

β -HALOVINYLLALDEHYDES – AS VERSATILE REACTIVE INTERMEDIATES IN THE SYNTHESSES OF CONDENSED FUSED RING POLYCYCLIC HETEROCYCLES

Batchu Chandra Sekhar, ^{†*} Sukuru Raghu Ramadas, and Devella Venkata Ramana^{††}

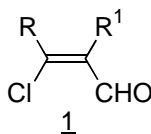
Department of Chemistry, Indian Institute of Technology, Chennai – 600 036, India

Dedicated to Prof. S. R. Ramadas on the occasion of his 70th birthday.

Abstract - New approaches for the syntheses of a wide range of mono and polycyclic heterocycles utilizing β -halovinylaldehydes are summarized. The syntheses of a variety of heterocycles employing this synthon are discussed vividly in this review with 80 reference citations.

INTRODUCTION

A number of reports have appeared describing Vilsmeier-Haack reaction of active methylene compounds.



[†] Present address: Dr. Reddy's Research Foundation, 7-1-27, Ameerpet, Hyderabad – 500 050, India.
^{††} Emeritus Scientist (CSIR, India).

These reactions lead mainly to the formation of β -halovinylaldehydes (**1**) which constitute a class of compounds that have served as useful intermediates for the synthesis of quite a variety of heterocycles. Because of the easy accessibility and high reactivity these β -halovinylaldehydes have been extensively employed as versatile reactive intermediates in the syntheses of large variety of aliphatic, aromatic, heterocyclic compounds. The addition-elimination followed by intramolecular aldol type of condensation of β -halovinylaldehydes with methyl mercaptoacetate or ethyl mercaptoacetate gave condensed 5 membered or 6 membered thiophene derivatives, respectively. Condensation and cyclization of β -halovinylaldehydes either with 1,2- or 1,4-dinucleophiles results in 5 or 7 membered heterocycles. Derivatives prepared in this fashion relate to patents or experiments to develop potent heterocycles, as well as studies on a new or efficient method for the synthesis of potential heterocycles aiming at agrochemicals or drugs. In spite of enormous number of review articles on the utility of these compounds in the synthesis of heterocycles, to our knowledge this subject has never been surveyed. The Vilsmeier-Haack reaction and its synthetic applications have been reviewed by Seshadri¹ and Weißenfels² in seventies only. However, these reviews are now obsolete. Therefore it is felt highly desirable to highlight in this review the reactions of β -halovinylaldehydes (leading to a variety of heterocycles) which have not been referred in the aforementioned two reviews.

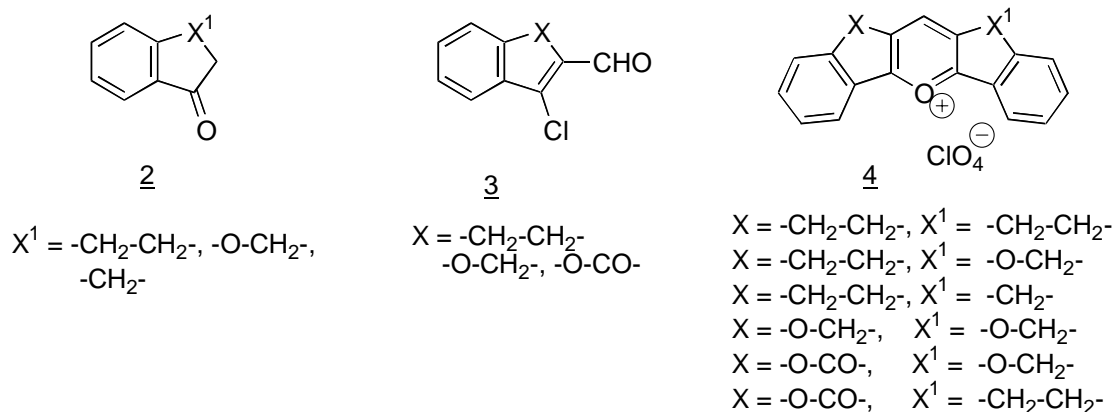
This review mainly refers to the following category of heterocycles prepared mostly based on the nature of the substrate employed or on the nature of the heterocycles formed.

1. Pyrylium salts.
2. Phthalides.
3. Benzofuran and benzopyran derivatives.
4. Thiophene derivatives.
5. Isoxazoles.
6. Thiadiazolium salts.
7. Fused pyrazoles.

8. Pyrimidine heterocycles.
9. Fused quinoline heterocycles.
10. Isoquinoline derivatives.
11. Tetracyclic 1,5-benzoxazepine, 1,5-benzothiazepine, 1,5-benzodiazepine derivatives.

1. PYRYLIUM SALTS

Polycyclic pyrylium perchlorates (**4**) were prepared³ in a novel manner by cyclization of β -chlorovinylaldehydes (**3**) with ketones (**2**) in presence of HClO_4 and acetic acid in a single pot reaction. The reaction involves the condensation of formyl function with active methylene group, followed by addition and elimination of chlorine (Scheme I).

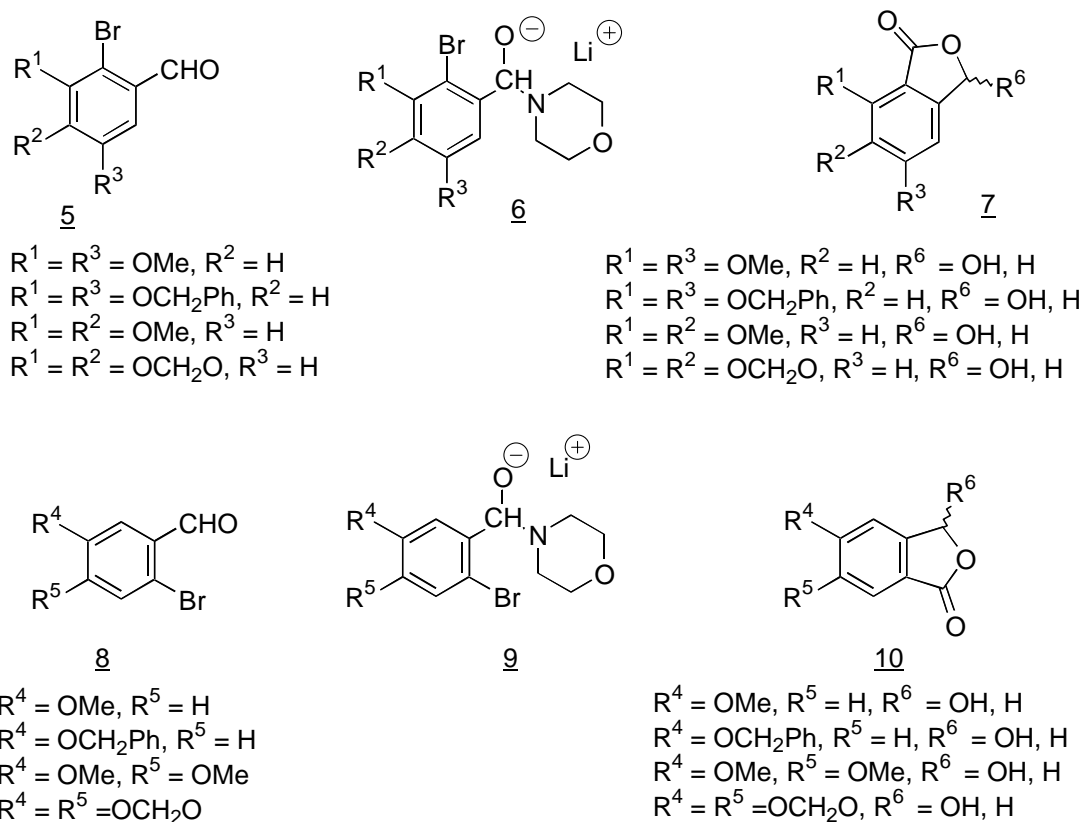


Scheme I

2. PHTHALIDES

Phthaldehydic acids and phthalides are useful synthons for a variety of natural products. A general and efficient method for the synthesis of phthaldehydic acid (**7**, **10**, $\text{R}^6=\text{R}^5=\text{OH}$) and phthalides (**7**, **10**, $\text{R}^6=\text{R}^5=\text{H}$), many of which are key intermediates in the synthesis of polycyclic aromatic natural products, have been prepared as shown below.⁴ In this method, *o*-bromobenzaldehydes (**5**, **8**) were first protected *in situ* as α -morpholino alkoxides (**6**, **9**) by reaction with lithium morpholide. Treatment of the α -morpholino alkoxides with *n*-butyllithium (to exchange bromine with lithium) followed by sequential

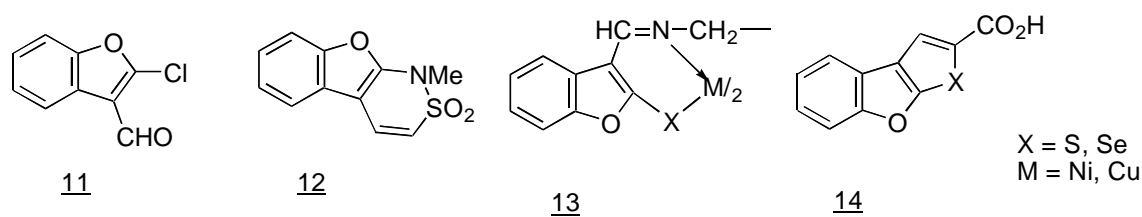
treatment with solid CO₂ and dilute acid afforded the phthaldehydic acids (**7**, **10**, R⁶=R⁵=OH) which on reduction with NaBH₄ furnished the desired phthalides (**7**, **10**, R⁶=R⁵=H) respectively (Scheme II).



Scheme II

3. BENZOFURAN AND BENZOPYRAN DERIVATIVES

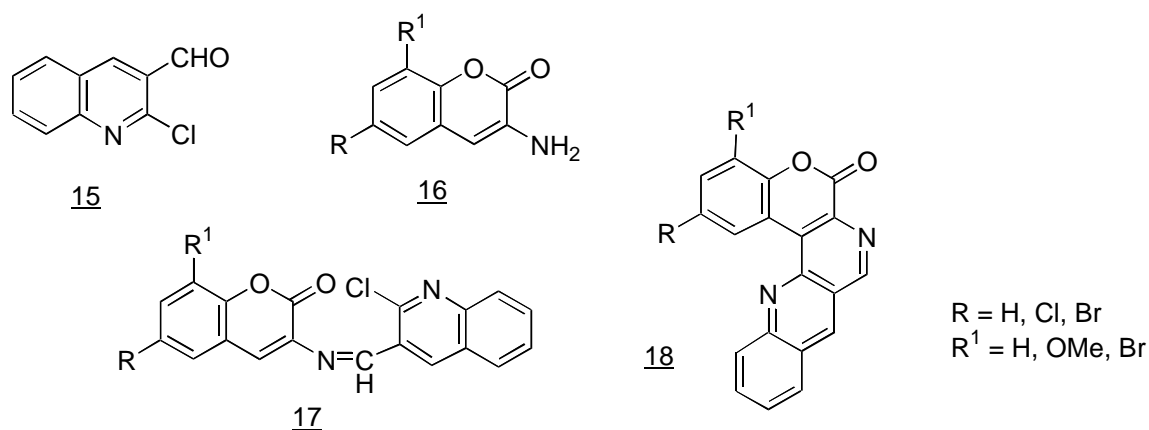
The synthesis of novel heterocyclic ring systems such as benzofurothiazine (**12**) is described⁵ from 2-chloro-3-benzofurancarboxaldehyde (**11**) with *N*-methylmethanesulfonamide followed by treatment with sodium hydride (Scheme III). Very recently a series of condensed heterocycles (**14**) and metal complexes (**13**) were also synthesized⁶ from mercapto- and selenobenzofurancarboxaldehydes (**11**) (Scheme III) adopting the same procedure.



Scheme III

Cyclodehydrochlorination method

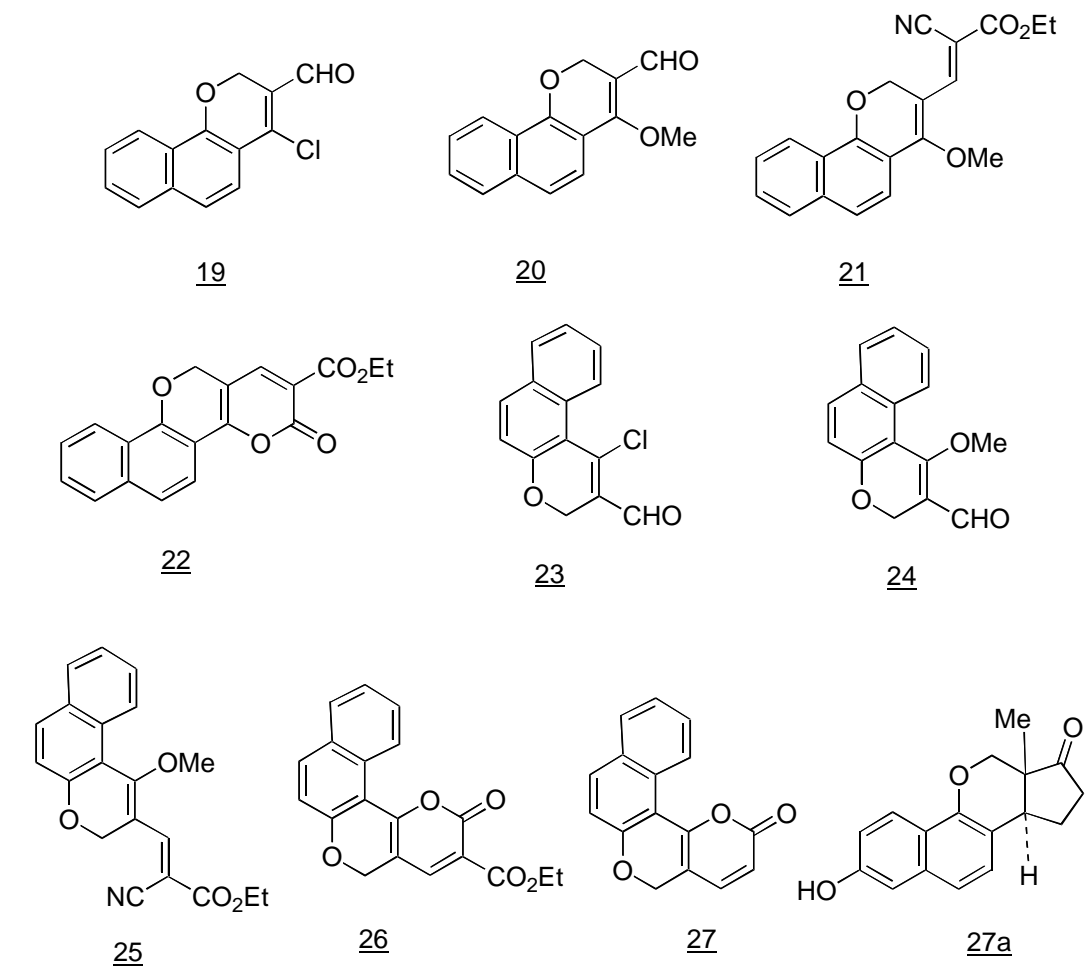
Prasad and Darbarwar have reported⁷ the synthesis of [1]benzopyrano[3,4-*h*]benzo[*b*]-1,6-naphthyridin-6-ones (**18**) from 3-aminocoumarins (**16**) and 2-chloro-3-formylquinoline (**15**). The reaction involves aldimine formation of the carboxaldehyde (**15**) in glacial acetic acid followed by cyclodehydrochlorination of the corresponding 3-(2-chloroquinolinylmethylidenamino)-2*H*-[1]benzopyran-2-ones (**17**) in dry pyridine (Scheme IV).



