Recent advances in the synthesis of benzimidazol(on)es *via* rearrangements of quinoxalin(on)es

Vakhid A. Mamedov*

This is the first review describing all the quinoxaline–benzimidazole rearrangements as a whole and the new quinoxalinone–benzimidazol(on)e rearrangements in particular when exposed to nucleophilic rearrangements for the synthesis of various biheterocyclic motifs. The scope of the rearrangements is illustrated by way of numerous examples of their application, and in doing so, the review contains over 131 references and covers all of the literature, from the first report of the rearrangement of 2,3-diphenylquinoxaline by Ogg and Bergstrom in 1931 up to more recent examples in the past few years. The mechanisms for the selected transformations are also discussed.

1 Introduction

Benzimidazole, firstly described by Hobrecker in 1872,[1] is an important privileged heterocyclic motif[2–5] and one of the most widely investigated scaffolds by synthetic chemists because of

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center of the Russian Academy of Sciences, Arbuzov str. 8, Kazan, 420088, Russian Federation. E-mail: mamedov@iopc.ru

Vakhid A. Mamedov graduated from the Azerbaijan State University in Baku (1981). After working for few years as research scientist at the Institutes of the Azerbaijan Academy of Sciences he moved (1985) to the A. E. Arbuzov Institute of Organic and Physical Chemistry (IOPC), Kazan Scientific Centre Russian Academy of Sciences, where he obtained his Ph.D. (1989) with Professor Il'dus A. Nuretdinov, and D.Sc. (1999) degrees in Chemistry collaborate with Professors Yakov A. Levin and Eugeniy A. Berdnikov. He spent his postdoctoral fellowship (1997–1998) with Professor Sadao Tsuboi at the Okayama University (Japan), working on synthetic approaches to the C-13 side chain of paclitaxel (Taxol) and docetaxel (Taxotere). He became head of the laboratory of the Chemistry of Heterocyclic Compounds in IOPC in 2002. He authored over 170 papers. Mamedov's research interests focus on organic synthesis methodology and development of new schemes for tandem transformations for synthesizing diversity-oriented heterocyclic systems.

its medicinal importance. The benzimidazole scaffold acts as an important class of heterocyclic compounds with a wide range of biological properties.[6] Benzimidazole derivatives are structural isosteres of naturally occurring nucleotides, which allow them to easily interact with the biopolymers of the living systems and different kinds of biological activity have been obtained. 2-Aminobenzimidazoles proved useful for acid/base catalysis and can substitute guanidinium groups in receptor molecules designed as phosphoryl transfer catalysts.[7] Some 2-amino-benzimidazoles displayed an appreciable antimicrobial effect and their corresponding carbamate derivatives have been synthesized for their significant antifilarial activity *in vivo*.[8] As to their high affinity towards a variety of enzymes and protein receptors, they could be considered as pivotal structures in drug design.[9] The optimization of benzimidazole-based structures has resulted in marketed drugs, *e.g.* omeprazole[10] and pimobendan[11] which are used as therapeutic agents in the treatment of peptic ulcer and congestive heart failure respectively. Benzimidazole derivatives proved of great interest because of their wide range of biological functions[12] and pharmacological applications.[13] They are an integral part of various clinical medicines[14] as well, for example 2-substituted benzimidazole, esomeprazole[15] is an anti-ulcer drug and albendazole[16] is used to treat parasitic diseases, whereas, 1,2-substituted benzimidazole, astemizole is an antihistamine drug (Fig. 1).[17] Many derivatives of benzimidazoles are well known for their antimicrobial,[18] anthelmintic,[19] antiviral,[20] and antifungal[21] activities. The antifungal agent benomyl was first reported as a fungicide against a wide range of agricultural fungal diseases.[22] Later on, it proved to be a potent antiproliferative agent against the Hela cancer cell line and could be partly used in cancer chemotherapy.[23] Benzimidazole derivatives with ester groups on the benzene ring possessed antifungal, insecticidal and herbicidal activities.[24] Besides, many dichlorobenzimidazoles appeared

very effective against methicillin resistant *Staphylococcus aureus* (MRSA).[25] Since 1985, benzimidazole containing compounds have been reported as well known anticancer agents.[26] The role of mammalian DNA topoisomerases as molecular targets for anticancer drugs received appreciation. Some benzimidazoles have been reported as topoisomerase inhibitors *e.g.* Hoechst 33258 and Hoechst 33342 (Fig. 1).[27]

Some widely used anticancer drugs such as RAF265 (CHIR-265; Novartis Pharmaceuticals, Basel, Switzerland) and AZD6244 (ARRY-142886; AstraZeneca, London, England) are known to contain a benzimidazole moiety. RAF265 resulted in the reduction of tumor cell growth and in tumor cell apoptosis.[28] Compound AZD6244 suppresses the growth of melanoma cells through the induction of cytostasis.[29] 2-Aryl-benzimidazole moiety proved to be a pharmacophore for a new class of DNA intercalating agents.[30] The importance of naphthalene benzimidazole compounds as antioxidants on hepatic cytochrome has been explored since 1997.[31] On the other hand, the antiviral activity of 5-chloro and 5,6-dichloro-2-substituted benzimidazole derivatives against several viruses, *e.g.* influenza, human cytomegalovirus, hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency retrovirus (HIV-1) was reported.[32] These compounds proved to be anticancer agents against breast and prostate cancer cell lines[33] as well as potential topoisomerase II inhibitors.[34] In 2010, a new series of 2-substituted benzimidazole derivatives with a 5-chloro or 5-underivatized carboxylic acid group exhibited antitumor activity against hepatocellular carcinoma (HEPG2), human breast adenocarcinoma (MCF7) and human colon carcinoma (HCT 116) cell lines.[35]

Telmisartan is a potent angiotensin II receptor antagonist in the treatment of essential hypertension.[36] It is one of the most
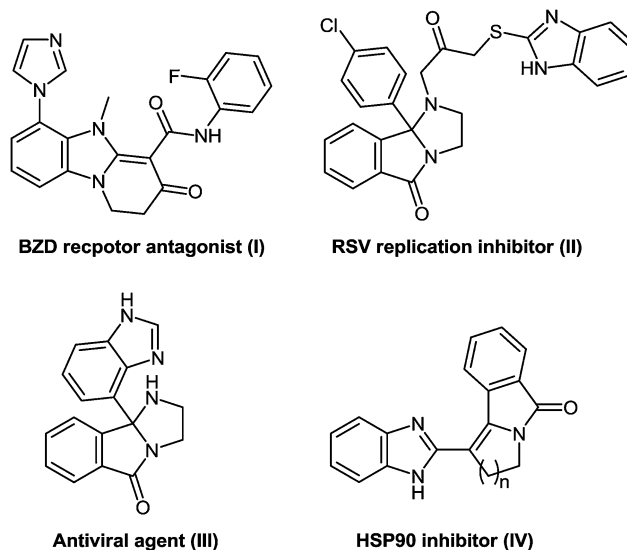
Fig. 2 Biologically active bis-heterocyclic compounds.

efficient drugs in its class, boasting the longest half-life, a high protein binding affinity, and a low daily dosage.[37] The drug is currently marketed under the brand name of Micardis and provides additional benefits against vascular and renal damage caused by diabetes and cardiovascular disease.[38]

Bis-heterocyclic compounds offer better binding opportunities with a enzyme active site due to its three dimensional special arrangement and consequently possess many intrinsic biological properties.[39] In particularly, bis-heterocycles comprising pyridobenzimidazoles (I) are ligands for the BZD site on GABA-A receptors and are therefore used for the
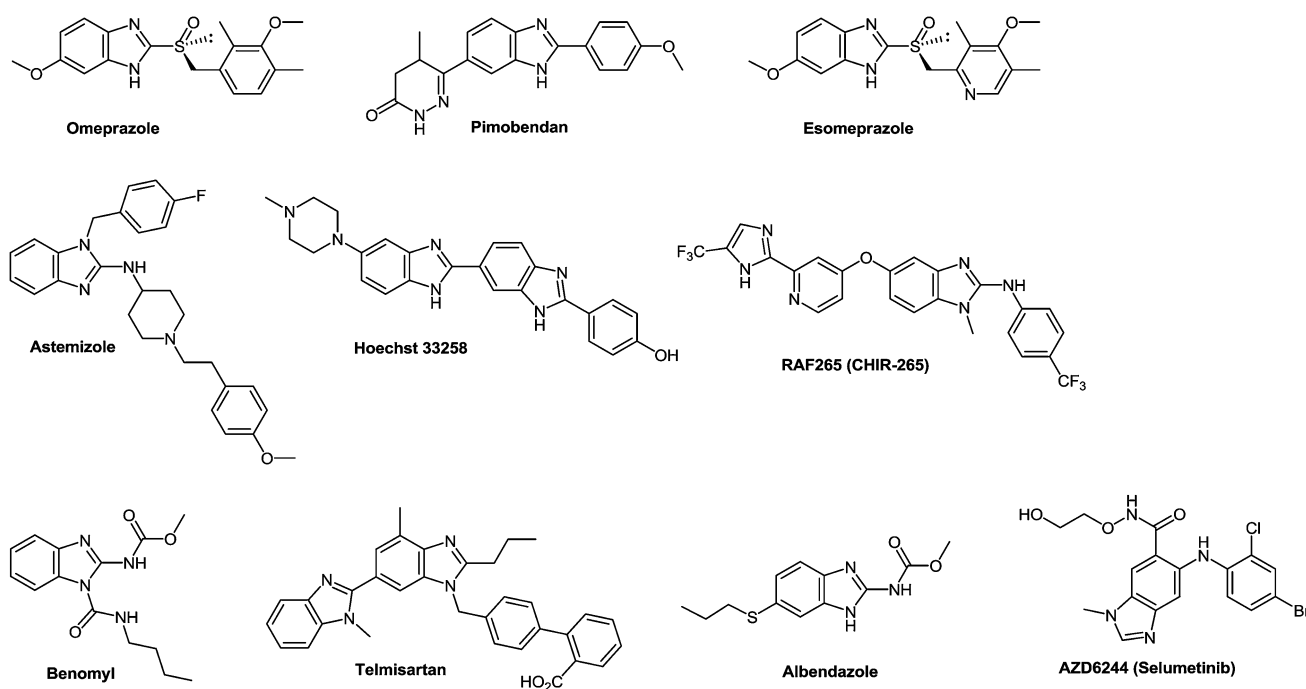
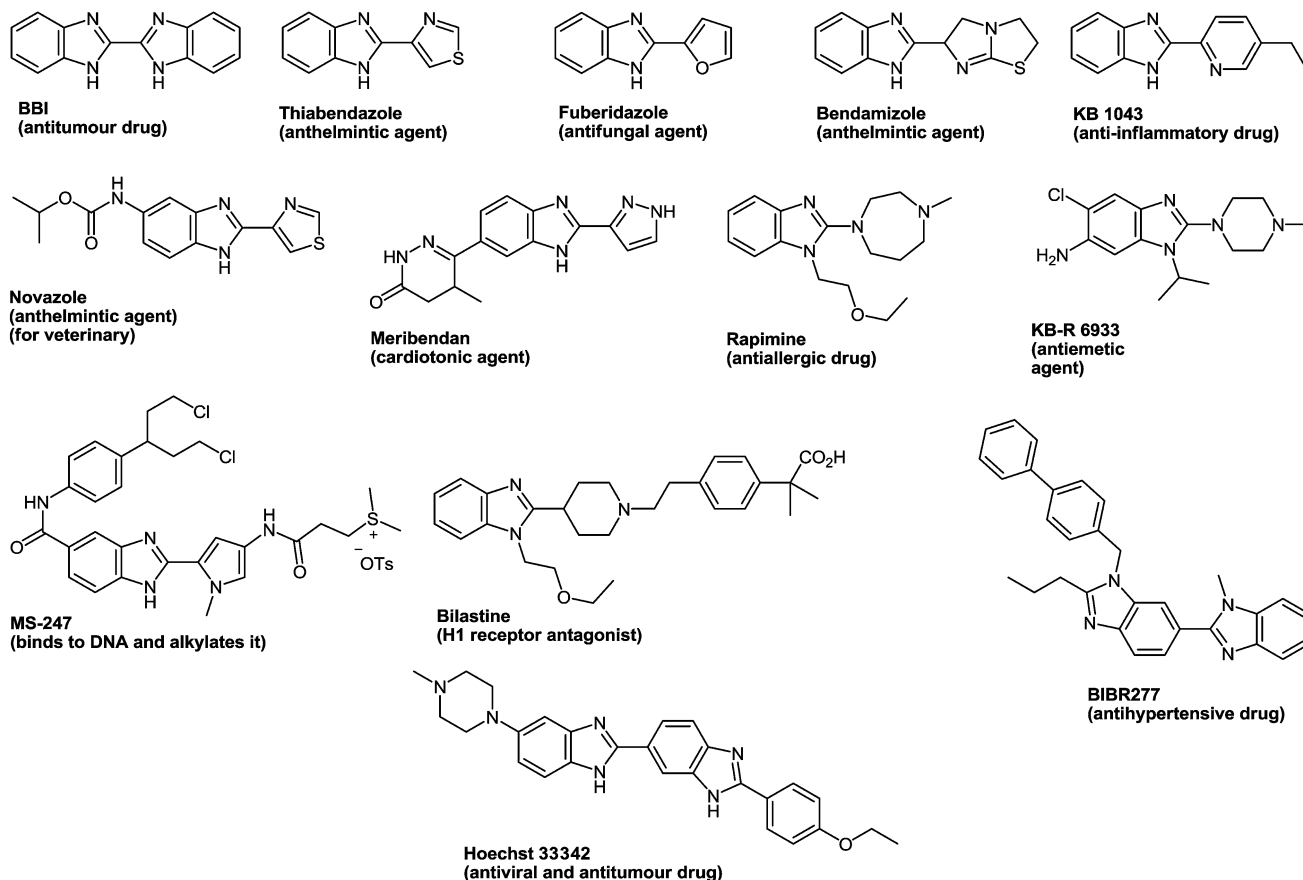**Fig. 1** Clinically used benzimidazoles from the current literature.

BBI
(antitumour drug)

Thiabendazole
(anthelmintic agent)

Fuberidazole
(antifungal agent)

Bendamizole
(anthelmintic agent)

KB 1043
(anti-inflammatory drug)

Novazole
(anthelmintic agent)
(for veterinary)

Meribendan
(cardiotonic agent)

Rapimine
(antiallergic drug)

KB-R 6933
(antiemetic agent)

MS-247
(binds to DNA and alkylates it)

Bilastine
(H1 receptor antagonist)

BIBR277
(antihypertensive drug)

Hoechst 33342
(antiviral and antitumour drug)

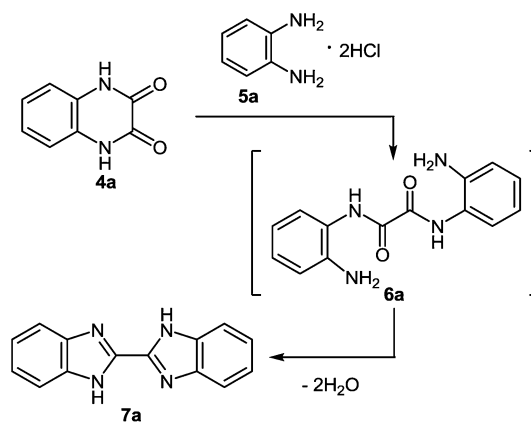**Fig. 3** Clinically used hetarylbenzimidazoles from the drug reference books by Mashkovskiy[43] and Negwer.[44]
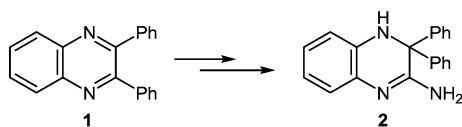
Scheme 1 Proposed benzyl → benzilic rearrangement.
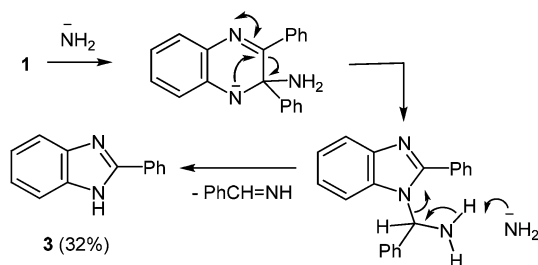
Scheme 2 Proposed mechanism of the rearrangement.

Scheme 3 Synthesis of 2,2′-bibenzimidazole.

treatment of disorders of the central nervous system including convulsion such as epileptic seizures, anxiety, depression, muscular spasm, and attention deficit hyperactivity disorder (Fig. 2).[40] Polycyclic bis-heterocycles with imidazopyridine or imidazoisoindole moieties (**II**) prove the basic structural frameworks of potent inhibitors of respiratory syncytical virus while some imidazoisoindoles (**III**) exhibit antiviral activity.[41]

Benzimidazoles in combination with the pyrrolo-isoidolones (**IV**) exhibit anticancer activity *via* the inhibition of the ATPase-type catalytic activity of the Hsp90 chaperone protein.[42]

The drug reference books by Mashkovskiy[43] and Negwer[44] comprise 92 benzimidazole derivatives used in medicine. However, only 13 of them (Fig. 3) include other heterocyclic rings directly connected with the benzimidazole system. This is apparently due to the fact that such compounds are mostly inaccessible. The analysis of the literary data shows that the
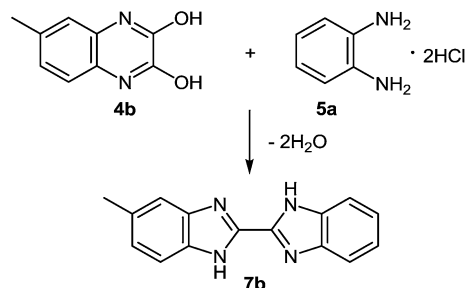
Scheme 4 Synthesis of an unsymmetrically substituted 2,2′-bibenzimidazole.

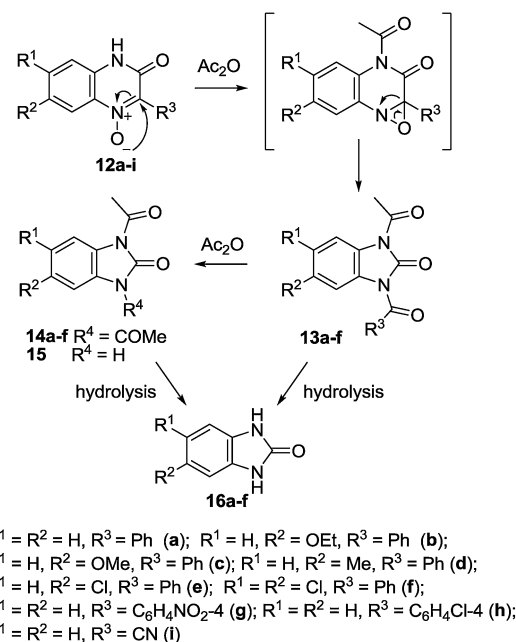methods of the synthesis of such compounds involve many steps, *i.e.* they are laborious, and the total yields of products never exceed 20% ± 25%.

There are two classical methods for benzimidazole synthesis, *i.e.* coupling of 1,2-diaminobenzenes (1,2-DABs) with carboxylic acids and of 1,2-DABs with aldehydes and ketones (the Phillips–Ladenburg and the Weidenhagen reactions, respectively).[45] The classical version of these reactions are limited by the use of high temperatures (sometimes, 250–300 °C) and by the low yields of products.[46] Actually, all the methods of benzimidazole synthesis which currently exist represent modifications of the reactions mentioned.[47]

The analysis of the data published has shown that the main drawback of these methods involve the impossibility to use them for synthesizing various types of benzimidazole derivatives. For example, it is no so easy task to enter any given heterocycle in position 2 of benzimidazole ring using of these methods. In addition to the methods mentioned, examples of the formation of benzimidazole derivatives by rearrangement of heterocyclic systems have been documented. Despite the fact that the publications on these reactions are much fewer as compared with the Phillips–Ladenburg and Weidenhagen reactions, they are more diverse but unfortunately not general. The generalization and systematization of the data published on the rearrangement reactions will considerably facilitate the quest of organic chemists for the methods of the synthesis of benzimidazole derivatives inaccessible by the Phillips–Ladenburg and Weidenhagen reactions. In this review, we will focus
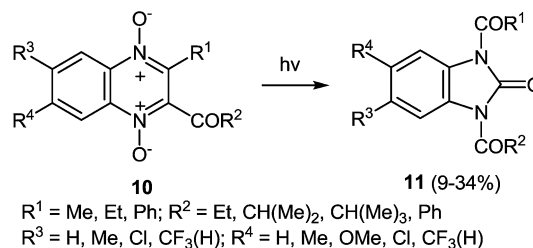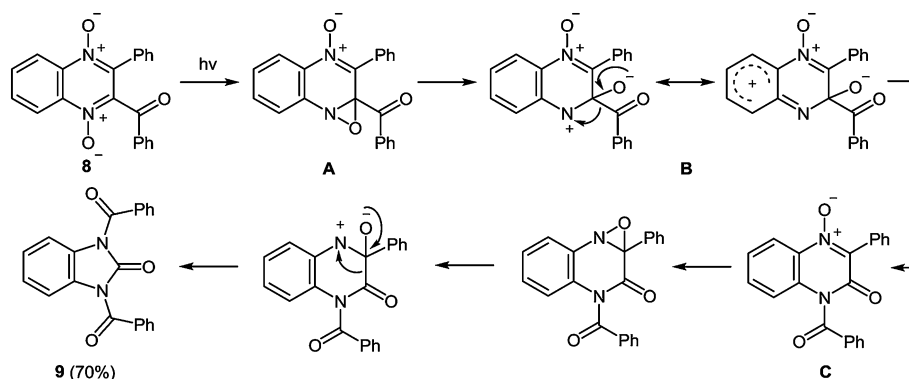
Scheme 6 Ring contraction of quinoxaline-di-*N*-oxide when exposed to light.

R^1 = Me, Et, Ph; R^2 = Et, CH(Me)$_2$, CH(Me)$_3$, Ph
R^3 = H, Me, Cl, CF$_3$(H); R^4 = H, Me, OMe, Cl, CF$_3$(H)

$R^1 = R^2$ = H, R^3 = Ph (**a**); R^1 = H, R^2 = OEt, R^3 = Ph (**b**);
R^1 = H, R^2 = OMe, R^3 = Ph (**c**); R^1 = H, R^2 = Me, R^3 = Ph (**d**);
R^1 = H, R^2 = Cl, R^3 = Ph (**e**); $R^1 = R^2$ = Cl, R^3 = Ph (**f**);
$R^1 = R^2$ = H, R^3 = C$_6$H$_4$NO$_2$-4 (**g**); $R^1 = R^2$ = H, R^3 = C$_6$H$_4$Cl-4 (**h**);
$R^1 = R^2$ = H, R^3 = CN (**i**)

Scheme 7 Proposed mechanism of the rearrangement of 3-hydroxy-2-*R*-quinoxaline-1-oxides when heated under reflux with acetic anhydride.

mainly on recent advances in the synthesis of benzimidazoles and benzimidazolones *via* new rearrangements of quinoxalinones when exposed to nucleophilic reagents and earlier works of importance will also be discussed.

Scheme 5 Proposed mechanism of the rearrangement of 2-benzoyl-3-phenylquinoxaline-di-*N*-oxide when exposed to sunlight.
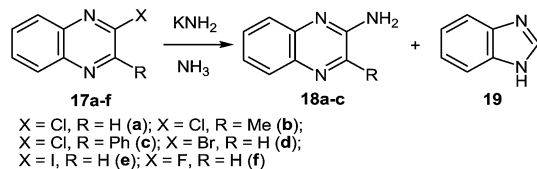
Scheme 8 The reaction of 2-haloquinoxalines with potassium amide.

X = Cl, R = H (**a**); X = Cl, R = Me (**b**); X = Cl, R = Ph (**c**); X = Br, R = H (**d**); X = I, R = H (**e**); X = F, R = H (**f**)

2 Synthesis of benzimidazoles

2.1 Rearrangement of quinoxalines (historical background)

First example. In 1931, Ogg and Bergstrom published a serious of papers aimed to demonstrate possible analogies between heterocyclic systems and their acyclic and alicyclic counterparts.[48] Quinoxaline, for example, was described as an "ammono glyoxal" and 2,3-diphenylquinoxaline **1** was considered to be the heterocyclic equivalent of benzyl. In an attempt to justify this hypothesis, the authors carried out the reaction of 2,3-diphenylquinoxaline **1** with potassium amide in liquid ammonia, anticipating a reaction similar to the benzyl → benzilic rearrangement, which would lead to the formation of 2,2-diphenyl-3-aminoquinoxaline **2** (Scheme 1). In fact the reaction lead to a new product – 2-phenylbenzimidazole **3** in an approximately 30% yield and the recovery of about 60% of unchanged 2,3-diphenylquinoxaline **1**.[49]

The formation of 2-phenylbenzimidazole **3** from 2,3-diphenylquinoxaline **1** and potassium amide involves the initial addition of an amide ion at the C(2) carbon atom, according to Ogg and Bergstrom had postulated, but with subsequent ring
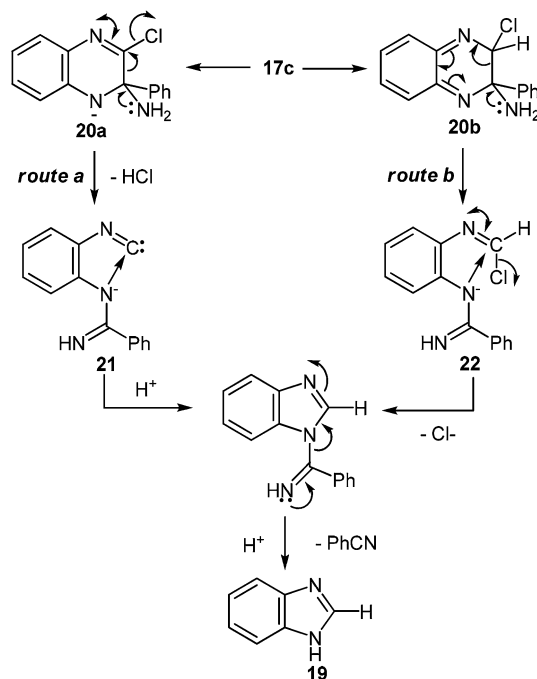
Scheme 9 Proposed mechanism of the rearrangement of 2-chloroquinoxalines into benzimidazole when exposed to potassium amide in liquid ammonia.
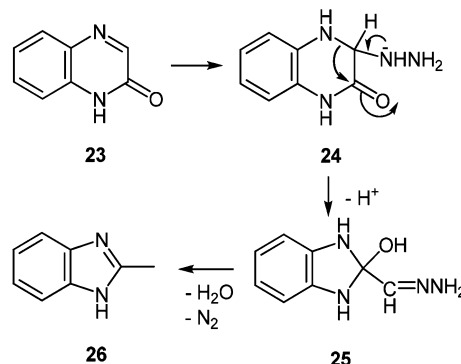

**Scheme 10** Hydrazinolysis of quinoxalin-2(1H)-one.
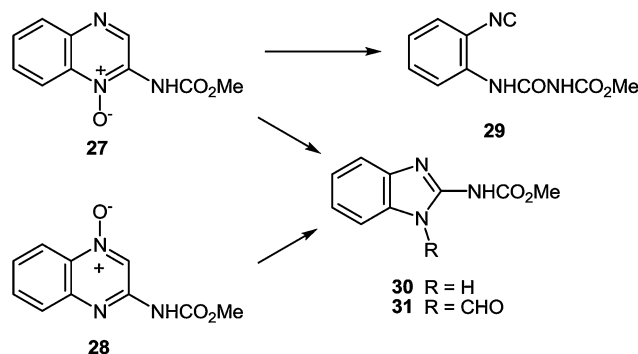
Scheme 11 Photolysis of the quinoxalin-2-ylcarbamate-N-oxides.

contraction, presumably with the elimination of benzylidenimine. This would result in the observed product **3**, rather than the phenyl migration of the benzyl acid-rearrangement type (Scheme 2).

Attempts to accomplish the ring contraction of 2,3-diphenylquinoxaline **1** to 2-phenylbenzimidazole **3** with other bases (KOH in H$_2$O or EtOH, NaOH in MeOH, NaH in toluene) were unsuccessful. The efficiency of KNH$_2$ appears to be specific.
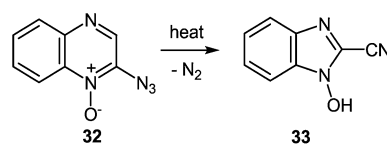

Scheme 12 Thermolysis of 2-azidoquinoxaline-1-oxide.

R = Ph, alkyl, alkoxy
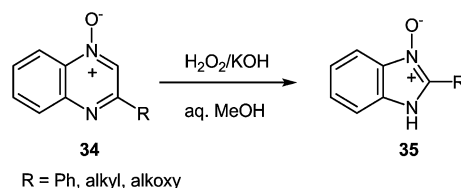
Scheme 13 Oxidation of quinoxaline-4-oxides.

Second example. Quinoxaline-2,3(1H,4H)-dione **4a** with 1,2-DAB dihydrochloride was shown to interact with the formation of the highly labile compound **6a**. As a result of "ammonolysis" this compound was spontaneously dehydrated and cyclised to form compound **7a** (Scheme 3).[50]
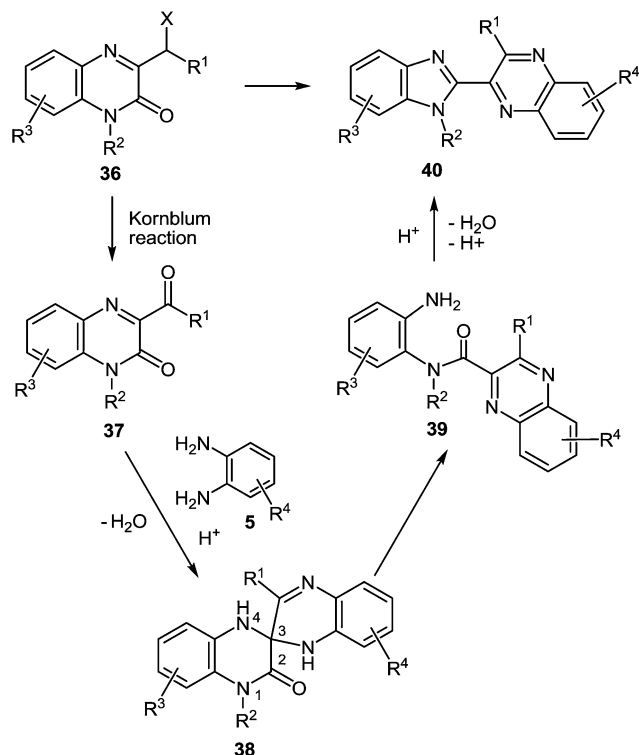
This reaction sequence has been used for the preparation of an unsymmetrically substituted 2,2′-bibenzimidazole, since 2,3-dihydroxy-6-methylquinoxaline **4b** and 1,2-DAB dihydrochloride reacted to form 5-methyl-2,2′-bibenzimidazole **7b** (Scheme 4).[50]

Third example. Exposure to sunlight of a methanolic solution of 2-benzoyl-3-phenylquinoxaline di-N-oxide **8** in a Pyrex flask for 12 h, resulted in the precipitation of 1,3-dibenzoyl-benzimidazolone **9** in 70% yield.[51] This rearrangement can be considered to involve two nitrone functions in one molecule. It is generally accepted that the irradiation of nitrones leads to oxazirane intermediates with further thermal and photochemical rearrangements.[52] Hence, it is reasonable to assume that, on irradiation, **8** is transformed into the isomeric oxazirane **A**. Considering the mechanism for the formation of **9** from oxazirane **A**, the authors favor intermediate **B** arising from the thermal heterolytic N–O bond fission of the oxirane ring, as suggested by Splitter and Calvin[52c] for the thermal decomposition of 2,3-diaryloxaziranes. In this case the positive charge on the nitrogen is delocalized by resonance with the adjacent aromatic ring, and then be assumed to undergo 1,2-benzoyl migration to an electron-deficient nitrogen **C**. The driving force for this shift is supplied by the negative charge on the oxygen (Scheme 5). When this mechanism is applied to the nitrone system at positions 3 and 4 the observed product **9** would be formed by ring contraction.

