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Advances in the synthesis of benzimidazol-2-ones

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Known methods for the synthesis of benzimidazol-2-ones are considered and integrated. Approaches based on transformations of aniline derivatives, N,N′-disubstituted ureas and halobenzenes are analyzed. Methods involving rearrangements of heterocyclic compounds, such as benzodiazepinones, benzodiazepinediones, quinoxalinones and tetrazolones, as well as fused and spirocyclic systems incorporating a benzimidazole moiety, are presented. A separate section is devoted to rearrangements of anthranilic acid derivatives giving benzimidazol-2-ones. The mechanisms of formation of these compounds are discussed; the attention is focused on rearrangements of quinoxalinones giving rise to bis-heterocyclic systems.
The bibliography includes 181 references.

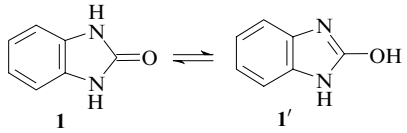
Contents

I. Introduction 968
II. Methods based on aniline and its derivatives 970
III. Methods based on halobenzenes 976
IV. Methods based on rearrangements of heterocyclic systems 980
V. Methods based on rearrangements of anthranilic acid 991
VI. Other methods 992

I. Introduction

A great deal of attention is currently being paid to the development of methods for the synthesis of derivatives of 1,3-dihydro-2*H*-benzimidazol-2-one (hereinafter, benzimidazol-2-one, **1**) (Scheme 1) because many representatives of this class exhibit diverse biological activity.

Scheme 1



1 **1′**

For example, the benzimidazol-2-one moiety is present in pharmacophoric compounds, such as calcitonin gene-related peptide receptor (CGRP) antagonists (structures **2a** – **c**),[1] p53-Mdm antagonists (**3**),[2] human cannabinoid receptor 2 (hCB2) antagonist (**4**),[3] opioid receptor 1 (NOP) antagonists (**5a** – **c**),[4, 5] HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) (**6a**,**b**),[6] D-amino acid oxidase (DAAO) inhibitors (**7a** – **c**),[7] respiratory syncytial virus (RSV) inhibitor (**8**),[8] mycobacterium tuberculosis enzyme inhibitor (**9**),[9] p38 MAP kinase inhibitor (**10**)[10] and antibacterial agents (**11a**,**b**).[11] Benzimidazol-2-one derivatives (*e.g.*, compound **12**) are selective peroxisome proliferator-activated receptor γ modulators (SPPARγMs) and can be used as potential therapeutic agents for the treatment of type 2 diabetes mellitus (T2DM).[12] Besides, these compounds exhibit activity as progesterone receptor antagonists (**13a** – **d**, **14a**,**b**)[13, 14] and selective vasopressin 1a receptor antagonists (**15**),[15] possess antitumour activity (**16**)[16] and play an important role in K^+ channel activation (**17a** – **c**).[17, 18] Benzimidazol-2-one derivatives have been also used over 30 years as pigments with a broad range of hues in watercolor painting and as colourants in electrophotographic toners and developers because of their durability and light resistance.[19 – 23]

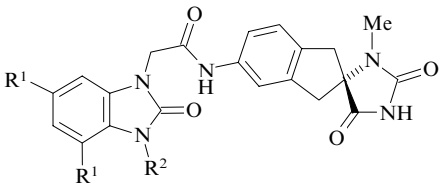
In recent years, numerous methods for the synthesis of functionalized benzimidazol-2-ones have been described in the literature. Although unsubstituted benzimidazol-2-one (**1**) was synthesized for the first time by Rudolph[24] more than a century ago (in 1879) from ethyl (2-aminophenyl)-carbamate (*o*-aminophenylurethane), chemists seek to

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Current research interests: organic synthesis, reactivity and mechanisms of organic reactions, development of new tandem transformation protocols for the synthesis, of diversity-oriented heterocyclic systems.

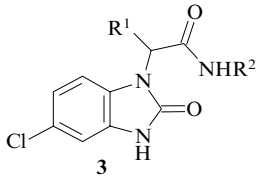
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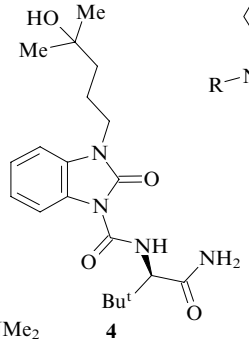
Structures 2 – 17



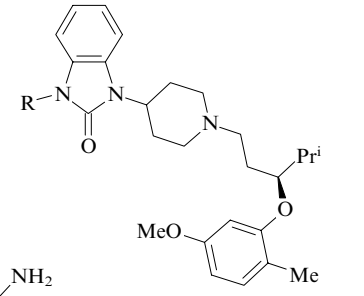
2a: R^1 = H, R^2 = 2-Py;
2b: R^1 = R^2 = Me;
2c: R^1 = Me, R^2 = $CH_2C(O)NMe_2$



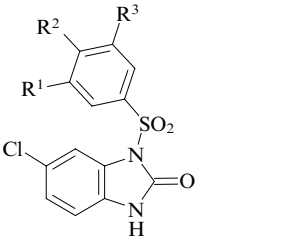
3
(R^1 = Ar, CH_2Ar;
R^2 = $(CH_2)_nAr$, Alk, Cy)



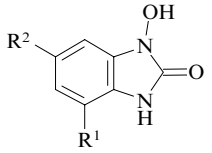
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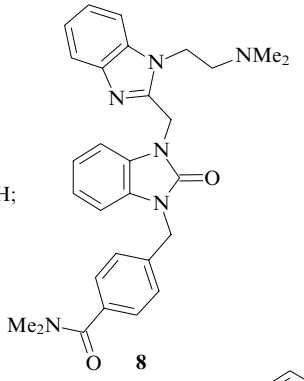
(+)-**5a**: R = $CH_2C(O)NHMe$;
(+)-**5b**: R = CH_2CH_2OMe;
(+)-**5c**: R =



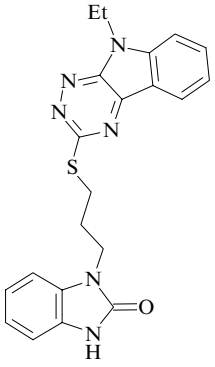
6a: R^1 = R^3 = Me, R^2 = H;
6b: R^1 = H, R^2 = R^3 = Me



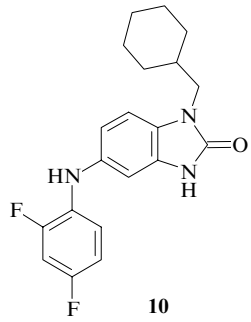
7a: R^1 = R^2 = H;
7b: R^1 = OMe, R^2 = H;
7c: R^1 = R^2 = F



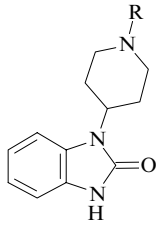
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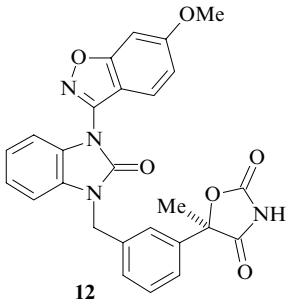
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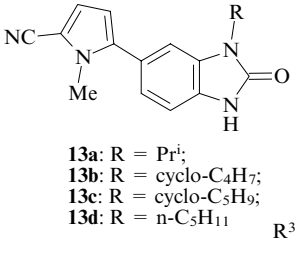
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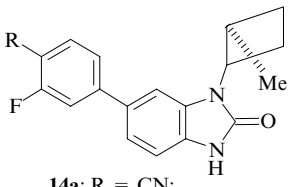
11a: R = $C(O)OCH_2C_6H_4NO_2$-4;
11b: R = C_6H_3F-2-NO_2-4



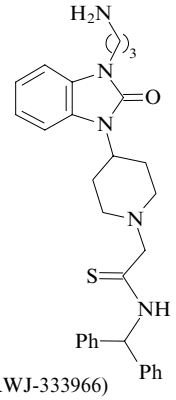
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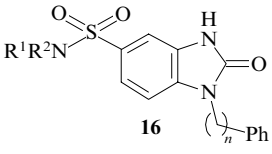
13a: R = Pr^i;
13b: R = cyclo-C_4H_7;
13c: R = cyclo-C_5H_9;
13d: R = n-C_5H_{11}



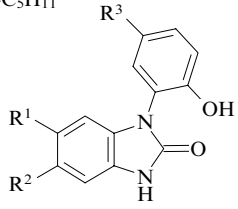
14a: R = CN;
14b: R = OH



15 (RWJ-333966)



16
(n = 1, 2; R^1R^2N = Pr^iNH,
PhNH, morpholino, *etc.*)



17a: R^1 = H, R^2 = CF_3, R^3 = Cl (NS 004);
17b: R^1 = H, R^2 = R^3 = CF_3 (NS 1619);
17c: R^1 = Cl, R^2 = H, R^3 = OH

Py is pyridyl, Cy is cyclohexyl

develop new and improve the already available approaches to the preparation of these compounds.

There are two main methods for the synthesis of N-substituted benzimidazol-2-ones. One of them is based on the selective alkylation or arylation of nitrogen atoms in benzimidazol-2-ones.[13,25,26] Another method involves the nucleophilic substitution of 2-fluoronitrobenzenes with amines followed by reductive cyclization in the presence of a carbonyl source, *e.g.*, 1,1′-carbonyldiimidazole (CDI).[10,27–29] In the former case, a special strategy for the protection of NH groups is often required. The latter method is not always applicable because of a limited number of available 2-fluoronitrobenzene derivatives. It should be noted that each method has its specific features associated with the nature of the reagents, as well as with the character of sources of nitrogen and carbonyl function used in the synthesis. Apart from these two approaches, there are many other strategies for the preparation of unsymmetrical benzimidazol-2-ones, for example, reactions accompanied by rearrangements of different heterocyclic systems.

Before the publication of this review, no analysis of all available methods for the synthesis of benzimidazol-2-ones, including the discussion of advantages and limitations of each method and the lines of the development of new procedures for the preparation of previously inaccessible derivatives, has been reported in the literature. Previous reviews on quinoxalines[30–32] and benzimidazoles[33,34]

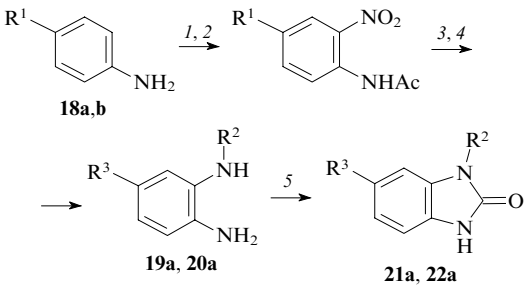
included separate sections dealing with the synthesis of benzimidazol-2-ones. Besides, a mini review devoted to this field of research was published in 2016.[35] However, these reviews consider only selected approaches to the synthesis of this important type of compounds and, even more so, do not give any predictions on the development of new methods. The goal of this review is to perform a comprehensive analysis of different synthetic approaches to benzimidazol-2-ones. The data are classified according to the type of the starting compounds. The review first addresses methods involving the cyclization step, then those involving rearrangements giving benzimidazol-2-ones and finally procedures which do not belong to the above-mentioned groups.

II. Methods based on aniline and its derivatives

II.1. Synthesis from anilines

There are only two works,[12, 36] in which monosubstituted anilines **18a**,**b** were used for the synthesis of benzimidazol-2-ones through multistep transformations. In both cases, the synthesis strategy involved the protection of the amino group in the first step, the introduction of the nitro group in the second one, the reduction of the nitro group in the third step and deprotection of the amino group in the fourth one. In the final step, *o*-diaminobenzenes containing two (**19a**) or one (**20a**) NH_2 groups were cyclized using CDI as the carbonyl source to form benzimidazol-2-ones **21a** and **22a**, respectively (Scheme 2, Table 1).

Scheme 2



II.2. Synthesis from *o*-diaminobenzenes

One of the most commonly used methods for the synthesis of benzimidazol-2-one derivatives is based on transformations of *o*-diaminobenzenes **19** (Scheme 3, Table 2). Both unsubstituted diaminobenzene **19b** ($R^1 = R^2 = H$) [37 – 41, 43, 44, 48, 49] and its different derivatives [42, 45 – 49] are utilized as the starting compounds. This method was employed to synthesize benzimidazol-2-one (**1**) in high yield using urea as the cross-linking agent, the reaction being performed in various solvents under rather severe conditions, whereas the reaction with the use of CDI took place at room temperature (see Table 2). Similar procedures were developed for the synthesis of nitrogen-substituted *o*-diaminobenzenes **20** (Scheme 4, Table 3). Urea,[37 – 42] CDI,[43 – 46, 50] phosgene,[47] ethyl cyanoformate,[48] carbon dioxide,[49] di-*tert*-butyl dicarbonate [$(Boc)_2O$],[51] *N*,*N*′-disuccinimidyl carbonate (DSC) [52] and triphosgene [53 – 56] served as the carbonyl source. The diversity of products **21** and **22** formed in these reactions is determined by the nature

Table 2. Transformation of *o*-diaminobenzenes **19** containing free amino groups into benzimidazol-2-ones (see Scheme 3).

R^1	R^2	Reagents and conditions (*a*)	Yield (%)	Ref.
H	H	Urea, ethylene glycol, 130 – 140 °C	79	37
H	H	Urea, glycol, 130 – 140 °C, 1 h; then 170 °C, 7 h	90	38
H	H	Urea, pentan-1-ol, 130 °C, 2 h	89	39
H	H	Urea, K_2CO_3, DMF, 135 – 140 °C	94	40
H	H	Urea, butan-1-ol, Δ, 10 h	94	41
H	CO_2Et	Urea, xylene, 40 °C, 12 h	93	42
H	H	CDI, DMF, 20 °C, 22 h	98	43
H	H	CDI, 2-methyltetrahydrofuran, 20 °C, 48 h	98	44
H	F	CDI, THF, 20 °C, 2.5 h	83	45
H	CF_3	CDI	–	46
H	CO_2H	Phosgene, AcOH	–	47
H	OMe	Ethyl cyanoformate, LiBr, dioxane, 100 – 105 °C, 1 h	78	48
H, Me	H, Me, Hal, NO_2, Bz	CO_2 (2 MPa), $[Bu^n_4N^+]_2[WO_4]^{2-}$ (cat.)	70 – 99	49

Scheme 3

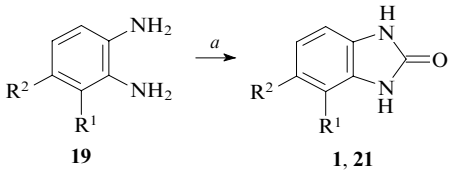
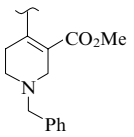
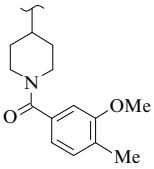
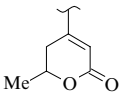
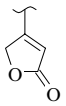
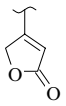
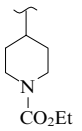
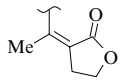


Table 1. Transformation of anilines **18a**,**b** into benzimidazol-2-ones (see Scheme 2).

Compounds	R^1, R^2, R^3	Reagents and conditions	Yield [a] (%)	Ref.
18a, **19a**, **21a**	$R^1 = R^3 = CF_3$, $R^2 = H$	1) Ac_2O, AcOH , 0 °C; 2) HNO_3, AcOH, 20 °C; 3) H_2, Pd/C, MeOH; 4) NaOH, MeOH; 5) CDI, THF	–	12
18b, **20a**, **22a**	R^1 = Br, R^2 = Me, R^3 = 3-$O_2NC_6H_4$	1) Ac_2O, Δ; 2) HNO_3 (conc.); 3) Fe, AcOH, H_2O; then $CH(OEt)_3$, $NaBH_4$, EtOH, Δ; 4) 3-$O_2NC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, PhMe, EtOH, H_2O, 85 °C; then 1 M HCl, Δ; 5) CDI, THF	85	36

Note. A dash indicates that the yield was not reported in the original publication. [a] Hereinafter, the product yield is given for the cyclization step.

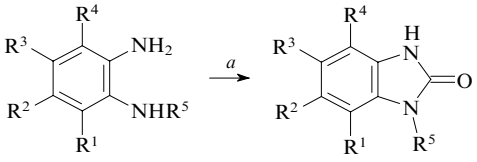
Table 3. Transformation of nitrogen-substituted *o*-diaminobenzenes **20** into benzimidazol-2-ones (see Scheme 4).

R^1	R^2	R^3	R^4	R^5	Reagents and conditions (*a*)	Yield (%)	Ref.
H	H	H	H	Ar	CDI, THF (anh.), 20 °C or DMF (anh.), 90 °C, 2 h	61 – 80	50
H	H	H	H		1) $(Boc)_2O$, DCM; 2) TFA	91	51
H	H	H, F, Me	H, Me		DSC, MeCN, 20 °C	–	52
H, Cl, NO_2	H, Me	H	H		Triphosgene, TEA, DCM, 0 °C	55 – 66	53
H	Me	H	H		Triphosgene, TEA, DCM, 0 °C	68	53
NO_2	H	H	H		Triphosgene, TEA, DCM, 0 °C	55	53
H	H	H, F	H		Triphosgene, TEA, DCM, 0 °C	–	54
H	H	H	H	4-ClC_6H_4	Triphosgene, TEA, THF (anh.), 20 °C	98	55
H	H	Cl	H	Ph	Triphosgene, TEA, THF (anh.), 20 °C	97	55
H	H, NO_2	H, Cl, Me	H		Triphosgene, TEA, DCM	52 – 65	56

Note. TEA is triethylamine, DCM is dichloromethane.

of the starting *o*-diaminobenzenes, which are often difficult to prepare and which require a certain strategy to control the regioselectivity of the processes.

Scheme 4



20 **22**

Apart from the above-mentioned sources of the carbonyl group, 4-nitrophenyl chloroformate was employed for the construction of immobilized benzimidazol-2-ones **23** from *o*-diaminobenzenes **24** applied onto a support (Scheme 5).[57] Blanco-Canosa and Dawson accomplished an efficient solid-phase peptide synthesis by the Fmoc strategy (Fmoc is fluoren-9-ylmethyloxycarbonyl) to prepare thioester peptide precursor **25** for use in chemical cross-linking. In this process, the closure of the benzimidazolone ring afforded the product in 67% – 90% yield depending on the nature of the substituent R (R = H, Alk, CH_2Ar); the cleavage of compound **26** to free amine proceeded with a yield of 90%.

