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Advances in the synthesis of benzimidazolones *via* rearrangements of benzodiazepinones and quinoxalin(on)es

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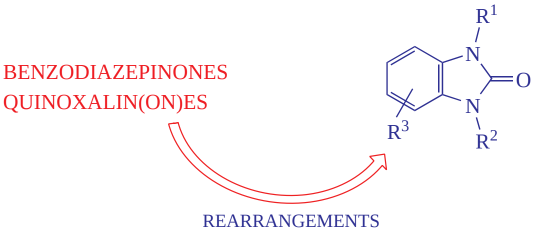
The review critically analyzes methods for the preparation of benzimidazolones proceeding *via* the rearrangements of benzodiazepinones and quinoxalin(on)es, highlights recent advances in the synthesis of bi- and tri-heterocyclic systems with the benzimidazolone moiety, and the advantages and major challenges in their biomedical applications.



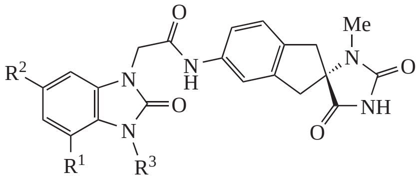
Introduction

Benzimidazol-2-ones are important heterocycles with an embedded cyclic urea scaffold widely distributed in a variety of pharmacological compounds, such as calcitonin gene-related peptide (CGRP) receptor antagonists **1**,[1] p53-Mdm antagonists **2**,[2] cannabinoid receptor 2 (hCB2) antagonists **3**,[3] opioid receptor-like 1 (NOP) agonists **4**,[4,5] non-nucleoside HIV-1 RT (NNRTIs) inhibitors **5**,[6] D-amino acid oxidase (DAAO) inhibitors **6**,[7] respiratory syncytial virus (RSV) fusion inhibitors **7**,[8] as well as *Mycobacterium tuberculosis* enzyme inhibitors **8**,[9] p38 MAP kinase inhibitors **9**,[10] and antibacterial agents **10**.[11] Benzimidazolone carboxylic acid derivatives are potential therapeutic agents of selective peroxisome proliferator-activated receptor γ modulators (SPPARγMs),[12] and may be used to treat type II diabetes mellitus (T2DM).[12] Benzimidazol-2-ones play important role as progesterone receptor antagonists **12**, **13**[13,14] selective

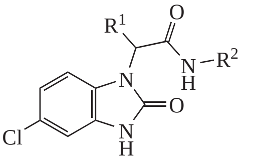
Professor **Vakhid A. Mamedov** graduated from Azerbaijan State University in Baku (1981) and received his PhD (1989) and Dr. Sci. (1999) degrees in chemistry at the A. E. Arbuzov Institute of Organic and Physical Chemistry (IOPC), Kazan Scientific Centre of the Russian Academy of Sciences. He spent 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 Chemistry of Heterocyclic Compounds at IOPC in 2002. He was principal tutor of 13 post-graduates and 24 graduate students, both in Russia and Japan, one of them got Dr. Sci. degree in 2014 under his leadership. He has authored over 180 papers and reviews in peer-reviewed journals and is the author of one monograph. Mamedov's research interests focus on the methodology of organic synthesis and development of new schemes of the tandem transformations for synthesizing the diversity-oriented heterocyclic systems.

Dr. **Nataliya A. Zhukova** graduated from Kazan State Technological University in 2002. In 2009, she received her PhD degree from A. E. Arbuzov Institute of Organic and Physical Chemistry (IOPC), Kazan Scientific Centre of the Russian Academy of Sciences, under the supervision of Professor Vakhid A. Mamedov. Since 2015, she is a senior researcher of the Laboratory of Chemistry of Heterocyclic Compounds at IOPC. Her scientific interests include the chemistry of N,S-containing heterocycles – potential biologically active compounds.

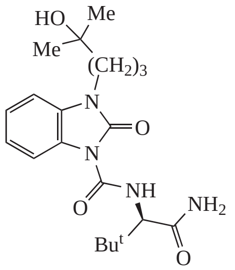
Professor **Oleg G. Sinyashin** graduated from Kazan State University (KSU) in 1978. He received his PhD degree from KSU in 1981 and Dr. Sci. degree in chemistry in 1990. He was elected a corresponding member of the Russian Academy of Sciences in 1997, and a full member of the Russian Academy of Sciences in 2006. The most part of his professional career is connected with A. E. Arbuzov Institute of Organic and Physical Chemistry (IOPC), Kazan Scientific Centre of the Russian Academy of Sciences. He began working as a junior researcher at IOPC in 1981 and became its director in 2001. In addition, he is the head of the Laboratory at IOPC since 1996 and head of the Department of Organic Chemistry at the Kazan National Research Technological University since 2001. He was the coordinator of many Russian and several international projects. He was awarded with the State Prize of the Republic of Tatarstan in science and technology (1997). His research interests cover chemistry of organophosphorus compounds, synthesis, structure and properties of organometallic compounds, chemistry of fullerenes, electrosynthesis of organic and organoelement compounds. He has authored over 400 publications including one monograph, articles in refereed journals, patents and conference reports.



1a $R^1 = R^2 = H$, R^3 = 2-pyridyl
1b $R^1 = R^2 = R^3 = Me$
1c $R^1 = R^2 = Me$, $R^3 = CH_2C(O)NMe_2$



2
$R^1 = Ar$, CH_2Ar
$R^2 = (CH_2)_nAr$, Alk, cyclohexyl



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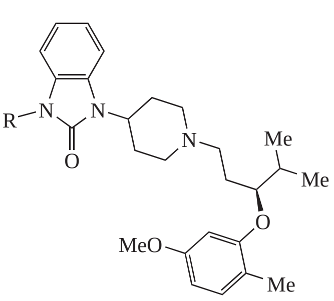
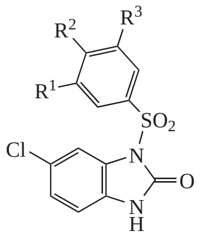
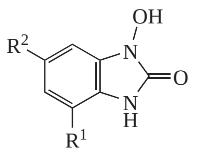


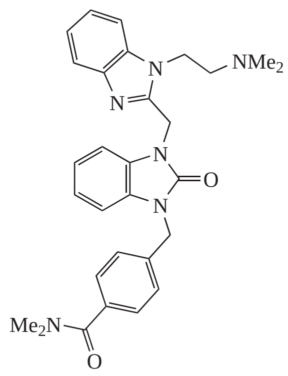
(+)-**4a** $R = CH_2CONHMe$
(+)-**4b** $R = CH_2CH_2OMe$
(+)-**4c** R = (1,2,4-triazol-5-yl)methyl



5a $R^1 = R^3 = Me$, $R^2 = H$
5b $R^1 = H$, $R^2 = R^3 = Me$



6a $R^1 = R^2 = H$
6b $R^1 = OMe$, $R^2 = H$
6c $R^1 = R^2 = F$



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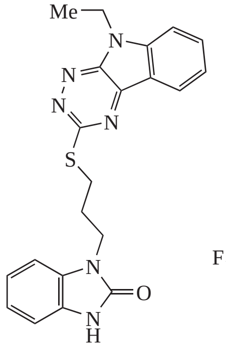
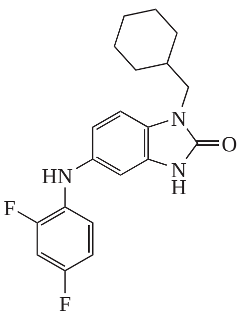


8
(SID 7975595)



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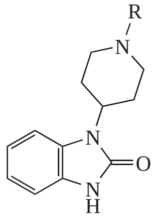
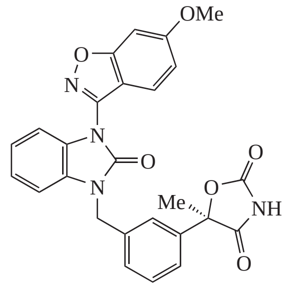


10a $R = 4\text{-}O_2NC_6H_4CH_2OC(O)$
10b $R = 2\text{-}F\text{-}4\text{-}O_2NC_6H_3$



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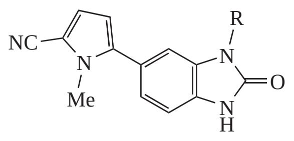
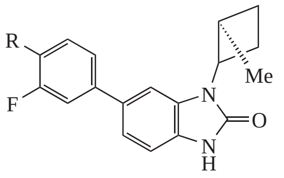
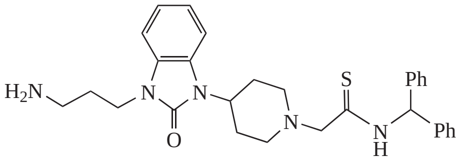


