Russian Chemical Reviews **79** (5) 351 – 370 (2010) © 2010 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2010v079n05ABEH004089

New and modified classical methods for the synthesis of quinoxalines

D F Saifina, V A Mamedov

Contents

I.	Introduction	351
II.	The condensation of *o*-phenylenediamine and its derivatives with various two-carbon unit donors	352
III.	Synthesis of quinoxalines based on aniline derivatives	363
IV.	Synthesis of quinoxalines based on heterocyclic systems devoid of the pyrazine fragment	366

Abstract. Published data on the synthesis of quinoxalines are generalized and described systematically; the key attention is given to the sources published in the last 10 – 15 years. Modifications of the classical synthetic routes and new methods little known to wide circles of chemists are considered. The bibliography includes 122 references.

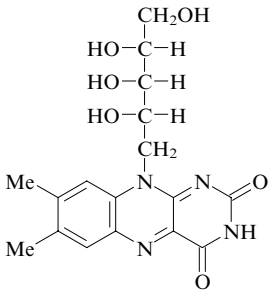
I. Introduction

Quinoxaline derivatives are fragments of many biologically active and pharmacologically important compounds,[1–4] including riboflavin (vitamin B_2), agonists and antagonists of various receptors, agents with high antibacterial or antiviral activities (echinomycin, lenomycin, actinomycin).[5] Also, they are known to be applied as dyes, effective electroluminescent materials,[6] organic semiconductors,[7] building blocks in the synthesis of anionic receptors,[8] cavitands[9,10] and DNA-binding agents.[11,12]

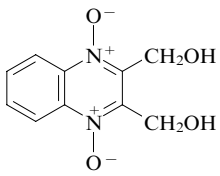
Examples of biologically active compounds containing quinoxaline fragments are presented below.

This diversity of useful synthetic quinoxaline derivatives accounts for the appearance of modifications of the classical synthetic methods and the search for new methods ensuring the availability of the corresponding functionalized quinoxalines.

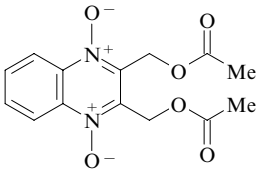
The methods of synthesis and the chemistry of quinoxalines are the subjects of some chapters in books.[13,14] Since then, an extensive series of studies on the methods of synthesis of functionalized quinoxalines have been published; they were mainly concerned with modified Körner[15] and Hinsberg methods,[16] *i.e.*, the reactions of 1,2-arylenediamines with dicarbonyl compounds.



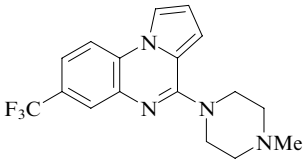
Riboflavin (vitamin B_2)



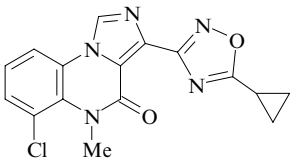
Dioxidine, an antibacterial agent



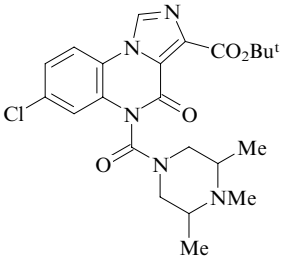
Quinoxidine, an antibacterial agent



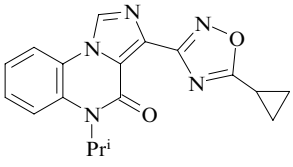
CGS 12066B, a type 1B serotonin receptor agonist



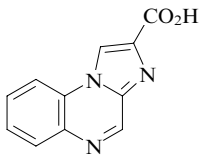
U-80447, an antidepressant, an anxiolytic drug



U-97775, an anxiolytic drug, a $GABA_A$ receptor ligand



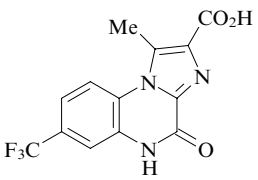
Panadiplon U-78875, an anxiolytic drug, benzodiazepine agonist



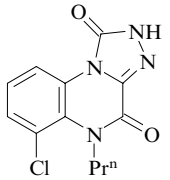
Diazoquinast, an antiallergic agent

D F Saifina, V A Mamedov A E Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, ul. Akad. Arbuzova 8, 420088 Kazan, Russian Federation.
Fax (7-843) 273 22 53, tel. (7-843) 272 73 04,
e-mail: dsaifina@iopc.ru (D F Saifina),
mamedov@iopc.ru (V A Mamedov)

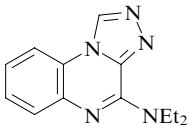
Received 17 July 2009
Uspekhi Khimii **79** (5) 395 – 415 (2010); translated by Z P Svitanko



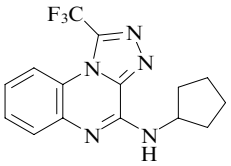
LU73068, an anticonvulsant, glycine/NMDA receptor antagonist



REV3164, RH3164, an antiallergic agent, anticonvulsant



CP-41475, an antidepressant, central nervous system stimulant



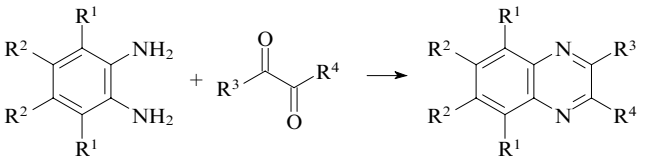
CP-68247, A_1 adenosine receptor antagonist

This review presents three main approaches to the synthesis of quinoxalines: (i) condensation of *o*-phenylenediamine (*o*-PDA) and its derivatives with various two-carbon unit donors, (ii) cyclization of aniline derivatives, (iii) reactions of various heterocyclic systems devoid of the pyrazine fragment.

II. The condensation of *o*-phenylenediamine and its derivatives with various two-carbon unit donors

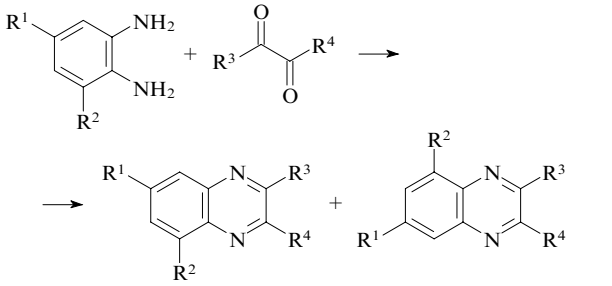
The main route for constructing the quinoxaline system is the reaction of 1,2-arylenediamines with various two-carbon unit donors: α-diketones (path *a*), oxalic acid derivatives (path *b*), pyruvic acid derivatives (path *c*), α-halocarbonyl compounds (path *d*), epoxides (path *e*), dihalides (path *f*), alkenes (path *g*), alkynes (path *h*), α-hydroxy ketones (path *i*), ketones (path *j*), heterocyclic systems (path *k*).

Path a. In most cases, this path is implemented by the reaction of *o*-PDA with various diketones in boiling acetic acid or ethanol, which gives the corresponding quinoxalines in good yields.[17–21] The substituents in the diketone may be represented by alkyl, aryl and hetaryl fragments.[21–30] The reaction of diketone containing ferrocenyl fragment with *o*-PDA was carried out in boiling dioxane under nitrogen; 3-phenyl-2-ferrocenylquinoxaline was obtained in 65% yield.[29]



R^1	R^2	R^3	R^4	Yield (%)	Ref.
H	H	Me	Me	91	19
H	H	H	Me	77	19
H	H	3-$O_2NC_6H_4$	3-$O_2NC_6H_4$	85	21
Br	H	pyrrol-2-yl	pyrrol-2-yl	—	23
H	H	*o*-$(CH_2)_2C_6H_4(CH_2)_2$		86	25
H	$OC_{12}H_{25}$-n	2′,6-bipyridin-2-yl	2-pyridyl	74	26
H	H	2,2-dimethyl-1,3-dioxolanyl	2,2-dimethyl-1,3-dioxolanyl	98	27
H	H	Fc	Ph	65	29

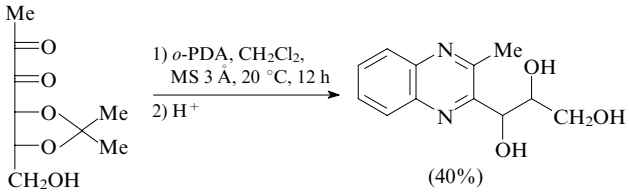
The use of unsymmetrically substituted *o*-phenylenediamines and 1,2-diketones may lead to the formation of two regioisomeric products.[24, 29, 30]



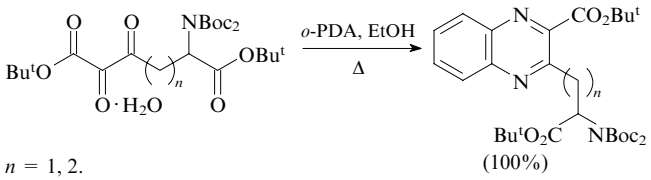
R^1	R^2	R^3	R^4	Total yield (%)	Ref.
NO_2	H	Me	Me	87	18
F	H	Ph	4-HOC_6H_4	94	24
CF_3	NO_2	Ph	Ph	75	30
CF_3	NO_2	Me	Me	72	30
CF_3	NO_2	H	H	68	30
CF_3	NO_2	Me	H	75	30
CF_3	NO_2	Ph	H	66	30
F	H	Ph	6-hydroxy-2-naphthyl	58	24
F	H	Ph	4′-hydroxybiphenyl-4-yl	80	24
F	H	Ph	4-hydroxyphenyl	93	24
NO_2	H	Fc	Ph	73	29
CO_2H	H	Fc	Ph	81	29

The structure and the ratio of the products formed upon the reaction of unsymmetrical 1,2-arylenediamines with diketones are determined by the nature of substituents: electron-donating substituents in diamines activate the amino groups, whereas in diketones they decrease the electrophilicity of the carbonyl groups. For electron-withdrawing substituents, the opposite trend is observed.

Sugars containing an α-dicarbonyl function can also act as two-carbon unit donors. The reaction of 1-deoxy-4,5-*O*-isopropylidene-D-*erythro*-hexo-2,3-diulose with aromatic diamines (the Maillard reaction) in chloroform in the presence of molecular sieves (MS) results in the formation of quinoxaline derivative with polyoxyalkyl substituents.[31]

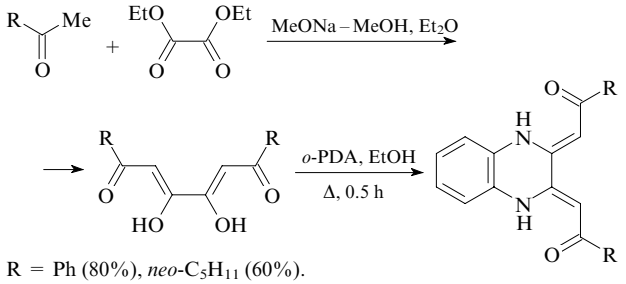


A vicinal tricarbonyl compound comprising an activated carboxylate fragment and a formally dicarbonyl fragment can serve as the electrophilic component. By reactions of diamines with vicinal tricarbonyl derivatives of α-amino acids, a number of new heterocyclic α-amino acids, in particular those with quinoxaline fragment, were obtained.[32, 33]



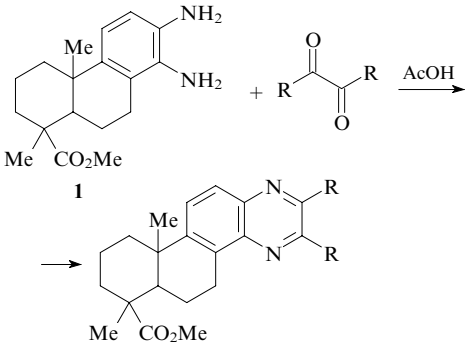
n = 1, 2.

Tetraketones synthesized from methyl ketone and diethyl oxalate are condensed on refluxing with *o*-PDA in ethanol[34,35] with participation of the most electrophilic (second and third) carbonyl carbon atoms.



R = Ph (80%), *neo*-C_5H_{11} (60%).

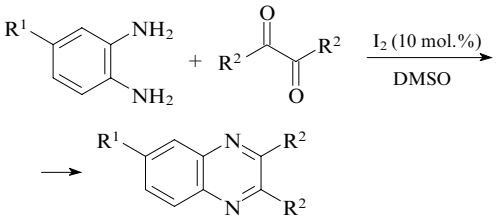
Various biologically active fragments can be introduced into a quinoxaline system not only using a dicarbonyl reagent but also by means of functionalized aromatic diamines. Quinoxalines containing a hydrogenated naphthalene fragment were prepared in moderate yields (42% – 70%) by the reaction of abietic acid derivative **1** with 1,2-diketones.[36] When present in subtoxic concentrations, these compounds inhibit the replication of chicken pox virus and cytomegalovirus.



1

R = Me (61%), Ph (79%); R – R = $(CH_2)_4$ (42%).

The introduction of catalytic amounts of iodine to the reactions of aliphatic and aromatic diketones with substituted *o*-diamines reduces the reaction time and ensures the synthesis of quinoxalines at room temperature in high yields without by-products.[37]

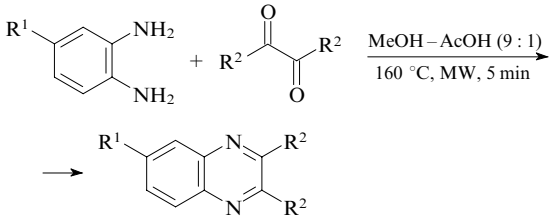


R^1 = H: R^2 = Ph (95%), 4-$MeOC_6H_4$ (92%), 4-MeC_6H_4 (90%), 2-furyl (90%); R^1 = Bz: R^2 = Ph (85%), 4-$MeOC_6H_4$ (88%), 4-MeC_6H_4 (86%), 2-furyl (86%); R^1 = Me: R^2 = Ph (90%), 4-$MeOC_6H_4$ (90%), 4-MeC_6H_4 (91%), 2-furyl (89%).

More *et al.*[38] studied these reactions in various solvents (polar protic and aprotic, non-polar). The highest rates were attained in polar solvents (the reactions are completed in 15 – 20 min), the highest reaction rates being observed in acetonitrile. The optimal iodine concentration was 10 mol.%, a decrease in the concentration resulting in longer reaction times. Electron-donating substituents in *o*-diamine increased the product yield, while electron-withdrawing groups decreased the yield. The substituents in aromatic diketones induce the opposite trend. Nevertheless, the changes in the yields are insignificant and the yields are high. In the case of unsymmetrical 1,2-diketones, different diamines give rise to 1 : 1 isomer mixtures formed in a nearly quantitative yield.

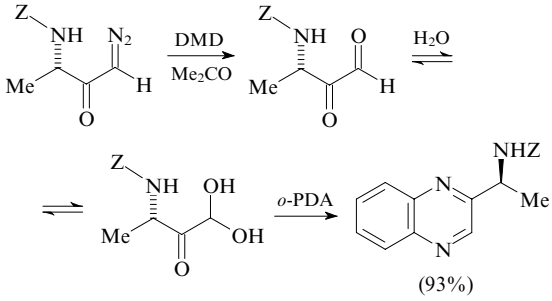
The role of iodine in the formation of the quinoxaline system is not entirely clear; according to publications,[37,38] it serves as a mild Lewis acid.

Functionalized quinoxalines were also obtained in high yields from 1,2-diketones under microwave radiation (MW).[39] Microwave radiation reduces the reaction time, increases the yields and rules out the formation of by-products and polymerization products typical of thermally induced reaction. Note also that this method ensures high yields of not only quinoxalines containing electron-donating groups but also of those with electron-withdrawing groups; the use of unsymmetrical ketones gives rise to 1 : 1 isomer mixtures.



