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Advances in the synthesis of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines

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This review is intended to generalize and systematize available information on the synthesis of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines. Relevant studies published in the last 10 – 15 years, as well as earlier studies less familiar to the broad chemical community, are surveyed. Major methods of formation of the imidazoquinoxaline system from substituted quinoxalines and imidazoles according to the type of bond being formed are presented. Special focus is placed on the radically new methods that enable the synthesis of various derivatives of these heterocyclic systems from available and inexpensive reagents. The mechanisms of formation of these compounds are discussed. Information on the biological activity of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines and examples of pharmaceuticals based on them are reported.
The bibliography includes 179 references.

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I. Introduction

Heterocyclic systems containing the quinoxaline moiety are widely used in practice. Many of them have high biological activity (for example, antitumour,[1,2] antiviral,[3] antibacterial,[4,5] antiinflammatory[6]) or are inhibitors of kinases, enzymes that catalyze phosphate group transfer from ATP.[7–9] Quinoxalines are used as antibiotics,[10,11] dyes,[12,13] electroluminescent materials,[14,15] organic semiconductors,[16] DNA-binding agents,[17] as well as 'building blocks' in synthesis of anion[18] and cavitand[19,20] receptors, corrosion inhibitors,[21] *etc*. Among the derivatives annulated at bond *a* of the quinoxaline ring, imidazoquinoxalines hold a special place, since many pharmaceuticals based on them have been developed. In particular, drugs U-80447 and U-97775, which have a sedative effect, are imidazo[1,5-*a*]-quinoxaline derivatives, and antiallergic drug Dazoquinast and compound LU-73068, an anticonvulsant and glycine antagonist, are imidazo[1,2-*a*]quinoxaline derivatives (Fig. 1).[22]

In the last years, interest in imidazoquinoxalines continues unabated due to the search for compounds with antitumour activity,[23–29] which selectively act on the central nervous system[30,31] and inhibit poly(ADP-ribose) polymerase.[32] This circumstance attracts the attention of organic chemists to the development of new methods of synthesis of different imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines. However, currently, information on the synthesis of such compounds remains fragmentary. In monograph[33] (1979), data on different imidazoquinoxaline systems have been reported, mainly covering the period from 1965 to 1975, although the first publication[34] on the synthesis of imidazo[1,5-*a*]quinoxalines appeared in 1951 and that on the synthesis of imidazo[1,2-*a*]quinoxalines, in 1962.[35] In review[36] dealing with the combinatorial synthesis of the most important bicyclic structures, selected methods of

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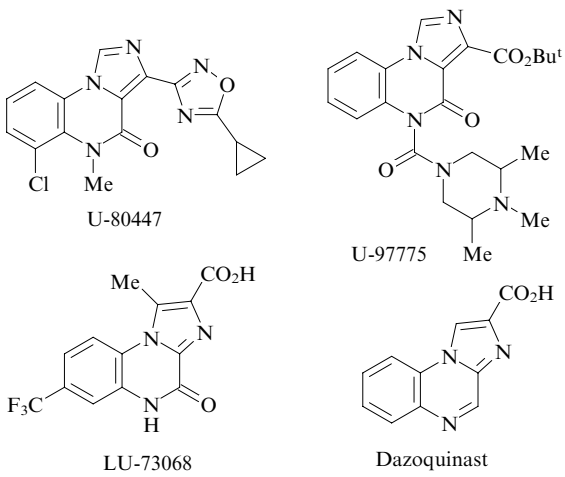
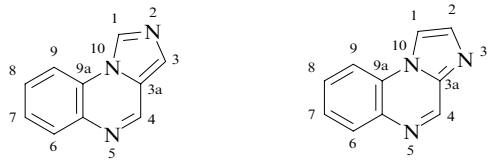


Figure 1. Imidazoquinoxaline-based drugs.

synthesis of about twenty fused heterocycles, including imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines, have been considered. The authors present available data without their comparative analysis.

In the present review, we consider all possible variants of assembly of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxaline skeletons from various fragments.

Imidazoquinoxaline structures



Imidazo[1,5-*a*]quinoxaline Imidazo[1,2-*a*]quinoxaline

The principle of systematization of data is the same as used in our previous reviews [37, 38] focusing on pyrrolo[1,2-*a*]quinoxalines. Formation of the structure of each heterocyclic system is considered without including the benzene ring. The corresponding figures show all possible assembly variants in which quinoxaline or imidazole derivatives act as the initial compounds.

II. Synthesis of imidazo[1,5-*a*]quinoxalines on the basis of quinoxaline derivatives

As shown by analysis of the structures (Fig. 2), the imidazo[1,5-*a*]quinoxaline system can be formed from quinoxaline derivatives (labelled with the subscript Q) in the following ways:

— through intramolecular cyclization with formation of the N(10)–C(1), C(1)–N(2), N(2)–C(3) or C(3)–C(3a) bonds (variants $\mathbf{A1_Q}$–$\mathbf{A4_Q}$);

— through different intermolecular condensations of quinoxaline derivatives

a) with equivalents of monoatomic carbon synthons accompanied by the formation of the N(10)–C(1) and C(1)–N(2) or N(2)–C(3) and C(3)–C(3a) bonds (variants $\mathbf{B1_Q}$ and $\mathbf{B3_Q}$),

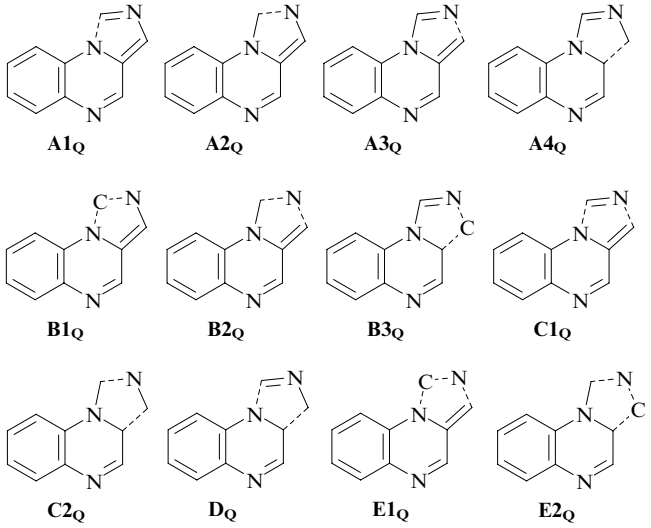


Figure 2. Possible variants of construction of the imidazo[1,5-*a*]-quinoxaline system on the basis of quinoxaline derivatives (the forming bonds are shown by the dashed lines).

b) with equivalents of monoatomic nitrogen-containing synthons accompanied by the formation of the C(1)–N(2) and N(2)–C(3) bonds (variant $\mathbf{B2_Q}$),

c) with diatomic molecules accompanied by the formation of the C(1)–N(2) and C(3)–C(3a) or N(10)–C(1) and N(2)–C(3) bonds (variants $\mathbf{C2_Q}$ and $\mathbf{C1_Q}$),

d) with triatomic molecules accompanied by the formation of the N(10)–C(1) and C(3)–C(3a) bonds (variant $\mathbf{D_Q}$);

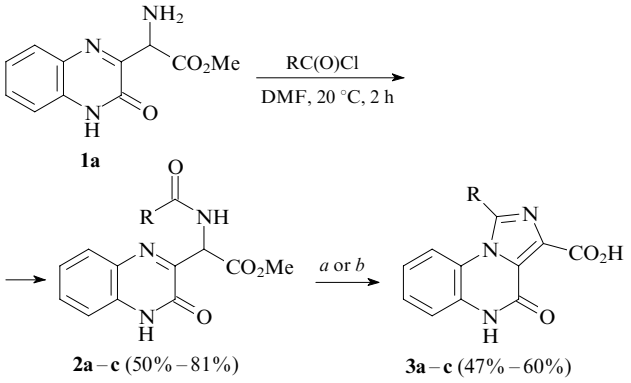
— through the three-component reaction leading to the formation of the N(10)–C(1), C(1)–N(2) and N(2)–C(3) or C(1)–N(2), N(2)–C(3) and C(3)–C(3a) bonds (variants $\mathbf{E1_Q}$ and $\mathbf{E2_Q}$).

1. Methods of formation of the N(10)–C(1) bond (variant $\mathbf{A1_Q}$)

Imidazole ring annulation according to variant $\mathbf{A1_Q}$ can be a result of the nucleophilic attack of the nitrogen atom in the 1- or 4-position of quinoxaline at the electrophilic carbon atom of the C–N–C moiety of the substituent at the C(2) or C(3) atom. Such substituents are acylaminomethyl, isocyanatomethyl, benzylaminomethyl, *etc.* groups. As a rule, the methods of synthesis corresponding to this variant are rather simple from the preparative point of view, and the reactions proceed in high yields. The starting reactants can be, for example, 3-aminomethylquinoxalines **1** (Scheme 1).[39, 40] In particular, their reaction with carboxyl chlorides yields acylated derivatives **2**; when heated for a while in alcohol solutions in the presence of potassium hydroxide, the latter undergo intramolecular cyclization to give imidazo[1,5-*a*]quinoxalines **3**. The major disadvantage of this method is that the corresponding starting compounds are obtained by multistage reactions.

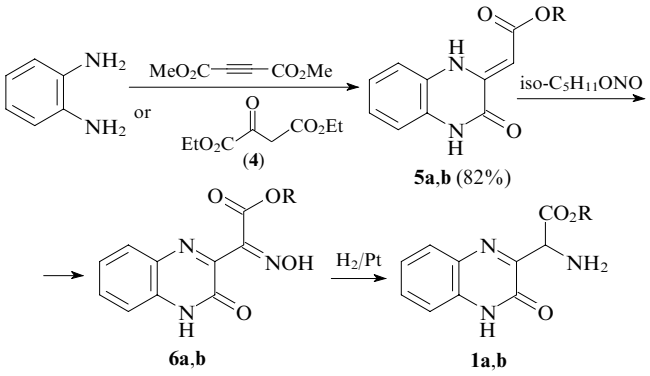
Two procedures of synthesis of aminomethylquinoxalines **1** have been developed. One of them involves three stages: 1) condensation of ethyl ethoxalylacetate (**4**) or dimethyl acetylenedicarboxylate with *o*-phenylenediamine to give quinoxalines **5**; 2) the reaction of the latter with isopentyl nitrite and 3) reduction of resulting oximes **6** (Scheme 2).[39, 40]

Scheme 1



(*a*) KOH, EtOH, H_2O, 4 h; (*b*) NaOH, MeOH, H_2O, 2 h;
2, **3**: R = Et (**a**), Ph (**b**), Bn (**c**)

Scheme 2

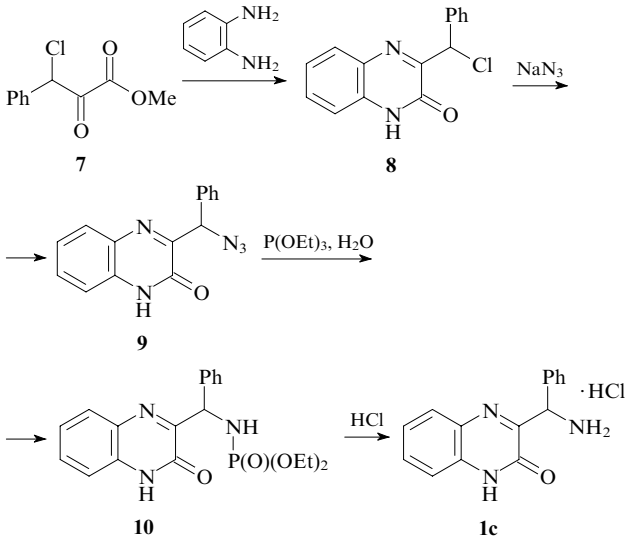


R = Me (**a**), Et (**b**)

The other procedure comprising four stages involves the following reactions: 1) condensation of methyl chlorophenylpyruvate (**7**), synthesized by the Darzan reaction from methyl dichloroacetate and benzaldehyde,[41] with *o*-phenylenediamine to give 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one (**8**);[42] 2) the reaction with sodium azide to give corresponding azide **9**; 3) Staudinger reaction with triethyl phosphite yielding phosphoramidate **10** and 4) the reaction of the latter with dry HCl, which leads to target amine **1c** in the form of hydrochloride (Scheme 3).[43]

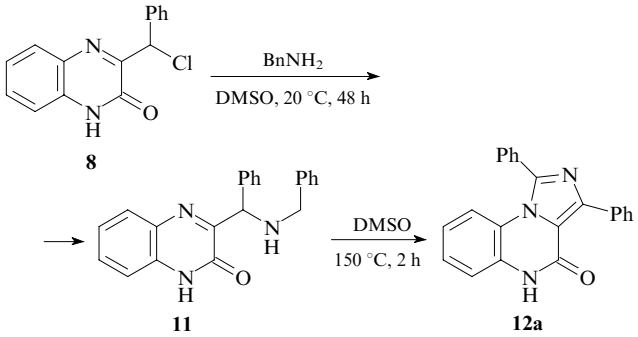
When heated for 2 h or thermolyzed for 10 min at 225 ± 3 °C, 3-(α-benzylaminobenzyl)quinoxalin-2(1*H*)-one (**11**), synthesized by the reaction of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one (**8**) and benzylamine in DMSO at room

Scheme 3



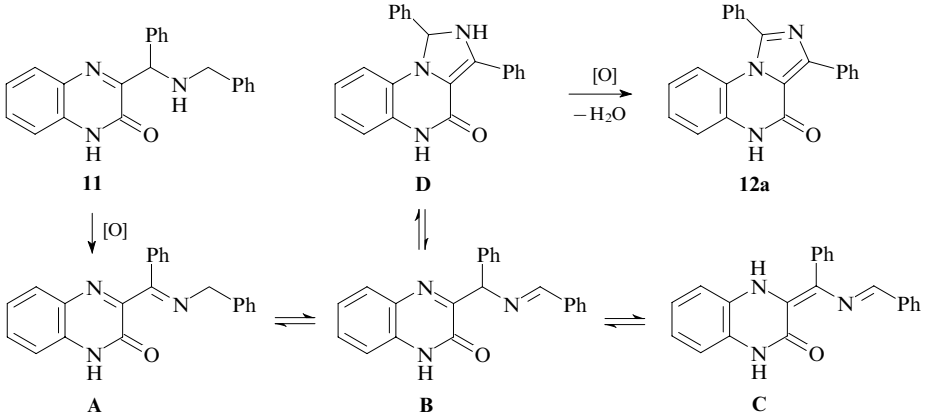
temperature, undergoes intramolecular cyclocondensation to give imidazoquinoxaline **12a** (Scheme 4).[44]

Scheme 4



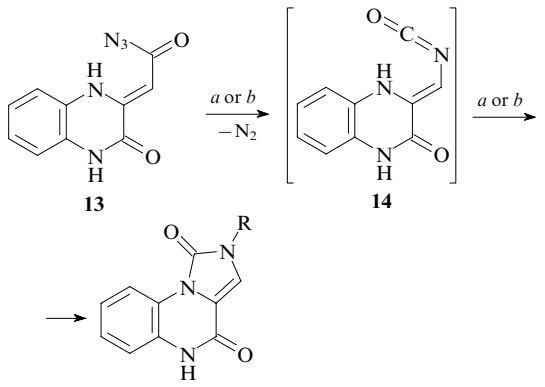
Annulation of the imidazole ring to compound **11** evidently occurs through the oxidation of the latter to imine **A** which can also exist as tautomers **B** and **C**. The nucleophilic attack of the N(4) atom at the carbon atom of the imine moiety in structure **B** leads to the closure of the imidazole ring to form dihydroimidazoquinoxaline system **D**, and further oxidation of the latter under the reaction conditions leads to tricyclic compound **12a**. Air oxygen or a solvent (dimethyl sulfoxide) can act as an oxidant in this case (Scheme 5).

Scheme 5



Heating 3-(azidocarbonylmethylene)-1,2,3,4-tetrahydroquinoxalin-2-one (**13**), synthesized from the corresponding hydrazide, in xylene or acetic anhydride first presumably induces the Curtius rearrangement to give isothiocyanate **14**, and the closure of the imidazole ring in it leads to imidazo[1,5-*a*]quinoxalinediones **15** in high yields.[45] The reaction in xylene yields imidazoquinoxalinedione **15a** with unsubstituted imidazole nitrogen atom, and the reaction in acetic anhydride affords its acetylated derivative **15b** (Scheme 6).

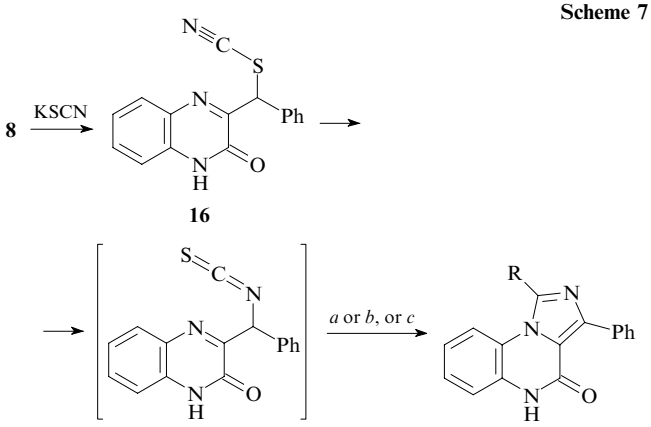
Scheme 6



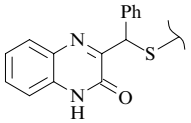
(*a*) xylene, Δ (for **15a**); (*b*) Ac_2O, Δ (for **15b**); R = H (**a**), Ac (**b**)

Quinoxaline-containing thiocyanate **16**, which forms in the reaction of 3-(α-chlorobenzyl)quinoxalinone **8** with potassium thiocyanate, isomerizes into the S-analogue of thiocyanate **14** — isothiocyanate **17**. The latter acts as a starting compound for the synthesis of imidazo[1,5-*a*]quinoxalines **12b**,**c** and **18** through intramolecular cyclization. The direction of the process depends on the reaction conditions (temperature, pH of a medium, solvent). Thermolysis of compound **16** in the absence of the solvent leads to 1-sulfanylimidazoquinoxaline **12b**, isomeric to compounds **16** and **17**, in quantitative yield. Heating thiocyanate **16** in the presence of Et_3N in DMF gives compound **18** in 60% yield, while heating in DMSO leads to imidazo[1,5-*a*]quinoxaline **12c** (yield 11%) in a mixture with other products (Scheme 7).[46]

Scheme 7

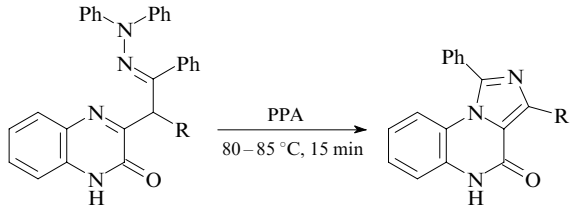


(*a*) 225 °C, 5 min (for **12b**); (*b*) DMSO, 150 °C, 1 h (for **12c**);
(*c*) Et_3N or DMF, 150 °C, 1 h (for **18**);

R = SH (**12b**), H (**12c**),  (**18**)

Under the action of polyphosphoric acid (PPA), hydrazones **19a**,**b** lose diphenylamine and convert into imidazo[1,5-*a*]quinoxalines **20a**,**b** (Scheme 8).[47]

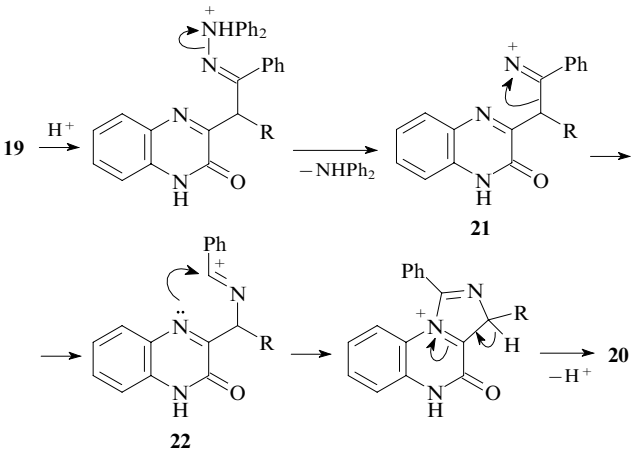
Scheme 8



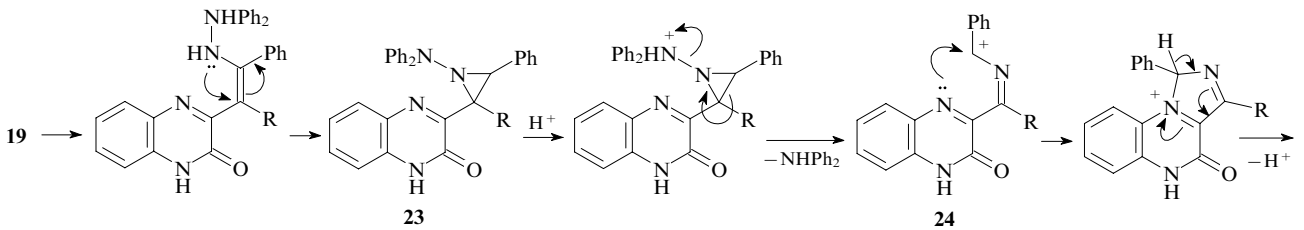
R = Me (**a**), Bn (**b**)

The authors believe that compounds **20** form as a result of generation of nitrenium ion **21** after diphenylamine elimination (just as it happens in the Schmidt reaction[48,49]), migration of the alkyl group to the nitrogen atom and closure of the imidazole ring in carbocation **22** (Scheme 9).

