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REVIEW

Synthetic Strategies Towards Benzoxazole Ring Systems: A Review

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A review on the various synthetic strategies towards the formation of benzoxazole ring systems is described.

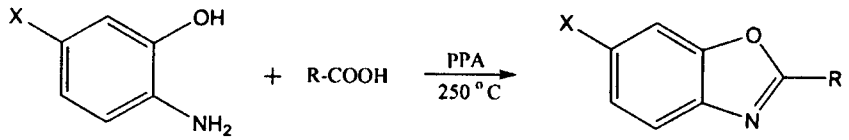
Key Words: Synthetic strategies, Benzoxazoles, Review.

Benzoxazole is an important heterocyclic ring system and the targets containing benzoxazole moiety, either isolated from natural products or accessed by total synthesis, possess most remarkable and a wide range of biological activities[1]. The biological and analytical importance of benzoxazoles has been well documented[2]. The benzoxazole scaffold is also found in many biologically active compounds such as anticancer agents[3], gram-positve antibacterials[4], antimicrobial[5], polycyclic and polyether antibiotics[6, 7], antiparasitics[8], antiinflammatories[9], anticonvulsants[10], H_2-antagonists[11], elastase inhibitors[12], whitening agents[13], bis-benzoxazole natural products[14], polybenzoxazole and azole polymers[15], crown-ether cyanine dyes[16], synthetic heat resistant fibers[17], optical bleaching agents[18], etc., all containing the benzoxazole fragment. These examples highlight the level of interest in new synthetic approaches to benzoxazole derivatives and have prompted researchers around the globe to synthesize and to explore the wide applicability of this important pharmacophoric scaffold.

The benzoxazoles are usually prepared by the condensation of *o*-aminophenols with carboxylic acids with various leaving groups or carboxylic acid itself[19] or other typical methods cited[20]. Time, necessity and the development of novel and useful synthetic reagents have enhanced the scope for the outcome of various synthetic methodologies for the benzoxazole ring systems. In this review, the various methods that have been published so far are categorized which provides some insight into the logic of synthesis in general, and the methods available are conveniently classified and presented, according to the conditions under which they are synthesized.

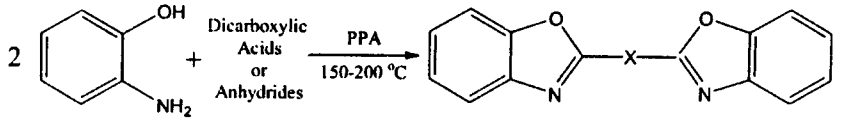
Thermal Cyclizations

By Polyphosphoric Acid: The condensation of *o*-aminophenol (**1**, X = H) or its chloro derivative with a carboxylic acid in the presence of polyphosphoric acid at 250°C giving 2-substituted benzoxazoles (2, X = H or Cl; R = Ph) was reported by Hein *et al.*[21]



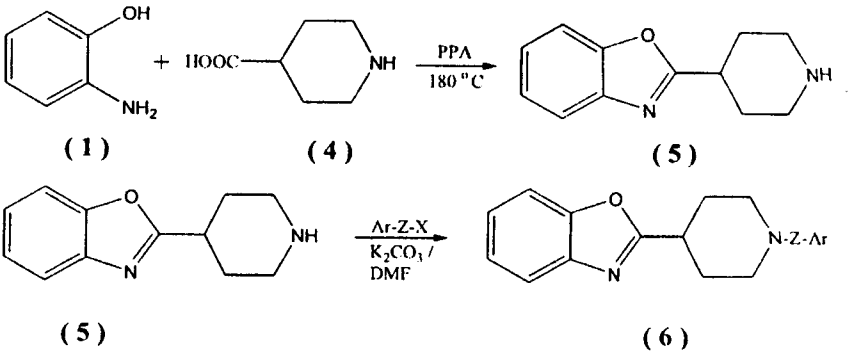
(1) (2)

Nyilas and Pinter[22] have shown the synthesis of the bis-benzoxazoles (**3**) in fair to excellent yields by inter-molecular condensation of two molecules of **1** with one molecule of dicarboxylic acid or its anhydride in polyphosphoric acid (PPA) at temperatures ranging from 150–200°C. The connecting unit, *i.e.*, X in **3**, linking the two benzoxazole nuclei has been varied from simple alkane chains to aryl chains [*i.e.*, X = $(CH_2)_2$, $(CH_2)_4$, $(CH_2)_6$, $(CH_2)_8$, C_6H_{10}, C_6H_8, *o*-, *m*- and *p*-phenylene].



(1) (3)

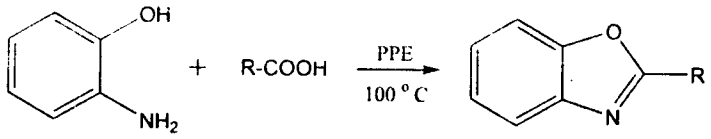
Similarly, synthesis of a series of piperidinobenzoxazoles (**6**) have been reported by Orjales *et al.*[23] Thus, condensation of **1** with 4-piperidinecarboxylic acid (**4**) in polyphosphoric acid at 180°C gave 2-(4-piperidinyl)benzoxazole (**5**). The compound **5** was then reacted with aryl halides (Z = CH_2, $(CH_2)_2$, $CH(C_6H_5)$, $(CH_3)_2O$; Ar = Ph, 4-Cl-C_6H_4-, 4-F-C_6H_4-, 4-MeO-C_6H_4-, 4-t-Bu-C_6H_4-) to give the title 2-substituted piperidinylbenzoxazoles (**6**).



(1) (4) (5)

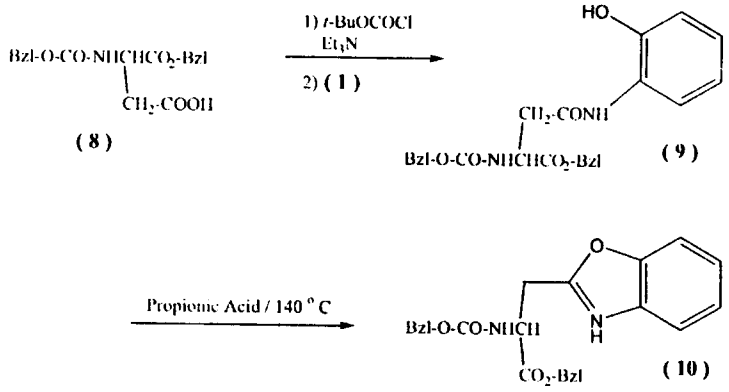
(5) (6)

By Polyphosphate Ester: Polyphosphate ester mediated synthesis of 2-substituted benzoxazoles (**7**) was reported[24] by heating a mixture of **1** and free carboxylic acids [R = Me, Ph, Cl, NO_2, 4-(NHCOCH$_3$)-C_6H_4-] under mild conditions, *i.e.*, at 100°C.