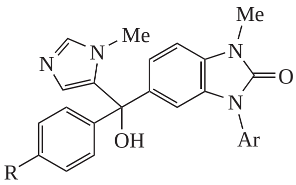
12a $R = Pr^i$
12b R = cyclobutyl
12c R = cyclopentyl
12d $R = CHEt_2$



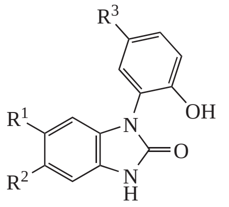
13a R = CN
13b R = OH



14
(RWJ-333966)



15a R = CN, Ar = $3\text{-}ClC_6H_4$
15b R = Cl, Ar = $3\text{-}EtOC_6H_4$



16a $R^1 = H$, $R^2 = CF_3$, $R^3 = Cl$ (NS004)
16b $R^1 = H$, $R^2 = R^3 = CF_3$ (NS1619)
16c $R^1 = Cl$, $R^2 = H$, $R^3 = OH$

vasopressin 1a receptor antagonist **14**,[15] in the selective inhibition of farnesyltransferase (FTase) **15**,[16] and the activation of K^+ channels **16**.[17,18]

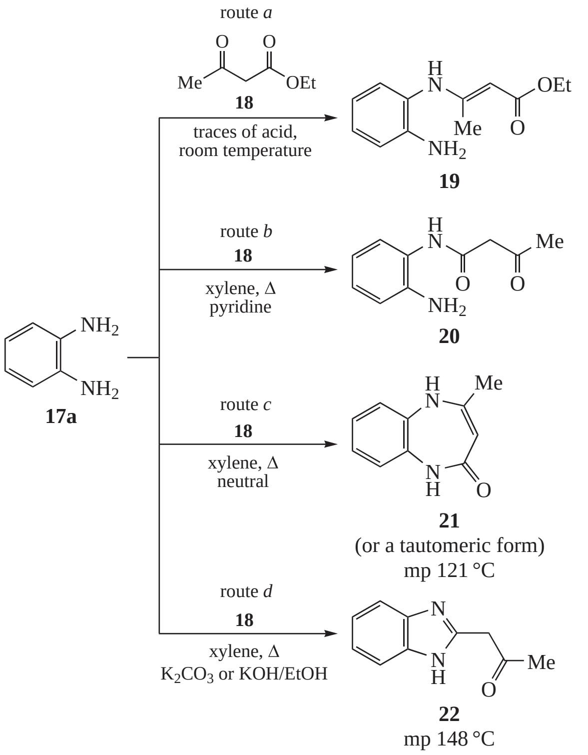
Benzimidazol-2-one derivatives have been used for over thirty years as pigments with a broad range of hues in watercolor painting and electrophotographic developer toner due to their durability and light resistance.[19–23]

Two typical methods are usually employed for the synthesis of N-substituted 1,3-dihydrobenzimidazol-2-ones. The first method is the selective alkylation or arylation of nitrogen atoms in 1,3-dihydrobenzimidazol-2-ones.[13,24,25] The second method involves the nucleophilic substitution of fluorine atom in 2-fluoronitrobenzenes with amines and subsequent reductive cyclization with the suppliers of carbonyl group, *e.g.*, carbonyldiimidazole.[10,16,26–28] The first method often requires a strategy for the protection of NH groups, and the second is problematic because of the limitations of the substituted derivatives of 2-fluoronitrobenzenes. In addition, there are other approaches for obtaining unsymmetrical 1,3-dihydrobenzimidazol-2-ones, *e.g.*, reactions proceeding with the rearrangements of different heterocyclic systems. Surprisingly, such methods are still not reviewed. Some subsections concerning benzimidazolones in reviews on quinoxalines[29–31] or benzimidazoles[32,33] do not generalize all the means of synthesizing 1,3-dihydrobenzimidazol-2-ones, and do not allow one to make predictions about possible new methods. Herein, we attempt to fill in this blank.

Synthesis of benzimidazolones *via* rearrangement of benzodiazepinones

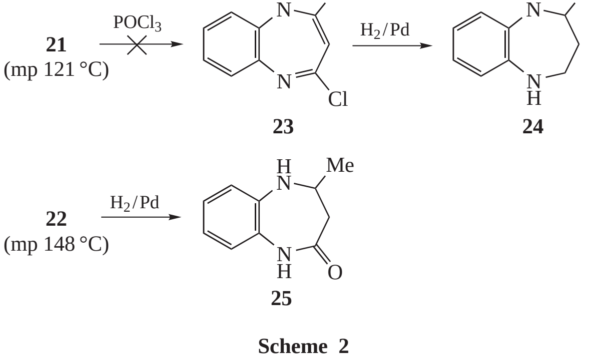
In the presence of traces of acid, the reaction between 1,2-diaminobenzene (1,2-DAB) **17a** and ethyl acetoacetate **18** at room temperature affords ethyl β-(*o*-aminoanilino)crotonate **19** (Scheme 1, route *a*).[34,35] The same reactants in boiling xylene containing pyridine give *o*-aminoaceto anilide **20** (Scheme 1, route *b*).[36]

According to Sexton,[34] the addition of ester **18** to 1,2-DAB **17a** in boiling xylene under neutral conditions leads to 4,7-dihydro-5-methyl-1*H*-2,3-benzo-1,4-diazepin-7-one **21** (or its tautomeric form) with the mp 121 °C (Scheme 1, route *c*). Meanwhile, if ester **18** is previously kept over potassium carbonate or if ethanolic potassium hydroxide solution is added to the reaction mixture, the product could be isomeric 2-acetonylbenzimidazole **22** with mp 148 °C (Scheme 1, route *d*).



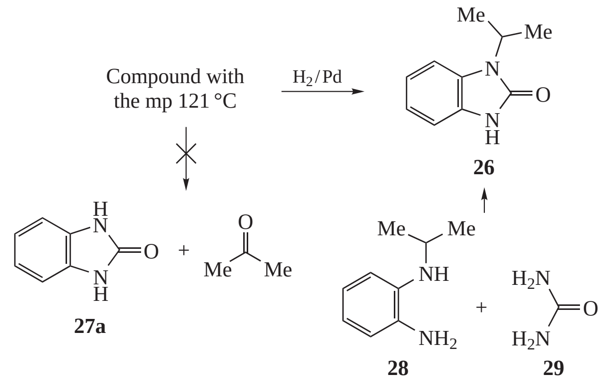
Scheme 1

The supposed diazepine (mp 121 °C) reacted with phosphoryl chloride in the presence of dimethylaniline to produce a chloro compound, in which the chlorine atom could be replaced with an amino group by treatment with ethanolic ammonia. However, on catalytic reduction and dehalogenation, this chloro compound absorbed only 2 mol of hydrogen instead of the three to be expected for 7-chloro-5-methyl-2,3-benzo[*b*][1,4]diazepiane **23** with the formation of 2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-[1,4]diazepine **24**. Therefore, both Sexton's compounds[34] were re-examined by Davoll.[37] The compound with the mp 148 °C absorbed 1 mol of hydrogen over palladium, the product being truly 4-methyl-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one **25** (Scheme 2). Hence, the compound with the mp 148 °C is dihydrodiazepine **21**, which has also been prepared by the counter synthesis from 1,2-DAB and ketene.[38]



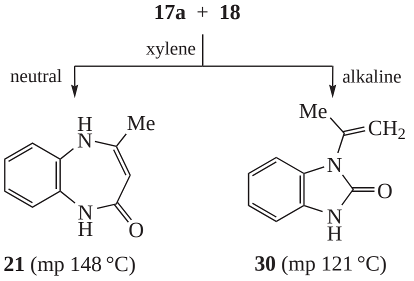
Scheme 2

On reduction, the compound with the mp 121 °C also absorbed 1 mol of hydrogen to give a product resembling the starting material in its UV absorption spectrum and solubility in alkali, however, it was not hydrolyzed into benzimidazol-2-one **27a** and acetone (Scheme 3) by dilute acid. The assumption that the product of the hydrogenation of compound with the mp 121 °C is 1-isopropylbenzimidazol-2-one **26** rather than diazepine **25** has been confirmed with the counter synthesis of product **26** from *N*-isopropyl-*o*-phenylenediamine **28** and urea **29** (see Scheme 3).[39]