Ring contraction also occurs on irradiation of quinoxaline di-N-oxide of the type **10**, the product of the reaction being a 1,3-disubstituted benzimidazolone **11** (Scheme 6).[51b]

Fourth example. When heated with acetic anhydride, quinoxaline 1-oxides **12a–i** bearing a substituent at C(2), a carbonyl at C(3), and a free hydrogen at N(4) are transformed into l-acetyl-3-

Scheme 14 The reaction sequence of the rearrangement.
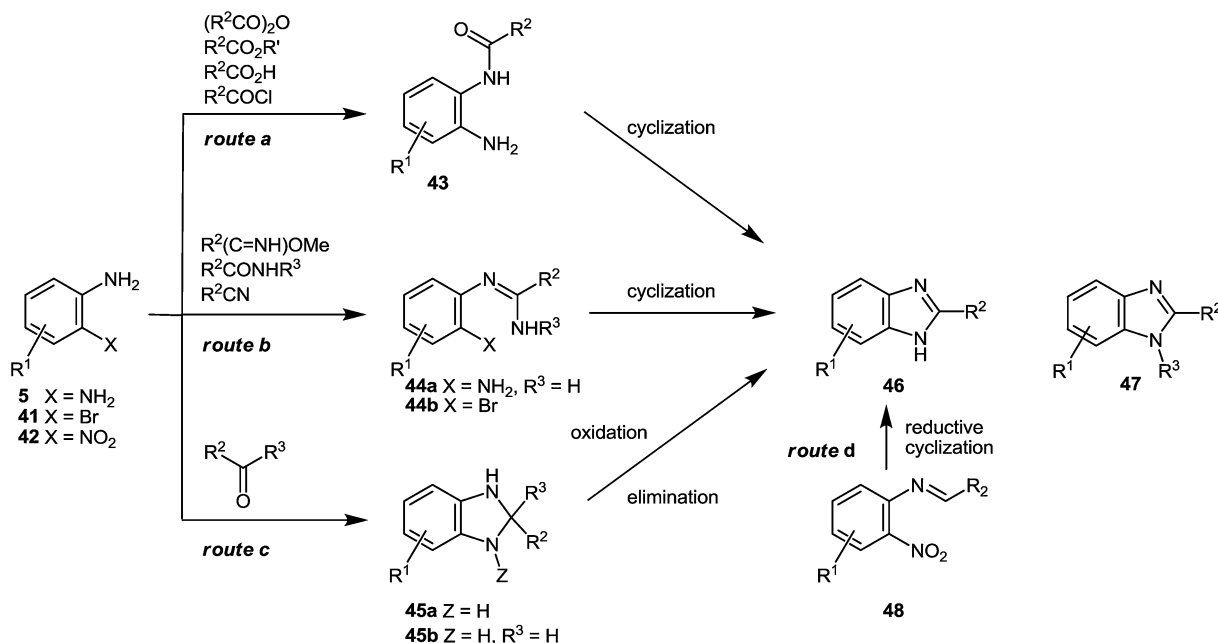
Scheme 15 Common strategies for the synthesis of benzimidazoles.
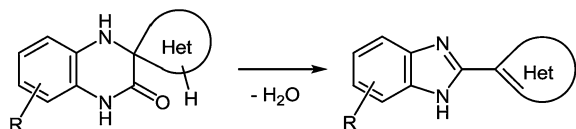
Scheme 16 Schematical presentation of the rearrangement.

acetyl-2-benzimidazolinones or 1,3-diacetyl-2-benzimidazolones depending on the nature of substituents at C(2), C(6) and C(7).[53]

For example, when 3-hydroxy-2-phenyl- (**12a**), 7-ethoxy-3-hydroxy-2-phenyl- (**12b**) and 3-hydroxy-7-methyl-2-phenyl-quinoxaline-1-oxide (**12d**) are heated with acetic anhydride under reflux for 4 h, they yield l-acetyl-3-benzoyl-2-benzimidazolone (**13a**) and its 5-ethoxy- and 5-methyl-l-acetyl-3-benzoyl derivatives **13b** and **13d**, respectively. The latter on hydrolysis with aqueous alkali lose their acetyl and benzoyl groups and yield benzimidazolone **16a** and its 5-ethoxy- (**16b**) and 5-methyl- (**16d**) derivatives (Scheme 7). 3-Hydroxy-2-(4-nitrophenyl)quinoxaline-1-oxide **12g** remained unchanged even on prolonged heating under reflux with acetic anhydride. However, when the two reactants are heated together in a sealed tube at 180 °C for 12 h, the products of the reaction are 1,3-diacetyl- and l-acetyl-2(3H)-benzimidazolones **14a** and **15** with 4-nitrobensoic acid. Similarly, 2-cyano-3-hydroxyquinoxaline 1-oxide **12i** failed to react with acetic anhydride under ordinary conditions of reflux. However, in a sealed tube at 180 °C, 1,3-diacetyl-2-benzimidazolone **14a** was produced as well.

Fifth example. In every the cases when the 2-chloroquinoxaline **17a–c** was heated with potassium amide in liquid ammonia at low temperature, benzimidazole **19** as well as the corresponding 2-aminoquinoxalines **18a–c** were formed (Scheme 8).[54] This indicates that the presence of a substituent at position 3 (Me or Ph) does not prevent ring contraction and that it is the carbon atom 3 in the quinoxaline ring which is eliminated. Considering the mechanism of this ring contraction it seems likely that there occurs an initial attack of the amide ion at position 3, which results in the intermediate **20** (Scheme 9).[54]

At present, it is yet unclear whether isonitrile **21** (Scheme 9, route a) or iminochloride **22** (Scheme 9, route b) is involved in the course of this reaction. It is tentatively suggested that this
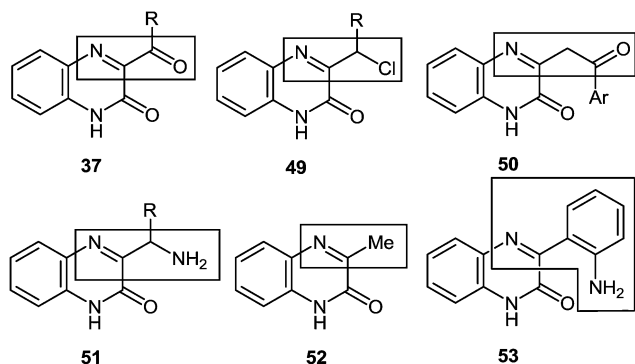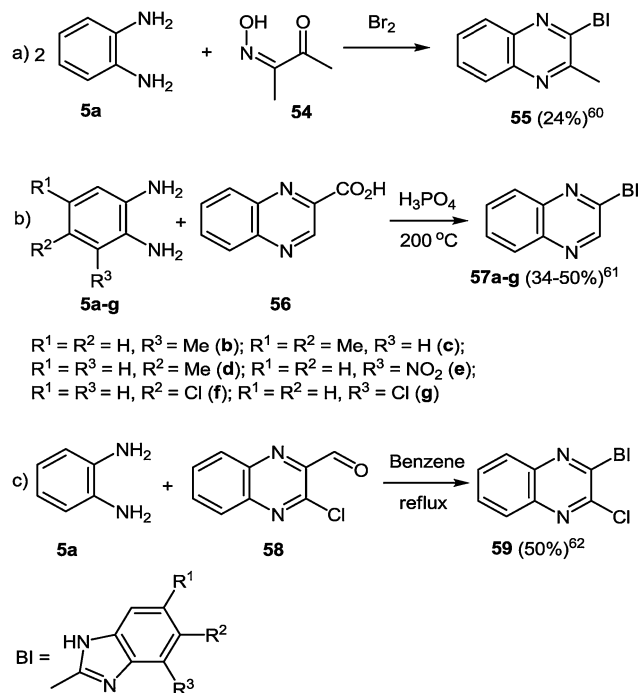

Scheme 17 Benzimidazolylquinoxaline synthesis routes according to the ref. 60–62.

ring contraction occurs as shown below (Scheme 9). The formation of a nitrile has been confirmed by the fact that with **17a** it is possible to isolate benzamidine, which is probably formed by the addition of potassium amide to benzonitrile.

It should be pointed out that with 2-chloroquinoxaline the main product is benzimidazole, and only some 2-amino-quinoxaline is formed. Under these conditions 2-bromo- (**17d**) and 2-iodo- (**17e**) quinoxaline are almost exclusively converted

Fig. 4 Schematical presentation of the quinoxalin-2-ones as functional ketones.
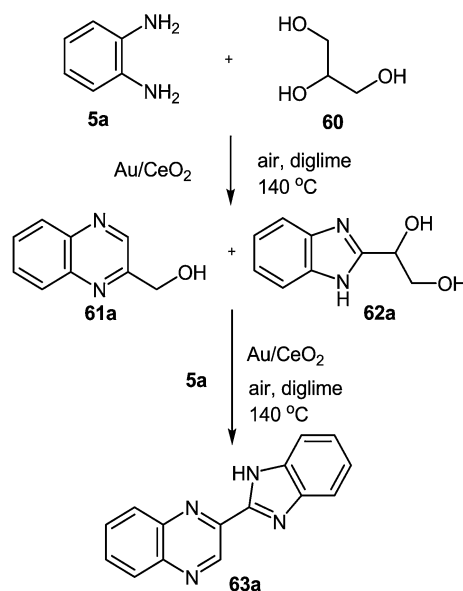
Scheme 18 New one-pot two step process for the synthesis of benzimidazolylquinoxalines starting from glycerol.

into benzimidazole, whereas with 2-fluoroquinoxaline **17f** only a trace of benzimidazole is formed.[54]

Sixth example. The hydrazinolysis of quinoxalin-2(1*H*)-one **23** in boiling 50% aqueous hydrazine lead to the formation of 2-methylbenzimidazole **26**.[55] This reaction has once again demonstrated the strong tendency of hydrazine to bring about ring transformation. This is assumed to occur by an initial addition of hydrazine at the C=N bond of **24**, resulting in the 3,4-addition analogues to addition reactions in 6- and 7-oxopteridines with nucleophilic reagents.[56] As above, the ring contraction into **25**, and the reductive conversion of the –HC= N–NH$_2$ into a methyl group by a Wolff–Kishner type process, together with dehydration, produced **26** (Scheme 10).

Seventh example. Photolysis of the quinoxalin-2-ylcarbamate *N*-oxides **27** and **28** in various solvents (*e.g.*, methanol) gives the benzimidazol-2-ylcarbamates **30** and **31**. Under acidic conditions the 1-oxide **27** yields the isonitrile **29** (Scheme 11).[57]

Eighth example. A further case of ring contraction has been reported on the thermolysis of 2-azidoquinoxaline 1-oxide **32** when 2-cyano-1-hydroxybenzimidazole **33** is formed (Scheme 12).[58]

Oxidation of 2-phenylquinoxaline-4-oxide **34** with a 30% aqueous hydrogen peroxide in acetic acid[59] or formic acid[60] results in the 1,4-dioxide, which on reduction with sulfurous acid in methanol yields 2-phenylquinoxaline-1-oxide. However,

treatment of the 4-oxide **34** with a 30% aqueous hydrogen peroxide in methanol and the presence of potassium hydroxide brings about 2-phenylbenzimidazole-3-oxide **35**. This is a general reaction of 2-alkyl- and 2-alkoxyquinoxaline 4-oxide (Scheme 13).[61]

As evident from the above eight examples of recycling of quinoxaline derivatives, the first two and the sixth one lead to the 2-substituted benzimidazoles, and the third and fourth ones result in the *N*-substituted benzimidazolones. All of them except the last one are special cases, *i.e.* implemented as the special representatives of the benzimidazole derivatives. As for the fourth example, the possibility of this reaction is limited to the synthesis of the derivatives of benzimidazolones with substituents only on the benzene ring. As a result of rearrangement they are eliminated as substituents at position 3 of the starting compounds. Thus, none of these methods of the synthesis of benzimidazole derivatives can compete with the classical Phillips–Ladenburg and Weidenhagen reactions.

2.2 Principles of the method

Quinoxalin-2(1*H*)-ones **37** can be converted into substituted benzimidazoles **40** following the reaction sequence, first reported in 2000,[62] and shown in Scheme 14. Firstly, 3-α-chloro (or bromo)benzylquinoxalin-2(1*H*)-ones **36** are oxidized with the Kornblum type reactions[63] or the direct oxidation of 3-benzyl (or
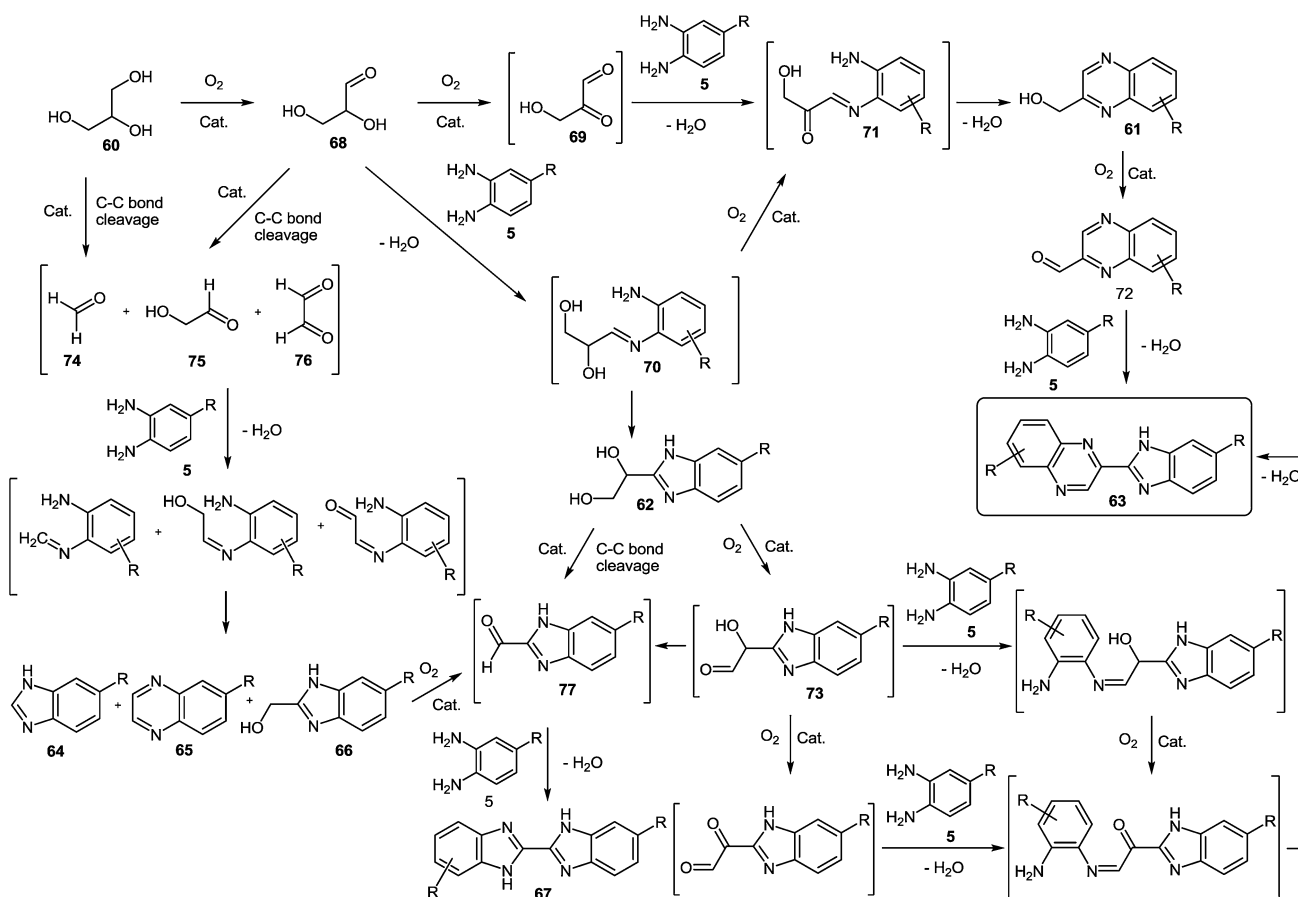
Scheme 19 Proposed benzimidazolylquinoxalines synthesis mechanism starting from 1,2-DAB derivatives and glycerol.
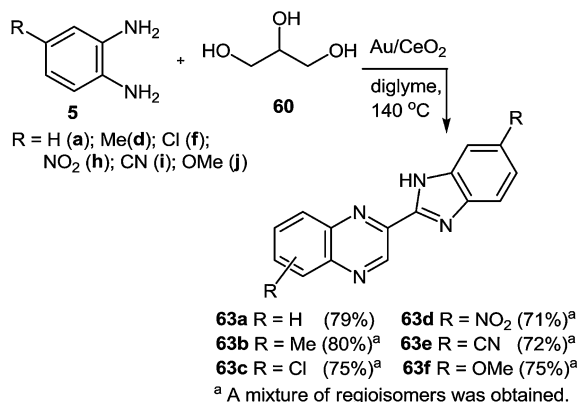
Scheme 20 Synthesis of benzimidazolylquinoxaline derivatives starting from 1,2-DABs and glycerol with Au/CeO$_2$ as a catalyst.

alkyl) quinoxalin-2(1*H*)-ones **36** with the help of GrO$_3$ in acetic acid with water[62d,64] to give 3-aroyl- or 3-alkanoylquinoxalin-2(1*H*)-ones **37**. 3-Aroyl- or 3-alkanoylquinoxalin-2(1*H*)-ones **37** react with 1,2-DABs **5** to give the spiro-quinoxalinone derivative **38**. The spiro-quinoxalinone derivative **38** is then heated in acetic acid to give the benzimidazole derivative **40** through the proceeding cascade reactions involving: (a) acid-catalyzed ring-opening of spiro-compound **38** with the formation of quinoxaline derivative **39**, (b) the intramolecular nucleophilic attack by the amino moiety on the carbonyl group leading to the formation of the final product **40** with the elimination of water. Practically for every case the spiro-compound **38** can be isolated and individually characterized, but the quinoxaline derivative **39** can only be rarely isolated. The sequence is thus based on the combination of the following facts:

(i) The presence of the carbonyl group at position 3 of quinoxalin-2(1*H*)-ones **37**, according to the principle of Ogg and Bergstrom[48] allows to consider them as the hetero analogues of α-diketones (see Sections 4 and 10).

(ii) The susceptibility of these systems to the reactions of the usual α-diketones, according to the Hinsberg reaction[65] involves spiro-quinoxaline derivatives with at least one mobile hydrogen atom in the spiro-forming component.[62]

(iii) The susceptibility of the spiro-quinoxaline derivatives **38** towards the acid-catalyzed ring-opening with the formation of quinoxaline derivatives **39**, and the intramolecular ring closure reaction with the formation of benzimidazole derivatives **40**.

In the reactions above aroyl- and alkanoylquinoxalinones were dealt with as hetero analogues of α-diketones. Accordingly, we assume the 3-(α-haloalkyl)- and 3-(α-halobenzyl)quinoxalin-2(1*H*)-ones, 3-(α-aminobenzyl)quinoxalin-2(1*H*)-ones and 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones to be analogues of α-haloketones, α-aminoketones and β-diketones, respectively.

2.3 Advantages of the method

The present method for the synthesis of substituted benzimidazoles starting from quinoxalin-2(1*H*)-one derivatives has the following characteristics or distinct advantages over the
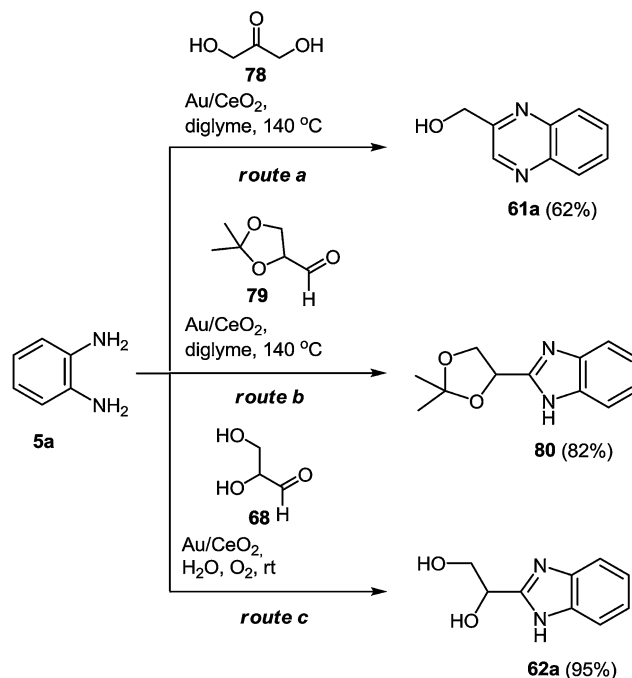
Scheme 21 Possible synthetic routes to yield the intermediate quinoxaline **60a** or benzimidazoles **79**, **61a**.

previously used routes (the Phillips–Ladenburg and the Weidenhagen reactions) or their numerous variations.

(A) Firstly, the acid-catalyzed rearrangement of spiro-quinoxalinone derivative **38** through the *o*-aminoanylide quinoxaline 2-carboxylic acid **39** involves a milder reaction condition and provides almost quantitative yields of the benzimidazole derivative **40** (Scheme 14). Most of the popular approaches generally involve the condensation of an arylenediamine with a carbonyl equivalent (Scheme 15). For example, the reaction of 1,2-DABs with carboxylic acid or acid chloride results in intermediate amide **43**. In order to produce benzimidazole **46** the latter in turn could undergo a cyclodehydration reaction at elevated temperatures under strong acidic or alternatively under harsh dehydrating conditions,
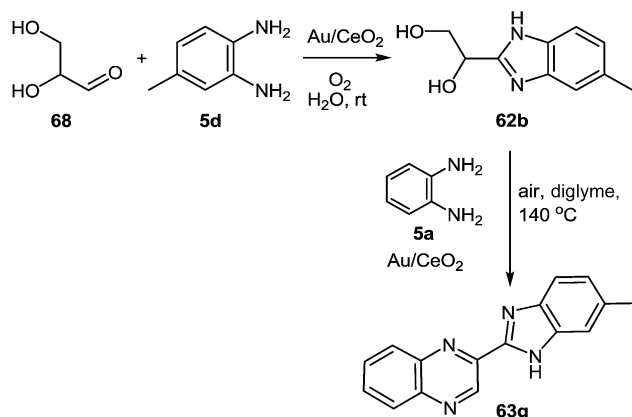

**Scheme 22** New one-pot two-step process to produce benzimidazolylquinoxalines starting from glyceraldehyde.

(Scheme 15, route a). Similarly, esters, lactones and anhydrides could generate benzimidazoles via the cyclization of amide **43**, although given the rather harsh reaction conditions required and the poor diversity profile of the final products their scope might be limited. For instance, the reaction of 1,2-DABs with aliphatic esters and lactones involves the use of strong mineral acids such as hydrochloric acid, sulfuric acid, hot glacial acetic acid or polyphosphoric acid under very high temperatures, i.e. the conditions are not absolutely compatible with a broad range of functional groups and desirable substrates. Aromatic esters require temperatures of up to 250–300 °C, thus rendering the synthesis of 2-arylbenzimidazoles almost impractical.[46a] However, the reaction of aromatic esters with 1,2-DABs under the Weinreb conditions could provide access to 2-arylbenzimidazoles.[46b] In the class of acid anhydrides of monobasic acids, only acetic anhydride has been practically used in the preparation of 2-methylbenzimidazoles. Cyclic anhydrides of dibasic acids have also been used in the synthesis of benzimidazoles, although high temperatures and strong acids are usually necessary to convert the intermediate N-(o-aminophenyl)-imide into the desired benzimidazole.[47a,b] Besides, a mixture of regioisomeric benzimidazoles could result from the reaction of nonsymmetric anhydrides with arylenediamines.

In the presence of HCl the reaction of 1,2-DABs with amides[66] and nitriles[67] at 200–250 °C could also afford 2-substituted benzimidazoles with the general structure **46** via the cyclization of intermediate amidine **44a** (Scheme 15, route b). Alternatively, upon the formation and subsequent cyclization of amidine **44a** under milder conditions[68] the reaction of 1,2-DABs with an imidate could afford benzimidazole **46** as well. Although the imidate route could provide access to a diverse set of 2-substituted benzimidazoles starting from several commercially available aliphatic and aromatic nitriles,
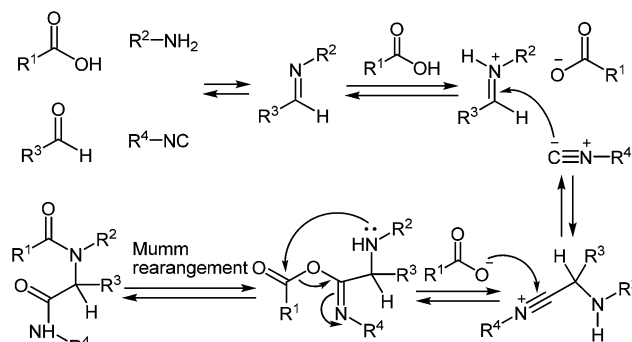
Scheme 24 Mechanism of the four-component Ugi reaction.
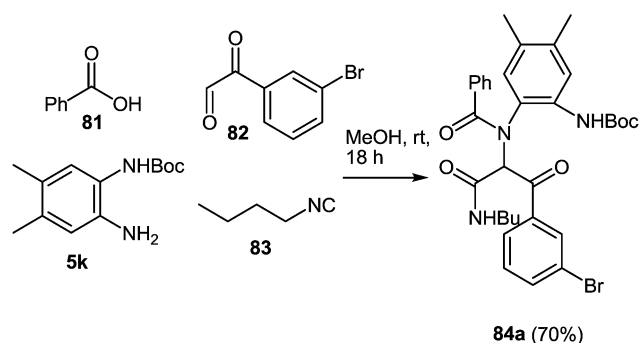
Scheme 25 Four-component one-pot Ugi reaction.

the hydroscopic nature of the intermediate imidates might be of concern, particularly in a high throughput set-up. The palladium catalyzed intramolecular N-arylation reaction of the o-bromophenylamidine precursors of type **44b**, resulting from
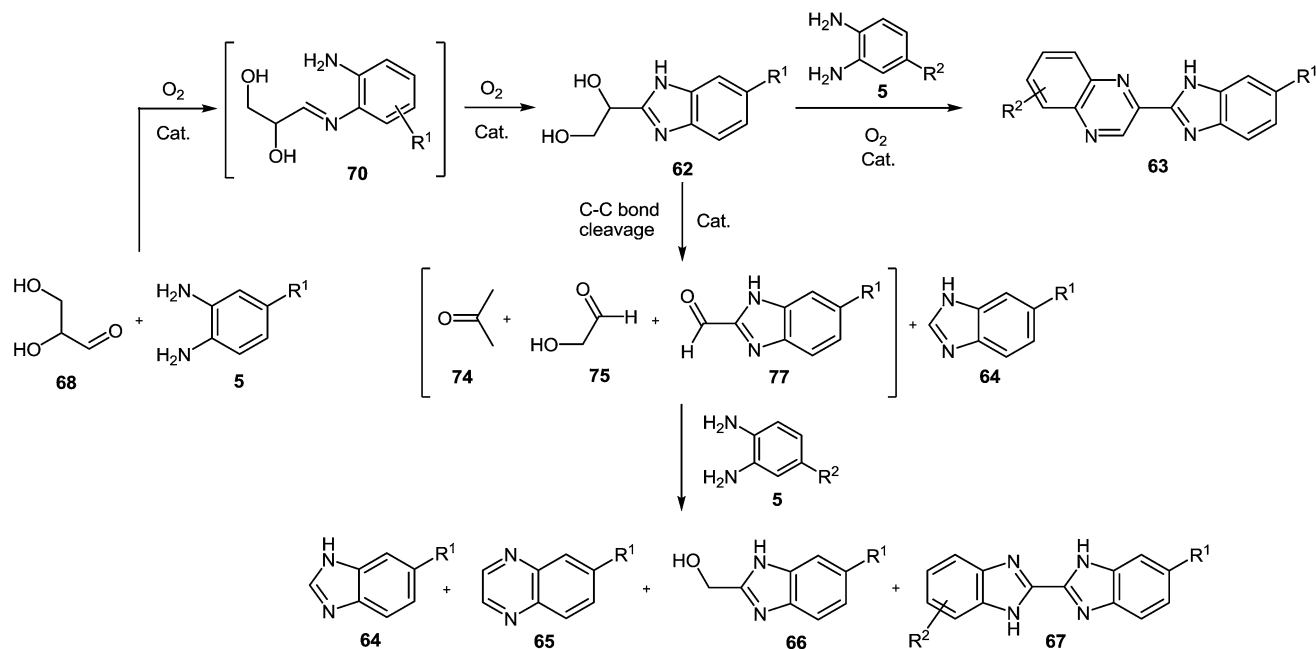
Scheme 23 Proposed benzimidazolylquinoxalines synthesis mechanism from 1,2-DABs and glyceraldehyde.

the assisted $POCl_3$ condensation of bromoaniline **41** and an amide, has been recently developed providing entry to *N*-substituted benzimidazoles with the general structure **47**.[69] Despite the somewhat harsh conditions required to generate the intermediate amidine precursors, this method proves successful in the regioselective synthesis of *N*-substituted benzimidazoles which is a current limitation as regards many other approaches.

Aldehydes and, to a lesser extent, ketones can also afford benzimidazoles when condensed with 1,2-DABs (Scheme 15, route c). Although the reaction of ketones with 1,2-DABs in the presence of HCl at 250–300 °C can yield benzimidazole **46** due to the aromatization of intermediate benzimidazoline **45a**, their use has been rather limited.[1b,70] Furthermore, since the aromatization of benzimidazoline **45a** occurs *via* the elimination of an alkyl group, a mixture of benzimidazoles could result from non-symmetric ketones. Alternatively, aldehydes have been used more extensively in the preparation of 2-substituted benzimidazoles according to the Weidenhagen's method.[71]
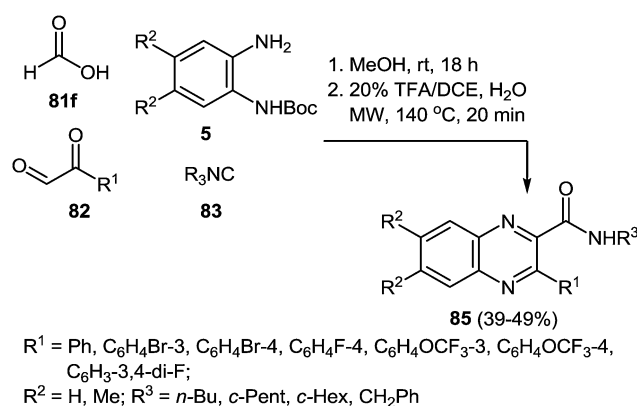
For example, condensation of 1,2-DABs with an aldehyde, followed by the oxidation of the intermediate benzimidazoline **45b** could afford benzimidazole **46** as well. While the oxidation can proceed spontaneously by disproportionation, this can lead to some of side products. Oxidative methods usually require heating in nitrobenzene or DMF at elevated temperatures, as well as the use of metal ions, iodine, organic oxidants or inorganic sulfites when heated.[72] However, for the synthesis of *N*-substituted and N–H benzimidazoles one mild set of oxidation conditions utilizing oxone has been recently described.[72]

Method of reductive cyclization of *N*-benzylidene-2-nitroanilines **48** (R^2 = Ar), prepared from *o*-nitroaniline **42** and benzaldehydes (Scheme 15, route d) could be a viable alternative to the widely used 1,2-DAB based synthetic methods. But according to our knowledge, it was not as yet been studied to date. Triethylphosphite,[73] triruthenium dodecacarbonyl[74] in the presence of carbon monoxide, and recently, phenylmagnesium chloride[75a] have been successfully utilized as the reducing agents for this transformation. The reaction presumably proceeds *via* an *in situ* aryl nitro reduction, followed by an intramolecular cyclization,[75] and results in benzimidazole **46** (R^2 = Ar). This strategy requires the preparation and isolation of the corresponding *N*-benzylidene-2-nitroanilines **48** before subjecting them to cyclization conditions though it could obviate the preparation and isolation of the intermediate 1,2-DABs in particular those that are water-soluble or prone to air-oxidation.