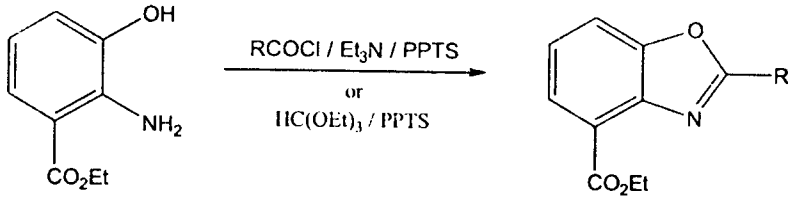


(1) (7)

By Propionic Acid: Nestor (Jr.) *et al.* reported[25] the use of propionic acid as an acid catalyst for thermal cyclization leading to benzoxazole formation. In a typical reaction, α-benzyl N-(benzyloxycarbonyl)-D-aspartate **(8)** was reacted with isobutyl chloroformate in presence of triethylamine and dry THF followed by the addition of **1** to give the intermediate **(9)**, which on cyclization in presence of propionic acid at 140°C yielded benzyl N-(benzyloxycarbonyl)-3-(2-benzoxazolyl)-D-alaninate **(10)**.



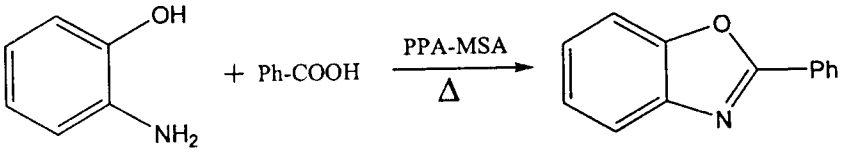
By Pyridinium *p*-toluenesulfonate: Pyridinium *p*-toluenesulfonate (PPTS) mediated synthesis of 2-substituted benzoxazoles was reported by Goldstein and Dambek[26]. Thus, condensation of methyl-2-amino-3-hydroxybenzoate **(11)** was reacted with the acid chlorides or the *ortho*-acetal in the presence of PPTS as an acid catalyst gave the corresponding methyl-2-substituted-4-benzoxazole-carboxylates (**12**, R = H, Me, *t*-Bu, Ph, 4-MeO-C_6H_4-, 4-NO_2-C_6H_4-, 2-furoyl and 3-pyridyl).



(11) (12)

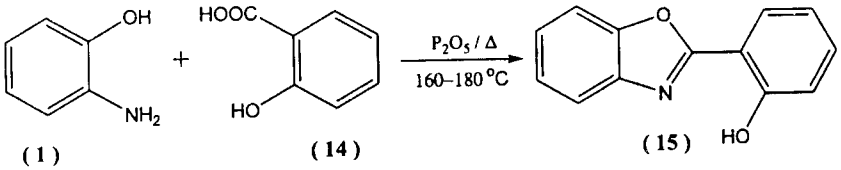
By PPA-Methanesulfonic Acid Mixture: Similary, reported is the preparation of 2-phenylbenzoxazole **(13)** by So and Heeschen[27] through the condensation of **1** with benzoic acid in the presence of polyphosphoric acid-methanesulfonic

acid (PPA-MSA), which is found to be an effective and convenient alternative to PPA[21]



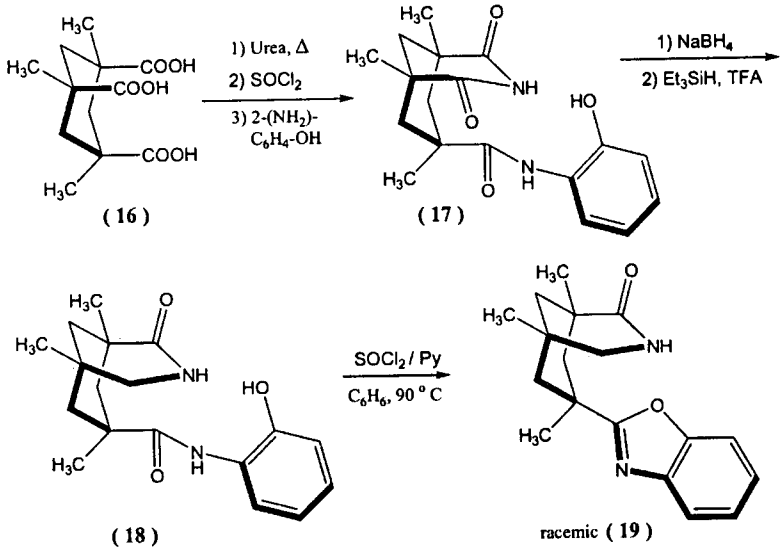
(1) (13)

By Phosphorous Pentoxide: Wronski[28] reported the synthesis of 2-(*o*-hydroxyphenyl)benzoxazole **(15)** by heating a mixture of **1**, salicylic acid **(14)** and phosphorous pentoxide at 160–180°C for 2 h.



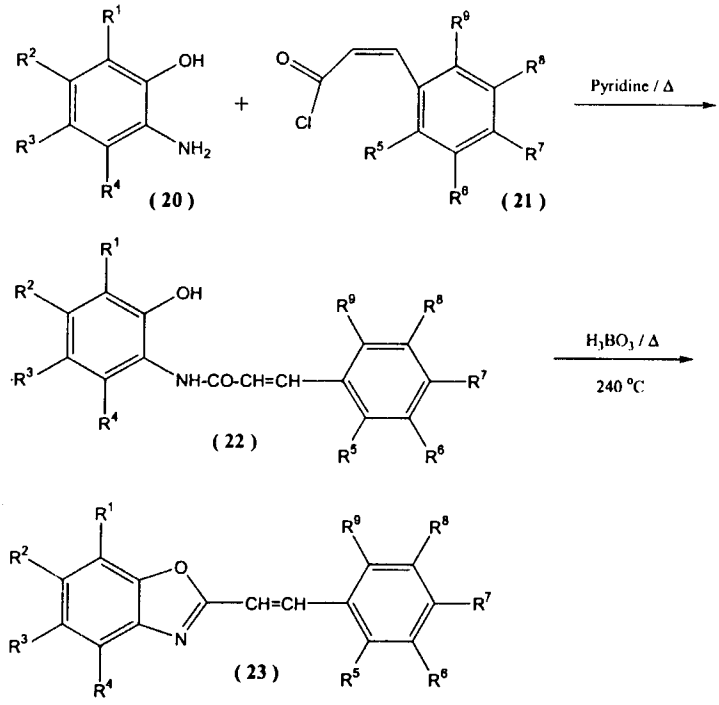
(1) (14) (15)

By Thionyl Chloride: Thionyl chloride mediated thermal cyclization in the formation of the racemic auxiliary **(19)** has been reported by Stack *et al.*[29] Thus, the Kemp's triacid **(16)** was heated with urea in triglyme at 200°C, followed by treatment with thionyl chloride and then with **1** gave **17**. Reduction of one of the imide carbonyl of **17** with sodium borohydride and triethylsilane in trifluoroacetic acid provided the lactam amide **18**. Heating **18** with thionyl chloride and pyridine in benzene at 90°C afforded the recemic auxiliary **19**.

