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HETEROCYCLES DIRECTLY LINKED TO 3-POSITION OF 1-BENZOPYRAN-4-ONES

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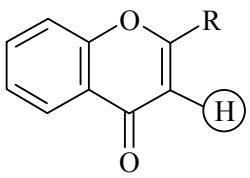
Abstract – Syntheses and some important reactions of the title systems are reviewed.

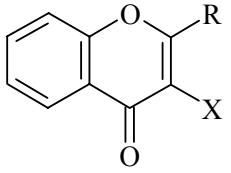
1. INTRODUCTION

1-Benzopyran-4-one (chromone) moiety is a component of many biologically active substances of both natural and synthetic origins. Several other heterocyclic compounds are also bestowed with some biological activities. So a lot of interest centers on the synthesis and chemistry of a variety of heterocycles linked with or without any tether to the 2- or 3-position of a chromone moiety with the aim of obtaining molecules of potential medicinal applications. The present review gives an account of the synthesis and a few important reactions of the titled system **A** where the ring H representing a heterocycle of one or more than one like or unlike heteroatom is linked directly (not through any tether) to the 3-position of a chromone moiety. The general methods for construction of the assemblage **A** are (i) simple elaboration of an appropriate functional group X of 3-functionalised chromone **B** to a heterocyclic ring without affecting the chromone moiety, (ii) acylation of the ketomethylene group of ω-hetaryl-2-hydroxyacetophenone **C** followed by ring closure and (iii) preparation of the disubstituted chromone **D** with its CX being a functionality capable of intramolecular reaction with a phenolic hydroxy group, either or both of Y and Z heteroatomic species, Z a nucleophilic centre and A a 2-4 carbon chain. The system **C** can be obtained by (a) reaction of salicyloyl chloride with a heterocycle having an active methyl group as a substituent in the presence of a base and (b) nucleophilic substitution of bromine of *o*-hydroxyphenacyl bromide with an appropriate heterocycle. The aromatic ketone of the type **C** can also be prepared by Houben Hoesch synthesis involving a polyhydroxybenzene and a hetarylacetonitrile. The system **D** is mostly available from the appropriate chromone derivatives, and **D** gives rise to **A** *via* the intermediate **E**. Alkyl, alkoxy, halogen and many other substituents in the benzene ring of chromone remain unaffected in most of the

reactions by which the chromone system is transformed into titled system **A**. So a 2-unsubstituted 4-oxo-4*H*-1benzopyran-3-yl moiety having no or the above named substituents in the benzene ring is abbreviated as 'Chr' whereas 2-substituted one is drawn as such. This review presented in the following few sections and subsections based on the nature, number and relative position of the heteroatoms in the ring H, covers the literature upto Volume **139** of *Chemical Abstracts*.



A



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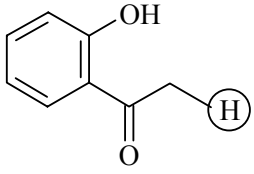
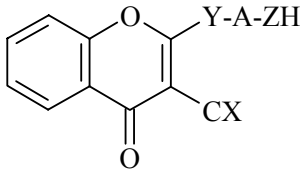
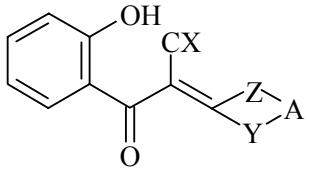


C



D



E

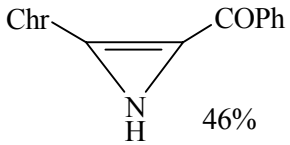
II. NITROGEN HETEROCYCLES

II.1. Heterocycles containing one N Atom

N-pyridinium phenacylide, prepared *in situ* from 1-phenacylpyridinium bromide under reflux in dry acetone containing anhydrous K_2CO_3, undergoes nucleophilic 1,2-addition to the nitrile functionality of 3-cyanochromone (**2**) followed by cyclisation and isomerisation to give the 2-azirine (**6**) which due to extended π-conjugation is more stable than the corresponding 1-azirine.[1] The anil (**3**) (Ar = Ph, C_6H_4OMe-*p*) and hydrazone (**4**) on treatment with *N*-aroylalanine Ar'CONHCH(Me)CO_2H (Ar' = C_6H_4X-*p*; X = H, Me, OMe, Cl, Br, NO_2) in CH_2Cl_2 containing chlorosulfonylmethylene(dimethyl)-ammonium chloride give respectively the azetidin-2-ones (**7**) (85-90%)[2] and (**8**) (80-85%).[3] 3-Amino-2-(4-bromophenyl)chromone condenses with 2,4-dimethoxytetrahydrofuran and hexa-2,5-dione in boiling Ac_2O to give 3-(1-pyrrolyl)flavones (**9**) and (**10**) respectively.[4] Trimethylamine catalysed condensation of chromone with isatin or 1-alkylisatin (Baylis-Hillman reaction) in MeOH at room temperature gives the indole (**11**) (R = H, Me, $PhCH_2$) which on refluxing in acetic anhydride affords the indolo[2,3-*b*][1]-benzopyran system.[5]

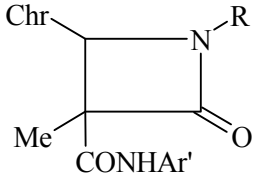
Chr—X

1 X = CHO
2 X = CN
3 X = CH=NAr
4 X = CH=NNMe$_2$
5 X = CON$_3$

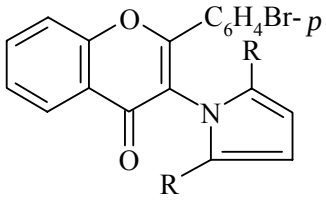


46%

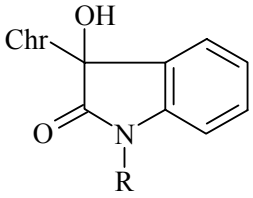
6



7 R = Ar
8 R = NMe$_2$

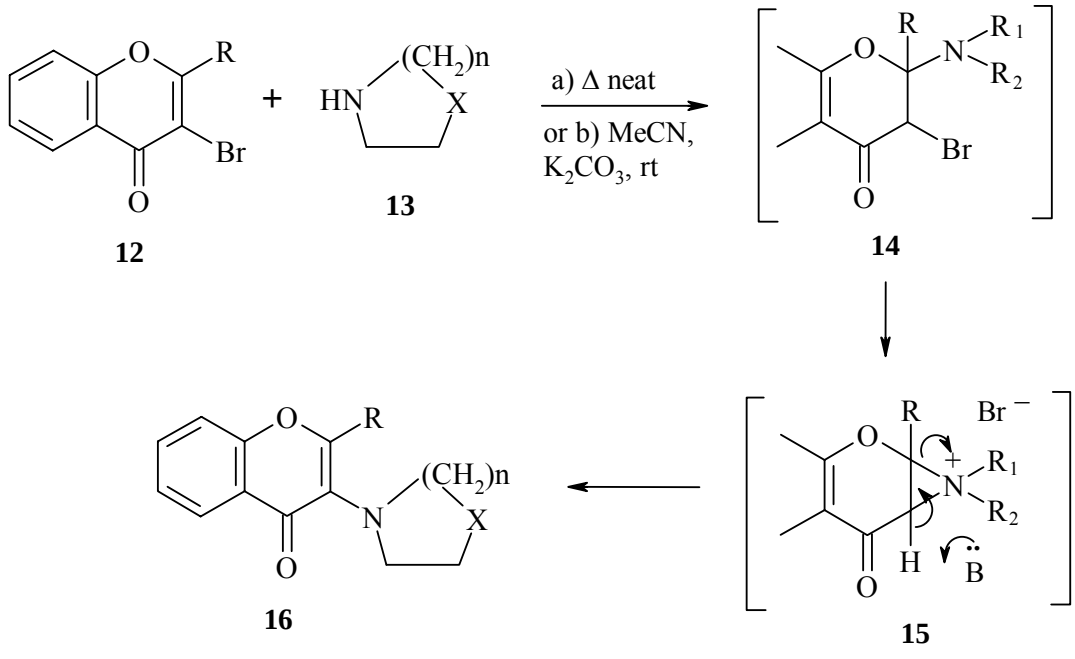


9 R = H, 28%
10 R = Me, 28%



11 R = H, 78%
R = Me, 85%
R = $PhCH_2$, 83%

3-Chlorochromone or 3-bromochromone (**12**) (R = H, Me) when either heated neat or treated in MeCN containing K_2CO_3 at room temperature with pyrrolidine (**13**) (n = 1, X = CH_2) gives 3-(1-pyrrolidinyl)-chromone (**16**).[6,7] Here the secondary amine undergoes 1,4-addition to the α,β-unsaturated ketone functionality of **12**, the resultant adduct (**14**) by an intramolecular S_N2 reaction forms the aziridinium intermediate (**15**), the latter in the presence of a base collapsing to **16** (Scheme 1). The pyrrolidinylchromone (**16**) (R = H, Me; n = 1, X = CH_2) is also obtained by heating the appropriate 3,3-dibromochromanone in MeCN with pyrrolidine in the presence of K_2CO_3, the reaction involving nucleophilic substitution of one bromine of dibromochromanone by the secondary amine and subsequent dehydrobromination of the resultant 3-bromo-3-(1-pyrrolidinyl)chromanone.[8] The heterocycles represented by the general structure (**16**) and synthesised from the appropriate 3-chloro(or bromo)-chromone and cyclic amine[6,7] are listed in Table 1. The compounds (**16**) when prepared from 3,3-dibromochromanone and the cyclic secondary amine[8] are obtained in 85% yield.



