DOI 10.1007/s10593-019-02501-w

Chemistry of Heterocyclic Compounds **2019**, *55*(7), 584–597

REVIEW

Dedicated to Professor V. A. Mamedov on his 60th anniversary

New achievements in the synthesis of pyrrolo[1,2-*a*]quinoxalines

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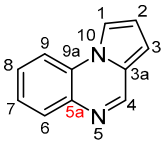
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2019, *55*(7), 584–597

Submitted January 29, 2019
Accepted after revision May 1, 2019



This review article describes methods for the preparation of pyrrolo[1,2-*a*]quinoxalines, covering literature sources from the last 10 years. The attention was largely paid to new, original methods for the synthesis of pyrrolo[1,2-*a*]-quinoxalines on the basis of pyrrole and quinoxaline derivatives, as well as multicomponent reactions leading to the formation of both pyrrole and quinoxaline rings.

Keywords: pyrrolo[1,2-*a*]quinoxalines, pyrroles, quinoxalines, biological activity.

Pyrrolo[1,2-*a*]quinoxalines have been characterized with respect to a broad range of biological properties.[1] During the last decade, derivatives of this tricyclic system have been studied as antiparasitic (antimalarial, anti-Leishmania) agents,[2] as well as data have been obtained on their antifungal activity.[3] Derivatives of pyrrolo[1,2-*a*]quinoxalines have been applied as ligands of 5-HT_3 receptors,[4] inhibitors of human protein kinase CK2, AKT kinase,[5] enzymes RAD51,[6] FAAH, and MAGL,[7] as well as the protein tyrosine phosphatase 1B.[8] Some of these compounds have been shown to possess analgesic,[9] antileukemic,[10] and tuberculostatic activity.[11] 4-(2-Arylidenehydrazinyl)pyrrolo-[1,2-*a*]quinoxalines have been used as fluorescent probes.[12] All of these applications provide motivation for synthetic chemists to develop new, simple methods for the preparation of pyrrolo[1,2-*a*]quinoxaline derivatives. The earlier review articles[13] on methods for the synthesis of this class of compounds covered publications from 1950–2009. The current review reflects the most recent achievements over the last 10 years, with the main emphasis on new, original methods that are applicable to the formation of pyrrolo[1,2-*a*]quinoxaline system.

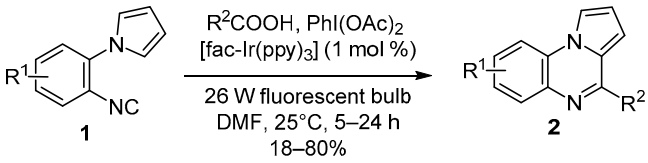
1. SYNTHESIS STARTING FROM PYRROLE DERIVATIVES

1.1. Intramolecular cyclization of functionalized pyrroles

Syntheses of pyrrolo[1,2-*a*]quinoxalines on the basis of pyrroles have been accomplished by using various approaches to the formation of pyrazine ring. One of these approaches involves intramolecular cyclization of functionalized *N*-phenylpyrroles, leading to the closure of pyrazine ring and formation of C(3a)–C(4) bond (Scheme 1), C(4)–C(5) bond (Scheme 3), or N(5)–C(5a) bond (Schemes 4, 5) of the pyrrolo[1,2-*a*]quinoxaline system.

Intramolecular cyclization of 1-(2-isocyanophenyl)-1*H*-pyrroles **1**, induced by irradiation with visible light, occurred under mild conditions in the presence of carboxylic acid derivatives and led to pyrrolo[1,2-*a*]-quinoxalines **2** bearing various functional groups at position 4 (Scheme 1).[14]

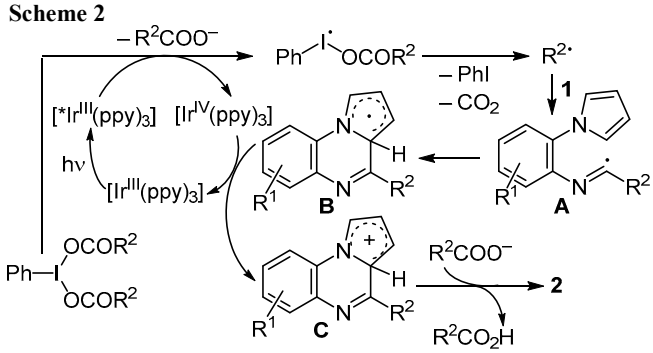
Scheme 1



R^1 = H, Hal, Me, OMe, Ac, CO_2Me
R^2 = Alk, Bn, $(CH_2)_2COMe$, $(CH_2)_nHet$, $(CH_2)_n(NHBoc)CO_2R^3$ (R^3 = Bn, All)

The reaction proceeded according to a radical mechanism in the presence of iridium catalyst and $PhI(OAc)_2$, as shown in Scheme 2. The initial interaction of $PhI(OAc)_2$ with carboxylic acid resulted in the formation of the respective phenyliodonium(III)dicarboxylate ($PhI(OCOR)_2$). This

Scheme 2



* Here and further the corresponding author is marked with*.

phenyliodonium derivative acted as a single electron oxidant on the Ir(III) complex, giving the intermediate [Ph–I–OC(O)R]•. The subsequent decarboxylation of this intermediate gave an alkyl radical that attacked the starting isonitrile **1**, transforming it into the imidoyl radical **A**, which underwent an intramolecular homolytic aromatic substitution with the formation of radical σ-complex **B**. This radical complex was oxidized by Ir(IV) complex to cation **C**, the aromatization of which led to 4-substituted pyrrolo[1,2-*a*]quinoxaline **2** (Scheme 2).[14]

Analogous processes were used to obtain fused quinoxalines **3**–**9**, which are shown in Figure 1, from the appropriate derivatives of imidazole, benzimidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, and tetrazole.[14]

Previously it has been shown that intramolecular cyclization of 2-ethoxycarbonyl-*N*-(2-nitrophenyl)pyrroles led to the closure of pyrazine ring and formation of pyrrolo-[1,2-*a*]quinoxalinone derivatives **10** (transformation *xv*, Scheme 3).[13a] Specific precursors of pyrrolo[1,2-*a*]-quinoxalinones containing ester groups at various positions of the benzene and pyrrole rings were synthesized. Additional pharmacophoric groups were introduced into the synthesized (ethoxycarbonyl)pyrrolo[1,2-*a*]quinoxalinones, and the antileucemic activity of the obtained derivatives was studied.[10]

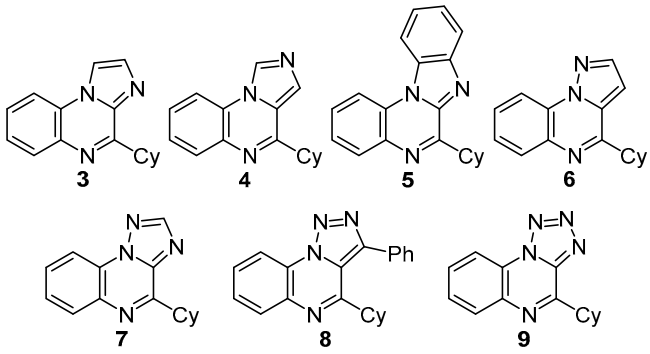
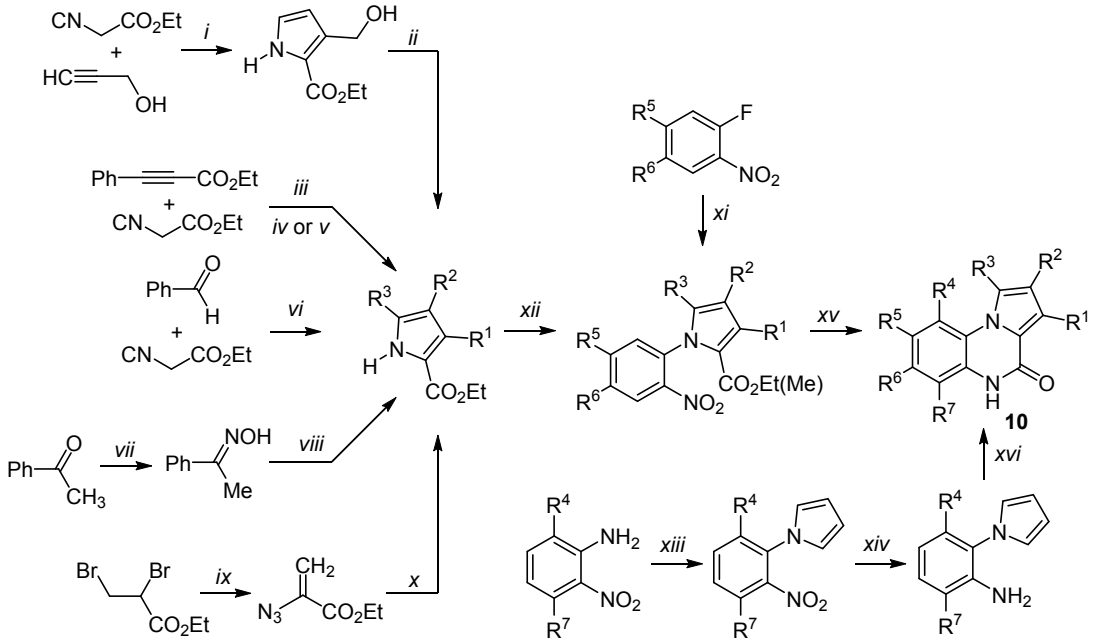


Figure 1. Fused quinoxalines **3**–**9**, obtained in reactions of 1-(2-isocyanophenyl)-1*H*-pyrrole aza analogs with cyclohexylcarboxylic acid (CyCOOH) under the conditions given in Scheme 1.