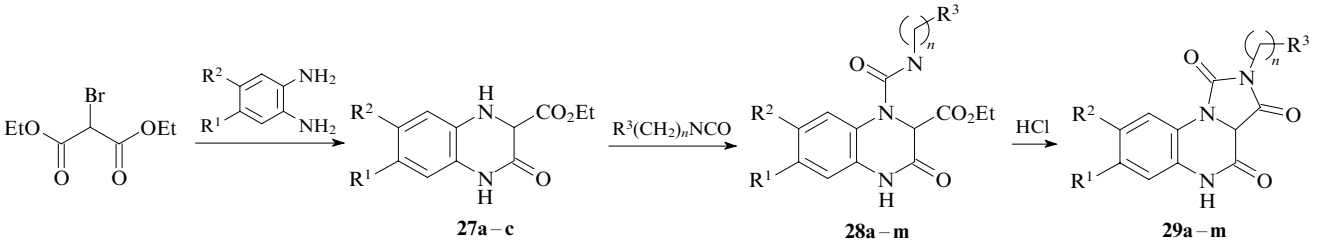
Scheme 9



Scheme 10



Scheme 12

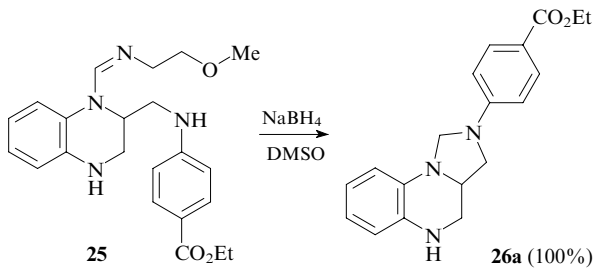


Another way can be suggested through the intermediate formation of aziridine derivative **23** and the acid-catalyzed opening of the aziridine ring at the C(2)–C(3) bond with removal of diphenylamine and formation of carbocation **24** (Scheme 10).

2. Method of formation of the C(1)–N(2) bond (variant $A2_Q$)

Intramolecular cyclization involving the amine nitrogen atom of the substituent in the 2-position and the carbon atom of the imine moiety of the substituent in the 1-position in tetrahydroquinoxaline **25** leads to hydrogenated imidazo[1,5-*a*]quinoxaline **26a** in quantitative yield (Scheme 11).[50]

Scheme 11



3. Method of formation of the N(2)–C(3) bond (variant $A3_Q$)

The reaction of diethyl bromomalonate and *o*-phenylenediamines gives tetrahydroquinoxalin-2-ones **27a–c**, which are then introduced into the aminoacylation reaction.[51] On heating in 2 M HCl, carbamoyl derivatives **28a–m** undergo intramolecular amidation to give imidazo[1,5-*a*]quinoxalines **29a–m** (Scheme 12, Table 1).[52]

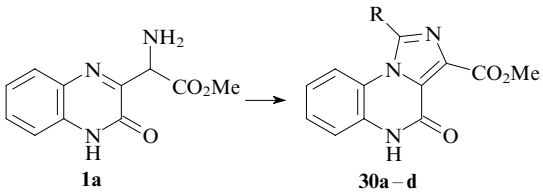
Table 1. Yields of imidazo[1,5-*a*]quinoxalines **29** (see Scheme 12).[52]

Substrate **27**	R^1	R^2	Products **28**, **29**	R^3	*n*	Yield of **29** (%)
a	H	H	**a**	Ph	0	85
	H	H	**b**	C_6H_4Me-4	0	80
	H	H	**c**	C_6H_4OMe-4	0	80
	H	H	**d**	C_6H_4Cl-4	0	90
	H	H	**e**	Et	0	50
	H	H	**f**	Ph	1	90
	H	H	**g**	CO_2Et	1	50
	H	H	**h**	CO_2H	1	40
b	Cl	H	**i**	Ph	0	70
	Cl	H	**j**	C_6H_4Me-4	0	80
	Cl	H	**k**	CO_2Et	1	40
	Cl	H	**l**	CO_2H	1	60
c	Me	Me	**m**	Ph	0	80

4. Methods of formation of the N(10)–C(1) and C(1)–N(2) bonds (variant $B1_Q$)

Only one of the three possible variants of formation of the imidazo[1,5-*a*]quinoxaline system on the basis of reactions of quinoxaline and equivalents of monoatomic synthons (see Fig. 2) is known. This variant corresponds to the formation of the bond of the C(1) carbon atom with two nitrogen atoms in the 2- and 10-positions. In particular, the condensation of 3-aminomethylquinoxalin-2(1*H*)-one **1a** with triethyl orthoformate or triethyl orthoacetate in the presence of *p*-toluenesulfonic acid (TsOH) upon heating under reflux for 2–3 h leads to imidazoquinoxalines **30a–c** (Scheme 13).[30,31] 1-Hydroxy derivative of imidazoquinoxaline **30d** is synthesized from amine **1a** by the reaction with 1,1′-carbonyldiimidazole (Im_2CO) in methanol in the presence of KOH.[43]

Scheme 13



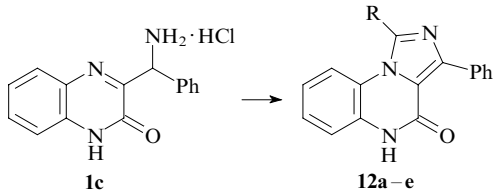
Product **30**	R	Reagent	Conditions	Yield (%)
a	H	$HC(OEt)_3$	TsOH, Δ, 2–3 h	85
b	Me	$MeC(OEt)_3$	TsOH, Δ, 2–3 h	62
c	CH_2Cl	$ClCH_2C(OEt)_3$	TsOH, Δ, 2–3 h	72
d	OH	Im_2CO	KOH, MeOH	53

The reaction of 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one hydrochloride (**1c**) with triethyl orthoformate does not require additional acid catalysis. The reaction lasts for 6 h to yield imidazoquinoxaline **12c**.[43] Refluxing of compound **1c** with acetic anhydride for 4 h leads to 1-methylimidazoquinoxalin-4-one **12d**.[43] Aromatic aldehydes can also be used as the equivalents of monoatomic synthons. As distinct from the above reactions, the reaction of compound **1c** with aromatic aldehydes requires longer time. In particular, the reaction of 4-methoxyethoxybenzaldehyde with quinoxaline **1c** in boiling dioxane lasts for 15 h to give *p*-methoxyphenylimidazoquinoxalin-4-one **12e** in high yield.

Decreasing the reaction duration to 9 h in the case of benzaldehyde gives 1-phenylimidazoquinoxaline **12a** in only 58% yield. Amine hydrochloride **1c** reacts with carbon

disulfide in methanol in the presence of KOH to give 1-sulfanylimidazoquinoxaline **12b** (Scheme 14).[43]

Scheme 14

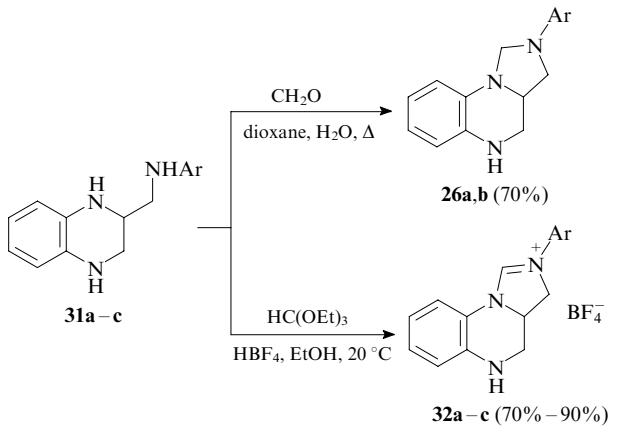


1c **12a–e**

Product **12**	R	Reagent	Conditions	Yield (%)
a	Ph	PhCHO	dioxane, Δ, 9 h	58
b	SH	CS_2	KOH, MeOH	90
c	H	$HC(OEt)_3$	6 h	84
d	Me	Ac_2O	Δ, 4 h	53
e	C_6H_4OMe-4	4-$MeOC_6H_4CHO$	dioxane, Δ, 15 h	93

The reaction of arylaminomethyltetrahydroquinoxalines **31a–c** with formaldehyde leads to hexahydroimidazoquinoxalines **26a**,**b** and the reaction with triethyl orthoformate in the presence of tetrafluoroboric acid gives imidazolium salts **32a–c** (Scheme 15).[53, 54]

Scheme 15



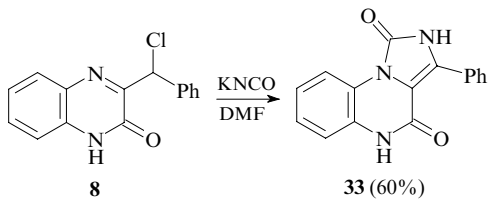
31a–c **26a**,**b** (70%) **32a–c** (70%–90%)

Ar = $C_6H_4CO_2Et$-4 (**a**), C_6H_4Me-4 (**b**), C_6H_4Cl-4 (**c**)

5. Methods of formation of the N(10)–C(1) and N(2)–C(3) bonds (variant $C1_Q$)

There are two possible ways of designing imidazo[1,5-*a*]quinoxalines according to variants **C**: the introduction of the C(1)–N(2) or N(2)–C(3) fragment into quinoxaline derivatives. However, only the first one (variant $\mathbf{C1_Q}$) has been described in the literature. Evidently, this is due to the ease of synthesis of appropriate starting quinoxalines.[41, 42] In particular, the reaction of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one (**8**) with potassium isothiocyanate in boiling DMF for 6 h leads to 3-phenylimidazoquinoxaline-1,4-dione (**33**) (Scheme 16).[43]

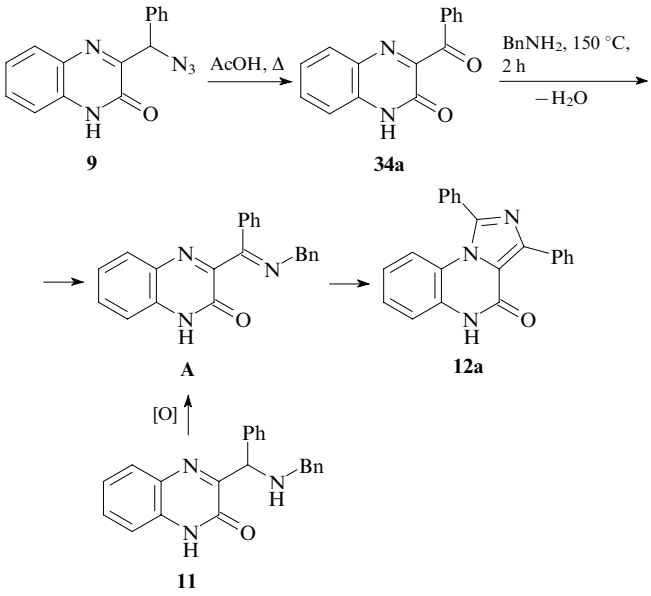
Scheme 16



8 **33** (60%)

The reaction of heterocyclic ketone **34a** with benzylamine on heating in DMSO affords imidazoquinoxaline **12a** in quantitative yield. This result is yet another evidence that the formation of imidazoquinoxaline **12a** in the reaction of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one (**8**) with benzylamine in DMSO also occurs through amine **11** and intermediate imine **A** (see Scheme 5).[44] 3-Benzoylquinoxalin-2(1*H*)-one (**34a**) readily forms upon thermolysis of azide **9** in boiling acetic acid (Scheme 17).[55]

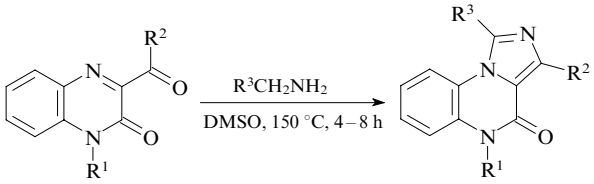
Scheme 17



9 **34a** **A** **12a** **11**

Analogously, N-alkylated derivatives **34c–h** and 3-acetylquinoxalin-2-one (**34b**) [instead of 3-benzoylquinoxalin-2-one (**34a**)] react with 3-aminomethylpyridine (β-picolylamine) (instead of benzylamine) to give imidazo[1,5-*a*]quinoxalin-4-ones **35a–l** (Scheme 18, Table 2).[56–58]

Scheme 18



34a–h **12a**, **35a–l**

In addition, compounds containing two benzoylquinoxaline moieties were introduced into this reaction. This enabled the synthesis of bis(imidazoquinoxaline)s in which the quinoxaline moieties are linked with each other through various spacers. In particular, the reaction of α,ω-bis(3-benzoylquinoxalin-2-on-1-yl) derivatives **36a–e** with benzyl- and picolylamines on heating in DMSO yields α,ω-bis(1,3-diphenyl- and 1-pyridyl-3-phenylimidazo[1,5-*a*]quinoxalin-4-on-5-yl) derivatives **37a–g** (Scheme 19).[44, 56, 57, 59]

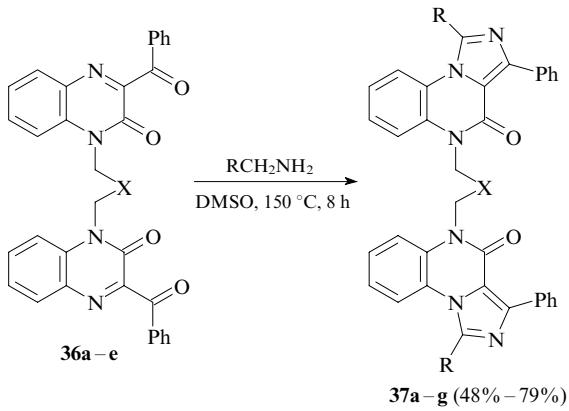
The second approach to the synthesis of bis(imidazoquinoxaline)s is based on the use of a compound containing two aminomethyl moieties, 1,3-di(aminomethyl)benzene (**38**).

Table 2. Yields of imidazo[1,5-*a*]quinoxalines **12a** and **35** (see Scheme 18).[56–58]

Substrate **34**	R^1	R^2	Product	R^3	Yield (%)
a	H	Ph	**12a**	Ph	98
	H	Ph	**35a**	3-Py	66
	H	Ph	**35b**	3-Py	63
b	H	Me	**35c**	Ph	40
	H	Me	**35d**	3-Py	51
c	Me	Ph	**35e**	3-Py	65
d	Et	Ph	**35f**	Ph	76
	Et	Ph	**35g**	3-Py	66
e	Pr^n	Ph	**35h**	Ph	75
	Pr^n	Ph	**35i**	3-Py	51
f	n-C_6H_{13}	Ph	**35j**	3-Py	57
g	n-C_9H_{19}	Ph	**35k**	3-Py	51
h	n-$C_{18}H_{37}$	Ph	**35l**	3-Py	44

Note. Py is pyridyl.

Scheme 19

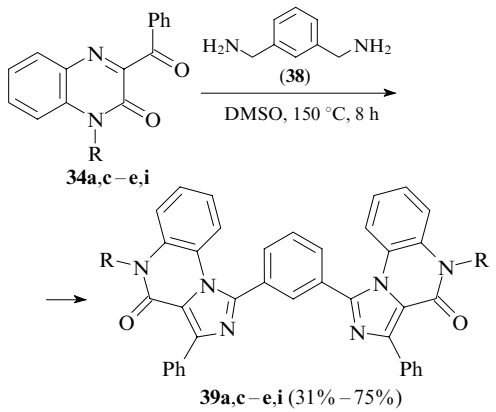


36a–e **37a–g** (48%–79%)

R = Ph: X = CH_2OCH_2 (**a**), $(CH_2OCH_2)_2$ (**b**), $(CH_2OCH_2)_3$ (**c**), $(CH_2)_4$ (**d**), C_6H_4-1,3 (**e**); R = 3-Py: X = $(CH_2)_4$ (**f**), $(CH_2OCH_2)_3$ (**g**)

It reacts with 3-benzoylquinoxalin-2-ones **34a**,**c**–**e**,**i** to give *m*-phenylenebis(imidazo[1,5-*a*]-quinoxalin-4-one)s **39a**,**c**–**e**,**i**.[44, 56, 59] These compounds are of interest as bidentate chelating agents and precursors of macrocycles (Scheme 20).

Scheme 20

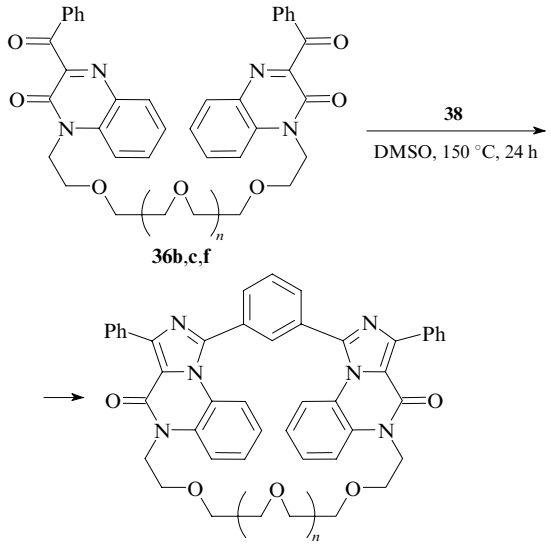


34a,c–e,i **39a,c–e,i** (31%–75%)

R = H (**a**), Me (**c**), Et (**d**), Pr^n (**e**), Bn (**i**)

An original method of constructing new types of crown ether derivatives **40b**,**c**,**f** is a combination of the above approaches to the synthesis of bis(imidazo[1,5-*a*]quinoxaline)s.[56] However, from compounds **36b**,**c**,**f**, these macrocycles are obtained in low yields. The yield of products **40** insignificantly increases when the reaction is carried out in the presence of alkali metal salts ($LiClO_4$, NaCl, KI) as template agents (Scheme 21).[56]

Scheme 21

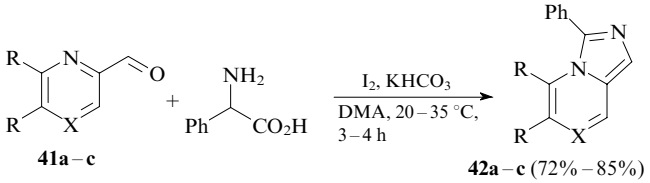


36b,c,f **40b,c,f** (8%–14%)

n = 0 (**b**), 1 (**c**), 2 (**f**)

The method of formation of the N(10)–C(1) and N(2)–C(3) bonds suggested by the authors of this review [56] has been successfully used for imidazo[*a*]annulation of quinoxaline, quinoline and pyridine derivatives.[60] The starting compounds are quinoxaline- (**41a**), quinoline- (**41b**) and pyridine-2-carbaldehydes (**41c**) (instead of 3-benzoylquinoxalinone derivatives) and phenylglycine (instead of benzyl- and picolylamines). The reactions have been carried out under milder conditions than in Ref. 56 (DMSO, 150 °C) and have afforded products **42a**–**c** in rather high yields (Scheme 22).