(B) Secondly, the synthesis of substituted benzimidazoles can be accomplished starting from the quinoxalin-2(1*H*)-one derivative **36** easily available with the use of various preparatively simple ways under mild conditions from corresponding substituted 1,2-DABs and pyruvates. In doing so as a result of the rearrangement substituents of the benzene ring of the quinoxalinone system appeared to be on the benzene ring of the benzimidazole ring. As a result of the rearrangement the substituent R^2 at position N(1) of the quinoxalin-2(1*H*)-one system are transferred to the *N* atom of benzimidazole system.
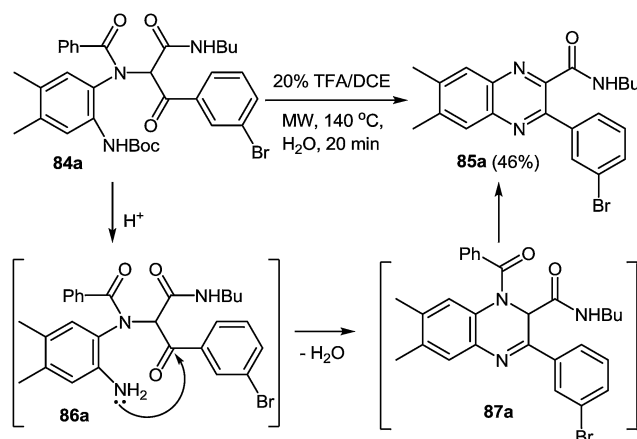
Scheme 26   Conversion of Ugi adduct into quinoxaline **85a** *via* intermediates **86a** and **87a**.

R^1 = Ph, C_6H_4Br-3, C_6H_4Br-4, C_6H_4F-4, $C_6H_4OCF_3$-3, $C_6H_4OCF_3$-4, C_6H_3-3,4-di-F;
R^2 = H, Me; R^3 = *n*-Bu, *c*-Pent, *c*-Hex, CH_2Ph

Scheme 27   Study of the reaction scope.

(C) The route **36** to **40** clearly shows that a benzyl (or haloalkyl) group can be converted (by use of the Kornblum reaction) into a ketone group necessary for the introducing of quinoxaline ring in to position 2 of quinoxalinone **37** according to the Hinsberg reaction.[65] In this reaction compound **37** formally acts as the hetero analogue of α-diketone.

(D) As can be seen from the reaction depicted in Scheme 14, the key step in this case is the formation of spiro-compound **38**. As a result of the cascade reaction this compound is transformed into a benzimidazole derivative **40**, with a heterocyclic system. This system acts as a spiro-fragment in the intermediate compound **38**. The result makes it possible to propose the main principle for this rearrangement. Any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one with at least one mobile hydrogen atom in their spiro-forming components can be converted into the benzimidazole derivative with the spiro-forming component at position 2 (Scheme 16).[76]

(E) The understanding of the reaction mechanism makes it possible for us to make a bold assumption as seen from Fig. 4, all the reactions of aroyl- and alkanoylquinoxalines when interacting with 1,2-DABs at the initial stage behave as hetero analogues of α-diketones, *i.e.*, as iminoketones (see Sections 4
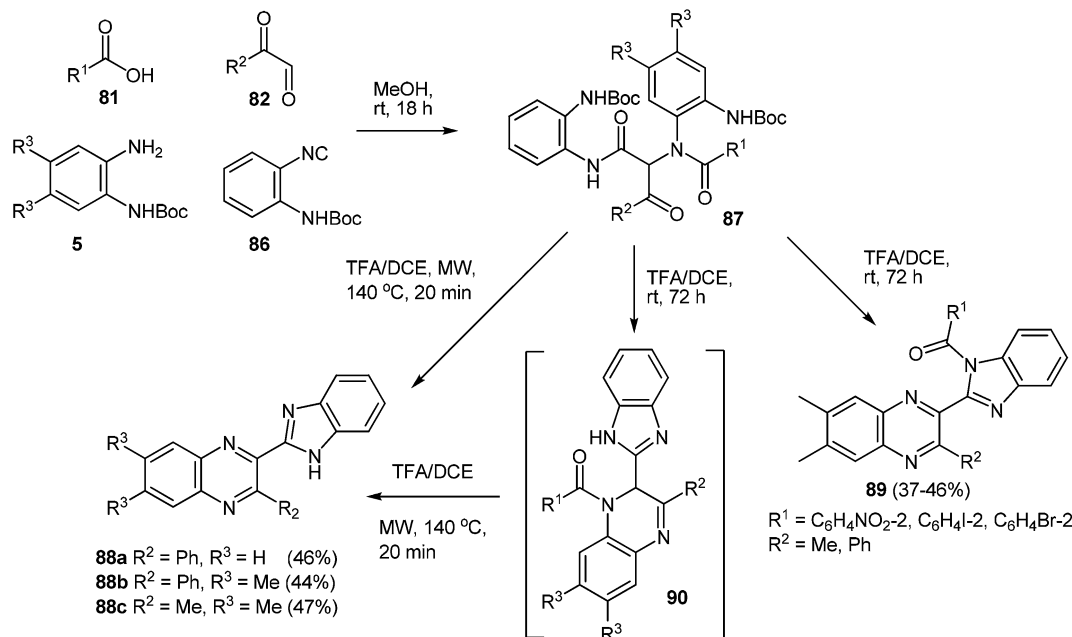
Scheme 28 Synthesis of 2-benzimidazolylquinoxalines.
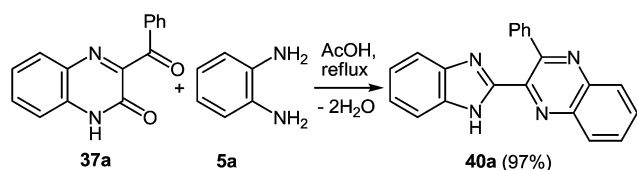
Scheme 29 Rearrangement of 3-benzoylquinoxalin-2(1*H*)-one.

and 10). Then the problem appears, why other quinoxaline derivatives with certain substituents do not behave like α-haloketones **49** (see Section 5), β-diketones **50** (see Section 6), α-aminoketones **51** (see Section 7), methyl ketones **52** (see Section 8), *o*-aminoaldehydes (or ketones) **53** (see Section 9), *etc.*

3   Synthesis of 2-(benzimidazol-2-yl) quinoxalines

3.1   From glycerol and 1,2-diaminobenzenes with use of gold catalysis

Methods for the synthesis of these hetarylquinoxalines are limited. An option involves the reaction of the 1,2-DAB **5a** with 3-hydroxyimino-2-butanone **54** and bromine in a one-pot reaction (Scheme 17a).[77] Another possibility is to react 1,2-DABs **5a–g** with quinoxalin-2-carboxylic acid **56**, but this synthetic route needs to be performed in a polyphosphoric acid media at 200 °C (Scheme 17b).[78] A third route is to react the 1,2-DAB **5a** with quinoxalin-2-carboxaldehyde **58** in benzene at reflux temperature (Scheme 17c).[79] In all the three cases the yield of the target product remains very low.
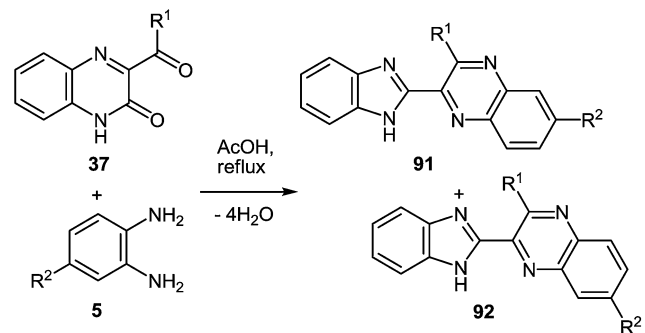
A gold catalyst (Au/CeO₂) was used to synthesize benzimidazolylquinoxalines by two novel methods in a multistep one-pot methodology.[80] The first method involved the oxidative

coupling of glycerol **60** with 1,2-DAB **5a** performed at 140 °C using diglyme as a solvent and lead to the benzimidazolylquinoxaline compound **63a** through the formation of intermediates **61a** and **62a** (Scheme 18). Herein, the benzimidazolylquinoxaline possesses the same substituents in both heterocycles. After that to expand the synthetic scope, an alternative route that allows
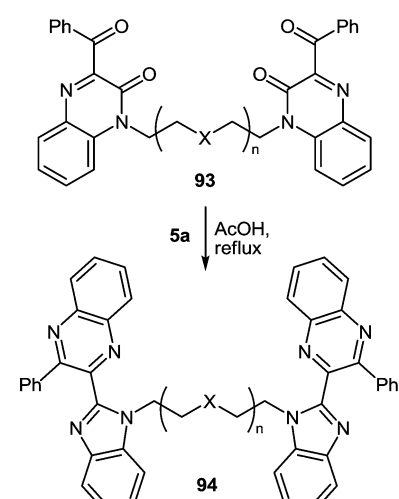
Table 1 Acid-catalyzed rearrangement of quinoxalin-2-ones when exposed to 1,2-DAB **5a**

Entry	Substrate	R¹	R²	Product	Yield (%)	Ref.
1	**37b**	H	C_6H_4F-4	**40b**	94	83
2	**37c**	H	C_6H_4Cl-4	**40c**	97	
3	**37d**	H	C_6H_4Br-4	**40d**	95	
4	**37e**	H	C_6H_4I-4	**40e**	93	
5	**37f**	H	$C_6H_4NO_2$-4	**40f**	92	
6	**37g**	H	CH_2Ph	**40g**	81	82
7	**37h**	H	CH_2CH_2Ph	**40h**	87	
8	**37i**	H	*n*-Pr	**40i**	82	
9	**37j**	H	Me	**40j**	72	81
10	**37k**	Et	Me	**40k**	99	
11	**37l**	Me	Ph	**40l**	81	79
12	**37m**	Et	Ph	**40m**	79	
13	**37n**	*n*-Pr	Ph	**40n**	87	
14	**37o**	*n*-Bu	Ph	**40o**	87	
15	**37p**	*n*-Pent	Ph	**40p**	86	
16	**37q**	CH_2Ph	Ph	**40q**	56	
17	**37r**	COMe	Ph	**40r**	81	

Table 2 Acid-catalyzed rearrangement of quinoxalin-2-ones when exposed to 3,4-diaminotoluene **5d** and 4-nitro-1,2-DAB **5h**

| Entry	37	R^1	5	R^2	Products (yield)	Ref.
1	**37a**	Ph	**5d**	Me	**91a + 92a** (82%)	79
2	**37g**	CH$_2$Ph	**5d**	Me	**91b + 92b** (34%) (44%)	82
3	**37a**	Ph	**5h**	NO$_2$	**91c + 92c** (39%) (44%)	79
4	**37b**	C$_6$H$_4$F-4	**5h**	NO$_2$	**91d + 92d** (47%) (38%)	83
5	**37c**	C$_6$H$_4$Cl-4	**5h**	NO$_2$	**91e + 92e** (42%) (36%)	
6	**37d**	C$_6$H$_4$Br-4	**5h**	NO$_2$	**91f + 92f** (45%) (43%)	
7	**37e**	C$_6$H$_4$I-4	**5h**	NO$_2$	**91g + 92g** (44%) (45%)	
8	**37g**	CH$_2$Ph	**5h**	NO$_2$	**91h + 92h** (36%) (49%)	82
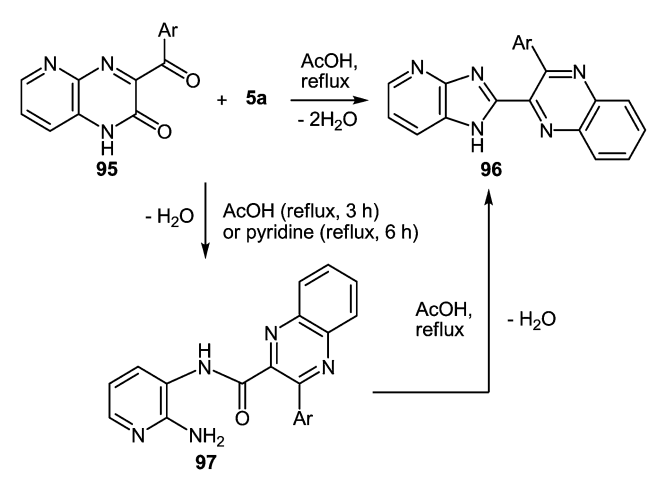
Table 3 Preparation of the symmetric benzimidazolemonopodands

Entry	Substrate	X	n	Product	Yield (%)
1	**93a**	O	1	**94a**	80
2	**93b**	O	2	**94b**	75
3	**93c**	CH$_2$	1/3	**94c**	69
4	**93d**	CH$_2$	4/3	**94d**	72
5	**93e**	CH$_2$	8/3	**94e**	73
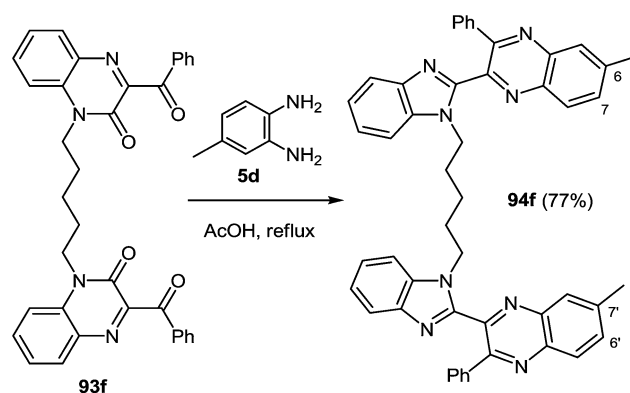
Scheme 30 Preparation of the nonsymmetric benzimidazole-monopodand.

combining different substituents in both heteroaromatic moieties was designed.

However, at the beginning of the reaction, the quinoxalin-2-ylmethanol **61a**, formed by oxidative coupling between glycerol **60** and 1,2-DAB **5a**, and the 1-(1*H*-benzo-[*d*]imidazol-2-yl)ethane-1,2-diol **62a**, which could be produced through the oxidation of one of the primary alcohol groups of glycerol and subsequent coupling with 1,2-DAB **5a**, were the predominant products (Scheme 18). Both compounds (**61a** and **62a**) exhibited a primary and unstable character and after one hour of reaction, the concentrations of both intermediates began to decrease, due to their conversion into 2-(1*H*-benzo[*d*]imidazol-2-yl)quinoxaline **63a**, produced through oxidation-cyclization of

Table 4 Synthesis of 2-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)-3-arylquinoxalines

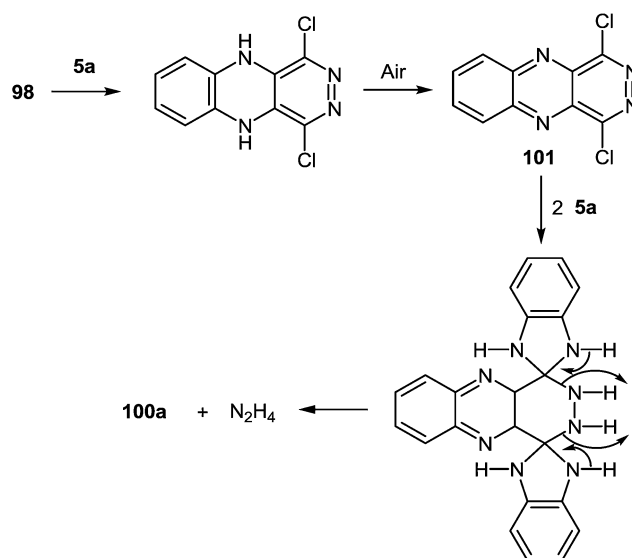| Entry	Substrate	Ar	Product	Yield (%)
1	**95a**	Ph	**96a**	69
2	**95b**	C$_6$H$_4$F-4	**96b**	44
3	**95c**	C$_6$H$_4$Cl-4	**96c**	41
4	**95d**	C$_6$H$_4$Br-4	**96d**	43
5	**95a**	Ph	**97a**	64^a, 72^b
6	**97a**	Ph	**96a**^{a}	84

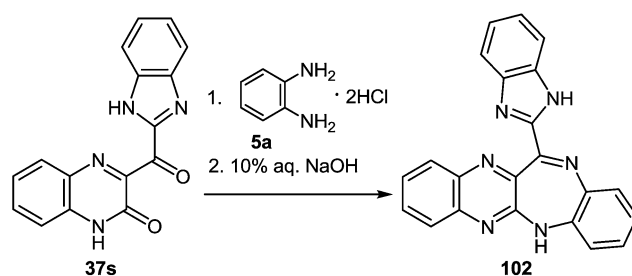^{a} Obtained in refluxing pyridine. ^{b} Obtained in refluxing AcOH.

61a and **62a** with another 1,2-DAB molecule **5a**. Other byproducts such as 1H-benzo[d]imidazole **64a**, quinoxaline **65a**, (1H-benzo[d]imidazol-2-yl)methanol **65a** and 1H,1′H-2,2′-bibenzo[d]-imidazole **66a** were also detected in the reaction media (Scheme 19). The proposed mechanism (Scheme 19) of the processes involves the oxidation of glycerol **60** to glyceraldehyde **68** and subsequently to the dicarbonyl compound **69**.

Both compounds can condense with 1,2-DAB to produce the imine intermediates **70** and **71**, with **70** converted into product **71** by fast oxidation of the remaining hydroxyl group. Later, product **71** follows a condensation reaction to yield hydroxymethylquinoxaline intermediate **61**, which can be further oxidized to 2-carboxaldehydequinoxaline **72**, which couples with another molecule of 1,2-DAB to reach the benzimidazolylquinoxaline derivative **63**. Besides, the imine intermediate **71** can result in the dihydroxybenzimidazole intermediate **62**, which through a subsequent oxidative coupling with 1,2-DAB produces the benzimidazolylquinoxaline derivative **63**. On the other hand, the formation of the byproducts detected by gas chromatography could be due to the oxidative cleavage of glycerol **60**, glyceraldehyde **68**, the dihydroxybenzimidazole intermediate **62**, and the α-hydroxycarbonylbenzimidazole intermediate **73** into different carbonyl compounds such as **73**, **74**, **75**, and **76**. Later the coupling with 1,2-DAB produces the byproducts **64**, **65**, **66**, and **67** through cyclization in minor amounts.

In Scheme 20, good yields of benzimidazolylquinoxaline derivatives were obtained. However, with electron-withdrawing substituents such as nitro, chloro or nitrile groups, the yields of quinoxaline derivatives were slightly lower with respect to those of 1,2-DAB or with respect to 1,2-DABs with electron-

Fig. 5 Tautomerism in imidazopyridines.

2-(1H-imidazo[4,5-b]pyridin-2-yl)-3-arylquinoxalines
96a-d

2-(1H-imidazo[5,4-b]pyridin-2-yl)-3-arylquinoxalines
96′a-d

Scheme 31 The reaction of tetrachloropyridazine and 1,2-DAB.

Scheme 32 Displacement of hydrazine hydrochloride from 1,4-dichloropyridazino[4,5-b]quinoxaline by 1,2-DAB.

Scheme 33 The interaction of 3-benzimidazoylquinoxalin-2(1H)-one **37s** with 1,2-DAB dihydrochloride as described in literature.[95]
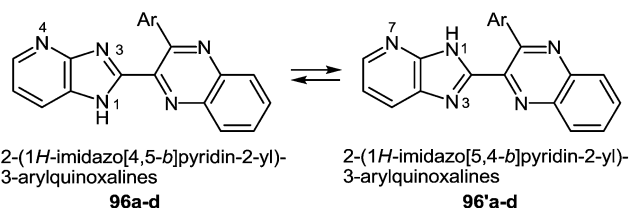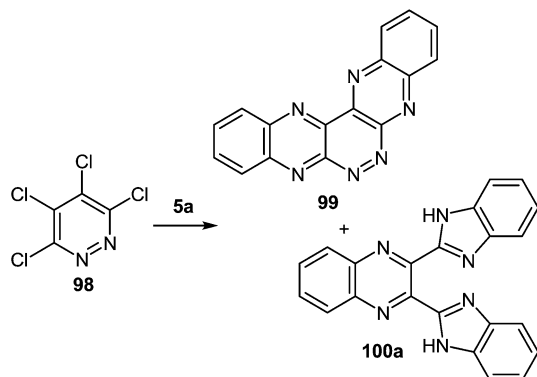
donating substituents such as methyl and methoxy. In all these cases the reactions proceed with the formation of regioisomers of benzimidazolylquinoxalines.

To develop a method for the synthesis of the 2-benzimidazolylquinoxaline derivatives with different substituents in the benzimidazole and quinoxaline fragments the conditions for the formation of the assumed intermediate products of the reaction, i.e. hydroxymethylquinoxaline **61a**, 1-(1H-benzo[d]imidazol-2-yl)ethane-1,2-diol **62a**, and its protected derivative **80** were investigated (Scheme 21).[80]

Following the optimization of the reaction conditions with different substrates, the results presented in Scheme 22 showed that only the reaction between glyceraldehyde and 1,2-DAB (Scheme 21, route c) in the presence of Au/CeO₂, oxygen pressure, and at room temperature, produced the benzimidazole intermediate **62** with a high selectivity with complete conversion. Consequently, the synthesis of the benzimidazole intermediate from glyceraldehyde and 1,2-DAB derivative was chosen as the optimum first step of the reaction.

This second process involves two sequential steps with very different reaction conditions. In the first one, glyceraldehyde is coupled with an 1,2-DAB derivative in the presence of Au/CeO₂
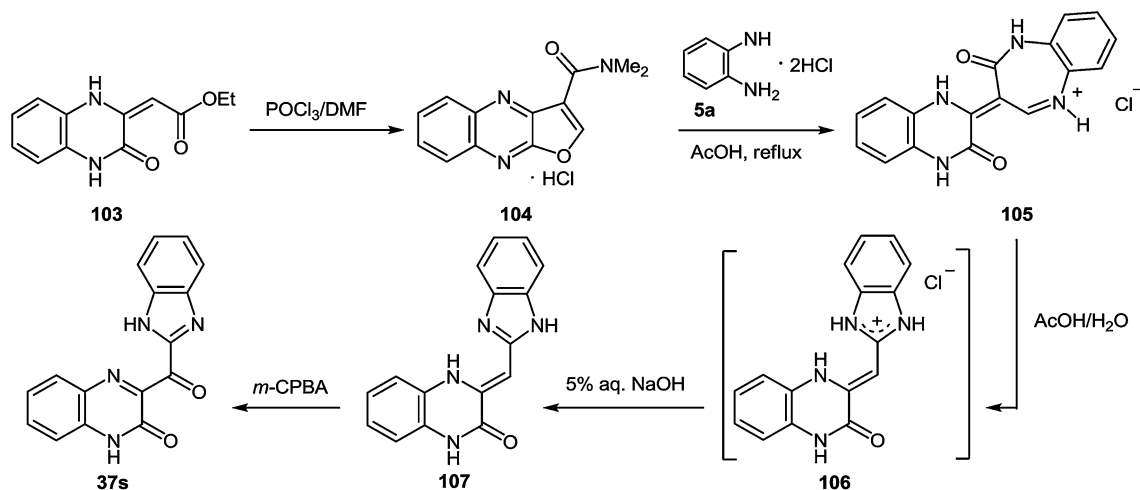
Scheme 34 The general scheme of the synthesis of 3-benzimidazoylquinoxalin-2(1H)-one **37s** starting with quinoxalin-2(1H)-one derivative **103** according to the references [95,97] The geometry of C=C double bond for quinoxaline derivative **107** is strongly supported by gauge-independent atomic orbital calculations.[99]
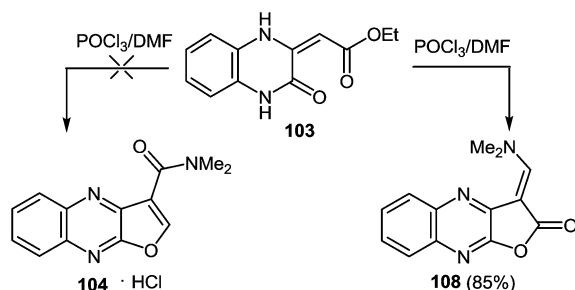
Scheme 35 The reaction of 3-ethoxycarbonylmethylene-3,4-dihydroquinoxalin-2(1H)-one **103** with the Vilsmeier reagent.

Scheme 36 A plausible mechanism for the formation of furo[2,3-b]quinoxalin-2-one derivative **108**.

to produce the intermediate **62** under very mild reaction conditions (room temperature, 3 bar O_2, and water as a solvent). After the complete conversion of g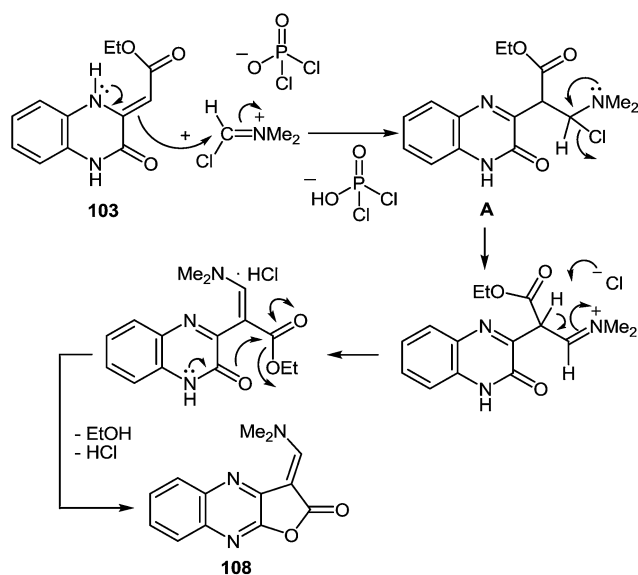lyceraldehyde, a solution of the second 1,2-DAB molecule **5d** in diglyme is added, and the temperature is increased to 140 °C while the water is removed by a Dean–Stark system. The main product observed under these conditions is the benzimidazolylquinoxalines **63g** (Scheme 22), which is formed by oxidative coupling between the intermediate **62** and the 1,2-DAB molecule **5d**.[80] Both routes were applied to the synthesis of different benzimidazolylquinoxalines derivatives, obtained in yields between 60 and 80%.

As can be seen from the reaction mechanism (Scheme 23) and from the data in the Scheme 20, this method cannot be used effectively in the case of the synthesis of substituted derivatives of 2-benzimidazolylquinoxalines, as the reactions of mono-substituted derivatives of 1,2-DAB proceed with the formation of the mixtures of regioisomers, which are difficult to separate. The problem is further complicated with the diversely substituted derivatives of 1,2-DAB. Expensive (Au) and environmentally unsafe (CeO$_2$) catalyst also limits the possibilities of this method.

3.2 Via the isocyanide based multi-component reactions (IMCRs)

IMCRs are considered as a principal field of study for the generation of both new chemo type diversity and preferred methodologies to produce known heterocycles.[81] In particular, the Ugi reaction, is extremely versatile enabling access to the numerous of small molecules through a various strategies that include post-condensation modifications of the Ugi adduct and use of variety of nucleophiles, which can trap nitrilium intermediate both intra- and intermolecularly (Scheme 24). Several groups have developed concise methodologies that enable access to diazepines,[82] ketopiperazines,[83] imidazolines,[84] β-lactams[85] hydantoins, etc.[86] The final ring closure is accomplished
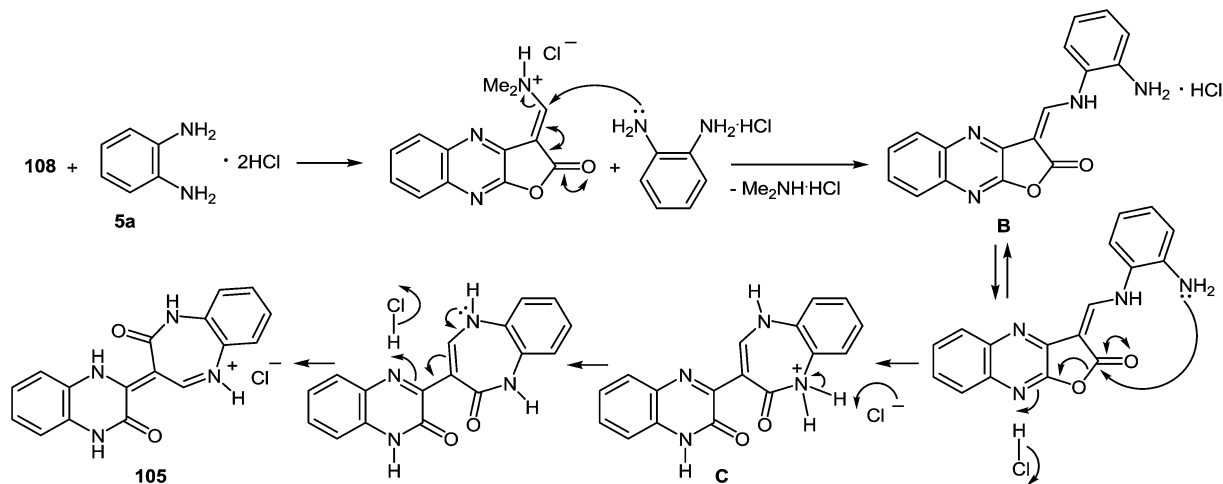
Scheme 37 A possible mechanism of the formation of benzodiazepin-2(1H)-one derivative **105**.

through the amide bond formation in the Ugi/deprotect/cyclize strategies.[81e,f]

When 3-bromophenyl glyoxaldehyde **82** and N-Boc-(4,5-dimethyl)-1,2-DAB **5k** were used instead of amine and aldehyde components in the above reaction the process proceeded smoothly in methanol at ambient temperature resulting in the Ugi adduct **84** in a 70% yield (Scheme 25). The treatment of **84** with TFA provides **85a** in good yield, which is the first reported synthesis of quinoxalines derived in one step with the use of the Ugi reaction, assuming to proceed unexpectedly through intermediates **86** and **87** with the elimination of a benzoyl group (Scheme 26).[82] The final product is appreciably different from the Ugi precursor, which provides a unique opportunity to achieve such a difference.

One pot procedure results in a higher overall yield of **85a** (46%) when compared to that of the two step process (34%) (Scheme 26).[87]

As to the scope of the reaction, various aldehydes, 1,2-DABs and isonitriles were used to produce a set of diversified quinoxalines and, the transformation worked equally well for all inputs (Scheme 27).[87]

In the same reaction conditions, it was assumed that the use of isonitrile **86** (o-N-Boc-phenylisonitrile)[88] usually facilitates access to 2-benzimidazolylquinoxalines **88**.

