The Chemistry of 4H-3,1-Benzoxazin-4-ones

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Received February 18, 1999

Contents

The present review covers the synthesis and reactions of 4H-3,1-Benzoxazin-4-ones. Only those with carbon substituents at the 2-position are included. Literature corverage includes publications primarily from the mid 1960's to May 1998.

1. Introduction.

4H-3,1-Benzoxazin-4-ones as a class have been known for more than a century. The phenyl derivative **1** was first synthesized in 1883 [1] and the methyl analog **2** seventeen years later [2]. Members of this family have been given the common name "acylanthranils" presumably from their early syntheses from 2,1-benzisoxazole (anthranil) and an acylating agent.

1	R = Ph
2	R = Me

3

4	R = H
5	R = Me
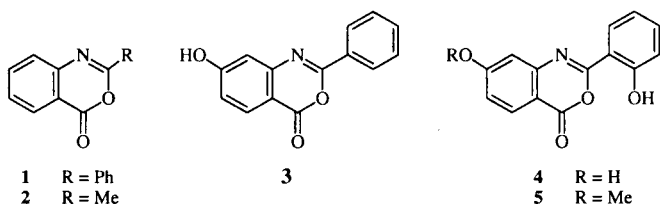
Compounds possessing this ring system are found in nature. The phytoalexins isolated from infected carnations [3,4] are dianthalexin (**3**) and hydroxylated analogs **4** and **5**.

4H-3,1-Benzoxazin-4-ones have been used as linking-units in thermally stable polymers [5] and have been shown to possess biological activity. They are potent inactivators of chymotrypsin [6,7,8] as well as inhibitors of human leukocyte elastase [7,9,10] and HSV-1 protease [11].

## 2. Synthesis of 4H-3,1-Benzoxazin-4-ones.

2.1 From Anthranilic Acids.

By far the most popular and versatile route to the 3,1-benzoxazin-4-one nucleus relies on anthranilic acid or its derivatives as a convenient starting material. Simple 2-substituted derivatives **7** are best prepared by reacting an anthranilic acid **6** with an appropriate anhydride at elevated temperatures. Lower molecular weight anhydrides are usually employed as the solvent [12-19] although co-solvents such as chloroform [20], dioxane [21] and toluene [22] have been successfully used. Yields

6
X = H, halo, OMe, COOH, NO₂

7
R = Me, Et, n-Pr, Ph, CF₃
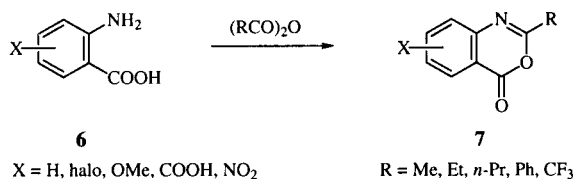
are generally high and fall between 80-95%.

Orthoesters can also be used as a cyclizing agent in the conversion of anthranilic acid to acylanthranils. Heating **6** with 1.5-4 equivalents of an orthoester over a period of 1-2 hours provides the desired product in high yield. When microwave irradiation is used instead of classical heating, reactions are complete within 1-5 minutes [23].

Although these methods provide benzoxazinones in a straightforward manner, the lack of a wide variety of readily

R	Yield (%)
H	80
Me	87
Et	90
Pr	78
Bu	75
Ph	91
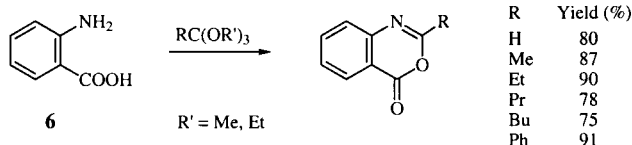
available anhydrides or orthoesters limits the generality of the reactions. A vast array of acid chlorides are either commercially available or easily prepared. Anthranilic acid (6) reacts with two equivalents of an acid chloride in pyridine solution to give the benzoxazinone in good yield.

Mechanistically, the first equivalent of acid chloride acylates the amine to give an N-acylanthranilic acid then the second equivalent forms an anhydride with the acid group to produce an intermediate 8. Cyclization then occurs by an intramolecular nucleophilic displacement of carboxylate ion from the anhydride moiety by the carbonyl oxygen of the amide function [24,25].
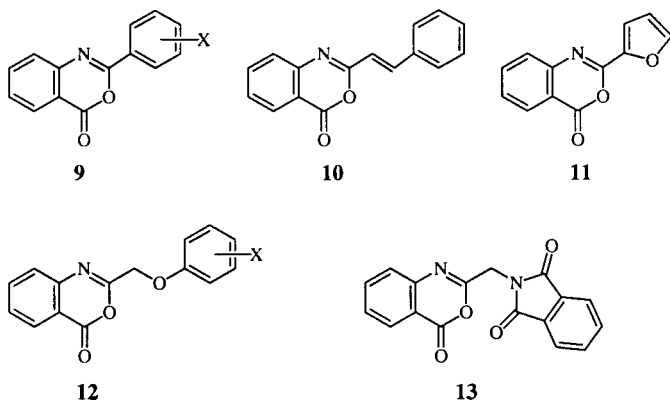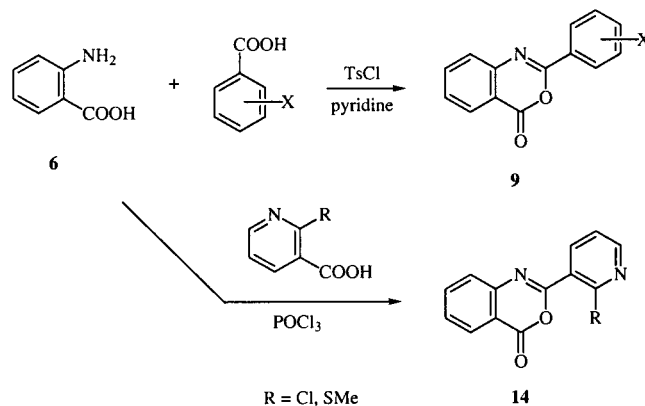
solvent. This route is less suitable for the preparation of 2-alkyl-3,1-benzoxazin-4-ones due to the susceptibility of the products to hydrolyze, however, the 2-cyclohexyl analog [33] as well as the ether and phthalimide derivatives 12 and 13 have been reported [34,35].

A closely related synthesis of 2-phenyl-3,1-benzoxazin-4-ones 9 uses the reaction of 6 with two equivalents of an ortho or para-substituted benzoic acid (X = H, Cl, Me, OMe, NO$_2$) in the presence of tosyl chloride to produce the product in 33-62% yield [39]. Another variation of the theme reacts equimolar quantities of 6 and a benzoic, cinnamic or nicotinic acid in phosphorus oxychloride solvent. Although the products are isolated in low yield (4-29%), the interesting pyridyl analogs 14 are able to be prepared [40]. Higher yields probably would have been realized if two equivalents of the carboxylic acid were used.

N,N-Dimethylchlorosulfitemethaniminium chloride (15) can be employed as an activating agent in the reaction

This procedure is generally used for the synthesis of 2-aryl-3,1-benzoxazin-4-ones. 2-Phenyl analogs 9 containing a variety of substituents (X = H, Cl, Br, Me, OMe, CF$_3$, NO$_2$, COOH) at the ortho, meta or para positions have been successfully prepared [24-29]. Also, both α- and β-naphthyl analogs [30] as well as the styryl derivative 10 [24,31,32] and furyl (11) [24] derivatives have been synthesized. Yields of the reactions generally fall between 75-90%. This technique has been applied to the synthesis of dianthalexin (3) and five other oxygenated analogs [24b]. Modifications of this method use N,N-dimethylaniline [36], tetrahydrofuran/sodium carbonate (powder) [37] or phase transfer conditions [38] to replace the pyridine as the

R = Cl, SMe   14

between 6 and a benzoic acid. The initially formed anhydride-like species 16 acylates 6 an nitrogen with loss of SO$_2$ and DMF to give the N-acylanthranilic acid 17. Subsequent activation of the carboxylic acid group of 17 with another molecule of 15 produces another anhydride-like intermediate which then cyclizes to 9 (X = H, Cl, Me, NO$_2$). These products are isolated in 67-84% yield. Additionally, the corresponding 2-(3-pyridyl) analog 9, (X = 3-N) and 2-methyl derivative 2 are formed in 78% and 52% yield respectively [41].

The interesting aminobenzoxazinone derivative 19 is readily prepared from the reaction of equimolar quantities of 3-trifluoromethylanthranilic acid (18) and a

X = H, Me, OMe, NO$_2$
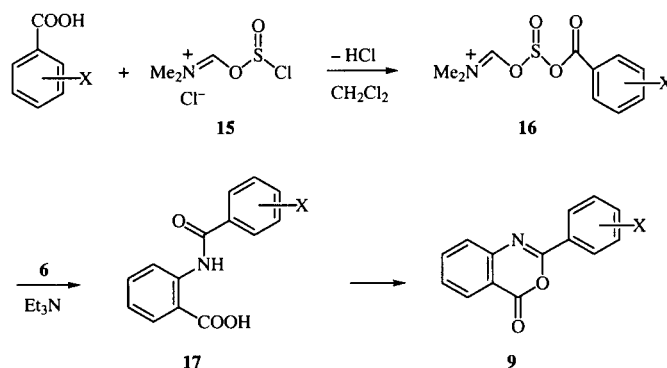
Boc-protected amino acid with two equivalents of isobutyl chloroformate in the presence of *N*-methylmorpholine [42,43]
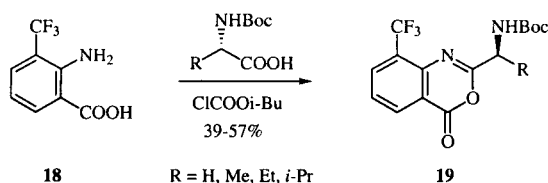
Anilines condense with 4,5-dichloro-1,2,3-dithiazolium chloride (20) to give iminodithiazoles. Anthranilic acid behaves differently. When a methylene chloride solution of 6 and 20 is treated with pyridine, 2-cyano-3,1-benzoxazin-4-one (22) is produced in 46% yield. A similar reaction using triphenylphosphine instead of pyridine gives the analogous 3,1-benzothiazin-4-one (23) in 69% yield. The delicate intermediate iminodithiazole 21 can be isolated if four equivalents of 6 are used without the addition of pyridine. Heating 21 in toluene affords 22 in 99% yield whereas treating 21 with two equivalents of triphenylphosphine produces 23 in quantitative yield [44,45].
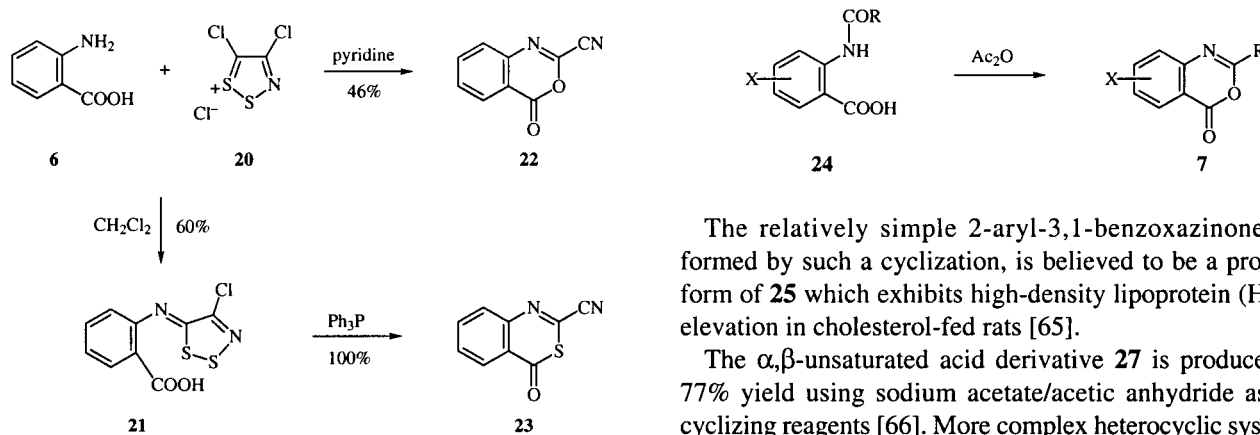
## 2.2 From *N*-Acylanthranilic Acids.

As discussed earlier, reactions of anthranilic acids with excess acylating agents proceed *via* initial *N*-acylation followed by cyclization. It stands to reason that starting from an *N*-acylanthranilic acid a variety of reagents can be used to effect the cyclodehydration to the benzoxazin-4-one.

The most widely used reagent for this purpose is acetic anhydride. The reaction is performed by simply refluxing a solution of 24 in acetic anhydride for about one hr then removing the solvent and crystallizing the product 7. The cyclization can accommodate a wide variety of acyl groups where R can be a simple hydrogen, alkyl or substituted phenyl [46-52] or more complex functionalities like chloroalkyl (CH_2Cl and $CH(Me)Cl$) [53-57], styryl [58], trifluoromethyl [59], phalimidomethyl [60], COOEt [61,62], 2-thienyl, pyridyl and thiadiazole [50,63,64]. The aromatic substituent X can be either an electron donating or withdrawing group.

