1*H*-Benzimidazole-2-acetonitriles as Synthon in Fused Benzimidazole Synthesis

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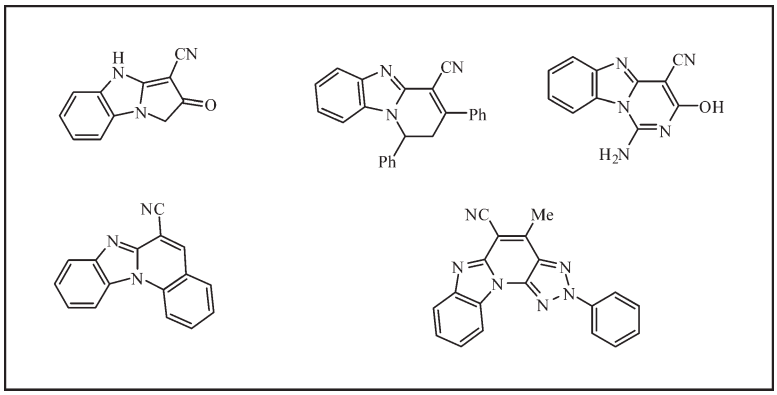

This review summarizes the methods for preparing 1*H*-benzimidazole-2-acetonitriles and their reactions in the past years, some of which have been applied to the synthesis of biologically active molecules. The main reactions are divided into several groups according to some types of the fused benzimidazoles.

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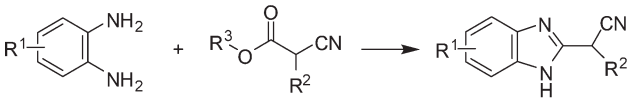
Contents **Page**

1. INTRODUCTION

1*H*-Benzimidazole-2-acetonitriles are convenient precursors which have been extensively utilized in heterocyclic synthesis. Many reactions were developed in the last decades for which the reactivity of 1*H*-benzimidazole-2-acetonitriles towards diverse reagents was utilized for the synthesis of nitrogen bridged heterocycles. From the point of view for biological activities, benzimidazole derivatives are useful intermediates and subunits for the development of molecules having pharmaceutical or biological interests [1,2]. Also, substituted benzimidazole derivatives have found applications in diverse therapeutic areas such as antiulcer drugs, anticancer drugs, antiviral drugs, and antiprotozoan species [3–6]. The main purpose of this review is to present a survey of the literature on the synthesis and reactions of 1*H*-benzimidazole-2-acetonitriles during the last decades.

Scheme 1



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2. METHODS FOR SYNTHESIS OF 1*H*-BENZIMIDAZOLE-2-ACETONITRILES

Two major approaches have been developed for the synthesis of 1*H*-benzimidazole-2-acetonitriles. The first approach involves the construction of the 1*H*-benzimidazole-2-acetonitriles by cyclization of *o*-phenylenediamine derivatives with reagents such as cyanoacetic acid ester, ethyl 2-cyanoacetimidate, and cyanoacetamide. The second method entails ring transformation of benzodiazepine-3-carbonitrile.

2.1. From *o*-phenylenediamine derivatives. 1*H*-Benzimidazole-2-acetonitriles **1** were synthesized by fusion of *o*-phenylenediamines and cyanoacetate at high temperature (Scheme 1) [7–15].

Katsuyama and Kubo have been reported the synthesis of 5-hydroxymethyl-1*H*-benzimidazole-2-acetonitrile **2** starting from 3,4-diaminobenzoic acid (Scheme 2) [16].

Ethyl 2-cyanoacetimidate hydrochloride was converted into 1*H*-benzimidazole-2-acetonitrile **3** by fusion with 1,2-phenylenediamine (Scheme 3) [17].

Compound **3** was prepared by condensation of 1,2-phenylenediamine with cyanoacetamide in an inert organic solvent (Scheme 4) [18].

Cyclocondensation of enaminonitriles (R = CO_2Et, Bz) with *o*-pheylenediamine gave 1*H*-benzimidazole-2-acetonitrile **4** (Scheme 5) [19].

2.2. Ring transformation of benzodiazepine-3-carbonitrile. Treatment of benzodiazepine-3-carbonitrile **5** with methoxyamine hydrochloride resulted in the ring transformation of oxime **6** whose hydrolysis and neutralization gave the target molecule (Scheme 6) [20,21].

Ring cleavage of benzodiazepines **7** (R = Me, Et) with methylamine provided dihydropyrimidines **8**, which underwent ring transformations and hydrolysis to furnish 2-(1*H*-benzo[*d*]imidazol-2-yl)-3-(methylamino)acrylonitrile **9** (Scheme 7) [22].

3. SYNTHESIS OF FUSED BENZIMIDAZOLES

3.1. Pyrrolobenzimidazoles. Elwan has reported the synthesis of pyrrolo[1,2-*a*]benzimidazoles **12**. The reaction of 1*H*-benzimidazole-2-acetonitrile **3** with hydrazonoyl halides (**10a**, X = Cl; R_1 = Me; R_2 = H, Cl, Me; **10b**, X = Br; R_1 = Ph; R_2 = H, NO_2, Me) in the presence of triethylamine led to the formation of pyrrolo[1,2-*a*]benzimidazoles **12**. It has been suggested that the reaction starts from the nucleophilic substitution of the halogen with the benzimidazole carbanion to provide intermediate **11**, which upon dehydration gives the pyrrolobenzimidazoles **12** (Scheme 8) [23].

Awadallah *et al*. revised the structure of **12** into the 3-arylazo-2-methylpyrrolo[1,2-*a*]benzimidazoles (**13**, Ar = 4-Cl-C_6H_4, 4-Br-C_6H_4) by the X-ray crystallography (Scheme 9) [24].

On the other hand, the reaction of hydrazonoyl chlorides (**14** X = Cl; R_1 = Et; R_2 = H, Cl, Me, NO_2; R_2 = H; R_1 = Me; R_2 = Cl) with 1*H*-benzimidazole-2-acetonitrile **3** in the presence of sodium ethoxide yielded the pyrazolopyrrolobenzimidazole **16** *via* the intermediates **15** (Scheme 10) [23,25].

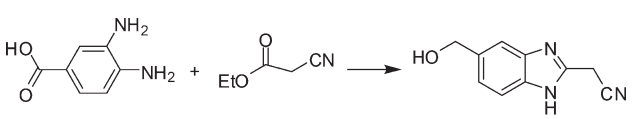
Condensation of the benzimidazoline **17** with the 2-aminothiophene-3-carboxylates **18** [R_1 = Ph, R_2 = H (**18a**); $R_1R_2 = (CH_2)_4$ (**18b**)] in DMF at 100°C provided the tetrahydropyrrolothienopyrimidinediones **19** in 42–67% yields. The reaction of compound **17** with triethylamine produced pyrrolobenzimidazole **20**. This reactivity was explained in terms of steric factors of **17** in which the substituent shields the heterocyclic nitrogen atom and hinders intramolecular alkylation (Scheme 11) [26].

Reaction of dichloromaleimide with 1*H*-benzimidazole-2-acetonitriles followed by intramolecular cyclization of **21** furnished 1,3-dioxo-1,3-dihydropyrrolo [3′,4′:4,5]pyrrolo[1,2-*a*]benzimidazoles **22** (R = H, Me) [27] (Scheme 12).

The pyrrolo[1,2-*a*]benzimidazole-3-carbonitrile **24** was prepared by reaction of compound **3** with oxalic acid bis(*p*-tolylimidoyl) chloride **23** in the presence of triethylamine (Scheme 13) [28].

Treatment of 1-alkyl-4,5-dichloro-3-nitropyridazin-6-one (**25**, R_1 = Et, Me) with ambident nucleophiles (*i.e*., 1*H*-benzimidazole-2-acetonitriles) in the presence of potassium carbonate led to selective substitution of a chorine

Scheme 2



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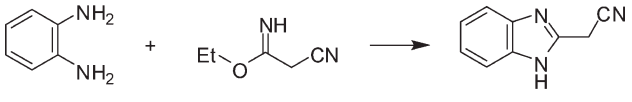
Scheme 3



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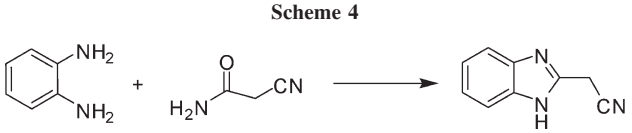
Scheme 4



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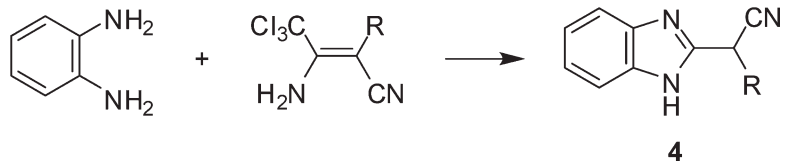
Scheme 5



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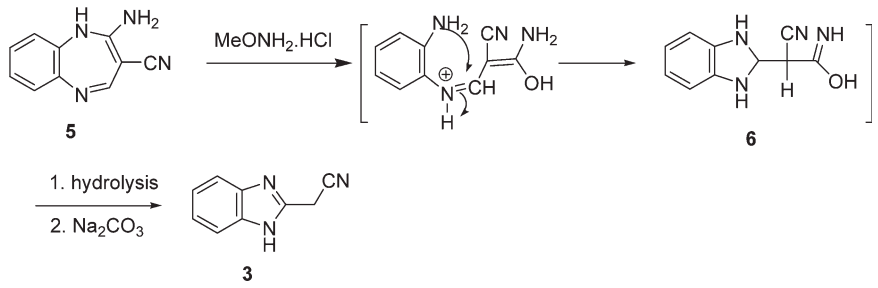
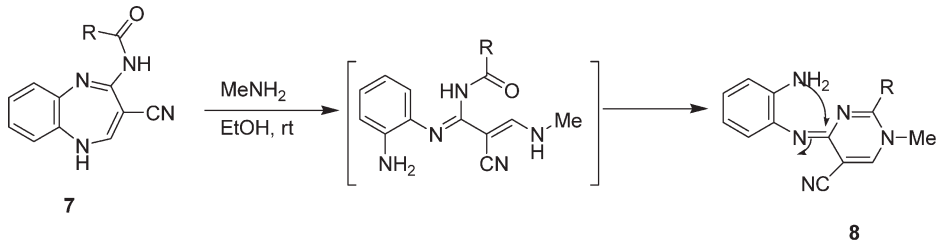
Scheme 6

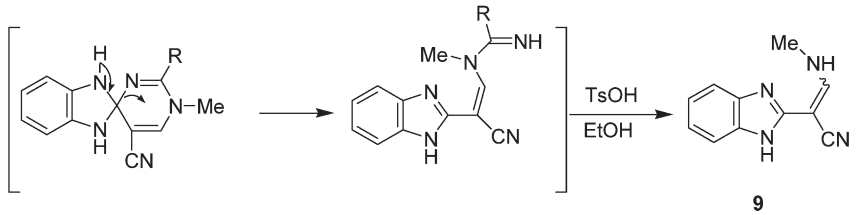


5 **6** **3**

Scheme 7



7 **8**



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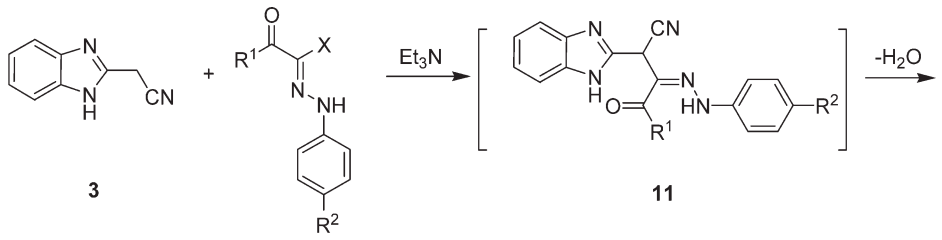
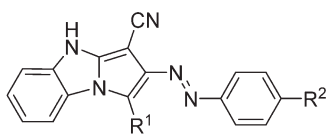
Scheme 8



3 **10** **11**



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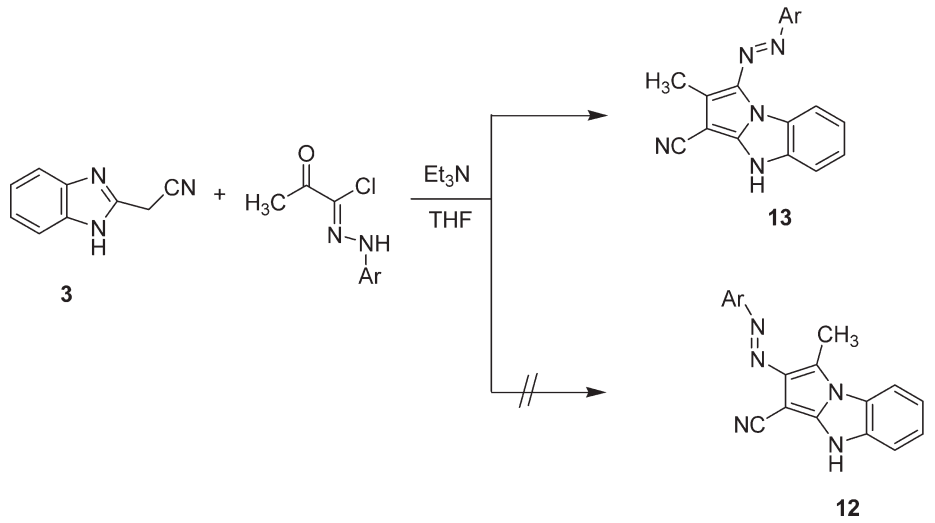
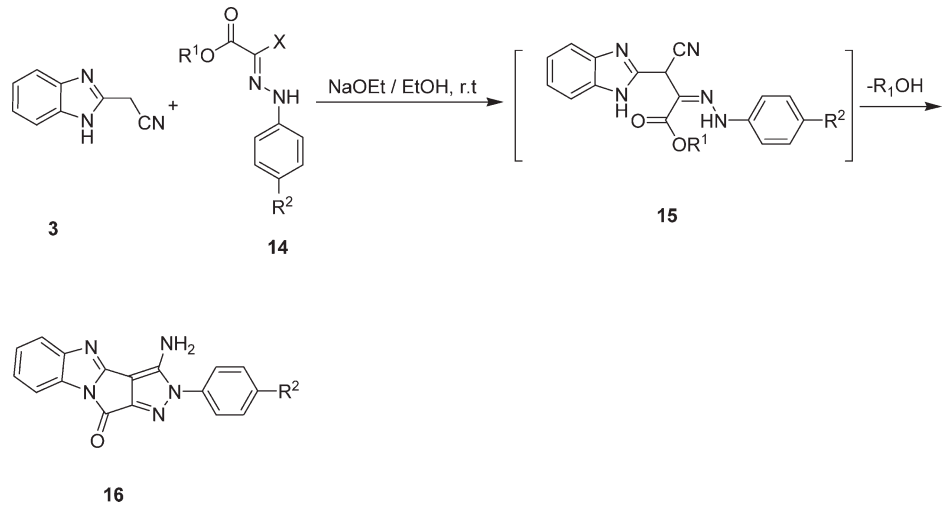
Scheme 9



