Gary M. Coppola

Department of Metabolic and Cardiovascular Diseases, Novartis Pharmaceuticals Corporation, 556 Morris Ave., Summit, NJ 07901

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The present review covers the synthesis and reactions of 2-hetero-4*H*-3,1-benzoxazin-4-ones which include oxygen, sulfur and nitrogen substituents. Literature coverage includes publications primarily from the mid 1960's to December 1999.

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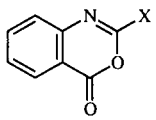
4*H*-3,1-Benzoxazin-4-ones (**1**) have been known for more than a century. They are found in nature [1,2] and have been used as linking units in polymer chemistry [3] and as key intermediates in organic synthesis [4]. The susceptibility of the C-4 carbonyl to nucleophilic attack allows this class of compounds to be extremely potent serine protease inhibitors, inactivating enzymes such as chymotrypsin [5], human leukocyte elastase (HLE) [6,7], pancreatic elastase [8], cathepsin G [9,10] and C1r serine protease [11,12].

Scheme 1



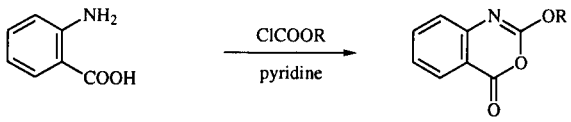
1

A recent review [4] covered the chemistry of **1** where X was limited to carbon-containing substituents. This review extends the scope to include the synthesis and reactions of 2-hetero substituted 4*H*-3,1-benzoxazin-4-ones containing oxy, mercapto and amino functionality (**1**, X = OR, SR, NR_2).

Oxygen.

Anthranilic acid (**2**) contains nearly all the functionality present in the 4*H*-3,1-benzoxazin-4-one system. Only the introduction of the 2-carbon atom with its associated substituent is required to complete the heterocycle. The most expeditious method for preparing 2-alkoxy-4*H*-3,1-benzoxazin-4-ones (**3**) is to treat an anthranilic acid with 4 equivalents of an appropriate chloroformate in pyridine at temperatures ranging from 0 °C to room temperature. A wide range of substituents can be tolerated and yields are generally good. Table 1 lists yields for some simple 2-alkoxy derivatives of **3**. The cyclization can accommodate both electron donating and withdrawing groups in the aromatic ring. Anthranilic acids with substituents such as 4,5-dimethoxy [15,16], 4-chloro [15], 6-methyl [17] and 4- or 5-nitro [14,18] produce the corresponding benzoxazinones in acceptable yield.

Scheme 2



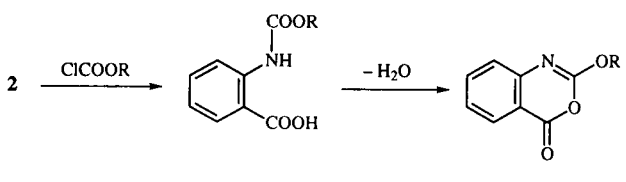
2 **3**

Table 1
2-Alkoxy-4*H*-3,1-benzoxazin-4-ones (**3**)

3	R	Yield (%)	Reference
a	Me	47	10
b	Et	90	13,14,15
c	*n*-Pr	60	10
d	*i*-Bu	66	10
e	allyl	16	10
f	Ph	81	10

Although **3** can be prepared in a one-pot reaction, in certain cases where the chloroformate is either expensive or difficult to prepare it is advantageous to perform the synthesis in a stepwise manner. Treating anthranilic acid (**2**) with a slight excess of the chloroformate in either pyridine [19] or in tetrahydrofuran in the presence of potassium carbonate [20] affords the 2-carboalkoxyaminobenzoic acid **4** in good yield. A dehydrative cyclization produces the product **3**. Reagents such as concentrated sulfuric acid [14], acetic anhydride [21], ethyl chloroformate [19], phosphorus oxychloride [16], thionyl chloride [20], or the carbodiimides DCC [16] or EDCI [14,20] have been used to effect the cyclization.

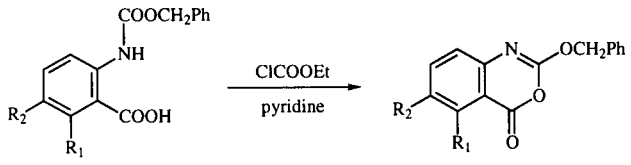
Scheme 3



4 **3**

This is a particularly useful method to prepare 2-benzyloxy analogs **6** [19]. Carboalkoxylation of an appropriate anthranilic acid derivative with Cbz-Cl in pyridine furnishes **5** in 41-73% yield. Treatment of **5** with ethyl chloroformate in pyridine produces the 2-benzyloxy analogs **6** in high yields.

Scheme 4



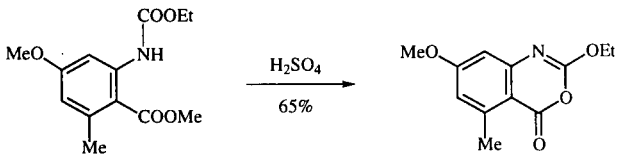
5 **6**

6	R_1	R_2	Yield (%)
a	H	H	95
b	Me	H	69
c	H	Me	84

This methodology is also useful for the preparation of more exotically substituted benzoxazinones. Coupling **7** with the mixed anhydride of either Boc-*L*-alanine or Boc-*L*-valine (generated *in situ* with isobutyl chloroformate) gives the peptide-like compounds **8**. Cyclization of **8** with ethyl chloroformate in pyridine and triethylamine affords **9a** or **9b** in 20% yield. These compounds exhibit HLE inhibitory activity [18].

It is not imperative to have a free acid for cyclization to occur. Stirring **10** in concentrated sulfuric acid at room temperature for 2 hours gives **11** in 65% yield [14].

Scheme 6



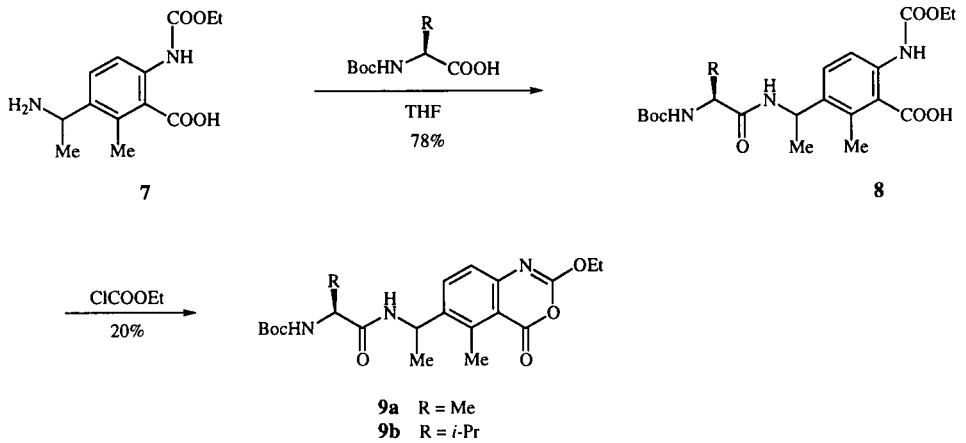
10 **11**

Several other strategies which proceed through a 2-carboalkoxyamino benzoic acid (**4**) have been successful. Treatment of anthranilate **12** with trichloromethyl chloroformate (diphosgene) in tetrahydrofuran followed by the imidazolyl alcohol **13** affords carbamate **14** in 81% yield. Hydrolysis of the ester to acid (61% yield) then carbodiimide cyclization furnishes **15** in 71% yield [14].

Substituted anthranils provide an alternate source of anthranilic esters. Reaction of **16** with ethanol in the presence of sodium bicarbonate gives ethyl anthranilate **17** in 76% yield. Carbamylation of **17** with diphosgene followed by ethanol affords **18** then reduction of the nitro group and cyclization with concentrated sulfuric acid produces the benzoxazinone **19** in about 50% yield [14].

Curtius rearrangement of phthalate **20** results in the formation of isocyanate **21**. This intermediate is usually not isolated but heated with an alcohol in toluene to give carbamate **22** directly. Standard cyclization with sulfuric acid gives the 2-alkoxybenzoxazinone **23** [14,22].