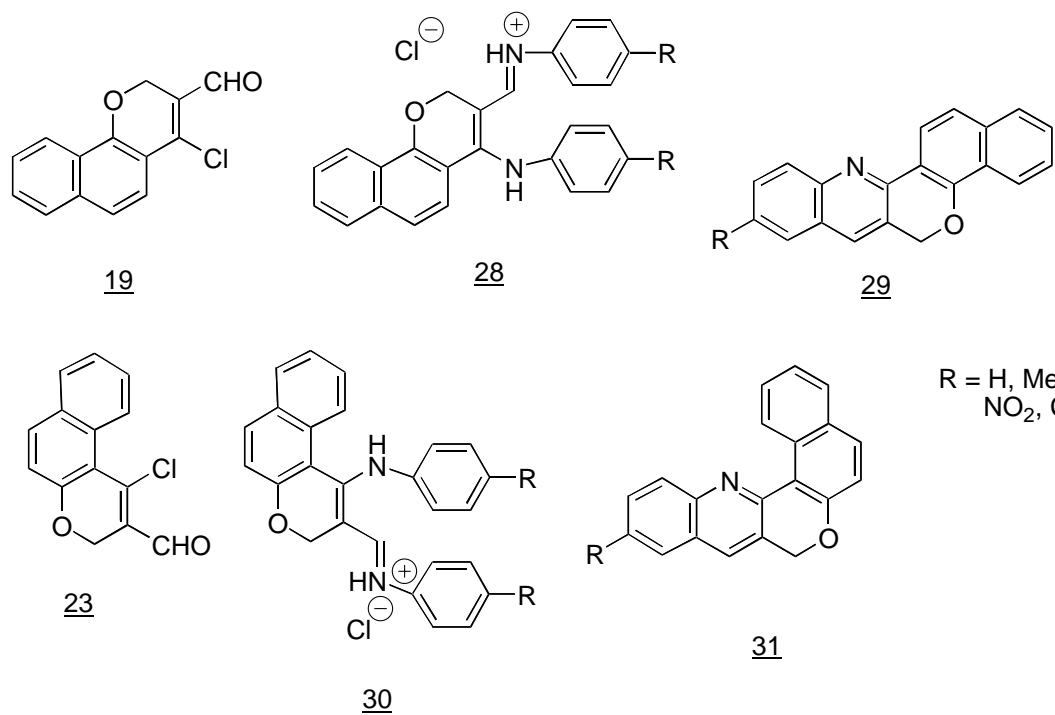
Scheme IV

Thermal Cyclization

Polycyclic coumarin analogs of potent carcinogenic oxacoumarins (**22**, **26**, **27**) (Scheme V) have been synthesized⁸ starting from chloro aldehydes (**19**) and (**23**). The chloro aldehydes (**19**) and (**23**) were converted to methoxy derivatives (**20**) and (**24**) by conventional procedure which on condensation with cyanoacetic ester gave the nitrile derivatives (**21** and **25**) which on further heating in pyridine furnished the corresponding major ester derivatives (**22**, **26**), along with a minor decarboxylated derivative (**27**). It is interesting to mention here that **19** would serve as a very useful intermediate for the synthesis of 11-oxaequilin (**27a**).



Scheme V



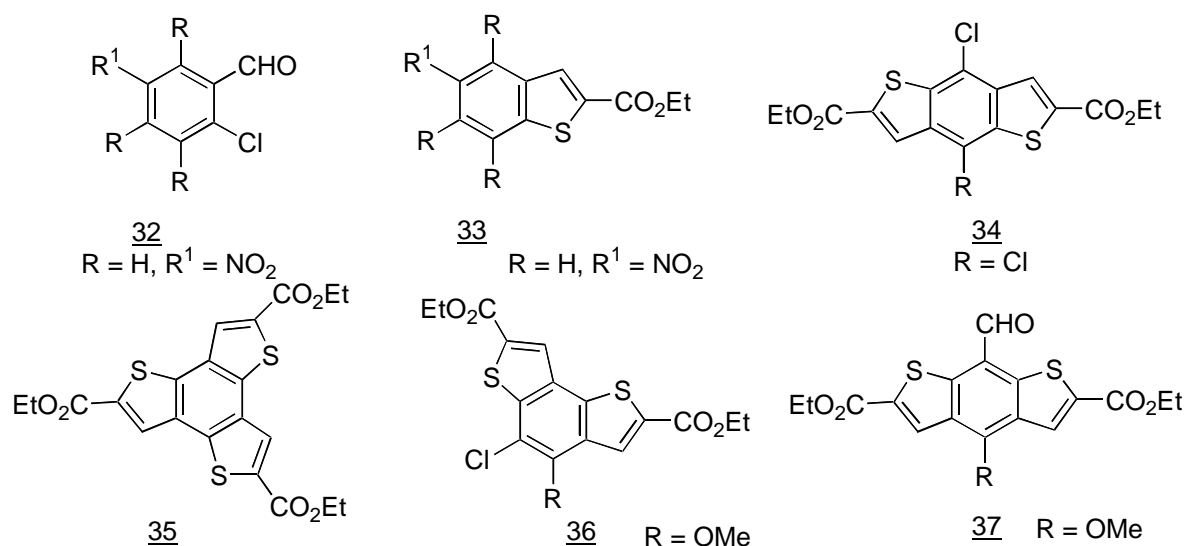
Scheme VI

Syntheses of naphthopyranoquinolines (**29** and **31**) (Scheme VI) having bay region and Fjord region in the molecules were recorded⁸ by the thermal cyclization of enaminoimine hydrochlorides (**28** and **30**). The chloro aldehydes (**19** and **23**) on reaction with substituted anilines afforded enaminoimine hydrochloride (**28**) and (**30**), which on thermolysis underwent ring closure, with the elimination of arylamine hydrochloride to afford the corresponding naphthopyranoquinolines (**29** and **31**) (Scheme VI).

4. THIOPHENE DERIVATIVES

Employing Intramolecular Aldol Condensation Concept

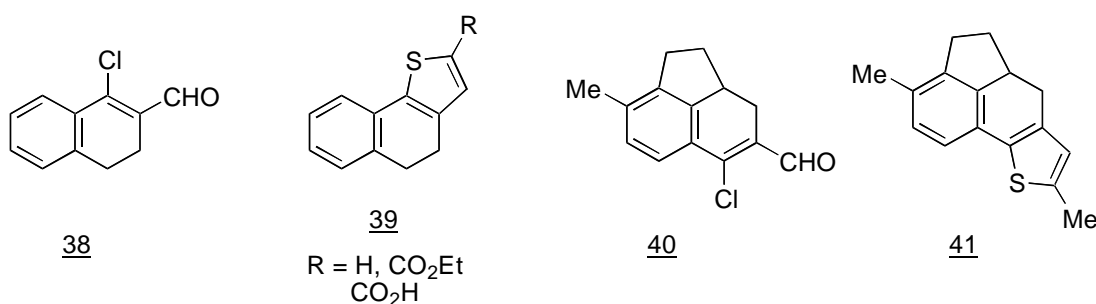
β -Halovinylaldehydes were thiolated into condensed thiophene derivatives initially. For example, the substituted chlorobenzaldehydes (**32**) were converted into the thiophene derivatives⁹ in a single step (**33-37**) on reaction with ethyl mercaptoacetate in presence of triethylamine. The mechanism of the reaction involves the addition and elimination one, followed by intramolecular aldol type of condensation as shown below (Scheme VII).



Scheme VII

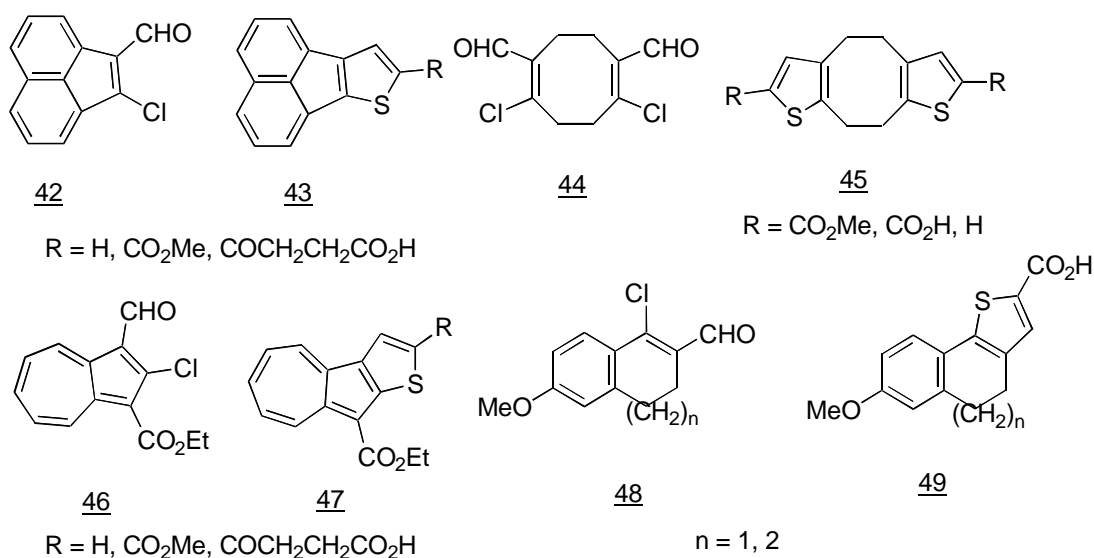
Carbocyclic Thiophenes

Recently the preparation of thiophene (**39**) from the reaction of 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde (**38**) with ethyl mercaptoacetate and sodium ethoxide was reported.¹⁰ The reaction is nothing but an extension of Wagner thiophene synthesis.⁹ Hence the methodology is also extended to the synthesis of polycyclic thiophene derivatives (**41**) from β -chloroaldehydes (**40**) by the action of ethyl bromoacetate or ethyl α -bromopropionate and sodium sulfide in DMF.¹¹ (Scheme VIII).



Scheme VIII

Condensation of acenaphthochloroaldehydes (**42**) with methyl mercaptoacetate, triethylamine and KOH in aqueous pyridine gave acenaphthothiophenes, (**43**).¹² One should note that such a simple procedure for such polycyclic thiophenes is made possible only through β -chlorovinylaldehydes serving as suitable synthons. Several interesting carbocyclic thiophene derivatives (**45**, **47**) from β -chloroaldehydes (**44**, **46**) have also recently been prepared (Scheme IX).^{13, 14} The syntheses of naphthothiophenecarboxylic acid

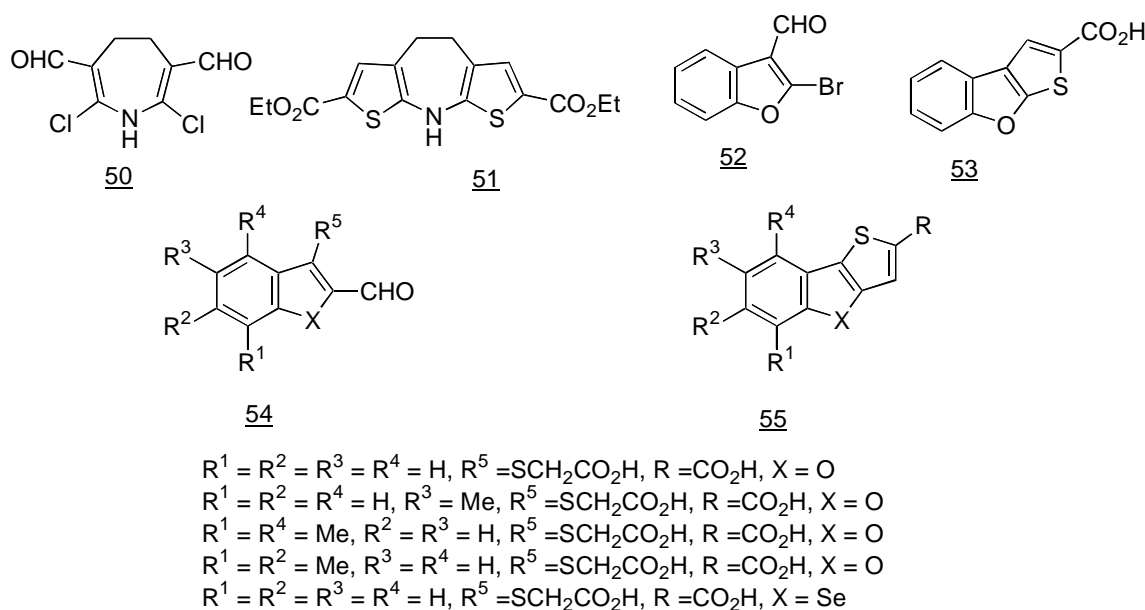


Scheme IX

derivatives (**49**) were also achieved¹⁵ from the corresponding chloroaldehydes (**48**) by the condensation of thioglycolic acid in weakly basic medium followed by cyclization employing 30% aq. KOH (Scheme IX). These reactions indicate the importance of β -chlorovinylaldehyde as excellent and versatile synthons.

