-5*H*-1-benzazepine-2,6,8-trione⁹² with azadiene (**1c**) proceeds similarly to give the corresponding aromatized cycloadducts with respective yields of 48-58 and 56%.

The behavior of quinoline-4,5,8-triones in their cycloaddition reactions differed considerably from those of quinoline-2,5,8-triones⁹³ (Scheme 66). Thus, treatment of **74a-b** with azadiene (**1c**) gives hydroquinones (**75a-b**), as major products, which were accompanied by small amounts of their oxidized forms (**76a-b**). Formation of hydroquinones (**75**) occurs after dimethylamine elimination from the corresponding tautomer of the primary cycloadduct. Moreover, small amounts of the 1,5-regioisomers are obtained (respective yields 7% and 4%). Formation of the latter contrasts with the complete regioselectivity found, in similar reactions, with quinoline-2,5,8-triones. Compounds (**75a-b**) are quantitatively oxidized to **76a-b** by treatment with MnO₂ in chloroform. When quinones (**74a**) or (**74c**) and azadiene (**1l**) are reacted under the same conditions, equimolar mixtures of fully aromatized cycloadducts (**76c-d**) and hydroquinones (**77a-b**) are obtained. Compounds (**77**) result from their oxidizing role to form quinones (**76**). From the similar orientation of the regiochemistry of quinoline-4,5,8-triones and quinoline-2,5,8-triones, it appears that CO-4 and CO-2 have the same complementary effect.



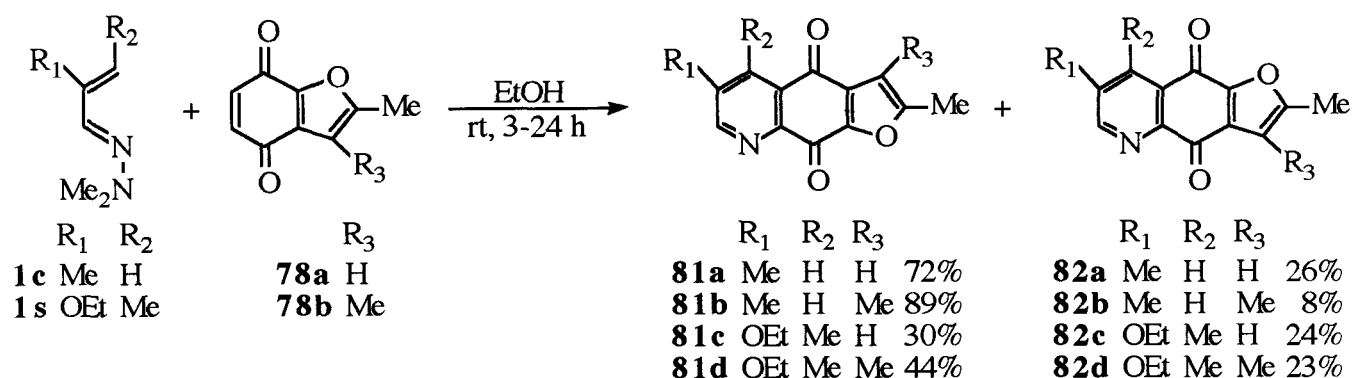
Scheme 66

Various furoquinolinediones are prepared through Diels-Alder reactions between azadienes and benzofuranediones.⁴¹ The synthetic potential of these dienophiles is recently reviewed.⁹⁴ Starting from the C-4 substituted azadiene (**11**), an inseparable mixture of the stable regioisomeric dihydro cycloadducts was obtained (Scheme 67).



