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Recyclization reactions leading to benzimidazoles

V A Mamedov, A M Murtazina

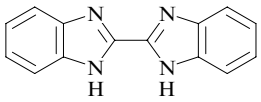
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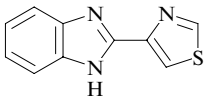
Abstract. The published data on the recyclization reactions that afford benzimidazoles are generalized and systematized. Both classical and new methods of benzimidazole synthesis are considered. Attention is focused on the publications over the recent 10 – 15 years; of the earlier publications, only those unknown to the wide circle of chemists are analyzed. The bibliography includes 143 references.

I. Introduction

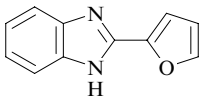
The benzimidazole system is a constituent of many physiologically active substances including vitamin B_{12},[1] compounds that exhibit antiviral[2,3] and antitumour activities,[4–6] preparations used in veterinary,[7–10] fungicides,[11] *etc*. The drug reference books by Mashkovskii[12] and Negwer[13] comprise 89 benzimidazole derivatives used currently in medicine. However, only 11 of them (see below) include other heterocyclic rings directly fused with the benzimidazole system. Probably, this is associated with the fact that such compounds are hardly accessible. Indeed, the analysis of the literature data shows that the methods of synthesis of such compounds involve many steps, are labourious, and the total yields of products never exceed 20% – 25%.



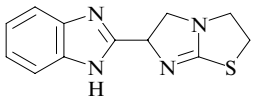
BBI, the antitumour drug



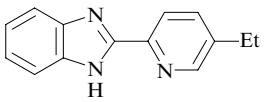
Thiabendazole,
the anthelmintic agent



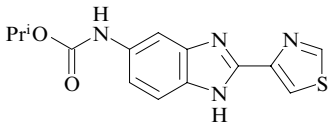
Fuberidazole,
the antifungal agent



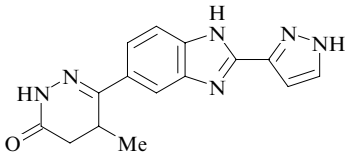
Bendamizole, the anthelmintic agent



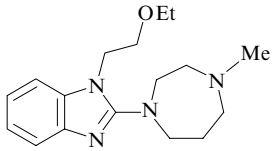
KB 1043,
the anti-inflammatory drug



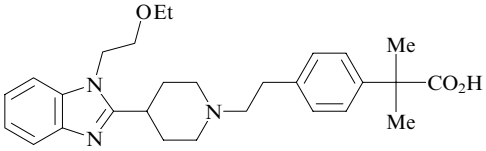
Novazole, the anthelmintic
agent (for veterinary)



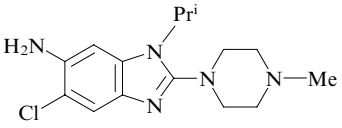
Meribendan, the cardiotonic agent



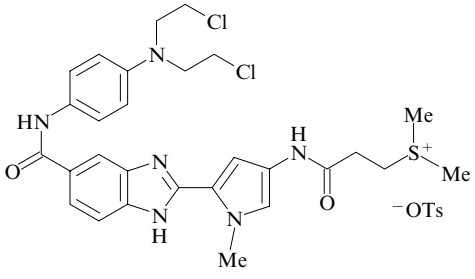
Rapimine, the antiallergic drug



Bilastine, the H_1 receptor antagonist



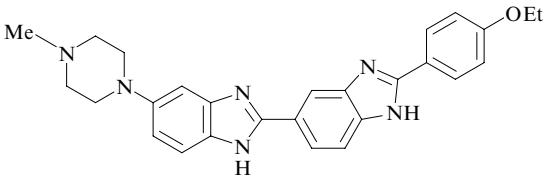
KB-R 6933, the antiemetic agent



MS-247, binds to DNA and alkylates it

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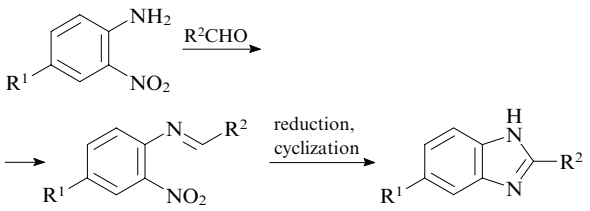
Received 8 July 2010
Uspekhi Khimii **80** (5) 419 – 442 (2011); translated by T Ya Safonova



H342, the antiviral and antitumour drug

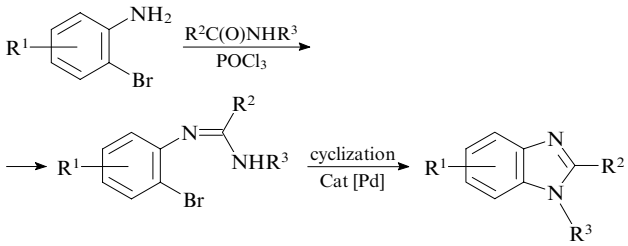
There are two classical methods for benzimidazole synthesis, namely, coupling of *o*-diaminobenzenes with carboxylic acids and of *o*-phenylenediamine (*o*-PDA) with aldehydes and ketones (the Phillips–Ladenburg and the Weidenhagen reactions, respectively).[14] The necessity of using high temperature (sometimes, 250–300 °C) and the low yields of products limited the use of these reactions in their classical versions.[15,16] Virtually all the currently existing methods of benzimidazole synthesis represent modifications of the mentioned reactions.[17–19] Scheme 1 shows the general strategy of benzimidazole synthesis. In the reaction with *o*-PDA, it is possible to use esters, lactones, anhydrides[14] in place of acids (or their chlorides), but this requires more drastic conditions (pathway *a*).[20,21] Amides, nitriles and imidates can also be introduced in the reaction with a diamine (pathway *b*); however, in this case, the formation of benzimidazoles is the result of cyclization of the intermediate amidine. The Weidenhagen reaction with aldehydes and, to a lesser extent, ketones afforded the final products following the oxidation step (pathway *c*). As a rule, in addition to the target products, the oxidation afforded numerous side products, because oxidation requires heating of the reaction mixture to the solvent boiling point (nitrobenzene or DMF) or the use of metal ions, molecular iodine, organic oxidants or inorganic hydrogensulfites at high temperatures. Nonetheless, several examples of milder oxidation of dihydrobenzimidazoles are known; they include the use of oxone,[22] $NaHSO_3$,[23–25] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[26–28] 1,4-benzoquinone,[29] atmospheric air,[30] $Fe(NO_3)_3$,[31] $FeCl_3 \cdot 6H_2O$,[32] $In(OTf)_3$,[33] $Yb(OTf)_3$,[34] $Sc(OTf)_3$,[35,36] $KHSO_4$,[37] SO_2,[38–40] $Me_2S^+BrBr^-$ (Ref. 41), $Na_2S_2O_3$,[42] $PhI(OAc)_2$,[43–49] $Mn(OAc)_3$,[50] $Ba(MnO_4)_2$,[51] NiO_2,[52] I_2,[53] benzofuroxan,[54] thianthrene radical cation[55] as oxidants or catalysts (promoters).

An alternative method is the reduction of Schiff bases derived from 2-nitroanilines and aldehydes (a modification of the Weidenhagen reaction). Dodecacarbonyltriruthenium[56] in the presence of carbon monoxide, phenylmagnesium chloride[57] and transition metal compounds[58,59] were used in this reaction as the reducing agents.



R^2 = Me: R^1 = H, Me, EtO, Cl; R^1 = H: R^2 = Ph, 4-MeC_6H_4, 4-$Pr^iC_6H_4$, 2-$EtOC_6H_4$, 4-ClC_6H_4, 3-BrC_6H_4.

Recently, a method of synthesis of N-substituted benzimidazoles has been proposed,[20,21] which was based on the palladium compound-catalyzed intramolecular arylation of *N*-(*o*-bromophenyl)amidines prepared by fusing *o*-bromoaniline with amides.

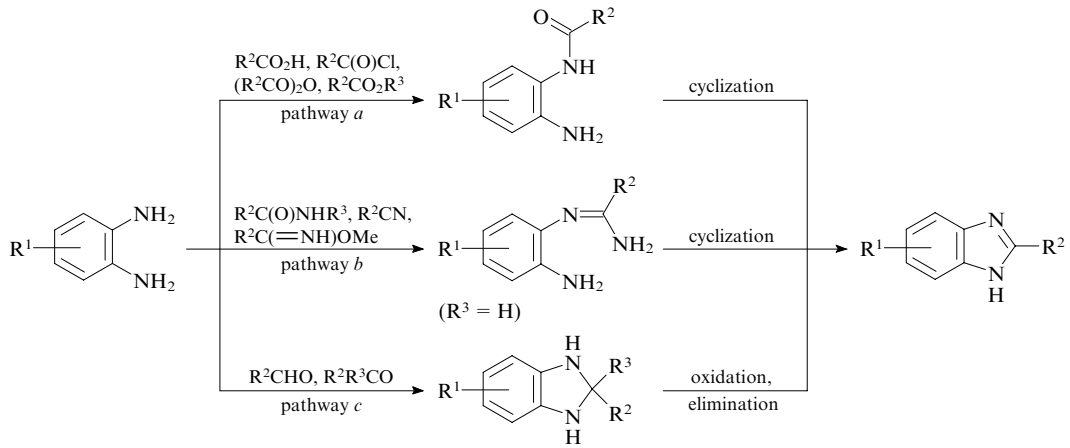


R^1 = H, 3-Me, 5-OMe, 5-NO_2; R^2 = Me, Et, Pr^i, Bn, Ph; R^3 = Me, Ph.

The analysis of published data has shown that the main drawback of the listed methods was their limited use in the synthesis of benzimidazole derivatives. For instance, for synthetic chemists it is a challenge to introduce a heterocycle into position 2 of benzimidazole.

In addition to the mentioned methods, examples of the formation of benzimidazole derivatives by recyclization of heterocyclic systems are documented. Although 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 published data on the recyclization reactions will considerably facilitate the quest of organic chemists for the methods of synthesis of benz-

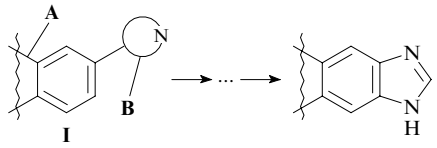
Scheme 1



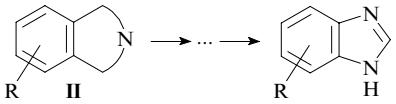
R^1 = H, 4-Me, 4-Cl, 4-NO_2, *etc.*; R^2 = Alk, Ar; R^3 = H, Alk, Ar.

imidazole derivatives inaccessible by the Phillips–Ladenburg and Weidenhagen reactions.

Recyclization reactions to produce benzimidazole derivatives may be divided into two groups. The first group includes the reactions of compounds with the general formula **I**, in which the carbocyclic system **A** and the N-heterocyclic fragment **B** are non-fused.



The second group includes the reactions of compounds with the general formula **II**, *i.e.*, fused bi-, tri- and tetracyclic systems containing at least one N-heterocycle.

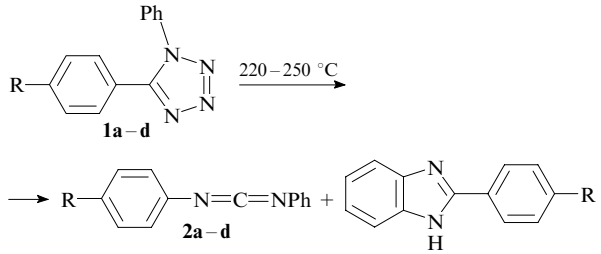


II. Recyclization of heterocyclic compounds with substituents containing a benzene ring

These processes mainly include the compounds capable of elimination of neutral molecules such as N_2 and CO_2 or those capable of undergoing photochemical isomerization to form benzimidazole derivatives.

1. Recyclization under conditions of thermolysis

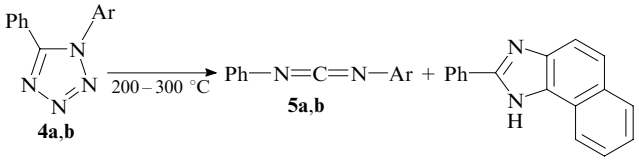
Pyrolysis of 1,5-diaryltetrazoles **1** affords carbodiimides **2** and, in addition, 2-aryl-substituted benzimidazoles **3**, albeit in low yields. This was explained by the competition of two reactions. One reaction involves the migration of aryl groups from the carbon atom to the nitrogen atom and the other includes cyclization without migration. Studying the effect of substituents has shown that the highest yield (19%) of 2-arylbenzimidazole **3b** was achieved with *para*-chloro derivative **1b**. The Cl atom in the *para*-position of the benzene ring retarded the C → N migration of the phenyl group in the Beckmann rearrangement as well as the formation of carbodiimide relative to cyclization.[60]



3a–d [12% (**a**), 19% (**b**), 8% (**c**), traces (**d**)]

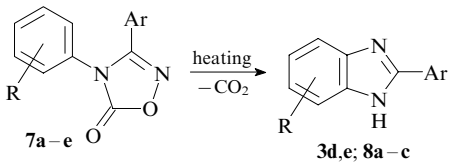
R = H (**a**), Cl (**b**), Me (**c**), NO_2 (**d**).

The thermal decomposition of diaryltetrazoles containing phenyl, naphthyl (**4a**,**b**) and 1-phenanthryl groups produced diarylcarbodiimides **5** and 2-arylbenzobenzimidazoles **6**, for example,[61]



Ar = 1-Naph (**a**), 2-Naph (**b**).

Pyrolysis of 1,2,4-oxadiazol-5-ones **7a–e** proved to be more efficient for the synthesis of benzimidazole derivatives as compared with pyrolysis of tetrazoles. The rearrangement of compounds **7** afforded benzimidazole derivatives **3d**,**e**, **8a–c** in high yields.[62,63]

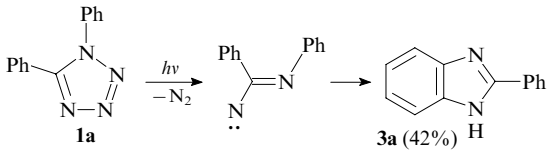


Compound **7**	R	Ar	*T*/°C	Product	Yield (%)
a	2-Me	Ph	220	**8a**	91
b	2-NO_2	Ph	255	**8b**	78
c	4-NO_2	Ph	230	**8c**	75
d	H	$C_6H_4NO_2$-4	220	**3d**	74
e	H	C_6H_4OMe-4	190	**3e**	14

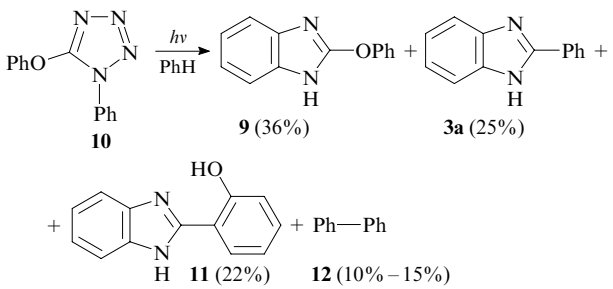
Further modification of this method was based on the transformations of oxadiazolones or the corresponding thiones in dioxane under the action of either radical generating agents (for example, peroxides) or under photolytic conditions. This was successfully employed in the synthesis of various 2-(thiazol-4-yl)benzimidazole derivatives.[64]

2. Recyclization under photolytic conditions

The formation of benzimidazole as a result of tetrazole photolysis was described for the first time in 1967.[65] 2-Phenylbenzimidazole (**3a**) was obtained as the only photolysis product of 1,5-diphenyltetrazole (**1a**).

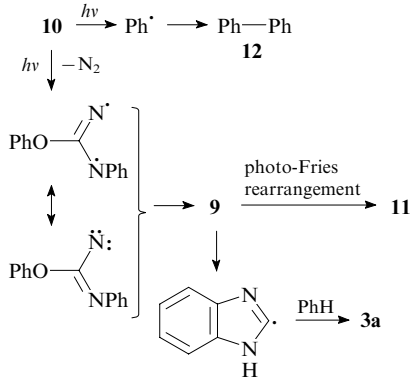


Similarly, 2-phenoxybenzimidazole (**9**) was synthesized in the photolysis of 1-phenyl-5-phenoxytetrazole (**10**) in acetonitrile. In benzene, this reaction afforded additionally three products (**3a**, **11**, **12**) along with compound **9**.[66,67]

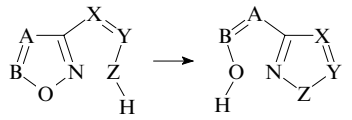


The formation of compounds **3a** and **11** was explained by the extrusion of nitrogen followed by the photochemical decomposition of 2-phenoxybenzimidazole (**9**), which results in a mixture of other benzimidazoles (**3a**, **11**). This is the first example of the photo-Fries rearrangement accompanied by the heterocyclic fragment migration (Scheme 2). Aryl–oxygen bond cleavage is a rationale for the formation of biphenyl (**12**).