Heterocyclic Thiophene

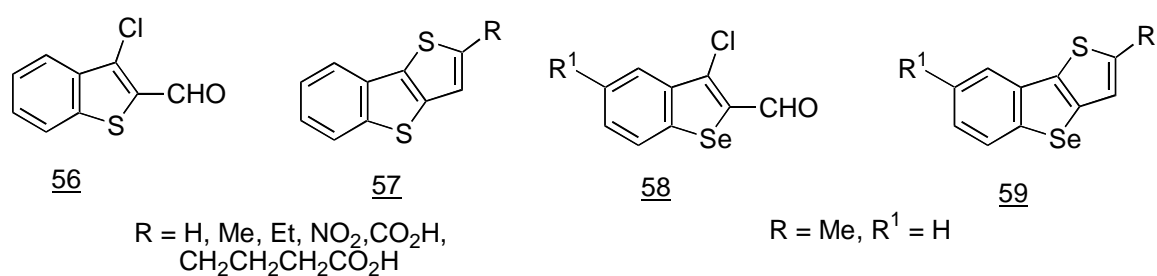
Aubert *et al.*¹⁶ have reported novel heterocyclic systems such as bithiophene isosteres of dibenzo[*b,f*]azepins. Bis- β -chlorovinylaldehydes (**50**) were converted in a single step into the dithieno[*b,f*]azepins (**51**) by condensation with ethyl 2-mercaptoacetate and triethylamine in pyridine. Recently the thienobenzofurancarboxylic acid (**53**) was obtained in a simple way from 2-bromobenzofuran-3-carboxaldehyde (**52**) by condensing it with mercaptoacetic acid.¹⁷ Quite similar to this procedure is the reported¹⁸ syntheses of thienobenzofurans and its derivatives (**55**) from β -chloroaldehydes (**54**) (Scheme X).



Scheme X

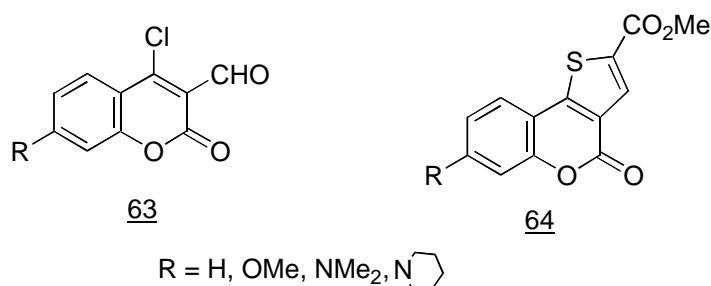
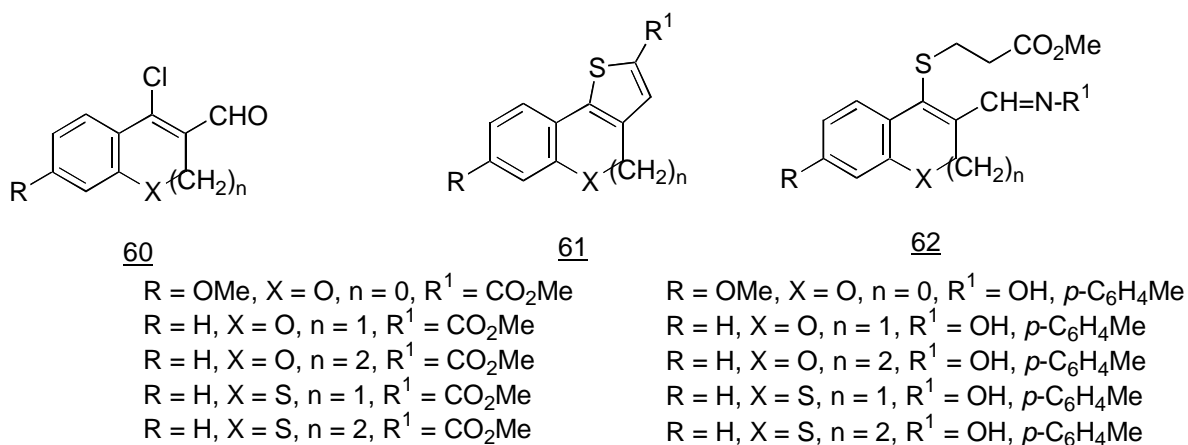
Interesting thienobenzothiophene derivatives (**57**) were prepared from 2-formyl-3-chlorobenzo[*b*]-thiophene (**56**) by condensation with thioglycolic acid, followed by ring closure in strongly alkaline medium. Several electrophilic substitution reactions of **57** including formylation, acetylation,

succinylation, nitration and bromination were also described.¹⁹ The synthesis of benzoselenopheno[3,2-*b*]thiophene (**59**) by cycloaddition of **58** with thioglycolic acid was investigated.¹⁸ Refluxing **58** with copper-quinoline gave the desired heterocycle (**59**) (R=H, R¹=Me). This was acylated under Friedel-Crafts condition to **59** (R=Ac, R¹=Me) which was reduced to **59** (R=Et, R¹=Me) (Scheme XI).



Scheme XI

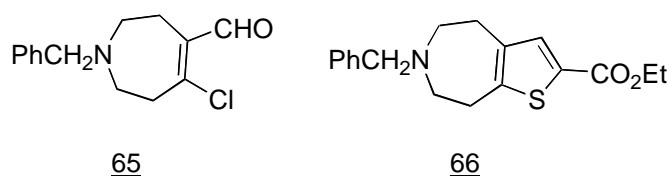
A simple and convenient method for the preparation of another class of condensed thiophene derivatives (**61**) has been reported from our laboratories²⁰ starting with heterocyclic β -chlorovinylaldehydes (**60**) and



Scheme XII

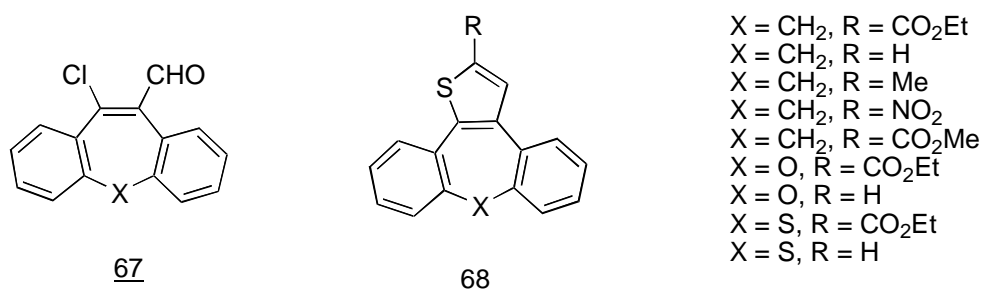
methyl mercaptoacetate in a single step quite recently (Scheme XII). The condensation of β -chlorovinylaldehydes with methyl β -mercaptoacetate as a possible route to the synthesis of hitherto unknown 11-thiasteroids (**62**) was also attempted,²¹ though unsuccessful, from our laboratory. Chloroformylcoumarins (**63**) on reaction with methyl thioglycolate in presence of triethylamine and KOH afforded thienocoumarincarboxylates (**64**). Interestingly, the fluorescence properties of these compounds were reported earlier by Weißenfels *et al.*²² in 1989 (Scheme XII).

The preparation of thienoazepines (**66**) and its derivatives was achieved²³ from chloroformyl derivative (**65**) and mercaptoacetic acid in pyridine and triethylamine (Scheme XIII) as shown below.



Scheme XIII

Condensation of tricyclic heterocyclic β -chloroaldehydes (**67**) with sodium sulfide or selenide and ethyl bromoacetate resulting in the formation of the complex tetracyclic heterocycles (**68**) was described²⁴ (Scheme XIV) for the first time as the simplest method.

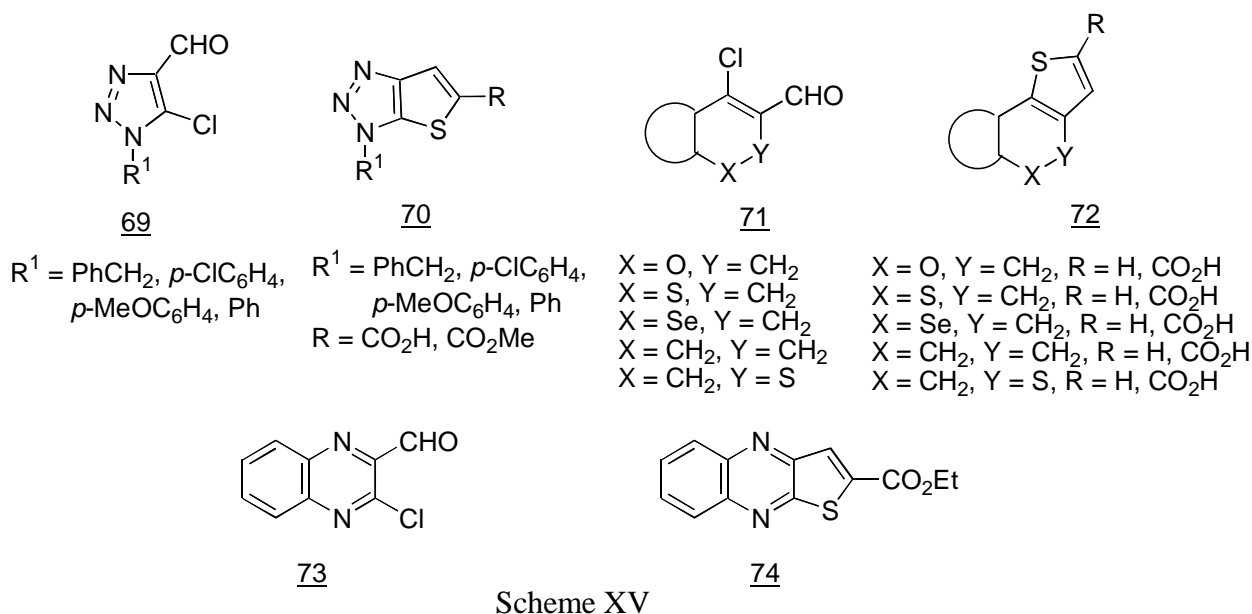


X = CH₂, R = CO₂Et
X = CH₂, R = H
X = CH₂, R = Me
X = CH₂, R = NO₂
X = CH₂, R = CO₂Me
X = O, R = CO₂Et
X = O, R = H
X = S, R = CO₂Et
X = S, R = H

Scheme XIV

Fused thienoazoles (**70**) that are of interest as a potential source of thienyl nitrones have been synthesized²⁵ from 5-chloro-4-formyltriazoles (**69**) by reaction with methyl mercaptoacetate and Na₂CO₃. However, the attempted decarboxylation led to the decomposition of the ring system (Scheme XV). Novel

heterocyclic systems having a condensed thiophene ring such as thienobenzopyran, thienobenzothiopyran, benzodithiophene (**72**) and their preparations were described²⁶ from chloroformyl derivatives (**71**) via condensation with thioglycolic acid followed by treatment with concentrated KOH. Thienoquinoxalinecarboxylates (**74**) were achieved²⁷ from quinoxalinechloroaldehydes (**73**) and ethyl mercaptoacetate (Scheme XV) adopting exactly the above mentioned methodology.



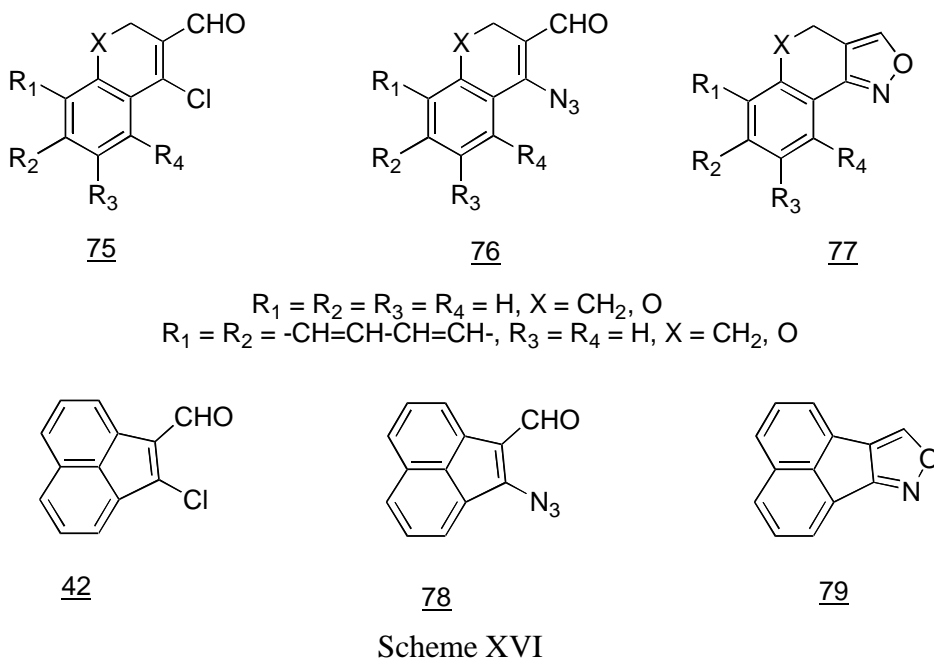
In conclusion it is to be pointed out that the condensation of chloro aldehydes either with mercapto acids or esters in presence of base was utilized in the synthesis of a variety of fused polycyclic heterocycles as discussed above.

5. ISOXAZOLES

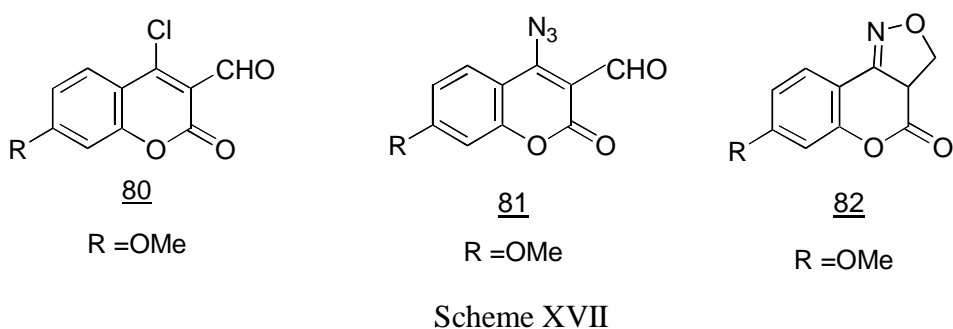
Cyclization via Azidolysis

Polycyclic isoxazoles (**77**) were obtained²⁸ by thermal cyclisation of azido aldehydes (**76**). For example, the β -chlorovinylaldehydes (**75**) and (**42**) were converted to azido aldehydes (**76**) and (**78**) by reaction

with NaN_3 in DMSO. The azides were cyclized thermally to isoxazoles (**77**) and (**79**) by reflux in dichloromethane (Scheme XVI).

