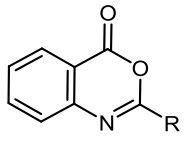
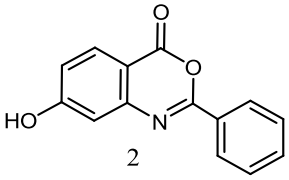
INTRODUCTION

4H-3,1-benzoxazinones as a class have been known for more than a century. The phenyl derivative 1a was first synthesized [128] and the methyl analog 1b seventeen years later [54]. Members of this family have been given the common name “acylanthranils” presumably from their early synthesis from 2,1-benzisooxazole (anthranil) and an acylating agent. Compounds possessing this ring system are found in nature. e.g. Phytoalexins avenalumin [202] and Dianthalexins 2 [52,147], and some hydroxylated derivatives of this last compound 3,4 [224].



1

a, R= ph
b, R= CH_3



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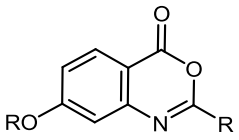


3, R= H
4, R=Me

The present review will covers this important field of fused heterocycles with nearly all the chemistry (synthesis and reactions) as well as its applications. For 4H-3,1-benzoxazin-4-one derivatives only those with carbon substituents at 2-position will he mentioned.

1. Importance of 4H-3,1-benzoxazin-4-ones

1.1 Pharmaceutical applications of 4H-3,1-benzoxazin-4-ones

The 4H-3,1-benzoxazin-4-one core is a key structural fragment in a range of biologically active compounds. Work by medicinal chemists had led to a number of drugs. Related uses being found for this class of heterocyclic systems.

4H-3,1-benzoxazin-4-ones have attracted considerable attention as inhibitors of Serine proteases. The interaction of 3,1-benzoxazin-4-ones with serine proteases involves enzyme acylation due to the nucleophilic attack of the active site of serine on the lactone carbon, ring cleavage, and subsequent deacylation of the acylenzyme formed [139,295]. Hays et al. have screened a series of 2-substituted 4H-3,1-benzoxazin-4-ones as inhibitors of Clr serine protease of the complement system.

Particularly, 2-aryl-4H-3,1-benzoxazin-4-ones act as Clr Serine protease inhibitors [133]. Also it was converted into the corresponding 4(3H)-quinazolin-4-ones interaction with 4-amino-1-phenyl-2,3-dimethyl pyrazolin-5-one (aminoantipyrine), which act as Non-Steroidal anti-inflammatory agents [118, 123].

In a modem fashion, 4H-3,1-benzoxazin-4-ones core linked to heterocycle or heteroaryl were disclosed as Serine hydrolase inhibitors. They were evaluated in a human sputum neutrophil elastase assay [274].

Chiral 2-alkylamino 4H-3,1-benzoxazin-4-one derivatives were reported as inhibitors or potent inactivatores of Standard Serine Proteases of the Chemotrypsin superfamily [215,289,180].

A series of 2-amino substituted 4H-3,1-benzoxazin-4-one derivatives was reported as inhibitors for human protease, and some of them demonstrate Anti-Viral activity in cell culture, with selectivities related to chemotrypsin and Elastase and stability with respect to hydrolysis in human plasma [8,137,138 ,149]. Also a combination of 4H-3,1-benzoxazin-4-one with 2-aminothiadiazole gives substituted quinazolinone which act as potent Anticonvulsants and Enzyme inhibitors [275].

5-Methyl-4H-3,1-benzoxazin-4-one derivatives are acomplished as specific inhibitors of Human. Leukocyte Elastase (HLE), where they showed strong and highly specific inhibition of Human Sputum Elastase (HSE), which is equivalent to HLE [302].

Moreover, 2-substituted-4H-3,1-benzoxazin-4-one derivatives showed good Cytotoxic activity [236], Herbicidal properties and inhibition of Herpes simplex virus type 1 (HSV-1) protease [145,167]. A series of 4H-3,1-benzoxazin-4-ones with different aromatic substitution pattern were evaluated as HIV-1 Reverse transcriptase inhibitors [244].

2-Aryl-substituted 4H-3,1-benzoxazin-4-ones act as novel active substances for the cardiovscular system. They exhibit relaxing effect on smooth musculature in particular and markedly increase coronary flow through Langendorff hearts [304].Moreover, they are used in t treatment of Obesity and also found to be novel specific Puromycin sensitive aminopeptidase inhibitors [153,307]. Nevertheless, they exhibit biological activates towards anti-elastases. [69].

Clearly, some 2-substituted 4H-3,1-benzoxazin-4-ones have the ability to lower the levels of cholesterol and triglycerides in plasma, and to raise the proportion of total cholsterol carried by high-density lipoproteins [124].

The importance of these 4H-3,1-benzoxazin-4-one also resides in that, these compounds is useful precursors for the preparation of other pharmaceutically active heterocyclic compounds, mainly quinazoline derivatives [68].

For example, 2-styryl-4-(3R)-quinazolinone bearing 5-,6-, 7-, 8-Cl, 6-Br, 6-F, 6-NH_2, 6-OMe, 6-OH, 6-OEt act as new class of Anti-Miotic Anti-Cancer agents which inhibited Tubulin polymerization. Extensive structure activity relationship studies suggest that, the entire quinazolinon structure was required, but activity was further enhanced by halides or small hydrophobic substituents at position-6 [169].

While, substituted 2-(1-adamantyl)-4H-3,1-benzoxazin-4-ones and 2-(1-adamantyl)-3-amino or alkyl-3,4-dihydroquinazolin-4-ones are found to exhibit a broad spectrum Anti-Tumor activity with full panel (MG-MID) median growth inhibition (GI_{50}), some of them showed moderate selectivity towards Leukemia Cell Lines, and some of them possess moderate Anti-HIV-l potency [112].

1.2 Industrial applications

4H-3,1-benzoxazin-4-ones containing at 2-position Ph, m-, p-tolyl, p-chlorophenyl, m-nitrophenyl, or m-methoxyphenyl are additives comprising surfactants, carboxypolymers, polysaccharides and/or polyalicylene glycols. amount of 5-7% of this compounds have good storage stability in detergent components containing a peroxygen bleach, such as Na perborate tetrahydrate, dissolve rapidly in water, and provide good bleaching of stained textiles during laundering a dispersion of 100g sodium-Dedecylbenzene-sulfoflate in 800g molten 2-phenyl-4H-3,1-benzoxazin-4-one was prepared at 130 °C, cooled and milled to give particles with av. diameter 0.5-1mm [219,235].

2-Alkyl and 2-aryl-4H-3,1-benzoxazin-4-ones are widely used in the synthesis of polymeric materials and optical bleaching agents [41,127]. Some 4H-3,1-benzoxazin-4- ones bearing sulfonylamino groups are used as fluorescent dyes [181].

Recently, 4H-3,1-benzoxazin-4-one derivatives with (2-aryl) vinyl substituent at 2-position were reported as useful UV absorber having absorption in the long-wavelength region for cosmetics [293].

(2,2'-Di-(4H-3,1-benzoxazin-4-one))-m- or p-phenylenes were used for improving the light-fastness of textile materials, where they are used for increasing the light-fastness of textiles and producing textiles which protect the wearer from the solar UV radiation [220].

2. Synthesis of 4H-3,1-benzoxazin-4-ones

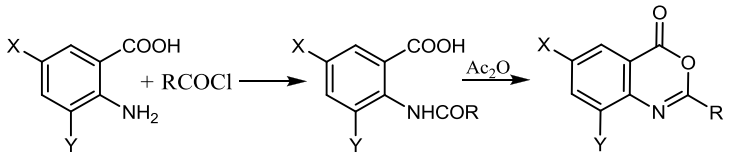
4H-3,1-benzoxazinones comprise a relatively large group of substances which have come to be known were synthesized as follows:

2.1 From anthranilic acids

By far the most popular and versatile route to the 3,1-benzoxazinone nucleus relies on anthranilic acid or its derivatives as a convenient starting material.

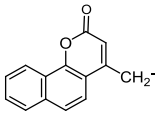
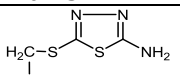
2.1.1 Via the action of acid chlorides on anthranilic acid

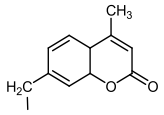
2-Alky, -aryl and -aryalkyl 4H-3,1-benzoxazinenes 1 have been obtained by heating anthranilic acid or substituted anthranilic acid with acid chlorides. Here, a vast array of acid chlorides are either commercially available or easily prepared.



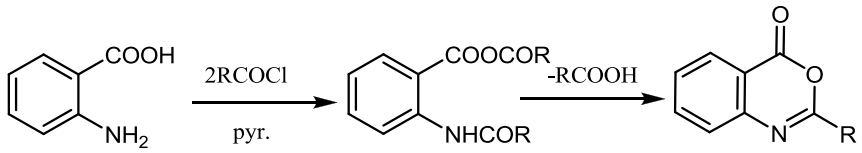
1 a-z_{12}

The compounds thus obtained are collected in the following table

	X	Y	R	Reference
a	H	H	-C_6H_5	[128, 36]
b	H	H	-CH_3	[315, 75]
c	Br	H	-CH_3	[266]
d	H	H	-C_3H_7(iso)	[121]
e	H	H	-CH_2COCH_3	[96]
f	H	H	-$CH_2C_6H_5$	[96]
g	H	H	-C_3H_7(n)	[119, 126]
h	H	H	-CH_2CI	[256]
i	H	H	-$C_{10}H_7$(α)	[88]
j	Br	Br	-CH_3	[161]
k	H	H		[110]
l	Br	Br	-C_6H_5	[162]
m	I	H	-CH_3	[213]
n	NO_2	H	-C_3H_7(n)	[64]
0	CH_3	H	-$C_6H_4C_4H_9$(t)(4)	[141]
p	H	H	C_4H_3S	[107]
q	I	H	C_6H_5	[131]
r	H	H		[44]
s	H/Br Br/Cl	H/Br H	-C_6H_4.C1(4)	[188]
t	H/Br	H/Br	C_6H_5- -C_6H_4CI (o, m,p)	[188]
u	H	H	-C_6H_4.I(o)	[148]
v	I	H	-C_6H_5	[4]
w	I	H	-CH_2Cl	[90]
x	H	H	-C_2H_5	[30]
y	$NHSO_2R$	H	-CH_3	[310]
z	H	H	-C_6H_4.$NHSO_2R$	[51]

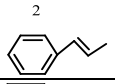
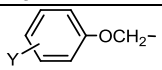
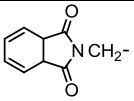
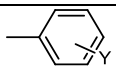
	X	Y	R	Reference
z_1	H	H		[285]
Z_2	CH_3	H	$-C_6H_4.C_4H_9t(4)$	[141]
Z_3	H	H	$-CH=CH_2$	[176]
Z_4	H	H	$-C_{10}H_7(\beta)$	[210]
Z_5	Br	Br	C_4H_3S	[162]
Z_6	Br/H	Br/H	$-CH_3$	[171]
Z_7	Cl	Cl	$-C_6H_5$	[214]
Z_8	H	OCH_3	$C_6H_4Br(4)$, $C_6H_4Br(2)$, $C_6H_4C1(3)$, $C_6H_4F(2)$, $C_6H_4C1(4)$, $C_6H_4C1(2)$	[155]
Z_9	H	OCH_3	- CH_3, C_2H_5, C_4H_9, C_6H_5, $C_6H_4Br(4)$, $C_6H_4Cl(4)$, - $C_6H_4Br(2)$, $C_6H_4Cl(2)$, $C_6H_4F(2)$, $C_6H_4CH_3(2)$, $C_6H_4(OCH_3)(2)$	[156]
z_{10}	H	Cl/CH_3	- $C_6H_4Br(2)$, $C_6H_4Cl(2)$, $C_6H_4F(2)$, $C_6H_4CH_3(2)$, $C_6H_4(OCH_3)(2)$	[156]
	F	H	$-CH_2CH_2ph$, Bu, Ph, 	[327]
z_{11}	H	H	C_4H_3O	[193]
z_{12}	2-aminobenzoic acid	Ph		
	CH_3	H		[61]

Although these methods provide benzoxazinones in a straight forward manner, the lack of a wide variety of readily available acid chlorides limits the generality of this method. As a modification of literature methods [326,313], 2- aryl-4H-3, 1-benzoxazin-4-ones 5 were obtained via reaction of anthranilic acid with two equivalents of an acid chloride in pyridine solution.

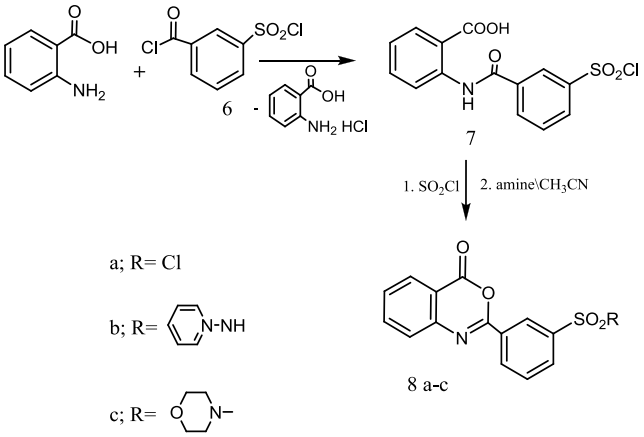


5 a-g

The compounds thus obtained are collected in the following table

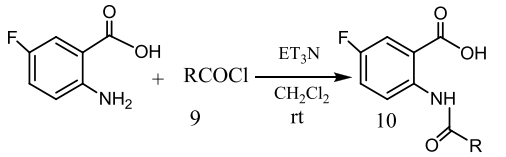
	X	R	Ref.
a	H	 Y= H, Cl, Br, Me, OMe, CF_3, NO_2, COOH(at o-, m-,p-)	[36,147, 141,173,133,239]
b	H		[36,297,265,267]
c	H		[36]
d	H	 Y= H, Me, OMe, NO_2	[36]
e	H		[277, 183]
f	H	 Y H, 3-F, 2-F, 3-OMe, 4-OMe, 2-OMe, 3-OH, 4-OH, 2,5-Di-OH, 2-OH	[273]
g	NO_2	$-C_6H_5$	[175]

In contrast, the 3-chloro sulphonylbenzoyl chloride 6 reacts with 2 equivalents of anthranilic acid to give N-(3-chlorosulphonylbenzoyl)anthranilamide (7), which furnishes the 3-(4-oxo-4H-3,1-benzoxazin-2-yl)benzenesuphonyl chloride (8a) on treatment with thionyl chloride. 4H-3,1-benzoxazinones 8b,c are obtained on treatment of 8a with aniline and piperidine at 20 °C in acetonitrile [296].



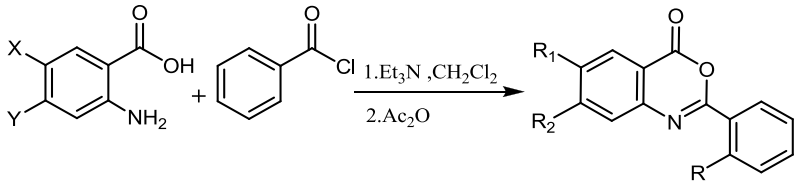
8 a-c

On the other hand, 5-fluoroanthranilic acid reacts with acid chlorides 9 in the presence of triethylamine and methylene chloride at room temperature to afford 10, which on heating with acetic acid anhydride for 1hour produces the 6-fluoro-2-substituted benzoxazinones 11 [327].



R= C_4H_9, C_6H_5, $-CH_2CH_2Ph$, $C_4H_3S.CH_2$ - 11

The reaction of acid chlorides with anthrailic acids can be performed as a one-pot reaction. Thus the reaction of substitute anthranilic acid with to 2-substituted benzoyl chlorides 12 in presence of Et_3N and CH_2C_{12} followed by addition of acetic acid anhydride and affords disubstituted benzoxazinones 13[261].



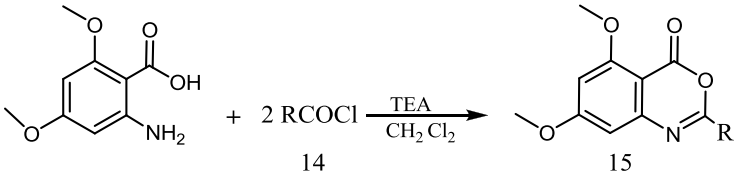
13 a-g

The compounds thus obtained are collected in the following table

	X	Y	R	R_1	R_2
a	Br	H	CH_3	Br	H
b	Br	H	CH_3	C_6H_4.Cl(4)	H
c	H	Br	H	H	Br
d	H	Br	H	H	C_6H_4.Cl(4)
e	H	H	CH_3	H	H

	X	Y	R	R_1	R_2
f	OCH_3	H	OCH_3	OCH_3	H
g	OCF_3	H	CH_3	OCF_3	H

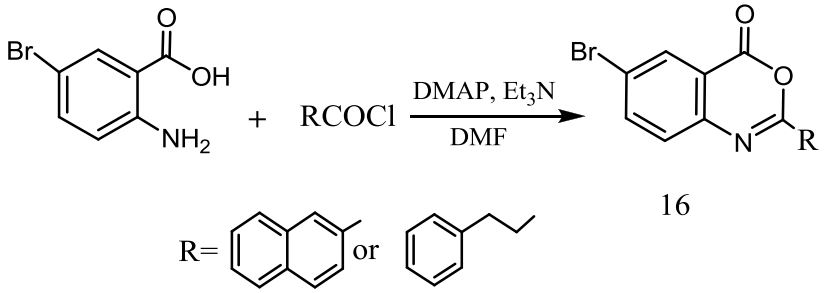
If 4,6-dimethoxyanthranilic alkanoyl chlorides 14 in TEA and acid is reacted with CH_2CI_2 at 40 °C, 4H-3,1-benzoxazin-4-one derivatives 15 is produced [136].



14 15

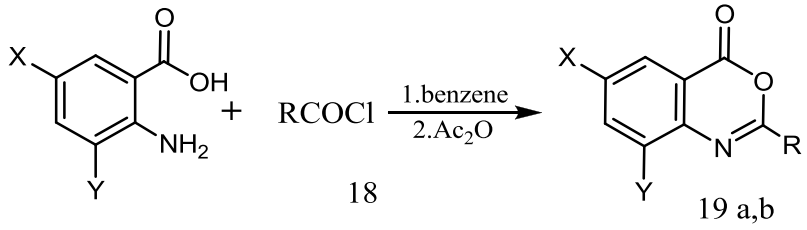
R= Me, Et, n-Pr, i-Pr, n-Bu, i-Bu

5-Bromoanthranilic acid is cyclized with 2- naphthoyl and/or phenethyloyl chloride by heating the mixture with DMPA and triethyl amine in DMF and furnishes 16 [322]



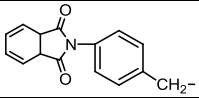
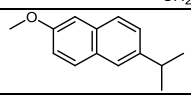
16

Moreover, reaction of anthranilic acids 17 with synthesized acid chlorides 18 was carried out in boiling benzene followed by refluxing in acetic acid anhydride to afford benzoxazinone derivatives 19.



17 18 19 a,b

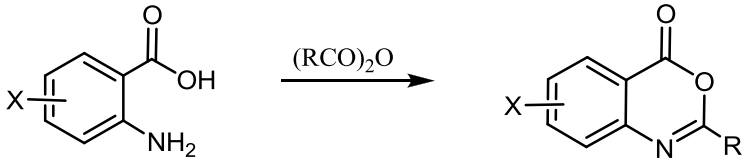
The compounds thus obtained are collected in the following table

	X	Y	R	Ref.
a	H	H		[42]
b	Cl	Cl		[14]

2.1.2 Via the action of acid anhydrides on anthranilic acid

Simple 2-substituted derivatives 20 are best prepared by reacting an anthranilic acid derivative with an appropriate anhydride at elevated temperatures. Lower

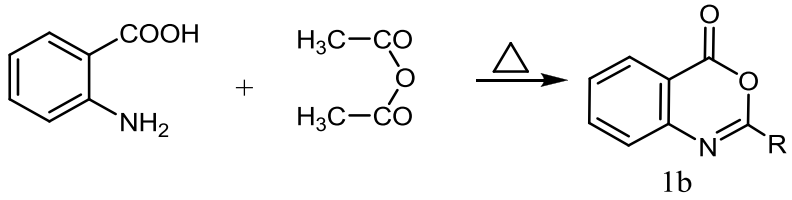
molecular weight anhydrides are usually employed as the solvents [57, 249, 243, 178, 23, 35, 111].



20

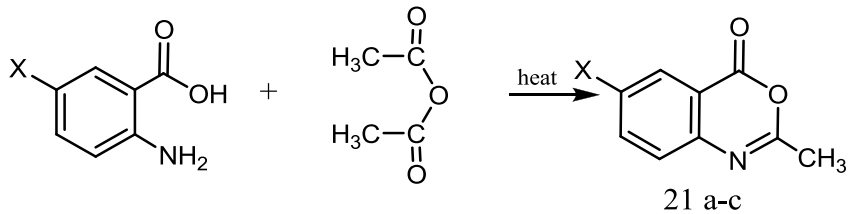
X=H,halogen,OMe,NO_2 R=Me,Et,n-Pr,Ph,CF_3

2-Methyl-4H-3,1-benzoxazin-4-one (1b) are obtained by heating anthranilic acid with acetic anhydride [200].



1b

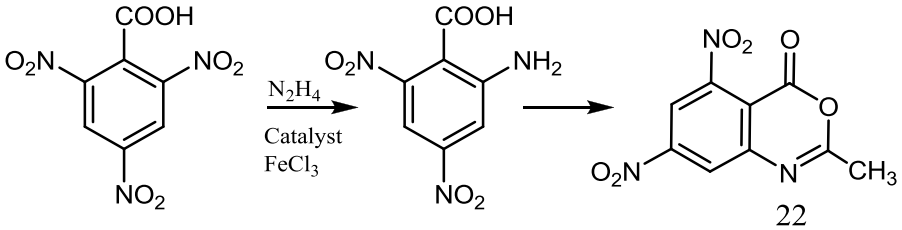
Recently, 2-methyl-6-halo-4H-3,1-benzoxazin-4-ones 21 are obtained by heating 5- haloanthranilic acid with acetic acid anhydride for two hours.



21 a-c

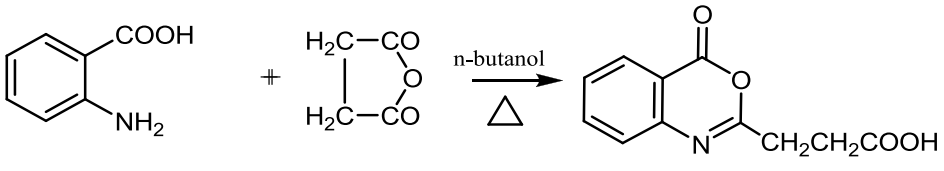
a, X= H, Br [182]
b, X =Cl [250]
C, X =I [279]

2-methyl-5,7-dinitro-4H-3,1- benzoxazin-4-one (22) is prepared in the same way by generating 4,6-dinitroanthranilic acid (catalytic reduction of 2,4,6-trinitrobenzoic acid) followed by heating with acetic acid anhydride [177].



22

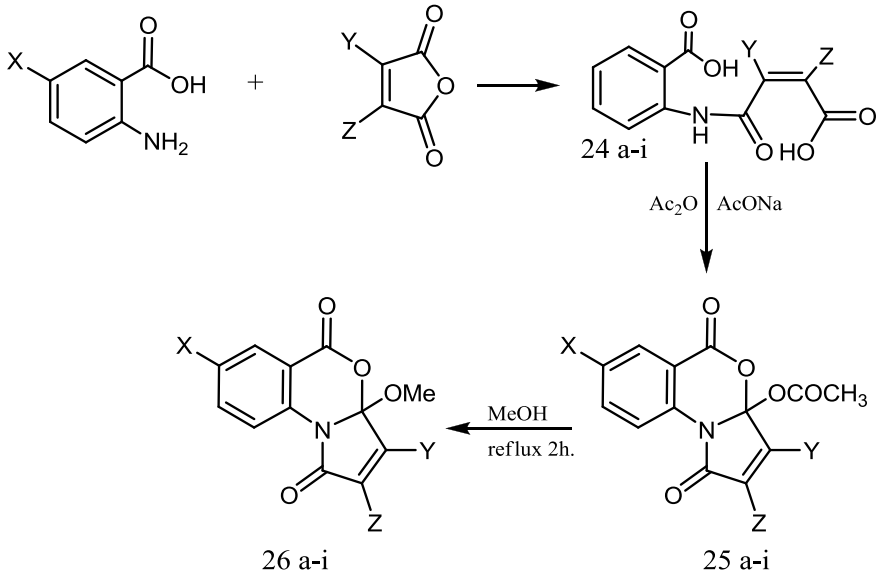
Similarly, 2-(β-carboxyethyl)-4H-3, 1-benzoxazin-4-one (23) has been obtained by heating anthranilic acid with succinic acid anhydride in n-butanol [119].



23

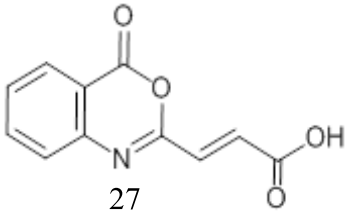
Also co-solvents as chloroform, dioxane, toluene, and orthoesters are used successfully as cyclizing agents [26, 45, 306].

In addition, a series of o-carboxymaleanilic acids 24 are prepared by reacting anthranilic acid with maleic anhydride, methylmaleic anhydride, or phenylmaleic anhydride, which intermolecularly dehydrated to afford pyrrolobenzoxazinones 25. Which underwent solvolysis via refluxing with anhydrous methanol furnishes 26 [40].



	X	Y	Z
a	H	H	H
b	Cl	H	H
c	Br	H	H
d	I	H	H
e	H	Me	H
f	H	H	Me
g	H	Ph	H
h	H	Me	Me
i	H	o-C_4H_4	o-C_4H_4

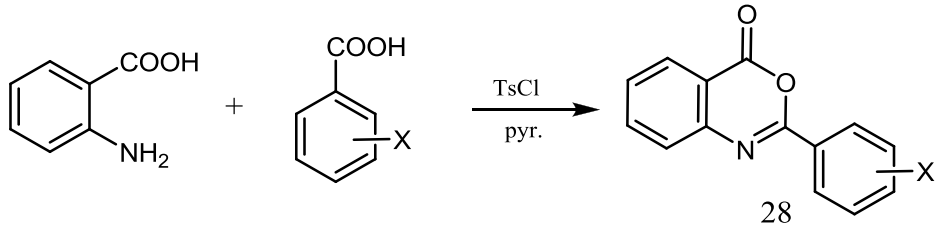
Under identical conditions, o-carboxyfumaranilic acid afforded 2-carboxyvinylbenzoxazinone 27 which does not further cyclized due to its cis-geometry [40].



27

2.1.3 Via reaction of anthranilic acid with aromatic carboxylic acid

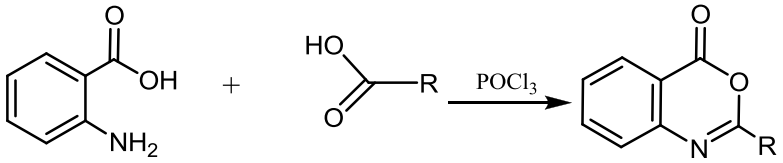
A closely related synthesis of 2-phenyl-4H-3,1- benzoxazin-4-one 28 uses the reaction of anthranilic acid with two equivalents of an ortho or para substituted benzoic acid (X= H, Cl, Me, OMe, NO_2) in the presence of tosyl chloride [255].



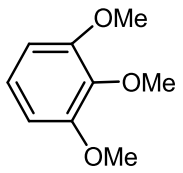
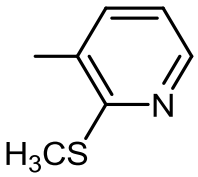
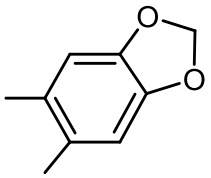
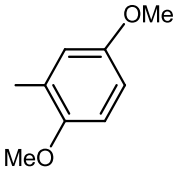
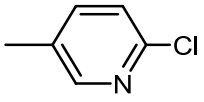
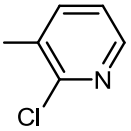
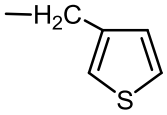
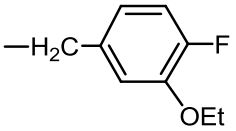
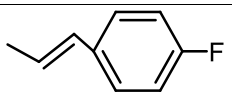
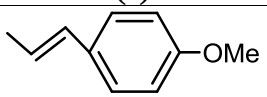
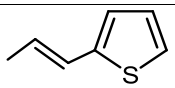
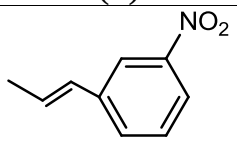
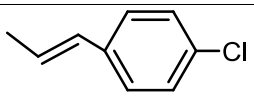
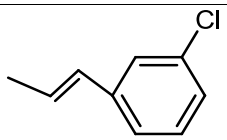
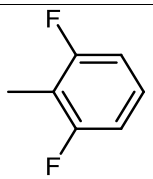
28

X= H, Cl, Me, OMe, NO_2

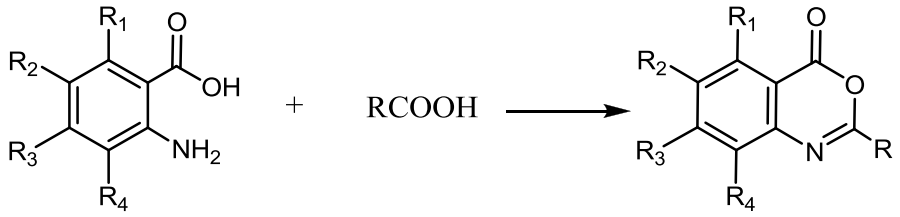
Starting from anthranilic acid on one hand and the aromatic carboxylic acids 29 on the other hand, where the preliminary chlorination to furnish the acid chloride is not necessary when the reaction proceed to yield benzoxazinone derivatives 30 a-o as a final product is performed in phosphoryl chloride under nitrogen atmosphere [260].