Scheme 2



Studies of the photochemical (λ = 254 nm) behaviour of 5-phenyl-1,2,4-oxadiazoles revealed the dependence on the nature and position of substituents in the heterocycle and also on the solvent used.[68, 69] Thus compounds **13a**,**b** underwent photorearrangement to afford benzimidazoles **14a**,**b**; at the same time, in the irradiation of oxadiazole **13c**, no indole formation as a result of rearrangement involving the side chain was observed (Scheme 3). This difference lies in specific features of the electronic structure of the these oxadiazoles.



In compounds **13a**,**b**, the triad XYZ is NCC, two carbon atoms of the substituent constituting part of the benzene ring.

These molecules include a 6π-electron system that comprises a heterocycle and a side chain, which is favourable for the Boulton–Katritzky rearrangement,[70] whereas molecule **13c** is devoid of such a π-electron system.

Several parallel reactions occurred during irradiation of 1,2,4-oxadiazoles. If a group capable of tautomerization (NHR, OH; for example, compound **13a**) was present in position 3, then the photoisomerization took place to afford 1,3,4-oxadiazole **15** as the result of standard ring contraction–expansion processes. On the other hand, if photoisomerization was impossible and the solvent exhibited nucleophilic properties (like MeOH), then the reaction of the latter with intermediates that appeared upon photolysis of the O–N bond in the heterocycle resulted in open-chain products **16**, **17**. The oxadiazole **13c** hydrolysis products also contained yet another open-chain compound and a quinazolone derivative.

When anhydrous MeCN served as the solvent in place of MeOH, benzimidazole **14b** was the main photolysis product of oxadiazole **13b**.

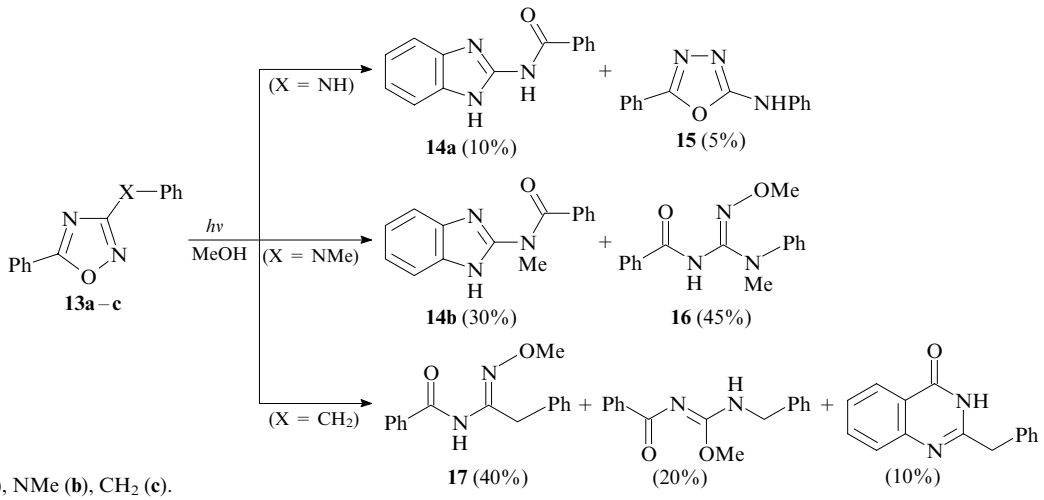
As is seen from the above data, the listed syntheses of benzimidazole derivatives cannot be used as preparative methods because almost all reactions are low-yielding. On the other hand, all benzimidazole derivatives obtained in this way can easily and in good yields be synthesized by the Phillips–Ladenburg and Weidenhagen reactions; this is why the classical versions of synthesis are the methods of choice.

3. Ring expansion of 1-aryldiaziridinimines affording benzimidazoles, indazoles and dibenzodiazepines

Under the action of bases, *N′*-Aryl-*N*-hydroxyguanidine *O*-sulfonic acids **18a–f** were transformed into (*N*-arylimino)diaziridines in good yields. The products represented a mixture of isomers **19a–f** and **20a–f**,† which could easily be separated by crystallization and column chromatography (Scheme 4).[71] Base-induced 1,3-elimination of sulfuric acid from guanidine derivatives **18** affords predominantly (*N*-arylimino)diaziridines **19**. Good yields of compounds **19** were obtained from *N*-hydroxyguanidines provided that the two *ortho*-positions of the aryl group are substituted as in compounds **18d–f**. The yellow colour of non-purified iminodiaziridines **19e**,**f** suggested the presence of side prod-

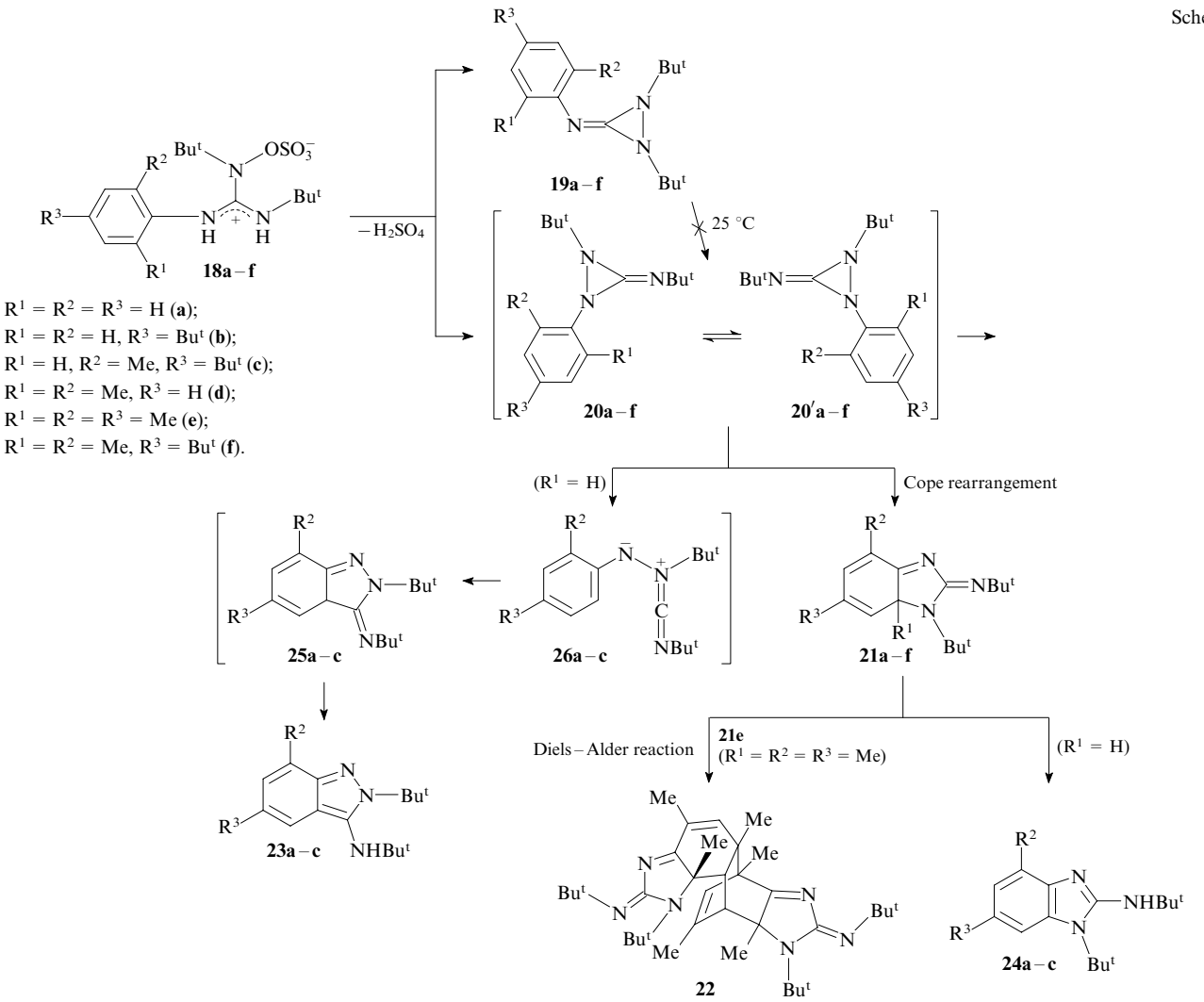
† Compounds **20** undergo very rapid degenerate valence isomerization (**20** ⇄ **20′**).[71]

Scheme 3



X = NH (**a**), NMe (**b**), CH_2 (**c**).

Scheme 4



ucts that turned out to be 2-imino-2,3-dihydro-3a*H*-benzimidazoles **21e**,**f**. At room temperature, compound **21e** slowly dimerized to **22** by the mechanism of the Diels–Alder cycloaddition, whereas, as expected, compound **21f** containing a bulky *tert*-butyl substituent in position 5 did not undergo dimerization. In those cases where the *ortho*-positions were free, for instance, in compounds **18a**,**b**, the predominant products were 3-amino-2*H*-indazoles **23a**,**b**, respectively. For guanidine derivative **18c**, the main product was 2-aminobenzimidazole **24c**.

Scheme 4 shows the possible methods for synthesizing the derivatives of benzimidazoles **21**, **24** and indazoles **23**. (*N′*-Arylimino)diaziridines **19** may be excluded from consideration as the intermediates, because compounds **19a**,**e** were stable and were recovered from the reaction mixtures.

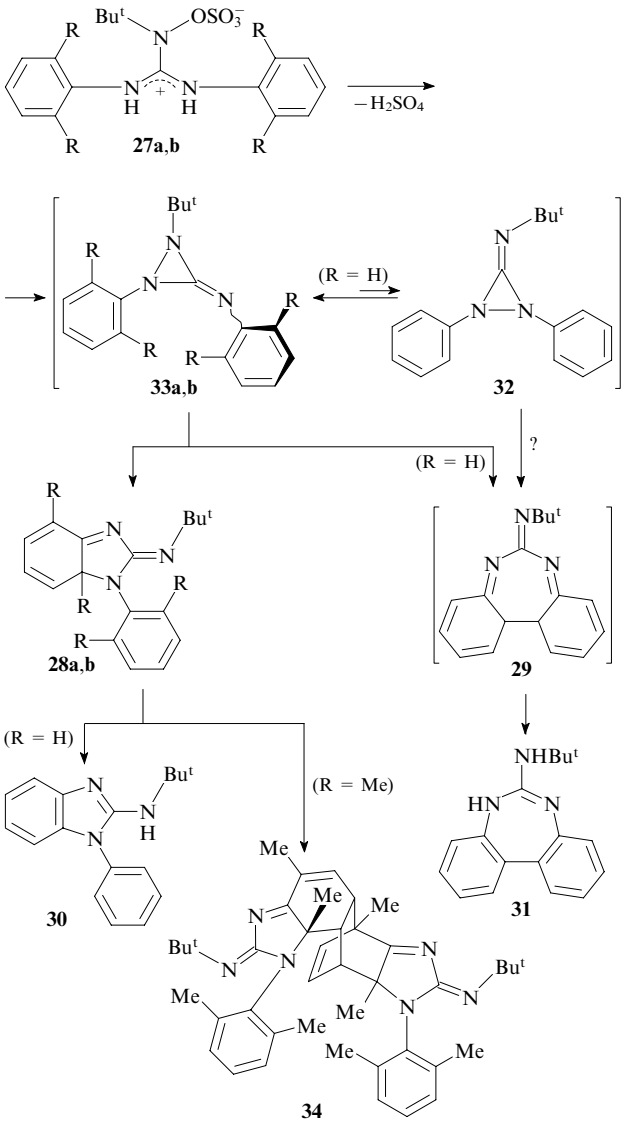
The ring expansion in compounds **20** to afford 3-amino-2*H*-indazoles **23** was observed only in those cases where at least one *ortho*-position in the benzene ring remained unsubstituted. In this case, the initial step can be considered as a formal [1,3] shift (**20** → **25**). The two *ortho*-substituents preclude this process. However, *ortho*-substituents had an insignificant effect, if at all, on the Cope rearrangement of compounds **20** to form 2,3-dihydro-3a*H*-benzimidazoles **21**. Probably, azomethinimines **26** are intermediates in this step due to the presence of the co-planar benzene ring and azomethinimine fragment.[72] Apparently, the co-planarity is violated in compounds with two *ortho*-substituents, which is the reason for competition between the formation reactions of benzimidazoles and indazoles. *ortho*-Substituents impede the Cope rearrangement in aziridines **20** to a lesser

Table 1. The yield and the ratio of products for the reaction of *N*-hydroxyguanine *O*-sulfonic acids **18** and **27** with strong bases.[71]

Starting compound	Reaction conditions [a]	Total yield (%)	Products	Ratio of products
18a	A	80–89	**19a**, **23a**, **24a**	from 15 : 83 : 2 to 11 : 87 : 2
18b	A [b]	91	**19b**, **23b**, **24b**	4 : 71 : 25
18c	A [b]	86	**19c**, **23c**, **24c**	6 : 9 : 85
18d	A	72	**19d**	
	B	80	**19d**	
	C	64	**19d**	
18e	A	67	**19e**, **21e**	98 : 2
	D	67	**19e**, **21e**	72 : 28
18f	A [b]	75–78	**19f**, **21f**	from 98 : 2 to 86 : 14
27a	A	91	**30**, **31**	85 : 15
	E	98	**30**, **31**	25 : 75
27b	A	54	**28b**, **34**	96 : 4

[a] A, KOH (40%) in MeOH; B, KOH (50%) in H_2O; C, NaH in THF; D, Bu^tOK in Et_2O, −78–25 °C; E, aqueous NaOH (2 M); [b] at 0 °C.

Scheme 5



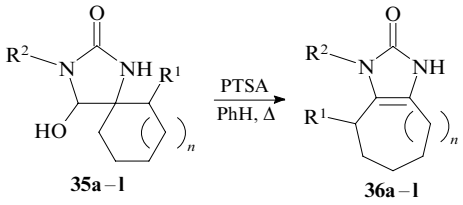
R = H (**a**), Me (**b**).

extent than the ring opening; this is why the yield of benzimidazole **24c** approached 85%, whereas the yield of indazole **23c** fell to 9% (Table 1).

The addition of a strong base to *N*,*N*-diphenyl-*N*-hydroxyguanidine *O*-sulfonic acid (**27a**) brings about transient deep yellow colouration, which suggests the formation of intermediates **28** and **29** and, further, 2-aminobenzimidazole **30** and 6-amino-5*H*-dibenzo[*d*,*f*]-1,3-diazepine **31**, respectively. In the case of dilute aqueous NaOH, diazepine **31** prevailed in the mixture, whereas concentrated methanolic NaOH favours the preferential formation of 2-aminobenzimidazole **30** (Scheme 5). The absence of isomeric 2-anilino-1-*tert*-butylbenzimidazole ruled out the attack of the electrophilic nitrogen atom from compound **27a** on the benzene ring. The unexpected formation of diazepine **31** can be due to *i*) the base-catalyzed C—C-coupling to afford dibenzodiazepine **29** from diphenyl(hydroxy)guanidine *O*-sulfonic acid **27a**, thus bypassing the formation of diaziridine **32**; *ii*) [1,3] shift in diaziridine **33a** to afford diaziridine **32** followed by the divinylcyclopropane–cyclopentadiene rearrangement of the latter to diazepine **29** and *iii*) [3,5] sigmatropic shift in diaziridine **33** to form diazepine **29**. A small fraction of compound **33b** underwent dimerization to adduct **34** (see Table 1).[71]

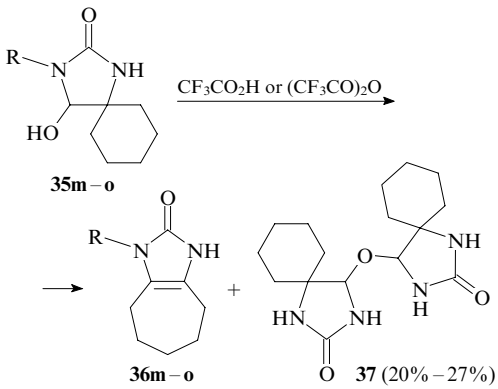
4. Acid-catalyzed recyclization of 4-hydroxyimidazolidinones

Recyclization of spirocyclic 4-hydroxyimidazolidin-2-one derivatives **35a-l** to 2(3*H*)-imidazolinone derivatives **36a-l** *d*-fused with 6-, 7- or 8-membered carbocycles occurred on refluxing in benzene for 48 h in the presence of *p*-toluenesulfonic acid (PTSA).[73,74]



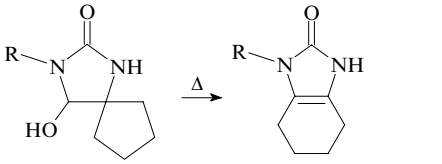
Product **36**	R^1	R^2	*n*	Yield (%)	Product **36**	R^1	R^2	*n*	Yield (%)
a	H	Me	0	66	**g**	H	$CH_2C_6H_4Cl$-4	1	58
b	H	Bu^n	0	62	**h**	H	$(CH_2)_3Ph$	1	93
c	H	Bn	0	45	**i**	Me	Bu^n	1	54
d	H	Me	1	39	**j**	Me	$(CH_2)_3Ph$	1	53
e	H	Bu^n	1	38	**k**	H	Bu^n	2	61
f	H	Bn	1	58	**l**	H	$(CH_2)_3Ph$	2	60

Analogous derivatives **35m–o** when refluxed in CH_2Cl_2 for 48 h with equimolar amounts of trifluoroacetic acid/trifluoroacetic anhydride afforded mixtures of diastereomers of ether **37** (yield 20%–27%) and rearrangement products (**36m–o**) (50%–55%). At the same time, treatment of compounds **35m(n)** with trifluoroacetic acid at room temperature for 24 h (refluxing for 72 h) resulted only in imidazolinones **36m(n)** in the yields of 81% and 73%, respectively. As can be seen, the difference in the reaction conditions (in dichloromethane in the presence of trifluoroacetic acid/trifluoroacetic anhydride, or in trifluoroacetic acid) affected the rate of competitive reactions.



