CARBAZOLE-1,4-DIONES : SYNTHESES AND PROPERTIES

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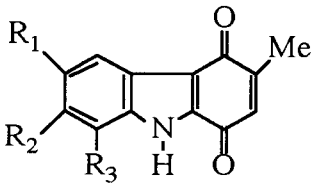
Abstract- The synthetic approaches to carbazole-1,4-diones are described. Their synthetic usefulness in hetero Diels-Alder reactions towards azadienes, their behavior as precursors for carbazole-4,5-diones as well as their biological properties are reported.

INTRODUCTION

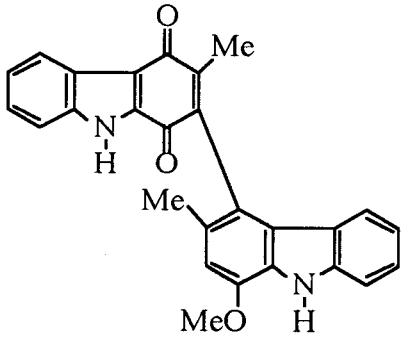
The carbazole-1,4-dione structure is common to numerous biologically active alkaloids. Moreover, it represents an interesting precursor for several other heterocyclic compounds. The first isolation of a carbazolequinone, murrayaquinone-B (**Ib**), was reported in 1983 by Furukawa *et al.*[1] Until now, thirteen naturally occurring carbazole-1,4-dione alkaloids were described in the literature. Thus, murrayaquinones-A to E (**Ia-e**) and pyrayaquinones-A to C (**II**) and (**III**), respectively, have been isolated from the root or stem barks of *Murraya euchrestifolia* Hayata,[1-5] while bikoeniquinone-A (**IV**), bismurrayaquinone-A (**V**), koeniginequinone-A (**If**) and koeniginequinone-B (**Ig**) have been extracted from the root or stem bark of *Murraya koenigii* Spreng.[6] Finally, clausenaquinone-A (**VI**) has been isolated from the stem bark of *Clausena excavata*[7] (Scheme 1).

Several works have been devoted to these alkaloids or their analogues and various synthetic approaches were employed. In addition to Furukawa review[8] on natural carbazolequinones, this paper describes syntheses of all carbazole-1,4-diones reported to date, including our recent work on 2- and 3-bromocarbazolequinones. We also present the efficient use of the latter as dienophiles towards 1- or 2-azadienes, the behavior of some carbazole-1,4-diones as precursors for carbazole-3,4-diones and their biological properties.

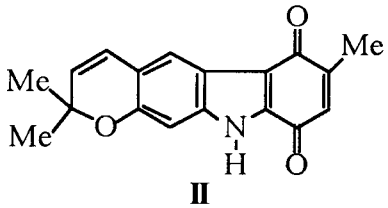


I

a: R_1=H, R_2=H, R_3=H: murrayaquinone-A
b: R_1=H, R_2=OMe, R_3=prenyl: murrayaquinone-B
c: R_1=H, R_2=OMe, R_3=geranyl: murrayaquinone-C
d: R_1=H, R_2=OH, R_3=geranyl: murrayaquinone-D
e: R_1=H, R_2=OH, R_3=prenyl: murrayaquinone-E
f: R_1=H, R_2=OMe, R_3=H: koeniginequinone-A
g: R_1=OMe, R_2=OMe, R_3=H: koeniginequinone-B



IV
bikoeniquinone-A



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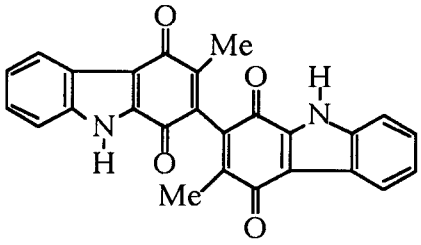
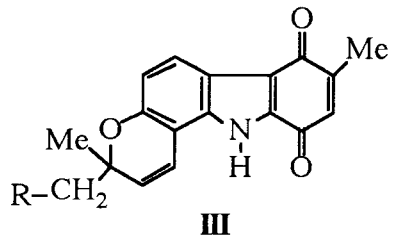
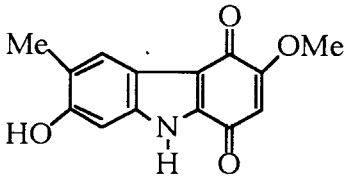
pyrayaquinone-A



V
bismurrayaquinone-A



III
a: R=H: pyrayaquinone-B
b: R=prenyl: pyrayaquinone-C



VI
clausenaquinone-A

Scheme 1

SYNTHESES

Synthetic approaches to carbazole-1,4-diones might be classified as follows :

1 - Condensation of diquinones with primary amines

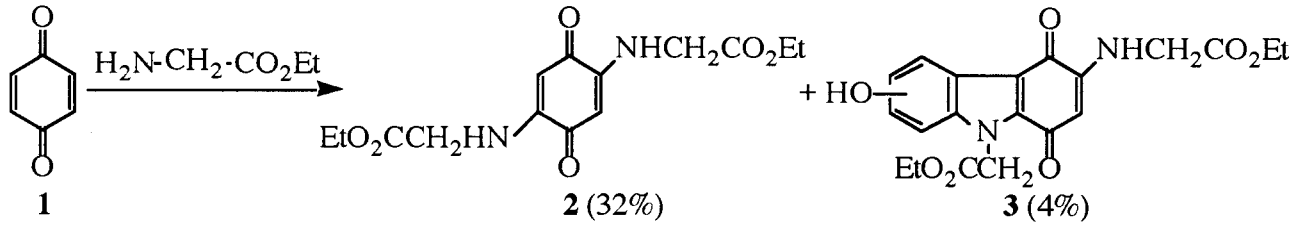
2 - Oxidation of tetrahydrocarbazol-1-ones and hydroxy- or methoxycarbazoles

3 - Cyclodehydrogenation of anilinobenzoquinones with palladium (II) diacetate.

4 - Miscellaneous syntheses

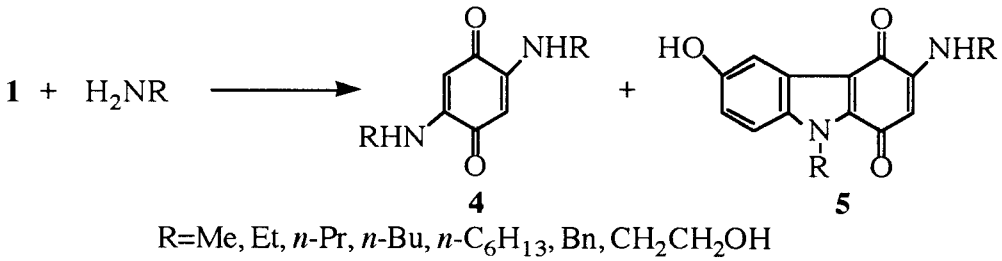
1- Condensation of diquinones with primary amines :

Cranwell and Haworth[9] have described the reaction of α-amino acid esters with quinones. They found that the condensation of *p*-benzoquinone (**1**). with glycine ethyl ester afforded a mixture of the expected 2,5-dicarbethoxymethylaminobenzoquinone (**2**) as the major product and carbazolequinone (**3**) as the minor one. These authors have not assigned the hydroxyl group position of **3** (Scheme 2).



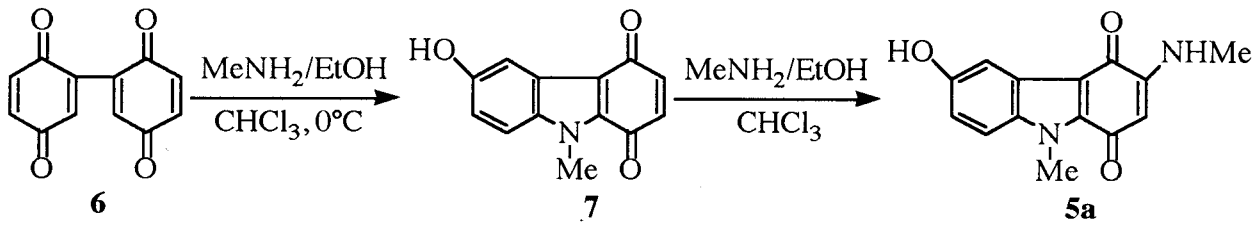
Scheme 2

On the other hand, Ott *et al.*[10] have investigated the reaction of **1** with primary amines. They obtained two kind of products : 2,5-bis(alkylamino)quinones (**4**) and carbazolequinones (**5**) (Scheme 3).



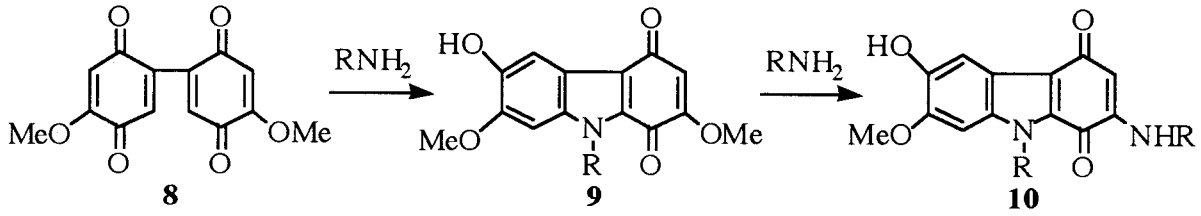
Scheme 3

Moreover, they showed the influence of the solvent on the respective yields of **4** and **5**. For example, performing the reaction with methylamine in pyridine or DMF, the corresponding compounds (**4a**) and (**5a**) (R=Me) were obtained in 62% and 19% yields respectively, while this ratio was reversed to 16% and 78% yields when a mixture of chloroform-ethanol was used. The structure of compounds (**5**) was proved both by spectroscopic methods and by comparison with a sample of 6-hydroxy-9-methyl-3-methylamino-1,4-carbazolequinone (**5a**) prepared from diquinone (**6**) as shown in Scheme 4.



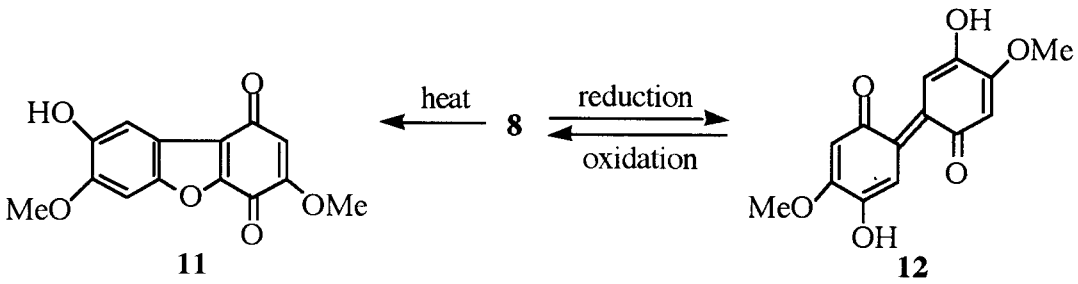
Scheme 4

Then, this last reaction was largely studied by Hammam *et al.*[11] Thus, 4,4'-dimethoxydiquinone (**8**) was reacted with primary amines to give carbazolequinones (**9**) (Scheme 5). However, the use of aliphatic amines afforded compounds (**10**) in which the quinonoid methoxyl substituent of **9** was replaced by an alkylamino group.



Scheme 5

Moreover, two side reactions were observed by these authors. Indeed, upon heating, dimethoxydiquinone (**8**) isomerised to a rearranged product (**11**) while primary aromatic amines substituted in the *ortho*-position did not react with diquinone (**8**), the latter being transformed by reduction, in the presence of ethanol, into a blue violet compound (**12**) (Scheme 6).