Scheme 22



41a–c **42a–c** (72%–85%)

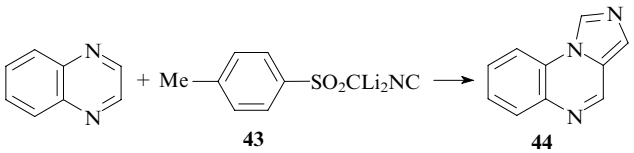
R–R is benzo: X = N (**a**), CH (**b**); R = H, X = N (**c**);
DMA is dimethylacetamide

6. Methods of formation of the N(10)–C(1) and C(3)–C(3a) bonds (variant D_Q)

All known D_Q-type methods of synthesis of imidazoquinoxalines (see Fig. 2) involve the reaction of quinoxaline derivatives with synthetic equivalents of the $^{2-}C(R)-N{=}C^{+}$ fragment; as such, methyl isocyanides are usually used. The principle possibility of implementing this approach was demonstrated for the first time in 1980 by the reaction of unsubstituted quinoxaline with dilithium

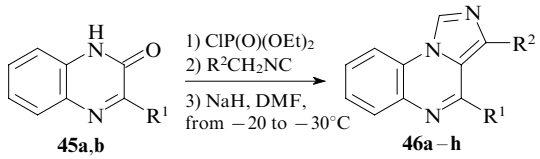
derivative **43**, readily generated from *p*-toluenesulfonylmethyl isocyanide (TsMIC) under the action of two Bu^nLi equivalents in THF at −70 °C.[61] The yield of imidazo[1,5-*a*]quinoxaline (**44**) was 30% (Scheme 23).

Scheme 23



Quinoxalin-2(1*H*)-ones of different structure react with methyl isocyanides under the action of bases to form imidazo[1,5-*a*]quinoxaline derivatives.[60–76] The reaction is usually carried out in the presence of diethyl chlorophosphite at low temperatures. The *in situ* formed diethyl quinoxalinylphosphonate (see below) readily reacts with substituted methyl isocyanides, and 1,3-dipolar cycloaddition thereby leads to annulation of the imidazole ring. By this method, quinoxalinones **45a**,**b** have been converted into imidazo[1,5-*a*]quinoxalines **46a**–**h** with different substituents in the 3-position (Scheme 24).[62, 63]

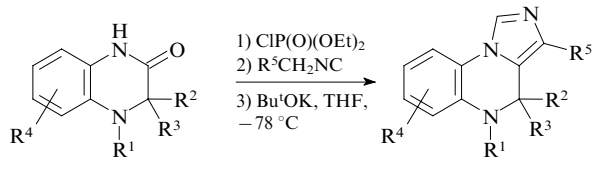
Scheme 24



45: R^1 = H (**a**), Me (**b**);
46: R^1 = H: R^2 = CO_2Et (**a**), CO_2Pr^i (**b**), CO_2Bu^t (**c**);
R^1 = Me: R^2 = CO_2Et (**d**), CO_2Pr^i (**e**), CO_2Bu^t (**f**), 5-cyclopropyl-1,2,4-oxadiazol-3-yl (**g**), 5-methyl-1,2,4-oxadiazol-3-yl (**h**)

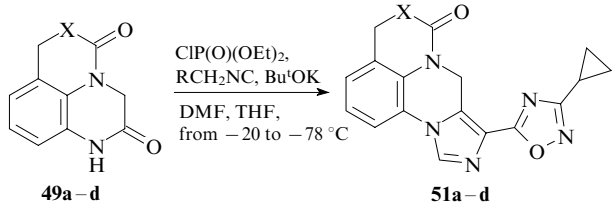
The reaction of substituted dihydroquinoxalin-2(1*H*)-ones **47** under these conditions leads to corresponding dihydroimidazoquinoxalines **48**.[64–70] The number of imidazo[1,5-*a*]quinoxaline derivatives thus synthesized amounts to several hundreds (Scheme 25).

Tricyclic compounds **49a**–**d** and **50a**–**d**, containing the quinoxalin-2(1*H*)-one moiety with the carbonyl group at the C(4) atom reacts with isocyanides in the presence of potassium *tert*-butoxide to form tetracycles **51a**–**d** and **52a**–**d**, respectively (Schemes 26 and 27).[67, 71] The latter have been synthesized both in the racemic form (**52a**,**d**) and as optical isomers with the *S* (**52b**) and *R* configuration (**52c**) of the asymmetric centre.



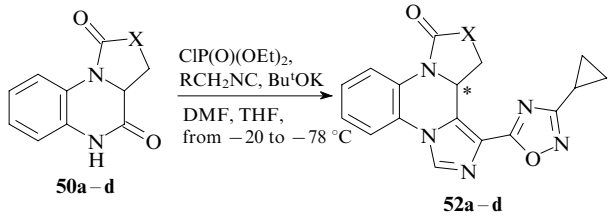
R^1 = Ac, Bz, Boc, C(O)Et, $C(O)CF_3$, $C(O)NMe_2$, $C(O)NEt_2$, pyrrolidinocarbonyl, morpholinocarbonyl, piperidinocarbonyl, 2-furylcarbonyl, *etc.*; R^2, R^3 = H, Me; R^4 = H, Me, F, Cl; R^5 is 5-X-1,2,4-oxadiazol-3-yl (X = Et, Pr^i, cyclo-C_3H_5), CO_2Bu^t, Ar; Boc = $C(O)OBu^t$

Scheme 26



X = NBoc (**a**, 22%), NPr^i (**b**), NMe (**c**), O (**d**, 32%);
R is 3-cyclopropyl-1,2,4-oxadiazol-5-yl

Scheme 27

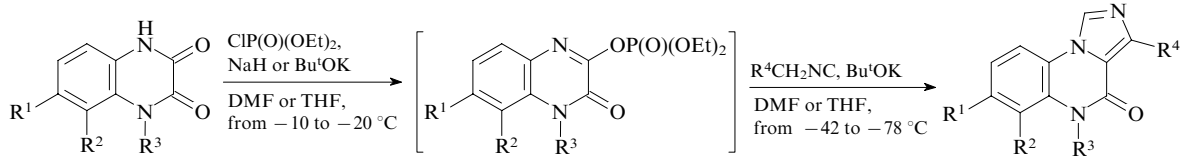


X = CH_2 (*R*,*S*) (**a**, 47%), CH_2 (*S*) (**b**, 46%), CH_2 (*R*) (**c**, 46%), O (**d**, 10%);
R is 3-cyclopropyl-1,2,4-oxadiazol-5-yl

A method of synthesis of imidazoquinoxalin-4-ones that affords these heterocyclic systems with different substituents in the 3-, 5-, 6- and 7-positions has been well developed.[64, 69, 72–77] The method is based on the reaction of quinoxaline-2,3-dione derivatives **53** with diethyl chlorophosphite leading to diethyl quinoxalinyl phosphates **54**. The latter, without isolation, are introduced into the reaction with substituted methyl isocyanides in the presence of a base leading to products **55** (Scheme 28).

Quinoxaline-2,3-diones **53**, containing necessary substituents in the benzo moiety, are synthesized in three stages from *o*-halonitrobenzenes. The transformations involve the substitution of an amino group for the halogen atom to

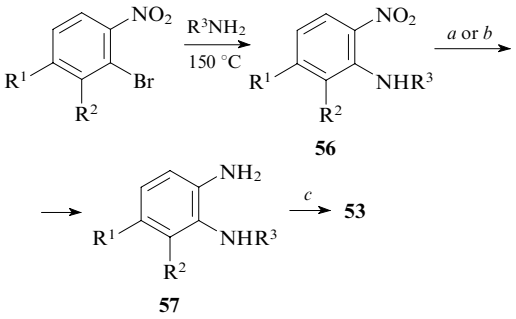
Scheme 28



R^1, R^2 = H, Cl, F, Me; R^3 = Me, Pr^i, Bu^t, Bn, $PhCH_2CH_2$, 2-$PyCH_2$, 2-$MeOC_6H_4CH_2$, cyclo-$[O(CH_2CH_2)_2N]CH_2CH_2$, cyclo-$C_3H_5CH_2CH_2$; R^4 = CO_2Et, 5-cyclopropyl-1,2,4-oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, C_6H_4X (X = H, F, Cl, OMe, CF_3)

form compounds **56**, the reduction of the nitro group to the amino group and condensation of substituted diaminobenzenes **57** with oxalyl chlorides (Scheme 29).[64]

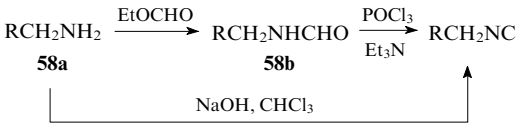
Scheme 29



(*a*) H_2, 5% Pd/C, EtOH; (*b*) H_2, 5% Pt/S/C, EtOH;
(*c*) $EtO_2CC(O)Cl$ or $(COCl)_2$, $EtNPr^i_2$, PhMe

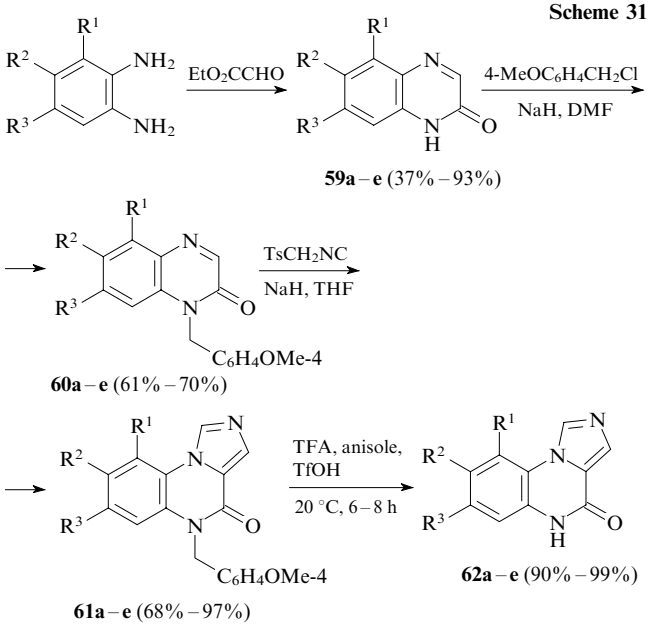
Two classical methods based on methylamines **58a** have been developed for preparation of substituted methyl isocyanides — the second component of the reaction shown in Scheme 28. The first method consists of one stage, namely, treatment of amines with chloroform in the presence of alkalis; the second method consists of two stages. The reaction with ethyl formate leads to formamides **58b**, which are then dehydrated by treating with phosphorus oxochloride in the presence of triethylamine (Scheme 30).[64]

Scheme 30



Two decades after the first example of annulation of the imidazole moiety[61] to bond *a* of quinoxaline under the action of dilithium salt **43**, a new procedure has been suggested in which the initial compounds are quinoxalinones **59**.[78–81] Protected *N*-(4-methoxybenzyl)quinoxalinones **60** are introduced into the reaction with TsMIC in THF in the presence of NaH, which leads to imidazoquinoxaline **61** in high, sometimes quantitative, yields. The

Scheme 31

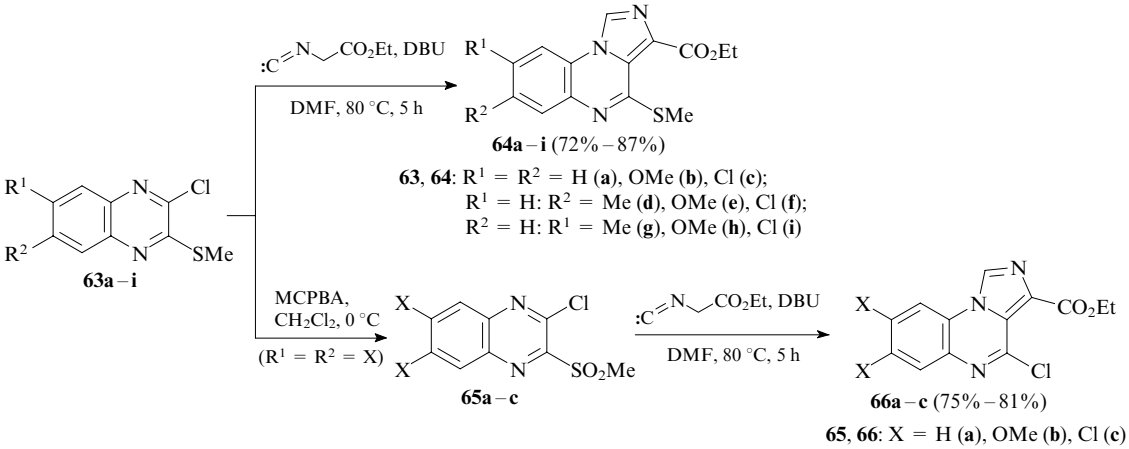


$R^1 = R^2 = H$: R^3 = H (**a**), OMe (**b**), Cl (**c**);
R^1 = H, $R^2 = R^3$ = OMe (**d**); $R^1 = NO_2$, $R^2 = R^3$ = H (**e**)

protective group is removed under the action of trifluoroacetic acid (TFA), anisole and trifluoromethanesulfonic acid (TfOH). This method is simple and enables the synthesis of different initial N(1)-alkylated quinoxalin-2(1*H*)-ones through condensation of *o*-phenylenediamines and ethyl glyoxalate with subsequent introduction of the protective *p*-methoxybenzyl group. The method has opened a new way to the synthesis of numerous imidazo[1,5-*a*]quinoxalines **62** with the free 1- and 3-positions (Scheme 31).

When quinoxaline has an easily leaving group in the 2-position, annulation of the imidazole ring according to variant $\mathbf{D_Q}$ can also occur, which is demonstrated by Scheme 32.[82] The reaction of 2-methylsulfanyl-3-chloroquinoxalines **63a–i** with ethyl isocyanoacetate leads to 4-methylsulfanylimidazoquinoxalines **64a–i**, whereas the reaction of the products of oxidation of compounds **63a–c**, sulfones **65a–c**, gives 4-chloroimidazoquinoxalines **66a–c**.[80]

Scheme 32

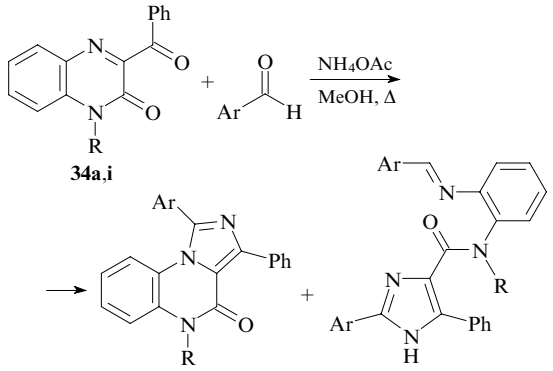


MCPBA is *m*-chloroperoxybenzoic acid, DBU is 1,5-diazabicyclo[5.4.0]undec-7-ene

7. Method of formation of the N(10)–C(1), C(1)–N(2) and N(2)–C(3) bonds (variant $E1_Q$)

It should be noted that the examples of **E**-type formation of bonds in imidazo[1,5-*a*]quinoxalines are limited to variant $E1_Q$. The three-component reaction of 3-benzoylquinoxalin-2(1*H*)-one (**34a**) with aromatic aldehydes and NH_4OAc in boiling methanol is the only example of E_Q-type synthesis of the imidazo[1,5-*a*]quinoxaline system.[83] This reaction leads not only to imidazo[1,5-*a*]quinoxaline derivatives **12a** and **67a–g** but also to 2,4,5-trisubstituted imidazoles **68a–h**, sometimes as major products. It should be noted that the reaction of N-alkylated 3-benzoylquinoxalin-2(1*H*)-one **34i** yields only imidazo[1,5-*a*]quinoxaline **67g**. As distinct from variant $C1_Q$ of synthesis of imidazo[1,5-*a*]-quinoxalines where aminomethyl derivatives are used to introduce the C(1)–N(2) fragment into 3-benzoylquinoxalin-2(1*H*)-one, in this case the reaction involves different substituted aldehydes, including pyridine-3-carbaldehyde, and inexpensive and readily available ammonium acetate. This approach is attractive since it enables the introduction of a definite substituent in any position of imidazo[1,5-*a*]quinoxalines under relatively mild conditions (Scheme 33).

Scheme 33



Compound **34**	R	Ar	Products [yield (%)]
a	H	Ph	**12a** (26) + **68a** (49)
	H	4-BrC_6H_4	**67a** (33) + **68b** (47)
	H	4-$O_2NC_6H_4$	**67b** (17) + **68c** (47)
	H	4-FC_6H_4	**67c** (26) + **68d** (45)
	H	4-ClC_6H_4	**67d** (28) + **68e** (40)
	H	4-IC_6H_4	**67e** (29) + **68f** (44)
	H	3-Py	**67f** (42) + **68g** (38)
i	Bu^n	Ph	**67g** (42) + **68h** (traces)

III. Synthesis of imidazo[1,5-*a*]quinoxalines based on imidazole derivatives

Design of the imidazo[1,5-*a*]quinoxaline system on the basis of imidazole derivatives (labelled with the subscript I) has been much less studied than the synthesis based on quinoxaline derivatives. Three variants of assembly of such a tricyclic system are mainly used: intramolecular cyclization of imidazole derivatives with formation of the C(4)–N(5) and C(9a)–N(10) bonds (variants $A2_I$ and $A4_I$, respectively) and intermolecular condensation with equivalents of monoatomic carbon synthons with the simultaneous formation of the C(3a)–C(4) and C(4)–N(5) bonds (variant $B1_I$) (Fig. 3). Other routes are represented by single examples.

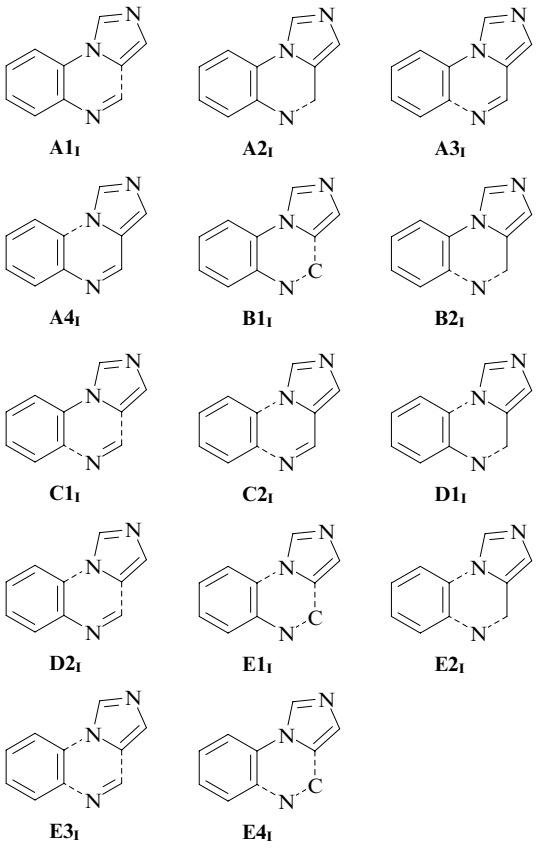
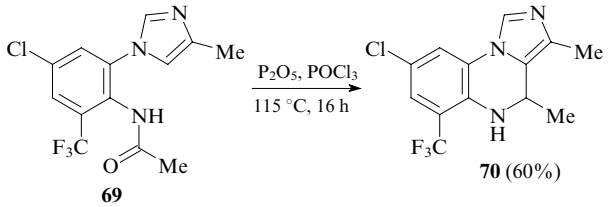


Figure 3. Possible variants of construction of the imidazo[1,5-*a*]-quinoxaline system on the basis of imidazole derivatives.

1. Method of formation of the C(3a)–C(4) bond (variant $A1_I$)

As distinct from imidazo[1,2-*a*]quinoxaline derivatives for which the method of construction of the heterocycle through the formation of the C(3a)–C(4) bond is basic (see Section V.1), there are only two publications describing the $A1_I$-type synthesis of representatives of the tricyclic imidazo[1,5-*a*]quinoxaline system.[30,84] The condensation of acetamide **69** in a mixture of phosphorus(V) oxide and oxochloride on heating leads to imidazo[1,5-*a*]quinoxaline **70** (Scheme 34).