Product **36**	R	Reaction conditions	Yield (%)
m	CH_2NBn_2	CH_2Cl_2, Δ, 48 h	52
	CH_2NBn_2	20 °C, 24 h	81
n	piperidinomethyl	CH_2Cl_2, Δ, 48 h	50
	piperidinomethyl	Δ, 72 h	73
o	morpholinomethyl	CH_2Cl_2, Δ, 48 h	55

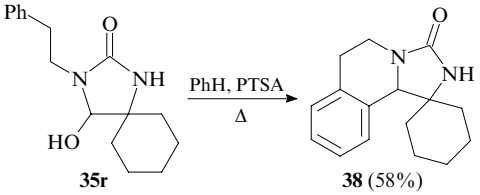
Several 1-substituted 5-hydroxy-2-oxoimidazoline-4-spirocyclopentanes were also studied aimed at determining the size effect of the carbocycle spiro-fused to the position 5 of imidazolinone. Thus under the above conditions, compounds **35p**,**q** afforded only the rearrangement products of imidazolinones **36p**,**q** rather than product **37**. This suggests that the carbocycle in the position 5 exerts the steric effect on the attack by trifluoroacetic acid.



35p,**q** **36p**,**q** (64% – 71%)

R = CH_2NBn_2 (**p**), CH_2NMeBn (**q**).

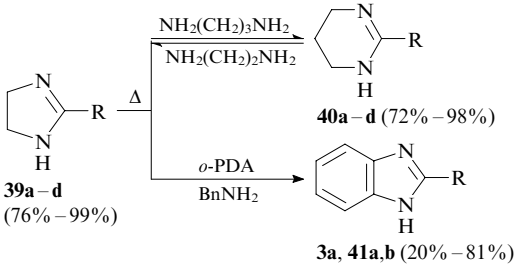
Spiro-fused imidazolidinone **35r** gave was annulated imidazolinone **38** as the sole reaction product.



35r **38** (58%)

5. Transamination reactions of 2-substituted 4,5-dihydroimidazoles

Transamination can be considered as an analogue of recyclization. Heating of 2-substituted 4,5-dihydroimidazoles **39a** – **d** with an excess of propane-1,3-diamine results in transamination and the imidazole ring expansion to the pyrimidine ring (**40a** – **d**). The reaction of the resulting pyrimidines (**40**) with ethylene-1,2-diamine affords the corresponding 4,5-dihydroimidazole derivatives (**39**) in high yields. When aromatic 1,2-diamine, *e.g.*, *o*-PDA, was used in the reaction with 4,5-dihydroimidazoles **39**, benzimidazole derivatives **3a**, **41a**,**b** formed. In the synthesis of substituted benzimidazoles, benzylamine was used as the solvent. Thus heating of dihydroimidazole **39a** with 2 equiv. of *o*-PDA in benzylamine afforded 2-methylbenzimidazole (**41a**) in the yield of 75%. Such transamination reaction can be employed for 1,2- and 1,3-diamines. No reaction was observed for 1,4- and 1,6-diamines.[75] The expected reaction product of imidazoline **39a** with 1,4-diaminobutane, namely, 2-methyl-4,5,6,7-tetrahydro-1,3-diazepine, was synthesized earlier using acetamidine hydrochloride in place of compound **39a**.[76]



39a – **d** (76% – 99%) **40a** – **d** (72% – 98%) **3a**, **41a**,**b** (20% – 81%)

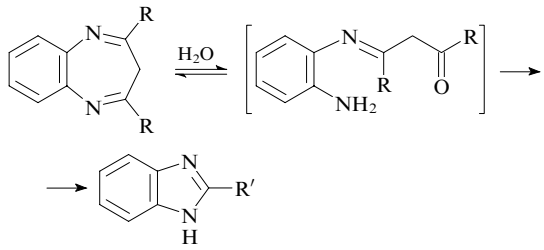
for **39**, **40**: R = Me (**a**), Ph (**b**), n-$C_{17}H_{35}$ (**c**), H (salt with HOAc) (**d**); for **41**: R = Me (**a**), n-$C_{17}H_{35}$ (**b**).

III. Recyclization of fused heterocyclic systems

1. Benzo derivatives of seven-membered heterocycles: 1,5-benzo[*b*]diazepines in the synthesis of benzimidazoles

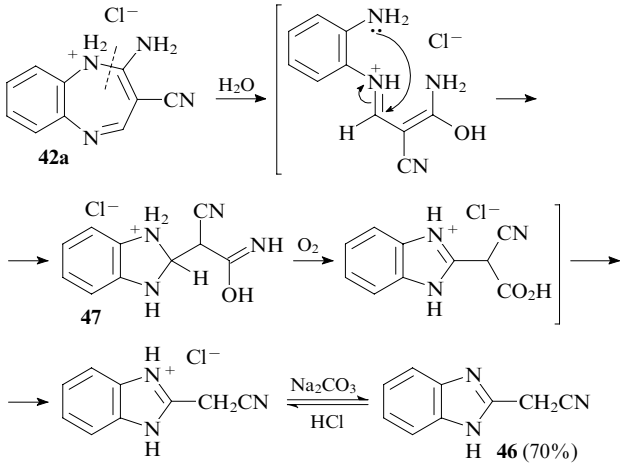
a. The behaviour of diazepines under hydrolytic conditions

1,5-Benzo[*b*]diazepines pertain to heterocyclic systems capable of undergoing recyclization under various conditions to form benzimidazole derivatives. The main reason for this is the proneness of the imine fragment in 1,5-benzo[*b*]diazepines to undergo acid or alkaline hydrolysis to give a system with a free amino group and a fragment containing different electrophilic centres including those leading to the benzimidazole system.[77 – 82] In the general form, this process can be presented as follows:



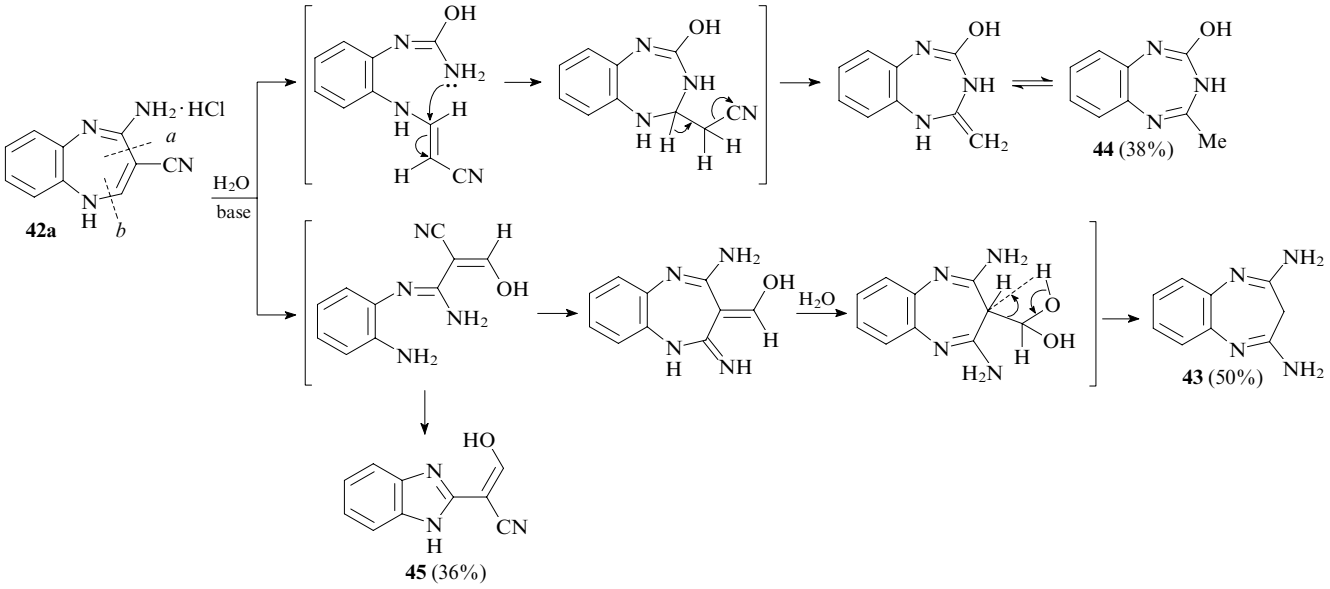
Heating of compound **42a** in 3% aqueous NaOH for 15 min at 100 °C produced 2,4-diamino-3*H*-1,5-benzodiazepine (**43**).[83, 84] Heating of the same compound in 0.3% aqueous NaOH (pH 8.5) afforded another product, 2-hydroxy-4-methyl-3*H*-1,3,5-benzotriazepine (**44**). On heating in water or in aqueous ammonia or 2-aminopiperidine, diazepine **42a** was transformed into 2-substituted benzimidazole **45**. The putative mechanisms for the formation of these compounds were proposed that involved the C – C (*a*) and C – N (*b*) bond cleavage in the diazepine ring of compound **42a** (Scheme 6) depending probably on the basicity of the medium.[84]

Heating of diazepine **42a** in aqueous 0.1 M HCl at 100 °C produced 2-cyanomethylbenzimidazole (**46**) in a good yield. Probably, the C(4) – N(5) bond in diazepine **42a** was cleaved, which was followed by the benzimidazole ring closure, oxidation of intermediate product **47** with atmospheric oxygen and decarboxylation.[85]



42a **47** **46** (70%)

Scheme 6



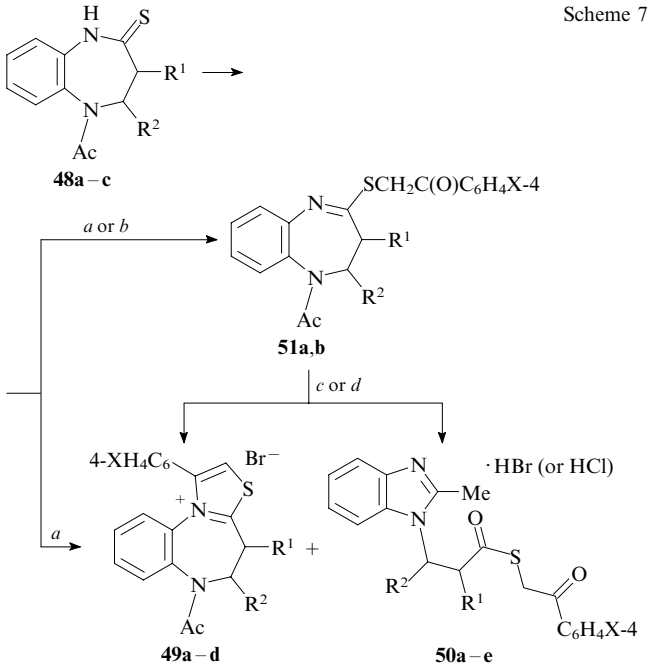
It deserves mention that heating of benzimidazole **45** (prepared by hydrolysis of compound **42a** in a weakly alkaline solution) in hydrochloric acid (pH 1) afforded no benzimidazole **46**.

A method was developed for synthesizing new tricylic thiazolobenzodiazepine derivatives and benzimidazoles based on substituted 1,5-benzo[*b*]diazepine-2-thiones.[86] The thiazole ring was formed as the result of condensation–cyclization of the corresponding thiolactams **48a–c** with an excess (1.5 equiv.) of 2,4′-dibromoacetophenone or 2-bromoacetophenone in boiling anhydrous butan-2-one. Scheme 7 shows the reaction sequence in the synthesis of tricyclic derivatives.

The formation of a mixture of tricyclic compounds **49a–d** in the yields of 31%–48% and benzimidazole derivatives **50a–e** in the yields of 34%–50% suggests that as regards energy, these two cyclization routes are equally probable.

Heating of benzodiazepine derivative **51a** with an excess of concentrated hydrochloric acid in butan-2-one also afforded N-substituted benzimidazole **50e**, which was not accompanied by the formation of tricyclic derivatives. Heating of compound **51b** with an equivalent amount of 40% aqueous HBr also afforded both tricyclic derivative **49b** and benzimidazole **50b** in approximately equal yields. Under these conditions, benzodiazepine derivative **51a** did not react. Generally, derivatives of 3*H*- and 2,3-dihydro-1*H*-1,5-benzodiazepine with the structure similar to that of compounds **48a–c** underwent either decomposition or isomerization to benzimidazoles on heating in an acidic medium.[87] The analogous transformations to 2-methylbenzimidazole derivatives were also observed for several N(5)-acetyl-substituted 1,5-benzodiazepin-2-ones, when the acylation or bromination reactions were carried out in the presence of concentrated sulfuric acid.[88,89] The formation of five-membered rings was favoured by the basic or acidic hydrolysis, which provided activation of the amide bond or the N=C bond in the original 1,5-benzodiazepine and subsequent cyclization with loss of water. The presence of an acetyl substituent at the N(5) atom favoured the formation of benzimidazole derivatives. However, no formation of benzimidazole derivatives was observed in the

Scheme 7



Starting compound	R^1	R^2	Reagent (X)	Reaction conditions	Product	Yield (%)
48a	H	Me	Br	*a*	**51a**·HBr	92
	H	Me	Br	*b*	**51a**	67
48b	Me	H	H	*b*	**51b**	65
	Me	H	Br	*a*	**49a** + **50a**	42 + 34
	Me	H	H	*a*	**49b** + **50b**	48 + 46
48c	H	H	Br	*a*	**49c** + **50c**	31 + 38
	H	H	H	*a*	**49d** + **50d**	29 + 47
51a	H	Me	Br	*c*	**50e**	50
51b	Me	H	H	*d*	**49b** + **50b**	43 + 40

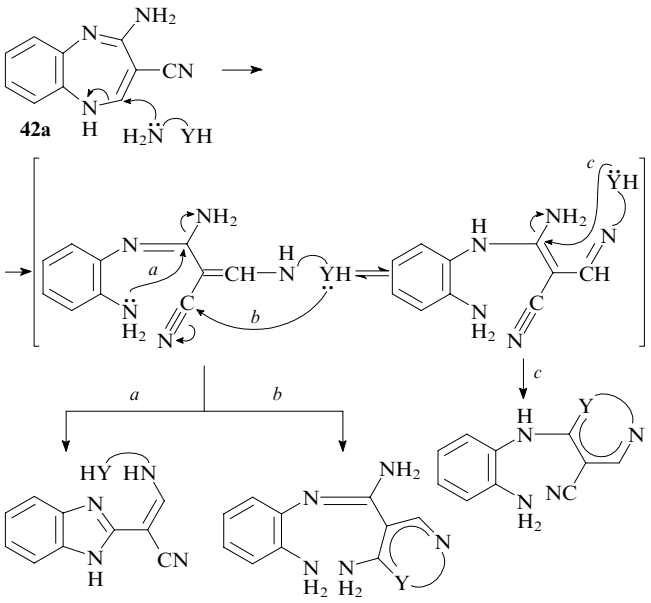
Note. X = Br, $BrCH_2C(O)C_6H_4Br$-4 reagent; X = H, $BrCH_2C(O)Ph$ reagent; (*a*) refluxing in EtC(O)Me; (*b*) K_2CO_3, EtC(O)Me, 20–25 °C; (*c*) excess of concentrated HCl, EtC(O)Me, refluxing; (*d*) 1 equiv. HBr (40%), EtC(O)Me, refluxing.

synthesis of the thiazolobenzodiazepine system from 1,5-benzodiazepine-2-thiones and aliphatic α-halo ketones.

b. Reactions of benzodiazepines with N-nucleophiles

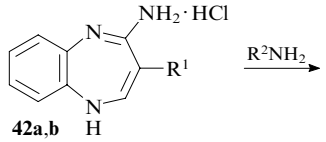
Due to the presence of three electron-deficient carbon atoms, namely, C(2), C(4) and CN, carbonitrile **42a** acts as an efficient Michael acceptor with respect to nitrogen-containing nucleophiles ($H_2N\overset{\frown}{}YH$) such as amines, hydroxylamines, hydrazines and amidines. The intermediate formed upon the diazepine ring opening under the action of a nucleophile was capable of recyclization by one of the three pathways (*a*, *b*, *c*) shown in Scheme 8.[77]

Scheme 8

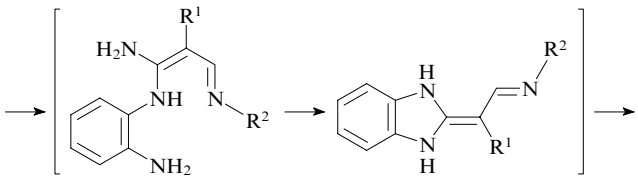


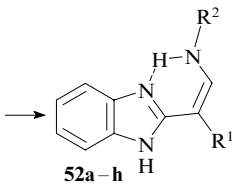
c. Reactions of benzodiazepines with amines

Refluxing of a suspension of benzodiazepine hydrochloride **42a** or **42b** in methanol with aromatic amines such as aniline, *p*-anizidine, *m*-toluidine and *m*-chloroaniline afforded substituted benzimidazoles **52a**–**h**.[90] Such a transformation proceeds probably *via* open-chain addition products in which the *ortho*-amino group attacks the amidine carbon atom.