Scheme 3

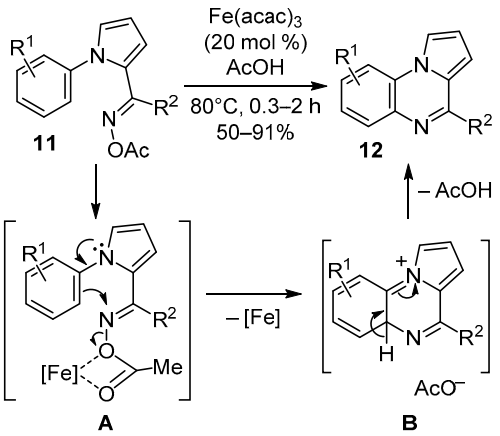


i: Ag_2CO_3, dioxane, 80°C, 2 h
ii: 1. MnO_2, $CHCl_3$, Δ, 2.5 h;
2. $KMnO_4$, Me_2CO/H_2O, 40°C, 2 h, rt, 1 h;
3. EtOH, $SOCl_2$, Δ, 3 h
iii: dppp, dioxane, 100°C
iv: 1. Ag_2CO_3, dioxane or NMP, 25°C; 2. 80°C
v: Cu_2O, phenanthroline, dioxane, 100°C
vi: DBU, THF, 50°C
vii: H_2NOH, HCl, pyridine, EtOH, Δ
viii: 1. $EtO_2C{\equiv}CO_2Et$, DABCO, PhMe, 80°C;
2. 170°C, MW 45 min
ix: NaN_3, DMF, 65°C
x: $PhCOCH_2CO_2Et$, $Mn(OAc)_3{\cdot}2H_2O$, 40°C
xi: methyl pyrrole-2-carboxylate, Cs_2CO_3, DMF, Δ, 2 h
xii: 2-fluoronitrobenzene, Cs_2CO_3, DMF, Δ, 1.5 h
xiii: DMTHF, AcOH, Δ, 1 h
xiv: $CuSO_4$–$NaBH_4$, EtOH, 0°C, 1 h
xv: Fe, AcOH, 2 h, 28–92%
xvi: $(Cl_3CO)_2CO$, PhMe, Δ, 4 h, 48–81%

Reaction	R^1	R^2	R^3	R^4	R^5	R^6	R^7
i, *ii*, *xii*, *xv*	CO_2Et	H	H	H	H	H	H
iii, *xii*, *xv*	CO_2Et	Ph	H	H	H	H	H
iv or *v* or *vi*, *xii*, *xv*	Ph	CO_2Et	H	H	H	H	H
vii, *viii*, *xii*, *xv*	CO_2Et	H	Ph	H	H	H	H
ix, *x*, *xii*, *xv*	H	CO_2Et	Ph	H	H	H	H
xi, *xv*	H	H	H	H	CO_2Et	H	H
xi, *xv*	H	H	H	H	H	CO_2Et	H
xiii, *xiv*, *xvi*	H	H	H	CO_2Et	H	H	H
xiii, *xiv*, *xvi*	H	H	H	H	H	H	CO_2Et

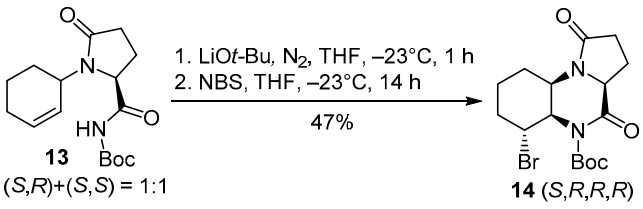
1-(*N*-Arylpyrrol-2-yl)ethanone-*O*-acetyloximes **11** underwent intramolecular cyclization in the presence of Fe(III) compounds, giving pyrrolo[1,2-*a*]quinoxalines **12** (Scheme 4).[15] The proposed reaction mechanism included an initial coordination of pyrrole derivative with Fe(III) ion, leading to acetoxy group activation with the formation of the intermediate **A**, which underwent cyclization to the intermediate **B**, followed by deprotonation (Scheme 4).[15]

Scheme 4



Intramolecular cyclization of the diastereomeric mixture of *tert*-butyl-1-(cyclohex-2-enyl)-5-oxopyrrolidine-2-carbonylcarbamate **13** in the presence of base, followed by treatment with *N*-bromosuccinimide, resulted in pyrazine ring closure and the formation of pyrrolo[1,2-*a*]quinoxaline system. The resulting product **14** was obtained as enantiomerically pure (*S*,*R*,*R*,*R*)-isomer, and the unreacted *S*,*S*-isomer of the starting amide was also isolated (Scheme 5).[16]

Scheme 5

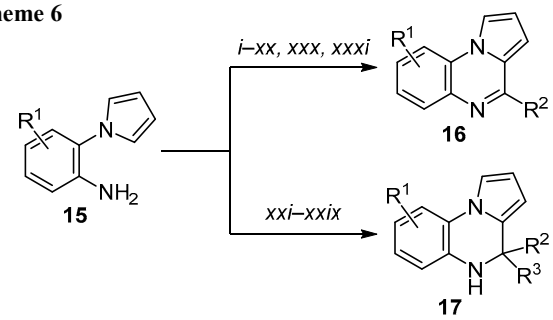


1.2. Cyclization of *N*-(2-aminophenyl)pyrroles

N-(2-Aminophenyl)pyrroles were found to be convenient reagents for the synthesis of pyrrolo[1,2-*a*]quinoxalines. The reaction of *N*-(2-aminophenyl)pyrroles with equivalents of one-atom synthons led to the formation of C(3a)–C(4) and C(4)–N(5) bonds of the pyrrolo[1,2-*a*]quinoxaline system. The reaction of *N*-(2-aminophenyl)pyrroles with acetic anhydride[17] or triphosgene[2a,7,10,12] (transformation *xvi,* Scheme 3) provided pyrrolo[1,2-*a*]quinoxalines **10**, some of which were converted into more complex derivatives for biological activity studies.

Other original methods have been recently developed for the synthesis of pyrrolo[1,2-*a*]quinoxalines **16**, **17** from *N*-(2-aminophenyl)pyrroles **15** (Scheme 6, Table 1), with a prominent role played by the use of new one-carbon synthons (Table 1, transformations *i–xii*). When cyclic compounds, methyl aryl ketones, alkenes, and alkynes were used (transformations *i–v*),[18–21] pyrrolo[1,2-*a*]quinoxalines containing a functional group at position 4 were formed. Condensation reactions involving oxygen-containing heterocyclic compounds (oxetane, tetrahydrofuran, tetrahydropyran, 1,3-dioxolane) led to the formation of pyrrolo[1,2-*a*]quinoxalines containing a hydroxyalkyl substituent (hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxyethoxy group, respectively) at position 4 (transformation *i*).[18] Replacement of tetrahydrofuran with tetrahydrothiophene led to the formation of pyrrolo[1,2-*a*]-quinoxaline bearing a propylthiol substituent (transformation *i*).[18] A distinct feature of these transformations was the fact that mild reaction conditions and room temperature were sufficient. The reaction of *N*-(2-aminophenyl)pyrroles with cyclobutanone oximes (R = H, Bn, methoxybenzyl, methoxynaphthyl) enabled the preparation of pyrrolo[1,2-*a*]-quinoxalines bearing a β-cyanoethyl substituent at position 4 (transformation *ii*).[19]

Scheme 6



The proposed reaction mechanism (Scheme 7) involved the formation of radical species from cyclic reagents during the first step (tetrahydrofuranyl radical **A** or γ-cyanopropyl radical **A'**), which attacked position 2 of the pyrrole moiety in *N*-(2-aminophenyl)pyrrole, leading to the formation of intermediates **B** and **B'**. The intermediate **B** through its protonated form **C** was further transformed by closure of pyrazine ring and cleavage of tetrahydrofuran ring, resulting in the formation of 4,5-dihydropyrroloquinoxaline **D**, the oxidation of which led to the final product (Scheme 7). Another route for the transformation of intermediate **B** can be associated with the initial oxidation into intermediate **E**, followed by spirocyclization, tetrahydrofuran ring disclosure in the spiro compound **F**, and deprotonation of the intermediate **G** (Scheme 7).[18] In the reaction with cyclobutanone oximes, intermediate **B'** was oxidized into the hydroperoxide **C'** that underwent elimination of a water molecule and was converted into the oxo derivative **D'**, with subsequent intramolecular cyclocondensation leading to the final product (Scheme 7).[19]

Another method for introducing a functional group at position 4 of the pyrrolo[1,2-*a*]quinoxaline system based on the condensation of *N*-(2-aminophenyl)pyrroles with methyl aryl ketones,[20a] ethenes or ethynes[21] at heating in

Table 1. Reactants, reaction conditions, and yields in the cyclization reaction of *N*-(2-aminophenyl)pyrroles