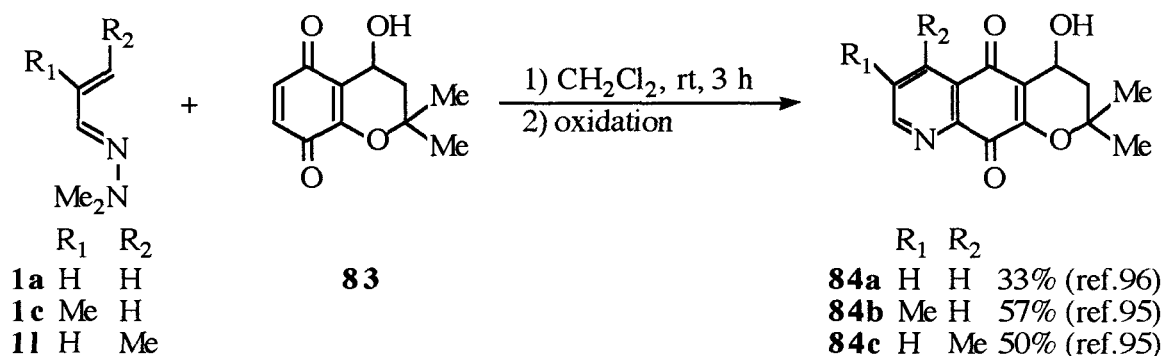
Scheme 67

On the other hand, the more reactive C-3 substituted azadienes (**1c**) or (**1s**) generate directly aromatized cycloadducts. Average to good regioselectivities are observed, but unfortunately separation of the regioisomers failed (Scheme 68). In agreement with the electron donor effect of the ring oxygen atom, the nucleophilic C-4 end of azadienes adds preferentially to C-5 of the quinones. The same regioselectivity is predicted by the FMO theory (larger coefficient values at C-4 for dienes and at C-5 for dienophiles). In order to improve the cycloaddition regioselectivity, brominated quinones are used. Thus, starting from 5- or 6-bromobenzofuran-4,7-diones, the corresponding furoquinolinediones (**81**) and (**82**) are respectively obtained as a single regioisomer and in most cases with higher yields. The FMO theory fails to explain the reversed regiochemistry since larger orbital coefficient values, calculated by the PM3 method, are always located at C-5 of bromoquinones.



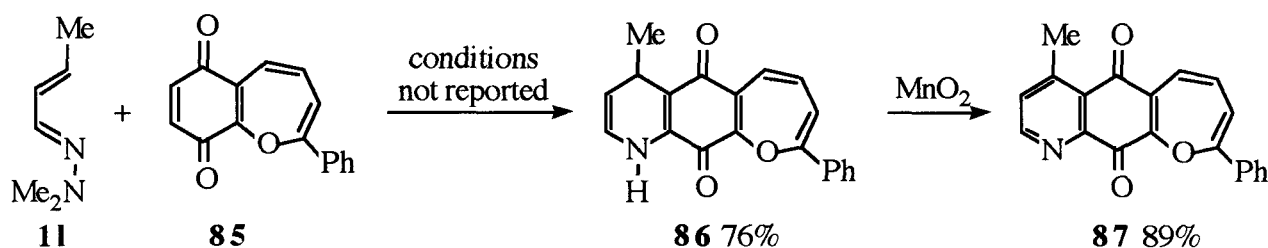
Scheme 68

The influence of a pyran ring on the regiochemistry of the Diels-Alder reaction with azadienes (**1a**), (**1c**) or (**11**) is evaluated.^{95,96} In all experiments fully aromatized cycloadducts are obtained after *in situ* oxidation with Ag₂O/SiO₂ or DDQ (Scheme 69). The regiochemistry observed can be rationalized from the electron-donating effect of the ring oxygen atom. In contrast with juglone, the non coplanar hydroxyl group cannot be chelated with the adjacent quinonic carbonyl. For this reason it has no influence on the regiochemistry. To corroborate this regioselectivity, the theoretical chemical hardness concept is successfully developed.⁹⁶



