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SYNTHETIC UTILITIES OF *O*-PHENYLENEDIAMINES: SYNTHETIC APPROACHES FOR BENZIMIDAZOLES, QUINOXALINES AND BENZO[1,5]DIAZEPINES

Magdy Ahmed Ibrahim*

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, 11711, Cairo, Egypt
*E-mail: magdy_ahmed1977@yahoo.com

Abstract – This review represents the methods developed for the synthesis of benzimidazoles, quinoxalines and benzo[1,5]diazepines from the condensation of *o*-phenylenediamines with a variety of electrophilic reagents.

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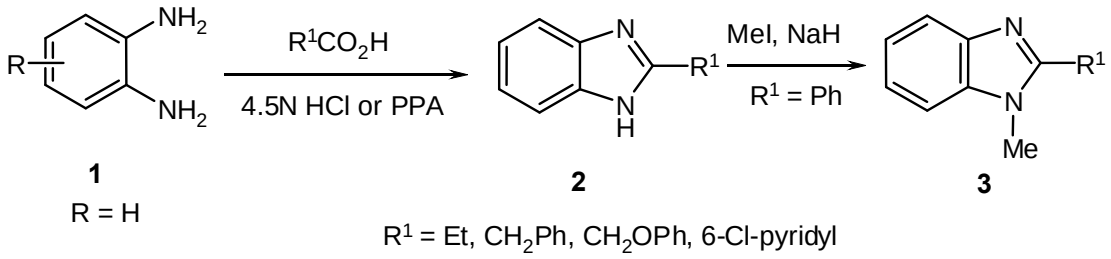
1. INTRODUCTION

Heterocycles make up an exceedingly important class of compounds due to their expansive range of applications. They are predominant among all types of pharmaceuticals, agrochemicals and veterinary products.[1–7] This comes as no surprise, since the most potent natural compounds and alkaloids are heterocyles. Nitrogen heterocycles in particular exhibit diverse biological and pharmacological activities[8–10] due in part to the similarities with many natural and synthetic molecules with known biological significance.[11] *o*-Phenylenediamines are good starting materials for the synthesis of a variety of heterocyclic rings especially benzimidazoles, quinoxalines and 1,5-benzodiazepines. The present review concerted on the utilities of *o*-phenylenediamines in the synthesis of benzimidazoles, quinoxalines and 1,5-benzodiazepines *via* chemical reactions with bifunctional electrophiles.

2. SYNTHETIC APPROACHES FOR BENZIMIDAZOLE DERIVATIVES

Benzimidazole nucleus is a constituent of several natural and non-natural products such as Vitamin B12,[12] marine alkaloid kealiiquinone,[13] benzimidazole nucleosides.[14] Some of their derivatives are marketed as anti-fungal agents such as Carbendazim[15] and anti-helmintic agents such as Mebendazole and Thiabendazole.[16] Benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry, encompassing a plethora of useful biological activities such as antimicrobial,[17–19] anticancer[20–22] and anti HIV.[23–25] Benzimidazoles are fundamental structural units not only in the pharmaceutical industry but also in several other fields such as agricultural, electronic, and polymer chemistry.[26–29]

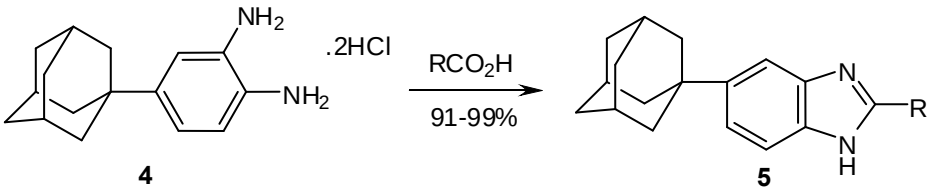
Condensation reactions of *o*-phenylenediamines with mono electrophilic reagents represent one of the most important routes for the synthesis of benzimidazole derivatives. Carboxylic acids are the most important, thus, 1*H*-benzimidazole derivatives **2** were synthesized *via* condensation reactions of *o*-phenylenediamine **1** with carboxylic acid derivatives in the presence of 4.5N HCl or polyphosphoric acid (PPA). Methylation of compound **2** (R=Ph) gave the corresponding *N*-methylbenzimidazole **3**.[30-36]



1 R = H **2** **3**

R^1 = Et, CH_2Ph, CH_2OPh, 6-Cl-pyridyl

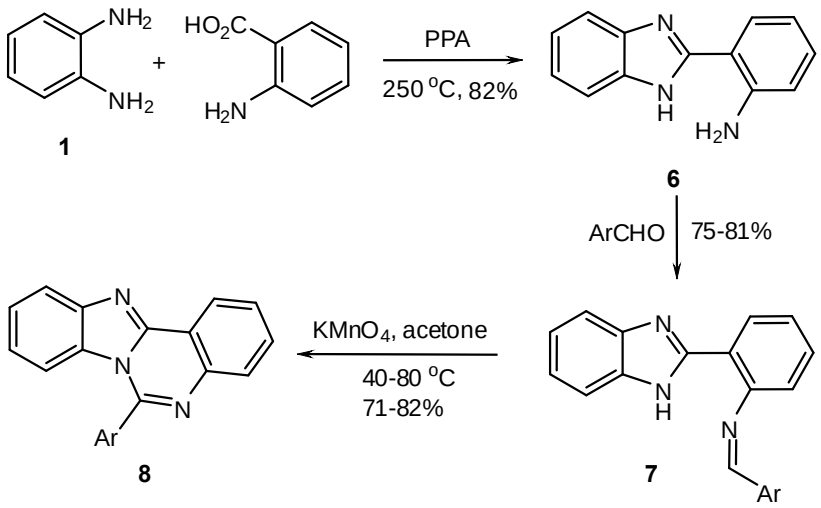
Also, fusion of 4-(1-adamantyl)-1,2-diaminobenzene dihydrochloride **4** with a variety carboxylic acids yielded the corresponding 5-(1-adamantyl)benzimidazoles **5**.[37]



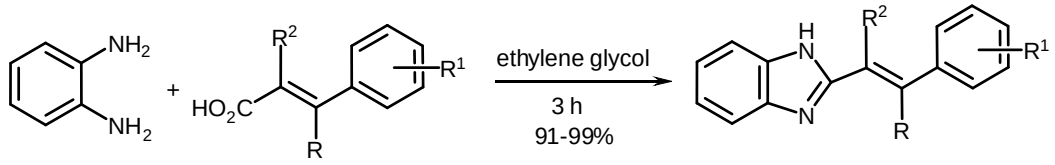
4 **5**

R = 1-adamantyl, *o*-ClC_6H_4, *p*-ClC_6H_4, CH_2OPh

Condensation of **1** with anthranilic acid in PPA at 250 °C gave 2-(*o*-aminophenyl)benzimidazole **6**.[38,39] Ten new 2-*o*-arylideneaminophenylbenzimidazoles **7** were prepared *via* the condensation of **6** with various aryl aldehydes. 6-Arylbenzimidazo[1,2-*c*]quinazolines **8** as antimicrobial agents were obtained through oxidative cyclization of compounds **7**.[39]



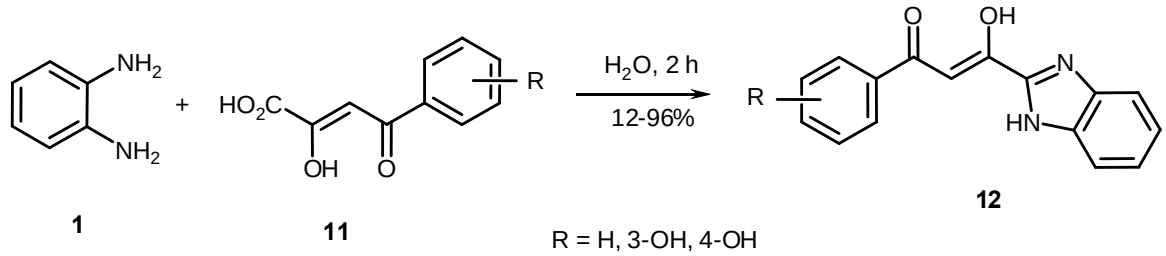
Condensation of *o*-phenylenediamine **1** with cinnamic acid derivatives **9** in boiling ethylene glycol gave 2-styrylbenzimidazole **10** in 91-99% yields.[40]



1 **9** **10**

R = H, Me, Ph
R^1 = H, 4-Me, 2-Cl, 4-Cl, 3-NO_2, 4-NO_2
R^2 = H, Me, Ph

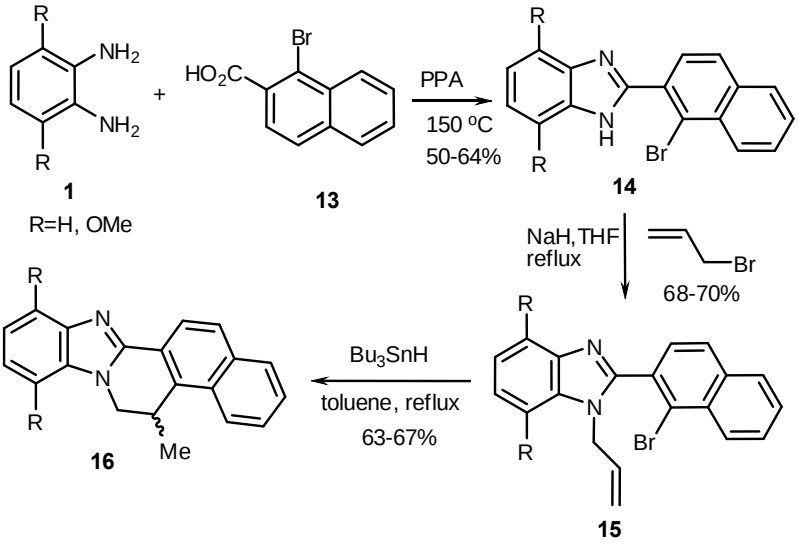
Likewise, condensation of **1** with α-hydroxycinnamic acids **11** in boiling water afforded 1-(1*H*-benzimidazol-2-yl)-2-(hydroxyphenyl)ethane derivatives **12**.[40]



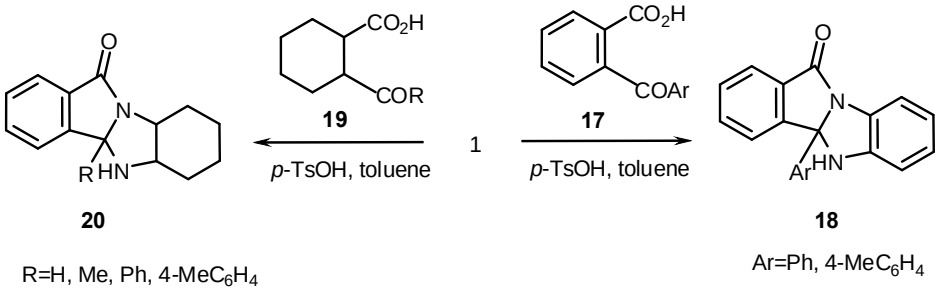
1 **11** **12**

R = H, 3-OH, 4-OH

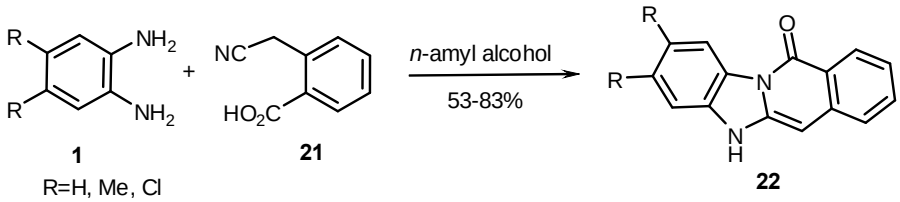
Heating *o*-phenylenediamines **1** with 1-bromo-2-naphthoic acid **13** in PPA gave 2-(1-bromo-2-naphthyl)-1*H*-benzimidazoles **14** which underwent *N*-allylation using allyl bromide in sodium hydride/THF to give 1-allyl-2-(1-bromo-2-naphthyl)benzimidazoles **15**. Bu_3SnH mediated cyclization of **15** in refluxing toluene afforded compounds **16**.[41]



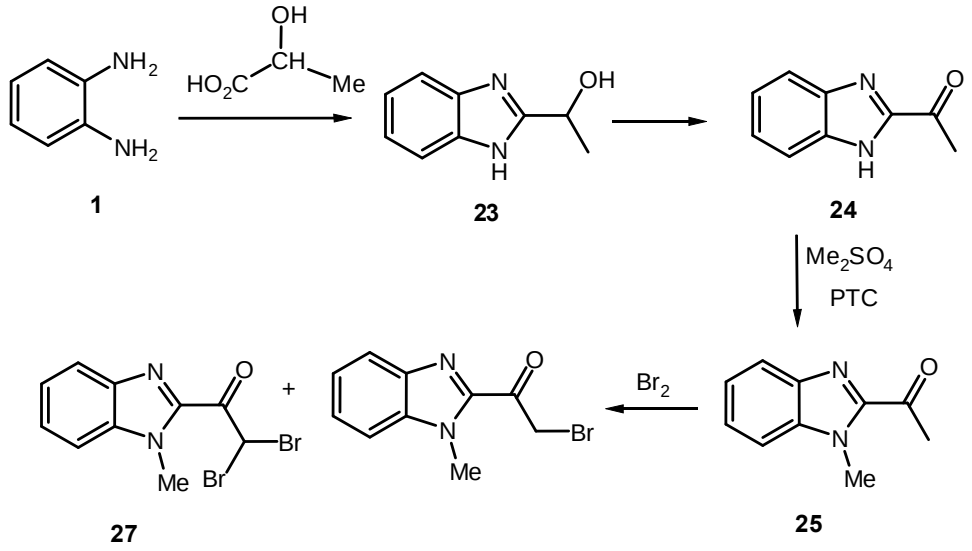
Condensation of *o*-phenylenediamine **1** with *o*-acylbenzoic acids **17** in refluxing toluene using catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) led to the formation of isoindolobenzimidazoles **18** in reasonable yields. Similar, condensation of **1** with aroylcyclohexane-2-carboxylic acids **19** gave hexahydroisoindolobenzimidazoles **20**.[42,43]



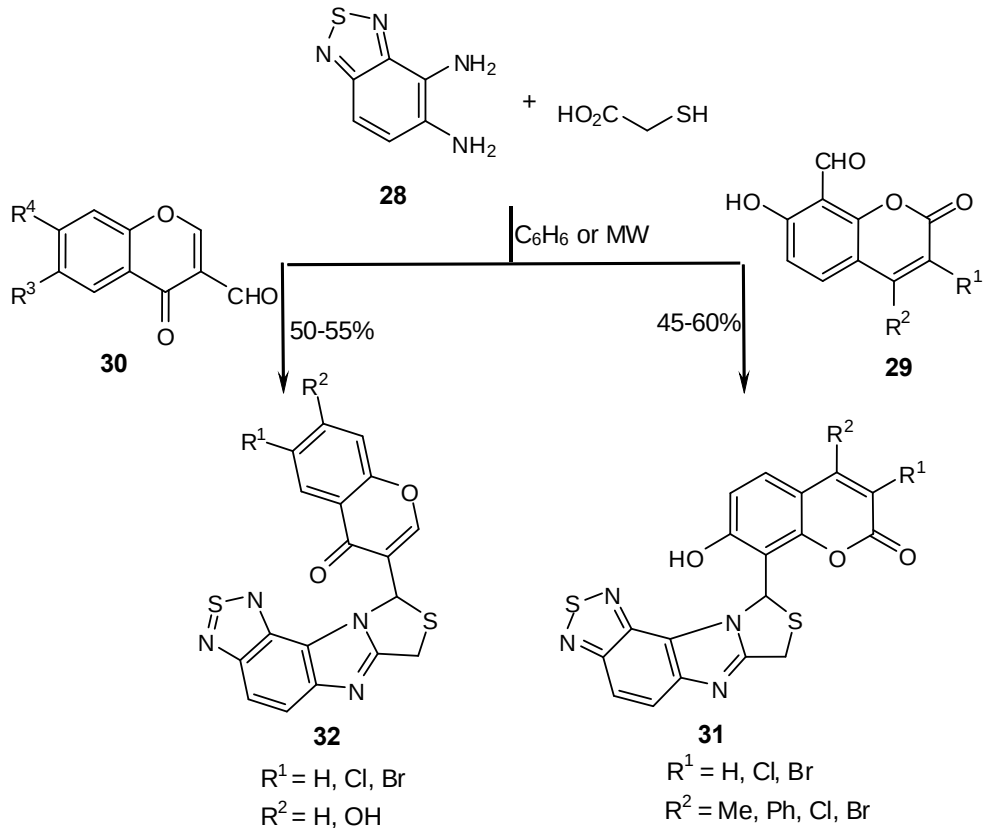
Substituted 5*H*-benzimidazo[l,2-*b*]isoquinolin-11-ones **22** were synthesized in good yields (53-83%) by refluxing the appropriate *o*-phenylenediamines **1** with α-(*o*-carboxyphenyl)acetonitriles **21** in *n*-amyl alcohol.[44]



Reaction of **1** with lactic acid gave 2-(α-hydroxyethyl)benzimidazole **23**. Compound **23** on oxidation with acid dichromate yielded 2-acetylbenzimidazole **24** which underwent *N*-methylation with dimethylsulfate in acetonitrile/potassium carbonate/triethylbenzyl ammonium chloride (as a phase-transfer catalyst), yielding the corresponding *N*-methylated compound **25**. Bromination of **25** in acetic acid gave monobromoacetyl derivative **26** and its dibromo derivative **27**.[45]

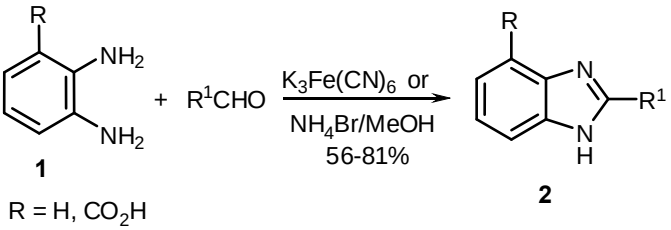


2,1,3-Benzothiadiazole-4,5-diamine **28** was condensed with various substituted coumarin-8-carboxaldehyde **29** and chromone-3-carboxaldehyde **30** in the presence of mercaptoacetic acid, in benzene under reflux, to give the corresponding coumarinylbenzothiadiazoles **31** and chromenylbenzothiadiazoles **32**, respectively.[46]



