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# Synthesis of pyrido[1,2-*a*]benzimidazoles and other fused imidazole derivatives with a bridgehead nitrogen atom

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**Abstract. Main methods for the synthesis of fused imidazole derivatives with a bridgehead nitrogen atom are systematically considered and summarized. The reaction mechanisms that underlie the methods for the synthesis of pyrido[1,2-*a*]-benzimidazoles and related compounds are described. Biological properties and mechanisms of the biological activity of fused azaheterocycles are discussed. The bibliography includes 152 references.**

## I. Introduction

Nitrogen-containing heterocycles have attracted considerable attention of researchers in organic chemistry and allied sciences (medicine, pharmacology, genetics and so on) over a long period of time. Among these compounds, polycyclic imidazole derivatives containing a nitrogen atom common to several rings find most use at the present time,[1, 2] because they are bioisosteric analogues of nitrogenous bases of nucleic acids. In addition, these heterocyclic systems exhibit high fluorescence activity due to the presence of a conjugation system and chromophore groups.[3, 4] Hence, these compounds can be used as fluorescent labels in genetic investigations.

It should be noted that, although these compounds are widespread in nature,[5, 6] they are mainly prepared by synthetic methods. There is voluminous literature on the methods for the synthesis of these compounds and their biological activity. However, there are no reviews on this subject. The goal of our review is to consider the known synthetic approaches to fused imidazole derivatives with a bridgehead nitrogen atom and summarize data on the mechanisms of the biological activity of these compounds.

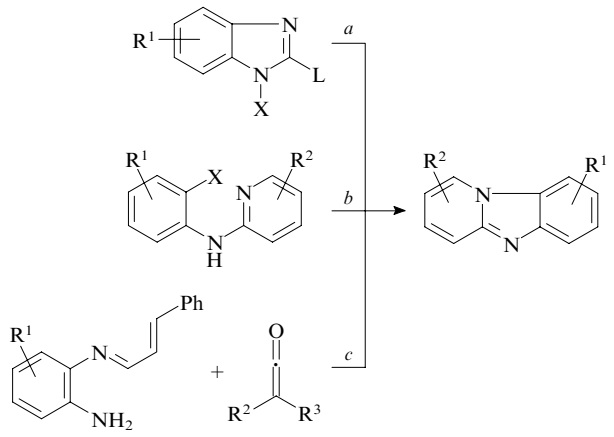
Methods for the synthesis of pyrido[1,2-*a*]benzimidazoles are most widely covered in the literature. Hence, the procedures for the formation of this heterocyclic system are considered in this review in most detail. Based on the analysis of the literature, three approaches to these derivatives can be distinguished:

1) methods for the synthesis of fused polyheterocycles based on the formation of the pyridine ring (Scheme 1, path *a*);

2) methods for the formation of the imidazole ring in a polyfused structure (see Scheme 1, path *b*);

3) synthetic approaches resulting in the simultaneous formation of several heterocycles in a fused system (see Scheme 1, path *c*).

Scheme 1




These methods are also used for the synthesis of related fused polycyclic structures. The data will be considered in terms of this classification.

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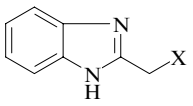
## II. Formation of polyfused azaheterocycles based on substituted benzimidazoles

As mentioned above, one of approaches to pyrido[1,2-*a*]-benzimidazoles and related polycyclic imidazole derivatives with a bridgehead nitrogen atom is based on the α-annulation of an azaheterocycle to benzimidazole. This group of methods includes reactions of substituted benzimidazoles with different reagents, whose nature dictates the reaction conditions.

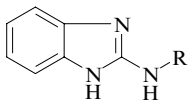
### 1. Condensation of benzimidazoles with bifunctional reagents

Numerous synthetic methods, which are well covered in the literature and are widely used in the practice for the construction of pyrido[1,2-*a*]benzimidazoles and related systems, are based on the cyclocondensation of benzimidazoles with bifunctional reagents.[7–15]

In the overwhelming number of studies, 2-substituted benzimidazoles served as the starting compounds in these transformations. The latter can act as C,N- (structure **A**) or N,N-dinucleophiles (structure **B**). These substrates can be used to synthesize various polyfused systems by reactions of such bifunctional reagents as alkoxy- and alkylsulfanylethylenes, cyano- and oxovinylamines and derivatives of α,β-unsaturated carboxylic acids.



**A**



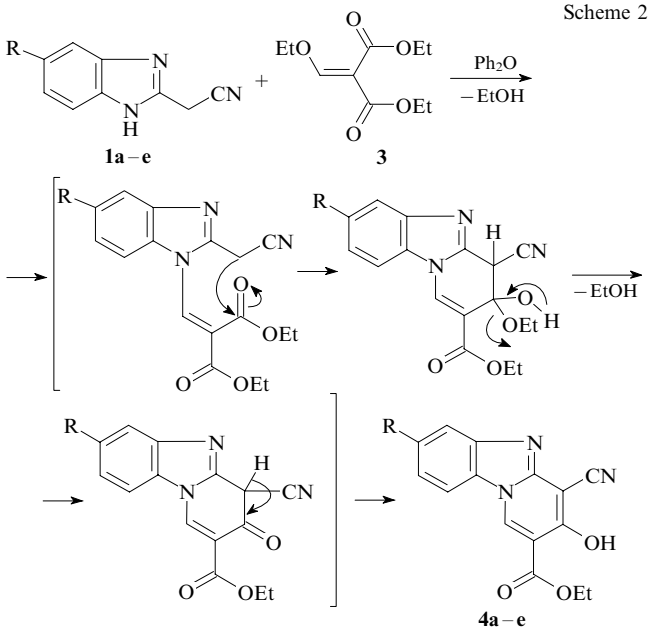
**B**

X = H, CN, Bz, Ac, C(O)Et; R = H, $CH_2CH_2OH$, $CH(NH_2)_2$

The reactions of alkoxyethylenes containing a good nucleofuge at the double bond with 1*H*-benzimidazol-2-ylacetonitriles **1** (see Ref. 16) and 1*H*-benzimidazole-2-amine (**2a**)[17] involve the nucleophilic vinylic substitution followed by the cyclization of the condensation product. Thus, compounds **1a–e** react with diethyl ethoxymethylenemalonate (**3**) in diphenyl ether at 250 °C within 5 min to form the target products **4a–e** in 70%–80% yields (Scheme 2).[16]

The reactions of 1*H*-benzimidazole-2-amine (**2a**) with α,β-unsaturated carboxylic acid esters **3** and **5** at 110–120 °C afford 3-substituted 4-oxopyrimido[1,2-*a*]benzimidazoles **6** and **7** within 0.5–1.25 h (Scheme 3).[17] It should be noted that amino derivative **8** predominates in the mixture of products obtained in the reaction with the use of reagent **5**.

Scheme 2



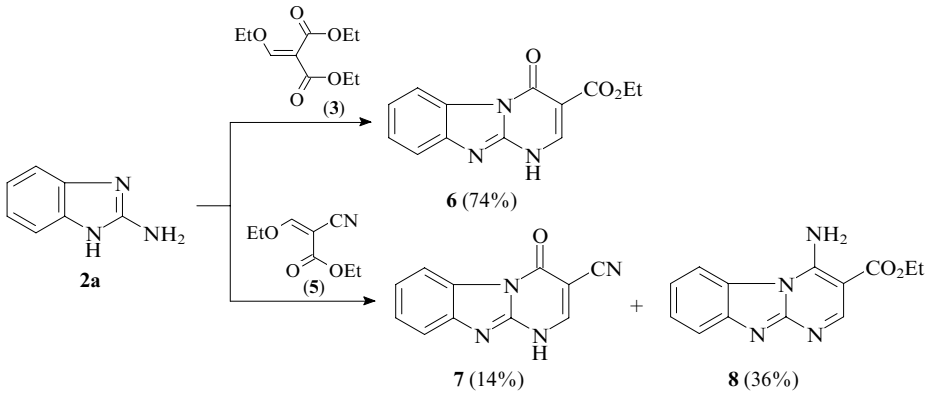
**1a–e** **3** **4a–e**

R = H (**a**), Me (**b**), Cl (**c**), OMe (**d**), $NO_2$ (**e**)

The [3 + 3]-cyclocondensation of the 1*H*-2-R-benzimidazole dianion, which is generated by the abstraction of two protons from the methylene (in compound **1a**) or methyl (in compound **9**) group and the amino group, with α-oxoketene dithioacetals **10a**,**b** was described by Panda *et al.*[18] Depending on the nature of the substituent in position 2 of benzimidazole ($CH_2CN$ or Me), pyrido[1,2-*a*]benzimidazoles are produced through different pathways (Scheme 4).

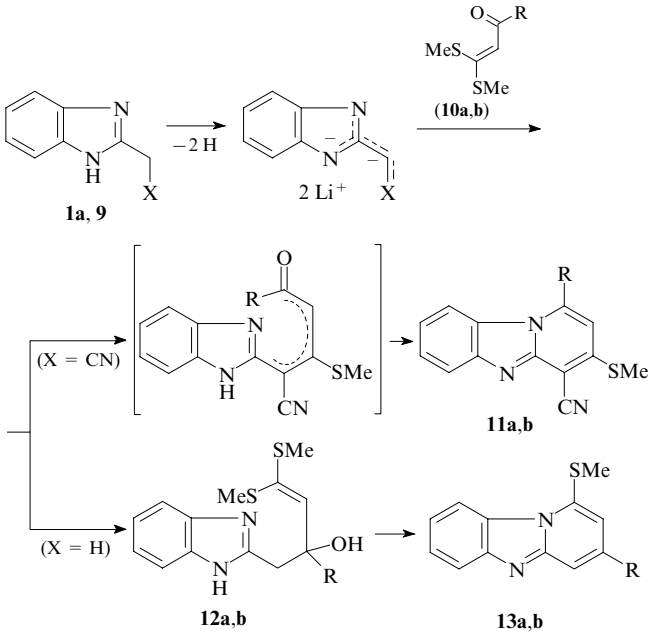
Thus, the electron-withdrawing cyano group in compound **1a** contributes to the stabilization of the dianion, resulting in that its cyclocondensation with 3,3-bis(methylsulfanyl)-1-phenylprop-2-en-1-one (**10b**) or 4,4-bis(methylsulfanyl)but-3-en-2-one (**10a**) proceeds in one step through 1,4-addition–elimination followed by heterocyclization. The dianion was prepared by the addition of lithium diisopropylamide (LDA) to a solution of compound **1a** in THF at 0 °C followed by the addition of a solution of dithioacetal **10** in THF. After 12 h, the reaction mixture was treated with $NH_4Cl$, and products **11a**,**b** were extracted with chloroform. The yields of compounds **11a**,**b** were 72% and 76%, respectively.

Scheme 3



**2a** **6** (74%) **7** (14%) **8** (36%)

Scheme 4

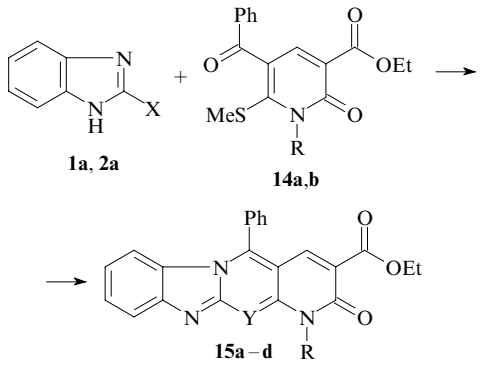


X = CN (**1a**), H (**9**); **10**–**13**: R = Me (**a**), Ph (**b**)

The reaction of the 2-methyl-1*H*-benzimidazole dianion (**9**) with dithioacetals **10a**,**b** begins by going through the 1,2-addition to form 1-(1*H*-benzimidazol-2-yl)-4,4-bis(methylsulfanyl)but-3-en-2-ols **12a**,**b** as intermediates. The latter undergo cyclization under heating to 90–100 °C in 85% phosphoric acid for 4–5 h. The target products **13a**,**b** were isolated in 70% yield.

The selective cyclocondensation of N-substituted 5-benzoyl-3-ethoxycarbonyl-6-methylsulfanyl-1,2-dihydropyridin-2-ones (**14a**,**b**) with benzimidazoles **1a** and **2a** produced a series of new tetracyclic systems **15a**–**d** (Scheme 5).[19] The reaction was performed by heating the reactants under reflux in hexanol for 4 h (for compound **1a**) or in isopropyl alcohol for 7 h (for compound **2a**). The yields of the products varied from 45% to 56%.

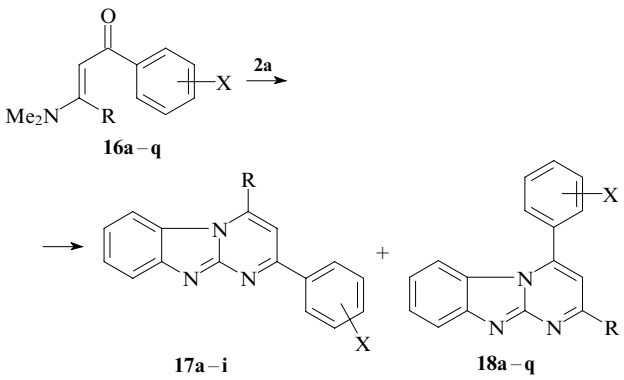
Scheme 5



X = $CH_2CN$ (**1a**), $NH_2$ (**2a**); Y = C(CN) (**15a**,**b**), **N** (**15c**,**d**);
R = Me (**14a**, **15a**,**c**), Et (**14b**, **15b**,**d**)

The selectivity of the cyclocondensation of benzimidazolamine **2a** with 3-(dimethylamino)-1-phenylprop(or but)-2-en-1-ones **16a**–**q** containing a substituted benzene ring was investigated by Tseng *et al.*[20] The dimethylamino group at the double bond in these compounds is a good leaving group. The reactions of compounds **16a**–**f** containing the unsubstituted double bond (R = H) give pyrimido[1,2-*a*]-benzimidazoles **17a**–**f** and **18a**–**f** in an equimolar ratio in a total yield of 41%–56%. In the case of R = Me or Ph (compounds **16g**–**q**), only products **18g**–**q** were isolated. Depending on the nature of the substituent in the aromatic moiety of **16**, the reaction can afford products **17g**–**i** as an impurity (1%–2%). The reaction is performed by heating the starting compounds under reflux in glacial acetic acid for 4–5 h (Scheme 6).