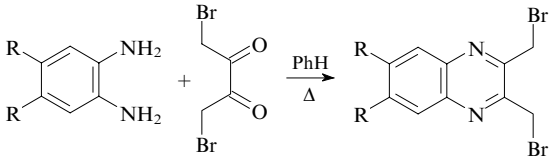
R^2 = Ph: R^1 = NH_2 (99%), Cl (96%), CO_2Me (98%), OMe (97%), F (99%), CN (99%); R^1 = NH_2, R^2 = 2-pyridyl (98%); R^2 = 2-furyl: R^1 = Cl (85%), CO_2Me (96%).

Diketones can also be generated *in situ*. For example, α-keto aldehyde obtained by oxidation of (*N*-benzyloxycarbonyl-L-alanyl)diazomethane with dimethyldioxirane (DMD) is subjected to condensation with *o*-PDA in ethanol at room temperature to give optically active quinoxalines with a chiral amino acid or peptide aminoalkyl fragment in the side chain, the products being formed in high yields.[40]



Z is benzyloxycarbonyl.

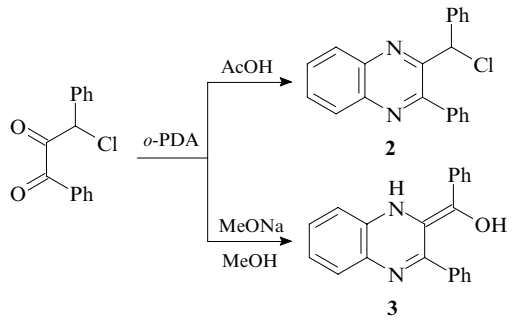
The condensation of 1,2-diaminobenzenes with 1,4-dibromobutane-2,3-dione, containing two α-halocarbonyl fragments together with the dicarbonyl fragment, in boiling benzene occurs exclusively at the α-dicarbonyl fragment[41]



R = H (92%), Me (93%), Cl (90%).

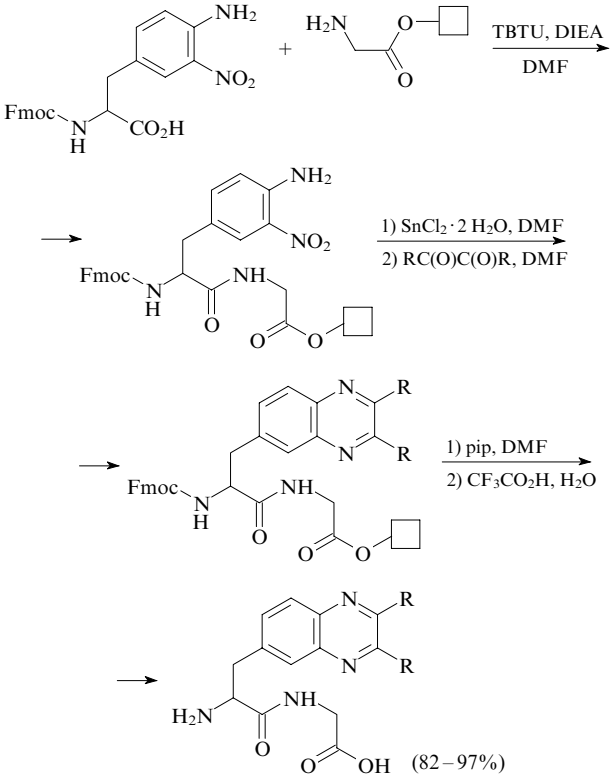
and results in 2,3-bis(bromomethyl)quinoxalines formed in high yields without bromoacylquinoxaline and bis-quinoxaline.

Note that the reaction route and the structure of products formed from compounds containing both diketone and α-halocarbonyl fragments depend on the solvent.



For example, the reaction of 3-chloro-1,3-diphenylpropane-1,2-dione with *o*-PDA in acid medium (acetic acid) involves the α-diketone fragment and gives quinoxaline **2**, while in a basic medium (MeONa in MeOH), the reaction involves the α-chloro ketone fragment to give dihydroquinoxaline **3**.[42]

The solid-phase synthesis of quinoxaline-containing peptides comprises the following sequence of transformations: (i) the addition of peptide containing a β-(4-amino-3-nitrophenyl)alanine residue to the Wang resin; (ii) reduction of the nitro group with tin(II) chloride; (iii) reaction of the diamine thus formed with a dicarbonyl compound.[43]

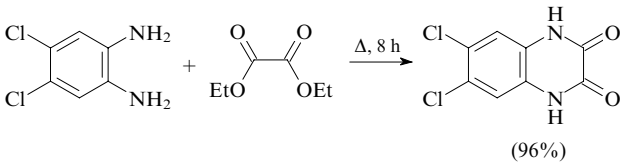


R = Me, Ph, 4-MeOC$_6$H$_4$, 2-furyl, 2-pyridyl, *etc*; TBTU is 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate; DIEA is ethyldi(isopropyl)amine, Fmoc is fluorenylmethoxycarbontyl; □ is solid support.

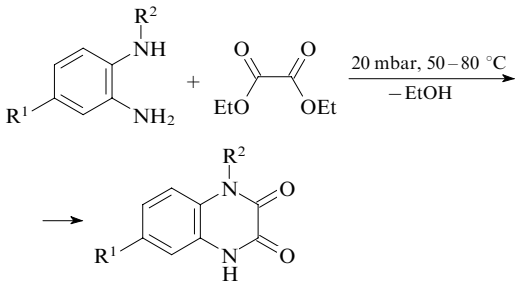
Note in conclusion that in quinoxaline synthesis, α-diketones can be involved in the formation of a benzene rather than pyrazine ring. Thus 2,3-dicyanoquinoxalines were prepared by the Wittig reaction of 2,3-bis(bromomethyl)-5,6-dicyanopyrazine with 1,2-dicarbonyl compounds.[44]



Path b. Oxalic acid derivatives are also used as two-carbon unit donors; these compounds react with *o*-PDA to afford tetrahydroquinoxaline-2,3-diones.[1,45,46] Usually, ring closure is induced by strong acids or by heating (in some cases, refluxing).

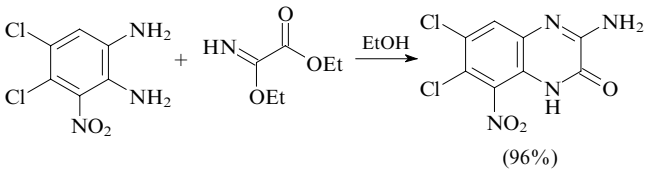


1,2,3,4-Tetrahydroquinoxaline-2,3-diones can be prepared without a catalyst or heating by conducting the reaction on a rotary evaporator.[47] The excess of diethyl oxalate serves as a mild solvent and can easily be separated from the target product by washing with ether. Since the products are efficiently separated (precipitated and evaporated), the possibility of side reactions is eliminated.



R^1	R^2	Yield (%)
H	H	40
H	Ph	37
Cl	H	59
Cl	$(CH_2)_2CN$	41
Me	H	27
CF_3	$(CH_2)_2CN$	29

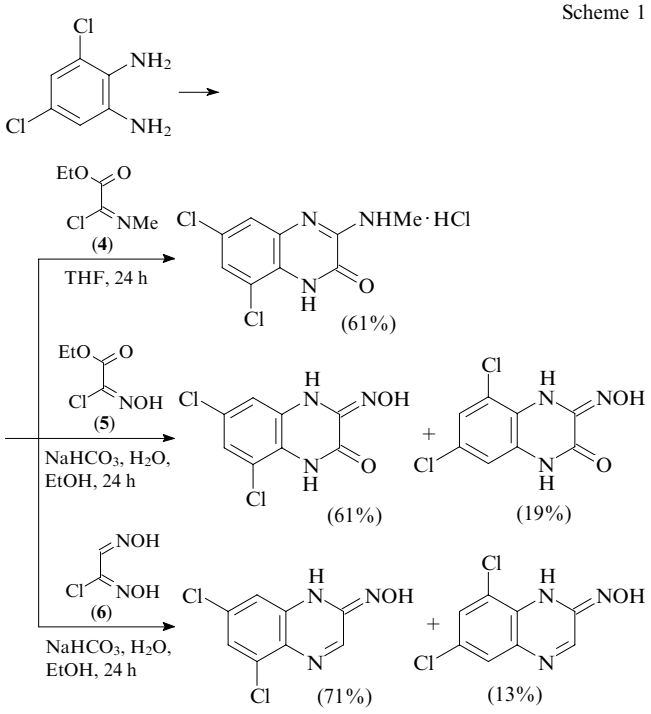
More rarely, oxalic acid itself[48] and oxalyl chloride[49] are used to prepare tetrahydroquinoxaline-2,3-diones. The use of oxalomonoimidic acid diethyl ester results in 3-aminoquinoxalin-2(1*H*)-one in high yield.[50]



Oxalic acid derivatives **4**–**6**;† were used[51,52] in reactions with substituted *o*-PDA; in some cases, this gave isomeric mixtures of products (Scheme 1).

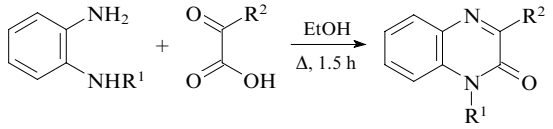
† Compound **6**, an aldehydo acid derivative, should strictly speaking be considered together with keto acids but it is more convenient to combine it with reagents **4** and **5** within the same scheme.

Scheme 1



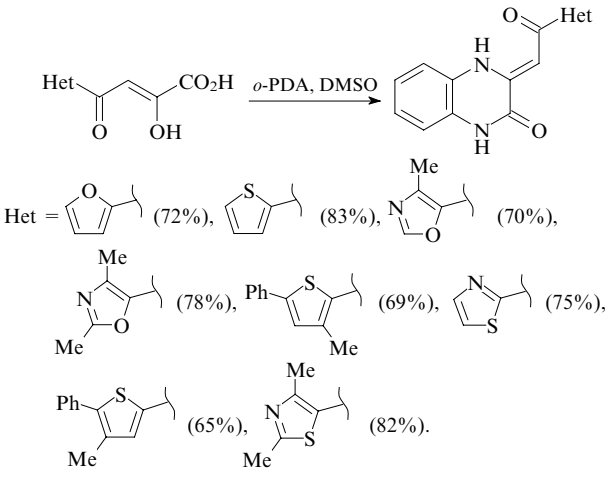
The ratio of the products depended not only on the electronic effects of substituents in diamines, but also on steric factors and activity of the imino and hydroxyimino derivatives used. Thus the reaction is less selective for more reactive hydroxymoyl chlorides where a considerable amount of the minor isomer is formed.

Path c. The Hinsberg reaction (heating of *o*-PDA with α-keto acids) has been known for more than a century and still remains the most practicable method for the preparation of quinoxalin-2(1*H*)-ones.[53, 54]



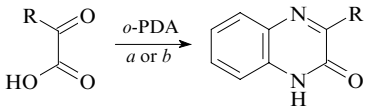
R^1 = H: R^2 = Bn (45%), Me (68%); R^1 = Me: R^2 = Me (77%), Bn (20%); R^1 = Bn, R^2 = Me (14%).

Due to the presence of α- and β-dicarbonyl fragments in hetaroylpyruvic acids, their reactions with *o*-PDA are expected to give both quinoxalines and benzodiazepine



derivatives. However, as in the reactions with aroylpyruvic acids, only quinoxalin-2(1*H*)-one derivatives were isolated.[55, 56]

Conducting the reaction of α-keto acids with *o*-PDA under enzymatic catalysis in the presence of *Saccharomyces cerevisiae* at room temperature and pH 7 allows one to avoid the formation of by-products and gives quinoxalin-2(1*H*)-ones in quantitative yields.[57] Note that the course of the reaction may be affected by not only the enzyme but also the enzyme carrier.

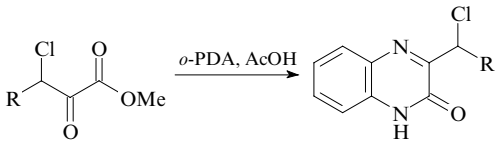


R = Me, Et, Bn, $(CH_2)_2CO_2H$, CH_2CO_2H, OH;
(*a*) *Saccharomyces cerevisiae*, 20 °C, 72 h (yields 92% – 95%);
(*b*) MW, 3.5 – 13 min (yields 86% – 91%).

Microwave irradiation of the reaction mixture also minimizes the formation of by-products.[57] Microwave radiation reduces the reaction time to several minutes and allows the reaction to be carried out without a solvent, which makes the workup easier.

When comparing these two variants of performing the reaction, note that although the biocatalytic process provides the target products in quantitative yields, it requires labour-consuming product purification and much time for the reaction to be completed, whereas the microwave-assisted reaction is a facile process resulting in quinoxalin-2(1*H*)-ones in high yields within several minutes.

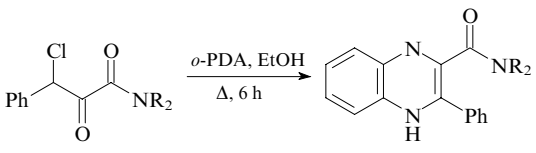
The reactions of *o*-PDA with aryl- and alkylchloropyruvates acid esters afford quinoxalin-2(1*H*)-ones **7**.[58, 59] In this case, the formation of the quinoxaline ring involves the α-keto group of the ester rather than the α-chloro ketone fragment.



7

R = Et (77%), Pr^n (74%), n-C_5H_{11} (70%), n-C_6H_{13} (75%), n-C_9H_{19} (76%), Bn (82%), $(CH_2)_2Ph$ (85%).

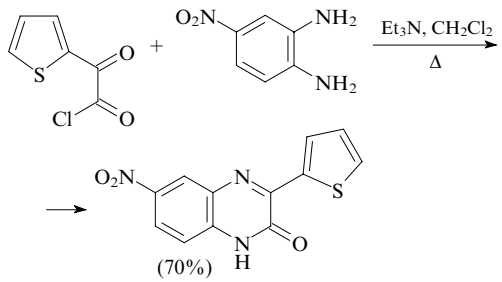
In the case of chlorophenylpyruvamides, the reaction with *o*-PDA involves the α-chloro ketone fragment, giving rise to 1,4-dihydroquinoxalines **8**, which is due to relatively easy alkylation of the amino group unlike transamidation of the amide group.[58]



8

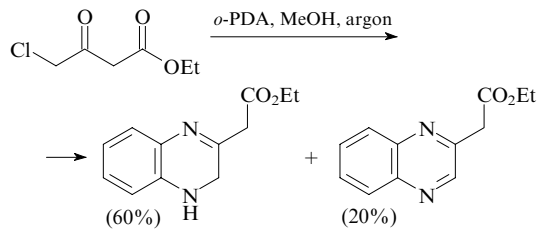
R = Me (56%), Et (55%), Pr^i (71%).

The use of α-keto acid chlorides also affords the corresponding quinoxalin-2(1*H*)-ones.[60]

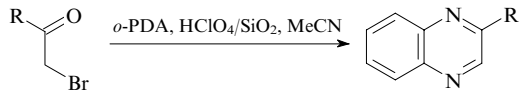


Path d. Yet another way of synthesizing quinoxaline derivatives is the reaction of *o*-PDA and its derivatives with α-halocarbonyl compounds,[61–63] resulting in 1,2-dihydro derivatives in moderate yields, and subsequent transformation of these products to aromatic quinoxalines by means of oxidants (in the presence of catalysts or without catalysts).

The presence of α-halocarbonyl and β-dicarbonyl fragments in ethyl 4-chloro-3-oxobutyrate implies that the reaction with *o*-PDA would give both quinoxaline and benzodiazepine moieties. However, only quinoxaline derivatives were isolated under reaction conditions in 80% overall yield.[62]



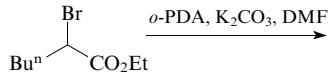
When catalytic amounts of perchloric acid adsorbed on SiO_2 ($HClO_4/SiO_2$) are used in the reaction of α-bromoketones and 1,2-diamines in acetonitrile, the target quinoxalines are formed within 15 min,[64] whereas without catalyst, no reaction products are detected even after 5 h.