On the other hand, aliphatic and aromatic aldehydes were good precursors for the formation of benzimidazole heterocycles. Thus, condensation of *o*-phenylenediamines **1** with aromatic aldehydes, in

the presence of potassium ferrocyanide (acted as an oxidant in different solvents) or strongly acidic conditions gave 2-aryl-1*H*-benzimidazoles **2** in good yields.[47,48]

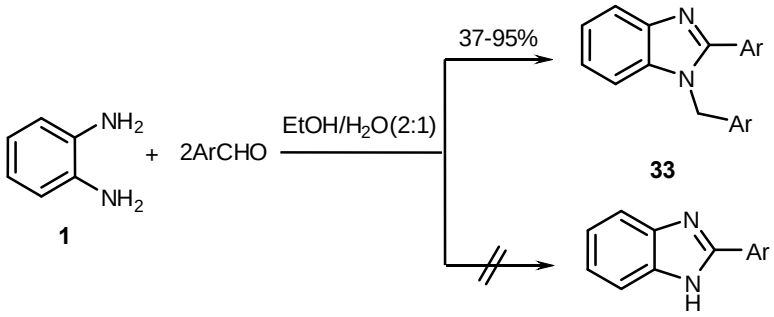


1 **2**

R = H, CO_2H

R^1= 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-HO-C_6H_4

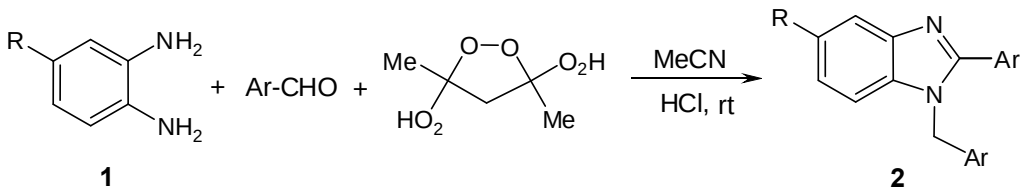
Also, it was reported that condensation of *o*-phenylenediamine **1** with some aromatic aldehydes in aqueous ethanol gave 2-aryl-1-arylmethyl-1*H*-benzimidazoles **33** in 37-95% yields not the other expected products **2**.[49,50]



1 **33** **2**

Ar= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)C_6H_3$, 3-ClC_6H_4, 4-ClC_6H_4, 4-HOC_6H_4

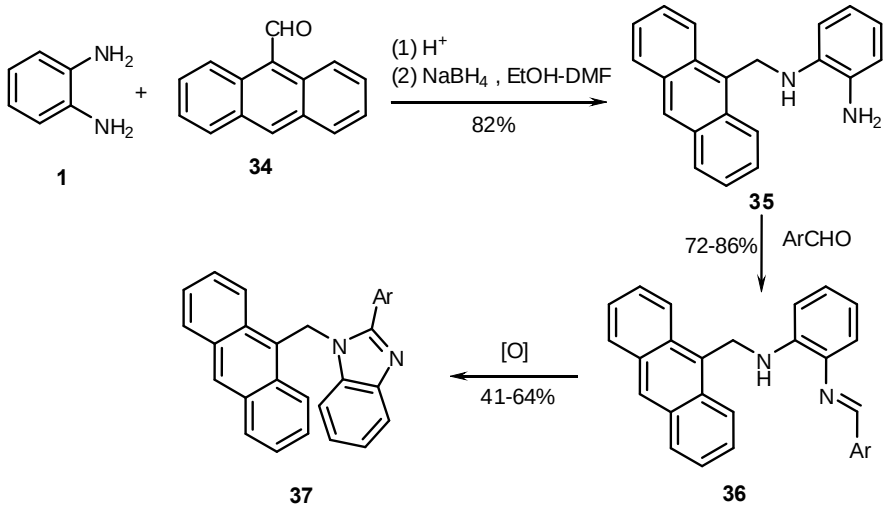
The catalytic effect of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane in the presence of HCl has been explored in one-pot condensation reaction of **1** with a variety of aldehydes into their corresponding 2-aryl-1-arylmethylimidazoles **2**. The reactions were conducted under mild conditions in MeCN at room temperature to afford the products in excellent yield.[51]



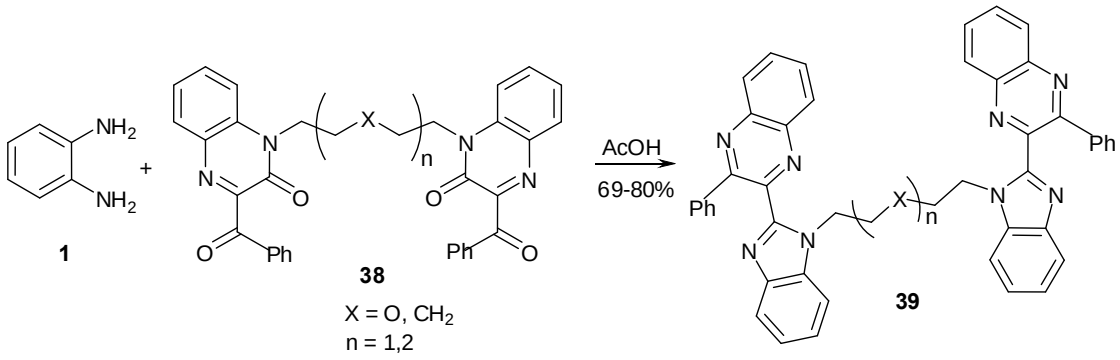
1 **2**

R=H, Me

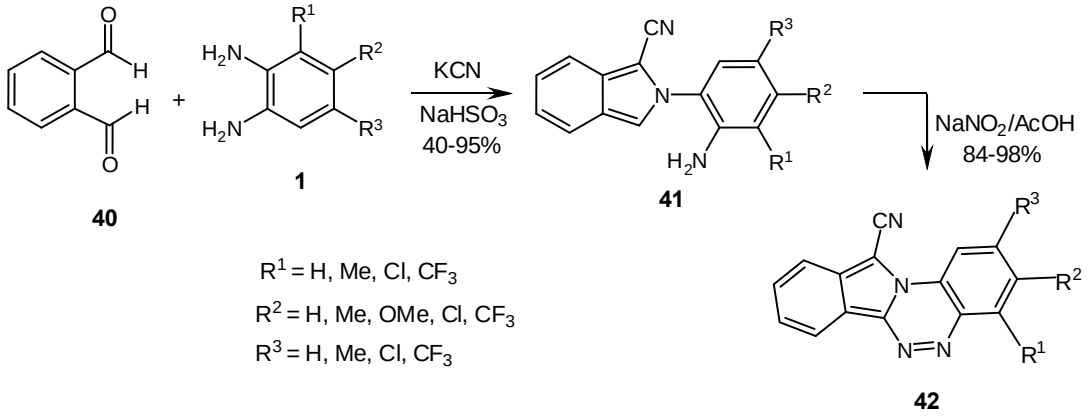
Compound **1** reacted with an equimolar amount of anthracene-9-carbaldehyde **34** to give *N*-(9-anthrylmethyl)benzene-1,2-diamine **35**. Reactions of **35** with a series of substituted salicylaldehydes afforded *N*-(9-anthrylmethyl)-*N*′-arylmethylidenebenzene-1,2-diamines **36** which underwent oxidation with atmospheric oxygen to the corresponding benzimidazole derivatives **37**.[52]



Reaction of **1** with *bis*-(3-benzoylquinoxaline) derivatives **38** in acetic acid under reflux gave *bis*-(benzimdizaolyl) derivatives **39**.[53]

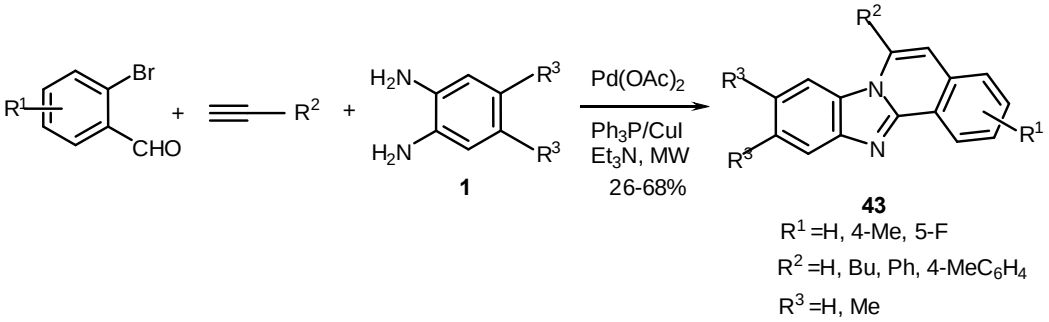


Condensation of **1** and phthaloyldicarboxaldehyde **40** in the presence of potassium cyanide and sodium hydrogen sulfite gave 2-(2-aminoaryl)-1-cyanoisoindoles **41**. Diazotization of the latter compound gave isoindolo[2,1-*c*]benzo[1,2,4]triazines **42**.[54]

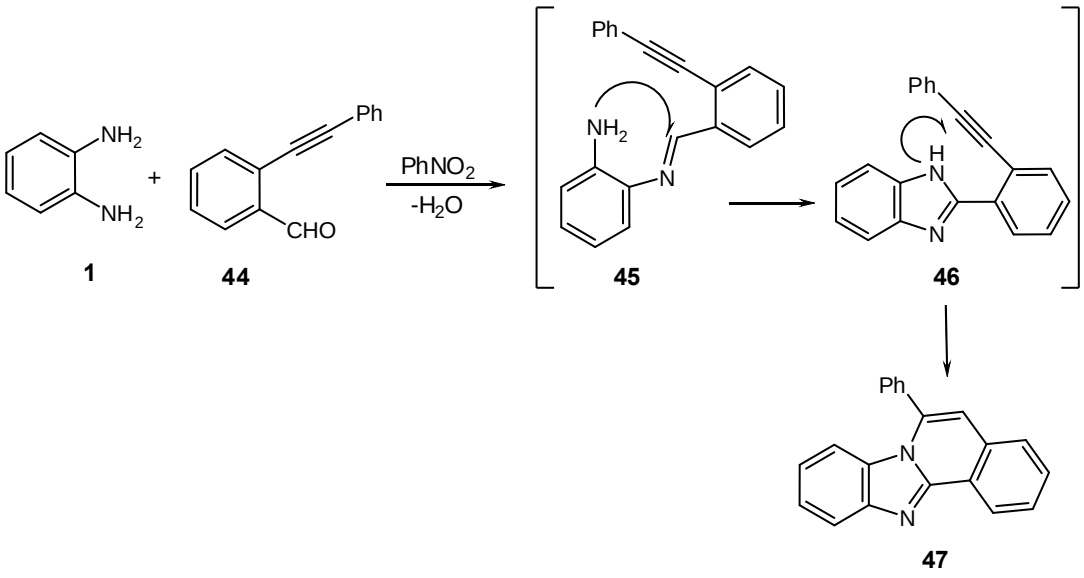


Direct and efficient syntheses of the benzimidazo[2,1-*a*]isoquinolines **43** have been achieved with 2-bromoarylaldehydes, terminal alkynes and *o*-phenylenediamines **1** in the presence of palladium acetate as

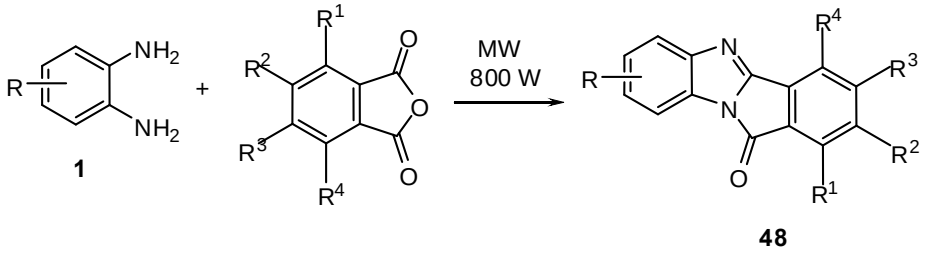
a catalyst under microwave irradiation process.[55]



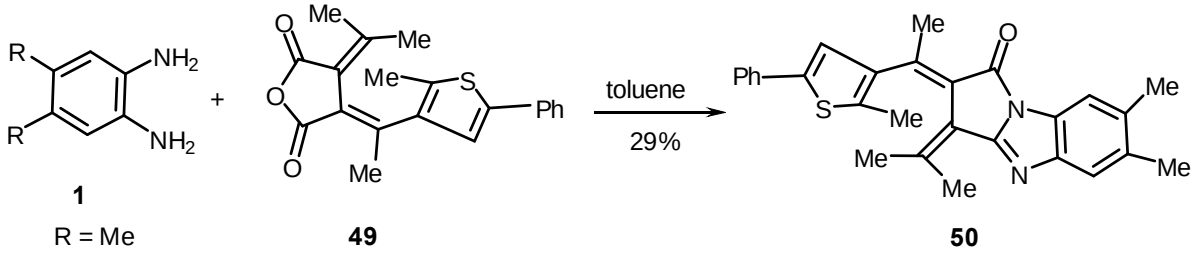
Condensation of **1** with 2-(2-phenylethynyl)benzaldehyde **44** in refluxing nitrobenzene resulted in an oxidative cyclization to give 6-phenylbenzimidazo[2,1-*a*]isoquinoline **47** *via* intermediates **45** and **46**.[56]



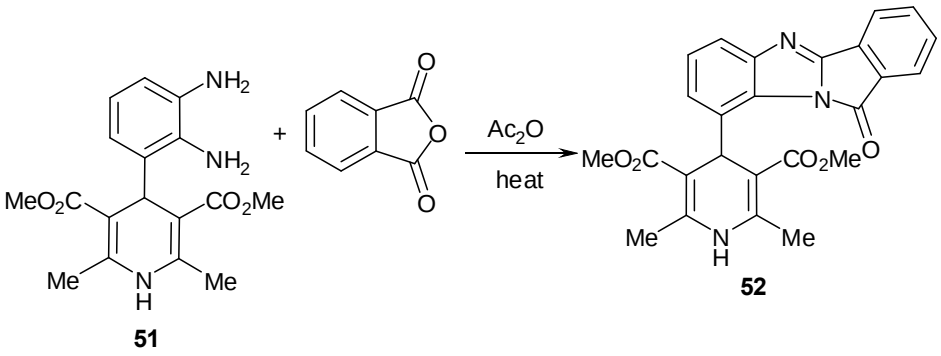
Cyclic anhydrides on treatment with *o*-phenylenediamines under different reaction conditions also afforded benzimidazole derivatives. Thus, 11*H*-isoindolo[2,1-*a*]benzimidazol-11-one derivatives **48** were mostly prepared from the condensation reaction of **1** and aromatic anhydrides on the surface of silica gel impregnated with $ZnCl_2$ under solvent free microwave irradiation conditions or at 140-150 °C.[57,58]



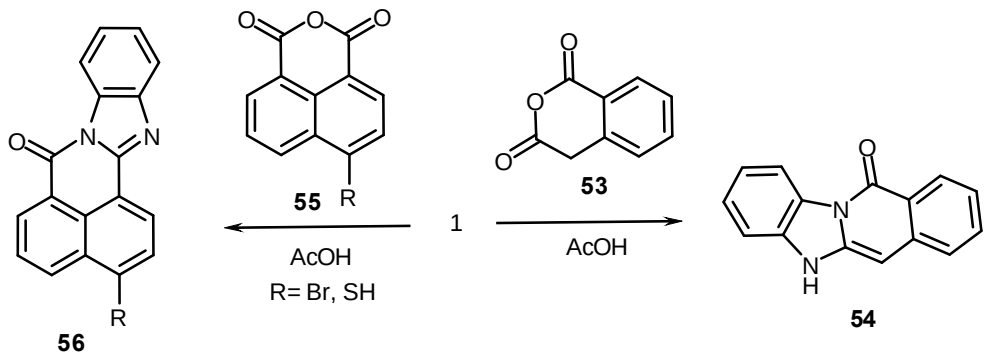
Benzimidazolo[1,2-*a*]pyrrolidin-2-one derivative **50** was prepared from the reaction of **1** with *E*-fulgide **49** in boiling toluene.[59]



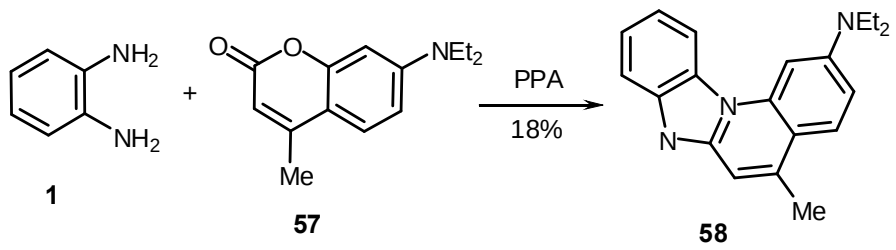
Similarly, isoindolobenzimidazolone **52** was prepared from heating phthalic anhydride with the pyridylphenylenediamine derivative **51** in boiling acetic anhydride.[60]



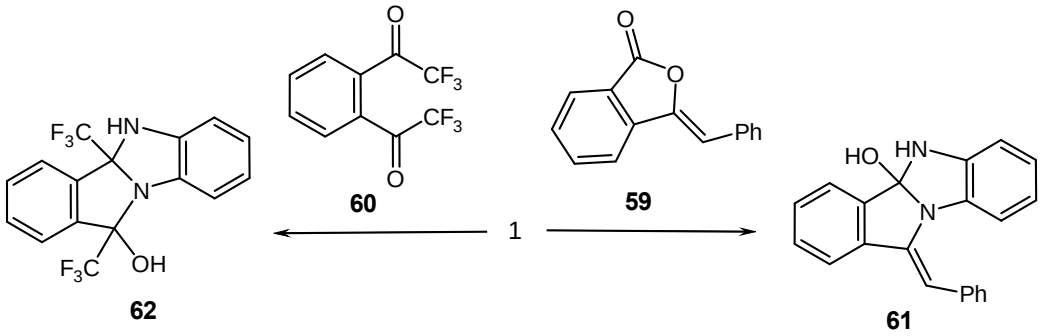
Refluxing isochroman-1,3-dione **53** with *o*-phenylenediamine **1** in glacial acetic acid gave 11*H*-benzimidazo[1,2-*a*]isoquinolin-11-one **54**.[61] Also, treatment of **1** with 1,8-naphthoic anhydride derivatives **55** gave the pentacyclic fused system; 7*H*-benzimidazo[2,1-*a*]benzo[*d*,*e*]isoquinolin-7-ones **56**.[62,63]