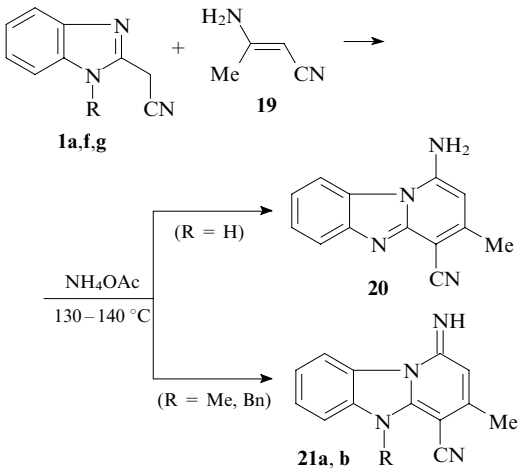
Scheme 6



R = H: X = 3-$CF_3$ (**a**), 3-Cl (**b**), 4-Cl (**c**), 4-Me (**d**), 3-OMe (**e**), H (**f**); R = Me: X = 3-$CF_3$ (**g**), 3-Cl (**h**), 4-Me (**i**), 4-Cl (**j**), H (**k**); R = Ph: X = 3-$CF_3$ (**l**), 3-Cl (**m**), 4-Cl (**n**), 4-Me (**o**), 3-OMe (**p**), H (**q**)

It was shown[21] that benzimidazole **1a** reacts with an equimolar amount of β-aminocrotonic acid nitrile (**19**) in the presence of ammonium acetate upon heating (130–140 °C) to form pyridobenzimidazole **20** (Scheme 7). Under similar conditions, N-substituted benzimidazoles **1f**,**g** give products **21a**,**b** in 64% and 47% yields, respectively.

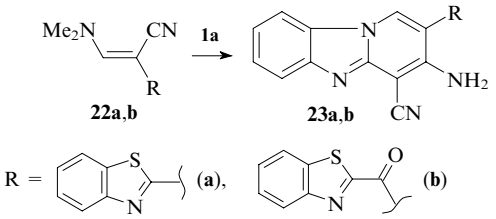
Scheme 7



R = H (**1a**), Me (**1f**, **21a**), Bn (**1g**, **21b**)

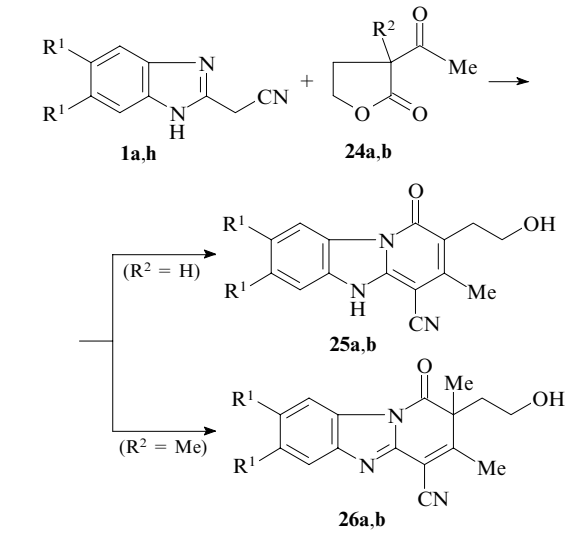
Pyrido[1,2-*a*]benzimidazoles containing the benzothiazole (**23a**) or benzothiazol-2-ylcarbonyl (**23b**) moiety as the substituent were synthesized by heating compound **1a** with (dimethylamino)acrylonitriles **22a**,**b** in ethanol in the presence of catalytic amounts of piperidine.[22,23] The yield of product **23a** was 81% (Scheme 8).

Scheme 8



Fused polyheterocycles with a bridgehead nitrogen atom are often synthesized by the reactions of benzimidazoles with carbonyl derivatives of tetrahydrofuran, 4*H*-chromene or 1,3-oxazole. Thus, the cyclocondensation of compounds **1a**,**h** with 3-acetyldihydrofuran-2(3*H*)-ones **24a**,**b** performed by heating on an oil bath in the presence of ammonium acetate for 1 h affords heterocyclic systems **25a**,**b** and **26a**,**b** (Scheme 9).[24]

Scheme 9

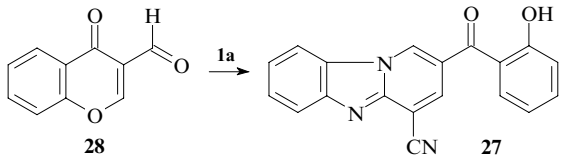


$R^1$ = H (**1a**, **25a**, **26a**), Me (**1h**, **25b**, **26b**); $R^2$ = H (**24a**), Me (**24b**)

Either 1,5-dihydro- (**25**) or 1,2-dihydropyrido[1,2-*a*]benzimidazoles (**26**) are produced depending on the nature of the substituent in compound **24**. The yields of the products vary from 37% to 90%.

Substituted pyrido[1,2-*a*]benzimidazole **27** was synthesized in 87% yield starting from compound **1a** and 4-oxo-4*H*-chromene-3-carbaldehyde (**28**) (Scheme 10).[25] The reaction proceeds in DMF in the presence of an excess of trimethylchlorosilane at 25 °C during a long period of time (12–24 h).

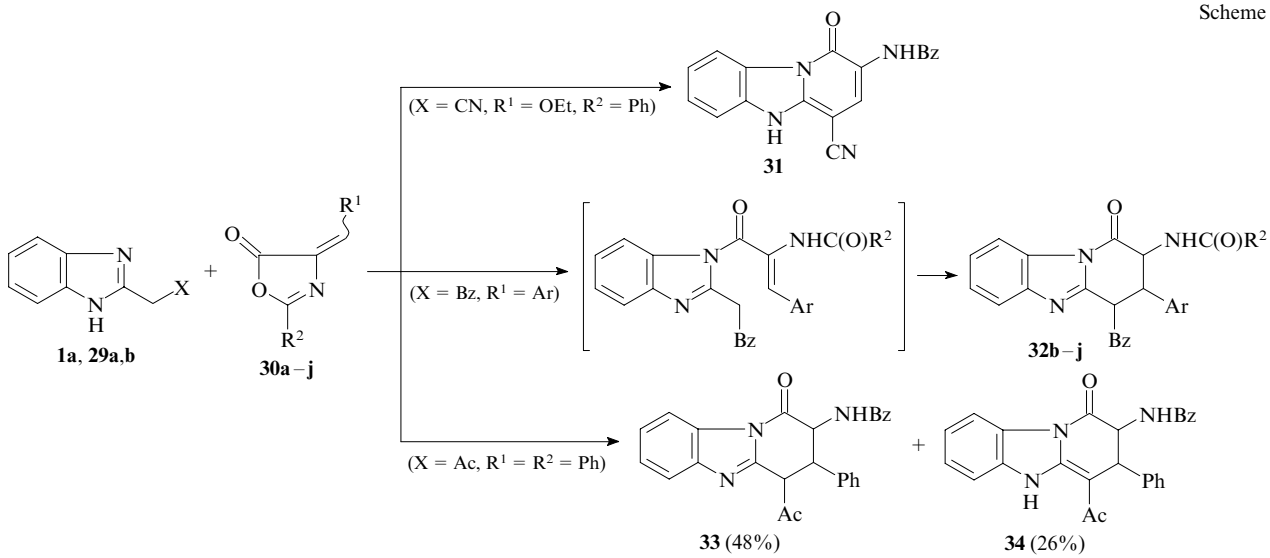
Scheme 10



In the studies,[24,26,27] the pyrido[1,2-*a*]benzimidazole system was constructed by heating 1*H*-benzimidazoles **1a** or **29a**,**b** with 1,3-oxazol-5-(4*H*)-one derivatives **30a**–**j** under reflux in pyridine or chlorobenzene for 1–2 h (Scheme 11). The authors noted the regioselectivity of the formation of the pyridine ring in the reactions with the use of substrates **1a** and **29a**. Under these conditions, the former substrate reacts with 1,3-oxazol-5(4*H*)-one **30a** to give pyrido[1,2-*a*]benzimidazole **31**, whereas the reactions of the latter with aryl-substituted 1,3-oxazol-5(4*H*)-ones **30b**–**j** afford products **32b**–**j** in yields from 70% to 95%. By contrast, the reaction of 1*H*-2-acetylmethylbenzimidazole (**29b**) with 1,3-oxazol-5(4*H*)-one **30b** is complicated by prototropic isomerism resulting in the formation of a mixture of isomers.[27] The isomers were separated by fractional crystallization in chlorobenzene, in which tautomer **34** having an enamine structure is much more readily soluble. It was found that compounds **33** and **34** are stable in solutions in DMSO-$d_6$ for 3 h. This made it possible to identify the products by $^1$H NMR spectroscopy.

The microwave-induced (MW-induced) reaction of benzimidazole-2-amine (**2a**) with 1,3-oxazol-5(4*H*)-ones **30b**–**e**,**k**,**l** in ethylene glycol was documented.[28] The reac-

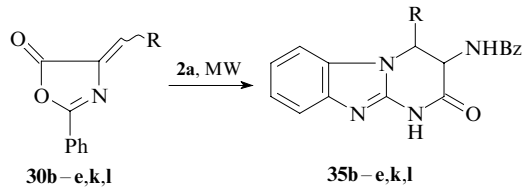
Scheme 11



**29**: X = Bz (**a**), Ac (**b**); **30**, **31**: $R^2$ = Ph: $R^1$ = OEt (**a**), Ph (**b**), 4-$MeOC_6H_4$ (**c**), 4-$ClC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), 3-Py (**f**), 4-Py (**g**); $R^2$ = Me: $R^1$ = Ph (**h**), 4-$MeOC_6H_4$ (**i**), 4-$ClC_6H_4$ (**j**); Py is pyridyl

tion proceeded at 110 °C within 4 – 9 min and gave products **35b** – **e**,**k**,**l** in 71% – 81% yields (Scheme 12).

Scheme 12

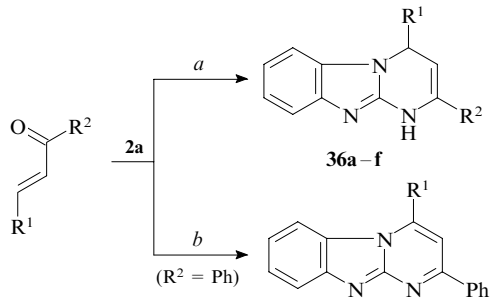



**30b** – **e**,**k**,**l** **35b** – **e**,**k**,**l**

R = Ph (**b**), 4-MeOC$_6$H$_4$ (**c**), 4-ClC$_6$H$_4$ (**d**), 4-O$_2$NC$_6$H$_4$ (**e**), 3,4,5-(MeO)$_3$C$_6$H$_2$ (**k**), 2-Th (**l**); Th is thienyl

Data on the construction of fused azaheterocycles by the annulation of a pyrimidine ring onto benzimidazolamine **2a** in the course of the thermal [29] or microwave-induced [30] condensation with α,β-unsaturated ketones (Scheme 13) are available in the literature. Thus, one isomer was shown [29] to be formed on heating compound **2a** with α,β-unsaturated ketones under reflux in n-butanol or DMF (conditions *a*). After cooling, the corresponding product **36** precipitated (yields 39% – 80%).

Scheme 13




**36a** – **f**

**37a**,**g** – **j**

R$^1$ = R$^2$ = Ph (**a**); R$^1$ = 3,4-Cl$_2$C$_6$H$_3$, R$^2$ = 3,4-(MeO)$_2$C$_6$H$_3$ (**b**); R$^1$ = 2-Th, R$^2$ = 4-FC$_6$H$_4$ (**c**); R$^1$ = Ph, R$^2$ = n-C$_6$H$_{11}$ (**d**); R$^2$ = Me: R$^1$ = Ph (**e**), 4-ClC$_6$H$_4$ (**f**); R$^2$ = Ph: R$^1$ = 4-MeOC$_6$H$_4$ (**g**), 3-O$_2$NC$_6$H$_4$ (**h**), 2-HOC$_6$H$_4$ (**i**), R$^1$ = 3-ClC$_6$H$_4$ (**j**)

This reaction was also performed in ethanol under microwave irradiation at 25 °C for 3 – 4 min (conditions *b*) in the presence of a catalytic amount of piperidine.[30] In this case, substituted pyrimido[1,2-*a*]benzimidazoles **37a**,**g** – **j** were synthesized in 70% – 87% yields. The formation of aromatic compounds **37** is apparently attributed to the presence of atmospheric oxygen as an oxidant, whose effect is enhanced under microwave irradiation.

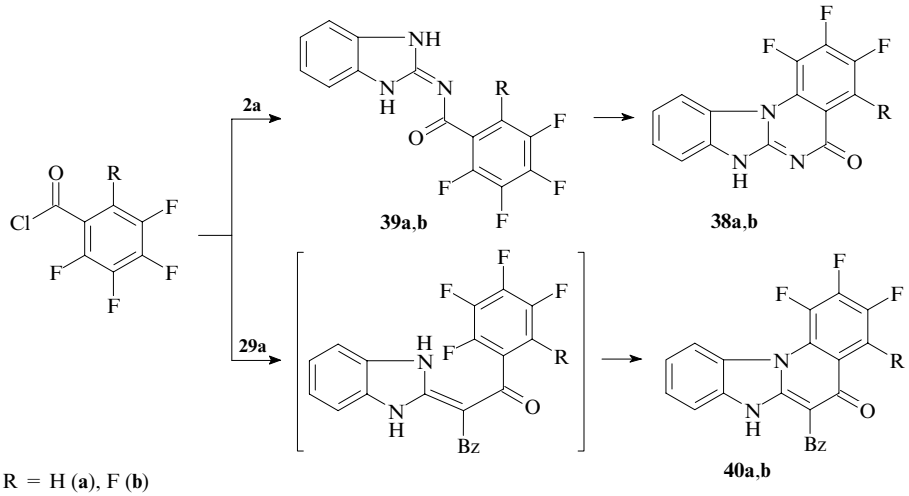
Polyfluorobenzoyl chlorides were used in the [3 + 3]-cyclocondensation with 2-substituted benzimidazoles. Thus, the two-step synthesis of benzimidazo[3,2-*a*]quinazolin-4-ones **38a**,**b** through the formation of intermediates **39a**,**b** (Scheme 14) was documented.[31] The latter were produced by the condensation of benzimidazolamine **2a** with tetra- and pentafluorobenzoyl chlorides under reflux in toluene for 2 h. The thermal cyclization of intermediates **39** in diphenyl ether affords products **38** in yields of at most 72% within 3 h (for compound **39a**). By contrast, the reaction of 1*H*-2-(1*H*-benzimidazol-2-yl)-1-phenylethanone (**29a**) with tetra- and pentafluorobenzoyl chlorides takes place in one step to give products **40a**,**b** in 73% and 81% yields, respectively.[32] The reaction was performed in the presence of triethylamine in a mixture of toluene and dichloromethane at room temperature for 24 h.

Esters of malonic acid derivatives or aliphatic 3-oxo acids are often used as 1,3-dielectrophiles. Thus, the condensation of 1*H*-benzimidazol-2-ylacetonitrile (**1a**) or ethyl 1*H*-benzimidazol-2-ylacetate (**29c**) with bis(2,4,6-trichlorophenyl) alkylmalonates (**41a** – **e**) or phenylmalonate (**41f**) affords compounds **42a** – **k**.[33] The subsequent deoxychlorination of the latter by heating under reflux in $POCl_3$ for 0.6 h gives products **43a** – **k** (Scheme 15).

