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Advancements in the synthesis of fused tetracyclic quinoline derivatives

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Fused tetracyclic systems containing a quinoline nucleus represent an important class of heterocyclic bioactive natural products and pharmaceuticals because of their significant and wide-spectrum biological properties. Several of these compounds have been obtained with diverse pharmacological and biological activities, such as antiplasmodial, antifungal, antibacterial, potent antiparasitic, antiproliferative, anti-tumor and anti-inflammatory activities. This information will be beneficial for medicinal chemists in the field of drug discovery to design and synthesize new fused tetracyclic quinolines as potent therapeutical agents. This review article provides a comprehensive report regarding the methods developed for the synthesis of fused tetracyclic quinolines reported so far (till October 2019). The article includes synthesis by one-pot domino reaction, microwave synthesis using a catalyst, using ionic liquids, photocatalytic synthesis (UV radiation), Pfitzinger reaction, I_2-catalyzed cyclization reaction, Wittig reaction, cascade reaction, imino Diels–Alder reaction, Friedel–Crafts reaction, CDC reaction, solvent-free reactions and using small chiral organic molecules as catalysts. To the best of our knowledge, this is the first review focused on the synthesis of fused tetracyclic quinolines along with mechanistic aspects.

1. Introduction

Quinoline, a well known heterocyclic compound, itself has few applications in chemical domains, but many of its derivatives are useful in diverse applications including pharmaceuticals, agrochemicals, materials and dyestuffs. Today they are available as drugs. The prominent ones are the fluoroquinolone antibiotics (Ciprofloxacin and its analogs), antimalarials (Quinine, Chloroquine, Quinidine, Mefloquine, Primaquine, Amodiaquinine), antibacterials (Sparfloxacin, Gatifloxacin), a cholesterol lowering agent (Pitavastatin), an antiviral agent (Saquinavir), an anthelmintic agent (Oxamniquine), an antifungal–antiprotozoal agent (Clioquinol), a local anesthetic (Dibucaine), an antiretroviral agent (Saquinavir), an anti-asthmatic (Montelukast), antipsychotics (Aripiprazole, Brexpiprazole), an anti-TB agent (Bedaquiline), anticancer agents (Camptothecin, Irinotecan, Topotecan), antiglaucoma (Cartiolol) and cardiotonic (Vesnarinone) agents, protein kinase inhibitors (Lenvatinib, Bosutinib and Cabozantinib), and a farnesyl transferase inhibitor for leukemia (Tipifarnib). Moreover, several quinolines have been reported to display various useful biological and pharmacological activities as antiinflammatory agents,[1,2] antipsychotics,[3] antiprotozoals,[4–9] antituberculosis agents,[10–12] anti-Alzheimers agents,[13] anti-HIV agents,[14–16] antiasthmatics,[17] potent melanin-concentrating hormone 1 receptor (MCH1R) antagonists,[18–22] antioxidants,[23] antivirals,[24] antifungals,[25,26] Src kinase inhibitors,[27] antihypertensive agents,[28] anti-microbials,[29–31] antibiotics,[32] tyrokinase PDGF-RTK inhibiting agents,[33] agents for treatment of lupus[34,35] and neurodegenerative diseases[36] and efflux pump inhibitors.[37]

Fused tetracyclic systems containing a quinoline moiety are an important class of organic molecules since many of them exhibit excellent biological activities. They have been well established to be useful as potent topoisomerase I and II inhibitor, antifungal, antiplasmodial, antibacterial, potent antiparasitic, antiproliferative, anti-inflammatory and anti-tumor agents.[38–43] In addition, mappicine ketone, as fused quinoline natural product, is an antiviral lead compound with selective activities against herpes viruses HSV-1 and HSV-2 and human cytomegalovirus (HCMV).[44] A fused quinoline alkaloids cryptolepine, neocryptolepine, and isocryptolepine are antimalarial natural products having cytotoxic activities.[45,46] The chemical structures of these natural products are shown in Fig. 1.

Due to their tremendous pharmacological and biological importance, chemists have developed a large number of protocols for the synthesis of fused tetracyclic systems comprising quinoline nucleus, to the best of our knowledge,

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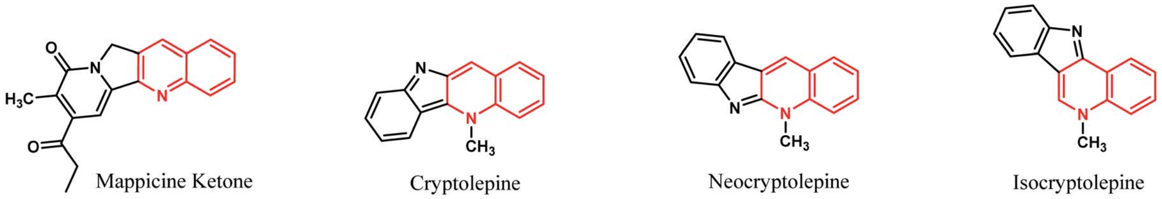

Fig. 1 Structures of natural products containing quinoline ring.

this has never been reviewed. The present review article provides, for the first time, a comprehensive compilation of synthetic methods on the synthesis of these tetracyclic ring systems, as a significant family in the field of organic chemistry.

2. Synthesis of tetracyclic quinolines

2.1. Tetracyclic quinolines with one heteroatom

2.1.1. Isoindolo[2,1-*a*]quinolines. A novel series of tetracyclic isoindolo[2,1-*a*]quinoline-5,11-dione derivatives **3** have been synthesized and evaluated as potent inhibitors of human topoisomerase-II and DNA-gyrase by Sui *et al.*[47] On heating 2-aminoacetophenones **1** with phthalic anhydrides **2** at reflux in xylene in the presence of TEA, as a base catalyst, the tetracyclic products **3** were obtained in 35–74% yields (Scheme 1). Only in one case the imide intermediate **5** was isolated. The isolation of

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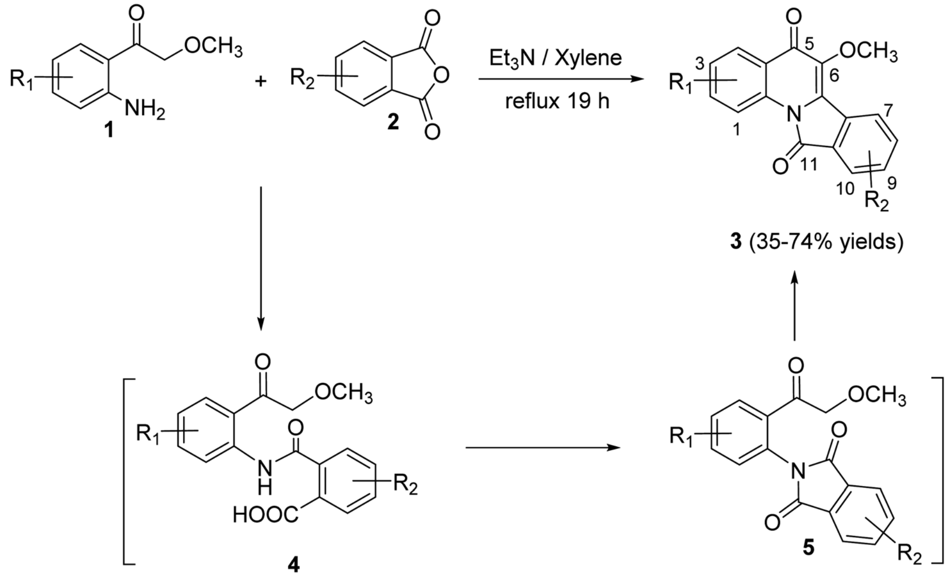
Mariam Abdullah AL-Sheikh was born in 1972 in Makkah-Kingdom of Saudi Arabia. She received her B.Sc. degree in pure chemistry and MSc degree in Organic Chemistry from the University of King AbdulAziz-Jeddah-Saudi Arabia, involving a dissertation entitled "Novel synthesis of heterocyclic compounds containing nitrogen and/ or sulphur" in 1999. Also, she obtained her PhD in 2003 from the University of King AbdulAziz on utility of α-enones in the synthesis of some new heterocyclic compounds under the supervision of Prof. Mohamed Hilmy Elnagdi and Prof. Ebtisam Hafez. In, 2009 and 2013 the University of King AbdulAziz awarded her the University Prize designated for research and academic science. This prize has been given to the best organic researcher scientist in the University. She is currently working as Associate Professor of Organic Chemistry at University of King AbdulAziz. Her current research interest is focused in the development of new synthetic methodology in organic chemistry, which includes the chemistry of nitrogen- and sulfur-containing compounds for the synthesis of biologically active heterocycles.

Hanadi Yousef Medrasi was born in 1976 in Makkah-Kingdom of Saudi Arabia. She obtained her MSc degree in Organic Chemistry from the University of King AbdulAziz-Jeddah-Saudi Arabia, involving a dissertation entitled "Novel approaches to functionally substituted condensed azoles and azines" in 2003. She received her PhD degree from the University of King AbdulAziz-Jeddah-Saudi Arabia, completing her doctoral thesis on alkylation reactions of arenes in 2010. In, 2013 the University of King AbdulAziz awarded her the University Prize designated for the outstanding organic researcher scientist. She is currently working as Assistant Professor of Organic Chemistry at the University of Jeddah, Saudi Arabia. Her research interests include the study of synthesis and reactivity of biologically important heterocycles and organic chemistry education.



3	R1	R2
a	2,4-(OMe)$_2$	H
b	2,4-(OMe)$_2$	8,9-Cl$_2$
c	2,4-(OMe)$_2$	9-*t*-Bu
d	2,4-(OMe)$_2$	8-*t*-Bu
e	2,4-(OMe)$_2$	8,9-Me$_2$
f	2,4-(OMe)$_2$	8,9-(OMe)$_2$
g	2,4-F$_2$	H

Scheme 1 Synthesis of isoindolo[2,1-*a*]quinoline-5,11-diones **3**.

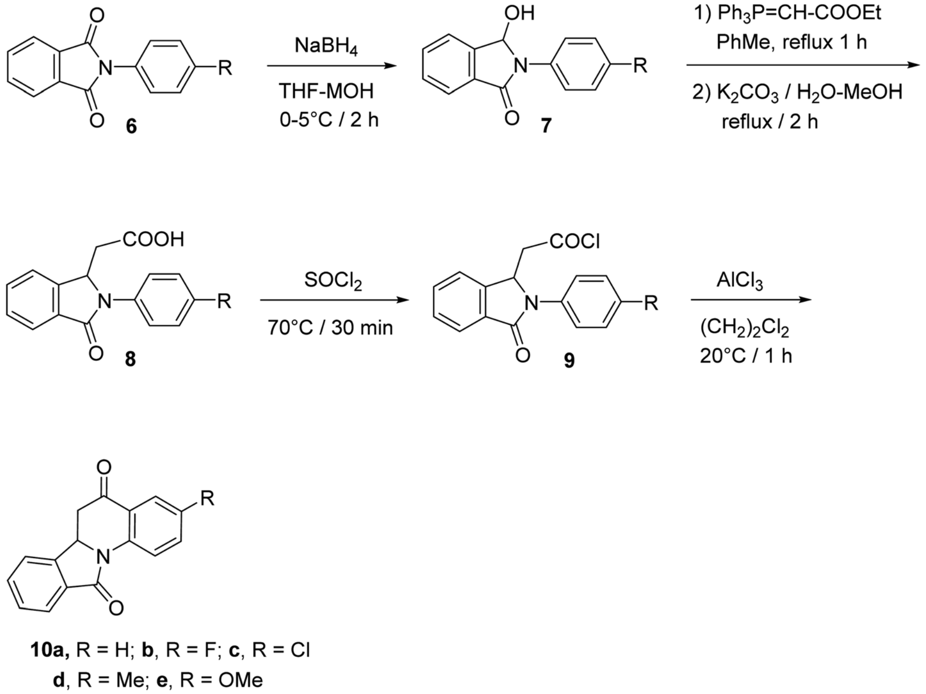
5 confirmed that imide formation occurs prior to intramolecular cyclization of the amide in **4** to form the quinoline nucleous (Scheme 1).

The synthetic method to tetracyclic 3-substituted-6,6*a*-dihydroisoindolo[2,1-*a*]quinoline-5,11-diones **10** is outlined in Scheme 2.[48] Reduction of 2-arylisoindolo-1,3(2*H*)-diones **6** with sodium borohydride ($NaBH_4$) in THF/MeOH at 0–5 °C produced 2-aryl-3-hydroxy-isoindolin-1-ones **7**, which converted into 2-aryl-3-oxo-isoindole-1-acetic acids **8** by a Wittig reaction and subsequent hydrolysis. Treatment **8** with thionyl chloride at 70 °C gave the corresponding 2-aryl-3-oxo-isoindole-1-acetyl chlorides **9**, which underwent an intramolecular Friedel–Crafts reaction in 1,2-dichloroethane with $AlCl_3$ as a catalyst to give the desired isoindolo[2,1-*a*]quinolines **10**. These synthesized products exhibited a protective effect against N_2-induced hypoxia.

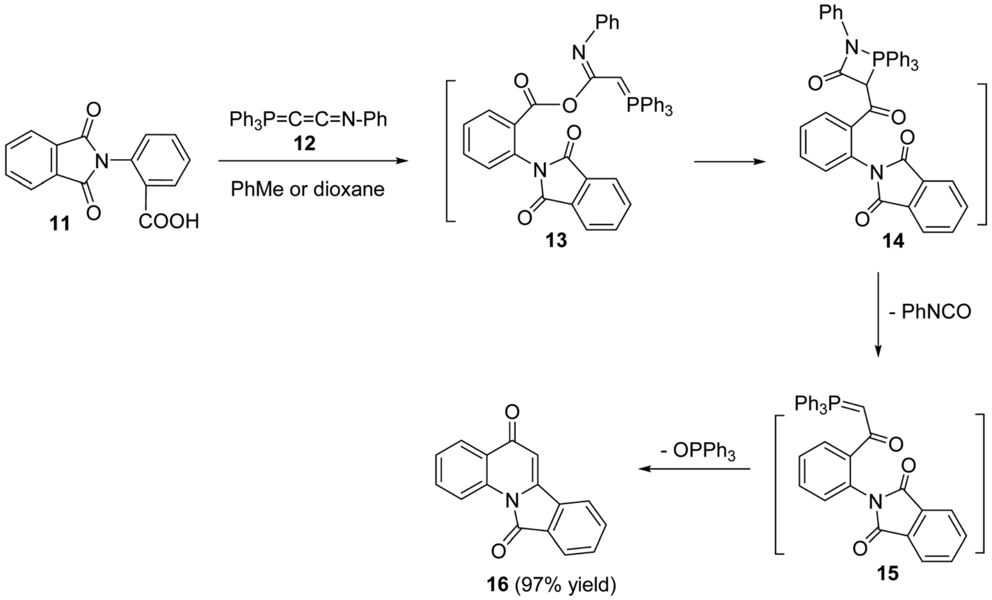
In 1994, Kumar and coworkers[49] have reported an efficient synthesis of isoindolo[2,1-*a*]quinoline-5,11-dione (**16**) *via* the reaction of 2-(1,3-dioxoisoindolin-2-yl)benzoic acid (**11**) with *N*-phenyl(triphenylphosphoranylidine)ethenimine (**12**) (Scheme 3). When a mixture of **11** and **12** was refluxed in toluene or dioxane, the desired isoindolo[2,1-*a*]quinoline-5,11-dione (**16**) was obtained in 97% yields. The time of reaction was not reported. The plausible mechanism of this reaction includes the initial protonation of *N*-phenyl(triphenylphosphoranylidine)ethenimine (**12**) by **11** to give the *O*-acyl-imidate **13**. Then, a migration of the ester C=O group from oxygen to C-7 led to the formation of the intermediate **14**, which eliminates a molecule of phenyl isocyanate to afford the acylphosphorane **15**. Subsequent cyclization of **15** *via* the intramolecular Wittig reaction on the imide C=O gave the tetracyclic product **16** (Scheme 3).

In 1997, Kim and Keum[50] developed another method for the synthesis of isoindolo[2,1-*a*]quinolines **16** utilizing 2-(2-

Kamal Usef Sadek was born in El-Minia (1947) and has received B.Sc. degree (honour) in Applied Chemistry from Assiut University (1969) followed by MSc and PhD from Cairo University (1980) under the supervision of Prof. M. H. Elnagdi. He was appointed as a demonstrator of Chemistry in Assiut University then he shifted to the Department of Chemistry, El-Minia University (1975). Since then he was appointed as lecturer (1980), associate Prof. (1985) and Full Professor (1990). In 1987 he was awarded the Alexander von Hmboldt fellowship with Prof. W. Weigrebe in Pegensburg University and have several studies leaves with Prof. M. Regitz of Kuierslautern University and Prof. H. H. Otto in Freiburg University. Currently, he is working in developing green technologies for the synthesis of biologically active heterocycles.



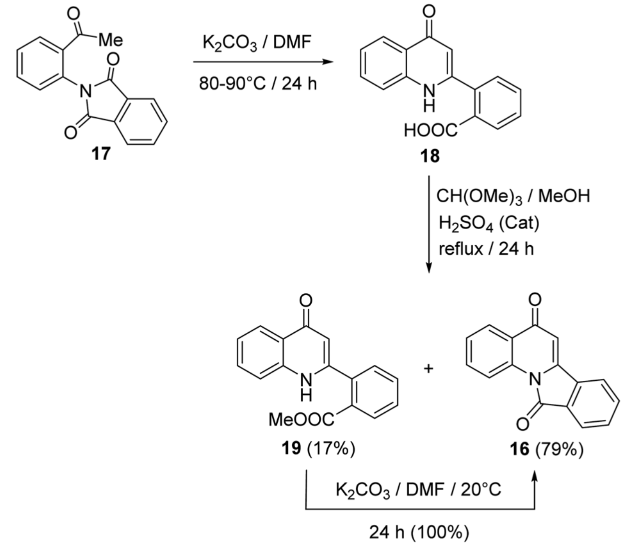
Scheme 2 The synthetic route to tetracyclic isoindolo[2,1-*a*]quinolines **10**.



Scheme 3 An efficient synthesis of isoindolo[2,1-*a*]quinolines **16** from **11**.

acetylphenyl)isoindoline-1,3-dione (**17**) as starting material. When **17** was heated in DMF in the presence of a catalytic amount of K_2CO_3 at 80–90 °C, it underwent intramolecular cyclization to produce the 2-(4-oxo-1,4-dihydro-quinolin-2-yl) benzoic acid (**18**), in 74% yield. Refluxing **18** with trimethyl orthoformate in MeOH in the presence of H_2SO_4 as an acidic catalyst gave a mixture of methyl 2-(4-oxo-1,4-dihydroquinolin-2-yl)benzoate (**19**) (17% yield) and tetracyclic isoindolo[2,1-*a*] quinoline-5,11-dione (**16**) (79% yield). On the other hand, when **19** was treated with K_2CO_3 in DMF at room temperature, it was converted quantitatively into the desired product **16** (Scheme 4).

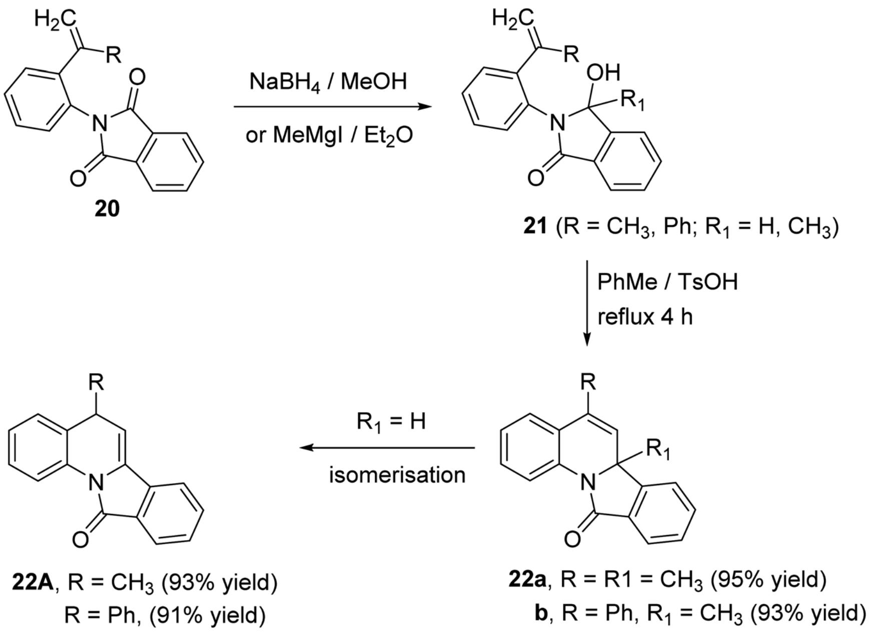
A novel route for the synthesis of 6*a*-methyl-5-substituted-isoindolo[2,1-*a*]quinoline-11(6*aH*)-ones **22** has been developed utilizing *N*-aryl-phthalimides **20** as the key precursors.[51] The reaction of **20** with sodium borohydride in dry MeOH at 10 °C or the Grignard reagent (MeMgI) in dry ether afforded the corresponding alcohols **21**. When compounds **21** ($R_1 = CH_3$) were



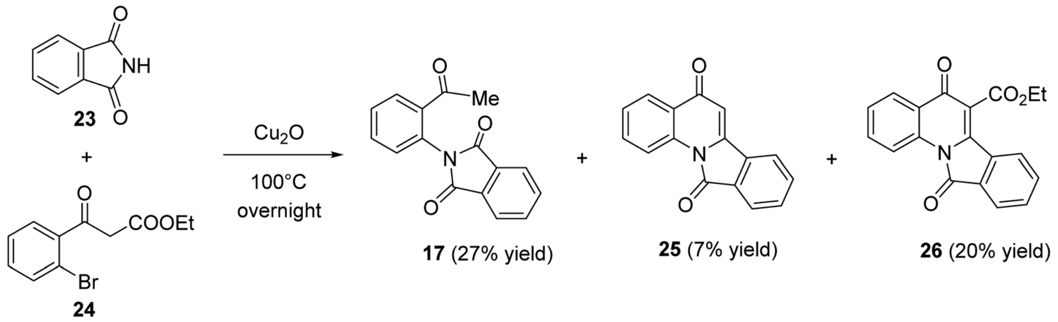
Scheme 4 Synthesis of isoindolo[2,1-*a*]quinolines **16** from **17**.

refluxed in toluene in the presence of *p*-toluene-sulfonic acid (TsOH), as catalyst, they underwent intramolecular ring closure to the isoindolo[2,1-*a*]quinolines **22** (Scheme 5). In case of **21** ($R_1 = H$), the isoindoloquinolines **22** were obtained which were rapidly isomerized, under these reaction conditions, to give the stable enamides **22A**, namely, 5-substituted-isoindolo[2,1-*a*]quinolin-11(5*H*)-ones.

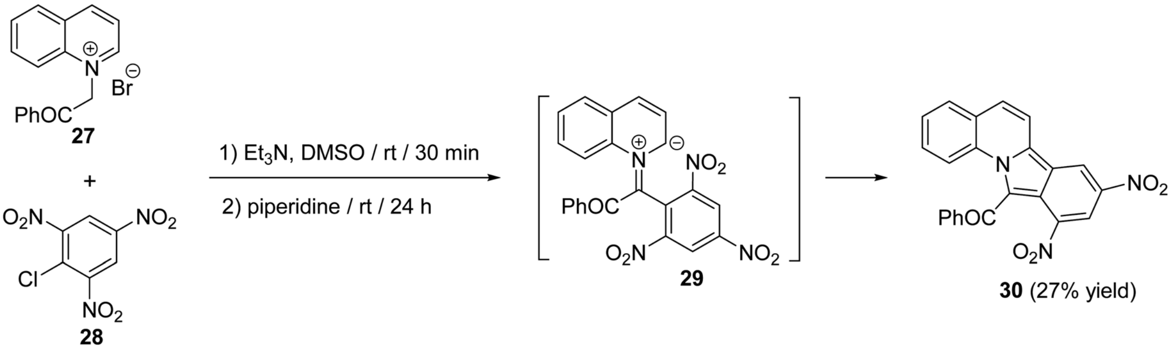
Heating a neat mixture of phthalimide (**23**) with ethyl bromobenzoylacetate (**24**) in the presence of Cu(I) oxide at 100 °C produced the 2-acetylphenylphthalimide (**17**) as the major product (27% yield), *via* the coupling reaction followed by the deethoxycarbonylation process, along with isoindolo[2,1-*a*]quinoline-5,11-dione (**25**) (7% yield) which formed *via* the coupling reaction followed by the deethoxycarbonylation and intramolecular cyclo-dehydration process, and ethyl 5,11-dioxo-5,11-dihydroisoindolo[2,1-*a*]quinoline-6-carboxylate (**26**) (20% yield) (Scheme 6). The product **26** was assumed to be formed through the coupling reaction followed by a thermal cyclo-dehydration reaction.[50]



Scheme 5 Synthesis of isoindolo[2,1-*a*]quinolines **22** from phthalimides **20**.



Scheme 6 Synthesis of 5,11-dihydroisoindolo[2,1-*a*]quinoline-5,11-diones **25** and **26**.

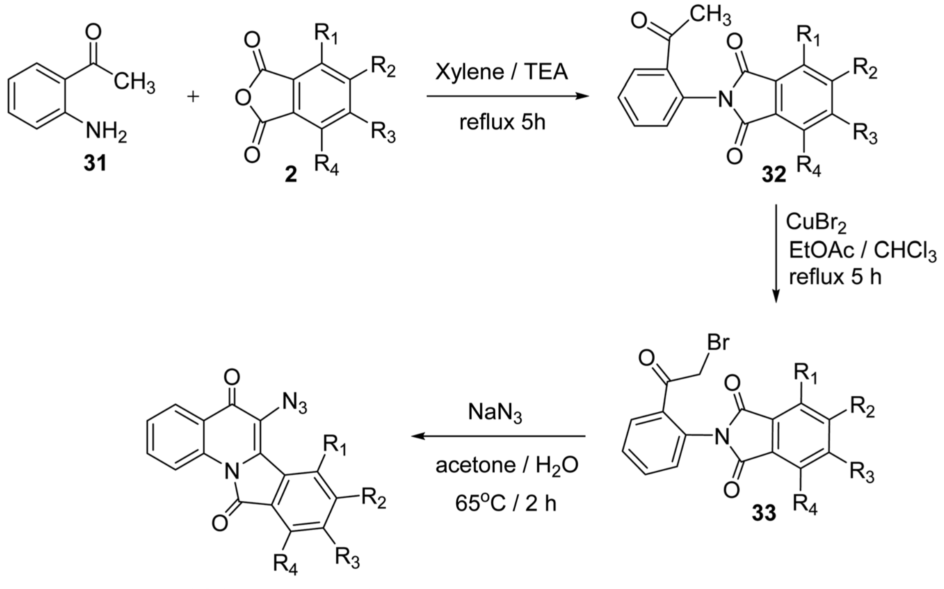


Scheme 7 Synthesis of 11-benzoyl-8,10-dinitroisoindolo[2,1-*a*]quinoline (**30**).

A simple route for the synthesis of 11-benzoyl-8,10-dinitroisoindolo[2,1-*a*]quinoline (**30**) has been reported by Reuschling and Kröhnke.[52] Reacting *N*-phenacylquinolinium bromide (**27**) with picryl chloride (**28**) at room temperature, under basic conditions, afforded the respective tetracyclic product **30** in low yield (27%), *via* intermediacy **29** (Scheme 7).

Alkhathlan and his group[53] have described the synthesis of 6-azido-isoindolo[2,1-*a*]quinoline,11-diones **34**. On reacting 2-aminoacetophenone (**31**) with phthalic anhydride derivatives **2** in xylene in the presence of a catalytic amount of Et_3N under reflux for 5 h, 2-(2-acetylphenyl)-isoindolo-1,3-diones **32** were obtained. Bromination of **32** with $CuBr_2$ in a EtOAc/$CHCl_3$ mixture under reflux for 5 h gave the corresponding bromo derivatives **33**. When the bromo compounds **33** were heated with sodium azide in a mixture of acetone/H_2O at 65 °C for 2 h, they underwent intramolecular cyclocondensation to furnish directly the new tetracyclic ring system **34** in 42–76% yields (Scheme 8). Attempts to isolate the azido analogs of **34** by conducting the reaction at different reaction conditions were failed.

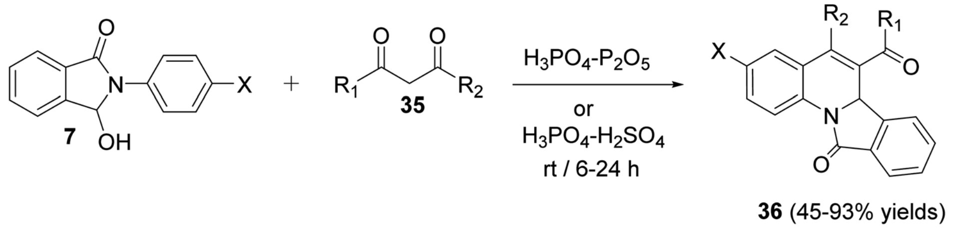
In 2009, Zhang *et al.*[54] have described as the first one-pot synthesis of isoindolo[2,1-*a*]quinolin-11-ones **36** by reacting 2-aryl-3-hydroxy-isoindol-1-ones **7** with 1,3-dicarbonyls **35** *via* coupling of *N*-acyliminium ion intermediates **37** with **35** followed by intramolecular Friedel–Crafts reaction catalyzed by H_3PO_4–P_2O_5 or H_3PO_4–H_2SO_4. Reactions were carried out by



34 (42-76% yields)

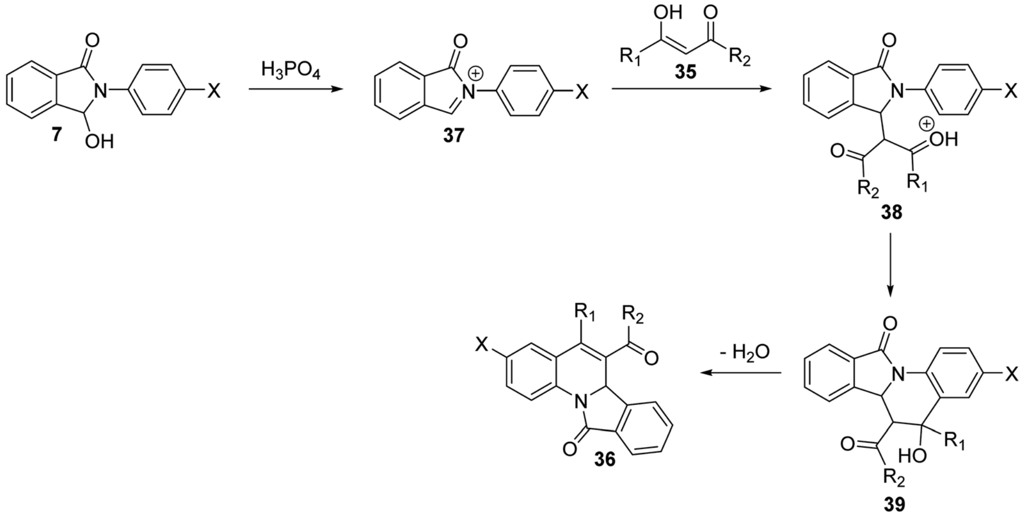
34	R_1	R_2	R_3	R_4
a	H	H	H	H
b	NO_2	H	H	H
c	H	NO_2	H	H
d	Cl	Cl	Cl	Cl

Scheme 8 Synthesis of 6-azido-isoindolo[2,1-*a*]quinoline-5,11-diones **34**.



36	X	R_1	R_2
a	H	Me	OEt
b	Me	Me	OEt
c	Cl	Me	OEt
d	MeO	Me	OEt
e	H	Me	Me
f	Me	Me	Me
g	H	Ph	Me
h	Me	Ph	Me
i	Cl	Ph	Me

Scheme 9 One-pot synthesis of isoindolo[2,1-*a*]quinolin-11-ones **36** by reacting **7** with **35**.

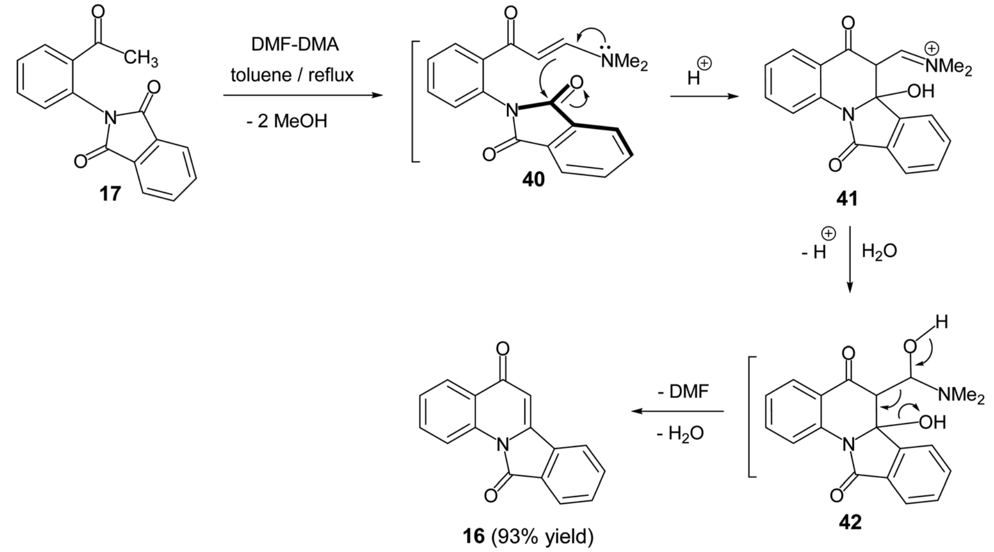


Scheme 10 A plausible mechanism for the formation of isoindolo[2,1-*a*]quinolin-11-ones **36**.

stirring **7** with **35** under the catalysis of H_3PO_4–P_2O_5 or H_3PO_4–H_2SO_4 at room temperature for 6–24 h to give the desired isoindolo[2,1-*a*]quinoline-11-ones **36** in 45–93% yields (Scheme 9). The structures of all the newly synthesized compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and MS. Furthermore, X-ray crystallographic analysis was performed to determine the absolute configuration of the products **36**. A plausible mechanism for the formation of **36** is given in Scheme 10. The reaction was initiated by the formation of an *N*-acyliminium intermediate **37** which was reacted with **35** to give the intermediate **38**. Intramolecular Friedel–Crafts reaction between the protected aniline and the ketone gave the desired tetracyclic product **36**.

In 2011, Svete and his co-workers[55] reported that the treatment of 2-(2-acetylphenyl)-1*H*-isoindole-1,3(2*H*)-dione (**17**) with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in refluxing toluene resulted in the formation of the isoindolo[2,1-*a*]quinoline-5,11-dione (**16**) in 93% yield (Scheme 11). The mechanism of this reaction began with the formation of enaminone **40**, which next underwent intramolecular cyclization to give the intermediate **41**. The formed adduct **41** was subsequently underwent β-elimination of DMF and H_2O to furnish the desired tetracyclic **16** (Scheme 11).

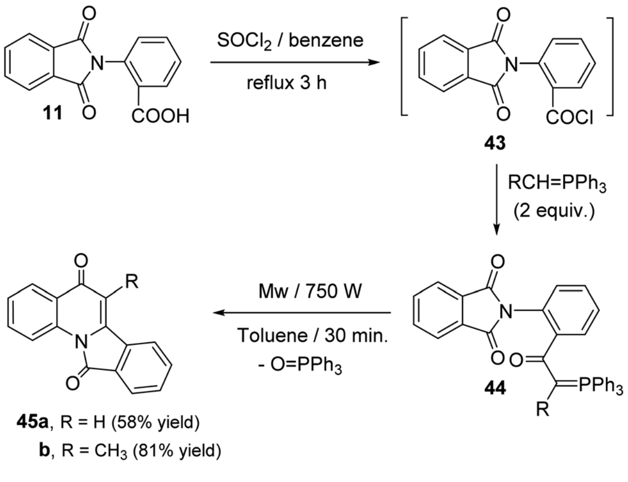
Sakhautdinov *et al.*[56] have described the synthesis of isoindolo[2,1-*a*]quinoline-5,11-diones **45** *via* intramolecular cyclization of *N*-[2-(triphenyl-λ^5-phosphanylidene)acetyl]-phthalimides **44** under microwave-heating. Refluxing a mixture of *o*-phthalimidobenzoic acid (**11**) and $SOCl_2$ in dry benzene for 3 h afforded the corresponding acid chlorides intermediate **43**, and the latter was reacted *in situ* with alkylidenephosphorane (2 equiv.) to give keto-stabilized phosphorus ylides **44**. The compounds **44** when heated in dry toluene in the presence of a catalytic amount of benzoic acid (5 mol%) at reflux



Scheme 11 Synthesis of isoindolo[2,1-*a*]quinoline-5,11-dione (**16**).

temperature under argon atmosphere for 56 h, they underwent intramolecular cyclization to afford the tetracyclic products **45** in low yields (15–27% yields). Interestingly, it was observed that use of microwave irradiation gave much faster reaction and improved the yields, thereby allowing rapid access to this class of compounds **45**. Thus, the ylides **44** when heated in dry toluene for 30 min under microwaves, they underwent intramolecular cyclization followed by elimination of a triphenylphosphine oxide (O=PPh$_3$) molecule to afford tetracyclic isoindolo[2,1-*a*]quinoline-5,11-diones **45**, in good yields (Scheme 12). However, one drawback of this methodology is electron-acceptor substituents on the ylide carbon atom hamper the intramolecular cyclization process.

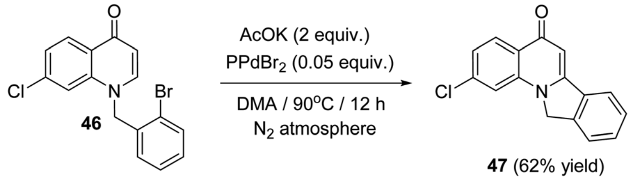
In 2014, Fu *et al.*[57] have described a new and efficient synthesis of 2-chloro-isoindolo[2,1-*a*]quinoline-5(11*H*)-one (**47**) through the intramolecular Heck coupling cyclization of 1-(2-bromobenzyl)-7-chloroquinolin-4(1*H*)-one (**46**). The reaction was carried out by heating **46** (1 equiv.) with AcOK (2 equiv.) as the base and PdBr$_2$ (0.05 equiv.) as the catalyst in DMA at 90 °C under N$_2$ atmosphere for 12 h to provide the tetracyclic product **47** in 62% yield (Scheme 13). Noticeably, a definite mechanism for the synthesis of compound **47** has not been reported.



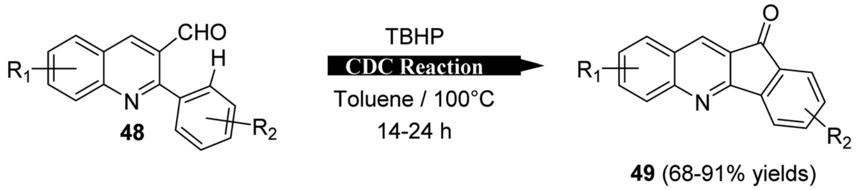
Scheme 12 Microwave-assisted synthesis of isoindolo[2,1-*a*]quinoline-5,11-diones **45**.

2.1.2. Indino[1,2-*b*]quinolines. Recently, Mishra *et al.*[58] have developed an eco-friendly, metal-free and TBHP-promoted economical method for the synthesis of 11*H*-indeno[1,2-*b*]quinolin-11-ones **49**, as antibacterial agent. The reactions were carried out by heating a solution of 2-aryl-quinoline-3-carbaldehyde derivatives **48** (1 equiv.) and *tert*-butyl hydroperoxide (TBHP) (3 equiv.) in toluene at 100 °C for 14–24 h and furnished the desired tetracyclic indenoquinolinones **49** in 68–91% yields (Scheme 14). Depending on product formation, they suggested the free radical mechanism of this reaction in Scheme 15.

An interesting utility of Pfitzinger reaction for construction of tetracyclic quinolines has been reported by Deady *et al.*[59] This protocol implies Pfitzinger reaction of isatin-7-carboxylic acids **50** and 1-indanones **51** to prepare analogues of the topoisomerase inhibitor 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboamides **56**. The one-pot reaction between **50** and **51** in NaOH (10%) at 90 °C under nitrogen atmosphere afforded tetracyclic 11*H*-indeno-[1,2-*b*]quinoline-6,10-dicarboxylic acids **52**, in 64–78% yields. Selective decarboxylation of **52**, followed by oxidation of CH$_2$ group in **53** with KMnO$_4$ produced 11-oxo-11*H*-

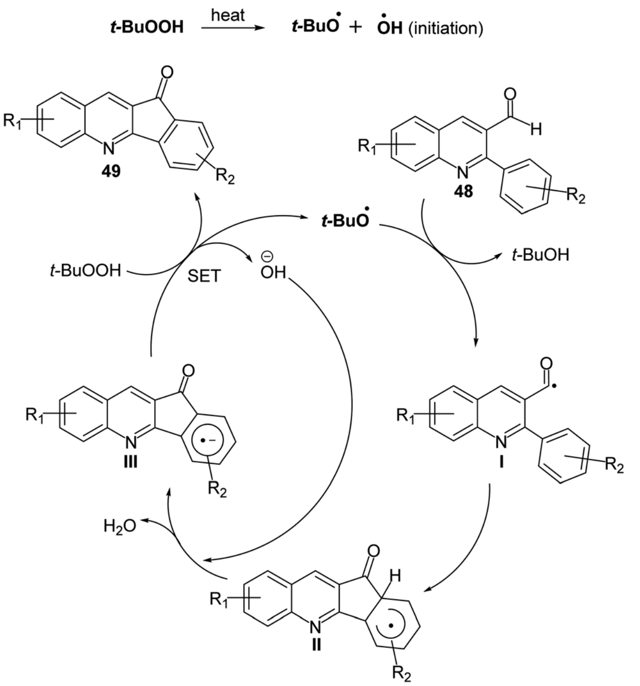


Scheme 13 Synthesis of 2-chloro-isoindolo[2,1-*a*]quinoline-5(11*H*)-one (**47**) *via* intramolecular Heck coupling cyclization of **46**.



49	R1	R2		R1	R2
a	H	H	h	7-CH_3	H
b	H	2-Br	i	8-OCH_3	H
c	H	2-Cl	j	6-Me	H
d	H	2-F	k	7-Cl	H
e	H	2-Me	l	8-CH_3	2-OCF_3
f	H	2-OCF_3	m	8-OMe	2-OCF_3
g	7-OCH_3	H	n	6-Me	2-OCF_3
			o	6-Et	2-OCF_3

Scheme 14 Synthesis of indeno[1,2-*b*]quinolin-11-ones **49** *via* intramolecular CDC reaction.



Scheme 15 Proposed mechanism for the formation of indeno[1,2-*b*]quinolin-11-ones **49** *via* intramolecular CDC reaction.

indeno-[1,2-*b*]quinoline-6-carboxylic acids **54**, in 15–79% yields. Refluxing **54** with 1,1′-carbonyl-diimidazole (CDI) in dioxan gave the corresponding imidazolide intermediate **55**, which was coupled, *in situ*, with *N*,*N*-dimethylethylenediamine in CH_2Cl_2 at room temperature to give the required tetracyclic 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamides **56**, in 31–90% yields (Scheme 16).