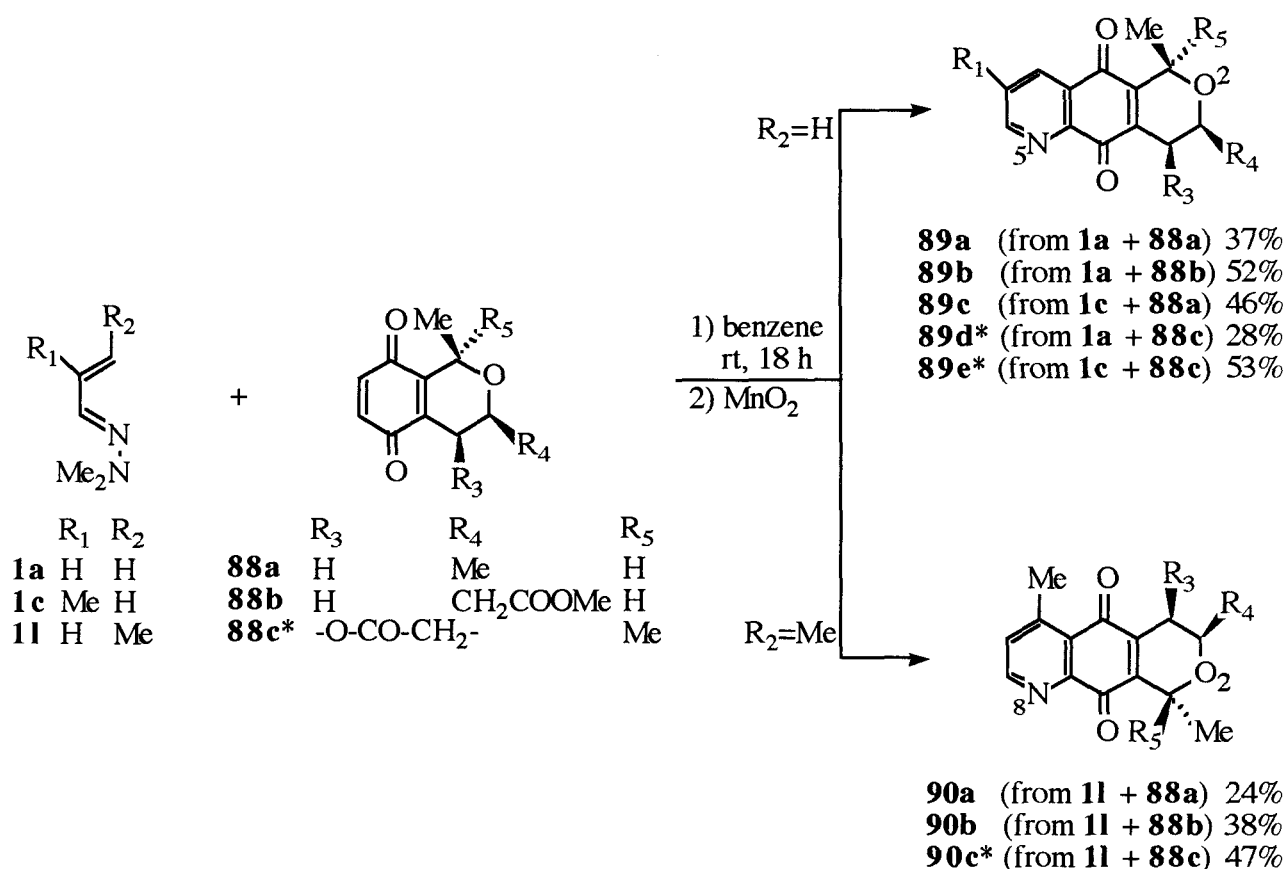
Scheme 69

Reaction of azadiene (**11**) with *p*-benzoquinono[*b*]oxepine (**85**) proceeds regioselectively to form the dihydro derivative (**86**) in 76% yield, which affords after oxidation with MnO₂ the 1-azanaphthoquinono[*b*]oxepine (**87**) in 89% yield⁹⁷ (Scheme 70). The regiochemistry of this cycloaddition agrees with the orientational effect of the ring oxygen atom.



