SYNTHESIS OF AZACHRYSENES AND MULTI-NITROGENATED DERIVATIVES

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Abstract. *Azachrysenes are aromatic tetracyclic structures where one carbon atom is replaced by nitrogen in any symmetrically distinct position of the fused aromatic ring. They can be considered analogs of azasteroids, with recognized potential as drug candidates. The present review surveys the work carried out over the last three decades on the synthesis of mono-, di-, tri- and penta-azachryzene derivatives. Although a diversity of synthetic approaches were described in the literature, there are no recent review articles on this subject.*

Contents

References

1. Introduction

Azachrysenes (aza-analogs of chrysene, Figure 1), are tetracyclic aromatic compounds where one of carbon atoms in the structure is replaced by nitrogen. The substitution pattern in rings A to D has been used to shape the properties of these *N*-heterocycles, namely as drug candidates, where these compounds can be considered as privileged structures.[1,2] Their unique structure also makes them valuable intermediates in the synthesis of azasteroids.[3]

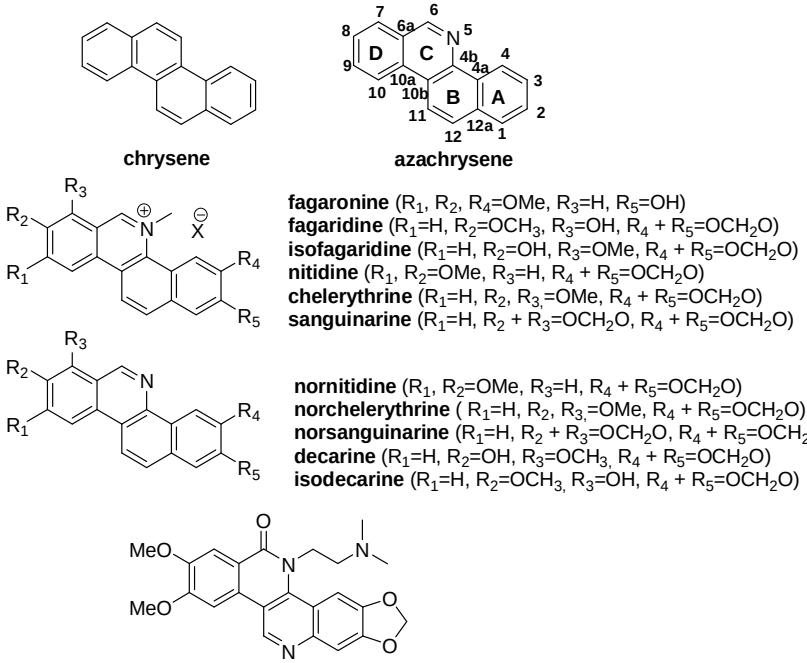


Figure 1

The azachrysene scaffold, also referred as benzophenanthridine, was extensively studied in the last decades[2,4] and received significant attention due to the widespread occurrence in nature and broad range of biological properties. Compounds with this core-structure are known to inhibit leukaemia[5] and to act as antimicrobial[6], anticancer[7], muscle relaxant[8], anti-inflammatory[9] and cardiotonic agents.[10] Some analogues behaved as potent inducers of apoptosis in HCT116 and SW620 cell lines, highlighting their potential relevance in colon cancer.[11] Among the compounds referred in Figure 1, Isofagaridine displayed in vitro cytotoxicity when tested against different cancer cell lines and behaved as a Topoisomerase I inhibitor.[12] Pre-clinical in vitro and in vivo studies on Sanguinarine showed that this compound causes apoptosis in human cancer cells and is also an important drug candidate for cancer treatment.[13] Chelerythrine, is a potent protein kinase C inhibitor[14] and Nitidine inhibits topoisomerases I/II.[15]

Substituted diaza- and triazachrysenes are less known and their synthesis and biological properties are mainly reported in patented work. Compounds with this core structure (e.g., ARC-111, Figure 1) proved to be potent topoisomerase-targeting agents with exceptional cytotoxic activity and have been studied as anticancer agents.[16]

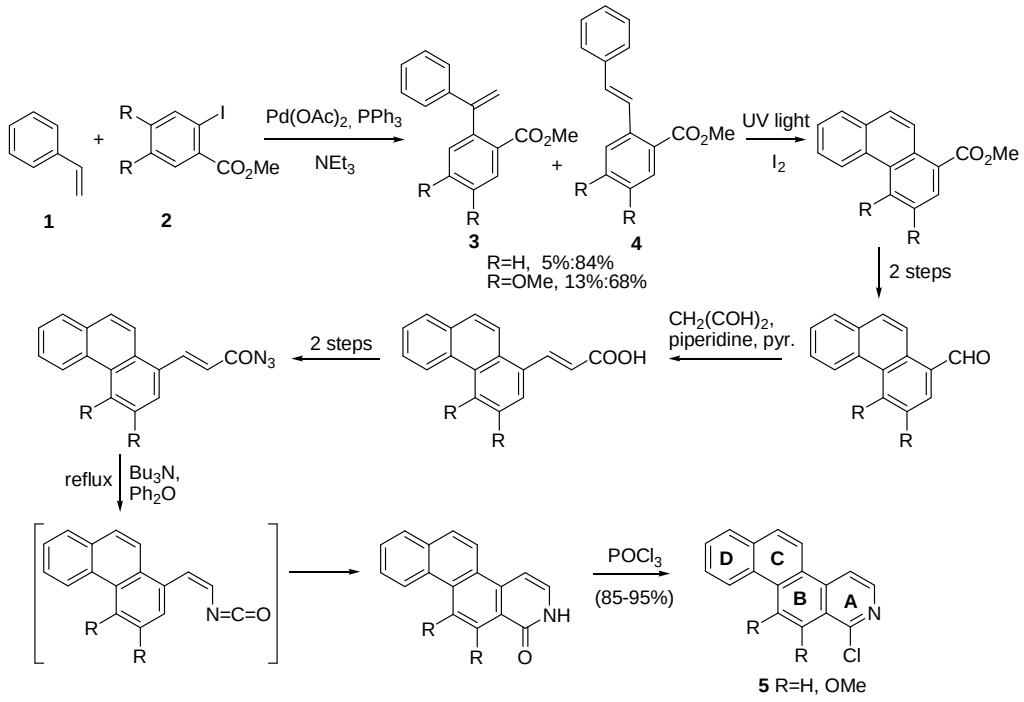
The preparation of multi-nitrogenated azachrysene derivatives is a significant challenge and only a few synthetic methodologies were designed to generate the tetracyclic core. The synthetic approaches are usually based on cyclization reactions to generate rings B- or C- either through free radical-mediated, aryne-mediated, Bischler-Napieralski, or transition metal-catalysed reactions. The synthesis usually requires several steps to generate the product but in a few examples the reagents evolve to the product in a single step or by a cascade reaction.

2. Synthesis of monoazachrysene derivatives

In the past, various synthetic methods were described in the literature for the preparation of azachrysene derivatives. Former work was reported in a previous review[2] and this section will focus on the synthetic approaches leading to 2-, 5- and 6-azachrysenes.

2.1. 2-Azachrysene

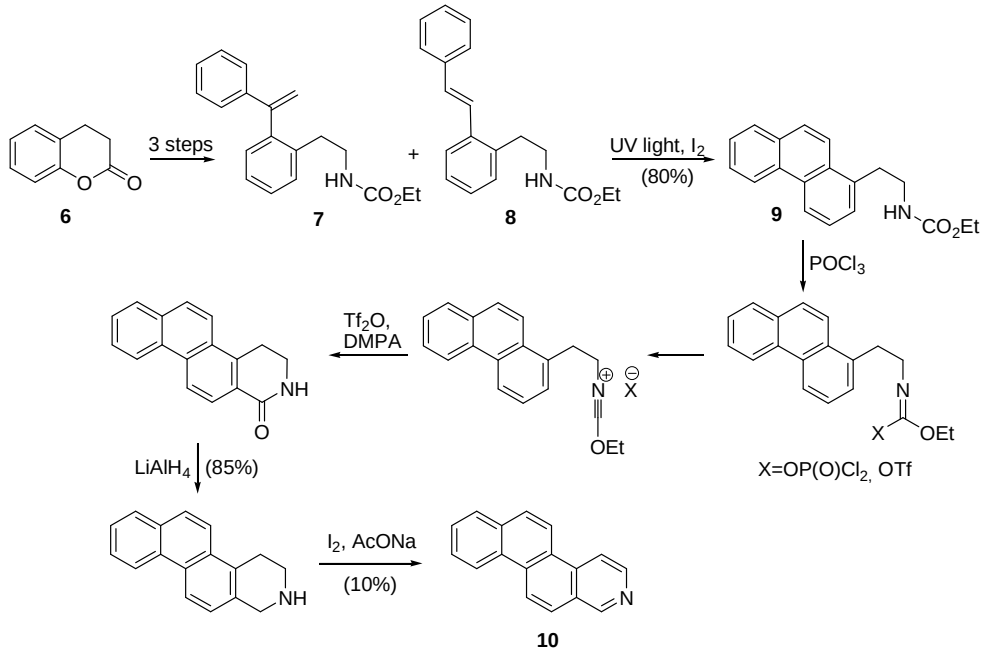
Estévez *et al*[17] described an efficient synthesis of 2-azachryses **5**, from *o*-styrylbenzoic esters **4** (Scheme 1).



Scheme 1

These compounds were prepared by Heck coupling of methyl *o*-iodobenzoates **2** to styrenes **1**. In this reaction, the 9-coupling product **3** was also formed but in a minor extent. Esters **4** were transformed into the phenanthrenylbenzoic acids and then into the target compounds **5** by a six-steps sequence including a Bischler-Napieralski cyclization. The halogen in position 1 of the tetracyclic skeleton is a versatile feature and allowed the formation of a diversity of derivatives.

The same research group reported another procedure[18] involving the Heck coupling reaction between 2-(2-ethoxycarbonylaminoethyl)phenyl esters and styrenes to give [2-(2-styrylphenyl)ethyl]carbamic acid ethyl esters **8** (Scheme 2). These compounds were cyclized to (2-phenanthren-1-yl-ethyl)carbamic acid ethyl esters **9**, from which 2-azachrysenes **10** were obtained in a five-steps sequence.



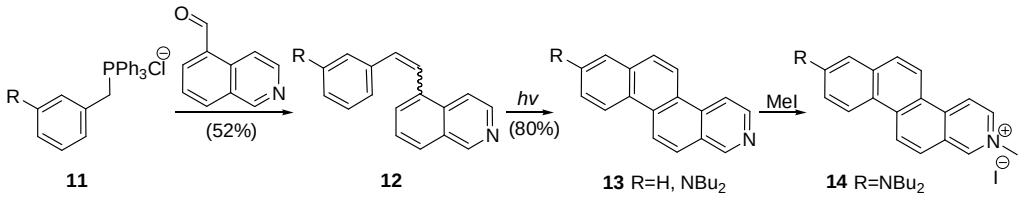
Scheme 2

2-Azachrysene **13** was obtained by a Wittig condensation of benzyltriphenylphosphonium chloride **11** with isoquinoline-5-carbaldehyde, followed by a photochemical cyclization of the mixture of diastereoisomeric alkenes **12**.[19] Methylation of **13** with MeI in THF led to the salt **14** (Scheme 3).

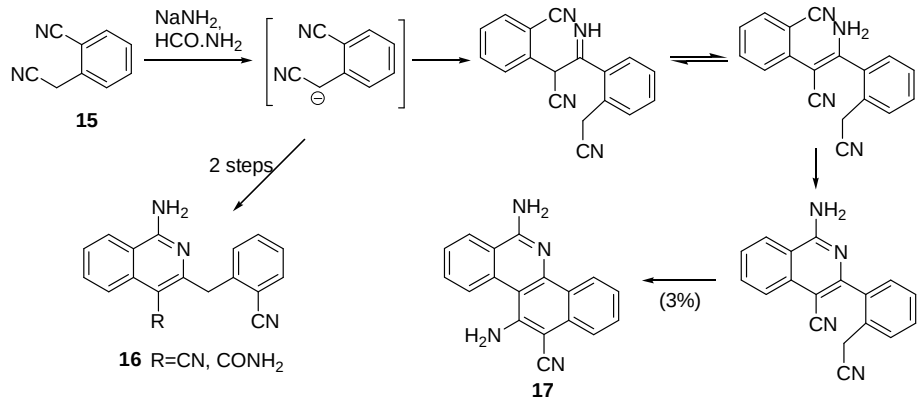
2.2. 5-Azachrysene

Elvidge *et al*[20] generated two dimeric cyclisation products when *o*-cyanobenzyl cyanide **15** was treated with sodamine in formamide solution. The use of a strong base was important in the synthesis of the major product, the 3-benzylisoquinoline **16**, formed by nucleophilic attack of the methylene carbanion to the cyano group of another cyanomethylene substituent. The azachrysene **17** was isolated in only 3% yield when the

carbanion attack occurred to the aromatic cyano group, followed by two intramolecular cyclization reactions (Scheme 4).

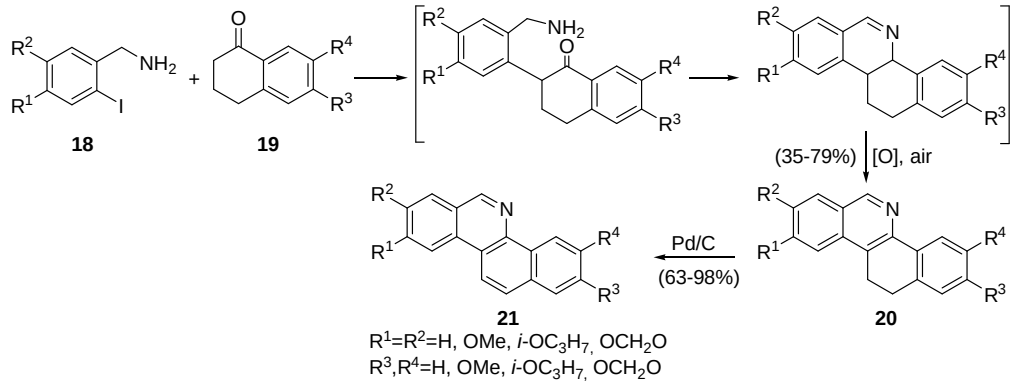


Scheme 3



Scheme 4

Roussi *et al*[21] reported the formation of dihydrobenzo[*c*]phenanthridines **20** when substituted iodobenzylamines **18** were reacted with different tetralones **19** (Scheme 5).