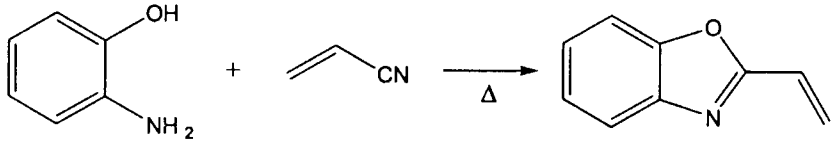


(16) (17) (18) racemic (19)

By Orthoboric Acid: Buell[30] has reported the preparation of a series of 2-styrylbenzoxazoles of the general formula **23** through the dehydration of the corresponding 2′-hydroxycinnamanilides **(22)** in a patented procedure. Thus, substituted *o*-aminophenol (**20**, $R^1 = R^2 = R^3 = R^4 = H$; $R^1 = R^3 = R^4 = H$; $R^2 = NO_2$; $R^1 = R^2 = R^4 = H$; $R^3 = NO_2$; $R^1 = Br$; $R^2 = R^4 = H$; $R^3 = NO_2$; $R^1 = R^4 = H$; $R^2 = NO_2$; $R^3 = Cl$) was reacted with substituted cinnamoyl chlorides (**21**, $R^5 = R^6 = R^7 = R^8 = R^9 = H$; $R^5 = OEt$; $R^6 = R^7 = R^8 = R^9 = H$; $R^5 = R^6 = R^8 = R^9 = H$; $R^7 = NO_2$; $R^5 = R^8 = R^9 = H$; $R^6 = Me$; $R^7 = NO_2$) in pyridine to get the 2′-hydroxycinnamanilides **(22)**. Dehydration of **22** was done by fusing with H_3BO_3 at 240°C to get the title 2-styrylbenzoxazoles **(23)**.

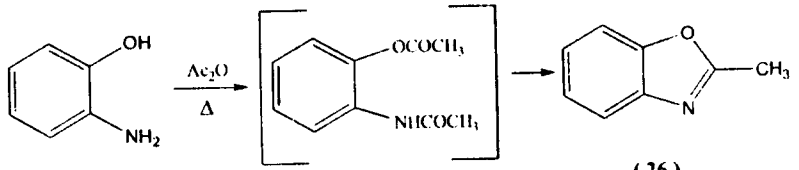


The synthesis of 2-vinylbenzoxazole **(24)** by the reaction of **1** with acrylonitrile was reported by Shono and Oda[31].



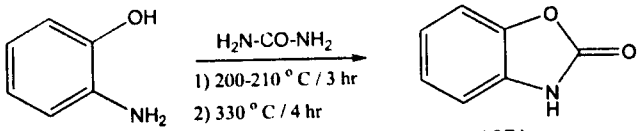
(1) **(24)**

By Direct Condensation: Preparation of 2-methylbenzoxazole **(26)** *via* the intermediacy of O,N-diacetyl derivative **25** by heating **1** with acetic anhydride was reported by Theilacker[32]. Formation of 2-methyl-5-methoxy-and 2-methyl-5-ethoxybenzoxazoles analogously has been reported by Takahashi *et. al.*[33]



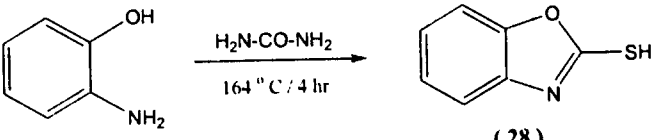
(1) (25) (26)

Takahashi and Yoneda reported[34] that when **1** was heated at 200–210°C for 3 h and an additional 1 h at 330°C with urea until no more ammonia evolved, this in turn on distillation *in vacuo* gave benzoxazoles-2-(3H)-one **(27)**.



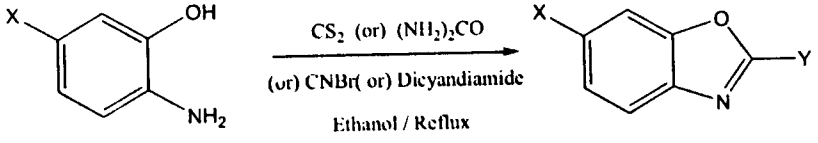
(1) (27)

Synthesis of benzoxazole-2-thiol **(28)** was reported by Linko[35], through the reaction of **1** and urea at 164°C for 4 h, followed by treatment with conc. sulfuric acid.



(1) (28)

Preparation of various 2,5-disubstituted benzoxazoles (**30**, X = Cl or COOH or CO_2Bu; Y = OH or SH or NH_2 or —NH—C=NH—NH_2) was reported by Nagano *et al.*[36], by the condensation of substituted **1** (*i.e.*, **29**, X = same as in **30**) or its hydrochloride salt with CS_2 or NH_2—CO—NH_2 or CNBr or dicyandiamide in ethanol.

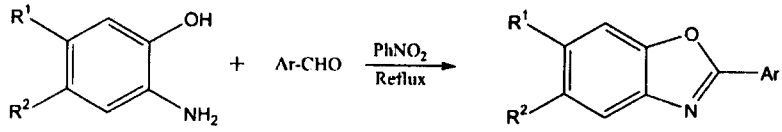


or
its HCl Salt

(29) (30)

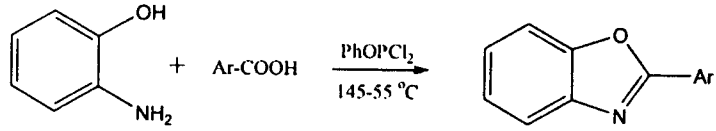
Somayajulu and Subba Rao[37] reported the formation of a variety of 2-aryl-benzoxazoles (**32**, $R^1 = R^2 = H$; Ar = Ph, 2-HO-C_6H_4-, 3-HO-C_6H_4-, 3,4-(OCH_2O)-C_6H_3-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2,4-Cl_2-C_6H_3-, 3,4-Cl_2-C_6H_3-, 4-Br-C_6H_4-, 2-NO_2-C_6H_4-, 3-NO_2-C_6H_4-, 4-NO_2-C_6H_4-, 2,3-HO-(NO_2)-C_6H_3-, 4-Me_2N-C_6H_4-, (-naphthyl; $R^1 = H$, $R^2 = Cl$, Ar = Ph, 3-HO-C_6H_4-, 4-Cl-C_6H_4-, 4-NO_2-C_6H_4-; $R^1 = H$, $R^2 = NO_2$, Ar = Ph, 4-MeO-C_6H_4-, 4-Cl-C_6H_4-, 4-NO_2-C_6H_4-, 2,4-Cl_2-C_6H_3-; $R^1 = NO_2$, $R_2 = H$, Ar = Ph, 4-MeO-C_6H_4-, 4-Cl-C_6H_4-,

4-NO_2-C_6H_4-) in good yields by the condensation of equimolar proportions of **31** and aromatic aldehydes by refluxing in excess of nitrobenzene for 1–5 h.



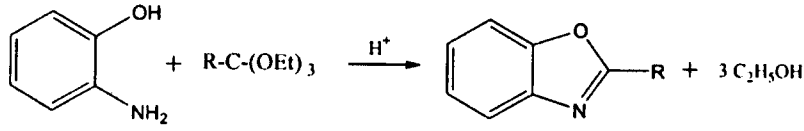
(31) (32)

A new convenient method for the synthesis of benzoxazoles by direct condensation reaction was reported by Chiriac[38]. Thus, 2-arylbenzoxazoles (**33**) were prepared by heating a mixture of **1** and the respective aromatic carboxylic acids (Ar = Ph, tolyl, anisyl, halophenyl, dichlorophenyl) in the presence of $PhOPCl_2$ at 145–155°C.



