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METHODS FOR THE SYNTHESIS OF HALOIMIDAZOLES (REVIEW)

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Published information on methods for the synthesis of haloimidazoles is summarized and classified.

Keywords: bromoimidazoles, imidazoles, iodoimidazoles, fluoroimidazoles, chloroimidazoles, photosynthesis.

Haloimidazoles form an important group of compounds used as synthons for the production of various derivatives of imidazole and condensed heterocyclic systems based on imidazole, including those with a nodal nitrogen atom. Some derivatives of haloimidazoles have high biological activity and have found use as drugs for the treatment of hypertonia [1] and also as chemical agents for the protection of plants [2].

Papers on the synthesis of haloimidazoles, mostly published before the middle of the twentieth century, are found in the monograph [3] and in the reviews [4-6]. However, the most important researches on the development of methods for the production of these compounds were executed in the last 55-60 years. This review is devoted to discussion of these methods.

1. SYNTHESIS OF FLUOROIMIDAZOLES

As will be described below, the direct halogenation of imidazoles by the respective halogens or halogen-releasing reagents (sodium hypochlorite, N-halosuccinimides, PCl_5, etc.) used for the production of bromo-, iodo-, and chloroimidazoles is not used for the synthesis of fluoroimidazoles.

The chief method for the synthesis of these compounds is the photochemical cleavage of imidazolediazonium fluoroborates.

The method was first proposed for the transformation of aromatic amines **1** into the fluoroarenes **3** through the diazonium salts **2** [7, 8]. Here it was established that salts of type **2** are more stable compounds than salts of the $ArN_2^+X^-$ type, where X is a halogen.

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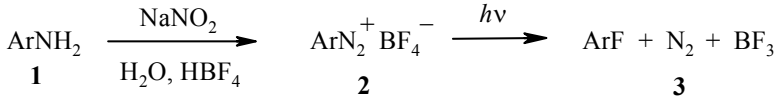
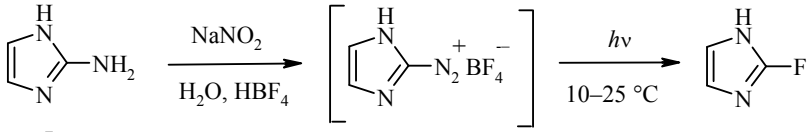


Unlike aromatic amines, aminoimidazoles are unstable. Their diazotization in the examples presented below (Section 1.1) was therefore conducted with sodium nitrite in 50% aqueous HBF_4 in a stream of nitrogen at −5 to −10°C. The obtained imidazolediazonium fluoroborates were irradiated without isolation by a 450 W mercury lamp. As a result of the photochemical reaction the diazo group is replaced by a fluorine atom with the formation of the corresponding 2-fluoro- or 4(5)-fluoroimidazole.

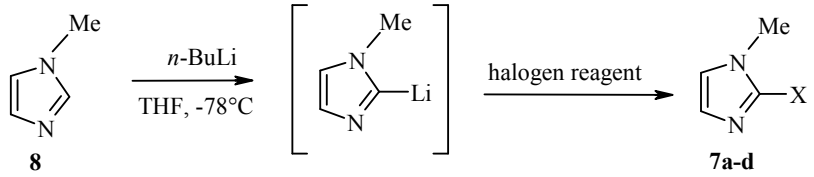
1.1. Synthesis of 2-Fluoroimidazoles

The first representative of this group of compounds, 2-fluoroimidazole **4**, was synthesized with a yield of 30% from 2-aminoimidazole **5** through the salt **6** [9, 10].



2-Fluoro-4(5)-methylimidazole [11] and 2-fluorobenzimidazole [12] were obtained according to a similar scheme, while 2-chloroimidazole [13] and 2-chloro-1-methylimidazole [13, 14] were obtained by diazotization of the corresponding amine in HCl (section 2.1).

