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β–HALOVINYLALDEHYDES – AS VERSATILE REACTIVE INTERMEDIATES IN THE SYNTHESES OF CONDENSED FUSED RING POLYCYCLIC HETEROCYCLES

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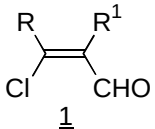
Dedicated to Prof. S. R. Ramadas on the occasion of his 70th birthday.

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.



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[††] 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 Seshadri[1] and Weiβenfels[2] 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.

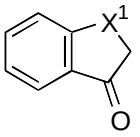
This review mainly refers to the following category of heterocycles prepared mostly based on the nature of the substrate employed or on the nature of the heterocycles formed.

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 prepared[3] 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).



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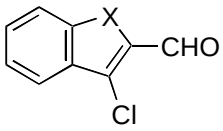
X^1 = $-CH_2-CH_2-$, $-O-CH_2-$, $-CH_2-$



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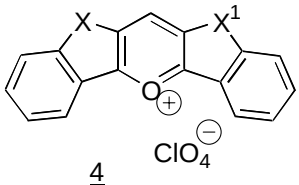
X = $-CH_2-CH_2-$, $-O-CH_2-$, $-O-CO-$



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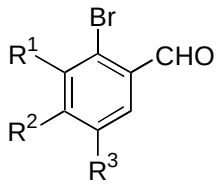
X = $-CH_2-CH_2-$, X^1 = $-CH_2-CH_2-$
X = $-CH_2-CH_2-$, X^1 = $-O-CH_2-$
X = $-CH_2-CH_2-$, X^1 = $-CH_2-$
X = $-O-CH_2-$, X^1 = $-O-CH_2-$
X = $-O-CO-$, X^1 = $-O-CH_2-$
X = $-O-CO-$, X^1 = $-CH_2-CH_2-$

Scheme I

2. PHTHALIDES

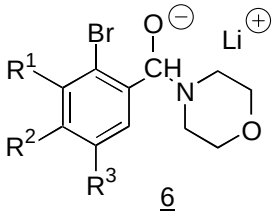
Phthaldehydic acids and phthalides are useful synthons for a variety of natural products. A general and efficient method for the synthesis of phthaldehydic acid (**7**, **10**, R^6=R^5=OH) and phthalides (**7**, **10**, R^6=R^5=H), many of which are key intermediates in the synthesis of polycyclic aromatic 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 CO_2 and dilute acid afforded the phthaldehydic acids (**7, 10,** R^6=R^5=OH) which on reduction with $NaBH_4$ furnished the desired phthalides (**7, 10,** R^6=R^5= H) respectively (Scheme II).



5

$R^1 = R^3 = OMe, R^2 = H$
$R^1 = R^3 = OCH_2Ph, R^2 = H$
$R^1 = R^2 = OMe, R^3 = H$
$R^1 = R^2 = OCH_2O, R^3 = H$



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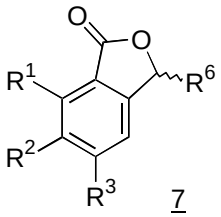
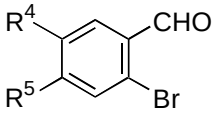


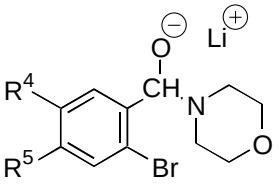
7

$R^1 = R^3 = OMe, R^2 = H, R^6 = OH, H$
$R^1 = R^3 = OCH_2Ph, R^2 = H, R^6 = OH, H$
$R^1 = R^2 = OMe, R^3 = H, R^6 = OH, H$
$R^1 = R^2 = OCH_2O, R^3 = H, R^6 = OH, H$



8

$R^4 = OMe, R^5 = H$
$R^4 = OCH_2Ph, R^5 = H$
$R^4 = OMe, R^5 = OMe$
$R^4 = R^5 = OCH_2O$



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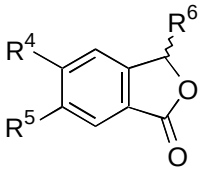


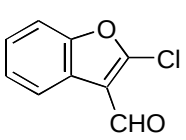
10

$R^4 = OMe, R^5 = H, R^6 = OH, H$
$R^4 = OCH_2Ph, R^5 = H, R^6 = OH, H$
$R^4 = OMe, R^5 = OMe, R^6 = OH, H$
$R^4 = R^5 = OCH_2O, R^6 = OH, H$

Scheme II

3. BENZOFURAN AND BENZOPYRAN DERIVATIVES

The synthesis of novel heterocyclic ring systems such as benzofurothiazine **(12)** is described[5] 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 synthesized[6] from mercapto- and selenobenzofurancarboxaldehydes **(11)** (Scheme III) adopting the same procedure.



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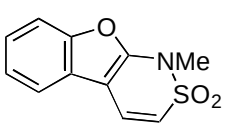

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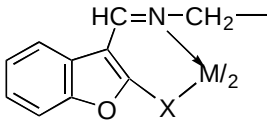

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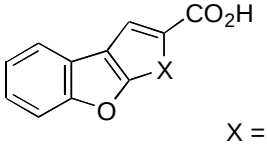


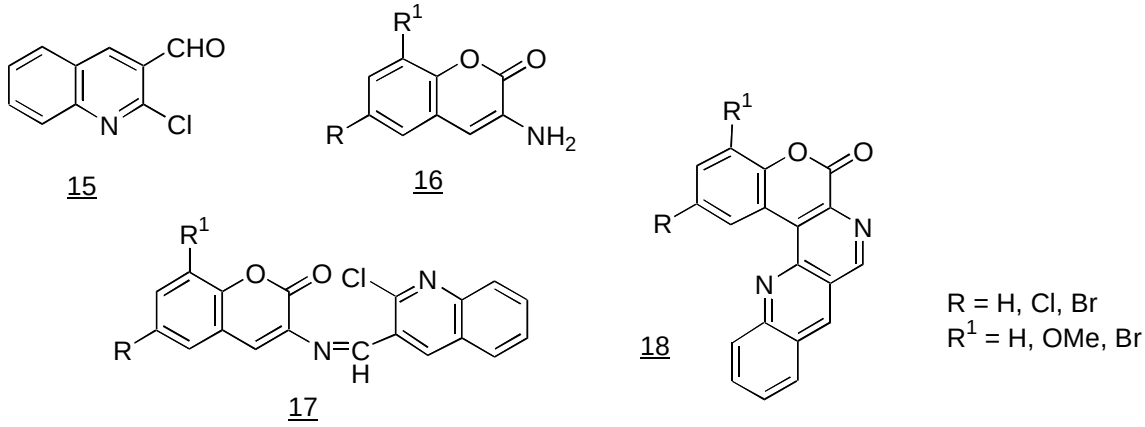
14

X = S, Se
M = Ni, Cu

Scheme III

Cyclodehydrochlorination method

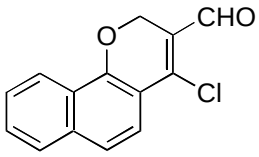
Prasad and Darbarwar have reported[7] the synthesis of [1]benzopyrano[3,4-*h*]benzo[*b*]-1,6-naphthyridin-6-ones **(18)** from 3-aminocoumarins **(16)** and 2-chloro-3-formylquinoline **(15)**. The reaction involves aldimine formation of the carboxaldehyde **(15)** in glacial acetic acid followed by 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 synthesized[8] 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)**.



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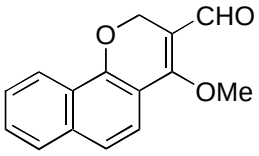

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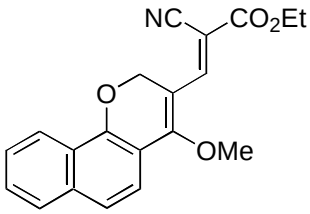

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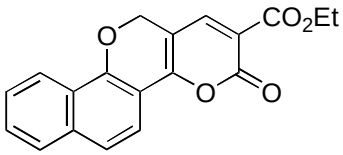

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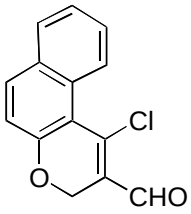

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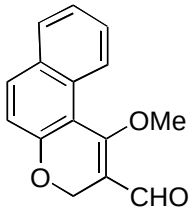

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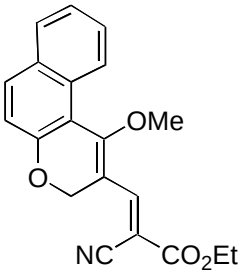

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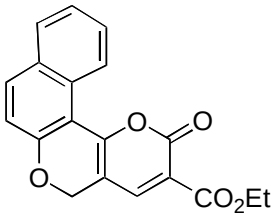

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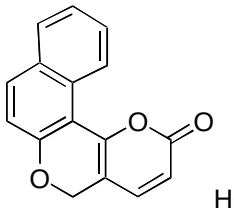

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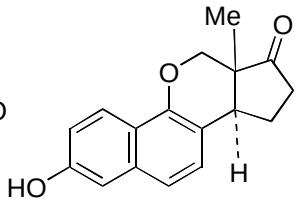
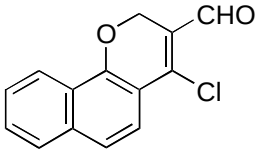