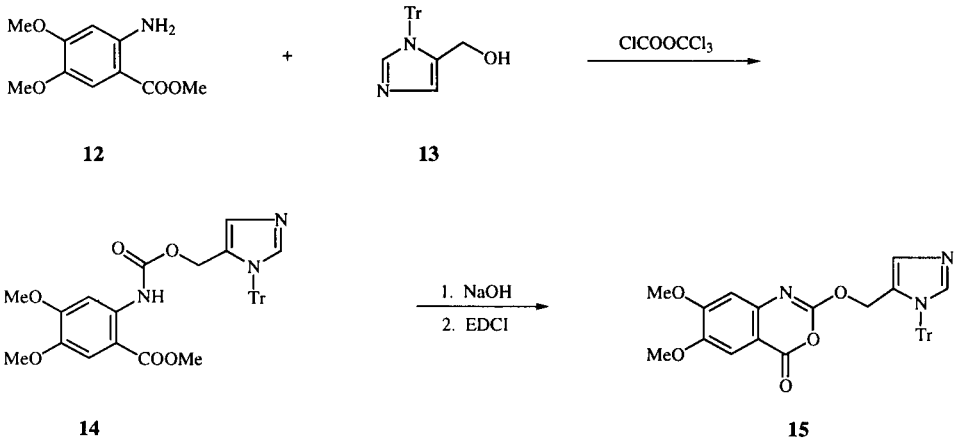
Scheme 5



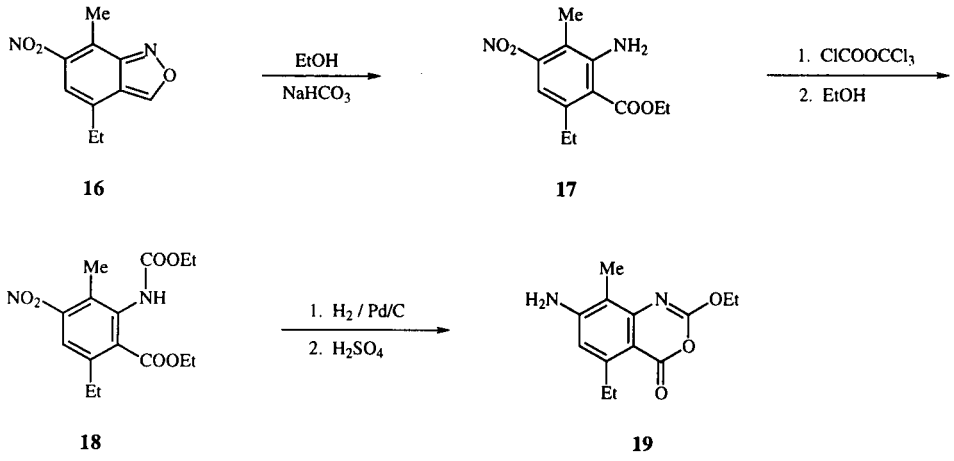
7 **8**

9a R = Me
9b R = *i*-Pr

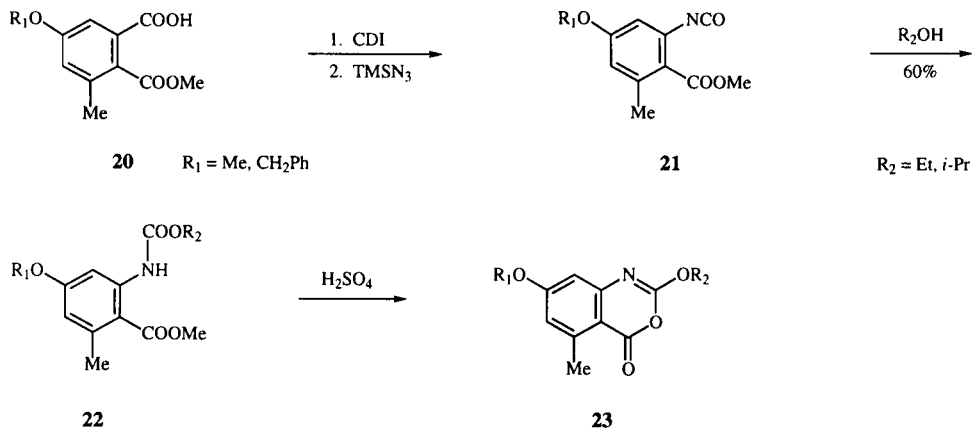
Scheme 7



Scheme 8

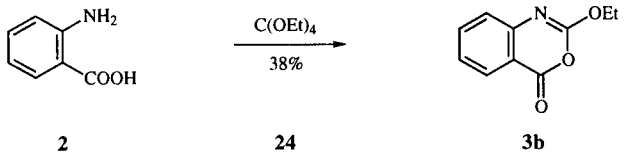


Scheme 9



It has also been reported that heating anthranilic acid with tetraethylorthocarbonate (**24**) affords 2-ethoxy-4*H*-3,1-benzoxazin-4-one (**3b**) in 38% yield [23].

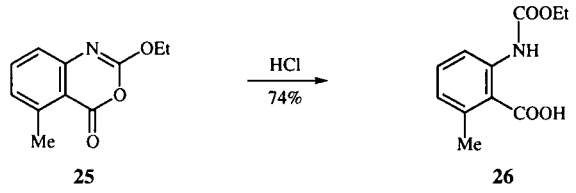
Scheme 10



2 **24** **3b**

2-Alkoxybenzoxazin-4-ones can be hydrolyzed to the corresponding 2-carboalkoxyamino benzoic acid under either acidic or basic conditions. For example, treating **25** with 4*N* hydrochloric acid in tetrahydrofuran for 15 minutes affords **26** in 74% yield [17]. Alternatively, 1*N* sodium hydroxide in tetrahydrofuran can be used. Under anhydrous conditions 2-alkoxy-3,1-benzoxazin-4-ones are stable to acid. In fact, the hydrochloride salt of 7-amino-2-ethoxy-4*H*-3,1-benzoxazin-4-one can be formed by treatment of the free base with 3% hydrogen chloride in dioxane [14].

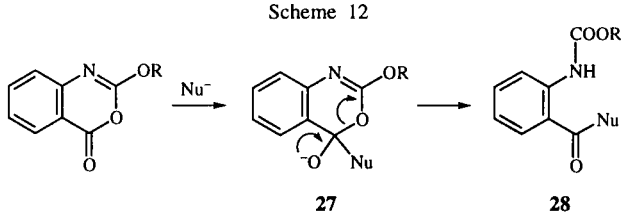
Scheme 11



25 **26**

The 2-alkoxybenzoxazinone system may be considered an enolically trapped form of isatoic anhydride. Its carbonyl is highly electrophilic and is therefore susceptible to nucleophilic attack (**27**). Subsequent ring opening of the heterocycle produces the anthranilate derivative **28**.

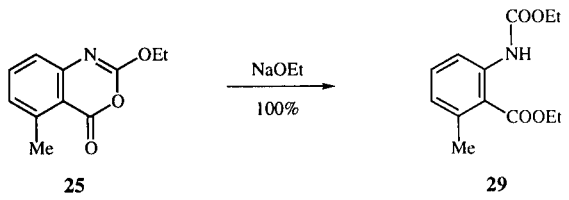
Scheme 12



27 **28**

Consequently, treating **25** with ethanolic sodium ethoxide at 0 °C for 2 hours results in the formation of ethyl anthranilate derivative **29** in quantitative yield [17].

Scheme 13

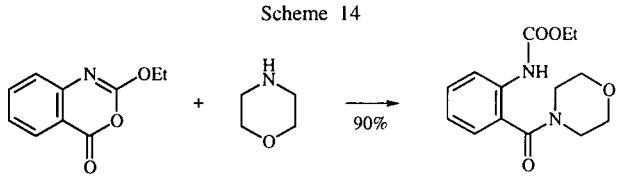


25 **29**

Many researchers have taken advantage of this special reactivity to acylate enzymes which contain an OH (usually from serine) in their active site. A variety of 2-alkoxy-4*H*-3,1-benzoxazin-4-ones have been designed to inhibit enzymes such as chymotrypsin [8,24], thrombin [25], cathepsin G [10], HSV-1 protease [26], protac^{R} [27], human leukocyte proteinase 3 [19], HLE [20] and pancreatic elastase [8].

Amine nucleophiles react with equal facility with 2-alkoxybenzoxazinones. Treatment of **3b** with morpholine in acetone produces **30** within 15 minutes and in 90% yield [28].

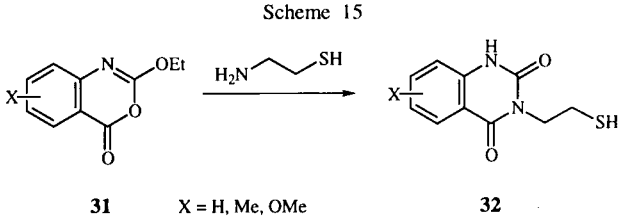
Scheme 14



3b **30**

With primary amines, however, the reaction does not stop at the anthranilamide but continues and cyclizes with the carbethoxy group to give quinazoline-2,4-diones. Thus, benzoxazinones **31** when reacted with cysteamine affords the 3-mercaptoethylquinazoline-2,4-diones **32** in 34-81% yield [29,30]. These compounds possess immunostimulant activity.

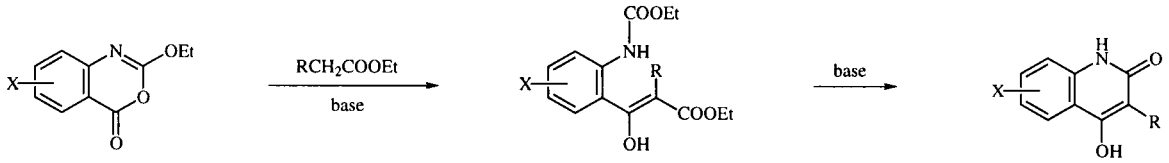
Scheme 15



31 X = H, Me, OMe **32**

Benzoxazinones **31** also react with anions of active methylenes to give β-ketoesters **33** (enolic form shown) in 50-99% yield. Conditions to generate the anions are either sodium hydride in benzene or potassium *t*-butoxide in *t*-butanol or tetrahydrofuran. Treatment of **33** with sodium hydride in alcohol-benzene, sodium alkoxide in alcohol or potassium *t*-butoxide in tetrahydrofuran results in cyclization to the 4-hydroxyquinolin-2-ones **34** which are isolated in 76-100% yield [15].