12 **13** **14** **15** **16**

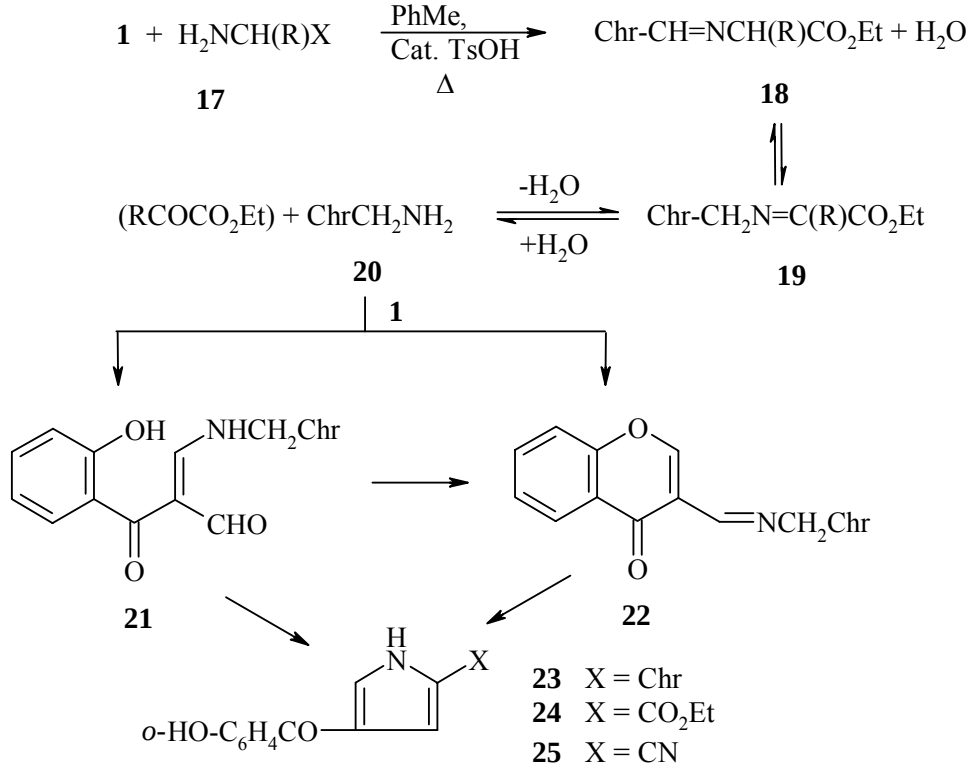
Scheme 1

Table 1. 3-(1-pyrrolidinyl-, 1-piperidinyl-, 1-morpholinyl- and 1-piperazinyl-) chromone (**16**)

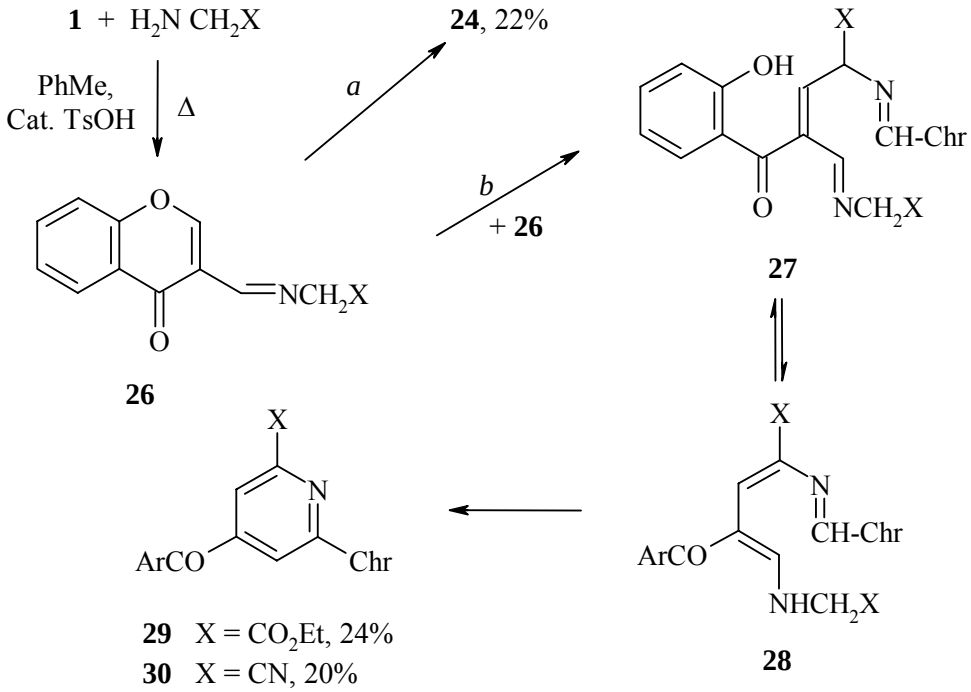
Entry	R	n	X	Method	Yield (%)	Ref.
1	H	1	CH_2	b	43	7
2	Me	1	CH_2	a	86	6
3	H	2	CH_2	a	~ 80	6
4	H	2	CH_2	b	70	7
5	Me	2	CH_2	a	~ 80	6
6	H	2	O	a	~ 80	6
7	Me	2	O	a	72	6
8	H	2	NMe_2	a	~ 80	6
9	Me	2	NMe_2	a	45	6

Nitrogen heterocycles result from the reaction of 3-formylchromone (**1**) with various bifunctional nucleophiles of the type (**17**) (R = H, Me, Ph; X = CO_2Et, CN).[9,10] The pyrrole (**23**) is obtained in 39-44% yield by heating 3-formylchromone (**1**) with ethyl 2-amino-2-phenylethanoate (**17**, R = Ph, X = CO_2Et) as well as ethyl 2-aminopropanoate (**17**, R = Me, X = CO_2Et) under reflux in toluene containing catalytic amount of *p*-toluenesulfonic acid. It is presumed to arise *via* initial condensation between the aldehyde (**1**) and amine (**17**) (X = CO_2Et) to **18** followed by hydrolysis of the tautomeric azomethine (**19**) to 3-aminomethylchromone (**20**). Interaction of **20** with a second molecule of 3-formylchromone (**1**) gives **21** that cyclises to the pyrrole (**23**). The alternative cyclisation of the azomethine (**22**) to 23 would represent a disfavoured process (Scheme 2).

Interaction of 3-formylchromone (**1**) with ethyl 2-aminoethanoate (**17**, R = H, X = CO_2Et) gives a mixture of the aroylpyrrole (**24**) and the chromone linked pyridine (**29**).[9,10] The former arises through intramoelcular Michael addition of the initially formed condensate (**26**) followed by pyran ring opening and prototopy (Scheme 3 – path *a*). Michael addition of a second molecule of **26** to the α,β-unsaturated carbonyl functionality of **26** with concomitant opening of the pyran ring gives **27** which through tautomerism (→**28**), electrocyclisation and elimination of H_2NCH_2X produces **29** (Scheme 3 – path *b*). 2-Aminoethanonitrile (**17**, R = H, X = CN) with 3-formylchromone (**1**) produces the pyridine (**30**) in complete exclusion of the pyrrole (**25**).[10]