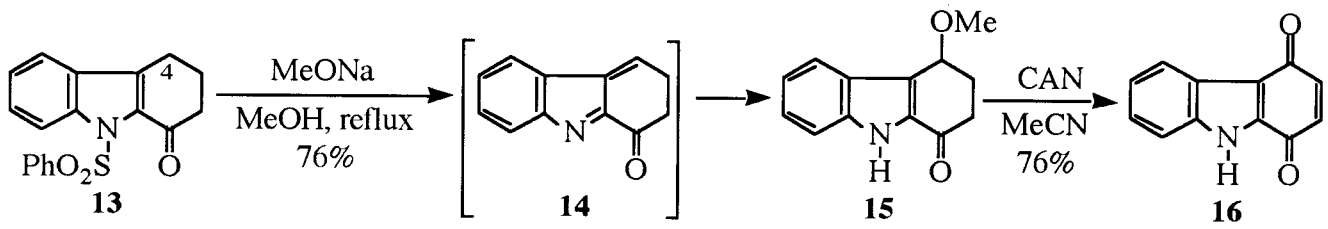
Scheme 6

In the course of these investigations, Hamman *et al.* showed also that compound (**8**) or its 3,3'-dihalogenated derivative reacted with various aliphatic or aromatic amines,[11a-c] amino acids,[11d] 2-aminothiazoles[11e] and peptides[11f] to afford the corresponding carbazolequinone. In the aim of spectral investigations, Issa et *al.*[12] have prepared some other carbazolequinones, using the Hammam approach.[11]

2 - Oxidation of tetrahydrocarbazol-1-ones and hydroxy- or methoxycarbazoles

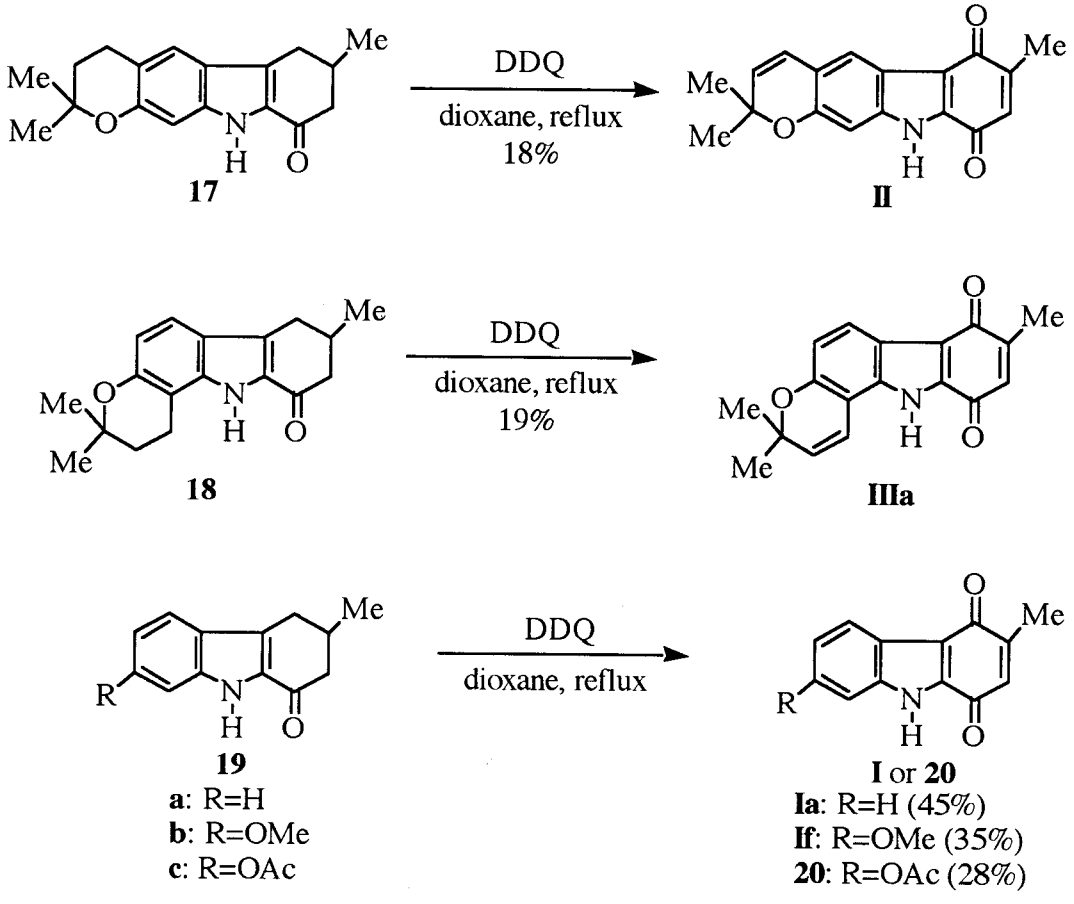
This method was the most widely used for the synthesis of naturally occurring carbazolequinones. Different strategies have been described for the obtention of the intermediates tetrahydrocarbazolones and hydroxy- or methoxycarbazoles. Oxidation of these ones was performed with an appropriate oxidant including ceric ammonium nitrate (CAN),[13,14] 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[15] pyridinium chlorochromate (PCC),[16,17] silver(II) oxide (AgO),[18] [bis(trifluoroacetoxy)iodo]benzene (PIFA),[19] photooxidation[20] and Frémy's salt.[6b,21-27]

The unsubstituted carbazolequinone (**16**) was prepared by oxidation of 4-methoxy-1,2,3,4-tetrahydro-1-oxocarbazole (**15**) with CAN in acetonitrile.[13] Compound (**15**) was obtained from **13** through a base catalyzed 1,4-elimination of benzenesulfinic acid, leading to the intermediate (**14**) which underwent, in the reaction condition, a nucleophilic addition of methanol providing **15** (Scheme 7).



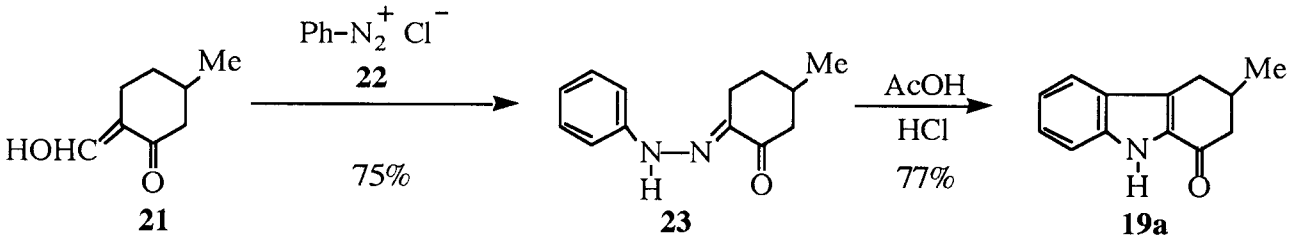
Scheme 7

In contrast, Ramesh and Kapil[15] have performed the synthesis of pyrayaquinones-A (**II**) and -B (**IIIa**), murrayaquinone-A (**Ia**), koeniginequinone-A (**If**) and carbazolequinone **20**, through the direct oxidation of the corresponding 1-oxotetrahydrocarbazoles (**17**) to (**19**) with DDQ in dioxane (Scheme 8).



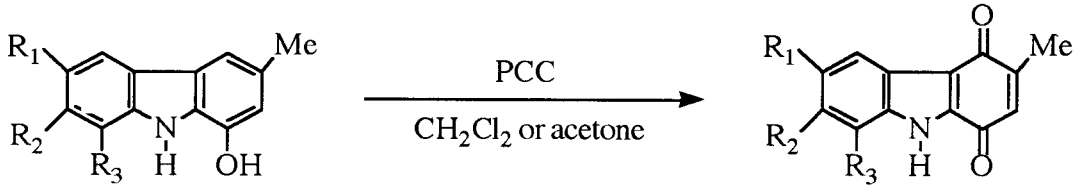
Scheme 8

Compounds (**17**) and (**18**) were prepared by condensation of 1-oxo-1,2,3,4-tetrahydro-3-methyl-7-hydroxycarbazole with 2-methylbut-3-en-2-ol in the presence of BF_3 etherate while 1-oxo-1,2,3,4-tetrahydro-3-methylcarbazoles (**19**) were obtained through a Japp-Klingemann condensation followed by Fischer indolization,[28] as describded for compound (**19a**) in Scheme 9. Thus, 2-hydroxymethylene-5-methylcyclohexanone (**21**), prepared from 3-methylcyclohexanone, was condensed with phenyldiazonium chloride (**22**) to give phenylhydrazone (**23**) which was cyclized with a mixture of acetic acid and concentrated HCl.



Scheme 9

In another approach, Ramesh and Kapil[16] have synthesized murrayaquinones-A (**Ia**) and -B (**Ib**), koeniginequinone-A (**If**), pyrrayaquinone-B (**IIIa**) and some other carbazolequinones by dehydrogenation of the corresponding 1-oxotetrahydrocarbazoles with 5% Pd-C in a sealed tube under vacuum at 170-180°C, then oxidation of the resulting 1-hydroxycarbazoles (**24**) with PCC (Scheme 10).



24

a: R_1=H, R_2=OH, R_3=H
b: R_1=H, R_2=OAc, R_3=H
c: R_1=OAc, R_2=OH, R_3=H
d: R_1=R_2=R_3=H
e: R_1=H, R_2=OMe, R_3=prenyl
f: R_1=H, R_2=OMe, R_3=H
g: R_1=H, R_2, R_3=$OC(CH_3)_2CH$=CH

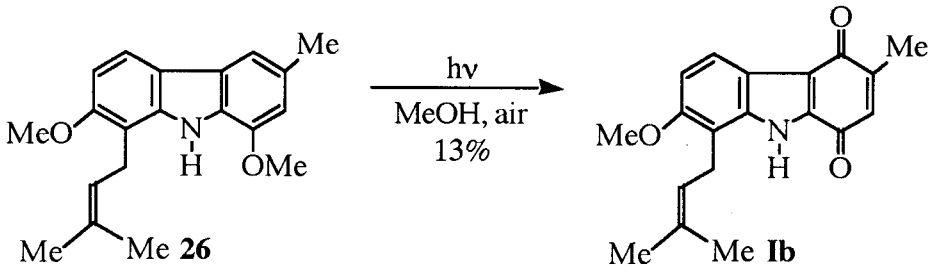
25 or **Ia** or **Ib** or **If** or **IIIa**

a: (25%)
b: (40%)
c: (30%)
Ia: (40%)
Ib: (32%)
If: (35%)
IIIa: (30%)