Scheme 16

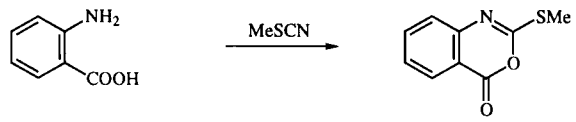


31 X = H, Cl, OMe; R = CN, COOEt, SO_2Me, COMe, COPh **33** **34**

Sulfur.

Only a few examples for the preparation of 2-alkylthio-4*H*-3,1-benzoxazin-4-ones are described in the literature. Thermolysis of anthranilic acid in the presence of methyl thiocyanate produces 2-methylthio-4*H*-3,1-benzoxazin-4-one (**35**) in 45% yield [31].

Scheme 17

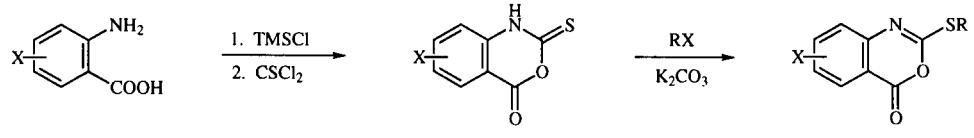


2 **35**

Alternatively, treatment of an anthranilic acid with chlorotrimethylsilane followed by thiophosgene affords the 2-thioisatoic anhydride **37**. Alkylation on sulfur with a variety of alkylating agents in the presence of potassium carbonate in acetone furnishes the 2-alkylthiobenzoxazinones **38** in 37-93% yield. These derivatives have been shown to possess HLE inhibitory activity [20].

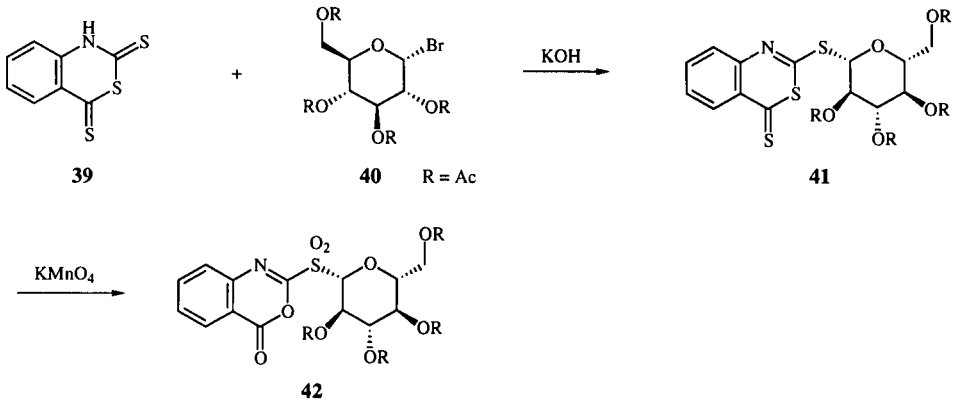
More complex glycoside derivatives are available *via* thioisatoic anhydride derivatives **39**. Alkylation of the 2-thiocarbonyl of **39** with tetra-O-acetyl-α-*D*-glucopyranosyl bromide (**40**) in the presence of potassium hydroxide or potassium carbonate affords S-glycoside **41** in 47% yield. Oxidation of **41** with potassium permanganate in acetic acid/water gives the sulfone **42** in 46% yield [32].

Scheme 18



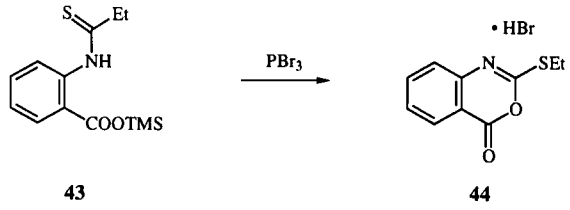
36 X = H, Me, Et, OMe, NMe_2, NHAc **37** **38** R = Me, Et, *i*-Pr, CH_2Ph, CH_2COOEt

Scheme 19



Exposure of trimethylsilylanthranilate **43** to phosphorus tribromide at room temperature for 24 hours gives the 2-ethylthiobenzoxazinone **44** as its hydrobromide salt in 40-60% yield [33].

Scheme 20



Nitrogen.

The bulk of the chemistry of 2-hetero benzoxazin-4-ones is associated with 2-amino derivatives since these compounds are more stable than the corresponding 2-carba, oxy or thio analogs. The most convenient method of preparation is from anthranilic acids. Introduction of a simple NH_2 into the 2-position is readily accomplished by treating an appropriate anthranilic acid **45** with two equivalents of cyanogen bromide in aqueous sodium hydroxide at temperatures between 0 °C and room temperature. Yields of 2-amino-4*H*-3,1-benzoxazin-4-ones (**46**) are listed in Table 2.

Scheme 21

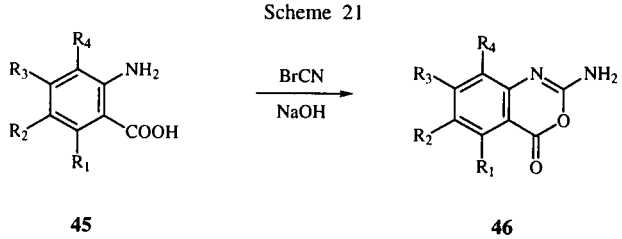


Table 2

2-Amino-4*H*-3,1-benzoxazin-4-ones

46	R_1	R_2	R_3	R_4	Yield (%)	Reference
a	H	H	H	H	95	34,35
b	Me	H	H	H	90	20
c	Et	H	H	H	54	20
d	H	Me	H	H	68	10
e	H	H	NO_2	H	14	36
f	H	OMe	OMe	H	90	37
g	COOH	H	H	H	-	38
h	H	COOH	H	H	-	38
i	H	H	H	COOH	-	38

Secondary aminobenzoxazinones **47** are also available from **2** in one step by treating the appropriate anthranilic acid with an alkyl or aryl isocyanate in solvents such as benzene [39], acetone [40], pyridine [26], and aqueous ethanol or acetic acid [41] (Table 3). Optimal results are obtained when two equivalents of isocyanate are used in protic solvents.

Scheme 22

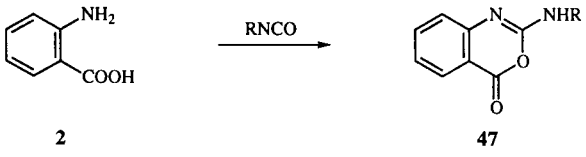


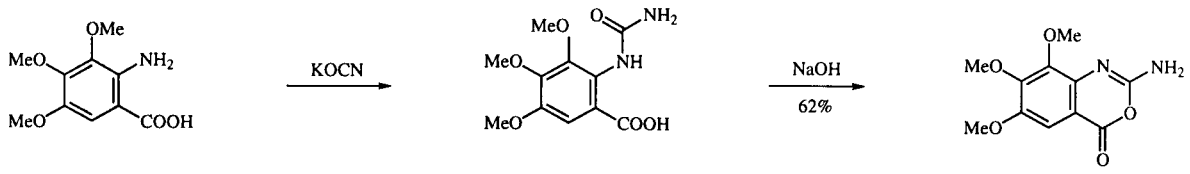
Table 3

Monosubstituted-2-amino-4*H*-3,1-benzoxazin-4-ones from **2**

47	R	Yield (%)	Reference
a	Me	90	41
b	Et	30	39
c	*n*-C_4H_9	85	41
d	C_6H_{11}	80	41
e	Ph	85	40

The conversion of anthranilic acids to 2-aminobenzoxazinones can also be accomplished in a stepwise manner. Reacting **48** with potassium cyanate at *p*H 5.6-6.0 forms the ureidobenzoic acid **49** which cyclizes to **50** when the *p*H is raised to 8.1 [42].

Scheme 23

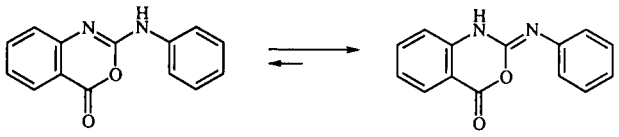


48 **49** **50**

A similar strategy has been used for the preparation of monosubstituted 2-aminobenzoxazinones **53**. The requisite *N*-substituted ureidobenzoic acid **52** is generated from an anthranilic acid or ester (**51**) upon treatment with an appropriate isocyanate. The most general method of cyclization uses concentrated sulfuric acid as the dehydrating agent. This procedure works well for both acids (**52**, R_1 = H) [43,44,45] and esters (**52**, R_1 = Me) [12,20,46,47,48] where R_2 is either alkyl or substituted phenyl. Aryl substituted **52** (R_2 = phenyl or tetrazolyl) acids [49,50] and esters [51,52] can also be cyclized in the presence of PPA at elevated temperatures. Under milder conditions, ureidobenzoic acids are cyclized to **53** using acetic anhydride [53] or the water-soluble carbodiimide EDCI [22,54,55]. Polymer-bound EDCI has also been proven an effective dehydrating agent which is easily removed from the reaction mixture [56].