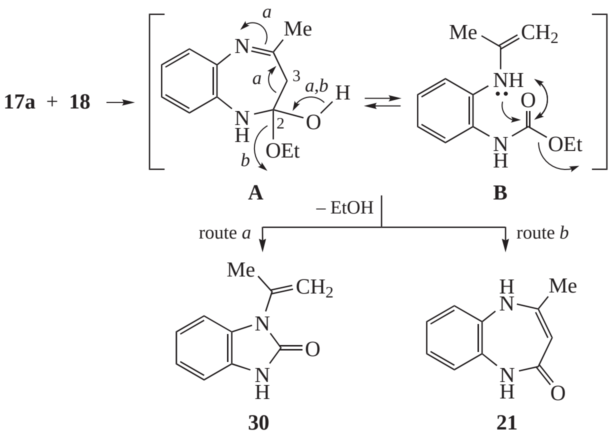
Scheme 3

Thus, the structures of the reaction products of 1,2-DAB **17a** with ethyl acetoacetate **18** have been shown to differ from those previously assigned by Sexton.[34] The product with the mp 148 °C is benzodiazepine derivative **21**, and the product with the mp 121 °C is 1-isopropenylbenzimidazol-2-one **30**[37,39] rather than 2-acetonylbenzimidazole **22**[34] (Scheme 4).



Scheme 4

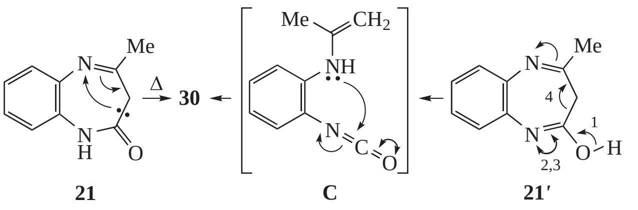
As shown in Scheme 5, formation of compound **30** in the reaction of 1,2-DAB **17a** with ethyl acetoacetate **18** occurs through the intermediate generation of the reaction hemiaminal derivative **A** at the initial stages, whose transformation proceeds not with the elimination of a molecule of ethanol or water, but with



Scheme 5

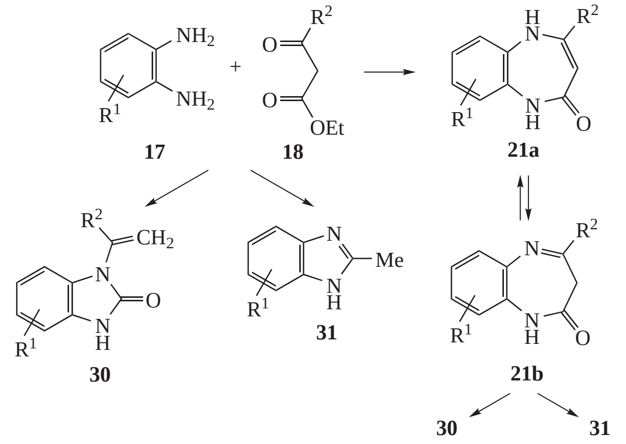
the C(2)–C(3) bond breakage leading to carbamate **B**. Further intramolecular amidation results in the benzimidazolone **30**.

Although in the literature[40,41] the thermal rearrangement of diazepine **21** is presented as the 1,3-sigmatropic one (Scheme 6), we cannot exclude a mechanism involving the C(2)–C(3) bond breakage under the investigated conditions as in the above case. To this, the intermediate formation of the more reactive isocyanate **C** can occur (see Scheme 6) (intramolecular cyclization of isocyanates with the formation of amide function are well known).[42–45]



Scheme 6

Depending on the reaction conditions, dihydrobenzodiazepinone **21**, 2-methylbenzimidazole **31** and vinylbenzimidazol-2-one **30** derivatives can be formed (Scheme 7).[46–49]



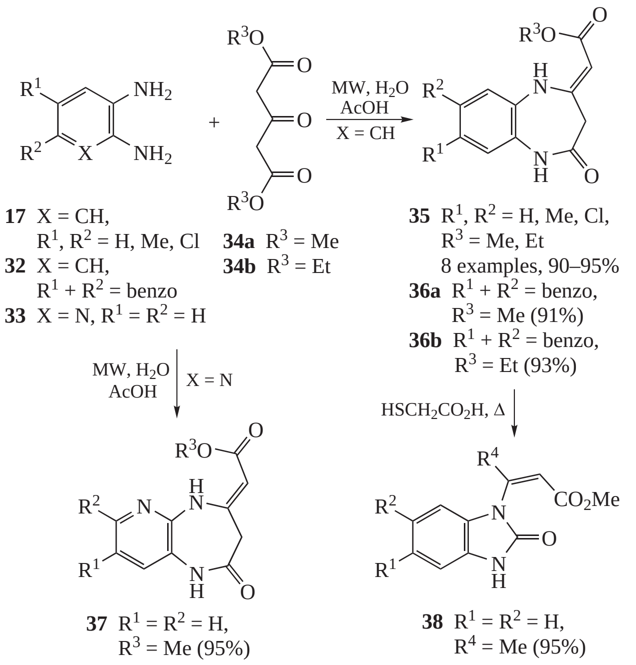
Scheme 7

It should be pointed out that formation of 1-isopropenylbenzimidazol-2-ones **30**[37,39] rather than 2-acetonylbenzimidazoles **22**[34] (see Scheme 4) is characteristic of other analogues of 1,2-DAB **17** and ethyl acetoacetate **18** as well.

The vicinal diamino group can be a part of condensed and heterocyclic systems attached to a fragment of ethyl acetoacetate in the molecule of alicyclic and cyclic compounds. In many cases the intermediates formed at an initial stage, the diazepine derivatives, on the way to the benzimidazolone derivatives are stable compounds and can be isolated and characterized.

The acid-catalyzed reactions of derivatives of 1,2-DAB **17** and its naphtho- (**32**) and pyrido- (**33**) analogues with acetonedicarboxylates **34** lead to 1,5-benzo- (**35**), naphtho- (**36**) and pyrido- (**37**) diazepines by irradiation in a Biotage Initiator 2.0 microwave oven for 3 min at 200 °C either in acetic acid or in water containing catalytic amounts of acetic acid (Scheme 8).[50] Diazepine **35** ($R^1 = R^2 = H$, $R^3 = Me$) when boiling in DMF in the presence of thioglycolic acid undergoes rearrangement giving the corresponding benzimidazolone derivative **38**. In all cases, the reactions proceed quantitatively.

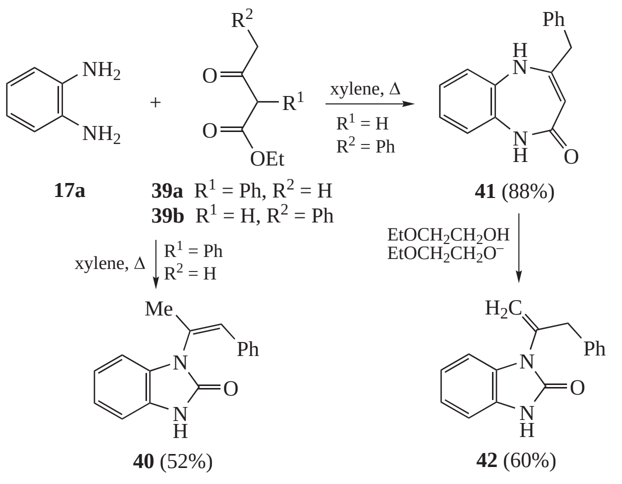
Reactions of 1,2-DAB **17a** with ethyl acetoacetate derivatives, namely α- and γ-phenylacetoacetic esters (**39a** and **39b**, respectively), in boiling xylene proceed in a different way (Scheme 9) to afford a rearrangement product **40** and the corresponding diazepine **41**, respectively. For rearrangement of the latter, its boiling in 2-ethoxyethanol is necessary.[51]