The thermal cyclocondensation of N,N-dinucleophiles with aliphatic and cyclic carboxylic acid esters [34, 35] is an example of the synthetic approach to fused azaheterocycles with a bridgehead nitrogen atom. Thus, the reactions of 1*H*-benzimidazole-2-amines **2a** – **c** with ethyl acetoacetate (**44a**), its trifluoromethyl analogue **44b** and ethyl 2-oxocycloalkanecarboxylates **44c**,**d** in the absence of a solvent at 130 °C gave products **45a** – **g** in 14% – 36% yields within 1.25 h (Scheme 16).

The synthesis of 1,3-diphenyl-1*H*-benzo[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyridine-5-carbonitrile (**46a**) by the reaction of substituted 5-chloro-1*H*-pyrazole-4-carbaldehydes **47a** – **d** with benzimidazol-2-ylacetonitriles **1a**,**h** was described in several publications. The reaction is performed

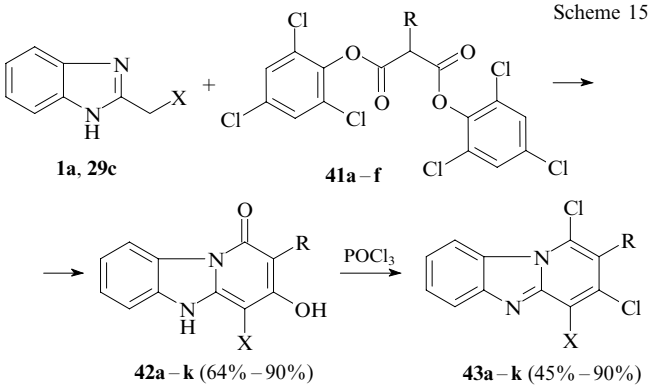
Scheme 14




**39a**,**b** **38a**,**b** **40a**,**b**

**38** – **40**: R = H (**a**), F (**b**)

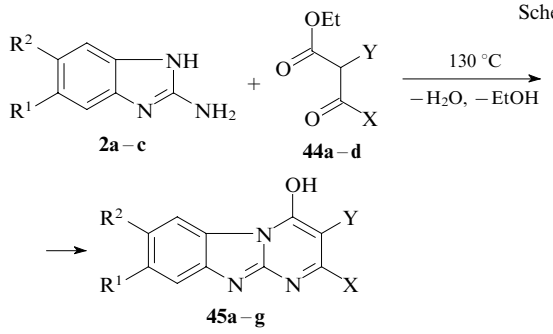
Scheme 15



**1a**, **29c** **41a–f** **42a–k** (64%–90%) **43a–k** (45%–90%)

X = CN (**1a**), $CO_2Et$ (**29c**); **41**: R = Me (**a**), Et (**b**), $Pr^i$ (**c**), $Bu^n$ (**d**), Bn (**e**), Ph (**f**); **42**, **43**: X = CN: R = Me (**a**), Et (**b**), $Pr^i$ (**c**), $Bu^n$ (**d**), Bn (**e**), Ph (**f**); X = $CO_2Et$: R = Me (**g**), Et (**h**), $Pr^i$ (**i**), Bn (**j**), Ph (**k**)

Scheme 16



**2a–c** **44a–d** **45a–g**

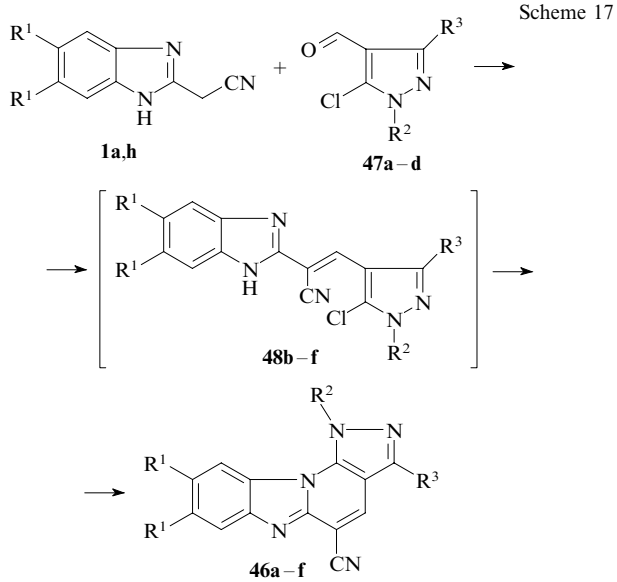
**2**: $R^1$ = $R^2$ = H (**a**), Me (**b**); $R^1$ = Cl, $R^2$ = H (**c**);
**44**: Y = H: X = Me (**a**), $CF_3$ (**b**); X–Y = $(CH_2)_4$ (**c**), $(CH_2)_3$ (**d**);
**45**: $R^1$ = $R^2$ = H: Y = H, X = Me (**a**); Y = H, X = $CF_3$ (**b**); X–Y = $(CH_2)_4$ (**c**), $(CH_2)_3$ (**d**); $R^1$ = $R^2$ = Me, Y = H: X = Me (**e**), $CF_3$ (**f**); $R^1$ = Cl, $R^2$ = Y = H, X = Me (**g**)

by heating in ethanol or DMF in the presence of pyridine,[36] piperidine or triethylamine as the catalyst [37, 38] (Scheme 17).

The yield of products **46** varies from 63% to 84%. It was noted [37, 38] that the reaction performed by heating in dioxane or ethanol in the absence of catalysts stops at intermediates **48**. Compounds **48b–e** were isolated in the individual state. Their cyclization takes place under reflux in DMF in the presence of triethylamine.[38]

It was shown that a five-membered heterocycle can be annulated with benzimidazole by the reaction of compound **1a** with chlorine-substituted arylhydrazones **49a–d** as 1,2-dielectrophiles.[39] The heating of the starting compounds under reflux in chloroform in the presence of triethylamine results in the formation of pyrrolo[1,2-*a*]benzimidazoles **50** or pyrazolo[3,4:3′,4′]pyrrolo[1,2-*a*]benzimidazoles **51** in 72%–82% yields depending on the nature of the substituent in arylhydrazone **49** (Scheme 18). The change of the solvent (the use of THF instead of chloroform) made it possible to decrease the reaction temperature to 25 °C.[40] However, in the latter case a mixture of isomers **50** and **52** was obtained, with the latter predominating. For example, the yields of compounds **52a** and **52b** were 65% and 75%, respectively, while the corresponding isomers **50b**,**d** were isolated as by-products. Attempts to extend the range of 1,3-dinucleophilic substrates for the reactions with chlorine-containing hydrazones **49a**,**b** failed. For instance, the reaction of benzimidazolamine **2a** with compound **49a** stops at the condensation product.

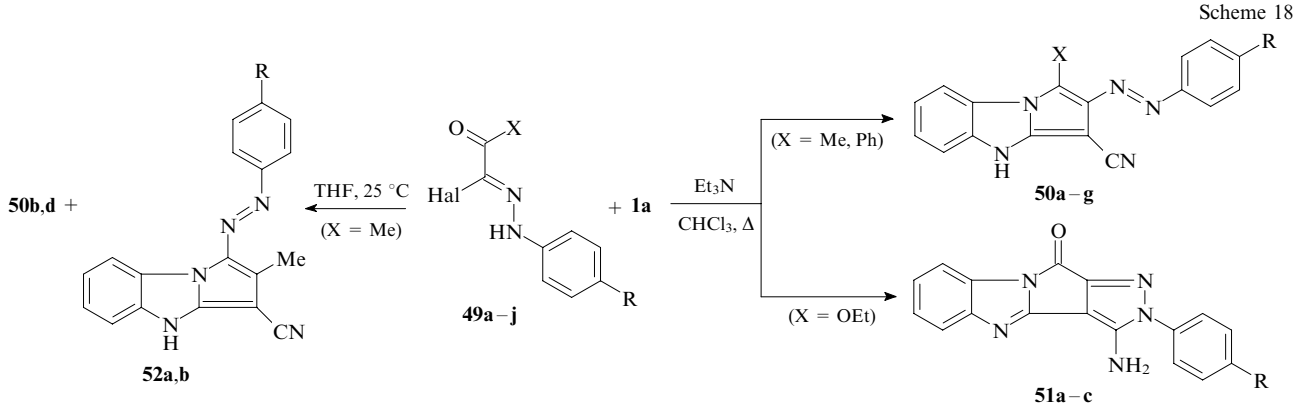
Scheme 17



**1a**,**h** **47a–d** **48b–f** **46a–f**

**47**: $R^2$ = $R^3$ = Ph (**a**); $R^3$ = Me: $R^2$ = Ph (**b**), 4-$MeC_6H_4$ (**c**), 4-$FC_6H_4$ (**d**); **46**, **48**: $R^1$ = H: $R^2$ = $R^3$ = Ph (**a**); $R^2$ = Ph, $R^3$ = Me (**b**); $R^2$ = 4-$MeC_6H_4$, $R^3$ = Me (**c**); $R^1$ = $R^3$ = Me: $R^2$ = Ph (**d**), 4-$MeC_6H_4$ (**e**), 4-$FC_6H_4$ (**f**)

Scheme 18

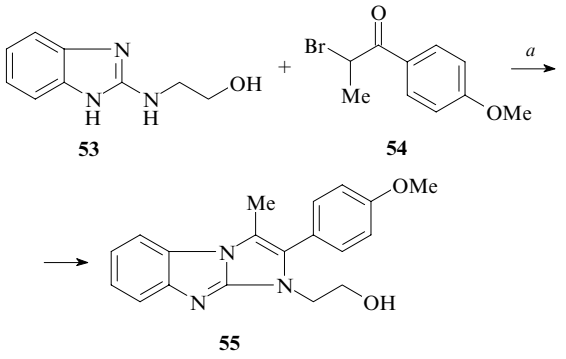


**50b**,**d** + **52a**,**b** **49a–j** + **1a** **50a–g** **51a–c**

Hal = Cl, X = Me: R = H (**49a**, **50a**), Cl (**49b**, **50b**, **52a**), Me (**49c**, **50c**), Br (**49d**, **50d**, **52b**); Hal = Br, X = Ph: R = H (**49e**, **50e**), $NO_2$ (**49f**, **50f**), Me (**49g**, **50g**); Hal = Cl, X = OEt: R = H (**49h**, **51a**), Cl (**49i**, **51b**), Me (**49j**, **51c**)

The reaction of 2-(1*H*-benzimidazole-2-amino)ethanol (**53**) with α-bromo ketone **54** is another example of the annulation of a five-membered ring onto the imidazole moiety.[41] Initially, the reactants were refluxed in isopropyl alcohol for 5 h. Then the alcohol was distilled off and the mixture was heated in aminoethanol for 3 h. The resulting 2-[2-(4-methoxyphenyl)-3-methyl-1*H*-imidazo[1,2-*a*]benzimidazol-1-yl]ethanol (**55**) was obtained in 42% yield (Scheme 19).

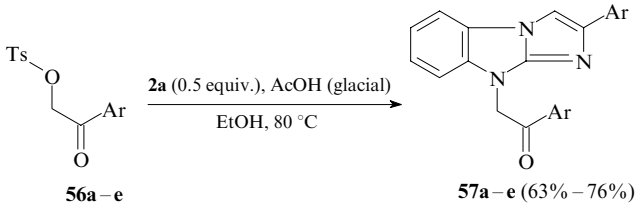
Scheme 19



(*a*) 1) $Pr^iOH$, Δ, 5 h; 2) $NH_2(CH_2)_2OH$, Δ, 3 h

The reaction of N,N-dinucleophile **2a** with aromatic ketones **56a – e** gave imidazo[1,2-*a*]benzimidazoles **57a – e** (Scheme 20).[42]

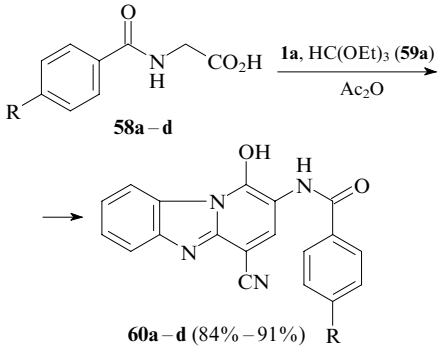
Scheme 20



**56**, **57**: Ar = Ph(**a**), 4-$MeC_6H_4$ (**b**), 4-$MeOC_6H_4$ (**c**), 4-$ClC_6H_4$ (**d**), 2-Th (**e**)

Multicomponent one-step reactions resulting in the formation of fused polycyclic systems containing a benzimidazole moiety are widely covered in the literature. Elgemeie *et al.*[43] descibed the reaction of benzimidazolylacetonitrile **1a** with benzoylaminoacetic acid derivatives **58a – d** and triethyl orthoformate (**59a**) performed by heating in acetic anhydride (Scheme 21). The yields of annulated products **60a – d** were rather high.

Scheme 21

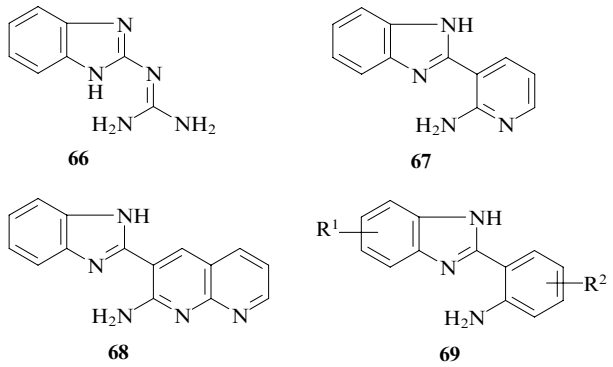


**58**, **60**: R = H (**a**), Me (**b**), OMe (**c**), Cl (**d**)

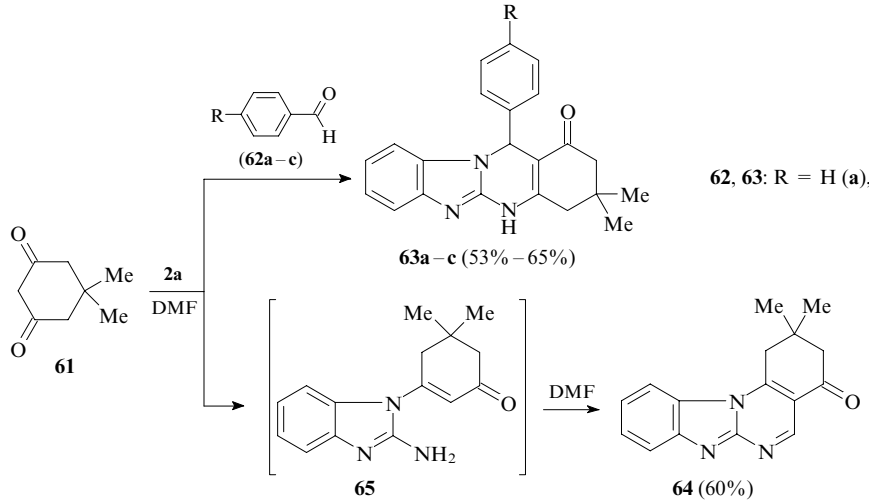
The heating of benzimidazolamine **2a** with dimedone (**61**) and benzaldehyde derivatives **62a – c** under reflux in DMF for a few minutes afforded 12-aryl-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[1,2-*b*]quinazolin-1(2*H*)-ones (**63**) in moderate yields (Scheme 22).[44]

The reaction in the absence of aromatic aldehyde gives cyclocondensation product **64**, which is formed by the reaction of intermediate **65** with a solvent molecule.