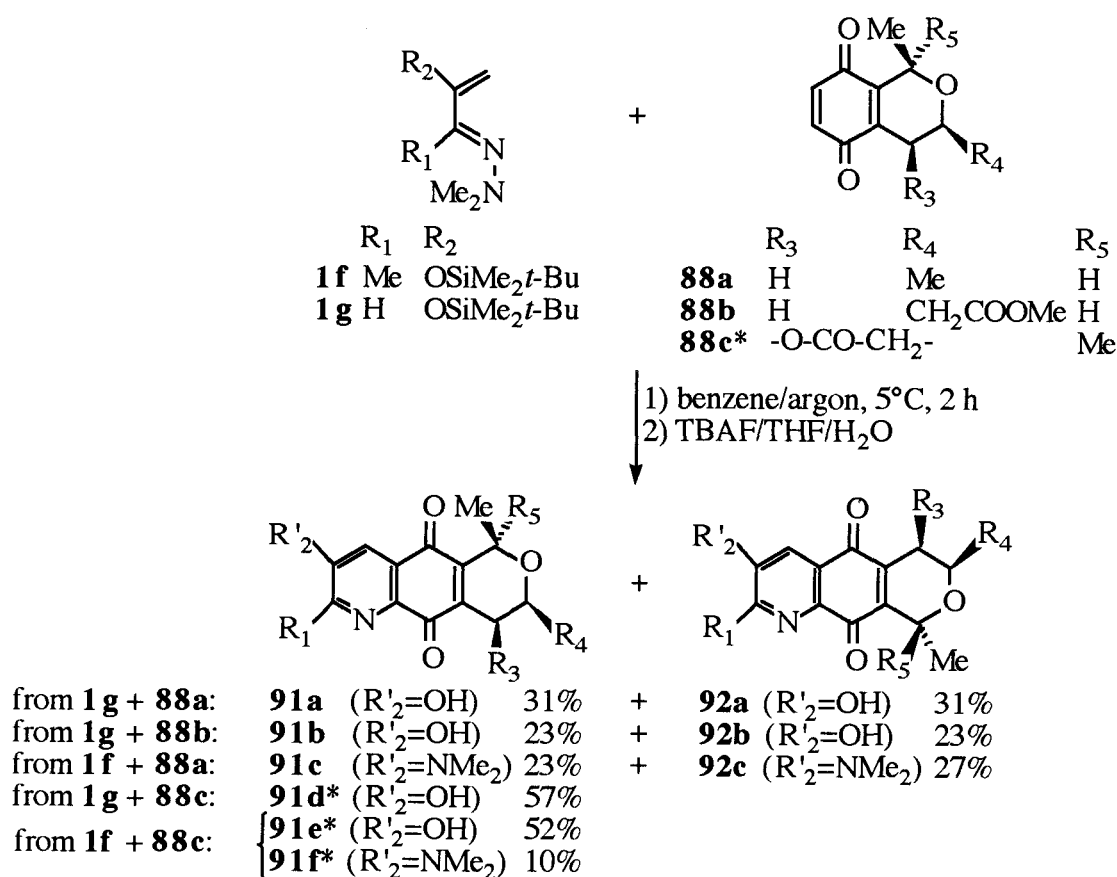
Scheme 70

When isochromanquinones (**88a-c**) are submitted to cycloaddition reactions with azadienes (**1a**), (**1c**) or (**1l**) azabenzisochromanquinones (**89**) and (**90**) are obtained. The regioselectivity of these reactions depends on the diene substituent and the structural symmetry of the starting quinone.²² Using azadienes (**1a**) or (**1c**), the 2,5-regioisomeric cycloadducts are formed while **1l** leads to formation of 2,8-derivatives. This inversion of the regiochemistry is not well explained by the authors. In the case of **88b**, the primary cycloadduct which is stable at -20°C is characterized before its oxidation (Scheme 71).