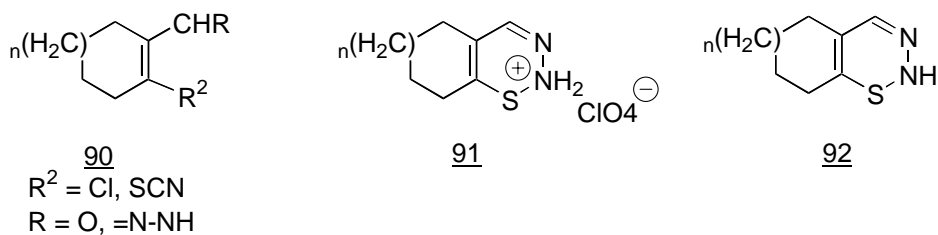


Quite similar to the above method it is found possible²⁹ to prepare the benzopyranoisoxazoles (**82**). The synthesis of 7-substituted benzopyranoisoxazole (**82**) was thus achieved from the corresponding chloroaldehydes (**80**) by reaction with sodium azide, followed by cyclization of **81** in high boiling solvent (Scheme XVII).



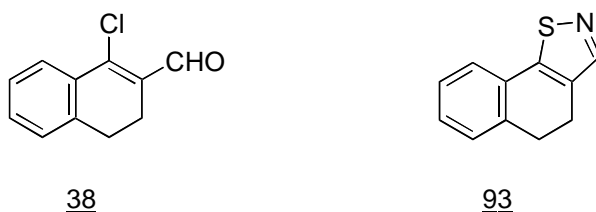
Cyclization via Aldimine

A modification of the above mentioned methodology to obtain isoxazole derivatives lies in the synthesis of 5-anilinothiazolo[5,4-d]isoxazole (**84**) from 4-chloro-2-anilinothiazole-5-carboxaldehyde (**83**) by treatment with NH_2OH in alcohol (Scheme XVIII)³⁰ in a single pot reaction.



Scheme XX

Nematicidal naphtho[2,1-*d*]isothiazoles (**93**) was obtained in a simple way³³ from the reaction of naphthalenechloroaldehydes (**38**) with S and NH₃ (Scheme XXI). **38** is a very useful intermediate for the synthesis of compounds of the type (**93**).

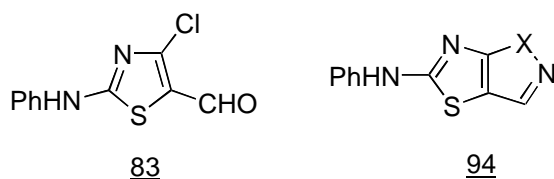


Scheme XXI

7. FUSED PYRAZOLES

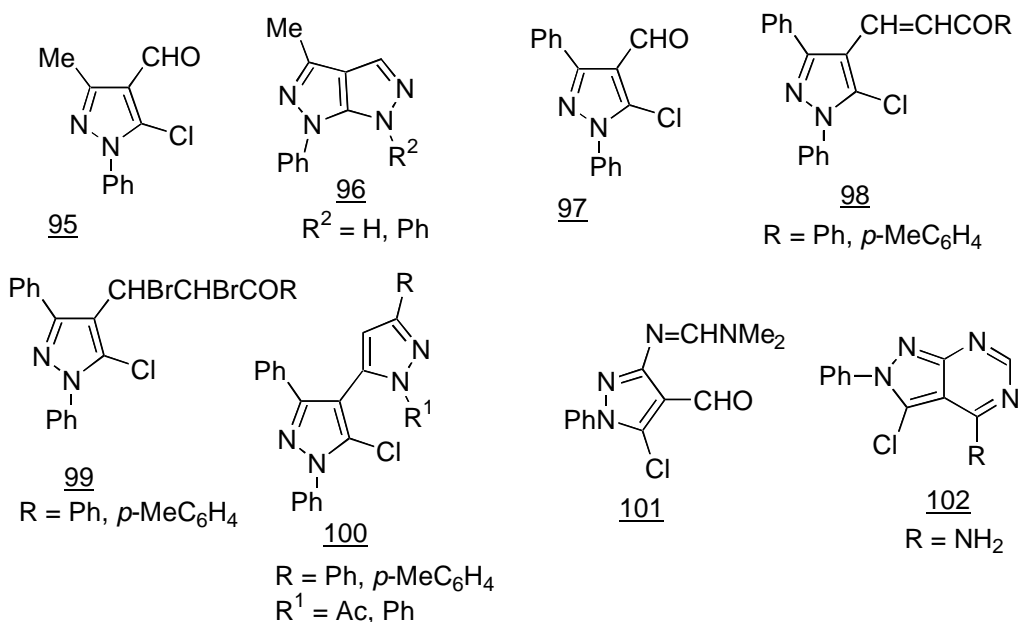
Cyclocondensation

Although recent publications disclosed a variety of applications of β -halovinylaldehydes to the field of heterocyclic chemistry, only a few examples were reported on the introduction of pyrazole moiety to five, six and seven membered heterocycles. Recently a versatile new synthesis of fused heterocycles such as pyrazolothiazole (**94**, X = NH, NPh), thiazoloisoxazole (**94**, X = O) were successfully prepared³⁴ by the condensation of chloroaldehyde (**83**) with NH₂NH₂, phenylhydrazine and NH₂OH, using the same synthetic strategy as discussed above (Scheme XXII).



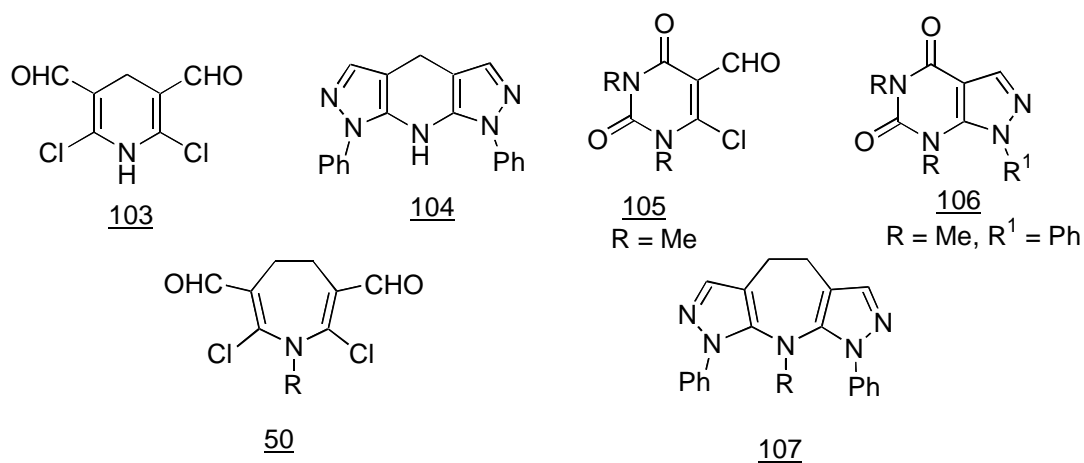
Scheme XXII

Recently, cyclocondensation of chloropyrazolecarboxaldehyde (**95**) with NH_2NH_2 has afforded pyrazolopyrazole³⁵ (**96**) (Scheme XXIII). β -Chlorovinylenones (**98**) are found to be suitable substrates for synthesis of pyrazole derivatives.³⁶ For example, very recently pyrazolylpropenone (**98**), prepared by condensation of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (**97**) with RCOMe followed by bromination of the resulting ketones gave dibromo derivatives (**99**) which in turn on reaction with RNHNH_2 furnished pyrazolylpyrazole (**100**, $\text{R} = \text{Ph}$) (Scheme XXIII). Similarly, amidinealdehydes (**101**) are also utilized in heterocyclic synthesis. Recently pyrazolopyrimidines (**102**) and their corresponding *N*-oxides are prepared by the condensation of amidinealdehyde (**101**) with $\text{NH}_2\text{OH}\cdot\text{HCl}$ in a simple manner.³⁷



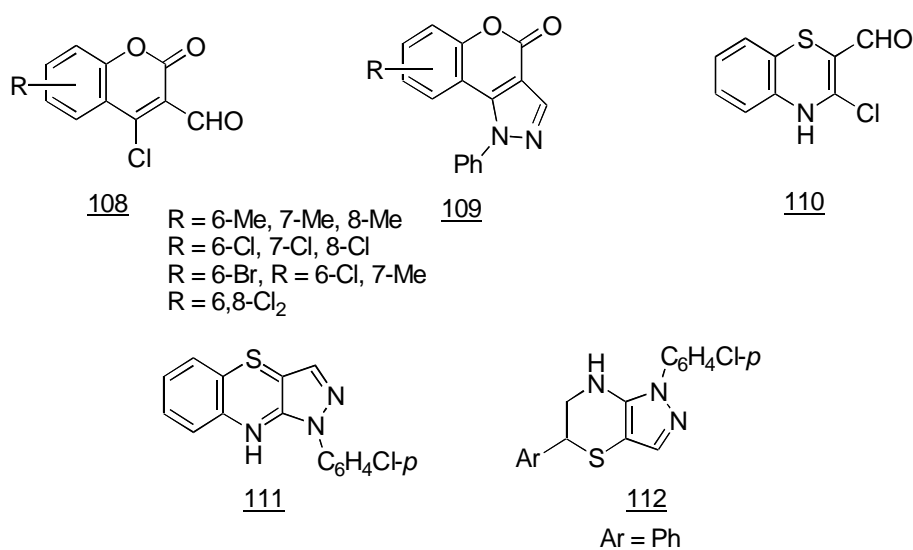
Scheme XXIII

Diformyldihydropyridine (**103**) on condensation with phenylhydrazine gave dipyrazolopyridine (**104**) in a single pot reaction³⁸ (Scheme XXIV). Reactions of 1,3-disubstituted 6-chloro-5-formyluracils (**105**) with phenylhydrazine or methylhydrazine afforded 1,5,7- and 2,5,7-trisubstituted, 4,6-dioxo-4,5,6,7-tetrahydropyrazolo(3,4-*d*)pyrimidine (**106**). Detailed investigations by Senda and Hirota³⁹ indicated that the reaction products (**106**) may occupy the substituent at 1 or 2 position depending upon the nature of NH_2NH_2 employed (Scheme XXIV). The synthesis of dipyrazoloazepines (**107**) has also been achieved¹⁶ by the condensation of di- β -chlorovinylaldehyde of azepine (**50**) with $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (Scheme XXIV) in the same way as described above.



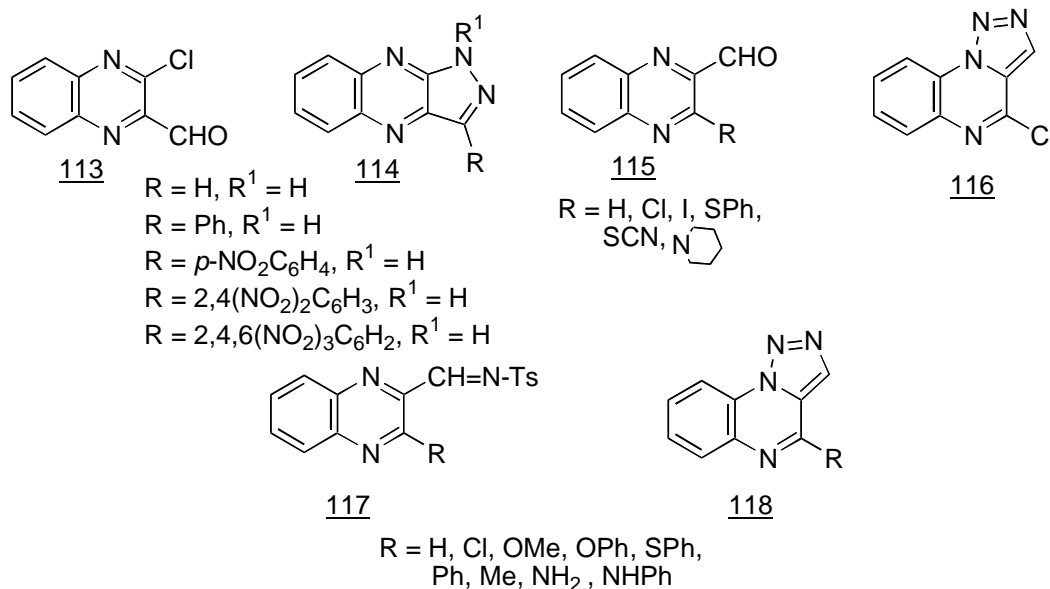
Scheme XXIV

The syntheses of coumarinoisoxazoles and coumarinopyrazoles (**109**) have been achieved⁴⁰ by heating the



Scheme XXV

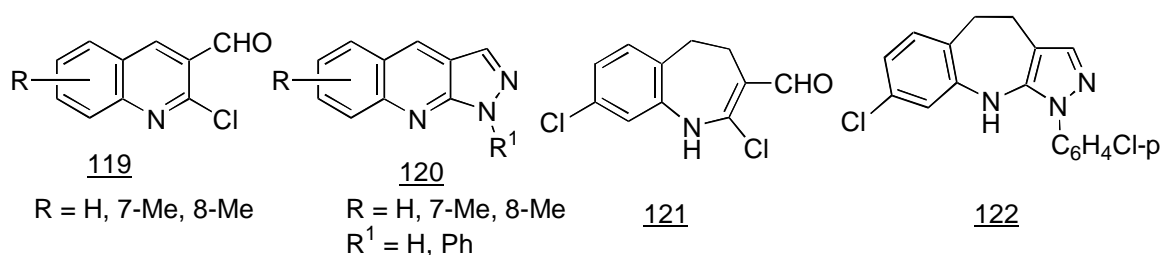
oximes of 4-chloro-3-formylcoumarins (**108**) directly in ethanol in presence of sodium acetate. Similarly, more heterocycles (**111**, **112**) are prepared⁴¹ from thiazinechloraldehyde (**110**) (Scheme XXV) by adopting the same synthetic strategy.



Scheme XXVI

Quinoxalinecarboxaldehyde (**113**) on condensation⁴² with NH₂NH₂ in ethanol gave pyrazoloquinoxalines (**114**). Several interesting triazoloquinoxaline (**116**, **118**) syntheses utilizing quinoxalinechloraldehydes (**115**, **117**) as starting materials have also been reported^{27, 43} (Scheme XXVI).