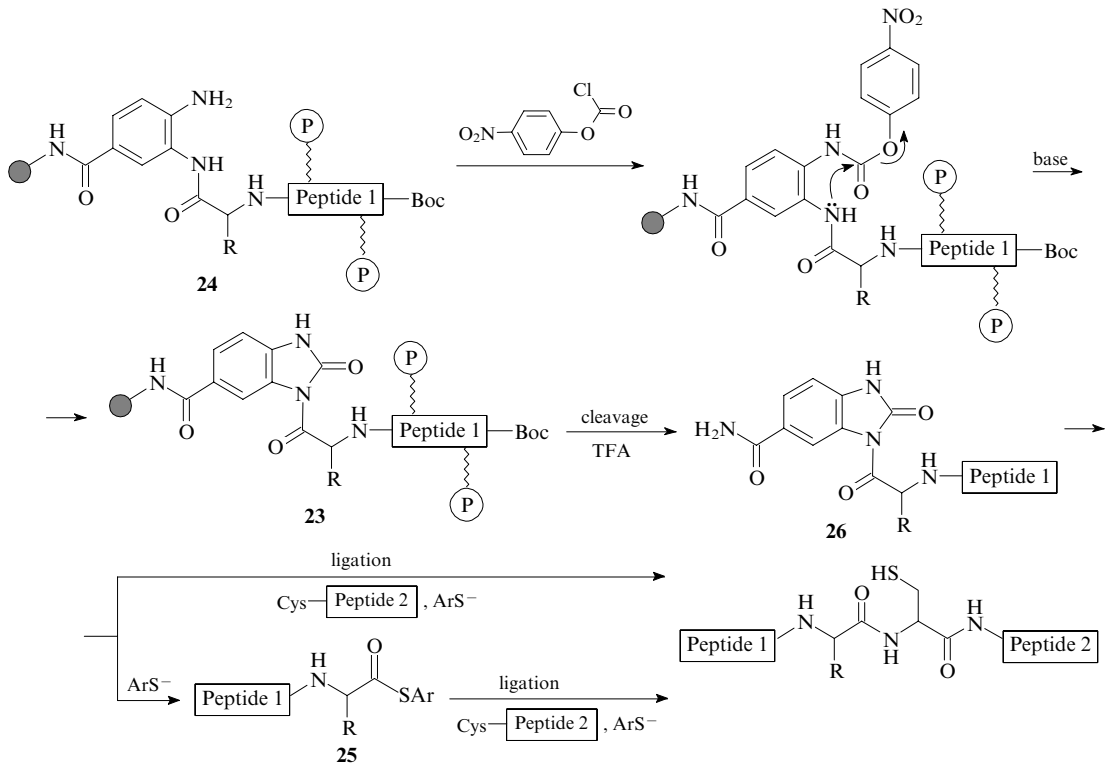
Fused compounds containing the *o*-diaminobenzene moiety also react with the carbonyl sources to give annulated benzimidazolones. For example, the annulation of 1,2-diaminobenzothiophene dihydrochloride (**27**) with urea affords benzo[*b*]thiophene[3,2-*e*]benzimidazolone (**28**) (Scheme 6).[58]

Mastalerz and Oppel[59] employed the reaction of hexaammonium triptycene hexachloride (**29**) with CDI to incorporate benzimidazolone units into a rigid D_{3h}-symmetric scaffold giving rise to triptycene tris(imidazolone) **30** (Scheme 7).[60]

II.3. Synthesis from *o*-nitroanilines

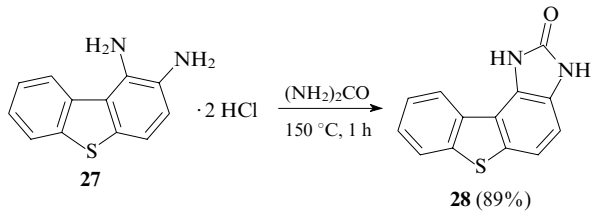
The synthesis of benzimidazol-2-ones from *o*-nitroanilines containing the secondary (**31a**, $R^3 \neq H$) or primary (**32a**,**b**, $R^3 = H$) amino group is performed as follows. First, a carbonyl-containing substituent is introduced at the amino group of the starting compound. In some cases, this step is followed by the one-step intramolecular reductive cyclization involving the amino group that formed (Scheme 8, Table 4). This procedure was used to synthesize benzimida-

Scheme 5



● is the Rink linker; (P) is a polymer; R = H, Alk, CH_2Ar; TFA is trifluoroacetic acid

Scheme 6

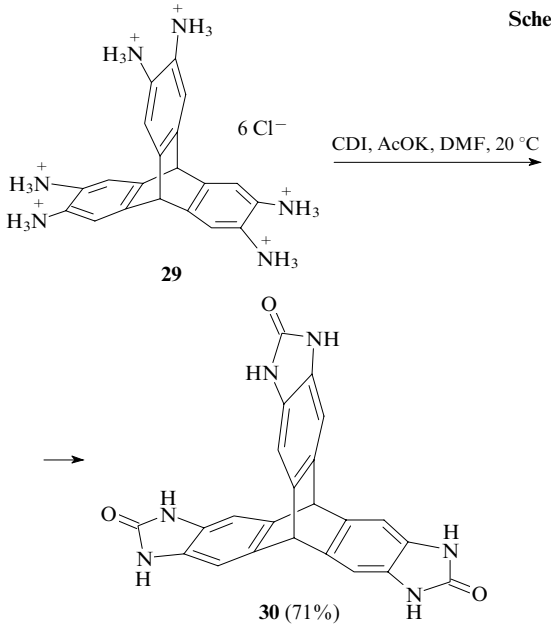


zol-2-one **22b**.[45] A similar approach was employed to prepare products **22c**,**d** containing the amidomethyl substituent at the nitrogen atom; this substituent was introduced in the final step of the process.[2]

The heating of four isomeric monoethoxycarbonylamino derivatives **33**–**36**, which are easily generated from 5-amino-4-carbamoyl-1-(2-nitrophenyl)-1*H*-1,2,3-triazole (**37**), under reflux in DMF for 4–5 h affords one and the same product — 1-(5-carbamoyl-1,2,3-triazol-4-yl)benzimidazolone **38** (Scheme 9).[61]

The formation of NH-triazoles **35** and **39** from compounds **34** and **40**, respectively, can be explained as follows: the reaction begins with the Dimroth rearrangement[62] giving intermediates **41** and **42** followed by their isomerization to tertiary amines (Scheme 10). The unusual

Scheme 7



N(1)–N(5)-ethoxycarbonyl shift is apparently attributed to the polar nature of the solvent.

Scheme 8

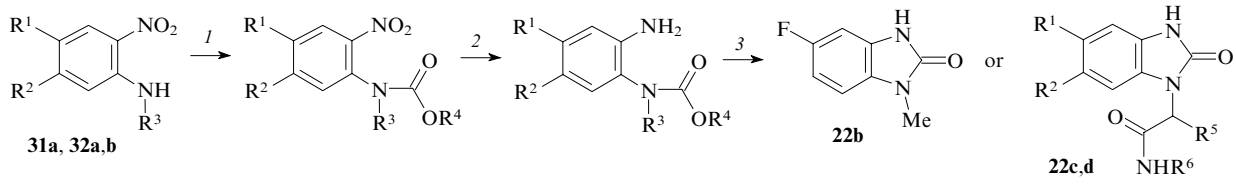
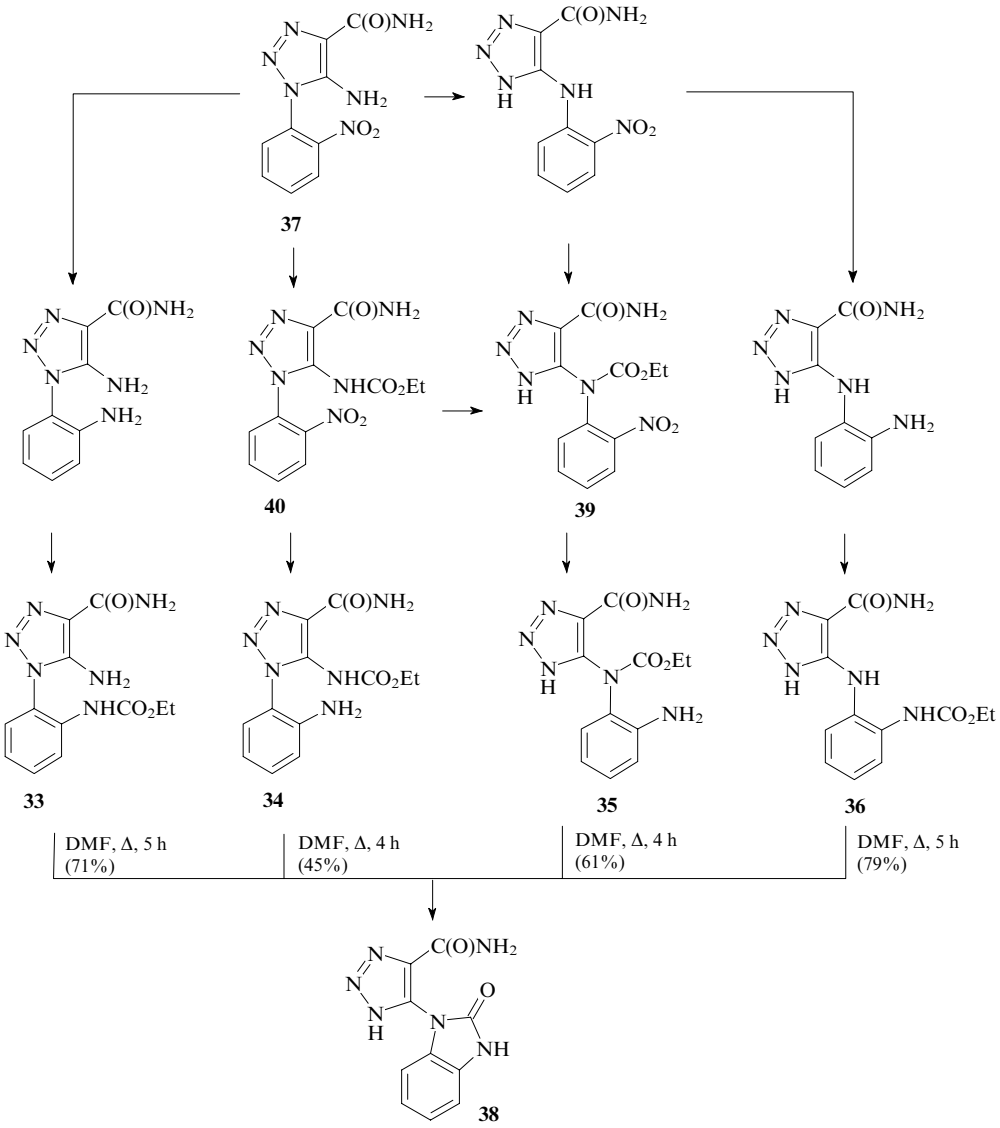


Table 4. Synthesis of benzimidazol-2-ones **22b – d** from *o*-nitroanilines **31a** and **32a**,**b** (see Scheme 8).

Substrate	Product **22**	R^1	R^2	R^3	R^4	R^5	R^6	Reagents and conditions	Yield (%)	Ref.
31a	**b**	F	H	Me	Bu^t	–	–	1) $(Boc)_2O$, TEA, DMAP, 2-methyltetrahydrofuran; 2) H_2, Pd/C, EtOH; 3) NaH, THF, DMF	99	45
32a	**c**	Cl	H	H	Me	Alk, Bn, Ar	Alk, Cy, Bn, $Ph(CH_2)_2$	1) $ClCO_2Me$; 2) Zn; 3) R^5CHO, R^6NC, THF, 20 °C; then TBD or K_2CO_3, MW	31 – 65	2
32b	**d**	H	F	H	Me	Ar, 1-(4-ClC_6H_4)-cycloprop-1-yl	Alk, Cy	1) $ClCO_2Me$; 2) Zn; 3) R^5CHO, R^6NC, THF, 20 °C; then TBD or K_2CO_3, MW	30 – 40	2

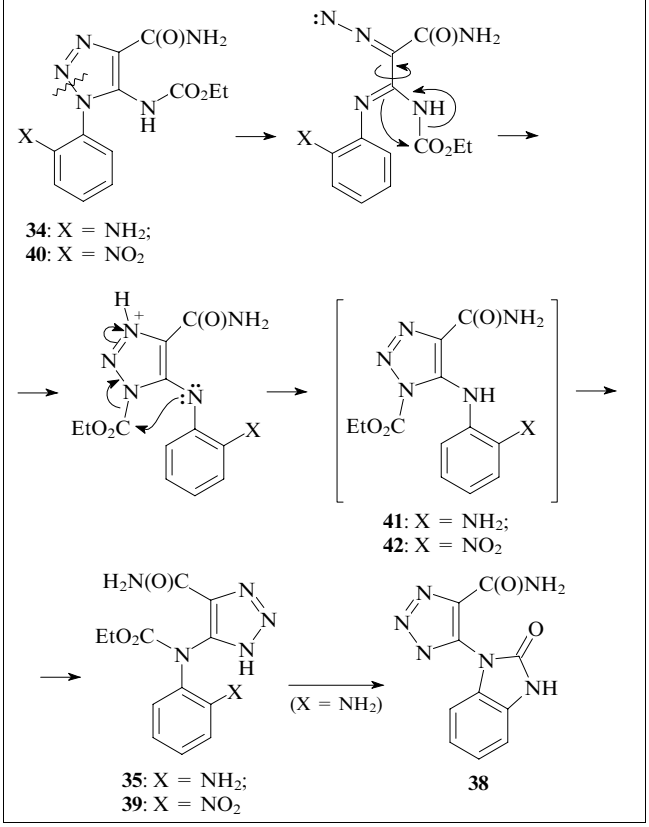
Note. DMAP is 4-dimethylaminopyridine, MW is microwave radiation, TBD is 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

Scheme 9

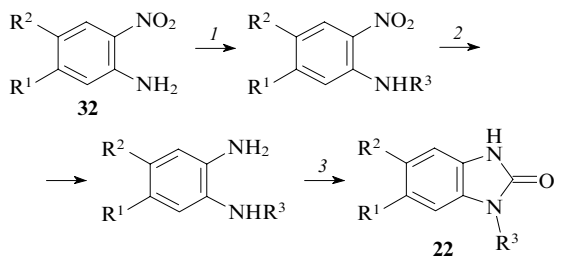


In other procedures, which utilize *o*-nitroanilines **32** as the starting compounds for the preparation of products **22**, the first step involves the reaction at the amino group (alkylation or acylation) followed by the two-step process, resulting in the reduction of the nitro group and the intermolecular ring closure (Scheme 11, Table 5).[63 – 66] The major requirement for the reactant utilized in intramolecular reductive cyclization is the presence of a good leaving group (usually, an alkoxy group) adjacent to the carbonyl function.

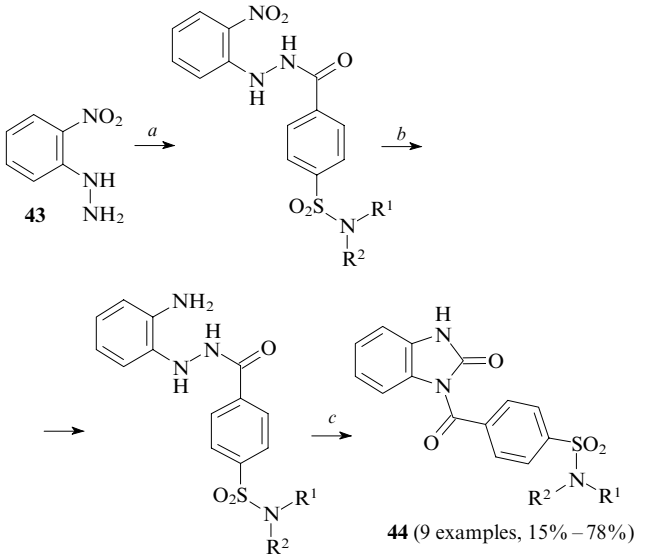
Scheme 10



Scheme 11



Scheme 12



(*a*) 3-$R^1R^2NSO_2C_6H_4C(O)Cl$, TEA, Et_2O; (*b*) H_2, Pd/C, MeOH;
(*c*) $ClCO_2Et$, PyH, Δ;
R^1 = H, Me, Et; R^2 = H, Me, Et, Pr^n, Pr^i, Bu^n, 2-Py

o-Nitrophenylhydrazine (**43**) was subjected to a similar series of transformations to prepare benzimidazolones **44** containing sulfonylamide substituents at the nitrogen atom (Scheme 12).[67] In the final cyclization step, ethyl chloroformate served as the carbonyl source.

The presence of more complex 3-(4-benzylpiperidin-1-yl)-prop-1- (**45a**) and 4-(4-benzylpiperidin-1-yl)but-1-ynyl (**45b**),[68] as well as 4-[3-(4-acetylpiperazin-1-yl)-3-oxoprop-1-enyl]-2-chlorophenylthiol (**46**)[69] pharmacophoric substituents in *o*-nitroanilines does not interfere with the preparation of the corresponding benzimidazol-2-one derivatives **47a**,**b** and **48** under standard conditions (Scheme 13).

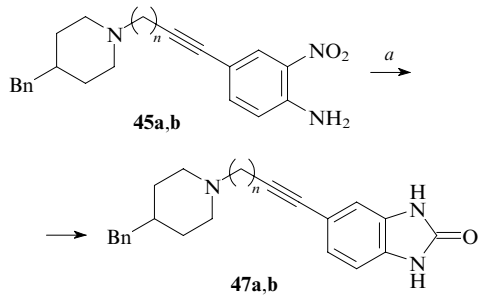
Apart from the above-mentioned sources of the carbonyl group, dimethyl carbonate (DMC) was used for the construction of benzimidazol-2-ones. The reaction of this compound with *o*-nitroaniline derivatives **32** proceeds in the presence of copper acetate as a non-toxic and cheap catalyst and polymethylhydrosiloxane (PMHS) as a reducing agent. A large series of N,N′-dimethylated benzimidazol-2-ones **49**

Table 5. Transformation of *o*-nitroanilines **32** into benzimidazol-2-ones (see Scheme 11).

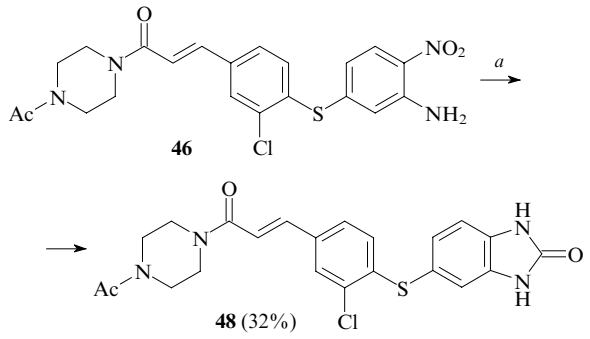
R^1	R^2	R^3	Reagents and conditions	Yield (%)	Ref.
Cl	H	$ArSO_2$	1) $ArSO_2Cl$, NaH, dioxane, 0 – 5 °C, 30 min; 2) Zn/HCl, EtOH, 80 °C; 3) 20% phosgene solution in PhMe, 2 M HCl, Δ	15 – 86	6, 63
Cl	H	R^4CH_2 (R^4 = Ar, Cy)	1) R^4CH_2Br, K_2CO_3, DMF, Δ, 2 h; 2) Zn/HCl, EtOH, 80 °C, 1 h; 3) 20% phosgene solution in PhMe, 2 M HCl, Δ, 4 h	45 – 91	64
H	Cl	2,6-$F_2C_6H_3CH_2$	1) 2,6-$F_2C_6H_3CH_2Br$, K_2CO_3, DMF, Δ, 2 h; 2) Zn/HCl, EtOH, 80 °C, 1 h; 3) 20% phosgene solution in PhMe, 2 M HCl, Δ, 4 h	76	64
H	EtO_2C	Pr^i	1) $NaBH_4$, PTSA, Me_2CO, THF; 2) $Na_2S_2O_4$, EtOH, H_2O, Δ; 3) triphosgene, DCM, 20 °C	–	65
H	EtO_2C	Pr^iO_2C	1) $Pr^iOC(O)Cl$, TEA, DCM; 2) $Na_2S_2O_4$, EtOH, H_2O, Δ; 3) CDI, THF	–	65
H	Me	Pr^i	1) Pr^iI, K_2CO_3, DMF; 2) $Na_2S_2O_4$, EtOH, H_2O; 3) CDI, THF	–	66

Note. PTSA is *p*-toluenesulfonic acid.

Scheme 13



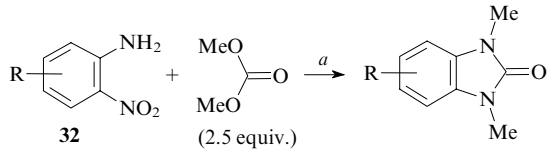
(*a*) 1) Fe/H$^+$, EtOH, Δ; 2) CDI, THF;
n = 1 (**a**, 65% yield), 2 (**b**, 61%)



(*a*) 1) $SnCl_2$, EtOH, Δ; 2) CDI, THF, Δ

(12 examples) were prepared in good yields by one-pot tandem reactions (Scheme 14).[70]

Scheme 14



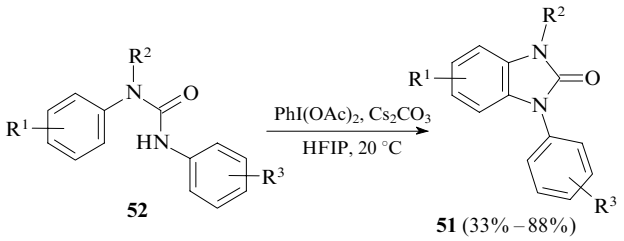
(*a*) $Cu(OAc)_2 \cdot H_2O$ (5 mol.%), PMHS (2 equiv.), 100 °C, 20 h;
R = H, Alk, OAlk, Hal, CN, NO_2, NH_2, Bz (at different positions)

The proposed mechanism for the formation of benzimidazol-2-one **49a** (R = H) involves the initial transformation of *o*-nitroaniline (**32c**) into *o*-diaminobenzene (**19b**) using a reducing agent (PMHS) and a copper ion — an unprecedented reduction catalytic system (Scheme 15). Apparently, copper hydride is generated as a catalytically active species from PMHS and copper acetate,[71] like in the synthesis of 1,3-dimethylbenzimidazol-2(3*H*)-ones **49** from *o*-diaminobenzenes.[72] Besides, in this process Cu^{2+} acts as a Lewis acid by enhancing the polarization of the carbonyl group of DMC, resulting in the activation of the carboxymethylation (like in phosgene) and methylation (like in methyl halides and dimethyl sulfate)[73, 74] activity of this reagent. The carbonylation of compound **19b** with DMC produces active intermediate carbamate ester **50**. Then the intramolecular nucleophilic cyclization in the presence of a copper complex with DMC affords monomethylated compound **22e**,[73] which is further methylated with dimethyl carbonate in the presence of a copper catalyst to form dimethylated product **49a**.