The Ugi reaction proceeded smoothly and upon microwave irradiation of Ugi products **87** with a 20% TFA/DCE, 2-benzimidazolylquinoxalines **88a–c** were obtained in good yield (Scheme 28).[87] 2-Benzimidazolylquinoxaline products **89** were observed with bulky o-substituted aromatic acids which had retained the benzoyl group through an internal acyl-transfer from the nitrogen obtained from the original Ugi amine input to the adjacent benzimidazole. Low yields of the desired products (39–49% in the cases of quinoxaline derivatives, and 37–46% in the case of 2-benzimidazolylquinoxalines) and the limited availability of mono- and di-variously-substituted derivatives of o-N-Boc-phenylisonitrile **86** and N-Boc-1,2-DAB limits the possibility of this approach to the synthesis of bicyclic derivatives of quinoxalines and 2-benzimidazolylquinoxalines variously substituted by quinoxaline and benzimidazole.

4 Synthesis of 2-hetarylquinoxalines *via* rearrangements

4.1 Synthesis of 2-(benzimidazol-2-yl)quinoxalines and their aza-analogues

One of the common reactions of α-diketones in the chemistry of heterocycles is the Hinsberg reaction,[65] *i.e.*, the synthesis of quinoxalines by the interaction of 1,2-DABs with α-dicarbonyl compounds.

Thus a series of reactions according to Hinsberg were carried out.

The reaction of quinoxalin-2-one **37a** (see Subsection 2.2) with 1,2-DAB **5a** in boiling acetic acid leads to the corresponding 2-benzimidazolylquinoxaline **40a** in a 97% yield (Scheme 29).[62a]

Tables 1 and 2 show that a variety of quinoxalinones **37a–r** and 1,2-DABs **5a**, **d**, **h** are compatible with these reaction conditions, with diverse 2-benzimidazolyl substituted quinoxalines in good yields. The reactions of 3-phenylacetylquinoxalin-2(1H)-one **37g** with 3,4-diaminotoluene **5d**, or 4-nitro-1,2-DAB **5h**, produce a mixture of two isomers in almost equal amounts (Table 2),[62d,89] as evident from the ^{1}H NMR spectra of the crude products.

This is because the fact that the probability of an initial attack of the amino group on the C(3) atom of the quinoxalin-2(1H)-one system and on the aroyl- or alkanoyl group during the rearrangement is nearly the same (Table 1).[62a,b,d,e,90]

Table 1, shows that it makes no deference for the reaction whether or not there is a substituent of quinoxalin-2(1H)-ones at position 1. The same process is successful with N-alkylated derivatives of quinoxalin-2(1H)-ones, producing N-alkylated derivatives of benzimidazole as well. All these reactions involve the formation of 2-(benzimidazol-2-yl)quinoxalines almost in quantitative yields.

The reaction proceeds with the compounds with two quinoxalin-2(1H)-one moieties in their composition, and, what kind of spacer connects these two fragments makes no difference. In all cases the reactions proceed smoothly with the

formation of benzimidazolemonopodands with the terminal quinoxaline fragments (Table 3).[62c,d,91]

When the reaction of 1,5-bis(3-benzoylquinoxalin-2(1*H*)-on-1-yl)pentane **93f** with the 3,4-diaminotoluene **5d** was carried out under the same conditions the formation of a single product mainly the benzimidazolemonopodand **94f** with the terminal 6- and 7′-dimethylquinoxaline rings in a 77% yield actually occurs (Scheme 30).[62c]

These systems contain methyl groups at C(6) and C(7′), and not at the C(6), C(6′) and C(7), C(7′) positions. The probability of an initial attack on the amino group on the C(3) atom or on the benzoyl group is roughly the same. Otherwise, the formation of three products of rearrangement could be observed in approximately equal amounts.

The use of aza-analogues of quinoxalinones **37** – pyrido[2,3-*b*]pyrazin-3(4*H*)-ones **95** instead of quinoxalinones **37** in the rearrangement considered above makes it possible to synthesize aza-analogues of benzimidazoles – 1*H*-imidazo[4,5-*b*]pyridines **96** which are not easily accessible by classical Phillips–Ladenburg[3a,46b,47c,92b–e] and Weidenhagen[71,72,74,92e–g] reactions. The formation of 2-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)-3-arylquinoxalines **96a–d** from pyrido[2,3-*b*]pyrazin-2(1*H*)-ones **95a–d** and 1,2-DAB **5a** proceeds in AcOH under reflux for 35–47 h. It should be noted, that the reaction with refluxed AcOH for 3 h leads to the formation of 2-amino-3-azaanylide-quinoxaline-3-phenyl-2-carboxylic acids **97**. This has been illustrated by the reaction of 2-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)-3-phenylquinoxaline **95a** and 1,2-DAB **5a** (Table 4).[62f]
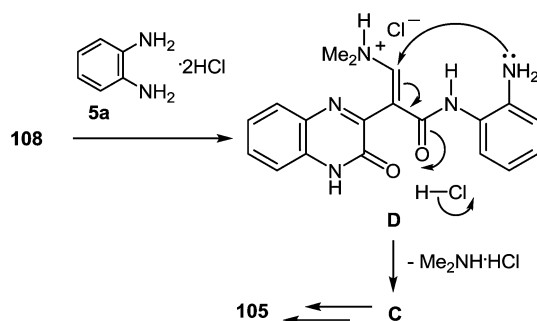
Scheme 38 A possible alternative mechanism for the formation of benzodiazepin-2(1*H*)-one derivative **105**.
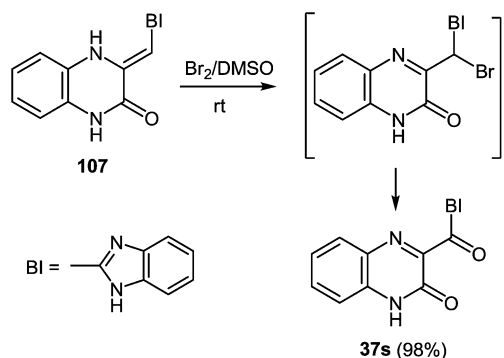
Scheme 39 The synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s**.
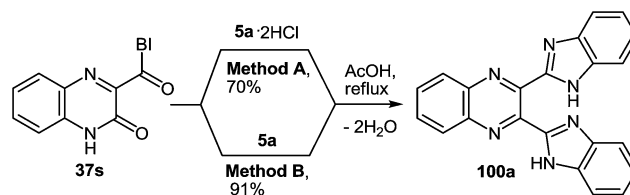
Scheme 40 The quinoxalinone-benzimidazole rearrangement in the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s** with both 1,2-DAB dihydrochloride and 1,2-DAB.

Table 5 Scope of 1,2-DABs in 2,3-bis(benzimidazol-2-yl)quinoxaline formation
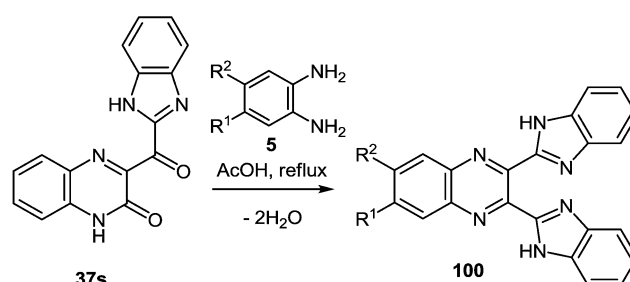
Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**5c**	Me	Me	**100b**	90
2	**5d**	Me	H	**100c**	86
3	**5f**	Cl	H	**100d**	89
4	**5h**	NO$_2$	H	**100e**	83
5	**5l**	CO$_2$H	H	**100f**	76
6	**5m**	COPh	H	**100g**	80

Compounds **96a–d**, in contrast to the compounds **40a–d** with the benzimidazole system in the investigated solutions of DMSO-d_6 exist as a tautomeric mixture of **96a–d** ⇆ **96′a–d**, resulting in the dissymmetric 1*H*-imidazo[4,5-*b*]pyridine system (Fig. 5). Benzimidazoles as imidazoles with a *N*-hydrogen ring are subjected to tautomerism, which becomes evident in

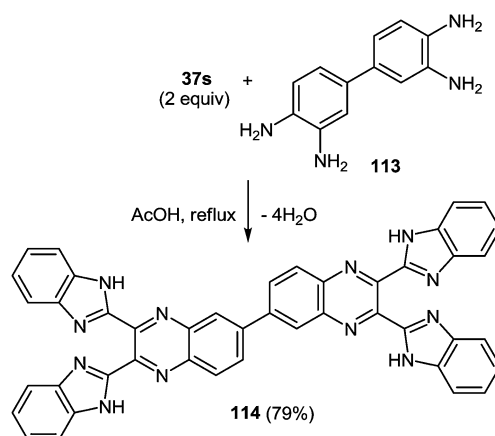**Scheme 41** The formation of 2,2′,3,3′-tetra(benzimidazol-2-yl)-6,6′-biquinoxaline.
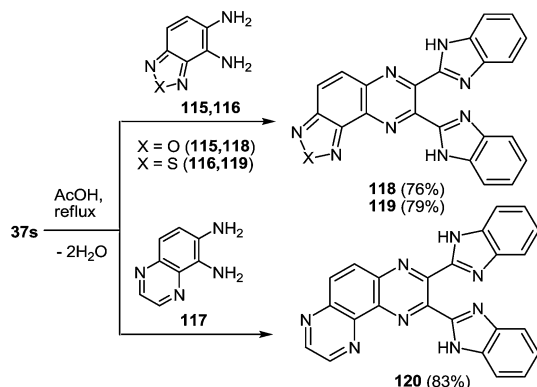
Scheme 42 The quinoxalinone-benzimidazole rearrangement in the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1H)-one **37s** with benzo[c]furane-4,5 − **115**, benzo[c]thiene-4,5 − **116** and quinoxaline-5,6 − **117** diamines.
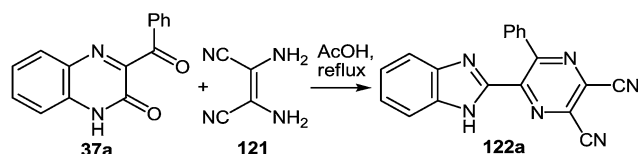
Scheme 43 Acid-catalyzed rearrangement.

unsymmetrically substituted compounds.[93] In the cases of imidazo[4,5-b]pyridines **96a–d** the dissymmetry was caused by the nitrogen atom of the pyridine ring.

4.2 Synthesis of 2,3-bis(benzimidazol-2-yl)quinoxalines

It is not a simple task to obtain high results in the synthesis of heterocyclic systems with two directly connected benzimidazole fragments with the known methods (by Phillips–Ladenburg[3a,46b,47c,92b–e] and Weidenhagen[71,72,74,92e–g] reactions). At least twice as many labor-consuming classical methods of the synthesis of benzimidazoles are involved.

It should be pointed out that there was only one paper[94] in which the formation of 2,3-bis(benzimidazol-2-yl)quinoxaline **100a** as a by product in the reaction of tetrachloropyridazine **98** and 1,2-DAB **5a** in N-methylpyrrolidone at 115 °C for 17 h has been described (Scheme 31). The yield of the main product of this reaction 5,6,7,8,13,14-hexaazapentaphene **99** obtained as a free base after treatment of the corresponding hydrochloride with aqueous sodium hydroxide is 15%. The yield of the by-product – 2,3-bis(benzimidazol-2-yl)quinoxaline **100a** has not been given in this paper. Therefore this method cannot be used as a preparative one for the synthesis of 2,3-bis(benzimidazol-2-yl)quinoxalines. The synthesis of other heterocyclic systems with two benzimidazole fragments cannot be used either.

It was suggested that the quinoxaline residue of the product **100a** was formed by the initial nucleophilic attack on position 4 and 5 of tetrachloropyridazine **98** by 1,2-DAB. Further the aerial oxidation, resulting in an intermediate 1,4-dichloropyridazino[4,5-b]quinoxaline **101** which might react with two more

molecules of 1,2-DAB to give the pyridazine-ring-opened system **100a** (Scheme 32).

As seen from the above data (see Section 4.1), the rearrangement proceeds very well with different aroyl- and alkanoyl-derivatives of quinoxalinones and as a result various benzimidazole derivatives are obtained. A further analysis of this

Table 6 Synthesis of 5,6-dicyano-3R-1H,1'H-spiro[pyrazine-2,2'quinoxalin]-3'(4'H)-ones
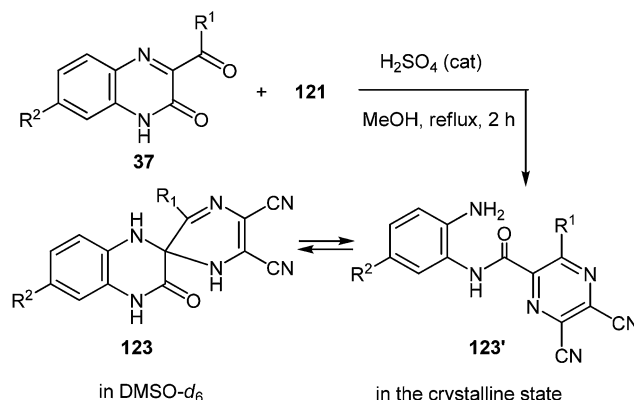
Entry	Substrate	R¹	R²	Product	Yield (%)
1	**37a**	Ph	H	**123a**	96, 74[a], 91[b]
2	**37b**	C₆H₄F–4	H	**123b**	92, 85[a], 88[b]
3	**37c**	C₆H₄Cl–4	H	**123c**	93, 82[a]
4	**37d**	C₆H₄Br–4	H	**123d**	93, 77[a]
5	**37e**	C₆H₄I–4	H	**123e**	95, 77[a]
6	**37t**	Ph	COPh	**123f**	95, 61[a]
7	**37u**	Ph	CO₂H	**123g**	89, 64[a]
8	**37g**	CH₂Ph	H	**123h**	95, 60[a]
9	**37j**	Me	H	**123i**	75, 61[a]

[a] p-TsOH was used instead of H₂SO₄. [b] HCl was used instead of H₂SO₄.

Table 7 Acid-catalysed rearrangement of 5,6-dicyano-3R-1H,1'H-spiro[pyrazine-2,2'-quinoxalin]-3'(4'H)-ones
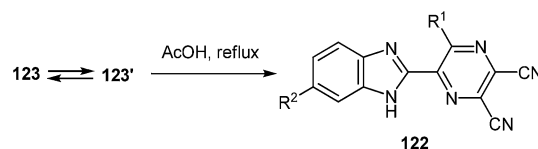
Entry	R¹	R²	Time	Product	Yield (%)
1	Ph	H	10 min	**122a**	90
2	C₆H₄F–4	H	10 min	**122b**	90
3	C₆H₄Cl–4	H	10 min	**122c**	91
4	C₆H₄Br–4	H	10 min	**122d**	89
5	C₆H₄I–4	H	10 min	**122e**	92
6	Ph	COPh	3 h	**122f**	89
7	Ph	CO₂H	3 h	**122g**	85
8	CH₂Ph	H	10 min	**122h**	92
9	Me	H	10 min	**122i**	93

Table 8 The synthesis of 4-alkyl-5,6-dicyano-1H,1'H-spiro[pyrazine-2,2'-quinoxalin]-3'-ones and 1-alkyl-2-(pyrazin-2-yl)benzimidazoles

37
37o R = n-Bu
37v R = n-Oct
37w R = n-Non
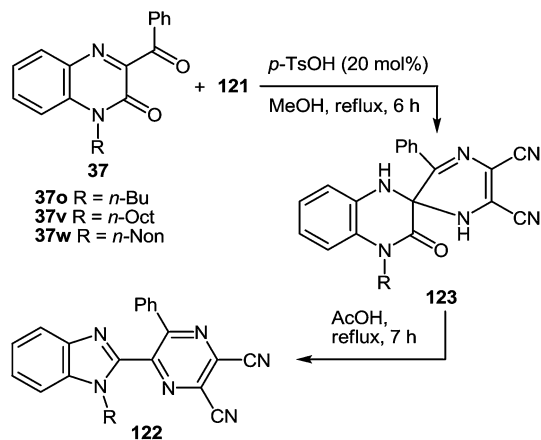
Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
1	n-Bu	123j	95	4	n-Bu	122j	58
2	n-Oct	123k	94	5	n-Oct	122k	60
3	n-Non	123l	97	6	n-Non	122l	60

strategy led us to examine how this rearrangement would proceed, if 3-hetaroylquinoxalin-2(1H)-ones were used instead of alkanoyl- or aroylquinoxalin-2(1H)-ones. Among heteroaroyl groups the benzimidazoyl group was of primary interest since on the one hand, the successful course of the reactions of the 3-(benzimidazo-2-yl)quinoxalin-2(1H)-one[95] with 1,2-DABs opens up a new and effective way of obtaining 2,3-bis(benzimidazol-2-yl)quinoxaline derivatives. The latter are inaccessible by any other known methods of constructing the benzimidazole system. On the other hand, this could prove whether the interaction of 3-(benzimidazo-2-yl)quinoxalin-2(1H)-one with 1,2-DAB dihydrochloride resulted in the benzodiazepine derivative, as previously cited in literature[95] (Scheme 33).

Kurasawa in his work[95] showed that the reaction of 3-benzimidazoylquinoxalinone 37s with 1,2-DAB dihydrochloride in boiling acetic acid resulted in a benzodiazepine derivative 102 (Scheme 33).

Since this is contrary to the above findings on the reactions of aroylquinoxalin-2(1H)-ones with 1,2-DAB,[62,96] proceeding with the formation of 2-benzimidazolylquinoxaline derivative it was decided to examine the results described in paper.[95] To this end, it was planned to synthesize 3-benzimidazoylquinoxalinone according to the following Scheme 34 described by Kurasawa.[95,97]

As depicted in Scheme 34 compound 103 at the very first stage to react with the Vilsmeier reagent [DMF–POCl$_3$, 1 : 1], at a temperature on water bath for 2 h, to give 3-(N,N-dimethylaminocarbonyl)furo[2,3-b]quinoxaline hydrochloride 104 (83%).[97a] After a detailed study of the structure of the reaction product, with the involvement of IR data[98] it was concluded that there was no compound 104, but its isomer – 1-N,N-dimethylaminomethylene-1,2-dihydrofuro[2,3-b]quinoxalin-2-one 108 (Scheme 35).

Apparently the formation of the furo[2,3-b]quinoxalin-2-one derivative 108 proceeds via the initial formation of compound A according to the first stage of the aliphatic Vilsmeier reaction, performed on the methylene group of the substituent at position 3 of quinoxalin-2(1H)-one 103. The latter undergoes intramolecular cyclization with the subsequent elimination of EtOH and HCl, results in the final product 108 (Scheme 36).

The next stage of the synthesis of 3-benzimidazoylquinoxalin-2(1H)-one 37s according to Scheme 34 is the reaction of 104 with 1,2-DAB dihydrochloride in acetic acid which resulted in the ring transformation to afford 3-(3,4-dihydroquinoxalin-2(1H)-on-3-yl)-1,2-dihydro-1,5-benzodiazepin-2(1H)-one hydrochloride 105.[97b]

The reaction of 108 with 1,2-DAB dihydrochloride in the same conditions afforded a compound, which was identified by NMR spectroscopy as 3-(3,4-dihydroquinoxalin-2(1H)-on-3-yl)-1,2-dihydro-1,5-benzodiazepin-2(1H)-onium chloride 105.[97b] The formation of benzodiazepin-2(1H)-one derivative 105 can be due to the attack of the amino group of 1,2-DAB dihydrochloride on the activated carbon atom of the N,N-dimethylaminomethylene group of furo[2,3-b]quinoxalin-2-one derivative 108 by the HCl and results in the formation of intermediate B. The latter undergoes intramolecular ring closure and ring opening processes, by the addition of the nitrogen atom of the second amino group of 1,2-DAB to the
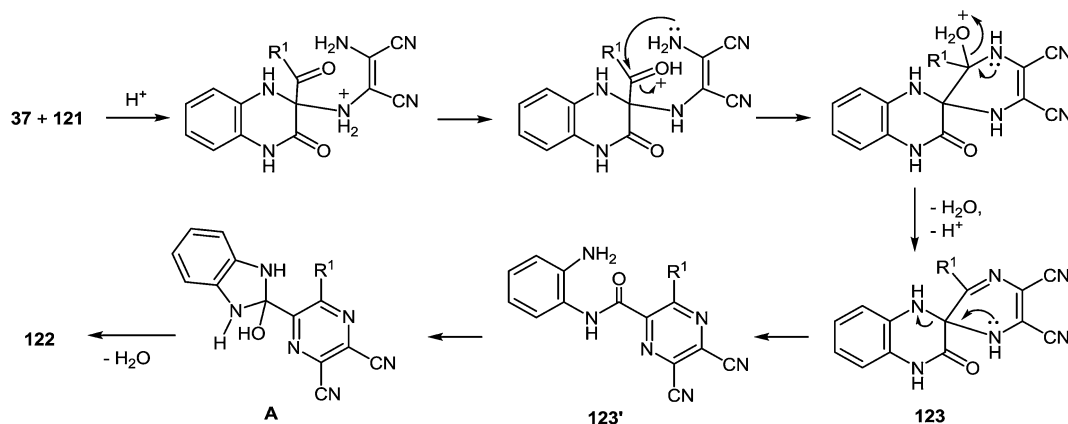
Scheme 44 A plausible mechanism for the formation of 2-(pyrazin-2-yl)benzimidazoles 122.

Table 9 Rearrangement of 3-benzoylquinoxalin-2(1H)-one and its derivatives in three component one-pot reaction

37,124,125
37a R = H, Z = O
37o R = n-Bu, Z = O
124 R = H, Z = NC₆H₄Me-2
125 R = H, Z = NC₆H₄Me-4

126
126a R¹ = Ph
126b R¹ = C₆H₄Br-4
126c R¹ = C₆H₄NO₂-4
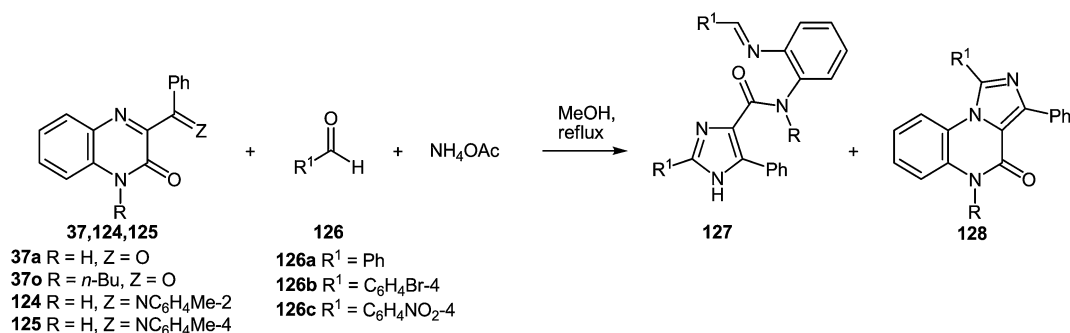
Entry	Substrates	Ratio **1/2**/NH₄OAc	Time (h)	Products	Ratio **127/128**[a]	Total yield (%) **127 + 128**
1	**37a**	**126a**	1/1/2	9	**127a + 128a** 2/1	5 (7)[b]
2	**37a**	**126a**	1/1/10	9	**127a + 128a** 1.8/1	30
3	**37a**	**126a**	1/2/10	7	**127a + 128a** 2/1	79 (79)[c]
4	**37a**	**126a**	1/3/10	7	**127a + 128a** 2/1	52
5	**37a**	**126b**	1/2/10	7	**127b + 128b** 1.4/1	83
6	**37a**	**126c**	1/2/10	7	**127c + 128c** 2.7/1	70
7	**37o**	**126a**	1/2/10	7	**127d + 128d**[d] Trace/1	52
8	**124**	**126a**	1/2/10	7	**127a + 128a** 1/1.2	61
9	**125**	**126a**	1/2/10	7	**127a + 128a** 4/1	64
10	**125**	**126b**	1/2/10	7	**127b + 128b** 2/1	59

[a] The ratio of compounds **127** and **128** was determined by ¹H NMR spectroscopy. [b] Isolated yield after reflux for 15 h. [c] Isolated yield when the reaction was carried out in the presence of L-proline. [d] Isolated yield of **128d** = 42%.

carbonyl group of the furan ring. The cleavage of the C–O bond results in the intermediate **C**. The 1,5-benzodiazepine system **C** is subsequently transformed into the final product **105** as shown above (Scheme 37).

A possible mechanism for the formation of benzodiazepin-2(1H)-one derivative **105** (Scheme 38) can be alternatively written as follows; the amination with 1,2-DAB dihydrochloride would occur at the carbonyl carbon of **108**, forming the corresponding amide of 1,2-DAB and the subsequent intramolecular Michael addition of mono-N-acylated 1,2-DAB **D** to form the 1,5-benzodiazepine system **C**, subsequently transformed into the final product **105** (Scheme 38).

Heating at reflux of the benzodiazepine derivative **105** in the aqueous acetic acid solution affected ring transformation as has been shown in paper[95] to give **106**, the treatment of which with a 5% sodium hydroxide yielded a free base **107** (Scheme 34). The final stage of the synthesis of 3-benzimidazoylquinoxalin-2(1H)-one **37s** according to Scheme 34 involves the oxidation of compound **107** with m-chloroperbenzoic acid (m-CPBA).[95] According to this method the yield of the desired product is approximately 40%, therefore it was used the method of oxidation for the synthesis of 3-benzimidazoylquinoxalin-2(1H)-one **37s**, which has been recently developed for similar compounds. This includes the treatment of 3-(α-bromobenzyl)quinoxalin-2(1H)-ones with DMSO.[63b] The reaction of 3-(benzimidazol-2-yl)methylenequinoxalin-2(1H)-one **107** with an equimolar amount of bromine in DMSO at room temperature for

24 h results in ketone **37s** with a quantitative yield. According to the Kornblum oxidation[100] the formation of the latter can be represented as an oxo-dehydrohalo-bisubstitution[101] formed in situ 3-(α-bromomethylimidazol-2-yl)quinoxalin-2-(1H)-one (Scheme 39).
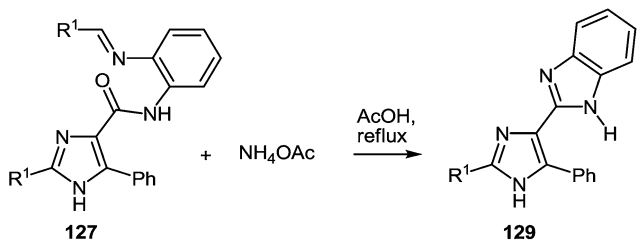
As expected the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1H)-one **37s** with 1,2-DAB dihydrochloride, proceeds with the formation of 2,3-bis-(1H-benzimidazol-2-yl)quinoxaline **100a** (Scheme 40), but not of the benzodiazepine derivative **102**, as described.[95] In this reaction when 1,2-DAB is used instead of 1,2-DAB dihydrochloride the yield of compound **100a** is almost quantitative.

Thus, the reactions of 3-benzimidazoylquinoxalin-2(1H)-one **37s** with both 1,2-DAB dihydrochloride and 1,2-DAB proceed according to the new quinoxalinone-benzimidazole rearrangement. There occurs the formation of 2,3-bis-(1H-benzimidazol-2-yl)quinoxaline **100a** and not of the benzodiazepine derivative **102**, as has been previously described. The reactions of synthesis of 3-benzimidazoylquinoxalin-2(1H)-one **37s** starting from 3-ethoxycarbonylmethylene-3,4-dihydroquinoxalin-2(1H)-one through the 3-(3,4-dihydroquinoxalin-2(1H)-on-3-yl)-1,2-dihydro-1,5-benzodiazepin-2(1H)-one hydrochloride **105** and 3-(benzimidazol-2-yl)methylen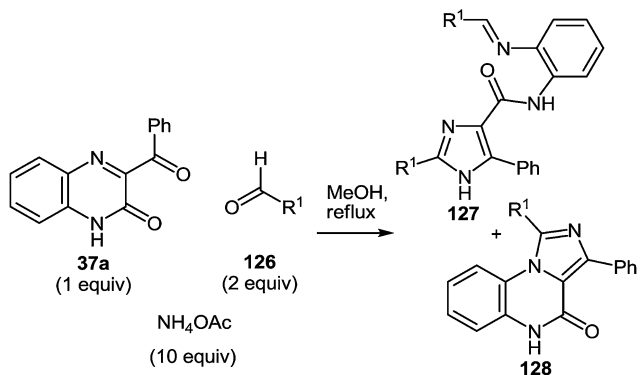equinoxalin-2(1H)-one **107** have also been reexamined and the published results[95,97] appropriately amended. A simple and efficient one-pot method for the synthesis of 3-benzimidazoylquinoxalin-2(1H)-one **37s** directly from 3-(benzimidazol-2-yl)methylenequinoxalin-2(1H)-one **107** has been described.

Table 10 3-Aroylquinoxalin-2(1H)-one derivatives as hetero analogues of α-diketones in the synthesis of functionalized imidazoles

Entry	Substrate	R[1]	Products (yield)
1	**126a**	Ph	**127a + 128a** (49%) (26%)
2	**126b**	C_6H_4Br-4	**127b + 128b** (47%) (33%)
3	**126c**	$C_6H_4NO_2$-4	**127c + 128c** (47%) (17%)
4	**126d**	C_6H_4F-4	**127e + 128e** (45%) (26%)
5	**126e**	C_6H_4Cl-4	**127f + 128f** (40%) (28%)
6	**126f**	C_6H_4I-4	**127g + 128g** (44%) (29%)
7	**126g**	Py-3	**127h + 128h** (38%) (42%)

Table 11 Synthesis of 2-(imidazol-4-yl)benzimidazoles **129a–d**

Entry	Substrate	R[1]	Product	Yield (%)
1	**127a**	Ph	**129a**	94
2	**127c**	$C_6H_4NO_2$-4	**129b**	99
3	**127e**	C_6H_4F-4	**129c**	98
4	**127h**	Py-3	**129d**	95

3-(Benzimidazo-2-yl)quinoxalin-2(1H)-one **37s** reacted not only with 1,2-DAB **5a** and its substituted analogues **5c, d, e, h, l, m** in AcOH at reflux. The formation of 2,3-bis(benzimidazol-2-yl)quinoxalines **100b–g** was observed in excellent 76–90% isolated yields (Table 5).[86]

The scope of the methodology, was studied first with respect to the 3,3′-diaminobenzidine **113** (Scheme 41). As seen, this chemistry is not limited to mono- and disubstituted systems, a compound with two 1,2-diaminobenzene fragments is an acceptable substrate as well.[102]

Investigations were also carried out with respect to the condensed 1,2-DABs. The 3-(benzimidazo-2-yl)quinoxalin-2(1H)-one **37s** was allowed to react with benzo[c]furane-4,5-diamine **115**, benzo[c]thiene-4,5-diamine **116** and quinoxaline-5,6-diamine **117** in AcOH at reflux (Scheme 42).[102] The isolated yields of the di(benzimidazol-2-yl)quinoxalines **118–120** proved high enough as well.

Thus, the results of the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1H)-one **37s** with a variety of 1,4-di-N-nucleophiles confirm the hypothesis, which has been proposed earlier (Scheme 16).[76]

Thus, we have developed a simple, mild and high yielding one-pot method to prepare quinoxalines and tethered quinoxaline-benzimidazoles. In this case the scope of the rearrangement was extended to other 1,4-di-N-nucleophiles, which enables a simple and efficient method for the preparation of a series of 2,3-bis(benzimidazol-2-yl)quinoxalines as well as of di(benzimidazol-2-yl)-furo[3,4-f]-, thieno[3,4-f]- and pyrazino[2,3-f]quinoxalines. This was accomplished by the rearrangement of 3-benzimidazoylquinoxalin-2(1H)-one on exposure to 1,2-DAB and its substituted and condensed derivatives. Considering the well documented medicinal utility of benzimidazoles and quinoxalines, these compounds consisting from the combination of the two scaffolds afford new opportunities to investigate their biological activity.