Ahmed *et al.* have reported⁴⁴ the synthesis of 1*H*-pyrazolo[3,4-*b*]quinoline (**120**) from 2-chloro-3-quinolinecarboxaldehyde (**119**) in the same fashion as mentioned above (Scheme XXVII). Chlorophenylpyrazolobenzazepine (**122**) was synthesized from reaction of chloroformylbenzazepine (**121**) and *p*-chlorophenylhydrazine. The reaction involves condensation of the formyl function, followed



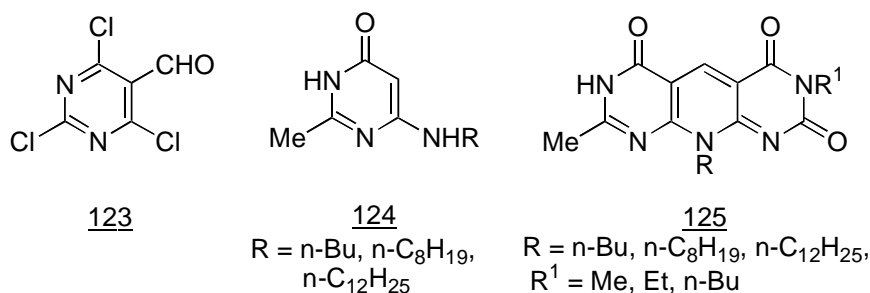
Scheme XXVII

by cyclisation. This method constitutes as an extension of previously described reactions.

8. PYRIMIDINE HETEROCYCLES

Cyclocondensation

Pyrimidine derivatives continue to be of an interest due to their wide range of biological activities and also due to the synthetic challenge posed by the naturally occurring complex molecules containing the pyrimidine ring. Apart from the synthesis of complex heterocycles containing a uracil moiety (nucleoside and nucleotide analogues) the various ring transformation of these compounds are of particular interest. A new type of pyridodipyrimidinetriones (**125**) were prepared very recently by Yoneda⁴⁵ by the condensation of 6-aryl- or alkylamino-2-methylpyrimidin-4(3*H*)-ones (**124**) with 2,4,6-trichloropyrimidine-5-carboxaldehyde (**123**) (Scheme XXVIII). Pyridodipyrimidines thus obtained showed strong ability to oxidise alcohols under neutral conditions to yield the corresponding carbonyl compounds and a significant autorecycling in the oxidation was also noticed.

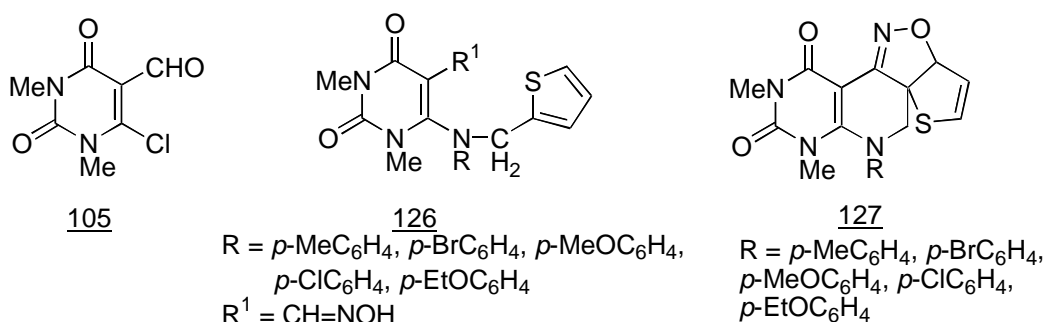


Scheme XXVIII

Intramolecular Cycloaddition

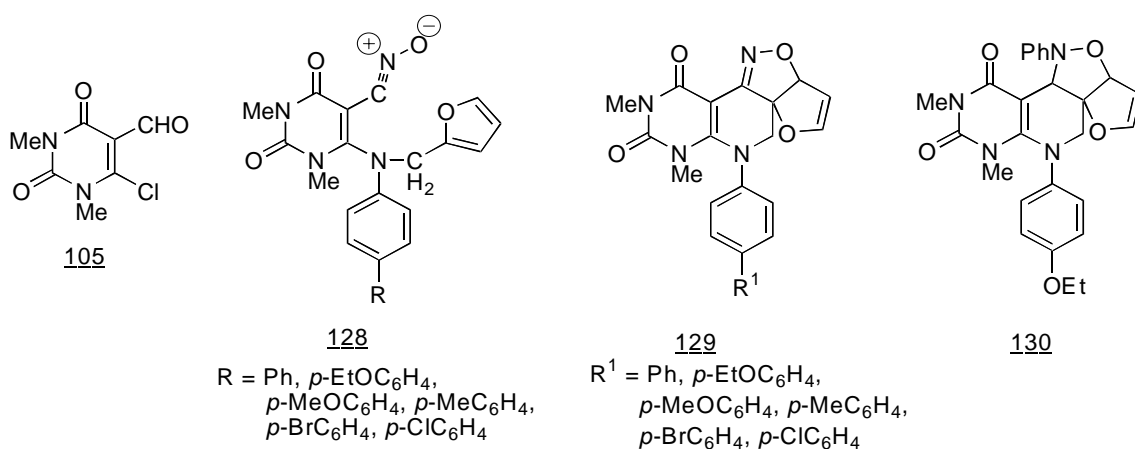
Very recently Sandhu⁴⁶ has demonstrated an efficient and facile synthesis of novel thienoisoxazolopyridopyrimidines (**127**) from 6-chloro-5-formyl-1,3-dimethyluracil (**105**) via intramolecular cycloaddition of thiophene and nitrile oxide or nitron groups bounded to 1,3-dimethyluracils. The readily available 6-chloro-5-formyl-1,3-dimethyluracil (**105**) was treated with 2-anilinomethylthiophenes (obtained from the corresponding thiophene Schiff bases by reduction with

NaBH₄) to afford the substituted formyluracils (**126**, R¹ = CHO) in good yields. The corresponding oximes [**126**, R¹ = (-CH=NOH)] were obtained in 50% yield by condensation of (**126**, R¹ = CHO) with NH₂OH.HCl. The nitrile oxides generated *in situ* from **126** underwent cyclisation to afford novel heterocycles (**127**) in good yields (Scheme XXIX). It is interesting to note that thiophene which has only little π-character (typical of a double bond) and which is a relatively inert ring systems in this case underwent facile intramolecularly cycloaddition with the corresponding dipoles.



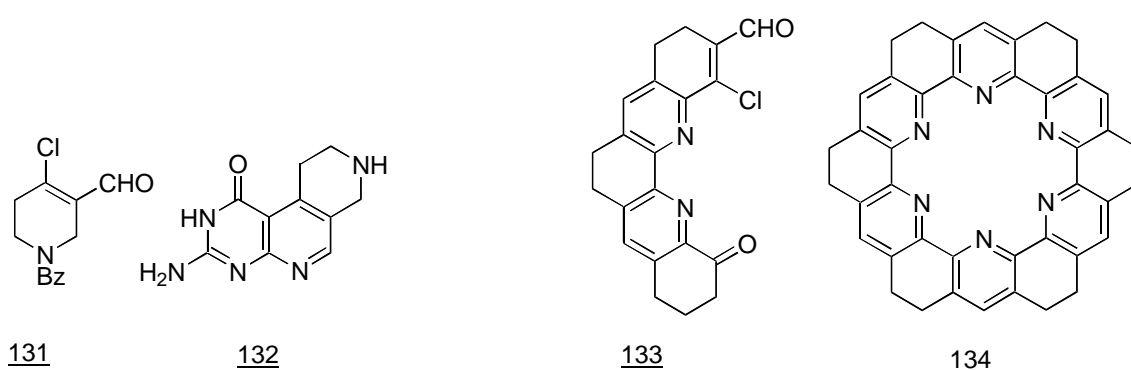
Scheme XXIX

Syntheses of several novel condensed pyridopyrimidines (**129**, **130**) have recently been prepared⁴⁷ *via* the intramolecular cycloadditions with chloroformyl uracils (**105**) and furfurylarylamines as an extension of the same synthetic strategy as discussed above by the same authors⁴⁷ (Scheme XXX).



Scheme XXX

Recently the synthesis of a substituted tetrahydropyrimidonaphthyridine (**132**) as a tricyclic 5-deaza nonclassical folate was reported by Ahaam⁴⁸ by the condensation of 2,4,6-triaminopyrimidine with tetrahydropyridine chloroaldehyde (**131**). The condensation was regiospecific and afforded only the substituted angular tetrahydro pyrimidonaphthyridine in fairly good yields (Scheme XXXI). Dibenzophenanthroline system (**133**) as synthetic precursors of hexaaza-kekulene was achieved by Ransohoff.⁴⁹ From **133**, a product was obtained from which the dodecahydrohexaazakekulene structure (**134**) is suggested on the basis of ¹H-NMR spectral data (Scheme XXXII).



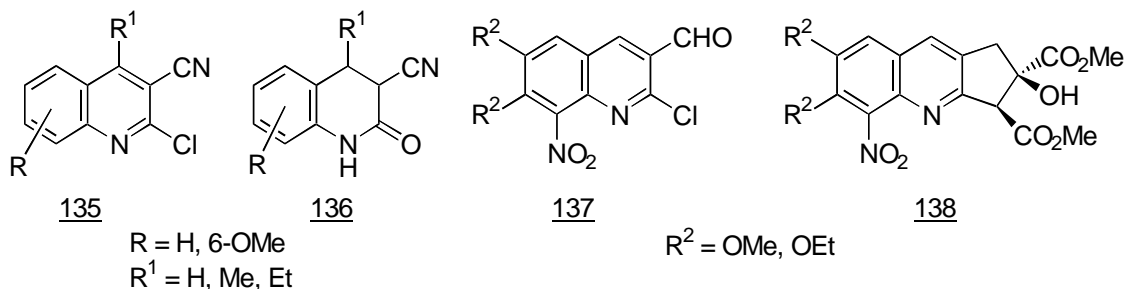
Scheme XXXI

Scheme XXXII

9. FUSED QUINOLINE HETEROCYCLES

Cyclopentaquinoline

Quinoline derivatives were known to possess a diverse spectrum of pharmacological activity. 2-Chloroquinoline-3-carboxaldehydes have been demonstrated to be versatile intermediates for functional group interconversions and for the synthesis of fused quinolines. Syntheses of several new ring systems

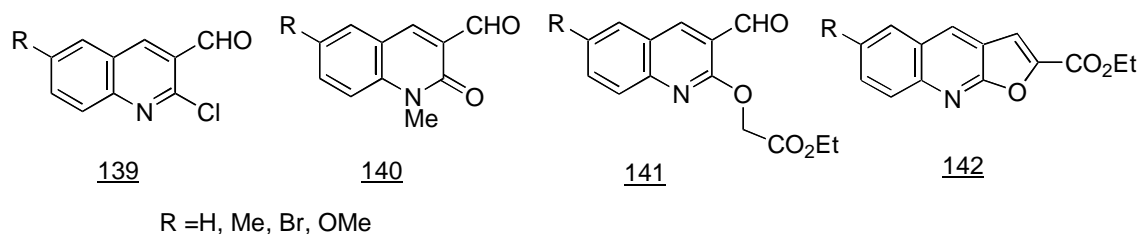


Scheme XXXIII

based on quinoline chloroaldehydes have been recently reported. For example, very recently Bhaduri⁵⁰ has achieved novel syntheses of 3-cyano-3,4-dihydroquinolin-2[1*H*]-one (**136**) and derivatives of cyclopentaquinolines (**138**) from chlorocynoquinolines. Reduction of quinolines (**135**) with sodium borohydride gave the corresponding 1,4-dihydroquinolines, decomposition of which on storage gave dihydroquinolines (**136**). Condensation and cyclisation of formylquinolines (**137**) with methyl acetoacetate gave cyclopentaquinolines (**138**) (Scheme XXXIII).

Furoquinolines

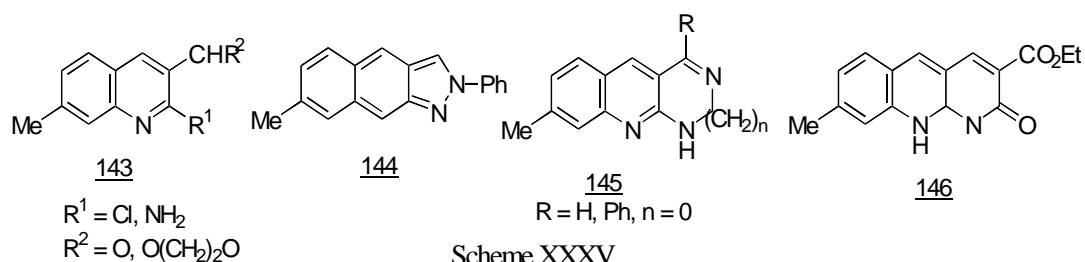
Pawar *et al.*⁵¹ have reported the synthesis of linear furoquinoline derivative (**142**) from 2-chloroquinoline-3-carbaldehyde derivatives (**139**). Hydrolysis of **139** with 6*N* HCl gave 2-oxo-3-formyl-1-methyl-1,2-dihydroquinoline (**140**), which on treatment with ethyl chloroacetate in presence of base gave the aryloxy ester (**141**). The cyclisation of **141** with sodium acetate in acetic anhydride gave furoquinoline derivative (**142**) (Scheme XXXIV).



