Synthesis of some Heterocyclic Compounds Containing Nitrogen and studying their Biological Activity

Thesis

Submitted by

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تخليق بعض المركبات النيتروجينية غير متجانسة الحلقة ودراسة الأثر البيولوجي لها

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بكالوريوس علوم – كيمياء

للحصول على

درجة ماجستير العلوم في الكيمياء

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قسم الكيمياء

كلية العلوم - جامعة عين شمس

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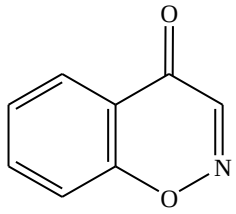
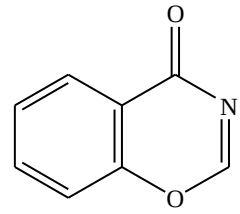
Introduction

BENZOXAZINONE

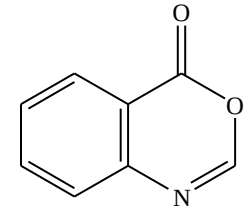
The keto derivatives of the different isomeric benzoxazines ***viz***. benzoxazinones are heterocyclic compounds comprising a benzene ring fused with six-membered ring containing two hetero atoms i.e., oxygen and nitrogen the diverse benzoxazinones can be represented as follows:



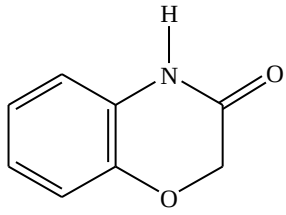
1,2,4-Benzoxazinone
(1,2-Benzoxazin-4-one)



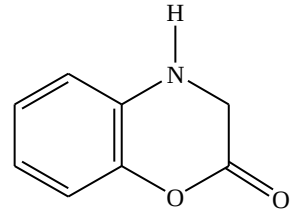
1,3,4-Benzoxazinone
(1,3-Benzoxazin-4-one)



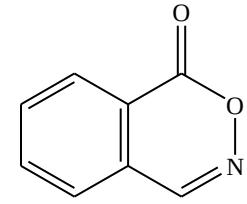
3,1,4-Benzoxazinone
(3,1-Benzoxazin-4-one)



1,4,3-Benzoxazinone
(1,4-Benzoxazin-3-one)



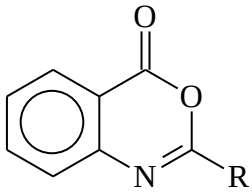
1,4,2-Benzoxazinone
(1,4-Benzoxazin-2-one)



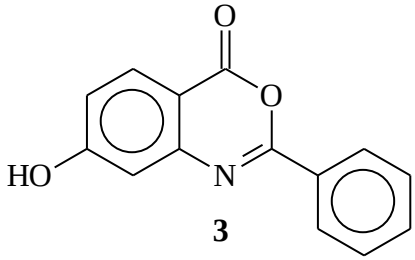
2,3,1-Benzoxazinone
(2,3-Benzoxazin-1-one)

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[(116)] and the methyl analog **2** seventeen

years later[38]. Members of this family have been given the common name "acylanthranils" presumably from their early synthesis from 2,l-benzisoxazole (anthranil) and an acylating agent.



1 R =Ph
2 R =Me



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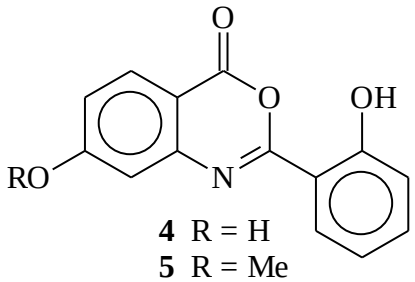


4 R = H
5 R = Me

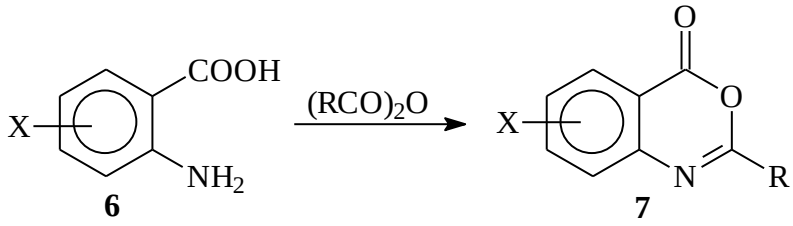
Compounds possessing this ring system are found in nature. The phytoalexins isolated from infected carnations[34,211] are dianthalexin **3** and hydroxylated analogs **4** and **5**.