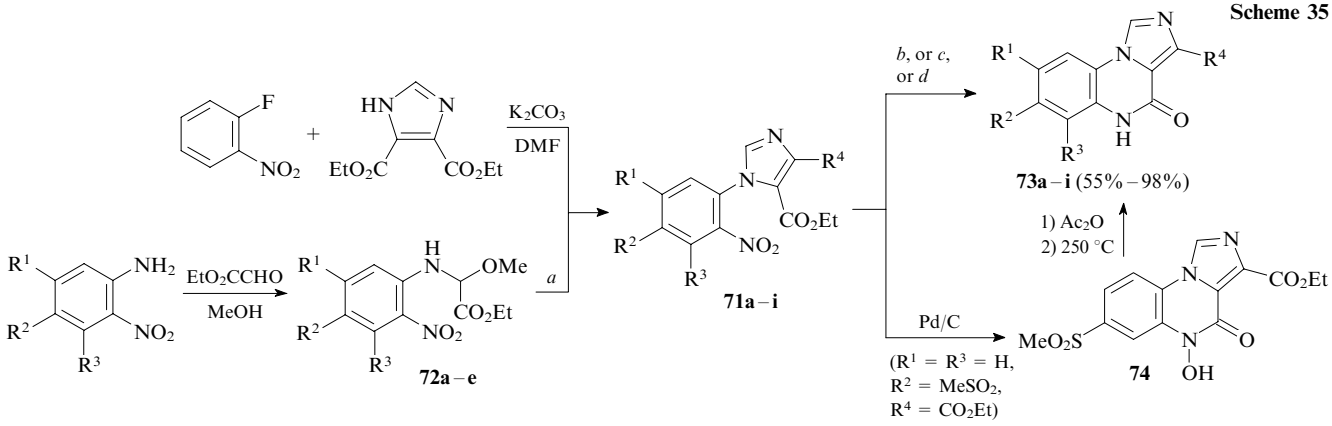
Scheme 34



2. Methods of formation of the C(4)–N(5) bond (variant $A2_I$)

Reductive cyclization of 1-(2-nitrophenyl)-5-ethoxycarbonylimidazoles **71** is used rather often for constructing the imidazo[1,5-*a*]quinoxaline ring. Compounds **71** are synthe-

Scheme 35



(*a*) $TsCH_2NC$, K_2CO_3, EtOH, 50 °C, 4 h; (*b*) Pd/C, EtOH; (*c*) Fe, AcOH, 105 °C, 6–12 h; (*d*) $Na_2S_2O_4$, AcOH, H_2O, 105 °C, 6 h

72: $R^1 = R^2 = OMe$, $R^3 = H$ (**a**); $R^1 = NHMe$, $R^3 = H$: $R^2 = H$ (**b**), F (**c**), Cl (**d**); $R^1 = R^2 = H$, $R^3 = CO_2Et$ (**e**);
71, **73**: $R^1 = R^3 = H$, $R^4 = CO_2Et$: $R^2 = H$ (**a**), SO_2Me (**b**); $R^1 = R^2 = OMe$, $R^3 = R^4 = H$ (**c**); $R^2 = R^3 = H$, $R^1 = Cl$, $R^4 = CO_2Et$ (**d**); $R^1 = R^2 = R^4 = H$: $R^3 = Cl$ (**e**), CO_2Et (**i**); $R^1 = NHMe$, $R^3 = R^4 = H$: $R^2 = H$ (**f**), F (**g**), Cl (**h**)

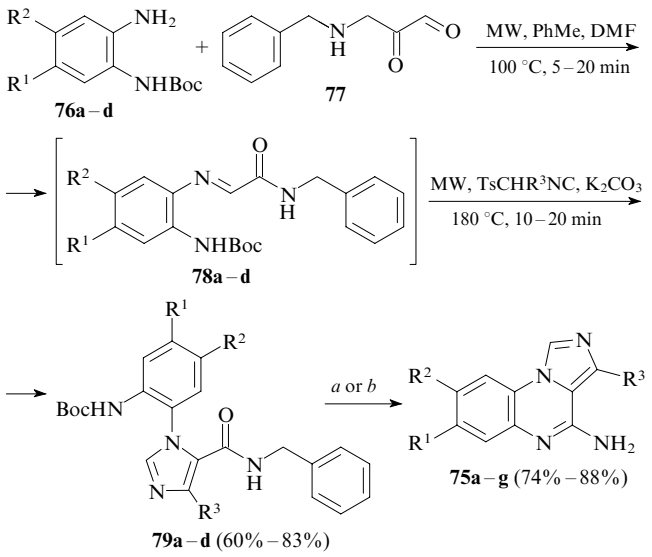
sized by two methods: 1) from *o*-fluoronitrobenzenes by the reaction with 4,5-diethoxycarbonylimidazole in the presence of K_2CO_3 (Refs 85 and 86) or Cs_2CO_3 (Ref. 87) in DMF; 2) in two stages — by the reaction of *o*-nitroanilines with ethyl glyoxylate followed by cyclization of the resulting α-methoxy-α-(2-nitroanilino)acetates **72**.[88,89] The cyclization of compounds **71** gives imidazo[1,5-*a*]quinoxalines **73** (R^2 = H, OMe).[85,87–91] Once the benzene ring of molecule **71** has the acceptor methylsulfonate group, the reduction mainly leads to 5-hydroxyimidazoquinoxaline **74**, which is then converted in two stages into imidazoquinoxaline **73b** (acylation with acetic anhydrides and subsequent thermolysis).[85,86]

The reduction with sodium dithionite in aqueous acetic acid gives imidazoquinoxaline **73c** in nearly quantitative yield.[86] It should be noted that this method is universal for synthesis of derivatives of other heterocyclic systems, in particular, thiazolo[3,4-*a*]-,[92] pyrrolo[1,2-*a*]- (Ref. 93) and indolo[1,2-*a*]quinoxalines.[94] Their formation depends on the type of heterocyclic moiety in compounds **71** (Scheme 35).

A convenient method of synthesis of pharmacologically attractive imidazoquinoxaline derivatives **75a–g** has been described.[95] The method involves the three-component reaction of *N*-Boc-*o*-phenylenediamines **76a–d** with glyoxylic acid derivatives, namely, with ethyl glyoxylate (see Section IV) and benzylglyoxylamide (**77**), with the participation of tosylmethyl isocyanides. The reaction is carried out under microwave irradiation (the Van Leusen modification[96]). It is likely that, first, the condensation of aldehyde at the free amino group of compounds **76a–d** leads to imines **78a–d**, which are cyclized to give imidazole derivatives **79a–d**. Removal of the Boc protective group from the nitrogen atom of compounds **78a–d** promotes further cyclization, which occurs either spontaneously with formation of heterocycle **75a** (see also Section IV) or under microwave irradiation in acid conditions. In the latter case, compounds **75b–f** are formed. It should be noted that the formation of the imidazoquinoxaline system by this method occurs rapidly and is highly effective (Scheme 36).

The strategy of Van Leusen[96] served as a basis for the development of a one-pot process, which made it possible to synthesize imidazo[1,5-*a*]quinoxalines with the use of phenylglyoxaldehyde instead of benzylglyoxylamide (see Section IV).[97]

Scheme 36



(*a*) 10% TFA, CH_2Cl_2, 20°C (for **a**);
(*b*) MW, 60–140 °C (for **b**–**f**)

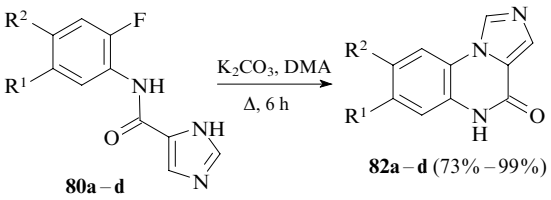
75, **79**: $R^3 = H$: $R^1 = R^2 = H$ (**a**), Me (**b**); $R^1 = F$, $R^2 = H$: $R^3 = Ph$ (**c**), Me (**d**); $R^1 = OMe$, $R^2 = H$: $R^3 = C_6H_4Br$-4 (**e**), $C_6H_3(OMe)_2$-3,4 (**f**); $R^1 = R^2 = H$, $R^3 = Et$ (**g**);
76, **78**: $R^1 = R^2 = H$ (**a**), Me (**b**); $R^2 = H$: $R^1 = F$ (**c**), OMe (**d**)

3. Methods of formation of the C(9a)—N(10) bond (variant $A4_I$)

The intramolecular nucleophilic substitution of the fluorine atom in 1*H*-imidazole-5-carboxyl-2-fluoroanilides **80a–d** and **81a–h** in the presence of a base leads to imidazo[1,5-*a*]-quinoxalines containing a hydrogen atom (**82a–d**, Scheme 37) or aminocarbonylmethyl group in the 5-position (**83a–h**, Scheme 38) according to variant $A4_I$ (see Fig. 3).[81,98–100] The cyclization of anilides **80a–d**

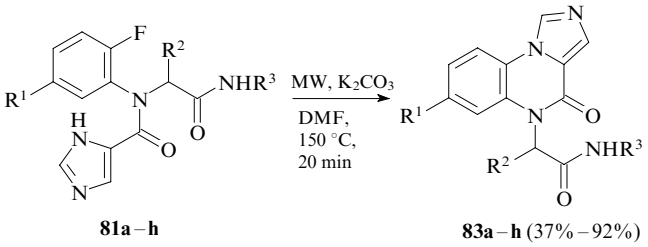
proceeds in boiling dimethylacetamide for 6 h, and the cyclization of derivatives **81a–h** in DMF under microwave irradiation at 150 °C for 20 min gives the products in high yields.

Scheme 37



R^1 = H: R^2 = H (**a**), Br (**b**); R^1 = Br, R^2 = F (**c**); R^1 = F, R^2 = Br (**d**)

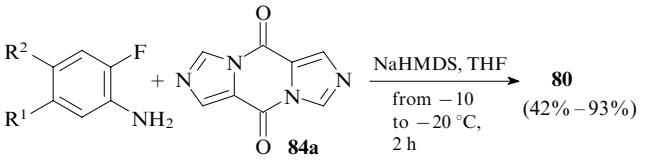
Scheme 38



R^1 = H, R^2 = cyclo-C_3H_5: R^3 = Bu^t (**a**), C_6H_4OMe-4 (**b**), $CH_2C_6H_4OMe$-4 (**c**), Me (**d**); R^1 = R^2 = H: R^3 = $CH_2C_6H_4OMe$-4 (**e**), Bu^t (**f**); R^3 = Bu^t: R^1 = H, R^2 = C_6H_4OMe-4 (**g**); R^1 = CF_3, R^2 = cyclo-C_3H_5 (**h**)

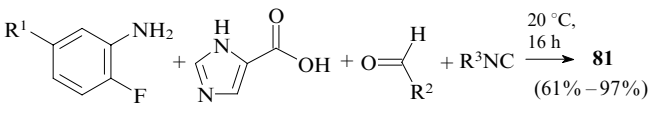
Anilides **80** have been synthesized through acylation of *o*-fluoroanilines by carbonylimidazole dimer (diimidazo[1,5-*a*:1,5-*d*]-pyrazine-5,10-dione, **84a**) in the presence of sodium hexamethyldisilazide (NaHMDS) (Scheme 39).[81,99]

Scheme 39



Compounds **81** are synthesized by the Ugi reaction, which is a multicomponent process involving *o*-fluoroaniline, aldehyde, isocyanide and 1*H*-imidazole-5-carboxylic acid. The reaction is initiated by condensation of aniline with aldehyde leading to the corresponding imine, which successively reacts with the acid and isocyanide to give target compounds **81**. Trifluoroethanol is used as a solvent in this reaction (Scheme 40).[100]

Scheme 40



4. Methods of formation of the C(3a)–C(4) and C(4)–N(5) bonds (variant $B1_I$)

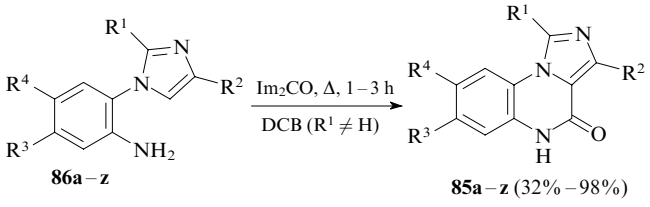
An efficient $B1_I$-type method of synthesis of imidazo[1,5-*a*]-quinoxalines **85a–z** is the reaction of 2-(1*H*-imidazol-1-yl)aminobenzenes **86a–z** with 1,1′-carbonyldiimidazole (Scheme 41, Table 3).[101–106] The reaction proceeds in boiling *o*-dichlorobenzene (DCB) to give target products in moderate to high yields.

Table 3. Imidazo[1,5-*a*]quinoxalines **85** prepared by Scheme 41.[101–106]

Compounds **85**, **86**	R^1	R^2	R^3	R^4
a	Ph	H	H	H
b	Me	H	NO_2	2-methyl-imidazol-1-yl
c	Me	H	H	H
d	Et	Me	H	H
e	Et	Me	H	morpholin-4-yl
f	Et	Me	H	4-methyl-2-ethyl-imidazol-1-yl
g	Me	H	H	Im
h	Et	Me	H	Im
i	Et	H	H	Im
j	Me	H	H	2-methylimid-azol-1-yl
k	morpholin-4-yl–methyl	H	H	H
l	Et	Me	H	pyrrolidin-1-yl
m	cyclo-C_5H_9	H	CO_2Me	Me
n	morpholin-4-yl	H	CO_2Me	Me
o	tetrahydro-furan-3-yl	H	CO_2Me	Me
p	morpholin-4-yl	H	CO_2Me	Cl
q		Me	CO_2Me	Me
r		H	CO_2Me	CH_2OMe
s	cyclohexan-1-on-4-yl	H	CO_2Me	Me
t	3-Th[a]	H	$C(O)NMe_2$	H
u	3-ClC_4H_6	H	$C(O)NMe_2$	H
v	Pr^i	H	Cl	H
w	4-MeC_6H_4	H	$C(O)NMe_2$	H
x	Pr^i	H	CO_2Et	H
y	$CHEt_2$	H	$C(O)NMe_2$	H
z	$CHEt_2$	H	CO_2Et	H

[a] Th is thienyl.

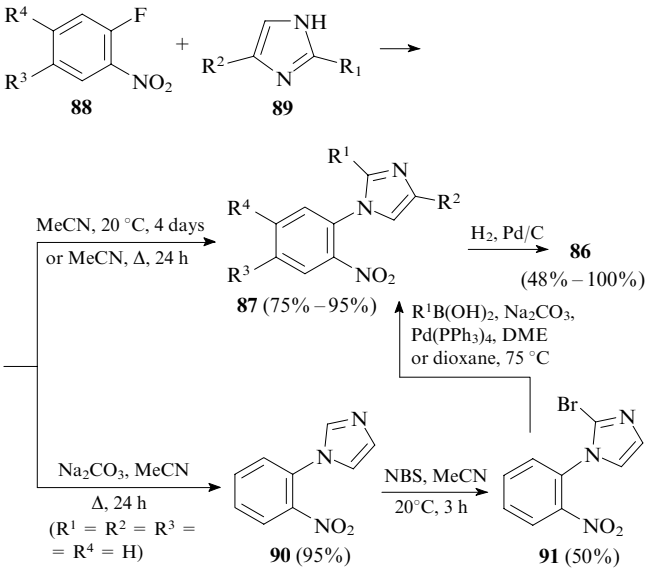
Scheme 41



Necessary starting compounds **86** are synthesized by either a two- or a four-stage method. The last stage in both cases is the catalytic reduction of 1-(2-nitrophenyl)-imidazoles **87**. In the first method, compounds **87** are formed through the nucleophilic substitution of the fluorine atom in *o*-fluoronitrobenzenes **88** by imidazoles **89**.[101–104] The second method consists of the following stages: 1) the arylation of imidazole with *o*-fluoronitrobenzene in the presence of sodium carbonate, 2) the bromination of 2-

nitrophenylimidazole **90** with bromosuccinamide, 3) the introduction of an alkyl or aryl fragment into the imidazole ring of 2-bromo derivative **91** by the Suzuki cross-coupling reaction leading to products **87** (Scheme 42).[98] The availability of the starting compounds, the ease of each stage and high yields allow easy variation of substituents in the 2-position of the imidazole ring, which leads to different 1-substituted imidazo[1,5-*a*]-quinoxalines **85**.[101–106]

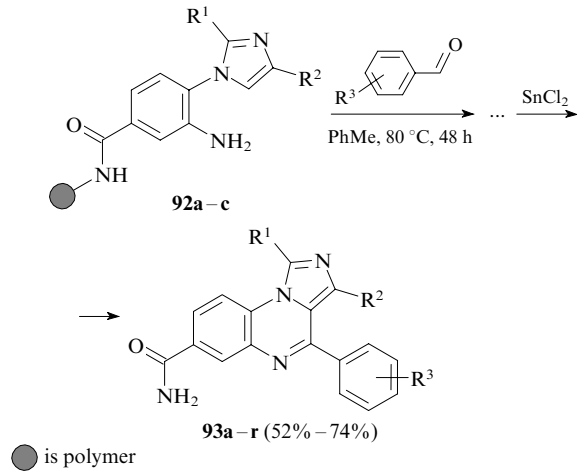
Scheme 42



DME is dimethoxyethane, NBS is *N*-bromosuccinamide

A structural specific feature of 2-(1*H*-imidazol-1-yl)aminobenzene derivatives **92** makes it possible to use them in the Pictet–Spengler reaction[107,108] with aldehydes. However, as distinct from β-arylethylamines (key compounds of the Pictet–Spengler reaction) giving tetrahydroisoquinoline derivatives, these compounds form corresponding imidazo[1,5-*a*]quinoxalines **93a–r** (Scheme 43, Table 4).[109] The reaction occurs in the solid phase, and all stages of formation of 2-(1*H*-imidazol-1-yl)aminobenzene derivatives **92a–c** are carried out with the participation of a fluoronitrobenzene derivative attached to a polymer substrate through the carbamoyl bond. Tin chloride is used as a reducing agent.

Scheme 43



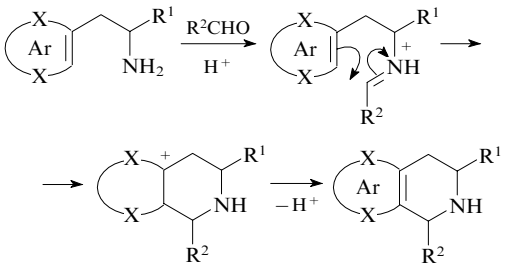
● is polymer

Table 4. Yields of imidazo[1,5-*a*]quinoxalines **93** (see Scheme 43).[109]

Substrate **92**	R^1	R^2	Product **93**	R^3	Yield (%)
a	Ph	Me	**a**	4-Me	72
	Ph	Me	**b**	H	73
	Ph	Me	**c**	4-OEt	74
	Ph	Me	**d**	4-NO_2	70
	Ph	Me	**e**	2-OH	73
	Ph	Me	**f**	4-Cl	74
b	Me	H	**g**	4-Me	50
	Me	H	**h**	H	52
	Me	H	**i**	4-NO_2	45
	Me	H	**j**	4-OEt	57
	Me	H	**k**	2-OH	52
	Me	H	**l**	4-Cl	54
c	Et	Me	**m**	4-Me	73
	Et	Me	**n**	H	72
	Et	Me	**o**	4-NO_2	65
	Et	Me	**p**	4-OEt	70
	Et	Me	**q**	2-OH	71
	Et	Me	**r**	4-Cl	72

An efficient method of selective synthesis of the oxidized and reduced forms of imidazo[1,5-*a*]quinoxalines *via* modified Pictet–Spengler reaction of 2-imidazolyl anilines with arylaldehydes (the possible mechanism is shown in Scheme 44) has been described.[110] The reaction proceeds under mild conditions and affords the products in high yields if the imidazole ring contains electron-donating substituents in the 2- and 4-positions, which facilitates electrophilic aromatic substitution at the 5-position of imidazole.