29 $30_{a\text{-}o}$

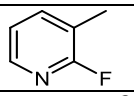
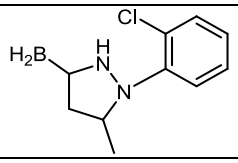
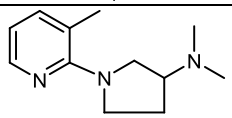
 (a)	 (b)	 (c)	 (d)
 (e)	 (f)	 (g)	 (h)
 (i)	 (j)	 (k)	 (l)
 (m)	 (n)	 (o)	

Recently, heteroarylbenzoxazinones 33 a-c were prepared by heterocyclization of heterocarboxylic acids 32a,b with substituted anthranilic acids 31a,b. If the benzoxazinone 33a is combined with 3-(dimethylamino) pyrrolidine gives 4H-3,1-benzoxazin-4-one derivative 33e.

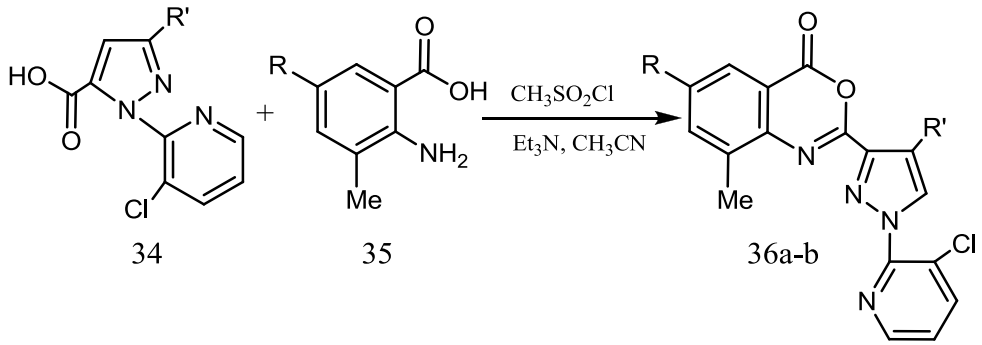


31 32 33a-c

The compounds thus obtained are collected in the following table

	R^1	R^2	R^3	R^4	R	Ref.
a	Et	H	OMe	H		[274]
b	H	CN	H	Me		[190]
c	Et	H	OMe	H		[274]

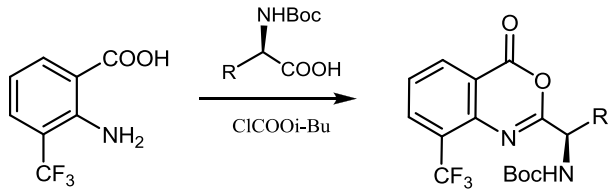
Another variation of this method uses the coupling of the pyrazole acid 34 with anthranilic acids 35 in acetonitrile and triethyl amine in presence of methanesulphonyl chloride to obtain the 4H-3,1- benzoxazin-4-one derivatives 36.



34 35 36a-b

2.1.4 Reaction of substituted anthranilic acid with Boc-protected amino acids

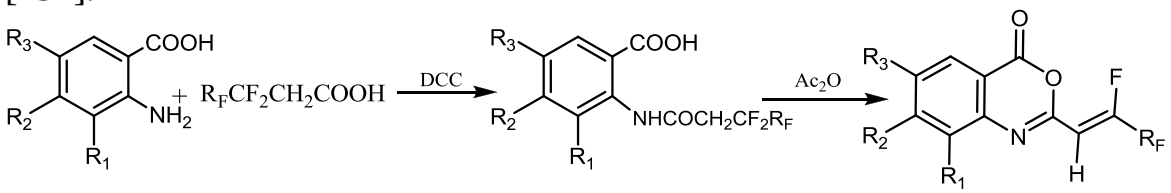
The interesting aminobenzoxazirione derivative 37 was readily prepared from the reaction of equimolar quantities of 3-trifluoromethylanthranilic acid and Bocprotected amino acid with two equivalents of isobutylformate in the presence of N-methylmorpholine with complete retention of the chiral information [66, 67].



R= H, Me, Et, i-Pr 37

2.1.5 Reaction of substituted anthranilic acid with 2,2-dihydro fluoroalkanoic acid

2-[(z)-1-hydrofluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones 38 are obtained via condensation of 2,2-dihydropolyfluoro alkanoic acid with anthranilic acid or its derivatives in the presence of N,N'-dicyclohexylcarbodimide (DCC) in CH_2C12 [194].



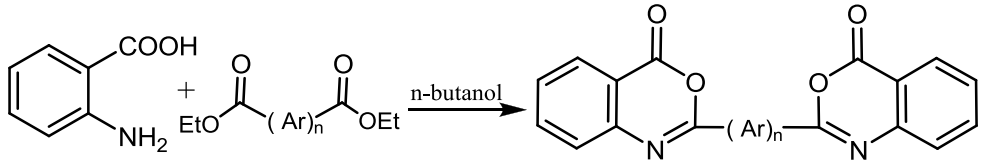
a-d e-j 38

a, R_1=R_2R_3=H b, R_1=H, R_2=R_3=OCH_3
c, R_1=R=H, R_2=Cl d, R_1=R_3=Br, R_2=H

R_F, e=C_5F_{11}, f = CF_6C_1, g = C_3F_7,
h=CF_2C_1, I = CF_2Br, j = CF_3

2.1.6 Synthesis of Bis(411)-3,1-benzoxazin-4-one derivatives :-

Bis(4H)-3,1-benzoxazin-4-one derivatives 39 are prepared from interaction of terephthaloyl chloride with diethyloxalate or anthranilic acid [201].



39

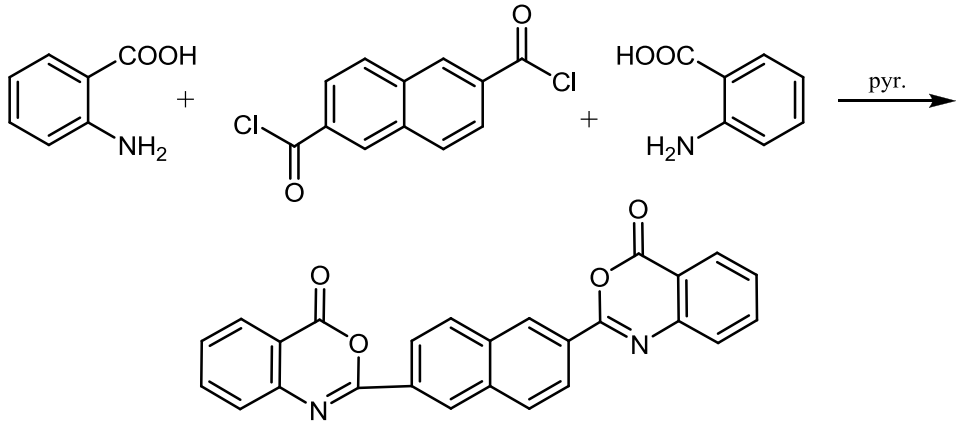
a, n= 0 in case of diethyloxalate

b,n=1 in case of terephthaloyl chloride which gave 2,2'-p-phenylene bis-(6-substituted)-3,1-benzoxazin-4-one.

General formula (39; R1, R2= C1-C10 hydrocarbyl, C1-C3 alkoxy, C1-C4 acyl, halogen, nitro, Ar C6-C12 aromatic hydrocarbon group n= 0,1) were prepared and used as light stabilizer for polyester fibers' [201].

Similarly a sunscreen contains a cyclic imino ester (40) (R = divalent aromatic hydrocarbyl) as a UV absorbent, has been obtained via interaction of 2,6-naphthalene dicarboxylic acid chloride with anthranilic acid in pyridine [324].

It is resistant to water, not readily soluble in organic solvents, fats, oils, and nonirritating to the skin. It prevents skin rash and acts as skin conditioner.

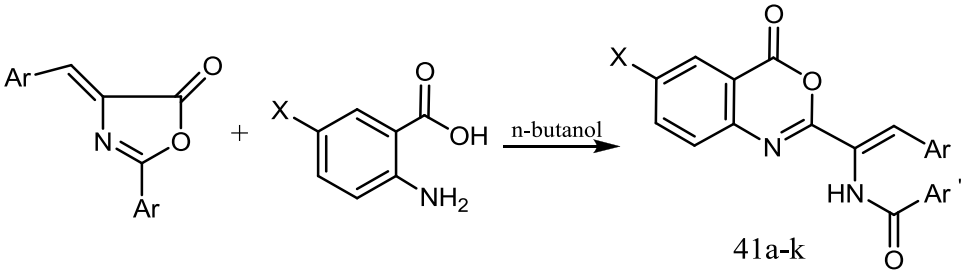


40

2.1.7 From interaction of anthranilic acid with heterocyclic compounds

2.1.7.1 From 4-arylidene-2-aryl-oxazoIin-5-one

2-substituted-4H-3,1-benzoxazin-4-ones 41 were obtained via interaction of 4-arylidene-2-aryl- oxazolin-5-one with anthranilic acid in boiling butanol.



41a-k

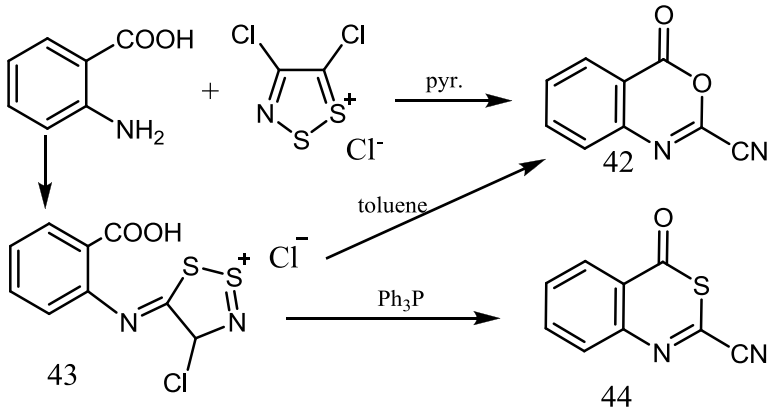
The compounds thus obtained are collected in the following table

	X	Ar	Ar	Ref
a	H	$C_6H_4.(OCH_3)(4)$	C_6H_5	[84]
b	H	$C_6H_4.NO_2(3)$	C_6H_5	[84]
c	H	$C_6H_4.(OCH_3)(4)$	$C_6H_4.(OCH_3)(4)$	[84]
d	H	$C_6H_4.C_{10}H_7$ (2)	C_6H_5	[94]
e	H	$C_6H_2.(OCH_3)_3(3,4,5)$	$C_6H_4.Cl(2)$	[94]
f	H	$C_6H_2.(OCH_3)_3(3,4,5)$	$C_6H_4.Cl(2)$	[94]
g	H	$C_6H_2.(OCH_3)_3(3,4,5)$	C_6H_5	[99]
h	H	$C_6H_4.Cl(4)$	C_6H_5	[99]
i	H	$C_6H_4C_{10}H_7(l)$	C_6H_5	[6]
j	H	2-furyl	C_6H_5	[6]
k	Br	C_6H_5	C_6H_5	[217]

2.1.7.2 From iminodithiazole

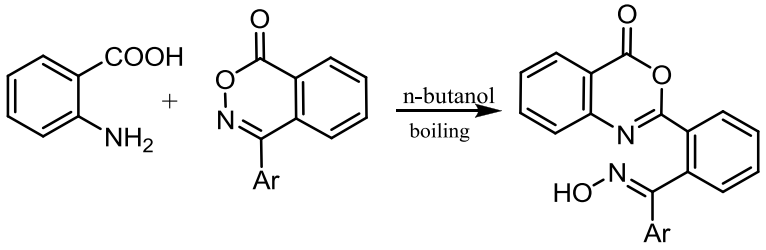
Iminodithiazole obtained from condensation of anilines with 4,5-dichloro-1,2,3-dithiazolium. Chloride were reacted with a solution of anthranilic acid (in

methylene chloride) in the presence of pyridine to produce 2-cyano-3,1-benzoxazin-4-one (42). A similar reaction of using triphenyl phosphine instead of pyridine yielded the analogous 3,1-benzothiazin-4-one 44. The delicate intermediate iminodithiazole 43 can be isolated if four equivalents of anthranilic acid are used without the addition of pyridine. Heating of 43 in toluene afforded 42, while treating 43 with two equivalents of triphenyl phosphine produces 44 [47, 48].



2.1.7.3 From (4H)-3,2-benzoxazin-4-one

2-substituted-4H-3,1-benzoxazin-4-ones 45 have been obtained when 1-substituted-4H-3,2-benzoxazin-4- one derivatives were allowed to react with anthranilic acid in boiling n-butanol.

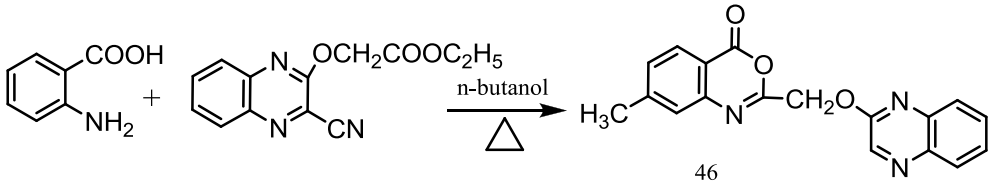


45a,b

Ar		Ref.
a,	$-C_6H_3(CH_3)_2(3,4)$	[99]
b,	$-C_6H_4.C_6H_4(4)$	[100]

2.1.7.4 From 3- methyl-2-(ethoxycarbonylmethoxy) quinoxaline

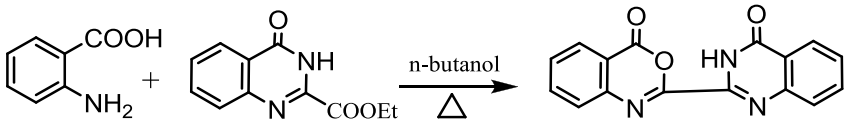
Substituted-4H-3,1-benzoxazin-4-one 46, which bearing a hetaryl moiety at 2-position, are synthesized via interaction of 2-(ethoxycarbonyl methoxy)-3-methylquinoxaline with anthranilic acid in boiling butanol at 120 °C [210].



46

2.1.7.5 From 2-ethoxycarbonyl-4(3H)-quinazolin-4-one

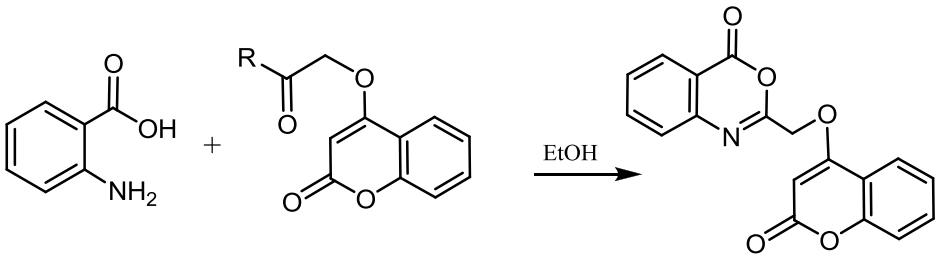
2-[4(3H)-oxoquinazol-2-yl]-(4H)-3,1-benzoxazin-4-one (47) are synthesized via interaction of 2- ethoxycarbonyl-4(3H)-quinazolinone with anthranilic acid by fusion at 170 °C or by refluxing in n-butanol for 3 hr [19].



47

2.1.7.6 From substituted coumarin

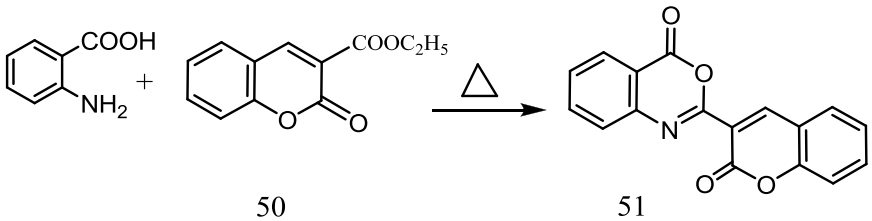
4H-3,1-benzoxazin-4-one derivative 49 is resulted from the interaction of anthranilic acid with (2- oxo-2H-chromen-4-yloxy)acetyl chloride 48a or the ester 48b in boiling ethanol [27].



48a,b 49

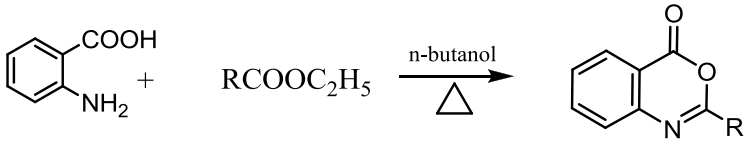
a; R= Cl b; R= OEt

While, 4H-3,1-benzoxazin-4-one 51 bearing coumarin-3-yl moiety at position-2 was obtained via interaction of 3-ethoxycarbonyl coumarin 50 with anthranilic acid by fusion at 150 °C or refluxing in n-butanol [102].



50 51

Similarly, 2-cyanomethyl, acetonyl andlor ethoxycarbonyl-4H-3,1-benzoxazin-4-one 52 were obtained via interaction of ethylcyanoacetate, ethylacetoacetate and diethyloxalate with anthranilic acid in boiling butanol.

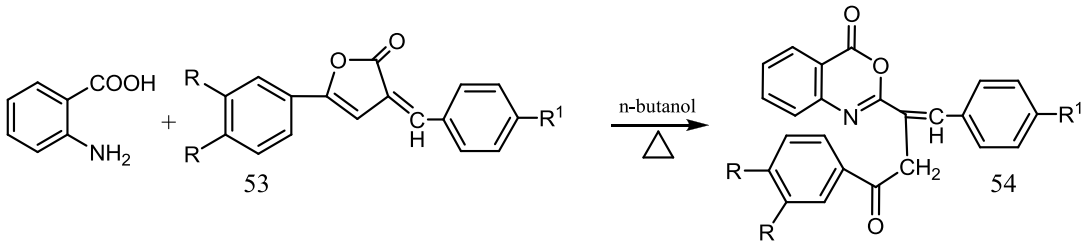


52a-c

	R	Ref.
a	-CH_2CN	[212]
b	-CH_2COCH_3	[96]
c	-$COOC_2H_5$	[19]

2.1.7.7 From hetero-ring opening of furanone derivatives

Hetero-ring opening of the furanone derivatives 53 with anthranilic acid in boiling butanol affords the 4H-3,1-benzoxazin-4-one derivatives 54 [284].

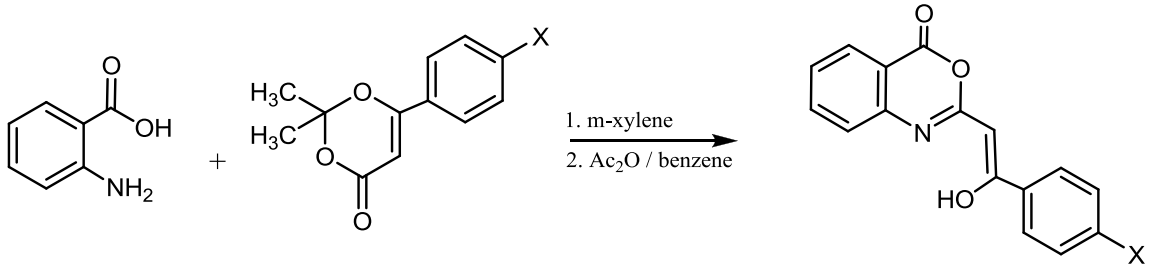


53 54

R= C1, Me; R^1 = Cl, NO_2, OCH_3, H

2.1.7.8 From hetero-ring opening of 1,3-dioxin-4-one derivatives

2-Substitutedphenylvinyl-4H-3,1-benzoxazin-4- one derivatives 56 were synthesized via refluxing anthranilic acid with 2,2-dimethyl-6-phenyl-[1,3]dioxin- 4-one derivative 55 in m-xylene, followed by dehydration [309].



55 56

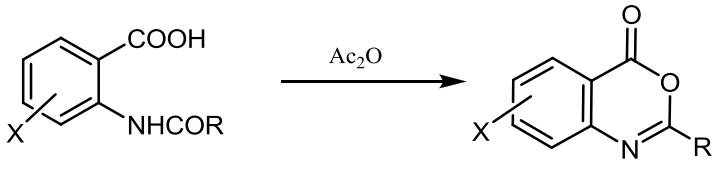
X = H, Me, OMe, OEt, Cl, Br

2.2 From N-acylanthranilic acid

Starting from an N-acylanthranilic acid a variety of reagents can be used to affect cyclodehydration to the benzoxazin-4-one.

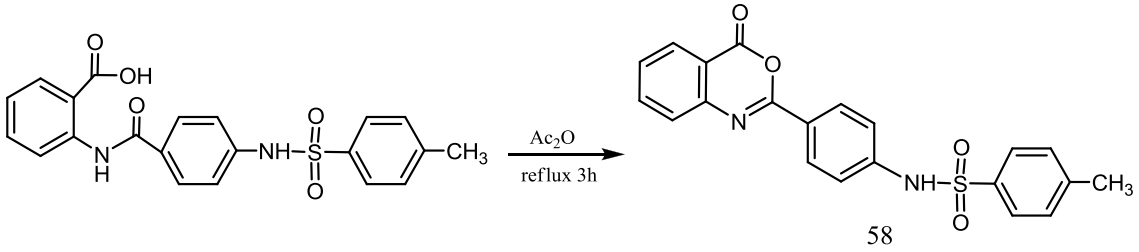
2.2.1 Acetic anhydride as cyclizing agent

Acetic anhydride is the most widely used reagent for this purpose, the cyclization can accommodate a wide variety of acyl groups (X = electron donating or withdrawing group, R = alkyl, substituted phenyl, CH_2Cl , $CH(CH_3)Cl$, styryl , trifluoromethyl , phthalimidomethyl , COOEt , 2-thienyl , pyridyl or thiadiazole) [71,163].



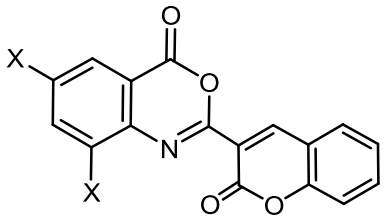
57

Also, aromatic systems containing thionylamino functionality at position-2 was introduced to obtain derivative 58 [15].



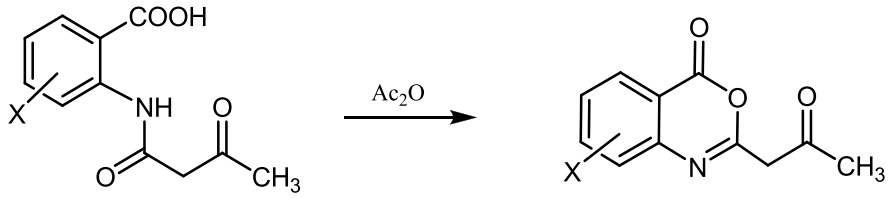
58

More complex heterocyclic systems such as a coumarin can be introduced into the 2-position of the benzoxazinone affording 59 [269].



X= H, Br 59

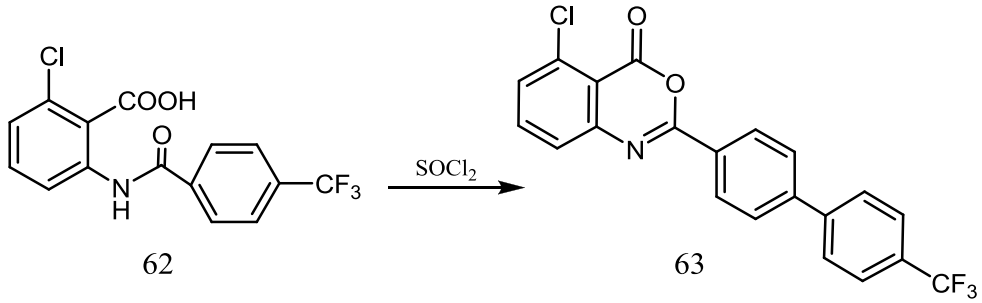
Anthranilic acid can also be acylated at nitrogen with either diketene [72, 73] or 2,2,6-trimethyl-4H-1,3-dioxin-4-one (diketene acetone adduct) [63] to give 60 which when exposed to acetic anhydride cyclizes to the 2-acetonyl derivative 61.



60 61

2.2.2 Thionyl chloride as cyclizing agent

Refluxing a solution of substituted N-acylanthranilic acid 62 with a small excess of thionyl chloride in 1,2-dichloroethane produces the benzoxazin-4-one derivative 63 [144].

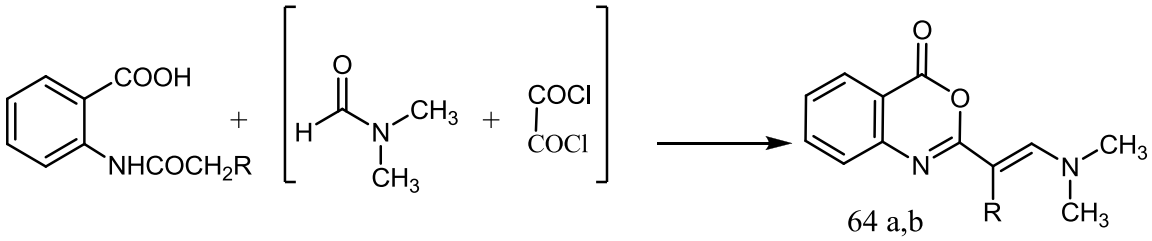


62 63

2.2.3 Vilsmeier reagents as cyclizing agent

Vilsmeier reagents generated front e.g. N,N-dimethyl formamide and oxalyl chloride, were reacted with N-acetylanthranilic acid to produce the 2-(2'-dimethylamino)ethenyl-4H-3,1-benzoxazin-4-one (64a). Similarly, N-

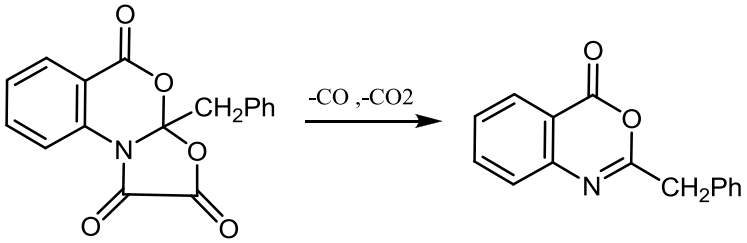
phenylacetyl anthranilic acid gave 2-(2'- dimethylamino-1'-phenyl)ethenyl-4H-3,1-benzoxazin-4- one (64b) [46].



64 a,b

a, R=H b, R=Ph

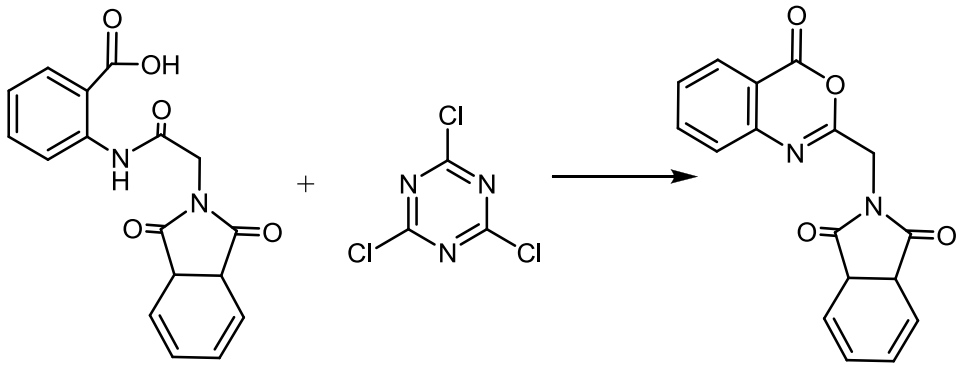
Reaction of N-acetylated anthranilic acids and oxalyl chloride alone give the fused oxazolidine-4,5-dione (65) [46].



65 66

2.2.4 Cyanuric chloride as cyclizing agent

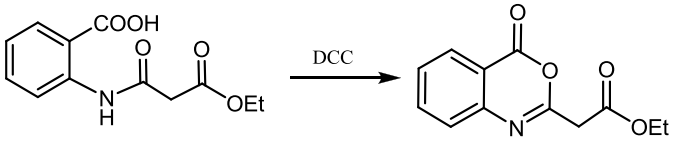
2-(N-phthaloylmethyl)-4H-3,1-benzoxazin-4-one 68 are prepared via reaction of the acyl chloride derivative N-phthaloylglycine with anthranilic acid in chloroform and N-phthaloylanthranilic acid 67 is generated. It reacted with cyanuric chloride to form the final product [272].