R^1 = CN (**a**), CO_2Et (**b**).

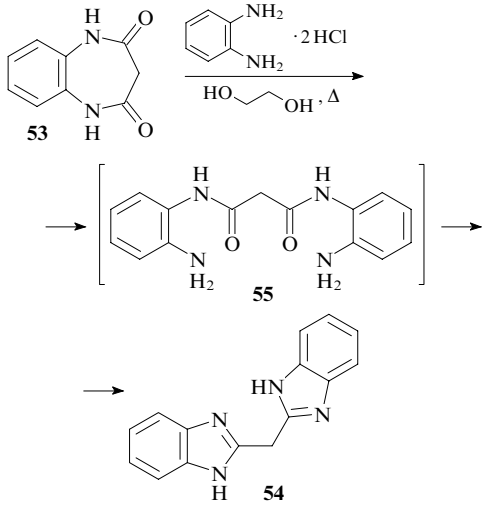




Product **52**	R^1	R^2	Yield (%)
a	CN	Ph	55
b	CN	C_6H_4Me-4	53
c	CN	C_6H_4Me-3	55
d	CN	C_6H_4Cl-3	48
e	CO_2Et	Ph	48
f	CO_2Et	C_6H_4Me-4	62
g	CO_2Et	C_6H_4Me-3	65
h	CO_2Et	C_6H_4Cl-3	24

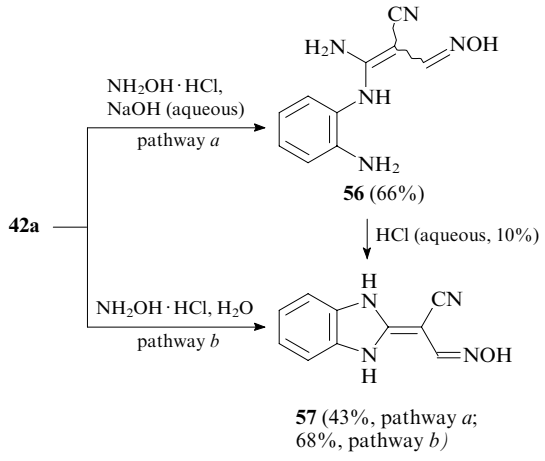
However, the reaction of simple aliphatic amines ($MeNH_2$, $EtNH_2$) with compounds such as **42a**,**b** produced no benzimidazole derivatives, altough the reaction of diazepine **42a** with methoxyamine hydrochloride in hot water afforded the corresponding benzimidazole **52i** (R^1 = CN, R^2 = MeO) as the main product (yield 36%) and 2-(1-cyano-2-hydroxyvinyl)benzimidazole as the side product (4%).[85]

Refluxing of *o*-phenylenemalonamide (**53**) with *o*-PDA hydrochloride in ethylene glycol afforded 2,2′-methylenedibenzimidazole (**54**) *via* intermediate malonamide **55**.[91]

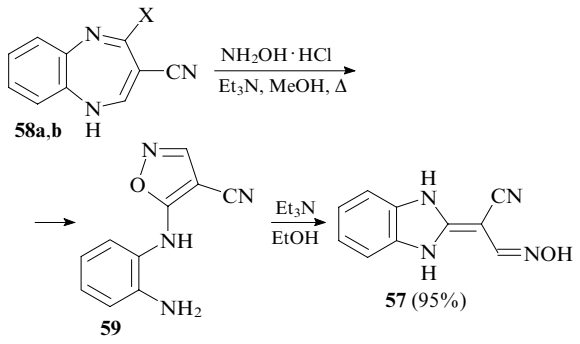


d. Reactions of benzodiazepines with hydroxylamines

The reaction of benzodiazepine **42a** with hydroxylamine hydrochloride in hot aqueous NaOH (pH 8.5) afforded open-chain adduct **56**. This reaction carried out in ethanol containing triethylamine as the base produced oxime **56** in the higher yield. Compound **56** was easily transformed into 2,3-dihydro-1*H*-benzimidazole derivative **57** upon treatment with 10% hydrochloric acid at room temperature. Heating of benzodiazepine **42a** with hydroxylamine hydrochloride in water afforded solely compound **57**.[77,92]

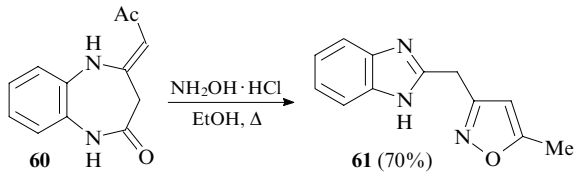


Heating of benzodiazepines **58a**,**b** with hydroxylamine hydrochloride in the presence of triethylamine in methanol afforded anilinoisoxazole **59** in moderate yields (58% and 65%); on boiling in ethanol with an excess of triethylamine, product **59** was converted to 2,3-dihydro-1*H*-benzimidazole derivative **57**. The formation of isoxazole **59** probably proceeded *via* an open-chain intermediate with the structure similar to that of compound **56**.[92]



X = $NHCO_2Et$ (**a**), NHC(O)NHEt (**b**).

The use of benzodiazepin-2-one **60** in place of derivatives **42a** and **58a**,**b** afforded exclusively benzimidazole **61** in a good yield.[93]

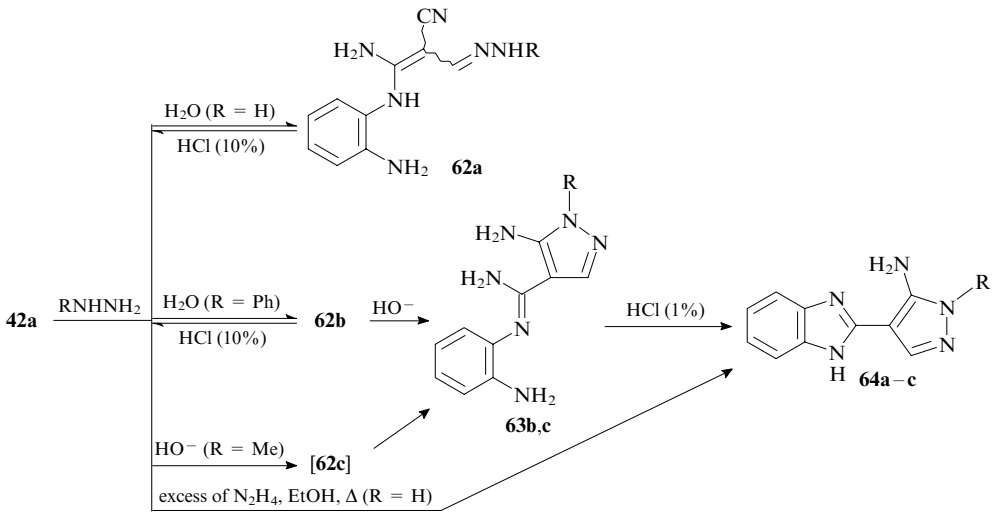


e. Reactions with hydrazines

Reactions of benzodiazepine **42a** with hydrazine and its monosubstituted derivatives were studied in sufficient detail.[94] The products of these reactions differed from those obtained in the reaction of diazepine **42a** with hydroxylamine and the reactions of other 1,5-benzodiazepines with hydrazines.[95,96] Upon the treatment with an excess of hydrazine hydrate or phenylhydrazine in water at room temperature, diazepine **42a** quickly transformed to hydrazone **62a** or **62b**, which could be isolated in the form of yellow powder in a good yield. Compound **62a** transformed to original diazepine **42a** under the action of 10% hydrochloric acid, whereas treatment of compound **62b** with HCl afforded a mixture of diazepine hydrochloride **42a** and pyrazole derivative **63b** together with the starting material (according to ^1H NMR spectra, the percentage of compounds **62b**, **42a** and **63b** was 30%, 26% and 44%, respectively). Treatment of compound **62b** with an alkali resulted in pyrazole **63b** in a good yield. The reaction of benzodiazepine **42a** with methylhydrazine in the presence of alkali to afford methylpyrazole **63c** probably proceeded *via* intermediate **62c**, which could not be isolated. Heating of compounds **63b**,**c** in dilute hydrochloric acid transformed them to benzimidazoles **64b**,**c**, respectively. It was also found that prolonged heating of benzodiazepine **42a** with an excess of hydrazine hydrate in ethanol produced benzimidazole **64a** (Scheme 9).[77,97]

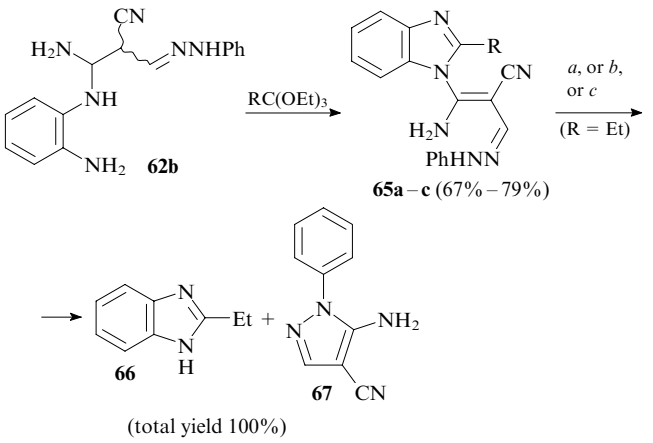
The reaction of phenylhydrazone **62b** with orthoesters afforded benzimidazole derivatives **65a**–**c**. On heating up to 100 °C in protic solvents such as n-butanol or water, the latter derivatives were transformed to 2-substituted benzimidazoles and 5-amino-4-cyano-1-phenylpyrazole. A mechanism of the C–N bond cleavage was proposed in which the important role was played by the OH group of the

Scheme 9



For **62**–**64**: R = H (**a**), Ph (**b**), Me (**c**).

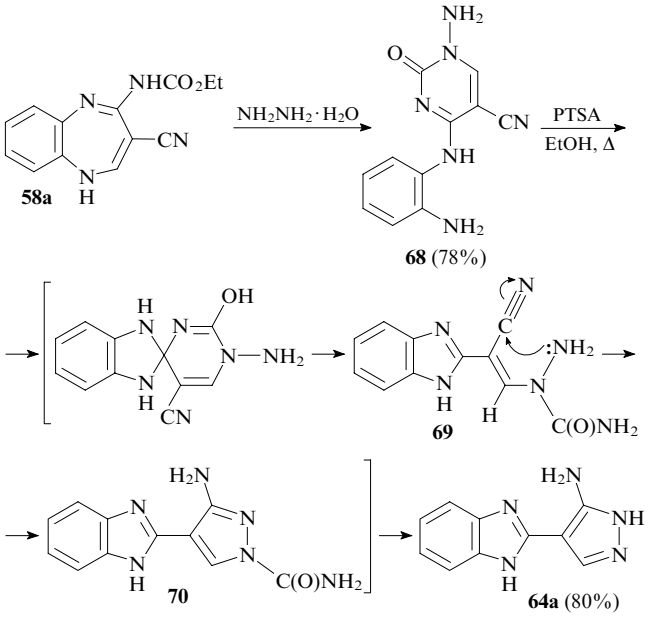
solvent.[98] This transformation was studied in detail for benzimidazole **65c** (**65c** → **66** + **67**).



R = H (**65a**), Me (**65b**), Et (**65c**); (*a*) Bu^{n}OH, Δ, 5 h; (*b*) H_2O, Δ, 7 h; (*c*) DMF, Δ, 2.5 h.

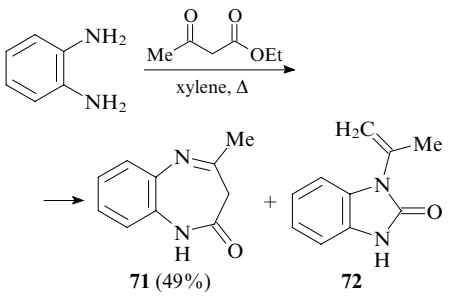
Hydrazine hydrate readily reacted with benzodiazepine **58a** in ethanol at room temperature to form pyrimidine **68**.[97] This afforded benzimidazol **64a** on refluxing in ethanol in the presence of *p*-toluenesulfonic acid (Scheme 10). No formation of pyrimido[1,6-*a*]benzimidazole was observed. This can be explained by the reaction of the cyano group with the hydrazine fragment in intermediate **69** to form pyrazole ring **70**; its hydrolysis afforded pyrazolylbenzimidazole **64a**.

Scheme 10

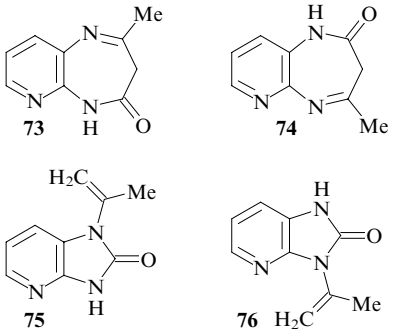


f. Thermal rearrangement of fused dihydrodiazepinones

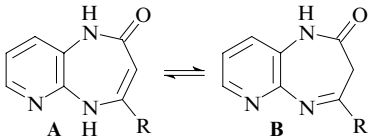
The coupling of ethyl acetoacetate with *o*-PDA in boiling xylene produced benzodiazepinone derivative **71** as the major product and *N*-isopropenylbenzimidazolin-2-one (**72**) as the side product.[99]



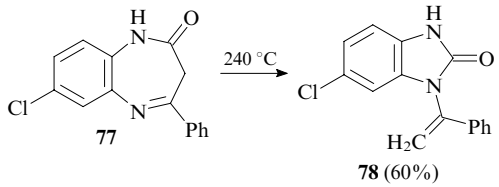
The appearance of a rearrangement side product was also observed in the reaction of ethyl acetoacetate with 2,3-diaminopyridine; however, in this case, due to the asymmetric structure of the heteroaromatic diamine, two theoretically possible diazepine derivatives **73**, **74** and, correspondingly, two possible imidazolinone derivatives **75**, **76** formed.[100]



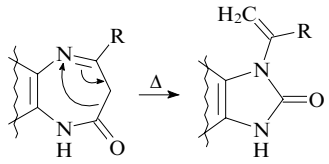
The synthesis of benzimidazoles was also carried out at the melting temperatures of diazepines. The general character of processes for such systems was demonstrated irrespective of the substituent at the endocyclic double bond of the diazepine ring in the alkene (**A**) or azomethine (**B**) form.



For example, on melting of diazepine **77,** the rearrangement occurred to afford 2,3-dihydro-1*H*-benzimidazol-2-one **78**.[101]

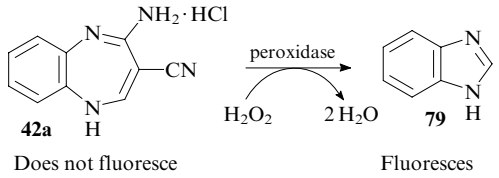


Although the mechanism of this rearrangement is not yet entirely clear, its ease and high yields allowed the concerted mechanism to be assumed irrespective of the nature of substituent R



This reaction route as such is a unique example of the [1,3] sigmatropic shift from the carbon atom to the nitrogen atom.