Scheme 44

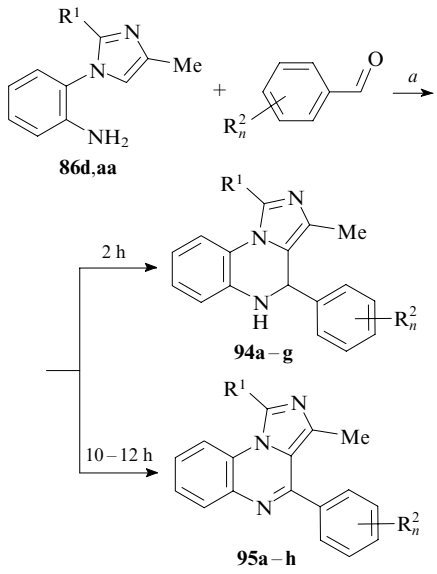


X = N, CH

The reaction of 2-(1*H*-imidazol-1-yl)aminobenzenes **86d**,**aa** with substituted benzaldehydes in the presence of benzotriazole and TsOH in toluene for 2 h leads to dihydroimidazoquinoxalines **94a–g** in high yield (Scheme 45, Table 5).[110] The best condition for the formation of imidazoquinoxalines **95a–h** is to increase the reaction duration to 12 h, which ensures the complete conversion of the intermediate dihydro derivative. Thus, varying the reaction time allows one to stop the reaction after the formation of compound **94** or **95**.

Both 4,5-dihydro derivatives **94** and imidazo[1,5-*a*]quinoxalines **95** are obtained in high yields and under mild conditions. Aniline **86d** with two electron-donating groups in the imidazole ring reacts more readily than aniline **86aa,** containing only the methyl group in this ring. The reaction of *p*-bromobenzaldehyde with *N*-(2-aminophenyl)imidazole ($R^1 = R^2 = H$ in formula **86**, see Scheme 41) does not lead to corresponding dihydroimidazo[1,5-*a*]quinoxaline **94**.

Scheme 45



(*a*) benzotriazole, 10% TsOH, PhMe, 25 °C;
R^1 = Et (**86d**), H (**86a**)

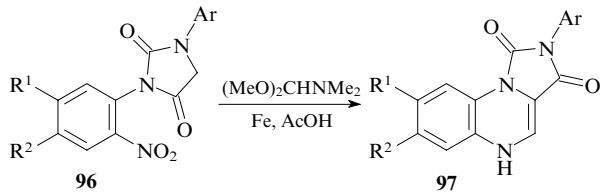
Table 5. Yields of compounds **94** and **95** (see Scheme 45).[110]

Compound **94**	R^1	R^2_n	Yield (%)	Compound **95**	R^1	R^2_n	Yield (%)
a	Et	4-Br	88	**a**	Et	4-Br	86
b	Et	4-NO_2	90	**b**	Et	4-F	88
c	Et	2,4-Cl_2	86	**c**	Et	4-Me	80
d	Et	3-Cl	84	**d**	H	4-NO_2	83
e	Et	3-NO_2	85	**e**	H	4-CN	82
f	Et	3-OMe	80	**f**	H	4-CF_3	82
g	H	4-OMe	77	**g**	H	3-NO_2	78
				h	H	2,4-Cl_2	75

At the same time, aldehydes with electron-donating substituents and halogen atoms ensure the highest yield of imidazo[1,5-*a*]quinoxalines **95**.[110]

The use of 1-(*o*-nitrophenyl)imidazole-2,5-diones **96** and dimethylformamide dimethyl acetal has been patented as another source of structural fragments necessary for **$B1_I$**-type construction of the tricyclic system.[111–115] The condensation of these reactants in acetic acid in the presence of iron powder has been used to obtain a large number of imidazoquinoxaline-2,3-diones **97** with a variety of substituents. Unfortunately, the yields of the products have not been specified in patents [111–115] (Scheme 46).

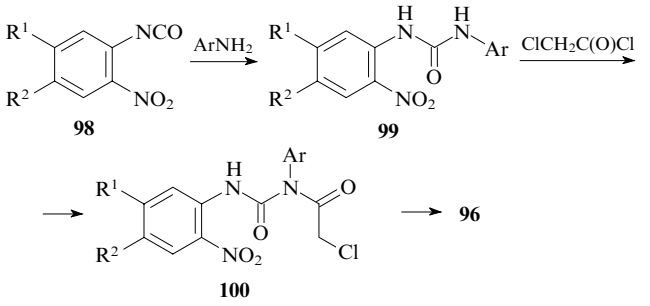
Scheme 46



Ar = C_6H_4X (X = H, F, Cl, Br, Me, Et, Pr^n, OMe, OEt, OPr^n, OPr^i, OAc, NH_2), C_6H_3XY (X = F, Br; Y = Me, OEt), 2-Th;
R^1, R^2 = H, Me, Cl, Br, CO_2Et

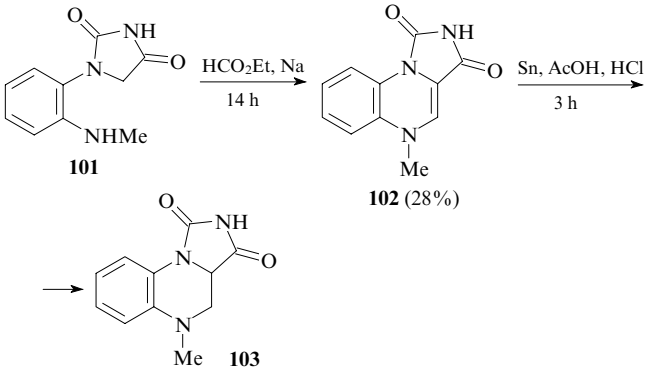
Compounds **96** have been synthesized from 2-nitrophenyl isocyanates **98** through the formation of corresponding urea derivatives **99**: they react with acetic chloride to give compounds **100**, which undergo cyclization to yield compounds **96**. This method,[111–115] as well as variant **$A3_Q$** using quinoxaline derivatives,[51] has been developed in detail precisely for the synthesis of 2,3-dioxoimidazoquinoxalines (Scheme 47).

Scheme 47



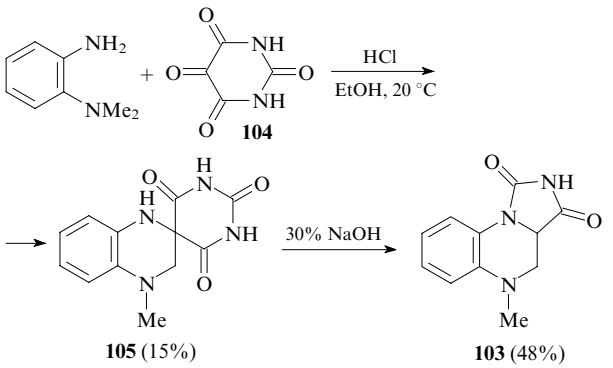
The reaction of 1-(*o*-methylaminophenyl)imidazole-2,5-dione **101** with ethyl formate under the action of sodium yields 1,3-dioxoimidazoquinoxaline **102**, which is reduced by tin in a mixture of acetic and hydrochloric acids to give imidazoquinoxaline **103** (Scheme 48).[34]

Scheme 48



When elucidating the structure of the compound resulting from the alkaline hydrolysis of the product of the reaction of alloxan (**104**) with *o*-dimethylaminoaniline, Rudy and Cramer [116] found a new method of synthesis of dihydroimidazoquinoxaline **103**. This method is a promising approach to synthesis of spiro-fused quinoxaline **105** (Scheme 49).

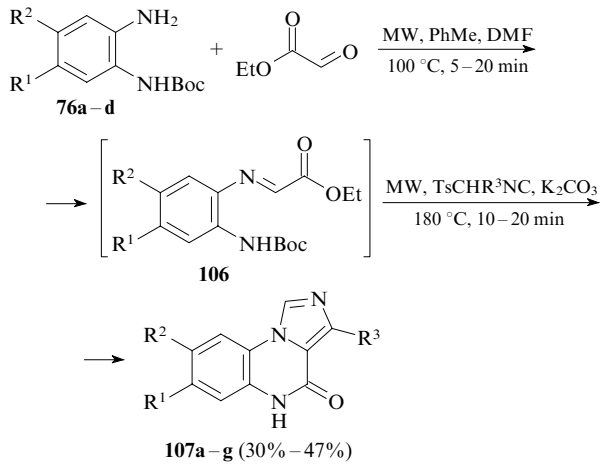
Scheme 49



IV. Other methods of synthesis of imidazo[1,5-*a*]quinoxalines

Three-component condensation of *N*-Boc-*o*-diaminobenzenes **76**, ethyl glyoxylate and substituted tosyl isocyanates in the presence of potassium carbonate on heating and under microwave irradiation (the Van Leusen strategy mentioned above) has been described.[95] The reaction proceeds as a one-pot process, but in two stages; cyclization of intermediates **106** leads to imidazo[1,5-*a*]quinoxalin-4-ones **107a–g** (Scheme 50).

Scheme 50

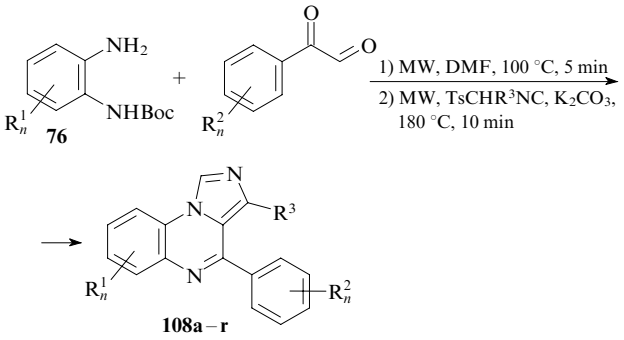


76a–d → **106** → **107a–g** (30%–47%)

107: $R^1 = R^2 = H$: $R^3 = H$ (**a**), Et (**b**); $R^1 = R^2 = R^3 = Me$ (**c**); $R^2 = R^3 = H$: $R^1 = F$ (**d**), OMe (**f**); $R^2 = H$: $R^1 = F$, $R^3 = Et$ (**e**); $R^1 = OMe$, $R^2 = H$, $R^3 = Me$ (**g**)

The use of phenyl-substituted glyoxals rather than ethyl glyoxylate under analogous conditions leads to 4-arylimidazo[1,5-*a*]quinoxalines **108a–r** (Scheme 51, Table 6).[97]

Scheme 51



76 → **108a–r**

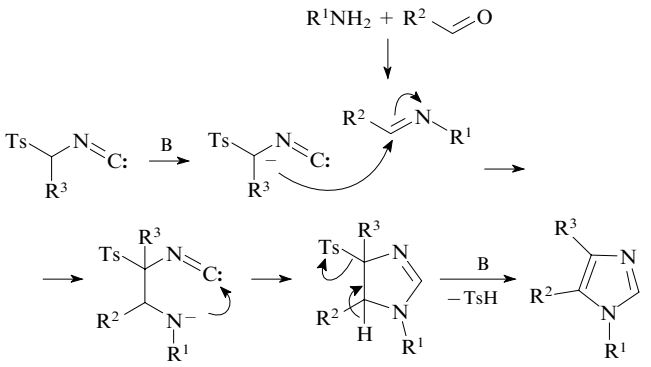
This method enables the introduction of diverse substituents into the heterocycle, no matter whether they have electron-donating or electron-withdrawing properties. The only limitation found by the authors is related to the use of 2-substituted phenylglyoxaldehydes. In this case, the yield of the product is considerably reduced (imidazoquinoxaline **108q**) or the product does not form (the synthesis of compound **108r** was unsuccessful). This is caused by the extreme sensitivity of the reaction to steric factors. Variation of the substituent in isocyanide also has an effect on the yield of the product. In particular, the use of aryl-substituted *p*-tosylmethyl isocyanides ($R^3 = Ar$) leads to an increase in the yield of compounds **108g**,**k**,**o**. At the same time, ethyl-substituted *p*-tosylmethyl isocyanides ($R^3 = Et$) give products **108h–j** in considerably lower yields.

Table 6. Yields of compounds **108** (see Scheme 51).[97]

Compound **108**	R^1_n	R^2_n	R^3	Yield (%)
a	H	H	H	67
b	H	4-CF_3	H	61
c	H	4-OMe	H	52
d	H	3-NO_2	H	53
e	5-OMe	H	H	58
f	4-Br	H	H	66
g	H	H	Ph	74
h	H	H	Et	33
i	5-F	4-OMe	Et	40
j	4,5-Me_2	3,4,5-$(OMe)_3$	Et	39
k	5-OMe	4-OMe	Ph	71
l	5-OMe	4-CF_3	Ph	66
m	4-Br	3,4,5-$(OMe)_3$	Ph	59
n	4-Br	4-F	4-BrC_6H_4	65
o	4,5-Me_2	3,4,5-$(OMe)_3$	4-BrC_6H_4	70
p	4,5-Me_2	3-NO_2	4-BrC_6H_4	55
q	5-OMe	2-F	4-BrC_6H_4	13
r	H	2-OMe	H	0

Formation of the imidazole ring in this case is shown in Scheme 52. It involves the formation of Schiff bases in the reaction of amine with aldehyde with subsequent cyclization initiated by tosylmethyl cyanide.[96]

Scheme 52



B is base

Closure of bonds in synthesis of imidazoquinoxalines **108**, according to the fragmental approach used by us, is shown in Fig. 4.

V. Synthesis of imidazo[1,2-*a*]quinoxalines based on quinoxaline derivatives

Among possible variants of assembly of imidazo[1,2-*a*]quinoxalines shown in Fig. 5, the following methods are

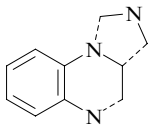


Figure 4. Scheme of formation of the imidazo[1,5-*a*]quinoxaline system in synthesis of compounds **108**.

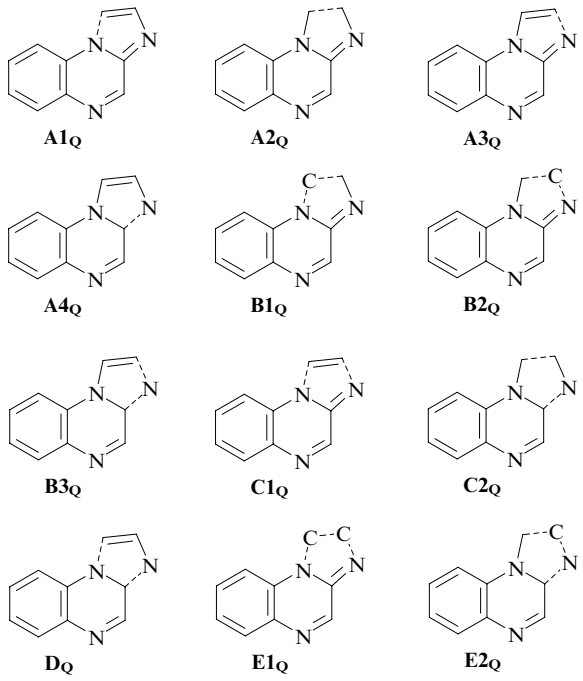


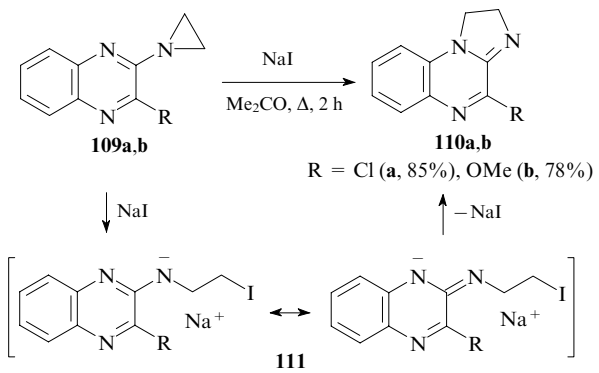
Figure 5. Possible variants of construction of the imidazo[1,2-*a*]-quinoxaline system on the basis of quinoxaline derivatives.

known: methods based on intramolecular cyclization with formation of the N(10)–C(1) and C(2)–N(3) bonds (variants **A1Q**, **A3Q**), on intermolecular condensation of quinoxaline derivatives with formation of the C(2)–N(3) and N(3)–C(3a) bonds (variant **B3Q**) and the N(10)–C(1) and C(2)–N(3) bonds (variant **C1Q**), as well as on the processes that occur in the three-component system involving the formation of the N(10)–C(1), C(1)–C(2) and C(2)–N(3) bonds (variant **E1Q**).

1. Methods of formation of the N(10)–C(1) bond (variant A1Q)

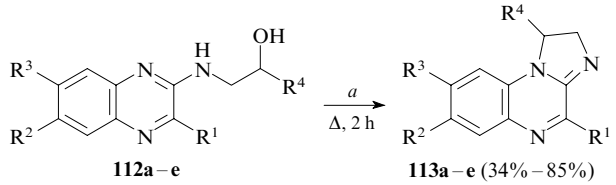
Variant **A1Q** of synthesis of imidazo[1,2-*a*]quinoxalines can be exemplified by the rearrangement of 2-(aziridino)quinoxaline derivatives **109a**,**b** by the Gabriel–Heine reaction.[117] This method has been used to synthesize, for the first time, dihydroimidazo[1,2-*a*]quinoxalines **110a**,**b** (Scheme 53).[35] The method consists in the opening of the aziridine ring and closure of the imidazole ring in intermediate compounds **111**.

Scheme 53



2-(2-Hydroxyethylamino)quinoxalines **112a–e** are cyclized into 1,2-dihydroimidazo[1,2-*a*]quinoxalines **113a–e** under the action of dehydrating agents, such as thionyl chloride, HCl or phosphorus(V) oxochloride (Scheme 54).[90, 103, 118, 119]

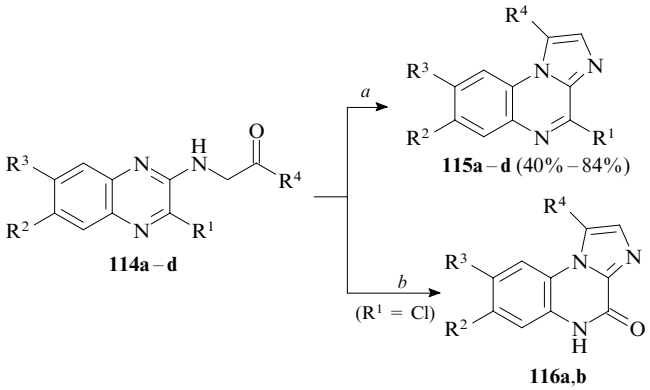
Scheme 54



(*a*) $SOCl_2$ or HCl, MeOH (for **a**), $POCl_3$ (for **b**–**e**);
R^1 = Cl, R^2 = NO_2, R^3 = F, R^4 = Et (**a**); R^2 = R^3 = R^4 = H: R^1 = H (**b**), Me (**c**), Ph (**d**); R^1 = R^2 = R^3 = Cl, R^4 = Me (**e**)

Intramolecular cyclocondensation of 1-[(quinoxalin-2-yl)amino]alkan-2-ones **114a–d** in the presence of trifluoroacetic anhydride leads to formation of aromatic imidazoquinoxalines **115a–d**.[103, 120–122] At the same time, cyclization of chloro derivatives **114a**,**b** in boiling xylene in the presence of TsOH leads to imidazo[1,2-*a*]quinoxalin-4(5*H*)-ones **116a**,**b** (Scheme 55).[120]

Scheme 55

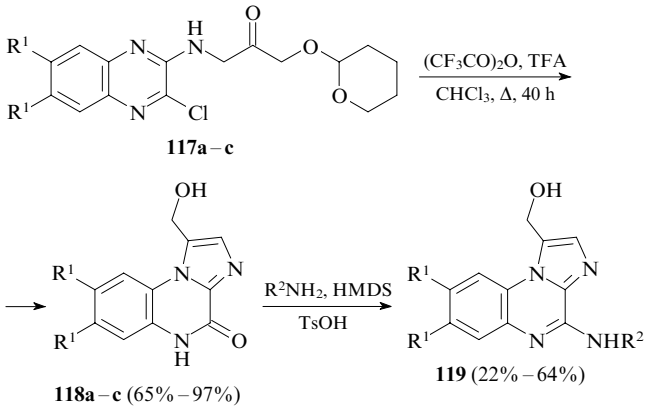


(*a*) $(CF_3CO)_2O$, Δ, 8 h or $(CF_3CO)_2O$, TFA, 20 °C, 5–24 h;
(*b*) TsOH, xylene, Δ, 24 h;
114, **115**: R^1 = Cl, R^2 = R^3 = H: R^4 = Bu^i (**a**), $BnCH_2$ (**b**), Me (**c**);
R^1 = OH, R^2 = F, R^3 = NO_2, R^4 = Et (**d**);
116: R^2 = R^3 = H: R^4 = Bu^i (**a**), $BnCH_2$ (**b**)