67 68

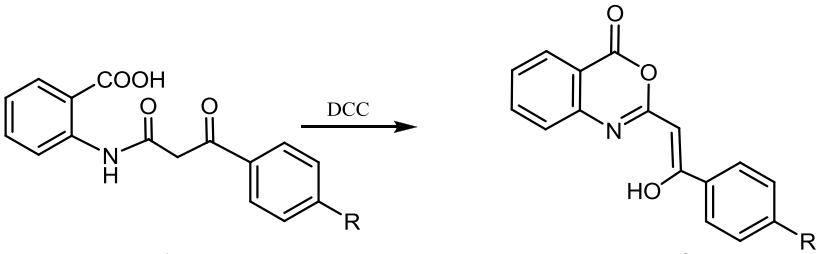
2.2.5 Dicyclohexylcarbodiimide as cyclizing agent

N,N'-dicyclohexylcarbodiimide (DCC) is used for dehydration of N-acylanthranilic acid 69 to obtain the 2- ethoxycarbonylmethyl-4H-3,1-benzoxazin-4-one 70. Where, N-acylanthranilic acid 69 was obtained via reaction of anthranilic acid with diethylmalonate [303].



69 70

Dehydration of N-acylanthranilic acid 71 to benzoxazinone 72 using DCC is achieved in higher yield and shorter reaction time as compared to the conversion with acetic acid anhydride as dehydrating agent [309].

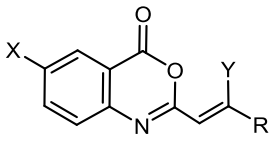


71 72

R= H, Me, OMe, OEt, Cl, Br

2.3 From 2-methyl-4H-3,1-benzoxazin-4-one

2-styryl or substituted styryl-4H-3,1-benzoxazin-4-ones 73 have been obtained, via interaction of 2- methyl-4H-3,1-benzoxazin-4-one with aromatic aldehydes and /or ketones in the presence of anhydrous zinc chloride at 170 °C.

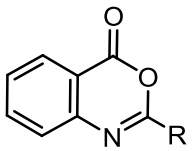


73

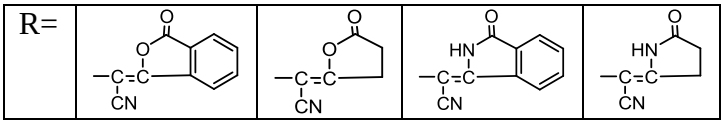
The compounds thus obtained are collected in the following table

	X	Y	R	Ref.
a	Br	H	C_6H_5 , $C_6H_4.OCH_3(4)$, $C_6H_4.NO_2(4)$, $C_6H_3(O_2CH_2)(3,4)$, $C_6H_4N(CH_3)_2(4)$, -CH=CH-C_6H_5	[266]
b	H	CH_3CO	C_6H_5, $C_6H_4.OH(4)$, $C_6H_4.NO_2(3)$, $C_6H_4.OCH_3(4)$, -CH=CH-C_6H_5 , $C_6H_3(O_2CH_2)(3,4)$	[96]
c	H	C_6H_5	$C_6H_4.OCH_3(4)$, $C_6H_4.OH(2)$, $C_6H_4N(CH_3)_2(4)$, -CH=CH-C_6H_5	[92]
d	H	H	$OC_6H_4.C1(4)$, C_6H_5 , $C_6H_3(O_2CH_2)(3,4)$	[101]
e	H	H	$C_4H_3O(2)$	[203]

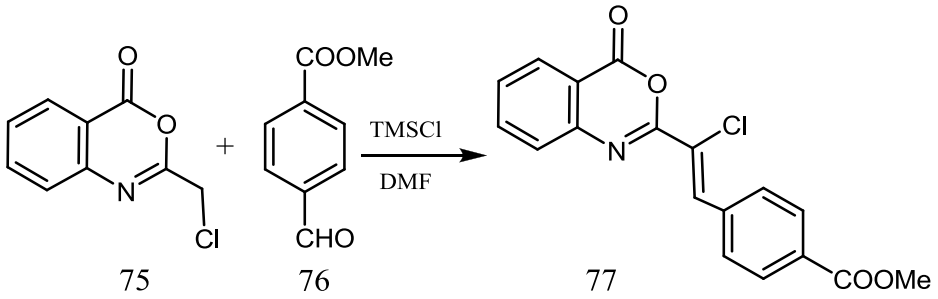
Similarly, 2-cyanomethyl-(4H)-3,1-benzoxazin-4- one has been reacted with phthalic anhydride, succinic anhydride, phthalimide and succinimide to give the benzoxazinone derivatives 74 [212].



74



A more recent concept uses the idea of reaction of aldehydes with chloromethyl benzimidazole, meanwhile the 2-[(2-aryl-1-chloro)vinyl]-4H-3,I-benzoxazin-4-one 77 is obtained via interaction of 2-chloromethyl analog 75 with aldehyde 76 in presence of chlorotriethylsilane [262].



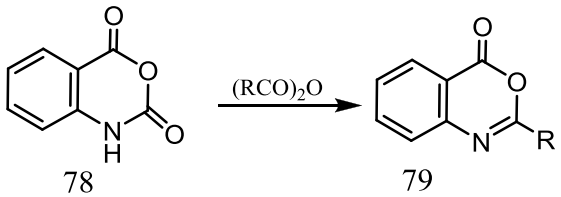
75 76 77

2.4 From isatoic anhydrides

Isatoic anhydrides are noted for their versatility in heterocyclic synthesis, so it is no surprise that 4H-3,1- benzoxazin-4-one heterocycle can be obtained from the closely related 2H-3,1-benzoxazin-2,4(1H)-dione (78) system.

2.4.1 Reaction of isatoic anhydride with acid anhyd rides

When isatoic anhydride 78 is refluxed in acetic anhydride [297], acetic acid anhydride/ pyridine [166, and 301] or stirred with trifluoro acetic acid anhydride/pyridine at room temperature [321] the corresponding benzoxazinone 79 is isolated in high yield.

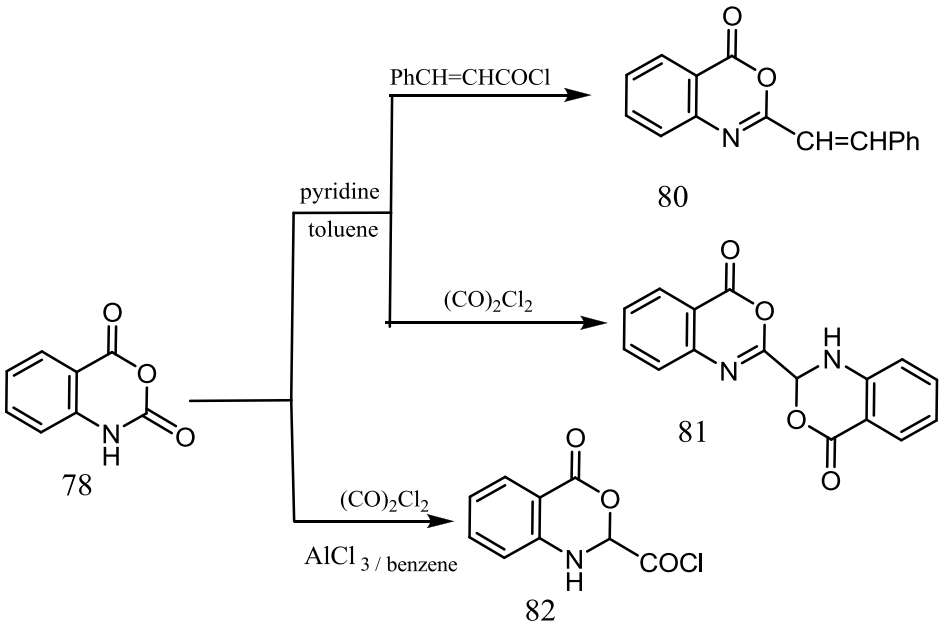


78 79

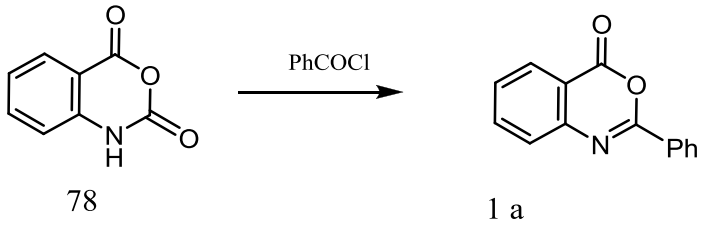
R = CH_3, Ph, CF_3, COCl, $C_6H_4.NH_2(2)$, CH2CH(CH3)COOEt

2.4.2 Reaction of isatoic anhydride with acid chlorides

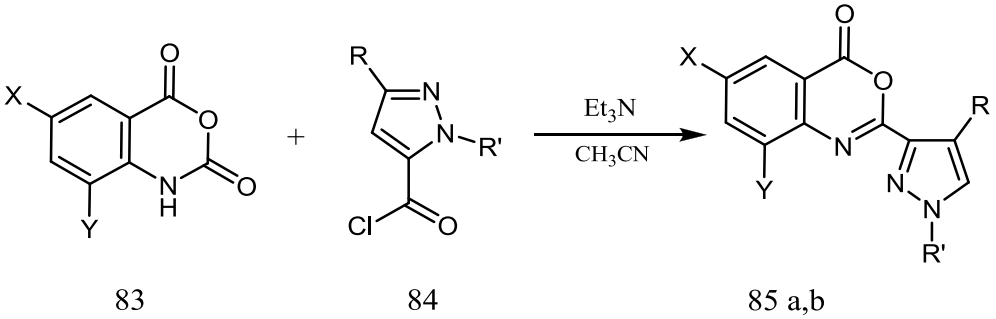
Likewise, refluxing a mixture of isatoic anhydride 78 and either cinnamoyl chloride or oxalyl chloride in pyridine/toluene solvent produces the 2-styryl analog 80 or the bis-3,1-benzoxazin-4-one 81 [166]. If the reaction with oxalyl chloride carried out in benzene using anhydrous aluminium chloride or 4-(dimethylamino)pyridine as an additive, the 2- chloroformyl derivative 82 is isolated [301].

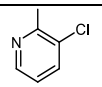


Isatoic anhydride also reacts with acid chlorides at elevated temperature to give 3,l-bezoxazin-4-one. Thus, heating compound 78 and benzoyl chloride results the 2- phenylbenzoxazinone 1a [142, 143].

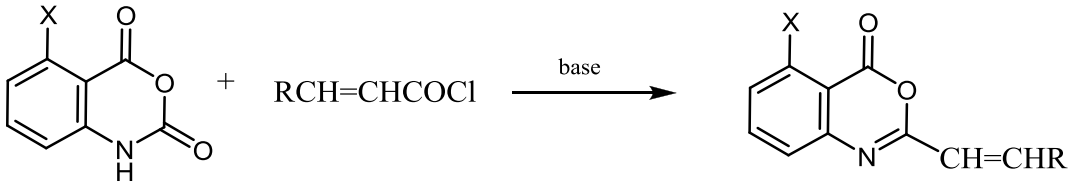


Coupling of trifluoromethyl-substituted isatoic anhydride 83 with pyrazole acid chlorides 84 affords benzoxazinones 85 in modest yield.



	X	Y	R	R’	Ref.
a	CF_3	Me	OCR_3, CF_3, Br, Cl, OCF_2H, OCH_2CF_3		[192]
B	H	H	CF_3	C_6H_5	[191]

Condensation of isatoic anhydride 86 with 3-substituted-acryloyl chloride 87 under basic condition yields the arylvinyl-4H-3,1-benzoxazin-4-ones 88 [293].

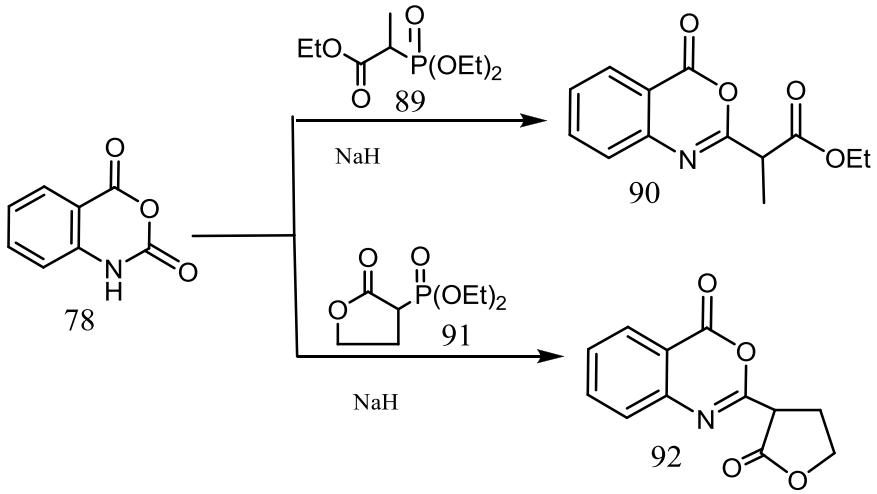


86 87 a,b 88 a,b

	X	R
a	H	Ph, $CH_3.C_6H_4(4)$, $OCH_3.C_6H_4(4)$, CI $.C_6H_4(4)$, $Br.C_6H_4(4)$, $(OCH_3)_2.C_6H_3(2,4)$, $C_4H_3O(2)$
b	Cl	Ph, $CH_3.C_6H_4(4)$, $OCH_3.C_6H_4(4)$

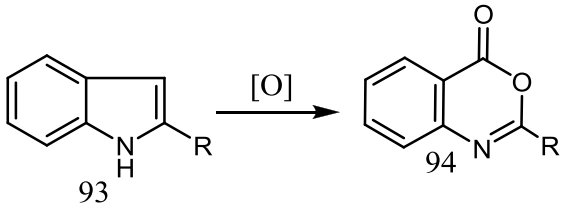
2.4.3 Reaction of isatoic anhydride with phosphoryl- stabilized anions

Reaction of isatoic anhydride 78 with phosphoryl-stabilized anions bearing no α-hydrogen atoms led to the formation of 3,1-benzoxazin-4-one. Consequently, when compound 78 is allowed to react with the anion of ethyl2-diethylphosphonopropanoate (89) or α-diethyl phosphono--butyrolactone 91 in benzene, it produces 90 and 92 respectively [204, 205].



2.5 Oxidation of indoles

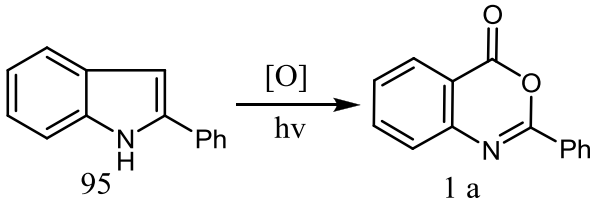
2-substituted indoles 93 were readily oxidized With m-chloroperoxybenzoic acid [55] or p-chloroperoxybenzoic acid [53] and the corresponding benzoxazinone 94 are produced.



93 94

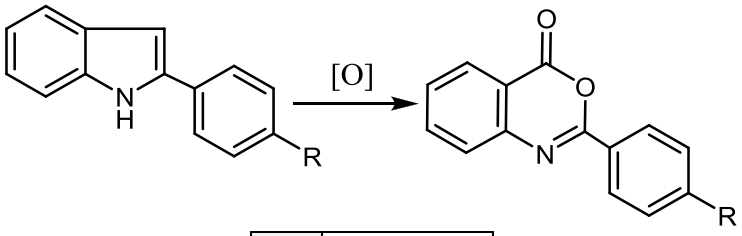
R= i-Pr, t-Bu, Ph, 2-pyridyl

A similar transformation is accomplished by the photooxygenation of 2-phenylindole 95 in methanol using Rose Bengal as a sensitizer [129].



95 1 a

In a closely related transformation, the oxidation of 2-phenylindolenin-3-one 96 with m-chlorobenzoic acid in chloroform affords 1a [259]. Whereas, oxidation of 4-dimethylamino analog 97 with hydrogen peroxide in N,N-dimethylformamide furnishes 98 [10].

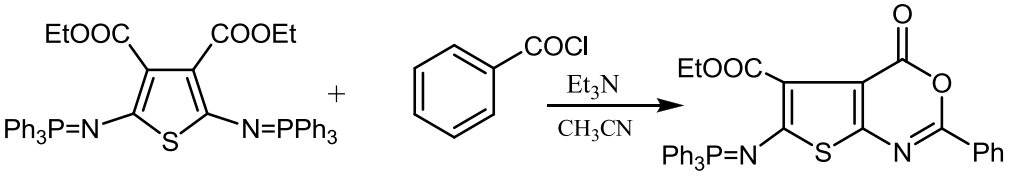


	R
1a	H
96	H
97	NMe_2
98	NMe_2

2.6 Miscellaneous

2.6.1 From β-(Triphenylphosphoranylidene)amino esters

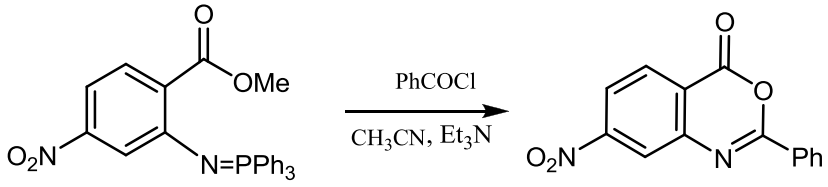
β-(Triphenylphosphoranylidene)amino ester derivative 99 is treated with 1 equivalent of benzoyl chloride and triethylamine in acetonitrile and the oxazinone derivative 100 is generated [314].



99 100

2.6.2 From iminophosphorane

Similarly, treatment of iminophosphorane 101 with benzoyl chloride in acetonitrile in the presence of small excess of triethyl amine yielded 7-nitro-2-phenyl- 4H-3,1-benzoxazin-4-one (102) [314].

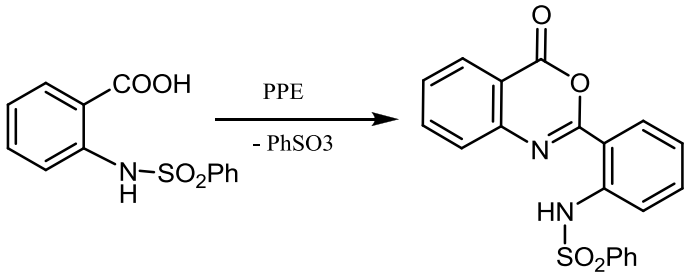


101 102

This reaction is used for the production of heteroannulated 3,1-benzoxazin-4-ones, where the benzene ring is replaced with thiophene, thiazole, and pyridazine [314].

2.6.3 From N-benzenesulphonylanthranilic acid

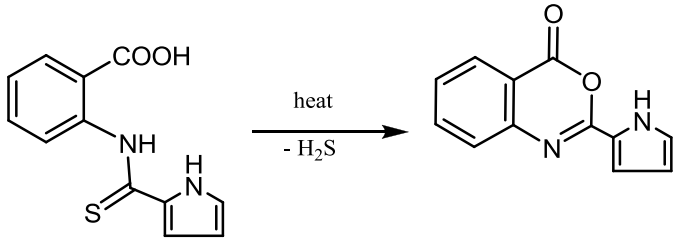
The self condensation of 2-molecules of N-benzenesulphonyl anthranilic acid 103 in polyphosphate ester (PPE) results in the formation of 2-substituted phenyl-4H-3,1-benzoxazin-4-one 104 [312].



103 104

2.6.4 From thioamide derivatives

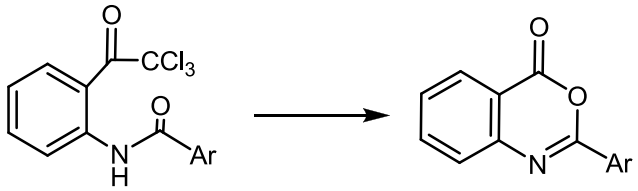
Heating thioamide derivative 105 in refluxing t-butylbenzene causes cyclization to occur with loss of hydrogen sulphide and produces 2-pyrrolyl-4H-3,1- benzoxazin-4-one 106 [195].



105 106

2.6.5 From electrochemical trichloroacetylanilides

The electrochemical reduction of several o-trichloroacetylanilides, 2-$CCl_3CO.C_6H_4.NHCOAr$ (Ar =Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$), on mercury pool in acetonitrile, yields 4H-3,1-benzoxazin-4-ones 107 [216].

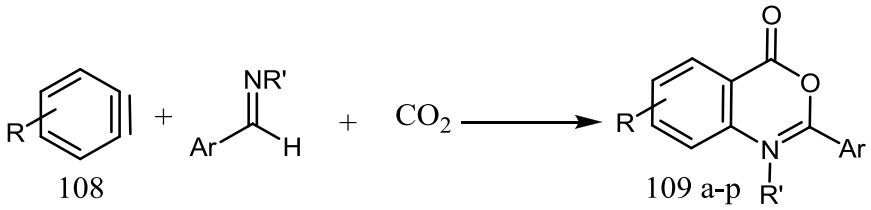


107

Ar= Ph, $C_6H_4.CH_3(4)$, $C_6H_4.OCH_3(4)$

2.6.6 CO_2 Incorporation reaction using arynes

The CO_2 incorporation reaction based upon three component assembly by the use of arynes and imines produced benzoxazinones 109 . The reaction carried out by in situ generated benzyne 108 which reacted with aryl imines under a CO2 atmosphere (1 atm) [323].



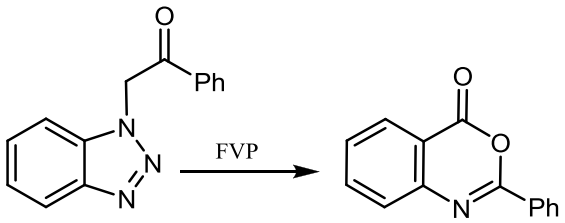
108 109 a-p

	R	R’	Ar
a	4- CH_3	Me	2,4,6-$(CH_3)_3.C_6H_2$
b	4-F	Me	2,4,6-$(CH_3)_3.C_6H_2$
c	6- CH_3	Me	2,4,6-$(CH_3)_3.C_6H_2$
d	3- OCH_3	Me	2,4,6-$(CH_3)_3.C_6H_2$
e	4,5- $(CH3)_2$	Me	2,4,6-$(CH_3)_3.C_6H_2$
F	3,6- $(CH_3)_2$	Me	2,4,6-$(CH_3)_3.C_6H_2$
g	H	H	2,4-$(CH_3O)_2.C_6H_3$
h	H	H	2,4-$(CH_3)_2.C_6H_3$
i	H	H	4-$(CH_3O).C_6H_4$
j	H	H	C_6H_5
k	H	H	1-naphthyl
l	H	H	2-thienyl
m	H	H	4-$CF_3.C_6H_4$
n	H	Bn	4-$CH_3O.C_6H_4$
o	H	n-Bu	H
P	H	i-Pr	H

2.6.7 From 2-(1H-1,2,3-benzotrizol-1-yl)phenylethanone

Homogenous flash vacuum pyrolysis reaction of 2-(1 H-1,2,3-benzotriazol-1 -yl)phenyl ethanone is considered as one-pot synthesis of 2-phenyl-4H-3,1

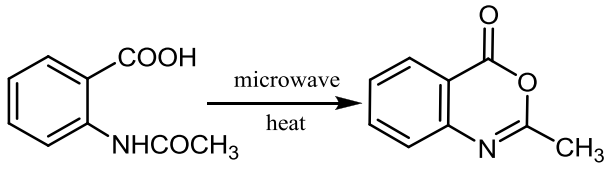
benzoxazin-4-one (1a). Where the benzotriazole underwent acyl migration followed by elimination of diazomethane and rearrangement of the intermediate formed [218].



1 a

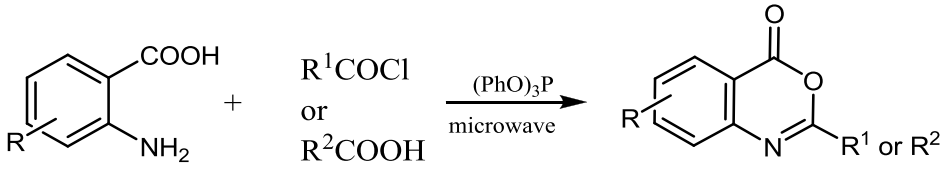
2.6.8 From heating of acetylanthranilic acid by microwave

The benzoxazinone 1b was obtained via heating of acetylanthranilic acid under microwave heating conditions [300].



1 b

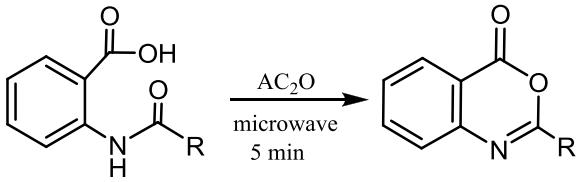
On the other hand, the 4H-3,1-benzoxazin-4-one derivatives 110 can be obtained via applying optimized microwave reaction conditions to a variety of anthranilic acids and both acyl chlorides (R^1COCl) and carboxylic acids (R^2CO_2H) in the presence of the coupling reagent triphenyl phosphite [193].



110

R	R^1	R^2
H	Ph	Ph
H	$C_4H_3O(2)$	Bn
H		$(CH_3)_3CH$
H		C_3H_5
H		Et
4- Me		Me
4-Cl		$(CH_3)_2CHCH_2$
2-amino nicotinic acid		Ph

A fast synthesis of 2-substituted-4H-3,1- benzoxazin-4-one 112 is achieved from the reaction of acetic acid anhydride with 2-acylaminobenzoic acid 111 under microwave and solvent-free conditions [251].

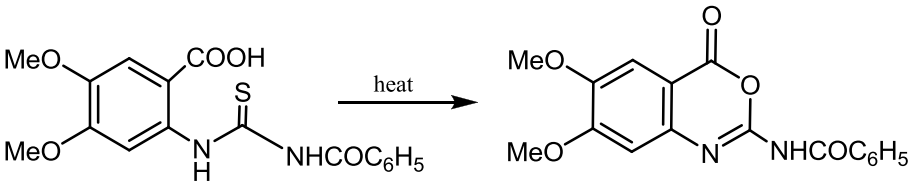


111 112

R = n-Pr, Ph, -CH=CH-Ph

2.6.9 Thermolysis of 2-(3-benzoylthioureido)-4,5-dimethoxy benzoic acid

2-benzoylamino-6,7-dimethoxy-4H-3,1-benzoxazin-4-one (113) is prepared by thermal treatment of benzoic acid derivative [138].

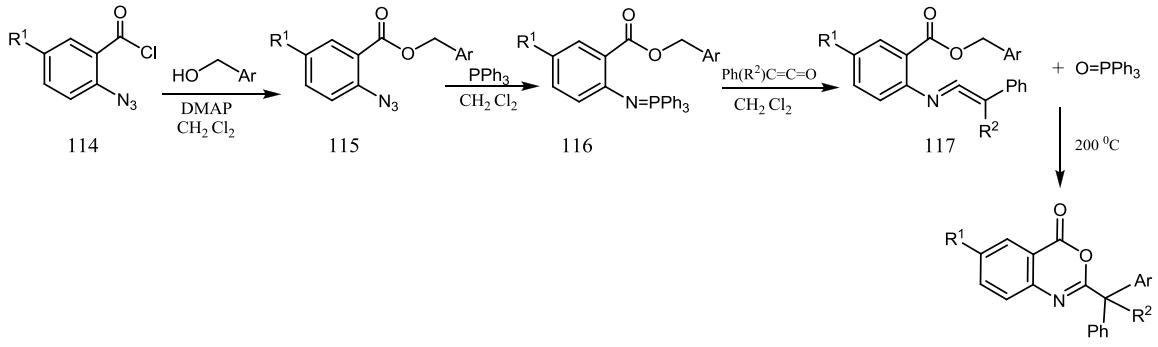


113

The inactivation of Chymotrypsin and human Leukocyte elastase by compound 113 is reported [138].

2.6.10 Thermally induced cyclization of ketenimines

4H-3,1-benzoxazin-4-one 118 is prepared based on the thermally induced cyclization of N-(2-benzyloxycarbonyl)phenyl keter.imines 117, generated from the interaction of 2-azidobenzoyl chlorides 114 with benzylic alcohols [13].



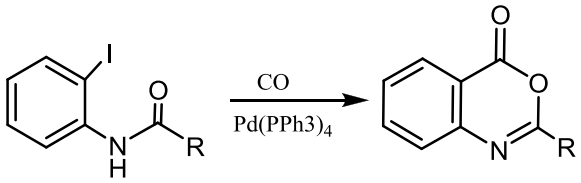
114 115 116 117 118

R^1	R^2	Ar
H	Me	4-MeC_6H_4
CI	Ph	4-OMe C_6H_4
		3,4-$(OMe)_2C_6H_4$
		3,5-$(OMe)_2C_6H_4$

2.6.11 From o-iodoaniline

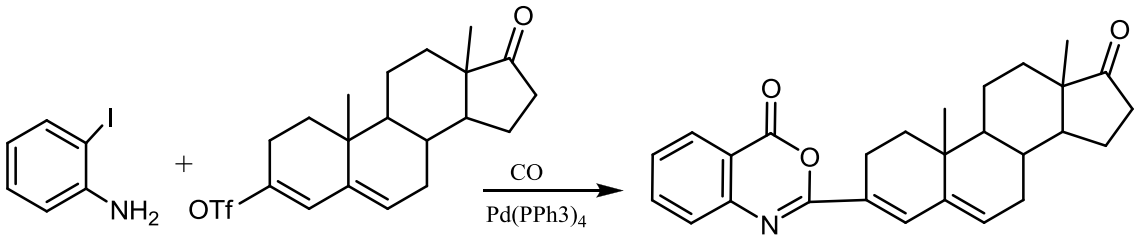
In all the syntheses of 4H-3,1-benzoxazin-4-ones presented so far the common scenario begins with materials which have the amine and carbonyl carbon

(which will ultimately become the 1- and 4-positions of the product) already positioned appropriately on the benzene ring. An alternate strategy takes advantage of carbonylation methodology which allows for the attachment of the carbonyl function onto a simpler aniline derivative. This is elegantly demonstrated by the reaction of an o-acylamidophenyl iodide 119 in the presence of potassium carbonate and palladium catalyst under an atmosphere of carbon monoxide which produces the benzoxazinone derivatives 120 [59].