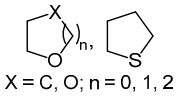
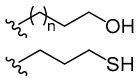
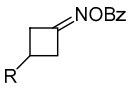
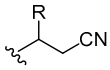
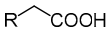
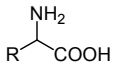
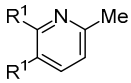
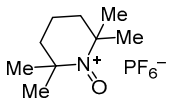
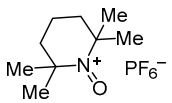
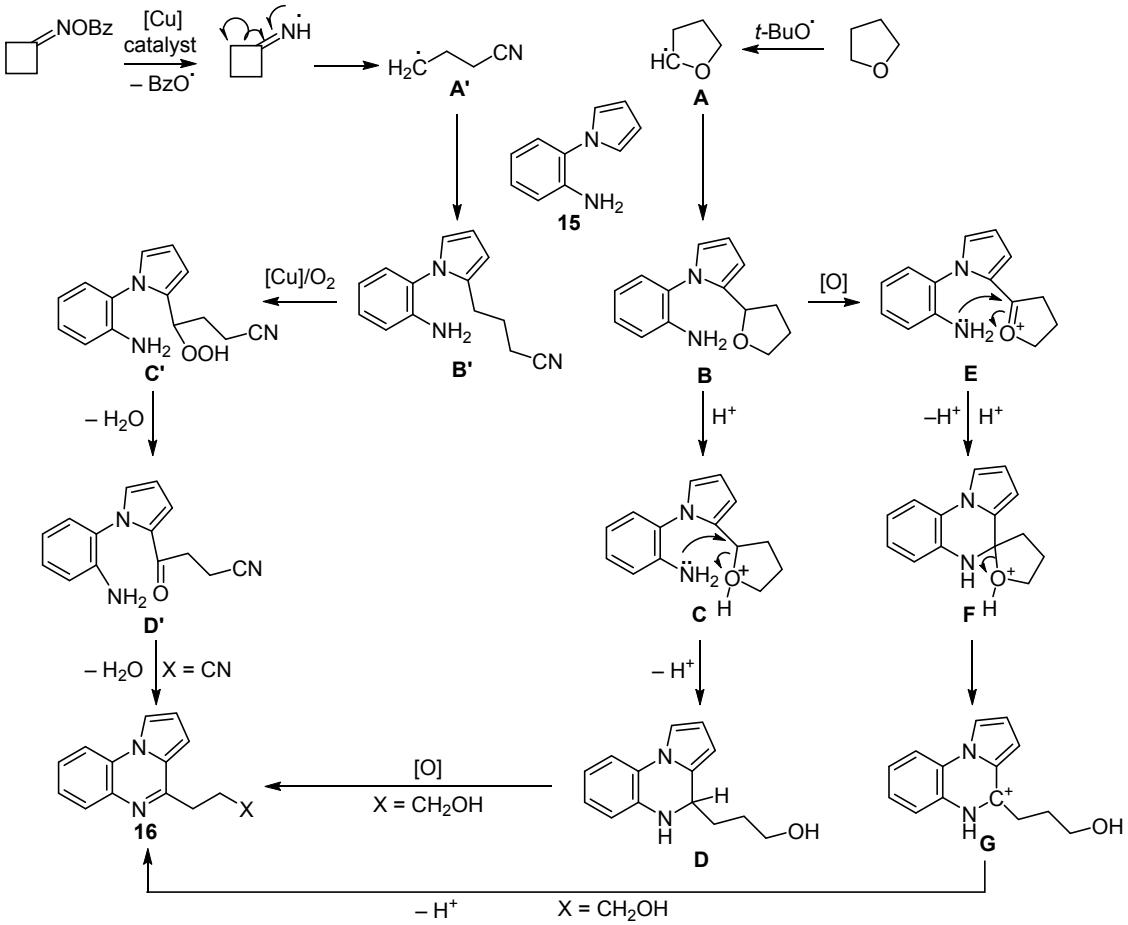
Reaction conditions	Reactant	R^2 or R^2/R^3	Catalyst	Solvent	Oxidant	Temperature, °C	Time, h	Yield, %
i	 X = C, O; n = 0, 1, 2		*t*-BuOOH, $FeCl_3$, CF_3SO_3H	*t*-BuOH	–	25	10	44–85[18]
ii			$Cu(OPIV)_2$	*N*-methyl-pyrrolidone	O_2 (from cylinder)	80	8	43–80[19]
iii		 Ar	I_2	DMSO	–	120	6	72–90[20a]
iv					IBX*, O_2 (air)	100	12	84–89[21]
v					O_2 (air)		10	86–91[21]
vi		C_1–C_6 Alk			O_2 (air)	160	16–64	53–93[22]
vii		Ar	I_2	MeCN	I_2	80	5–8	82–92[23a]
viii				*o*-xylene	O_2 (from cylinder)	140	12	81–95[23b]
ix		Ar, Het	$FeCl_3$	DMF	O_2 (air)	100	24	72–98[24a]
x			$CuSO_4$, ligand**	DMF	O_2	130	8	72–92[24b]
xi		C_1–C_6 Alk, Ph	–	DCE–H_2O	$(NH_4)S_2O_8$	80	10	53–92[24c]
xii		Py, Qu	CF_3CO_2H, $Cu(OAc)_2$	DMF	O_2 (from cylinder)	120	12	52–82[25]
xiii		Ar, Het	Amberlite IR-120H	–	–	100	4	65–92[26a]
xiv		Ar	CF_3CO_2H	CH_2Cl_2	$KMnO_4$	0–25	5–30	60–76[26b]
xv		Ar, Alk, Het	–	*o*-xylene	O_2 (1 bar)	140	24	40–90[26c]
xvi		Ar, Het	$Cu(OTf)_2$	EtOH	-	25	1-2	75-96[26d]
xvii		Ar	 (100 mol %)	MeCN	–	25	18	76–96[27a]
xviii		Ar	$AlCl_3$/BtH	THF		25	8–10	85-–91[27b]
xix		Ar, Het	*p*-DBSA***	EtOH	$KMnO_4$	25	0.5	40–90[27c]
xx		Ar, Het	I_2	DMSO	O_2 (air)	120	12	50–81[20b]
xxi		H/Ar	 (1 mol %)	MeCN	–	25	18–24	75–92[27a]
xxii		H/Ar, H/Alk, H/Het	$AlCl_3$/BtH	THF	–	25	1–2	65–92[27b]
xxiii		H, Ar, Het, Alk	$[PrPy]HSO_4$ $nSiO_2$	H_2O	–	70	0.2–0.9	85–99[28a]
xxiv		H/Ar, H/Het	$B(OMe)_3$ Ligand*[4]	CH_2Cl_2	–	–40	15	72–94[28b]
xxv		Me/Ar	*p*-DBSA	EtOH	–	25	0.5	82–86[27c]
xxvi		Alk/Alk	CF_3CO_2H, MW	$CHCl_3$	–	85	0.2	72–90[29]

Table 1 (continued)

Reaction conditions	Reactant	R^2 or R^2/R^3	Catalyst	Solvent	Oxidant	Temperature, °C	Time, h	Yield, %
xxvii	R—≡—R^1	Me/Alk	[Au]*[5]	PhMe	–	80	1-6	20–95[30a]
xxviii	R—≡—H	Me/Alk	[Au]*[6]	PhMe	–	100	24	48–97[30b]
xxix			$PtBr_2$	MeOH	–	25–80	6–24	67–98[30c]
xxx	DMSO	H	AcOH	DMSO	DMSO, O_2	130	20	59–87[31]
xxxi			AcOH, Fe			100	12	45–82[25]

* IBX = 2-iodoxybenzoic acid.
** Ligand = 2,2'-bipyridyl.
*** *p*-DBSA = dodecylbenzenesulfonic acid.
*[4] Ligand = 1,1'-bi-2-naphthol.
*[5] [Au] = [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{MeCN}]SbF_6.
*[6] [Au] = $Ph_3PAuNTf_2$.

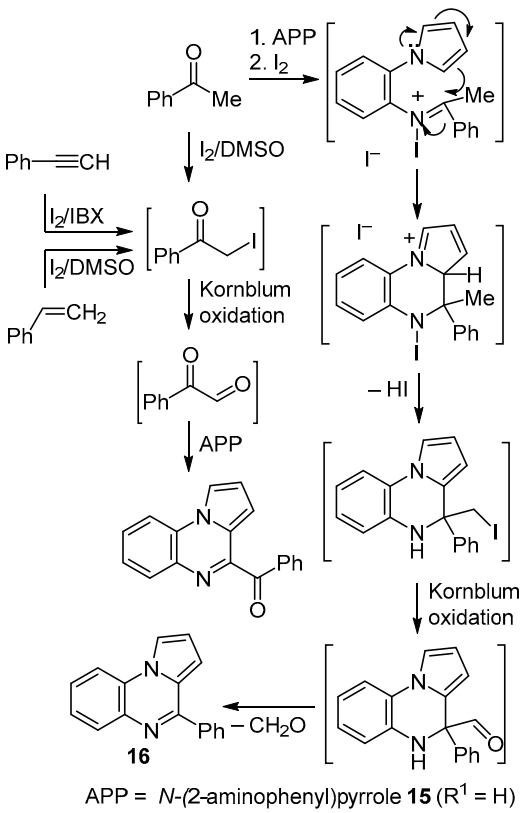
Scheme 7



the presence of iodine and resulted in the formation of aryl (pyrroloquinoxalin-4-yl) ketones in high yields (Table 1, transformations *iii*–*v*). The most probable route of reaction involved the transformation of starting ketones, ethenes, and ethynes into iodoacetophenone, followed by its oxidation to oxophenylacetaldehyde, which further participated in a Pictet–Spengler reaction with *N*-(2-aminophenyl)pyrroles (Scheme 8).[20a,21]

Elemental iodine acted as a catalyst in this case, since the eliminated HI was oxidized by DMSO to I_2.[20a,21] It is interesting to note that the interaction of *N*-(2-aminophenyl)pyrroles **15** with aryl methyl ketones in DMSO in the presence of I_2 at 120°C can lead to different products. On the one hand, those are the already mentioned arylpyrroloquinoxalin-4-yl ketones (Table 1, transformation *iii*),[20a] while on the other hand also 4-arylpyrroloquinoxalines (Table 1, transformation *xx*) can be obtained.[20b] The formation of various products was caused by the order in which reactants were added. In the first case, the aryl methyl ketone was heated in DMSO in the

Scheme 8



presence of elemental iodine in catalytic amounts, followed by the addition of *N*-(2-aminophenyl)pyrrole.[20a] In the second case, the aryl methyl ketone and *N*-(2-aminophenyl)pyrrole were heated in DMSO and only then treated with catalytic amounts of elemental iodine.[20b] For this reason, iodination and the subsequent Kornblum reaction led to different products (Scheme 8).