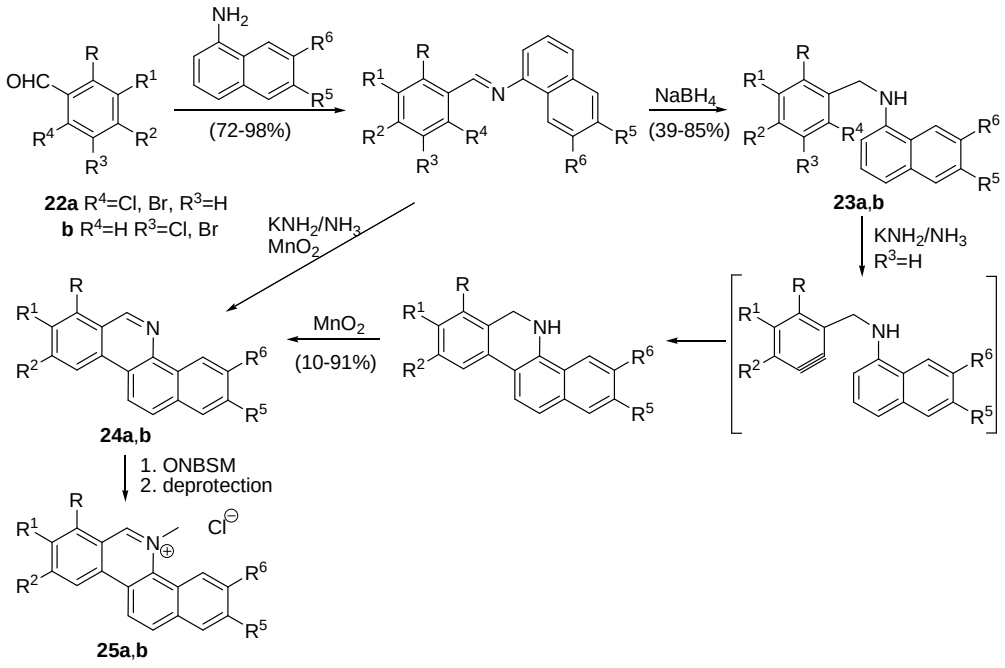


Scheme 5

The reaction proceeded by nucleophilic attack of the enolate of **19** to the iodobenzene, followed by intramolecular cyclization between the amino and carbonyl groups with elimination of water, to yield the 2-aryltetralones. Dehydrogenation of the tetracyclic ring **20** in the presence of Pd/C, gave the benzo[*c*]phenanthridines (or 5-azachrysene) **21**.

Kessar *et al*[22] synthesized several benzo[*c*]phenanthridine alkaloids (Scheme 6). The reaction was initiated by the synthesis of the Schiff base when the haloaldehyde **22** and naphtylamines were refluxed in ethanol followed by reduction with sodium borohydride leading to **23**. Reaction of this compound with KNH_2/NH_3 and manganese dioxide in chloroform led to the 5-azachrysene **24**. Compound **24** was also isolated in 63% yield from direct cyclization of the Schiff base induced by KNH_2/NH_3 followed by MnO_2. An analogue of compound **24**, with a non-aromatic **A** ring, was prepared and isolated in good yield from the corresponding analogue of **23**, by an oxidative coupling process promoted by phenyliodine(III)-bis(trifluoroacetate) (PIFA).[23]

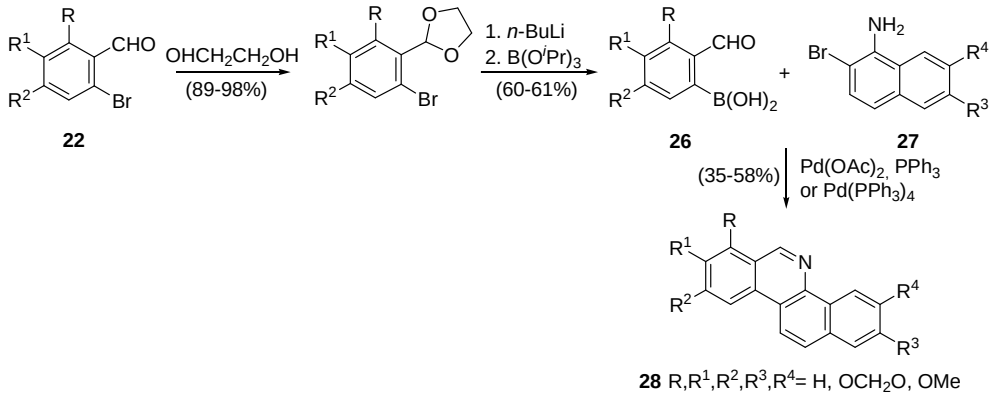
The imine was also reduced to amine by dimethylamineborane to give the key intermediate **23** in good yield (Scheme 6).[24] The subsequent step also involved a benzyne intermediate generated by treatment of the substituted benzylamine with LDA. Oxidation with manganese dioxide afforded 5-azachrysene **24** that was methylated with methyl 2-nitrobenzenesulfonate (ONBSM) to give **25**.



Scheme 6

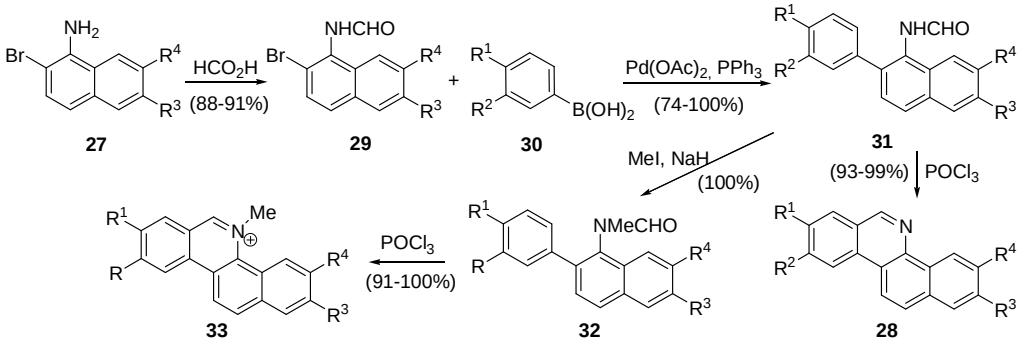
Benzo[*c*]phenanthridine alkaloids were prepared, from bromonaphthylamine **27**.[26] The first approach involved the 2-formylphenylboronic acid **26** that was synthesized from bromobenzaldehyde **22** after

protection and deprotection of the benzaldehyde group (Scheme 7). Reaction of **26** with 2-bromonaphthylamine **27** gave azachrysenes **28** in 35-58% yield in the presence of palladium acetate and triphenylphosphate. This reaction was accompanied by extensive deboronation with significant formation of piperonal as a side product.



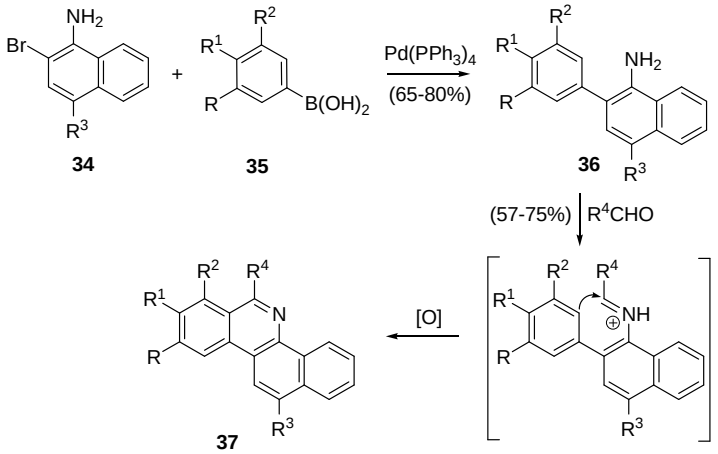
Scheme 7

Protection of the 1-amino group in **27** by formylation (**29**) prior to the Suzuki coupling led to much better yields of the coupled products **31** (Scheme 8).[26] These compounds were then methylated using iodomethane and sodium hydride leading to formamides **32**. Naphthalenes **31** and **32** were used as precursors of azachrysenes **28** and **33** respectively, using the Bischler-Napieraski reaction.



Scheme 8

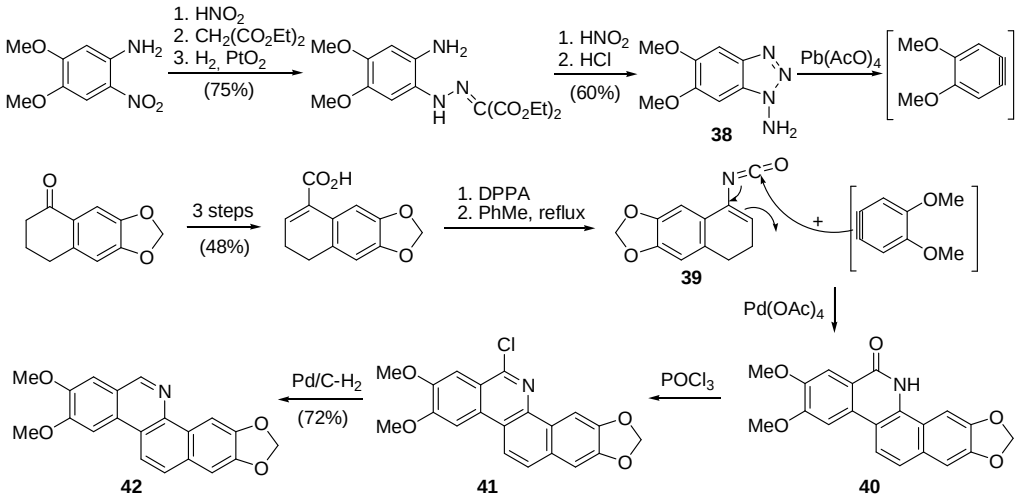
Kundu *et al*[27] also developed an efficient and versatile method for the synthesis of benzophenanthridines upon reaction of phenylboronic acid **35** and bromonaphthylamines **34** (Scheme 9). The synthesis of compound **36** occurs in a single step, via Suzuki coupling. Combining amine **36** with aldehydes led to the formation of azachrysene **37** via π-cyclization of the intermediate imine, followed by spontaneous air oxidation.



R, R^1, R^2=H, CH_3, OCH_3, R^3=H, 3,4-$(OCH_3)_2C_6H_3$, 3,4,5-$(CH_3)_3C_6H_2$
R^4=H, 4-$OEtC_6H_4$, 4-OHC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$(CH_3)_2NC_6H_4$, 3,4-$(OCH_3)_2C_6H_3$

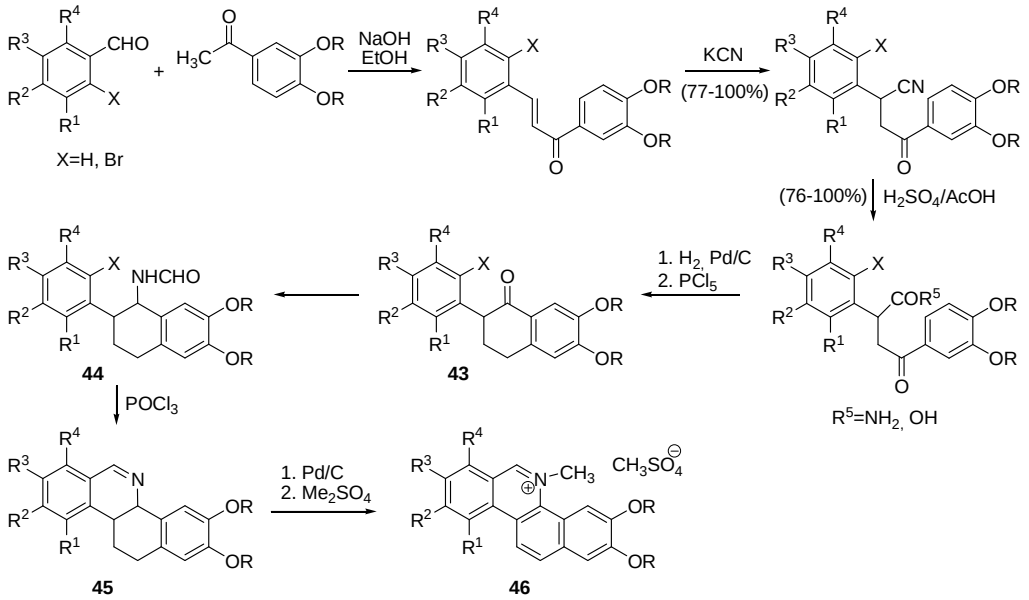
Scheme 9

The synthesis of *N*-nornitidine **42** was reported by Rigby *et al*[28] and is based on the [4+2] cycloaddition of a substituted benzyne with an appropriate vinyl isocyanate (Scheme 10). *N*-Aminobenzotriazole **38**, used as the benzyne precursor, was obtained in two steps from nitroaniline, in 45% overall yield. On the other hand, vinyl isocyanate **39**, obtained via modified Curtius rearrangement, was neither isolated nor characterized and was immediately reacted with the benzyne leading to the cycloaddition product **40** after slow addition of a slight excess of $Pb(OAc)_4$. Subsequent exposure of **40** to refluxing $POCl_3$ generated the aromatic chlorobenzophenanthridine **41** in 45% yield. Finally, hydrogenolysis of **41** under standard conditions gave *N*-nornitidine **42**.



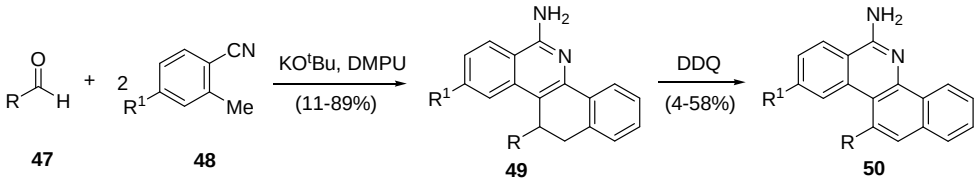
Scheme 10

Ishii *et al*[29] also used the 2-aryl-1-tetralone intermediate as a strategy to produce a number of benzophenanthridines (Scheme 11). 2-Aryl-1-tetralone derivatives **43** were obtained from chalcones via 2,4-bisaryl-4-oxobutyronitriles, followed by hydrolysis, hydrogenation using Pd/C and cyclization with phosphorus pentachloride. Compounds **43** were used as precursors of **44**, that were cyclized to the tetrahydrobenzophenanthridines **45** by the Bischler-Napieralski reaction using phosphorus oxychloride. Aromatization and quaternization afforded benzophenanthridine alkaloids **46**.



Scheme 11

Clement *et al*[30] reported a simple one-step synthesis of 6-aminobenzo[*c*]phenanthridines **50** that involved condensation of aromatic aldehydes **47** with 2-methylbenzonitrile **48** (2 equiv.) to give the fused ring system **49** (Scheme 12).