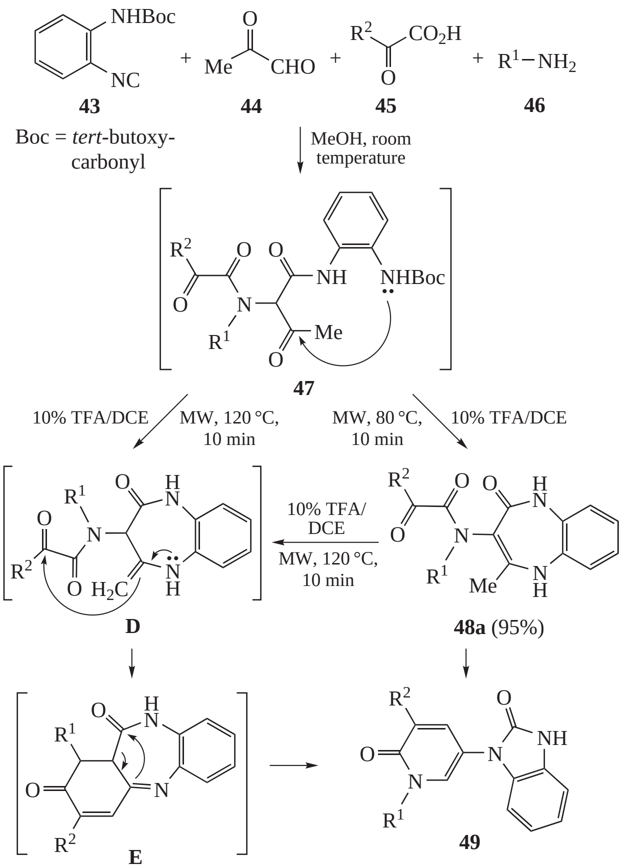
Scheme 8

Hulme and coworkers reported[53,54] that replacement of the commercially available isonitriles by *o*-*N*-Boc-phenylisonitrile **43**, bearing an additional masked amino group,[52] in multicomponent reactions (MCR) of isonitriles, pyruvic aldehyde **44**, phenylglyoxylic acid **45** and amine **46** allows one to perform a domino process combining two modified multicomponent Ugi reactions in one pot, with the formation of compounds **47**[53,54] (Scheme 10). In the course of consecutive processes including the intramolecular attack of the anilinic amine onto the pyruvaldehyde carbonyl group in the presence of 10% TFA/DCE the intermediate **D** would form. Subsequent formation of benzodiazepine tricyclic species **E** (*cf.* ref. 55) is followed by its rearrangement under microwave irradiation at 120 °C to afford biheterocyclic compound **49** (see Scheme 10). Upon experimenting with lower temperatures (80 °C) the expected kinetic product **48a** ($R^1 = 3\text{-}BrC_6H_4$, $R^2 = 4\text{-}FC_6H_4CH_2$) was obtained in an almost quantitative amount.

1,2-DAB **17a** can react not only with ethyl acetoacetate **18** and its acyclic derivatives **34**, **39**, but also with its carbo- and heterocyclic analogues, such as 2-ethoxycarbonylcycloalkanones,[39] methyl 4-oxotetrahydrothiophene-3-carboxylates,[56] N-substituted 3-ethoxycarbonyl-4-piperidone,[39] and 1-*N*,*N*-dimethylaminomethylene-1,2-dihydrofuro[2,3-*b*]quinoxalin-2-one.[57,58]



Scheme 9

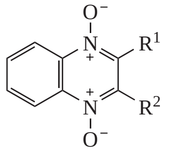


$R^1 = Ph(CH_2)_2$, $MeO(CH_2)_2$, Ph, 2,6-$Cl_2C_6H_3CH_2$, 2-furyl
$R^2 = Bu^i$, Ph, 2-furyl, 2-thienyl
7 examples, 47–58%
$R^1 = 3\text{-}BrC_6H_4$, $R^2 = 4\text{-}FC_6H_4CH_2$
(88% from **48a**)

Scheme 10

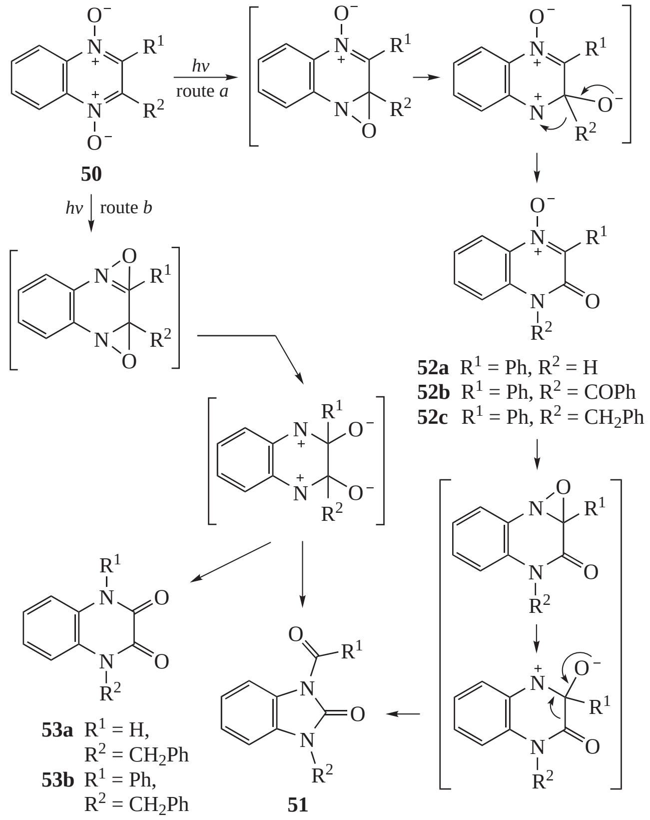
Synthesis of benzimidazolones *via* rearrangement of quinoxalin(on)es

From quinoxaline N*-oxides.* Quinoxaline l,4-dioxides and monoxides were successfully photolyzed to yield a variety of products depending on the structures of the substrates.[59–62] 2-Aroyl-3-arylquinoxaline 1,4-dioxides **50** (R^1 = Ar, R^2 = COAr) were reported to give 1-aroylbenzimidazol-2-ones **51**.[60,61,63] Analogous 2- or 3-alkylated compounds behave similarly to **50** (R^1 = Alk, R^2 = COAr).[62] However, compounds lacking aryl substituents or a CO group as part of R^1 or R^2 failed to rearrange. The mechanism suggested by Haddadin and coworkers[60–62] for the reaction is shown in Scheme 11 (route *a*). In looking for support for this mechanism, synthesis of the proposed intermediate **52b** was attempted, without success. To clarify the mechanism of the rearrangement, the behaviour of four quinoxaline 1,4-dioxides **50a–d** was studied.[64]



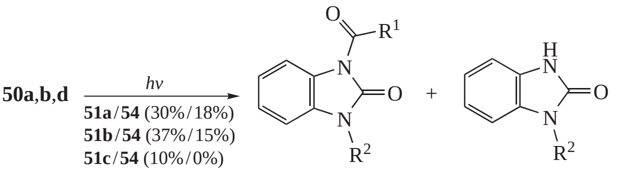
50a R^1 = Me, $R^2 = CH_2Ph$
50b R^1 = Ph, $R^2 = CH_2Ph$
50c R^1 = H, $R^2 = CH_2Ph$
50d R^1 = C(O)Ph, $R^2 = CH_2Ph$

The dominant features of these compounds are the presence of benzyl substituent and (with the exception of **50d**) the lack of CO group. The essential feature of mechanism (Scheme 11, route *a*) is the migration of a CO carbon to an electron-deficient nitrogen. It was interesting to see whether benzyl group behaves similarly, knowing that 2,3-dialkyl- or 2,3-diaryl analogues of **50** do not undergo such a rearrangement.[64]