Boiling compounds **117a–c** with trifluoroacetic anhydride and trifluoroacetic acid leads to formation of 1-hydroxymethylimidazo[1,2-*a*]quinoxalin-4(5*H*)-ones **118a–c**, the products of cyclization and hydrolysis. These derivatives react with primary amines in the presence of hexamethyldisilazane (HMDS) and TsOH at room temperature to form corresponding 4-amino derivatives **119** (Scheme 56).[123]

2-(2,2-Dialkoxyethylmino)quinoxalines **120** with R^3 = H, Cl, $N(CH_2CH_2)_2NBoc$ are cyclized under the action of HCl or TsOH to form imidazo[1,2-*a*]quinoxalines **121**.[91, 119, 124–126] The oxidation of compound **121** (R^1 = R^2 = Cl, R^3 = R^4 = H) by magnesium monoperoxyphthalate leads to corresponding imidazo[1,2-*a*]quinoxalin-4(5*H*)-one **122** (R^1 = R^2 = Cl).[124]

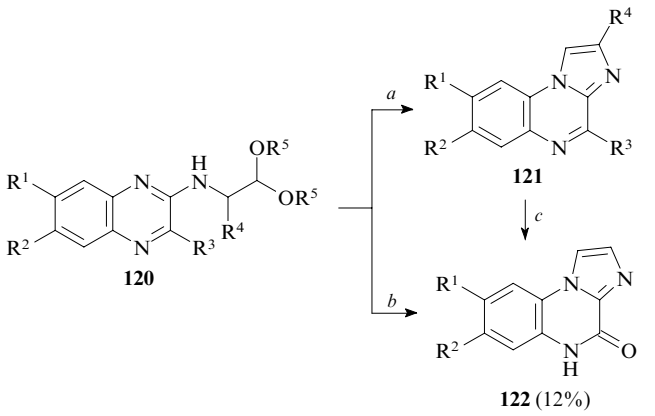
Scheme 56



R^1 = H (**a**), Me (**b**), Cl (**c**); R^2 = Bu^n, Bu^i, Bn, cyclo-C_5H_9, cyclo-C_6H_{11}

Imidazoquinoxalin-4-ones **122** also form when 3-chloroquinoxalines **120** (R^3 = Cl) are treated with 48% HBr solution[124] or when quinoxalin-2-ones **120** (R^3 = OH) are heated for a long time in hydrochloric acid (Scheme 57).[125, 126]

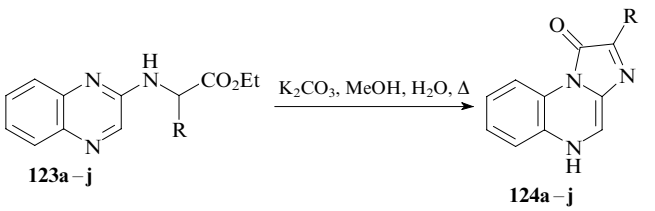
Scheme 57



(*a*) HCl or TsOH, Δ (for R^3 = H, Cl, $N(CH_2CH_2)_2NBoc$;
(*b*) 48% HBr, Δ, 4 h or HCl, Δ, 24 h (for R^3 = Cl, OH);
(*c*) $Mg(O_2CC_6H_4CO_3H\text{-}4)_2$, 55 °C, 18 h (for R^1 = R^2 = Cl, R^3 = R^4 = H);
R^1 = H, F, Cl; R^2 = H, F, Cl, CF_3; R^3 = H, Cl, OH, $N(CH_2CH_2)_2NBoc$; R^4 = H, C_6H_4X (X = H, 2-F, 3-F, 4-F, 3-Cl, 4-Cl, 4-Me, 3-OMe, 4-OEt), 2-Th, 5-methylthiophen-2-yl; R^5 = Me, Et

Annulation of the imidazole ring is a result of intramolecular condensation involving the imine nitrogen atom of the quinoxaline system and the carbon atom of not only the alkyl halide, ketone and aldehyde groups but also of the ester group and acetylene moiety. In particular, the condensation of ethyl esters of α-substituted *N*-(quinoxalin-2-yl)glycines **123a–j** in aqueous methanol in the presence of potassium carbonate leads to imidazoquinoxalinones **124a–j** (Scheme 58).[125, 126]

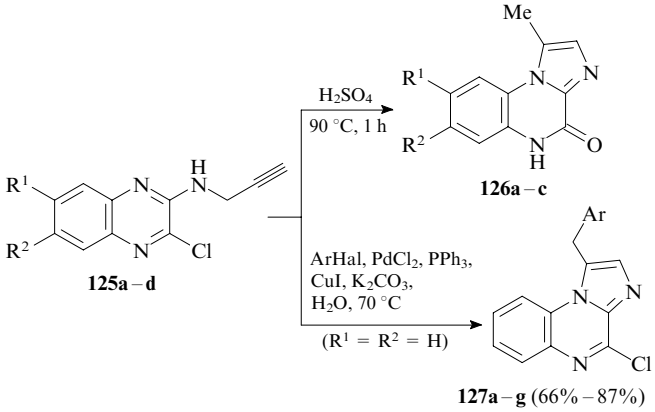
Scheme 58



R = Ph (**a**), 2-Th (**b**), 5-methylthiophen-2-yl (**c**), C_6H_4X [X = 3-OMe (**d**) 4-OEt (**e**), 3-F (**f**), 4-F (**g**), 3-Cl (**h**), 4-Cl (**i**), 4-Me (**j**)]

3-Chloroquinoxalines **125a**,**b** with the propargylamino group in the 2-position are cyclized under the action of concentrated sulfuric acid into imidazoquinoxalines **126a**,**b**,[127] accompanied by hydrolysis and elimination of the chlorine atom. Analogously, benzo[*g*]quinoxaline **125c** converts into benzo[*g*]imidazo[1,2-*a*]quinoxaline **126c** in 30% yield (Scheme 59).[128] The use of the palladium–copper catalyst enables the cyclization of compound **125d** under milder conditions, which leads to the retention of the chlorine atom in the molecule. Owing to the presence of aryl iodides (bromides) in the reaction mixture, quinoxaline **125d** converts into 1-benzyl-substituted imidazo[1,2-*a*]quinoxalines **127a–g** in one-pot process. The use of iodine analogues instead of bromonitrobenzenes allows one to increase the yield of compounds **127a**,**b** by 20%.[129]

Scheme 59

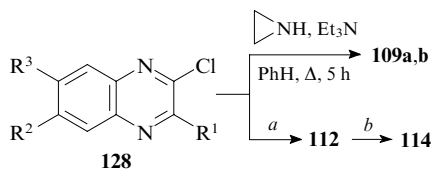


125: R^2 = Cl: R^1 = H (**a**), Cl (**b**); R^1–R^2 is benzo (**c**); R^1 = R^2 = H (**d**);
126: R^2 = Cl: R^1 = H (**a**), Cl (**b**); R^1–R^2 is benzo (**c**);
127: Ar = $C_6H_{5-n}X_n$ [X_n = 2-NO_2 (**a**), 4-NO_2 (**b**), 2-NO_2-4-Cl (**c**), 4-NO_2-2-Cl (**d**), 4-Ac (**e**), 2-CHO (**f**), 4-CN (**g**)]; Hal = Br, I

It is likely that ring closure in these reactions occurs through the intermediate formation of the corresponding acetonylamino derivatives of quinoxalin-2(1*H*)-one and benzo[*g*]quinoxalin-2(1*H*)-one.

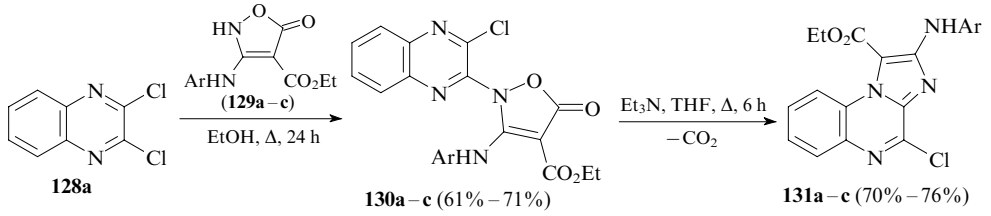
Precursors of imidazoquinoxalines — compounds **109a**,**b** and **112** — have been synthesized from chloroquinoxalines **128** and corresponding amines in the presence of Et_3N. To oxidize aminoalcohols **112** to ketones **114**, different oxidative systems have been used: a complex of trime-

Scheme 60



(*a*) $NH_2CH_2CHR^4OH$, Et_3N, dioxane or $CHCl_3$, Δ;
(*b*) $Me_3N\cdot SO_3$, Et_3N, DMSO, 20 °C, 8 h; or CrO_3–Py; or $(COCl)_2$, DMSO

Scheme 61



129–131: Ar = 3-MeC_6H_4 (**a**), 4-BrC_6H_4 (**b**), 4-$O_2NC_6H_4$ (**c**)

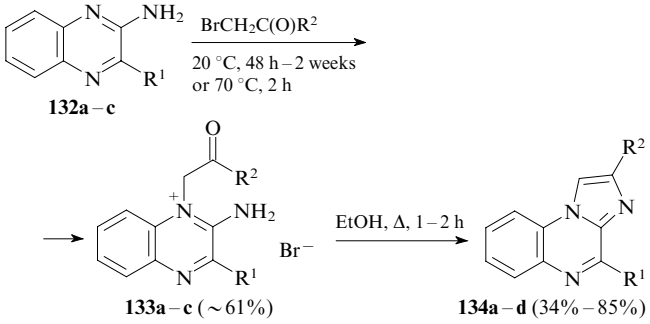
thylamine and sulfuric anhydride in DMSO, chromium(VI) oxide in pyridine (Sarett method),[130, 131] and dichloroxalate in DMSO (Swern method) (Scheme 60).[103, 120, 122]

The reaction of 2,3-dichloroquinoxaline **128a** with arylaminoisoxazolones **129a–c** gives oxazolylquinoxalines **130a–c**, which rearrange on heating in THF in the presence of triethylamine into imidazoquinoxalines **131a–c** with elimination of CO_2 (Scheme 61).[132]

2. Method of formation of the C(2)—N(3) bond (variant $A3_Q$)

The reaction of 2-aminoquinoxalines **132a–c** with bromoacetaldehyde and ethyl bromopyruvate gives salts **133a–c**, which undergo intramolecular cyclization on heating in ethanol to give imidazoquinoxalines **134a–d** (Scheme 62).[39, 122, 133]

Scheme 62



132: R^1 = NHMe (**a**), NHEt (**b**), Cl (**c**);
133: R^2 = CO_2Et: R^1 = NHMe (**a**), NHEt (**b**); R^1 = Cl, R^2 = H (**c**);
134: R^2 = CO_2Et: R^1 = NHMe (**a**), NHEt (**b**), OH (**d**); R^2 = H, R^3 = Cl (**c**)

3. Method of formation of the C(2)—N(3) and N(3)—C(3a) bonds (variant $B3_Q$)

Heating 1,4-bis(aroylmethyl)quinoxalin-2,3-diones **135a–j** in acetic acid in the presence of ammonium acetate leads to 2-aryl-5-aroylmethylimidazo[1,2-*a*]quinoxaline-4-ones **136a–j** ($B3_Q$-type cyclization, see Fig. 5), whereas expected 1,5-diarylbis(imidazo[1,2-*a*:2′,1′-*c*])quinoxalines **137** are not identified in the reaction mixture. Starting compounds **135** have been obtained by alkylation of quinoxalinediones **138a**,**b** with aroylmethyl bromides (Scheme 63).[134]

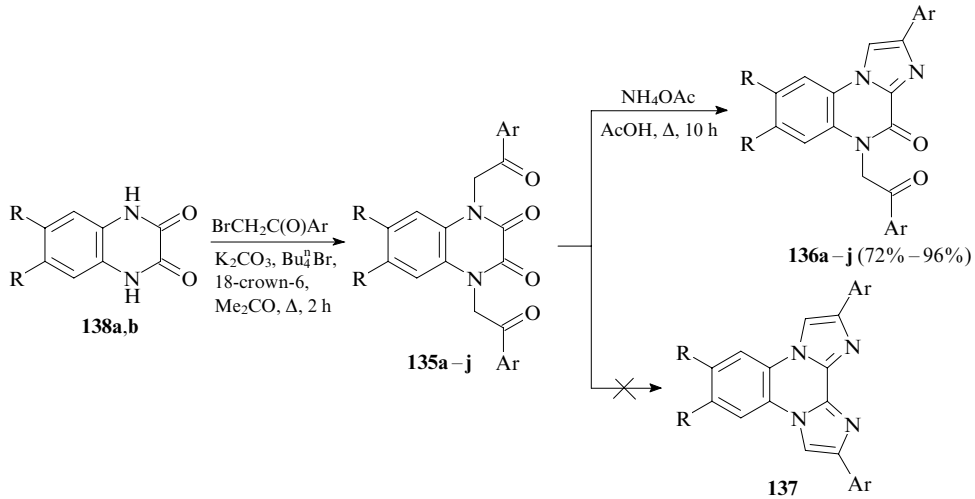
4. Methods of formation the N(10)—C(1) and C(2)—N(3) bonds (variant $C1_Q$)

Imidazoquinoxalines can be synthesized from aminoquinoxalines **132** and bromoketones or ketoaldehydes without isolation of corresponding quaternized derivatives **133** (see Scheme 62). This method was used to synthesize compounds **139a–h** from 2-aminoquinoxaline (**132d**) and compounds **140a–c** from 3-chloro derivative **132c** (Scheme 64).[126, 135, 136]

5. Method of formation of the N(10)—C(1) and N(3)—C(3a) bond (variant D_Q)

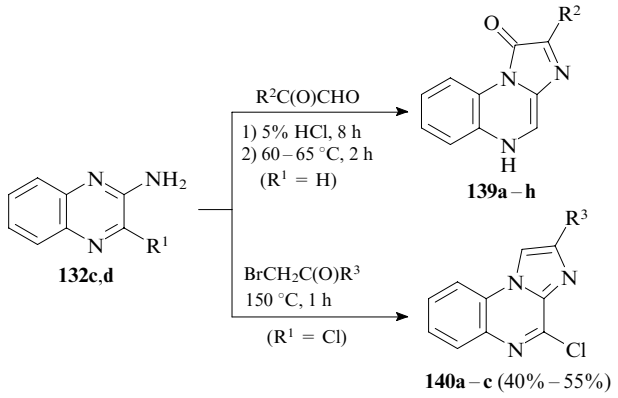
Refluxing 2,3-dichloroquinoxaline (**128a**) with two equivalents of arylaminoisoxazolone **129a** in ethanol for 48 h in the absence of bases (see Section V.2) leads to bis(imidazo)quinoxaline system **141** (Scheme 65).[132]

Scheme 63



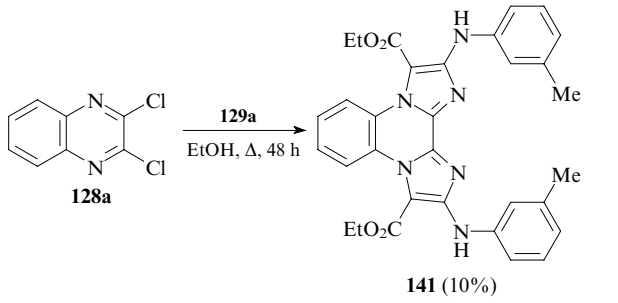
R = H: Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-ClC_6H_4 (**d**), 4-FC_6H_4 (**e**); R = NO_2: Ar = Ph (**f**), 4-$MeOC_6H_4$ (**g**), 4-BrC_6H_4 (**h**), 4-ClC_6H_4 (**i**), 4-FC_6H_4 (**j**)

Scheme 64



132: R^1 = Cl (**c**), H (**d**);
139: R^2 = Me (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**), 2,4-$F_2C_6H_3$ (**c**), 2,6-$F_2C_6H_3$ (**d**); 3-$EtOC_6H_4$ (**e**), 3-EtC_6H_4 (**f**), 4-MeO-3-FC_6H_3 (**g**), F_3CO (**h**);
140: R^3 = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 2-Th (**c**)

Scheme 65

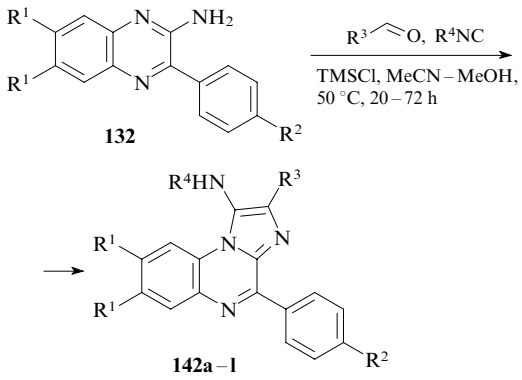


6. Method of formation of the N(10)–C(1), C(1)–C(2) and C(2)–N(3) bonds (variant $E1_Q$)

The multicomponent reaction of 2-amino-3-arylquinoxalines **132** with aldehydes and isocyanides under the conditions of the Groebke–Blackburn–Bienaymé reaction [137–139] leading to 1-aminoimidazo[1,2-*a*]quinoxalines **142a–l** is an example of synthesis of such compounds according to variant $\mathbf{E1_Q}$ (Scheme 66, Table 7).[140, 141]

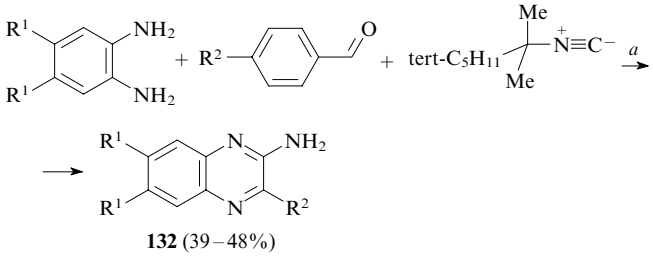
It should be noted that starting 2-aminoquinoxalines **132** for this reaction have also been obtained in a multicomponent system by the modified Groebke–Blackburn–Bienaymé reaction, using *o*-phenylenediamines as one of the reactants (Scheme 67).

Scheme 66



TMS is trimethylsilyl

Scheme 67



(*a*) 1) HCl, MeOH, 8 h; 2) DDQ, 20 °C, 3 h;
DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

VI. Synthesis of imidazo[1,2-*a*]quinoxalines on the basis of imidazole derivatives

The known variants of assembly of the imidazo[1,2-*a*]quinoxaline system from imidazoles involve different intramolecular cyclizations of imidazole derivatives accompanied by the formation of the C(3a)–C(4), C(4)–N(5) and C(9a)–N(10) bonds (variants $\mathbf{A1_I}$, $\mathbf{A2_I}$ and $\mathbf{A4_I}$, respectively), as well as intermolecular cyclizations of imidazole derivatives with different equivalents of monoatomic carbon synthons accompanied by the formation of the C(3a)–C(4) and C(4)–N(5) bonds (variant $\mathbf{B1_I}$) and with equivalents of triatomic nitrogen–carbon synthons accompanied by the formation of the C(4)–N(5) and C(9a)–N(10) bonds (variant $\mathbf{D1_I}$) (Fig. 6).