II.4. Synthesis from N,N′-disubstituted ureas

Recently, Yu *et al.*[75] reported a radically new approach to the synthesis of N,N′-disubstituted benzimidazol-2-ones **51** by the direct intramolecular oxidative C – H-amidation of *N*,*N*′-diarylureas **52** using cheap $PhI(OAc)_2$ as an oxidizing agent in the absence of metal-complex catalysts in 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) (26 examples, Scheme 16). This method can be used to introduce various substituents at nitrogen atoms and into the benzene ring of the benzimidazolone scaffold. The drawback of this approach is that it is difficult to prepare starting *N*,*N*′-diarylureas containing particular substituents.

Scheme 16



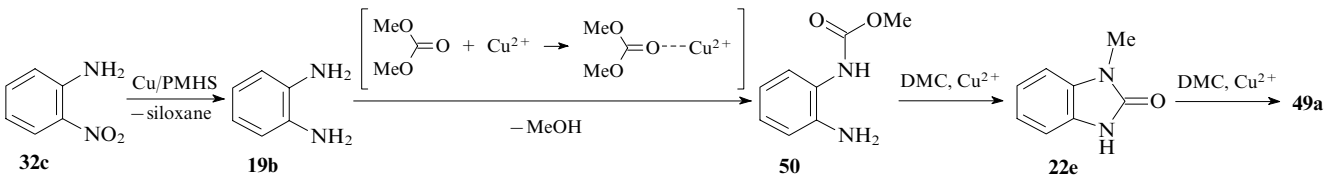
R^1 = H, Hal; R^2 = Alk, cyclo-Alk, Ar, CH_2Ar;
R^3 = H, Me, CO_2Alk, Hal (R^1 and R^3 at different positions)

The direct intramolecular oxidative cyclization using 3-aryl-1-(benzyloxy)ureas **52**, which are generated from phenyl isocyanates **53** or anilines **18**, instead of *N*,*N*′-diarylureas in the presence of $Pb(OAc)_4$ (Ref. 76) affords benzimidazol-2-one derivatives **54** (28 examples, Scheme 17).[7] The subsequent removal of the benzyl protecting group by catalytic hydrogenation gives the target 1-hydroxy-1*H*-benzimidazolones **55** — D-amino acid oxidase inhibitors.

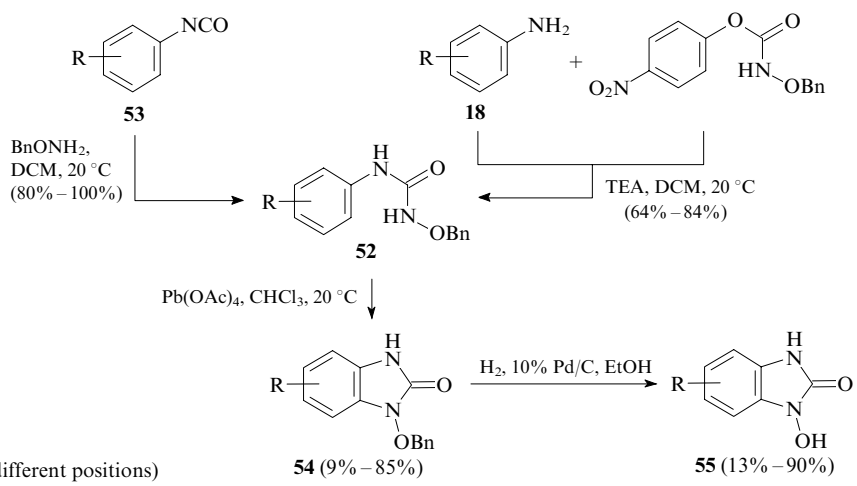
1-Alkoxybenzimidazol-2-ones **56** were synthesized also by the cyclization of *N*-alkoxy-*N*-chloro-*N*′-arylureas **57**, which contain the nitro group or the chlorine atom in the *ortho* and *para* positions of the aryl substituent, with sodium acetate (Scheme 18).[77]

The treatment of diazenes **58a – e** with zirconium tetrachloride in dichloromethane at room temperature leads to intramolecular cyclization giving the corresponding *N*-alkoxycarbonylaminobenzimidazol-2-ones **59a – e** (Scheme 19).[78] It should be noted that product **59e** was obtained as the only regioisomer when using diazene **58e** as the starting compound. In the case of diazene **58f** (R^1 = H,

Scheme 15

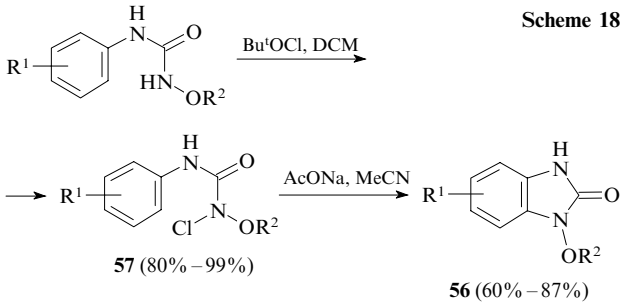


Scheme 17



R = H, Alk, OAlk, Hal (at different positions)

Scheme 18



R^1 = H, 2-NO_2, 4-NO_2, 2-Cl, 4-Cl;
R^2 = Et, Pr^i, CMe_2CO_2Me, $(CH_2)_2Ph$

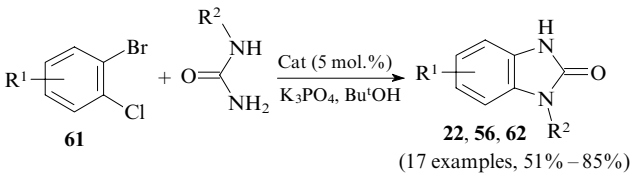
R^2 = OMe, R^3 = Me), the intermolecular rather than intramolecular reaction presumably proceeds: the first step affords benzimidazol-2-one **59f** (sufficiently activated due to the presence of the electron-donating methoxy group in the benzene ring), which then reacts with a molecule of the starting diazene **58f** to form benzimidazol-2-one **60**. Attempts to isolate benzimidazol-2-one **59f** in the individual state failed.

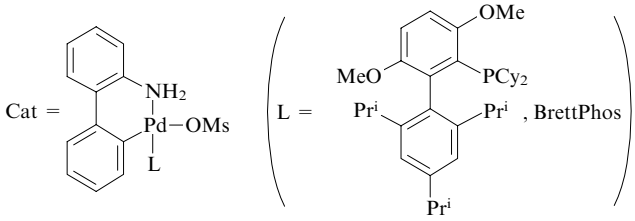
III. Methods based on halobenzenes

III.1. Synthesis from *o*-dihalobenzenes

The synthesis of benzimidazol-2-ones **22** (R^2 = Alk), **56** (R^2 = OAlk) and **62** (R^2 = Hal, CN, *etc.*) using *o*-dihalo-

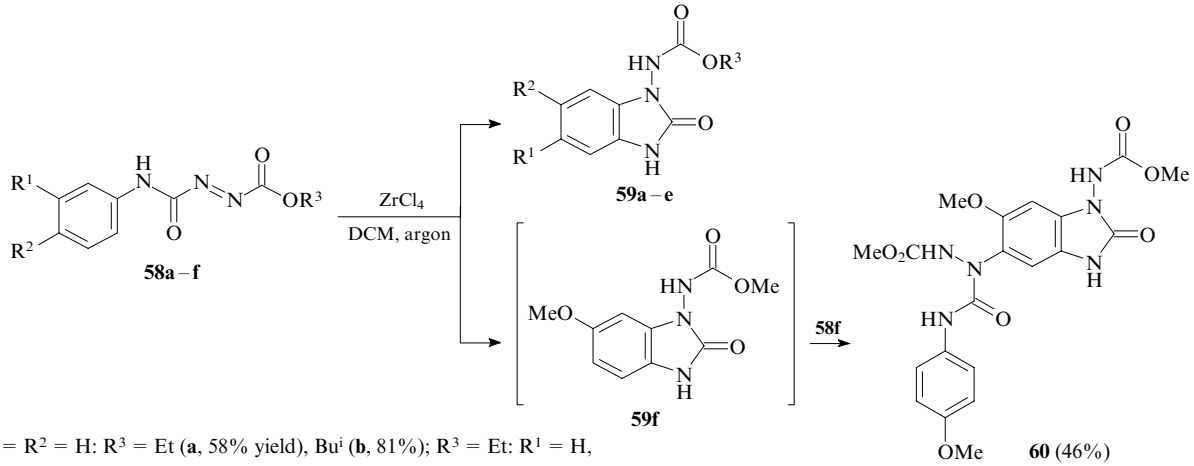
Scheme 20





R^1 = Alk, Ar (at different positions); R^2 = Alk, Hal, OAlk, CN, NHPiv, C(O)[$N(CH_2)_4$-cyclo]; Ms = SO_2Me, Piv = C(O)Bu^t

Scheme 19



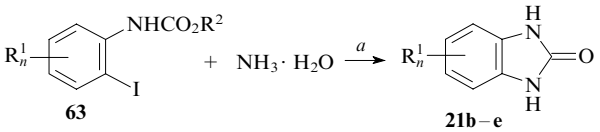
R^1 = R^2 = H: R^3 = Et (**a**, 58% yield), Bu^i (**b**, 81%); R^3 = Et: R^1 = H, R^2 = Me (**c**, 58%); R^1 = H, R^2 = F (**d**, 74%); R^1 = Cl, R^2 = H (**e**, 62%); R^1 = H, R^2 = OMe, R^3 = Me (**f**)

benzenes **61** as the starting compounds is based on two discrete palladium-catalyzed reactions giving rise to two C – N bonds and is characterized by high regioselectivity (Scheme 20).[79] This is due to chemoselectivity of two radically different catalytic processes, namely, the oxidative addition of the Pd catalyst to the Ar – Br bond in the presence of the Ar – Cl bond, which is favourable for the formation of the C – N bond with NH_2 nitrogen atoms of urea. The advantages of this method are that it is a one-step process, which utilizes the commercially available Pd catalyst and simple starting compounds, and that it provides a selective route to a number of benzimidazol-2-one derivatives, including those having a complex structure.

III.2. Synthesis from *o*-haloarylcarbamates

The essence of this approach is that the C – N bond is formed in the first step *via* the reaction of aqueous ammonia with 2-iodophenylcarbamates **63** (Scheme 21)[80] or of

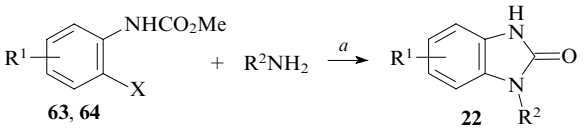
Scheme 21



(*a*) CuI – L-proline, NaOH, DMSO, 20 °C → 130 °C;
R^1_n = 5-Ac (**b**, 72% yield), 5-NO_2 (**c**, 78%), 5-C(O)NHPr^n (**d**, 74%), 4,6-Me_2 (**e**, 76%); R^2 = Alk

amines with methyl 2-haloarylcarbamates **63** and **64** (Scheme 22)[81] in the presence of a base using the

Scheme 22



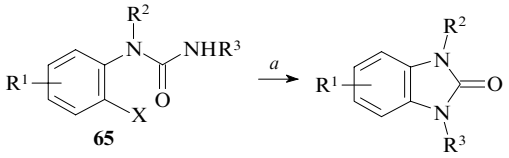
(*a*) CuI – L-proline, K_3PO_4, DMSO, 50 °C → 130 °C;
for X = Br (**64**, 9 examples, 62% – 82% yield): R^1 = H, Me, OMe, Ac, CO_2Me, C(O)NHPr^n, NO_2, CH_2OTBS (at different positions); R^2 = Alk, All, Bn, CH_2CO_2H, CH_2Het; for X = I (**63**, 7 examples, 66% – 85% yield): R^1 = H, OMe, Ac, Br (at different positions); R^2 = Alk, All, Bn, CyC_6H_4, cyclo-[$CH(CH_2CH_2)_2NBoc$];
TBS = $SiMe_2Bu^t$

CuI – L-proline system as a catalyst followed by the intramolecular amidation involving the introduced amino group. Products **21b – e** and **22** were synthesized by this method in good yields.

III.3. Synthesis from *o*-haloarylureas

The intramolecular closure of the imidazolone ring in compounds **65** involving the terminal nitrogen atom of the urea moiety and the halogen atom in 2-position (Scheme 23, Table 6) was described in publications.[82 – 86]

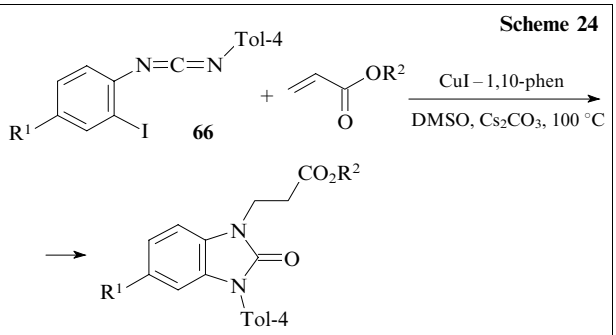
Scheme 23



III.4. Synthesis from *o*-iodophenylcarbodiimides

The reaction of *o*-iodoarylcarbodiimides **66** with α,β-unsaturated esters in the presence of CuI as a catalyst and 1,10-phenanthroline (phen) as a ligand produced 1,3-disubstituted benzimidazolone derivatives **67**.[87] This reaction performed in a system additionally containing Cs_2CO_3 affords target products in higher yields (Scheme 24).[87]

Scheme 24



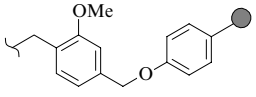
67 (5 examples, 62% – 70%)

R^1 = H, Me, F; R^2 = Me, Et, Bu^n; Tol = C_6H_4Me

III.5. Synthesis from *o*-halonitrobenzenes

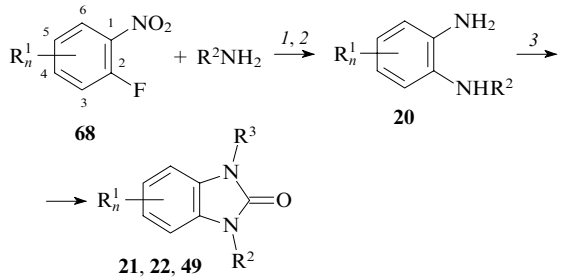
One of convenient methods for the synthesis of benzimidazol-2-ones is based on the use of *o*-halonitroben-

Table 6. Transformation of *o*-haloarylureas **65** into benzimidazol-2-ones (see Scheme 23).

R^1	R^2	R^3	X	Reagents and conditions (*a*)	Yield (%)	Ref.
H, Me, OMe, CF_3, F, NO_2	Alk, CH_2Ar	H	Br	CuI, H_2O, TMEDA, 120°C	51 – 92	82
H, F, Me	Bn, Ar	H	Cl	$Pd(OAc)_2$ (1 mol.%), X-Phos (3 mol.%), $NaHCO_3$ (300 mol.%), Pr^{i}OH, 83 °C	91 – 92	83
H, Hal, CF_3, OMe, CO_2Me	H	Alk, Ar, Het	Br, I	CuI, DBU, DMSO, MW, 120 °C	54 – 95	84
H, Cl, Br	H, Me, Bn, PMB, C_6H_4Br-4	Ar	F, Cl, Br, I	KOH (2 equiv.), DMSO, 40 °C	–	85
Cl, F, CF_3		H	Cl	$Pd(OAc)_2$, X-Phos, $NaHCO_3$, THF	–	86

Note. TMEDA is *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, X-Phos is 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene, PMB is *p*-methoxybenzyl.

Scheme 25



Scheme 26

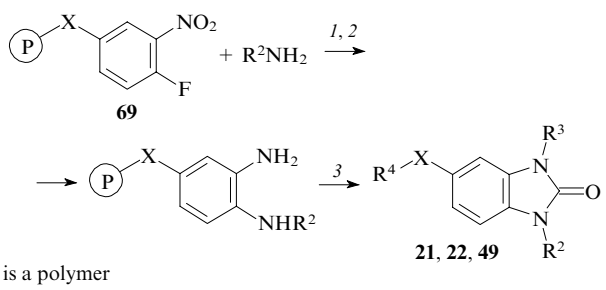
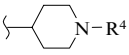
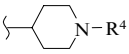
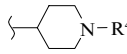
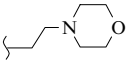
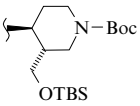
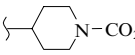
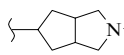
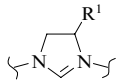
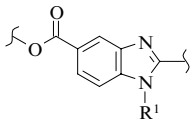


Table 7. Transformation of *o*-fluoronitrobenzenes **68** into benzimidazol-2-ones (see Scheme 25).

