Recent advances on the synthesis of azoles, azines and azepines fused to benzimidazole

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Abstract
The current review article represents a survey covering the literatures on azoles, azines and azepines fused to the a face of a benzimidazole moiety since 1980. Synthetic routes leading to benzimidazole fused with different ring systems; five-, six-, and seven-membered heterocyclic rings, containing one-, two- and three-heteroatoms were reported utilizing simple reactive benzimidazole synthons

Keywords: Benzimidazoles, triheterocycles, synthesis, azoles, azines, azepines

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1. Introduction

In the recent years, many biologically active fused benzimidazoles exhibiting interesting medicinal properties for the potential treatment of human diseases have been disclosed. For example, pyrrolobenzimidazoles,1-5 thiazolobenzimidazoles,6 pyrimidobenzimidazoles,7 and pyridobenzimidazoles8 were reported as potent antitumor agents. Furthermore, pyrrolobenzimidazoles,9 pyridobenzimidazoles,10 were found to be useful in treating central nervous system disorder. Pyridobenzimidazoles have also anxiolytic activity in humans,11-13 and pyrimidobenzimidazoles were anti-rheumatic agents.14 Also, 1,2,4-triazinobenzimidazoles were found to be aldose reductase inhibitors15 and to possess antimicrobial activity.16

There are a large number of pharmacologically interesting benzimidazole molecules fused to a five membered rings containing one heteroatom (pyrrolobenzimidazoles), two heteroatoms (pyrazolo-, imidazo-, oxazolo- and thiazolo-benzimidazoles) and three heteroatoms (triazolo-, thia diazolo- and oxadiazolo-benzimidazoles). Also, several benzimidazole moieties are fused to a six membered ring containing one heteroatom (pyridobenzimidazoles), two heteroatoms (pyrimido-, pyrazino-, thiazino-benzimidazoles) and three heteroatoms (triazinobenzimidazoles). Seven membered rings fused to benzimidazole (azepino-, diazepino-, triazepino- and thiazepino- benzimidazoles) are also well known.

As a continuation of our very recently published review article concerning the synthesis of benzimidazole-based polyheterocycles,17 herein we wish to publish our current review reporting the numerous publications declaring various synthetic routes to the benzimidazole-based triheterocycles that are mentioned above, since 1980, utilizing simple reactive benzimidazole synthons.

2. Synthesis of Azolo-fused-benzimidazoles

2.1. Pyrrolobenzimidazoles

3-Hydroxypyrrolo[1,2-α]benzimidazoles 3 were prepared by Michael-type addition of benzimidazole 1 to α,β-unsaturated carbonyl compounds 2 in refluxing dioxane in the presence of Et₃N (Scheme 1).18
**Scheme 1**

Treatment of 1-benzyl-1H-benzimidazole 4 with phenacyl bromide 5 gave the benzimidazolium salt 6. An oxidant promoted 1,3-dipolar cycloaddition of 6 to activated alkenes was developed for the preparation of 4H-pyrrolo[1,2-a]benzimidazole derivatives 7 in moderate yields under mild conditions. In the presence of a suitable oxidant, alkenes could be used as dipolarophiles successfully. Moreover, CrO₃/Et₃N has been proved to be a more effective dehydrogenating reagent than MnO₂ (Scheme 2).

**Scheme 2**

Reaction of 1-benzyl-1H-benzimidazole 4 with 2-(bromoacetyl)thiophene 8 gave the benzimidazolium salt 9 which on treatment with activated acetylenes 10 resulted in the formation of thenoylpyrrolo[1,2-a]benzimidazole derivatives 11 (Scheme 3).

**Scheme 3**

Alkylation of 2-benzylbenzimidazole 12 with propargyl bromide 13 in refluxing ethanol gave
1-(2-propynyl)-2-benzylbenzimidazole 14 which upon treatment with KOH in THF at 20 °C gave pyrrolo[1,2-\(a\)]benzimidazole derivative 15 in 81% yield. Treatment of 14 with MeI in ethanolic KOH gave 2-methylpyrrolo[1,2-\(a\)]benzimidazole 16 (Scheme 4).\textsuperscript{21}

Scheme 4

Fusion of 2-cyclopropylbenzimidazoles 17 with ammonium iodide at 150 °C with no solvent resulted in the formation of a mixture of the 2,3-dihydro-1\(H\)-pyrrolo[1,2-\(a\)]benzimidazoles 18 and 19. Yield and reaction time was greatly affected by the type of electron withdrawing and electron donating groups R\textsuperscript{1} and R\textsuperscript{2} (Scheme 5).\textsuperscript{22}

Scheme 5

The reaction of 2-benzyl-1-dialkylaminoethylbenzimidazoles 20 with phenacyl bromides 5 in refluxing acetone gave the quaternary salts 21 in high yields. Cyclization of the salts 21 proceeded smoothly upon boiling in water in the presence of sodium carbonate to give the pyrrolo[1,2-\(a\)]benzimidazoles 22 (Scheme 6).\textsuperscript{23}
Rhodium-catalyzed microwave irradiation of N-allyl benzimidazoles 23 using 5 mol% of [RhCl(coe)$_2$]$_2$ (coe = cis-cyclooctene) in the presence of tricyclohexylphosphine hydrochloride (HCIPCy$_3$) gave the corresponding dihydropyrrolobenzimidazoles 24 in moderate to excellent yields after 20 min (Scheme 7).\(^{24}\)

Cyclization of the amidine 25 with strong base such as sodium methoxide in DMF at 150 °C was reported to give the pyrrolo[1,2-\(a\)]benzimidazole 26 in 75% yield via loss of HF (Scheme 8).\(^{25}\)

Pyrrolo[1,2-\(a\)]benzimidazolium salt 28 was prepared in high yield and selectivity from the catalytic ring closing of 1-(3-butenyl)-3-methylbenzimidazolium bromide 27 using nickel dicyclooctadiene, Ni(COD)$_2$, as catalyst in DMF at 70 °C (Scheme 9).\(^{26}\) The reaction proceeded...
through azolium, C2–H, oxidative addition to Ni(0) followed by intramolecular insertion of the N-alkenyl double bond into the Ni hydride to give an intramolecularly bound carbene–Ni–alkyl intermediate A. Reductive elimination of the linked carbene and alkyl groups B gave the fused-ring azolium product 28 and regenerated the Ni(0) catalyst. The catalyst was formed in situ from Ni(COD)2 and ligand L (where L = IMes, SMes, PPh3, PCy3, PCy2(biphenyl), P(t-Bu)3 in DMF.26

Scheme 9

The N-arylpyrrolidine derivative 29 was cyclized to pyrrolo[1,2-α]benzimidazole 26 in low yield by heating in formic acid in the presence of hydrogen peroxide at 70 °C (Scheme 10).27

R = Me

Scheme 10

Treatment of 3-(N-pyrrolidinyl)-4-nitrotoluene 30 with ZnCl2/AC2O followed by treatment with a mixture of AC2O, dimethylaminopyridine (DMAP) and Et3N gave pyrrolo[1,2-α]benzimidazole 31 in 53% yield (Scheme 11).28,29

Scheme 11

Cyclocondensation of 2-(1H-benzimidazol-2-yl)-4-chloro-3-oxobutanenitrile 32 in refluxing dioxane in the presence of triethylamine gave the pyrrolo[1,2-α]benzimidazol-2-one derivative 33 (Scheme 12).30
Scheme 12

1-Carboxymethylbenzimidazolium chlorides 34 were converted into 4-methyl-4H-pyrrolo[1,2-α]benzimidazol-2(1H)-one derivatives 35 in fair yields by treating 34 with \(N, N'\)-carbonyldiimidazole (CDI) in DMF at room temperature followed by addition of Et\(_3\)N and heating the mixture at 70 °C for 5 h (Scheme 13).\(^{31}\)

\[
\begin{align*}
1) & \text{CDI, DMF, rt} \\
2) & \text{Et}_3\text{N, 70 °C} \\
\text{R}^1 = \text{H; } & \text{R}^1 = \text{H, R}^2 = \text{Me; } \text{R}^1 = \text{Me, R}^2 = \text{H; } \text{R}^1 = \text{R}^2 = \text{Me}
\end{align*}
\]

Scheme 13

Reaction of \(o\)-phenylenediamines 36 with maleic anhydrides 37 gave \(N\)-(\(o\)-aminophenyl)-maleimides 38 which were cyclized to give pyrrolobenzimidazoles 39 (Scheme 14).\(^{32}\)

\[
\begin{align*}
\text{R} = \text{H, NO}_2; & \text{R}^1 = \text{H, Cl, Me} \\
\text{R}^2 = \text{R}^3 = \text{Me; } & \text{R}_2 = \text{OMe, R}_3 = \text{Ph}
\end{align*}
\]

Scheme 14

Cyclocondensation of \(γ\)-lactones 40 with \(o\)-phenylenediamine 36 in refluxing aq. HCl gave the benzimidazoles 41 which were cyclized by thionyl chloride in DMF to give pyrrolobenzimidazoles 42. Pyrrolobenzimidazoles 44 were prepared by condensing \(o\)-phenylenediamine with 2-alkyl-4-oxopentanoic acid 43 at 180-200 °C (Scheme 15).\(^{33}\)
Scheme 15

Reaction of benzimidazolium salts 45 with aq. NaHCO₃ afforded the pyrrolobenzimidazole derivatives 46 (Scheme 16).³⁴

Scheme 16

Inaba et al. reported the ring-opening reaction of cyclopropane dicarboxylate 48 on heating with 2-chlorobenzimidazole 47 in N-methylpyrrolidinone (NMP) at 120 °C using sodium hydride to provide the pyrrolo[1,2-a]benzimidazole derivative 49 in 56% yield (Scheme 17).³⁵

Scheme 17

Reaction of 1-but-3-enylbenzimidazole 50 with xanthates 51 using 10-camphorsulfonic acid (CSA) in dichloromethane (DCM) under reflux condition gave the pyrrolo[1,2-a]benzimidazole derivatives 52 in 37-57% yields. The reaction proceeded via radical chain mechanism initiated by a small amount of lauroyl peroxide to give 52 (Scheme 18).³⁶
1,3-Dipolar cycloaddition reaction between fluorinated vinyl tosylate and the benzimidazolium salts 53 afforded 4H-pyrrolo[1,2-a]benzimidazoles 55 (Y = H) in 10-68% yields via elimination of TsOH and HF molecules from the 3+2 cycloadduct intermediates 54 (Scheme 19). Benzimidazolium bromide 53 reacted also with 1-chloro-1,2,2-trifluoroethene to produce 55 (Y = F) in 45-80% yields via elimination of HCl and HF molecules from the intermediate 54 (Scheme 19).

