

## 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, pyrrolbenzimidazoles,<sup>1-5</sup> thiazolobenzimidazoles,<sup>6</sup> pyrimidobenzimidazoles,<sup>7</sup> and pyridobenzimidazoles<sup>8</sup> were reported as potent antitumor agents. Furthermore, pyrrolbenzimidazoles,<sup>9</sup> pyridobenzimidazoles,<sup>10</sup> were found to be useful in treating central nervous system disorder. Pyridobenzimidazoles have also anxiolytic activity in humans,<sup>11-13</sup> and pyrimidobenzimidazoles were anti-rheumatic agents.<sup>14</sup> Also, 1,2,4-triazinobenzimidazoles were found to be aldose reductase inhibitors<sup>15</sup> and to possess antimicrobial activity.<sup>16</sup>

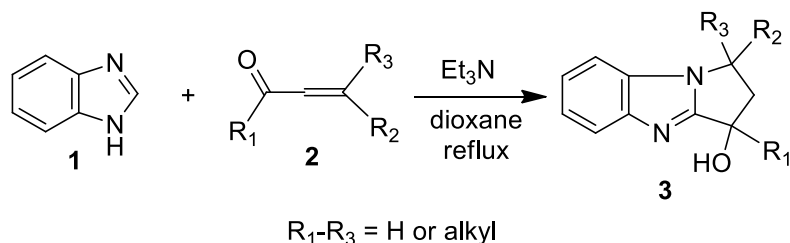
There are a large number of pharmacologically interesting benzimidazole molecules fused to a five membered rings containing one heteroatom (pyrrolbenzimidazoles), two heteroatoms (pyrazolo-, imidazo-, oxazolo-, and thiazolo-benzimidazoles) and three heteroatoms (triazolo-, thiadiazolo- and oxadiazolo-benzimidazoles). 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,<sup>17</sup> 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

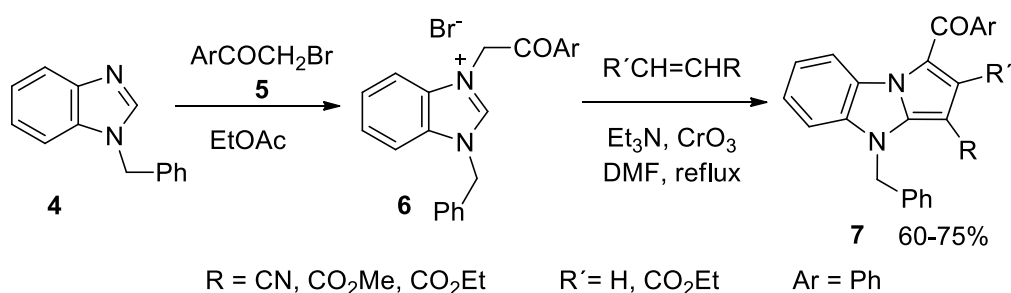
### 2.1. Pyrrolbenzimidazoles

3-Hydroxypyrrolo[1,2-*a*]benzimidazoles **3** were prepared by Michael-type addition of benzimidazole **1** to  $\alpha,\beta$ -unsaturated carbonyl compounds **2** in refluxing dioxane in the presence of Et<sub>3</sub>N (Scheme 1).<sup>18</sup>



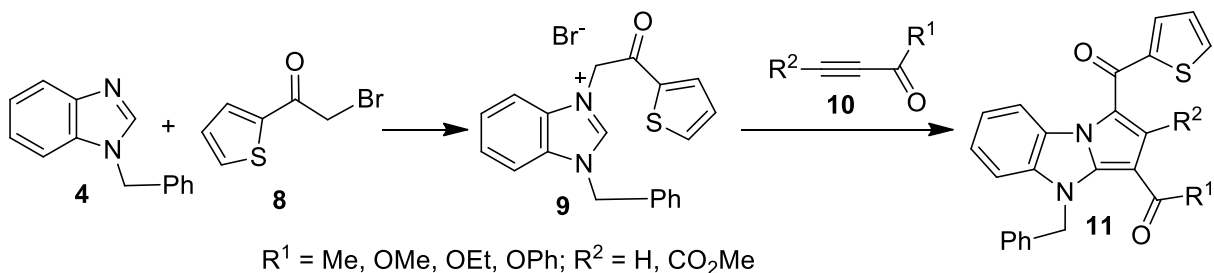
### Scheme 1

Treatment of 1-benzyl-1*H*-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 4*H*-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, CrO<sub>3</sub>/Et<sub>3</sub>N has been proved to be a more effective dehydrogenating reagent than MnO<sub>2</sub> (Scheme 2).<sup>19</sup>



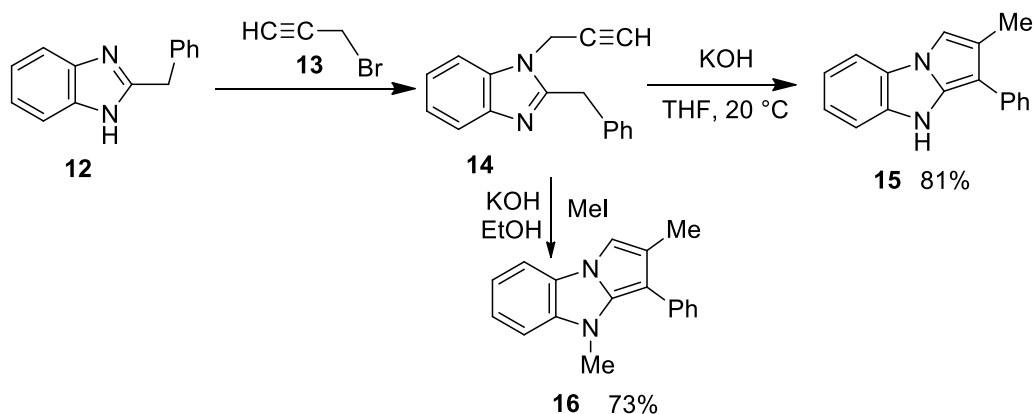
### Scheme 2

Reaction of 1-benzyl-1*H*-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).<sup>20</sup>



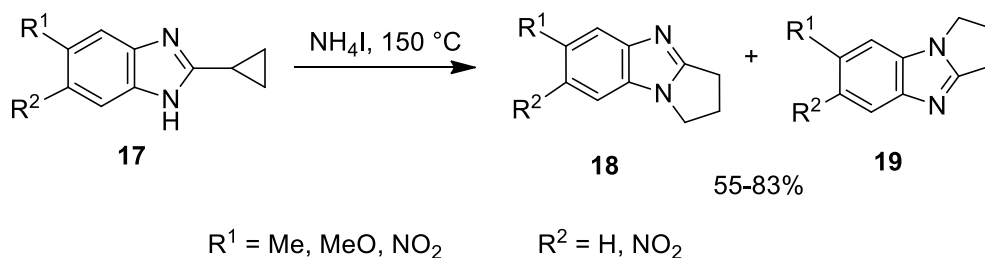
## Scheme 3

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).<sup>21</sup>



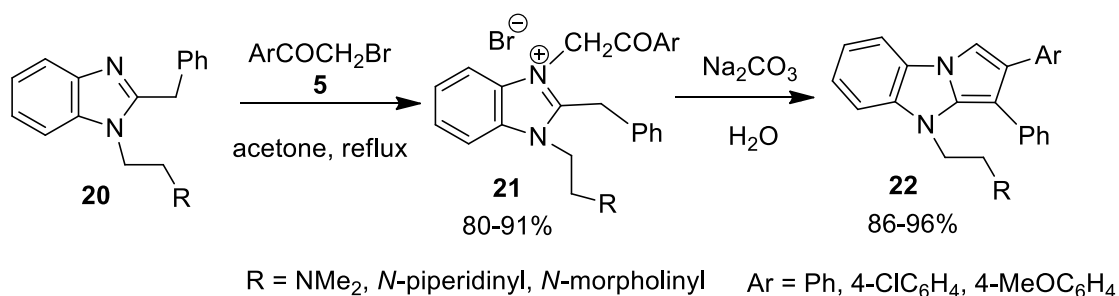
## Scheme 4

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<sup>1</sup> and R<sup>2</sup> (Scheme 5).<sup>22</sup>



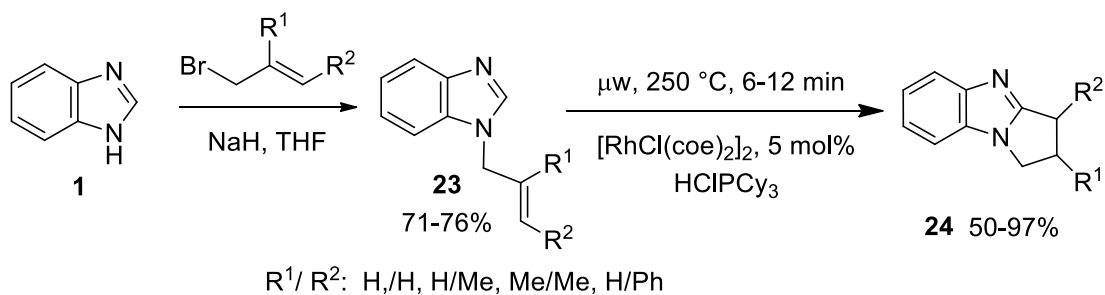
## Scheme 5

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).<sup>23</sup>



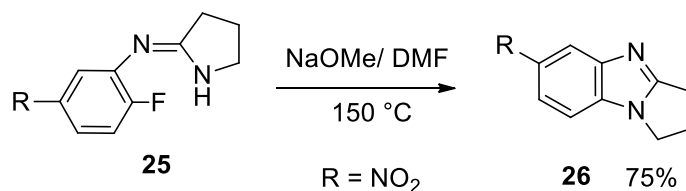
### Scheme 6

Rhodium-catalyzed microwave irradiation of *N*-allyl benzimidazoles **23** using 5 mol% of [RhCl(coe)<sub>2</sub>]<sub>2</sub> (coe = *cis*-cyclooctene) in the presence of tricyclohexylphosphine hydrochloride (HCIPCy<sub>3</sub>) gave the corresponding dihydropyrrolobenzimidazoles **24** in moderate to excellent yields after 20 min (Scheme 7).<sup>24</sup>



### Scheme 7

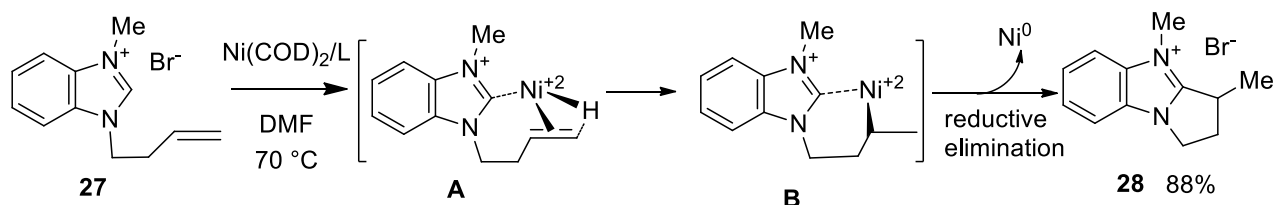
Cyclization of the amidine **25** with strong base such as sodium methoxide in DMF at 150 °C was reported to give the pyrrolo[1,2-*a*]benzimidazole **26** in 75% yield *via* loss of HF (Scheme 8).<sup>25</sup>



### Scheme 8

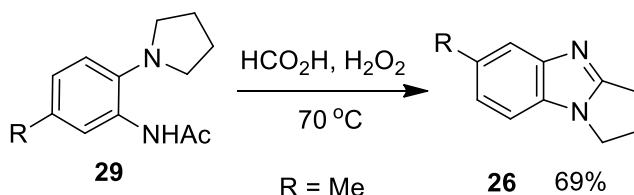
Pyrrolo[1,2-*a*]benzimidazolium salt **28** was prepared in high yield and selectivity from the catalytic ring closing of 1-(3-butenyl)-3-methylbenzimidazolium bromide **27** using nickel dicyclooctadiene, Ni(COD)<sub>2</sub>, as catalyst in DMF at 70 °C (Scheme 9).<sup>26</sup> The reaction proceeded 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)<sub>2</sub> and ligand L (where L = IMes, SMes, PPh<sub>3</sub>, PCy<sub>3</sub>, PCy<sub>2</sub>(biphenyl), P(t-Bu)<sub>3</sub> in DMF).<sup>26</sup>



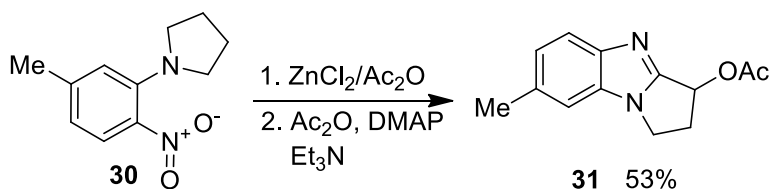
### Scheme 9

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



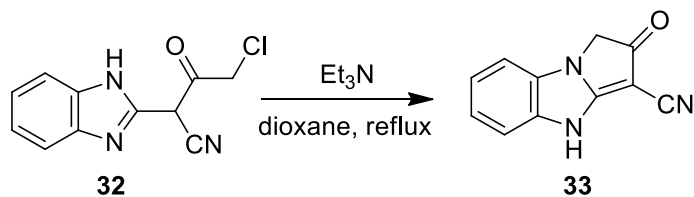
### Scheme 10

Treatment of 3-(*N*-pyrrolidinyl)-4-nitrotoluene **30** with ZnCl<sub>2</sub>/Ac<sub>2</sub>O followed by treatment with a mixture of Ac<sub>2</sub>O, dimethylaminopyridine (DMAP) and Et<sub>3</sub>N gave pyrrolo[1,2-*a*]benzimidazole **31** in 53% yield (Scheme 11).<sup>28,29</sup>



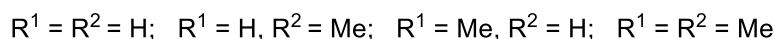
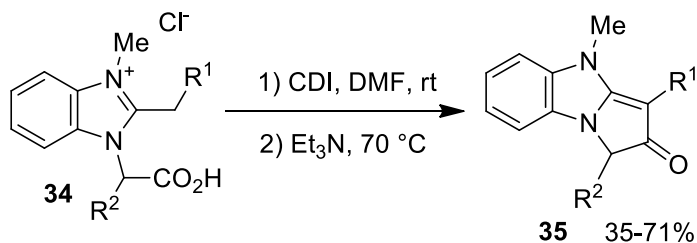
### Scheme 11

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



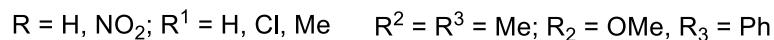
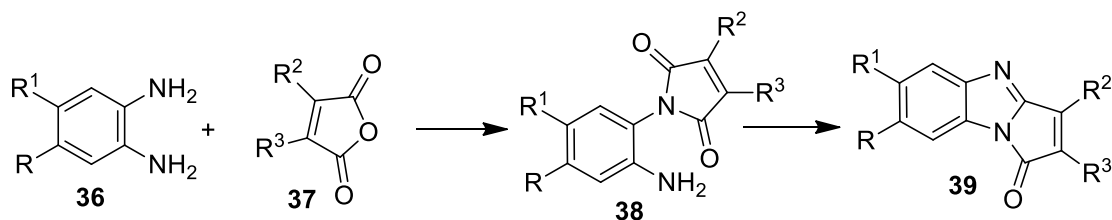
### Scheme 12

1-Carboxymethylbenzimidazolium chlorides **34** were converted into 4-methyl-4*H*-pyrrolo[1,2-*a*]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<sub>3</sub>N and heating the mixture at 70 °C for 5 h (Scheme 13).<sup>31</sup>



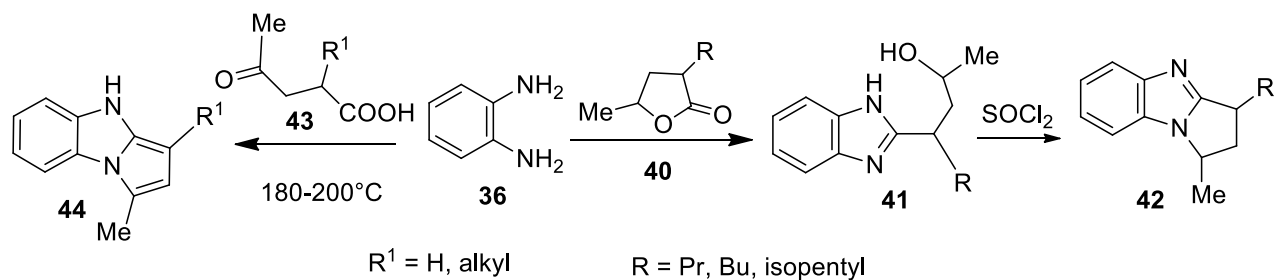
### Scheme 13

Reaction of *o*-phenylenediamines **36** with maleic anhydrides **37** gave *N*-(*o*-aminophenyl)-maleimides **38** which were cyclized to give pyrrolobenzimidazoles **39** (Scheme 14).<sup>32</sup>



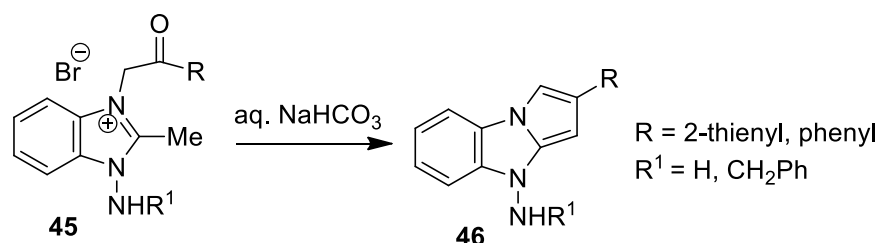
### Scheme 14

Cyclocondensation of  $\gamma$ -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).<sup>33</sup>



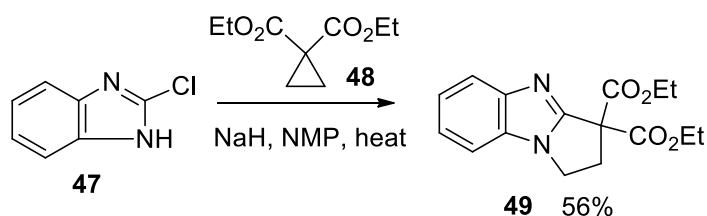
### Scheme 15

Reaction of benzimidazolium salts **45** with aq.  $\text{NaHCO}_3$  afforded the pyrrolobenzimidazole derivatives **46** (Scheme 16).<sup>34</sup>



### Scheme 16

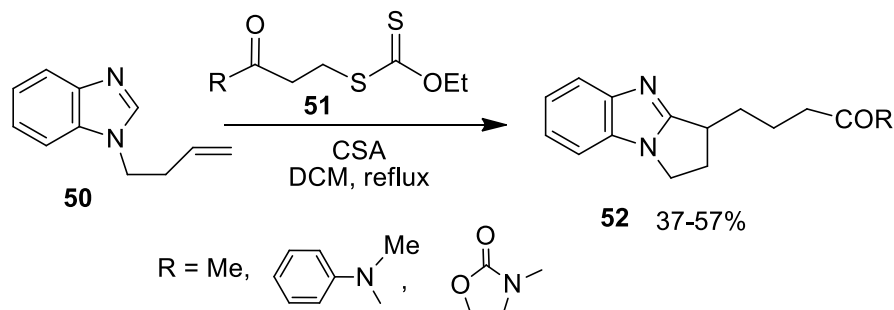
Inaba *et al.* reported the ring-opening reaction of cyclopropane dicarboxylate **48** on heating with 2-chlorobenzimidazole **47** in *N*-methylpyrrolidine (NMP) at 120 °C using sodium hydride to provide the pyrrolo[1,2-*a*]benzimidazole derivative **49** in 56% yield (Scheme 17).<sup>35</sup>



### Scheme 17

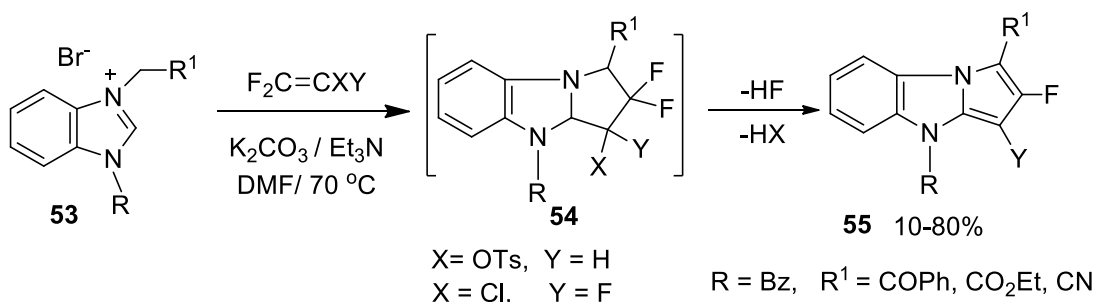
Reaction of 1-but-3-enylbenzimidazole **50** with xanthates **51** using 10-camphorsulfonic acid (CSA) in dichloromethane (DCM) under reflux condition gave the pyrrolo[1,2-*a*]benzimidazole derivatives **52** in 37-57% yields. The reaction proceeded *via* radical chain mechanism initiated by a small amount of lauroyl peroxide to give **52** (Scheme 18).<sup>36</sup>





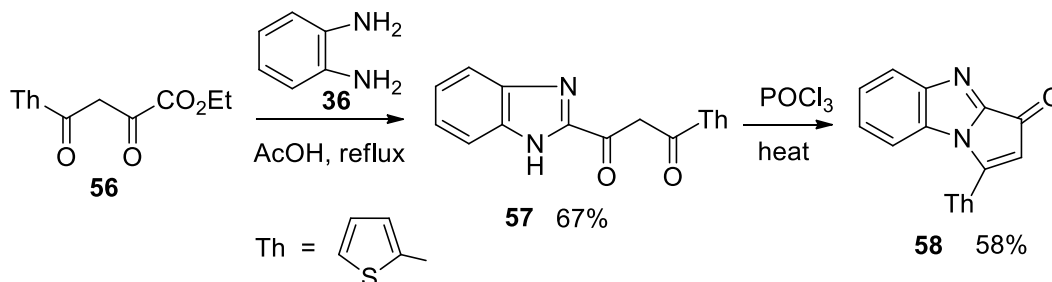
Scheme 18

1,3-Dipolar cycloaddition reaction between fluorinated vinyl tosylate and the benzimidazolium salts **53** afforded 4*H*-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).<sup>37</sup> 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).<sup>38</sup>



Scheme 19

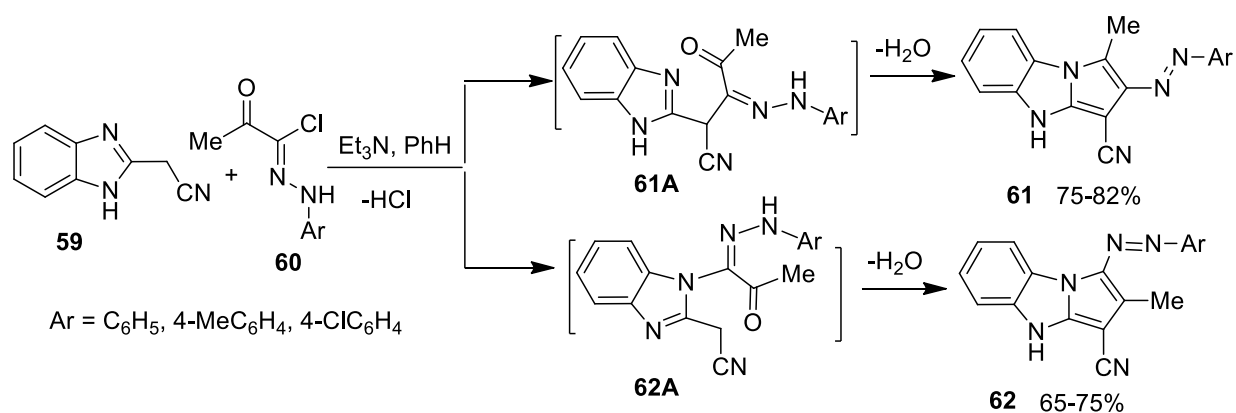
Condensation of ethyl 2-thienoylpyruvate **56** with *o*-phenylenediamine **36** in glacial acetic acid under reflux gave the corresponding 2-[(2-thienoyl)acetyl]benzimidazole **57**. Pyrrolo[1,2-*a*]benzimidazole derivative **58** was prepared in 58% *via* heating of compound **57** with phosphorus oxychloride on a water bath (Scheme 20).<sup>39</sup>



Scheme 20

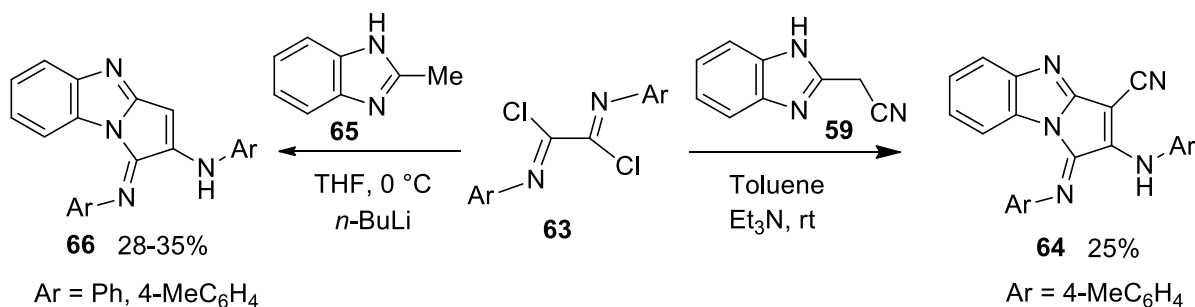
Reaction of 2-cyanomethylbenzimidazole **59** with hydrazonoyl halides **60** in the presence of triethylamine apparently led to the formation of pyrrolo[1,2-*a*]benzimidazoles **61** *via* the initial

exocyclic *C*-attack (Scheme 21).<sup>40</sup> However, later Awadallah *et al.* repeated the above reaction and they found that the product was 3-aryloxy-2-methylpyrrolo[1,2-*a*]benzimidazoles **62** rather than 2-aryloxy-3-methylpyrrolo[1,2-*a*]benzimidazoles **61** based on X-ray crystallography *via* the initial endocyclic *N*-attack (Scheme 21).<sup>41</sup>



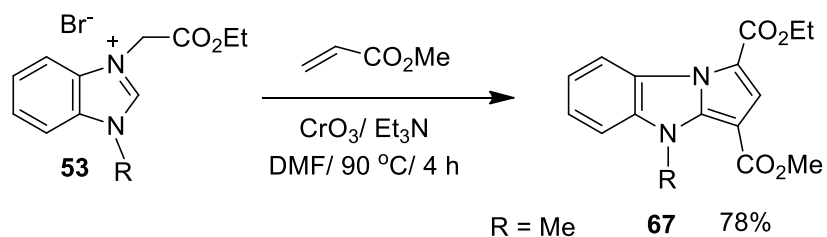
### Scheme 21

Pyrrolo[1,2-*a*]benzimidazol-2-amine derivative **64** was prepared in a moderate yield by reaction of 2-cyanomethylbenzimidazole **59** with oxalbis(*p*-tolylimido) dichloride **63** in toluene in the presence of triethylamine at room temperature (Scheme 22).<sup>42</sup> 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-1*H*-pyrrolo[1,2-*a*]benzimidazole-2-amines **66** in moderate yields (Scheme 22).<sup>43</sup>



