Synthetic routes to benzimidazole-based fused polyheterocycles

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Abstract

The review article represents a survey covering the synthetic strategies leading to benzimidazole-based fused polyheterocyclic systems utilizing simple reactive benzimidazole synthons since 1980. The polyheterocyclic systems are classified based on the number of rings; tetra-, penta-, hexa- and hepta-fused ring systems. Among each polyheterocyclic system, further classification according to the number of heterotoms; two-, three-, four-, five-, six- and seven heteroatoms is considered.

Keywords*:* Polyheterocycles, fused benzimidazoles, synthesis, cyclization

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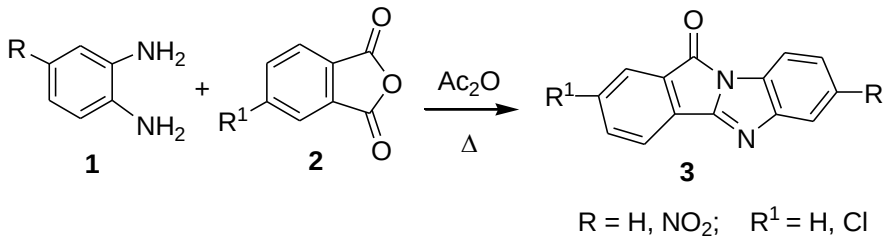
1. Introduction

There is a growing interest over the past years for the synthesis of benzimidazole-based heterocycles due to the crucial role of benzimidazole unit in the functions of biologically important molecules.[1-3] Benzimidazole-based ployhetrocycles has exhibited interesting biological properties. For example, benzimidazoquinazolines,[4-8] benzimidazoisoquinolines[9] and benzimidazo[2,1-*a*]isoindolones[10] were reported as potent antitumor agents. Benzimidazo[2,1-*b*]quinazolines are potent immuno-suppressors[11] and benzimidazo[2,1-*b*]benzo[*f*]isoquinoline ring system[12] is present in pharmacologically active compounds. Isoindolo[2,1-*a*]benzimidazoles are also known to be sedatives and tranquilizers.[13] There have been a number of practically important routes to benzimidazole-based polyheterocycles, *e.g.* (*i*) the reaction of benzaldehyde derivatives with benzimidazoles containing an activated methylene group at position 2, (*ii*) the reaction of coumarins with *o*-phenylenediamines, (*iii*) the reaction of 2-azidoanilines with substituted cinnamaldehydes, (*iv*) the reaction of 2-(2-aminoaryl(hetaryl))benzimidazoles with haloketones, (*v*) the reaction of *o*-phenylenediamines with phthalic anhydrides, (*vi*) metal-catalyzed cyclization of alkynylaniline derivatives and (*vii*) the reaction of 2-(hydroxymethylene)-3-keto steroids with funtionalized benzimidazoles. Such reactions provide convenient strategies for synthesis of annulated benzimidazole polyheterocycles. This review covers the literature from 1980 to 2009.

2. Tetracyclic fused benzimidazoles

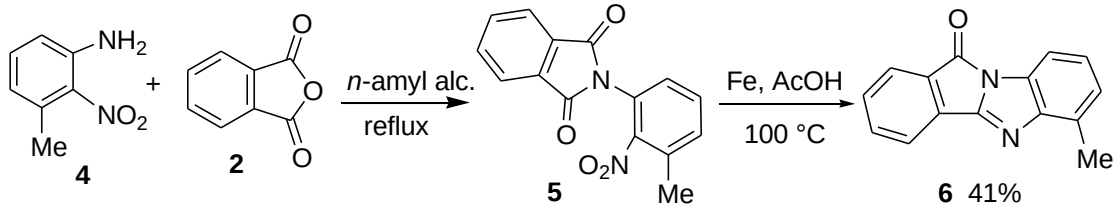
2.1. With two heteroatoms

2.1.1. Isoindolo-benzimidazoles. The preparation of isoindolo[2,1-*a*]benzimidazol-11-one derivatives was mostly performed from the condensation reaction of *o*-phenylenediamines with phthalic anhydrides. Thus, heating a mixture of *o*-phenylenediamines **1** with phthalic anhydrides **2** in acetic anhydride at 140-150 °C gave 11*H*-isoindolo[2,1-*a*]benzimidazol-11-one derivatives **3** (Scheme 1).[14,15]



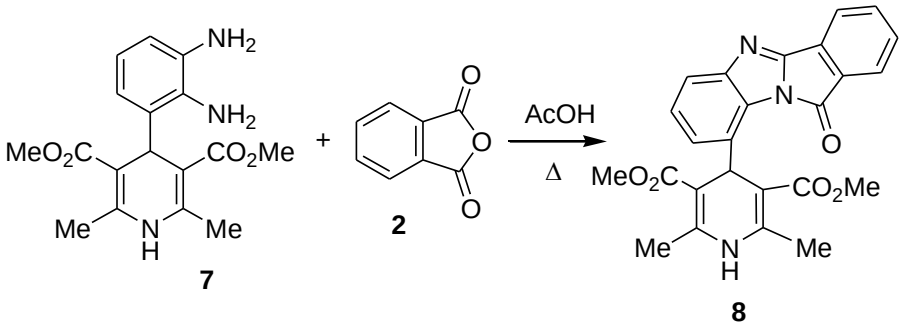
Scheme 1

Heating of 2-nitro-3-methylaniline **4** and phthalic anhydride **2** in *n*-amyl alcohol gave *N*-(2-nitro-3-methylphenyl)phthalimide **5**. Reaction of **5** with iron powder in 50% aqueous acetic acid at 100 °C gave 6-methyl-11-oxoisoindolo[2,1-*a*]benzimidazole **6** (Scheme 2).[16]



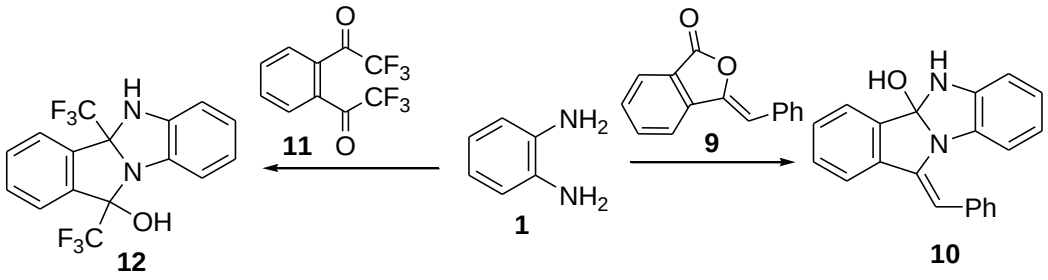
Scheme 2

The isoindolobenzimidazolone derivative **8** was obtained similarly from heating of phthalic anhydride **2** with the pyridyl-phenylenediamine derivative **7** (Scheme 3). [17]



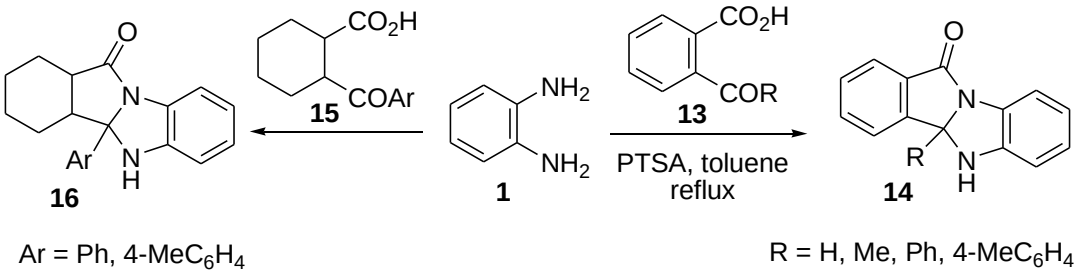
Scheme 3

The hydroxyisoindolobenzimidazole derivatives **10** and **12** were synthesized from *o*-phenylenediamine **1** and 3-benzylidenephthalide **9** and with the 1,2-di(triflouroacetyl)benzene **11**, respectively (Scheme 4).[18,19]



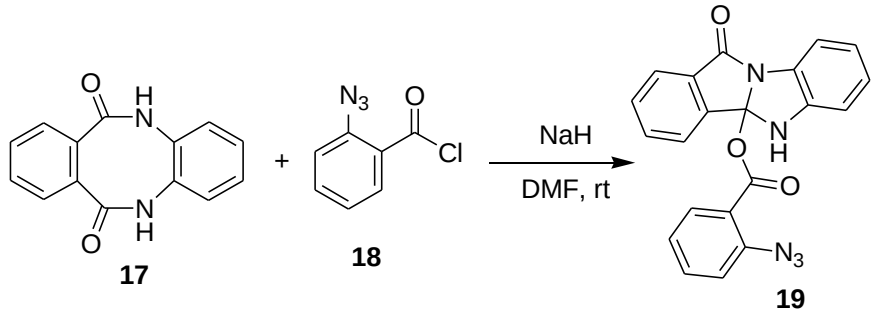
Scheme 4

Condensation of *o*-phenylenediamine **1** with *o*-acylbenzoic acids **13** in refluxing toluene using catalytic amount of *p*-toluenesulfonic acid (PTSA) under azeotropic condition for removal of water, led to the formation of isoindolobenzimidazoles **14** in reasonable yields (Scheme 5).[20,21] Similar condensation of **1** with aroylcyclohexane-carboxylic acids **15** gave the hexahydroisoindolobenzimidazoles **16** (Scheme 5).[22,23]



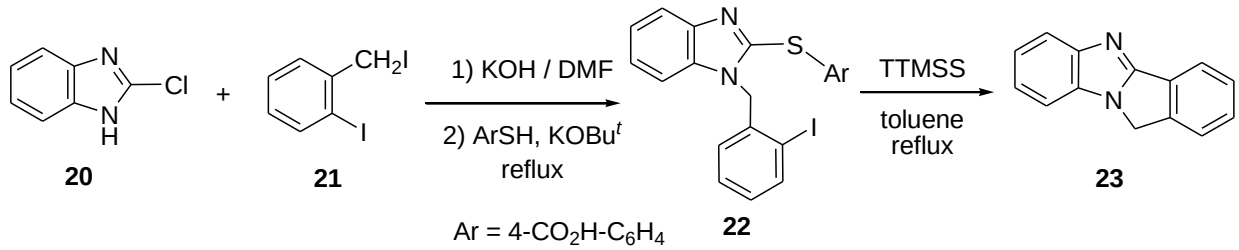
Scheme 5

Reaction of dibenzo[*b*,*f*][1,4]diazocine-6,11-(5*H*,12*H*)-dione **17** with 2-azidobenzoyl chloride **18** in DMF and NaH afforded only 30% yield 4b-[(2-azidobenzoy1)oxy]-5*H*-isoindolo[2,1-*a*]benzimidazol-11(4b*H*)-one **19** *via* transannular cyclization (Scheme 6).[24]



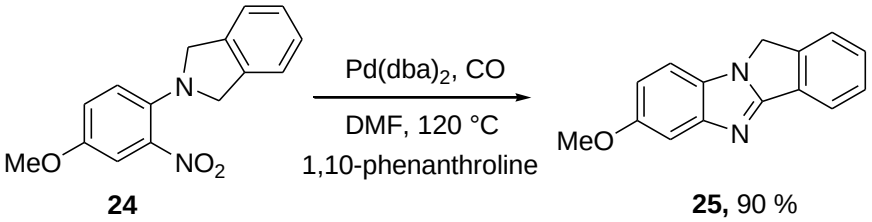
Scheme 6

The parent 11*H*-isoindolo[2,1-*a*]benzimidazole could also be obtained *via* an intramolecular aryl radical cyclization as shown in Scheme 7. Thus, heating a mixture of 2-chlorobenzimidazole **20**, arenethiol and 2-iodobenzyl iodide **21** in DMF in the presence of KOH / KOBu^t under reflux gave a quantitative yield of the 2-arylthio-1-benzyl-1*H*-benzimidazole derivative **22**. Five-membered cyclisation with the radical precursor **22** using *tris*-(trimethylsilyl)silane (TTMSS) in toluene at reflux afforded a low yield (20%) of the cyclised product 11*H*-isoindolo[2,1-*a*]benzimidazole **23** *via* a homolytic aromatic substitution by aryl radical at C-2 of benzimidazole ring (Scheme 7).[25]



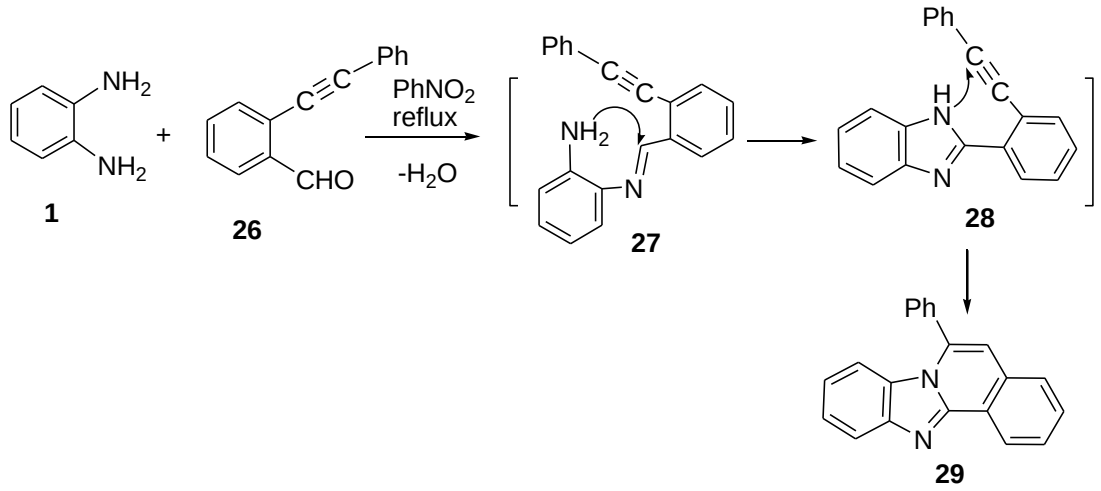
Scheme 7

7-Methoxy-11*H*-isoindolo[2,1-*a*]benzimidazole **25** was prepared in 90% yield from palladium-catalyzed annulation of 2-(4-methoxy-2-nitrophenyl)-2,3-dihydro-1*H*-isoindole **24** by heating in DMF using *bis*-(dibenzylideneacetone)palladium [Pd(dba)$_2$] and 1,10-phenanthroline at 120 °C and the solution was saturated with CO under pressure (Scheme 8).[26]



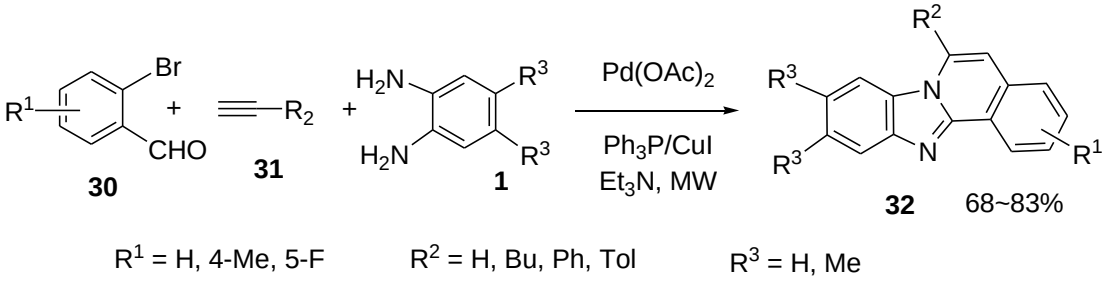
Scheme 8

2.1.2. Benzimidazo[2,1-*a*]isoquinolines. Condensation of *o*-phenylenediamine **1** with 2-(2-phenylethynyl)benzaldehyde **26** in refluxing nitrobenzene resulted in an oxidative cyclization to give 6-phenylbenzimidazo[2,1-*a*]isoquinoline **29** *via* the intermediates **27** and **2**8 (Scheme 9).[27]



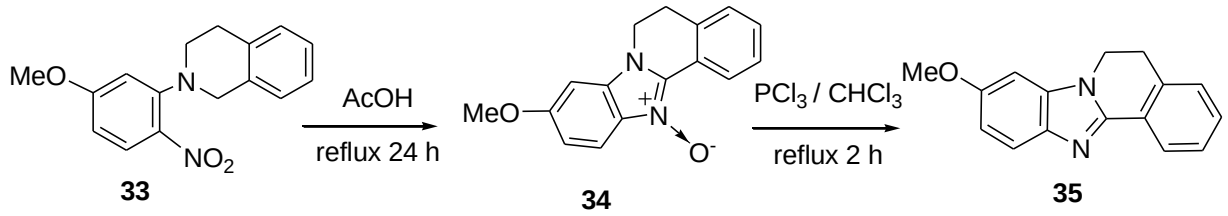
Scheme 9

Direct, efficient syntheses of the benzimidazo[2,1-*a*]isoquinolines **32** have been achieved with 2-bromoarylaldehydes **30**, terminal alkynes **31**, and 1,2-phenylenediamines **1** by a microwave-accelerated tandem process in which a Sonogashira coupling, 5-endo cyclization, oxidative aromatization, and 6-endo cyclization could be performed in a single synthetic operation (Scheme 10).[28]



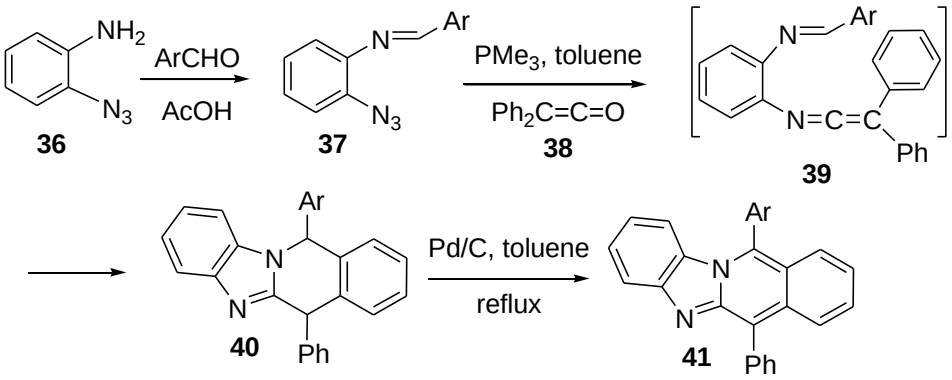
Scheme 10

Heating of *N*-(5-methoxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **33** in acetic acid resulted in an intramolecular cyclization to give the benzimidazo[2,1-*a*]isoquinoline-*N*-oxide **34** which upon deoxygenation *via* heating with PCl_3 in chloroform gave the benzimidazo[2,1-*a*]isoquinoline derivative **35** (Scheme 11).[29]



Scheme 11

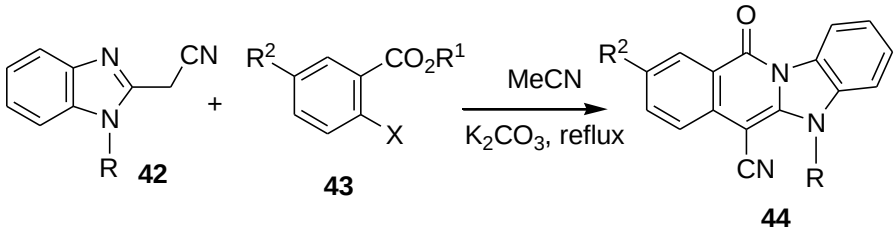
The reaction of 2-azidoaniline **36** with aromatic aldehydes gave N-(2-azidophenyl)imines **37** which upon reaction with trimethylphosphine followed with diphenylketene **38**, the corresponding 6,11-dihydrobenzimidazo[1,2-*b*]isoquinolines **40** were isolated in excellent yields *via* a formal [4+2] intramolecular cycloaddition of ketenimine with imine function of the intermediates **39**. Refluxing of **40** with Pd/C in toluene gave benzimidazo[1,2-b]isoquinolines **41** in good yields (Scheme 12).[30,31]



Ar = 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-MeC_6H_4

Scheme 12

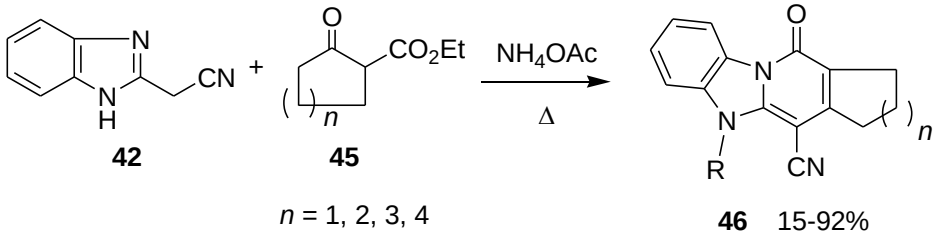
2-Benzimidazoleacetonitrile **42** condensed with 2-haloaromatic esters **43** in refluxing acetonitrile containing K_2CO_3 to give the benzimidazo[1,2-*a*]isoquinolones **44** (Scheme 13).[32-34]



R = Me; R^1 = Me, Et; R^2 = H, NO_2; X = Cl, F

Scheme 13

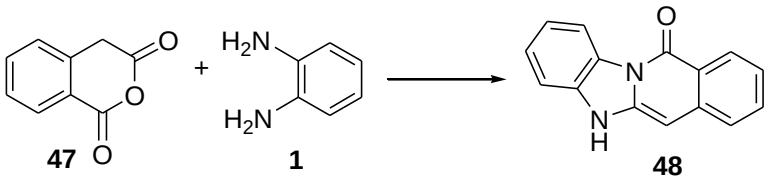
Benzimidazo[1,2-*a*]isoquinolines **46** were prepared in reasonable yield by condensing 2-benzimidazoleacetonitrile **42** with ethyl cycloalkanone-2-carboxylates **45** in the presence of ammonium acetate at 140 °C (Scheme 14).[35,36]



n = 1, 2, 3, 4

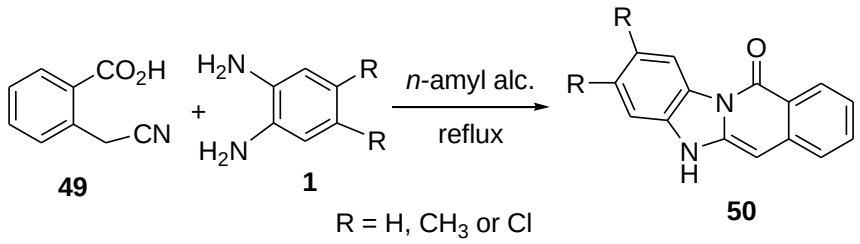
Scheme 14

Refluxing of isochroman-1,3-dione **47** with *o*-phenylenediamine **1** in acetic acid gave 11*H*-benzimidazo[1,2-*a*]isoquinolin-11-one **48** (Scheme 15).[37]