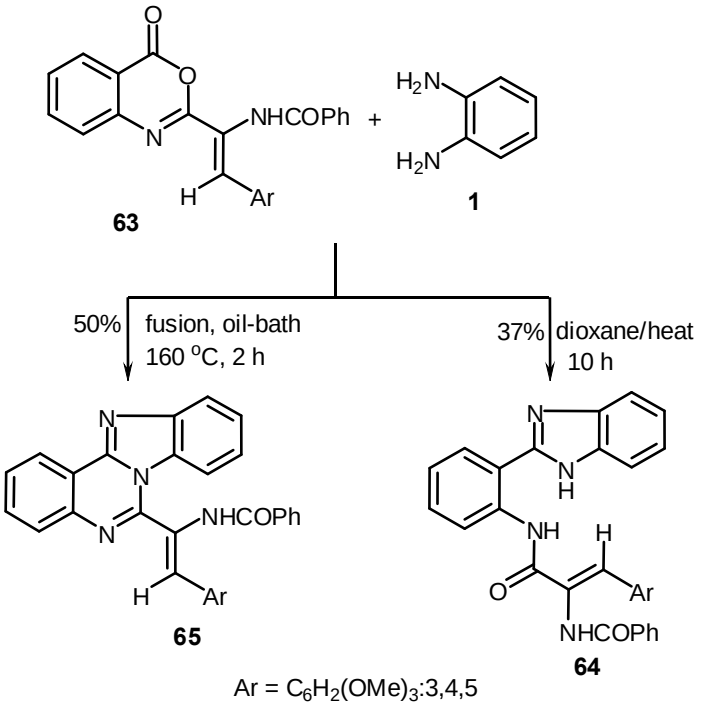
Likewise, 2-*N*-ethylamino-5-methylbenzimidazo[1,2-*a*]quinoline **58** was formed in 18% yield when 7-diethylamino-4-methylcoumarin **57** reacted with compound **1** in the presence of PPA at 240 °C.[64]



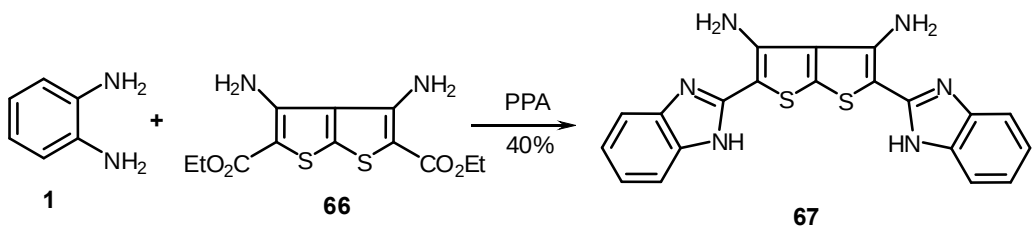
The hydroxyisoindolobenzimidazole derivatives **61** and **62** were synthesized from condensation of **1** and 1,2-di(triflouroacetyl)benzene **59** and 3-benzylidenephthalide **60**, respectively.[65,66]



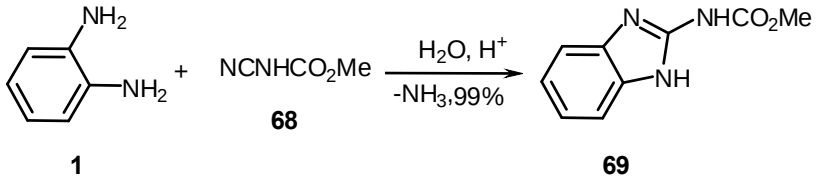
Reaction of **1** with benzoxazinone **63** in boiling dioxane gave benzimidazole derivative **64**, while, in the absence of solvents at 160 °C in an oil bath benzimidazo[1,2-*c*]quinazoline derivative **65** was obtained.[67]



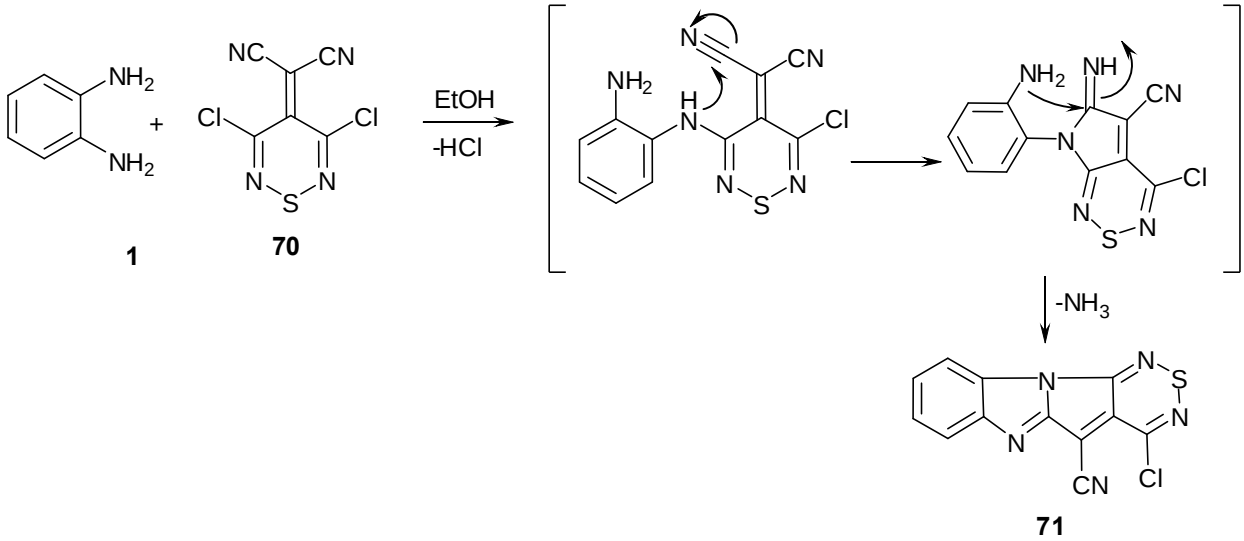
Reaction of **1** with 3,4-diamino-2,5-dicarbethoxythieno[2.3-*b*]thiophene **66** in PPA gave 3,4-diamino-2,5-dihetarylthieno[2,3-*b*]thiophenes **67**.[68]



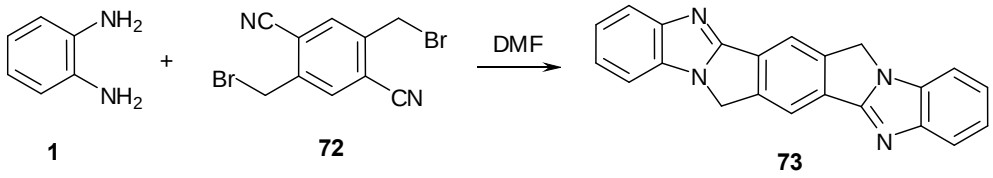
Reaction of **1** with methyl cyanocarbamate **68** in acidic medium gave methyl 2-benzimidazolylcarbamate **69**.[69]



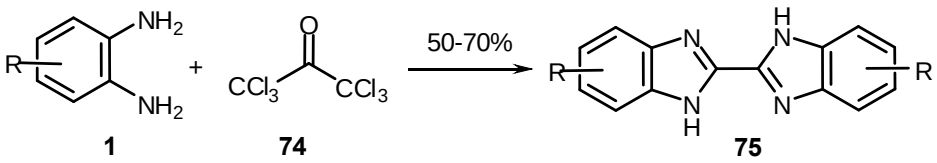
Reaction of **1** with (3,5-dichloro-4*H*-1,2,6-thiadiazin-4-ylidene)propanedinitrile **70** in ethanol at 20 °C gave 4-chloro-5-cyano-1,2,6-thiadiazino[3',4':5,4]pyrrolo[1,2-*a*]benzimidazole **71** *via* loss of HCl and NH_3 molecules.[70]



Reaction of **1** with 2,5-*bis*(bromomethyl)benzene-1,4-dinitrile **72** in boiling DMF led to the formation of polycyclic skeleton **73**.[71]



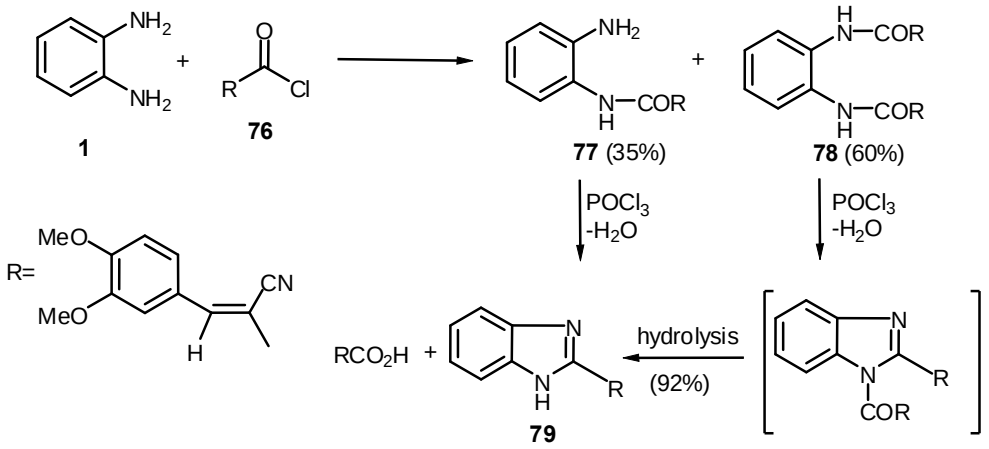
Cyclocondensation of **1** with hexachloroacetone **74** in ethylene glycol at 40–50 °C led to substituted *bis*-benzimidazoles **75**.[72]



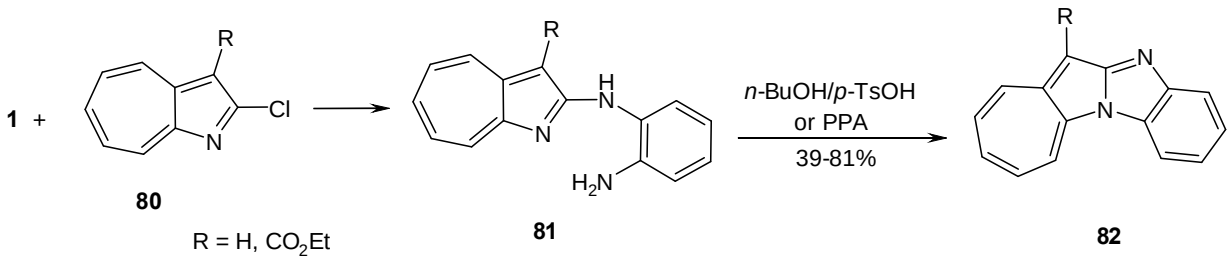
X=3-Me, 4-Me, 4-Cl, 4-MeO, 3-OH

Reaction of *o*-phenylenediamine **1** with acid chloride **76** gave a mixture of monosubstituted derivative **77** and *N*,*N*'-disubstituted derivative **78**. Treatment of both **77** and **78** with $POCl_3$ yielded the same

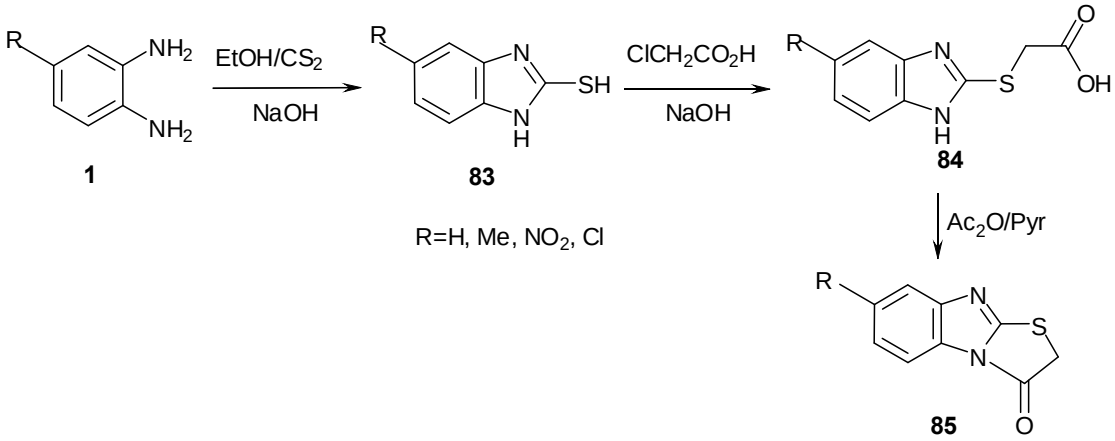
benzimidazole derivative **79**.[73]



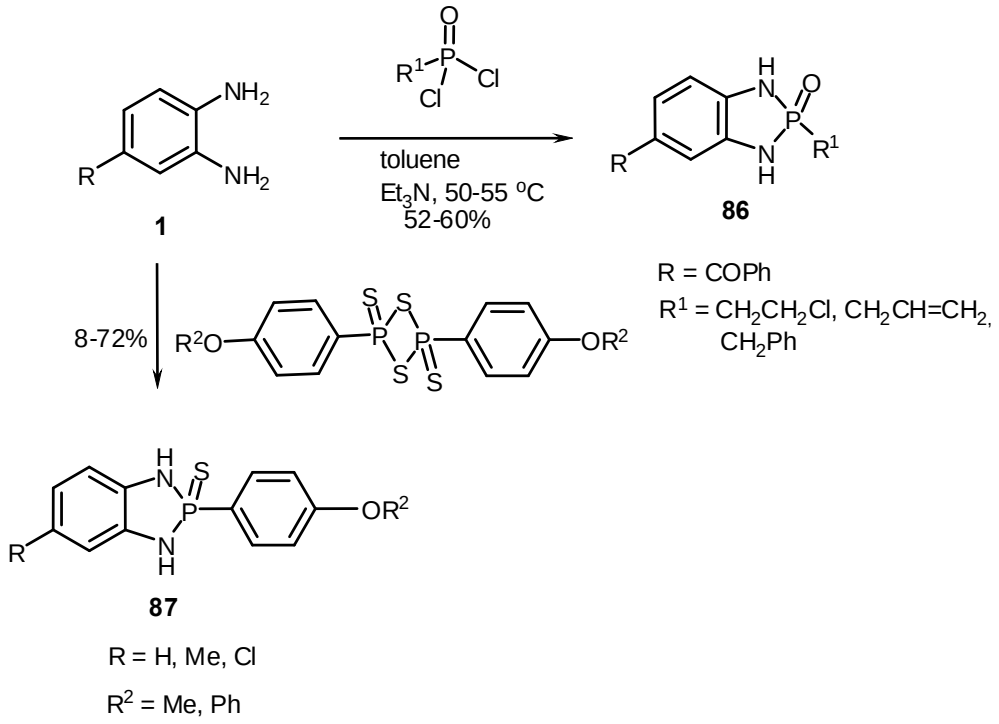
Chlorocyclohepta[*b*]pyrroles **80** reacted with *o*-phenylenediamine **1** to give 2-(2-aminoanilino)-cyclohepta[*b*]pyrroles **81** in good yields. Treatment of **81** with PPA or *p*-TsOH in *n*-butanol afforded cycloheptapyrrolobenzimidazoles **82** in good yields.[74]



1*H*-Benzimidazole-2-thiols **83** were prepared by refluxing ethanol–water solution of sodium hydroxide, carbon disulfide and 4-(un)substituted-1,2-diaminobenzenes. The reaction between chloroacetic acid and **83** (R=H) in the presence of sodium hydroxide led to (benzimidazol-2-ylthio)acetic acids **84**. 1,3-Thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones **85** were obtained by heating **84** and acetic anhydride in pyridine medium at 100 °C.[75]



In a similar manner for the synthesis of benzimidazoles, reaction of *o*-phenylenediamine **1** with phosphonyl dichloride in dry toluene in the presence of triethylamine gave the corresponding 2-(2-chloroethyl/allyl/benzyl)-2,3-dihydro-5-benzoyl-1*H*-1,3,2-benzodiazaphosphole-2-oxide **86**.[76] Also, treatment of **1** with 2,4-*bis*(4-methoxyphenyl)-l,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) afforded 1,3-dihydro-1,3,2-benzodiazaphosphole-2-sulfide-2-*p*-alkoxy(phenoxy)phenyl **87**.[77]



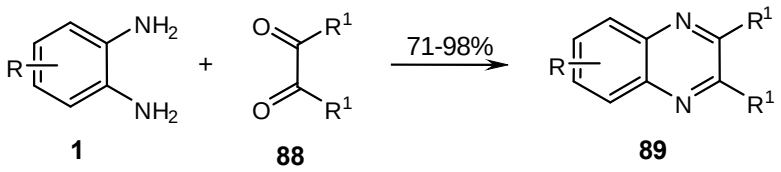
1 **86** **87**

3. SYNTHETIC APPROACHES FOR QUINOXALINE DERIVATIVES

Quinoxaline derivatives are the subject of considerable interest from both academic and industrial perspective.[78-84] Quinoxalines possessing broad spectrum of biological activities including antiviral, antibacterial, anti-inflammatory, askinase inhibitors, anticancer, antitumor, antidepressant, antimycobacterial, cadiotonic and anthelmintic agents.[85-94] Also, quinoxalines have been reported for their applications in dyes,[95] pharmaceuticals[96] and have also been used as building blocks for the synthesis of organic semiconductors.[97,98] Moreover, quinoxaline ring is a part of various antibiotics such as Echinomycin, Levomycin and Actinoleutin[99,100] that are known to inhibit growth of gram positive bacteria and are active aganist various transplantable tumors.[101]

A variety of synthetic strategies have been developed for the preparation of quinoxaline derivatives. One of the most common methods is the double condensation between aryl-1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid for 2-12 h, to produce quinoxalines in 34-85% yields.[102] From the synthesis standpoint, this traditional process generally requires high reaction temperature, strong acidic media, and mostly long reaction time.