Condensation of ethyl 2-thienoylpyruvate 56 with o-phenylenediamine 36 in glacial acetic acid under reflux gave the corresponding 2-[(2-thienoyl)acetyl]benzimidazole 57. Pyrrolo[1,2-a]benzimidazole derivative 58 was prepared in 58% via heating of compound 57 with phosphorus oxychloride on a water bath (Scheme 20).
Reaction of 2-cyanomethylbenzimidazole 59 with hydrazonoyl halides 60 in the presence of triethylamine apparently led to the formation of pyrrolo[1,2-a]benzimidazoles 61 via the initial exocyclic C-attack (Scheme 21). However, later Awadallah et al. repeated the above reaction and they found that the product was 3-arylazo-2-methylpyrrolo[1,2-a]benzimidazoles 62 rather than 2-arylazo-3-methylpyrrolo[1,2-a]benzimidazoles 61 based on X-ray crystallography via the initial endocyclic N-attack (Scheme 21).

Scheme 21

Pyrrolo[1,2-a]benzimidazol-2-amine derivative 64 was prepared in a moderate yield by reaction of 2-cyanomethylbenzimidazole 59 with oxalbis(p-tolylimidoyl) dichloride 63 in toluene in the presence of triethylamine at room temperature (Scheme 22). Furthermore, treatment of 2-methylbenzimidazole 65 with n-butyl lithium in THF at 0 °C followed by addition of 63 resulted in the formation of 1-arylimino-1H-pyrrolo[1,2-a]benzimidazole-2-amines 66 in moderate yields (Scheme 22).

Scheme 22

When a mixture of the benzimidazolium bromide 53 and methyl acrylate in DMF in the presence of triethylamine was treated with chromium trioxide, the 4-methylpyrrolo[1,2-a]benzimidazole-1,3-dicarboxylate 67 was isolated in a good yield (Scheme 23).
Scheme 23

Heating the benzimidazolium salts 68 with aqueous sodium carbonate in the presence of sodium bisulfite gave 2-phenylpyrrolo[1,2-a]benzimidazoles 69 in low yields (Scheme 24).^45

Scheme 24

Reaction of benzimidazole-2-carboxaldehyde 70 with trans-1-amino-2,3-diphenylaziridine 71 gave 1-[1-allyl-1H-benzimidazol-2-yl-methylidene]-2,3-diphenyl-1-aziridinamine 72 which underwent thermolysis facilitated intramolecular 1,3-dipolar cycloaddition followed by loss of N2 to give the cyclopropapyrrolo[1,2-a]benzimidazole 73 (Scheme 25) in excellent yield.^46

Scheme 25

2.2. Pyrazolobenzimidazoles

1-Amino-3-alkylbenzimidazolethione 74 was transformed to 1-amino-3-alkyl-2-(methylthio)benzimidazolium salt 75 upon treatment with methyl iodide. The latter salt reacted with different active methylenes to give the corresponding 2-substituted methylene-benzimidazoline derivatives 76 which underwent base or acid catalyzed cyclization to give 2-aminopyrazolo[1,5-a]benzimidazoles 77 and pyrazolo[1,5-a]benzimidazol-2-ones 78, respectively. Compounds 78 underwent N- and O-methylation when treated with methyl iodide under basic condition to give the corresponding pyrazolo[1,5-a]benzimidazoles 79 and 80 (Scheme 26).^47
Acetylation of 1-amino-2-methylbenzimidazole 81 with acetic anhydride gave the N,N-diacylated derivative 82. The latter was alkylated with alkyl iodide to give benzimidazolium salts 83 which were cyclized with acetic anhydride to give pyrazolobenzimidazoles 85 in good yields. Pyrazolobenzimidazoles 85 were alternatively obtained via alkylation of 1-amino-2-methylbenzimidazole 81 with alkyl iodide to give benzimidazolium salts 84 followed by reflux in acetic anhydride (Scheme 27). 48 3-(α-Bromoacetyl)pyrazolo[1,5-a]benzimidazole 86 was obtained by brominating 3-acetylpyrazolo[1,5-a]benzimidazoles 85 with bromine in AcOH (Scheme 27).
Treatment of 1-amino-2-methylbenzimidazolium chlorides **87** with acetic anhydride in the presence of potassium carbonate under reflux afforded a mixture of pyrazolo[1,5-\(a\)]benzimidazoles **88** and pyrrolo[1,2-\(a\)]benzimidazoles **89** (Scheme 28).\(^{50}\)

**Scheme 28**

Pyrazolo[1,5-\(a\)]benzimidazoles **92** were prepared in moderate yields by reacting 1-aminobenzimidazole derivative **90** with phenacyl bromides **5** to form the thiadiazino- and selenadiazino-benzimidazoles **91**, which underwent ring contraction to give **92** (Scheme 29).\(^{51,52}\)

**Scheme 29**

Ring contraction of 1,2,4-triazepino[2,3-\(a\)]benzimidazol-4-ones **93** in acetic anhydride afforded pyrazolo[1,5-\(a\)]benzimidazole derivatives **96** in low to high yields probably according to the mechanism depicted in Scheme 30.\(^{53}\)

**Scheme 30**
Free radical oxidation of anilinopyrazoles 97 by dibenzoyl peroxide or lead(IV) oxide resulted in the formation of the pyrazolo[1,5-a]benzimidazoles 98 in moderate yields (Scheme 31).54

![Scheme 31](image)

Scheme 31

4H-Pyrazolo[1,5-a]benzimidazoles 100 were prepared in moderate to good yields by hydrogenation of the hydrazones 99 in acetic acid containing Pt-metal (Scheme 32).55

![Scheme 32](image)

Scheme 32

When 5-amino-l-(α-chlorophenyl)pyrazoles 101 were heated with copper(II) oxide in DMF and anhydrous K2CO3, the 4H-pyrazolo[1,5-a]benzimidazoles 102 were formed. Treatment of 102 (R = CN) with sodium azide gave 3-(tetrazol-5'-yl)-4H-pyrazolo[1,5-a]benzimidazole 103. Basic hydrolysis of 102 (R = CO2Et) led to 4H-pyrazolo[1,5-a]benzimidazole-3-carboxylic acid 104. When 104 was heated above its melting point in vacuo, it smoothly decarboxylated to give the parent 4H-pyrazolo[1,5-a]benzimidazole 105 (Scheme 33).56

![Scheme 33](image)
Flash vacuum pyrolysis (FVP) of 1-(2-azidophenyl)pyrazoles 106 or photolysis at 254 nm in ethanol and diethylamine gave the pyrazolo[1,5-α]benzimidazoles 105 in reasonable yields via the intermediate 2-(1-pyrazolyl)phenylnitrene 107 (Scheme 34).57,58

Scheme 34

The hydrazine derivative 108 was cyclocondensed with ethyl 3-ethoxy-3-iminopropanoate hydrochloride 109 to give the ethoxypyrazolinone derivative 110 which was hydrogenated in acetic acid in the presence of Pd/C and then cyclized by refluxing in HOAc after removal of Pd/C to give the pyrazolobenzimidazole derivative 111 (Scheme 35).59

Scheme 35

2.3. Imidazobenzimidazoles

Imidazo[1,5-α]benzimidazole derivative 113 was prepared by reaction of 2-aminomethylbenzimidazole 112 with acetic anhydride (Scheme 36).60

Scheme 36
Reaction of 1,2-diaminobenzimidazole 114 with one equivalent of 1-phenyl-2-bromo-3-phenylpropanone 115 in methanol led to the formation of 2-phenyl-3-benzyl-9-aminoimidazo[1,2-a]benzimidazole 116 (Scheme 37).61

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{H} & \quad \text{Ph} \\
114 & \quad 115 \\
\rightarrow & \quad 116
\end{align*}
\]

Scheme 37

Treatment of 2-aminobenzimidazole 117 with ethyl bromopyruvate 118 in THF at room temperature followed by reflux in ethanol gave the imidazo[1,2-a]benzimidazole 119 in low yield (Scheme 38).62

\[
\begin{align*}
\text{N} & \quad \text{NH} \\
\text{H} & \quad \text{CO}_2\text{Et} \\
117 & \quad 118 \\
\rightarrow & \quad 119
\end{align*}
\]

Scheme 38

2-(Chloromethyl)imidazo[1,2-a]benzimidazole 122 was prepared by condensation of 1-methyl-2-aminobenzimidazole 120 with 1,3-dichloroacetone 121 (Scheme 39).63

\[
\begin{align*}
\text{N} & \quad \text{NH} \\
\text{Me} & \quad \text{Cl} \\
120 & \quad 121 \\
\rightarrow & \quad 122
\end{align*}
\]

Scheme 39

Treatment of 2-aminobenzimidazole 117 with 2-bromoacetaldehyde diethylacetal in a solution of NaOMe in MeOH under reflux gave 2-amino-1-(2,2-diethoxyethyl)benzimidazole 123. Refluxing the latter compound 123 in HCl afforded imidazo[1,2-a]benzimidazole 124 which on treatment with dimethyl sulfate in aq. NaOH gave a mixture of 1-methylimidazo[1,2-a]benzimidazole 125 and 9-methylimidazo[1,2-a]benzimidazole 126 (Scheme 40).64
Scheme 40

When 2-aminobenzimidazole 117 was refluxed with 2-bromoacetylnaphthalene or 3-bromoacetylpyrazole derivatives 127 or 128 in ethanol, it afforded the 1H-imidazo[1,2-a]benzimidazole derivatives 129 and 130, respectively, in good yields (Scheme 41).65,66

Scheme 41

Photolysis of 1-(4,5-dihydro-1H-imidazol-2-yl)benzotriazole 131 in acetonitrile at 254 nm for 18 h gave dihydroimidazo[1,2-a]benzimidazole 133 in good yield. The reaction took place via the diradical intermediate 132 (Scheme 42).67

Scheme 42

Treatment of the diimidoyl dichlorides 63 with 2-aminobenzimidazole 117 in refluxing THF in the presence of Et₃N resulted in the formation of the 3H-imidazo[1,2-a]benzimidazol-2-
amines 134 in good yield. Acylation of the latter 134 (Ar = 4-tolyl) with acetyl chloride in the presence NaN(SiMe₃)₂ at low temperature gave 9-acetyl-3H-imidazo[1,2-a]benzimidazole 135 in 53% yield (Scheme 43). ⁶⁸

