Synthesis of some heterocyclic compounds of expected biological activity

Thesis submitted by

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M.Sc. (Chemistry 2006)

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Acknowlegement

‘‘I do thank god for all gifts be gave me’’

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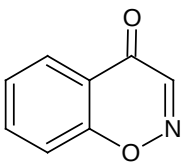
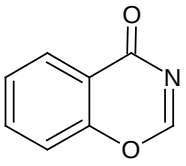
The author

Benzoxazinones

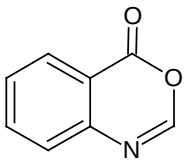
The keto derivatives of the different isomeric benzoxazinones are heterocyclic compounds comprising a benzene ring fused with six-member ring containing two hetero atoms i.e., oxygen and nitrogen some benzoxazinones can be represented as follow:



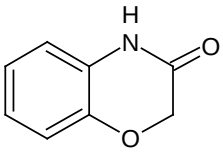
1,2-Benzoxazin-4-one



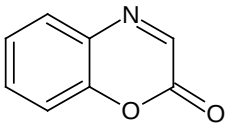
1,3-Benzoxazin-4-one



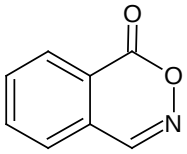
3,1-Benzoxazin-4-one



1,4-Benzoxazin-3-one

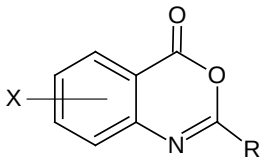


1,4-Benzoxazin-2-one



2,3-Benzoxazin-1-one

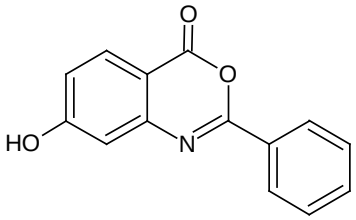
4H-3,1-benzoxazin-4-ones as a class have been known for more than a century. The phenyl derivative **1** was first synthesized in 1883 [97] and the corresponding methyl analog **2** seventeen years later [28]. Members of this family have been given the common name "acylanthranils" presumably from their early synthesis from 2,1benzisoxazole (anthranil) and an acylating agent.



1

a- R= Ph

b- R= Me



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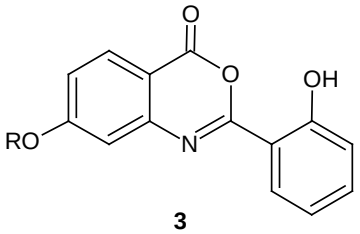


3

a- R = CH_3

b- R = H

Compounds possessing this ring system are found in nature. The phytoalexins isolated from infected carnations [27,172] are dianthalexin **3** and hydroxylated analogs **4.**

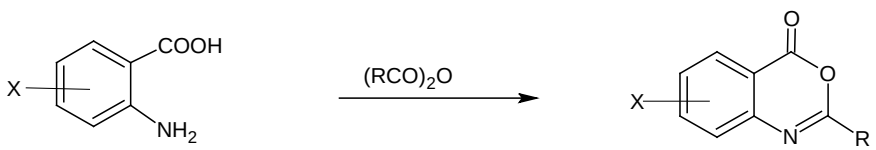
4H-3,1-benzoxazin-4-ones have been used as linking units in thermally stable polymers [286] and have been shown to posses

biological activity. They are potent in activators of chymotrypsin [7,109, 233] as well as inhibitors of human leucocyte elastase [142, 228, 233] and HSV-1 protease [128]

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

i- Via cyclization of N-acylanthranilic acids with acetic anhydride:

The most popular and versatile route to the 3,1-benzoxazin-4-ones nucleus relies on anthranilic acid or its substituted derivatives are best prepared by reacting the anthranilic acid **4** with an appropriate anhydride at elevated temperature. Low molecular weight anhydrides are usually employed as the solvent [17,25, 40,71, 140, 180, 190] also co-solvents such as chloroform [19], dioxane [29] and toluene [244] have been successfully used. Yields are generally high and fall between 80-95%.