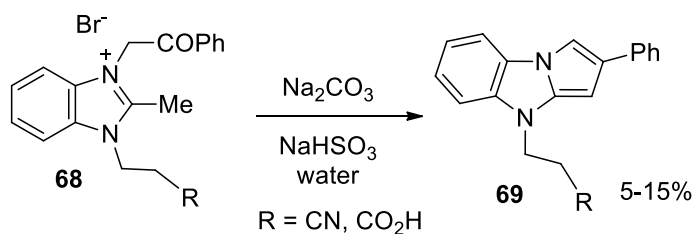
### Scheme 22

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).<sup>44</sup>



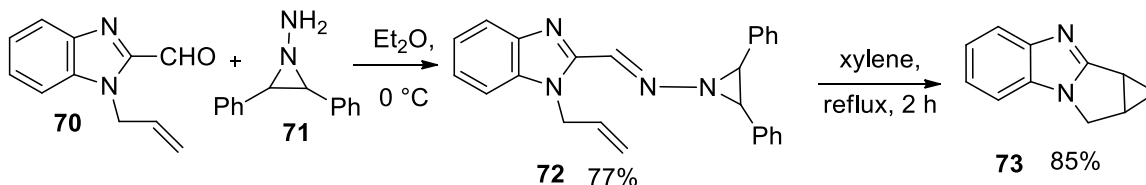
Scheme 23

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).<sup>45</sup>



Scheme 24

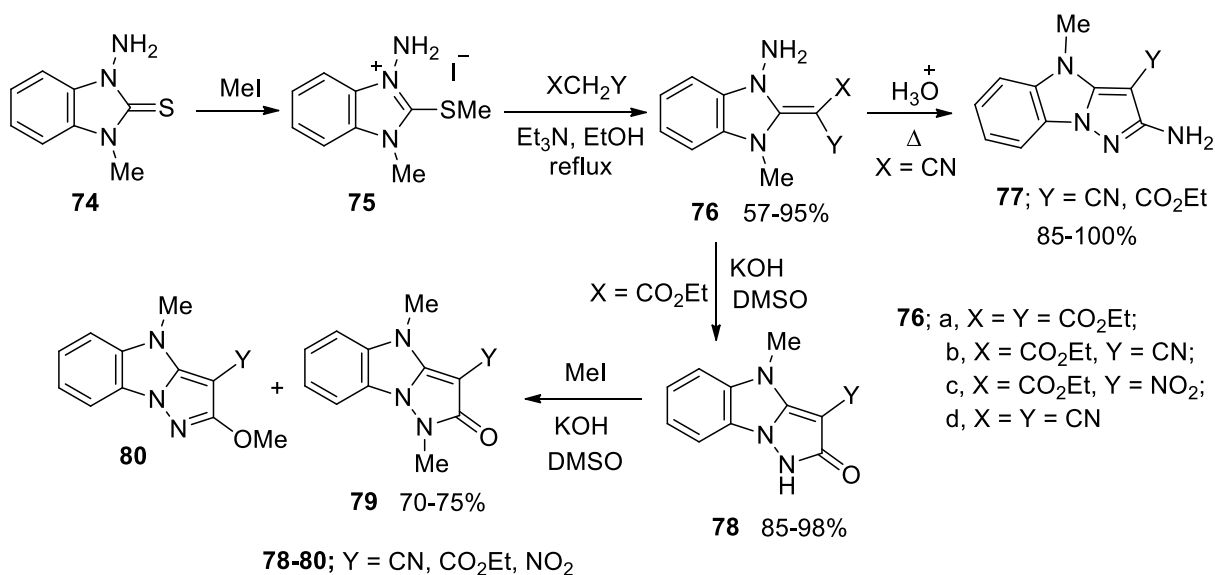
Reaction of benzimidazole-2-carboxaldehyde **70** with *trans*-1-amino-2,3-diphenylaziridine **71** gave 1-[1-allyl-1*H*-benzimidazol-2-yl-methylidene]-2,3-diphenyl-1-aziridinamine **72** which underwent thermolysis facilitated intramolecular 1,3-dipolar cycloaddition followed by loss of  $\text{N}_2$  to give the cyclopropapyrrolo[1,2-*a*]benzimidazole **73** (Scheme 25) in excellent yield.<sup>46</sup>



Scheme 25

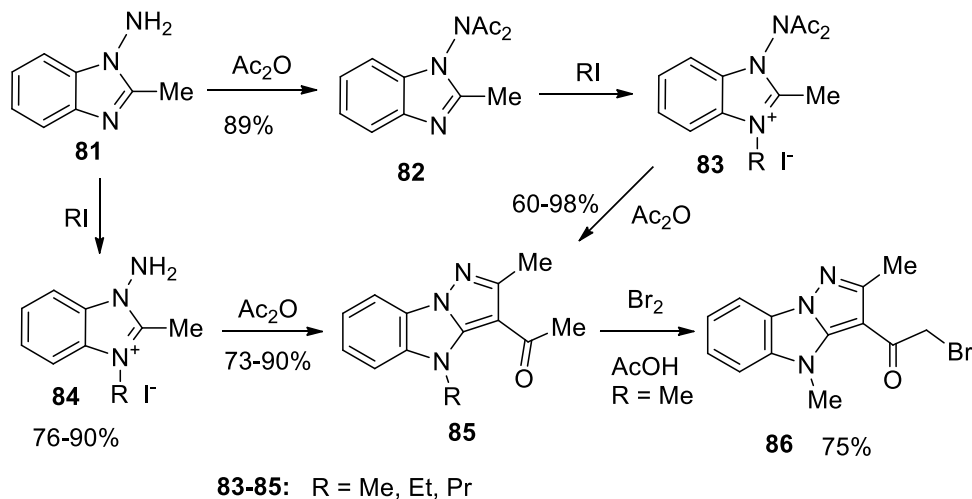
## 2.2. Pyrazolobenzimidazoles

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 methylenebenzimidazoline 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).<sup>47</sup>



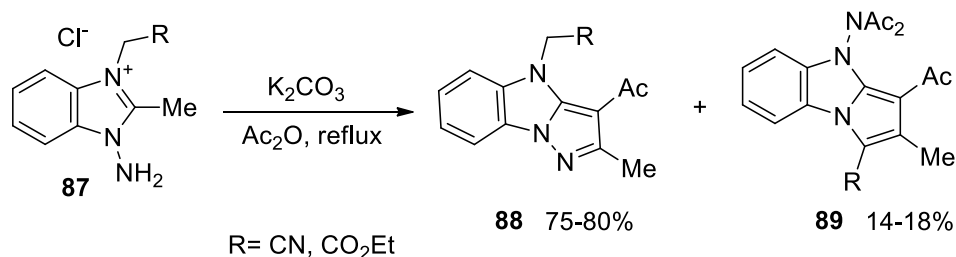
## Scheme 26

Acylation 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).<sup>48</sup> 3-( $\alpha$ -Bromoacetyl)pyrazolo[1,5-*a*]benzimidazole **86** was obtained by brominating 3-acetylpyrazolo[1,5-*a*]benzimidazoles **85** with bromine in AcOH (Scheme 27).<sup>49</sup>



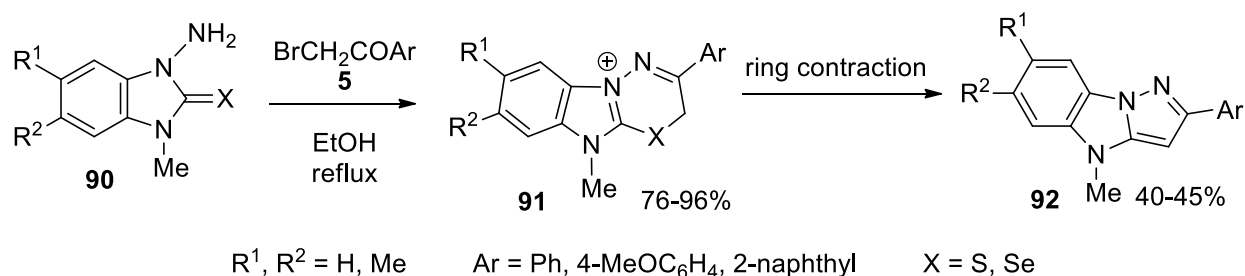
## Scheme 27

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).<sup>50</sup>



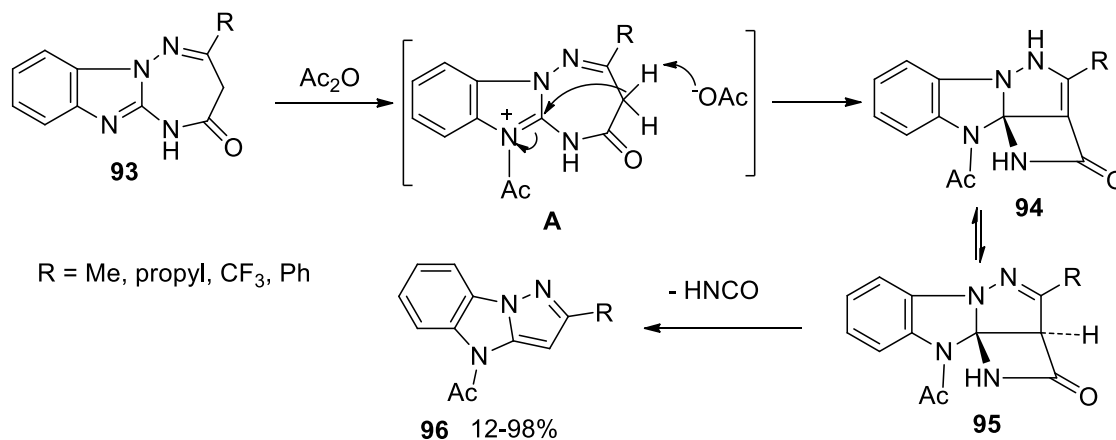
Scheme 28

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).<sup>51,52</sup>



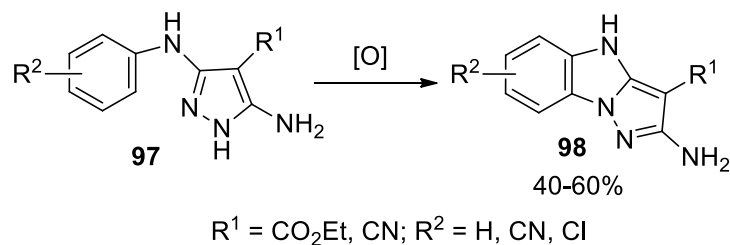
Scheme 29

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.<sup>53</sup>



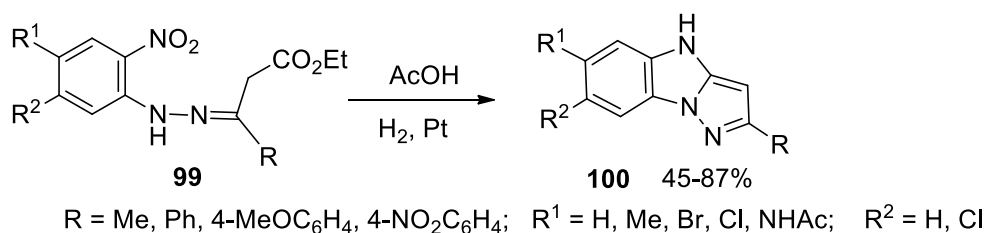
Scheme 30

Free radical oxidation of anilopyrazoles **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).<sup>54</sup>



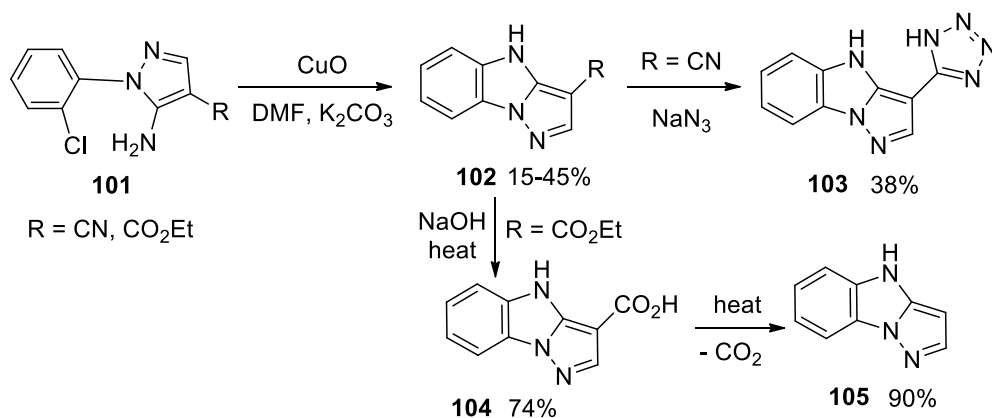
Scheme 31

4*H*-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).<sup>55</sup>



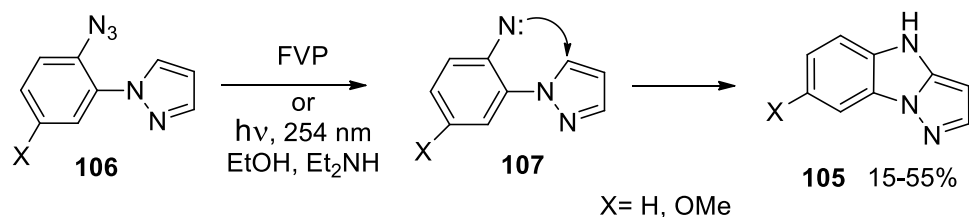
Scheme 32

When 5-amino-1-(*o*-chlorophenyl)pyrazoles **101** were heated with copper(II) oxide in DMF and anhydrous  $\text{K}_2\text{CO}_3$ , the 4*H*-pyrazolo[1,5-*a*]benzimidazoles **102** were formed. Treatment of **102** ( $R = \text{CN}$ ) with sodium azide gave 3-(tetrazol-5'-yl)-4*H*-pyrazolo[1,5-*a*]benzimidazole **103**. Basic hydrolysis of **102** ( $R = \text{CO}_2\text{Et}$ ) led to 4*H*-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 4*H*-pyrazolo[1,5-*a*]benzimidazole **105** (Scheme 33).<sup>56</sup>



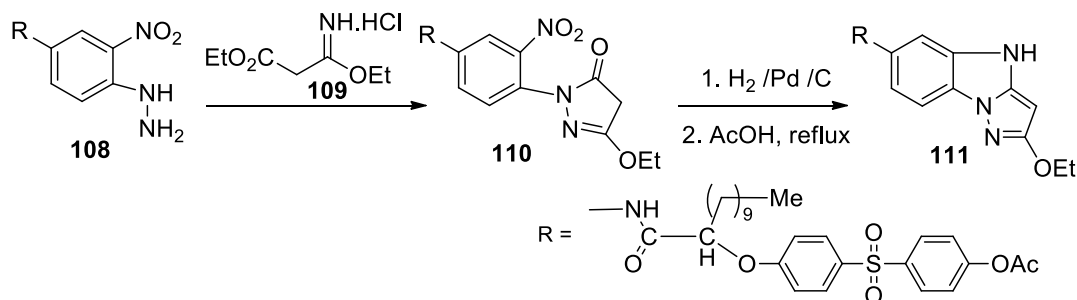
Scheme 33

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



Scheme 34

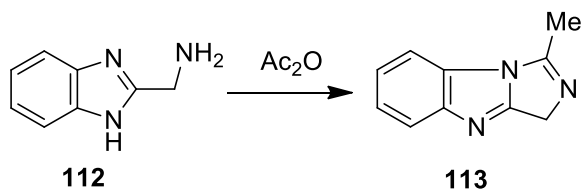
The hydrazine derivative **108** was cyclocondensed with ethyl 3-ethoxy-3-iminopropanoate hydrochloride **109** to give the ethoxypyrazolinone derivative **110** which was hydrogenated in acetic acid in the presence of Pd/C and then cyclized by refluxing in HOAc after removal of Pd/C to give the pyrazolobenzimidazole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



Scheme 35

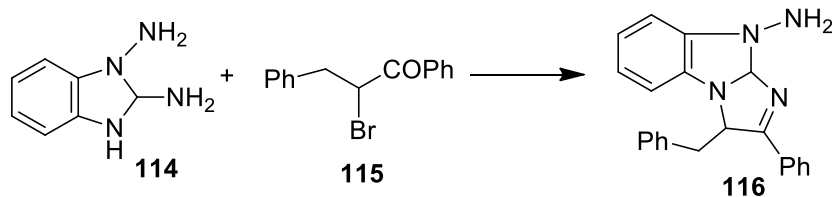
### 2.3. Imidazobenzimidazoles

Imidazo[1,5-*a*]benzimidazole derivative **113** was prepared by reaction of 2-aminomethylbenzimidazole **112** with acetic anhydride (Scheme 36).<sup>60</sup>



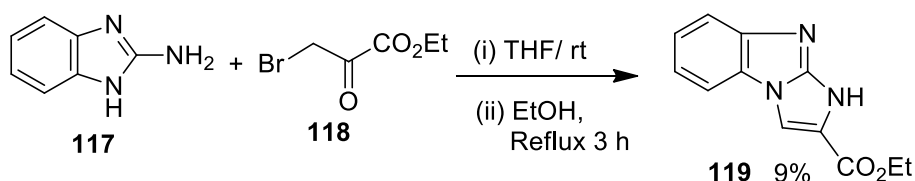
Scheme 36

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).<sup>61</sup>



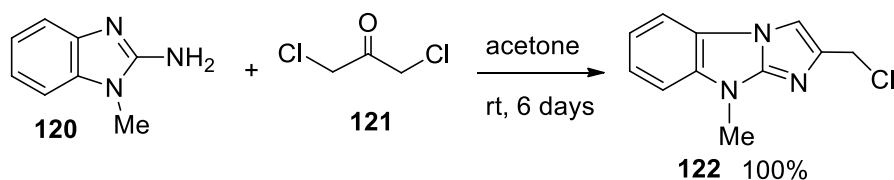
Scheme 37

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).<sup>62</sup>



Scheme 38

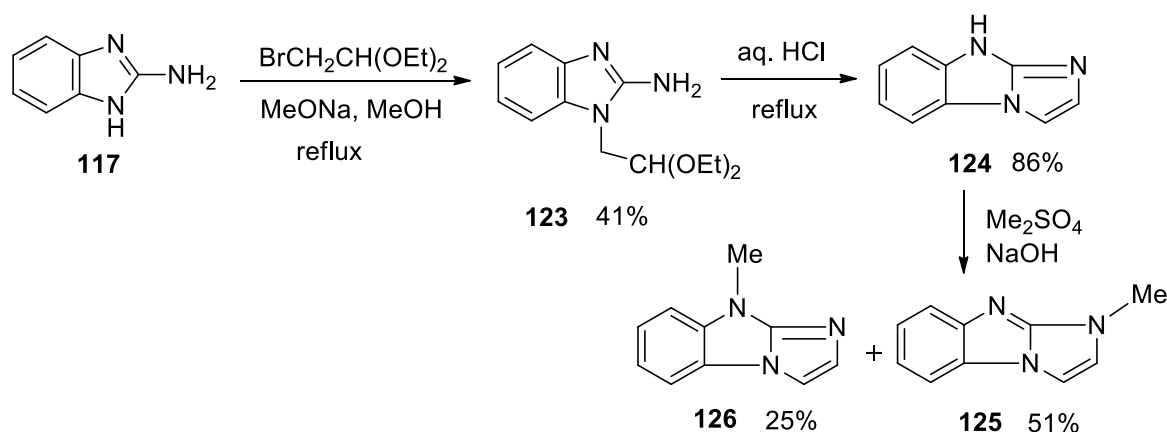
2-(Chloromethyl)imidazo[1,2-*a*]benzimidazole **122** was prepared by condensation of 1-methyl-2-aminobenzimidazole **120** with 1,3-dichloroacetone **121** (Scheme 39).<sup>63</sup>



Scheme 39

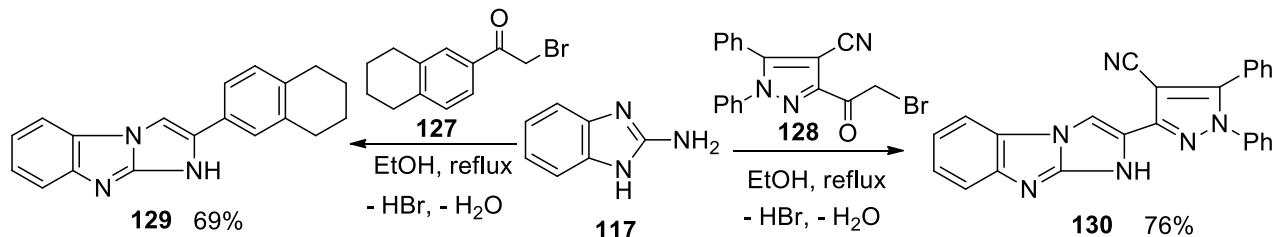
Treatment of 2-aminobenzimidazole **117** with 2-bromoacetaldehyde diethylacetal in a solution of NaOMe in MeOH under reflux gave 2-amino-1-(2,2-diethoxyethyl)benzimidazole **123**. Refluxing the latter compound **123** in HCl afforded imidazo[1,2-*a*]benzimidazole **124** which on treatment with dimethyl 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).<sup>64</sup>





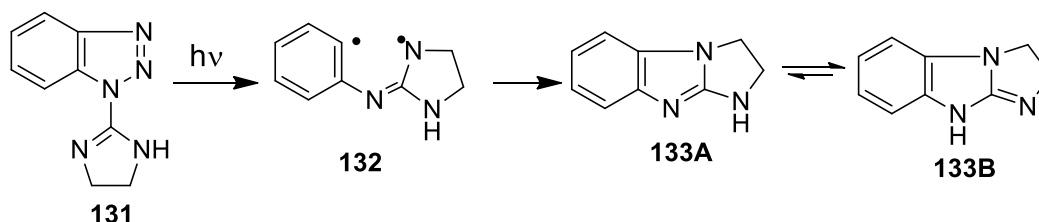
Scheme 40

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



Scheme 41

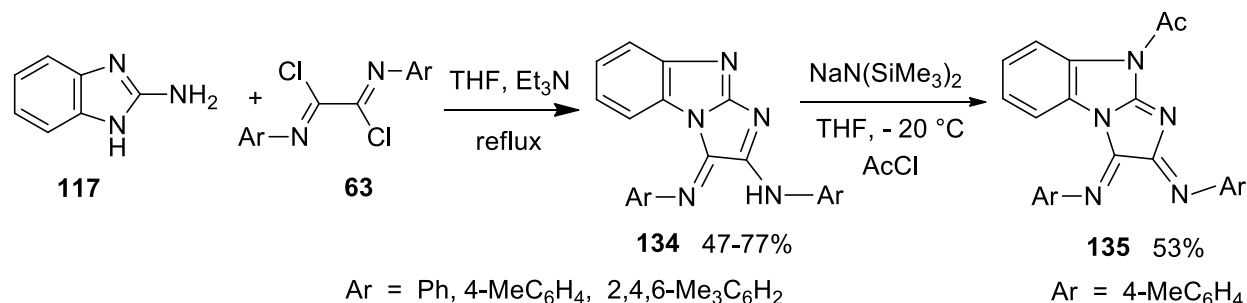
Photolysis of 1-(4,5-dihydro-1*H*-imidazol-2-yl)benzotriazole **131** in acetonitrile at 254 nm for 18 h gave dihydroimidazo[1,2-*a*]benzimidazole **133** in good yield. The reaction took place via the diradical intermediate **132** (Scheme 42).<sup>67</sup>



Scheme 42

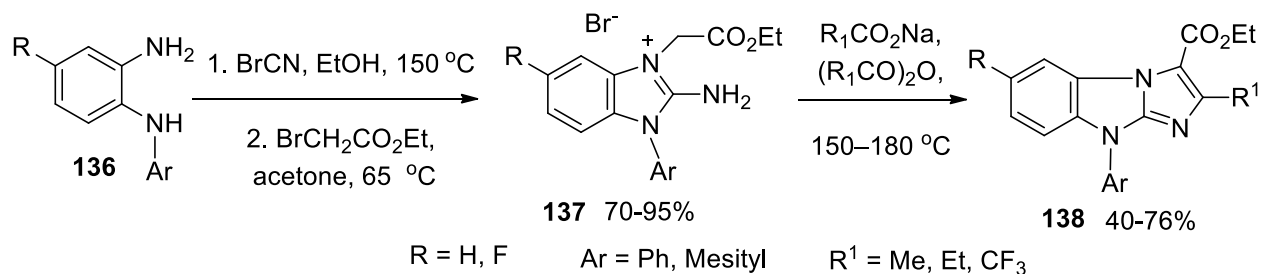
Treatment of the diimidoyl dichlorides **63** with 2-aminobenzimidazole **117** in refluxing THF in the presence of Et<sub>3</sub>N resulted in the formation of the 3*H*-imidazo[1,2-*a*]benzimidazol-2-

amines **134** in good yield. Acylation of the latter **134** (Ar = 4-tolyl) with acetyl chloride in the presence  $\text{NaN}(\text{SiMe}_3)_2$  at low temperature gave 9-acetyl-3*H*-imidazo[1,2-*a*]benzimidazole **135** in 53% yield (Scheme 43).<sup>68</sup>



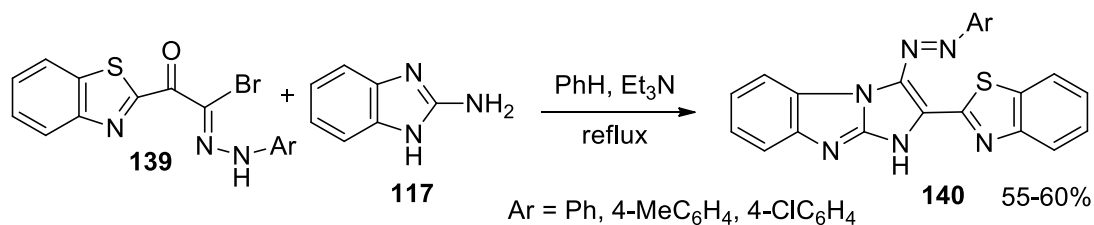
### Scheme 43

2-Aminobenzimidazolium bromides **137** were formed by reaction of *o*-(*N*-aryl)phenylenediamines **136** with cyanogen bromide in ethanol at  $150^\circ\text{C}$ , 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).<sup>69</sup>



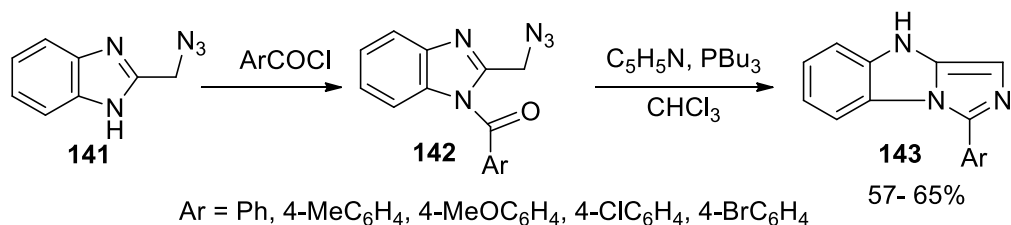
### Scheme 44

Treatment of hydrazoneyl bromides **139** with 2-aminobenzimidazole **117** in refluxing ethanol furnished 3-arylaazo-1*H*-imidazo[1,2-*a*]benzimidazoles **140** (Scheme 45).<sup>70</sup>



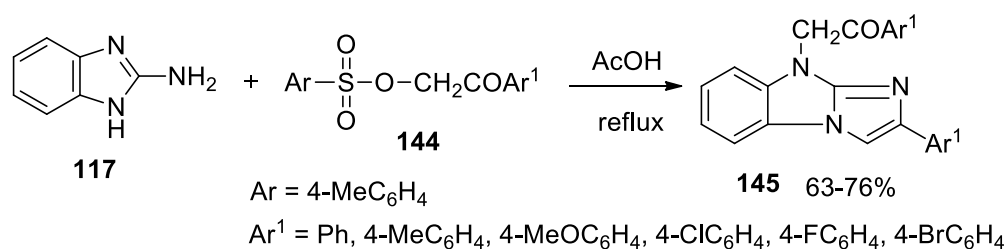
### Scheme 45

2-Azidomethylbenzimidazole **141** reacted with benzoyl chlorides and gave the benzoyl(azidomethyl)benzimidazoles **142** which reacted with tributylphosphine to give the corresponding 3-aryl-9*H*-imidazo[1,2-*a*]benzimidazoles **143** (Scheme 46).<sup>71</sup>



### Scheme 46

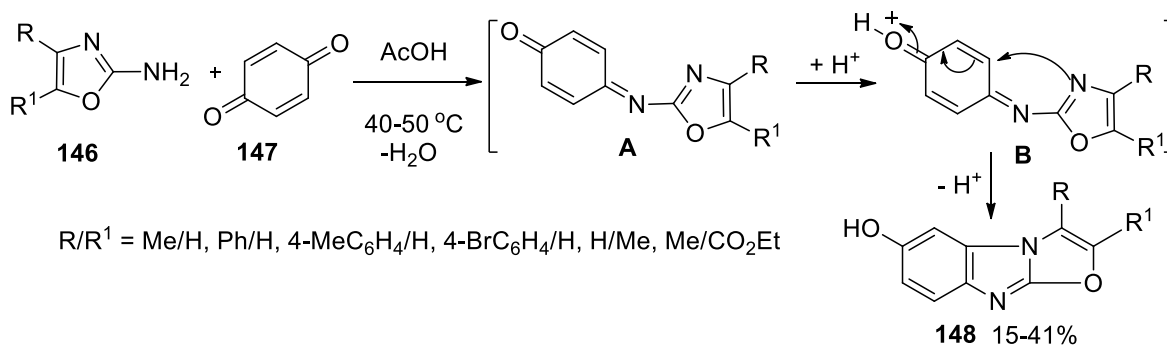
2,9-Disubstituted imidazo[1,2-*a*]benzimidazoles **145** were obtained regioselectively in good yields by heating a mixture of 2-aminobenzimidazole **117** and  $\alpha$ -tosyloxy ketones **144** in acetic acid (Scheme 47).<sup>72</sup>