Scheme 10



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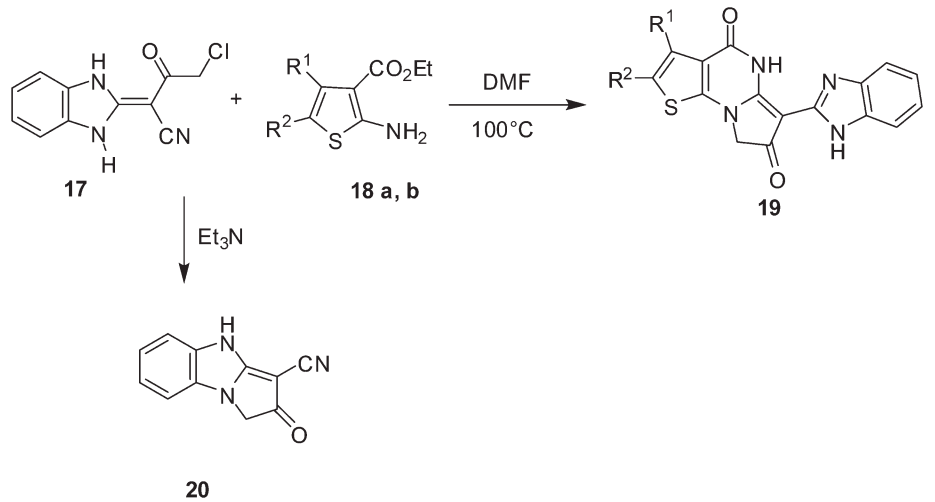
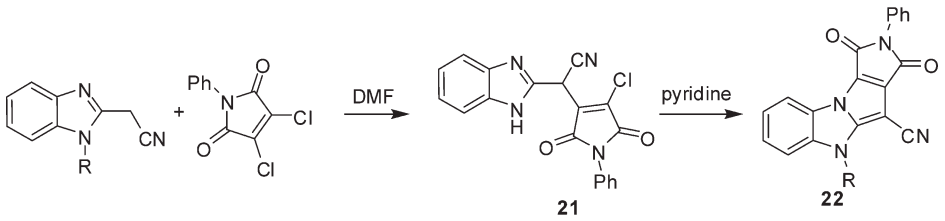
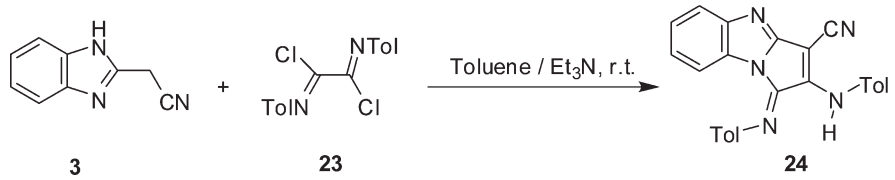


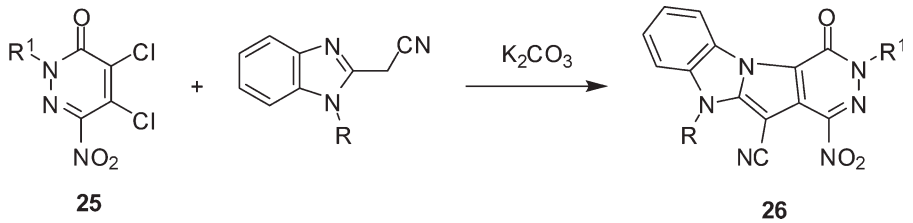
Scheme 12



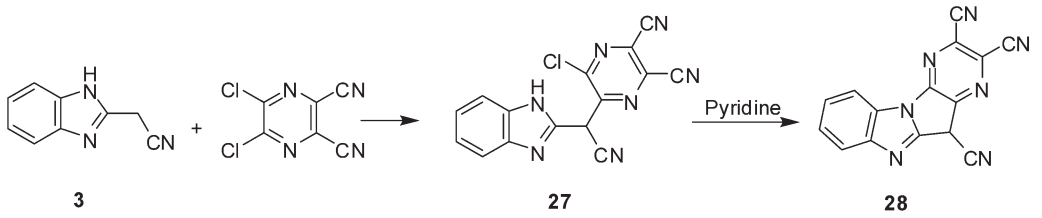
Scheme 13



Scheme 14



Scheme 15

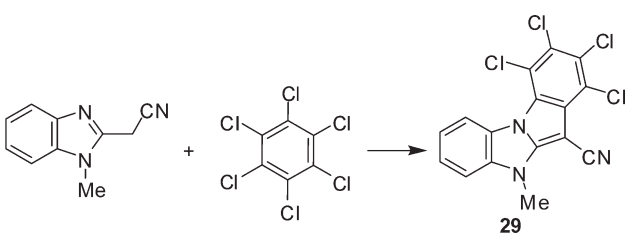


atom by the quaternary carbon atom of the carbanion formed from a substituted acetonitrile **26** (Scheme 14) [29].

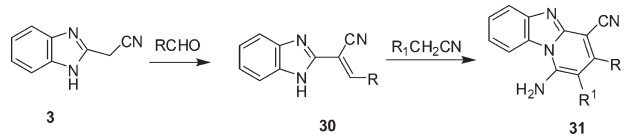
Reaction of 2,3-dichloro-5,6-dicyanopyrazine with **3** led to α-(3-chloro-5,6-dicyanopyrazin-2-yl)-α-(2-azaheteroaryl)acetonitriles **27**. Subsequent heating in pyridine causes an intramolecular cyclization to yield condensed pyrrolo[*b*]pyrazine **28** (Scheme 15) [30].

The nucleophilic substitution reaction of hexachlorobenzene with 1-methyl-1*H*-benzimidazole-2-acetonitrile yielded the condensed indole **29** (Scheme 16) [31].

Scheme 16



Scheme 17



3.2. Pyridobenzimidazoles. Condensation of the pyridine ring with benzimidazole, that is, the passage to pyridobenzimidazoles, extended the spectrum of biological activity [32,33]. The main methods for preparation of pyridobenzimidazoles starting from 2-cyanomethylbenzimidazoles can be occurred *via* Knoevenagel reaction followed by cyclocondensation, Michael addition, reaction with enaminones, and cyclocondensation with β-dicarbonyl compounds.

3.2.1. Knoevenagel reaction. Cyclization of **30** with malononitrile or ethyl cyanoacetate (R = aromatic subs.; R_1 = CN, CO_2Et) in ethanol in the presence of piperidine produced pyridobenzimidazoles **31**(Scheme 17) [34].

Highly fluorescent 7-(diethylamino)benzimidazo[1,2-*a*]quinoline-3-carbonitrile **33** was prepared by cyclization of 4-(diethylamino)-2-methoxybenzaldehyde **32** with **3** (Scheme 18) [35].

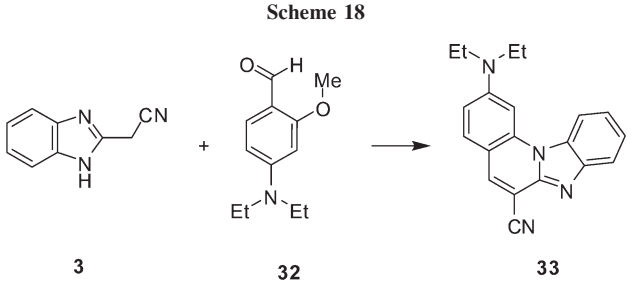
Reaction of the **3** with 2,6-dihalobenzaldehydes (**34**, X = F, Cl, Br) in dioxane led to cinnamonitriles **35** and intramolecular cyclization in DMF benzo[4,5]imidazo[1,2-*a*]quinoline-6-carbonitriles **36** which was obtained directly by refluxing in DMF containing triethylamine (Scheme 19) [36,37].

1-Aryl-3-chloro-4-isoquinolinecarbaldehydes (**37**; R = 4-chlorophenyl, 2,3-dichlorophenyl, 3- and 4-nitrophenyl) were condensed with **3** in DMF to produce diheteroarylpropenenitriles (**38**, same R), which cyclized to yield **39** (same R) [38] (Scheme 20).

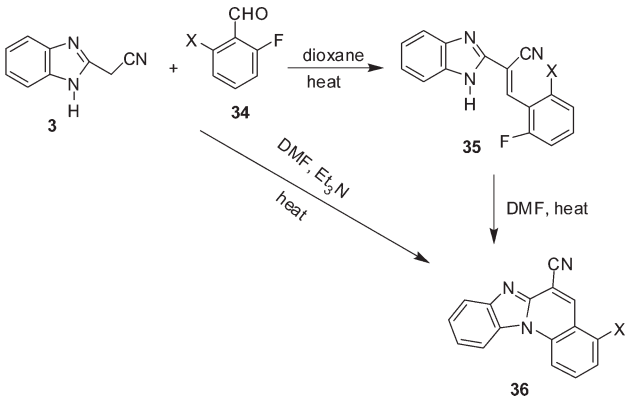
The condensation of 1-phenylpyrazole-4-carboaldehydes (**40**, R = Me, Ph) with benzimidazole-2-acetonitrile **3** led to the formation of fluorescent 3-methyl-1-phenyl-1*H*-pyrazolo[4.3:5,6]pyrido[1,2-*a*]benzimidazole-5-carbonitrile **41**. Similar condensation of 2-chloro-7-methylquinoline-3-carbaldehyde **42** furnished the corresponding 1,2-fused benzimidazo heterocycle **43** (Scheme 21) [39,40].

Chromenes (**44**, R = H, Cl, Br, Me, Et) reacted with **3** in ethylene glycol to yield pyridobenzimidazoles **45** in 65–80% yields (Scheme 22) [41].

Scheme 18



Scheme 19



Ring transformations of pentose glycals (**46**, R_1 = H, R_2 = BnO; R_1 = BnO, R_2 = H) with **3** furnished the pyridiobenzimidazoles **47** (Scheme 23) [42,43].

Vilsmeier-Haack reaction of 3-β-acetoxyandrostan-17-one **48** with phosphorus oxychloride and DMF produced 3-β-acetoxy-17-chloro-16-formyl-5α-androst-16-ene **49**. Reaction of **49** with 1*H*-benzimidazole-2-acetonitrile **3** in refluxing ethanolic solution furnished benzimidazolopyridoandrostane **51** in 82% yield, However, the intermediate **50** was yielded in 70% in the presence of piperidine (Scheme 24) [44].

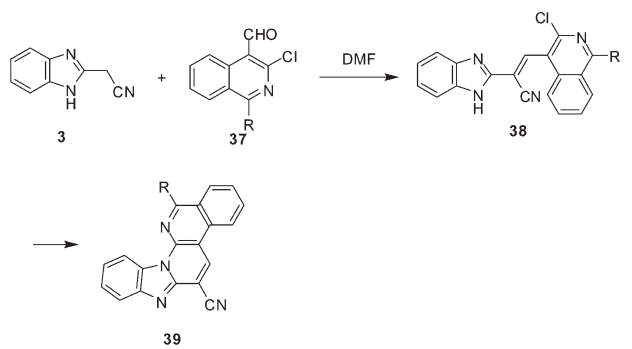
3.2.2. Michael addition. Michael addition of **3** to chalcone in ethanol having a catalytic amount of piperidine led to the formation of pyridobenzimidazole **52** (Scheme 25) [45,46].

Addition of 1*H*-benzimidazole-2-acetonitrile **3** to arylidenemalononitrile **53** produced 1-amino-3-aryl pyrido[1,2-*a*]benzomidazole-2,4-dicarbonitrile **54** (R = aryl). Compounds **54** reacted with formamide yielding 4-amino-5-arylpyrimido[5′,4′:5,6]pyrido[1,2-*a*]benzimidazole-6-carbonitrile **55** (R = aryl) [47,48] (Scheme 26).

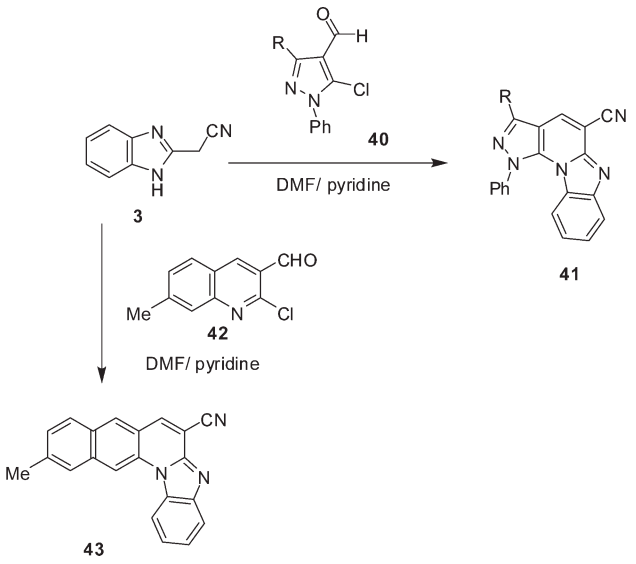
Reaction of arylidene-1*H*-benzimidazol-2-ylacetonitriles **56** with 1*H*-benzimidazole-2-acetonitrile **3** furnished pyrido[1,2-*a*]benzimidazole **57** (Scheme 27) [49].