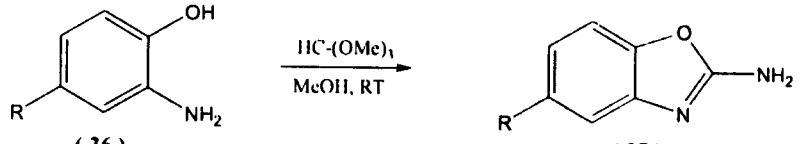
(1) (33)

A new synthesis of benzoxazole rings has been reported by Jenkins *et al.*[39a] by the condensation of **1** with the orthoformate (**34**, R = H, Me or Et) in the presence of sulfuric acid to give the benzoxazoles (**35**, R = same as in **34**). In the same manner, the syntheses of 6-nitro-, 5-methyl-, 5-chloro-6-methyl-, 5-chloro-7-methyl- and 5-methyl-7-chlorobenzoxazoles were reported[39b]



(1) (34) (35)

Kunz *et al.*[40] reported the synthesis of 5-substituted-benzoxazoles (**37**, R = same as in **36**) by the cyclocondensation of 4-substituted-2-aminophenols (**36**, R = NHCOMe, COPh, Br, Cl, iodo, cyano, methyl, methoxy, nitro, propionyl) with trimethyl orthoformate in methanol at room temperature.

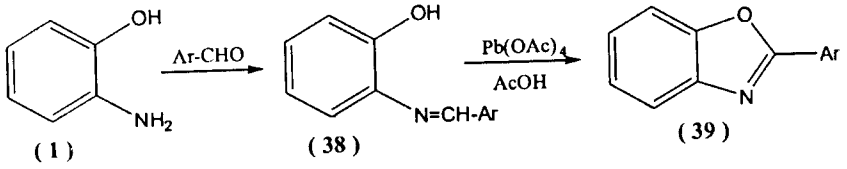


(36) (37)

Oxidative Cyclization from Schiff Bases

Stephens[41] reported the preparation of certain nitro-substituted benzoxazoles of the type **39** (Ar = 4-NO_2-C_6H_4-, 3-NO_2-C_6H_4-, 4-Cl-C_6H_4-). Thus, condensation of **1** with aromatic aldehyde (Ar = same as in **39**) gave the corresponding N-arylidene derivative (**38**, *i.e.*, commonly known as Schiff's base). The com-

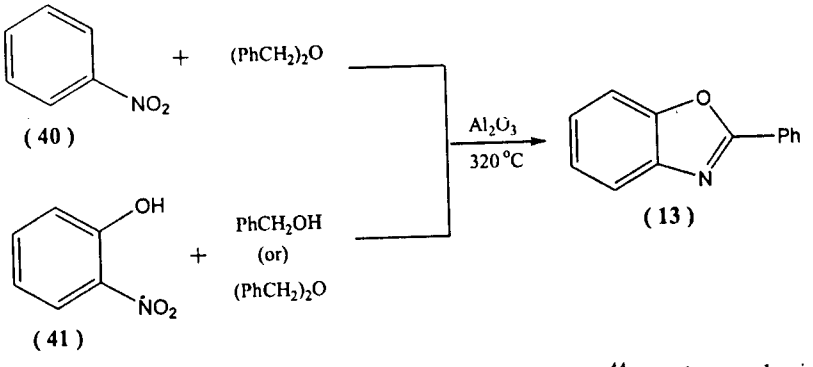
pound **38** on oxidative cyclization in the presence of $Pb(OAc)_4$ in hot glacial acetic acid gave the title compound **39**. Further, in a patented procedure, Dyson and Stephens reported[42] that PbO_2 or red lead in glacial acetic acid with or without the addition of acetic anhydride may be substituted for $Pb(OAc)_4$ for use in the oxidative cyclization of the Schiff bases to benzoxazoles.



(1) (38) (39)

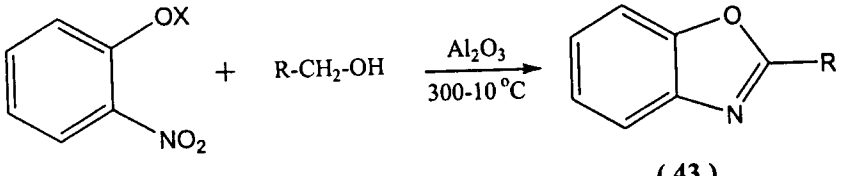
Catalytic Synthesis

Synthesis of 2-phenylbenzoxazole **(13)** was reported by Kozlov *et al.*[43], passing a mixture of nitrobenzene **(40)** and benzyl ether over activated Al_2O_3 at 320°C at a velocity of 0.2 g/min in 10% yield. The same compound was also reported to have obtained in 30–34% yield by treating *o*-nitrophenol **(41)** with benzyl alcohol or benzyl ether under similar conditions mentioned above.



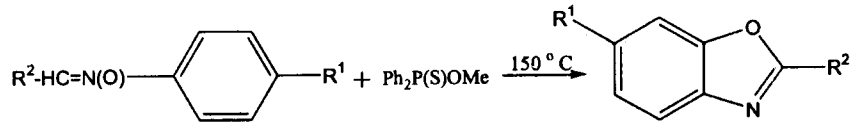
(40) (13) (41)

A new method was developed by Kozlov and Kiselev[44] for the synthesis of 2-substituted benzoxazoles **(43)** by the reaction of *o*-nitrophenol (**41**, X = H) or *o*-nitroanisole (**42**, X = Me) with aliphatic alcohols in the presence of a catalyst such as Al_2O_3, Cu-Al_2O_3 (30% Cu), Cu-Al_2O_3 (75% Cu) etc.



(41 or 42) **(43)**

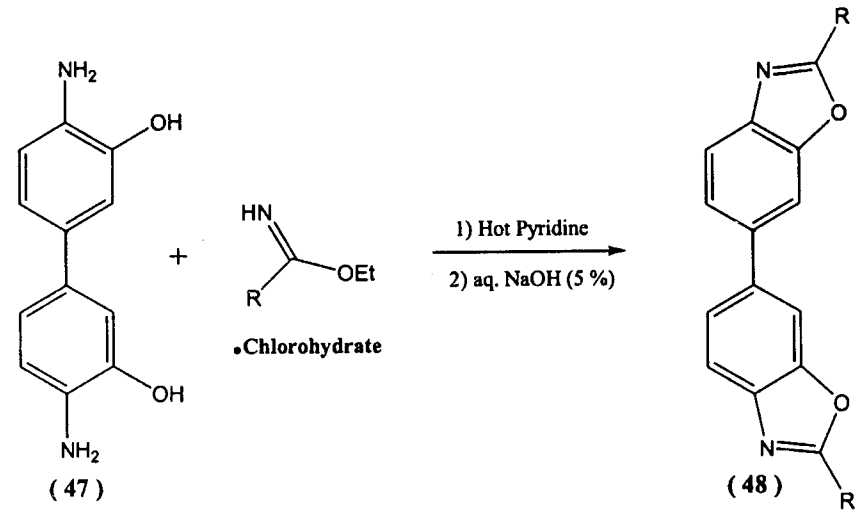
Reactions of (-N-diarylnitrones (**44**, R^1 = H or Me; R^2 = Ph, 4-Cl-C_6H_4-, 4-Me-C_6H_4-, 4-MeO-C_6H_4-) with *o*-methyl diphenylphosphinothioate **(45)** giving benzoxazoles (**46**, R_1 and R_2 = same as in **44**) in fairly good yields was reported by Yoshifuji *et. al.*[45]