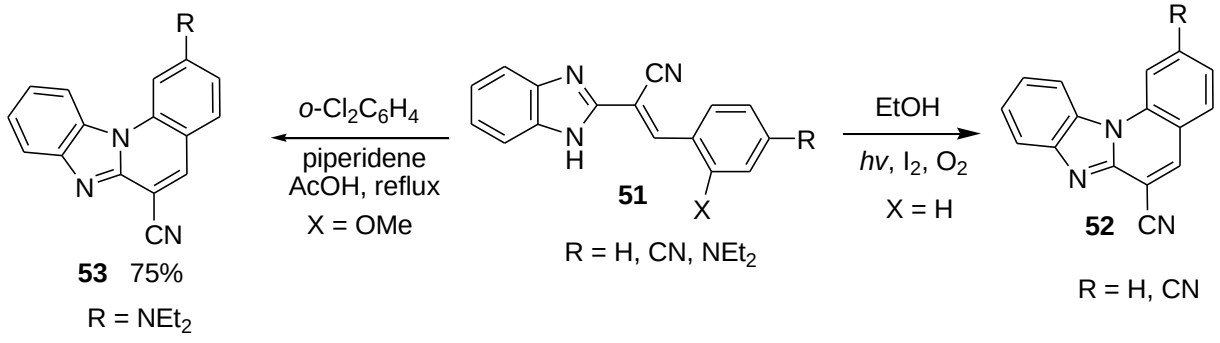
Scheme 15

Substituted 5*H*-benzimidazo[l,2-*b*]isoquinolin-11-ones **50** were synthesized in good yields (53-83%) by refluxing, in *n*-amyl alcohol, the appropriate *o*-phenylenediamine **1** with α-(*o*-carboxyphenyl)acetonitriles **49** (Scheme 16).[38]



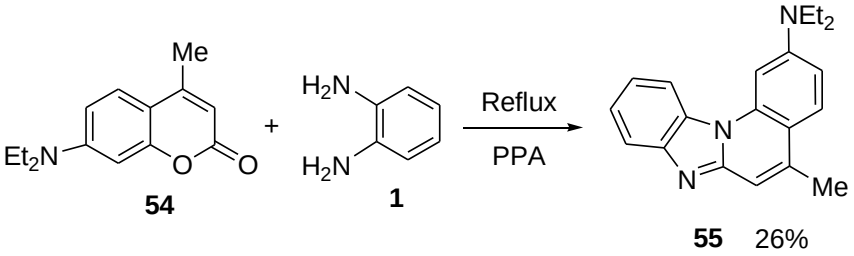
Scheme 16

2.1.3. Benzimidazo[1,2-*a*]quinolines. Photochemical cyclization of arylidene-1*H*-benzimidazol-2-ylacetonitriles **51** yielded the bezimidazo[1,2-*a*]quinoline derivatives **52** (Scheme 17).[39] Highly fluorescent 7-(diethylamino)benzimidazo[1,2-*a*]quinoline-3-carbonitrile **53** was prepared in 75% yield by cyclization of the arylidene-1*H*-benzimidazol-2-ylacetonitrile **51** (X = OMe, R = NEt_2) under refluxing *o*-dichlorobenzene in the presence of piperidine and acetic acid (Scheme 17).[40]



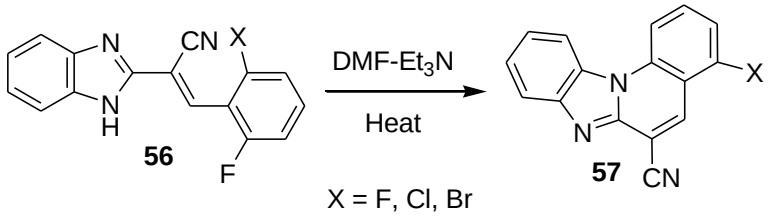
Scheme 17

2-*N*-Ethylamino-5-methylbenzimidazo[1,2-*a*]quinoline **55** was formed in 18% yield when 7-diethylamino-4-methylcoumarin **54** reacted with *o*-phenylenediamine **1** in the presence of polyphosphoric acid (PPA) at 240 °C (Scheme 18).[41]



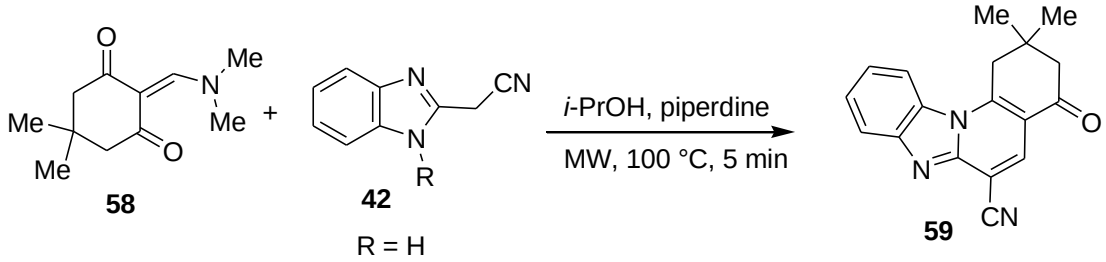
Scheme 18

Arylidene-1*H*-benzimidazol-2-ylacetonitriles **56** underwent an intramolecular cyclization when heated in DMF containing triethylamine to give the benzimidazo[1,2-*a*]quinoline-6-carbonitriles **57** (Scheme 19).[42,43]



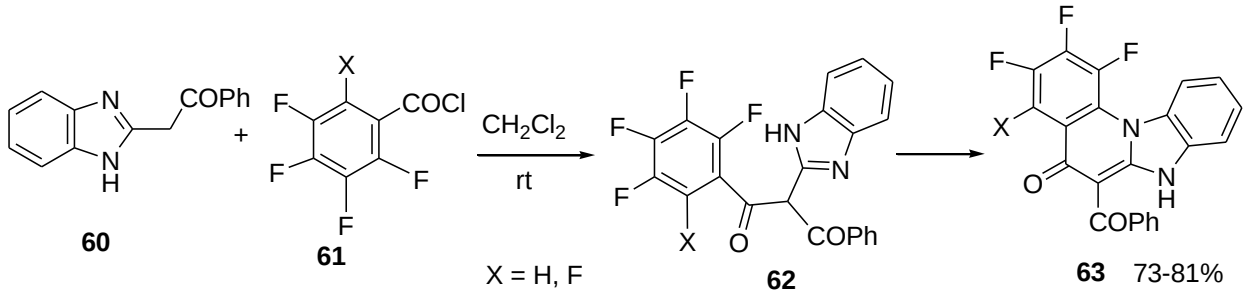
Scheme 19

Microwave irradiation of 2-(*N*,*N*-dimethylamino)methylene-5,5-dimethylcyclohexane-1,3-dione **58** and 2-benzimidazoleacetonitrile **42** in *iso*-propanol and a catalytic amount of piperidine led to the formation of tetrahydrobenzimidazo[1,2-*a*]quinoline derivative **59** (Scheme 20).[44]



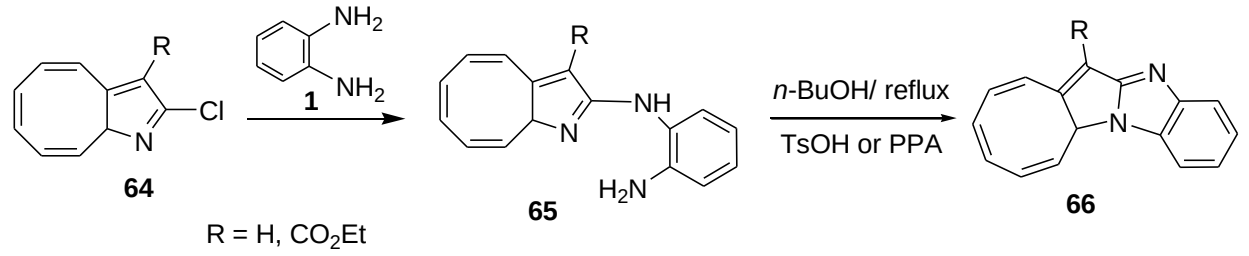
Scheme 20

Room-temperature reactions of polyfluorobenzoyl chlorides **61** with 2-benzoylmethylbenzimidazole **60** in dichloromethane in the presence of triethylamine afforded tetracyclic imidazoquinolines **63** in 73-81% yields *via* the intermediate **62** (Scheme 21).[45]



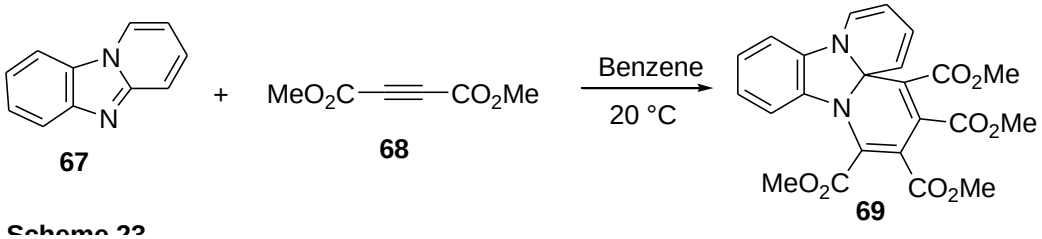
Scheme 21

2.1.4. Fused macroheterocycles with two heteroatoms. Chlorocyclohepta[*b*]pyrroles **64** reacted with *o*-phenylenediamine **1** to give 2-(2-aminoanilino)cyclohepta[*b*]pyrroles **65** in good yields. Treatment of **65** (R = H) with polyphosphoric acid (PPA) afforded cycloheptapyrrolobenzimidazole **66** (R = H) in good yields and when **65** (R = CO_2Et) was treated with TsOH in *n*-butanol under reflux the ester derivative **66** (R = CO_2Et) was obtained (Scheme 22).[46]



Scheme 22

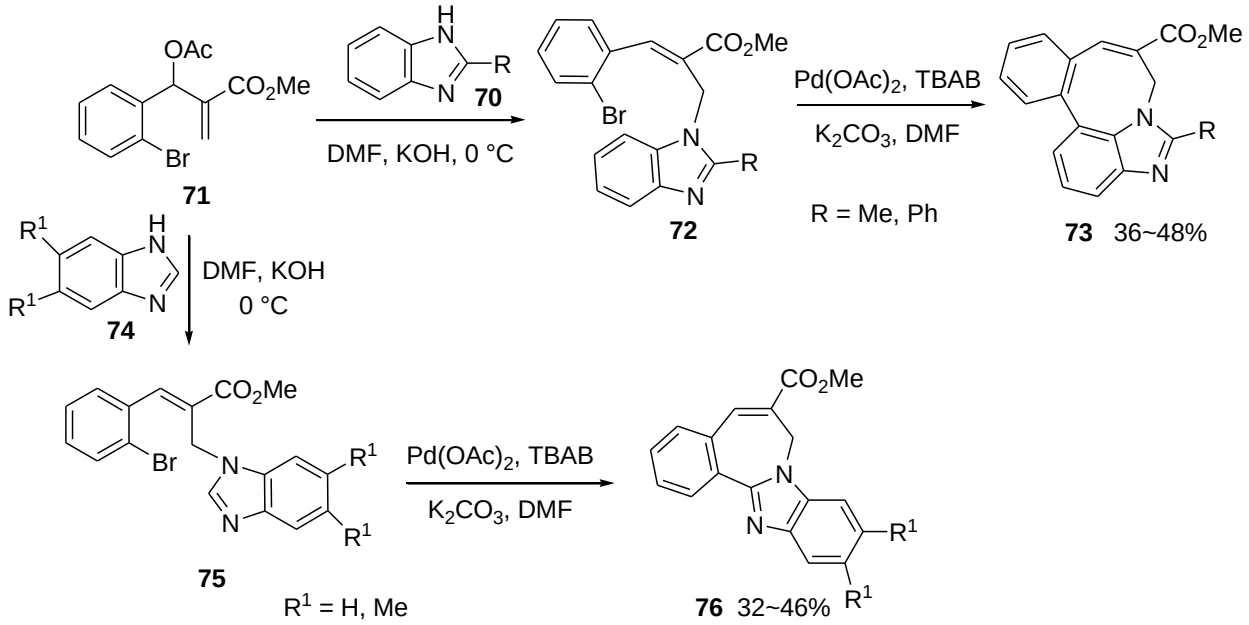
Treatment of pyrido[1,2-*a*]benzimidazole **67** with dimethyl acetylenedicarboxylate **68** in benzene for 5 h at 20 °C gave the *bis*-pyridobenzimidazole derivative **69** in 44% yield (Scheme 23).[47]



Scheme 23

Scheme 23

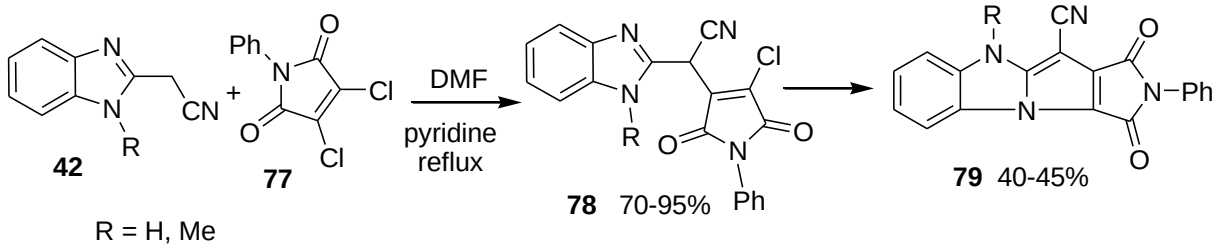
The reaction of Baylis–Hillman acetate **71** with 2-substituted benzimidazoles **70** in DMF and K_2CO_3 at room temperature gave the benzimidazole-attached Baylis–Hillman adducts **72** in 67–89% yields. The tetracyclic compounds containing eight-membered ring; benzoazocino-benzimidazole derivatives **73** were formed, in 36–48% yields, from the intramolecular palladium catalyzed cyclization of **72**. Similarily, the seven-membered ring compounds **76** were obtained from the reaction of **71** with 2-unsubstituted benzimidazoles **74** in DMF and K_2CO_3 at room temperature to give the adducts **75**. Intramolecular Pd-catalyzed cyclization of **75** resulted in the formation of benzo[3,4]azepino[1,2-*a*]benzimidazole derivatives **76** in reasonable yields. The latter results show that 2-position of benzimidazole is more reactive than that of 7-position (Scheme 24).[48]



Scheme 24

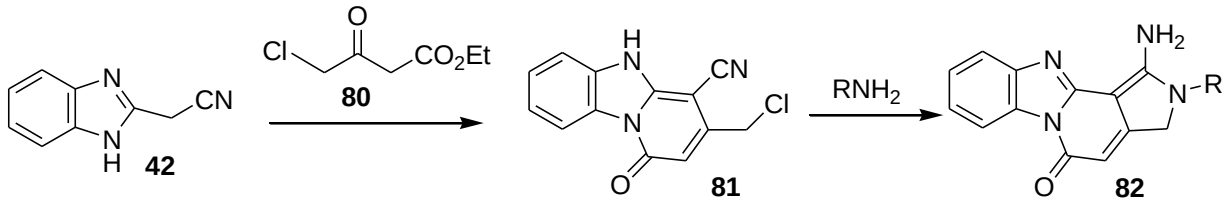
2.2. With three heteroatoms

2.2.1. Pyrrolo-[3',4':4,5]pyrrolo[1,2-*a*]benzimidazoles. Condensation of 2-cyanomethyl-benzimidazoles **42** with dichloromaleimide derivative **77** afforded the (1*H*-benzimidazol-2-yl)-(3-pyrrolyl)acetonitriles **78**. Intramolecular cyclization of **78** gave 1,3-dioxo-1,3-dihydropyrrolo[3',4':4,5]pyrrolo[1,2-*a*]benzimidazoles **79** (Scheme 25).[49]



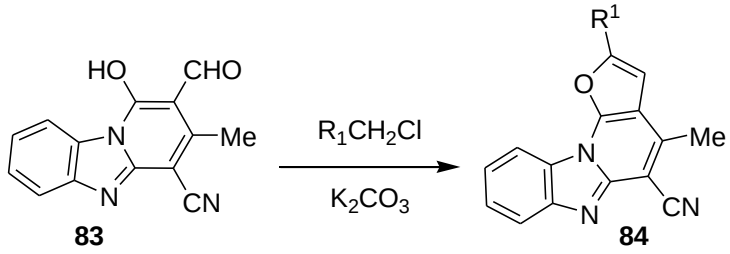
Scheme 25

2.2.2. Pyrrolo[3',4':3,4]pyrido[1,2-*a*]benzimidazoles. Condensation of 2-benzimidazole-acetonitrile **42** with ethyl 4-chloro-3-oxobutanoate **80** led to 3-chloromethylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **81** which upon amination with primary amines yielded pyrrolo[3',4':3,4]pyrido[1,2-*a*]benzimidazoles **82** (Scheme 26).[50]



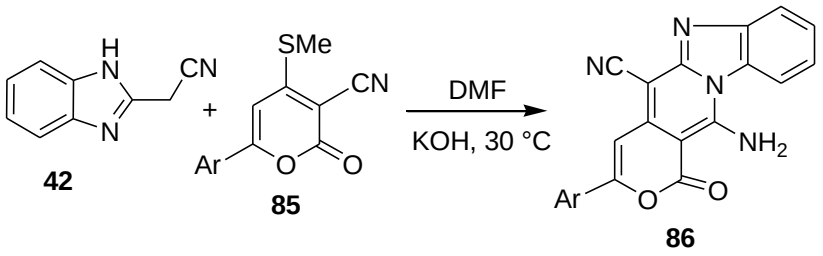
Scheme 26

2.2.3. Furo[3',2':5,6]pyrido[1,2-*a*]benzimidazoles. Furo[3',2':5,6]pyrido[1,2-*a*]benzimidazole derivatives **84** were prepared by reaction of the hydroxy aldehyde **83** with activated alkyl halides in the presence of K_2CO_3 (Scheme 27).[51]



Scheme 27

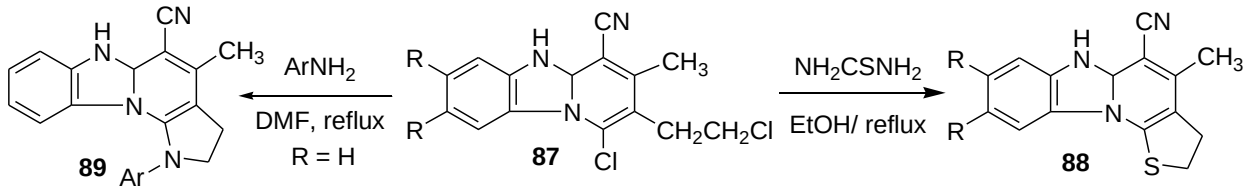
2.2.4. Pyrano[4,3-*d*]pyrido[1,2-*a*]benzimidazoles. Reaction of 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-ones **85** with 2-cyanomethyl-benzimidazole **42** in DMF and KOH at 30 °C led to the formation of pyrano[4,3-d]pyrido[1,2-*a*]benzimidazoles **86** in low yields (7-20%) (Scheme 28).[52]



Ar = 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$

Scheme 28

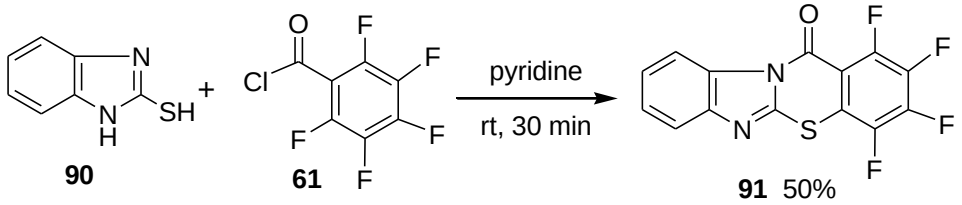
2.2.5. Thieno[2,3-*b*]pyrido[1,2-*a*]benzimidazoles. Badawey *et al* reported the reaction of chloropyrido[1,2-*a*]benzimidazole derivatives **87** with thiourea in refluxing ethanol to give thieno[2,3-*b*]pyrido[1,2-*a*]benzimidazole derivatives **88**. Treatment of **87** with anilines in refluxing DMF gave the 1*H*-pyrrolo[2,3-*b*]pyrido[1,2-*a*]benzimidazole derivatives **89** (Scheme 29).[53]



Ar = 4-ClC_6H_4, 4-F-C_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$ R = H, Me

Scheme 29

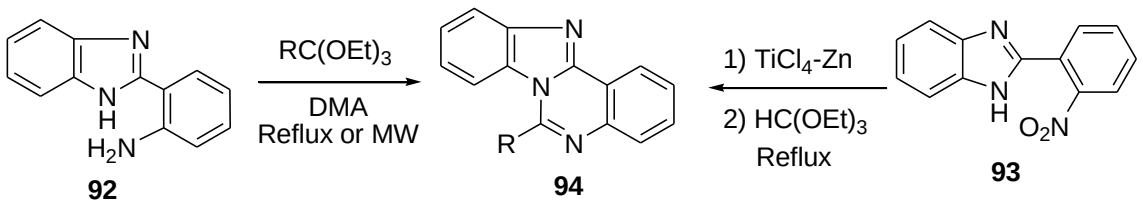
2.2.6. Benzimidazo[2,1-*b*]-1,3-benzothiazine. Reaction of benzimidazole-2-thiol **90** with pentafluorobenzoyl chloride **61** in pyridine at room temperature for 30 minutes gave 1,2,3,4-tetrafluoro-12*H*-benzimidazo[2,1-*b*][1,3]benzothiazin-12-one **91** in 50% yield (Scheme 30).[54]