The formation of pyridobenzimidazole **61** can be achieved by addition of active methylene component **3**

Scheme 20



Scheme 21



to 4-ethoxymethylene-2-phenyl-5-oxazolone **58** to form the intermediate **59**, which underwent intramolecular acylation at the nitrogen atom of benzimidazole nucleus with cleavage of oxazolone ring to form intermediate **60**. Finally, elimination of ethanol furnished pyridobenzimidazole **61** (Scheme 28) [50].

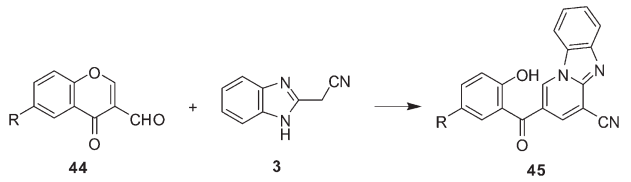
Ethyl 2-cyano-3-(5-chloro-1,3-diphenylpyrazol-4-yl)acrylate **62** underwent Michael addition with **3** to produce pyrido[1,2-*a*]benzimidazole **63** (Scheme 29) [51].

Cyclocondensation of 3-aryl-2-(2-benzimidazolyl)acrylonitrile **64** (R = 1-naphthyl, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4) with ethyl acetoacetate and cyanoacetohydrazide gave pyridobenzimidazolones **65**, and aminopyridobenzimidazoles **66**, respectively (Scheme 30) [52].

Treatment of 1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α,α-*D*-altropyranosid-3-yl)-4-phenyl-but-3-yn-2-one **67** with **3** produced benz[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile derivative **68** (Scheme 31) [53].

3.2.3. Reaction with enaminones. Enaminone derivatives are highly reactive intermediates and are extensively used for the synthesis of heterocyclic compounds. Dawood *et al*., have reported the synthesis of pyrido[1,2-*a*]benzimidazole derivative **70** by reaction of 1-(benzo[d]thiazol-2-yl)-3-(dimethylamino)prop-2-en-1-one **69** with **3** in ethanol in the presence of piperidine (Scheme 32) [54].

Scheme 22



The reaction of enaminonitrile **71** with **3** was also conducted in refluxing ethanol in the presence of a catalytic amount of piperidine to afford 3-amino-2-(benzothiazol-2-yl)carbonylpyrido[1,2-*a*]-benzimidazole-4-carbonitrile **72** (Scheme 33) [55].

Also, treatment of enaminonitrile [2-(benzothiazol-2-yl)-3-(*N*,*N*-dimethylamino)-prop-2-enenitrile] **73** with **3** in refluxing ethanol in the presence of catalytic amount of piperidine afforded 3-amino-2-(benzothiazol-2-yl)pyrido[1,2-*a*]benzimidazol-4-carbonitrile **74** (Scheme 34) [56].

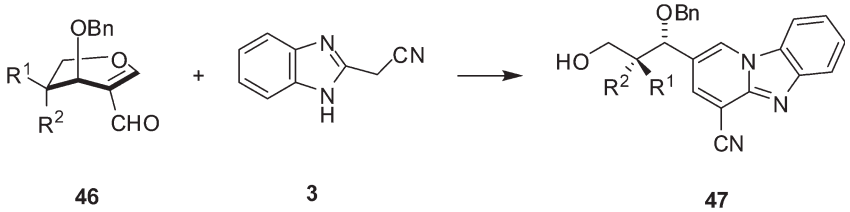
Pyrido[1,2-*a*]benzimidazoles **76** were synthesized by reacting 3-aryl-2-(*N*,*N*-dimethylamino)methylene-3-oxopropanenitriles **75** with **3** [31,55,57]. Elmaati *et al*. in 2002 have been reported the synthesis of pyridobenzimidazole **78**. Reaction of enaminone of acetoacetanilide **77** with **3** yielded the target compound **78** (Scheme 35) [57].

Hassanien in 2005, reported the reaction of methyl 2-benzoyl-3-dimethylaminopropenoate **79** with 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile **3** in refluxing acetic acid in the presence of ammonium acetate to produce methyl 4-cyano-3-phenylbenzimidazo[1,2-*a*]pyridine-2-carboxylate **80**, but not **81** (Scheme 36) [58].

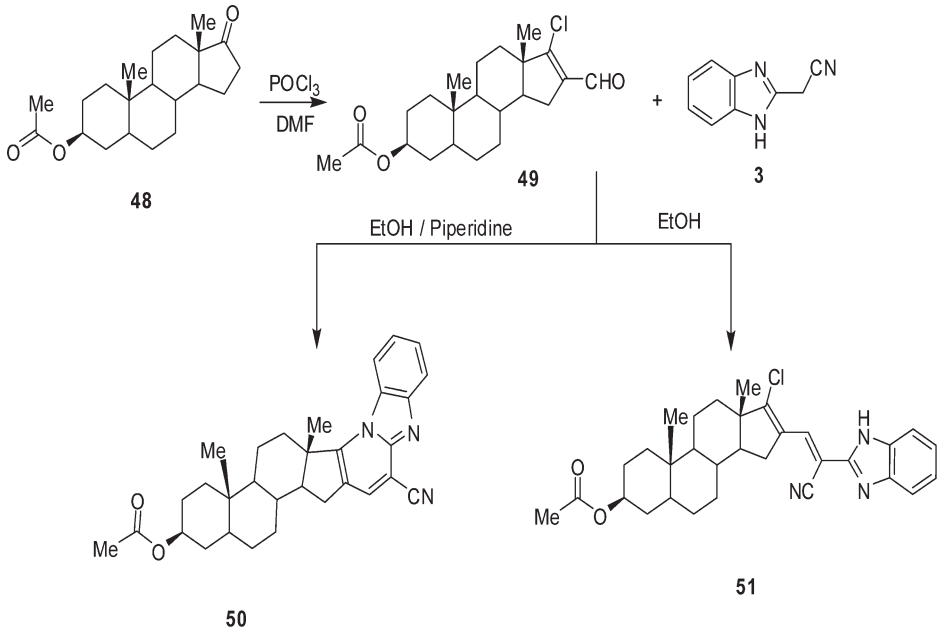
Microwave irradiation of dimedone **82**, dimethylformamidedimethyl acetal and **3** in iso-propanol and a catalytic amount of piperidine led to the formation of tetrahydrobenzo[4,5]imidazo[1,2-*a*]quinolin-6-yl cyanide **83** (Scheme 37) [59].

The enaminone 2-dimethylaminomethylene-1,3-indandione **84** reacted with **3** to produce indenofluorene **85** [33], while its reaction with 2-dimethylaminomethylene-3-(phenylhydrazono)indan-1-one **86** furnished diazaindenofluorene derivative **87** (Scheme 38) [60].

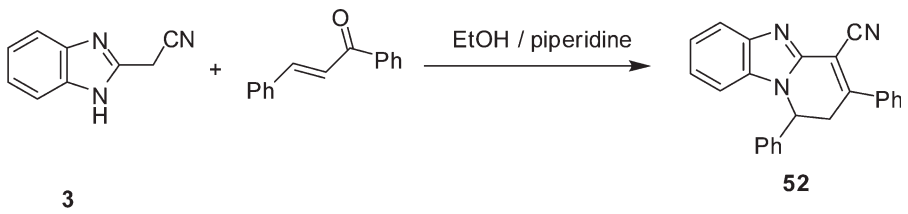
Scheme 23



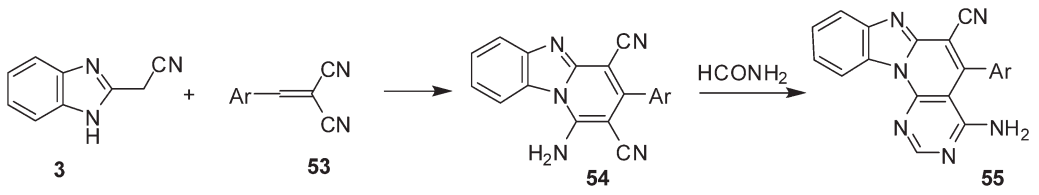
Scheme 24



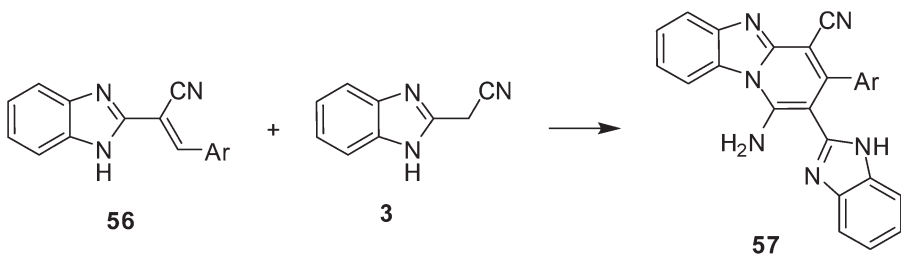
Scheme 25



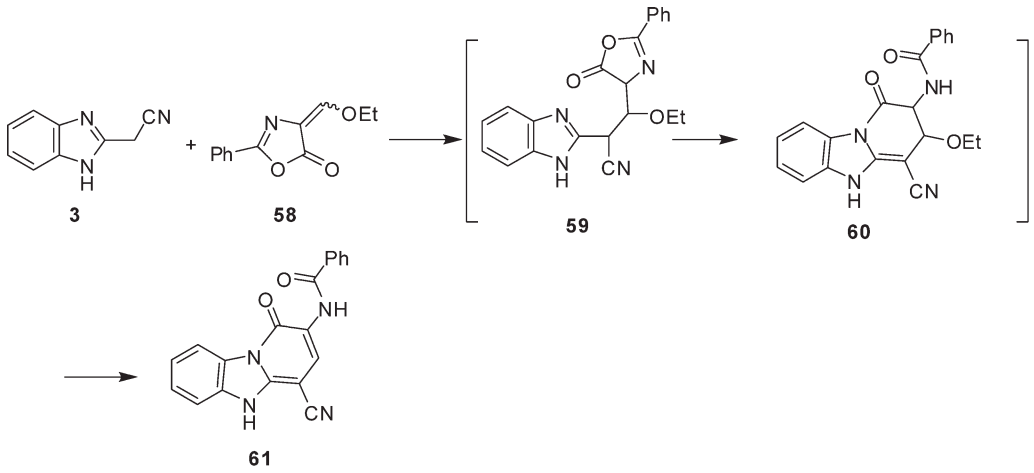
Scheme 26



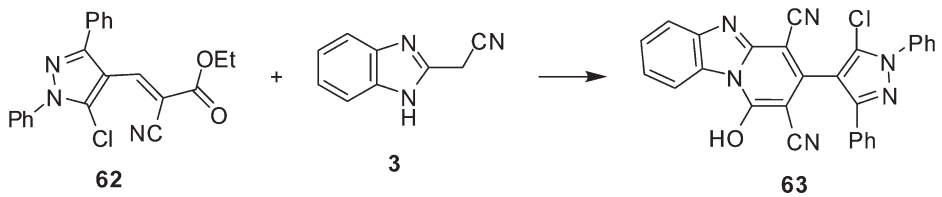
Scheme 27



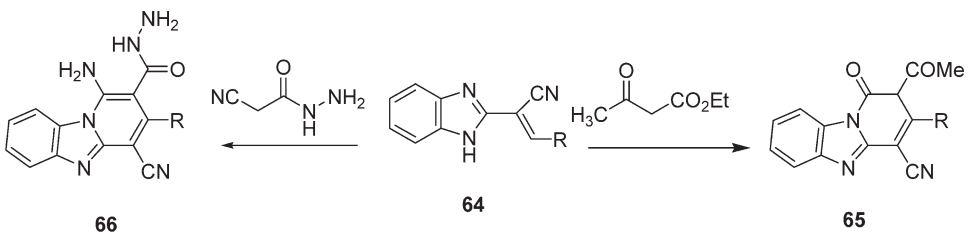
Scheme 28



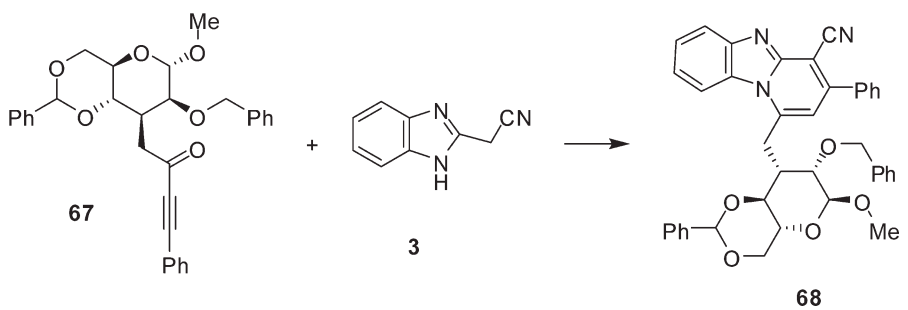
Scheme 29



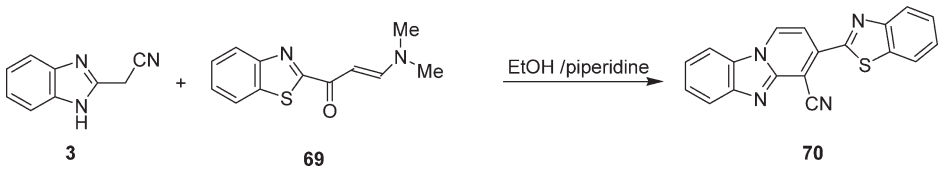
Scheme 30



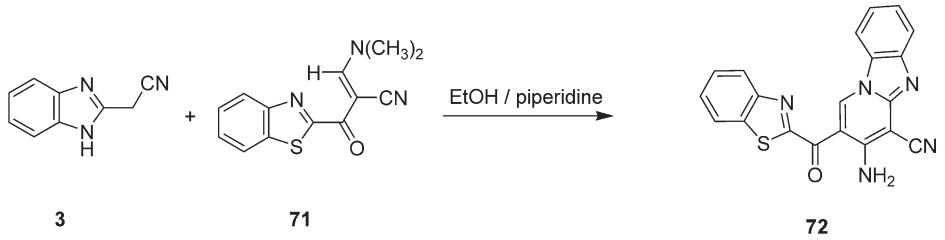
Scheme 31



Scheme 32

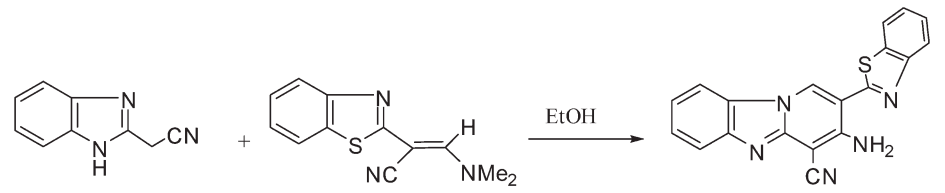


Scheme 33



3 **71** **72**

Scheme 34



3 **73** **74**

Benzo[4,5]imidazo[1,2-*a*]pyridine-2,4-dicarbonitrile **89** was obtained *via* treatment of enaminone **88** with 1*H*-benzimidazole-2-acetonitrile **3** in ethanol and has a catalytic amount of piperidine (Scheme 39) [61,62].