2.1.3. Indino[1,2-*c*]quinolines.

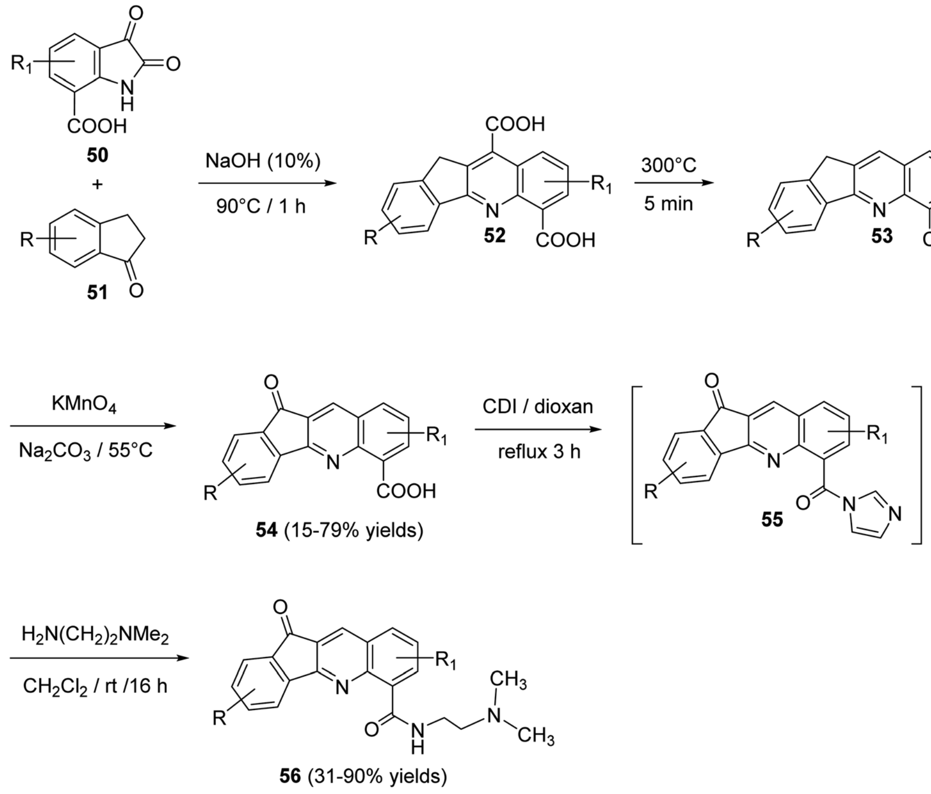
Tseng *et al.*[60] reported synthesis and antiproliferative evaluation of some 6-amino-11*H*-indeno[1,2-*c*]quinolin-11-ones **61** from reaction of isatin (**57**) with substituted phenylacetic acids **58.** Heating a mixture of **57** and **58** in the presence of a catalytic amount of CH_3CO_2Na at 200 °C produced 3-aryl-2-hydroxy-quinoline-4-carboxylic acid derivatives **59**, which were chlorinated with $POCl_3$ at 150 °C to give 6-chloro-indeno[1,2-*c*]quinoline-11-ones **60**, in 88–91% yields. On heating **60** with cyclic secondary amines in ethoxyethanol at 200 °C, the corresponding 6-amino-indeno[1,2-*c*]quinoline-11-ones **61** were obtained in 55–83% yields (Scheme 17).

Chen *et al.*[61] reported synthesis of a series of novel tetracyclic 6-amino-9-chloro-11*H*-indeno[1,2-*c*]quinoline-11-ones **65**, as potential anticancer agents, through the Pfitzinger synthetic reaction of isatin (**57**) and 4-chlorophenyl-acetic acid (**62**). At first, a mixture of **57** and **62** was stirred at 200 °C with sodium acetate to produce 3-(4-chlorophenyl)-2-hydroxy-quinolin-4-carboxylic acid (**63**) as a key intermediate. Treatment of **63** with $POCl_3$ at 150 °C afforded 6,9-dichloro-11*H*-indeno[1,2-*c*]quinoline-11-one (**64**), in 30% yield. Reaction of **64** with an appropriate primary and secondary amines in DMF at 150 °C gave the corresponding side chain tetracyclic compounds **65** in 18–86% yields (Scheme 18).

2.2. Tetracyclic quinolines with two heteroatoms

2.2.1. Indolo[2,3-*b*]quinolines.

In 2004, Chen's group[62] reported an efficient synthesis of some 11-substituted-6*H*-indolo[2,3-*b*]quinolines **70a–c**, starting from 4-hydroxy-quinolin-2(1*H*)-one (**66**). In this cascade reaction, the hydroxyquinoline **66** was methylated with Me_2SO_4 in acetone in the presence of K_2CO_3 to produce 4-methoxy-quinoline-2(1*H*)-one (**67a**). Refluxing **66** with aniline or *p*-anisidine in Ph_2O yielded 4-anilino-quinolin-2(1*H*)-one (**67b**) or its 4-methoxy derivative **67c**, respectively. Heating **67a–c** with $POCl_3$ at 90 °C afforded the 2-chloroquinolines **68a–c**. Treatment of **68a–c** with 1*H*-benzo[1,2,3]triazole in ethoxyethanol at reflux temperature gave the corresponding triazoles **69a–c**, which underwent decomposition reaction in polyphosphoric acid (PPA) to afford the respective tetracyclic indolo[2,3-*b*]quinolines **70a–c**, in 32–56% yields (Scheme 19). The products exhibited selective cytotoxicities for K-562, HL-60, RPMI-8226 and MOLT-4.



56	R	R_1		R	R_1
a	H	H	h	4-CH_3	H
b	1-OMe	H	i	4-Cl	H
c	2-OMe	H	j	H	8-OMe
d	2-Cl	H	k	H	8-Cl
e	3-OMe	H	l	2,3-$(OMe)_2$	H
f	3-OH	H			
g	3-Me	H			

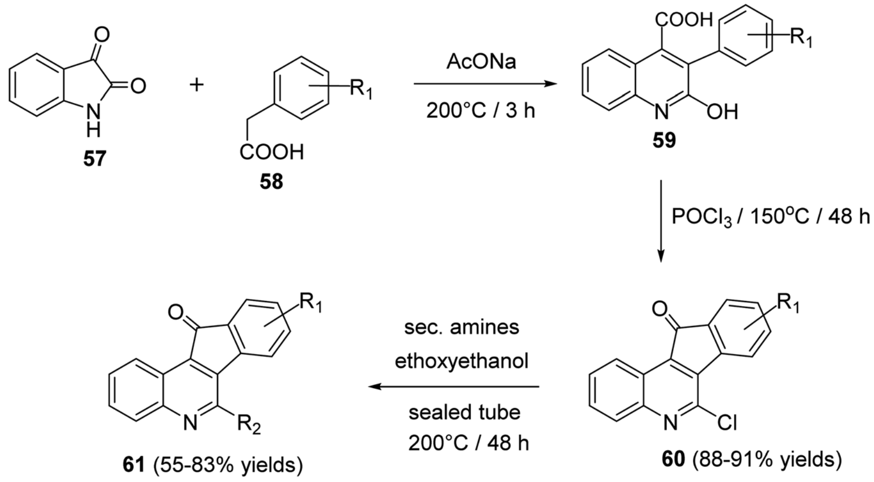
Scheme 16 Synthesis of 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamides **56**.

In 2018, Salman *et al.*[63] have developed a simple and regioselective synthesis of two series of 10*H*-indolo[3,2-*b*]quinolines **75** and 6*H*-indolo[2,3-*b*]quinolines **76** *via* palladium catalyzed Suzuki reaction of 2,3-dihaloquinolines with 2-bromophenylboronic acid, followed by double C–N coupling. The Suzuki reaction of 2-chloro-3-bromoquinoline (**71**) and 3-bromo-2-iodoquinoline (**73**) with 2-bromophenylboronic acid gave 3-(2-bromophenyl)-2-chloroquinoline (**72**) and 3-bromo-2-(2-bromophenyl)quinoline (**74**) in 75 and 60% yield, respectively (Scheme 20).

The double carbon–nitrogen coupling reaction was performed by heating **72** and **74** with various amines in the presence of the catalyst tris(dibenzylideneacetone)-dipalladium [$Pd_2(dba)_3$] with the base NaO^tBu in toluene at 100 °C to give the desired 10*H*-indolo[3,2-*b*]quinolines **75** and 6*H*-indolo[2,3-*b*] quinoline **76**, in moderate to excellent yields (Scheme 21).[63]

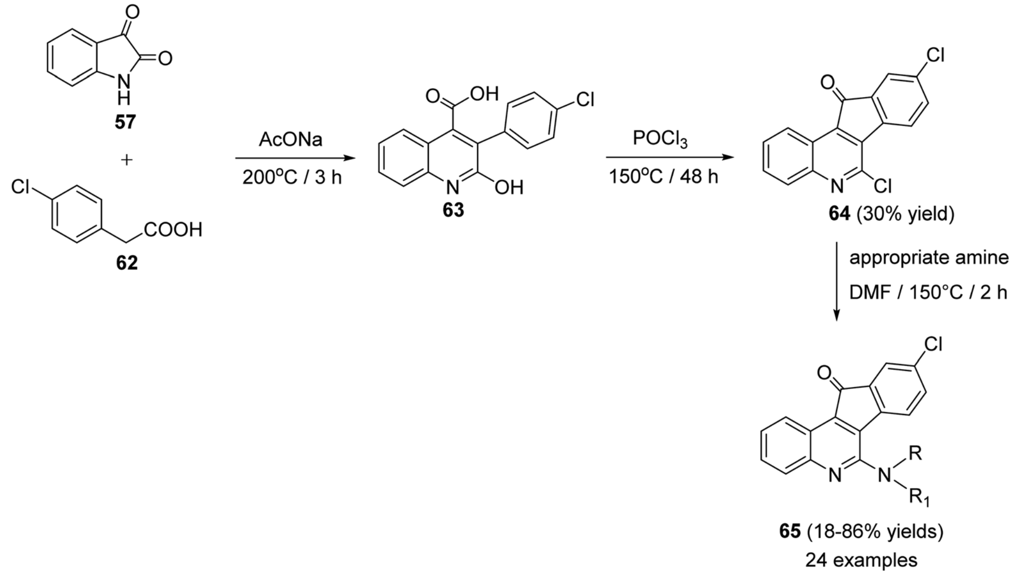
Peczyńska-Czoch and his group[64a,b] have described the synthesis of 6*H*-indolo[2,3-*b*]-quinolines **79** and **84**, as novel and more efficient DNA Topoisomerase I1 inhibitors, *via* the methods showed in Schemes 22 and 23. Heating the chloroquinolines **77** with 1*H*-benzo[1,2,3]triazole at 110–120 °C gave the corresponding triazoles **78** (Scheme 22). However, compounds **83** were prepared by heating chloroquinoline derivatives **80** with 4-methyl-3-nitroaniline (**81**) at 150–160 °C, followed by the reduction of the NO_2 group in intermediate **82** and diazotization of the amino obtained (Scheme 23). Subsequent decomposition of triazoles **78** and **83** in polyphosphoric acid (PPA) at 130–180 °C afforded the respective indolo[2,3-*b*] quinolines **79** and **84**, respectively, in low yields.

Wang *et al.* and Lu *et al.*[43,65a–d] developed an efficient protocol for the synthesis of a series of 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolines (neocryptolepines) **89** with different substituents on the quinoline ring, as useful scaffold for the synthesis of anticancer and antimalaria agents. In this cascade reaction, various *N*-methyl-anilines **85** were treated with *N*-chlorosuccinimide (NCS) in CH_2Cl_2 at room temperature, followed by the addition of methyl 1*H*-indole-3-carboxylate (**86**) producing the corresponding methyl 2-((4-substituted phenyl)(methyl) amino)indole-3-carboxylates **87.** Upon refluxing **87** in diphenyl ether at 250 °C, it underwent intramolecular cyclization to give the tetracyclic ketones **88** in 68–98% yields. Chlorination of **88** was carried out in $POCl_3$ under reflux conditions to yield the



61	R1	R2
a	9-OMe	NH_2
b	9-OMe	piperazino
c	9-OMe	morpholino
d	9-OMe	piperidino
e	9-OMe	4-methylpiperazino
f	9-OMe	3-methylpiperazino

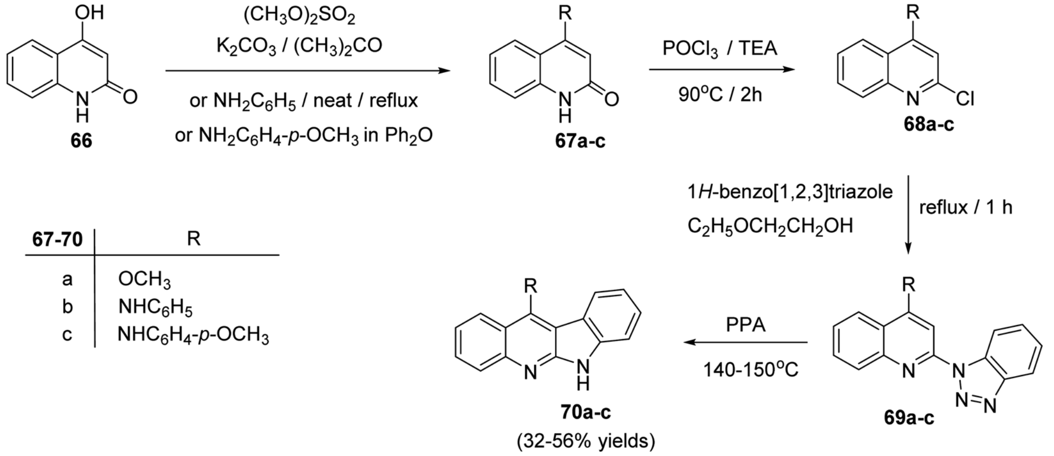
Scheme 17 Synthesis of indeno[1,2-*c*]quinolines **61**.



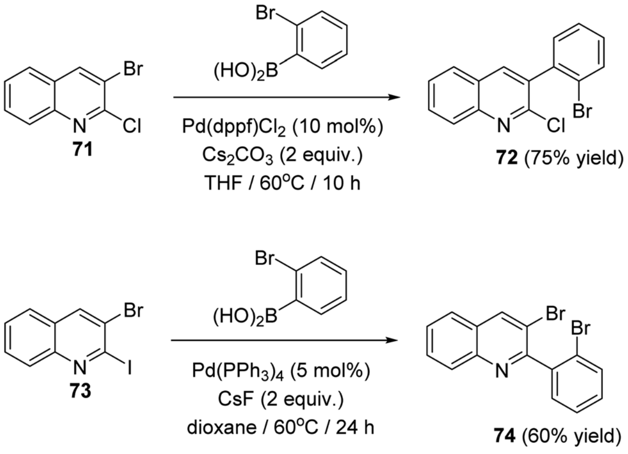
Scheme 18 Synthesis of 6-amino-9-chloro-11*H*-indeno[1,2-*c*]quinoline-11-ones **65**.

desired 11-chloroneocryptolepines **89** in 67–94% yields, with high purity (Scheme 24).

Ali *et al.*[66] reported synthesis of highly substituted indolo[2,3-*b*]quinolines **92** *via* metal-free, one-pot annulation reaction of substituted indoles **90** with 1-(2-tosylaminophenyl)-ketones **91**. The reaction occurs *via* an activation of C-2 and C-3 of indoles **90** by molecular iodine and Cs_2CO_3, as a base catalyst, followed by *in situ* reaction with 1-(2-tosylamino-phenyl)ketones **91** in acetonitrile at 90 °C to afford polyfunctionalized indolo[2,3-*b*] quinolines **92**, in moderate to excellent yields (Scheme 25). In this reaction, electrophilic addition of iodonium ion to the 3-position of indoles **90** afforded cation intermediate **I**. 2-Amination of **I** with **91** gives **II**, which undergoes elimination of one molecule of HI in the presence of base to furnish **III**. Subsequent alkylation, followed by detosylation of **III** in the presence of HCl (12 M) affords **92** (Scheme 25).



Scheme 19 Synthesis of indolo[2,3-*b*]quinoline derivatives **70a–c**.



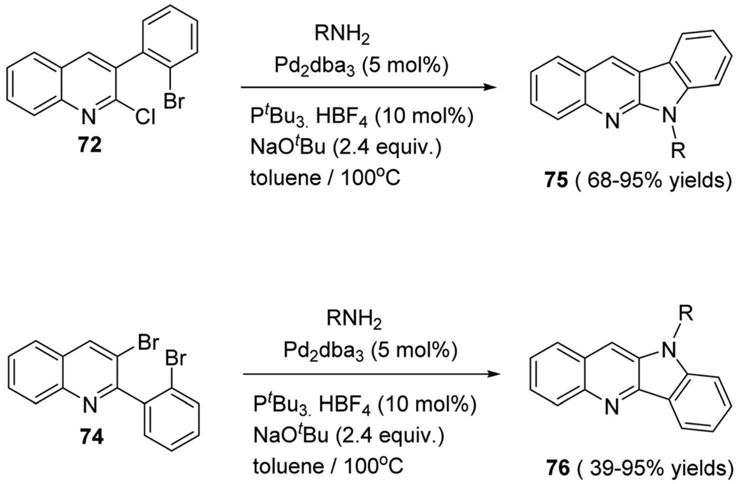
Scheme 20 Chemoselective Suzuki reaction of 2,3-dihaloquinsolines **71** and **73**.

In 2015, Pal *et al.*[67] have developed a new one-pot strategy for the synthesis of novel 11-carboxymethyl substituted 6*H*-indolo[2,3-*b*]quinolines **95**, as potential inducers of apoptosis, involving Pd(II)-catalyzed intramolecular oxidative C3–H alkenylation of the indole ring of (*E*)-alkyl-3-(2-(1*H*-indol-2-ylamino)phenyl)acrylates **94** followed by desulfonylation. In the present study, the starting material **94** was prepared *via* I_2-mediated addition of sulfonamide derivative **93** to indoles **90**. Heating a mixture of **93** (1 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.50 mol) and trifluoroacetic acid (TFA) (1.20 mol) in CH_3CN at 60 °C under an aerobic atmosphere for 5–7 h afforded the target tetracyclic products **95** in 52–89% yields (Scheme 26). A mechanism for the Pd(II)-catalyzed formation of **95** is outlined in Scheme 27.

Ghorbani-Vaghei and Malaekehpoor[68] described a simple and one-pot synthesis of novel 6*H*-indolo[2,3-*b*]quinolines **98** from the reaction of indole-3-carbaldehyde (**96**) with various aryl amines **97**, under mild conditions, utilizing *N*-bromosuccinimide (NBS) as an efficient catalyst. NBS initially catalyzed the formation of Schiff base **I** and then a 3-bromoindolinium cation intermediate **II**. The intermediate **II** on the subsequent nucleophilic attack by an another mole of aniline, followed by intramolecular cyclization and oxidation produces **98**. Reaction is outlined in Scheme 28.

A novel and efficient method for the synthesis of 11-substituted-6*H*-indolo[2,3-*b*]quinolines **103** *via* thermolysis of the carbodiimide **100**, which represents a new way of generating biradicals from unsaturated molecules having two nitrogen atoms in the conjugated system, is reported by Wang *et al.*[69] Thus, thermolysis of the carbodiimide **100**, having a different substituents at the acetylenic terminus, in refluxing *p*-xylene at 138 °C produced **103** in 16–91% yields. Apparently, a two-step biradical pathway through **101** or a one-step intramolecular Diels–Alder reaction produced the intermediate **102**, which on subsequent tautomerization under the reaction conditions affords the final product **103** (Scheme 29). An especially attractive feature of this synthetic method is the possibility of placing a wide variety of substituents at different positions of the 6*H*-indolo[2,3-*b*]quinoline structure by selecting suitable fragments.

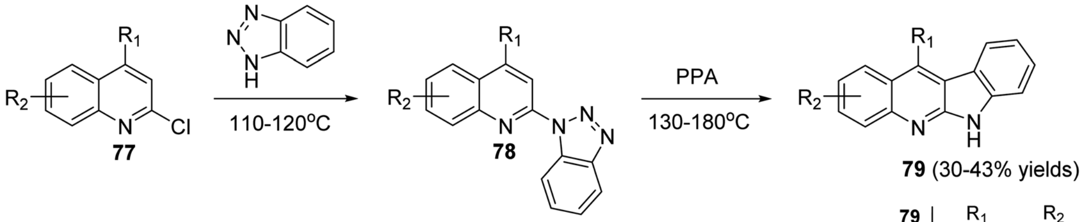
On heating 1-(2-alkynyl)phenyl-3-aryl-2-methylisothioureas **104** with $[Pd(\eta^3\text{-}C_3H_5)\text{–}Cl]_2$ (5 mol%) in the presence of Cs_2CO_3 (2 equiv.), CuTC (copper thiophene-carboxylate) (1.1 equiv.) and 1,4-bis(diphenylphosphino)butane (dppb) (0.3 equiv.) in xylene at 130 °C, a wide range of the desired tetracyclic adduct 6-methyl-indolo[2,3-*b*]quinolines **105** were obtained in 33–76% yields (Scheme 30).[70] Importantly, a variety of electron-rich aryl groups on the aryl ring (Ar) promoted this process. However, substrates bearing an electron-withdrawing group decreased the chemical yields. In fact, the reaction of isothiourea bearing a 3,5-bis(trifluoromethyl)phenyl group afforded no cyclized adduct. Respecting to the substituent (R) on the alkynyl group, both phenyl and alkyl groups were tolerated under these reaction conditions. In the suggested reaction mechanism, the oxidative addition of MeS–C bond to Pd(0), followed by ligand exchange with CuTC gave the alkenylpalladium complex **II**. Subsequent nucleophilic attack of the aryl group to the Pd(II) complex followed by reductive elimination of



75	R
a	4-CH$_3$-C$_6$H$_4$
b	4-OCH$_3$-C$_6$H$_4$
c	4-OEt-C$_6$H$_4$
d	3,5-(OMe)$_2$-C$_6$H$_3$
e	naphthyl
f	4-F-C$_6$H$_4$
g	4-Cl-C$_6$H$_4$
h	4-methoxybenzyl

76	R		R
a	4-CH$_3$-C$_6$H$_4$	i	benzyl
b	4-*t*-Bu-C$_6$H$_4$	j	3-methoxybenzyl
c	4-OMe-C$_6$H$_4$	k	allyl
d	3-OMe-C$_6$H$_4$	l	cyclopentyl
e	2-OMe-C$_6$H$_4$	m	*n*-hexyl
f	3,5-(OMe)$_2$-C$_6$H$_3$	n	*n*-heptyl
g	4-F-C$_6$H$_4$		
h	4-Cl-C$_6$H$_4$		

Scheme 21 Synthesis of 10*H*-indolo[3,2-*b*]quinolines **75** and 6*H*-indolo[2,3-*b*]quinolines **76**.

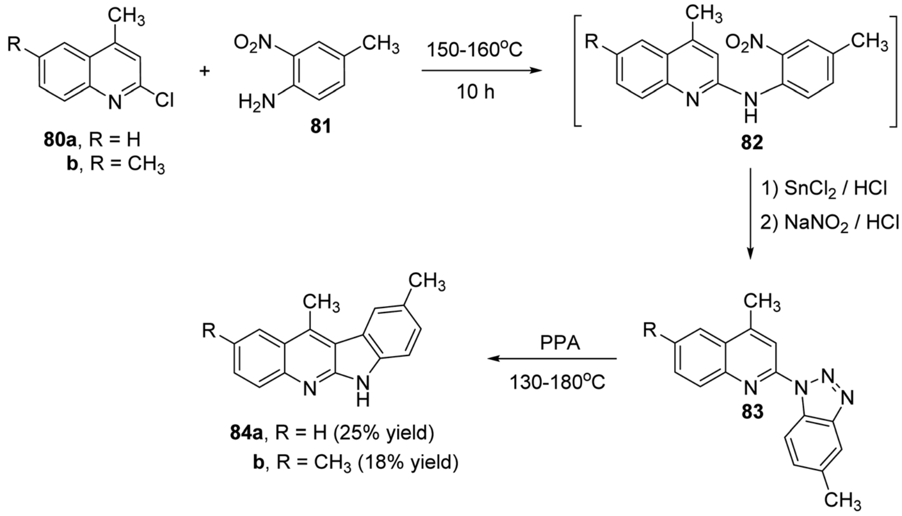


79	R$_1$	R$_2$
a	H	H
b	CH$_3$	H
c	CH$_3$	2-CH$_3$
d	CH$_3$	4-CH$_3$

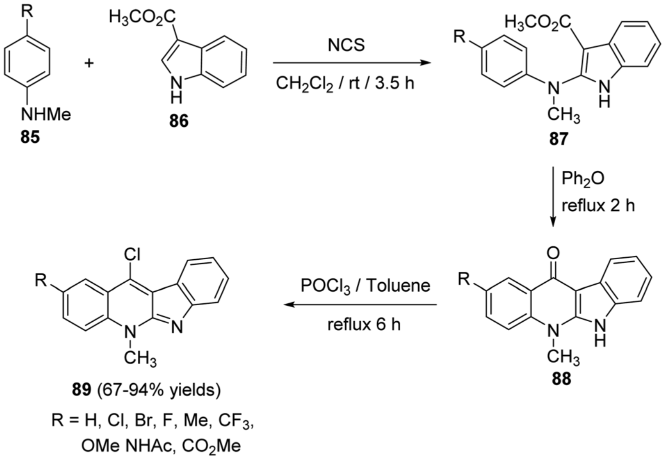
Scheme 22 Synthesis of 6*H*-indolo[2,3-*b*]quinolines **79**.

the resulting Pd-complex provided the tetracyclic product **105** (Scheme 31).

Recently, Patel *et al.*[71] have described an elegant and green approach for the synthesis of 11-aryl-6*H*-indolo[2,3-*b*]quinolines **108** from 2-(phenylethynyl)anilines **106** and aryl isothiocynates **107**. The *in situ* generated *o*-alkynylthioureas, obtained by reacting **106** and **107**, underwent efficient cascade cyclization in the presence of Ag$_2$CO$_3$, as the catalyst, in DMSO to give 11-aryl-6*H*-indolo[2,3-*b*]quinolines **108**, in 59–83% yields, under microwave conditions (30 min reaction time at 130 °C, 150 W, closed vial) (Scheme 32). The authors examined the electronic effect of substituents R$_3$ on the aryl isothiocynates **107**, R$_2$ present on the other phenyl ring of 2-(phenylethynyl)anilines **106** and R$_1$ substituents present on the amine bearing ring of 2-(phenylethynyl)anilines **106** on the product yields and they found that when substituents R$_2$ and R$_3$ are electron-donating groups the products were obtained in better yields compared to electron-withdrawing substituents. On the other hand, R$_1$ substituents showed a trend on the product yields opposite to that of substituents R$_2$ and R$_3$. A plausible reaction mechanism has been proposed as outlined in Scheme 33. Reaction of **106** and **107** gives thiourea intermediate **I**, which is desulfurized in the presence of Ag$_2$CO$_3$ to a carbodiimide intermediate **II**. Intramolecular cyclization of **II** formed a carbene-type intermediate **III**. The latter **III** undergoes further cyclization *via* carbene C–H insertion to afford a non-aromatic tetracyclic intermediate **IV**, which is aromatized to furnish the desired tetracyclic product **108**.



Scheme 23 Synthesis of 6*H*-indolo[2,3-*b*]quinolines **84**.

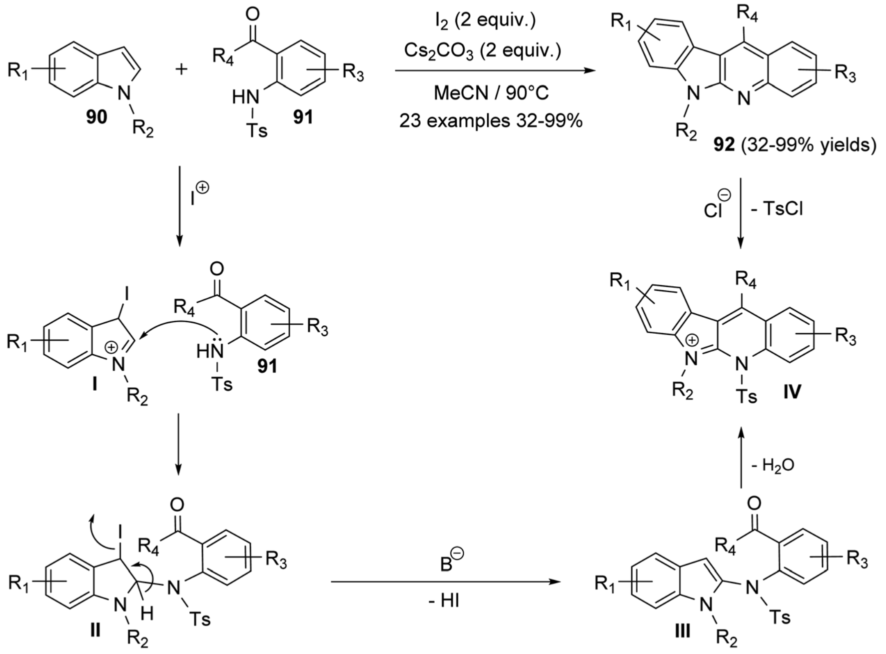


Scheme 24 Synthesis of 11-chloroneocryptolepines **89**.

In 2019, Kundal *et al.*[72] reported a novel, general and efficient method for the synthesis of diversely substituted indolo[2,3-*b*]quinolines **111** through a two-step domino reaction. First, the starting 3-indolines **110** were prepared by Pd-catalyzed domino Heck–Suzuki coupling of 2-bromo-*N*-propargylanilides **109** with aryl boronic acids (Scheme 34). Next, when the 3-indolines **110** were subjected to the oxidative cross-dehydrogenative coupling (CDC) between allylic C sp^3–H of the indoline ring and the free NH_2 group in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2 equiv.) in CH_2Cl_2 at room temperature, the fused tetracyclic indolo[2,3-*b*]quinolines **111** were produced in quantitative yields within one hour (Scheme 34). Gratifyingly, it was found that there was no significant electronic effect of the substituent on the aryl ring on the olefinic motif during the formation of C–N bond. DDQ has been proven as an efficient metal-free oxidant for CDC reactions of C–C bond formation reactions, but the formation of the C–N bond *via* DDQ-mediated cross-dehydrogenative coupling (CDC) has been relatively rare. Therefore, this strategy for the preparation of indolo[2,3-*b*]quinolines **111** should be very attractive in the modern context of organic chemistry research. A plausible mechanism for the DDQ-mediated oxidative C–H amination is outlined in Scheme 35.

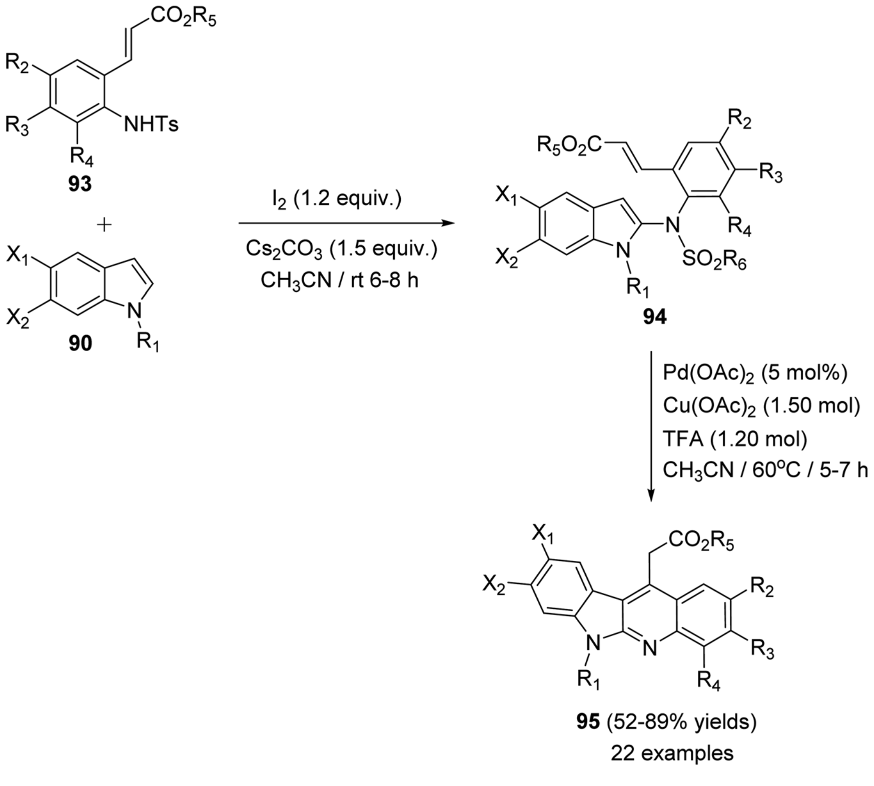
A novel and divergent approach for the synthesis of 5-methyl-5*H*-indolo[2,3-*b*]quinoline alkaloid cryptotackieine **127** was reported.[73] The reaction was performed in eight steps, starting from (2-nitrobenzyl)triphenylphosphonium bromide (**117**). First, condensation of **117** with *o*-azidobenzaldehyde (**118**) in the presence of anhydrous K_2CO_3 and catalytic amounts of dibenzo-18-crown-6 gave the 1-azido-2-(2-nitrostyryl)benzene (**119**). Staudinger reaction between the azide **119** and triphenylphosphine in dry CH_2Cl_2 at room temperature for 5 h followed by hydrolysis of the resulting iminophosphorane **120** provided the 2-(2-nitrostyryl)aniline (**121**). One-pot conversion of **121** into the 3-(2-nitrophenyl)quinoline-2(1*H*)-one (**123**) was performed by sequential treatment with bis(trichloromethyl) carbonate (triphosgene) and further microwave-promoted cyclization of the resulting 1-isocyanate-2-(2-nitrostyryl)-benzene (**122**). Conversion of the quinoline **123** into 1-methylquinoline-2-one **126** was performed by the three-step sequence: (i) methylation with CH_3I in DMF at 60 °C for 2 h to give 1-methyl-3-(2-nitrophenyl)quinoline-2(1*H*)-one (**124**); (ii) reduction of the nitro group in **124** with H_2 in the presence of Pd/c (10%) in EtOH at room temperature for 5 h to give 3-(2-amiophenyl)-1-methyl-quinoline-2(1*H*)-one (**125**) and (iii) diazotization followed by the reaction with NaN_3 furnished 3-(2-azidophenyl)-1-methyl-quinoline-2(1*H*)-one (**126**). Finally, when a solution of the iminophosphorane derived from **126** and Me_3P in nitrobenzene was heated under microwave irradiation at 180 °C for 30 min, the required 5-methyl-5*H*-indolo-[2,3-*b*]quinoline (**127**) was obtained in 40% yield (Scheme 36). The conversion of **126** into **127** represents the first example of an intramolecular aza-Wittig reaction involving a 2-pyridone carbonyls group.

A new, efficient and four-step formal synthesis of alkaloid cryptotackiene **127**, a linear 5-*N*-methyl-5*H*-indolo[2,3-*b*]

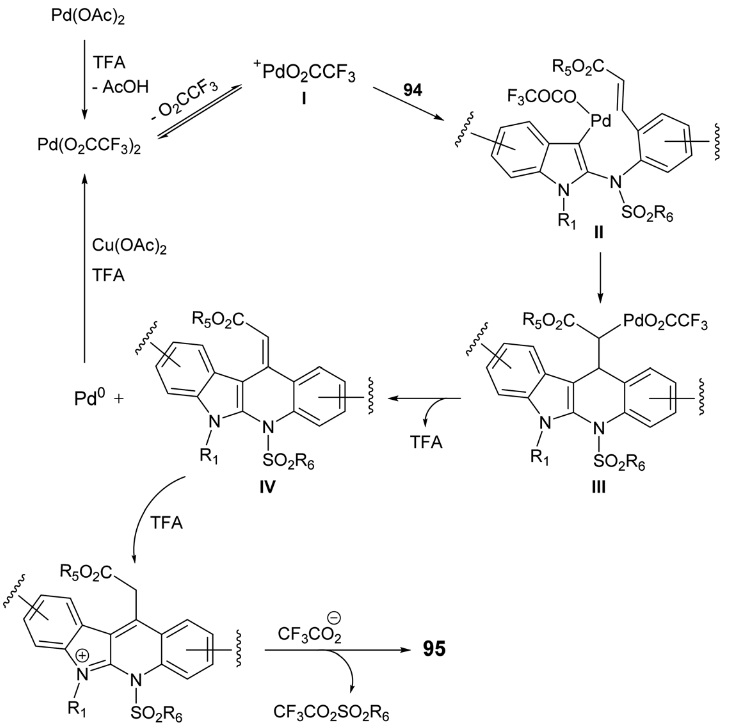


Scheme 25 Molecular iodine catalyzed synthesis of polyfunctionalized indolo[2,3-*b*]-quinolines **92**.

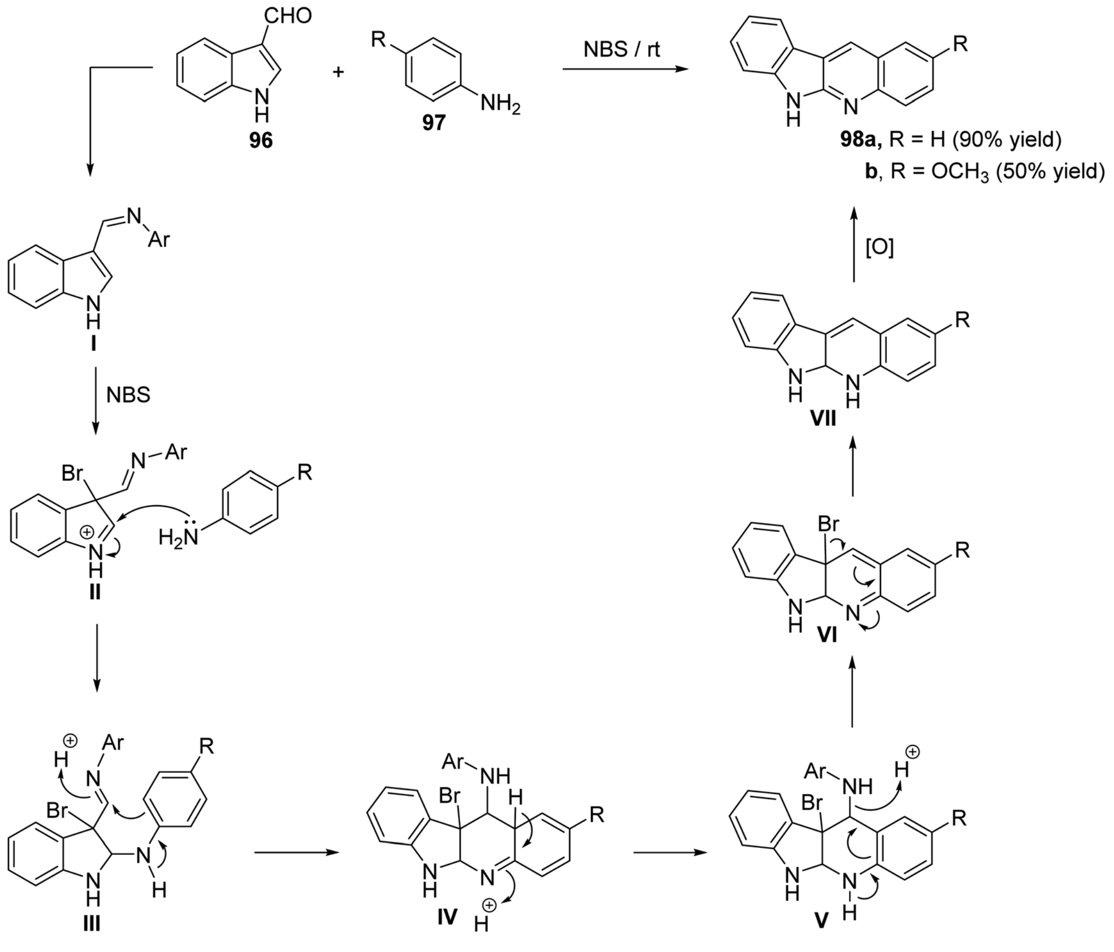
quinoline alkaloid, isolated from the West African shrub *Cryptolepis sanguinolenta*, is reported.[74] It should be noted that the cryptotackiene has been reported to display strong antiplasmodial activity. First, the starting 3-bis[(methylsulfanyl)-methylene]-2-oxindole (**128**) was subjected to conjugate addition with cyclohexanone (**129**) in DMF in the presence of NaH to afford the required 3-[(methylthio)(2-oxocyclohexyl)-methylene]indolin-2-one (**130**). Heterocyclization of the latter adduct **130** was performed by heating with $AcONH_4$ in dry DMSO in the presence of 4 Å molecular sieves at 120–130 °C for



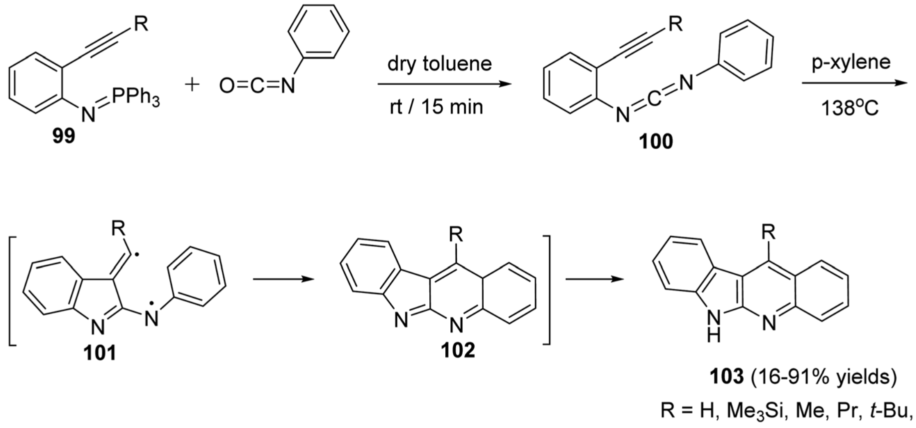
Scheme 26 Pd-mediated synthesis of 11-carboxymethyl substituted 6*H*-indolo[2,3-*b*]-quinolines **95**.



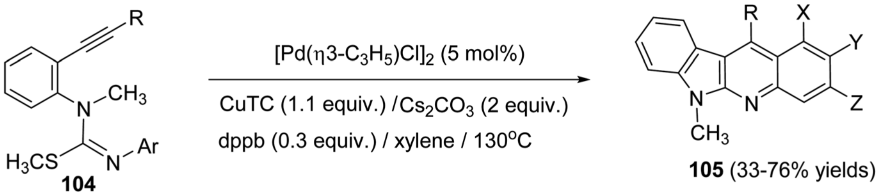
Scheme 27 Proposed reaction mechanism for the formation of 11-carboxymethyl substituted 6*H*-indolo[2,3-*b*]quinolines **95**.



Scheme 28 NBS catalyzed synthesis of novel indolo[2,3-*b*]quinolines **98**.



Scheme 29 Synthesis of 6*H*-indolo[2,3-*b*]quinolines **103** *via* thermolysis of *N*-[2-(1-alkynyl)-phenyl]-*N*-phenylcarbodiimides **100**.

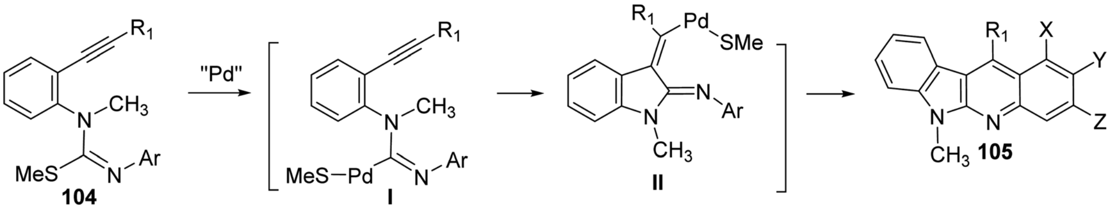


105	R	X	Y	Z
a	4-Me-C_6H_4	H	Me	H
b	4-OMe-C_6H_4	H	OMe	H
c	4-NMe_2-C_6H_4	H	NMe_2	H
d	4-Cl-C_6H_4	H	Cl	H
e	4-CN-C_6H_4	H	CN	H
f	3,5-Me_2-C_6H_3	Me	H	Me
g	3-OMe-C_6H_4	OMe	H	H
h	C_6H_5	H	H	H

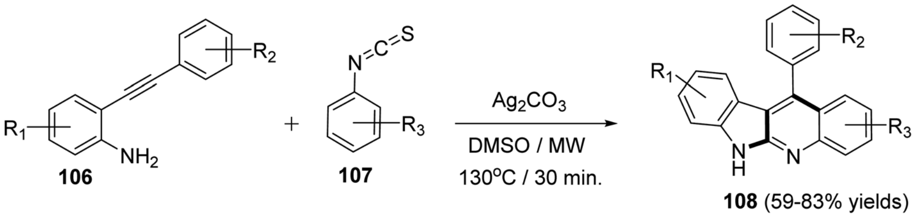
Scheme 30 Synthesis of 6-methyl-indolo[2,3-*b*]quinolines **105** by Pd-catalyzed annulation of unsaturated isothioureas.

12 h to give the 11-(methylthio)-2,3,4,6-tetrahydro-1*H*-indolo[2,3-*b*]quinoline (**131**). Dethiomethylation of **131** with Raney Ni in EtOH at reflux temperature for 6 h gave 2,3,4,6-tetrahydro-1*H*-indolo[2,3-*b*]quinoline (**132**). Subsequent dehydrogenation of **132** with DDQ in refluxing 1,4-dioxane furnished the requested 6*H*-indolo[2,3-*b*]quinoline (**133**) in 88% yield (Scheme 37). Finally, indoloquinoline **133** was converted into 5-methyl-5*H*-indolo[2,3-*b*]quinoline (cryptotackiene) (**127**) by heating with dimethylsulfate in toluene in sealed tube at 150–160 °C. Compound **127** was found to be identical in all respects with the one prepared by heating **133** with methyl iodide in EtOH in closed glass tube at 100 °C (Scheme 37).