Scheme 11

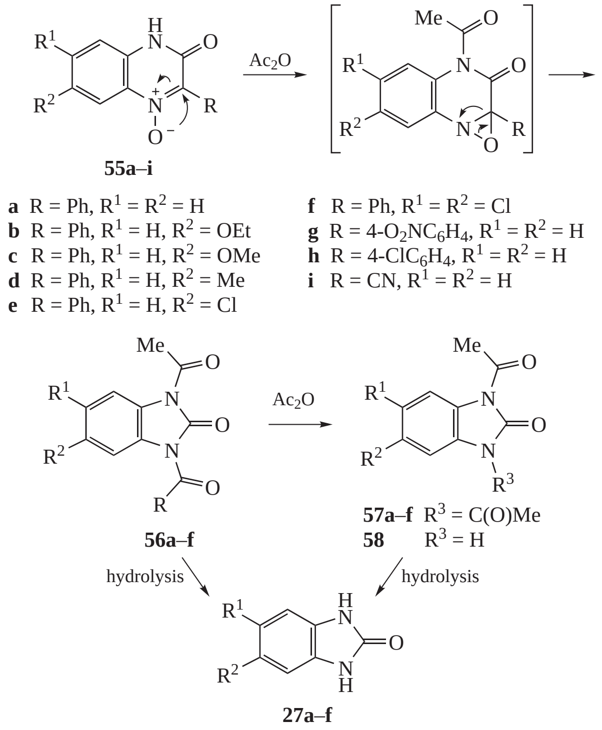
The benzyl group was capable of migration as anticipated. Compounds **50a** and **50b** on photolysis in methanol gave corresponding 1-acyl-3-benzylbenzimidazolones **51a**,**b** (Scheme 12).[64] An accompanying product in each case was the hydrolyzed *N*-benzylbenzimidazolone **54**. In the case of **50d** the isolated product agrees with a higher migratory aptitude for a benzoyl compared with a benzyl substituent. The product **51c** hydrolyzes completely to unsubstituted benzimidazolone **27a** instead of **54**. However, compound **50c** did not behave similarly but afforded 1-benzyl-2,3-quinoxalinedione **53a**. The rearrangement of **50b** can be explained by Scheme 11 (route *a*) and provides a possibility of testing the proposed stepwise mechanism by the direct synthesis of intermediate **52c**. Benzylation of 3-phenylquinoxalin-2-one 4-oxide **52a** is possible although it failed. When intermediate **52c** was photolyzed under the conditions used for **50b**, it failed to give **51b** and **54**, but instead gave **53b**. The results of the photolysis of **52c** show that it cannot be an intermediate in the photolysis of **50b**, and that this photolysis does not proceed by the stepwise mechanism shown in Scheme 11 (route *a*). More likely mechanism for the photolysis of compounds mentioned previously[60,61] and the photolysis of **50a–c** was suggested.[64] It involves the simultaneous excitation of both nitrone functions at 1- and 4-positions (route *b*). This scheme can also account for the formation of **53a** from **50c** by assuming a different mode of migration in the charged intermediate.



51a R^1 = Me, $R^2 = CH_2Ph$ **54** $R^2 = CH_2Ph$
51b R^1 = Ph, $R^2 = CH_2Ph$
51c R^1 = Ph, $R^2 = C(O)CH_2Ph$

Scheme 12

Ahmad and coworkers reported[65] that quinoxaline 1-oxides **55a**–**i**, bearing a substituent at C(2), a carbonyl at C(3), and a free hydrogen at N(4), when heated with acetic anhydride, are transformed into 1,3-diacylbenzimidazol-2-ones depending on the nature of substituents at C(2), C(6), and C(7). For example, 3-hydroxy-2-phenylquinoxaline 1-oxide **55a**, 7-ethoxy-3-hydroxy-2-phenylquinoxaline 1-oxide **55b** and 3-hydroxy-7-methyl-2-phenylquinoxaline 1-oxide **55d** on reflux with acetic anhydride afforded 1-acetyl-3-benzoylbenzimidazol-2-one **56a**, or 5-ethoxy- and 5-methyl-1-acetyl-3-benzoylbenzimidazol-2-ones **56b** and **56d**, respectively, which on hydrolysis with aqueous alkali lost their acyl groups and yielded benzimidazol-2-one **27a** or 5-ethoxy- (**27b**) and 5-methyl- (**27d**) derivatives (Scheme 13).[65] 3-Hydroxy-2-(4-nitrophenyl)quinoxaline 1-oxide **55g** remained unchanged even on prolonged reflux with acetic anhydride. However, when the two reactants were heated together in a sealed tube at 180 °C for 12 h, the products of the reaction were 1,3-diacetyl- and 1-acetylbenzimidazolin-2(3*H*)-ones **57a** and **58**, respectively, along with 4-nitrobenzoic acid. Likewise, 2-cyano-3-hydroxyquinoxaline 1-oxide **55i** failed to react with acetic anhydride under ordinary reflux conditions. However in a sealed tube at 180 °C, it also gave 1,3-diacetylbenzimidazol-2-one **57a**.

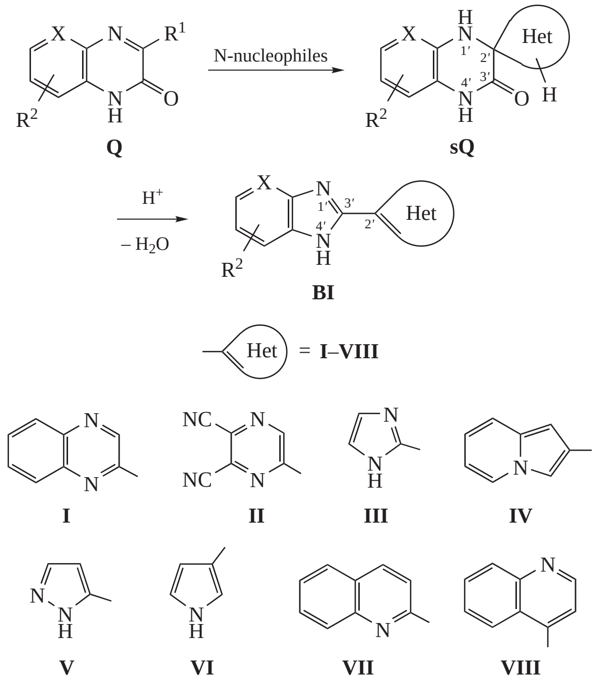


a R = Ph, $R^1 = R^2$ = H
b R = Ph, R^1 = H, R^2 = OEt
c R = Ph, R^1 = H, R^2 = OMe
d R = Ph, R^1 = H, R^2 = Me
e R = Ph, R^1 = H, R^2 = Cl
f R = Ph, $R^1 = R^2$ = Cl
g R = 4-$O_2NC_6H_4$, $R^1 = R^2$ = H
h R = 4-ClC_6H_4, $R^1 = R^2$ = H
i R = CN, $R^1 = R^2$ = H

Scheme 13

Under certain conditions not only quinoxaline *N*-oxides but also the functionally substituted quinoxalin-2(1*H*)-ones underwent rearrangements giving benzimidazol-2-ones.

From quinoxalinones. Mamedov and coworkers reported[66–78] that quinoxalin-2(1*H*)-ones **Q** (X = CH, R^2 = H, Me, Cl, *etc.*) and their aza-analogues (X = N, R^2 = H)[71] with the imine function between the C(3) and N(4) atoms of the pyrazine ring depending on the nature of substituents R^1 at the 3-position behave like imino analogues of α-chloro ketones [in the case of R^1 = CH(Cl)Ph],[66] α-amino ketones [in the case of R^1 = $CH(NH_2)Ph$],[67] α-azido ketones [in the case of R^1 = $CH(N_3)(CH_2)_nPh$],[68] α-diketones [in the case of R^1 = C(O)Ar, C(O)Alk],[69–74] β-diketones [in the case of R^1 = $CH_2(CO)Ar$],[76,77] usual ketones (in the case of R^1 = Me),[75] and 2-aminobenzaldehydes (in the case of R^1 = 2-$H_2NC_6H_4$)[78] and undergo novel acid-catalyzed rearrangement in the reactions with various N-nucleophiles resulting in 2-heteroaryl substituted benzimidazole derivatives (Scheme 14).