3.2.4. Reaction with β-dicarbonyl compounds. 3-Methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **90** (prepared by the condensation of **3** and ethyl acetoacetate) is formylated with DMF-$POCl_3$ to 2-formyl-3-methylpyrido[1,2-*a*]benzimidazol-4-carbonitrile **91**(Scheme 40) [63].

1-Oxo-*1H,5H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles **94** by fusing **3** with some ethyl acetoacetate **92** in the presence of ammonium acetate or with ethyl β-aminocrotonate **93** (R = H, R_1 = Me) [64] (Scheme 41).

Pyrido[1,2-*a*]benzimidazole-4-carboxylic acid **95** was prepared in excellent yield by condensation of **3** with acetyl acetone followed by hydrolysis of the nitrile group by sulfuric acid (Scheme 42) [65,66].

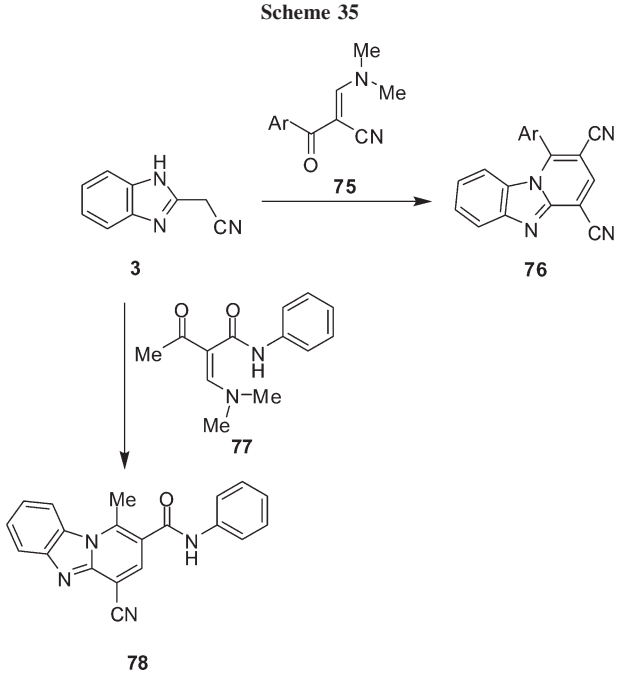
Pyrrolo[3′,4′:3,4]pyrido[1,2-*a*]benzimidazoles **97** [R = Bu, Bn, $MeOCH_2CH_2$, $O(CH_2CH_2)_2NCH_2CH_2$, 2-furyl-CH_2, 4-MeC_6H_4, 2-MeC_6H_4] were prepared in two steps. The condensation of **3** with ethyl 4-chloro-3-oxobutanoate led to the formation of 3-chloromethyl-1,5-dihydro-1-oxopyrido[1,2-*a*]benzimidazole-4-carbonitrile **96**. Amination of **96** with primary amines yielded **97** (Scheme 43) [67].

Condensation of benzimidazole **98** with ethoxymethylenemalonic acid esters (**99**, R = Et, Me) and acetoacetic ester gave the corresponding pyrido[1,2-*a*]benzimidazoles **100**, **101** (Scheme 44) [7].

Cycloalkylpyrido[1,2-*a*]benzimidazoles **102–104** were prepared by reaction of **3** with dimethyl 2-oxocyclopentane-1,3-dicarboxylate, dimethyl 3-oxocyclopentane-1,2-dicarboxylate, or methyl 2-oxocyclohexanecarboxylate in the presence of two equivalent of ammonium acetate at 140°C, these compounds exhibited a good *in vitro* antineoplastic activity especially against most of the leukemia cell lines (Scheme 45) [68–70].

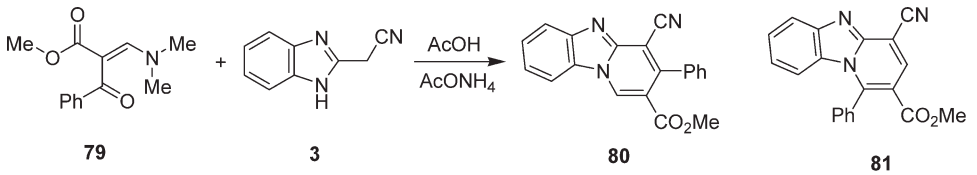
3.2.5. C-acylation. 2-Chloronicotinoyl chloride reacted with 1-methyl-benzimidazole-2-acetonitriles, to give 97% conjugated nitrile **105** which cyclized on heating to give the corresponding 1,8-naphthyridine **106** in high yield (Scheme 46) [71].

Scheme 35



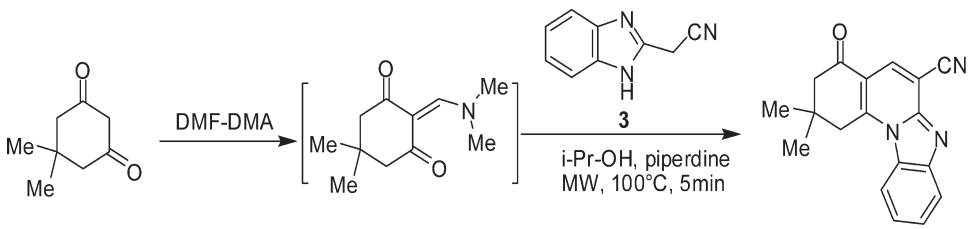
3 **76** **78**

Scheme 36



79 3 80 81

Scheme 37



82 83

1-Methyl-benzimidazole-2-acetonitriles condensed with 2-haloaromatic esters (**107**, X = Cl, F; R = H, O_2N; R_1 = Me, Et) in refluxing acetonitrile containing potassium or cesium carbonate to give condensed isoquinolones **108** (Scheme 47) [72–74].

3-Hydroxy-*1H,5H*-pyrido[1,2-*a*]benzimidazol-1-ones (**110**, R = Et, Bu, $PhCH_2$, Ph) were prepared by cyclization of 1*H*-benzimidazole-2-acetonitrile with the dicarboxylate **109** (Scheme 48) [75,76].

Condensed azine **112** was prepared by cyclization of the corresponding benzothiophene **111** in refluxing ether (Scheme 49) [77].

3.2.6. Miscellaneous methods. A one-step synthesis of benzimidazolo[1,5-*a*]pyridine **114** was reported. The reaction of 2-(2-phenylhydrazono)malononitrile **113** with **3** in refluxing ethanol yielded the target molecule **114** (Scheme 50) [78].

2-Imino-*N*′-*p*-arylpropanehydrazonoyl cyanide (**115**, R = Me, OMe, NO_2) were condensed with **3** in acetic acid to give the corresponding 3-methylpyrido[1,2-*a*]benzimidazoles **116** which then oxidized with cuprous acetate in DMF to triazolo[4,5-*b*]pyrido[1′,2′-*a*]benzimidazoles **117** (Scheme 51) [79].

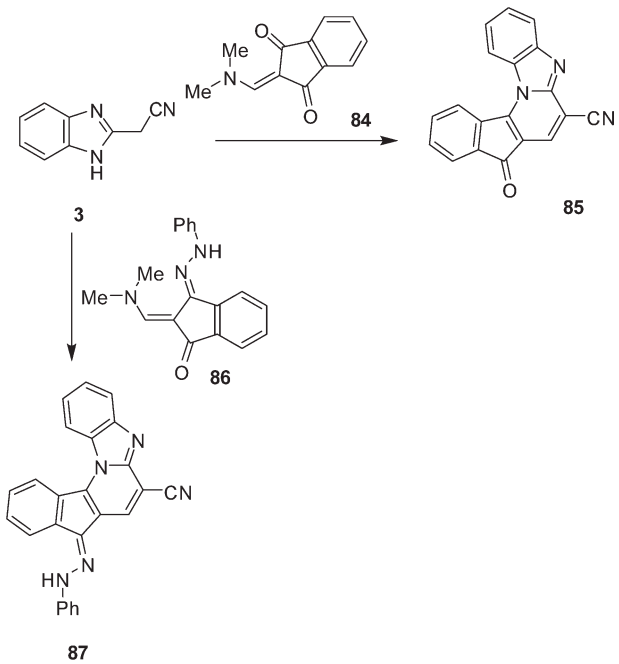
Reaction of **3** with 3-aminobut-2-enenitrile **118** afforded 1-amino-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **119** (Scheme 52) [80].

Compound **3** reacted with sodium salts of 3-hydroxymethylene-2-alkanones (**120**, R = H, Me, R_1 = Me, aryl) in piperidine acetate and aqueous ethanol to yield two isomeric structures **121** and **122**. The X-ray analysis confirmed the presence of **121** in the solid state (Scheme 53) [81].

The cycloannulation of dianion **123** derived from **3** with the acyclic ketene dithioacetals (**124**, R = Ph, Me) produced 4-cyano-1-phenyl (or 1-methyl)-3-(methylthio)-pyrido[1,2-*a*]benzimidazoles **125** in good yields *via* the intermediate **124** (Scheme 54) [82].

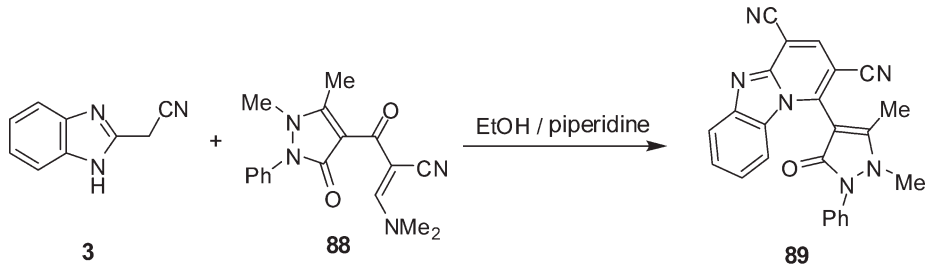
Benzimidazole-2-acetonitriles (R = H, Me) were treated with carbon disulphide and dimethyl sulfate to furnish thioesters **126**. Reactions of (**126**, R = H, Me) with methyl 2-cyano-3,3-bis(methylthio)acrylate (**127a**, X = CO_2Me), 2-[bis(methylthio)methylene]malononitrile (**127b**, X = CN), and 2-(ethoxymethylene)malononitrile gave pyridobenzimidazoles (**128**, R_1 = SMe, Z = O, NH; R_1 = H, Z = NH) (Scheme 55) [83].