27a

Scheme V



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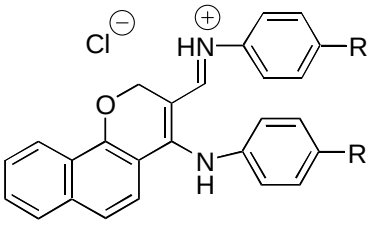

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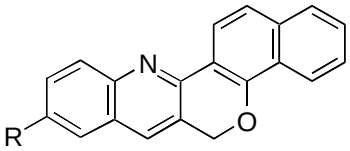

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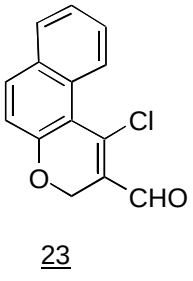

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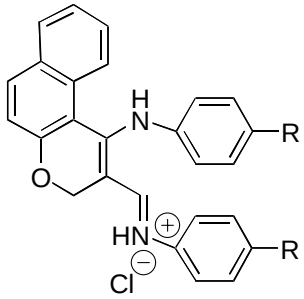

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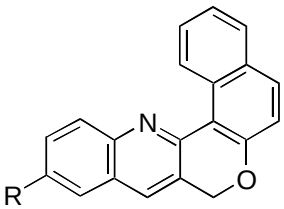


31

R = H, Me, OMe, Cl, NO_2, CO_2Et

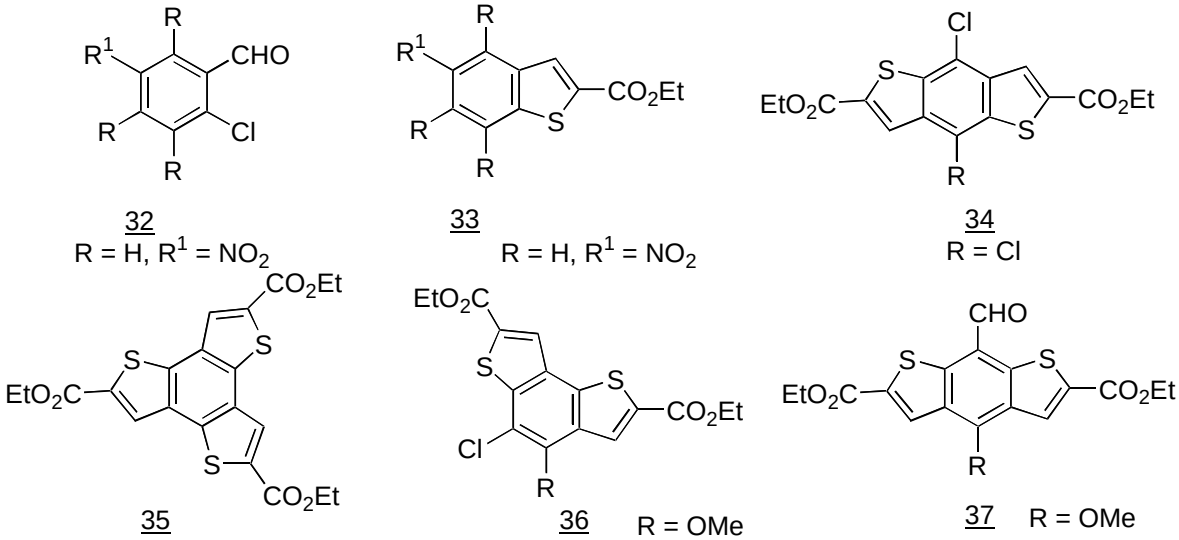
Scheme VI

Syntheses of naphthopyranoquinolines **(29** and **31)** (Scheme VI) having bay region and Fjord region in the molecules were recorded[8] 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

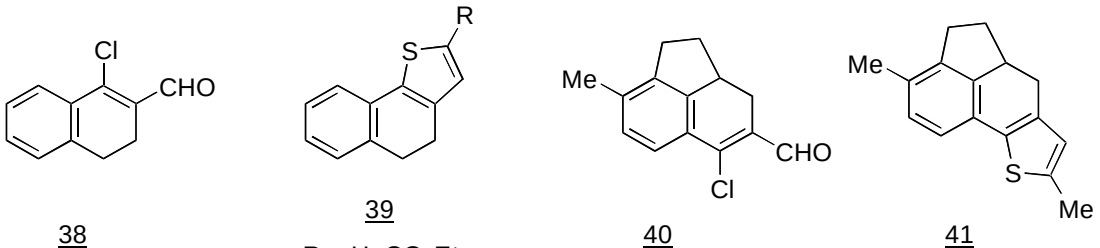
β-Halovinylaldehydes were thiolated into condensed thiophene derivatives initially. For example, the substituted chlorobenzaldehydes **(32)** were converted into the thiophene derivatives[9] in a single step **(33-37)** on reaction with ethyl mercaptoacetate in presence of triethylamine. The mechanism 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).

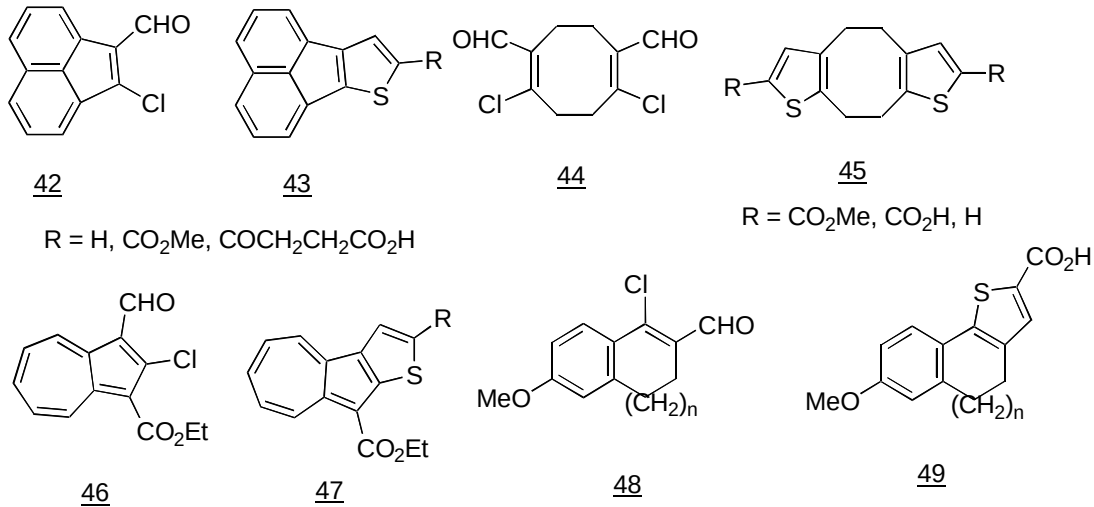


38 39 40 41

R = H, CO_2Et CO_2H

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



42 43 44 45

R = H, CO_2Me, $COCH_2CH_2CO_2H$

R = CO_2Me, CO_2H, H

46 47 48 49

R = H, CO_2Me, $COCH_2CH_2CO_2H$

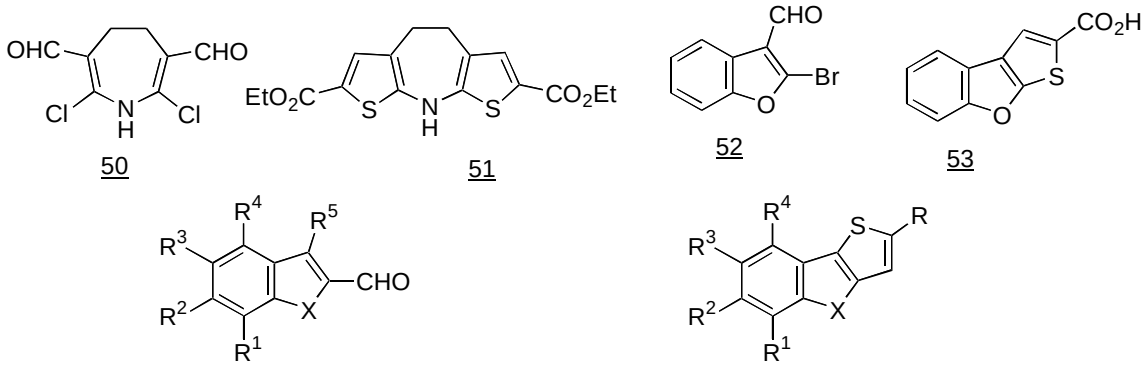
n = 1, 2

Scheme IX

derivatives **(49)** were also achieved[15] 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 bisthiophene 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 reported[18] syntheses of thienobenzofurans and its derivatives **(55)** from β-chloroaldehydes **(54)** (Scheme X).