Scheme 71

Finally, azadienes (**1f-g**) give 1:1 mixtures of 2,5- and 2,8-regioisomers. Their separation is performed with their *O*-benzyl derivatives for **91a+92a** and their *O*-methyl in the case of **91b+92b**. Formation of **91c+92c** results from a nucleophilic substitution of the silyloxy or the hydroxyl group by the liberated dimethylamine. Moreover, the lactone ring by increasing the dissymmetry of quinone (**88c**) affords a complete regioselectivity (Scheme 72).

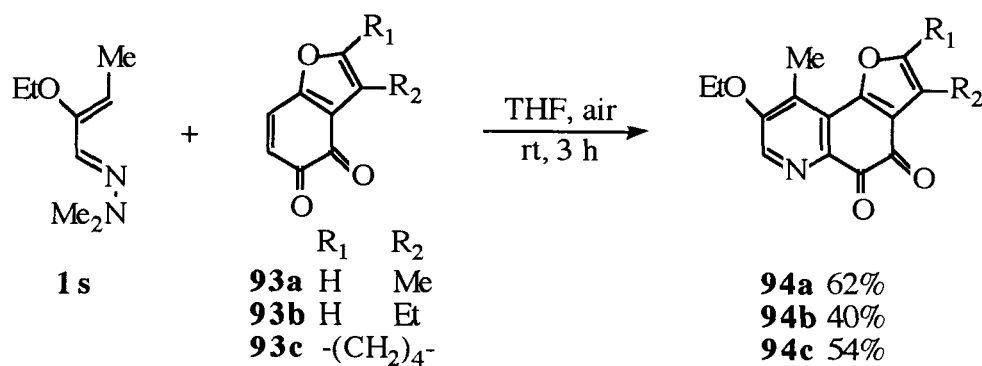


(*mixture of enantiomers)

Scheme 72

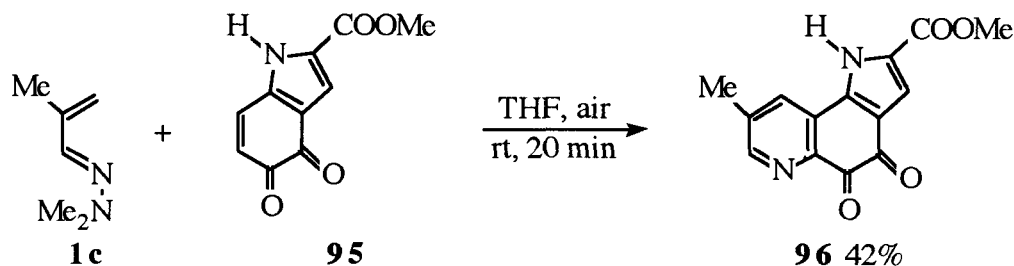
Unsymmetrical 1,2-quinones

The ability of benzo[*b*]furan-4,5-diones to undergo Diels-Alder reactions was recently reviewed.⁹⁴ In that field, our group was the first to use the α,β -unsaturated *N,N*-dimethylhydrazone (**1 s**) as a diene⁹⁸ (Scheme 73). In the experimental conditions employed, neither primary adducts nor dihydro derivatives were isolated. Furoquinolinediones (**94**) were directly obtained after spontaneous elimination of dimethylamine and oxidation. These cycloadditions were totally regioselective, the C-4 nucleophilic end of azadiene (**1 s**) adding exclusively at C-7 of quinone, in agreement with the electronic resonance theory.³⁸ This orientation of the regiochemistry was also supported by experiments on the nucleophilic addition of dimethylamine on quinones (**93**).⁹⁸