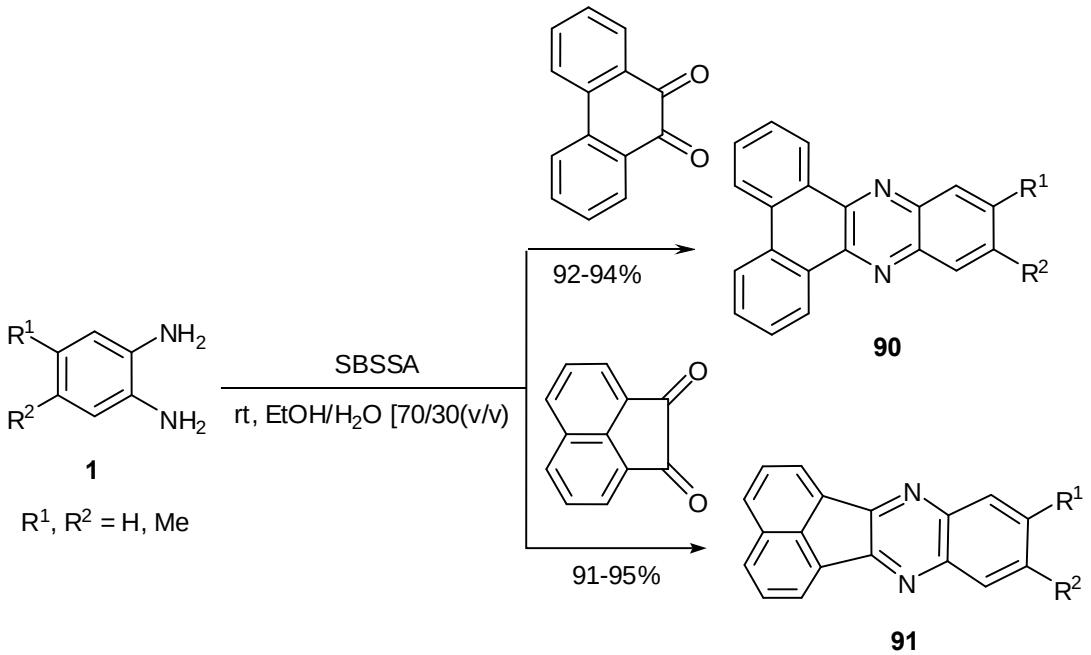
A number of methods have been developed to improve the reaction conditions and yields. Thus, clay-catalyzed condensation of *o*-phenylenediamine **1** with 1,2-diketones **88** gave 2,3-disubstituted quinoxaline **89**. In the presence of catalytic amounts NH_4Cl[103] or cerium trichloride[104] the yield was improved in a very short time. Moreover, under microwave irradiation, quinoxaline derivatives **89** were obtained in 71-98% yields.[105-107] Also, reaction of **1** with 1,2-diketones **88** in DMSO in the presence of iodine as a catalyst gave quinoxaline derivatives **89** in 85-95% yields.[108]



1 **88** **89**

R = H, Me, Cl, NO_2
R^1 = Me, Ph, *p*-$MeOC_6H_4$
p-MeC_6H_4, *p*-ClC_6H_4, furyl)

2,3-Disubstituted quinoxalines **89** (68-93% yields) were also prepared from reaction of **1** with benzil **88** at room temperature in the presence of different catalysts such as oxalic acid, $ZnCl_2$, $Mn(OAc)_2$, $CoCl_2$, $Ni(OAc)_2$ or silica bonded S-sulfonic acid (SBSSA).[109,110] Similarly, dibenzo[a,c]phenazine derivatives **90** and acenaphtho[1,2-*b*]quinoxaline derivatives **91** were efficiently prepared from condensation of **1** with phenanthrene-9,10-dione and acenaphene-1,2-dione in the presence of SBSSA.[110]



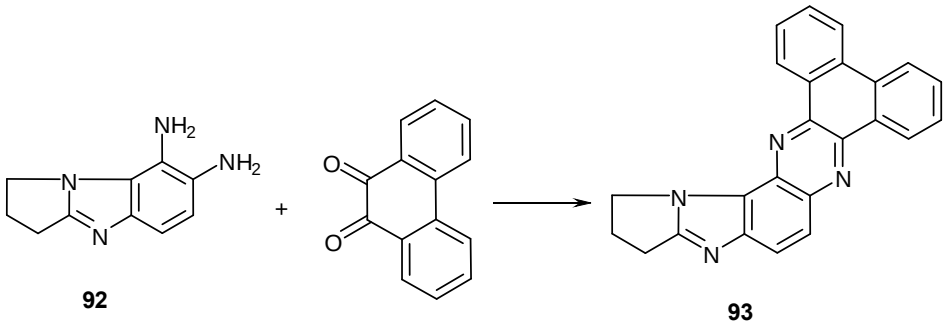
1

R^1, R^2 = H, Me

90

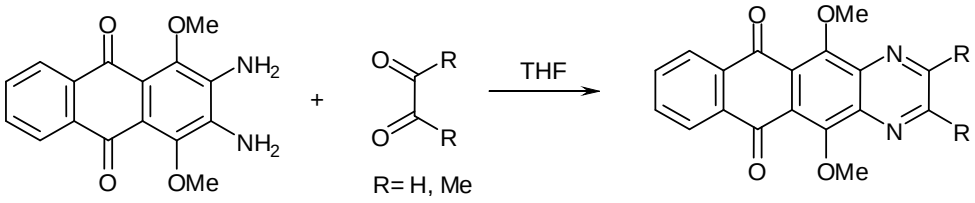
91

Diaminopyrrolobenzimidazole **92** underwent condensation reaction with phenanthrene-9,10-dione in AcOH at reflux to give hepta-fused-heterocyclic system **93**.[111]



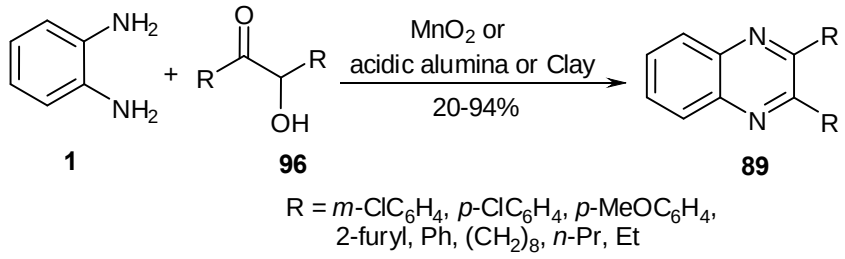
92 **93**

Condensation of *O*,*O*-dimethyl derivative of diaminoquinazirin **94** with glyoxal or diacetyl in THF gave naphtha[2,3-*g*]quinoxaline-6,11-dione derivatives **95**.[112]



94 **95**

Microwave-assisted reaction of *o*-phenylenediamine **1** with α-hydroxy ketones (acyloins such as benzoin) **96** in the presence of MnO_2,[113] acidic alumina,[114] or Clay,[115] as a catalyst gave 2,3-disubstituted-quinoxaline **89**. The reaction was supposed to be carried out *via* a tandom oxidation process of acyloin to the corresponding 1,2-dicarbonyl compounds.

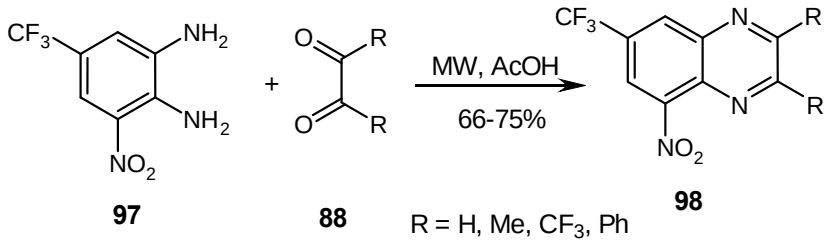


1 **96** **89**

R = *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, 2-furyl, Ph, $(CH_2)_8$, *n*-Pr, Et

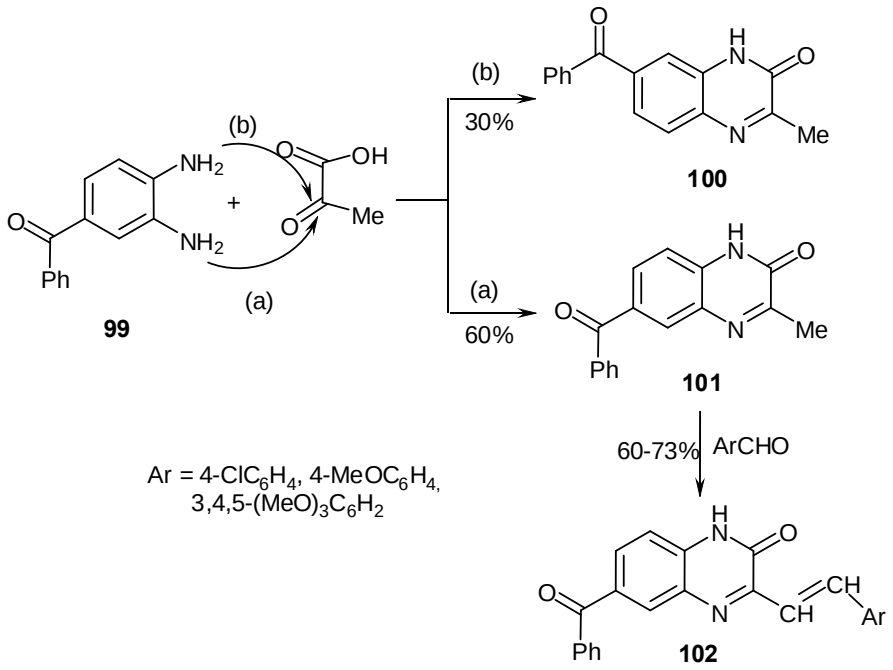
It was found that, in symmetrical diamines the product will be same irrespective of which amine participates first in the reaction as reported above. In case of unsymmetrical diamines, the substituents influence initial participation of a particular amino group in the reaction, resulting in region-specific products. The electron withdrawing/donating nature of substituents in diamine influenced the nucleophilicity of the amine group. Thus, reaction of 3-nitro-5-trifluoromethyl-1,2-phenylenediamine **97** with 1,2-diketones **88** gave quinoxaline derivatives **89** in 82-88% yields using MW and 66-75% yields under thermal conditions. It is presumed that the amino group meta to CF_3 and NO_2 groups participates initially in the Schiff base formation, while the other amino group could not participates initially because it is *ortho* to nitro and *para* to CF_3 group which are considered to be powerful electron withdrawing

groups and may reduce the nucleophilicity of amine. Hence the formation of other region isomer to compound **98** was not seen.[116]

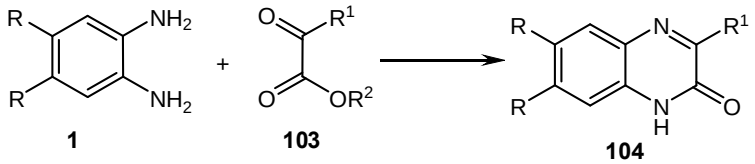


97 **88** R = H, Me, CF_3, Ph **98**

Condensation of 4-benzoyl-1,2-phenylenediamine **99** with pyruvic acid in acetic acid at room temperature gave a mixture of 3-methylquinoxalinone **100** and the corresponding isomer **101**. 6-Benzoyl-3-substituted-styryl-2(1*H*)-quinoxalinones **102** were obtained *via* fusion of **101** with aromatic aldehydes in the presence of piperidine at 160 ºC.[117]



1,2-Dihydro-3-substitutedquinoxalin-2-ones **104** were prepared by condensation of α-ketocarboxylic acids or corresponding esters **103** with diamine **1**.[118-130]



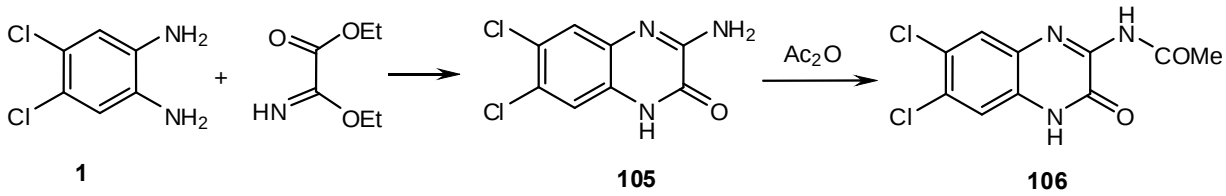
1 **103** **104**

R = H, Me, Cl

R^1 = H, Me, Et, Ph, CH_2Cl, CH_2Br, $CHBr_2$, CH_2CO_2Et, $CH_2CH_2CO_2Et$, $CH(CH_3)CO_2Et$

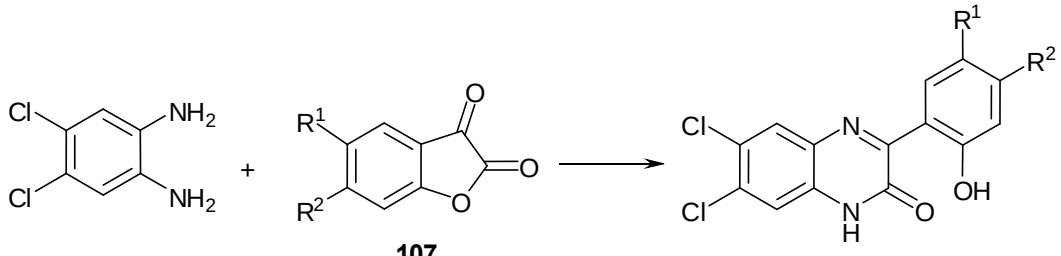
R^2 = H, alkyl

Instead of α-ketocarboxylic acids or α-ketoesters**,** it is possible to use great variety of functional derivatives (e.g. oxalomonoimidic acid diethylester) to react with *o*-phenylenediamine **1** to produce 3-aminoquinoxalin-2-one **105** which on acetylation gave 3-acetylamino analogs **106**.[131-133]



1 **105** **106**

Also, treatment of **1** with coumarandione **107** yielded 3-(2-hydroxyphenyl)quinoxalin-2-ones **108**.[134]

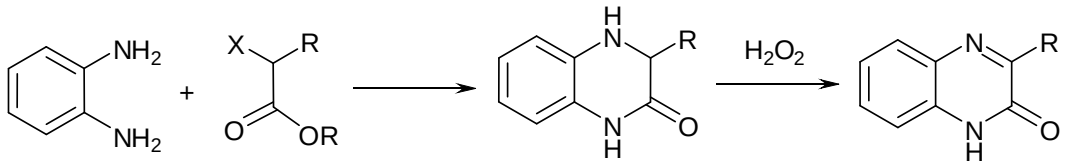


1 **107**

R^1 = H, Me
R^2 = H, MeO

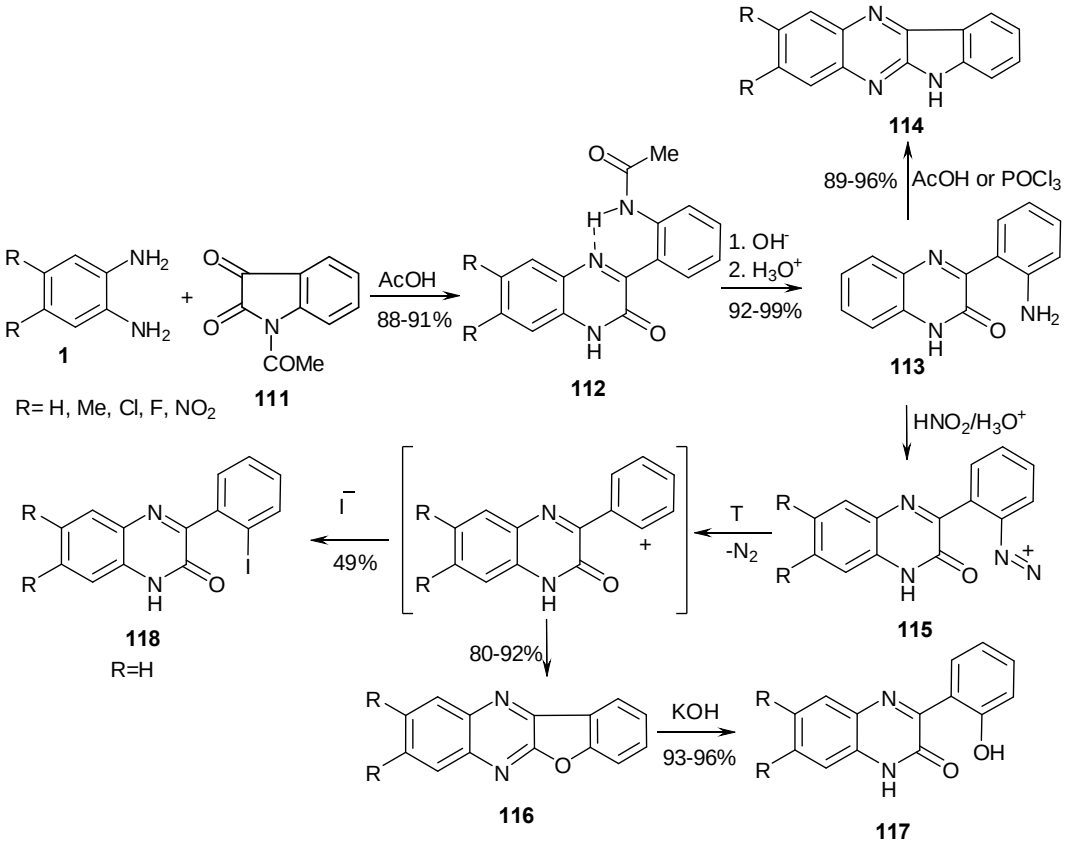
108

Haloesters are also very good starting compounds when reacted with *o*-phenylenediamine **1** to produce tetrahydroquinoxalines **109** which on dehydrogenation by hydrogen peroxide gave compounds **110**.[135]