In the initially formed intermediate 8 where now the two acyl functionalities are different, the *O*-acyl is always eliminated over the *N*-acyl group. Furthermore, once the benzoxazinone is formed no transacylation occurs. For example, heating the parent system 7 (X = R = H), 1 or 2 with propionic anhydride does not result in the formation of any 2-ethyl-3,1-benzoxazin-4-one [46].

The relatively simple 2-aryl-3,1-benzoxazinone 26, formed by such a cyclization, is believed to be a prodrug form of 25 which exhibits high-density lipoprotein (HDL) elevation in cholesterol-fed rats [65].

The α,β-unsaturated acid derivative 27 is produced in 77% yield using sodium acetate/acetic anhydride as the cyclizing reagents [66]. More complex heterocyclic systems

25 → **26**

34 → **35**

X = H, Cl, I, Me, Et, OMe, CF$_3$, COOH, NO$_2$
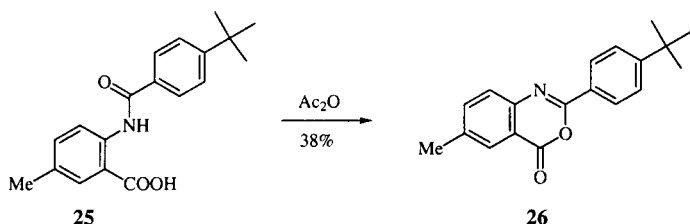
such as a coumarin can be introduced into the 2-position of the benzoxazinone affording **28** in 75-82% yield [67].

27

28 X = H, Br
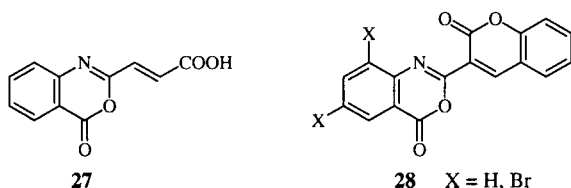
The unusual transformation **29**→**30** proceeds by initial formation of the benzoxazinone ring where both the OH and NH of the hydroxylamine are acetylated. Elimination of acetate, forming an intermediate acylaldimine, followed by readdition of acetate to the α-carbon produces the product **30** [68].


29 → **30**
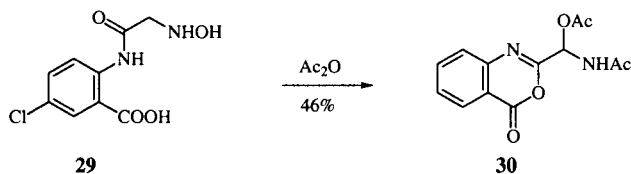
Acylation of anthranilic acid with succinic anhydride affords **31** in 95% yield. Esterification of the alkyl carboxylate followed by refluxing in acetic anhydride for one hr furnishes **33** in nearly quantitative yield [69].

H$^+$
MeOH ⌐ **31** R = H
       └ **32** R = Me

33
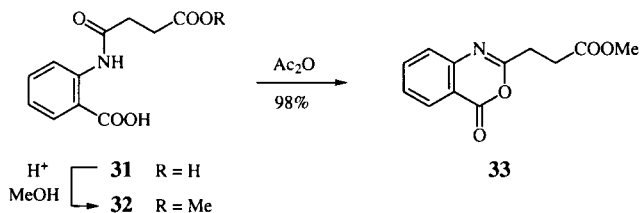
Anthranilic acids can also be acylated on nitrogen with either diketene [70,71] or 2,2,6-trimethyl-4H-1,3-dioxin-4-one (diketene acetone adduct) [72] to give **34** which, when exposed to acetic anhydride, cyclizes to the 2-acetonyl derivative **35** in yields of 8-85%.

Although acetic anhydride appears to be the reagent of choice in the cyclodehydration of N-acylanthranilic acids to benzoxazinones, other acid activating or dehydrating
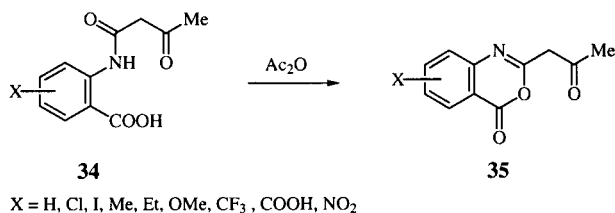
agents have been used to effectively accomplish the same transformation. The action of benzoyl chloride on N-benzoylanthranilic acid furnishes **1** in 81% yield [24a]. The same conversion using methyl isothiocyanate affords **1** in 30% yield [73]. Tosyl chloride [74] and ethyl chloroformate [75] have been used to cyclize N-acetylanthranilic acid to **2**. Heating N-benzoyl- or N-acetylanthranilic acid in pyridine in the presence of triphenyl phosphite gives **1** and **2** in 96% and 90% yields respectively [76]. Using Boc$_2$O, one equivalent of pyridine and a catalytic quantity of 4-(dimethylamino)pyridine in dioxane gives **1** and **2** in 90% and 88% yields respectively [77].

Acylation of methyl anthranilate with (S)-N-Boc-alanine under standard peptide-coupling conditions furnishes **36** in 72% yield. Hydrolysis of the ester to acid **37** and subsequent treatment with Boc$_2$O as above affords **38** in 92% yield. Other amino acids such as phenylglycine, methionine, valine and proline also work well (90-94% yield) [78].

LiOH ⌐ **36** R = Me
      └ **37** R = H

38
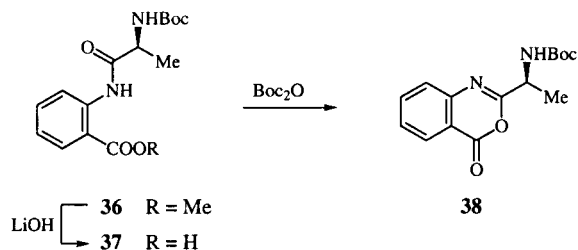
A variety of N-aroylanthranilic acids have been cyclodehydrated to the corresponding 2-substituted phenyl-3,1-benzoxazin-4-one with concentrated sulfuric acid [79,80]. This method is not suitable for the preparation of 2-alkyl analogs due to the ease of hydrolytic cleavage of the heterocyclic ring under the reaction conditions.

Refluxing a solution of **39** with a small excess of thionyl chloride in 1,2-dichloroethane for one hr produces the benz-

39 → **40**
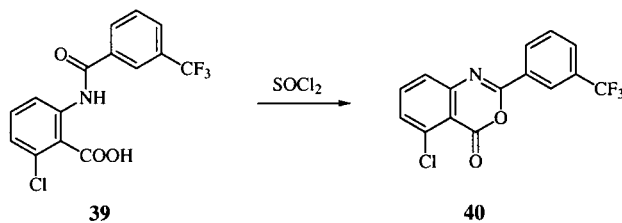
oxazinone **40** in 92% yield [50a]. This method is relatively mild and can be used to prepare benzoxazinones where the 2-substituent contains a β-dicarbonyl moiety [50b].

The herbicidal 2-dichloromethyl-3,1-benzoxazin-4-one (**42**) is prepared by cyclodehydration of **41** with *N,N*-dicyclohexylcarbodiimide at room temperature for three hours [81].

41   **42**
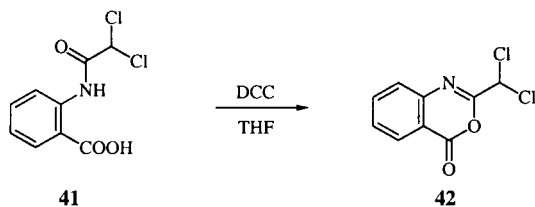
N-acylanthranilic acids, under Vilsmeier-Haack conditions (oxalyl chloride/*N,N*-dimethylformamide) [82] or upon reaction with the solid Vilsmeier salt **44** in refluxing acetonitrile for 10 minutes, rapidly form enamino benzoxazinone derivatives **45** in good yields [83].

43   **44**   **45**   R = H   77%
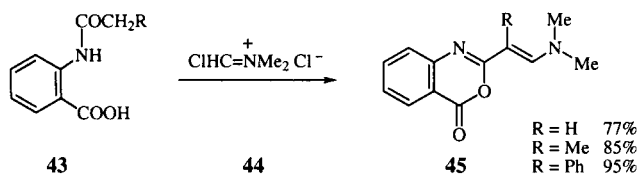   R = Me   85%
                                                      R = Ph   95%

2.3 From Isatoic Anhydrides.

Isatoic anhydrides are noted for their versatility in heterocyclic syntheses so it is no surprise that the 4H-3,1-benzoxazin-4-one heterocycle can be obtained from the closely related 2H-3,1-benzoxazine-2,4(1H)-dione system. When isatoic anhydride (**46**) is refluxed in acetic anhydride for 4-6 hours [84], refluxed in acetic anhydride/pyridine for 2 hours [85] or stirred with trifluoroacetic anhydride/pyridine at room temperature for 15 minutes [86] the corresponding benzoxazinone **2** or **47** is isolated in high yield.

46   **2**   R = Me
   **47** R = CF₃
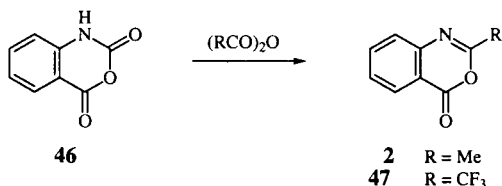
Isatoic anhydride also reacts with acid chlorides at elevated temperatures to give 3,1-benzoxazin-4-ones. Thus, heating **46** and benzoyl chloride at 197-215° for 6 hours

gives the 2-phenyl analog **1** in 94% yield [87,88]. Likewise, refluxing a mixture of **46** and either cinnamoyl chloride or oxalyl chloride in pyridine/toluene solvent produces the 2-styryl analog **10** or the bis-3,1-benzoxazin-4-one **48** in 93% and 86% yields respectively [85a]. If the reaction with oxalyl chloride is carried out in benzene using anhydrous aluminum chloride or 4-(dimethylamino)pyridine as an additive, the 2-chloroformyl derivative **49** is formed [85b].

48   **49**
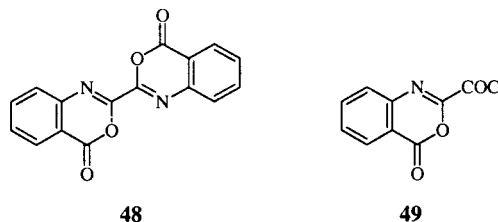
Thermolysis of isatoic anhydride in boiling 1-methylnaphthalene affords aminophenylbenzoxazinone **51** in 25% yield [89]. The product is believed to arise from a Diels-Alder-like reaction off two molecules of ketenimine **50**, one which behaves as a diene and the other a dienophile. Pyrolysis of **46** in diethylphthalate or ethyl anisate produces **52** (60% yield) and **53** (37% yield).

46   **50**   **51**

52 R₁ = COOEt R₂ = H
53 R₁ = H   R₂ = OMe
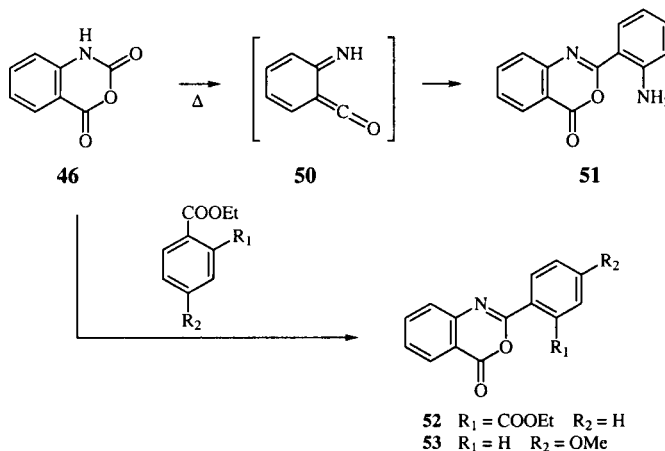
Reactions of isatoic anhydride with phosphoryl-stabilized anions bearing no α-hydrogen atoms leads to the formation of 3,1-benzoxazin-4-ones. Consequently, when **46** is allowed to react with the anion of ethyl 2-diethylphosphonopropanoate or α-diethylphosphono-γ-butyrolactone in refluxing benzene (3-5 hours), products **54** or **55** are obtained in 64% and 91% yield respectively [90,91].

2-Isocyanatobenzoyl chloride (**56**), prepared from **46** and thionyl chloride, reacts with phenylmagnesium bromide at the more reactive isocyanato group to give **1** in 70% yield. The 5-chloro derivative affords **57** in 40% yield [92]. In a similar

54   **46**   **55**
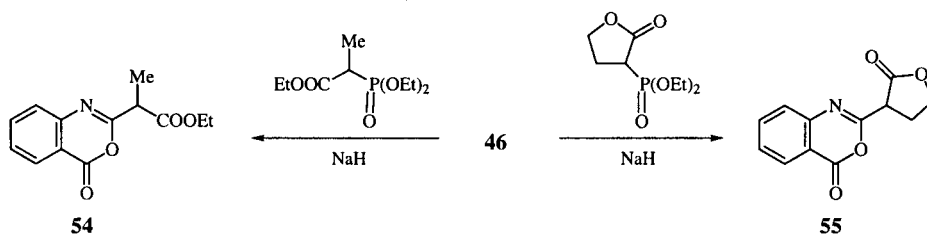
fashion, cyanotrimethylsilane reacts with **56** in refluxing chloroform to produce the 2-cyano derivtive **22** in 54% yield [93].