Vanelle *et al.*[75] have reported an original, rapid and easy two-step synthesis of new substituted indolo[2,3-*b*]quinolines based on TDAE strategy from reaction between 1-methylisatin (**134**) and substituted *o*-nitrobenzyl chlorides **135** followed by a one-pot reduction-intramolecular cyclization-double-dehydration reaction. First, reaction of **134** (3 equiv.) with **135** in DMF in the presence of TDAE at −20 °C for 1 h gave the corresponding α-hydroxy lactame **136** (Scheme 38). Reduction of the nitro aromatic group in **136** with iron in AcOH acid at 110 °C for 48 h



Scheme 31 A suggested mechanism for the Pd-catalyzed formation of 6-methyl-indolo[2,3-*b*]quinolines **105**.



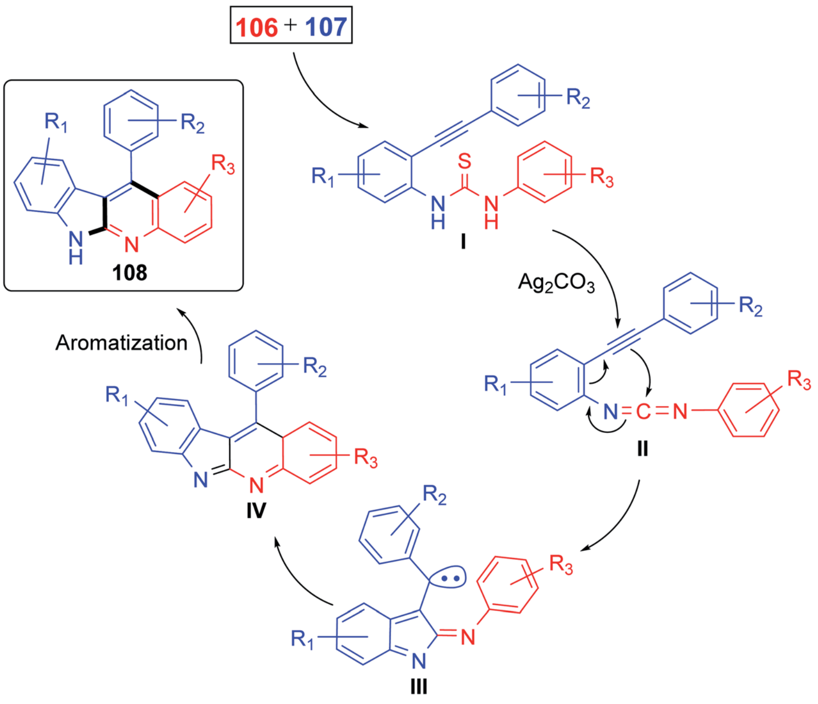
108	R$_1$	R$_2$	R$_3$		R$_1$	R$_2$	R$_3$
a	H	4-Me	2-Me	h	9-Me	H	2-F
b	H	4-OMe	2-Me	i	9-F	H	2-Me
c	H	4-Me	2-F	j	9-F	H	2-F
d	H	4-OMe	2-F	k	9-Me	4-Me	H
e	H	4-F	2-Me	l	9-F	4-F	H
f	H	4-F	2-F	m	9-Me	4-Me	2-Me
g	9-Me	H	2-Me	n	9-F	4-F	2-F

Scheme 32 A green method for the synthesis of 11-aryl-6*H*-indolo[2,3-*b*]quinolines **108** under microwave heating.

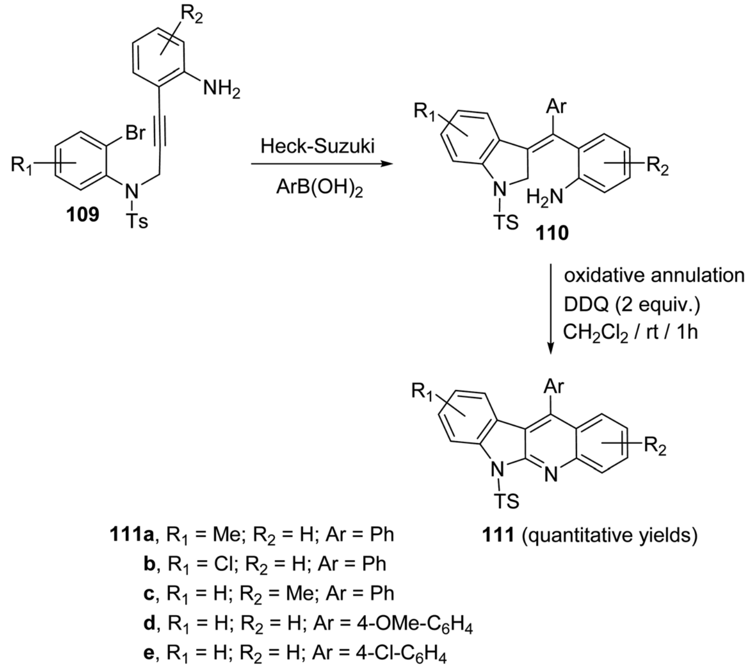
gave the desired 6-methyl-6*H*-indolo[2,3-*b*]quinolines **139** in 33–65% yields (Scheme 38). The latter step involves the nucleophilic attack of NH$_2$ group on lactam C=O group in intermediate **137**, followed by the acid-promoted double dehydration of the resulting 5*a*,6,10*b*,11-tetrahydro-6-methyl-5*H*-indolo[2,3-*b*]quinoline-5*a*,10*b*-diols intermediate **138** (Scheme 38).

A convenient, short and high yielding approach for the synthesis of 6*H*-indolo[2,3-*b*]quinoline (**145**) is described utilizing Wittig reaction and one-pot reduction–cyclization–dehydration method as the key steps.[76] By condensation of isatin (**57**) with (2-nitrobenzyl)-triphenylphosphonium bromide (**140**) in CHCl$_3$ in the presence of Et$_3$N at room temperature for 3 h, the corresponding Wittig product, namely 3-(2-nitrobenzylidene)indolin-2-one (**141**), was formed. Reduction of **141** with Fe/AcOH in the presence of a catalytic amount of HCl at 120 °C for 24 h gave 6*H*-indolo[2,3-*b*]quinoline (**145**) in 77% yield (Scheme 39). In the last step, reduction of NO$_2$ group followed by isomerization of C–C double bond, cyclization and then dehydration took place in one-pot to afford the aromatized tetracyclic product **145** through intermediates **142–144.**

A facile synthesis of 6*H*-indolo[2,3-*b*]quinolines **145** utilizing a Perkin reaction followed by a one-pot double reduction, double cyclization and isomerization has been reported by Tilve *et al.*[77] Condensation of *o*-nitrobenzaldehyde (**146**) with *o*-



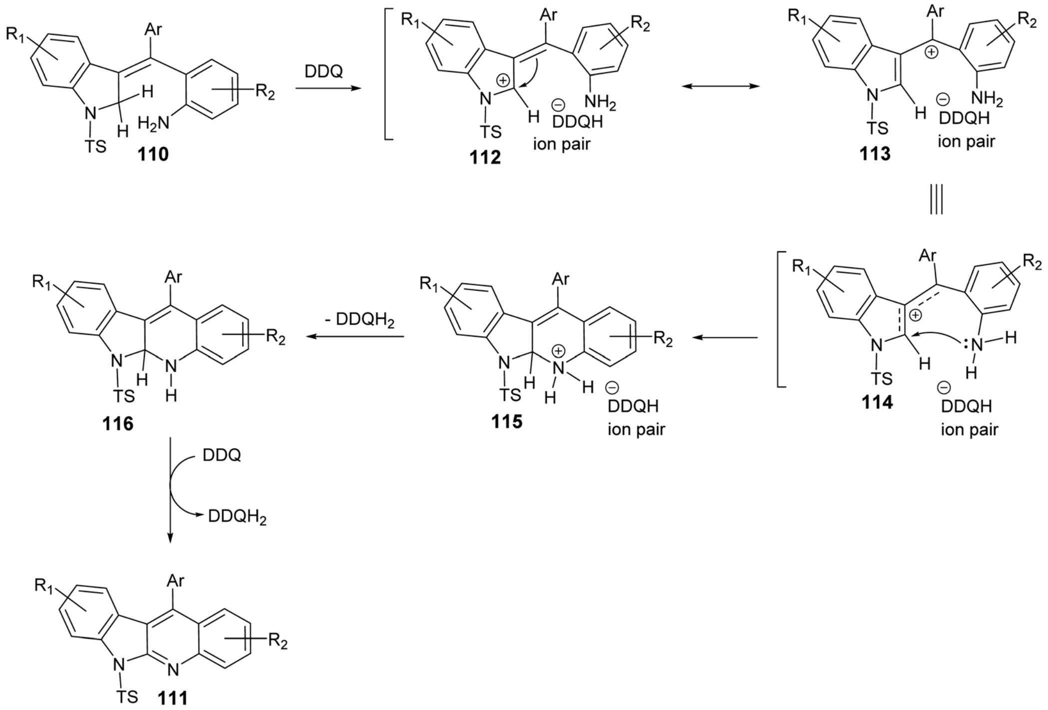
Scheme 33 Proposed mechanistic pathway.



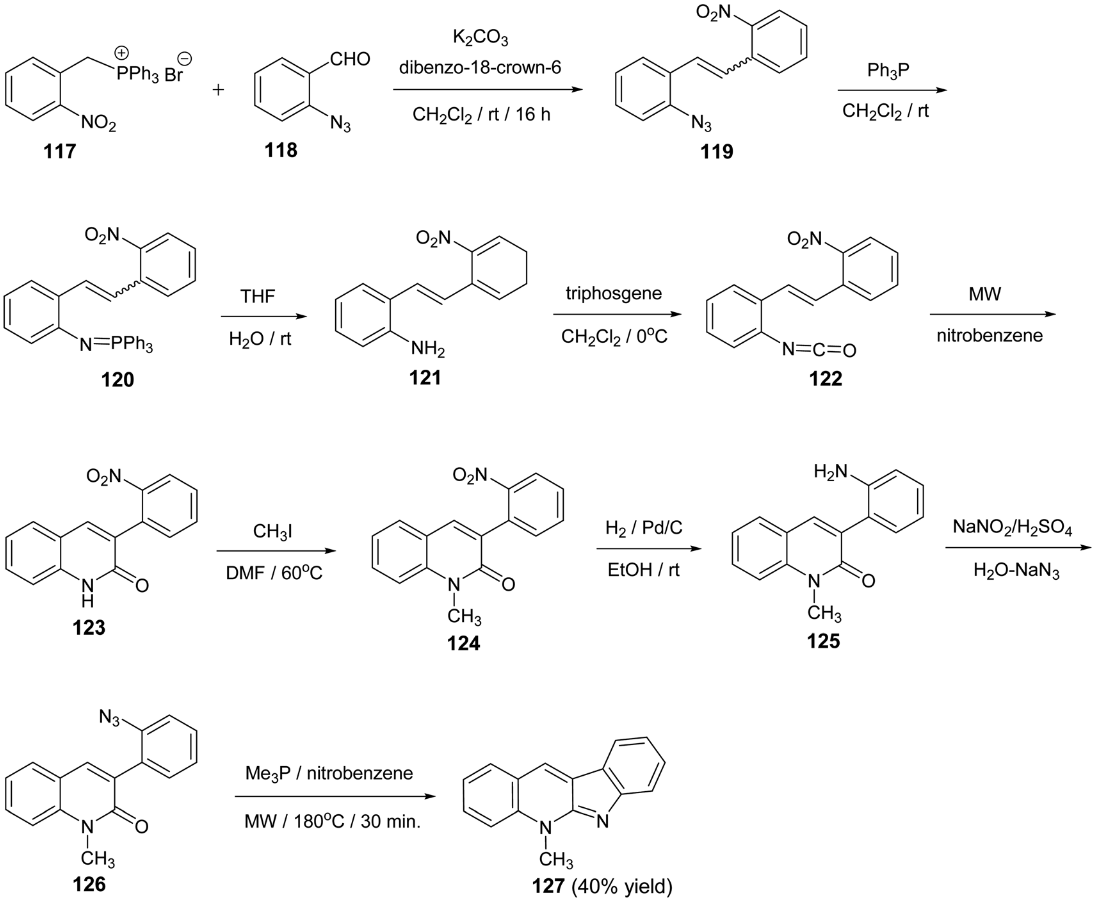
Scheme 34 Synthesis of indolo[2,3-*b*]quinolines **111** *via* Heck–Suzuki coupling and DDQ-mediated C–H amination.

nitrophenyl-acetic acid (**147**) in the presence of Ac_2O and Et_3N under reflux for 5 h afforded the corresponding 2,3-bis(2-nitrophenyl)acrylic acid (**148**), which on esterification gave the ester **149.** Reduction of **149** with Fe/AcOH in presence of HCl at 120 °C for 24 h furnished the required 6*H*-indolo[2,3-*b*]quinoline (**145**) in 74% yield (Scheme 40). In this step, four reactions had happened in a tandem manner, that is, reduction of both the NO_2 groups, cyclization, isomerization of the intermediate *E*-amide to the *Z*-amide followed by a second cyclization.

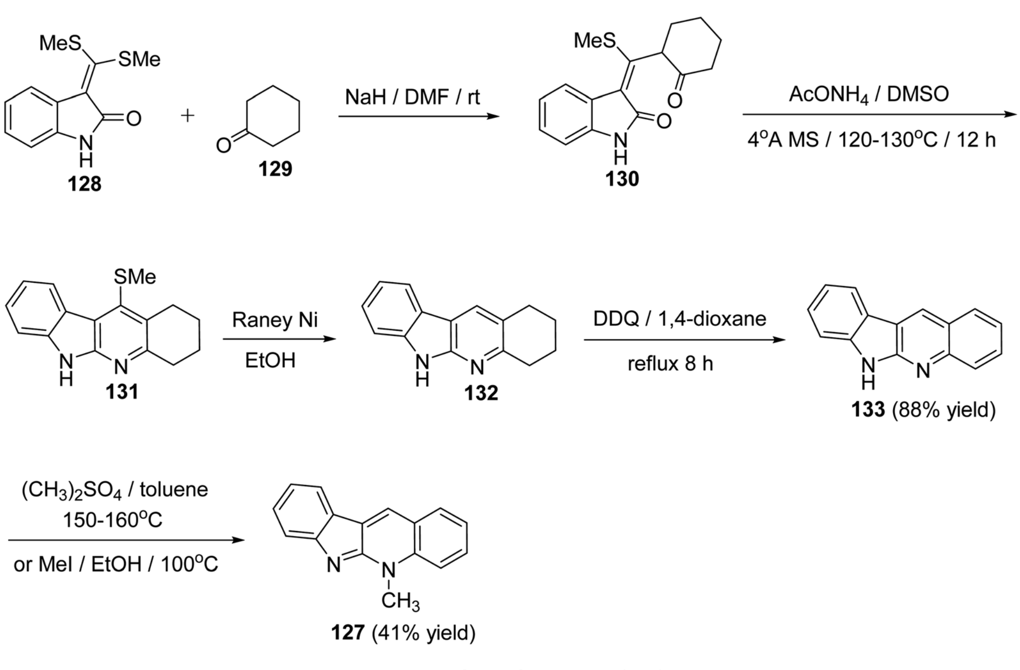
An easy and one-pot procedure for the synthesis of a series of novel 6*H*-indolo[2,3-*b*]quinolines **150** with different substituents on quinoline ring was reported by Parvatkar *et al.*[78] This



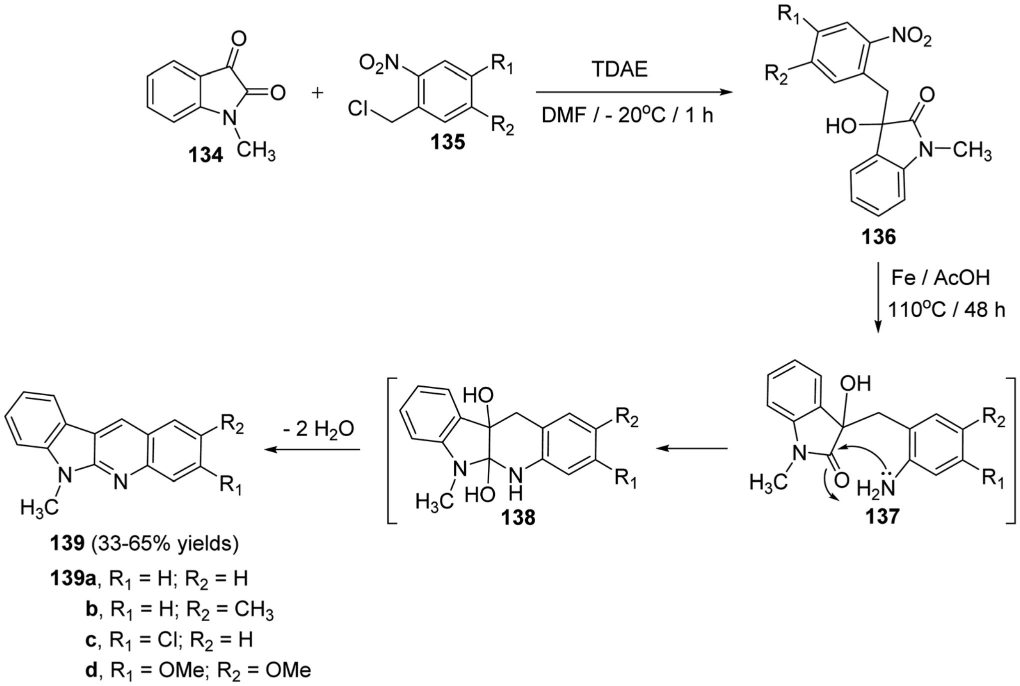
Scheme 35 A suggested mechanism for the DDQ-mediated oxidative C–H cycloamination.



Scheme 36 A novel approach for the synthesis of 5-methyl-5*H*-indolo[2,3-*b*]quinoline (**127**).



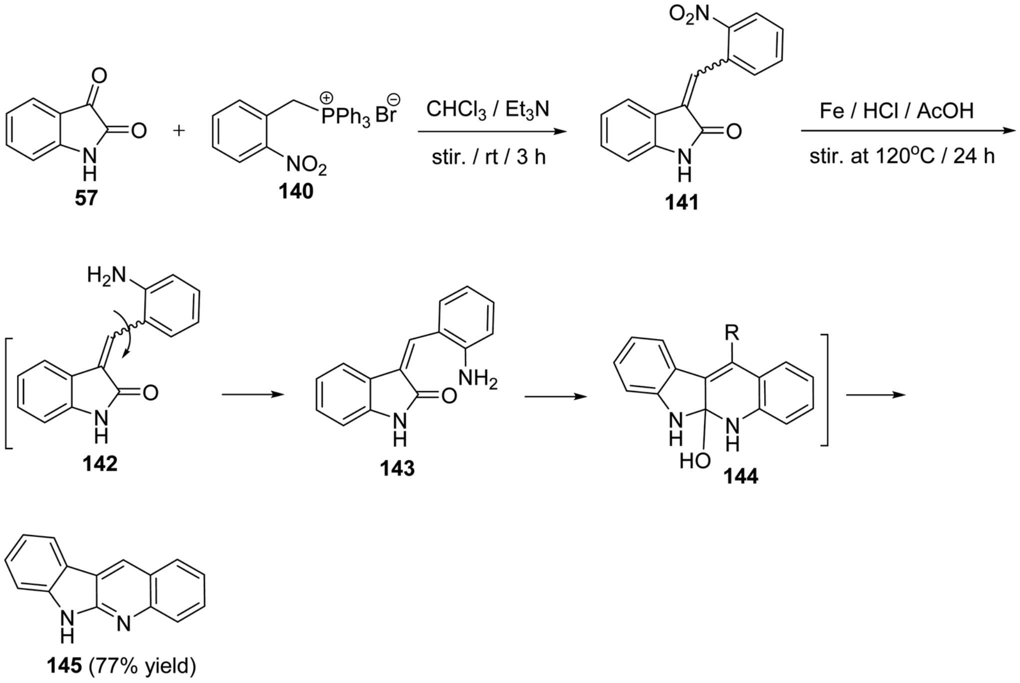
Scheme 37 A four-step formal synthesis of 5-methsyl-5*H*-indolo[2,3-*b*]quinoline (**127**).



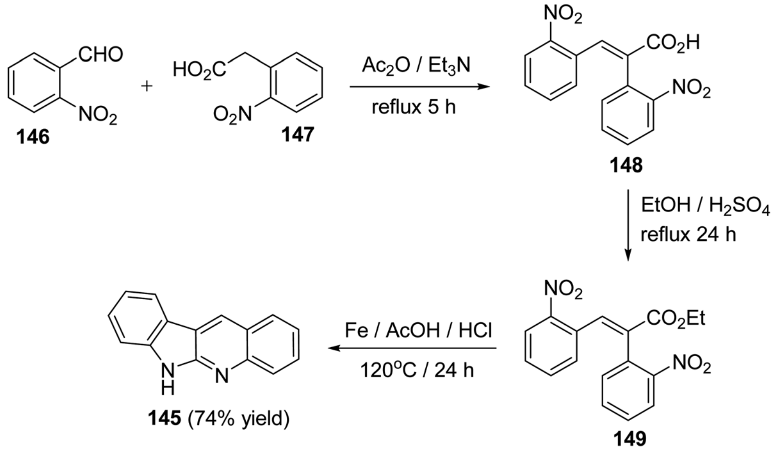
Scheme 38 Synthesis of 6-methyl-6*H*-indolo[2,3-*b*]quinolines **139** *via* one-pot reduction–cyclization–dehydration reactions of α-hydroxy lactams **136**.

synthetic method involves refluxing of indole-3-carboxyaldehyde (**96**) (1 equiv.) with aryl amines **97** (2 equiv.) in diphenyl ether in the presence of a catalytic amount of I_2 (0.1 equiv.) for 12 h to afford 6*H*-indolo[2,3-*b*]quinolines **150** in 38–45% yields (Scheme 41). A suggested mechanism for the formation of **150** is given in Scheme 42.

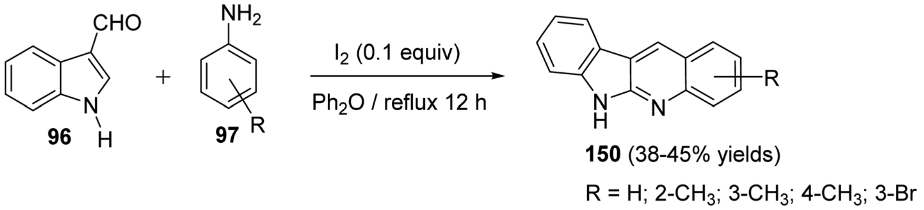
In 2010, Haddadin and his co-workers[79] have described a highly efficient, easy and three-step protocol for the synthesis of biologically active 6*H*-indolo[2,3-*b*]quinolines **162.** An



Scheme 39 A short and convenient method for the synthesis of 6*H*-indolo[2,3-*b*]quinoline (**145**).



Scheme 40 A new synthesis of 6*H*-indolo[2,3-*b*]quinolines **145**.



Scheme 41 A novel and one-pot synthesis of different 6*H*-indolo[2,3-*b*]quinolines **150** using I_2 as a catalyst.

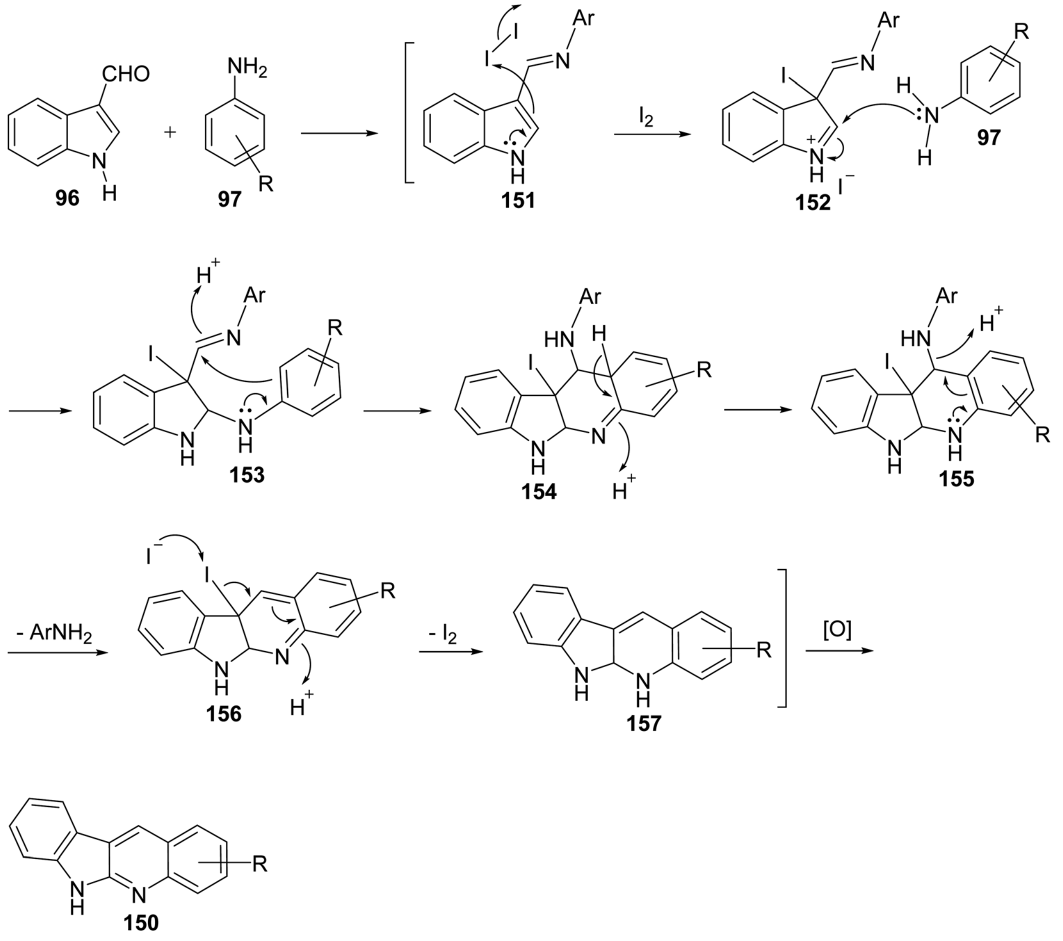
optimized route to **162** is outlined in Scheme 43. Condensation of *o*-aminobenzaldehydes **158** with *o*-nitroaryl acetonitriles **159** in refluxing methanolic KOH afforded a series of novel 2-amino-3-(2-nitroaryl)quinolines **160**. Reduction of **160** with Zn/AcOH afforded the corresponding 3-(2-aminoaryl)quinolin-2-amines **161**. Diazotization of **161** followed by intramolecular cyclization under acidic conditions gave the desired tetracyclic 6*H*-indolo- [2,3-*b*]quinolines **162** in 54–79% yields (Scheme 43).

A convenient method for preparation of 6*H*-indolo[2,3-*b*] quinolines **150** utilizing ruthenium-exchanged FAU-Y zeolite (RuY) as a recyclable heterogeneous catalyst is reported.[80] Reaction of indole-3-carbaldehyde (**96**) (1 equiv.) with aryl amines **97** (1 equiv.) in refluxing dioxane in the presence of Ru^{3+} exchanged FAU-Y zeolite (RuY, 0.1 g, activated at 550 °C for 3 h) for 4–6 h gave 6*H*-indolo[2,3-*b*]quinolines **150** in 50–65% isolated yields (Scheme 44). A mechanism for the RuY catalyzed formation of the 6*H*-indolo[2,3-*b*]-quinolines **150** is outlined in Scheme 45.

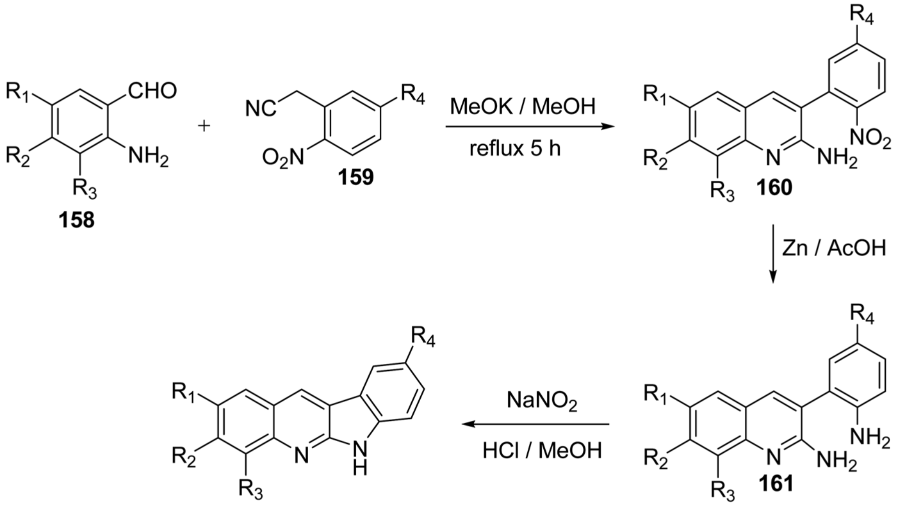
Seidel *et al.*[81] have described a new acid-catalyzed indole annulation with secondary aminobenzaldehydes **163** for the rapid and one-step synthesis of neocryptolepine and various analogues, a bioactive materials as promising lead for new antimalarial agents. Condensation of **163** with indoles **164** in the presence of one equivalent of *para*-toluene sulfonic acid (*p*-TSA) in EtOH under reflux gave neocryptolepine analogues (5-methyl-5*H*-indolo[2,3-*b*]-quinolines) **165** in 56–77% yields (Scheme 46). Condensation of **163** with **164** is expected to form azafulvenium ion **166** which undergoes direct ring-closure to furnish **167**. Subsequent oxidation of **167** completes the synthesis of the desired products **165** (Scheme 47). Interestingly, the oxidized products **165** were obtained directly and the putative intermediate **167** was not isolated, presumably because it undergoes facile oxidation by air.

A simple and concise two-step approach for the synthesis of 6*H*-indolo[2,3-*b*]-quinolines **171** is reported using an alkylation of 1*H*-indoles **164** at its more reactive 3-position and domino reduction–intramolecular cyclization–aromatization approach.[82] Alkylation of indoles **164** was performed using 2-nitrobenzyl bromide (**168**) in the presence of methylmagnesium bromide (MeMgBr), as the base, in a mixture of acetone–H_2O (4 : 1) at 80 °C for 40 h to yield 3-(2-nitrobenzyl)-1*H*-indoles **169.** Reductive cyclization of **169** with triphenylphosphine in refluxing diphenyl ether for 4–6 h provided the tetracyclic compound **170,** which underwent oxidation followed by aromatization under reaction conditions to give the desired products **171** in 55–63% yields (Scheme 48). A suggested mechanism for the formation of **171** is depicted in Scheme 49.

An efficient and straightforward synthesis of 6*H*-indolo[2,3-*b*]quinolines **173** in one-pot by alkylation–dehydration–cyclization–aromatization method utilizing pivalic acid with indoles **164** and *o*-aminobenzaldehyde (**172**) is described by Kadam and Tilve.[83] Thus, refluxing **164** with **172** in the presence of pivalic acid in Ph_2O for 6 h gave the tetracyclic 6*H*-indolo[2,3-*b*]quinolines **173** (Scheme 50). In the proposed reaction mechanism, the alkylation of **164** with **172**, followed by dehydration and



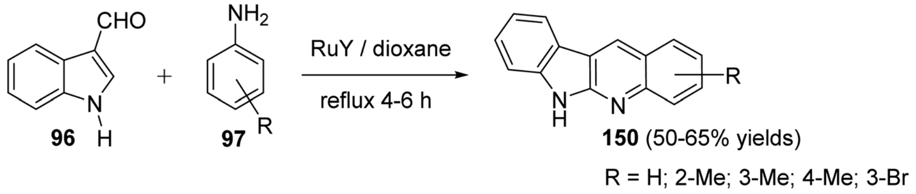
Scheme 42 Postulated mechanism for the formation of **150**.



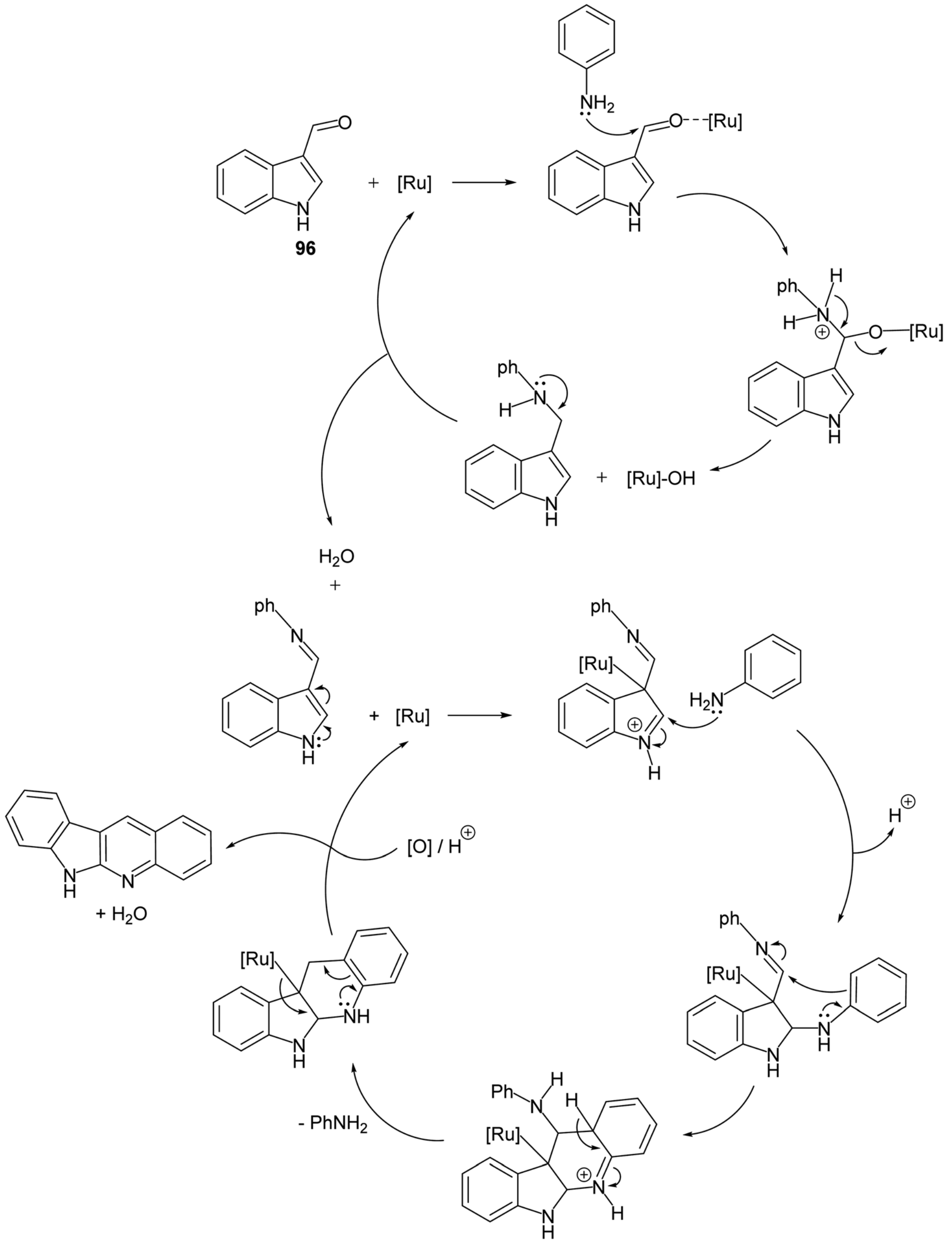
Scheme 43 Route toward the synthesis of **162**.

cyclization gives dihydroindolo-quinoline intermediate **178**, which oxidizes under reaction conditions to furnish the final product indoloquinolines **173** (Scheme 51).

A facile and iron-mediated synthesis of 6*H*-indolo[2,3-*b*] quinolines **180** by reaction of 2-amino-α-phenylbenzene methanol **179** and various indoles **90** was developed by Wang *et al.*[84]

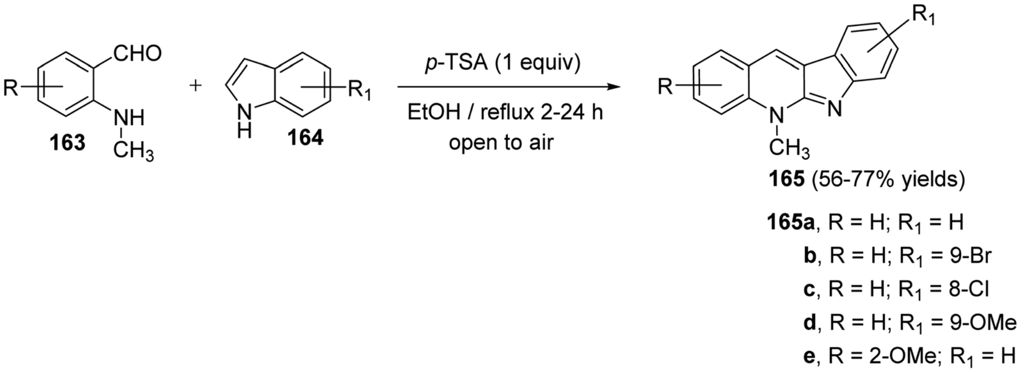


Scheme 44 RuY catalyzed synthesis of 6*H*-indolo[2,3-*b*]quinolines **150**.

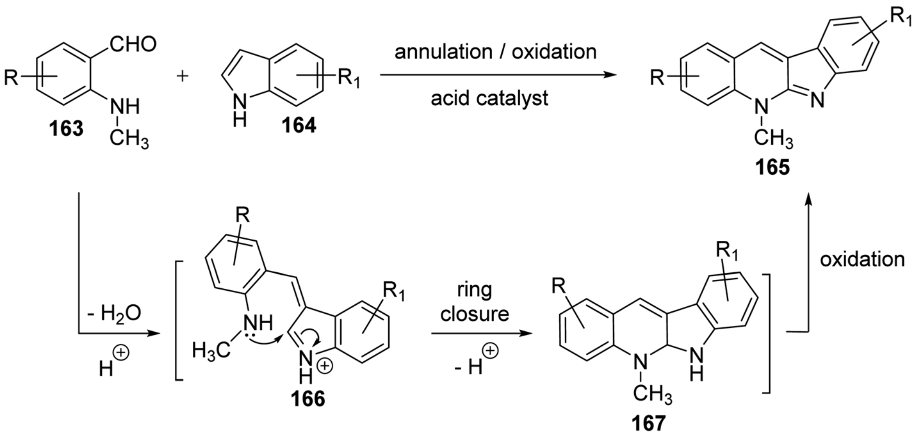


Scheme 45 Proposed mechanistic pathway for the RuY catalyzed formation of 6*H*-indolo- [2,3-*b*]quinoline **150**.

This synthetic approach proceeded by heating a mixture of **179** (1.5 equiv.), **90** (1 equiv.) and $FeCl_3$ (2.5 equiv.) in MeOH at 80 °C for 2 h (Scheme 52). In the present study, the target products have been prepared through a new approach in 34–83% yields. When the metal salt was replaced with $FeCl_2$ or absent, the desired products **180** were not obtained. This indicated that

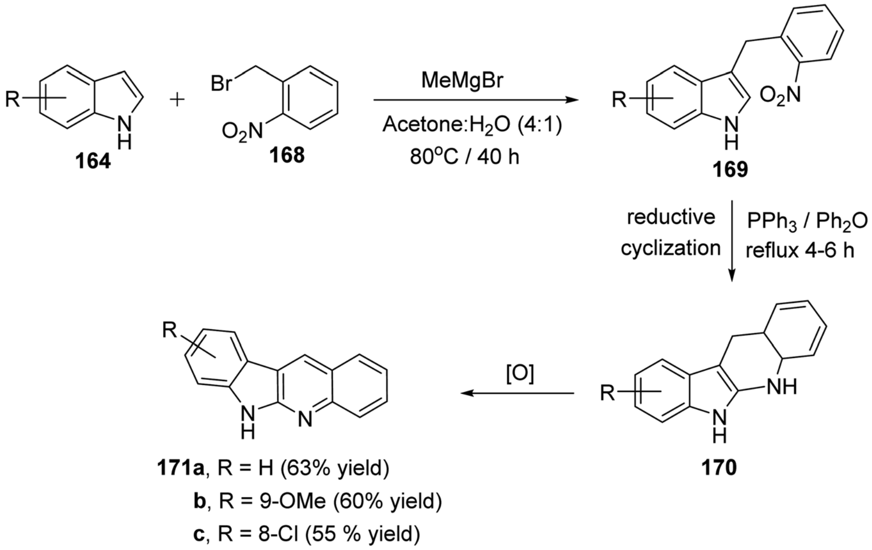


Scheme 46 One-step synthesis of 5-methyls-5*H*-indolo[2,3-*b*]quinolines **165**.

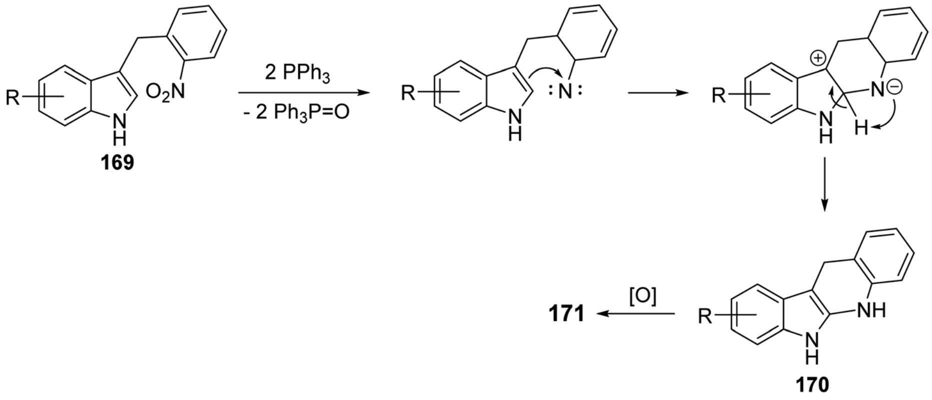


Scheme 47 Proposed synthesis of 5-methyl-5*H*-indolo[2,3-*b*]quinolines **165**.

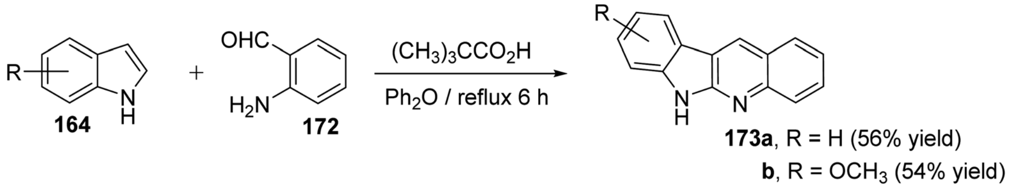
$FeCl_3$ played the role of an oxidant in the process of reaction rather than the function of catalysis. The authors also studied the influence of electronic effects on these reactions. The indoles bearing electron-withdrawing groups (EWG) on the benzene ring (R_2) seemed to be less efficient than electron-donating groups (EDG) and resulted in low yields. A mechanism for the iron-promoted synthesis of 6*H*-indolo[2,3-*b*] quinolines **180** is proposed as shown in Scheme 53. Firstly,



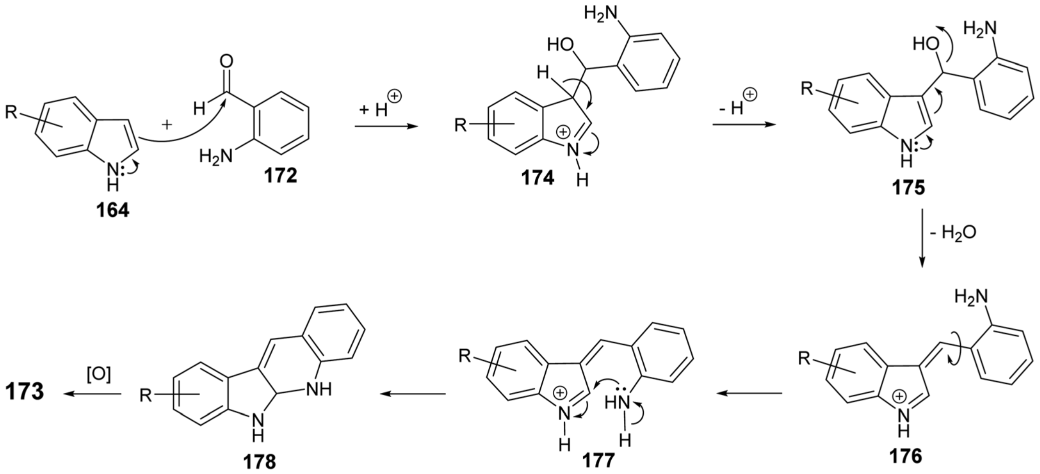
Scheme 48 A concise synthesis of 6*H*-indolo[2,3-*b*]quinolines **171**.



Scheme 49 Proposed mechanism for the formation of 6*H*-indolo[2,3-*b*]quinolines **171**.