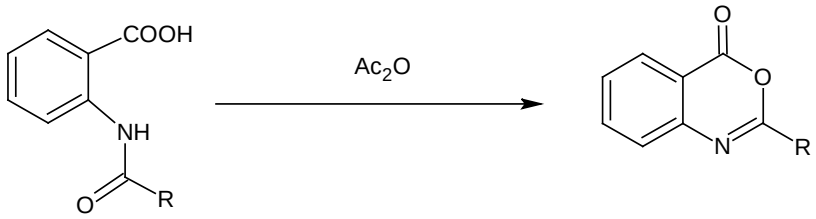
4 **5**

X = H, COOH, OMe, NO_2, Cl, Br

R = Me, Et, n-Pr, Ph, CF_3

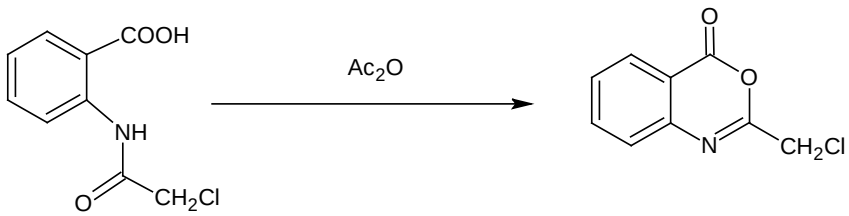
Also reactions of anthranilic acid or its derivatives **4** with excess acylating agents via N-acylation give N-acylanthranilic acid **6** that undergoes ring cyclization to afford the formation of 4H-3,1-benzoxazin-4-ones. The most widely used cyclizing agent is the acetic anhydride. The cyclization can accommodate a wide variety of

acyl groups where R can be simple hydrogen, alkyl or substituted phenyl [8, 47, 106, 155, 216, 253] or more complex functionalities chloroalkyl [12, 74, 95, 102, 196] styryl [76], trifluromethyl[209], phthalimidomethyl[165], 2-thienyl, pyridyl and thiadiazole [106, 114, 180].



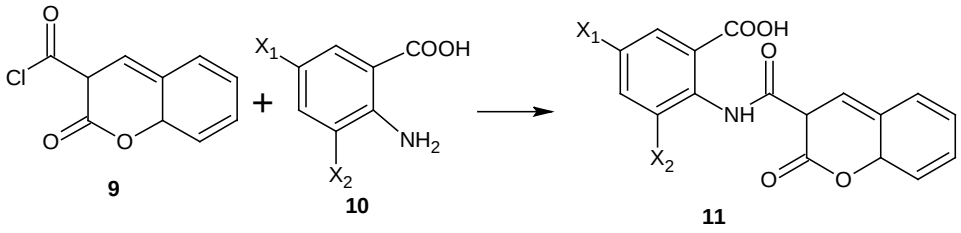
6

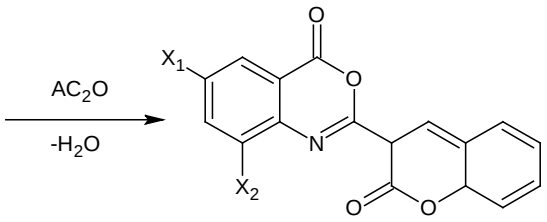
Treatment of chloroacetylanthranilic **7** acid with acetic anhydride afforded 2-(chloromethyl)-4H-3,1-benzoxazin-4-one **8.** [175]



7 **8**

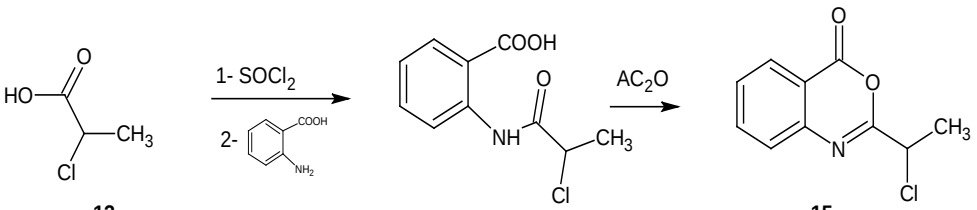
Treating 3-coumarincarbonyl chloride **9** with anthranilic acid derivatives **10** gave the corresponding amides **11** which were cyclised with acetic anhydride to give 2-coumarinyl-4-H-3,1-benzoxazin-4-ones (X1, X2 = H, Br) **12** [209]