Scheme 43

2-Aminobenzimidazolium bromides 137 were formed by reaction of o-(N-aryl)phenylenediamines 136 with cyanogen bromide in ethanol at 150°C, followed by alkylation with ethyl bromoacetate in acetone at reflux. Condensation with acid anhydrides along with their respective sodium salts afforded the imidazo[1,2-a]benzimidazole esters 138 (Scheme 44). ⁶⁹

Scheme 44

Treatment of hydrazonoyl bromides 139 with 2-aminobenzimidazole 117 in refluxing ethanol furnished 3-arylazo-1H-imidazo[1,2-a]benzimidazoles 140 (Scheme 45). ⁷⁰

Scheme 45
2-Azidomethylbenzimidazole 141 reacted with benzoyl chlorides and gave the benzoyl(azidomethyl)benzimidazoles 142 which reacted with tributylphosphine to give the corresponding 3-aryl-9H-imidazo[1,2-a]benzimidazoles 143 (Scheme 46).\(^{71}\)

Scheme 46

2,9-Disubstituted imidazo[1,2-a]benzimidazoles 145 were obtained regioselectively in good yields by heating a mixture of 2-aminobenzimidazole 117 and α-tosyloxy ketones 144 in acetic acid (Scheme 47).\(^{72}\)

Scheme 47

2.4. Oxazolobenzimidazoles
Reaction of 2-aminooxazoles 146 with p-benzoquinone 147 in acetic acid at 40-50°C for one hour gave the corresponding 6-hydroxyoxazolo[3,2-a]benzimidazoles 148 in moderate yields according to the mechanism shown in Scheme 48.\(^ {73}\)

Scheme 48
Benzimidazo[2,1-b]benzoxazole 150 was prepared photolytically at 360 nm from 1-(2-benzoxazolyl)benzotriazole 149 (Scheme 49).\textsuperscript{74}

Scheme 49

3-Cyanomethylene-1,3-oxazolo[3,2-a]benzimidazole 153 was obtained by condensation of 2-alkylthiobenzimidazoles 151 with 4-hydroxy-4-methylpent-2-ynenitrile 152 in acetonitrile containing LiOH (Scheme 50).\textsuperscript{75}

Scheme 50

2,3-Dihydrooxazolo[3,2-a]benzimidazole derivatives 153 were also obtained by heating 2-aminobenzimidazoles 117 with 4-hydroxy-2-alkynenitrile derivatives 152 in DMF probably according to the mechanism illustrated in Scheme 51.\textsuperscript{76}

Scheme 51
1-Substituted benzimidazoles 156 were readily annulated regio- and stereoselectively when treated with α,β-acetylenic-γ-hydroxy nitrile 152 under mild conditions, at 20-25°C without catalyst and without solvent, to form 3-cyanomethylene-2,2-dimethyl-1,3-oxazolo[3,2-a]benzimidazoles 157 in excellent yields (Scheme 52).77

![Scheme 52](image)

The reaction of 2-chloro-1-phenacylbenzimidazole 158 with sodium benzoate, as a base, in DMF gave 2-phenyloxazolo[3,2-a]benzimidazole 159 in 76% yield (Scheme 53).78

![Scheme 53](image)

Condensation of o-phenylenediamine 36 with (S)-lactic acid in 4N HCl at reflux gave 2-(hydroxyethyl)benzimidazole 160 in 85% yield. Heating the latter compound 160 with benzaldehyde dimethyl acetal using a catalytic amount of p-toluenesulfonic acid gave the oxazolo[3,4-a]benzimidazole derivative 161 (Scheme 54).79,80

![Scheme 54](image)

Heating a mixture of 2-(hydroxymethyl)benzimidazole 162 and benzaldehyde dimethyl acetals 163 in dry toluene and a catalytic amount of p-toluenesulfonic acid for 48 h gave the oxazolo[3,4-a]benzimidazole derivatives 164 (Scheme 57).81
2.5. Thiazolobenzimidazoles

Reaction of hydrazonoyl bromides 139 with benzimidazole-2-thiol 165 in ethanolic triethylamine solution at reflux gave the thiazolo[3,2-\(\alpha\)]benzimidazoles 166 in good yields (Scheme 56).82-84

Benzimidazole-2-thiol 165 reacted similarly with bis-hydrazonoyl chlorides 167 in refluxing ethanol in the presence of triethylamine to give 2,3-bis(arylhydrazono)-2,3-dihydrothiazolo[3,2-\(\alpha\)]benzimidazoles 168 in high yields (Scheme 57).85,86

Refluxing of oxal-bis(arylimidoyl) dichlorides 63 in THF with benzimidazole-2-thiol 165 in the presence of Et\(_3\)N afforded the thiazolo[3,2-\(\alpha\)]benzimidazole derivatives 170 (Scheme 58).68
Scheme 58

When a mixture of benzimidazole-2-thiol 165 and the maleimide derivatives 171 was heated in acetic acid in the presence of sulfuric acid, it furnished the thiazolo[3,2-a]benzimidazole derivatives 173 in moderate yields via Michael-type addition followed by ring opening of the intermediate 172 (Scheme 59).87

Scheme 59

Thiazolo[3,4-a]benzimidazoles 175 were prepared by heating a mixture of o-phenylenediamine, 2-mercaptoacetic acid and the appropriate carbonyl compounds 174 in benzene under conventional reflux or microwave irradiation (Scheme 60).88-92

Scheme 60

Condensation of 2-mercaptobenzimidazoles 165 with chloroacetic acid and acetic anhydride gave the thiazolo[3,2-a]benzimidazol-3(2H)-ones 177 in good yields.93-96 Reaction of 165 with α-bromoketones 5 followed by polyphosphoric acid (PPA) yielded the thiazolo[3,2-
Condensation of \textbf{165} with 1,2-dibromoethane in ethanol yielded the thiazolo[3,2-\textit{a}]benzimidazole derivatives \textbf{180} (Scheme 61).\textsuperscript{103}

\begin{align*}
R = & \text{H, Me, Br, Cl, F, NO}_2; \\
\text{Ar} = & \text{Ph, 4-ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4
\end{align*}

\textbf{Scheme 61}

2,3-Dihydrothiazolo[3,2-\textit{a}]benzimidazole \textbf{182} was prepared by condensation of 2-(1,2-dibromoethyl)pyridine \textbf{181} in DMF with 2-mercaptobenzimidazole \textbf{165} (Scheme 62).\textsuperscript{104-106}

\begin{align*}
\text{DMF} 
\end{align*}

\textbf{Scheme 62}

Treatment of benzimidazole-2-thiol \textbf{165} with 1,3-dichloroacetone \textbf{121} gave 1-(2-benzimidazolylthio)-3-chloro-2-propanone hydrochloride \textbf{183}. Cyclization of \textbf{183} in sulfuric acid followed by basic work up provided 3-chloromethylthiazolo[3,2-\textit{a}] benzimidazole \textbf{184}.\textsuperscript{107-109} An efficient regioselective synthesis of 2-methoxycarbonylthiazolo[3,2-\textit{a}] benzimidazoles \textbf{186} from benzimidazole-2-thiols \textbf{165} and \(\alpha\)-chlorooaldehyde ester \textbf{185} was reported (Scheme 63).\textsuperscript{110}
Scheme 63

Treatment of 2-(allylthio)benzimidazole 187 with iodine in CHCl₃ and then with aqueous potassium hydroxide gave the thiazolo[3,2-α]benzimidazole 188 (Scheme 64).¹¹¹

Scheme 64

2-Methoxy-7-trifluoromethyl-2,3-dihydrothiazolo[3,2-α]benzimidazole 190 was prepared in 78% yield by the intermolecular cyclization of 1-(2,2-dimethoxyethyl)-2-mercaptobenzimidazole 189 using diethyl ether-boron trifluoride in dry dichloromethane (DCM) (Scheme 65).¹¹²

Scheme 65

The reaction between 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine 191 and mercaptoacetic acid under reflux gave the thiazolobenzimidazole derivative 193 (Scheme 66).¹¹³
Scheme 66

The reaction of benzimidazole-2-thiol 165 with bromomalononitrile 194 in cold ethanolic potassium hydroxide solution afforded 2-dicyanomethylthiobenzimidazole 195 which underwent cyclization when treated with ethanolic sodium acetate at reflux to give 3-aminothiazolo[3,2-a]benzimidazole-2-carbonitrile 196 (Scheme 67). Heating benzimidazole-2-thiol 165 with acetophenones in acetic acid afforded 2-benzimidazolylthioacetophenone derivatives 197 in very good yield. Reaction of 197 in acetic anhydride afforded 2-benzoyl-3-methylthiazolo[3,2-a]benzimidazoles 198 in high yield (Scheme 67).

Scheme 67

Treatment of thiazolinethione derivative 199 with iodomethane in anhydrous acetone at room temperature afforded quantitatively the thiazolium iodide 200. Heating 200 in methanol then treatment of the cold product with aqueous sodium bicarbonate gave 3-methylthiazolo[3,2-a]benzimidazole 201 in 100% yield. Alternatively, 3-methylthiazolo[3,2-a]benzimidazole 201 was obtained in 95% by refluxing 202 in ethanolic KOH solution (Scheme 68).
Scheme 68

Exposure of 1-alkynyl[4-(trifluoromethyl)phenyl](tetrafluoroborato)-\(\lambda^3\)-bromanes 203 to benzimidazole-2-thiol 165 in dichloromethane (DCM) at 0 °C under argon resulted in a domino Michael addition–carbene rearrangement–cyclization reaction to produce directly thiazolo[3,2-\(a\)]benzimidazoles 204 in high yields (Scheme 69).\(^1\) The epoxyphosphonate 205 reacted with 165 in refluxing toluene in the presence of tosyl alcohol to give the thiazolo[3,2-\(a\)]benzimidazole 206 in good yield (Scheme 69).\(^2\)

Scheme 69

2.6. Triazolobenzimidazoles

Heating benzimidazole-2-thiol 165 with hydrazonoyl halides 207 in chloroform in the presence of Et\(_3\)N gave the 1,2,4-triazolo[4,3-\(a\)]benzimidazoles 210 through the spiro intermediate 208 which underwent ring opening to yield the thiohydrazide 209 (Scheme 70).\(^3\)