4.3 Synthesis of 2-(pyrazin-2-yl)benzimidazoles

Further exploration of the above strategy with the use of diaminomaleonitrile instead of 1,2-DABs has led to the development of a novel, simple method for the synthesis of 2-benzimidazolylpyrazines. In this case the results of study on a novel rearrangement of 3-aroyl- and alkanoylquinoxalin-2(1H)-ones and 2,3-diaminomaleonitrile as a N-nucleophile under the acid catalysis condition are presented.[103]

Regardless of the molar ratio of the reagents (1 : 1, 1 : 1.1, 1 : 2; **37a** : **121**) and reaction time (3, 9 or 17 h) the reaction of 3-benzoylquinoxalin-2(1H)-one (3-BQ) **37a** with 2,3-diaminomaleonitrile **121** proceeded in the same way with the formation of a ∼45% yield of the rearrangement product **122a** (Scheme 43), whereas 50% of 3-benzoylquinoxalin-2(1H)-one **37a** reverted. Diaminomaleonitrile **121** apparently undergoes polymerization. Adding a second equivalent of diaminomaleonitrile **121** to the reaction mixture obtained after boiling the equimolar ratio of reagents in acetic acid for 5 h did not lead to an increased yield of the desired product. Neither did the boiling for an additional 5 h.

In order to improve the yield of the rearrangement product there were used the principles of the previously proposed hypothesis (Scheme 16).[76] In accordance with this hypothesis here appeared the problem of the synthesis of the spiro[pyrazine-2,2′-quinoxalin]-3′(4′H)-one derivative. For this purpose the necessary pyrazine ring system at position 2 of quinoxalin-2(1H)-one **37a** via the modified Körner and Hinsberg[104] reaction
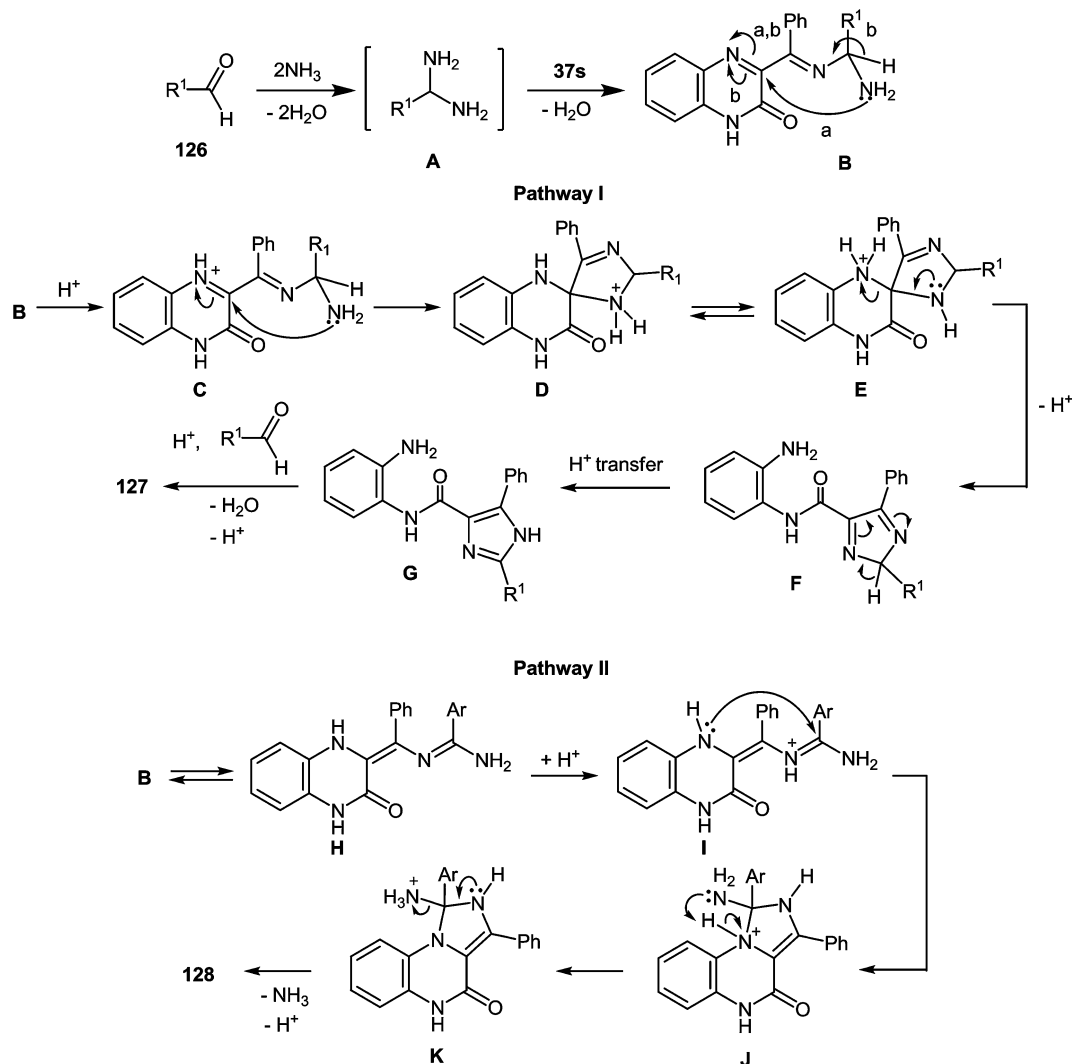
Scheme 45 A plausible mechanism for the formation of imidazoles. *Pathway I* – acid catalysis through ring-closure and ring-opening processes. *Pathway II* – *via* a novel acid catalysis imidazoannulation of quinoxalin-2(1H)-ones.
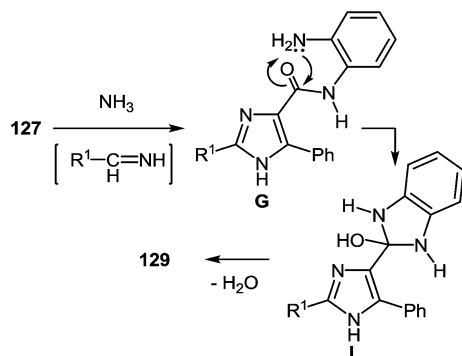
Scheme 46 A possible mechanism for the formation of 2-(imidazol-4-yl)benzimidazoles **129**.

(the synthesis of quinoxalines by condensation of α-dicarbonyl compounds with 1,2-DAB) has been installed. This was achieved by the reaction of **37a** with diaminomaleonitrile **121** in a boiling

solution of MeOH in the presence of a catalytic amount of H_2SO_4. In this reaction the 3-BQ **37a** was considered as an heteroanalogue of an α-dicarbonyl compound. The reaction proceeded smoothly for 2 h to give the desired spiro-compound, 5,6-dicyano-3R-1H,1′H-spiro[pyrazine-2,2′-quinoxalin]-3′(4′H)-one **123a** in 96% yield (Table 6, entry 1). The optimum molar ratio of reagents **37a**:**121** was 1.0 : 1.1. Under these conditions other 3-aroyl- (**37a–e, t, u**) and 3-alkanoyl- (**37g, i**) derivatives of quinoxalin-2(1H)-ones behaved similarly resulting in high (75–96%) yields of the corresponding spiro-derivatives on reaction with diaminomaleonitrile **121** (Table 6). These examples of the reactions of **37a, d** with **121** showed that increasing the reaction time up to 10 h resulted in a mixture of the products of rearrangement of **122a, d** and spiro-derivatives of quinoxalinones **123a, d** in a ratio of ∼1 : 3 (yield 89%), and up to 20 h in a ratio of ∼1 : 1 (yield 97%). When carrying out the reactions of quinoxalines **37a–e, g, j, t, u** with diaminomaleonitrile **121** for 6 h in the presence of p-TsOH (20 mol%) as a catalyst the formation of spiro-compounds **123a–i** occurred in yields of 60–85% (Table

6). The reactions of quinoxalin-2(1H)-ones **37a, b** with **121** show that in the presence of catalytic amounts of HCl, spiro-compounds **123a–b** are formed in 2 h and the yields of products were 91% and 88%, respectively (Table 6, entries 1 and 2).

Spiro-compounds **123a–e, h, i** without substituents on the benzene ring of the quinoxaline system were quantitatively transformed into the desired 2-(pyrazin-2-yl)benzimidazole **122a–e, h, i** in boiling AcOH in 10 min (Table 7, entries 1–5, 8, 9). The substituted spiro-derivatives of quinoxalin-2(1H)-ones **123f, g** underwent the rearrangement only after 3 h in boiling AcOH (Table 7, entries 6, 7).

The formation of spiro-compounds also proceeded with the N-alkylated derivatives of quinoxalin-2(1H)-ones **37o, v, w** to give N-alkylated spiro[pyrazine-2,2'-quinoxalin]-3'(4'H)-ones **123j–l** (Table 8). p-TsOH was more suitable as the catalyst for these cases. It should be pointed out that the rearrangement of N-alkylated spiro-compounds **123j–l** was slower than with non-alkylated spiro-compounds **123a–i**. Thus, boiling the spiro-compounds **123j–l** for 5 min resulted in the formation of the product of rearrangement in a ~25% yield, 30 min: ~50%, 3 h: ~75%, 7 h: ~100%.

It is worthy of note that the products of the reaction of 3-aroyl(alkanoyl)quinoxalin-2(1H)-ones **37a–e, g, i, t, u** and N-alkyl-3-BQs **37o, v, w** with diaminomaleonitrile **121** in DMSO-d_6 exist solely in spiro-cyclic-forms **123a–l**, whereas in the crystalline state they exist only as open chain forms **123'a–l**.[103]

Based of the chemistry of quinoxalinones,[105] diaminomaleonitrile,[106] and the above data, it is reasonable to assume that as the first step the formation of 2-(pyrazin-2-yl)benzimidazoles **122** involves addition of the amino group of diaminomaleonitrile **121** to the C(3) atom of quinoxalin-2(1H)-one **37**. The next step involves a nucleophilic attack of the second amino group of **121** on the benzoyl carbonyl group to form the spiro-quinoxaline derivative **123**. Rearrangement of the spiro-quinoxalinone **123** is then assumed to occur according to Scheme 46, which proceeds via cascade reactions involving: (a) acid-catalyzed ring-opening with cleavage of the C(3)–N(4) bond in the spiro-compound **123** with the formation of an intermediate quinoxaline derivative **123'**, (b) intramolecular nucleophilic attack by the amino group on the carbonyl group with the formation of intermediate hydroxy-derivative **A**, and (c) elimination of water leading to the final product **122** (Scheme 44).

An efficient and versatile metal-free method for the preparation of a series of 2-(pyrazin-2-yl)benzimidazoles has been developed. This was accomplished by the novel rearrangement of 3R-5,6-dicyano-1H,1'H-spiro[pyrazine-2,2'-quinoxalin]-3'(4'H)-ones easily obtained from 3-aroyl- and 3-alkanoylquinoxalin-2(1H)-ones on exposure to diaminomaleonitrile. The key advantages are the simplicity of the operation, high yields, easy availability of 3-aroyl- and alkanoylquinoxalin-2(1H)-ones, as well as the simple work-up and purification of the products.
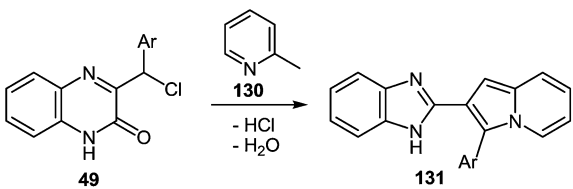
4.4 Synthesis of 2-(imidazol-4-yl)benzimidazoles

In continuation of the efforts to develop quinoxalin-2(1H)-one.[62c,f,107] based on synthetic methodologies, a simple, mild and expeditious synthesis of 2,4,5-trisubstituted imidazoles in high yields with 3-aroylquinoxalin-2(1H)-ones as hetero analogues of α-diketones has been developed (Table 9).[108]

To determine the scope and generality of this reaction, various substituted aldehydes and 3-pyridinecarboxaldehyde were utilized. The desired products were obtained and the results are summarized in Table 10.
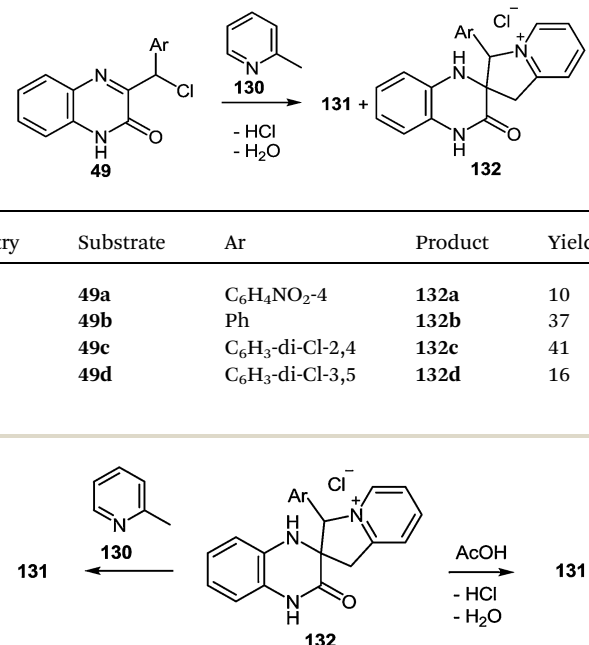
The presence of the o-iminoanilide substituent at position 4 of imidazoles **127** makes it possible to use them in further syntheses. Based on the four imidazole derivatives **127a, c, e, h** it was shown that the reaction of these compounds with

Table 12 Synthesis of benzimidazoles from quinoxalinones and α-picoline via rearrangement
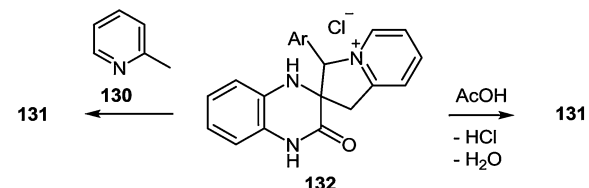
Entry	Substrate	Ar	Product	Yield (%)
1	**49a**	C$_6$H$_4$NO$_2$-4	**131a**	72
2	**49b**	Ph	**131b**	78
3	**49c**	C$_6$H$_3$-di-Cl-2,4	**131c**	76
4	**49d**	C$_6$H$_3$-di-Cl-3,5	**131d**	65
5	**49e**	CH$_2$Ph	**131e**	70

Table 13 Reaction of 3-(α-chloro)benzylquinoxalin-2(1H)-ones **49** with in α-picoline **130**

Entry	Substrate	Ar	Product	Yield (%)
1	**49a**	C$_6$H$_4$NO$_2$-4	**132a**	10
2	**49b**	Ph	**132b**	37
3	**49c**	C$_6$H$_3$-di-Cl-2,4	**132c**	41
4	**49d**	C$_6$H$_3$-di-Cl-3,5	**132d**	16

Scheme 47 The rearrangement of spiro-quinoxalinones **132**.
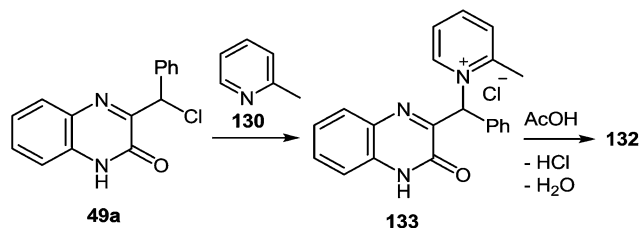
Scheme 48 The synthesis and rearrangement of 2-methyl-1-[(3-oxo-3,4-dihydroquinoxalin-2-yl)(phenyl)methyl]pyridinium chloride **133**.
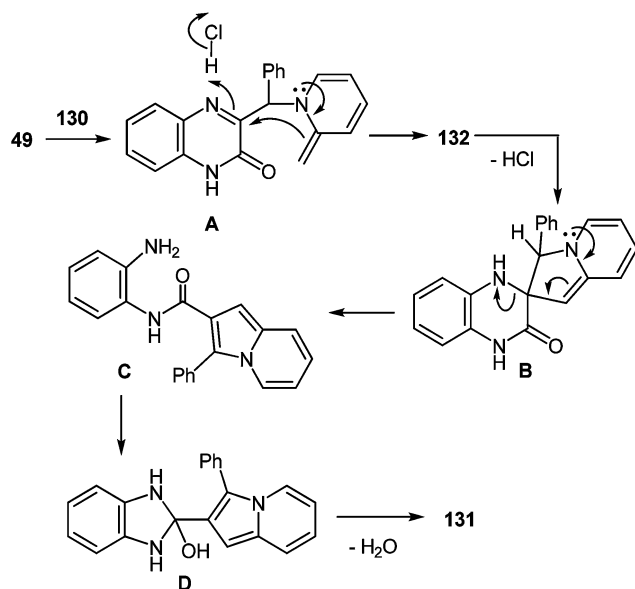
Scheme 49 Proposed mechanism of the rearrangement.

ammonium acetate in acetic acid proceeds with the formation of 2-(imidazol-4-yl)benzimidazoles **129a–d** in almost quantitative yields (Table 11).

A plausible mechanism for the synthesis of imidazoles, imidazo[1,5-a]quinoxalin-4(5H)-ones and benzimidazoles has been proposed (Scheme 45). The formation of the diamine intermediate **A** takes place during the initial stage of the reaction. Intermediate **A** condenses with the 3-benzoylquinoxalin-2(1H)-one **37s** followed by dehydration to afford the imino intermediate **B**, which is transformed in two different ways (*pathway I* and *pathway II*). *Pathway I* proceeds by cascade reactions involving: (a) acid-catalyzed ring-closure of intermediate **C** with the formation of spiro-compound **D**, (b) acid-catalyzed ring-opening of spiro-compound **E** with the formation of the imidazole derivative **F**, which is rearranged into the imidazole derivative **G** *via* a [1,5] hydrogen shift, and (c) reaction of the latter with the aldehyde to form compound **127**. *Pathway II* involves the tautomerism of intermediate **B** with the formation of compound **H**, which under acid catalysis undergoes intramolecular cyclization to give **I**. The final product **128** is formed following the elimination of ammonia through intermediates **J** and **K**.

It is apparent that the formation of 2-(imidazol-4-yl)benzimidazoles **129a–d** involves the ammonolysis of imidazoles **127a, c, d, g** to form the corresponding o-aminoanilide derivative **G** as the first step. The next step involves an intramolecular nucleophilic attack by the amino group on the carbonyl group with the formation of the intermediate hydroxy-derivative **L**, and then the elimination of water. This leads to the formation of the final product **129** (Scheme 46).

This was accomplished by the novel ring-opening of 3-aroylquinoxalin-2(1H)-ones on exposure to diaminoaryl-methanes intermediately generated from arylaldehydes and ammonium acetate. The introduction of the o-iminoanilide fragment at position 4 of the imidazole derivatives with the help of this method makes it possible to synthesize 2-(imidazol-4-yl)benzimidazoles. The simplicity of this method, high yields, easy work-up and purification of compounds by crystallization are the key advantages.

Table 14 Synthesis of 3′-aryl-1,2,3,4,4′,5′-hexahydro[quinoxalin-2,5′-pyrazol]-3-ones
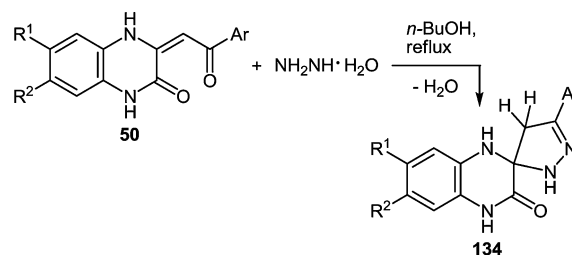
Entry	Substrate	R^1	R^2	Ar	Product	Yield (%)
1	**50a**	H	H	Ph	**134a**	81
2	**50b**	Me	Me	Ph	**134b**	76
3	**50c**	H	Cl	Ph	**134c**	64
4	**50d**	NO_2	H	Ph	**134d**	73
5	**50e**	H	H	C_6H_4Me-4	**134e**	77
6	**50f**	H	H	C_6H_4Cl-4	**134f**	73

Table 15 Synthesis of 2-(pyrazol-3-yl)benzimidazoles
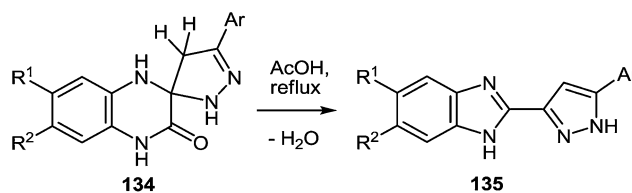
| Entry	Substrate	R^1	R^2	Ar	Product	Yield (%)
1	**134a**	H	H	Ph	**135a**	99
2	**134b**	Me	Me	Ph	**135b**	99
3	**134c**	H	Cl	Ph	**135c**	98
4	**134d**	NO_2	H	Ph	**135d**	96
5	**134e**	H	H	C_6H_4Me-4	**135e**	99
6	**134f**	H	H	C_6H_4Cl-4	**135f**	85

5 Synthesis of 2-(3-arylindolizin-2-yl) benzimidazole

One of the common reactions of α-haloketones in the chemistry of heterocycles is the Chichibabin reaction, that is, the synthesis of indolizines by interaction of α-picoline with α-haloketones. It was carried out in a series of reactions according to Chichibabin. Thus, the reaction of quinoxalin-2-one **49** (see Subsection 2.3E) with α-picoline **130** at reflux results in high yields of the corresponding 2-(indolizinyl)benzimidazoles **131** (Table 12). As is evident from the structure of compounds **131**, the C(2)–C(3)–C(Cl)Ar and N=C–Me fragments of quinoxaline **49** and α-picoline **130** are involved in constructing the two new heterocyclic rings.[89,107a,109]

Initially, a complete dissolution of compounds **49** is observed in refluxing the α-picoline solution. After that there rapidly occurs an abundant precipitation of crystals which gradually dissolve during the course of the reaction. The yield of crystalline products with a precise melting point, are obtained, for example, after refluxing quinoxalin-2(1H)-one **49c** in α-picoline **130** for 1 h, and the yield is 41% (Table 13).

It should be noted that spiro-compound **132** is quantitatively transformed into 2-(3-arylindolizin-2-yl)benzimidazole **131** not only in boiling α-picoline, but also in acetic acid (Scheme 47).

A first-stage product resulting from the nucleophilic displacement of the Cl atom by the pyridine *N* atom of α-picoline under milder reaction conditions than are required for the formation of a spiro-compound or its rearrangement into a benzimidazole derivative was isolated and characterized. For instance, when 3-(α-chlorobenzyl)quinoxalin-2(1H)-one **49a** was stirred in α-picoline **130** at 50 °C for 3 h (Scheme 48), it was possible to obtain the first stage product of the reaction, that is, compound **133**, which in boiling acetic acid is transformed into a rearrangement product **132** in quantitative yields.[89]

The formation of the rearrangement product can be represented by Scheme 49. According to this scheme, the initial step involves the nucleophilic displacement of the Cl atom by the pyridine *N* atom, which is followed by a cascade transformation. The latter involves: (a) dehydrochlorination with the abstraction of a methyl H atom of α-picoline, (b) intramolecular
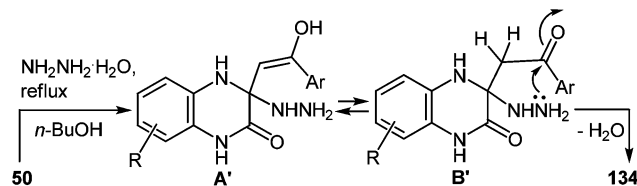
Scheme 51 Proposed mechanism of the rearrangement with the initial attack on the C(3) atom of the quinoxalin-2(1H)-one.
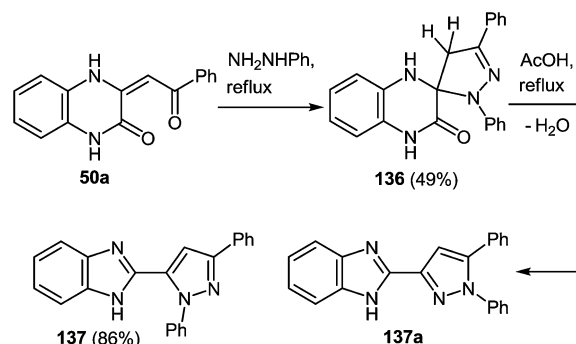
Scheme 52 Phenylhydrazine as nucleophilic reagent in the rearrangement of 3-arylacylidene-3,4-dihydroquinoxalin-2(1H)-one.
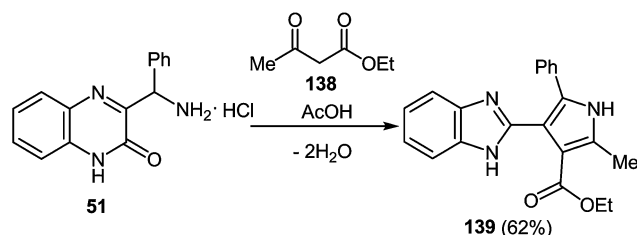
Scheme 53 The rearrangement of 3-(α-aminobenzyl)quinoxalin-2-(1H)-one hydrochloride in the reaction with acetoacetic ester.

nucleophilic addition of the methylidene C atom of the α-picoline fragment to the azomethine C atom of the quinoxaline system (spiro-compound **B**), (c) cleavage of the C(3)–N(4) bond
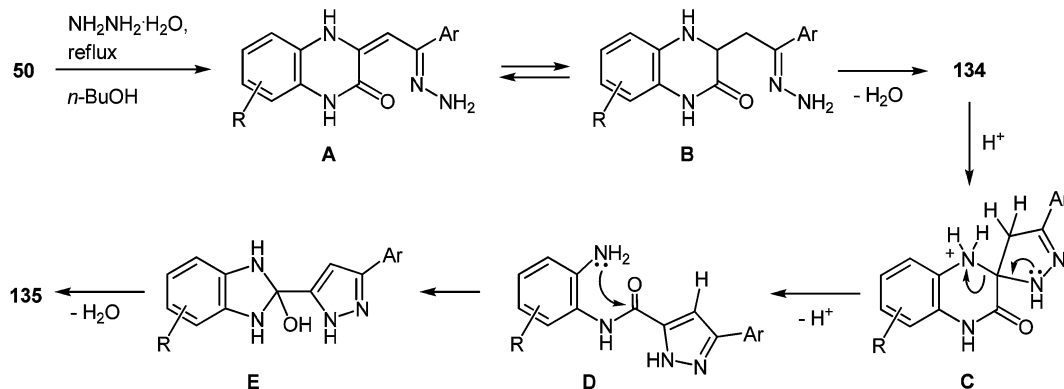
Scheme 50 Proposed mechanism of the rearrangement with the initial attack on the aroyl carbonyl group.

(*N*-substituted 1,2-DAB **C**), (d) closure of a five-membered ring (benzimidazoline **D**), and (e) elimination of water.

According to this scheme, the initial step involves the nucleophilic displacement of the Cl atom by the pyridine *N* atom, which is followed by a cascade transformation. The latter involves: (a) dehydrochlorination with the abstraction of a methyl H atom of α-picoline, (b) intramolecular nucleophilic addition of the methylidene C atom of the α-picoline fragment to the azomethine C atom of the quinoxaline system (spiro compound **B**), (c) cleavage of the C(3)–N(4) bond (*N*-substituted 1,2-DAB **C**), (d) closure of a five-membered ring (benzimidazoline **D**), and (e) elimination of water.

3-(α-Haloarylmethyl)- and 3-(α-halophenethyl)quinoxalin-2(1*H*)-ones, as well as their various derivatives have been shown to react with α-picolines, providing high yields of 3-aryl- and 3-alkylindolizinylbenzimidazoles.

6   Synthesis of 2-(pyrazol-3-yl) benzimidazoles

One of the most popular reactions of β-diketones in heterocyclic chemistry is the Knorr reaction, that is, the synthesis of pyrazoles by interaction of β-diketones with hydrazines. It has been described that the interaction of 3-(arylacylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones **50** (see Subsection 2.3E) with hydrazine hydrate in boiling butanol solution proceeds with the formation of 3′-aryl-1,2,3,4,4′,5′-hexahydro[quinoxalin-2,5′-pyrazol]-3-ones **134a–f** in good yields (Table 14).[76a,107a,110]

Boiling spiro-quinoxalin-2,5′-pyrazol-3-ones **134a–f** in an acetic acid solution for 8 h results in the acid catalysis rearrangement with the release of water and the formation of corresponding 2-(pyrazol-3′-yl)benzimidazoles in quantitative yields (Table 15).

Thus, both the formation of spiro-quinoxalinones **134a–f** and their rearrangement into the corresponding pyrazolylbenzimidazoles **135a–f** proceed in high yields (Table 14 and 15). As is evident from the structure of compounds **135a–f**, the C(2)–C(3)=CH–C(O)–Ar fragment of quinoxalines **50a–f** and hydrazine hydrate are involved in the formation of the heterocyclic systems.

On the basis of the known chemistry of hydrazines,[111] ketones,[112] and quinoxalinones[105] it is reasonable to assume that the first stage of the reaction mechanism involves the addition of the hydrazine to the carbonyl group of the 3-arylacylidene fragment of quinoxalin-2(1*H*)-one **50** with the formation of intermediate **A** capable of reversible tautomerization to intermediate **B**. The next step involves a nucleophilic attack of the amino group on the C(3) atom of the quinoxalin-2(1*H*)-one to form the spiro-quinoxaline derivative **134**. Rearrangement of the spiro-quinoxaline is then assumed to occur according to Scheme 50, which proceeds by cascade reactions involving: (a) acid-catalyzed ring-opening in spiro-compound **C** with the intermediate formation of pyrazolo derivative **D**, (b) intramolecular nucleophilic attack by the amino group on the carbamoyl carbonyl group with the intermediate formation of hydroxy-derivative **E**, and (c) elimination of water leading to

the formation of the final product **135**. It was shown that the reaction does not proceed in neutral or aprotic solvents.

It should be pointed out that the formation of spiro-quinoxaline derivative **134** could be due to the Michael addition of hydrazine to the partially positive C(3) atom of the quinoxalin-2(1*H*)-one **50** in the first stage of the reaction mechanism with the formation of intermediate **A′** capable of reversible tautomerization to intermediate **B′**. Then cyclization involves the nucleophilic attack of the amino group on the carbonyl group of the 3-arylacylidene fragment of quinoxalin-2(1*H*)-one (Scheme 51).

It is worth noting that the reaction of phenylhydrazine with 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-one **50a** proceeds similarly to the reaction with hydrazine hydrate. This involves the formation of spiro-compound **136**, which rearranges into pyrazolylbenzimidazole **137**, and no other possible regioisomer **137a**, in boiling acetic acid (Scheme 52).

This was accomplished *via* a novel quinoxalinone-benzimidazole rearrangement of 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones on exposure to hydrazine hydrate and phenylhydrazine. The reaction is readily applicable to large scale synthesis.