Scheme 30

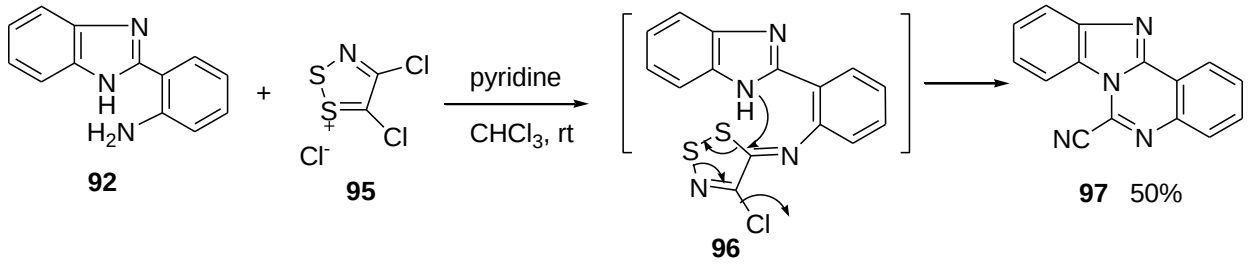
2.2.7. Benzimidazo[1,2-*c*]quinazolines. The benzimidazo[1,2-*c*]quinazoline derivatives **94** were obtained in high yields from the cyclocondensation reaction of 2-(2-aminophenyl)benzimidazole **92** with *ortho*-esters in dimethylacetamide (DMA) under microwave irradiation.[55] The same

product **94** (R = H) was prepared from treatment of 2-(2-nitrophenyl)benzimidazole derivative **93** with triethyl-*ortho*formate in the presence of $TiCl_4$-Zn (Scheme 31).[56,57]



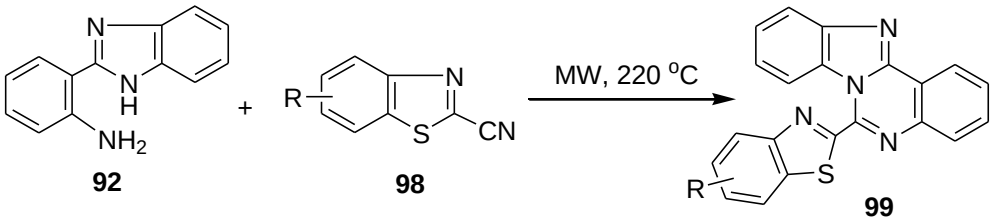
Scheme 31

6-Cyanobenzimidazo[1,2-*c*]quinazoline **97** was prepared in 50% yield by treatment of 2-(2-aminophenyl)benzimidazole **92** with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) **95**, in chloroform at room temperature in the presence of pyridine, *via* the intermediate **96** (Scheme 32).[58]



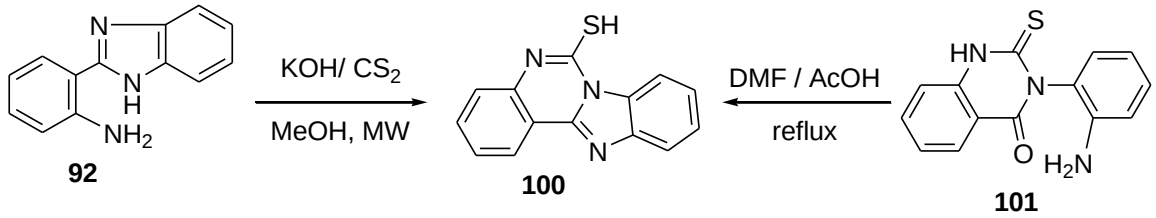
Scheme 32

The cyano group in position 2 of the benzothiazole ring is very reactive and its transformation into acid, amide, amidine and imidate may be easily realised. Thus, microwave irradiation of 2-cyanobenzothiazole **98** with 2-(2-aminophenyl)benzimidazole **92** at 220 ^oC (150 Watt), in the presence of graphite, resulted in the formation of 6-(2-benzothiazolyl)benzimidazo[1,2-*c*]quinazolines **99** in good yields (Scheme 33).[59]



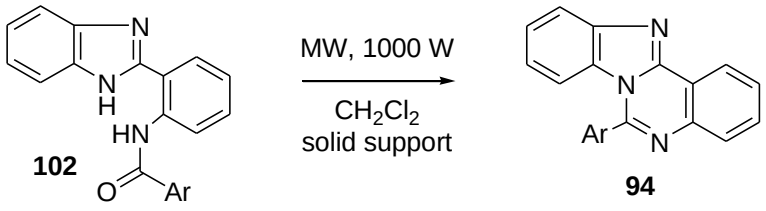
Scheme 33

The 6-mercaptobenzimidazo[1,2-*c*]quinazoline **100** was easily accomplished by the reaction of **92** with carbon disulphide in the presence of methanolic potassium hydroxide either under microwave irradiation at 60 ºC or conventional heating (Scheme 34).[60,61] Compound **100** was alternatively prepared by cyclization of 3-(2-aminophenyl)-4-oxoquinazoline-2-thione **101** in refluxing DMF in the presence of acetic acid (Scheme 34).[62]



Scheme 34

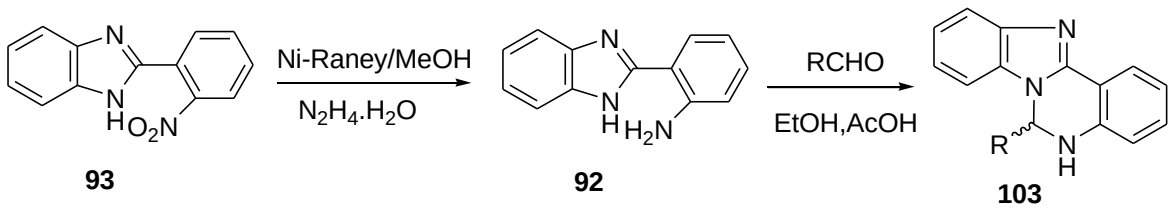
Mahana *et al*. reported the conversion of 1*H*-2-benzimidazol-2-ylbenzanilides **102** into 6-arylbenzimidazo[1,2-*c*]quinazolines **94** under microwave irradiation using SiO_2-MnO_2 (95 : 5 mixture) as solid inorganic support (Scheme 35).[63]



Ar = C_6H_5, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 35

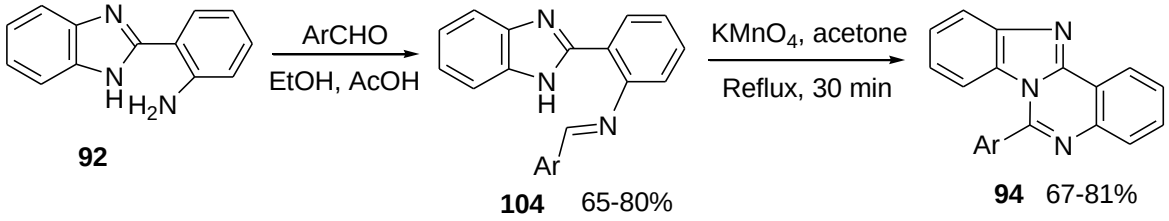
Benzimidazo[1,2-*c*]quinazolines **103** was readily prepared in high yield by reduction of 2-(2-nitrophenyl)benzimidazole **93** followed by reaction of the obtained 2-(2-aminophenyl)benzimidazole **92** with aldehydes in ethanol/acetic acid mixture (Scheme 36).[64]



R = 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 3,4,5-$(OMe)_3C_6H_2$

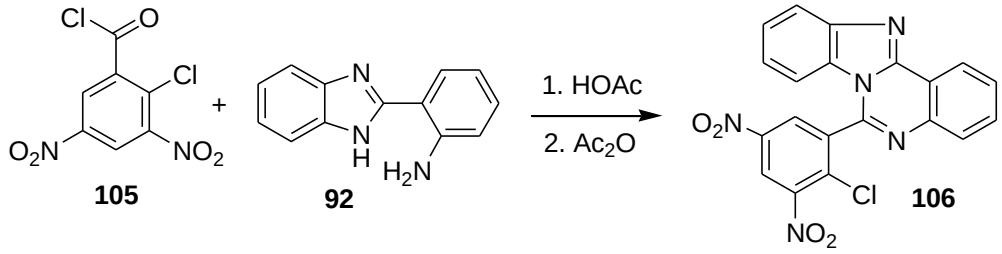
Scheme 36

2-(*o*-Arylideneaminophenyl)benzimidazoles **104** were synthesized *via* the condensation between 2-(*o*-aminophenyl)benzimidazole **92** and various aldehydes in refluxing ethanol in the presence of catalytic amount of acetic acid. Oxidative cyclization of 2-(*o*-arylideneaminophenyl)-benzimidazoles **104** using potassium permanganate in refluxing acetone resulted in the formation of 6-arylbenzimidazo[1,2-*c*]quinazolines **94** (Scheme 37).[65]



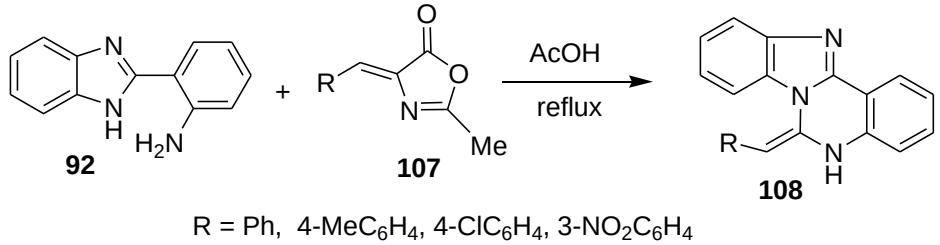
Scheme 37

Benzimidazo[1,2-*c*]quinazoline **106** derivative was prepared by the reaction of the benzoyl chloride derivative **105** with 2-(2-aminophenyl)benzimidazole **92** in acetic acid / acetic anhydride mixture (Scheme 38).[66]



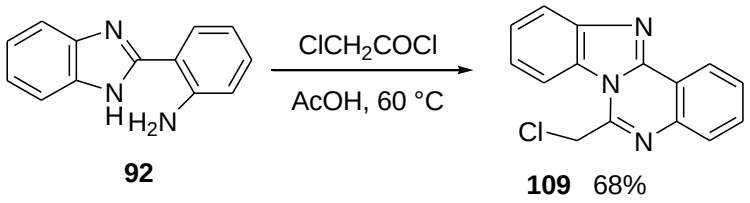
Scheme 38

Condensation of 2-(2-aminophenyl)benzimidazole **92** with 4-arylideneoxazolin-5-ones **107** in acetic acid resulted in the formation of the 6-arylidene-benzimidazo[1,2-*c*]quinazolines **108** (Scheme 39).[67]



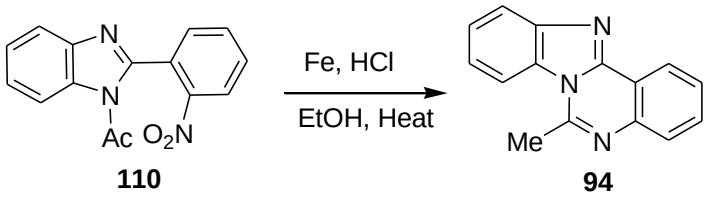
Scheme 39

Heating a mixture of 2-(2-aminophenyl)benzimidazole **92** and chloroacetylchloride in glacial acetic acid on water-bath at 60 °C gave 6-chloromethylbenzimidazo[1,2-*c*]quinazoline **109** in 68% yield (Scheme 40).[68]



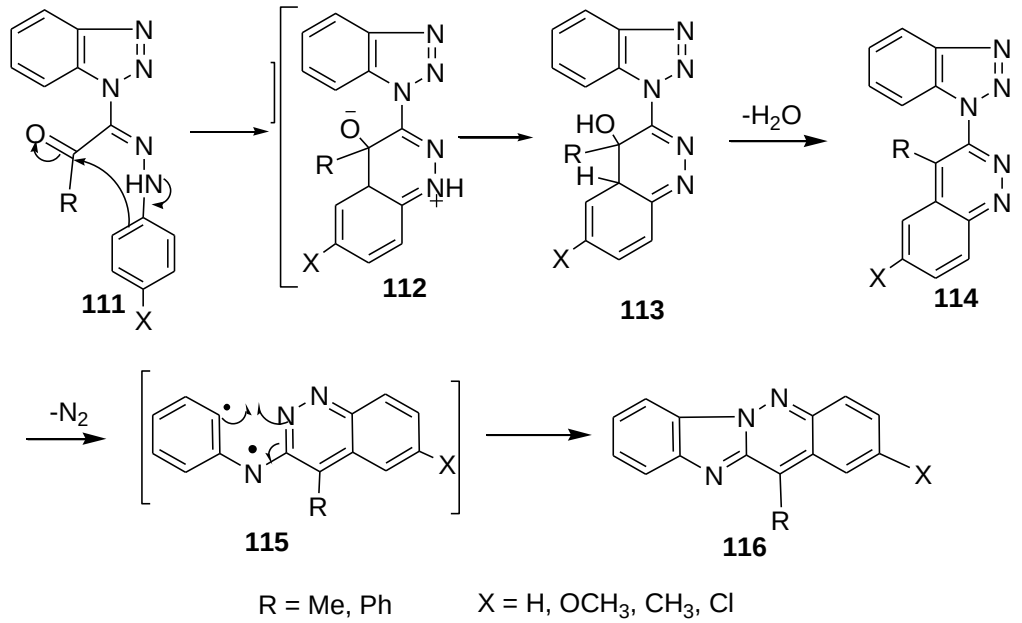
Scheme 40

Reductive cyclization of 1-acetyl-2-(2-nitrophenyl)benzimidazole **110** in the presence of iron powder and HCl in refluxing ethanol produced benzimidazo[1,2-*c*]quinazoline **94** (R = Me) in 46% yield (Scheme 41).[69]



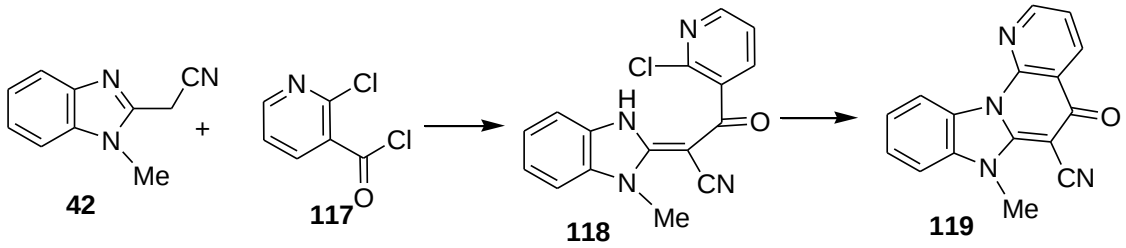
Scheme 41

2.2.8. Benzimidazo[1,2-*b*]cinnolines. The pyrolysis of arylhydrazonobenzotriazoles **111** resulted in the formation of the benzimidazo[1,2-*b*]cinnoline derivatives **116** *via* intramolecular nucleophilic addition involving the arylhydrazono group and the ketone carbonyl moiety followed by cyclization and subsequent elimination of H_2O and N_2 from the intermediates **112-115** according to the mechanism outlined in Scheme 42.[70]



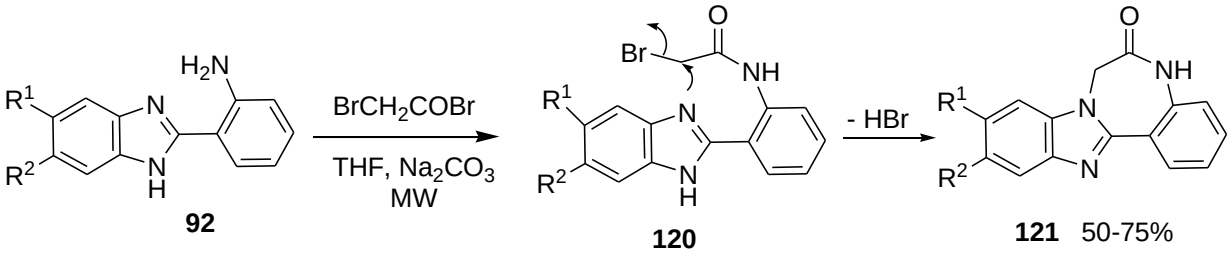
Scheme 42

2.2.9. Pyridopyridobenzimidazoles. Reaction of 2-chloronicotinoyl chloride **117** with 2-benzimidazoleacetonitrile **42** gave the conjugated nitrile **118** in 97% yield**,** which was then cyclized on heating to give the corresponding fused tetraheterocyclic system **119** in high yield (Scheme 43).[71]



Scheme 43

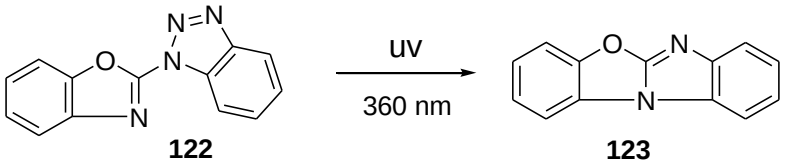
2.2.10. Fused macroheterocycles with three heteroatoms. The synthesis of 5*H*-benzimidazo[1,2-*d*]-1,4-benzodiazepin-6(7*H*)-ones **121** was readily accomplished by reaction of 2-(2-aminophenyl)-1*H*-benzimidazole derivatives **92** and 2-bromoacetyl bromide *via* the intermediate **120**, under microwave irradiation conditions at 300 W in THF and sodium carbonate (Scheme 44).[72]



R^1, R^2 : H, Me, F, Cl, Br

Scheme 44

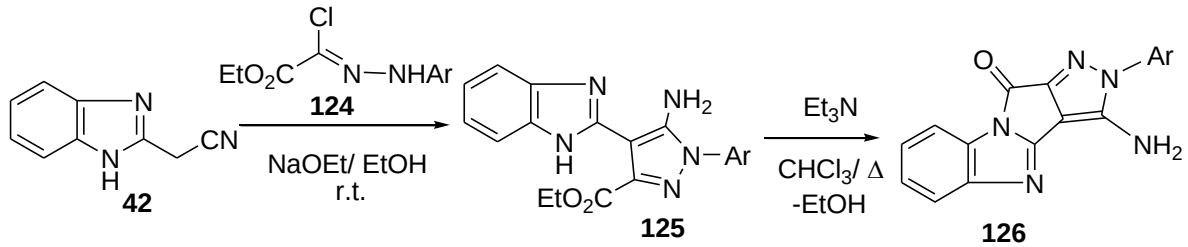
2.2.11. Benzimidazo[2,1-*b*]benzoxazoles. Benzimidazo[2,1-*b*]benzoxazole **123** was prepared photolytically at 360 nm from 1-(2-benzoxazolyl)benzotriazole **122** (Scheme 45).[73]



Scheme 45

2.3. With four heteroatoms

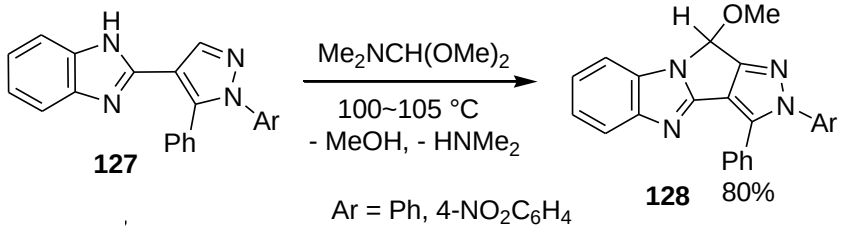
2.3.1. Pyrazolo[3,4:4`,3`]pyrrolo[1,2-*a*]benzimidazoles. Treatment of hydrazonoyl chlorides **124** with 2-cyanomethylbenzimidazol **42** in ethanolic sodium ethoxide solution at room temperature afforded ethyl 5-amino-1-aryl-4-(benzimidazol-2-yl)pyrazole-3-carboxylate **125**. Heating **125** in chloroform in the presence of triethylamine yielded 1-amino-2-arylpyrazolo[3,4:4`,3']pyrrolo[1,2-*a*]benzimidazoles **126** *via* loss of ethanol (Scheme 46).[74]



Ar = C_6H_5, 4-ClC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4

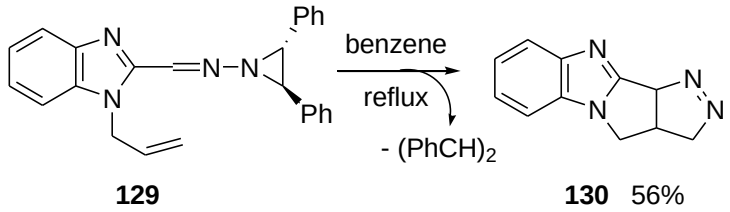
Scheme 46

Condensation of pyrazolylbenzimidazoles **127** with dimethylformamide-dimethylacetal (DMF-DMA) at 100~105 °C led to the formation of pyrazolo[3,4:3`,4`]pyrrolo[1,2-*a*]benzimidazole derivatives **128** in 80% yield (Scheme 47).[75]



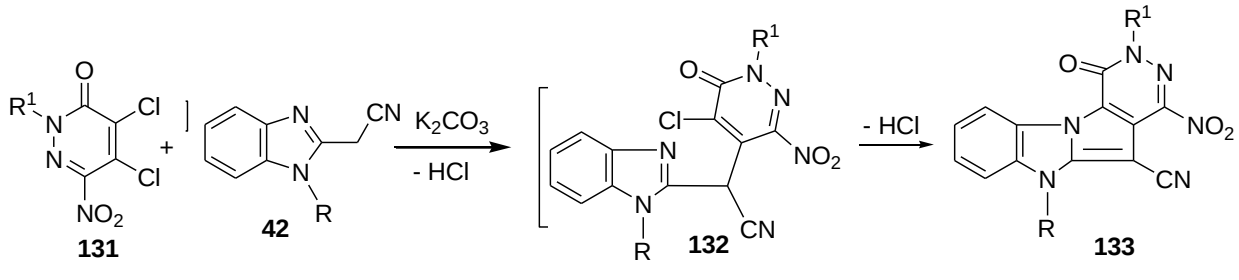
Scheme 47

Refluxing the benzimidazole-2-Eschenmoser hydrazone **129** in benzene for three hours gave 3,3*a*,4,10*b*-tetrahydropyrazolo[3',4':3,4]pyrrolo[1,2-*a*]benzimidazole **130** in 56% yield *via* the 1,3-dipolar intramolecular [3+2] cycloaddition with thermal cleavage of **129** to generate *trans*-stilbene (Scheme 48).[76]