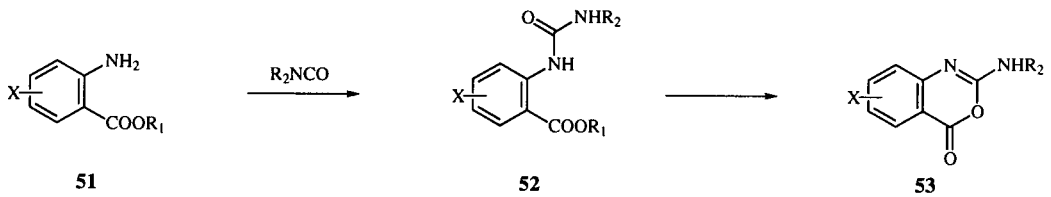
It should be mentioned here that although the 2-anilino derivative has been depicted in the literature as structure **54**, spectral evidence suggests that it exists predominantly as the exocyclic imino tautomer **55** [50].

Scheme 25



54 **55**

Scheme 24



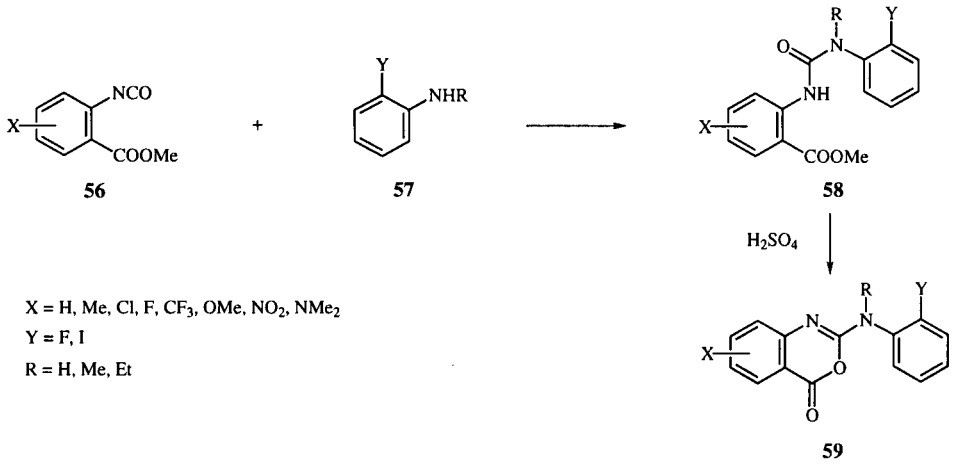
51 **52** **53**

R_1 = H, Me
X = H, Me, Cl, OMe, CF_3, NMe_2, NO_2
R_2 = alkyl, aryl, CH_2COOEt, $(CH_2)_3Cl$, $(CH_2)_3COOH$

An alternate method of constructing the ureidobenzoate intermediate is to reverse the positions of the reactive groups in the starting materials. Consequently, reaction of the 2-carbomethoxyphenyl isocyanate **56** with aniline **57** produces the desired intermediate **58** which is readily cyclized to **59** with sulfuric acid [12,47]. This method is particularly useful when 2-*N*,*N*-disubstituted aminobenzoxazinones are desired.

Structures such as **62** are amenable for the construction of combinatorial libraries on solid support. Immobilizing the amino acid on Wang or Sasrin resin then converting the amine to an isocyanate affords **63**. Reaction with an anthranilic acid produces the resin-bound ureidobenzoic acid **64**. Dehydrative cyclization with *N*,*N*'-diisopropylcarbodiimide (DIC) followed by release of the product from the resin with trifluoroacetic acid gives the products **66** [60].

Scheme 26

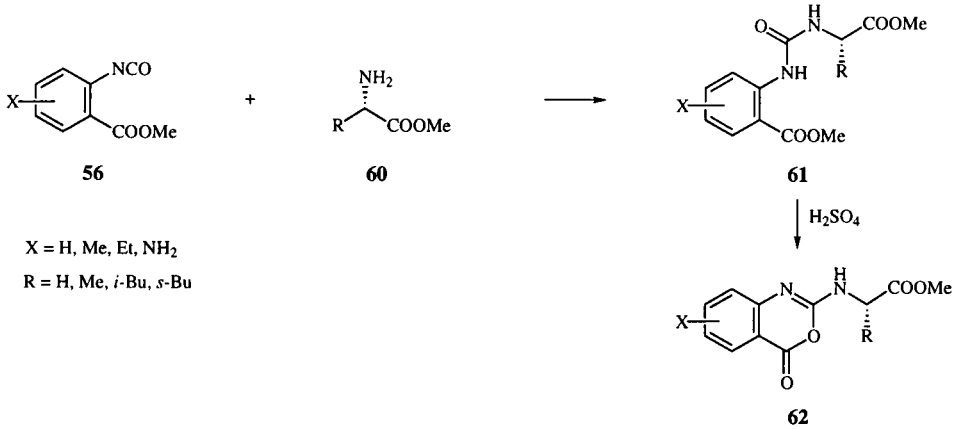


The reaction can accommodate amino acids (**60**) and peptides to produce exotically substituted benzoxazinones **62** in good yields [20,48]. Derivatives of this type are potent HLE inhibitors. If the aromatic ring contains a 7-amino group which is acylated with an amino acid, the resulting highly water soluble compounds have been shown to possess HLE as well as human suptum elastase (HSE) activity [57,58,59].

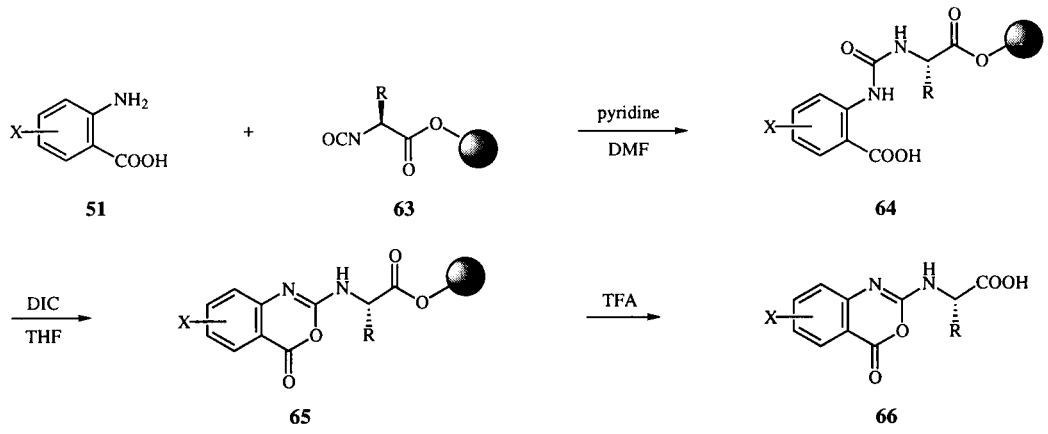
Once again, the reactive groups can be reversed. Reaction of isocyanate **56** with resin-bound amino acid **67** produces ureidobenzoate **68**. Hydrolysis of the ester with potassium trimethylsilanoate to acid **64** followed by cyclization with DIC, acetic anhydride or *p*-toluenesulfonyl chloride gives the benzoxazinones **65** [61].

Still other permutations are possible such as immobilizing the anthranilic acid **51** on resin *via* a heteroatom attachment (X = O, S, N) to its aromatic ring. The benzoxazinone can then be constructed by previously described methodology [61].

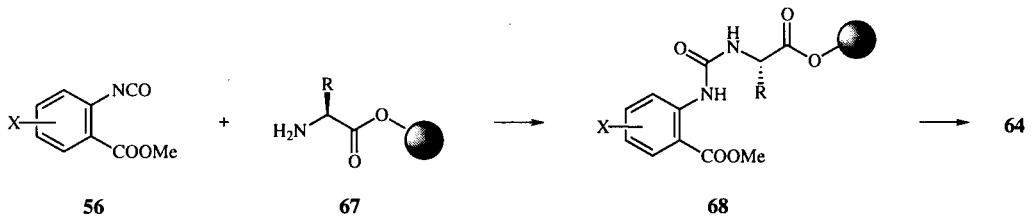
Scheme 27



Scheme 28



Scheme 29

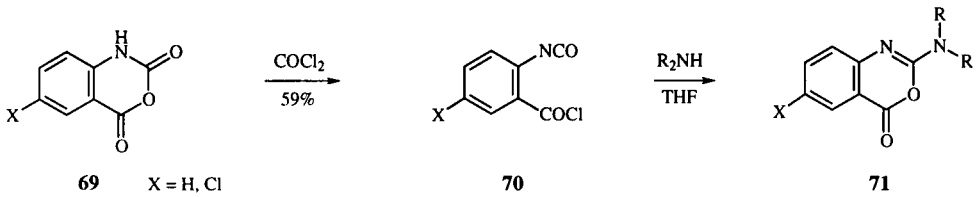


Yet another strategically similar approach utilizes isatoic anhydrides as the anthranilate source. Treatment of an isatoic anhydride **69** with phosgene in the presence of a catalytic amount of dimethylformamide results in the formation of *o*-cyanatobenzoyl chloride **70**. Addition of two equivalents of an amine (one equivalent is an HCl scavenger) to **70** at room temperature gives **71** directly in high yield. This is an excellent method for the preparation of 2-*N*,*N*-dialkylaminobenzoxazinones and has been used to synthesize diethyl, di-*n*-butyl, diisopropyl, diisobutyl, pyrrolidino, piperidino and morpholino analogs [20,62,63].