R^1_n	R^2	R^3	Reagents and conditions	Yield (%)	Ref.
H, or 4-F, or 5-F	Alk, cyclo-Alk	H	1) DMF, N_2, 20 °C or $PhNH_2$, Bu^tOK, DMF, N_2, 20 °C (50% – 80% yield); 2) $NaBH_4$, Pd/C, MeOH, THF or H_2 (~2 atm), Pd/C, MeOH, 20 °C (40% – 90%); 3) CDI, THF, N_2, 20 °C	40 – 80	88
4-F,5-NHPh (see [a])	$CH_2C_6H_{11}$-cyclo	H	1) DMF, 20 °C, 14 h (90%); then *N*-methylpiperazine, Hünig's base, DMF, 100 °C, 24 h (64%); 2) H_2, 10% Pd/C, EtOAc, 20 °C, 16 h (75%); 3) CDI, THF, 16 h	65	10
4-OMe	All	H	1) 20 °C, 1.5 h (97%); 2) Fe, NH_4Cl, EtOH, H_2O, 100 °C, 22 h (83%); 3) CDI, THF, 50 °C, 2 h	45	28
3-F	 (see [b])	H	1) KI, Na_2CO_3, DMF, 50 °C; 2) H_2, 5% Pd/C, MeOH, 20 °C; 3) CDI, MeCN, 40 °C; then NaOH, EtOH, Δ	42	29
4-Me	 (see [b])	H	1) KI, Na_2CO_3, DMF, 50 °C, 15 h (84%); 2) H_2, 5% Pd/C, MeOH (100%); 3) CDI, MeCN, 40 °C, 36 h (76%); then 2.5 M NaOH (aq.), Δ, 15 h	100	89
5-F,4-Me	 (see [a])	H	1) DIEA, DMF, 80 °C, 38 h (64%); 2) $N_2H_4 \cdot H_2O$, Ni-Ra, EtOH, 45 °C, 50 min (92%); 3) CDI, THF, 45 °C, 80 min (77%); then 20% TFA in DCM, 20 °C, 1 h	94	89
H		H	1) K_2CO_3, THF, 20 °C, 20 h (97%); 2) H_2 (4 atm), Pd/C, THF, 20 °C, 5 h; 3) CDI, THF, 20 °C, 20 h	83	3
H	C_6H_4Cl-3	Me	1) KF, 180 °C, 44 h (97%); 2) HCl, $SnCl_2 \cdot 2H_2O$, EtOH, 0 – 20 °C (97%); 3) CDI, DCM, Δ, 2 h; then EtOH, Δ, 2 h (73%); then MeI, NaH, DMF, 20 °C, 1 h	94	90
5-CO_2Me	Pr^i	Me	1) DCM, 22 °C, 2 h (91%); 2) H_2, Pd/C, 22 °C, 1 h (100%); 3) phosgene, PhMe, DCM, 20 °C, 16 h	56	91
H or 5-CN	Ar	H	1) K_2CO_3, DMA, 120 °C (26% – 46%); 2) H_2, Pd/C; 3) phosgene	31 – 66	92
H		H	1) Bu^nOH, Na_2CO_3; 2) $N_2H_4 \cdot H_2O$, Ni-Ra, EtOH; 3) DSC, DMF	91	93
5-CO_2Me	Alk, cyclo-Alk, Ar	see [d]	1) DMF, 20 °C; then PS trisamine, DMF, 50 °C; 2) H_2, $Pd(OH)_2$, DMF; 3) triphosgene, $CHCl_3$, 20 °C; then PS trisamine, $CHCl_3$, 30 °C; then R^5Br, PS-BEMP, DMF, $CHCl_3$; then PS-MTU, DMF, $CHCl_3$, 50 °C (see [e])	42 – 64	94
4-F, or 5-F, or 3-F		H	1) Na_2CO_3, KI, CyOH, MW, 180 °C, 10 min; 2) Zn, 1 M HCl, MeOH; 3) triphosgene, TEA, THF, 20 °C, 2 h	50 – 60	95, 96
H	 (see [c])	H	1) Na_2CO_3, KI, CyOH, MW, 180 °C, 10 min (90%); 2) Zn, 1 M HCl, MeOH; 3) triphosgene, TEA, THF, 20 °C, 2 h; then 4 M HCl, dioxane, 20 °C	82	97

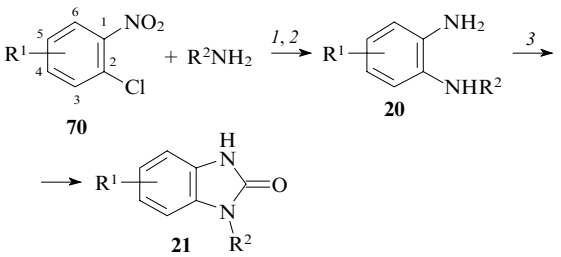
Note. The positions of the substituents R^1_n in the substrate are given; Hünig's bases are sterically hindered amines [dicyclohexylethylamine and diisopropylethylamine (DIEA)]; Ni-Ra is Raney nickel. [a] In the product, the 4-methylpiperazine group is present instead of the fluorine atom in 5-position; [b] in compounds **20** and **68**, $R^4 = CO_2Et$; in the product, $R^4 = H$; [c] in compounds **20** and **68**, R^4 = Boc; in the product, $R^4 = H$. [d] $R^3 = CH_2Alk$, CH_2Ar, CH_2Het, CH_2CO_2Et, $CH_2C(O)Het$; [e] PS trisamine, PS-BEMP, PS-MTU is polystyrene modified with amine, phosphazene base and methylurea, respectively.

Table 8. Transformation of immobilized *o*-fluoronitrobenzenes **69** into benzimidazol-2-ones (see Scheme 26).

Polymer	X	R^2	R^3	R^4	Reagents and conditions	Yield (%)	Ref.
MBHA-Resin	 [R^1 = Alk, Bn, $(CH_2)_2Ph$]	Alk, Bn	All, Ar	H	1) DIEA, DMF, 20 °C, 20 h; 2) $SnCl_2 \cdot 2H_2O$, DMF, 20 °C, 14 h; 3) CDI, 20 °C; then R^3Hal (Hal = I, Br), DBU, THF; then HF, anisole, 0 °C, 7 h	60 – 72	98
Poly-ethylene-glycol (PEG)	 [R^1 = cyclo-C_5H_9, $(CH_2)_2OMe$]	Alk, cyclo-Alk, CH_2Het, CH_2Ar	H	Me	1) DCM, 20 °C, 12 h; 2) Zn, HCO_2NH_4, MeOH, 20 °C, 30 min; 3) triphosgene, DCM, 20 °C, 12 h; then MeOH, KCN	72 – 84	99
		Alk, cyclo-C_5H_9	Alk, Ar	Me	1) DCM, 20 °C, 12 h; 2) Zn, HCO_2NH_4, MeOH, 20 °C, 30 min; 3) triphosgene, DCM, 20 °C, 12 h; then R^3Hal (Hal = I, Br), NaH, DCM, 20 °C, 12 h; then MeOH, KCN	64 – 73	99
U-ROMP-Resin		Bu^n	H	Me	1) TEA, DCM, 20 °C, 3 h; 2) $SnCl_2 \cdot 2H_2O$, THF, 20 °C, 36 h; 3) triphosgene, TEA, DCM, 20 °C, 4 h; then 0.5 M NaOMe in MeOH, THF, 50 °C, 90 min	82	100
Wang resin		Cy, Bn	H	H	1) DMSO, 20 °C, 24 h; 2) $SnCl_2 \cdot 2H_2O$, DMF, 40 °C, 12 h; 3) ethyl cyanoformate, THF, DCM, DMF, 20 °C, 24 h; then TFA, DCM, 20 °C, 2 h	86	101

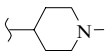
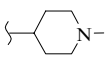
zenes,[3, 10, 28, 29, 88 – 105] usually 2-fluoro derivatives (Schemes 25 and 26; Tables 7 and 8) and more rarely 2-chloro derivatives (Scheme 27, Table 9), as the starting compounds.[102 – 104] The first step involves the nucleophilic displacement (*via* the S_NAr mechanism) of the halogen atom with the amino group followed by the reduction of the nitro group to form N-substituted *o*-diaminobenzenes. In the third step, the cyclization with carbonyl sources takes place. This method is applicable to both usual *o*-fluoronitrobenzenes **68** containing different substituents in the benzene ring (see Scheme 25) and their immobilized analogues **69** (see Scheme 26) and was employed to synthesize a wide range of benzimidazol-2-ones containing free NH groups (**21**), as well as benzimidazol-2-ones substituted at one (**22**) or both (**49**) nitrogen atoms. In the case of *o*-chloronitrobenzenes **70**, the reaction affords products in rather low yields (see Scheme 27 and Table 9).

Scheme 27



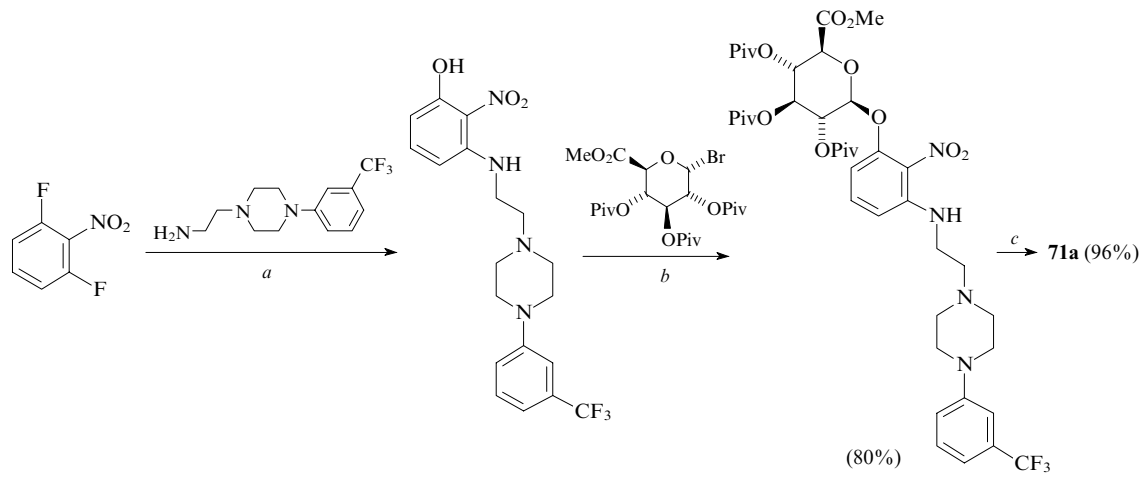
The advantage of this approach is that it can be employed to synthesize any N-substituted benzimidazol-2-one due to the ability of the halogen atom to be involved in

Table 9. Transformation of *o*-chloronitrobenzenes **70** into benzimidazol-2-ones (see Scheme 27).

R^1	R^2	Reagents and conditions	Yield (%)	Ref.
5-CO_2Me	Alk, cyclo-Alk, Bn, Ph	1) AcONa, MeCN, H_2O, Δ, 17 – 24 h (for alkylamines); or DIEA, 70 °C, MeOH, DMF, Δ, 18 h (for cycloalkylamines); or DMSO (DMF), 8 h (for aniline and benzylamine); 2) $Pd(OH)_2$, MeOH, 20 °C, 5 h; 3) CDI, dioxane (anh.), 20 °C, 24 h	81	102
5-OPh	CH_2Cy	1) Hünig's base, DMF, 100 °C, 24 h; 2) H_2, 10% Pd/C, EtOAc, 20 °C, 16 h; 3) CDI, THF, 12 h	78	10
H	 (see [a])	1) KI, Na_2CO_3, CyOH, MW, 180 °C, 10 min; 2) Zn, 1 M HCl, MeOH, 50 °C; 3) CDI, MeCN; then 1 M NaOH, 100 °C	–	103
4-Me	 (see [b])	1) K_2CO_3, DMF, 70 °C; 2) Fe, HCl (conc.), EtOH, Δ, 3.5 h; 3) triphosgene, AcOEt, 20 °C; then Pd/C, HCO_2H, MeOH, Δ	25	104
H	$(CH_2)_2NHR^3$ (see [c])	1) K_2CO_3, DMF, 70 °C; 2) EtOH, 10% Pd/C, HCO_2NH_4, −70 °C; 3) triphosgene, DIEA, AcOEt, 0 °C; then TFA, DCM	20	104

Note. The position of the substituent R^1 is given for the starting compound. [a] In compounds **20** and **70**, R^3 = CO_2Et; in the product, R^3 = H; [b] in compounds **20** and **70**, R^3 = Bn; in the product, R^3 = H; [c] in compounds **20** and **70** R^3 = Boc; in the product, R^3 = H.

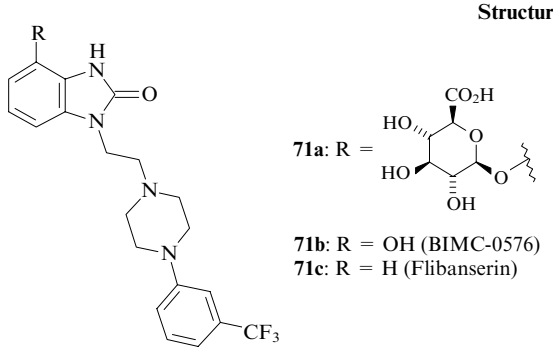
Scheme 28



(*a*) 1) 45 °C, 1 h; 2) $MeSO_2(CH_2)_2OH$, NaH, DMSO, 0 °C, 1 h; (*b*) Ag_2CO_3, HMTTA, MeCN; (*c*) 1) H_2, Pd/C; 2) $Cl_3C(O)CO_2CCl_3$, TEA; 3) LiOH; HMTTA is 1,1,4,7,10,10-hexamethyltriethylenetetramine

S_NAr reactions with virtually all amines. An example is the unique synthesis of glucuronide **71a** (Scheme 28).[105]

Structures 71



71a: R =

71b: R = OH (BIMC-0576)
71c: R = H (Flibanserin)

This compound is an analogue of hydroxy derivative **71b** (BIMC-0576) — a metabolite of the antidepressant Flibanserin (**71c**).

IV. Methods based on rearrangements of heterocyclic systems

IV.1. Transformations of benzodiazepinones and benzodiazepinediones

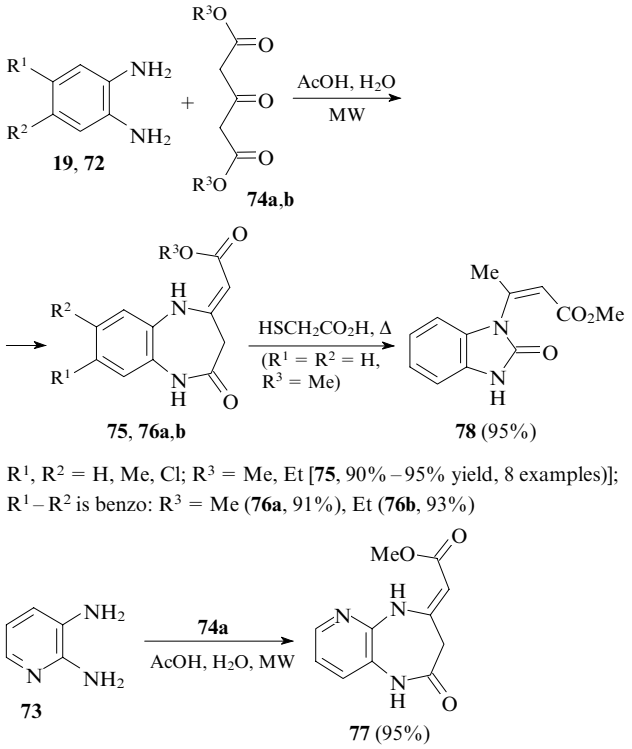
IV.1.a. Benzodiazepinones

Microwave-assisted acid-catalyzed reactions of *o*-diaminobenzenes **19** (R^1, R^2 = H, Me, Cl) and their naphtho (R^1–R^2 are benzo, **72**) and pyrido analogues (**73**) with acetonedicarboxylates **74a**,**b** [R^3 = Me (**a**), Et (**b**)] produce 1,5-benzo- (**75**), naphtho- (**76a**,**b**) and pyridodiazepines (**77**) (Scheme 29).[106] Diazepine **75a** (R^1 = R^2 = H, R^3 = Me) undergoes a rearrangement upon heating under reflux in DMF in the presence of thioglycolic acid to give the corresponding benzimidazolone derivative **78**. In all cases, the reactions afford target products in quantitative yield.

The benzodiazepinone system can be formed in the course of the reaction. Thus, the reaction of 3-(dimethylaminomethylene)furo[2,3-*b*]quinoxalin-2(3*H*)-one (**79**) with *o*-diaminobenzene dihydrochloride in AcOH produces chloride **80** (Scheme 30).[107,108] The formation of this product can be attributed to the attack of the amino group of *o*-diaminobenzene on the activated carbon atom of the *N,N*-dimethylaminomethylene moiety of furo[2,3-*b*]quinoxalin-2-one hydrochloride **81** giving rise to intermediate **82.** The latter undergoes intramolecular ring closure and opening through the attachment of the nitrogen atom of the second amino group of *o*-diaminobenzene to the carbonyl group of the furan ring, resulting in the cleavage of the C–O bond and the formation of intermediate **83**. 1,5-Benzodiazepine system **83** is further transformed into final product **80**.

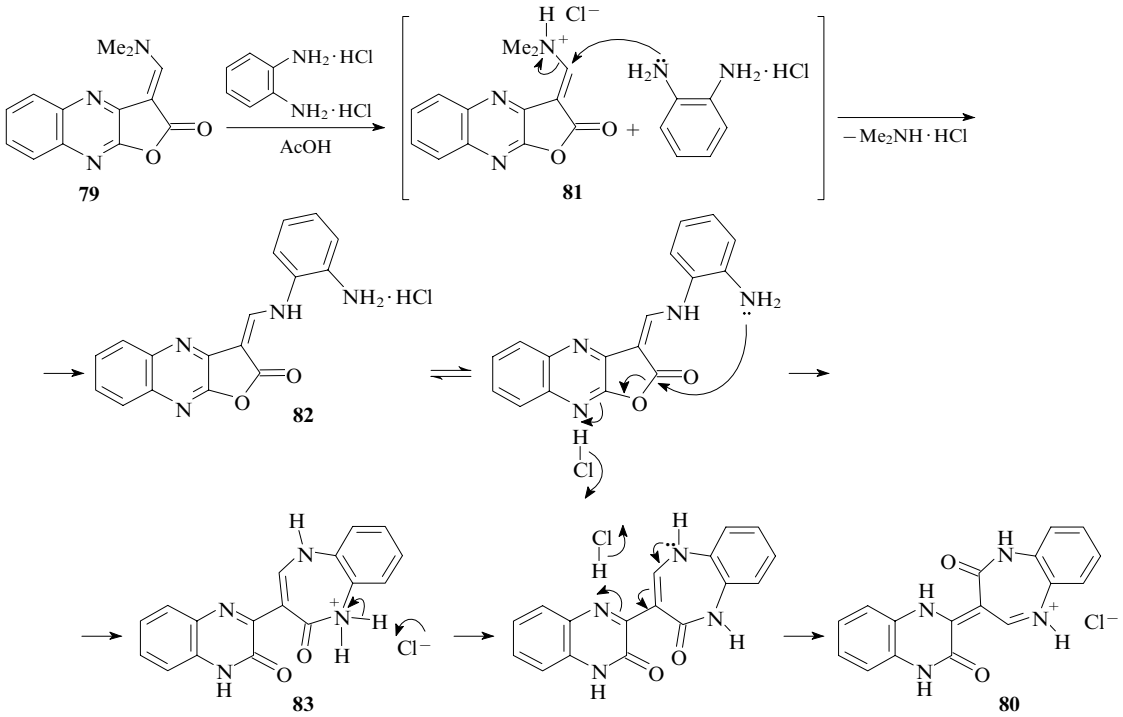
An alternative mechanism for the formation of benzodiazepine **80** involves the amidation of the carbonyl carbon atom of compound **79** with *o*-diaminobenzene dihydrochloride giving amide **84**. The subsequent intramolecular

Scheme 29

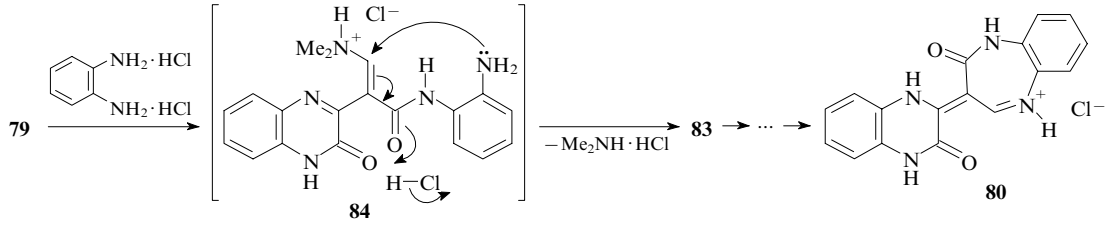


R^1, R^2 = H, Me, Cl; R^3 = Me, Et [**75**, 90%–95% yield, 8 examples)]; R^1–R^2 is benzo: R^3 = Me (**76a**, 91%), Et (**76b**, 93%)

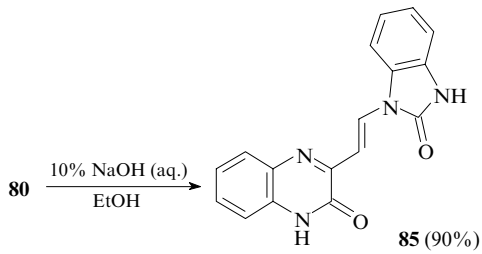
Scheme 30



Scheme 31



Scheme 32



Michael addition of this mono-N-acylated diaminobenzene affords 1,5-benzodiazepine system **83** (Scheme 31).[107, 108]

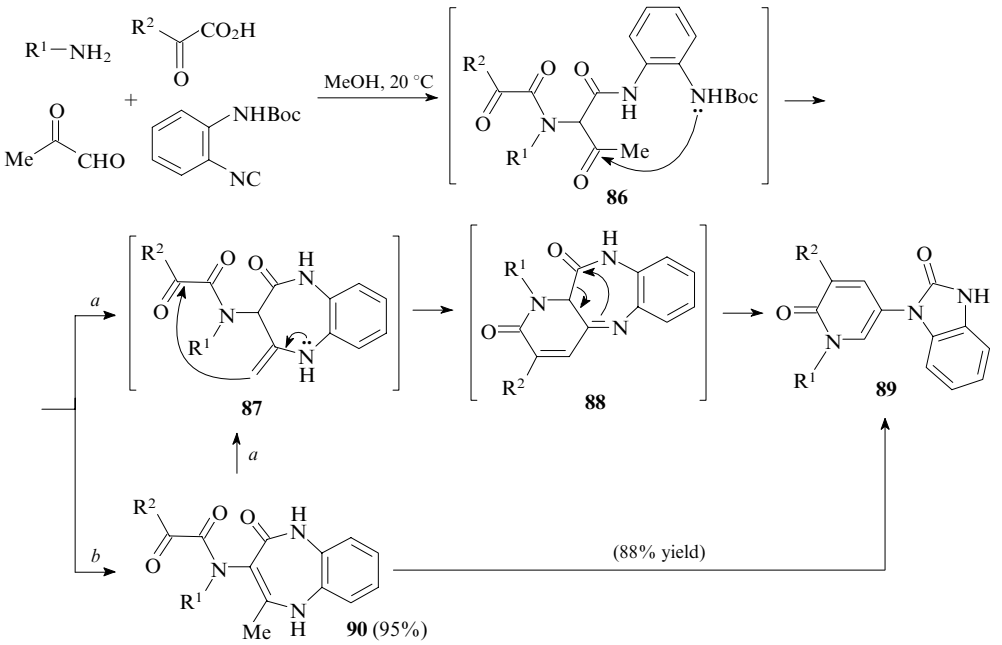
The treatment of benzodiazepine **80** with a 10% aqueous NaOH solution in EtOH produces 3-[2-(benzimidazol-2-on-1-yl)vinyl]-1*H*-quinoxalin-2-one (**85**) in high yield (Scheme 32).[107, 108]

o-*N*-Boc-Phenylisonitriles containing an additionally protected amino group[109] were used in the Ugi multicomponent reaction involving pyruvic aldehyde (2-oxopropanal), derivatives of glyoxalic acid and primary amines to prepare compounds **86**, which can be easily utilized in subsequent transformations (Scheme 33).[110, 111] The intramolecular attack of the aniline amino group on the carbonyl group (of the pyruvic aldehyde residue) in the presence of 10% trifluoroacetic acid in dichloroethane resulted in the transformation of compounds **86** into intermediates **87**. The acid-catalyzed aldol condensation (in the case under consideration, the imino-aldol process)[112] involving these intermediates provides an unprecedented route to tricyclic intermediate **88** containing the benzodiazepine moiety. Under the reaction conditions, the latter can be rearranged to form heterocyclic system **89** (7 examples, 47% – 58% yield) containing pyridone and benzimidazolone moieties. At lower temperature (80 °C instead of 120 °C), compound **86** (R^1 = C_6H_4Br-3, R^2 = $CH_2C_6H_4F$-4) is transformed into plausible kinetic product **90** in nearly quantitative yield.