Scheme XXXIV

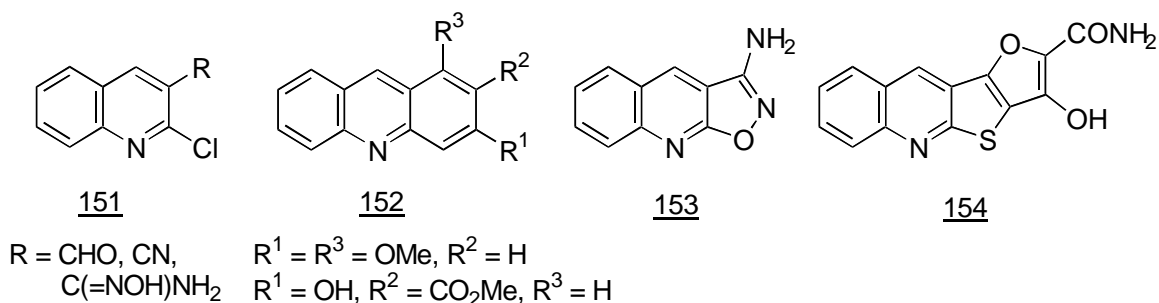
Pyrazoloquinoline

A versatile new synthesis of quinolines and related fused pyridines have been achieved by Cohn⁵² from quinolinechloroaldehydes. In the case of β -chlorovinylaldehydes, as the aldehydes (**143**, $R^2 = O$) are



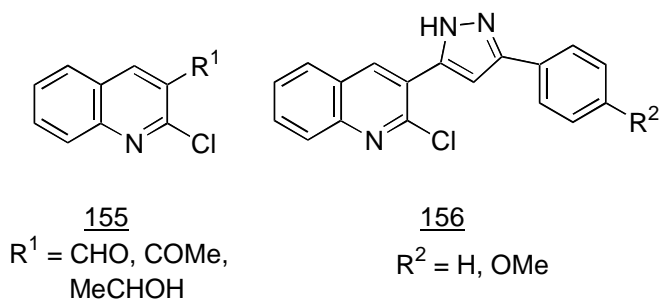
Scheme XXXV

A number of tri- and tetracyclic heterocycles have been synthesized from 2-chloro-3-formylquinoline. For example, Bhaduri⁵⁶ has reported the synthesis of isoxazoloquinoline (**153**), furothienoquinoline derivatives (**154**) (Scheme XXXVII) from 2-chloro-3-cyanoquinolines. Reactions of 2-chloro-3-cyanoquinoline (**151**) with NH_2OH followed by further ring closure in presence of Na_2CO_3 gave **153**. Condensation of **151** with methyl acetoacetate in presence of dry pyridine gave a number of quinoline derivatives (**152**) (Scheme XXXVII).



Scheme XXXVII

Further a number of reactions of 2-chloro-3-formylquinolines, directed towards obtaining quinoline derivatives in which 3- position is attached to heterocycles and alicycles are described by Bhaduri⁵⁷ very recently. Interestingly, in none of these reactions, the nucleophilic displacement of chlorine is observed (Scheme XXXVIII) by the author.⁵⁷

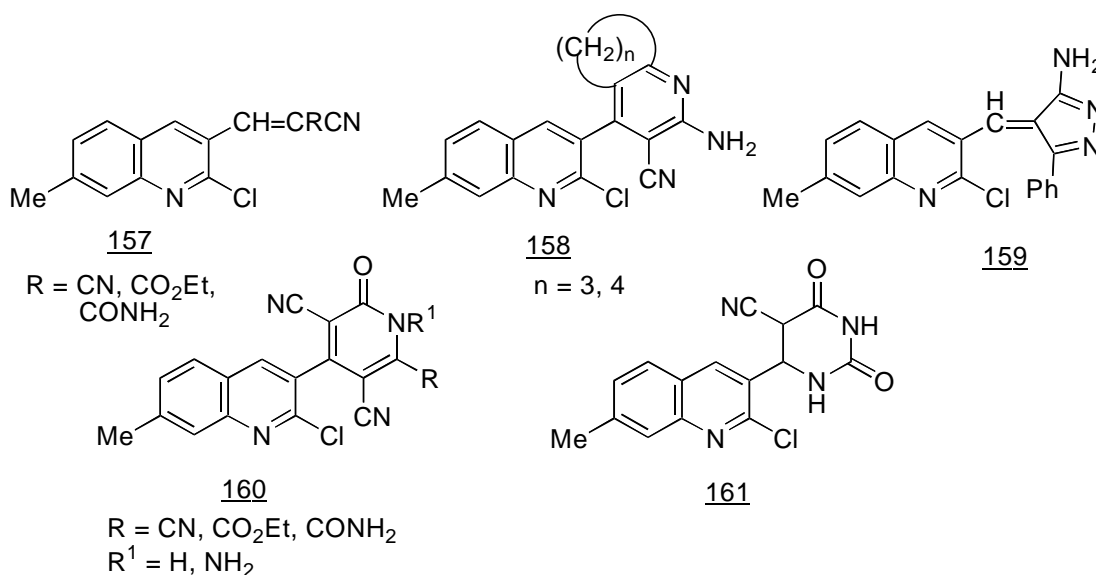


Scheme XXXVIII

2-Chloro-3-formylquinoline (**155**, $\text{R}^1 = \text{CHO}$) on reaction with methylmagnesiumiodide gave the secondary alcohol which on oxidation with pyridine chlorochromate gave 3-acyl-2-chloroquinoline (**155**,

$R^1 = \text{Ac}$). The base catalyzed condensation of **155** with aromatic aldehydes gave the chalcones and the ring closure of these chalcones with $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ gave the pyrazole derivatives (**156**).

Several new pyrimidine, pyridine and pyrazole derivatives of potential synthetic and biological importance have been synthesized very recently by Elgemele⁵⁸ from activated β -chlorovinyl nitriles. Cyanomethylenequinolin-3-yl derivatives (**157**) are easily prepared through a Knoevenagel condensation of chloroformylquinoline with malononitrile and ethyl cyanoacetate. Further treatment of **157** with cycloalkanone and ammonium acetate afforded the cyanopyridine **158** in good yield. Similarly, the condensation of **157** with urea or thiourea yielded the cyanopyrimidine derivatives (**161**). Cyclocondensation of **157** with ethyl cyanoacetate yielded dicyanoquinolinylpyridones (**160**) and monocyanoquinolinylpyrimidone (**161**) (Scheme XXXIX).

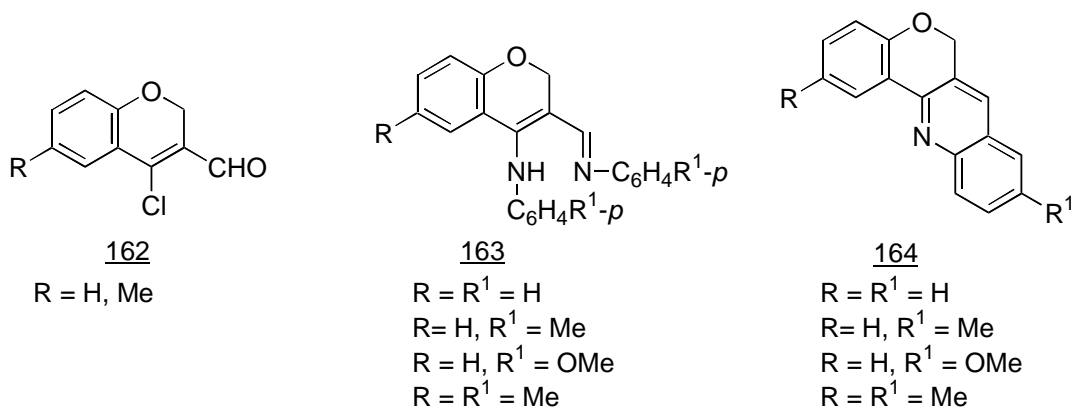


Scheme XXXIX

Thermal cyclisation

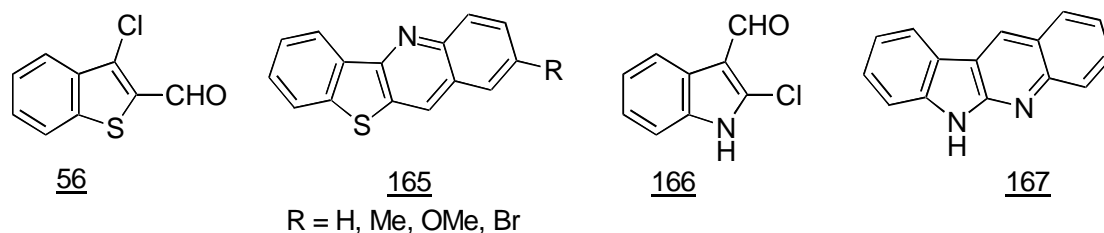
Syntheses of several quinoline derivatives starting from β -halovinylaldehydes have been published appeared in literature. One of the interesting examples of the utility of β -halovinylaldehydes for quinoline synthesis, is the reaction of 4-chloro-chromene-3-carboxaldehyde (**162**) with anilines. Balasubramanian⁵⁹

has reported a simple and convenient synthesis of a series of benzopyranoquinolines (**164**) based on thermal transformation of enaminoimines (**163**). This transformation parallels the reactions of β -chloroacroleins and anilines (Scheme XL).



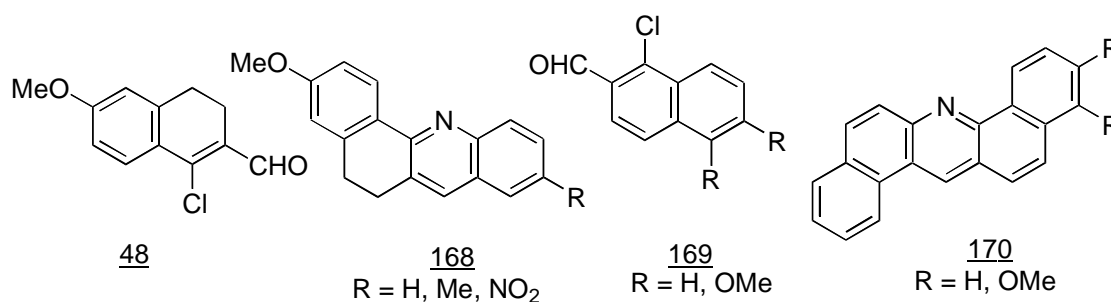
Scheme XL

Other interesting examples employing similar procedures have appeared in recent literature. For example, benzothienoquinolines (**165**) have been reported⁶⁰ from the reaction of chlorobenzothienoquinoline carbaldehyde (**56**) with anilines at 170°C in 70 – 90% yield *via* the corresponding arylimine derivatives. Similarly reaction of 2-chloroindole-3-carboxaldehyde (**166**) with aniline has been reported⁶¹ to yield indoloquinoline (**167**) utilizing almost the same concept (Scheme XLI).



Scheme XLI

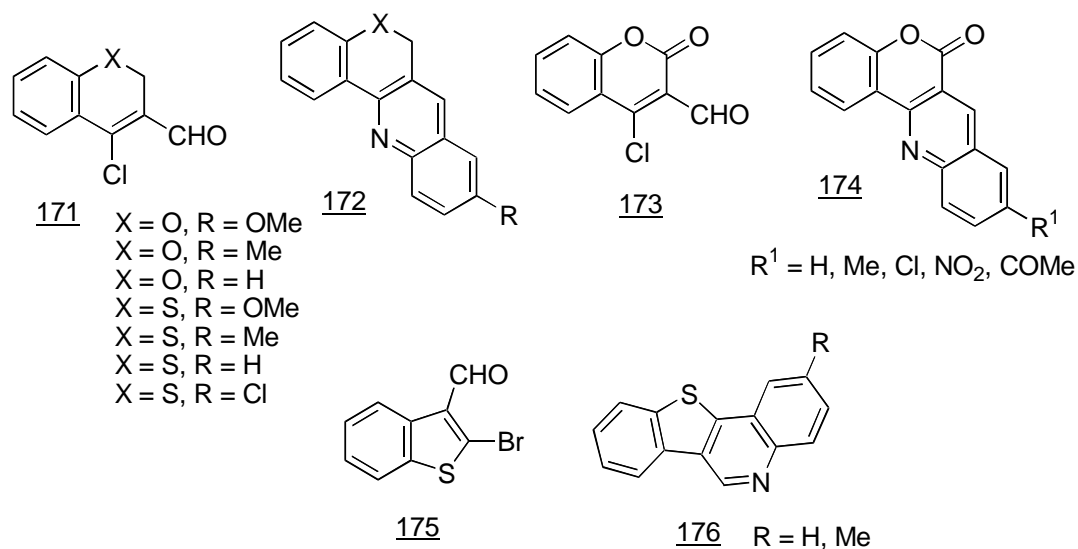
Dihydronaphthoquinolines are relatively rare polycyclic heterocyclic compounds. A facile and convenient methodology for the synthesis of dihydronaphthoquinolines has been successfully achieved recently by Ray⁶² utilizing almost the same synthetic strategy. Condensation of chloroaldehydes (**48**) with aniline in ethanol gave 90% of anil derivatives, which on pyrolysis at 250°C underwent cyclization to yield **168** in 70% yield. Dihydrodiols and diol epoxides of dibenzacridines with defined stereochemistry are expected to be proximate and ultimate carcinogens. Very recently Ray⁶³ has also obtained in one step the synthesis of dibenzacridine derivatives (**170**) from the corresponding anil hydrochlorides by heating them just above their melting points for 3 min. The anil derivatives are obtained in excellent yields from the chloroaldehydes (**169**) by reaction with 2-naphthylamine (Scheme XLII).



Scheme XLII

Photocyclisation

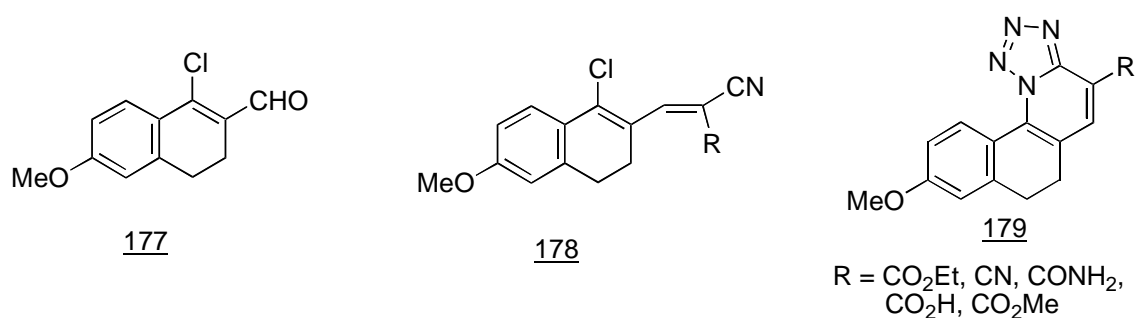
There has been considerable interest in the study of photochemical cyclization of imines derived from aromatic aldehydes or ketones and arylamines. Non oxidative photocyclisations have been synthetically exploited well in the field of stilbene in the same review. However, reports on analogous studies involving ω -haloazahexatriene are lacking. A very good example of such novel transformation encountered in an attempted photocyclization of *n*-arylimines derived from 4-chloro-3-formylbenzopyrans and benzothiopyrans (**171**) (Scheme XLIII) has been reported very recently by Balasubramanian.⁶⁴ Other interesting examples utilizing the same approaches have appeared recently.⁶⁵ For example, 4-chloro-2-oxo-2*H*-chrome-3-carboxaldehyde (**173**) on reaction with aromatic amines gave benzopyranoquinolines (**174**). Similarly, benzothienoquinolines (**176**) were also obtained⁶⁶ by condensation of 2-bromo-3-formylbenzothiophene (**175**) with aniline (Scheme XLIII).