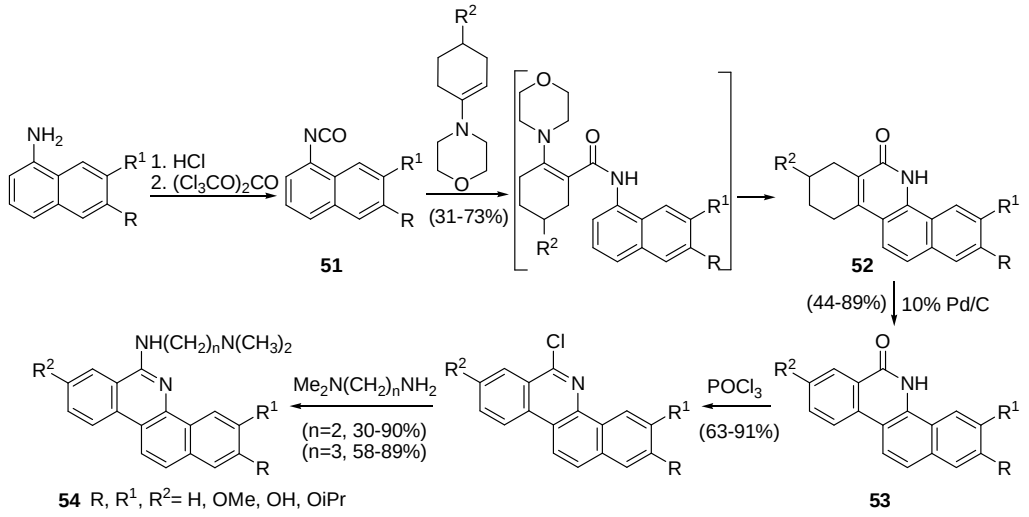
R=H, C_6H_5, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-$OEtC_6H_4$, 4-$OEtC_6H_4$, 2,3-$(MeO)_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 2,5-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3,5-$(MeO)_2C_6H_3$, 2,3,4-$(MeO)_3C_6H_2$, 2,4,5-$(MeO)_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$, 3,4,5-$(MeO)_3C_6H_2$, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 2-thienyl, 4-(2-propyl)phenyl, 1-naphthyl, 3-OH-4-$OMeC_6H_3$, 4-OH-3-$OMeC_6H_3$, 3-OH-2,4-$OMeC_6H_2$, 4-OH-3,5-$OMeC_6H_2$, 3,4-methylenedioxyphenyl, 4-$Me_2NC_6H_4$, R^1=H, OMe

DMPU=1,3-dimethyl-3,4,5,6-tetrahydropyrimidine-2-(*1H*)-one

Scheme 12

The fully aromatized structure was accessible through subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Benzophenanthridine **50** (R=R[1]=H, 41%), was also prepared from naphthylamine and 2-chlorobenzonitrile, in a single step, in the presence of a mixture of sodium and lithium amide in liquid ammonia.[31]

Bisagni *et al*[32] synthesized benzophenanthridin-6(*5H*)-ones **53** where the key step was the preparation of tetrahydrobenzo[*c*]phenanthridin-6(*5H*)-ones **52** from 1-naphthylisocyanates **51** and a morpholino enamine (Scheme 13). Dehydrogenation of ring D with Pd/C yielded the final product **53**. Subsequent chlorination followed by reaction with alkylamines led to 6-amino-substituted benzo[*c*]phenanthridine derivatives **54** bearing a (dimethylamino)alkylamino side chain at the 6-position.

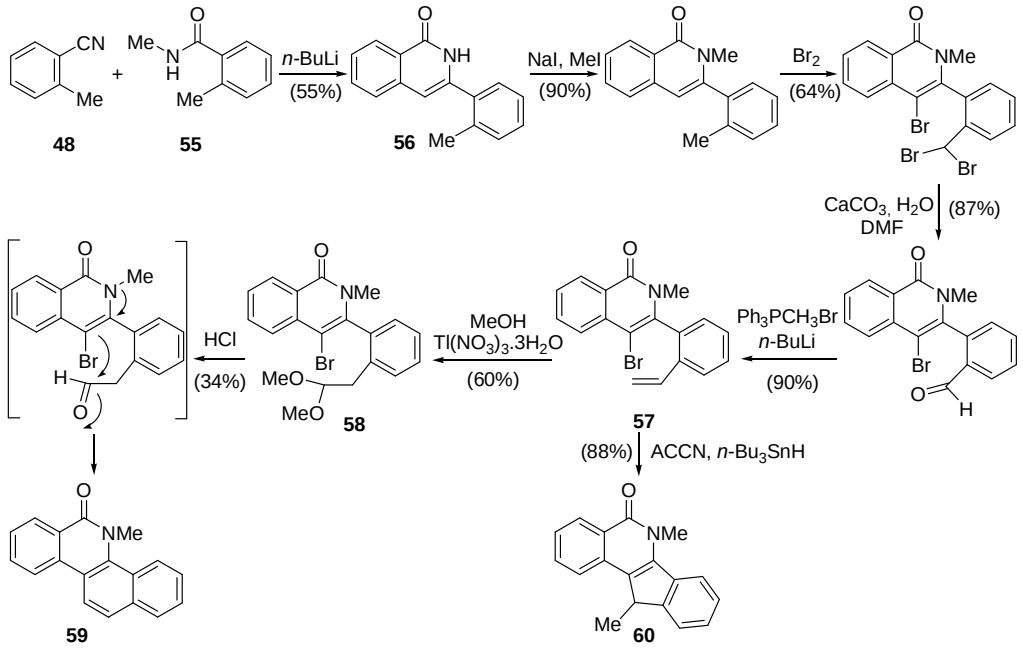


Scheme 13

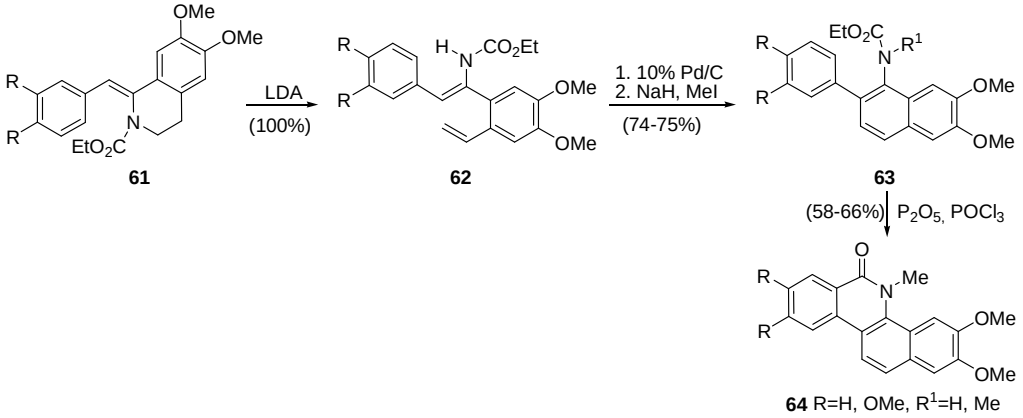
The benzo[*c*]phenanthridone skeleton **59** was synthesized by Cho *et al*[33] from *o*-methylbenzonitrile **48** and *N*-methyl-*o*-toluamide **55** in seven steps (Scheme 14). Amide **55** was basified with *n*-butyl lithium to give the dianion which was reacted with *o*-methylbenzonitrile **48** to afford the 3-(2-methyl)phenylisoquinolin-1(*2H*)-one **56**. The reaction proceeded in four steps involving methylation of the amide nitrogen, bromination followed by aldehyde formation and Wittig reaction, ultimately leading to styrene **57**. Oxyfunctionalization of **57** with thallium trinitrate in methanol gave the acetal **58**, which was then hydrolyzed with 10% HCl to provide the desired 5-methylbenzo[*c*]phenanthridin-6-one **59**, in 34% yield. Radical cyclization of styrene **57** with tributyl tin hydride in the presence of azobiscyclohexanecarbonitrile (ACCN) led to the selective formation of 6,11-di-methyl-6,11-dihydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one **60**, and not to the benzophenanthridone **59**. The authors also realized that the indeno[1,2-*c*]isoquinolin-5-one **60** showed excellent in vitro antitumor activity when compared to benzophenanthridone **59**.

Estévez *et al*[34] described the transformation of 1-benzylisoquinolines into benzo[*c*]phenanthridones through the C-N cleavage by LDA, in 1-benzylidine derivatives **61** (Scheme 15). Compounds **62** were

transformed into naphtalenes **63** by a Bichler-Napieralski reaction followed by cyclization to the corresponding tetrasubstituted benzo[*c*]phenanthridones **64**.



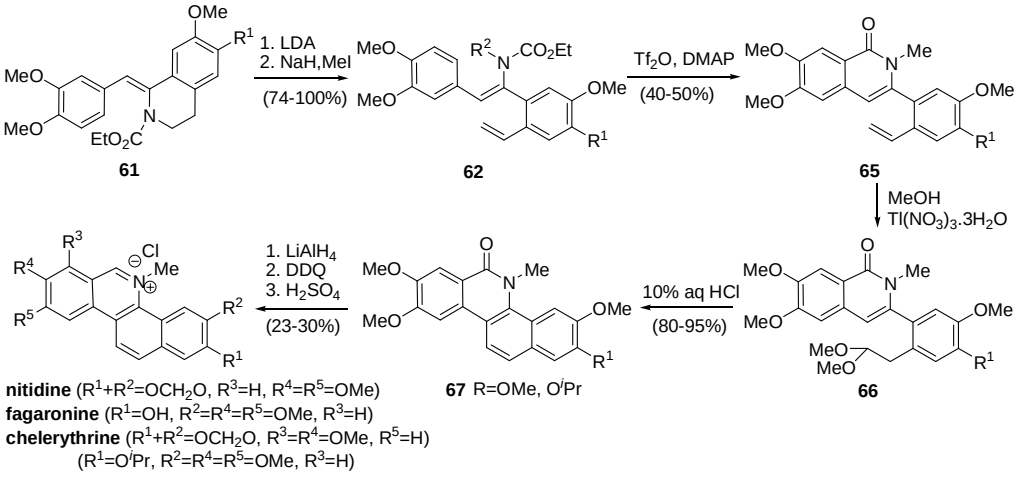
Scheme 14



Scheme 15

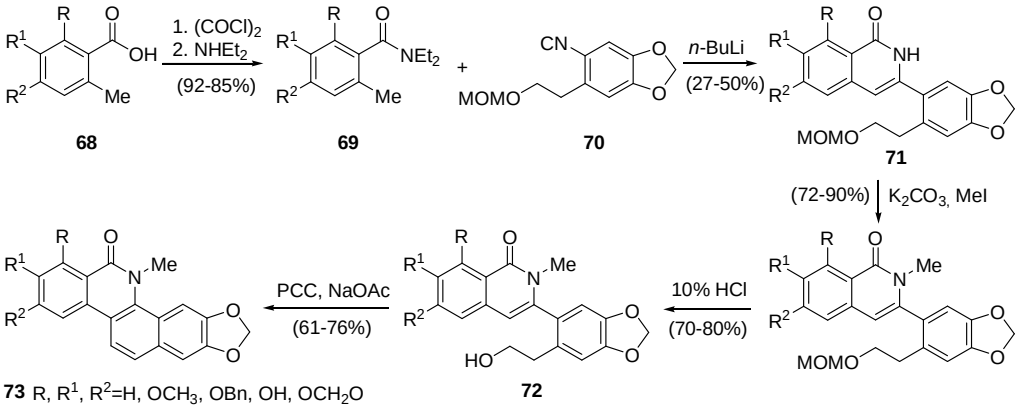
Two years later these authors described a modification of this approach that provides access to vinylphenylisoquinolinones **65**, and a new method for the total synthesis of benzophenanthridones **67** (Scheme 16).[35] Compound **62** was reacted with triflic anhydride (Tf_2O) and *N*,*N*-dimethylaminopyridine (DMAP) and the Bischler-Napieralski cyclization afforded vinylphenylisoquinolinones **65**. Treatment with

thallium (III) trinitrate in methanol afforded the acetal **66**, which undergoes hydrolysis, cyclization, and dehydration on addition of 10% hydrochloric acid, leading to **67**. Successive reduction with $LiAlH_4$ and oxidation with DDQ produced nitidine, fagaronine or chelerythrine, depending on the substitution pattern.



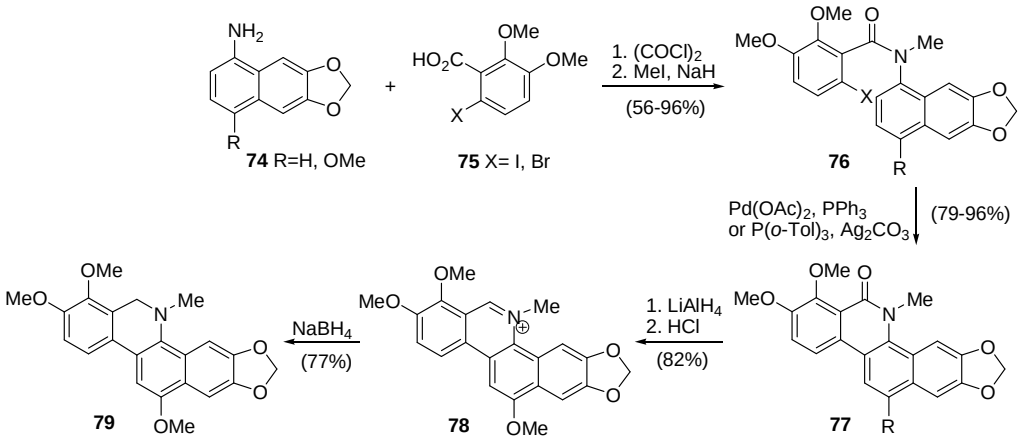
Scheme 16

Eight years later, a novel synthesis of benzo[*c*]phenanthridin-6-one **73** was published by Cho (Scheme 17).[36] The initial step was the coupling between *o*-toluamide **69** and benzonitrile **70** to produce 3-arylisoquinoline **71**. *o*-Toluamides **69** were synthesized in good yield from the corresponding substituted benzoic acids **68** by treatment with oxalyl chloride followed by diethylamine. Compound **72** was formed after *N*-methylation and hydrolysis of the MOM protecting group with HCl. The alcohol functional group in **72** was oxidized with PCC ultimately leading to the aromatized benzo[*c*]phenanthridine **73**. The catalytic hydrogenation reaction of **73** (R^1=OBn) with 5% Pd/C removed the benzyl group to give the oxyterihanine (R^1=OH) in 53% yield.[36b]



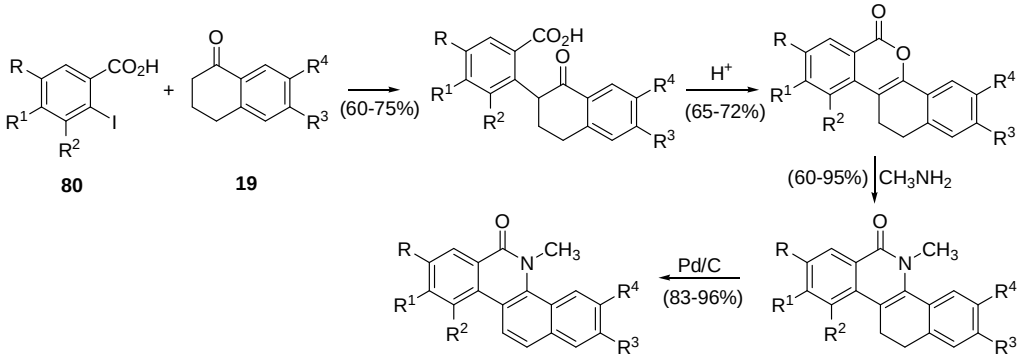
Scheme 17

A convenient and versatile synthesis of benzophenanthridones **77**, was reported by the internal biaryl coupling reaction of haloamides **76** using a palladium reagent (Scheme 18).[37] Compound **76** resulted from treatment of **75** with oxalyl chloride followed by addition of amine **74** and trimethylamine. Methylation with methyl iodide in the presence of sodium hydride in DMF gave the iodoamide or bromoamide **76**. The coupling reaction of haloamides **76** was performed using $Pd(OAc)_2$, PPh_3 or P(*o*-Tol)$_3$ and Ag_2CO_3 affording chelerythrines **77**. Reduction of **77** with $LiAlH_4$ followed by treatment with HCl gave benzophenanthridine **78**, which was reduced with $NaBH_4$ to afford 12-methoxydihydrochelerythrine **79**, isolated in 77% yield.