The oxidative decomposition of benzodiazepine hydrochloride **42a** under the action of hydrogen peroxide afforded benzimidazole (**79**) in low yields. This reaction was used for the fluorimetric determination of hydrogen peroxide due to the strong fluorescence of benzimidazole.[102]

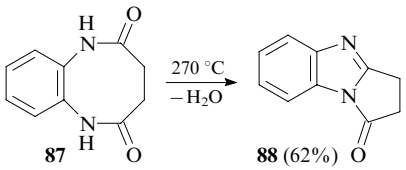


2. Benzo derivatives of eight-membered and larger heterocycles

a. Dibenzo[*b*,*f*]-1,4-diazocines in the synthesis of benzimidazoles

Heating of dibenzo[*b*,*f*]-1,4-diazocine-6,11(5*H*,12*H*)-dione (**80**) to its melting point (300 °C) resulted in the diazocine ring contraction, which was accompanied by dehydration to form isoindolo[2,1-*a*]benzimidazol-11-one (**81**) (Scheme 11).[103] An analogous ring contraction to afford compound **82** occurred when dibenzodiazocine **80** was treated with phosphorus pentachloride. Boiling of compound **80** in 10% aqueous NaOH produced benzimidazole derivative **83a**. Methyl ester of this acid (**83b**) can be obtained from acid chloride **82**. As the result of alkali-catalyzed hydrolysis, 5,12-dimethyldibenzo[*b*,*f*]-1,4-diazocine-6,11-dione (**84**) transformed to a zwitter-ionic derivative of benzimidazole **85**; prolonged heating of the latter at 320 °C afforded benzimidazole **86** (see Scheme 11).

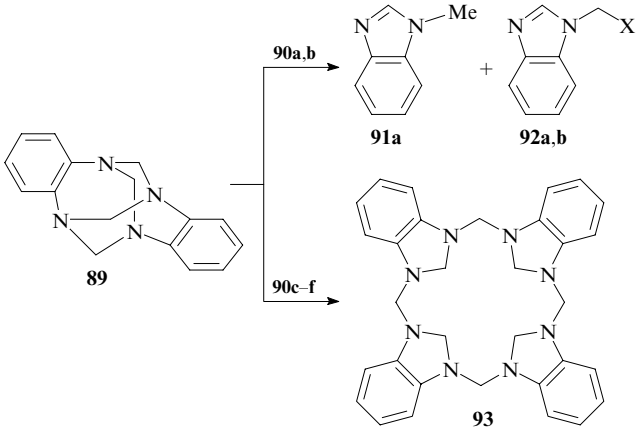
When heated to the melting temperature, benzodiazocine **87**, like dibenzo derivative **80**, underwent ring contraction to form pyrrolobenzimidazolinone **88**.



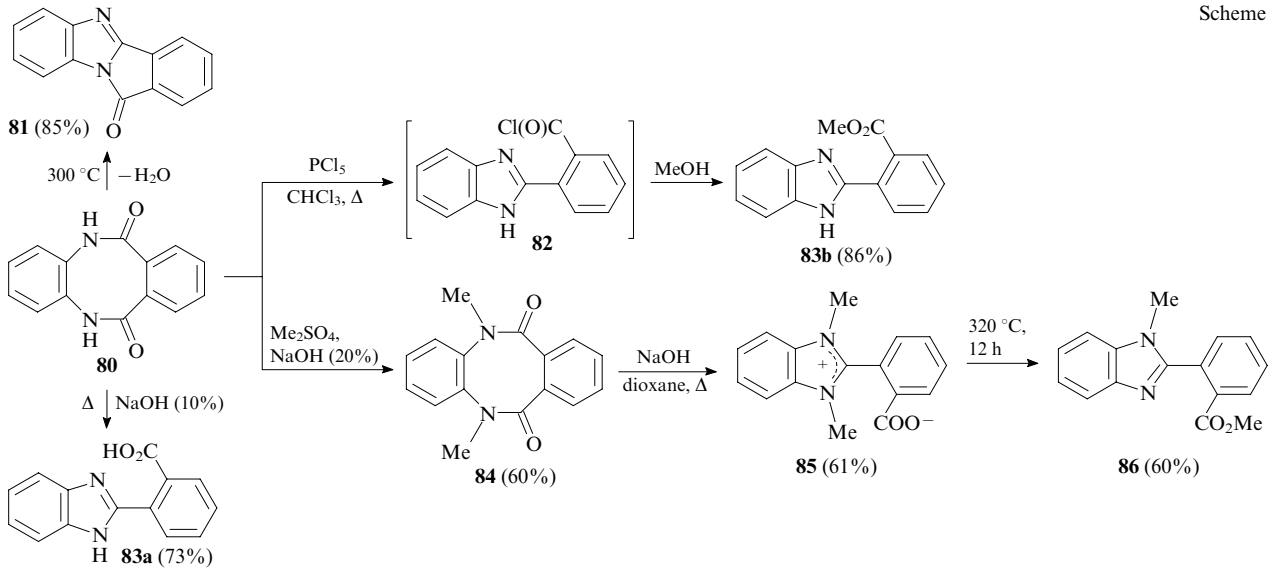
b. Dimethanodibenzo[*d*,*i*]-1,3,6,8-tetraazecine in the synthesis of benzimidazoles

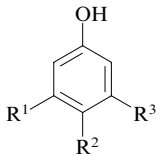
Dimethanodibeno[*d*,*i*]-1,3,6,8-tetraazecine (DMDBTA, **89**) was obtained for the first time by Fischer back by the end of the 19th century by condensation of *o*-PDA with formaldehyde;[104] however, the reactivity and synthetic prospects of this compound still remain unexplored.

In place of the expected symmetrical N,N-disubstituted benzimidazoles,[105] other benzimidazole derivatives formed in the reaction of DMDBTA with phenols. Thus the reactions with electron-rich phenols (for example, **90a**,**b**) afforded 1-methylbenzimidazole (**91a**) and the corresponding *ortho*-aminomethylated products **92a**,**b**, whereas the reactions with electron-deficient phenols (for example, **90c**–**f**) afforded cyclodimerization product **93**.[106]



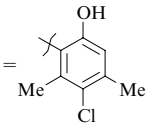
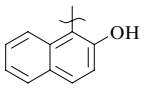
Scheme 11





90a–f

($R^1 = R^3 = Me$, $R^2 = Cl$ (**a**); $R^1–R^2$ is benzo, $R^3 = H$ (**b**); $R^1 = R^3 = H$: $R^2 = H$ (**c**), Me (**d**), Cl (**e**), NO_2 (**f**));

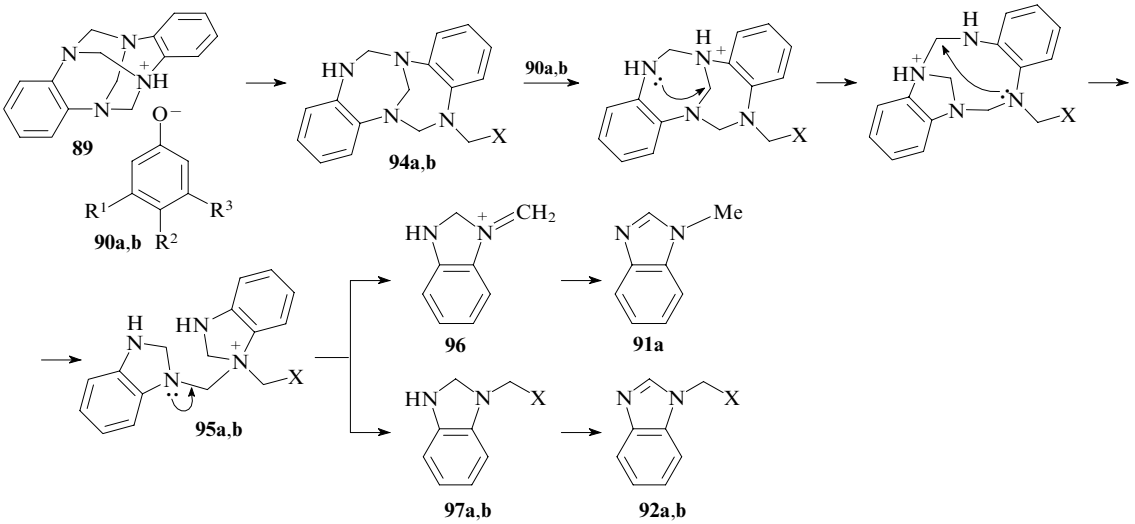
X =  (**92a**, 35%),  (**92b**, 46%).

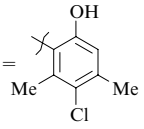
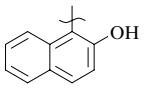
The putative mechanism of formation of products **91a**, **92a**,**b** (Scheme 12) includes the protonation, in the initial step, of at least one of two DMDBTA nitrogen atoms. This activates the methylene group for the electrophilic attack at the *ortho*-position of the aromatic ring of phenols **90a**,**b** to afford adducts **94a**,**b** (in Schemes 12 and 13, the ions formed from compounds **89** and **90** appear under the same numbers). Further protonation of compounds **94a**,**b** brings about recyclization of seven-membered rings to five-membered ones to afford compounds **95a**,**b**. In turn, the latter decomposed to benzimidazole derivatives **96** and **97a**,**b** and transformed further to final products **91a** and **92a**,**b**.[106]

Scheme 13 shows the putative mechanism of formation of tetramer **93**. As in the case of compounds **91a**, **92a**,**b**, the nitrogen atom from DMDBTA is protonated in the initial step to activate the neighbouring methylene groups. After this, the electrophilic methylene group is subjected to the attack by one of the nitrogen atoms from another DMDBTA molecule. The consecutive opening of seven-membered rings and closure of benzimidazole rings led first to compound **98** and then to the final macrocycle (**93**).[106]

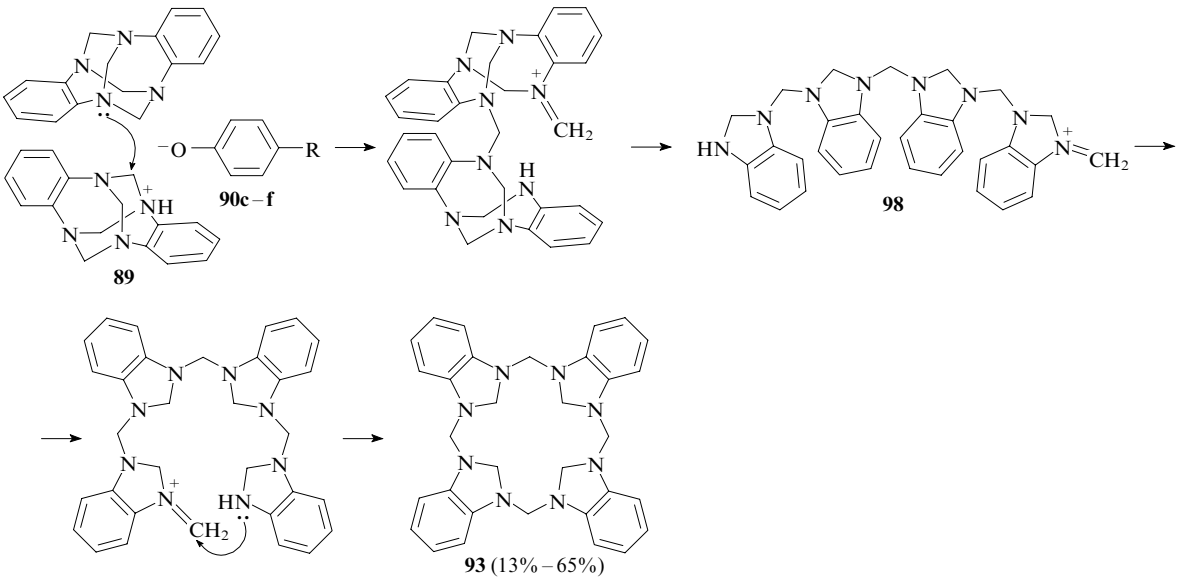
The reaction of DMDBTA (**89**) with benzotriazole in dioxane produced 1,3-bis(benzotriazol-1-ylmethyl)-2,3-dihy-

Scheme 12



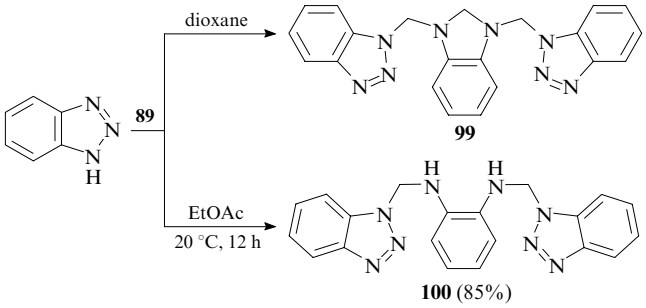
For **92**, **94**, **95**, **97**: X =  (**a**),  (**b**).

Scheme 13



93 (13% – 65%)

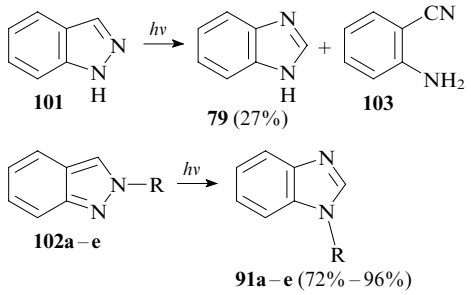
dro-1*H*-benzimidazole (**99**) in moderate yield. The use of ethyl acetate, where compound **89** was more stable than in dioxane, in an attempted increase in the product yield afforded however *N*,*N*′-bis(benzotriazol-1-ylmethyl)-1,2-diaminobenzene (**100**) in place of the expected compound **99** in good yield (85%).[107, 108]



3. Benzo derivatives of five-membered heterocycles

a. Recyclization under photocatalytic conditions

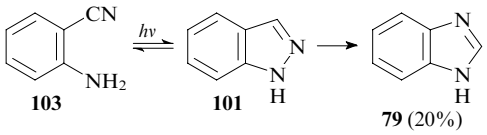
Photolysis of indazoles **101**, **102a**–**e** produced benzimidazole **79** and its 1-alkyl derivatives **91a**–**e**, respectively, in moderate yields. The results of these reactions considerably depended on the position of substituents in the heterocycle. In the absence of substituents, benzimidazole formed together with traces of 2-aminobenzonitrile (**103**).[63, 109, 110]



R = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**), Bn (**e**).

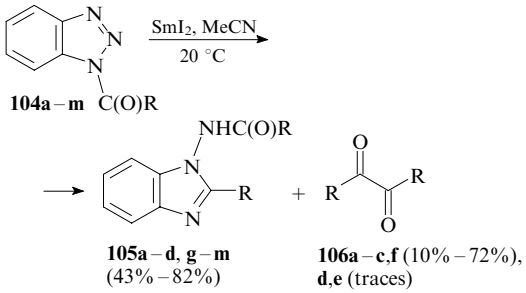
The high yields of compounds **91** deserve mention; however, original indazoles **102** are not easily accessible.