New methods have been developed for the synthesis of pyrrolo[1,2-*a*]quinoxalines **16** containing alkyl, aryl, and hetaryl substituents at position 4. Primary alcohols,[22] benzylamines,[23] aryl- and hetarylacetic acids, alkyl- and arylaminoacetic acids[24] were used as novel sources of single carbon atom synthons for the closure of pyrazine ring (Table 1, transformations *vi*–*xi*). During the optimization of reaction conditions for the process *xi* (Table 1), the reaction was found to proceed with a higher yield in the absence of a catalyst.[24c] The possible mechanism of these transformations includes the oxidation of alcohols (RCH_2OH), oxidative decarboxylation of substituted acetic (RCH_2COOH) or aminoacetic acids ($RCH(NH_2)COOH$) with the formation of aldehydes (RCH=O), or oxidative condensation of benzylamines ($ArCH_2NH_2$) with the formation of azomethines Ar–CH=N–CH_2Ar. The obtained aldehydes or imines subsequently reacted with *N*-(2-aminophenyl)pyrrole.[22–24]

π-Electron-deficient heterocycles containing methyl groups (α-picoline and 2-methylquinoline), as well as the respective 5- and 6-substituted derivatives containing Me, Et, and CN groups participated in an oxidative condensation with *N*-(2-aminophenyl)pyrroles **15**, forming 4-(pyridin-2-yl)- and 4-(quinolin-2-yl)pyrrolo[1,2-*a*]quinoxalines (Table 1, transformation *xii*).[25] The reaction proceeded with good to high yields in acidic medium when a copper salt was added as a catalyst. The presence of acid facilitated the tautomerization of methylpyridine and methylquinoline into the corresponding methylidene forms, which were further oxidized with air oxygen in the presence of catalyst to the pyridine- and quinoline-carbaldehydes. The subsequent Pictet–Spengler reaction led to 4,5-dihydropyrroloquinoxalines, which were then oxidized with [Cu]/O_2 system to the final products.

Various aldehydes have been previously used in reactions with *N*-(2-aminophenyl)pyrroles **15** to obtain pyrrolo[1,2-*a*]quinoxalines **16**, **17**.[13a] New condensation procedures have been developed over the last 10 years, including those that require catalysts, such as Lewis acids, strong organic acids, ionic liquids, and metal ions (Table 1, transformations *xiii*, *xiv*, *xvi*, *xviii*, *xix*, *xxii*–*xxiv*).[26–28] In a number of cases, the reactions proceeded in the presence of oxidants (O_2, I_2, $KMnO_4$) that were necessary to oxidize the initially formed 4,5-dihydro derivatives of pyrrolo[1,2-*a*]-quinoxalines **16**. Under milder conditions (in the absence of oxidants and at lower temperature) the reaction could be terminated at the stage of 4,5-dihydropyrrolo[1,2-*a*]-quinoxalines **17** (Table 1, transformations *xxi*–*xxiv*).[27,28]

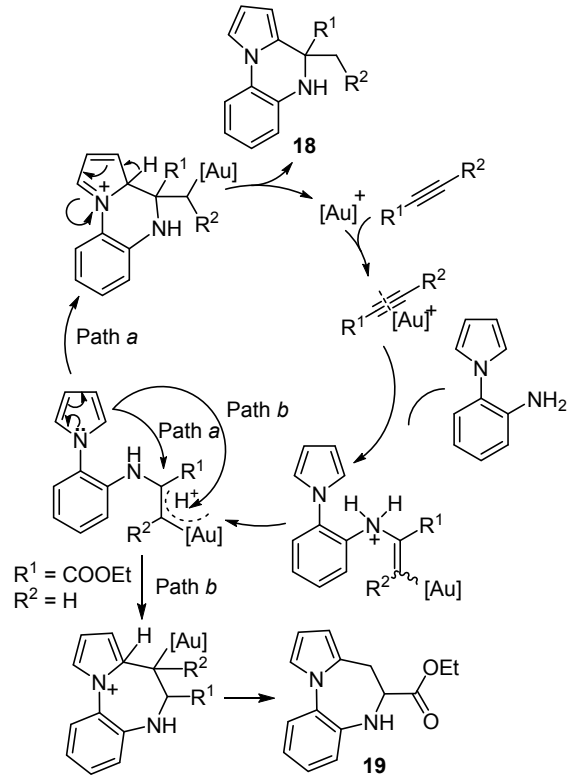
A method has been proposed for the preparation of 4,5-dihydropyrrolo[1,2-*a*]quinoxalines **17** from *N*-(2-aminophenyl)pyrroles **15** and aldehydes in aqueous medium in the presence of an ionic liquid.[28a] When $AlCl_3$ was used as catalyst in the presence of benzotriazole (BtH), the reaction led to the formation of 4,5-dihydropyrrolo[1,2-*a*]-quinoxalines in 1–2 h, while increasing the reaction duration to 8–10 h provided access to aromatic derivatives (Table 1, transformations *xxii* and *xviii*).[27b] The initiation of Pictet–Spengler reaction was achieved by using oxoammonium salt, depending on the amount of which either pyrrolo[1,2-*a*]quinoxalines **16** or their 4,5-dihydro derivatives **17** were isolated (Table 1, transformations *xvii* and *xxi*).[27a] The copper-catalyzed condensation of *N*-(2-aminophenyl)pyrroles **15** and aromatic aldehydes produced pyrrolo[1,2-*a*]quinoxalines **16** in 1–2 h at room temperature (Table 1, transformation *xvi*).[26d]

The interaction of ketones with *N*-(2-aminophenyl)-pyrroles led to 4,4'-disubstituted 4,5-dihydropyrrolo[1,2-*a*]-quinoxalines (Table 1, transformations *xxv* and *xxvi*).[27c,29] At the same time, derivatives of pyrrolo[1,2-*a*]quinoxalines could be obtained after microwave irradiation for 12 min in the presence of an acidic catalyst.[29]

Terminal alkynes in the presence of catalytic amounts of Au or Pt salts participated in hydroamination/hydroarylation reactions with *N*-(2-aminophenyl)pyrroles **15** according to the Markovnikov's rule, resulting in the formation of 4-methyl-4'-substituted 4,5-dihydropyrrolo[1,2-*a*]quinoxalines (Table 1, transformations *xxvii*–*xxix*).[30] The use of [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{MeCN}]SbF_6 as catalyst not only allowed to significantly reduce the reaction time, but also to use 1,2-disubstituted acetylenes as starting materials.[30a] The presence of an ethoxycarbonyl substituent in the terminal acetylene led to a different mechanistic route and, instead of pyrrolo[1,2-*a*]quinoxaline **18** (Scheme 9,

path *a*), gave pyrrolo[1,2-*a*]benzo[1,5]diazepine derivative **19** (Scheme 9, path *b*).[30a]

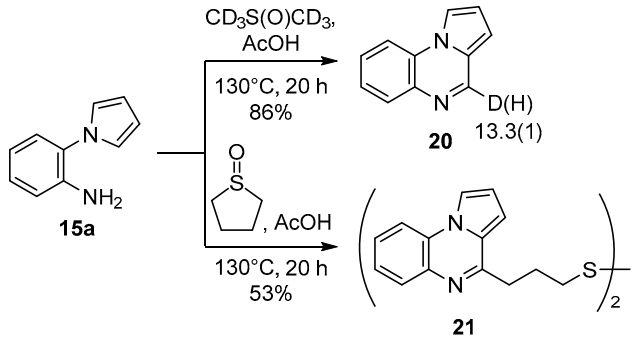
Scheme 9



Dimethyl sulfoxide was used not only as solvent, but also as a reactant that provided a single carbon atom synthon during the pyrazine ring closure in reactions with *N*-(2-aminophenyl)pyrroles **15**. This allowed to obtain pyrrolo[1,2-*a*]quinoxalines unsubstituted at position 4 (Table 1, transformation *xxx*).[31] The reaction proceeded in the absence of metal-based catalysts and met the criteria of green chemistry. For the purpose of mechanistic studies,[31] the reaction of *N*-(2-aminophenyl)pyrroles **15** with DMSO was performed in the presence of radical traps, which indeed reduced the yields of pyrroloquinoxalines. This observation provided evidence about the role of radical intermediates in this reaction. An isotopic experiment was performed to elucidate the origin of carbon atom at position 4 of the pyrroloquinoxaline product formed in this reaction: *N*-(2-aminophenyl)pyrrole (**15a**) was reacted with deuterated dimethyl sulfoxide. The resulting mixture contained 4-deuterio- and 4*H*-pyrroloquinoxalines **20** in 13.3:1 ratio, indicating that the single carbon atom source during the synthesis of pyrrolo[1,2-*a*]quinoxalines was DMSO (Scheme 10).[31]