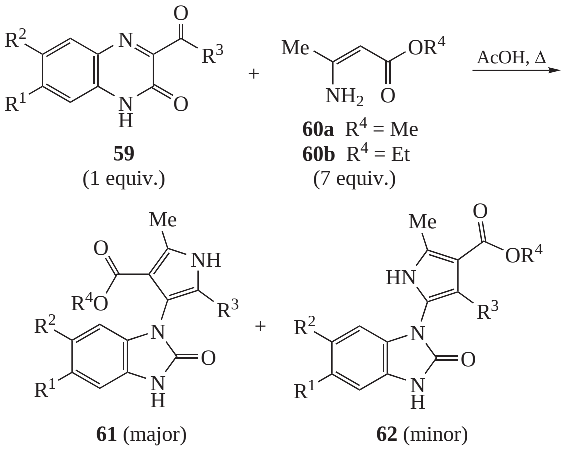


Scheme 14

The transformation proceeds through the heteroarylspiroquinoxalin-3′(4′*H*)-ones **sQ**, whose formation occurs as one of the classic reactions of the synthesis of heterocycles. In the syntheses of spiro[quinoxaline-2,2′-quinoxalin]-3′(4′*H*)-ones **sQI**, spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones **sQII** and spiro[imidazoline-5,2′-quinoxalin]-3′(4′*H*)-ones **sQIII**, the derivatives of quinoxalin-2(1*H*)-one with R^1 = C(O)Ar and C(O)Alk were the heteroanalogues of α-diketones in the Hinsberg–Körner[79,80] and Debus–Radziszewski–Japp[81–83] reactions. In the syntheses of spiro[indolizine-2,2′-quinoxalin]-3′(4′*H*)-ones **sQIV**, the derivatives of quinoxalin-2(1*H*)-one with R^1 = CH(Cl)Ar acted as heteroanalogues of α-chloro ketones in the Chichibabin[84] reaction. In the syntheses of spiro[pyrazoline-5,2′-quinoxalin]-3′(4′*H*)-ones **sQV** and spiro[pyrroline-3,2′-quinoxalin]-3′(4′*H*)-ones **sQVI**, the derivatives of quinoxalin-2(1*H*)-one with R^1 = $CH_2C(O)Ar$ and R^1 = $CH(NH_2)Ar$ served as heteroanalogues of β-diketones and α-amino ketones in the Knorr[85,86] reactions. In the syntheses of 1*H*,1′*H*-spiro[quinoline-2,2′-quinoxalin]-3′(4′*H*)-ones **sQVII** and 2,3-dihydro-1*H*,1′*H*-spiro[quinoline-4,2′-quinoxalin]-3′(4′*H*)-ones **sQVIII**, the derivatives of quinoxalin-2(1*H*)-one with R^1 = Me and with R^1 = 2-$H_2NC_6H_4$ served as heteroanalogues of usual ketones[87] in the modified Friedländer reaction and heteroanalogues of 2-aminobenzaldehydes in the Friedländer[78] reaction. The second stage of the process involves a fundamentally new acid-catalyzed rearrangement[87,88] (*Mamedov Heterocycle Rearrangement, Type 1*) of heteroarylspiroquinoxalin-3′(4′*H*)-ones **sQ**(**I**–**VIII**) in the benzimidazole derivatives **BI**(**I**–**VIII**) (Scheme 14).

The key step of this rearrangement (see Scheme 14) comprised a contraction of the pyrazine ring of the quinoxalin-2-one system in intermediate spiroquinoxalin-2(1*H*)-one derivatives **SQ**.[33,87,88] It was also shown that the necessary prerequisite 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 in Scheme 14, the formation of water molecule takes place with the involvement of the oxygen atom of the carbonyl group. It was assumed that if the spiro-quinoxalinone derivative without mobile hydrogen atom 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 proceed without any water elimination and with the preservation of the carbonyl oxygen atom, probably quinoxalinone-benzimidazolone. To confirm this assumption it was necessary to prepare the spiro-derivatives of the quinoxalinone lacking mobile hydrogen atoms. To this end, after analyzing all the possible nucleophilic reagents, the enamines as C,N-nucleophiles have been used.

Previously, Mamedov and coworkers reported[89] that the reaction of 3-acylquinoxalin-2(1*H*)-ones **59** with the commercially available enamines [methyl- (**60a**) and ethyl- (**60b**) 3-aminocrotonates] as C,N-nucleophiles under the acid catalysis conditions proceeds so fast that it appears impossible to allocate the expected spiro-compound which immediately underwent the rearrangement giving the corresponding *N*-(pyrrol-3-yl)benzimidazol-2-ones **61** as major and *N*-(pyrrol-2-yl)benzimidazol-2-ones **62** as minor products in the overall 89–99% yields (Scheme 15).



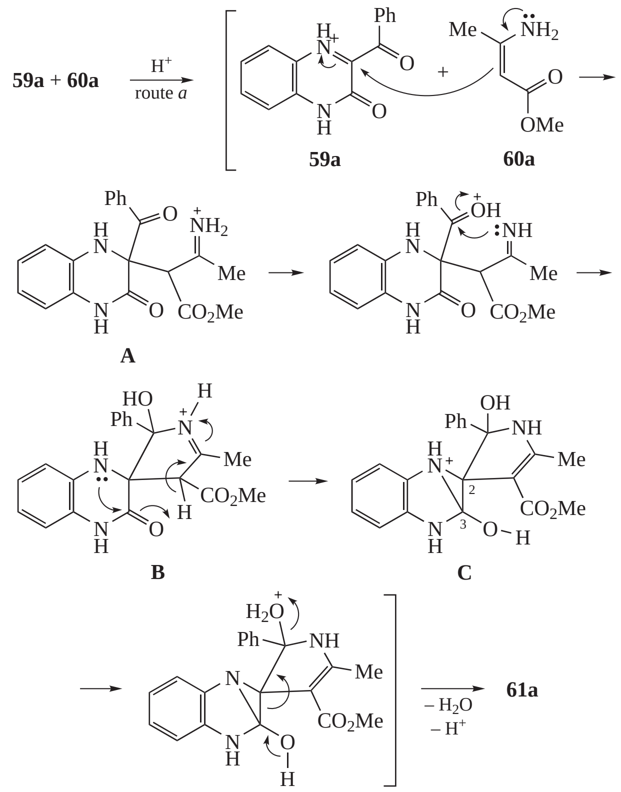
16 examples, 89–99%

R^1, R^2 = H, Me, C(O)Ph, CO_2H
R^3 = Pr, Ph, 4-HalC_6H_4 (Hal = F, Cl, Br, I)
R^4 = Me, Et

Scheme 15

A plausible reaction mechanism for the formation of *N*-pyrrolyl-benzimidazol-2-ones **61** and **62** has been proposed (Schemes 16 and 17). The process occurs in two directions (routes *a* and *b*), differing at their initial stages. In the case of the formation of *N*-(pyrrol-3-yl)benzimidazol-2-ones **61**, the interaction between **59a** and **60a** (Scheme 16) starts according to the acid-catalyzed Michael type mechanism[90–93] leadings to species **A**. The intramolecular cyclization of **A** *via* the attack by the imine nitrogen on the nearby C(O)Ph moiety affords the spiro-quinoxaline derivative **B**. The rearrangement of the latter is then assumed to occur according to Scheme 5, *i.e.*, by cascade reactions: (i) the intramolecular nucleophilic attack by the amino group on the carbonyl group with the intermediate formation of the hydroxy derivative **C**, (ii) 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 final product **61a**.

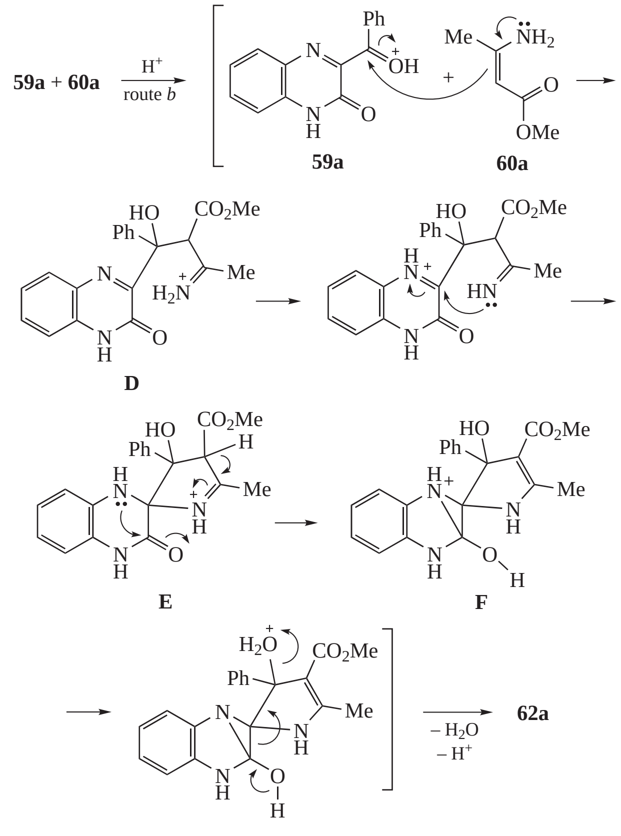
In the case of the formation of *N*-(pyrrol-2-yl)benzimidazol-2-ones **62** at its initial stage, a nucleophilic attack by the enamino double bond of **60a** on the electron deficient benzoyl carbonyl group of **59a** occurs, which leads to species **D** (Scheme 17). This brings about the rearrangement product *via* intermediates **E** and **F**.