Scheme 73

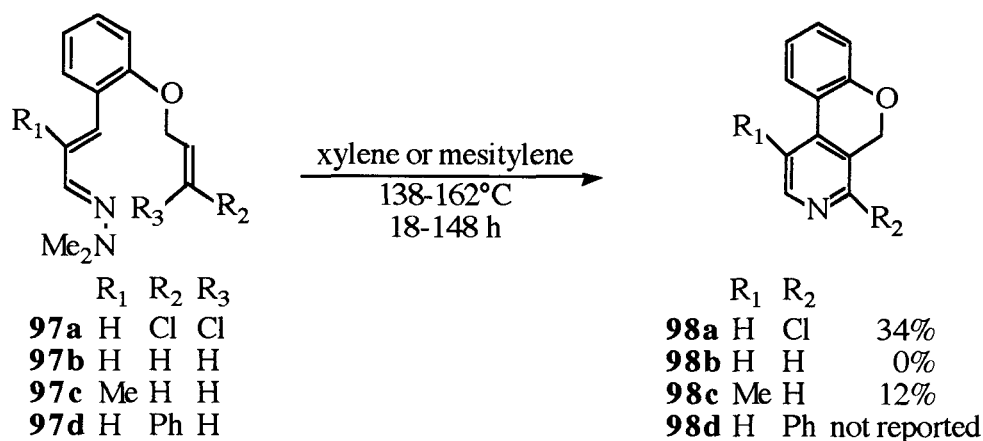
In continuation of our work focused on heterocyclic *o*-quinones, we recently explored the chemical behavior of an *o*-indoloquinone (**95**) towards azadiene (**1c**)⁹⁹ (Scheme 74). As observed with benzo[*b*]furan-4,5-diones the fully aromatized pyrroloquinolinequinone (**96**) was directly obtained through a totally regioselective [4+2] process. The moderate yield of these reactions can be attributed to the lower stability of the *ortho* quinonic structures comparatively to the *para* ones.



Scheme 74

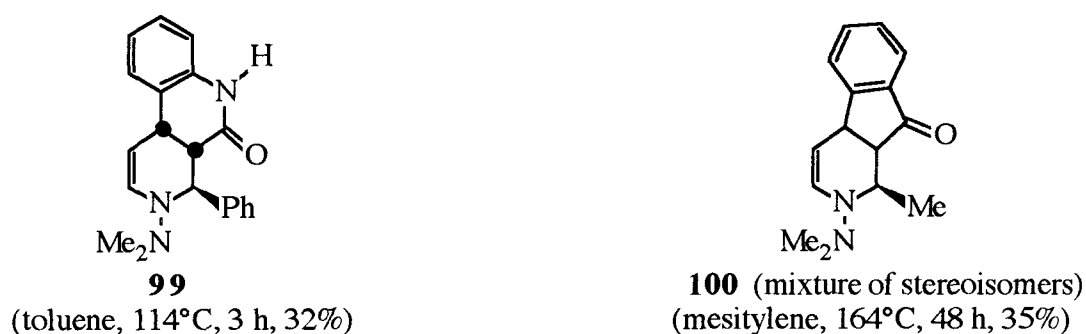
IV. INTRAMOLECULAR DIELS-ALDER REACTIONS

The first example of this type of reaction was described in 1988 for the synthesis of some annelated pyridines.¹⁰⁰ Heating cinnamoyl hydrazones bearing an unsaturated chain at the *ortho* position induces smooth intramolecular [4+2] cycloadditions¹⁰⁰ (Scheme 75). With inactivated allyl ether chains (**97b-c**), the starting compounds are poor Diels-Alder substrates. In the case of **97d** the primary cycloadduct is stable enough to be isolated (138°C, 18 h, 80%). The aromatized structure (**98d**) is further obtained after treatment with 10% Pd/C in xylene at 138°C.