Scheme 2

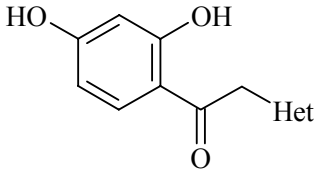


For **28-30** : Ar=C_6H_4OH-*2*

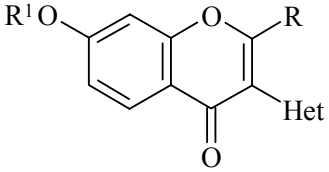
Scheme 3

2,4-Dihydroxy-ω-(2-pyridyl)acetophenone (**31**) (Het = 2-pyridyl), obtained by Houben-Hoesch reaction between resorcinol and pyridine-2-acetonitrile, undergoes ring closure to give in ~ 80% yield the chromone (**32**) (R = R^1 = H) by ethyl orthoformate or formic-acetic anhydride and to **32** (R = Me, R^1 = Ac) by acetic anhydride in refluxing pyridine containing catalytic amount of piperidine.[11,12] 3-Bromoflavone (**12**) [R = $C_6H_4S(=O)_2Me$-*p*], prepared from 2-hydroxy-4'-methylmercaptylchalcone by sequential treatment with iodine, NBS and oxone, gives the corresponding 3-(3-pyridyl)flavone (42%) on $Pd(PPh_3)_4$ catalysed Suzuki coupling with lithiated trimethyl pyridine-3-boronate in boiling PhMe - EtOH containing Na_2CO_3.[13] The dihydroxyacetophenone (**31**) (Het = 2-quinolyl), derived from resorcinol and quinolin-2-acetonitrile, cyclises with refluxing $HC(OEt)_3$ or Ac_2O to give **32** (R = R^1 = H or R = Me, R^1 = Ac) in 80-86% yield.[14]

A cursory report on the formation of the 1,4-dihydropyridine (**34**) by reacting 3-formylchromone (**1**) with two molar proportion of β-aminocrotonic acid derivatives (**33**) in AcOH had been made.[15] Later on, the same reaction of **1** with **33** (E = CO_2Me, CO_2Et) in acetic acid at 60ºC is reported to give a mixture of the dihydropyridines (**34**) and (**35**), both of which can be dehydrogenated by manganese dioxide.[16] 3-Formyl-chromone on condensation with methyl acetoacetate and liquor ammonia in boiling methanol is reported[17] to give (**34**, E = CO_2Me), though the present author gets only the benzopyranopyridine (**36**) in complete exclusion of **34** from the above reaction.[18] The dihydropyridine (**34**) (E = CO_2Et) is, however, obtained by heating on water bath a mixture of **33** (E = CO_2Et) and **37** (R = OEt) dissolved in DMF and it is smoothly dehydrogenated by palladised charcoal.[19] The piperidinylchromone (**16**) (R = H, n = 2, X = CH_2) (Table 1 – entries 3 and 4), obtainable by heating 3-bromochromone[6,7,20,21] as well as 3,3-dibromochromanone[8] with piperidine, on treatment with oxalic acid gives chromone.[21] 1-(2-Hydroxy-phenacyl)pyridinium bromide on refluxing in Ac_2O forms 1-(2-methyl-4-oxo-4*H*-1-benzopyran-3-yl)-pyridinium bromide (60%).[22]



31



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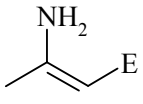

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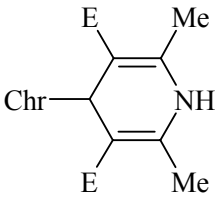
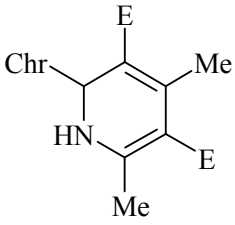
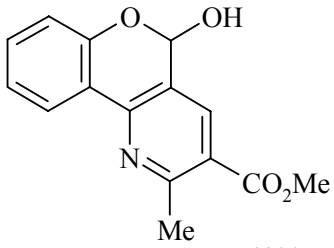


34 E = CO_2Me, 70%
E = CO_2Et, 51%



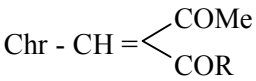
35 E = CO_2Me, 19%
E = CO_2Et, 23%



43%

36

Substituent E	Yield (%) of **34**	**35**
CO_2Me	70	19
CO_2Et	51	23



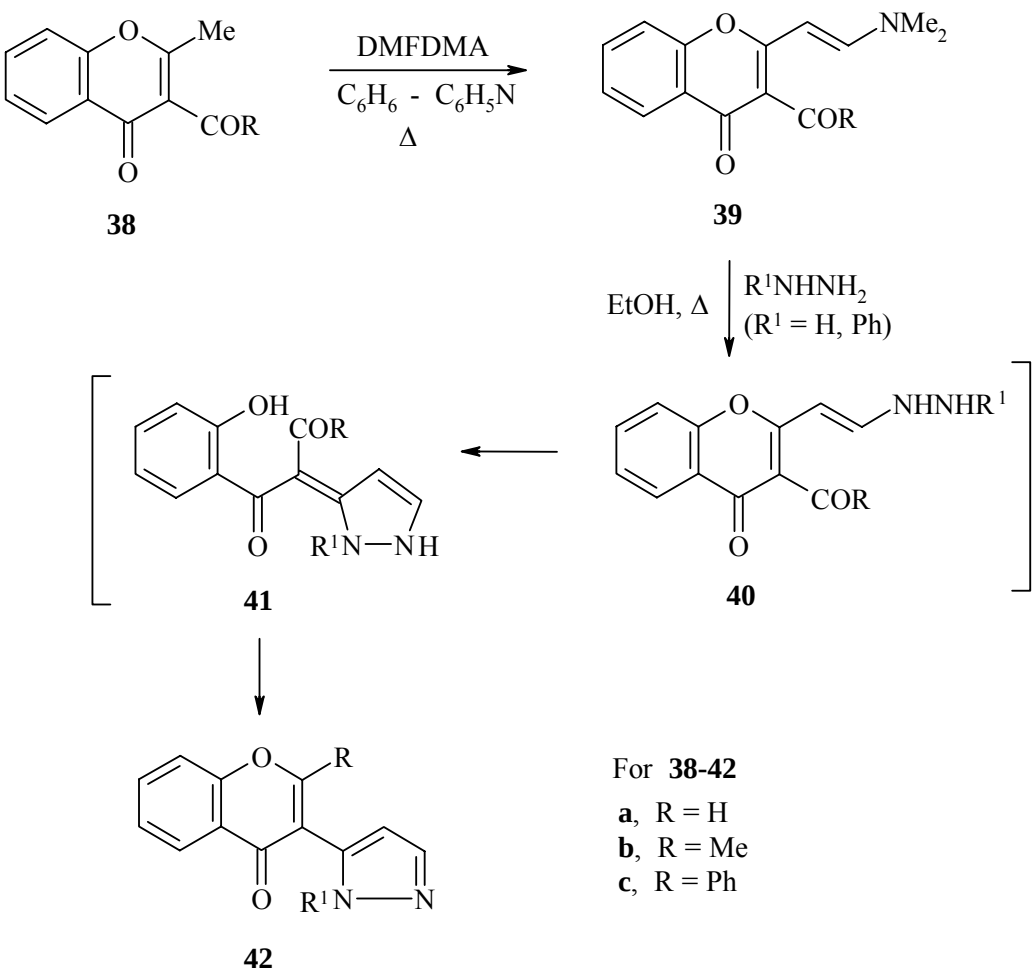
37

II.2. Heterocycles containing two N Atoms

II.2.1. Pyrazoles

3-Acyl-2-methylchromone (**38**) on warming with dimethylformamide dimethyl acetal (DMFDMA) in benzene-pyridine gives the enamine (**39**) in 53-66% yield. Hydrazine well as phenylhydrazine in refluxing ethanol undergoes 1,6-addition to the α,β,γ,δ-unsaturated carbonyl functionality of **39** with expulsion of dimethylamine, the resultant intermediate (**40**) by an intramolecular 1,4-addition followed by pyran ring opening (→ **41**) and recyclisation gives the pyrazole (**42**) (Scheme 4). Hydrazine gives an intractable tar with **39a** whereas the other two members (**39b** and **39c**) give the corresponding pyrazoles (**42**) (R^1 = H). All the members of the enamine (**39**) give with phenylhydrazine the corresponding 1-phenylpyrazoles (**42**) (R^1 = Ph).[23] 3-(β-Dimethylaminoacryloyl)chromone, derived from 3-acetyl-chromone and DMFDMA in boiling benzene, reacts with phenylhydrazine under reflux in ethanol giving a mixture of pyrazole (**42**) (R = H, R^1 = Ph) and 1-phenylamino-3-salicyloylpyridin-4(1*H*)-one.[24] The enamine (**39**) (CN in place of COR), derived likewise from 3-cyano-2-methylchromone and DMFDMA, gives under similar conditions the pyrazole (**42**) (R = NH_2) with H_2NNHR^1 (R^1 = H, Ph) by a mechanism similar to that depicted in Scheme 4.[25] The prepared pyrazoles (**42**) are tabulated in Table 2.