Scheme 10

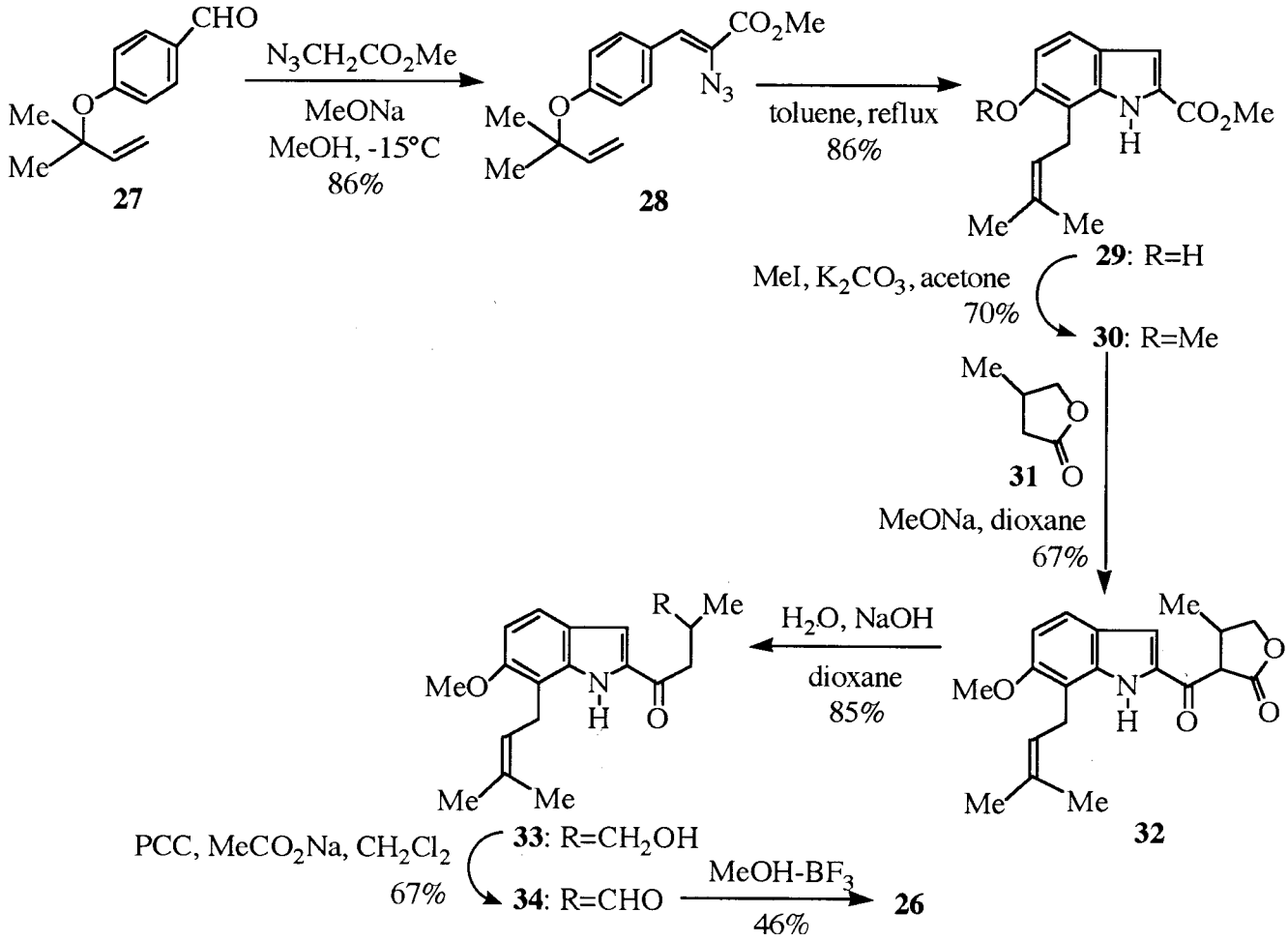
More recently, Saha and Chowdhury[6b] have confirmed the assigned structures of koeniginequinone-A (**If**) and -B (**Ig**) by synthesis starting from 3-methoxy or 3,4-dimethoxy phenyldiazonium chloride and **21** as described above.[28] The yield of the final oxidation step was increased by the use of Frémy's salt (77% and 72% for **If** and **Ig** respectively).

Martin and Moody[20] have also prepared murrayaquinone-B (**Ib**) by photooxidation of the 1-methoxycarbazole (**26**) (Scheme 11).



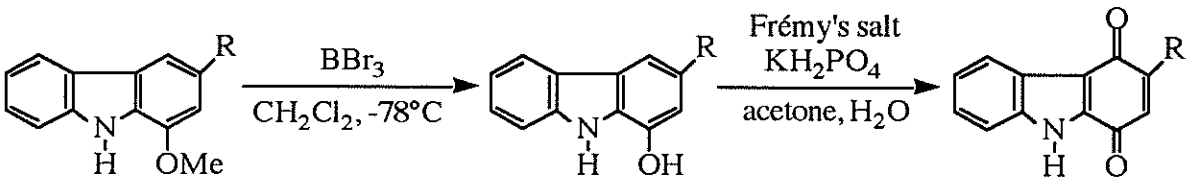
Scheme 11

The synthesis of **26** (Scheme 12) involved, in the key step, the formation of the indole derivative (**29**) *via* sequential indolization and regioselective Claisen rearrangement of the azidocinnamate (**28**) prepared from **27**. Conversion of **29** into **26** was carried out by Claisen condensation of the indole ester (**30**) with 4-methylbutyrolactone (**31**) to give the lactone (**32**) which was converted to the alcohol (**33**) by hydrolysis and decarboxylation. Oxidation of **33** with PCC gave the corresponding aldehyde (**34**) which was finally cyclized into the required methoxycarbazole (**26**) by stirring at room temperature in the presence of a BF_3 methanol complex.



Scheme 12

Moreover, Martin and Moody[21] have synthesized carbazolequinone (**16**) and murrayaquinone-A (**Ia**) through demethylation of methoxycarbazoles (**35**) with BBr_3 followed by oxidation of the resulting hydroxycarbazoles (**36**) and (**24d**) with Frémy's salt (Scheme 13).



35

a: R=H
b: R=Me

36: R=H (100%)
24d: R=Me (86%)

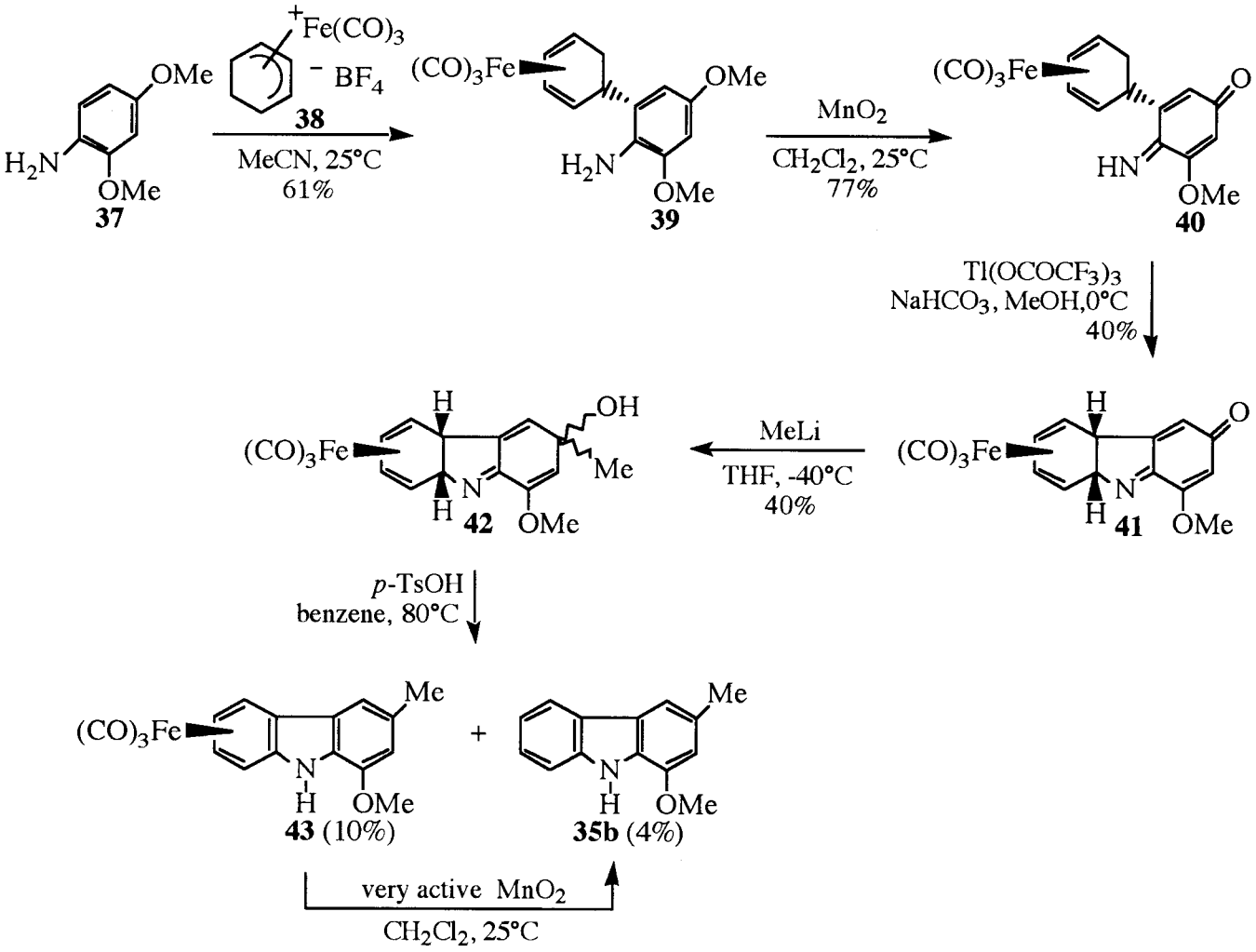
16: R=H (85%)
Ia: R=Me (40%)

Scheme 13

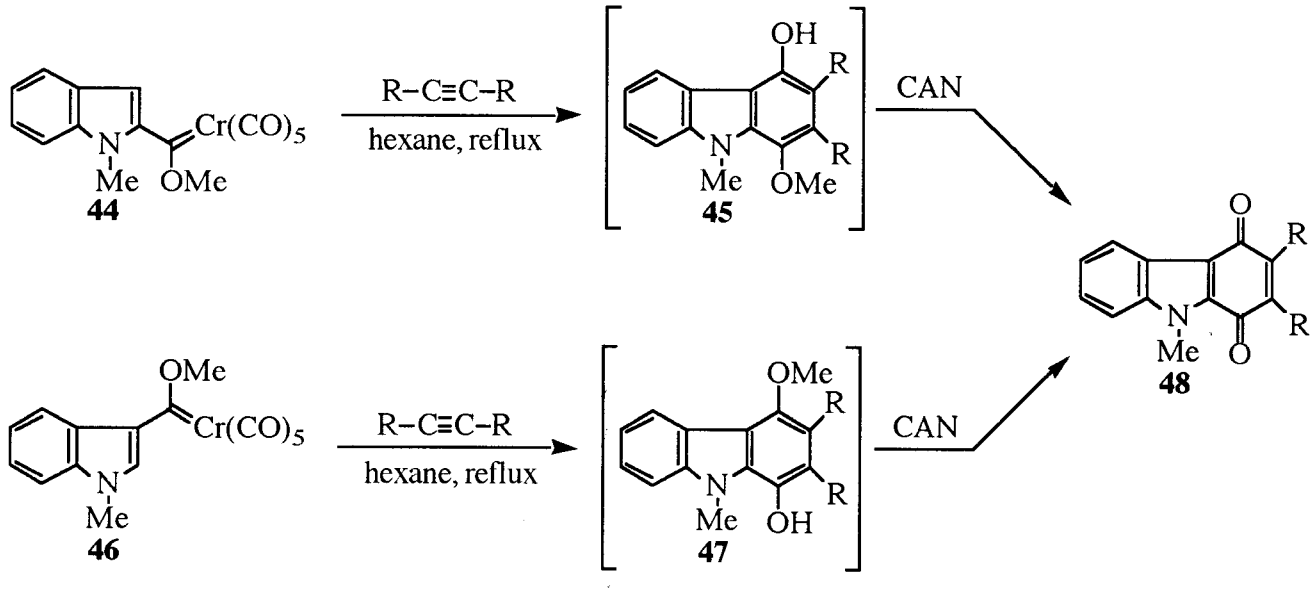
Knölker and Bauermeister[22] have also prepared murrayaquinone-A (**Ia**) from murrayafoline-A (**35b**) as described in Scheme 13. To obtain **35b**, they developed a methodology based on consecutive iron-induced C-C and C-N bond formation (Scheme 14). The key steps of this synthetic approach were an electrophilic substitution of the arylamine (**37**) by the iron complex cation (**38**) to give regio- and stereoselectively the iron complex (**39**) followed by an oxidative cyclization of this intermediate with manganese dioxide and thallium (III) trifluoroacetate to afford the iminoquinone complex (**41**). Then, a nucleophilic addition of methyllithium followed by treatment of the resulting complex (**42**) with *p*-toluenesulfonic acid gave in addition to the expected murrayafoline-A (**35b**), the iron complex (**43**) which was finally converted into **35b** with very active manganese dioxide.

