The synthesis of quinones

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Reviewing the literature published between 1 January 1996 and 30 June 1998

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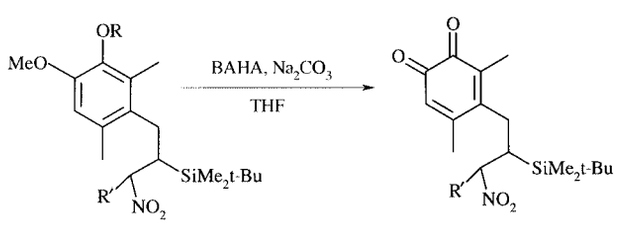
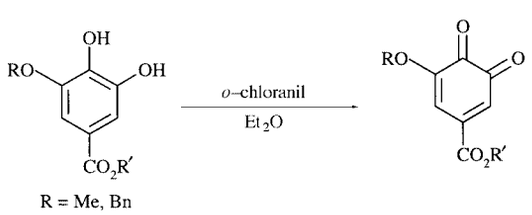
1 Synthesis of benzoquinones

1.1 Synthesis of benzo-1,2-quinones

During the period under review few references have appeared on the synthesis of benzo-1,2-quinones; those that have appeared mostly concern the oxidation of 1,2-dihydroxylated benzenes. Oxidation of 1-hydroxy or 1-*tert*-butyldimethylsilyloxy-2-methoxybenzene with tris(4-bromophenyl)aminium hexachloroantimonate (BAHA, Weitz' aminium salt) in THF gave benzo-1,2-quinones in 70% yields (Scheme 1).[1] The oxidation of monoprotected gallates with *o*-chloranil (tetrachlorobenzo-1,2-quinone) has been reported to give benzo-1,2-quinones in excellent yield (76–87%) (Scheme 2).[2] The electrochemical oxidation followed by electrochemical reduction of 2,3,4-trihydroxybenzophenones in the presence of amino alcohols or amines in one-pot gives 2,4-dihydroxy-3-aminobenzophenone derivatives in 15–60% yield *via* the intermediacy of the benzo-3,4-quinone (Scheme 3).[3] The oxidation of mononuclear phenols to 1,2-quinones by transition-metal-mediated hydroperoxide has been reviewed.[4]

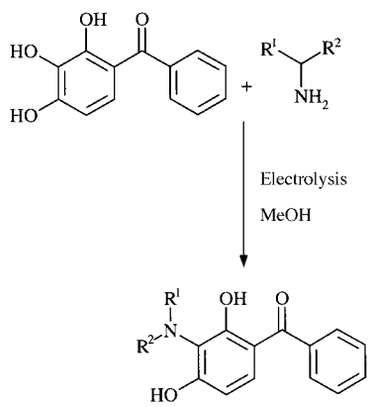


Scheme 1



R = Me, Bn

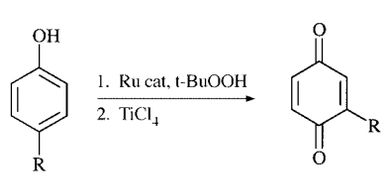
Scheme 2



Scheme 3

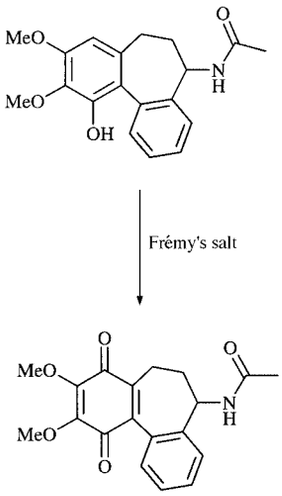
1.2 Synthesis of benzo-1,4-quinones

Several techniques have appeared for the oxidation of phenols to benzoquinones with most of the examples described being benzo-1,4-quinones. Ruthenium catalysed oxidation of 4-substituted phenols with *tert*-butyl hydroperoxide in ethyl acetate or benzene followed by treatment with titanium tetrachloride gives high yields (70–80%) of 2-substituted benzo-1,4-quinones with the 4-substituent of the phenol migrating to the 2-position of the benzo-1,4-quinone (Scheme 4).[5] Polymer supported vanadium complexes have been reported as catalysts for the *tert*-butyl hydroperoxide oxidation of phenols to benzo-1,4-quinones in 65–95% yields.[6] A mixture of cobalt and manganese salts of *p*-aminobenzoic acid supported on silica gel catalyses the oxidation of phenols to benzo-1,4-quinones in 36–65% yield.[7] Phenols have been oxidised to benzo-1,4-quinones in a two step procedure *via para*-sulfinylation followed by a Pummerer rearrangement induced by trifluoroacetic anhydride on the resulting *p*-sulfinylphenols;[8] overall yields for this process are moderate. The highly oxygenated aromatic ring of 1-demethylthiocolchicine was oxidised to the 1,4-quinone by Frémy's salt[9] (Scheme 5).



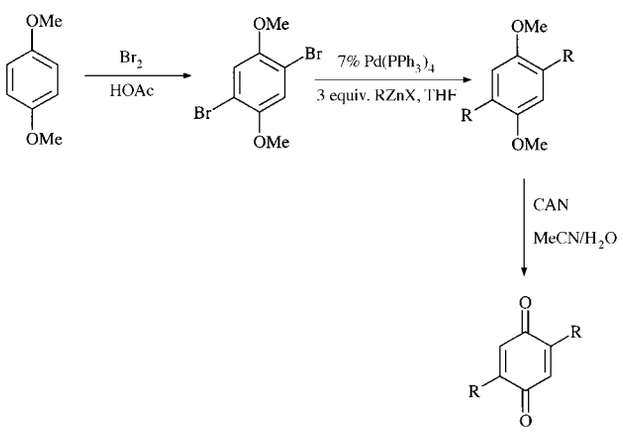
Scheme 4

The oxidation of 1,4-dioxygenated benzenes remains the most widely reported route to benzo-1,4-quinones. For hydroquinones oxidants utilised include: copper(II) sulfate on alumina[10] (yields 92–98%), ferric chloride in DMF[11] (yields 9–36%), ceric ammonium nitrate (CAN) in acetonitrile–water[12–14] (yields 70–95%), silver(I) oxide in benzene[15–18] (yields 50–90%) and sodium hypochlorite[19] (yield 95%). 2-Alkyl-3,5,6-trichlorobenzo-1,4-quinones have been prepared from 2-alkylhydroquinones in low yield by reaction with chlorine gas in refluxing

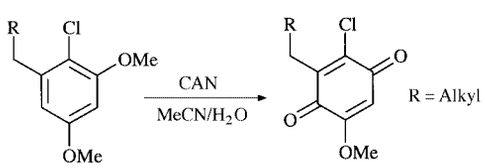


Scheme 5

aqueous acetic acid.[20] 1,4-Dimethoxybenzenes are also readily oxidised to benzo-1,4-quinones; CAN in acetonitrile–water[21,22] is the most commonly reported oxidant, THF–water has also been used.[23] This transformation is at the heart of an elegant synthesis of symmetrical 2,5-disubstituted benzo-1,4-quinones from 1,4-dimethoxybenzene *via* a palladium catalysed double Negishi coupling[23] (Scheme 6). For R = Aryl the yields of the coupling are good (53–93%), for R = Alkyl yields are moderate (30–42%); the yields for the CAN oxidation are good (65–95%). 1,3-Dimethoxy-5-alkyl-4-chlorobenzenes have been oxidised by CAN in acetonitrile–water to give 3-methoxy-5-alkyl-6-chlorobenzo-1,4-quinones[24] which may then be hydrolysed to 3-methoxy-5-alkyl-6-hydroxybenzo-1,4-quinones (Scheme 7).