Scheme 18

Roussi *et al*[21] also reported the formation of benzo[*c*]phenanthridones **81** starting with an $S_{RN}1$ reaction between 2-iodobenzoic acids **80** and the enolate of tetralones **19** (Scheme 19). This procedure is similar to that used for the synthesis of dihydrobenzo[*c*]phenanthridines **20** described in Scheme 5 and involved irradiation of the reagents followed by reflux in benzene containing *p*-toluenesulfonic acid. The ester evolved to the amide upon heating with methylamine, in a sealed container.

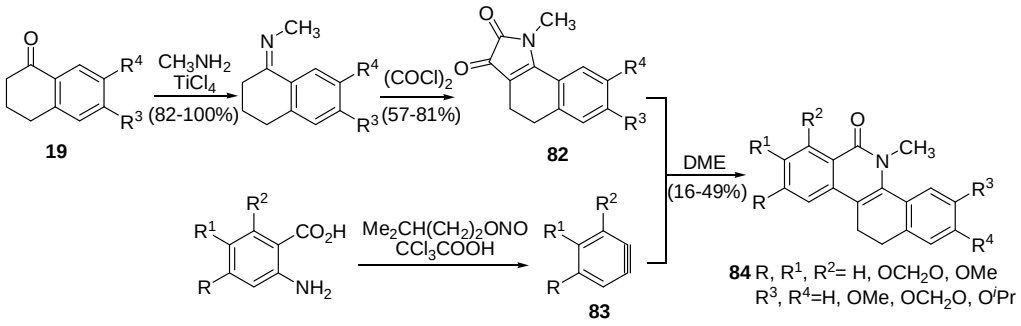


81 R=R^1=R^2=H, OMe, R^3, R^4=H, OMe, O^{i}C$_3$H$_7$

Scheme 19

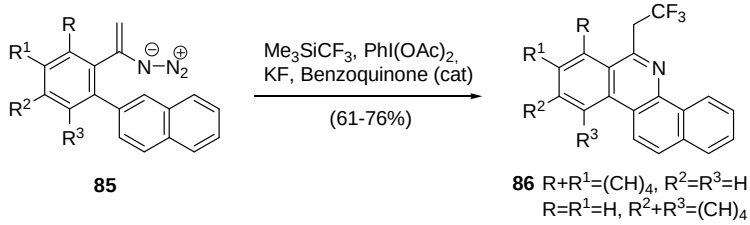
The fully aromatic system was obtained after treatment with Pd/charcoal.

Castedo *et al*[38] developed a highly convergent strategy to benzo[*c*]phenanthridones based on the ability of dihydronaphthalenopyrrolinediones to undergo [4+2] cycloadditions with the highly electrophilic benzyne system (intramolecular benzyne cycloaddition) (Scheme 20). The tetralone **19** was converted into the *N*-methylimine and then treated with oxalyl chloride under carefully controlled conditions to provide the dihydronaphthalenopyrrolinedione **82**. Reaction with benzyne **83**, was performed in 1,2-dimethoxyethane (DME) under reflux conditions, and was initiated by nucleophilic attack of the enamine to the electrophilic benzyne, followed by elimination of carbon monoxide, producing the dihydrobenzo[*c*]phenanthridin-6(5*H*)-one **84**.



Scheme 20

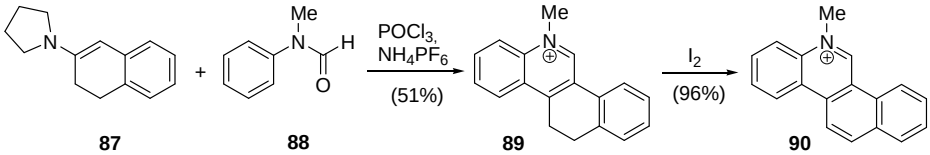
Chiba *et al*[39] prepared benzo[*c*]phenanthridines **86** by an oxidative radical perfluoroalkylation of biarylvinyl azides **85** (Scheme 21). Readily available and easily handled Me_3SiCF_3 was used as the perfluoroalkyl radical source under oxidative conditions in the presence of $PhI(OAc)_2$ and KF with a catalytic amount of benzoquinone.



Scheme 21

2.3. 6-Azachrysene

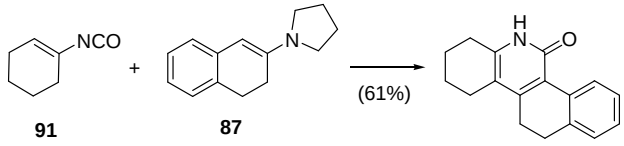
The reaction between 2-(1-pyrrolidino)-3,4-dihydronaphtalene **87** and *N*-methylformanilide **88** in the presence of phosphorus oxychloride afforded the 11,12-dihydro-6-methylbenzo[*i*]phenanthridinium hexafluorophosphate **89**, isolated after addition of ammonium hexafluorophosphate (Scheme 22).[40] Oxidation to the aromatic quaternary benzo[*i*]phenanthridine **90** occurred in excellent yield in the presence of iodine.



87 **88** **89** **90**

Scheme 22

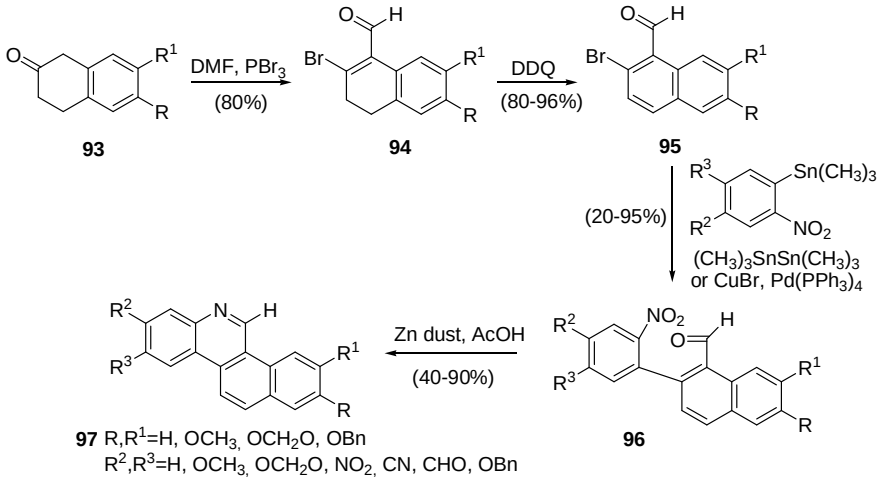
Rigby *et al*[41] reported the synthesis of 7,8,9,10,11,12-hexahydrobenzo[*i*]phenanthridin-5(*6H*)-one **92**, in a single step, from the reaction of vinyl isocyanate **91** with enamine **87** (Scheme 23).



91 **87** **92**

Scheme 23

The synthesis of substituted benzo[*i*]phenanthridines **97** was also performed from the substituted *β*-tetralone **93** under bromo-Vilsmeier conditions leading to aldehyde derivatives **94** (Scheme 24).[42] Treatment of this compound with DDQ in toluene provided the bromo-naphthaldehydes **95**. Stille coupling of **95** with various trimethyl(*ortho*-nitrophenyl)stannanes gave **96**, and reduction of the nitro group with zinc dust in acetic acid followed by intramolecular cyclization with the carbonyl group, provided the benzo[*i*]phenanthridines **97** in yields ranging from 40-90%. The synthesized compounds were evaluated as topoisomerase I-targeting agents and the substituent in the 8-position was important for the pharmacological activities that were evaluated.

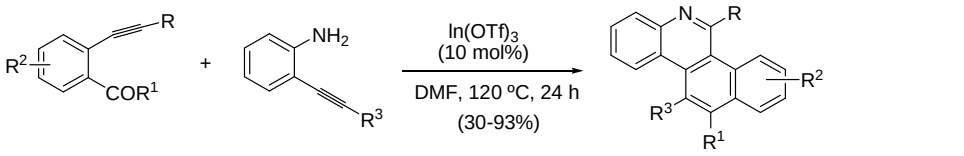


93 **94** **95** **96**

97 R,R^1=H, OCH_3, OCH_2O, OBn
R^2,R^3=H, OCH_3, OCH_2O, NO_2, CN, CHO, OBn

Scheme 24

Yanada *et al*[43] reported the synthesis of compounds **100** via a domino intramolecular nucleophilic attack/intermolecular cycloaddition/dehydration process from the indium(III)-catalyzed tandem reaction of *ortho*-alkynylbenzaldehydes **98** and *ortho*-alkynylanilines **99** (Scheme 25).



98 **99** **100** R=Ph, Bu, R^1=H, Me
R^2=H, 4-Me, 5-F, 6-F, R^3=Bu, $SiMe_3$

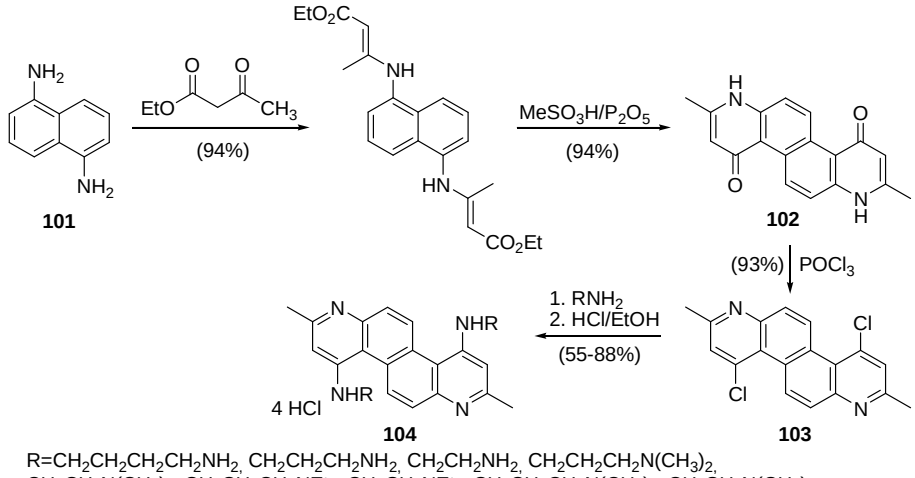
Scheme 25

3. Synthesis of diazachrysene derivatives

Diazachrysene derivatives are also known compounds, but only three examples (1,10-, 2,4-, and 4,10-diazachrysenes) were previously reported in the literature.[4a-b] This section highlights the advancements in the synthesis of other diazachrysene derivatives.

3.1. 1,7-Diazachrysene

The only representative example of this heterocyclic system reported in the literature was prepared from 1,5-diaminonaphthalene **101** (Scheme 26)[44] used as a precursor of intermediate **102**, generated via a Conrad-Limpah reaction. Compound **102** was reacted with $POCl_3$ to give the dichloride **103**. Nucleophilic substitution with a variety of diamines, followed by HCl salt formation, led to 1,7-bis(aminoalkyl)diazachrysene tetrahydrochloride **104**.



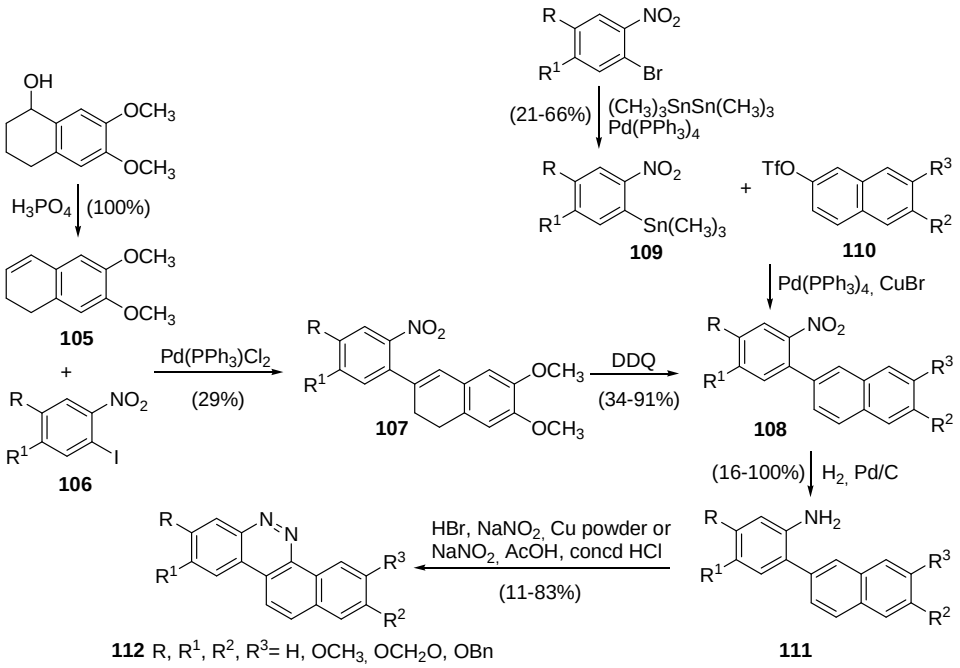
101 **102** **103** **104**

R=$CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2NH_2$, $CH_2CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2NEt_2$, $CH_2CH_2NEt_2$, $CH_2CH_2CH_2N(CH_2)_4$, $CH_2CH_2N(CH_2)_4$, $CH_2CH_2CH_2N(CH_2)_5$, $CH_2CH_2N(CH_2)_5$, $CH_2CH_2CH_2N(CH_2CH_2)_2O$, $CH_2CH_2N(CH_2CH_2)_2O$

Scheme 26

3.2. 5,6-Diazachrysene

LaVoie *et al*[45] reported the synthesis of substituted dibenzo[*c*,*h*]cinnolines **112** (Scheme 27) and evaluated these compounds as topoisomerase I-targeting anticancer agents. The reaction sequence started with the coupling of **105** with *o*-iodonitrobenzene **106**, under conditions analogous to those used in the Heck reaction, leading to **107**. Oxidation of **107** with DDQ provided the naphthyl derivatives **108**. These compounds were also obtained by a different synthetic approach (Scheme 27) involving substituted *ortho*-nitroarylstannanes **109**. Stille coupling with naphthalene derivatives **110** led to **108**. Reduction of the nitro group followed by diazotization of the aniline **111** led to the benzo[*c*,*h*]cinnolines **112**.