1 R = H
57 R = Cl

22

56
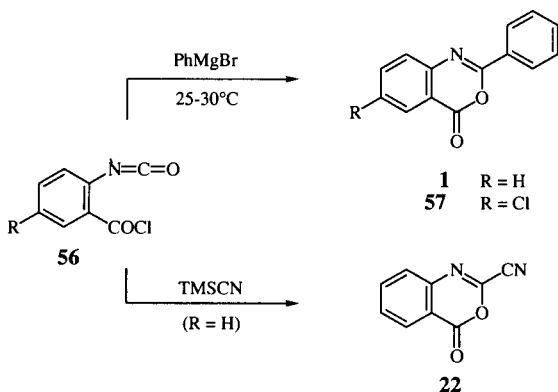
2.4 Oxidation of Indoles.

2-Substituted indoles **58** are readily oxidized with *m*-chloroperoxybenzoic acid [94] or monoperphthalic acid [95] to the corresponding benzoxazinone in low yield. A similar transformation can be accomplished by the photooxygenation of 2-phenylindole in methanol using Rose Bengal as a sensitizer [96].

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

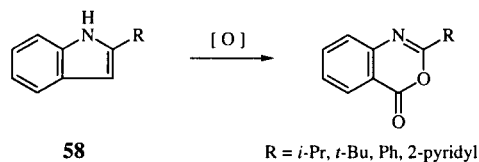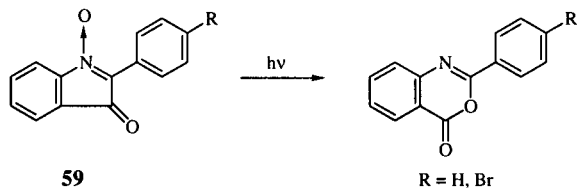On the other hand, photolysis of 2-phenylisatogen (**59**), which is a potential intermediate in the conversion of **58**→**1**, in cyclohexane results in the formation of **1** in 93% yield [97,98]. The reaction proceeds much better in non polar solvents as evidenced by an identical reaction in ethanol which produces **1** in only 53% yield.

59   R = H, Br

In a closely related transformation, the oxidation of 2-phenylindolenin-3-one (**60**) with *m*-chloroperoxybenzoic acid in chloroform affords **1** [99] whereas oxidation of the 4-dimethylamino analog **61** with 30% hydrogen peroxide in dimethylformamide furnishes **62** [100].

60   R = H
61   R = NMe$_2$

1   R = H (71%)
62   R = NMe$_2$ (60%)
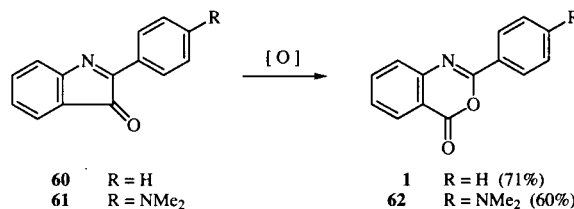
2.5 Other Syntheses.

Pyrolysis of 1,2,3-benzotriazin-4-ones **63** in 1-methylnaphthalene generates the same type of intermediate **50** that isatoic anhydrides do and consequently undergo the same [4+2] cycloaddition to give **51**, **64a** or **64b** in moderate yields [89,101]. Performing the pyrolysis in refluxing anisaldehyde results in the formation of 2-(4-methoxyphenyl) derivative **65** in 22% yield.

63   **50**   **51**   X = H   (44%)
                               64a X = Cl   (40%)
                               64b X = OMe (38%)

65
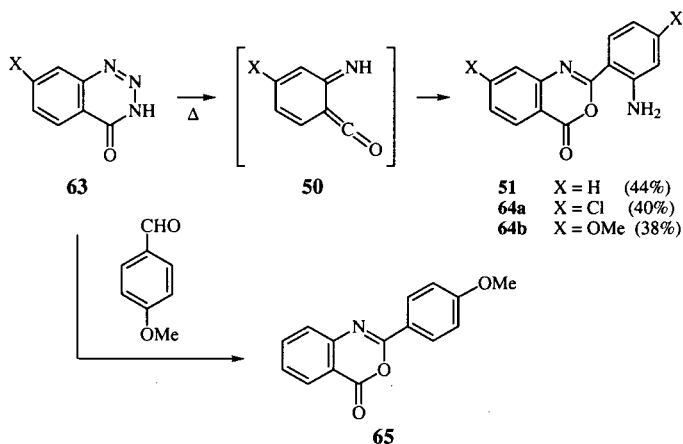
Condensation of 2-azidobenzoic acid (**66**) with a functionalized benzaldehyde at 115-120° produces 2-phenyl-3,1-benzoxazin-4-ones in 60-72% yield [102]. The reaction is believed to proceed by initial formation of an oxatriazoline species **67** which, under anchimeric assistance of the carbonyl group, loses elements of nitrous oxide followed by dehydration to form the product.
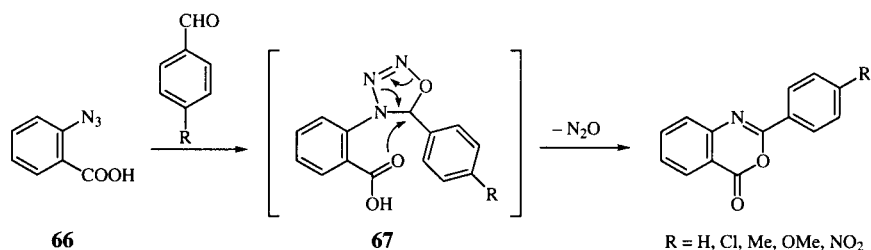
When equimolar amounts of *N*-aroylanthranilamides **68** and triethyloxonium fluoroborate are refluxed in methylene chloride for one hr, the corresponding 2-phenyl-3,1-benzoxazin-4-ones **9** are exclusively formed in moderate yield [103].
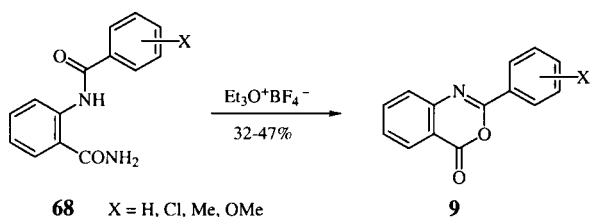
Electrochemical cyclization of *o*-trichloroacetanilides **69** produces a mixture of 2-phenyl-3,1-benzoxazin-4-ones (40-45%) and the corresponding *o*-dichloroacetylanilide (38-46%) as a result of dehalogenation of **69** [104].

Treatment of iminophosphorane **70** with benzoyl chloride in acetonitrile in the presence of a small excess of triethylamine gives the 7-nitro-2-phenylbenzoxazinone **71** in 42% yield. In the absence of the tertiary amine the yield falls to 13%. The method is useful for the production of heteroannulated 3,1-benzoxazin-4-ones where the benzene ring is replaced with thiophene, thiazole and pyridazine [105].
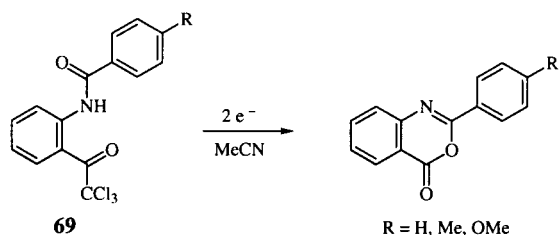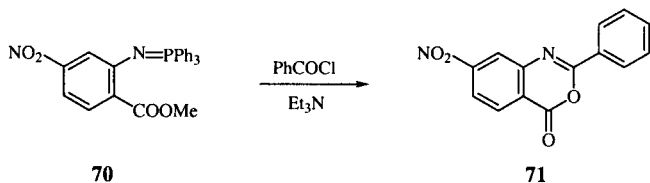

The self-condensation of two molecules of *N*-benzenesulfonylanthranilic acid (**72**) in polyphosphate ester at 120° results in the formation of **73** in 38% yield [106].
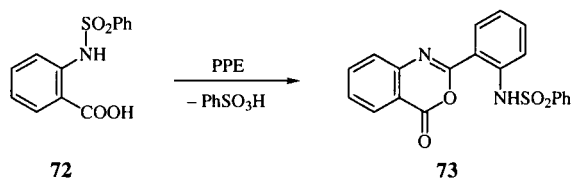
In an interesting series of rearrangements 2-phenylisatogen (**59**), in the presence of sulfuric acid in methanol, is converted to 3-benzoyl-2,1-benzisoxazole (**74**). A thermal rearrangement of **74** in acetic anhydride/pyridine affords **1** in 93% yield [107].
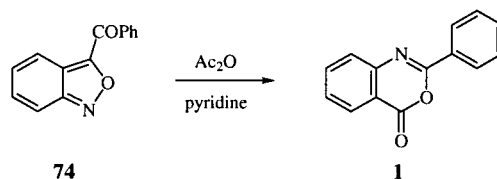
Heating thioamide **75** in refluxing *t*-butylbenzene causes cyclization to occur with loss of hydrogen sulfide to produce the 2-pyrrolyl-3,1-benzoxazin-4-one **76** in 94% yield. Alternatively, briefly heating **75** with concentrated hydrochloric acid in acetic acid furnishes the corresponding 3,1-benzothiazin-4-one **77** in 89% yield [108].
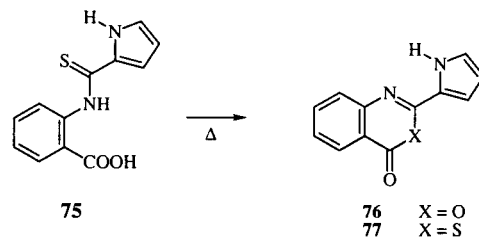
In all the syntheses of 3,1-benzoxazin-4-ones presented so far the common scenario begins with starting materials which have the amine and carbonyl carbon (which will ultimately become the 1- and 4-positions of the product)

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 **78** in the presence of potassium carbonate and palladium catalyst under an atmosphere of carbon monoxide.

A three-component reaction, using 2-iodoaniline (**80**) as the aromatic anchor, an aryl iodide or vinyl triflate (as precursors of the substituent at the 2-position), and carbon monoxide to supply the 4-carbonyl, allows access to a variety of 2-aryl or vinyl-3,1-benzoxazine-4-ones under relatively mild conditions[109]. A good example of this methodology at work is the reaction of **80** with triflate **81** to give the steroidal benzoxazinone **82** in 78% yield.

3. Spectral Characteristics.

The nature of the skeletal components of the 3,1-benzoxazin-4-one system makes characterization of the compounds easy by spectral methods. The presence of a lactone c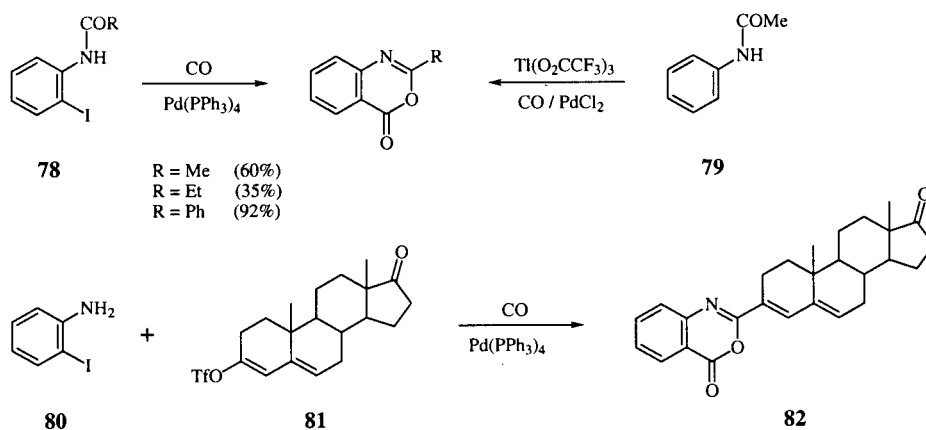arbonyl makes infrared spectroscopy an obvious tool for initial identification. The C=O absorption is generally observed between 1770-1750 cm^{-1}. The parent compound (where the 2-substituent = H) has been reported to have a carbonyl stretching frequency at 1755 cm^{-1} [23]. 2-Alkyl analogs fall within a relatively narrow wavelength of 1765-1758 cm^{-1} [23,111] whereas 2-aryl derivatives, depending on the nature of their substitution, spread throughout the general range [24a,39]. A secondary band associated with the C=N double bond is seen at 1650-1615 cm^{-1} [36,56,112].

78   R = Me   (60%)
      R = Et   (35%)
      R = Ph   (92%)

79

80   +   81   →   82

Table 1

Comparison of Preparations for the Commonly Used Benzoxazin-4-ones

2-Substituent	Method	Yield (%)	Reference
CH₃	A	100	22
	B	90	23
	D	85	285
Ph	A	100	22
	B	94	23
	C	90	24a
	D	81	46
CF₃	A	40	20
	D	90	59
	E	86	207

Methods: (A) anthranilic acid + anhydride; (B) anthranilic acid + orthoester; (C) anthranilic acid + acid chloride; (D) *N*-acylanthranilic acid + acetic anhydride; (E) *N*-acylanthranilic acid + thionyl chloride.