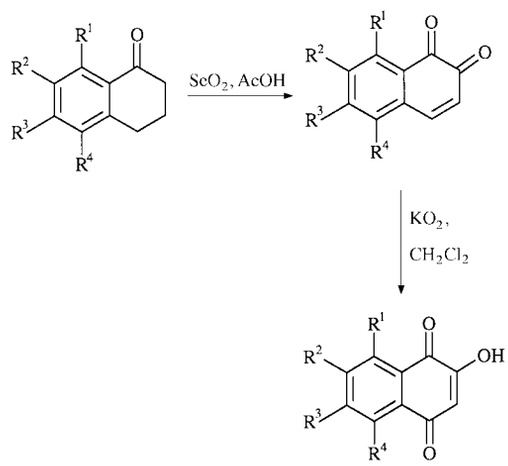
Scheme 6



Scheme 7

2 Synthesis of naphthoquinones

Naphthols may be oxidised to naphtho-1,2-quinones by peroxides under transition metal catalysis, this topic has recently been reviewed.[4] 2-Methylnaphthalene has been oxidised to a mixture of 2-methylnaphtho-1,4-quinone and 6-methylnaphtho-1,4-quinone in aqueous acetonitrile solution by potassium persulfate in the presence of the water-soluble metalloporphyrins MnTPPS (TPPS = tetrasodium *meso*-tetrakis(*p*-sulfonatophenyl)porphyrin) and FeTMPS (TMPS = octasodium *meso*-tetrakis(3,5-disulfonatomesityl)porphyrin) in moderate to excellent yields (37–100%) though in small scale reactions.[25] 2,3-Dimethylnaphthalene has been oxidised to 2,3-dimethylnaphtho-1,4-quinone with chromium trioxide in acetic acid.[26] Naphtho-1,4-quinones may readily be prepared by the CAN oxidation of 1,4-dimethoxynaphthols in a similar manner to 1,4-dimethoxybenzenes.[27,28] Naphtho-1,2-quinones have been prepared from 1-tetralones by oxidation with selenium dioxide in acetic acid in good yields (60–78%), subsequent oxidation with potassium superoxide in dichloromethane yields 2-hydroxynaphtho-1,4-quinones in excellent yields (95–98%)[29] (Scheme 8).



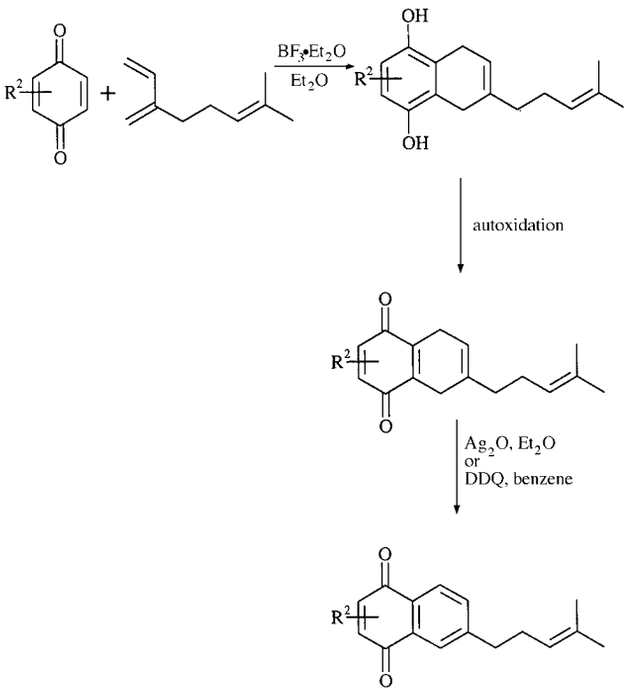
Scheme 8

The [4+2] cycloadditions continue to be an important route to naphtho-1,4-quinones. A series of terpenylnaphthoquinones have been prepared by reaction between benzo-1,4-quinone, 2-methylbenzo-1,4-quinone and α-myrcene to give the dihydronaphthoquinone followed by silver oxide or DDQ oxidation[30] (Scheme 9). The addition of 2-(*p*-tolylsulfinyl)-benzo-1,4-quinone to 1-[(trimethylsilyl)oxy]buta-1,3-diene gave naphtho-1,4-quinone by thermal elimination of the sulfinyl and trimethylsiloxy groups at room temperature.[31] The reaction of *o*-quinodimethanes with dienophiles has also been used to prepare naphtho-1,4-quinones and two interesting methods for the preparation of *o*-quinodimethanes from α,α′-dibromo-3,6-dimethoxy-*o*-xylene have appeared. The first method[26] utilises sodium hydroxymethanesulfonate (Rongalite) to prepare the sultine which may be isolated by chromatography and stored. Thermolysis of the sultine occurs in refluxing toluene with extrusion of SO_2 to give the *o*-quinodimethane which may be readily trapped by dienophiles, in this case fullerenes. Deprotection and oxidation give the naphthoquinone (Scheme 10). The second method uses activated nickel to prepare the *o*-quinodimethane in the presence of fumaronitrile as the dienophile to give 2,3-dicyano-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene in 71% yield. Aromatisation with *N*-bromosuccinimide–triethylamine followed by oxidation with CAN gave 6,7-dicyanonaphtho-1,4-quinone in 76% yield.[28]

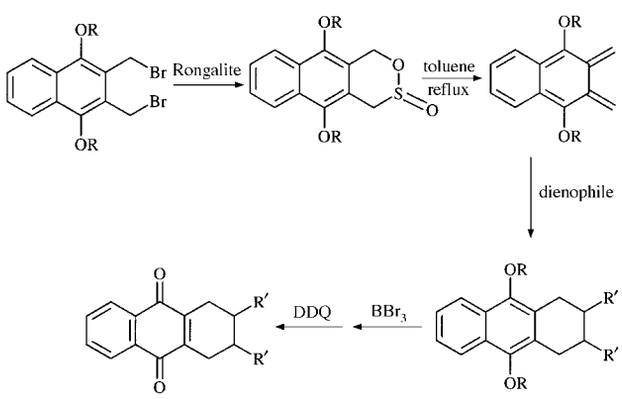
2.1 Substitution of benzoquinones and naphthoquinones

The [2+2] cycloaddition of styrenes with quinones has been reported[32,33] to proceed under Lewis acid ($MeAlCl_2$, $TiCl_4$, $SnCl_4$ or $BF_3{\cdot}OEt_2$) catalysis to give cyclobutanes which upon treatment with protic acid rearrange cleanly to dihydrobenzofurans (Scheme 11).

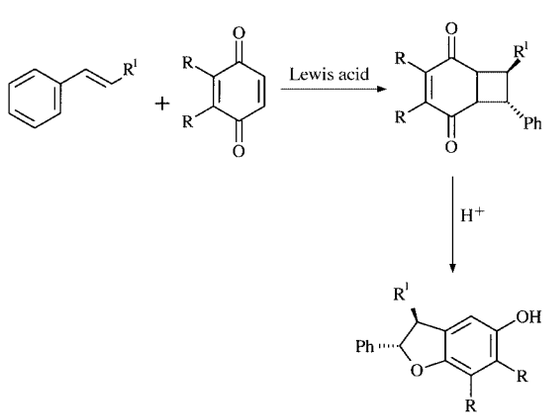
The [4+2] cycloaddition of naphtho-1,2-quinone with levopimaric acid, or one of its esters, gives a dihydronaphtho-1,2-quinone polycyclic adduct which on treatment with alcoholic sodium hydroxide with exclusion of oxygen gives a high yield of the quinone[34] (Scheme 12).



Scheme 9

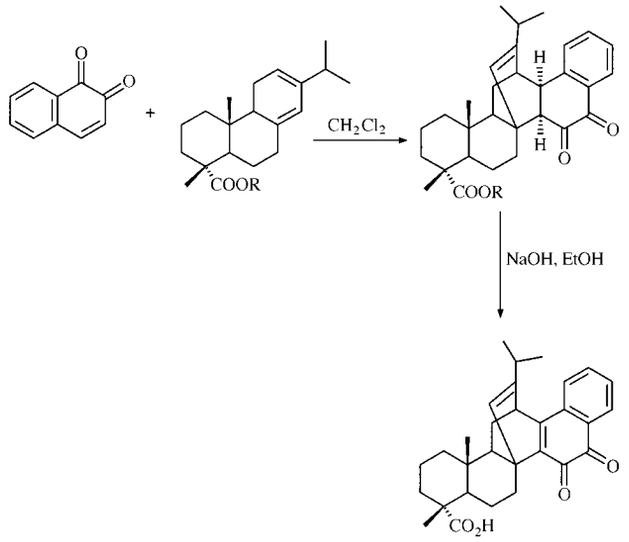


Scheme 10



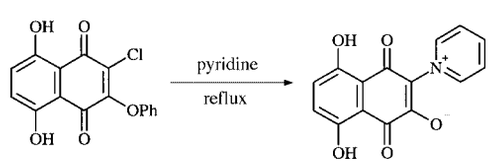
Scheme 11

Aza-substituted quinones can be prepared by direct addition of nitrogen nucleophiles to quinones, aziridinyl quinones have been prepared in poor to moderate yields (2–37%) by the direct addition route.[35] A general route to (alkylamino) naphthoquinones *via* alkylamine addition to bromonaphthoquinones in good to excellent (51–92%) yields has been reported.[36] The direct addition of hydrazoic acid (generated from sodium azide and strong acid) to naphthoquinones in a polar solvent such as methanol, at room temperature or above, gives good to