### Scheme 47

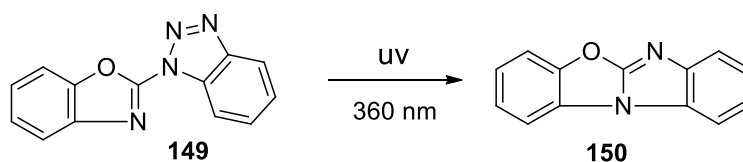
## 2.4. Oxazolobenzimidazoles

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.<sup>73</sup>



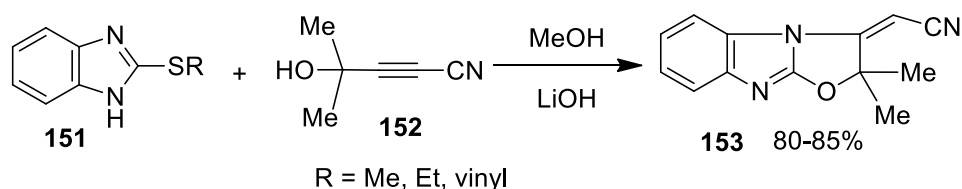
### Scheme 48

Benzimidazo[2,1-*b*]benzoxazole **150** was prepared photolytically at 360 nm from 1-(2-benzoxazolyl)benzotriazole **149** (Scheme 49).<sup>74</sup>



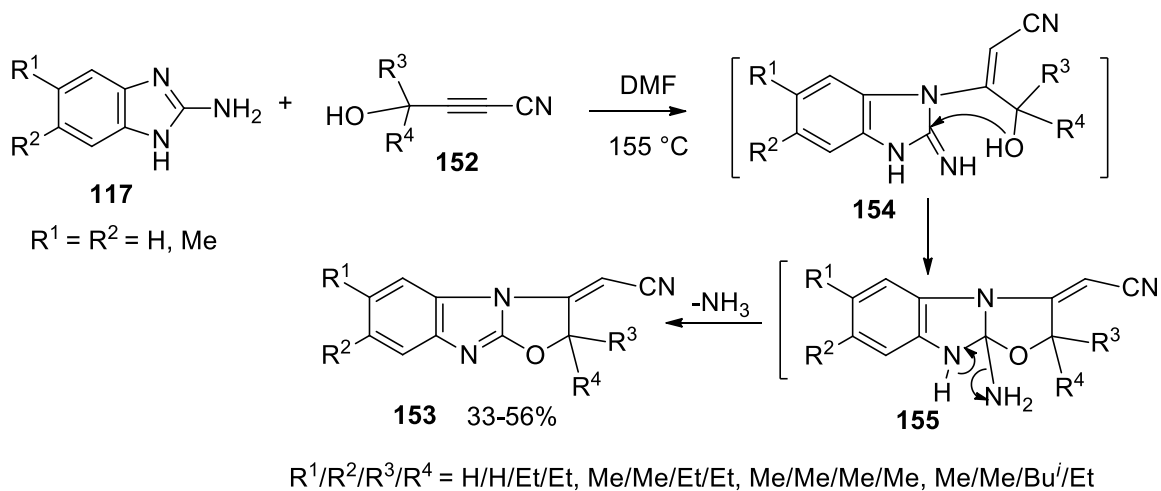
### Scheme 49

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).<sup>75</sup>



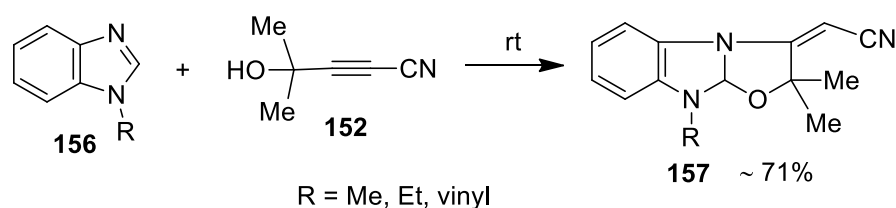
### Scheme 50

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.<sup>76</sup>



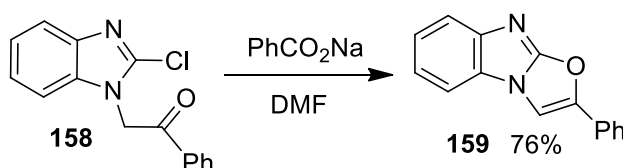
### Scheme 51

1-Substituted benzimidazoles **156** were readily annulated regio- and stereoselectively when treated with  $\alpha,\beta$ -acetylenic- $\gamma$ -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).<sup>77</sup>



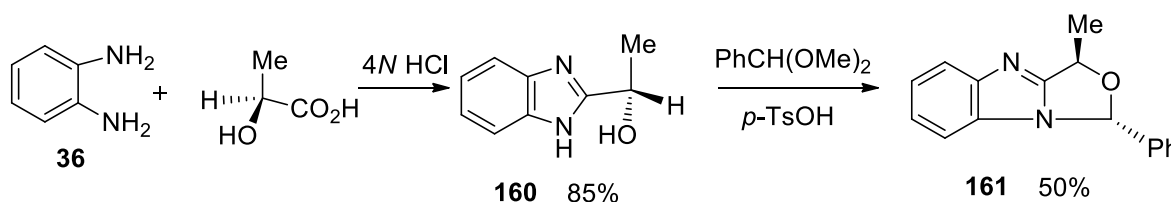
### Scheme 52

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).<sup>78</sup>



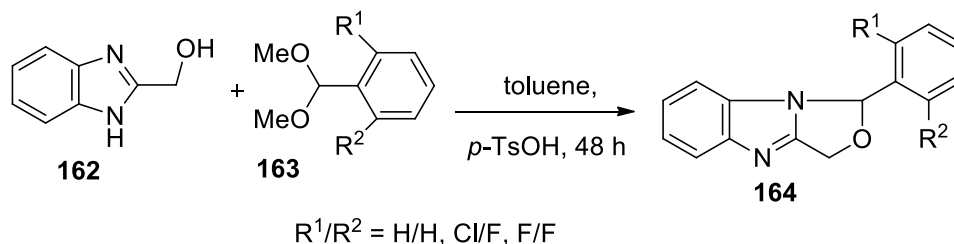
### Scheme 53

Condensation of *o*-phenylenediamine **36** with (*S*)-lactic acid in 4*N* 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).<sup>79,80</sup>



### Scheme 54

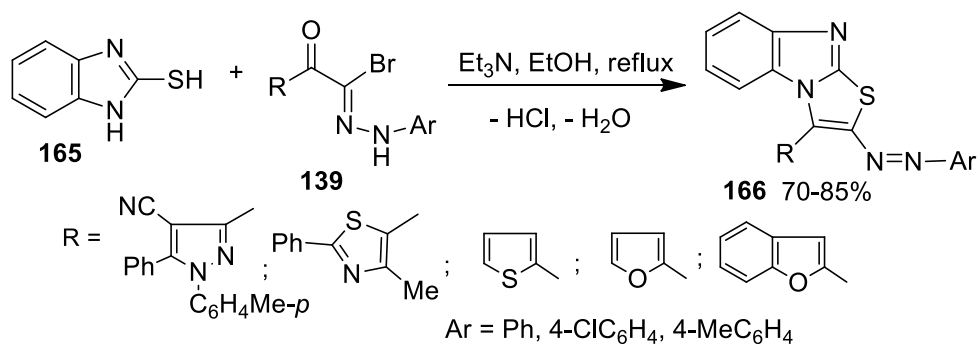
Heating a mixture of 2-(hydroxymethyl)benzimidazole **162** and benzaldehyde dimethyl acetals **163** in dry toluene and a catalytic amount of *p*-toluenesulfonic acid for 48 h gave the oxazolo[3,4-*a*]benzimidazole derivatives **164** (Scheme 57).<sup>81</sup>



Scheme 55

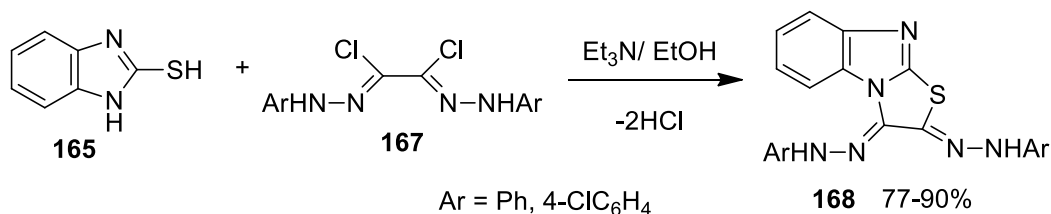
## 2.5. Thiazolobenzimidazoles

Reaction of hydrazoneyl bromides **139** with benzimidazole-2-thiol **165** in ethanolic triethylamine solution at reflux gave the thiazolo[3,2-*a*]benzimidazoles **166** in good yields (Scheme 56).<sup>82-84</sup>



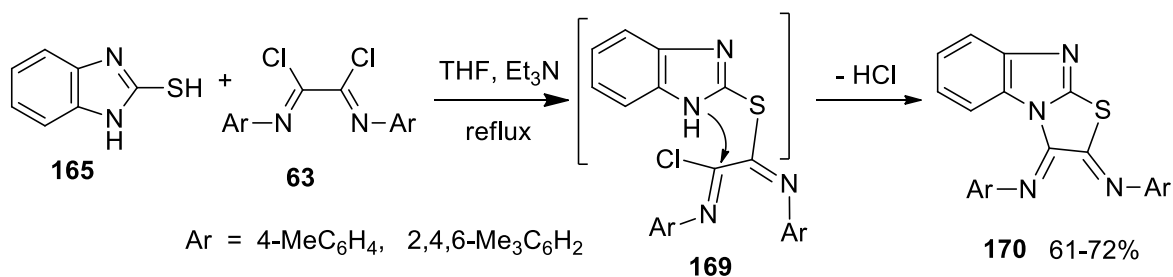
Scheme 56

Benzimidazole-2-thiol **165** reacted similarly with *bis*-hydrazoneyl chlorides **167** in refluxing ethanol in the presence of triethylamine to give 2,3-*bis*-(arylhyazone)-2,3-dihydrothiazolo[3,2-*a*]benzimidazoles **168** in high yields (Scheme 57).<sup>85,86</sup>



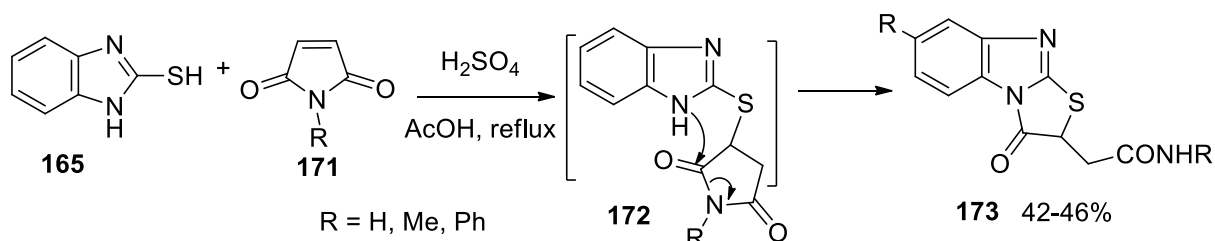
Scheme 57

Refluxing of oxal-*bis*-(arylimidoyl) dichlorides **63** in THF with benzimidazole-2-thiol **165** in the presence of Et<sub>3</sub>N afforded the thiazolo[3,2-*a*]benzimidazole derivatives **170** (Scheme 58).<sup>68</sup>



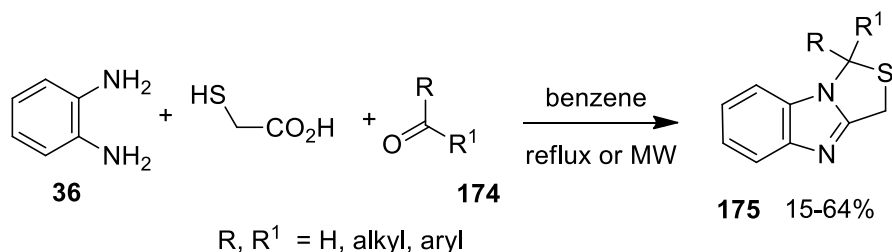
## Scheme 58

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).<sup>87</sup>



## Scheme 59

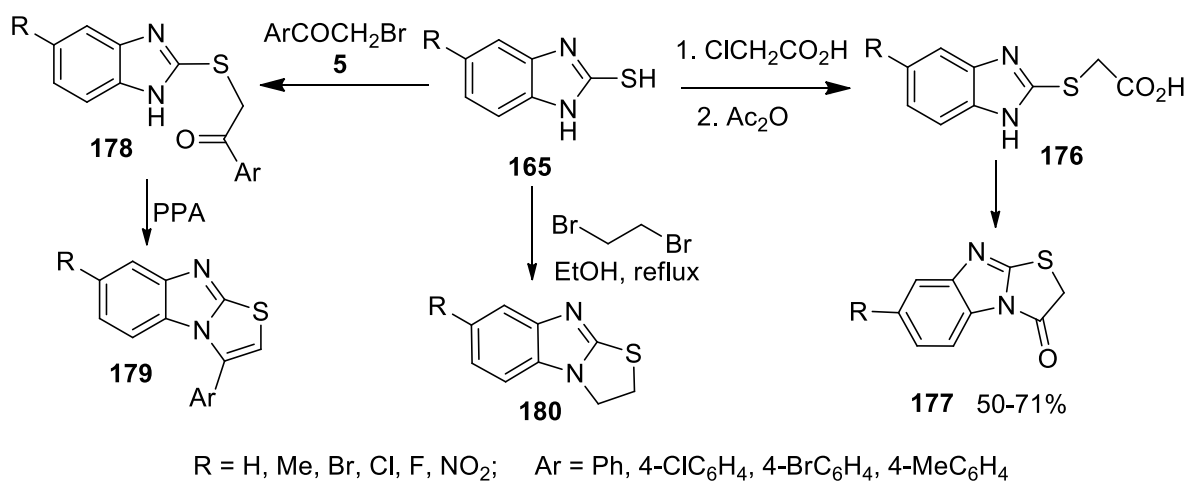
Thiazolo[3,4-*a*]benzimidazoles **175** were prepared by heating a mixture of *o*-phenylenediamine, 2-mercaptoacetic acid and the appropriate carbonyl compounds **174** in benzene under conventional reflux or microwave irradiation (Scheme 60).<sup>88-92</sup>



## Scheme 60

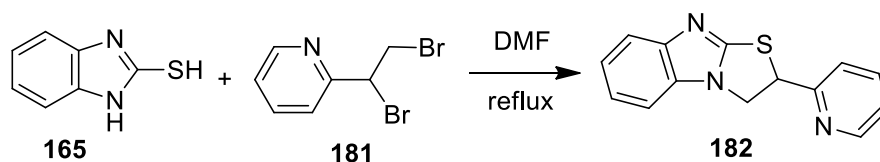
Condensation of 2-mercaptobenzimidazoles **165** with chloroacetic acid and acetic anhydride gave the thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones **177** in good yields.<sup>93-96</sup> Reaction of **165** with  $\alpha$ -bromoketones **5** followed by polyphosphoric acid (PPA) yielded the thiazolo[3,2-

*a*]benzimidazoles **179**.<sup>97-102</sup> Condensation of **165** with 1,2-dibromoethane in ethanol yielded the thiazolo[3,2-*a*]benzimidazole derivatives **180** (Scheme 61).<sup>103</sup>



### Scheme 61

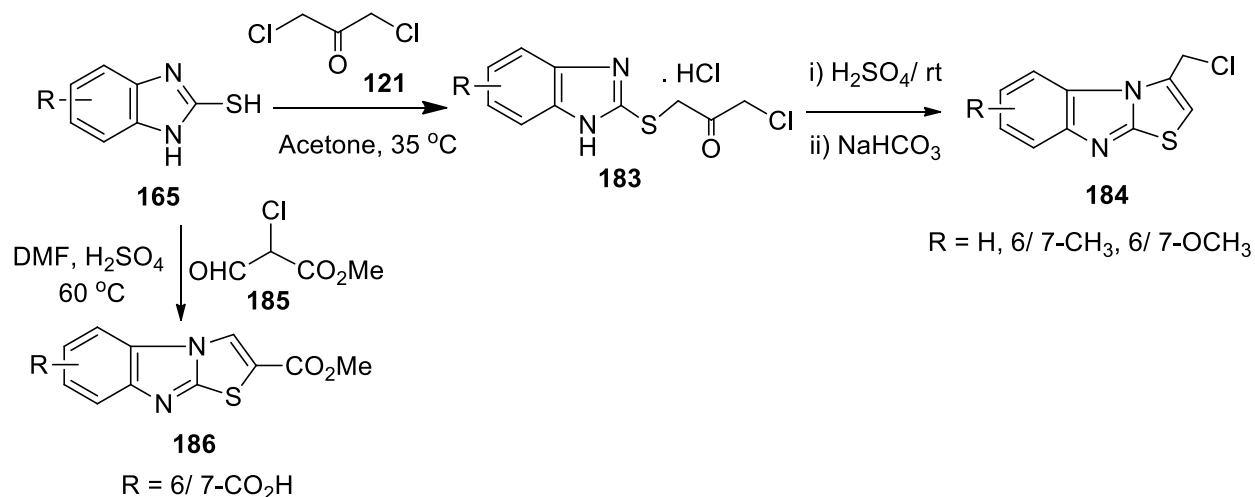
2,3-Dihydrothiazolo[3,2-*a*]benzimidazole **182** was prepared by condensation of 2-(1,2-dibromoethyl)pyridine **181** in DMF with 2-mercaptobenzimidazole **165** (Scheme 62).<sup>104-106</sup>



### Scheme 62

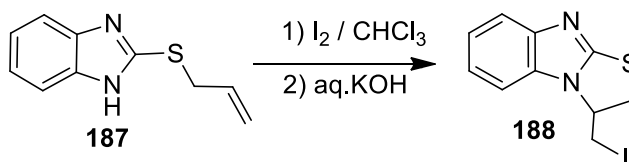
Treatment of benzimidazole-2-thiol **165** with 1,3-dichloroacetone **121** gave 1-(2-benzimidazolylthio)-3-chloro-2-propanone hydrochloride **183**. Cyclization of **183** in sulfuric acid followed by basic work up provided 3-chloromethylthiazolo[3,2-*a*] benzimidazole **184**.<sup>107-109</sup> An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





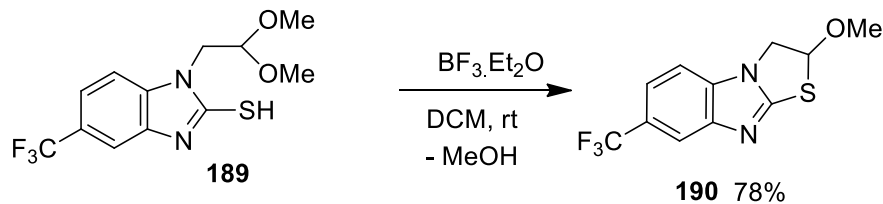
### Scheme 63

Treatment of 2-(allylthio)benzimidazole **187** with iodine in  $\text{CHCl}_3$  and then with aqueous potassium hydroxide gave the thiazolo[3,2-*a*]benzimidazole **188** (Scheme 64).<sup>111</sup>



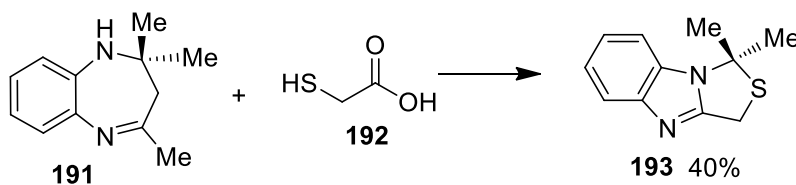
### Scheme 64

2-Methoxy-7-trifluoromethyl-2,3-dihydrothiazolo[3,2-*a*]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).<sup>112</sup>



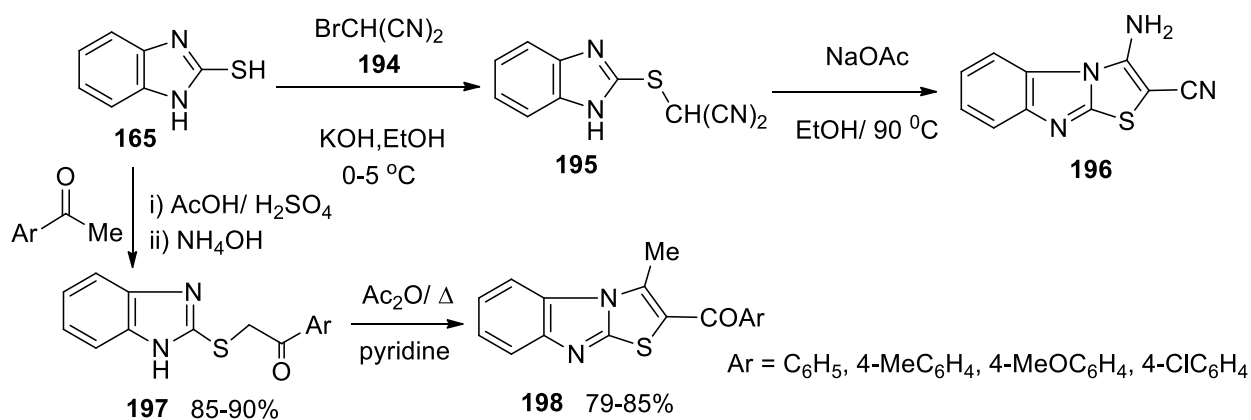
### Scheme 65

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



### 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).<sup>114</sup> 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).<sup>115</sup>

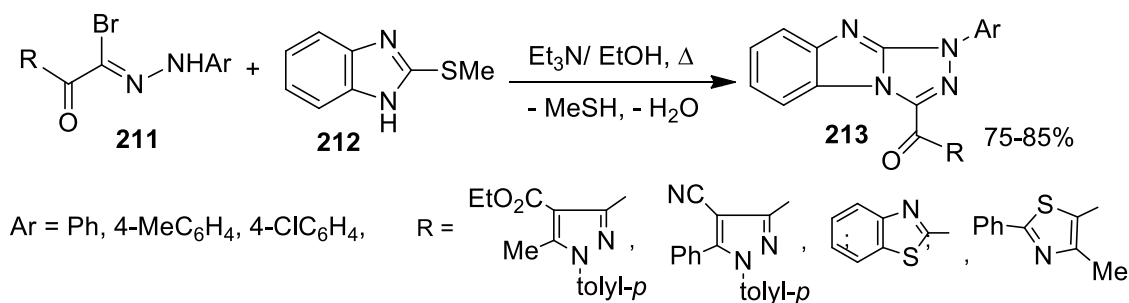


### Scheme 67

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.<sup>116-118</sup> Alternatively, 3-methylthiazolo[3,2-*a*]benzimidazole **201** was obtained in 95% by refluxing **202** in ethanolic KOH solution (Scheme 68).<sup>119</sup>

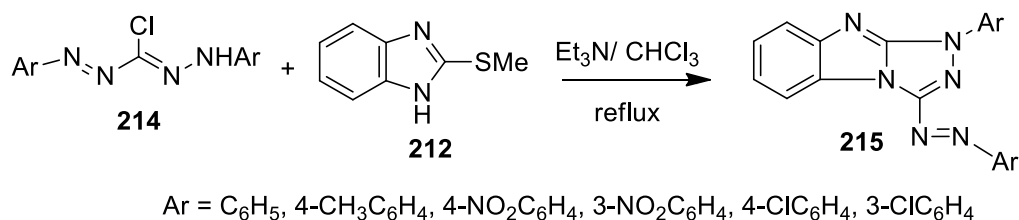


Similarly, the hydrazonoyl bromides **211** reacted with 2-methylthiobenzimidazole **212** in refluxing ethanol in the presence of triethylamine to give 1,2,4-triazolo[4,3-*a*]benzimidazole derivatives **213** (Scheme 71).<sup>70,84,123,124</sup>



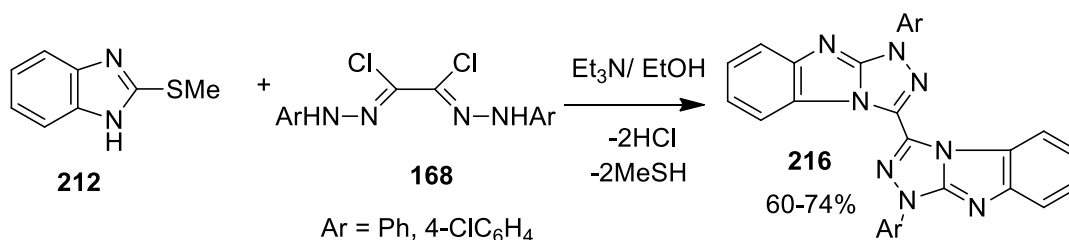
Scheme 71

3-Arylo[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).<sup>125</sup>



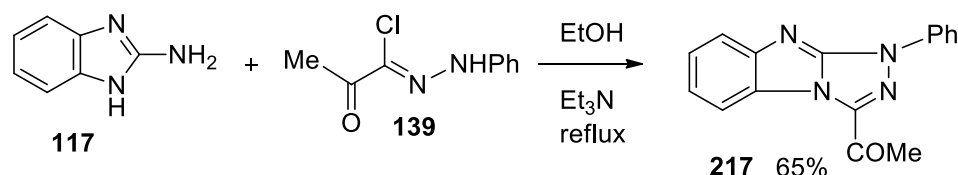
Scheme 72

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).<sup>85</sup>



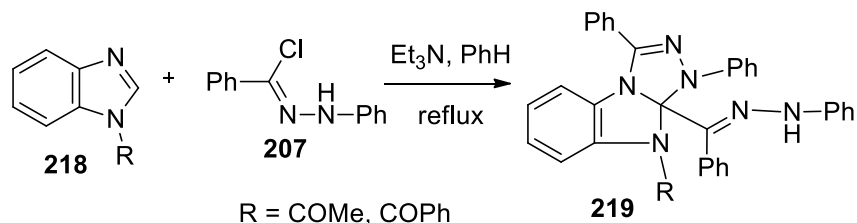
Scheme 73

Reaction of 2-aminobenzimidazole **117** with the hydrazonoyl chloride **139** gave 1-phenyl-3-acetyl-1,2,4-triazolo[4,3-*a*]benzimidazole **217** (Scheme 74).<sup>126</sup>