In a number of studies,[45 – 52] the following 1,5-N,N-dinucleophiles were used as substrates for the α-annulation of a six-membered heterocycle to 2-substituted 1*H*-benzimidazoles: *N*-(1*H*-benzimidazol-2-yl)guanidine (**66**),[45, 46] 3-(1*H*-benzimidazol-2-yl)pyridine-2-amine (**67**),[47] 3-(1*H*-



Scheme 22



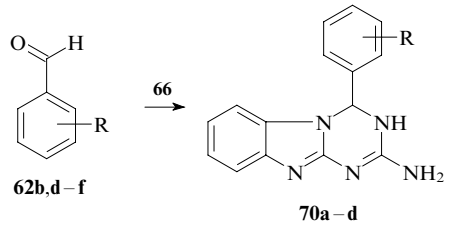
**62**, **63**: R = H (**a**), OMe (**b**), $NO_2$ (**c**)

benzimidazol-2-yl)-1,8-naphthyridine-2-amine (**68**)[48] and 2-(1*H*-benzimidazol-2-yl)aniline ($R^1 = R^2 = H$, **69a**).[49]

Monoelectrophilic carbonyl compounds, such as aromatic ketones,[48] aldehydes[45–48] and triethoxyalkanes,[50] were used as reagents.

For example, substituted 1,3,5-triazino[1,2-*a*]benzimidazoles **70** were synthesized from *N*-(1*H*-benzimidazol-2-yl)guanidine (**66**) by heating with benzaldehydes **62b**,**d**–**f** under reflux in ethanol.[45,46] The yields of the products varied from 43% to 84% (Scheme 23).

Scheme 23

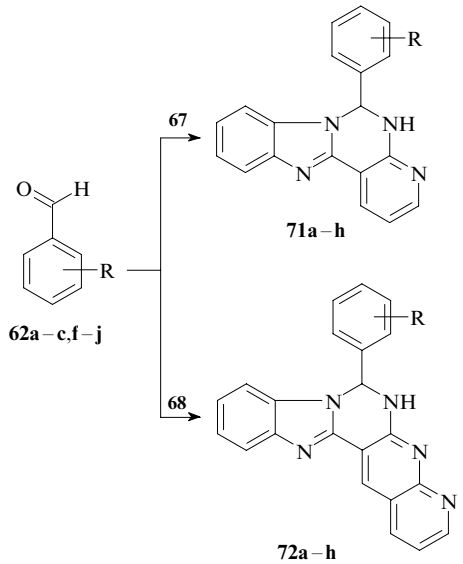


**62b**,**d**–**f** **70a**–**d**

R = 4-OMe (**62b**, **70a**), 2-$NO_2$ (**62d**, **70b**), 2-$CO_2H$ (**62e**, **70c**), 4-Cl (**62f**, **70d**)

The reactions of 3-(1*H*-benzimidazol-2-yl)pyridine-2-amine (**67**)[47] or 3-(1*H*-benzimidazol-2-yl)-1,8-naphthyridine-2-amine (**68**)[48] with substituted benzaldehydes **62a**–**c**,**f**–**j** were performed under reflux in glacial acetic acid for 2 h. Cyclocondensation products **71a**–**h** and **72a**–**h** were synthesized in 50%–65% and 60%–85% yields, respectively (Scheme 24).

Scheme 24

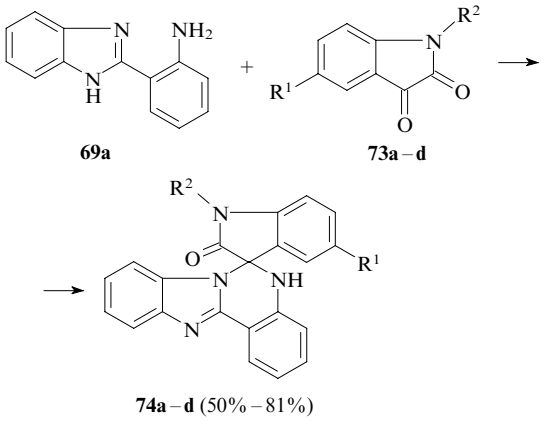


**62a**–**c**,**f**–**j** **71a**–**h** **72a**–**h**

R = H (**62a**, **71a**, **72a**), 4-OMe (**62b**, **71b**, **72b**), 4-$NO_2$ (**62c**, **71c**, **72c**), 4-Cl (**62f**, **71d**, **72d**), 4-Me (**62g**, **71e**, **72e**), 4-Br (**62h**, **71f**, **72f**), 3-$NO_2$ (**62i**, **71g**, **72g**), 2-Th (**62j**, **71h**, **72h**)

Under similar conditions, 2-(1*H*-benzimidazol-2-yl)aniline (**69a**) reacts with substituted isatins **73a**–**d** to give 5,6-dihydrospiro(benzo[4,5]imidazo[1,2-*c*]quinazoline-6,3′-indolin)-2′-ones **74a**–**d** in yields from moderate to high (Scheme 25).[49]

Scheme 25

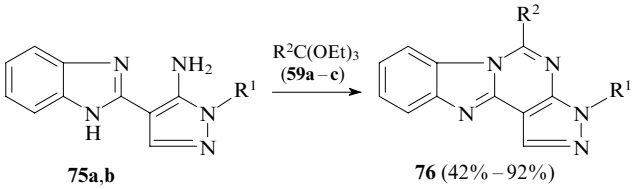


**69a** **73a**–**d** **74a**–**d** (50%–81%)

**73**, **74**: $R^1$ = H: $R^2$ = H (**a**), Me (**b**), Br (**c**); $R^1 = R^2$ = Me (**d**)

The cyclocondensation products of 4-(1*H*-benzimidazol-2-yl)pyrazole-5-amines **75a**,**b** with orthoesters **59a**–**c** were prepared under reflux in the absence of a solvent.[50] These reactions produce pyrazolo[3′,4′:4,5]pyrimido[1,6-*a*]benzimidazoles **76** (Scheme 26).

Scheme 26

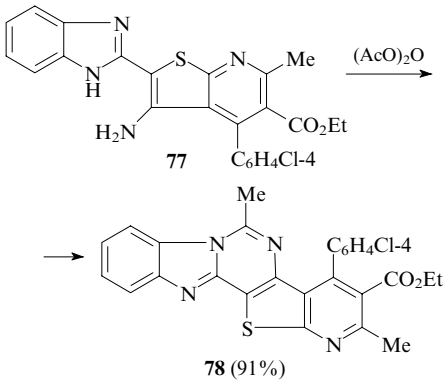


**75a**,**b** **76** (42%–92%)

$R^1$ = Me (**75a**), Ph (**75b**); $R^2$ = H (**59a**), Me (**59b**), Et (**59c**)

The condensation of 2-(1*H*-benzimidazol-2-yl)thieno[2,3-*b*]pyridine-3-amine **77** with acetic anhydride was performed by heating for 4 h to prepare 7*H*-pyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[1,6-*a*]benzimidazole **78** in high yield (Scheme 27).[51]

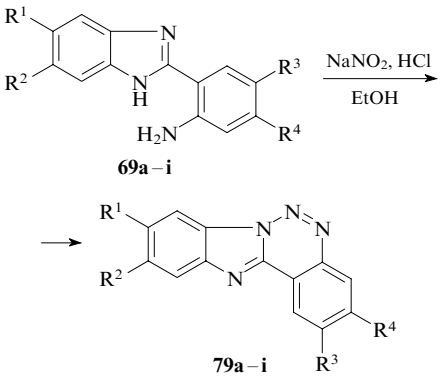
Scheme 27



**77** **78** (91%)

The synthesis of fused polyazaheterocycles containing the 1,2,3-triazine ring was documented.[51,52] For instance, the diazotization of substituted 2-(1*H*-benzimidazol-2-yl)anilines **69a**–**i** affords compounds **79a**–**i** in 92%–98% yields (Scheme 28).

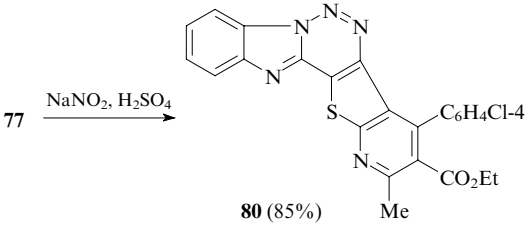
Scheme 28




$R^2 = R^3 = R^4 = H$: $R^1$ = H (**a**), Cl (**b**), Me (**c**);
$R^3 = R^4 = H$: $R^1 = R^2$ = Cl (**d**), Me (**e**); $R^1 = R^2 = R^4 = H$, $R^3$ = Cl (**f**); $R^1 = R^2 = R^3 = H$: $R^4$ = Cl (**g**), Me (**h**), F (**i**)

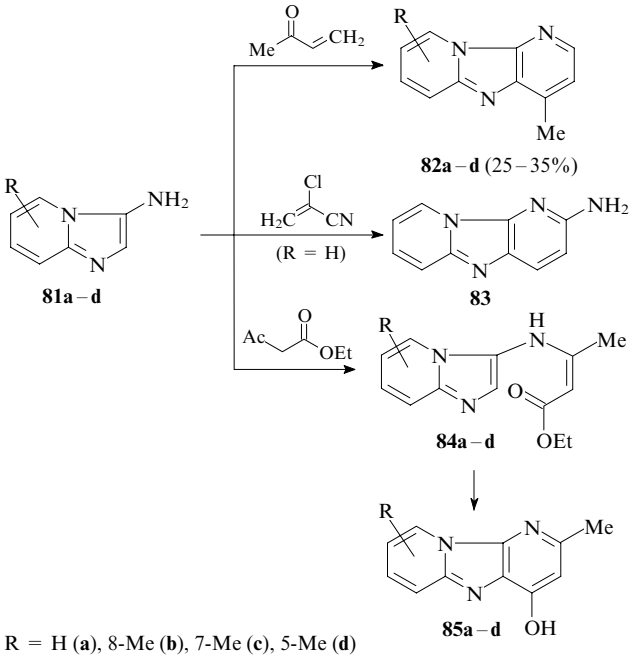
The diazotization of 2-(1*H*-benzimidazol-2-yl)thieno[2,3-*b*]pyridine-3-amine **77** gives product **80** (Scheme 29).[51]

Scheme 29




In a number of studies, polyfused imidazole derivatives were synthesized with the use of imidazo[1,2-*a*]pyridine-3-amines **81** instead of 2-substituted 1*H*-benzimidazoles.[53] The condensation of the latter with methyl vinyl ketone was performed in ethanol in the presence of aqueous iron(III) chloride and anhydrous zinc(II) chloride by heating to 65 – 70 °C for 12 h. The yields of products **82a – d** were

Scheme 30




R = H (**a**), 8-Me (**b**), 7-Me (**c**), 5-Me (**d**)

low (Scheme 30, hereinafter, the numbers at the substituents indicate their positions in the initial heterocyclic system). The reaction of compound **81a** with 2-chloroacrylonitrile produces pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridine-2-amine (**83**) in 35% yield.

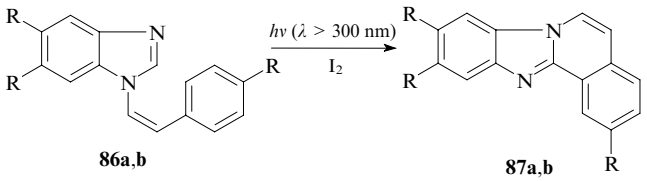
The heating of the reaction mixture of imidazo[1,2-*a*]pyridine-3-amines **81a – d** with ethyl 3-oxobutyrate under reflux in anhydrous ethanol overnight resulted in the formation of intermediate condensation products **84a – d**. The heating of the latter in Dowtherm A (an azeotropic mixture of diphenyl and diphenyl oxide) for 0.5 h gave compounds **85a – d** in high yields (80% – 95%) (see Scheme 30).

## 2. Intramolecular cyclization of substituted benzimidazoles

Fused polycyclic imidazole derivatives with a bridgehead nitrogen atom are often synthesized by the intramolecular cyclization of substituted benzimidazoles. Monosubstituted benzimidazoles can contain a substituent in either position 1 or 2 of the imidazole ring. In the former case, a polyfused structure is produced through the C – C bond formation, whereas the α-annulation of a heterocycle containing a substituent in position 2 to 1*H*-benzimidazole proceeds through the C – N bond formation.

The photochemical cyclization of styrylbenzimidazoles **86a**,**b** giving benzimidazo[2,1-*a*]isoquinolines **87a**,**b** is an example of the synthesis of fused polycyclic imidazole derivatives from N-substituted benzimidazoles.[54] The reaction is induced by irradiation of a solution of the starting compounds in ethanol in the presence of one equivalent of iodine (Scheme 31).

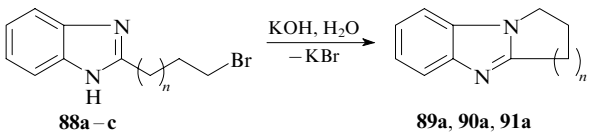
Scheme 31




R = H (**a**), Me (**b**)

The dehydrogenation and dehydrohalogenation are the main processes accompanying the formation of the C – N bond in 2-substituted 1*H*-benzimidazoles. A method for the synthesis of fused tricyclic systems based on the intramolecular dehydrohalogenation of 2-(ω-bromoalkyl)-1*H*-benzimidazoles **88a – c** was described.[55] The cyclization takes place in ethanolic KOH; the yields of products **89a – 91a** vary from moderate to high (Scheme 32).