Scheme 12

excellent yields (58–97%) of 2-aminonaphtho-1,4-quinones.[37] Addition of hydrazoic acid to benzoquinones under the same conditions at −78 °C gives azidobenzohydroquinones in good to excellent yields. It has been reported that on prolonged heating in neat pyridine or 3-picoline, the pyridine/picoline added to 2-chloro-3-phenoxynaphthazarin to give the 3-pyridinium-1-yl-2-naphthoxide in 50% yield[38] (Scheme 13). The proposed mechanism postulates initial action of pyridine on the 2 position followed by loss of Cl^-, the chloride then attacks the aromatic ring of the phenoxy group resulting in C–O bond cleavage leaving the oxygen attached to the quinone. 2-Oxo-3-(pyridinium-1-yl)naphtho-1,4-quinone betaines are obtained in moderate to good yield (25–80%) by oxidation of naphtho-1,4-quinones with iodine–MnO_2 or hydrogen peroxide in the presence of substituted pyridines.[39] Pyridines have been added to *p*-chloranil and *p*-fluoranil (tetrachloro- and tetrafluoro-benzo-1,4-quinone) under mild conditions to give pyridinium-oxy zwitterionic quinones.[40]

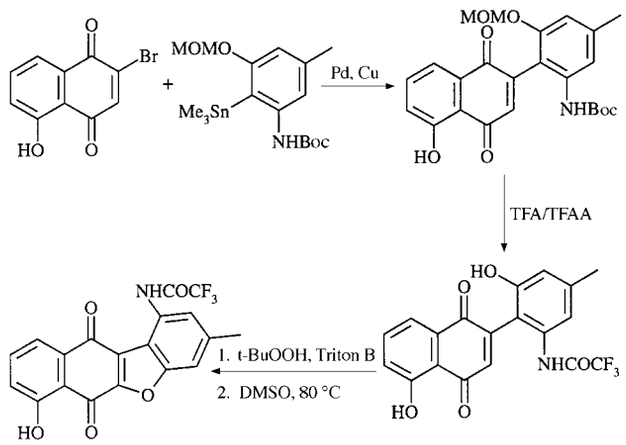


Scheme 13

Two reports of new methods of halogenation of quinones have appeared: naphthoquinones have been chlorinated in good to excellent yields (50–98%) by mercury(II) chloride or copper(II) chloride in acetic acid in the presence of catalytic quantities of iodine.[41] Benzo-1,4-quinones and naphthoquinones have been brominated with bromine adsorbed on neutral alumina and iodine monobromide in acetic acid in good to excellent yields (63–97%); the reaction is accelerated by microwave irradiation.[42] Microwave irradiation has also been used to accelerate the selective mercuration of naphtho-1,4-quinone with arylmercury(II) chlorides (also generated by microwave irradiation). The reaction, which takes 12 hours by conventional chemistry, is complete in 2–3 minutes and good to excellent yields (64–85%) of 2-[arylmercury(II)]naphtho-1,4-quinones are produced.[43]

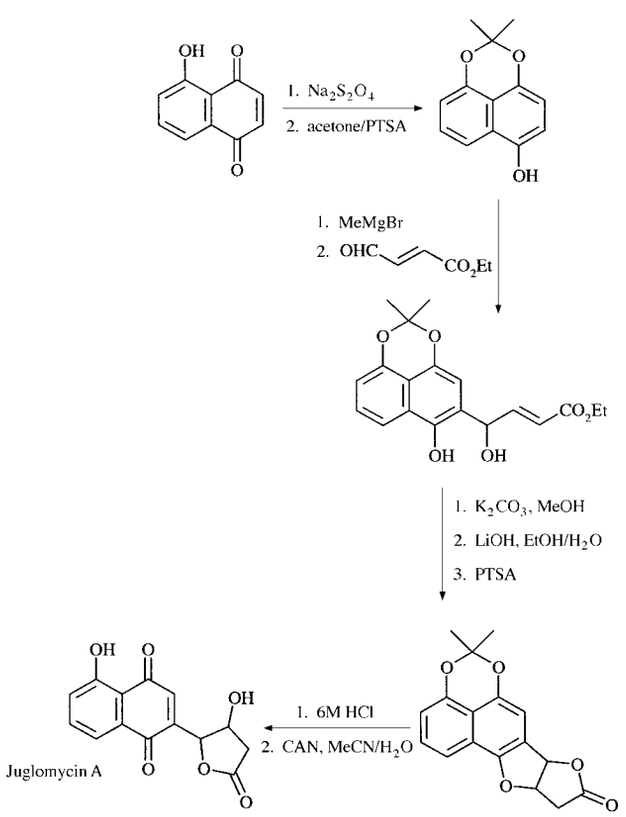
The reaction of benzo-1,4-quinone with a monoamide of oxalic acid and ammonium persulfate in the presence of catalytic silver nitrate gave the acylated benzo-1,4-quinone in 62% yield *via* the acylated hydroquinone;[23] in the absence of the silver the hydroquinone was isolated. 2,6-Dimethoxybenzo-1,4-quinone has been prenylated to give a (1:1) mixture of mono- and di-prenylated dimethoxybenzoquinones by prenyl

bromide–zinc in THF.[44] The palladium catalysed coupling of naphthoquinone-2-triflates with stannanes has been reported to give 2-alkyl- and 2-arylnaphthoquinones in good (45–73%) yields,[45] the addition of LiCl to the reaction mixture gives 2-chloronaphtho-1,4-quinone as the major product. 2-Bromonaphthoquinones have been reacted with aryl stannanes under palladium and copper catalysis to give high yields of 2-arylnaphthoquinones[46] which were then reacted with *t*-BuOOH and Triton B to give the 2-aryl-3-hydroxyquinone[47] (Scheme 14).



Scheme 14

Two syntheses of the antibacterial agent Juglomycin A have appeared, one asymmetric[48] in 4 steps from 5-methoxy-1-naphthol, the other racemic[49] in 6 steps from juglone (Scheme 15).

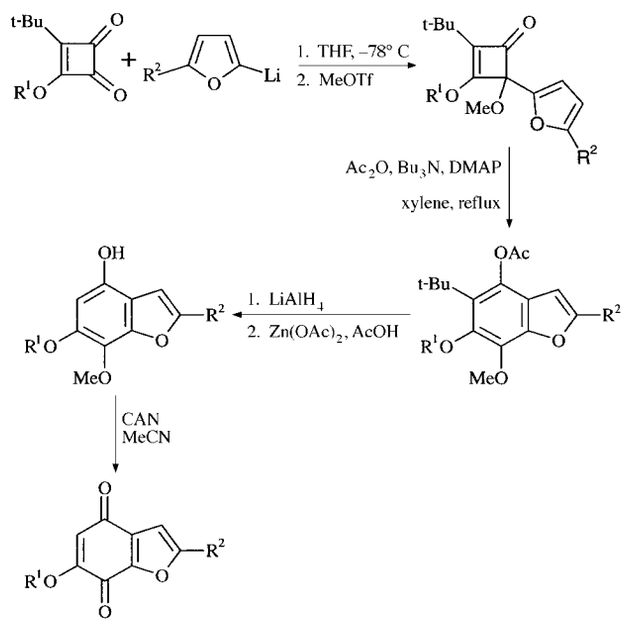


Scheme 15

3 Synthesis of heterocyclic quinones

3.1 Synthesis of five-membered heteroaromatic quinones

Fused five-membered heterocyclic quinones continue to be significant targets for synthesis and many reports have appeared in which such heterocyclic quinones are prepared. However only a few reports concern the synthesis of oxygen containing heterocyclic quinones. The addition of 2-lithiofurans to *tert*-butylcyclobutenediones followed by quenching with methyl triflate and thermolysis in the presence of acetic anhydride gives 4-acetoxy-7-methoxybenzofurans. Deprotection followed by oxidation with CAN gives the benzo[*b*]furandione in good yields[50] (Scheme 16). 2-Lithiofuran and functionalised cyclobutenediones are also the starting point for a synthesis of phenanthrafuranoquinones.[51] A functionalised benzo[*b*]-naphtho[2,3-*d*]furan has been prepared by cyclisation of a 2-aryl-3-hydroxyquinone[47] (Scheme 14).