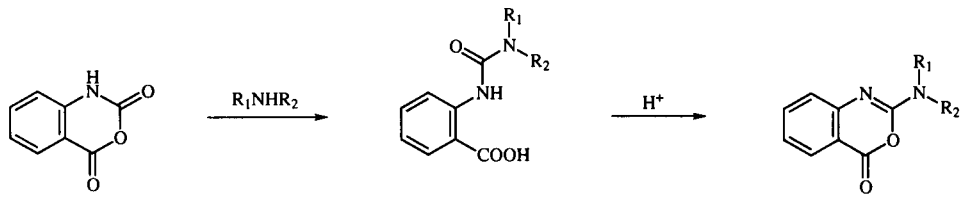
The preparation of *o*-cyanatobenzoates is not limited to the use of anthranilates as starting materials. As previously mentioned, Curtius rearrangement of phthalate **20** produces the isocyanate **21**. Reaction of **21** with amines gives the corresponding uereidobenzoate which is subsequently cyclized to the 2-aminobenzoxazinone with sulfuric acid [22,48].

In some instances amines open isatoic anhydride in an "abnormal" fashion to give ureidobenzoic acids **72**. Cyclization with either sulfuric acid or perchloric acid affords the benzoxazinones **73** [20,64].

Scheme 30



Scheme 31



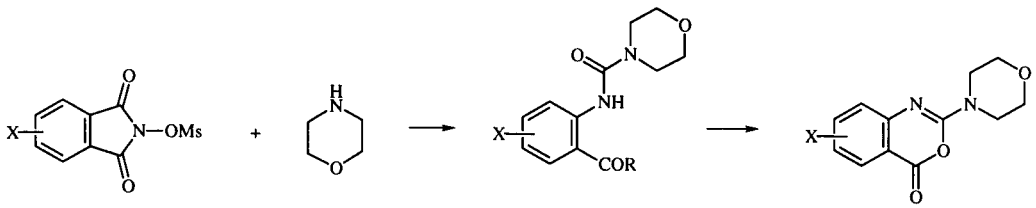
69 72 73

Reaction of morpholine with *N*-(mesyloxy)phthalimide (**74**) in acetone affords ureidobenzamide **77** in high yield. Acidic hydrolysis of **77** with 0.25 *M* hydrochloric acid gives the carboxylic acid **75** whereas treatment with 0.25 *M* ethanolic hydrochloric acid produces ester **76**. Cyclization of **75**→**78** is effected with acetic anhydride whereas **76** or **77** requires sulfuric acid [10,28]. The initial formation of **77** can be rationalized by nucleophilic attack of morpholine at the lactam carbonyl of **74** followed by ring cleavage, elimination of methanesulfonic acid, Lossen rearrangement to 2-isocyanatomorpholinobenzamide and addition of morpholine to the isocyanate. Other amines such as diethylamine, methyl cyclohexylamine and pyrrolidine have been used successfully in this reaction.

ily displaced with amines at 0 °C to ambient temperature to give aminobenzoxazinones **73** (*e.g.* R_1 = H, R_2 = Me, 64%; R_1 = R_2 = Et, 73%) [65]. Amino acid esters [20] and peptides [48] have also been used to displace the benzotriazole.

Thermolysis of the *cis*-tetra-azene **81** in refluxing benzene leads to the formation of 2-phthalimido-4*H*-3,1-benzoxazin-4-one (**82**) in approximately 60% yield. The *cis* disposition of the groups allows one phthalimido group to act as an internal nucleophile triggering a Curtius-type rearrangement in the other phthalimido group to generate an intermediate *o*-cyanatophthalimidobenzamide which then undergoes a 1,5-shift of the remaining phthalimido group leading to the product [66,67].

Scheme 32



74 X = H, Me

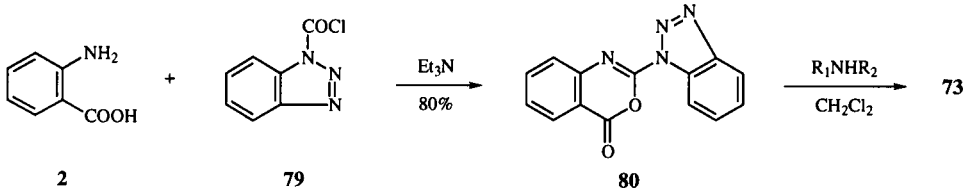
75 R = OH
76 R = OEt
77 R = morpholino

78

The interesting and versatile 2-(1-benzotriazolyl)-4*H*-3,1-benzoxazin-4-one (**80**) is readily prepared by treating anthranilic acid with two equivalents of 1-benzotriazole carboxylic acid chloride (**79**) in benzene or toluene in the presence of triethylamine. The benzotriazol group is eas-

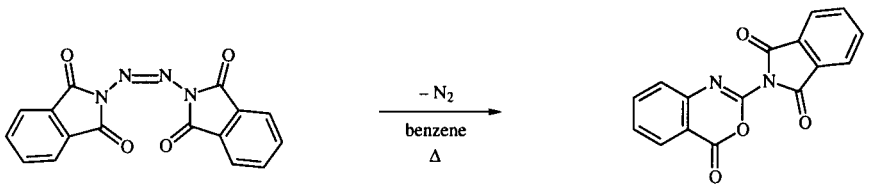
Thermolysis of benzotriazinone **83** in the presence of either phenyl or 3-chlorophenyl isocyanate produces the corresponding 2-phenylimino-3,1-benzoxazin-4-one **55** or **84** in 80% yield [68,69].

Scheme 33



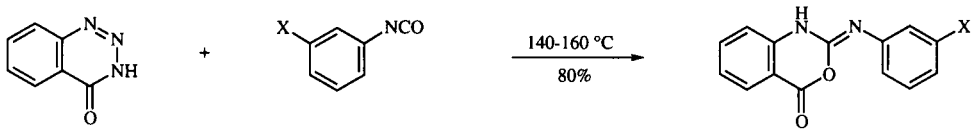
2 79 80

Scheme 34



81 82

Scheme 35

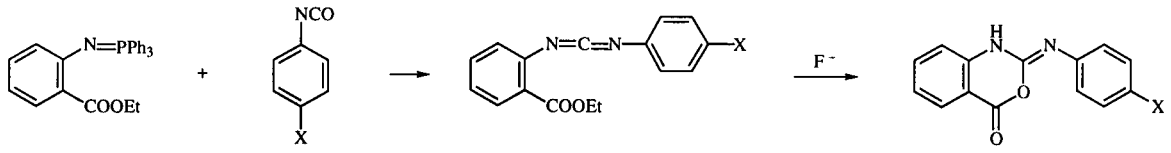


83 55 X = H 84 X = Cl

Reaction of imino-phosphorane **85** with an aryl isocyanate in tetrahydrofuran at 0 °C produces an intermediate carbodiimide **86** which is not isolated. Treatment of the reaction mixture with tetrabutylammonium fluoride facilitates cyclization to **87** as a result of its increasing the electrophilic character of the central carbon atom of the carbodiimide [70].

Using a similar strategy but a different reactant, one can directly synthesize compounds **55** or **92** in one pot. Reaction of **90** with a dithiocarbamate **91** in the presence of mercuric oxide in either dimethylformamide or acetone affords benzoxazinones **92**. The reaction initially forms a thiourea derivative similar to **88** which then is converted to a carbodiimide similar to **89** prior to cyclizing. The

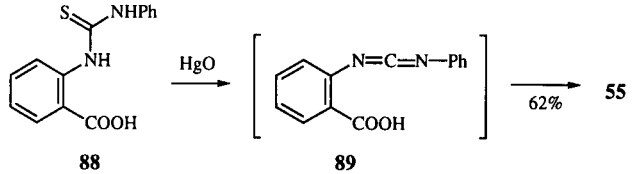
Scheme 36



85 X = H, Cl, OMe 86 87

Treatment of thiourea **88**, which is available from the reaction of potassium anthranilate with phenyl isothiocyanate, with mercuric oxide in acetone readily loses hydrogen sulfide to form carbodiimide **89**. Spontaneous cyclization with the carboxylic acid gives **55** [34,71].

Scheme 37



88 89

R group can be substituted phenyl [72], benzenesulfonyl [73], 1,3,4-oxadiazole [74], 4-arylthiazole [75] and benzothiazole [76].

Thermal cyclization of thiourea **93** in refluxing toluene gives the 2-benzoylaminobenzoxazinone **94** (67% yield) which is a potent chymotrypsin inactivator [37].

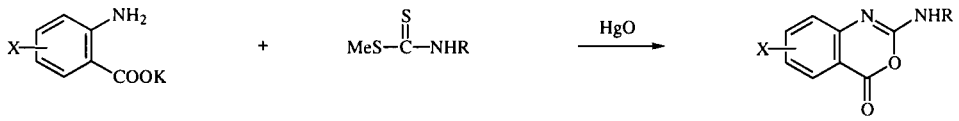
Ureidobenzonitrile **95**, which is readily prepared from anthranilonitrile and 2-chloroethyl isocyanate, when heated with concentrated hydrochloric acid is converted to 2-(2-chloroethylamino)-4*H*-3,1-benzoxazin-4-one (**96**) in 81% yield [77].