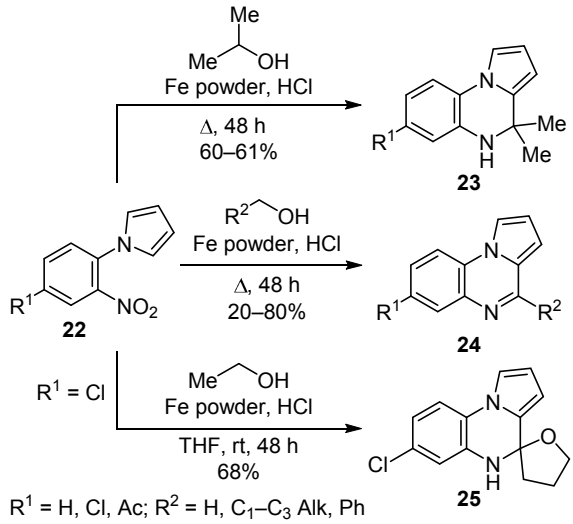
It has been proposed[31] that a methyl radical was formed under the reaction conditions, which then reacted with oxygen, resulting in the formation of a peroxide radical followed by generation of formaldehyde that participated in the cyclization with *N*-(2-aminophenyl)pyrroles **15**. The interaction of *N*-(2-aminophenyl)pyrroles **15** with tetrahydrothiophene oxide did not produce the expected 4-mercaptopropylpyrrolo[1,2-*a*]quinoxaline, but rather its oxidation product – the respective disulfide **21** (Scheme 10).[31] The cyclization into pyrrolo[1,2-*a*]quinoxalines by the action of DMSO could be also achieved at lower temperature and in a shorter time by using a catalyst (Table 1, transformation *xxxi*).[25]

Scheme 10



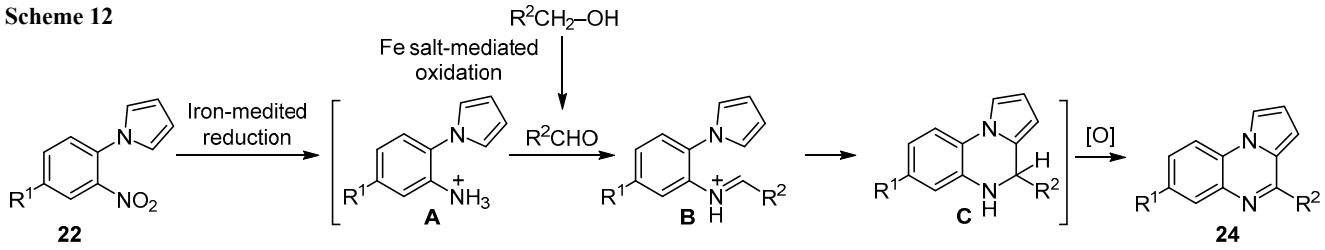
The synthesis of pyrrolo[1,2-*a*]quinoxalines can be also accomplished from the typically more available *N*-(2-nitrophenyl)pyrroles **22**, using various alcohols as sources of the single carbon atom synthon for the formation of C(3a)–C(4) and C(4)–N(5) bonds in the pyrrolo[1,2-*a*]quinoxaline system (Scheme 11). The reaction proceeded in the presence of Fe(0) source in acidic medium. The use of MeOH in a reaction with *N*-(2-nitrophenyl)pyrrole led to unsubstituted pyrrolo[1,2-*a*]quinoxaline.[32] The use of isopropanol (a secondary alcohol) resulted in the formation of 4,4-dimethyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalines **23**, while the use of primary alcohols allowed to obtain 4-substituted pyrrolo[1,2-*a*]quinoxalines **24**.[32] Performing the reaction in THF gave 5'*H*-spirofuranpyrrolo[1,2-*a*]-quinoxaline **25** in a good yield.

Scheme 11



The proposed mechanism of this cascade reaction is shown in Scheme 12 and includes the reduction of nitro group to an amino group (intermediate **A**). The ferric salt formed in this process oxidized the alcohol to aldehyde,

Scheme 12



which further participated in a condensation with *N*-(2-aminophenyl)pyrrole and formed the iminium salt **B**. The subsequent steps of cyclization (intermediate **C**) and aromatization led to the target product – pyrroloquinoxaline **24**.[32]

Thus, based only on the reactions of *N*-(2-aminophenyl)pyrroles **15** with aldehydes, ketones, and arylacetic acids or their bisderivatives, a library of pyrrolo[1,2-*a*]quinoxalines **26a**–**p** bearing alkyl, aryl, hetaryl- (Fig. 2, compounds **26a**–**h**),[20b,24b,26a,d,27a,c] spirohetaryl- (compound **26i**),[26a] and polycondensed carbocyclic substituents (compounds **26j**–**l**) at position 4, was obtained.[26b,27c] In addition, bispyrroloquinoxalines linked by rigid spacers (compounds **26m**,**n**)[27a,b] or flexible chains (compounds **26o**,**p**)[28] were obtained.

It should be noted that some methodologies are universally applicable and enable the preparation of indolo[1,2-*a*]-,[23,24c,27,29,30a] imidazo[1,5-*a*]-,[20a] and pyrazolo[1,5-*a*]quinoxalines[20a] by replacing the *N*-(2-aminophenyl)pyrroles **15** as starting materials with their condensed or aza analogs – *N*-(2-aminophenyl)indoles, *N*-(2-aminophenyl)imidazoles, and *N*-(2-aminophenyl)pyrazoles, respectively.

1.3. Other syntheses on the basis of pyrrole derivatives

Amino acids **28** can provide a three-atom synthon by reacting with *N*-(2-halophenyl)pyrroles **27** in the presence of a copper catalyst, leading to the formation of 4-substituted pyrrolo[1,2-*a*]quinoxalines **12** (Scheme 13). The C(3a)–C(4) and N(5)–C(5a) bonds of the given heterocyclic system are formed in this process. The first step involves the formation of intermediate **A**, which is further transformed into the final product either by oxidation and cyclization through the intermediates **B** and **D** or by decarboxylation followed by cyclization through the intermediates **C** and **E**.[33] Pyrrolo[1,2-*a*]quinoxalines **12** were formed in good yields (46–78%), except for the cases when R^2 = Cy or Ph (35 and 12%, respectively). When this reaction was performed with *N*-(2-halophenyl)indoles as starting materials, derivatives of indolo[1,2-*a*]quinoxaline were obtained.[33]

The condensation of pyrrole-2-carbaldehyde (**29**) with 2-haloanilines **30** in the presence of a copper catalyst and hydrazide of salicylic acid or bipyridine as ligand led to pyrrolo[1,2-*a*]quinoxalines **31** (Scheme 14). The C(9a)–N(10) and C(4)–N(5) bonds of the tricyclic system were formed during this process.[34] The preparation of unsubstituted pyrrolo[1,2-*a*]quinoxaline was optimized with respect to the reaction conditions and by taking into account the effects of various catalysts and ligands on the final product yield. Thus, the reaction did not proceed in the absence of catalyst, when only the ligand was added. Replacing DMF as solvent with dioxane or PhMe gave a low yield (6 and 15%) of the unsubstituted pyrrolo[1,2-*a*]quinoxaline. Decreasing the temperature to 100°C also led to decrease of the yield. Good yields of pyrrolo[1,2-*a*]quinoxalines **31** were achieved by using 2-iodo- or 2-bromoanilines. The use of 2-chloroaniline gave trace amounts of pyrrolo[1,2-*a*]quinoxaline.