Various 3-(4-pyrazolyl)chromones have been synthesised by treating some simple condensates of the aldehyde (**1**) with diazoalkanes.[26-28] All these syntheses are performed by treating the olefinic substrates dissolved in CH_2Cl_2 with an ethereal solution of excess diazoalkane at 5ºC for 10-24 hr. Thus, **37** (R = Me, Ph) with CH_2N_2 affords a mixture of the pyrazole (**44**) and dihydrofuran (**45**). Here diazomethane undergoes 1,3-dipolar cycloaddition to the exocyclic olefinic bond of **37**; the resultant 1-pyrazoline intermediate (**43**) (non-isolable) undergoes (i) base catalysed deacetylation to **44**, diazomethane or **43** itself functioning as the base (Scheme 5 – path *a*) and (ii) a formal 1,5-sigmatropic shift of the carbonyl group accompanied by nitrogen extrusion to form **45** (path *b*). The 1-pyrazoline (**43**) derived from **37**

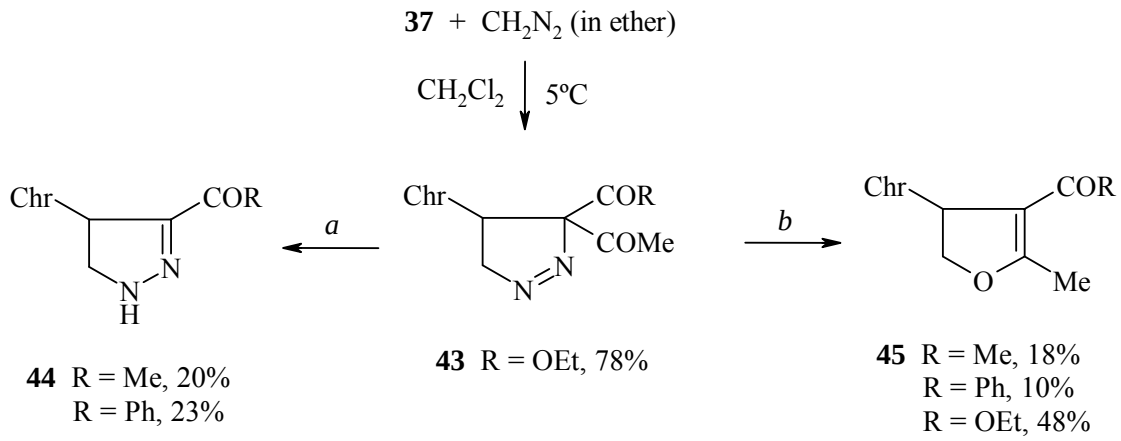


Scheme 4

Table 2. 5-(4-Oxo-4*H*-1-benzopyran-3-yl)pyrazoles (**42**)

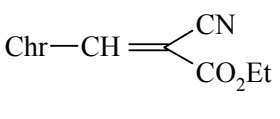
Substituents		Yield (%)	Ref.
R	R^1		
H	H	—	23
Me	H	62	23
Ph	H	69	23
H	Ph	35	23
H	Ph	14	24
Me	Ph	79	23
Ph	Ph	82	23
NH_2	H	62	25
NH_2	Ph	66	25

(R = OEt) and diazomethane is isolable and this on heating at its melting point affords **45** (R = OEt) (path *b*) in complete exclusion of **44** (R = OEt) and any *C*-methylated product of **37** (R = OEt).[27]



Scheme 5

The chromone derivative (**46**) on treatment with diazomethane gives a little amount of the pyrazoline (**47**)[27] (*vide infra*). The condensate (**37**) (R = Me) on treatment with phenyldiazomethane gives the pyrazole (**48**) along with other products[28] (*vide* section III). The nitrilimine (**49**) undergoes cycloaddition with CH_2=CHR (R = CH_2Br, COMe, CN, CO_2Me, Ph) in dry benzene at room temperature giving the pyrazoline (**50**).[29] Similar cycloaddition of DMAD with **49** also gives a pyrazole derivative.[29] Cyclisation of ω-hetarylresacetophenone (**31**) (Het = 1-phenylpyrazol-4-yl), obtained by reacting resorcinol with 1-phenylpyrazol-4-acetonitrile in the presence of hydrogen chloride, by acetylation in xylene at 130ºC gives the pyrazole (**32**) (R = Me, R^1 = Ac).[30] The chalcone derived from 3-acetyl-2-methylchromone **38** (R = Me) and an aromatic aldehyde reacts with hydrazine or phenylhydrazine under reflux in EtOH giving in nearly 50% yield 2-methyl-3-(1-unsubstituted or 1-phenyl-5-aryl-4,5-dihydropyrazol-3-yl)chromone.[31]



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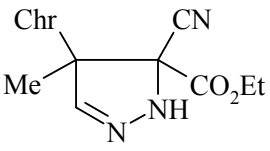
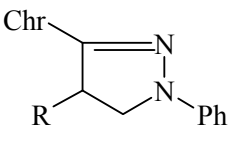


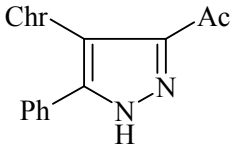
25%

47



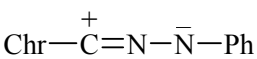
50

R	Yield (%)
CH_2Br	55
Ac	60
CN	61
CO_2Me	65
Ph	50



5%

48



49

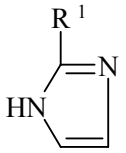
II.2.2. Imidazoles

ω-Bromo-2-hydroxyacetophenone on heating with the imidazole (**51**) (R^1 = H, Me) in DMF at 60ºC gives the phenacylimidazole (**52**) which reacts with a boiling ethanolic solution of an aldehyde R^2CHO (R^2 = H, Me, Ph) giving the chromanone linked imidazole (**53**).[32] The compound (**52**) (R^1 = H) gives **54** (R^1 = R^2 = H) with triethyl orthoformate, **54** (R^1 = H, R^2 = Me or Ph) with acetic or benzoic anhydride[32] under refluxing condition of the reagent used in excess. ArCOCl [Ar = C_6H_4Cl-*2* or *3*, $C_6H_4NO_2$-*3*, C_6H_4OMe-*3*, $C_6H_3(OMe)_2$-*3,5*, $C_6H_2(OMe)_3$-*3,4,5*] reacts with **52** (R^1 = H) ($ClCH_2CH_2Cl$, montmorillonite-KSF, Et_3N, rt) giving **54** (R^1 = H, R^2 = Ar) in 42-86% yield.[33] 2-Methyl(or 1,2-dimethyl)imidzole reacts with 2-acetoxy(or benzoxy)benzoyl chloride in MeCN-NEt_3 at room temperature to give the imidazole (**55**) (X = NH or NMe, R^1 = Me or Ph, R^2 = H) in 20-30% yield.[34] The benzimidazole (**56**) (X = NH, NMe; R^1 = H, Me, CF_3; R^2 = OH, OAc, O_2CF_3) is obtained in 60-99% yield by cyclisation of the hetarylacetophenone (**31**) (Het = 1-unsubstituted or 1-methylbenzimidazol-2-yl) respectively with $HC(OEt)_3$, Ac_2O, $(F_3CCO)_2O$ in pyridine at 2-3ºC.[35]

3-Formylchromone (**1**) on condensation with *o*-phenylenediamine (**58**) (X = NH) in refluxing benzene gives the dihydrotetraaza[14]annulene (**59**),[36] not the previously suggested 6,11-dihydro[1]benzopyrano-[2,3-*b*][1,5]benzodiazepin-13(5a*H*)-one.[37-39] The compound (**59**) on oxidation with chloranil (xylene, Δ)[37] or refluxing nitrobenzene[39] or on digestion in acetic acid[36,38] gives in nearly 85% yield the benzimidazole (**56**) (X = NH, R^1 = R^2 = H). It is cursorily reported that **1** when heated with **58** (X = NH, NPh) in the solvent medium RH (R = OMe, OEt, OCH_2Ph, SPh, SCH_2Ph, NHPh etc.) forms **60** which on treatment with chloranil in rfluxing xylene gives **56** (X = NH, NPh; R^1 = R^2 = H).[36] The compound resulting from the treatment of acetal corresponding to the aldehyde (**1**) with *o*-phenylenediamine in benzene and subsequent digestion in acetic acid[40] should also be assigned the structure (**56**) (X = NH, R^1 = R^2 = H). The benzimidazole of the type (**56**) (X = NPh, R^1 = NMe_2) is obtained by reacting 2-dimethylamino-3-formylchromone with **58** (X = NPh) in acetic acid.[41] A mixture of 3-formylchromone (**1**), benzil and ammonium acetate in refluxing acetic acid affords the trisubstituted imidazole (**57**) (X = NH, R^1 = R^2 = H) (63%).[42]

II.2.3. Pyrimidines

The enamine (**39**) (R = H, Me, Ph) on reacting with guanidine carbonate in refluxing ethanol produces the corresponding 2-amino-4-(4-oxo-4*H*-1-benzopyran-3-yl)pyrimidine (**61**).[23] NH_4OAc as well as 2-amino-3-formylchromone (**63**) (X = O) on refluxing with 3-cyanochromone (**2**) in acetic acid affords the chromone linked pyrimidine (**65**).[43] The same pyrimidine (**65**) is also obtained by treating the aldehyde (**63**) (X = O) with *p*-toluenesulfonic acid in refluxing toluene[44] as well as by heating a solution of