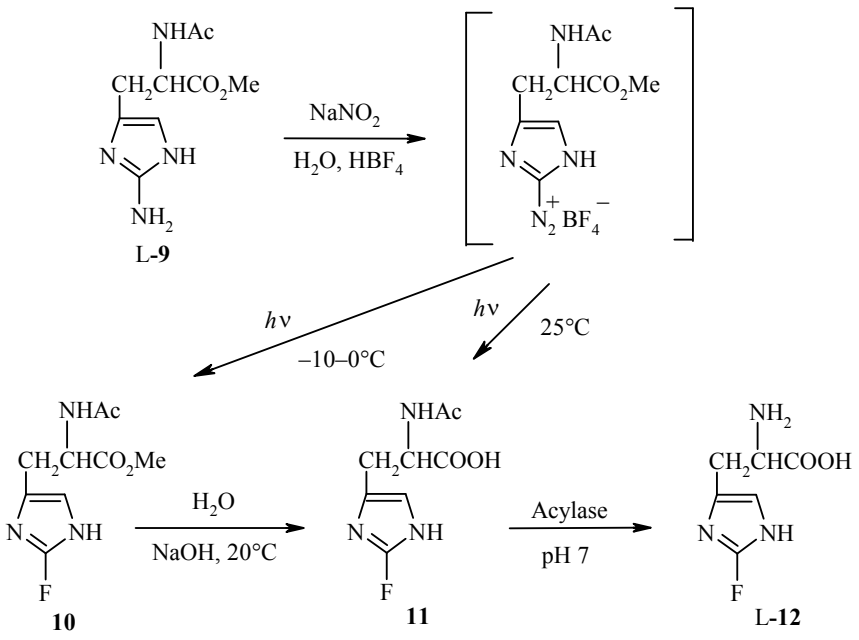
The general method for the synthesis of 2-halo-1-methylimidazoles **7a-d** (yields 55-80%) by lithiation of 1-methylimidazole **8** followed by treatment of the intermediate 2-lithio derivative with a halogen reagent ($FClO_3$, Br_2, I_2 [15], Cl_2, CCl_3COCl, CCl_4, C_2Cl_6) was used for the synthesis of 2-fluoro-1-methylimidazole **7a** [16].



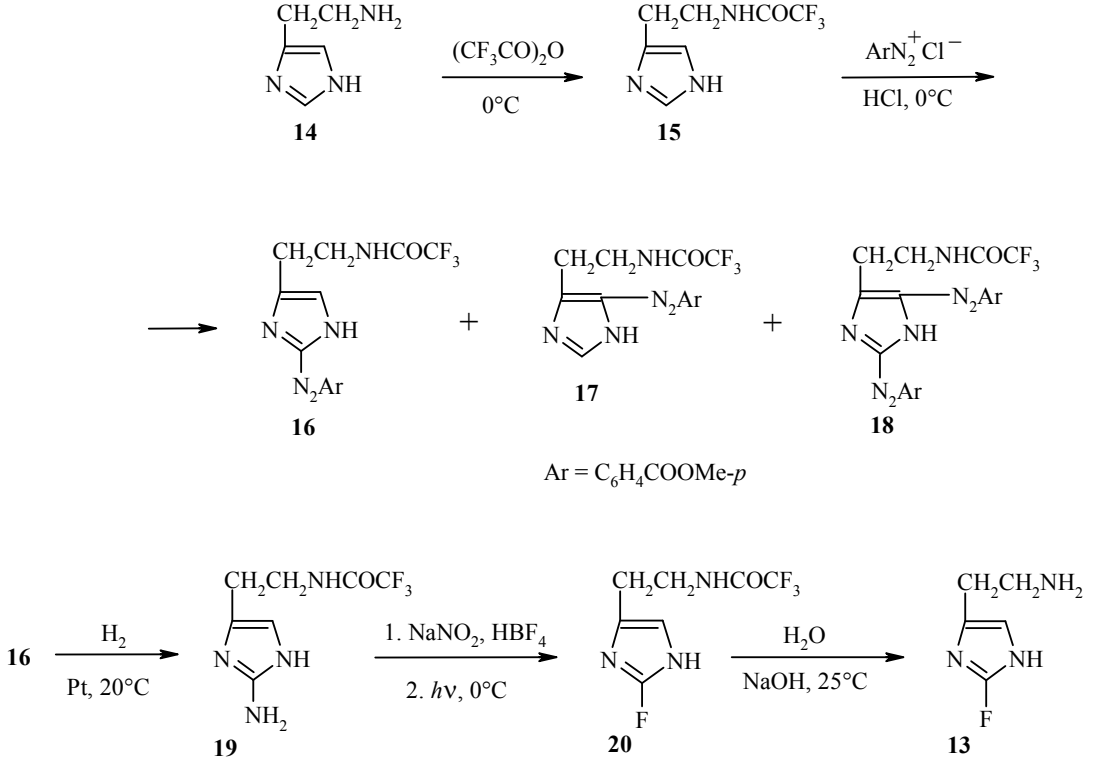
a X = F, **b** X = Br, **c** X = I, **d** X = Cl