By taking advantage of the strong *ortho*-directing effect of the oxygen atom, *N*-acetylaniline (**79**) can be thallated adjacent to the amide group and subsequently carbonylated under an atmosphere of carbon monoxide in the presence of catalytic amounts of palladium chloride to afford **2** in 40% yield [110]. The generality of this reaction has not been explored.

The ultraviolet spectra of 3,1-benzoxazin-4-ones shows a λ_{max} at 305-365 nm and 215-250 nm [24a,113,114].

The proton nmr spectra of benzoxazinones is obviously dependent on the nature of the substituent at the 2-position. For the simple CH_3 analog **2**, the methyl signal is observed at δ 2.47 ppm. The proton at position 5, due to its proximity to the carbonyl group falls at δ 8.16 ppm [23,109]. The carbon-13 chemical shifts for the carbon at position 2 are dependent on the substituent (see Table 2). The signal for the carbonyl carbon at position 4 is less variable and for the common derivatives falls between δ 159.1-156.6 ppm [23,109,115]. For the assignment of the remainder of the carbon shifts and for data on 18 additional compounds please see reference 115.

Table 2

¹³C-nmr Chemical Shifts for the Common
2-Substituted-3,1-benzoxazin-4-ones

| R	δ C2	δ C4
CH₃	160.1	159.1
t-C₄H₉	167.5	159.1
CF₃	146.2	156.6
Ph	156.3	158.7

High-resolution electron impact mass spectra of compounds 1 and 2 show a fragmentation pattern which involves the primary loss of CO_2 from both parent ions, $C_6H_5\bullet$ from 1 and Me• from 2. Also seen is a loss of ketene from compound 2. The ion RCO^+ is a major daughter [116].

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

Electrophilic reactions on the benzene ring of the benzoxazinone nucleus are rare and are probably unnessary due to the plethora of diversely substituted anthranilic acids which are available. This section will focus on the remaining reactive sites and feature the reactions at the C-4 and C-2 carbons of the heterocycle as well as the substituent attached to the 2-position.

4.1 Reactions at the 2-Substituent.

3,1-Benzoxazin-4-ones bearing an alkyl substituent at the 2-position are susceptible to oxidation at the methylene adjacent to the heterocyclic ring. Oxidation of the methyl analog 2 or benzyl analog 83 with selenium dioxide in either ethanol or acetic anhydride furnishes the 2-carboxaldehyde 84 [117] or 2-benzoyl derivative 85 [112] in 63% and 53% yields respectively.


2	R = H	84	R = H
83	R = Ph	85	R = Ph
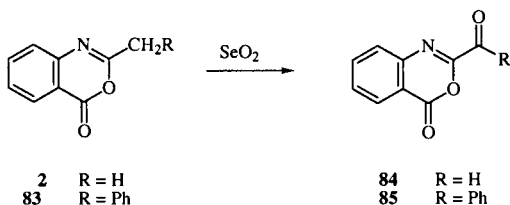
The 2-benzylbenzoxazinone 83, under Vilsmeier conditions is converted to 45 [83].

83   45
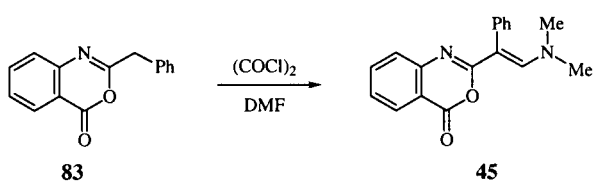
2-Styryl-3,1-benzoxazin-4-ones are readily available from the condensation of a 2-alkyl benzoxazinone with an aromatic aldehyde. This is accomplished by boiling a neat mixture of the benzoxazinone and an appropriate aldehyde for a period of 30 min to 4 hours and gives 86 in 40-80% yield [118-120]. In some instances the reaction is facilitated by the addition of anhydrous zinc chloride [121,124]. The zinc forms a coordination comples with the nitrogen of the benzoxazinone and subsequently loses hydrogen choloride forming a carbanion at the "benzylic" carbon. This species then condenses with the aldehyde to produce the product 86. This reaction is not only limited to aldehydes but ketones

such as acetone, benzophenone and acetophenone produce olefinic derivatives in 60-65% yield [125].

R = H, Me, Ph
X = H, Me, OH, OMe, NO_2, styryl, NMe_2

86
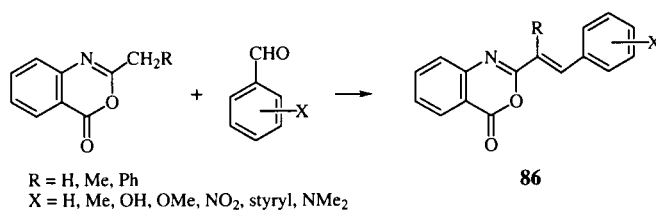
The reaction of 2-ethyl- or 2-cyanomethyl-3,1-benzoxazin-4-one with succinic anhydride and phthalic anhydride (not shown) or their corresponding imides in the presence of zinc chloride at 170-220° results in the formation of the methylene tetrahydrofuranone adduct 87 in 62-80% yield [124,126].

R = Me, CN   X = O, S   87
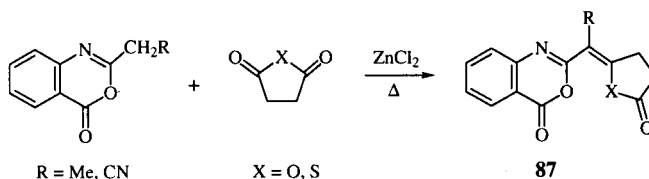
The same reaction of succinic, maleic or phthalic anhydride (not shown) with 2 or its 6-bromo derivative 88 produces the diketone 89 in 53-50% yield [123,125].

2	X = H	
88	X = Br	89
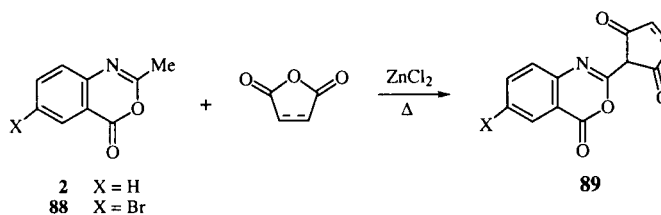
2-Styrylbenzoxazinones behave as dienes in the Diels-Alder reaction. Heating 10 or 90 with either maleic anhydride or N-phenylmaleimide in refluxing xylene (12-18 hours) affords the [4+2] adduct 91 in 40-60% yield [58,125].

10	R = H	X = O, N-Ph	
90	R = COMe		91
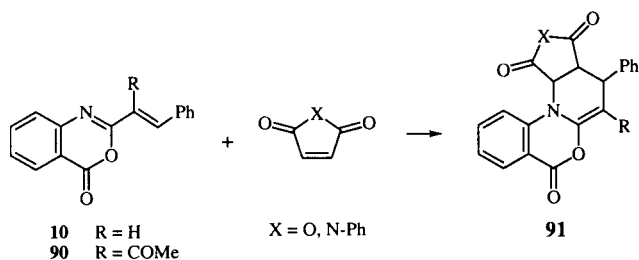
4.2 Reaction with Hydrogen Nucleophiles.

The benzoxazine nucleus is susceptible to attack by hydride reagents such as sodium borohydride. Reactions

are usually performed in ethanol, methanol or tetrahydro-furan and tend to give varying mixtures of *N*-alkylan-thranilic acids **92** and 2-acylaminobenzyl alcohols **93** [99,127,128].

X = H, Cl
R = Me, *t*-Bu, Ph, styryl, 2-thienyl, CF₃
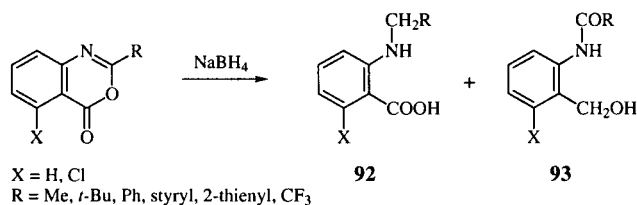
Catalytic hydrogenation of **2** in acetic acid affords *N*-acetyltoluidine (**94**) in 41% yield. A similar reduction of **1** gives *N*-benzoylbenzyl alcohol (**93**, R = Ph, X = H) in 16% yield. Hydrogenation of **95** under neutral conditions results in the initial reduction of the C=N bond then cyclization with the *o*-carboxylic acid group to furnish the tetracycle **96** in 40% yield [129].
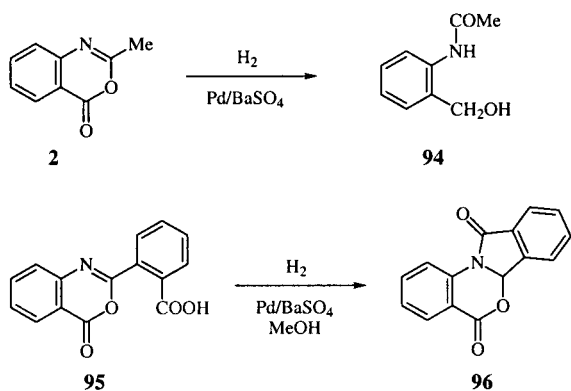
4.3 Reaction with Oxygen Nucleophiles.

The simplest and sometimes the most unwanted reaction of some 3,1-benzoxazin-4-ones is hydrolysis. The parent compound **7** (X = R = H) is moisture sensitive and extremely hygroscopic [23]. 2-Alkylbenzoxazinones are more prone to hydrolysis than their 2-aryl counterparts. In fact, 7-chloro-2-(3-methylphenyl)-4*H*-3,1-benzoxazin-4-one remains unchanged after standing in a sealed bottle for one year [130]. Exposure of solid **2** to moist air for 15 days results in the quantitative formation of *N*-acetylanthranilic acid (**98**) [131].

In aqueous solution **2** is hydrolyzed to **98** under either basic or acidic conditions. The reaction is stoichiometric, the kinetics is pseudo-first-order, and the rate constant (k) attains a minimum value at pH 6.8. Under basic conditions, nucleophilic attack occurs at C-4 (**99**) whereas under acidic conditions the nitrogen (N-1) is protonated thus activating C-2 to attack [132].

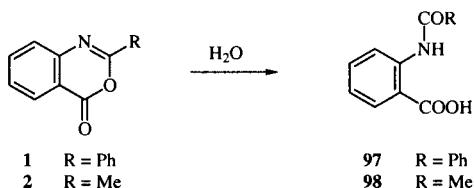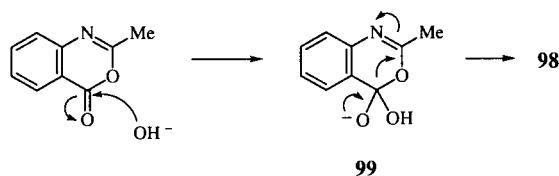Organic solvents have a profound effect on the rate of the hydrolysis of **2**. The rate constant in proton-acceptor solvents decreases in the order benzene > dimethyl sulfoxide > acetone > *N,N*-dimethylformamide > pyridine whereas for hydrolysis in proton donor solvents it decreases in the order benzene > chloroform > acetonitrile [133].

Incorporation of a carboxylic acid at position 8 **100** allows intramolecular protonation of N-1 which enhances susceptibility of nucleophilic attack at C-2 (and/or C-4). Consequently, the rate of hydrolysis of **100**→**101** is increased 250 fold over **2**→**98** at pH 6.8 [114,134].
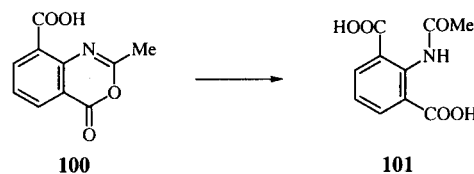
Hydrolysis of **1** also occurs under both basic and acidic conditions. Heating **1** with 2*N* sodium hydroxide affords *N*-benzoylanthranilic acid (**97**) in 96% yield [24,107]. Likewise, heating an acetone solution of **1** with 2.7*N* hydrochloric acid gives **97** in 99% yield [107].

3,1-Benzoxazin-4-ones can be considered as semiacid anhydrides which undergo many of the reactions of true acid anhydrides but at a slower rate. This special reactivity allows this class of compounds to be quite useful as serine protease inhibitors, inactivating enzymes such as chymotrypsin [8], human leucocyte elastase [9,10], porcine pancreatic elastase, cathepsin G [7] and C1r serine protease [27]. Mechanistically, the inactivation involves nucleophilic attack of the active site serine hydroxyl group on the C-4 carbonyl of the benzoxazinone which leads to ring opening and formation of an acylated enzyme (Figure 1). The chemical stability and potency of the benzoxazinones can be tuned by chosing substituents (R) which influence the reactivity of the carbonyl by electronic and steric effects.

Figure 1

Solution-phase reactions of acetylanthranil (**2**) with alcohols under basic conditions occur similarly by attack of alkoxide on the carbonyl to furnish *N*-acetylanthranilic esters **102** in high yields [85,135].