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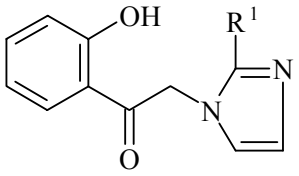

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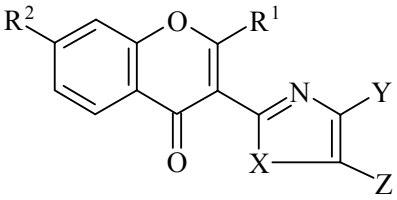
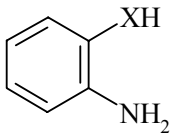


55 Y = Z = H
56 YZ = CH=CH-CH=CH
57 Y = Z = Ph



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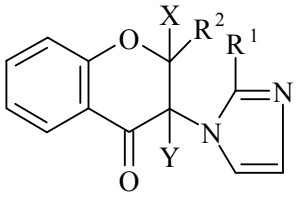
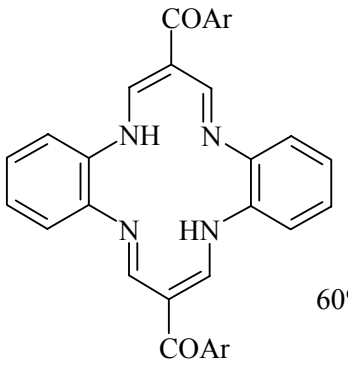


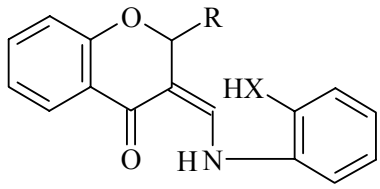
53 X = Y = H
54 XY = bond

Substituents		Yield (%)	
R	R^1	**53**	**54**
H	H	55	87
Me	H	70	—
H	Me	82	83
H	Ph	75	77
Me	Ph	—	29



59 Ar = C_6H_4OH-*o*

60%



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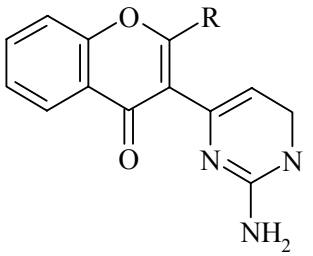
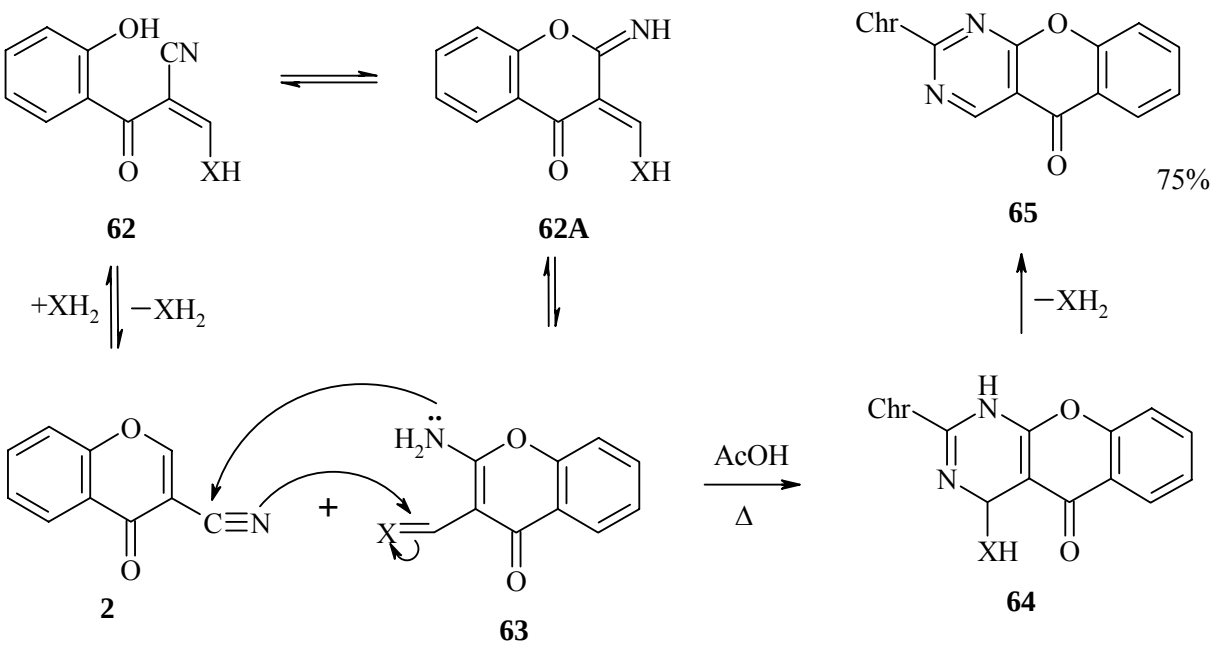


61 R = H, 42%
R = Me, 46%
R = Ph, 69%

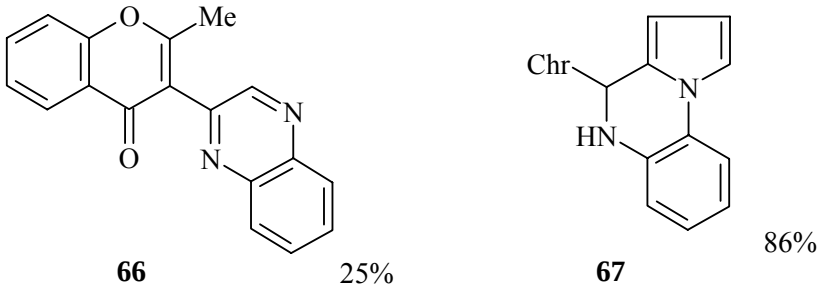
2-amino-3-iminomethylchromone (**63**) (X = NC_6H_4 Me-*p*) in DMF.[45] The pyrimidine (**65**) is formed *via* the intermediate (**64**) resulting from the condensatin of the nitrile (**2**) with 2-amino-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (**63**) (X = O) or its derivative (**63**, X = NC_6H_4 Me-*p*), both the reactants being interconvertible under the reaction conditions (Scheme 6). IR spectrum in KBr pellet of the compound (**63**) (X = NC_6H_4Me-*p*), assumed to arise from **2** and *p*-toluidine, shows the presence of NH, OH and CN groups compatible with the tautomeric structure (**62**) whereas ^{1}H-NMR spectrum indicates the compound to exist solely in its imino-enamine tautomeric form (**62A**) in its chloroform solution.[45] These findings support interconvertibility under suitable reaction conditions of **2** and **63** as envisaged in Scheme 6.



Scheme 6

II.2.4. Pyrazines

3-Bromo-2-methylchromone (**12**) (R = Me) with 1-methyl-1,4-diazacyclohexane (**13**) (n = 2, X = NMe) gives the piperizine (**16**) (Scheme 1, Table 1 – entry 9).[6] Condensation of 3-bromoacetyl-2-methylchromone (**38**) (R = CH_2Br) with *o*-phenylenediamine (**58**) (X = NH) in refluxing EtOH containing AcONa is followed by air oxidation to afford the quinoxaline (**66**).[46] Acetic acid catlysed condensation of 3-formylchromone with 1-(2-aminophenyl)pyrrole leads to the pyrrolo[1,2-*a*]quinoxaline (**67**).[47]

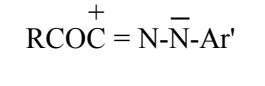


66 25% **67**

II.3. Heterocycles containing three or more N atoms

The nitrilimine (**68**) (R = Me, OEt; Ar' = C_6H_4Me-*p*, C_6H_4Br-*p*), prepared *in situ* from the corresponding hydrazonoyl bromide in $CHCl_3$ by treatment with NEt_3 at 0-5ºC, undergoes both [4+3] and [3+2] cycloaddition to the Schiff base (**3**), the latter process giving the 1,2,4-triazoline (**69**).[48] Ac_2O converts the acetophenone (**31**) (Het = 4-phenyl-1,2,4-triazol-3-yl) to the triazole (**32**) (R = Me, R^1 = Ac).[49] 3-(1-Tetrazolyl)chromone (**70**) (R = Me, Ph) is obtained by reacting the appropriately 2-substituted 3-aminochromone with sodium azide and ethyl orthoformate in AcOH.[50] 3-Cyanochromone (**2**) on

treatment with NaN_3 in THF containing anhydrous $AlCl_3$ gives the tetrazole (**71**) (R = H) which on treatment with dialkylamide $R^1CONR_2^2$ (R^1 = H, R^2 = Me, Et; $R^1 = R^2$ = Me) and $POCl_3$ in DMF at room temperature gives Chr-CONHN=C(R^1)NR_2^2 in ~ 80% yield, the latter being converted by $NaNO_2$ in AcOH at room temperature to the acid azide (**5**).[51,52] The tetrazole (**71**) (R = H) on treatment with NaOH undergoes pyran ring opening and subsequent deformylation to give 5-(2-hydroxyphenacyl)tetrazole which on acetylation (Ac_2O, Δ) forms the tetrazole (**71**) (R = Me).[52] The tetrazole (**71**) (R = H) reacts with *t*-butanol in CF_3CO_2H in the presence of 95% H_2SO_4 to give the alkylated tetrazole (**72**).[52]