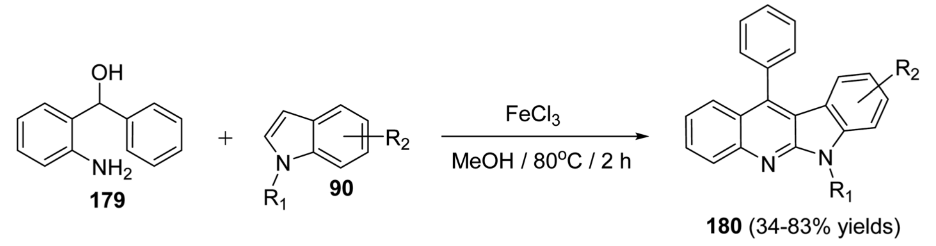
Scheme 50 A pivalic-acid assisted one-pot alkylation–dehydration–cyclization–aromatization method for the synthesis of 6*H*-indolo[2,3-*b*]quinolines **173**.



Scheme 51 A plausible mechanism for the synthesis of 6*H*-indolo[2,3-*b*]quinolines **173**.

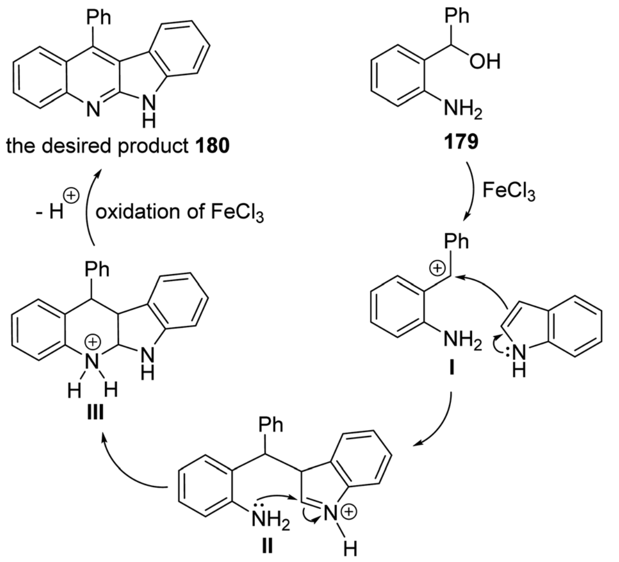
$FeCl_3$ may activate **179** to give intermediate **I,** which undergoes the Friedel–Crafts reaction to furnish intermediate **II**. The latter intermediate **II** undergoes intramolecular cyclization to afford intermediate **III**, which subsequently undergoes deprotonation and oxidation by $FeCl_3$ to afford the desired product **180**.

In 2016, Shi and Wang[85] have developed an environmentally friendly and efficient Rh(III)-catalyzed synthetic approach for 6*H*-indolo[2,3-*b*]quinolines **182** from various indoles **90** and benzo[*c*]isoxazole (**181**) using H_2O as an efficient solvent. This annulation procedure undergoes tandem C–H activation, cyclization, and condensation steps. The reaction was carried out by reacting 1-(pyridin-2-yl)-1*H*-indoles **90** (1.0 equiv.) with **181** (1.5 equiv.) in the presence of a catalytic amount of $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and AcONa (0.4 equiv.) in H_2O at 100 °C under Ar atmosphere for 12 h. The methodology furnished the desired tetracyclic **182** in 59–94% yields (Scheme 54). A control experiment showed that both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ were essential catalyst system for this transformation as their omission led to no formation of tetracyclic product **182.** In this work, the authors investigated the effect of additives in the present reaction and they have noted



180a, R_1 = Me; R_2 = H
b, R_1 = Bn; R_2 = H
c, R_1 = H; R_2 = H
d, R_1 = H; R_2 = 10-Me
e, R_1 = H; R_2 = 9-OMe
f, R_1 = H; R_2 = 8-F
g, R_1 = H; R_2 = 9-Br
h, R_1 = H; R_2 = 10-CO_2Me

Scheme 52 Iron-promoted synthesis of 6*H*-indolo[2,3-*b*]quinolines **180** from the reaction of **179** with different indoles **90**.

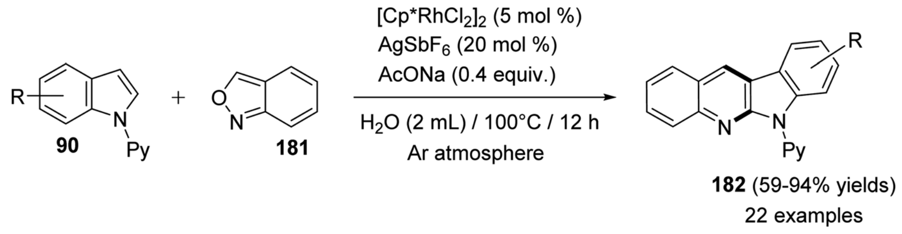


Scheme 53 Postulated mechanism for the construction of indolo[2,3-*b*]quinolines **180** from **179** and **90**.

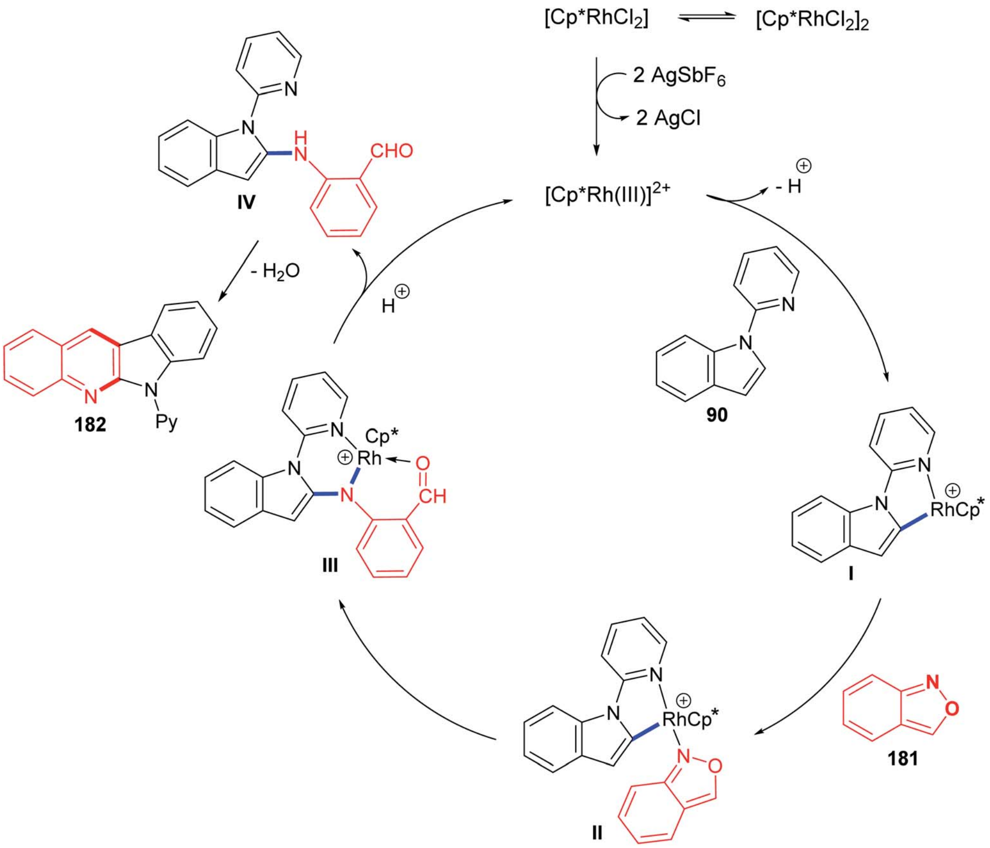
that the use of AcONa gave the best result as the yields of products **182** were increased. The mechanistic pathway for the reaction of **90** with **181**, using Rh(III) as a catalyst, is outlined in Scheme 55. First, indoles **90** reacted with Cp*Rh(III) *via* directed C–H cleavage to give intermediate **I.** The coordination of **181** to **I** yields intermediate **II.** Subsequently, the migration insertion of the coordinated **181** into the Rh–C bond gives intermediate **III.** Protonation of **III** provides the further intermediate **IV** and releases the Rh(III) species for the next catalytic cycle. Finally, the latter intermediate **IV** undergoes intramolecular cyclization *via* elimination of one molecule of H_2O to afford the final product **182.**

Yin *et al.*[86] developed a facile and efficient method for the synthesis of 6-substituted 6*H*-indolo[2,3-*b*]quinolines **185** from isoindigo derivatives **184**, prepared from isatins **57** and indolin-2-ones **183**, in the presence of $SnCl_2$, in combination with AcOH/HCl under heating at 120 °C for 12–24 h in moderate yields (60–74% yields) (Scheme 56). Pyrrole and pyridine rings are synchronously constructed in one-pot for these tetracyclic products. A possible reaction mechanism for the formation of **185** is presented as shown in Scheme 57. First, reduction of the carbon–carbon double bond in **184** by $SnCl_2$ in an acid medium affords the saturated 1,4-diketone intermediate **185.** Hydrolysis of the amide bond of **185**, followed by a decarboxylation yields the further intermediate **187.** Subsequent intramolecular cyclization/aromatization furnishes the target tetracyclic molecule **185** *via* intermediate **188.**

In 2017, Challa *et al.*[87] reported an efficient metal-free method for the synthesis of indolo[2,3-*b*]quinolines **190** under

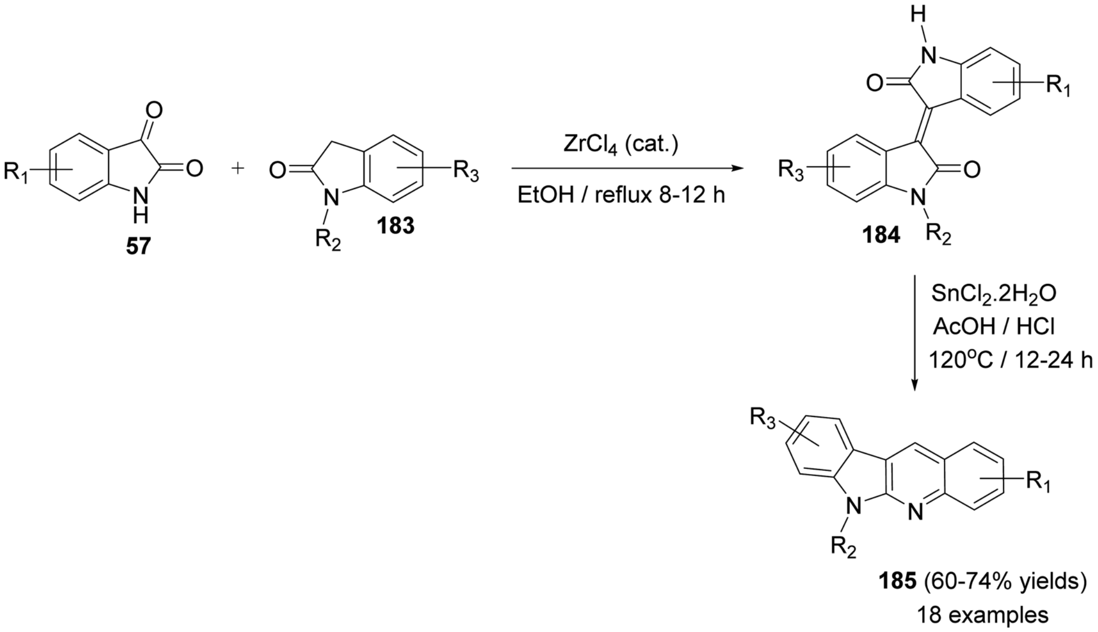


Scheme 54 Rh(III)-catalyzed C–H amination/annulation of substituted indole derivatives **90** with **181**.

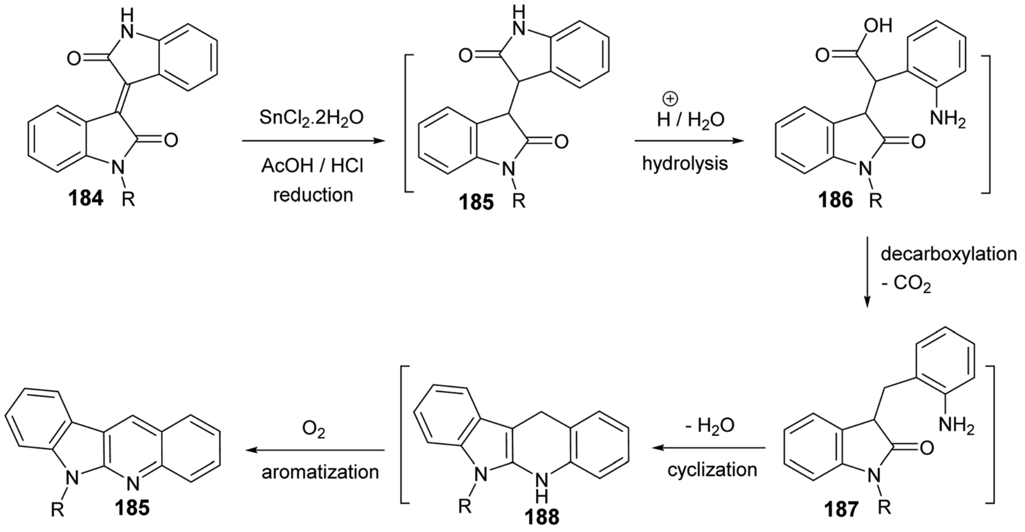


Scheme 55 Plausible catalytic cycle.

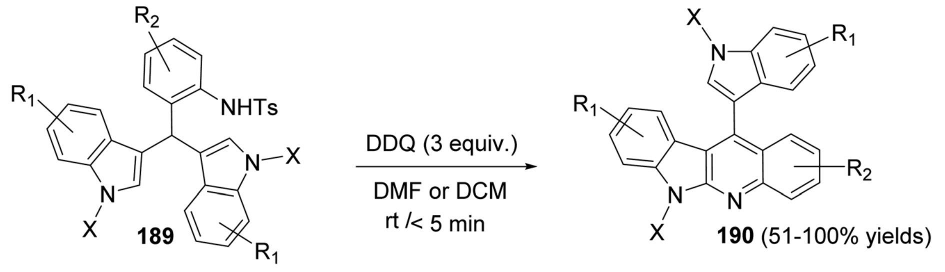
DDQ-mediated oxidative conditions from the easily accessible 3,3′-diindolylmethanes (DIMs). Treatment of 3,3′-diindolylphenylmethanes (DIPMs) **189** with DDQ (3 equiv.) at room temperature for <5 min using DCM or DMF as the solvent afforded the desired indolo[2,3-*b*]quinolines **190** in 51–100% yields (Scheme 58).



Scheme 56 Synthesis of 6-substituted-6*H*-indolo[2,3-*b*]quinolines **185** from isoindigo derivatives **184** in the presence of SnCl$_2$ in acidic media.



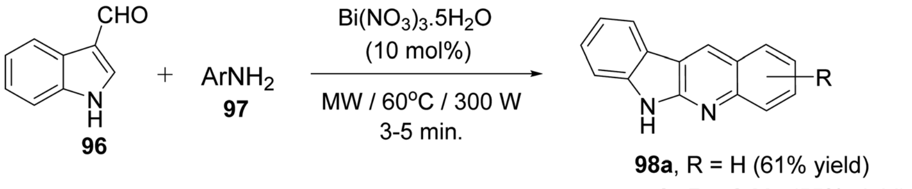
Scheme 57 A possible reaction mechanism for the formation of 6-substituted-6*H*-indolo-[2,3-*b*]quinolines **185**.



R_1 = H, Cl, Br, I, OMe, CN, CO_2Me, OBn
R_2 = H, OMe
X = H, Me, Ph

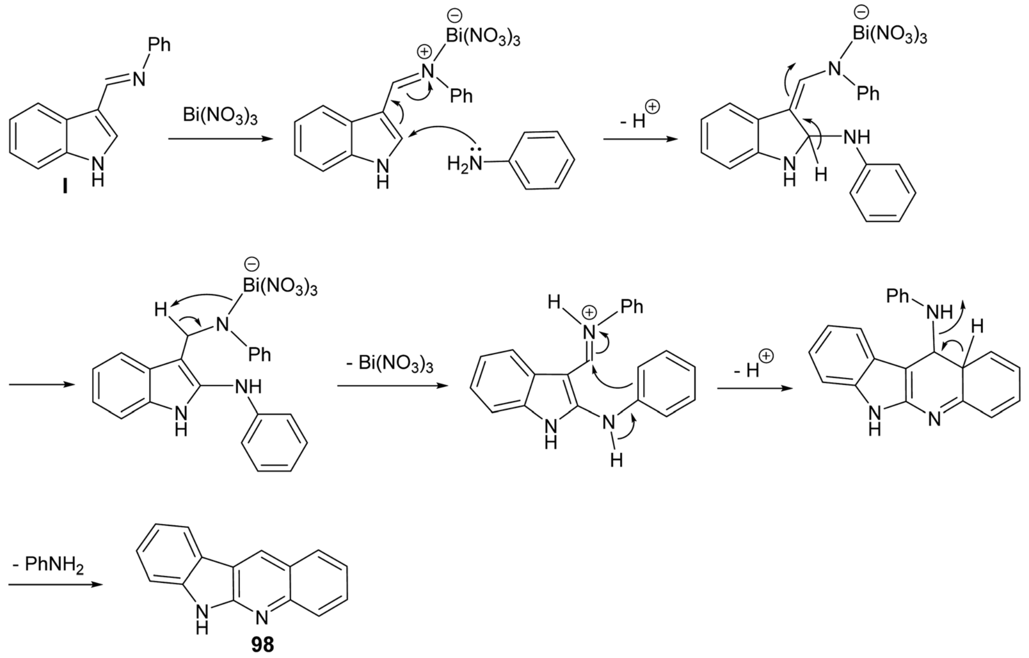
Scheme 58 Scope of DDQ-mediated intramolecular C2–N bond formation for the synthesis of indolo[2,3-*b*]quinolines **190**.

A clean and expeditious microwave-mediated one-pot methodology for the synthesis of a series of 6*H*-indolo[2,3-*b*]quinolines **98** using eco- and user-friendly bismuth-nitrate [$Bi(NO_3)_3\cdot 5H_2O$] as a catalyst under mild reaction conditions is reported.[88] A mixture of indole-3-carboxyaldehyde **96** (1 equiv.), aryl amines **97** (2 equiv.) and $Bi(NO_3)_3\cdot 5H_2O$ (10 mol%, 0.1 equiv.) in tightly sealed vessel under solvent-free condition were irradiated in microwave at 60 °C (300 W) for 3–5 min to provide different linear 6*H*-indolo[2,3-*b*]quinolines **98** in good yields (52–61% yields) (Scheme 59). Aryl amines containing electron-withdrawing or electron-donating groups and hetero-aryl moiety are compatible with these reaction conditions yielding the desired tetracyclic products in good yields within short period of time. In contrast to all available approaches, this is the fastest method reported so far for the synthesis of linear indolo[2,3-*b*]quinolines. A proposed mechanism for the Bi(III)-



98a, R = H (61% yield)
b, R = 2-Me (55% yield)
c, R = 3-Me (54 % yield)
d, R = 4-Me (56% yield)
e, R = 3-Br (58% yield),

Scheme 59 Microwave-mediated $Bi(NO_3)_3$-catalyzed synthesis of indolo[2,3-*b*]quinolines **98**.

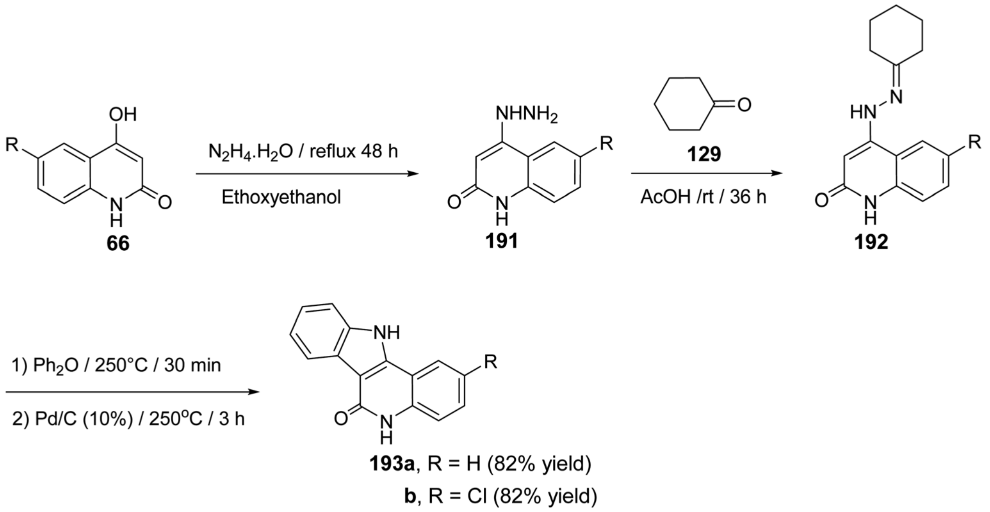


Scheme 60 Plausible reaction mechanism for Bi(III)-catalyzed synthesis of indolo[2,3-*b*]-quinolines **98** through activation of the *in situ* formed imine.

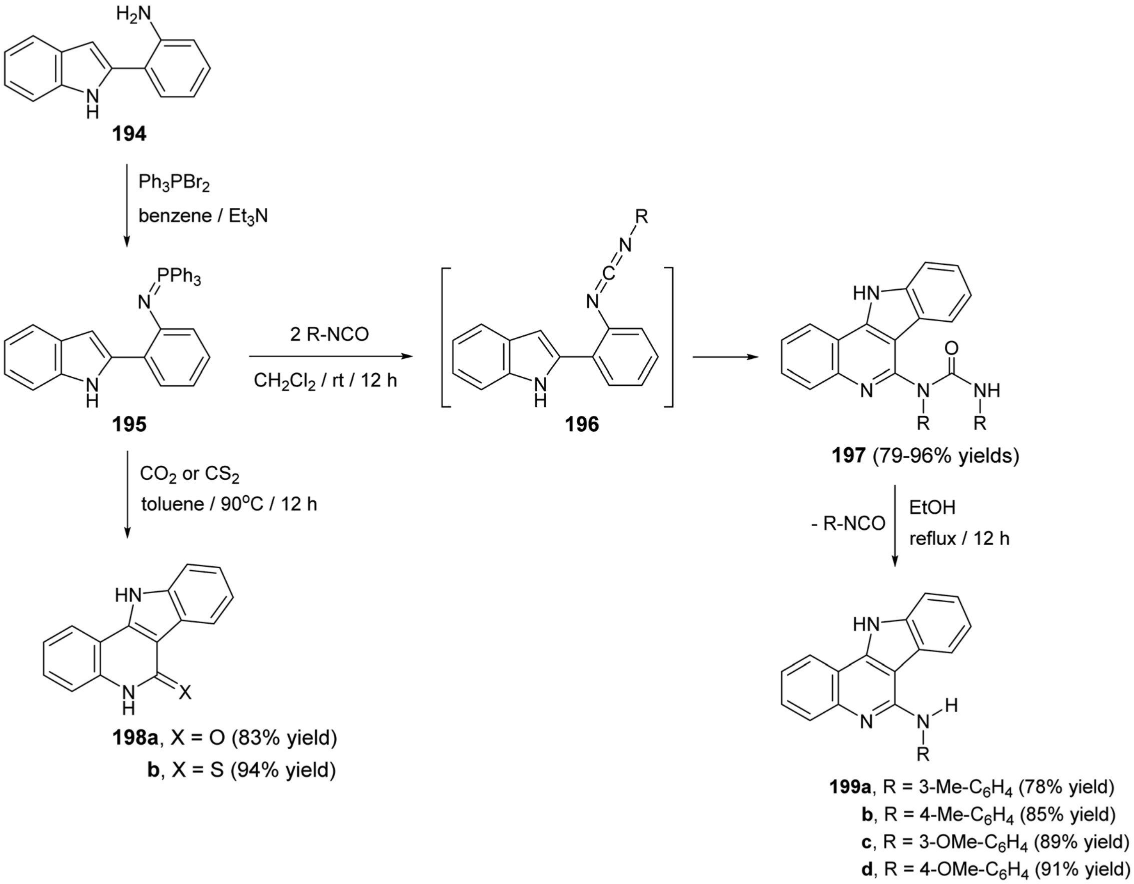
catalyzed for the formation of the indolo[2,3-*b*]quinolines **98** is given in Scheme 60.

2.2.2. Indolo[3,2-*c*]quinolines. The synthesis and cytotoxic activity evaluation of 5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6-ones **193** were reported by Chen and his co-workers[89] in 2002. The starting 4-hydrazinoquinolin-2(1*H*)-ones **191** were synthesized by refluxing 4-hydroxy-quinolin-2(1*H*)-ones **66** with hydrazine hydrate in ethoxyethanol as a solvent. Stirring **191** with cyclohexanone (**129**) in glacial AcOH at room temperature afforded the corresponding hydrazones **192.** The thermal Fischer indolization of **192** followed by the dehydrogenation gave the fused heterocyclic compounds **193**, in good yields (Scheme 61).

Molina *et al.*[90] have developed a new, simple and general methodology for the synthesis of indolo[3,2-*c*]quinolines **197**–**199**, bearing an amino, oxygen, or a sulfur atom at the 5-position. This approach based on the aza-Wittig type reaction of iminophosphoranes with hetero-cumulenes to afford the 2-azahexatriene moiety containing a cumulated double bond at one end and the C═C bond of the pyrrole ring at the other, which subsequently underwent ring closure to give the fused tetracyclic products **197–199.** Thus, iminophosphorane **195**, which was obtained from 2-(*o*-aminophenyl)indole (**194**) and

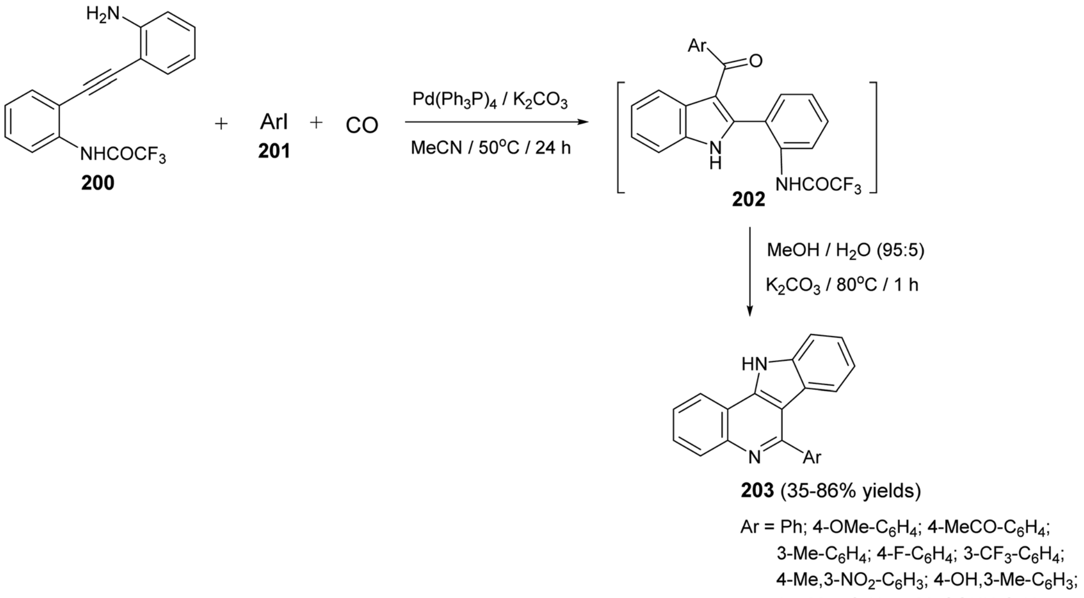


Scheme 61 Synthesis of 5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6-ones **193**.

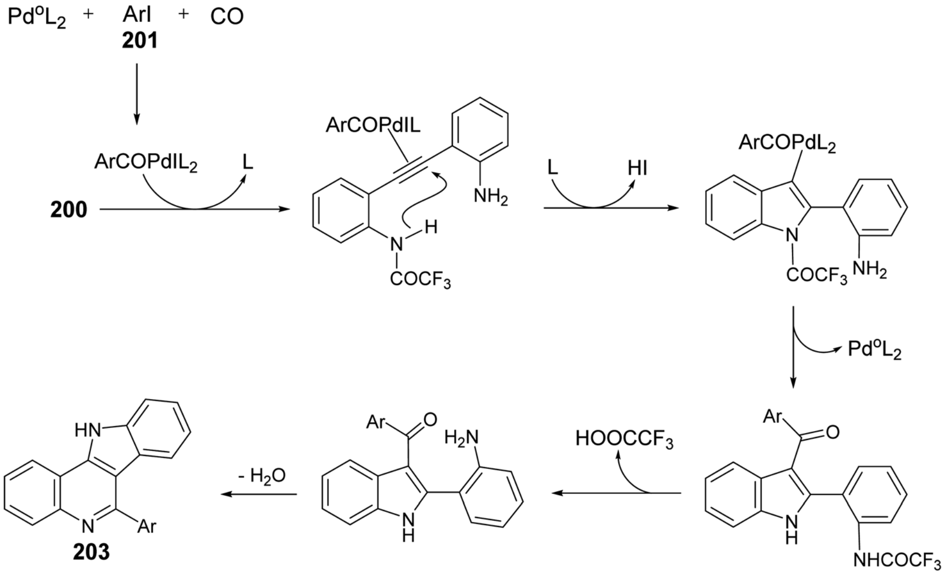


Scheme 62 A new methodology for the synthesis of indolo[3,2-*c*]quinolines **197–199**.

triphenylphosphine dibromide, reacted with aromatic isocyanates, (1 : 2) molar ratio, in dry CH_2Cl_2 at room temperature for 12 h to afford the new tetracyclic 5-[*N*-aryl-*N*(arylcarbamoyl)]-amino-11*H*-indolo[3,2-*c*]quinolines **197** in 79–96% yields (Scheme 62). The compounds **197** when heated in EtOH at reflux temperature for 12 h, they underwent elimination of the isocyanate to give 5-arylamino-11*H*-indolo[3,2-*c*]quinolines **199** in 78–91% yields (Scheme 62). The authors believed that the

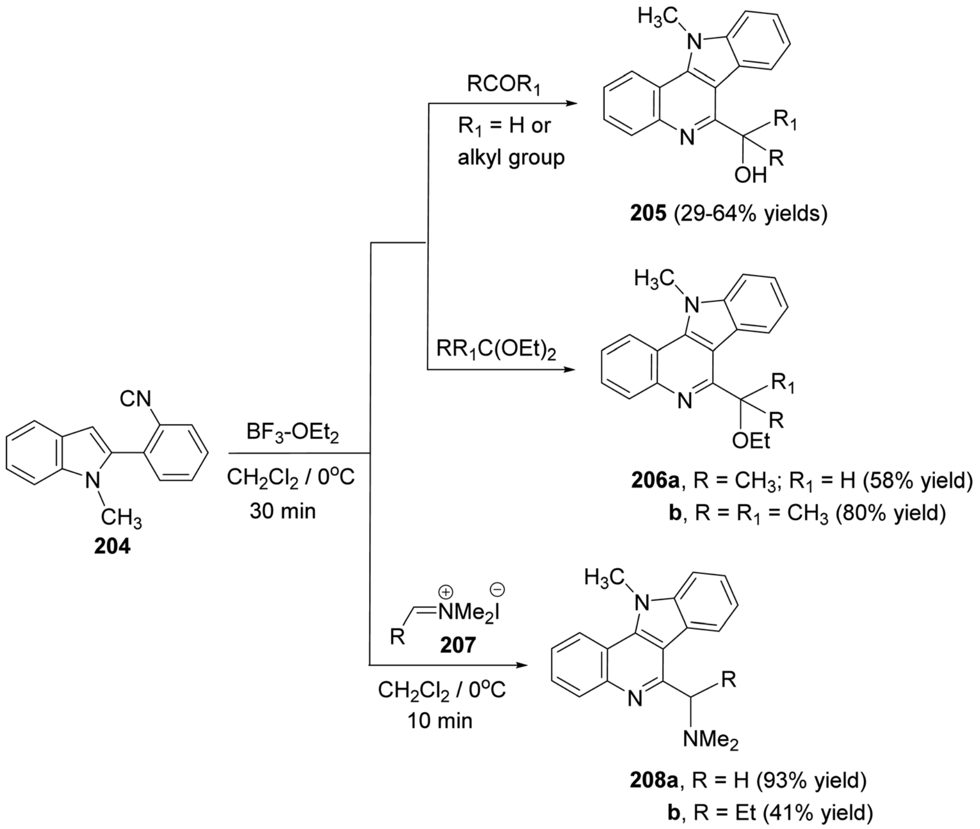


Scheme 63 A one-pot procedure for the synthesis of 6-aryl-11*H*-indolo[3,2-*c*]quinolines **203**.

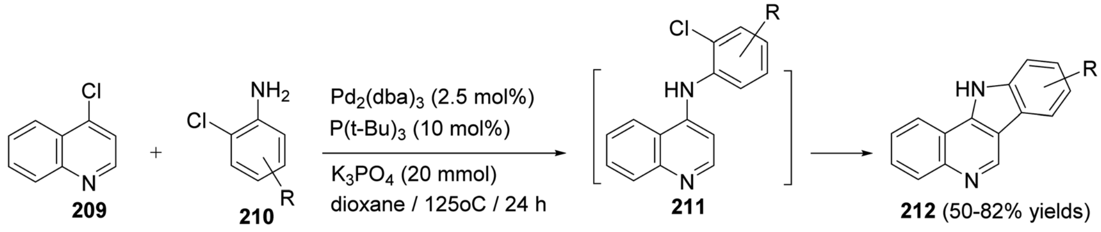


Scheme 64 A plausible reaction mechanism for the formation of **203**.

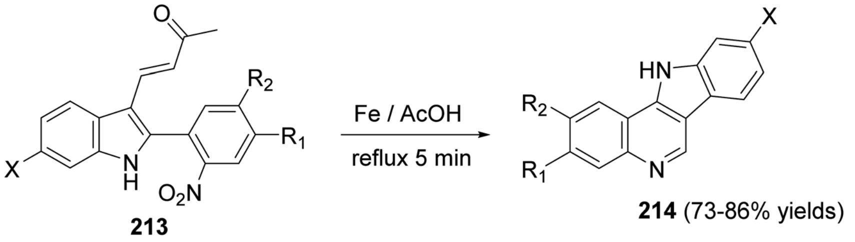
mechanism of the conversion of **195** into **197** involves initial aza-Wittig reaction to afford a carbodiimide **196**, as highly reactive intermediate, which underwent electrocyclic ring closure followed by 1,3-H shift with concomitant addition of the formed exocyclic NH group to the second molecule of the isocyanate. On the other hand, treatment of iminophosphorane **195** with an excess of CO_2 at 90 °C in a sealed vessel or CS_2 in toluene at 90 °C led to the formation of indolo-[3,2-*c*]quinolin-6-one **198a** and indolo[3,2-*c*]quinolin-6-thione **198b** in 83 and 94% yield, respectively (Scheme 62).



Scheme 65 A convenient synthesis of 6-substituted-11-methyl-11*H*-indolo[3,2-*c*]quinolines **205**, **206** and **208**.



Scheme 66 Synthesis of D-ring substituted 11*H*-indolo[3,2-*c*]quinolines **212** *via* auto-tandem Pd-catalyzed intermolecular C–N and intramolecular C–C bond formation.



214	X	R_1	R_2
a	H	H	H
b	H	OMe	H
c	H	OMe	OMe
d	Cl	H	H
e	Cl	OMe	OMe
f	Me	H	H
g	Me	OMe	OMe
h	Me	H	Cl
i	Me	H	Br

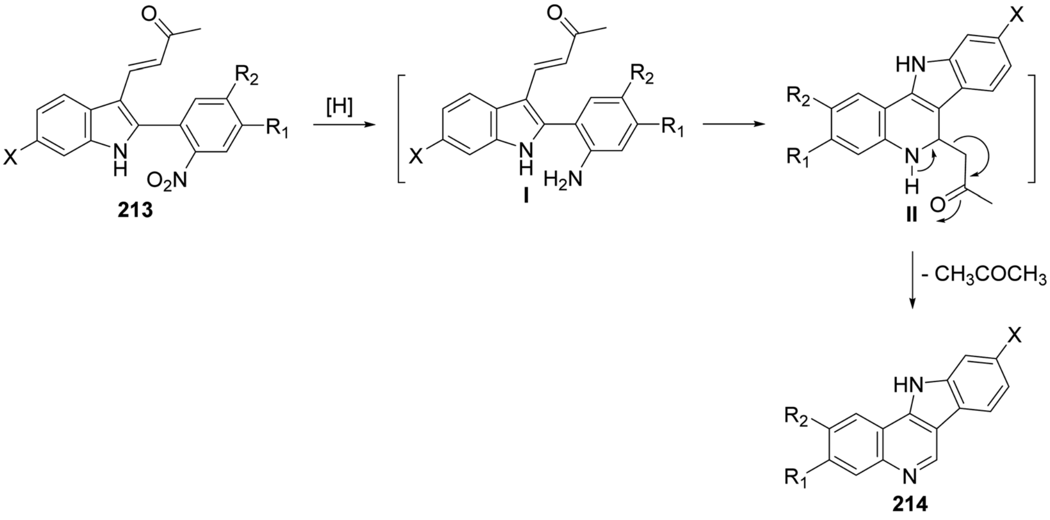
Scheme 67 Reductive cyclization of 2-(2-nitrophenyl)indoles **213** to indolo[3,2-c]quinolines **214**.

A one-pot and highly efficient procedure for the preparation of 6-aryl-11*H*-indolo[3,2-*c*]quinolines **203** *via* Pd-catalyzed carbonylative cyclization of *o*-(*o*-aminophenyl)-ethynyltrifluoro acetanilide **200** with aryl iodides **201** followed by the cyclization of the resultant 3-aroylindoles **202** was described.[91] By reaction of **200** with **201** in the presence of a catalytic amount of $Pd(Ph_3P)_4$ and K_2CO_3 in MeCN at 50 °C for 24 h, under a balloon of carbon monoxide, the corresponding *N*-(2-(3-aroyl-1*H*-indol-2-yl)phenyl)-2,2,2-trifluoro-acetamides **202** were obtained, *in situ*, which underwent basic hydrolysis followed by intramolecular cyclization to give the desired indolo[3,2-*c*]quinolines **203** in 35–86% yields (Scheme 63). A suggested mechanism for the formation of **203** is illustrated in Scheme 64.

A convenient synthetic method for the synthesis of 11*H*-indolo[3,2-*c*]quinolines carrying a different substituents at the 6-position, by electrophile-mediated cyclization reactions of 2-(2-isocyanophenyl)-1-methyl-1*H*-indole (**204**), was reported by Kobayashi and his group[92] in 2005. Treatment of **204** with various aldehydes (or ketones) and acetals in the presence of a catalytic amount of boron trifluoride–diethyl ether (BF_3–OEt_2) in CH_2Cl_2 at 0 °C for 30 min afforded 6-(1-hydroxy)-11-methyl-11*H*-indolo[3,2-*c*]quinolines **205** and 6-(1-ethoxyalkyl)-11-methyl-11*H*-indolo[3,2-*c*]quinolines **206**, respectively, in moderate to good yields (Scheme 65). However, the reaction of **204** with iminium salts **207** was carried out in the absence of catalyst in CH_2Cl_2 at 0 °C for 10 min to give 6-dimethylamino-methyl-11-methyl-11*H*-indolo[3,2-*c*]quinolines **208** in moderate to excellent yields.

Maes and his group[93] have developed the first synthesis of D-ring substituted 11*H*-indolo[3,2-*c*]quinolines **212** *via* auto-tandem Pd-catalyzed intermolecular carbon–nitrogen and intramolecular carbon–carbon bond formation. The reaction was carried out by heating 4-chloroquinoline (**209**) (2 mmol) with a wide variety of *o*-chloroanilines **210** (2.4 mmol) in the presence of $Pd_2(dba)_3$ (2.5 mol%), P(*t*-Bu)$_3$ (10 mol%) and K_3PO_4 (20 mmol) in dioxane at 125 °C for 24 h to give 11*H*-indolo[3,2-*c*]quinolines **212** in 50–82% yields, *via* intermediacy of **211** (Scheme 66). In the present work, the authors also reported that amine **211** is certainly an intermediate since TLC and MS analyses clearly revealed its presence during the process of the reaction and this reaction requires Pd catalysis since omitting the catalyst gave no **211** and **212**.

A simple and new synthesis of indolo[3,2-*c*]quinolines **214** *via* reductive cyclization of a series of 2-(2-nitrophenyl)indoles **213** was reported.[94] Treatment of **213** with Fe in AcOH under reflux for 5 min gave directly 11*H*-indolo[3,2-*c*]quinolines **214**, in one step, in high yields (Scheme 67). In the proposed reaction mechanism, the reduction of NO_2 group gave the corresponding

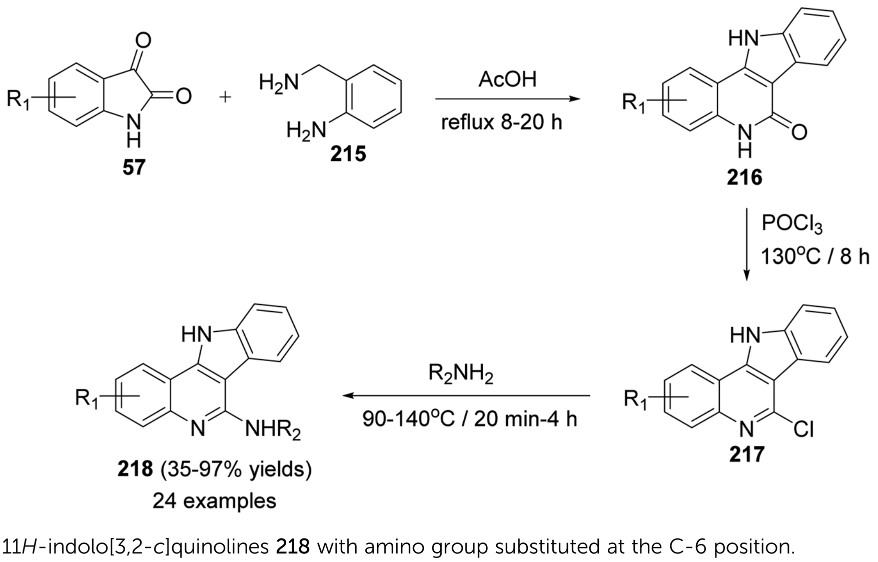


Scheme 68 The proposed mechanism of indolo[3,2-*c*]quinoline **214** formation.

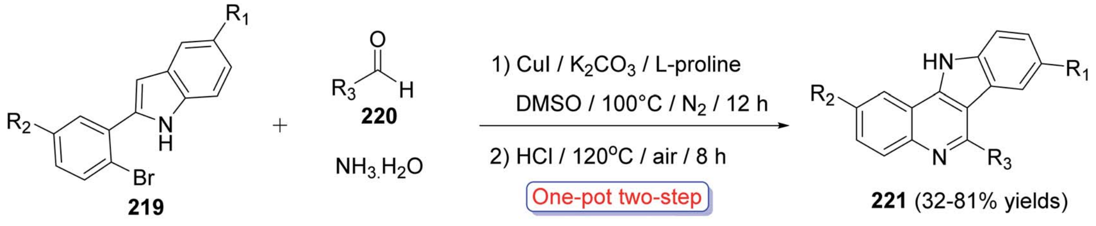
aniline intermediate **I**, which underwent intramolecular Michael addition to afford the intermediate 6-acetonyl-5,6-dihydro-11*H*-indolo[3,2-*c*]quinolines **II**. The aromatization of **II**, *via* elimination of one molecule of acetone, gave the desired indolo-[3,2-*c*]quinolines **214** (Scheme 68). The authors also reported that the reaction has a general character, electron-withdrawing halide substituents as well as electron-donating alkoxy and alkyl groups have no significant effect on the yields of products **214**.

In 2014, Inokuchi *et al.*[95] reported the synthesis of a new series of 6-amino-11*H*-indolo[3,2-*c*]quinolines **218**, with different substituents on the quinoline ring, utilizing isatins **57** and 2-aminobenzylamine (**215**) as starting materials. Thus, the reaction of **57** with **215** in AcOH under reflux for 8–20 h provided the 6-dihydro-11*H*-indolo[3,2-*c*]quinoline-6(5*H*)-ones **216**. Dehydrative chlorination of **216** was accomplished in $POCl_3$ at 130 °C for 8 h to afford the corresponding 6-chloro-11*H*-indolo[3,2-*c*]quinoline **217**. The 6-chloro compounds **217** when heated with the appropriate amines at 90–140 °C within 20 min to 4 h, they underwent the addition–elimination reaction of the anilines and alkyl amines to produce the new 6-amino-11*H*-indolo[3,2-*c*]quinolines **218** in 35–97% yields (Scheme 69).