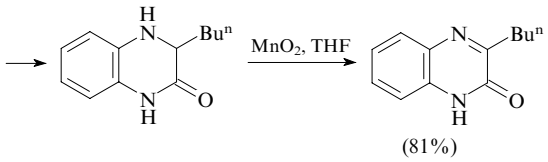


R = Ph (94%), 4-ClC_6H_4 (92%), 4-BrC_6H_4 (90%), 4-MeC_6H_4 (89%), 4-$MeOC_6H_4$ (87%), 2-furyl (87%).

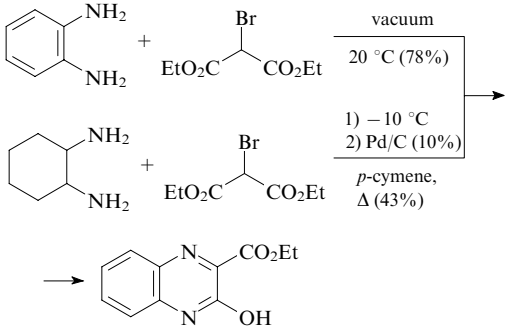
As opposed to other studied heterogeneous catalysts, the $HClO_4/SiO_2$-catalyzed reaction does not stop after condensation but proceeds further as oxidation and heterocycle aromatization. In the presence of this catalyst, atmospheric oxygen serves as the oxidant. In the absence of air, transformation to the aromatic form almost does not take place in the catalyzed reaction. The isolated dihydro derivative is also oxidized under similar conditions in the presence of $HClO_4/SiO_2$. The catalyst can easily be removed from the reaction mixture and used three times without loss of activity.

The reactions of *o*-PDA with compounds containing a halogen atom in the α-position to the ester group followed by oxidation of the dihydro product with manganese oxide provide quinoxalin-2(1*H*)-ones in high yields.[65]



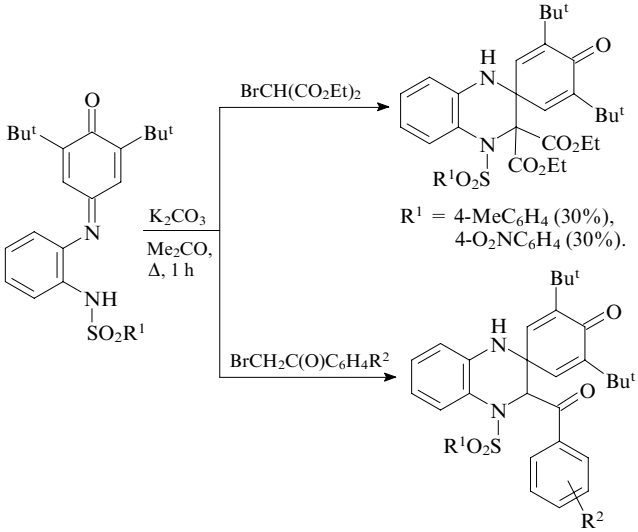


Quinoxaline derivatives can be obtained by reactions of α-halocarbonyl compounds with arylenediamines also without a catalyst. A one-pot method for the synthesis of substituted ethyl 3-hydroxyquinoxaline-2-carboxylates from *o*-PDA and diethyl bromomalonate without a solvent or catalyst at room temperature in a vacuum has been described.[66] All unsymetrically substituted 1,2-diamines afford isomer mixtures, while 4-nitro- and 4-benzoyl-1,2-phenylenediamines give only one isomer.



Stirring of *cis*-cyclohexane-1,2-diamine with diethyl bromomalonate at −10 °C for 15 min followed by treatment with 10% Pd/C in boiling *p*-cymene also results in quinoxaline in a 43% yield.[66]

α-Halocarbonyl compounds react with *o*-(*N*-sulfonyl)indoanilines to give spiroquinoxalines in moderate yields.[67] A necessary condition for the reaction to occur is high mobility of the *N*-methylene (or *N*-methine) hydrogen in the intermediate, which is attained through the effect of the electron-deficient aroyl or two ethoxycarbonyl groups.



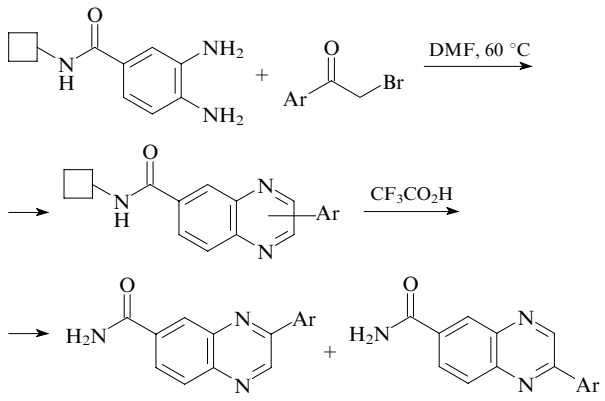
R^1 = 4-MeC_6H_4 (30%), 4-$O_2NC_6H_4$ (30%).

R^1 = 4-MeC_6H_4: R^2 = H (65%), 4-Br (50%), 3-NO_2 (40%), 3,4-Cl_2 (40%);
R^1 = 4-$O_2NC_6H_4$, R^2 = 4-Br (70%).

N-Allyl and *p*-nitrobenzyl *o*-(*N*-sulfonyl)indoaniline derivatives failed to be converted to the corresponding quinoxalines even on many-hour refluxing in pentachloro-

benzene or *o*-dichlorobenzene. The attempts to increase the mobility of methylene protons by replacing the vinyl and *p*-nitrophenyl groups by electron-withdrawing oxadiazole fragment did not induce the desired spirocyclization either.

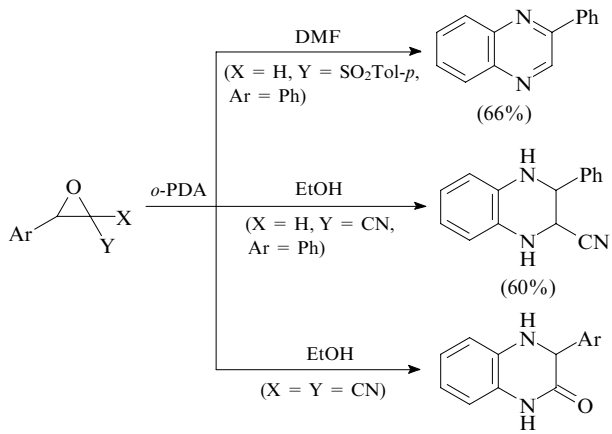
The use of *o*-PDA supported on SynPhase™ in the reaction with an α-bromo ketone affords isomeric quinoxalines in an overall yield of 86%.[68]



Ar = Ph, 2-$MeOC_6H_4$, 2,5-$(MeO)_2C_6H_3$, 4-MeC_6H_4, 4-FC_6H_4, 4-$Et_2NC_6H_4$, 4-PhC_6H_4.

Path e. Epoxides can also serve as two-carbon unit donors for the construction of a quinoxaline system. They react with *o*-PDA to give di- and tetrahydro derivatives in moderate yields. For preparing proper quinoxalines based on epoxides, a good leaving group at one of the oxirane ring atoms is required; in some cases, the use of catalysts is required.

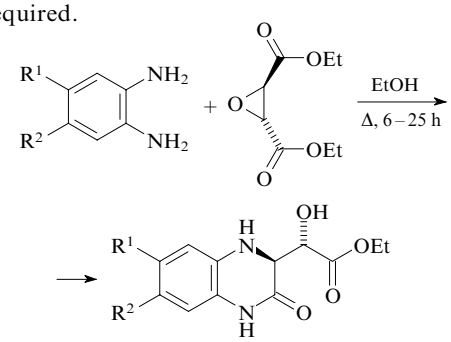
The condensation of 2-(*p*-tolylsulfonyl)-3-phenyloxirane with *o*-PDA on heating in DMF for 3 h furnishes 2-arylquinoxalines in 45%–66% yield.[69] Apparently, arylquinoxalines are formed upon the primary attack by the amino group on the C(3) carbon atom bearing the phenyl group with oxirane ring opening; this is followed by the attack by the second amino group on the carbonyl group formed, and, finally, oxidation of 1,2-dihydro derivative.



Ar = Ph (90%), 3-$O_2NC_6H_4$ (94%), 4-$MeOC_6H_4$ (91%).

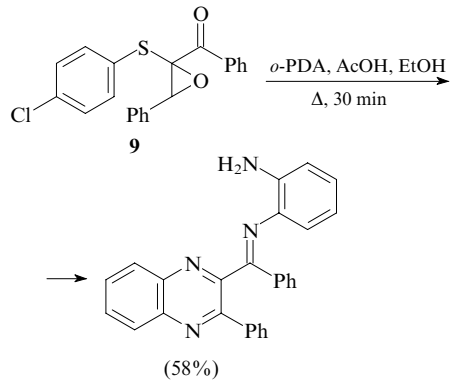
The application of this approach to 2-cyano- and 2,2-dicyano-3-aryloxiranes led to 3-aryl-2-cyano- and 3-aryl-2-oxo-1,2,3,4-tetrahydroquinoxalines, respectively, which are dehydrogenated to give aromatic derivatives on heating in ethanol in the presence of mercury oxide.

Diethyl (*R*,*R*)-oxirane-2,3-dicarboxylate obtained from diethyl (2*R*,3*R*)-(+)-tartrate reacts with *o*-PDA at elevated temperature under argon to give optically active tetrahydroquinoxalin-2-ones in good yields.[70] Note that whereas for *o*-PDA and its derivatives with electron-donating substituents, refluxing in ethanol is sufficient, for 1,2-diamino-4-nitrobenzene heating without a solvent at 155 °C is required.

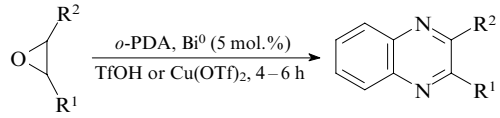


R^1 = R^2 = H (81%), Me (77%); R^1 = Me, R^2 = H (56%); R^1 = H: R^2 = OMe (81%), CF_3 (80%).

A series of new quinoxalines were prepared in 55%–61% yields by one-pot three-component condensation of epoxy ketones **9** with *o*-PDA in ethanol in the presence of catalytic amounts of acetic acid.[71] The authors assumed that the reaction occurs as a tandem process comprising the following sequence of transformations: acid-catalyzed aminolysis of oxirane, cyclization, elimination of benzenethiol, oxidation with air oxygen, condensation of the resulting aroylquinoxaline with the second *o*-PDA molecule. The formation of the product even at 1 : 1 reactant ratio shows that aroylquinoxaline is highly reactive and undergoes further condensation, resulting in imine. This might be due to protonation of the carbonyl carbon atom or the quinoxaline nitrogen atom with acetic acid, which increases the electrophilicity of the carbonyl function.



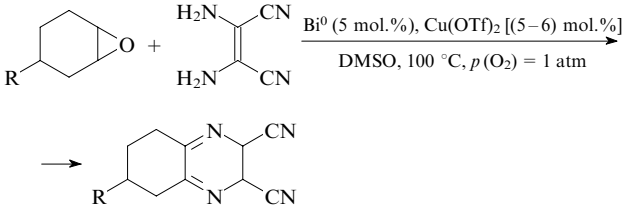
Different substituted quinoxalines can be obtained directly from simple epoxides or monosubstituted styrene oxides and *o*-arylenediamine using catalytic amounts of bismuth powder and copper triflate additives in DMSO.[72] The best results (yields 53%–70%) in the synthesis of quinoxalines were attained by using 1.5-fold excess of the



R^1 = Pr^n, R^2 = Bu^n (70%), R^1 = H: R^2 = Ph (64%), 4-ClC_6H_4 (65%).

diamine. In the absence of bismuth, DMSO or molecular oxygen, no quinoxalines were formed.

The reaction of 2,3-diaminomaleonitrile with cyclohexene oxide also leads to the corresponding hexahydroquinoxalines in 67% – 71% yield.[72]

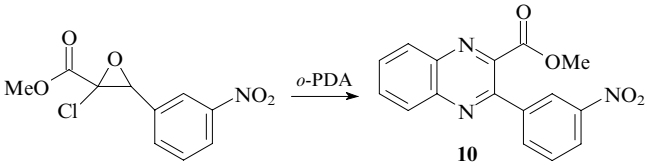


R = H (67%), CH_2=CH (71%).

For monosubstituted epoxides or cyclohexene oxide, $Cu(OTf)_2$ was added, while in the case of disubstituted epoxides, the use of a strong Brønsted acid (TfOH) was more beneficial. The required amount of acid to be added was calculated in view of the optimal ratio of the quinoxaline yield to the amount of the by-product formed in acid-catalyzed polymerization of epoxides.

It was assumed [72] that the reaction proceeds as the initial oxidation of epoxide with DMSO catalyzed by acid additives and resulting in the corresponding α-hydroxy ketone or α-hydroxy aldehyde. In the second step, this intermediate compound is oxidized to diketone or keto aldehyde under the action of the Bi^0/O_2 system and then condensed with *o*-PDA to give quinoxaline.

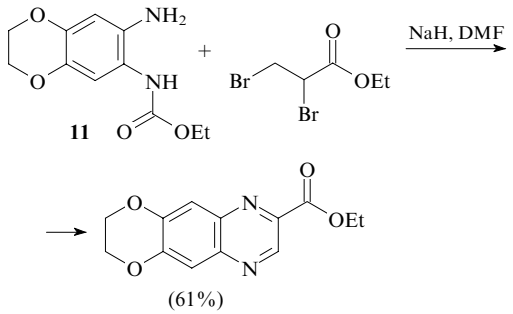
As noted above (see path *c*), the reaction of chloroarylpyruvates with *o*-PDA affords quinoxalin-2(1*H*)-ones **7**.[58] The chloro ketones used in these reactions are obtained by isomerization of chloro epoxides. However, chloro epoxide (unlike isomeric chloro ketone) is condensed with *o*-PDA to give quinoxaline **10**.[73]



10

Path f. Dihalides can also serve as bis-electrophiles for the construction of the quinoxaline system in the reaction with 1,2-arylenediamines and their derivatives.

For example, the oxidative condensation of *N*-(*o*-aminophenyl)carbamate **11** with ethyl 2,3-dibromopropionate in DMF in the presence of sodium hydride directly gives quinoxaline in one step.[74] Since carbamate **11** is readily oxidized with air, the condensation is carried out under argon and the subsequent workup is carried out in air to obtain the aromatic product.



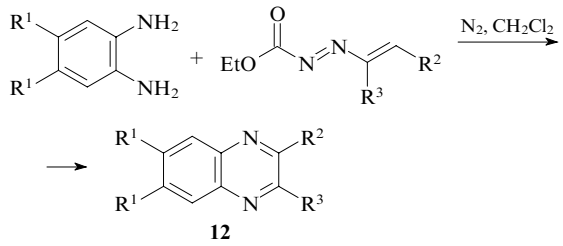
11

(61%)

The presence of two biselectrophilic fragments (α-halocarbonyl and α-dihalide) in 2,3-dibromopropionate implies the formation of a quinoxaline mixture. However, only one product was isolated; this fact was attributed [74] to fast elimination of hydrogen bromide under reaction conditions followed by the reaction of the unsaturated bromo ester formed *in situ* with *o*-PDA.

Path g. When activating groups are present, alkenes can also act as donors of a two-carbon fragment in the synthesis of quinoxaline derivatives.