2-Fluoro-5-iodo-1-methylimidazole (yield 49%) was synthesized similarly by the reaction of 2,5-diiodo-1-methylimidazole with BuLi followed by treatment of the 2-lithio derivative with $FClO_3$ [15].

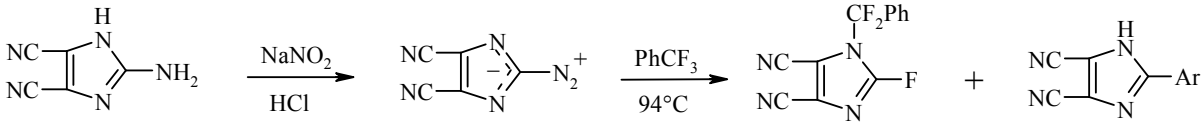
Methods for the production of important natural compounds 2-fluoro-substituted in the imidazole ring (L-histidine and histamine) were described in [17]. Here other derivatives of 2-fluoroimidazole were produced as intermediate compounds. Thus, the diazotization of α-(N-acetyl)-L-histidine L-**9** followed by photochemical cleavage of the intermediate diazonium salt at -10 to 0°C or at 25°C led to the formation of the ester **10** (yield 32%) and the acid **11**, which was treated without isolation with acylase, leading to fluoro-L-histidine L-**12** (yield 77% calculated on the ester **10**) [17].



The histamine **13**, 2-substituted with fluorine in the heterocycle, was synthesized from the histamine **14** in five stages. Azocoupling of N-trifluoroacetylhistamine **15** and arenediazonium chloride led to a mixture of azo and diazo products **16**-**18** (yield of required isomer **16** 72%). The amine **19** was obtained by the hydrogenation of compound **16** (yield 90%), and fluoro-N-trifluoroacetylhistamine **20** was obtained from it by diazotization and photochemical transformation (yield 37% calculated on the amine **19**). Hydrolysis of **20** gave the targeted fluorohistamine **13**, which was isolated in the form of the picrate [17].



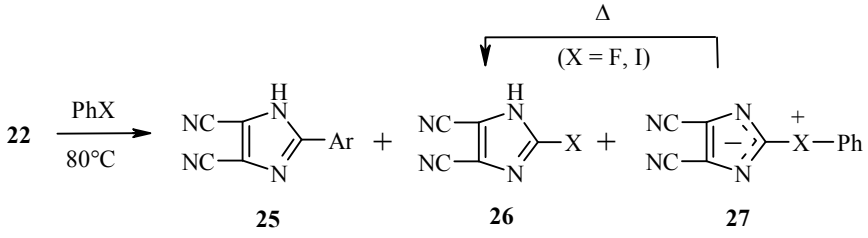
Diazotization of 2-amino-4,5-dicyanoimidazole (**21**) leads to a quantitative yield of the 2-diazo compound **22**, which has a zwitterionic structure and exhibits explosive characteristics [18, 19]. Pyrolysis of compound **22** at 94°C in $PhCF_3$ gave a mixture of products **23** and **24** with yields of 27 and 20% respectively [18].