The action of methyl or phenyl isocyanate on 2,1-benzisothiazol-3-ones **97** in the presence of triethylamine in either tetrahydrofuran or ethyl acetate affords the corresponding aminobenzoxazinones **99** in 15-70% yield [78]. Initial reaction of **97** with the isocyanate followed by ring

opening generates the charged species **98**. Intramolecular attack of the urea oxygen on the thio acid, with concomitant loss of sulfur, produces **99**.

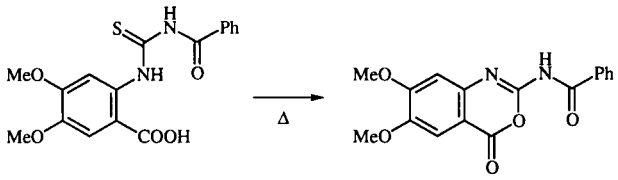
Base-catalyzed addition of hydroxide to the carbonyl of the indolylnitroxide **100** followed by ring expansion gives benzoxazinyl-2-nitroxide **101** [79,80].

Scheme 38



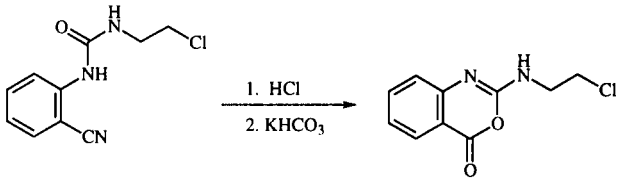
90 X = H, Cl, Me **91** **92**

Scheme 39



93 **94**

Scheme 40



95 **96**

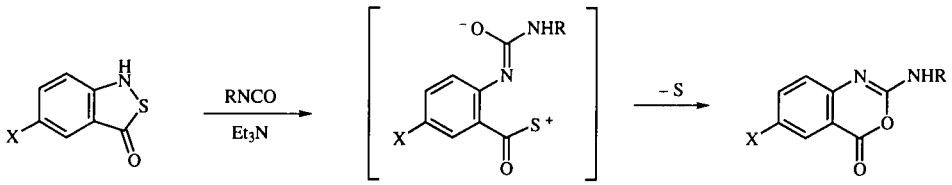
The condensation of anthranilic acid with *N*-alkyl carbamates in the presence of $POCl_3/ZnCl_2$ (3:1) at 80 °C produces a nearly 1:1 mixture of benzoxazinone **102** and quinazoline-2,4-dione **103** [81].

Bifunctional electrophilic reagents are capable of reacting with both functional groups of anthranilic acid to produce a variety of substituted 2-aminobenzoxazinones. *N*-(Dichloromethylene)sulfonamides **104**, when heated with **2** in benzene or toluene, are converted to 2-sulfonylamino-4*H*-3,1-benzoxazin-4-ones **105** in 48-93% yield [82,83]. Alkyl as well as aryl groups containing either electron donating or withdrawing substituents are tolerated.

Phosgene iminium chlorides **107** react exothermically with methyl anthranilate accompanied by strong gas evolution to give *N,N*-disubstituted 2-aminobenzoxazinones **108** as their hydrochloride salts. Treatment of the salts with triethylamine affords the free base [84,85].

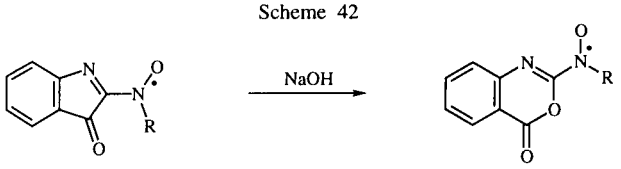
The *N*-acyl chloroformamidine **109** reacts with anthranilic acid by initial nucleophilic displacement of the chlorine atom followed by ring closure at the same carbon atom with elimination of pyrrolidine to furnish the 4-nitrobenzoylbenzoxazinone **110** in 31% yield [86].

Scheme 41



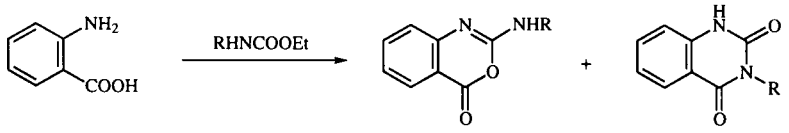
97 X = H, Cl R = Me, Ph **98** **99**

Scheme 42



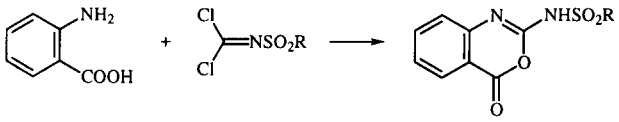
100 R = *i*-Pr, *t*-Bu, Ph **101**

Scheme 43



2 R = Me, Et, Pr **102** **103**

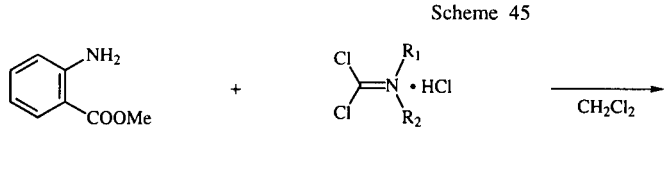
Scheme 44



2 **104** **105**

R = Me, Ph, 4-Cl-Ph, 4-MeO-Ph, 4-Me-Ph, 4-NO_2-Ph

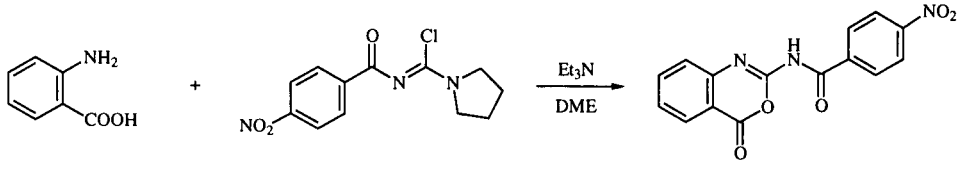
Scheme 45



106 **107** **108**

R_1	R_2	Yield (%)
Me	Me	81
morpholino		60
Me	Ph	62

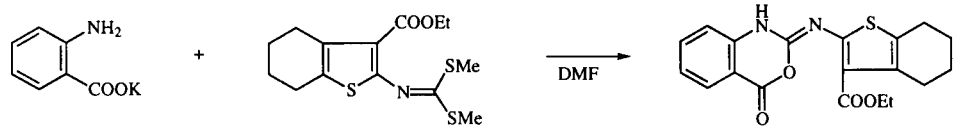
Scheme 46



2 **109** **110**

Condensation of thiophene-derived **111** with potassium anthranilate results in the formation of aryliminobenzoxazinone **112**. The product is isolated in 45% yield [87].

Scheme 47



90 (X = H) **111** **112**

By taking advantage of the *ortho*-directing influence of the oxygen atom, phenylurea **113** can be thallated adjacent to the urea function to generate the metalated species **114**. Carbonylation of **114** under an atmosphere of carbon monoxide in the presence of a catalytic amount of palladium chloride produces the 2-aminobenzoxazinones **92** [20,48]. The R group can be isopropyl, the amino acids glycine, valine, leucine or the dipeptides *L*-Leu-*L*-LeuOMe or *D*-Leu-*L*-LeuOMe. This method is particularly attractive in cases where the anthranilate starting material is not commercially available.

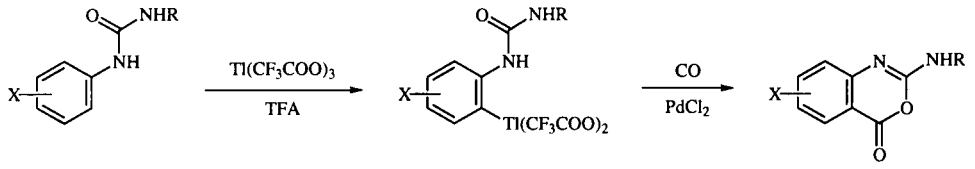
Reaction of 2-aminobenzoxazinones can be divided into two categories, those on the 2-amino group and those involving the heterocyclic ring.

Treatment of 2-aminobenzoxazinones with anhydrides provides *N*-acylated analogs [20]. Refluxing **117** with benzoic anhydride in toluene affords the *N*-benzoyl derivative **118** in 12-35% yield [10,37,88]. These compounds are potent chymotrypsin inactivators.

Condensing 2-alkylaminobenzoxazinones **47** with ethyl or *n*-butyl isocyanate in refluxing benzene produces the urea derivatives **119** in high yield [39,48].

Acylation of **47a** with 2-methylthiobenzoyl chloride (**120**) in pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine affords benzoylated analog **121** [47].

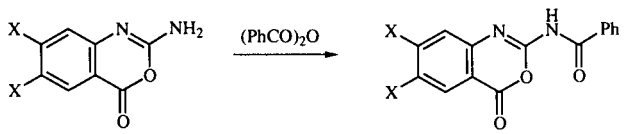
Scheme 48



113 **114** **92**

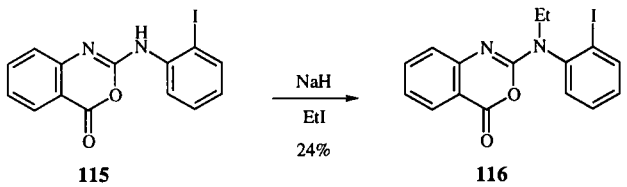
It has been reported that alkylation of **115** with ethyl iodide gives **116**, however, since 2-anilinobenzoxazinones have the capability to exist in the imino tautomer (*e.g.* **55**), it has not been rigorously established that the alkylation is as shown or on the ring nitrogen [76,77].