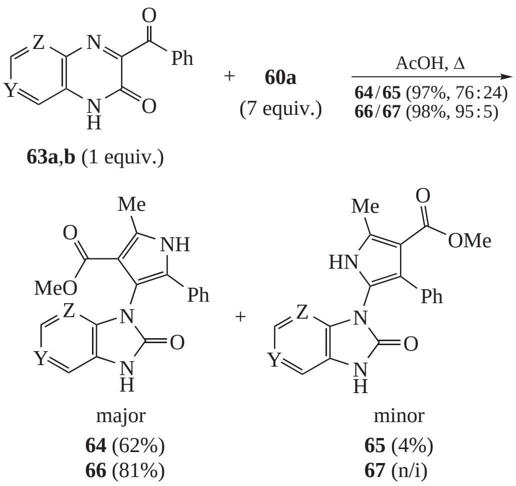
Scheme 16

This chemistry is not limited to quinoxalin-2(1*H*)-ones and 5- and 7-azaquinoxalin-2(1*H*)-ones, *e.g.*, 3-benzoylpyrido[3,2-*b*]pyrazin-2(1*H*)-one **63a** and 3-benzoylpyrido[3,4-*b*]pyrazin-2(1*H*)-one **63b** when subjected to the rearrangement afford easily separable regioisomeric products **64**/**65** and **66**/**67**, respectively, in overall quantitative yields (Scheme 18).[89]

In comparison with the existing methods, the present approach offers the following advantages: (i) it proceeds faster and provides good to excellent yields under mild conditions with no additional



Scheme 17



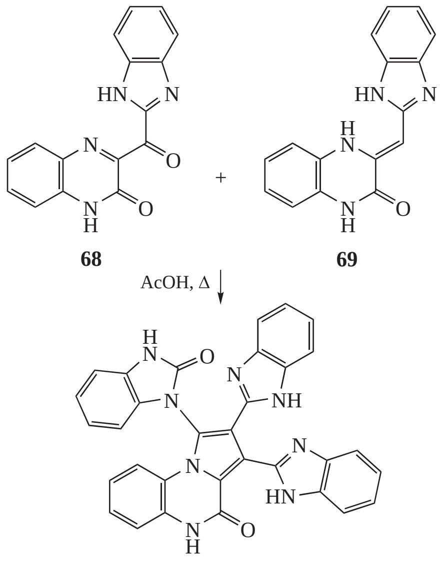
63a, **64**, **65** Z = N, Y = CH
63b, **66**, **67** Z = CH, Y = N

Scheme 18

activation modes such as microwave irradiation, (ii) it is very cost-effective and uses the inexpensive and available reagents, and (iii) it is applicable to a broad scope of substrates.

An effective synthesis strategy has been developed based on the novel quinoxalin-2(1*H*)-one/benzimidazol-2-one rearrangement that makes it possible to access *N*-pyrrolylbenzimidazol-2-ones from the readily available 3-aroylquinoxalin-2(1*H*)-ones with various substituents and available alkyl 3-aminocrotonates. The method is general and a wide variety of *N*-pyrrolylbenzimidazol-2-ones was prepared in good yields.

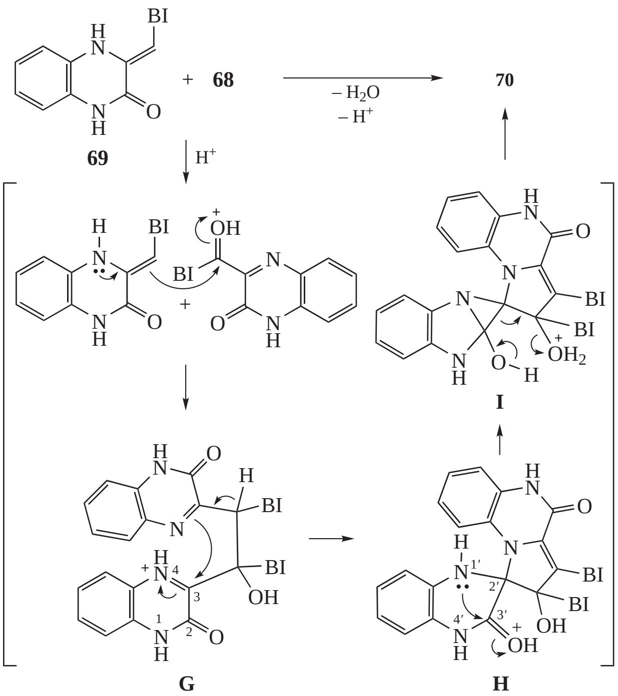
On using more complex reactants, more sophisticated products were thus obtained. Carrying out the reaction of 3-(benzimidazol-2-yl)quinoxalin-2(1*H*)-one **68** with 3-(benzimidazol-2-ylmethylidene)quinoxalin-2(1*H*)-one **69** in boiling AcOH led to pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one derivative **70** in a good yield (Scheme 19).[68]



70 (74%)

Scheme 19

The formation of compound **70** (Scheme 20) results from a cascade reaction that involves: (i) the intermolecular ene reaction[94–96] between enamine **69** and ketone **68** yielding compound **G**, (ii) the intramolecular ene reaction[97–99] giving the spiro-derivative quinoxalinono[2′,1]pyrrolo[1,2-*a*]quinoxaline **H**, and (iii) a new quinoxalinono-benzimidazolono rearrangement in the spiro-forming fragment (Scheme 20). Unlike the rearrangements discussed above (Scheme 14), in which the opening of the pyrazine ring of quinoxalinone system of spiro-derivatives occurs between the C(1) and N(2) atoms, in this case the opening of the pyrazine ring of quinoxaline system of spiro-derivative **H** occurs between the C(2) and C(3) atoms, through the intermediate formation of fused spiro-aziridino[2′,1]pyrrolo[1,2-*a*]quinoxaline **I** (see Scheme 20).

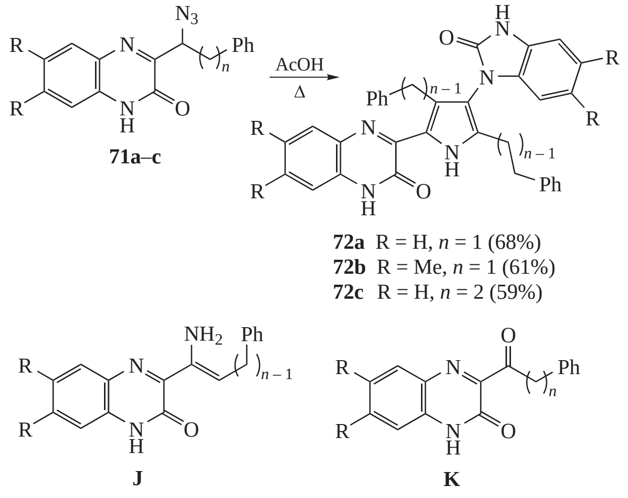


BI = benzimidazol-2-yl

Scheme 20

Enamines for the rearrangement can be generated *in situ* by the decomposition of azides (Scheme 21).[100] In this case the final products **72a–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. Thus, the new rearrangement of quinoxalinones makes it possible to simultaneously construct two various new heterocyclic systems under one-pot reaction conditions.

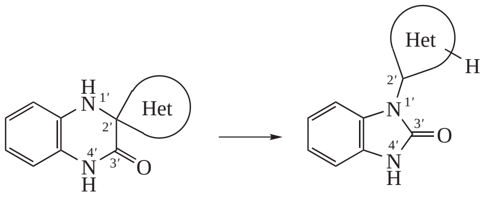
The fact that formation of the benzimidazolone derivatives in the reactions of the self-condensation of 3-(α-azidophenylalkyl)-quinoxalin-2(1*H*)-ones **71** (see Scheme 21) and in the condensa-



72a R = H, *n* = 1 (68%)
72b R = Me, *n* = 1 (61%)
72c R = H, *n* = 2 (59%)

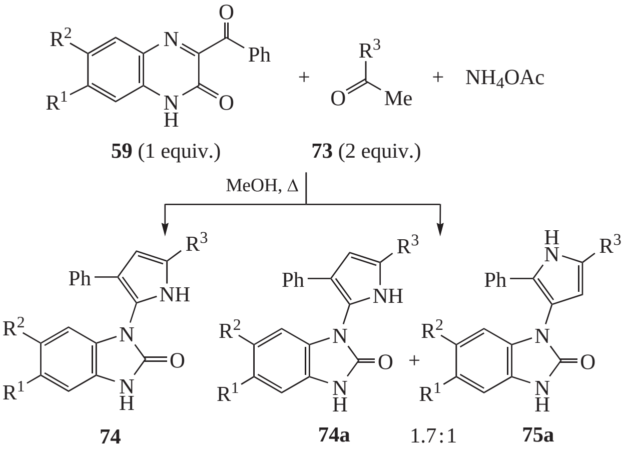
Scheme 21

tion of 3-(benzimidazol-2-yl)quinoxalin-2(1*H*)-one **68** with its predecessor, 3-(benzimidazol-2-ylmethylidene)quinoxalin-2(1*H*)-one **69** (see Scheme 19), gives reason to propose a new 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' (*Mamedov Heterocycle Rearrangement, Type 2*)[30,31] (Scheme 22).