Irradiation of a degassed solution of 2-aminobenzonitrile (**103**) in acetonitrile led to indazole (**101**); upon further irradiation, the latter was transformed to benzimidazole (**79**).[111]



b. Samarium diiodide-induced recyclization of *N*-acylbenzotriazoles

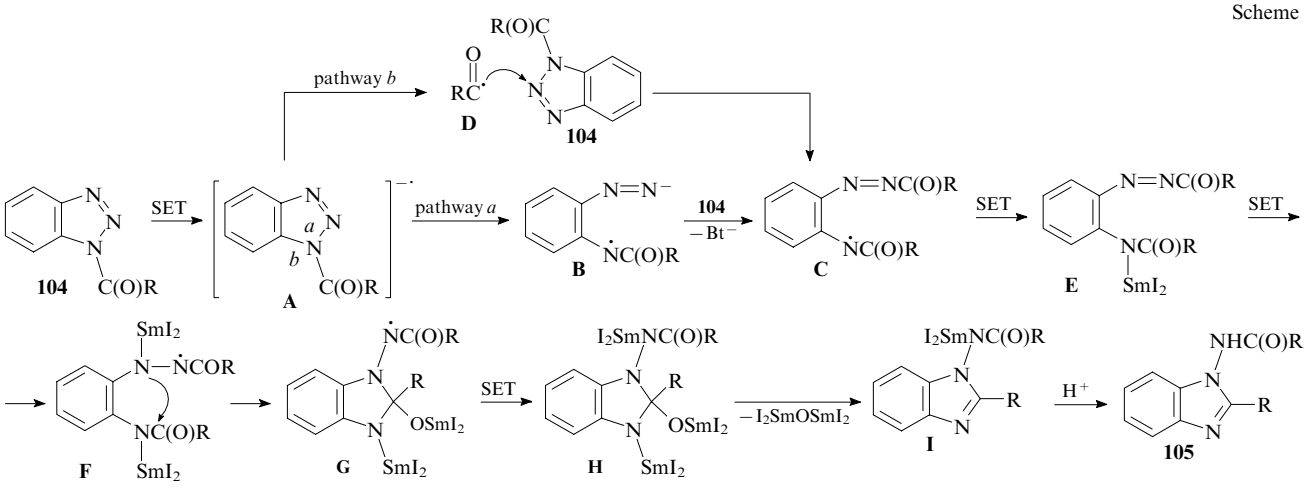
The interaction of *N*-acylbenzotriazoles **104a**–**m** with samarium diiodide in acetonitrile at room temperature led to recyclization of the benzotriazole ring to afford 1-acylamino-2-alkyl(aryl)benzimidazoles **105a**–**m**.[112] Alkanoyl derivatives of benzotriazole **104g**–**m** transformed exclusively to benzimidazoles in the yields of 60%–82%, whereas aroyl derivatives **104a**–**e** afforded, in addition to benzimidazoles, the corresponding α-diketones (**106a**–**c**,**f**) in the yields of 10%–72% (compounds **106d**,**e** formed only in trace amounts and no benzimidazole **105f** was detected at all).



R = Ph (**a**), C_6H_4Cl-3 (**b**), C_6H_4Cl-4 (**c**), C_6H_4Me-4 (**d**), C_6H_4Cl-2 (**e**), C_6H_4OMe-4 (**f**), Bu^n (**g**), n-C_6H_{13} (**h**), n-C_8H_{17} (**i**), n-$C_{16}H_{33}$ (**j**), cyclo-C_6H_{11} (**k**), Et (**l**), Me (**m**).

Scheme 14 shows one of the possible reaction routes.[112–115] The cleavage of the N–N bond in the transient radical anion **A** (pathway *a*) results in the formation of radical anion **B**; the latter is then acylated by

Scheme 14

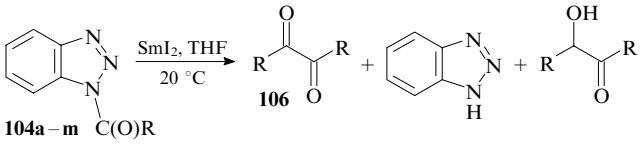


SET is single-electron transfer; Bt is benzotriazol-1-yl.

another molecule of compound **104** to afford intermediate **C**. This can also be obtained as a result of the N—C bond cleavage in radical anion **A** (pathway *b*) to form acyl radical **D**, which attacks the N—N bond in another molecule of compound **104**. Intermediate **C** uptakes the second electron from SmI_2 to transform to compound **E**. The N=N bond in the latter compound is reduced by the equivalent amount of SmI_2 to afford radical **F**. The amino group in the aromatic ring is involved in the intermolecular attack on the carbonyl carbon atom in such a way as to preferentially produce a five-membered ring in intermediate **G**. Upon the transfer of the next electron from SmI_2 to the nitrogen atom (structure **H**), the abstraction of $I_2SmOSmI_2$ leads to benzimidazole **I**. Subsequent protonation furnishes final product **105**.

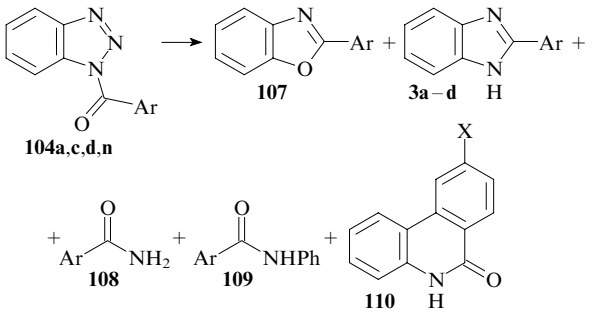
Thus, the first example of the benzotriazole ring opening under the action of a unique reducing agent, SmI_2 in acetonitrile, is described. Recyclization is a convenient method for the preparation of 1-acylamino-2-alkyl(aryl)-benzimidazoles **105**.[112–115] This is one of rare examples where all three nitrogen atoms remain incorporated in the new compound after the recyclization.

If THF was used as the solvent in this reaction in place of acetonitrile, no benzimidazole derivatives formed. The predominant reaction product was α-diketone **106**.



c. Gas-phase thermolysis of 1-aroylbenzotriazoles

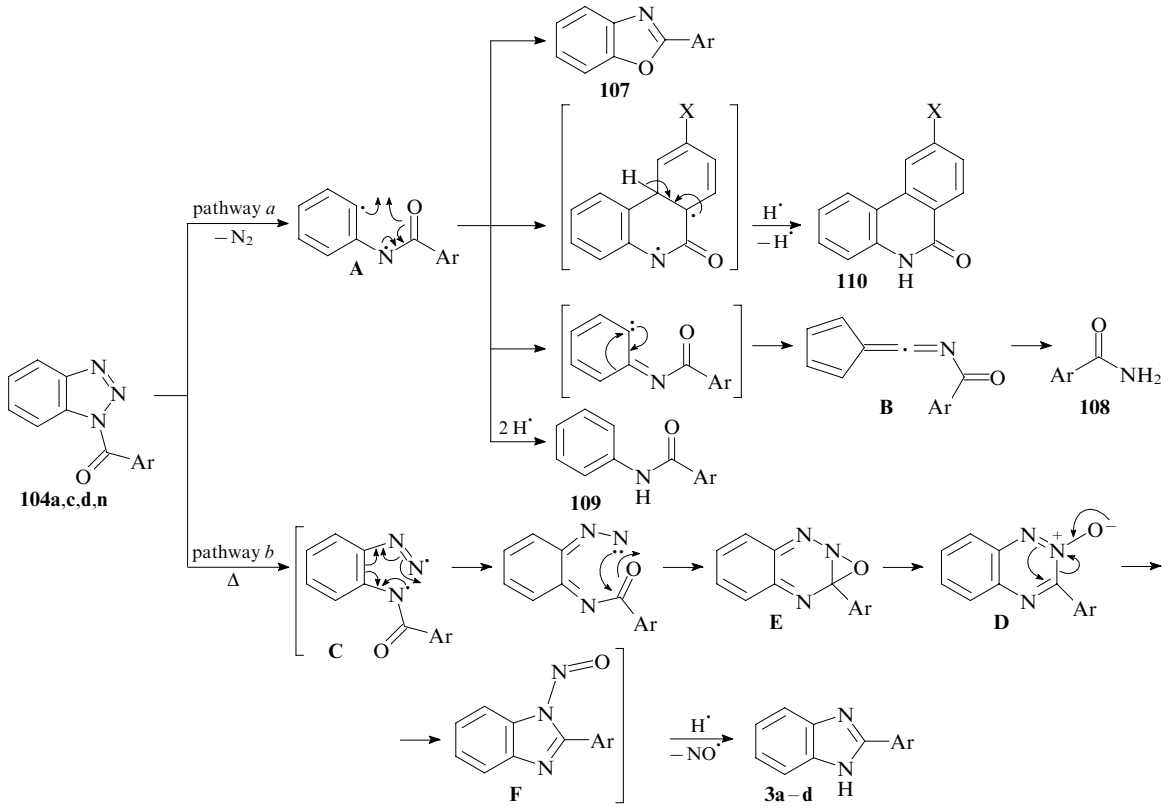
As a result of gas-phase thermolysis, *N*-aroylbenzotriazoles **104a**,**c**,**d**,**n** afforded derivatives of benzoxazoles **107**, benzimidazoles **3a–d**, benzamides **108**, benzanilides **109** and phenanthridones **110**.[116]



Triazole **104**	Ar	Yield of products (%)					
		107	**3**	**108**	**109**	**110**	(X)
a	Ph	3	11 (**c**)	5	23	7	(H)
c	C_6H_4Cl-4	5	5 (**a**)	2	6	5	(Cl)
d	C_6H_4Me-4	4	14 (**b**)	22	6	5	(Me)
n	$C_6H_4NO_2$-4	20	4 (**d**)	18	6	4	(NO_2)

Scheme 15 shows the putative pathways for the synthesis of compounds **3**, **107**–**110**. Pathway *a* includes the extrusion of an N_2 molecule to produce biradical **A**. The latter can undergo both the cyclization to form benzoxazole derivatives **107** and phenanthridone **110** and the rearrangement to form benzamide **108** *via* carbene and *N*-aroylcyclopentadienylketenimine **B**. The addition of two hydrogen atoms to biradical **A** affords benzanilide **109**. Pathway *b* that explains the formation of 2-arylbenzimidazoles **3** involves the N—N bond cleavage in the benzotriazole ring to form biradical **C**. The latter transforms to 3-aryl-

Scheme 15

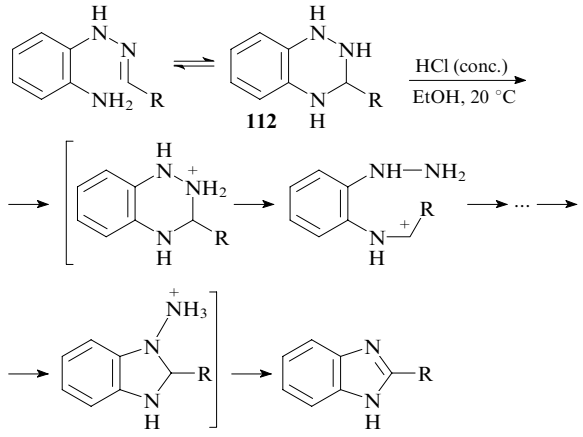


1,2,4-benzotriazine 2-oxide **D** *via* intermediate **E**. The rearrangement of intermediate **D** to **F** proceeds with the elimination of the NO$^{\bullet}$ radical, whereas the addition of H$^{\bullet}$ leads to benzimidazole **3**.

4. Benzo derivatives of six-membered heterocycles including quinoxalines

a. Acid-catalyzed rearrangement of 3,4-dihydro-1,2,4-benzotriazines

The treatment of aldehyde 2-aminophenylhydrazones with concentrated hydrochloric acid in EtOH at room temperature afforded 2-substituted benzimidazoles **3a**, **41a**, **66**, **79**, **111** with simultaneous evolution of ammonia.[117]



112

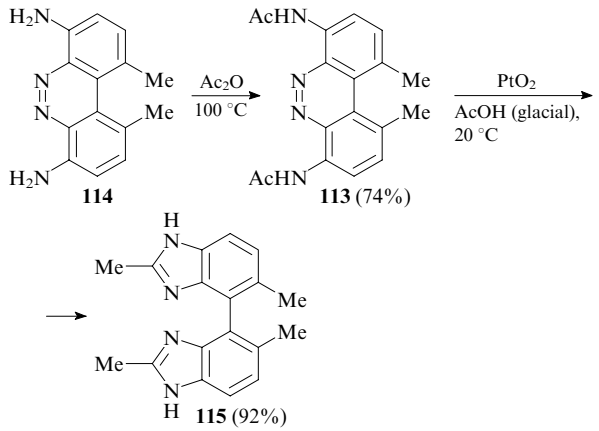
3a, **41a**, **66**, **79**, **111** (R = Bn)

R = H, Me, Et, Bn, Ph.

The putative reaction mechanism includes the acid-catalyzed migration of the alkylidene or arylidene group from the hydrazine nitrogen atom to the amine nitrogen atom through the protonation of 1,2,3,4-tetrahydro-1,2,4-benzotriazines **112**. This kind of migration was described by Abramovich and Schofield[118] and later by Boido and Sparatore.[119] The migration was followed by the ring closure that involved the second nitrogen atom of the hydrazine group.

b. Reductive recyclization of *N*,*N*′-diacetamidodimethylbenzo[*c*]cinnoline

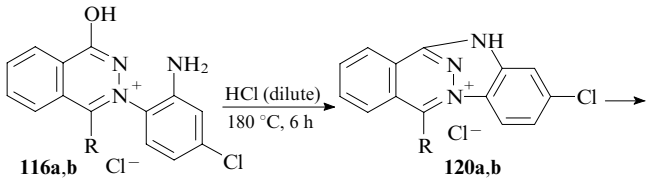
N,*N*′-Diacetyl-4,7-diamino-1,10-dimethylbenzo[*c*]cinnoline (**113**) prepared by acetylation of the corresponding diamino derivative (**114**) underwent recyclization upon reduction in the presence of platinum oxide to afford 2,2′,5,5′-tetramethyl-4,4′-bibenzimidazole (**115**) in a high yield.[120]



114 **113** (74%) **115** (92%)

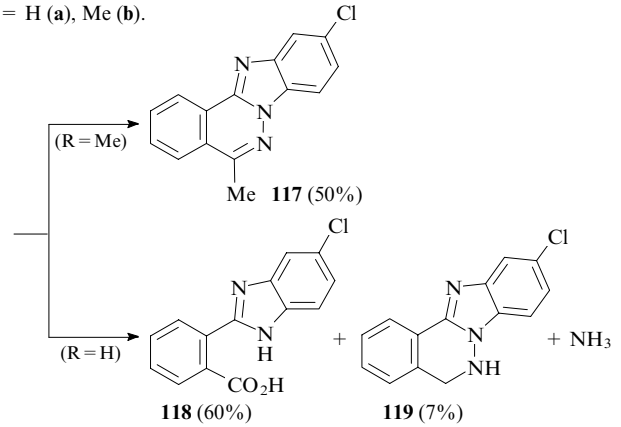
c. Acid-catalyzed recyclization of 3-(*o*-aminophenyl)phthalaz-1-ones

3-(*o*-Aminophenyl)phthalaz-1-ones **116a**,**b** underwent quite unexpected transformations on heating in a sealed tube with dilute hydrochloric acid at 180 °C for 6 h; moreover, the reaction pathways for compounds **116a** and **116b** differed substantially.[121] Thus compound **116b** gave tetracyclic derivative **117**, whereas compound **116a** afforded carboxylic acid **118** (as a result of elimination of the N(2) atom in the form of ammonia) and tetracyclic compound **119**. 2′-Amino-3-phenylphthalaz-1-one sulfate behaved similarly. In the reactions of both **116a** and **116b**, one water molecule was lost from the 2′-amino and 1-hydroxy groups in the first step. The resulting compound (**120a**) was so unstable that immediately eliminated the N(2) atom in the form of ammonia and transformed to oxidation (**118**) and reduction (**119**) products. Compound **120b** was more stable due to the presence of a methyl group in position 4; in the methylene form it reacts to form compound **117** as a result of rearrangement.



116a,**b** **120a**,**b**

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

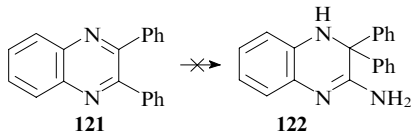


117 (50%) **118** (60%) **119** (7%)

Not only phthalazines and their derivatives could undergo recyclization to form benzimidazole derivatives, but their closest structural analogues, quinoxalines, as well.

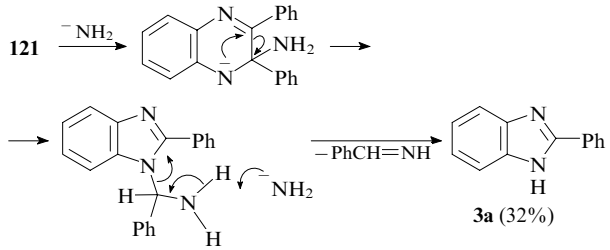
d. Recyclization of quinoxalines

In 1931, Ogg and Bergstrom[122] published a study in which they demonstrated the possible analogy between heterocyclic compounds and their acyclic and alicyclic counterparts. For example, they considered quinoxaline as 'ammonoglyoxal' and 2,3-diphenylquinoxaline (**121**) as the heterocyclic analogue of benzil. To check the hypothesized analogy, Taylor and McKillop[123] studied the reaction of diphenylquinoxaline (**121**) with potassium amide in ammonia and assumed that a certain transformation similar to the benzilic acid rearrangement could occur to afford 3-amino-2,2-diphenyl-1,2-quinoxaline (**122**). However, instead of the expected compound (**122**), they isolated 2-phenylbenzimidazole (**3a**) in a yield of ~30% and ~60% of compound **121** was recovered.