(44) (45) (46)

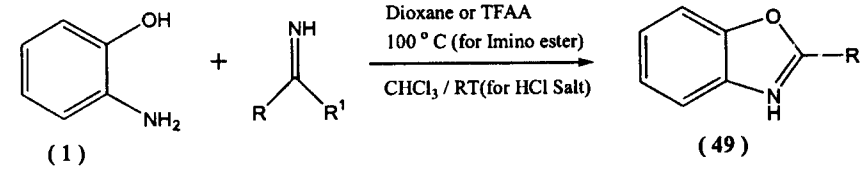
From Imino Esters

A method for the preparation of 2,2′-dialkyl, 2,2′-diaryl-6,6′-dibenzoxazoles (**48**, R = CF_3, C_3F_7, Pr, Ph, $PhCH_2$) was reported by Gitina *et al.*[46] In a typical experiment the chlorohydrate of ethyl ester of iminoacetic acids (R = same as in **48**) was added to a stirred solution of 3,3′-dihydroxybenzidine (**47**) in hot pyridine, followed by treatment with 5% aq. NaOH to gave the title compounds **48** in high yields.

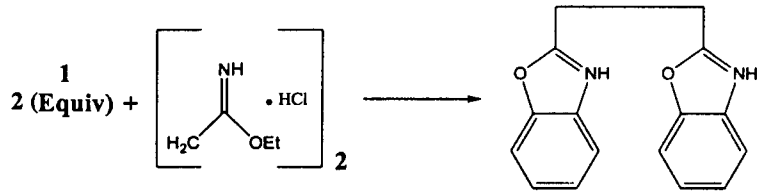


(47) (48)

Braz *et al.*[47] reported the synthesis of 2-substituted benzoxazoles (**49**, R = Me or CF_3) from the reaction of **1** with imino esters (R = Me or CF_3) or its hydrochloride salts. They have also reported the formation of α,ω-bis(benzoxazol-2-yl)alkanes (**50**) by the reaction of esters of aliphatic bis(imino-carboxylic acids) with two moles of **1**.



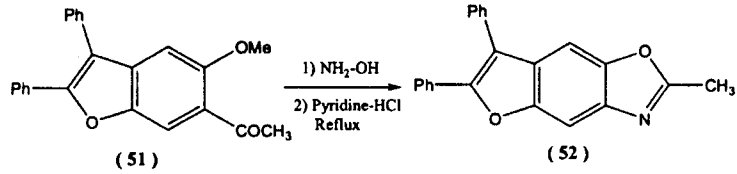
(1) or its HCl salt (49)



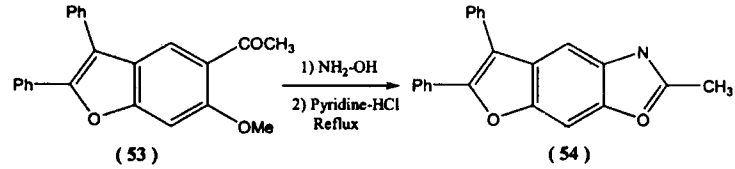
(50)

From Hydroxybenzofurans

Hishmat *et al.*[48] reported the formation of benzoxazoles from the reactions of substituted hydroxybenzofurans. Thus, 6-acetyl-5-methoxy-2,3-diphenylbenzofuran (**51**) was converted to the oxime, which on treatment with freshly prepared pyridine hydrochloride under reflux gave 2-methyl-6,7-diphenylfuro(2,3-f]-benzoxazole (**52**). Similarly, the isomeric 2-methyl-5,6-diphenylfuro(3,2-f]benzoxazole (**54**) was also prepared from the corresponding 5-acetyl-6-methoxy-2,3-diphenylbenzofuran (**53**) *via* its oxime.



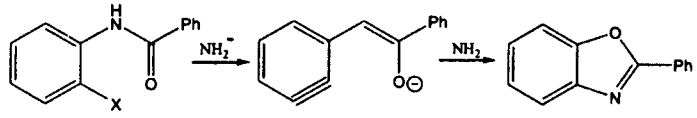
(51) (52)



(53) (54)

Aryne Mediated Synthesis

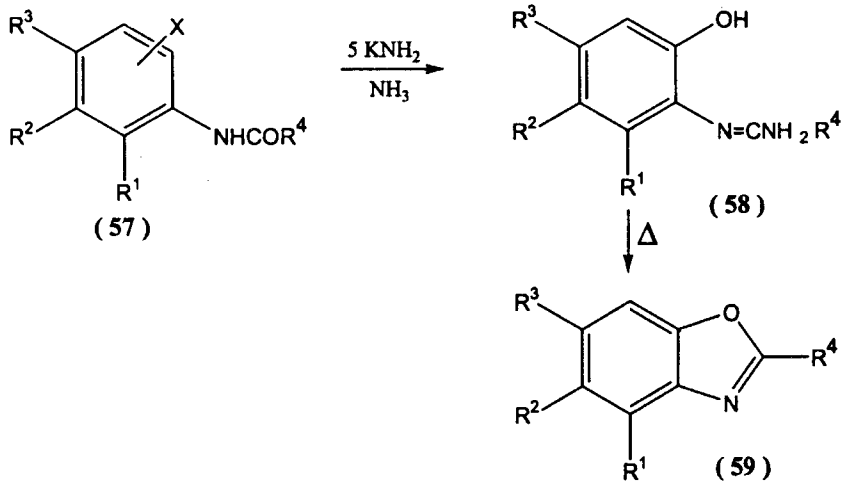
Synthesis of 2-phenylbenzoxazole (**13**) by a ring closure reaction *via* an aryne intermediate (**56**) has been reported by Bunnett and Hrutfiord [49]. Thus, benz-(2-bromo)-anilide (**55**, X = Br) and its chloro analogue (**55**, X = Cl) were converted into 2-phenylbenzoxazole (**13**) in 72 and 69% yields respectively by the action of potassium amide in liquid ammonia.



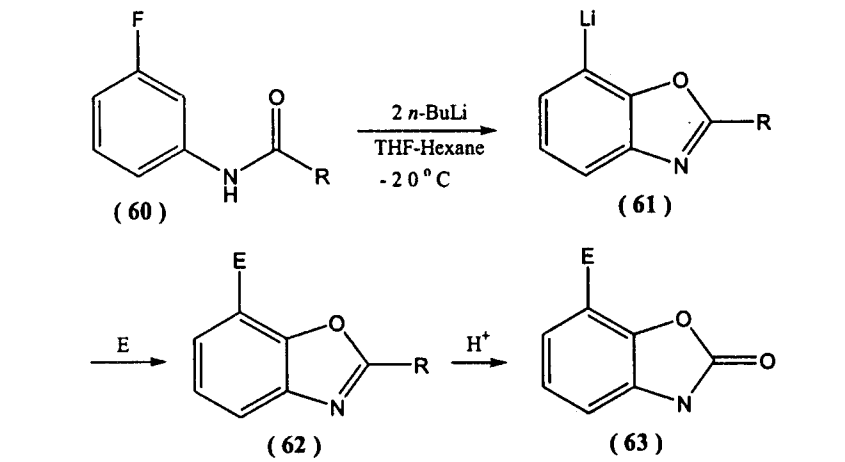
(55) (56) (13)

El-Sheikh *et al.*[50] reported the preparation of several benzoxazole derivatives (**59**, R^1-R^4 same as in **57**) through either sublimation or acidic hydrolysis of (*o*-hydroxyphenyl)benzamidines (**58**, R^1-R^4 same as in **57**) generated from *o*-and *m*-halobenzamides (**57**, R^1 = H or Me; R^2 = H; R^3 = H or Me or MeO; R^4 = H,

Me, Ph, 4-MeO-C_6H_4-, 4-Me-C_6H_4-, 3-Me-C_6H_4- or (-$C_{10}H_7$-; X = 2-Cl, 2-Br, 3-Cl or 3-Br) under aryne-forming conditions. Evidence was also provided for the initial formation of benzoxazoles in these reactions as reported by previous workers[49] under aryne-forming conditions which get readily aminated to the corresponding hydroxyphenyl amidines under the highly basic reaction conditions employed in the aryne-forming reactions.