IV.1.b. 1,5-Benzodiazepine-2,4-diones

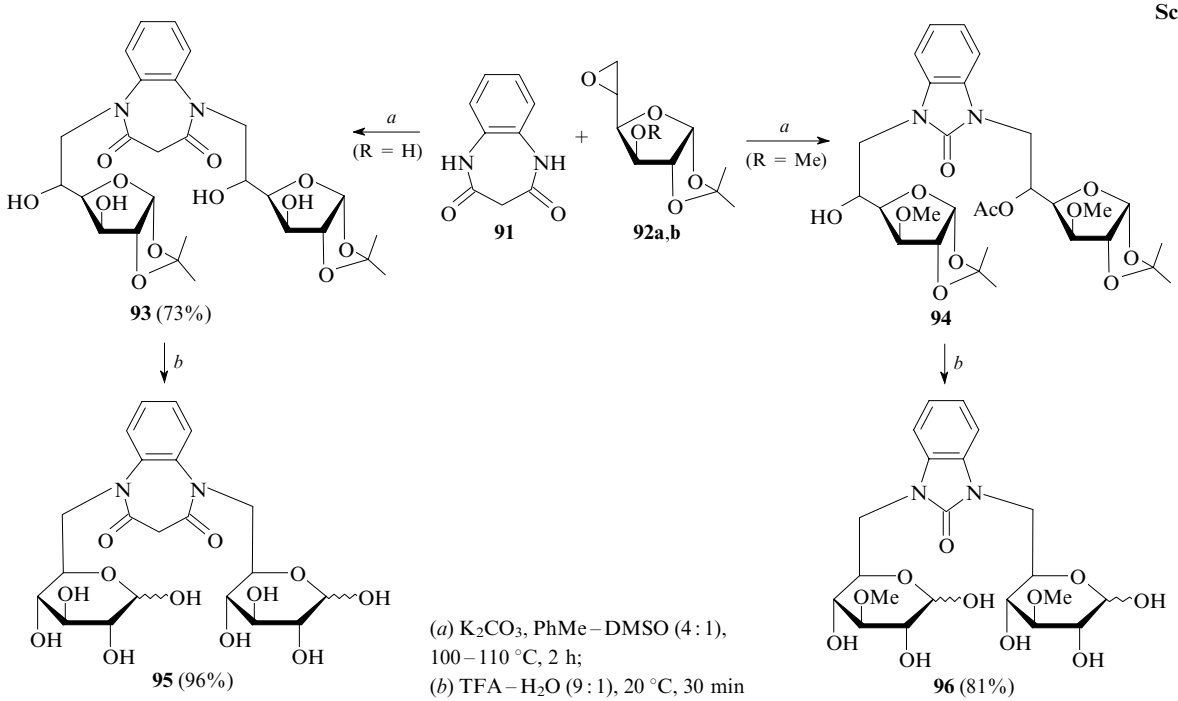
1,5-Benzodiazepine-2,4-dione (**91**) also undergoes a rearrangement to a benzimidazolone derivative. The heating of this heterocyclic compound under reflux with 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**92a**, R = H)[113] in the presence of K_2CO_3 in a toluene – DMSO system (4 : 1) for 2 h affords the expected N,N′-bis derivative **93** (Scheme 34).[114] It should be noted that, under comparable conditions, the reaction with a more lipophilic homologue containing the methylated OH group — 3-*O*-methyl-5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**92b**) —

Scheme 33



(*a*) 10% TFA, DCE, MW, 120 °C, 10 min; (*b*) 10% TFA, DCE, MW, 80 °C, 10 min; R^1 = $(CH_2)_2Ph$, $(CH_2)_2OMe$, Ph, C_6H_4Br-3, $CH_2C_6H_3Cl_2$-2,6, 2-Fu; R^2 = Bu^i, Ph, 2-Fu, 2-Th, $CH_2C_6H_4F$-4; DCE is dichloroethane, Fu is furyl, Th is thienyl

Scheme 34

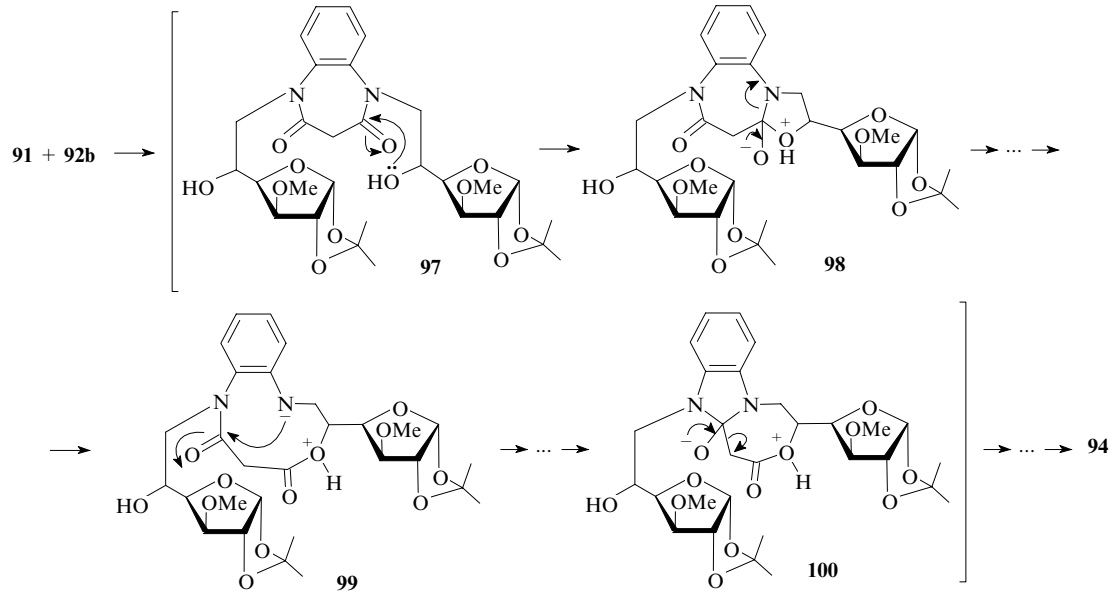


(*a*) K_2CO_3, PhMe – DMSO (4 : 1), 100 – 110 °C, 2 h;
(*b*) TFA – H_2O (9 : 1), 20 °C, 30 min

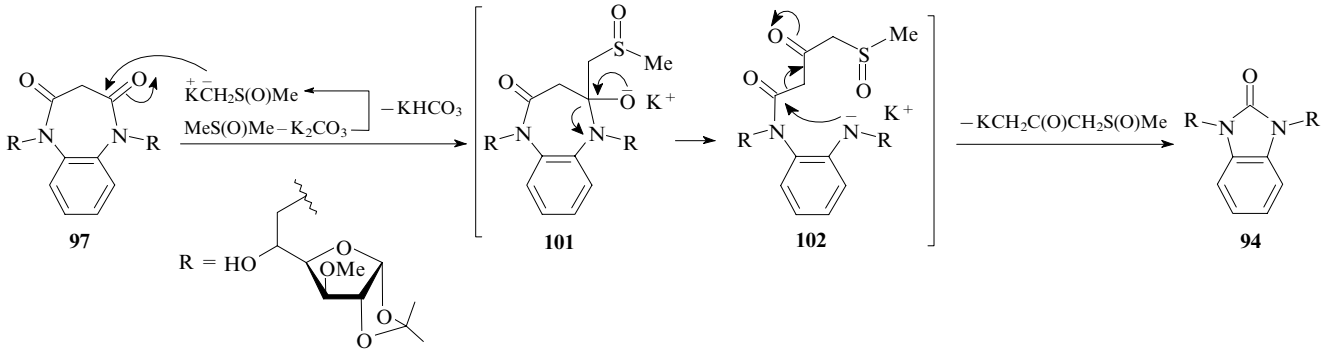
gives exclusively product **94** in moderate yield (see Scheme 34). The subsequent rearrangement of D-glucofuranose to D-glucopyranose and the removal of the isopropylidene protection from compounds **93** and **94** in a TFA – H_2O mixture (9 : 1)[115] produced *N*,*N*′-bis(6-deoxy-D-glucopyranos-6-yl)-1,5-benzodiazepine-2,4-dione (**95**) and *N*,*N*′-bis(6-deoxy-3-*O*-methyl-D-glucopyranos-6-yl)-benzimidazolone (**96**), respectively.[114]

The most probable mechanism for this transformation is shown in Scheme 35. The first reaction step is assumed to form intermediate **97** similar to compound **93**. The next step involves the intramolecular attack of the OH group at the C(5) atom of carbohydrate on the carbonyl group of diazepine-2,4-dione giving intermediate **98**. [Compound **93** is less prone to this attack because of the formation of intramolecular hydrogen bonds between OH groups at the C(3) and C(5) atoms, resulting in a decrease in the nucleophilicity of the OH group at the C(5) atom.] The subsequent N(1) – C(2) bond cleavage of derivative **98** affords intermediate **99**, which contains an NH group deprotonated in

Scheme 35



Scheme 36



the presence of a basic catalyst (potassium carbonate). The attack of this group on the remaining carbonyl function gives rise to tricyclic compound **100**. Finally, the C(3) – C(4) bond cleavage of the oxazepine ring yields product **94**. It is noteworthy that this rearrangement differs from the known rearrangements of 1,4- and 1,5-benzodiazepines,[116–118] but it has been observed in the condensation reactions of 1,5-benzodiazepine-2,4-dione **91** with other 3-*O*-alkyl-α-D-glucofuranoses, in particular, with 3-O-allyl and 3-O-octyl derivatives.[113] This rearrangement did not occur in the reaction of benzodiazepine **91** with carbohydrate **92a**.

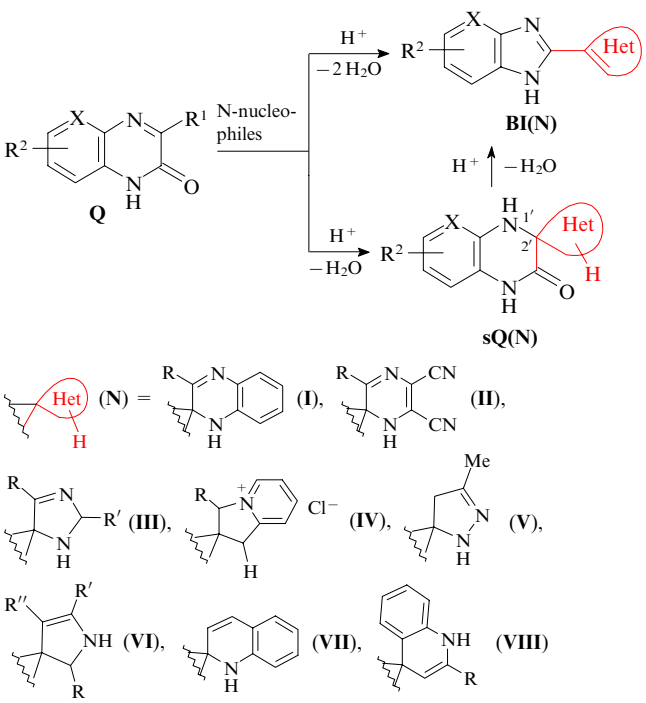
An alternative mechanism for the transformation of 1,5-benzodiazepine-2,4-dione into benzimidazol-2-one in the presence of K_2CO_3 in a toluene – DMSO mixture (4 : 1) is shown in Scheme 36. The first step involves the intermolecular attack of a base [K_2CO_3 or a product of its reaction with DMSO — $K^+ {}^-CH_2S(O)Me$] on the carbonyl group of diazepine-2,4-dione **97** giving rise to intermediate **101**. In the next step, the N(1) – C(2) bond is cleaved to form intermediate **102** containing the anionic nitrogen atom. This nitrogen atom attacks the carbonyl group that remained intact to form the structure of benzimidazolone derivative **94** accompanied by the elimination of 1-(methylsulfinyl)propan-2-one as 3-(methylsulfinyl)-2-oxopropylpotassium.

IV.2. Transformations of quinoxalinones

IV.2.a. Mamedov rearrangement

Earlier, we have demonstrated[119–131] that, depending on the nature of R^1 in 3-position, quinoxalin-2(1*H*)-ones **Q** (X = CH: R^2 = H, Me, Cl, *etc.*) and their aza analogues (X = N, R^2 = H)[124] containing the imino group [C(3)=N(4) bond] in the pyrazinone ring behave as heteroanalogues of α-chloro ketones [if R^1 = CH(Cl)Ph],[119] α-amino ketones (if R^1 = $CH(NH_2)Ph$),[120] α-azido ketones [if R^1 = $CH(N_3)(CH_2)_nPh$],[121] α-diketones [if R^1 = C(O)Ar, C(O)Alk],[122–127] β-diketones [if R^1 = $CH_2C(O)Ar$],[129, 130] simple ketones (if R^1 = Me)[128] and 2-aminobenzaldehydes (*e.g.*, if R^1 = $C_6H_4NH_2$-2),[131] *i.e.*, undergo an acid-catalyzed rearrangement in the presence of different N-nucleophiles to give 2-hetaryl-substituted benzimidazoles **BI** (Scheme 37). It should be noted that if the R^1 moiety in the structure **Q** contains electrophilic substituents (or reaction centres), not only aromatic diamines, such as *o*-diaminobenzenes, 2,3-diaminopyridine and 4,5-diaminopyrimidine, but also α-picolines and other amines, *e.g.*, hydrazine, arylmethanediamines (generated *in situ*) and 2,3-diaminomaleonitrile, can be utilized as N-nucleophiles. If the R^1 group in the structure **Q** contains nucleophilic substituents (or reaction centres), spiro-fused quinoxalinones **sQ** are generated through either the attack of the

Scheme 37



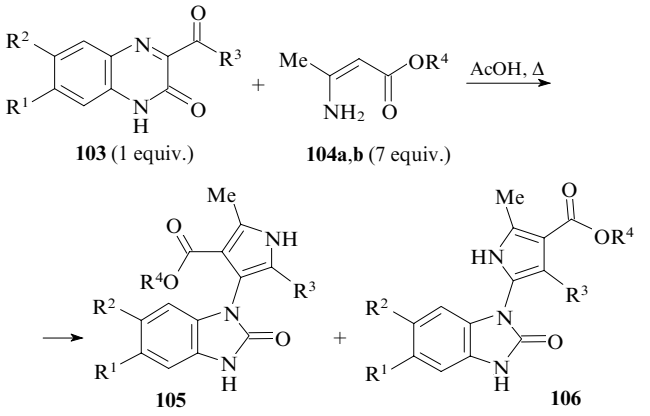
amino nitrogen atom or the attack of the C(2) atom of the enamine moiety (that is generated *in situ* by the reaction of quinoxalinones with ketones) on the C(3) atom of quinoxalinone.

The reaction proceeds through the formation hetaryl-spiroquinoxalin-3′(4′*H*)-ones **sQ** generated by one of the classical reactions in the synthesis of heterocycles. In the case of spiro[quinoxaline-2,2′-quinoxalin]-3′(4′*H*)-ones **sQ(I)**, spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones **sQ(II)** and spiro[imidazoline-5,2′-quinoxalin]-3′(4′*H*)-ones **sQ(III),** quinoxalin-2(1*H*)-ones derivatives with R^1 = C(O)Ar and C(O)Alk are utilized as heteroanalogues of α-diketones in the Hinsberg–Körner [132, 133] and Debus–Radziszewski–Japp reactions.[134–136] In the case of spiro[indolizine-2,2′-quinoxalin]-3′(4′*H*)-ones **sQ(IV)**, quinoxalin-2(1*H*)-one derivatives with R^1 = CHClAr act as heteroanalogues of α-chloro ketones in the Chichibabin reaction.[137] In the case of spiro[pyrazoline-5,2′-quinoxalin]-3′(4′*H*)-ones **sQ(V)** and spiro[pyrroline-3,2′-quinoxalin]-3′(4′*H*)-ones **sQ(VI)**, quinoxalin-2(1*H*)-one derivatives with R^1 = $CH_2C(O)Ar$ and R^1 = $CH(NH_2)Ar$ are heteroanalogues of β-diketones and α-amino ketones in the Knorr reaction.[138, 139] In the case of hydrogenated 1*H*,1′*H*-spiro[quinoline-2,2′-quinoxalin]-3′(4′*H*)-ones **sQ(VII)** and 1*H*,1′*H*-spiro[quinoline-4,2′-quinoxalin]-3′(4′*H*)-ones **sQ(VIII)**, quinoxalin-2(1*H*)-one derivatives with R^1 = Me and R^1 = 2-$NH_2C_6H_4$ can be considered as heteroanalogues of simple ketones [128] in the modified Friedländer reaction and of 2-aminobenzaldehydes [131] in the classical Friedländer reaction. In the second step, a new acid-catalyzed rearrangement of heteroaryl-spiroquinoxalin-3′(4′*H*)-ones **sQ(I–VIII)** takes place accompanied by the pyrazine ring contraction of the quinoxalin-2-one system giving benzimidazole derivatives **BI(I–VIII)** (Mamedov rearrangement of type 1) [140, 141] (see Scheme 37).

It should be noted that the presence of at least one labile hydrogen atom in the spiro-forming component responsible for water elimination is a necessary condition for this rearrangement. As can be seen in Scheme 37, the carbamoyl oxygen atom is involved in the formation of H_2O. Two situations are possible for spiro derivatives of quinoxalinone lacking labile hydrogen atoms in the spiro moiety: either these derivatives do not undergo a rearrangement or the carbamoyl oxygen atom will remain unchanged in the rearrangement. In order to confirm this assumption, spiro derivatives of quinoxalinone lacking labile hydrogen atoms were synthesized. Based on the analysis of potential nucleophilic reagents, we chose enamines as C,N-nucleophiles for the synthesis of these compounds.