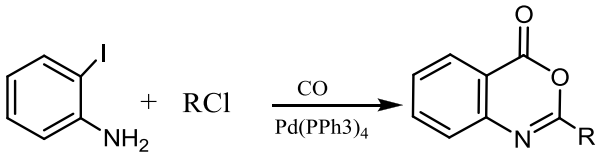
119 R= Me, Et, Ph 120

A three-component reaction, using o-iodoaniline as the aromatic anchor, an aryl iodide or vinyl triflate (as precursors of the substituent at 2-position), and carbon monoxide to supply the 4-carbonyl, allows access to a variety of 2-aryl or 2-vinyl-4H-3,1-bezoxazin-4-ones [59]. A good example of this methodology at work is the reaction of o-iodoaniline with triflate 121 to give the steroidal benzoxazinone 122.

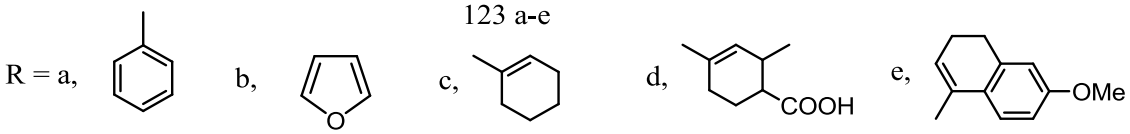


121 122

Similarly, employing o-iodoaniline as building- block, unsaturated halides are used as percursors of the substituent at 2-position of oxazinone nucleus, and carbon monoxide in the presence of potassium carbonate and catalytic amount of $Pd(PPh_3)_4$. Such a process can be easily fulfilled to afford 4H-3,1-benzoxazin-4-one derivatives 123 containing an unsaturated unit, linked to C-2 [22].



123 a-e



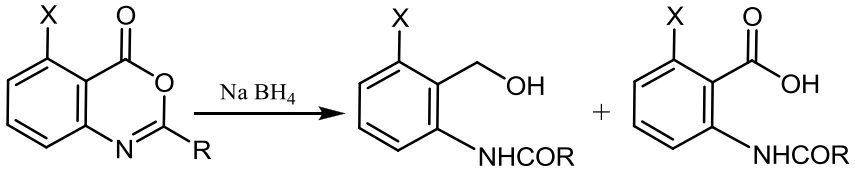
3. Reactions of 4H-3,1-benzoxazin-4-ones

4H-3,l-benzoxazin-4-one derivatives can be considered as semi-acid anhydrdes formcd by cyclodehydration of acylanthranilic acids. They undergo many reactions of true acid anhydrides, but at slower rate [117].

Electrophilic reactions on the benzene ring of the benzoxazinone nucleus are rare and are probably unnecessary due to the plethora of diversely substituted anthranilic acids which are available. We will concern on the remaining reactive sites and feature the reactions at the C-4 and C-2 carbons of our heterocycle.

3.1 Reactions with Hydrogen nucleophiles

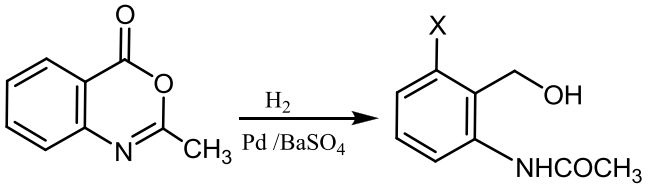
Benzoxazinone nucleus is susceptible to attack by hydride reagents as sodium borohydride and tend to give varying mixture of 2-acylaminobenzyl alcohol 124 and N-alkylanthranilic acid 125 [24].



124 125

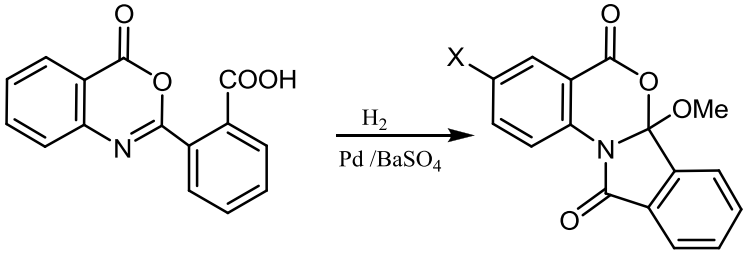
R = Me, t-Bu, CF3, Ph, styryl, 2-thienyl

In contrast, catalic hydrogenation of 2-methyl-4H-3,1-benzoxazin-4-one (1b) in acetic acid affords only N-acetyl toluidine 126 [56].



1 b 126

Similary, hydrogenation of benzoxazinone 5a under neutral conditions resulted in the initial reduction of C=N bond then cyclization with o-carboxylic acid group and furnished the tetracycle 127 [56].

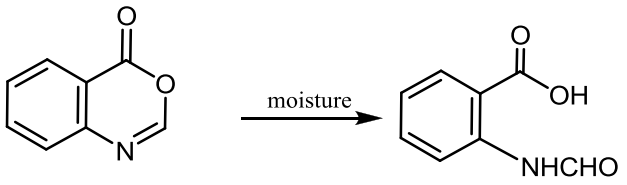


5 a 127

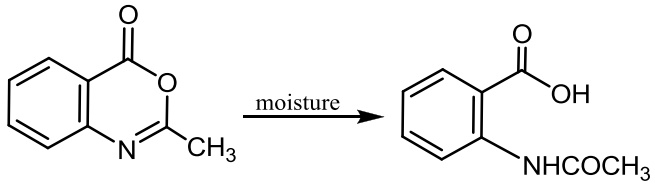
3.2 Reactions with Oxygen nucleophiles

The simplest and sometimes the most unwanted reaction of some 4H-3,1-benzoxazin-4-ones is hydrolysis. Where, the 4H-3,1-beoxin-4-ones are exceedingly labile to hydrolysis and the initial cleavage to N-acylanthranilic acids parallels that of benzoxazoles to acylarninophenol.

However, their sensitivities to hydrolysis vary greatly. 4H-3,1Benzoxazinone (formanthranil) 128 and acetanthi-anil lb undergo cleavage by atmosphere moisture. The higher 2- alkylbenzoxazinoes are increasingly stable and the 2-aryl/and 2-styrylbenzoxaziones can be handled without special precautions [75].



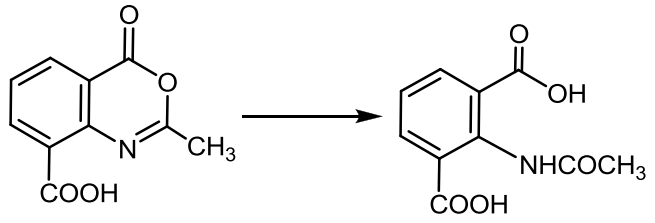
128 129



1 b 130

Kinetic studies for hydrolysis of 4H-3,1 bcnzoxin-4-one in dilute buffers at 0.1 M ionic strength and D_2O was reported. The bases in the buffers were catalysts Sand the second order rate constants obeyed a Bronsted relation with isotope effect on the OH term. Hydrolysis under acidic and basic conditions in O-enriched H_20 indicated attack at C_2 and C_4, respectively. R-substituted 2-phenyl-4H-3, 1 -benzoxazin-4-one (R=H, p-Br, p-Me, p-MeO) showed Hammett p values under acidic and basic conditions (-0.38 and +0.71). Strong acid media inhibited hydrolysis of the phenyl and p-MeO derivatives in accordance with extensive protonation of N_1 and a lowering of the H_2O activity with the increased acidity [320].

Incorporation of a carboxylic acid at 8-position allows intramolecular protonation of N_1, which enhances susceptibility attack at C-2 and/or C-4 [80].



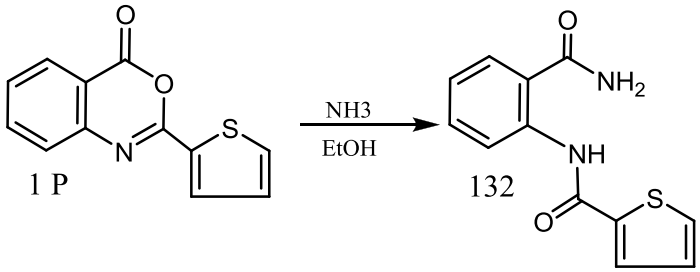
20 131

3.3 Reactions with nitrogen nucleophiles

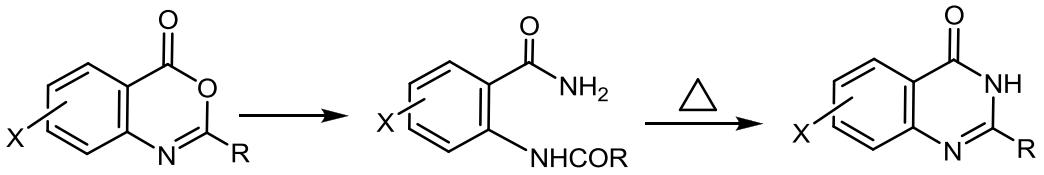
Reaction of 4H-3,1-benzoxazin-4-ones with amines is the most interesting, because of the wide range of heterocycles that can be produced either directly or through further transformations of the initially formed products.

3.3.1 Ammonlysis

The interaction of 4H-3,1-benzoxazin-4-one derivative 1p with ammonia in ethanol produces compound 132 [76].



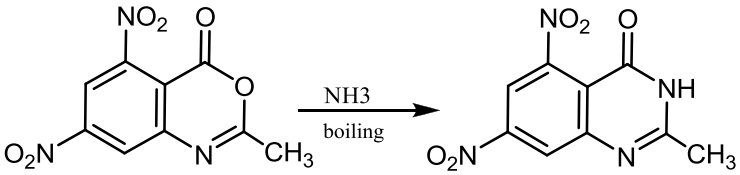
Ammonia (The simplest of amines) or ammonium hydroxide, when allowed to react with benzoxazinone deriative 133 over a period of 1-3 hours, the anthranilamide 134 is produced in good yield [233,230,317]. This in turn, can be cyclized to 3-unsubstituted-4(3H)-quinazolone 135 under thermal conditions (240-280 ^{0}C) or with acetic anhydride. quinazolone can also be produced after longer reaction times with ammonium hydroxide (6-24h.) [199,233,230] or by heating with formamide (170-175°C) [120, 119] or ammonium acetate at 130-135°C [37,169].



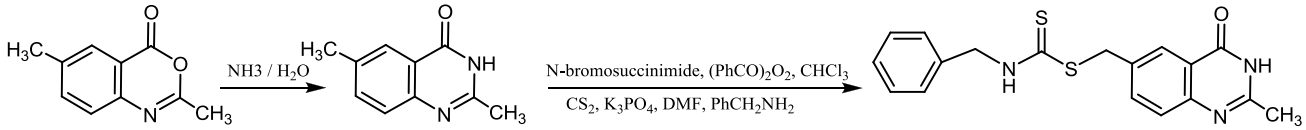
X= H ,Cl ,Br ,Me

R = alkyl ,PhY (Y =Br ,NHMe) ,CH_2CN

Boiling 4,6-dinitro-2-methyl-4H-3,1-benzoxazin-4-one (22) with aqueous ammonia; suffered recyclization into the corresponding quinazolone derivative 136 [177].

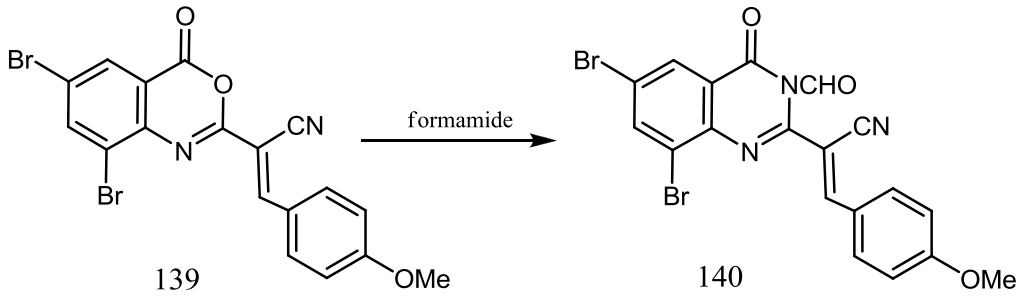


2,6-Dimethyl-4(3H)-quinazolinone (137) is produced via interaction of 2,6-dimethyl benzoxazinone $1z_{12}$ with 25% aqueous ammonia in ethanol at room temperature for 48 hours. The obtained quinazolone 137 is converted to an interesting 6-substituted quinazolone derivative 138, which is known as a Cytotoxic active compound [61].



1 z_{12} 137 138

In contrast, 4H-3,1-benzoxazin-4-one derivative 139 is formylated on treatment with excess of formamide and yielded the N-formyl-quinazolinone derivative 140 [108].

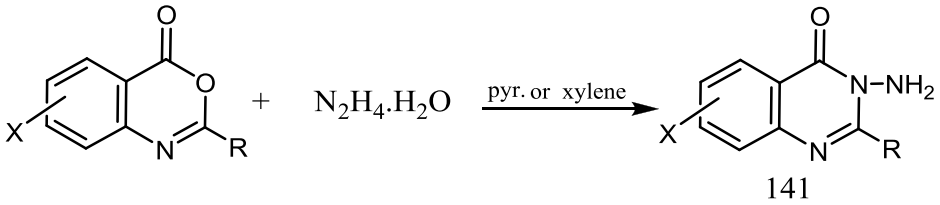


139 140

3.3.2 Hydrazinolysis

3.3.2.1 Reactions with hydrazine hydrate

Heating 4H-3,1-benzoxazin-4-ones in neat hydrazine hydrate or in pyridine or xylene solutions produces the 3-amino-4-quinazolones 141 [57,26, 306, 305, 185, 270,271, 208, 78, 283].

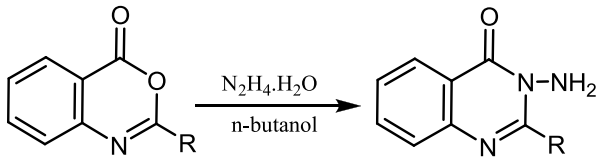


141

X=H, halo, Me, NO_2
R=Me, Et, i-Pr, CF_3, Ph, 2-furyl

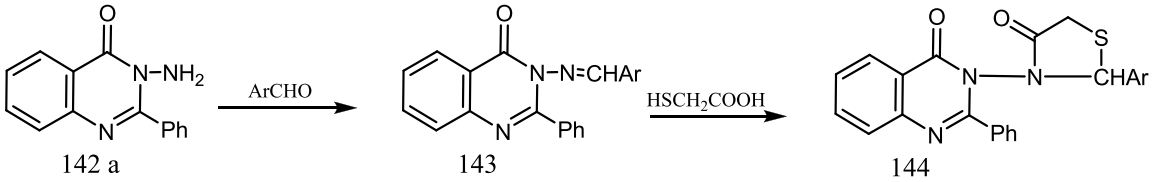
It was found that, cyclization on both nitrogens of the hydrazine to form a 1,3,4-benzotriazepin-5-one is not observed [305].

Similarly, heating benzoxazinone derivatives 1a,b with hydrazine hydrate in n-butanol afford 3-aminoquinazolone derivatives 142 [211,210,158].



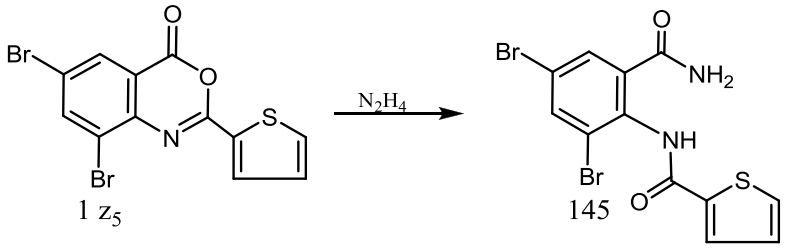
142 a,b

The quinazolone 142a is reacted with aromatic aldehydes and produces the corresponding benzylidene aminoquinazolinone derivatives 143, which in turn cyclized to thiazolone derivative 144 by its interaction with thioglycolic acid [158].



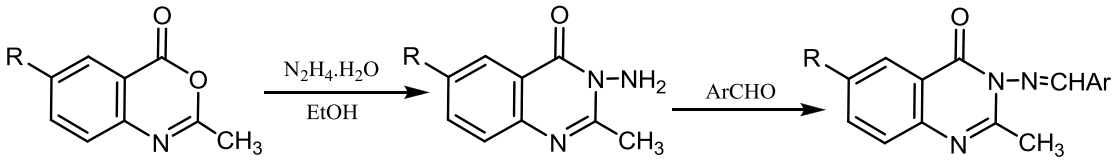
142 a 143 144

On the other hand, treatment of the benzoxazinone derivative $1z_5$ with hydrazine hydrate in ethanol affords the (thienoylamino) dibromobenzamide 145 [162].



1 z_5 145

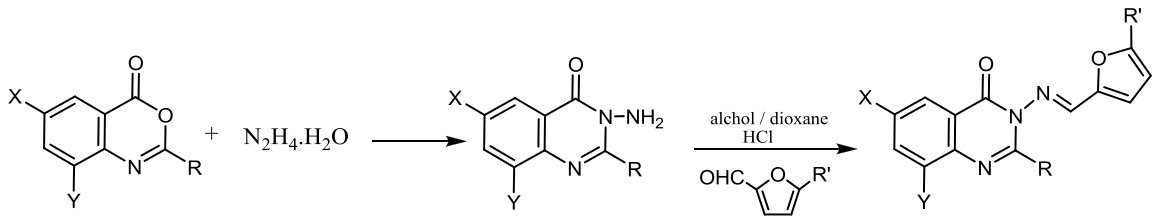
Compounds 1b and 1c undergo heteroring opening with hydrazine and give 2-methyl-3 -amino-4(3H)-quinazolone. Compounds 146 condensed with aromatic and aldehydes and give 2-styryl-3-benzyiidene imino-4(3H)-quinazolone derivatives 147 (Ar=phenyl, substituted phenyl R=H, Br) [29].



1 b or 1c 146 147

R =H ,Br

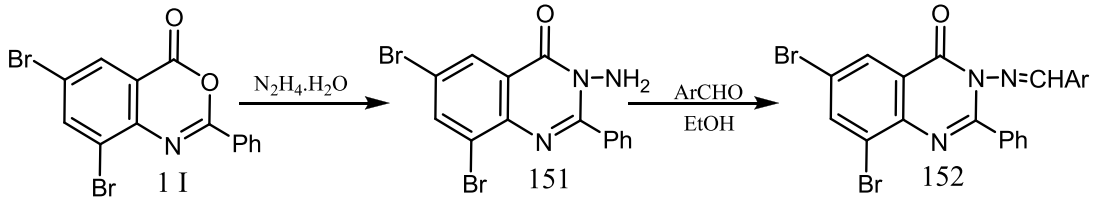
Condensation of substituted 4H-3,1-benzoxazin-4-ones 148 with hydrazine hydrate produce 3-amino-substituted quinazolinone 149. This compounds 149 treated with furan-2-aldehydes in the presence of acid catalyst forming substituted-furyl-quinazolin-4(3H)-ones 150 [254].



148 149 150

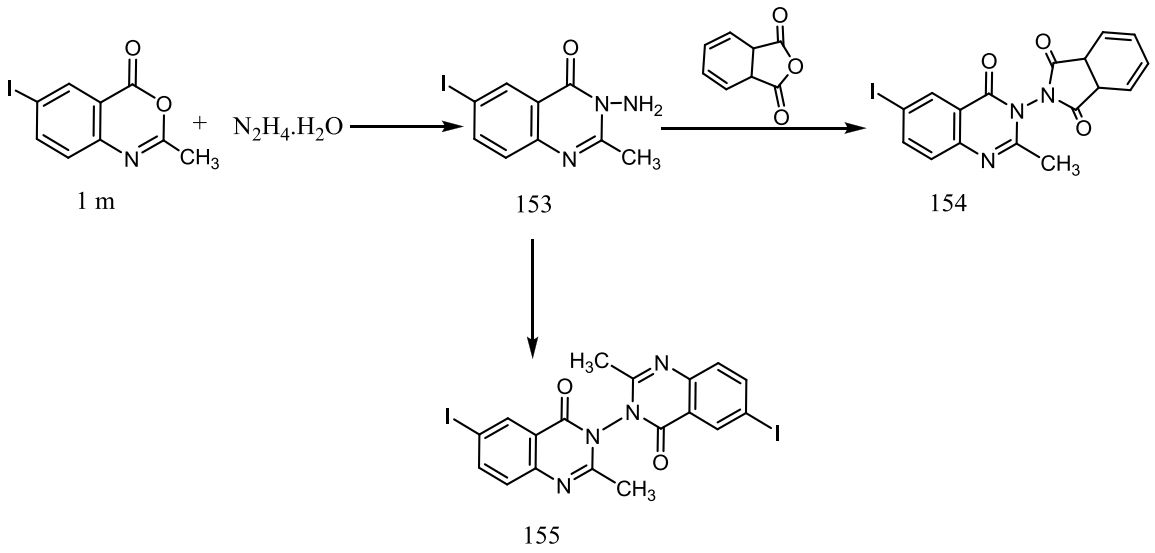
X/Y =H,Br & R =Ph, Me, n-Pr & R’ =H, Me, NO_2

A series of novel hydrazones 152 are synthesized by condensation of 3-amino-6,8-dibromo-2-phenylquinazolin-4(3H)-ones 151 with different aromatic aldehydes via cyclized intermediate 6,8-dibromo-2-phenyl-4H-3,1-benzoxazin-4-one(11). The obtained hydrazones 152 are screened for its Antimicrobial activity [242].

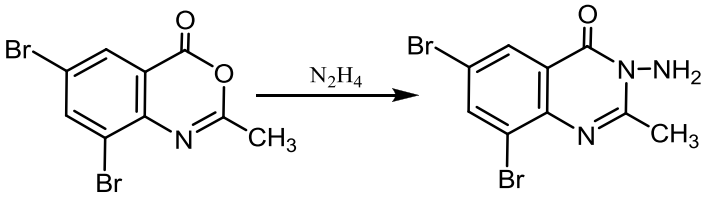


Ar = Ph, $C_6H_4.OCH_3(4)$, $C_6H_4.OH(2)$, $C_6H_4.N(CH_3)_2(4)$, $C_6H_4.NO_2(3)$, $C_6H_4.CH_3(4)$, $C_6H_4.OH(4)$, $C_6H_4.Cl(4)$, $C_6H_4.NO_2(4)$, $C_6H_2(OCH_3)_3(3,4,5)$, $C_6H_3.OH(4).OCH_3(3)$, -CH=CHPh

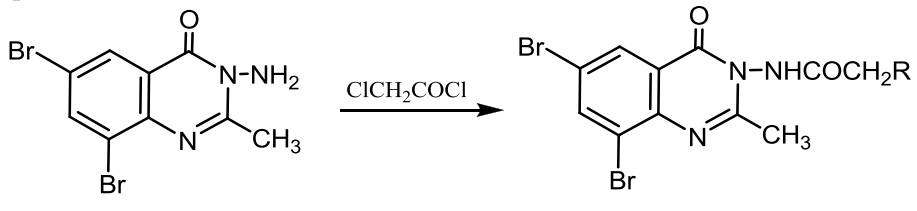
Also compound 1m reacts with hydrazine hydrate in ethanol and yields aminoidometyl quinazolone 153, which reacts with phthalic anhydride and gives phthalimidoquinazolinone 154. And with a second molecule of 6-iodo-2-methyl-4H-3,1-benzoxazin-4-one 1m yields4-oxoquinazolinylquinazolinone 155 [213].



6,8-Dibromo-2-methyl-4H-3,1-benzoxazin-4-one (1j) reacts with hydrazine hydrate in ethanol and gives 3-amino- 6 ,8-dibromo-2-methyl-4(3H)-quinazolinone (156) [270,271].



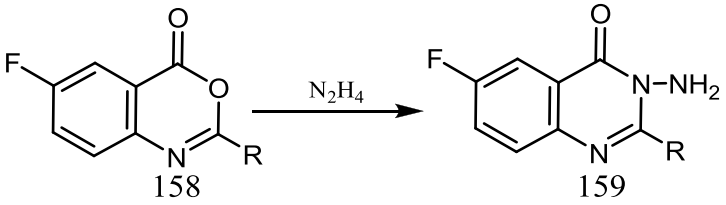
Compound 156 reacts with chloro acetyl chloride and gives N-chloroacetyl quinazolinone derivative 157a [270,271].



a	R=Cl	e	R=Et_2N
b	R=BuS	f	R=morpholinyl
c	R=t-BuS	g	R= piperidinyl
d	R=Me_2N	h	R= N^4 phenylpiperazinyl

Compounds 157b-h are prepared by eventual reaction of 157a with the appropriate mercaptan or secondary amines, are tested for lethal toxicity in mice, antifungal activity in vitro (Currularia lunata and Dreschlera halodis), Analgesic activity in mice and Antiflammatory activity in rats [270,271].

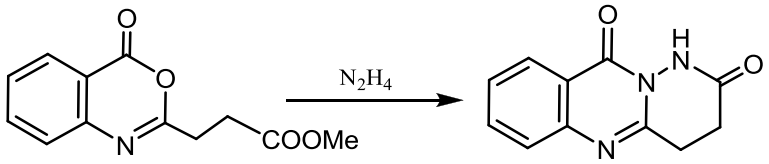
In similar way as mentioned above, 6-fluoro-2- substituted 4H-3,1-benzoxazine-4-ones 158 has reacted with hydrazine hydrate and compound 159 is generated [325, 327].



158 159

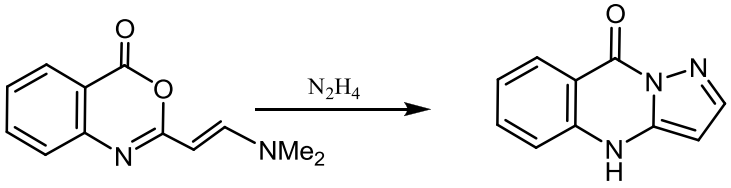
R = $PhCH_2CH_2$, Bn, Ph, 2-thiophenemethylene

4H-3,1-benzoxazin-4-ones with additional reactive functionalities at 2-position undergo further cyclization when exposed to hydrazine hydrate, and form a variety of interesting heterocycles 163-167.