50 51 52 53

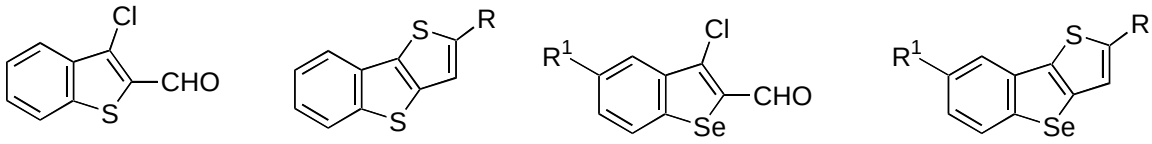
54 55

$R^1 = R^2 = R^3 = R^4 = H$, $R^5 = SCH_2CO_2H$, $R = CO_2H$, X = O
$R^1 = R^2 = R^4 = H$, $R^3 = Me$, $R^5 = SCH_2CO_2H$, $R = CO_2H$, X = O
$R^1 = R^4 = Me$, $R^2 = R^3 = H$, $R^5 = SCH_2CO_2H$, $R = CO_2H$, X = O
$R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = SCH_2CO_2H$, $R = CO_2H$, X = O
$R^1 = R^2 = R^3 = R^4 = H$, $R^5 = SCH_2CO_2H$, $R = CO_2H$, X = Se

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,

succinoylation, 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, R^1=Me). This was acylated under Friedel-Crafts condition to **59** (R=Ac, R^1=Me) which was reduced to **59** (R=Et, R^1=Me) (Scheme XI).



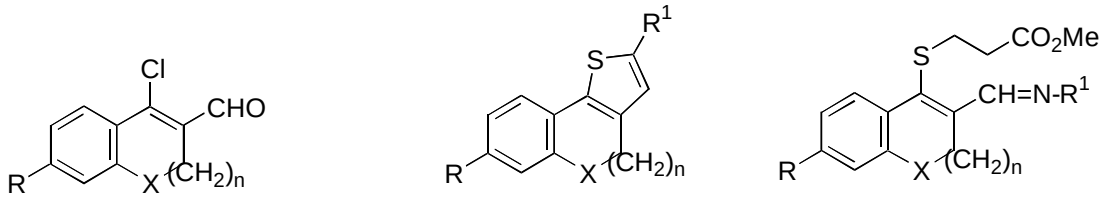
56 57 58 59

R = H, Me, Et, NO_2,CO_2H, $CH_2CH_2CH_2CO_2H$

R = Me, R^1 = H

Scheme XI

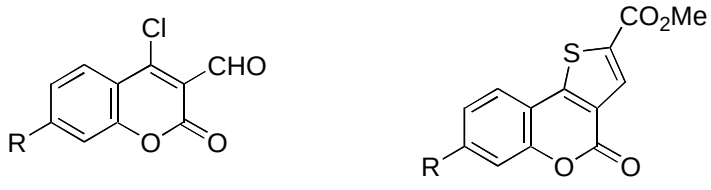
A simple and convenient method for the preparation of another class of condensed thiophene derivatives **(61)** has been reported from our laboratories[20] starting with heterocyclic β-chlorovinylaldehydes **(60)** and



60 61 62

R = OMe, X = O, n = 0, R^1 = CO_2Me
R = H, X = O, n = 1, R^1 = CO_2Me
R = H, X = O, n = 2, R^1 = CO_2Me
R = H, X = S, n = 1, R^1 = CO_2Me
R = H, X = S, n = 2, R^1 = CO_2Me

R = OMe, X = O, n = 0, R^1 = OH, *p*-C_6H_4Me
R = H, X = O, n = 1, R^1 = OH, *p*-C_6H_4Me
R = H, X = O, n = 2, R^1 = OH, *p*-C_6H_4Me
R = H, X = S, n = 1, R^1 = OH, *p*-C_6H_4Me
R = H, X = S, n = 2, R^1 = OH, *p*-C_6H_4Me



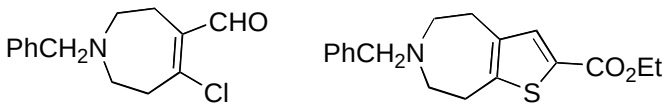
63 64

R = H, OMe, NMe_2, N⬠

Scheme XII

methyl mercaptoacetate in a single step quite recently (Scheme XII). The condensation of β-chlorovinylaldehydes with methyl β-mercaptopropionate 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 Weiβenfels *et al.* [22] in 1989 (Scheme XII).

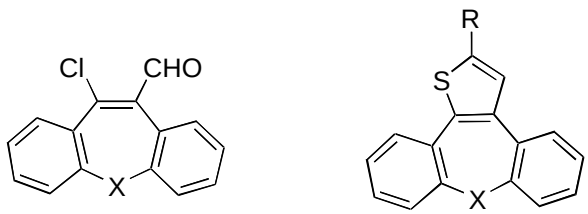
The preparation of thienoazepines **(66)** and its derivatives was achieved[23] from chloroformyl derivative **(65)** and mercaptoacetic acid in pyridine and triethylamine (Scheme XIII) as shown below.



65 66

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 described[24] (Scheme XIV) for the first time as the simplest method.



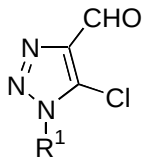
67 68

X = CH_2, R = CO_2Et
X = CH_2, R = H
X = CH_2, R = Me
X = CH_2, R = NO_2
X = CH_2, R = CO_2Me
X = O, R = CO_2Et
X = O, R = H
X = S, R = CO_2Et
X = S, R = H

Scheme XIV

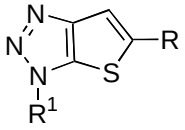
Fused thienoazoles **(70)** that are of interest as a potential source of thienyl nitrones have been synthesized[25] from 5-chloro-4-formyltriazoles **(69)** by reaction with methyl mercaptoacetate and Na_2CO_3. However, the attempted decarboxylation led to the decomposition of the ring system (Scheme XV). Novel

heterocyclic systems having a condensed thiophene ring such as thienobenzopyran, thienobenzothiopyran, benzodithiophene **(72)** and their preparations were described[26] from chloroformyl derivatives **(71)** *via* condensaion with thiogycolic acid followed by treatment with concentrated KOH. Thienoquinoxalinecarboxylates **(74)** were achieved[27] from quinoxalinechloroaldehydes **(73)** and ethyl mercaptoacetate (Scheme XV) adopting exactly the above mentioned methodology.



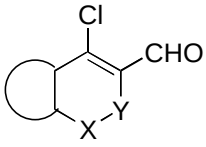
69

R^1 = $PhCH_2$, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, Ph



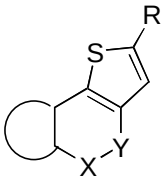
70

R^1 = $PhCH_2$, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, Ph
R = CO_2H, CO_2Me



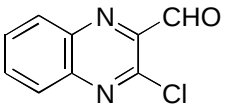
71

X = O, Y = CH_2
X = S, Y = CH_2
X = Se, Y = CH_2
X = CH_2, Y = CH_2
X = CH_2, Y = S

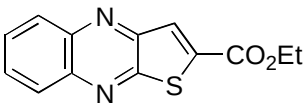


72

X = O, Y = CH_2, R = H, CO_2H
X = S, Y = CH_2, R = H, CO_2H
X = Se, Y = CH_2, R = H, CO_2H
X = CH_2, Y = CH_2, R = H, CO_2H
X = CH_2, Y = S, R = H, CO_2H



73



74

Scheme XV

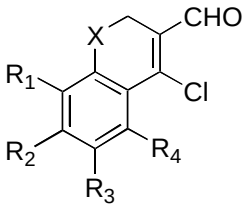
In conclusion it is to be pointed out that the condensation of chloro aldehydes either with mercapto acids or esters in presence of base was utilized in the synthesis of a variety of fused polycyclic heterocycles as discussed above.

5. ISOXAZOLES

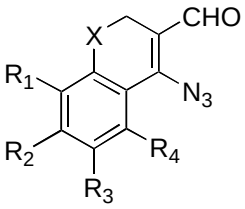
Cyclization *via* Azidolysis

Polycyclic isoxazoles **(77)** were obtained[28] 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

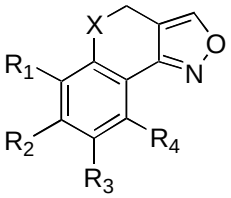
with NaN_3 in DMSO. The azides were cyclized thermally to isoxazoles **(77)** and **(79)** by reflux in dichloromethane (Scheme XVI).



75

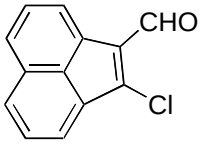


76

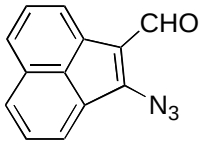


77

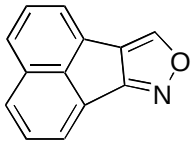
$R_1 = R_2 = R_3 = R_4 = H$, X = CH_2, O
$R_1 = R_2$ = -CH=CH-CH=CH-, $R_3 = R_4 = H$, X = CH_2, O



42



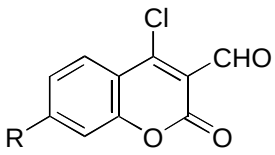
78



79

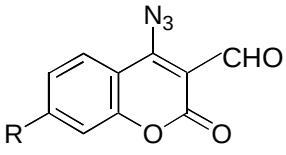
Scheme XVI

Quite similar to the above method it is found possible[29] 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).