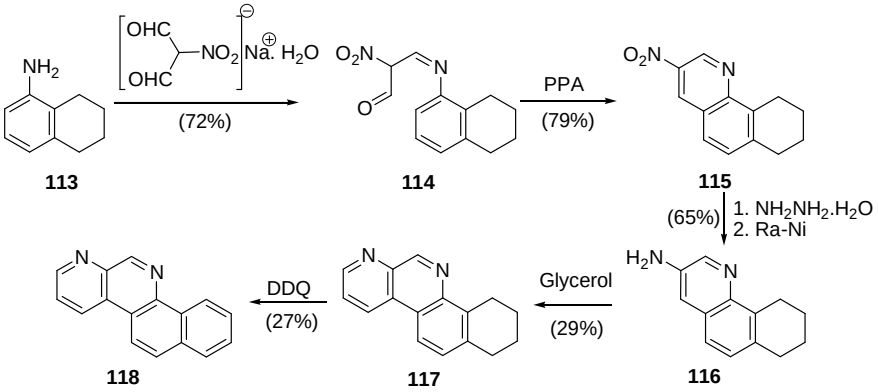
Scheme 27

3.3. 5,7-Diazachrysene

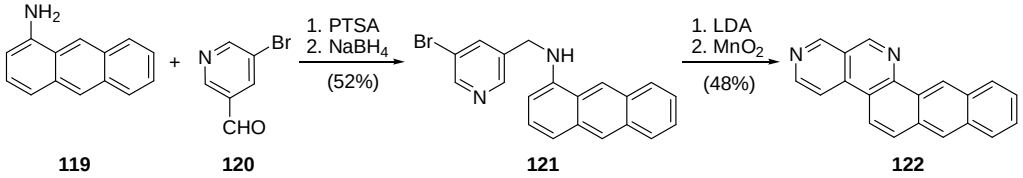
Takeuchi *et al*[46] combined 5-aminotetralin **113** with sodium nitromalonaldehyde monohydrate to give compound **114**. Cyclization using polyphosphoric acid (PPA) (Scheme 28) led to **115**. The nitro group in **115** was reduced to the amine **116** with Raney nickel, followed by the Skraup reaction to give compound **117**. Naphto[2,1-*f*][1,7]naphthyridine **118** was obtained by dehydrogenation of **117** using DDQ.

3.4. 5,8-Diazachrysene

Acid catalyzed condensation of 1-aminoanthracene **119** and 5-bromonicotinaldehyde **120** followed by reduction with sodium borohydride in methanol afforded compound **121** (Scheme 29). Cyclization with excess LDA and manganese dioxide dehydrogenation led to diazachrysene **122**.[47]



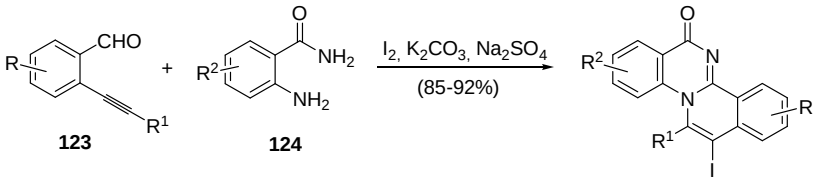
Scheme 28



Scheme 29

3.5. 5,10b-Diazachrysene

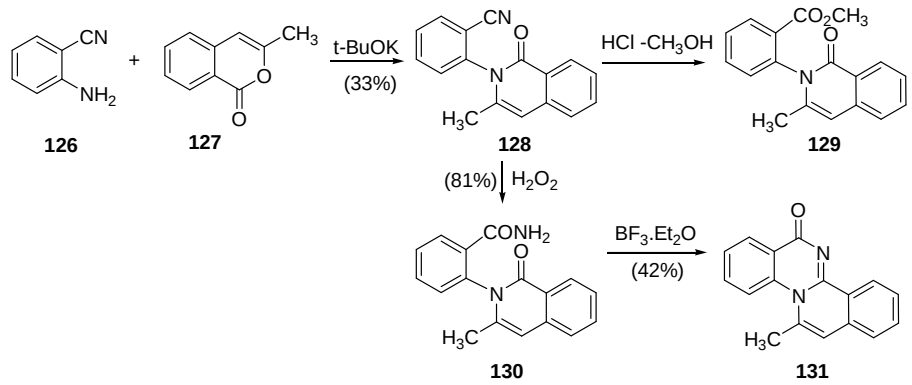
An efficient iodine-mediated electrophilic tandem cyclization between substituted 2-alkynylbenzaldehydes **123** and 2-aminobenzamides **124** led to isoquinoline-fused quinazolinones **125** (Scheme 30).[48] The presence of the iodo group confers an advantage for further derivatization via robust cross coupling reactions, that were exemplified by Sonogashira and Suzuki cross-coupling reactions.



125 R= H, 4,5-$(OMe)_2$, 5-F, 5-OMe
R^1=Ph, 4-^{t}BuC$_6$H$_4$, 4-MeC$_6$H$_4$, R^2=H, 5-NO_2

Scheme 30

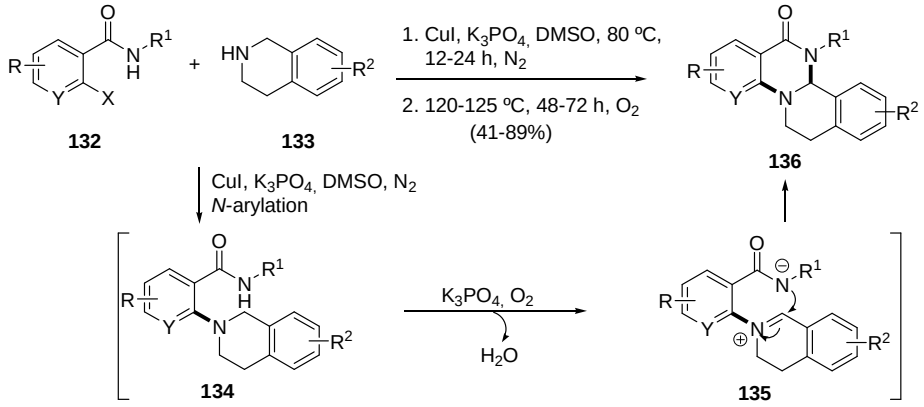
The reaction of 2-aminobenzonitrile **126** with 3-methylisocoumarin **127** in the presence of potassium *tert*-butoxide gave the isocarbostyril **128** (Scheme 31).[49] Attempts to induce ring closure of **128** to **131** by treatment with methanolic hydrogen chloride resulted in compound **129**. The novel ring system 12-methyl-6*H*-isoquino[2,1-*a*]quinazolin-6-one **131** was generated by treatment of **128** with alkaline hydrogen peroxide, leading to **130**, followed by cyclization of this compound with boron trifluoride etherate.



Scheme 31

Fu *et al*[50] report a novel and efficient copper-catalyzed one-pot synthesis of tetrahydroisoquinolino[2,1-*a*]quinazolinone derivatives **136** (Scheme 32). In this case copper-catalysed *N*-arylation of substituted 1,2,3,4-tetrahydroisoquinoline **133** with amide **132** provided **134**. Intramolecular aerobic oxidation of **134** in the presence of base (two or four equivalents of K_3PO_4) led to **135**. Intramolecular nucleophilic attack of the amide nitrogen to the imine carbon in **135** led to the *N*-fused heterocycles **136**.

The enantioselective C-N bond-forming reaction to produce **136** was described in the literature and was also catalyzed by chiral phosphate anions,[51] palladium(II)-porphyrin complex,[52] tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^+SbCl_6^-$)[53] or iodine(III).[54]

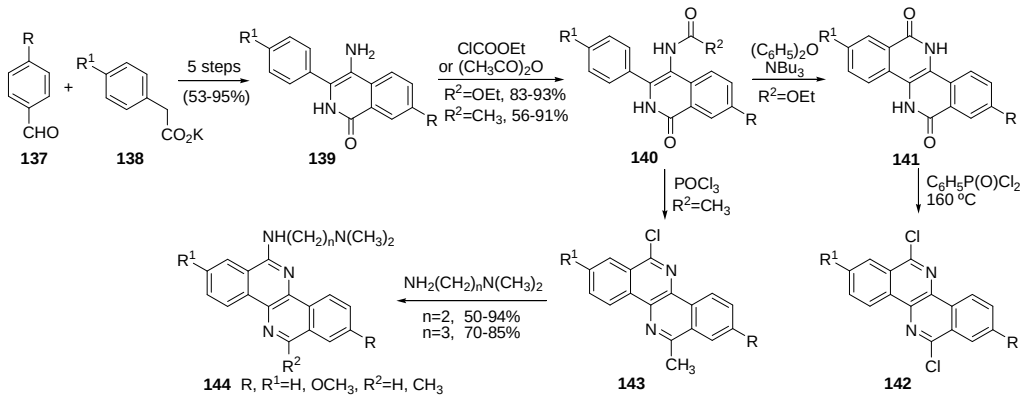


Scheme 32

3.6. 5,11-Diazachrysene

The synthesis of dibenzo[*c*,*h*]-1,5-naphthyridine derivatives was reported to occur from substituted benzaldehydes **137** and arylacetic acid **138** (Scheme 33).[55] The 4-amino-3-aryl-isoquinolin-1-(*2H*)-ones **139** were prepared in five steps and then combined with ethyl chloroformate or acetic anhydride leading to the acylated derivatives **140**. Thermal cyclisation of compounds **140** (R^2=OEt) provided dibenzo[*c*,*h*]-1,5-

naphthyridinediones **141**. Compounds **140** (R^2=CH_3) were used as precursors of dibenzo[*c*,*h*]-1,5-naphthyridine derivatives **144** in another five steps. The different amino substituted derivatives **144** were obtained from the chloro-substituted analogues **143** by reaction with 2-dimethylaminoethylamine or 3-dimethylaminopropylamine under reflux conditions.



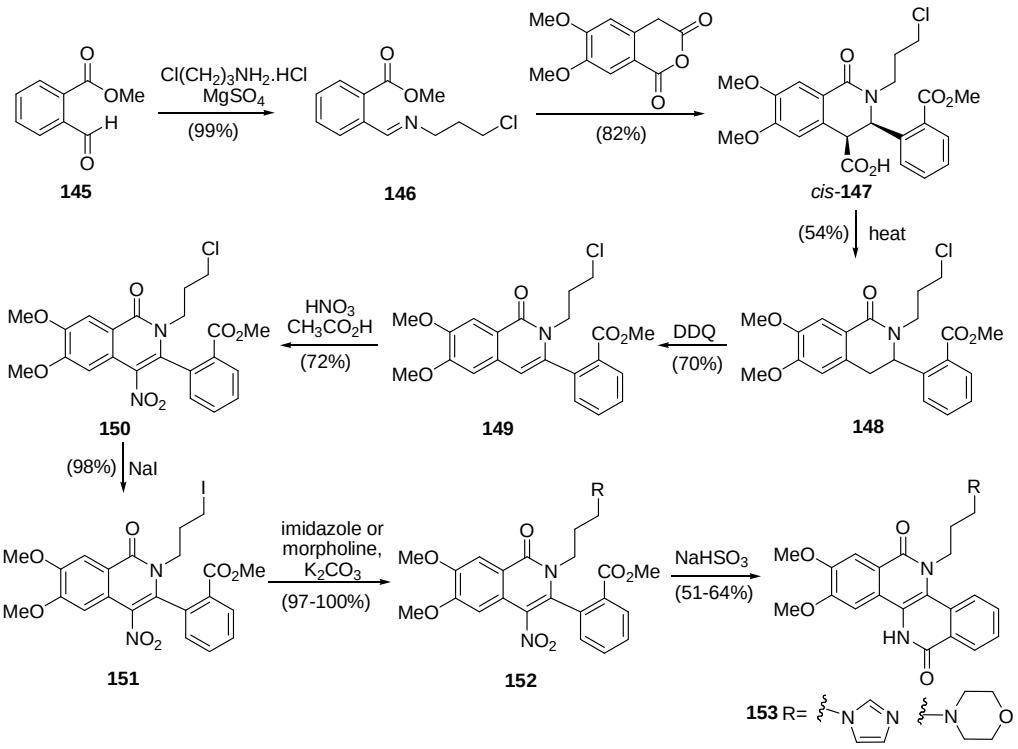
Scheme 33

Cushman *et al*[56] recently reported another alternative for the synthesis of dibenzo[*c*,*h*]-1,5-naphthyridinediones **153**, analogous to **141**, where one of the isoquinolinone nitrogens was replaced by an aminopropyl side chain (Scheme 34). The synthetic approach involved the reaction of **145** with 3-chloropropylamine, followed by reaction of the resulting Schiff base **146** with 4,5-dimethoxyhomophthalic anhydride to produce the *cis*-isoquinolonic acid **147**. Thermal decarboxylation of **147** led to dihydroisoquinolone **148**, that was treated with DDQ to provide the dehydrogenated isoquinolone **149**. The nitration of compound **149** occurred in the 3-position yielding **150**. The Finkelstein reaction of **150** with sodium iodide led to **151**, which was further reacted with imidazole or morpholine to give amines **152**. Reduction of the nitro group with sodium bisulfite resulted in the formation of the dibenzo[*c*,*h*]-1,5-naphthyridinediones **153**. The compounds prepared were evaluated for their Topoisomerase I inhibitory and antiproliferative activities.