Scheme 32

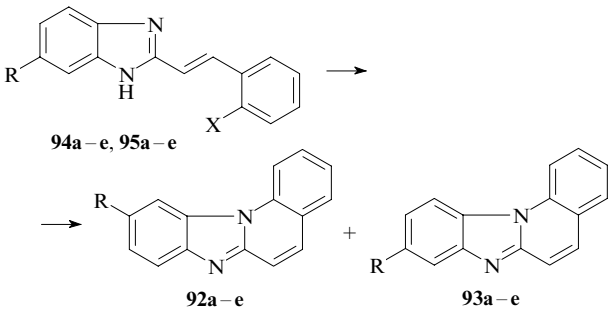



*n* = 1 (**88a**, **89a**, yield 43%), 2 (**88b, 90a**, yield 87%), 3 (**88c, 91a**, yield 94%)

Isomeric benzimidazo[1,2-*a*]quinolines **92a – e** and **93a – e** were synthesized by the photochemical dehydrogenation (dehydrohalogenation) of 2-styryl- and 2-(*o*-chloro-

styryl)-1*H*-benzimidazoles **94a–e** and **95a–e**, respectively (Scheme 33).[56]

Scheme 33

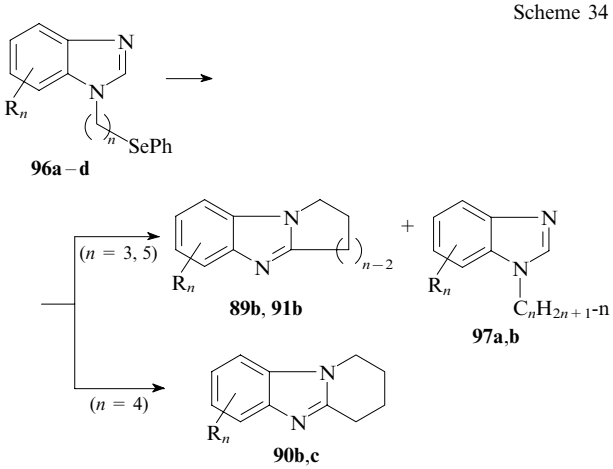



X = H (**94**), Cl (**95**); R = C(=N$^+$H$_2$Cl$^-$)NHPr$^i$ (**a**), C(=N$^+$H$_2$Cl$^-$)NH$_2$ (**b**), cyclo-(C=N$^+$H(Cl$^-$)CH$_2$CH$_2$NH) (**c**), C(=N$^+$H$_2$Cl$^-$)NHN(CH$_2$CH$_2$)$_2$O (**d**), CN (**e**)

The reactions were performed under irradiation of solutions of the starting compounds using a mercury lamp in the presence of iodine (5 mol.%) in ethanol at room temperature. Benzimidazo[1,2-*a*]quinoline derivatives were obtained as an inseparable mixture of two structural isomers (**92**, **93**) in a ratio of ~1.5 : 1. Only products **92e** and **93e** were isolated in 20% and 12% yields, respectively.

Heterocyclic systems containing five- (**89**), six- (**90**) and seven-membered (**91**) saturated rings [1,2-*a*]-fused to benzimidazole were synthesized by the intramolecular radical cyclization of phenylselenyl-substituted benzimidazoles **96a–d** accompanied by the C–C bond formation.[57] The reactions proceed in the presence of tri-n-butylstannane and camphorsulfonic acid necessary for the quaternization of position 3 of the imidazole ring in compounds **96**, as well as of 1,1′-azobis(cyclohexanecarbonitrile) acting as an aza initiator (Scheme 34).

Scheme 34



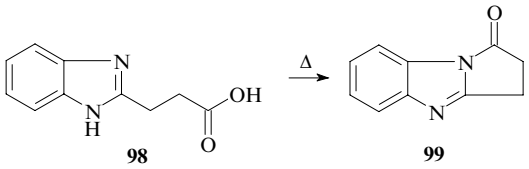

| Starting compound | *n* | R$_n$ | Products [yield (%)] |
|---|---|---|---|
| **96a** | 3 | 5,6-Me$_2$ | **89b** (32) + **97a** (54) |
| **96b** | 4 | 5,6-Me$_2$ | **90b** (69) |
| **96c** | 5 | 5,6-Me$_2$ | **91b** (63) + **97b** (21) |
| **96d** | 4 | 4,7-(OMe)$_2$ | **90c** (70) |

The target products were prepared by heating the reactants under reflux in toluene for 18 h. The radical cyclization of selenides **96a**,**b** used for the formation of five- and seven-membered rings affords products of elimination of the SePh group (compounds **97a**,**b**), compound **97a** being the major product in the former case.

In some cases, 1*H*-benzimidazoles containing a substituent with the terminal carboxy group in position 2 serve as substrates for the intramolecular cyclization. The intramolecular dehydration was induced by heating to high temperatures[58] or using microwave radiation.[59]

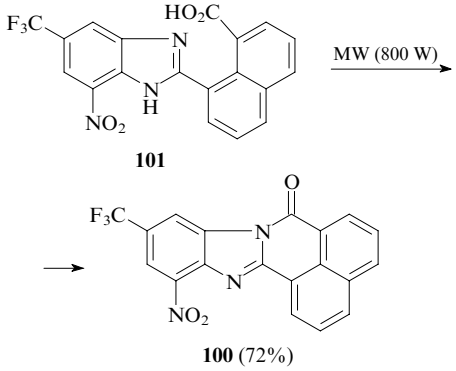
It was shown[58] that the dihydropyrrole ring can be subjected to α-annulation by the reaction of 3-(1*H*-benzimidazol-2-yl)propionic acid (**98**) with dicyclohexylcarbodiimide as the dehydrating agent in pyridine at 5–10 °C. The cyclization affords 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one (**99**) in 78% yield (Scheme 35).

Scheme 35



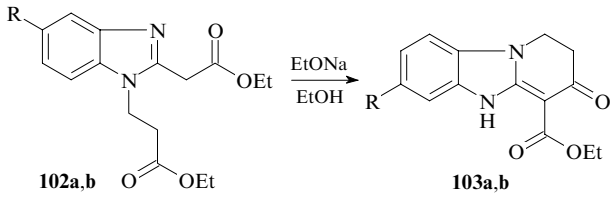

Fused polycyclic system **100** was constructed by the microwave-induced reaction of 8-[7-nitro-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]-α-naphthoic acid (**101**) on silica gel in the presence of zinc(II) chloride.[59] The reaction proceeds under heating within a few minutes (Scheme 36).

Scheme 36




Methods for the synthesis of polycyclic imidazole derivatives with a bridgehead nitrogen atom from 1,2-disubstituted benzimidazoles are described in the literature.[60–62] The presence of ester substituents in compounds **102a**,**b** made it possible[60,61] to perform the Dieckmann reaction and prepare ethyl 3-oxo-1,2,3,5-tetrahydropyrido[1,2-*a*]-benzimidazole-4-carboxylates **103a**,**b** in good yields. The reaction proceeds after the treatment of the starting substrate with a freshly prepared solution of sodium ethoxide in ethanol (Scheme 37).

Scheme 37

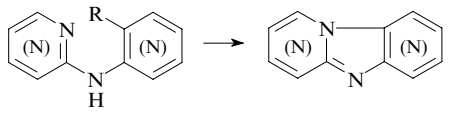



R = H (**a**, 66%), F (**b**, 88%)

## III. Formation of the imidazole ring in fused heterocycles with a bridgehead nitrogen atom

Another group of methods for the synthesis of fused polycyclic imidazole derivatives includes methods based on the intramolecular cyclization of *N*-(2-R-phenyl)hetaryl-2-amines (Scheme 38) or related imines using different conditions.†

Scheme 38

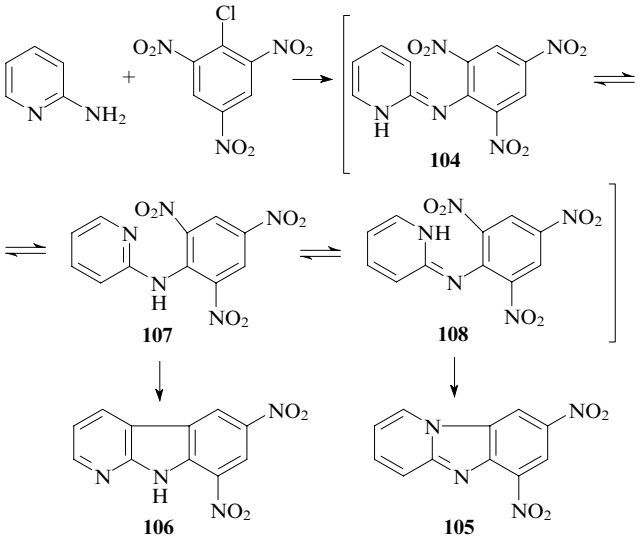


R = H, $NO_2$, Cl, Br, $NH_2$

The starting compounds are usually prepared by reactions of heteroaromatic compounds containing an amino group in the *ortho* position with respect to the endocyclic nitrogen atom with different halogen-substituted arenes[63–65] or by reactions of 2-halohetarenes with amino or carboxy derivatives of heterocycles.[66–69] The subsequent cyclization can be based on the non-activated replacement of halogen[68,70–72] or hydrogen in the presence of catalysts,[67] the opening–closure of the pyridine ring,[73,74] the activated nucleophilic substitution[74] and photocyclization.[75–81]

This method for the synthesis of fused azaheterocycles with a bridgehead nitrogen atom was described for the first time by Morgan and Stewart.[63–65] Thus, the condensation of 2-chloro-1,3,5-trinitrobenzene and 2-aminopyridine proceeds through the intermediate formation of 2,4,6-trinitro-*N*-(pyridin-2(1*H*)-ylidene)aniline (**104**), which undergoes cyclization (Scheme 39).

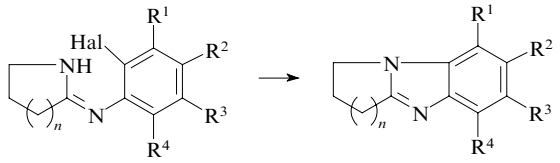
Scheme 39



Initially, the reactants are fused at 105–120 °C for 2 h, which is followed by the thermal cyclization (heating under reflux in naphthalene or dimethylaniline). The nucleophilic substitution of the nitro group affords 6,8-dinitropyrido[1,2-*a*]benzimidazole (**105**) in 60% yield as a mixture with isomeric 6,8-dinitro-9*H*-pyrido[2,3-*b*]indole (**106**). The formation of the latter is attributed to the prototropic tautomerism of compound **104**, which is responsible for the cyclization either at position 3 of the pyridine ring (from tautomer **107**) or at the endocyclic nitrogen atom of the pyridine ring (from tautomer **108**).

Nazarenko *et al.*[66] developed a method for the synthesis of fused azaheterocycles **89** and **91** based on the activated nucleophilic substitution — the intramolecular dehydrohalogenation. Thus, the intramolecular cyclization of 2-chloro-*N*-[(2*E*)-azepan-2-ylidene]anilines **109g,h** is performed by heating with sodium methoxide under reflux in DMF, whereas fluorine-containing substrates **109a–f** are heated in the absence of a solvent to 150 °C. Products **89c** and **91c–i** are formed in high yields (Scheme 40).

Scheme 40

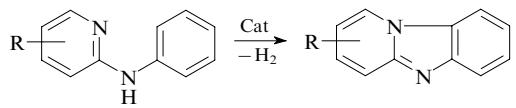


**109a–h** **89c**, **91c–i** (72%–81%)

| Starting imine **109** | Hal | Product | *n* | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|---|---|---|
| **a** | F | **89c** | 1 | $NO_2$ | H | H | H |
| **b** | F | **91c** | 3 | H | H | $NO_2$ | H |
| **c** | F | **91d** | 3 | H | F | H | H |
| **d** | F | **91e** | 3 | H | H | H | F |
| **e** | F | **91f** | 3 | F | F | H | H |
| **f** | F | **91g** | 3 | F | F | F | F |
| **g** | Cl | **91h** | 3 | H | H | $CF_3$ | H |
| **h** | Cl | **91i** | 3 | H | H | $SO_2NEt_2$ | H |

Prostakov *et al.*[67] proposed the catalytic dehydrocyclization of (2-pyridyl)anilines **110a–c** for the formation of the imidazole ring in fused polycyclic structures **111a–c** (Scheme 41).

Scheme 41



**110a–c** **111a–c**

R = H (**a**), 3-Me (**b**), 5-Me (**c**); Cat is the industrial catalyst K-16

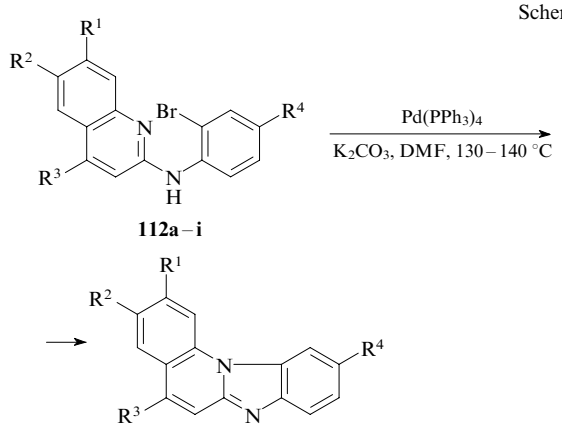
This method has found little use because of the drastic conditions (the reaction temperature is 560–580 °C) and low yields of the reaction products (9%–27%).

The catalytic dehydrohalogenation of quinoline-substituted *o*-bromoanilines **112a–i**, which were synthesized according to a reported procedure,[68] gave fused polycyclic azaheterocycles **113a–i** (Scheme 42).[69]

A $Pd^0$ complex with triphenylphosphine was used as the catalyst for this reaction. The reaction was performed in the presence of anhydrous $K_2CO_3$ in DMF at 130–140 °C for 12 h.

† The notation (N) inside the ring indicates that the ring can contain nitrogen atoms which are not shown in the structural formula.

Scheme 42



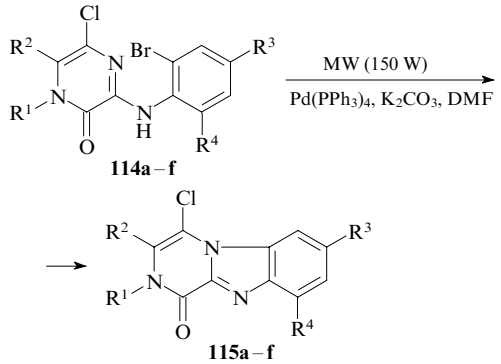

**112a–i**

**113a–i** (70%–93%)

$R^1 = R^2 = R^3 = H$: $R^4$ = Me (**a**), $Pr^i$ (**b**), OMe (**c**); $R^2 = R^3 = R^4 = H$, $R^1$ = OMe (**d**); $R^1 = R^2 = R^4 = H$, $R^3$ = Me (**e**); $R^1 = R^2 = H$, $R^3$ = Me: $R^4$ = Me (**f**), $Pr^i$ (**g**), OMe (**h**); $R^1 = H$, $R^2 = R^3 = R^4$ = Me (**i**)

This procedure was improved by Alen *et al.*,[70] who suggested the microwave-induced Buchwald–Hartwig cyclization with compounds **114a–f**. This made it possible to decrease the reaction time to 0.4 h. Pyrazino[1,2-*a*]benzimidazol-1(2*H*)-ones **115a–f** were synthesized in yields from moderate to high (Scheme 43).