4H-3,1-Benzoxazin-4-ones have been used as linking units in thermally stable polymers[286] and have been shown to posses biological activity. They are potent in activators of chymotrypsin[10,133,277] as well as inhibitors of human leukocyte elastase[171,272,277] and HSV-l protease[158].

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

1.1 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.Simple2-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[20,29,52,84,97,169,224,232] although co-solvents such as chloroform[23], dioxane[39] and toluene[287] have been successfully used. Yields are generally high and fall between 80-95%.

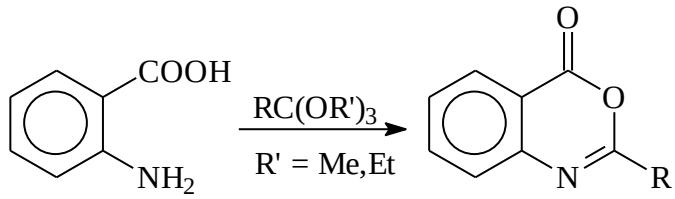


6 X = H, halo, OMe, COOH, NO2

7 R = Me, Et, n-Pr, Ph, CF3

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[167].

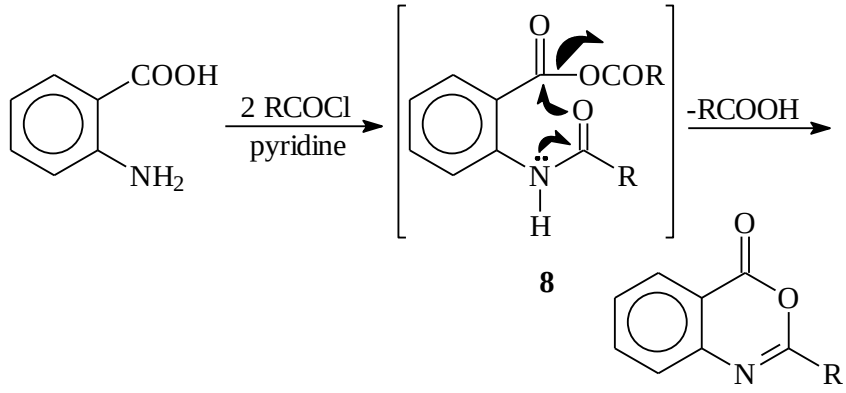
Although these methods provide benzoxazinones in a straightforward manner, the lack of a wide variety of readily available anhydrides or orthoesters limits the generality of the reactions. A vast array of acid chlorides are either commercially available or easily prepared. Anthranilic acid **6** reacts with two equivalents of an acid chloride in pyridine solution to give the benzoxazinone in good yield.



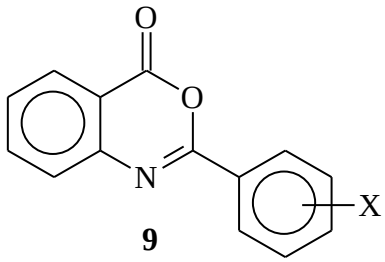
6

R	Yield %
H	80
Me	87
Et	90
Pr	78
Bu	75
Ph	91

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 intermolecular nucleophilic displacement of carboxylate ion from the anhydride moiety by the carbonyl oxygen of the amide function[32,225].



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 *artho*, *meta* or *para* positions have been successfully prepared[32,78,123,164,225]. Also, both α- and β-naphthyl analogs[195] as well as the styryl derivative **10**[32,279,280] and furyl derivatis **11**[32] 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[132]. Modifications of this method use *N*,*N*-dimethylaniline[50], tetrahydrofuran/sodium carbonate[212] or phase transfer conditions[130] to replace the pyridine as the 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[252] as well as the ether and phthalimide derivatives **12** and **13** have been reported[172,261].