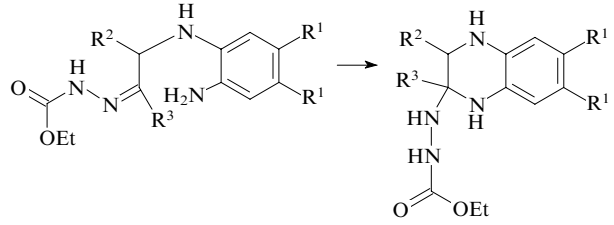
The reaction of 1,2-diazabuta-1,3-dienes containing a phosphine oxide or phosphonate fragment with 1,2-phenylenediamines at room temperature leads to quinoxalines **12** in high yields.[75]



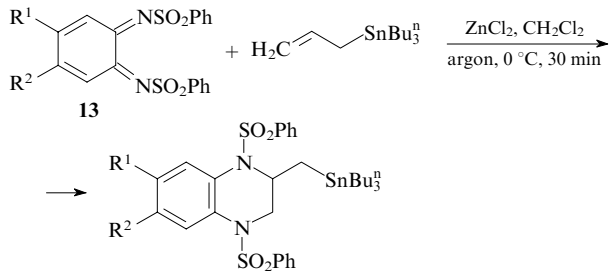
12

R^1	R^2	R^3	Yield (%)
H	$P(O)Ph_2$	Me	81
H	$P(O)(OEt)_2$	Me	83
H	$P(O)Ph_2$	Ph	91
H	$P(O)(OEt)_2$	Ph	98
Me	$P(O)Ph_2$	Me	90
Cl	$P(O)Ph_2$	Me	93
Cl	$P(O)Ph_2$	Ph	89

The authors suggested that the first reaction step consists of a nucleophilic attack by one *o*-PDA amino group on the terminal carbon atom of the heterodiene system to give the intermediate 1,4-adduct (hydrazone), and the nucleophilic attack by the second amino group on the hydrazone carbon atom followed by elimination of the hydrazinecarboxylate fragment results in 2-phosphorylated tetrahydroquinoxalines.

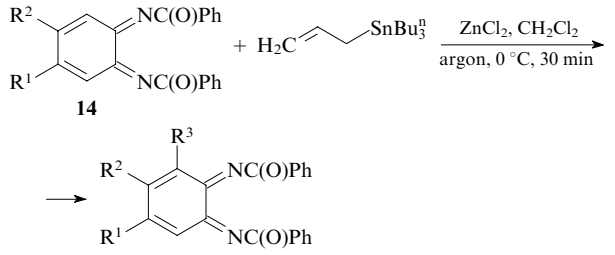


Another example of using alkene for preparing quinoxalines is the addition of allyltri(n-butyl)stannane to *o*-quinonediimines **13** in the presence of $ZnCl_2$.[76] Although the reaction products are formally the Diels – Alder adducts, it should be noted that in the absence of a Lewis acid, no cyclocondensation takes place; therefore, according to authors' opinion, the reaction follows an ionic mechanism. Other Lewis acids ($AlCl_3$, Me_2AlCl, $TiCl_4$) also promote the reaction, but still less efficiently than $ZnCl_2$.



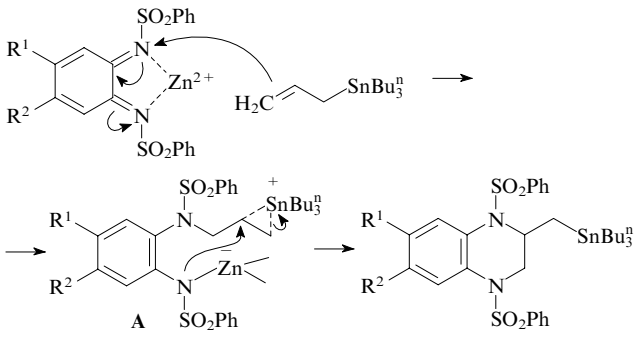
R^1	R^2	Yield (%)
Cl	H	98
Br	H	72
Me	H	72
Cl	Cl	82
Me	Me	44

Note that in the case of *N*-benzoyl substituents in *o*-quinonediimines **14**, allylated amides are formed under conditions of this reaction.[76]

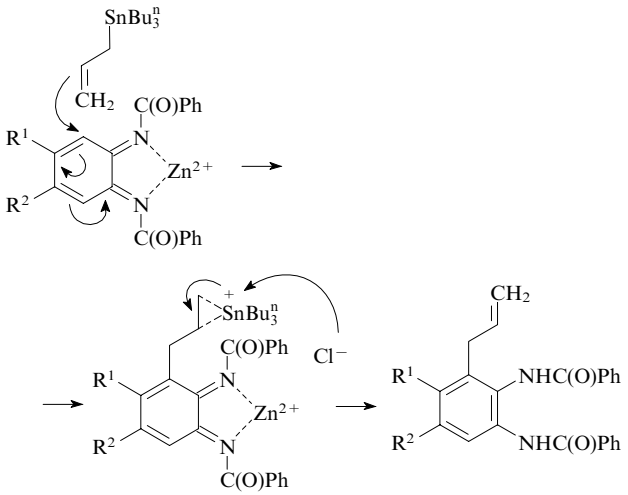


Substrate **14**		Product			
R^1	R^2	R^1	R^2	R^3	yield (%)
H	H	H	All	H	61
Me	H	Me	All	H	68
Cl	H	Cl	All	H	68
Cl	Cl	Cl	Cl	All	77
Me	Me	Me	Me	All	69

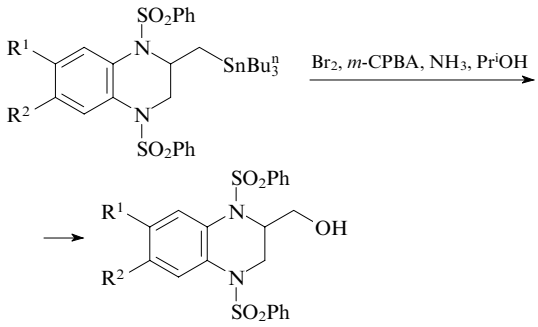
The authors suggested that the first reaction step includes coordination of the Lewis acid to quinoneimine, the site of the primary attack by allylstannane depending on the basicity of quinoneimine nitrogen atoms. The sulfonyl substituent is more electrophilic than the benzoyl substituent; therefore, allylstannane attacks it to give intermediate carbocation **A** stabilized through hyperconjugation.



The imide nitrogen atom bearing a benzoyl substituent is more basic; therefore, the reaction with allylstannane occurs as 1,4- or 1,6-addition depending on the substituent in the benzene ring.



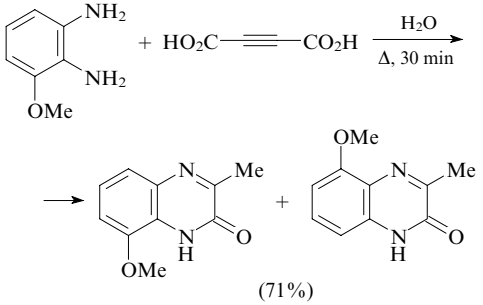
Treatment of the resulting quinoxalines with bromine in isopropyl alcohol in the presence of ammonia and *m*-chloroperoxybenzoic acid (*m*-CPBA) results in the corresponding alcohols in high yields.



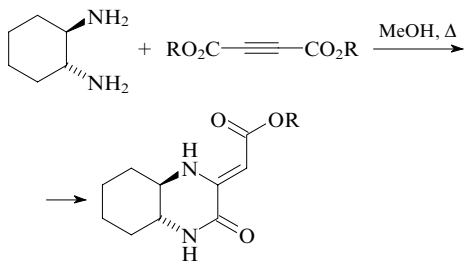
The proposed method provides the route to tetrahydroquinoxalines in high yields but it requires expensive reagents and is applicable only to a limited range of derivatives.

Path h. Unlike alkenes considered above, acetylenedicarboxylic acid and its derivatives react with 1,2-phenylenediamines to provide the ester carbon atom and the triple bond carbon atoms as electrophilic centres for the construction of the quinoxaline ring.[77]

The reaction of 2,3-diaminoanisole with acetylenedicarboxylic acid gave a mixture of two isomeric products in approximately equal amounts.[78] Their separation was attained owing to their different acidity: at pH 8 one isomer passed to the solution and the other one remained in the precipitate.

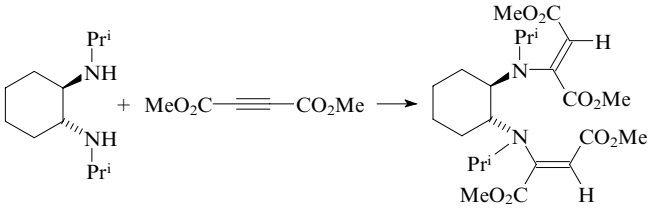


The use of *trans*-(1*R*,2*R*)-diaminocyclohexane in the reactions with acetylenedicarboxylic acid derivatives carried out on refluxing in methanol also yields decahydroquinoxaline derivatives in good yields.[79]



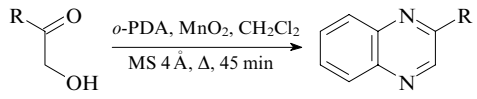
R = Me (65%), Et (68%).

However, in the case of di(isopropylamino)cyclohexane, no quinoxaline formation was observed but the addition product of two acetylene molecules to nitrogen atoms was isolated;[79] this is obviously due to steric hindrance caused by the isopropylamino groups at the asymmetric carbon atoms.



Path i. When α-hydroxy ketones are used as donors of the bis-electrophilic fragment, the formation of the quinoxaline system requires the presence of MnO_2 as the oxidant.[80]

Thus α-hydroxy ketones are oxidized by MnO_2 and the keto aldehydes formed *in situ* then react with aromatic 1,2-diamines to give quinoxalines in the one-pot process.[81]



R = Me (79%), Ph (79%), 2-furyl (89%), cyclo-C_6H_{11} (78%).

When the reaction of hydroxyacetone with *o*-PDA is performed in the presence of 15 equiv. of MnO_2 in dichloromethane, 2-methylquinoxaline is produced in 43% yield. The addition of acid or base or replacement of the solvent did not improve the result, moreover, azobenzene was formed as a by-product resulting from oxidative coupling of diamine. When a twofold excess of diamine was used, the target product was formed in a 79% yield within an hour.

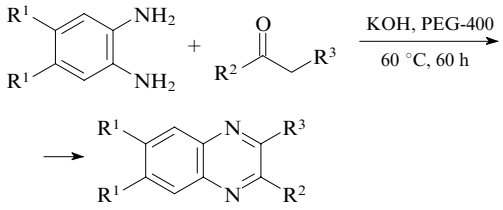
Both alkyl and aryl-substituted α-hydroxy ketones are converted to quinoxalines in good yields under these conditions. The advantages of this method are the possibility of preparing highly reactive keto aldehydes *in situ* and the ease of product isolation, in particular, after completion of the reaction, the oxidant and the by-product are removed by filtering and evaporation.

When methyl glycolate (R = OMe) was used for the synthesis of quinoxalin-2(1*H*)-one, the product was formed in only 36% yield, because oxidation of methyl glycolate was slower than that of α-hydroxy ketones and the azo compound was formed faster than quinoxaline.

Path j. Ketones containing α-methylene group can also act, under certain conditions, as donors of two-carbon fragment for constructing the quinoxaline system.

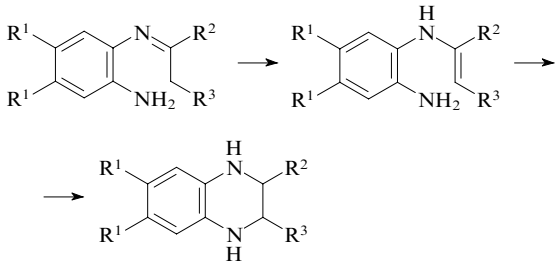
o-Phenylenediamine reacts with a number of ketones in poly(ethylene glycol) (PEG-400) at 60 °C in the presence of KOH to give the corresponding quinoxalines in high yields; the optimum reactant ratio is 1 : 2 and the optimum reaction time is 60 h.[82]

Note that performing the process under argon leads to a slight decrease in the product yield; increase in the reaction temperature to 100 °C also decreases the product yield. On increasing the KOH : diamine ratio from 1 : 1 to 3 : 1, the product yield increases, while in the absence of KOH, cyclization giving quinoxaline does not take place.



R^1	R^2	R^3	Yield (%)
H	Ph	Me	72
H	4-$MeOC_6H_4$	Me	59
H	4-ClC_6H_4	Me	54
H	Ph	Pr^n	73
H	Ph	n-C_6H_{13}	65
H	Ph	CH_2Bn	68
H	Ph	Ph	67
H	Pr^i	Ph	75
H	Et	Ph	56
H	Me	Bu^n	30
H	n-C_5H_{11}	Bu^n	31
Me	Ph	Me	54
Me	4-$MeOC_6H_4$	Me	74
Me	4-ClC_6H_4	Me	49
Me	Ph	Ph	71
Me	Pr^i	Ph	95

It was suggested[82] that the process starts with condensation of the ketone with the diamine to give ketimine, which undergoes intramolecular hydroamination as the enamine tautomer followed by dehydrogenation, the role of KOH being to activate the amino groups and to facilitate the tautomerization of the ketimine.

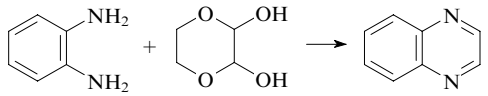


The reaction is applicable to alkyl aryl ketones; in the case of acetophenone, the product yield is only 20%.

The reaction of *o*-PDA with 1-phenylbutan-2-one results in only one regioisomer, 3-ethyl-2-phenylquinoxaline. Low yields and reaction rates were observed when *o*-PDA reacted with non-activated dialkyl ketones; however, in this case, too, only one regioisomer was formed from unsymmetrical ketones.

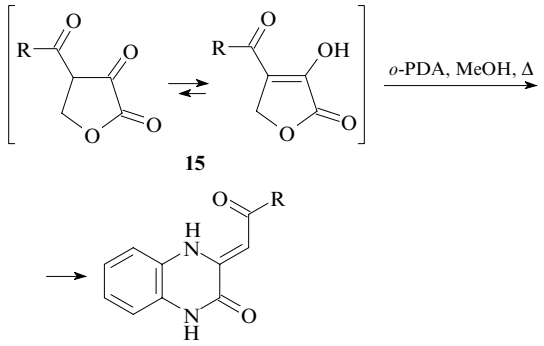
Path k. Some heterocyclic derivatives can also serve as two-carbon unit donors; under the action of *o*-PDA, they usually undergo ring cleavage to give substituted quinoxalines.

Thus 2,3-dihydroxy-1,4-dioxane, a stable synthetic equivalent of anhydrous glyoxal, reacts with *o*-PDA at room temperature in ethanol to give quinoxaline in high yield within 30 min.[83]



(95%)

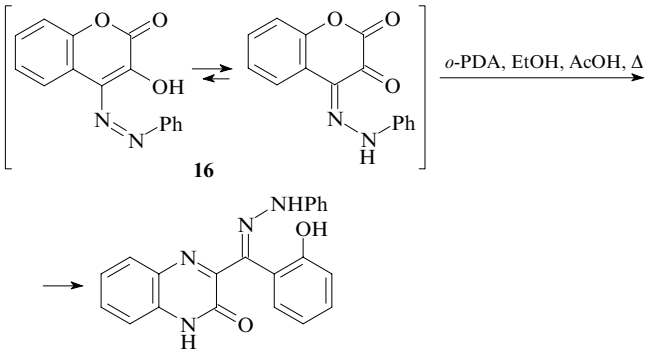
The condensation of α-keto-β-substituted γ-butyrolactones (3-hydroxyfuran-2(5*H*)-ones) **15** with *o*-PDA results in 3-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones.[84] The authors assumed that the reaction starts with the nucleophilic attack by the amino group on the keto group of furanone to give Schiff's base. Then the attack by the second amino group on the lactone carbonyl group results in ring opening. The process is completed by retro-aldol condensation with evolution of formaldehyde, which was identified as a reaction product with dimedone in an ethanolic solution.