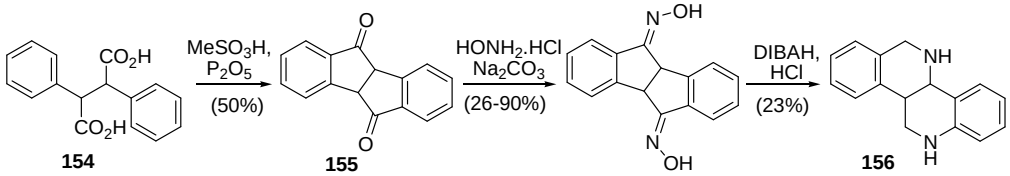
3.7. 5,12-Diazachrysene

Papageorgiou *et al*[57] described the synthesis of *cis*-4b,5,6,10b,11,12-hexahydro-5,12-diazachrysene **156**. The reaction proceeded by intramolecular cyclization of 2,3-diphenylsuccinic acid **154** in the presence of methanesulfonic acid (Scheme 35). The reductive Beckmann rearrangement of the oxime converted indeno[2,1-*a*]indene-5,10-dione **155** to the 5,12-diazachrysene **156**.

Another procedure for the synthesis of 5,12-diazachrysene was described from a readily available indole **157** (Scheme 36).[58] Reaction with aromatic aldehydes led to 10-benzylidene-5-methyl-5,10-dihydroindeno[1,2-*b*]indole **158** that was oxidized with hydrogen peroxide to give the dioxodibenzo[*b*,*f*]azocine **159**. Refluxing **159** with ethylamine generated the new diazachrysene **160**, isolated in 50% yield. This compound exhibited strong yellow fluorescence under ultraviolet light.



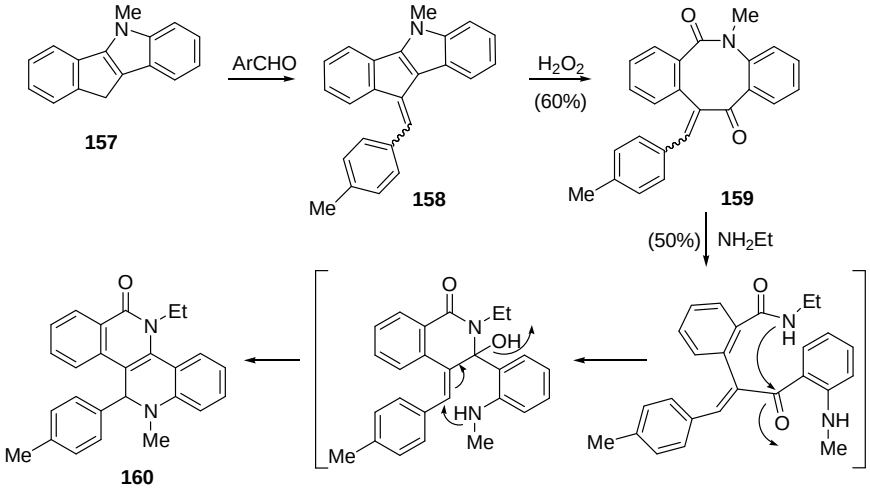
Scheme 34



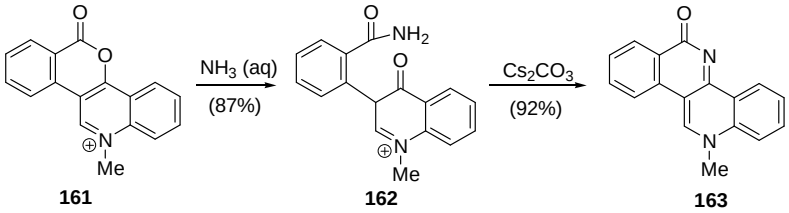
Scheme 35

Mackay *et al*[40] reported the synthesis of 6-methyl-12-oxodibenzo[*c*,*h*][1,6]naphthyridine **163** in three steps from the benzopyrano[4,3-*c*]quinolinium phosphodichloridate **161** (Scheme 37). Cleavage of the lactone moiety by ammonia solution yielded the amide **162**. The aromatic dibenzo[*c*,*h*][1,6]naphthryridine **163** was obtain in high yield by intramolecular cyclisation in the presence of caesium carbonate, with subsequent dehydration.

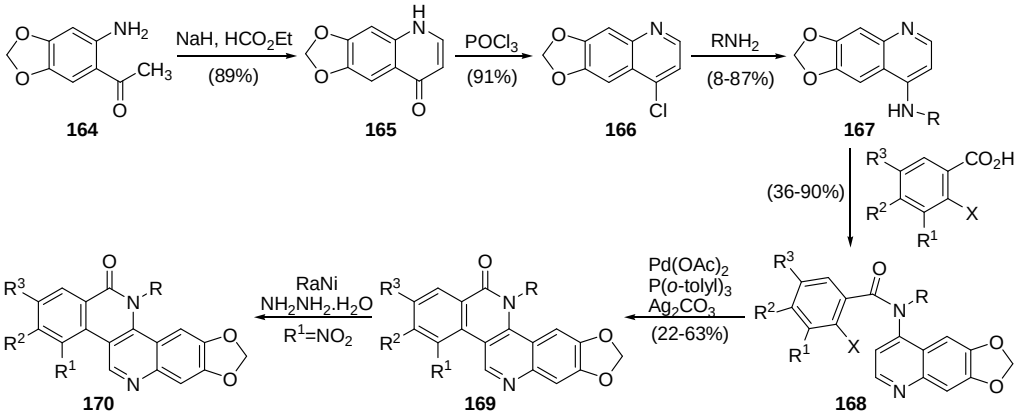
LaVoie *et al*[16a,59] described the synthesis of analogues of ARC-111 (**170**) with NH_2, *N*-alkyl, *N*,*N*-dialkyl, pyrrolidinyl, piperidinyl and piperazinyl substituents at the 2-position of a 5-ethyl group (Scheme 38). Compound **165**, prepared by reaction of *o*-aminoacetophenone **164** with ethyl formate in sodium hydride, was used as the starting material. Chlorination of **165** with phosphoryl chloride provided 4-chloro-6,7-methylenedioxyquinoline **166**, used as the precursor of 4-aminoquinolines **167** after heating with primary amines.



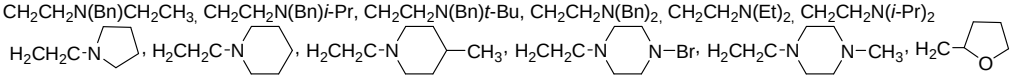
Scheme 36



Scheme 37



R= $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2N(CH_3)_2$, $CHCH_3CH_2N(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2N(Bn)CH_3$, $CH_2CH_2N(Bn)CH_2CH_3$, $CH_2CH_2N(Bn)i\text{-}Pr$, $CH_2CH_2N(Bn)t\text{-}Bu$, $CH_2CH_2N(Bn)_2$, $CH_2CH_2N(Et)_2$, $CH_2CH_2N(i\text{-}Pr)_2$

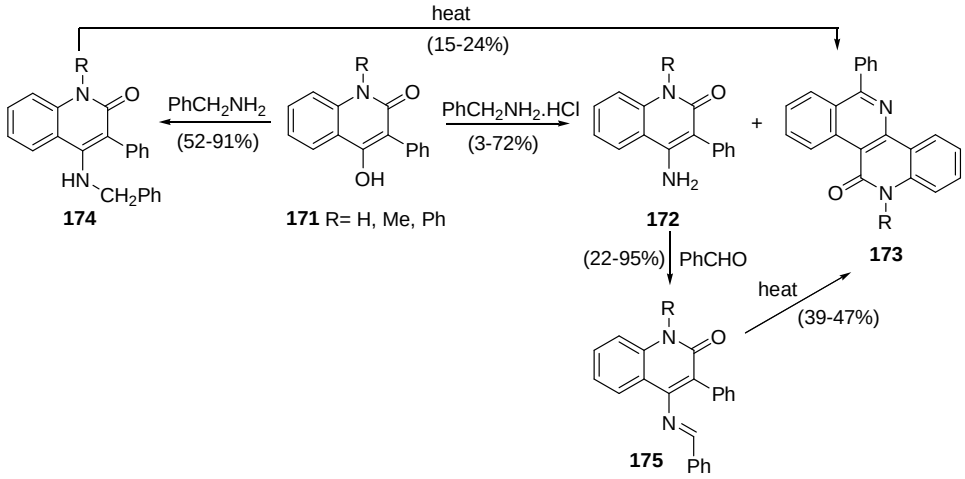


R^1, R^2, R^3=H, NO_2, OCH_3, NH_2, X=I, Br

Scheme 38

The conversion of benzoic acid to the acid chloride using oxalyl chloride, followed by immediate reaction with **167** provided variable yields of the amides **168**. The Heck reaction was used for the cyclization of these benzamides to generate 5,12-diazachrysene-6-ones **169**, that were reduced with Ra-Ni in the presence of hydrazine to give the corresponding amino analogues **170**.

Kappe *et al*[60] reported the synthesis of a 5,12-diazachrysene **173**, initially as a by-product in the reaction between 4-hydroxy-3-phenyl-2-quinolone **171** with benzylamine (Scheme 39). They realized that the dibenzo[*c*,*h*][1,6]naphthyridine **173** could also be synthesized by thermolysis of **174**. The primary amine in the 4-position of 2-quinolone **172** allowed the preparation of different imines by condensation with aldehydes and compounds **175** were cyclized to **173** upon heating.



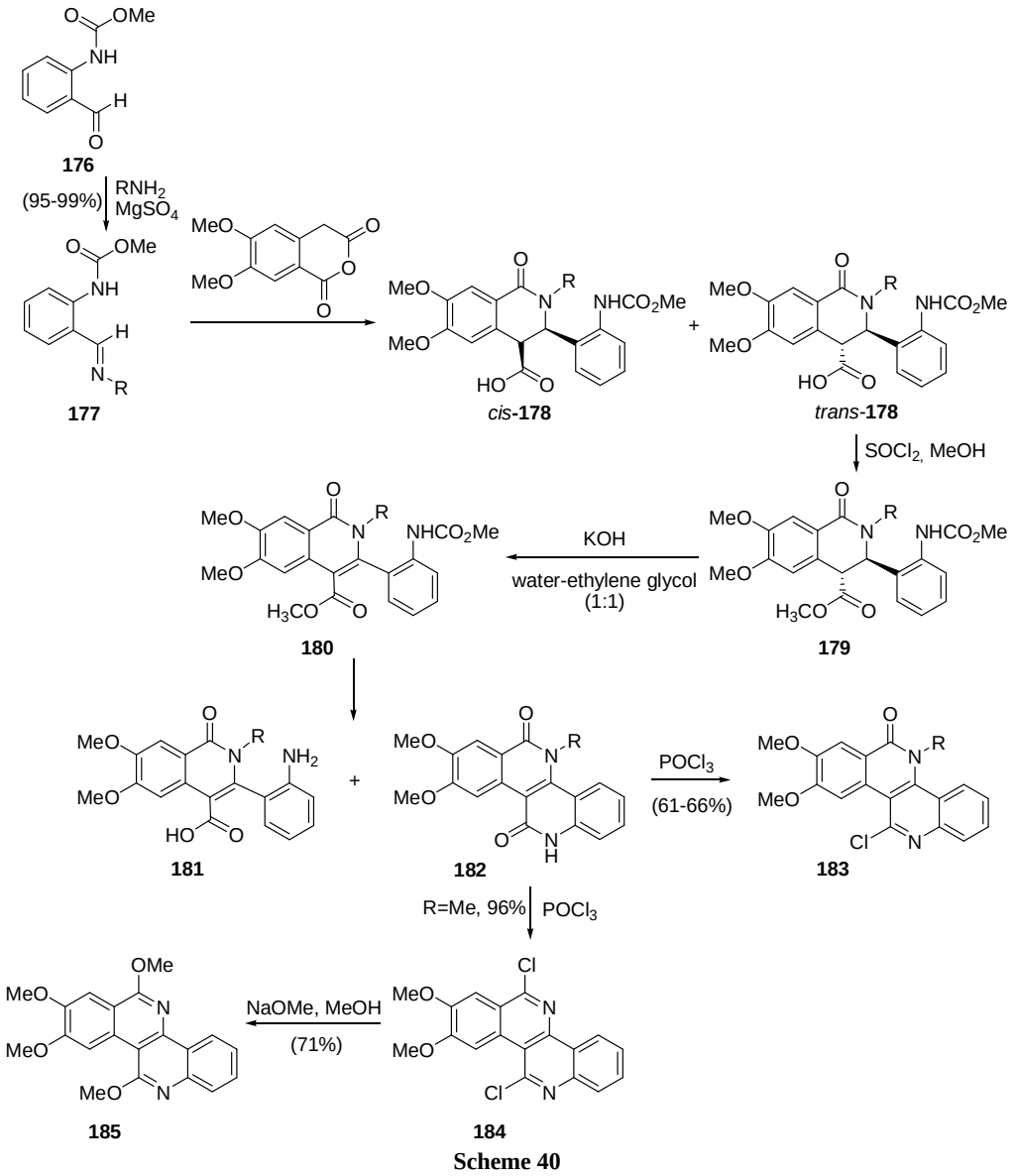
Scheme 39

Dibenzo[*c*,*h*][1,6]naphthyridinediones **182** with various side chains attached to the isoquinoline lactam were synthesized from the *N*-protected *o*-aminobenzaldehyde **176** (Scheme 40).[61] Imine **177**, isolated from the reaction of aldehyde **176** with different primary amines followed by reaction with 4,5-dimethoxyhomophthalic anhydride led to a mixture of *cis*- and *trans*-**178** (isolated by filtration or by evaporation of the filtrate and recrystallization of the crude product, respectively). The reaction proceeded to naphthyridinediones **182** and this compound was reacted with $POCl_3$ to yield chloronaphthyridinones **183** or the dichloride **184**, as shown in Scheme 40. The reaction of dichloride **184** with sodium methoxide gave the tetramethoxydibenzonaphthyridine **185**.