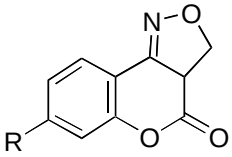
80

R =OMe



81

R =OMe



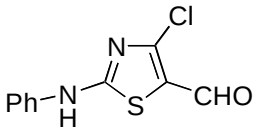
82

R =OMe

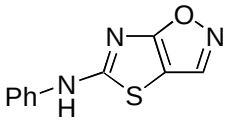
Scheme XVII

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.



83

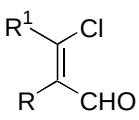


84

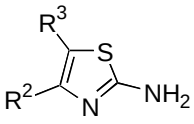
Scheme XVIII

6. THIADIAZOLIUM SALTS

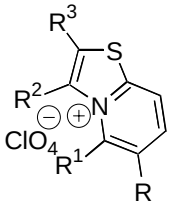
Shulga and Chuiguk[31] have observed the synthesis of thiazolo[3,2-*a*]pyrimidinium salts **(87-89)** from β-chloroaldehydes **(85)** with 2-aminothiazole **(86)**. The reaction involves the condensation of carboxaldehydes followed by addition and elimination of chlorine. Benzothiazole **(88)** and naphthothiazole **(89)** were synthesised adopting identical sequence of reactions on the appropriate β-chloroaldehydes (Scheme XIX).



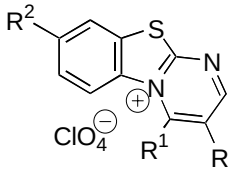
85



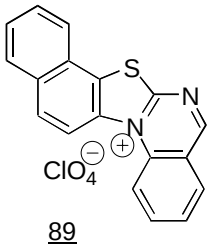
86



87



88



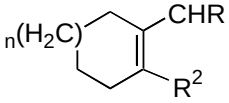
89

R = R^1 = Me, R^2 = R^3 = H
R = R^1 = Me, R^2 = Ph, R^3 = H
R = R^1 = $(CH_2)_4$, R^2 = Ph, R^3 = H
R = R^1 = R^2 = R^3 = Me
R = R^1 = R^2 = Me, R^3 = H

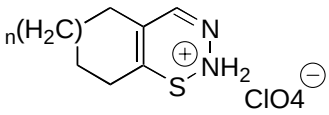
R = R^1 = Me, R^2 = H, NO_2
R = R^1 = CH=CH, R^2 = NO_2

Scheme XIX

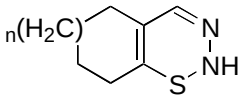
Novel heterocyclic 8 electron systems namely 1,2,3-thiadiazolium salts **(91)** were found possible[32] by treating the chlorocycloalkenealdehydes **(90**, R^2 = Cl, R = O**)** with KSCN to give the corresponding sulfocyanide **(90**, R^2 = SCN, R = O**)** which in turn led to hydrazones, when treated with hydrazine **(90**, R^2 = SCN, R = =N-NH_3). The hydrazones thus formed underwent cyclization with $HClO_4$ to yield **91**. Treatment of **91** with a weak base gave **92** in fairly good yield (Scheme XX).



90
R^2 = Cl, SCN
R = O, =N-NH



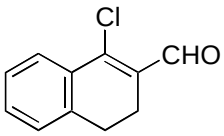
91



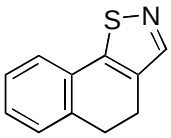
92

Scheme XX

Nematicidal naphtho[2,1-*d*]isothiazoles **(93)** was obtained in a simple way[33] from the reaction of naphthalenechloroaldehydes **(38)** with S and NH_3 (Scheme XXI). **38** is a very useful intermediate for the synthesis of compounds of the type **(93)**.



38



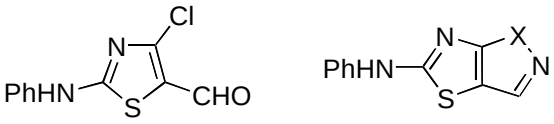
93

Scheme XXI

7. FUSED PYRAZOLES

Cyclocondensation

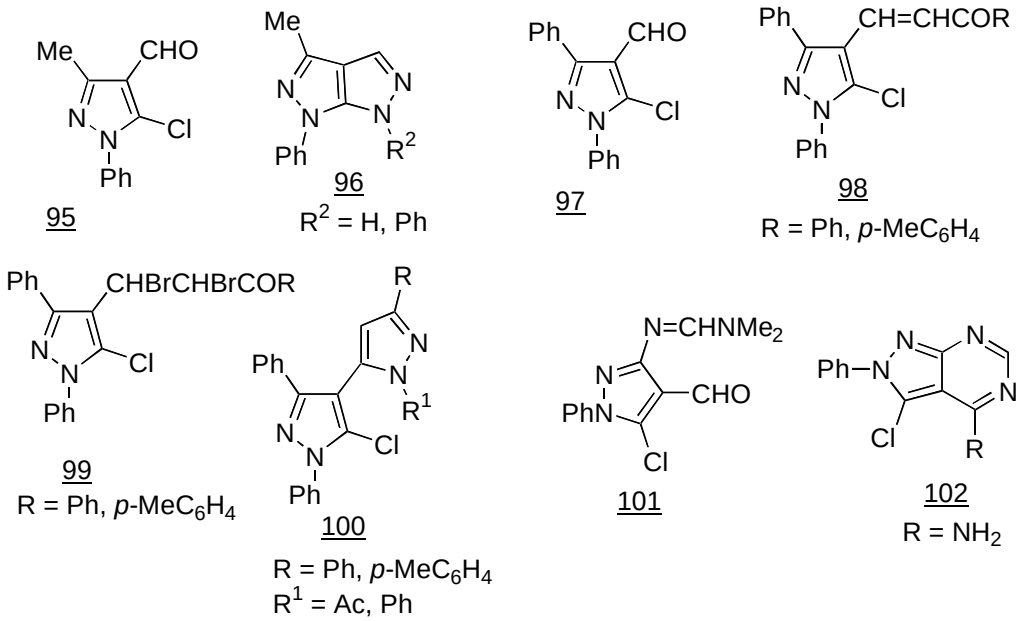
Although recent publications disclosed a variety of applications of β-halovinylaldehydes to the field of heterocyclic chemistry, only a few examples were reported on the introduction of pyrazole moiety to five, six and seven membered heterocycles. Recently a versatile new synthesis of fused heterocycles such as pyrazolothiazole **(94**, X = NH, NPh**)**, thiazoloisoxazole **(94**, X = O**)** were successfully prepared[34] by the condensation of chloroaldehyde **(83)** with NH_2NH_2, phenylhydrazine and NH_2OH, using the same synthetic strategy as discussed above (Scheme XXII).



83 94

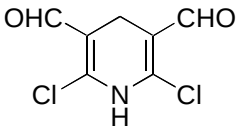
Scheme XXII

Recently, cyclocondensation of chloropyrazolecarboxaldehyde **(95)** with NH_2NH_2 has afforded pyrazolopyrazole[35] **(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 R-$NHNH_2$ furnished pyrazolylpyrazole **(100,** R = Ph**)** (Scheme XXIII). Similarly, amidinealdehydes **(101)** are also utilized in heterocyclic synthesis. Recently pyrozolopyrimidines **(102)** and their corresponding *N*-oxides are prepared by the condensation of amidinealdehyde **(101)** with $NH_2OH.HCl$ in a simple manner.[37]

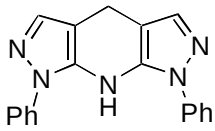


Scheme XXIII

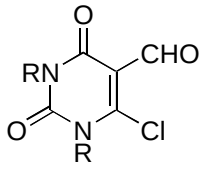
Diformyldihydropyridine **(103)** on condensation with phenylhydrazine gave dipyrazolopyridine **(104)** in a single pot reaction[38] (Scheme XXIV). Reactions of 1,3-disubstituted 6-chloro-5-formyluracils **(105)** with phenylhydrazine or methylhydrazine afforded 1,5,7- and 2,5,7-trisubstituted, 4,6-dioxo-4,5,6,7-tetrahydropyrazolo(3,4-*d*)pyrimidine **(106)**. Detailed investigations by Senda and Hirota[39] 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 achieved[16] by the condensation of di-β-chlorovinylaldehyde of azepine **(50)** with NH_2NH_2. H_2O (Scheme XXIV) in the same way as described above.