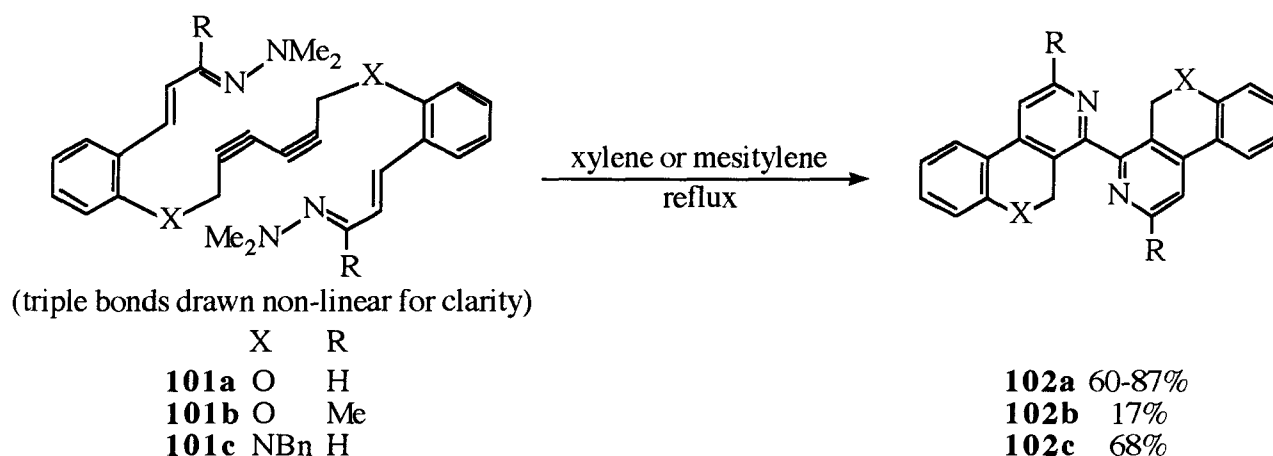
Scheme 75

Two other examples of stable tetrahydro derivatives (**99**) and (**100**) are reported in the same paper (Scheme 76).



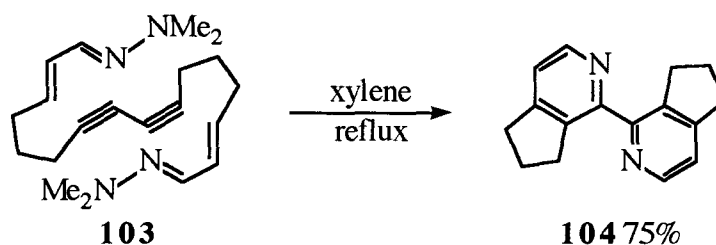
Scheme 76

To obtain compounds (**98**), [4+2] cycloadditions are also performed with structures containing a triple bond in the aliphatic chain. Thus, **98b** and **98d** are directly isolated in 48 and 74% yields respectively. This methodology was also applied to the synthesis of the monoterpene alkaloid actinide (200°C, 6 h, 46%).¹⁰⁰ Recently, a new route to 2,2'-bipyridines based on a double intramolecular Diels-Alder reaction was reported¹⁰¹ (Scheme 77).