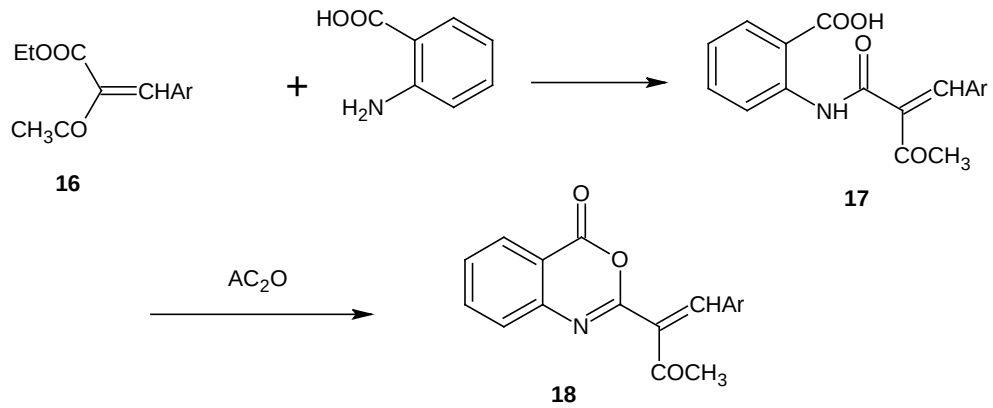


12

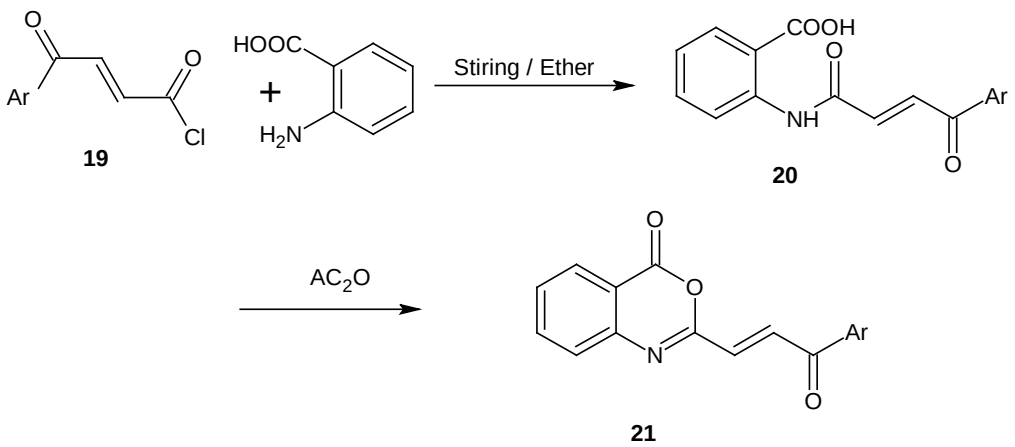
Treating 2-chloropropanoic acid **13** with thionyl chloride then anthranilic acid gave the intermediate **14** which cyclised on treatment with acetic anhydride to afford 2-(1-chloroethyl)-4-H-3,1-benzoxazin-4-one **15** [207].