Bauta *et al.*[14] have reported the synthesis of carbazolequinones (**48**) by oxidation of hydroxycarbazoles (**45**) or (**47**) with CAN. The precursors (**45**) or (**47**) were prepared through a regioselective reaction of indolecarbene chromium complexes (**44**) or (**46**) with alkynes (Scheme 15).

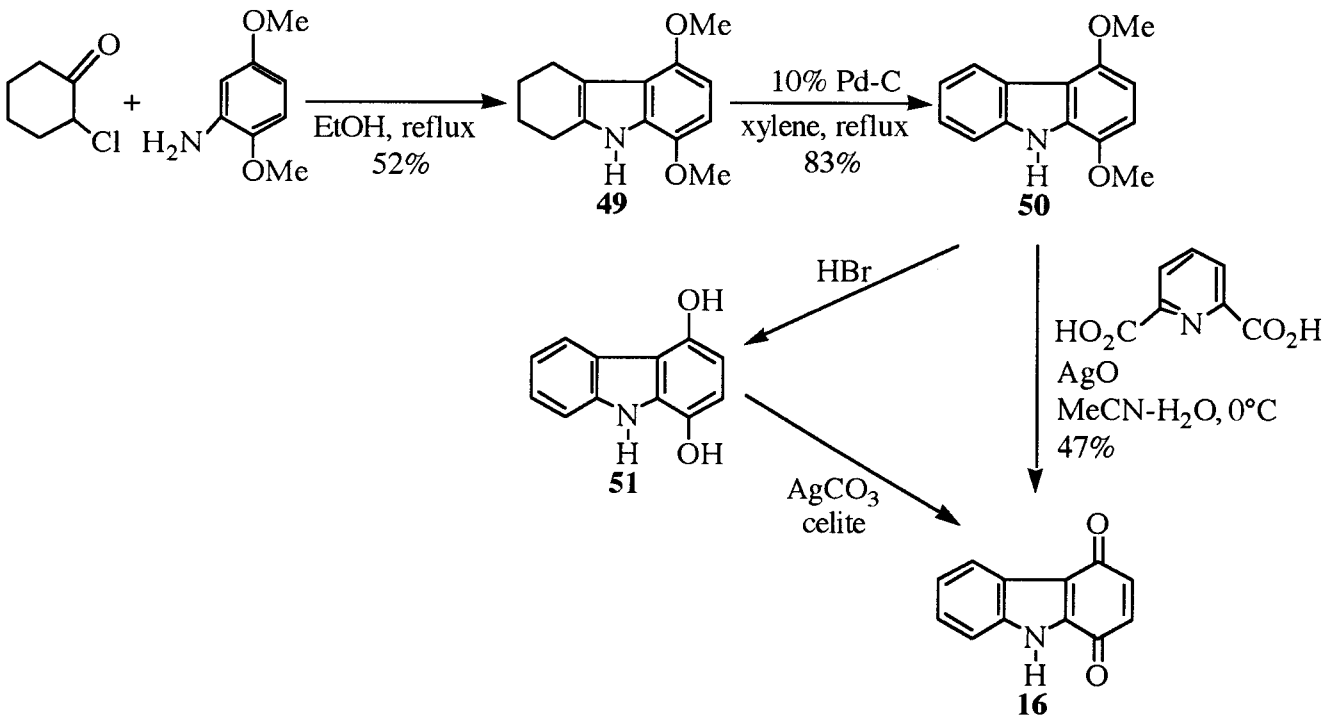
Another access to the unsubstituted carbazolequinone (**16**) was developed by Parrick and Yahya[18] (Scheme 16). Condensation of 2-chlorocyclohexanone with 2,5-dimethoxyaniline gave the intermediate (**49**) which was readily dehydrogenated to dimethoxycarbazole (**50**). The latter was converted to quinone (**16**), either directly by oxidation with silver (II) oxide in the presence of pyridine-2,6-dicarboxylic acid or, in a lower yield, by demethylation followed by oxidation with silver carbonate on celite.



Scheme 14



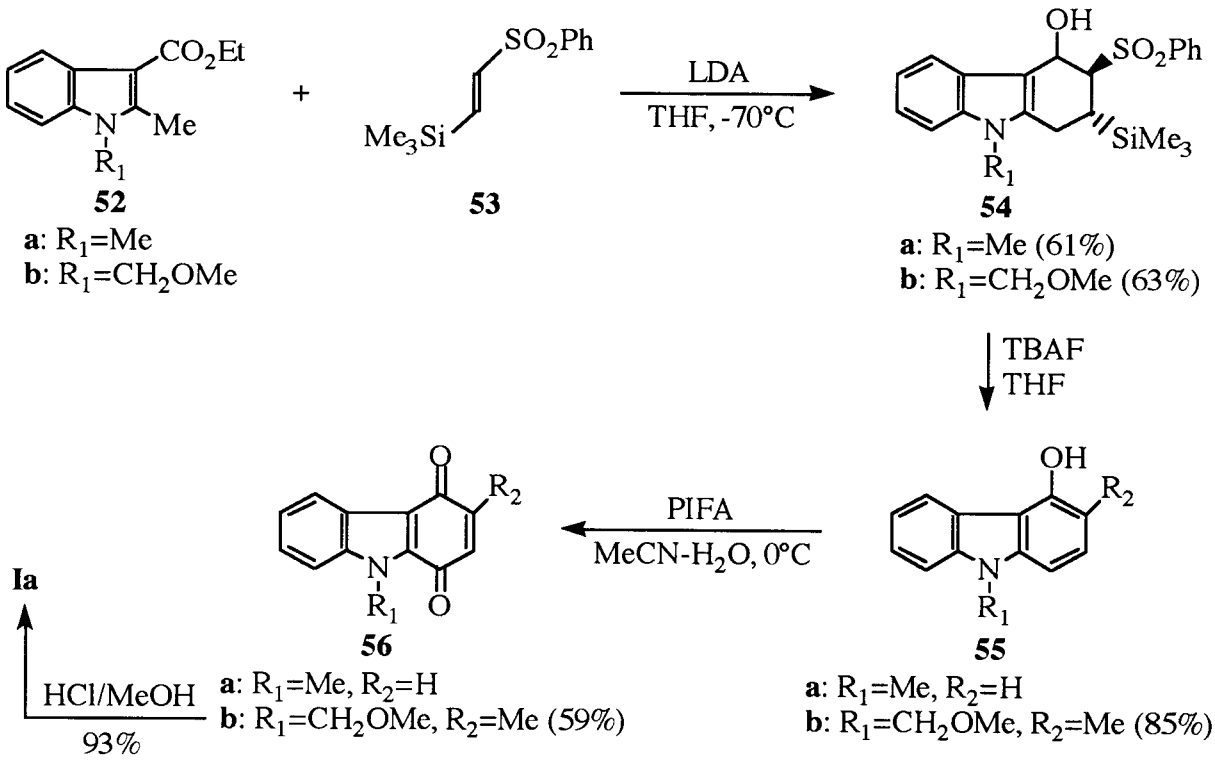
Scheme 15



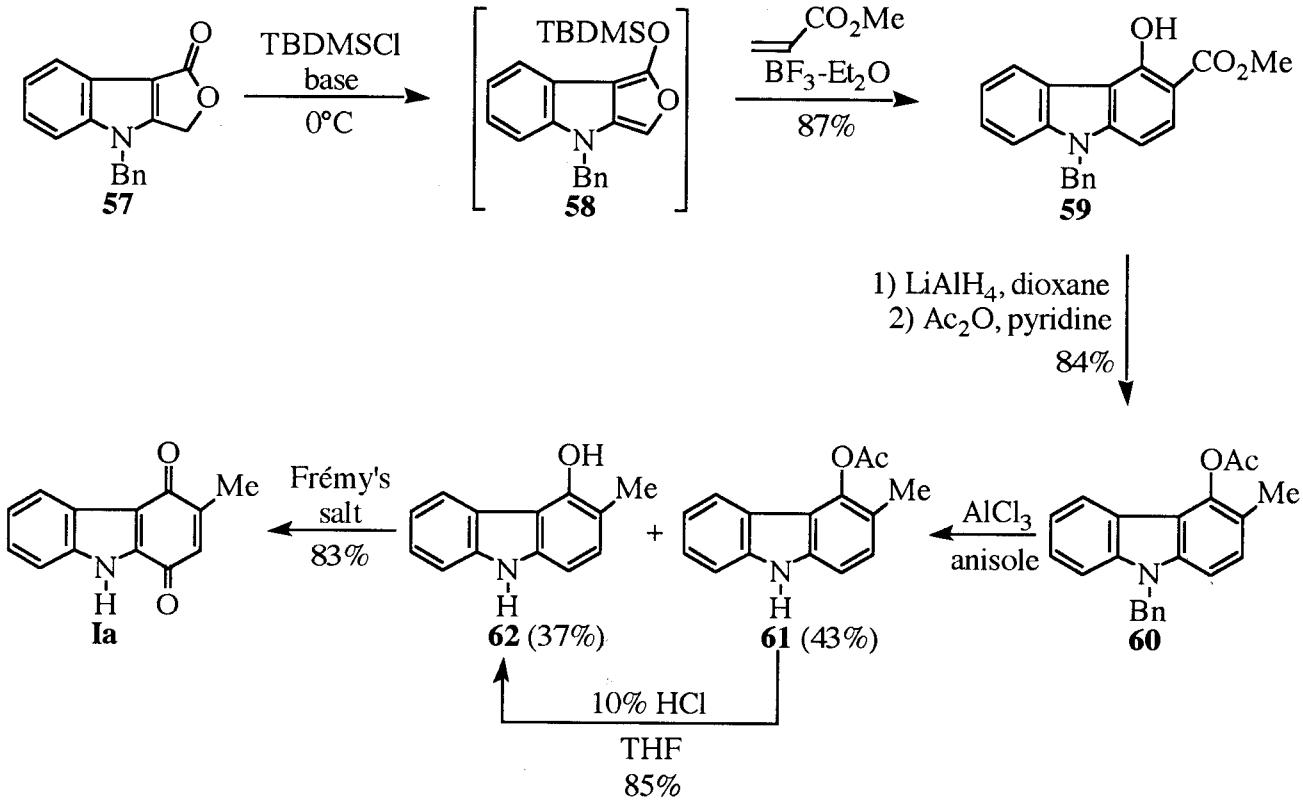
Scheme 16

Hanaoka *et al.*[19] have described the synthesis of carbazolequinone (**56a**) through an anionic cycloaddition of the indole ester (**52a**) with phenyl β-trimethylsilylvinyl sulfone (**53**) (Scheme 17). The resulting cycloadduct (**54a**) was treated with tetrabutylammonium fluoride (TBAF) to afford the phenol (**55a**) which was oxidized with PIFA to provide the expected quinone (**56a**). In this case, only the yield of the cycloaddition step was reported. This methodology was also applied to the synthesis of murrayaquinone-A (**Ia**) using **52b** as the starting material. After reaction with **53**, the resulting cycloadduct (**54b**) was methylated at C-3 with methyl iodide to give a mixture of two diastereomers (56%) which was treated with TBAF to give **55b**. Then, oxidation with PIFA and final deprotection with HCl in MeOH afforded murrayaquinone-A (**Ia**).

On the other hand, Miki and Hachiken[23] have employed Frémy's salt to oxidize, in the last step, methylcarbazole (**62**) into murrayaquinone-A (**Ia**) (Scheme 18). Their approach to the 4-hydroxycarbazole structure involved a Diels-Alder reaction between methyl acrylate and indole (**58**) which was prepared from lactone (**57**). The cycloaddition gave regioselectively carbazole (**59**). After reduction, acetylation and debenzylation of **59**, a mixture of compounds (**61**) and (**62**) was obtained. Further deacetylation of **61**, performed with hydrochloric acid, gave another amount of **62**.