21 **22** **23** **24a,b**

24 a Ar = $C_6H_4CF_3$-*o*; **b** Ar = $C_6H_4CF_3$-*p*

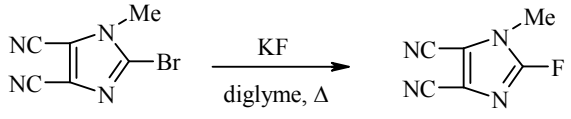
The pyrolysis of compound **22** by heating in halobenzenes takes place in a more complicated manner. In this case mixtures of compounds of types **25**-**27** are formed. During pyrolysis in fluorobenzene the yield of the mixture of products **25** amounted to 50% (ratios of *o*-, *m*-, and *p*-isomers 58:34:8) [18]. Compounds **27** (X = F, I) could not be isolated since they are converted into 2-fluoro(iodo)-1-phenylimidazoles **26** (yields ~23%) under the reaction conditions [18].



25 **26** **27**

25 Ar = C_6H_4X-*o*, C_6H_4X-*m*, C_6H_4X-*p*; **25**–**27** X = F, Cl, Br, I

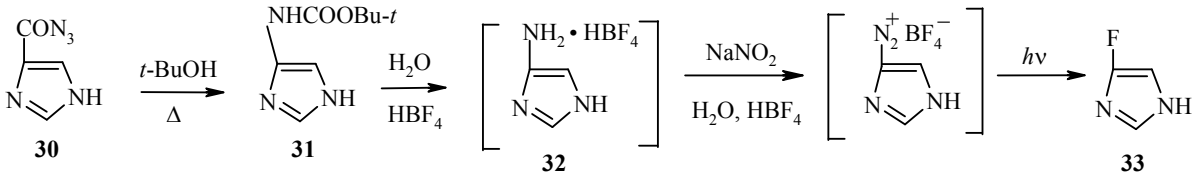
The reaction of 2-bromo-1-methylimidazole **28** with KF in diglyme in the presence of 18-crown-6 ether leads to the 2-fluoro derivative **29** with a yield of 89% [20].



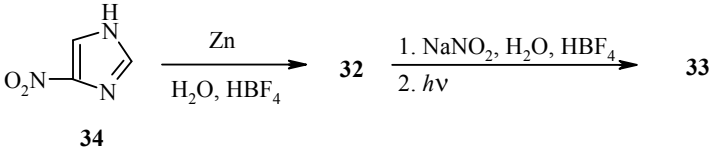
28 **29**

1.2. Synthesis of 4(5)-Fluoro- and 4,5-Difluoroimidazoles

Ways of producing 4(5)-fluoroimidazoles from derivatives of imidazole-4(5)-carboxylic acid and 4(5)-nitroimidazoles have been described. Thus, the azide of imidazole-4(5)-carboxylic acid **30** was converted into 4(5)-fluoroimidazole (**33**) through the *tert*-butyl carbamate **31** (yield 41%), hydrolysis of the latter to the hydrofluoroborate **32** by aqueous HBF_4, and subsequent diazotization and photochemical cleavage with a yield of 41% on the carbamate **31** [9, 10].

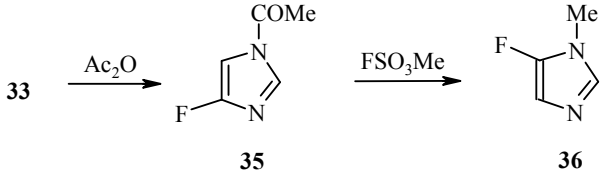


A simpler method for the synthesis of compound **33** is based on the use of the readily obtainable 4(5)-nitroimidazole (**34**), the reduction of which with zinc dust in 50% aqueous HBF_4 gave the hydrofluoroborate **32**. The latter is converted into the fluoroimidazole **33** as described above with a yield of 17-40% on the nitro compound **34** [17, 21, 22].

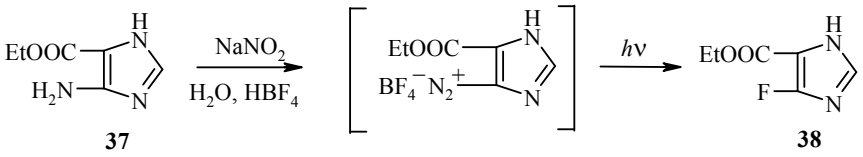


The NO_2 group was replaced by fluorine in a similar way during the synthesis of 1-methyl-substituted 4-fluoro- and 5-fluoroimidazoles [11, 14] and also of 4(5)-fluoro-2-methylimidazole [23]. The yields of the products amounted to 20-25% on the initial nitroimidazoles.