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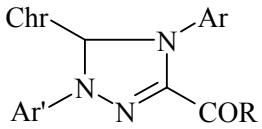
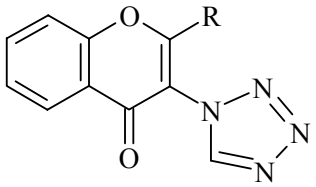
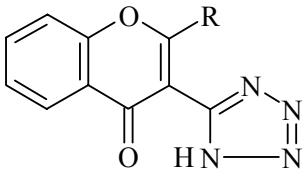


69

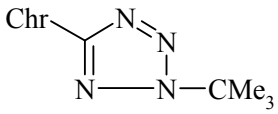
R	Ar	Ar'	Yield (%)
Me	C_6H_4OMe-*p*	C_6H_4Me-*p*	45
Me	C_6H_4OMe-*p*	C_6H_4Br-*p*	45
Me	C_6H_4OEt-*p*	C_6H_4OMe-*p*	40
OEt	C_6H_4OMe-*p*	C_6H_4Br-*p*	40
OEt	C_6H_4OMe-*p*	C_6H_4Me-*p*	45
OEt	C_6H_4OEt-*p*	C_6H_4Br-*p*	45



70 R = Me, 64%
R = Ph, 54%



71 R = H, 80%
R = Me, 64%



77%

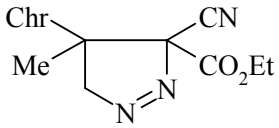
72

III. OXYGEN HETEROCYCLES

III.1. Heterocycles containing one O atom

Formation of chromonyldihydrofuran (**45**) by treating **37** (R = Me, Ph, OEt) with diazomethane has been mentioned in section II.2.1. Diazomethane brings about *C*-methylation of the cyano ester (**46**), the resultant β-methylacrylic ester reacts further with diazomethane furnishing *via* the 1-pyrazoline (**73**) (non-isolable), the 2-pyrazoline (**47**), the dihydrofuran (**74**) and a stereoisomeric mixture of the cyclopropane (**75**). The dihydrofuran (**74**) on heating in an oil bath at 180ºC for 30 min. isomerises to cyclopropane (**75**) through a reversed alkoxycarbonylcyclpropane → 5-alkoxy-2,3-dihydrofuran rearrangement.[27] The cyclopropane (**76**), derived from **37** (R = Me) and phenyldiazomethane, thermally (~200ºC) rearranges to the *trans*-dihydrofuran (**77**).[28] The compound (**31**) (Het = 2-benzofuryl, 5-ethoxy-2-furyl), derived from resorcinol and the apropriate hetarylacetonitrile, on acetylation (Ac_2O, Δ) gives the furylchromone **32** (R = Me, R^1 = Ac).[30] The chalcone, prepared from 2-benzyloxyacetophenone and

benzofuran-2-aldehyde, on expoxidation and subsequent treatment with $BF_3.Et_2O$ affords 3-(2-benzofuryl)chromone (~ 50%).[53,54]



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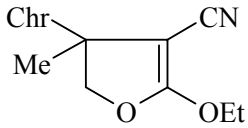

24%

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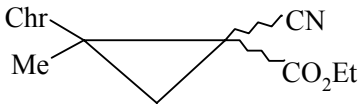

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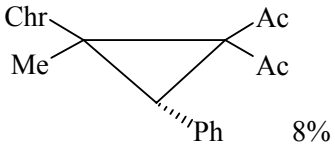

8%

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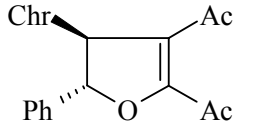
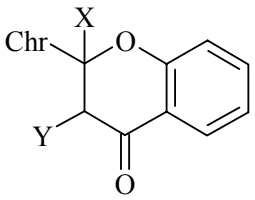


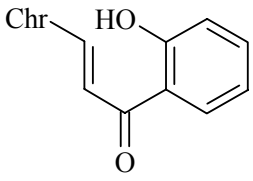
80%

77

EtONa in refluxing EtOH brings about self-condensatin of chromone to chromanylchromone (**78**) (44%).[55] 3-Formylchromone when refluxed in ethanol containing triethylamine[56] or stirred with neutral Brockman alumina in dichloromethane at room temperature[57] forms **78** respectively in 10 and 6% yields along with other products. In the preparation of 3-formylchromone by Vilsmeier-Haack reactin of *o*-hydroxyacetophenone, a small amount of the chromone derivative (**80**) is obtained as a byproduct which on heating with 83% H_3PO_4 gives **78** (20%).[58] 2-Hydroxychromanone when heated over its melting point transforms into **80** (51%) which on selenium dioxide oxidation in refluxing isoamyl alcohol gives the 3,2'-bichromone **79** (20%).[59] The enamine (**81**), prepared by refluxing a benzene solution of 2-hydroxyacetophenone and DMFDMA, on treatment with $POCl_3$ in dioxan at room temprature gives chromone (20%) and chlorochromene (**82**) (5%), the latter on oxidation with PDC in pyridine at room temperature gives the bichromone (**79**) (16%).[60] The enamine (**81**) on anodic oxidation in tetraethylammonium perchlorate – acetonitrile by controlled potential electrolysis gives 3,3'-bichromone (**83**) (R = R^1 – R^4 = H).[61] Ullmann coupling of 3-bromo(or iodo)flavone catalysed by finely divided copper at 200-210ºC[62,63] or in the refluxing DMF medium[63] leads to 3,3'-biflavone **83** (R = C_6H_4X-*p*, X = NH_2, NO_2, Cl, OMe). Silylation of flavanones with Me_3SiNMe_2 in the presence of TsOH followed by treatment with Ag_2O also affords **83**.[64] The biflavone (**83**) (R = Ph, C_6H_4OMe-*p*; R^1 = R^3 = OMe; R^2 = R^4 = H) has been prepared via Baker-Venkatraman rearrangement (NaH, PhMe, Δ) of the diester **84** prepared from pholoroglucinol.[65] Condensatin of 3-formylchromone with dimidone in pyridine at room temperature gives the oxygen heterocycle (**85**).[66-68] 3-Formylchromone when heated at 80-100ºC with *p*-cresol in the presence of anhydrous $AlCl_3$ gives the 9*H*-xanthene derivative (**86**).[69] 3-Acylchromone (**87**) (R = H, Me, Ph) condenses with barbituric acid in boiling AcOH-Ac_2O to give the heterocycle (**88**) (~ 60%).[66]



78 X = Y = H
79 XY = bond



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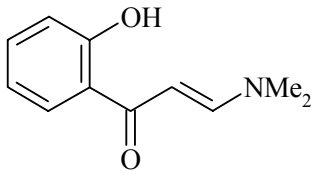

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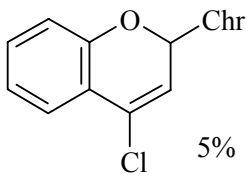

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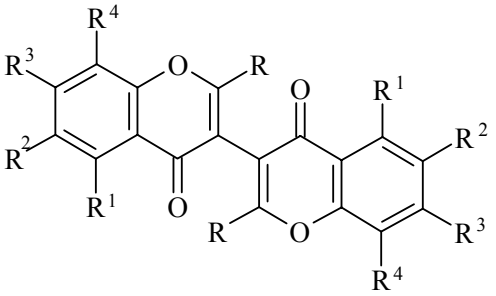
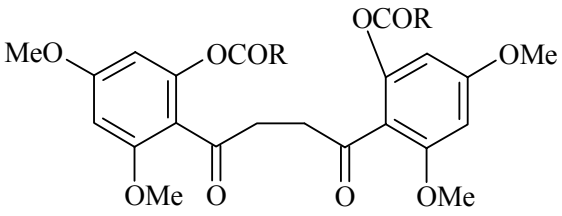


83

R	R^1	R^2	R^3	R^4	Yield (%)
$C_6H_4NH_2$-*4*	H	Cl	H	H	75
$C_6H_4NO_2$-*4*	H	Cl	H	H	80
C_6H_4Cl-*4*	H	Cl	H	NO_2	73
C_6H_4OMe-*4*	H	H	MeO	H	86
Ph	MeO	H	MeO	H	90
C_6H_4OMe-*4*	MeO	H	MeO	H	89
Ph	H	H	H	H	80