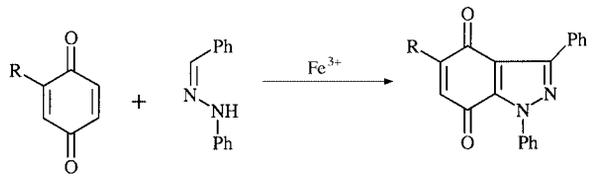


Scheme 16

A series of benzo[*b*]thiophene-4,7-quinones have been prepared by oxidative demethylation of the corresponding 4,7-dimethoxybenzo[*b*]thiophenes with CAN.[52] A small series of naphtho[2,3-*b*]thiophene-4,9-quinones has been prepared using classical Friedel–Crafts or directed lithiation strategies and were found to possess *in vitro* trypanocidal and antiplasmodial activity.[53] Friedel–Crafts approaches have also been used to prepare a number of polycyclic thiophene-containing quinones[54] including benzothieno[2,3-*b*]naphtho-1,4-quinone, benzothieno[2,3-*b*]anthra-1,4-quinone, benzothieno[2,3-*b*]-phenanthro-1,4-quinone, 4,10-dihydrothieno[3′,2′:4,5]benzo-[1,2-*b*][1]benzothiophene-4,10-dione, 4,10-dihydrothieno-[3′,2′:4,5]benzo[1,2-*b*][1]benzothiophene-4,10-dione and 6,12-dihydrobenzo[1,2-*b*:4,5-*b*′]bis([1]benzothiophene)-6,12-dione.

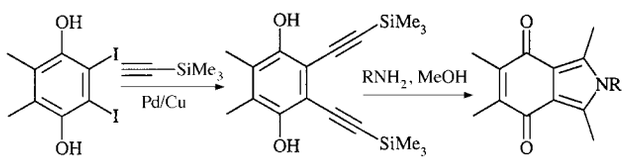
By far the largest class of heterocyclic quinones are those containing nitrogen. Much synthetic effort continues to be directed towards the kinamycin antibiotics and mitomycin antitumour agents producing complex polycyclic molecules containing indolylquinone substructures.

Simpler nitrogen-containing heterocyclic quinones have also been reported. 3-Ethyloxindole-4,7-quinone has been prepared in four steps from 4,7-dimethoxyisatin.[55] The first reported example of the aza-Nenitzescu reaction between *p*-benzoquinones and benzaldehyde phenylhydrazone gives 1,3-diphenylindazol-4,7-diones,[56] though yields are moderate (Scheme 17). Indazol-4,7-diones have also been prepared by the reaction of diazoalkanes with *p*-benzoquinones, also in moderate yields.[57] The reaction of tosylmethylisocyanide (TosMIC) with naphtho-1,4-quinone has been reported to give *2H*-benzo-[*f*]isoindol-4,9-dione in 49% yield.[58] Similar products have been prepared by the palladium–copper catalysed coupling of 2,3-diiodo-5,6-dimethylhydroquinone with trimethylsilylacetylene



Scheme 17

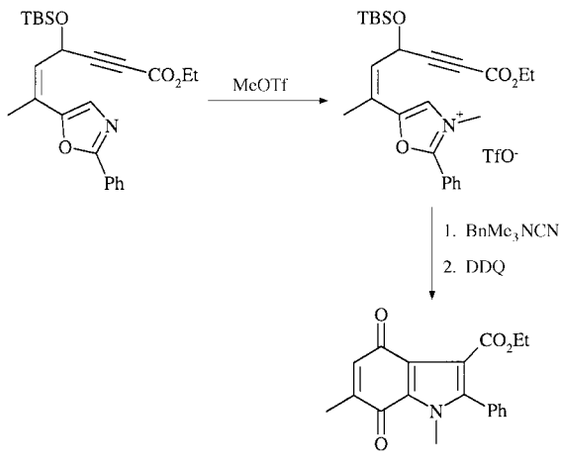
to give 2,3-bis[(trimethylsilyl)ethynyl]-5,6-dimethylhydroquinones followed by reaction with alkylamines in methanol; yields are of the order of 50% with respect to the starting hydroquinone[59] (Scheme 18). The reaction of 2,3-diazidonaphthoquinone with triphenylphosphine gives the phosphorane of 2-aminonaphthotriazole-4,9-dione in near quantitative yield. The compound is surprisingly stable and may be hydrolysed by 1 M HCl to the free 2-amino derivative.[60]



Scheme 18

Rearrangement with benzyltrimethylammonium cyanide of the oxazolium salt, produced by alkylation of the alkenyl, alkynyl oxazole with methyl triflate, followed by DDQ oxidation gives the 1-methyl-2-phenyl-3-ethoxycarbonylindolequinone in 63% yield after chromatography[61] (Scheme 19). 3,4-Disubstituted indole-6,7-quinones and 4,8-disubstituted indole-4,5-quinones have been synthesised as models for the novel organic cofactor TTQ of bacterial amine dehydrogenases. The final step of the sequence is oxidation of the 5- or 8-hydroxyindole with Frémy's salt to give the required *o*-quinone in good yield (69–87%).[62] Pyrroloquinolinequinone (PQQ) is another cofactor of bacterial dehydrogenases containing an indole-*o*-quinone moiety; a synthesis of three isomeric analogues, has been reported[63] (Scheme 20). An indole-*o*-quinone moiety was also used as an advanced intermediate in the synthesis of marine alkaloids based on the 1,3,4,5-tetrahydropyrrolo[4,3,2-*d*,*e*]quinoline nucleus;[64] the quinone being produced by deprotection of the *o*-dimethoxy compound with boron tribromide and aerial oxidation (Scheme 21).

Carbazolequinones have been prepared in good yield by the reaction of 2-lithio-1-methylindoles with 3-*tert*-butyl-4-isopropoxycyclobut-3-ene-1,2-dione followed by acetic anhydride quench, thermolysis and CAN oxidation[50] (Scheme 22). Similar compounds have been prepared by deprotection with acid of



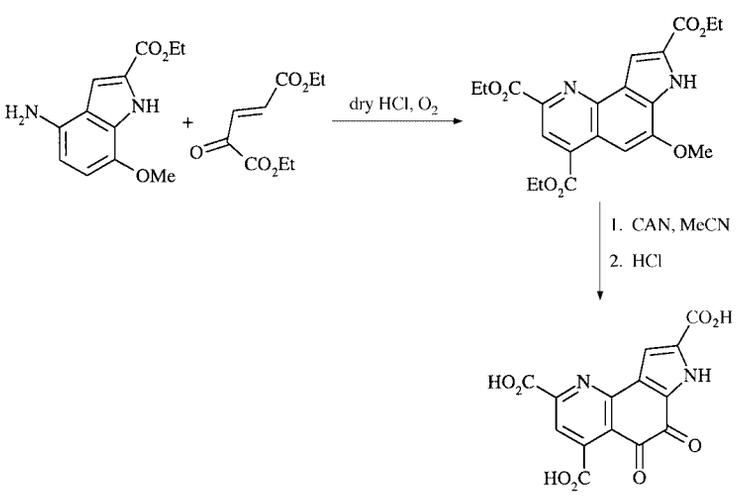
Scheme 19

the Boc-protected naphthoquinones described in Scheme 15[47] which then spontaneously cyclise to give high yields (80%) of the corresponding carbazolequinone.

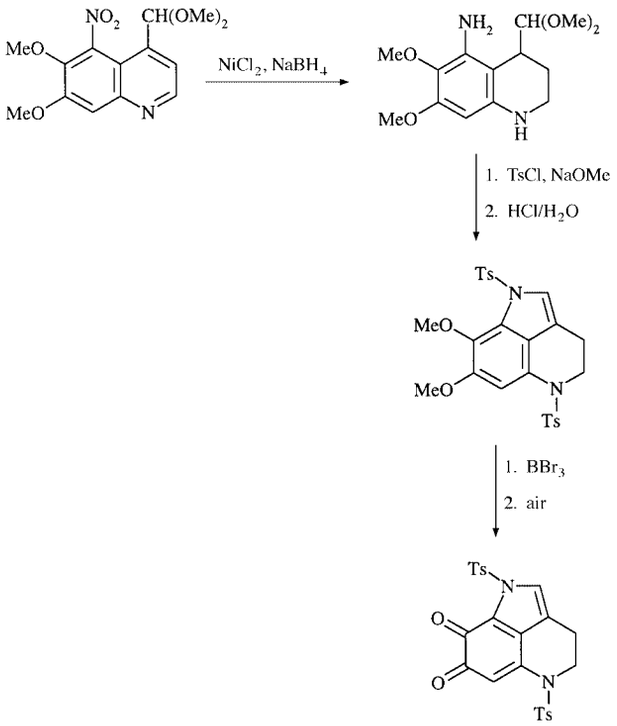
The mitomycin series continues to be of interest and syntheses of tricyclic indolequinones related to mitosenes continue to appear. An aziridinomitosene analogue has been prepared from 4,5,7-trioxygenated-6-methylindole-2-carbaldehyde by reaction with dimethylvinylsulfonium iodide followed by ring opening with sodium azide, mesylation, oxidation and ring closure with triphenylphosphine[65] (Scheme 23). A mesylated indolequinone has been prepared as a precursor of a cyclopropyl quinomethane species which is a nucleophile trap structurally related to the A-ring of CC-1065. The starting point of the synthesis is a tricyclic indolyl ketone (Scheme 24) and the quinone moiety is introduced by oxidation of the 4-aminoindole with Frémy's salt.[66]