A convenient and highly selective synthesis of 11*H*-indolo[3,2-*c*]quinolines **221** through Cu-catalyzed one-pot two-step cascade reactions of 2-(2-bromoaryl)-1*H*-indoles **219** with aldehydes **220** and aq. NH_3 was developed by Guo *et al.*[96] in 2015. First, indoles **219** were treated with **220** and aq. NH_3 in the presence of CuI, K_2CO_3, and L-proline under nitrogen at 100 °C for 12 h. Then, the reaction mixture was acidified with HCl and stirred at 120 °C for 8 h under air to provide the required tetracyclic product **221** in modest to good yields (32–81%) (Scheme 70). A mechanism for the Cu-catalyzed formation of **221** is outlined in Scheme 71. For aldehydes **220**, it was found that alkenyl- and aryl-substituted aldehydes usually afforded the



Scheme 69 Synthesis of 11*H*-indolo[3,2-*c*]quinolines **218** with amino group substituted at the C-6 position.

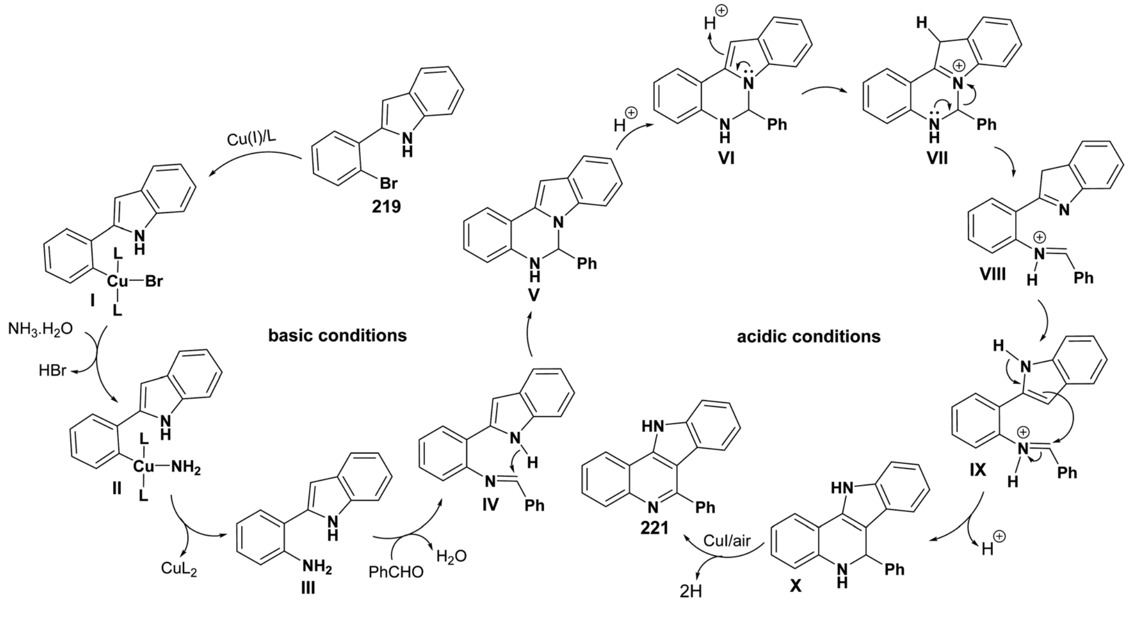


221	R_1	R_2	R_3
a	H	H	Ph
b	H	H	4-Me-C_6H_4
c	H	H	4-OMe-C_6H_4
d	H	H	4-Cl-C_6H_4
e	H	H	1-naphthyl
f	H	H	thienyl
g	H	H	styryl
h	H	H	propyl
i	H	H	H
j	Cl	H	Ph
k	H	OMe	Ph
l	H	OMe	4-Cl-C_6H_4
m	H	Cl	Ph
n	H	Cl	4-OMe-C_6H_4
o	H	Cl	styryl

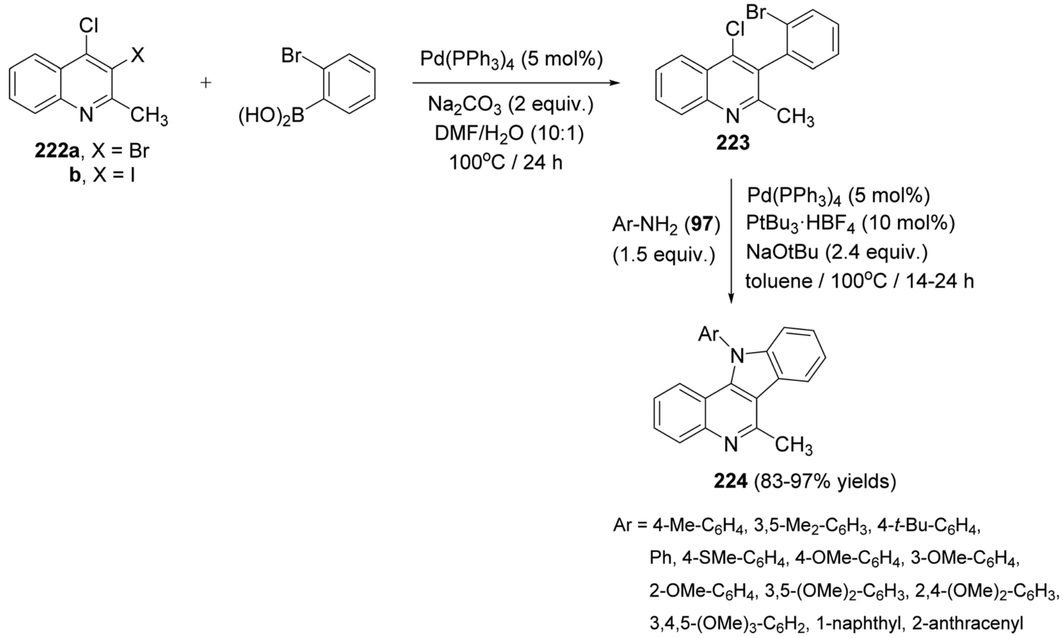
Scheme 70 One-pot two-step synthesis of **221** from **219**, **220** and aq. NH_3.

products **221** in yields higher than alkyl-substituted aldehydes. For indoles **219**, different substituents (R_1 and R_2 group) exhibited a slight influence on the yields of the products **221**.

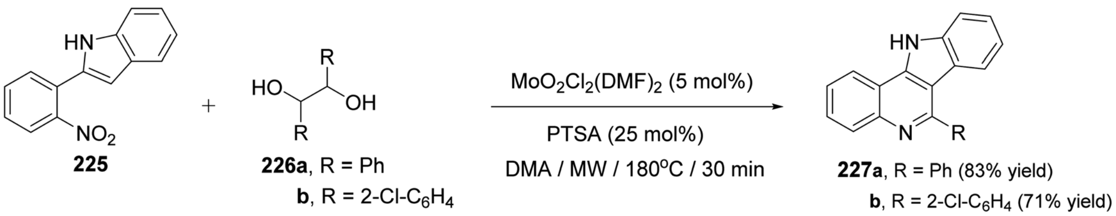
In 2017, Langer *et al.*[97] have developed a new and convenient synthesis of 11-aryl-11*H*-indolo[3,2-*c*]quinolines **224** by chemoselective Suzuki reaction of *o*-dihalo-quinolines with *o*-bromophenylboronic acid, followed by double carbon–nitrogen coupling with primary amines. The chemoselective Suzuki reaction of 3,4-dihalo-2-methylquinolines **222** with *o*-bromophenylboronic acid in the presence of $Pd(PPh_3)_4$ (5 mol%) and Na_2CO_3 (2 equiv.) in DMF/H_2O (10 : 1) at 100 °C for 24 h afforded 3-(2-bromophenyl)-4-chloro-2-methylquinoline (**223**). Heating **223** with various electron-poor, -neutral and -rich arylamines **97** (1.5 equiv.) in the presence of Pd_2dba_3 (5 mol%), $PtBu_3 \cdot HBF_4$ (10 mol%), and



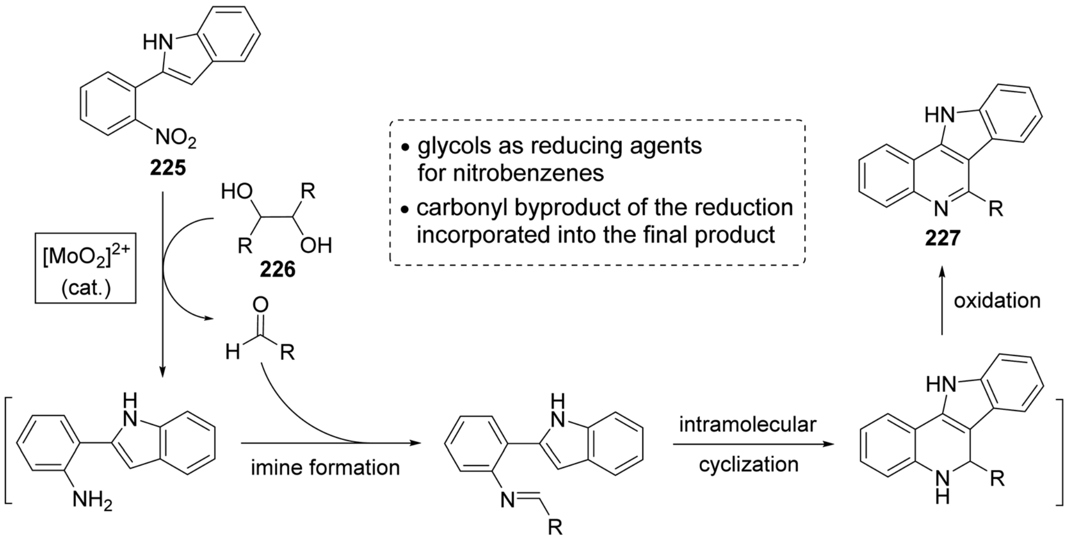
Scheme 71 Plausible mechanism for the formation of **221**.



Scheme 72 A new and convenient synthesis of 11-aryl-11*H*-indolo[3,2-*c*]quinolines **224**.

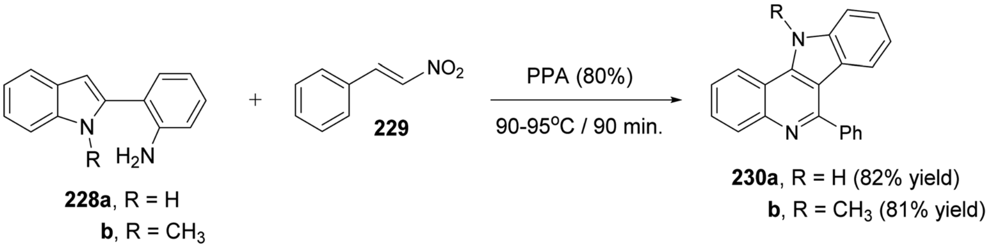


Scheme 73 Synthesis of indolo[3,2-*c*]quinolines **227** from 2-(2-nitrophenyl)indole (**225**).

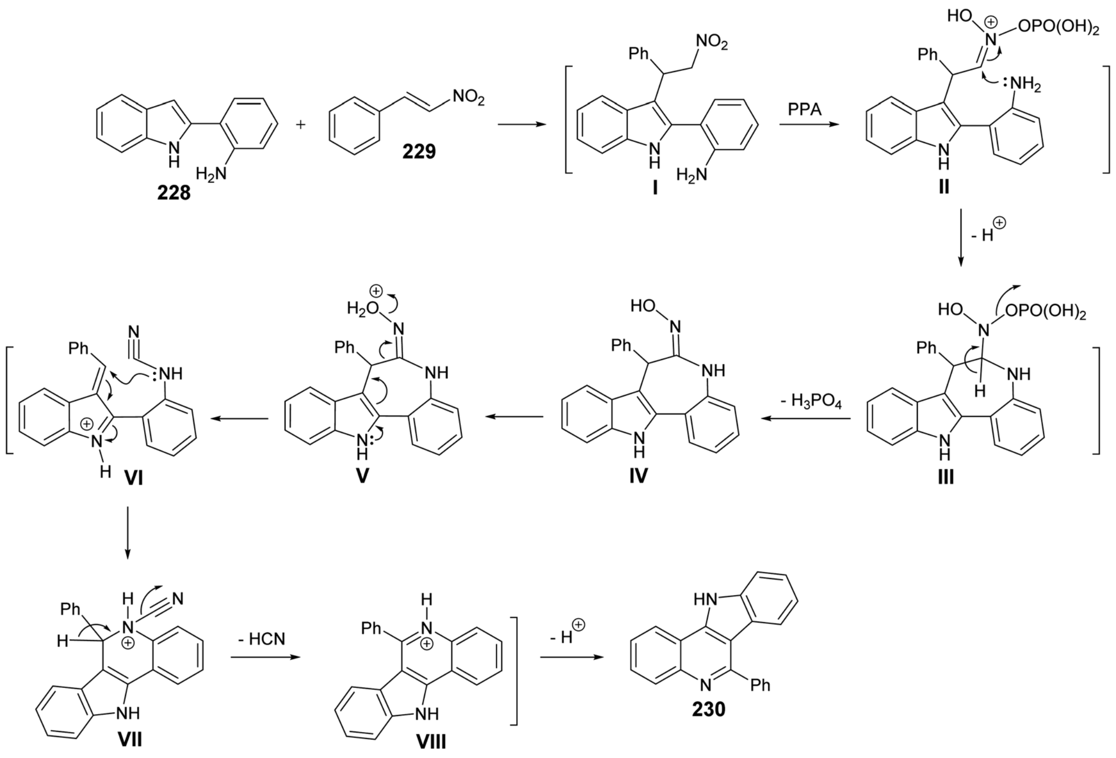


Scheme 74 A plausible mechanism for the formation of **227** from **225** and **226**.

NaO^{t}Bu (2.4 equiv.) in toluene at 100 °C for 14–24 h furnished the novel tetracyclic indolo[3,2-*c*]-quinolines **224** in 83–97% yields (Scheme 72). In this approach, the substituents located at the 11 position are installed directly, thereby avoiding the problem of selectivity in the alkylation of the 11-unsubstituted heterocyclic compounds.



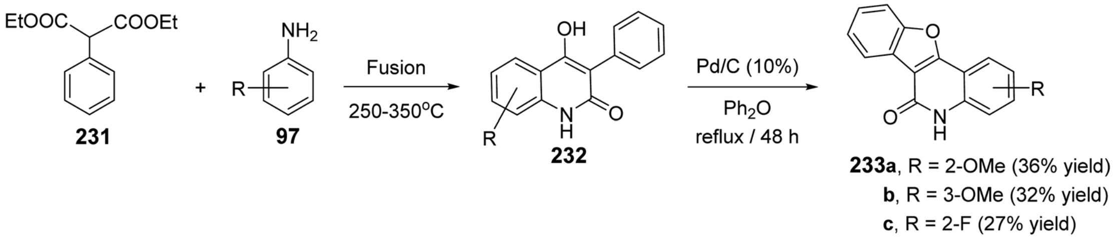
Scheme 75 Synthesis of indolo[3,2-c]quinolines **230** *via* PPA-mediated cyclization reaction between **228** and **229**.



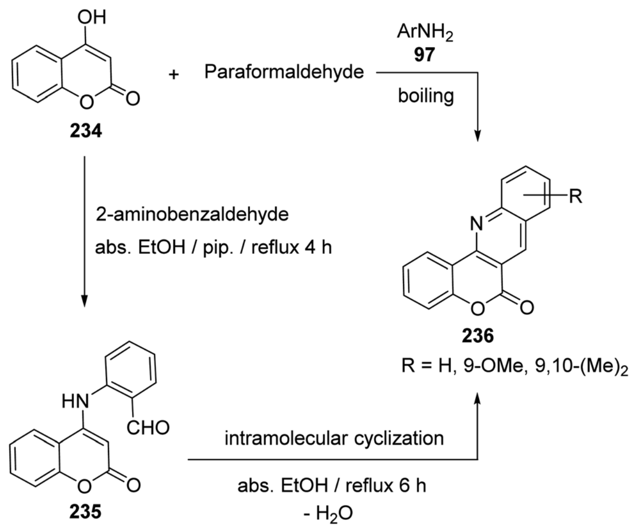
Scheme 76 A plausible mechanism for the formation of **230**.

In the same year, Sanz *et al.*[98] have reported a novel domino nitro reduction, imine formation, intramolecular cyclization, oxidation for the efficient, clean and one-pot synthesis of indolo[3,2-*c*]quinolines **227** from easily available nitrobenzenes as the nitrogen source and glycols as the carbonyl source and reducing agents. The process utilizes the carbonyl byproduct of the initial dioxomolybdenum(VI)-catalyzed reduction of nitrobenzenes with glycols as a reagent for the imine generation. This method represents the first sustainable domino reaction in which the waste byproduct of a reaction has been used as a reactant for the next step and included into the final product. This synthetic method proceeded by treatment 2-(2-nitrophenyl)indole (**225**) (1 equiv.) with secondary glycols **226** (2.2 equiv.) in the presence of a catalytic amount of a dioxomolybdenum(VI) complex and PTSA (25 mol%) in DMA as solvent and under MW irradiation at 180 °C for 30 min to give the new indolo[3,2-*c*]quinolines **227** in high yields (Scheme 73). A suggested mechanism for the synthesis of **227** is outlined in Scheme 74.

Very recently, Aksenov and his coworkers[99] have reported a one-pot synthesis of indolo[3,2-*c*]quinolines **230** *via* PPA-mediated unexpected cyclization reaction between 2-(2-aminophenyl)indoles **228** and 2-nitrostyrene (**229**). The reaction was carried out by heating a mixture of **228** and **229** in PPA (80%) at 90–95 °C for 90 min (Scheme 75). The mechanistic pathway for the formation of **230** *via* cyclization of **228** with **229** is given in Scheme 76. The reaction of **228** with **229** gave the nitroalkane intermediate **I**. In the PPA medium, nitroalkane **I** is exist in the phosphorylated *aci* form **II**, with a highly electrophilic C═N bond, which underwent intramolecular *N*-Nef reaction to provide the corresponding cyclic aminal intermediate **III**. Subsequent elimination of H_3PO_4 afforded cyclic imidoxime intermediate **IV**. The latter **IV** was protonated in acidic medium to give intermediate **V**, which further underwent a seven-membered ring cleavage (Werner rearrangement) to provide *N*-cyano-aniline **VI**. A subsequent *6-endo-trig* cyclization of the resulting **VI** involving the iminium moiety of the indole to yield



Scheme 77 Pd-catalyzed synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-ones **233**.

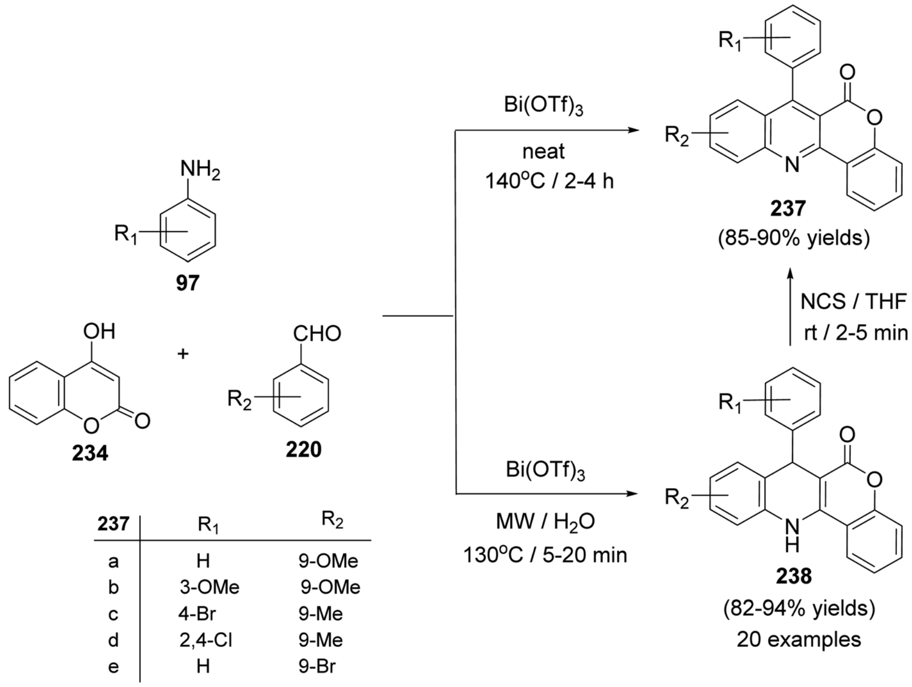


Scheme 78 Synthesis of 6*H*-chromeno[4,3-*b*]quinoline-6-ones **236**.

the indoloquinoline core in the form of *N*-cyano-ammonium **VII**. The elimination of HCN afforded 5*H*-indolo[3,2-*c*]quinolin-11-ium ion **VIII**, which underwent deprotonation, under basic conditions during the post-reaction work-up, to afford the desired tetracyclic indolo[3,2-*c*]quinolines **230**.

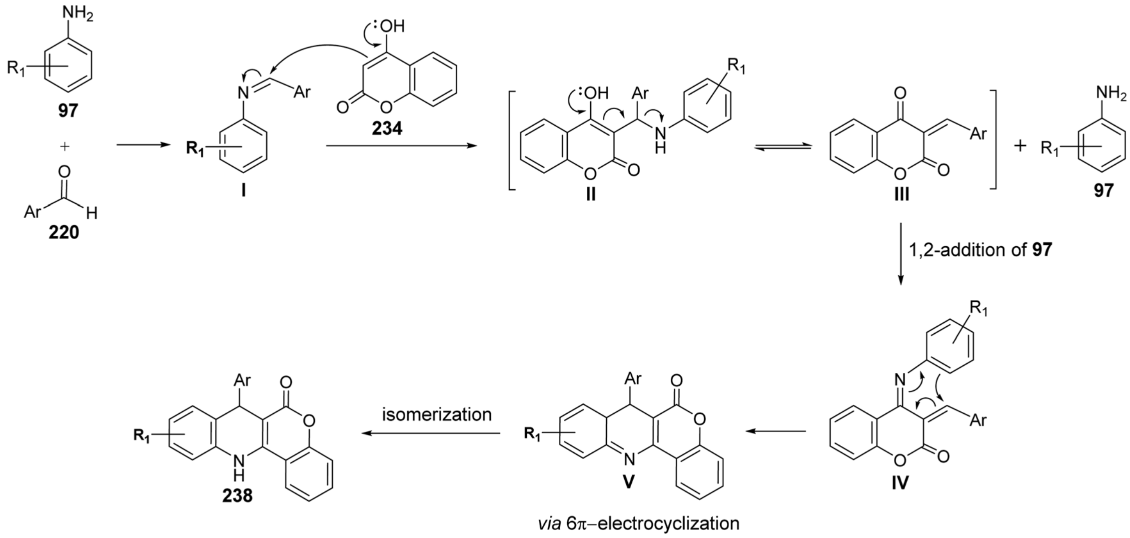
2.2.3. Benzofuro[3,2-*c*]quinolines. The synthesis of certain benzofuro[3,2-*c*]quinolin-6(5*H*)-ones **233** *via* Pd-catalyzed cyclodehydrogenation of 4-hydroxy-3-phenyl-quinolin-2(1*H*)-ones **232** was reported.[89] Fusion of diethyl 2-phenylmalonate (**231**) with anilines **97** at 250–350 °C leading to the formation of **232.** Refluxing **232** in diphenyl ether in the presence of a catalytic amount of Pd/C (10%) gave the respective tetracyclic products **233**, in low yields (27–36%) (Scheme 77).

2.2.4. Chromenoquinolines. Buu-Hoi *et al.*[100] have reported the first synthesis of 6*H*-chromeno[4,3-*b*]quinoline-6-ones **236,** which are analogues of the carcinogenic dibenzacridines and benzacridines, *via* reaction of 4-hydroxycoumarin (**234**) with paraformaldehyde and primary arylamines **97** (Scheme 78). The novel synthesis of this ring system has developed by Tabaković

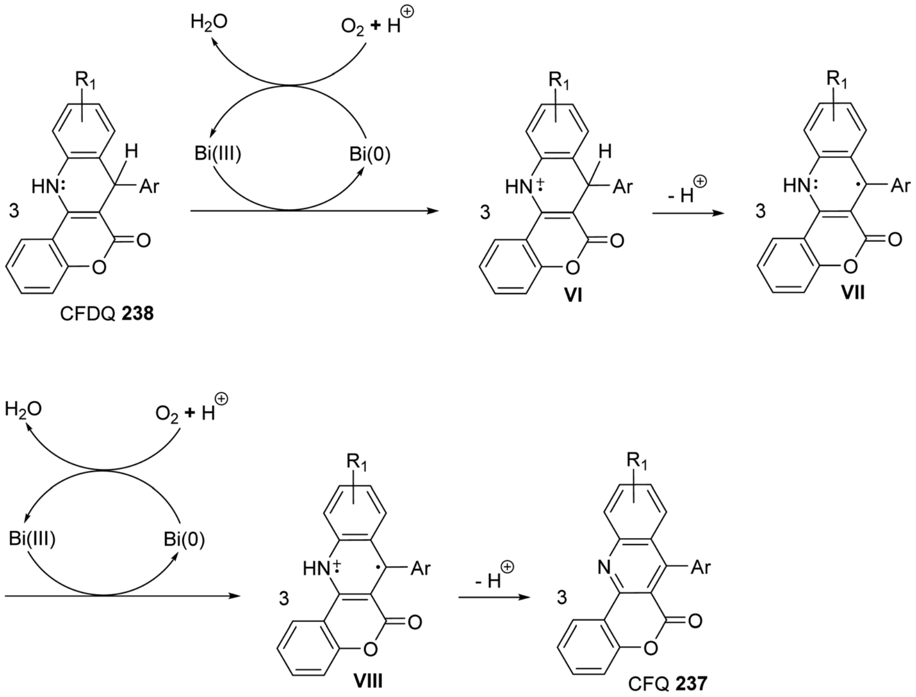


237	R1	R2
a	H	9-OMe
b	3-OMe	9-OMe
c	4-Br	9-Me
d	2,4-Cl	9-Me
e	H	9-Br

Scheme 79 Synthesis of CFQ **237** and CFDQ **238**.



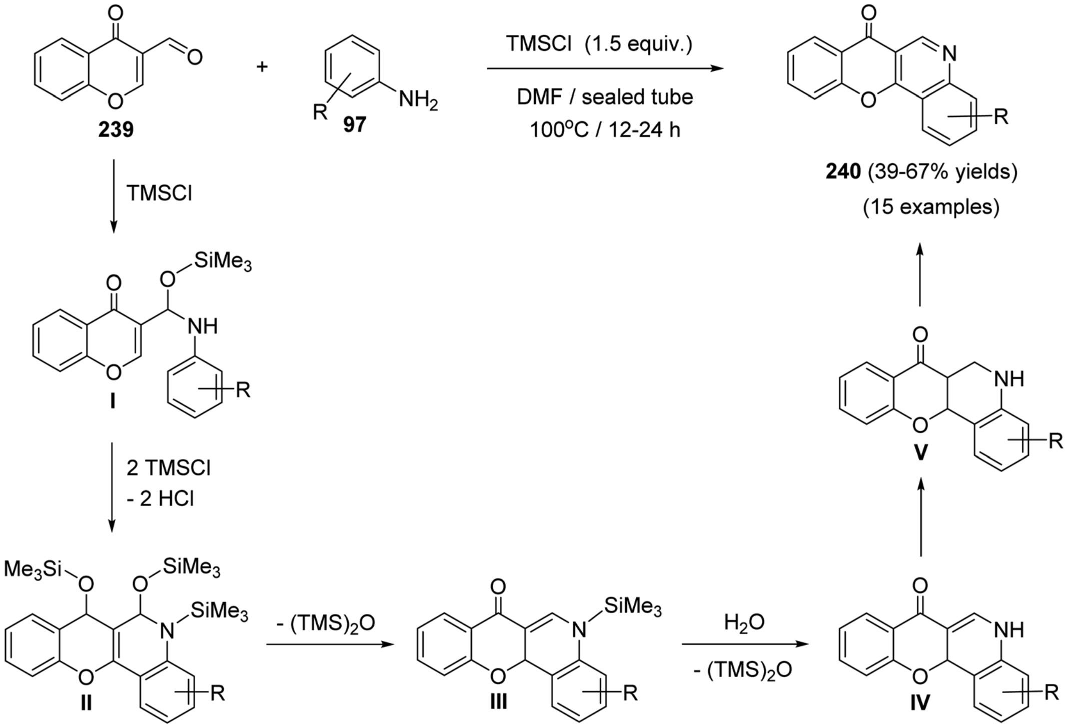
Scheme 80 Possible mechanism for the formation CFDQ **238**.



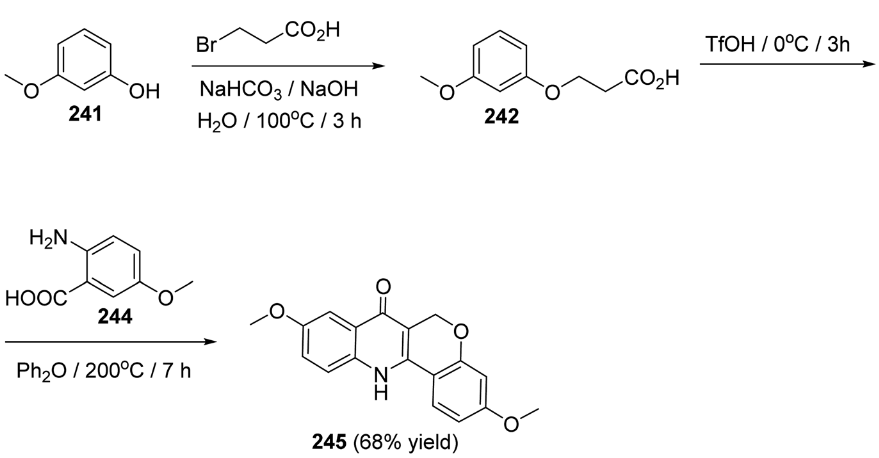
Scheme 81 Plausible mechanism for the formation CFQ **237** from CFDQ **238**.

et al.[101] The reaction was carried by refluxing a 1 : 1 molar ratio of **234** with 2-aminobenzaldehyde in abs. EtOH in the presence of a catalytic amount of piperidine to give 2-((2-oxo-2*H*-chromen-4-yl)amino)benzaldehyde (**235**), which was converted to the tetracyclic products **236** (after refluxing 6 h) by losing a molecule of H_2O *via* formation of intramolecular Schiff base (Scheme 78).

A facile one-pot, three-component reaction of 4-hydroxycoumarin (**234**), aromatic amines **97** and aromatic aldehydes **220** using an environmentally benign bismuthtriflate $Bi(OTf)_3$ as a catalyst under neat and conventional heating conditions at 140 °C produced the coumarin fused quinoline (CFQ), namely 7-aryl-6*H*-chromeno[4,3-*b*]quinoline-6-ones **237**, in 85–90% yields (Scheme 79). On the other hand, microwave (MW) assisted multicomponent reactions of the same combination in the presence of $Bi(OTf)_3$ as a catalyst in H_2O at 130 °C gave coumarin fused dihydroquinolines (CFDQ) **238**, in 82–94% yields (Scheme 79).[102] Authors also reported an alternative and rapid route for the synthesis of CFQ **237** by stirring CFDQ **238** in the presence of *N*-bromosuccinamide (NBS) in THF at room temperature (Scheme 79). The plausible mechanism for the formation of CFDQ **238** is described in Scheme 80. Initially,



Scheme 82 TMSCl-mediated synthesis of **240** from **239**.

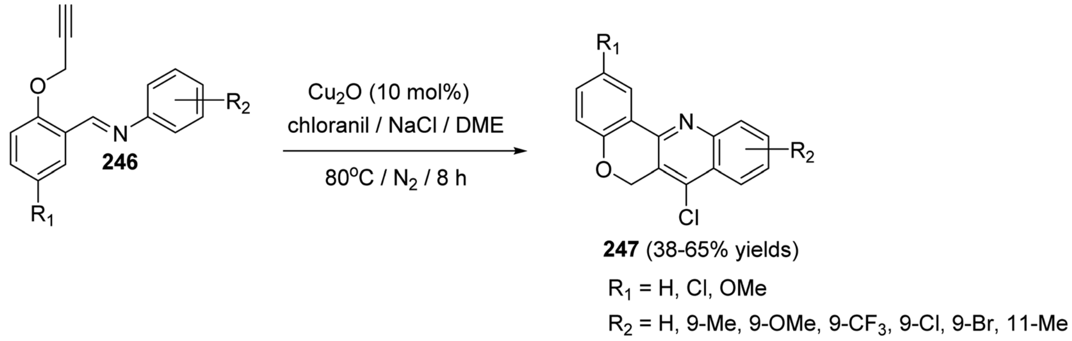


Scheme 83 Three steps synthesis of 3,9-dimethoxy-6,12-dihydro-6*H*-chromeno[4,3-*b*]-quinoline-7-one (**245**).

aldehyde **220** condensed with aromatic amine **97** to form an imine **I.** Nucleophilic addition of **234** to intermediate **I** afforded an unstable intermediate **II**, which in equilibrium with intermediate **III.** Subsequent, 1,2-addition of the aromatic amines **97** to **III**, followed by 6π-electrocyclization and isomerisation yielded products (CFDQ) **238**. The formation of **237** can be explained *via* the formation of **238**, followed by free radical mechanism involving Bi(III)/Bi(0) as outlined in Scheme 81. The fluorescence property studies of the synthesized CFDQ **238** and CFQ **237** in different solvents showed that CFDQ **238** are more fluorescent than the CFQ **237**.

Plaskon *et al.*[103] have described a versatile and facile method for the synthesis of 7*H*-chromeno[3,2-*c*]quinolin-7-ones **240** utilizing chlorotrimethylsilane (TMSCl) as a potential promoter and water scavenger. On heating a solution of 4-oxo-4*H*-chromene-3-carbaldehyde (**239**) and anilines **97** in the presence of TMSCl in DMF at 100 °C, the tetracyclic products **240** were obtained in 39–67% yields (Scheme 82).

The synthesis of 3,9-dimethoxy-6,12-dihydro-6*H*-chromeno[4,3-*b*]quinoline-7-one (**245**), as a new class of estrogen receptor β-selective ligands, was achieved in three steps as shown in Scheme 83. Reactions were carried out by heating 3-methoxyphenol (**241**) with 3-bromo-propanoic acid under basic

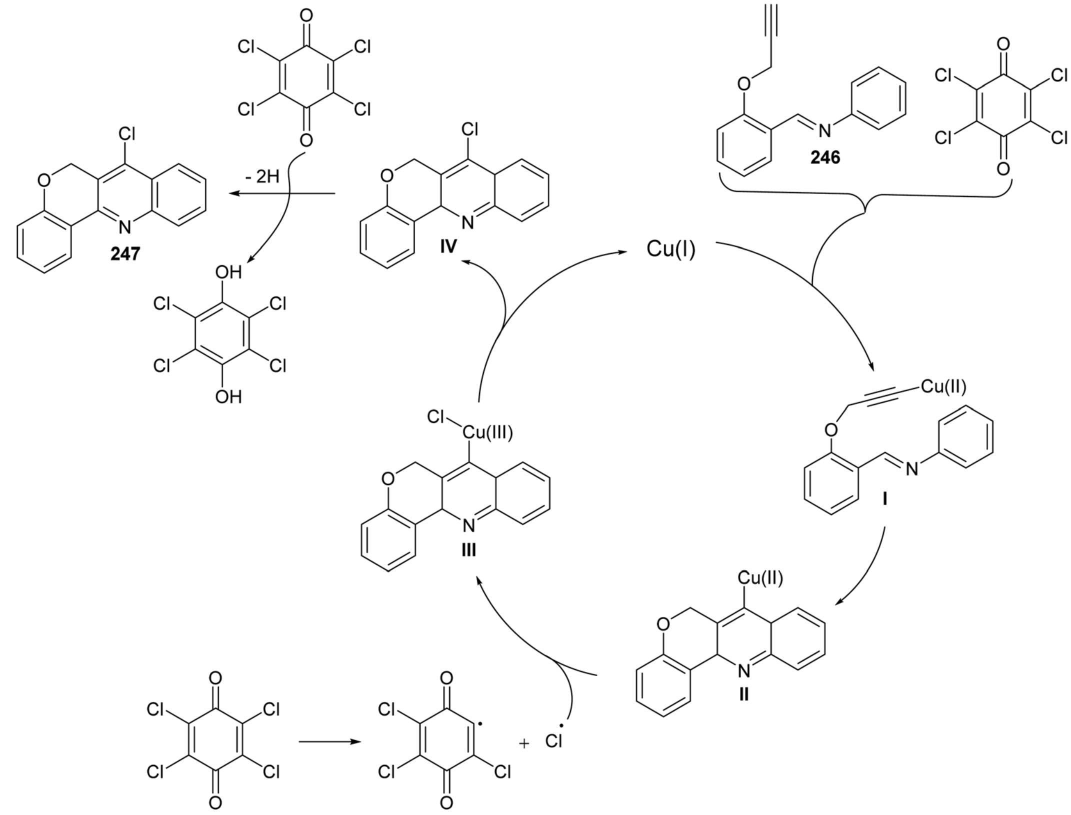


Scheme 84 Synthesis of 7-halogenated-6*H*-chromeno[4,3-*b*]quinolines **247** *via* Cu-catalyzed cascade reaction.

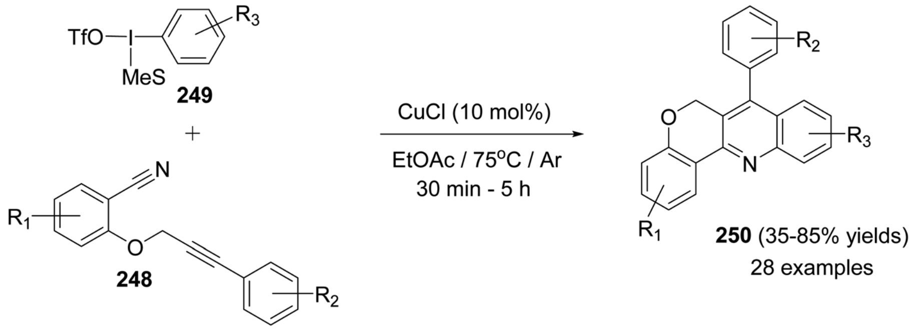
conditions at 100 °C for 3 h to give the corresponding 3-(3-methoxyphenoxy)propanoic acid (**242**), which underwent intramolecular Friedel–Crafts acylation when treated with TfOH at 0 °C for 3 h to provide 7-methoxychroman-4-one (**243**). By condensation of **243** with 5-methoxyanthranilic acid (**244**) in diphenyl ether at 200 °C for 7 h, the desired tetracyclic product **245** was formed in 68% yield (Scheme 83).[104]

In 2016, Bao *et al.*[105] have developed a new, efficient and convenient halogenation method to synthesize 7-halogenated chromeno[4,3-*b*]quinolines **247** through Cu-catalyzed cascade reactions (intramolecular aza-Diels–Alder reaction of Schiff base, followed by chlorination utilizing chloranil) (Scheme 84). The reaction was carried out by treatment Schiff base **246** (1 equiv.) with a mixture of Cu_2O (10 mol%), *p*-chloranil (*p*-CHL) (2 equiv.), and NaCl (1.5 equiv.), as an additive, in dimethoxyethane (DME). The mixture was heated at 80 °C under a nitrogen atmosphere for 8 h to give the new tetracyclic product **247** in satisfactory yields (38–65%) (Scheme 84). In the proposed reaction mechanism, the reaction of Schiff base substrate **246** with a Cu(I) species in the presence of chloranil produced Cu(II) acetylide **I**, which undergoes intramolecular aza-Diels–Alder reaction to give intermediate **II**. The Cl radical originated from *p*-CHL reacts with intermediate **II** to afford intermediate **III**, which subsequently undergoes reductive elimination reaction to give a chlorinated intermediate **IV** and Cu(I) species. Oxidation of intermediate **IV** with *p*-CHL occurs to provide the desired tetracyclic product **247** (Scheme 85).

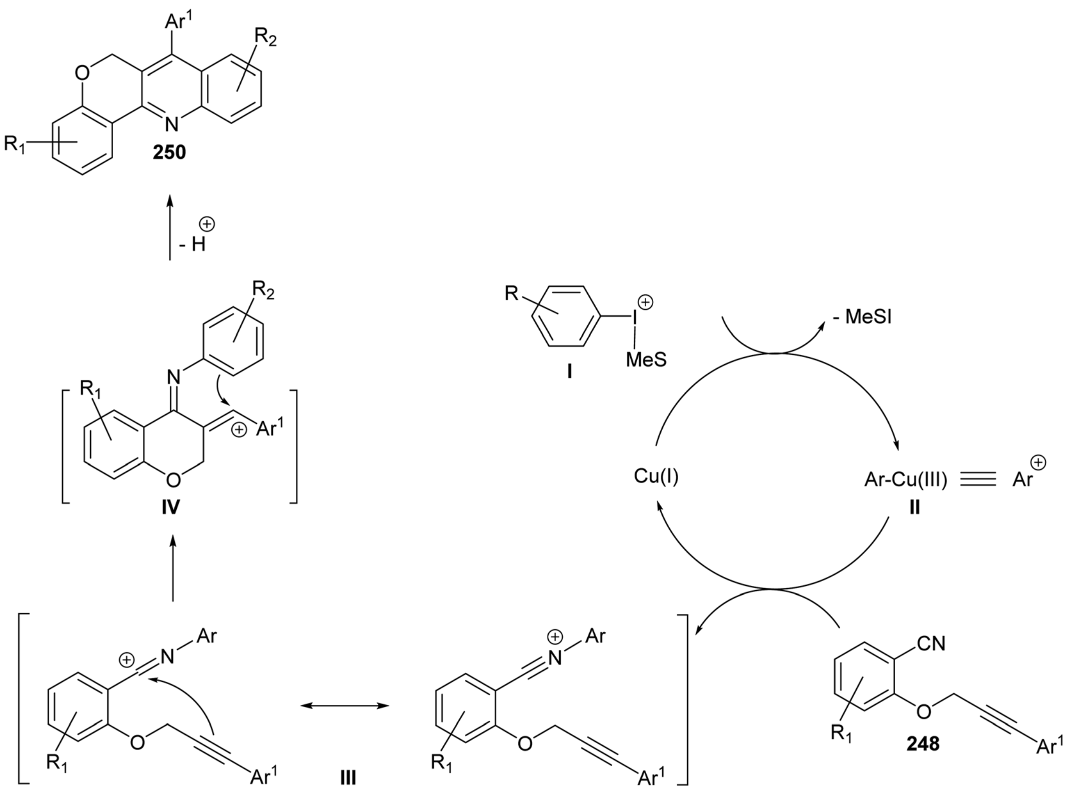
In the same year, Novák and his group[106] reported the development of a novel and highly modular Cu-catalyzed oxidative transformation for the construction of chromeno-



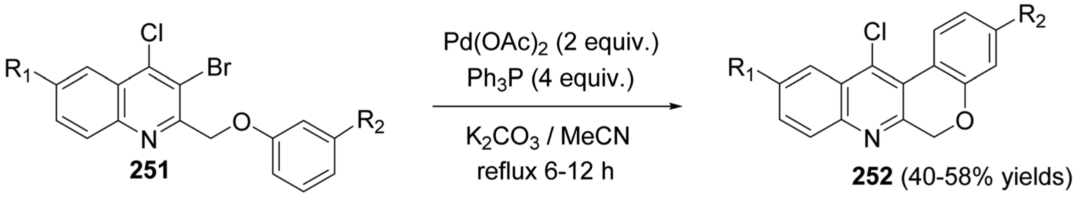
Scheme 85 A suggested mechanism for the formation of **247** from **246**.



Scheme 86 Highly modular synthesis of chromeno[4,3-*b*]quinolines **250** *via* arylation-ring closure.

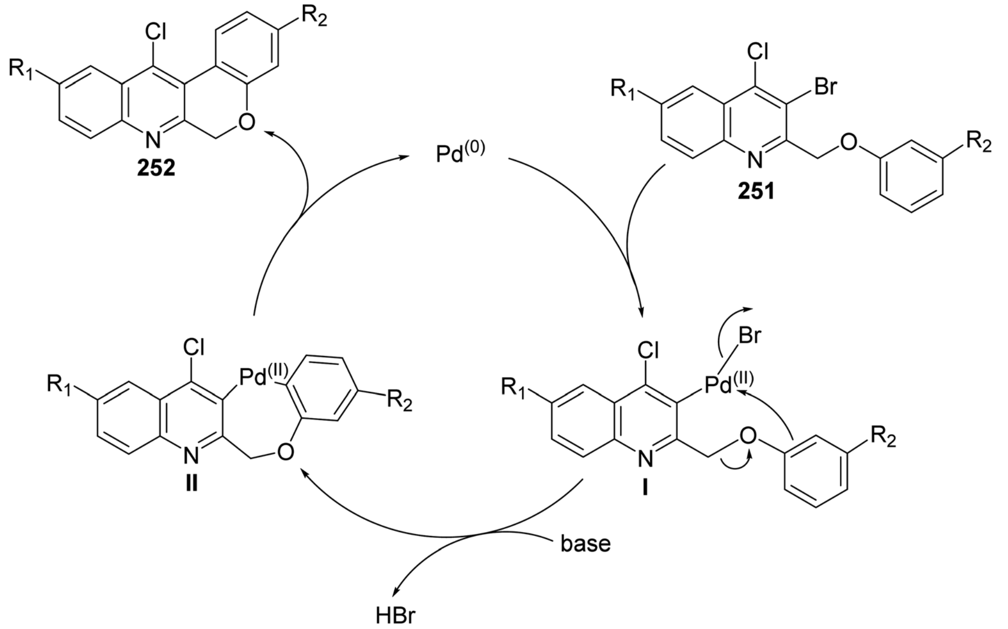


Scheme 87 A plausible mechanism for the formation of chromeno[4,3-*b*]quinolines **250** *via* arylation–cyclization reaction.