Under acid catalysis, the reaction of 3-aroyl- and 3-alkanoylquinoxalin-2(1*H*)-ones **103** with commercially available enamines [methyl (**104a**) and ethyl 3-aminocrotonates (**104b**)] proceeds so rapidly that the expected spiro compound cannot be isolated because it is immediately rearranged to the corresponding *N*-(pyrrol-3-yl)benzimidazol-2-ones **105** (as major products) and *N*-(pyrrol-2-yl)benzimidazol-2-ones **106** (as minor products) in a total yield of 89%–99% (16 examples, Scheme 38).[142]

Scheme 38

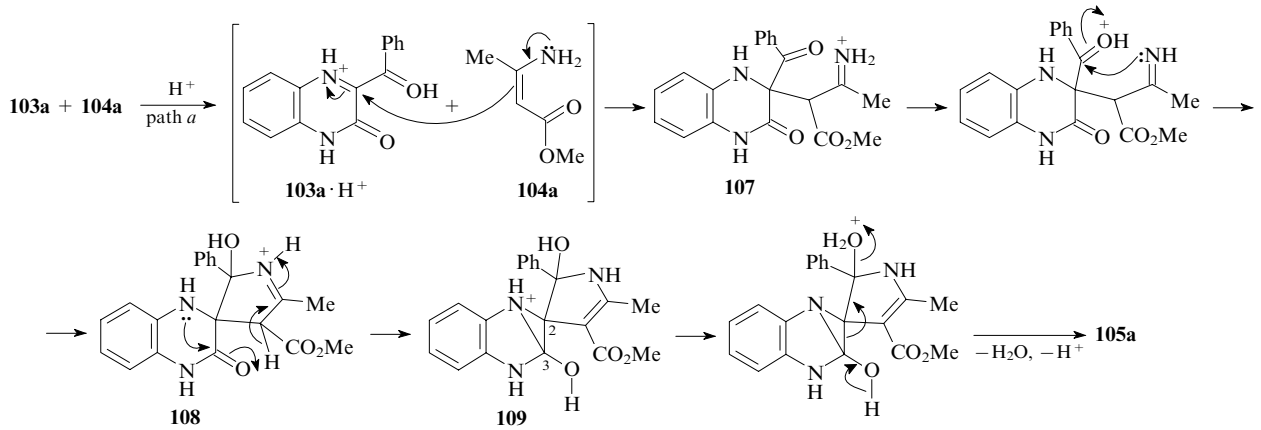


R^1, R^2 = H, Me, Bz, CO_2H; R^3 = Pr^n, C_6H_4X-4 (X = H, F, Cl, Br, I); R^4 = Me, Et

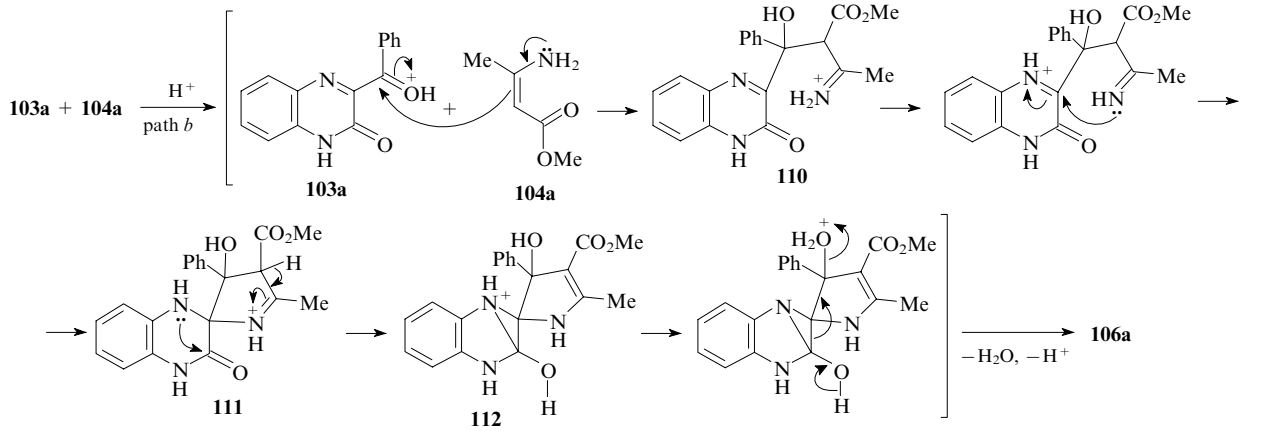
The plausible mechanism of the formation of *N*-pyrrolylbenzimidazol-2-ones **105** and **106**, which differ by the initial step (paths *a* and *b*), is shown in Schemes 39 and 40, respectively, in relation to selected compounds. In the former case (see Scheme 39), the first step of the transformation involves the acid-catalyzed reaction of substrate **103a** (R^1 = R^2 = H, R^3 = Ph) with methyl 3-aminocrotonate (**104a**), resulting in the nucleophilic attack of the double bond of enamine **104a** on the electron-deficient double bond of the imine carbon atom of compound **103a** to give intermediate **107**. After the attack of the imine nitrogen atom on the carbonyl carbon atom of the benzoyl moiety, intermediate **107** undergoes intramolecular cyclization to form spiro derivative of quinoxaline **108**. The rearrangement of intermediate **108** occurs as a series of cascade processes: 1) the intramolecular attack of the amino group on the carbonyl group of the carbamoyl moiety to form intermediate hydroxy derivative **109**, 2) the ring opening *via* the C(2)–C(3) bond cleavage in intermediate **109**, 3) the water elimination giving final product **105a**.

The first step of another reaction pathway (path *b*) involves the nucleophilic attack of the double bond of enamine **104a** on the carbon atom of the electron-deficient carbonyl group of the benzoyl moiety of substrate **103a**

Scheme 39



Scheme 40



giving rise first to compound **110** and then to intermediates **111** and **112**. This transformation affords *N*-(pyrrol-2-yl)benzimidazol-2-one **106a** (see Scheme 40).

As opposed to the above-considered rearrangement (see Scheme 37), in which the pyrazine ring opening of the quinoxalinone system of spiro derivatives **sQ** is accompanied by the cleavage of the bond between the C(1) and N(2) atoms, the ring opening in spiro derivatives **108** (see Scheme 39) and **111** (see Scheme 40) involves the C(2)—C(3) bond cleavage through the formation of spirocyclic intermediates **109** and **112**, respectively.

Not only quinoxalin-2(1*H*)-ones but also their aza analogues, such as 3-benzoylpyrido[3,2-*b*]pyrazin-2(1*H*)-one (**113a**) and 3-benzoylpyrido[3,4-*b*]pyrazin-2(1*H*)-one (**113b**), are rearranged to easily separable regioisomeric products **114a**,**b** and **115a**,**b**, with the former predominating (Scheme 41).

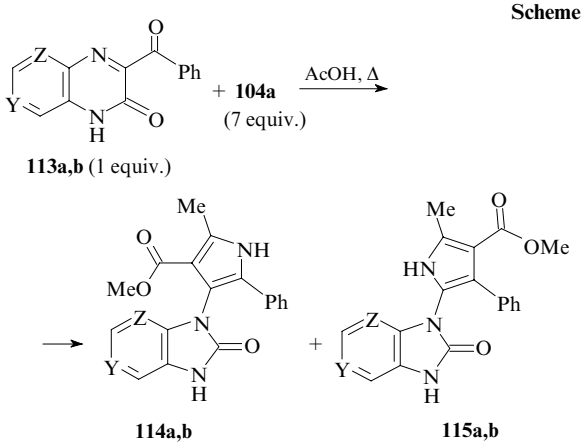
The method under consideration has the following advantages over conventional methods for the synthesis of benzimidazol-2-ones:

1) the reaction proceeds under mild conditions, affords products in good yields and does not require microwave irradiation or other procedures for reactant activation;

2) it is cost-effective because it utilizes cheap, commercially available reagents;

3) it has a wide substrate scope, including 3-aroyl(alkanoyl)quinoxalin-2(1*H*)-ones, 3-benzoylpyrido[3,2-*b*]pyrazin-2(1*H*)-one and 3-benzoylpyrido[3,4-*b*]pyrazin-2(1*H*)-one, as well as structurally diverse enamines.

Scheme 41



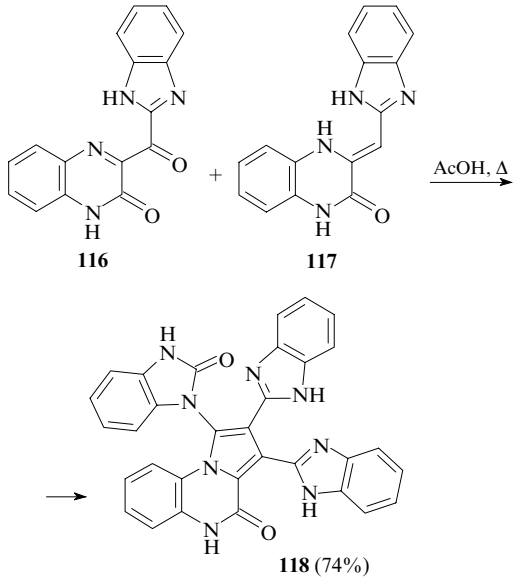
Compounds **113**–**115**	Z	Y	Yield (%)		**114**:**115**
			114	**115**	
a	N	CH	62	4	76:24
b	CH	N	81	Traces	95:5

Therefore, the above-described rearrangement provided the basis for an effective approach to the synthesis of *N*-pyrrolylbenzimidazolones from available 3-aroylquinoxalin-2(1*H*)-ones containing different substituents and commercial reagents — methyl and ethyl 3-aminocrotonates. This approach can be employed to prepare a wide variety of

N-pyrrolylbenzimidazol-2-ones and holds promise not only for organic synthesis but also for medicinal chemistry because the resulting compounds contain pharmacophoric moieties or their combinations.

The rearrangement using enamine-containing heterocyclic compounds instead of commercially available enamines is applicable to the synthesis of more complex heterocyclic systems which are difficult or impossible to prepare by other known methods. For example, the reaction of 3-(benzimidazol-2-ylcarbonyl)quinoxalin-2(1*H*)-one (**116**) with 3-(benzimidazol-2-ylmethylene)quinoxalin-2(1*H*)-one (**117**) in refluxing acetic acid affords pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one derivative **118** in good yield (Scheme 42).[121]

Scheme 42

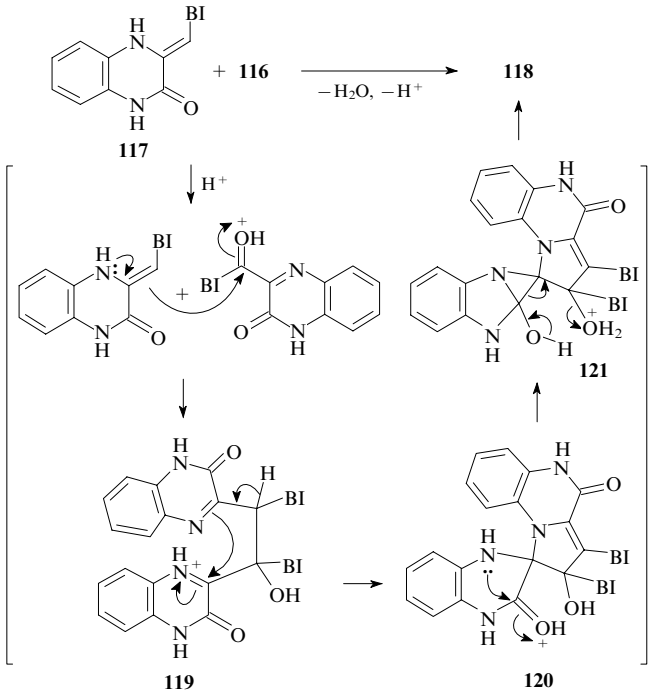


The formation of compound **118** proceeds through the following transformations: 1) the intermolecular ene reaction[143–145] between enamine **117** and ketone **116** giving intermediate **119**; 2) the intramolecular ene reaction[146–148] yielding spiro derivative of quinoxalino[2′,1]pyrrolo[1,2-*a*]quinoxaline **120** and 3) a new quinoxalinone-benzimidazolone rearrangement involving intermediate **121** (Scheme 43, BI is benzimidazol-2-yl).

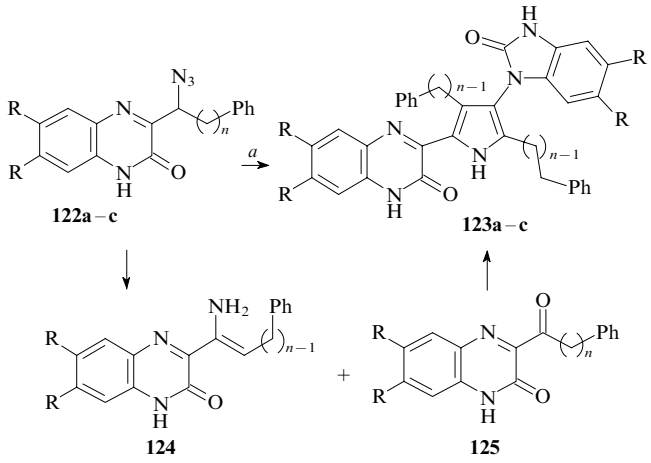
Enamines generated *in situ* through decomposition of azides **122a–c** can also be involved in this rearrangement. In this case, final products **123a–c** are generated *via* intermolecular condensation of enamine **124** with appropriate ketone **125**, which are formed under the reaction conditions (Scheme 44).[149] Consequently, this rearrangement allows the simultaneous one-step construction of two different heterocyclic systems.

The formation of benzimidazol-2-one derivatives *via* the condensation of 3-(benzimidazol-2-ylcarbonyl)quinoxalin-2(1*H*)-one (**116**) with its precursor — 3-(benzimidazol-2-ylmethylene)quinoxalin-2(1*H*)-one (**117**) (see Scheme 42) — and the self-condensation of 3-(α-azidophenylalkyl)quinoxalin-2(1*H*)-ones **122** (see Scheme 44) led us to a new hypothesis: any spiro derivative of 1,2,3,4-tetrahydroquinoxalin-3-one lacking labile hydrogen atoms in the spiro-forming component can be rearranged to a benzimidazolone derivative containing the spiro-forming moiety in 1-position (Mamedov rearrangement of type 2)[150] (Scheme 45).

Scheme 43

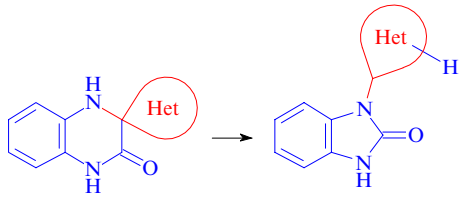


Scheme 44



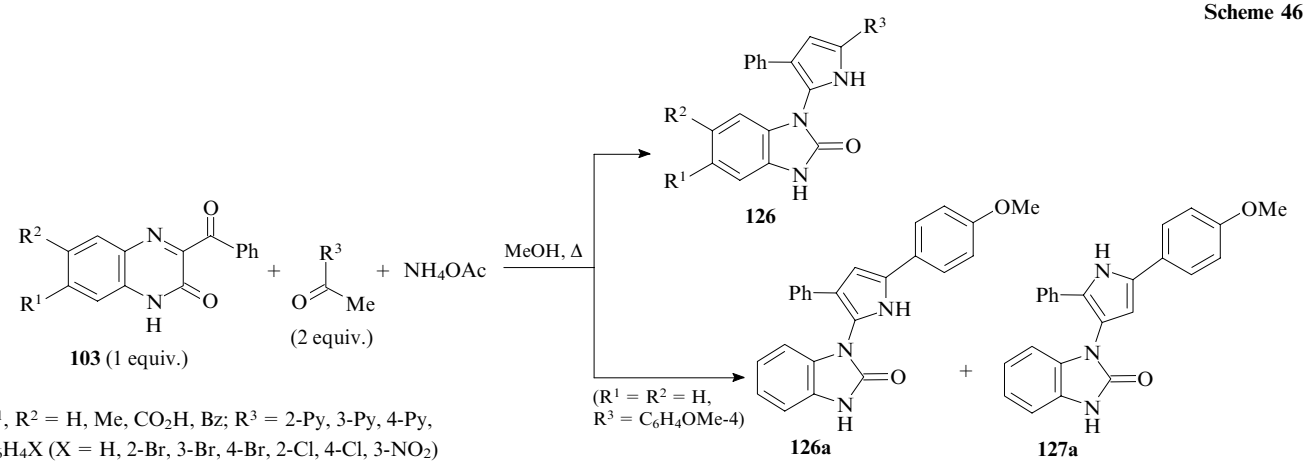
(*a*) AcOH, Δ; *n* = 1: R = H (**a**, 68% yield), Me (**b**, 61%); *n* = 2, R = H (**c**, 59%)

Scheme 45

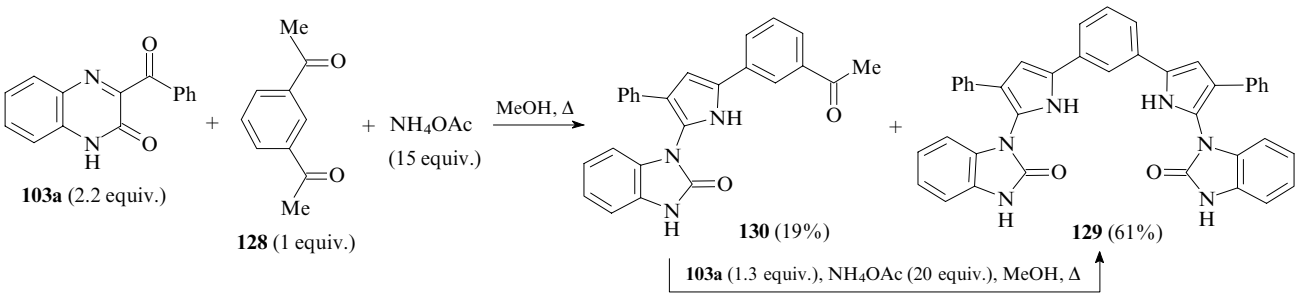


The above-considered reactions of 3-aroyl- and 3-alkanoylquinoxalinones can also be performed using enamines generated *in situ* from ketones containing the activated methylene group and amines. For example, Scheme 46 shows the structures of *N*-pyrrolylbenzimidazolones **126**, which are produced by the three-component reaction of 3-benzoylquinoxalinones **103** with different ketones and

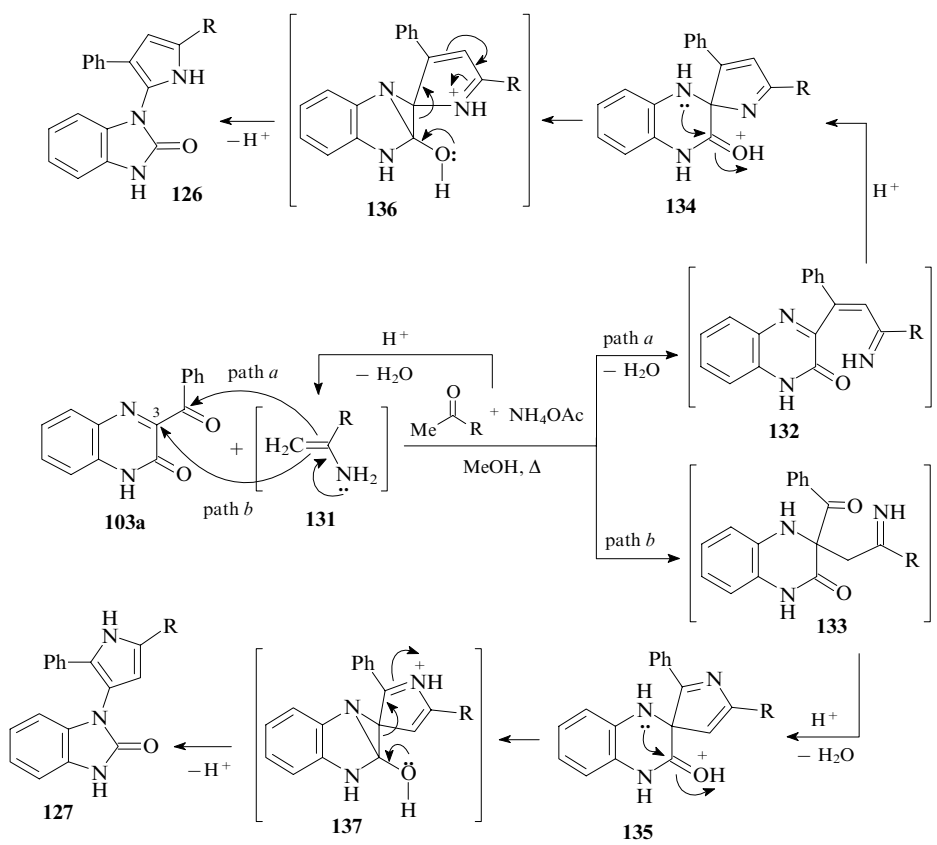
Scheme 46



Scheme 47



Scheme 48



ammonium acetate.[150] The rearrangement readily occurs with acetophenones, including those containing electron-withdrawing and electron-donating substituents, and heteroaromatic ketones. The reaction of *p*-methoxy-substituted acetophenone with 3-benzoylquinoxalinone (**103a**)

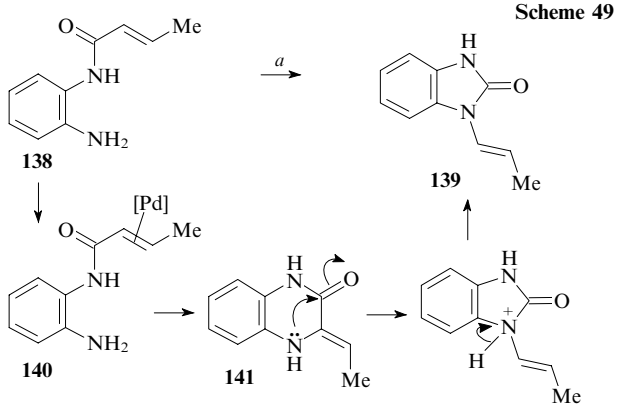
afforded a mixture of regioisomeric products **126a** and **127a** in a total yield of 92% in 1.7 : 1 ratio.