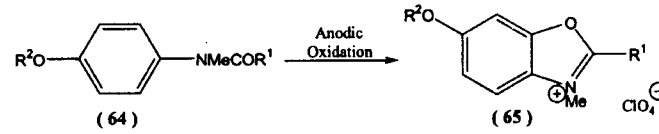


The preparation and electrophilic trapping of 7-lithiated benzoxazoles generated *via* benzyne cyclization has been reported by Clark and Caroon [51]. Treatment of N-substituted-*m*-fluoroanilines (**60**, R = *t*-Bu, O-*t*-Bu or Ph) with 2.5 equivalents of *n*-BuLi followed by aqueous work up gave the 7-lithiated benzoxazole (**61**, same as in **60**). Addition of electrophiles to **61** (R = *t*-Bu) gave the adduct **62** (R = *t*-Bu; E = Et, SCH_3, CHOH(4-C_6H_4-, 4-*t*-Bu-C_9H_9OH). Compound **62** upon hydrolysis and mild acidic work up afforded 7-substituted 2-benzoxazolinones **63** [E = Me, CH(OH)C_6H_5-, CONH-(4-Cl-C_6H_4-), SCH_3.].



Anodic Oxidation

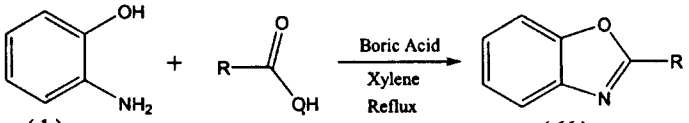
Anodic oxidation of N-methylcarbanilides **64** (R^1 = Me, Ph, 4-NO_2-C_6H_4-, 4-MeO-C_6H_4-; R^2 = Me or Et), with an alkoxy group *para* to the nitrogen atom giving the intra-molecular cyclization products, N-methylbenzoxazolium perchlorates (**65**, R^1 and R^2 same as in **64**) was reported by Ohmori *et al.*[52] The process of cyclization was investigated by cyclic voltametry, controlled potential electrolysis and open circuit relaxation experiments using an optically transparent glassy carbon electrode.



(64) (65)

Boric Acid Catalysed Synthesis

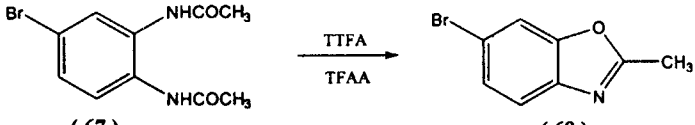
A facile, practical and economic method for the synthesis of a variety of 2-substituted benzoxazoles (**66**) has been reported by Masanao *et al.*[53] Thus, direct condensation of **1**, aryl carboxylic acid (R = Ph, 4-Cl-C_6H_4-, 4-MeO-C_6H_4-, 4-NO_2-C_6H_4-, 4-NMe_2-C_6H_4-, cinnamyl, ethylphenyl, 3-pyridyl, 3-furyl, 2-furyl) and boric acid in equimolar amounts, in refluxing xylene gave 2-substituted benzoxazoles (**66**, R = same as in aryl carboxylic acid above) in good to moderate yields.



(1) (66)

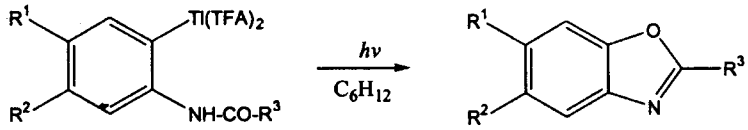
Thallium Mediated Synthesis

The formation of 4-acetamido-6-bromo-2-methylbenzoxazole (**68**) by thallium (III) trifluoroacetate (TTFA) promoted oxidative intra-molecular cyclization of 1,2-diacetamido-4-bromobenzene (**67**) in trifluoroacetic acid was reported by Lau and Basiulis[54].



(67) (68)

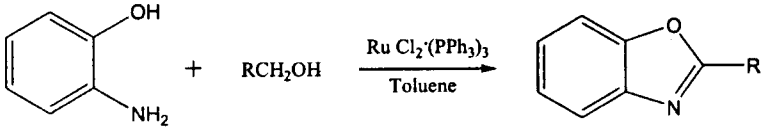
Preparation of benzoxazoles (**70**, R_1 = R_2 = H or Me; R_3 = Me, Ph or 4-Cl-C_6H_4) from anilides (**69**, R^1, R^2 and R^3 = same as in **70**) by regiospecific *ortho*- thallation, followed by photolysis of the resulting arylthallium intermediates or *o*-thallated anilides in cyclohexane suspension have been reported by Taylor *et al.*[55]



(69) (70)

Ruthenium-Complex Catalyzed Synthesis

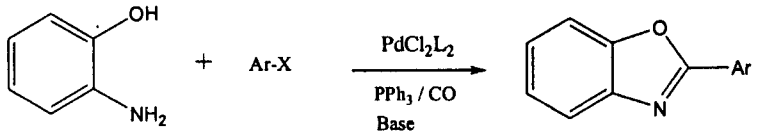
Kondo *et al.*[56] reported the first example of the ruthenium-catalyzed facile synthesis of benzoxazoles. The condensation reaction of **1** with various primary alcohols (R = Ph, 4-Me-C_6H_4-, *n*-propyl, benzyl, cinnamyl) in toluene in an autoclave, under an argon atmosphere by the use of a catalytic amount of the ruthenium-complex gave the title compounds (**71**, R = same as above in case of alcohols) in high yields.



(1) (71)

Palladium-Catalyzed Carbonylation and Condensation

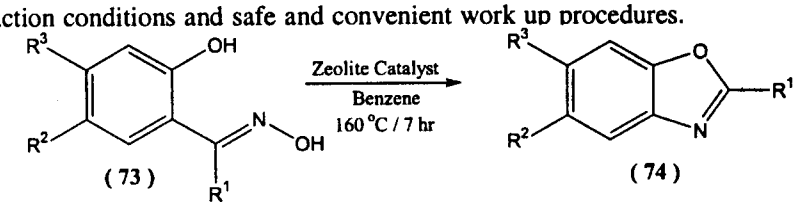
A new synthetic method was reported by Perry *et al.*[57], in which 2-aryl-benzoxazoles (**72**, Ar = Ph, 4-Cl-C_6H_4-, 4-Me-C_6H_4-, 4-MeO-C_6H_4-, 4-CN-C_6H_4, 4-Ac-C_6H_4-, 4-NO_2-C_6H_4-, biphenyl, 2-furyl, 2-pyridyl) can be prepared by the palladium-catalyzed condensation of aryl halides (Ar = same as in **72**) with **1** followed by dehydrative cyclization. A wide variety of functional groups can be tolerated by this method on either aromatic ring and gives good to excellent yields of title compounds. This synthetic procedure nicely complements those derived from benzoic acid intermediates where such compounds are unavailable or synthetically difficult to obtain.