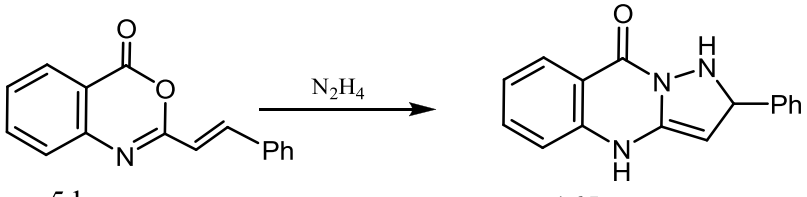
160 163

[38]



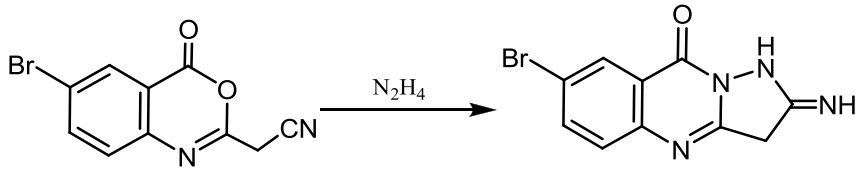
161 164

[46]



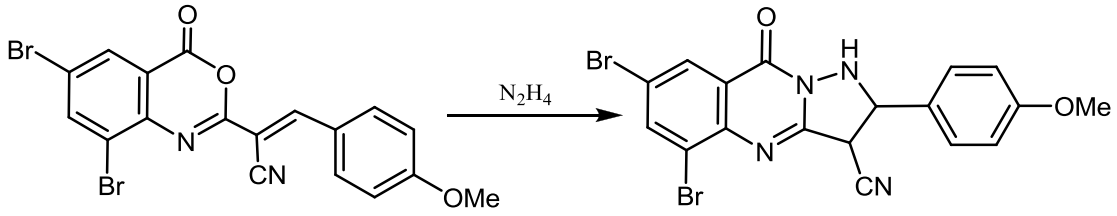
5 b 165

[169]



162 166

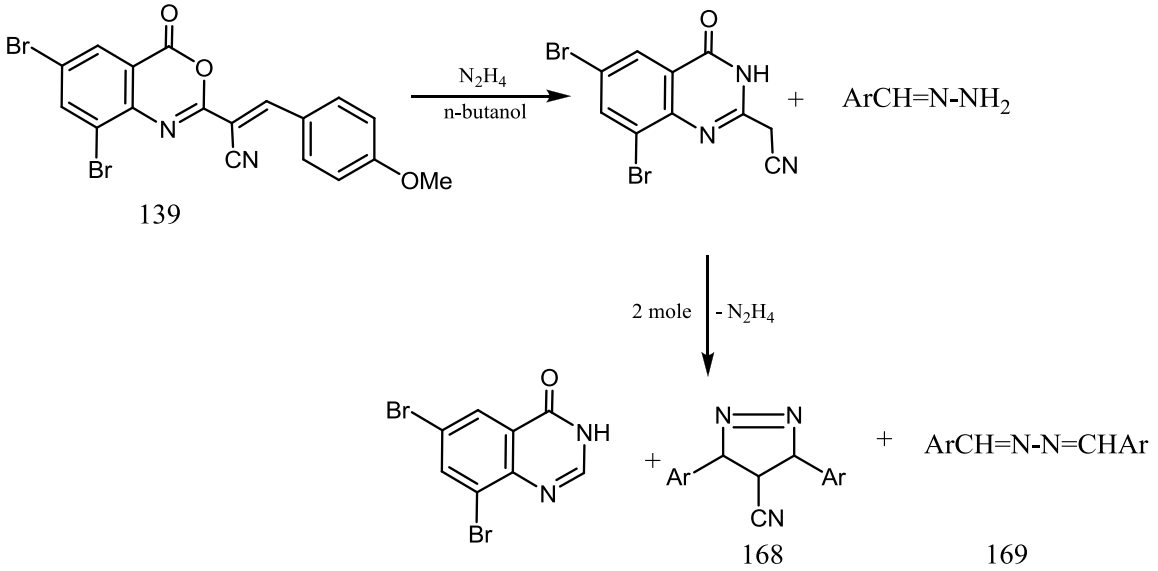
[16,17]



139 167

[108]

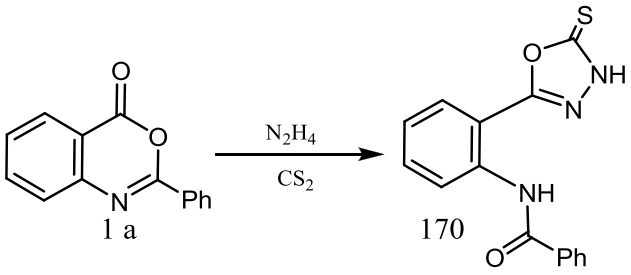
On the other hand, when the reaction of 4H-3,1- benzoxazin-4-one 139 with hydrazine hydrate is conducted in n-butanol, a mixture of 3,5 -bis-(4-methoxyphenyl)-1H-pyrazole-4-carbonitrile (168) and N,N-bis-(4-methoxybenzylidene)hydrazine (169) is obtained [108].



Ar = $C_6H_4.OCH_3(4)$

3.3.2.2 Reaction with hvdrazine hydrate in presence of carbondisulphide

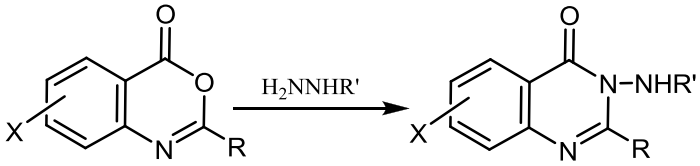
When the reaction of 4H-3,1-benzoxazin-4-one 1a with hydrazine hydrate is conducted in the presence of carbon disulphide in alcoholic potassium hydroxide, the 1,3,4-oxadiazolin-5-thione 170 is produced directly [164].



1 a 170

3.3.2.3 Reaction with subsitituted hydrazines

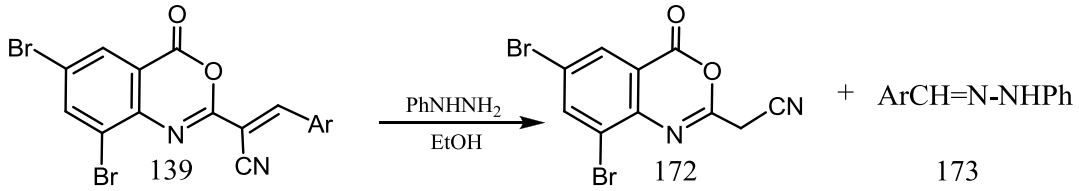
Substituted hydrazines react likewise in solvents such as benzene, pyridine, ethanol, or acetic acid to furnish 3-N-substituted quinazolone derivatives 171, where R can be phenyl [213], acyl [5], (C= XNHR (X= O or S) [158], and others [9,299].



171

R=Me, Et, i-Pr, CF3, Ph, 2-furyl
R'=Ph, CH_3CO, CONHR,CSNHR

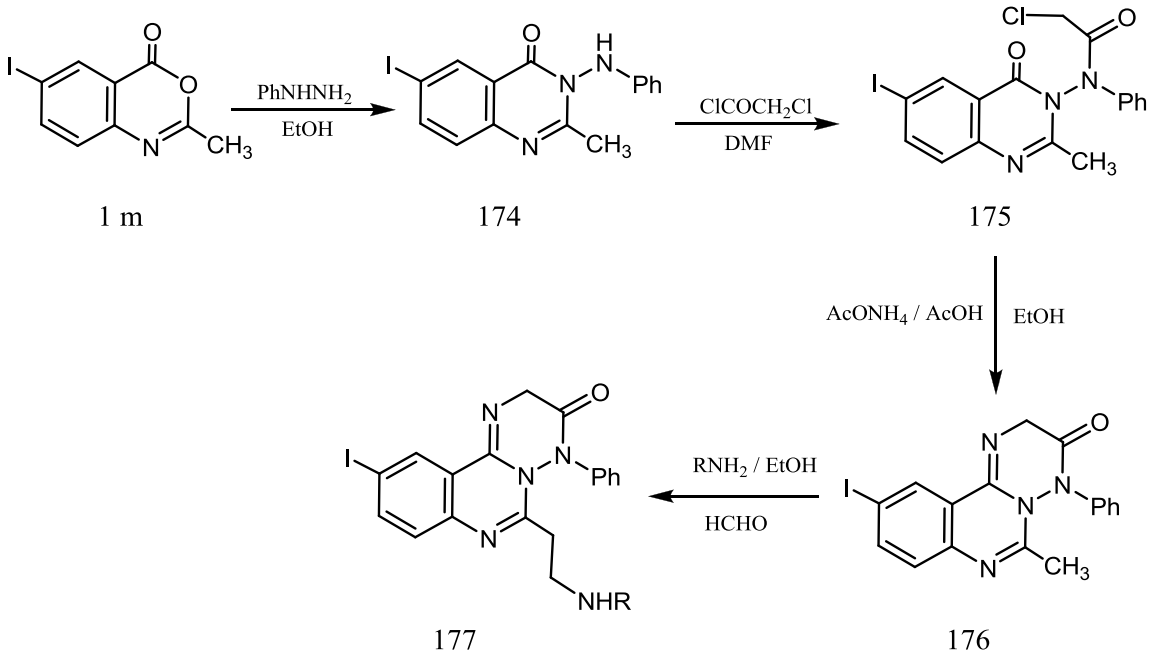
4H-3,1-benzoxazin-4-one 139 is reacted with phenyl hydrazine in the same manner like reaction with hydrazine hydrate, it gives a mixture of carbonitrile 172 and hydrazine derivative 173 [108].



139 172 173

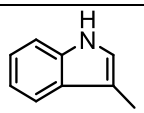
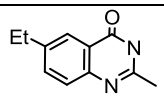
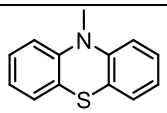
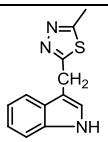
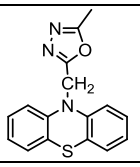
Ar = $C_6H_4.OCH_3(4)$

Hydrazinolysis of benzoxazinone derivative 1m using phenyl hydrazine furnishes the quinazolinone derivative 174. It is used in synthesizing some triazino-quinazoline derivatives 177 by introducing aromatic nuclei via Mannich reaction with arylamines [279].

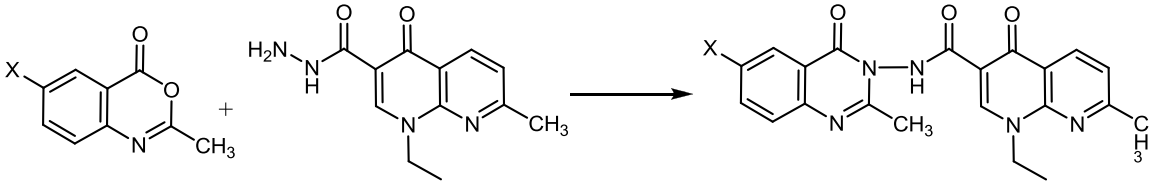


1 m 174 175

176 177

R						
						

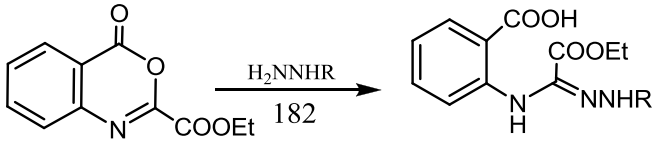
Interaction of 2-methyl-4H-3,1-benzoxazin-4-one derivatives 178 with nalidixic acid hydrazide 179 yield substituted 3,1-quinazol-4-one derivatives of nalidixic acid 180, which exhibited inhibitory activity against A. hydrophila [135].



178 179 180

X= H ,I ,NO_2

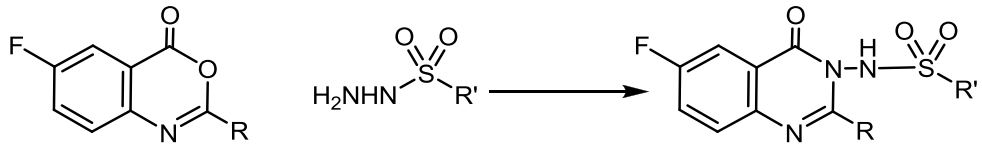
When 2-ethoxycarbonyl-4H-3,1-benzoxazine-4-one (181) treated with substituted hydrazines 182, the hydrazones 183 are isolated [229].



181 183

R= Ph, COPh, COpy.

Combining 4H-3,1-benzoxazin-4-ones 184 acid substituted sulphonylhydrazides 185 devoid of solvents, followed by heating at 160 °C (oil bath) gave compounds 186 as the major products [327].

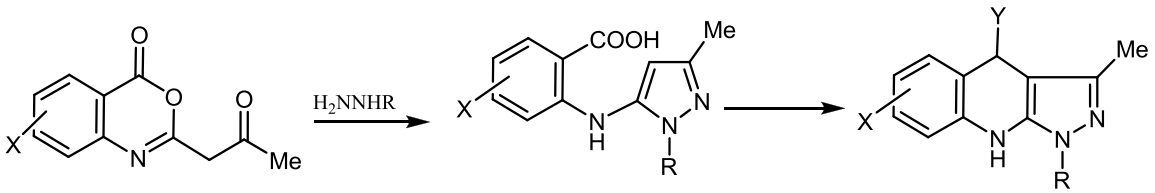


184 185 186

R = phenethyl, Bn, Ph, 2-thiophene-methylene

R= 4-COOH.Ph, 3-COOH,Ph, 4-NHCOMe.Ph, 4-OCF_3,Ph, 3,4-di-Cl.Ph, 4-CN.Ph, 4-Cl.Ph, Bn, 3-$N0_2$-4-Cl.Ph, 4-t.Bu, 2,4-di-Cl.Ph

Reactions of acetonyl benzoxazinones 61 with methylhydrazine or various phenylhydrazines affording the pyrazolyl anthranilic acids 187. Cyclization of these intermediates with a mixture of phosphours pentoxide and polyphosphoric acid providing the 4-hydroxypyrazolo [3,4- d]quinazoline 188 (Y= OH) [63,288], whereas cyclization with phosphours oxychloride gives the 4-chioro analog 188 (Y= Cl) [73,72].



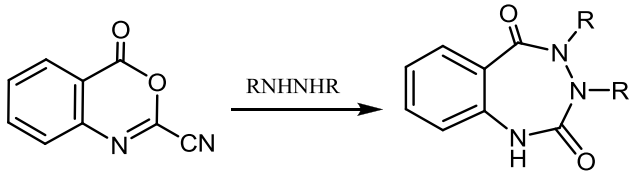
61 187 188

R = Me, Ph

X= H, Cl, I, Me, Et, OMe, CF_3, COOH, NO_2

Y= OH, Cl

Symmetrically disubstituted hydrazines are reacted with cyano derivative 189 with loss of HCN to produce 1,3,4- benzotriazepin-2,5-diones 190 [292].

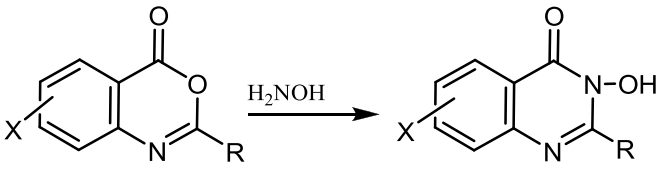


189 190

R= Me, Et, i-Pr

3.3.2.4 Reactions with hydroxylamine hydrochloride

Reaction of 4H-3,1-benzoxazine-4-one derivatives 191 with hydroxylamine hydrochloride in refluxing pyridine afford 3-hydroxy-4-quinazolinone derivatives 192 [50, 92,121, 161].



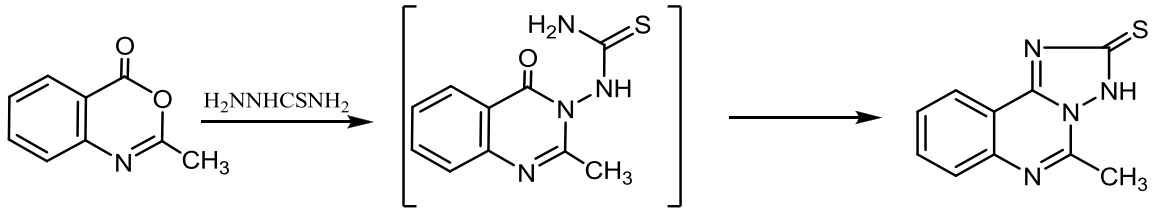
191 192

R=Mc, Et, i-Pr, CF_3, Ph, 2-furyl

X=H, halo, Me, NO_2

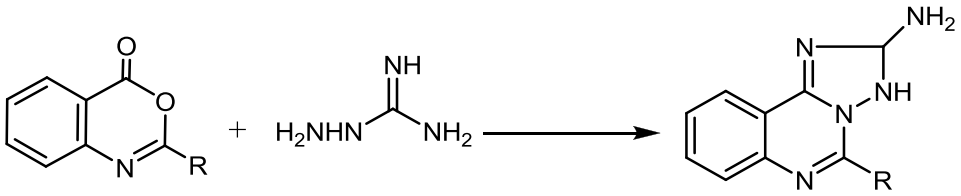
3.3.2.5 Reactions with thiosemicarbazide and aminoguanidines

If heating 2-methyl-4H-3,1-benzoxazin-4-one (1b) with thiosemicarbazide in acetic acid in the presence of fused sodium acetate, the conversion does not stop at the thiocarbamide intermediate 193 but continues to cyclodehydrate providing 194 [159].



1 b 193 194

In a similar fashion, refluxing 2- phenyl (or methyl)-4H-3,1-benzoxazin-4-ones (1a or 1b) with aminoguanidine in pyridine to afford the amino derivatives 195 [71].



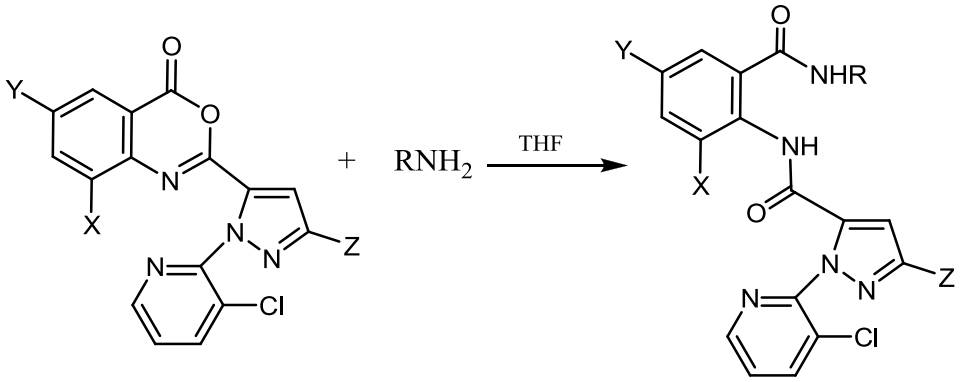
1b or 1a 195

R=Me,Ph

3.3.3 Aminolysis

3.3.3.1 Reactions with primary nonaromatic amines

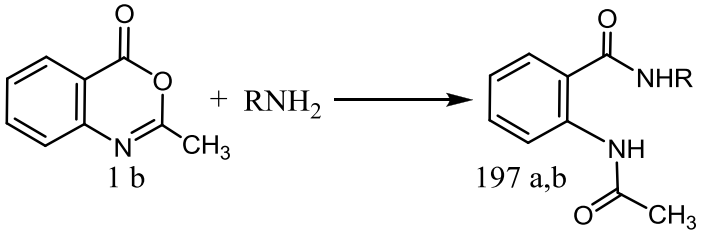
In many cases, acylanthranilamides are the products of the interaction of 4H-3,1-benzoxazin-4-ones with primary amines (due to the weak nucleophilicity of primary amines in comparison with aromatic amines and consequenly depend on the mode of attacking the benzoxazinone moiety).Reacion of 4H-3,1-benzoxazinone 36 with isopropyl amine and/or methylamine in THF produced the corresponding pyridylpyrazole anthranilic diamides 196. Compounds 196 have insecticidal potency and a Calcium mobilization threshold (CMT).



36 196 a,b

a; X= C1, Me	[190,192]
Y=H,Cl	
Z=CF_3	
R=i-Pr	
b ; X=CH_3	[191]
Y=H,Cl,Br,I,CF_3	
Z=Br,CI, CF_3, OCH_3, OCF_2H,	
OCH_2CF_3 R = Me, i-Pr	

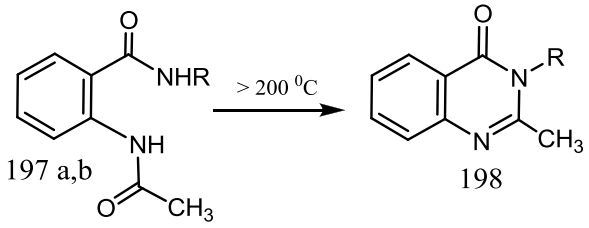
Reactions of 4H-3,1-benzoxazin-4-one 1b with isopropyl amine and/or t-butylamine produces N-acylanthranilamide 197 [114,118].



1 b 197 a,b

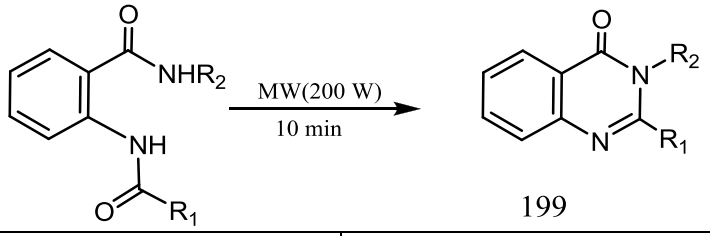
a, R= -$CH(CH_3)_2$ b, R= -$C(CH_3)_3$

N-acylanthranilamide 197 requires temperatures above 200 °C to affect cyclization into 3-substituted quinazolinone derivative 198 [115, 117].

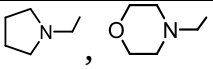


197 a,b 198

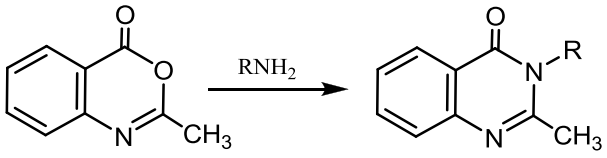
Instead of using high temperature to effect cyclization, microwave-assisted cyclocondensation is used to obtain 2,3-disubstituted quinazolinone 199 [179].



199

R1 = Me, Et	R2 = Me, n-Bu, Et_3N, 

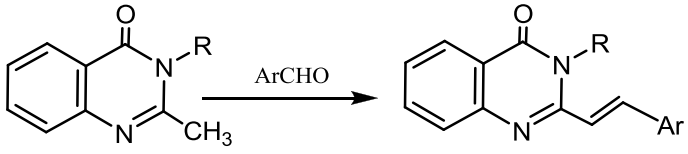
Simple straight-chain alkylamines as methyl and n-butyl amines react with benzoxazinone 1b to afford 3-substituted-4-quinazolinones 200 [207].



1 b 200

R = Me, n-Bu

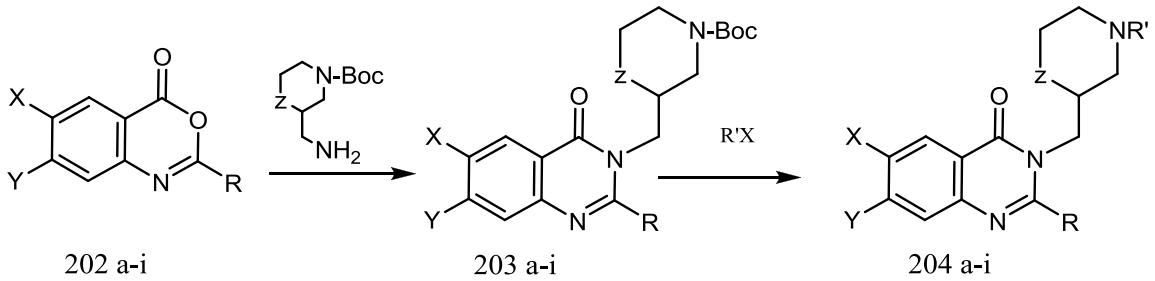
2-Methyiquinazolinone 200 can be easily homologated to styryl derivative 201 by refluxing it with an appropriate aldehyde [32].



200 201

R=Me, n-Bu Ar=Ph, naphthyl, 2-furyl

4H-3,1-benzoxazin-4-one 202 furnishing 3-substituted quinazolin-4(3H)-one 204 via insertion of Boc-protected aminomethylpiperidine or 3-aminomethylmorpholine, led to intermediate 203 which is deprotected and subsequently is alkylated using reductive amination or nucleophilic substitution conditions [261].

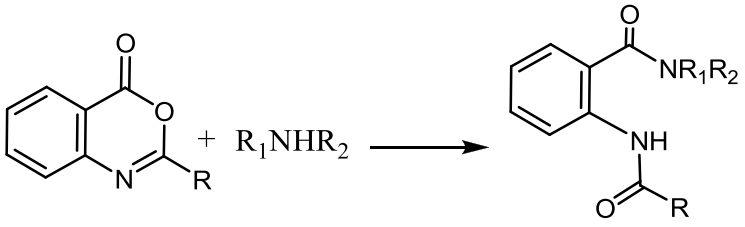


The compounds thus obtained are collected in the following table

	X	Y	Z	R	R’
a	$C_6H_4Cl(4)$	H	CH_2	$C_6H_4CH_3(2)$	Et,i-Pr, $(CH_2)_3CH$-, $(CH_2)_2OCH_3$, $(CH_2)_2F$, $EtCF_3$,n-Pr-CF_3
b	$C_6H_4Cl(4)$	H	CH_2	$C_6H_4OCH_3(2)$	Et
c	$F.C_6H_4$ (4)	H	CH_2	i-Pr	Et
d	H	H	CH_2	$C_6H_4CH_3(2)$	i-Pr
e	OCH_3	H	CH_2	$C_6H_4OCH_3(2)$	Et
f	OCH_3	H	CH_2	$C_6H_4CH_3(2)$	Et
g	$F.C_6H_4$ (4)	H	CH_2	$C_6H_4CH_3(2)$	H, i-Pr
h	Br	H	O	$C_6H_4CH_3(2)$	Bn, H, i-Pr
i	H	$C_6H_4Cl(4)$	CH_2	$C_6H_4OCH_3(2)$	Et

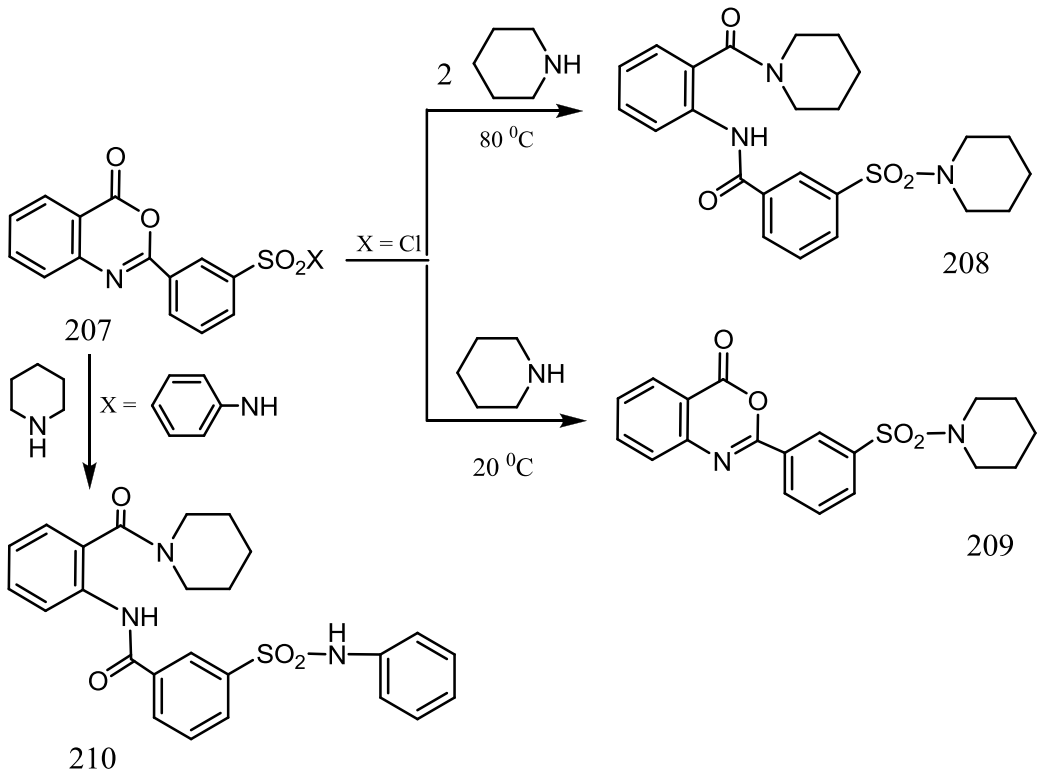
3.3.3.2 Reactions with secondary amines

In a similar fashion, as isopropyl and/or t-butylamines are reacted with 4H-3,1-benzoxazin-4-ones 205 and produce N-acylanthranilamides 206. Also secondary amines such as dimethylamine, morpholine, piperidine, and pyrrolidine are reacting and produce N-acylanthranilamides 206 [71].



205 206

4H-3,1-benzoxazin-4-ones 207 with sulphonyl group introduced at 2-position are reacting with piperidine under differenet reaction conditions leading to 208-210. It gives an idea about the extent of the reactivity of the benzoxazinone fragment, where the chlorosulphonyl group is more reactive than the benzoxazinone fragment toward amines [294].

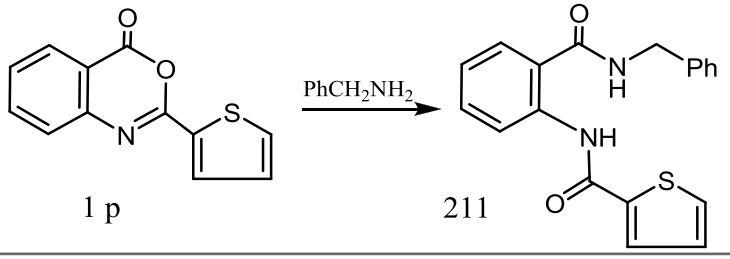


207 208 209 210

3.3.3.3 Reactions with alkylamines

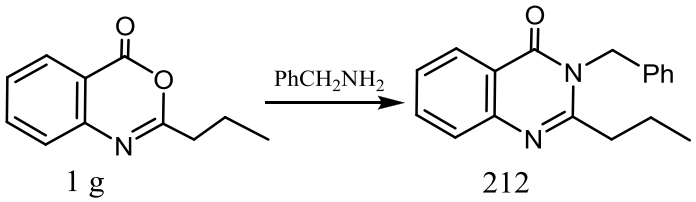
3.3.3.3.1 Reactions with benzylamine

Treatment of benzoxazinone 1p with benzylamine in ethanol affords N-acylanthranilamides 211 [76].