Scheme 38

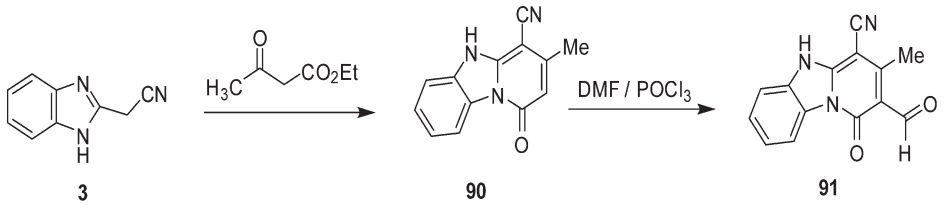


85

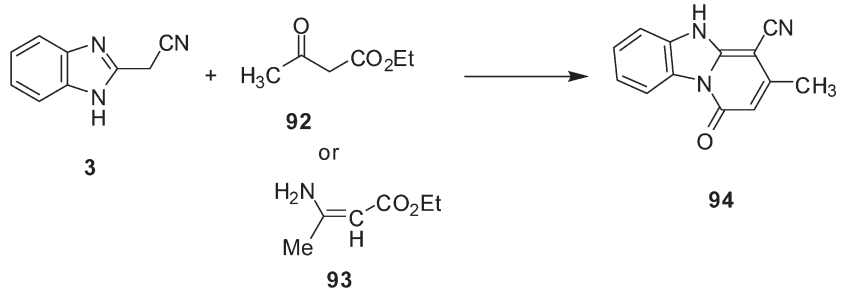
Scheme 39



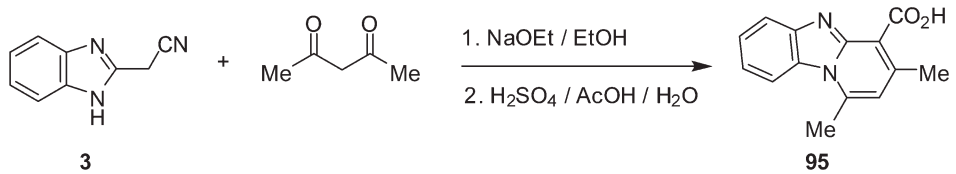
Scheme 40



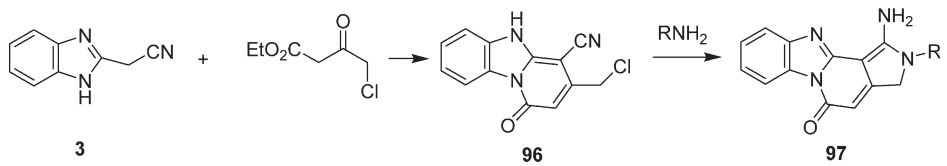
Scheme 41



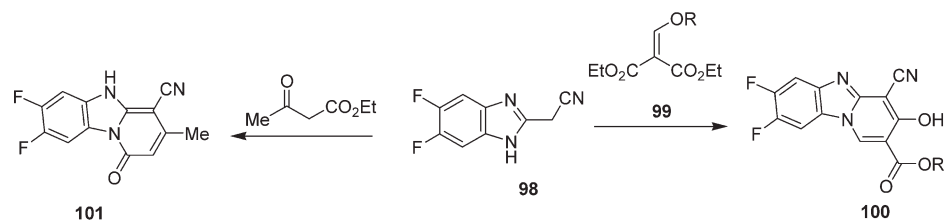
Scheme 42



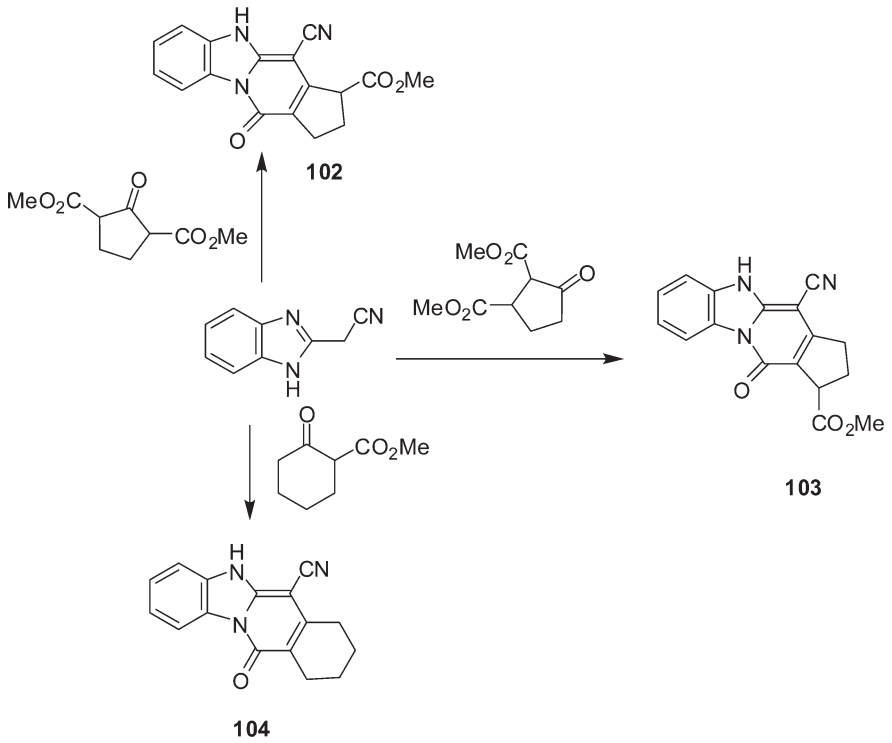
Scheme 43



Scheme 44



Scheme 45



The reaction of **3** with triethyl orthoformate and hippuric acid derivatives in refluxing acetic anhydride afforded pyrido[1,2-*a*]benzimidazole derivatives **131** *via* the intermediates **129** then **130**. The latter cyclizes *via* water elimination to yield pyrido[1,2-*a*]benzimidazole derivatives **131** (Scheme 56) [84].

Thermal condensation of **3** with diethyl ethoxymethylenemalonate in diphenyl ether at 240–250°C gave 75% yield ethyl 4-cyano-3-hydroxypyrido[1,2-*a*]benzimidazole-2-carboxylate **132** (Scheme 57) [33].

Base-catalyzed condensation-cyclization of **3** with 4-(methylthio)-2-oxo-6-aryl-2*H*-pyran-3-carbonitriles (**133**, Ar = aryl, 3-pyridyl, 4-pyridyl) led to the formation of pyrido[1,2-*a*]benzimidazoles **134** as a major product and pyrano[4,3-*d*]pyrido[1,2-*a*]benzimidazoles **135** as a minor one (Scheme 58) [85].

Reactions of 2-chlorobenzonitriles (**136**, R = H, NO_2) and 2-chloro-3-quinolinecarbonitrile with 1*H*-benzimidazole-2-acetonitriles (R_1 = H, Me, Et) gave condensed isoquinolinimines (**137**; R = H, NO_2; X = NH, NMe, NEt) and condensed 1,8-naphthyridinimines (**138**; X = NMe) [86] (Scheme 59).

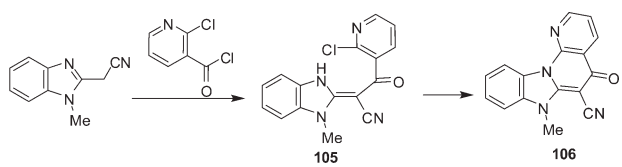
2-(2-Hydroxyethyl)-1-oxo-pyrido[l,2-*a*]benzimidazole-4-carbonitrile **139** was prepared by reacting **3** with 2-acetylbutyrolactone in the presence of ammonium acetate, whereas the 2-benzamido compound **140** was obtained by reacting **3** with 4-ethoxymethylene-2-phenyloxazolin-5-one (Scheme 60) [87].

Cyanamide in the presence of methanol, s-triazine and **3** gave primary product cyanoethene **141** which was stabilized *via* intermediate **142** to give pyridobenzimidazole **143** (Scheme 61) [88].

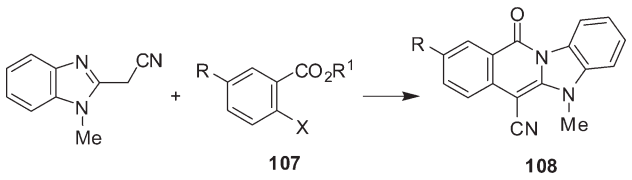
The reaction of 3-methylthio-4-phenyl-1,2-dithiolium perchlorate **144** with **3** in a mixture of acetonitrile/dioxane in the presence of triethylamine gave two products. The major product was cyanopyridobenzimidazole **145** formed by initial reaction of acetonitrile at the unsubstituted 5-position of the dithiole ring, followed by ring opening and recyclization. The other product was dithiole **146** (Scheme 62) [89].

Reactions of **3** with diketene in acetic acid at room temperature gave *C*-acetoacetyl derivative **147** which easily cyclized to give 4-cyano-3-methylpyrido[1,2-*a*]benzimidazole-1(5*H*)-one **148** (Scheme 63) [90].

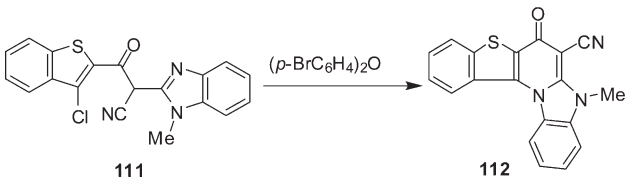
Scheme 46



Scheme 47



Scheme 49



The nucleophilic attack of carbanion of 1*H*-benzimidazole-2-acetonitriles (R = H, Me) at C-4 of pyrimidine ring in **149** led to the formation of the non-isolated intermediate **150**, which underwent intramolecular cyclization through acylation at the nitrogen atom of benzimidazole leading to pyridopyrimidine **151** (Scheme 64) [91].

3.3. Pyrimidobenzimidazoles. A one-step synthesis of azolo[5″,1″:3′,4′][1,2,4]triazino[5′,6′:4,5]pyrimido[1,6-*a*]benzimidazoles (**155**, Z = N, CH) has been achieved by the reaction of ethyl 2-cyanomethyl-1*H*-benzimidazole-1-carboxylate **152** with heterocyclic diazonium salts **153** through the formation of the intermediate **154** (Scheme 65) [92].

Acylation of 2-(1*H*-imidazol-2-yl)acetonitriles (R = H, Me) by haloalkyl isocyanates (**156**, Ar = Ph, 4-tolyl, 4-anisyl) followed by heterocyclization of **157** afforded 1,2,3,5-tetrahydrobenzo[4,5]imidazo[1,2-*c*]pyrimidines **158** (Scheme 66) [93].

Compound **3** reacted with ethyl chloroformate in the presence of triethylamine to give *N*- and *C*-acyl derivatives **152** and **159** respectively, which separated by fractional crystallization from dioxane. Reaction of C-acyl derivative **159** with guanidine sulfate in dry pyridine and sodium methoxide gave 1-amino-3-hydroxy-4-cyanopyrimidino[1,6-*a*]benzimidazole **160** (Scheme 67) [94].

Abdelhamid *et al*. have reported the synthesis of benzimidazo[1,2-*c*]pyrimidine-4-carbonitriles **162**. Treatment of 2-(1-ethoxycarbonyl)benzimidazoylacetonitrile **152** with isothiocyanates (R = Me, Ph) in the presence of potassium hydroxide gave the target compounds **162** in good yield *via* the formation of thioanilide intermediate **161** (Scheme 68) [95,96].

The reaction of **3** with sulfur, arylisothiocyanates, and carbon disulfide has been reported by Ivachtchenko *et al*. [97] and Badawy *et al*. [98] to give **163** which underwent methylation to give **164** (Scheme 69).

The mechanism of the reaction has described as follows (Scheme 70):

Five-component condensation of isothiocyanates (R_1 = 4-EtO, 3-MeO), sulfur, 1*H*-benzimidazole-2-acetonitrile **3**, triethylamine, and carbon disulfide furnished triethylammonium 3-aryl-[1,3]thiazolo[4′,5′:4,5]pyrimido[1,6-*a*]benzimidazole-2(3*H*)-thioxo-5-thiolates **166**, the alkylation of **166** led to 3-aryl-5-R-thio-[1,3]thiazolo[4′,5′:4,5]pyrimidino[1,6-*a*]benzimidazole-2(3*H*)-thiones **167** (R_2 = Me, 2-(methyl)-1,3-dioxolane, CH_2CO_2Et) [97] (Scheme 71).

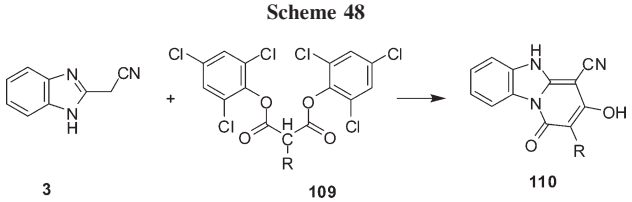
A buffered solution of 1,2,4-triazole-5-diazoium salt **168** was coupled with 1-methylbenzimidazole-2-yl-acetonitrile **3** to yield the corresponding hydrazones **169**, intramolecular cyclization of the latter compound gave triazolo[5,1-*c*]-1,2,4-triazine **170**. Similarly, indazole-3-diazonium chloride **171** also coupled readily with **3** to yield hydrazone **172** which cyclized in refluxing pyridine to produce 1,2,4-triazino[3,4-*b*]indazole **173** in to two tautomeric forms [99] (Scheme 72).

Compound **3** reacted with a variety of *N*-acyl imidates (**174**, R_1 = Me, Et; R_2 = Me, Et, Ph) under microwave irradiation in open vessels to give the corresponding pyrimido[1,6-*a*]benzimidazoles **175** [100] (Scheme 73).

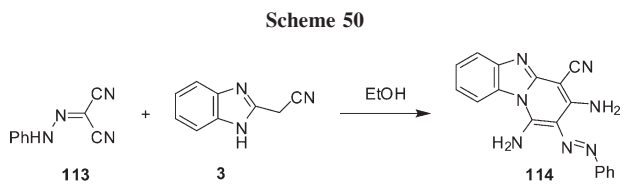
Compound **3** condensed with aminoesters (**176**, R_1 = Ph, 4-$EtOC_6H_4$, 2- and 4-ClC_6H_4, 2,5-$Cl_2C_6H_3$, 2-naphthyl, PhNMe; R_2 = alkyl) to give 60–75% cyanoketones **177**, which underwent acid-catalyzed intramolecular cycloaddition to give 78–87% title compounds (**178**, R_1 = Ph, 4-$EtOC_6H_4$, 2-ClC_6H_4, PhNMe). Refluxing (**178**, R_1 = Ph) with anhydrides or acid chlorides gave 72–98% tetracyclic cyclocondensation products (**179**, R_3 = Me, Et, 2-XC_6H_4; X = H, F, Cl, Br, iodo) [101] (Scheme 74).