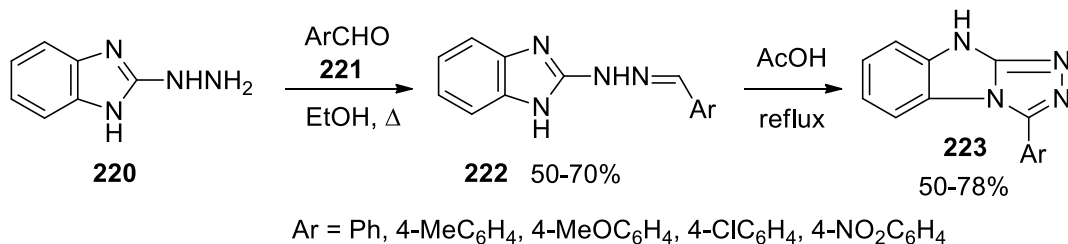
### Scheme 74

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



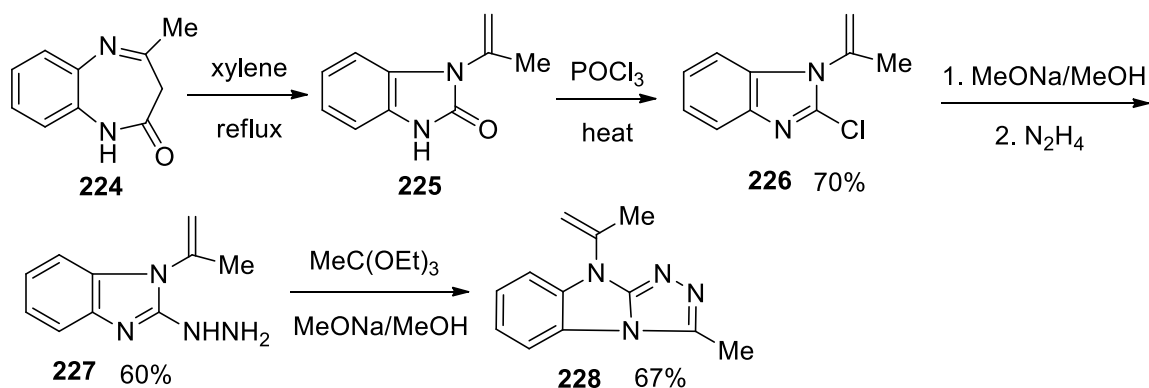
### Scheme 75

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



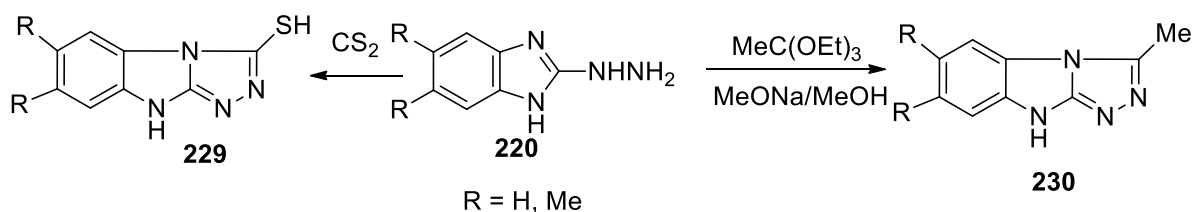
### Scheme 76

Heating 4-methyl-1,5-benzodiazepin-2-one **224** in xylene induced rearrangement into the 1-( $\alpha$ -methylvinyl)benzimidazole **225**. Treatment of **225** with POCl<sub>3</sub> gave the 2-chlorobenzimidazole derivative **226** which on reaction with sodium methoxide followed by hydrazine then triethyl *ortho*-acetate afforded the 9-( $\alpha$ -methylvinyl)triazolobenzimidazole **228** (Scheme 77).<sup>129</sup>



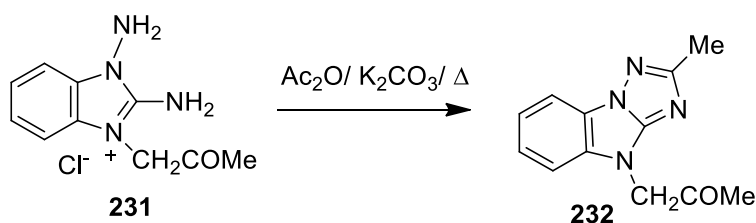
Scheme 77

Cyclisation of 2-hydrazinobenzimidazoles **220** with  $\text{CS}_2$  and with triethyl orthoacetate gave the corresponding triazolobenzimidazoles **229** and **230**, respectively (Scheme 78).<sup>130,131</sup>



Scheme 78

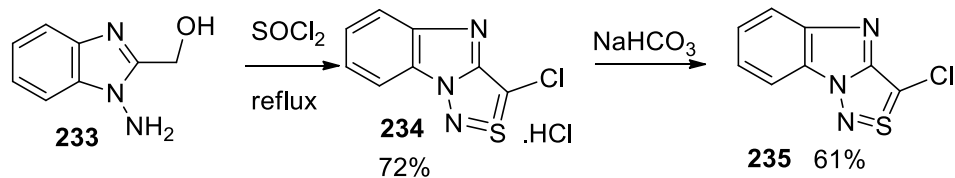
Cyclization of 1,2-diaminobenzimidazolium salt **231**, by boiling it in acetic anhydride in the presence of  $\text{K}_2\text{CO}_3$  gave the triazolobenzimidazole derivative **232** (Scheme 79).<sup>132</sup>



Scheme 79

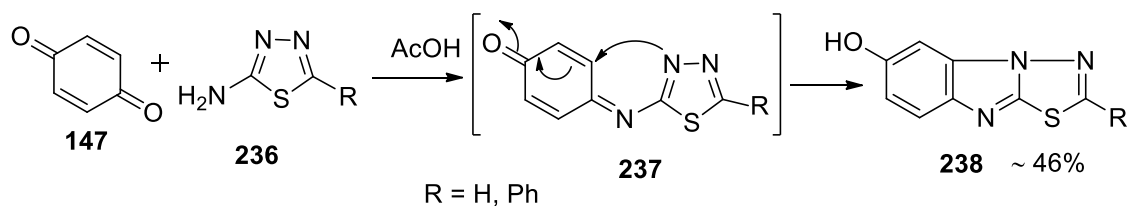
## 2.7. Thiadiazolobenzimidazoles

Reaction of (1-amino-1*H*-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).<sup>133-135</sup>



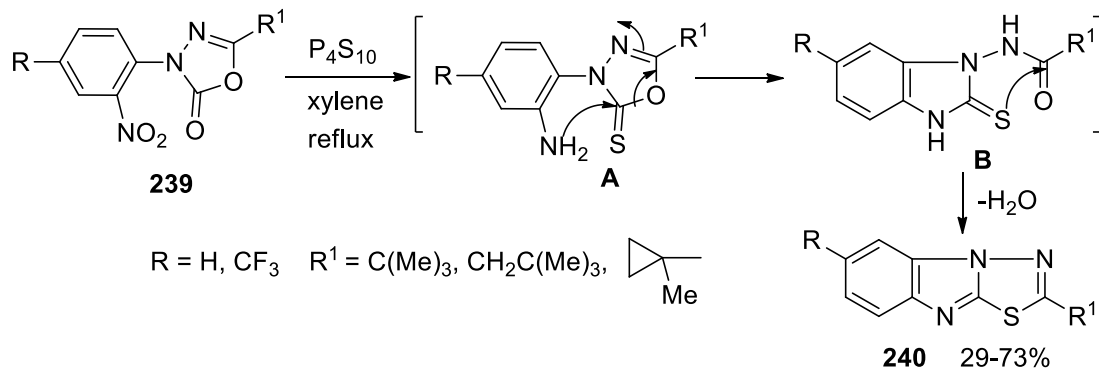
Scheme 80

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-*a*]benzimidazoles **238** (Scheme 81).<sup>136</sup>



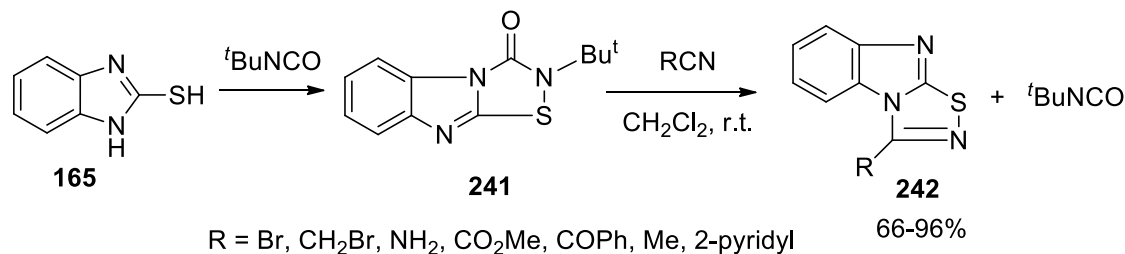
Scheme 81

The reaction of 1,3,4-oxadiazolinones **239** with phosphorus pentasulfide ( $\text{P}_4\text{S}_{10}$ ) in refluxing xylene gave 1,3,4-thiadiazolo[3,2-*a*]benzimidazoles **240** probably according to the mechanism shown in Scheme 82.<sup>137</sup> After an induction period of approximately 10 hrs, the system,  $\text{P}_4\text{S}_{10}$ -refluxing xylene, generated  $\text{H}_2\text{S}$  which, in turn, was capable of reducing the nitro group.



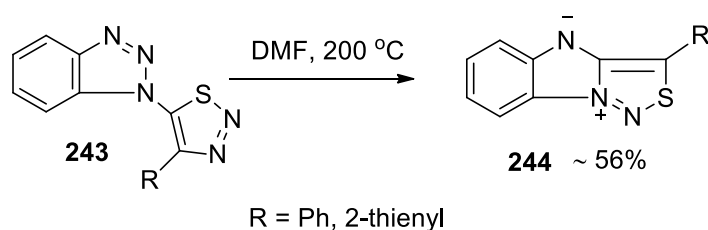
Scheme 82

Amidation of 2-mercaptobenzimidazole **165** by *tert*-butyl isocyanate followed by cyclization gave 2-*tert*-butyl-1,2,4-thiadiazolo[4,5-*a*]benzimidazole **241** which on treatment with nitriles afforded the 1,2,4-thiadiazolo[4,5-*a*]benzimidazoles **242** (Scheme 83).<sup>138-140</sup>



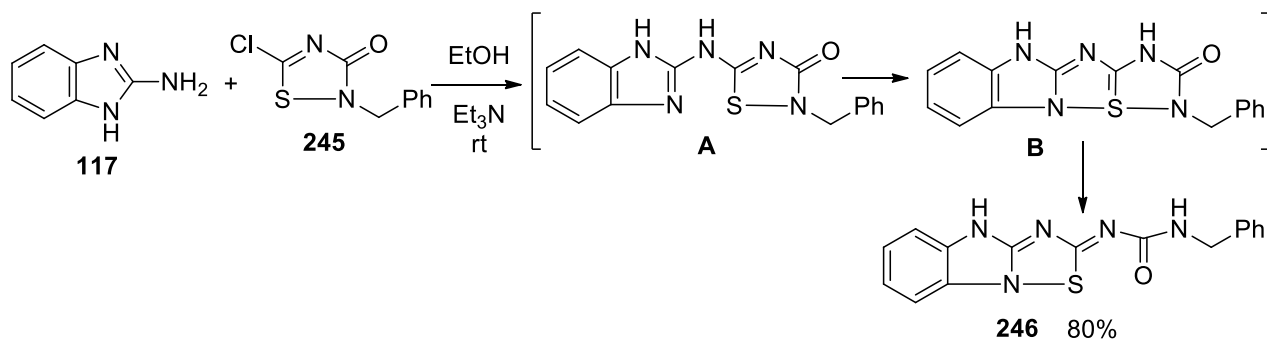
## Scheme 83

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).<sup>141</sup>



## Scheme 84

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).<sup>142</sup>

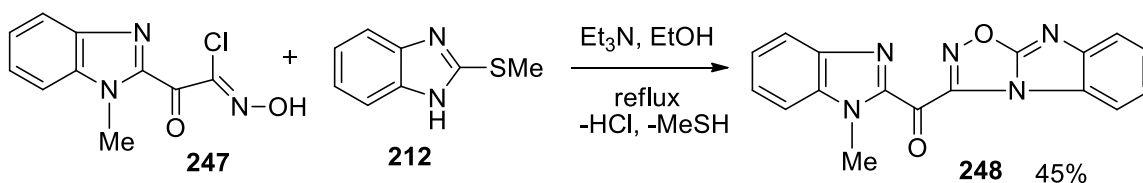


## Scheme 85

## 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).<sup>143</sup>



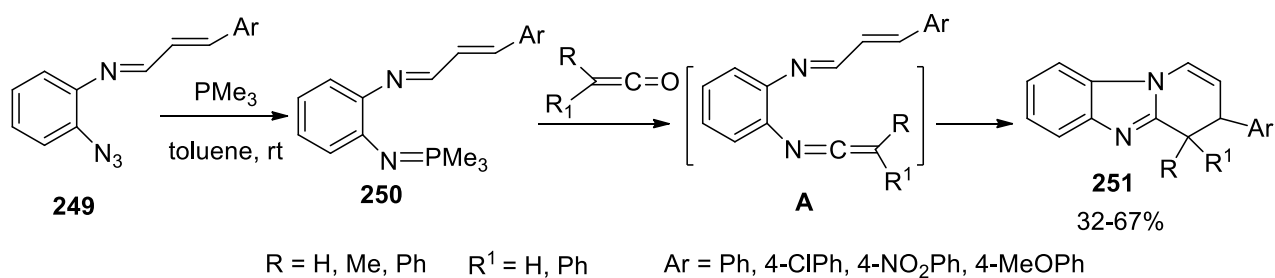


Scheme 86

### 3. Synthesis of Azino-fused-benzimidazoles

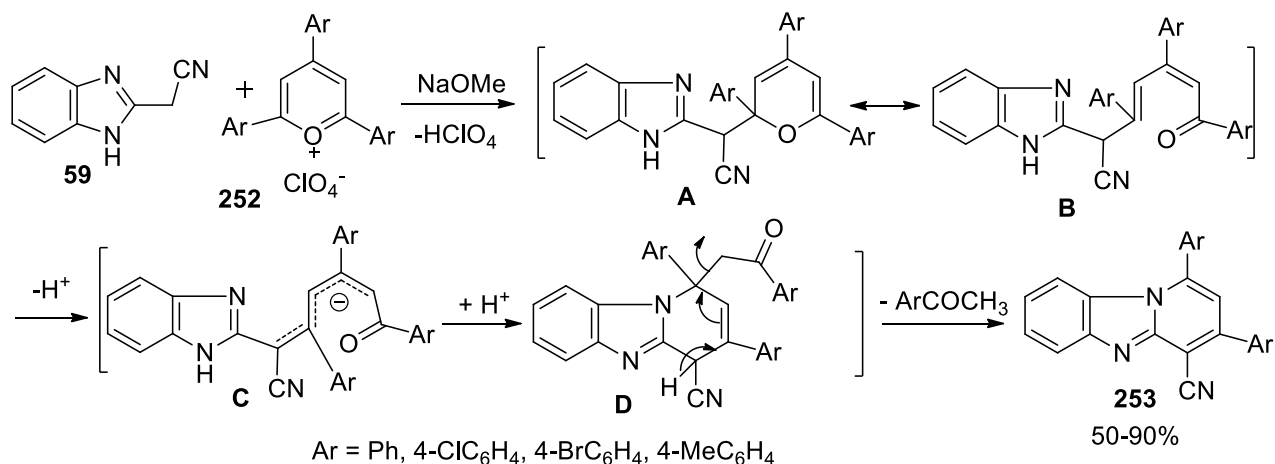
#### 3.1. Pyridobenzimidazoles

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).<sup>144</sup>



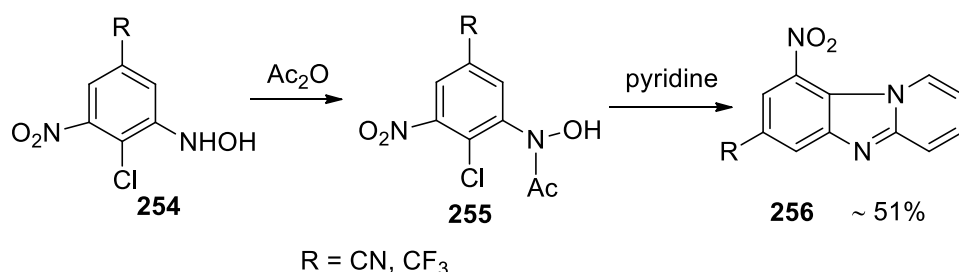
Scheme 87

Cyclocondensation and ring opening of triarylpyrylium 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.<sup>145</sup>



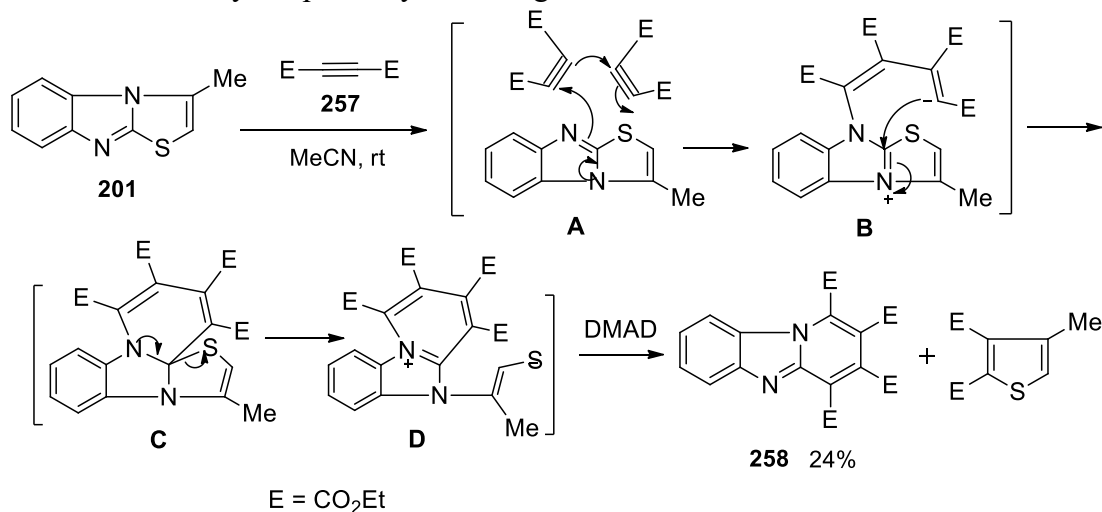
Scheme 88

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).<sup>146</sup>



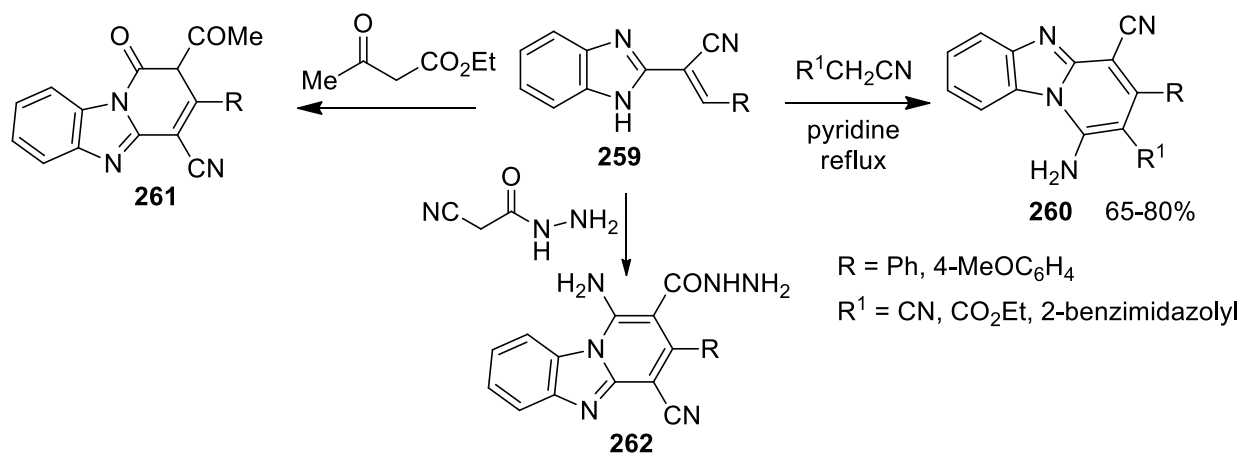
### Scheme 89

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.<sup>147</sup>



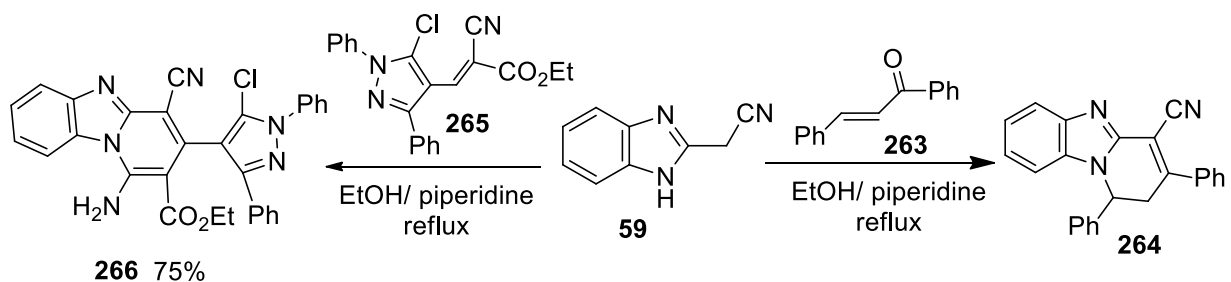
### Scheme 90

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 cyanoaceto-hydrazide to give the pyridobenzimidazole derivatives **261** and **262**, respectively (Scheme 91).<sup>148-150</sup>



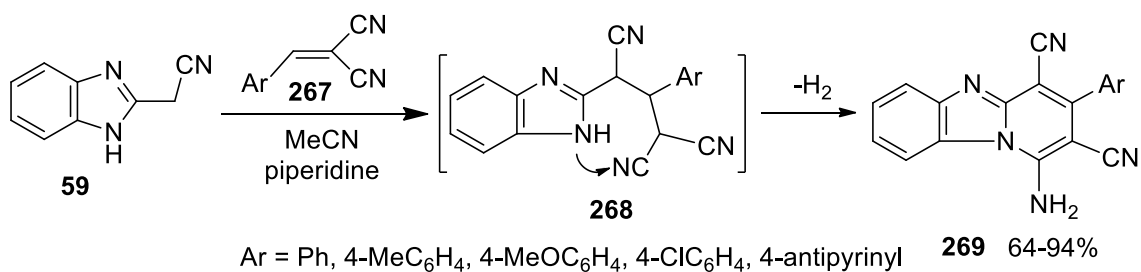
Scheme 91

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).<sup>151-153</sup>



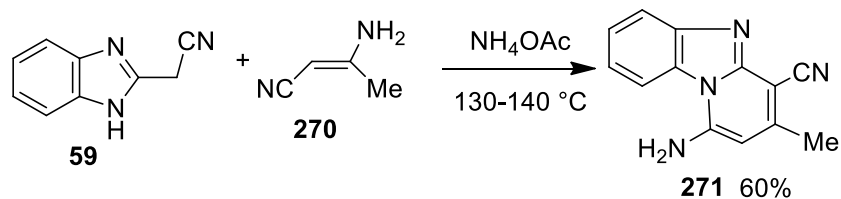
Scheme 92

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).<sup>154,155</sup>



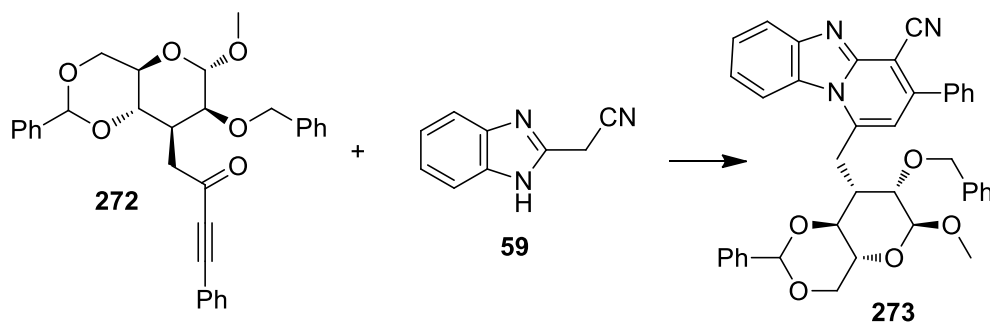
Scheme 93

Heating a mixture of 2-benzimidazoleacetonitrile **59** and  $\beta$ -aminocrotonitrile **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).<sup>156</sup>



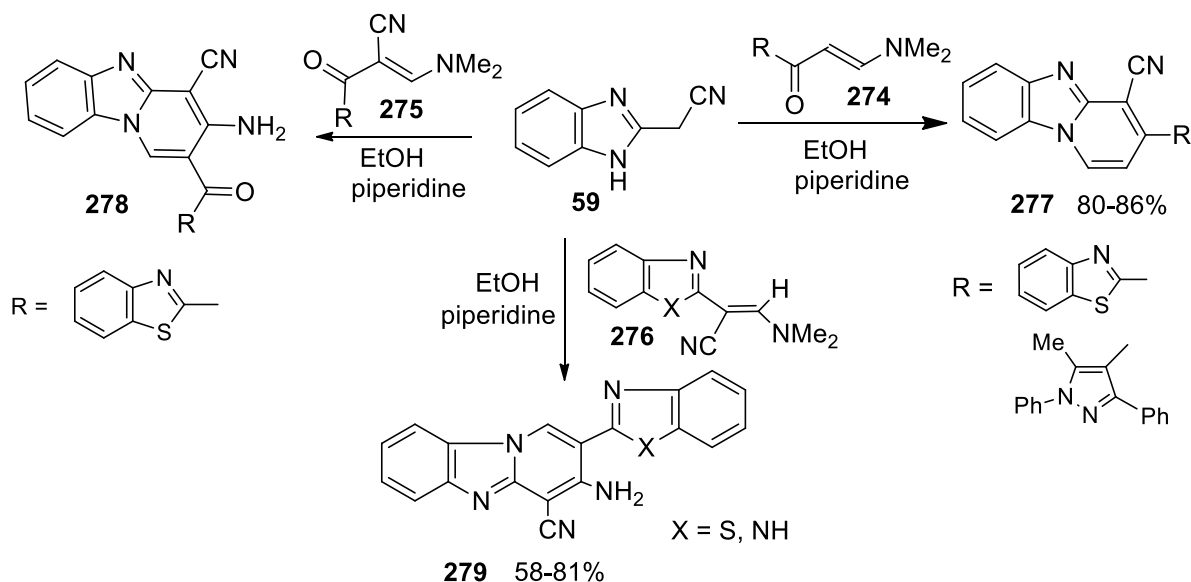
### Scheme 94

Treatment of 2-benzimidazoleacetonitrile **59** with the phenylacetylene derivative **272** produced the pyrido[1,2-*a*]benzimidazole-4-carbonitrile derivative **273** (Scheme 95).<sup>157</sup>



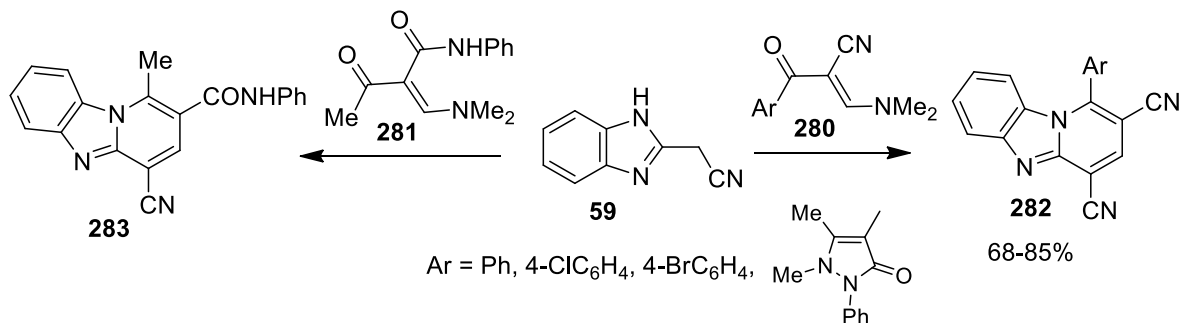
### Scheme 95

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).<sup>158-162</sup>



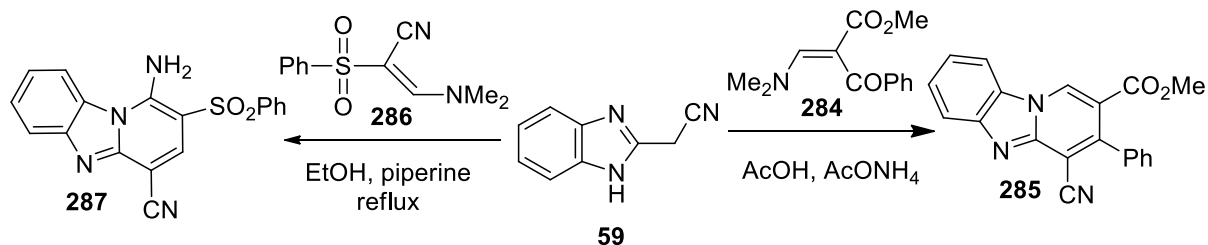
### Scheme 96

Pyrido[1,2-*a*]benzimidazoles **282** and **283** were synthesized by reacting 2-benzimidazoleacetonitrile **59** with the enaminones **280** and **281**, respectively, in refluxing pyridine or ethanol/piperidine (Scheme 97).<sup>163-166</sup>



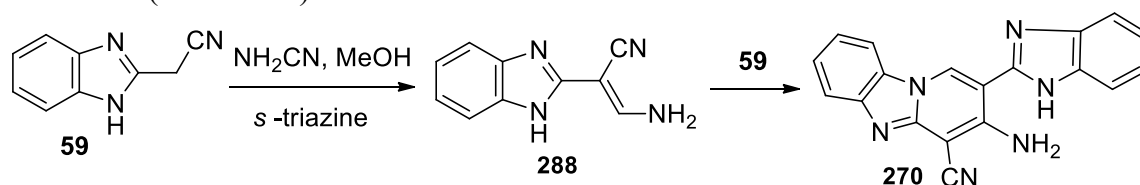
### Scheme 97

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-*a*]pyridine-2-carboxylate **285**.<sup>167</sup> Heating a mixture of 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile **286** with 2-benzimidazoleacetonitrile **59** in ethanol and piperidine afforded the pyrido[1,2-*a*]benzimidazole derivative **287** (Scheme 98).<sup>168</sup>