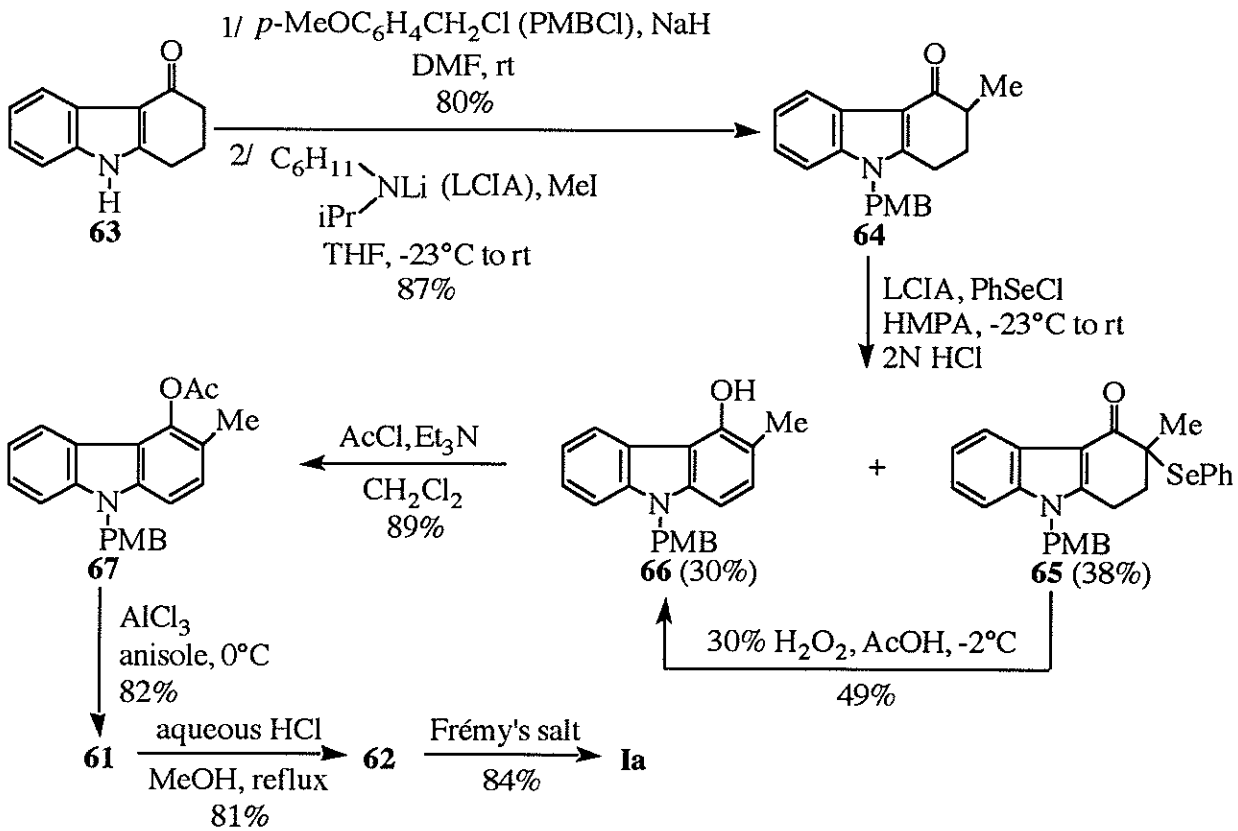
Scheme 17



Scheme 18

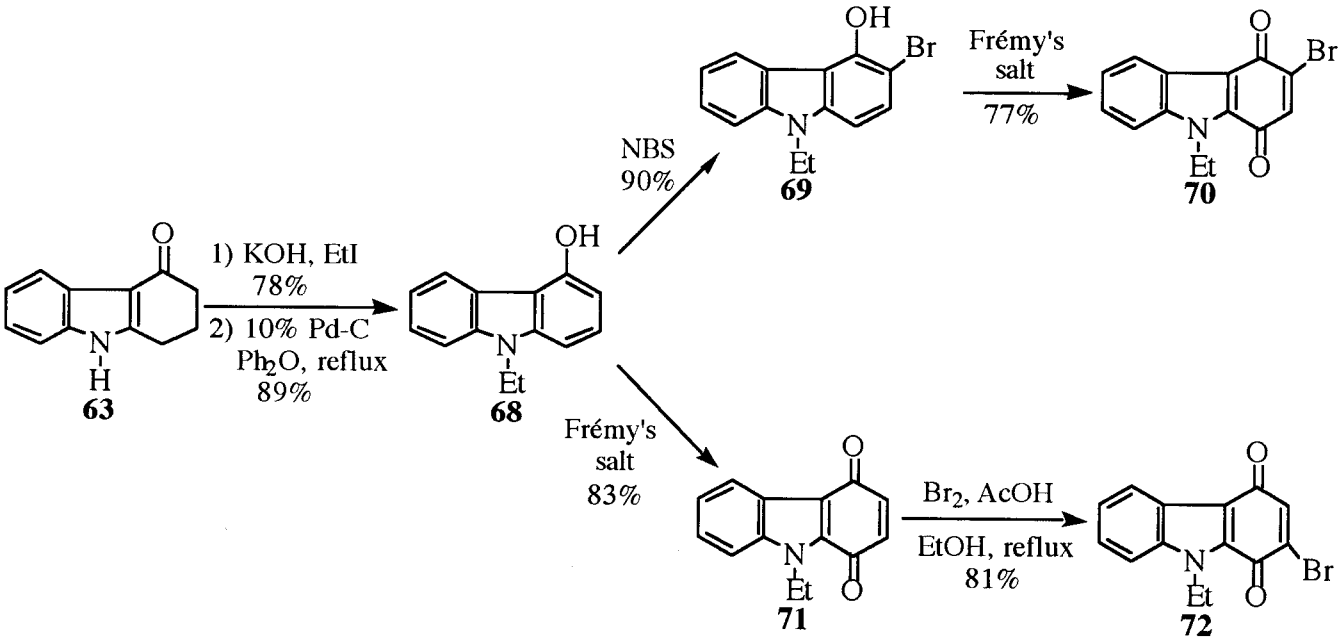
Another example of preparation of murrayaquinone-A (**Ia**) involving an oxidation step with Frémy's salt was reported by Matsuo and Ishida.[24] Their synthetic approach to the title compound started with tetrahydrocarbazolone (**63**) (Scheme 19) which has been prepared in several ways : from 1,3-cyclohexanedione monophenylhydrazone by Fischer indolization,[29] by treatment of 3-(2-iodo-phenyl)amino-2-cyclohexen-1-one with sodium hydride-copper (I) iodide[30] and also by photocyclization[31] or palladium-catalyzed[32] cyclization of 3-(2-bromophenyl) amino-2-cyclohexen-1-one.

Methylation at C-3 of tetrahydrocarbazolone (**63**) was performed as shown in Scheme 19 through protection of the NH group, treatment with methyl iodide in the presence of a base then, with phenylselenenyl chloride. A mixture of compound (**65**) and the aromatized product (**66**) was obtained. The selenenylated derivative (**65**) was converted into **66** by oxidation and elimination reaction with H_2O_2-AcOH. Oxidation of **66** with Frémy's salt gave the corresponding quinone in good yield, but attempts to remove the N-protecting group in this quinone failed. Then, by a sequence of acetylation, deprotection of the nitrogen atom and hydrolysis of the ester group, **66** was converted to **62**, which was finally oxidized with Frémy's salt to give the desired murrayaquinone-A (**Ia**).



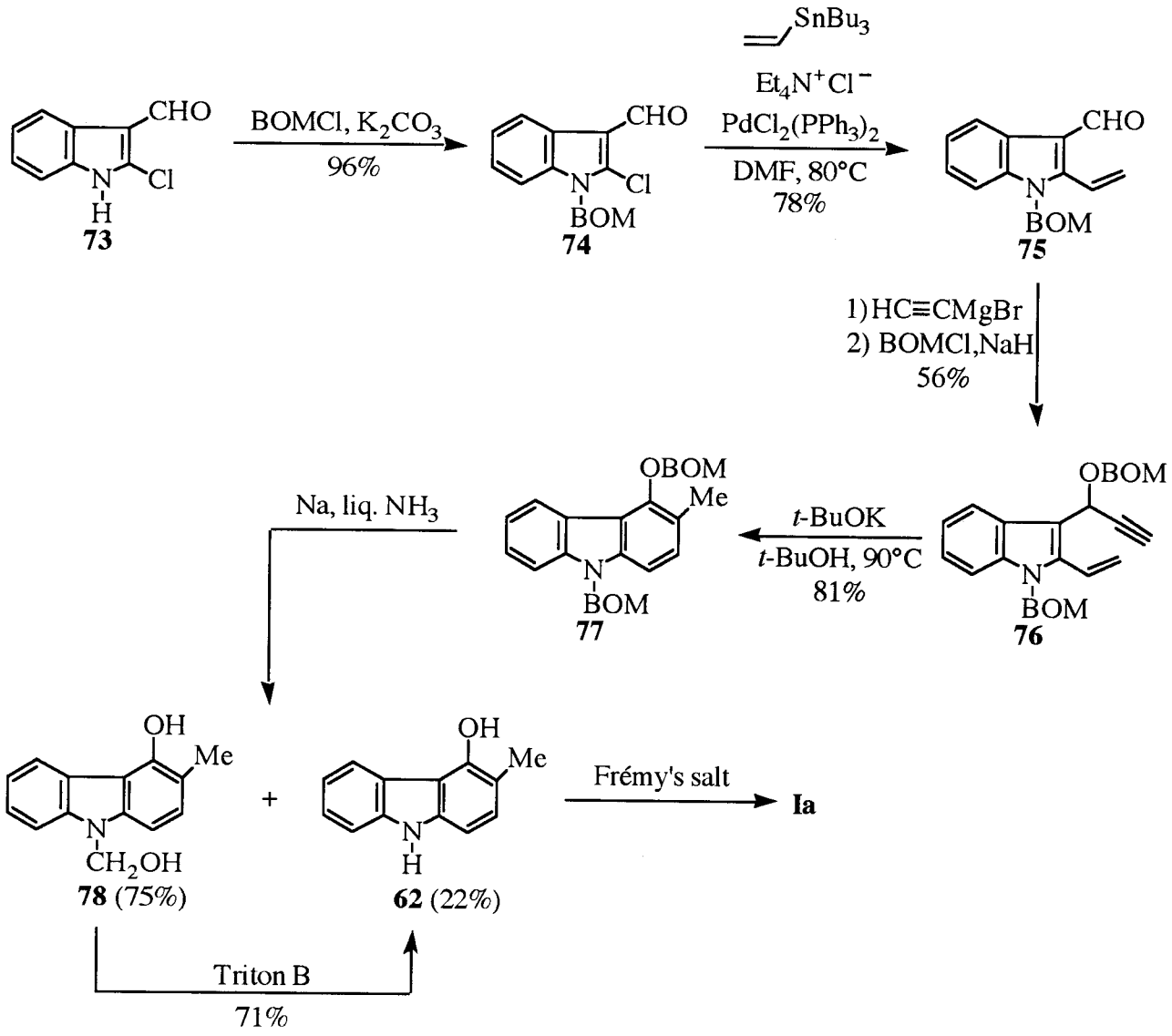
Scheme 19

In order to obtain 2- or 3-carbazolequinones (**70**) and (**72**) as efficient dienophiles towards 1- or 2-azadienes, Fillion *et al.*[25] have performed the synthesis of carbazolequinones (**70**), (**71**) and (**72**) (Scheme 20). Starting from tetrahydrocarbazolone (**63**), prepared following a Fischer indolization from 1,3-cyclohexanedione monophenylhydrazone, an N-ethylation followed by a dehydrogenation in the presence of 10% Pd-C yielded 4-hydroxycarbazole (**68**). Bromination of **68** with NBS gave 3-bromo-4-hydroxycarbazole (**69**) which was oxidized with Frémy's salt into 3-bromocarbazolequinone (**70**). On the other hand, oxidation of **68** with Frémy's salt gave carbazolequinone (**71**) which, upon treatment with bromine in acetic acid, afforded 2-bromocarbazolequinone (**72**).