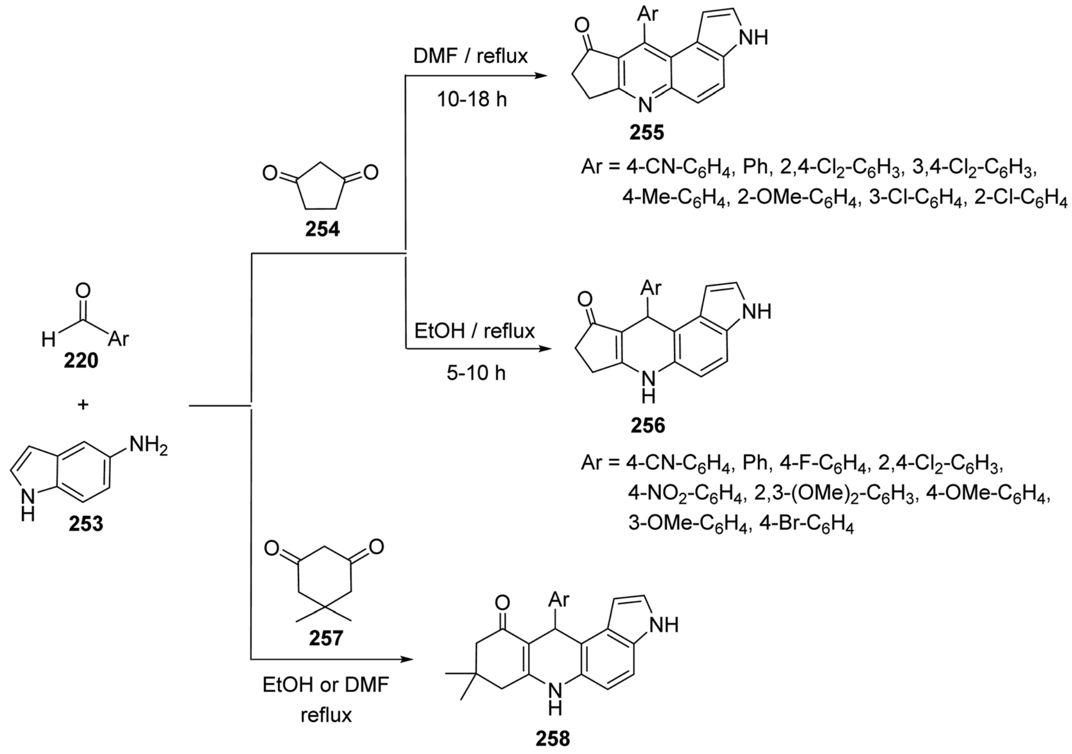
252	R_1	R_2
a	H	H
b	H	Me
c	H	OMe
d	OMe	H
e	OMe	Me
f	OMe	OMe

Scheme 88 Cyclization of 2-[(3-substituted-phenoxy)methyl]quinolines **251** to chromeno-[3,4-*b*]quinolines **252**.



Scheme 89 Proposed mechanism for the formation of tetracyclic **252** from **251**.

[4,3-*b*]quinolines **250**, starting from arylpropynyloxybenzonitriles **248** and arylmesityl-iodonium triflates **249**. Reaction of nitriles **248** with **249** in EtOAc in the presence of a catalytic amount of CuCl (10 mol%) at 75 °C for 30 min – 5 h afforded the polyfunctionally substituted chromeno[4,3-*b*]quinolines **250** in 35–85% yields (Scheme 86). A plausible mechanism was proposed (Scheme 87).

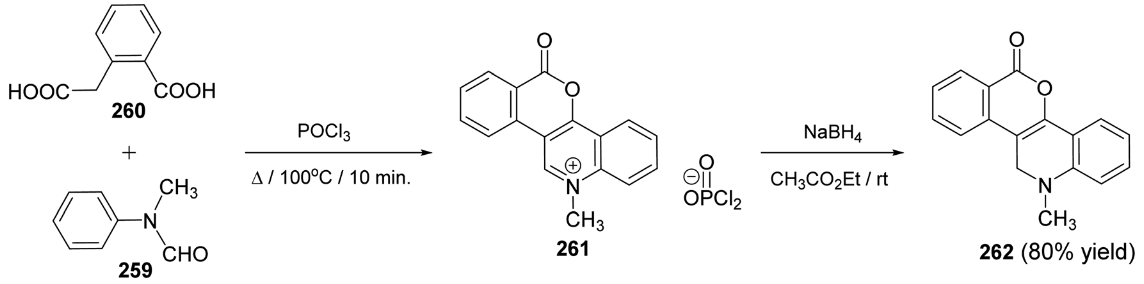


Ar = 4-CN-C_6H_4, Ph, 2,4-Cl_2-C_6H_3, 3,4-Cl_2-C_6H_3, 4-Me-C_6H_4, 2-OMe-C_6H_4, 3-Cl-C_6H_4, 2-Cl-C_6H_4

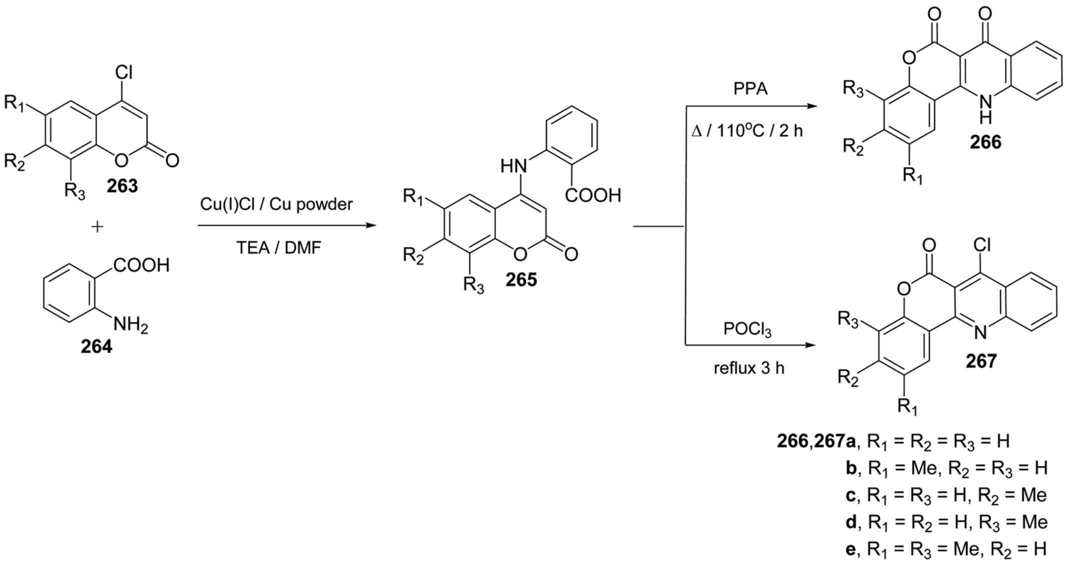
Ar = 4-CN-C_6H_4, Ph, 4-F-C_6H_4, 2,4-Cl_2-C_6H_3, 4-NO_2-C_6H_4, 2,3-$(OMe)_2$-C_6H_3, 4-OMe-C_6H_4, 3-OMe-C_6H_4, 4-Br-C_6H_4

Ar = 4-Br-C_6H_4, 3-OMe-C_6H_4, 3,4-Cl_2-C_6H_3, 4-Me-C_6H_4, 2-OMe-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 3,4-Me_2-C_6H_3, 3,4-$(OMe)_2$-C_6H_3, 2-F-C_6H_4

Scheme 90 One-pot synthesis of cyclopenta[*b*]pyrrolo[3,2-*f*]quinolins **255** and pyrrolo-[3,2-*a*]acridines **258** under catalyst-free conditions.



Scheme 91 Synthesis of benzopyrano[4,3-*c*]quinoline (**262**) from *N*-methylformanilide (**259**) and homophthalic acid (**260**).



Scheme 92 Synthesis of benzopyrano[4,3-*b*]quinoline derivatives **266** and **267**.

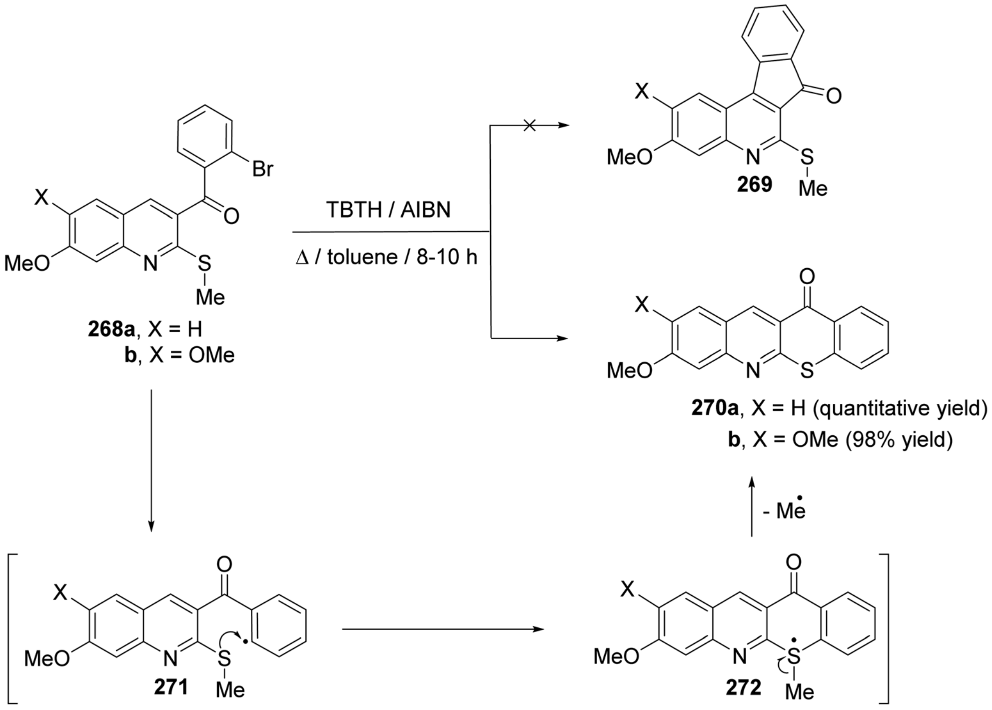
Morris and Jackson[107] reported the Pd-catalyzed intramolecular cyclization of 2-[(3-substituted-phenoxy)methyl] quinolines **251** to prepare chromeno[3,4-*b*]quinolines **252**. The cyclization was carried out, under typical Heck conditions, by refluxing a mixture of appropriate quinoline **251** (1 equiv.), $Pd(OAc)_2$ (2 equiv.), triphenylphosphine (4 equiv.) and K_2CO_3 (20 equiv.) in CH_3CN for 6–12 h under an atmosphere of nitrogen (Scheme 88). It was found that compound **251** containing a strong electron-withdrawing groups on the phenoxy ring retarded the cyclization and no products were obtained after heating at reflux for a long time, while electron-donating groups increased the rate of the reaction and produced the desired products **252** in reasonable yields (40–58% yields). A proposed mechanism for the formation of tetracyclic chromeno [3,4-*b*]quinolines **252** from **251** is shown in Scheme 89.

2.2.5. Cyclopenta[*b*]pyrrolo[3,2-*f*]quinolines.

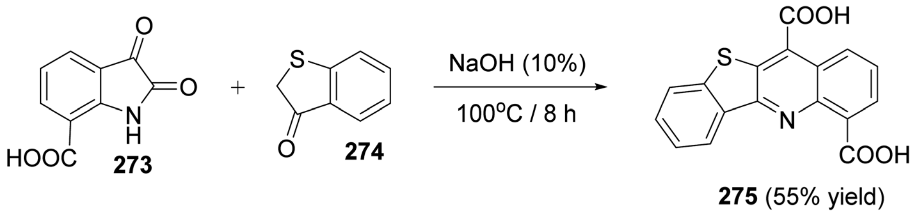
A combinatorial synthesis of fused heterocyclic compounds, cyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-ones **255**, 10-aryl-6,7,8,10-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-ones **256** and 8,9-dihydro-8,8-dimethyl-11-aryl-3*H*-pyrrolo[3,2-*a*]acridin 10(6*H*,7*H*,11*H*)-ones **258**, *via* three-component reaction of 1*H*-indol-5-amine (**253**), aromatic aldehydes **220** and 1,3-dicarbonyl compounds **254**, **257**, under catalyst-free conditions, has been reported by Zhou *et al.* in 2013.[108] It was interesting that the designed reactions gave un-aromatized or aromatized products depending on the reaction temperature and the type of 1,3-dicarbonyl compounds. Treatment of aromatic aldehydes **220**, 1*H*-indol-5-amine (**253**), and cyclopentane-1,3-dione **254** in refluxing DMF, without catalyst, resulted in the aromatized cyclopenta[*b*] pyrrolo[3,2-*f*]quinolin-9(3*H*)-ones **255**, in high yields (83–92%). When the same reaction was carried out in refluxing EtOH, without catalysts, the un-aromatized 10-aryl-6,7,8,10-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-ones **256** were obtained in 84–96% yields (Scheme 90). On the other hand, when 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**257**) was subjected to react with **220** and **253**, under catalyst-free conditions, the un-aromatized 11-aryl-8,9-dihydro-8,8-dimethyl-3*H*-pyrrolo[3,2-*a*]acridin-10(6*H*,7*H*,11*H*)-ones **258** were obtained, whether they were refluxed in DMF or EtOH (Scheme 90).

2.2.6. Benzopyranoquinolines.

Meth-Cohn[109] has developed an approach for the synthesis of 12-methyl-6-oxo-11,12-dihydro-6*H*-[2]benzopyrano[4,3-*c*]quinoline (**262**), in high yield. The reaction was accomplished by heating a mixture of *N*-methylformanilide (**259**) and homophthalic acid (**260**) in $POCl_3$ at 100 °C for 10 min to give 12-methyl-6-oxo-6*H*-[2]benzopyrano [4,3-*c*]quinolinium phosphorodichloridate (**261**). The salt **261**



Scheme 93 A regioselective synthesis of new benzothiopyrano[2,3-*b*]quinolines **270**.



Scheme 94 A one-pot synthesis of benzothieno[3,2-*b*]quinoline-4,11-dicarboxylic acid (**275**).

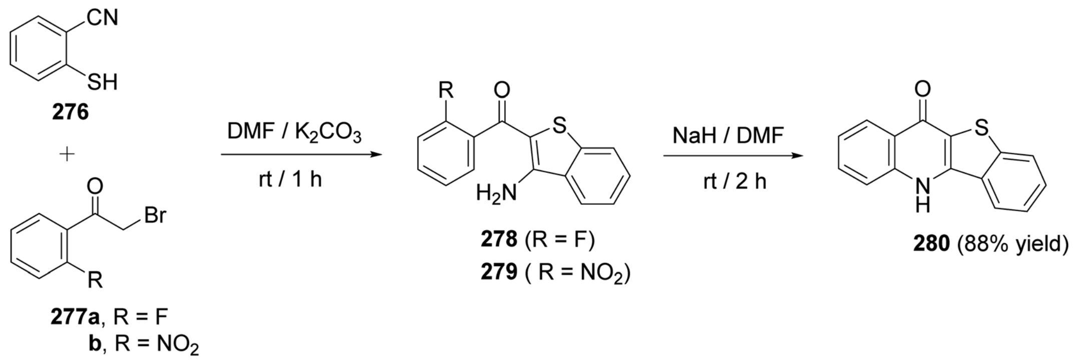
showed kinetic presence for attack at the quinoline α-position. Thus, reduction of **261** with sodium borohydride in ethyl acetate at room temperature produced the desired benzopyranoquinoline **262** Scheme 91).

Ullmann Jordan condensation reaction of 4-chlorocoumarins **263** with anthranilic acid (**264**) afforded 4-(2′-carboxyphenylamino)-2*H*-[1]benzopyran-2-ones **265**. When compounds **265** were heated with polyphosphoric acid (PPA) at 110 °C for 2 h, they underwent intramolecular cyclocondensation to furnish directly the tetracyclic ring system namely 7,12-dihydro-6*H*-[1]benzopyrano[4,3-*b*]quinoline-6,7-diones **266** in ~90% yields (Scheme 92). On the other hand, refluxing **265** with phosphoryl chloride ($POCl_3$) for 3 h afforded 7-chloro-benzo-pyrano[4,3-*b*]quinoline-6-ones **267** in ~80% yields (Scheme 92).[110]

2.2.7. **Benzothiopyranoquinolines.** In 2003, Junjappa and his coworkers[111] have reported a simple and highly efficient regioselective synthesis of new benzothiopyrano[2,3-*b*]quinolines **270** through TBTH/AIBN-mediated radical cyclization of the corresponding 3-(2-bromobenzoyl)-2-methylthioquinoline derivatives **268a, b**. As shown in Scheme 93, the reaction proceeded by heating a solution of **268a, b** (1 equiv.), TBTH (2.5 equiv.) and AIBN (catalytic) in toluene for 8–10 h under nitrogen atmosphere. The products were found to be not the tetracyclic quinolines **269**, but were characterized as the novel benzothiopyrano[2,3-*b*]quinolines **270a, b** on the basis of their spectral and analytical data. The proposed mechanistic pathway for radical cyclization of **268a, b** is outlined in Scheme 93. The initially formed *o*-benzoyl radical **271** undergoes radical translocation by attack on the methylthio group (MeS–) to afford radical intermediate **272**, which on loss of the methyl radical gives the benzothiopyranoquinolines **270a** and **270b** in quantitative and 98% yield, respectively.

2.2.8. **Benzothienoquinolines.** Deady *et al.*[112] reported a one-pot, two-component synthesis of benzothieno[3,2-*b*]quinoline-4,11-dicarboxylic acid (**275**), as a new class of putative topoisomerase inhibitors, by the reaction of isatin-7-carboxylic acid (**273**) and benzo[*b*]thiophen-3(2*H*)-one (**274**). The reaction takes place at 100 °C for 8 h using NaOH (10%) as a base delivering the benzo-thieno[3,2-*b*]quinolines **275** in 55% yield (Scheme 94).

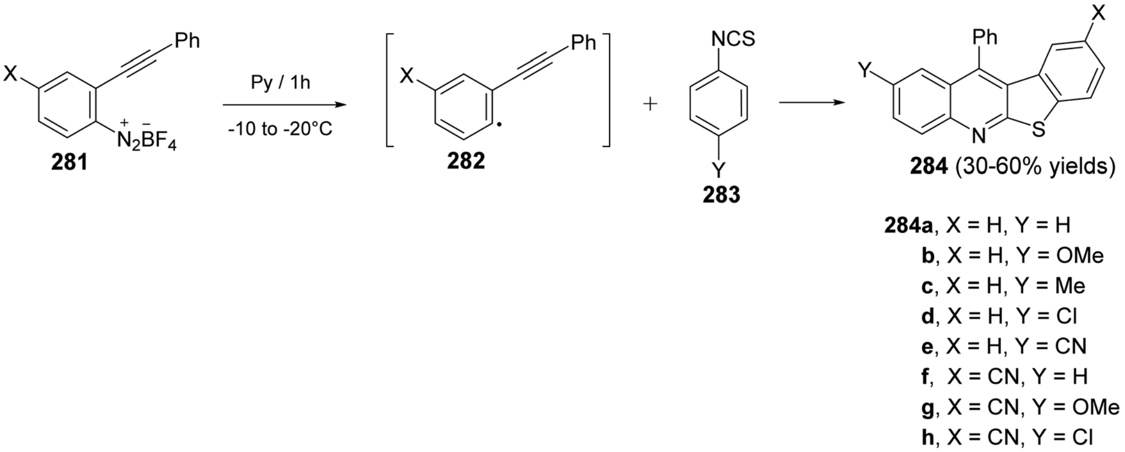
In 2000, Rádl *et al.*[113] developed a new procedure for the synthesis of benzothieno-[3,2-*b*]quinoline-11(5*H*)-one (**280**) in



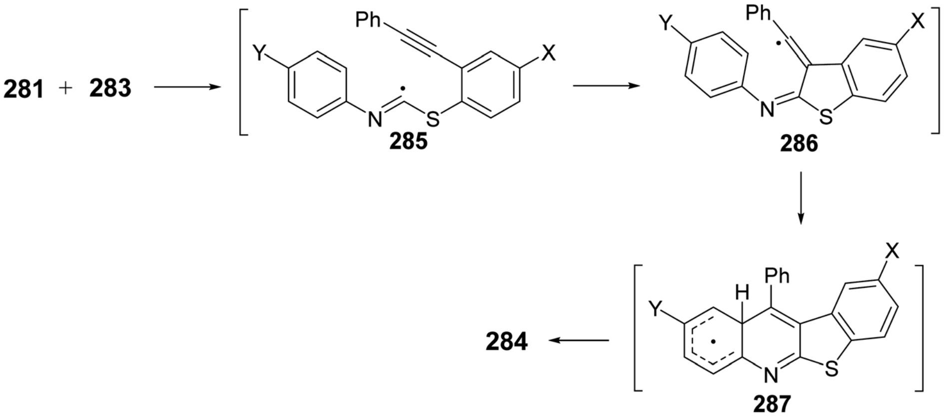
Scheme 95 A new method for the synthesis of benzothieno[3,2-*b*]quinoline-11(5*H*)-one (**280**).

88% yield, as shown in Scheme 95. Treatment of 2-mercaptobenzonitrile **276** with phenacylbromides **277a, b** in DMF in the presence of K_2CO_3 at room temperature for 1 h gave the corresponding benzothiophenes **278, 279.** When these compounds were stirred with NaH in DMF at room temperature for 2 h, they underwent intramolecular nucleophilic cyclization to provide the desired tetracyclic **280** (Scheme 95).

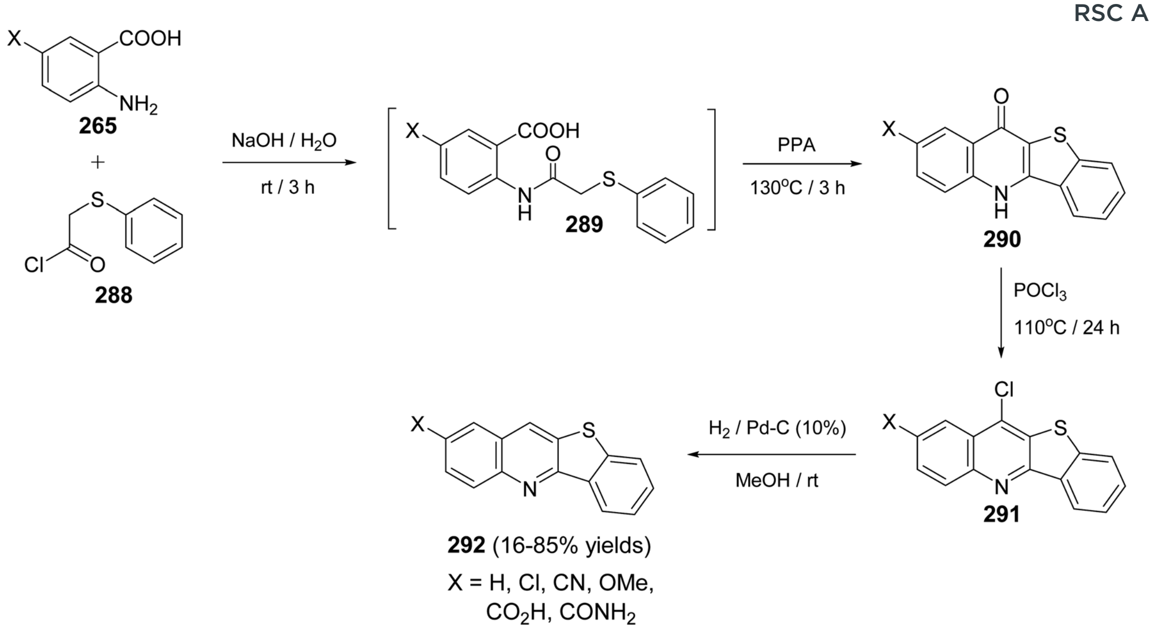
In the same year, Zanardi *et al.*[114] have devised a novel protocol for the one-pot construction of benzothieno[2,3-*b*] quinolines **284** based on a radical cascade reaction of the 2-(phenylalkynyl)aryl radicals **282** with some aryl isothiocyanates **283.** The aryl radicals **282** were easily generated upon portionwise addition of the diazonium tetrafluoroborate **281** (1 equiv.) to a stirred pyridine solution of **283** (3 equiv.) at −10 to −20 °C. After one hour, the reaction mixture was normally subjected to



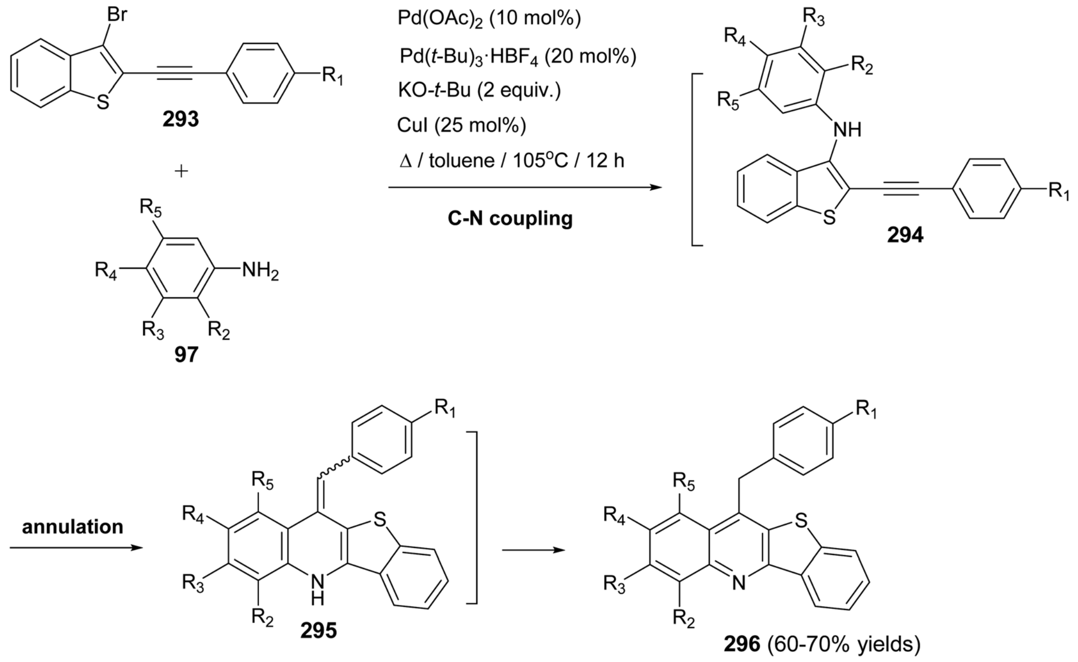
Scheme 96 Synthesis of benzothieno[2,3-*b*]quinolines **284** *via* reaction of 2-ethynylaryl radicals **282** with aryl isothiocyanates **283**.



Scheme 97 Reaction mechanism for the formation of benzothieno[2,3-*b*]quinolines **284**.

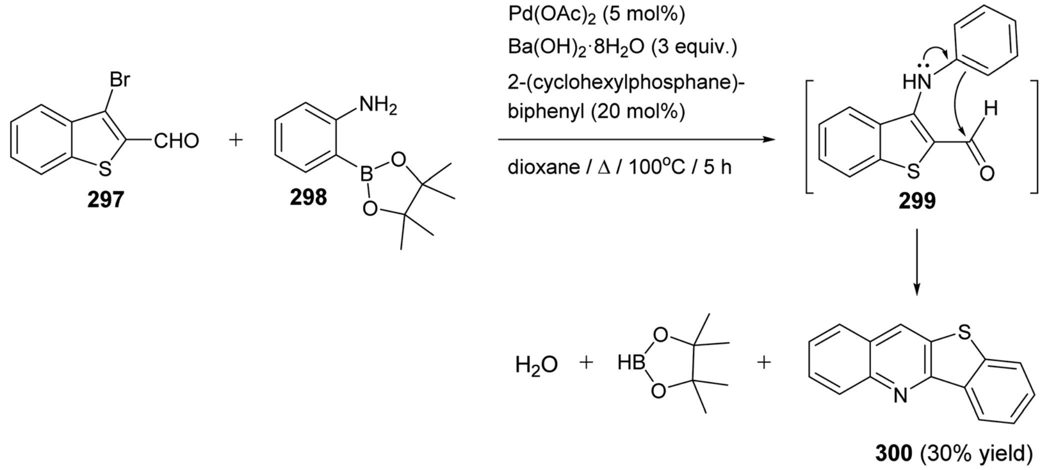


Scheme 98 Synthesis of benzothieno[3,2-*b*]quinolines **292** from **265** and **288**.



296	R_1	R_2	R_3	R_4	R_5
a	H	H	H	OMe	H
b	H	H	OMe	H	H
c	H	H	H	Me	H
d	H	H	H	Et	H
e	H	H	H	OEt	H
f	H	H	Me	H	Me
g	H	H	OMe	H	OMe
h	Me	OMe	H	OMe	H
i	Me	OMe	H	H	H
j	Me	H	H	OEt	H
k	OMe	H	H	$CH(Me)_2$	H
l	Me	H	H	F	H
m	OMe	H	CF_3	H	H

Scheme 99 A highly efficient synthesis of new benzothieno[3,2-*b*]quinolines **296** *via* the Pd-catalyzed reaction of **293** with **97**.



Scheme 100 One-pot synthesis of benzothieno[3,2-*b*]quinoline (**300**).

chromatographic separation to give the desired benzothieno[2,3-*b*]quinolines **284** in 30–60% yields (Scheme 96). The reaction mechanism for the formation of **284** is outlined in Scheme 97. The aryl radicals **282** attacks the sulfur atom of the isothiocyanate **283** giving α-sulfanylimidoyl radical **285.** Subsequent tandem 5-*exo-dig* cyclization onto the adjacent ethynyl moiety gave a linear 1-phenylvinyl radical **286.** The latter intermediate **286** underwent intramolecular 6-membered cyclization onto the isothiocyanate ring to give the benzothienoquinolines **284**, through the cyclohexadienyl radical **287.**

Zhu *et al.*[115] in 2007, synthesized benzothieno[3,2-*b*]quinolines **292** by the reaction of anthranilic acid derivatives **265** with 2-(phenylthiol)acetyl chloride (**288**). In this reaction the substituted anthranilic acids **265** were acylated with **288** under basic conditions to give the intermediates **289.** These intermediates **289** then underwent a double intramolecular cyclization reaction with polyphosphoric acid (PPA) at 130 °C for 3 h to furnish benzothieno[3,2-*b*]quinoline-11(5*H*)-ones **290.** Chlorination of **290** with $POCl_3$ at 110 °C for 24 h provided the corresponding chloro compounds **291,** which hydrogenated in H_2 atmosphere on Pd/C (10%) in MeOH at room temperature to give the desired tetracylic benzothieno[3,2-*b*]quinoline derivatives **292** in 16–85% yields (Scheme 98).

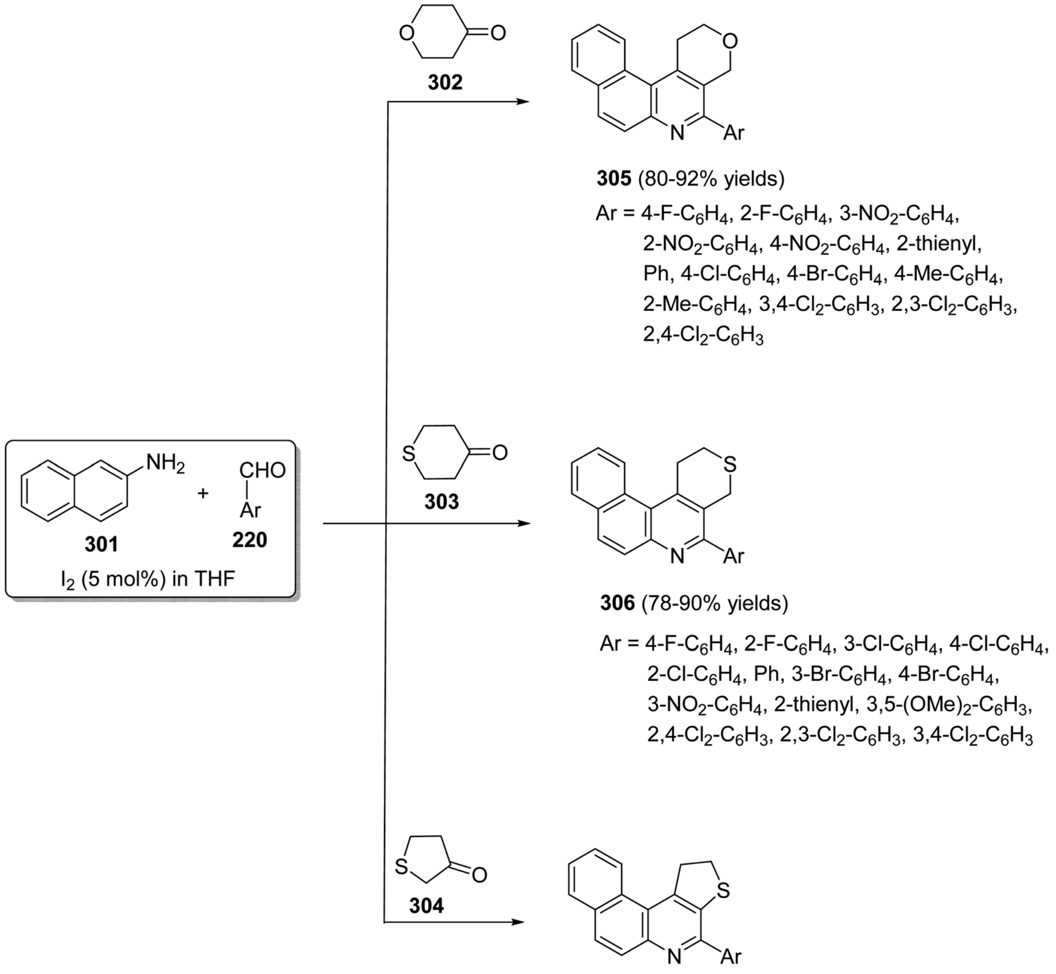
Langer and his group,[116] developed a highly efficient synthesis of new benzothieno-[3,2-*b*]quinolines **296** *via* the Pd-catalyzed reaction of 2-alkynyl-3-bromobenzothiophenes **293** with anilines **97.** When a mixture of **293** (1 equiv.), **97** (1.3 equiv.), $Pd(OAc)_2$ (10 mol%), $Pd(t\text{-}Bu)_3\cdot HBF_4$ (20 mol%), KO-*t*-Bu (2 equiv.) and CuI (25 mol%) was heated in toluene at 105 °C for 12 h, the desired benzothieno[3,2-*b*]quinolines **296** were indeed produced in 60–70% yields *via* intermediates **294** and **295** (Scheme 99).

A new one-pot method for the synthesis of benzothieno[3,2-*b*]quinoline (**300**) from the reaction of 3-bromobenzo[*b*]thiophene-2-carbaldehyde (**297**) with 2-aminophenylpinacolborane (**298**) under Suzuki coupling conditions utilizing a stereochemically hindered ligand, 2-(cyclo-hexylphosphane)biphenyl and $Ba(OH)_2\cdot 8H_2O$, as the base, was reported by Castanheira and co-workers[117] in 2014. This synthetic approach proceeded by heating a mixture of **297** (1 equiv.), **298** (1 equiv.), $Pd(AcO)_2$ (5 mol%), 2-(cyclohexylphosphane)-biphenyl (20 mol%), $Ba(OH)_2\cdot 8H_2O$ (3 equiv.) in dioxane at 100 °C for 5 h to give the tetracyclic product **300** in 30% yield (Scheme 100). The formation of **300** is assumed to proceed *via* a Pd-catalyzed C–N coupling followed by an intramolecular cyclization that probably occur by nucleophilic attack of the activated *ortho* position of the diarylamine intermediate **299** on the aldehydic carbonyl group, after deboronation (Scheme 100).

In 2009, Wang's group[118] have developed a simple and efficient route for construction of several tetracyclic quinolines *viz.* benzo[*f*]pyrano[3,4-*c*]quinolines **305**, benzo[*f*]thiopyrano[3,4-*c*]quinolines **306** and benzo[*f*]thieno[2,3-*c*]quinolines **307** *via* three-component reaction of aromatic aldehydes **220,** naphthalene-2-amine (**301**) and heterocyclo-ketones **302–304,** including tetrahydropyran-4-one **302**, tetrahydrothiopyran-4-one **303** and dihydro-thiophen-3(2*H*)-one **304**, in THF catalyzed by molecular iodine (5 mol%) at reflux temperature (Scheme 101). The mechanism involves the condensation reaction between amine **301** and aromatic aldehydes **220** to form the imine **I,** which reacts with iodine to produce the activated intermediate **II.** The enol form of cyclic ketones **302–304** attacks the latter intermediate **II** to give intermediate **III,** followed by an intramolecular cyclization to produce **IV.** Subsequent dehydration of **IV** affords dihydroquinoline **V,** which then undergoes air auto-oxidation to produce aromatized tetracyclic quinolines **305–307** (Scheme 102).

2.3. Tetracyclic quinolines with three heteroatoms

2.3.1. Furothiopyrano[2,3-*b*]quinolines. Recently, Singh and his co-workers[119] have reported a facile synthesis of tetracyclic, furothiopyrano[2,3-*b*]quinoline derivatives **312** *via* base-free I_2-catalyzed cyclization reactions of 3-homoallylquinolin-2-thiones **311.** The starting 3-homoallylquinoline-2-thinoes **311** were prepared, in two steps, from reaction of 2-chloroquinoline-3-carbaldehydes **308** with allyl bromides **309** in DMF (Barbies reaction), followed by treatment with Na_2S in



305 (80-92% yields)

Ar = 4-F-C_6H_4, 2-F-C_6H_4, 3-NO_2-C_6H_4, 2-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2-thienyl, Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Me-C_6H_4, 2-Me-C_6H_4, 3,4-Cl_2-C_6H_3, 2,3-Cl_2-C_6H_3, 2,4-Cl_2-C_6H_3

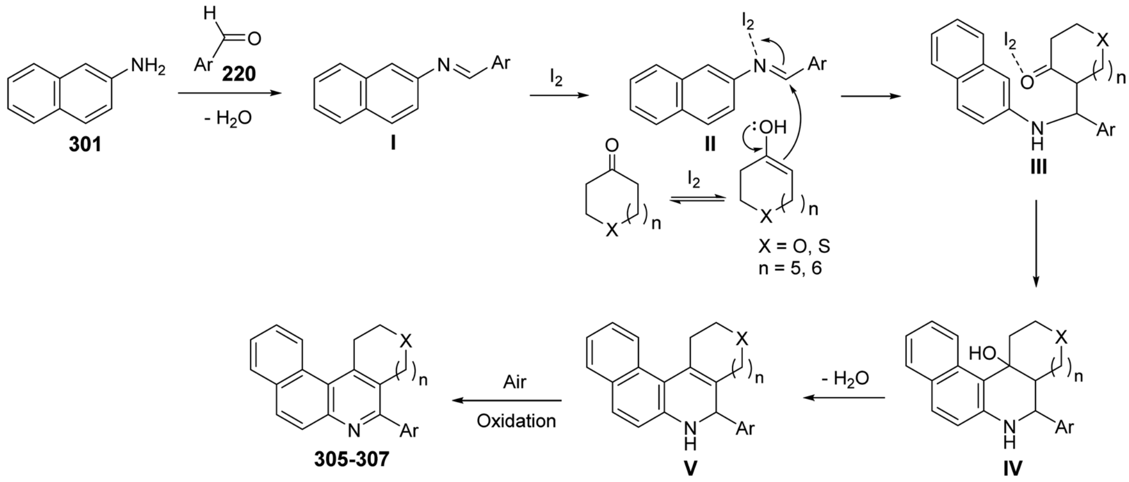
306 (78-90% yields)

Ar = 4-F-C_6H_4, 2-F-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2-Cl-C_6H_4, Ph, 3-Br-C_6H_4, 4-Br-C_6H_4, 3-NO_2-C_6H_4, 2-thienyl, 3,5-$(OMe)_2$-C_6H_3, 2,4-Cl_2-C_6H_3, 2,3-Cl_2-C_6H_3, 3,4-Cl_2-C_6H_3

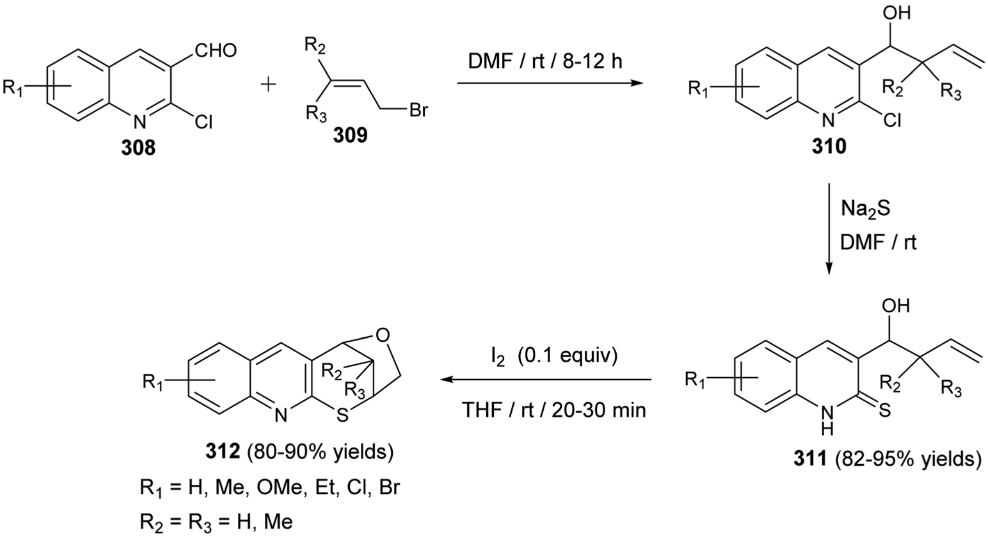
307 (76-86% yields)

Ar = 2,4-Cl_2-C_6H_3, 2-OMe-C_6H_4, Ph, 3,5-$(OMe)_2$-C_6H_3, 3-Br-C_6H_4, 2,3-Cl_2-C_6H_3, 2-NO_2-C_6H_4, 2-Br-C_6H_4, 4-Cl-C_6H_4

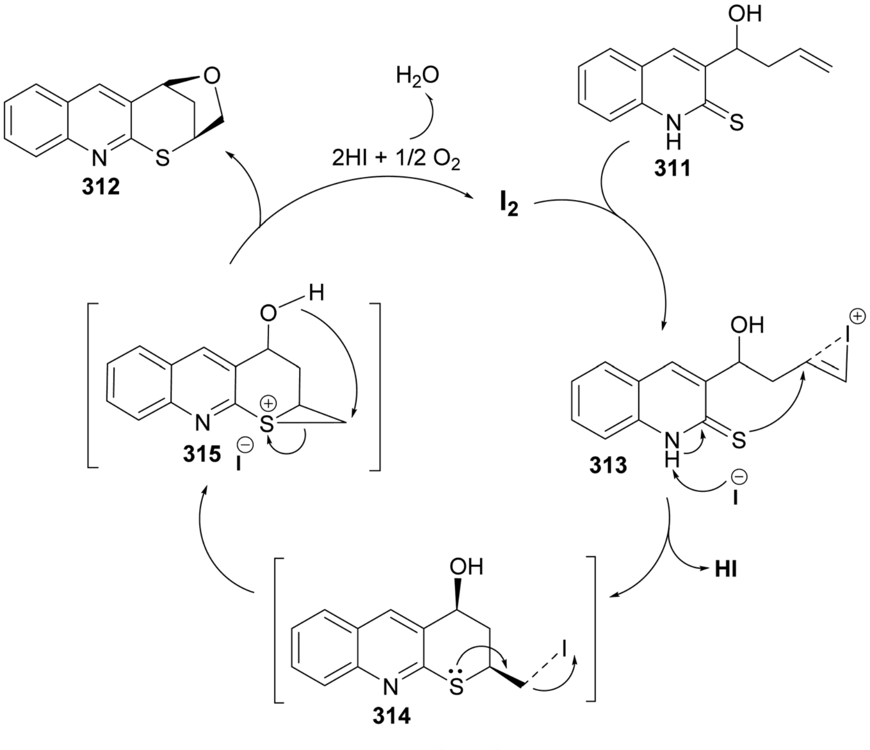
Scheme 101 Molecular iodine catalyzed synthesis of fused tetracyclic quinolines 305–307.