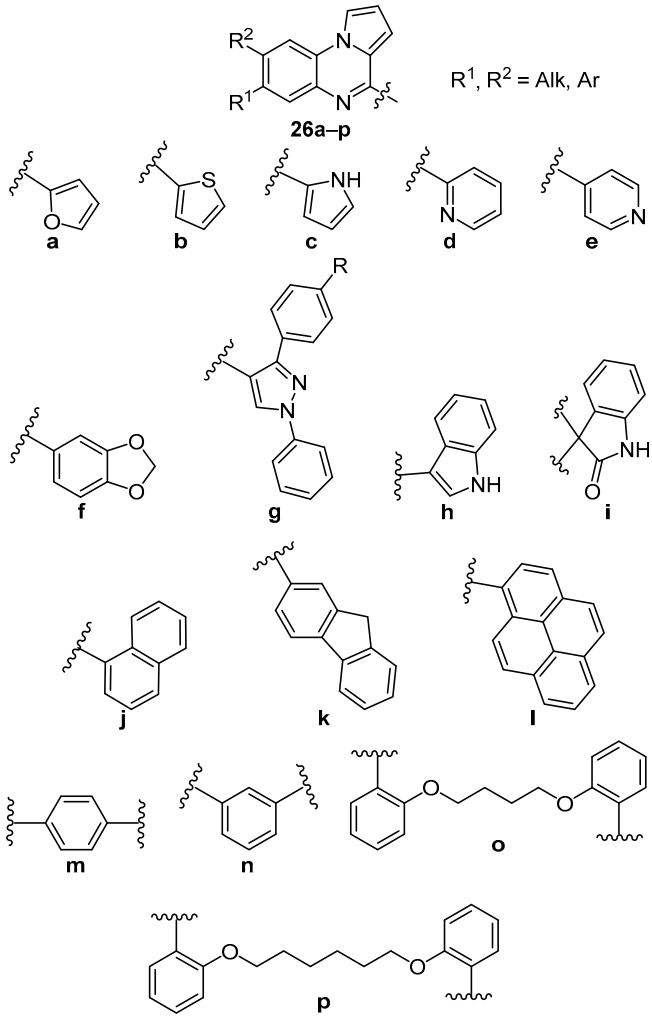
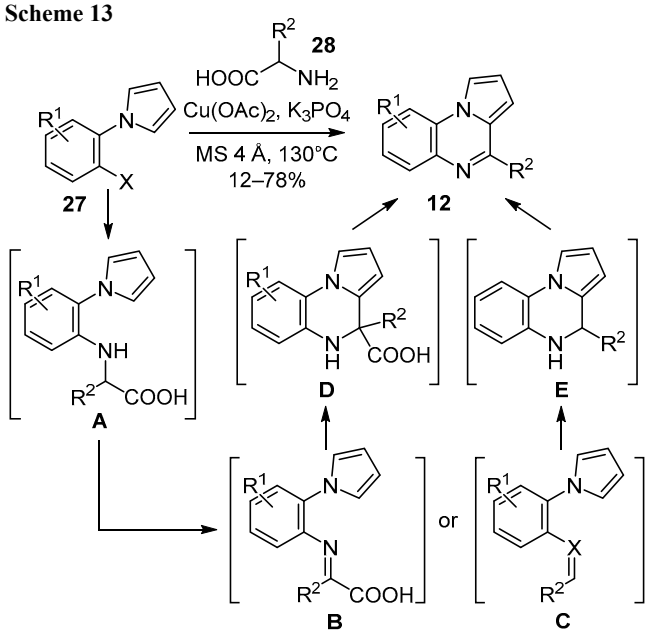


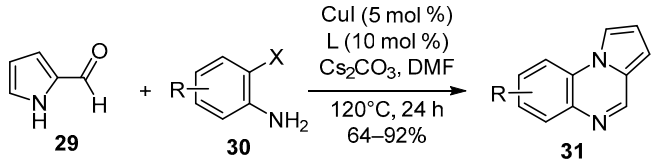
Figure 2. The heterocyclic substituents **a**–**h**, spirohetaryl substituent **i**, and condensed carbocyclic substituents **j**–**l**, introduced at position 4 of pyrrolo[1,2-*a*]quinoxalines, as well as spacers **m**–**p** linking two pyrroloquinoxalin-4-yl moieties.

Scheme 13



R^1 = H, Me, F, Cl, CN, CF_3, OCF_3; X = Br, I; R^2 = Alk, Cy, Ph

Scheme 14

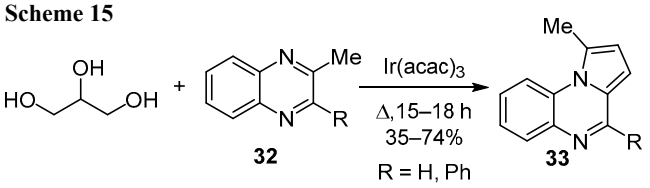


L = 2-hydroxybenzohydrazide or 2,2'-bipyridine
X = I, Br; R = H, Me, F, Cl, Br, CF_3

2. SYNTHESIS ON THE BASIS OF QUINOXALINE DERIVATIVES

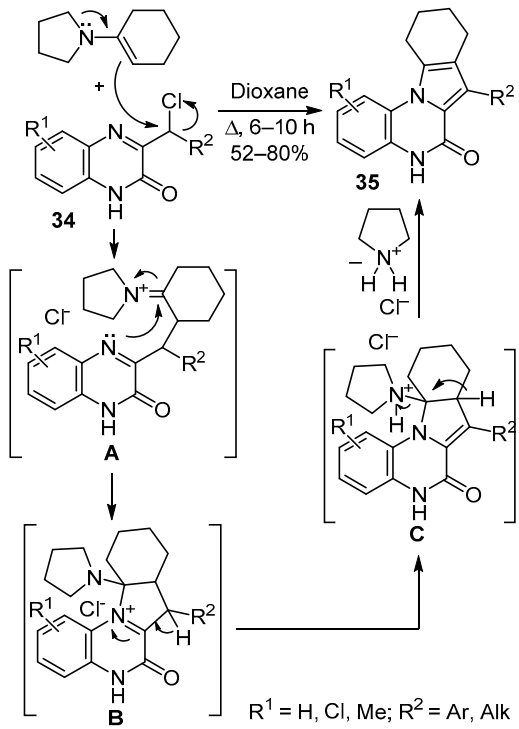
The condensation of 2-methylquinoxalines **32** with glycerol in the presence of an iridium catalyst led to annulation of a pyrrole ring, with the formation of C(1)–N(10) and C(2)–C(3) bonds in tricyclic system **33** (Scheme 15).[35]

Scheme 15



The reaction of 3-(α-chlorobenzyl)quinoxalin-2-ones **34** with 1-(cyclohexen-1-yl)pyrrolidines upon heating produced tetrahydroindolo[1,2-*a*]quinoxalin-6(5*H*)-ones **35** (Scheme 16).[36] Their formation included a Stork alkylation with the formation of intermediate **A** and an intramolecular nucleophilic attack by ring nitrogen atom at the iminium group, leading to the intermediate **B**, and aromatization with elimination of pyrrolidinium chloride from the intermediate **C**.

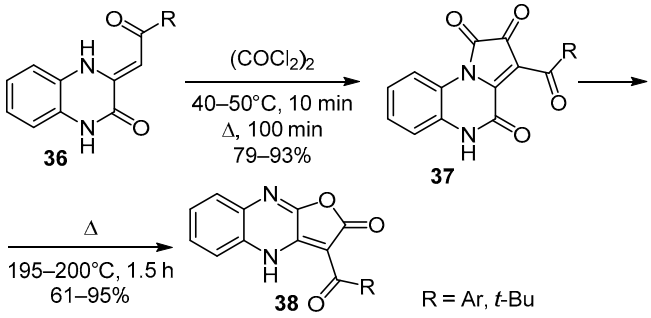
Scheme 16



R^1 = H, Cl, Me; R^2 = Ar, Alk

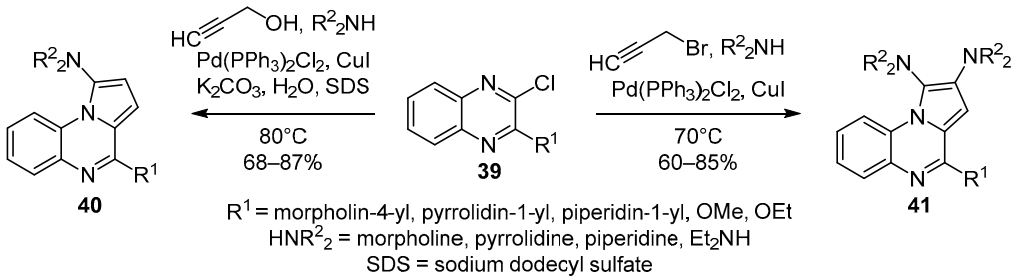
The reaction of 3-(acylmethylidene)quinoxalin-2-ones **36** with oxalyl chloride led to the formation of pyrrolo[1,2-*a*]-quinoxaline-1,2,4-triones **37** in high yields (Scheme 17).[37] Thermolysis of the obtained polycarbonyl compounds **37** resulted in recyclization into furo[3,2-*b*]quinoxalin-2(4*H*)-ones **38** (Scheme 17).[37]

Scheme 17

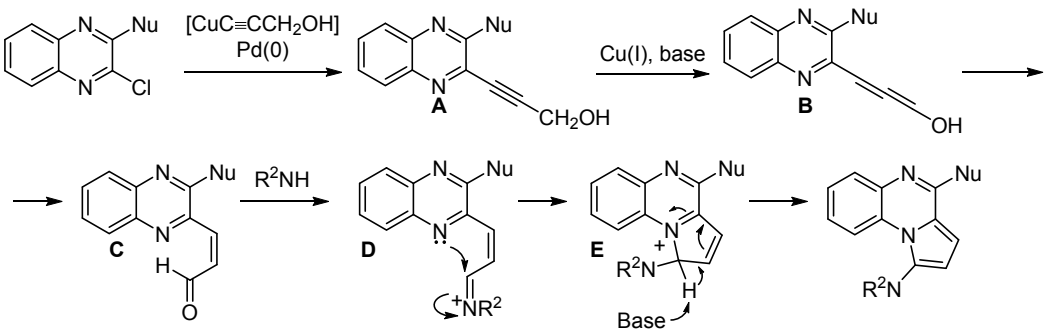


A three-component condensation of 3-alkoxy-2-chloro- and 2-chloro-3-dialkylaminoquinoxalines **39** with propargyl alcohol and secondary amines was achieved by heating in the presence of palladium catalyst and a base in H_2O medium and led to annulation of a pyrrole ring, with the formation of C(1)–N(10) and C(3)–C(3a) bonds of a tricyclic system (Scheme 18).[38] Pyrrolo[1,2-*a*]quinoxalines **40** formed in this way contained a dialkylamino group at position 1. The replacement of propargyl alcohol with propargyl bromide and performing the reaction in an excess of secondary amine allowed to obtain 1,2,4-tri-