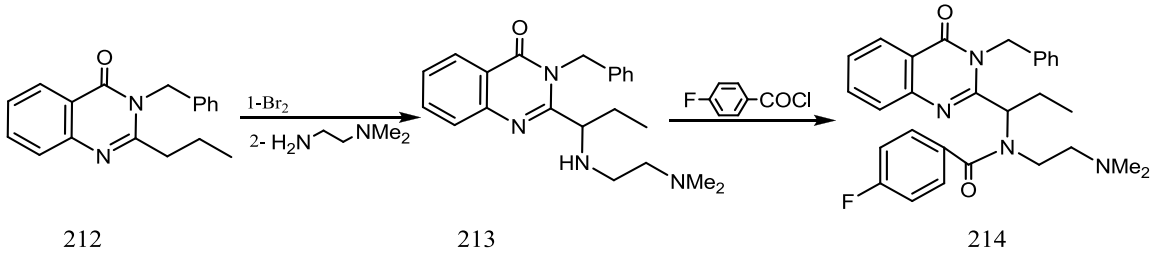


1 p 211

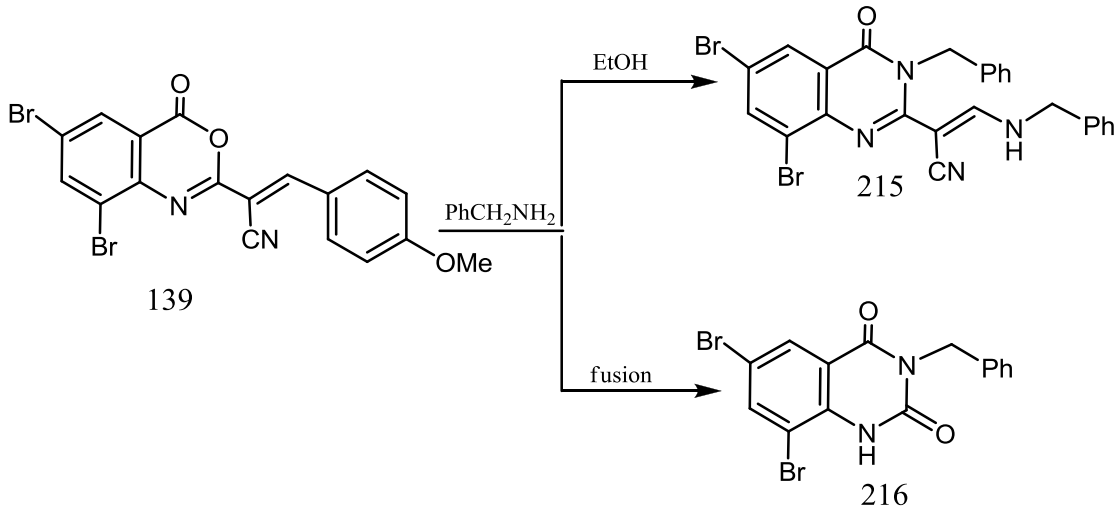
On the other hand, treatment of 2-propyl-4H-3,1-benzoxazin-4-one (1g) with benzylamine yields 3-benzyl quinazolinone 212 [126].



Bromination of quinazolinone 212 followed by addition of N,N-dimethyl ethylene diamine produces 213. The latter quinazolinone 213 reacts with 4-fluorobenzoyl chloride to furnish 214. Comnound 214 is a biologically active compound and useful in trearment of Cancer, Hyperplasmia, Restenosis immune disorders and inflammation [126].

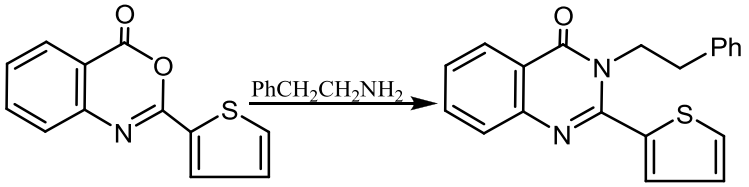


2-Substituted acrylonitril-4H-3,1-benzoxazin-4-one 139 reacts with benzylamine under different reaction conditions in order to give a mixture of N-benzylquinazolinone derivative 215 and quinazolin-2,4-dione 216 [108].



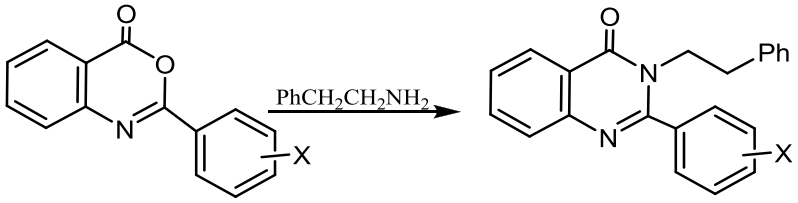
3.3.3.3.2 Reactions with phenylethylamine

Search for novel drug-like Calcilytics identified a new quinazolinone derivative 217 formed via heating 4H-3,1- benzoxazin-4-one 1p with phenethylamine [319].



1 p 217

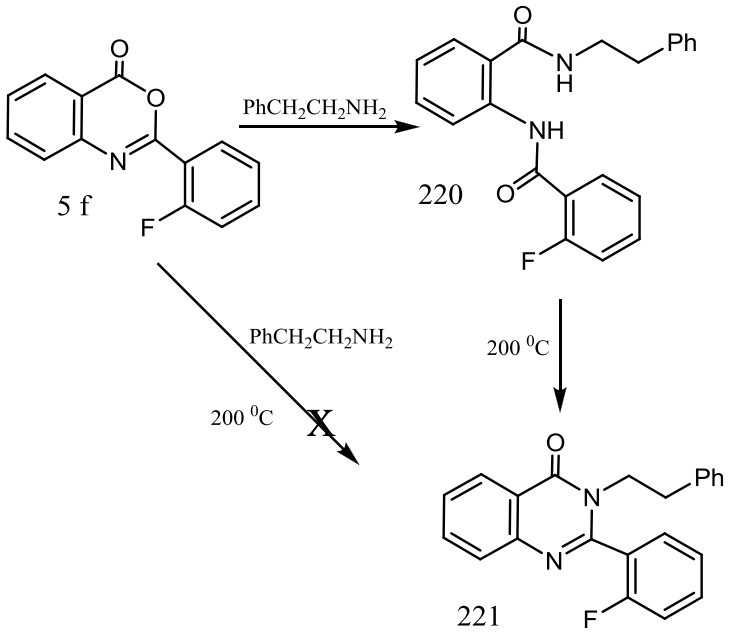
Similarly, refluxing 2-phenyl (or substituted phenyl)-4H- 3,1-benzoxazin-4-ones 218 with a 10 fold excess of phenethylamine for 2-3 hours at 200 °C produce the corresponding 4(3H)-quinazolin-4-one derivatives 219 [273].



218 219

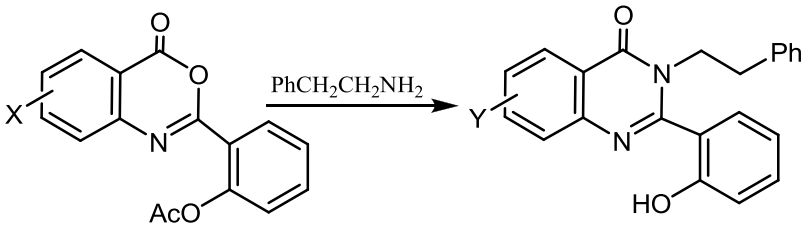
X = H, 3-F, 3-OMe, 4-OMe, 2-OH, 3-OH, 4-OH, 2,5-di-OH

Similarly, fusion of 2-(2-fluorophenyl)-substituted benzoxazinone 5f and phenethylamine at 200 °C, resulted in the dominant nucleophilic displacement of fluorine substituent with the amino moiety .For preservation of the 2-(2-fluorophenyl) fragment, synthesis of the intermediate bisamide 220 was carried out in pyridine at 120 °C followed by thermal cyclization to 2-(2-fluorophenyl)-3 -phenethyl-3H-quinazolin-4-one (221) [273, 313].



Benzoxazinones 222 bearing fluorine at 5, 7, or 8- position are submitted to the latter reaction with phenethylamine lead to amino-substituted quinazolinones 223 (where undesired nucleophilic displacement of the fluorine by the amine

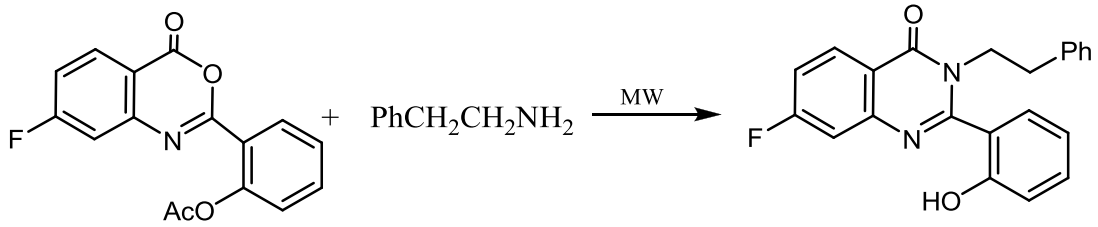
occurs), probably due to the reaction conditions (elevated temperature and absence of solvent) [273].



222 223 a-c

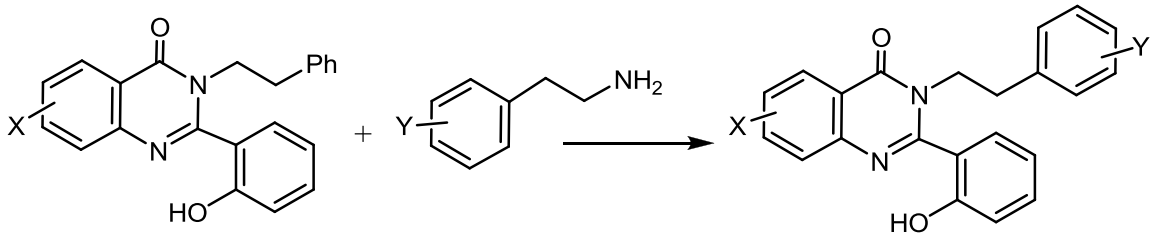
a	X= 5-F	Y= 5-$PhCH_2CH_2NH$
b	X= 7-F	Y= 7- $PhCH_2CH_2NH$
c	X= 8-F	Y= 8- $PhCH_2CH_2NH$

Applying microwave irradiation to the above benzoxazInone 222b results 7-fluoro-substituted quinazolinone 224, whereas 5- and 8-fluoro-substituted benzoxazinones 222a,c still produce products of nucleophilic displacement 223 a,c [273].



222 b 224

A series of 2-(2-hydroxyphenyl)-3-phenethylquinazolin-4(3H)-one 227 are prepared in the same fashion starting from 2-(2-hydroxyphenyl) substituted benzoxazinones 225 and phenethyl amines 226 [273].

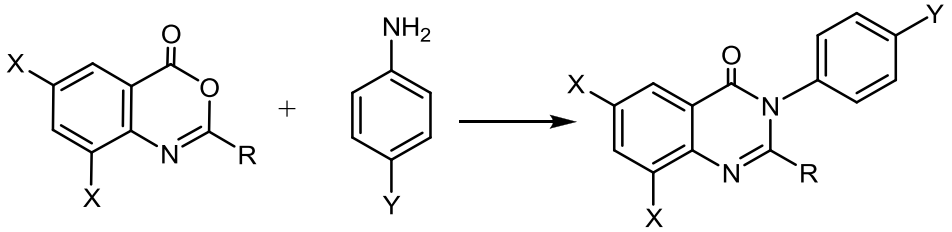


225 226 227 a-j

	X	Y
a	8-Me	H
b	7-F	H
c	7-Cl	3-F
d	6-Cl	H
e	5-Me	3-F
f	H	3-Cl
g	6-Me	H
	X	Y
h	5-Me	3-F
i	6-F	H
j	6-F	3-F

3.3.3.4 Reactions with anilines

Several experimental conditions for the reactions of anilines with 4H-3,1-benzoxazin-4-ones are reported. The reactants can be combined neat at room temperature [249], at elvated temperature ranging from 150- 220 °C [287, 282, 152, 157] or at 150-180°C in the presence of zinic chloride [87, 214, 7]. Alternatively, the reaction can be performed in solvents such as pyridine [296,280], dioxane [90,16,17], acetic acid [206], dimethylformamide or ethanol [90,154]. Substituted anilines 229 afforded quinazolinones 230 when reacted with substituted benzoxazinones 228.



228 229 230 a-h

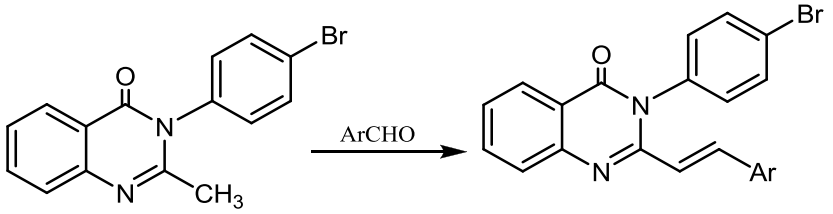
X=H, halo

R= Me, CH_2CI, Ph, CH_2Ph, COOEt

	Y	Ref.
a	Halo	[90]
b	Me	[154]
c	OH	[183, 281, 182]
d	OMe	[258]
e	Phenoxy	[33]
f	NO_2	[11,286]
g	SO_2NH_2	[231,232,33]
h	COOEt	[23,207]

3.3.3.4.1 Reactions with p-bromoanilines

p-Bromoaniline for example, reacts with benzoxazinone 1b in ethanol and affords 3-(bromophenyl)-2-methyl-3H- quinazolin-4-one (231) [122].



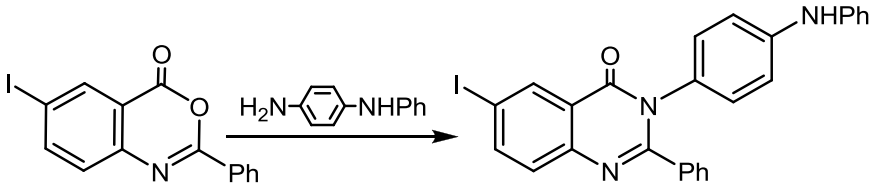
231 232

Ar = Ph, 4-C1.Ph, 2-theinyl, 4-OMePh

3.3.3.4.2 Reactions with p-aminodiphenylamine

In similar fashion, interaction of 2-phenyl-6-iodo-4H-3,1-benzoxazin-4-one (1q) with p-aminodiphenylamine yields 6-iodo-2-phenyl-3-(4'-phenylaminophenyl)-quinazolin-4-one

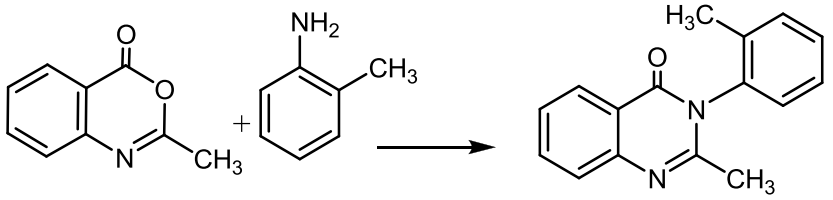
(233) [131].



1 q 233

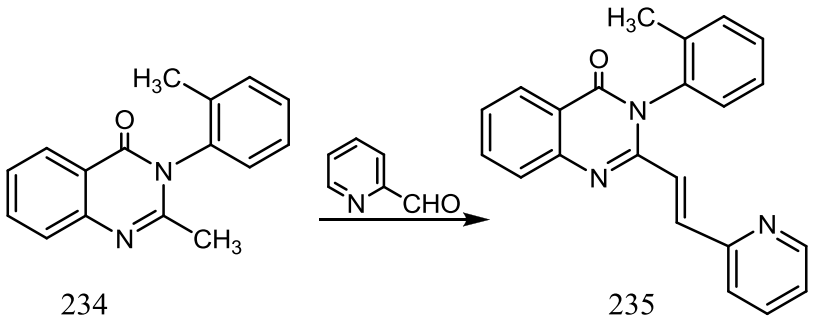
3.3.3.4.3 Reactions with o-toluidine

Refluxing a mixture of benzoxazinone 1b and o-toluidine in toluene under azeotropic conditions furnishes the CNS agent Methaqualone 234 [257].



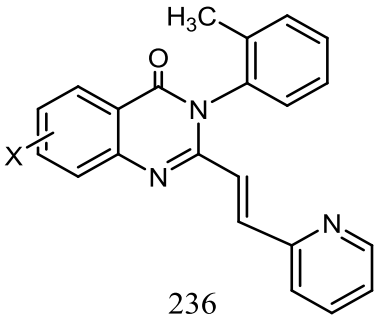
1 b 234

The above reaction also can be conducted in acetic acid followed by condensation of the produced quinazolinone 234 with 2-pyridinecarboxaldehyde in the presence of zinc chloride and provided 2 [(pyridine-2-yI)vinyl]-3 -(2-methylphenyl)-quinazolin-4(3H)-one (235), which is known as Piriqualone and it was tested as anticonvulsant agent [318].



234 235

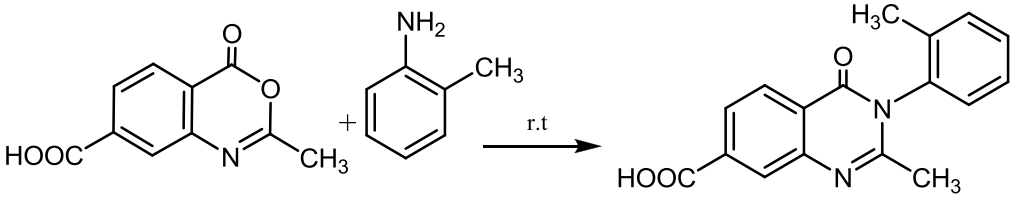
Starting from substituted 2-methyl-4H-3, 1-benzoxazin-4-ones, a series of 3-(2-methylphenyl)-2- [(2-pyridyl)vinyl] quinazolones 236 is obtained [318].



236

X = 6-CR_3, 6-F, 6-Cl, 7-Cl, 8-Cl, 6,8-Cl_2, 6-Br, 8-OCR_3. 6,7-$(OCH_3)_2$

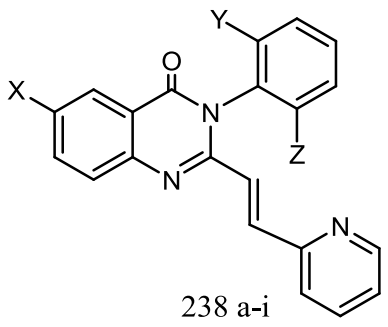
7-Carboxyquinazolone 237 is synthesized by mixing benzoxazinone 20 and o-toluidine at room temperature for 3-4 hours [249].



30 237

3.3.3.4.4 Reactions with 2-substituted and/or 2,6-disubstituted anilines

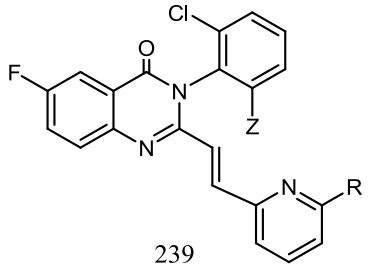
A variety of 2-substituted and/or 2,6-disubstituted anilines interact with substituted 4H-3, 1 -benzoxazin-4-ones to produce quinazolinone derivatives 238 [318].



238 a-i

	X	Y	Z		X	Y	Z
a	H	F	H	g	F	Cl	H
b	H	Cl	H	h	F	Br	H
c	H	Br	H	i	H	H	H
d	H	CF_3	H	j	H	CH_3	CH_3
e	H	OCH_3	H	k	H	Cl	Cl
f	F	F	H	L	F	F	F

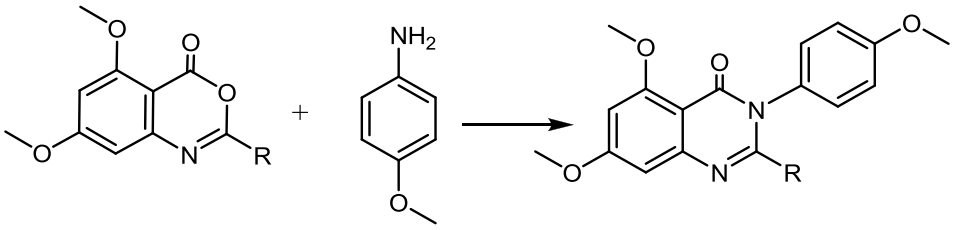
In a similar fashion, a series of 3-(2-chlorophenyl)-2- substituted quinazolones 239 is prepared and their biological activity are tested. They are identified as antagonist template for AMPA receptors (play an important role in pharmacological studies of glutamate receptors) [65].



239

R		
H	CH_3OCH_2	piperidine
CH_3	$CH_3CH_2OCH_2$	$(CH_3)_2CHNHCH_2$
CHO	CH_2F	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2$
CH_2NH_2	CN	$(C_2H_5)_2NCH_2$
COOH	$COOCH_3$	$(CH_3)_2NCH_2$
CH_2OH	$C_2H_5NCH_2$	CH_3NHCH_2
$AcOCH_2$	pyrrolidine	

5,7-Dimethoxy-2-substituted benzoxazinones 240 are reacted with p-methoxyaniline either via refluxing in xylene for 4 hours or in acetic acid at 60 °C for 24 hours and afforded 3-(4-methoxy phenyl)-4(3H)-quinazolinone 241 [136].

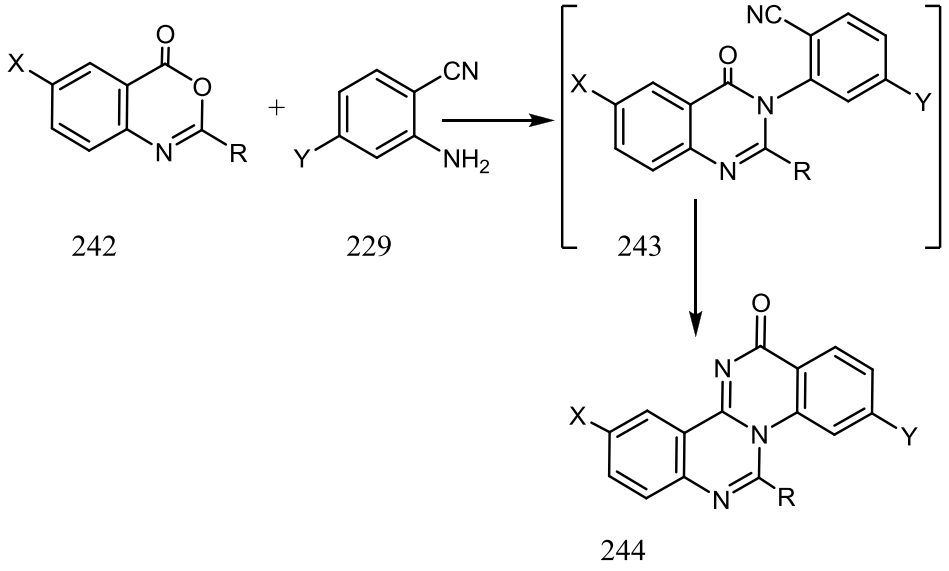


240 241

R = H, Me, Et, n-Pr, n-Bu, i –Bu

3.3.3.4.5 Reactions with anilines containing reactive function groups

3.3.3.4.5.1 Reaction with 2-cyanoanilines

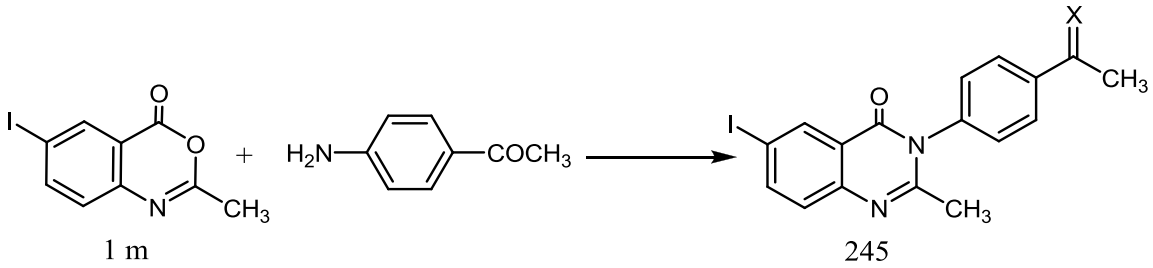


242 229 243 244

X= H, Cl , Me & Y = H, Cl, Me & R= Me ,n-Pr, i-Pr

3.3.3.4.5.2 Reactions with p-aminoacetophenone

Benzoxazinone 1m condenses with 4-amino acetophenone in n-butanol and gives 2-methyl-6-iodo-3-(4'- acetylphenyl)-quinazol-4-one (245a,b) [130].



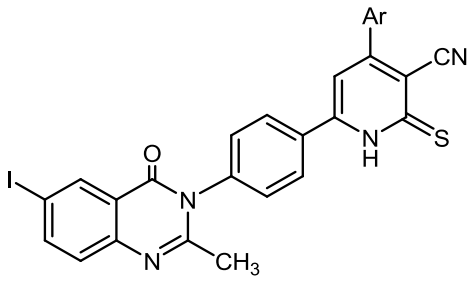
1 m 245

a ; X= O

b; X= $NNHCONH_2$

The semicarbazone 245b was obtained from 245a by refluxing with an equimolar amount of semicarbazide hydrochloride in ethanol [130].

Cyanopyridin-2-(1H)-thione derivatives were obtained via the reaction of arylmethylene-cyanothioacetamide ($ArCH=C(CN)CSNH_2$) with the active methylene carbonyl quinazolone 245b. An assay for Antitumor activity showed that compound 246 (Ar= 4-$OCH_3C_6H_4$) has a significant activity against Ehrlich Acites Carcinoma tumor cells (in vitro) and displayed a significant percent of the nonviable tumor cells to about 40% and 80% at concentration of 10 and 100mg, respectively [130].

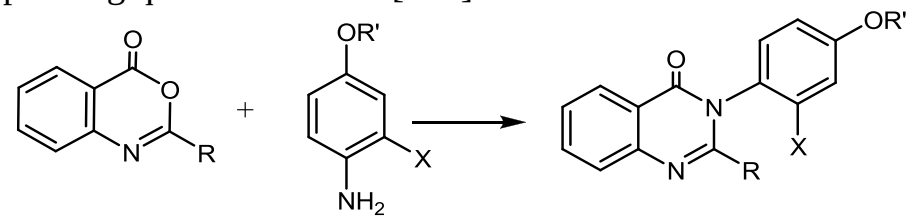


246

Ar= Ph, 4-pyridyl, 2-thienyl

3.3.3.4.5.3 Reactions with 4-hydroxyanilines

Treatment of 4H-3,1-benzoxazin-4-ones 247 with 4- hydroxyanilines 248 yield the corresponding quinazolone 249 [245].

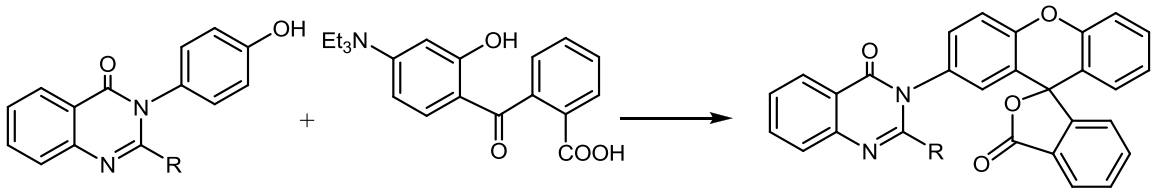


247 248 249

R = Me, Ph, CH_2Cl, CH_2Ph

a; R'= H, X=H b; R'= Me, X= NO_2

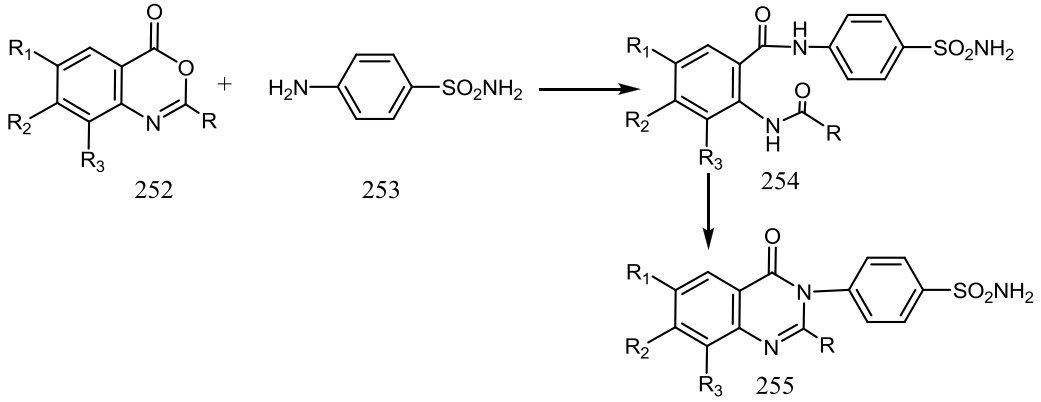
The latter quinazolones 249 react with 2-(4- diethylamino-2-hydroxybenzoyl)benzoic acid (250) in the presence of sulphoric acid to produce fluorans 251 [245].