Scheme 70
Similarly, the hydrazonoyl bromides 211 reacted with 2-methylthiobenzimidazole 212 in refluxing ethanol in the presence of triethylamine to give 1,2,4-triazolo[4,3-\(a\)]benzimidazole derivatives 213 (Scheme 71).\(^{70,84,123,124}\)

![Scheme 71](image)

3-Arylazo[1,2,4]triazolo[4,3-\(a\)]benzimidazoles 215 were prepared from the reaction of 3-chloro-1,5-diarylformazans 214 with 2-methylthiobenzimidazole 212 in refluxing chloroform and triethylamine (Scheme 72).\(^{125}\)

![Scheme 72](image)

Bis-hydrazonoyl chlorides 168 reacted with 2-methylthiobenzimidazole 212 in 1:2 molar ratio in refluxing ethanol in the presence of triethylamine to give 1,1'-diaryl-3,3'-bi-1,2,4-triazolo[4,5-\(a\)]benzimidazoles 216 (Scheme 73).\(^{85}\)

![Scheme 73](image)
Reaction of 2-aminobenzimidazole 117 with the hydrazonoyl chloride 139 gave 1-phenyl-3-acetyl-1,2,4-triazolo[4,3-α]benzimidazole 217 (Scheme 74).126

Scheme 74

1,3-Dipolar cycloaddition reaction of 1-acylbenzimidazoles 218 with two equivalents of hydrazonoyl chloride 207 in refluxing benzene and Et$_3$N gave the triazolobenzimidazole derivatives 219 (Scheme 75).127

Scheme 75

Reaction of 2-hydrazinobenzimidazole 220 with aromatic aldehydes 221 in refluxing ethanol afforded the corresponding aryldrazones 222 which, in turn, were cyclized upon heating in acetic acid to afford 3-aryl-9H-1,2,4-triazolo[4,3-α]benzimidazoles 223 (Scheme 76).128

Scheme 76

Heating 4-methyl-1,5-benzodiazepin-2-one 224 in xylene induced rearrangement into the 1-(α-methylvinyl)benzimidazole 225. Treatment of 225 with POCl$_3$ gave the 2-clorobenzimidazole derivative 226 which on reaction with sodium methoxide followed by hydrazine then triethyl ortho-acetate afforded the 9-(α-methylvinyl)triazolobenzimidazole 228 (Scheme 77).129
Scheme 77

Cyclisation of 2-hydrazinobenzimidazoles 220 with CS\textsubscript{2} and with triethyl orthoacetate gave the corresponding triazolobenzimidazoles 229 and 230, respectively (Scheme 78).\textsuperscript{130,131}

Scheme 78

Cyclization of 1,2-diaminobenzimidazolium salt 231, by boiling it in acetic anhydride in the presence of K\textsubscript{2}CO\textsubscript{3} gave the triazolobenzimidazole derivative 232 (Scheme 79).\textsuperscript{132}

Scheme 79

2.7. Thiadiazolobenzimidazoles

Reaction of (1-amino-1H-benzimidazol-2-yl)methanol 233 with thionyl chloride at reflux afforded 3-chlorobenzimidazo[1,2-c]-1,2,3-thiadiazolium chloride 234. Treatment of the salt 234 with sodium bicarbonate gave 3-chlorobenzimidazo[1,2-c]-1,2,3-thiadiazole 235 (Scheme 80).\textsuperscript{133-135}
Condensation of 2-amino-1,3,4-thiadiazoles 236 with \( p \)-benzoquinone 147 in acetic acid gave 6-hydroxy[1,3,4]thiadiazolo[3,2-\( \alpha \)]benzimidazoles 238 (Scheme 81).\(^{136}\)

Amidation of 2-mercaptobenzimidazole 165 by \( \text{tert} \)-butyl isocyanate followed by cyclization gave 2-\( \text{tert} \)-butyl-1,2,4-thiadiazolo[4,5-\( \alpha \)]benzimidazole 241 which on treatment with nitriles afforded the 1,2,4-thiadiazolo[4,5-\( \alpha \)]benzimidazoles 242 (Scheme 83).\(^{138-140}\)
Thermal rearrangement of 1-(1,2,3-thiadiazol-5-yl)-1,2,3-benzotriazoles 243 afforded zwitterionic [1,2,3]thiadiazolo[3,4-\(a\)]benzimidazol-8b-ium-4-ides 244 (Scheme 84).\(^{141}\)

1,2,4-Thiadiazolo[2,3-\(a\)]benzimidazole derivative 246 was prepared in high yield from the reaction of 1,2,4-thiadiazol-3-(2\(H\))-one 245 with 2-aminobenzimidazole 117 via rearrangement of the adduct A through hypervalent sulfur intermediates B (Scheme 85).\(^{142}\)

2.8. Oxadiazolobenzimidazoles
Refluxing 2-(1-methylbenzimidazolyl)carbonylhydroximoyl chloride 247 with 2-methylthio-benzimidazole 212 in ethanol and triethylamine gave the benzimidazo[1,2-\(d\)]-1,2,4-oxadiazole 248 (Scheme 86).\(^{143}\)
3. Synthesis of Azino-fused benzimidazoles

3.1. Pyridobenzimidazoles

Treatment of \(N\)-(2-azidophenyl)imines \(249\) with trimethylphosphine in toluene gave the phosphazenes \(250\). Reaction of \(250\) with ketenes led to the formation of the nonisolable ketenimines \(A\) which underwent [4+2] intramolecular cycloaddition to give the corresponding 3-aryl-3,4-dihydropyrido[1,2-\(a\)]benzimidazoles \(251\) (Scheme 87).\(^\text{144}\)

![Scheme 87](image)

Cyclocondensation and ring opening of triarylpypyrylium salts \(252\) with 2-benzimidazoleacetonitrile \(59\) gave pyrido[1,2-\(a\)]benzimidazole-4-carbonitriles \(253\) via loss of acetophenones probably according to the mechanism depicted in Scheme 88.\(^\text{145}\)

![Scheme 88](image)
Acylation of arylhydroxylamines 254 gave the N-acetyl derivatives 255, which on reaction with pyridine afforded the pyrido[1,2-\(a\)]benzimidazoles 256 (Scheme 89).\textsuperscript{146}

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{Cl} \\
\text{NH}_{\text{OH}} & \quad \text{Ac}_2\text{O} \\
254 & \quad \text{R = CN, CF}_3 \\
\text{O}_2\text{N} & \quad \text{Cl} \\
\text{N-OH} & \quad \text{Ac} \\
255 & \\
\text{pyridine} & \quad \text{NO}_2 \\
256 & \quad \sim 51\% \\
\end{align*}
\]

Scheme 89

Diels-Alder cycloaddition of 3-methylthiazolo[3,2-\(a\)]benzimidazole 201 with dimethyl acetylenedicarboxylate (DMAD) 257 in acetonitrile gave the pyrido[1,2-\(a\)]benzimidazole derivative 258 in 24% yield probably according to the mechanism outlined in Scheme 90.\textsuperscript{147}

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{Me} \\
258 & \quad \text{E} = \text{CO}_2\text{Et}
\end{align*}
\]

Scheme 90

Cyclization of benzylidene-1\(H\)-benzimidazol-2-ylacetonitriles 259 with activated acetonitriles in ethanol in the presence of piperidine gave pyridobenzimidazoles 260. Compound 259 reacted also with ethyl acetoacetate and with cyanoacetohydrazide to give the pyridobenzimidazole derivatives 261 and 262, respectively (Scheme 91).\textsuperscript{148-150}
**Scheme 91**

Michael-type addition of 2-benzimidazoleacetonitrile 59 to chalcone 263 in ethanol and piperidine led to the formation of pyridobenzimidazole 264. Also, analogous reaction of 59 with ethyl 2-cyanoacrylate derivative 265 yielded the pyridobenzimidazole derivative 266 in 75% yield (Scheme 92).\(^{151-153}\)

**Scheme 92**

Treatment of 2-benzimidazoleacetonitrile 59 and benzylidinemalononitriles 267 in acetonitrile containing piperidine under reflux afforded the polysubstituted pyrido[1,2-\(a\)]benzimidazoles 269 in moderate to good yields via cyclization followed by loss of hydrogen from the intermediate 268 (Scheme 93).\(^{154,155}\)

**Scheme 93**

\[Ar = \text{Ph, 4-MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{antipyrinyl} \]
Heating a mixture of 2-benzimidazoleacetonitrile 59 and β-aminocrotononitrile 270 in the presence of ammonium acetate at 130-140 °C afforded 1-amino-3-methylpyrido[1,2-\(a\)]benzimidazole-4-carbonitrile 271 (Scheme 94).\(^{156}\)

![Scheme 94](image)

Scheme 94

Treatment of 2-benzimidazoleacetonitrile 59 with the phenylacetylene derivative 272 produced the pyrido[1,2-\(a\)]benzimidazole-4-carbonitrile derivative 273 (Scheme 95).\(^{157}\)

![Scheme 95](image)

Scheme 95

The reaction of heteroaryl enamines 274, 275 and 276 with 2-benzimidazoleacetonitrile 59 was conducted in refluxing ethanol in the presence of piperidine to afford the corresponding pyrido[1,2-\(a\)]benzimidazoles 277-279 (Scheme 96).\(^{158-162}\)
Scheme 96

Pyrido[1,2-\textit{a}]benzimidazoles 282 and 283 were synthesized by reacting 2-benzimidazoleacetonitrile 59 with the enamines 280 and 281, respectively, in refluxing pyridine or ethanol/piperidine (Scheme 97).\textsuperscript{163-166}

Scheme 97

Reaction of methyl 2-benzoyl-3-dimethylaminopropenoate 284 with 2-benzimidazoleacetonitrile 59 in refluxing acetic acid in the presence of ammonium acetate gave methyl 4-cyano-3-phenylbenzimidazo[1,2-\textit{a}]pyridine-2-carboxylate 285.\textsuperscript{167} Heating a mixture of 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile 286 with 2-benzimidazoleacetonitrile 59 in ethanol and piperidine afforded the pyrido[1,2-\textit{a}]benzimidazole derivative 287 (Scheme 98).\textsuperscript{168}
Scheme 98

Treatment of 2-benzimidazoleacetonitrile 59 withcyanamide in the presence s-triazine gave the enamionitrile derivative 288 which reacted again with 59 to give pyridobenzimidazole derivative 270 (Scheme 99). 169