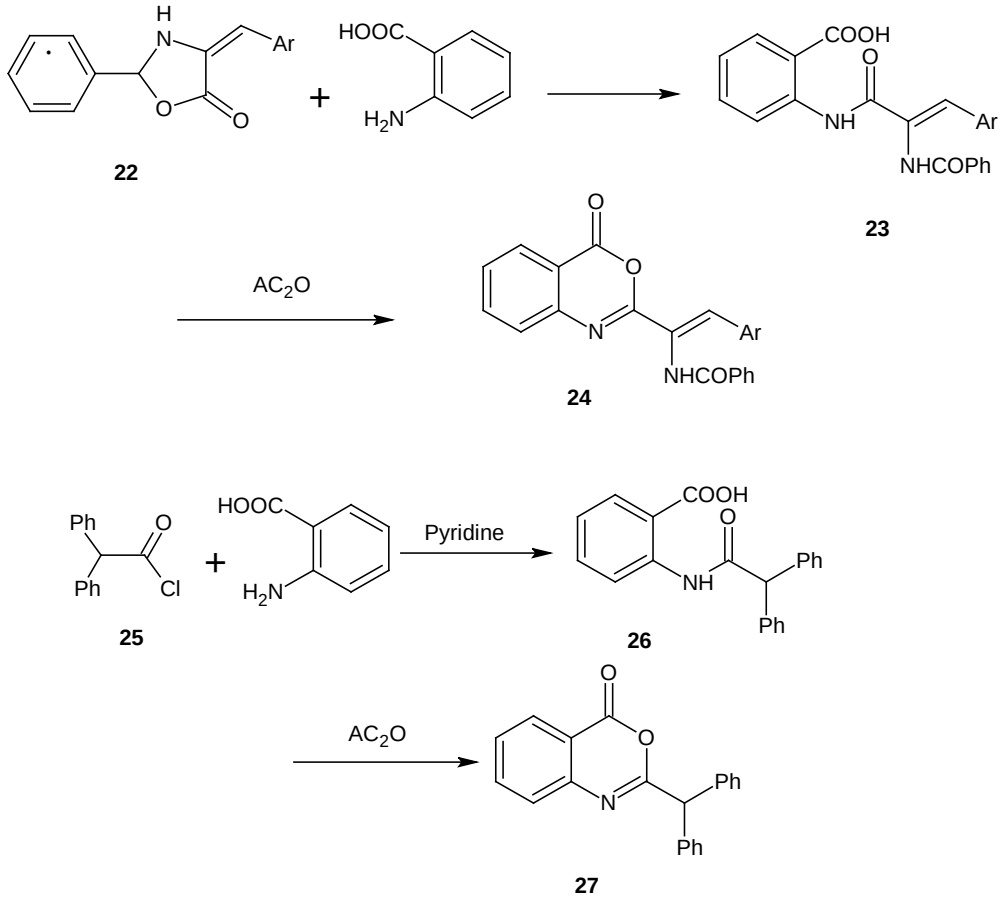


2-(α-Acetylstyryl)-4H-3,1-benzoxazi-ones **18** have been prepared via cyclization of **17** by the effect of acetic anhydride [74]. Compound **17** is obtained by the reaction of anthranilic acid and **16**.



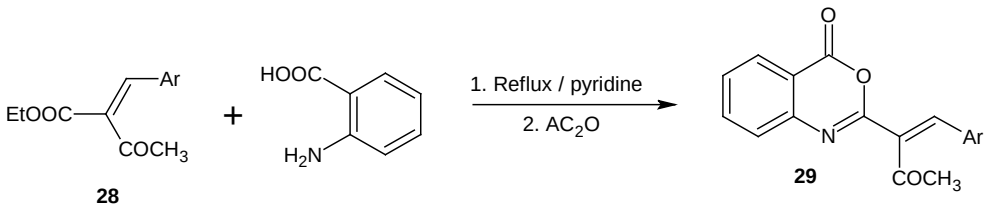
To introduce more complex system at 2-position Sammour et al and Soliman et al have been reported the preparation of a number of 4H-3,1-benzoxazin-4-one derivatives that are summarized as follow.





22 **23** **24** **25** **26** **27**

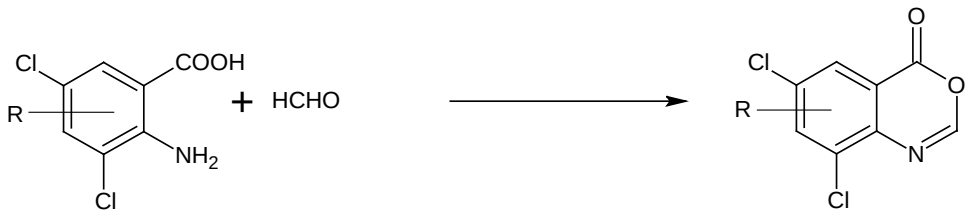
In a similar approach, the preparation of 2-(acetylstyryl)- 4H-3,1-benzoxazin-4-ones **29** have been prepared via reaction of anthranilic acid with the acetyl derivative **28** [74]



28 **29**

ii- Via condensation of anthranilic acid derivatives with formaldehyde

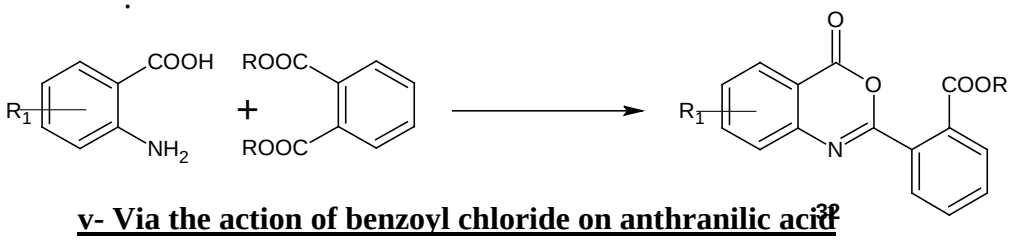
An early method for preparation of 4H-3,1-benzoxazin-4-one derivatives **31** was achieved by condensation of a number of chloro-anthranilic acid derivatives **30** with formaldehyde. [97,250]



30 **31**

iv- Via the action of diphthalate ester on substituted anthranilic acid:

4H-3,1-benzoxazin-4-one derivative **34** were prepared by cyclo-condensation of substituted anthranilic acid with diethyl phthalate [154].