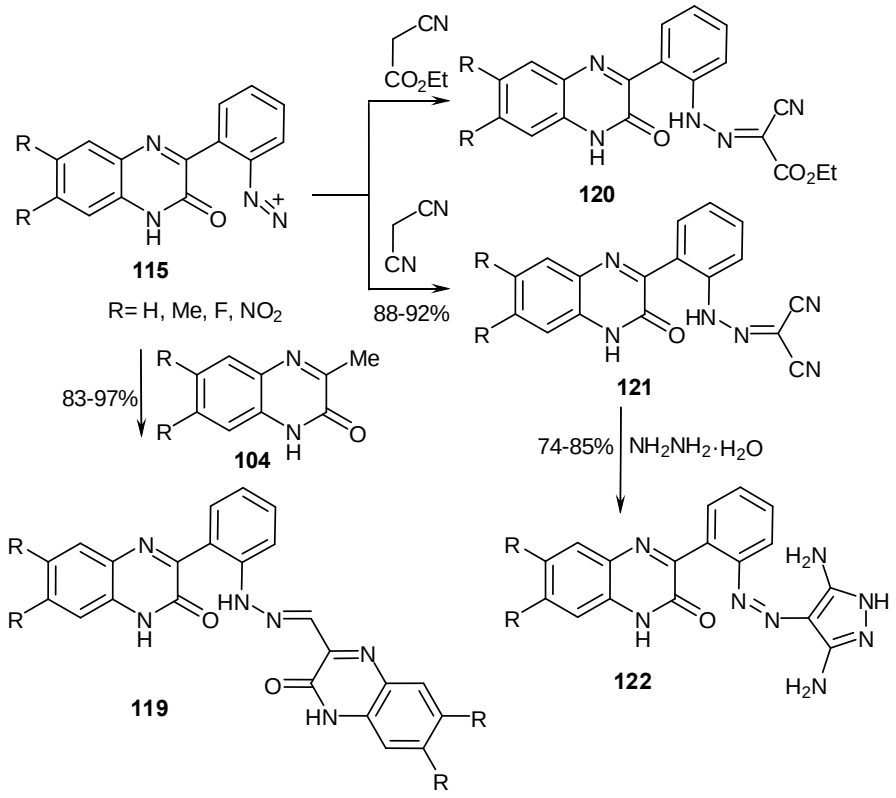


1 **109** **110**

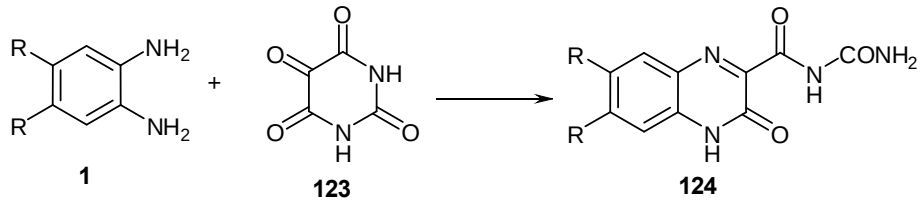
3-(2-Acetylaminophenyl)-1,2-dihydroquinoxaline-2-ones **112** were prepared by the reaction of *N*-acetylisatin **111** with 1,2-diamines **1** in acetic acid under reflux. The corresponding amino derivative **113** was then prepared by alkaline hydrolysis of **112**. Boiling amino derivative **113** in acetic acid or phosphorus oxychloride furnished the fused system; indolo[2,3-*b*]quinoxalines **114**. The diazotization of compound **114** afforded solution of the corresponding diazonium salts **115**, which under thermal decomposition yielded [1]benzofuro[2,3-*b*]quinoxalines **116**. Compounds **116** were split in alkaline medium into the 3-(2-hydroxyphenyl)-1,2-dihydroquinoxalin-2-ones **117.** During decomposition of **115** with the presence of iodide ions, 3-(2-iodophenyl)-1,2-dihydroquinoxalines **118** were obtained.[136-139]



Coupling of diazonium salts **115** with 6,7-disubstituted-3-methyl-1,2-dihydroquinoxalin-2-ones, ethyl cyanoacetate and malononitrile gave the corresponding hydrazones **119-121**. Hydrazones **121** were cyclized with hydrazine hydrate to the corresponding pyrazole derivatives **122**.[139]



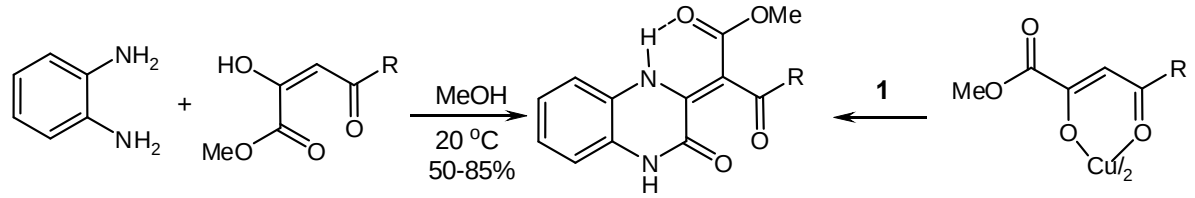
Instead of α-keto-carboxylic acids or α-ketoesters, it is possible to use great variety of functional derivatives including ureides and lactams (e.g. alloxane **123**) to produce quinoxalines **124**.[140,141]



1 **123** **124**

R= H, Me

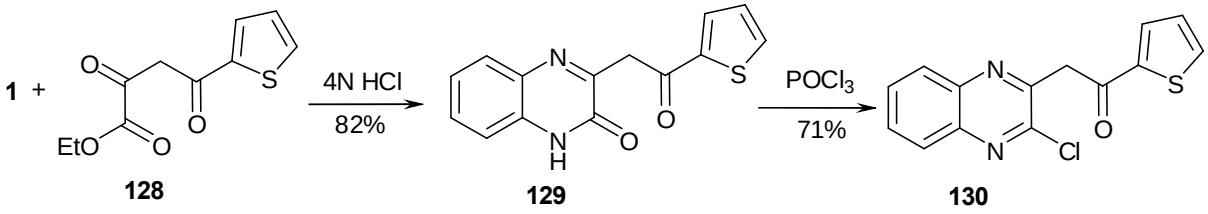
Condensation of **1** with polyfluoroacyl pyruvates **125** resulted in the formation of 3-(2-oxofluoro-alkylidene)-1,2,3,4-tetrahydroquinoxalin-2-ones **126** in 50-85% isolated yields. The same products **126** were obtained from chelates **127** and diamine **1**.[142]



1 **125** **126** **127**

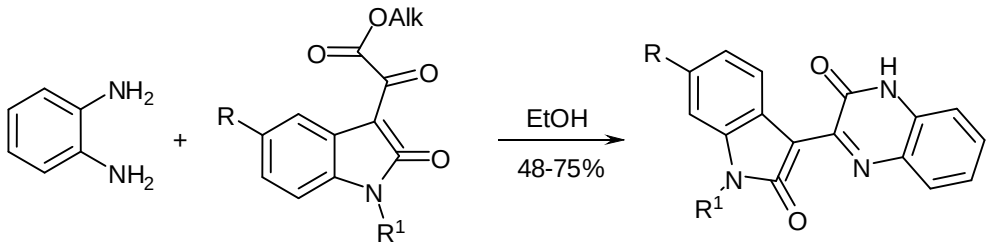
R= CHF_2, CF_3, C_4F_9, C_6F_5

Reaction of **1** with 2-thienoylpyruvate **128** gave 2-chloro-3-(2'-thienoylmethyl)quinoxaline **130** *via* treatment of 2-hydroxy-3-(2'-thienoylmethyl)quinoxaline **129** with phosphorus oxychloride.[143]



128 **129** **130**

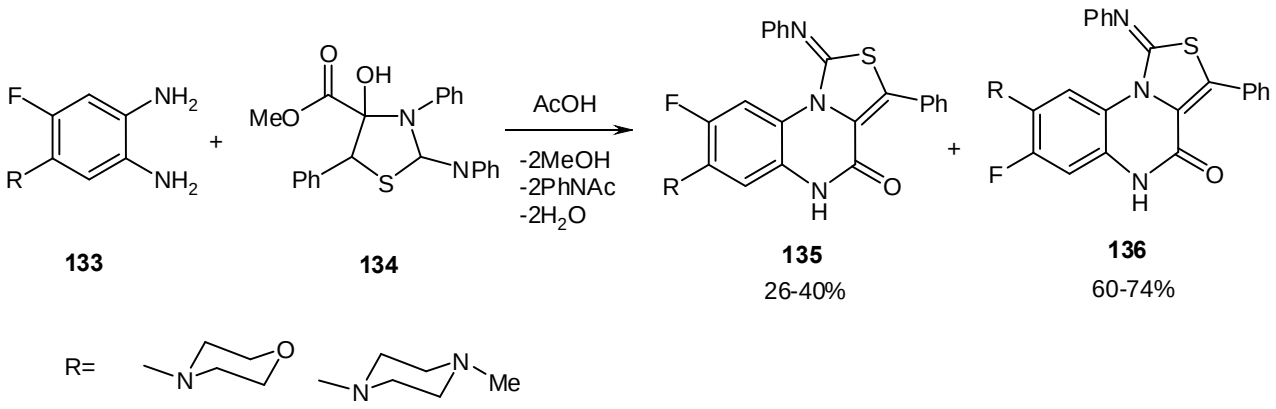
Treatment of 2-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetic acid esters **131** with *o*-phenylenediamine **1** gave the corresponding 3-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3,4-dihydroquinoxaline-2(1*H*)-ones **132**.[144]



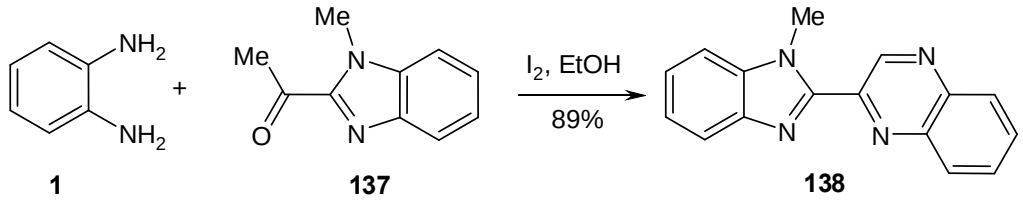
1 **131** **132**

Alk = Me, Et R = H, Br R^1 = H, COMe

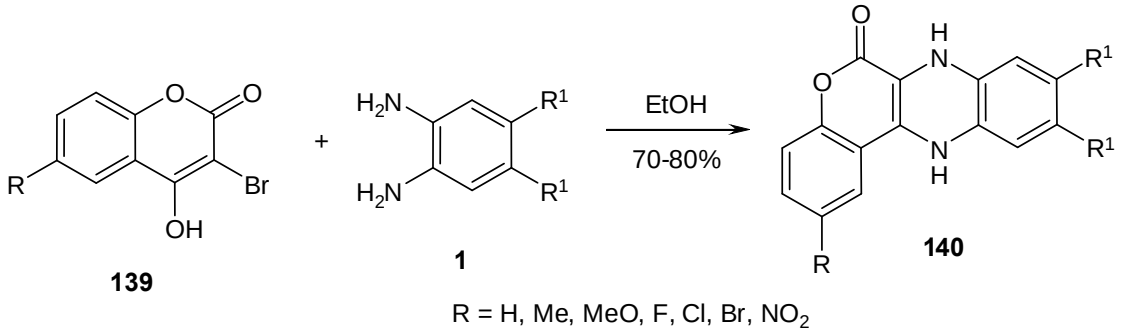
Condensation of 5-fluoro-4-moephilino- and 5-fluoro-4-(4-methylpiperazino)-1,2-phenylenediamines **133** with 4-hydroxy-3,5-diphenyl-2-phenyliminothiazolidine **134** gave a region-isomeric mixture of 8-fluoro-3-phenyl-1-phenyliminothiazolo[3,4-*a*]quinoxalin-4(5*H*)-ones **135** and 7-fluoro-3-phenyl-1-phenylimino-thiazolo[3,4-*a*]quinoxalin-(5*H*)-ones **136**. Herein again, the use of unsymmetrically substituted 1,2-phenylenediamines resulted in the formation of a mixture of two isomeric thiazoloquinoxalones **135** and **136** in a ratio 2:3.[145]



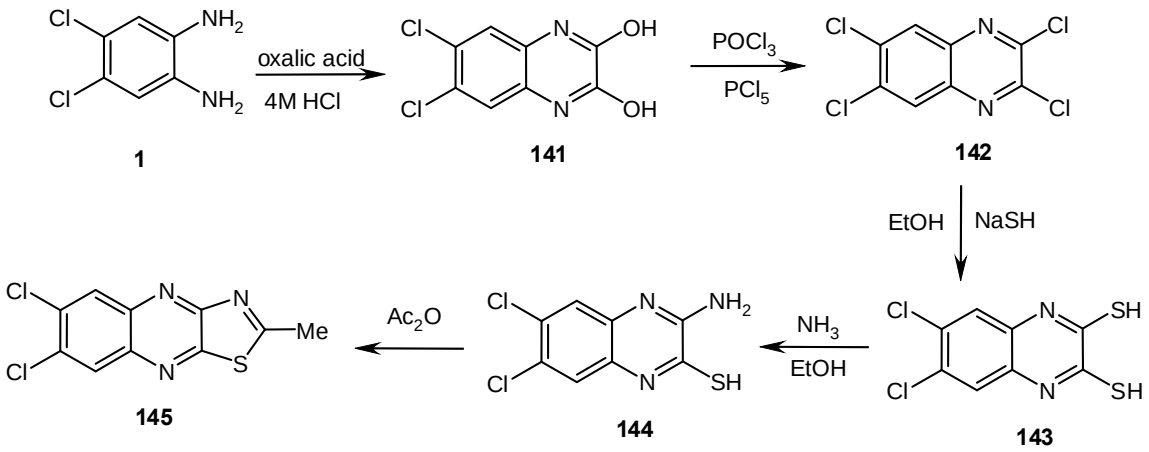
Reaction of **1** with 1-(1-alkyl/aralkyl-1*H*-benzimidazol-2-yl)ethanone **137** in ethanol containing iodine gave 2-(1-methyl-1*H*-benzimidazole-2-yl)quinoxaline **138**.[146]



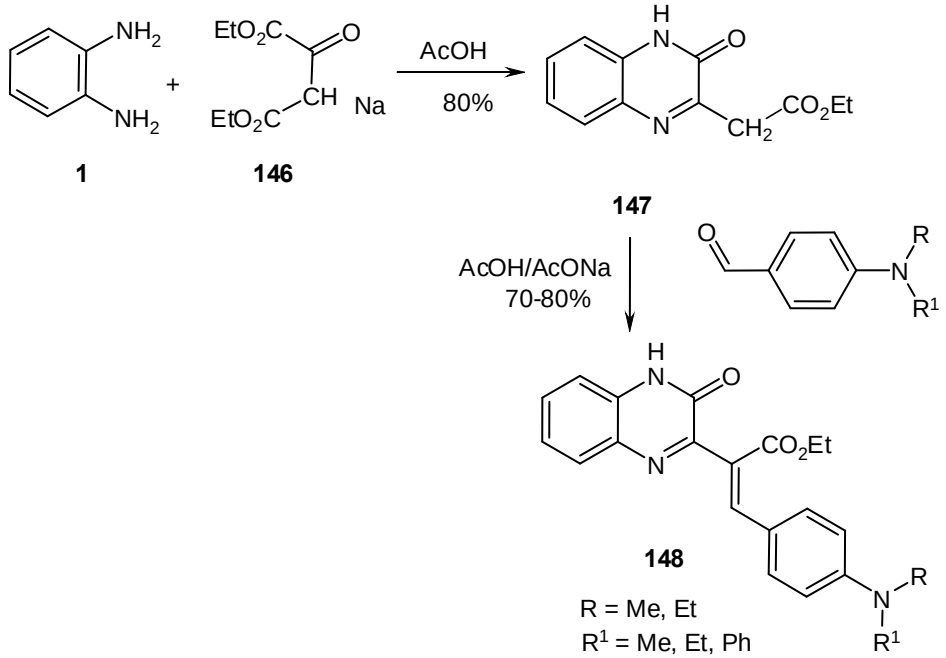
Literature survey reveals that quinoxaline having coumarine constituent possesses antibacterial activity.[147] *o*-Phenylenediamines **1** on reaction with various substituted 4-hydroxycoumarin **139** in ethanol under reflux afforded 2,9,10-trisubstituted-6-oxo-7,12-dihydrochromeno[3,4-*b*]quinoxalines **140** in 70-80% yields.[148]



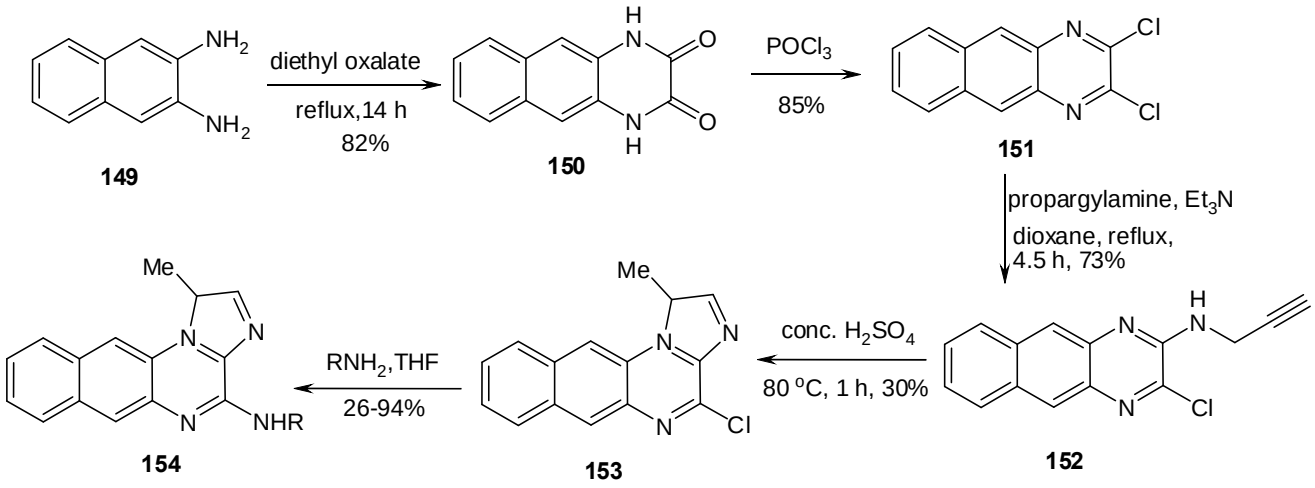
2,3-Dihydroxy-6,7-dichloroquinoxaline **141** was synthesized in good yield by condensation of corresponding diamine **1** with oxalic acid in refluxing 4*M* hydrochloric acid.[149] Chlorination of **141** gave 2,3,6,7-tetrachloroquinoxaline **142**, which on subsequent reaction with sodium hydrogen sulfide gave of 2,3-dimercapto-6,7-dichloroquinoxaline **143** in quantitative yield.[150] Partial ammonolysis of compound **143**, using alcoholic ammonia, yielded 2-amino-3-mercapto-6,7-dichloroquinoxaline **144** in 70% yield. Acetylation of **144** using acetic anhydride under reflux afforded 2-methyl-6,7-dichlorothiazolo[4,5-*b*]-quinoxaline **145** in 71% yield.[151]