Table 7. Yields of compounds **142** (see Scheme 66).[140, 141]

Compound **142**	R^1	R^2	R^3	R^4	Time /h	Yield (%)
a	H	H	4-FC_6H_4	$Pr^iO(CH_2)_3$	20	65
b	H	H	Pr^n	4-$MeOC_6H_4CH_2$	48	45
c	H	H	4-$Bu^nOC_6H_4$	$Pr^i(CH_2)_2$	48	52
d	H	H	3,4,5-$(MeO)_3C_6H_2$	4-$MeOC_6H_4CH_2$	72	68
e	Me	H	3-Py	$EtO(CH_2)_3$	20	73
f	Me	H	4-$Pr^iOC_6H_4$	EtO_2CCH_2	48	56
g	Me	H	1-methylimidazol-3-yl	cyclo-C_5H_9	72	34
h	Me	H	4-NCC_6H_4	Bu^t	20	72
i	Me	CO_2Me	Pr^n	Bu^t	48	64
j	Me	H	Pr^n	Bu^t	48	71
k	Me	H	1,3-dimethylimidazol-4-yl	$EtO(CH_2)_3$	72	49
l	H	Ph	Ph	cyclo-C_7H_{13}	–	33

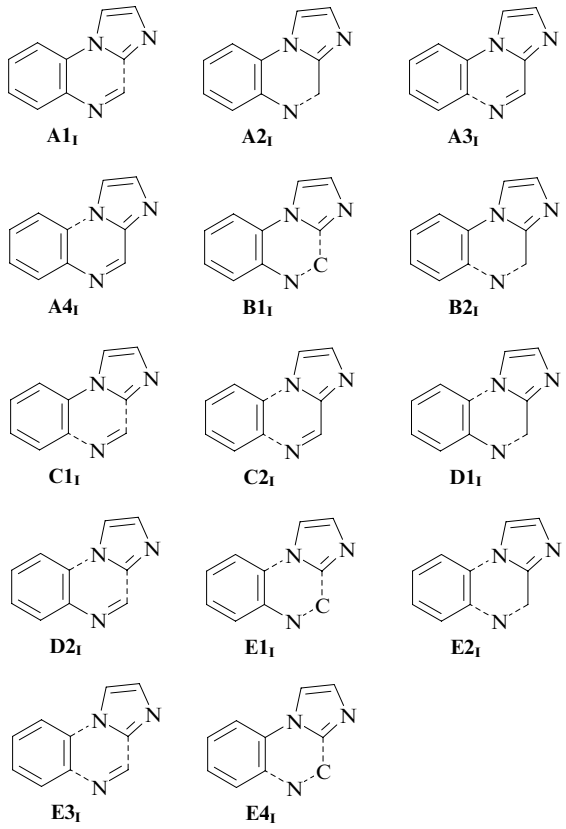
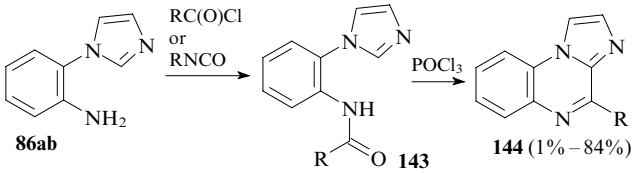


Figure 6. Possible variants of construction of the imidazo[1,2-*a*]-quinoxaline system on the basis of imidazoles.

1. Method of formation of the C(3a)—C(4) bond (variant $A1_I$)

One of the key methods of synthesis of imidazo[1,2-*a*]quinoxalines on the basis of imidazoles is $A1_I$-type synthesis. In this case, imidazole ring annulation is a result of formation of the C(3a)—C(4) bond. In particular, 1-(2-acylaminophenyl)- or 1-(2-amino-carbonylaminophenyl)imidazoles **143**, obtained by the reaction of *N*-(2-aminophenyl)imidazole **86ab** and acetyl chlorides or isocyanates, are converted under the action of phosphorus(V) oxochloride into 4-substituted imidazoquinoxalines **144**.[142–152] More than 100 imidazo[1,2-*a*]quinoxalines have been synthesized by this method (Scheme 68).

Scheme 68

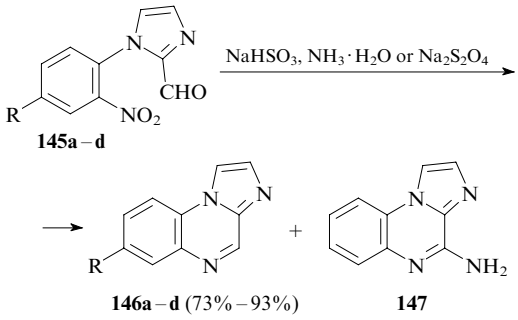


R is Alk, cycloalkyl, XC_6H_4 (X = Me, Bu^t, Ph, Cl, Br, F, NO_2), AlkNH, ArNH, chloroalkyl, alkoxyalkyl

2. Methods of formation of the C(4)—N(5) bond (variant $A2_I$)

The reduction of 1-(2-nitrophenyl)-2-formylimidazoles **145b–d** by sodium hydrosulfite in an aqueous ammonia leads to imidazo[1,2-*a*]quinoxalines **146b–d** in high yields.[153,154] It is likely that the products are generated through the $A2_I$-type intramolecular cyclization of the corresponding amino derivatives. In the case of compound **145a**, 4-aminoimidazo[1,2-*a*]quinoxaline **147** was isolated in 3% yield as a side product.[155] However, the reduction of compound **145a** by sodium dithionite leads only to imidazo[1,2-*a*]quinoxaline **146a** in 50% yield (Scheme 69).[153]

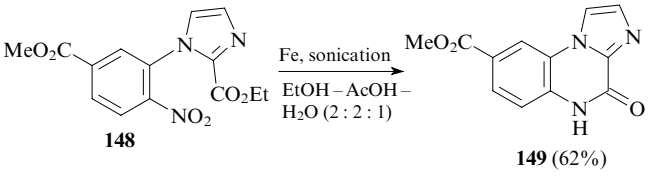
Scheme 69



R = H (**a**), Me (**b**), OMe (**c**), Br (**d**)

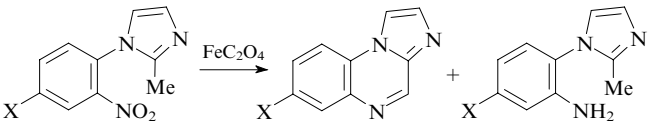
The reduction of nitro ester **148** by iron powder in aqueous ethanolic acetic acid under ultrasonic activation for 4 h is accompanied by intramolecular cyclization to give imidazoquinoxalin-4-one **149** in good yield (Scheme 70).[156]

Scheme 70



It is known that the appropriately arranged methyl group in one ring and the nitro group in the other ring react with each other in the presence of iron oxalate to form an extra central ring.[157] According to this methodology, 2-methyl-1-(2-nitrophenyl)-imidazoles **150a**,**e** in the presence of iron oxalate are transformed into imidazo[1,2-*a*]quinoxalines **146a**,**e** (Scheme 71).[158] However, the cyclization competes with the reduction of the nitro group to the amino group to give compounds **151a**,**e**.

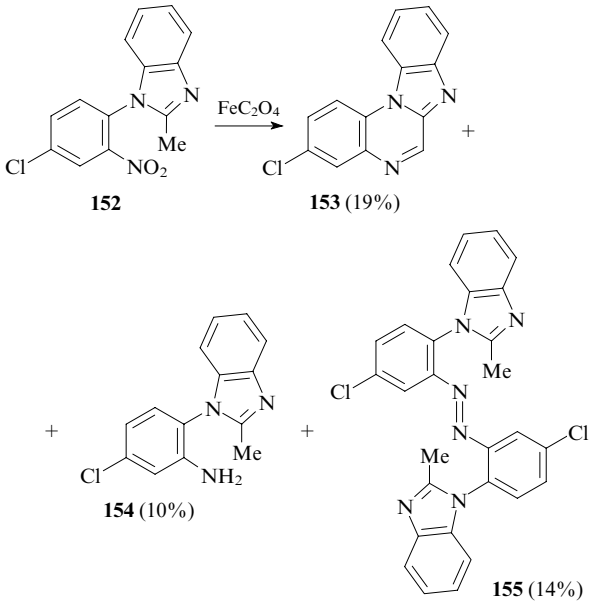
Scheme 71



X = H (**a**), Cl (**e**)

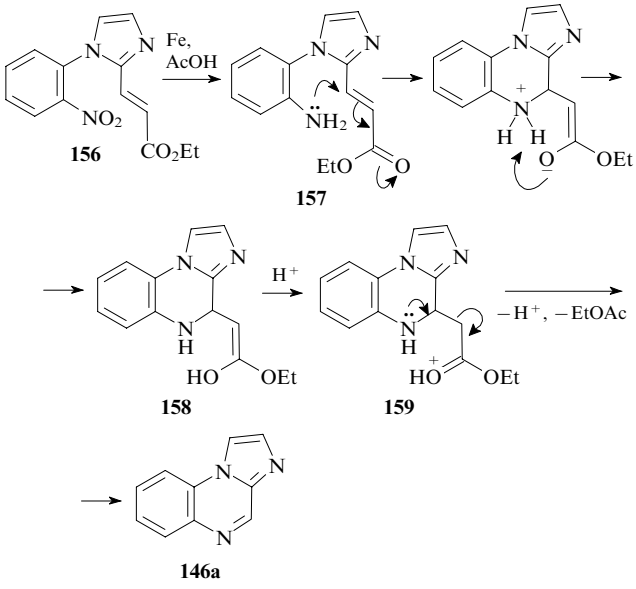
Benzannulated analogue **152** gives, under these conditions, a mixture of benzimidazoquinoxaline **153**, primary amine **154** and azo compound **155** in 19%, 10% and 14% yields, respectively (Scheme 72).[158]

Scheme 72



The presence of the ethoxycarbonylvinyl moiety in the 2-position of the imidazole ring spatially close to the nitro group of compound **156** facilitates intramolecular cyclization. It occurs through the Michael nucleophilic addition of the amino group generated by the reduction of the NO_2 group. This reaction leads to annulation of the pyrazine ring in intermediate **157** to give tricycle **158**. The elimination of ethyl acetate from cation **159** contributes to the formation of unsubstituted imidazo[1,2-*a*]quinoxaline **146a** (Scheme 73).[159]

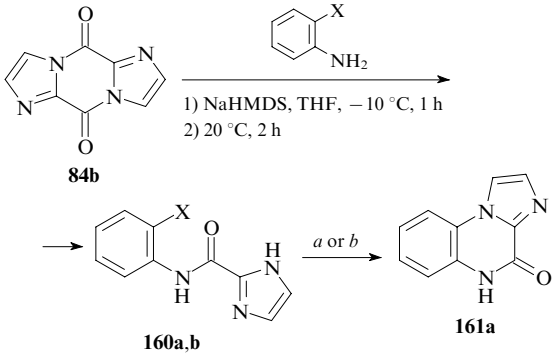
Scheme 73



3. Methods of formation of the C(9a)–N(10) bond (variant $A4_I$)

$A4_I$-type methods of synthesis are common for imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines. When kept in boiling dimethylacetamide in the presence of NaH for 6 h, anilide **160a** converts into imidazo[1,2-*a*]quinoxalin-4-one (**161a**) in 80% yield (Scheme 74, conditions *a*).[121,160] It has been shown that a combination of pyrrole-2-carbohydrazide attached to a polystyrene substrate (PSP) with CuI is a regenerable heterogeneous catalytic system for Ullmann C–N coupling in an aqueous medium. It allows one to aminate functionalized haloarenes with anilines, benzylamines, aliphatic amines and even imidazole. In the last case, compound **160b** can be converted into imidazo[1,2-*a*]quinoxalin-4-one (**161a**) *via* an alternative route without using air-sensitive NaH and an organic solvent, DMA. The reaction proceeds in water, which makes the process much more effective and environmentally safe (conditions *b* in Scheme 74).[161] Initial anilides **160** have been synthesized by acylation of *o*-haloanilines with diimidazo[1,2-*a*;1′,2′-*d*]-pyrazine-5,10-dione (**84b**).

Scheme 74

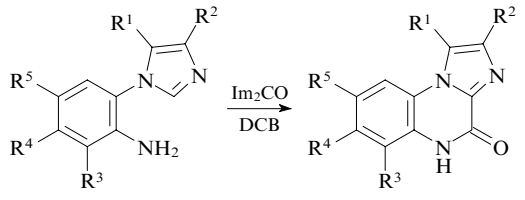


160: X = F (**a**), I (**b**);
(*a*) NaH, DMA, Δ, 6 h (from **160a**, yield 80%); (*b*) CuI, PSP, Bu^n_4Br, K_3PO_4, H_2O, 120 °C, 8 h (from **160b**, yield 54%)

4. Methods of formation of the C(3a)–C(4) and C(4)–N(5) bonds (variant $B1_I$)

The reaction of 1-(2-aminophenyl)imidazoles **162a–m** with carbonyldiimidazole on heating in dichlorobenzene leads to imidazoquinoxalin-4-ones **161a–m** (Scheme 75) (Refs 80, 101, 103, 104, 162–166). The yields vary from moderate to high.

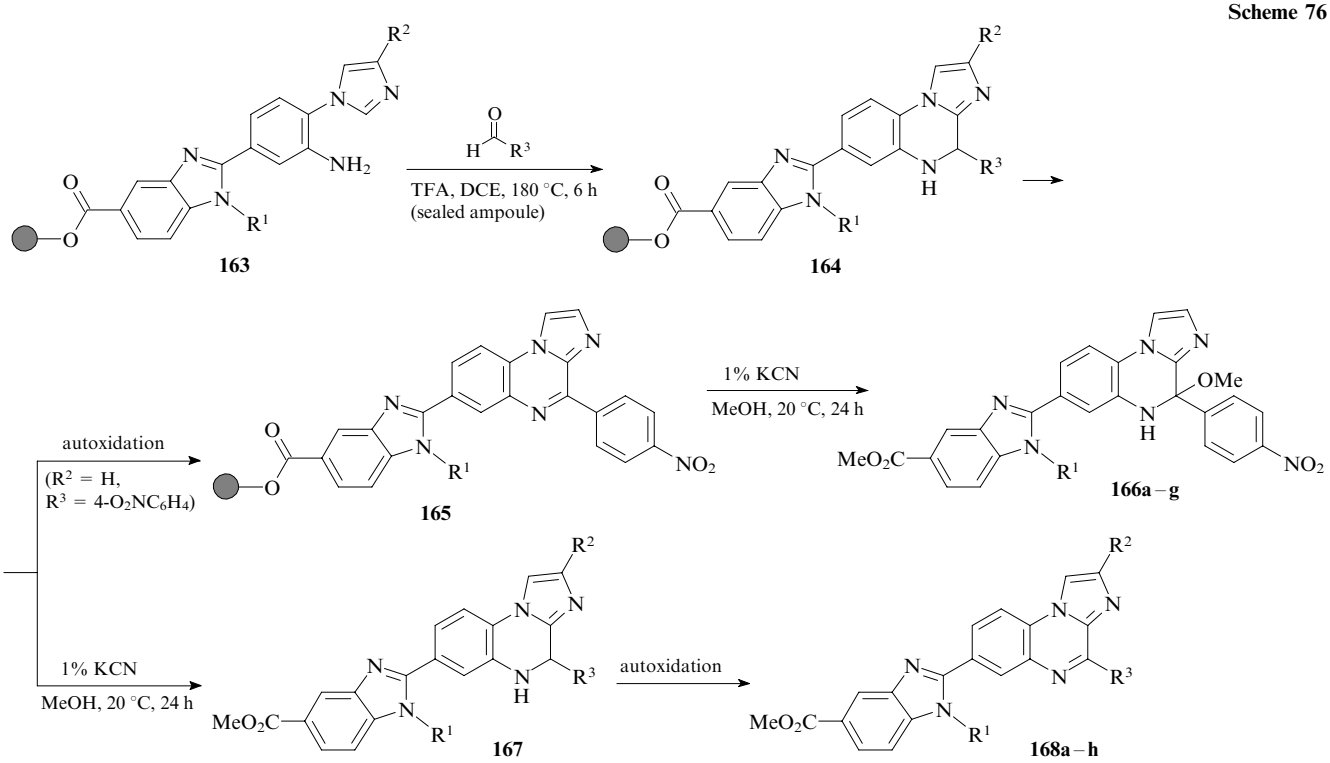
Scheme 75



$R^1 = R^2 = R^3 = R^5 = H$: R^4 = H (**a**), F (**b**), Cl (**c**);
$R^1 = R^2 = R^3 = H$: $R^4 = NO_2$, R^5 = H (**d**); $R^4 = NO_2$, R^5 = Im (**e**);
$R^4 = CF_3$, R^5 = Im (**f**); R^1 = Me, $R^2 = CO_2Et$, R^3 = H:
$R^4 = R^5$ = H (**g**); $R^4 = CF_3$, R^5 = H (**h**); $R^4 = SO_2Me$, R^5 = H (**i**);
R^4 = H, R^5 = Im (**j**); $R^1 = R^3 = R^4 = R^5$ = H, R^2 = Me (**k**);
R^1 = Et, $R^2 = CO_2Et$, $R^3 = R^5$ = H, $R^4 = CF_3$ (**l**);
R^1 = Me, $R^2 = CO_2Et$, R^3–R^4 is benzo, R^5 = H (**m**)

The Pictet–Spengler reaction[107,108] of compounds **163,** with the unsubstituted 2-position in the imidazole ring, and aldehydes yields imidazo[1,2-*a*]quinoxaline **164**.[166] The reaction is carried in the solid phase. Compounds **163** are synthesized in four stages from an *o*-phenylenediamine derivative attached to a polymeric support through an

Scheme 76



163 **164** **165** **166a–g** **167** **168a–h**

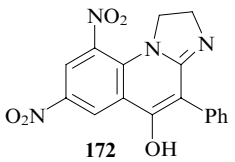
166: R^1 = Pr^i (**a**, 60%), iso-C_5H_{11} (**b**, 70%), cyclo-C_6H_{11} (**c**, 73%), cyclo-C_8H_{15} (**d**, 62%), $(CH_2)_3OMe$ (**e**, 67%), 2-(cyclohexen-1-yl)ethyl (**f**, 79%), 2-(tetrahydrofuran-2-yl)ethyl (**g**, 70%); **168**: R^1 = 2-(cyclohexen-1-yl)ethyl: R^2 = H, R^3 = Ph (**a**, 70%); R^2 = H, R^3 = 4-$MeOC_6H_4$ (**b**, 82%); R^2 = H, R^3 = Pr^n (**c**, 65%); R^2 = Me, R^3 = Ph (**d**, 58%); R^2 = Me, R^3 = 4-$MeOC_6H_4$ (**e**, 67%); R^2 = Me, R^3 = n-C_6H_{13} (**f**, 56%); R^2 = Me, R^3 = 4-$O_2NC_6H_4$ (**g**, 69%); R^1 = Bu^n, R^2 = Me, R^3 = 4-$O_2NC_6H_4$ (**h**, 65%); DCE is dichloroethane

ester group in the 5-position of the benzimidazol-2-yl moiety.[166] In the case of electron-withdrawing substituents in the 4-position of the benzene ring of substituent R^3 and in the absence of a substituent in the 2-position of imidazoquinoxalines **164** (R^2 = H, R^3 = 4-$O_2NC_6H_4$), autoxidation occurs to form compounds **165**. The product is removed from the polymer support with a 1% potassium cyanide solution in methanol at room temperature. Compounds **165** add methanol at the C=N bond, which is favoured by the presence of an electron-withdrawing substituent, to form compounds **166a–g**. Under the same conditions, compounds **164** are first converted into dihydroimidazoquinoxalines **167**, which are oxidized to products **168a–h** (Scheme 76).