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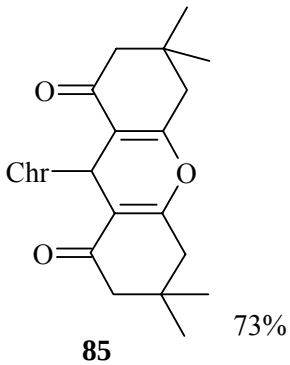

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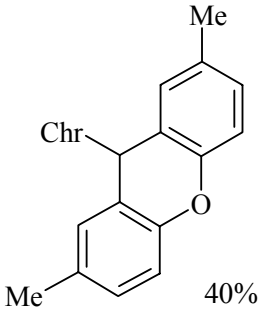

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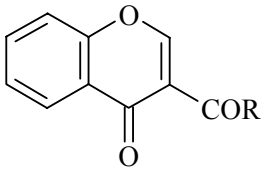

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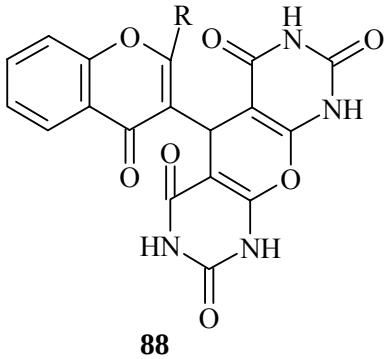
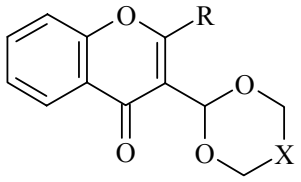


88

III.2. Heterocycles containing two O atoms

The aldehyde (**1**) with the diol $HOCH_2$-X-CH_2OH (X = bond, CH_2, CMe_2) under azeotropic conditions in refluxing C_6H_6 containing TsOH gives the acetal (**89**) (R = H) (~ 90%)[40,70] whereas 3-acetyl(or benzoyl)-chromone gives a variable mixture of the acetal (**89**) and ketal (**90**) (R = Me or Ph).[70] Silica gel[71] as well as clay[72] mediated acetalisation of **1** also produces **89** (R = H, X = bond) in 71-91% yield. The acetal (**89**) (R = H, X = bond) gives with nitrogen nucleophiles the same products as are obtained from the corresponding aldehyde (**1**).[40] The acetal (**89**) (R = H, X = bond) gives with diazomethane the 1-pyrazoline (**91**) that survives crystallisation from ethyl acetate but yields on heating at 160-170ºC the

acetal **89** (R = Me, X = bond) (70%) admixed with a little quantity (8%) of 5-salicyloylpyrazole; the latter compound can be had in a better yield (13%) by percolating a solution of **91** in ethyl acetate through a column of neutral Brockman alumina.[73] The acetal (**89**) (R = H) can be lithiated at pyran 2-position by LTMP in THF at –78ºC and this lithiated compound (**89**) (R = Li) is capable of capturing an electrophile like $ClCO_2Et$, $ClSiMe_3$, MeCHO, PhCOCN giving (**89**) [R = CO_2Et, $SiMe_3$, MeCH(OH), PhCO]; LDA gives poor yields of these 2-substituted chromones and some intractable products. In every case, **89** (R as above, X = CH_2) is accompanied by the dimer (**92**) arising due to incomplete metalation of **89** (R = H, X = CH_2) and subsequent interaction of the metalated compound with the unmetalated one.[70]



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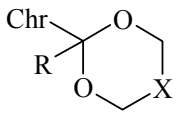

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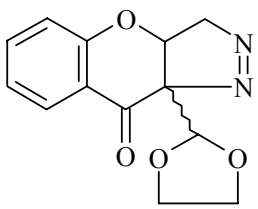
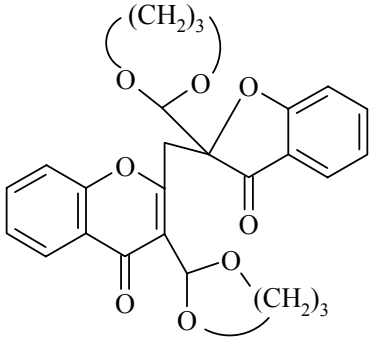


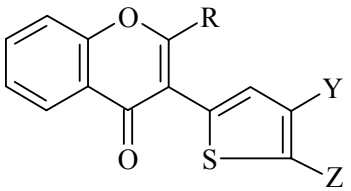
91 80%



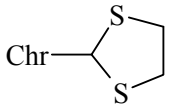
92 40%

IV. SULPHUR HETEROCYCLES

$Pd(PPh_3)_4$ catalysed Suzuki coupling in boiling PhMe-EtOH containing Na_2CO_3 of 3-iodochromone with 2-thienylboronic acid gives the thiophene **93**[74] and that of the bromoflavone **12** (R = $C_6H_4SO_2Me$-*p*) with benzthiophene-2-boronic acid gives **94**.[13] *p*-Toluenesulphonic acid catalysed condensation of **1** with ethane-1,2-dithiol in refluxing C_6H_6 forms the dithiolane **95**.[40]



93 R = Y = Z = H, 70%
94 R = $C_6H_4SO_2Me$-*p*, YZ = CH=CH-CH=CH, 56%

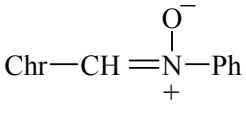


82%
95

V. HETEROCYCLES CONTAINING N AND O ATOMS

[3+2] Cycloaddition of *C*-(4-oxo-4*H*-1-benzopyran-3-yl)-*N*-phenylnitrone (**96**) with styrene as well as acrylonitrile in refluxing benzene[48] and microwave induced cycloaddition between the nitrone **96** with the olefin (**97**) (R^1 = H, Me; R^2 = CO_2Me, CH_2Br, CN) in the absence of any solvent are reported[75] to form the isoxazolidine derivative, the stereochemistry of the adduct not being delineated. Ishar *et al.*[76] have investigated the complete peri-, regio- and stereo-selectivities of the cycloaddition reactions of **96** with

electron rich as well as electron deficient olefins. The nitrone (**96**) existing only in the *Z*-isomeric form undergoes frontier-orbital (LUMO-dipole HOMO-dipolarophile) controlled *exo*-selective 1,3-dipolar cycloaddition; significant amounts of *endo*-adducts are obtained only in the cases of dipolarophiles bearing polar substituents. Thus, **96** with the olefin (**97**) (R^1 = H; R^2 = OEt, O-*i*Bu, CN, Ph, CO_2Et, COMe, $CONH_2$) in dry CH_2Cl_2 at room temperature gives the isoxazolidines (**98**) (*exo*-adduct) and (**99**) (*endo*-adduct) together with small amounts of 3-formyl-2-phenylaminochromone and the benzopyrandione (**101**) (Table 3), the latter two compounds resulting from the initial electrocyclisation of **96**. The compound (**100**) results from heating **96** with methyl methacrylate (**97**) (R^1 = Me, R^2 = CO_2Me) in benzene in a sealed tube. Under the same conditions **96** gives a mixture of **102-104** with ethyl crotonate, and **105** and **106** with dihydrofuran.[76]



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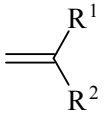

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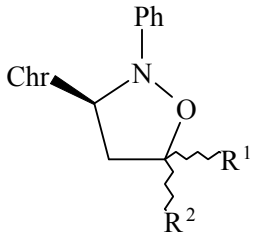
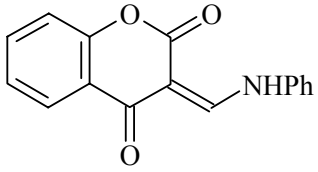


98 β - R^2
99 α - R^2
100 R^1 = β-Me, R^2 = α-CO_2Me, 60%



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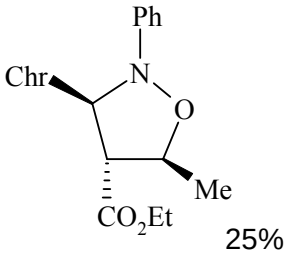
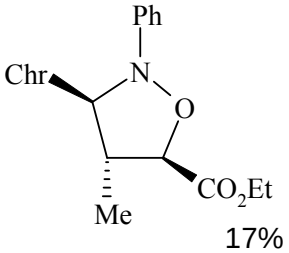