Scheme 50



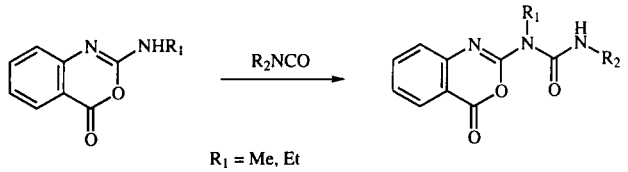
117 X = H, OMe **118**

Scheme 49



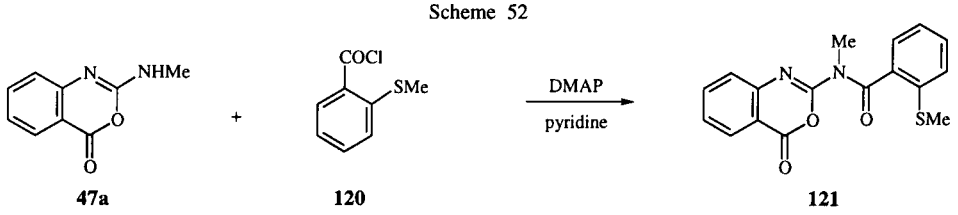
115 **116**

Scheme 51



47 R_1 = Me, Et; R_2 = Et, *n*-Bu **119**

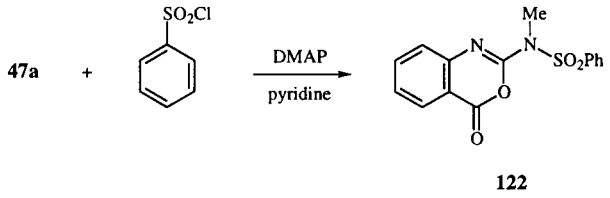
Scheme 52



47a 120 121

Under similar conditions, **47a** can also be sulfonylated with benzenesulfonyl chloride to yield the sulfonamide **122** [55]. Both **121** and **122** are C1r protease inhibitors.

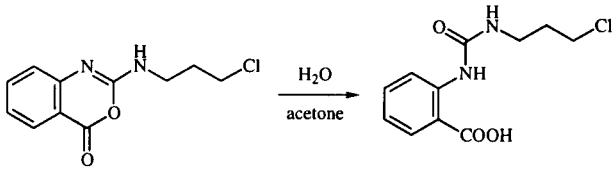
Scheme 53



122

Hydrolysis of 2-aminobenzoxazinones occurs under, neutral, acidic or basic conditions. Simply refluxing a solution of **123** in aqueous acetone for 1 hour results in formation of ureidobenzoic acid **124** in 74% yield [46].

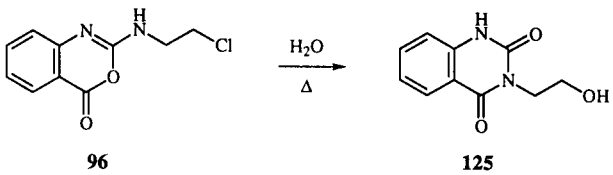
Scheme 54



123 124

Heating **96** in water for 2 hours results in hydrolysis, cyclization of the ureidobenzoic acid to the quinazoline-2,4-dione system, with further hydrolysis of the alkyl chloride to alcohol and furnishes **125** in 83% yield [77].

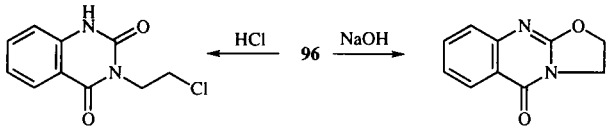
Scheme 55



96 125

Heating **96** with concentrated hydrochloric acid for 1 hour gives 3-chloroethylquinazoline-2,4-dione (**126**) in 90% yield. Conversely, brief treatment of **96** with 10% aqueous sodium hydroxide in ethanol affords **127** in 72% yield [77].

Scheme 56



126 127

In a likewise fashion **128**, when treated with dilute hydrochloric acid for 2-3 minutes, provides **129** in nearly quantitative yield. However, heating **128** in concentrated hydrochloric acid for 15 minutes or allowing the mixture to stand at room temperature for 15 hours gives the quinazoline-2,4-dione **130** in 70% yield [44].

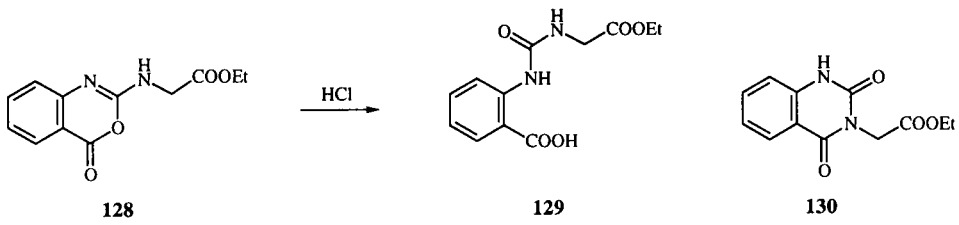
2-Anilinobenzoxazinones can also be converted to the corresponding 3-phenylquinazoline-2,4-diones with PPA at elevated temperatures [49,50,51].

The kinetics and mechanism for the hydrolysis of **46a** at a *p*H range of 0.5 to 12.6 has been studied in detail [35]. At low *p*H protonation of the nitrogen is the initiating step. Within a series of aromatic carboxy derivatives **46g**, **46h** and **46i** it was found that the carboxylate at the 5-position (**46g**) has no effect on the hydrolysis whereas the 8-carboxy derivative **46i** has a marked effect in the rate of hydrolysis due to the intramolecular protonation of the ring nitrogen [38].

Under anhydrous conditions in aprotic solvents, exposure of 2-aminobenzoxazinones to hydrochloric acid results in the formation of their hydrochloride salts [34,48,63].

In alcoholic solvents under anhydrous conditions in the presence of hydrochloric acid or *p*-toluenesulfonic acid, 2-aminobenzoxazinones are converted to the ureidobenzoates **52** in high yield [28,44]. If the hydrochloride salt of the aminobenzoxazinone is used, simply stirring in alcohol will effect the same transformation [36].

Scheme 57



128 129 130

Scheme 58

46g 46i

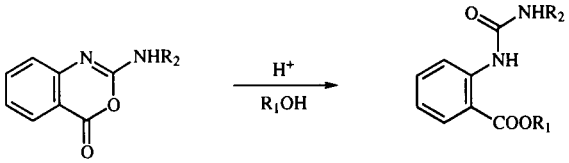
Scheme 60

73 131

R_1, R_2 = H, Me, Et, $(CH_2)_2Cl$, CH_2COOEt, Ph, morpholino

R_3, R_4 = H, Me, Ph, CH_2Ph, CH_2COOEt, morpholino

Scheme 59



47 52

R_1 = Me, Et

R_2 = H, CH_2COOEt

Amines react with 2-aminobenzoxazinones at the C-4 carbonyl *via* simple nucleophilic attack [89] to provide ureidobenzamides **131** usually in high yield. Primary and secondary alkylamines react with **73** at room temperature in solvents such as acetone [28], dioxane [71] and water [89]. Reaction of **73** with anilines, on the other hand, requires more forcing conditions such as refluxing in either benzene [77] or ethanol [43], or heating neat at 100 °C for 3 minutes [44,46]. Using the hydrochloride salts **108** requires the use of either 2 equivalents of the amine or 1 equivalent of amine and 1 equivalent of sodium acetate in ethanol [84].

Portionwise addition of **55** to a cold solution of hydrazine hydrate in ethanol followed by brief refluxing affords hydrazide **132** in 74% yield. Further refluxing of **132** in ethanol for 1 hour results in cyclization with loss of aniline to give the 3-aminoquinazoline-2,4-dione **133** in 78% yield [90].

Treatment of hydrochloride salt **108** with 3 equivalents of methylhydrazine in ethanol forms ureidohydrazide **134**. Thermal cyclization in dimethylformamide with loss of dimethylamine furnishes the 1,3,4-benzotriazepine-2,5-dione **135** in 79% yield [85].

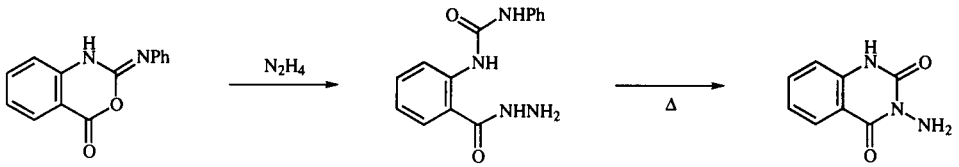
Fusion of **55** with ammonium acetate or formamide at 150 °C gives the 2-anilino-4-quinazolone **136** in about 50% yield [40,43,91,92].

Refluxing a solution of **46a** with sulfonamide **137** in either pyridine or pyridine/dimethylformamide (1:3) directly forms the 3-phenylquinazoline-2,4-diones **138** in 40-75% yield [93].