Scheme 22

Recently, Mamedov and coworkers reported[101] that the above reactions of 3-acylquinoxalinones proceed equally well with enamines generated *in situ* from ketones with an activated methylene group and amines. For example, Scheme 23 shows the structural variations which are tolerated by these three-component reactions of 3-benzoylquinoxalinones (3-BQ) **59** with various ketones **73** and ammonium acetate.[101] Acetophenones (with electron-withdrawing and electron-donating substituents) and heteroaromatic ketones were converted into the corresponding products in good to excellent yields (see Scheme 23).



13 examples, 59–84%

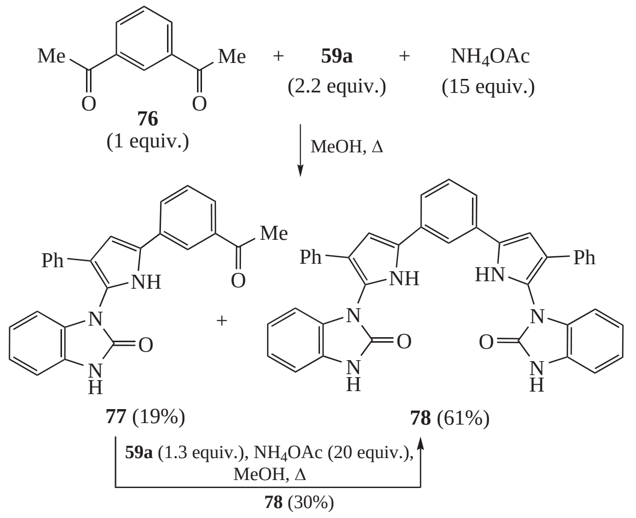
R^1, R^2 = H, Me, CO_2H, C(O)Ph
R^3 = 4-pyridyl, 3-pyridyl, 2-pyridyl, Ph, 4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 3-$O_2NC_6H_4$

92% combined
R^1 = R^2 = H
R^3 = 4-$MeOC_6H_4$

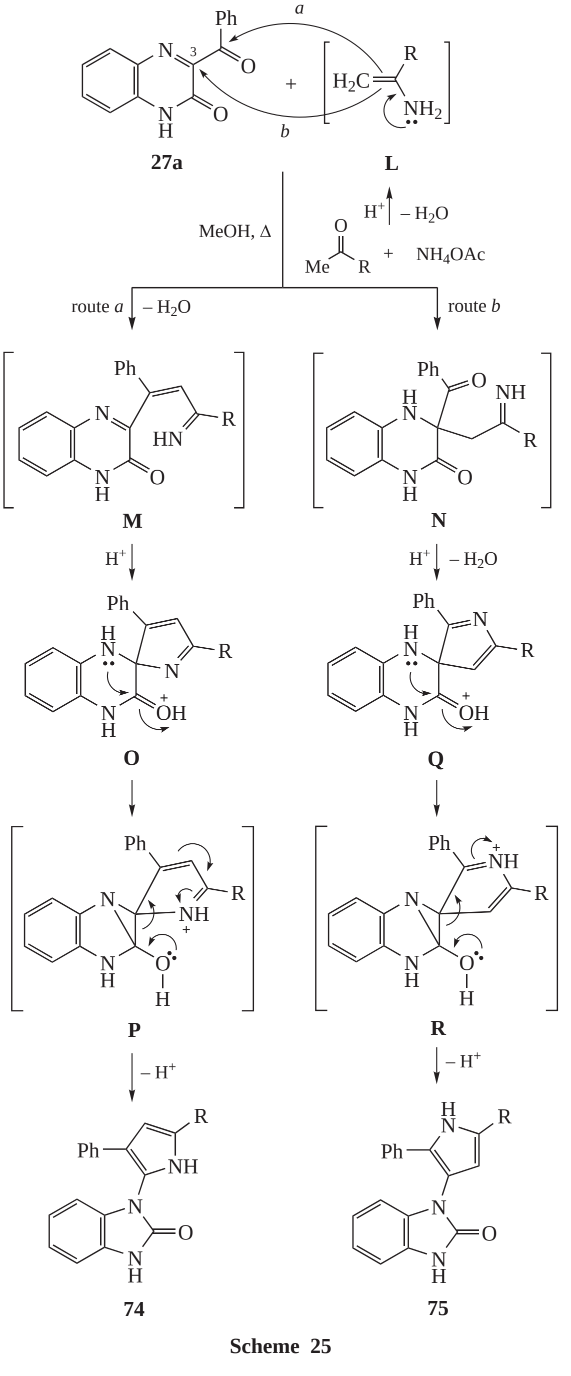
Scheme 23

Moving from acetophenone **73a** (R^3 = Ph) to 1,3-diacetylbenzene **76** (Scheme 24) would allow the anticipated cascade process with two MCR modifications to occur in one pot with the formation of compound **78**, with two 1-(pyrrol-2-yl)benzimidazolone cores in the benzene ring as a major product and compound **77** with one 1-(pyrrol-2-yl)benzimidazolone core as a minor product.[101] The reaction between acetophenone derivative **77** and 3-BQ **59a** in the presence of NH_4OAc can also produce **78** in a 30% yield.

The known chemistry of ketones,[102] imines,[103] quinoxalines,[29] and enamines[104–107] allows one to propose a plausible reaction course (Scheme 25), although the exact mechanism of this reaction is yet unclear. Intermediate **L** formed at the initial



Scheme 24



Scheme 25

stage reacts with the 3-BQ **59a** in two different directions (routes *a* and *b*) to give isomeric spiro[pyrrole-2,2′-quinoxalin]-3-one derivative **O** and spiro[pyrrole-3,2′-quinoxalin]-3-one derivative **Q** through the intermediates **M** and **N**, respectively. The latter are formed by the initial attack of enamine on the benzoyl carbonyl carbon atom (route *a*) and on the C(3) atom of the quinoxalinone system (route *b*), respectively. Then, both routes *a* and *b* proceed by cascade reactions involving: (i) the consecutively acid-catalyzed ring-closure of quinoxaline derivatives **M**, **N** to corresponding spiro-derivatives **O**, **Q** followed by formation of intermediates **P**, **R** with the aziridine ring system, (ii) the acid-catalyzed ring-opening in intermediates **P**, **R** with the formation of the final 1-(pyrrol-2-yl)- **74** and 1-(pyrrol-3-yl)-benzimidazolone **75** derivatives, respectively.

An important three-component reaction of 3-benzoylquinoxalinones, various methyl (het)aryl ketones and ammonia has been developed. The method makes it possible to access substituted 1-(pyrrolyl)benzimidazolone derivatives *via* multicomponent reactions from easily available 3-benzoylquinoxalinone precursors in the presence of various methyl (het)aryl ketones and ammonia in 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. Importantly, the method can be used for the synthesis of a wide range of benzimidazolone derivatives, since various methyl ketones are commercially available or can be easily obtained.

Conclusions

This review has presented the recent progress in the synthesis of benzimidazolones based on the rearrangements of benzodiazepinones and quinoxalin(on)es. These results indicate the importance and utility of various old and new rearrangements, not only in the preparation of 1*H*-benzimidazol-2(3*H*)-one as a parent molecule, but also for construction of its N-substituted derivatives, ranging from simple monocyclic compounds to complex polycyclic and spiro-systems. In many cases, the synthesis occurs regioselectivity and the products possess biological activity or are potential intermediates in the synthesis of physiologically active compounds including analogues of the currently used medicinal preparations.

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