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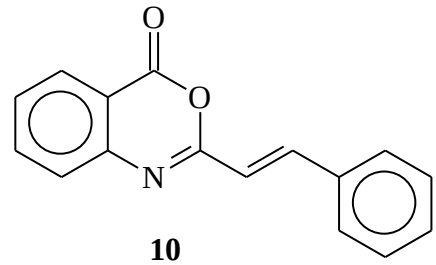

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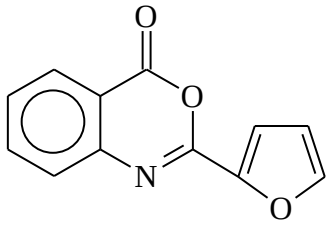

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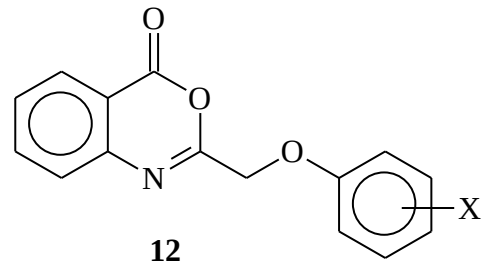
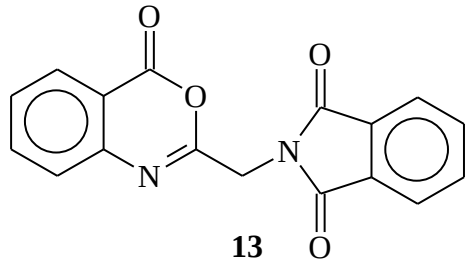