Scheme 18



Scheme 19



(dialkylamino) derivatives of pyrrolo[1,2-*a*]quinoxaline **41**. When the reaction was performed with propargyl bromide in MeCN, DMF, or H_2O, similarly to the case with propargyl alcohol, a pyrrolo[1,2-*a*]quinoxaline derivative unsubstituted at position 2 was formed.[38]

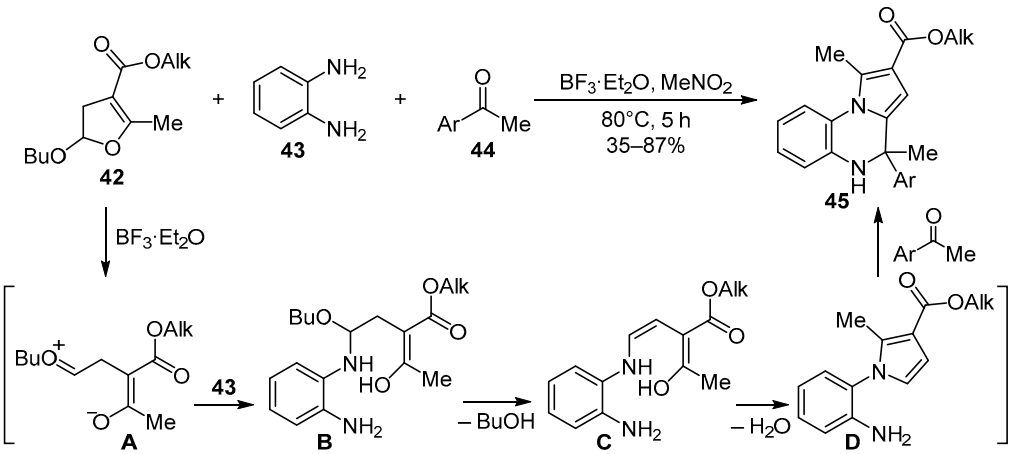
A possible route for the synthesis of pyrrolo[1,2-*a*]-quinoxalines, involving a Sonogashira reaction with the formation of alkyne **A**, its Cu(I)-catalyzed isomerization into allene **B** and further to ketone **C** is shown in Scheme 19. A reaction of the latter with amines gave the iminium intermediates **D**, which underwent intramolecular heterocyclization to the pyrroloquinoxalines **E**, followed by base-catalyzed aromatization.[38a]

3. MULTICOMPONENT REACTIONS INVOLVING SIMULTANEOUS FORMATION OF PYRROLE AND PYRAZINE RINGS

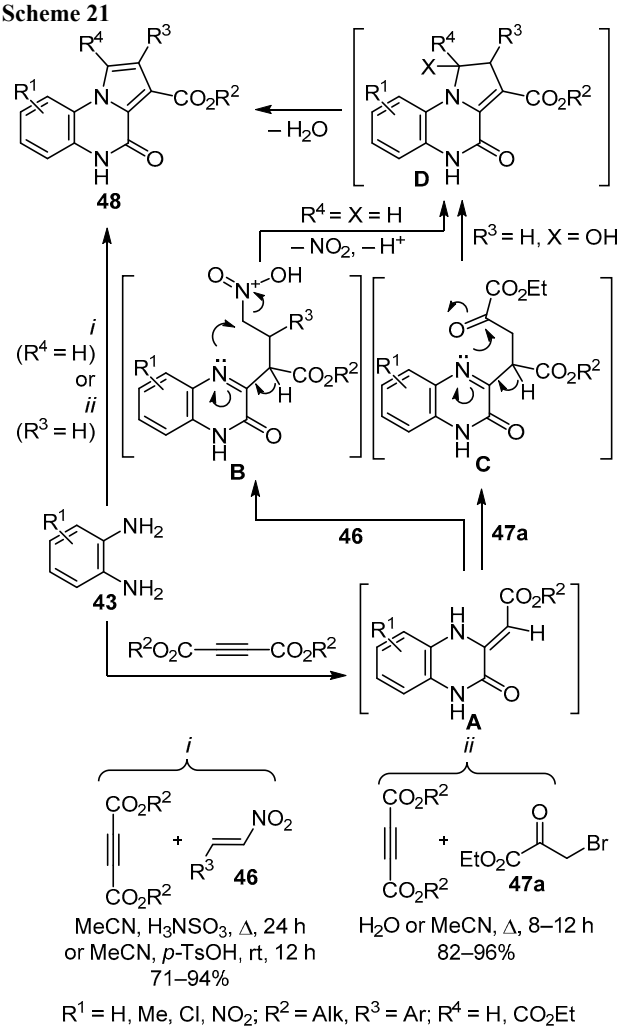
The three-component reaction between 4-alkoxycarbonyl-2-butoxy-5-methyl-2,3-dihydrofuran **42**, *o*-phenylenediamine (**43**), and methyl aryl(hetaryl) ketone **44** proceeded upon heating in the presence of $BF_3 \cdot Et_2O$ and led to the formation of 4,5-dihydropyrrolo[1,2-*a*]quinoxaline derivatives **45** (Scheme 20).[39] The selection of cyclic ketones (cyclohexanone, cycloheptanone, cyclooctanone) as starting materials led to the formation of the respective spirocycloalkanepyrrolo[1,2-*a*]quinoxalines.[39] The assembly of a tricyclic system apparently occurred as a result of dihydrofuran ring opening in the presence of $BF_3 \cdot Et_2O$, with the formation of intermediate **A**. The latter reacted with *o*-phenylenediamine (**43**), producing the intermediate **B**. Elimination of a butanol molecule gave the enamine **C**, which was cyclized to the *N*-(2-aminophenyl)pyrrole **D**. The subsequent condensation with ketones resulted in pyrazine ring closure.

A three-component condensation of dialkylacetylene dicarboxylates and *o*-phenylenediamines **43** with (*E*)-nitrostyrenes[40] **46** or ethyl bromopyruvate[41] (**47a**) gave high yields of pyrrolo[1,2-*a*]quinoxalin-4-ones **48** containing substituents at 2,3- or 1,3- positions of the five-membered ring, respectively (Scheme 21). Quinoxaline derivatives were formed at the first step (intermediate **A**). The reaction of enamine **A** with *E*-nitrostyrene **46** in acidic medium led

Scheme 20



Scheme 21

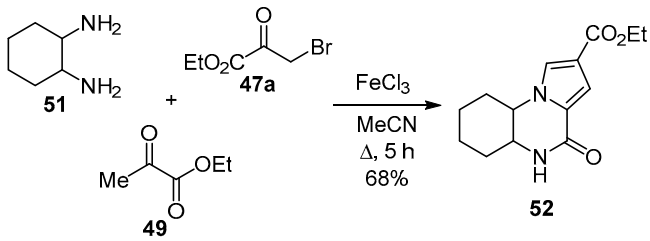


to the intermediate **B**, while a reaction with ethyl bromopyruvate (**47a**) gave the intermediate **C**, both of which underwent intramolecular cyclization with the elimination of nitrogen dioxide in the case of intermediate **A**, resulting in the formation of 1,2-dihydropyrroloquinoxaline **D** (Scheme 21). Oxidative dehydrogenation or dehydration of the intermediate **D** gave pyrrolo[1,2-*a*]quinoxalin-4-one **48**. Performing the reaction in H_2O led to a more rapid formation of pyrrolo[1,2-*a*]quinoxalines, compared to the reactions in MeCN.[41]

The three-component reaction betweeen *o*-phenylenediamines **43**, ethyl pyruvate (**49**), and bromocarbonyl compounds **47** gave high yields of 2-aryl(ethoxycarbonyl)-pyrrolo[1,2-*a*]quinoxalin-4-ones **50** (Scheme 22). AT the first step of this reaction, also a quinoxaline derivative (intermediate **A**) was formed, which further reacted with bromocarbonyl compounds **47** in the presence of $FeCl_3$ and was converted into the salt **B** that underwent dehydrobromination with the formation of intermediate **C**. Intramolecular cyclization of the latter led to 1,2-dihydropyrrolo[1,2-*a*]quinoxalines **D**, while their subsequent oxidation gave pyrroloquinoxalin-4-ones **50**.[42]