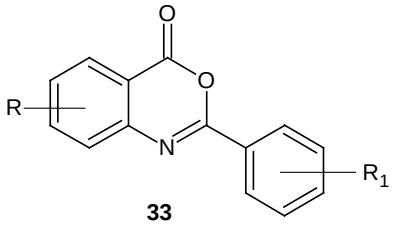


37

v- Via the action of benzoyl chloride on anthranilic acid derivatives:-

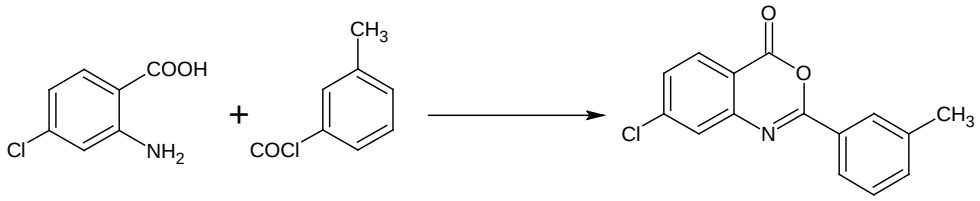
2-Phenyl-4H-3,1-benzoxazin-4-one derivatives **33** were synthesized via benzoylation of anthranilic acid derivatives using aqueous alkali

in an immiscible organic solvent and phase-transfer catalyst followed by cyclization of the product N-benzoylanthranilic acids [101].



33

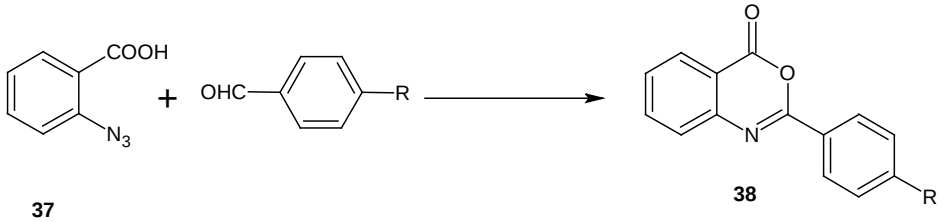
In a similar manner, 7-chloro-2-(3-methylphenyl)- 4H-3,1-benzoxazin-4-one **36** was obtained by condensation of 3-methylbenzoylchloride **35** and 2-amino-4-chlorobenzoic acid **34** [132].



34 **35** **36**

vi- Via cyclization of o-substituted aryl azide:

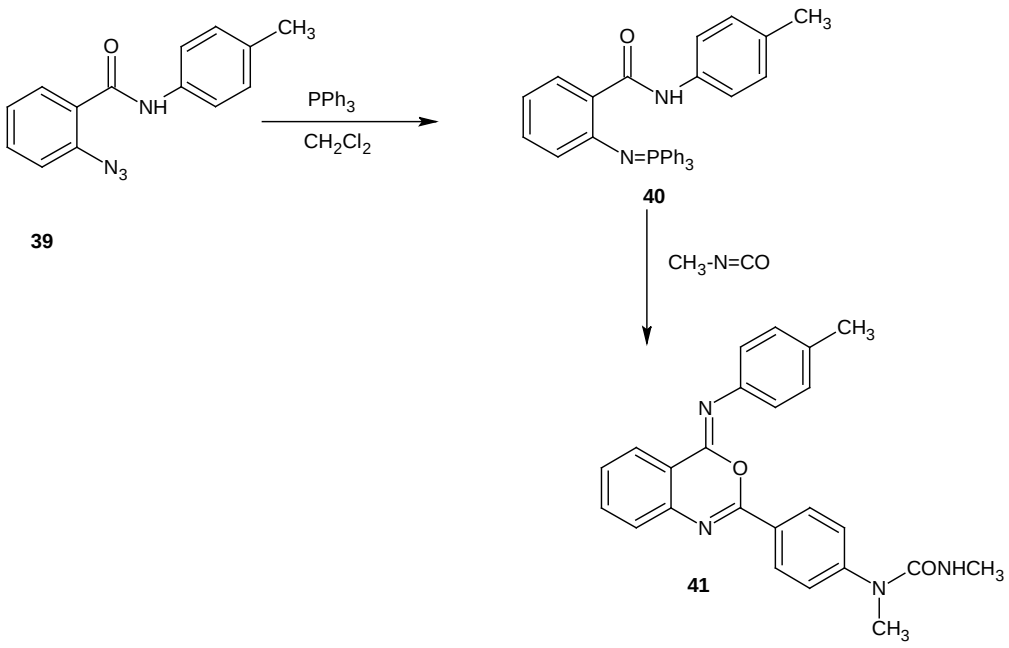
4H-3,1-Benzoxazin-4-ones **38** were prepared by cyclising o-substituted aryl azide **37** with aromatic aldehydes [193].