Scheme 43




**114a–f**

**115a–f**

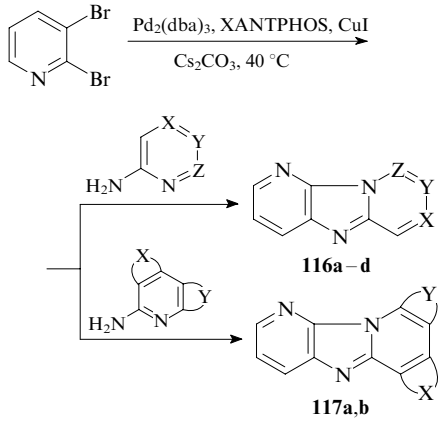
$R^1 = R^2$ = Ph, $R^3 = R^4 = H$ (**a**); $R^1$ = 4-$MeOC_6H_4CH_2$, $R^2 = R^4 = H$: $R^3 = H$ (**b**), CN (**c**), Me (**d**), $OCF_3$ (**e**); $R^1$ = 4-$MeOC_6H_4CH_2$, $R^2 = H$, $R^3 = R^4 = F$ (**f**)

The Pd-catalyzed formation of intermolecular and then intramolecular C–N bonds was laid at the basis of the one-pot synthesis of fused polycyclic imidazole derivatives with a bridgehead nitrogen atom, *viz.*, compounds **116** and **117**.[71,72] The synthesis was performed in the presence of 9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene (XANTPHOS) (Scheme 44).

The cyclocondensation of 2-aminoazines with 2,3-dibromopyridine was performed under a nitrogen atmosphere in the presence of the orthogonal Pd–Cu catalyst at 140 °C for 24 h.[71] The yields of fused azaheterocycles **116** and **117** were from 44% to 88%.

The intramolecular cyclization of *N*-(5-nitro-2-pyridyl)-*o*-phenylenediamine (**118a**), which was produced from 2-chloro-5-nitropyridine and *o*-phenylenediamine (**119a**), was performed under reflux in an ethanol–HCl mixture

Scheme 44



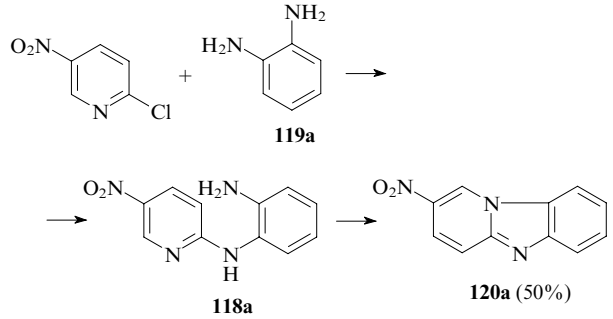

**116a–d**

**117a,b**

**116**: X = Y = Z = CH (**a**); X = N, Y = Z = CH (**b**); X = Y = CH, Z = N (**c**); X = Z = CH, Y = N (**d**); **117**: X = 2H, Y is benzo (**a**); Y = 2H, X is benzo (**b**); dba is dibenzylideneacetone

for 18 h.[73] This reaction gave 2-nitropyrido[1,2-*a*]benzimidazole (**120a**) in moderate yield (Scheme 45).

Scheme 45



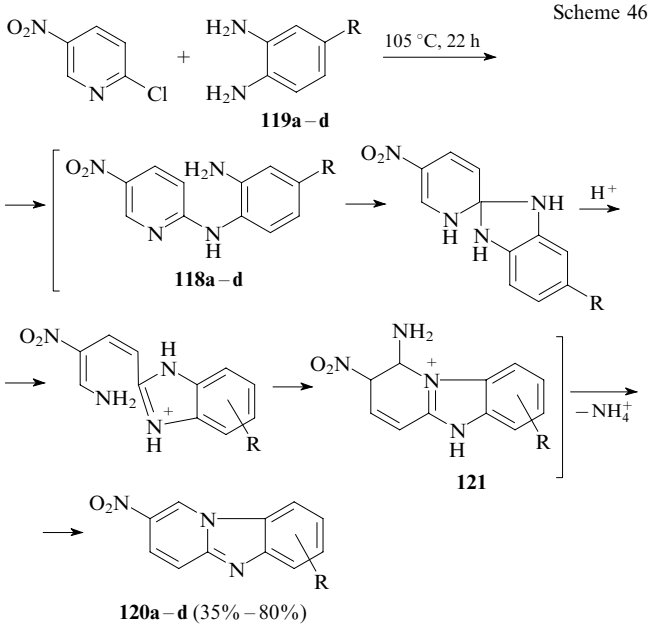
**119a**

**118a**

**120a** (50%)

More recently, Sundberg and Ellis[74] extended the range of amines **119** introduced in this reaction and prepared pyrido[1,2-*a*]benzimidazoles **120b–d**. The reaction was performed in an HCl–EtOH–$H_2O$ mixture by long-term

Scheme 46




**119a–d**

**118a–d**

**121**

**120a–d** (35%–80%)

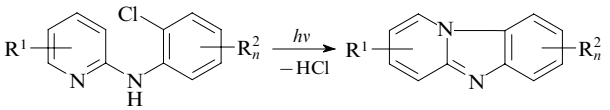
R = H (**a**), Cl (**b**), Me (**c**), $NO_2$ (**d**)

heating on an oil bath. The following reaction mechanism was proposed (Scheme 46).

The first step involves the activated replacement of the chlorine atom in position 2 of pyridine. In the second step, intermediate product **118** undergoes the intramolecular cyclization according to the $S_NANRORC$ mechanism accompanied by the opening–closure of the pyridine ring. In the final step, an ammonium ion is eliminated from intermediate salt **121**. It was noted [74] that, as opposed to the regioselective reaction of 4-nitro-*o*-phenylenediamine (**119d**) with 2-chloro-5-nitropyridine, the corresponding reactions of 4-chloro (**119b**) and 4-methyl derivatives (**119c**) give equimolar mixtures of isomeric pyrido[1,2-*a*]-benzimidazoles containing substituents in positions 7 and 8 of the heterocycle.

An interesting procedure for the construction of fused polyheterocyclic systems with a bridgehead nitrogen atom based on the photoinduced non-activated replacement of chlorine was proposed by Frolov an co-workers.[75–81] For example, the heteroatomic photocyclization of *N*-(2-chlorophenyl)pyridine-2-amines (**122a–h**) under irradiation using a mercury lamp for 4–6 h in *tert*-butanol affords compounds **123a–h** in 8%–60% yields (Scheme 47).[75–77]

Scheme 47



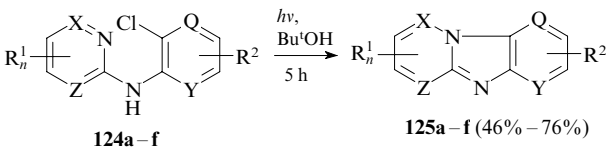
**122a–h** **123a–h**

$R^1$ = H: $R_n^2$ = H (**a**), 4-F (**b**), 4-Cl (**c**), 5-Cl (**d**), 6-Cl (**e**), 4,5-$Cl_2$ (**f**); $R_n^2$ = H: $R^1$ = 5-Cl (**g**), 4-Me (**h**)

Baklanov and Frolov noted [75] that the photocyclization competes with the photoinduced dechlorination. In addition, product **123** is produced along with a small amount of the corresponding pyrido[2,3-*b*]indole due to the prototropic isomerism of the starting substrate **122**.

The heteroatomic photocyclization of dihetarylamines **124a–f** can also be used for the synthesis of other fused imidazole derivatives with a bridgehead nitrogen atom:[78–81] pyrido[2′,3′:4,5]- (**125a**) and pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines (**125b**), pyrimidino[1,2-*a*]benzimidazoles (**125c**), pyridazino[1,6-*a*]benzimidazoles (**125d**), pyrido[2′,3′:4,5]- (**125e**) and pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyrimidines (**125f**) (Scheme 48).

Scheme 48



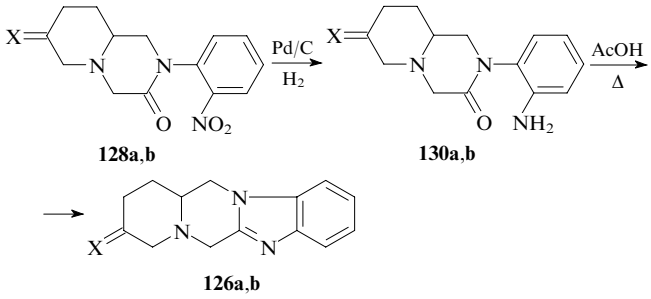
**124a–f** **125a–f** (46%–76%)

X = Z = Q = CH, Y = N, $R^2$ = 5-Cl (**a**); X = Z = Y = CH, Q = N, $R_n^1$ = $R^2$ = H [**b**, yield (46%)]; X = Y = Q = CH, Z = N, $R^2$ = H (**c**); X = N, Y = Z = Q = CH, $R_n^1$ = $R^2$ = H (**d**); X = Q = CH, Z = Y = N, $R^2$ = H, $R_n^1$ is a substituent in position 5 (**e**); X = Y = CH, Z = Q = N, $R^2$ = H, $R_n^1$ = 1,3-$Me_2$ [**f**, yield (76%)]

In our opinion, the formation of the imidazole ring by the reductive amination of pyridinium salts, which can be easily synthesized from cheap and readily available reagents, is among the most promising synthetic approaches to polyfused azaheterocycles.

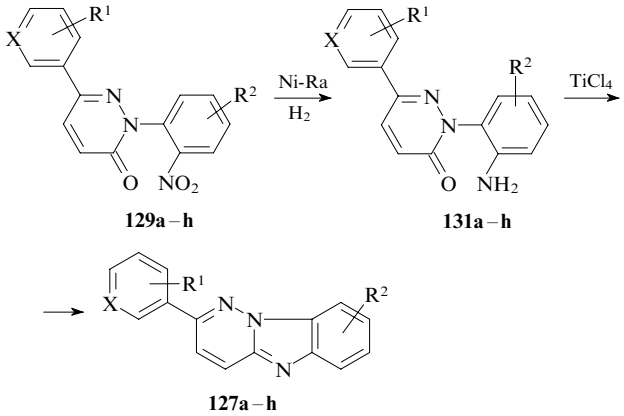
In the classical interpretation, the term 'reductive amination' is applicable to reactions accompanied by the condensation of the carbonyl group of the molecule with the amino group that is formed in the course of the reduction. This method was used to synthesize fused polycyclic imidazole derivatives (for example, compounds **126a,b** and **127a–h**) in two steps.[82, 83] Thus, the catalytic hydrogenation of the $NO_2$ groups of compounds **128a,b** and **129a–h** in the presence of Pd/C (Ref. 81) or Raney nickel [83] affords reduction products **130a,b** and **131a–h** which undergo intramolecular cyclization with the use of $TiCl_4$ in acetic acid (Scheme 49).

Scheme 49



**128a,b** **130a,b** **126a,b**

X = $OCH_2CH_2O$ (**a**), O (**b**)



**129a–h** **131a–h** **127a–h**

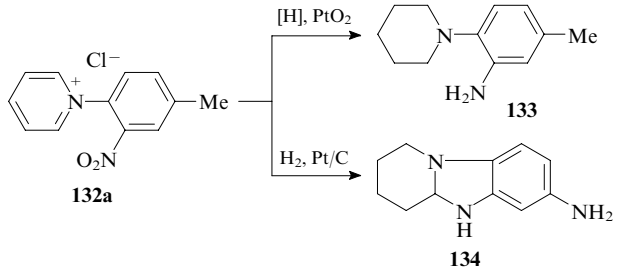
X = CH, $R^1$ = H: $R^2$ = H (**a**), 4-$NH_2$ (**b**), 4-Cl (**c**); X = CH, $R^2$ = H: $R^1$ = 3-Me (**d**), 3-Cl (**e**), 4-Cl (**f**), 2-Cl (**g**); X = N, $R^1$ = $R^2$ = H (**h**)

However, this procedure is not extended to 1-(2-nitrophenyl)pyridinium salts, because the generation of a carbonyl derivative under basic conditions can lead to the opening of the pyridine ring to form glutaconic aldehyde.[84] Hence, it is more correct to use the term 'reductive intramolecular cyclization', which involves the simultaneous reduction and nucleophilic substitution of hydrogen, instead of the term 'reductive amination' for reactions accompanied by the reduction of 1-(2-nitrophenyl)pyridinium salts.

It should be noted that there are few publications devoted to the use of the reductive cyclization for the synthesis of fused polycyclic imidazole derivatives with a bridgehead nitrogen atom, which is apparently associated with the fact that this process is poorly known. An analysis of the data published in the literature shows that the successful reductive cyclization depends on numerous factors, primarily, on the nature of the reducing agent.

The use of various systems, such as $H_2$–Pt/C, $H_2$–Pd/C,[85] $H_2$–$PtO_2$,[86] phenylhydrazine–acetic acid[85,87] and $SnCl_2$–HCl,[88–92] for the reduction of 1-(2-nitrophenyl)pyridinium salts **132** was described in the literature. However, it is not always possible to perform the simultaneous reduction and intramolecular cyclization. Thus, the hydrogenation of salt **132a** on $PtO_2$ in ethanol results only in the reduction of the nitro group to the amino group and of the pyridine ring to the piperidine ring (compound **133**) (Scheme 50).[86]

Scheme 50



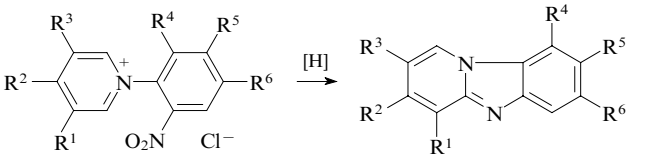

**132a** **133** **134**

The target benzimidazole derivative was not isolated from the reaction mixture. Cyclization product **134** was synthesized by the reduction of pyridinium salt **132a** under conditions of catalytic hydrogenation with the use of Pt/C or Pd/C as the catalyst. In this case, the reductive cyclization was accompanied by the reduction of the heterocyclic moiety (see Scheme 50).[85]

The use of phenylhydrazine[85,87] as a reducing agent made it possible to synthesize fused systems **135b–d** by heating the reactants under reflux in acetic acid. However, the low yields of the products (40%–53%)[85] are indicative of the low efficiency of this reducing system as applied to the synthesis of fused azaheterocycles (Scheme 51, Table 1).

Good results were obtained with the use of the $SnCl_2$–HCl system. The reaction with this reducing agent made it possible to synthesize substituted pyrido[1,2-*a*]benzimidazoles **135b**,**e–m** in high yields (91%–98%) under mild conditions (20 °C, 10–15 min) in one step (see Scheme 51 and Table 1).[88–90,93–95]

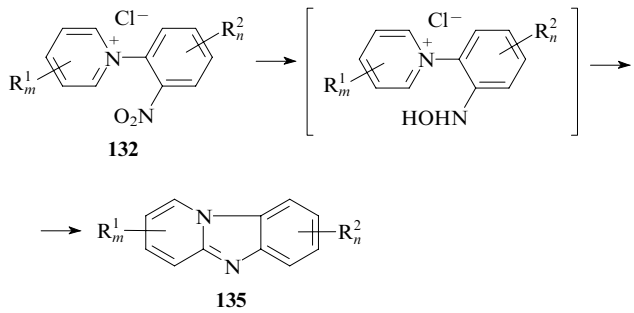
Scheme 51




**132b–l** **135b–m**

According to the results of the study,[96] the possible mechanism of the reductive cyclization of pyridinium salts can be represented by Scheme 52.