(1) (72)

Zeolite Catalyzed Synthesis

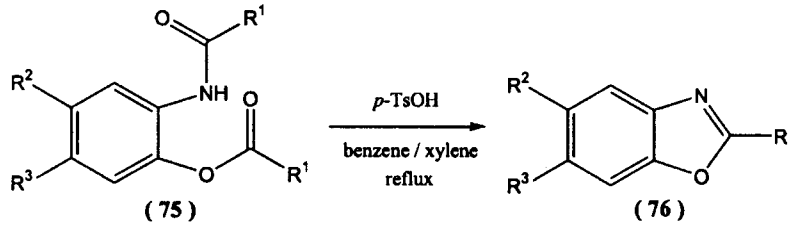
Bhawal *et al.*[58] established a facile heterogeneous catalytic method for the synthesis of a variety of benzoxazoles (**74**, R^1 = Me or Et; R^2 = H, Cl or Me; R^3 = H or OH) starting from *o*-acylphenol oximes (**73**, R^1-R^3 same as in **74**) *via* Beckmann rearrangement using commercially available H-Y zeolite catalyst. The obvious advantages of heterogeneous catalysis in terms of easy separation, consistent yields and recyclability of the catalyst are noteworthy, apart from mild reaction conditions and safe and convenient work up procedures.



(73) (74)

PTSA-Promoted Synthesis

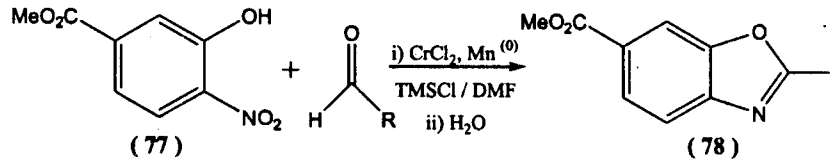
DeLuca and Kerwin[59] demonstrated the formation of benzoxazoles (**76**, R^1 = Me, Et, *t*-Bu, Ph, 4-Cl-C_6H_4-or 4-NO_2-C_6H_4-; R^2, R^3 = H or nitro) by treating N,O-diacylated 2-aminophenols (**75**, R^1-R^3 = same as in **76**) by the use of *para*-toluenesulfonic acid in refluxing benzene or xylene. These reactions are operationally simple and proceed with excellent yields. Further, these reactions can be used to prepare a wide variety of benzoxazoles and may have particular utility in cases where diacylation of starting *o*-aminophenol is contemplated, such as in solid phase synthesis.



(75) (76)

Chromium-Manganese Redox-Coupled Synthesis

A procedure was developed for the one-pot preparation of benzoxazoles (**78**, R = ethyl, *i*-propyl, 1-methylpropyl, butyl, heptyl, cyclohexyl, Ph, 4-MeO-C_6H_4-, 3,5-$(MeO)_2$-C_6H_3-, 2-OH-C_6H_4-) from *o*-hydroxy nitroarene (**77**) and benzaldehydes (R = same as in **78**) by Hari *et al.*[60] This process employs a domino reaction process made possible by a Cr/Mn redox couple. Highest yields are obtained for *o*-hydroxy nitroarenes substituted with an electron-withdrawing group at the *para* position. The dependence of the reaction on aldehyde structure and also on the *o*-hydroxy nitorarene has also been studied. Further, this reaction should be a useful alternative to other currently available methods for benzoxazole formation, particularly in cases where chemoselectivity and sensitivity to the harsh conditions typically employed are issues[27, 53, 56, 57]



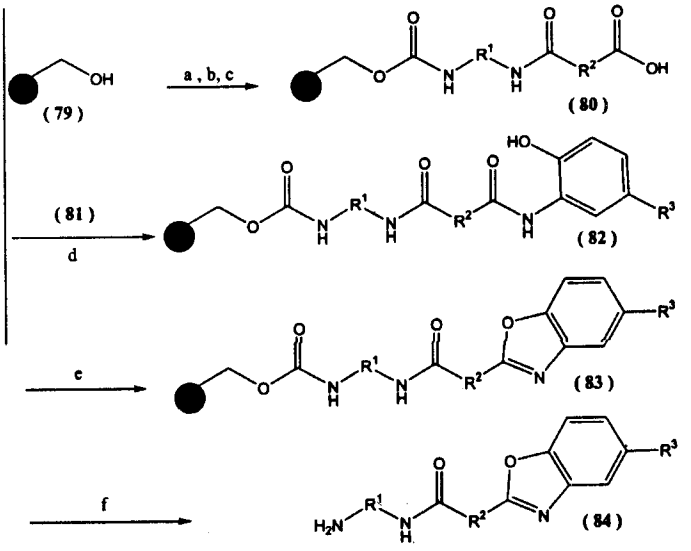
(77) (78)

Solid Phase Synthesis

A convenient procedure for the generation of a series of various substituted benzoxazoles is the synthesis of these compounds on a solid phase. The technique is especially useful for many synthetic transformations, since excess reagents can be used to drive the reactions to completion and the excess reagents and soluble byproducts are easily removed[61]. The following are the methods in solid phase technique for the synthesis of title benzoxazoles

By Mitsunobu Reaction: Wang and Hauske[62] reported, for the first time, a very convenient methodology for the solid phase synthesis of benzoxazoles *via*

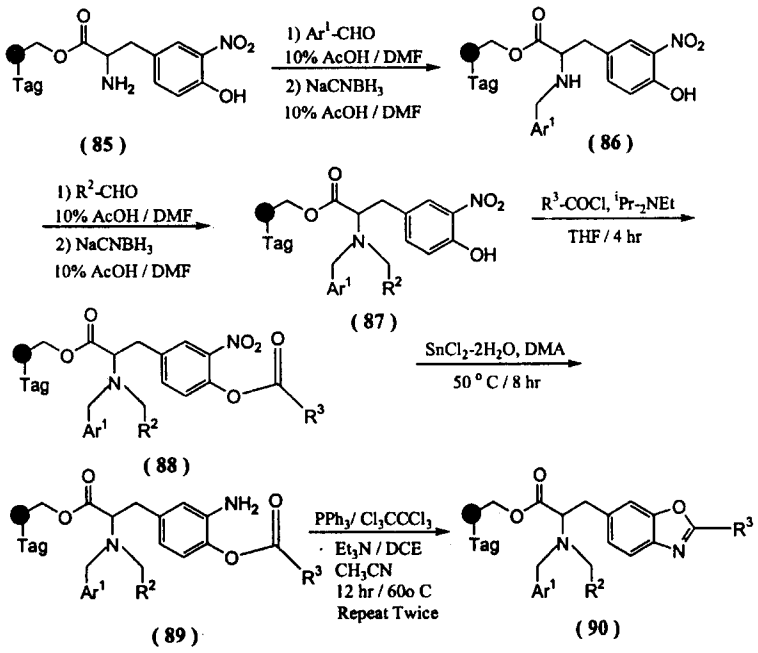
Mitsunobu reaction conditions and the procedure has been applied to the synthesis of a combinatorial library with satisfactory results. Thus, Wang resin **79** was converted to carboxy functionalized resin **80**. The latter was reacted with *o*-aminophenols (**81**, R^3 = H, Me, *t*-butyl, etc.) to get the 2-amidophenol attached to a solid support **82**. The compound **82** was cyclodehydrated under Mitsunobu's condition to give the corresponding benzoxazole attached to the solid support **83** in high yields and high purity. The solid support was delinked to get the free benzoxazoles **84**.