3.8. 6,12-Diazachrysene

LaVoie *et al*[62] performed the synthesis of several 6-substituted dibenzo[*c*,*h*][2,6]naphthyridin-5-ones **193** that can be considered reversed lactam analogues of ARC-111 and these compounds were evaluated for their topoisomerase I-targeting activity and citotoxicity (Scheme 41). 6,7-Methylenedioxy-4-quinolinecarboxylic acid **188** was prepared from **186** after two sequential oxidation steps. Compound **190** was prepared by hydrolysis of *o*-iodoacetamide **189** using aqueous NaOH. The amide **191** was obtained by

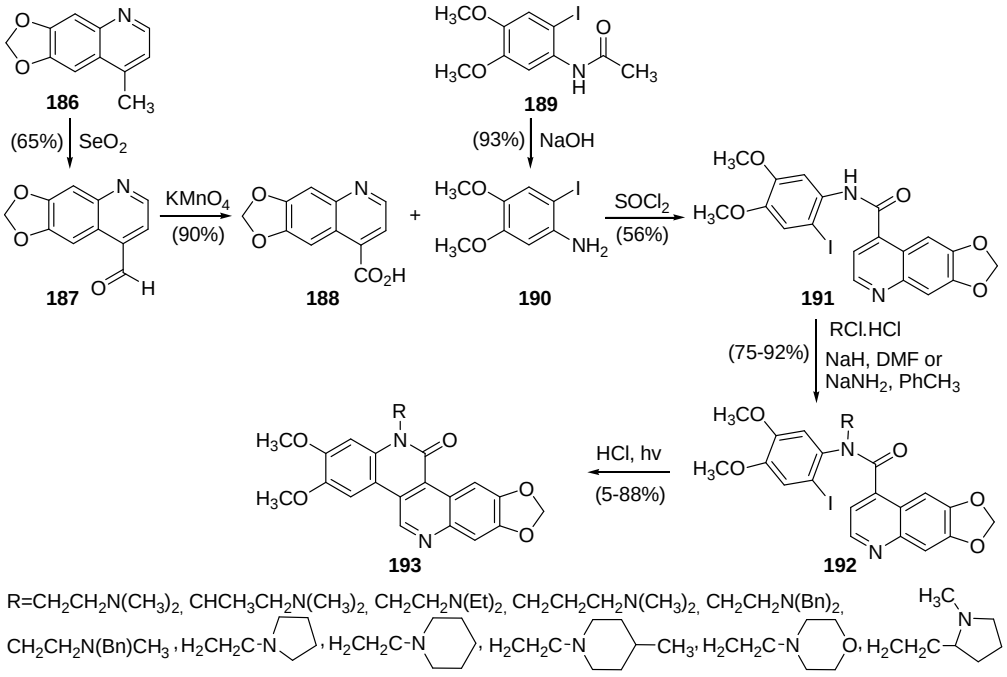
coupling **188** and **190** using thionyl chloride. Treatment with sodium hydride led to the amide anion, which was reacted with substituted alkyl halides to form tertiary amide intermediates **192**. Photocyclization of **192** in the presence of HCl provided the desired products **193**.



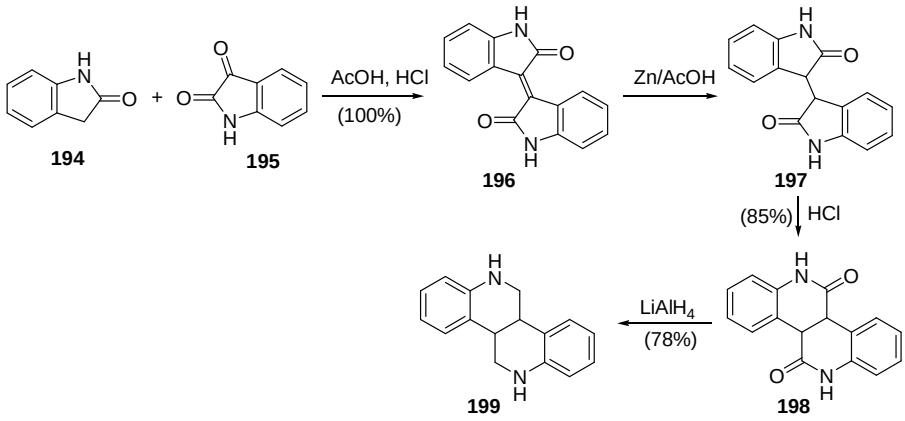
Scheme 40

Papageorgiou *et al*[63] report a new class of diazachrysenes starting from oxindole **194** and isatine **195** to generate isoindigo **196** (Scheme 42). The double bond in **196** was reduced with Zn in AcOH affording **197**

as a 1:1 mixture of the *meso* and racemic form. Refluxing in HCl gave a diastereoisomerically pure δ-lactam **198** that was treated with $LiAlH_4$ to yield the corresponding hexahydro-diazachrysene **199**.



Scheme 41

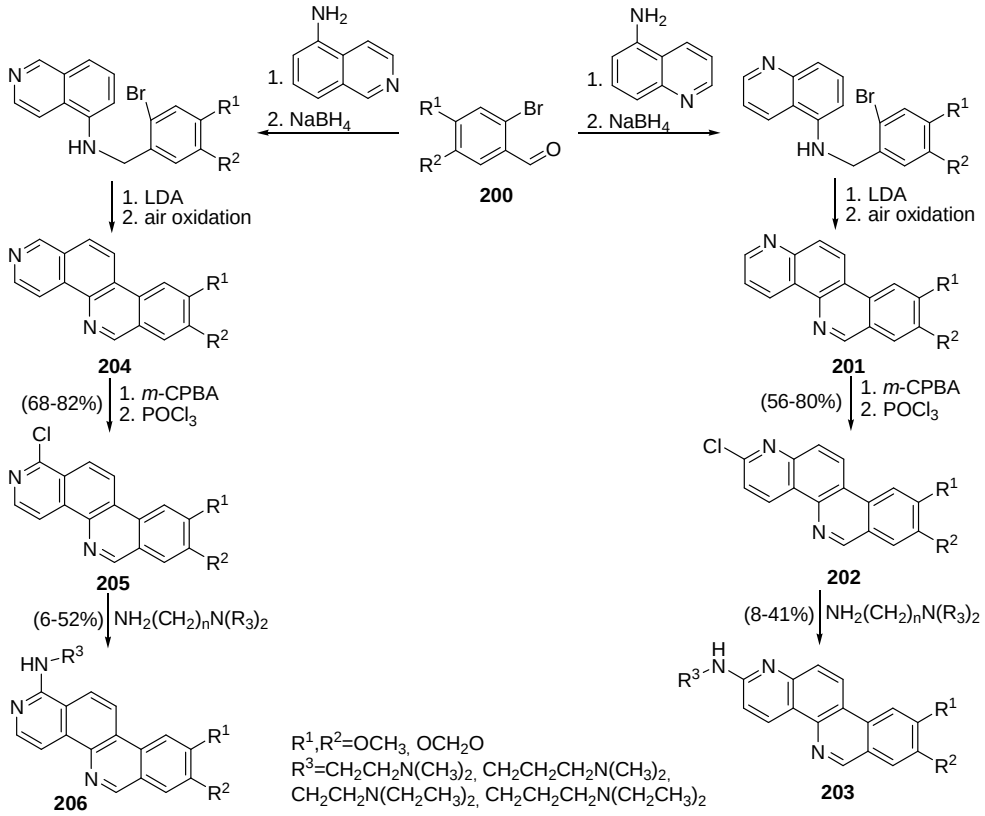


Scheme 42

3.9. 7,11- and 8,11-Diazachrysene

Tillequin *et al*[64] recently published the synthesis and biological activities of a new series of benzo[*c*][1,7] and [1,8]phenanthrolines substituted at C1 and C2 by dialkylaminoalkyl side chains (Scheme

43). Condensation of the 2-bromoaldehyde **200** with the 5-amino-quinoline or isoquinoline gave access to the corresponding Schiff bases. After reduction of the imine function with $NaBH_4$, treatment with an excess of LDA allowed the intramolecular cyclization to compound **201** or **204**. A spontaneous air oxidation step, followed by oxidation with *m*-CPBA, and reaction with $POCl_3$ originated the chloro derivatives **202** or **205**. Finally, heating these compounds with primary alkylamines generated the corresponding substituted benzo[*c*]phenanthrolines **203** or **206** in low to moderate yields (6-52%).

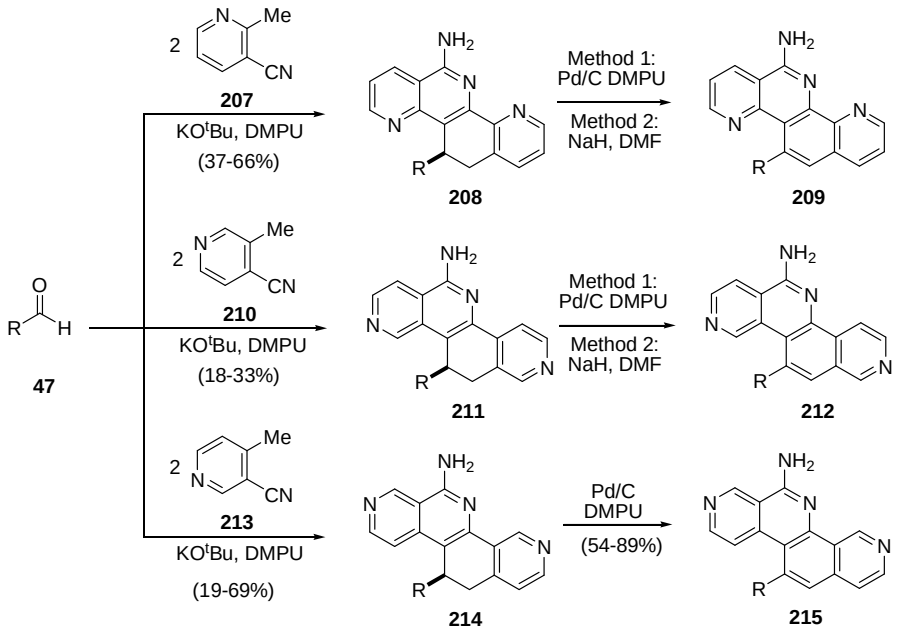


Scheme 43

4. Synthesis of triazachrysene derivatives

4.1. 1,5,10-, 2,5,9- and 3,5,8-Triazachrysene

Based on the synthesis of benzo[*c*]phenanthridines **49** (Scheme 12), Clement *et al*[65] recently reported a novel class of triazachrysenes (Scheme 44) with high cytotoxic potential as was demonstrated by preliminary in vitro studies. The process involved a base-catalyzed condensation of various aldehydes **47** with two equivalents of methyl-cyanopyridine **207**, **210** or **213** in 1,3-dimethyltetrahydropyrimidin-2-one (DMPU), used as solvent. The 11-substituted 6-amino-11,12-dihydropyridophenanthrolines **208**, **211** or **214** were oxidized with Pd/C in DMPU to provide the fully aromatic triazachrysenes **209**, **212** or **215**.

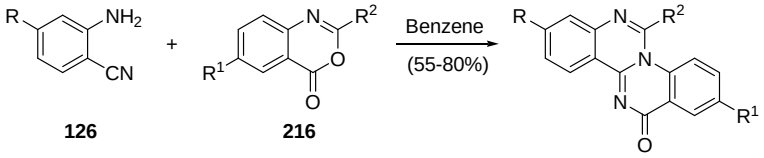


R=H, C_6H_5, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2,3-$(MeO)_2C_6H_3$, 2,5-$(MeO)_2C_6H_3$, 2,4,6-$(MeO)_3C_6H_2$, 3,4,5-$(MeO)_3C_6H_2$, furyl, thienyl, biphenyl, propyl, 3-BrC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4, 4-FC_6H_4

Scheme 44

4.2. 4b,6,11-Triazachrysene

Refluxing substituted 2-aminobenzonitriles **126** with 4*H*-3,1-benzoxazin-4-one **216** in benzene gave the 13*H*-quinazolino[3,4-*a*]quinazolin-13-ones **217** (Scheme 45) in a one-pot reaction.[49]



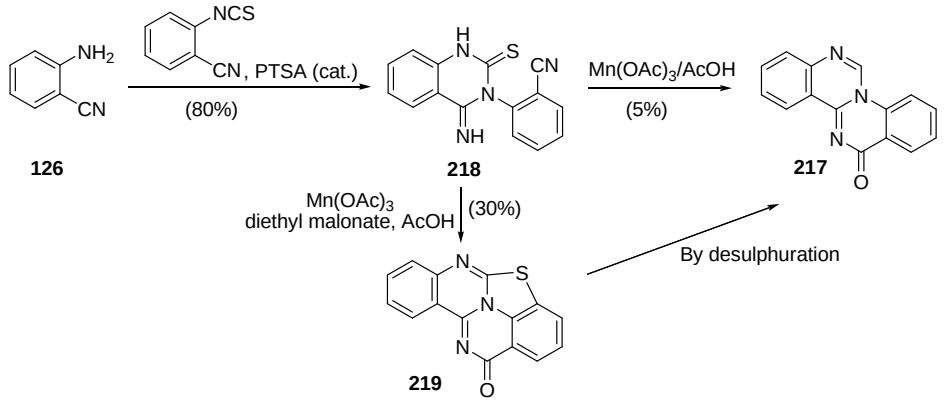
217 R,R^1=H, CH_3, Cl, R^2=CH_3, Isopr, Pro

Scheme 45

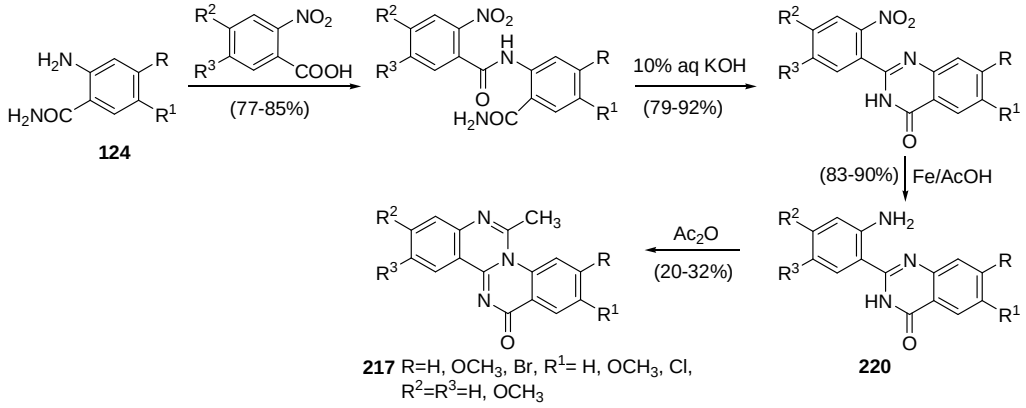
The 13*H*-quinazolino[3,4-*a*]quinazolin-13-one **217** was alternatively synthesized from **218**, prepared by reaction of 2-aminobenzonitrile **126** with 2-cyanophenyl isothiocyanate and a catalytic amount of *p*-toluenesulphonic acid (PTSA) (Scheme 46).[66] Reaction of **218** with manganese(III)acetate in acetic acid led to a poor yield of the tetracyclic product **217**. The reaction of compound **218** with manganese(III)acetate and diethyl malonate in acetic acid also generated the triazachrysene **219**, used as a precursor of **217** by desulphuration. In both cases, compounds **217** and **219** were isolated after column chromatography.