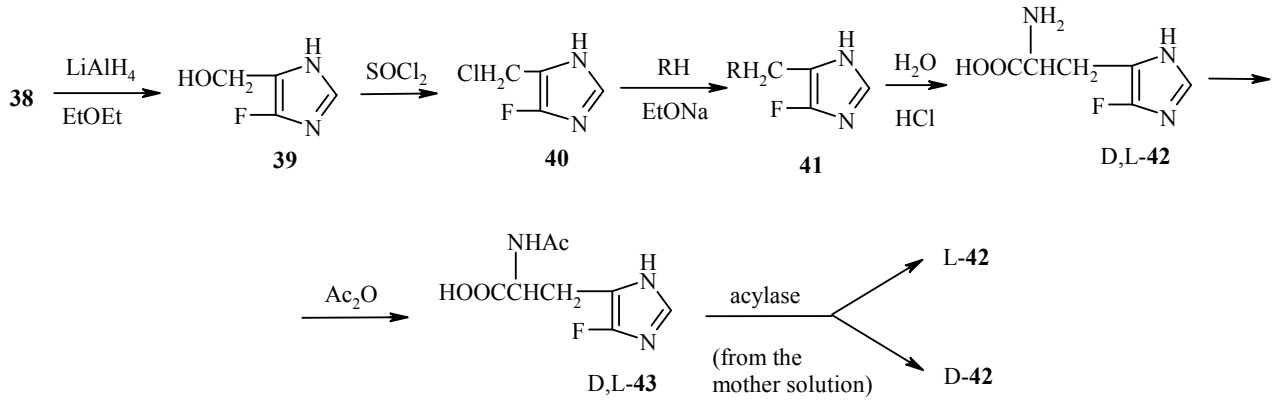
The acetylation of 4(5)-fluoroimidazole (**33**) gave 1-acetyl-4-fluoroimidazole **35** (yield 80%), the treatment of which with methyl fluorosulfonate led to 5-fluoro-1-methylimidazole **36** (yield 79%) [11].



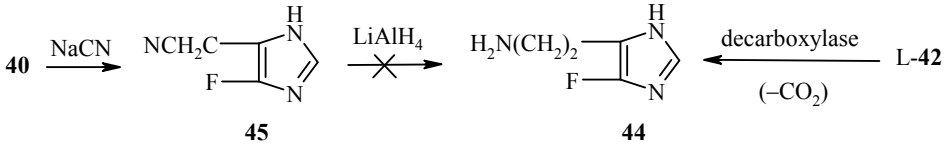
The synthesis of histidine and histamine derivatives 4-fluoro-substituted in the imidazole ring was realized through a series of 4(5)-fluoro-substituted derivatives of imidazole [9, 10]. Thus, the key product ethyl 4(5)-fluoroimidazole-5(4)-carboxylate (**38**) was obtained with a yield of 39% by diazotization of the ester of the amino acid **37** followed by photolysis of the intermediate diazonium salt [9, 10].