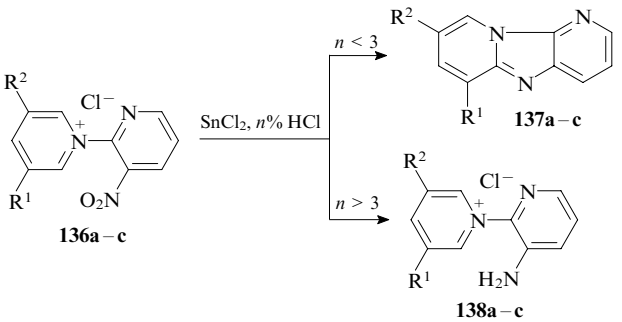
Scheme 52




**132** **135**

The $SnCl_2$–HCl system was used also to reduse *N*-(3-nitro-2-pyridyl)pyridinium salts **136a–c**.[91,92] It was noted that pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines **137a–c** or

Scheme 53




**136a–c** **137a–c** **138a–c**

$R^1$ = H: $R^2$ = H (**a**), Me (**b**); $R^1$ = $R^2$ = Me (**c**)

**Table 1**. Reductive cyclization of arylpyridinium salts **132**.

| Compounds **132**, **135** | Reducing agent | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | Ref. |
|---|---|---|---|---|---|---|---|---|
| **b** | $PhNHNH_2$ | H | H | H | H | H | $NO_2$ | 85 |
| | $SnCl_2$–HCl [a] | H | H | H | H | H | $NO_2$ | 89, 90, 94 |
| **c** | $PhNHNH_2$ | H | H | H | $NO_2$ | H | $NO_2$ | 85 |
| **d** | $PhNHNH_2$ (see [b]) | H | $SiMe_2Ph$ | Me | H | H | $NO_2$ | 87 |
| **e** | $SnCl_2$–HCl | H | H | H | H | H | $CF_3$ | 90, 94 |
| **f** | $SnCl_2$–HCl | Me | H | Me | H | H | CN | 95 |
| **g** | $SnCl_2$–HCl | Me | H | Me | H | CN | CN | 95 |
| **h** | $SnCl_2$–HCl | Me | H | H | H | H | $CF_3$ | 95 |
| **i** | $SnCl_2$–HCl | H | H | H | H | H | CN | 90, 94 |
| **j** | $SnCl_2$–HCl [c] | H | H | H | H | CN | CN | 88, 94 |
| **k** | $SnCl_2$–HCl | H | H | H | H | H | $CO_2H$ | 95 |
| **l** | $SnCl_2$–HCl | H | H | H | H | H | $CO_2NH_2$ | 95 |

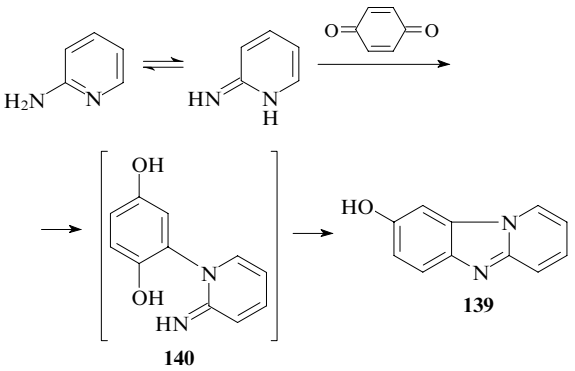
[a] In addition, product **135m** with $R^6$ = $NH_2$ was obtained;[91–93] [b] a mixture of isomers containing a methyl group in positions 2 and 4 in a ratio of 1.2 : 1 is formed; [c] in this case, pyridinium bromide was used.

*N*-(3-amino-2-pyridyl)pyridinium salts **138a–c** are formed depending on the concentration (higher or lower than 3%) of hydrochloric acid.[92] The yields of cyclization products **137a–c** are 79%–91% (Scheme 53).

The third approach to the synthesis of fused polyheterocyclic systems through the formation of the imidazole ring, which radically differs from the above-considered two procedures, is based on the condensation of *p*-quinones with 2-aminopyridine.[97–100]

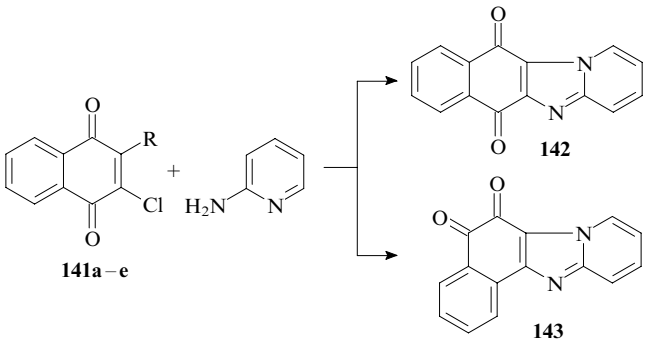
Schmid and Czerny[97] showed that pyrido[1,2-*a*]benzimidazole **139** can be prepared by the condensation of *p*-benzoquinone with 2-aminopyridine through the formation of intermediate **140**. The reaction was performed by heating the starting compounds under reflux in acetic acid (Scheme 54).

Scheme 54



Attempts to perform this reaction with 1,4-naphthoquinone failed. Further efforts to use 1,4-naphthoquinones as reagents for the synthesis of fused polycyclic imidazole derivatives with a bridgehead nitrogen atom were made by Truitt *et al.*[98] Thus, the heating of 2-acetamido-3-chloro-1,4-naphthoquinone (**141a**) under reflux with 2-aminopyridine in butanol for 4 h afforded benzimidazole derivative **142** in 50% yield (Scheme 55).

Scheme 55

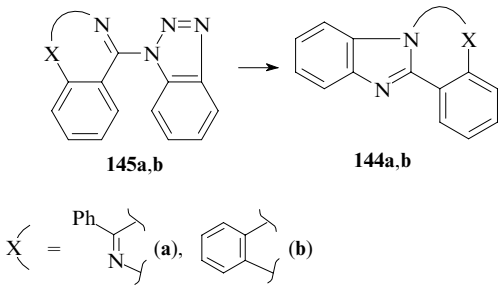


R = NHAc (**a**), Cl (**b**), OH (**c**), OEt (**d**), OAc (**e**)

More recently, Mosby and Boyle[99,100] found that this reaction can give several products. It was shown that the reaction pathway depends on the nature of the substituent in position 2 of naphthoquinone **141**. Thus, it was shown that the reaction of 2-aminopyridine with compounds **141a**,**b** gives not a product having a linear structure (compound **142**), as it was described by Truitt *et al.*,[98] but a product having an angular structure (compound **143** in Scheme 55). The use of another solvent (ethanol instead of butanol) led to an increase in the yield of angular isomer **143** from 67% to 81%. The reactions of 1,4-naphthoquinones **141c–e** containing a hydroxy, ethoxy or acetoxy group produced linear isomer **142**.

Another method for the synthesis of fused azaheterocycles, such as benzimidazo[1,2-*c*]quinazoline (**144a**)[101] and -[1,2-*f*]phenanthridine (**144b**),[102] is based on the photolysis of 4-(1*H*-benzotriazol-1-yl)quinazoline (**145a**) and 6-(1*H*-benzotriazol-1-yl)phenanthridine (**145b**), respectively (Scheme 56) resulting in the formation of the imidazole ring.

Scheme 56

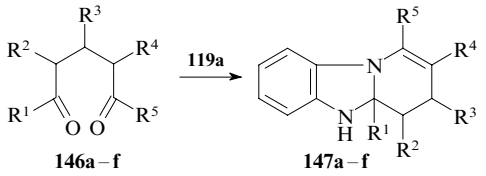


Product **144a** was synthesized in 80% yield by irradiation ($\lambda > 290$ nm) of a solution of the starting compound in benzene under an argon atmosphere at 30–40 °C.[101] The photolysis ($\lambda = 254$ nm) of compound **145b** was performed in acetonitrile; product **144b** was also generated in good yield.[102]

## IV. Simultaneous formation of two heterocycles in a polyfused system

One of the most well-characterized methods for the synthesis of fused heterocycles resulting in the simultaneous formation of the pyridine and imidazole rings is based on the reaction of 1,5-diketones with dinucleophiles (*o*-phenylenediamines). For instance, the cyclization of substituted pentane-1,5-diones **146a–f** with *o*-phenylenediamine (**119a**) affords substituted tetrahydropyrido[1,2-*a*]benzimidazoles **147a–f** (Scheme 57).[103–106]

Scheme 57



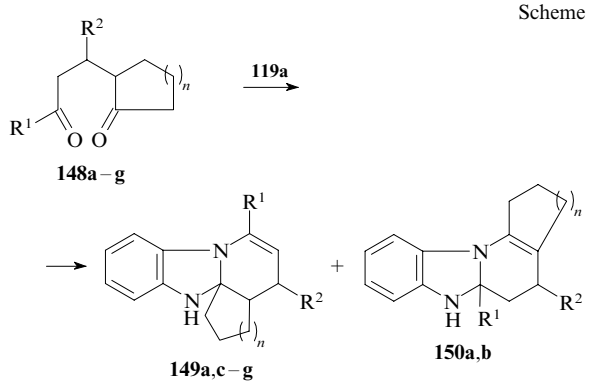
$R^1 = R^5 = Ph$, $R^2 = R^3 = R^4 = H$ (**a**); $R^1–R^2 = (CH_2)_4$: $R^3 = R^5 = Ph$, $R^4 = H$ (**b**); $R^3 = H$, $R^4–R^5$ are 1′,2′-(3′,4′-dihydronaphtho) (**c**); $R^3 = Ph$, $R^4–R^5$ are 1′,2′-(3′,4′-dihydronaphtho) (**d**); $R^1–R^2$ are 2,2-dimethyl-3-oxatetrahydrobenzo, $R^3 = Ph$, $R^4–R^5$ are 1′,2′-(3′,4′-dihydronaphtho) (**e**); $R^1–R^2 = R^4–R^5$ are 1′,2′-(3′,4′-dihydronaphtho), $R^3 = H$ (**f**)

The reaction is performed under reflux in xylene for 5–10 h in the presence of *p*-toluenesulfonic acid with distillation as an azeotrope with water. It was noted that the yield of target compounds **147** depends on the structure and varies from 62% to 95%.

More recently, Donchak *et al.*[107] studied the cyclocondensation of unsymmetrical γ-oxopropylcyclopentanones (**148a–c**) and -hexanones (**148d–g**) with diamine **119a** and

found that the reaction pathway depends on the ring size and the nature of substituents in the diketone (Scheme 58).

Scheme 58

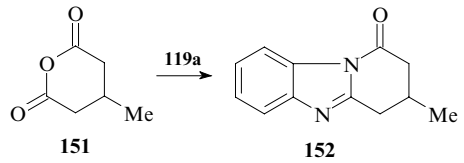


$n$ = 1 : $R^1$ = $R^2$ = Ph (**a**); $R^1$ = 4-$MeOC_6H_4$, $R^2$ = H (**b**); $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = Ph (**c**); $n$ = 2: $R^1$ = 4-$MeOC_6H_4$, $R^2$ = Ph (**d**); $R^1$ = 4-$O_2NC_6H_4$, $R^2$ = Ph (**e**); $R^1$ = 2-$O_2NC_6H_4$, $R^2$ = H (**f**); $R^1$ = 2-$O_2NC_6H_4$, $R^2$ = Ph (**g**)

Thus, the condensation of cyclohexanones **148d–g** is the regiospecific reaction resulting in the closure of the azole ring onto the alicyclic moiety to form only compounds **149d–g**. The heterocyclization of cyclopentanone derivatives **148a–c** can follow both pathways, whose ratio depends on the nature of the substituent $R^1$. For example, the reaction of cyclopentanone **148a** gives compounds **149a** and **150a** in a ratio of 3 : 7, the reaction of *p*-nitro-substituted analogue produces compound **149c**, whereas the reaction of *p*-methoxy-substituted 1,5-diketone **148b**, which does not contain a substituent in position 3, affords only product **150b**. The yields of the reaction products are 35%–80%.

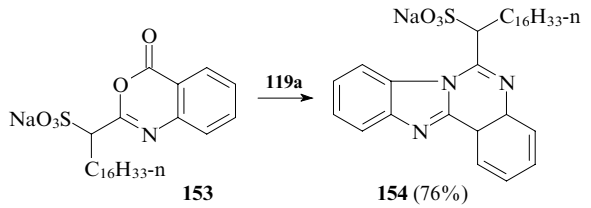
The heating of *o*-phenylenediamine (**119a**) with 4-methyldihydro-2*H*-pyran-2,6(3*H*)-dione (**151**) under reflux in xylene results in the formation of 3-methyl-3,4-dihydropyrido[1,2-*a*]benzimidazol-1(2*H*)-one (**152**) in 10% yield (Scheme 59).[108]

Scheme 59



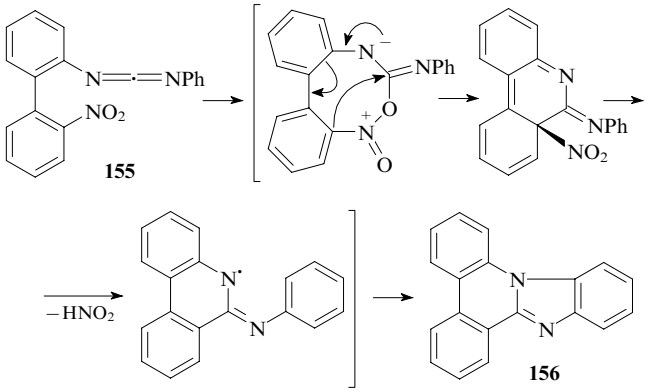
The fusion of 4*H*-3,1-benzoxazin-4-one **153** with diamine **119a** on an oil bath for 2 h yielded the sodium salt of dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline sulfonate **154** (Scheme 60).[109]

Scheme 60



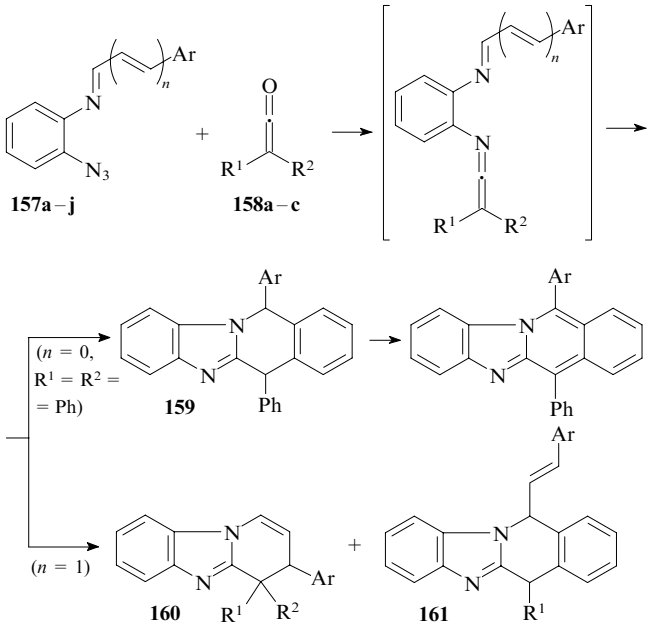
Another approach to the simultaneous formation of the imidazole and pyridine rings in fused azaheterocyclic systems is based on the intramolecular cyclization of carbodiimide **155**, which takes place during its pyrolysis (750 °C, 0.0015 mm Hg).[102, 110] The proposed reaction mechanism is shown in Scheme 61.[110] The yield of benzimidazo[1,2-*f*]phenanthridine (**156**) is 45%.