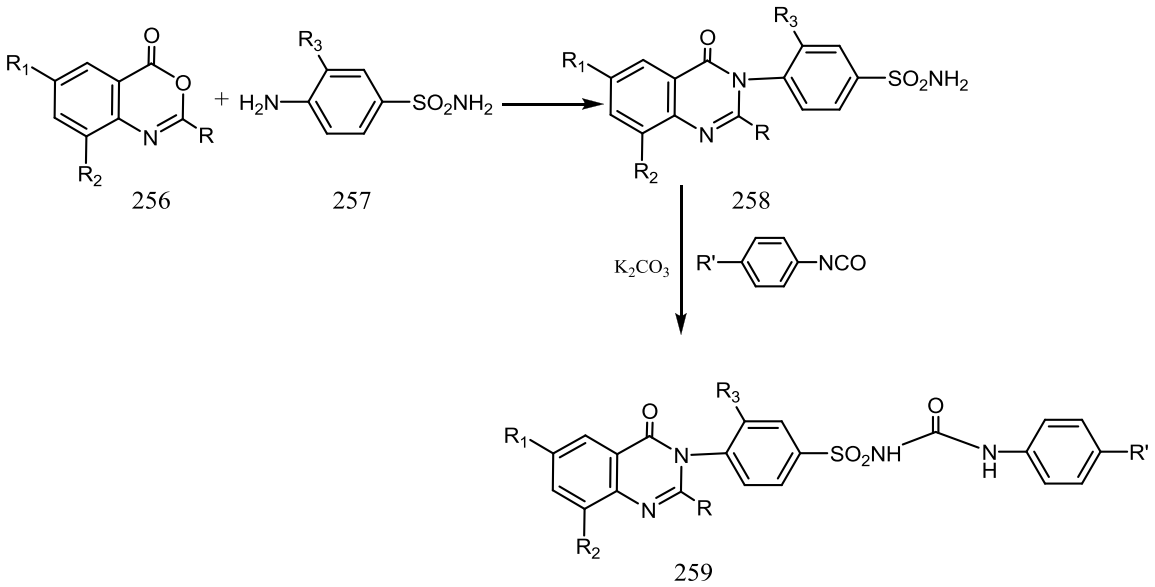
249 250 251

3.3.3.4.5.4 Reactions with sulphanilamide

3-(4-sulphamoylphenyl)-4(3H)-quinazolin-4-ones (255; R = alkyl; R^1 = H, Me, halo; R^2 = H, Cl, NO_2 R^3= H, halo) are synthesized by condensation of sulphanilamide with various 4H-3, 1-benzoxazin-4-ones 252. 2-amido-N-(4-sulphamoyl phenyl)benzamides are isolated as reaction intermediates. Some of quinazolone derivatives 255 showed significant anticonvulsant effects against pentetrazoll- induced avulsions [111].



Similarly, 1- [4-(4'-oxo-2-methyl/ phenyl-4-(3H)-quinazolin-yl)-3-aryl ureas (259; R = Me, Ph; R^3 = H, Me; R^2= H, Me; R^1,R^2= H, Br) are prepared by reaction of corresponding quinazolinone-sulphanilamides 258 with aryl isocyanates in the presence of K_2CO_3 in acetone solution. the corresponding quinazolinones are obtained from interaction the corresponding 4H-3,1-benzoxazin-4-ones 256 [221].

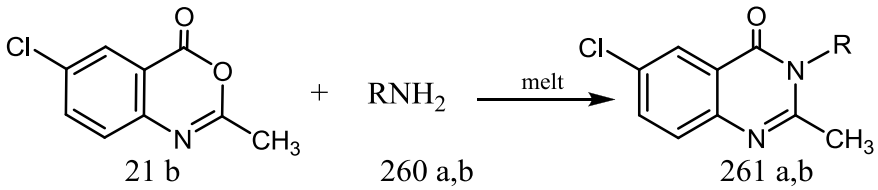


Both the oral and i.p. $LD^{(50)}$ values for 259 in mice were 1600 to >2000 and 600 to 800 mg/Kg. This compounds were evaluated for their hypoglyceamic activity against the streptozotocin induced diabetic rats. (259; R = Ph; R^3= H, Me; R^1= R^2= H) decreased the blood sugar level significantly both in normal and streptozotocin-induced diabetic rats. The other compounds showed significant hypoglyceamic activity [221].

3.3.3.5 Reactions with amino heterocyclic compounds

Amino heterocycles such as pyridine, pyrimidine [277,31],pyrazole [247], thiazole [277,113], or 1,3,4-thiadiazole [243, 298, 238] have been successfully useful to prepare 3-heterosubstituted quinazolone with high biological activity [11, 276, 187].

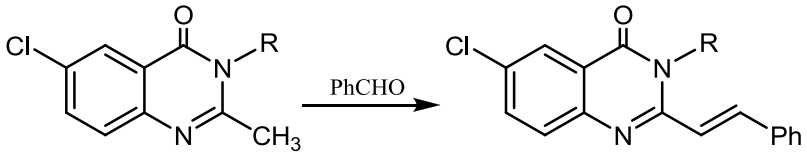
Fusion of 6-chloro-2-methyl-4H-3,1-benzoxazin-4-one 21b with heterocyclic amines 260 produces 3-heterocyclic-2- methylquinazolone derivatives 261 [252].



21 b 260 a,b 261 a,b

a;R=5-indazolyl
b; R= 1-ethyl-5-pyrazolyl

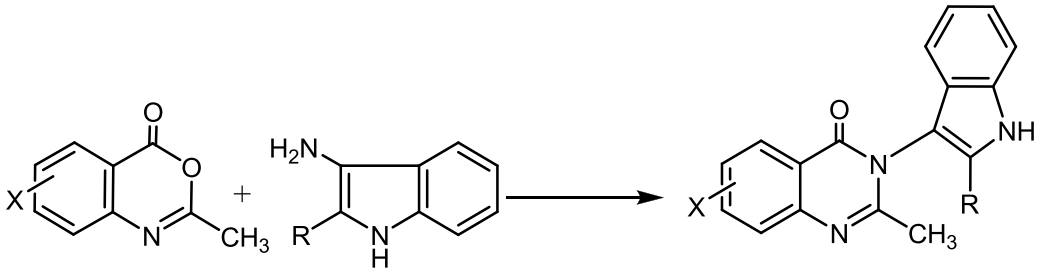
Refluxing equimolar amounts of 2-methyl quinazolone 261 and benzaldehyde in glacial acetic acid; the 3-heterocyclo-2-styrylquinazolinones 262 are generated [253].



261 a,b 262 a,b

a; R= 5-indazolyl
b; R= 1-ethyl-5-pyrazolyl

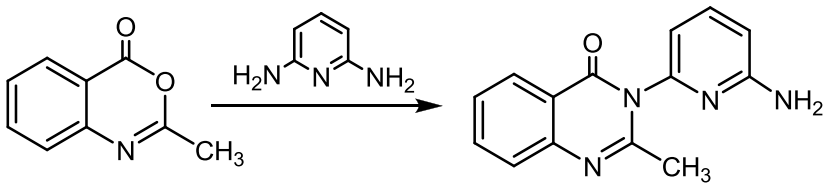
Reaction of 4H 3,1-benzoxazin-4-ones 1a,c,m with 2- substituted-3-aminoindoles 263 in dry pyridine produce 2- methyl-3 -(2'-substItutedindol-3-yl)-4(3H)-quinazolinone 264 [184].



1 a,c,m 263 264

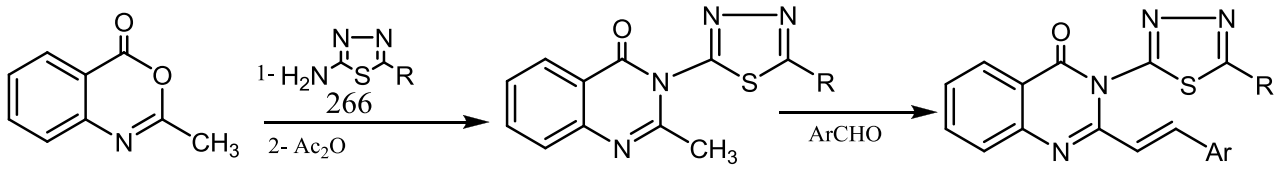
X= H, 6-I, 6-Br
R= H, Me

Also 4H-3,1-benzoxazin-4-one 1b is reacted with 2,6- pyridindiamine to furnish 3-substituted quinazolone 265 [290].



1b 265

Synthesis of 3-(1',3',4'-thiadiazolyl)-2-styrylquinazolin-4(3H)-ones (268) is accomplished by a three-step procedure, the intermediate 3 -(1,3 4-thiadiazoloIyl)-2-methyl quinazolinones 267 is obtained by refluxing 2-methyl-4H-3,1-benzoxazin-4-one 1b with thiadiazole-amino derivatives 266 [168].



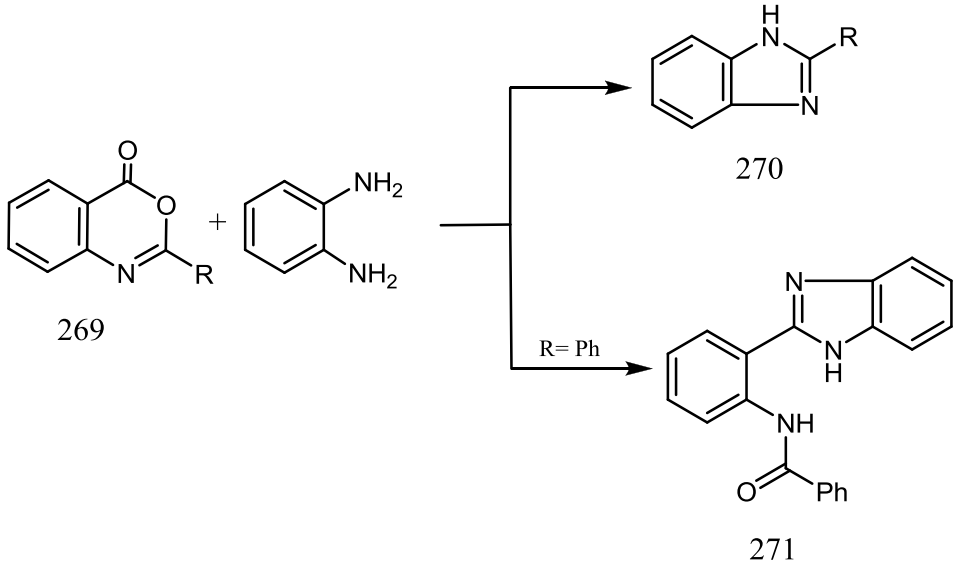
1 b 267 a-r 268 a-r

	R	Ar		R	Ar		R	Ar
a	Ph	4-ClC_6H_4	g	Ph	3-ClC_6H_4	m	Ph	4-pyridyl
b	4-$OCH_3C_6H_4$	4-ClC_6H_4	h	4-$OCH_3C_6H_4$	3-ClC_6H_4	n	4-$OCH_3C_6H_4$	4-pyridyl
c	4-$CH_3C_6H_4$	4-ClC_6H_4	i	4-$CH_3C_6H_4$	3-ClC_6H_4	o	4-$CH_3C_6H_4$	4-pyridyl
d	4-ClC_6H_4	4-ClC_6H_4	j	4-ClC_6H_4	3-ClC_6H_4	p	4-ClC_6H_4	4-pyridyl
e	3-ClC_6H_4	4-ClC_6H_4	k	3-ClC_6H_4	3-ClC_6H_4	q	3-ClC_6H_4	4-pyridyl
f	-CH=CHPh	4-ClC_6H_4	l	-CH=CHPh	3-ClC_6H_4	r	-CH=CHPh	4-pyridyl

3.3.3.6 Reactions with diamines

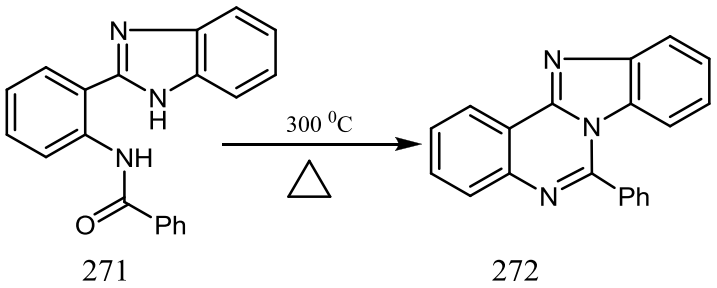
3.3.3.6.1 Reactions with o-phenylenediamine

If refluxing benzoxazinone derivatives 269 with o-phenylenediamine in chloroform, 2-substituted benzamidazoles 270 are formed. Conversally, heating the above mixture in polyphosphoric acid at 200 °C provided 271 [250,163].

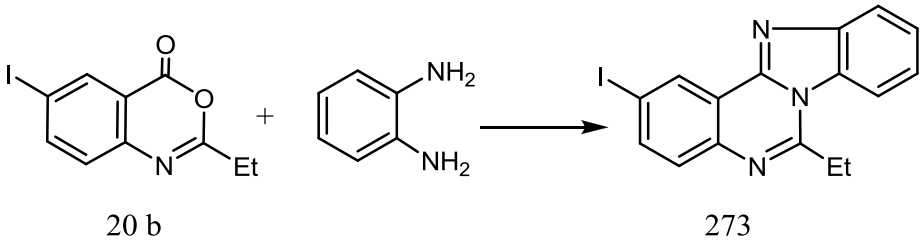


R = Me, Ph, CH2Ph

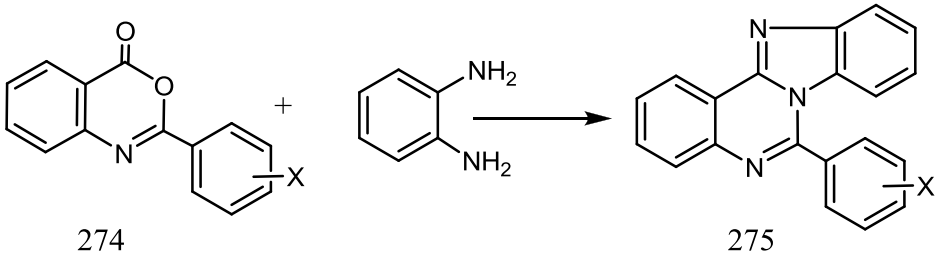
If compound 271 is heated at 300 °C in a sublimation apparatus it cyclodehydrated and benzimidazo quinazoline 272 is produced [250].



Refluxing a mixture of 2-ethyl-6-iodo-4H-3,1- benzoxazin-4-one (20b) and o-phenylenediamine in acetic acid in the presence of fused sodium acetate resulted the formation of tetracyclic compound 273 [30].

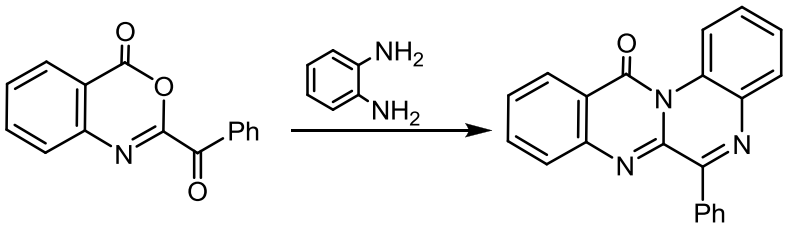


Cyclocondensatin of 2-aryl benzoxazinones 274 (R = Ph or substituted Ph) with o-phenylenediamine catalyzed by orthophosphoric acid yield analgos benzoimidazo quinazolinoneS 275 [237].



X= H, 2-OH, 4-NO_2

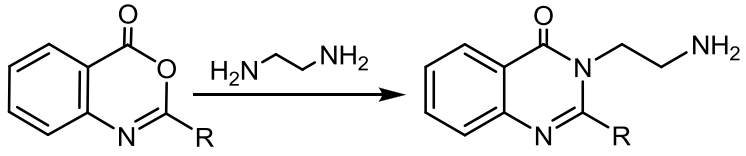
4H-3,1-benzoxazin-4-ones (276) reacts with o-phenylenediamine to afford 277 [250].



276 277

3.3.3.6.2 Reactions with ethylenediamine

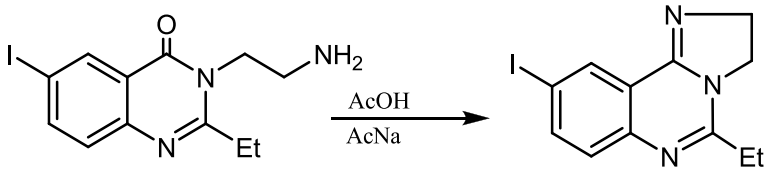
2-Methyl-4H-3,1-benzoxazin-4-one 1b as well as 2- phenyl analog 1a are reacting with ethylenediamine and produce the conesponding 3-functionalized quinazolones 278 [239,114,118, 74].



1a or 1b 278

R = Me, Ph

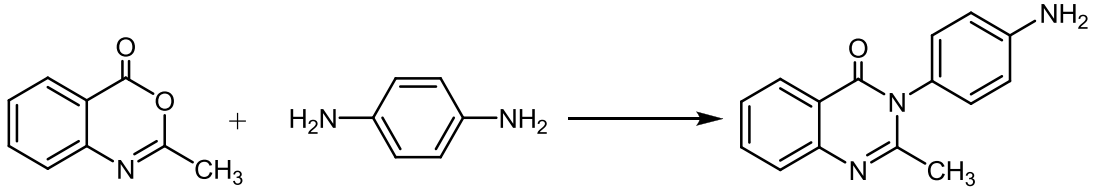
Analogs such as this have the added capability to react further and generated more complex heterocyclic systems [250]. For example, heating quinazolinone 279 in acetic acid in the presence of fused sodium acetate, cyclodehydration occurred and the imidazolo quinazoline 280 is generated [30].



279 280

3.3.3.6.3 Reactions with p-phenylenediamine

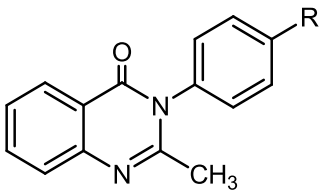
Interaction of 2-methyl-4H-3,1-benzoxazin-4-one (1b) with p-phenylenediamine affords quinazolinone 281 [146].



1 b 281

Treatment of quinazolinone 281 with alkyl isocyanates followed by cyclocondensation with phenacyl bromides or chloroacetic acid furnished

quinazolinones 282 bearing heterocyclic moieties with high biological activities [146].

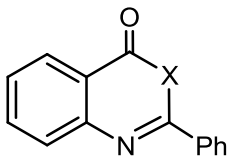


282 a-c

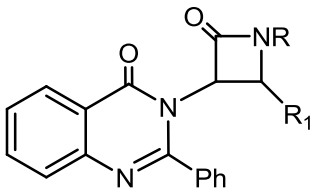
a	b	c
R = NHCSNHR[1]	R = 3-alkyl- 4-aryl-2, 3-dihydrothiazol-2-ylideneamino	R=3-alkyl-4-oxo-thiazolidin-2-ylideneamino
R[1] = Me, Et, Bu, CH2Ph		

3.3.3.7 Reactions with aminoacids

1 ,4-Disubstituted 3-[3'-(2'-phenyl-4-oxo-quinazolinyl)]- 2-azetidinones 284 [240], were prepared by cyclocondensation of Schiff's bases RN= CHR_1 (same R groups) with ketenes , the ketene was prepared by treating 1a (X =O) with H_2NCH2COOH to give 283b (X = NCH_2COOH) which was converted to the acid chloride 283c (X = NCH_2COCl). Treatment of the acid chloride with Et_3N gave 283d (X = NCH=CO) in situ. Compounds 284 showed antiimplantation acitivity in rats [240].



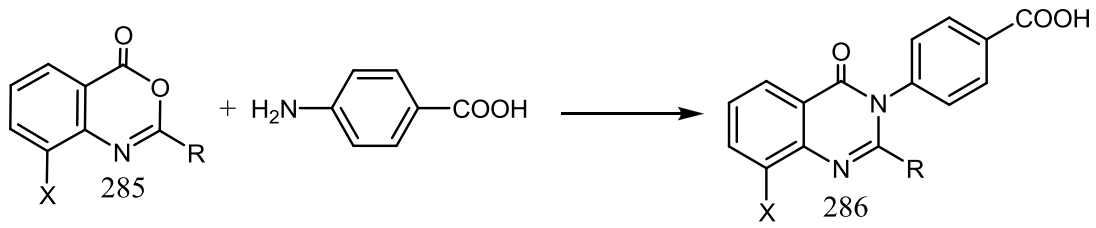
283 a-d



284

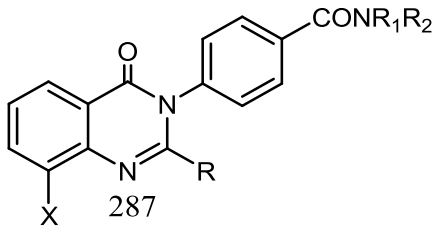
R	R_1
Ph	Ph
4-$OMeC_6H_4$	2-$CH_3C_6H_4$
2-$NO_2C_6H_4$	3-$CH_3C_6H_4$
2-FC_6H_4	4-ClC_6H_4

In the same manner, carboxyphenylquinazolones 286 has been obtained via cyclocondensation of 2-aryl or alkyl-8- bromo-4H-3,1-benzoxazin-4-one 285 with p-aminobenzoic acid [225].



X = H ,Br & R = Ph ,CH_2Cl

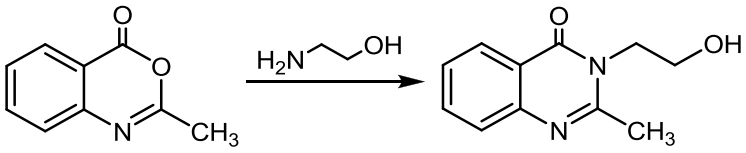
2(phenyl/chloromethyl)-3-[4-(N,N-disubstituted amino carbonyl)Phenyl]-8-substituted 4(3H)quinazolones 287 are synthesized by treating carboxyquinazolinone 286 with $SOCl_2$ in benzene and with the different secondary amines. All quinazolinones 287 are screened for toxicity, central nervous system, cardiovascular and anti-inflammatory activites. Most of these compounds are found to be non-toxic and stimulant in nature. Some of this compounds also exhibited cardiovascular and anti-inflammatory activities [225].



X = H, Br
R = Ph, CH_2Cl
R_1R_2N = morpholino, N-Me piperazino, Et_2N, $(HOCH_2CH_2)_2N$, piperidino,N-phenylpiperazino

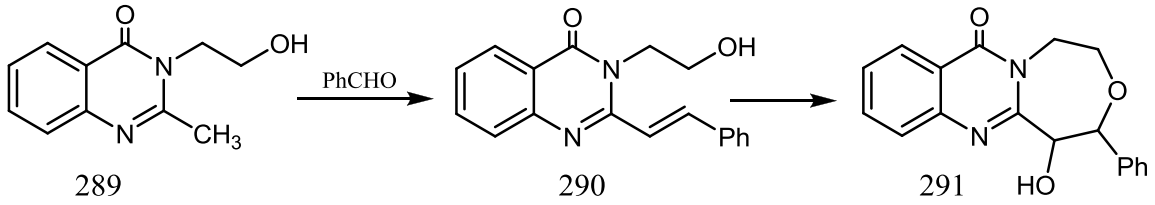
3.3.3.8 Reactions with aminoalcohols

2-Methyl-4H-3,1-benzoxazin-4-one 1b reacts with ethanolamine to produce the corresponding 3-hydroxyethyl quinazolone 289 [71].



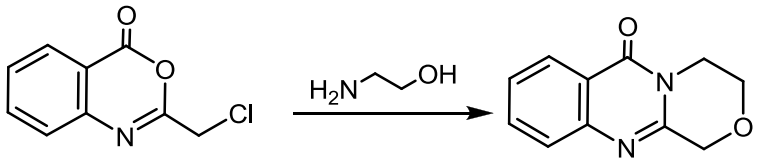
1 b 289

Heating of the resulting quinazolinone 289 with benzaldehyde yields the styryl derivative 290. Epoxidation of the double bond, then treatment of the product with sodium methoxide afforded 291 as a result of intramolecular attack of ethanol group on the epoxide [81].



289 290 291

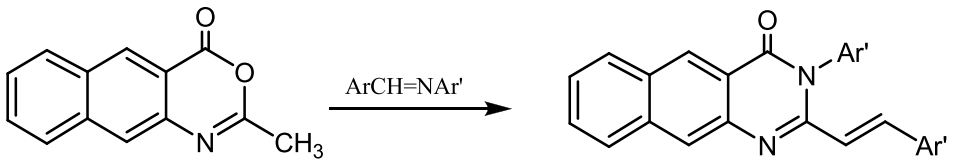
Heterocondensed quinazolones 1 ,4-oxazino[3 ,4-b] quinazolin-6-one 292 has been obtained (chloromethyl)-4H-3,1 -benzoxazin-4-one 1h with ethanol amine followed by base-catalyzed cyclization [227].



1 h 292

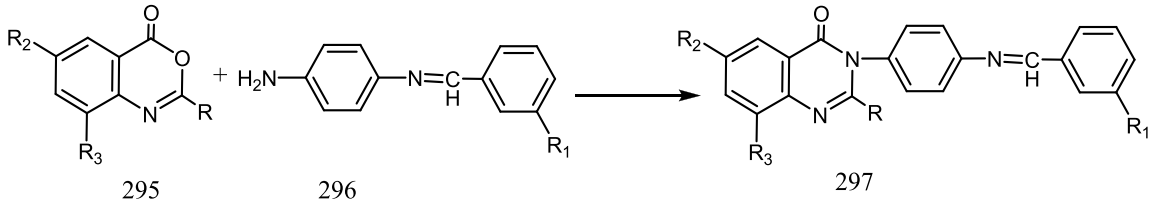
3.3.3.9 Reactions with Schiff's bases

Condensation of methylnaphthoxazinone 293 with ArCH=NAr' (Ar, Ar' substituted phenyl) in acetic acid yield benzoquinazolones 294 [186].



293 294

Similarly, compounds 297 are prepared by reaction of 4H-3,1-benzoxazin-4-one derivatives 295 with Schiff's base 296. Compounds 297 are tested for Anthelmintic, Virucidal and Bactericidal activity [278].



295 296 297

R = Me,Ph

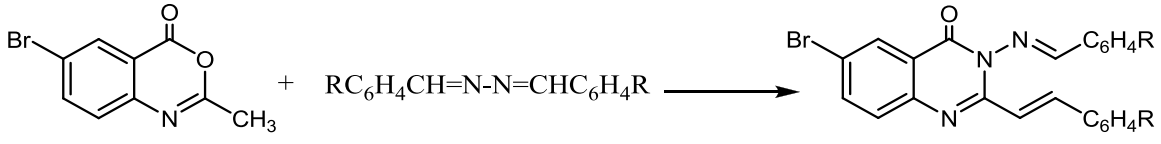
R_1 = 3-NO_2, 4-OH, 4-NMe_2, 2-OH, 4-Cl

R_2 = H, Br

R_3= H, Br

3.3.3.10 Reactions with azines

6- Bromo-2-methyl-4H-3,1-benzoxazin-4-one (1c) undergoes hetero-ring opening followed by recyclization and condensation when treated with azines 298 and yielded 3-arylideneamino-substituted quinazolin-4-(3H)one 299. The reaction involves a cleavage of the azine into its amine and arylidene moieties which are smoothly incorporated into 1c via nucleophilic attack of the amine at position-4 and condensation of the aldehyde with a reactive methyl group at position-2 respectively [77].

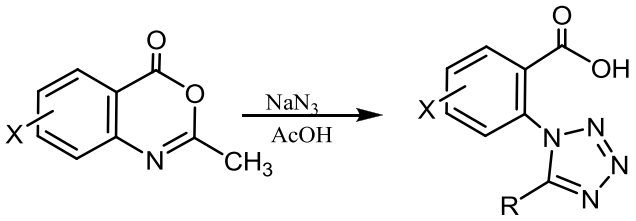


1 c 298 299

R = H, 4-OMe

3.3.3.11 Reactions with sodium azide

Treatment of 4H-3, 1-benzoxazin-4-ones 300 with hydrazoic acid (generated with sodium azide in acetic acid) [163, 203, 28, 119, 109, 43, 86] or directly with sodium azide in dimethylformamide [132] resulted in the formation of the tetrazolyl benzoic acids 301.

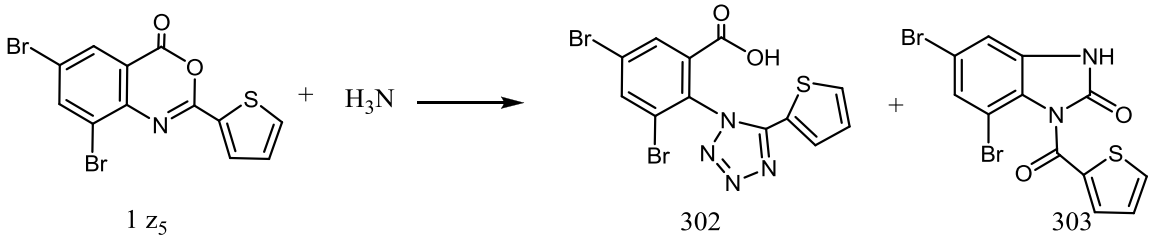


300 301

X = H, Me, Br

R= H, Me, pr, ph, styryl, 2-thienyl

Reaction of compound $1z_5$ with HN_3 gave the tetrazole 302 along with the benzimidazolone 303 [162].