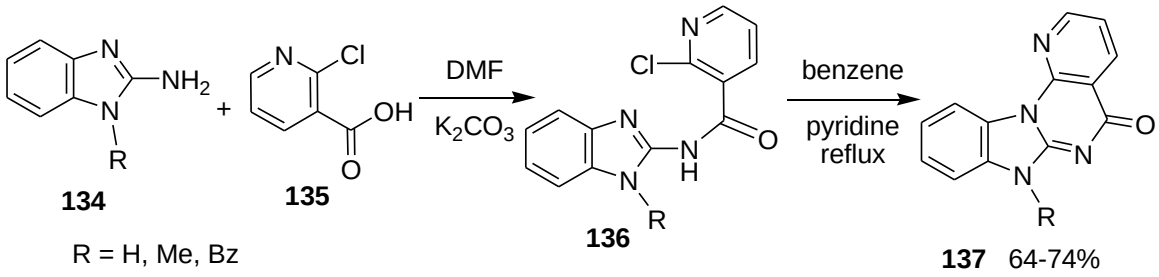
Scheme 48

2.3.2. Pyridazino-pyrrolo-benzimidazoles. Treatment of 4,5-dichloropyridazine **131** 2-cyanomethylbenzimidazoles **42** in the presence of potassium carbonate led to the formation of pyridazino-pyrrolo-benzimidazoles **133** *via* loss of HCl from the intermediate **132** (Scheme 49).[77]



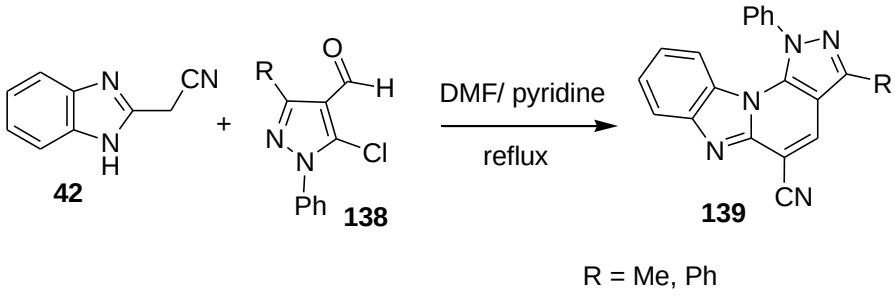
Scheme 49

Treatment of 2-aminobenzimidazoles **134** with 2-chloronicotinic acid **135** in DMF, in the presence of K_2CO_3, gave the amides **136** which upon reflux in benzene and pyridine afforded the 5-oxopyrido[3',2 ':5,6]pyrimido[1,2-*a*]benzimidazoles **137** (Scheme 50).[78,79]



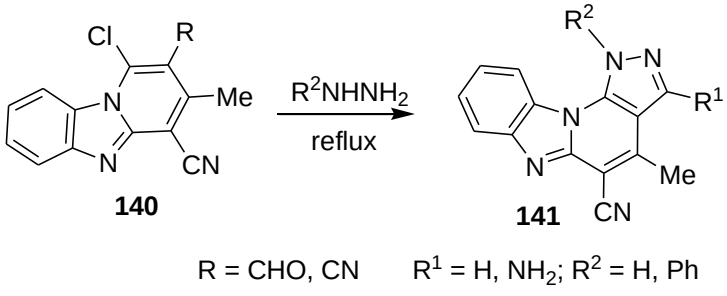
Scheme 50

2.3.3. Pyrazolo[4.3:5,6]pyrido[1,2-*a*]benzimidazoles. The condensation of 5-chloro-4-formylpyrazoles **138** with 2-benzimidazoleacetonitrile **42** in pyridine-DMF mixture led to the pyrazolo[4.3:5,6]pyrido[1,2-*a*]benzimidazoles **139** in high yields (Scheme 51).[80,81]



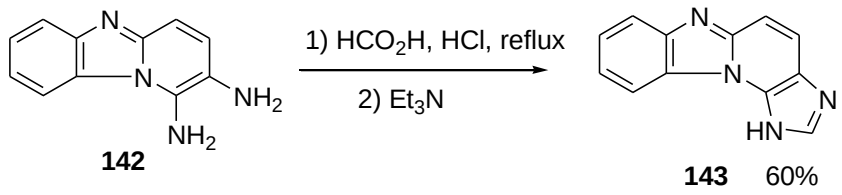
Scheme 51

Pyrazolo[4',3':5,6]pyrido[1,2-*a*]benzimidazoles **141** were prepared by the condensation of pyridobenzimidazoles **140** with hydrazines (Scheme 52).[82]



Scheme 52

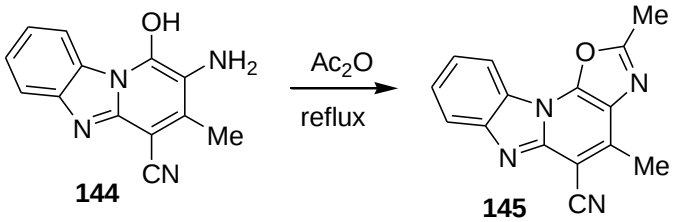
2.3.4. Imidazo[4',5':5,6]pyrido[1,2-*a*]benzimidazoles. Heating a mixture of the diaminopyridobenzimidazole **142** and formic acid in the presence of aq. HCl at reflux condition followed by neutralization with Et_3N gave 60% yield of 1*H*-imidazo[4',5':5,6]pyrido[1,2-*a*]benzimidazoles **143** (Scheme 53).[83]



142 **143** 60%

Scheme 53

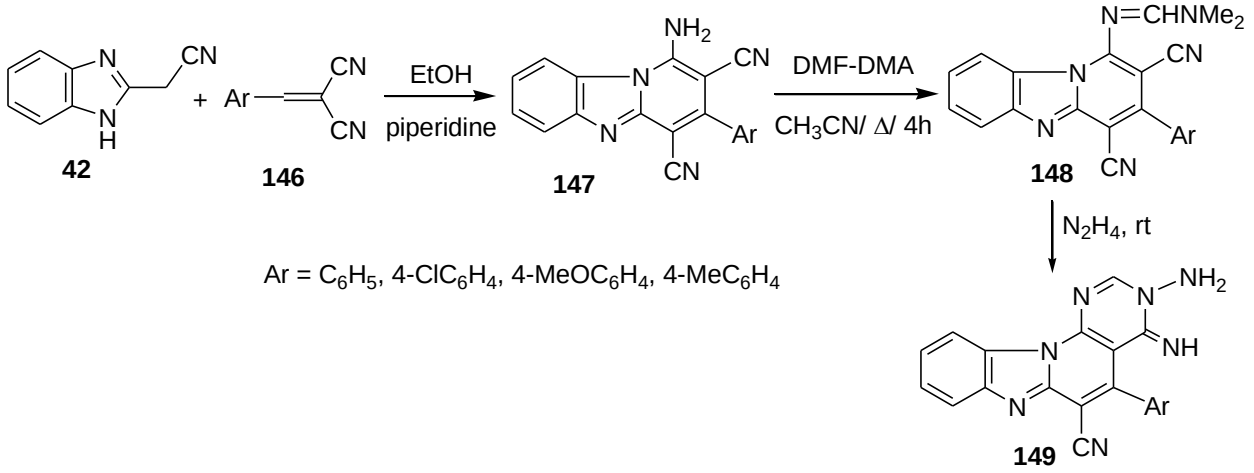
2.3.5. Oxazolo[4',5':5,6]pyrido[1,2-*a*]benzimidazoles. The condensation of 2-amino-1-hydroxypyrido[1,2-*a*]benzimidazole **144** with acetic anhydride at reflux yielded 2,4-dimethyloxazolo[4',5':5,6]pyrido[1,2-*a*]benzimidazole **145** which was used as fluorescent brighteners for polyester fibers (Scheme 54).[84]



144 **145**

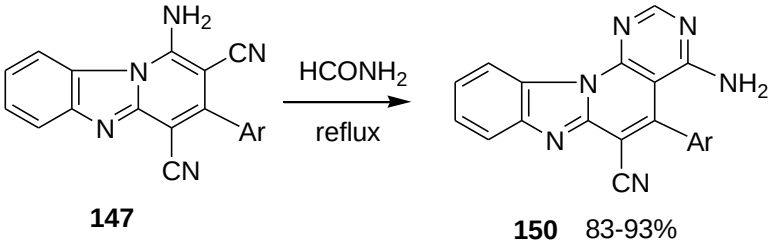
Scheme 54

2.3.6. Pyrimido-pyrido-benzimidazoles. Treatment of 2-benzimidazoleacetonitrile **42** with arylidenemalononitrile **146** in ethanol containing piperidine gave 1-aminopyrido[1,2-*a*]benzimidazole-2,4-dicarbonitriles **147** which upon heating with dimethylformamide-dimethylacetal (DMF-DMA) in dioxane gave the corresponding *N*,*N*-(dimethylaminomethylene)amino derivatives **148**. Condensation of **148** with hydrazine hydrate in ethanol at room temperature afforded 3-amino-4-imino-5-aryl-6-cyanopyrimido[5`,4`:5,6]pyrido[1,2-*a*]benzimidazoles **149** (Scheme 55).[85]



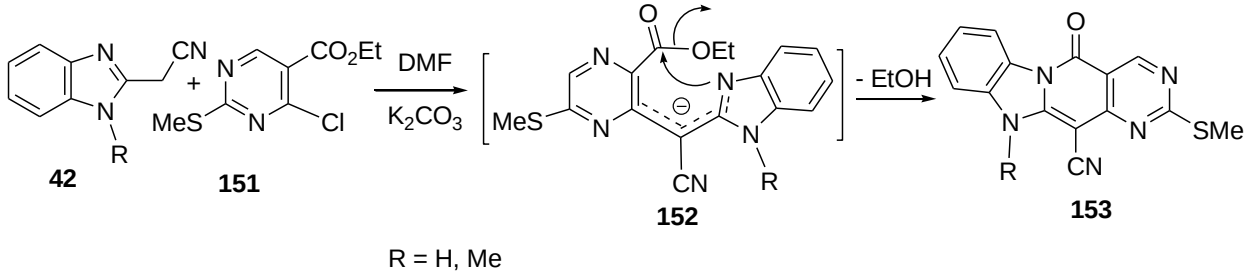
Scheme 55

1-Aminopyrido[1,2-*a*]benzomidazole-2,4-dicarbonitriles **147** underwent cyclocondensation reaction when heated with formamide to yield the pyrimido[5',4':5,6]pyrido[1,2-*a*]benzimidazoles **150** in 83-93% yields (Scheme 56).[86,87]



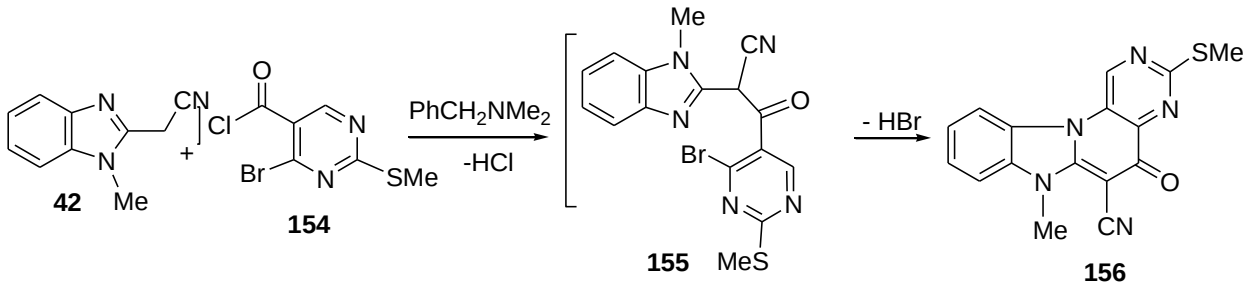
Scheme 56

Reaction of 2-cyanomethylbenzimidazoles **42** with ethyl 4-chloro-2-methylthio-5-pyrimidine-carboxylate **151** in refluxing DMF in the presence of K_2CO_3 led to the formation of the 3-methylthio-5-cyano-12-oxopyrimido[4',5'-4,5]pyrido[1,2-*a*]benzimidazoles **152** in 85-88% yields *via* the intermediate **152** (Scheme 57).[88]



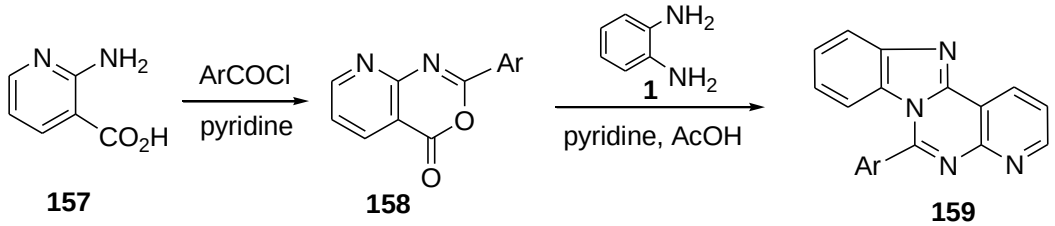
Scheme 57

7-Methyl-3-(methylthio)-5-oxo-6-cyanopyrimido[4',5':5,6]pyrido[1,2-*a*]benzimidazole **156** was prepared from the reaction of 2-benzimidazoleacetonitrile **42** with 4-bromo-2-methylsulfanyl-5-pyrimidinoyl chloride **154** in the presence of *N*,*N*-dimethylbenzylamine followed by intramolecular cyclization of the intermediate **155** (Scheme 58).[89]



Scheme 58

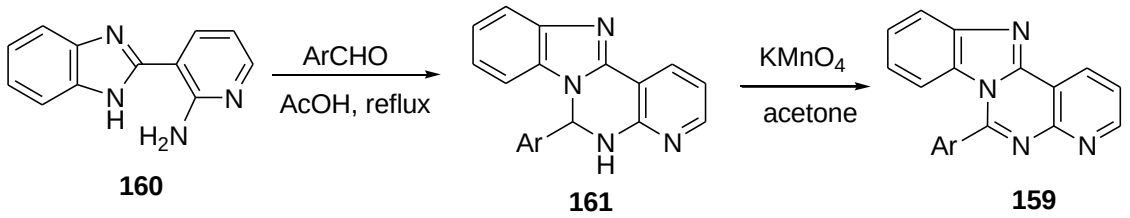
2.3.7. Pyrido-pyrimido-benzimidazoles. 2-Aminonicotinic acid **157** reacted with aromatic acid chlorides in pyridine to give 2-arylpyrido[2,3-*d*][1,3]oxazin-4-ones **158**. Treatment of the latter compounds **158** with *o*-phenylenediamines **1** in pyridine gave the 6-arylpyrido[2',3':4,5]pyrimido[1,6-*a*]benzimidazoles **159** (Scheme 59).[90]



Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

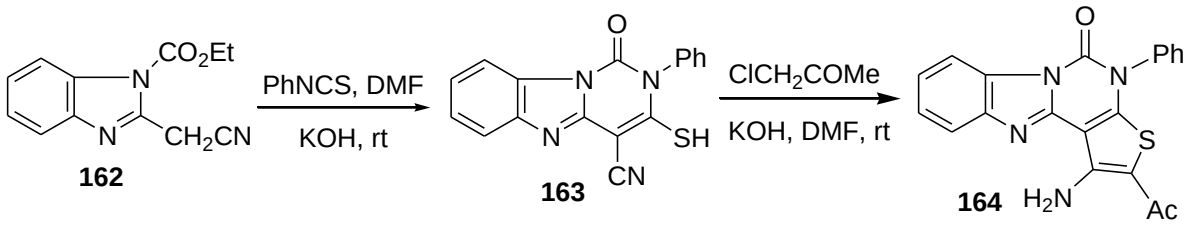
Scheme 59

Compounds **159** were alternatively accomplished by refluxing 2-(2-amino-3-pyridyl)benzimidazole **160** with aromatic aldehydes in acetic acid to give 5,6-dihydropyridopyrimidobenzimidazoles **161**. Oxidation of the latter compounds **161** with $KMnO_4$ in acetone afforded 6-arylpyrido[2',3':4,5]pyrimido[1,6-*a*]benzimidazoles **159** (Scheme 60).[91]



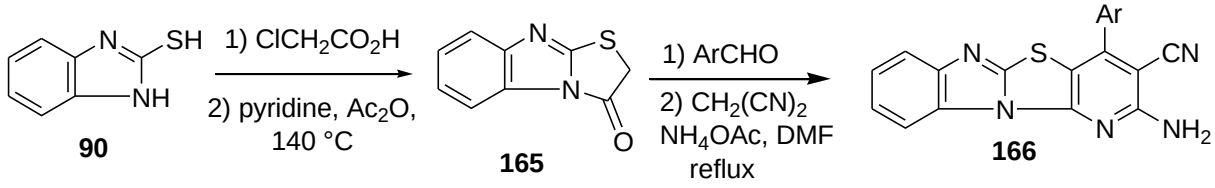
Scheme 60

2.3.8. Thieno[2`,3`:3,4]pyrimido[1,6-*a*]benzimidazoles. Reaction of 1-ethoxycarbonyl-2-benzimidazoleacetonitrile **162** with phenylisothiocyanate in DMF in the presence of KOH gave 4-cyano-3-mercaptopyrimido[1,6-*a*]benzimidazole **163.** Treatment of **163** with chloroacetone in DMF and potassium hydroxide at room temperature yielded 2-acetyl-3-amino-10-oxo-11-phenylthieno[2`,3`:4,5]pyrimido[1,6-*a*]benzimidazole **164** (Scheme 61).[92]



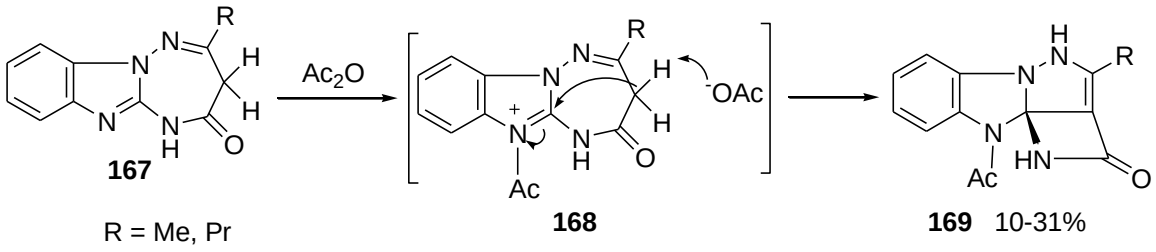
Scheme 61

2.3.9. Pyrido[2`,3`:4,5]thiazolo[2,3-*a*]benzimidazoles. Heating a mixture of 2-mercaptobenzimidazole **90** with chloroacetic acid in the presence of acetic anhydride gave 4-oxo-3,4-dihydro-5*H*-thiazolo[2,3-*a*]benzimidazole **165**. Treatment of **165** with aromatic aldehydes, malononitrile and ammonium acetate in refluxing DMF yielded 2-amino-3-cyano-4-arylpyrido[2`,3`:4,5]thiazolo[2,3-*a*]benzimidazoles **166** in reasonable yields (Scheme 62).[93]



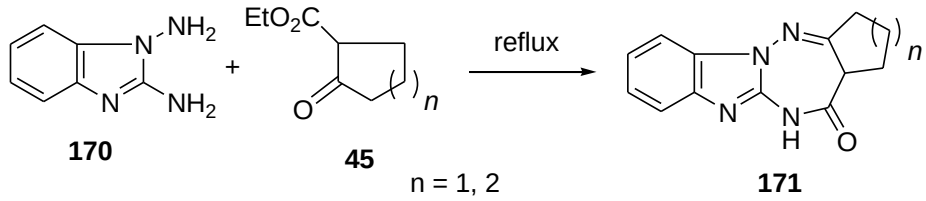
Scheme 62

2.3.10. Azeto[3',2':4,5]pyrazolo[1,5-*a*]benzimidazoles. Treatment of 2-alkyl-3*H*-[1,2,4]triazepino[2,3-*a*]benzimidazol-4-one **167** with acetic anhydride gave 3-alkyl-10-acetyl-4H-azeto[3',2':4,5]pyrazolo[1,5-*a*]benzimidazol-2-ones **169** in low yields *via* ring contraction ionic mechanism of the intermediate **168** as shown in Scheme 63.[94]



Scheme 63

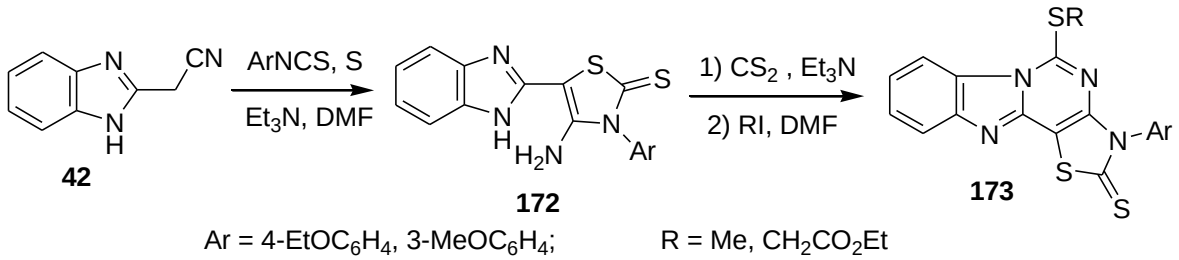
2.3.11. Fused macroheterocycles with four heteroatoms. Cycloalkano-1,2,4-triazepino[2,3-*a*]benzimidazolones **171** were prepared in low yields by condensing 1,2-diaminobenzimidazole **170** with 5 equivalents of ethyl cycloalkanone-2-carboxylates **45** at reflux temperature (Scheme 64).[95]