The use of 1,3-diacetylbenzene (**128**) containing an additional acetyl group instead of acetophenone (R^3 = Ph) in this reaction resulted in the expected cascade process that produced compound **129** containing two 1-(pyrrol-2-yl)-benzimidazolone moieties in the benzene ring (the major product) and compound **130** bearing one such moiety (the minor product).[150] It was shown that the reaction of acetophenone **130** with substrate **103a** in the presence of ammonium acetate (the reactant ratio is given in Scheme 47) gave dimer **129** in 30% yield.

Based on the known reactions of ketones,[151] imines[152] and enamines,[153–156] a plausible mechanism of this reaction can be proposed (Scheme 48), though it was not ultimately established. Intermediate **131**, which is formed in the initial step of the process reacts with 3-benzoylquinoxaline **103a** *via* two pathways (paths *a* and *b*) through the formation of intermediates **132** and **133** followed by the formation of isomeric derivatives of spiro[pyrrole-2,2′-quinoxalin]-3-ones **134** and spiro[pyrrole-3,2′-quinoxalin]-3-ones **135**. Intermediates **132** and **133** are generated *via* the initial attack of enamine on the carbonyl carbon atom of the benzoyl group (path *a*) and on the C(3) atom of the quinoxalinone system (path *b*), respectively. Both path *a* and path *b* are cascade transformations involving the following steps: 1) the acid-catalyzed ring closure of quinoxaline derivatives **132** and **133** to form spiro derivative **134** and **135**, respectively, followed by the formation of intermediates **136** and **137** containing the strained aziridine system; 2) the acid-catalyzed aziridine ring opening in intermediates **136** and **137** giving the final 1-(pyrrol-2-yl)- (**126**) and 1-(pyrrol-3-yl)benzimidazolones **127**.

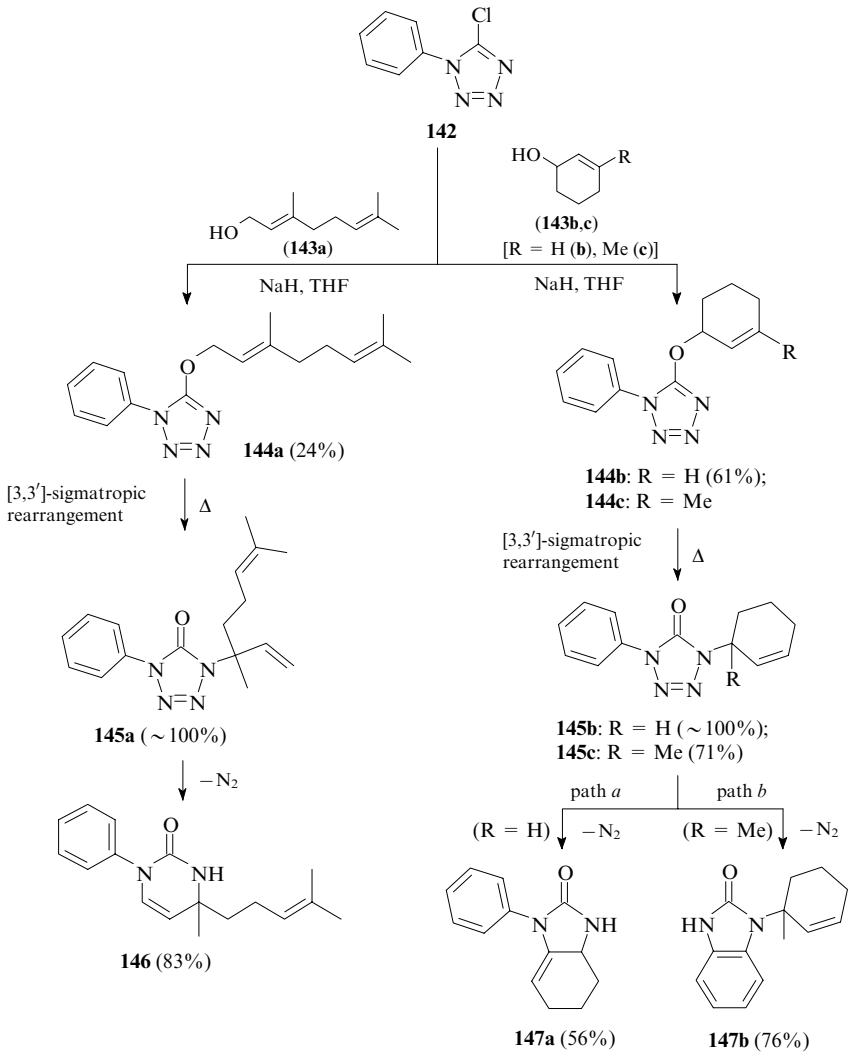
Therefore, a convenient method for the synthesis of 1-pyrrolybenzimidazolone derivatives in good yields was developed based on the three-component reaction of readily available 3-benzoylquinoxalinones, aryl(hetaryl) methyl

Scheme 49



(*a*) $Pd(PPh_3)_2Cl_2$ (5 mol.%), Xantophos, Bu^{t}ONa, PhMe (anh.), 80 °C

Scheme 50



ketones and ammonium acetate. Enamines generated *in situ* from ketone and ammonia readily react with 3-benzoylquinoxalinones to form pyrrolylbenzimidazolones. An important advantage of this method is that it is applicable to the synthesis of a wide range of benzimidazolone derivatives because it can utilize various methyl ketones, both commercially available and synthetic.

IV.2.b. Pd-Catalyzed rearrangement

Heating of (*E*)-*N*-(2-aminophenyl)but-2-enamide (**138**) with $Pd(PPh_3)_2Cl_2$ or the ligand Xantophos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] in the presence of Bu^tONa as a base in dry toluene resulted in the rearrangement giving compound **139** in 67% yield (Scheme 49).[157] According to the mechanism proposed by Banerji and Pramanik,[157] π-Pd complex **140** undergoes the insertion of the NH_2 group to form quinoxalinone **141** followed by the pyrazine ring contraction.

IV.3. Transformations of tetrazolone derivatives

The reactions of 5-chloro-1-phenyltetrazole (**142**) with allyl alcohols **143a**–**c** gave 5-allyloxy-1-phenyltetrazoles **144a**–**c** (Scheme 50). 1-Allyl-4-aryltetrazolones **145a**–**c** are produced from compounds **144a**–**c** in quantitative yield through the thermal Claisen [3,3′]-sigmatropic rearrangement.[158–162]

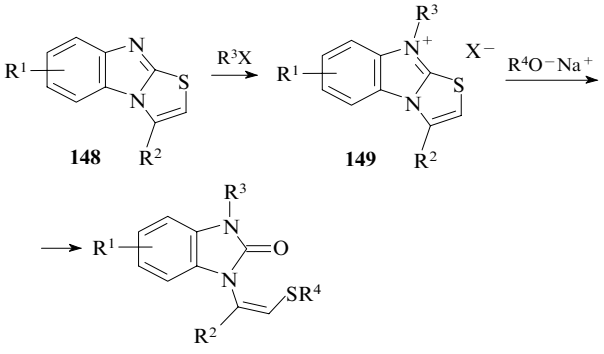
The photolysis of tetrazolones **145a**,**b** affords compounds **146** and **147a** according to a known scheme proposed earlier for other 1-allyl-4-phenyl-1,4-dihydro-5*H*-tetrazol-5-ones.[163, 164] Under the same conditions, the reaction of tetrazolone **145c**, which was synthesized using bulky 3-methylcyclohex-2-enol, gives benzimidazolone **147b**, *i.e.*, the cyclization involves the phenyl substituent of a short-lived intermediate that is formed upon extrusion of N_2 (see Scheme 50).[165] This unexpected cyclization pathway is attributed to steric hindrance created by the methyl group bonded to the allylic carbon atom in compound **145c**; otherwise, the photolysis would afford a pyrimidinone derivative.

IV.4. Rearrangements of fused heterocycles and spiro compounds containing the benzimidazole system

IV.4.a. Thiazolo[3,2-*a*]benzimidazolium salts

Thiazolo[3,2-*a*]benzimidazoles **148** are readily transformed into thiazolo[3,2-*a*]benzimidazolium salts **149** (Scheme 51), and the reaction of the latter with sodium alkoxide is accompanied by the unusual C–O bond cleavage to form

Scheme 51



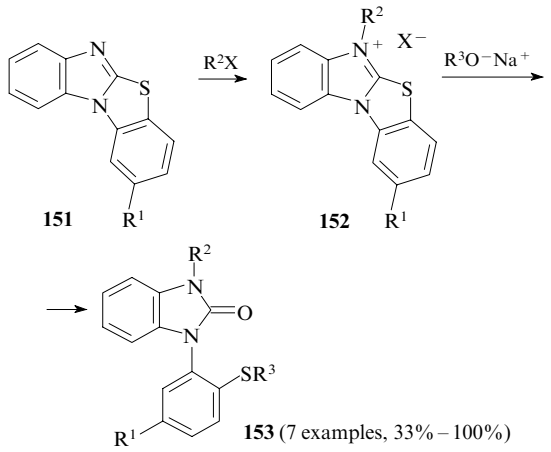
150 (17 examples, 52% – 100%)

R^1 = H, F, Cl; R^2 = Ar, Alk; R^3 = Alk, CH_2Ar; R^4 = Me, Bn

benzimidazol-2-one derivatives **150** containing various N-thioalkenyl substituents.[166]

A similar transformation was described for benzo analogues.[166] Thus, the transformation of benzimidazo[2,1-*b*][1,3]benzothiazoles **151** produced salts **152**, which were transformed into N-aryl-substituted benzimidazolones **153** containing alkylsulfanyl groups in the *ortho* position (Scheme 52).

Scheme 52

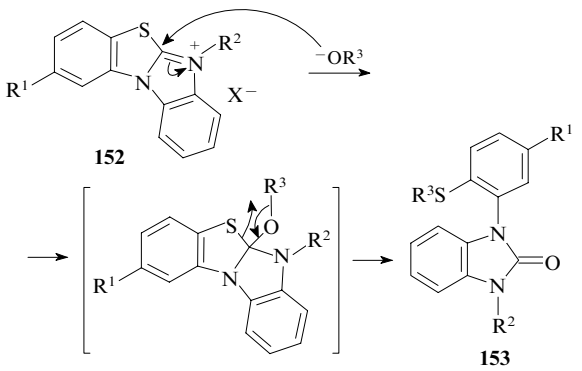


153 (7 examples, 33% – 100%)

R^1 = H, Cl; R^2 = Alk, CH_2Ar; R^3 = Alk

The mechanism of this transformation is shown in Scheme 53 in relation to salt **152**. In the first step, the alkoxide anion attacks the sp^2-hybridized carbon atom bonded to three heteroatoms, including the quaternized nitrogen atom. Then the R^3-O bond in this part of the molecule is cleaved, resulting in the formation of the carbonyl group of benzimidazolone and the migration of the substituent R^3 to the sulfur atom.

Scheme 53

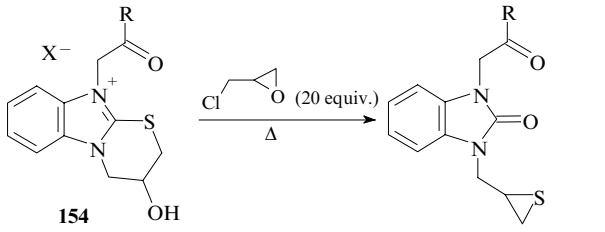


IV.4.b. Hydroxybenzimidazo[2,1-*b*]thiazinium salts

The reaction of 3-hydroxybenzimidazo[2,1-*b*]thiazinium salts **154** with epichlorohydrin proceeds *via* thiazine ring transformation to form substituted 1-(2,3-epithiopropyl)-benzimidazol-2-ones **155** (Scheme 54).[167]

Kuethe *et al.*[168] proposed a mechanism for the formation of compounds **155** presented in Scheme 55. This mechanism involves the formation of intermediate **156**, but the pathway of the formation of the final product was not explained. In our opinion, the more probable reaction pathway involves the formation of intermediates shown in Scheme 56.

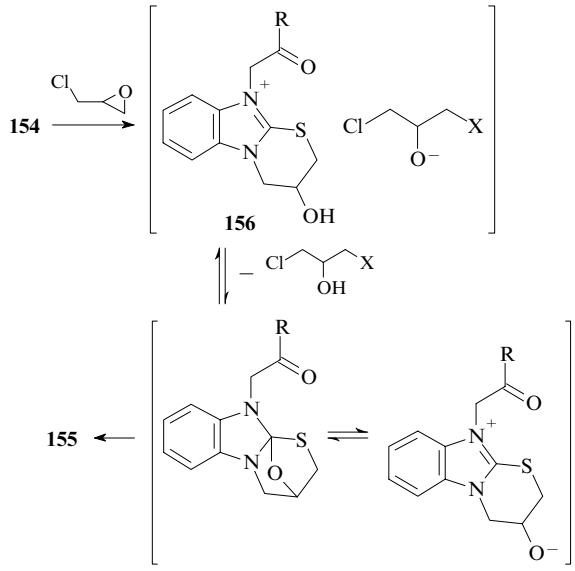
Scheme 54



154 **155** (6 examples, 75%–85%)

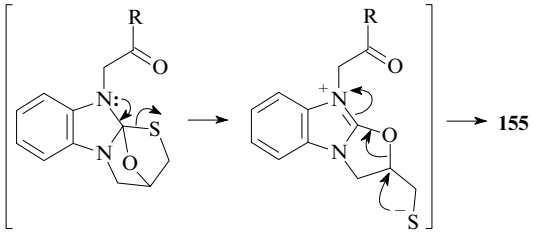
R = OAlk, Ar, Het; X = Br, I

Scheme 55

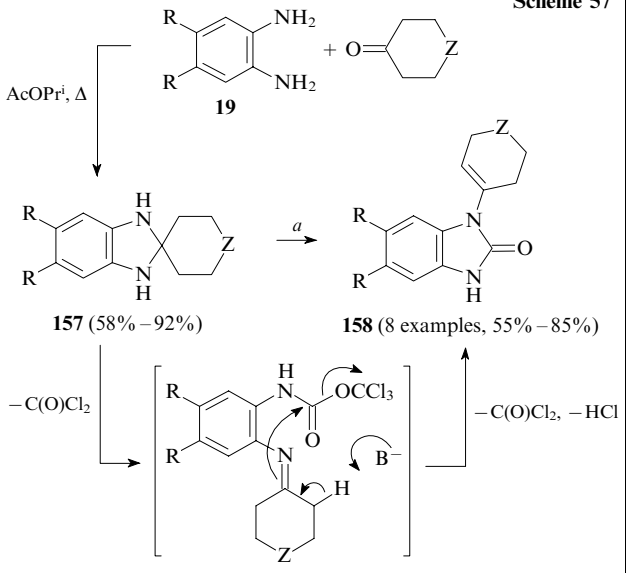


The proposed procedure can be used to introduce functional groups that are unstable in an alkaline medium into thiirane derivatives.

Scheme 56



Scheme 57

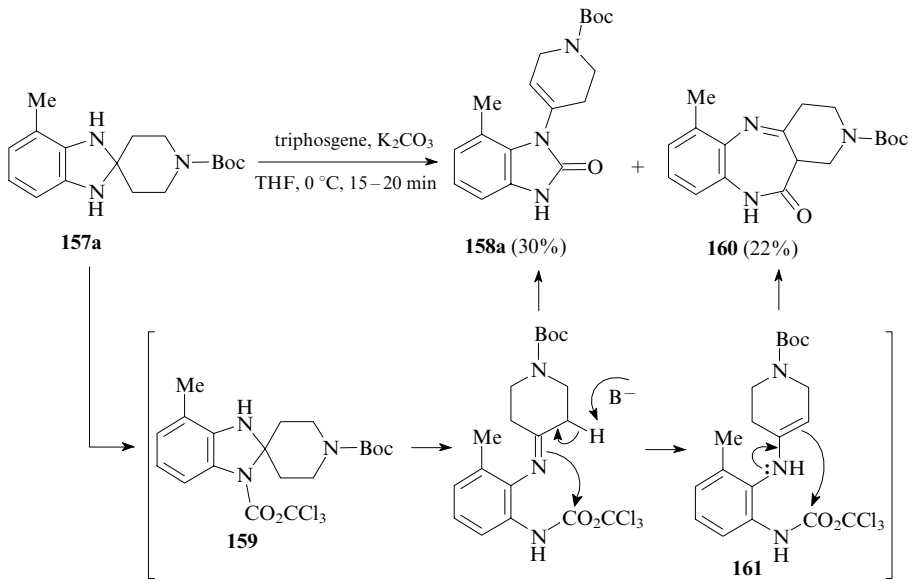


(*a*) triphosgene, K_2CO_3, THF, 0 °C, 15–20 min; R = H, Cl; Z = NCO_2Et, NCO_2Bn, NBz, NBn, NBoc, O, S, CH_2; B^- is a base

IV.4.c. Spiro-fused benzimidazolines

It was found [168] that the reaction of symmetrical spiro-fused benzimidazolines **157**, which can be easily generated from commercially available diaminobenzenes **19** and cyclic ketones, with triphosgene in the presence of potassium carbonate proceeds *via* the rearrangement into *N*-alkenylbenzimidazol-2-ones **158** (Scheme 57).

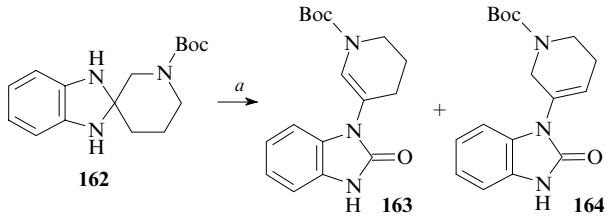
Scheme 58



Kuethe *et al.*[168] investigated the mechanism of transformation and studied the effect of the substituent in the benzene ring on the regioselectivity of the rearrangement (Scheme 58). The activation was found to occur at the less sterically demanding nitrogen atom of spiro-benzimidazoline **157a** to give intermediate **159**. The subsequent ring opening, tautomerization and cyclization afford benzimidazolone **158a**. The formation of benzoazepinone **160** can only be explained by intramolecular cyclization of enamine **161** and it represents the only case, in which the formation of this type of products was detected (see Scheme 58).