7   Synthesis of 2-(pyrrol-3-yl) benzimidazole

One of the most popular reactions of α-aminoketones in heterocyclic chemistry is another Knorr reaction, that is, the synthesis of pyrroles by the interaction of α-aminoketones with β-dicarbonyl compounds. Assuming that 3-(α-aminobenzyl)quinoxalin-2-(1*H*)one is the very analog of α-amineketones we have carried out the reaction of 3-(α-aminobenzyl)quinoxalin-2-(1*H*)-one hydrochloride **51** (see Subsection 2.3E) with acetoacetic ester **138** in the boiling acetic acid. Reaction proceeds with the contraction of the pyrazine ring system as a result of the rearrangement involving C(2)-C(3)-C(NH₂)Ph and the C(2)-
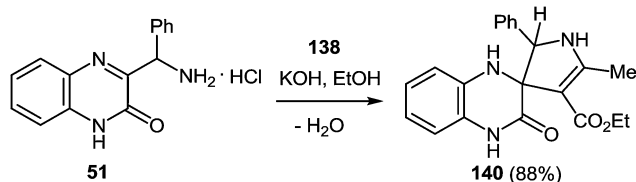
Scheme 54   The synthesis of spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′*H*)-one.
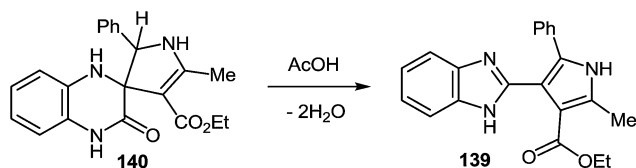
Scheme 55   Acid-catalyzed rearrangement of spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′*H*)-one **140**.

C(3) fragments of the quinoxalinone system and acetoacetic ester, respectively, with the formation of 2-(5-methyl-2-phenyl-4-ethoxycarbonyl-pyrrol-3-yl)benzimidazole **139** (Scheme 53).[76b]

Instead of the 3-(α-aminobenzyl)quinoxalin-2-(1H)-one **51** hydrochloride in the reaction with acetoacetic ester **138** its free base is used. This has no significant effect on the yield of the product of the rearrangement, which is apparently associated with the occurrence of various acid catalyzed side reactions involving acetoacetic ether.

To improve the yield of the product of the rearrangement the main principle of this rearrangement, proposed above was used (see Subsection 2.3D). In accordance with the above principle the spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′H)-one **140** was synthesized. The 3-(α-aminobenzyl)quinoxalin-2(1H)-one **51**, was considered to be the hetero analogue of α-aminocarbonyl compound according to the Knorr reaction[113] (*i.e.* obtaining pyrroles by the condensation of α-aminoketones with ketones containing an activated methylene group). Thus, at position 2 of quinoxalinone **51** the necessary pyrrolidine system has been set up with the help of the reaction of the compound **51** with acetoacetic ester **138** in EtOH in the presence of KOH. The reaction proceeds smoothly with the formation of the desired spiro-compound – 5-methyl-2-phenyl-4-ethoxycarbonyl-1′H-spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′H)-one **140** with high yields (88%) (Scheme 54). It should be noted that the reaction proceeds well enough both at room temperature (12 h) and by reflux (4 h).

Boiling the compound **140** in acetic acid for 1 h leads to the expected benzimidazole **139** in quantitative yields (Scheme 55).

The formation of the rearrangement product in the reaction of 3-(α-aminobenzyl)quinoxalin-2(1H)-one **51** with acetoacetic ester can be represented as shown below in Scheme 58. According to the scheme, the formation of spiro-compound **140** occurs at the initial stage. In reaction conditions it further undergoes acid-catalyzed rearrangement. The latter involves the disclosure of the pyrazine ring of the quinoxalin-2(1H)-one system on the N(1)–C(2) bond in the intermediate salt **A** and the
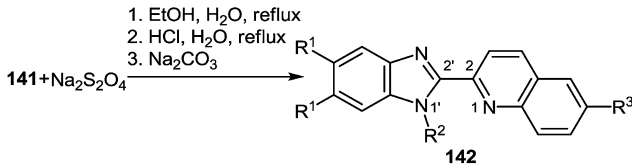
closure of the imidazole ring of the benzimidazole system with the newly formed amino group and the carbonyl group of carbamoyl fragment in the pyrrole derivative **B** (Scheme 56).

It should be pointed out that other substituted derivatives of 3-(α-aminobenzyl)quinoxalin-2-(1H)-one also successfully react not only with acetoacetic ester but with other esters of β-oxoacids, resulting in corresponding derivatives of 2-(pyrrol-3-yl) benzimidazole in high yields.

8 Synthesis of 2-(benzimidazol-2-yl) quinolines

One of the most popular reactions of usual ketones in the heterocyclic chemistry is the Friedländer reaction, that is, the

Table 16 One-pot synthesis of 2-(benzimidazol-2-yl)quinolines from 3-(β-2-nitrostyryl)quinoxalin-2(1H)-ones

Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**141a**	H	H	H	**142a**	80
2	**141b**	H	Me	H	**142b**	76
3	**141c**	H	Et	H	**142c**	74
4	**141d**	H	*n*-Pr	H	**142d**	53
5	**141e**	H	*n*-Bu	H	**142e**	69
6	**141f**	H	*n*-Pent	H	**142f**	70
7	**141g**	H	*n*-Hex	H	**142g**	54
8	**141h**	Me	H	H	**142h**	79
9	**141i**	H	H	Cl	**142i**	59
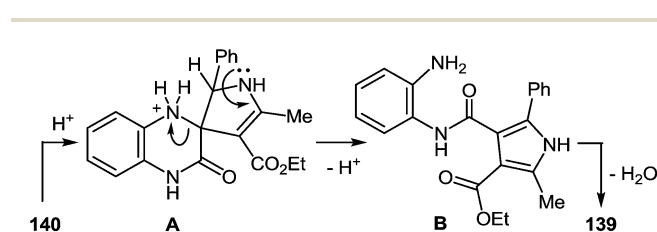
Scheme 56 Proposed mechanism of the rearrangement.
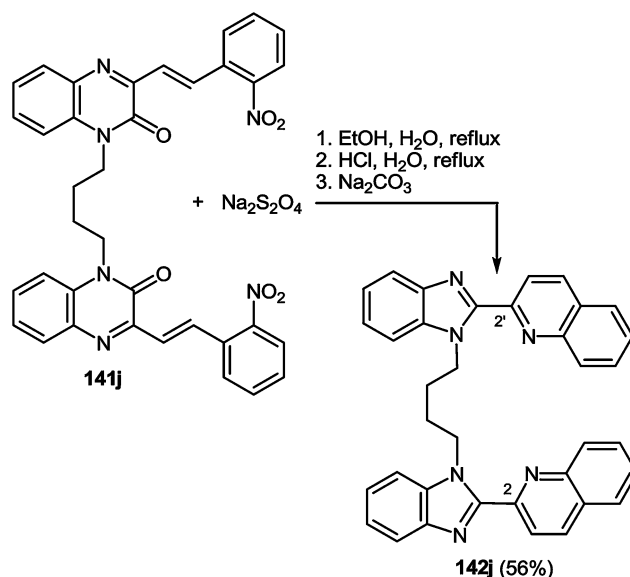
Scheme 58 Synthesis of 1,4-bis[2-(quinolin-2-yl)-1H-benzimidazol-1-yl]butane.

Scheme 57 Synthesis of 3-(β-2-nitrostyryl)quinoxalin-2(1H)-ones.
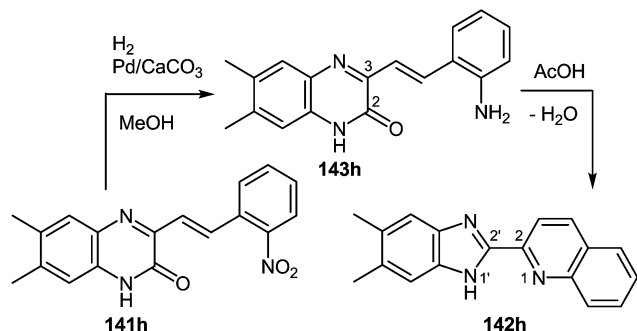
Scheme 59 Synthesis of 2-(benzimidazol-2-yl)quinoline from 3-(β-2-nitrostyryl)-6,7-dimethylquinoxalin-2(1*H*)-one *via* corresponding amino derivative.
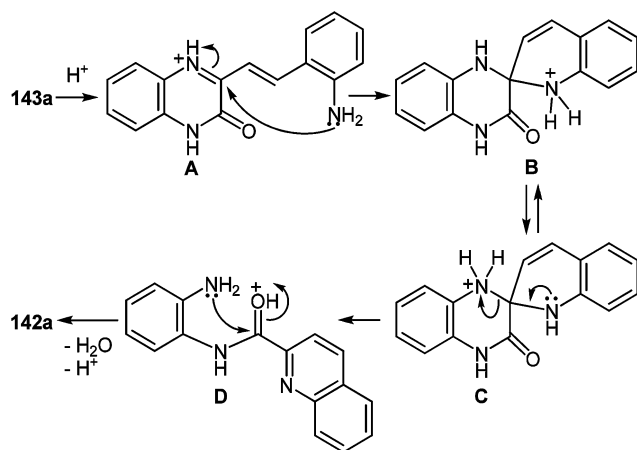
Scheme 60 Proposed mechanism of the rearrangement.

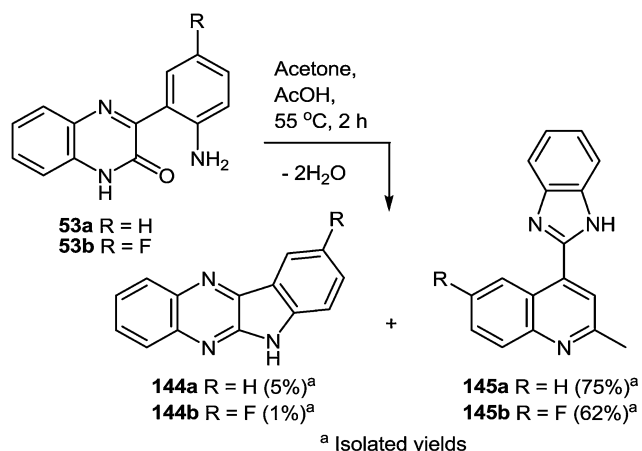**Scheme 61** The reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones derivatives **53a, b** with acetone.

synthesis of quinolines by their interaction with *o*-acylarylamines in basic or acid catalysis conditions.

This reaction has been modified according to the system based on aromatic aldehydes **126** and 3-methylquinoxalinones **52** (see Subsection 2.3E), easily available from methylpyruvates

Table 17 Reaction of 3-(2-aminophenyl)-quinoxalin-2(1*H*)-ones **53a, b** with acetophenones **146a–f**
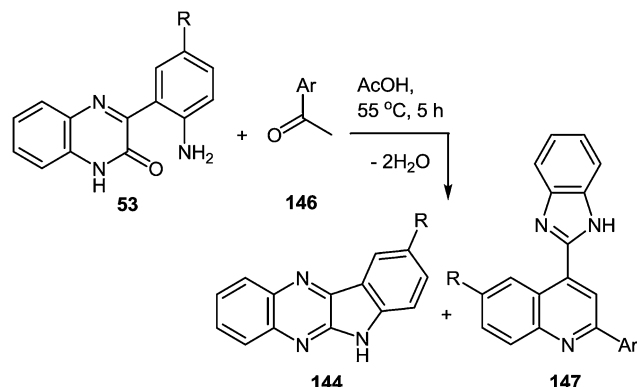
Entry	53	R	146	Ar	Products	Yield (%)	
						144	147
1	**53a**	H	**146a**	Ph	**144a + 147a**	6	80
2	**53a**	H	**146b**	C6H4Br-4	**144a + 147b**	4	76
3	**53a**	H	**146c**	C6H4Br-3	**144a + 147c**	4	78
4	**53a**	H	**146d**	C6H4Br-2	**144a + 147d**	4	73
5	**53a**	H	**146e**	C6H4Cl-4	**144a + 147e**	4	77
6	**53a**	H	**146f**	C6H4Cl-2	**144a + 147f**	4	71
7	**53b**	F	**146a**	Ph	**144b + 147g**	1	68
8	**53b**	F	**146b**	C6H4Br-4	**144b + 147h**	1	66
9	**53b**	F	**146c**	C6H4Br-3	**144b + 147i**	1	64
10	**53b**	F	**146d**	C6H4Br-2	**144b + 147j**	1	61
11	**53b**	F	**146e**	C6H4Cl-4	**144b + 147k**	2	65
12	**53b**	F	**146f**	C6H4Cl-2	**144b + 147l**	1	62

and 1,2-DABs. The first stage of the modification involves the formation of *o*-nitrostyryl derivatives of quinoxalin-2(1*H*)-one **141** (Scheme 57).[107c]

The second stage is based on the reduction of *o*-nitrostyryl derivatives **141** when exposed to Na2S2O4 (sodium hydrosulfate, sodium dithionate). *O*-Aminonitrostyryl derivatives of quinoxalin-2(1*H*)-one, obtained in these conditions immediately undergo acid-catalyzed rearrangement with the formation of corresponding benzimidazolyl quinoline derivatives. As is evident from the structure of compounds **142**, the C(2)–C(3) fragment and the β-2-nitrostyryl substitute at position 3 of the quinoxalin-2(1*H*)-one system, are involved in constructing two new heterocyclic systems (Table 16).

This reaction also proceeded with a compound **141j** possessing two 3-(β-2-nitrostyryl)quinoxalin-2(1*H*)-one fragments, with the formation of a benzimidazole-monopodand with terminal benzimidazole fragments at C(2) and C(2′) positions of the quinoline ring system (Scheme 58).

To investigate the reaction mechanism, the reduction of 3-(β-2-nitrostyryl)-6,7-dimethylquinoxalin-2(1*H*)-one **141h** with hydrogen using a 10 mol% Pd/CaCO3 as the catalyst in methanol has been performed and the corresponding 3-(β-2-aminostyryl)-6,7-dimethylquinoxalin-2(1*H*)-one **143h** obtained. When boiled in AcOH for 3 h the latter was transformed into 2-(benzimidazol-2-yl)quinoline **142h** (Scheme 59).
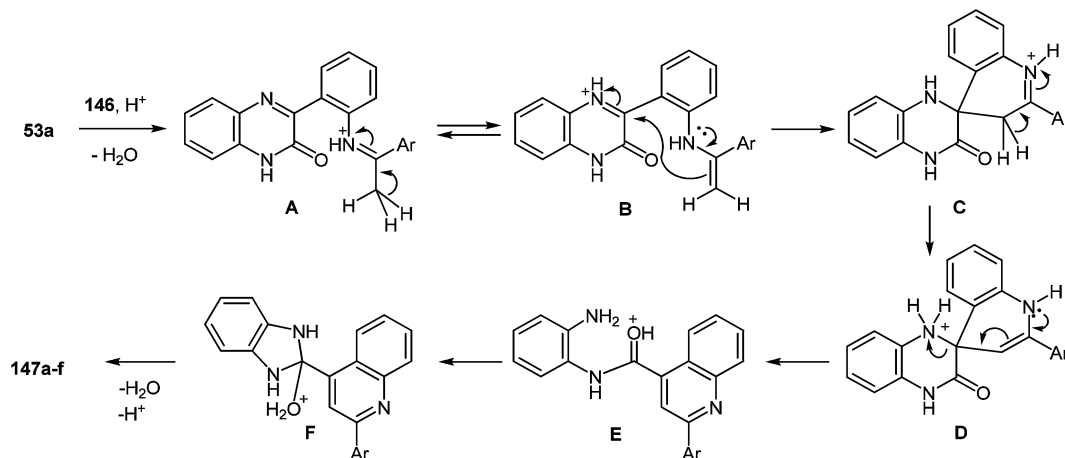
Scheme 62 A plausible mechanism for the formation of 4-(benzimidazol-2-yl)quinolines **147**.
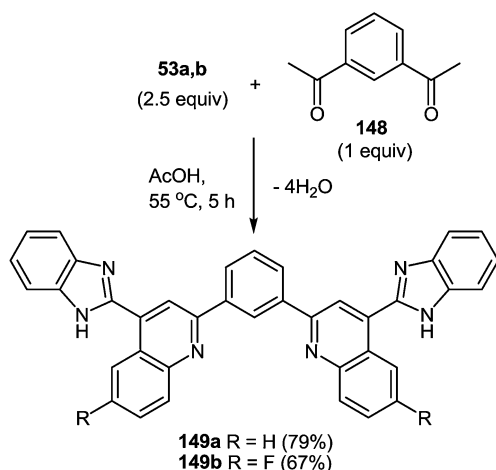
Scheme 63 Reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones **53a, b** with 1,3-diacetylbenzene **148**.
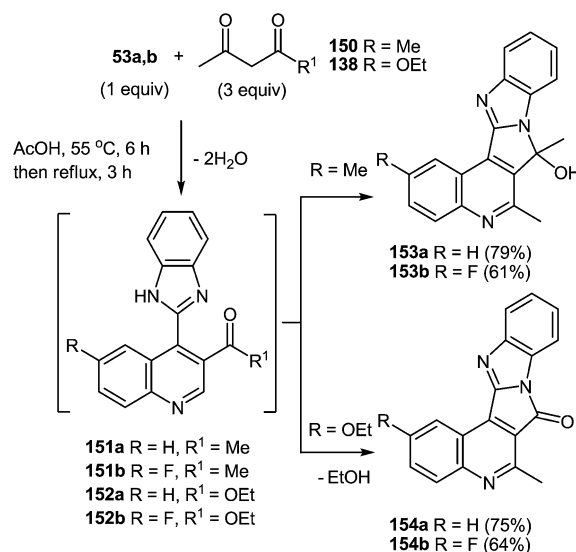
Scheme 64 Reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones **53a, b** with acetylacetone **150** and ethyl acetoacetate **138**.

The known chemistry of aniline,[114] azadienes,[115] and quinoxalinones,[105,116] allows to assume that the first stage of this reaction involves the nucleophilic attack of the amine group on the C(3) atom of the quinoxalin-2(1*H*)-one of **A** to form the spiro-quinoxaline derivative **B**. Rearrangement of the spiro-quinoxaline is then assumed to occur according to Scheme 60 by cascade reactions involving: (a) acid-catalysed ring-opening with cleavage of the C(3)–N(4) bond in the spiro-compound **C** leading to the formation of the quinoline derivative **D**, and (b) intramolecular nucleophilic attack by the amino group on the carbamoyl carbonyl group with the formation of the final product **142** following the elimination of water.

This protocol includes a novel acid-catalyzed rearrangement of 3-(β-2-aminostyryl)quinoxalin-2(1*H*)-ones. The simplicity of the reaction design and the possibility of introducing a variety of substituents at any position of both the benzimidazole and quinoline ring systems makes this method a useful tool for constructing these medicinally and technically (organic emitting materials) relevant compounds. The reaction is readily applicable to large-scale synthesis.

9 Synthesis of 4-(benzimidazol-2-yl) quinolines

3-(β-2-Nitrostyryl)quinoxalin-2-(1*H*)-ones **141**, are easily obtained from 3-methylquinoxalin-2(1*H*)-one **52** (see Subsection 2.3E) and *o*-nitrobenzaldehyde **126,** and when exposed to sodium dithionite are converted into 2-(benzimidazol-2-yl) quinolines **142**.[107c] The process occurs under reduction conditions in a cascade of the modified Friedländer reaction and the new acid-catalyzed rearrangement through the intermediately formed products – 3-(β-2-aminostyryl)quinoxalin-2(1*H*)-ones **143** (Scheme 59).

The structure of the compound **142** shows that the *o*-aminostyryle substituent and the C(2), C(3) atoms of the amide and imine fragments of the pyrazine ring of quinoxalin-2(1*H*)-one **143** (Scheme 59) are involved in the construction of two new
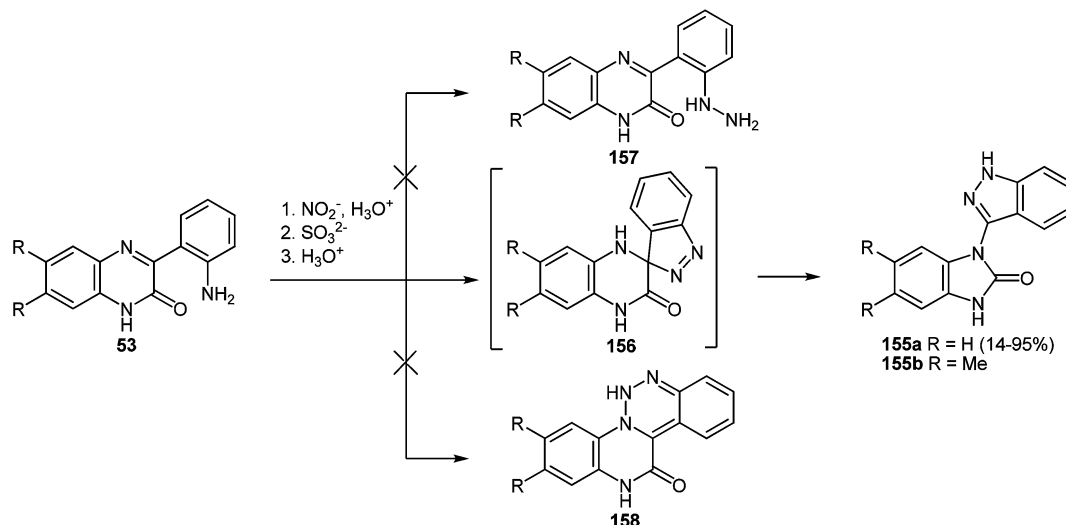
Scheme 65 Reaction of 3-(2-aminophenyl)quinoxalin-2(1H)-ones **53** with NaNO₂ in acidic medium.

heterocyclic systems. In this case, the formation of the pyridine ring of the quinoline system occurs as a result of the proceeding new rearrangement.[96,117,118] As seen from the Table 16, the atoms C(2) and C(3) of the quinoxalin-2(1H)-one system become the atoms C(2′) and C(2) of the benzimidazole and quinoline systems of the compounds **142** respectively.

Following the line of logics demonstrated in the papers[62c–f,76,102,103,107,108a] and specifically in the paper[107c] on the new rearrangement of the quinoxalin-2(1H)-one derivatives, it was proposed that in the latter reaction 3-(2-aminophenyl)qui-noxalin-2(1H)-one derivatives **53** can be used instead of 3-methylquinoxalin-2(1H)-one **52** and o-nitrobenzaldehyde **126** derivatives as the hetero analogues of o-amino aromatic alde-hydes and ketones bearing an active α-methylene functionality. The ketones can be condensed with compounds **53** capable of providing a two-carbon fragment in the construction of the quinoline system, which makes it possible to synthesize the 4-(benzimidazol-2-yl)quinolines **145,147,149** isomeric to the 2-(benzimidazol-2-yl)quinolines **142**.

The reaction of 3-(2-aminophenyl)quinoxalin-2(1H)-one **53a** with acetone in acetic acid proceeded with the formation of the ~88% yield of the crude product, which contains ~90% of the quinoline **145a** and ~10% of the quinoxaline **144a** derivatives as a result of the rearrangement and as a result of the intra-molecular cyclocondensation of the quinoxaline derivative **53a** (Scheme 61).[119,120]

The procedure was extended to 3-(2-amino-5-fluorophenyl) quinoxalin-2(1H)-one **53b** and various acetophenones **146a–f**. The reactions proceeded very efficiently, and led to the forma-tion of the corresponding 4-(benzimidazol-2-yl)quinolines **147a–l** as major and 6H-indolo[2,3-b]quinoxaline **144a–b** as minor products (Table 17).

Based on the known chemistry of amines,[121] enolizable ketones,[122] enamines,[123] quinoxalinones,[105,116] and the previous reports[62e,f,102,103,107,108a] a plausible mechanism for the reaction of the formation of 4-(benzimidazol-2-yl)quinolines

147 has been proposed (Scheme 62). The reaction starts with the condensation of ketones with 3-(2-aminophenyl)quinox-alin-2(1H)-one **53a** to form imine **A**, which is transformed to intermediate **B** by tautomerization. Subsequently interme-diate **B** is easily cyclized through the intramolecular nucleo-philic addition to give the spiro-quinoxaline derivative **C**. The rearrangement of the spiro-quinoxalinone **C** is then assumed to occur according to Scheme 64, which proceeds by cascade reactions involving: (a) the ring-opening with the cleavage of the C(3)–N(4) bond in the spiro-compound **D** with the inter-mediate formation of the quinoline derivative **E**, (b) the intramolecular nucleophilic attack by the amino group on the carbonyl group with the intermediate formation of the hydroxyl-derivative **F**, and (c) the elimination of water leading to the formation of the final product **147**. All the stages of the reaction involve acid-catalyzed processes.

This chemistry is not limited to mono- and disubstituted systems, and a compound with two acetyl fragments, namely 1,3-diacetylbenzene **148** is an acceptable substrate as well (Scheme 63).

The scope of this chemistry was also expanded on the compounds with two same and two different carbonyl groups in their compositions. The 3-(2-aminophenyl)quinoxalin-2(1H)-ones **53a, b** were allowed to react with 1,3-pentanedione **150** and ethyl acetoacetate **138**, in AcOH, but in these cases with acetyl and ester groups at position 3 of the quinoline system there occurs the formation of benzimidazolo[2,1-a]pyrrolo[3,4-c] quinoline derivatives **153a,b** and **154a,b** instead of the expected 4-(benzimidazol-2-yl)quinolines **151a,b** and **152a,b** corre-spondingly (Scheme 64).[102]

Thus, an efficient synthesis for structurally diverse 4-(benzimidazol-2-yl)quinolines via reactions of 3-(2-amino-phenyl)quinoxalin-2(1H)-ones and ketones, including acetone, acetophenones, 1,3-pentanedione and ethyl acetoacetate has been developed. The selective formation of the very different quinoline derivatives depends on the structure of ketones. The

Table 18 Synthesis of *N*-pyrrolylbenzimidazol-2-ones 160 and 161
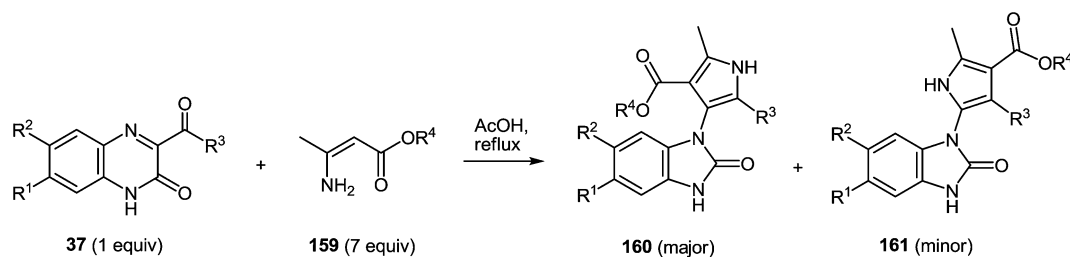
Entry	37	R^1	R^2	R^3	159	R^4	Products (yield)	Overall yield (160/161)^a
1	37a	H	H	Ph	159a	Me	160a + 161a (45%) (n/i)	97%, 78 : 22
2	37b	H	H	C$_6$H$_4$F-4	159a	Me	160b + 161b (42%) (n/i)	94%, 74 : 26
3	37c	H	H	C$_6$H$_4$Cl-4	159a	Me	160c + 161c (52%) (n/i)	97%, 72 : 28
4	37d	H	H	C$_6$H$_4$Br-4	159a	Me	160d + 161d (51%) (n/i)	97%, 70 : 30
5	37e	H	H	C$_6$H$_4$I-4	159a	Me	160e + 161e (53%) (n/i)	98%, 75 : 25
6	37i	H	H	*n*-Pr	159a	Me	160f + 161f (39%) (n/i)	97%, 91 : 9
7	37x	Me	Me	Ph	159a	Me	160g + 161g (62%) (n/i)	97%, 83 : 17
8	37t	COPh	H	Ph	159a	Me	160h + 161h (43%) (n/i)	97%, 79 : 21
9	37a	H	H	Ph	159b	Et	170i + 171i (58%, 24%) (4%)	99%, 78 : 22
10	37b	H	H	C$_6$H$_4$F-4	159b	Et	160j + 161j (59%) (n/i)	96%, 77 : 23
11	37c	H	H	C$_6$H$_4$Cl-4	159b	Et	160k + 161k (61%, 40%) (5%)	97%, 67 : 33
12	37d	H	H	C$_6$H$_4$Br-4	159b	Et	160l + 161l (56%, 38%) (4%)	99%, 67 : 33
13	37e	H	H	C$_6$H$_4$I-4	159b	Et	160m + 161m (56%) (n/i)	98%, 60 : 40
14	37x	Me	Me	Ph	159b	Et	160n + 161n (65%) (n/i)	99%, 84 : 16
15	37t	COPh	H	Ph	159b	Et	160o + 161o (41%) (n/i)	98%, 72 : 28
16	37u	CO$_2$H	H	Ph	159b	Et	160p + 161p (77%)	89%, 75 : 25, (inseparable mixture)

^{a} Ratio determined by the ^{1}H NMR of the crude products.

key steps are assumed to involve the new acid-catalyzed rearrangement of the spiro-quinoxalinone derivatives formed *in situ* from the reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones and ketones under the modified Friedländer reaction.

It should be pointed out that in an attempt to prepare 3-(2-hydrazinophenyl)quinoxalin-2(1*H*)-one 157 by reduction of corresponding diazonium salt from 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones 53 with sodium sulfite instead of the intended product 157 a compound with the molecular formula C$_{14}$H$_{10}$N$_4$O has been isolated, which the authors[124] considered to be 6*H*-quinoxalino[1,6-*c*][1,2,3]benzotriazin-13(12*H*)-one 158. However, later[125] it proved that the structure proposed by the authors[124] was incorrect. By NMR spectroscopy[125] and by X-ray analysis[126] it was shown that the correct structure is 1-(1*H*-indazol-3-yl)-1*H*-benzimidazol-2(3*H*)-one 155 (Scheme 65). The formation of the 1*H*-benzimidazol-2(3*H*)-one derivative 155 as a consequence of the principle suggested above proceeds through the spiro-compound 156 without any mobile hydrogen atom in their spiro-forming component.