Badawey *et al*. [102] reported that **3** (R = H, Me) was allowed to react with ethoxycarbonylisocyanate at

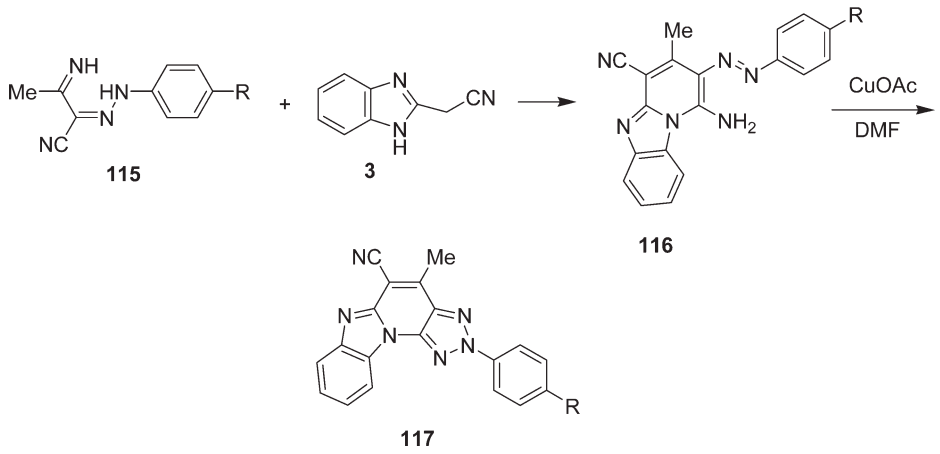
Scheme 48



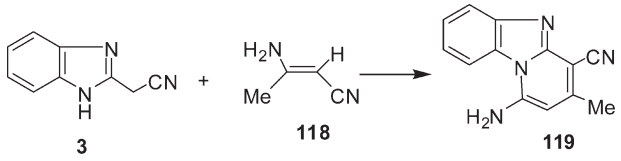
Scheme 50



Scheme 51



Scheme 52

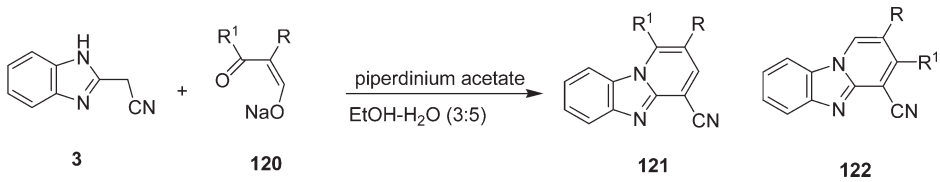


room temperature to afford the intermediate **180**, which was readily cyclized in boiling bromobenzene to the corresponding 7,8-disubstituted-1,3-dioxo-*2H*,*5H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitrile **181** in excellent yield (Scheme 75).

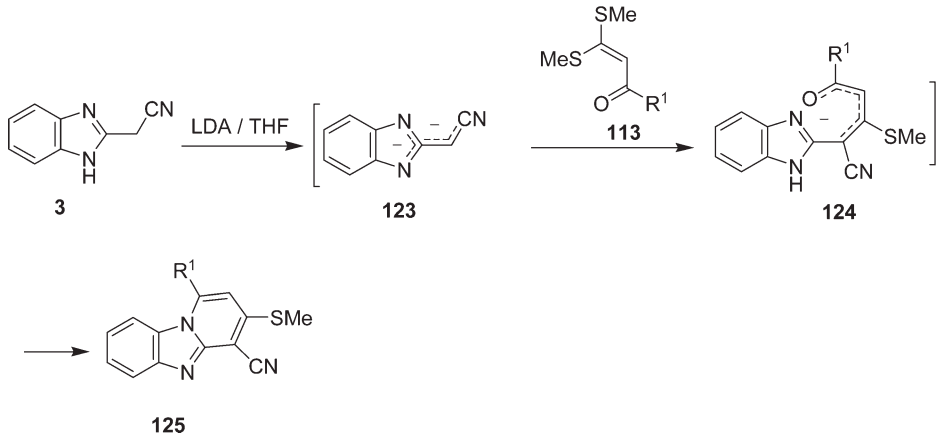
Reaction of **3** with cyanoamide (**182**, R = SMe, SCH_2Ph, 4-phenylpiperazino, Me, 4-MeC_6H_4, 4-ClC_6H_4, 2-furyl, 2-thienyl; R_1 = SMe, SCH_2Ph, OMe) and β-diketones (**183**, R_2 = Me, Ph) gave the pyrimido[1,6-*a*]benzimidazole-4-carbonitrile **184**(Scheme 76) [103].

Compound **3** and 2-(2,2,2-trifluoro-*N*-methylacetamido)benzoyl chloride **185** gave the 1-acylbenzimidazole **186**, which was cyclized with sodium *t*-butoxide in pyridine to give quinolone **187**, which was cyclized with

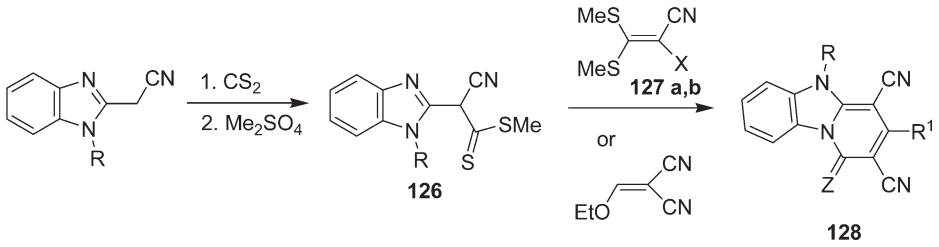
Scheme 53



Scheme 54



Scheme 55



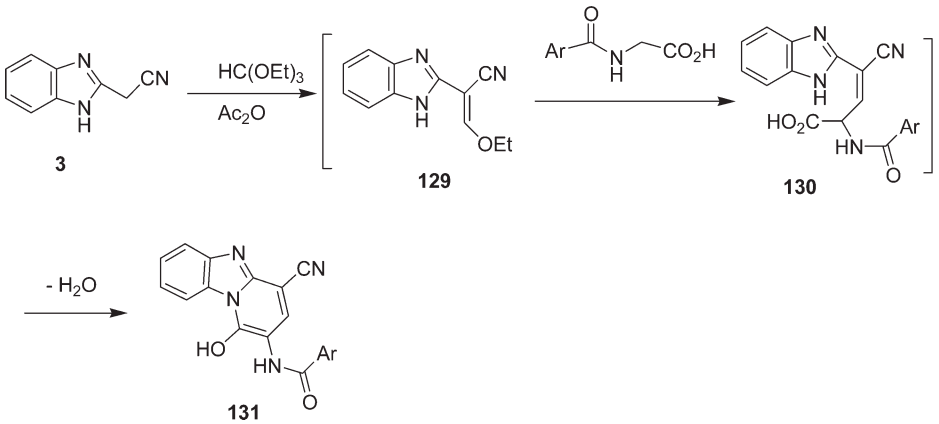
acid chlorides, anhydrides, or triethylorthoformate to give **188** (Scheme 77) [104].

Pyrimido[1,6-*a*]benzimidazole **189** was prepared by heating of **3** with trichloroacetonitrile followed by cyclocondensation with triethylorthoformate (Scheme 78) [105].

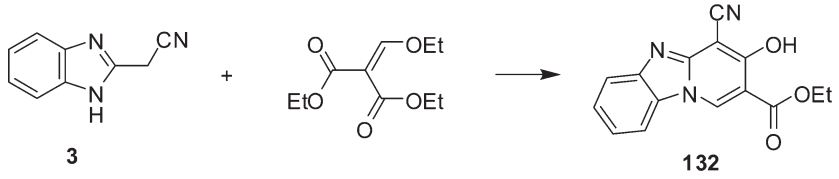
2-Amino-3-(benzimidazol-2-yl)-1,8-naphthyridine **190** was obtained by condensation of 2-aminonicotinaldehyde with **3**. 7-Arylbenzimidazo[1′,2′:1,6]pyrimido[4,5-*b*][1,8]naphthyridines (**192**, R = Ph, 4-MeC_6H_4, 2-thienyl, *etc*.) were prepared by oxidation of the 6,7-dihydro derivatives **191**, which were obtained by condensation of benzaldehydes with 2-amino-3-(2-benzimidazolyl)-1,8-naphthyridine **190** (Scheme 79) [106].

Pyrroloquinoline **194** was prepared in good yield by treating 1*H*-benzimidazole-2-acetonitrile **3** with quinoline derivative **193** in refluxing pyridine containing sodium *t*-butoxide. Cyclization of **194** by refluxing acetic anhydride gave 85% **195** (Scheme 80) [107].