15

R = Ph (85%), 4-ClC_6H_4 (49%), 3,4-$(MeO)_2C_6H_3$ (85%), Bu^t (68%), EtO (41%).

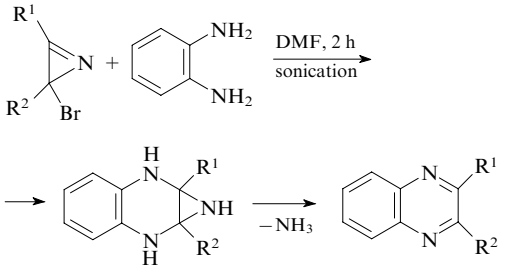
Similarly to butyrolactones, phenylhydrazine **16** (2*H*-chromene derivative) reacts with *o*-PDA in a boiling EtOH – AcOH mixture with ring cleavage giving rise to quinoxalin-2(1*H*)-one **17**.[85]



16

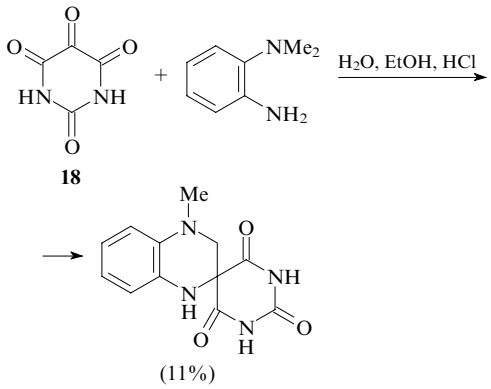
17 (80%)

2-Halo-2*H*-azirines can also function as the starting compounds in quinoxaline synthesis.[86] At room temperature and even at 65 °C, the expected products are not formed, but they are formed in good yields when the reaction is carried out in DMF in an ultrasonic bath.



R^1	R^2	Yield (%)
Ph	CO_2Et	86
CO_2Me	Bz	73
CO_2Me	CO_2Me	69
Me	CO_2Me	80

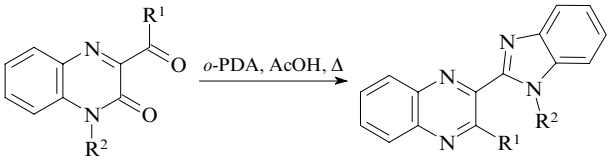
The reaction of alloxan (**18**) with *o*-PDA derivatives in ethanol in the presence of hydrochloric acid gives spiroquinoxalines in low yields apart from other products.[87]



18

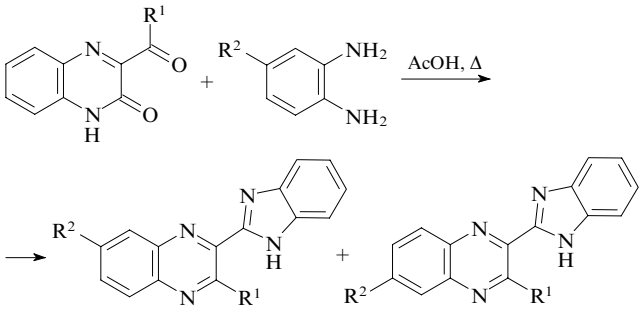
(11%)

In 2000, a fundamentally new reaction was discovered, taking place in the 3-aroyl(alkanoyl)quinoxalin-2(1*H*)-one – 1,2-arylenediamine system[88,89] with pyrazine ring contraction to give the corresponding 2-benzimidazolylquinoxalines in good yields.[90–93] The quinoxaline ring is formed in this case with participation of the imine carbon atom of the pyrazine ring and the α-carbon atom of the 3-substituent in the quinoxalin-2(1*H*)-one system.



R^1	R^2	Yield (%)
Ph	H	97
Ph	Me	81
Ph	Et	79
Ph	Pr^n	87
Ph	Bu^n	87
Ph	n-C_5H_{11}	86
Ph	Bn	56
Me	H	72
Me	Et	99
Pr^n	H	75
Bn	H	81
CH_2Bn	H	87

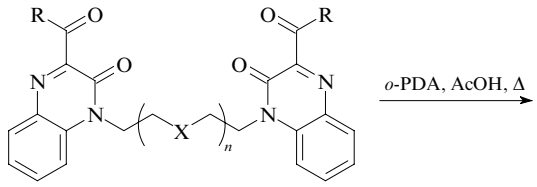
The use of this reaction allows one to introduce the benzimidazole system into the quinoxaline molecule. The use of unsymmetrically substituted 1,2-arylenediamines results in a mixture of isomers in approximately equal amounts.[92–94]

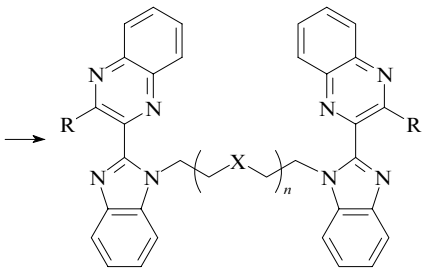


R^1	R^2	Total yield (%)
Ph	NO_2	83
Ph	Me	82
Bn	NO_2	85
Bn	Me	78
Me	NO_2	52
Me	Me	72

In view of the formation of isomer mixture irrespective of the nature of substituents in the quinoxalin-2(1*H*)-ones and 1,2-arylenediamines used, the reaction mechanism was described[93] as follows: first, the amino group of *o*-PDA attacks either the C(3) atom of the quinoxaline system or the alkanoyl (aroyl) carbon atom; this is followed by cascade transformation comprising the formation of spiroquinoxaline **A**, opening of the pyrazine ring of the quinoxaline system to give quinoxaline-2-carboxylic acid *o*-aminoanilide **B**, intramolecular electrophilic addition of the amine nitrogen atom to the carbamoyl carbonyl group, ring contraction and elimination of water (Scheme 2).

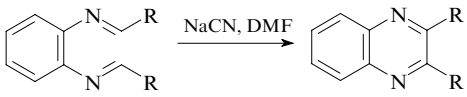
A similar reaction occurs for compounds with two terminal benzoyl- or acetylquinoxalin-2(1*H*)-one fragments.[92,95]





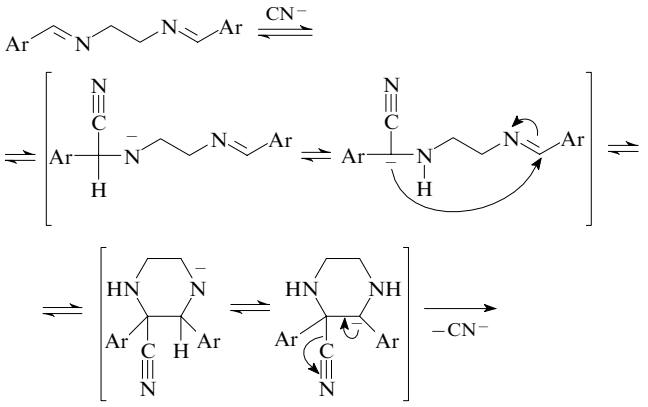
R = Ph, X = O: n = 1 (80%), 2 (75%); R = Ph, X = CH_2: n = 1/3 (69%), 4/3 (72%), 8/3 (73%); R = Me, X = O, n = 1 (75%).

Path l. Yet another approach to the synthesis of quinoxalines is intramolecular cyclization of various *o*-PDA derivatives with appropriate functional groups. Thus when dialdimines are used in cyanide-catalyzed aldimine coupling (analogue of benzoin condensation), intramolecular cyclization takes place to give quinoxaline derivatives.[96] The most effective solvents are methanol and DMF in which sodium cyanide is readily soluble.

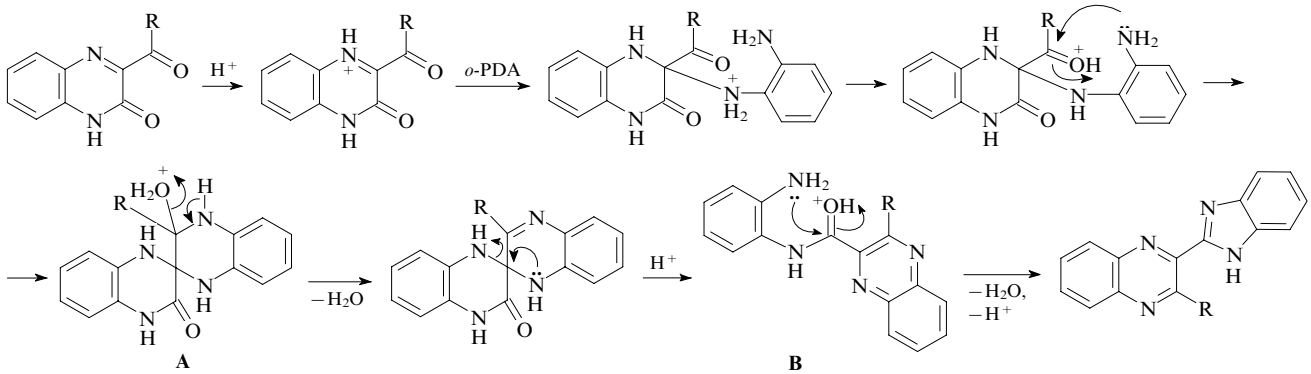


R = 2-HOC_6H_4 (88%), 2-furyl (53%), 2-HO-3-$MeOC_6H_3$ (65%).

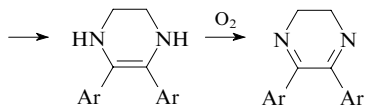
The authors assumed that the reaction proceeds through the initial addition of the cyanide anion to the imino group followed by the nucleophilic attack on the carbon atom by the second imino group and elimination of the catalyst.



Scheme 2



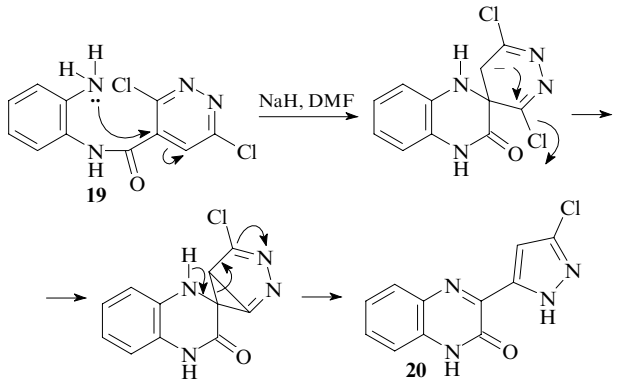
R = Alk, Ar.



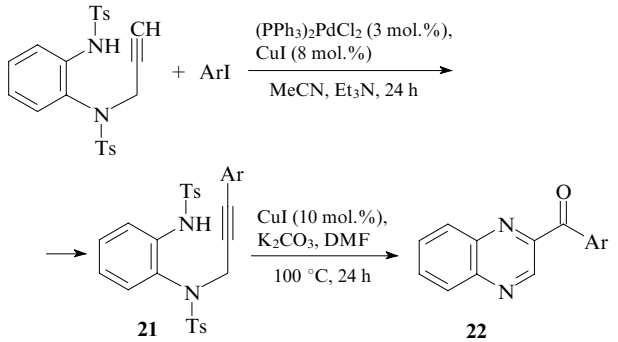
In the presence of atmospheric oxygen, oxidative cyclization takes place to give diimino derivatives; under phase transfer conditions amino-imine derivatives can be obtained; cyclization of unsymmetrical dialdimines provides a route to unsymmetrical quinoxalines.

Note that vanillin (4-hydroxy-3-methoxybenzaldehyde) and related aldehydes do not undergo benzoin condensation, whereas dialdimines based on vanillin are coupled to give quinoxalines.

On heating with sodium hydride in DMF, 2-aminoanilide **19** experiences the pyridazine ring rearrangement to give quinoxalin-2(1*H*)-one **20**.[97]



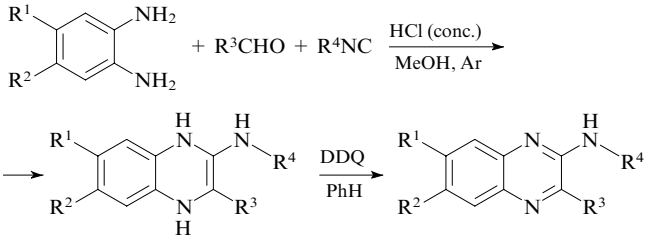
In di(*p*-tosyl)amides **21**, ring closure takes place under the action of K_2CO_3 and CuI to give 2-aroylquinoxalines **22**.[98]



Ar	Yield (%)	
	21	**22**
Ph	43	46
3-ClC_6H_4	60	60
4-MeC_6H_4	60	53
2-MeC_6H_4	55	50
4-$MeOC_6H_4$	41	40
2-$MeOC_6H_4$	52	49
1-Naphthyl	59	44
2-Thienyl	65	45

It is noteworthy that C-arylation of terminal alkynes (Sonogashira reaction) requires both palladium(II) complex and copper(I) iodide as the catalyst, whereas cyclization requires only CuI (without CuI the cyclic product is not formed). When potassium carbonate is replaced by triethylamine, no cyclic product is formed either.

Path m. Recently, a new multicomponent reaction was proposed,[99,100] including the condensation of 1,2-arylenedimines, aldehydes and isocyanides to give 1,4-dihydroquinoxalines, which are oxidized on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the corresponding aromatic derivatives of 2-aminoquinoxalines.



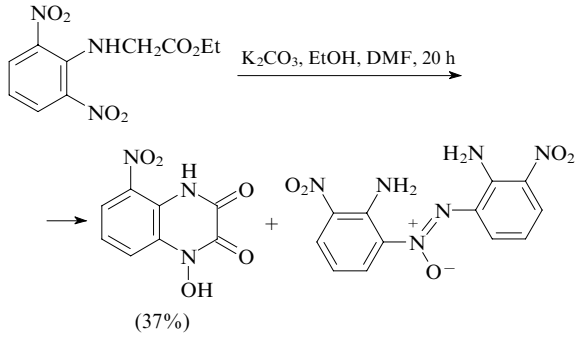
R^1	R^2	R^3	R^4	Yield (%)
H	H	Ph	$Ph(CH_2)_2$	54
Me	Me	Ph	$Ph(CH_2)_2$	50
Me	H	Ph	cyclo-C_5H_9	53
Me	Me	1-methylpyrazol-5-yl	$Ph(CH_2)_2$	43
Me	Me	3-pyridyl	$Ph(CH_2)_2$	33
H	H	Ph	$MeO(CH_2)_2$	48
CO_2H	H	Ph	cyclo-C_5H_9	35
H	H	2-thienyl	$MeO(CH_2)_2$	43

III. Synthesis of quinoxalines based on aniline derivatives

The use of aniline derivatives for the synthesis of quinoxalines, unlike 1,2-arylenediamines, implies regioselective reaction.

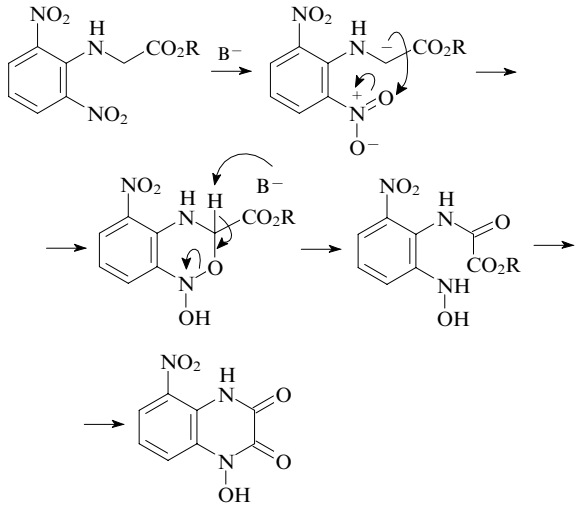
The possible starting compounds include *o*-nitroanilines (path *n*), anilines with a terminal nitro group in the substituent (path *o*), *o*-halogenated anilines (path *p*), α-arylliminooximes (path *q*).