10 Synthesis of 1-pyrrolylbenzimidazolones and their aza-analogues *via* new rearrangements

Scheme 16 shows that the key step of the reactions above, involved a novel acid-catalyzed rearrangement of intermediate spiro-quinoxalin-2(1*H*)-one derivatives with a contraction of
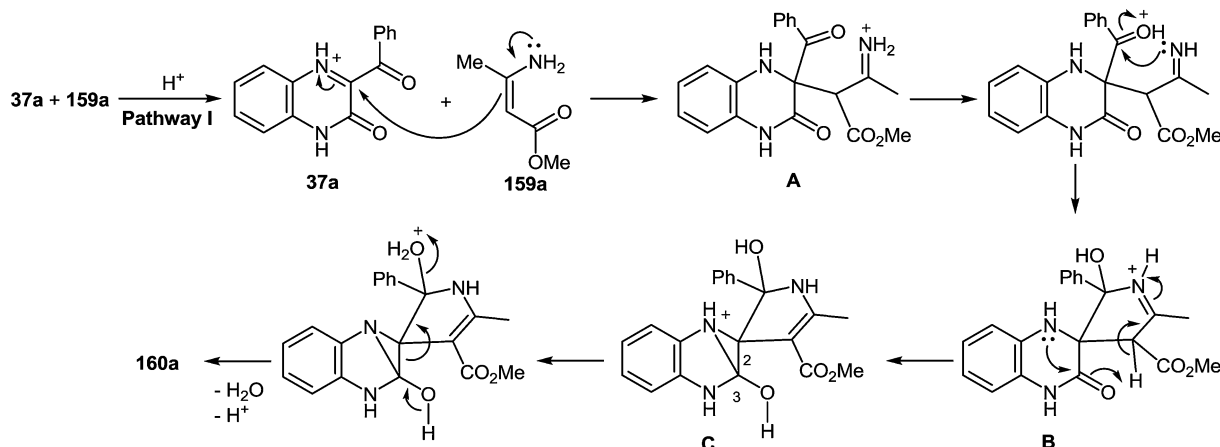
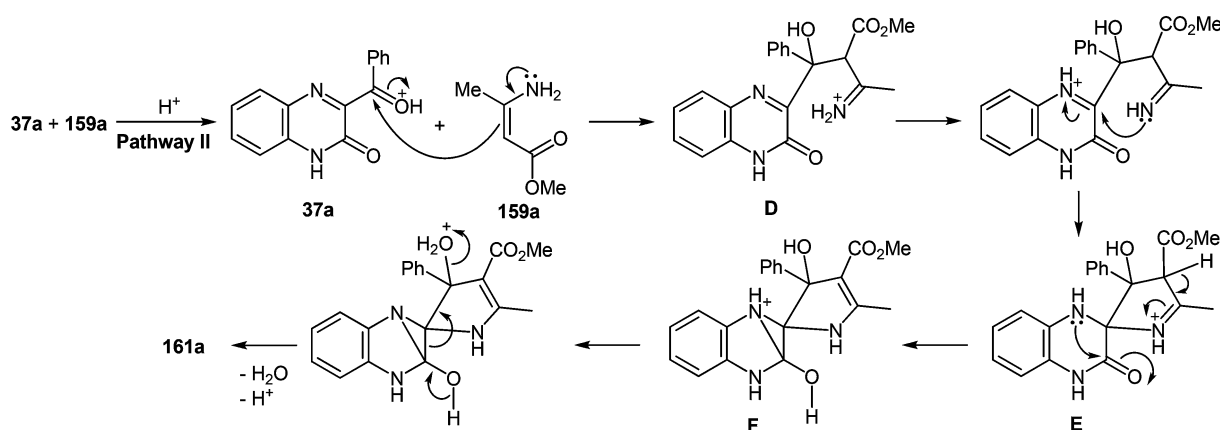**Scheme 66** Proposed mechanisms for the formation of **160a** (*pathway I – via* an initial attack on the C(3) atom of quinoxalin-2(1*H*)-one).

the pyrazine ring of the quinoxalin-2-one system. It was also shown that the necessary condition for the rearrangement is the presence of at least one mobile hydrogen atom in the spiro-forming fragment, which is responsible for the elimination of water. As can be seen from Scheme 16 the formation of water takes place with the involvement of the oxygen atom of the carbonyl group. We assumed that if the spiro-quinoxalinone derivative with no mobile hydrogen atom in the spiro-fragment was subjected to rearrangement, there might probably be two options. The first one is that the rearrangement would not occur at all, the second one is that another rearrangement would take place without any water elimination and with the preservation of the carbonyl oxygen atom, probably quinoxalinone-benzimidazolone. To confirm this assumption it was necessary to synthesize a spiro-derivative so the quinoxalinone without any mobile hydrogen atoms. To this end, after analyzing all the possible nucleophilic reagents, we have chosen the enamines as CN-nucleophiles. The reaction of 3-aroyl- and alkanoylquinoxalin-2(1*H*)-ones with the commercially available enamines (methyl- (**159a**) and ethyl- (**159b**) 3-aminocrotonates) as CN-nucleophiles under the acid catalysis condition proceeds so fast that it appears impossible
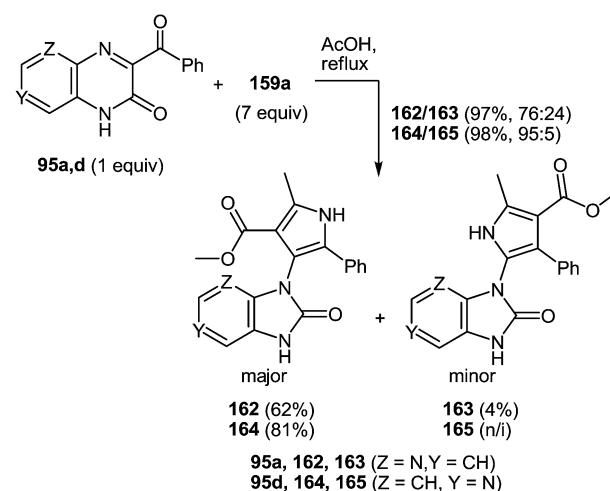
Scheme 68 Synthesis of *N*-pyrrolyl-1*H*-imidazo[5,4-*b*]- (**162/163**) and *N*-pyrrolyl-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-ones (**164/165**).

to allocate the expected spiro-compound which are immediately subjected to the rearrangement with the formation of the corresponding *N*-(pyrrol-3-yl)benzimidazol-2-ones (**160**) as

Scheme 67 Proposed mechanisms for the formation of **161a** (*pathway II – via* an initial attack on the C atom of benzoyl group).
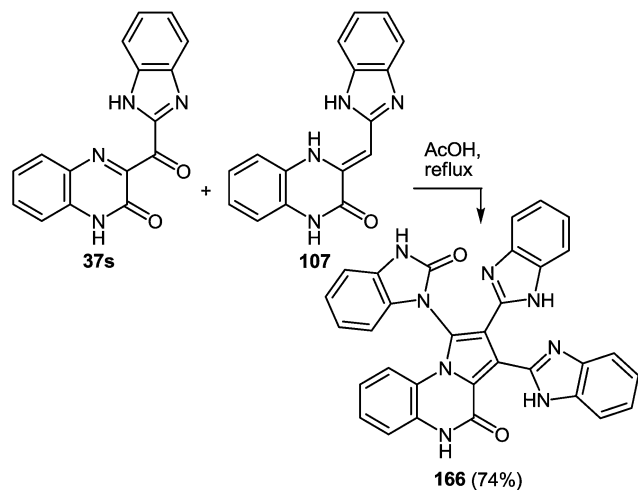
Scheme 69 The formation of 1-(benzimidazol-2-on-1-yl)-2,3-(dibenzimidazol-2-yl)pyrrolo[1,2-*a*]quinoxaline-4(5*H*)-one **166**.
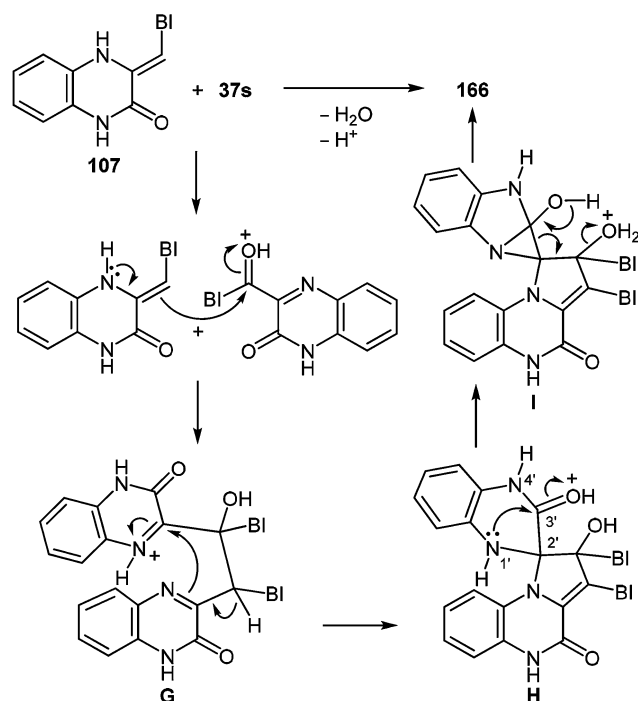
Scheme 70 A plausible mechanism for the formation of pyrrolo[1,2-*a*]quinoxaline-4(5*H*)-one **166**.

major and *N*-(pyrrol-2-yl)benzimidazol-2-ones (**161**) as minor products with the overall 89–99% yields (Table 18).[127]

A plausible reaction mechanism for the formation of *N*-pyrrolylbenzimidazol-2-ones **160** and **161** has been proposed (Scheme 66). The formation of *N*-pyrrolylbenzimidazol-2-ones occurs in two different ways (*pathway I* and *pathway II*), differing at their initial stage of the process. In the case of the formation of *N*-(pyrrol-3-yl)benzimidazol-2-ones **160** the reaction starts (Scheme 68) with the acid catalyzed subsequent Michael type of the reaction[128] between **37a** and **159a** involving a nucleophilic attack by the enamino double bond (of **159a**) on

the electron deficient double bond (of **37a**), which leads to the formation of **A**. The intramolecular cyclization of **A** involving the attack by the imine nitrogen on the nearby –C(O)Ph moiety affords the spiro-quinoxaline derivative **B**. The rearrangement of the spiro-quinoxalinone **B** is then assumed to occur according to Scheme 68, which proceeds by cascade reactions involving: (a) the intramolecular nucleophilic attack by the amino group on the carbonyl group with the intermediate formation of the hydroxy-derivative **C**, (b) the ring-opening with the cleavage of the C(2)–C(3) bond in the hydroxy-derivative **C** with the elimination of water leading to the formation of the final product **160a**.

In the case of the formation of *N*-(pyrrol-2-yl)benzimidazol-2-ones **161** at its initial stage there occurs a nucleophilic attack by the enamino double bond (of **159a**) on the electron deficient benzoyl carbonyl group (of **37a**) which leads to the formation of **D** (Scheme 68, *pathway II*). This brings about the rearrangement product *via* intermediates **E** and **F** (Scheme 67).

This chemistry is not limited to the quinoxalin-2(1*H*)-ones and the 5- and 7-aza-quinoxalin-2(1*H*)-ones, namely 3-benzoyl-pyrido[3,2-*b*]pyrazin-2(1*H*)-one **95a** and 3-benzoylpyrido[3,4-*b*]pyrazin-2(1*H*)-one **95d** subjected to the rearrangement with the formation easily separable regioisomeric products **162/163** and **164/165** with overall quantitative yields (Scheme 68).[129]
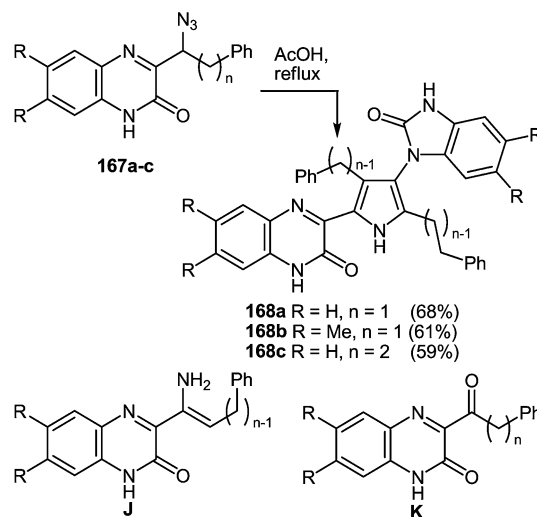
Scheme 71 A new quinoxalinone–benzimidazolone rearrangement proceeding under self-condensation of 3-(α-azidophenylalkyl)quinoxalin-2(1*H*)-ones.
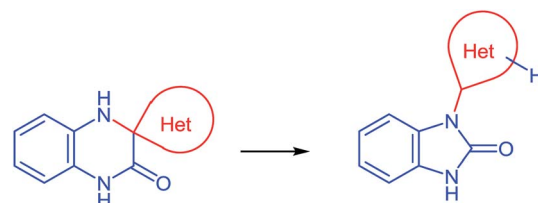
Scheme 72 A schematic presentation of the spiro-1,2,3,4-tetrahydroquinoxalin-3-one → benzimidazolone rearrangement.

Table 19 Synthesis of 1-(pyrrolyl)benzimidazolones

| Entry	37	R^1	R^2	146	R^3	Time (h)/NH$_4$OAc (eq.)	Product	Yield (%)
1	37a	H	H	146a	Ph	20/20	169a	65
2	37a	H	H	146b	C$_6$H$_4$Br-4	14/15	169b	81
3	37a	H	H	146c	C$_6$H$_4$Br-3	20/20	169c	66
4	37a	H	H	146d	C$_6$H$_4$Br-2	20/20	169d	62
5	37a	H	H	146e	C$_6$H$_4$Cl-4	14/15	169e	79
6	37a	H	H	146f	C$_6$H$_4$Cl-2	20/20	169f	63
7	37a	H	H	146g	C$_6$H$_4$NO$_2$-3	20/20	169g	59
8	37a	H	H	146h	C$_6$H$_4$OMe-4	14/15	169h + 170h	92^a
9	37a	H	H	146i	Py-2	20/20	169i	79
10	37a	H	H	146j	Py-3	20/20	169j	73
11	37a	H	H	146k	Py-4	20/20	169k	76
12	37u	CO$_2$H	H	146a	Ph	14/15	169l	62
13	37u	CO$_2$H	H	146b	C$_6$H$_4$Br-4	14/15	169m	84
14	37t	COPh	H	146b	C$_6$H$_4$Br-4	24/25	169n	12^b
15	37x	Me	Me	146b	C$_6$H$_4$Br-4	24/25	169o	63

^{a} Formed two isomers in a 63 : 37 percentage ratio (based on ^{1}H NMR). ^{b} 55% of 37t was recovered.

In comparison with the existing methods, the present approach offers the following advantages: (i) it proceeds faster and affords good to excellent yields under mild conditions with no additional activation modes such as microwave irradiation, (ii) it is very cost-effective and uses the inexpensive easily and commercially available reagents, and (iii) it is applicable to a broader range of substrates, including 3-aroyl(alkanoyl)quinoxalin-2(1H)-ones, 3-benzoylpyrido[3,2-b]pyrazin-2(1H)-one and 3-benzoylpyrido[3,4-b]pyrazin-2(1H)-one and various enamines.

An effective synthesis strategy has been developed via the novel quinoxalin-2(1H)-one/benzimidazol-2-one rearrangement that makes possible a rapid access to the N-pyrrolylbenzimidazol-

2-ones from the readily available 3-aroylquinoxalin-2(1H)-ones with various substituents and commercially available methyl and ethyl-3-aminocrotonates. The methodology was found to be general and a wide variety of N-pyrrolylbenzimidazol-2-one derivatives were prepared in good yields. Due to the availability of the starting materials and the potential applications of the products, this method is highly perspective in organic synthesis and medicinal chemistry.

If instead of commercially available enamines the heterocyclic compound with an enamine fragment is used the rearrangement found allows to synthesize more complex heterocyclic system that are hard-to-reach by other known methods. Indeed, carrying out the reaction of 3-(benzimidazo-2-
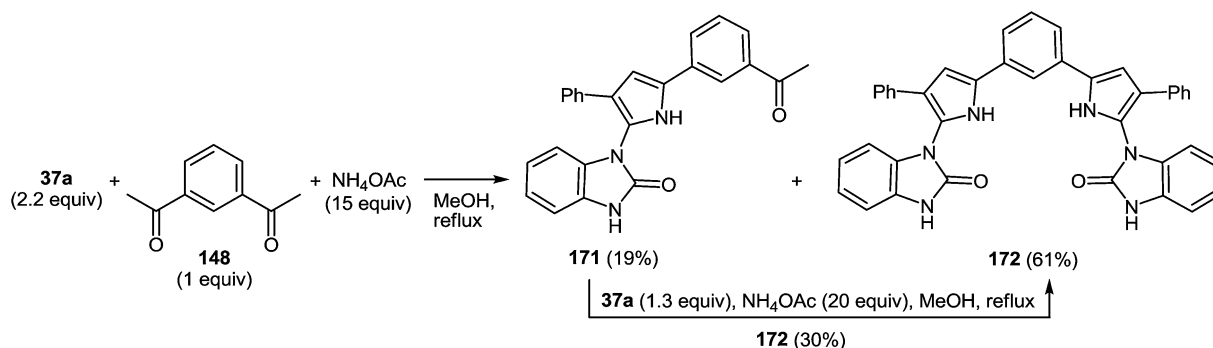
Scheme 73 Synthesis of 1-[5-(3-acetylphenyl)-3-phenylpyrrol-2-yl]benzimidazol-2(3H)-one **171** and 1,3-bis[2-(benzimidazol-2-on-1-yl)-3-phenylpyrrol-5-yl]benzene **172**.
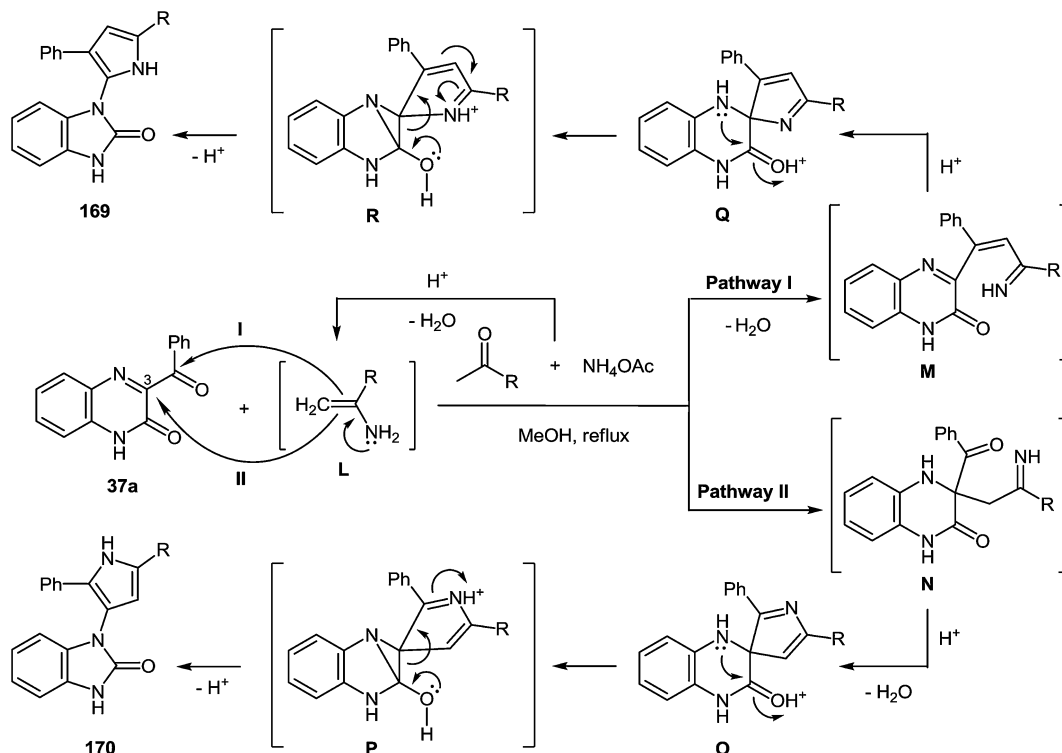
Scheme 74 A plausible mechanism for the formation of 1-(5-*R*-3-phenylpyrrol-2-yl)- (**169**) and 1-(5-*R*-2-phenylpyrrol-3-yl)- (**170**) benzimidazol-2(3*H*)-ones.

yl)quinoxalin-2(1*H*)-one **37s** with 3-(benzimidazol-2-yl)methylenequinoxalin-2(1*H*)-one **107** in boiling AcOH led to the derivative of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **166** in a good yield (Scheme 69).[102]

The formation of compound **166** occurs as a result of a cascade reaction involving: (a) the intermolecular ene reaction[130] between the enamine **107** and ketone **37s** with the formation of compound **G**, (b) the intramolecular ene reaction[131] wi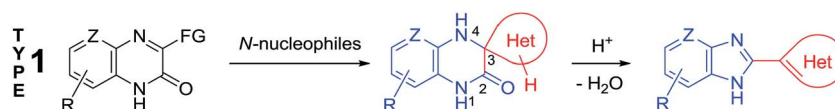th the formation of the spiro-derivative quinoxalinono[2′,1]pyrrolo[1,2-*a*]quinoxaline **H**, and (c) a new quinoxalinono-benzimidazolono rearrangement in the spiro-forming fragment. Unlike the rearrangements discussed above (see Sections 2.2 and 4–9), in which the opening of the pyrazine ring of the quinoxalinone system of spiro-derivative (Schemes 14, 46, 47, 51, 52, 58, 62 and 64) occurs between the C(3) and N(4) atoms, the opening of the pyrazine ring of the quinoxaline system of spiro-derivative **H** occurs in the new rearrangement between the C(2) and C(3) atoms, through the intermediate formation of fused spiro-aziridino[2′,1]pyrrolo[1,2-*a*]quinoxaline **I** (Scheme 70).

In this case 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s**, supplying two carbon atoms in the formation of the pyrrole ring

is subjected to a rearrangement (Scheme 69) different from that discussed above (see Section 4.2).

Enamines for the rearrangement can be generated from decomposition of azides. The above rearrangement was observed earlier in our group on the example of the self-condensation of 3-(α-azidophenylalkyl)quinoxalin-2(1*H*)-ones **167a–c** (Scheme 71) (see D. F. Saifina thesis pages 89–93 in chapter 4).[89] In this version of the rearrangement the enamines for the rearrangement can be generated *in situ* by the decomposition of azides. The final products **168a–c** are formed as a result of the intermolecular condensation of an enamine **J** and the corresponding ketone **K** formed *in situ* under the reaction conditions. In this case the new rearrangement of quinoxalinones makes it possible to simultaneously construct two various new heterocyclic systems under one-pot reaction conditions.

The fact that the formation of the benzimidazolone derivatives in the reactions of the self-condensation of 3-(α-azidophenylalkyl)quinoxalin-2(1*H*)-ones **167** (Scheme 73) and in the condensation of 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s** with its predecessor – 3-(benzimidazol-2-yl)methylenequinoxalin-2(1*H*)-one **107** (Scheme 71) gives reason for propose a new

Scheme 75 Schematical presentation of the rearrangement **TYPE 1**.
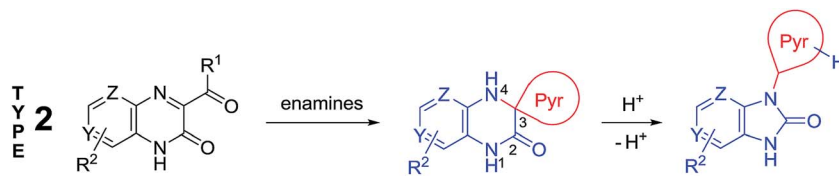
Scheme 76 Schematical presentation of the rearrangement **TYPE 2**.

hypothesis, that "*any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one without any mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazolone derivative with the spiro-forming component at position 1*" (Scheme 72).

The above reactions of 3-benzoyl-, 3-alkanoyl- quinoxalinones proceed equally well with enamines generated *in situ* from the ketones with an activated methylene group and amines.

Table 19 reports the structural variations which are tolerated by these three-component reactions of 3-aroylquinoxalinones with various ketones and ammonium acetate.

Acetophenones (electron-withdrawing and electron-donating substituents) and heteroaromatic ketones have resulted in the corresponding products in good to excellent yields (Table 19). The same is true for the different 3-BQs with various substituents with the exception of the PhC(O) group (Table 19, entry 14) in the benzene ring of the quinoxalin-2(1*H*)-one system.

The replacement of the commercially available acetophenone **146a** with 1,3-diacetylbenzene **148**, bearing an additional acetyl group, would allow the anticipated cascade process with two MCR modifications in one pot with the formation of compound **172**, with two 1-(pyrrol-2-yl)benzimidazolone cores in the benzene ring as a major product and compound **171** as a minor product with one 1-(pyrrol-2-yl)benzimidazolone core. It has been shown that acetophenone **171** with 3-BQ **37a** in the presence of NH₄OAc (the ratio of reagents is given in the Scheme 74) can also be transformed to **172** with a 30% yield (Scheme 73).

The known chemistry of ketones,[122] imines,[121] quinoxalines[105] and enamines[123] allows to propose a plausible reaction course (Scheme 74), although the exact mechanism of this reaction is yet unclear. Intermediate **L** formed at the initial stage of the processes reacts with the 3-BQ **37a** in two different ways (*pathway I* and *pathway II*) with the formation of an isomeric spiro[pyrrol-3,2′-quinoxalin]-3-one derivative **O** and a spiro[pyrrol-2,2′-quinoxalin]-3-one derivative **Q** through the intermediate **M** and **N**. The latter are formed by the initial attack of enamine on the benzoyl carbonyl carbon atom (*pathway I*) and on the C(3) atom of the quinoxalinone system (*pathway II*), respectively. Then, both *pathway I* and *pathway II* proceed by cascade reactions involving: (a) the consecutively acid-catalyzed ring-closure of quinoxaline derivatives **M, N** to spiro-derivatives **Q, O** followed by formation of intermediates **R, P** with the aziridine ring system; (b) the acid-catalyzed ring-opening in intermediates **R, P** with the formation of the final 1-(pyrrol-2-yl)-**169** and 1-(pyrrol-3-yl)benzimidazolone **170** derivatives.

An important three component reaction of 3-benzoylquinoxalinones, various methylaryl-(hetaryl)ketones and ammonia has been developed. The method allows the preparation of substituted 1-(pyrrolyl)benzimidazolone derivatives *via* multi-component reaction conditions from easily available 3-benzoylquinoxalinone precursors in the presence of various methylaryl(hetaryl)ketones and ammonia with good to excellent yields. Enamines could be generated *in situ* from ketones and ammonia, which smoothly react with 3-benzoylquinoxalinones to provide 1-(pyrrolyl)benzimidazolone derivatives. An important aspect of this method is that it can be used for the synthesis of a wide range of benzimidazolone derivatives, since various methylketones are commercially available and can easily be obtained through the various simple reactions.

11 Conclusion

Benzimidazol(on)es have taken a leading role in the recent literature because of their wide variety of applications in various disciplines like medicinal chemistry, organometallics, and material science. Several novel synthetic routes have been developed to achieve these skeletons. These newer synthetic routes are based on the combination of several interesting strategies such as tandem sequences, multicomponent reactions, and rearrangements. As is evident from the discussion in this review, these synthetic procedures offered easy access to benzimidazol(on)es from simple and readily available precursors. The development of these synthetic procedures is very useful especially for medicinal and material chemists. In this review we mainly focused our attention to two fundamentally new rearrangements of quinoxalinones and their aza-analogues discovered by us.

The first one can be schematically represented as **TYPE 1** on the Scheme 75: "*Any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one with at least one mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazole derivative with the spiro-forming component at position 2*".

The second one can be schematically presented as **TYPE 2** on the Scheme 76: "*Any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one without any mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazolone derivative with the spiro-forming component at position 1*".

Thus, the novel rearrangements presented raises no doubts as to its generality in the synthesis of benzimidazol(on)es. In accordance with the aim set both the first and the second component can be replaced when synthesizing any desired derivative of benzimidazole. *Via* these novel rearrangements 2-(benzimidazol-2-

yl)-quinoxalines and their aza-analogues (2-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)-3-arylquinoxalines), 2,3-bis(benzimidazol-2-yl)quinoxalines, 2-(pyrazin-2-yl)benzimidazoles, 2-(imidazol-4-yl)benzimidazoles, 2-(3-arylindolizin-2-yl)benzimidazole, 2-(pyrazol-3-yl)benzimidazoles, 2-(pyrrol-3-yl)benzimidazoles, 2-(benzimidazol-2-yl)quinolines, 4-(benzimidazol-2-yl)quinolines and their condensed analogues (benzimidazolo[2,1-*a*]pyrrolo[3,4-*c*]quinoline), *N*-pyrrolylbenzimidazol-2(3*H*)-ones and their aza analogues (*N*-pyrrolyl-1*H*-imidazo[5,4-*b*]pyridin-2(3*H*)-ones, *N*-pyrrolyl-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-ones), *N*-(1*H*-indazol-3-yl)benzimidazol-2(3*H*)-ones have been synthesized to date. These derivatives are shown in the review. We hope that in future these new rearrangements, based on the rearrangement of quinoxalin(on)e derivatives into benzimidazol(on)e derivatives, will find their worthy place in the chemistry of heterocyclic compounds, and will serve as a simple and efficient method for the synthesis of various benzimidazole derivatives, along with the classical Phillips–Ladenburg and Weidenhagen reactions.

Acknowledgements

Notes and references

1 (*a*) F. Hobrecker, *Ber. Dtsch. Chem. Ges.*, 1872, **5**, 290; (*b*) J. Wright, *Chem. Rev.*, 1951, **48**, 397; (*c*) K. Hofmann, *The Chemistry of Heterocyclic Compounds, Imidazole and its Derivatives, Part 1*, Interscience, London, 1953.

2 For selected reviews, see: (*a*) M. R. Grimmet, in *Comprehensive Heterocyclic Chemistry*, ed. K. T. Potts, Pergamon, Oxford, 1984, vol. 4; (*b*) M. R. Grimmet, in *Comprehensive Heterocyclic Chemistry II*, ed. I. Shinkai, Pergamon, Oxford, 1996, vol. 3.

3 For selected reviews, see: (*a*) N. Preston, *Chem. Rev.*, 1974, **74**, 279; (*b*) R. J. Sundberg and R. B. Martin, *Chem. Rev.*, 1974, **74**, 471.

4 J. A. Asensio, E. M. Sanchez and P. Gomez-Romero, *Chem. Soc. Rev.*, 2010, **39**, 3210.

5 *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, Germany, 2007.

6 S. Hirashima, T. Suzuki, S. Noji, I. Ando, M. Komatsu, S. Ikede and H. Hashimoto, *J. Med. Chem.*, 2006, **49**, 4721.

7 U. Scheffer, A. Strick, V. Ludwig, S. Peter, E. Kalden and M. W. Gobel, *J. Am. Chem. Soc.*, 2005, **127**, 2211.

8 E. Sener, I. Yalcin, O. Temiz, I. Oren, A. Akin and N. Ucarturk, *Il Farmaco*, 1997, **52**, 99.

9 P. Sharma, A. Kumar and M. Sharma, *Eur. J. Med. Chem.*, 2006, **41**, 833.

10 P. Lindberg, P. Nordberg, T. Alminger, A. Brandstrom and B. Wallmark, *J. Med. Chem.*, 1986, **29**, 1327.

11 R. Mannhold, *Drugs Future*, 1985, **10**, 570.

12 (*a*) N. Singh, A. Pandurangan, K. Rana, P. Anand, A. Ahmad and A. K. Tiwari, *Int. Curr. Pharm. J.*, 2012, **1**, 119; (*b*) C. Mukhopadhyay, S. Ghosh, S. Sengupta and S. De, *RSC Adv.*, 2011, **1**, 1033; (*c*) S. Demirayak, I. Kayagil and L. Yurttas, *Eur. J. Med. Chem.*, 2011, **46**, 411; (*d*) J. E. Payne, C. Bonnefous, K. T. Symons, P. M. Nguyen, M. Sablad, N. Rozenkrants, Y. Zhang, L. Wang, N. Yazdani, A. K Shiau., S. A. Noble, P. Rix, T. S. Rao, C. A. Hassig and N. D. Smith, *J. Med. Chem.*, 2010, **53**, 7739; (*e*) R. Sevak, A. Paul, S. Goswami and D. Santani, *Pharmacol. Res.*, 2002, **46**, 351; (*f*) L. K. Labanauskas, A. B. Brukstus, P. G. Gaidelis, V. A. Bucinskaite, E. B. Udrenaite and V. K. Dauksas, *Pharm. Chem. J.*, 2000, **34**, 353; (*g*) B. Can-Eke, M. O. Puskullu, E. Buyukbingol and M. Iscan, *Chem.–Biol. Interact.*, 1998, **113**, 65.

13 (*a*) S. Bhattacharya and P. Chaudhuri, *Curr. Med. Chem.*, 2008, **15**, 1762; (*b*) M. Boiani and M. Gonz'alez, *Mini-Rev. Med. Chem.*, 2005, **5**, 409; (*c*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.