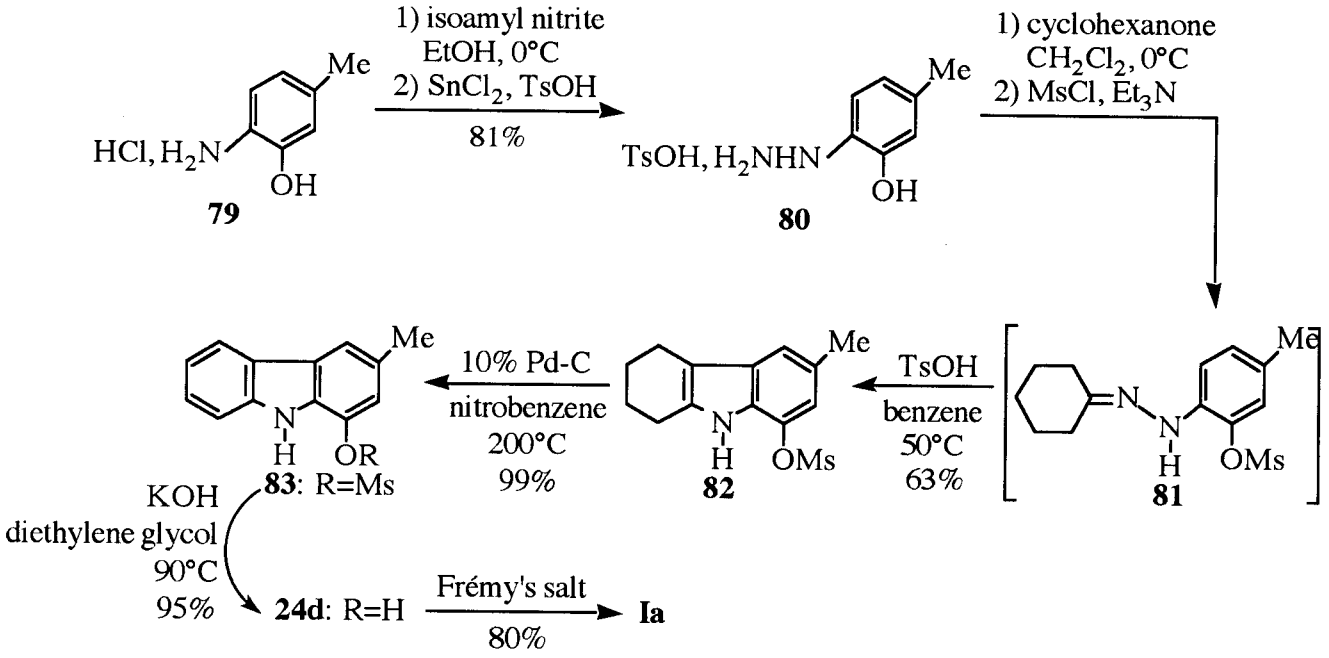
Scheme 20

Recently, Hibino *et al.*[26] have reported a new synthesis of murrayaquinone-A (**Ia**) starting from 2-chloro-3-formylindole (**73**) by an allene-mediated electrocyclic reaction involving the indole 2,3-bond (Scheme 21). After protection of the NH group with benzyloxymethyl chloride (BOMCl), the cross-coupling reaction of **74** with tributylvinyltin gave the 2-ethenylindole (**75**). The Grignard reaction of **75** with ethynylmagnesium bromide followed by treatment with benzyloxymethyl chloride afforded the 2-ethenyl-3-propargylindole (**76**), which was cyclized in the presence of potassium *tert*-butoxide to yield the 4-oxygenated carbazole (**77**). Deprotection of the latter gave a mixture of the hydroxycarbazoles (**62**) and (**78**). Further treatment of **78** with Triton B gave another amount of **62** which was converted into murrayaquinone-A (**Ia**) by oxidation with Frémy's salt.



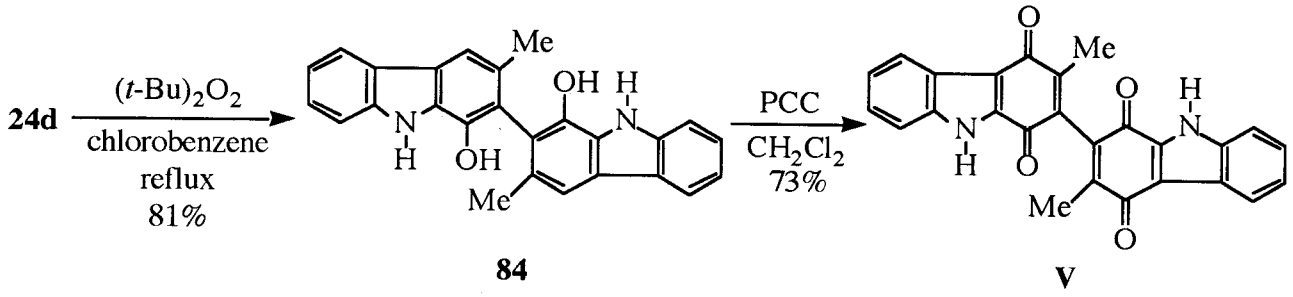
Scheme 21

Murakami *et al.*[27] have recently reported the synthesis of murrayaquinone-A (**Ia**) by oxidation of 1-hydroxycarbazole (**24d**) with Frémy's salt as previously described by Martin and Moody.[21] But, their methodology for the synthesis of this precursor was different. It was based on a Fischer indolization of 2-sulfonylphenylhydrazone (Scheme 22). Thus, 2-hydrazino-5-methylphenol *p*-toluenesulfonate (**80**), prepared from the aminophenol (**79**), was reacted with cyclohexanone to yield the corresponding hydrazone which gave **81** after protection of the OH group with methanesulfonyl chloride (MsCl). Compound (**81**) was then cyclized without purification by treatment with *p*-toluenesulfonic acid and the resulting tetrahydrocarbazole (**82**) was dehydrogenated to afford the 8-mesyloxy-6-methylcarbazole (**83**). Finally, hydrolysis of the mesyl group of **83** gave **24d**.



Scheme 22

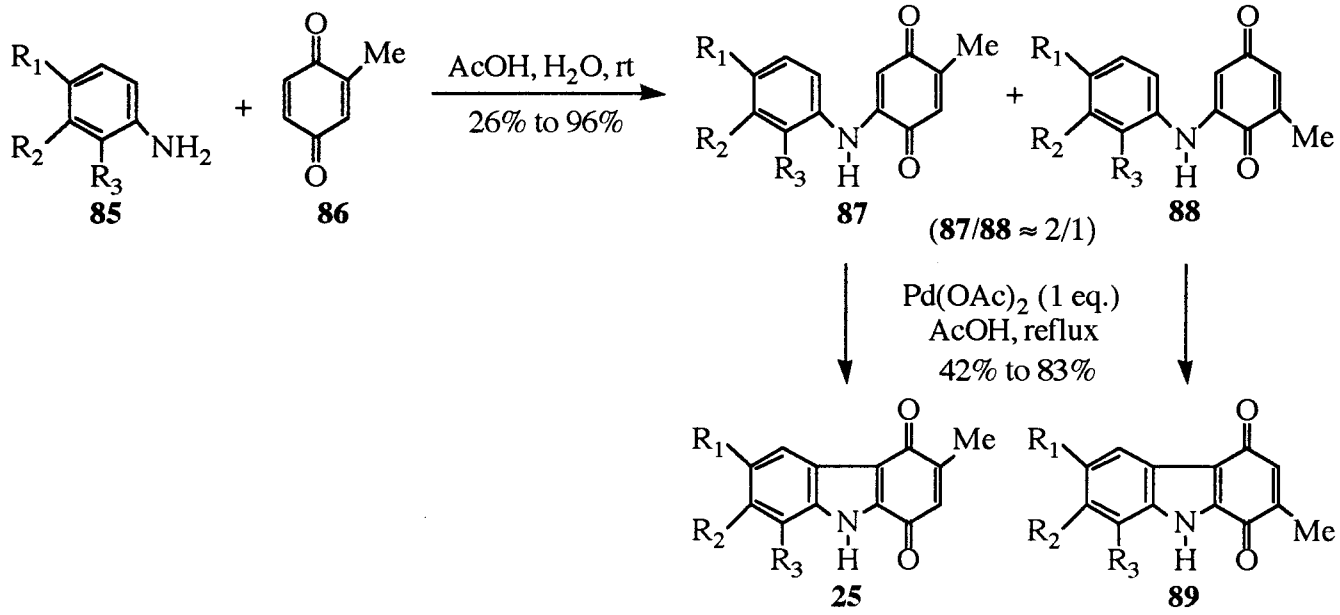
The first synthesis of bismurrayaquinone-A (**V**) was reported by Bringmann *et al.*[17] (Scheme 23). After an oxidative dimerization of 1-hydroxycarbazole (**24d**), the resulting dimer (**84**) was converted to the natural product by treatment with PCC. 1-Hydroxycarbazole (**24d**) was prepared by a Japp-Klingemann type condensation followed by cyclization (as shown in Scheme 9) and aromatization with 10% Pd-C.



Scheme 23

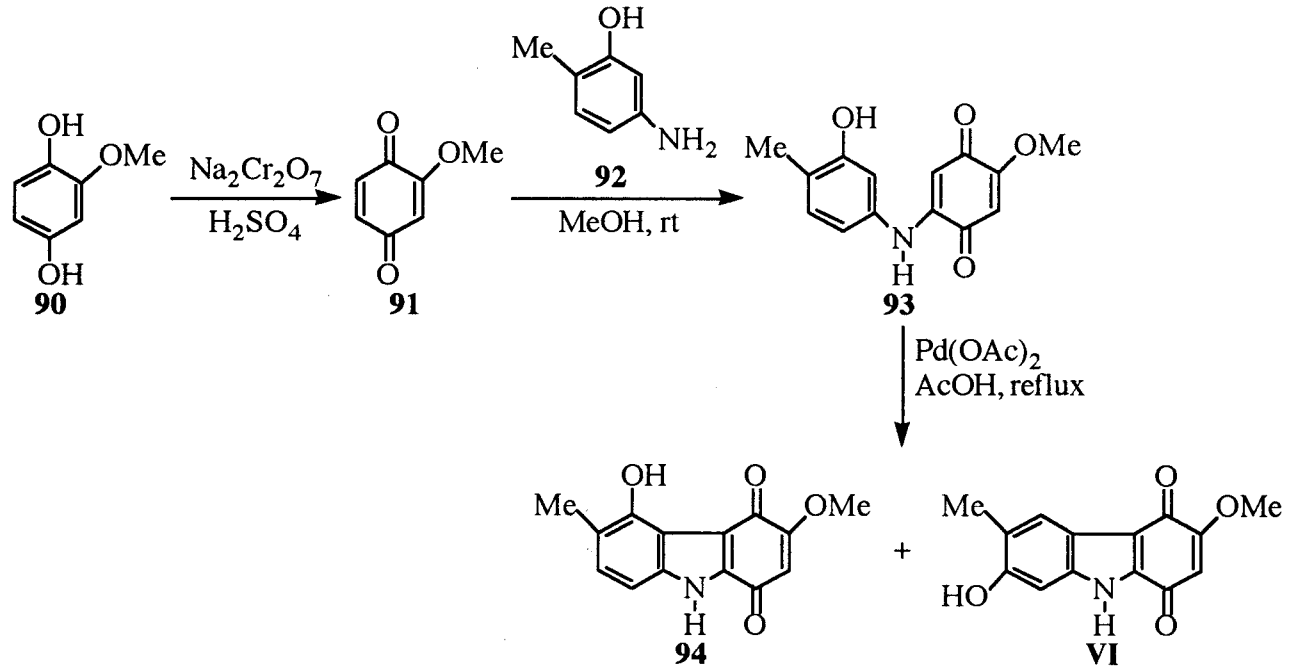
3-Cyclodehydrogenation of anilinobenzoquinones with palladium(II) diacetate.