Scheme 99

Reaction of 6-aryl-3-cyano-4-methylthio-2H-pyran-2-ones 289 with 2-benzimidazoleacetonitrile 59 in DMF and KOH at 30 °C led to the formation of the pyrido[1,2-α]benzimidazole derivatives 290 in moderate yields (Scheme 100). 170

Scheme 100

3-Formylchromenes 291 underwent ring opening when heated with 2-benzimidazoleacetonitrile 59 in ethylene glycol at 200-210 °C to give the pyridobenzimidazoles 292 in good yields. 171 Similar ring transformation occurred on the reaction of 2-formylglycals 293 with 59 when heated in chlorobenzene/AcOH in the presence of piperidine, to furnish the pyridobenzimidazoles 294 in moderate yields (Scheme 101). 172, 173
Scheme 101

7,8-Difluoro-3-methyl-1-oxo-4-cyano-1H,5H-pyrido[1,2-a]benzimidazole 295A was obtained in high yield by heating a mixture of 2-benzimidazoleacetonitrile 59 with ethyl acetoacetate at 140 °C in the presence of ammonium acetate.174,175 Pyrido[1,2-a]benzimidazol-1-ones 295B (R¹ = H, Bz) were obtained by fusing 2-benzimidazoleacetonitrile 59 with ethyl β-aminocrotonates 296 in the presence of NH₄OAc at 140 °C (Scheme 102).176

Scheme 102

Graebe-Ullmann thermolysis of 5-(1-benzotriazolyl)-spiro[2H-imidazo[4,5-b]pyridine-2,1'-cyclohexane] 297 followed by treatment with Na₂S₂O₄ in aq. THF gave 1,2-diaminopyrido[1,2-a]benzimidazole 298 in low yield (Scheme 103).177

Scheme 103
Condensation of 2-benzimidazoleacetonitrile 59 with diethyl 2-oxosuccinate 299, in ethanol and DMF in the presence of piperidine produced pyrido[1,2-a]benzimidazole derivative 300. In addition, thermal condensation of 59 with diethyl ethoxymethyleneumalonate 301 in diphenyl ether at 240-250 °C gave the pyrido[1,2-a]benzimidazole 302 (Scheme 104). 178 3-Hydroxypyrido[1,2-a]benzimidazol-1-ones 304 were prepared by heating 2-benzimidazoleacetonitrile 59 with substituted malonate esters 303 (Scheme 104). 179,180

![Scheme 104](image)

Scheme 104

Treatment of 1-aminobenzimidazoles 305 with α,β-unsaturated ketones 306 in the presence of zinc chloride as catalyst in refluxing acetone gave the corresponding pyridobenzimidazoles 307 via an intramolecular rearrangement of the intermediates A (Scheme 105). 181

![Scheme 105](image)

Scheme 105

Formation of 2-benzamido-1-oxo-1H,5H-pyrido[1,2-a]benzimidazoles 310 was achieved by the neat heating of 2-benzimidazoleacetonitrile 59 or ethyl 2-benzimidazoleacetate 308 with 4-ethoxymethylene-2-phenyl-5-oxazolinone 309 via loss of ethanol from the intermediates A (Scheme 106). 8b,182
Scheme 106

Reaction of 2-benzimidazoleacetonitrile 59 with sodium salts of 3-hydroxymethylene-2-alkanones 311 in piperidine acetate and aq. ethanol yielded the pyrido[1,2-\( \alpha \)]benzimidazoles 312. The other isomeric structure 313 was excluded based on the X-ray analysis (Scheme 107).\(^{183}\)

\[
\begin{align*}
\text{Scheme 107} \\
2-(2-Hydroxyethyl)pyrido[1,2-\( \alpha \)]benzimidazole-4-carbonitriles 315 were prepared from heating 2-benzimidazoleacetonitriles 59 with 2-acetylbutyrolactone 314 in the presence of ammonium acetate.\(^{184}\) Condensation of 59 with ethyl 4-chloro-3-oxobutanoate 316 in refluxing DMF and ZnCl\(_2\) led to 3-chloromethylpyrido[1,2-\( \alpha \)]benzimidazol-1-one-4-carbonitrile 317 (Scheme 108).\(^{185}\)
\end{align*}
\]
A highly efficient and regioselective annulation protocol for a series of pyrido[1,2-a]benzimidazoles 320 involving [3+3] cyclocondensation of 2-benzimidazoleacetonitrile 59 with a variety of α-oxoketene dithioacetals 318 has been reported (Scheme 109).186

Scheme 109

Reaction of chloromethylenemalononitriles 321 with 2-(nitromethylene)-benzimidazole 322 yielded the 4-nitropyrido[1,2-a]benzimidazole derivative 323 (Scheme 110).187

Scheme 110

Heating a mixture of 2-(2-arylhydrazono)malononitrile 324 with 2-benzimidazoleacetonitrile 59 in refluxing ethanol yielded the 2-arylazopyrido[1,2-a]benzimidazoles 325.188 However, condensation of the arylhydrazones 326 with 2-benzimidazoleacetonitrile 59 in refluxing acetic acid gave the 3-methyl-2-arylazopyrido[1,2-a]benzimidazoles 327 (Scheme 111).189

Scheme 111
Heating of 2-benzimidazoleacetonitrile 59 with triethyl orthoformate gave the intermediate ethoxycyronitrile derivative 328 which upon treatment with hippuric acid derivatives 329 in refluxing acetic anhydride afforded the pyrido[1,2-α]benzimidazole derivatives 331 in high yields via loss of water molecule from the intermediate 330 (Scheme 112). \(^\text{190}\)

\[
\begin{align*}
\text{Ar} = \text{Ph}, 4-\text{MeOC}_{6}H_{4}, 4-\text{MeC}_{6}H_{4}, 4-\text{ClC}_{6}H_{4}
\end{align*}
\]

**Scheme 112**

Polysubstituted pyrido[1,2-α]benzimidazoles 332 were efficiently produced in moderate yields in a one-pot, four-component reaction of pyridine or 3-picoline, chloroacetonitrile, malononitrile, and aromatic aldehydes in refluxing acetonitrile as outlined in Scheme 113. \(^\text{191}\)

\[
\begin{align*}
R = \text{H, Me} \\
\text{Ar} = \text{C}_{6}H_{5}, 4-\text{MeOC}_{6}H_{4}, 4-\text{MeC}_{6}H_{4}, 4-\text{NO}_{2}C_{6}H_{4}, 4-\text{BrC}_{6}H_{4}, 4-\text{C}_{2}H_{5}C_{6}H_{4}, 4-\text{iPrC}_{6}H_{4}
\end{align*}
\]

**Scheme 113**

Alkylation of 4,7-dimethoxy-1H-benzimidazole 333 using 1-iodo-4-(phenylselenanyl)-butane and sodium hydride gave the phenylselenide derivative 334. Radical cyclisation of 334 gave the pyrido[1,2-α]benzimidazole derivative 335 using Bu$_3$SnH, 1,1'-azobis(cyclohexanecarbonitrile) (ACN) and camphorsulfonic acid (CSA) under reflux in toluene (Scheme 114). \(^\text{192}\)

Scheme 114

Pyrido[1,2-α]benzimidazole derivatives 339 were prepared by reaction of the 2-bromopyridinium salts 336 with pyridine to give the fused heterocyclic bromide salt 338 which upon heating in basic solution underwent recyclization to form 339 (Scheme 115).

Scheme 115

3-(N-Piperidyl)-2-nitroaniline 340 underwent Michael-type addition with acrylonitrile, followed by hydrogenation then condensation with 3-ethoxy-3-iminopropanoate hydrochloride 109 to give 1-(2-cyanoethyl)-2-(ethoxycarbonylmethyl)-4-(N-piperidinyl)benzimidazole 341. Ethanolysis of the nitrile function and base-catalyzed cyclization of the resulted diester followed by amidation with 2,6-difluoroaniline gave the pyrido[1,2-α]benzimidazole derivative 342 (Scheme 116).

Scheme 116

Catalytic hydrogenation of 2-(N-cyanoethyl)-2-nitroaniline 343 and subsequent reaction with ethyl 3-amino-3-ethoxyacrylate hydrochloride 109 followed by ethanolysis of the cyano group in
ethanolic HCl gave the diester intermediate 344. The latter upon treatment with sodium ethoxide underwent Dieckmann cyclization to afford pyrido[1,2-a]benzimidazoles 345 (Scheme 117).196,197

![Scheme 117](image)

**Scheme 117**

The reaction of 2-amino-5-methylpyridine 346 with 1,2-cyclohexanediol 347 in the presence of a catalytic amount of RuCl2(PPh3)3 348 under reflux in diglyme for 24 h afforded 2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]benzimidazole 349 in 74% yield (Scheme 118).198

![Scheme 118](image)

**Scheme 118**

Pyrido[1,2-a]benzimidazole derivative 351 was obtained by photochemical cyclization of 2-chloro-N,N'-di(2-pyridyl)-1,4-phenylenediamine 350 (Scheme 119).199

![Scheme 119](image)

**Scheme 119**

Photo-induced cyclization of haloarylpyridylamines 352 gave the pyrido[1,2-a]benzimidazoles 353 (Scheme 120).200,201
The $N$-heterocyclic carbene of complex 355 was found to be an active catalyst in the Rh(I)-catalyzed intramolecular coupling of the alkenyl group of 1-(2,2-dimethylbut-3-enyl)-1$H$-benzimidazole 354 to the C–H bond of the benzimidazole moiety to give 2,2-dimethyl-1,2,3,4-tetrahydropyrido[1,2-$a$] benzimidazole 356 (Scheme 121).202,203

Scheme 121

Intramolecular radical addition of 2-thiophenoxybenzimidazole 357 was reported in the presence of cobaloxime 358 or Ph$_3$SnH/AIBN to give 3,3-dimethyl-1,2,3,4-tetrahydropyrido[1,2-$a$] benzimidazole 360. The yield of 360 was higher (81%) with using cobaloxime 358 than with Ph$_3$SnH/AIBN (64%) (Scheme 122).204