12

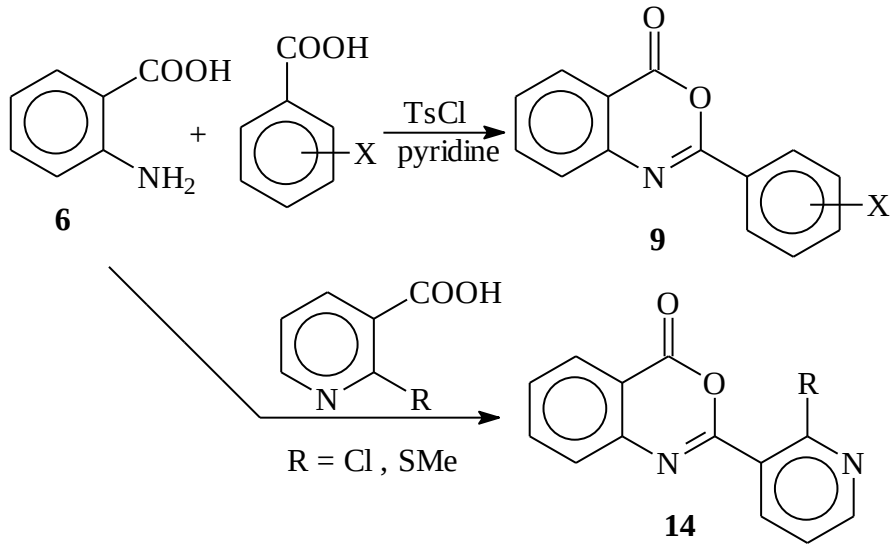
X = H , Me , OMe , NO_2



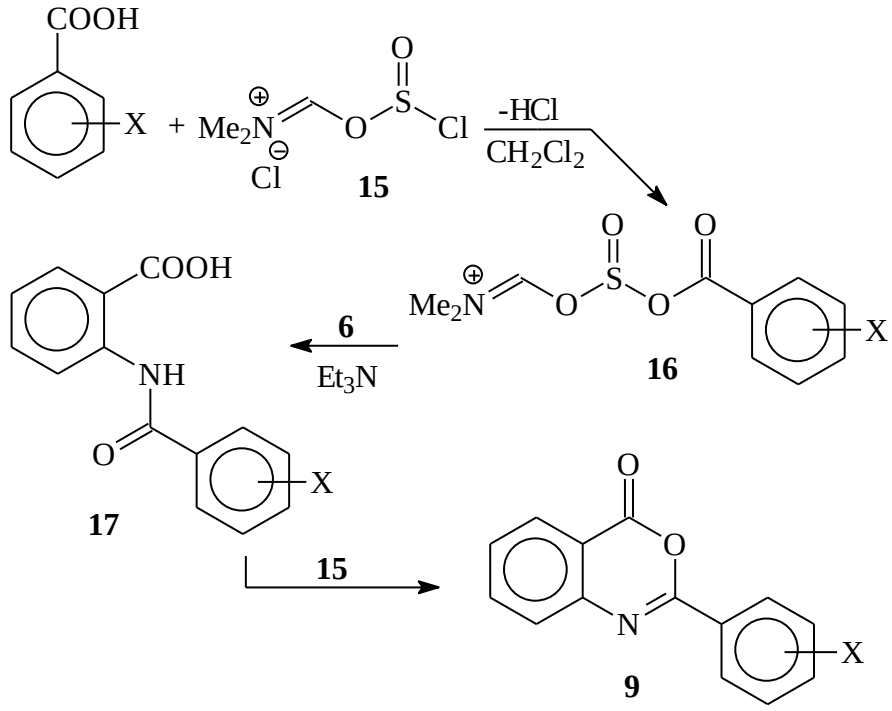
13

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[(235)]. 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

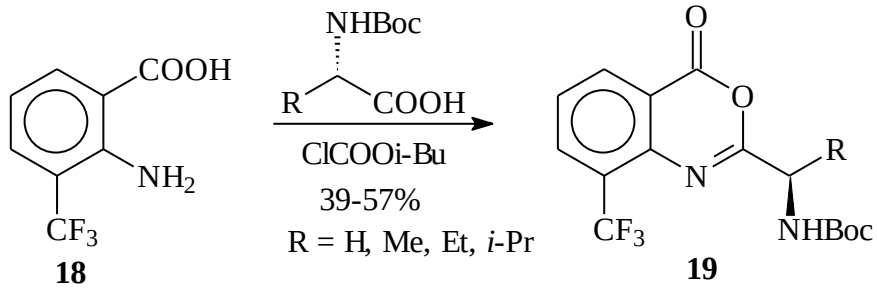
analogs **14** are able to be prepared[243]. Higher yields probably would have been realized if two equivalents of the carboxylic acid were used.



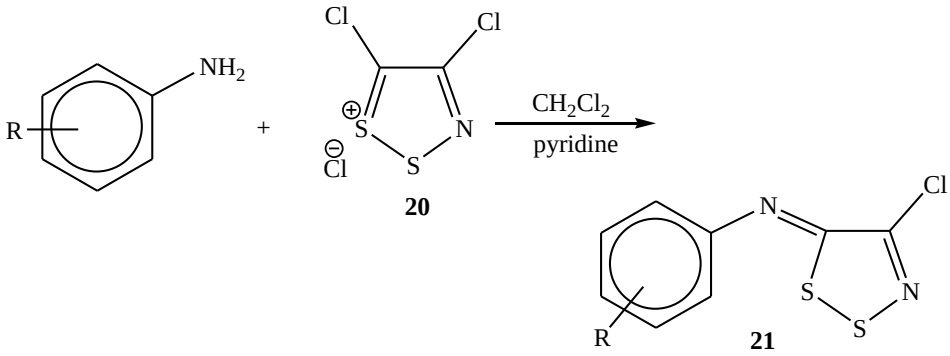
N,*N*-Dimethylchlorosulfitemethaniminium chloride **15** can be employed as an activating agent in the reaction between **6** and a benzoic acid. The initially formed anhydride-like species **16** acylates **6** on nitrogen with loss of SO_2 and DMF to give the *N*-acylanthranilic acid **17**. Subsequent 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[244].