Scheme XLIII

1,3-Dipolar cycloaddition

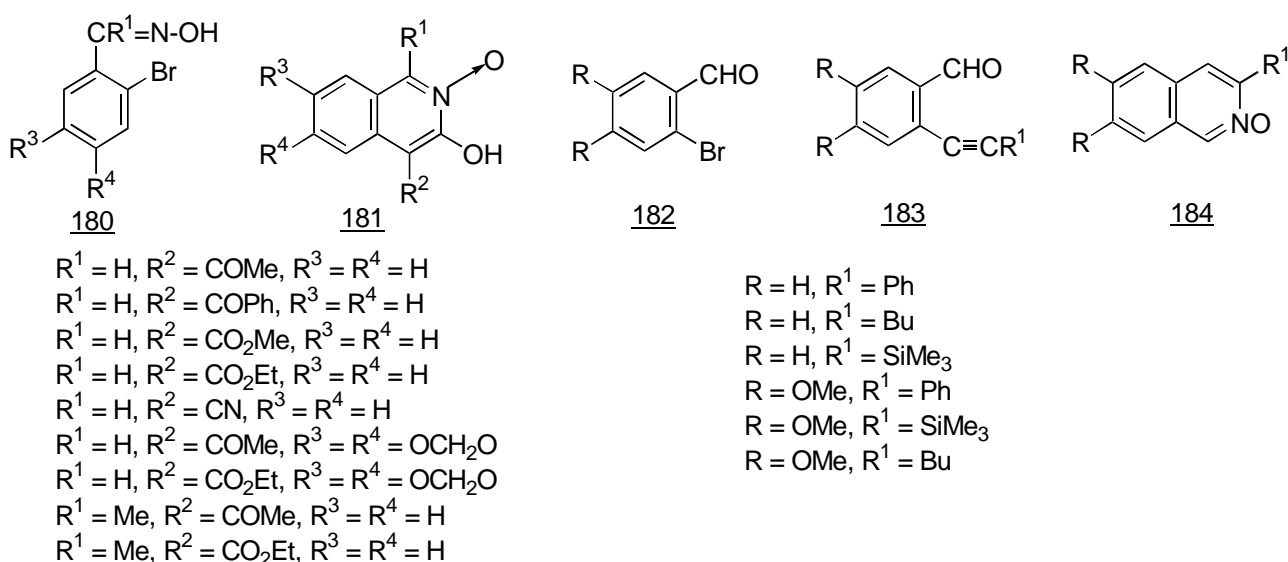
Ylidine malononitriles are versatile synthons in heterocyclic synthesis. Konwar *et al.*⁶⁷ have reported the synthesis of benzo[*h*]tetrazolo[1,5-*a*]-6,7-dihydroquinolines (**179**) utilizing intramolecular 1,3-dipolar cycloaddition reaction of ylidine malononitrile. Knoevenagel condensation of cyanomethylenes with 1-chloro-6-methoxy-3,4-dihydronaphthalene (**177**) gave ylidine malononitriles (**178**). The reaction of **178** with KN₃ in ethanol underwent facile halide displacement followed by cycloaddition to yield **179** (Scheme XLIV).



Scheme XLIV

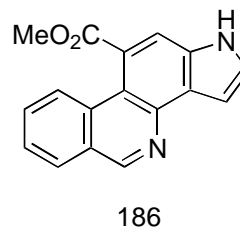
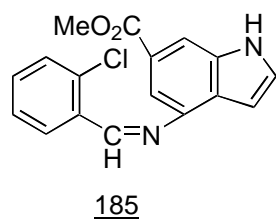
10. ISOQUINOLINE *N*-OXIDES

β -Chlorovinylaldehydes have been utilized to build up isoquinoline derivatives. Recently a simple one step synthesis of 3-hydroxyisoquinoline-*N*-oxide (**181**) has been achieved⁶⁸ by Cu catalysed condensation of β -dicarbonyl compounds, with 2-bromobenzaldoximes (**180**), in moderate to good yields (Scheme XLV). A facile synthesis of isoquinoline *N*-oxides from *o*-bromobenzaldehydes was successfully realised very recently by Yamanaka⁶⁹ in their studies concerning the application of Pd catalysed reactions of aryl halides with terminal acetylenes. The reaction of 2-bromobenzaldehyde (**182**) with phenylacetylene in DMF in presence of catalytic amount of dichlorobis(triphenylphosphine)palladium and CuI in triethylamine gave **183** in satisfactory yield. The aldoxime of **183** was heated with K₂CO₃ in ethanol, affording isoquinoline-2-oxide (**184**) in fairly good yield (Scheme XLV).



Scheme XLV

The synthesis of pyrrolophenanthridine (**186**) is described from the reaction of (chlorobenzylidene)indolamine (**185**) with NaNH₂ in liquid NH₃ by Balberkina⁷⁰ very recently utilizing the same procedure (Scheme XLVI).



Scheme XLVI

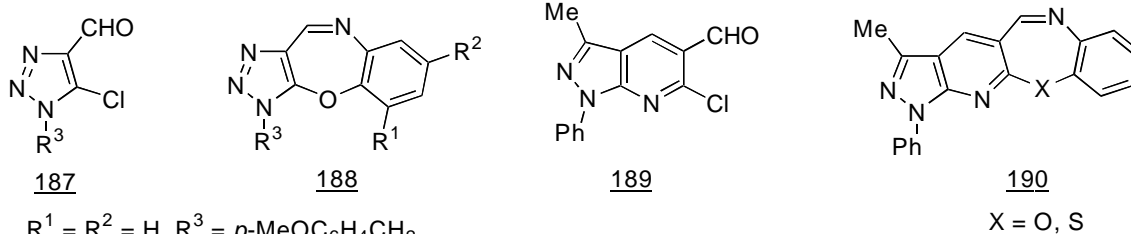
11. 1,5-BENZOXAZEPINES, 1,5-BENZOTHIAZEPINE AND 1,5-BENZODIAZEPINE DERIVATIVES

1,5-Benzoxazepines

Syntheses of vast number of polycyclic heterocyclic 1,5-benzoxazepines, 1,5-benzodiazepines and 1,5-benzthiazepine derivatives utilizing β -halovinylaldehydes as starting material have been well studied.⁷¹⁻⁷⁹

Many of these synthetic procedures are surveyed by Weißenfels² and Schulte.⁷¹ Hence these approaches will not be discussed in detail in this review. Only recent contributions appeared in this area that are of interest would be highlighted here.

A convenient synthesis of a novel tricyclic heterocyclic triazole ring system (**188**) from chlorotriazole carbaldehydes (**187**) and 2-aminophenols is described,⁷² under milder reaction conditions employing the

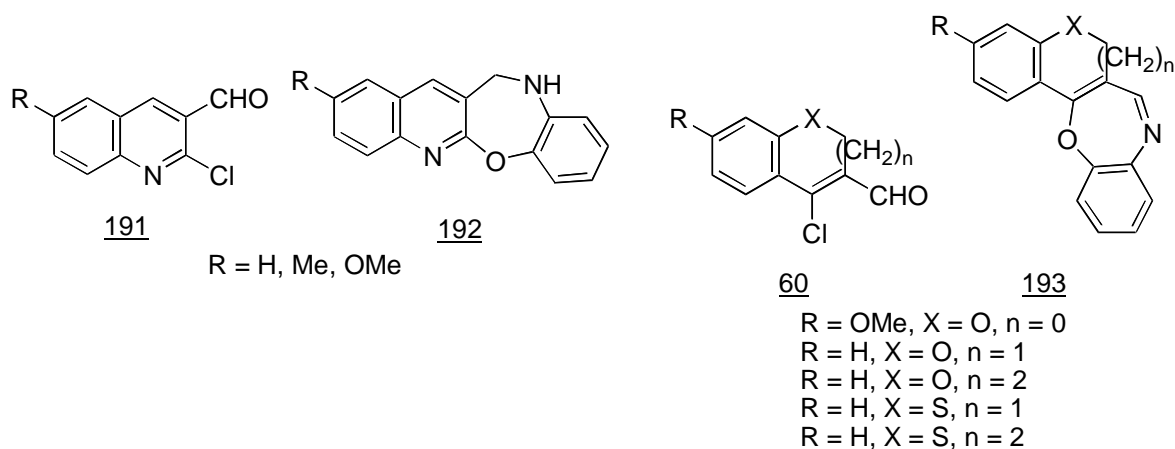


$R^1 = R^2 = H, R^3 = p\text{-MeOC}_6\text{H}_4\text{CH}_2$
 $R^1 = \text{Me}, R^2 = H, R^3 = p\text{-MeOC}_6\text{H}_4\text{CH}_2$
 $R^1 = H, R^2 = \text{Me}, R^3 = p\text{-MeOC}_6\text{H}_4\text{CH}_2$
 $R^1 = H, R^2 = \text{Cl}, R^3 = p\text{-MeOC}_6\text{H}_4\text{CH}_2$
 $R^1 = H, R^2 = H, R^3 = p\text{-ClC}_6\text{H}_4\text{CH}_2$
 $R^1 = \text{Me}, R^2 = H, R^3 = p\text{-ClC}_6\text{H}_4\text{CH}_2$
 $R^1 = H, R^2 = \text{Me}, R^3 = p\text{-ClC}_6\text{H}_4\text{CH}_2$
 $R^1 = H, R^2 = \text{Cl}, R^3 = p\text{-ClC}_6\text{H}_4\text{CH}_2$

Scheme XLVII

same strategy.⁷¹⁻⁷⁹ Reactions of chloropyrazolopyridinecarboxaldehydes (**189**) with 1,4-dinucleophiles like 2-aminophenol gave novel tetracyclic pyrazolopyrido[1,5]benzoxazepine and benzothiazepine (**190**) respectively (Scheme XLVII). Combination of intramolecular nucleophilic addition and aldehyde condensation reactions are involved to furnish these ring systems.⁷³

A facile one-pot synthesis of quinobenzoxazepines and its dihydroderivatives (**192**) are reported⁷⁶ by the condensation and subsequent cyclization reactions of 2-chloro-3-formylquinoline (**191**) with 2-aminophenol (Scheme XLVIII). A characteristic feature of the ¹H NMR spectra noticed in these 1,5-benzoxazepines is the high field resonance signals of the imine and C-13 protons relative to that shown by the corresponding Schiff bases.

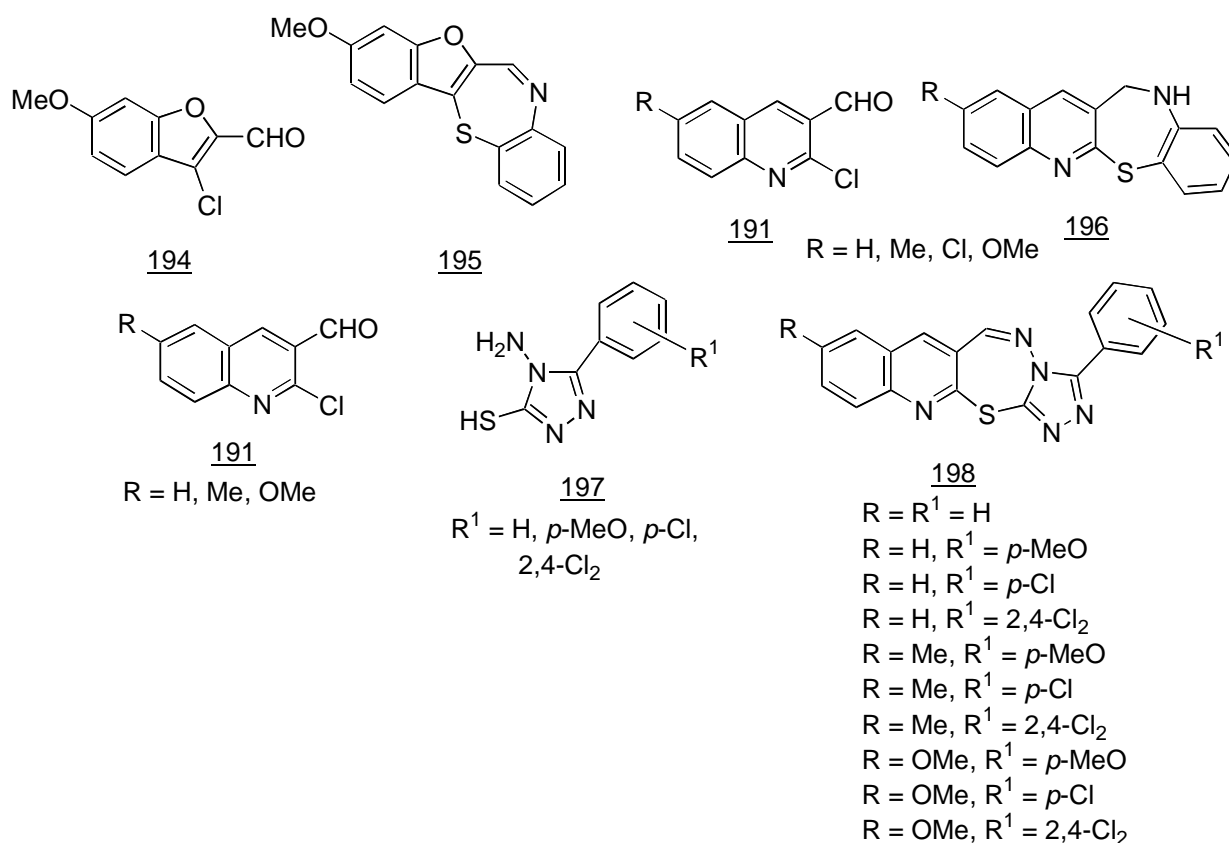


Scheme XLVIII

The synthesis of tetracyclic 1,5-benzoxazepine (**193**) has been described from our laboratory by condensation of chloraldehydes (**60**) with 2-aminophenol. And also studies on the reactivity of new types of tetracyclic-1,5-benzoxazepines (**193**) like catalytic hydrogenation and cyclofunctionalization with mercapto acids/esters are also investigated from our laboratory⁷⁹ (Scheme XLVIII) with little success.