103

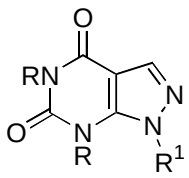


104



105

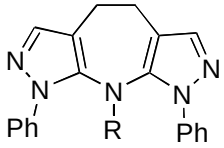
R = Me



106

R = Me, R^1 = Ph

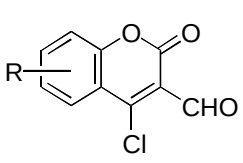
50



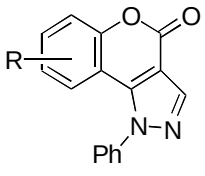
107

Scheme XXIV

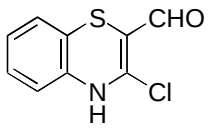
The syntheses of coumarinoisoxazoles and coumarinopyrazoles **(109)** have been achieved[40] by heating the



108

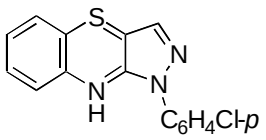


109

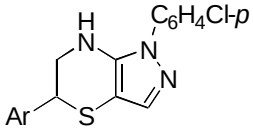


110

R = 6-Me, 7-Me, 8-Me
R = 6-Cl, 7-Cl, 8-Cl
R = 6-Br, R = 6-Cl, 7-Me
R = 6,8-Cl_2



111

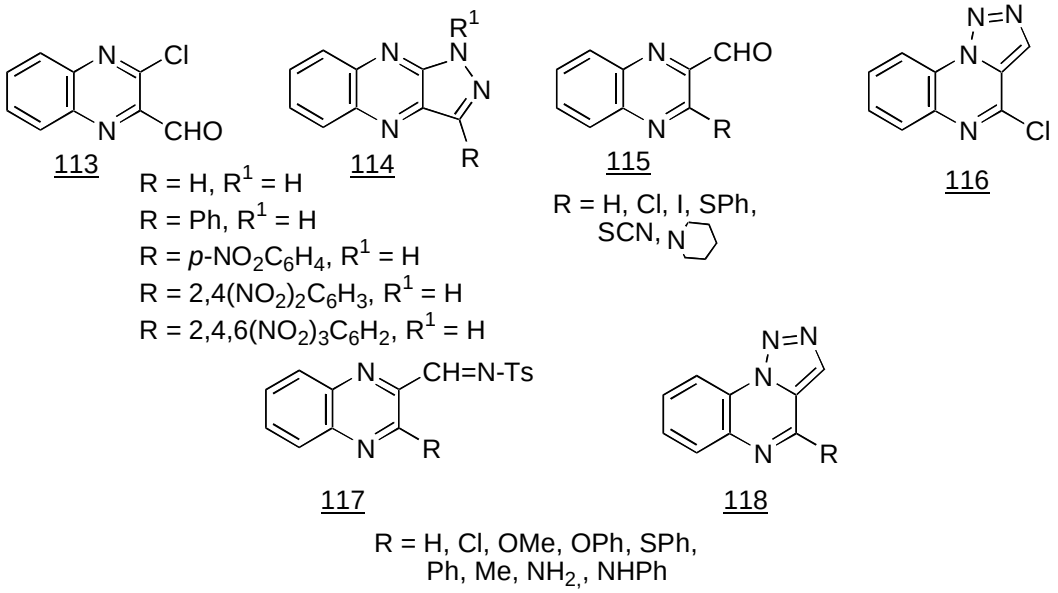


112

Ar = Ph

Scheme XXV

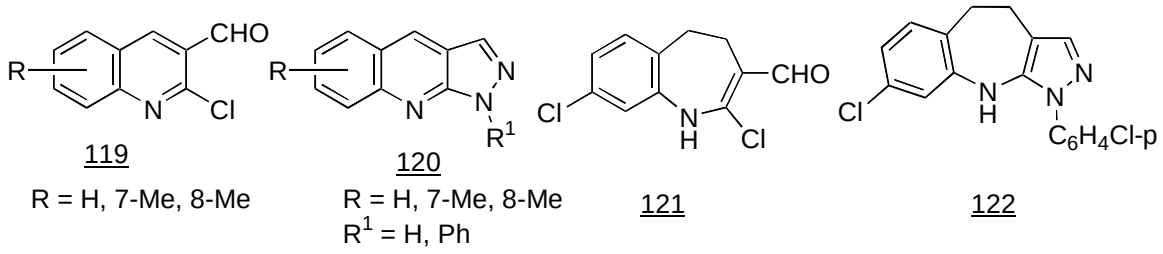
oximes of 4-chloro-3-formylcoumarins **(108)** directly in ethanol in presence of sodium acetate. Similarly, more heterocycles **(111, 112)** are prepared[41] from thiazinechloraldehyde **(110)** (Scheme XXV) by adopting the same synthetic strategy.



Scheme XXVI

Quinoxalinecarboxaldehyde **(113)** on condensation[42] with NH_2NH_2 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 reported[44] 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



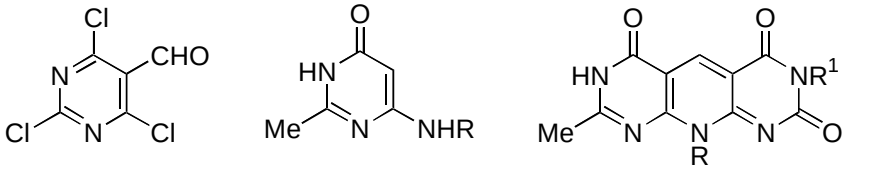
Scheme XXVII

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 Yoneda[45] 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.



123

124
R = n-Bu, n-C_8H_{19}, n-$C_{12}H_{25}$

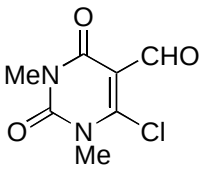
125
R = n-Bu, n-C_8H_{19}, n-$C_{12}H_{25}$,
R^1 = Me, Et, n-Bu

Scheme XXVIII

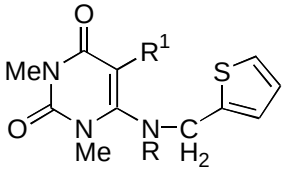
Intramolecular Cycloaddition

Very recently Sandhu[46] 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 nitrone 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

$NaBH_4$) to afford the substituted formyluracils **(126**, R^1 = CHO**)** in good yields. The corresponding oximes **[126**, R^1 = (-CH=NOH)**]** were obtained in 50% yield by condensation of **(126**, R^1 = CHO**)** with $NH_2OH.HCl$. 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.



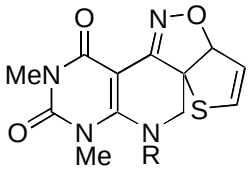
105



126

R = *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$EtOC_6H_4$

R^1 = CH=NOH

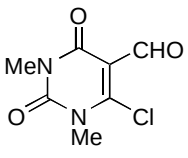


127

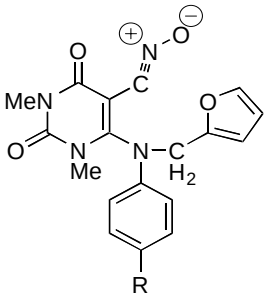
R = *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$EtOC_6H_4$

Scheme XXIX

Syntheses of several novel condensed pyridopyrimidines **(129, 130)** have recently been prepared[47] *via* the intramolecular cycloadditions with chloroformyl uracils **(105)** and furfurylarylamines as an extension of the same synthetic strategy as discussed above by the same authors[47] (Scheme XXX).

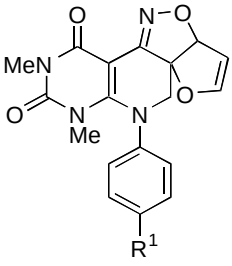


105



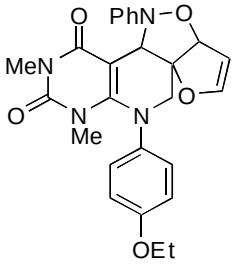
128

R = Ph, *p*-$EtOC_6H_4$, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4



129

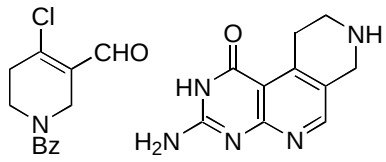
R^1 = Ph, *p*-$EtOC_6H_4$, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4



130

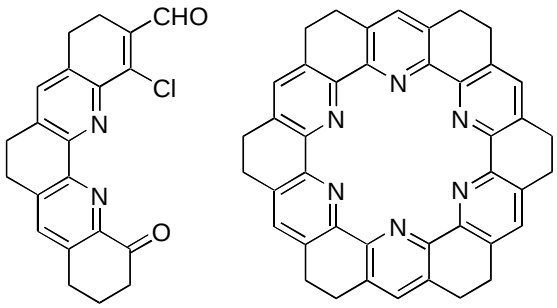
Scheme XXX

Recently the synthesis of a substituted tetrahydropyrimidonapthyridine **(132)** as a tricyclic 5-deaza nonclassical folate was reported by Ahaam[48] by the condensation of 2,4,6-triaminopyrimidine with tetrahydropyridine chloroaldehyde **(131)**. The condensation was regiospecific and afforded only the substituted angular tetrahydro pyrimidonapthyridine 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 ^{1}H-NMR spectral data (Scheme XXXII).