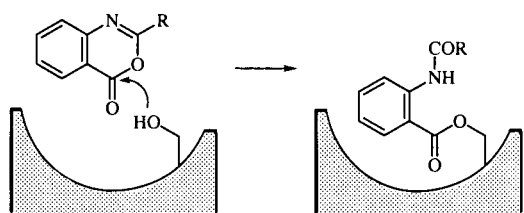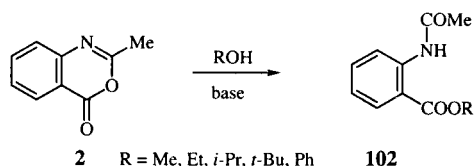**2**   R = Me, Et, *i*-Pr, *t*-Bu, Ph   **102**

Under neutral conditions, reactions of **2** with alcohols takes a different course. The nucleophile ROH undergoes an "abnormal" nucleophilic attack at the less electropositive C-2 center. This is thought to arise by hydrogen bonding of the alcohol to the nitrogen of the heterocycle then an intra-complex attack at the nearest electropositive carbon atom (**103**) [135]. The resulting transient intermediate **104** reacts further with alcohol then self-condenses to give the 4-quinazolone **105** in 69% yield [136]. This self-condensation occurs more readily in the solid state (exposure of **2** to methanol vapor) than it does in solution [137].

The yield of 4-quinazolone by this process is influenced by the nature of the solvent or the kind of substituents at position 2 or 5 in the benzoxazinone. The reaction occurs readily in methanol or ethanol and is hampered in iso-propanol and more strongly in *t*-butanol. In aprotic solvents, dimeric condensation does not occur. If the 5-position is substituted with Cl, the corresponding 4-quinazolone is formed exclusively with no by-products. If the 2-position is substituted with a straight chain alkyl group, the yield of 4-quinazolone is high. Conversely, a more bulky substituent such as *t*-butyl, phenyl or styryl inhibits formation of the 4-quinazolone even when a chlorine atom is present at position 5 [111].
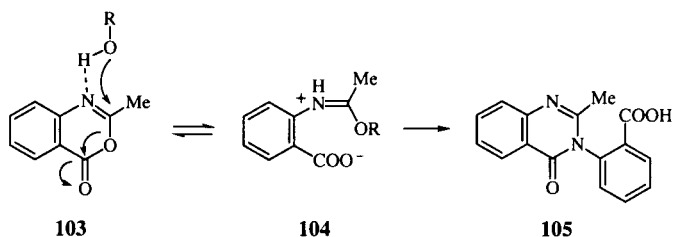
4.4 Reaction with Nitrogen Nucleophiles.

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

Ammonia (the simplest of amines) or ammonium hydroxide, when allowed to react with **7** over a period of 1-3 hours produces anthranilamide **106** in good yield [46,80,138,139]. This, in turn, can be cyclized to the 3-unsubstituted-4-quinazolone **107** under thermal conditions (240-280°) or with acetic anhydride. Quinazolone **107** can also be produced from **7** by longer reaction times with ammonium hydroxide (16-24 hr) [48,140] or by heating with formamide (170-175°) [17,33,141,142] or ammonium acetate at 130-150° [143,144]. One example has been reported which converts **2** to **107** (X = H, R = Me) using the complex [3THF•Mg$_2$Cl$_2$OTiNCO] in 38% yield [145].

7   **106**   **107**

X = H, Cl, Br, Me
R = alkyl, CH$_2$CN, PhY (Y = Br, NHMe)
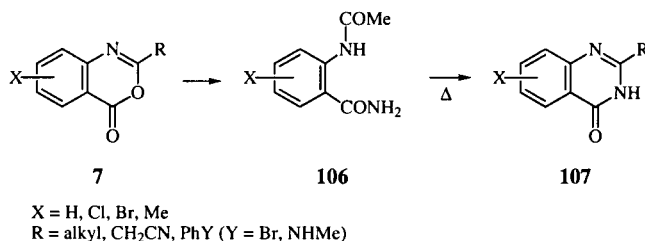
Solvent has a profound effect on the mode of reaction of **2** with ammonia. In benzene, anhydrous ammonia reacts at a slower rate (3 days) to produce quinazolone **107** (X = H, R = Me) as the sole product. The rate of conversion is six times faster in pyridine than in benzene. However, if water is added to the benzene system, the rate of reaction increases by orders of magnitude but the sole product is **106** (X = H, R = Me) [146]. The conversion is mechanistically similar to **103** where ammonia (instead of water) hydrogen bonds to the nitrogen atom of the heterocycle then undergoes "abnormal" nucleophilic addition to C-2 to form the amidine salt **108** (pathway A) which subsequently dehydrates to give the quinazolone.

103   **104**   **105**   **109**   **110**
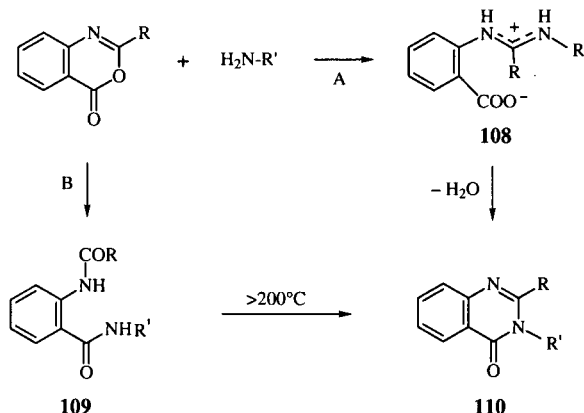
With primary aliphatic amines, the salt **108** can be isolated [147] and it has been shown that in solution **108** is readily converted to **110** even at room temperature. This mechanistically precludes pathway B because *N*-acylanthranilamides **109** require temperatures >200° to effect cyclization to **110**. Anilines also react by pathway A but at a slower rate [148,149].

Steric factors play an important role on the reaction pathway. Reaction of **2** with isopropylamine or *t*-butylamine exclusively follows pathway B to give **109** [150]. Amines having the general formula $H_2N(CH_2)_nH$ follow pathway A when n < 4 but follow pathway B when n ≥ 4. This crossover in selectivity is attributed to the $H_2N(CH_2)_4$ segment which forms a six-membered Newman coil which is held together by intramolecular van der Waals forces thus presenting the benzoxazinone with a rather bulky amine [147,151]. An identical reaction of **2** with $H_2N(CH_2)_3Si(OEt)_3$, which has no protons at the fourth position and cannot form a Newman coil, now follows pathway A and gives the amidine salt **108** in 95% yield. Likewise, when the amine $H_2N(CH_2)_nX$ possesses a terminal polar group (X = OH or COOH), the reaction follows pathway A due to interruption of the Newman coil by intermolecular hydrogen bonding [152,153].

Secondary amines such as dimethylamine, morpholine, piperidine and pyrrolidine almost always follow pathway B [150,154]. The nature of the substituent at the 2-position of the benzoxazinone affects the relative reactivity due to its influence on the electrophilicity at C-2 by electronic induction and/or resonance contribution. The order of reactivities for carbon substituents is CF_3>H>CH_3>Ph [59]. As a general rule, more reactive acetylanthranils favor pathway A whereas the less reactive benzoylanthranils (R = Ph) favor pathway B [59,148].

In contrast to the above observations, 6,8-dibromo-3,1-benzoxazin-4-one, whether substituted at position 2 with a methyl or phenyl, reacts slowly with primary amines in ethanol to afford the acyl anthranilamide via pathway B [120,155,156].

Experimental conditions for the reactions of anilines with benzoxazinones are quite varied. The reactants can be combined neat at room temperature [13], at elevated temperatures ranging from 150-220° [51,52,64,157] or at 150-180° in the presence of zinc chloride [121,158-160]. Alternatively, the reaction can be performed in solvents such as pyridine [161,162], dioxane [54,55], acetic acid [49], dimethylformamide [163] or ethanol [54,164]. The anilines can be sub-

stituted with a variety of substituents to afford quinazolones **111** where Y = halogen, methyl [54,163], hydroxy [35,165,166], methoxy [163,167], phenoxy [168], nitro [169,170], anilino [171], SO_2NH_2 [19,172] and COOEt [16,173,174]. The *ortho* and *meta* positions can also be substituted [158,159]. Aminoheterocycles such as pyridine, pyrimidine [34,175], pyrazole [176], thiazole [34,177] or 1,3,4-thiadiazole [14,31,178] have also been successfully used. Products derived from these reactions have found uses as antimalarials [179], psychotropic [169] or antiparkinsonian agents [180].

X = H, halogen
R = Me, CH_2Cl, Ph, CH_2Ph, COOEt

111
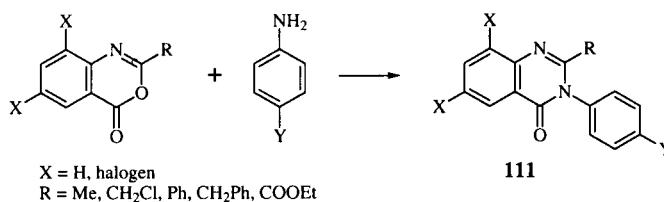
The CNS agent methaqualone (**113**) is easily prepared in 92% yield by refluxing a mixture of **2** and *o*-toluidine in toluene under azeotropic conditions [84]. The 7-carboxy analog **114** is synthesized in 68% yield by mixing **112** and *o*-toluidine at room temperature for 3-4 hours [13].

2   R = H
112   R = COOH

113   R = H
114   R = COOH
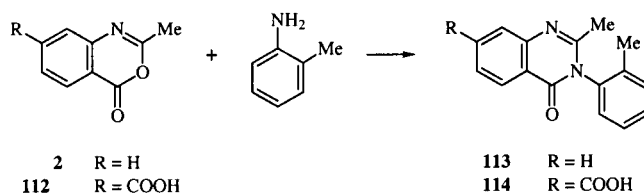
Reactions of benzoxazinones with anilines containing a reactive functional group at the *ortho* position adds another dimension to the basic transformation, that further cyclization to more complex heterocyclic systems is possible. An interesting example of this is the reaction of a benzoxazinone with a 2-cyanoaniline. When the reactants are refluxed in benzene for 24 hours, the quinazolino[3,4-a]quinazolin-13-one **117** is produced in 55-80% yield [181]. The reaction proceeds along pathway A to give amidine intermediate **108**. The amine nitrogen then attacks the nitrile to give the 4-iminoquinazoline **116** which then cyclizes to **117**.

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

115

116

117
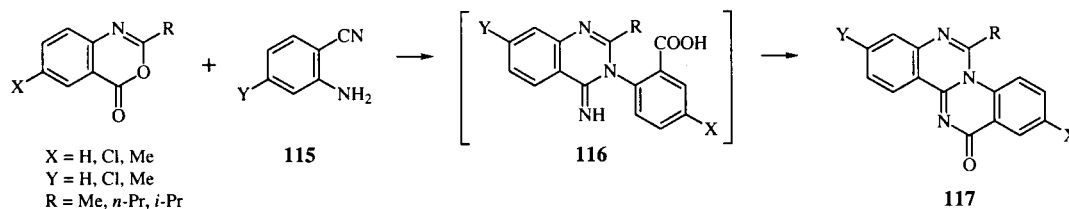
Under appropriate conditions, benzoxazinones are able to transfer its 2-carbon and its attached substituents to another molecule. When **1**, **2** or **83** is refluxed with *o*-phenylenediamine (**118**) in chloroform, 2-substituted benzimidazoles **119** are formed in high yield along with a small amount of anthranilic acid [112,182]. Conversely, heating the two reactants in polyphosphoric acid at 200° provides **120** in 90% yield.

119

118

R = Me, Ph, CH₂Ph

R = Ph

120
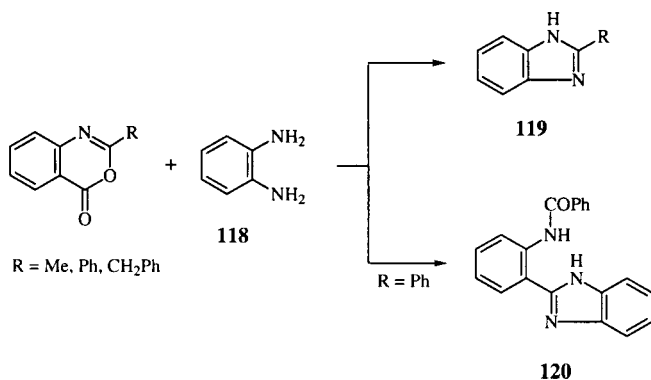
Refluxing a mixture of **121** and **118** in acetic acid in the presence of fused sodium acetate results in the formation of tetracycle **122** [183]. This heterocycle is probably formed by the cyclodehydration of an intermediate similar to **120**. In fact, if **120** is heated at 300° in a sublimation apparatus it cyclodehydrates to give a similar ring system [112].

121   **122**
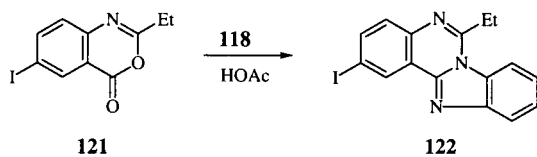
If the 2-substituent on the benzoxazinone contains a reactive group such as a carbonyl (*e.g.* **85**) the *o*-phenylenediamine, after forming the quinazolone, cyclodehydrates to afford **123** [112].