Under these conditions, spirobenzimidazoline **162** containing the unsymmetrically arranged piperidine moiety gives an inseparable mixture of regioisomers **163** and **164** in 2.5 : 1 ratio (in a total yield of 41%), which are also generated through the rearrangement (Scheme 59).

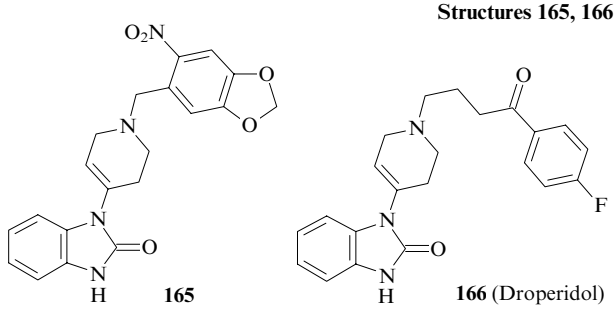
Scheme 59



(*a*) triphosgene, K_2CO_3, THF, 0 °C, 15 – 20 min

This strategy was employed to synthesize a μ-opioid receptor antagonist[104] (compound **165**) and Droperidol (**166**)[169] — the powerful antiemetic and antipsychotic drug currently used in medical practice.

Structures 165, 166



V. Methods based on rearrangements of anthranilic acid

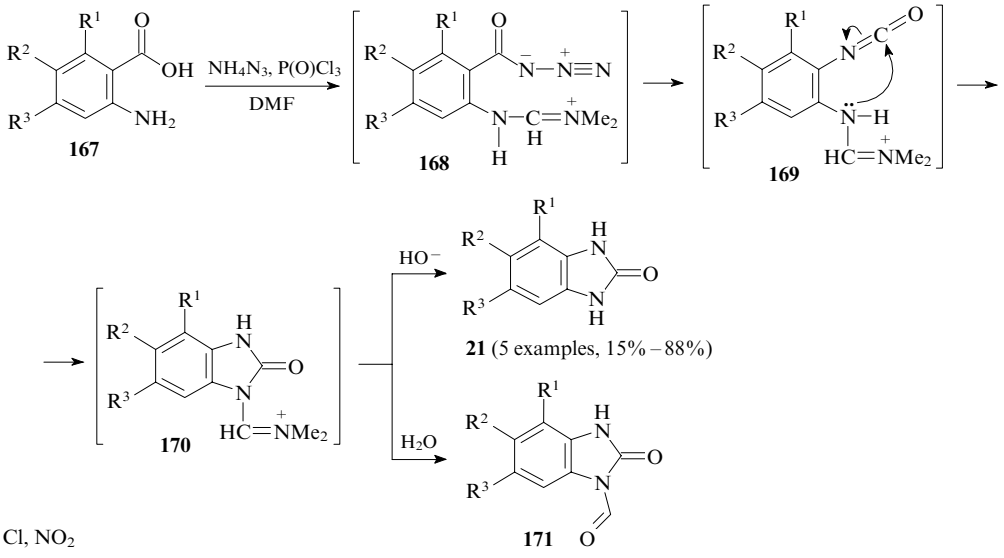
Apart from the above-considered approaches, the Curtius rearrangement of anthranilic acid derivatives is also employed to synthesize benzimidazol-2-ones. The latter step of this process involves intramolecular amidation of 2-isocyanatoanilines.

A facile general route to benzimidazol-2-ones was developed. This method is based on the one-pot process involving the *in situ* generation and cyclization of azides of *ortho*-substituted benzoic acid derivatives **167** (Scheme 60).[170] Ammonium azide and the Vilsmeier complex are utilized as reagents. (Ammonium azide is generated *in situ* under the reaction conditions in the presence of an appropriate derivative of anthranilic acid from powdered sodium azide and ammonium chloride in DMF.) Acyl azide **168** thus formed is a highly reactive intermediate and undergoes the Curtius rearrangement to give isocyanate **169**, which contains, instead of the amino group, a moiety that is generated by the reaction of this amino group with the Vilsmeier reagent. The presence of the iminium cation in the vicinity of the amino group does not interfere with intramolecular cyclization to benzimidazolone derivative **170**. Hydrolysis of the latter with 1 M NaOH affords final product 21. However, the hydrolysis of compound **170** in a neutral medium produces *N*-formyl derivative of benzimidazolone **171** (see Scheme 60). A similar process takes place with anthranilic acid derivatives containing different substituents in the benzene ring.

2-Amino-4,6-dichlorobenzoic acid (**167a**) is readily transformed into 4,6-dichlorobenzimidazol-2-one (**21f**) upon treatment with diphenylphosphoryl azide (DPPA) in the presence of triethylamine through the Curtius rearrangement of intermediate 2-amino-4,6-dichlorobenzoyl azide (**172a**) (Scheme 61).[171]

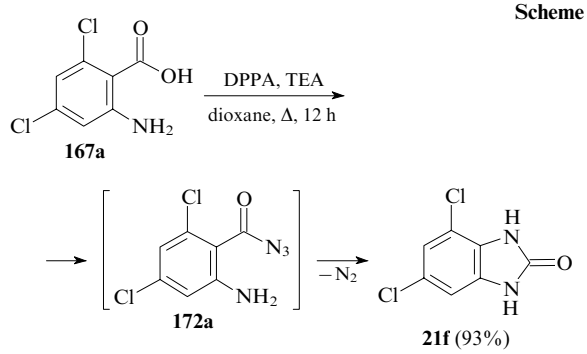
The treatment of substituted derivatives of phthalic anhydride **173a – d** with trimethylsilyl azide affords benzimidazol-2-ones **21g – j** in moderate yield through two successive Curtius rearrangements (Scheme 62).[172] The first rearrangement gives rise to benzoxazine-2,4-dione deriva-

Scheme 60



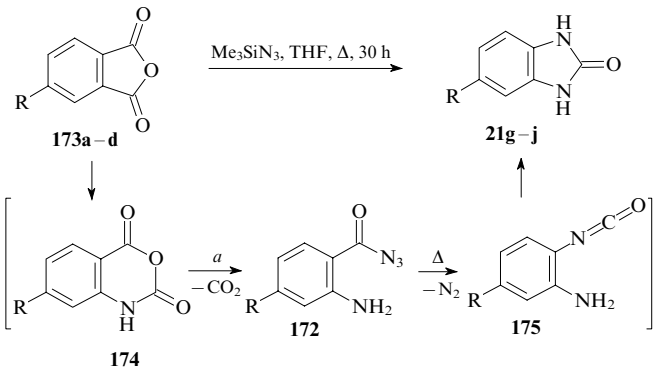
R^1, R^2, R^3 = H, Cl, NO_2

Scheme 61



tive **174** as an intermediate; the second rearrangement involving the intramolecular cyclization of isocyanate **175** produces benzimidazol-2-ones **21**.

Scheme 62



(*a*) Me_3SiN_3; R = H (**173a**; **21g**, 51% yield), Bu^t (**173b**; **21h**, 52%), Me (**173c**; **21i**, 77%), F (**173d**; **21j**, 50%)

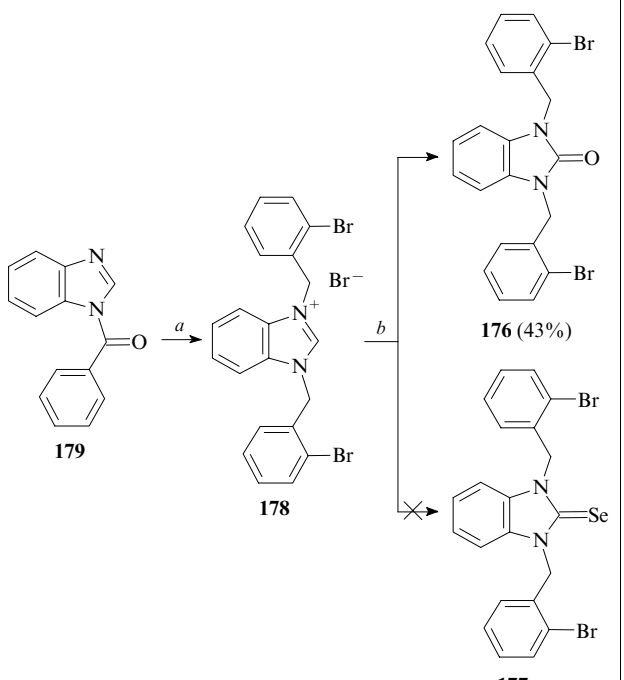
VI. Other methods

The unexpected formation of benzimidazol-2-one derivative **176** instead of its 2-selenium analogue **177** was observed in attempting to synthesize 1,3-bis(2-bromobenzyl)benzimidazole-2(3*H*)-selenone from 1,3-bis(2-bromobenzyl)benzimidazolium bromide **178**, which was generated from benzimidazole **179**. The reaction was performed using Na_2Se_2 in the presence of Bu^{t}OK (Scheme 63).[173] This fact can be apparently attributed to hydrolysis of salt **178**, especially since examples of such hydrolysis during the transformation of carbene into imidazolones were reported.[174]

Benzimidazolium salts **180** are readily transformed into N,N′-disubstituted benzimidazol-2-ones **49b–f** upon the treatment with a commercial bleach composed of an aqueous alkaline solution of hypochlorite or *N*-chlorosuccinimide (NCS) (Scheme 64).[175] This method is applicable to the preparation of a wide range of substrates using imidazolium salts with both simple and complex structures.

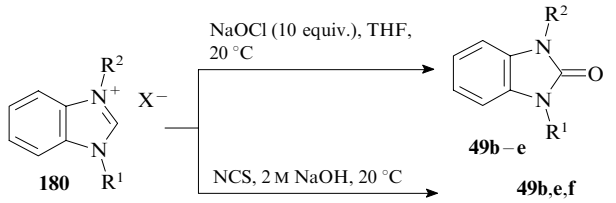
The plausible mechanism of the formation of benzimidazol-2-one derivatives involves the addition of the hydroxide ion to the cation of benzimidazolium salt **180** to form hydroxy derivative **181**.[176] The *ortho*-chlorination and base-induced elimination of HCl from intermediate **182** give rise to the carbonyl group. An alternative pathway involves the reaction of the cation of benzimidazolium salt **180** with a hypochlorite ion (that is formed *in situ* or directly upon the addition of the salt) giving intermediate **182**. The base-induced elimination of HCl from the latter intermediate affords the corresponding imidazolone (Scheme 65).[177]

Scheme 63



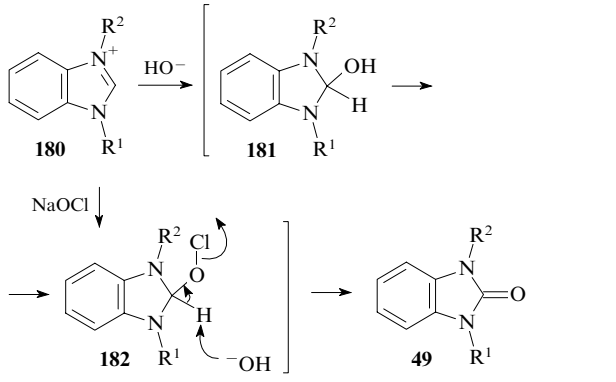
(*a*) 2-$BrC_6H_4CH_2Br$, dioxane, Δ; (*b*) Na_2Se_2, Bu^{t}OK, THF, 20 °C

Scheme 64



R^1 = Me: R^2 = Bn [**b**, 85% yield (conditions *a*) and 84% yield (conditions *b*)], $CH_2O(CH_2)_2SiMe_3$ (**c**, 79%), $CH_2C_6H_4OMe$-4 [**e**, 81% (conditions *a*) and 83% (conditions *b*)], CH_2OMe (**f**, 81%); R^1 = R^2 = Bn (**d**, 88%)

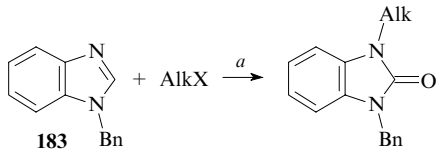
Scheme 65



Benzimidazolones can be synthesized by the oxidation of benzimidazolium salts in the presence of metal-containing catalysts. For instance, N-substituted benzimidazole **183** was initially quaternized with alkyl halides, and then the salts were oxidized *in situ* with DTBP in the presence of CuI

as a catalyst and imidazole as a ligand. This procedure was used to synthesize a series of *N*-alkyl-*N*′-benzylbenzimidazol-2-ones **49** (Scheme 66).[177]

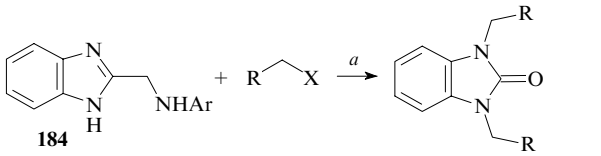
Scheme 66



(*a*) DTBP (2 equiv.), CuI (20 mol.%), imidazole (1 equiv.), PivOH (1.2 equiv.), hexane, DMA, 120 °C, 24 h; X = Cl, Br, I;
DTBP is di-*tert*-butyl peroxide, DMA is dimethylacetamide

Aminomethylbenzimidazoles **184** react with commercially available arylmethyl halides to form N,N′-disubstituted benzimidazol-2-ones (Scheme 67).[178] It should be noted that n-hexyl halide also gives a benzimidazol-2-one derivative, though in low yield (13%). However, the reaction with such halide as 4-nitrobenzyl bromide ($R = C_6H_4NO_2$-4) containing an electron-withdrawing group affords 4-nitrobenzaldehyde as the major reaction product.

Scheme 67

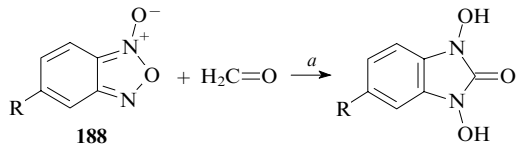


(*a*) 1) MeCN, 70 °C; 2) K_2CO_3, MeCN, H_2O; X = Cl, Br;
$R = X_nC_6H_{5-n}$ (X = 2,4-F_2, 2,4-Cl_2, 3,4-Cl_2, 2-F, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 4-Me, 4-OMe), n-C_5H_{11}

The possible mechanism of the transformation is presented in relation to the reaction of benzimidazole **184a** [Ar = $C_6H_3(CF_3)_2$-3,5] with 2,4-difluorobenzyl bromide (Scheme 68). This mechanism involves the formation of double salt **185a**, which readily undergoes the transformation into the corresponding pseudo-base **186** in the presence of water. Compound **186** is stabilized *via* elimination of *N*-methyl-*N*-(2,4-difluorobenzyl)-3,5-bis(trifluoromethyl)aniline hydrobromide (**187**), which acts as a 2,4-difluorobenzylating agent to form product **49g**.[178]

The reaction of benzofuroxans **188** with formaldehyde in the presence of bases proceeds exothermically to give dihydroxybenzimidazol-2-ones **189** (Scheme 69). These compounds can be alkylated and acylated at hydroxy groups and bind isocyanates and acrylonitriles to form various derivatives.[179]

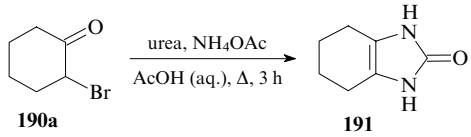
Scheme 69



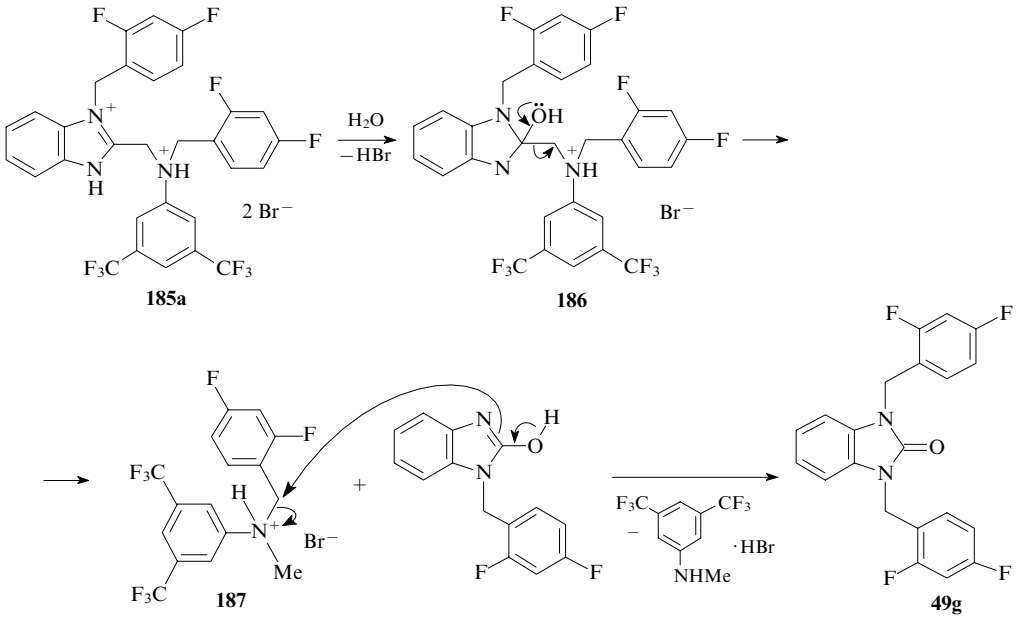
(*a*) 1) HO^-; 2) H_3O^+; 3) MeOH, H_2O; R = H, Cl, Me, OMe, CO_2H, $C(O)NH_2$

In addition to the above-considered methods for the synthesis of benzimidazol-2-ones, mention should also be made of the procedure for the preparation of imidazol-2-ones and tetrahydrobenzimidazol-2-ones based on the reaction of α-bromo ketones with urea and ammonium acetate in boiling aqueous acetic acid. This procedure provides a simple route to imidazol-2-ones containing different substituents. For instance, the reaction of α-bromocyclohexanone (**190a**) produced tetrahydrobenzimidazol-2-one **191** (Scheme 70).[180] Unfortunately, the authors did not report the yield.

Scheme 70

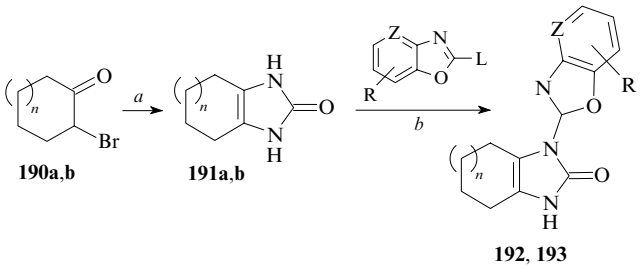


Scheme 68



This approach was employed to synthesize a series of 4,5,6,7-tetrahydrobenzimidazol-2-ones **192** and 3,4,5,6,7,8-hexahydrocycloheptaimidazolones **193** — a new type of ligands for brain $GABA_A$ receptors (Scheme 71).[181]

Scheme 71



190a,b **191a,b** **192**, **193**

(*a*) urea, NH_4OAc, AcOH (aq.), Δ, 3 h; (*b*) 1) LDA, THF, 20 °C, 20 min; 2) THF, 0.5 – 2 h; LDA is lithium diisopropylamide; *n* = 1 (**190a**, **191a**, **192**), 2 (**190b**, **191b**, **193**); L = Cl, SMe; **192**: Z = CH, N; R = H, F, OMe (at different positions); **193**: Z = CH, CF, N; R = H, F, Me, OMe (at different positions)

* * *

This review covers recent advances in the synthesis of benzimidazol-2-ones based on reactions of aniline and its derivatives (*o*-diaminobenzenes, *o*-nitroanilines, N,N′-disubstituted ureas), halobenzenes (*o*-dihalobenzenes, *o*-haloaryl carbamates, *o*-iodophenylcarbodiimides, *o*-halonitrobenzenes), α-bromocyclohexanone, anthranilic acid derivatives and various heterocyclic systems. Rearrangements of benzodiazepinones, quinoxalinones, tetrazolones, as well as of fused and spirocyclic compounds containing the benzimidazole moiety, hold the most important place among these methods. These results attest to significance and usefulness of various rearrangements for the synthesis of not only 1*H*-benzimidazol-2(3*H*)-one but also its N-derivatives, from simple monocyclic compounds to polycyclic and spiro systems. In many cases, the reactions are regioselective and produce compounds that exhibit biological activity or can be utilized as intermediates for the synthesis of physiologically active compounds, including analogues of currently used drugs.

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