37 **38**

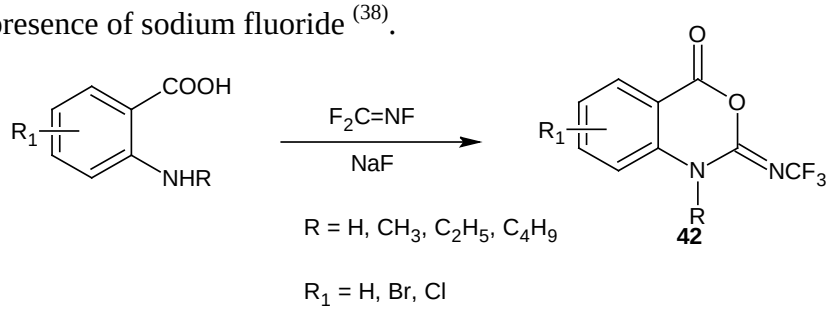
The aza-Wittig reaction of iminophosphoranes derived from 4H-3,1-benzoxazin-4-one with heterocumulenes leads functionalized quinazolines. Thus N-p-tolyl-o-azidobenzamide **39** was treated with PPh_3 in methylene chloride to afford the iminophosphorane

derivative **40** which reacted with methyl isocyanate as an example of heterocumulene to give iminobenzoxazine derivative **41** [67, 167].



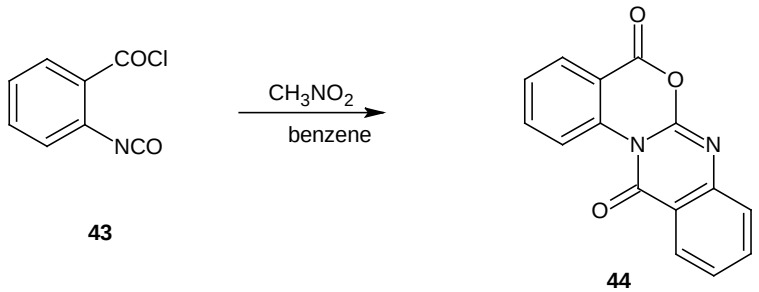
vii- Via the action of F_2C=NF on anthranilic acid:

2-(trifluoromethylimino)- 4H-3,1-benzoxazin-4-one derivatives **42** were synthesized by the action of F_2C=NF on anthranilic acid in the presence of sodium fluoride [38].



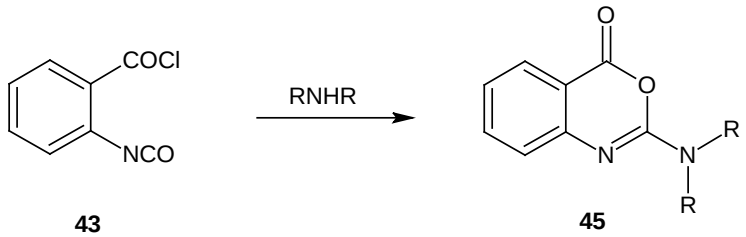
viii- Via reaction between isocyanate derivatives and nitromethane:

Treatment of o-isocyanate-benzoyl chloride **43** with nitromethane in benzene yielded the tetracyclic product of 4H-3,1-benzoxazin-4-one **44**. [2, 160]



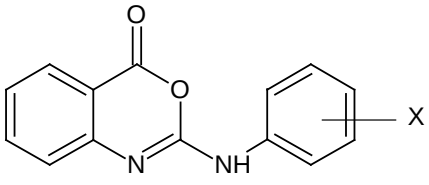
43 **44**

On the other hand 2-dialkylamino-4H-3,1-benzoxazin-4-one derivatives **45** were obtained from the reaction of o-isocyanato-benzoylchloride **43** and dialkylamines [242].



43 **45**

2-Substituted 4H-3,1-benzoxazin-4-ones **46** were prepared by the action of phenylisocyanate on 1,2,3-triazin-4-one [111].



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