1,5-benzothiazepine

The synthesis of tetracyclic 1,5-benzothiazepine (**195**) starting from 3-chloro-6-methoxybenzofuran-2-carboxaldehyde (**194**) and 2-aminothiophenol was achieved very recently from our laboratory.⁷⁸ More examples of synthetic applications of 2-chloro-3-formylquinolines (**191**) were described by Paradisi and Zecchini.⁷⁷ These authors reported the synthesis of quinobenzothiazepine (**196**) and its derivatives (Scheme XLIX) from the results of the condensation of 2-chloroquinoline-3-carboxaldehyde with *o*-aminophenol. Rao *et al.* recently have successfully synthesized⁸⁰ novel tetracyclic system such as quino[3,2-*f*]-1,2,4-triazolo[3,4-*b*]thiadiazepines (**198**) by cyclocondensation reaction of quinoline-carboxaldehyde (**191**) with aminomercaptophenyltriazoles (**197**) in DMF.

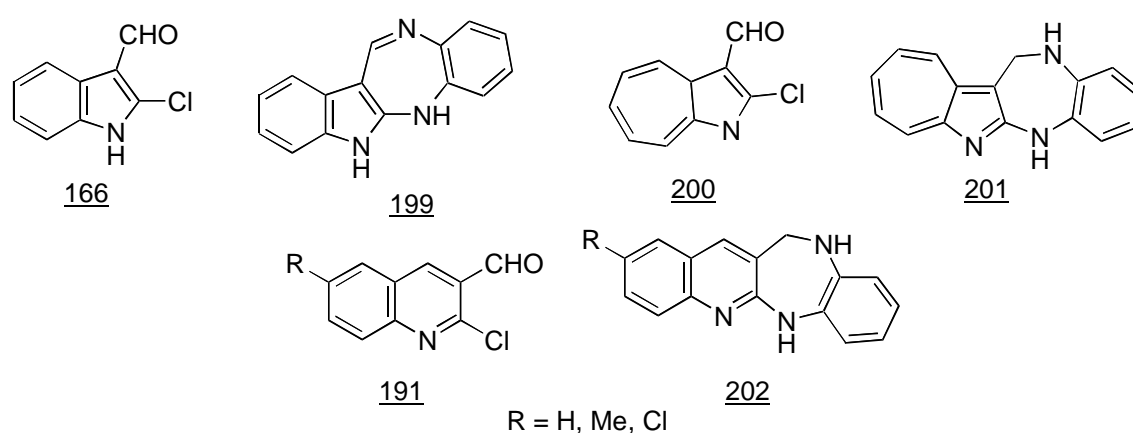


Scheme XLIX

1,5-benzodiazepine

2-Chloroindole-3-carboxaldehyde (**166**) on reaction with *o*-phenylenediamine underwent condensation and cyclization spontaneously affording indolobenzodiazepine⁷¹ (**199**) (Scheme L).

Heterocycles are also obtained using azaazulene skeleton (**201**) and three syntheses in an efficient manner are reported⁷⁴ very recently, from the reactions of 2-chlorocyclohepta[*b*]pyrrole-3-carbaldehyde (**200**) with *o*-phenylenediamine. The synthesis of novel fused tetracyclic quinoline derivatives (**202**) is described⁷⁵ by the condensation of quinoline chloroaldehyde (**191**) and *o*-phenylenediamine. The intermediate benzimidazoline derivative is oxidized followed by simultaneous reduction of quinobenzodiazepine to its dihydro derivative (**202**) (Scheme L).



Scheme L

ACKNOWLEDGEMENT

The inter library loan services from the McGoogan library of Medicine, University of Nebraska, Medical Centre, Omaha, U.S.A. is gratefully acknowledged.

REFERENCES

1. S. Seshadri, *J. Scient. Ind. Res.*, 1973, **32**, 128.
2. M. Pulst and M. Weißenfels, *Z. Chem.*, 1976, **16**, 337.
3. J. Andreeux, J. P. Battioni, M. Giraud, and D. Molho, *Bull. Soc. Chim. Fr.*, 1973, No. 6, Pt. 2, 2093.
4. K. A. Sinha Babu and T. R. Borchardt, *J. Org. Chem.*, 1983, **48**, 2356.
5. G. M. Coppola, *J. Heterocycl. Chem.*, 1981, **18**, 845.
6. V. P. Litvinov, V. Yu. Mortikov, and A. F. Vaisburg, *Izv. Akad. Nauk. SSSR. Ser. Khim.*, 1990, **2**, 422.

7. K. Rajendra Prasad and M. Darbarwar, *Org. Prep. Proced. Int*, 1995, **27**, 547.
8. Md. I. Sami, G. K. Kar, and J. K. Ray, *Tetrahedron*, 1992, **48**, 5199.
9. R. Ernst and W. Claus, *Ger. Offen., D.E.*, 1,902,050, 1970, 8 pp, (*Chem. Abstr.*, 1970, **73**, 87909g).
10. K. Clarke, D. N. Gregory, and R. M. Scrowston, *J. Chem. Soc., Perkins Trans. 1*, 1973, 2956.
11. G. Kirsch and P. Cagniant, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, 1975, **281C**, 393.
12. K. G. Kar, G. B. Chatterjee, and J. K. Ray, *Org. Prep. Proced. Int*, 1988, **20**, 213.
13. J. F. Muller, J. M. Mager, and D. Cagniant, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, 1978, **286**, 241.
14. K. Yamane, K. Fujimori, and T. Takeuchi, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 2437.
15. M. Ghosh, R. Mukherjee, B. G. Chatterjee, and J. K. Ray, *Indian J. Chem., Sect B.*, 1981, **20B**, 243.
16. T. Aubert, M. Fernier, I. Mounier, and R. Guillard, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2095.
17. V. P. Litvinov, V. Yu. Mortikov, and A. F. Vaisburg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, **2**, 424.
18. P. Cagniant, G. Kirsch, and L. Perrin, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, 1973, **271**, 1561.
19. A. Ricci, D. Balucani, and Bettelli, *Gazz. Chim. Ital.*, 1971, **101**, 774.
20. B. Chandra Sekhar, D. V. Ramana, and S. R. Ramadas, *Sulfur Lett.*, 1989, **9**, 271.
21. B. Chandra Sekhar, D. V. Ramana, and S. R. Ramadas, *Sulfur Lett.*, 1989, **10**, 149.
22. M. Weißenfels, A. Hantschmann, T. Steinfuehrer, and E. Birkner, *Z. Chem.*, 1989, **10**, 166.
23. R. Sauter, G. Griss, W. Grell, R. Hurnaus, B. Eisele, W. Haarmann, and E. Rupprecht, *Ger. Offen. D.E.*, 3,105,858, 1981, 66 pp, (*Chem. Abstr.*, 1982, **97**, 216151a).
24. P. Cagniant and G. Kirsch, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, 1976, **283**, 683.
25. J. Becher, P. H. Oksen, and K. Brøndums, *Heterocycles*, 1986, **24**, 2299.
26. R. Ricci, D. Balucani, C. Rossi, and A. Croisy, *Boll. Sci. Fac. Chim. Ind. Bologna*, 1969, **27**, 279.
27. E. Lippmann and W. Shilov, *Collect. Czech. Chem. Commun.*, 1984, **49**, 1304.
28. Md. I Sami, G. K. Kar, and J. K. Ray, *Org. Prep. Proced. Int.*, 1991, **23**, 186.
29. Hantschmann, Achim, Steinfuehrer, Torsten, Weissenfels, Manfred, *Ger (East) DD 281, 390*, 1990, (*Chem. Abstr.*, 1991, **114**, 185482x).

30. R. A. Pawar, *Indian. J. Chem., Sect. B*, 1989, **28**, 866.
31. S. I. Shulga and V. A. Chuiguk, *Ukr. Khim. Zh.*, 1973, **39**, 66.
32. G. Entenmann, *Synthesis*, 1973, **4**, 225.
33. H. Adolf, H. Fleig, and H. Hagen, *Ger. Offen.*, 2,626,967, 1977, 11 pp. (*Chem. Abstr.*, 1978, **88**, 136608d).
34. R. A. Pawar and A. P. Rajput, *Indian J. Chem., Sect. B*, 1989, **28B**, 866.
35. Abd. El. Latif, F. M., *Asian. J. Chem.*, 1993, **5**, 184.
36. A. G. El-Shekeil, P. S. Babaqi, M. A. Hassan, and S. A. Shiba, *Proc. Pak. Acad. Sci.*, 1988, **25**, 25.
37. S. B. Barnela, R. S. Pandit, and S. Seshadri, *Indian J. Chem., Sect. B*, 1976, **14B**, 668.
38. M. Weibenfels and S. Kaubisch, *Z. Chem.*, 1982, **22**, 23.
39. S. Senda, K. Hirota, and G. N. Yang, *Chem. Pharm. Bull.*, 1972, **20**, 399.
40. S. R. Moorthy, V. Sundara Moorthy, and N. V. Subba Rao, *Indian J. Chem.*, 1973, **11**, 854.
41. O. Aki and Y. Nakagawa, *Chem. Pharm. Bull.*, 1972, **20**, 1325.
42. V. D. Romanenko and S. I. Burmistrov, *Khim. Geterotsikl. Soedin.*, 1973, **6**, 852.
43. E. Lippmann and M. Vogel, *J. Prakt. Chem.*, 1987, **329**, 101.
44. M. A. Farghaly, S. N. Habid, B. A. Ali Hazzaa, S. El, and A. Ola, *Alexandria. J. Pharm. Sci.*, 1989, **3**, 84.
45. K. Moriyama, T. Nagamatsu, and F. Yoneda, *J. Heterocycl. Chem.*, 1986, **23**, 241.
46. D. Prajapathi and J. S. Sandhu, *Synthesis*, 1988, **4**, 342.
47. D. Prajapathi, P. Bhuyan, and J. S. Sandhu, *J. Chem. Soc., Perkin Trans.1*, 1988, 607.
48. A. Gangjee and A. K. Ohemeng, *J. Heterocycl. Chem.*, 1985, **22**, 1153.
49. J. Ransohoff, E. Butler, and A. H. Staab, *Tetrahedron Lett.*, 1985, **26**, 6179.
50. Neelima, B. Bhat, and A. P. Bhaduri, *J. Heterocycl. Chem.*, 1986, **23**, 409.
51. R. A. Powar, P. B. Bajare, and S. B. Mundade, *J. Indian Chem. Soc.*, 1990, **67**, 685.
52. R. Hayes and O. Meth-Cohn, *Tetrahedron Lett.*, 1982, **23**, 1613.
53. Neelima, B. Bhat, and A. P. Bhaduri, *J. Heterocycl. Chem.*, 1984, **21**, 1469.

54. A. M. Farghally, N. S. Habid, A. A. B. Hazzaa, and O. L. El-Sayed, *J. Pharm. Belg.*, 1985, **40**, 366.
55. N. M. Fathy, A. S. Aly, F. Abd-El-Motti, and F. M. E. Abdel-Megeid, *Egypt J. Chem.*, 1986, **29**, 609.
56. R. P. Srivastava, Neelima, and A. P. Bhaduri, *J. Heterocycl. Chem.*, 1987, **24**, 219.
57. R. P. Srivastava, Neelima, and A. P. Bhaduri, *Indian J. Chem., Sect B*, 1987, **26B**, 418.
58. M. N. Fathy and G. H. Elgemeie, *J. Chem. Eng. Data*, 1988, **33**, 218.
59. K. K. Balasubramanian, G. V. Bindu Madhavan, M. Nair, and B. Venugopalan, *Synthesis*, 1977, **9**, 611.
60. A. Ya. Bushkov and O. I. Lantsova, *Khim. Geterotsikl. Soedin.*, 1985, **2**, 273.
61. K. E. Schulte, J. Reisch, and U. Stoess, *Arch. Pharm.*, 1972, **305**, 523.
62. J. K. Ray, S. Sharma, and G. B. Chatterjee, *Synth. Commun.*, 1979, **9**, 727.
63. K. G. Kar, C. A. Karmakar, and J. K. Ray, *Tetrahedron Lett.*, 1989, **30**, 223.
64. K. S. Swaminathan, R. S. Ganesh, C. S. Venkatachalam, and K. K. Balasubramanian, *Tetrahedron Lett.*, 1983, **24**, 3653.
65. H. Dieter, *Arch. Pharm.*, 1987, **320**, 595.
66. R. Neidlein and H. Heid, *Synthesis*, 1977, **1**, 65.
67. D. Konwar and R. C. Baruah, *Indian J. Chem., Sect B. Org. Chem. Incl. Med. Chem.*, 1997, **36B**, 918.
68. A. McKillop, *Synthesis*, 1977, **1**, 760.
69. T. Sakamoto, Y. Kondo, N. Miura, K. Hayashi, and H. Yamanaka, *Heterocycles*, 1986, **24**, 2311.
70. E. P. Baberkina, R. N. Akhvlediani, V. N. Buyanov, E. F. Kuleshova, and N. N. Suvorov., *Zh. Org. Khim.*, 1988, **24**, 2440.
71. K. E. Schulte, J. Reisch, and U. Stoess, *Arch. Pharm.*, 1972, **305**, 523.
72. E. F. Nielsen and E. B. Pedersen, *Chem. Scr.*, 1986, **26**, 343.
73. A. Simay and K. Takacs, *J. Heterocycl. Chem.*, 1982, **19**, 809.
74. N. Abe and Y. Emoto, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1543.
75. K. Rama Rao, P. B. Sattur, and N. Bhanumati, *Heterocycles*, 1986, **24**, 1683.
76. G. P. Zecchini, I. Torrini, and M. P. Paradisi, *Heterocycles*, 1987, **26**, 2443.

77. I. Torrini, G. P. Zecchini, and M. P. Paradisi, *Heterocycles*, 1988, **27**, 401.
78. B. Chandra Sekhar, D. V. Ramana, and S. R. Ramadas, *Sulfur Lett.*, 1987, **6**, 149.
79. B. Chandra Sekhar, *Syntheses and Reactions of New Types of Fused Ring Heterocycles Containing Oxygen, Nitrogen and Sulfur Atoms*, Ph.D. Thesis, IIT – Madras, 1989.
80. G. R Rao and K. R. Srinivasa, *Indian J. Pharm. Sci.*, 1991, **53**, 37.