The interesting aminobenzoxazinone derivative **19** is readily prepared from the reaction of equimolar quantities of 3-trifluoromethylanthranilic acid **18** and a Boc-protected amino acid with two equivalents of isobutyl chloroformate in the presence of *N*-methylmorpholine[62,81].

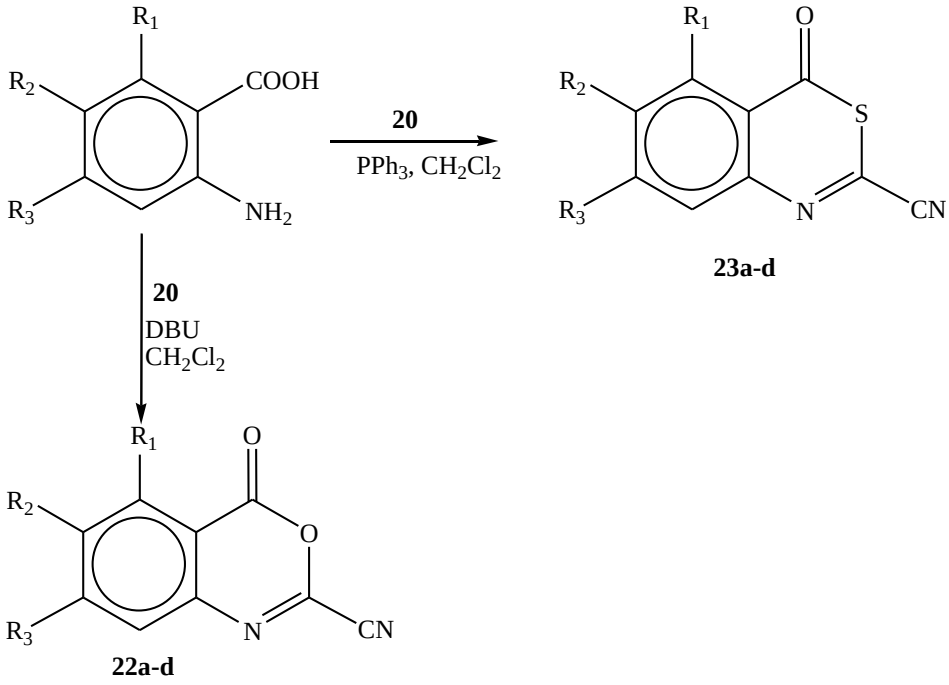


Aniline can be condensed with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) **20** in dichloromethan at room temperature knowed by addition of pyridine to give imino-1,2,3-dithiazoles **21**[269].



20 **21**

F.R. Alexandre et al observed that anthranilic acid and its benzo derivative (eg. 4-chloro and 4,5-dimethoxy anthranilic acid) behave differently to all the aniline investigated and did not give the analogous imines **21** but rather 2-cyano-3,1-benzoxazin-4-one derivatives **22**, and with triphenyl phosphine it give 2-cyano-3,1-benzothiazin-4-one **23**[11,115].



Compound	R_1	R_2	R_3	yield
22a	H	OCH_3	OCH_3	31
22b	OCH_3	OCH_3	OCH_3	43
22c	H	H	H	26
22d	H	H	CH_3	20
23a	H	OCH_3	OCH_3	67
23b	OCH_3	OCH_3	OCH_3	55
23c	H	H	H	28
23d	H	H	CH_3	38

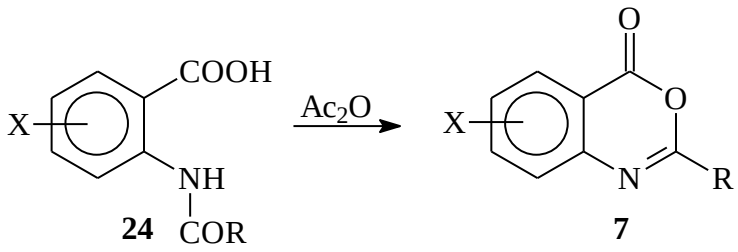
1.2 From N-Acylanthranilic Acids.