Path n. The reductive cyclization of *o*-nitroaniline derivatives is used most widely . In the presence of bases, various *N*-methyl-substituted *o*-nitroanilines give 1-hydroxyquinoxaline-2,3(1*H*,4*H*)-diones and azobenzene derivatives (in the given example, the latter was detected but the yield was not determined).[101]



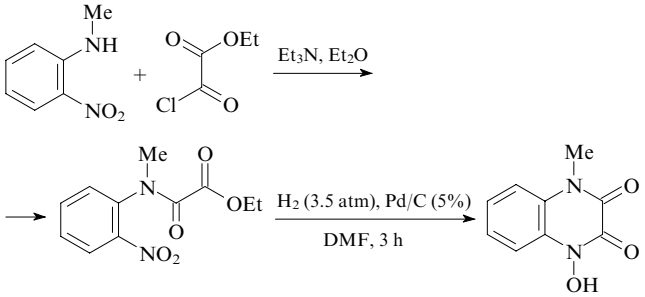
Note that in the absence of the second substituent in the *o*-position to the amino group, benzimidazoles are formed under reaction conditions. Potassium carbonate proved to be most effective among the compounds studied for the formation of quinoxaline rather than benzimidazole system.

It is assumed [101] that quinoxalines are formed as a result of intramolecular redox process followed by cyclization.



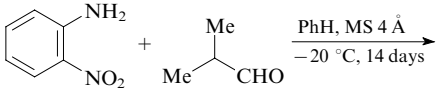
B^- is base.

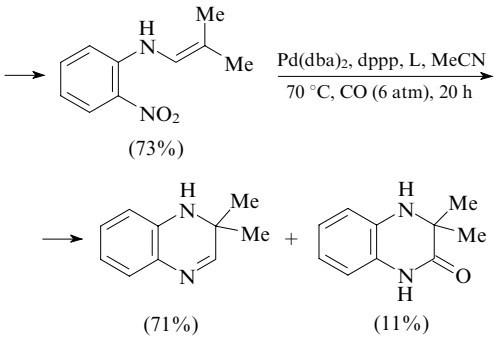
Quinoxaline-2,3(1*H*,4*H*)-diones **23** can be obtained in high yields also by a different method, namely, hydrogenation of *o*-nitroaniline derivatives containing a carboxyl or ester residue under the action of reducing systems such as palladium on charcoal, tin in acidic medium or $NaHCO_3 - Na_2S - MeOH$.[49]



23 (85%)

Palladium-catalyzed reductive N-heteroannulation of enamines obtained from *o*-nitroaniline yields a mixture of 1,2-dihydroquinoxalines and dihydroquinoxalinones.[102]





dba is dibenzylideneacetone, dppp is 1,3-bis(diphenylphosphino)propane, L is 1,10-phenanthroline.

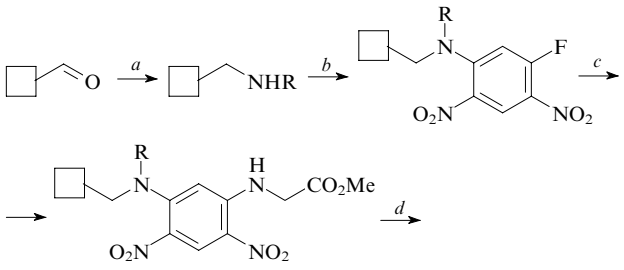
It is worth noting that heterocyclization of enamines in the presence of ruthenium catalyst at 60 atm gives benzimidazole as the major product.

Enamines with electron-withdrawing substituents other than the nitro group in the *o*-position of the benzene ring do not undergo heteroannulation to give quinoxalines.

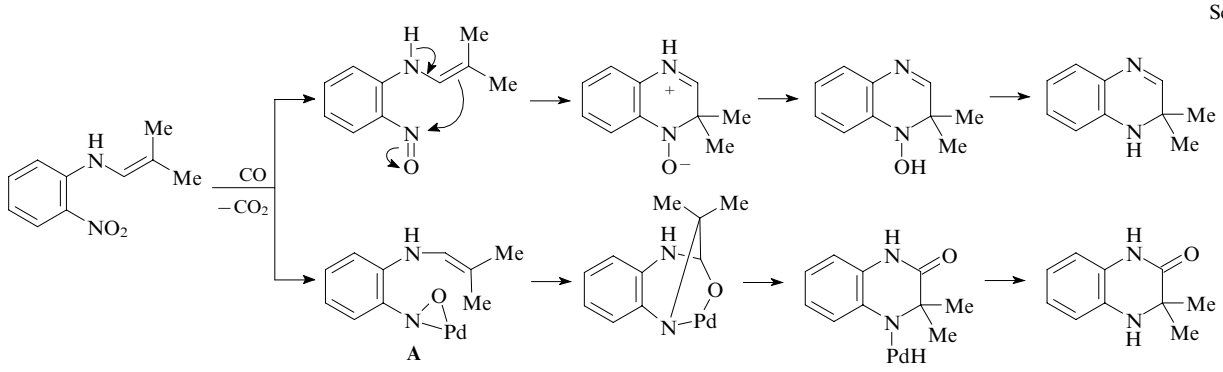
Although the reaction mechanism is not entirely clear, in the authors' opinion,[102] the reaction occurs as initial deoxygenation of the nitro compound in the presence of a catalyst to give the nitrosoaryl derivative followed by cyclization involving the neighbouring enamine fragment and catalyst-induced deoxygenation.

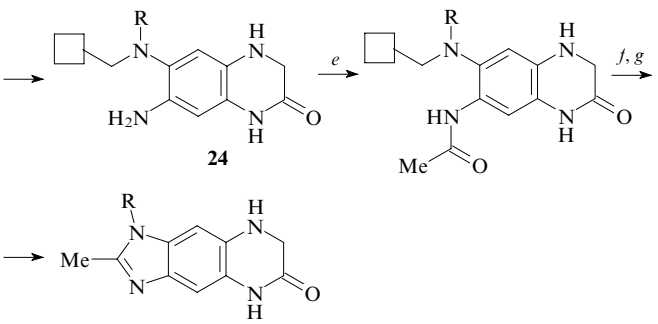
Yet another possible route includes the insertion of enamine to palladium derivative **A** to give bicyclic complex, which undergoes β-elimination followed by reductive elimination (Scheme 3).

The primary amines supported on 2-(3-methoxyphenoxy-4-formyl)ethylpolystyrene react with 2,4-dinitro-1,5-difluorobenzene followed by replacement of the second fluorine atom by an amino acid residue, reduction of nitro groups and cyclization to give tetrahydroquinoxalinones **24**.[103]



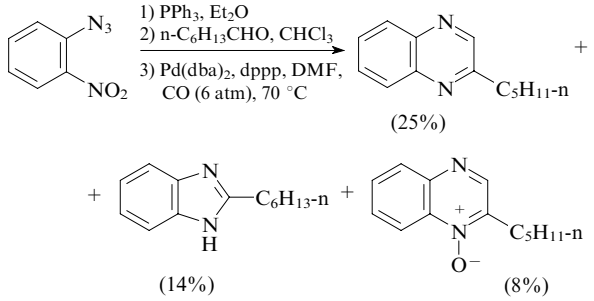
Scheme 3



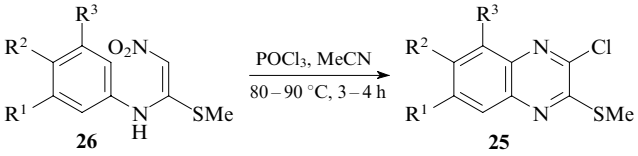


R is 3-(4-methylpiperazin-1-yl)propyl, 2-2(chlorophenyl)ethyl;
(*a*) RNH_2, $HC(OEt)_3$, $Na(CN)BH_3$; (*b*) 1,5-F_2-2,4-$(NO_2)_2C_6H_2$, Et_3N;
(*c*) $H_2NCH_2CO_2Me$; (*d*) $SnCl_2 \cdot 2H_2O$, *N*-methylmorpholine;
(*e*) AcOH, $C(=NPr^i)_2$; (*f*) $CF_3CO_2H - CH_2Cl_2 - Et_3SiH$ (10 : 3 : 1);
(*g*) 4 M HCl, dioxane – MeOH (2 : 1), 50 °C.

1-Azido-2-nitrobenzenes when react with triphenylphosphine and heptanal in the presence of palladium catalyst are also subject to annulation to give a mixture of quinoxaline and benzimidazole derivatives.[102]



Path o. Quinoxalines can be prepared using not only *o*-nitroanilines but also aniline derivatives with a terminal nitro group in the substituent. Thus a new regioselective method for the synthesis of 3-chloro-2-methylthioquinoxalines **25** by heteroannulation of a number of *N*,*S*-ketene acetals **26** was developed.[104]

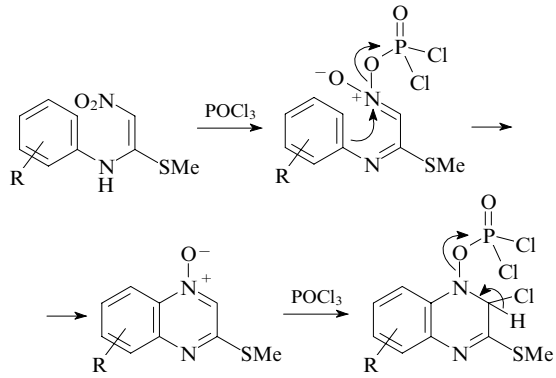


R^1	R^2	R^3	Yield (%)
MeO	H	H	70
MeO	MeO	H	75
MeO	H	MeO	71
H	H	H	50

The use of *N*,*S*-acetal under the Vilsmeier reaction conditions gave quinoxaline in 60% yield rather than the expected quinoline. It was found that the reaction with $POCl_3$ occurs smoothly also in acetonitrile in the absence of DMF; the yield then increases to 70%.

Under the same conditions, other substituted *N*,*S*-acetals were investigated. Compounds with activating *para*-substituents relative to the position involved in cyclization produce the corresponding quinoxalines in high yields. In the case of 3-fluoro derivative, two isomers are formed upon cyclization in the *ortho*- and *para*-positions to the substituent.

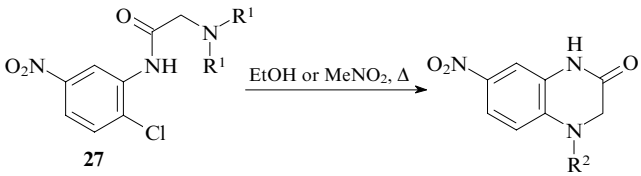
A supposed [104] mechanism of the transformation of *N*,*S*-acetals to quinoxalines includes the initial formation of quinoxaline *N*-oxide upon cyclization of the acetal followed by chlorination in position 3 and oxygen extrusion.



R = Alk, OAlk, Hal.

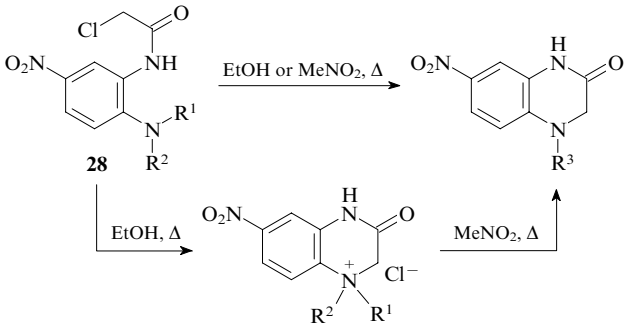
Path p. One more widely accepted method is based on aniline derivatives containing good leaving groups; the pyrazine ring is completed in this case as a result of both intra- and intermolecular reactions.

Thus heating of aminoacetanilides **27** induces their cyclization to tetrahydroquinoxalin-2-one derivatives.[105] This intramolecular aromatic nucleophilic substitution requires the presence of halogen-activating electron-withdrawing substituents.



R^1 = Me, $R^1 - R^1$ = $(CH_2)_n$ (n = 4–6), *o*-$(CH_2)_2C_6H_4CH_2$;
R^2 = Me (91%), $(CH_2)_4Cl$ (82%), $(CH_2)_5Cl$ (85%), $(CH_2)_6Cl$ (82%), *o*-$(CH_2)_2C_6H_4CH_2Cl$ (70%), *o*-$(CH_2)_2C_6H_4CH_2OEt$ (65%).

The intramolecular nucleophilic substitution in isomeric chloroacetanilides **28** also results either in 3-oxoquinoxalinium salts or directly in tetrahydroquinoxalin-2-ones depending on substituents and experimental conditions.

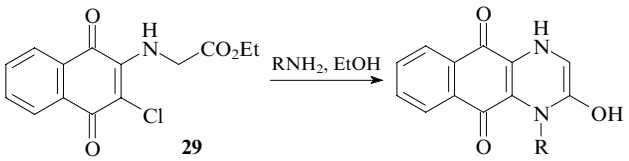


R^1 = R^2 = Me; $R^1 - R^2$ = $(CH_2)_5$, $(CH_2)_6$, *o*-$(CH_2)_2C_6H_4CH_2$;
R^3 = Me (98%), $(CH_2)_5Cl$ (91%), $(CH_2)_6Cl$ (90%),
o-$(CH_2)_2C_6H_4CH_2Cl$ (84%), *o*-$(CH_2)_2C_6H_4CH_2OEt$ (75%).

On refluxing in nitromethane, quinoxalinium salts, like acetanilides, are converted to the corresponding quinoxalines in high yields (77% – 98%). 3,4-Dihydroquinoxali-

nones tend to be oxidized in air and can be converted to aromatic derivatives.

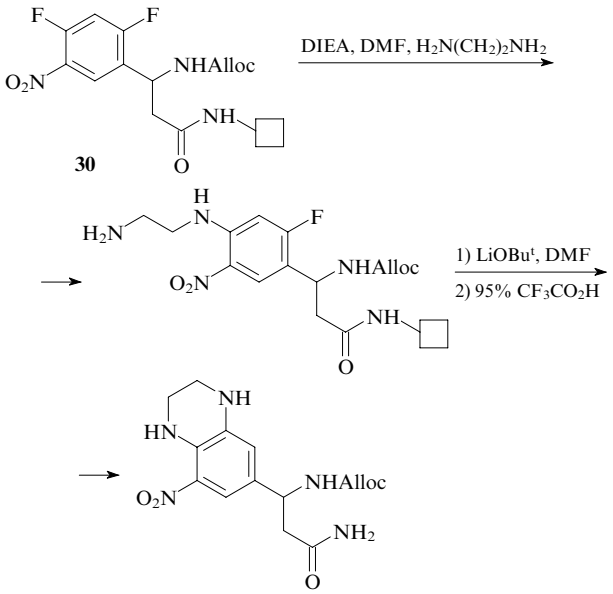
The reaction of esters **29** with primary aromatic and aliphatic amines affords benzoquinoxalines in high yields.[106]



29

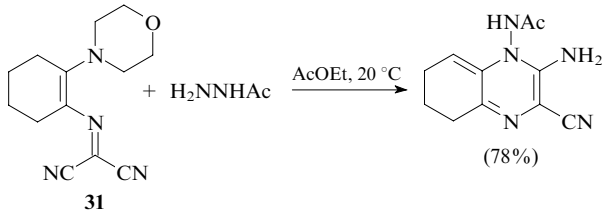
R = $(CH_2)_2OH$ (67%), $(CH_2)_3OH$ (90%), Pr^i (70%), Bu^i (81%), Bu^t (85%), Ph (88%), 2-$MeOC_6H_4$ (68%), 4-HOC_6H_4 (84%), 3,4-$(MeO)_2C_6H_3(CH_2)_2$ (75%).