Palladium-assisted cyclization of arylamino-1,4-benzoquinones constitutes another important route to carbazole-1,4-dione derivatives. Thus, Furukawa *et al.*[2,33] have reported the synthesis of murrayaquinone-A (**Ia**), pyrayaquinone-A (**II**) and -B (**IIIa**) and several analogues, using methyl-1,4-benzoquinone (**86**) and a series of arylamines (**85**) as starting materials. The first step of the reaction gave a mixture of regioisomers (**87**) and (**88**), which upon treatment with an equimolar amount of $Pd(OAc)_2$ in acetic acid afforded carbazolequiones (**25**) and (**89**) (Scheme 24).



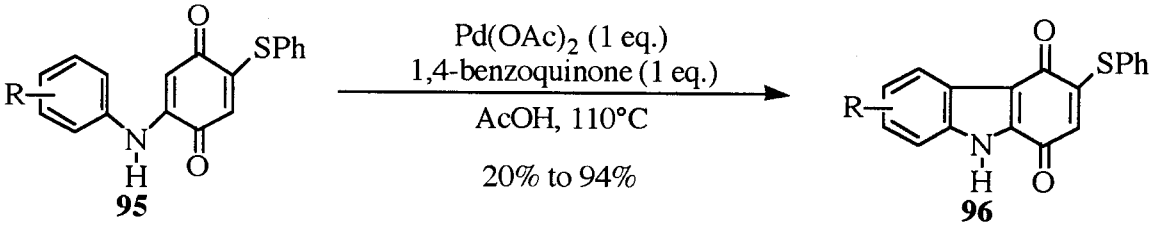
Scheme 24

In order to confirm the structure of clausenaquinone-A (**VI**), Wu *et al.*[7] performed its total synthesis from 2-methoxyhydroquinone (**90**) and 5-amino-*o*-cresol (**92**) (Scheme 25). Oxidation of **90** with chromic acid gave the methoxyquinone (**91**), which upon condensation with **92** afforded the arylaminobenzoquinone (**93**). Treatment of **93** with $Pd(OAc)_2$ in acetic acid led to the formation of two regioisomers : carbazolequinone (**94**) and clausenaquinone-A (**VI**), in a 1:1 ratio.



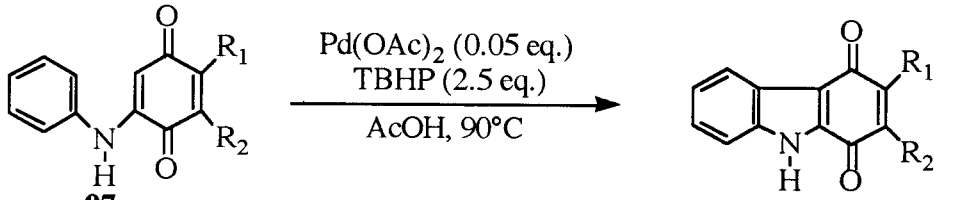
Scheme 25

Moreover, Bittner *et al.*[34] have synthesized a series of 3-phenylthiocarbazolequinones (**96**) by treatment of 5-anilino-2-phenylthio-1,4-benzoquinones (**95**) with $Pd(OAc)_2$ (Scheme 26). The reaction required stoichiometric amounts of $Pd(OAc)_2$ even in the presence of 1,4-benzoquinone as a reoxidant.



Scheme 26

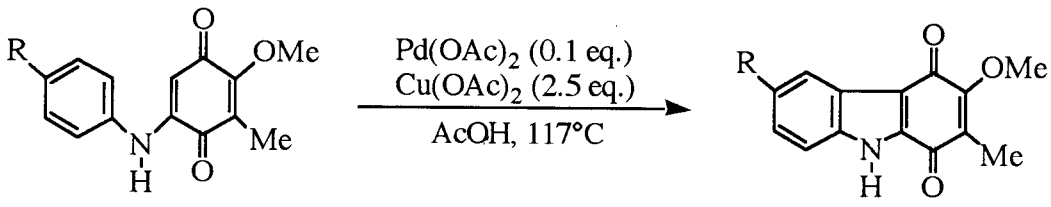
The catalytic cylization of arylaminoquinones with $Pd(OAc)_2$ in the presence of a reoxidant was also described by Akermark *et al.*[35] They reported the synthesis of murrayaquinone-A (**Ia**) and its regioisomer **98** using $Pd(OAc)_2$ in a catalytic amount (0.05 eq.) and an excess of *tert*-butyl hydroperoxide (TBHP) (2.5 eq.) as a reoxidant (Scheme 27). The yields were approximately the same as found in the stoichiometric reactions.



98: R_1=H, R_2=Me (60%)
Ia: R_1=Me, R_2=H (67%)

Scheme 27

Knölker *et al.*[36] have recently reported the effective use of cupric acetate as a reoxidant in a palladium-catalyzed oxidative cyclization of the anilinobenzoquinones (**99**) (Scheme 28).



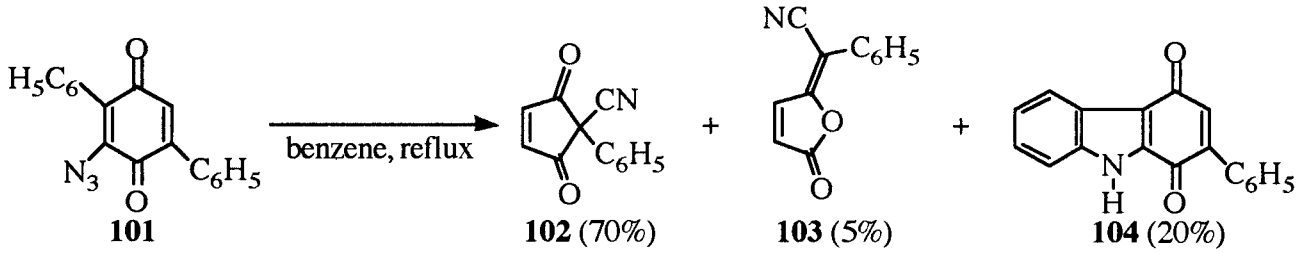
a: R=H
b: R=OMe

a: R=H (71%)
b: R=OMe (73%)

Scheme 28

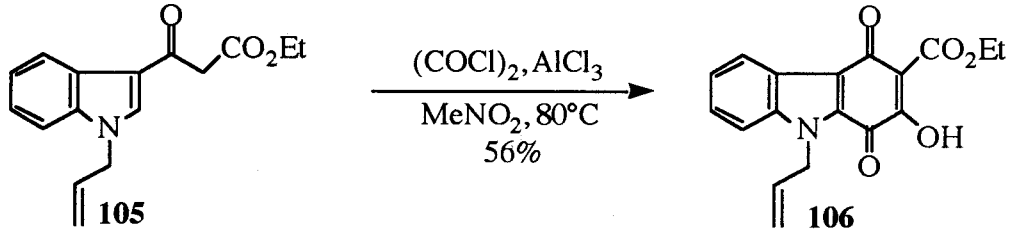
4 - Miscellaneous syntheses :

In their investigations on the thermal decomposition of monoazido-1,4-diquinone, Moore *et al.*[37] have reported the formation of a carbazolequinone starting from 2-azido-3,6-diphenyl-1,4-benzoquinone (**101**) (Scheme 29). Indeed, in refluxing benzene, decomposition of **101** gave, in addition with the expected cyclopentenedione (**102**), two minor products : compound (**103**) and 2-phenylcarbazolequinone (**104**).



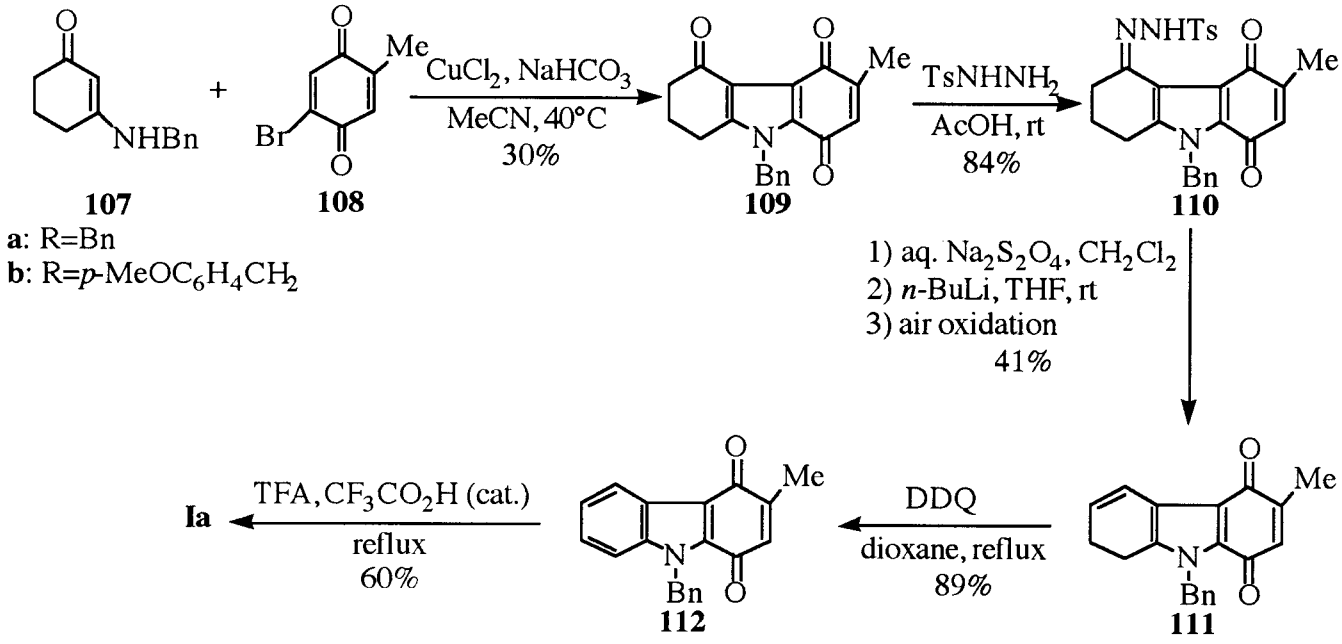
Scheme 29

As part of their work on the electrophilic bis-acylation of aromatic substrates, Sartori *et al.*[38] have devised a method affording hydroxyquinones in high yields and complete selectivity using aromatic and heteroaromatic β-keto esters. Thus, the regioselective bis-acylation of the β-keto ester (**105**) with oxalyl chloride in the presence of aluminum trichloride afforded **106** (Scheme 30).