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[11,64,131,184,189,264,304] or more complex functionalities like chloroalkyl (CH_2Cl and CH(Me)Cl)[15,87,114,120,245], styryl[90], trifluoromethyl[256], phthalimidomethyl[198], COOEt[44,227], 2-thienyl, pyridyl and thiadiazole[131,137,224]. The aromatic substituent X can be either an electron donating or withdrawing group.

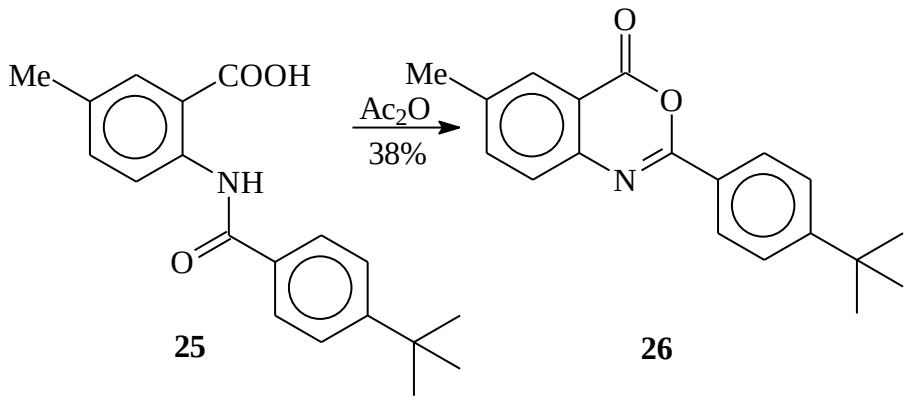
In the initially formed intermediate **8** where now the two acyl functionalities are different, the *O*-acyl is always eliminated over the *N*-acyl group. Furthermore, once the benzoxazinone is formed no transacylation occurs. For example, heating the parent system **7** (X = R = H), **1** or **2** with

propionic anhydride does not result in the formation of any 2-ethyl-3,1-benzoxazin-4-one[64].



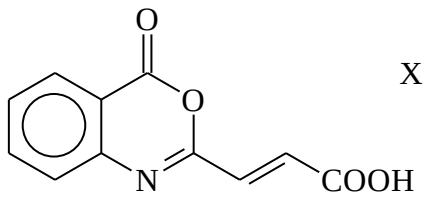
24 **7**

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[113].



25 **26**

The α,β-unsaturated acid derivative **27** is produced in 77% yield using sodium acetate/acetic anhydride as the cyclizing reagents[34]. More complex heterocyclic systems such as a coumarin can be introduced into the 2-position of the benzoxazinone affording **28** in 75-82% yield[157].



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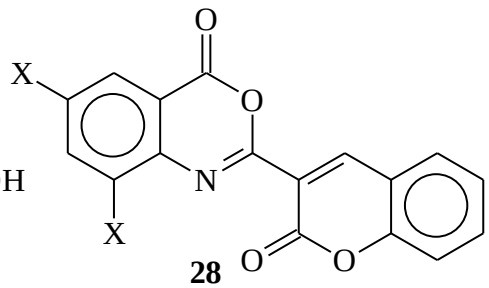
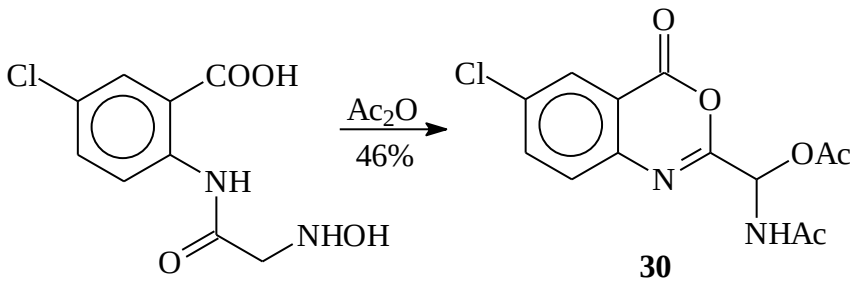


28

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**[38].



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[35].