Venkateswarlu *et al*[67] described the synthesis of quinazolino[3,4-*a*]quinazolin-13-ones **217**, by reaction of 2-(2-aminophenyl)quinazolin-4(*3H*)-one **220** with acetic anhydride followed by cyclization onto

N1 (Scheme 47). The substituted derivatives **220** were obtained from 2-aminobenzamides **124** and 2-nitrobenzoic acids in three consecutive steps.



Scheme 46

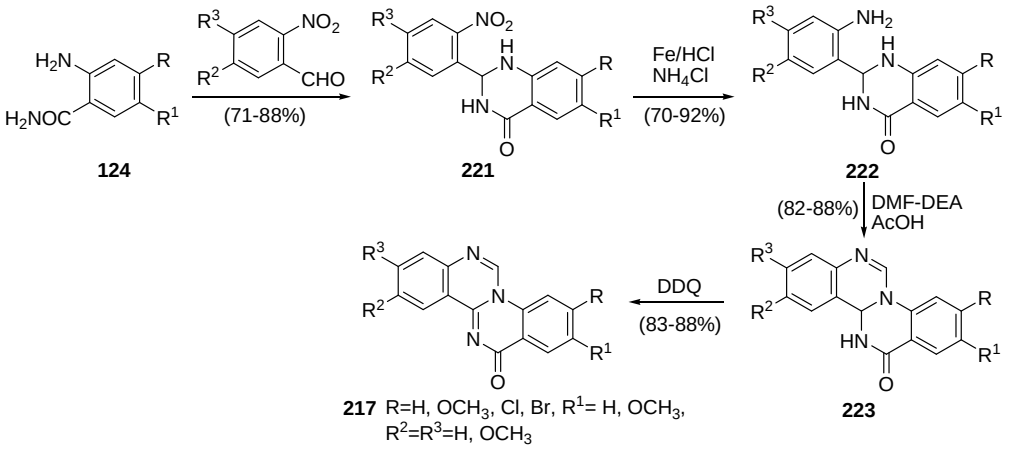


Scheme 47

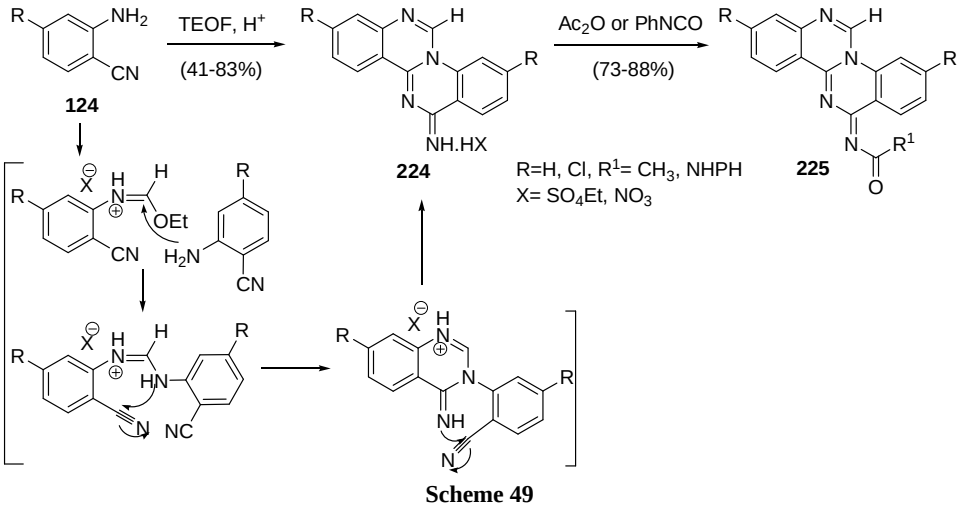
The same authors described the synthesis of quinazolino[3,4-*a*]quinazolin-13-ones **217** from the dihydro- precursors **223**.[68,69] These compounds were obtained by reaction of 2-(2-aminophenyl)-2,3-dihydroquinazolin-4(*1H*)-one **222** with dimethylformamide-dimethylacetal (DMF-DMA) followed by intramolecular cyclization (Scheme 48). The aniline moiety in **222** arised from reduction of the nitro functional group in **221**, using iron powder. Compounds **221** were obtained by refluxing 2-aminobenzamides **124** and 2-nitrobenzaldehyde. This reaction sequence provided the selective formation of quinazolino[3,4-*a*]quinazolin-13-ones **217**, isolated in very good yield.

Proença *et al*[70] described the formation of triazachrysenes **224** via dimerization of anthranilonitrile through a tandem process (Scheme 49). The sequence involved reaction of 2-aminobenzonitrile **124** with triethyl orthoformate (TEOF), using a protic acid as catalyst. The dimeric structures **224** were formed through a cascade reaction, initiated by the acid catalysed nucleophilic attack of a second molecule of

anthranilonitrile **124** to the imidate. Two consecutive intramolecular cyclization processes led to the final structure **224**, always isolated as a salt. Combining compound **224** with acetic anhydride or phenylisocyanate gave the acylated product **225** isolated in good yield.



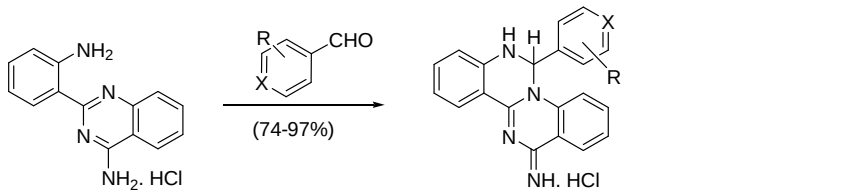
Scheme 48



Scheme 49

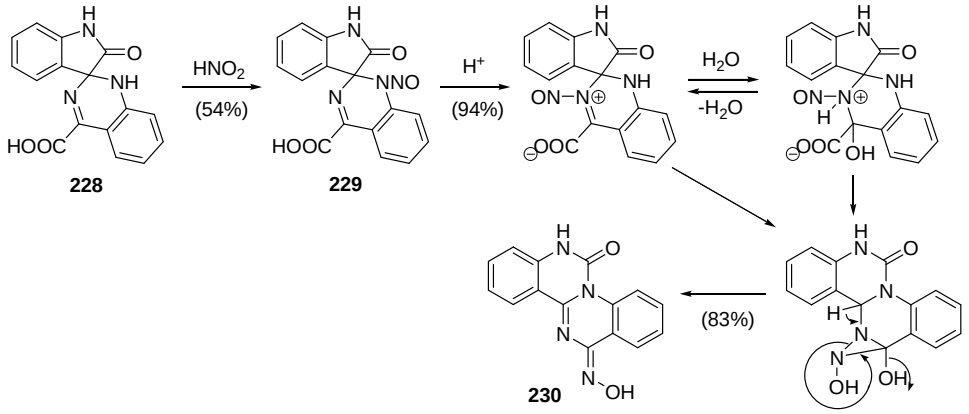
More recently, this group also synthesized a novel and highly stable tetracyclic structure **227** (Scheme 50), from the reaction of the hydrochloride salt of quinazoline **226** with aromatic aldehydes, under reflux or microwave irradiation.[71]

Bergman *et al*[72] reported the synthesis of the hydroximino triazachysene **230** from isamic acid **228** (Scheme 51). This compound could easily be converted to *N*-nitrosoisamic acid **229**, which when heated in ethanol underwent a ring expansion to a 13-hydroximino compound **230**. The structure of this compound was confirmed by X-ray spectroscopic analysis.



226 **227** R=H, 2-Cl, 3-Cl, 4-Cl, 4-CN, 4-NO_2, 2-OMe, 3-OMe, 4-OMe, 4-OH, 2-Me, 3,4-OH, X=CH, N

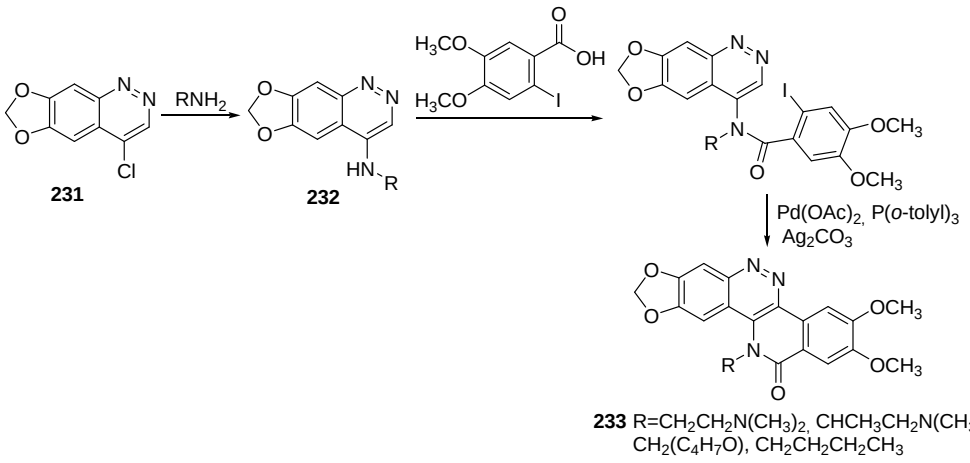
Scheme 50



Scheme 51

4.3. 5,6,11-Triazachrysene

A series of triazachrysenes **233**[16a] was synthesized by conversion of 4-chloro-6,7-methylenedioxycinnoline **231** into the substituted 4-aminoquinolines **232**, in the presence of a primary amines, under reflux (Scheme 52).



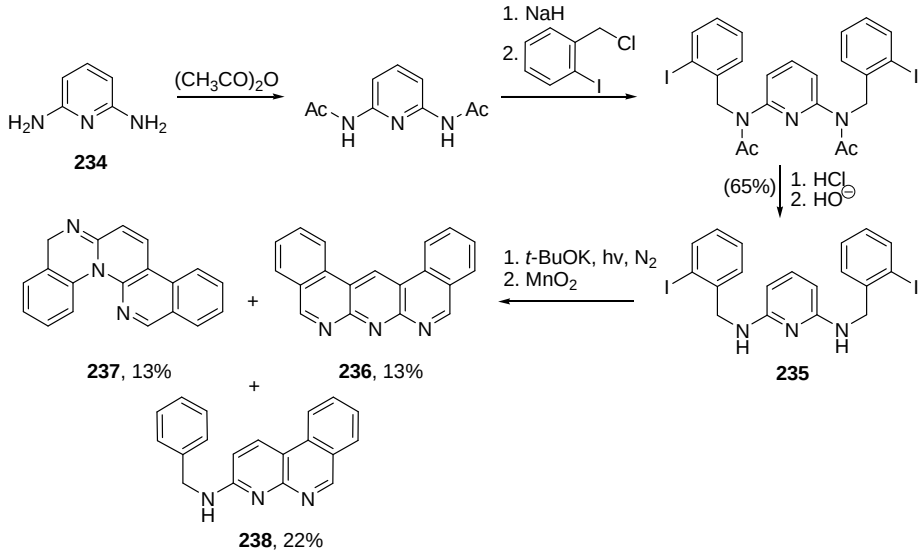
233 R=$CH_2CH_2N(CH_3)_2$, $CHCH_3CH_2N(CH_3)_2$, $CH_2(C_4H_7O)$, $CH_2CH_2CH_2CH_3$

Scheme 52

Condensation with a substituted benzoic acid followed by the Heck reaction led to 5,6,11-triazachrysen-12-ones **233**.

4.4. 7,10a,11-Triazachrysene

Pierini *et al*[73] presented the synthesis of novel triazachrysenes **237** by an intramolecular radical nucleophilic substitution reaction. The photostimulated reaction of diamine **235** was carried out in $NH_{3(l)}$ (used as solvent), and the double cyclization products **236** (C-C coupling) and **237** (C-N coupling) were both formed in 13% yield, together with the monocyclization-reduction product **238** (22%) (Scheme 53). These authors also reported that the use of DMF as solvent did not improve the yield of cyclic products **237** and **238**. The substrate **235** was prepared through a three-step synthetic strategy from 2,6-diaminopyridine **234** with an excess of acetic anhydride. The dianion, generated by addition of NaH, was reacted with *o*-iodobenzyl chloride followed by acetal cleavage with HCl, leading the final product **235**.



Scheme 53

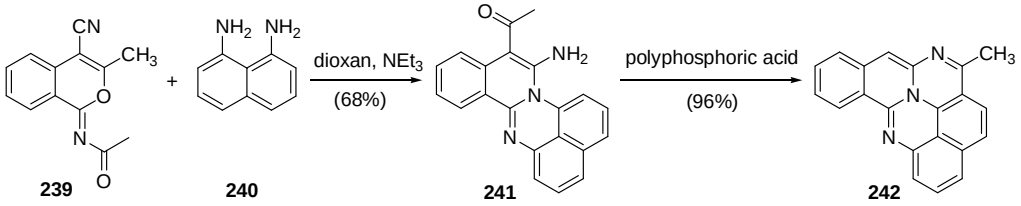
4.5. 7,13,13d-Triazachrysene

The isocoumarin derivative **239** was reacted with 1,8-naphthalenediamine **240** under basic conditions to give 12-acetylisoquino[2,1-a]perimidin-13-amine **241** (Scheme 54). When **241** was heated with polyphosphoric acid, a new hexacyclic system, 7,13,13d-triazachrysene **242** was isolated in good yield.[74]

5. Synthesis of pentaazachrysene derivatives

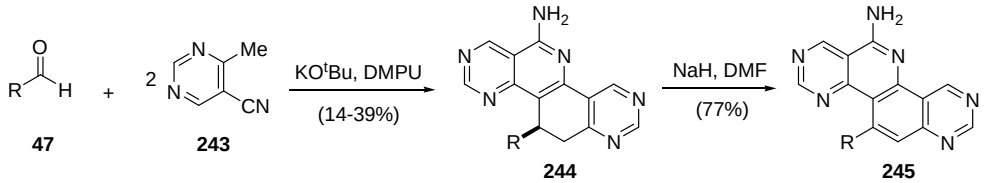
5.1. 1,3,5,8,10-Pentaazachrysene

Clement *et al*[65b] reported the synthesis of pentaazachrysenes **245** (Scheme 55) by a base-catalyzed condensation of aldehydes **47** with two equivalents of 4-methyl-5-cyanopyrimidine **243** followed by dehydrogenation. The fully aromatic ring system **245** was isolated in 77% yield.



239 **240** **241** **242**

Scheme 54



47 **243** **244** **245**

Scheme 55

6. Conclusions

In the present review, we presented the synthesis of a selection of mono-, di-, tri- and penta-azachrysene derivatives reported during the last three decades. Different synthetic approaches to the nitrogenated tetracyclic skeleton have been reported but the most common route involves the construction of either ring B or C in the final cyclization step.

Several strategies including metal-catalyzed reactions, MCR, microwave-irradiation or conventional heating methods have been successfully employed to prepare these diversely decorated skeletons, which are of significant importance for pharmaceutical as well as agrochemical industries.

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