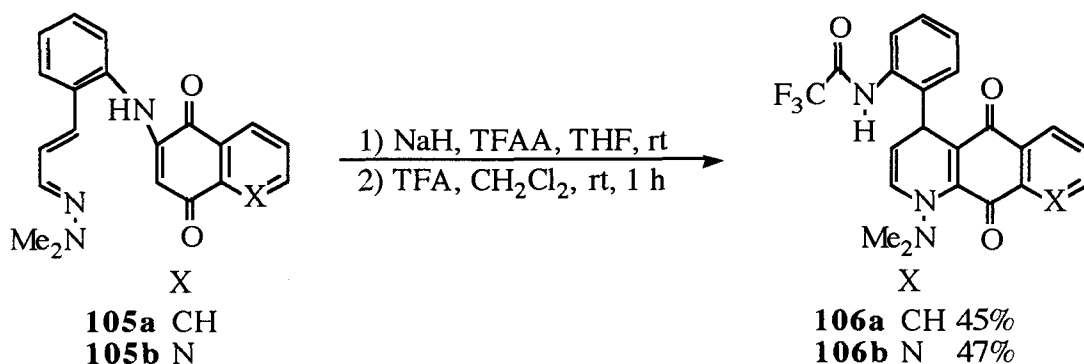
Scheme 77

Finally, when azadiene fragments are connected to alkyne dienophiles by simple alkyl chains, the corresponding substrate readily undergoes the desired double intramolecular Diels-Alder reaction¹⁰¹ (Scheme 78).



Scheme 78

In the last report, an intramolecular [4+2] cycloaddition was observed with a quinonic dienophile¹⁰² (Scheme 79).



Scheme 79

The cycloadditions are performed through a trifluoroacetylation of the secondary amino group followed by treatment with an excess of trifluoroacetic acid. Under these conditions the primary cycloadducts, which cannot be isolated, suffer elimination of trifluoroacetamide to form **106a-b**. These structures are useful intermediates in the synthesis of benzo- or pyrido[*b*]acridine-6,11-diones.

CONCLUSION

The dimethylamino substituent introduced at N-1 atom of the vinyl imine system plays the double role of an activating group for the cycloaddition reaction and a leaving one for a subsequent aromatization of the cycloadduct. The best reactivity in Diels-Alder reactions is obtained with 1-azadienes bearing at C-3 an electron-releasing substituent.

Such heterodienes constitute, through [4+2] cycloadditions, a very efficient approach to nitrogen containing six membered heterocycles. Therefore, their usefulness was largely exploited in inter- and intramolecular Diels-Alder reactions with various dienophiles among which quinones are the most widely employed.

Non-quinonic dienophiles afford generally with moderate to good yields dihydro cycloadducts which are easily aromatized by oxidative treatment. Totally regioselective [4+2] cycloadditions, in agreement with electronic resonance and FMO orbital theories, are obtained with unsymmetrical dienophiles.

The use of quinonic dienophiles may be hampered by the tendency of the primary cycloadducts to liberate dimethylamine, which then adds to the starting quinone or to the reaction product affording a yield decrease. For this reason, several experiments were attempted to solve the problem of dimethylamine addition. The first of them was based on its elimination from the reaction mixture by mean of an inert gas stream or by addition of acetic anhydride. But, these modifications lack general value. Good results are also obtained by carrying out the reaction on a silica gel support, but this method is restricted to cases where the cycloaddition is very fast. Addition of a chloroformylpolystyrene scavenger resin provides a convenient and efficient manner to minimize or suppress dimethylamine side-products. However, this method is not suitable for the less reactive azadienes for which reflux conditions must be employed.

In an alternative approach, the dimethylamino activating group can be replaced by an acetyl amino moiety which does not deliver nucleophilic species into the reaction medium. Unfortunately this modification results in a generally diminished reactivity of the azadiene system.²⁰

On the other hand, [4+2] cycloadditions carried out under ultrasonic irradiation exhibit sonochemical effects, even if sometimes modest, when quinonic dienophiles are used. The latter may generate radical-cations from azadienes.^{103,104} Therefore, the redox properties of Diels-Alder partners should be of importance and the role of sonication would be to enhance a single electron transfer process probably involved in the reaction mechanism.

The regiochemistry observed with unsymmetrical quinones is generally dependent on their structure and favored regioisomers correspond to those predicted by theories. In view to find complete regioselective pathways, the best strategy is the use of quinones substituted by a halogen as a blocking atom on the reactive double bond. Furthermore, this method presents the advantage of a help in the aromatization step which follows the Diels-Alder reaction.

Finally, intramolecular Diels-Alder reactions between the azadiene fragment and the connected alkene or alkyne dienophile are a useful method for the synthesis of annelated pyridinic structures.

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