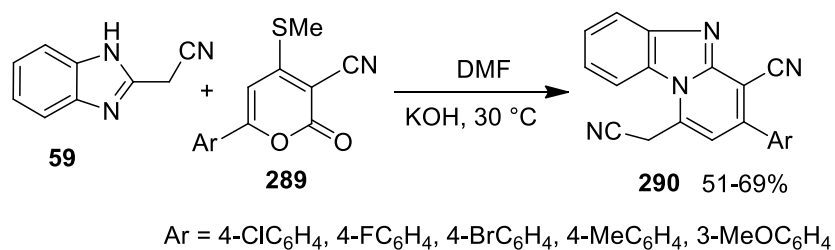
## Scheme 98

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



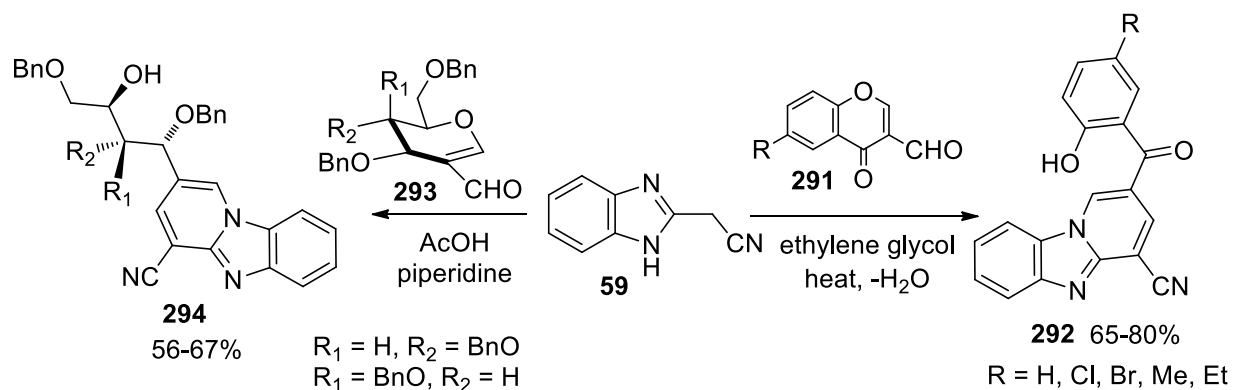
## Scheme 99

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



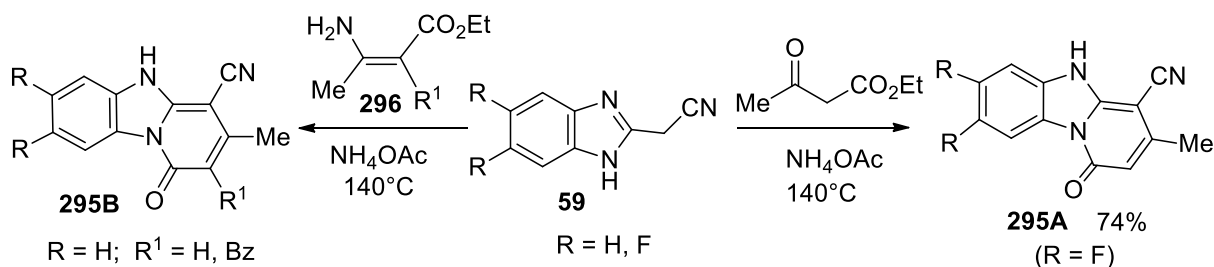
## Scheme 100

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.<sup>171</sup> Similar ring transformation occurred on the reaction of 2-formylglycols **293** with **59** when heated in chlorobenzene/AcOH in the presence of piperidine, to furnish the pyridobenzimidazoles **294** in moderate yields (Scheme 101).<sup>172,173</sup>



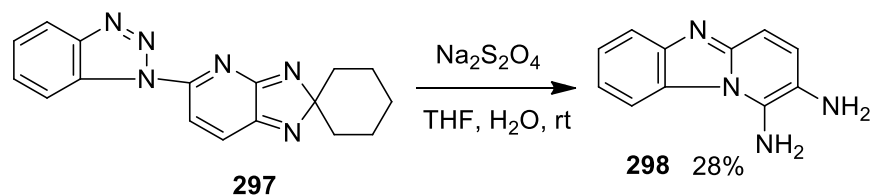
## Scheme 101

7,8-Difluoro-3-methyl-1-oxo-4-cyano-1*H*,5*H*-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.<sup>174,175</sup> Pyrido[1,2-*a*]benzimidazol-1-ones **295B** (R<sup>1</sup> = H, Bz) were obtained by fusing 2-benzimidazoleacetonitrile **59** with ethyl β-aminocrotonates **296** in the presence of NH<sub>4</sub>OAc at 140 °C (Scheme 102).<sup>176</sup>



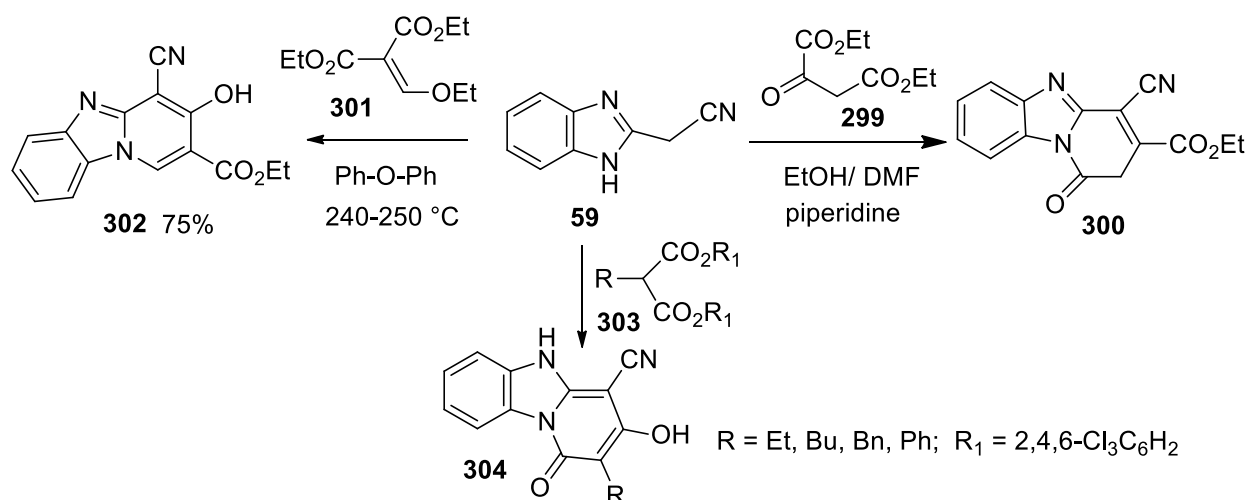
## Scheme 102

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



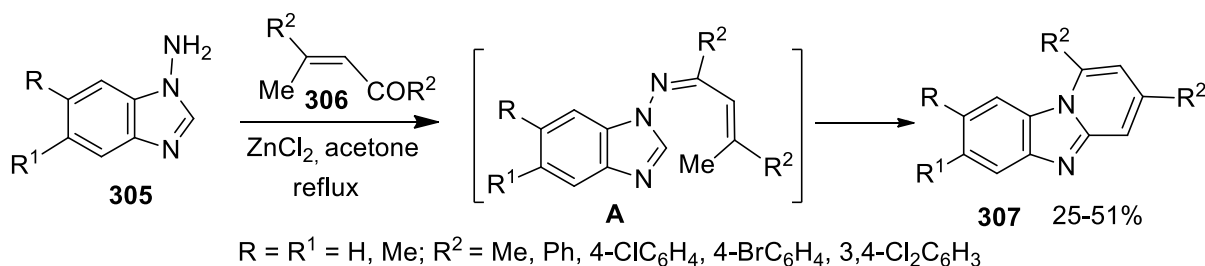
## Scheme 103

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 ethoxymethylenemalonate **301** in diphenyl ether at 240-250 °C gave the pyrido[1,2-*a*]benzimidazole **302** (Scheme 104).<sup>178</sup> 3-Hydroxypyrido[1,2-*a*]benzimidazol-1-ones **304** were prepared by heating 2-benzimidazoleacetonitrile **59** with substituted malonate esters **303** (Scheme 104).<sup>179,180</sup>



Scheme 104

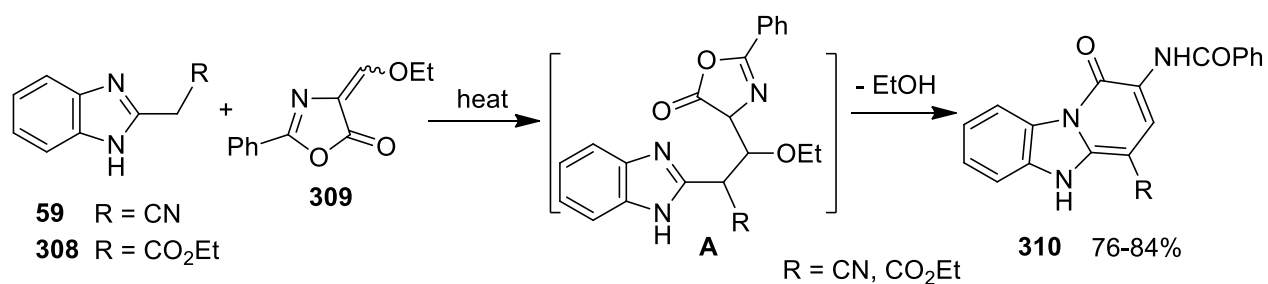
Treatment of 1-aminobenzimidazoles **305** with  $\alpha,\beta$ -unsaturated ketones **306** in the presence of zinc chloride as catalyst in refluxing acetone gave the corresponding pyridobenzimidazoles **307** via an intramolecular rearrangement of the intermediates **A** (Scheme 105).<sup>181</sup>



Scheme 105

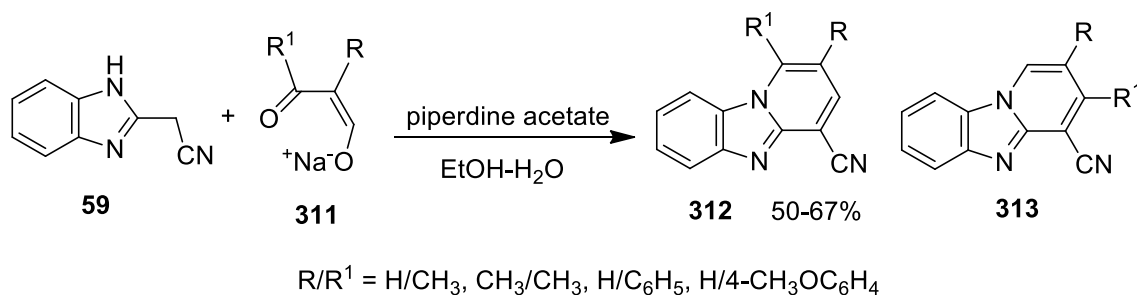
Formation of 2-benzamido-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazoles **310** was achieved by the neat heating of 2-benzimidazoleacetonitrile **59** or ethyl 2-benzimidazoleacetate **308** with 4-ethoxymethylene-2-phenyl-5-oxazolinone **309** via loss of ethanol from the intermediates **A** (Scheme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





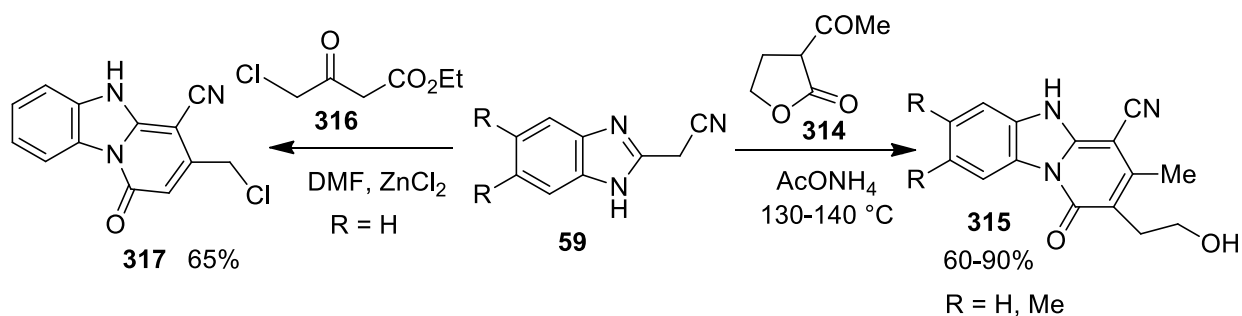
## Scheme 106

Reaction of 2-benzimidazoleacetone nitrile **59** with sodium salts of 3-hydroxymethylene-2-alkanones **311** in piperidine acetate and aq. ethanol yielded the pyrido[1,2-*a*]benzimidazoles **312**. The other isomeric structure **313** was excluded based on the X-ray analysis (Scheme 107).<sup>183</sup>



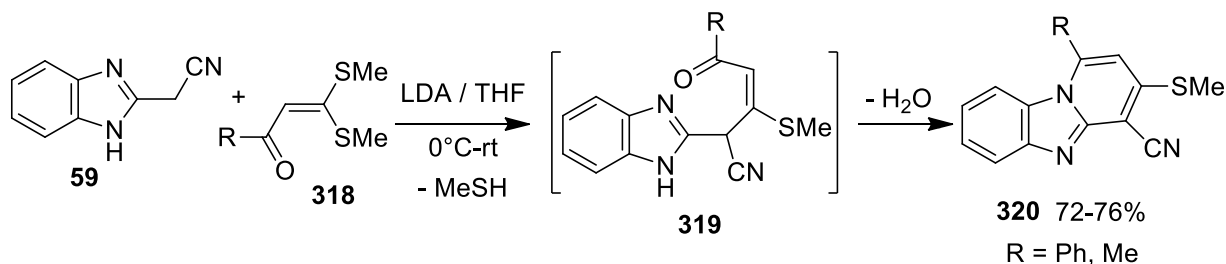
## Scheme 107

2-(2-Hydroxyethyl)pyrido[1,2-*a*]benzimidazole-4-carbonitriles **315** were prepared from heating 2-benzimidazoleacetone nitriles **59** with 2-acetylbutyrolactone **314** in the presence of ammonium acetate.<sup>184</sup> Condensation of **59** with ethyl 4-chloro-3-oxobutanoate **316** in refluxing DMF and ZnCl<sub>2</sub> led to 3-chloromethylpyrido[1,2-*a*]benzimidazol-1-one-4-carbonitrile **317** (Scheme 108).<sup>185</sup>



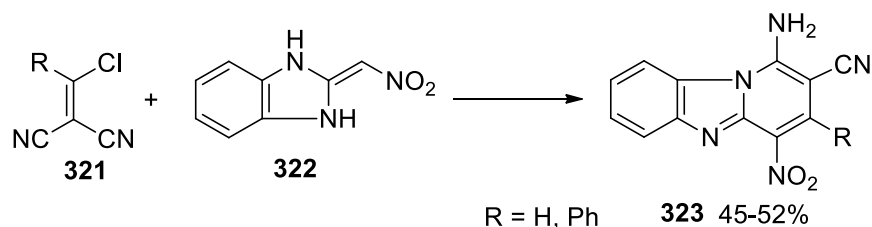
## Scheme 108

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  $\alpha$ -oxoketene dithioacetals **318** has been reported (Scheme 109).<sup>186</sup>



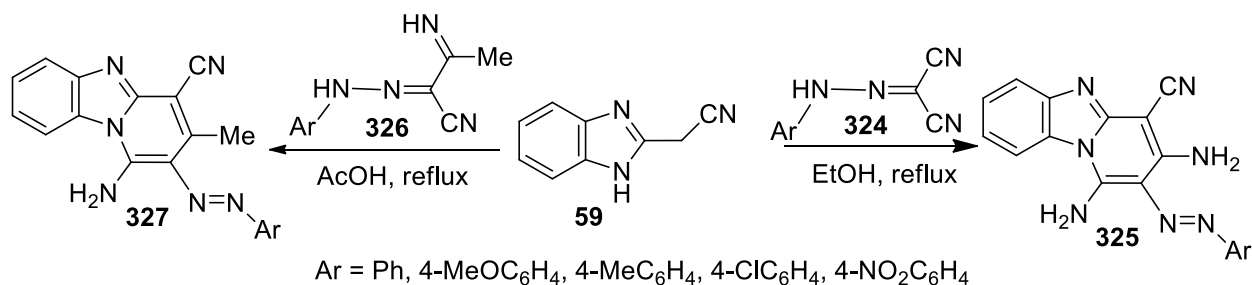
Scheme 109

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



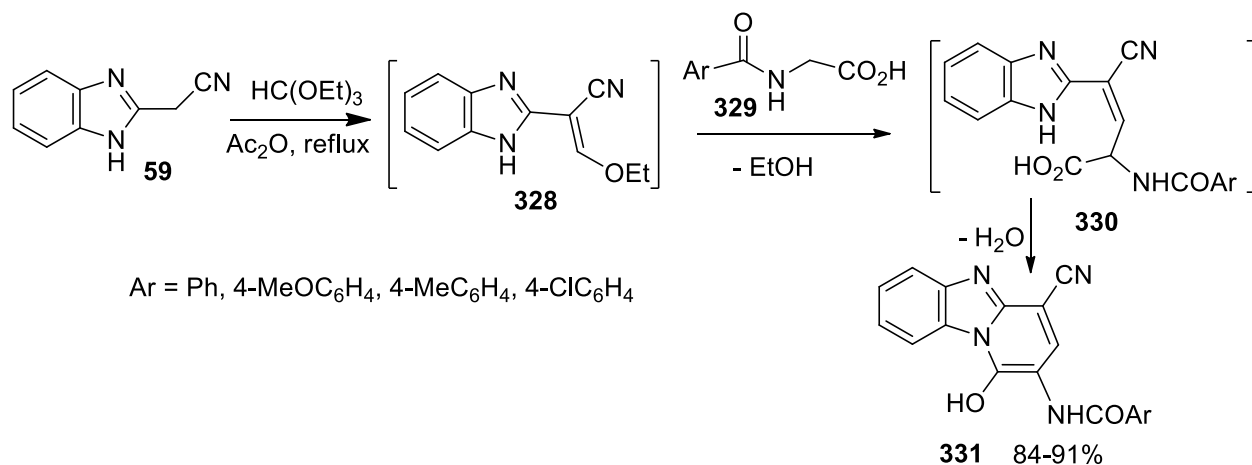
Scheme 110

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**.<sup>188</sup> 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).<sup>189</sup>



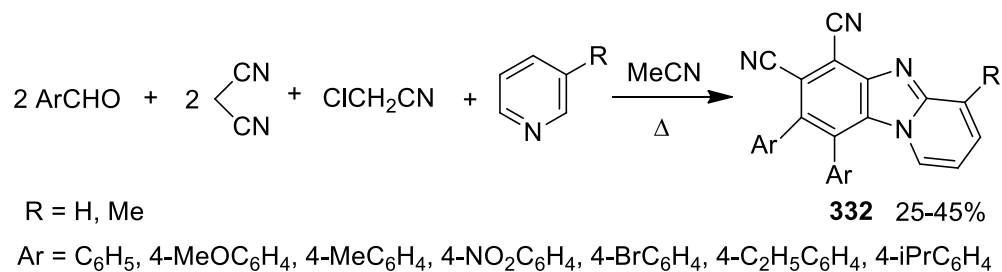
Scheme 111

Heating of 2-benzimidazoleacetonitrile **59** with triethyl orthoformate gave the intermediate ethoxyacrylonitrile derivative **328** which upon treatment with hippuric acid derivatives **329** in refluxing acetic anhydride afforded the pyrido[1,2-*a*]benzimidazole derivatives **331** in high yields *via* loss of water molecule from the intermediate **330** (Scheme 112).<sup>190</sup>



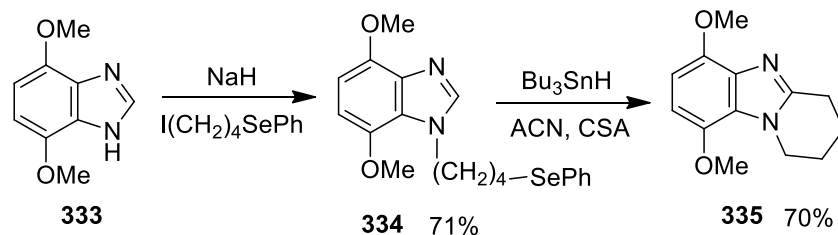
### Scheme 112

Polysubstituted pyrido[1,2-*a*]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.<sup>191</sup>



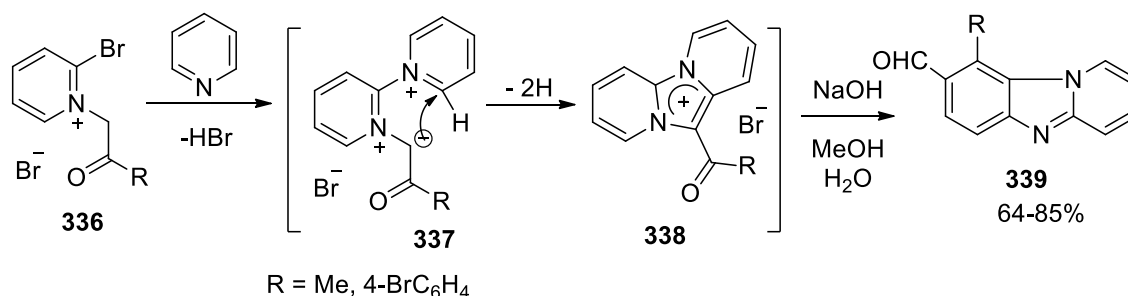
### Scheme 113

Alkylation of 4,7-dimethoxy-1*H*-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-*a*]benzimidazole derivative **335** using Bu<sub>3</sub>SnH, 1,1'-azobis(cyclohexanecarbonitrile) (ACN) and camphorsulfonic acid (CSA) under reflux in toluene (Scheme 114).<sup>192</sup>



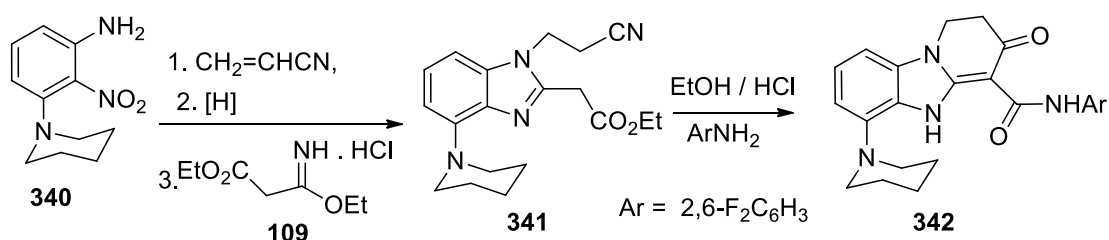
## Scheme 114

Pyrido[1,2-*a*]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).<sup>193</sup>



## Scheme 115

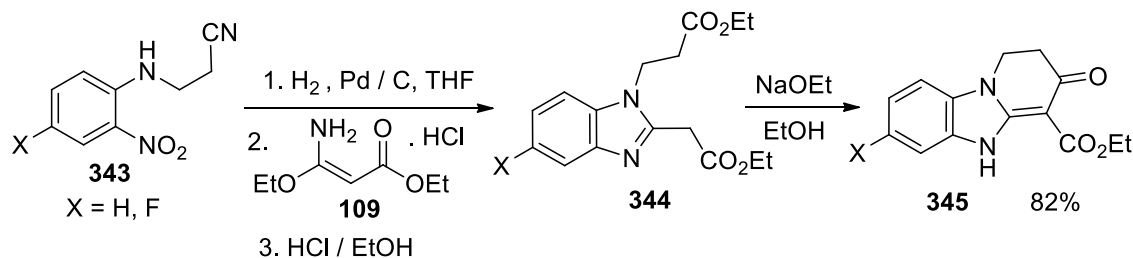
3-(*N*-Piperidyl)-2-nitroaniline **340** underwent Michael-type addition with acrylonitrile, followed by hydrogenation then condensation with 3-ethoxy-3-iminopropanoate hydrochloride **109** to give 1-(2-cyanoethyl)-2-(ethoxycarbonylmethyl)-4-(*N*-piperidinyl)benzimidazole **341**. Ethanolsis of the nitrile function and base-catalyzed cyclization of the resulted diester followed by amidation with 2,6-difluoroaniline gave the pyrido[1,2-*a*]benzimidazole derivative **342** (Scheme 116).<sup>194,195</sup>



## Scheme 116

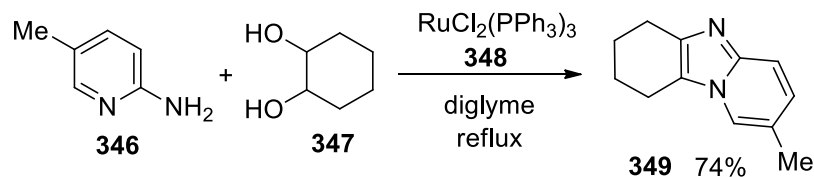
Catalytic hydrogenation of *N*-cyanoethyl-2-nitroaniline **343** and subsequent reaction with ethyl 3-amino-3-ethoxyacrylate hydrochloride **109** followed by ethanolsis of the cyano group in

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).<sup>196,197</sup>



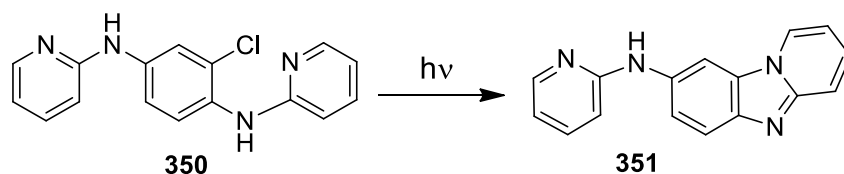
**Scheme 117**

The reaction of 2-amino-5-methylpyridine **346** with 1,2-cyclohexanediol **347** in the presence of a catalytic amount of  $\text{RuCl}_2(\text{PPh}_3)_3$  **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).<sup>198</sup>



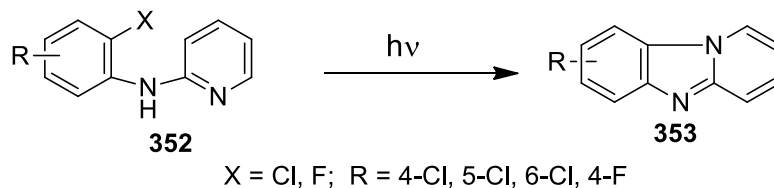
**Scheme 118**

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).<sup>199</sup>

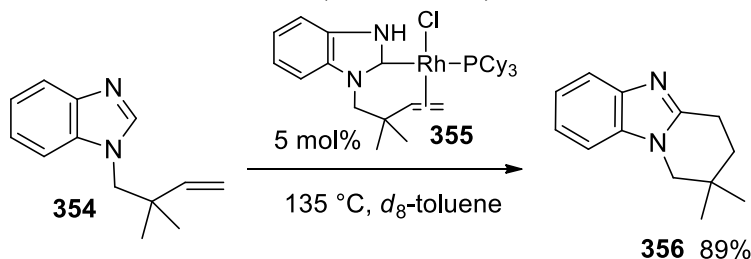


**Scheme 119**

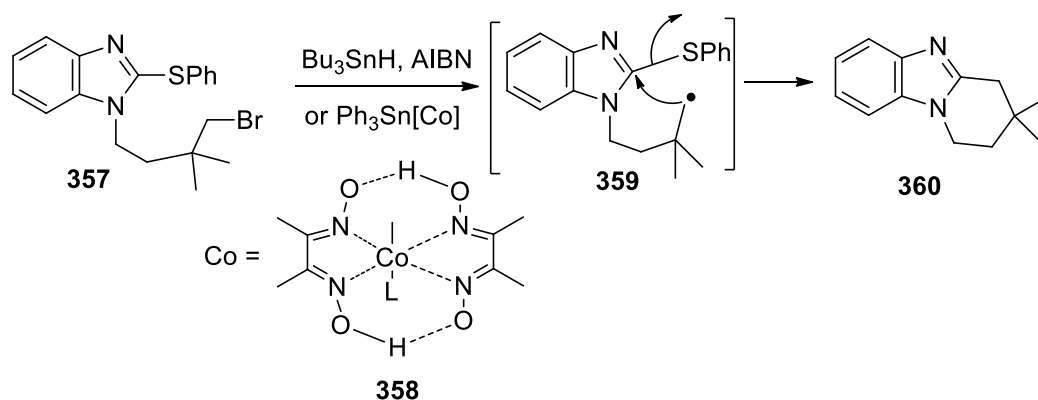
Photo-induced cyclization of haloarylpyridylamines **352** gave the pyrido[1,2-*a*]benzimidazoles **353** (Scheme 120).<sup>200,201</sup>