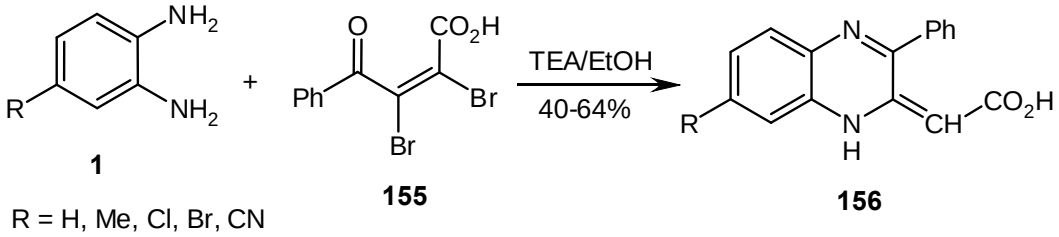
Ethyl quinoxalin-3(4*H*)-on-2-ylacetate **147** was synthesized by reaction of **1** with sodium salt of diethyl oxalacetate **146** (prepared from diethyl oxalate and ethyl acetate in benzene in the presence of sodium) in acetic acid. Condensation of **147** with dialkylaminobenzaldehydes afforded the styryl disperse dyes **148** in 70-80% yields.[152]



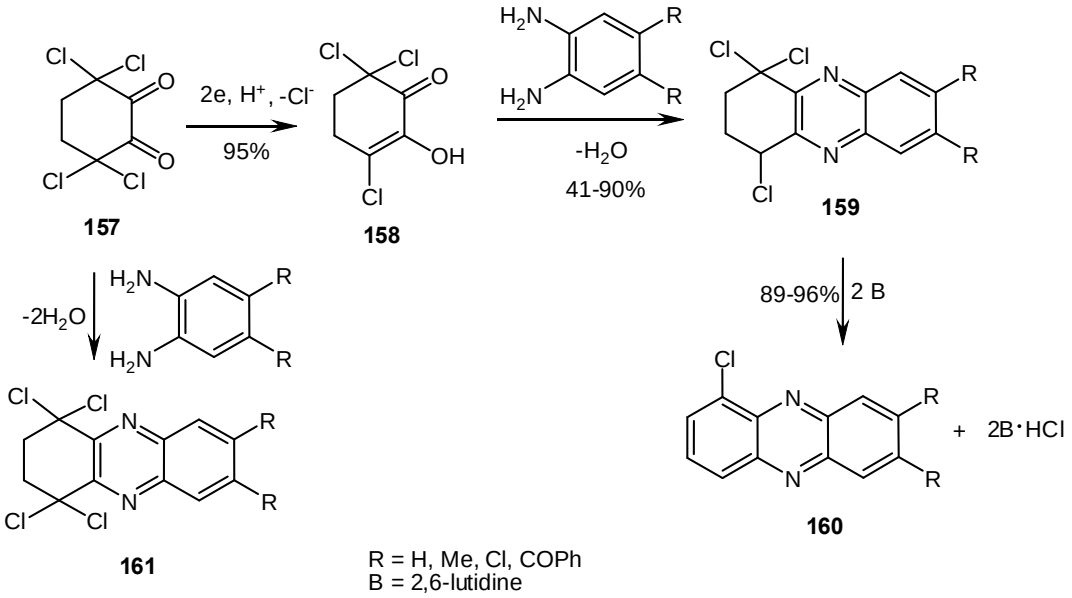
Commercially available 2,3-diaminonaphthalene **149** was reacted with diethyl oxalate to give annulated quinoxalinedione **150** which under treatment with phosphorus oxychloride under reflux afforded dichloro derivative **151**. Compound **151** was then reacted with propargylamine to give amino-chloro derivative **152**, which was cyclized under acidic conditions to provide 1-methyl-4-chlorobenzimidazoquinaxoline **153**. Compound **153** then served as a key intermediate to generate 4-amino-substituted analogues **154**.[153]



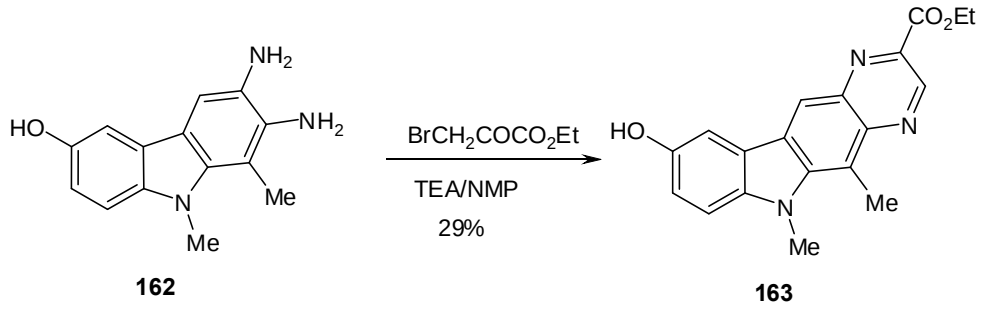
Reaction of **1** with 3-benzoyl-2,3-dibromopropionic acid **155**, in ethanol containing triethylamine, afforded 3-phenyl-2-carboxymethylene-1,2-dihydroquinoxalines **156**.[154]



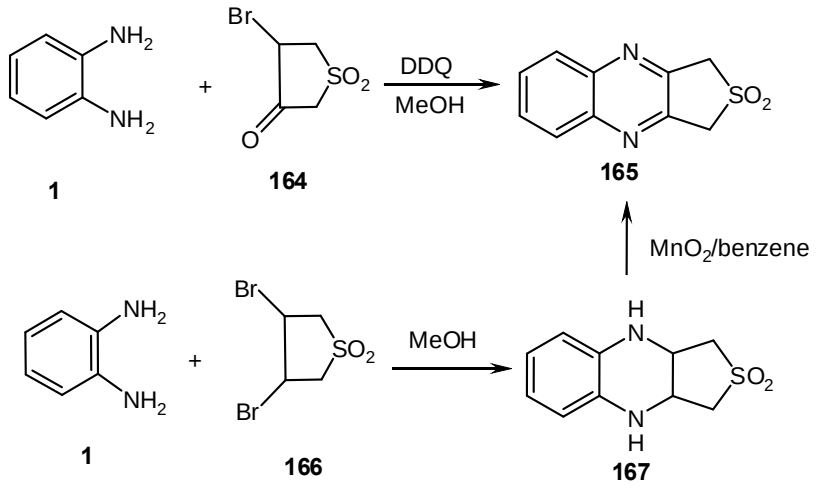
Condensation of **1** with 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **158**, prepared by electrochemical reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **157**, gave the corresponding intermediates **159** in high yields. Compounds **159** were converted into the corresponding 1-chlorophenazines **160** by simple treatment with 2,6-lutidine. Also, condensation of **1** with **157** gave the corresponding tetrachloro derivatives **161**.[155]



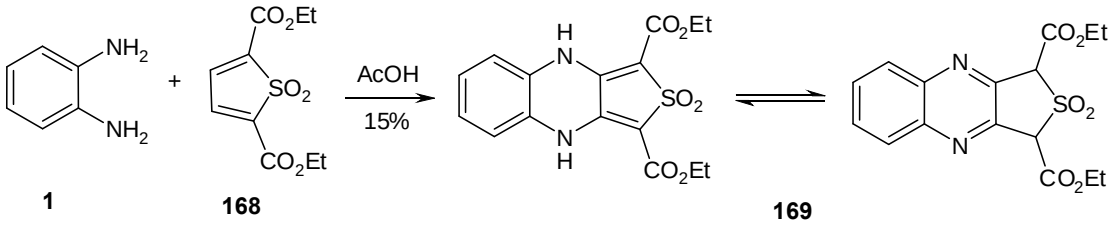
Treatment of diaminocarbazole derivative **162** with ethyl bromopyruvate in *N*-methylpyrrolidine (NMP) containing triethylamine gave the fused system **163** in 29% yield.[156]



The reaction of *o*-phenylenediamine **1** with 4-bromo-3-sulfolanone **164**, in the presence of dichloro-dicyanobenzoquinone (DDQ), yielded 1,3-dihydrothieno[3,4-*b*]quinoxaline-2,2-dioxide **165**. Compound **165** was also prepared from the reaction of 3,4-dibromosulfolane **166** with *o*-phenylenediamine **1**, followed by the dehydrogenation of tetrahydroquinoxaline intermediate **167**.[157,158]

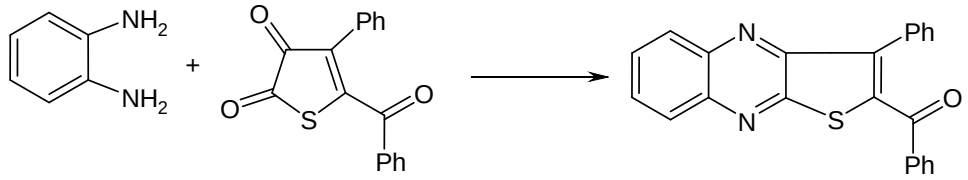


Diethyl dihydrothieno[3,4-*b*]quinoxaline-1,3-dicarboxylate **169** was obtained in 15% yield by the reaction of diester **168** and *o*-phenylenediamine **1** in acetic acid.[159]



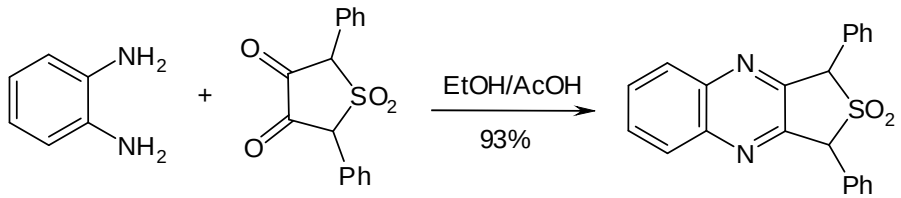
1 **168** **169**

Moreover, 2-benzoyl-3-phenylthieno[2,3-*b*]quinoxaline **171** was prepared *via* the condensation of thiophene-2,3-dione derivative **170** with *o*-phenylenediamine **1**.[160]



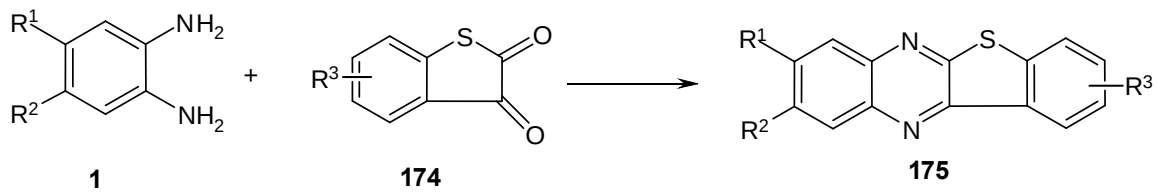
1 **170** **171**

Similarly, condensation of **1** with cyclic diketosulfone derivative **172** yielded 1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline derivative **173**.[161]



1 **172** **173**

Condensation of benzothiophene-2,3-diones **174** with compound **1** has been reported to give the corresponding benzothiopheno[2,3-*b*]quinoxalines **175**.[162]

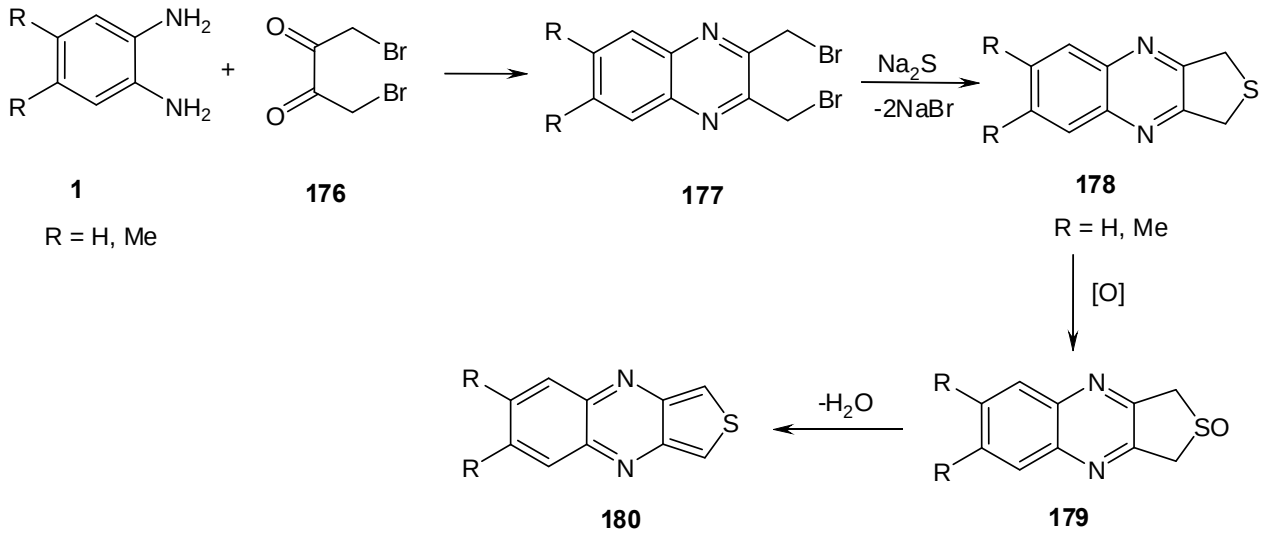


1 **174** **175**

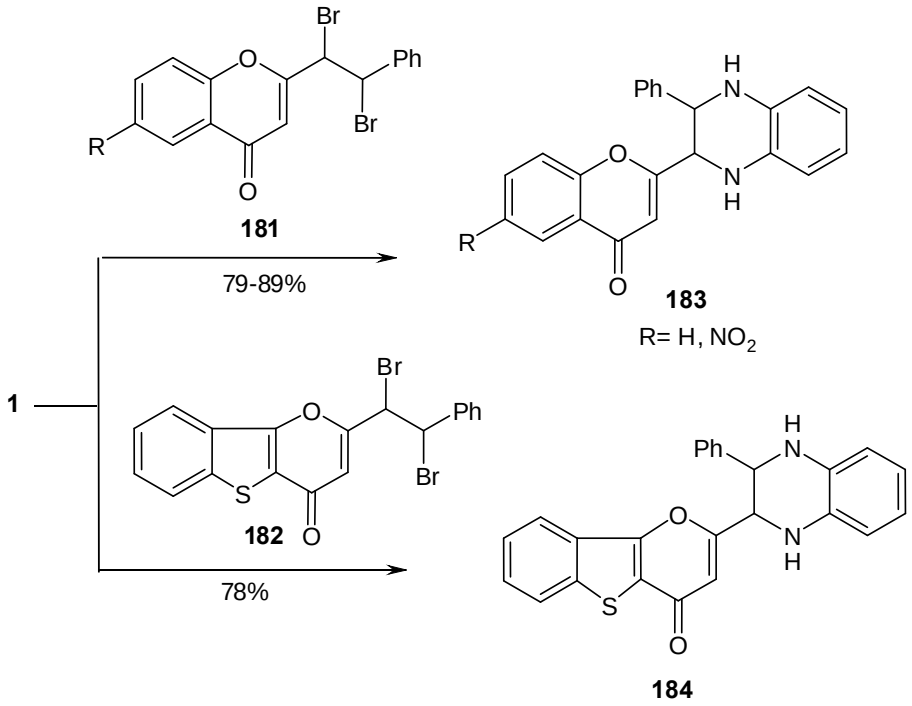
R^1, R^2 = H, Me ,OMe, NO_2, halo
R^3 = H, Me, Br

Reaction of 1,4-dibromo-2,3-butanedione **176** with *o*-phenylenediamine **1** gave 2,3-di(bromomethyl)-

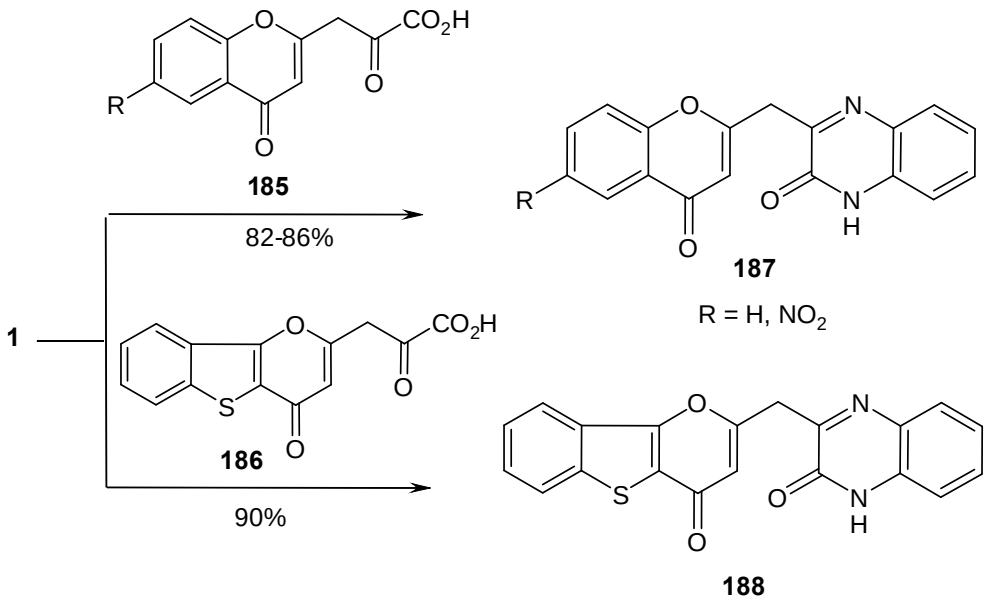
quinoxalines **177**. Compounds **177** were converted into the corresponding dihydrothienoquinoxalines **178** by treatment with anhydrous sodium sulfide. Oxidation of **178** afforded compound **179** which on dehydrogenation gave thieno[3,4-*b*]quinoxalines **180**.[163,164]



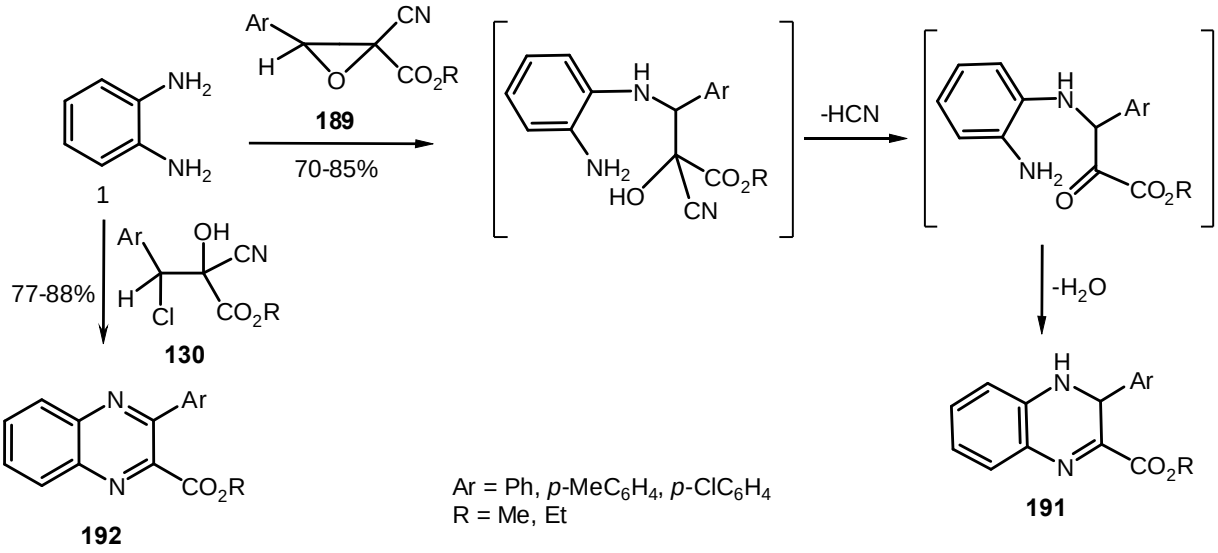
Reaction of **1** with 1,2-dibromophenylethane derivatives **181** and **182** gave tetrahydroquinoxaline derivatives **183** and **184,** respectively.[165]