Substituted tetrahydroquinoxalines are also formed upon cyclization of aniline derivatives containing a leaving group (halogen atom) not only in the *ortho*- but also in the *meta*-position.[107] The reaction of 3-amino-3-phenylpropionic acid derivative **30** immobilized on a solid substrate with the stoichiometric amount of primary diamine yields monosubstituted product. The subsequent dehydrofluorination induced by a strong base leads to the quinoxaline system *via* dehydrobenzene.[107]



Alloc = AllOC(O).

Apart from halogen atoms, morpholine can also function as the leaving group in the reactions of *ortho*-substituted tetrahydroanilines with amines. Thus the nucleophilic attack of the dinitrile **31** by hydrazines or hydrazides at room temperature in ethyl acetate provides the corresponding hydrogenated quinoxalines in high yields.[108]

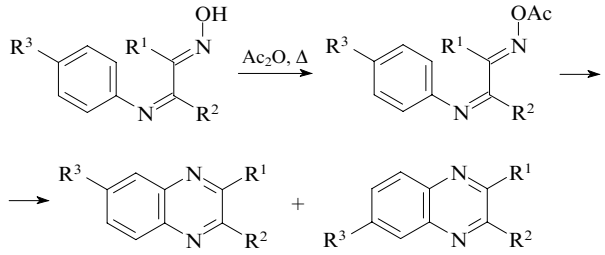


31

Path q. As regards regiochemistry, intramolecular cyclization of α-aryliminophenylhydrazones or oximes of α-dicarbonyl compounds with substituted anilines instead of *o*-diaminobenzenes or *o*-halonitrobenzenes is a promising method.

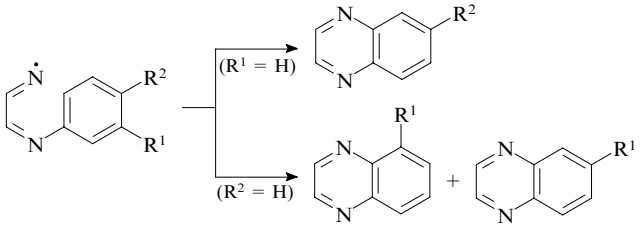
The refluxing of aryliminooximes in acetic anhydride yields a mixture of isomeric quinoxalines,[109] which allowed the authors to suggest that the reaction proceeds through the aryliminoiminyl radical resulting from homolytic cleavage of the N—O bond in the intermediate ester.[110, 111]

The one-pot process where oximes are employed instead of their esters (which are formed *in situ*) results in quinoxalines in comparable or higher yields under mild conditions.



R^1	R^2	R^3	Total yield (%)
Ph	Ph	H	57
Ph	Ph	MeO	65
Ph	Ph	Me	63
Ph	Ph	Cl	53
Me	Ph	H	66
Me	Me	H	16

When the benzene ring contains only a *para*-substituent, 6-substituted quinoxalines are obtained. In the case of *meta*-substituent, two isomers are formed as a result of attack to the *ortho*- and *para*-positions to the substituent, the former slightly predominating, which implies that the process occurs as aromatic substitution of the iminyl radical.



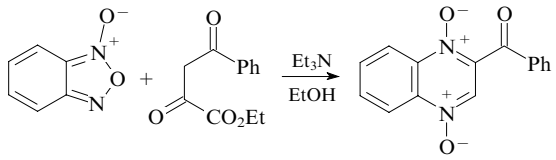
If the starting diketone is also unsymmetrical, the corresponding α-arylaminooxime, even when substituted only in the *para*-position, leads to a mixture of isomeric quinoxalines.

Although the researchers cited[109] assumed a radical mechanism for this reaction, a concerted process cannot be ruled out.

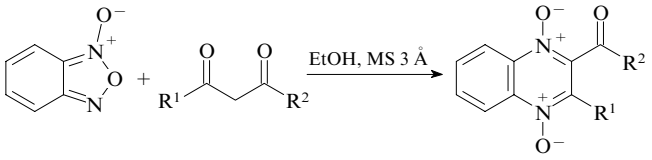
IV. Synthesis of quinoxalines based on heterocyclic systems devoid of the pyrazine fragment

A quinoxaline system can be constructed from various fused nitrogen-containing heterocycles devoid of a pyrazine fragment, for example, benzofuroxan (path *r*), benzimidazole (path *s*), azabicyclo[4.1.0]heptane (path *t*) and benzodiazepines (paths *u* and *v*).

Path r. A widely used method for the synthesis of quinoxaline 1,4-dioxides is the so-called Beirut reaction (also called Haddadin–Issidorides reaction), *viz*., the reaction of benzofurazan oxides with C-nucleophiles.[112–117]

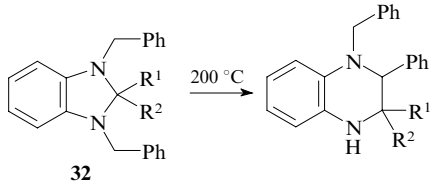


Silica gel can serve as the catalyst; however, the reaction time is 1–2 weeks. Molecular sieves, which reduced the reaction time to 1–3 days, proved to be more effective catalysts of this process.[118] The reaction efficiency also depends on the types of molecular sieves used; the best results were attained with the 3 A sieves (as a powder).



R^1	R^2	Yield (%)
Me	Et	82
Me	PhNH	88
Me	2-$MeOC_6H_4NH$	87
Me	4-$MeOC_6H_4NH$	80
Me	4-ClC_6H_4NH	84
Me	2-MeC_6H_4NH	85
MeO_2CCH_2	MeO	50
4-$O_2NC_6H_4$	EtO	83
Ph	PhNH	71

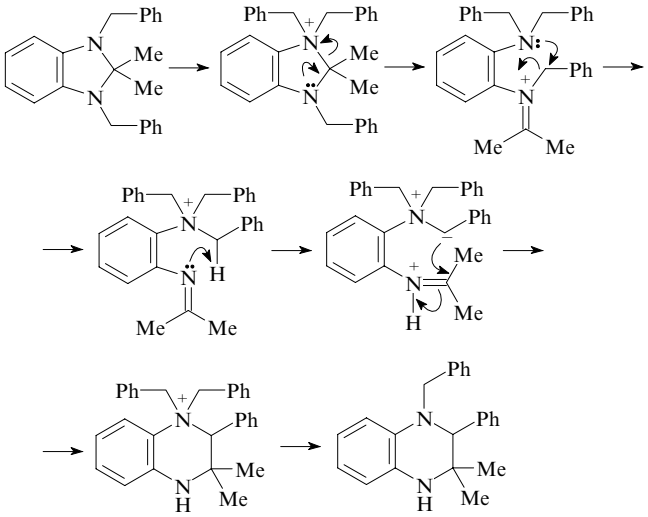
Path s. Benzimidazole containing, like benzofuroxan, two N atoms in positions 1 and 3 of the five-membered ring can also serve as the initial reagent in the quinoxaline synthesis. Thermolysis of 2,2-dialkyldihydrobenzimidazoles **32** was accompanied by their rearrangement to isomeric tetrahydroquinoxalines formed in low yields, which were isolated by column chromatography.[119]



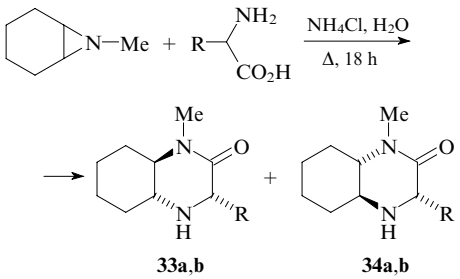
32

R^1 = Me: R^2 = Me (11%), Et (13%), Pr^n (10%);
$R^1–R^2$ = $(CH_2)_5$ (16%), $(CH_2)_4$ (14%).

The authors proposed a plausible mechanism for this reaction (shown using the dimethyl derivative as the example); however, they did not discuss what happened to the molecule that provides the benzyl cation in the first step. Note that the formation of the final product can be represented as a thermal isomerization of benzimidazole to quinoxaline without participation of the benzyl cation.



Path t. A quinoxaline-related system can emerge upon the expansion of not only five- but also a three-membered heterocycle. New *trans*-perhydroquinoxalin-2(1*H*)-ones were prepared by the reaction of aziridines with α-amino acids as a result of aziridine ring cleavage and pyrazine ring cleavage.[120] Note that the reaction is non-stereoselective and gives a mixture of products **33** and **34**.



33a,**b** **34a**,**b**

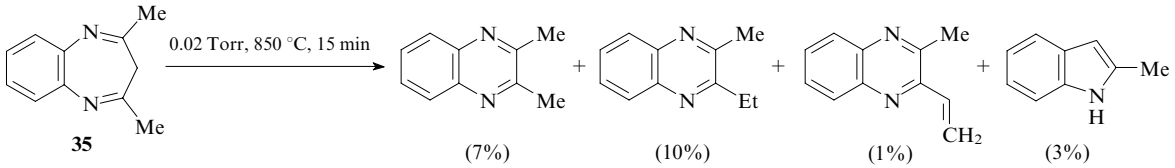
R = Me (**a**), Bn (**b**).

Compound	Yield (%)
33a	27
33b	26
34a	25
34b	23

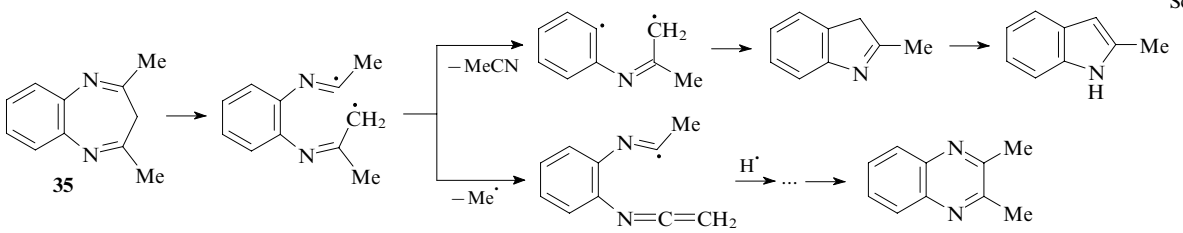
Path u. A quinoxaline ring can be obtained not only upon small ring expansion but also upon large ring contraction.

The gas-phase pyrolysis of 1,5-benzodiazepine **35** at 800–850 °C affords a mixture of heterocyclic products in low yields (Scheme 4).[121]

Scheme 4

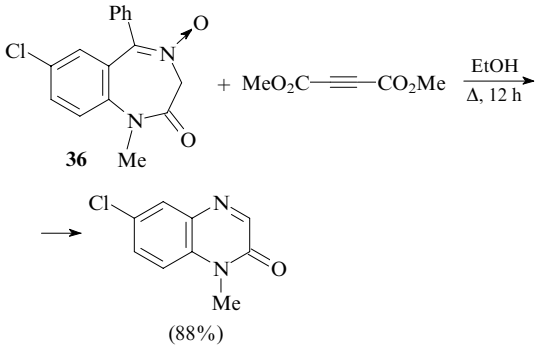


Scheme 5

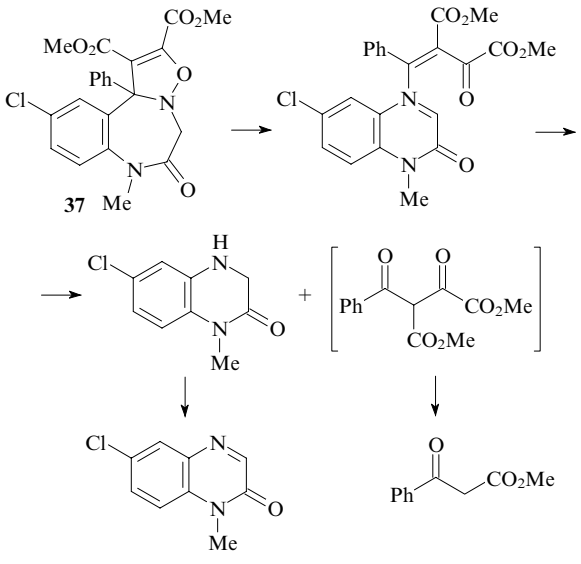


Only indole and quinoxaline derivatives could be identified in the mixture of pyrolysis products. The authors believe [121] that the formation of products is caused by homolytic cleavage of the benzodiazepine C(2)–C(3) bond to give imidoyl–azaallyl biradical pair. The β-cleavage of the imidoyl affords acetonitrile and the phenyl–azaallyl radical pair, which cyclizes to indole. The formation of dimethylquinoxaline is accompanied by loss of the C(1) fragment, possibly, upon β-cleavage of the initially formed biradical (Scheme 5).

Path v. 1,4-Benzodiazepine derivatives react with 1,3-dipolar reagents also with a rearrangement giving rise to quinoxalines in high yields. Thus *N*-oxide **36** undergoes 1,3-dipolar cycloaddition to dimethyl acetylenedicarboxylate in boiling ethanol for 12 h to be converted to quinoxaline rather than isoxazolidinobenzodiazepine.[122]



The authors assumed that the adducts formed in the 1,3-cycloaddition undergo the Beckmann rearrangement under the reaction conditions to give quinoxalines. Under mild conditions (stirring in EtOH or CH_2Cl_2 at room temperature for 3 days) adducts **37** and the rearrangement product



with the same molecular formula are obtained in good yields. The latter compound is also produced on short-term heating of the adduct in ethanol. On long-term heating in ethanol, both intermediates are converted to quinoxaline with evolution of methyl and ethyl benzoylacetates, which were detected by chromatography.

The information presented in the review demonstrates the application of a broad range of modern synthetic methods of organic chemistry for the preparation of diverse quinoxaline derivatives. The subsequent studies in this area will obviously be aimed at the synthesis and elucidation of useful properties of more complex quinoxaline derivatives and its fused analogues, which, in turn, will stimulate the development of convenient methods for their synthesis. We hope that this review will help synthetic chemists working in this field to achieve results on targeted synthesis of quinoxaline derivatives with a specified structure and will also attract attention of researchers working in other areas.