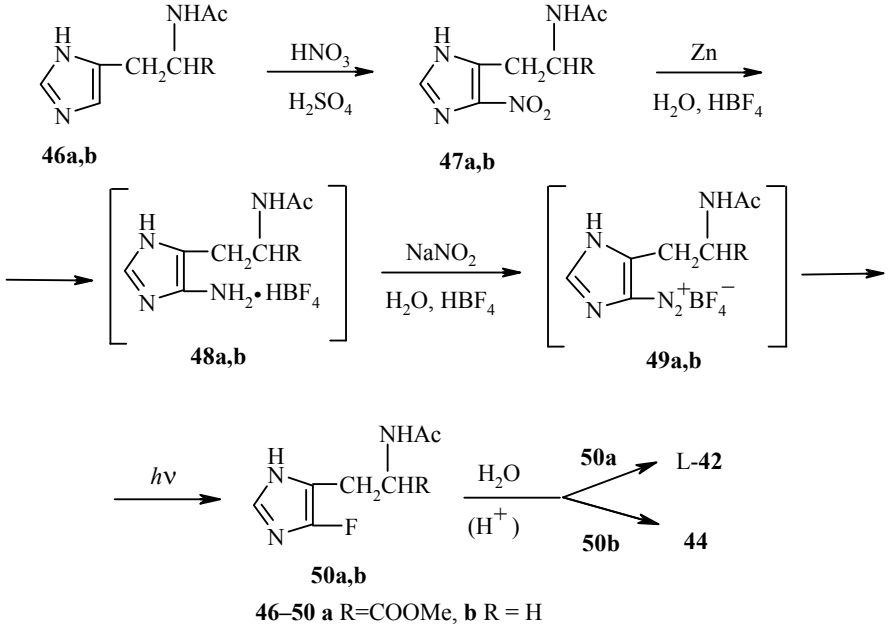
Reduction of the ester **38** with $LiAlH_4$ gave the alcohol **39** (yield 40%), treatment of which with $SOCl_2$ led to the chloromethyl derivative **40**, and this was then used further without purification. During the synthesis of fluoro-substituted histidine by the reaction of compound **40** with acetylaminomalonic ester the diester **41** was obtained (yield 26%), and the substituted D,L-histidine D,L-**42** was obtained from it by hydrolysis and decarboxylation (yield 82% on the ester **41**) [10]. The product was resolved into its antipodes by acetylation followed by deacetylation of the intermediate racemate D,L-**43** with acylase. The yield of fluoro-L-histidine L-**42** on the amino acid D,L-**42** amounted to 73%. The fluoro-D-histidine D-**42** was isolated from the mother solution after isolation of L-**42** with a yield of 41% on the racemate D,L-**42** [10].



In order to synthesize the fluorohistidine **44** from the chloromethyl-substituted compound **40** and NaCN the nitrile **45** was prepared (yield 18%). However, its reduction with $LiAlH_4$ did not lead to the desired product. (The oily product only contained traces of it.) By the other path – enzymatic decarboxylation of the fluoro-L-histidine L-**42** by the action of decarboxylase – it was possible to obtain the fluorohistamine **44** with a yield of 43% [10].

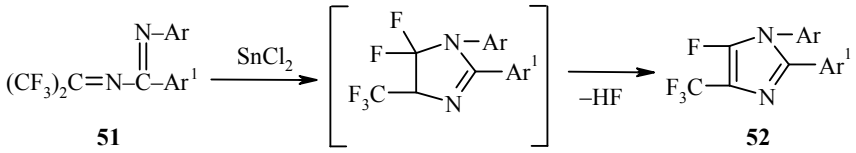


Simpler methods for the production of 4-fluoroimidazoles L-**42** and **44** are based on the nitration of the acetyl derivatives of histidine and histamine **46a** and **46b** respectively, leading to the nitro compounds **47a**,**b** with yields of 44-63%. By successive reduction of the products **47a**,**b**, diazotization, and photochemical cleavage the N-acetyl derivatives **50a**,**b** were synthesized with yields of 10-18% through the intermediate compounds **48a**,**b** and **49a**,**b**. Acid hydrolysis of these compounds gave the fluorohistidine L-**42** and fluorohistamine **44** [21].



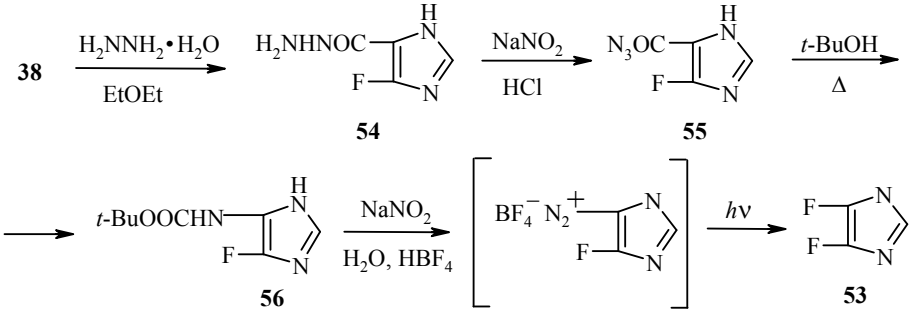
46–50 a R=COOMe, **b** R = H

The cyclization of the amidines **51** by the action of $SnCl_2$, resulting in the formation of 1,2-diaryl-4-fluoroimidazoles **52**, was described [23].