85   **123**
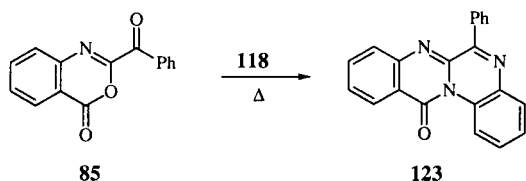
Treating **124** with indolylmagnesium bromide results in the formation of **125** which is isolated in 54% yield. Heating this compound with 6*N* hydrochloric acid causes cyclization to occur thus forming the indolo[2,1-*b*]quinazolone **126** [184].

124   **125**

126
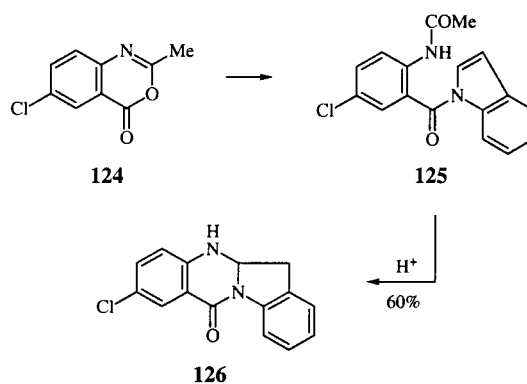
Primary non-aromatic amines react readily with 3,1-benzoxazin-4-ones to give a wide variety of 3-substituted-4-quinazolones **110**. Simple straight-chain alkyl amines as well as benzylic amines and heterocyclic-containing alkyl amines react with equal facility [18,120,185-191]. If the 2-substituent is a methyl (*e.g.* **127**), it can be homologated to the styryl derivative **128** simply by refluxing with an appropriate aldehyde for 10 minutes [192].


127   **128**
R = Me, *n*-Bu   Ar = phenyl, naphthyl, 2-furyl
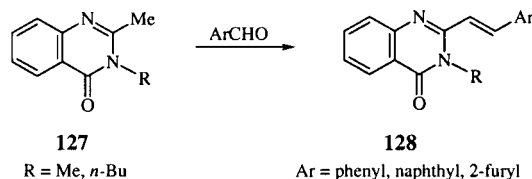
2-Methyl-3,1-benzoxazin-4-one (**2**), as well as the 2-phenyl analog **1**, reacts with ethanolamine or ethylenediamine to produce the corresponding 3-functionalized quinazolones **129** or **130** in good yields [28,153,171b].

2   **129** X = OH
                         130 X = NH₂
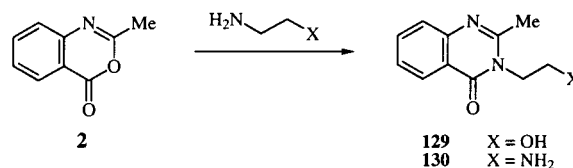
Analogs such as these have the added capability to react further and generate more complex heterocyclic systems. For example, derivative **131**, prepared in 65% yield from 2-ethyl-6-iodo-3,1-benzoxazin-4-one, when heated in acetic acid in the presence of fused sodium acetate, cyclodehydrates to afford tricycle **132** [183].

131   **132**
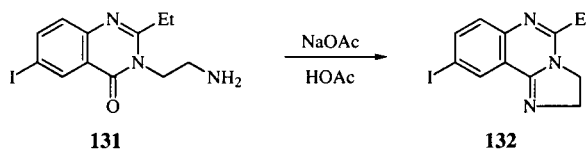
Reaction of 2-chloromethyl-3,1-benzoxazin-4-one (133) with ethanolamine in water followed by treatment with potassium hydroxide furnishes the 1,4-oxazino[3-4-b]-quinazolone 134 in 45% yield. The yield can be raised to 57% by a two-step sequence involving bromination of the 2-methyl group of 129 with N-bromosuccinimide then cyclizing with sodium hydroxide [53].

133 → 134
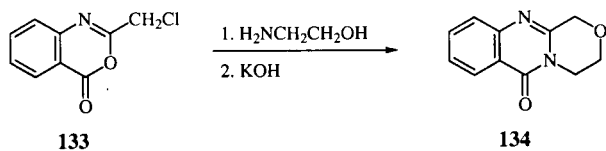
Heating 129 with benzaldehyde results in the formation of styryl derivatives 135 in 17% yield. Epoxidation of the double bond (72% yield) then treatment of the product with sodium methoxide affords 136 (63% yield) as a result of intramolecular attack of the ethanol group on the epoxide [193].

135 · 136
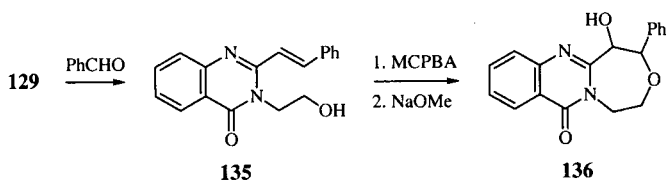
Benzoxazinones, when reacted with amino acids under fusion conditions at 190° or by refluxing in pyridine/water mixtures, produce quinazolone-3-acetic acid derivatives 137 in high yields. Glycine [143,194-196], longer-chained amino acids ($H_2N(CH_2)_nCOOH$) [152,197] and many of the natural α-alkyl amino acids [198-201] have been used in this reaction. The methyl ester 138 ($R_2 = H$) is prepared by refluxing a mixture of the benzoxazinone, glycine methyl ester hydrochloride and triethylamine in benzene [202] or by esterification of 137 with methanol in the presence of thionyl chloride [203].

R = Me, Pr, Ph
R_2 = H, alkyl
X = H, halogen

H^+, MeOH → 137 R' = H
                   138 R' = Me
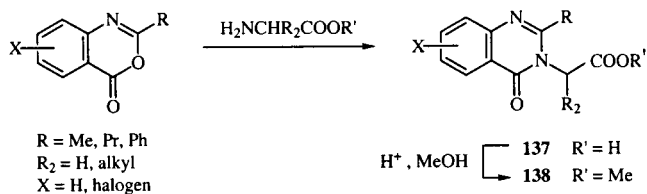
Once again, the incorporation of a "handle" capable of further reaction allows access to more complex heterocycles. Thus, reaction of 139 with glycine benzyl ester

hydrochloride in dimethylformamide affords 140 in 70% yield. Catalytic hydrogenation at 50 psi quantitatively reduces the nitro group and benzyl ester to give an intermediate which, when heated at 250°, cyclodehydrates to tetracycle 141 in 30-40% yield.

An alternate approach involves acylation of 51 with N-Boc-glycine under peptide coupling conditions (N,N-dicyclohexylcarbodiimide, methylene chloride) to give 142 in 60-70% yield. Removal of the protecting group under acidic conditions quantitatively provides 143. Intermediate 143 is also directly available from 51 in 90% yield by treatment with glycinyl chloride. Heating 143 in dimethylformamide at 95° results in the intramolecular attack of the glycyl amino group on C-4 of the heterocycle to give 141 in 93% yield [204].

139   51

140   142

141   143
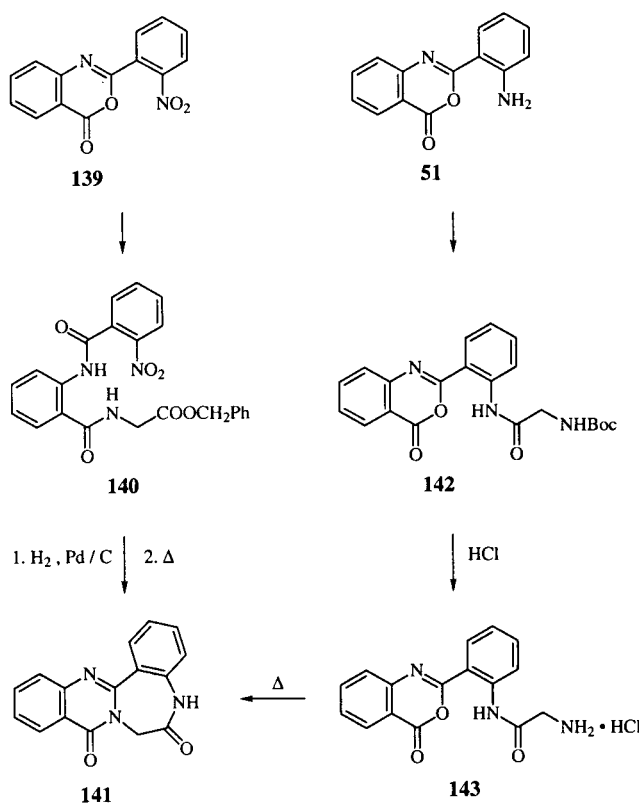
2-Trifluoromethyl-3,1-benzoxazin-4-one (47) reacts with 3-butenyl- or 4-pentenylamine to produce an N-acyl-anthranilamide which, when heated above 200°, forms the quinazolones 144 in good yields. Irradiation of these intermediates at 350 nm produces the respective photoadducts 145 in 95% (n = 1) and 88% (n = 2) yields [205].

The alkaloid rutaecarpine (149) and related analogs are synthesized using a three-reaction one-pot procedure starting from 47 and tryptamine (146). This sequence can provide the alkaloid in 99% overall yield [21,86,206].

47   **144**   n = 1, 2   **145**

146   **147**

148   **149**
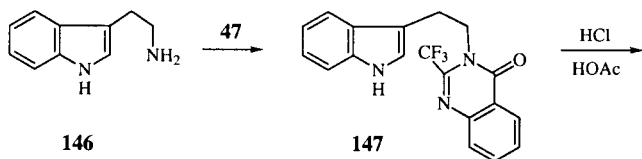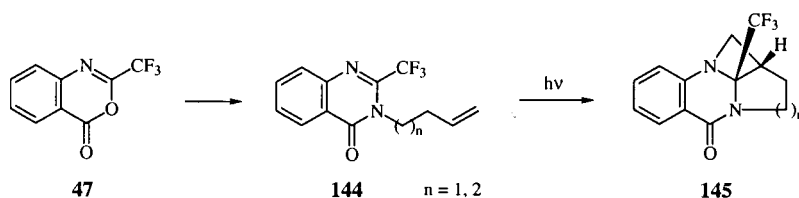
The rigid indomethacin analog **153** is readily constructed by the reaction of **150** with indoline **151**. After removal of the trifluoroacetyl group of **152** with ammonia, the biaryl bond is formed by treatment with isoamyl nitrite. Ester manipulation followed by aromatization of the indoline ring with manganese dioxide provides the final product **153** [207].

150   **151**

152   **153**
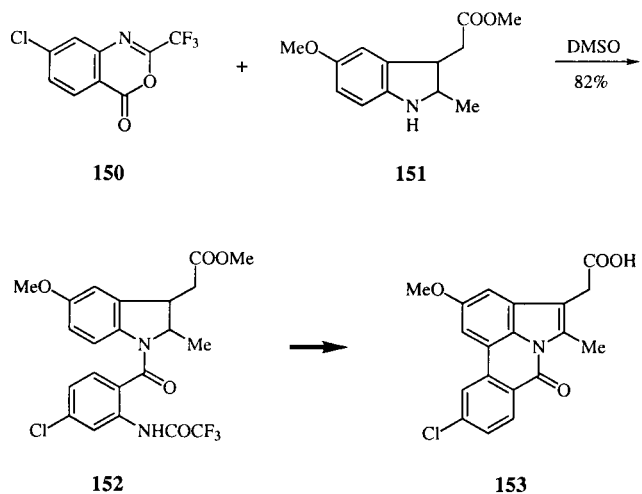
Reaction of benzoxazinones with hydroxylamine hydrochloride in refluxing pyridine affords 3-hydroxy-4-quinazolones **154a** in 45-93% yield [32,33,85,122,208]. Heating benzoxazinones in neat hydrazine hydrate or in pyridine or xylene solutions produces 3-amino-4-quinazolones **154b** in 55-83% yield [12,20,22,209-216].

Cyclization on both nitrogens of the hydrazine to form a 1,3,4-benzotriazepin-5-one is not observed [209]. Substituted hydrazines react likewise in solvents such as benzene, pyridine, ethanol or acetic acid to furnish **154c** where R_2 can be phenyl [122,217-220], acyl [216,220,221], COOEt [56,62], (C=X)NHR' (X = O or S) [216,221,222] and others [219,223,224].

X = H, halo, Me, NO_2 **154a**   Y = OH
R = Me, Et, Pr, i-Pr, CF_3, Ph, 2-furyl   **154b**   Y = NH_2
                                     154c   Y = NHR_2
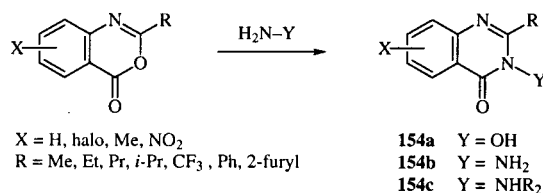
In the case of acylhydrazides, reaction with benzoxazinones in benzene produces the expected quinazolone **154c**, however, in ethanol the triazolylbenzoic acids **155** are formed in good yields. Treatment of one of the analogs with either acetic anhydride or diazomethane results in the formation of tricycle **156** [225].