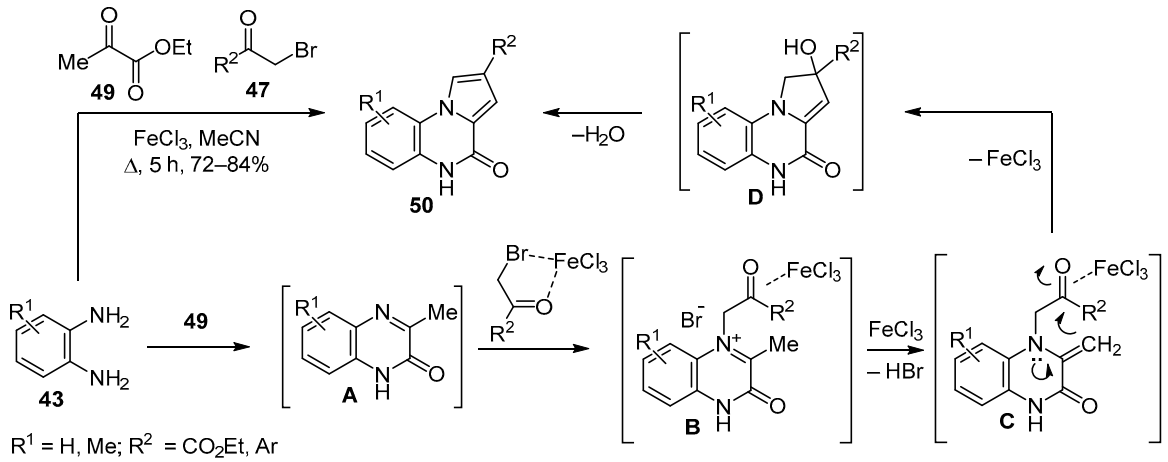
The applicability of the reaction between *o*-phenylenediamines **43**, ethyl pyruvate (**49**), and ethyl bromopyruvate (**47a**) in the presence of $FeCl_3$ was extended to cyclohexane-1,2-diamine (**51**). As a result, 5a,6,7,8,9,9a-hexahydropyrrolo[1,2-*a*]quinoxalin-4-one **52** was obtained (Scheme 23). Similar reaction with ethylenediamine led to the formation of pyrrolo[1,2-*a*]pyrazine derivative.[42]

Scheme 23

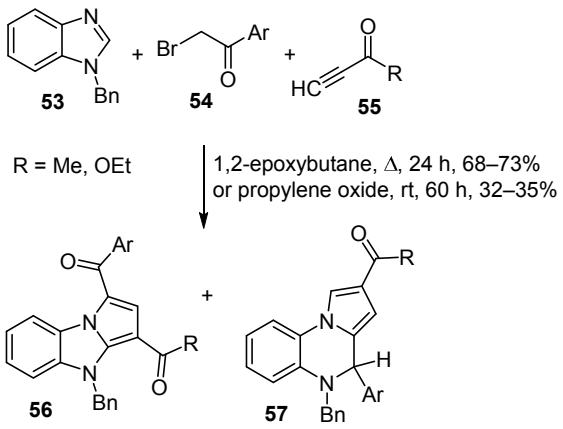


The three-component reaction of 1-benzylbenzimidazoles **53** with phenacyl bromides **54** and monosubstituted acetylenes **55** upon heating produced only pyrrolo[1,2-*a*]-benzimidazole derivatives **56** in good yields (68–73%), while at room temperature these reactants were converted into a mixture of pyrrolo[1,2-*a*]benzimidazole derivatives **56** and 4*H*-4,5-dihydropyrrolo[1,2-*a*]quinoxaline derivatives **57** in approximately equal amounts (32–35%) (Scheme 24).[43a]

Scheme 22



Scheme 24



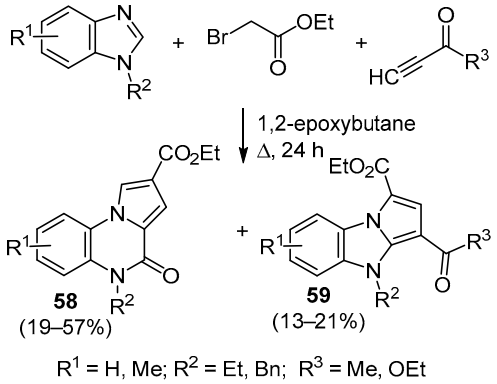
Scheme 25 shows a possible mechanism for such a three-component reaction. At the first step, formation of 1,3-dialkylbenzimidazolium salts occurred by alkylation of *N*-alkylbenzimidazoles with bromocarbonyl compounds, followed by deprotonation by the action of base, producing ylides **A**. The intermediates **A** participated in 1,3-dipolar cycloaddition reaction with acetylenes, with the formation of a key intermediate **B**. The formation of pyrrolo[1,2-*a*]quinoxaline derivatives (Scheme 25, path *a*) occurred as a result of imidazole ring opening that generated *N*-phenylpyrrole **C**, the cyclization of which gave pyrrolo[1,2-*a*]quinoxaline **D**.

Dehydration of pyrrolo[1,2-*a*]quinoxaline **D** led to the intermediate **E**. It has been proposed[43] that the formation of pyrrolo[1,2-*a*]quinoxaline **57** could result from the reduction of intermediate **E**, while intermediate **B** would serve as the hydride ion source. The second route of reaction (Scheme 25, path *b*) *via* the formation of pyrrolo-[1,2-*a*]benzimidazoles **56** could occur as a result of aromatization (oxidation) of the intermediate **B**.

The reaction of 3-butyn-2-one or ethyl propiolate with previously synthesized 1-benzyl-3-(phenacyl)benzimidazolium bromides led to the formation of a more complex reaction mixture, which yielded up to four pyrrolo[1,2-*a*]-quinoxaline derivatives. The product ratio changed depending on the reaction conditions (temperature, time, the choice of solvent, and the presence of a base).[43b]

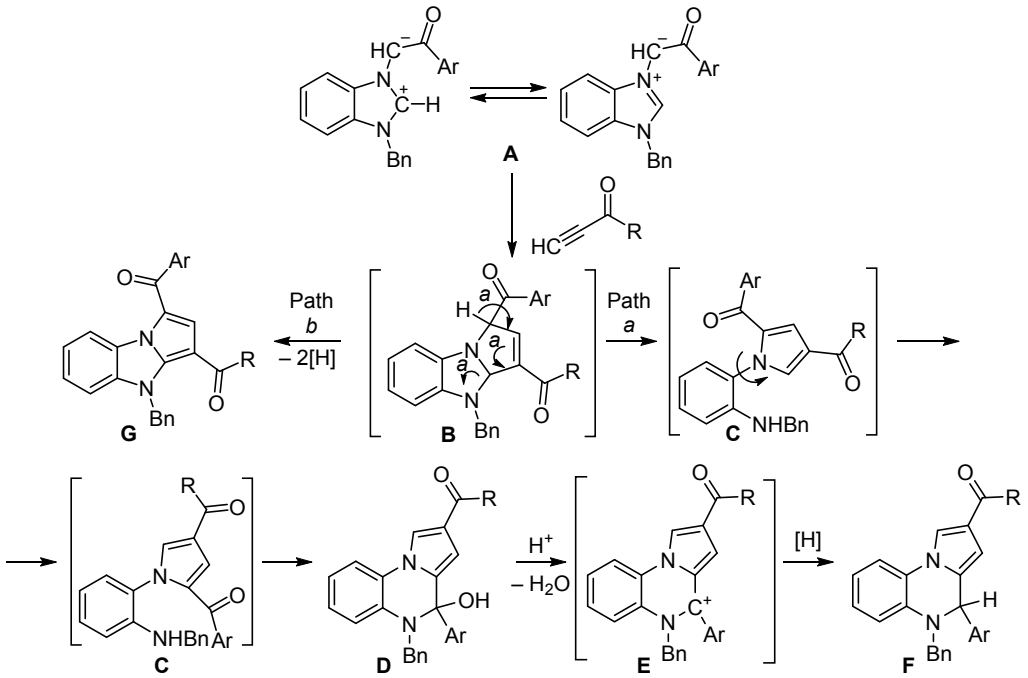
The use of α-bromo ketones instead of α-bromoacetates in the three-component reaction (Scheme 26) upon heating in 1,2-epoxybutane led exclusively to pyrrolo[1,2-*a*]-quinoxalin-4-ones **58** or a mixture of these products with a small amount of pyrrolo[1,2-*a*]benzimidazoles **59**.[44a]

Scheme 26



The introduction of dimethyl acetylenedicarboxylate in the three-component reaction produced an intractable product mixture. However, the reaction with separately prepared 1-alkyl-3-ethoxycarbonylmethylbenzimidazolium bromides also gave pyrrolo[1,2-*a*]quinoxalin-4-ones either as the sole products or containing small amounts of pyrrolo-[1,2-*a*]benzimidazole derivative.[44]

Scheme 25



Thus, in the time period covered in this review article, a range of new, original methods have been proposed for the synthesis of pyrrolo[1,2-*a*]quinoxalines. The main achievements in this direction are the following. First, the majority of the target products have been obtained in high yields (80% and higher). Second, methods have been developed for the introduction of various functional groups, as well as heterocyclic moieties into the molecules of pyrrolo[1,2-*a*]quinoxaline derivatives. Third, methods have been proposed that enable the preparation of pyrrolo[1,2-*a*]-quinoxalines using mild procedures, as well as under conditions that meet many of the green chemistry criteria. In addition, progress has been achieved in performing these three-component reactions as one-pot processes. The development has been especially rapid in the case of methods using metal complexes and other types of catalysts. The methods proposed for the preparation of pyrrolo[1,2-*a*]quinoxalines have been also used in the synthesis of other polycondensed tri- and tetracyclic heterocyclic systems, which are structurally related to pyrrolo[1,2-*a*]quinoxalines.

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