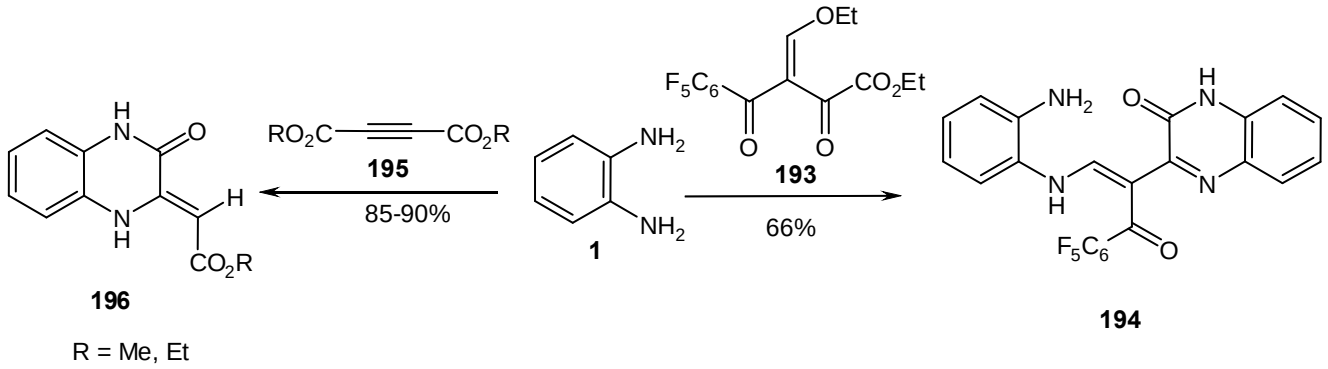
Reaction of pyruvic acids **185** and **186** with *o*-phenylenediamine **1** gave dihydroquinoxaline derivatives **187** and **188**, respectively.[165]



Reaction of *o*-phenylenediamine **1** with epoxides **189** and chlorocyanohydrins **190** gave 2-alkoxycarbonyl-3-aryl-3,4-dihydroqouinoxalines **191** and **192**, respectively.[166]



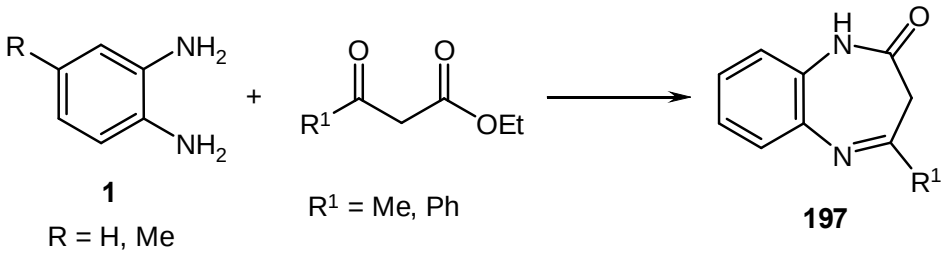
Reactions of *o*-phenylenediamine **1** with ethyl ethoxymethylidene-2,4-dioxo-4-pentafluoro phenylbutanoate **193** gave 3-[2-(2-aminophenylamino)-1-pentafluorobenzoylethenyl]-1,2-dihydro quinoxalin-2-one **194**. The reaction was accompanied by condensation at the α-oxoester to form quinoxaline moiety and the second molecule of *o*-phenylenediamine **1** underwent replacement to the ethoxy group leading to product **194**.[167] Reaction of **1** with dialkylacetylene dicarboxylate **195** gave 3,4-dihydro-3-(alkoxycarbonylmethylene)quinoxalin-2(1*H*)-one **196**.[168]



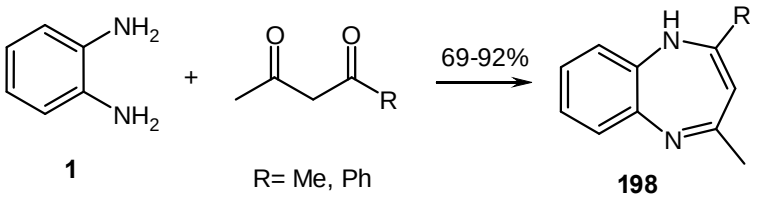
4. SYNTHETIC APPROACHES FOR BENZO[1,5]DIAZEPINE DERIVATIVES

Benzodiazepines and its derivatives constitute an important class of heterocyclic compounds which possess a wide range of therapeutic and pharmacological properties. Derivatives of benzodiazepines are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents.[169] In the last decade, the area of biological interest of 1,5-benzodiazepines has been extended to several diseases such as cancer, viral infection and cardiovascular disorders.[170]

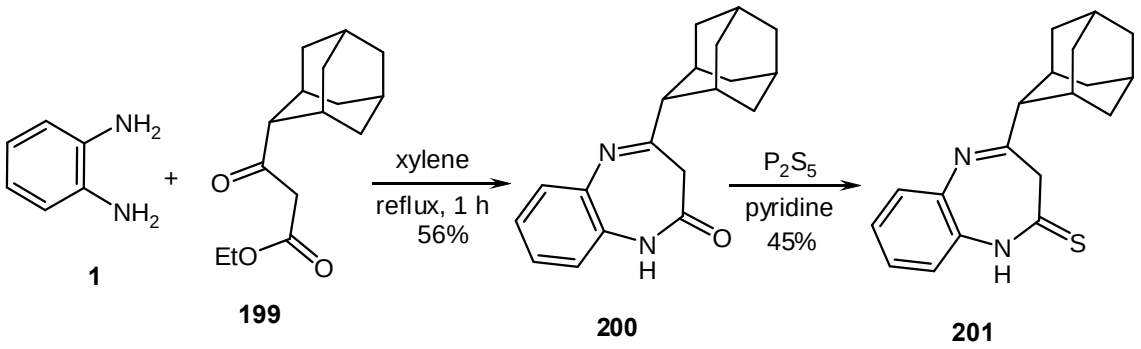
The most common route to benzodiazepines is the condensation reactions between *o*-phenylenediamines and 1,3-bifunctional electrophiles. Thus, 1,5-benzodiazepines **197** were prepared *via* treatment of *o*-phenylenediamine **1** with ethyl acetoacetate and ethyl benzoylacetate.[171,172]



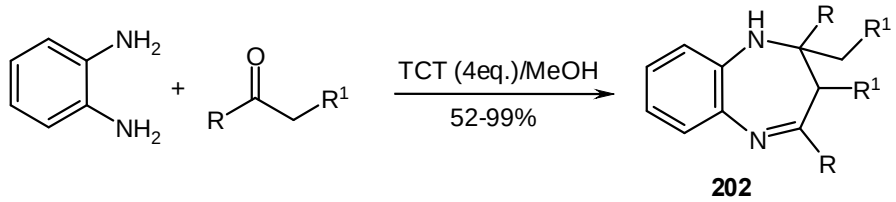
Similarly, heating **1** with acetyl/benzoyl acetone gave 1,5-benzodiazepines **198** in 69-92% yields.[173]



Also, treatment of **1** with 3-(l-adamantyl)-3-oxoethyl propionate **199**, in boiling xylene, led to 4-adamantyl-1,5-benzodiazepin-2-one **200**. Thionation the latter compound using phosphorus pentasulfide in boiling pyridine gave the corresponding thione derivative **201**.[173]

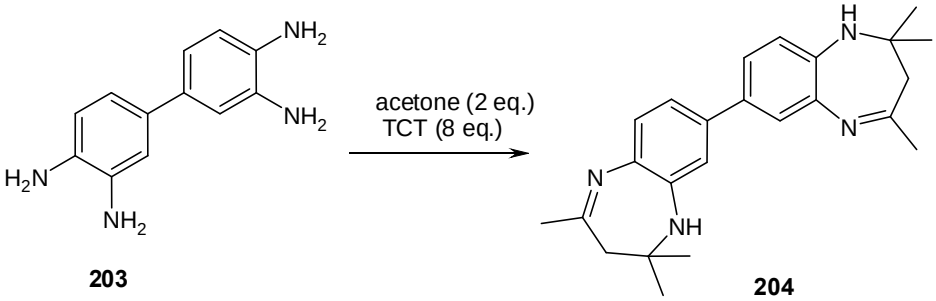


2,4,6-Trichloro-1,3,5-triazine (TCT) efficiently catalyzed the condensation reactions between *o*-phenylenediamine **1** and various enolizable ketones to afford 1,5-benzodiazepines **202** in good to excellent yields. This method achieves cheap catalyst and easy workup.[174]

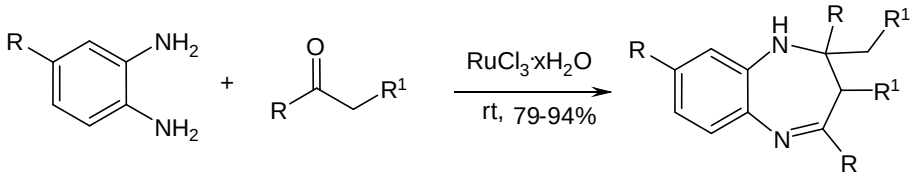


R = Me, Et, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-thienyl
R^1 = H, Me

Likewise, *bis*-benzodiazepine **204** was prepared in moderate yield from the reaction of *bis*-diamine **203** with acetone in the presence of TCT.[174]

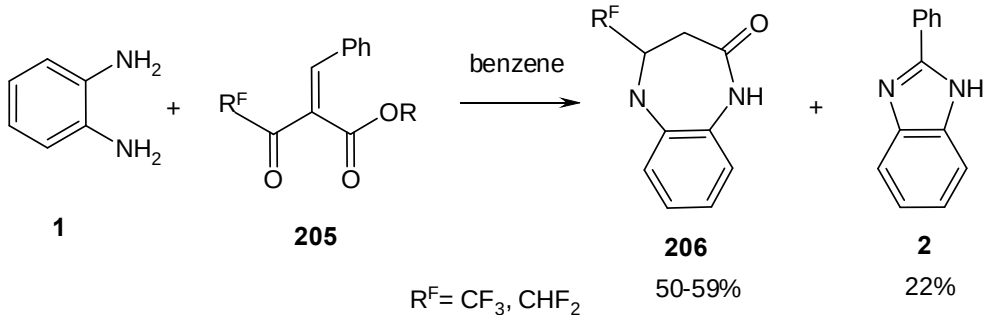


Also, 2,3-dihydro-1*H*-1,5-benzodiazepines **202** were synthesized in excellent yields (79-94%) *via* condensation of **1** with ketones having a hydrogen at α-position, using $RuCl_3 \cdot xH_2O$, ytterbium trichloride, sulfamic acid or *p*-nitrobenzoic acid as a catalyst.[175-178]

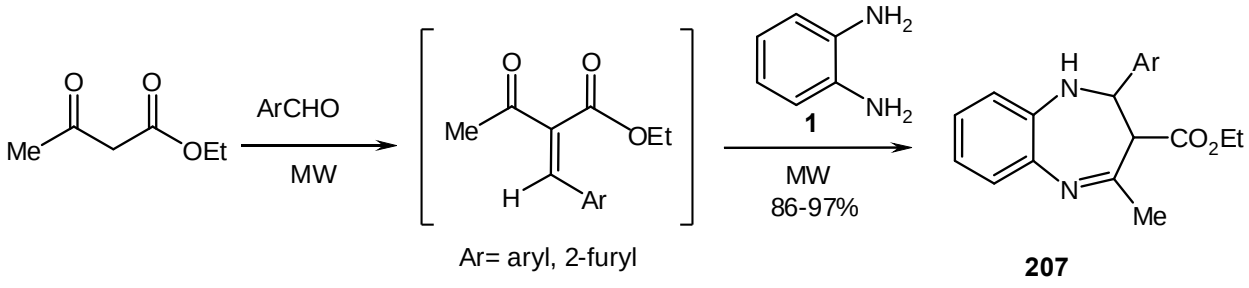


R = H, Me, Cl
R^1 = H, Me, Et, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$
R^2 = H, Me, $CHMe_2$

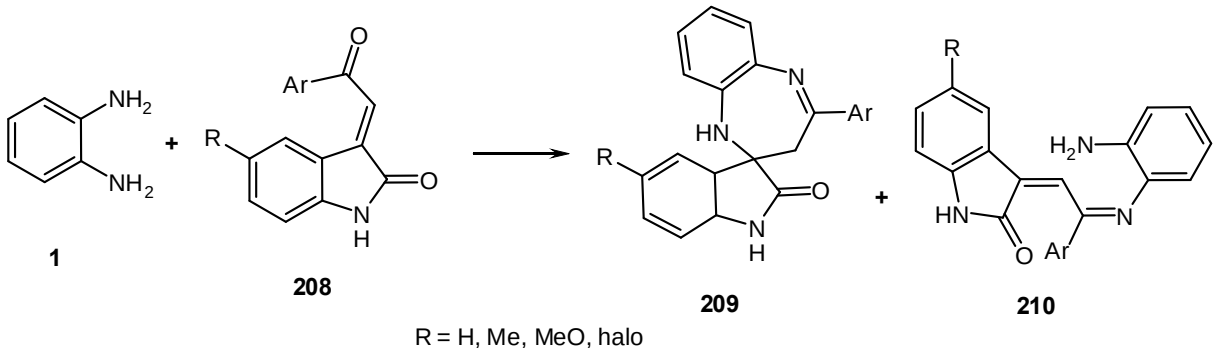
o-Phenylenediamine **1** on reaction with 2-benzylidene-3-oxoalkanoates **205** yielded benzodiazepines **206** together with benzimidazole **2**.[179]



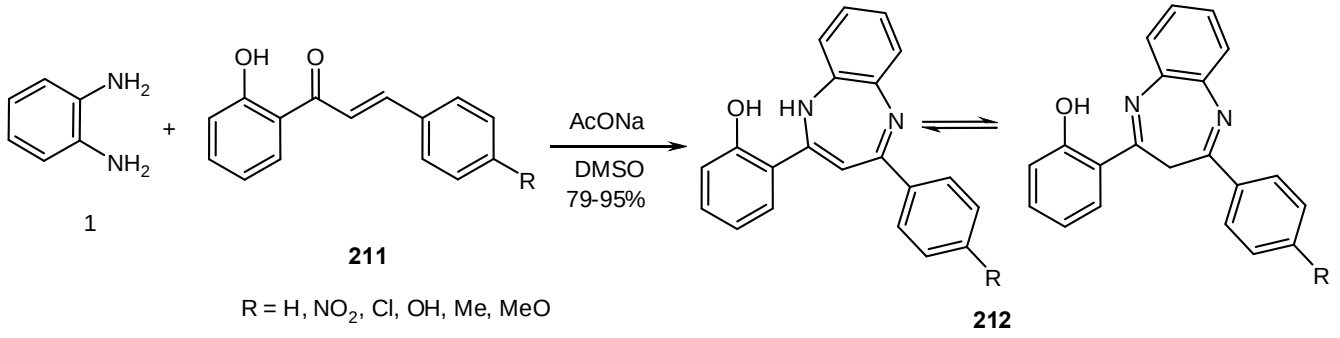
A convenient, solvent free and green approach for novel 1,5-benzodiazepines was achieved from the irradiation of ethyl acetoacetate and aromatic aldehydes for a sufficient interval of time followed by addition of *o*-phenylinediamine **1**, which condenses with the intermediate and afforded the desired product **207** in 86-97% yields.[180]



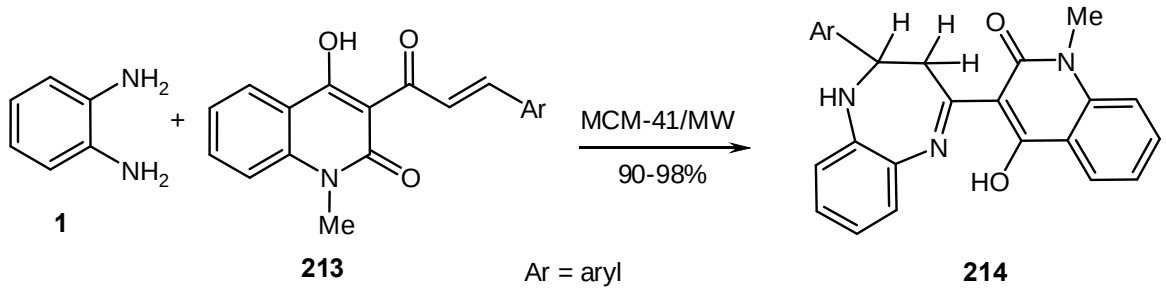
Treatment of **1** with 3-[2-oxo-2-aryl(hetaryl)ethylidene]-1*H*-indol-2-ones **208** gave 1,3-dihydrospiro[1,5-benzodiazepine-2,3'-indole]-2'(1'*H*)-one **209** together with 3-[2-(2-aminophenylimino)-2-arylethylidene]-2,3-dihydro-1*H*-indol-2-ones **210**.[181]