Ar = $C_6H_3Me_2$-*o*,*o*', $C_6H_2Me_3$-*o*,*o*',*p*; Ar^1 = Ph, C_6H_4Me-*p*, C_6H_4F-*p*, C_6H_4Cl-*p*

4,5-Difluoroimidazole **53** was synthesized from the ester **38** through the hydrazide **54** (yield 81%), the azide **55** (yield 88%), and the *tert*-butyl carbamate **56** (yield 94%). The target product **53** was obtaining by diazotization of the latter and photochemical cleavage of the diazoniun salt with a yield of 36% on the carbamate **56** [24].

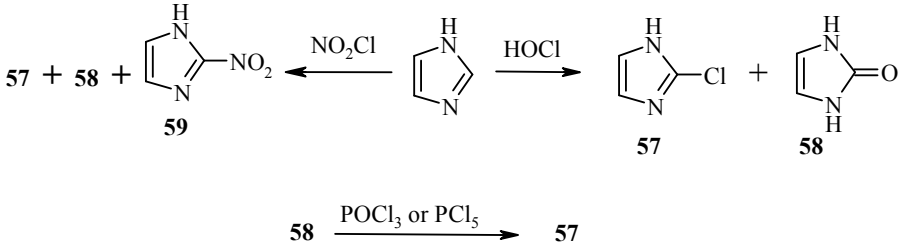


2,4(5)-Difluoro- and 2,4,5-trifluoroimidazoles were mentioned in a theoretical paper [25] without reference to the methods of synthesis.

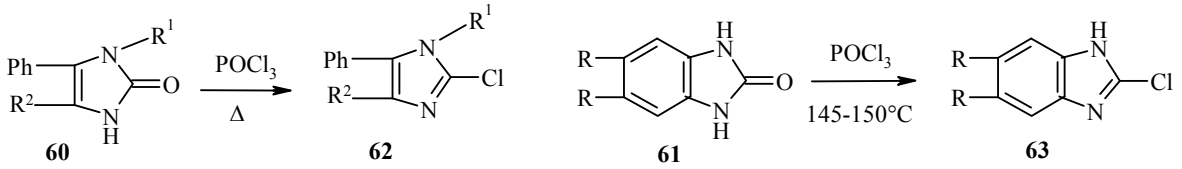
2. SYNTHESIS OF CHLOROIMIDAZOLES

2.1. Synthesis of 2-Chloroimidazoles

The chlorination of imidazole with chlorine has not been described. During chlorination with HOCl a mixture of 2-chloroimidazole (**57**) and imidazol-2-one (**58**) is formed [26], and with NO_2Cl a mixture of compounds **57**, **58**, and 2-nitroimidazole (**59)** is obtained [27]. Chloroimidazole **57** was also obtained with a yield of 25% by treating imidazolone **58** with $POCl_3$ [13] or PCl_5 [28]. The photochemical synthesis of 2-chloro- (**57**) and 2-chloro-1-methylimidazole (**7d**) [13] was mentioned above (see section 1.1).

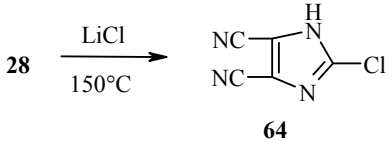


The alkylation of the chloride **57** gave its 1-alkyl-substituted derivatives (see Section 4.1). 2-Chloroimidazoles **62** (yields 59-99%) [29, 30] and 2-chlorobenzimidazoles **63** (yields 79-85%) [31] were produced by the reaction of imidazolones **60** and benzimidazolones **61** with $POCl_3$.