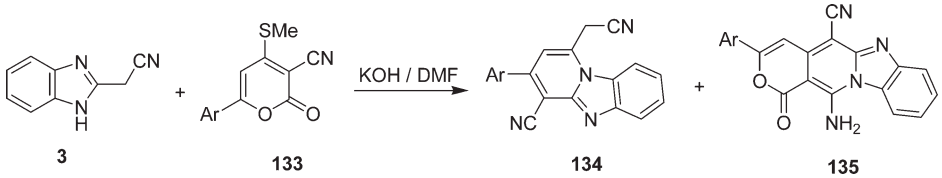
Scheme 56



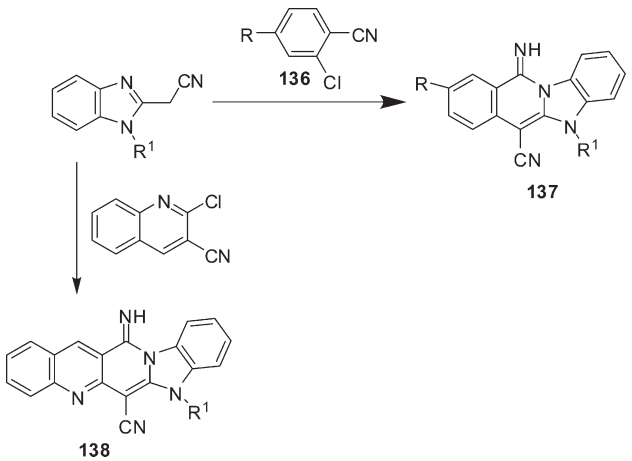
Scheme 57



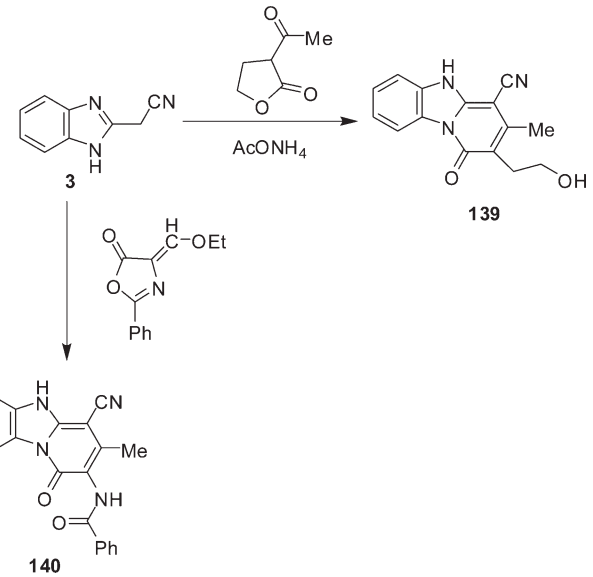
Scheme 58



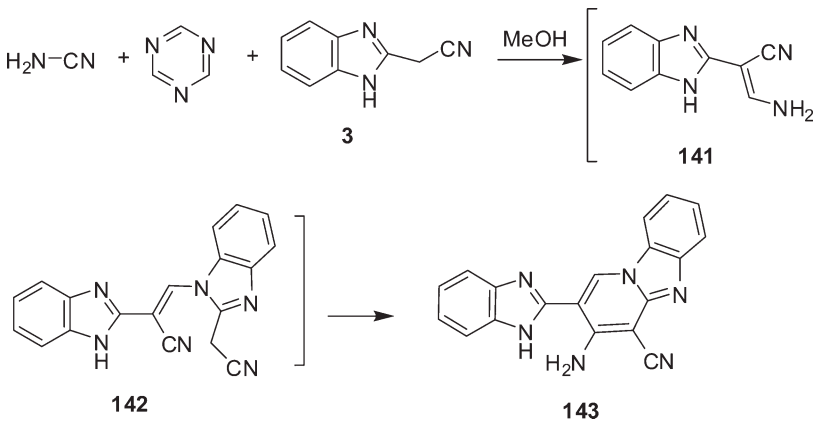
Scheme 59



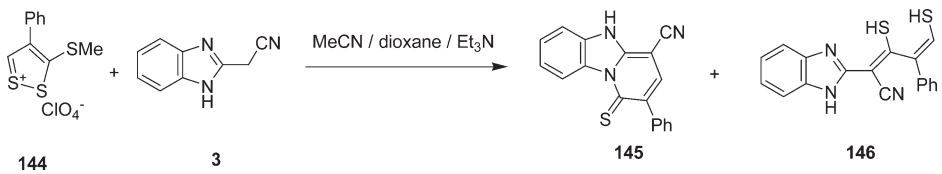
Scheme 60



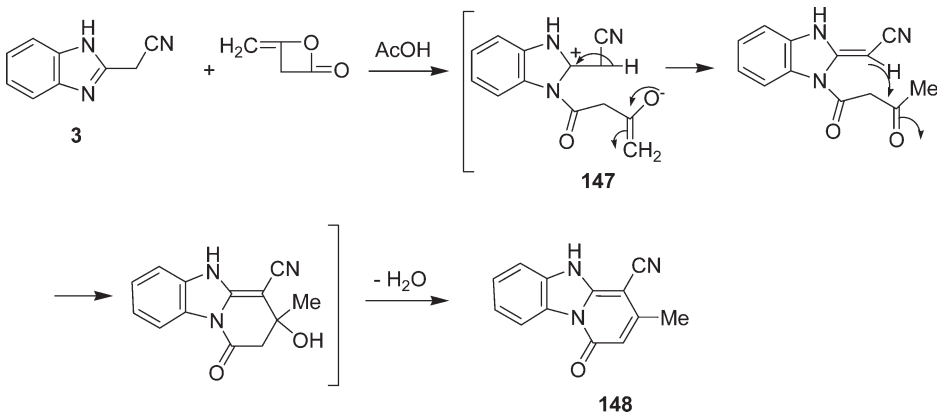
Scheme 61



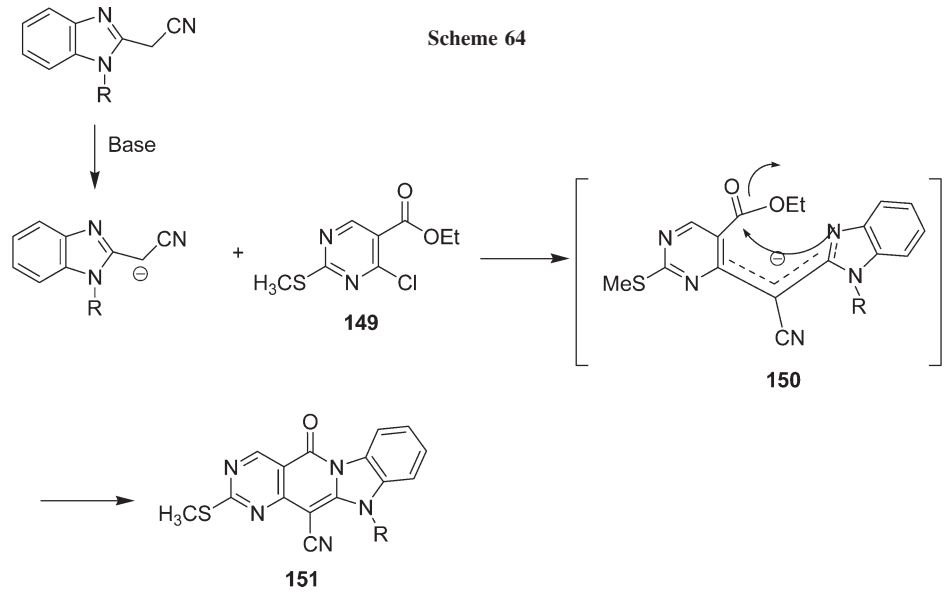
Scheme 62



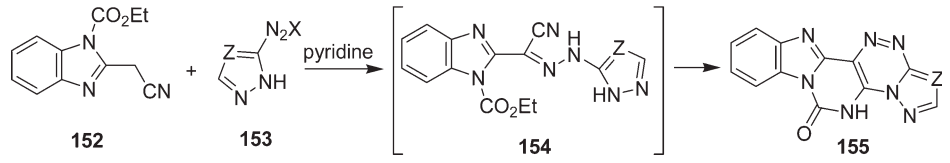
Scheme 63



Scheme 64



Scheme 65

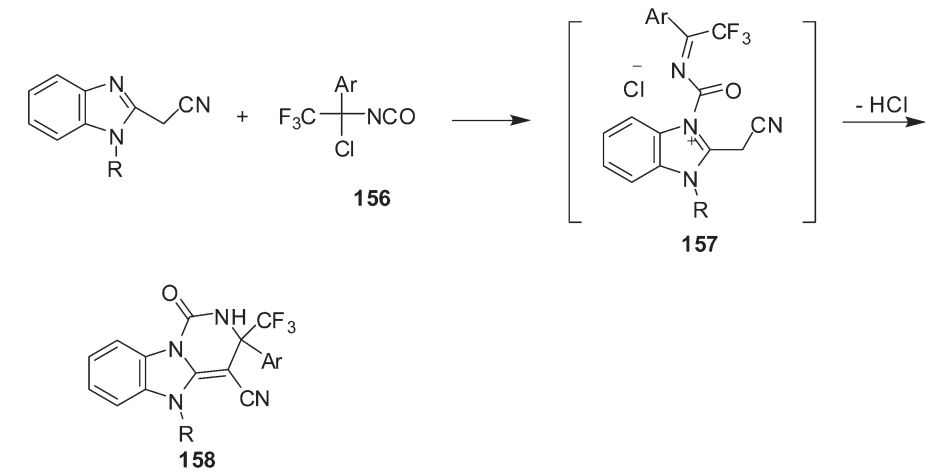


Benzimidazolylchromones (**198**, X = O, S) were prepared in high yields by cyclocondensation of hydroxy aromatic carboxylic acid methyl esters or 2-mercaptomethylbenzoate **197** with **3**. Acylation of **198** with acid chlorides (R = Me, Ph, Pr) gave benzimidazolobenzothiopyranopyrimidine **199** (Scheme 81) [108–110].

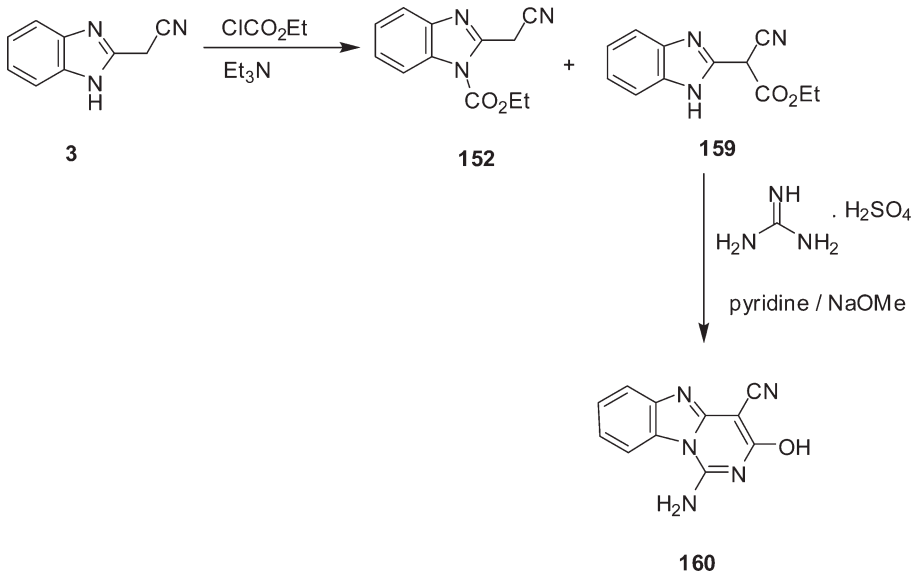
Cyclocondensation of **3** with hydrazones (**200**, R_1 = H, 2-, 3-, 4-Me, 4-Br) gave 90–99% **201** which were cyclized by acyl chlorides or anhydrides to give 80–94% **202** [R_1 as above, R_2 = H, Me, Et, Ph, 3,4,5-$(MeO)_3C_6H_2$] [110,111] (Scheme 82).

Treatment of 2,3,5-trimethyl-1,4-benzoquinone with **3** (R = H, Me) gave 2-amino-3-(benzimidazol-2-yl)benzo[*b*]furans **203** in high yield, respectively. Compound **203** were converted to 87–98% **204** (R_1 = R_2 = H; R_1 = Me, R_2 = Ac; R_1 = Et, R_2 = COEt; R_1 = Pr, R_2 =