5. Methods of formation of the C(4)–N(5) and C(9a)–N(10) bonds (variant $D1_I$)

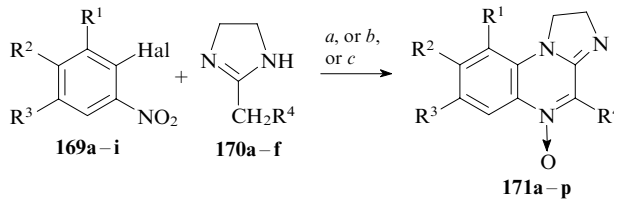
The reaction of 1,3-dinitro-4-fluorobenzene (**169a**) with cyclic amidine **170a** (tolazoline) yields imidazo[1,2-*a*]quinoxaline *N*-oxide **171a**. The reactions of compounds **169b–h** with imidazoles **170a–f**, are analogous and yield corresponding imidazo[1,2-*a*]quinoxaline *N*-oxides **171b–p** (Scheme 77, Table 8).[167–169]

Structure 172



172

Scheme 77



169a–i **170a–f** **171a–p**

(*a*) MeCN, Δ, 8 h; (*b*) EtOH, 24 h; (*c*) K_2CO_3, Pr^iOH, 50 h;
169: Hal = F, R^1 = R^2 = H: R^3 = NO_2 (**a**), H (**b**), Bz (**c**), 4-methyl-2-ethylaminothiazol-5-yl (**d**); Hal = F, R^1 = R^3 = H: R^2 = F (**e**), Cl (**f**); Hal = R^2 = R^3 = F, R^1 = H (**g**); Hal = Cl, R^2 = H: R^1 = NO_2, R^3 = CO_2Et (**h**); R^1 = CO_2Et, R^3 = NO_2 (**i**);
170: R^4 = Ph (**a**), 4-FC_6H_4 (**b**), H (**c**), 4-$H_2NC_6H_4$ (**d**), 3,4-$(MeO)_2C_6H_3$ (**e**), 3,4,5-$(MeO)_3C_6H_2$ (**f**)

It should be noted that the same reaction of isomer **169i** (Hal = Cl, R^1 = CO_2Et, R^2 = NO_2, R^3 = H) (rather than **169h**), which contains the ethoxycarbonyl group in the *ortho*-position to the chlorine atom, on refluxing in EtOH for 5 min leads to imidazoquinoline **172** — a carbon analogue of imidazo[1,2-*a*]quinoxaline.[168]

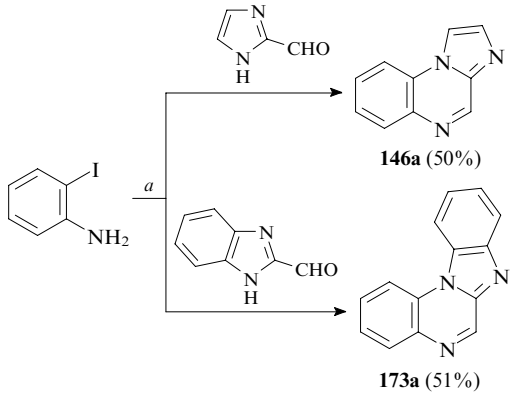
The condensation of *o*-iodoaniline with 2-formylimidazole in the presence of a copper catalyst results in imidazo[1,2-*a*]quinoxaline (**146a**). An analogous reaction with 2-formylbenzimidazole gives benzimidazo[1,2-*a*]quinoxaline (**173a**) (Scheme 78).[170]

Table 8. Yields of compounds **171** (see Scheme 77).[167–169]

Compound **171**	R^2	R^3	R^4	Yield (%)
a	H	NO_2	Ph	88
b[a]	H	CO_2Et	Ph	30
c	H	see[b]	H	2
d	H	H	4-FC_6H_4	36
e	H	H	4-$H_2NC_6H_4$	45
f	H	H	3,4-$(MeO)_2C_6H_3$	5
g	H	H	3,4,5-$(MeO)_3C_6H_2$	6
h	H	NO_2	4-FC_6H_4	20
i	H	NO_2	4-$MeOC_6H_4$	68
j	H	NO_2	3,4-$(MeO)_2C_6H_3$	20
k	H	Bz	4-$MeOC_6H_4$	16
l	H	Bz	3,4-$(MeO)_2C_6H_3$	11
m	H	Bz	Ph	14
n	F	H	Ph	52
o	Cl	H	Ph	see[c]
p	F	F	Ph	see[c]

[a] $R^1 = NO_2$, in the other cases, $R^1 = H$; [b] R^3 = 4-methyl-2-ethylaminothiazol-5-yl; [c] the yield is not specified in the original paper.

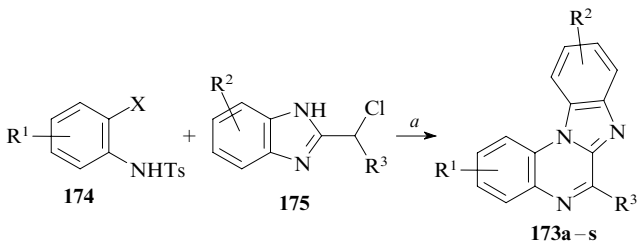
Scheme 78



(*a*) 10 mol.% CuI, 20 mol.% sparteine, 2 equiv. K_3PO_4, 130 °C, 24 h

There has been developed a convenient and efficient domino process for constructing benz[4,5]imidazo[1,2-*a*]quinoxalines **173** from *N*-tosyl-2-haloanilines **174** and 2-(chloromethyl)-1*H*-benzimidazoles **175** (Scheme 79, Table 9). This reaction proceeds under mild conditions and is catalyzed by copper salts, and the yields vary from moderate to quantitative. Such a Cu-catalyzed one-pot method can be used for synthesis of a large number of compounds with the aim of testing their biological activity.

Scheme 79



(*a*) $Cu(OAc)_2 \cdot H_2O$, L-proline, Cs_2CO_3, 80 °C; X = Cl, Br, I

Table 9. Yields of compounds **173** (see Scheme 79).[170,171]

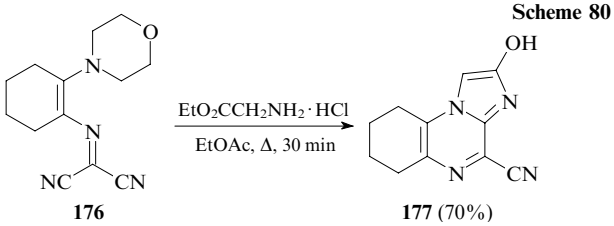
Compound **173**	R^1	R^2	R^3	X in substrate **174**	Time /h	Yield (%)
a	H	H	H	I	6	96
	H	H	H	Br	6	95
	H	H	H	Cl	15	46
b	4-Me	H	H	I	7	90
c	4-F	H	H	I	3	88
d	4-Cl	H	H	I	3	78
e	4-CF_3	H	H	I	2	85
f	5-Me	H	H	Br	6	94
g	4-F_3CO	H	H	Br	5	88
h	5-F	H	H	Br	3	84
i	5-Cl	H	H	Br	3	81
j	5-CF_3	H	H	Cl	3	72
k	Me	H	H	Cl	15	42
l	H	H	Me	I	6	71
	H	H	Me	Br	5	70
m	4-Cl	H	Me	I	3	64
n	H	5-Me	H	I	4	78
	H	5-Me	H	Br	5	70
o	4-Cl	5-Me	H	I	3	77
p	H	5,6-Me_2	H	I	4	85
q	4-Cl	5,6-Me_2	H	I	3	89
r	H	Cl	H	I	3	81
s	H	H	Ph	I	6	74

Studying the effect of the base nature on this process has shown that the use of caesium carbonate affords the target compounds in higher yields as compared with the reactions where K_2CO_3, K_3PO_4, KOH, Bu^tONa or Bu^tOK are used as a base. Six copper-containing catalysts have been tested: $Cu(OAc)_2 \cdot 2H_2O$, CuBr, CuI, CuCl, $CuBr_2$ and $CuCl_2 \cdot 2H_2O$. The best yields have been achieved with $Cu(OAc)_2 \cdot 2H_2O$. In addition, the effects of the solvent and ligand on the reaction efficiency have been studied. The use of DMSO, DMF, dioxane and toluene leads to benzimidazo[1,2-*a*]quinoxaline **173a** in good yield, whereas the reaction is almost absent in THF. The effect of the nature of the halogen atom in initial *N*-tosyl-2-haloanilines **174** on the yields of compounds **173** is as follows: when bromo and iodo derivatives are used, compounds **173** form in rather high yields (78% – 96%), while, in the reaction with *N*-tosyl-2-chloroanilines, good yields are achieved only when they contain electron-withdrawing substituent R^1 (otherwise, the yields are < 50%).[171]

VII. Other methods of synthesis of imidazo[1,2-*a*]quinoxalines

The imidazo[1,2-*a*]quinoxaline system can also be designed on the basis of compounds that contain neither the quinoxaline ring nor the imidazole ring. In particular, the reaction

Scheme 80



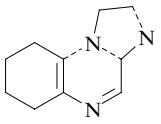


Figure 7. Scheme of formation of the imidazo[1,2-*a*]quinoxaline system in synthesis of compound **177**.

of compound **176** with ethyl glycinate hydrochloride leads to annulation of the imidazopyrazine system and formation of tetrahydroimidazoquinoxaline **177** (Scheme 80).[172]

Formation of tricycle **177** is schematically shown in Fig. 7.

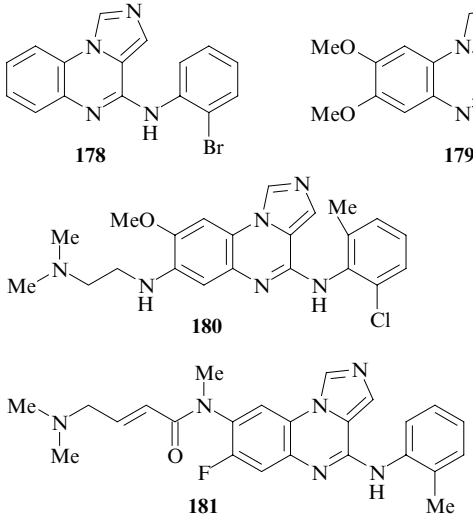
VIII. Biological activity of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines

Investigation of the biological activity of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines began almost simultaneously with the development of methods for their preparation. However, many data were published only in the patent literature. In the late 1980s and in the 1990s, major efforts were made to study the effect of these compounds on the central nervous system. The result of these works was the creation of drugs shown in Fig. 1.[22] The range of useful properties of such tricyclic systems has been extended in the last 10–15 years. Below, we present the structures of representatives of this class of compounds grouped by type of biological activity.

1. Kinase inhibition

Imidazo[1,5-*a*]quinoxalines **178**–**180**, containing an arylamine moiety in the 4-position, are inhibitors of the Src-family kinases p56Lck: the 50% inhibition concentrations (IC_{50}) of these compounds are 170.2, 2.0 and 1.7 nmol litre^{-1}, respectively.[80,150,173] The presence of an amide group in the 8-position, along with the 4-arylamine substituent, confers to compound **181** the ability to irreversibly inhibit Bruton's tyrosine kinase (BTK) (IC_{50} = 1.93 nmol litre^{-1}).[91] This compound is used in the treatment of rheumatoid arthritis.

Structures 178–181



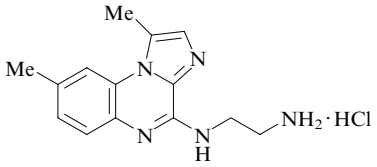
178 **179**

180

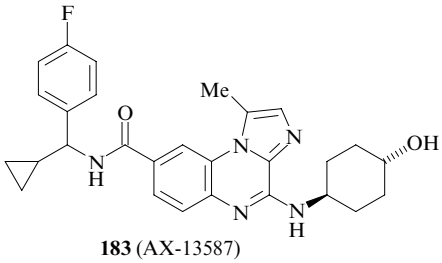
181

Among imidazo[1,2-*a*]quinoxalines, there are a highly efficient IkB-kinase inhibitor — compound **182** (BMS-345541)[174] — and a selective inhibitor of JNK1 kinase — compound **183** (AX-13587).[156]

Structures 182, 183



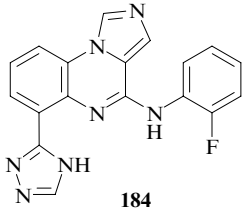
182 (BMS-345541)



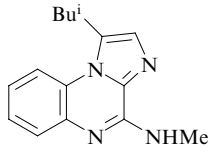
183 (AX-13587)

One of the important new areas of biological studies of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxaline derivatives focuses on their antitumour activity. New potent dual CK2 and PIM kinase inhibitors with the antiproliferative activity against cancer cells have been described,[87] for example, compound **184** (IC_{50} = 0.038 (PIM1), 0.043 (PIM2), 0.035 (CK2) mol litre^{-1}). 1-Isobutyl-4-methylaminoimidazo[1,2-*a*]quinoxaline (**185**, EAPBO-103) and 1-phenethyl-4-substituted imidazo[1,2-*a*]quinoxalines **186a–c** (EAPBO-201–203) show much higher activity (by a factor of 6–110 and 2–45) against melanoma (A375) than the antitumour drug fotemustine and immunomodulator imiquimod.[98] Compound **186c** also exhibits higher cytotoxic activity than imiquimod and fotemustine. 4-Methylamino-1-(2-methoxyphenyl)imidazo[1,2-*a*]quinoxaline (**187a**, EAPBO-503) is even more active against melanoma: its activity is 7–9 times higher than that of compound **186c**.[98,175] The metabolism and pharmacokinetics of these pharmaceuticals have been studied.[176,177] For compound **187a** and its metabolite — 1-(2-hydroxyphenyl)-4-methylami-

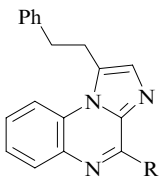
Structures 184–187



184

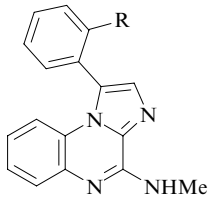


185 (EAPBO-103)



186a–c

R = Cl (**a**, EAPBO-201), NH_2 (**b**, EAPBO-202), NHMe (**c**, EAPBO-203)



187a,b

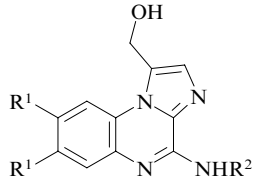
R = OMe (**a**, EAPBO-503), OH (**b**, EAPBO-603)

noimidazo[1,2-*a*]quinoxaline (**187a**, EAPBO-603)[177,178] — protocols for the quantification of them in human and rat plasma have been developed.[24]

2. Activity towards the A_1 adenosine and histamine receptors

Currently, study of the effect of the tricyclic compounds under consideration on the central nervous system are continued. 4-Alkylamino-1-hydroxymethylimidazo[1,2-*a*]-quinoxalines **188** are A_1 adenosine receptor antagonists, the compound with R^1 = Cl, R^2 is pyrrolidin-1-yl exhibiting the highest activity [inhibition constant (K_i), 7 nmol litre^{-1}].[123] It has been stated that the hydroxymethyl group in the 1-position displays the potent affinity toward the binding site of the receptor.[123]

Structures 188



188

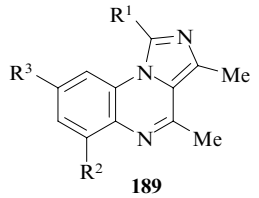
R^1 = H, Me, Cl; R^2 = Alk, cycloalkyl, azacycloalkylethyl

Imidazo[1,2-*a*]- and imidazo[1,5-*a*]quinoxalines have been studied as histamine receptor inhibitors.[90,179]

3. Phosphodiesterase inhibition

3,4-Dimethylimidazo[1,5-*a*]quinoxalines **189**, containing different substituents in the 1-, 6- and 8-positions, and above-mentioned imidazo[1,5-*a*]quinoxalines **188** are 10A phosphodiesterase (PDE10A) inhibitors and can be used for designing antischizophrenia drugs.[30,84]

Structures 189



189

R^1 = Ar, Het; R^2 = H, F, OH, OAlk, fluoroalkoxy;
R^3 = H, F, OH, OAlk, fluoroalkoxy, CF_3, morpholin-4-yl

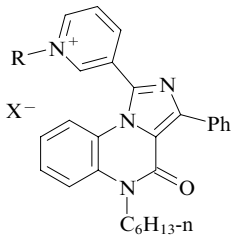
The presence of the pyrrolidine, morpholine, cyclohexane, piperidine, or azacycloheptane moiety in the 1-position of imidazo[1,5-*a*]-quinoxalin-4-ones, along with amide groups in the 7(8)-position, leads to inhibition of phosphodiesterase 9 (PDE9); therefore, such compounds are used for developing drugs that eliminate urination disorders.[105,106]

1-Isobutyl-4-methylaminoimidazo[1,5-*a*]quinoxaline (**185**) exhibits potent inhibitory properties against phosphodiesterase 4 (PDE4).[120]

4. Antimicrobial and antifungal activity

Imidazo[1,5-*a*]quinoxalin-4-ones **190a–c** with a quaternized pyridinium substituent in the 1-position have noticeable antimicrobial activity. The antibacterial activity of compounds **190** against *Staphylococcus aureus* is comparable with that of drugs ofloxacin and norfloxacin. In addition, bromide **190b** exhibits fungicidal activity (against *Candida albicans*) comparable with that of drug Amphotericin B, whereas iodide **190c** has no antifungal effect.[57] Both salts show significant antibacterial activity against soil bacterium *Bacillus cereus*.[57]

Structures 190



190a–c

R = Bn, X = Cl (**a**), R = n-C_9H_{19}: X = Br (**b**), I (**c**)

IX. Conclusions

As can be seen from the material presented in this review, imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines arouse a great deal of interest of researchers owing to the wide range of biological activity exhibited by them. For this reason, in addition to the improvement of the known methods of their synthesis, an intensive search is carried out for new preparative procedures that afford diverse derivatives.

Analysis of the efficiency of different methods of synthesis of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines demonstrates that there are currently 26 approaches corresponding to the retrosynthetic analysis of the structure of a heterocyclic system without including the benzene ring. Initial compounds are quinoxaline (see Figs 2 and 5) or imidazole derivatives (see Figs 3 and 6). For synthesis of imidazo[1,5-*a*]quinoxaline, seven approaches based on quinoxalines and four approaches based on imidazoles have been developed (Table 10); for synthesis of imidazo[1,2-*a*]quinoxalines, six approaches based on quinoxalines and five approaches based on imidazoles have been developed (Table 11).

These Tables demonstrate which methods of synthesis of imidazo[1,5-*a*]quinoxalines are most widely used, which of

Table 10. Comparison of different approaches to the synthesis of imidazo-[1,5-*a*]quinoxalines (see Figs 2 and 3).

Variant	Number of studies	Number of stages	Substituent variation positions	Ref.
$\mathbf{A1_Q}$	7	3–6	1–3	39, 40, 43–47
$\mathbf{A2_Q}$	1	3	2	50
$\mathbf{A3_Q}$	1	3	2	51
$\mathbf{B1_Q}$	5	4 or 5	1, 3	30, 31, 43, 53, 54
$\mathbf{C1_Q}$	6	3–5	1, 3, 5	43, 55, 57–60
$\mathbf{D_Q}$	20	4 or 5	3, 4, 6–9	61–80
$\mathbf{E1_Q}$	1	3–5	1, 5	83
$\mathbf{A1_I}$	2	3	—	30, 84
$\mathbf{A2_I}$	7	2	3, 6–9	85–91, 95, 97
$\mathbf{A4_I}$	4	2 or 3	6–9	81, 92–95
$\mathbf{B1_I}$	11	3–5	1–4, 6–9	34, 101–106, 109–115

Note. Here and in Table 11, a dash means that substituents cannot be varied.

Table 11. Comparison of different approaches to the synthesis of imidazo[1,2-*a*]quinoxalines (see Figs 5 and 6).

Variant	Number of studies	Number of stages	Substituent variation positions	Ref.
$\mathbf{A1_Q}$	13	4–5	1, 2, 4, 6–9	35, 91, 103, 118–126, 131
$\mathbf{A3_Q}$	3	3	2 or 4	39, 122, 133
$\mathbf{B3_Q}$	1	3	2, 6–9	134
$\mathbf{C1_Q}$	3	4	1, 2	126, 135, 136
$\mathbf{D_Q}$	1	1	—	132
$\mathbf{E1_Q}$	2	2	1, 2, 4, 6–9	140, 141
$\mathbf{A1_I}$	11	4	4	142–152
$\mathbf{A2_I}$	4	2	6–9	153–157
$\mathbf{A4_I}$	2	2	6–9	121, 160, 161
$\mathbf{B1_I}$	9	3	1, 2, 4, 6–9	80, 101, 103, 104, 162–166
$\mathbf{D1_I}$	4	1	1, 2, 4, 6–9	167–171

them require further development, and which methods remain unused. The formation of imidazo[1,5-*a*]quinoxalines **107** and **108** from compounds **76** and **105**, as well as the formation of imidazo[1,2-*a*]quinoxaline **177** from 1-morpholino-2-dicyanomethylideneiminocyclohexene (**176**) and ethyl glycinate hydrochloride,[172] offers great potential for creating imidazoquinoxaline systems from compounds containing neither the quinoxaline nor the imidazole ring.

We hope that information presented in this review will be helpful for researchers dealing with the chemistry of fused heterocycles not only to reduce the time for the search for and development of a synthetic approach to target compounds from readily available derivatives but also to invent radically new methods of synthesis of fused systems with a known combination of heterocycles. In our opinion, this work can stimulate synthetic organic chemists to design a wide range of new pharmaceutically promising compounds.

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