131 132

Scheme XXXI



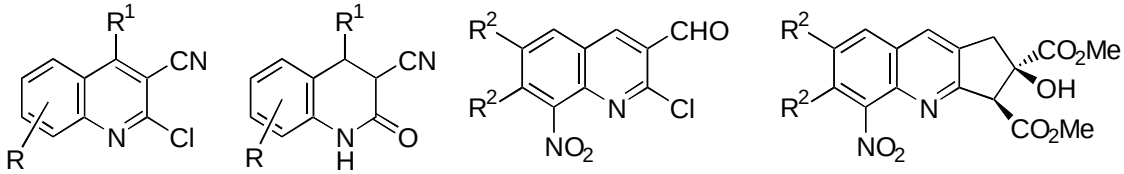
133 134

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



135 136 137 138

R = H, 6-OMe
R^1 = H, Me, Et

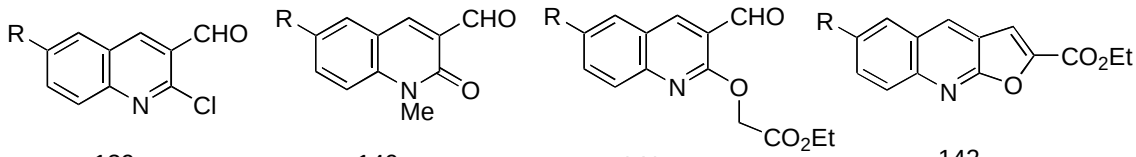
R^2 = OMe, OEt

Scheme XXXIII

based on quinoline chloroaldehydes have been recently reported. For example, very recently Bhaduri[50] has achieved novel syntheses of 3-cyano-3,4-dihydroquinolin-2[1*H*]-one **(136)** and derivatives of cyclopentaquinolines **(138)** from chlorocyanoquinolines. 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 6N 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).



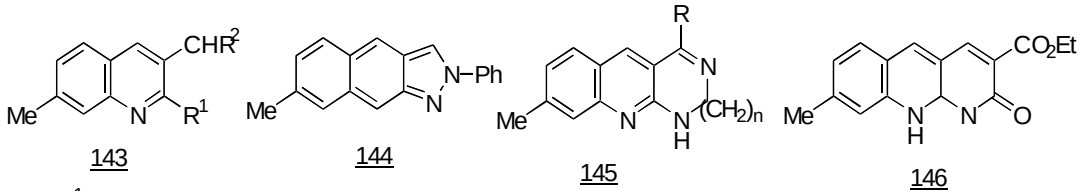
139 140 141 142

R =H, Me, Br, OMe

Scheme XXXIV

Pyrazoloquinoline

A versatile new synthesis of quinolines and related fused pyridines have been achieved by Cohn[52] from quinolinechloroaldehydes. In the case of β-chlorovinylaldehydes, as the aldehydes **(143**, R^2 = O**)** are



143 144 145 146

R^1 = Cl, NH_2
R^2 = O, $O(CH_2)_2O$

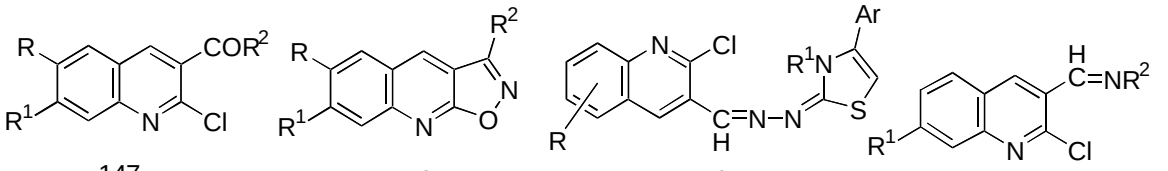
R = H, Ph, n = 0

Scheme XXXV

attacked at first the aldehydic function, by nitrogen nucleophiles, the corresponding acetals **[143**, R^2 = $O(CH_2)_2O$**]** underwent initial substitution at chlorine and the products **[143**, R^2 = $O(CH_2)_2O$, R^1 = Nu**]** undergo spontaneous cyclisation on deacetalisation with hot aqueous alcoholic mineral acids. In this way, the authors[52] have obtained in excellent yields the fused pyrazoles **(144)** and the diazepine **(145)** by the use of phenylhydrazine and ethylenediamine respectively (Scheme XXXV).

Isoxazolo- and thiazoloquinolines

Recently, isoxazolo[5,4-*b*]quinolines **(148)** have been obtained by Bhaduri[53] by reaction of 3-acyl- or aroyl-2-chloro-6-alkoxy or 6,7-dialkoxyquinolines **(147)** with NH_2OH (Scheme XXXVI). The method is of general applicability for obtaining this class of compounds and it involves the use of easily available starting materials. The synthesis involves the reaction of 2-chloro-3-formylquinolines with alkyl- or arylmagnesium halide to furnish the tertiary alcohols which on oxidation with pyridinium chlorochromate yielded 3-acyl- or aroyl 2-chloroquinolines **(147)** in good yields. Sayed[54] reported the synthesis of two series of substituted quinoline-3-carboxaldehydes. The first included derivatives of 2-chloroquinoline-3-carboxaldehyde thiocarbamoylhydrazone and the second involved substituted 2-chloroquinoline-3-carboxaldehyde(2,3-dihydrothiazol-2-ylidine) **(149)** from quinolinechloraldehyde **(147)** (Scheme XXXVI). Very recently, Fathy[55] has also obtained some reactions of 2-chloroquinoline-3-carboxaldehyde with hydrazine derivatives, NH_2OH and anilines utilizing more or less the same strategy **(150)**.



147
R = R^1 = OMe
R = OMe, R^1 = H
R = R^1 = OEt

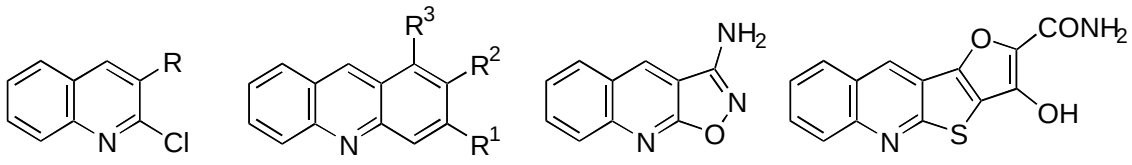
148
R = R^1 = OEt, R^2 = Me
R = R^1 = OMe, R^2 = Me
R = R^1 = OMe, R^2 = Ph
R = R^1 = OMe, R^2 = *p*-$MeOC_6H_4$
R = OMe, R^1 = H, R^2 = Me
R = OMe, R^1 = H, R^2 = Ph

149
R = H, 7-Me, 8-Me
R^1 = H

150
R^1 = Me, Cl
R^2 = NH_2, OH, NHPh,
$NHCONH_2$, $NHCSNH_2$,

SchemeXXXVI

A number of tri- and tetracyclic heterocycles have been synthesized from 2-chloro-3-formylquinoline. For example, Bhaduri[56] 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).



151 152 153 154

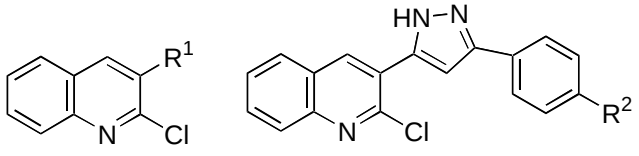
R = CHO, CN, C(=NOH)NH_2

$R^1 = R^3 = OMe$, $R^2 = H$

$R^1 = OH$, $R^2 = CO_2Me$, $R^3 = H$

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 Bhaduri[57] very recently. Interestingly, in none of these reactions, the nucleophilic displacement of chlorine is observed (Scheme XXXVIII) by the author.[57]



155

R^1 = CHO, COMe, MeCHOH

156

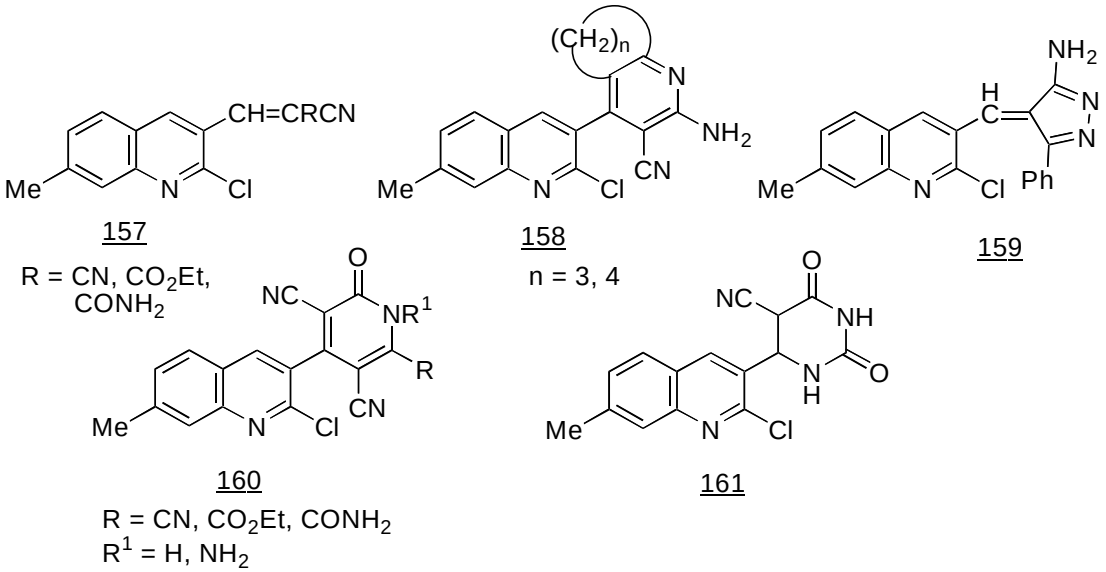
R^2 = H, OMe

Scheme XXXVIII

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

R^1 = Ac**)**. The base catalyzed condensation of **155** with aromatic aldehydes gave the chalcones and the ring closure of these chalcones with NH_2NH_2. H_2O gave the pyrazole derivatives **(156)**.