Scheme 102 A plausible mechanism for the synthesis of products 305–307.



Scheme 103 Synthesis of furothiopyrano[2,3-*b*]quinolines **312** *via* iodocyclization of 3-homoallylquinolin-2-thiones **311**.

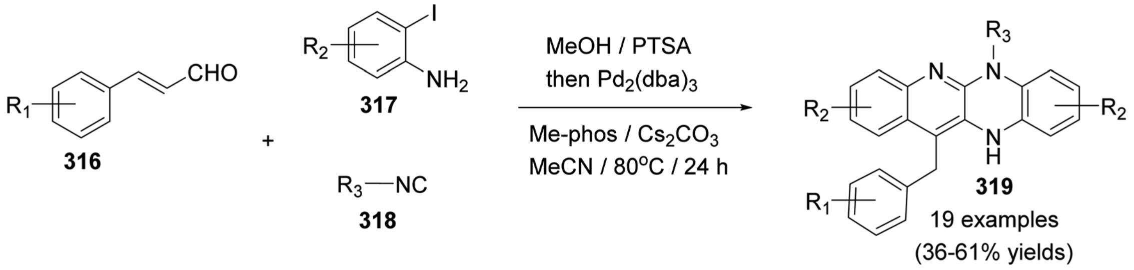


Scheme 104 Plausible mechanism for the formation of furothiopyrano[2,3-*b*]quinolines **312**.

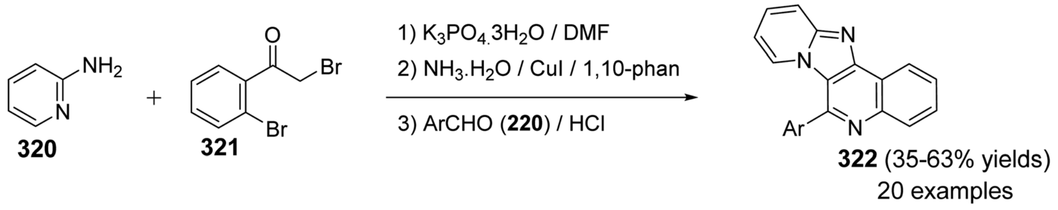
DMF at room temperature (Scheme 103). The cyclization reaction of **311** with I_2 in THF at room temperature afforded the required tetracyclic quinoline, furothiopyrano[2,3-*b*]quinolines **312**, in 80–90% yields (Scheme 103). All reactions were completed under aerobic conditions. The plausible mechanism for the formation of tetracyclic furothiopyranoquinolines **312** is shown in Scheme 104. The electrophilic addition of I_2 to olefinic bond of 3-homo-allaylquinoline-2-thiones **311** leads to the formation of iodonium ion **313**, which undergoes intramolecular attack by sulfide anion to give the tricyclic intermediate **314**. Neighboring group participation of sulfur atom on 2-iodomethyl carbon atom in **314** gives the sulfonium salt intermediate **315**. Finally, sulfonium salt ring open by the hydroxy group to give the tetracyclic ring system **312**.

2.3.2. Quinoxalino[2,3-*b*]quinolines.

In 2014, Che *et al.*[120] described a rapid synthesis of fused tetracyclic quinolines, 6,11-dihydroquinoxalino[2,3-*b*]quinolines **319**, a family of novel heterocycles with potential antitumor activity, *via* a sequential



Scheme 105 Synthesis of quinolino[3,2-*b*]quinoxalines **319** in one-pot process.

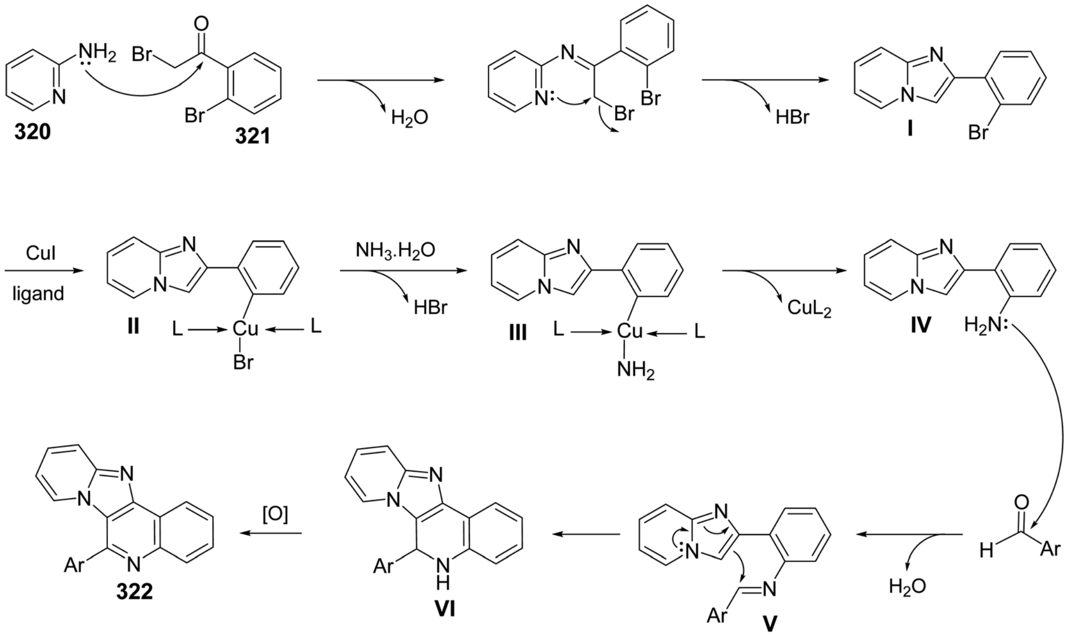


Scheme 106 Synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinolines **322**.

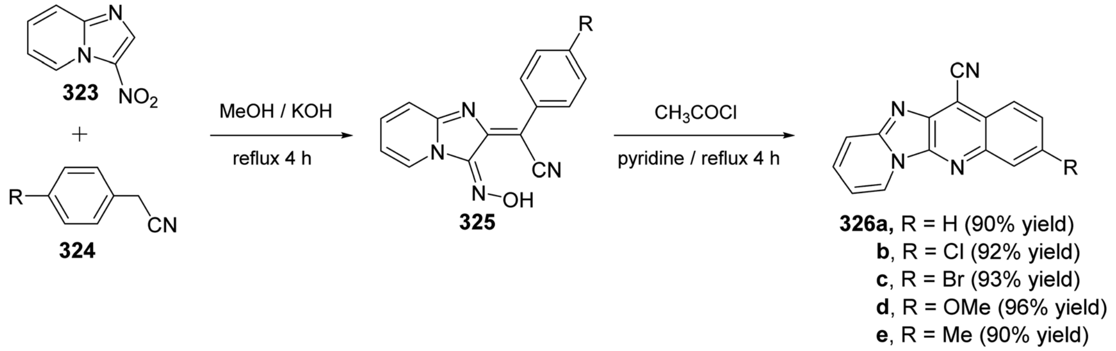
Ugi-variant multicomponent reaction and Pd-catalyzed bis-annulation in one-pot procedure. Reaction of cinnamic aldehydes **316**, two molecules of *o*-iodoanilines **317** and isocyanides **318** was carried out in MeOH at room temperature in the presence of *p*-toluenesulfonic acid (PTSA). The reaction mixture was then treated with $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2′-methylbiphenyl (Me-phos) and cesium carbonate ($CsCO_3$) in MeCN and refluxed to produce the desired tetracyclic 6,11-dihydroquinoxalino-[2,3-*b*]quinolines **319**, in 36–61% yields (Scheme 105). It was found that the electronic properties of substituents on the aromatic ring of cinnamic aldehyde had no effect on the reactivity, while the anilines with either electron-withdrawing or electron-donating group showed a slightly lower reactivity.

2.3.3. **Pyridoimidazoquinolines.** Tetracyclic ring system combining an imidazo[1,2-*a*]pyridine skeleton condensed with a quinoline nucleus are stimulating increasing interests since they are close isosteres of a series of powerful antiproliferative compounds such as datelliptium, pazellipticine as well as ellipticinem.[121]

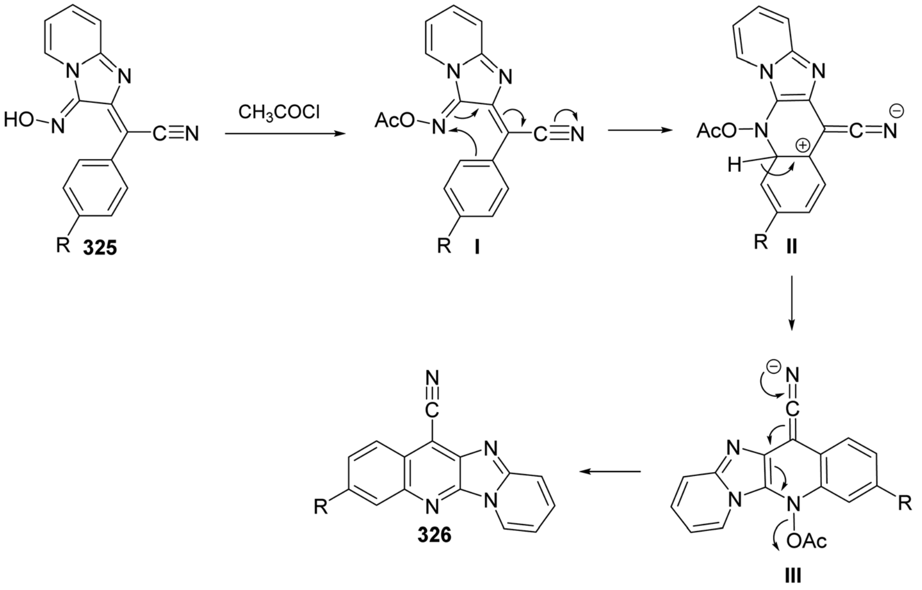
2.3.3.1. *Pyrido[2′,1′:2,3]imidazo[4,5-c]quinolines.* In 2015, Fan *et al.*[121] developed a facile and unprecedented methodology



Scheme 107 Plausible mechanism for the formation of pyrido[2′,1′:2,3]imidazo[4,5-c]-quinolines **322**.



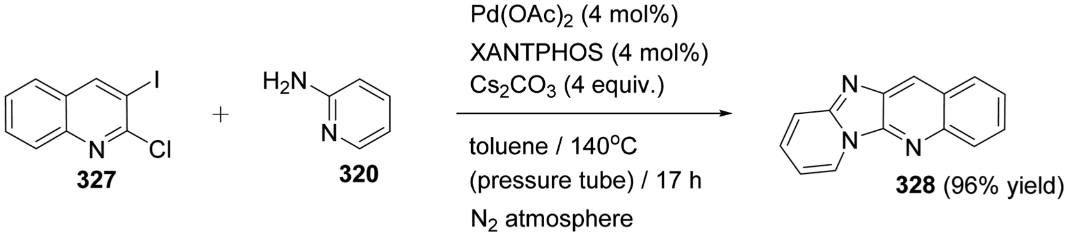
Scheme 108 Synthesis of new fluorescent tetracyclic compounds **326**.



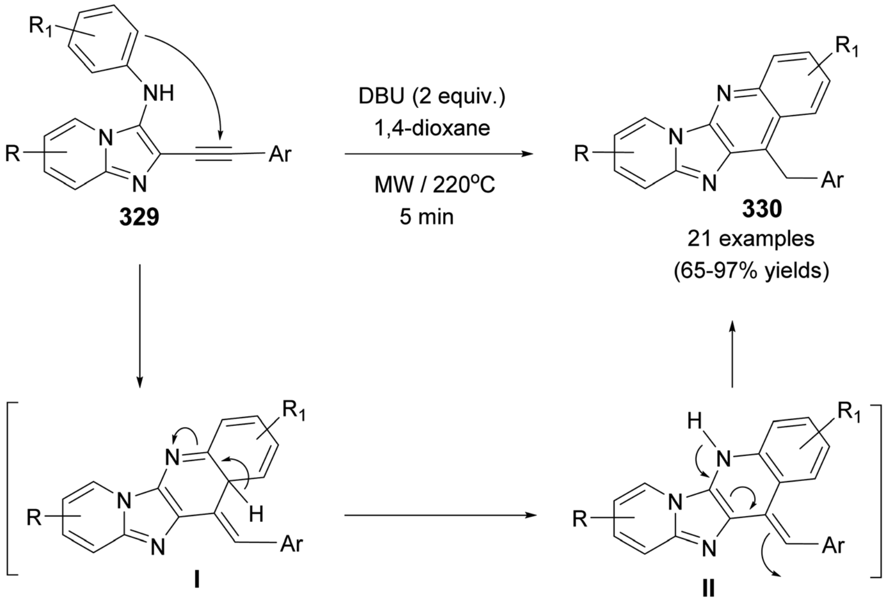
Scheme 109 Proposed mechanism for the formation of pyrido[2′,1′:2,3]imidazo[4,5-*b*]-quinolines **326**.

for the synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinolines **322** *via* Cu-catalyzed one-pot four-component sequential reactions of 2-aminopyridine (**320**), 2-bromophenacyl bromide (**321**), aldehydes **220** and aq. NH_3. The reactions were performed in three steps as shown in Scheme 106. (1) treatment of **320** with **321** in the presence of $K_3PO_4 \cdot 3H_2O$, as a base, in DMF at 80 °C for 4 h; (2) the reaction mixture was added with CuI, 1,10-phenanthroline (1,10-Phen) and aq. NH_3 and then stirred at 80 °C for 8 h; (3) finally, the resulting mixture was added with HCl and aldehydes **220** and then stirred at 80 °C under air for 4 h to produce the desired tetracyclic **322** in 35–63% yields. It was shown that phenyl substituted aldehydes with either electron-withdrawing or electron-donating substituents on the phenyl ring underwent this cascade process easily to furnish **322** in good yields. A plausible mechanism to account for the formation of **322** is suggested in Scheme 107. The reaction is presumed to take place by an initial condensation of **320** with **321** to afford 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**I**). The following Cu-catalyzed amination of **I** with NH_3, as the nitrogen source, through intermediates **II** and **III** gives 2-imidazo[1,2-*a*]pyridine-2-yl-phenylamine (**IV**). Condensation of **IV** with aldehydes **220** affords the corresponding imine intermediate **V**. The subsequent intramolecular nucleophilic cyclization of **V** affords **VI**, which then undergoes an oxidative dehydrogenation under these reaction conditions to give **322** as the final products.

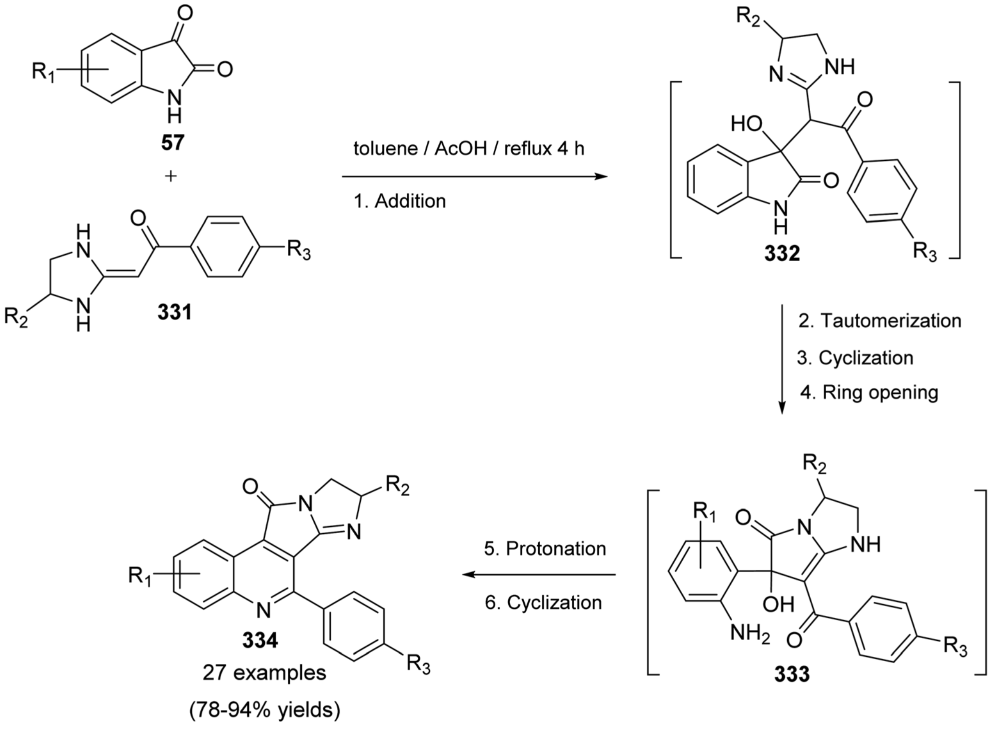
2.3.3.2. Pyrido[2′,1′:2,3]imidazo[4,5-b]quinolines. Rahimizadeh *et al.*[122] reported a new and efficient synthetic route for the synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinolines **326**, as novel tetracyclic ring system containing a quinoline nucleus which have strong fluorescence emission, utilizing (4-substituted) (3-hydroxyimino-2,3-dihydroimidazo[1,2-*a*]pyridin-2-yliden)methyl cyanides **325** as starting materials. The key intermediates **325** were synthesized by refluxing 3-nitro-imidazo[1,2-*a*]-pyridine **323** with arylacetonitriles **324** in MeOH in the presence of KOH for 4 h in excellent yields (Scheme 108). Acylation of hydroxyl group in **325** with acetyl chloride led to heterocyclization and afforded highly fluorescent **326** in 90–96% yields, *via* the intramolecular electrophilic aromatic substitution (Scheme 108). The proposed mechanism to explain the formation of **326** is shown in Scheme 109. Other reagents



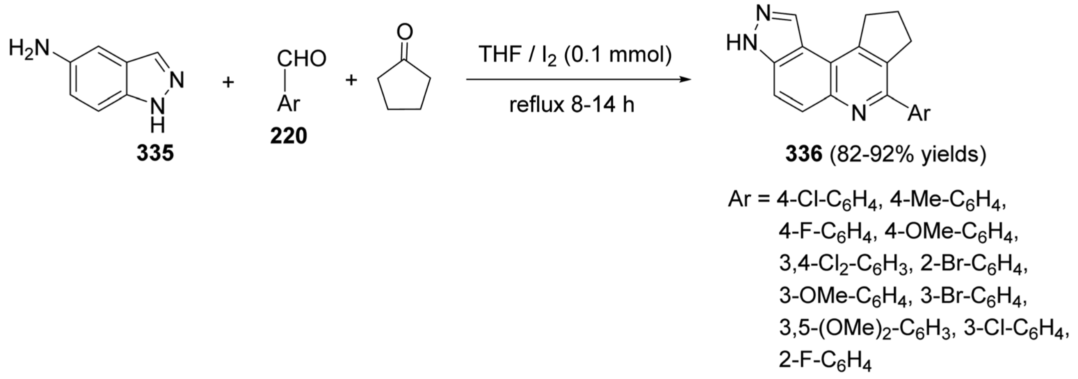
Scheme 110 Synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline (**328**) *via* auto-tandem amination on **327** with **320**.



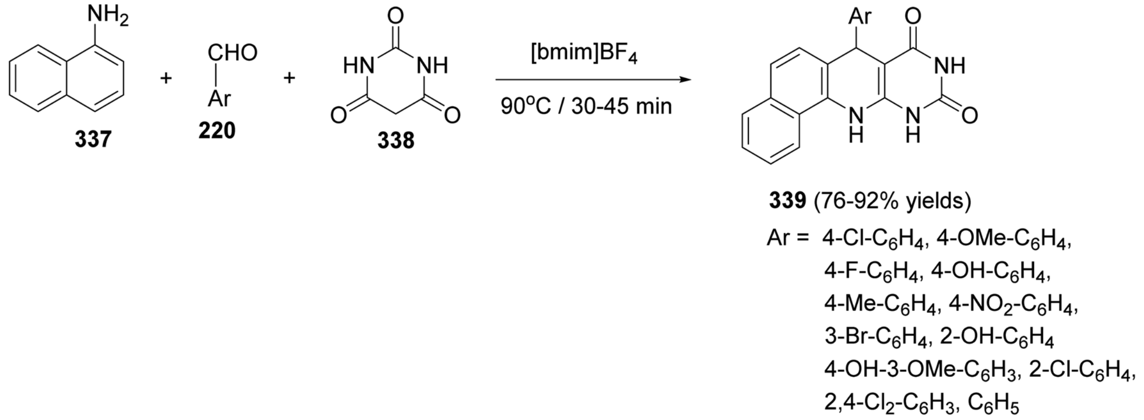
Scheme 111 DBU-catalyzed synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinolines **330**.



Scheme 112 Acetic acid catalyzed synthesis of imidazo[1′,2′:1,2]pyrrolo[3,4-c]quinolin-11-ones **334** *via* cascade of reactions.



Scheme 113 Molecular I2 catalyzed synthesis of cyclopenta[*c*]pyrazolo[4,3-*f*]quinolines **336**.



Scheme 114 Synthesis of benzo[*h*]pyrimido[4,5-*b*]quinoline-8,10-diones **339** in ionic liquid.

such as $POCl_3$ and $SOCl_2$ act in same way but the products **326** were obtained in low yields.

A new strategy for the synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline (**328**) *via* a regioselective auto-tandem Pd-catalyzed inter- and intramolecular double Buchwald–Hartwig amination of 2-chloro-3-iodoquinoline (**327**) with aminopyridine (**320**) was reported.[123] When a mixture of **327** (1 equiv.), **320** (1 equiv.), $Pd(OAc)_2$ (4 mol%), XANTPHOS (4 mol%), Cs_2CO_3 (4 equiv.) in toluene was heated at 140 °C (pressure tube) under N_2 atmosphere for 17 h, the tetracyclic **328** was obtained in 96% yield (Scheme 110).

Guillaumet *et al.*[124] have developed a rapid and efficient metal-free method for the synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinolines **330** from 2-(arylethynyl)imidazo[1,2-*a*]pyridin-3-amines **329** catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Microwave irradiation of **329** in 1,4-dioxane with a catalytic amount of DBU at 220 °C produced a series of unusual fused heterocyclic quinolines **330**, in 65–97% yields (Scheme 111). A proposed reaction pathway for the formation of **330** is shown in Scheme 111. The electron rich secondary amines **329** assists in the hydroarylation of the triple bond after deprotonation by DBU. Next, aromatization produces the respective pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinolines **330**.

2.3.4. Imidazo[1′,2′:1,2]pyrrolo[3,4-*c*]quinolines.

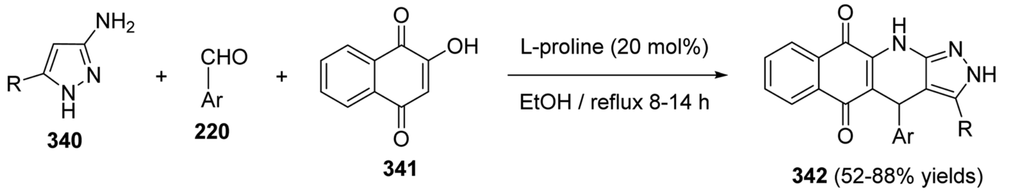
A simple and new synthetic route for the synthesis of imidazo[1′,2′:1,2]pyrrolo-[3,4-*c*]quinolin-11-ones **334** based on the cascade reaction of isatins with heterocyclic ketene aminals (HKAs) has developed by Yu *et al.*[125] in 2011. Refluxing a reaction mixture of isatins **57** and five-member heterocyclic ketene aminals (HKAs) **331** in toluene catalyzed by AcOH, forming the respective products **334** with good to excellent yields (78–94%) (Scheme 112). A suggested mechanism for the formation of **334** is shown in Scheme 112. At first, the α-C of **331** was added to the more electrophilic carbonyl center of **57** to furnish the intermediate **332**. This intermediate underwent imine–enamine tautomerization, intramolecular cyclization, dehydration, and ring-opening reactions to produce the further intermediate **333**. Finally, protonation of **333** followed by intramolecular cyclization resulted in the formation of the target tetracyclic **334**.

2.3.5. Cyclopenta[*c*]pyrazolo[4,3-*f*]quinolines.

A three-component imino Diels–Alder reaction of 1*H*-indazol-5-amine (**335**), aromatic aldehydes **220** and cyclopentanone in boiling THF catalyzed by molecular iodine led to the formation of a series of cyclopenta[*c*]pyrazolo[4,3-*f*]quinolines **336** in high yields (Scheme 113).[126]

2.3.6. Benzo[*h*]pyrimido[4,5-*b*]quinolines.

Guo and Yu[127] reported a three component reaction between 1-naphthylamine

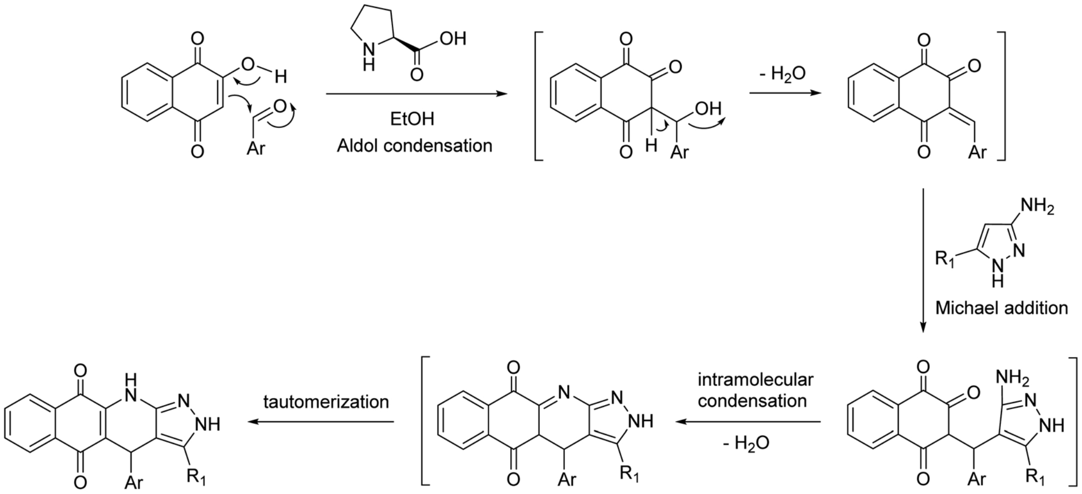


340 220 341

342 (52-88% yields)

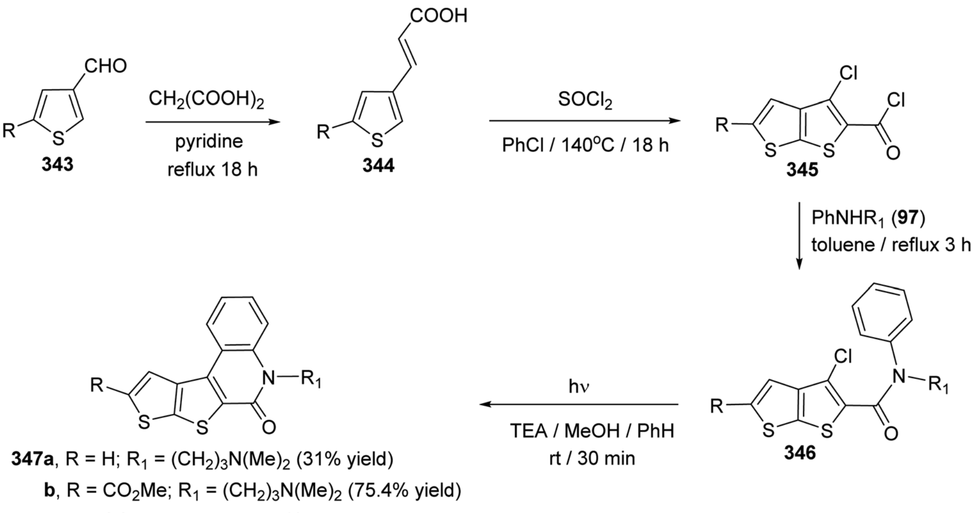
Ar = 4-F-C_6H_4, 4-Cl-C_6H_4,
4-Br-C_6H_4, 4-Me-C_6H_4,
4-NO_2-C_6H_4, 4-OMe-C_6H_4,
4-OH-C_6H_4, 3-NO_2-C_6H_4,
4-$(Me)_2CH$-C_6H_4, C_6H_5,
2,4-Cl_2-C_6H_3
R = H, CH_3

Scheme 115 L-Proline mediated synthesis of benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones **342**.



342

Scheme 116 Proposed mechanism for the formation of benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones **342**.



343 344 345 346

347a, R = H; R_1 = $(CH_2)_3N(Me)_2$ (31% yield)
b, R = CO_2Me; R_1 = $(CH_2)_3N(Me)_2$ (75.4% yield)
c, R = CO_2Me; R_1 = H (75.8% yield)
d, R = CONHPh; R_1 = H (40% yield)

Scheme 117 A multistep synthesis of thieno[3′,2′:4,5]thieno[2,3-*c*]quinolones **347**.

(**337**), aromatic aldehydes **220** and barbituric acid (**338**) in ionic liquid [bmim]BF_4, as a green solvent, produced a novel tetracyclic 7-aryl-11,12-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(7*H*,9*H*)-diones **339**, in 76–92% yields (Scheme 114).

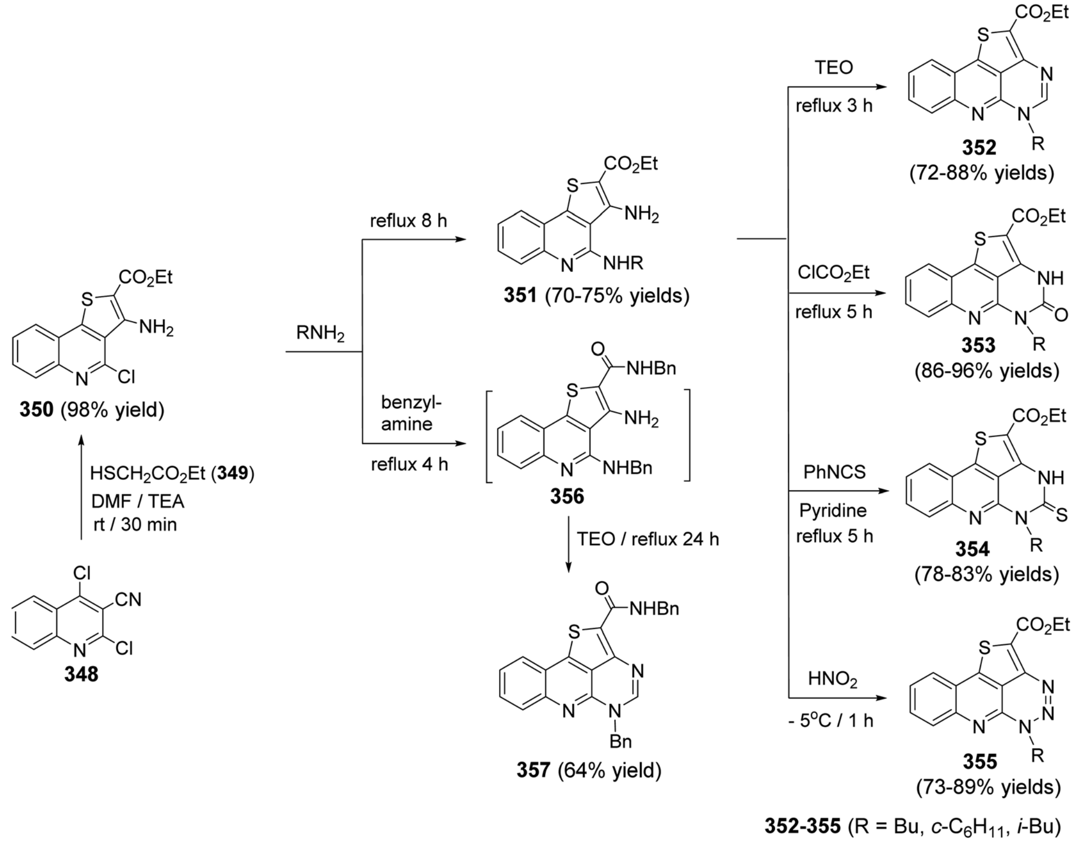
2.3.7. Benzo[*g*]pyrazolo[3,4-*b*]quinolines. In 2014, Karamthulla and coworkers[128] have described a L-proline mediated synthesis of 2*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10(4*H*,11*H*)-diones **342**, in 52–88% yields, *via* a three-component one-pot reaction of 3-aminopyrazoles **340**, aldehydes **220** and 2-hydroxy-1,4-naphthoquinone (**341**) in boiling ethanol (Scheme 115). The plausible mechanism for the formation of **342** is shown in Scheme 116. The reaction proceeds *via* domino aldol reaction/Michael addition/intramolecular condensation/tautomerism sequence to afford the desired products **342** regioselectively.

2.3.8. Thieno[3′,2′:4,5]thieno[2,3-*c*]quinolines. A multistep synthesis of novel thieno[3′,2′:4,5]thieno[2,3-*c*]quinolones **347** has been developed by Koružnjak *et al.*[129] Refluxing a solution of 5-substituted-thiophene-3-carboxaldehyde **343** and malonic acid in pyridine gave 5-substituted 3-(3-thienyl)acrylic acids **344**. When **344** was heated with $SOCl_2$ in the presence of a catalytic amount of pyridine in chlorobenzene at 140 °C, they underwent cyclization to give the corresponding 3-chloro-thieno[2,3-*b*]thiophene-2-carbonyl chlorides **345**. Reacting **345** with aniline derivatives **97** in refluxing toluene produced the 3-cholorothieno[2,3-*b*]thiophene-2-carboxamides **346**, which were photochemically dehydrohalogenated at room temperature to afford the respective tetracyclic **347**, in 31–76% yields (Scheme 117). The products **347** showed cytostatic activities against malignant cell lines and marked antitumor activity.

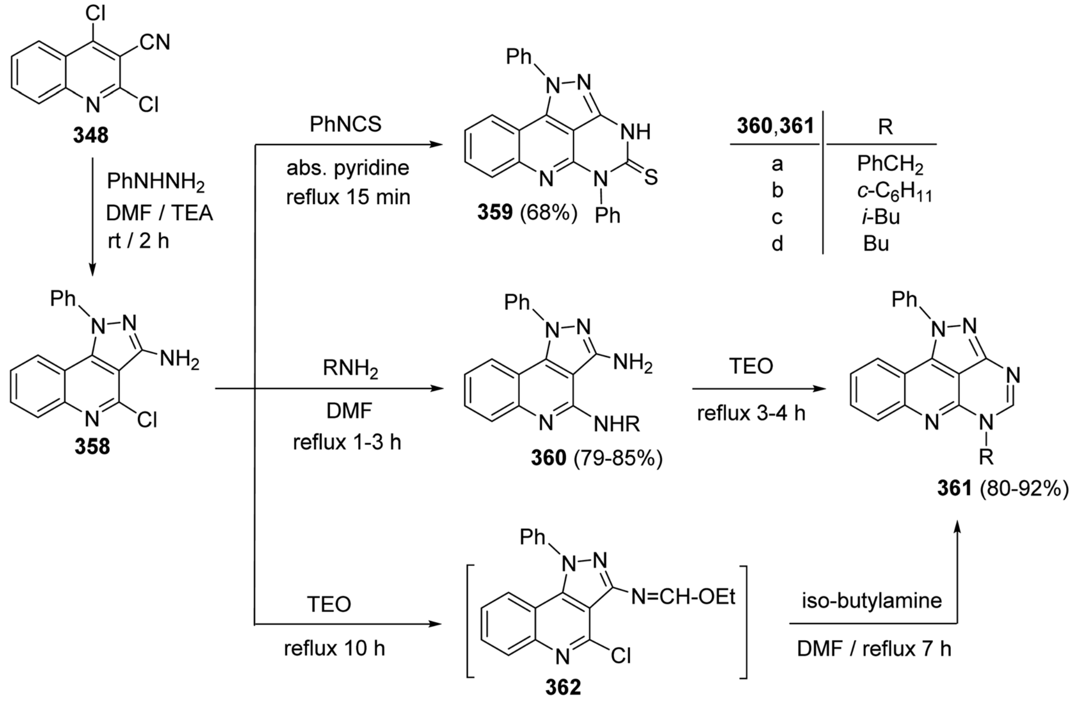
2.4. Tetracyclic quinolines with more than three heteroatoms

Since twenty-six years ago, Mekheimer and his group have developed different successful routes for the synthesis of a new tetracyclic systems containing the quinoline nucleus of biological importance utilizing for the first time 2,4-dichloroquinoline-3-carbonitrile (**348**) as a good precursor. It is well known that the chlorine atom at C-4 in **348** is more reactive than that at C-2 and is more easy to displace using nucleophiles.[130–134]

2.4.1. 1-Thia-3,5,6-triazaaceanthrylenes and 1-thia-3,4,5,6-tetraazaaceanthrylenes. Mekheimer *et al.*[135] have reported the synthesis of novel tetracyclic ethyl 5-alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylates and ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraaza-aceanthrylene-2-carboxylates using ethyl 3-amino-4-chloro-thieno[3,2-*c*]quinoline-2-carboxylate (**350**) as starting material, which was prepared from reaction of **348** with ethyl 2-mercaptoacetate (**349**) in DMF in the presence of TEA at room temperature in 98% yield (Scheme 118). Refluxing **350** in an excess of primary alkylamines furnished **351** in 70–75% yields, which were treated with an excess of TEO at reflux temperature to afford the angularly annulated tetracyclic ethyl 5-alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylates **352**



Scheme 118 Synthesis of ethyl 5-alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylenes **352–354**, **357** and ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylenes **355**.

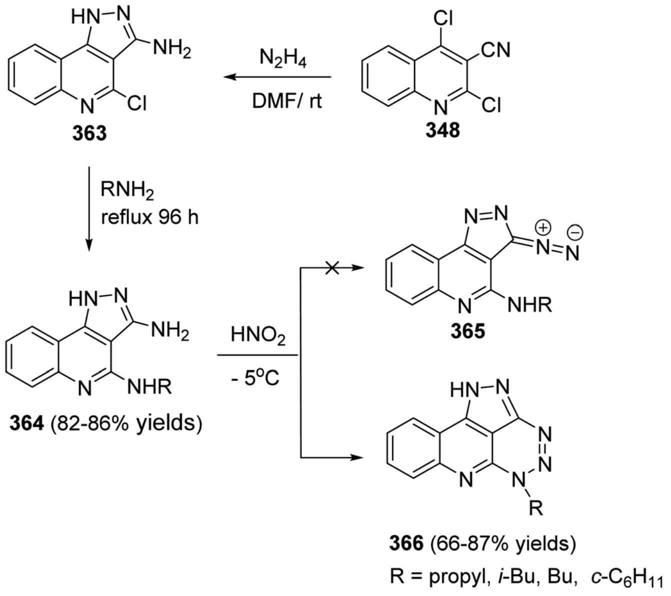


Scheme 119 Synthesis of 1,2,3,5,6-pentaazaaceanthrylenes **359** and **361**.

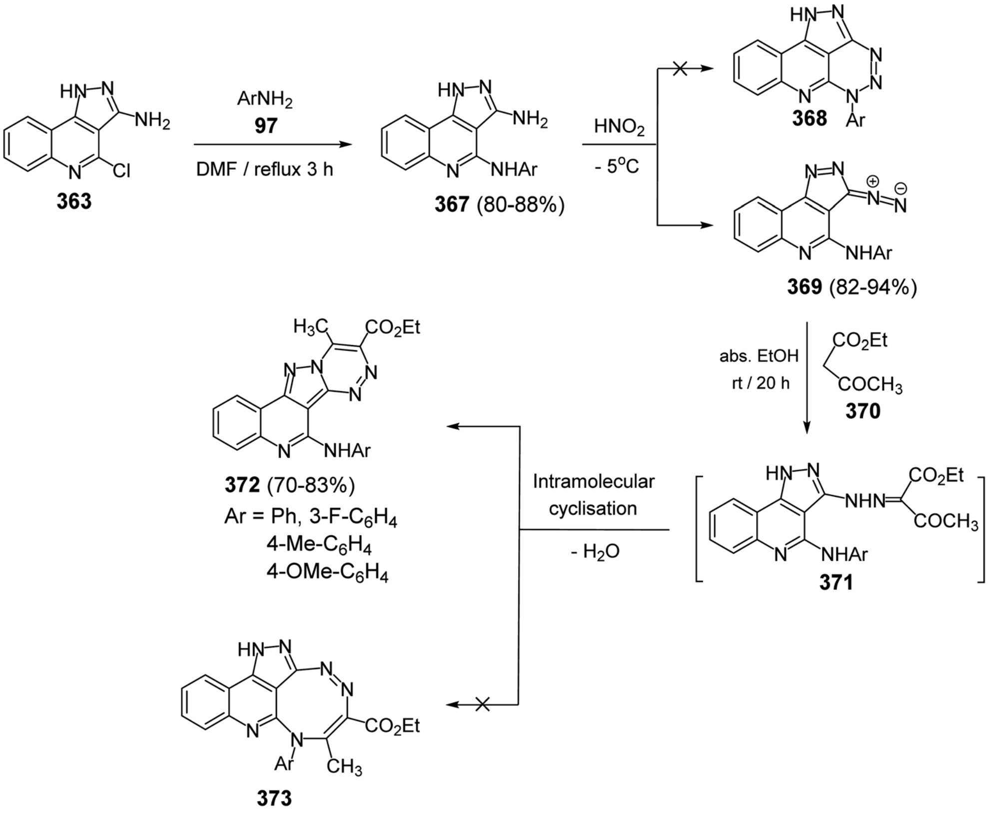
in 72–88% yields (Scheme 118). In contrast to the other amines, when **350** was reacted with excess of benzylamine, thieno[3,2-*c*] quinoline derivative **356** was obtained, as a viscous oil, which was refluxed with TEO to give 1-thia-3,5,6-triazaaceanthrylenes **357** in 64% yield (Scheme 118). Refluxing **351** with ethyl chloroformate and phenyl isothiocyanate furnished the new tetracyclic **353** and **354** in 86–96% and 78–83% yields, respectively. On the other hand, diazotization of **351** with $NaNO_2$ in H_2SO_4 (70%) at −5 °C gave the novel ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylene-2-carboxylates **355** in 73–89% yields (Scheme 118).

2.4.2. 1,2,3,5,6-Pentaazaaceanthrylenes. In 2003, Mekheimer *et al.*[136] described the synthesis of new tetracyclic ring systems combining both a pyrimidine and a pyrazoloquinoline moieties starting from 3-amino-4-chloro-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline (**358**), which was obtained by reaction of **348** with phenylhydrazine.[136] Reaction of **358** with phenyl isothiocyanate in absolute pyridine under reflux conditions led to the formation of 1,5-diphenyl-1,2,3,5,6-pentaazaaceanthrylene-4(3*H*)-thione (**359**) in 68% yield. When **358** was reacted with primary aliphatic amines in DMF at reflux temperature, the corresponding 3,4-diaminopyrazolo[4,3-*c*] quinolines **360** were obtained in 79–85% yields, which refluxed with an excess of TEO to afford the novel 1,2,3,5,6-pentaazaaceanthrylenes **361** in 80–92% yields (Scheme 119). Also, compounds **361** were prepared by an alternative route. As an example, reacting **358** with TEO under reflux conditions gave the intermediate 4-chloro-3-(ethoxymethyleneamino)-1-phenylpyrazolo-[4,3-*c*]quinoline (**362**), which then refluxed, *in situ*, with *iso*-butylamine in DMF to furnish the desired tetracyclic **361** (Scheme 119).