Scheme 122

Palladium-catalyzed intramolecular cyclization of 2-anilinopyridine 361 (X = Br; R = H) using palladium acetate and Na$_2$CO$_3$ in DMF at reflux gave pyrido[1,2-$a$]benzimidazole 362 (R
= H) in 59% yield. Also, catalytic cyclization of 361 (X = H; R = H, Me) in a continuous-flow quartz reactor containing K-16, as a dehydrogenating catalyst, at 560-580 °C gave the pyridobenzimidazoles 362 (R = H, Me) in 10-27% yields (Scheme 123).206

\[
\begin{array}{ccc}
\text{361} & \xrightarrow{\text{quartz reactor, } K-16 \text{ catalyst}} & \text{362} \\
X = H, Br & \text{560 °C} & R = H, Me \\
R = H, Me & \text{or } \text{Pd(OAc)}_2 / \text{Na}_2\text{CO}_3 & \text{DMF, reflux}
\end{array}
\]

Scheme 123

Condensation of 1,2-diaminobenzene 36 with the 5H-pyran-2,6-dione 363 gave the pyrido[1,2-a]benzimidazol-1-one 364,207 while condensation of 36 with 6-hydroxy-4-methyl-2-oxo-3-pyridine-carbonitrile 365 in 85% orthophosphoric acid afforded 3-methyl-1-oxo-1H,5H-pyrido[1,2-a]benzimidazole 366 (Scheme 124).208

\[
\begin{array}{ccc}
\text{366} & \xrightarrow{85\% \text{H}_3\text{PO}_4} & \text{365} \\
\text{36} & \xrightarrow{\text{363}} & \text{364} \\
Ar = 4-\text{MeOC}_6\text{H}_4
\end{array}
\]

Scheme 124

3.2. Pyrimidobenzimidazoles
Treatment of 2-aminobenzimidazole 117 with variety of enaminones 367, 368 and 369 in refluxing pyridine gave the corresponding pyrimido[1,2-a]benzimidazoles 370, 371 and 372, respectively (Scheme 125).160,163,165,168,209-213
Meziane et al reported the microwave-assisted synthesis of the pyrimido[1,6-a]benzimidazoles 376. Thus, heating of ethyl 2-(benzimidazol-2-yl)acetate 308 with N,N-dimethylformamide diethylacetal (DMF-DEA) at 90°C under microwave irradiation for 15 minutes gave the enamine derivative 373 which on treatment with the isocyanates or isothiocyanates 374 led to the formation of the pyrimido[1,6-a]benzimidazole 376 in good yields (Scheme 126).

Microwave assisted one-pot three component synthesis of 1,2-dihydro-pyrimido[1,2-a]benzimidazole-3-carbonitrile derivatives 379 were achieved in high yields. Thus, reaction of
carbonyl compounds 378, malonodinitrile and 2-aminobenzimidazole 117 in water under microwave gave pyrimido[1,2-a]benzimidazoles 379 (Scheme 127).\textsuperscript{215-217}

\begin{center}
\begin{align*}
\text{N} & \text{N} \\
\text{H} & \text{H} \\
117 & + \begin{array}{c}
\text{CN} \\
\text{X} \\
378
\end{array} \xrightarrow{\text{MW}} \begin{array}{c}
\text{N} \\
\text{N} \\
\text{H} & \text{H} \\
379 & \text{X} = \text{CN}, \text{CO}_2\text{Et}
\end{array}
\end{align*}
\end{center}

Carbonyl compd. = ArCHO, ArCOCH\textsubscript{3}, cyclopentanone, cyclohexanone, \(\alpha\)-tetralone

Ar = Ph, 4-ClC\textsubscript{6}H\textsubscript{4}, 4-BrC\textsubscript{6}H\textsubscript{4}, 4-FC\textsubscript{6}H\textsubscript{4}, 4-MeOC\textsubscript{6}H\textsubscript{4}, 4-MeC\textsubscript{6}H\textsubscript{4}, 2-ClC\textsubscript{6}H\textsubscript{4}, 2,4-Cl\textsubscript{2}C\textsubscript{6}H\textsubscript{3}

\textbf{Scheme 127}

The pyrimido[1,2-a]benzimidazoles 381 were synthesized through reaction of 2-aminobenzimidazole 117 with tetracyanoethylene 380 in ethyl acetate at room temperature \textit{via} loss of HCN and heterocyclization.\textsuperscript{218} When 2-aminobenzimidazole 117 was treated with (E)-3-(diethylamino)acrylonitrile 382 in refluxing pyridine it gave pyrimido[1,2-a]benzimidazol-4-amine 383 in 57% yield (Scheme 128).\textsuperscript{219}

\begin{center}
\begin{align*}
\text{N} & \text{N} & \text{CN} & \text{CN} \\
\text{H} & \text{H} & \text{N} & \text{N} \\
380 & \xrightarrow{\text{AcOEt, rt}} & 117 & \xrightarrow{\text{Et}_2\text{N, pyridine, reflux}} & 383 & 57\%
\end{align*}
\end{center}

\textbf{Scheme 128}

Fusion of 2-aminobenzimidazole 117 with methyl cinnamates 384 gave the pyrimido[1,2-a]benzimidazoles 385 (Scheme 129).\textsuperscript{220} The acetylenic aldehydes 386 and 3-phenylpropynenitrile 388 reacted by conjugate addition to 117 giving the pyrimido[1,2-a]benzimidazoles 387 and 389, respectively (Scheme 129).\textsuperscript{221}
Refluxing chlorooxazinediones 390 with \(\alpha\)-phenylenediamines 36 in THF in the presence of acetic acid gave pyrimidobenzimidazolodiones 391 in low yields (Scheme 130).  

Photo-irradiation of \(N,N'\)-(chlorophenylene)bis[dimethylpyrimidinamines] 392 gave pyrimidobenzimidazoles 393 (Scheme 131).

Photochemical cyclization of (2-chloroanilino)pyrimidines 394 in aqueous acetonitrile gave pyrimido[1,2-\(a\)]benzimidazoles 395 (Scheme 132).
Scheme 132

Reaction of ethyl 2-[(1H-benzimidazol-2-yl)sulfinylmethyl]-4-dimethylamino-5-pyrimidine-carboxylate 396 with alkanethiols in the presence of hydrochloric acid gave the pyrimido[1,2-a]benzimidazole-3-carboxylate 403 according to the mechanism shown in Scheme 133.226

Scheme 133

Treatment of 2-vinylbenzimidazoles 404 with bromine in chloroform gave 2-(1,2-dibromoethyl)-1H-benzimidazoles 405. Reaction of the latter compounds with benzonitriles and with aryl isocyanates under basic conditions yielded 1-phenylpyrimido[1,6-a]benzimidazole 407 and 2-phenylpyrimido[1,6-a]benzimidazole-3-one 408, respectively (Scheme 134).227
Scheme 134

Reaction of ethyl benzimidazole-2-acetate 308 with alkyl isocyanates gave the corresponding pyrimido[1,6-a]benzimidazoles 410 in excellent yields via loss of ethanol from 409 (Scheme 135).228

Scheme 135

Abdelhamid et al. reported the synthesis of pyrimido[1,6-a]benzimidazole-4-carbonitriles 413 from the reaction of 2-(1-ethoxycarbonyl)benzimidazolylacetonitrile 411 with isothiocyanates in the presence of KOH followed by HCl (Scheme 136).229,230

Scheme 136
Treatment of 2-benzimidazoleacetonitriles 59 or methyl 2-benzimidazoleacetate 308 with chloroalkyl isocyanates or carbodiimides 414 (Y = O, N-Ar'), in benzene in the presence of ethyl diisopropylamine furnished the pyrimido[1,6-a]benzimidazoles 416 via cyclization and loss of HCl from the benzimidazolium salt intermediate 415 (Scheme 137).231

![Scheme 137](image)

Reaction of ethyl 2-(1H-benzimidazol-2-yl)-2-cyanoacetate 417 with guanidine sulfate 418 in dry pyridine and sodium methoxide gave 1-amino-3-hydroxypyrimido[1,6-a]benzimidazole-4-carbonitrile 419 (Scheme 138).232

![Scheme 138](image)

2-Benzimidazoleacetonitrile 59 and its ester 308 reacted with N-acyl imidates 420 under microwave irradiation in open vessels to give the corresponding pyrimido[1,6-a]benzimidazoles 421 (Scheme 139).233

![Scheme 139](image)
Badawey et al. reported the reaction of 1H-benimidazoles 59 and 308 with ethoxycarbonyl isocyanate 422 at room temperature to afford the intermediate 423, which was readily cyclized in boiling bromobenzene to the corresponding 1,3-dioxopyrimido[1,6-a]benimidazole-4-carbonitrile 424 in excellent yields (Scheme 140).234

![Scheme 140](image)

The reaction of 2-aminobenzimidazole 117 with sulfones 425 proceeded at room temperature in acetonitrile to give tetrahydropyrimido[1,2-a]benimidazol-2-ol 426. Aromatization of the latter compounds 426 was performed under reflux in acetic acid via elimination of water and sulfinic acid to give 427. One-step procedure for the preparation of 427 in high yields from 2-aminobenzimidazole 117 and the sulfones 425 under reflux in water was also reported (Scheme 141).235 Condensation of 2-aminobenzimidazole 117 with diethyl ethoxymethylenemalonate 301 in dry methanol afforded 4-oxopyrimido[1,2-a]benimidazole-3-carboxylate 428 (Scheme 141).236

![Scheme 141](image)

3-(Trichloromethyl)pyrimido[1,6-a]benimidazole-4-carbonitrile 429 was prepared by heating of 2-benzimidazoleacetonitrile 59 with trichloroacetonitrile followed by triethyl orthoformate (Scheme 142).237 Reaction of dimethyl N-cyanodithioiminocarbonate 430 with 2-benzimidazoleacetonitrile 59 in the presence of KOH furnished 1-amino-4-cyano-3-(methylthio)pyrimido[1,6-a]benimidazole 432 (Scheme 142).238
Scheme 142

The reaction of 2-aminobenzimidazole 117 with the benzylidene derivatives 433, 267 and 434 in ethanol containing a catalytic amount of piperidine gave the corresponding pyrimido[1,2-\(a\)]benzimidazole derivatives 435, 436 and 437, respectively (Scheme 143).\(^{239-242}\)

Scheme 143

The condensation of 2-aminobenzimidazole 117 with chalcones 263 and with phenylhydrazonomalononitrile 324 gave pyrimido[1,2-\(a\)]benzimidazoles 438 and 440, respectively.\(^{243-246}\) Similar condensation of 117 with ethyl \(\alpha\)-(\(p\)-tolylazo)-\(\beta\)-oxobutyrate 441 in absolute ethanol afforded the pyrimido[1,2-\(a\)]benzimidazole-4-one 442 (Scheme 144).\(^{247}\)
Scheme 144