**Scheme 120**

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).<sup>202,203</sup>

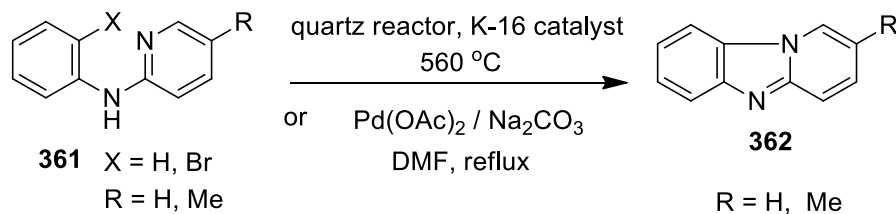
**Scheme 121**

Intramolecular radical addition of 2-thiophenoxybenzimidazole **357** was reported in the presence of cobaloxime **358** or  $\text{Ph}_3\text{SnH/AIBN}$  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  $\text{Ph}_3\text{SnH/AIBN}$  (64%) (Scheme 122).<sup>204</sup>

**Scheme 122**

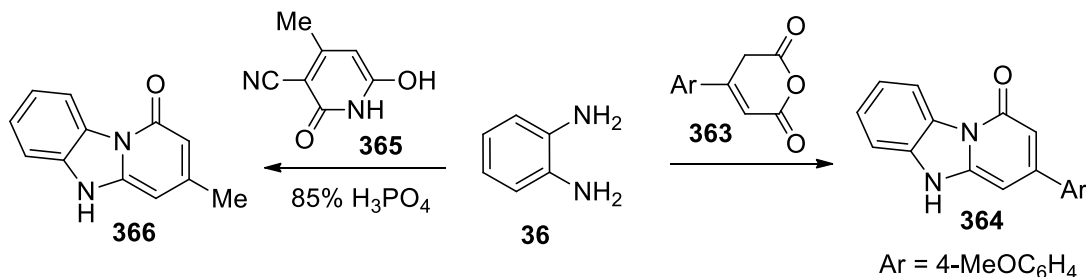
Palladium-catalyzed intramolecular cyclization of 2-anilinopyridine **361** (X = Br; R = H) using palladium acetate and  $\text{Na}_2\text{CO}_3$  in DMF at reflux gave pyrido[1,2-*a*]benzimidazole **362** (R =

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).<sup>206</sup>



### Scheme 123

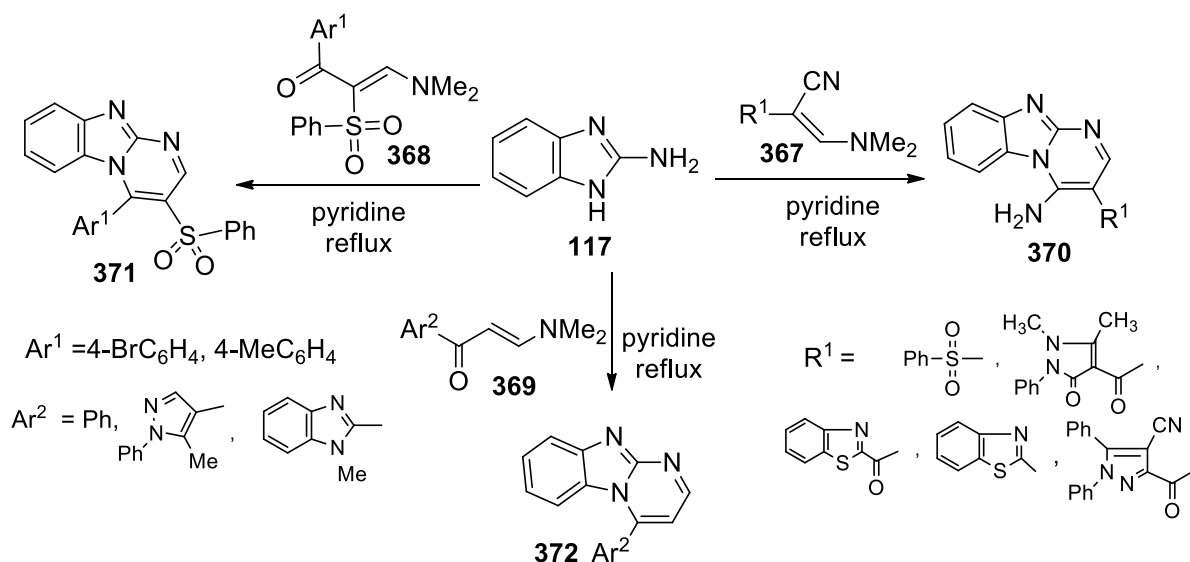
Condensation of 1,2-diaminobenzene **36** with the 5*H*-pyran-2,6-dione **363** gave the pyrido[1,2-*a*]benzimidazol-1-one **364**,<sup>207</sup> while condensation of **36** with 6-hydroxy-4-methyl-2-oxo-3-pyridine-carbonitrile **365** in 85% orthophosphoric acid afforded 3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole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



### Scheme 124

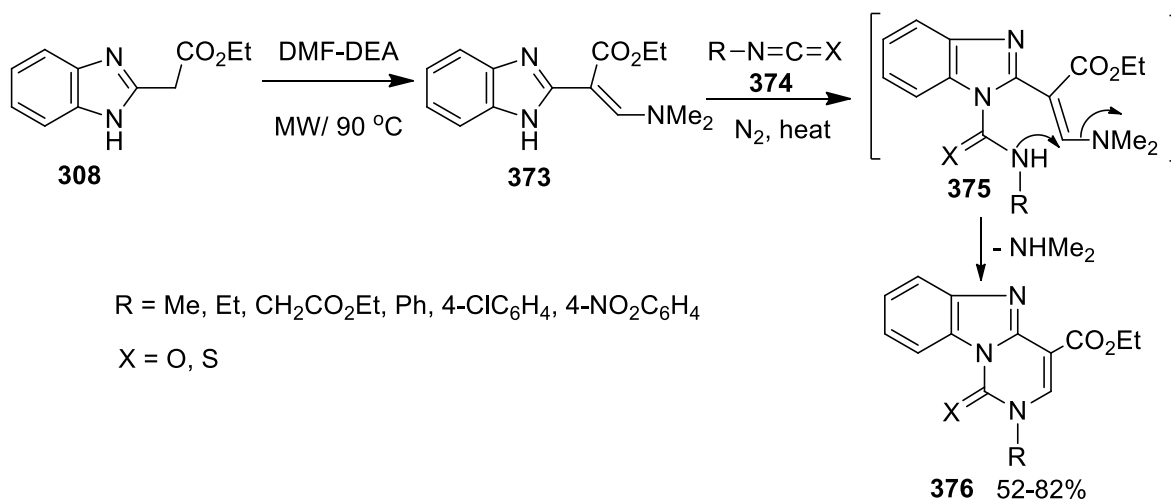
## 3.2. Pyrimidobenzimidazoles

Treatment of 2-aminobenzimidazole **117** with variety of enamines **367**, **368** and **369** in refluxing pyridine gave the corresponding pyrimido[1,2-*a*]benzimidazoles **370**, **371** and **372**, respectively (Scheme 125).<sup>160,163,165,168,209-213</sup>



### Scheme 125

Meziane *et al* reported the microwave-assisted synthesis of the pyrimido[1,6-*a*]benzimidazoles **376**.<sup>214</sup> 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).<sup>214</sup>

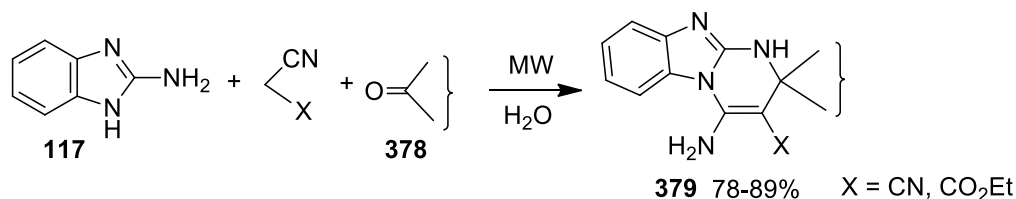


### Scheme 126

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



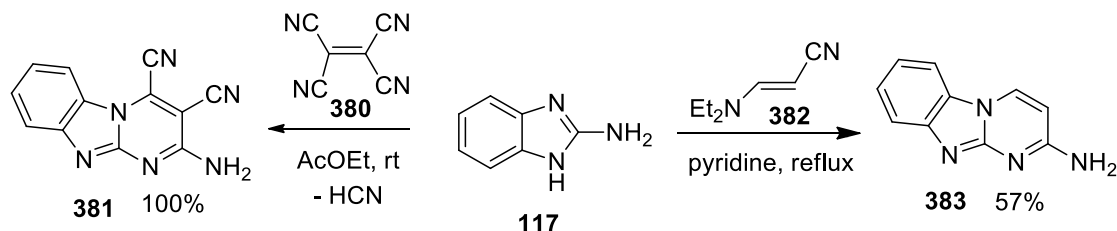
carbonyl compounds **378**, malonodinitrile and 2-aminobenzimidazole **117** in water under microwave gave pyrimido[1,2-*a*]benzimidazoles **379** (Scheme 127).<sup>215-217</sup>



Carbonyl compd. = ArCHO, ArCOCH<sub>3</sub>, cyclopentanone, cyclohexanone,  $\alpha$ -tetralone  
 Ar = Ph, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

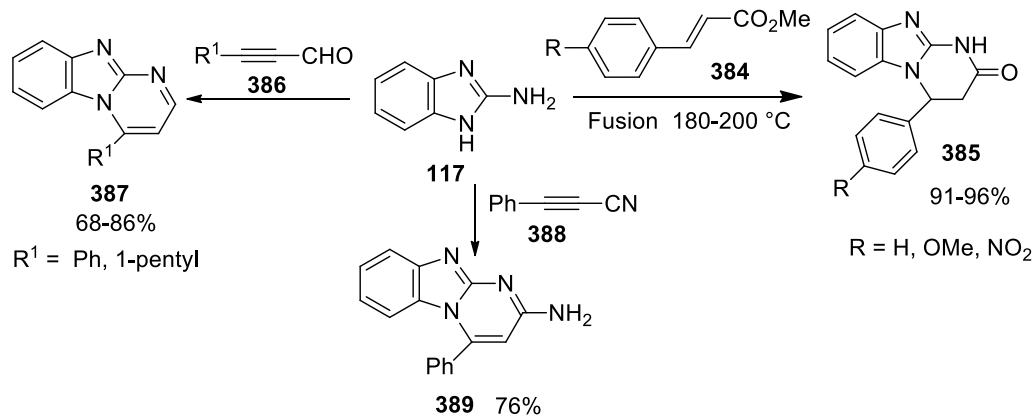
### Scheme 127

The pyrimido[1,2-*a*]benzimidazoles **381** were synthesized through reaction of 2-aminobenzimidazole **117** with tetracyanoethylene **380** in ethyl acetate at room temperature *via* loss of HCN and heterocyclization.<sup>218</sup> 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).<sup>219</sup>



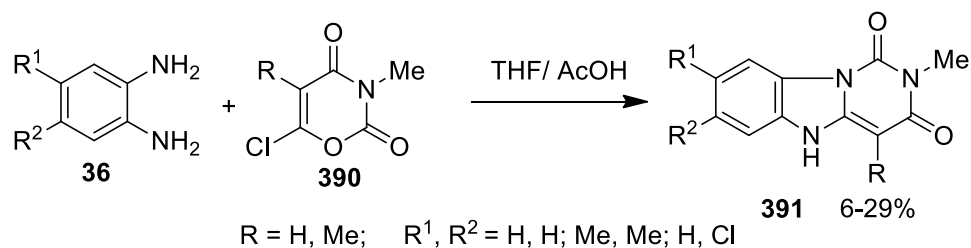
### Scheme 128

Fusion of 2-aminobenzimidazole **117** with methyl cinnamates **384** gave the pyrimido[1,2-*a*]benzimidazoles **385** (Scheme 129).<sup>220</sup> The acetylenic aldehydes **386** and 3-phenylpropenenitrile **388** reacted by conjugate addition to **117** giving the pyrimido[1,2-*a*]benzimidazoles **387** and **389**, respectively (Scheme 129).<sup>221</sup>



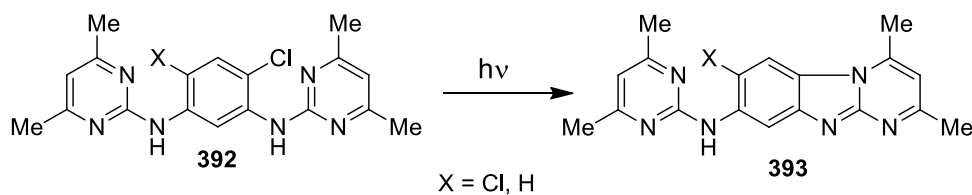
### Scheme 129

Refluxing chlorooxazinediones **390** with *o*-phenylenediamines **36** in THF in the presence of acetic acid gave pyrimidobenzimidazoles **391** in low yields (Scheme 130).<sup>222</sup>



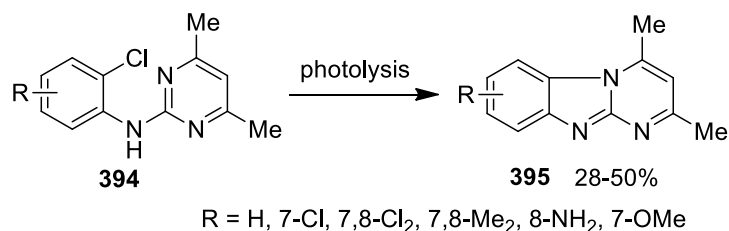
### Scheme 130

Photo-irradiation of *N,N'*-(chlorophenylene)bis[dimethylpyrimidinamines] **392** gave pyrimidobenzimidazoles **393** (Scheme 131).<sup>223</sup>



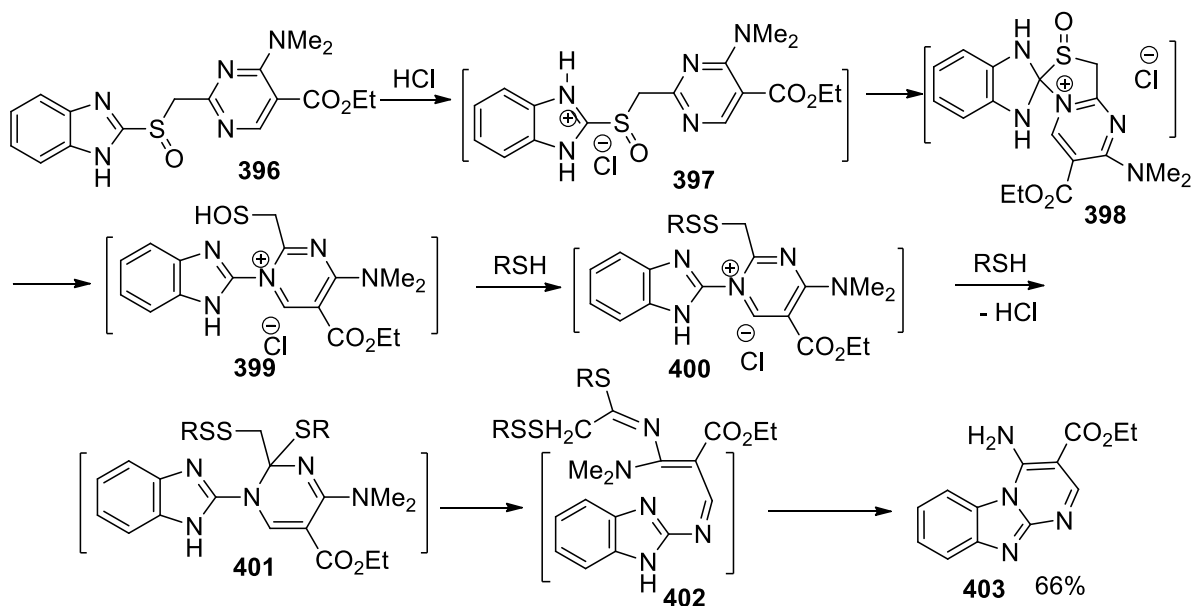
### Scheme 131

Photochemical cyclization of (2-chloroanilino)pyrimidines **394** in aqueous acetonitrile gave pyrimido[1,2-*a*]benzimidazoles **395** (Scheme 132).<sup>224,225</sup>



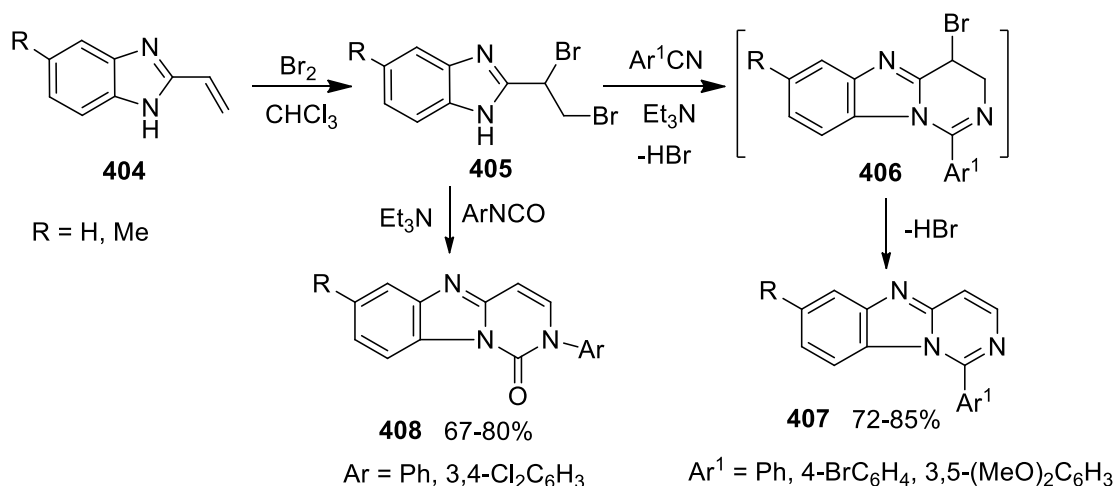
### Scheme 132

Reaction of ethyl 2-[(1*H*-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.<sup>226</sup>



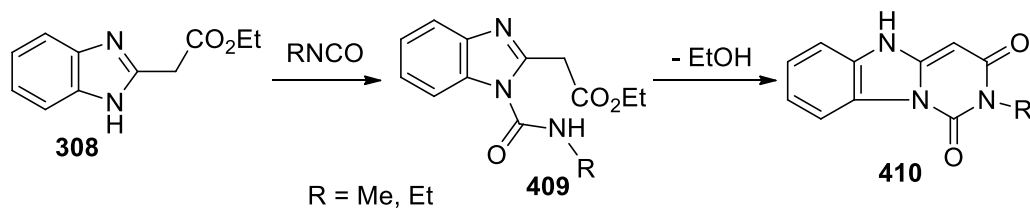
### Scheme 133

Treatment of 2-vinylbenzimidazoles **404** with bromine in chloroform gave 2-(1,2-dibromoethyl)-1*H*-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).<sup>227</sup>



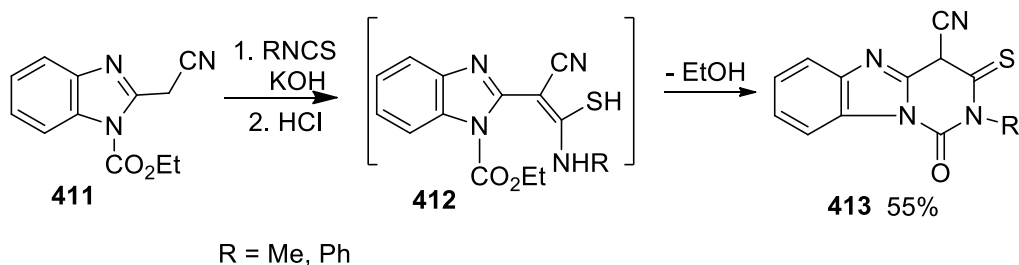
## Scheme 134

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).<sup>228</sup>



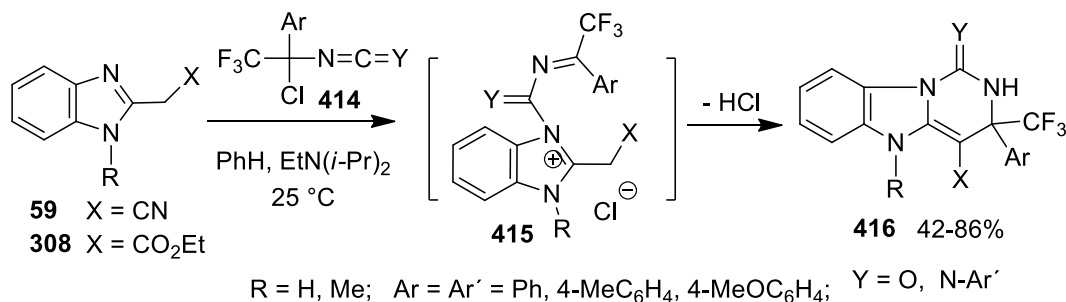
## Scheme 135

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).<sup>229,230</sup>



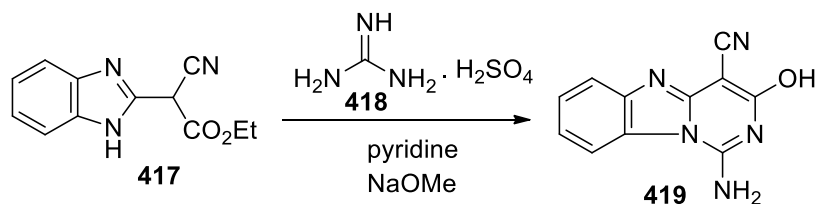
## Scheme 136

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).<sup>231</sup>



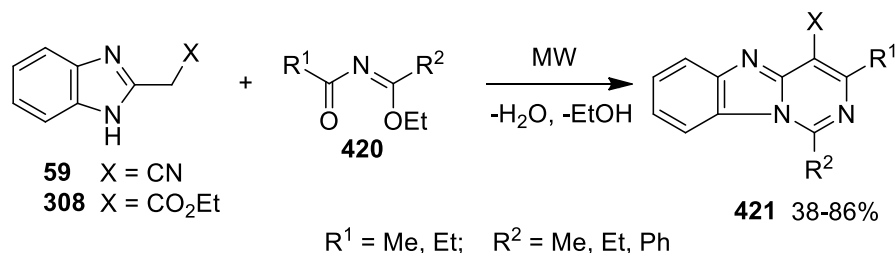
### Scheme 137

Reaction of ethyl 2-(1*H*-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).<sup>232</sup>



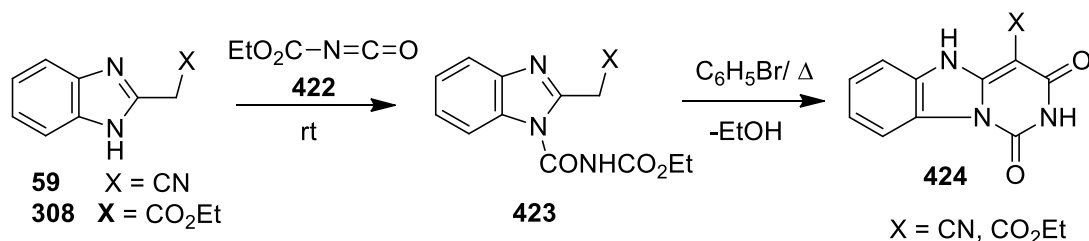
### Scheme 138

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).<sup>233</sup>



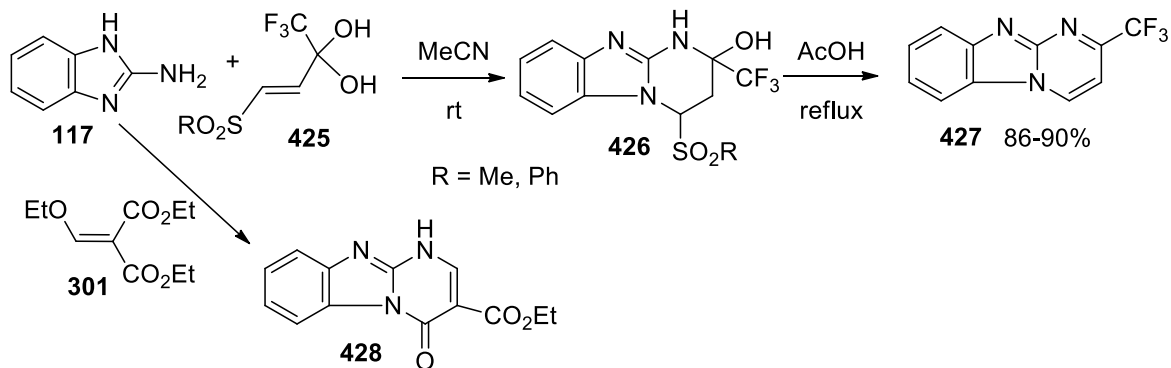
### Scheme 139

Badawey *et al.* reported the reaction of 1*H*-benzimidazoles **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-dioxypyrimido[1,6-*a*]benzimidazole-4-carbonitrile **424** in excellent yields (Scheme 140).<sup>234</sup>



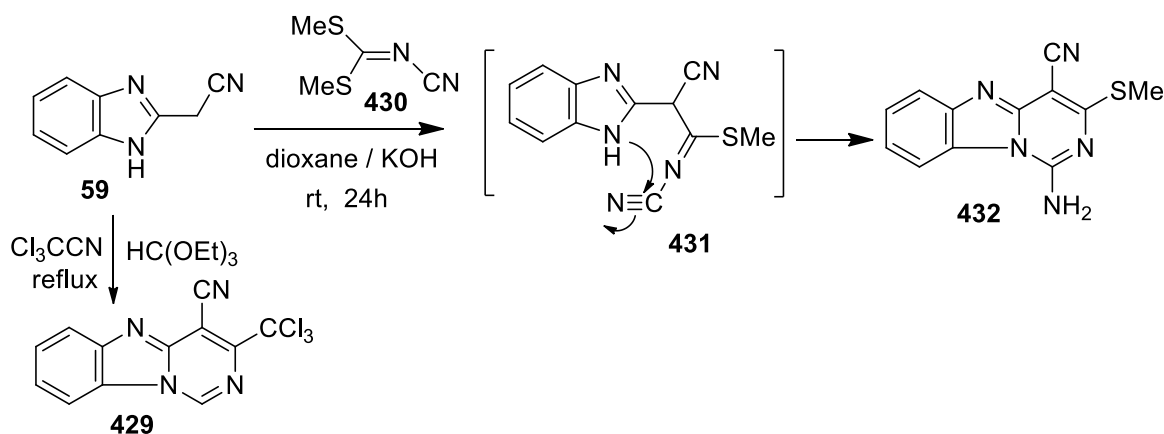
### Scheme 140

The reaction of 2-aminobenzimidazole **117** with sulfones **425** proceeded at room temperature in acetonitrile to give tetrahydropyrimido[1,2-*a*]benzimidazol-2-ol **426**. Aromatization of the latter compounds **426** was performed under reflux in acetic acid *via* elimination of water and sulfonic 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).<sup>235</sup> Condensation of 2-aminobenzimidazole **117** with diethyl ethoxymethylenemalonate **301** in dry methanol afforded 4-oxopyrimido[1,2-*a*]benzimidazole-3-carboxylate **428** (Scheme 141).<sup>236</sup>