3.2 Synthesis of six-membered heteroaromatic quinones

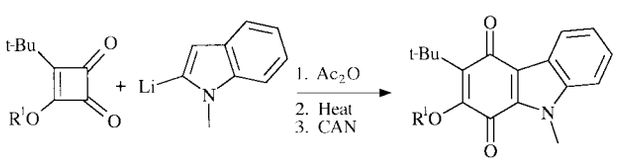
The majority of reports in the period under review of six-membered heteroaromatic quinones concern nitrogen containing heterocycles. A short series of 7-*N*-substituted quinoline-5,8-diones have been prepared from 8-hydroxy-2-methylquinoline as part of a total synthesis of the antitumour agent Lavendamycin.[67] The key step is the oxidation of the amide of the 5,7-bis(acylamino)-8-hydroxyquinoline with potassium dichromate in aqueous acetic acid to give the acylaminoquinolinediones in high (71–94%) yields. Some studies on the chemistry of these quinones have also been reported.[68] A series of 4,6-substituted-7-isopropoxyquinoline-5,8-diones have been prepared from lithiated



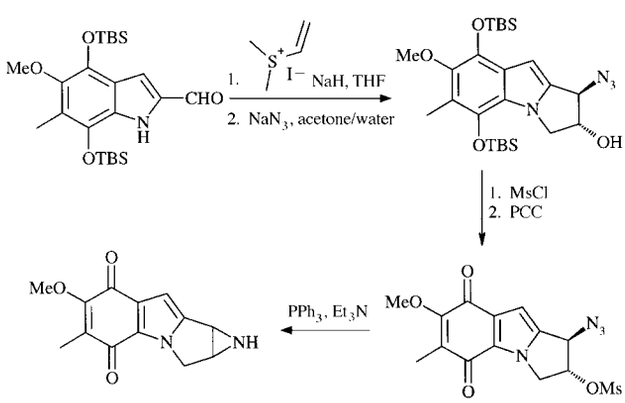
Scheme 20



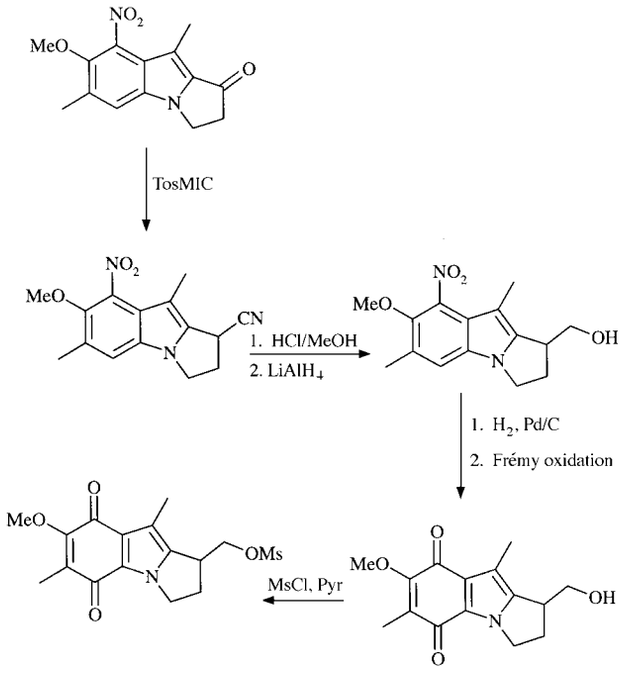
Scheme 21



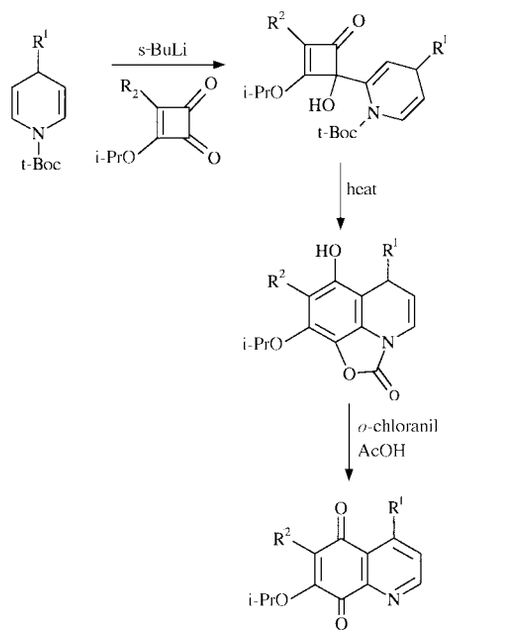
Scheme 22



Scheme 23



Scheme 24

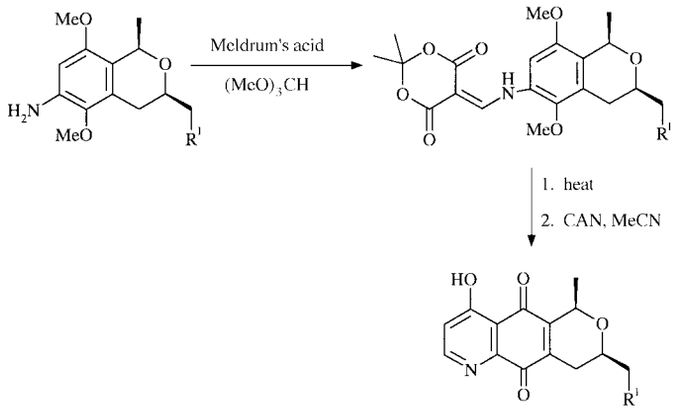


Scheme 25

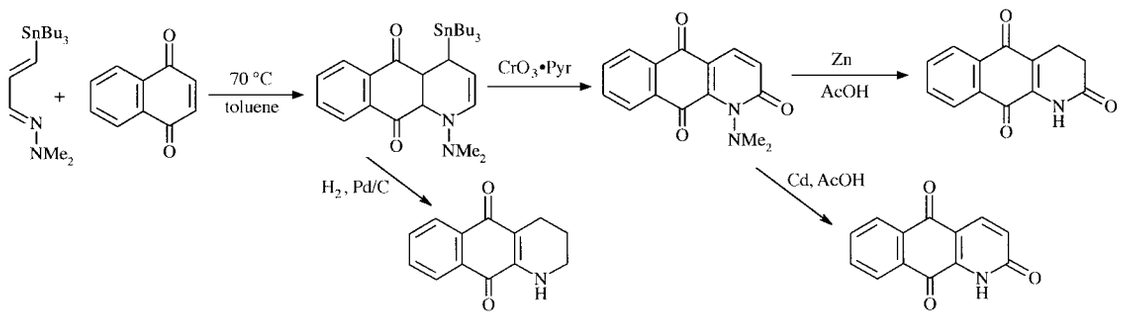
N-Boc-4-substituted-dihydropyridines and 3,4-disubstituted cyclobutenediones[69] (Scheme 25). A series of azabenzisochromanequinones have been prepared as analogues of the benzisochromanequinone antibiotics starting from a 6- or 7-aminochromane by condensation with Meldrum's acid and trimethyl orthoformate followed by a cyclisation reaction[70] (Scheme 26). 5,8-Dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione has been prepared in six steps, along with the isomeric 7,8-dione as part of a synthesis of the marine alkaloid Renierol.[71]

The reaction of 4-stannyl-1-azabutadienes with benzo-1,4-quinone or juglone gives adducts from which a number of azaanthraquinones can be prepared[72] (Scheme 27). The reaction of dimethoxycyclobutenediones with the lithium salts of *N*-arylpropargylamines followed by thermolysis gives dihydrophenanthridinediols which may be oxidised to give, depending on the *N*-substituent, piperidinequinones or phenanthridinequinones[73] (Scheme 28). The benzo[*b*]phenanthridinequinone phenanthroviridone has been prepared in five steps from 3-methoxy-5-methylbenzyl alcohol[74] (Scheme 29). The same compound has also been prepared in 11 steps by a palladium–copper catalysed coupling between 2-bromo-5-methoxynaphtho-1,4-quinone and a protected benzaldehyde stannane followed by amination and cyclisation.[46] A 1,2,3,4-tetrahydronaphtho[2,3-*c*]phenanthridine-7,12-dione has been prepared as an advanced intermediate in the synthesis of Dynemicin A by Diels–Alder reaction of dimethoxynaphthoquinone with a polycyclic pyrone followed by chloroimine formation with $POCl_3$ to give the aromatised product[75] (Scheme 30).