The reaction of the allenic nitriles 443 with 2-aminobenzimidazoles 117 in refluxing DMF led to 2-aminopyrimido[1,2-a] benzimidazole 445 in high yields (Scheme 145).248

Scheme 145

Reaction of 1-ethyl-2-aminobenzimidazole 446 and dimethyl acetylenedicarboxylate 257 at 130 °C afforded the methyl pyrimido[1,2-a]benzimidazol-4-carboxylate 447 in 59% yield. Similar treatment of 446 with diethyl (ethoxymethylene)malonate 301 gave ethyl 10-ethyl-4-oxo-4H-pyrimido[1,2-a]benzimidazol-3-carboxylate 448 in 71% yield (Scheme 146).62

Scheme 146
Reaction of 2-aminobenzimidazole 117 with 4-hydroxy-2-alkynenitrile 152 in ethanol under reflux gave excellent yields of 2-amino-4-(1-hydroxyalkyl)pyrimido[1,2-\(a\)]benzimidazole 450.\(^{76}\) In addition, the pyrimidobenzimidazole-2,4-dione 452 was prepared in 30% yield by treating 117 with diethyl diallylmalonate 451 (Scheme 147).\(^{249}\)

![Scheme 147](image1)

Refluxing 3-isothiocyanatobutanal 453 with \(o\)-phenylenediamines 36 in methanol at \(pH\) 5 gave the pyrimido[1,6-\(a\)]benzimidazole derivative 454 (Scheme 148).\(^{250,251}\)

![Scheme 148](image2)

Cyclocondensation of (2-benzimidazolylmethyl)triphenylphosphonium chloride 455 with benzoyl isothiocyanates in the presence of triethylamine gave pyrimido[1,6-\(a\)]benzimidazole derivative 456 (Scheme 149).\(^{252,253}\)

![Scheme 149](image3)
4-Amino-1H-1,5-benzodiazepine-3-carbonitrile 457 underwent ring opening when treated with hydroxylamine to yield 3-amino-3-(2-aminoanilino)-2-cyanopropenal oxime 458. Treatment of 458 with diluted hydrochloric acid gave 2-(2-benzimidazolinylidene)-2-cyanoethanal-oxime 459. Refluxing of 459 in triethyl orthoformate resulted in the formation of the pyrimido[1,6-a]benzimidazole derivative 460 (Scheme 150).

![Scheme 150](image)

The pyrimido[1,2-a]benzimidazole derivative 461 was prepared in 75% yield by cyclocondensation of 4-(ethoxymethylene)-2-phenyloxazol-5(4H)-one 308 with 2-aminobenzimidazole 117 under solventless domestic microwave heating via loss of ethanol from the intermediate 461A (Scheme 151).

![Scheme 151](image)

1,2-Diaminobenzimidazole 462 reacted with diethyl ethoxymethylene(malonate 301 to give the pyrimido[1,2-a]benzimidazole derivative 463 (Scheme 152).

![Scheme 152](image)
Pyrimido[1,2-\(a\)]benzimidazole derivatives 467-470, which are useful as neoplasm inhibitors, immuno-modulators, and antiallergic agents, were prepared via reaction of 2-aminobenzimidazole Schiff’s base 464 with active methylene compounds and with the cinnamoyl chlorides 465 (Scheme 153).

![Scheme 153](image)

3.3. Pyrazinobenzimidazoles

2-Acetylbenzimidazole 471 reacted with aromatic aldehydes to give 1-(benzimidazol-2-yl)-3-aryl-2-propenone 472. Reaction of 472 with phenacyl bromides 5 in acetone in the presence of potassium carbonate gave 1-[1-(2-aryl-2-oxoethyl)benzimidazol-2-yl]-3-arylpropenones 473 which upon heating with ammonium acetate in acetic acid gave 1-(2-arylvinyl)-3-arylpyrazino[1,2-\(a\)]benzimidazole derivative 474. Reaction of 471 with phenacyl bromides 5 gave 1-(2-aryl-2-oxoethyl)-2-acetylbenzimidazoles 475, which were then reacted with anilines in acetic acid to give 1-methylene-2,3-diaryl-1,2-dihydropyrazino[1,2-\(a\)]benzimidazoles 476 (Scheme 154).
Scheme 154

Pyrazino[1,2-\(a\)]benzimidazole 478 was prepared by heating 1-(2-pyrazinyl)benzotriazole 477 with polyphosphoric acid (PPA) at 180 °C (Scheme 155). 263

Scheme 155

Pyrazino[1,2-\(a\)]benzimidazole derivatives 479-481 were obtained from the reaction of 2-aminomethylbenzimidazole 112 with diethyl oxalate, phenacyl bromide 5 and with dibromoethane, respectively (Scheme 156). 60
Treatment of the 2-formylbenzimidazole 482 with primary amines and cyclohexyl isocyanide at 40 °C in methanol resulted in the formation of 3-oxo-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole-1-carboxamides 485 in good yields. Formation of 485 took place probably according to the mechanism depicted in Scheme 157.264

![Scheme 157](image)

3-Anilinopyrazinones 486 were easily converted into the pyrazino[1,2-a]benzimidazol-1(2H)-ones 487 by applying a microwave assisted Buchwald–Hartwig type cyclization using 10% Pd(PPh3)4 and anhydrous potassium carbonate in DMF at 150 °C and 150 Watts (Scheme 158).265

![Scheme 158](image)

### 3.4. Triazinobenzimidazoles

Treatment of ethyl 2-benzimidazolylacetate 308 with aryldiazonium salts in ethanolic sodium acetate solution yielded the arylhydrazones 488. Heating the latter hydrazones with ethyl chloroformate in pyridine afforded the 1,2,4-triazino[4,5-a]benzimidazole derivatives 489 (Scheme 159).266
Scheme 159

1,2,4-Triazino[2,3-α]benzimidazole derivative 493 was obtained selectively by the reaction of diethyl (E)-2,3-dicyanobutenedioate 490 with 1,2-diamino-1H-benzimidazole 462 in dimethyl sulfoxide at room temperature as outlined in Scheme 160.267

Scheme 160

3-Oxopropanenitriles 494 coupled smoothly with 1H-benzimidazole-2-diazonium sulfate 495 to afford the corresponding hydrazones 496. The latter hydrazones underwent intramolecular cyclization when heated in pyridine to give 1,2,4-triazino[4,3-α]benzimidazoles 497 in good yields (Scheme 161).268,269

Scheme 161
Benzimidazole-2-diazonium salt 495 was coupled with 2-benzimidazoleacetonitrile 59 to yield the hydrazone 498 which was cyclized under refluxing pyridine to produce the 1,2,4-triazino[4,3-\(a\)]benzimidazole 499 (Scheme 162).270

Scheme 162

The diazotized 2-nitroanilines 500 were coupled with \(N\)-ethoxycarbonylcyanoacetamide 501 to afford the corresponding hydrazones 502 which were cyclized into the nitrophenyltriazinediones 503. The latter were reduced to the corresponding aminophenyltriazinedione derivatives 504 which were then converted into the 1,2,4-triazino[2,3-\(a\)]benzimidazoles 505 (Scheme 163).271-274

Scheme 163

Heating benzoylpyruvic acid 507 with 1-amino-2-(\(N\)-methylamino)benzimidazole 506 produced the 1,2,4-triazino[2,3-\(a\)]benzimidazole derivative 508 (Scheme 164).275

Scheme 164
Heating 2-chloro-1-phenacylbenzimidazole 158, in refluxing DMF, with aminoguanidine 509 or with hydrazine hydrate led to 3-phenyl-1,4-dihydro-1,2,4-triazino[4,3-a]benzimidazole 510 in 49 and 86% yields, respectively (Scheme 165). 78

Scheme 165

The reaction of 2-hydrazinobenzimidazoles 220 with diethyl 2-oxomalonate 511 and with α-keto acids 513 in refluxing ethanol gave the corresponding 1,2,4-triazino[4,3-a]benzimidazol-4(10H)-ones 412 and 514, respectively. 276,277 Refluxing of 220 with diethyl oxalate in ethanol gave the 1,2,4-triazino[4,3-a]benzimidazole-3,4-dione 515 (Scheme 166). 128

Scheme 166

Condensation of hydrazines with N-propargyl-2-chlorobenzimidazole 516 resulted in the formation of 1,2,4-triazino[4,3-a]benzimidazole derivatives 517 (Scheme 167). 278

Scheme 167
Heating benzimidazole-1-acetonitriles $518$ and hydrazine in methanol gave 3-hydrazino-1,2,4-triazino[4,3-$a$]benzimidazole $519$ (Scheme 168).$^{279,280}$

**Scheme 168**

3.5. Thiazinobenzimidazoles

Michael-type addition of 2-mercaptobenzimidazole $165$ to ethyl propiolate in the presence of clay catalyst gave 4-oxothiazino[3,2-$a$]benzimidazole $520$. Alkylation of $165$ with epichlorohydrin $521$ in aqueous base gave the thiazino[3,2-$a$]benzimidazole derivative $522$. On the other hand, reaction of 2-mercaptobenzimidazole $165$ with acryloyl chlorides $523$ in pyridine and acetone afforded the $4H$-[1,3]thiazino[3,2-$a$]benzimidazol-4-ones $524$ (Scheme 169).$^{283}$

**Scheme 169**

Thiazino[3,2-$a$]benzimidazole derivatives $525$ and $526$ were prepared from the reaction of 2-mercaptobenzimidazoles $165$ with 3-chloropropanoic acid and 1,3-dibromopropane, respectively (Scheme 170).$^{284,285}$

**Scheme 170**
Bromination of 2-(allylthio)benzimidazoles 527 led to 2-[(2,3-dibromopropyl)thio]benzimidazoles 528 which were converted into the thiazino[3,2-a]benzimidazoles 529-531 in reasonable yields (Scheme 171).286,287

![Scheme 171]

Treatment of 1H-benzimidazol-2-ylmethanethiol 532 with tetracyanoethylene 380 gave 1-cyanodihydrothiazino[4,3-a]benzimidazole-2-carboxamide 533 (Scheme 172).288

![Scheme 172]

Heating 2-mercaptobenzimidazoles 165 with acetylenedicarboxylate esters 257 under microwave irradiation gave a mixture of 4-oxothiazino[3,2-a]benzimidazole-2-carboxylates 534 and 535 (Scheme 173).289,290

![Scheme 173]