Treatment of **46a** with cyanamide and sodium hydride in dimethylformamide affords the 3-cyanoquinazoline-2,4-dione **139** [52,94].

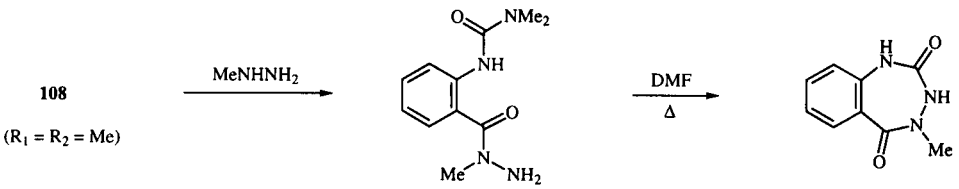
Addition of azide to **46a** results in the formation of 1-carbamoylbenzimidazol-2-one (**142**) in 76% yield. The product arises by initial nucleophilic addition of azide to the C-4 carbonyl to give an intermediate ureidoacid azide **140**. A Curtius rearrangement produces isocyanate **141** which is then attacked by the anilino urea nitrogen [94].

Scheme 61



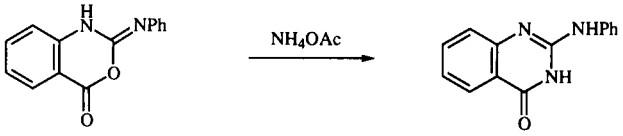
55 132 133

Scheme 62



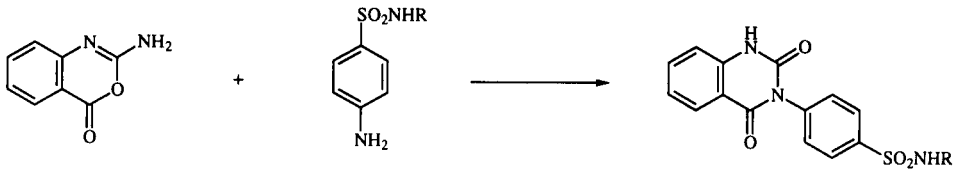
108 ($R_1 = R_2 = Me$) 134 135

Scheme 63



55 136

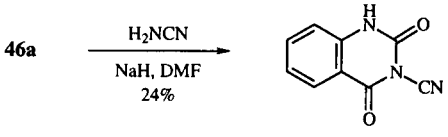
Scheme 64



46a 137 138

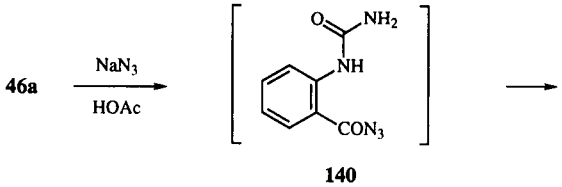
R = 2-pyridyl, 2-thiazolyl, 2-pyrimidinyl

Scheme 65



139

Scheme 66

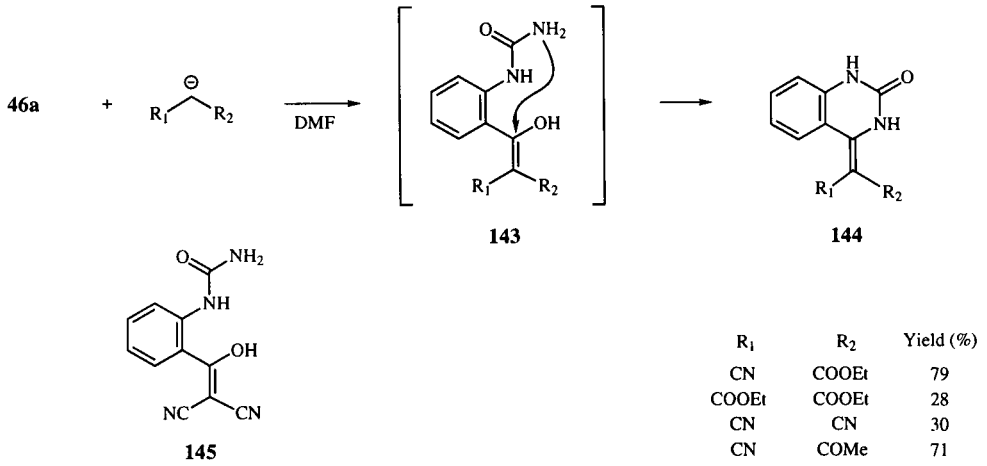


140 141 142

Anions of active methylenes react smoothly with **46a** at ambient temperature to furnish substituted 4-methylenequinazolone derivatives **144** in good yield [94]. Initial nucleophilic attack of the carbanion on the C-4 carbonyl generates intermediate **143** which then cyclizes with loss of water to form the product. Only in the case of malononitrile is the intermediate urea **145** able to be isolated in 56% yield. Cyclization of **145** with acetic anhydride gives the product **144** in 54% yield.

The nature of the skeletal components of the heterocyclic portion of 2-heterobenzoxazinones allows for facile characterization by spectral methods. In the infrared, three portions of the molecule are identifiable. The C=O and C=N double bonds are common to all. Measured in either nujol, chloroform or potassium bromide the carbonyl stretching frequency is generally observed between 1790-1725 cm^{-1}. A secondary band associated with the C=N double bond is seen at 1650-1630 cm^{-1}. The NH of the 2-amino

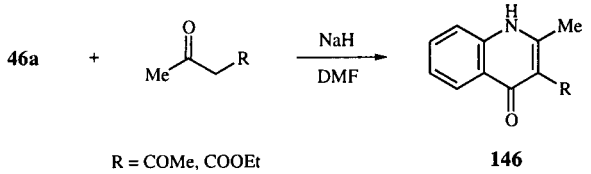
Scheme 67



R_1	R_2	Yield (%)
CN	COOEt	79
COOEt	COOEt	28
CN	CN	30
CN	COMe	71

Reaction of **46a** with the anion of acetylacetone or ethyl acetoacetate proceeds differently. The major product in each reaction is quinazoline-2,4-dione which is formed by rearrangement of **46a** promoted by the reacting nucleophile. The minor products are quinolones **146** which are isolated in about 25% yield. These are formed by attack of the anilino nitrogen of the initially generated ureido intermediate on the COMe carbonyl of the reacted nucleophile followed by loss of formamide.

Scheme 68



R = COMe, COOEt

146

Spectral Characteristics.

The crystal structure of 2-benzyloxy-5-methyl-4*H*-3,1-benzoxazin-4-one (**6b**) [19] and 2-(morpholin-4-yl)-4*H*-3,1-benzoxazin-4-one (**78**) [95] have been determined.

group is usually found between 3447-3280 cm^{-1} [19,70,-72,74,78].

The ultraviolet spectra of 2-benzyloxybenzoxazinones shows a λ_{max} at 314-323 nm and 247-252 nm [19]. ESR spectral data has been gathered for aminoxyl radical **101** [96].

The proton nmr spectra of 2-heterobenzoxazinones is obviously dependent on the functional groups decorating the periphery of the molecule. Signals for oxygen, sulfur and nitrogen-containing substituents are found in the expected regions of the spectrum. The carbon-13 chemical shifts for the carbonyl carbon at C-4 usually fall within a narrow range between δ 159.6-157 ppm. The signal for the carbon at position 2 is more variable and depends on the hetero substituent (see Table 4). For the assignment of the remainder of the carbon shifts and for data on additional analogs please see the references listed in Table 4.

It is interesting to note that carbon-13 shifts as well as carbonyl stretching frequencies of a variety of benzoxazinones have been used to estimate carbonyl reactivity and are useful in selection of parameters for structure-activity analysis of serine protease inhibitors [19,97].

Table 4
Carbon-13 Chemical Shifts for 2-Heterobenzoxazinones (**1**)

X	δC2	δC4	δC4a	Solvent	Reference
OEt	154.2	159.0	114.2	DMSO-d_6	97
OCH_2Ph	154.7	159.5	114.6	$CDCl_3$	19
SMe	163.3	158.0	115.3	DMSO-d_6	97
NH_2	155.4	159.6	112.5	DMSO-d_6	98
NHMe	154.7	159.5	112.5	DMSO-d_6	97
NHPh	150.6	159.0	113.7	DMSO-d_6	98

High resolution electron impact mass spectra of 2-phenyliminobenzoxazin-4-ones show an abundant fragment ion at $[C_8H_4NO_2]^+$ at *m/z* 146 (base peak). Surprisingly, the loss of CO_2 was not observed [99].

Conclusion.

Although 4*H*-3,1-benzoxazin-4-ones have been known for more than a century, only in the last 40 years have they been exploited for their biological and synthetic potential. The reactivity of the carbonyl can be tuned by varying the nature of the substituent in the 2-position thus making them excellent serine protease inhibitors capable of inactivating a wide variety of enzymes.

The 4*H*-3,1-benzoxazin-4-one heterocycle can be considered a protected and activated form of anthranilic acid. As shown in this review and in the previous review [4], the versatility of this heterocycle as a synthetic intermediate in the construction of numerous heterocyclic systems as well as acyclic products provides the chemist with alternative and often superior methods to achieve his or her goals. It is hoped that in the next 40 years the chemistry of benzoxazin-4-ones can continue to provide powerful techniques for the synthesis of medicinal and natural products.

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