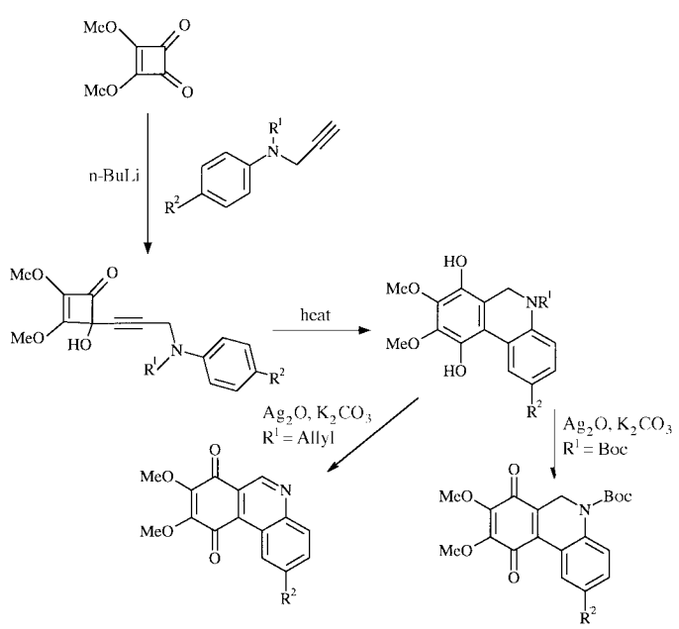
The synthesis of 4,7-phenanthroline-5,6-dione, an intermediate in the production of the diimine ligand PPZ (pyrazino[2,3-*f*][4,7]phenanthroline), in 50% yield from 2-methoxy-1,4-phenylenediamine by a double Skraup reaction



Scheme 26



Scheme 27



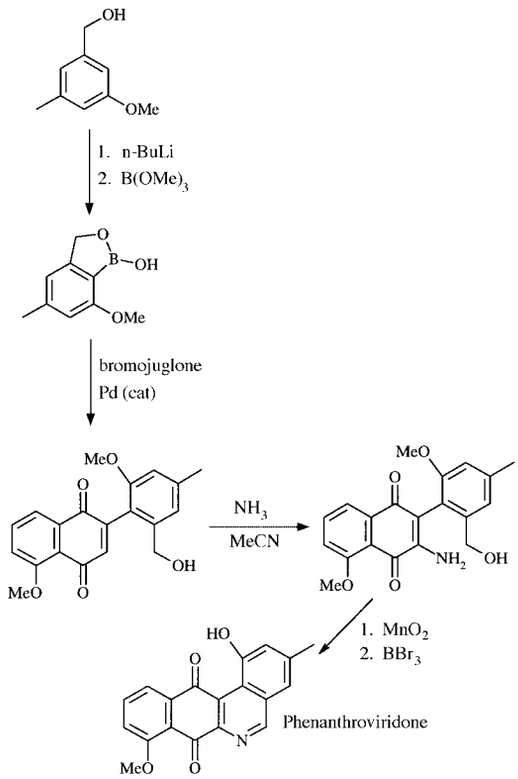
Scheme 28

followed by nitric acid oxidation has been reported.[76] 5,8-Dibromo-2-methyl-6*H*-pyrazolo[4,5,1-*de*]acridine-6,7,10-trione has been prepared in high (87%) yield by hypervalent iodine oxidation of the corresponding phenol[77] (Scheme 31). Novel 2,3-diheteroalkyl-substituted quinoxaline quinones have been prepared from 2,3-dichloro-5,8-dimethoxyquinoxaline by nucleophilic displacement of chlorine with alkoxide or thiolate anions followed by CAN oxidation.[78]

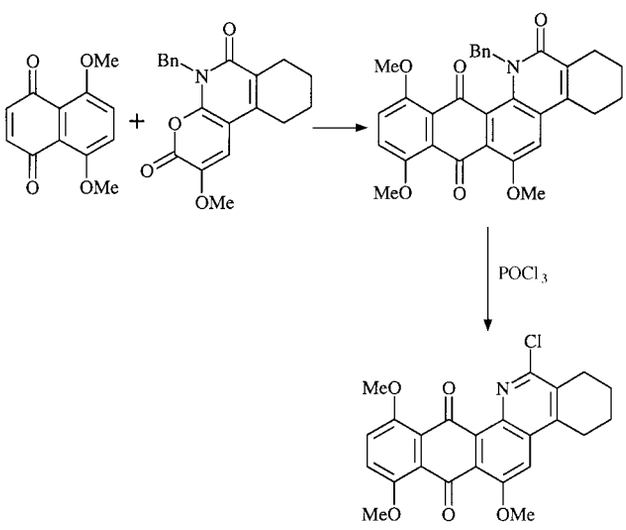
One example has been reported of the preparation in 44% yield of a (2,3-cholestano)-1,4-dithiaanthra-5,10-quinone from 2,3-dichloronaphtho-1,4-quinone and the salt generated by caesium hydroxide hydrolysis of (2,3-cholestano)-1,3-dithiole-2-one.[79]

3.3 Synthesis of saturated heterocyclic quinones

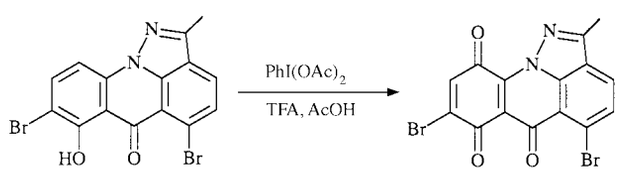
The hypervalent iodine oxidation of phenol derivatives bearing aminoquinones at the *ortho* position gives spiro-fused piperidinonaphthoquinones or tetrahydronaphtho[*a*][3]benzazepinediones depending on the phenolic substituent, *meta* substituted phenols give the azepinediones[80] (Scheme 32). The spirodienone phenols may be rearranged to the azepinediones



Scheme 29



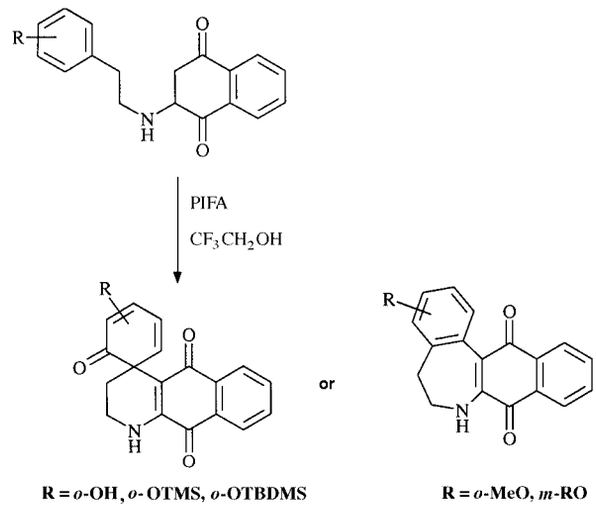
Scheme 30



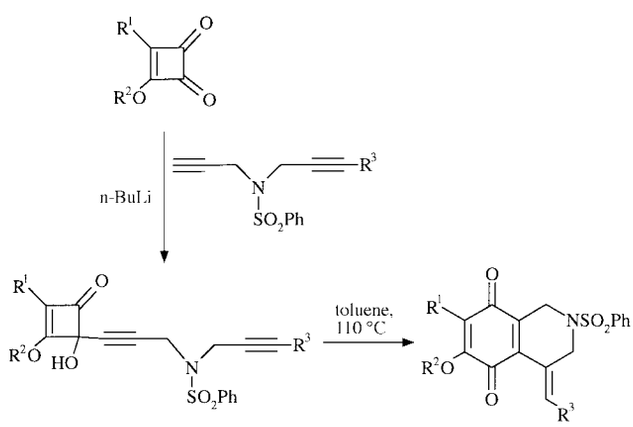
Scheme 31

with $BF_3{\cdot}Et_2O$. Heating mitoxantrone, a potently antitumour active tetrasubstituted anthraquinone in methanolic potassium hydroxide gave a high yield of a naphtho[2,3-*f*]quinoxaline-7,12-dione which retained some antileukaemic activity.[81] The addition of the lithium salts of 4-aza-1,6-diynes to cyclobutenediones gives 4-hydroxy-4-[aza-1,6-diynyl]cyclobutenols which give piperidinoquinones on thermolysis[73] (Scheme 33).