Several new pyrimidine, pyridine and pyrazole derivatives of potential synthetic and biological importance have been synthesized very recently by Elgemele[58] 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 derivates **(161)**. Cyclocondensation of **157** with ethyl cyanoacetate yielded dicyanoquinolinylpyridones **(160)** and monocyanoquinolinylpyrimidone **(161)** (Scheme XXXIX).

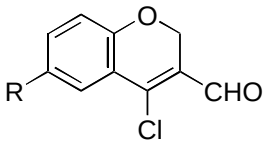


Scheme XXXIX

Thermal cyclisation

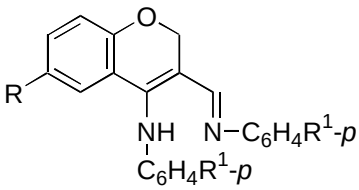
Syntheses of several quinoline derivatives starting from β-halovinylaldehydes have been published appeared in literature. One of the interesting examples of the utility of β-halovinylaldehydes for quinoline synthesis, is the reaction of 4-chloro-chromene-3-carboxaldehyde **(162)** with anilines. Balasubramanian[59]

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).



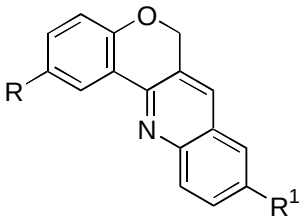
162

R = H, Me



163

R = R^1 = H
R= H, R^1 = Me
R = H, R^1 = OMe
R = R^1 = Me

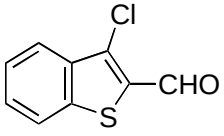


164

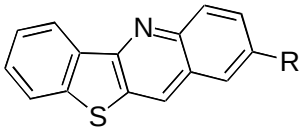
R = R^1 = H
R= H, R^1 = Me
R = H, R^1 = OMe
R = R^1 = Me

Scheme XL

Other interesting examples employing similar procedures have appeared in recent literature. For example, benzothienoquinolines **(165)** have been reported[60] from the reaction of chlorobenzo[*b*]thiophene carbaldehyde **(56)** with anilines at 170^{o}C in 70 – 90% yield *via* the corresponding arylimine derivatives. Similarly reaction of 2-chloroindole-3-carboxaldehyde **(166)** with aniline has been reported[61] to yield indoloquinoline **(167)** utilizing almost the same concept (Scheme XLI).

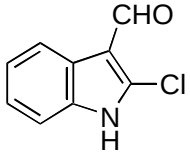


56

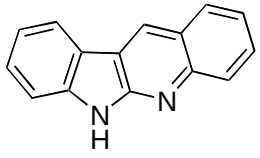


165

R = H, Me, OMe, Br



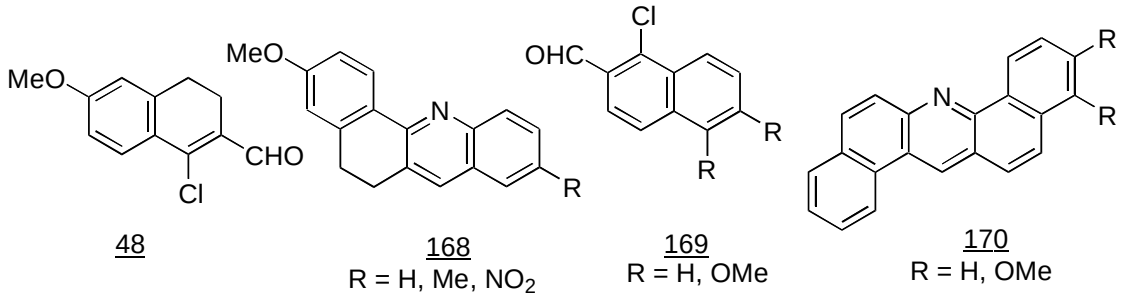
166



167

SchemeXLI

Dihydronaphthoquinolines are relatively rare polycyclic heterocyclic compounds. A facile and convenient methodology for the synthesis of dihydronaphthoquinolines has been successfully achieved recently by Ray[62] utilizing almost the same synthetic strategy. Condensation of chloroaldehydes **(48)** with aniline in ethanol gave 90% of anil derivatives, which on pyrolysis at 250^{o}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 Ray[63] 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).

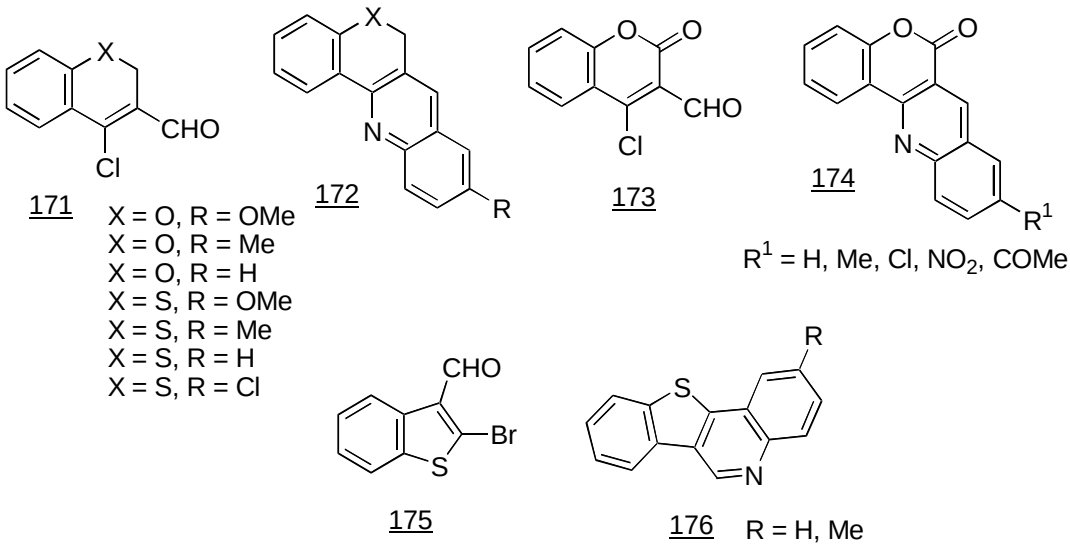


48 168 R = H, Me, NO_2 169 R = H, OMe 170 R = H, OMe

Scheme XLII

Photocyclisation

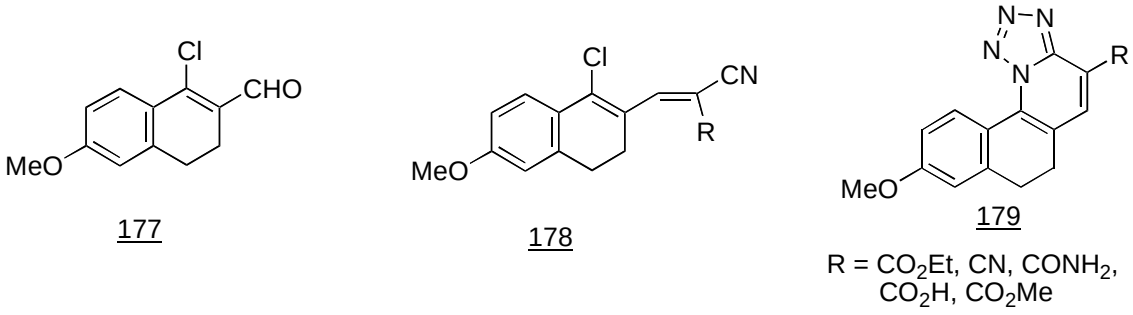
There has been considerable interest in the study of photochemical cyclization of imines derived from aromatic aldehydes or ketones and arylamines. Non oxidative photocyclisations have been synthetically exploited well in the field of stilbene in the same review. However, reports on analogous studies 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 obtained[66] by condensation of 2-bromo-3-formylbenzothiophene **(175)** with aniline (Scheme XLIII).



Scheme XLIII

1,3-Dipolar cycloaddition

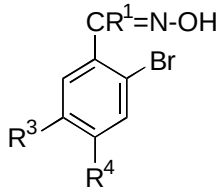
Ylidine malononitriles are versatile synthons in heterocyclic synthesis. Konwar *et al.*[67] have reported the synthesis of benzo[*h*]tetrazolo[1,5-*a*]-6,7-dihydroquinolines **(179)** utilizing intramolecular 1,3-dipolar cycloaddition reaction of ylidine malononitrile. Knoevenagel condensation of cyanomethylenes with 1-chloro-6-methoxy-3,4-dihydronapthalene **(177)** gave ylidine malononitriles **(178)**. The reaction of **178** with KN_3 in ethanol underwent facile halide displacement followed by cycloaddition to yield **179** (Scheme XLIV).



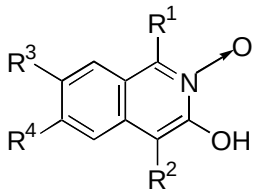
Scheme XLIV

10. ISOQUINOLINE *N*-OXIDES

β-Chlorovinylaldehydes have been utilized to build up isoquinoline derivatives. Recently a simple one step synthesis of 3-hydroxisoquinoline-*N*-oxide **(181)** has been achieved[68] 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 Yamanaka[69] 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 K_2CO_3 in ethanol, affording isoquinoline-2-oxide **(184)** in fairly good yield (Scheme XLV).