Scheme 66

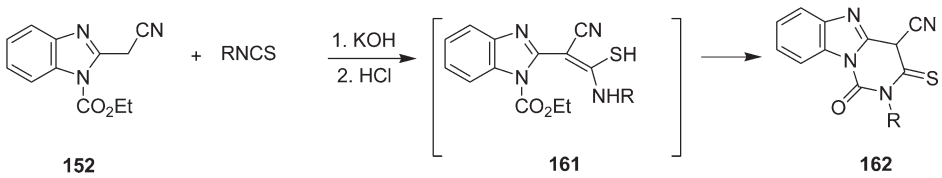


Scheme 67



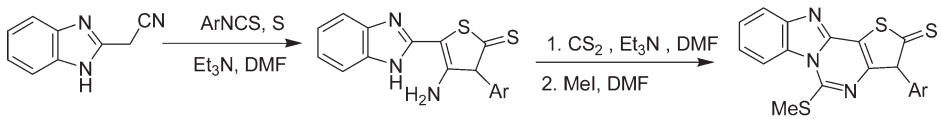
3 152 159 160

Scheme 68



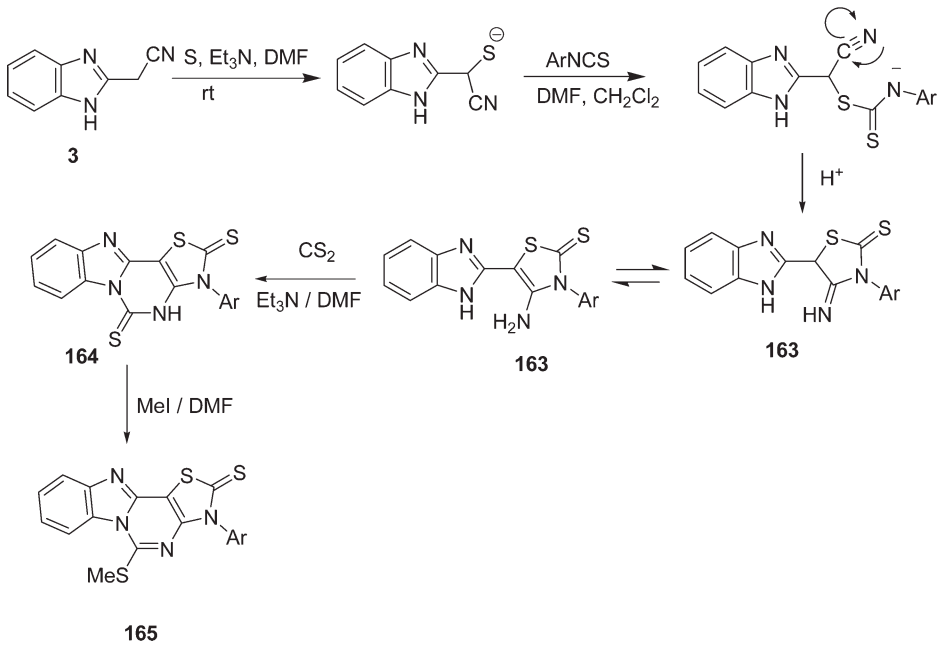
152 161 162

Scheme 69



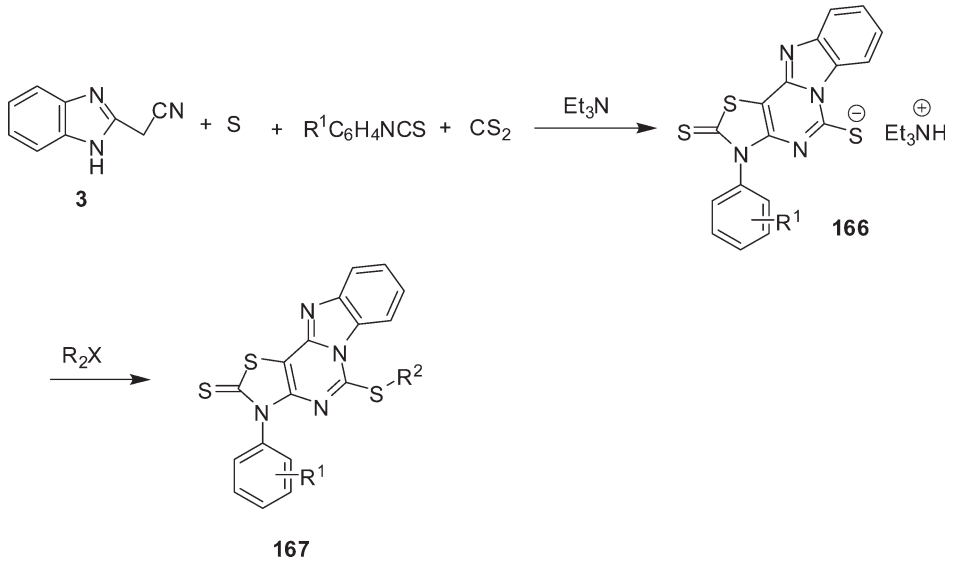
3 163 164

Scheme 70

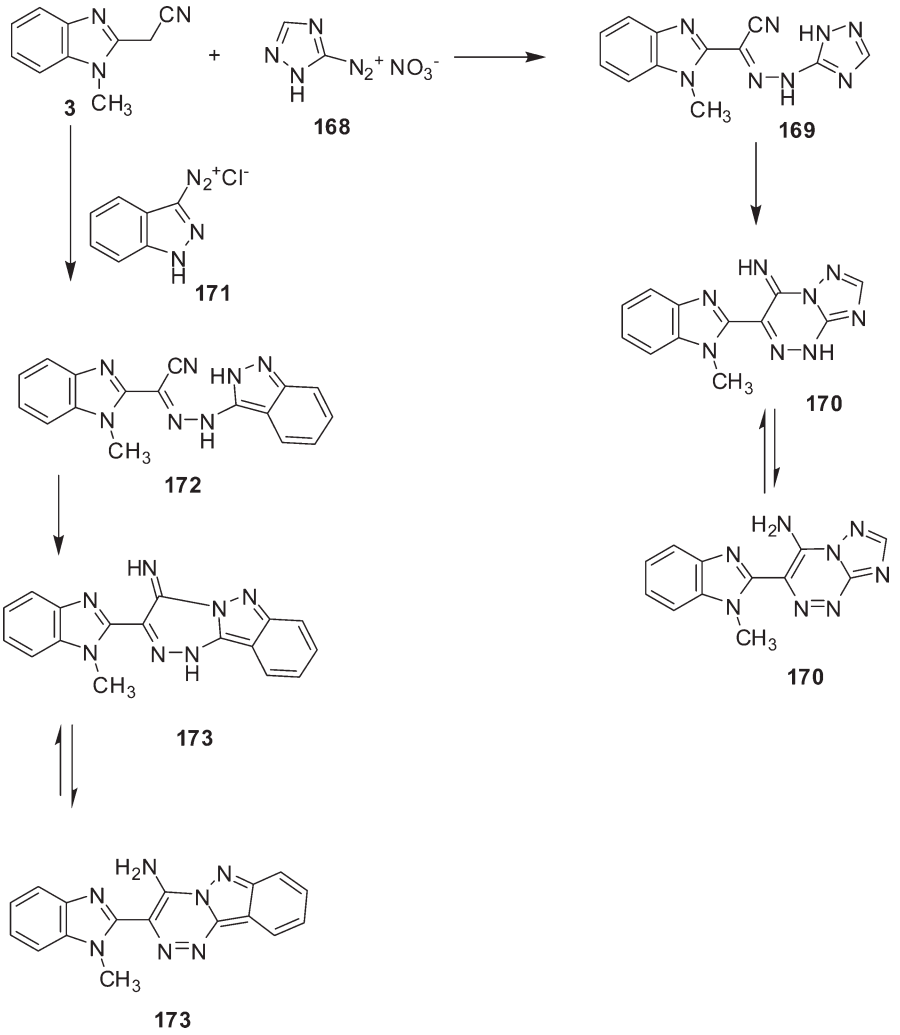


3 163 163 164 165

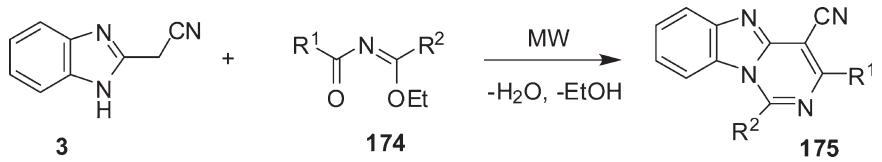
Scheme 71



Scheme 72

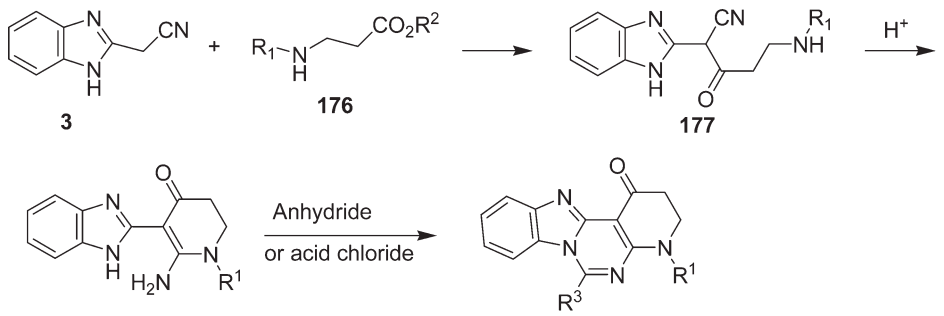


Scheme 73



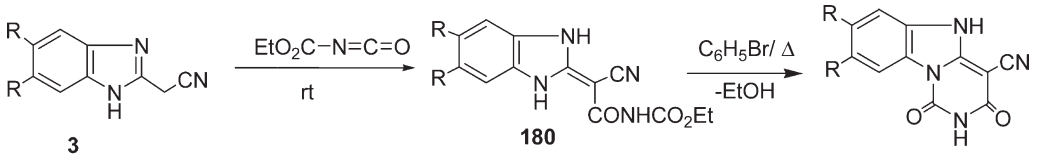
3 174 175

Scheme 74



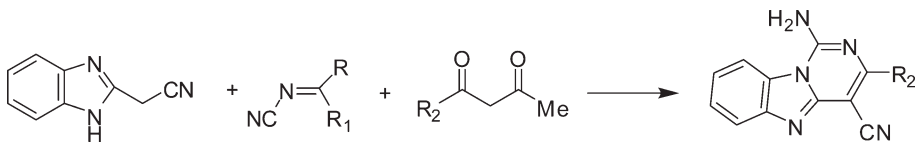
3 176 177 178 179

Scheme 75



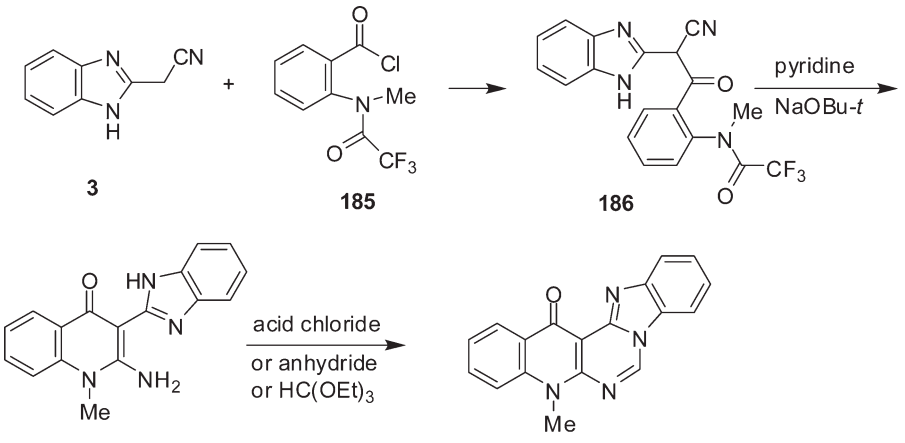
3 180 181

Scheme 76



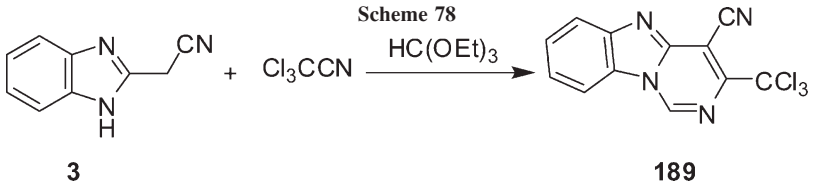
3 182 183 184

Scheme 77

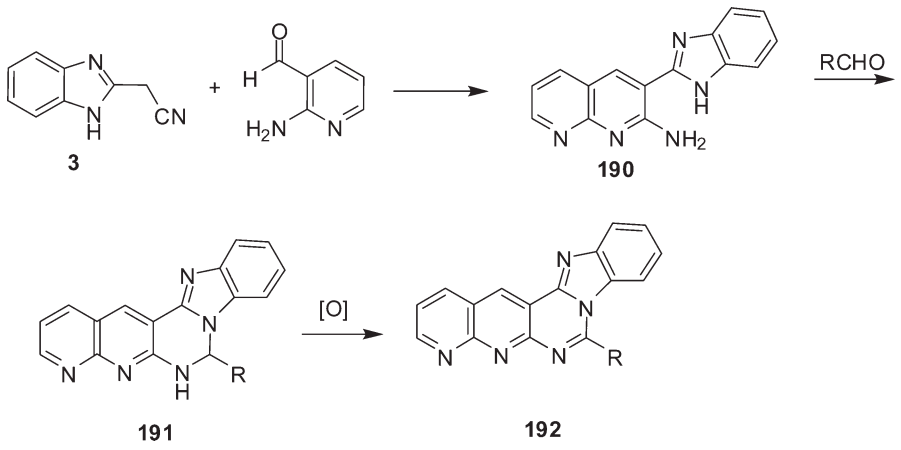


3 185 186 187 188

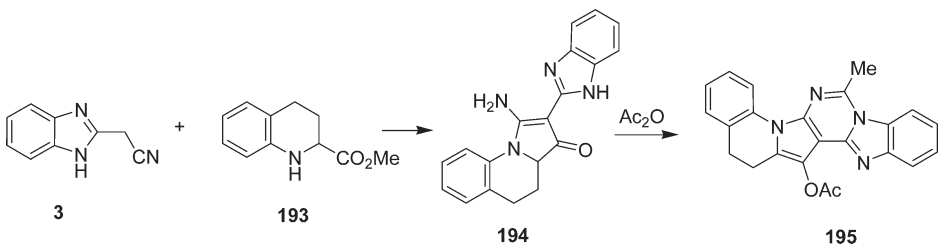
Scheme 78



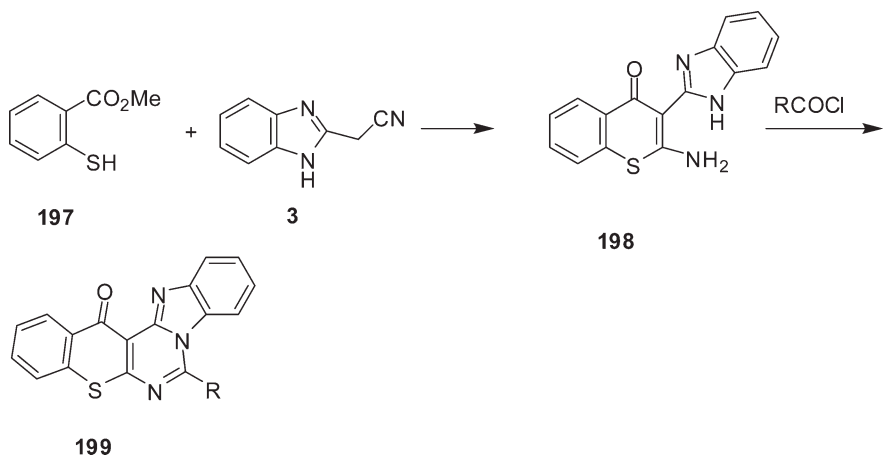
Scheme 79



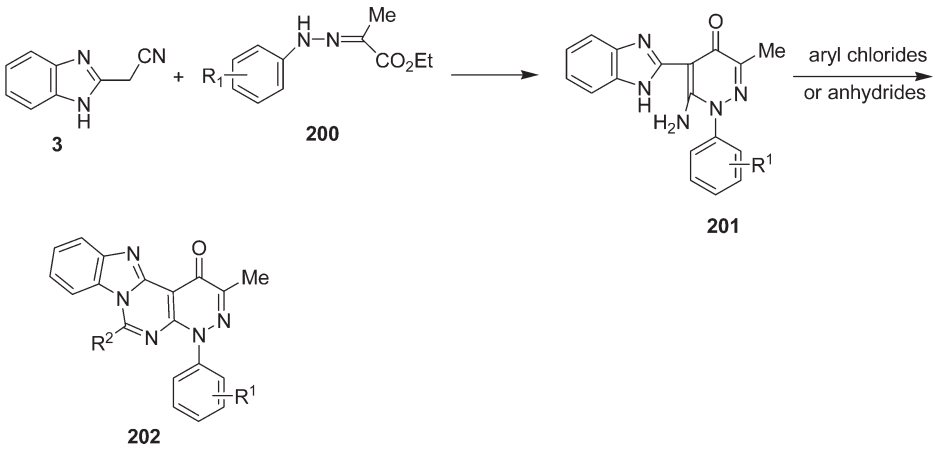
Scheme 80



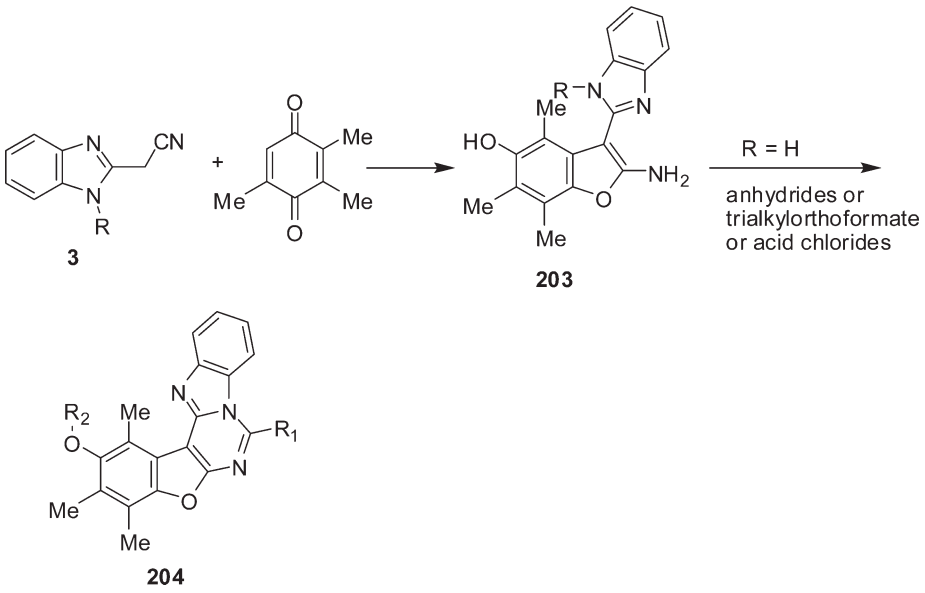
Scheme 81



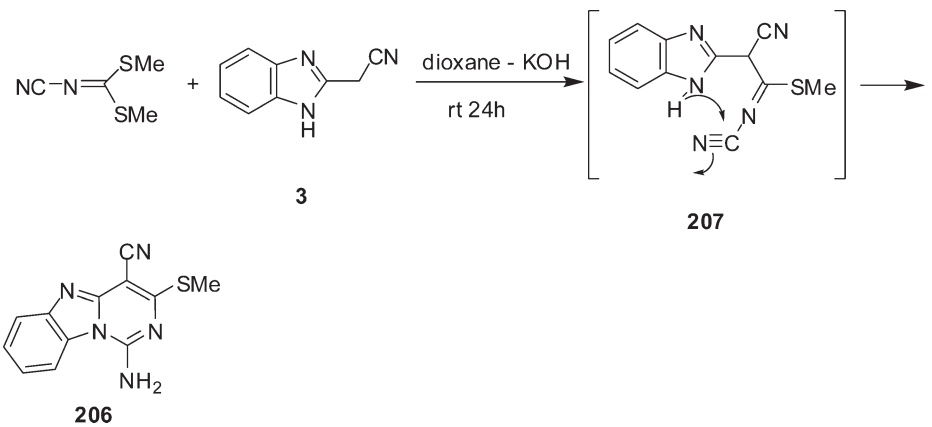
Scheme 82



Scheme 83



Scheme 84



COPr; R_1 = Ph, R_2 = Bz) by treatment with anhydrides trialkylorthoformate or acid chlorides (Scheme 83) [112].

Reaction of dimethyl *N*-cyanodithioiminocarbonate with **3** can be utilized for the synthesis of 2-amino-5-cyano-4-(methylthio)pyrimidino[1,6-*a*]benzimidazole **206**, by reaction in dioxane containing a catalytic amount of potassium hydroxide at room temperature (Scheme 84) [113].

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