R_1 = H, Me, Ph
R_2 = H, Me, CH_2CN,
CH_2NO_2, CH_2OPh

155

Ac_2O | R_1 = Me
         | R_2 = CH_2CN

156
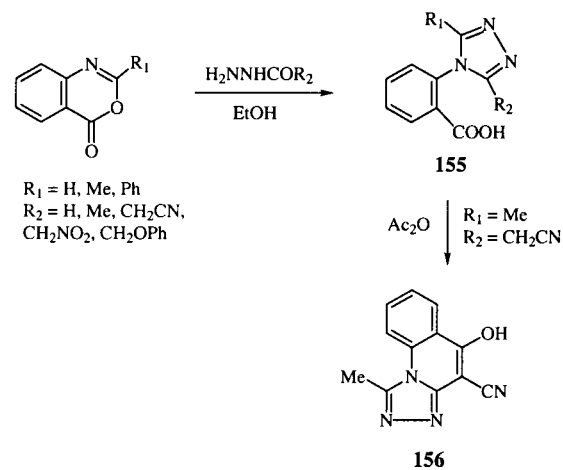
A similar raection of the 6-chloro derivative **157** with formic acid hydrazide followed by esterification with diazomethane gives triazolo ester **158**. Hydroxymethylation with paraformaldehyde to **159** then conversion of the alcohol to the chloride **160** with thionyl chloride and subsequent ammonolysis gives lactam **161** which is a critical intermediate in the synthesis of CNS-active triazolobenzodiazepines [226].
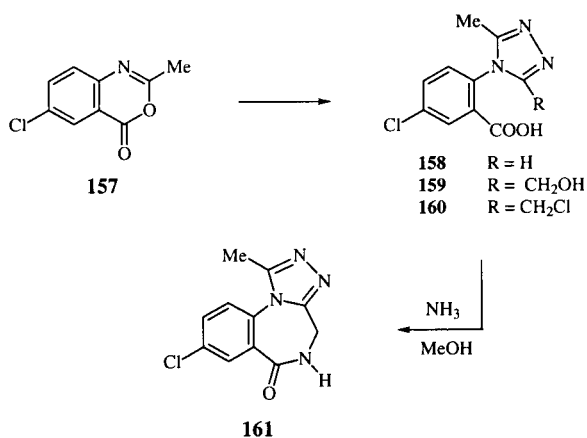
It seems most likely that reactions of benzoxazinones with hydrazines follow pathway A similar to **108** and in the case of the 2-ethoxycarbonyl derivative **162** the resulting amidrazones **163** are isolated in 90-98% yield [227,228]. On the other hand, 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one reacts with hydrazine following pathway B to give the anthranoylhydrazide in high yield [229].
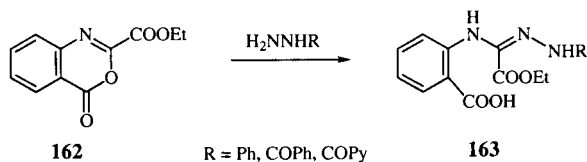
If the reaction of **1** with hydrazine is conducted in the presence of carbon disulfide in alcohloic potassium hydroxide, the 1,3,4-oxadiazoline-5-thione **164** is produced directly in 45% yield [230].
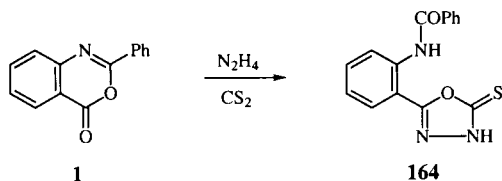
Benzoxazinones with additional reactive functionalities at the 2-position undergo further cyclization when exposed to hydrazine and form a variety of interesting heterocycles **167-170** [69,83,144,231].

Reactions of acetonyl benzoxazinones **35** with methyl-hydrazine or various phenylhydrazines affords the pyrazolyl anthranilic acid **171**. Cyclization of these intermediates with a mixture of phosphorus pentoxide and polyphosphoric acid provides the 4-hydroxypyrazolo[3,4-*b*]quinoline **172** [72,232] whereas cyclization with phosphorus oxychloride gives the 4-chloro analog **173** [70,71].
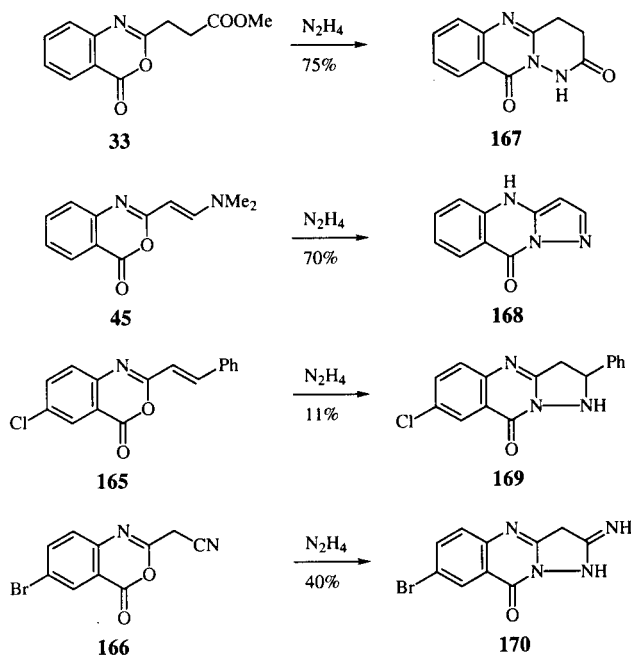
Symmetrical disubstituted hydrazines react with cyano derivative **22** with loss of HCN to produce 1,3,4-benzo-triazepin-2,5-diones **174** in 19-62% yield [93].
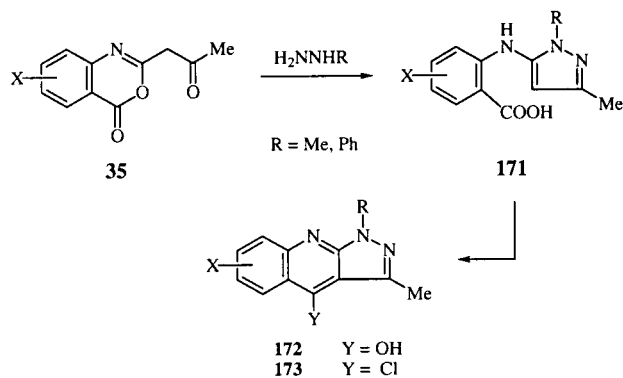
Heating **2** with thiosemicarbazide in acetic acid in the presence of fused sodium acetate does not stop at the thiocarbamide intermediate **154c**, but continues to cyclodehydrate
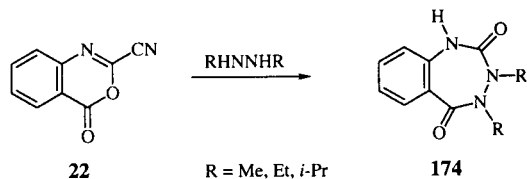
thus providing **175a** (X = H) in 50% yield [233]. In a similar fashion, refluxing 2-methylbenzoxazinones with aminoguanidine in pyridine affords the amino derivatives

175b in moderate yield [234]. 2-Phenylbenzoxazinones work in this reaction with equal facility.

X = H, Cl, Me, OMe, NO₂   Y = S, NH   **175a** Y = SH
                                        175b Y = NH₂
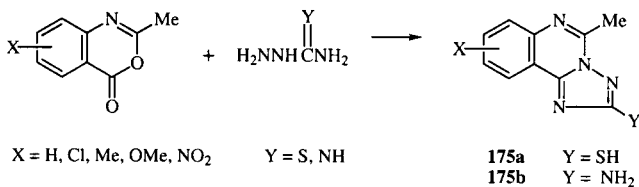
2-Methyl-3,1-benzoxazin-4-one (**2**) or its 6-bromo analog, when allowed to react with Schiff bases in acetic acid containing a catalytic amount of fused sodium acetate, produce 2-styryl quinazolones **176** in yields generally ranging between 50-75% [75,235-237]. The aryl groups Ar_1 and Ar_2 are usually substituted phenyl rings however the isoxazole heterocycle has been used as Ar_1 [238,239].

The reaction is believed to occur by addition of the imine to the C-4 carbonyl of **2** to generate species **177** which subsequently fragments to give the 2-methyl-4-quinazolone **178** and a benzaldehyde. Condensation of the aldehyde with **178** ultimately leads to **176**. This condensation has precedence as shown in the conversion of **127**→**128**. Additional support for this mechanism is given by the reaction of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one with benzylideneaniline where the 6,8-dibromo derivative of **178** (Ar_1 = Ph) is isolated in 60% yield [240]. The aldehyde is also detected in the reaction mixture.
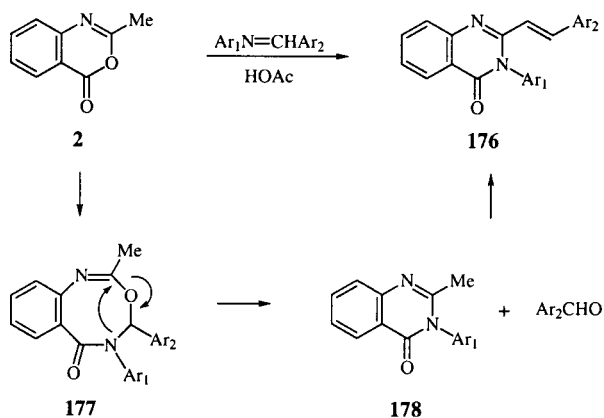
Treatment of benzoxazinones with either hydrazoic acid (generated with sodium azide in acetic acid) [63,113,119,141,241-243] or directly with sodium azide in dimethylformamide [244] results in the formation of the tetrazolyl benzoic acids **179** in good yields.

4.5 Reaction with Carbon Nucleophiles.

Grignard reagents and aryllithium's add readily to the C-4 carbonyl of benzoxazinones at temperatures ranging from -70° to 80°. It is generally found that adding aryl Grignard

X = H, Me, Br
R = H, Me, Pr, Ph, styryl, 2-thienyl   **179**
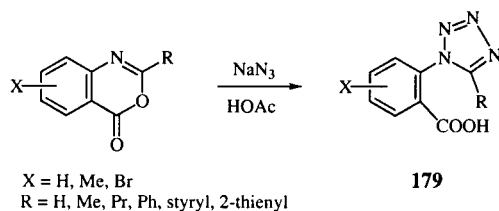
reagents under inverse addition conditions in conjunction with controlling the exotherm provides the acylated 2-aminobenzophenone derivatives **180** in high yields [15,245-248]. Aryl Grignard reagents, under normal addition mode, or aryllithium reagents tend to diminish the yield of **180** while increasing the amount of tertiary alcohol **181** [37,118]. Organometallics derived from furan, thiophene and pyrrole have been used successfully to give the heterocyclic analogs of **180** [37,249]. Using an excess of aryl or alkyl Grignard reagents, one usually obtains **181** along with its dehydration product **182** regardless of the mode of addition [92,250-253]. Treatment of carbinol **181** with acetic anhydride assists in the dehydration to the benzoxazine **182** [254]. The aminobenzophenone derivatives **180** are also available in 50-57% yield by a Friedel-Crafts arylation of the benzoxazinone with an aromatic hydrocarbon in the presence of aluminum chloride [122,251,252].

R_1 = Me, Ph, C_6H_{11} **180**   **181**
X = H, halo

182

The use of this methodology has played a critical role in the synthesis of a variety of heterocyclic and carbocyclic systems. For example, the reaction product of **2** and 4-chlorophenylmagnesium bromide, when treated with sodium methoxide, cyclizes to the 4-phenylcarbostyril **184**. This plus other derivatives are crucial intermediates

183   **184**

for the preparation of 4-phenyl-2-(1-piperazinyl)quino-lines which are novel antiulcer agents [255].

The 4-arylquinoline heterocycle comprising the hydrophobic domain of the HMG-CoA reductase inhibitor **188** is prepared from the reaction of **2** with 3,5-dimethyl-phenylmagnesium bromide. The acyl group of **185** is removed under acidic conditions and the resulting 2-aminobenzophenone **186** is condensed with methyl ace-toacetate to afford the quinoline **187** which is then elabo-rated using Wittig methodology to the final product [256].

(46%, not shown) as the result of displacement of the 7-methoxy group of the chromene [259].

2-Aminobenzophenones, derived from the hydrolysis of intermediates **192**, upon diazotization, cyclize to fur-nish fluorenones **193** in moderate yield [246,260,261]. The more complex acetylaminobenzophenone **195** is available from lithionaphthalene **194** and **2** in 78% yield. After removal of the acetyl group under basic conditions, ring closure by a hydroquinone-catalyzed Pschorr reaction with isoamyl nitrite gives **196** which is

The cyclization of 2-methoxyaminobenzophenones provides a biomimetic approact towards the synthesis of 9-acridones [257,258]. This is exemplified in the elegant construction of the acronycine skeleton. Both halves of the molecule are assembled by reaction of **2** with lithio-chromene **189**. Treating the resulting acetylaminoben-zophenone with sodium hydride causes cyclization with concomitant loss of the acetyl group to give a mixture of des-*N*-methylacronycine (**191**, 43%) and its linear isomer

used in the preparation of 1,7-dideoxy-3-demethylprek-inamycin [262].

The cardiotonic bemarinone (**199**) is readily prepared from benzoxazinone **197** in three steps [47].

197   198   199

Addition of **2** to an excess of *t*-butylmagnesium chloride produces the secondary alcohol **200** in 70% yield [263]. The first equivalent of Grignard reagent adds normally to **2** to generate *N*-acetyl-2-pivalophenone then the second equivalent of the reagent, instead of adding to the newly formed ketone, reduces the keto group presumably because of highly steric interactions between both ketone and organometallic.