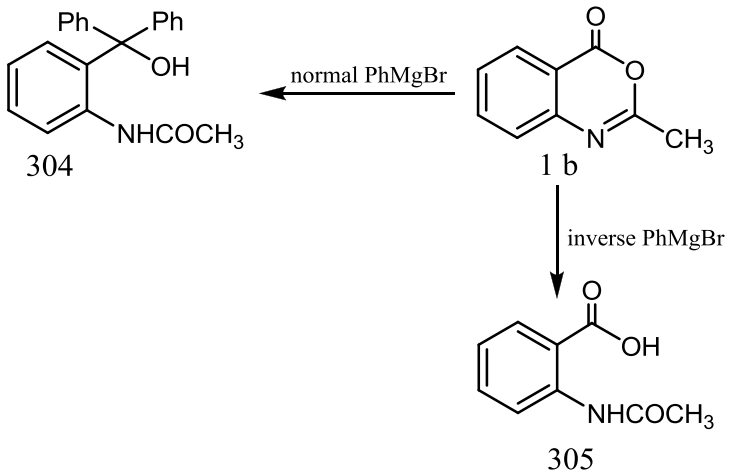


1 z_5 302 303

3.3.4 Reactions with carbon nucleophiles

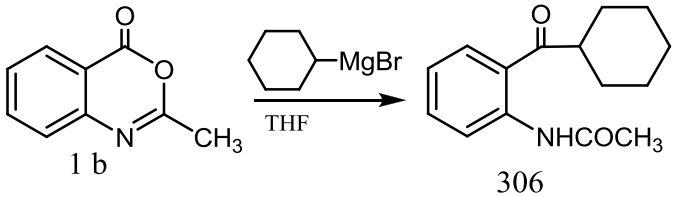
3.3.4.1 Reactions with Grignard reagents

The benzoxazinone 1b reacts with Grignard reagents in a fashion determined by the manner in which the reaction is carried out [315].



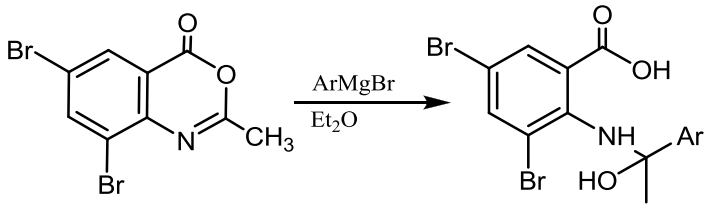
304 1 b 305

While this benzoxazinone 1b reacts with cyclohexyl magnesium bromide in THF to afford ketone 306 [62].



1 b 306

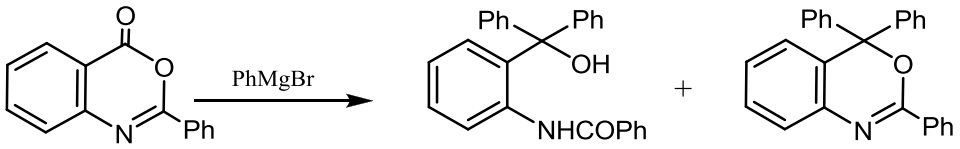
6,8-Dibromo analog 1j reacts with Grignard reagent and provide the unexpected products 307 [196].



1 j 307 a,b

a; Ar = Ph b; Ar = CH2Ph

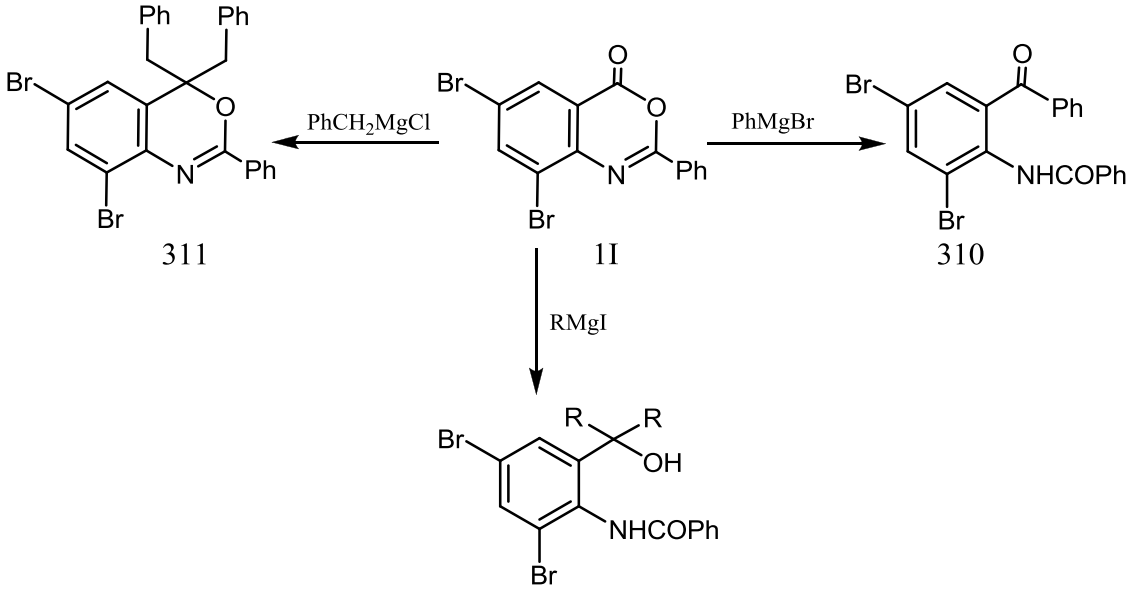
On the other hand, 2-phenyl-4H-3,1-benzoxazin-4-one 1a on reaction with phenyl magnesium bromide by either the normal or inverse addition method providing only 2- benzamidphenyl diphenyl carbinol 308 and its dehydration product 2,4,4-triphenyl-3,1-benzoxazone 309 [12].



1a 308 309

Similarly, 2-methyl-7-methoxy-4H-3, 1-benzoxazin-4-one reacts with p-methoxyphenyl magnesium bromide to give 2-acetamido-4,4-dimethoxybenzophenone [150].

6,8-Dibromo-2-phenyl-4H-3,1-benzoxazin-4-one (1I) reacts with different Grignard reagents affording different products 310-312 depending on the nature of the reagent and not on the reaction conditions [163].

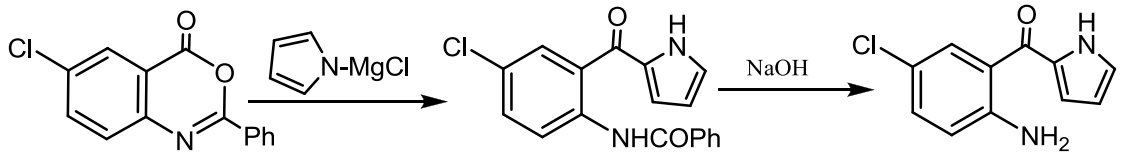


311 1I 310

312

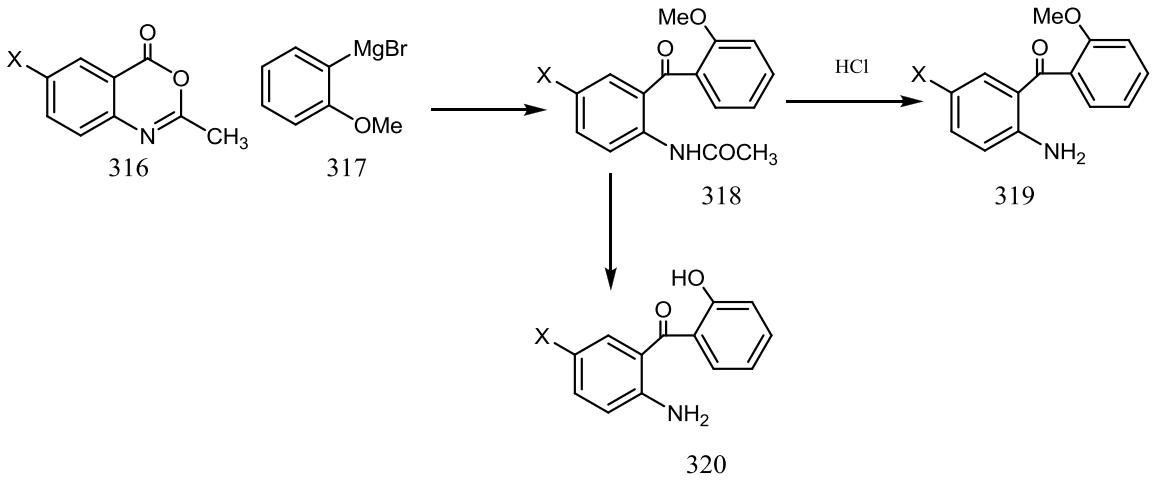
R = Et, 4-OMePh

Benzoxazinones 313 reacting with pyrrolyl Girgnard reagent followed by hydrolysis to afford 2-amino-5- chlorophenyl-2'-pyrrylketone 315 which is used as a key intermediate in the synthesis of HIV Tat-Antagonists [226].



313 314 315

6-Halo-2-methyl-4H-3, 1-benzoxazin-4-one 316 reacts with Grinard reagent 315 and produces ketone 318, which by hydrolysis gives the amines 319 and 320 [268].

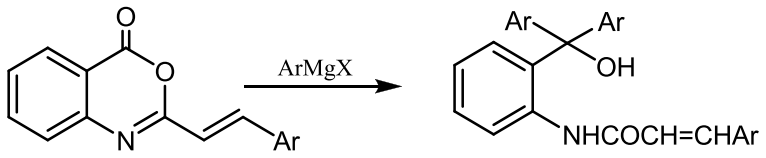


316 317 318 319

320

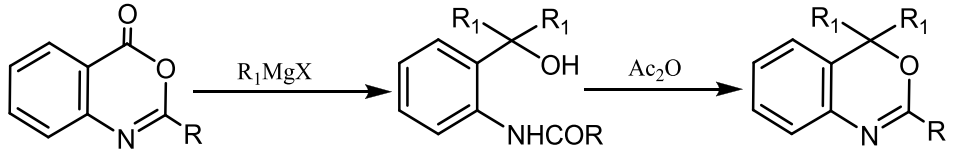
X = F, Cl, Br

The benzoxazinone 321 is reacted with Grignard reagents and gave the carbinols 322 which are identified as o-(cinnamoylamidophenyl)diarylcarbinols [**Error! eference source not found.**].



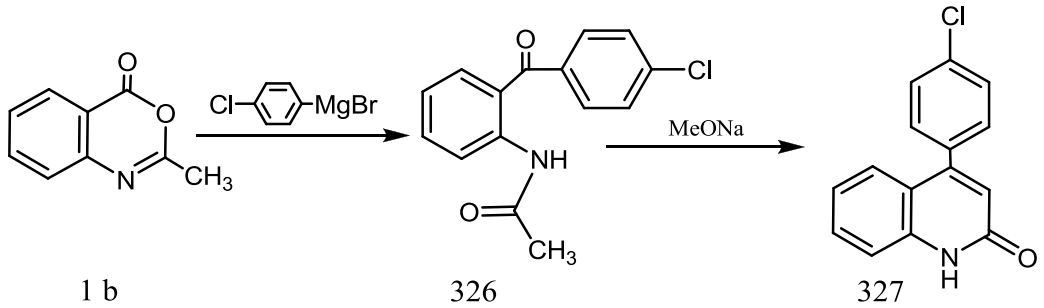
321 322

As a point of interest, 2-p-tolyl and/or p-chlorophenyl-4H-3,1-benzoxazin-4-ones 323 are reacted with PhMgBr or CH_3I and gave the carbinols o-[$HOC(R^1)_2$] C_6H_4NHCOR [324;R^1= CH_3, C_6H_5; R =$C_6H_4.CH_3$(4), C_6Cl(4)] which on heating with Ac_2O-AcONa are cyclized to 4,4-(diphenyl or dimethyl)-2-(p-tolyl or p-chlorophenyl)-3,1-benzoxazines 325 [329].



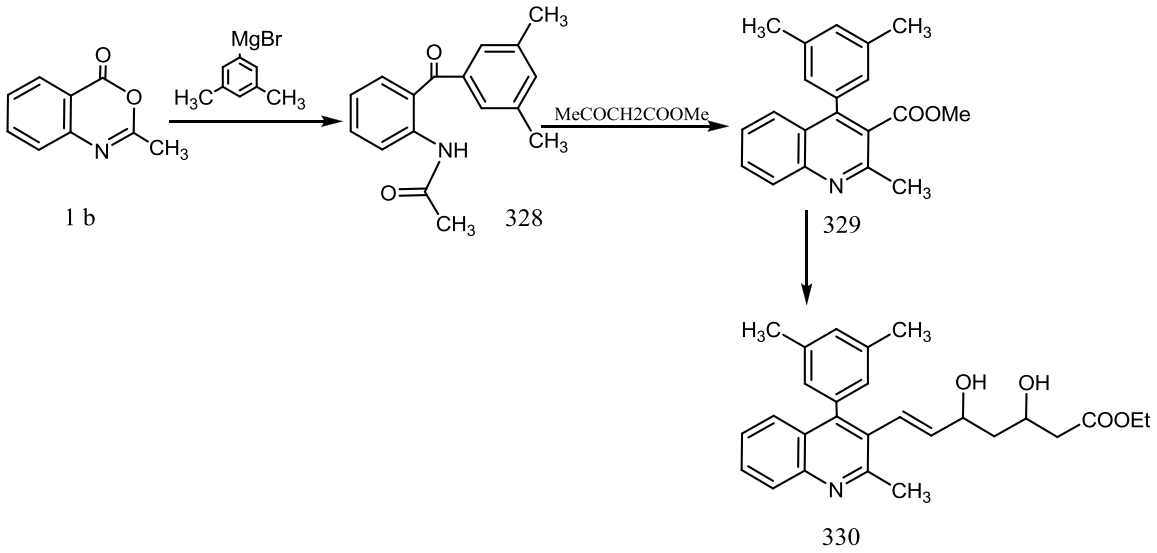
323 324 325

Reaction product 326 of benzoxazinone 1b and 4-chlorophenylmagnesium bromide are treated with sodium ethoxide and are cyclized to the 4-phenylcarbostyril 327 [151,197].

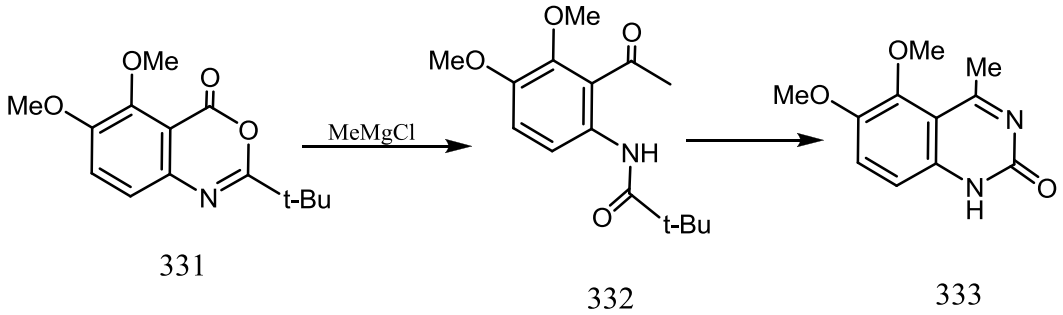


1 b 326 327

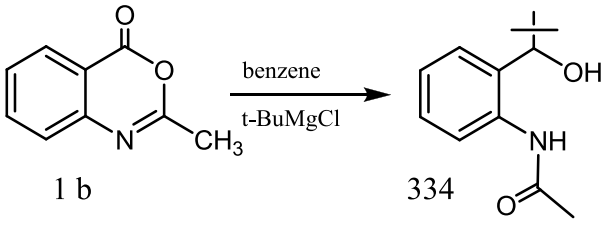
Bezoxazinone 1b reacts with 3,5-dimethylphenyl magnesium bromide and produces 328a. The acyl group of 328a is removed under acidic conditions and resulting 2- aminobenzophenone 328b. It condenses with methyl acetoacetate to afford the quinoline 329, which is then elaborated by using Wittig methodology to the 4-arylquinolin heterocycle 330. Compound 330 comprises the hydrophobic domain of reductase inhibitors [316].



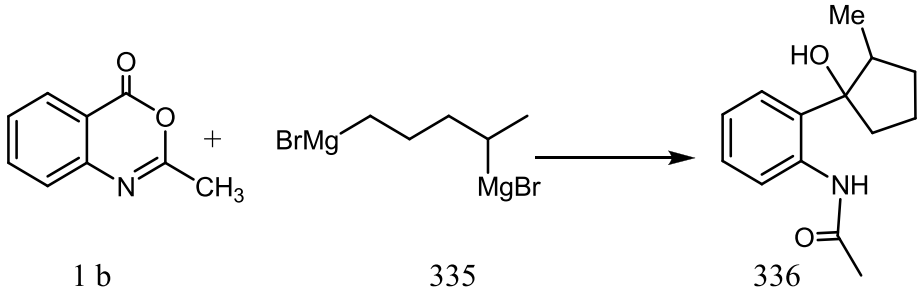
Cardiotonic bemarinone, 5,6-Dimethoxy-4-methyl-2(1H)- quinazolinone 333 is readily prepared from 4H-3,1-benzoxazinone 331 [70].



Addition of 2-methyl benzoxazinone 1b to an excess of t-butyl magnesium chloride produces the secondary alcohol 334. The first equivalent of Grignard reagent adds normally to 1b to generate N-acetylbenzophone derivative, then the second equivalent of the reagent instead of adding to the newly formed ketone, it reduces the keto group presumably because of highly steric interactions between both ketone and organometallic [328].

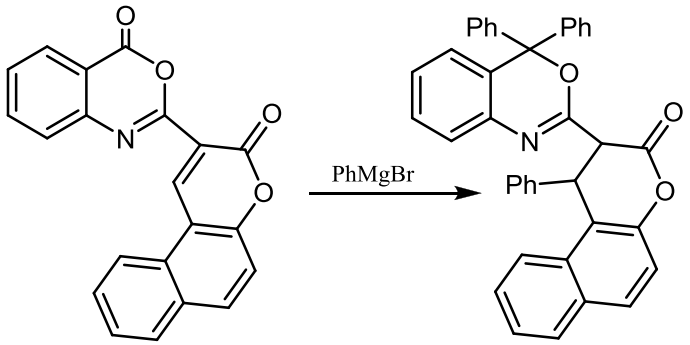


BisGrignard reagents such as 335 add to 2-methyl benzoxazinone 1b to give tertiary alcohol 336 [60].



1 b 335 336

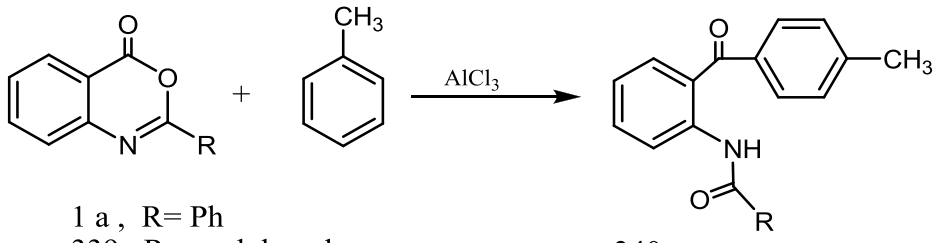
4H-3,1-Benzoxazin-4-ones 337 have bulky group at 2- position also react with Girgnard reagent PhMgBr and produce compound 338 [263].



337 338

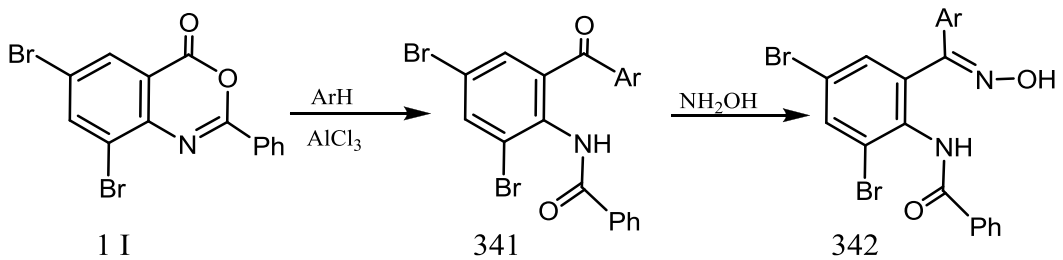
3.3.4.2 Friedel-Crafts reactions

2-Phenyl-4H-3, 1 -benzoxazin-4-one 1a and cyclohexyl-(4H)-3,1-benzoxazin-4-one 339 are reacted with toluene in the presence of anhydrous $AICl_3$ under Friedel-Crafts conditions to give 2-benzamido and 2-cyclohexylamido-p-methyl benzophenone 340 [265,267].



1 a , R= Ph
339 , R= cyclohexyl 340

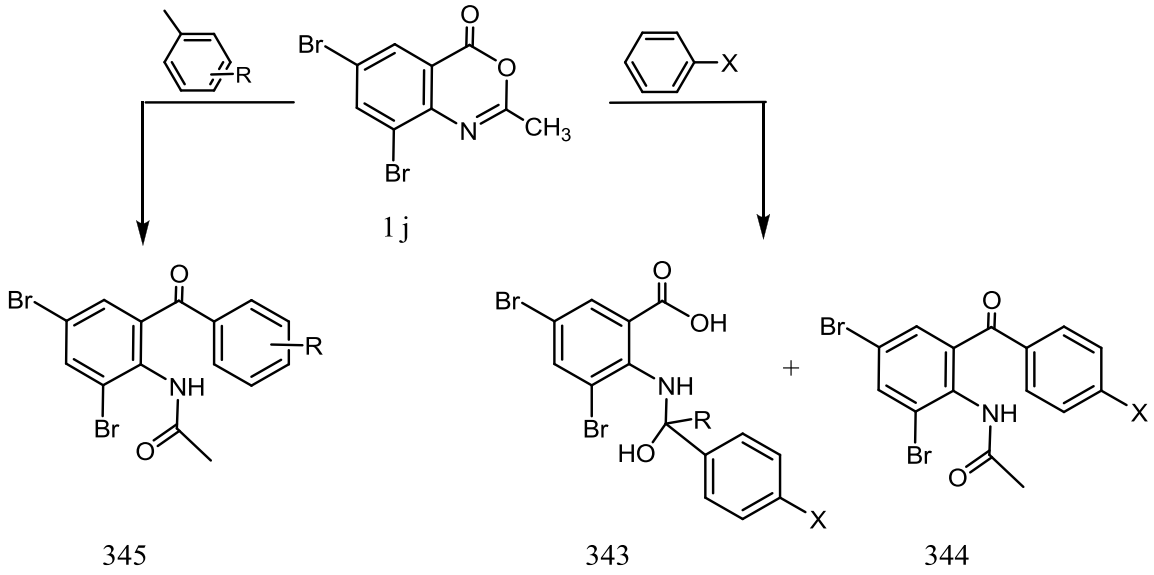
6, 8-Dibromobenzoxazinone 1I is submitted to arylation by applying Friedel-Crafts reaction conditions, benzophenone derivatives 341 are afforded. Compound 341a is reacted with hydroxylamine hydrochloride to yield oxime 342 [163].



1 I 341 342

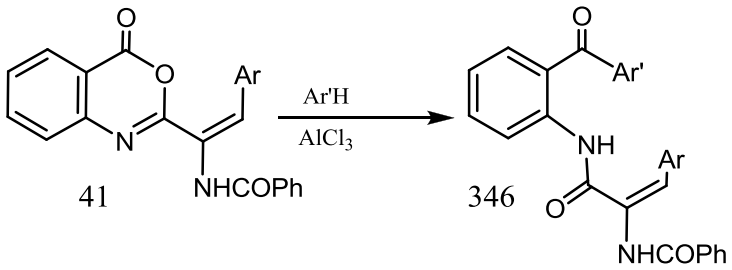
Ar = Ph, 4-$CH_3C_6H_4$, 3,4-di-MeC_6H_3, 2,4-di-MeC_6H_3, 2,6.di-MeC_6H_3

In contrast, 6,8-dibromo-2-methyl-4H-benzoxazin-4-one 1j arylated in different fashion; where it reacts with hydrocarbons namely, benzene, ethylbenzene, m- and p-xylene to afford either two benzophenone derivatives 343 and 344 in case of less bulky hydrocarbons (benzene, ethylbenzene) or only one product 345 in case of more bulky m- and p-xylene [196].



R = 3-Me, 4-Me X = H, Et

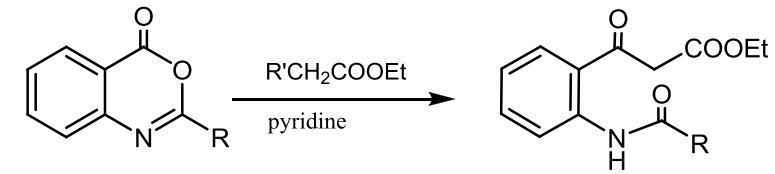
Also 4H-3,1-benzoxazin-4-ones 41 with bulky groups at 2-position arylated when submitted to react wits hydrocarbons under Friedel-Crafs reaction conditions producing benzophenone derivatives 346.



	Ar		Ar’		Ref.
a	4-$OCH_3C_6H_4$	3-$NO_2C_6H_4$	3-indolyl		[86]
b	1-naphthyl	2-furyl	2,4-di-MeC_6H_3	2,5-di-MeC_6H_3	[6]

3.3.4.3 Reactions with active methylene containing compounds

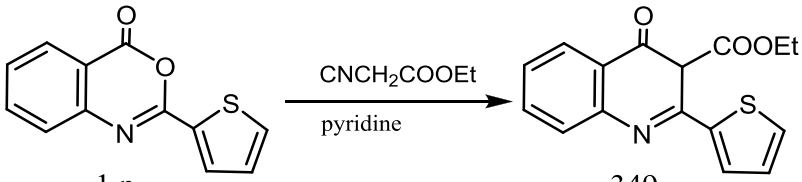
Reaction of benzoxazinones with active methylene containing compounds provide a variety of interesting results. Heating the benzoxazinones 347 with diethyl malonate, ethyl cyanoacetate, or ethyl acetoacetate in dry benzene produce. one and the same product 348 as the consequence of the loss of the R’ group [210, 265,26792, 212].



z 347 348

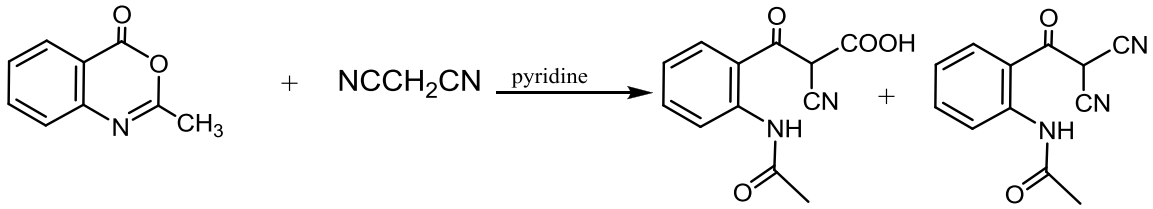
R = Ph, CH_2Ph, CH_2CN, 2-naphthyl
R'= COQEt, CN, COMe

An analogous reaction of thienyl derivative 1p with ethyl cyanoacetate affording the cyclized product 349 [163].



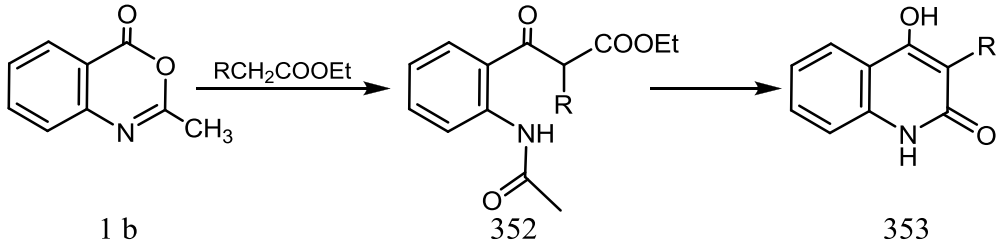
1 p 349

Under the same conditions, benzoxazinone 1b with malononitrile and a mixture of 350 and 351 is furnished [209].



1 b 350 351

Using potassium t-butoxide to generate the anion of the active methylene and running the reaction at room temperature, allow the R' group to be retained giving compound 352. That in turn, can be cyclized to the 4-hydroxy-2-quinoline 353 with either sodium alkoxide or 8% alcoholic hydrochloric acid [79].



1 b 352 353

R = COOEt, CN, COMe, SO_2Me

Recentely, [274] showed that the hit-to-lead optimization of the HNE inhibitor 5-methyl-2-(2-phenoxy-pyridin-3-yl)-benzo[d][1,3]oxazin-4-one is described. A structure–activity relationship study that focused on the 5 and 7 benzoxazinone positions yielded the optimized 5-ethyl-7-methoxy- benzo[d][1,3]oxazin-4-one core structure. 2-[2-(4-Methyl-piperazin-1-yl)-pyridin-3-yl] derivatives of this core were shown to yield HNE inhibitors of similar potency with significantly different stabilities in rat plasma.

More recently, Waisser et al. [311] showed that the new 3-benzyl-4-thioxo-2H-1,3-benzoxazine-2(3H)-ones and 3-benzyl-2H-1,3-benzoxazine-2,4(3H)-dithiones were synthesized. The compounds were tested for in vitro antimycobacterial activity against Mycobacterium tuberculosis, Mycobacterium kansasii and Mycobacterium avium. The replacement of the carbonyl group by the thiocarbonyl group increased the antimycobacterial activity. The most active derivatives were more active than isonicotinhydrazide (INH). The cytotoxicity and the antiproliferative activity were studied as well.