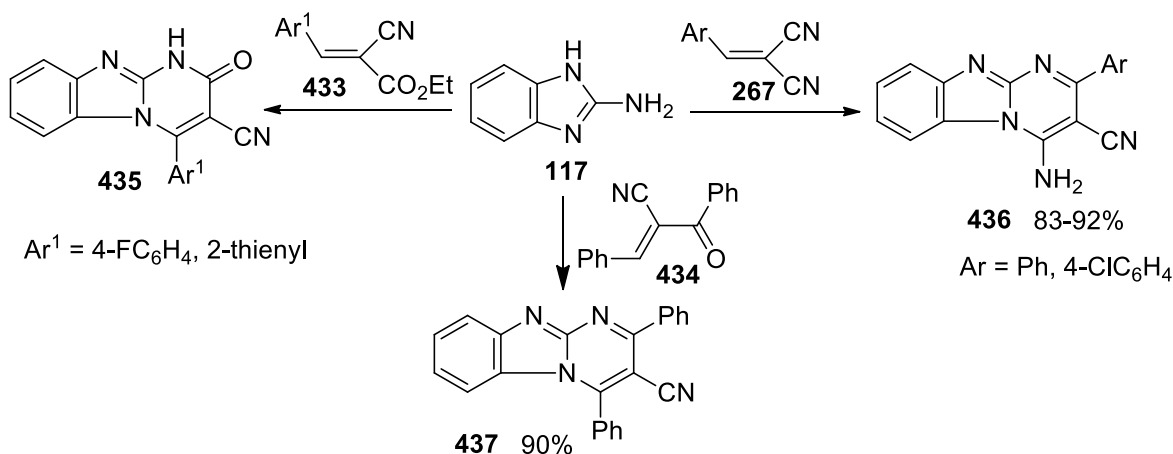
### Scheme 141

3-(Trichloromethyl)pyrimido[1,6-*a*]benzimidazole-4-carbonitrile **429** was prepared by heating of 2-benzimidazoleacetonitrile **59** with trichloroacetonitrile followed by triethyl orthoformate (Scheme 142).<sup>237</sup> 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*]benzimidazole **432** (Scheme 142).<sup>238</sup>



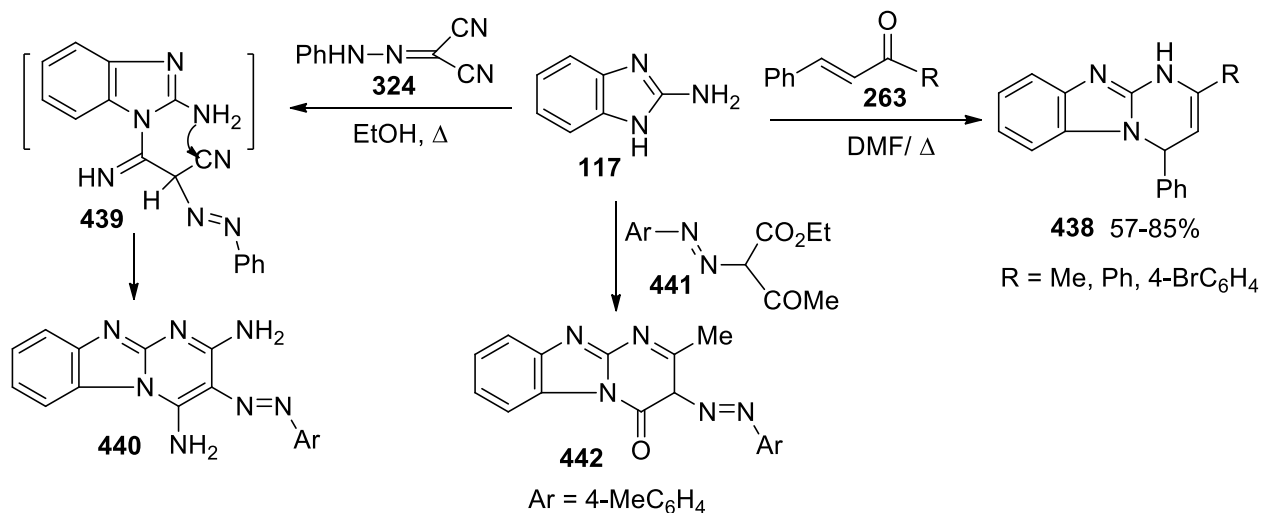
Scheme 142

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).<sup>239-242</sup>



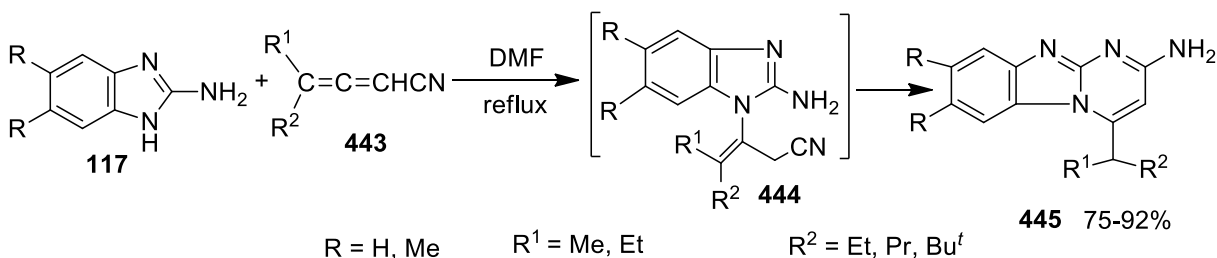
Scheme 143

The condensation of 2-aminobenzimidazole **117** with chalcones **263** and with phenylhydrazonomalononitrile **324** gave pyrimido[1,2-*a*]benzimidazoles **438** and **440**, respectively.<sup>243-246</sup> 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).<sup>247</sup>



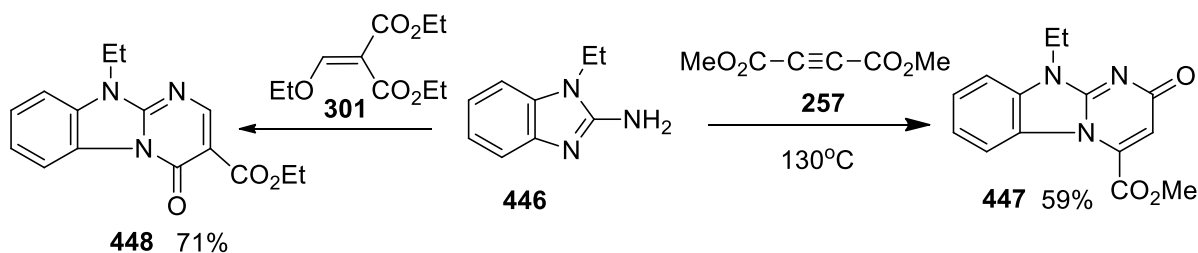
Scheme 144

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).<sup>248</sup>



Scheme 145

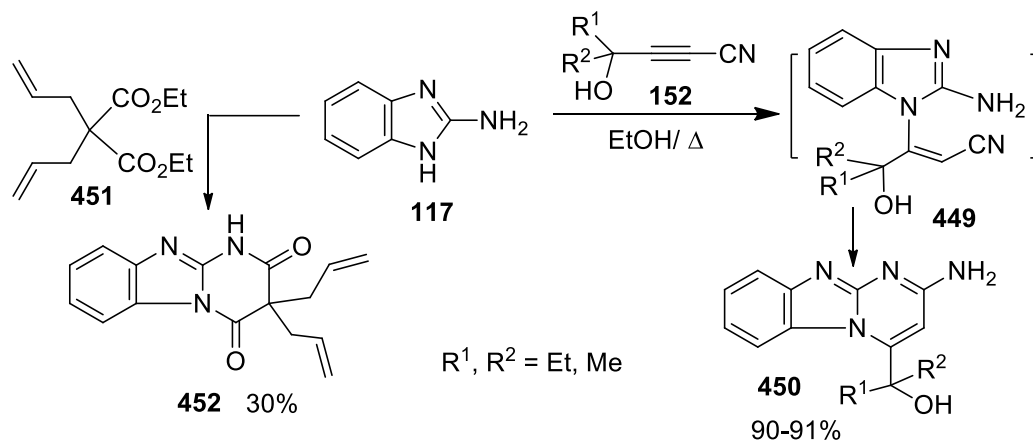
Reaction of 1-ethyl-2-aminobenzimidazole **446** and dimethyl acetylenedicarboxylate **257** at 130 °C afforded the methyl pyrimido[1,2-*a*]benzimidazol-4-carboxylate **447** in 59% yield. Similar treatment of **446** with diethyl (ethoxymethylene)malonate **301** gave ethyl 10-ethyl-4-oxo-4*H*-pyrimido[1,2-*a*]benzimidazol-3-carboxylate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



Scheme 146

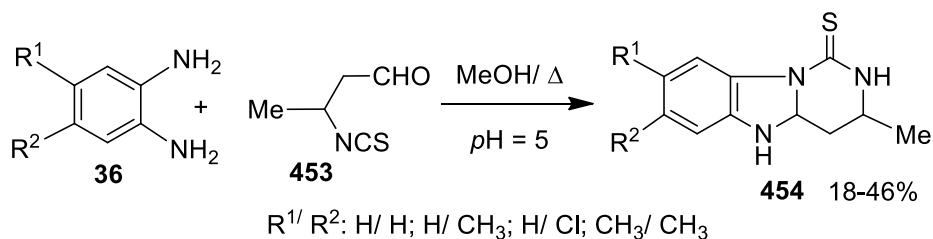


Reaction of 2-aminobenzimidazole **117** with 4-hydroxy-2-alkynenitrile **152** in ethanol under reflux gave excellent yields of 2-amino-4-(1-hydroxyalkyl)pyrimido[1,2-*a*]benzimidazole **450**.<sup>76</sup> In addition, the pyrimidobenzimidazole-2,4-dione **452** was prepared in 30% yield by treating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



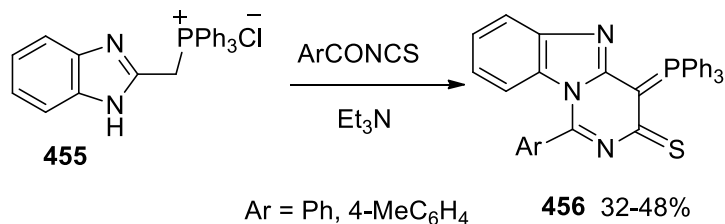
Scheme 147

Refluxing 3-isothiocyanatobutanal **453** with *o*-phenylenediamines **36** in methanol at pH 5 gave the pyrimido[1,6-*a*]benzimidazole derivative **454** (Scheme 148).<sup>250,251</sup>



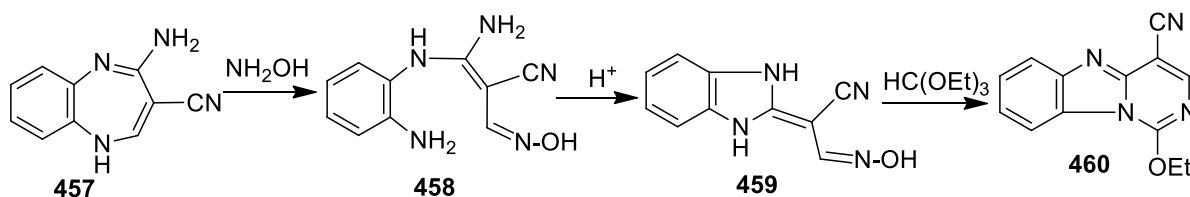
Scheme 148

Cyclocondensation of (2-benzimidazolymethyl)triphenylphosphonium chloride **455** with benzoyl isothiocyanates in the presence of triethylamine gave pyrimido[1,6-*a*]benzimidazole derivative **456** (Scheme 149).<sup>252,253</sup>



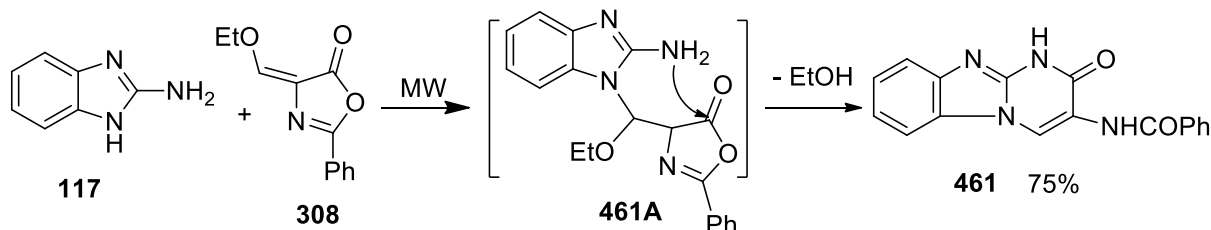
Scheme 149

4-Amino-1*H*-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).<sup>254</sup>



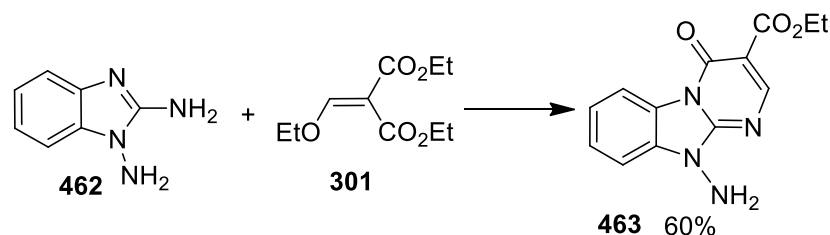
Scheme 150

The pyrimido[1,2-*a*]benzimidazole derivative **461** was prepared in 75% yield by cyclocondensation of 4-(ethoxymethylene)-2-phenyloxazol-5(4*H*)-one **308** with 2-aminobenzimidazole **117** under solventless domestic microwave heating *via* loss of ethanol from the intermediate **461A** (Scheme 151).<sup>255</sup>



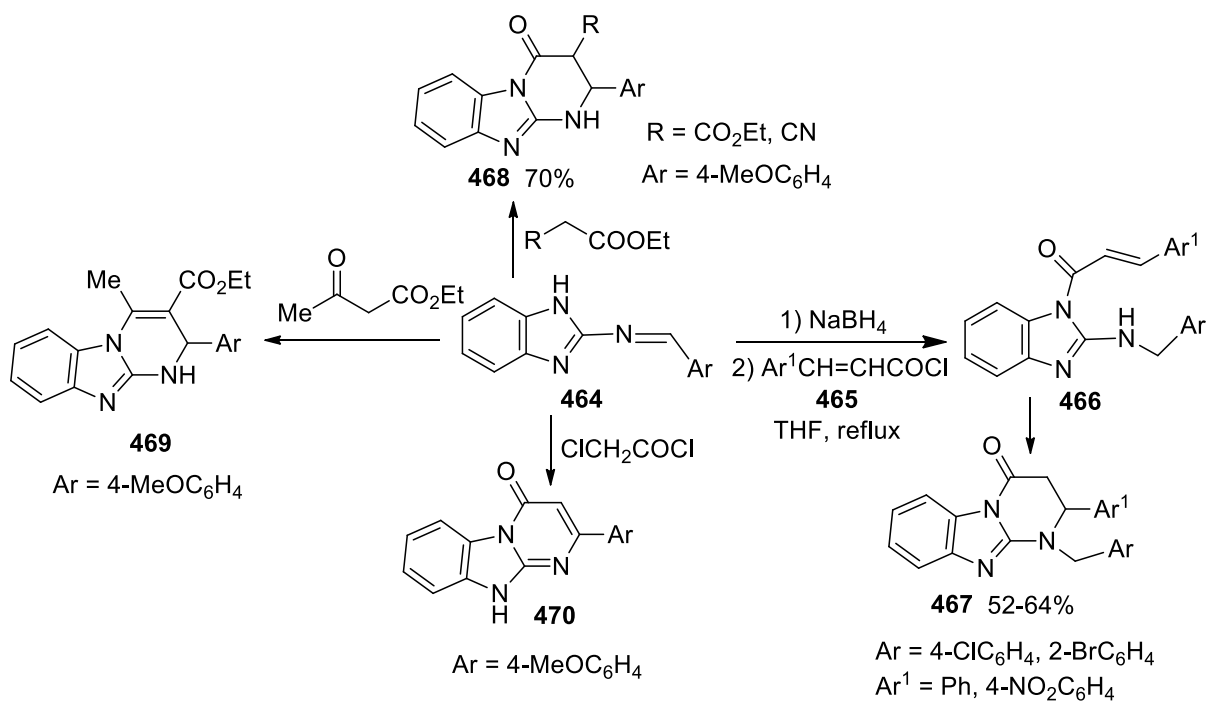
Scheme 151

1,2-Diaminobenzimidazole **462** reacted with diethyl ethoxymethylenemalonate **301** to give the pyrimido[1,2-*a*]benzimidazole derivative **463** (Scheme 152).<sup>256</sup>



Scheme 152

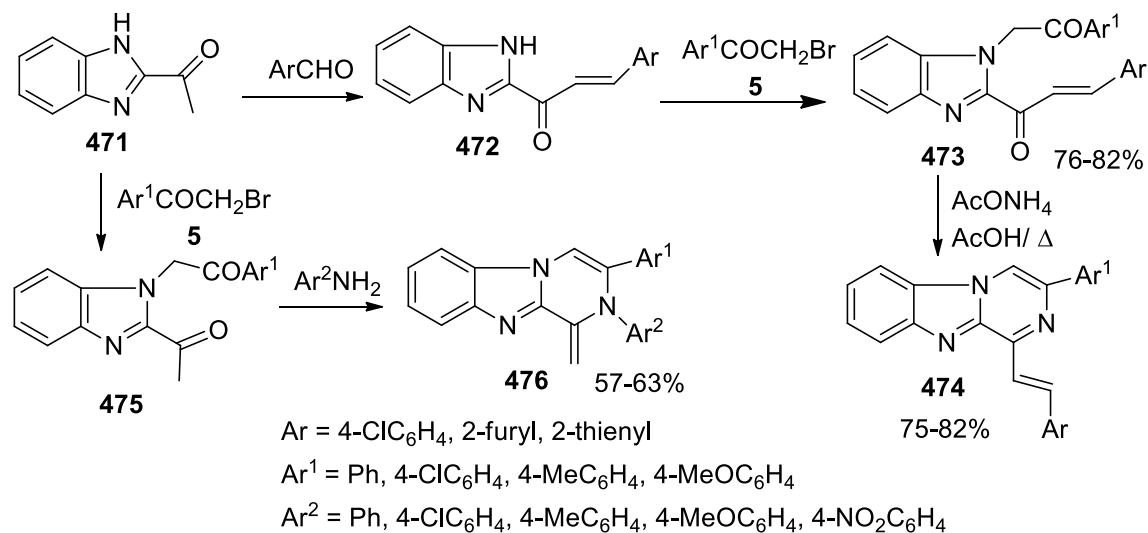
Pyrimido[1,2-*a*]benzimidazole derivatives **467-470**, which are useful as neoplasm inhibitors, immuno-modulators, and antiallergic agents, were prepared *via* reaction of 2-aminobenzimidazole Schiff's base **464** with active methylene compounds and with the cinnamoyl chlorides **465** (Scheme 153).<sup>257-261</sup>



Scheme 153

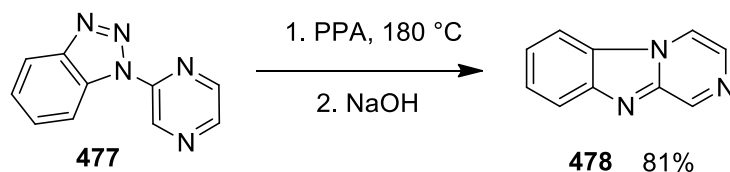
### 3.3. Pyrazinobenzimidazoles

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-arylpropanones **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).<sup>262</sup>



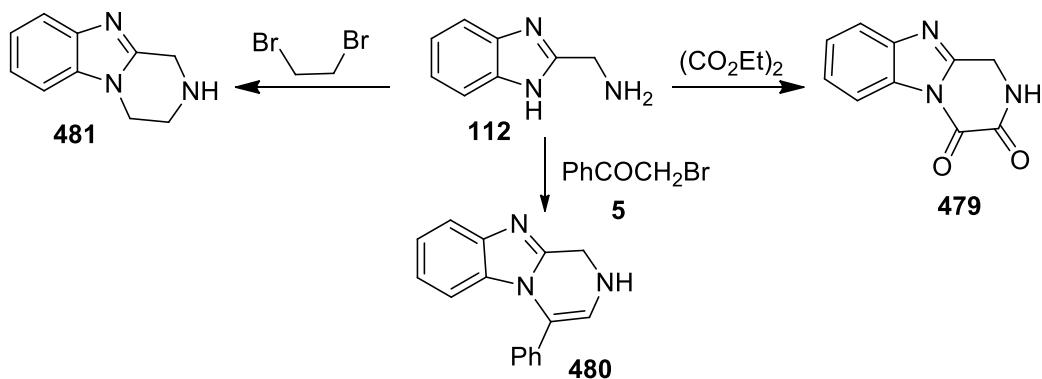
Scheme 154

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



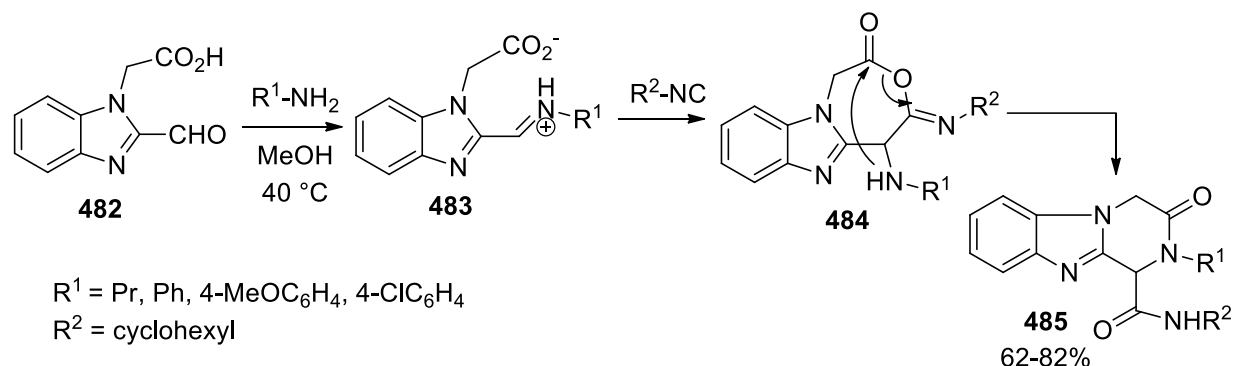
Scheme 155

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).<sup>60</sup>



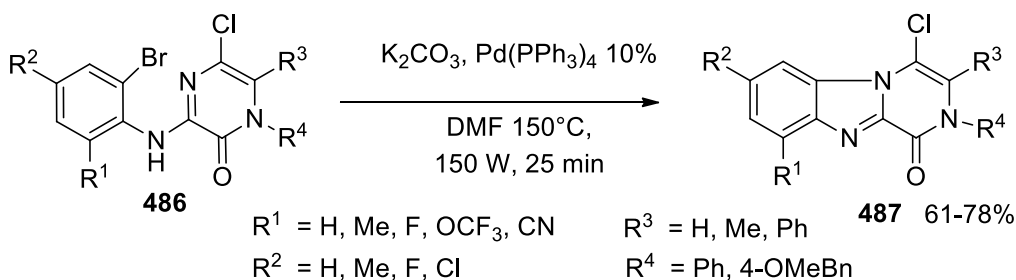
Scheme 156

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.<sup>264</sup>



### Scheme 157

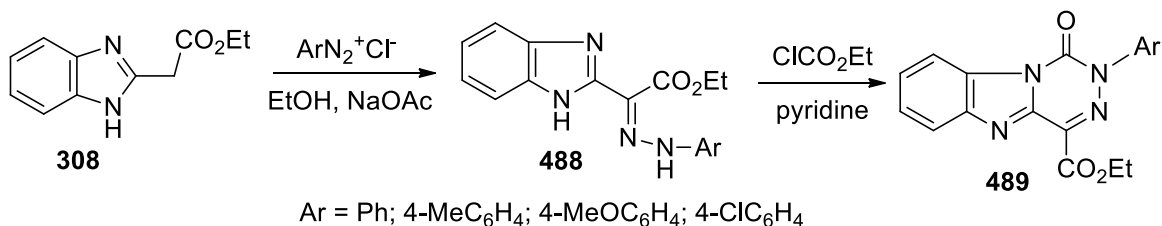
3-Anilinopyrazinones **486** were easily converted into the pyrazino[1,2-*a*]benzimidazol-1(*2H*)-ones **487** by applying a microwave assisted Buchwald–Hartwig type cyclization using 10%  $Pd(PPh_3)_4$  and anhydrous potassium carbonate in DMF at 150 °C and 150 Watts (Scheme 158).<sup>265</sup>



### Scheme 158

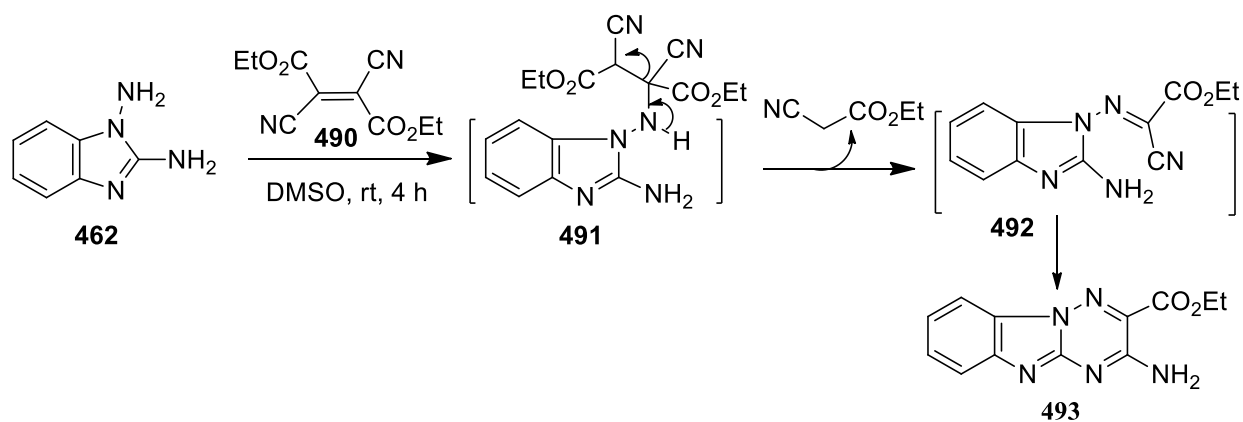
### 3.4. Triazinobenzimidazoles

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).<sup>266</sup>



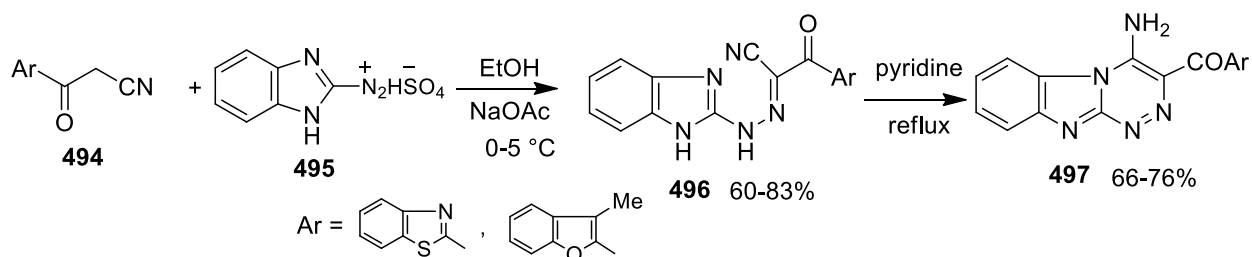
Scheme 159

1,2,4-Triazino[2,3-*a*]benzimidazole derivative **493** was obtained selectively by the reaction of diethyl (*E*)-2,3-dicyanobutenedioate **490** with 1,2-diamino-1*H*-benzimidazole **462** in dimethyl sulfoxide at room temperature as outlined in Scheme 160.<sup>267</sup>



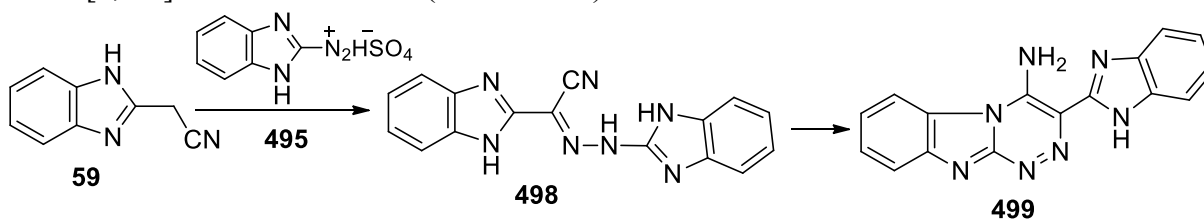
Scheme 160

3-Oxopropanenitriles **494** coupled smoothly with 1*H*-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-*a*]benzimidazoles **497** in good yields (Scheme 161).<sup>268,269</sup>