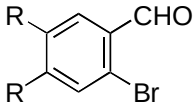


180

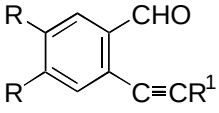


181

R^1 = H, R^2 = COMe, R^3 = R^4 = H
R^1 = H, R^2 = COPh, R^3 = R^4 = H
R^1 = H, R^2 = CO_2Me, R^3 = R^4 = H
R^1 = H, R^2 = CO_2Et, R^3 = R^4 = H
R^1 = H, R^2 = CN, R^3 = R^4 = H
R^1 = H, R^2 = COMe, R^3 = R^4 = OCH_2O
R^1 = H, R^2 = CO_2Et, R^3 = R^4 = OCH_2O
R^1 = Me, R^2 = COMe, R^3 = R^4 = H
R^1 = Me, R^2 = CO_2Et, R^3 = R^4 = H

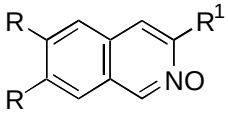


182



183

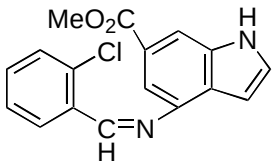
R = H, R^1 = Ph
R = H, R^1 = Bu
R = H, R^1 = $SiMe_3$
R = OMe, R^1 = Ph
R = OMe, R^1 = $SiMe_3$
R = OMe, R^1 = Bu



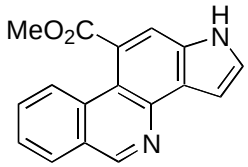
184

Scheme XLV

The synthesis of pyrrolophenanthridine **(186)** is described from the reaction of (chlorobenzylidine)indolamine **(185)** with $NaNH_2$ in liquid NH_3 by Balberkina[70] very recently utilizing the same procedure (Scheme XLVI).



185



186

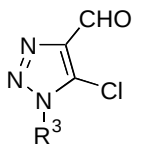
Scheme XLVI

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

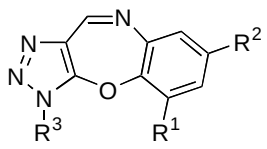
1,5-Benzoxazepines

Syntheses of vast number of polycyclic heterocyclic 1,5-benzoxazepines, 1,5-benzdiazepines 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 Weiβenfels[2] 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.

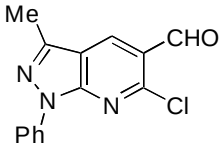
A convenient synthesis of a novel tricyclic heterocyclic triazole ring system **(188)** from chlorotriazole carbaldehydes **(187)** and 2-aminophenols is described,[72] under milder reaction conditions employing the



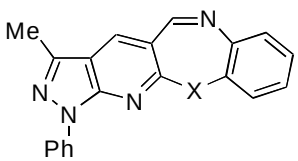
187



188



189



190

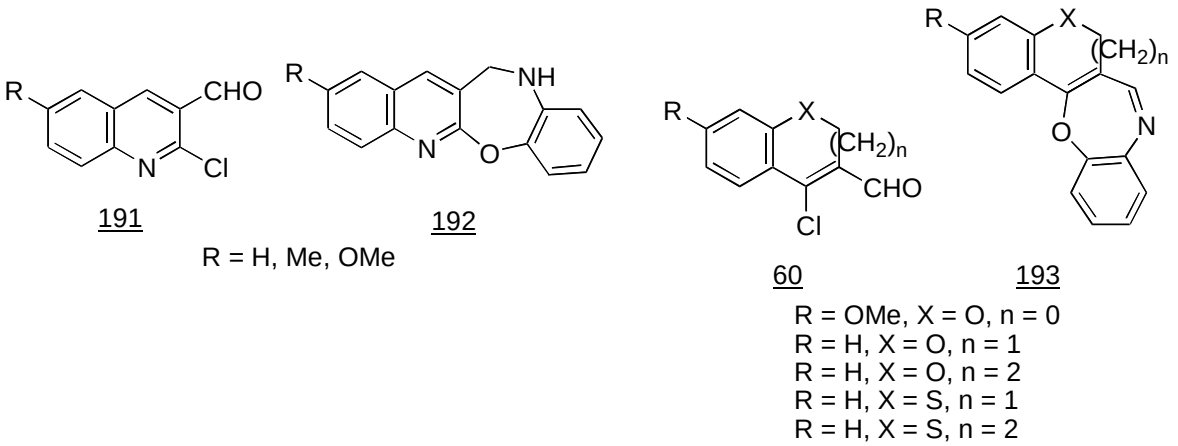
X = O, S

R^1 = R^2 = H, R^3 = *p*-$MeOC_6H_4CH_2$
R^1 = **Me,** R^2 = H, R^3 = *p*-$MeOC_6H_4CH_2$
R^1 = H, R^2 = Me, R^3 = *p*-$MeOC_6H_4CH_2$
R^1 = H, R^2 = Cl, R^3 = *p*-$MeOC_6H_4CH_2$
R^1 = H, R^2 = H, R^3 = *p*-$ClC_6H_4CH_2$
R^1 = Me, R^2 = H, R^3 = *p*-$ClC_6H_4CH_2$
R^1 = H, R^2 = Me, R^3 = *p*-$ClC_6H_4CH_2$
R^1 = H, R^2 = Cl, R^3 = *p*-$ClC_6H_4CH_2$

Scheme XLVII

same strategy.[71-79] Reactions of chloropyrazolopyridinecarboxaldehydes **(189)** with 1,4-dinuceophiles 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 reported[76] by the condensation and subsequent cyclization reactions of 2-chloro-3-formylquinoline **(191)** with 2-aminophenol (Scheme XLVIII). A characteristic feature of the ^{1}H 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.

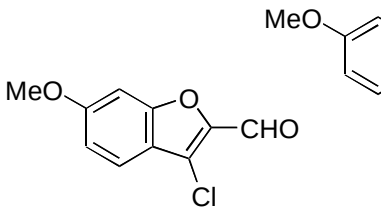


Scheme XLVIII

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 laboratory[79] (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 synthesized[80] 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.



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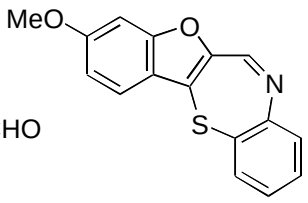

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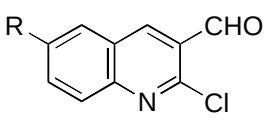
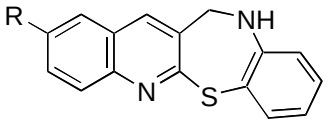


191

R = H, Me, Cl, OMe



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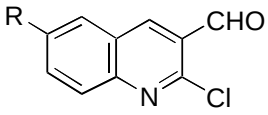
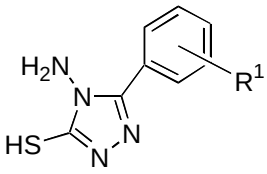


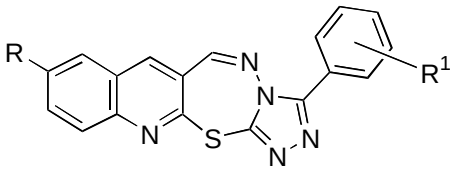
191

R = H, Me, OMe



197

R^1 = H, *p*-MeO, *p*-Cl, 2,4-Cl_2



198

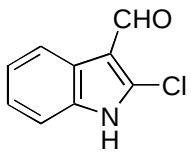
R = R^1 = H
R = H, R^1 = *p*-MeO
R = H, R^1 = *p*-Cl
R = H, R^1 = 2,4-Cl_2
R = Me, R^1 = *p*-MeO
R = Me, R^1 = *p*-Cl
R = Me, R^1 = 2,4-Cl_2
R = OMe, R^1 = *p*-MeO
R = OMe, R^1 = *p*-Cl
R = OMe, R^1 = 2,4-Cl_2

Scheme XLIX

1,5-benzodiazepine

2-Chloroindole-3-carboxaldehyde **(166)** on reaction with *o*-phenylenediamine underwent condensation and cyclization spontaneously affording indolobenzodiazepine[71] **(199)** (Scheme L).

Heterocycles are also obtained using azaazulene skeleton **(201)** and three syntheses in an efficient manner are reported[74] 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 described[75] 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).



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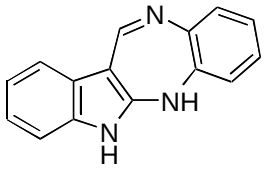

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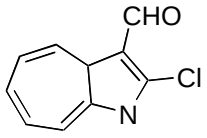
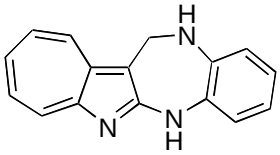


200



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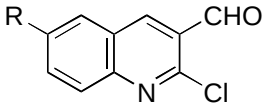

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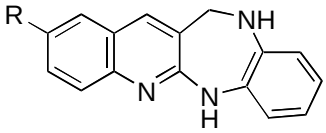

202

R = H, Me, Cl

Scheme L

ACKNOWLEDGEMENT

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