Scheme 61



Two heterocyclic moieties of the fused benzimidazo[1,2-*b*]isoquinoline system are formed by the reaction of *o*-phenylenediamine derivatives **157a–f** with ketene **158a**.[111] The reaction proceeds in a 1 M trimethylphosphine solution under reflux in toluene for 0.7 h. It was noted that products **159** are obtained after the isolation by chromatography in rather high yields (84%–92%) (Scheme 62).

Scheme 62



**157**: $n$ = 0: Ar = $R^3{}_nC_6H_{5-n}$ [$R^3_n$ = 4-Cl (**a**), 4-CN (**b**), 4-Me (**c**), 4-$NO_2$ (**d**), 3,5-$(OMe)_2$ (**e**), 2,6-$Cl_2$ (**f**)]; $n$ = 1: Ar = $R^3C_6H_4$ [$R^3$ = H (**g**), 2-OMe (**h**), 2-$NO_2$ (**i**), 4-OMe (**j**)];
**158**: $R^1$ = $R^2$ = Ph (**a**), H (**b**); $R^1$ = Me, $R^2$ = Ph (**c**)

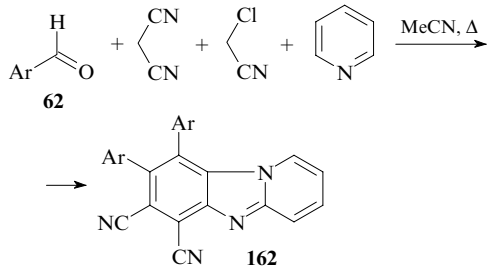
The aromatization of compounds **159** was performed under reflux in the presence of Pd/C in toluene for 16 h; the yields were 47%–67% (see Scheme 62).

More recently, the range of structures prepared according to this procedure was extended.[112] For instance, the reactions of *N*-(2-azidophenyl)imines **157g–j** with ketenes **158a–c** produced pyrido[1,2-*a*]benzimidazoles **160**. However, the reactions with the use of phenyl-substituted ketenes **158a**,**c** afforded mixtures of isomers **160** and **161**.

In some cases (if $R^3 = 2\text{-}NO_2$), they were produced in comparable yields. The high regioselectivity was observed only in the reaction giving pyrido[1,2-*a*]benzimidazoles **160** ($R^1 = R^2 = H$), which were isolated in 40% – 52% yields.

In the last decade, methods for the synthesis of pyrido[1,2-*a*]benzimidazoles based on one-step multicomponent reactions were reported.[113, 114] For example, pyrido[1,2-*a*]benzimidazoles **162** were synthesized by heating a mixture of substituted benzaldehydes **62** with malononitrile, chloroacetonitrile and an excess of pyridine under reflux in acetonitrile for 6 – 24 h (yields 20% – 51%) (Scheme 63).[114]

Scheme 63

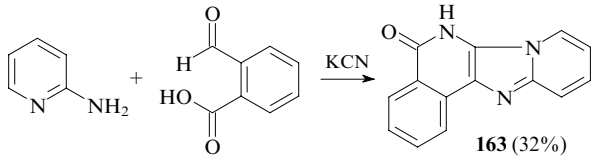


**62** **162**

Ar = Ph, 3-$MeC_6H_5$, 4-$MeC_6H_5$, 4-$EtC_6H_5$, 4-$Pr^iC_6H_5$, 4-$Bu^tC_6H_5$, 4-$MeOC_6H_5$, 4-$FC_6H_5$, 3-$ClC_6H_5$, 4-$ClC_6H_5$, 3-$BrC_6H_5$, 4-$BrC_6H_5$

The heating of 2-aminopyridine with 2-formylbenzoic acid and potassium cyanide in aqueous NaOH resulted in the formation of pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one (**163**) (Scheme 64).[115]

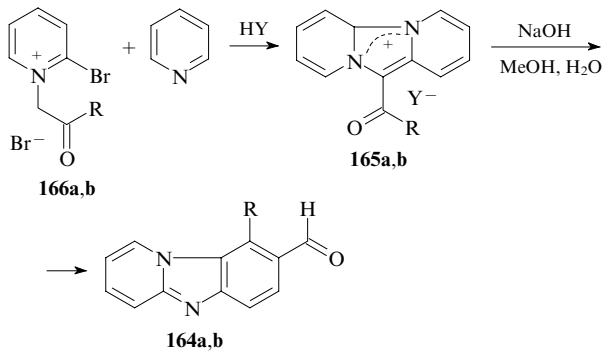
Scheme 64



**163** (32%)

An interesting approach to the synthesis of pyrido[1,2-*a*]benzimidazoles **164a**,**b** was proposed by Babaev and Tikhomirov.[116] These compounds are formed as a result of the previously unknown recyclization of 11-acyldipyrido[1,2-*a*:1,2-*c*]imidazolium cations (**165a**,**b**), which are generated from pyridinium salts **166a**,**b** (Scheme 65).

Scheme 65



**166a**,**b** **165a**,**b** **164a**,**b**

R = 4-$BrC_6H_4$ (**a**), Me (**b**); Y = Br (**165a**), $ClO_4$ (**165b**)

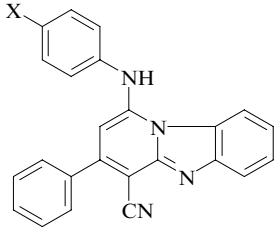
The products are formed in 93% (**164a**) and 43% (**164b**) yields after the addition of aqueous alkali to a solution of salts **165a**,**b** in methanol. The reaction is performed initially at room temperature and then by heating until product **164** precipitates, and the precipitate is purified by column chromatography.

## V. Biological activity of fused azaheterocycles

Fused polycyclic azaheterocycles have attracted great interest from pharmacologists due to a wide spectrum of biological activity of such derivatives. Some of these compounds exhibit antitumour (**167** – **169**),[14, 117, 118] immunomodulatory (**170**),[119] anti-inflammatory (**171**),[120] antibacterial and fungicidal (**172** – **174**)[121 – 123] activities. Drugs based on pyrido[1,2-*a*]benzimidazole **175** (commercial code RWJ 16979) have the anxiolytic effect[124 – 126] and are used as myorelaxant agents in the therapy of the central nervous system.[127 – 129]

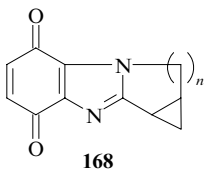
Several mechanisms of the biological activity of fused polycyclic imidazole derivatives with a bridgehead nitrogen atom were reported in the literature. Thus, the antitumour activity of this group of compounds is associated with the ability of their molecules to intercalate into the DNA double helix between pairs of complementary nitrogenous bases.[56] This results in DNA double-stranded breaks and triggers cell apoptosis.

The structural criteria for assessing the ability of a substance to intercalate into DNA are available. For



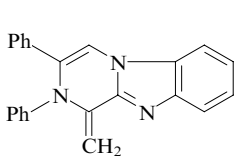
**167**

X = Cl (NSC 699944);
X = F (NSC 699948)

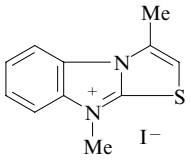


**168**

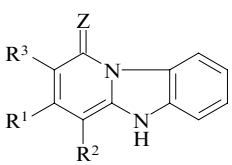
*n* = 1, 2



**169**

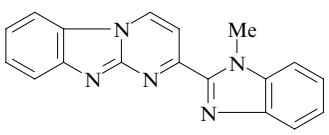


**170**

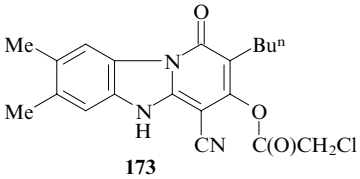


**171**

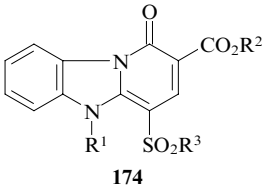
Z = O, NH; $R^1$ = H, Me;
$R^2$ = H, CN; $R^3$ = H, CN



**172**

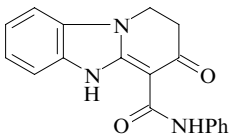


**173**



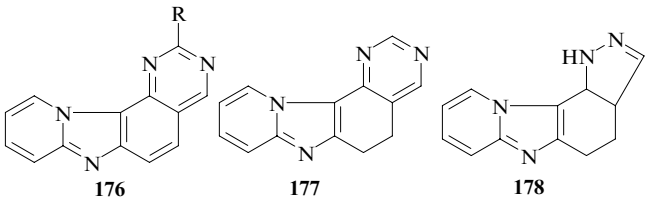
**174**

$R^1$, $R^2$, $R^3$ = Alk, Ar



**175** (RWJ 16979)

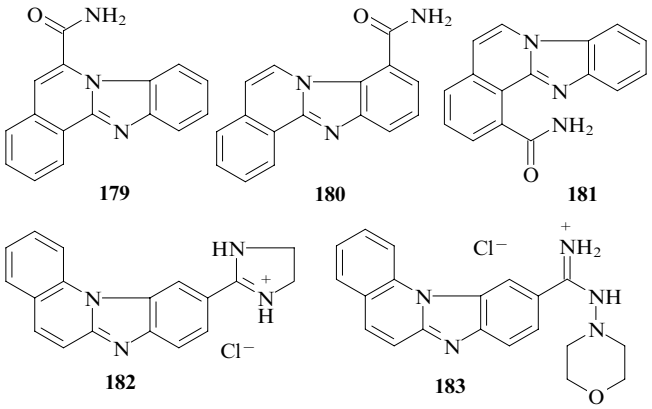
example, the presence of a planar system consisting of 3 or 4 fused heterocycles with a nitrogen atom common to several heterocycles is one of such criteria.[130–133] Biologically active compounds containing a planar polycyclic system can have this ability. Among these compounds are pyrido[1,2-*a*]benzimidazoles, benzimidazo[2,1-*a*]isoquinolines, benzimidazo[1,2-*c*]quinazolines, pyrimido[1,2-*a*]benzimidazoles, pyrido[1′,2′:1,2]imidazo[4,5-*h*]quinazolines, pyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazoles, imidazo[1,2-*a*]benzimidazoles and pyrazino[1,2-*a*]benzimidazoles.[41, 118, 134–140] It is believed that it is the presence of a system of fused aromatic azaheterocycles that is responsible for high biological activity of the compounds. For example, the cytotoxicity of pyrido[1′,2′:1,2]imidazo[4,5-*h*]quinazolines (**176**) against the HL60 and A2780 cell lines is 10 times higher than that of the corresponding hydrogenated derivatives **177** and **178** and is comparable with that of doxorubicin.[141]



**176** **177** **178**

R = H, $NH_2$

In several studies, it was shown that the introduction of $NH_2$,[134] $C(O)NH_2$ (Ref. 142) and Me (Ref. 143) groups into a heterocycle increases the cytotoxic activity of compounds against the following tumour cell lines: HL60 (leukemia), A2780 (ovarian carcinoma), SW620 (colon carcinoma) and so on. The activity depends also on the position of the functional group. Thus, the presence of the $C(O)NH_2$ group in position 1 or 11 of benzimidazo[2,1-*a*]isoquinolines **179** and **180** leads to an increase in the cytotoxic activity of compounds compared to that of 6-substituted derivatives **181**.[142]

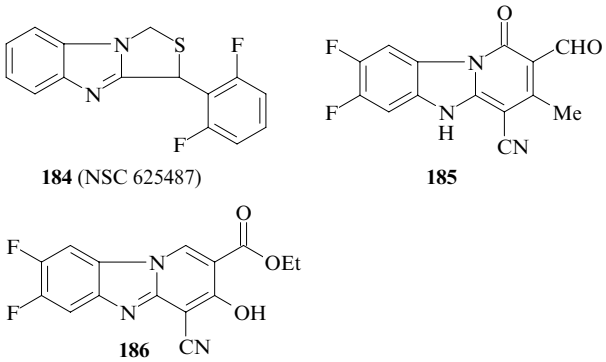


**179** **180** **181**

**182** **183**

Another way of influencing the cell reproduction and virus replication is to inhibit enzymes that play an important role in the DNA replication and transcription. For instance, compounds **182** and **183** can inhibit DNA topoisomerase II,[56] which leads to the termination of the cell cycle at the G2/M checkpoint (G2 is the post-synthetic period of the interphase and M is mitosis).[144]

The antibacterial activity of pyrimido[1,6-*a*]benzimidazole derivatives is also determined by the inhibition of enzymes, in particular, of the A subunit of DNA gyrase.[145] Compound **184** (NSC 625487) exhibits a similar effect.[146] Thus, it decreases cytopathic effects of human immunodeficiency virus (HIV) on the T lymphocyte cell culture due to the selective inhibition of HIV-1 reverse transcriptase. Fluorine derivatives **185** and **186** exhibit stable antiviral activity against a group of orthopoxviruses (variola virus).[147] By contrast, their fused bicyclic analogues did not display antiviral activity.[148]



**184** (NSC 625487) **185**

**186**

In sum, it should be noted that fused polycyclic azaheterocycles exhibit various biological activities. High antitumour and antimicrobial activities of this group of compounds, which are often higher than those of the known chemotherapeutic (etopside), antibacterial (gentamicin) and antifungal (nystatin) agents, were documented.

## VI. Conclusion

To summarize, polyfused imidazole derivatives with a bridgehead nitrogen atom attract great interest due to a wide range of biological activities. Hence, not only known methods for the synthesis of these compounds are improved but also new reactions are developed for the preparative synthesis of heterocyclic systems containing the imidazole moiety with a nitrogen atom common to several heterocycles. New papers on the development of approaches to the formation of pyrido[1,2-*a*]benzimidazole and related heterocyclic systems and investigations of their biological activity were published[149–152] during the preparation of this review. Although these data are not included in our review, they fit into the scope of the presented data , which confirms the validity of the proposed classification of the methods for the synthesis of these heterocycles.

The method for the synthesis of the target compounds is chosen by researchers based on their experience in performing particular chemical transformations, the available published data sources, reagents at hand and equipment. We hope that our review will be helpful for researchers working in the chemistry of fused heterocycles and allow one to save time for elaborating a synthetic approach to the required heterocyclic structures from readily available reagents. This will be helpful for the synthesis of a wide range of new biologically active compounds, which will contribute to the development of such areas as organic chemistry, medicine, cytogenetics and molecular biology.

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