Reaction of 3-methylthiazolo[3,2-a]benzimidazole 201 with two equivalents of methyl propiolate in refluxing acetonitrile gave the 1,4-thiazino[4,3-a]benzimidazole derivative 540 in reasonable yield and the mechanism of this reaction is depicted in Scheme 174.291
4. Synthesis of Azepino-fused-Benzimidazoles

4.1. Azepinobenzimidazoles

Treatment of 2-methylbenzimidazole 65 with ethyl 4-bromobutyrate in THF in the presence of NaH gave 1-(3-ethoxycarbonylpropyl)-2-methylbenzimidazole 541. Hydrolysis of the latter using NaOH followed by quaternization using alkyl halides gave the benzimidazolium salts 542. Treatment of the latter salts 542 with N,N'-carbonyldiimidazole (CDI) in acetonitrile at room temperature followed by addition of Et3N and heating the mixture at 70 °C gave 7,8,9,10-tetrahydro-5H-azepino[1,2-a]benzimidazol-7-one derivatives 543 (Scheme 175).31,292

Scheme 175
\textit{N}\text-(Haloaryl)amidines 544 underwent heterocyclization when heated in DMF in the presence of sodium methoxide to give the 7,8,9,10-tetrahydro-6\textit{H}-azepino[1,2-\textit{a}]benzimidazole derivatives 545 in high yields (Scheme 176).\textsuperscript{25,293}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textbf{544}}; \\
\node (B) at (2,0) {X = F, Cl}; \\
\node (C) at (2,-1) {R = F, CF\textsubscript{3}, SO\textsubscript{2}NEt\textsubscript{2}, NO\textsubscript{2}}; \\
\node (D) at (2,-2.5) {\textbf{545} 74-81\%}; \\
\draw[<->] (A) -- (B); \\
\draw[<->] (A) -- (C); \\
\draw[<->] (A) -- (D);
\end{tikzpicture}
\end{center}

\textbf{Scheme 176}

3-Methoxy-7,8,9,10-tetrahydro-6\textit{H}-azepino[1,2-\textit{a}]benzimidazole 547 was prepared from the reaction of mixture of \textit{N}\text-(2-(azepan-1-yl)-5-methoxyphenyl)acetamide 546, formic acid and H\textsubscript{2}O\textsubscript{2} at 40 °C as shown in Scheme 177.\textsuperscript{294}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textbf{546}}; \\
\node (B) at (2,0) {MeO \text{Ac}}; \\
\node (C) at (2,-0.5) {\text{HCO\textsubscript{2}H, H\textsubscript{2}O\textsubscript{2}}}; \\
\node (D) at (2,-1) {40 °C, 1h}; \\
\node (E) at (2,-1.5) {\textbf{547} 64\%}; \\
\draw[<->] (A) -- (B); \\
\draw[<->] (A) -- (C); \\
\draw[<->] (A) -- (D); \\
\draw[<->] (A) -- (E);
\end{tikzpicture}
\end{center}

\textbf{Scheme 177}

Fusion of a mixture of \textit{γ}-bromodipnone 549 and 1,2-dimethyl-1\textit{H}-benzimidazole 548 on an oil bath at 110 °C for 30 min afforded 11-methyl-7,9-diphenyl-6\textit{H},11\textit{H}-azepino[1,2-\textit{a}]-5-benzimidazolium bromide 550 in reasonable yield (Scheme 178).\textsuperscript{295}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textbf{548}}; \\
\node (B) at (2,0) {Br \text{ COPh}}; \\
\node (C) at (2,-0.5) {110 °C, \text{fusion}}; \\
\node (D) at (2,-1) {\textbf{550} 29\%}; \\
\draw[<->] (A) -- (B); \\
\draw[<->] (A) -- (C); \\
\draw[<->] (A) -- (D);
\end{tikzpicture}
\end{center}

\textbf{Scheme 178}

Treatment of 1\textit{H}-2-phenylthiobenzimidazole 551 with NaH in THF followed by adding 5-iodo-1-(phenylselenyl)pentane 552 under reflux gave 1-[5-(phenylselenyl)pentyl]-2-(phenylthio)-1\textit{H}-benzimidazole 553. Refluxing the latter 553 in toluene using Bu\textsubscript{3}SnH and AIBN
resulted in an intramolecular radical substitution of the intermediate 554 to give the 7,8,9,10-tetrahydro-6H-azepino[1,2-α]benzimidazole 555 in low yield (Scheme 179). 296

Scheme 179

The tetrahydro-6H-azepino[1,2-α]benzimidazole 555 was alternatively synthesized in a good yield by lithiation of either the N-alkylated 1H-benzimidazole 556 or 2-methylbenzimidazole 557 using lithium diisopropylamide (LDA) in THF at -78 °C (Scheme 180). 297

Scheme 180

Rhodium-catalysed reactions of N-(4-methylpent-4-enyl)-1,2-diaminobenzene 558 with hydrogen and carbon monoxide gave the 7,8,9,10-tetrahydro-7-methyl-6H-azepino[1,2-α]benzimidazole 561 in good yield. This product arised from initial highly regioselective aldehyde formation at the terminal carbon atom followed by cyclisation with subsequent oxidation to the benzimidazole 561 (Scheme 181). 298,299

Scheme 181

4.2. Diazepinobenzimidazoles
Reaction of 2-(ω-aminopropyl)benzimidazole 562 with carbon disulfide in alkaline ethanol gave the 1,3-diazepino[3,4-α]benzimidazole-2-thione 563 which on treatment with methyl iodide gave the 2-methylthio derivative 564 (Scheme 182). 300
4.3. Triazepinobenzimidazoles

Heating a mixture 1,2-diaminobenzimidazole 462 and 1,3-diketones 565 in polyphosphoric acid (PPA) at 110-115 °C or in the presence of ZnCl2 at 240-250 °C gave the corresponding 1,2,4-triazepino[2,3-a]benzimidazole derivatives 566 in good yields (Scheme 183).301

Scheme 183

When 1,2-diaminobenzimidazole 462 was treated with β-ketoesters 567 under reflux condition either in acetic acid or without solvent it gave the corresponding 1,2,4-triazepino[2,3-a]benzimidazol-4-ones 568 (Scheme 184).53,301-303

Scheme 184

2-Chlorobenzimidazole 47 was condensed with β-bromoketones 569 to give 1-(2-benzoylethyl)-2-chlorobenzimidazoles 570 which cyclized with hydrazines to give the corresponding 1,2,4-triazepino[4,3-a]benzimidazoles 571 (Scheme 185).304
Scheme 185

Reaction of 2-(benzylhydrazino)benzimidazole 572 with 4-phenyl-3-butyn-2-one 573 in DMF in the presence of Et$_3$N gave 73% of 1-benzyl-3-methyl-5-phenyl-1,2,4-triazepino[4,3-$a$]benzimidazole 574 (Scheme 186).$^{305}$

Scheme 186

Reaction of 2-hydrazonobenzimidazole 575 with tetracyanoethylene (TCNE) 380 gave the 1,2,4-triazepino[4,3-$a$]benzimidazole derivatives 576 (Scheme 187).$^{306}$

Scheme 187

4.4. Thiazepinobenzimidazoles

Reaction of 2-mercaptobenzimidazole 165 with two equivalents of tetracyanoethylene 380 in ethyl acetate at room temperature gave the 1,3-thiazepino[3,2-$a$]benzimidazole derivative 577 in low yield (Scheme 188).$^{307}$
Scheme 188

5. References


**Authors' Biographies**

**Kamal M. Dawood** was born in 1965 in Kafr-Elsheikh, Egypt. He graduated from Cairo University, Egypt in 1987 then he carried out his MSc and PhD studies under the supervision of Professor Ahmad M. Farag, Cairo University. He received his PhD in 1995 in the applications of hydrazonoyl halides in heterocyclic chemistry. In 1997 he was awarded the UNESCO Fellowship for one year at Tokyo Institute of Technology (TIT) and collaborated with Prof. Toshio Fuchigami in the field of ‘Electrochemical Partial Fluorination of Heterocyclic Compounds’. In 1999, he was awarded the JSPS (Japan Society for Promotion of Science) Fellowship for two years and worked again with Professor Fuchigami at TIT in the same field. He was awarded the Alexander von Humboldt Fellowship at Hanover University in 2004-2005 with Prof. Andreas Kirschning in the field of polymer supported palladium catalyzed cross coupling reactions and in 2007 and 2008 with Prof. Peter Metz at TU-Dresden, Germany, in the field of total synthesis of natural products. In 2002 he promoted to Associate Professor and in May 2007 he was appointed as Professor of Organic chemistry, Faculty of Science, Cairo University. In 2002 he received the Cairo University Award in Chemistry and in 2007 he received the State-Award in Chemistry. He is a member of the international Editorial Board of ISRN Organic Chemistry, part of the *International Scholarly Research Network* (ISRN), open access journals. He published more than 75 scientific papers and reviews in distinguished international journals. There are about 690 citations of his work from 1993 until 2010 (*h*-index 16).
Nehal M. Elwan was born in 1959 in Giza, Egypt. She graduated from Cairo University, Egypt in 1980 then she carried out her MSc and PhD studies under the supervision of Professors Hamdi M. Hassaneen and Ahmad S. Shawali (DSc.), Chemistry Department, Faculty of Science, Cairo University. She received her PhD in 1990 on the applications of hydrazonoyl halides in heterocyclic chemistry. In 1990 she was appointed as a lecturer of organic chemistry at Faculty of Science, Cairo University. In 1995 she was promoted to Associate Professor and in 2004 she was appointed as Professor of Organic chemistry, Faculty of Science, Cairo University. In 2005 she received the Cairo University Award in chemistry. Currently, she is the director of the Microanalysis Centre, Cairo University.

Bakr F. Abdel-Wahab was born in 1978 in Mansoura, Egypt. He is a researcher of organic chemistry at National Research Centre, Giza, Egypt. He has got his B.Sc. in 1999 from Chemistry Department, Faculty of Science, Mansoura University, Egypt. He received his M.Sc. in 2003 from Mansoura University under the supervision of Professor Fathy A. Amer. He has awarded his Ph.D. degree in 2007 from Ain-Shams University, Cairo under the supervision of Professor Maher A. El-Hashash (D.Sc). His current research interests cover the development and mechanistic aspects of organic reactions and their applications in medicinal chemistry. Currently, he is an assistant professor of organic chemistry at the Department of Chemistry, Faculty of Science and Arts, King Abdulaziz University, Khulais Branch, Saudi Arabia.