14 H. S. A. Elzahabi, *Eur. J. Med. Chem.*, 2011, **46**, 4025.

15 L. J. Scott, C. J. Dunn, G. Mallarkey and M. Sharpe, *Drugs*, 2002, **62**, 1503.

16 P. J. Venkatesan, *J. Antimicrob. Chemother.*, 1998, **41**, 145.

17 H. J. Al Muhaimeed, *J. Int. Med. Res.*, 1997, **25**, 175.

18 (*a*) S. Nakamura, *Chem. Pharm. Bull.*, 1955, **3**, 379; (*b*) A. Zeynep, A. Mehmet, K. Canan, Y. Sulhiye, B. Erdem and G. Hakan, *Arch. Pharm. Chem. Life Sci.*, 2006, **339**, 74; (*c*) T. Meral, G. Hakan, E. Rahmiye, E. Recep, K. Engin and A. Nurten, *Arch. Pharm. Pharm. Med. Chem.*, 1997, **330**, 372; (*d*) Z. M. Nofal, H. H. Fahmy and H. S. Mohamed, *Arch. Pharmacal Res.*, 2002, **25**, 28.

19 A. C. Cuckler and K. C. Mezey, *Arzneim. Forsch.*, 1966, **16**, 411.

20 (*a*) A. C. Hollinshead and P. K. Smith, *J. Pharmacol. Exp. Ther.*, 1958, **123**, 54; (*b*) D. C. O'Sullivan and A. K. Wallis, *J. Med. Chem.*, 1972, **15**, 103; (*c*) B. Simone, K. Mariola, G. Agata, K. Zygmunt, E. Henning, L. Paolo, G. Gilles and S. Frank, *ARKIVOC*, 2009, **iii**, 225; (*d*) R. Zou, K. Ayres, J. Drach and L. Townsend, *J. Med. Chem.*, 1996, **39**, 3477.

21 (*a*) W. W. Kilgore and E. R. White, *Bull. Environ. Contam. Toxicol.*, 1970, **5**, 67; (*b*) B. Maxwell and G. Brody, *Appl. Microbiol.*, 1971, **21**, 944; (*c*) E. I. Elnima, M. U. Zubair and A. A. Al-Badr, *Antimicrob. Agents Chemother.*, 1981, **19**, 29; (*d*) K. A. M. Walker, A. C. Braemer, S. Hitt, R. E. Jones and T. R. Mathews, *J. Med. Chem.*, 1978, **21**, 840; (*e*) C. J. Going and V. W. Mayer, *Mutat. Res.*, 1995, **343**, 185.

22 *The Pesticide Manual*, ed. C. Tomlin, Royal Society of Chemistry, British Crop Protection, 1994.

23 G. Kamlesh, B. Jamie, P. Austin, B. Julie, W. Leslie and P. Dulal, *Biochemistry*, 2004, **43**, 6645.

24 (*a*) O. Seckin, A. Dilek, Y. Sulhiye and G. Hakan, *Bioorg. Med. Chem.*, 2005, **13**, 1587; (*b*) G. Hakan, M. Tuncbilek, G. Ayhan and N. Altanlar, *Il Farmaco*, 1998, **53**, 415; (*c*) T. Hisano, M. Ichikawa, K. Tsumoto and M. Tasaki, *Chem. Pharm. Bull.*, 1982, **30**, 2996.

25 M. Tuncbilek, T. Kiper and N. Altanlar, *Eur. J. Med. Chem.*, 2009, **44**, 1024.

26 (*a*) E. A. Ibrahim, A. M. E. Omar and M. A. Khalil, *J. Pharm. Sci.*, 1980, **69**, 1348; (*b*) A. K. Piskin, A.-A. Zeynep, F. B. Atac, Y. Musdal and E. Buyukbingol, *Turk. J. Biochem.*, 2009, **34**, 39; (*c*) T. A. Heba, A. F. R. Fatma, M. R. Mostafa and I. E. Hoda, *Eur. J. Med. Chem.*, 2010, **45**, 2336; (*d*) S. Mohammad, M. M. Abdullah, M. A. Bakht and M. Jaseela, *Eur. J. Med. Chem.*, 2010, **45**, 114; (*e*) N. Boufatah, A. Gellis, J. Maldonado and P. Vanelle, *Tetrahedron*, 2004, **60**, 9131.

27 S. Alper, O. Temiz, E. Sener and I. Yalcin, *Il Farmaco*, 2003, **58**, 497.

28 K.-K. Wong, *Recent Pat. Anti-Cancer Drug Discovery*, 2009, **4**, 28.

29 N. K. Haass, K. Sproesser, T. K. Nguyen, R. Contractor, A. Medina, K. L. Nathanson, M. Herlyn and K. S. M. Smalley, *Clin. Cancer Res.*, 2008, **14**, 230.

30 W. A. Denny, G. W. Rewcastle and B. C. Baguley, *J. Med. Chem.*, 1990, **33**, 814.

31 (*a*) Z. Ates, B. C. Eke, S. Suzen, E. Buyukbingol and M. Iscan, *Il Farmaco*, 1997, **52**, 703; (*b*) Z. Ates-Alagoz and E. Buyukbingol, *Heterocycl. Commun.*, 2001, **7**, 455; (*c*) Z. Ates-Alagoz, B. C. Eke, T. Coban, M. Iscan and E. Buyukbingol, *Arch. Pharm.*, 2004, **337**, 188.

32 (*a*) S. Budow, M. Kozlowska, A. Gorska, Z. Kazimierczuk, H. Eickmeier, P. La Colla, G. Gosselin and F. Seela, *ARKIVOC*, 2009, **iii**, 225; (*b*) M. T. Migawa, J. Girardet, J. A. Walker, G. W. Koszalka, S. D. Chamberlain, J. C. Drach and L. B. Townsend, *J. Med. Chem.*, 1998, **41**, 1242; (*c*) A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Drach and L. B. Townsend, *J. Med. Chem.*, 1998, **41**, 1252.

33 M. Andrzejewska, L. Yepez-Mulia, R. Cedillo-Rivera, A. Tapia, L. Vilpo, J. Vilpo and Z. Kazimierczuk, *Eur. J. Med. Chem.*, 2002, **37**, 973.

34 A. Pinar, P. Yurdakul, I. Yildiz, O. Temiz-Arpaci, N. L. Acan, E. Aki-Sene and I. Yalcin, *Biochem. Biophys. Res. Commun.*, 2004, **317**, 670.

35 H. M. Refaat, *Eur. J. Med. Chem.*, 2010, **45**, 2949.

36 (*a*) W. Wienen, N. Hauel, J. C. A. Van Meel, B. Narr, U. Ries and M. B. Entzeroth, *J. Pharmacol.*, 1993, **110**, 245; (*b*) A. J. Battershill and L. J. Scott, *Drugs*, 2006, **66**, 51; (*c*) K. J. McClellan and A. Markham, *Drugs*, 1998, **56**, 1039.

37 (*a*) R. Cernes, M. Mashavi and R. Zimlichman, *Vasc. Health Risk Manage.*, 2011, **7**, 749; (*b*) M. Burnier and H. R. Brunner, *Lancet*, 2000, **355**, 637.

38 (*a*) S. C. Benson, H. A. Pershadsingh, C. I. Ho, A. Chittiboyina, P. Desai, M. Pravenec, N. Qi, J. Wang, M. A. Avery and T. W. Kurtz, *Hypertension*, 2004, **43**, 993; (*b*) R. A. Benndorf, T. Rudolph, D. Appel, E. Schwedhelm, R. Maas, F. Schulze, E. Silberhorn and R. H. Boger, *Metab., Clin. Exp.*, 2006, **55**, 1159; (*c*) J. F. E. Mann, R. E. Schmieder, M. McQueen, L. Dyal, H. Schumacher, J. Pogue, X. Wang, A. Maggioni, A. Budaj, S. Chaithiraphan, K. Dickstein, M. Keltai, K. Metsärinne, A. Oto, A. Parkhomenko, L. S. Piegas, T. L. Svendsen, K. K. Teo and S. Yusuf, *Lancet*, 2008, **372**, 547.

39 (*a*) A. Carta, S. Piras, G. Loriga and G. Paglietti, *Mini-Rev. Med. Chem.*, 2006, **6**, 1179; (*b*) B. P. Zambrowicz and A. T. Sands, *Nat. Rev. Drug Discovery*, 2003, **2**, 38.

40 S. Ohta, Y. Naita, T. Yuasa, S. Hatakeyama, M. Kobayashi, K. Kaibe, I. Kawasaki and M. Yamashita, *Chem. Pharm. Bull.*, 1991, **39**, 2787.

41 Y. Kuo-Long, R. L. Civiello, K. D. Combrink, H. B. Gulgeze, N. Sin, X. Wang, A. Nicholas and B. L. Venables, WO Pat., 2001/95910 A1, 2001.

42 D. F. Smith, L. Whitesell and E. Katsanis, *Pharmacol. Rev.*, 1998, **50**, 493.

43 *Lekarstvennye Sredstva*, ed. M. D. Mashkovskiy, Novaya Volna, Moscow, 2008.

44 M. Negwer and H.-G. Sharnow, *Organic-Chemical Drugs and Their Synonyms*, Wiley-VCH, Weinheim, 2001.

45 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Wiley, 2010, pp. 507–508.

46 (*a*) D. N. Gray, *J. Heterocycl. Chem.*, 1970, **7**, 947; (*b*) R. L. Hudkins, *Heterocycles*, 1995, **41**, 1045.

47 (*a*) V. Balasubramaniyan, P. Balasubramaniyan and S. V. Patil, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1990, **29**, 124; (*b*) M. S. Salakhov, V. S. Umaeva, Y. S. Salakhova and S. S. Idrisova, *Zh. Org. Khim.*, 1999, **35**, 421; (*c*) M. R. Grimmett, in *Best Synthetic Methods*, ed. O. Meth-Cohn and A. R. Katritzky, Academic Press, New York, 1997.

48 R. A. Ogg and F. W. Bergstrom, *J. Am. Chem. Soc.*, 1931, **53**, 1846.

49 E. C. Taylor and A. McKillop, *J. Org. Chem.*, 1965, **30**, 2858.

50 E. S. Lane, *J. Chem. Soc.*, 1955, 1079.

51 (*a*) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 1967, **8**, 753; (*b*) A. A. Jarrer, S. S. Halawi and M. J. Haddadin, *Heterocycles*, 1976, **4**, 1077.

52 (*a*) F. Krohnke, *Justus Liebigs Ann. Chem.*, 1957, **604**, 203; (*b*) J. Streith and C. Sigwatt, *Tetrahedron Lett.*, 1966, **13**, 1347; (*c*) J. S. Splitter and M. Calvin, *J. Org. Chem.*, 1965, **30**, 3427.

53 Y. Ahmad, M. S. Habib, A. Mohammady, B. Bakhtiari and S. A. Shamsi, *J. Org. Chem.*, 1968, **33**, 201.

54 P. T. Lont and H. C. Van der Plas, *Recl. Trav. Chim. Pays-Bas*, 1972, **91**, 850.

55 G. W. H. Cheeseman and M. Rafig, *J. Chem. Soc. C*, 1971, 452.

56 A. Albert and J. J. McCormack, *J. Chem. Soc.*, 1965, 6930.

57 R. A. Burrell, J. M. Cox and E. G. Savins, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2707.

58 R. A. Abramovitch and B. W. Cue, *Heterocycles*, 1973, **1**, 227.

59 E. Hayashi and C. Iijima, *Yakugaki Zasshi*, 1962, **82**(8), 1093; *Chem. Abstr.*, 1963, **58**, 4551.

60 Y. Ahmad, M. Habib, S. Ziauddin and B. Bakhtiari, *J. Org. Chem.*, 1966, **31**, 2613.

61 E. Hayashi and Y. Miura, *Yakudaku Zasshi*, 1967, **87**, 648; *Chem Abstr.*, 1967, **67**, 90775s.

62 (*a*) A. A. Kalinin, V. A. Mamedov and Y. A. Levin, *Chem. Heterocycl. Compd.*, 2000, **36**, 882; (*b*) V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, A. V. Chernova,

I. A. Litvinov, A. Ya and R. R. Shagidullin, *Russ. Chem. Bull.*, 2004, **53**, 164; (*c*) V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, E. A. Gorbunova and I. A. Litvinov, *Russ. J. Org. Chem.*, 2006, **42**, 1532; (*d*) A. A. Kalinin, O. G. Isaykina and V. A. Mamedov, *Chem. Heterocycl. Compd.*, 2007, **43**, 1307; (*e*) V. A. Mamedov, D. F. Saifina, I. K. Rizvanov and A. T. Gubaidullin, *Tetrahedron Lett.*, 2008, **49**, 4644; (*f*) V. A. Mamedov, N. A. Zhukova, T. N. Beschastnova, A. T. Gubaidullin, A. A. Balandina and S. K. Latypov, *Tetrahedron*, 2010, **66**, 9745.

63 (*a*) V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, I. A. Litvinov and Y. A. Levin, *Chem. Heterocycl. Compd.*, 2002, **38**, 1504; (*b*) E. A. Gorbunova and V. A. Mamedov, *Russ. J. Org. Chem.*, 2006, **42**, 1528; (*c*) V. A. Mamedov, A. M. Murtazina, D. I. Adgamova, N. A. Zhukova, T. N. Beschastnova, S. V. Kharlamov, I. K. Rizvanov and S. K. Latypov, *J. Heterocycl. Chem.*, 2014, **51**, 1664.

64 V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, O. G. Isaikina and I. A. Litvinov, *Russ. J. Org. Chem.*, 2005, **41**, 599.

65 O. Hinsberg, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 318.

66 S. von Niementowski, *Ber. Dtsch. Chem. Ges.*, 1897, **30**, 3062.

67 E. L. Hölljes and E. C. Wagner, *J. Org. Chem.*, 1944, **9**, 31.

68 F. E. King and R. M. Acheson, *J. Chem. Soc.*, 1949, 1396.

69 (*a*) C. T. Brain and S. A. Brunton, *Tetrahedron Lett.*, 2002, **43**, 1893; (*b*) C. T. Brain and J. T. Steer, *J. Org. Chem.*, 2003, **68**, 6814.

70 (*a*) J. B. Wright, *Chem. Rev.*, 1951, **48**, 397; (*b*) R. C. Elderfield and F. J. Kreysa, *J. Am. Chem. Soc.*, 1948, **70**, 44.

71 R. Weidenhagen, *Ber. Dtsch. Chem. Ges.*, 1936, **69**, 2263.

72 P. L. Beaulieu, B. Haché and E. von Moos, *Synthesis*, 2003, 1683.

73 J. I. G. Cadogan, R. Marshall, D. M. Smith and M. J. Todd, *J. Chem. Soc. C*, 1970, 2441.

74 S. Tolari, S. Cenini, C. Crotti and E. Gianella, *J. Mol. Catal.*, 1994, **87**, 203.

75 (*a*) W. Dohle, A. Staubitz and P. Knochel, *Chem.–Eur. J.*, 2003, **9**, 5323; (*b*) R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604; (*c*) R. J. Sundberg and T. Yamazaki, *J. Org. Chem.*, 1967, **32**, 290.

76 (*a*) V. A. Mamedov, A. M. Murtazina, A. T. Gubaidullin, E. A. Khafizova, I. K. Rizvanov and I. A. Litvinov, *Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 1645; (*b*) V. A. Mamedov, E. A. Khafizova, A. T. Gubaidullin, A. M. Murtazina, D. I. Adgamova, A. I. Samigullina and I. A. Litvinov, *Russ. Chem. Bull., Int. Ed.*, 2011, **60**, 368.

77 G. Sarodnick and G. Kempter, *Zeitschrift für Chemie*, 1982, **22**, 300.

78 (*a*) T. Mizutani, K. Yoshida and S. Kawazoe, *Drug Metab. Dispos.*, 1994, **22**, 750; (*b*) E. Novellino, B. Cosimelli, M. Ehlardo, G. Greco, M. Iadanza, A. Lavecchia, M. G. Rimoli, A. Sala, A. Da Settimo, G. Primofiore, F. Da Settimo, S. Taliani, C. La Motta, K. N. Klotz, D. Tuscano, M. L. Trincavelli and C. Martini, *J. Med. Chem.*, 2005, **48**, 8253.

79 E. Lippmann and W. Shilov, *Collect. Czech. Chem. Commun.*, 1984, **49**, 1304.

80 M. J. Climent, A. Corma, S. Iborra and S. Martínez-Silvestre, *ChemCatChem*, 2013, **5**, 3866.

81 (*a*) A. Domling, *Chem. Rev.*, 2006, **106**, 17; (*b*) C. Hulme and J. Dietrich, *Mol. Diversity*, 2009, **13**, 195; (*c*) L. El Kaim and L. Grimaud, *Tetrahedron*, 2009, **65**, 2153; (*d*) L. Banfi, R. Riva and A. Basso, *Synlett*, 2010, **1**, 23; (*e*) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **44**, 1947; (*f*) Z. Xu, M. Ayaz, A. Capelli and C. Hulme, *ACS Comb. Sci.*, 2012, **14**, 460; (*g*) Z. Xu, F. De Moliner, A. P. Capelli and C. Hulme, *Angew. Chem., Int. Ed.*, 2012, **51**, 8037.

82 (*a*) C. Hulme, J. Peng, S. Y. Tang, C. J. Burns, I. Morize and R. Labaudiniere, *J. Org. Chem.*, 1998, **63**, 8021; (*b*) Y. Huang, K. Khoury, T. Chanas and A. Doemling, *Org. Lett.*, 2012, **14**, 5916.

83 (*a*) C. Hulme, J. Peng, B. Louridas, P. Menard, P. Krolikowski and N. V. Kumar, *Tetrahedron Lett.*, 1998, **39**, 8047; (*b*) C. Hulme, J. Peng, G. Morton, J. M. Salvino, T. Herpin and R. Labaudiniere, *Tetrahedron Lett.*, 1998, **39**, 7227.

84 C. Hulme, L. Ma, J. Romano and M. Morrissette, *Tetrahedron Lett.*, 1999, **40**, 7925.

85 C. Hulme, L. Ma, M. P. Cherrier, J. J. Romano, G. Morton, C. Duquenne, J. Salvino and R. Labaudiniere, *Tetrahedron Lett.*, 2000, **41**, 1883.

86 (*a*) C. Hulme, L. Ma, J. J. Romano, G. Morton, S.-Y. Tang, M.-P. Cherrier, S. Choi, J. Salvino and R. Labaudiniere, *Tetrahedron Lett.*, 2000, **41**, 1889; (*b*) S. Pakornwit and M. Krasivan, *Tetrahedron Lett.*, 2014, **55**, 2299.

87 M. Ayaz, Z. Xu and C. Hulme, *Tetrahedron Lett.*, 2014, **55**, 3406.

88 S. Gunawan, M. Ayaz, F. De Moliner, B. Frett, C. Kaiser, N. Patrick, Z. Xu and C. Hulme, *Tetrahedron*, 2012, **68**, 5606.

89 D. F. Saifina, PhD dissertation, A. E. Arbuzov Institute of Organic and Physical Chemistry of Kazan Research Center of the Russian Academy of Sciences, Kazan, Russia, 2009.

90 A. A. Kalinin, PhD dissertation, Kazan State University, Kazan, Russia, 2000.

91 O. G. Isaykina, PhD dissertation, A. E. Arbuzov Institute of Organic and Physical Chemistry of Kazan Research Center of the Russian Academy of Sciences, Kazan, Russia, 2007.

92 (*a*) P. N. Preston, *Chem. Rev.*, 1974, **74**, 279; (*b*) A. Ladenburg, *Chem. Ber.*, 1875, **8**, 677; (*c*) M. A. Phillips, *J. Chem. Soc.*, 1928, **13**, 172; (*d*) M. A. Phillips, *J. Chem. Soc.*, 1928, **13**, 2393; (*e*) A. W. White, R. Almassy, A. H. Calvert, N. J. Curtin, R. J. Griffin, Z. Hostomsky, K. Maegley, D. R. Newell and B. T. Golding, *J. Med. Chem.*, 2000, **43**, 4084; (*f*) I. M. Elchaninov and M. M. Elchaninov, *Russ. J. Org. Chem.*, 2014, **50**, 1145; (*g*) B. H. Kim, R. Han, T. H. Han, Y. M. Jun, W. Baik and B. M. Lee, *Heterocycles*, 2002, **57**, 5.

93 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Wiley, 2010, pp. 462–463.

94 S. Kanoktanaporn, J. A. H. MacBride and T. J. King, *J. Chem. Res.*, 1980, **406**, 4901.

95 Y. Kurasawa, S. Shimabukuro, Y. Okamoto and A. Takada, *J. Heterocycl. Chem.*, 1985, **22**, 1461.

96 A. Hassner and I. Namboothiri, *Organic Syntheses Based on Name Reactions*, Elsevier, Amsterdam, 2012, pp. 299–300.

97 (*a*) Y. Kurasawa and A. Takada, *Heterocycles*, 1980, **14**, 281; (*b*) Y. Kurasawa, Y. Okamoto, K. Ogura and A. Takada, *J. Heterocycl. Chem.*, 1985, **22**, 661; (*c*) Y. Kurasawa, J. Satoh, M. Ogura, Y. Okamoto and A. Takada, *Heterocycles*, 1984, **22**, 1531.

98 L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Wiley, New York, 1975.

99 V. A. Mamedov, A. M. Murtazina, N. A. Zhukova, T. N. Beschastnova, I. K. Rizvanov and S. K. Latypov, *Tetrahedron*, 2014, **70**, 7567.

100 (*a*) N. Kornblum, W. J. Jones and G. J. Anderson, *J. Am. Chem. Soc.*, 1959, **81**, 4113; (*b*) N. Kornblum and H. W. Frazier, *J. Am. Chem. Soc.*, 1966, **88**, 865; (*c*) S. Chandrasekhar and M. Sridhar, *Tetrahedron Lett.*, 2000, **41**, 5423; (*d*) B. K. Bettadaiah, K. N. Burudutt and P. Srinivas, *J. Org. Chem.*, 2003, **68**, 2460.

101 *March's Advanced Organic Chemistry*, ed. M. B. Smith, Hooboken, New Jersey, 2013, pp. 1481–1483.

102 V. A. Mamedov, N. A. Zhukova, V. V. Sykaev, A. T. Gubaidullin, T. N. Beschastnova, D. I. Adgamova, A. I. Samigullina and S. K. Latypov, *Tetrahedron*, 2013, **69**, 1403.

103 V. A. Mamedov, N. A. Zhukova, T. N. Beschastnova, E. I. Zakirova, S. F. Kadyrova, E. V. Mironova, A. G. Nikonova, S. K. Latypov and I. A. Litvinov, *Tetrahedron Lett.*, 2012, **53**, 292.

104 (*a*) O. Hinsberg, *Liebigs Ann. Chem.*, 1887, **237**, 368; (*b*) S. N. Murthy, B. Madhav and Y. V. D. Nageswar, *Helv. Chim. Acta*, 2010, **93**, 1216.

105 G. W. H. Cheeseman and R. F. Cookson, in *Condensed Pyrazines*, ed. A. Weissberger and E. C. Taylor, Wiley-Interscience, New York, 1979.

106 (*a*) Y. Kubota, T. Shibata, E. Babamoto-Horiguchi, J. Uehara, K. Funabiki, S. Matsumoto, M. Ebihara and M. Matsui, *Tetrahedron*, 2009, **65**, 2506; (*b*) B. Gao, Q. Zhou, Y. Geng, Y. Cheng, D. Ma, Z. Xie, L. Wang and F. Wang, *Mater. Chem. Phys.*, 2006, **99**, 247; (*c*) R. Faust and C. Weber, *Tetrahedron*, 1997, **53**, 14655.

107 (*a*) V. A. Mamedov, D. F. Saifina, A. T. Gubaidullin, A. F. Saifina and I. K. Rizvanov, *Tetrahedron Lett.*, 2008, **49**, 6231; (*b*) V. A. Mamedov, A. M. Murtazina, A. T. Gubaidullin, E. A. Hafizova and I. K. Rizvanov, *Tetrahedron Lett.*, 2009, **50**, 5186; (*c*) V. A. Mamedov, D. F. Saifina, A. T. Gubaidullin, V. R. Ganieva, S. F. Kadyrova, D. V. Rakov, I. K. Rizvanov and O. G. Sinyashin, *Tetrahedron Lett.*, 2010, **51**, 6503.

108 (*a*) V. A. Mamedov, N. A. Zhukova, T. N. Beschastnova, A. T. Gubaidullin, D. V. Rakov and I. K. Rizvanov, *Tetrahedron Lett.*, 2011, **52**, 4280; (*b*) V. A. Mamedov, N. A. Zhukova, T. N. Beschastnova and A. T. Gubaidullin, *Russ. Chem. Bull., Int. Ed.*, 2011, **60**, 933.

109 V. A. Mamedov, D. F. Saifina, A. T. Gubaidullin, A. F. Saifina, I. K. Rizvanov and V. R. Ganieva, *Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 1986.

110 A. M. Murtazina, PhD dissertation, A. E. Arbuzov Institute of Organic and Physical Chemistry of Kazan Research Center of the Russian Academy of Sciences, Kazan, Russia, 2010.

111 (*a*) M. Behforouz, J. L. Bolan and M. S. Flynt, *J. Org. Chem.*, 1985, **50**, 1186; (*b*) J. Buckingham, *Q. Rev., Chem. Soc.*, 1969, **23**, 37; (*c*) L. A. Audrieth and B. A. Ogg, *The Chemistry of Hydrazines*, Wiley, New York, 1951.

112 (*a*) M. B. Smith, *March's Advanced Organic Chemistry*, Hooboken, New Jersey, 2013, pp. 1067–1248; (*b*) C. D. Gutsche, *The Chemistry of Carbonyl Compounds*, Prentice Hall, Englewood Cliffs, NJ, 1967.

113 (*a*) L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635; (*b*) A. Castro, D. D. Giannin and W. F. Greenlee, *J. Org. Chem.*, 1970, **35**, 2815; (*c*) A. F. Mironov, K. K. Alarkon and R. P. Evstigneeva, *Chem. Heterocycl. Compd.*, 1973, 1487.

114 (*a*) P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *J. Org. Chem.*, 2009, **74**, 8369; (*b*) L. Zhu and M. Zhang, *J. Org. Chem.*, 2004, **69**, 7371; (*c*) G. E. Ham, *J. Org. Chem.*, 1964, **29**, 3052; (*d*) E. Byun, B. Hong, K. A. De Castro, M. Lim and H. Rhee, *J. Org. Chem.*, 2007, **72**, 9815; (*e*) J. Marco-Contelles, E. Pérez-Mayoral, A. Samadi, M. do Carmo Carreiras and E. Soriano, *Chem. Rev.*, 2009, **109**, 2652; (*f*) M. Bian, W. Yao, H. Ding and C. Ma, *J. Org. Chem.*, 2010, **75**, 269; (*g*) T. Newhouse, C. A. Lewis, K. J. Eastman and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 7119.

115 (*a*) E. Bandini, G. Corda, A. D'Aurizio and M. Panunzio, *Tetrahedron Lett.*, 2010, **51**, 933; (*b*) V. Gouverneur and L. Ghosez, *Tetrahedron*, 1996, **52**, 7585; (*c*) Z. Bouaziz, P. Nebois and H. Fillion, *Tetrahedron*, 1995, **51**, 4057; (*d*) C. R. Berry and R. P. Hsung, *Tetrahedron*, 2004, **60**, 7629; (*e*) F. Palacios and G. Rubiales, *Tetrahedron Lett.*, 1996, **37**, 6379; (*f*) I. A. Motortna and D. S. Grierson, *Tetrahedron Lett.*, 1999, **40**, 7211; (*g*) M. A. Cuellar, L. K. Alegria, Y. A. Prieto, M. J. Cortes, R. A. Tapia and M. D. Preite, *Tetrahedron Lett.*, 2002, **43**, 2127.

116 V. A. Mamedov, A. A. Kalinin, V. V. Yanilkin, A. T. Gubaidullin, S. K. Latypov, A. A. Balandina, O. G. Isaikina, A. V. Toropchina, N. V. Nastapova, N. A. Iglamova and I. A. Litvinov, *Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 2616.

117 V. A. Mamedov and N. A. Zhukova, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and J. A. Joule, Elsevier, Amsterdam, 2013, vol. 25, pp. 1–45.

118 V. A. Mamedov and A. M. Murtazina, *Russ. Chem. Rev.*, 2011, **80**, 397.

119 (*a*) V. A. Mamedov, V. R. Galimullina, N. A. Zhukova, S. F. Kadyrova, E. V. Mironova, I. K. Rizvanov and S. K. Latypov, *Tetrahedron Lett.*, 2014, **55**, 4319; (*b*) V. A. Mamedov, S. F. Kadyrova, N. A. Zhukova, V. R. Galimullina, F. M. Polyancev and S. K. Latypov, *Tetrahedron*, 2014, **70**, 5934.

120 V. R. Galimullina, PhD dissertation, A. E. Arbuzov Institute of Organic and Physical Chemistry of Kazan Research

Center of the Russian Academy of Sciences, Kazan, Russia, 2015.

121 M. B. Smith, *March's Advanced Organic Chemistry*, Wiley, New York, 2001, pp. 1185–1187.

122 Z. Wang, *Comprehensive Organic Name Reactions and Reagents*, Wiley, Hoboken, New Jersey, 2009, pp. 1137–1142.

123 (*a*) Z. Rappoport, *The Chemistry of Enamines*, Wiley, Chichester, UK, 1994; (*b*) P. W. Hickmott, *Tetrahedron*, 1984, **40**, 2989; (*c*) P. W. Hickmott, *Tetrahedron*, 1982, **38**, 3363; (*d*) P. W. Hickmott, *Tetrahedron*, 1982, **38**, 1975.

124 I. Wiedermannová, J. Slouka, O. Humpa and K. Lemr, *J. Heterocycl. Chem.*, 2003, **40**, 357.

125 A. Lučka, I. Frišová and J. Slouka, *Magn. Reson. Chem.*, 2007, **45**, 46.

126 I. Frišová, Z. Trávníček, J. Slouka and P. Cankař, *ARKIVOC*, 2011, 127.

127 V. A. Mamedov, N. A. Zhukova, A. I. Zamaletdinova, T. N. Beschastnova, M. S. Kadyrova, I. K. Rizvanov, V. V. Syakaev and S. K. Latypov, *J. Org. Chem.*, 2014, **79**, 9161.

128 (*a*) S. Allu, S. Selvakumar and V. K. Singh, *Tetrahedron Lett.*, 2010, **51**, 446; (*b*) O. Andrei, A. Alexakis and G. Bernardinelli, *Org. Lett.*, 2003, **5**, 2559; (*c*) S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **9**, 2582; (*d*) S. Boncel, M. Mączka and K. Z. Walczak, *Tetrahedron*, 2010, **43**, 8450.

129 V. A. Mamedov, N. A. Zhukova, T. N. Beschastnova, V. V. Syakaev, D. B. Krivolapov, E. V. Mironova, A. I. Zamaletdinova, I. K. Rizvanov and S. K. Latypov, *J. Org. Chem.*, 2015, **80**, 1375.

130 (*a*) Y. Naruse, T. Suzuki and S. Inagaki, *Tetrahedron Lett.*, 2005, **46**, 6937; (*b*) G. Hilt and J. Treutwein, *Angew. Chem.*, 2007, **46**, 8500; (*c*) R. Shen, S. Zhu and X. Huang, *J. Org. Chem.*, 2009, **74**, 4118.

131 (*a*) G. E. Keck and R. R. Webb, *J. Am. Chem. Soc.*, 1981, **103**, 3173; (*b*) G. E. Keck and R. Webb, *Tetrahedron Lett.*, 1979, **20**, 1185; (*c*) W. Oppolzer, E. Pfenninger and K. Keller, *Helv. Chim. Acta*, 1973, **56**, 1807.