2   200
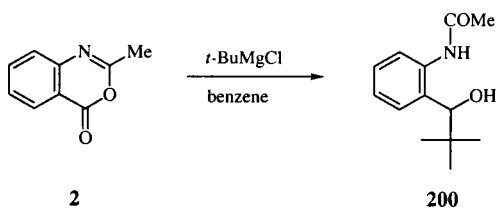
BisGrignard reagents such as **201** add to **2** to give an 82:18 mixture of tertiary alcohols **202** and **203**. It is believed that the more reactive secondary Grignard adds first to the benzoxazinone then, with the aid of chelation of the magnesium to oxygen, the primary Grignard adds intramolecularly to the ketone in a diastereoselective fashion [264].

201   202   203
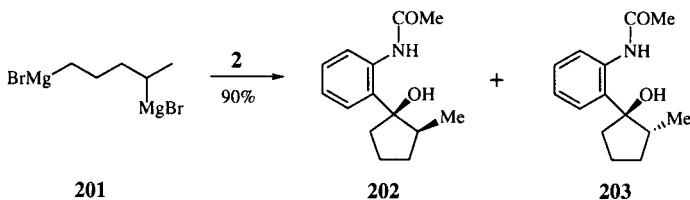
The reaction of benzoxazinones with active methylenes provides a variety of interesting results. Heating the benzoxazinone with diethyl maolnate, ethyl cyanoacetate or ethyl acetoacetate in dry pyridine gives one and the same product **204** (72-79% yield) as the consequence of the loss of the R' group [30,33,122,126].

R = Ph, CH$_2$Ph, CH$_2$CN, β-naphthyl
R' = COOEt, CN, COMe   **204**

However, an analogous reaction of thienyl derivative **205** with ethyl cyanoacetate affords the cyclized product **206** in 50% yield [63].

205   206
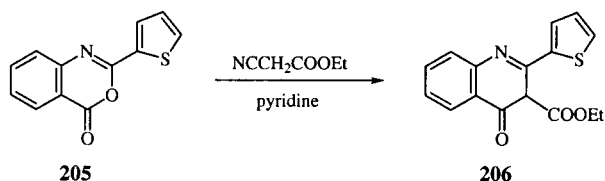
Additionally, reaction of **2** with malononitrile under similar conditions gives a mixture of **207** (64%) and **208** (41%) [253].

207   208
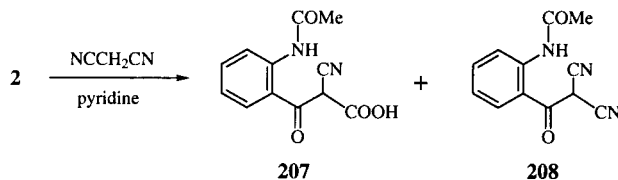
Using potassium *t*-butoxide in *t*-butanol to generate the anion of the active methylene and running the reaction at room temperature allows the R' group to be retaine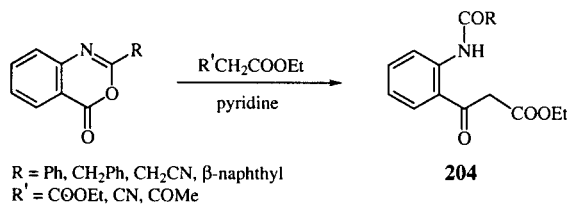d thus giving **209**. This, in turn, can be cyclized to the 4-hydroxy-2-quinolone **210** with either sodium alkoxide or 8% alcoholic hydrochloric acid [265].

R' = COOEt, CN,
COMe, SO$_2$Me   209   210
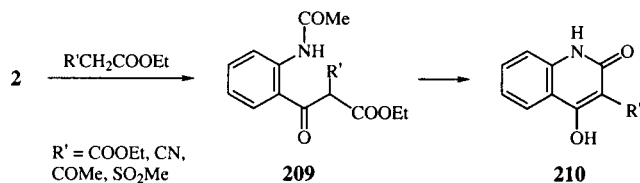
3-Amino-4-hydroxy-2-quinolones **212** are readily prepared in two steps from the reaction of a benzoxazinone with methyl isocyanoacetate. The initial 1,3-oxazole products **211** are isolated in 72-82% yield. Treatment of these intermediates with concentrated hydrochloric acid in methanol provides the product **212** in 81-98% yield [266].

Heating a mixture of **2** and either diethyl malonate, ethyl acetoacetate or acetylacetone in the presence of zinc chloride
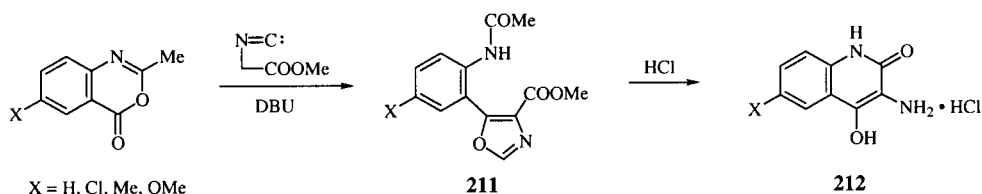
furnishes **213** in 55-65% yield [267]. These are excellent intermediates for the synthesis of spiroheterocycles.
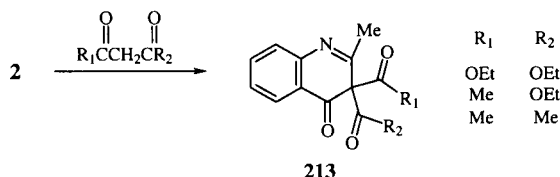
Dianions of *N*-substituted acetamides add to benzoxazinones at -70° to give the β-ketoamides **214** in 35-83% yield. Exposure of **214** to 4-(dimethylamino)pyridine in tetrahydrofuran results in cyclization to the 4-hydroxyquinoline **215** which is isolated in 30-88% yield. Some of these compounds have been shown to exhibit both analgesic and acute antiinflammatory activity [42,43,268-272].
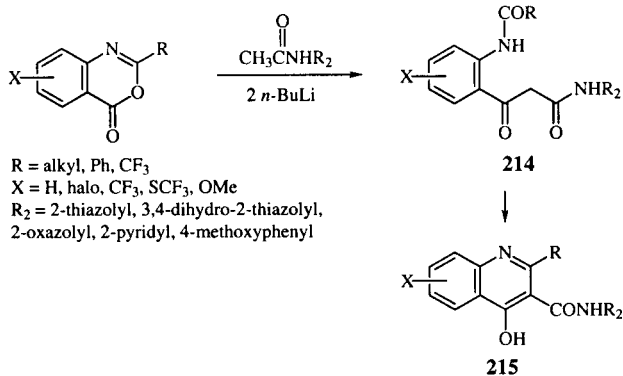
Treatment of 2-trifluoromethyl-3,1-benzoxazin-4-ones with phosphoranes **216** or **217** in boiling toluene solution affords the corresponding phosphoranes **218** in 70-99% yield [273,274]. Attempts to cyclize **218** to a quinoline results only in fragmentation.
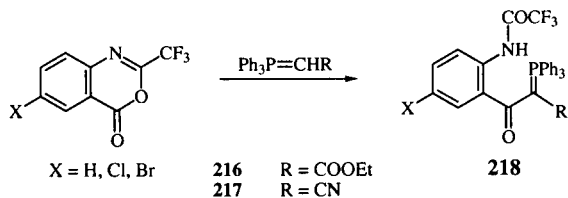
Enamines and ynamines react with 2-trifluoromethyl-3,1-benzoxazin-4-ones to form quinoline derivatives. For example, compounds **47** and **219** react with *N,N*-diethyl-1-propynylamine in ether at temperatures as low as -20° with vigorous evolution of carbon dioxide to give **220a** or **220b** in 94% and 85% yield respectively [275]. An analogous reaction with *N,N*-diethyl-1-butenamine retains the carboxyl group thus giving the 8-carboxyquinolines **221a** or **221b** in 65% and 48% yield respectively [276].
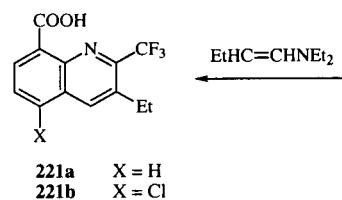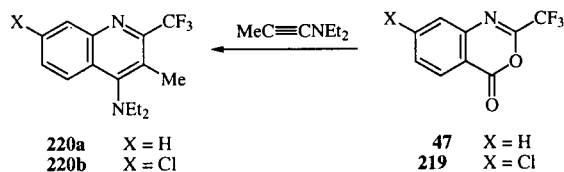
4.6 Other Reactions.

Primary, non-aromatic amines react with 2-cyanomethyl-3,1-benzoxazin-4-one (**222**) in refluxing dimethylformamide or ethanol to provide 2,4-quinazolinediones **224** in 52-81% yield [277,278]. Addition of the amine to the benzoxazinone follows pathway A to initially generate **108** which then undergoes the first stage of cyclization to **223**. Rather than dehydrate to form the 4-quinazolone **110** it loses acetonitrile to afford **224**.
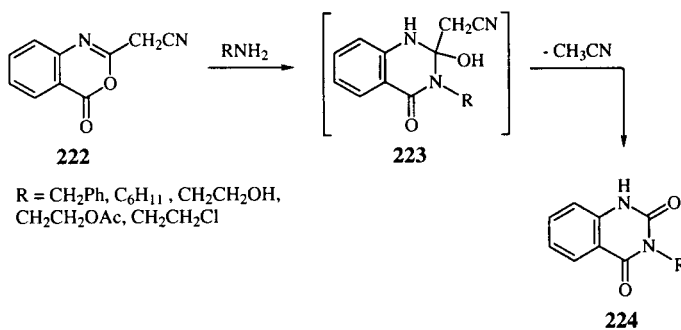
Thermolysis of *o*-azidophenylbenzoxazinones **225** in *o*-dichlorobenzene is complete within 5-10 minutes and affords indazolobenzoxazinones **227** in 62-92% yield. Treatment of *o*-nitrophenyl derivatives **226** with triethyl phosphite in boiling xylene only gives indazoloindazole-diones **228** in 87-91% yield. Compound **227** (X = H), upon prolonged heating in *o*-dichlorobenzene, does not rearrange to **228** to any appreciable extent, however, when treated with triethyl phosphite rapidly rearranges to **228** [279,280].

R = Me, Ph, CH₂Ph, CH₂CN

234

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| 225 | R = N₃ |
| 226 | R = NO₂ |

227
X = H, halo, NO₂, NHAc

228
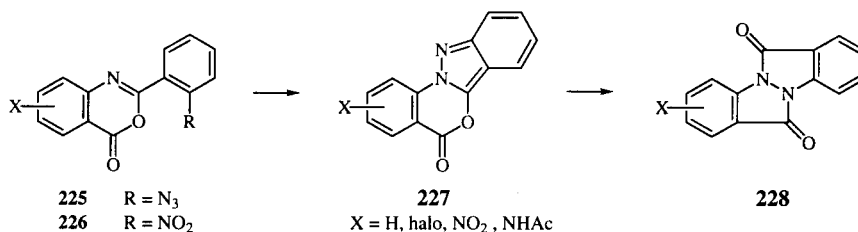
Reaction of **225** with triphenylphosphine at room temperature furnishes iminophosphorane **229** in 93% yield. Interaction of **229** with isocyanates directly produces **230** by way of an initial aza-Wittig reaction forming an intermediate carbodiimide [281].

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225　　Ph₃P / CH₂Cl₂　　**229**　　RNCO　　R = Me, aryl　　**230**
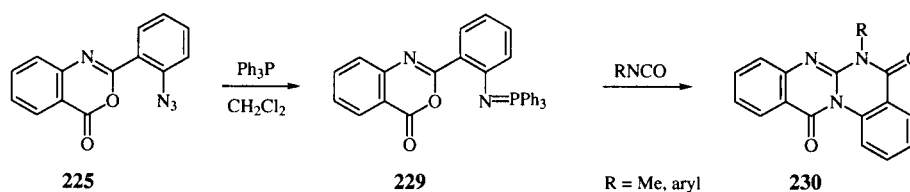
Isomerization of **231** under acidic conditions furnishes **232** in 95% yield. Further dehydration results in the formation of tetracycle **233** in 82% yield [282].

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231　　HCl　　**232**　　H₂SO₄ / HOAc　　**233**
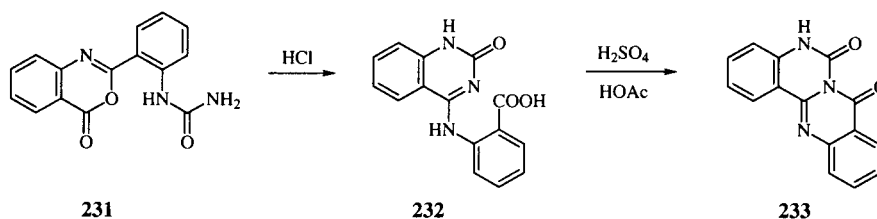
The 3,1-benzoxazin-4-one heterocycle can be converted to the corresponding 3,1-benzothiazine-4-thione **234** by treatment with phosphorus pentasulfide in refluxing xylene [122,142], triethylamine-solubilized phosphorus pentasulfide in acetonitrile [283] or Lawesson's reagent in benzene [284].

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