A number of reports have appeared detailing the construction of benzo- and/or naphtho[*c*]pyran ring systems containing

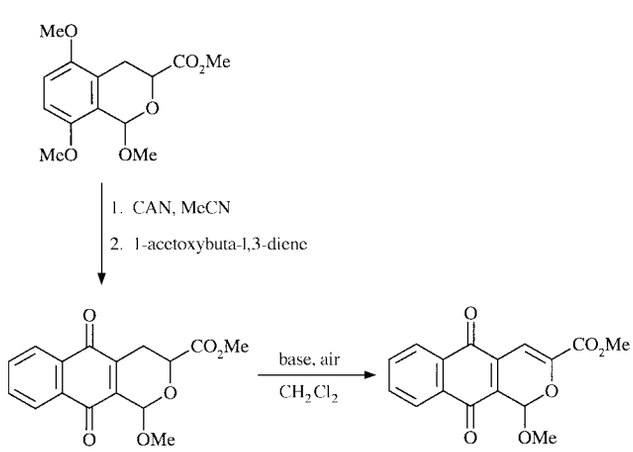


Scheme 32

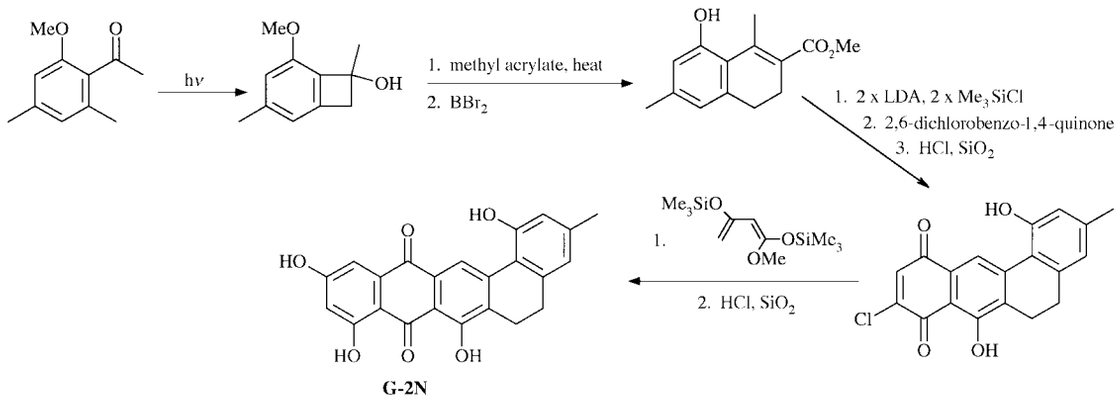


Scheme 33

an oxygen at the 4 position; this oxygen substituent appears to be important for biological activity. Three benzopyran quinones have been prepared from 2-hydroxymethyl-3,6-dimethoxystyrenes by a mercury mediated oxidative ring closure to the dimethoxybenzo[*c*]pyran followed by silver oxide oxidation.[82] Naphthoquinonepyrans have been prepared from benzopyran quinones (prepared from isochromanes) by [4+2] cycloaddition with 1-acetoxybuta-1,3-diene, these products undergo base catalysed aerial oxidation to the dehydroherbarin[83] (Scheme 34). The naphthopyran natural products Kalafungin[84] and Hongconin[85–87] have been the subject of a number of syntheses in which naphthopyran quinones are produced or have the clear



Scheme 34



Scheme 35

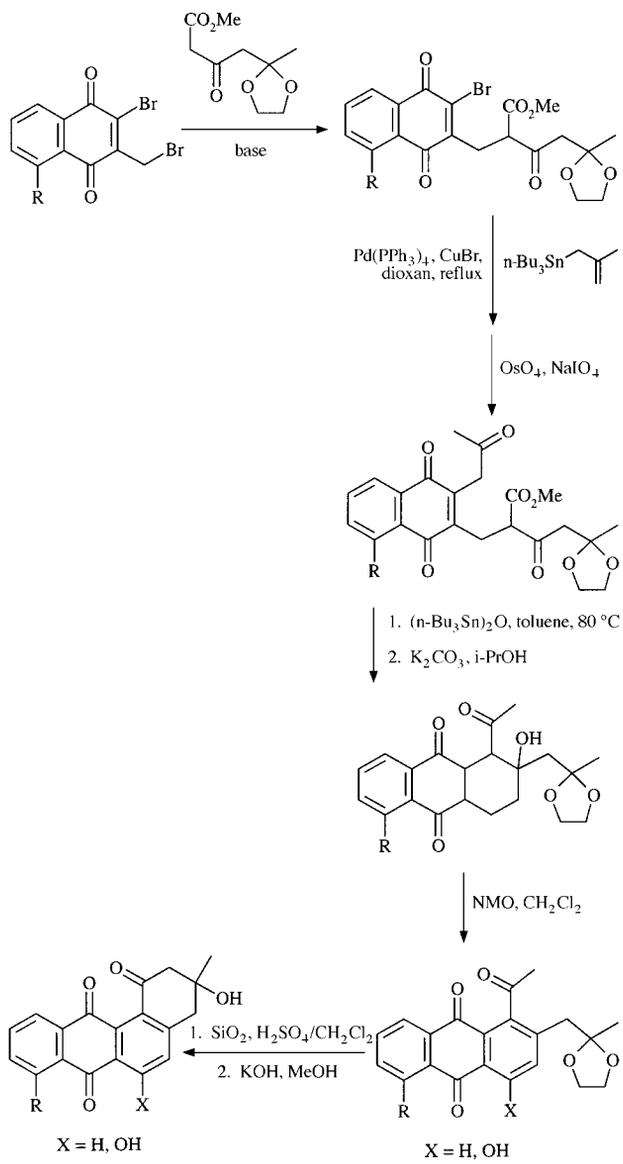
potential to be produced (as Hongconin is a naphthopyran hydroquinone, quinones are produced by accidental over oxidation of the desired products). Naphthoquinonepyrans have also been prepared by the photoannulation of 2-aryl-3-alkoxynaphtho-1,4-quinones in the presence of DDQ;[88] the reaction works best for benzyl or isopropyl ethers.

4 Synthesis of anthraquinones and anthracyclinones

Anthraquinones and anthracyclinones continue to be attractive targets for synthesis primarily because of the extensive range of biological activities which includes antitumour, antibacterial and antifungal effects.

At the simplest level of synthesis two methods have been reported for the preparation of anthraquinones by oxidation. Phenanthrene-9,10-quinone has been prepared in 66% yield by dihydroxy phenylselenonium benzenesulfonate oxidation of phenanthrene in refluxing dioxane–water.[89] Anthra-1,2,5,6-quinones have been prepared by oxidation of the corresponding 2,6-dihydroxyanthracenes.[90] Phenylseleninic anhydride [$(PhSeO)_2O$], potassium nitrosodisulfonate (Frémy's salt) and *tert*-butyl hydroperoxide with the Mimoun catalyst were compared as oxidants, but only phenylseleninic anhydride gave the expected compounds in good (70–76%) yields.

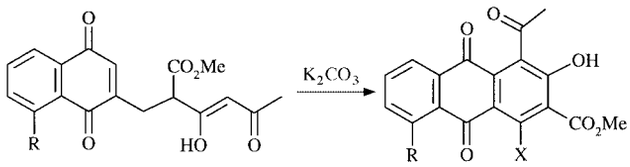
Diels–Alder approaches continue to be utilised to construct anthraquinones; a typical strategy has been adopted for the synthesis of the benzo[*a*]naphthacenequinone G-2N.[91] A substituted silylketene acetal was constructed and reacted with 2,6-dichlorobenzo-1,4-quinone to give a substituted chlorobenzoquinone, this product then underwent a second Diels–Alder with 1-methoxy-1,3-bis[(trimethylsilyl)oxy]buta-1,3-diene to give G-2N in 83% yield (Scheme 35). A series of thiazoloanthraquinones have been prepared in moderate yields (37–70%) by reaction of 4-methylene-5-(bromomethylene)-4,5-dihydrothiazole with naphthoquinones.[92] Similarly the reaction of polyfunctional silylketene acetals with naphthazarins or juglones followed by oxidative hydroxylation has been used to prepare kermesic acid derivatives.[93] 2-(*p*-Tolylsulfinyl)benzo-1,4-quinone has been shown to be a reactive dienophile for cycloaddition processes; reaction with styrenes gives phenanthrene-1,4-quinones[94] (though high pressures are required to achieve good yields), reaction with vinyl naphthalenes gives benzo[*c*]- and benzo[*a*]phenanthrene-1,4-quinones[95] and sequential reaction with two equivalents of 1-methoxycyclohexa-1,3-diene gives tetrahydronaphthacenequinones.[95] A double Diels–Alder approach has also been reported for the synthesis of 2,3-dimethoxy-6-methylanthra-9,10-quinone. Benzoquinone was reacted firstly with 2,3-dimethoxybuta-1,3-diene to give 6,7-dimethoxynaphthoquinone which was then reacted with isoprene to give, after aerial oxidation, the required product in 15% overall yield.[96] A series of 6-[(aminoalkyloxy)methyl]-4-demethoxy-6,7-dideoxydaunomycinones were prepared by a stereoselective double Diels–Alder approach from benzyne, 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane and a 1-acetylvinyl ester of a chiral auxiliary.[97] The synthesis of novel 7-aryl-7-deoxyanthracyclinones, a new class of anthracycline analogues, has been described.[98] The key intermediate tetracyclic ketone is prepared[99] in 48% yield by Diels–Alder reaction of 1-aryl-3-trimethylsiloxybuta-1,3-diene and 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,19-tetrone, ethynylation, hydration and