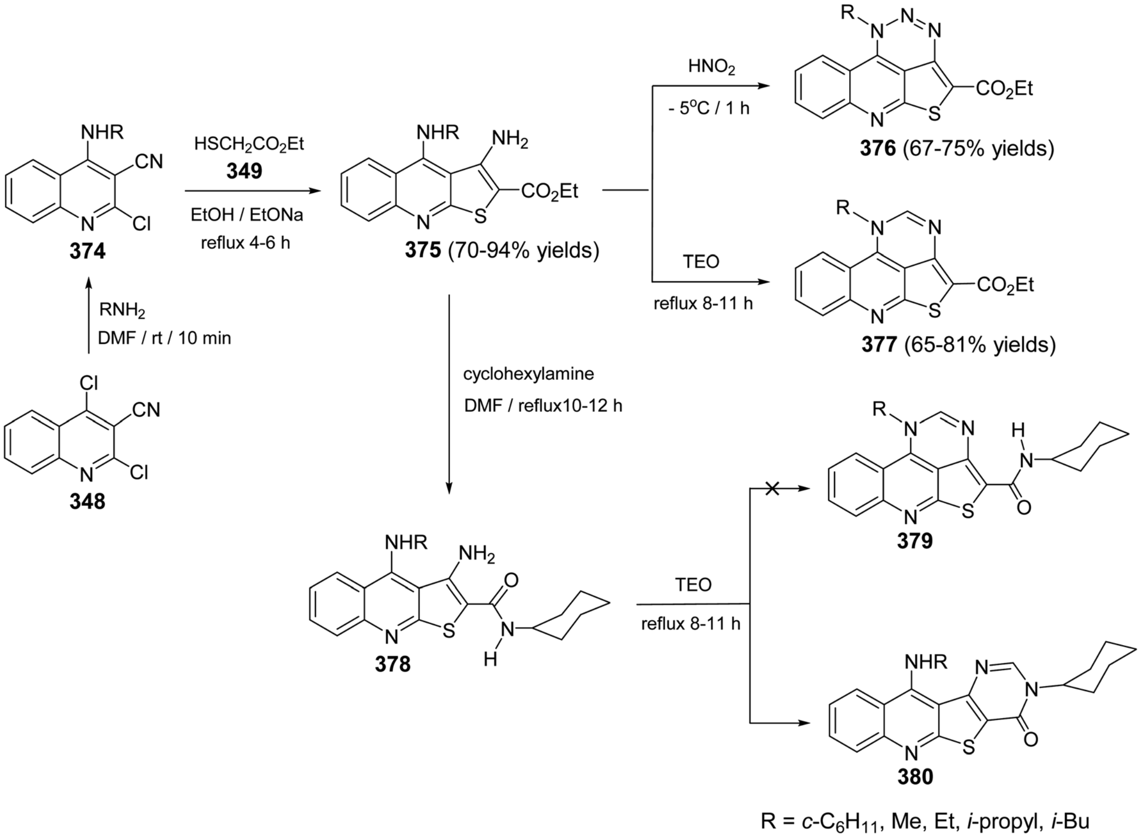
2.4.3. 1,2,3,4,5,6-Hexaazaaceanthrylenes and 5,7,8,10*a*,11-pentaazabenzo[*a*]fluorenes ring systems. The synthesis of new 5-alkyl-1,5-dihydro-1,2,3,4,5,6-hexaazaaceanthrylenes **366** was developed by Mekheimer[137] in 2001. Reactions were carried out by heating the key 3-amino-4-chloro-1*H*-pyrazolo[4,3-*c*]quinoline (**363**) with an excess of the primary alkylamines at reflux temperature to afford the corresponding 4-alkylamino-3-amino-1*H*-pyrazolo[4,3-*c*]-quinolines **364**, in 82–86% yields, which were



Scheme 120 Synthesis of 1,2,3,4,5,6-hexaazaaceanthrylenes **366** from **363**.



Scheme 121 Synthesis of 5,7,8,10*a*,11-pentaazabenzo[*a*]fluorenes **372**.



Scheme 122 Synthesis of novel 1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylenes **376**, 1*H*-5-thia-1,3,6-triazaacephenanthrylenes **377** and linear pyrimidothienoquinolines **380**.

transformed into the tetracyclic 5-alkyl-1,5-dihydro-1,2,3,4,5,6-hexaazaaceanthrylenes **366**, when treated with $NaNO_2$ in H_2SO_4 (70%) at −5 °C. The yields of the last step are 66–87% (Scheme 120). The author discarded the other possible structure **365** based on the spectral data.

On the other hand, reacting compound **363** with arylamines **97** in DMF under reflux conditions afforded the corresponding 4-arylamino-pyrazolo[4,3-*c*]quinolines **367** in 80–88% yields. Diazotisation of the amines **367** under ordinary conditions gave the 4-arylamino-3-diazo-1*H*-pyrazolo[4,3-*c*]quinolines **369** in 82–94% yields. Treatment the 3-diazo compounds **369** with ethyl acetoacetate (**370**) in absolute EtOH at room temperature gave the intermediate **371**, which then underwent intramolecular cyclo-condensation to afford directly the novel tetracyclic ring system **372** in 70–83% yields, for which the alternative isomeric structure **373** is theoretically possible (Scheme 121).[137]

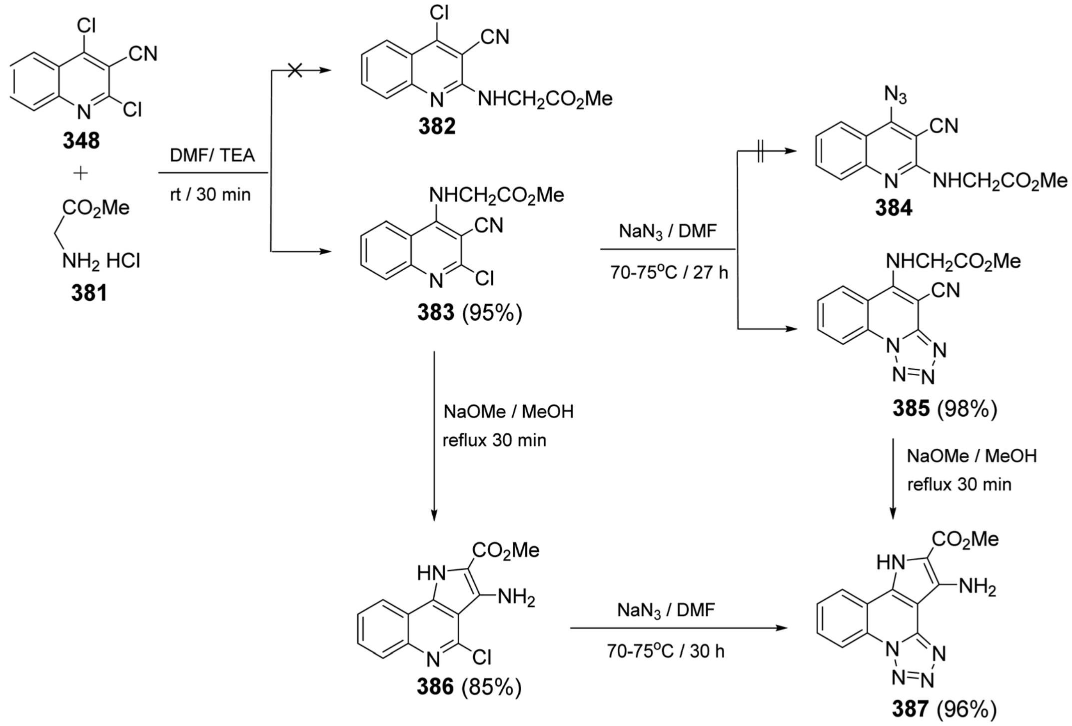
2.4.4. 5-Thia-1,2,3,6-tetraazaacephenanthrylenes and 5-thia-1,3,6-triazaacephenan-thrylenes.

Mekheimer *et al.*[138] have reported a new protocol for the construction of novel tetracyclic pyrimidothienoquinolines and 1,2,3-triazinothienoquinolines through 4-alkyl-amino-2-chloro-quinoline-3-carbonitriles **374**. By heating a mixture of **374** with ethyl 2-mercaptoacetate (**349**) and excess of sodium ethoxide in absolute EtOH at reflux temperature, 3-aminothieno[2,3-*b*]quinolines **375** were formed in 70–94% yields (Scheme 122). Diazotization of **375** resulted in the formation of 5-thia-1,2,3,6-tetraazaacephenanthryl-enes **376** in 67–75% yields (Scheme 122). However, when **375** were refluxed with TEO, 5-thia-1,3,6-triazaacephenanthrylenes **377** were indeed obtained in 65–81% yields (Scheme 122).[138] On the other hand, reaction of **375** with cyclohexylamine in DMF under reflux conditions afforded the corresponding amides **378**, which in treatment with an excess of TEO did not afford the perianellated tetracyclic system **379**, but furnished instead the unexpected linear isomeric pyrimidothienoquinoline derivatives **380** in good yields (Scheme 122).[138]

2.4.5. 1,4,5,6,6a-Pentaazabenzo[*a*]indacenes, 1,3,5,6-tetraazaaceanthrylenes and 5,7,9,11 tetraazabenzo[*a*]fluorenes.

The reaction of **348** with methyl glycinate hydrochloride (**381**) was investigated by Mekheimer[139] to synthesize the new 1,4,5,6,6*a*-pentaazabenzo[*a*]indacenes **387**. The reaction was carried out by treatment **348** with an excess of **381** in DMF in the presence of TEA at room temperature to afford one of the two isomeric structures **382** or **383** (Scheme 123). Spectral data could not unequivocally differentiate these isomers. To chemically verify the structure of **383**, tetrazolo[1,5-*a*]quinolines **385** was prepared, in 98% yield, by heating **383** with sodium azide in DMF at 70–75 °C (Scheme 123). The azidoquinolines **384** was ruled out based on the IR spectrum which has no azido band. When **383** was heated with sodium methoxide in MeOH at reflux temperature, it underwent intramolecular cyclization to provide methyl 3-amino-4-chloro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (**386**) in 85% yield. Refluxing **386** with sodium azide in DMF afforded the novel tetracyclic 1,4,5,6,6*a*-pentaazabenzo[*a*]indacenes **387** in 96% yield. Alternatively, compound **387** could also be obtained by refluxing **385** with sodium methoxide in MeOH (Scheme 123).

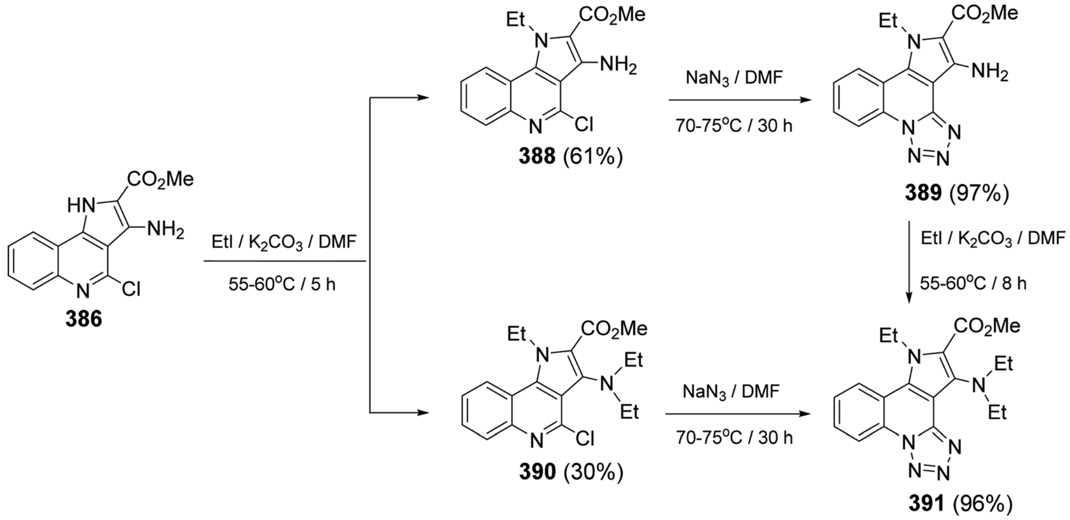
On the other hand, when a solution of **386** in dry DMF was treated with ethyl iodide in the presence of anhydrous K_2CO_3 at 55–60 °C, the methyl 3-amino-4-chloro-1-ethyl-pyrrolo-[3,2-*c*] quinoline-2-carboxylate (**388**), major product, was obtained in



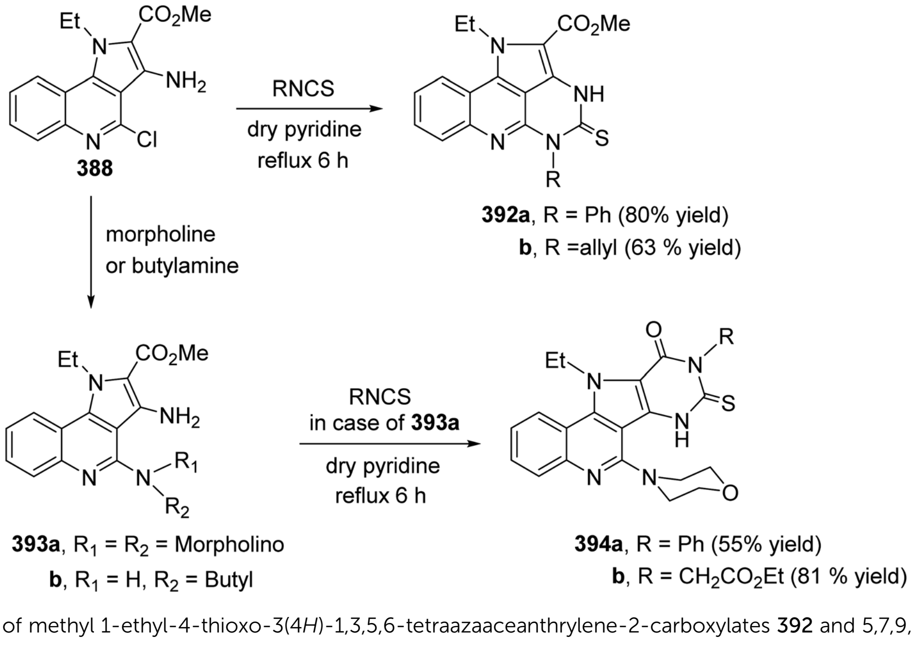
Scheme 123 Synthesis of methyl 3-amino-1,4,5,6,6*a*-pentaazabenzo[*a*]indacene-2-carboxylate (**387**).

61% yield. In addition to **388**, minor amounts of **390** was also obtained. Reaction of **388** and **390** with sodium azide, under similar reaction conditions as described before for the synthesis of **387**, yielded the novel tetracyclic systems **389** and its analog **391**, respectively, in quantitative yields (Scheme 124). Alternatively, compound **391** could also be obtained by heating a solution of **389** in dry DMF with ethyl iodide at 55–60 °C (Scheme 124).[139]

Also, Mekheimer and his co-workers[139] have reported the synthesis of novel tetracyclic systems incorporating a pyrimidine nucleus in addition to the pyrroloquinoline moiety utilizing the *N*-ethylpyrrolo[3,2-*c*]quinoline derivative **388** as starting material. Thus, reaction of **388** with isothiocyanates in dry pyridine under reflux conditions gave the corresponding novel methyl 1-ethyl-5-substituted-4-thioxo-3(4*H*)-1,3,5,6-tetraazaaceanthrylene-2-carboxylates **392** in 63–80% yields. On the other hand, treatment of **388** (1 equiv.) with morpholine (10 equiv.) in boiling absolute EtOH yielded the corresponding pyrrolo[3,2-*c*]quinoline derivative **393a**, in 79% yield, which reacted with isothiocyanates, under the same conditions described above, to yield the interesting 5,7,9,11-tetraazabenzo[*a*]fluorenes **394**, in 55–81% yields, as new model systems for pyrrolopyrimidoquinolines (Scheme 125). Furthermore, when **388** was heated in an excess of butylamine at reflux temperature, the versatile intermediate pyrrolo[3,2-*c*]quinolines **393b** was formed. Refluxing **393b** with ethyl chloroformate yielded the new methyl 5-butyl-1-ethyl-4-oxo-3(4*H*)-1,3,5,6-



Scheme 124 Synthesis of new 1,4,5,6,6*a*-pentaazabenzo[*a*]indacenes 389 and 391.

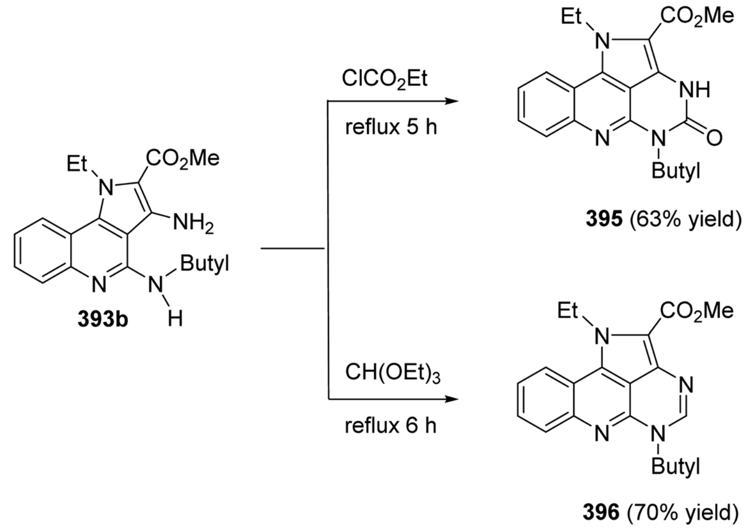


Scheme 125 Synthesis of methyl 1-ethyl-4-thioxo-3(4*H*)-1,3,5,6-tetraazaaceanthrylene-2-carboxylates 392 and 5,7,9,11-tetraazabenzo[*a*]fluorenes 394.

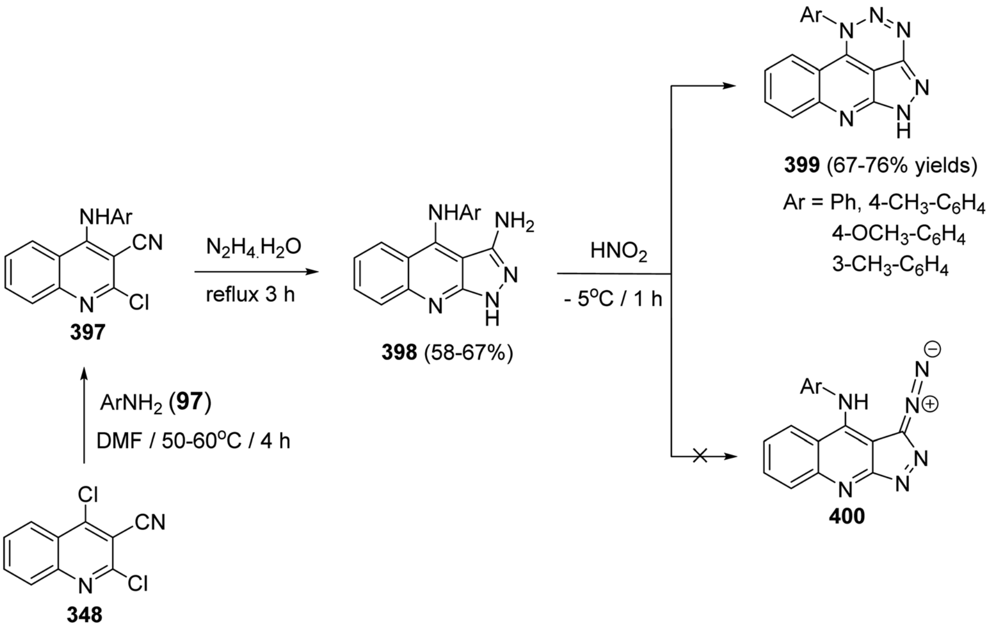
tetraazaaceanthrylene-2-carboxylate (**395**) in 63% yield. Meanwhile, refluxing **393b** with TEO afforded the methyl 5-butyl-1-ethyl-1,3,5,6-tetraazaaceanthrylene-2-carboxylate (**396**) in 70% yield (Scheme 126).

2.4.6. 1,2,3,4,5,6-Hexaazaacephenanthrylenes ring systems. Refluxing 4-amino-2-chloro-quinoline-3-carbonitriles **397** with an excess of hydrazine hydrate (80%) afforded 3-amino-4-arylamino-1*H*-pyrazolo[3,4-*b*]quinolines **398** in 58–67% yields. Diazotization of **398** yielded the new tetracyclic 1-aryl-1,5-dihydro-1,2,3,4,5,6-hexaazaacephenanthrylenes **399**, in 67–76% yields (Scheme 127). The other possible structure **400** was readily ruled out for the reaction products on the basis of spectral data.[140]

2.4.7. Isoxazolo[3′,4′:4,5]pyrrolo(or thieno)[2,3-*c*]quinolines. An efficient approach was developed by Mekheimer and co-workers[141] to synthesis the new tetracyclic isoxazolo[3′,4′:4,5]pyrrolo(or thieno)[3,2-*c*]quinolines **403**. By refluxing of **350** and **386** with primary aliphatic amines in DMF, the corresponding amines **351**, **401** were obtained, which were transformed into the 3-azido-pyrrolo(or thieno)quinolines **402** in 74–93% yields, when treated with sodium nitrite in H_2SO_4 (70%) at −5 °C, followed by reaction of the non-isolated pyrrolo(or thieno)quinoline diazonium sulfate with an aqueous solution of NaN_3



Scheme 126 Synthesis of methyl 5-butyl-1-ethyl-4-oxo-3(4*H*)-1,3,5,6-tetraazaaceanthrylene-2-carboxylate (**395**) and methyl 5-butyl-1-ethyl-1,3,5,6-tetraazaaceanthrylene-2-carboxylate (**396**).



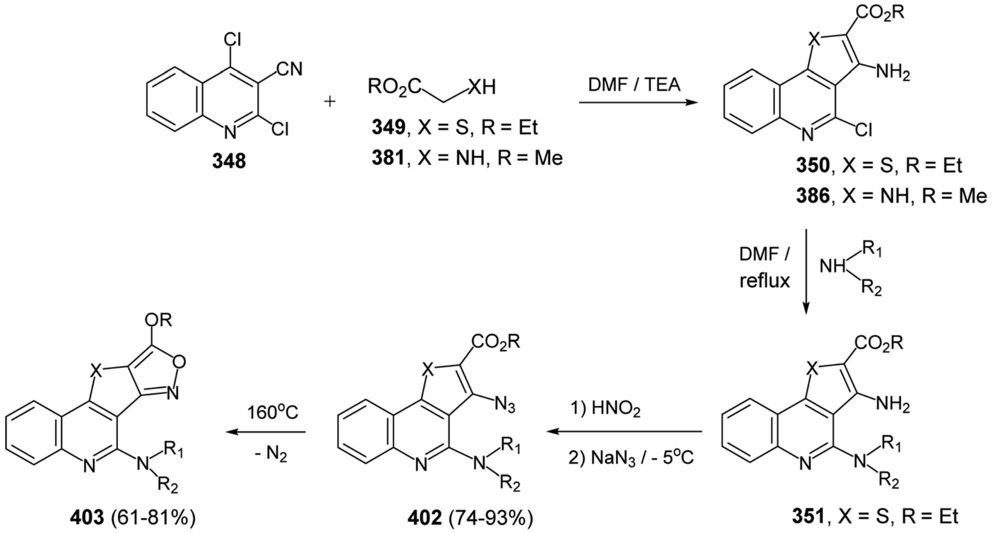
Scheme 127 Synthesis of 1-aryl-1,2,3,4,5,6-hexaazaacephenanthrylenes **399** from **348**.

at −5 °C. Conversion of azides **402** into the angular tetracyclic isoxazolo[3′,4′:4,5]pyrrolo(or thieno)[2,3-*c*]quinolines **403** was performed by refluxing in bromo-benzene (Scheme 128).

2.4.8. [1,2,4]Triazino[4′,3′:1,5]pyrazolo[4,3-*c*]quinolines.

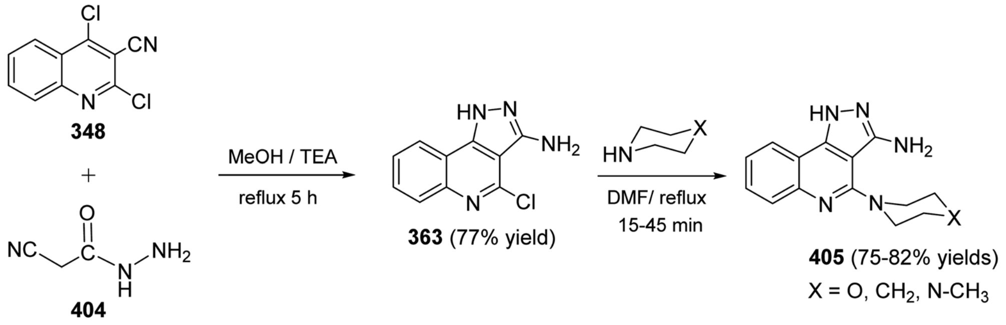
In 2017, Mekheimer *et al.*[142] have described the first synthesis of new four heterocyclic ring systems 10-amino-6,9-disubstituted-[1,2,4]triazino[4′,3′:1,5]pyrazolo[4,3-*c*]quinoline derivatives. Reacting **348** with cyanoacetic acid hydrazide (**404**) in refluxing MeOH in the presence of Et_3N gave the unexpected 3-amino-4-chloro-1*H*-pyrazolo[4,3-*c*]quinoline (**363**) (Scheme 129). The mechanism for the formation of **363** is shown in Scheme 130. Heating **363** with cyclic secondary amines (piperidine, morpholine and 1-methyl-piperazine) in DMF at reflux temperature furnished the corresponding 4-amino-pyrazolo[4,3-*c*]quinolines **405** (Scheme 129).

Then, compounds **363** and **405** were utilized as precursors for the synthesis of the new tetracyclic systems **413**. Diazotization of **363** and **405** yielded the corresponding diazonium salts **411**, which were then subjected to couple with different active methylene nitriles **412**, in aqueous EtOH containing sodium acetate, to give the novel perianellated tetracyclic ring system 10-amino-6,9-disubstituted-[1,2,4]triazino[4′,3′:1,5]pyrazolo[4,3-*c*]quinolines **413** (Scheme 131).[142] The structures of all the newly synthesized compounds were unambiguously confirmed by spectroscopic and analytical techniques. Furthermore, X-ray crystallographic analysis on compound **413c** was performed to determine the absolute configuration of the products **413**. The

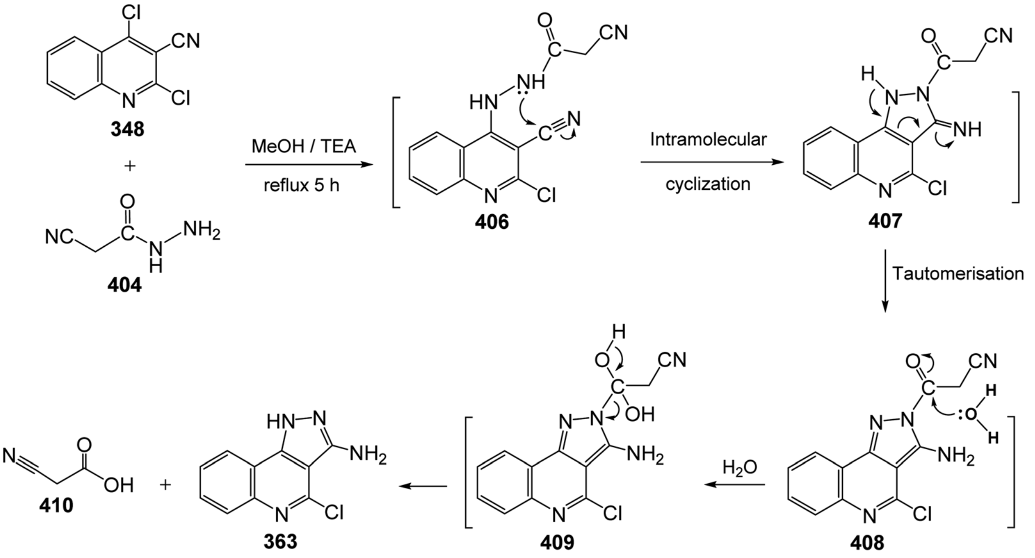


403	R	R1	R2	X
a	Et	H	Bu	S
b	Et	H	*i*-Bu	S
c	Et	H	*c*-C_6H_{11}	S
d	Et	morpholino		S
e	Et	4-methyl-piperidino		S
f	Me	morpholino		NH
g	Me	piperidino		NH

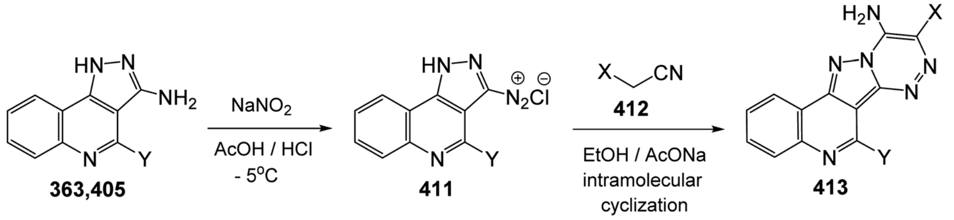
Scheme 128 Synthesis of isoxazolo[3′,4′:4,5]pyrrolo(or thieno)[3,2-*c*]quinolines **403**.



Scheme 129 Synthesis of 3-amino-1*H*-pyrazolo[4,3-*c*]quinoline derivatives **405**.

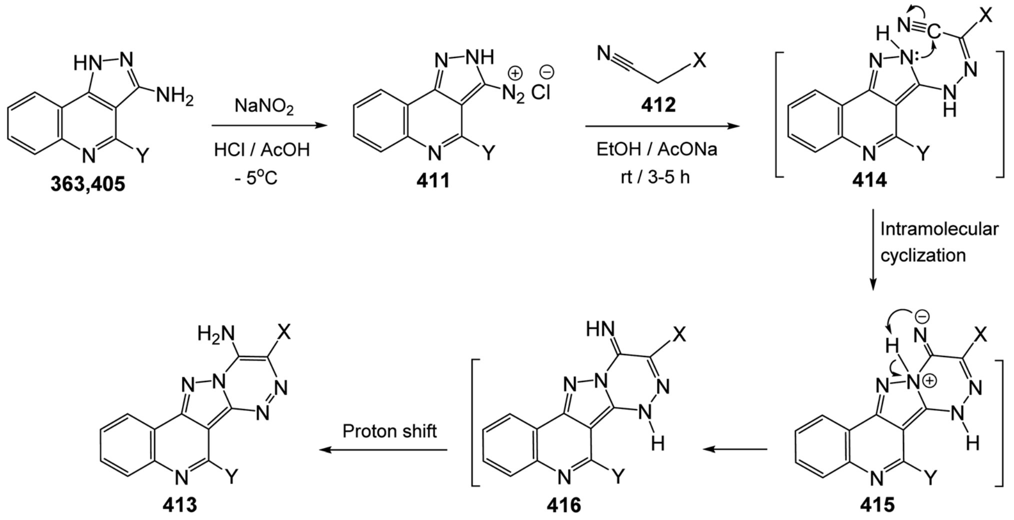


Scheme 130 Reaction mechanism for the formation of 3-amino-4-chloro-1*H*-pyrazolo-[4,3-*c*]quinoline (**363**).

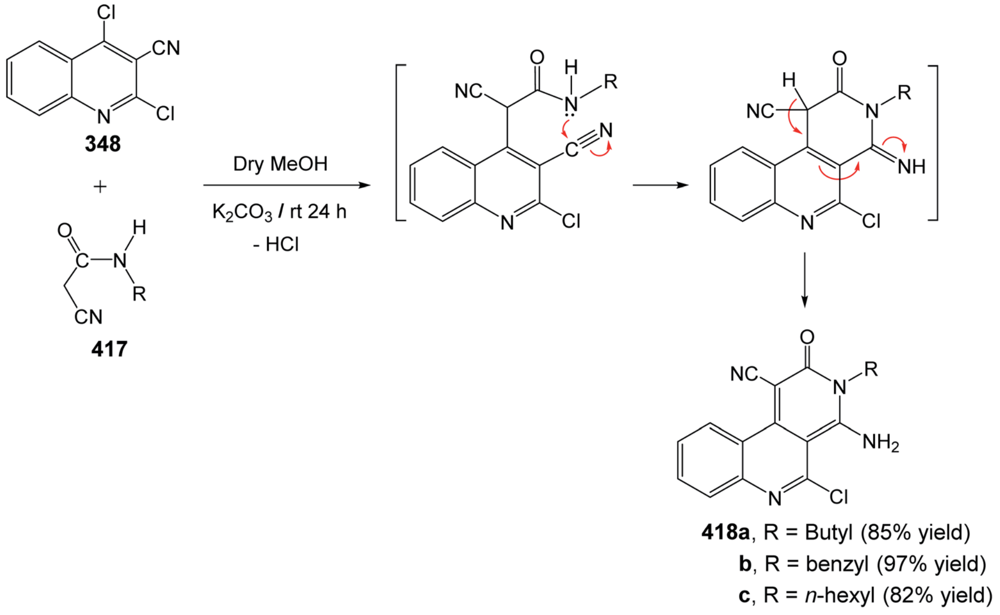


413	Y	X
a	Cl	$CSNH_2$
b	1-Methylpiperazino	CO_2Et
c	Piperidino	CN
d	Morpholino	$CONH_2$
		CONHPh

Scheme 131 Coupling reaction of **411** with active methylenes **412**.



Scheme 132 Reaction mechanism for the formation of 9-substituted-[1,2,4]triazino[4′,3′:1,5]-pyrazolo[4,3-*c*]quinolines **413**.

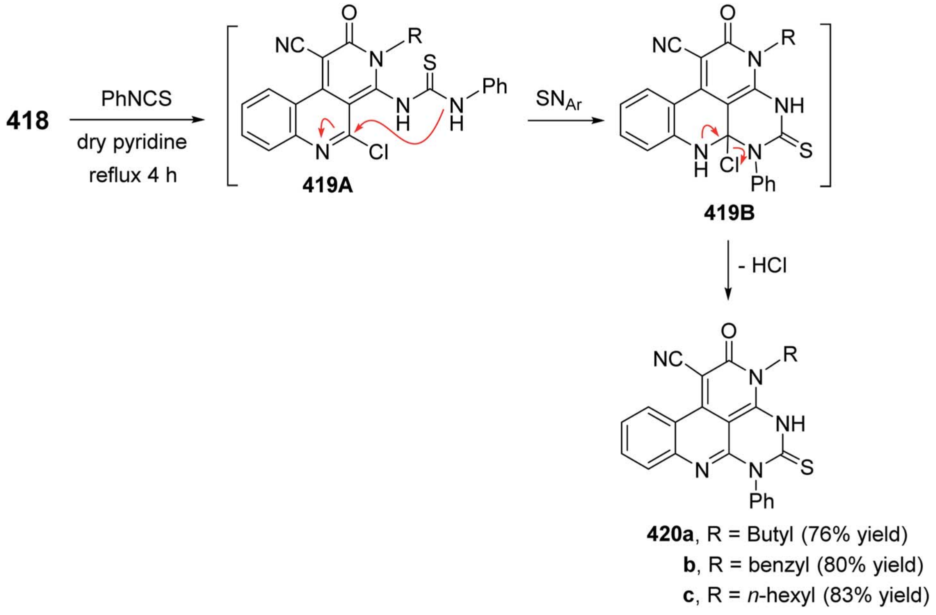


Scheme 133 Synthesis of 3-alkyl-4-amino-5-chloro-2-oxo-2,3-dihydrobenzo[*c*][2,7]naphthy-ridine-1-carbonitriles **418**.

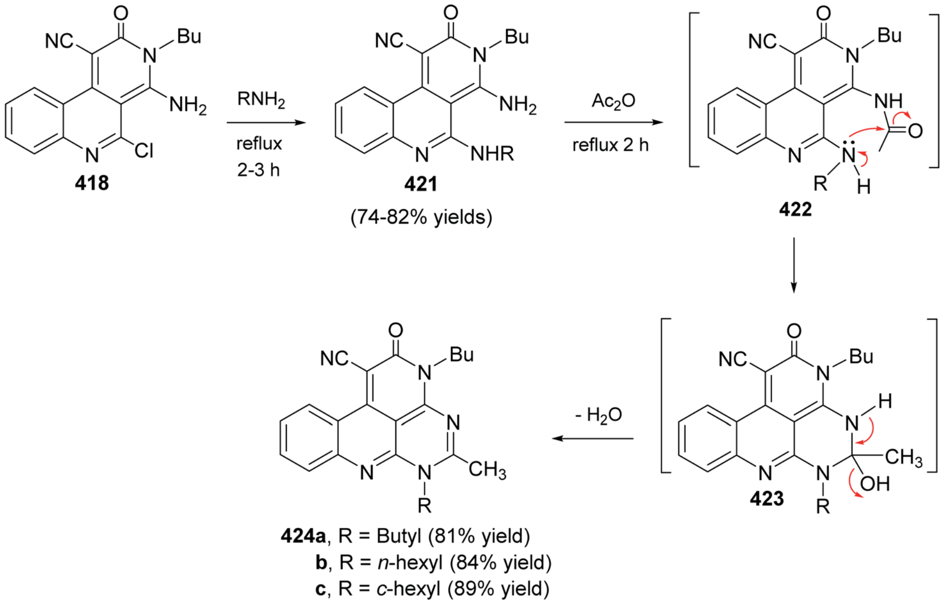
probable mechanism leading to the formation of 9-substituted-[1,2,4]triazino[4′,3′:1,5]pyrazolo[4,3-*c*]quinolines **413** is outlined in Scheme 132.

2.4.9. Benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridines. In 2018, Mekheimer and his group[143] have developed unprecedented synthesis of benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridines with structural analogy to pyrido[4,3,2-*mn*]-acridines present in the marine tetracyclic pyridoacridine alkaloids. Reaction of **348** with an equimolecular amount of cyanoacetamides **417** in absolute MeOH containing a catalytic amount of K_2CO_3 at room temperature gave the new benzo[*c*][2,7]naphthyridines **418**, only in one step (Scheme 133). When **418** were reacted with phenyl isothiocyanate in refluxing dry pyridine, the corresponding novel 3-alkyl-2-oxo-6-phenyl-5-thioxo-3,4,5,6-tetrahydro-2*H*-benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **420** were indeed formed in good yields, *via* intermediacy of **419** (Scheme 134).

When **421**, obtained by reacting **418** (R = butyl) with various alkyl amines, were heated with acetic anhydride under reflux conditions, the novel 3,6-dialkyl-5-methyl-2-oxo-3,6-dihydro-2*H*-



Scheme 134 Synthesis of 3-alkyl-2-oxo-6-phenyl-5-thioxo-3,4,5,6-tetrahydro-2*H*-benzo[*c*]-pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **420**.

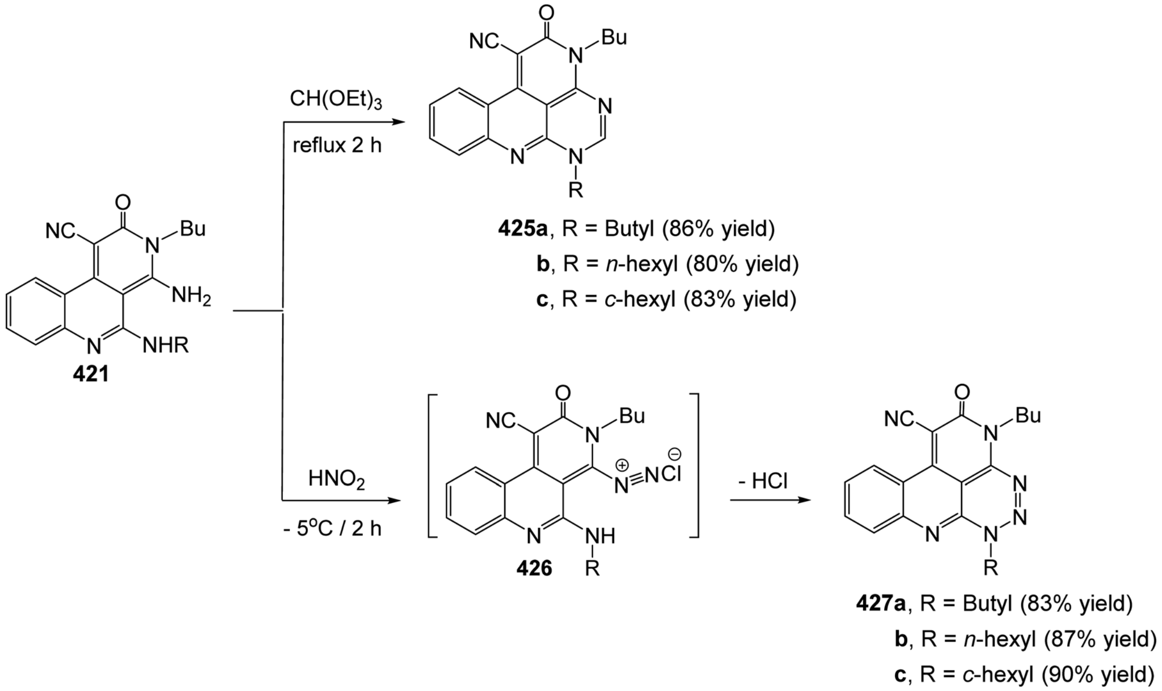


Scheme 135 Synthesis of 3,6-dialkyl-5-methyl-2-oxo-3,6-dihydro-2*H*-benzo[*c*]pyrimido-[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **424**.

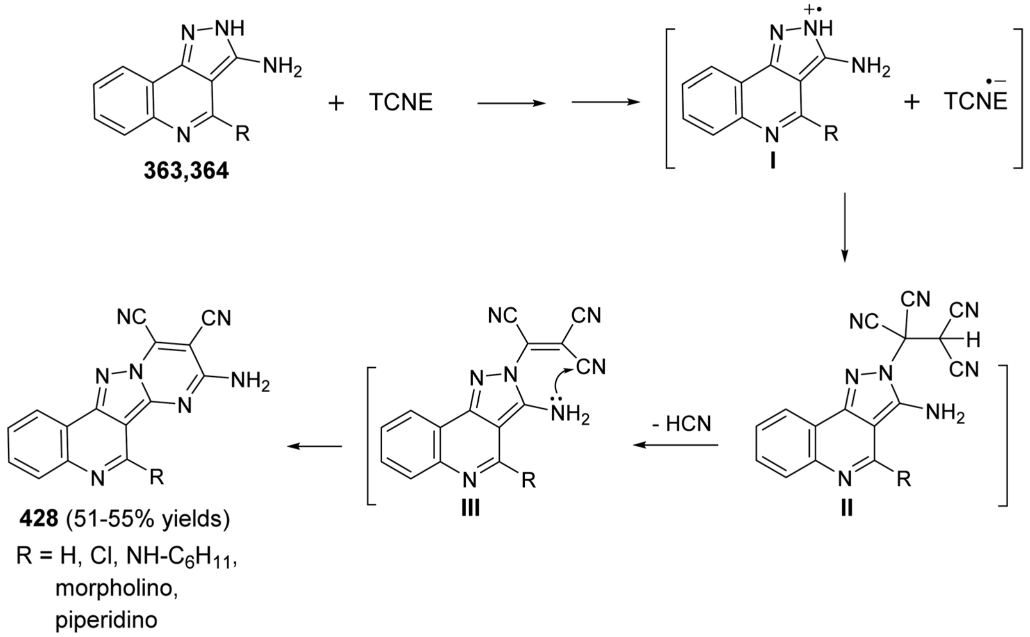
benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **424** were isolated in very good yields (Scheme 135).[143]

Moreover, refluxing **421** with TEO gave the new 3,6-dialkyl-2-oxo-3,6-dihydro-2*H*-benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **425** in 80–86% yields (Scheme 136). On the other hand, treatment of **421** with NaNO$_2$ in H$_2$SO$_4$ (70%) at −5 °C yielded the previously unreported 3,6-dialkyl-2-oxo-3,6-dihydro-2*H*-benzo[*c*][1,2,3]triazino[4,5,6-*ij*]-[2,7]naphthyridine-1-carbonitriles **427** in excellent yields (Scheme 136).[143]

2.4.10. Pyrimido[1′,2′:1,5]pyrazolo[4,3-*c*]quinolines. The synthesis of tetracyclic pyrimidopyrazoloquinolines **428** has described by Hassan and his group.[144] On reacting tetracyanoethylene (TCNE) (2 equiv.) (as π-acceptor) with pyrazolo[4,3-*c*] quinolines **363**, **364**[137] (1 equiv.) (as donor) in DMF furnished



Scheme 136 Synthesis of benzo[c]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **425** and benzo[c][1,2,3]triazino[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **427**.



Scheme 137 Synthesis of 8-amino-6-substituted-pyrimido[1′,2′:1,5]pyrazolo[4,3-c]quinoline-9,10-dicarbonitriles **428**.

a green colour, which rapidly disappeared to give the tetracyclic products, namely, 8-amino-6-substituted-pyrimido[1′,2′:1,5]pyrazolo[4,3-*c*]quinoline-9,10-dicarbonitriles **428**, in 51–55% yields. This behavior can be explained as due to initial formation of unstable charge-transfer complexes between TCNE and pyrazoloquinolines **363**, **364** followed by completion of electron transfer from **363**, **364** to TCNE leading to the formation of TCNE anion radical in contact with pyrazoloquinoline cation radical **I**. These radicals combine to furnish the adduct **II**. Elimination of one molecule of HCN gives **III** which undergoes intramolecular cyclization *via* attack of the amino group on the CN one to afford the pyrimidopyrazoloquinolines **428** (Scheme 137).

Conflicts of interest

There are no conflicts to declare.

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