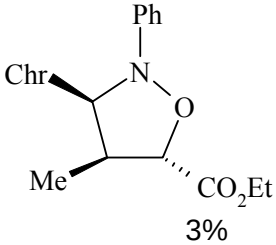
25%

102



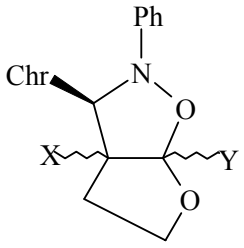
17%

103



3%

104



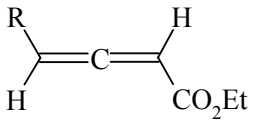
105 X = Y = β-H, 21%
106 X = Y = α-H, 4%

Regiospecific [3+2] cycloadditin in boiling C_6H_6 of the nitrone (**96**) to the 2,3-π bond of the allenic ester (**107**) (R = H, Me, Et) forms the cycloadduct (**108**) (non-isolable) which undergoes a series of tandem intramolecular transformations to afford the benzo[*b*]indolizine (**109**) together with a small quantity of the indole (**110**).[77] Morpholine (**13**) (n = 2, X = 0) with the chromone (**12**) (R = Me) gives the chromone linked morpholine (**16**) (Table 1 – entry 7).[6] Condensation of 3,3-dibromochromanone with morpholine also gives **16** (R = H, n = 2, X = O).[8] The anil (**3**) reacts with benzonitrile oxide (generated from benzhydroxamoyl chloride in $CHCl_3$ by treatment with NEt_3 at room temperature) giving the chromone linked 1,2,4-oxadiazoline (**111**).[29] The tetrazole (**71**) (R = H) on refluxing in Ac_2O produces the 1,3,4-oxadiazole (**112**).[52] Here Ac_2O acylates the 2- or 3-position of the tetrazole moiety of **71**; the resultant

Table 3. Yields of various products from reactions of nitrone (**96**) with monosubstituted olefins (**97**) (R_1 = H)

R_2 in **97**	Yield (%)			
	98	**99**	**101**	2-phenylamino-3-formylchrome
OEt	80	—	3	15
O*i*Bu	78	3	2	15
CN	47	40	trace	6
Ph	80	trace	2	15
CO_2Me	65	25	—	4
COMe	45	35	6	10
$CONH_2$	50	—	30	15

actyl derivative by a 1,5-sigmatropic shift of the acetyl carbonyl group accompanied by nitrogen extrusion forms **112**. 3-Formylchromone (**1**) reacts with $ArCONHNH_2$ (Ar = phenyl, 2- and 4-nitrophenyl, 2-phenyl-1,2,3-triazol-5-yl and 5-methyl-1-phenyl-1,2,3-triazol-4-yl) to give the corresponding hydrazone which on treatment with Ac_2O under heating or microwave irradiation gives 4,5-dihydro-1,3,4-oxadiazole derivative (**113**) in 60-70% yield.[78]



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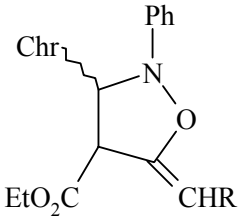

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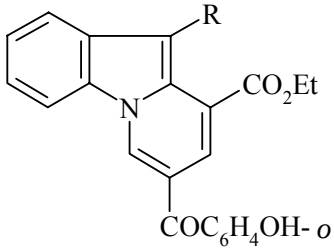
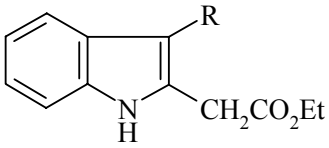
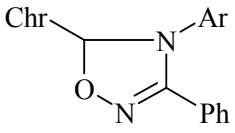


109 R = H, 35%
R = Me, 55%
R = Et, 60%

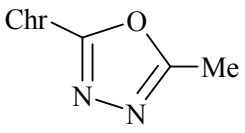


110 R = H, 5%
R = Me, ~1%
R = Et, <1%



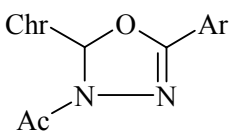
111

Ar	Yield (%)
C_6H_4OMe-*p*	70
C_6H_4OEt-*p*	65
C_6H_4Cl-*p*	60
Ph	60



72%

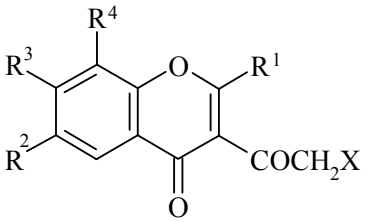
112



113

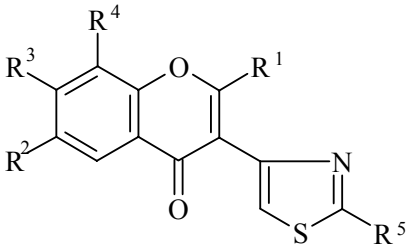
VI. HETEROCYCLES CONTAINING N AND S ATOMS

3-Acetylchromone (**114**) (R^1 = Me, R^2 = Cl, R^3 = H, Me; R^4 = H) on bromination with bromine in CCl_4 at room temperature gives the corresponding 3-bromoacetylchromone (**115**) which condenses with R^5C (=S)NH_2 [R^5 = Ar, NH_2, NHAr, $NHNH_2$] in boiling EtOH giving the thiazole (**116**).[79-81] The amine and hydrazine functionalities of (**116**) (R^5 = NH_2 and $NHNH_2$) have been further utilised for construction of several heterocycles.[80,81] Thioacetamide converts **115** (R^1 = H, Me; R^2-R^4 = H) into **116** (R^5 = Me).[46] The benzthiazole (**56**) (R^1 = H, R^2 = OH, X = S) is obtained in 78% yield by treating the acetophenone (**31**) (Het = 2-benzthiazolyl) with ethyl orthoformate in pyridine at 2-3ºC.[35] The ketone arising from Houben-Hoesch synthesis from pyrogallol and 2-methylthiazol-4-acetonitrile has been cyclised by Py-Ac_2O to the thiazole (**116**) (R^1 = R^5 = Me, R^2 = H, R^3 = R^4 = OAc) (76%).[82,83] The ketones (**31**) (Het = 2-phenyl-thiazol-4-yl and 2,4-dimethylthiazol-5-yl) obtained by treating resorcinol respectively with 2-phenyl-thiazole-4-acetonitrile and 2,4-dimethylthiazol-5-acetonitrile on acetylation (Ac_2O, Δ) cyclise to the corresponding chromonylthiazoles (**32**) (R = Me, R^1 = Ac)[30] analogous to **116**. Thioglycollic acid in C_6H_6 undergoes 1,4-addition to the imine (**3**, Ar = C_6H_4X-*p*; X = H, Cl, Me, OMe); the resultant adduct (**117**) (~ 98%) on prolonged refluxing in C_6H_6 affords thiazolidine derivative (**119**) (~ 35%) probably *via* the thazepine (**118**), the conversion (**118** → **119**) being regarded as a thermally induced thia-allylic rearrangement.[84] The chalcone Chr-CH=CH-CO-Ar, derived from 3-formylchromone and an aryl methyl ketone, condenses with 2-aminothiphenol (**58**, X = S) giving the 2,3-dihydro-1,5-benzothiazepine (**120**).[85,86]



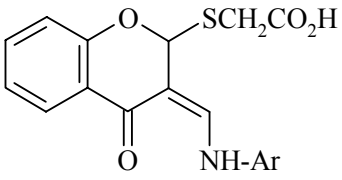
114 X = H
115 X = Br

R^1	R^2	R^3	Yield (%) of **115** (R^4=H)
H	H	H	~80
Me	H	H	77
Me	Me	H	70
Me	Cl	H	~80
Me	Cl	Me	~80



116

R^1	R^2	R^3	R^5	Yield (%) of **116** (R^4=H)
Me	H	H	Me	52
H	H	H	Me	33
Me	Cl	H	Ph	80
Me	Cl	Me	Ph	80
Me	Cl	H	$C_6H_4NO_2$-*p*	70
Me	Cl	Me	C_6H_4Cl-*p*	75
Me	Cl	Me	NH_2	90
Me	Cl	Me	NHPh	69
Me	Cl	Me	NHC_6H_4Me-*p*	95
Me	Cl	H	NH_2NH_2	88



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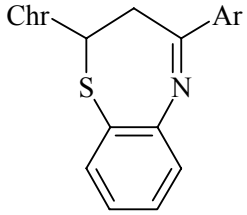

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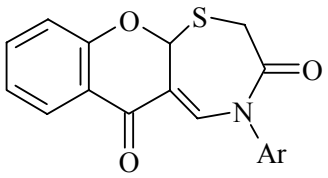

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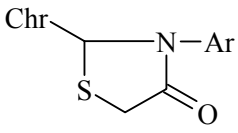

119

Ar	Yield (%)
Phenyl	52
p-Tolyl	63
p-Anisyl	68
p-Chlorophenyl	71
p-Bromophenyl	81
p-Fluorophenyl	76
1-Naphthyl	70
2-Naphthyl	72

ACKNOWLEDGEMENT

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