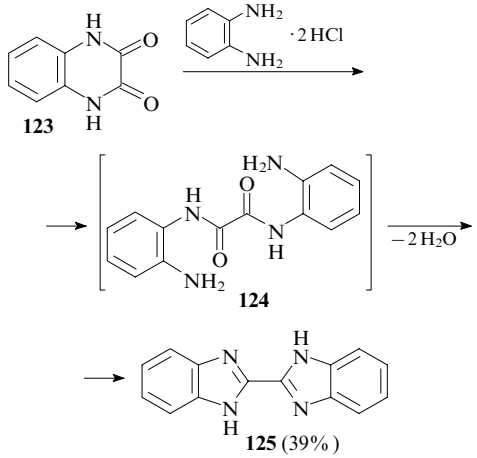
121 **122**

The mechanism of formation of 2-phenylbenzimidazole (**3a**) includes the primary addition of the amide ion to the C(2) atom of compound **121** (as postulated by Ogg and Bergstrom [122]). However, this was followed not by the phenyl group migration as in the benzilic acid rearrangement but by the ring contraction presumably as the result of elimination of benzylideneamine. All attempts to carry out the quinoxaline ring contraction (compound **121**) to afford the benzimidazole ring (**3a**) by employing other bases (KOH in water and ethanol, MeONa in methanol, NaH in toluene) failed.



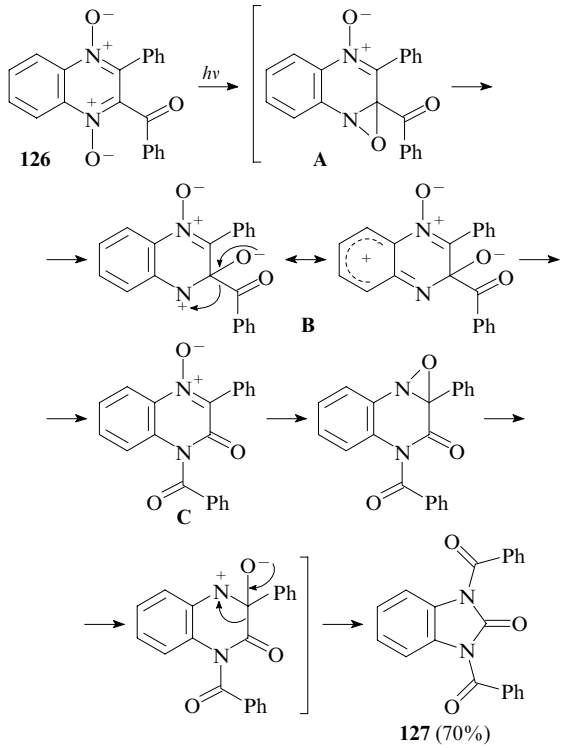
3a (32%)

It was shown that the reaction of quinoxaline-2,3-(1*H*,4*H*)-dione (**123**) with *o*-PDA afforded extremely unstable compound **124** as a result of 'ammonolysis', and the latter underwent spontaneous dehydration to form bibenzimidazole **125**.[91] This reaction sequence was also used in the synthesis of 2-(benzimidazol-2-yl)-5-methylbenzimidazole; however, its yield was not specified.[91]



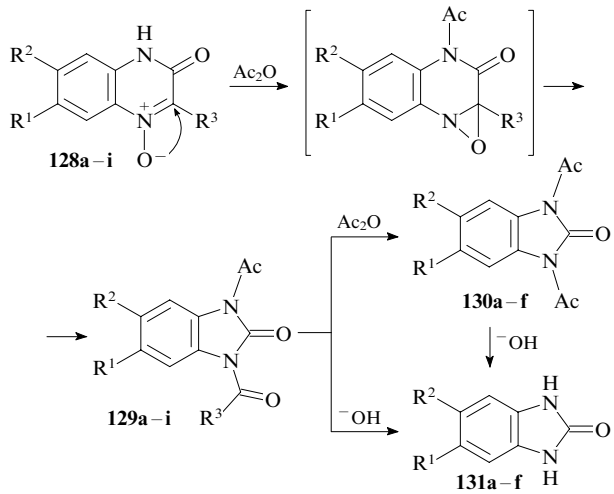
123 **124** **125** (39%)

The exposure of a solution of quinoxaline di-*N*-oxide **126** in methanol to sunlight for 12 h afforded 1,3-dibenzoylbenzimidazolone (**127**) in good yields.[124] Such a rearrangement was possible provided two nitrone fragments were present in a molecule. Generally, it was shown that photolysis of nitrones leads to oxaziridines, which in turn undergo further thermal or photochemical rearrangement. This is why it can be assumed that on irradiation, compound **126** is transformed into isomeric oxazirane **A**. In the studies of the mechanism of formation of benzimidazolone from oxaziridine **A,** an argument was put forward in support of intermediate **B** that appeared in the thermal cleavage of the N–O bond in the oxaziridine ring. Presumably, in intermediate **B** in which the positive charge on the nitrogen atom was delocalized due to the resonance with the conjugated aromatic system, the 1,2-benzoyl shift occurred to afford compound **C**. The driving force of this process was the negative charge on the oxygen atom.



126 **A** **B** **C** **127** (70%)

Refluxing of quinoxalin-2(1*H*)-one 1-oxide **128a** in acetic anhydride for 4 h afforded a compound with the composition $C_{16}H_{12}N_2O_3$, which was identified as **129a**. Refluxing for longer time or the use of excess Ac_2O produced diacetyl derivative **130a**. Compounds **128b–f,h** behaved in the similar fashion on refluxing in acetic anhydride yielding 2,3-dihydro-1*H*-benzimidazol-2-one derivatives **129b–f,h**, respectively. At the same time,



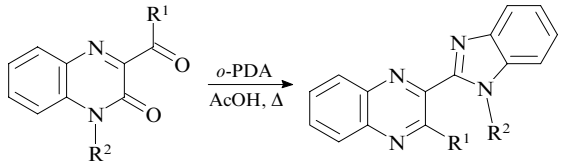
128a–i **129a–i** **130a–f** **131a–f**

R^3 = Ph: $R^1 = R^2$ = H (**a**); R^1 = EtO, R^2 = H (**b**); R^1 = MeO, R^2 = H (**c**); R^1 = Me, R^2 = H (**d**); R^1 = Cl, R^2 = H (**e**); $R^1 = R^2$ = Cl (**f**); $R^1 = R^2$ = H: $R^3 = C_6H_4NO_2$-4 (**g**), C_6H_4Cl-4 (**h**), CN (**i**).

quinoxalinone oxides **28g**,**i** transformed into 2,3-dihydro-1*H*-benzimidazol-2-one **130a** only on heating in a sealed tube at 180 °C for 12 h.[125] For compound **128g**, in addition to diacetyl derivative **130a**, the monoacetyl derivative was obtained. As a result of alkaline hydrolysis, compounds **129** and **130** transformed to N-unsubstituted 2,3-dihydro-1*H*-benzimidazol-2-ones **131**.

As follows from the aforementioned four examples of recyclization of quinoxaline derivatives, the former two led to C(2)-substituted benzimidazoles and the latter two afforded N-substituted benzimidazoles; moreover, the first three examples represent special cases, *i.e.*, they were implemented for a single derivative of this type. As to the fourth example, the potential of this reaction is limited to the synthesis of 2,3-dihydro-1*H*-benzimidazol-2-one containing substituents only in the benzene ring, because the substituent at C(3) atom of the starting compound is eliminated upon recyclization. Thus, none of these methods of synthesis of benzimidazole derivatives can compete with the classical Fillips–Ladenburg and Weidenhagen reactions.

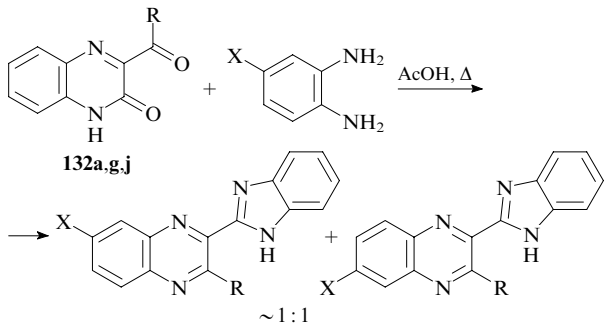
In 2000, a new in principle reaction of 3-aroyl(alkanoyl)quinoxalin-2(1*H*)-ones **132**[126–128] with 1,2-arylenediamines was discovered, *viz*., the pyrazine ring contraction affording the corresponding benzimidazol-2-ylquinoxalines **133** in high yields.[129–132] The formation of a new quinoxaline ring involved, in addition to the imine carbon atom, the α-carbon atom of the substituent in position 3 of quinoxalin-2(1*H*)-one.



132a–k **133a–k** (72%–99%)

R^1 = Ph: R^2 = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**), Bu^n (**e**), n-C_6H_{11} (**f**);
R^1 = Me, R^2 = H (**g**); R^1 = Pr^n, R^2 = H (**h**); R^1 = Me, R^2 = Et (**i**);
R^1 = Bn, R^2 = H (**j**); R^1 = $(CH_2)_2$Ph, R^2 = H (**k**).

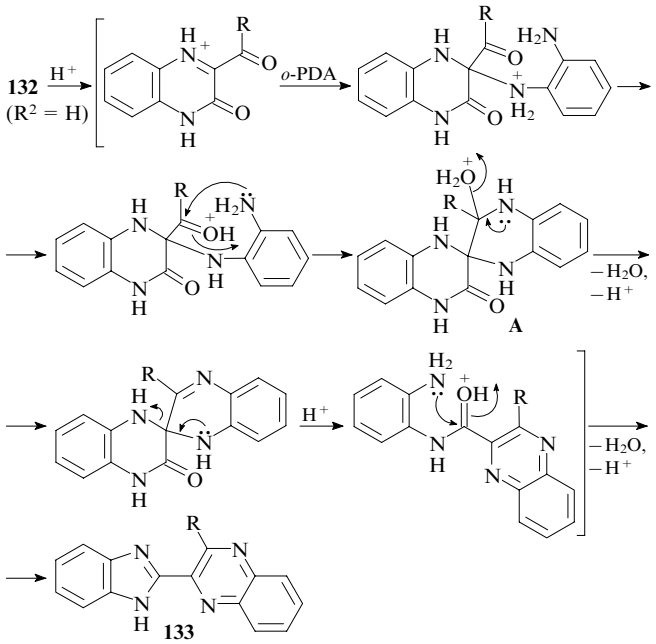
The use of asymmetrically substituted 1,2-arylenediamines in this reaction led to a mixture of isomers in the ratio ~ 1 : 1 and the total yield of 52%–85%.[131–135]



132a,**g**,**j**

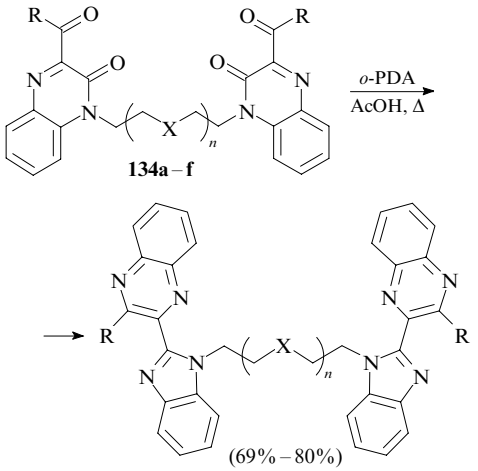
R = Ph: X = NO_2, Me; R = Bn, X = NO_2;
R = Me: X = NO_2, Me.

The formation of the isomeric mixture irrespective of the nature of substituents in quinoxalin-2(1*H*)-ones and 1,2-arylenediamines makes it possible to assume that the primary attack of the *o*-PDA amino group could be directed on either the C(3) carbon atom of the quinoxaline system or the aroyl(alkanoyl) carbon atom. This was followed by a cascade process that included the formation of spiroquinoxaline **A**, the intramolecular electrophilic addition of the amine nitrogen atom to the carbamoyl group, ring contraction and loss of water.[132, 135]



R = Alk, Ar.

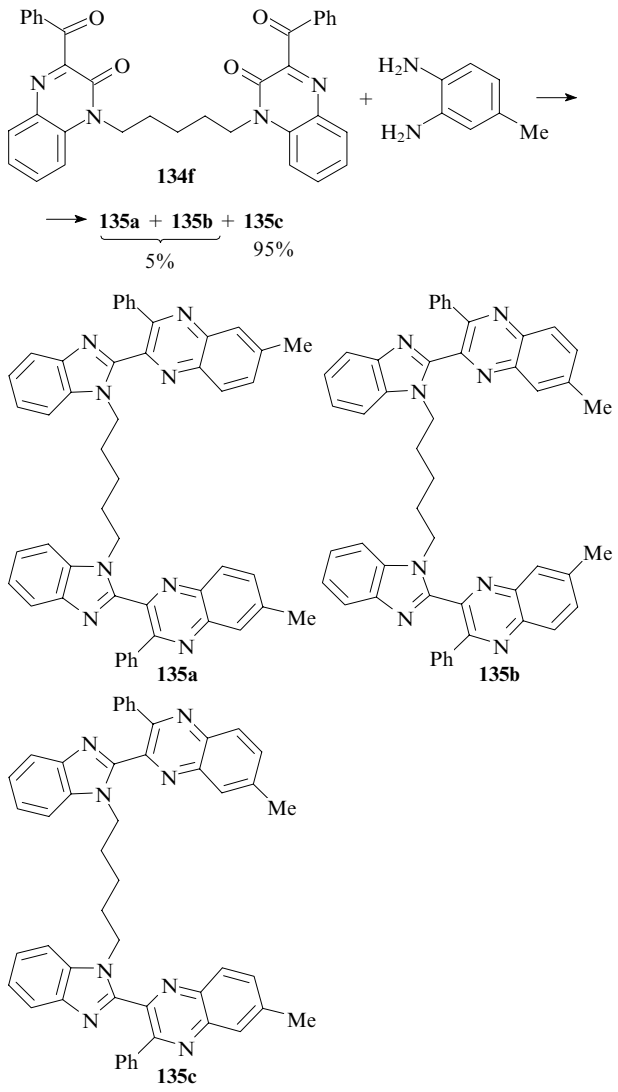
This reaction also proceeded with bisquinoxalin-2(1*H*)-ones **134a–f** containing a benzoyl (or acetyl) substituent.[131, 136]



134a–f

R = Ph, X = O: *n* = 1 (**a**), 2 (**b**); R = Ph, X = CH_2: *n* = 1/3 (**c**), 4/3 (**d**), 8/3 (**e**), 1 (**f**).

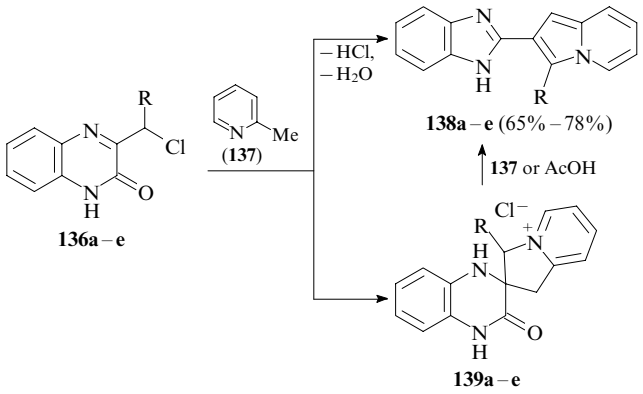
The use of asymmetrical 3,4-diaminotoluene in place of *o*-PDA in the reaction with bisquinoxalin-2(1*H*)-one **134f** containing a pentamethylene spacer resulted in the formation of a mixture of three rearrangement products **135a–c**, which differed in the position of methyl groups in the benzene ring of the quinoxaline system, where one of isomers prevailed.[136]



These results confirmed the assumption that the primary attack of the amino group of 1,2-diaminobenzene was directed on either the C(3) carbon atom of the quinoxaline system or the aroyl(alkanoyl) carbon atom.

Insofar as in the aforementioned reactions with 1,2-diaminobenzenes, aroyl- and alkanoylquinoxalinones (α-iminoketones) behaved in the initial step like α-diketones in the Hinsberg reaction, it is quite probable that other quinoxaline derivatives with certain substituents could behave as the heteroanalogues of halo ketones, β-diketones and common ketones. Studies of the behaviour of quinoxaline 3-haloalkyl and 3-halobenzyl derivatives (as the heteroanalogues of α-halo ketones), of aroylmethylidene-3,4-dihydroquinoxalinone derivatives (as the heteroanalogues of β-diketones) as well as of 3-methylquinoxalinone (as the heteroanalogue of methyl ketone) were carried out by examples of the reactions most widely used in the chemistry of heterocycles to check this assumption.