Scheme 64

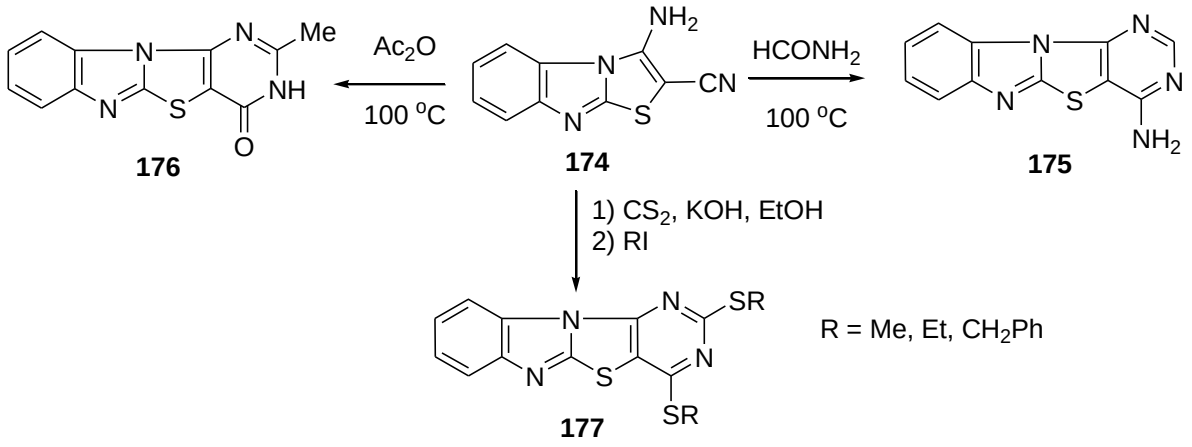
2.4. With five heteroatoms

2.4.1. 1,3-Thiazolo[4',5':4,5]pyrimido[1,6-*a*]benzimidazoles. Reaction of 2-benzimidazoleacetonitrile **42** with arylisothiocyanates in the presence of elemental sulfur and Et_3N in DMF at room temperature gave moderate yields of the thiazolylbenzimidazole derivatives **172**. Treatment of the latter compounds with carbon disulfide in DMF under reflux followed by *S*-alkylation afforded the thiazolo[4',5':4,5]pyrimido[1,6-*a*]benzimidazole-2(3*H*)-thiones **173** in 50-65% yields (Scheme 65).[96, 97]



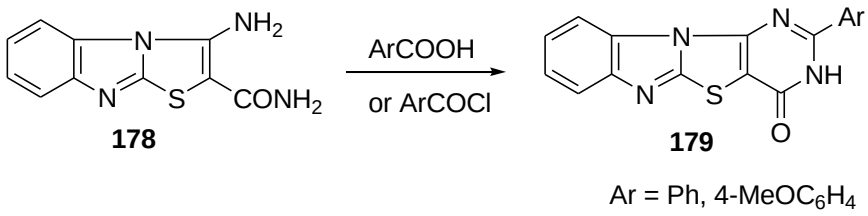
Scheme 65

2.4.2. Pyrimido[4`,5`:4,5]thiazolo[2,3-*a*]benzimidazoles. When 3-aminothiazolo[3,2-*a*]benzimidazole-2-carbonitrile **174** was treated with formamide and with acetic anhydride at 100 °C it gave the tetracyclic; pyrimido[4`,5`:4,5]thiazolo[2,3-*a*]benzimidazoles **175** and **176**, respectively (Scheme 66).[98,99] When the thiazolo[3,2-*a*]benzimidazole **174** was allowed to react with carbon disulphide followed with alkyl iodides in EtOH and KOH it gave the corresponding dialkylthio derivatives of pyrimido[4`,5`:4,5]thiazolo[2,3-*a*]benzimidazole **177** (Scheme 66).[100]



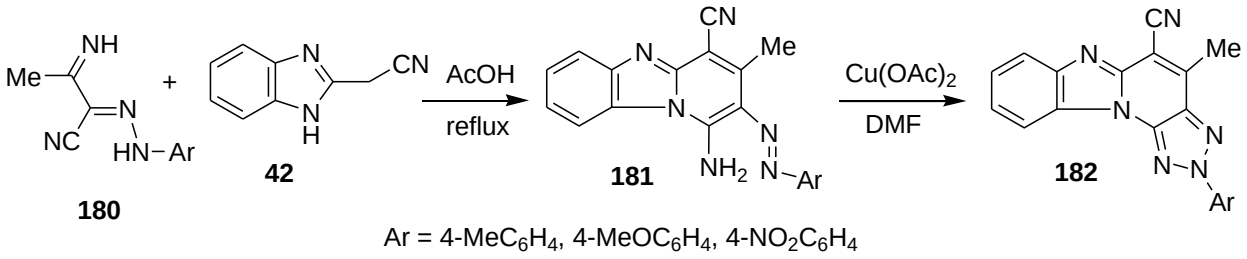
Scheme 66

Reaction of 3-aminothiazolo[3,2-*a*]benzimidazole-2-carboxamide **178** with aromatic carboxylic acids or with their chlorides afforded the corresponding pyrimido-fused derivatives **179** (Scheme 67).[101]



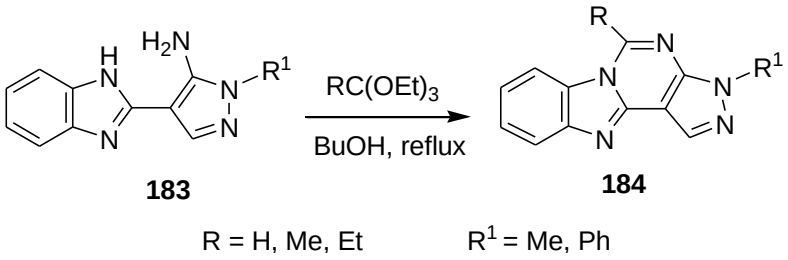
Scheme 67

2.4.3. Triazolo[4,5-*b*]pyrido[1`,2`-*a*]benzimidazoles. Condensation of 2-(arylhydrazono)-3-iminobutanenitrile **180** with 2-benzimidazoleacetonitrile **42** in acetic acid furnished the corresponding 3-methylpyrido[1,2-*a*]benzimidazoles **181**. Treatment of compounds **181** with cupric acetate in DMF resulted in their oxidative cyclization to give the *S*-triazolo[4,5-*b*]pyrido[1`,2`-*a*]benzimidazoles **182** (Scheme 68).[102]



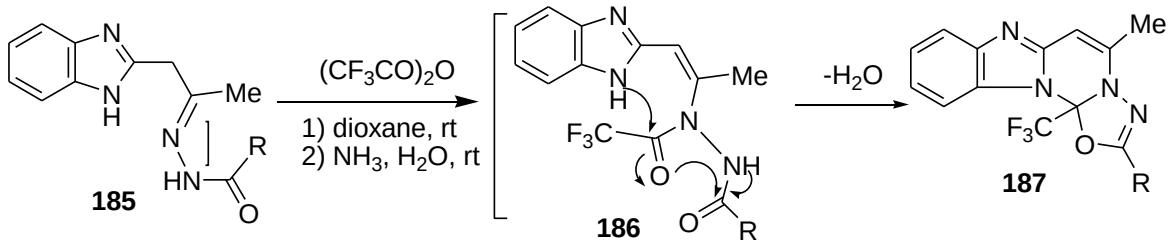
Scheme 68

2.4.4. Pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazoles. Reaction of 4-(2-benzimidazolyl)-1-methyl-5-aminopyrazole **183** with trialkylorthoformates in refluxing butanol gave the pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole derivatives **184** in good yields (Scheme 69).[103]



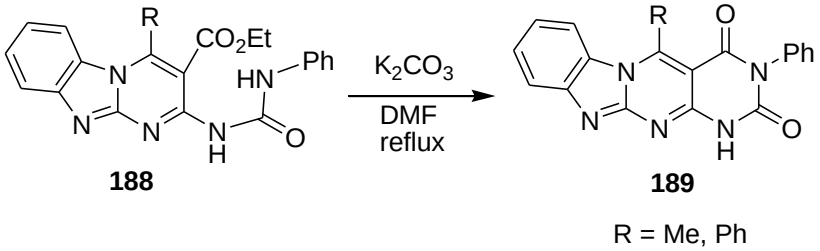
Scheme 69

2.4.5. 1,3,4-Oxadiazolo[2',3':2,3]pyrimido[1,6-*a*]benzimidazoles. The 1,3,4-oxadiazolo[2',3':2,3]pyrimido[1,6-*a*]benzimidazoles **187** were prepared by treatment of 2-acetonyl-1*H*-benzimidazolehydrazones **185** with trifluoroacetic anhydride in dioxane at room temperature *via* loss of water from the intermediate **186** (Scheme 70).[104]



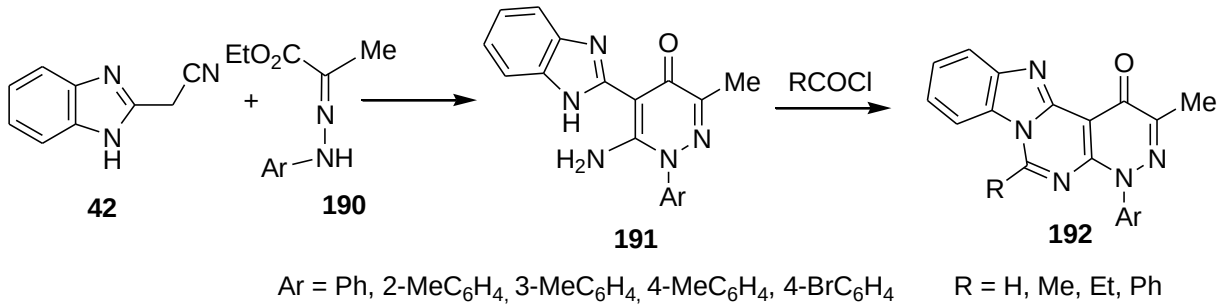
Scheme 70

2.4.6. Pyrimido[4',5':4,5]pyrimido[1,2-*a*]benzimidazole. Intramolecular cyclocondensation of pyrimidobenzimidazolylurea derivatives **188** under the action of K_2CO_3 in refluxing DMF gave the pyrimido[4',5':4,5]pyrimido[1,2-*a*]benzimidazole derivatives **189** in good yields (Scheme 71).[105]



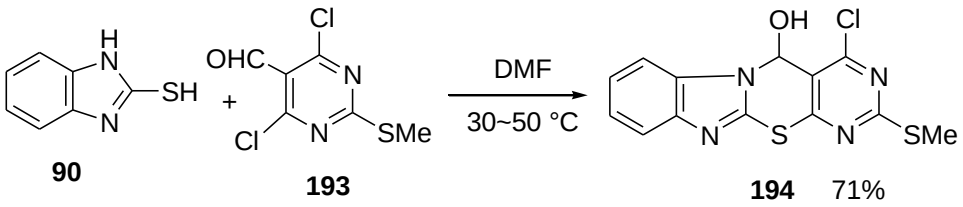
Scheme 71

2.4.7. Pyridazino-pyrimido-benzimidazoles. Reaction of 2-benzimidazoleacetonitrile **42** with arylhydrazones **190** gave the benzimidazolylpyridazines **191** in 90-99%, which were cyclized by acyl chlorides or anhydrides to give 80-94% of the pyridazinopyrimidobenzimidazoles **192** (Scheme 72).[106]



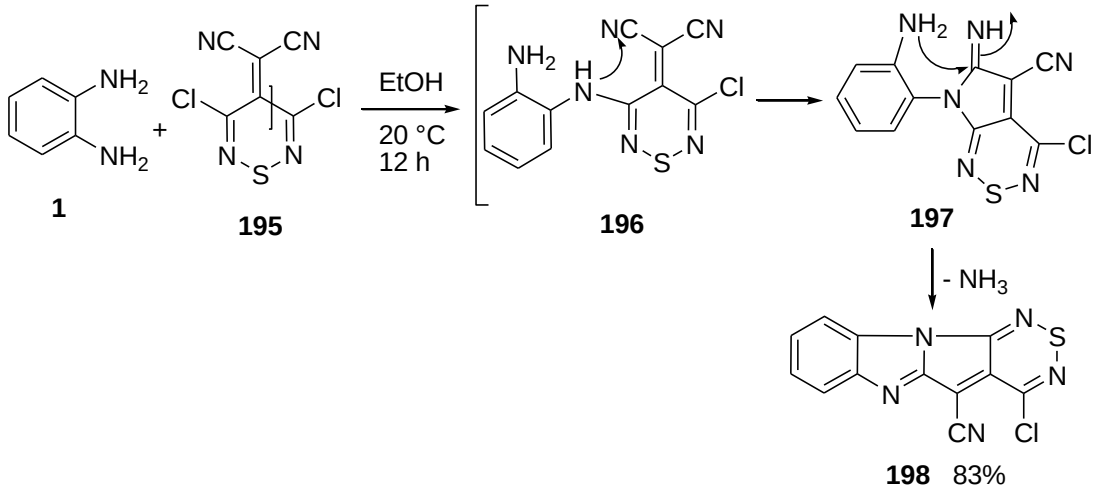
Scheme 72

2.4.8. Benzimidazo[2',1':2,3][1,3]thiazino[6,5-*d*]pyrimidine. Synthesis of 5*H*-benzimidazo[2',1':2,3][1,3]thiazino[6,5-*d*]pyrimidine **194** was reported *via* the cyclocondensation between 2-methylthiopyrimidine-5-carboxaldehyde **193** and 2-mercaptobenzimidazole **90** in DMF at 30-50 °C (Scheme 73).[107]



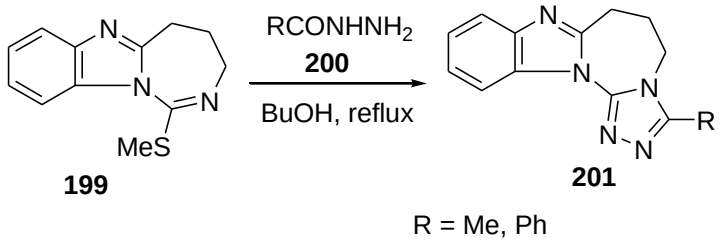
Scheme 73

2.4.9. Thiadiazino[3`,4`: 5,4]pyrrolo[1,2-*a*]benzimidazole. Reaction of (3,5-dichloro-4*H*-1,2,6-thiadiazin-4-ylidene)propanedinitrile **195** with 1,2-diaminobenzene **1** in ethanol at 20 °C gave 4-chloro-5-cyano-1,2,6-thiadiazino[3`,4`: 5,4]pyrrolo[1,2-*a*]benzimidazole **198** *via* loss of HCl and NH_3 molecules as shown in Scheme 74.[108]



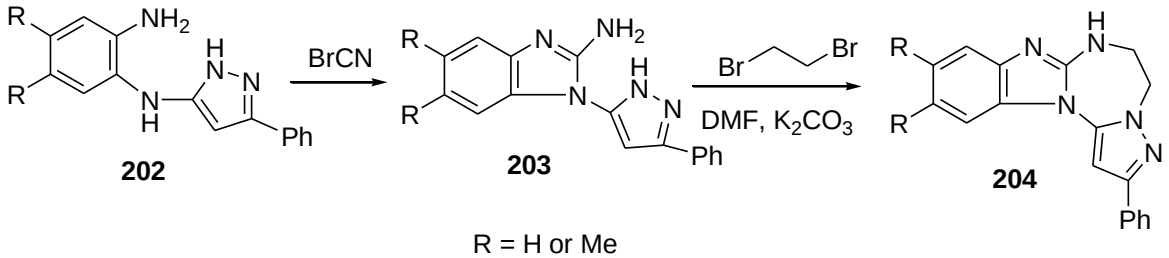
Scheme 74

2.4.10. Fused macroheterocycles with five heteroatoms. Reaction of the 1,3-diazepino[3,4-*a*]benzimidazole-2-thione **199** with acid hydrazides **200** in refluxing butanol gave the tetracyclic triazolo-diazepino-benzimidazole derivatives **201** (Scheme 75).[109]



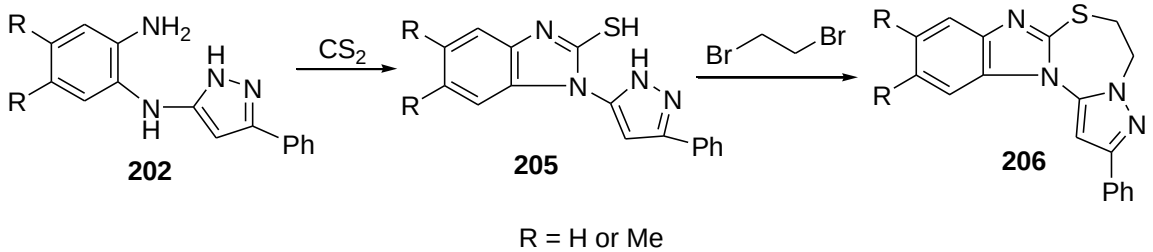
Scheme 75

Treatment of the pyrazoles **202** with cyanogen bromide afforded the 2-amino-1-(5 pyrazolyl)benzimidazoles **203** which upon treatment with 1,2-dibromoethane in the presence of 18-crown-6 in DMF and K_2CO_3 gave the pyrazolo[2,3-*a*]triazepino[3,2-*a*]benzimidazoles **204** (Scheme 76).[110]



Scheme 76

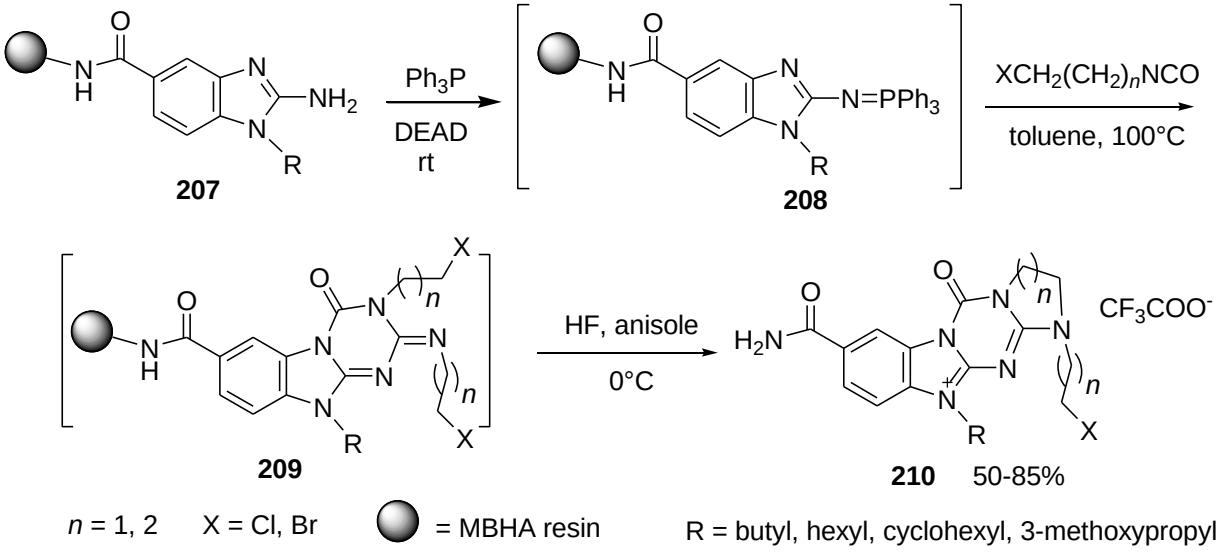
Reaction of the pyrazoles **202** with carbon disulfide yielded the 2-mercapto-1-(5 pyrazolyl)benzimidazoles **205**. When compounds **205** were treated with 1,2-dibromoethane in the presence of 18-crown-6, the pyrazolo[3,2-*d*][1,3,5]thiadiazepino[3,2-*a*]benzimidazoles **206** were obtained (Scheme 77).[110]



Scheme 77

Synthesis of the tetracyclic 1,3,5-triazino[1,2-a]benzimidazolium derivatives **210** starting from the methylbenzhydrylamine (MBHA) resin-bound benzimidazoles **207** was reported. Thus,

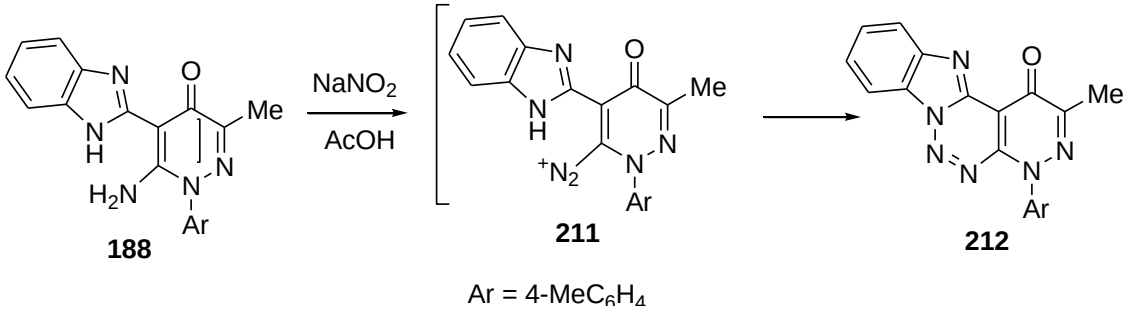
treatment of **207** with triphenylphosphine at room temperature to give the iminophosphorane intermediates **208** which upon heating with halogenoalkyl isocyanates followed by resin-cleavage using anhydrous HF and anisole at 0 °C gave **210** as outlined in Scheme 78.[111]



Scheme 78

2.5. With six heteroatoms

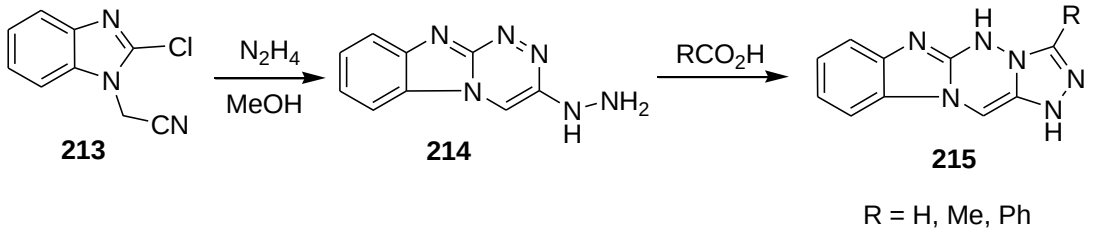
2.5.1. Benzimidazo[1,2-*c*]pyridazino[4,3-*e*]-l,2,3-triazines. Diazotization of 6-amino-benzimidazolylpyridazine **188** using sodium nitrite in acetic acid at 0-20 °C for 12 h followed by subsequent heating of the intermediate diazonium salt **211** yielded the benzimidazo[1,2-*c*]pyridazino[4,3-*e*]-l,2,3-triazine **212** in 68% yield (Scheme 79).[112]