Conditions: a) CDI, THF, RT, b) Diamine, THF, RT, c) Dicarboxylic anhydride, DMAP, Pyridine / CH_2Cl_2 (1:1), RT, d) PyBOP, NMM, DMF, RT, e)Ph_3P, DEAD, THF, RT, f) TFA / CH_2Cl_2, RT

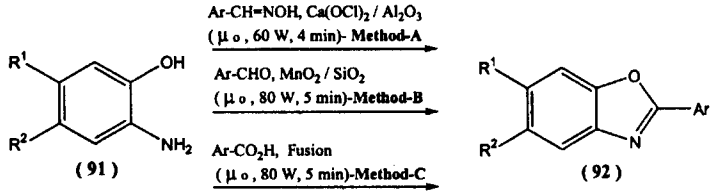
From 3-Nitrotyrosine: An efficient procedure for the solid-phase synthesis of benzoxazoles (**90**), where Ar^1 = 4-Cl-2-thienyl, 3,4-F_2-C_6H_3-, 2-benzofuryl, 3,4-(OCH_2O)-C_6H_3-, 2,3-Me_2-4-MeO-C_6H_2-, 2,3,4-$(MeO)_3$-C_6H_2-, 5-Me-2-furyl, 4-Cl-C_6H_4-, 2,4,6-$(Me)_3$-C_6H_2-, 4-CF_3-C_6H_4-, 1-Ph-3,5-Me_2-pyrazolyl, 2-furyl, 2-thienyl, 4-MeS-C_6H_4-, biphenyl, 3-(4-MeO-phenoxy)-C_6H_4-; R^2 = H, methyl, ethyl, 2-MeS-ethyl, propyl, 2-Me-propyl, 2,2-Me_2-propyl, cyclopropyl, 2-Et-3,3-Me_2-1-cyclohexenyl, cyclohexyl, benzyl; R^3 = cyclopropyl, *t*-butyl, 2-furyl, 3,5-$(MeO)_2$-C_6H_3-, 3-MeO-3-oxopropyl) on a solid support using 3-nitrotyrosine as a scaffold has been developed by Beebe *et al.*[63] The synthesis couples N-protected 3-nitrotyrosine to polystyrene *via* a Wang-type linker and the polymer supported 3-nitrotyrosine is deprotected and the resultant primary amine (**85**) converted to a tertiary amine (**87**) *via* sequential reductive alkylation using aromatic aldehydes to give **86** (Ar^1 = same as in **90**) followed by unhindered aliphatic aldehydes giving **87** (Ar^1 and R^2 = same as in **90**). The phenol (**87**) was then acylated to give **88** (Ar^1, R^2 and R^3 same as in **90**) and the nitro group of **88** is reduced using $SnCl_2$ to give the amino ester (**89**, Ar^1, R^2 and R^3 same as in **90**). The resulting

amino ester was then finally dehydratively cyclized to yield the benzoxazoles **(90).**



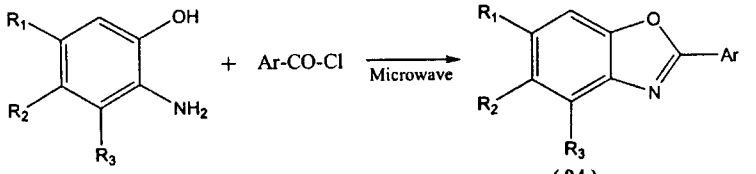
Microwave Assisted Synthesis

Three new methods to synthesise benzoxazole (**92**, where R^1 = H, Cl or NO_2; R^2 = H or NO_2; Ar = Ph, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 4-Me-C_6H_4-, 4-MeO-C_6H_4-, 2-NO_2-C_6H_4-, 3-NO_2-C_6H_4-, 4-NO_2-C_6H_4-, 3-OH-4-MeO-C_6H_3-, 3,4-$(MeO)_2$-C_6H_3-) by the reaction of *o*-aminophenol (**91**, R^1 and R^2 same as in 92) with aromatic oxime **(Method-A)** or aldehyde **(Method-B)** or carboxylic acid **(Method-C)** (Ar = same as in **92** for all the methods) on mineral supports using $Ca(OCl)_2$/ Al_2O_3 or MnO_2 / SiO_2 or by fusion "in dry media" were reported by Bougrin *et al.*[64] The reactions are activated under microwave irradiation. Further, reaction times are considerably shortened and the products are obtained in higher yields and better purity than compared to conventional heating.



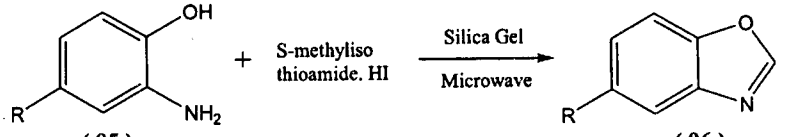
From Acyl Chlorides: A feasible and attractive protocol for the generation of benzoxazole libraries has been developed by R.S. Pottorf *et al.*[65] through the solution phase synthesis technique by the use of microwave assisted dielectric heating. The ease of synthesis and work up allowed the parallel synthesis of a

48-membered library of benzoxazoles quickly and efficiently. Thus *o*-aminophenols (**93**, $R^1 = R^2 = R^3 = H$; R^1 = 2-ethylpropyl; $R^2 = R^3 = H$; $R^1 = H$; $R^2 = SO_2Et$; $R^3 = H$; $R^1 = R^2 = H$; $R^3 = Me$; $R^1 = NO_2$; $R^2 = R^3 = H$; R^1 and $R^2 = C_4H_4$; $R^3 = H$ were reacted with acyl chlorides (Ar = Ph, 2-Br-C_6H_4-, 4-Ph-C_6H_4-, 4-NO_2-C_6H_4-, 3,4,5-$(MeO)_3$-C_6H_2-, 2-thienyl, 2-benzothienyl) in 1,4-dioxane or xylene in a sealed reaction vessel, under microwave heating at 210°C or 250°C for 15 min to give the corresponding 2-arylbenzoxazoles (**94**, R^1-R^3 same as in **93** and Ar = same as in case of acyl chlorides mentioned above) in high yields.



(93) (94)

From S-methylisothioamides: The synthesis of benzoxazoles (**96**) by the cyclocondensation reaction of *o*-aminophenols with S-methylisothioamide hydroiodides has been reported by Rostamizadeh and Derafshian[66]. Thus, the reaction of *o*-aminophenol (**95**, R = H, Me or Cl) with S-methylisothioamide on silica gel under microwave irradiation gave the benzoxazoles (**96**, R is same as in **95**).



(95) (96)

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