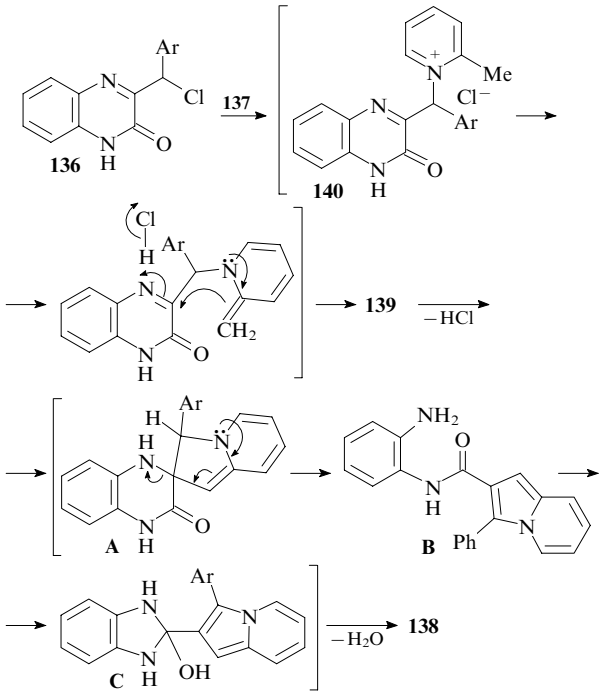
The first of the studied processes was the Chichibabin reaction (synthesis of indolizines by the reaction of halo ketones with α-picolines). The reaction of quinoxalin-2(1*H*)-ones **136a–e** with boiling α-picoline (**137**) (128 °C) for 9 h afforded benzimidazole derivatives **138a–e** in high yields *via* spirocompounds **139a–e** as in the case of the reaction of quinoxalinones with other dinucleophilic reagents.[137–139]



R = Ph (**a**), $C_6H_4NO_2$-4 (**b**), $C_6H_3Cl_2$-2,4 (**c**), $C_6H_3Cl_2$-3,5 (**d**), Bn (**e**).

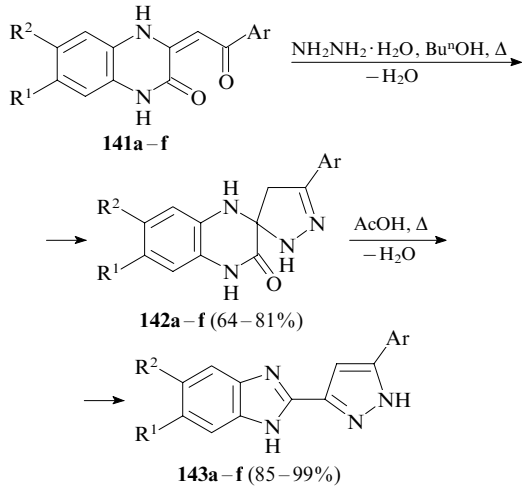
When this reaction was carried out under milder conditions, the product formed in the first step (**140**) could be isolated. This resulted from nucleophilic substitution of the pyridine nitrogen atom of α-picoline for the chlorine atom. Further stirring of compound **140** in α-picoline at higher temperature finally afforded either spiroquinoxaline **139** or benzimidazole derivative **138** depending on the reaction time and temperature.

The formation of the rearrangement product can be represented by the following scheme.[137,138] In the first step, the nucleophilic substitution of the pyridine ring nitrogen atom for the chlorine atom occurs. This is followed by a cascade reaction that involves dehydrochlorination with participation of a hydrogen atom of the a-picoline methyl group. After this, the intramolecular nucleophilic addition involving the methylene-group carbon atom of the picoline fragment and the imine nitrogen atom of the quinoxaline system affords spiro compound **A**. The N(1)–C(2) bond cleavage to form *o*-PDA N-substituted derivative **B** and ring closure to form benzimidazoline **C** followed by water loss complete the reaction.



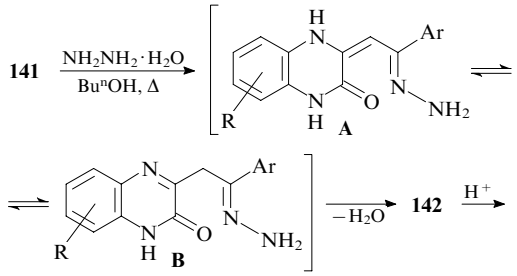
Thus, aroyl(alkanoyl)quinoxalinones and haloalkyl(halobenzyl)quinoxalinones were considered as the heteroanalogues of α-diketones and α-halo ketones. Following the same logics, the aroylmethylidenequinoxalinone derivatives can be considered as the analogues of β-diketones.

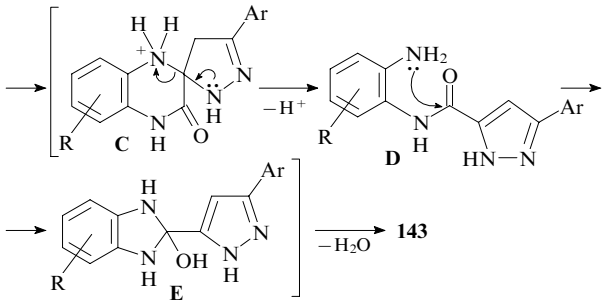
The second reaction used in testing the above assumption was the Knorr synthesis of pyrroles (the reaction of β-diketones with hydrazines). The reaction of aroylmethylidene-3,4-dihydroquinoxalin-2(1*H*)-ones **141a–f** with hydrazine hydrate in boiling n-butanol furnished spiro derivatives **142a–f** in good yields. Refluxing of the latter in acetic acid for 8 h resulted in elimination of a water molecule to afford the corresponding benzimidazoles **143a–f** in high yields as the result of the acid-catalyzed rearrangement.[140–142]



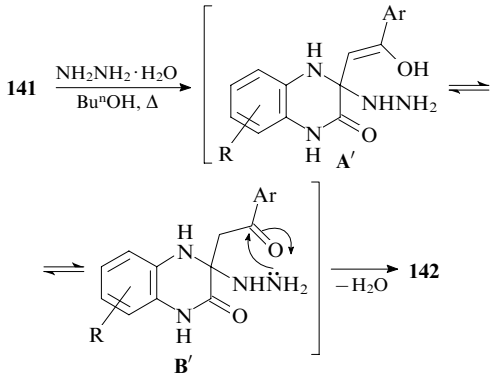
Ar = Ph: $R^1 = R^2 = H$ (**a**), Me (**b**); R^1 = Cl, R^2 = H (**c**);
R^1 = H, $R^2 = NO_2$ (**d**); $R^1 = R^2$ = H: Ar = C_6H_4Me-4 (**e**), C_6H_4Cl-4 (**f**).

The formation of the rearrangement product can be explained by the following reaction sequence. In the initial step, the nucleophilic addition of hydrazine to the carbonyl group of 3-aroylmethylidene moiety of quinoxalin-2(1*H*)-one **141** occurs to afford hydrazone **A**, which tautomerizes to intermediate **B**. The latter undergoes 5-*exo*-*trig*-cyclization, which is followed by the nucleophilic attack of the amino group of the hydrazone fragment on the C(3) atom of quinoxalin-2(1*H*)-one to afford spiro derivative **142**. This is followed by the pyrazine ring contraction to produce the imidazole ring as the result of a cascade reaction including the following steps: 1) acid-catalyzed pyrazinone ring opening in the intermediate **C** with the C(3)–N(4) bong cleavage to form pyrazole derivative **D**; 2) intramolecular nucleophilic addition of the nitrogen atom to the carbonyl group to form hydroxy derivative **E** and 3) elimination of water.[140–142]

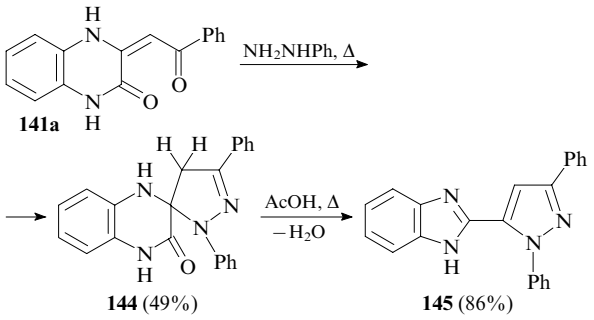




It should be noted that the formation of a spiro compound can also be explained by the Michael addition of hydrazine hydrate to the more electrophilic C(3) carbon atom of the quinoxalinone in the first step to afford intermediate **A′**, which can exist in the ketone form **B′** where the nucleophilic attack of the hydrazone amino group on the carbonyl carbon atom of the aroylmethylidene moiety occurs.

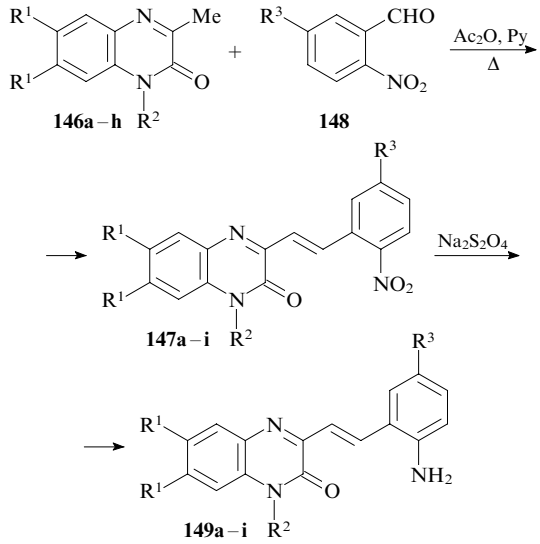


The reaction of 3,4-dihydroquinoxalin-2(1*H*)-one **141a** with phenylhydrazine proceeded similarly to the reaction with hydrazine hydrate to yield spiro compound **144**. The latter also underwent rearrangement in boiling acetic acid to give benzimidazole derivative **145** containing the 1,3-diphenylpyrazolyl fragment.[142]



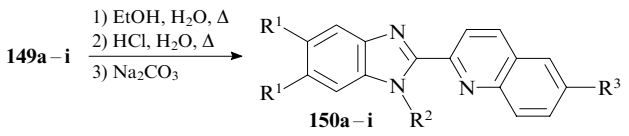
The synthesis of bisheterocyclic compounds comprising the benzimidazole system by the above reaction makes use of not only quinoxaline 3-aroyl–,[128–132] 3-alkanoyl-,[132,139] 3-α-halobenzyl-[137–139] or 3-aroylmethylidene derivatives[140–142] but 3-methylquinoxalin-2(1*H*)-one (**146a**) as well,[143] which is one of the simplest quinoxalin-2(1*H*)-one derivatives. The latter compound can be considered as an analogue of ordinary methyl ketones.

Verification of the above assumption also involved the use of the Friedlaender reaction, *i.e.*, the synthesis of quinolines by the reaction of ketones with *o*-acylarylamines under conditions of base and acid catalysis. The modification of the Friedlaender reaction to match the reaction under discussion included the formation of *o*-nitrostyryl derivatives from 3-methylquinoxalin-2(1*H*)-ones (**147**) by the reaction of the latter with corresponding substituted *ortho*-nitrobenzaldehyde **148** in the first step and the reduction of the product under the action of sodium dithionate in the second step.[143]



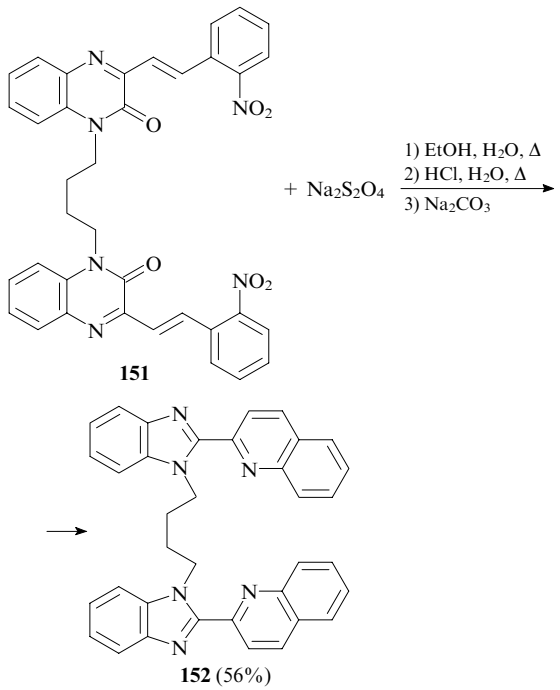
$R^1 = R^3 = H$: R^2 = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**), Bu^n (**e**), n-C_5H_{11} (**f**), n-C_6H_{13} (**g**); R^1 = Me, $R^2 = R^3$ = H (**h**); $R^1 = R^2$ = H, R^3 = Cl (**i**).

The synthesized *o*-aminostyryl derivatives **149** undergoes the acid-catalyzed rearrangement to afford 2-benzimidazol-2-ylquinolines **150a–i**.

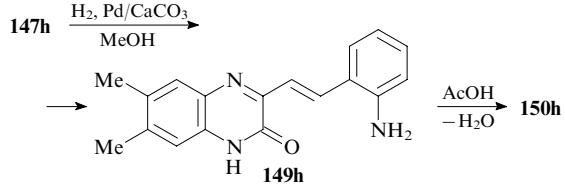


Compound **150**	R^1	R^2	R^3	Yield (%)
a	H	H	H	80
b	H	Me	H	76
c	H	Et	H	74
d	H	Pr^n	H	53
e	H	Bu^n	H	69
f	H	n-C_5H_{11}	H	70
g	H	n-C_6H_{13}	H	54
h	Me	H	H	79
i	H	H	Cl	59

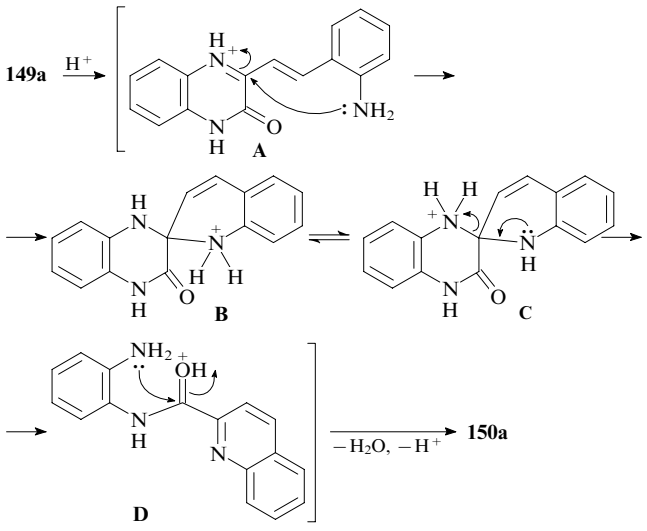
This reaction also proceeded with compounds containing two 3-(2-nitrostyryl)quinoxaline fragments. For example, in this reaction, derivative **151** readily transformed into bisimidazole **152**.



To demonstrate that the reaction proceeds *via ortho*-amino derivatives of 3-styrylquinoxalin-2(1*H*)-ones, the corresponding 3-(2-aminostyryl)-6,7-dimethylquinoxalin-2(1*H*)-one **149h** was synthesized by the reduction of nitro derivative **147h** in methanol by molecular hydrogen in the presence of 10 mol.% $Pd/CaCO_3$. Upon refluxing in AcOH for 3 h, compound **149h** transformed into 2-benzimidazol-2-ylquinoline **150h** in a good yield.[143]



In protonated amino derivative **A**, the nucleophilic attack of the *ortho*-amino group of the styryl fragment on the C(3) atom of quinoxalin-2(1*H*)-one occurred to afford spiro(quinoline-2,2′-quinoxaline)-3′(4′*H*)-one derivative **B**.



Next, the pyrazine ring contraction to the imidazole ring was observed as the result of acid-catalyzed opening of the pyrazinone ring in the intermediate compound **C** with the N(1)–C(2) bond cleavage and the formation of the quinoline derivative **D**. Later, the formation of the benzimidazole system proceeded similarly to the cases considered above.

Thus, unlike the recyclization reactions of heterocyclic compounds with benzene ring in substituents and the recyclization of benzo derivatives of five-, six- (including certain quinoxaline derivatives), seven-, eight-membered and larger heterocycles, the new recyclization reaction of 3-substituted quinoxalin-2(1*H*)-ones used in the synthesis of benzimidazoles is undoubtedly more general because, depending on the target, any required benzimidazole derivative can be synthesized by varying the first and(or) the second components.

* * *

The material presented in this review shows that despite the great diversity of reactions producing benzimidazoles, only few of them can serve as the basis for preparative synthesis since they are low-yielding, time-consuming, the starting-materials are difficult to obtain, *etc*. In this respect, the recyclization of quinoxaline derivatives to benzimidazole derivatives is extremely attractive. We hope that in future, this reaction will find its worthy place in chemistry of heterocyclic compounds and serve as a simple and efficient method of synthesizing various benzimidazole derivatives along with the classical Fillips–Ladenburg and Weidenhagen reactions.

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