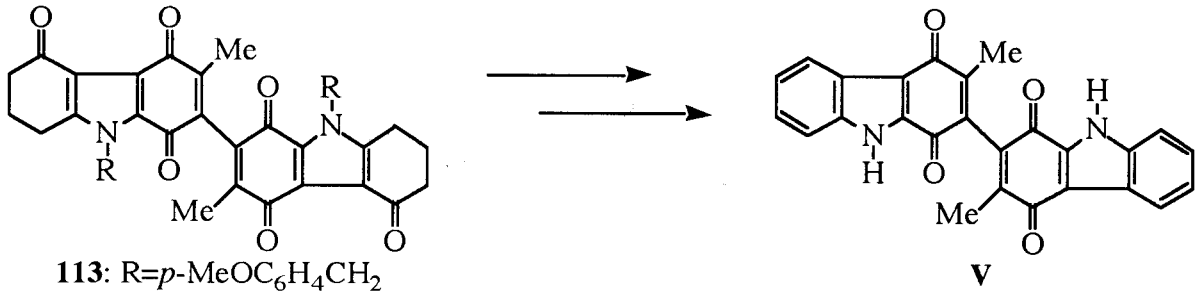
Scheme 30

Very recently, Murphy and Bertrand[39] (Scheme 31) have reported a new approach to the synthesis of murrayaquinone-A (**Ia**) and bismurrayaquinone-A (**V**) by an initial annelation of an aminocyclohexenone (**107**) with 2-methyl-5-bromobenzoquinone (**108**) followed by a series of functional group interconversions. The reaction between the *N*-benzyl enaminone (**107a**) and quinone (**108**) in the presence of sodium bicarbonate and copper (II) chloride, gave regioselectively the hexahydrocarbazoletrione (**109**), by Michael addition followed by an *in situ* reoxidation and subsequent dehalocyclization. Compound (**109**) was converted to the tosylhydrazone (**110**), then reduced with sodium dithionite and treated, without purification, with *n*-BuLi, to give, after air oxidation, compound (**111**). Then, **111** was dehydrogenated with DDQ and the resulting carbazolequinone (**112**) was deprotected to give murrayaquinone-A (**Ia**).



Scheme 31

When *N*-(*p*-methoxybenzyl) enaminone (**107b**) was employed, the annelation step gave the dimeric side-product (**113**) (Scheme 32) which was converted to bismurrayaquinone-A (**V**) using the strategy described in Scheme 31.



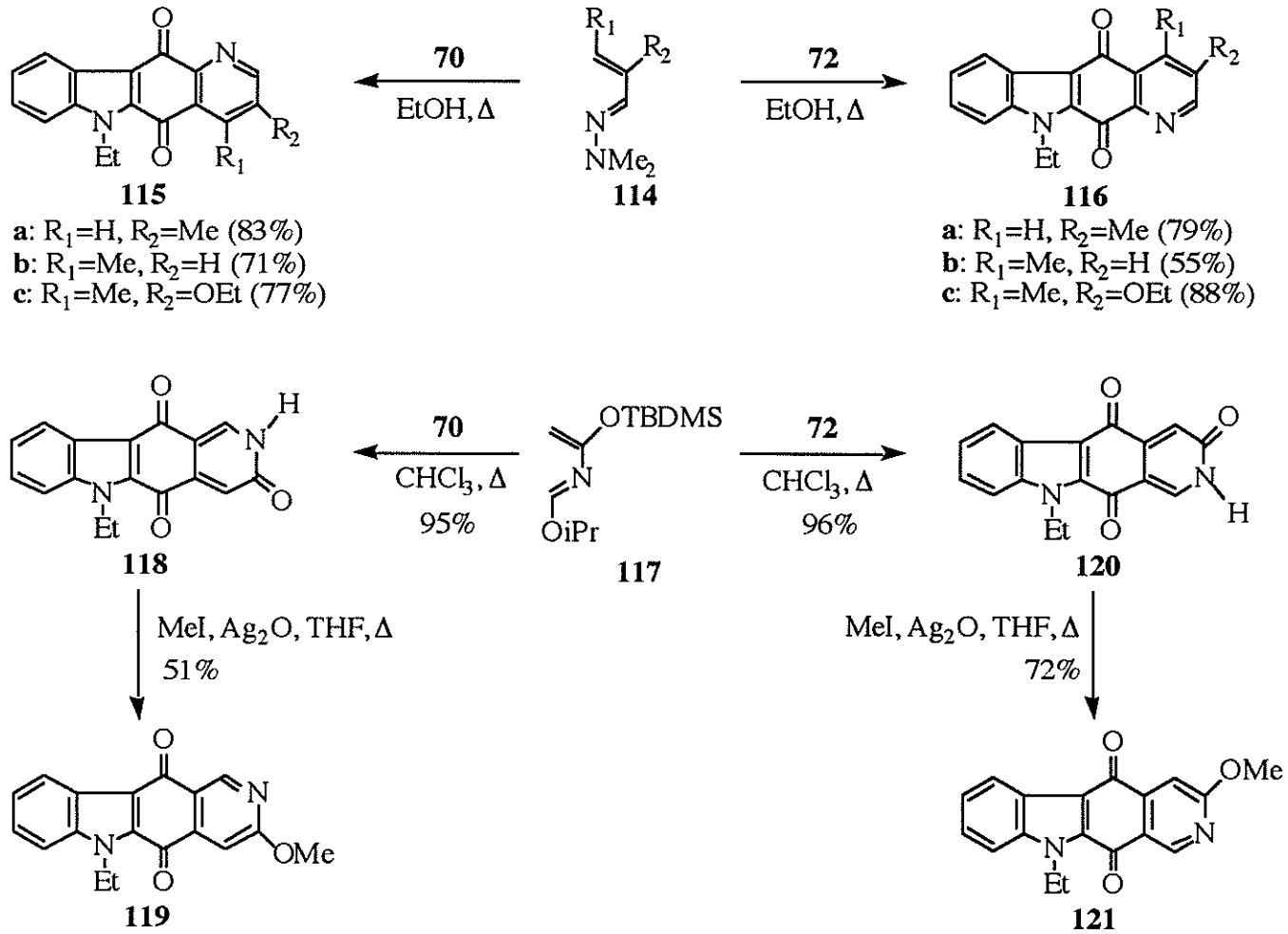
Scheme 32

PROPERTIES

1 - As efficient dienophiles towards 1- or 2-azadienes :

In continuation of their interest on heterocyclic quinones, Fillion *et al.*[25] developed a hetero Diels-Alder strategy based on the cycloadditions of carbazole-1,4-diones (**70**) and (**72**) towards azadienes (**114**) and (**117**) (Scheme 33). Thus, reactions with 1-azadienes (**114**), performed at reflux of ethanol, afforded regiospecifically the corresponding pyridocarbazolequinones (**115**) and (**116**). It appears that the unbrominated carbon of these quinones was exclusively attacked by the nucleophilic end of azadienes.

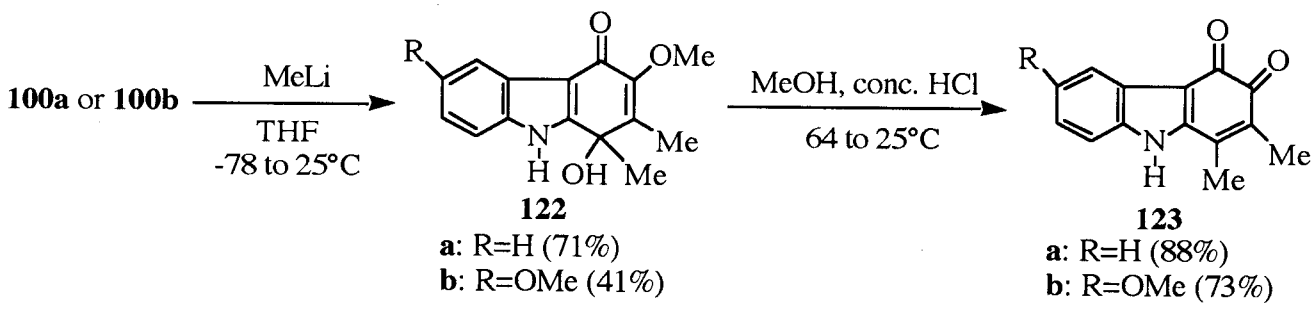
This orientational regiocontrol of the bromine atom was also applied in the cycloaddition with 2-azadiene (**117**). Indeed, compounds (**118**) and (**120**) were regiospecifically obtained in an excellent yield. Then, *O*-methylation of the lactam function, performed by treatment of **118** and **120** with silver oxide and methyl iodide in tetrahydrofuran (THF), gave the corresponding pyridocarbazolequinones (**119**) and (**121**).



Scheme 33

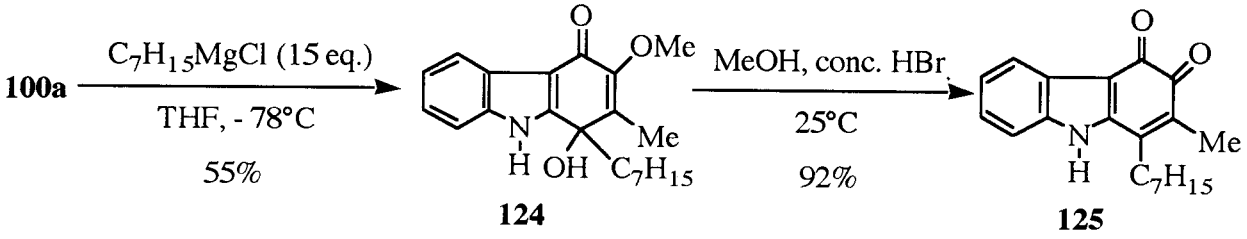
2 - As precursors for carbazole-3,4-diones :

Knölker *et al.*[36] reported the use of carbazole-1,4-diones as precursors for the synthesis of biologically active carbazole alkaloids. Indeed, the regioselective addition of methyllithium to **100a** or **100b** (Scheme 34) afforded respectively carbazomycin-G (**122a**) and -H (**122b**) which were previously isolated from streptoverticillium ehimense. Moreover, **122a** and **122b** were converted to carbazole-3,4-diones (**123a**) and (**123b**) respectively, by elimination of methanol under acidic conditions.



Scheme 34

On the other hand, the regioselective introduction of a heptyl side chain at C-1 in **100a** (Scheme 35) provided carbazolequinol (**124**) which upon treatment with concentrated hydrogen bromide in methanol gave carbazoquinocin-C (**125**), a natural product isolated from *streptomyces violaceus* 2448-SVT2.



Scheme 35

3 - Biological properties :

Some carbazole-1,4-dione alkaloids have been described for their pharmacological properties: Murrayaquinone-A (**Ia**) exhibited a cardiotonic activity,[40] while clausenaquinone-A (**VI**) inhibited the growth of tumor cells, like HCT-8, RPMI-7951 and TE671 with IC_{50} of 0.92, 0.22 and 3.82 μg/mL respectively[7] and showed also an inhibition of the rabbit platelet aggregation of 100 ± 0.8% at 10 μg/mL.

On the other hand, carbazolequinones (**9**) were found to possess interesting biological activities. Indeed, when nitrogen is substituted by a *para*-sulfophenyl group, an aqueous solution of **9** showed a tranquillizer property on mice with an effective dose of 250 mg/kg.[11c] Moreover, significant antibacterial and antifungal activities were observed for some carbazolequinones (**9**) substituted by a thiazole[11e] or a peptide[11f] moiety. In addition, these carbazolequiones showed also good vat-dyeing properties.[11a, b]

CONCLUSION

The carbazole-1,4-dione skeleton exists in a large number of biologically active alkaloids. Since their isolation, several synthetic approaches to these compounds or structural analogues have been reported. Three general methods have been used for this purpose. The condensation of diquinones with primary amines constitutes a concise synthesis of 6-hydroxycarbazole-1,4-diones with a wide variety of subtituents on the nitrogen atom. On the other hand, oxidation of tetrahydrocarbazolones and hydroxy- or methoxycarbazoles provides a convenient method to reach naturally occurring carbazolequinones and a range of substituted analogues. However, this methodology generally requires a sequence of several steps to obtain the intermediate structures. The more recent method is the cyclodehydrogenation of arylamino-1,4-benzoquinones with palladium (II) diacetate, which represents a facile one step oxidative coupling providing a series of substituted carbazole-1,4-diones. The process usually needs a stoichiometric quantity of $Pd(OAc)_2$. However, in some cases, the latter is successfully used in a catalytic amount in the presence of an oxidant. Finally, carbazole-1,4-diones can be considerate as potential therapeutic agents and direct precursors for biologically active carbazole alkaloids. Moreover, their use as dienophiles in Diels-Alder reactions may constitute an efficient route to their tetracyclic homologues, as it was already demonstrated by the synthesis of pyridocarbazolequinone derivatives.

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