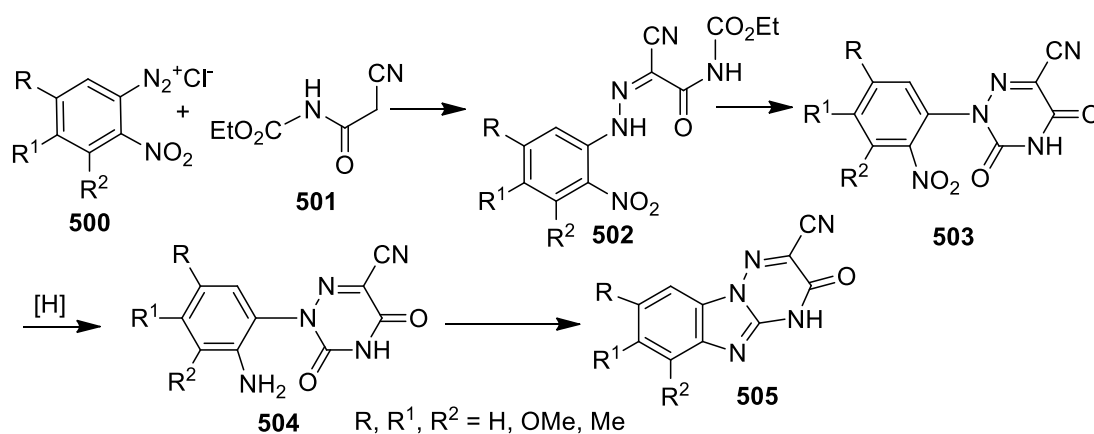
Scheme 161

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).<sup>270</sup>



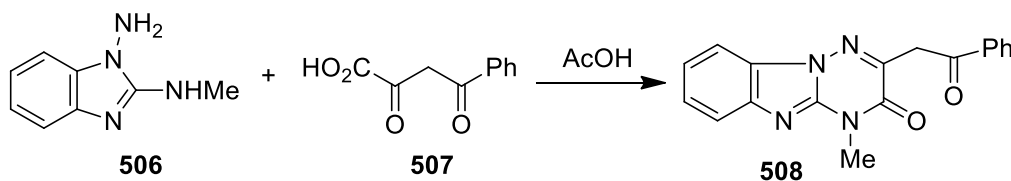
Scheme 162

The diazotized 2-nitroanilines **500** were coupled with *N*-ethoxycarbonylcynoacetamide **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).<sup>271-274</sup>



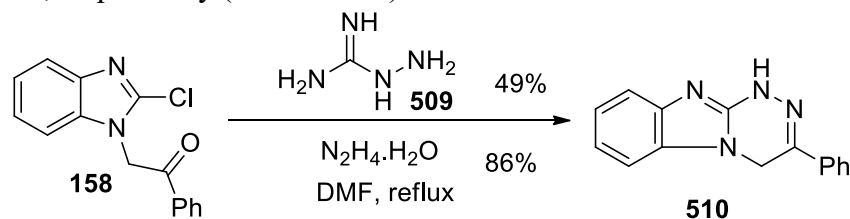
Scheme 163

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).<sup>275</sup>



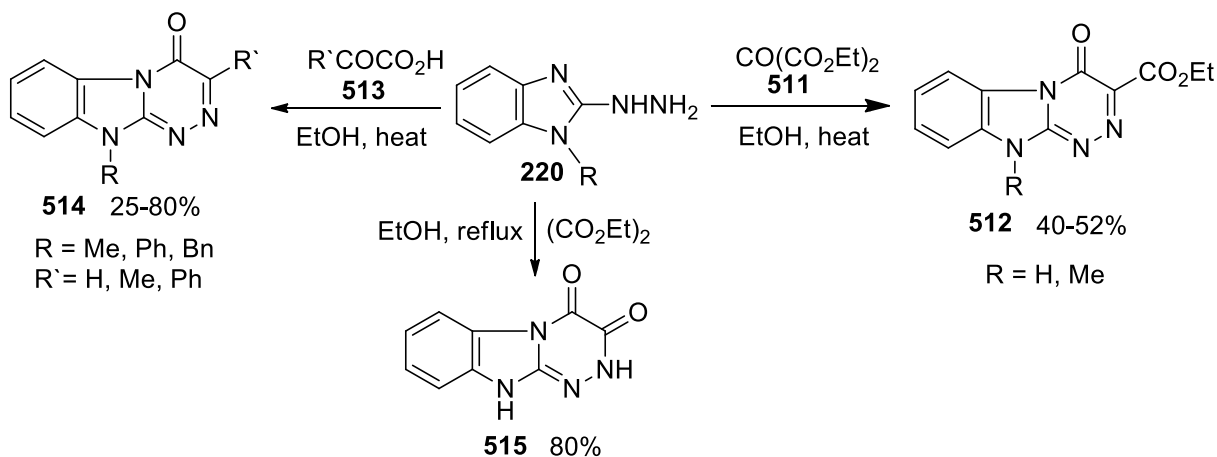
Scheme 164

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).<sup>78</sup>



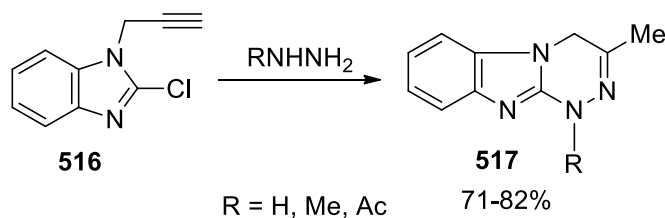
### Scheme 165

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



### Scheme 166

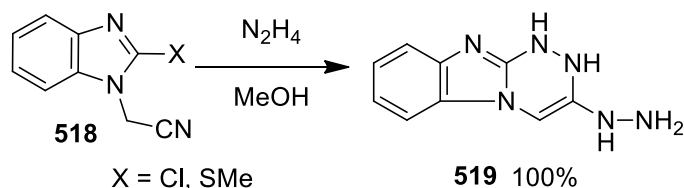
Condensation of hydrazines with *N*-propargyl-2-chlorobenzimidazole **516** resulted in the formation of 1,2,4-triazino[4,3-*a*]benzimidazole derivatives **517** (Scheme 167).<sup>278</sup>



### Scheme 167



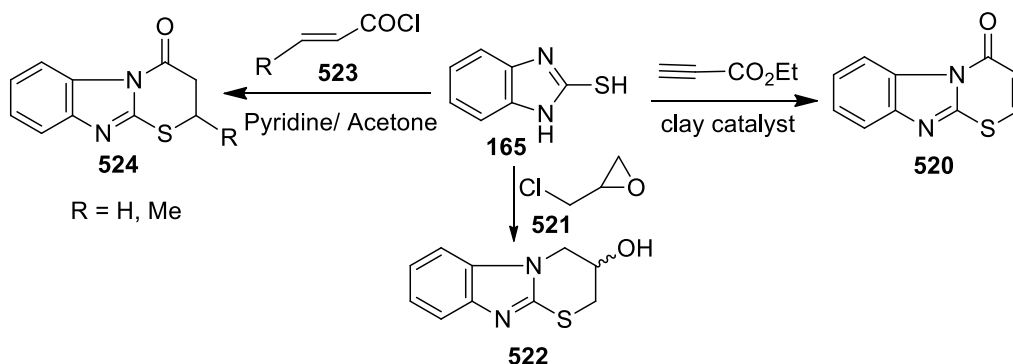
Heating benzimidazole-1-acetonitriles **518** and hydrazine in methanol gave 3-hydrazino-1,2,4-triazino[4,3-*a*]benzimidazole **519** (Scheme 168).<sup>279,280</sup>



Scheme 168

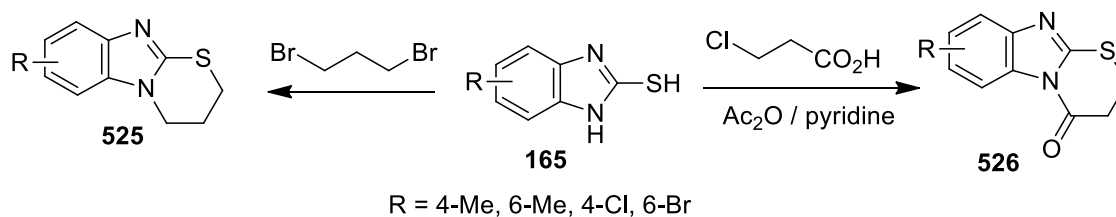
### 3.5. Thiazinobenzimidazoles

Michael-type addition of 2-mercaptobenzimidazole **165** to ethyl propiolate in the presence of clay catalyst gave 4-oxothiazino[3,2-*a*]benzimidazole **520**.<sup>281</sup> Alkylation of **165** with epichlorohydrin **521** in aqueous base gave the thiazino[3,2-*a*]benzimidazole derivative **522**.<sup>282</sup> On the other hand, reaction of 2-mercaptobenzimidazole **165** with acryloyl chlorides **523** in pyridine and acetone afforded the 4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones **524** (Scheme 169).<sup>283</sup>



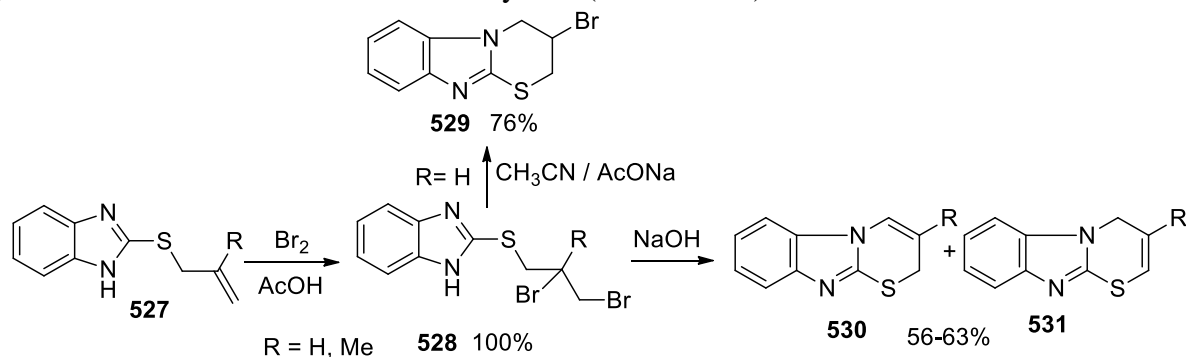
Scheme 169

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).<sup>284,285</sup>



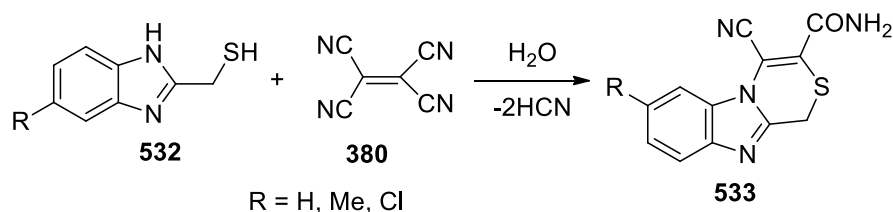
Scheme 170

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).<sup>286,287</sup>



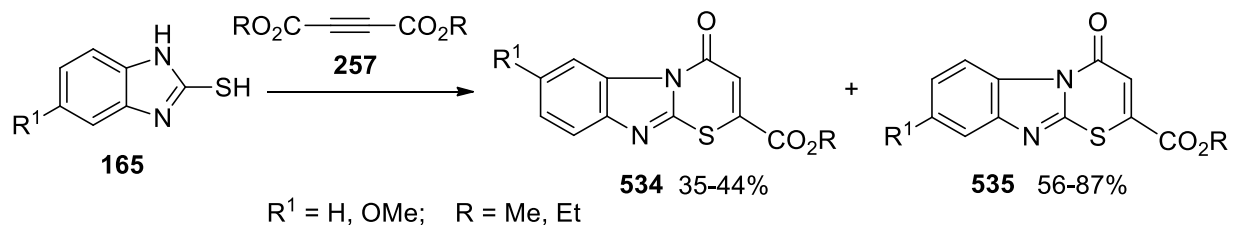
Scheme 171

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



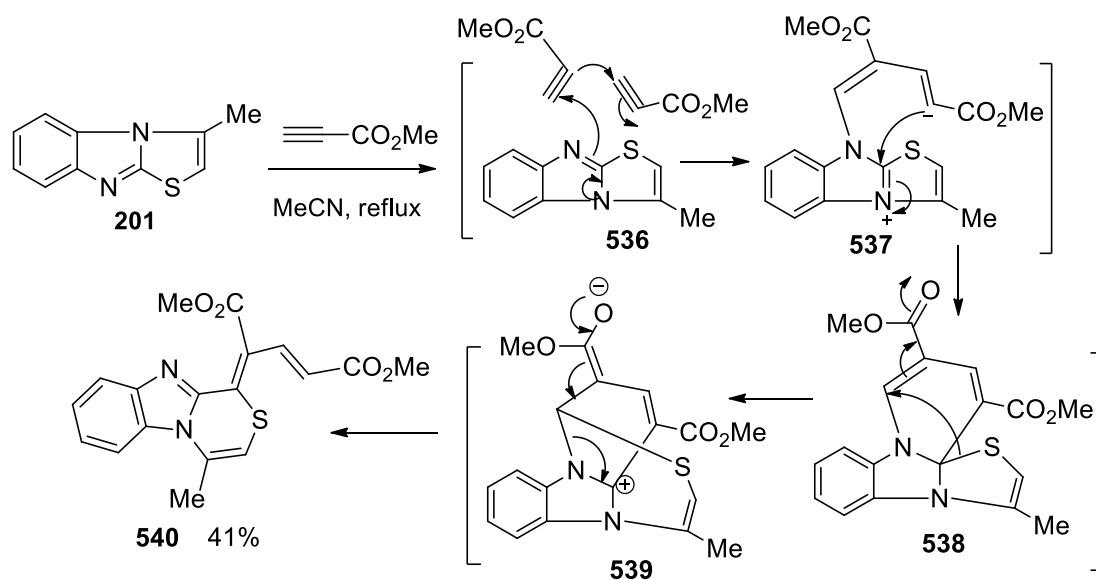
Scheme 172

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).<sup>289,290</sup>



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.<sup>291</sup>

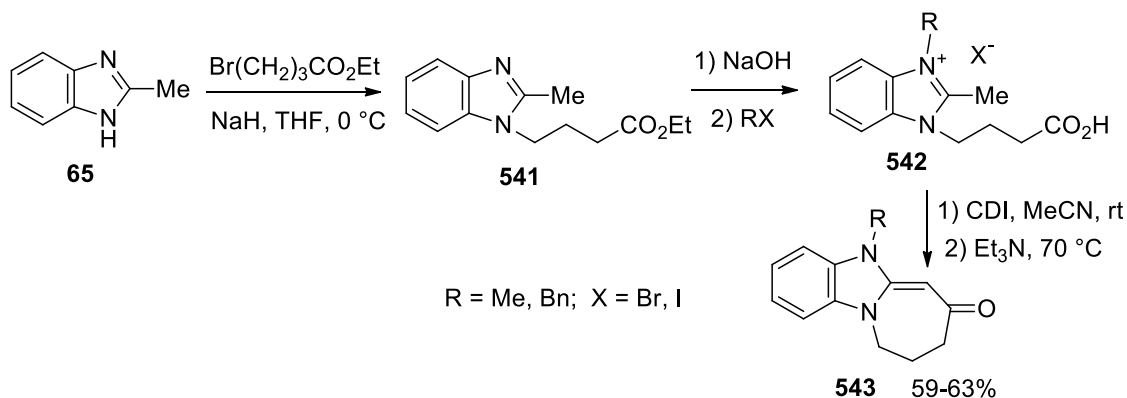


Scheme 174

## 4. Synthesis of Azepino-fused-benzimidazoles

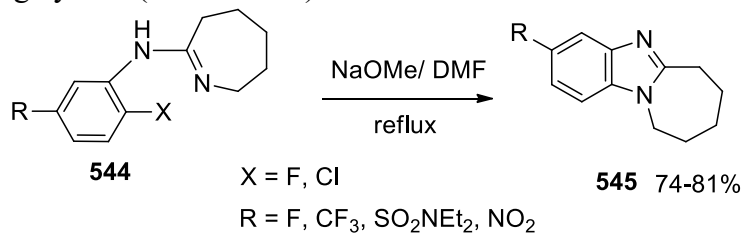
### 4.1. Azepinobenzimidazoles

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  $\text{Et}_3\text{N}$  and heating the mixture at  $70^\circ\text{C}$  gave 7,8,9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7-one derivatives **543** (Scheme 175).<sup>31,292</sup>



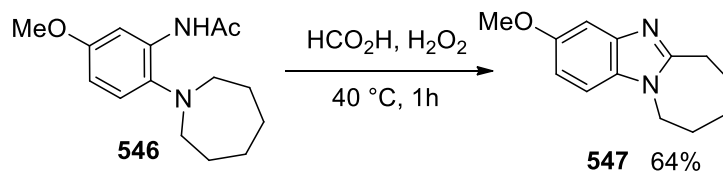
Scheme 175

*N*-(Haloaryl)amidines **544** underwent heterocyclization when heated in DMF in the presence of sodium methoxide to give the 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole derivatives **545** in high yields (Scheme 176).<sup>25,293</sup>



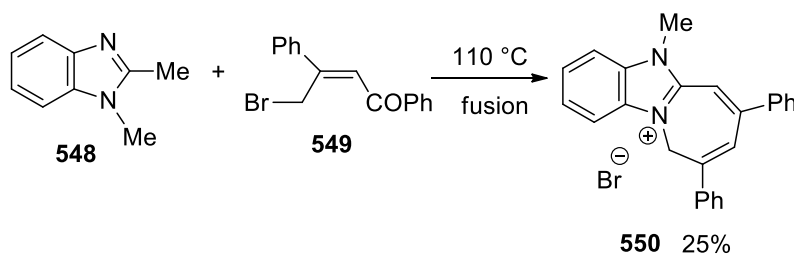
### Scheme 176

3-Methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole **547** was prepared from the reaction of mixture of *N*-(2-(azepan-1-yl)-5-methoxyphenyl)acetamide **546**, formic acid and H<sub>2</sub>O<sub>2</sub> at 40 °C as shown in Scheme 177.<sup>294</sup>



### Scheme 177

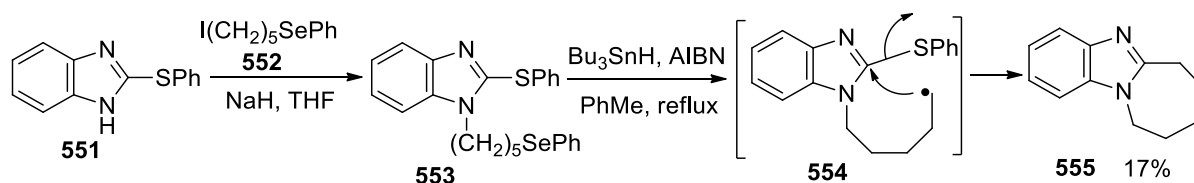
Fusion of a mixture of  $\gamma$ -bromodipnone **549** and 1,2-dimethyl-1*H*-benzimidazole **548** on an oil bath at 110 °C for 30 min afforded 11-methyl-7,9-diphenyl-6*H*,11*H*-azepino[1,2-*a*]-5-benzimidazolium bromide **550** in reasonable yield (Scheme 178).<sup>295</sup>



### Scheme 178

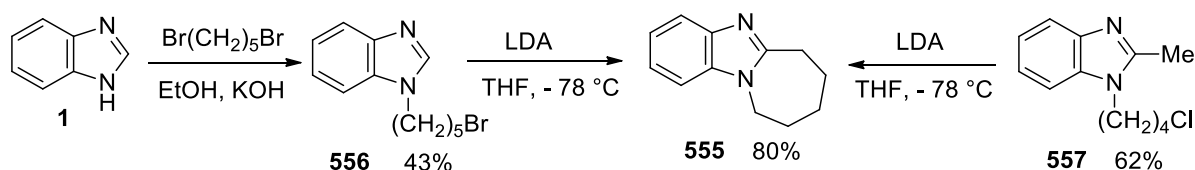
Treatment of 1*H*-2-phenylthioimidazole **551** with NaH in THF followed by adding 5-iodo-1-(phenylselenenyl)pentane **552** under reflux gave 1-[5-(phenylselenenyl)pentyl]-2-(phenylthio)-1*H*-benzimidazole **553**. Refluxing the latter **553** in toluene using Bu<sub>3</sub>SnH and AIBN resulted in

an intramolecular radical substitution of the intermediate **554** to give the 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole **555** in low yield (Scheme 179).<sup>296</sup>



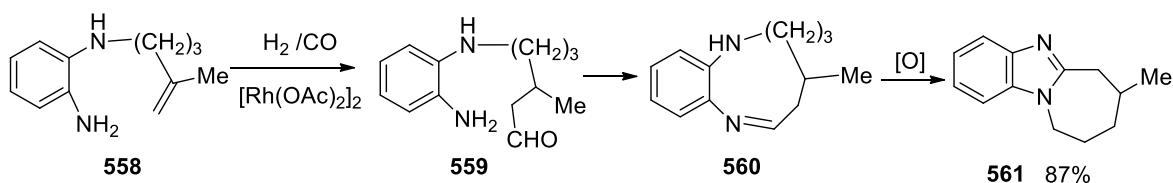
Scheme 179

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



Scheme 180

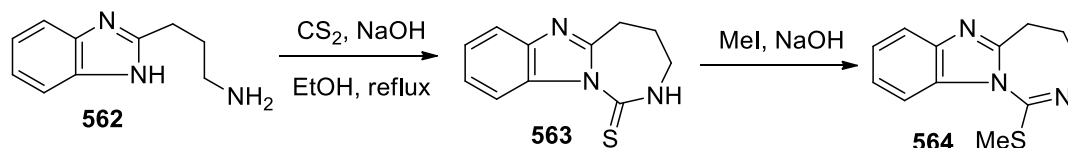
Rhodium-catalysed reactions of *N*-(4-methylpent-4-enyl)-1,2-diaminobenzene **558** with hydrogen and carbon monoxide gave the 7,8,9,10-tetrahydro-7-methyl-6*H*-azepino[1,2-*a*]benzimidazole **561** in good yield. This product arises from initial highly regioselective aldehyde formation at the terminal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



Scheme 181

#### 4.2. Diazepinobenzimidazoles

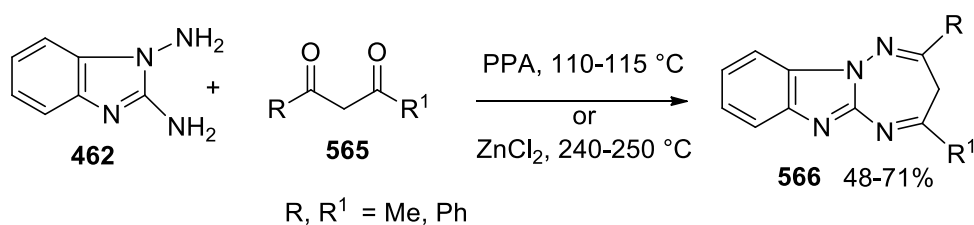
Reaction of 2-(ω-aminopropyl)benzimidazole **562** with carbon disulfide in alkaline ethanol gave the 1,3-diazepino[3,4-*a*]benzimidazole-2-thione **563** which on treatment with methyl iodide gave the 2-methylthio derivative **564** (Scheme 182).<sup>300</sup>



Scheme 182

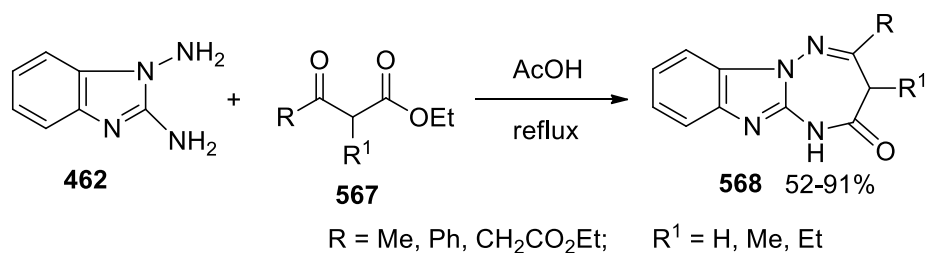
### 4.3. Triazepinobenzimidazoles

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  $\text{ZnCl}_2$  at 240-250 °C gave the corresponding 1,2,4-triazepino[2,3-*a*]benzimidazole derivatives **566** in good yields (Scheme 183).<sup>301</sup>



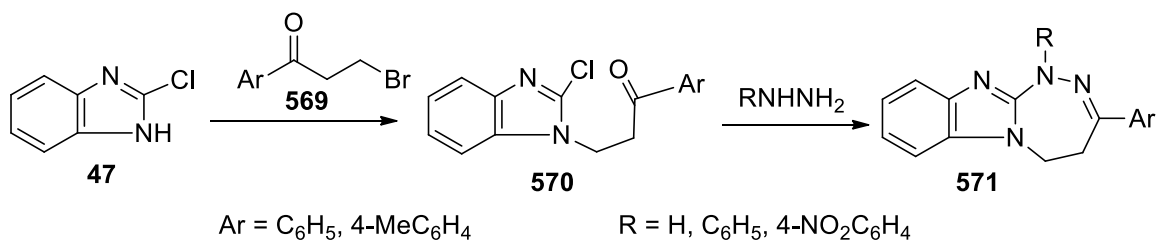
Scheme 183

When 1,2-diaminobenzimidazole **462** was treated with  $\beta$ -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).<sup>53,301-303</sup>



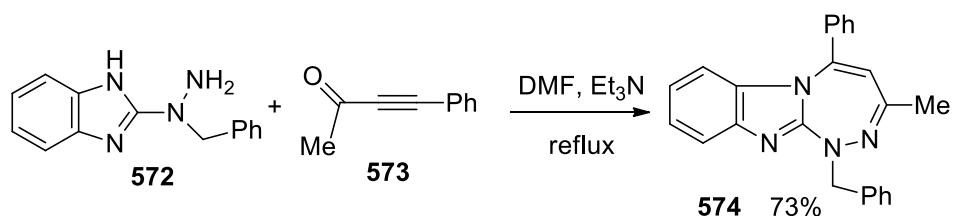
Scheme 184

2-Chlorobenzimidazole **47** was condensed with  $\beta$ -bromoketones **569** to give 1-(2-benzoyl-ethyl)-2-chlorobenzimidazoles **570** which cyclized with hydrazines to give the corresponding 1,2,4-triazepino[4,3-*a*]benzimidazoles **571** (Scheme 185).<sup>304</sup>



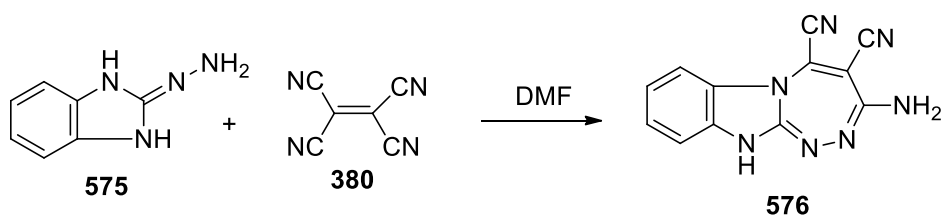
### Scheme 185

Reaction of 2-(benzylhydrazino)benzimidazole (**572**) with 4-phenyl-3-butyn-2-one (**573**) in DMF in the presence of Et<sub>3</sub>N gave 73% of 1-benzyl-3-methyl-5-phenyl-1,2,4-triazepino[4,3-*a*]benzimidazole (**574**) (Scheme 186).<sup>305</sup>



### Scheme 186

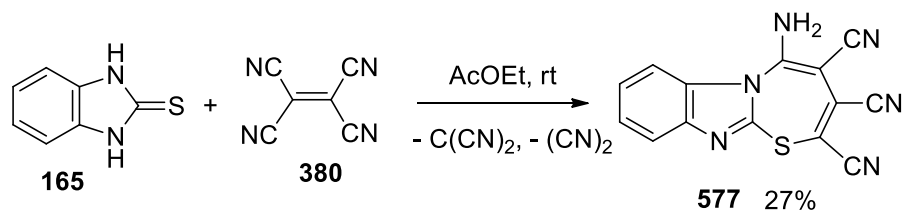
Reaction of 2-hydrazonobenzimidazole (**575**) with tetracyanoethylene (TCNE) (**380**) gave the 1,2,4-triazepino[4,3-*a*]benzimidazole derivatives (**576**) (Scheme 187).<sup>306</sup>



### 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).<sup>307</sup>



Scheme 188

## 5. References

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