Scheme 79

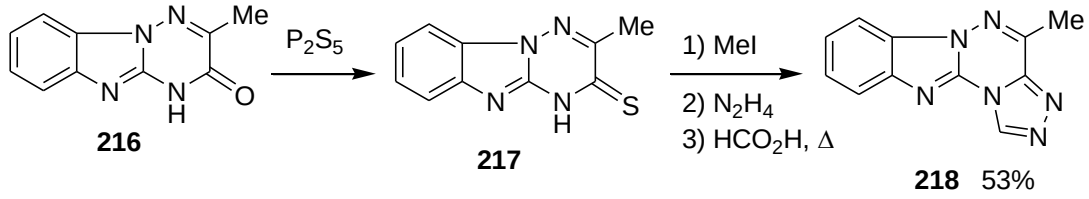
2.5.2. Triazolo-triazino-benzimidazoles. Treatment of 2-chloro-1-cyanomethylbenzimidazole **213** with hydrazine in boiling methanol gave 3-hydrazino-1,2,4-triazino[4,3-*a*]benzimidazole **214**. Reaction of **214** with carboxylic acids gave the triazolotriazinobenzimidazoles **215** in 70-

75% yield (Scheme 80).[113]



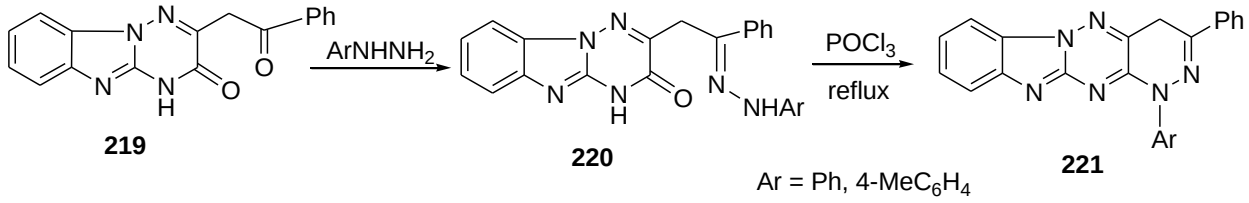
Scheme 80

Triazinone derivative **216** was converted into its thio-analogue **217** using phosphorus pentasulphide which was subsequently *S*-methylated then hydrazinated followed by cyclization *via* its reflux with formic acid to form 4-methyl-1,2,4-triazolo[4',3':4,5][1,2,4]triazino[2,3-*a*]benzimidazole **218** (Scheme 81).[114,115]



Scheme 81

2.5.3. Pyridazino[6,5-*a*]-1,2,4-triazino[2,3-*a*]benzimidazoles. Heating the ketone derivative **219** with arylhydrazines produced the arylhydrazones **220** which upon boiling in $POCl_3$ underwent cyclization into the pyridazino[6,5-*e*]-l,2,4-triazino[2,3-*a*]benzimidazoles **221** (Scheme 82).[116]

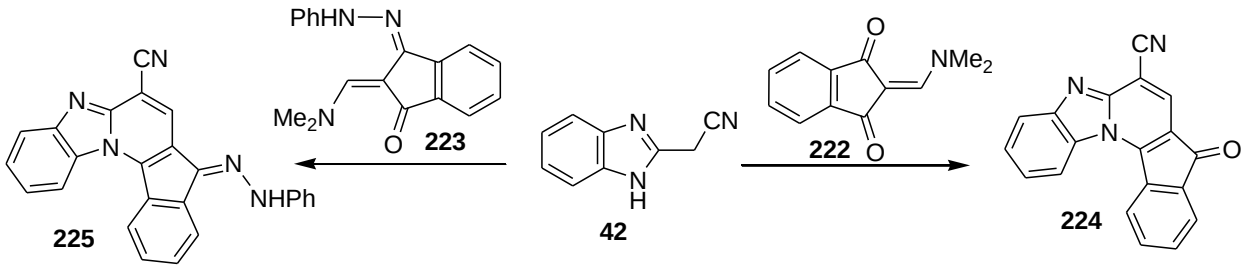


Scheme 82

3. Pentacyclic fused benzimidazoles

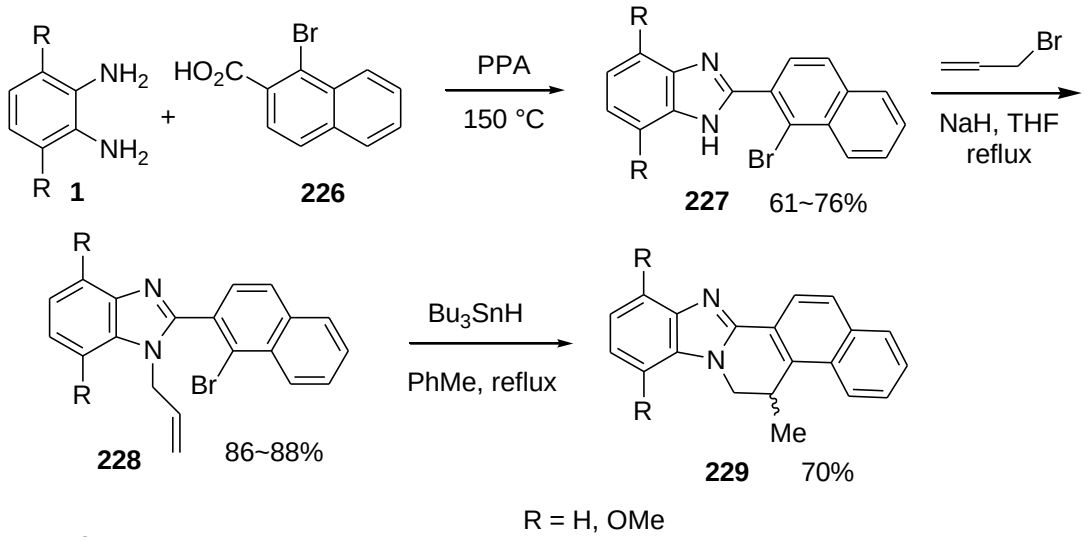
3.1. With two heteroatoms

Reaction of 2-benzimidazoleacetonitrile **42** with 2-dimethylaminomethylene-1,3-indandione **222** and with 2-dimethylaminomethylene-3-(phenylhydrazono)-indan-1-one **223** yielded the pentacyclic indeno-pyrido-benzimidazoles **224** and **225**, respectively (Scheme 83).[117]



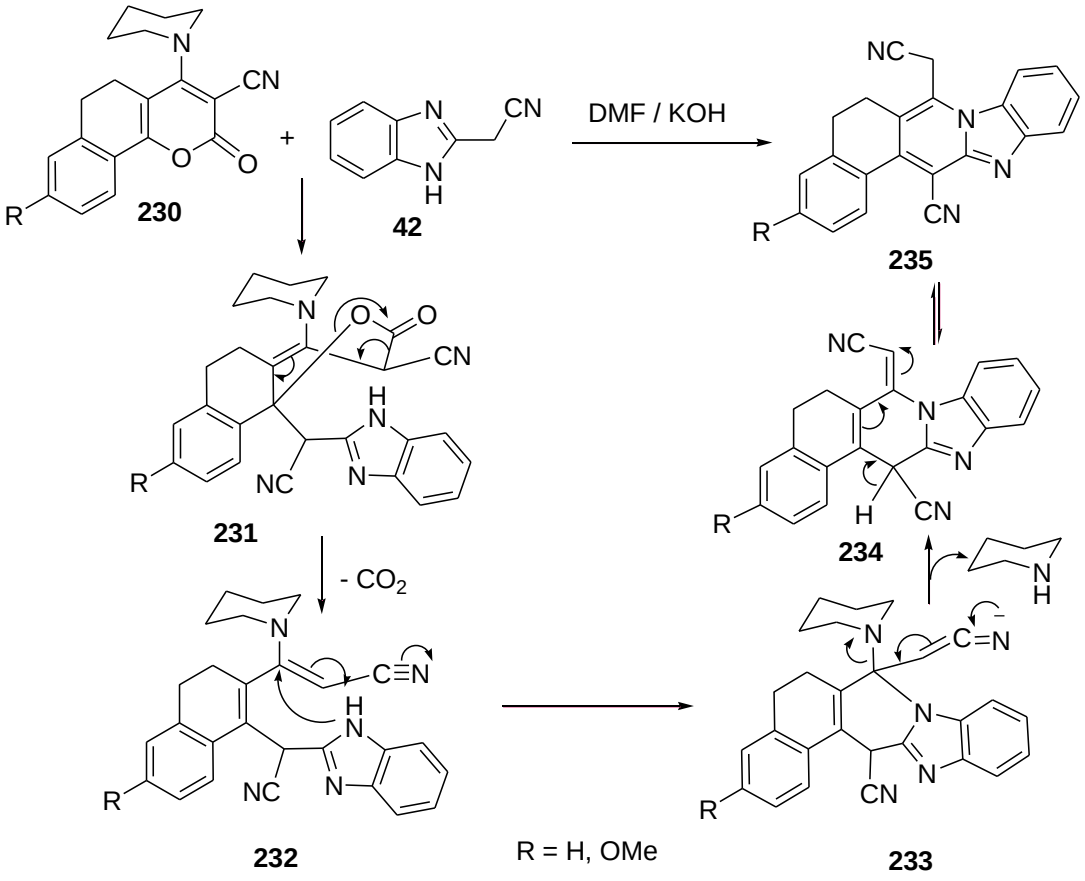
Scheme 83

The preparation of 5-methyl-5,6-dihydrobenzimidazo[2,1-*a*]benzo[*f*]isoquinolines **229** is achieved conveniently in three steps as shown in Scheme 84. Thus, heating of 1-bromo-2-naphthoic acid **226** with *o*-phenylenediamines **1** in polyphosphoric acid (PPA) gave 2-(1-bromo-2-naphthyl)-1*H*-benzimidazoles **227** which underwent *N*-allylation with sodium hydride and 3-bromoprop-1-ene in THF to give 1-allyl-2-(1-bromo-2-naphthyl)benzimidazoles **228** in 68–88% yield. Bu_3SnH mediated cyclization of **228** in refluxing toluene afforded compounds **229** (Scheme 84).[118]



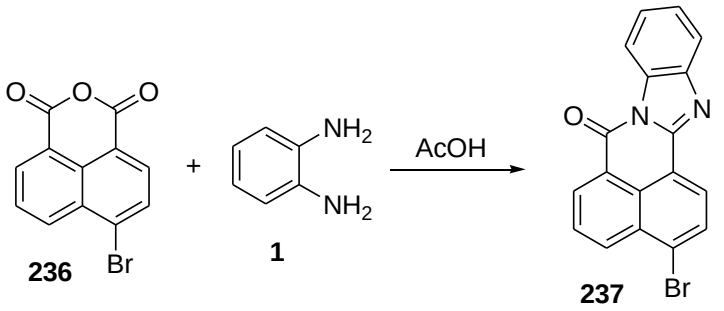
Scheme 84

(5,6-Dihydrobenzimidazo[1,2-*b*]benzo[*f*]isoquinolin-7-yl)-acetonitriles **235** were synthesized by the ring transformation of 4-(piperidin-1-yl)-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **230** with 2-benzimidazoleacetonitrile **42** in the presence of powdered KOH in DMF. In this reaction, the carbanion formed *in situ* attacks at C-10b with ring opening and loss of carbon dioxide to give **232** followed by ring closure involving the ring nitrogen of benzimidazole and C-4 of the chromene ring to yield **235** in good yields *via* loss of piperidine as depicted in Scheme 85.[119]



Scheme 85

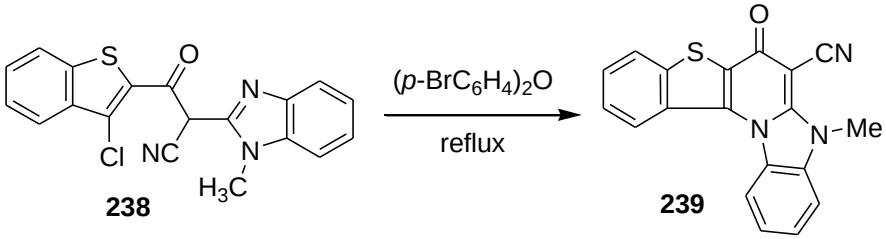
Treatment of 1,8-naphthoic anhydride derivative **236** with *o*-phenylenediamine **1** in glacial acetic acid gave the pentacyclic fused system; 7*H*-benzimidazo[2,1-*a*]benzo[*d,e*]isoquinolin-7-ones **237** (Scheme 86).[120]



Scheme 86

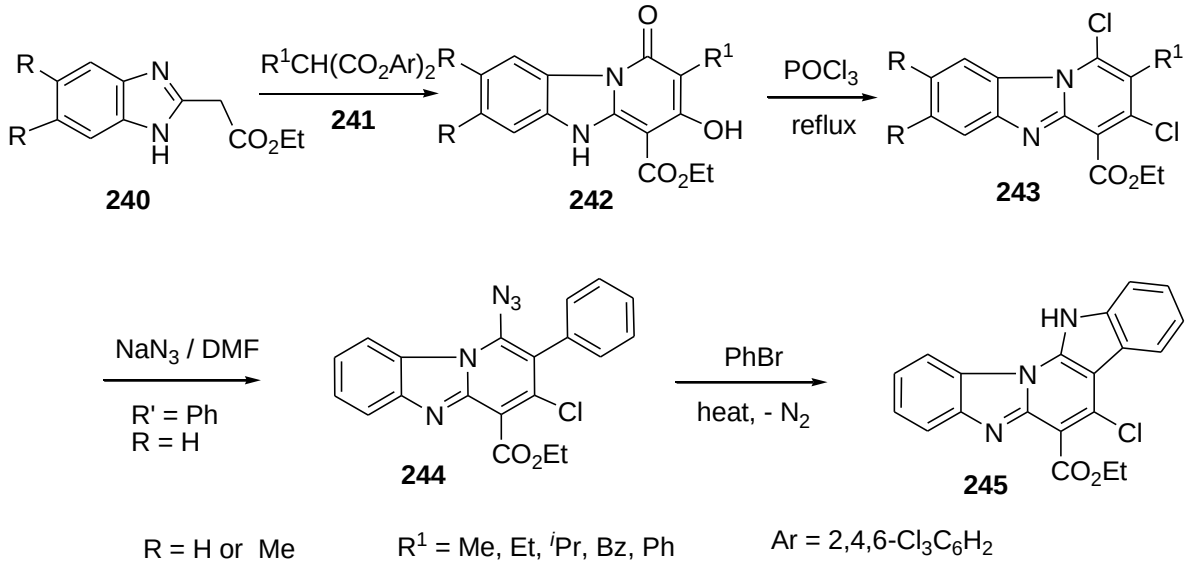
3.2. With three heteroatoms

3.2.1. Thieno[2,3-*b*]pyrido[1,2-*a*]benzimidazoles. Heating benzimidazolyl-benzothiophene derivative **238** in di(*p*-bromophenyl)ether at reflux produced the benzothieno[2,3-*b*]pyrido[1,2-*a*]benzimidazole derivative **239** (Scheme 87).[121]



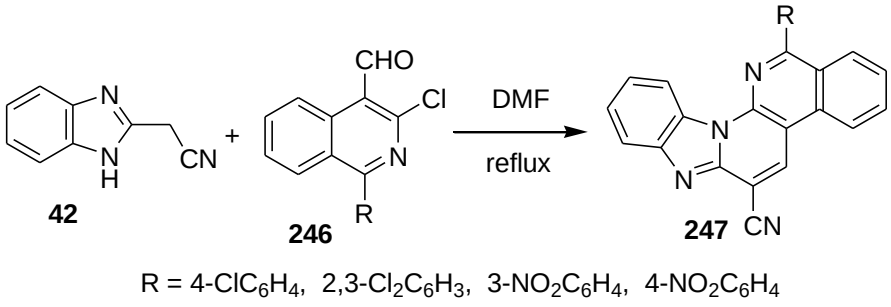
Scheme 87

3.2.2. Indolo[2,3-*b*]pyrido[1,2-*a*]benzimidazoles. Heating a mixture of ethyl benzimidazole-2-acetate **240** with the malonate esters **241** gave ethyl 3-hydroxy-1-oxo-pyrido[1,2-*a*]benzimidazole-4-carboxylates **242**. Heating the latter compounds **242** with $POCl_3$ gave the corresponding 1,3-dichloro derivatives **243**. Compound **243** (R = H, R^1 = Ph) was quantitatively converted into the 1-azido-3-chloropyrido[1,2-*a*]benzimidazole derivative **244** when treated with sodium azide in DMF. Refluxing the azido derivative **244** in bromobenzene gave the indolo[2,3-*b*]pyrido[1,2-*a*]benzimidazole derivative **245** (Scheme 88).[122]



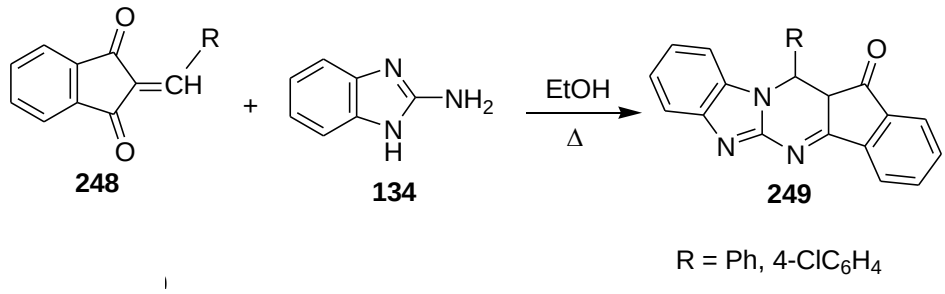
Scheme 88

3.2.3. Benzimidazo-pyrido-isoquinolines. 3-Chloroisoquinoline-4-carboxaldehydes **246** were condensed with 2-benzimidazoleacetonitrile **42** in DMF to give the benzimidazo-pyrido-isoquinolines **247** (Scheme 89).[123]



Scheme 89

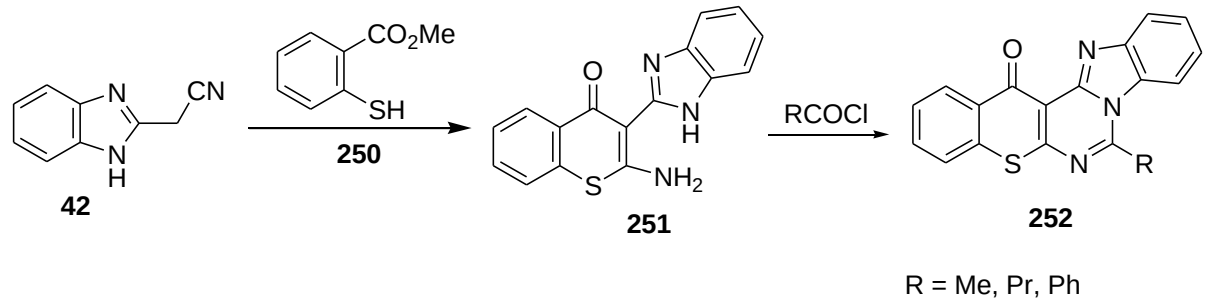
3.2.4. Indeno[1,2:4,5]pyrimido[1,2-*a*]benzimidazoles. Reaction of 2-arylideneindandiones **248** with 2-aminobenzimidazole **134** in refluxing ethanol yielded indeno[1,2:4,5]pyrimido[1,2-*a*]benzimidazole-13-ones **249** in high yields (Scheme 90).[124,125]



Scheme 90

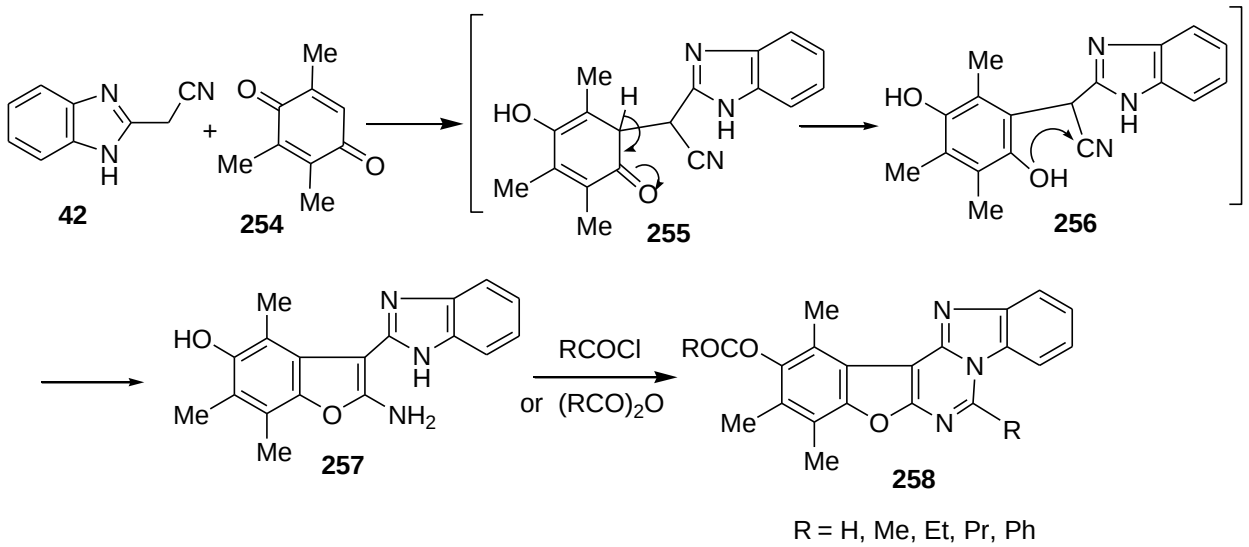
3.3. With four heteroatoms

2-Amino-3-(benzimidazol-2-yl)thiochroman-4-one **251** was prepared by cyclocondensation of methyl thiosalicylate **250** with 2-benzimidazoleacetonitrile **42**. Acylation of **251** with acid chlorides gave the benzimidazobenzothiopyranopyrimidines **252** (Scheme 91).[106,126]



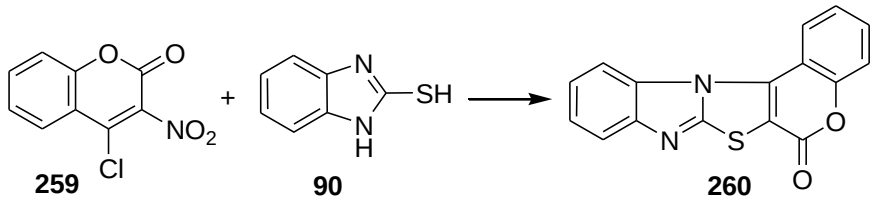
Scheme 91

Treatment of 2,3,5-trimethyl-1,4-benzoquinone **254** with 2-benzimidazoleacetonitrile **42** gave 2-amino-3-(2-benzimidazolyl)benzofuran **257** *via* the intermediates **255** and **256**. Treatment of compound **257** with acid anhydrides or acid chlorides afforded the benzofuro-pyrimido-benzimidazoles **258** (Scheme 92).[127]