References

1. R Sarges, H R Howard, R G Browne, L A Lebel, P A Seymour, B Koe *J. Med. Chem.* **33** 2240 (1990)
2. A Gomtsyan, E K Bayburt, R G Schmidt, G Z Zheng, R J Perner, S Didomenico, J R Koenig, S Turner, T Jinkerson, I Drizin, S M Hannick, B S Macri, H A McDonald, P Honore, C T Wismer, K C Marsh, J Wetter, K D Stewart, T Oie, M F Jarvis, C S Surowy, C R Faltynek, C-H Lee *J. Med. Chem.* **48** 744 (2005)
3. A Jaso, B Zarranz, I Aldana, A Monge *J. Med. Chem.* **48** 2019 (2005)
4. L E Seitz, W J Suling, R C Reynolds *J. Med. Chem.* **45** 5604 (2002)
5. A Dell, D H Williams, H R Morris, G A Smith, J Feeney, G C K Roberts *J. Am. Chem. Soc.* **97** 2497 (1975)
6. K R J Thomas, M Velusamy, J T Lin, C-H Chuen, Y-T Tao *Chem. Mater.* **17** 1860 (2005)
7. S Dailey, W J Feast, R J Peace, I C Sage, S Till, E L Wood *J. Mater. Chem.* **11** 2239 (2001)
8. J L Sessler, H Maeda, T Mizuno, V M Lynch, H Furuta *Chem. Commun.* 862 (2002)
9. J L Sessler, H Maeda, T Mizuno, V M Lynch, H Furuta *J. Am. Chem. Soc.* **124** 13474 (2002)
10. P P Castro, G Zhao, G A Masangkay, C Hernandez, L M Gutierrez-Tunstad *Org. Lett.* **6** 333 (2004)
11. K Toshima, R Takano, T Ozawa, S Matsumura *Chem. Commun.* 212 (2002)
12. L S Hegedus, M M Greenberg, J J Wendling, J P Bullock *J. Org. Chem.* **68** 4179 (2003)
13. *Heterocyclic Compounds. Six-membered Heterocycles Containing Two Hetero atoms and Their Benzo Derivatives* Vol. 6 (Ed. R C Elderfield) (New York: Wiley, 1957)
14. G W H Cheeseman, R F Cookson *Condensed Pyrazines* (New York, Chichester, Brisbane, Toronto: Wiley, 1979)
15. G Körner *Ber. Dtsch. Chem. Ges.* **17** (Referates) 572 (1884)
16. O Hinsberg *Ber. Dtsch. Chem. Ges.* **17** 318 (1884)

17. X Hui, J Desrivot, C Bories, P M Loiseau, X Franck, R Hocquemiller, B Figadére *Bioorg. Med. Chem. Lett.* **16** 815 (2006)
18. C Lovelette, W S Barnes, J H Weisburger, G M Williams *J. Agric. Food Chem.* **35** 912 (1987)
19. N J Leonard, J H Boyer *J. Am. Chem. Soc.* **72** 2980 (1950)
20. N Ocal, Z Turgut, S Kaban *J. Heterocycl. Chem.* **35** 1349 (1998)
21. V B Jigajinni, P N Preston, V K Shah, S W Simpson, I Soutar, N J Stewart *High Perform. Polym.* **5** 239 (1993)
22. G J Kirkovits, R S Zimmerman, M T Huggins, V M Lynch, J L Sessler *Eur. J. Org. Chem.* 3768 (2002)
23. D Aldakov, P Anzenbacher *Chem. Commun.* 1394 (2003)
24. D J Klein, D A Modarelli, F W Harris *Macromolecules* **34** 2427 (2001)
25. S A Fakhri, B H Yousefi *Acta Chim. Slov.* **47** 317 (2000)
26. M J Howard, F R Heirtzler, S I G Dias *J. Org. Chem.* **73** 2548 (2008)
27. I McCort, S Ballereau, A Duréault, J-C Depezay *Tetrahedron* **58** 8947 (2002)
28. Z Szgkelyhidi, J Pató, F Wáczek, P Bánhegyi, B Hegymegi-Barakonyi, D Erös, G Mészáros, F Hollósy, D Hafenbradl, S Obert, B Klebl, G Kéri, L Öfi *Bioorg. Med. Chem. Lett.* **15** 3241 (2005)
29. P Zanello, M Fontani, S Z Ahmed, C Glidewell *Polyhedron* **17** 4155 (1998)
30. G V Reddy, V V V N S Rama Rao, D Maitraie, S Ravikanth, R Yadla, S N Reddy, B Narsaiah, P S Rao *J. Fluorine Chem.* **124** 203 (2003)
31. M A Glomb, C Pfahler *Carbohydr. Res.* **329** 515 (2000)
32. R M Adlington, J E Baldwin, D Catterick, G J Pritchard *J. Chem. Soc., Perkin Trans. 1* 299 (2000)
33. R M Adlington, J E Baldwin, D Catterick, G J Pritchard *J. Chem. Soc., Perkin Trans. 1* 668 (2001)
34. V O Koz'minykh, O A Sof'ina, N M Igidov, E N Koz'minykh *Zh. Org. Khim.* **37** 1719 (2001) [a]
35. R Touzani, T Ben-Hadda, S Elkadiri, A Ramdani, O Maury, H Le Bozec, L Toupet, P H Dixneuf *New J. Chem.* **25** 391 (2001)
36. T Fonseca, B Gigante, M M Marques, T L Gilchrist, E Clercq *Bioorg. Med. Chem.* **12** 103 (2004)
37. R S Bhosale, S R Sarda, S S Ardhapure, W N Jadhav, S R Bhusare, R P Pawar *Tetrahedron Lett.* **46** 7183 (2005)
38. S V More, M N V Sastry, C-C Wang, C-F Yao *Tetrahedron Lett.* **46** 6345 (2005)
39. Z Zhao, D D Wisnoski, S E Wolkenberg, W H Leister, Y Wang, C W Lindsey *Tetrahedron Lett.* **45** 4873 (2004)
40. P Darkins, M Groarke, A McKervey, H M Moncrieff, N McCarthy, M Nieuwenhuyzen *J. Chem. Soc., Perkin Trans. 1* 381 (2000)
41. W-S Chung, J-H Liu *Chem. Commun.* 205 (1997)
42. V A Mamedov, V L Polushina, F F Mertsalova, I A Nuretdinov, A Kh Plyamovatyi *Izv. Akad. Nauk SSSR, Ser. Khim.* 1660 (1991) [b]
43. A Staszewska, P Stefanowicz, Z Szewczuk *Tetrahedron Lett.* **46** 5525 (2005)
44. J Jaung, M Matsuoka, K Fukunishi *J. Chem. Res. (S)* 284 (1998)
45. J J Li, K G Carson, B K Trivedi, W S Yue, Q Ye, R A Glynn, S R Millerv, D T Connor, B D Roth, J R Luly, J E Low, D J Heilig, W Yang, S Qin, S Hunt *Bioorg. Med. Chem.* **11** 3777 (2003)
46. J J Li, W S Yue *Tetrahedron Lett.* **40** 4507 (1999)
47. S-K Lin *Molecules* **1** 37 (1996)
48. S S Nikam, J J Cordon, D F Ortwine, T H Heimbach, A C Blackburn, M G Vartanian, C B Nelson, R D Schwarz, P A Boxer, M F Rafferty *J. Med. Chem.* **42** 2266 (1999)
49. B Loev, J H Musser, R E Brown, H Jones, R Kahen, F-C Huang, A Khandwala, P Sonnino-Goldman, M J Leibovitz *J. Med. Chem.* **28** 363 (1985)
50. C Gönczi, E Csikós, B Podányi, T Nusser, Z Böcskey, I Hermecz *J. Chem. Soc., Perkin Trans. 1* 1417 (2000)
51. É Csikós, C Gönczi, B Podányi, G Tóth, I Hermecz *J. Chem. Soc., Perkin Trans. 1* 1789 (1999)
52. S Gürsoy, M Koçak, Ö Bekaroğlu *Monatsh. Chem.* **131** 181 (2000)
53. K J Duffy, C Haltiwanger, Y Huang, A Konialian-Beck, J I Luengo *Tetrahedron Lett.* **39** 8017 (1998)
54. Y J L'Italien, C K Banks *J. Am. Chem. Soc.* **75** 3246 (1951)
55. K S Bozdyreva, I V Smirnova, A N Maslivets *Zh. Org. Khim.* **41** 1101 (2005) [a]
56. I A Tolmacheva, I V Mashevskaya, A N Maslivets *Zh. Org. Khim.* **38** 303 (2002) [a]
57. J Gris, R Glisoni, L Fabian, B Fernandez, A G Moglioni *Tetrahedron Lett.* **49** 1053 (2008)
58. V A Mamedov, I A Nuretdinov, F G Sibgatullina *Izv. Akad. Nauk SSSR, Ser. Khim.* 1412 (1989) [b]
59. D F Saifina, V R Ganieva, V A Mamedov *Zh. Org. Khim.* **45** 1252 (2009) [a]
60. D Sherman, J Kawakami, H-Y He, F Dhun, R Rios, H Liu, W Pan, Y-J Xu, S Hong, M Arbour, M Labelle, A J Duncton *Tetrahedron Lett.* **48** 8943 (2007)
61. S A Kotharkar, D B Shinde *Bioorg. Med. Chem.* **16** 6181 (2006)
62. P Puebla, Z Honores, M Medarde, E Caballero *J. Heterocycl. Chem.* **36** 1097 (1999)
63. B Insuasty, F Fernandez, J Quiroga, R Moreno *J. Heterocycl. Chem.* **35** 977 (1998)
64. B Das, K Venkaeswarlu, K Suneel, A Majhi *Tetrahedron Lett.* **48** 5371 (2007)
65. K S Kim, L Qian, E Bird, K E J Dickinson, S Moreland, T R Schaeffer, T L Waldron, C L Delaney, H N Weller, A V Miller *J. Med. Chem.* **36** 2335 (1993)
66. P Haldar, B Dutta, J Guin, J K Ray *Tetrahedron Lett.* **48** 5855 (2007)
67. S V Kurbatov, N I Vikrishchuk, V I Simakov, D N Kuznetsov, Yu A Zhdanov, L P Olekhnovich *Zh. Obshch. Khim.* **71** 1012 (2001) [c]
68. Z Wu, N J Ede *Tetrahedron Lett.* **42** 8115 (2001)
69. E C Taylor, C A Maryanoff, J S Skotnicki *J. Org. Chem.* **45** 2512 (1980)
70. K Woydowski, B Ziemer, J Liebscher *Tetrahedron: Asymmetry* **9** 1231 (1998)
71. M K Nasar, R R Kumar, S Perumal *Tetrahedron Lett.* **48** 2155 (2007)
72. S Antoniotti, E Dunach *Tetrahedron Lett.* **43** 3971 (2002)
73. V A Mamedov, L V Krokhina, A V Il'yasov *Khim. Geterotsikl. Soedin.* 1105 (1994) [d]
74. M Mateu, A S Capilla, Y Harrak, M D Pujol *Tetrahedron* **58** 5241 (2002)
75. D Aparicio, O A Attanasi, P Filippone, R Ignacio, S Lillini, F Mantellini, F Palacios, J M de los Santos *J. Org. Chem.* **71** 5897 (2006)
76. V Nair, R Dhanya, C Rajesh, M M Bhadbhade, K Manoj *Org. Lett.* **6** 4743 (2004)
77. N Kawahara, T Shimamori, T Itoh, H Takayanagi, H Ogura *Chem. Pharm. Bull.* **35** 457 (1987)
78. I Ya Postovskii, N G Koshel' *Khim. Geterotsikl. Soedin.* 981 (1970) [d]
79. N Nami, B Neumuller, M M Heravi, M Haghdadi *Mendeleev Commun.* **18** 153 (2008)
80. S A Raw, C D Wilfred, R J K Taylor *Org. Biomol. Chem.* **2** 788 (2004)
81. S A Raw, C D Wilfred, R J K Taylor *Chem. Commun.* 2286 (2003)
82. C S Cho, W X Ren, S C Shim *Tetrahedron Lett.* **48** 4665 (2007)
83. M C Venuti *Synthesis* 61 (1982)
84. A Amer, M Ventura, H Zimmer *J. Heterocycl. Chem.* **20** 359 (1983)
85. N Vinot, C Bellec, P Maitte *J. Heterocycl. Chem.* **20** 1645 (1983)
86. T M V D Pinho e Melo, C S J Lopes, A M Rocha Gonsalves, A M Beja, J A Paixao, M R Silva, L A da Veiga *J. Org. Chem.* **67** 66 (2002)
87. F E King, J W Clark-Lewis *J. Chem. Soc.* 172 (1953)
88. V A Mamedov, A A Kalinin, A T Gubaidullin, I A Litvinov, Ya A Levin *Khim. Geterotsikl. Soedin.* 1704 (2002) [d]
89. V A Mamedov, D F Saifina, E A Berdnikov *Khim. Geterotsikl. Soedin.* 574 (2007) [d]

90. A A Kalinin, V A Mamedov, Ya A Levin *Khim. Geterotsikl. Soedin.* 995 (2000) [d]
91. V A Mamedov, A A Kalinin, A T Gubaidullin, A V Chernova, I A Litvinov, Ya A Levin, R R Shagidullin *Izv. Akad. Nauk, Ser. Khim.* 159 (2004) [b]
92. A A Kalinin, O G Isaikina, V A Mamedov *Khim. Geterotsikl. Soedin.* 1539 (2007) [d]
93. V A Mamedov, D F Saifina, I Kh Rizvanov, A T Gubaidullin *Tetrahedron Lett.* **49** 4644 (2008)
94. V Balandina, V Mamedov, X Franck, B Figadere, Sh Latypov *Tetrahedron Lett.* **45** 4003 (2004)
95. V A Mamedov, A A Kalinin, A T Gubaidullin, E A Gorbunova, I A Litvinov *Zh. Org. Khim.* **42** 1543 (2006) [a]
96. B J E Reich, A K Justice, B T Beckstead, J H Reibenspies, S A Miller *J. Org. Chem.* **69** 1357 (2004)
97. G Heinisch, B Mutuszczak, K Mereiter *Heterocycles* **38** 2081 (1994)
98. R Mukhopadhyay, N G Kundu *Tetrahedron Lett.* **41** 9927 (2000)
99. M Krasavin, V Parchinsky *Synlett* 645 (2008)
100. M Krasavin, S Shkavrov, V Parchinsky, K Bukhryakov *J. Org. Chem.* **74** 2627 (2009)
101. P A Cafiero, C S French, M D McFarlane, R K Mackie, D M Smith *J. Chem. Soc., Perkin Trans. 1* 1375 (1997)
102. J M Wallace, B C G Soderberg, J Tamariz, N G Akhmedov, M T Hurley *Tetrahedron* **64** 9675 (2008)
103. A Mazurov *Tetrahedron Lett.* **41** 7 (2000)
104. C Venkatesh, B Singh, P K Mahata, H Ila, H Junjappa *Org. Lett.* **7** 2169 (2005)
105. S de Castro, R Chicharro, V J Arán *J. Chem. Soc., Perkin Trans. 1* 790 (2002)
106. V K Tandon, D B Yadav, H K Maurya, A K Chaturvedi, P K Shukla *Bioorg. Med. Chem.* **14** 6120 (2006)
107. S Dixon, X Wang, K S Lam, M J Kurth *Tetrahedron Lett.* **46** 7443 (2005)
108. D Legroux, J-P Schoeni, C Pont, J-P Fleury *Helv. Chim. Acta* **70** 187 (1987)
109. N P Xekoukoulotakis, C P Hadjiantoniou-Maroulis, A J Maroulis *Tetrahedron Lett.* **41** 10299 (2000)
110. H McNab *J. Chem. Soc., Perkin Trans. 1* 1941 (1982)
111. H McNab *J. Chem. Soc., Chem. Commun.* 422 (1980)
112. B Zarranz, A Jaso, I Aldana, A Monge *Bioorg. Med. Chem.* **11** 2149 (2003)
113. H Cerecetto, E Dias, R Di Maio, M Gonzalez, S Pacce, P Saenz, G Seoane *J. Agric. Food Chem.* **48** 2995 (2000)
114. K M Amin, M M F Ismail, E Noaman, D H Solimanb, Y A Ammard *Bioorg. Med. Chem.* **14** 6917 (2006)
115. A Atfah, J Hill *J. Chem. Soc., Perkin Trans. 1* 221 (1989)
116. P M Panasyuk, S F Mel'nikova, I V Tselinskii *Zh. Org. Khim.* **37** 937 (2001) [a]
117. P M Panasyuk, S F Mel'nikova, I V Tselinskii *Zh. Org. Khim.* **37** 938 (2001) [a]
118. T Takabatake, M Hasegawa *J. Heterocycl. Chem.* **24** 529 (1987)
119. G M Reddy, P L Prasunamba, P S N Reddy *Tetrahedron Lett.* **37** 3355 (1996)
120. D C Rees *J. Heterocycl. Chem.* **24** 1297 (1987)
121. C Despinoy, D Lloyd, H McNab, D Reed *Tetrahedron* **54** 9667 (1998)
122. T Miyadera, Y Kawano, T Hata, C Tamura, R Tachikawa *Chem. Pharm. Bull.* **25** 3247 (1977)

[a] — *Russ. J. Org. Chem. (Engl. Transl.)*
[b] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*
[c] — *Russ. J. Gen. Chem. (Engl. Transl.)*
[d] — *Chem. Heterocycl. Compd. (Engl. Transl.)*