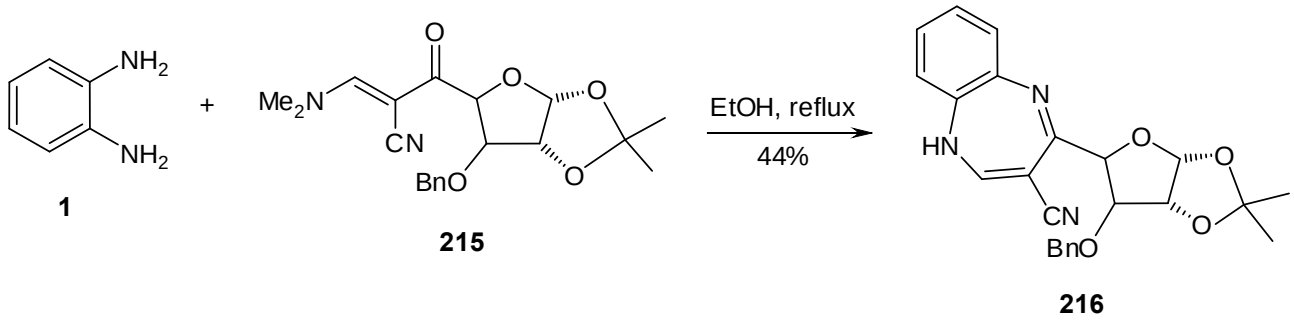
Reaction of *o*-phenylenediamine **1** with chalcones **211**, in ethanol under strongly acidic conditions or DMSO containing fused sodium acetate, gave 2-(2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-4-yl)-phenols **212**.[182]



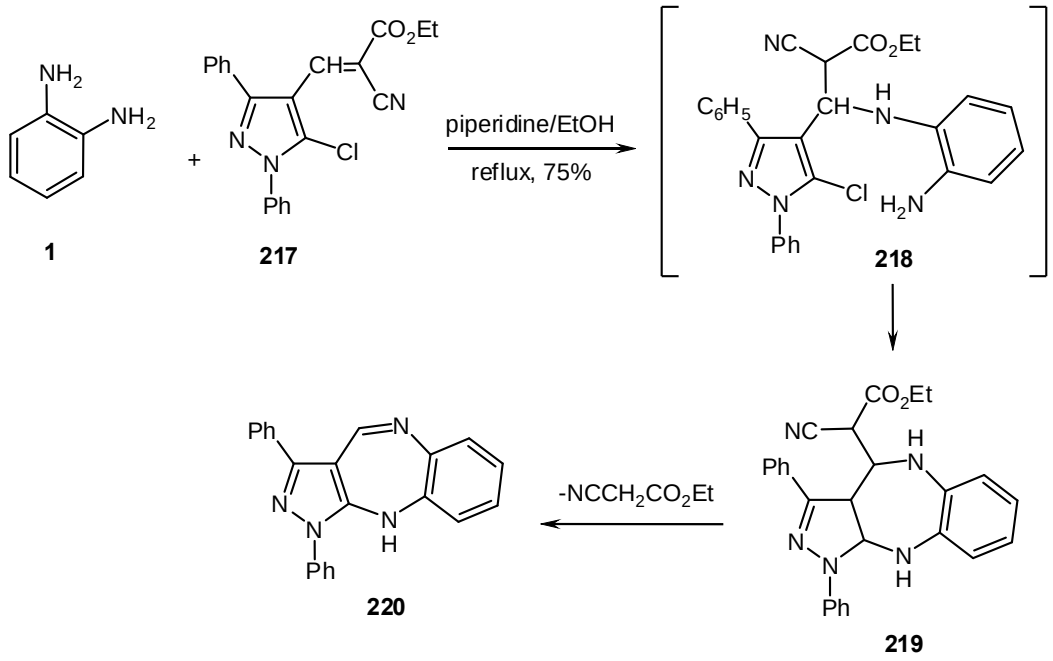
1,5-Benzodiazepines **214** were synthesized in excellent yields by treating **1** with 1*H*-2-oxo-4-hydroxy-quinolin-3-yl-3-aryl-2-propenones **213** using catalytic amount of mesoporous zeolite MCM-41.[183]



Reaction of **1** with enaminone **215** gave 4-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-*d*-xylotetrafuranos-4-yl)-1*H*-benzo[*b*][1,5]diazepine-3-carbonitrile **216**.[184]

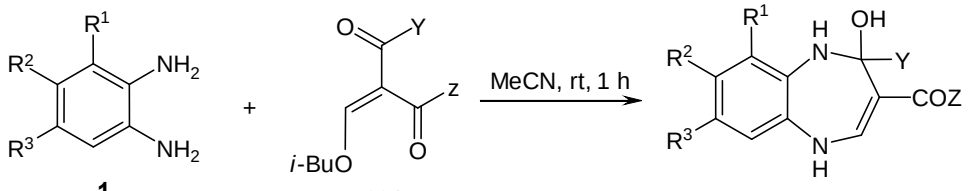


Condensation of **1** with ethyl 3-(5-chloro-1,3-diphenylpyrazole-4-methylidene)-2-cyanoacrylate **217** in boiling ethanol containing catalytic amount of piperidine afforded pyrazolo[3,4-*b*][1,5]benzodiazepine derivative **220** *via* the non isolable intermediates **218** and **219**.[185]



1 **217** **218** **219** **220**

The reaction of 3-(isobutoxymethylene)-pentane-2,4-dione derivatives **221** with various benzene-1,2-diamines gave 2,5-dihydro-2-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,5]diazepines **222** in moderate to high yields under very mild conditions.[186]

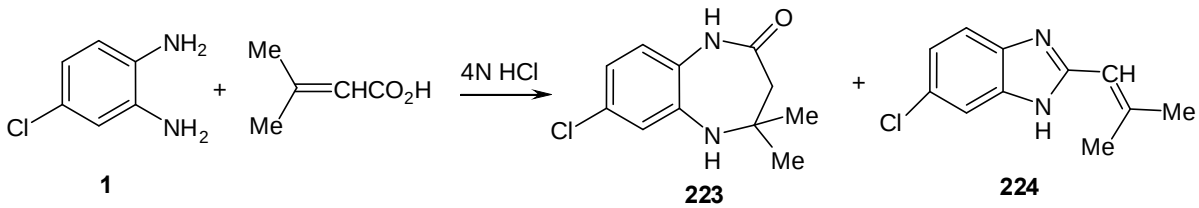


1 **221** **222**

R^1 = H, Me
R^2 = H, Me, Cl, NO_2, CO_2H, COPh, CO_2Me
R^3 = H, Me, Cl

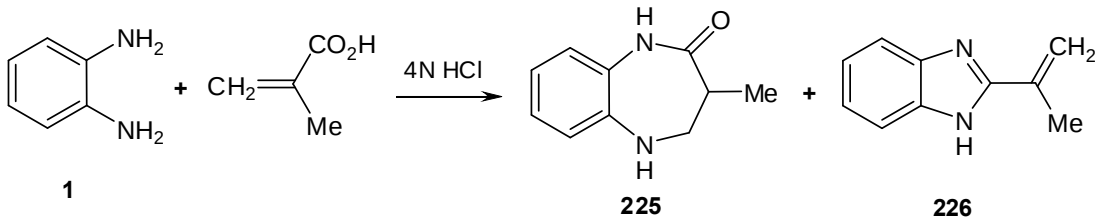
Y = CF_3, CF_2Cl, CF_2CF_3
Z = CCl_3, CF_3, CF_2Cl, CF_2CF_3

Methyl crotonic acid did not undergo any reaction with diamine **1** using 1:1 molar ratios of the reactants in 4*N* HCl under reflux. However, when the amount of methyl crotonic acid was doubled in the same experiment, the reaction occurred after thirteen hours of reflux and gave two pure crystalline products which were identified as 5-chloro-2-(1-isobutenyl)benzimidazole **223** and 7-chloro-4,4-dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one **224**.[187]



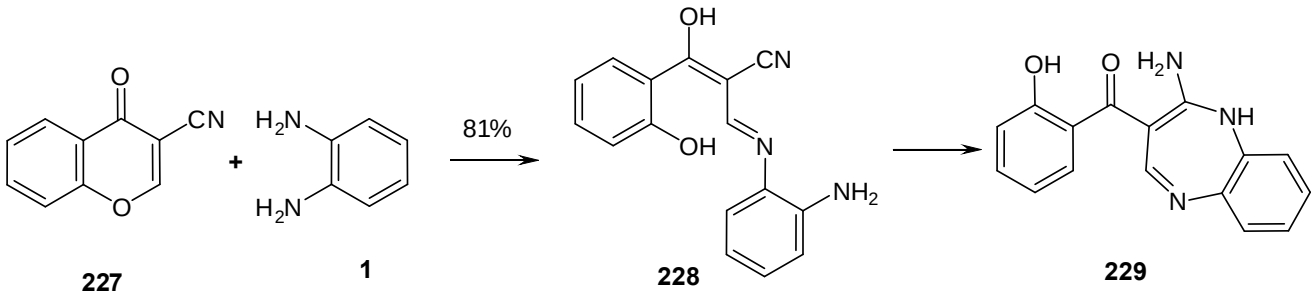
1 **223** 26% **224** 8%

Reaction of **1** and methacrylic acid gave 2-(2'-propenyl)benzimidazole **225** and 3-methyl-1,2,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one **226**.[187]



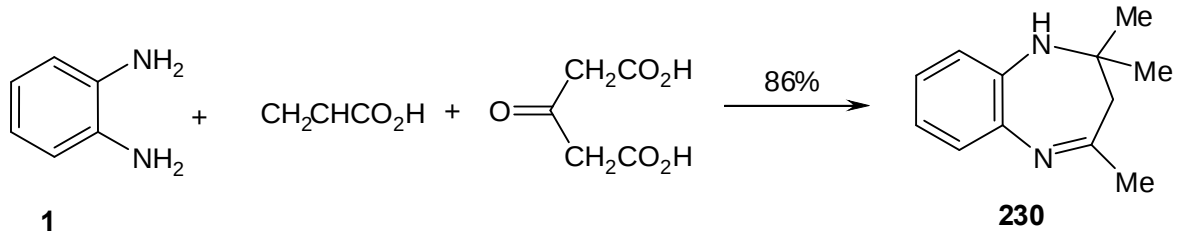
1 **225** **226**

Reaction of **1** with 3-cyanochromone **227** gave (2-amino-1*H*-benzo[*b*][1,5]diazepin-3-yl)-(2-hydroxyphenyl)methanone **229** *via* the non isolable intermediate 2-[(2-aminophenylimino)-methyl]-3-hydroxy-3-(2-hydroxyphenyl) acrylonitrile **228**.[188]



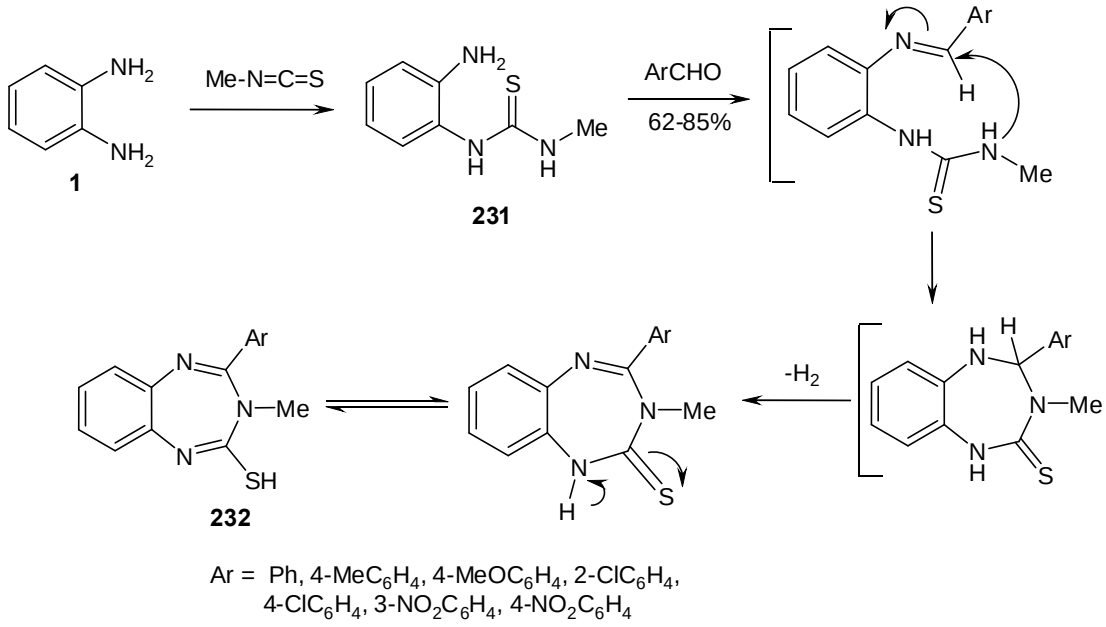
227 **1** **228** **229**

2,4,4-Trimethyl-3*H*-5-hydro-1,5-benzodiazepine **230** was obtained in 86% yield from the reaction of *o*-phenylenediamine **1** with acrylic acid at room temperature in the presence of acetonedicarboxylic acid (or acetone) as a catalyst.[189]

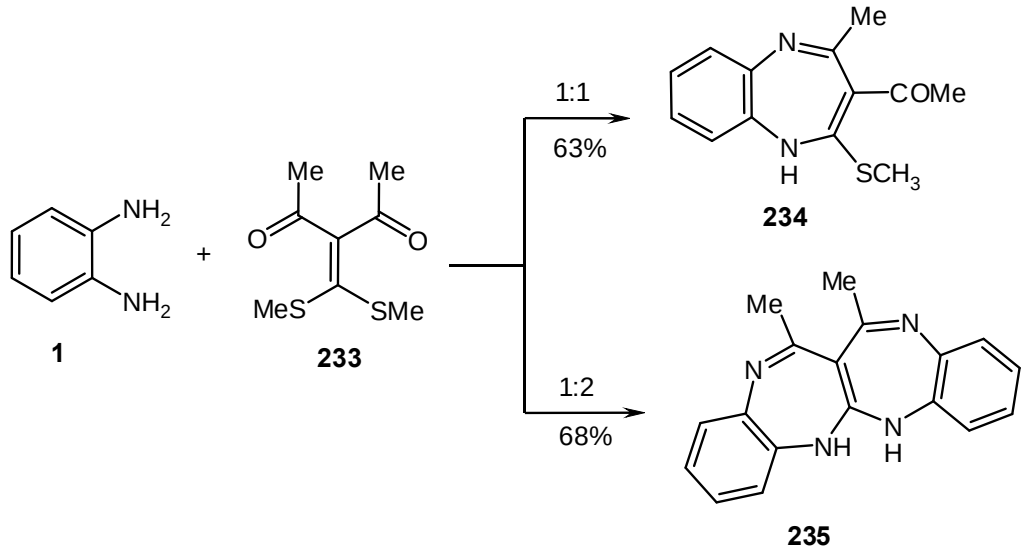


1 **230**

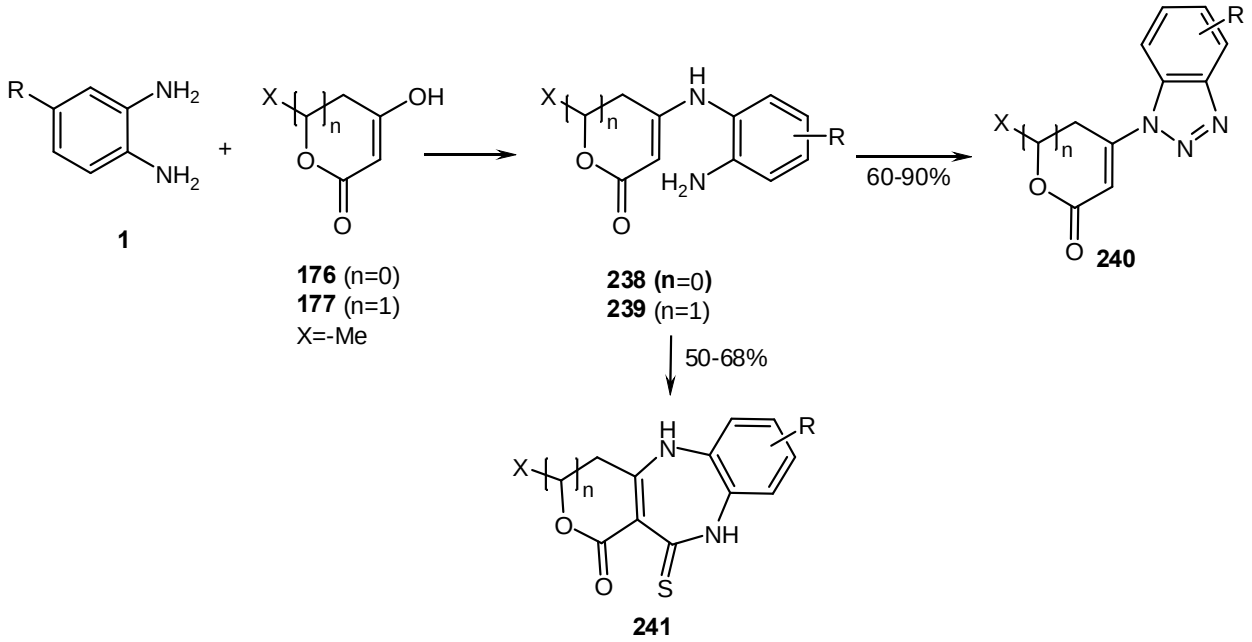
Reaction of **1** with methyl isothiocyanate gave *N*-(2-aminophenyl)-*N*'-methyl thiourea **231** which reacted with aromatic aldehydes in acetic acid to give 3-*N*-methyl-4-(substituted phenyl)-1,3,5-benzotriazepine-2-thiols **232** with 62-85% yield.[190]



Reaction of 2-acetyl-2-oxopropylidene *S*,*S*-acetal **233** with *o*-phenylenediamine **1**, in 1:1 or 1:2 molar ratios in refluxing acetonitrile gave benzdiazepene **234**, as well as benzodiazepino[5,6-*e*]benzodiazepine derivatives **235**, respectively.[191]



Reaction of **1** with tetronic acid **236** or pyrone **177** led to binucleophilic enaminone intermediates **238** and **239**, respectively. Under diazotization reaction, these two enaminones cyclized rapidly with good yields to generate benzotriazoles **240**. On the other hand, when enaminones **238** and **239** were allowed to react with carbon disulfide in dimethylsulfoxide in the presence of a catalytic amount of pyridine gave novel condensed benzobenzodiazepin-2-thiones **241** fused to dihydropyrone or tetronic acid moieties.[192]



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Magdy Ahmed Mohamed Ibrahim was born in Cairo, Egypt, in 1977. He received his B.Sc. degree in physics and chemistry (1999) and his M.Sc. degree in organic chemistry (2004). Also, he received his Ph.D. degree (2007) from the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. His research is focused on the synthesis of new heterocyclic compounds containing chromone, pyridine, quinolin-2(1*H*)-one and 1,2,4-triazine with expected biological activity. In addition, he published several review articles in the chemistry of chromone, 1,2,4-triazine and quinolin-2(1*H*)-one.