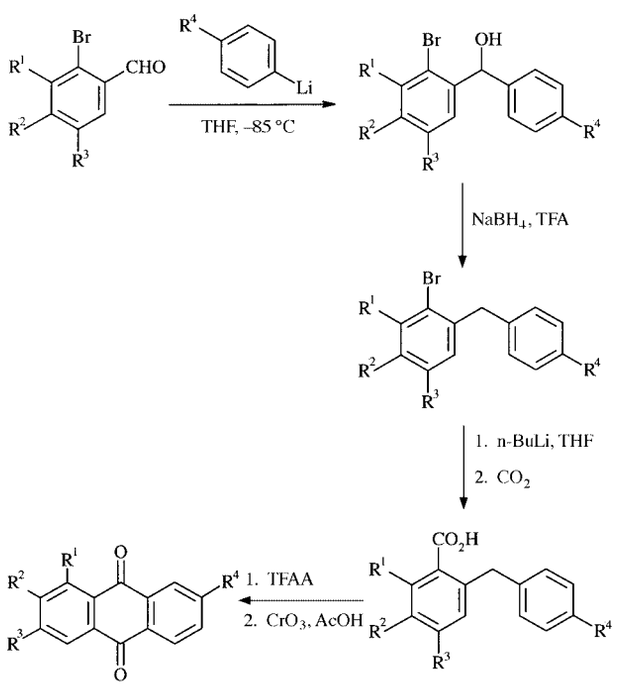
Scheme 36

oxidation gives the final product in 32% yield from the ketone.

The angucyclines are a group of antibiotics with a broad spectrum of biological activities comprising antitumour, enzyme inhibitory, antiviral and antifungal effects. A series of angucyclines have been prepared from 2-bromo-3-(bromomethyl)juglone by a sequence containing two successive aldol cyclisations and an aromatisation with *N*-methylmorpholine *N*-oxide which was also used to introduce the requisite phenolic hydroxy group[100] (Scheme 36). In a related piece of work a series of highly substituted anthraquinones have been prepared in high yield by base induced anionic cyclisation of a naphthoquinone also prepared from 2-bromo-3-(bromomethyl)-juglone[101] (Scheme 37). A straightforward and generally applicable synthesis of anthraquinones from *o*-bromodiphenylmethanes has been published, overall yields for the five step process are good (47–68%)[102] (Scheme 38).



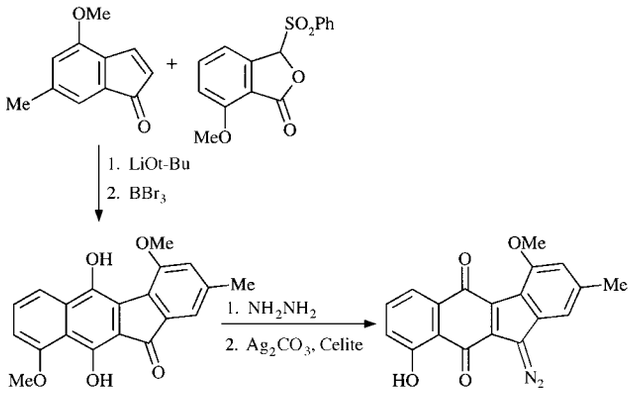
Scheme 37



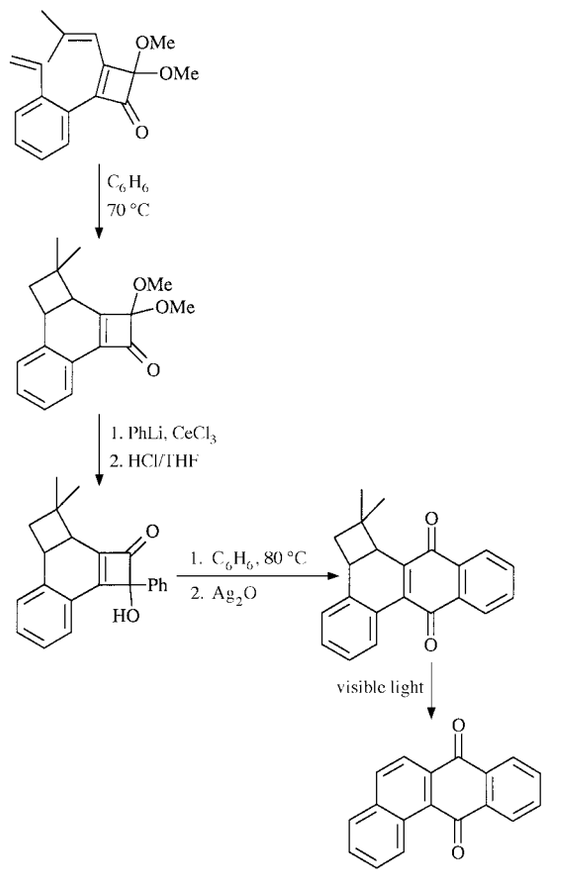
Scheme 38

The kinamycin family of antibiotics continues to be the target of synthetic strategies[103,104] and an elegant synthesis of the proposed structure of prekinamycin based on phthalide annelation methodology has appeared[105] (Scheme 39). However, the spectral properties of the compound prepared were not identical with those reported for prekinamycin.

A new method has been reported for the regiospecific synthesis of phenanthraquinones and related angularly fused polycyclic compounds from squaric acid derived cyclobutenones. The tetracyclic cyclobutenone, prepared by mild thermolysis of phenylcyclobutenone, is treated with aryl or alkynyllithiums (in some cases modified by addition of $CeCl_3$), thermolysed, oxidised with silver oxide and finally photofragmented to expel isobutylene and gives benzo[*a*]anthracene-7,12-diones, 2 or 3 substituted phenanthracene-1,4-diones and furanophenanthracenediones[106] (Scheme 40).



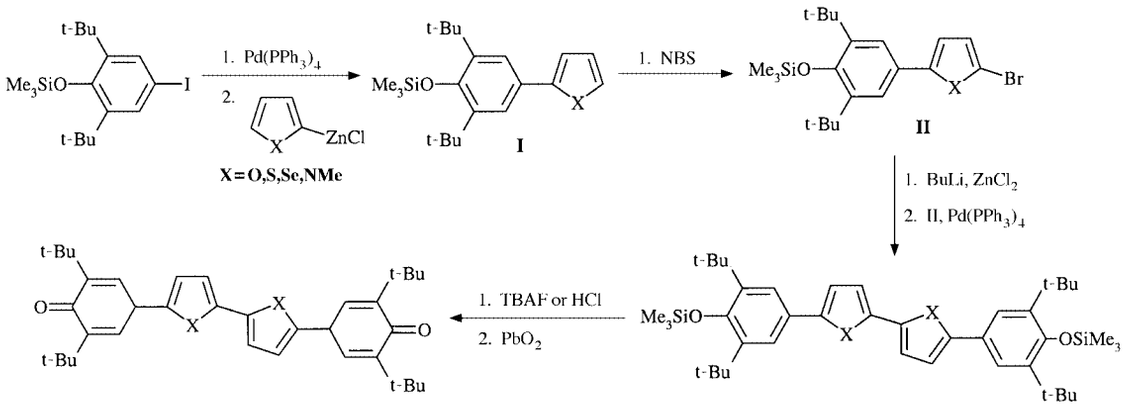
Scheme 39



Scheme 40

5 Synthesis of other polycyclic quinones

Extended quinones continue to be of interest as organic semiconductors and as dyes for laser-driven high-density optical storage devices. A range of heteroquaterphenoquinones have been synthesised by a palladium cross-coupling strategy (Scheme 41), the same products were also prepared by desilylation and oxidative dimerisation of intermediate (**I**) with potassium ferricyanide or lead(IV) oxide.[107] These compounds exhibit an intense absorption maximum in the near-infrared region and undergo amphoteric three stage redox reactions. A series of bipheno-4,4′-quinones have been prepared having the donor and acceptor substituents (alkylthio and halo) designed to decrease the intermolecular charge-transfer gap.[108] The quinones were prepared by either palladium catalysed cross-coupling and oxidation (CAN or potassium ferricyanide) of the protected phenols or oxidative coupling (DDQ) of the free phenols. The preparation of poly(anthra-9,10-quinone-2,6-diyl), *via* a precursor polymer, has been reported.[109]



Scheme 41

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