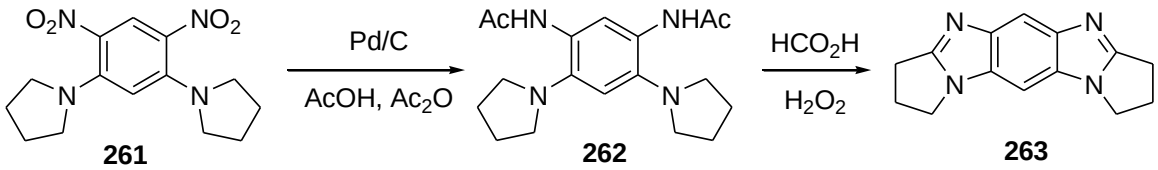
Scheme 92

4-Chloro-3-nitrocoumarin **259** underwent cyclization when treated with 2-mercaptobenzimidazole **90** to give the coumarino-thiazolo-benzimidazole **260** (Scheme 93).[124]



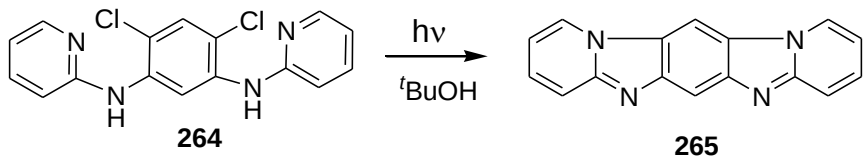
Scheme 93

Treatment of 1,5-dibromo-2,4-dinitrobenzene with pyrrolidine afforded **261**, which was converted to **262** by reduction followed by acylation. Heating of **262** with formic acid at 70 °C in the presence of H_2O_2 underwent cyclization into 3*H*,7*H*-1,2,8,9-tetrahydropyrrolo[1,2-*a*]-pyrrolo[1`,2`:1,2]imidazo[4,5-*f*]benzimidazole **263** in low yield (Scheme 94).[128-130]



Scheme 94

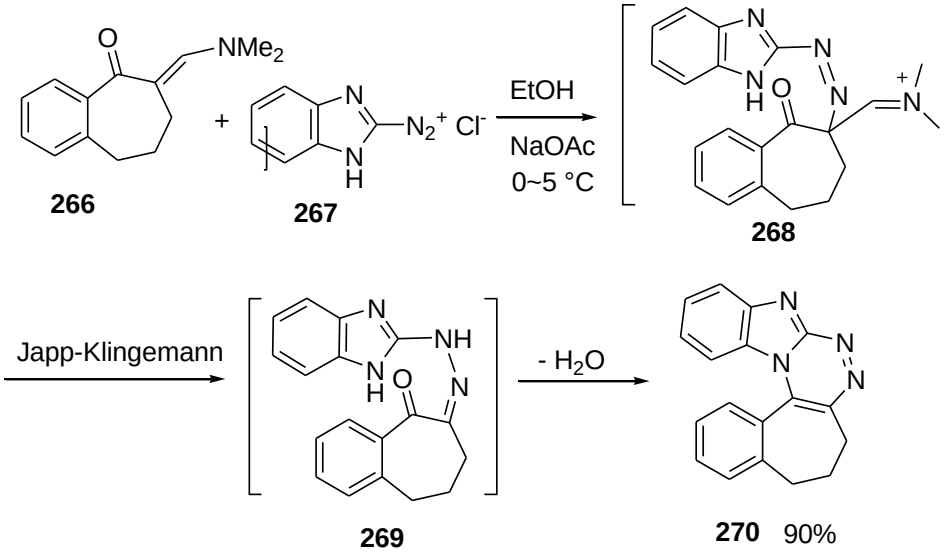
Photochemical irradition of 4,6-dichloro-1,3-(*N*,*N'*-di(2-pyridyl)benzenediamine **264** in 80% aq. *t*-butanol gave the linear fused-pentacyclic system **265** in 47% yield (Scheme 95).[131,132]



264 **265**

Scheme 95

Coupling of 2-dimethylaminomethylene-1-benzosuberone **266** with 2-aminobenzimidazole diazonium salt **267** gave 9,10-dihydro-8*H*-benzo[6',7']cyclohepta[1',2'-*e*]benzimidazo[2,1-*c*] [1,2,4]triazine **270**. The formation of the **270** is assumed to proceed *via* Japp–Klingemann-type cleavage of dimethylaminomethylene moiety from the intermediate **268** then loss of water from **269** (Scheme 96).[133]

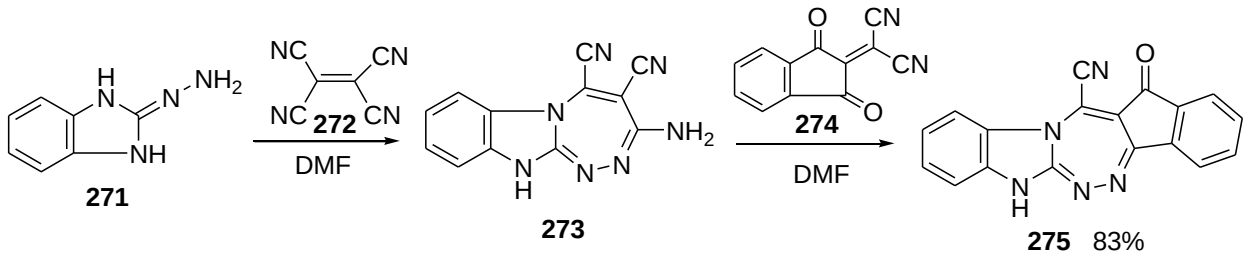


266 **267** **268**

269 **270** 90%

Scheme 96

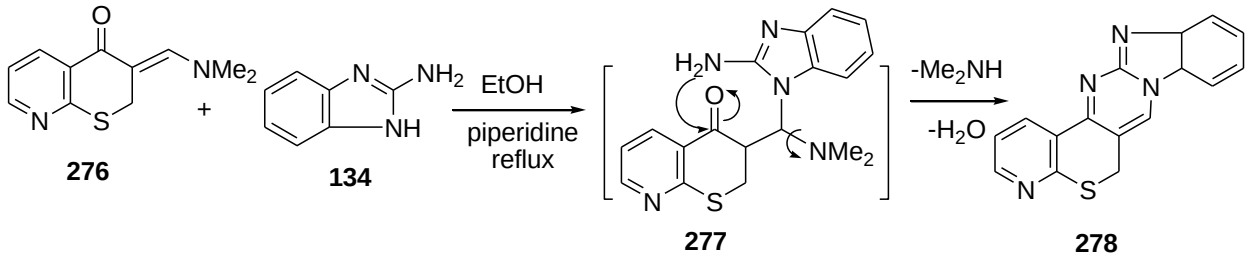
Reaction of 2-hydrazinobenzimidazole **271** with tetracyanoethylene (TCNE) **272** gave the 1,2,4-triazepino[1,2-*a*]benzimidazole derivs **273** that react with dicyanomethyleneindane-1,3-dione **274** to form the indeno-1,2,4-triazepino[1,2-*a*]benzimidazole derivative **275** in 83% yield (Scheme 97).[134]



Scheme 97

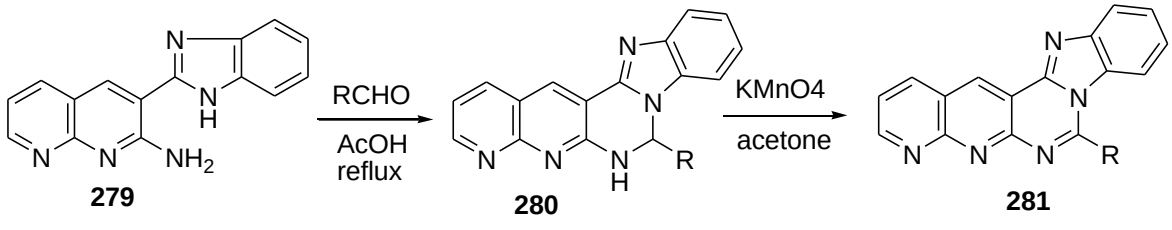
3.4. With five heteroatoms

Treatment of the enaminone **276** with 2-aminobenzimidazole **134** in refluxing ethanol in the presence of piperidine resulted in the formation of pyrido[2'',3'':2',3']-7H-thiopyrano[4',5':4,5]pyrimido[1,2-*a*]benzimidazole **278** *via* the initial attack of the endocyclic-NH of **134** to the exocyclic enamine moiety of **276** followed by the loss of dimethylamine and water molecules from the intermediate **277** (Scheme 98).[135]



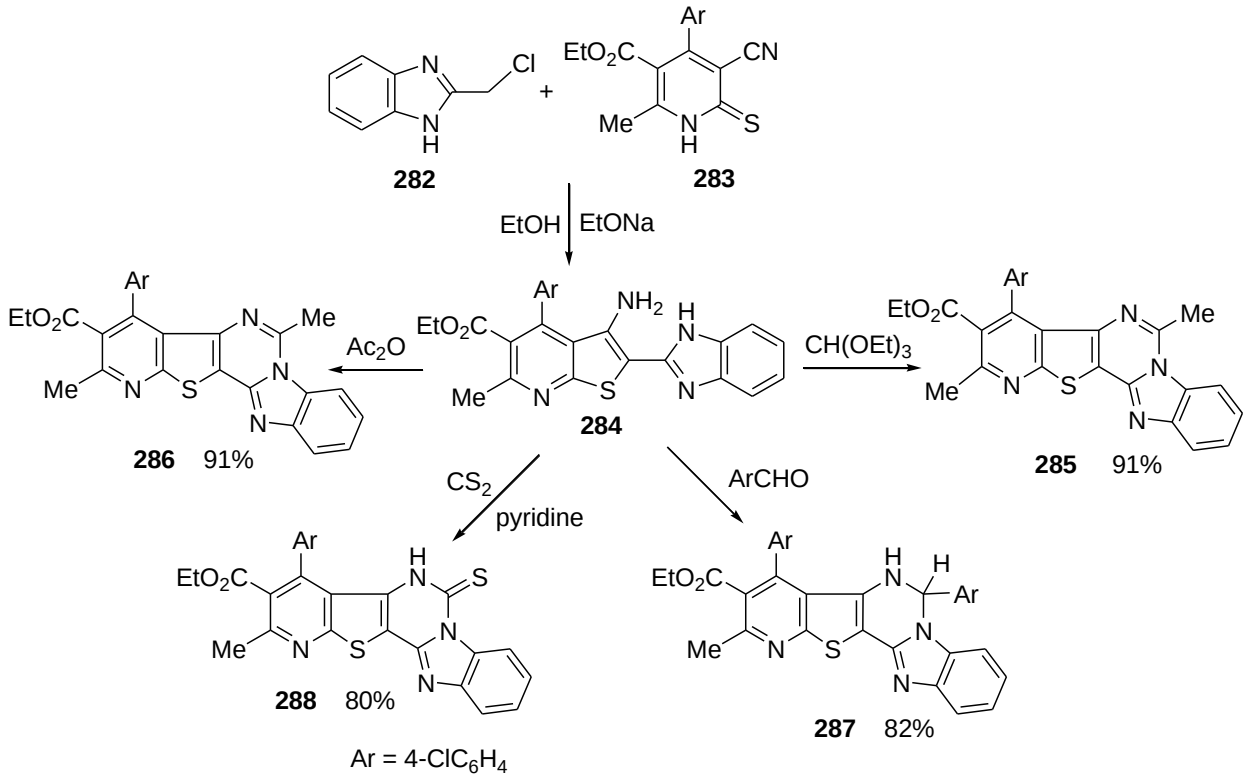
Scheme 98

Heating 2-amino-3-(2-benzimidazolyl)-1,8-naphthyridine **279** with aromatic aldehydes in acetic acid at reflux gave 6,7-dihydro-7-arylbenzimidazo[1',2':1,6]pyrimido[4,5-*b*][1,8]naphthyridines **280** which upon oxidation with $KMnO_4$ in acetone afforded 7-arylbenzimidazo[1',2':1,6]pyrimido[4,5-*b*][1,8]naphthyridines **281** (Scheme 99).[136]



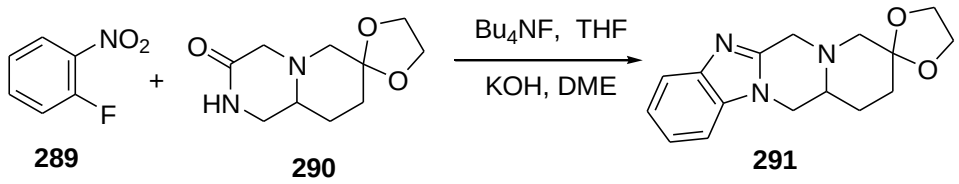
Scheme 99

Reaction of 2-chloromethylbenzimidazole **282** with 2-pyridinethione derivative **283** gave the theino[2,3-b]pyridine derivative **284**. Reaction of **284** with triethyl orthoformate, acetic anhydride, 4-chlorobenzaldehyde and carbon disulfide led to the formation of pyrido[3",2":4',5']thieno[3',2':4,5]pyrimido[1,6-a]benzimidazole derivatives **285, 286, 287** and **288**, respectively, in very high yields (Scheme 100).[137]



Scheme 100

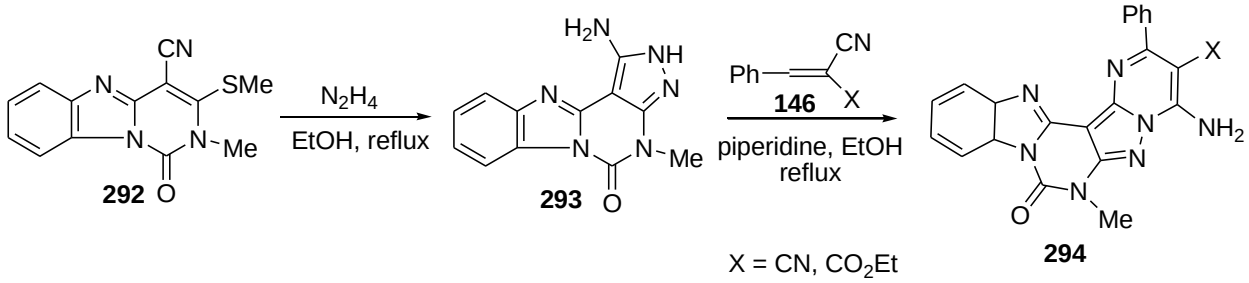
Synthesis of the pyrido[1',2':4,5]pyrazino[1,2-*a*]benzimidazole derivative **291** was reported from the reaction of lactam **290** with 2-fluoronitrobenzene **289** using KOH in dimethoxyethane (DME) in the presence of tetrabutylammonium fluoride, *via* elemination of HF followed by reduction of the nitro group then water elemination (Scheme 101).[138]



Scheme 101

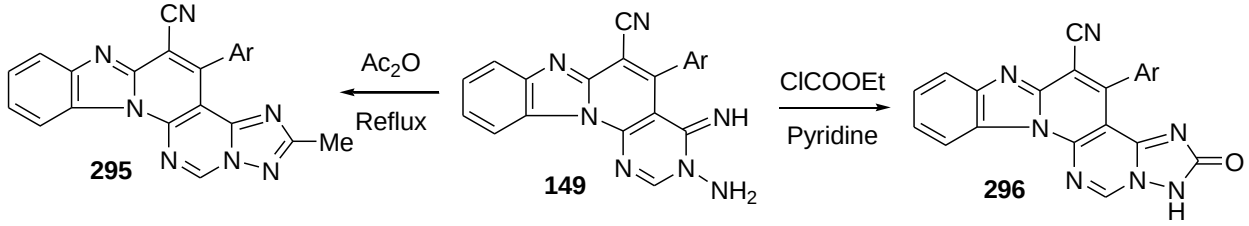
3.5. With six heteroatoms

Treatment of 3-methylthio-pyrimido[1,6-*a*]benzimidazole-4-carbonitrile **292** with hydrazine hydrate in refluxing ethanol gave the pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole derivative **293**. Reaction of **293** with the benzylidene derivatives **146** yielded pyrimido[2'',1'':5',6']pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazoles **294** (Scheme 102).[139]



Scheme 102

1,2,4-Triazolo-[2'',3'':6',1']pyrimido[4',5':2,3]pyrido[1,2-*a*]benzimidazoles **295** and **296** were synthesized by refluxing 3-amino-4-imino-5-aryl-6-cyanopyrimido[5',4':5,6]-pyrido[1,2-*a*]benzimidazole **149** with acetic anhydride and with ethyl chloroformate, respectively (Scheme 103).[85]

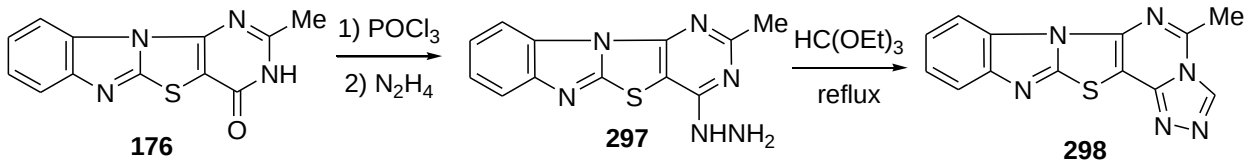


Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4; Ar` = Ph, 4-MeC_6H_4

Scheme 103

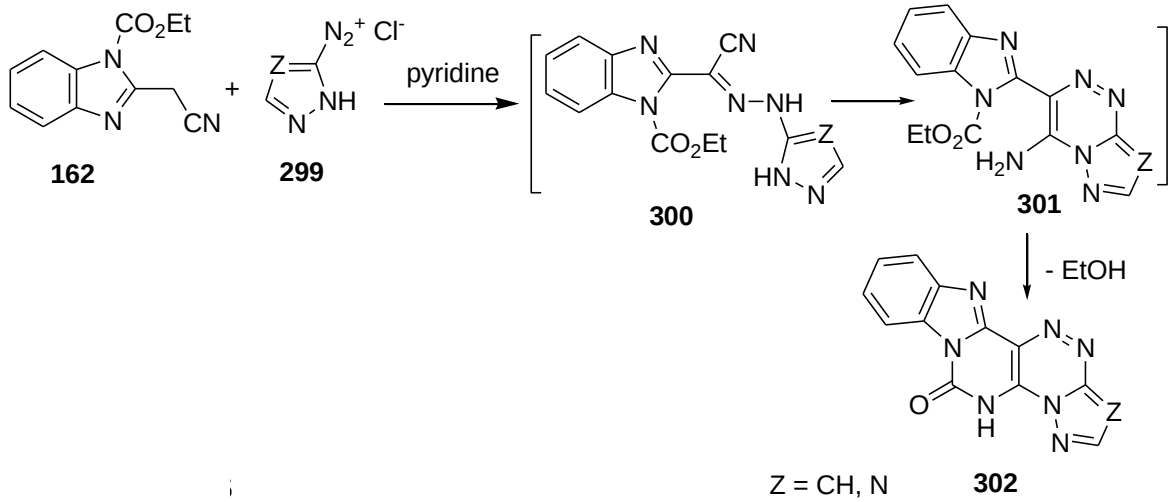
3.6. With seven heteroatoms

Heating 2-methyl-3*H*-pyrimido[4',5':4,5]thiazolo[3,2-*a*]benzimidazol-4-one **176** in $POCl_3$ followed by hydrazine hydrate gave 4-hydrazino-2-methylpyrimidino[4',5':4,5]thiazolo[3,2-*a*]benzimidazole **297**. Refluxing the latter **297** with triethylorthoformate afforded 5-methyl-1,2,4-triazolo[4'',3'':3',4']pyrimidino[5',6':5,4]-thiazolo[3,2-*a*]benzimidazole **298** in 49% yield (Scheme 104).[140]



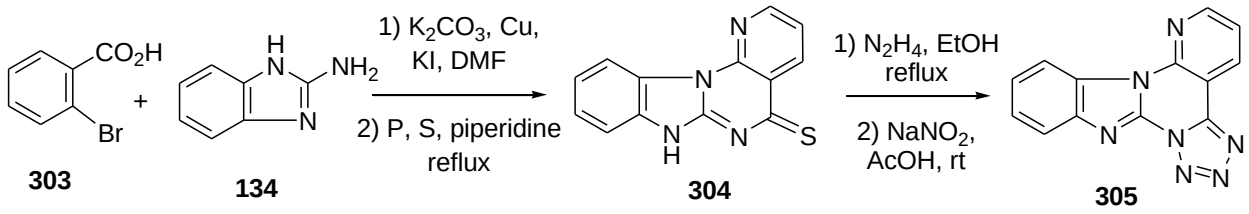
Scheme 104

Synthesis of azolo[5",1":3',4'][1,2,4]triazino[5',6':4,5]pyrimido[1,6-*a*]benzimidazoles **302** is performed in one-step by the reaction of ethyl 2-cyanomethyl-1*H*-benzimidazole-1-carboxylate **162** with the heterocyclic diazonium salts **299** *via* loss of ethanol from the intermediate **301** (Scheme 105).[141]



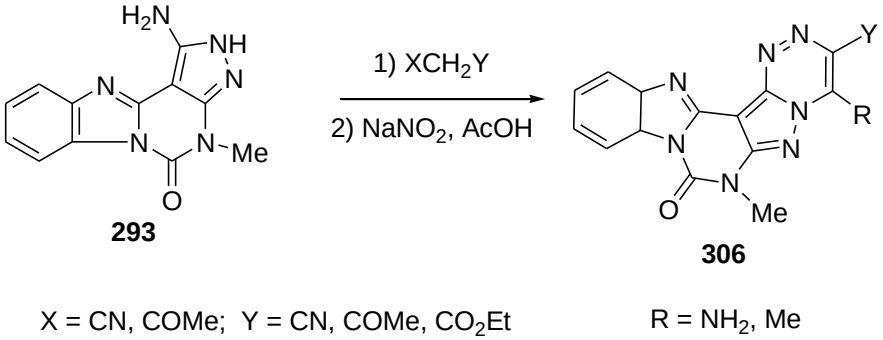
Scheme 105

Copper catalyzed cyclocondensation of 2-bromobenzoic acid **303** and 2-aminobenzimidazole **134** in K_2CO_3 and DMF at reflux afforded pyrido[3',2':5,6]pyrimido[1,2-*a*]benzimidazol-5(6*H*)-one **304** (X = O) which up on treatment with phosphorus and sulfur in refluxing pyridine gave 5-thione analogue **304** (X = S). Treatment of **304** (X = S) with hydrazine in refluxing ethanol followed by nitrosation gave the fused hexaazapentacyclic system **305** (Scheme 106).[142]



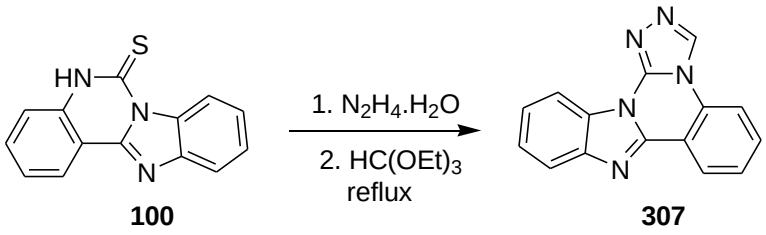
Scheme 106

Treatment of the pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole derivative **293** with active methylene derivatives in the presence of sodium nitrite and acetic acid yielded triazino[2",1":5',6']pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazoles **306** (Scheme 107).[139]



Scheme 107

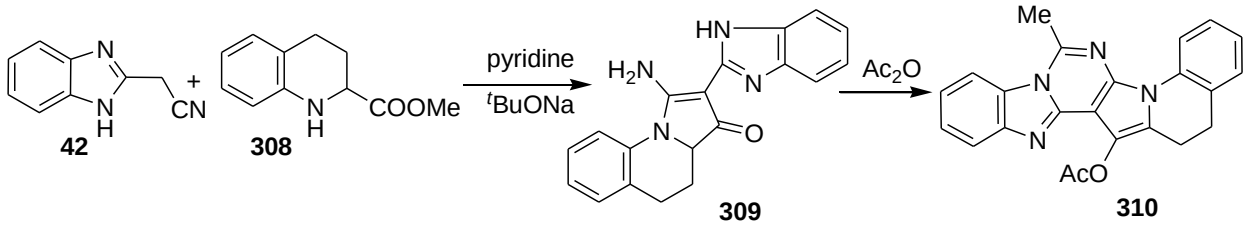
Heating benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thiones **100** with hydrazine hydrate in ethanol followed by adding triethylorthoformate at reflux gave benzimidazo[1,2-*c*]-1,2,4-triazolo[4,3-*a*]quinazoline **307** (Scheme 108).[62,143]



Scheme 108

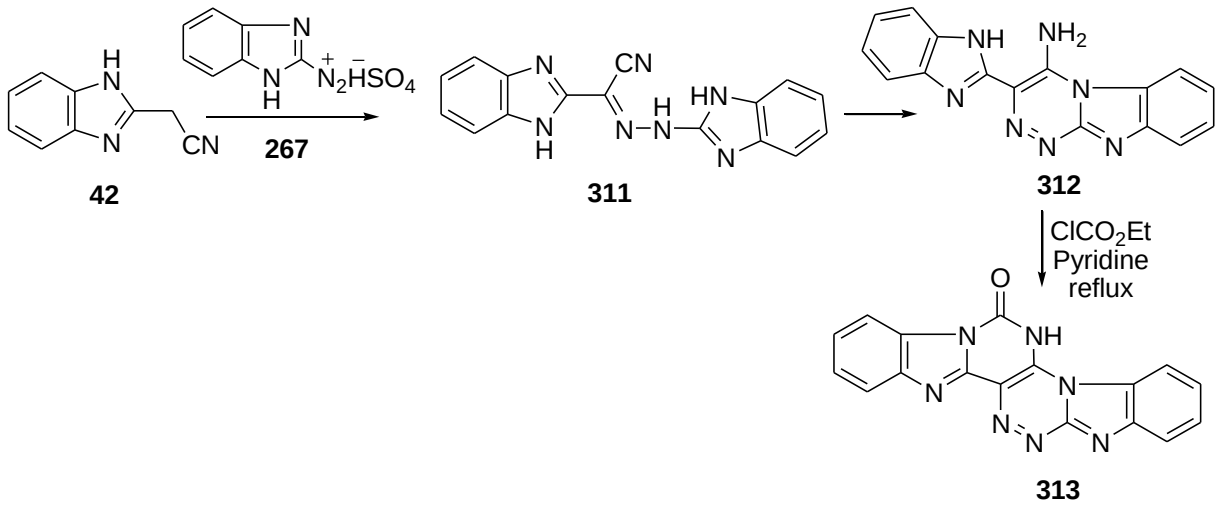
4. Hexa- and heptacyclic fused benzimidazoles

The pyrroloquinoline derivative **309** was prepared in good yield by treating 2-benzimidazoleacetonitrile **42** with methyl tetrahydroquinoline-2-carboxylate **308** in refluxing pyridine containing sodium *t*-butoxide. Cyclization of **309** was performed in refluxing acetic anhydride to give the hexacyclic fused system **310** (Scheme 109).[144]



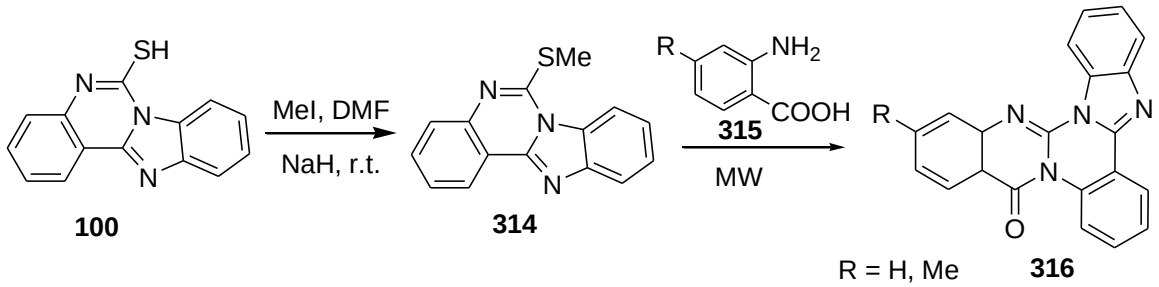
Scheme 109

Benzimidazole-2-diazonium salt **267** was coupled with 2-benzimidazoleacetonitrile **42** to yield the hydrazone **311** which was cyclized in refluxing pyridine to produce the 1,2,4-triazino[4,3-*a*]benzimidazole **312**. Heating the latter with ethyl chloroformate in refluxing pyridine produced the fused polyheterocycle **313** (Scheme 110).[145]



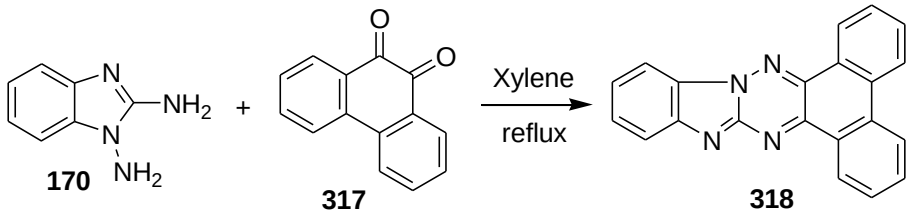
Scheme 110

Methylation of the mercaptobenzimidazo[1,2-*c*]quinazoline **100** with methyl iodide, in dimethylformamide, in the presence of sodium hydride gave the methylthio- derivative **314** in 95% yield. Thermal heating of benzimidazoquinazoline **314** and anthranilic acids **315**, neat at 120 °C or in butanol at reflux for 48 h, cannot give more than 50% of the polyheterocyclic skeleton: 5a,10,14b,15-tetraaza-benzo[*a*]indeno[1,2-*c*]anthracen-5-ones **316**. However, microwave irradiation of **315** with **314** on carbon graphite as support led to the formation of compounds **316** in good yields and in shorter times than for the purely thermal procedures (Scheme 111).[60]



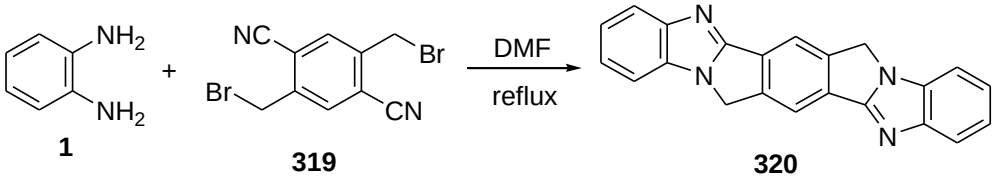
Scheme 111

Phenanthreno[9,10-*e*]-1,2,4-triazino[2,3-*a*]benzimidazole **318** was prepared by cyclocondensation of 1,2-diaminobenzimidazole **170** with phenanthrene-9,10-dione **317** in refluxing xylene (Scheme 112).[146]



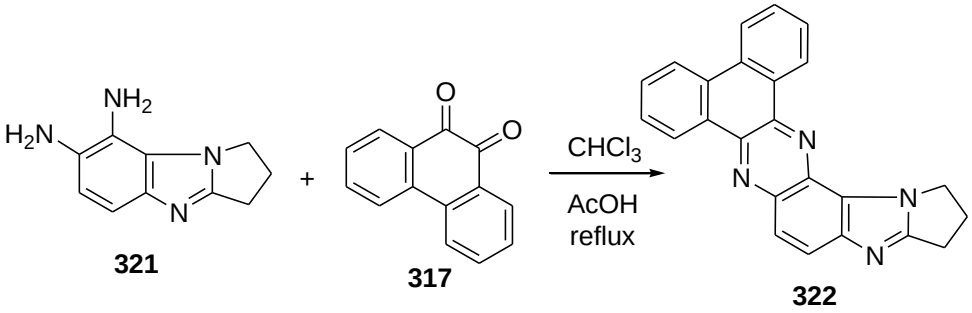
Scheme 112

Reaction of 2,5-*bis*(bromomethyl)benzene-1,4-dinitrile **319** with *o*-phenylenediamine **1** led to the formation of polycyclic skeleton **320** (Scheme 113).[147]



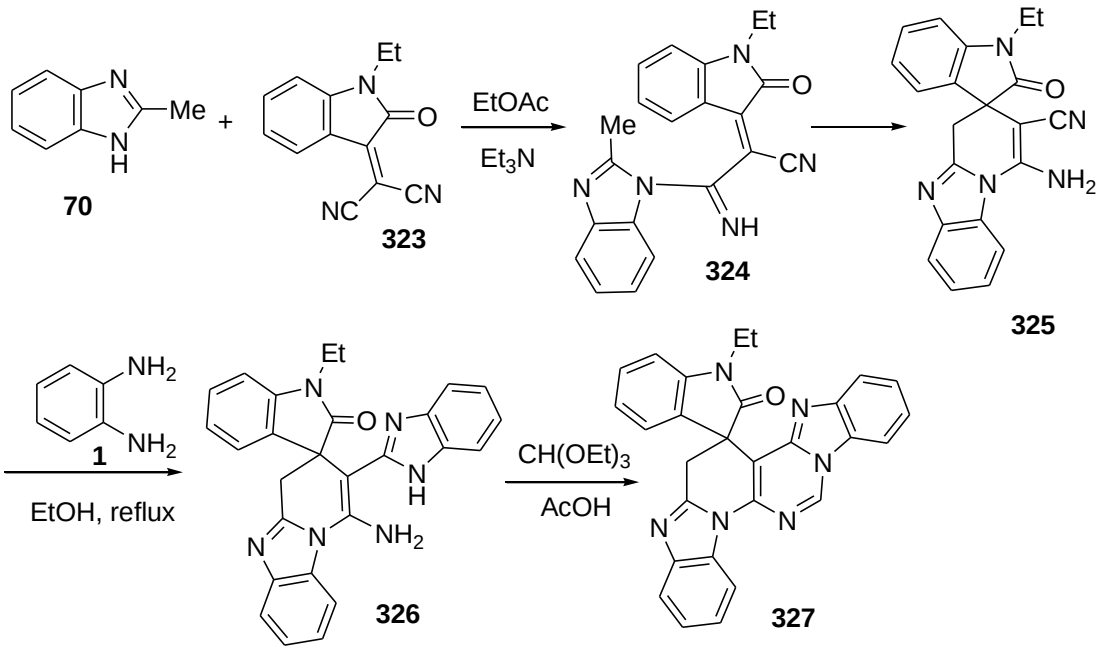
Scheme 113

Diaminopyrrolobenzimidazole **321** underwent a condensation reaction with phenanthrene-9,10-dione **317** in acetic acid at reflux to give the hepta-fused-heterocyclic system **322** (Scheme 114).[148]



Scheme 114

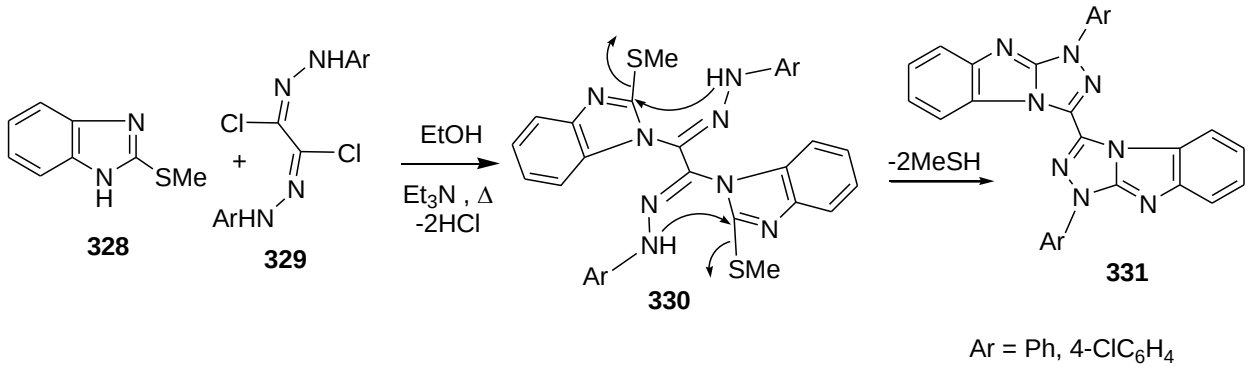
Reaction of 2-methylbenzimidazole **70** with 3-dicyanomethylidine-1-ethyl-2-oxoindoline **323**, in ethyl acetate and Et_3N, afforded 1-amino-2-cyano-3,4-dihydro-1'-ethylspiro{benzimidazo[1,2-*a*]pyridine-3,3'-indolin}-2'-one **325**. Reaction of **325** with *o*-phenylenediamine **1** in refluxing ethanol containing few drops of pyridine gave the benzimidazolyl spiropolyheterocycle **326** which reacts with triethylorthoformate to give the poly-fused heterocyclic system; 6,7-dihydro-1´-ethylspiro{benzimidazo[1',2':1,6]pyrido[2,3-*d*]benzimidazo[2",1"-*f*]pyrimidine-6,3'-indolin}-2'-one **327** in 45% yield (Scheme 115).[149]



Scheme 115

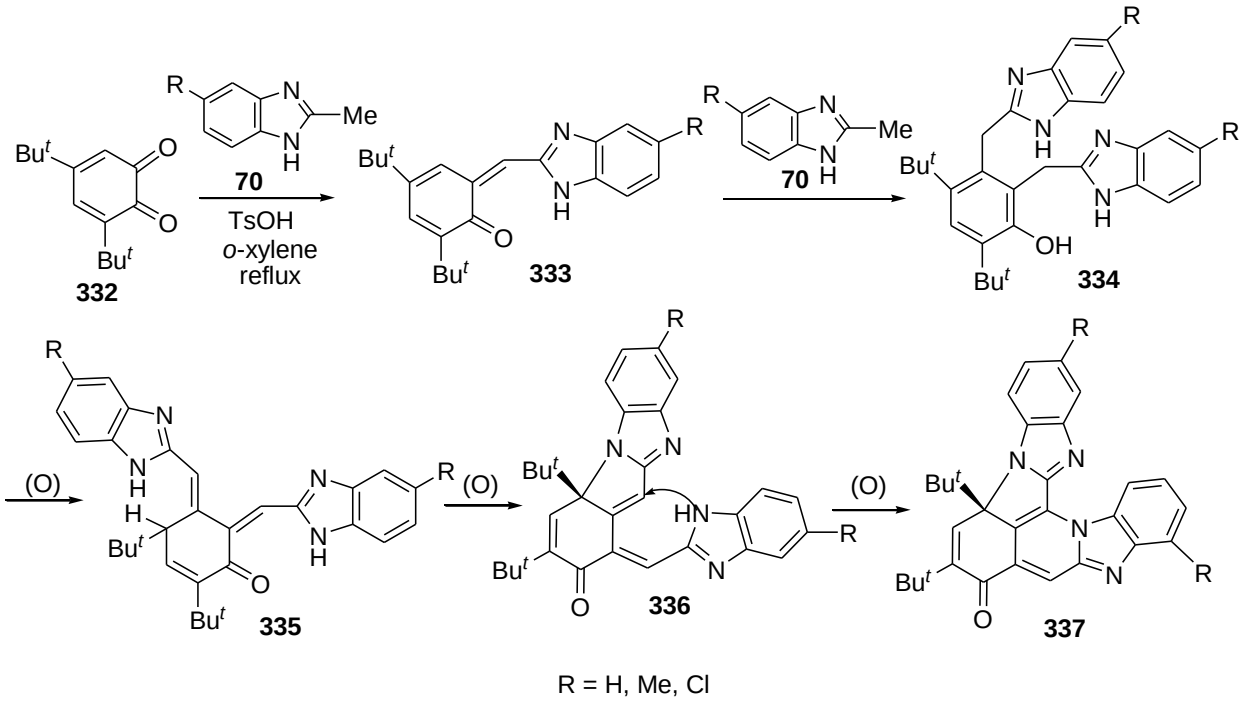
Bis-hydrazonoyl chlorides **329** reacted with 2-methylthiobenzimidazole **328** in 1:2 molar ratio in refluxing ethanol in the presence of triethylamine and gave 1,1`-diaryl-3,3`-bi-1,2,4-

triazolo[4,5-*a*]benzimidazoles **331** *via* loss of two molecules of MeSH from the intermediate **330** (Scheme 116).[150]



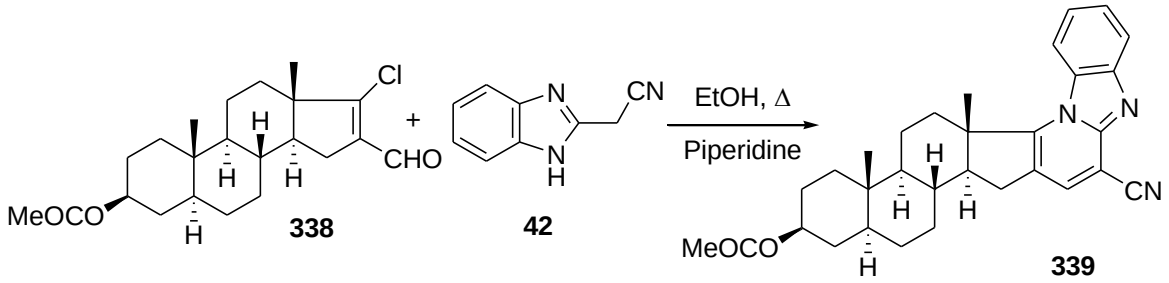
Scheme 116

Condensation of 3,5-di-(*tert*-butyl)-1,2-benzoquinone **332** with 2-methylbenzimidazoles **70** proceeded under reflux in *o*-xylene to yield the benzimidazolylidene derivative **333**. Reaction of the latter **333** with another molecule of 2-methylbenzimidazole **70** then rearranged to give the intermediate **334** which upon oxidation by an excessive amount of the *o*-quinone **332** gave rise to the polycyclic fused benzimidazoles **337** (Scheme 117).[151]



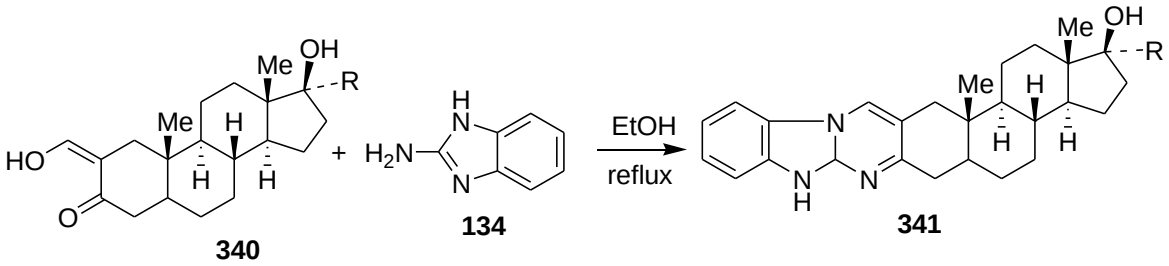
Scheme 117

Reaction of 3-β-acetoxy-17-chloro-16-formyl-5α-androst-16-ene **338** with 2-benzimidazoleacetonitrile **42** in refluxing ethanol in the presence of piperidine yielded the benzimidazopyridoandrostane derivative **339** in high yield (Scheme 118).[152]



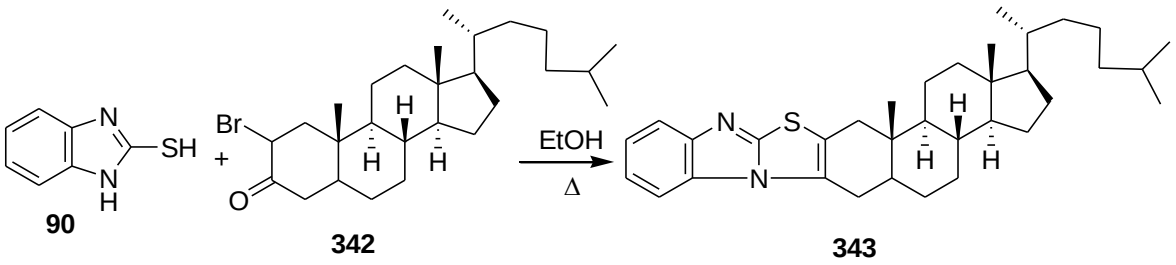
Scheme 118

Treatment of 2-hydroxymethylene-3-androstanone derivative **340** with 2-aminobenzimidazole **134** in refluxing ethanol gave the androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole derivatives **341** in excellent yields (Scheme 119).[153,154]



Scheme 119

Cyclocondensation reaction of 2-bromo-3-cholestanone **342** with 2-mercaptobenzimidazole **90** under refluxing ethanol gave the cholestano-thiazolo-benzimidazole derivatives **343** (Scheme 120).[155]



Scheme 120

5. References

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