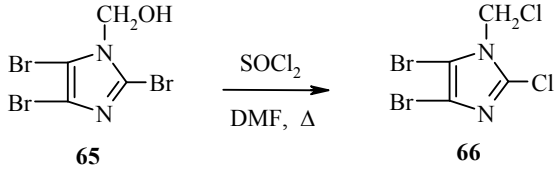


60, **62** R^1= H, Me; R^2 = H, Ph; **61**, **63** R = H, Me

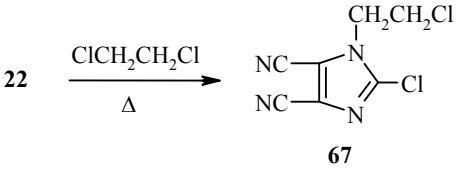
When 2-bromo-4,5-dicyano-1-methylimidazole (**28**) is heated with LiCl, the bromine atom is substituted by chlorine, and demethylation also occurs leading to the formation of the product **64** with a yield of 73% [20].



4,5-Dibromo-2-chloro-1-(chloromethyl)imidazole (**66**) was obtained by the reaction of 2,4,5-tribromo-1-hydroxymethylimidazole (**65**) with $SOCl_2$ [32].



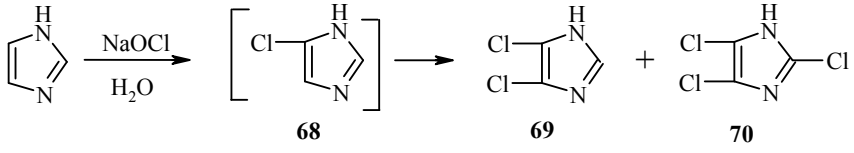
The pyrolysis of the diazo compound **22** in 1,2-dichloroethane takes place with simultaneous alkylation of the imidazole ring and substitution of the diazo group by a chlorine atom, resulting in the formation of the product **67** with a yield of 80% [18, 19].



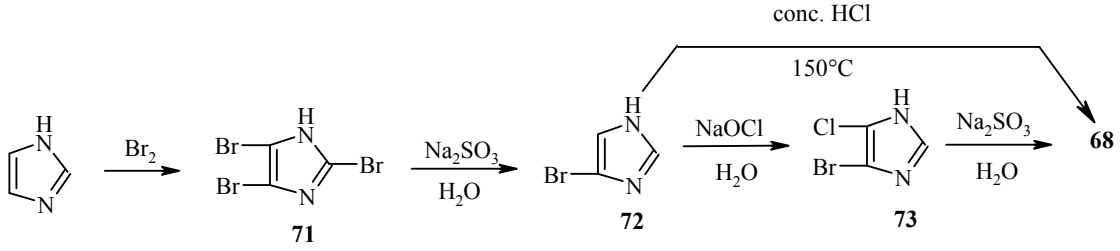
2.2. Synthesis of 4(5)-Chloro-, 4,5-Dichloro-, and 2,4,5-Trichloroimidazoles

2.2.1. Chlorination of Imidazoles

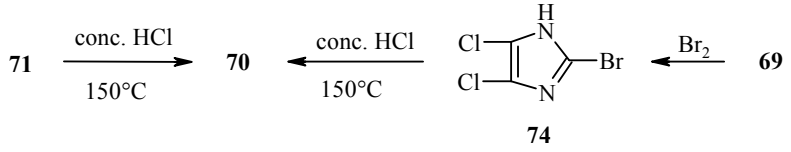
The chlorination of imidazole with NaOCl does not stop at the formation of 4(5)-chloroimidazole (**68**) but goes further and leads to 4,5-dichloro- (**69**) and 2,4,5-trichloroimidazoles and (**70**) with yields of 77 and 9% respectively [33].



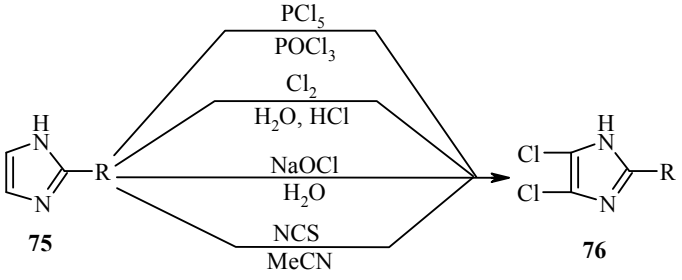
Since the dichloro and trichloro derivatives are not reduced by Na_2SO_3 to chloroimidazole **68** the latter was obtained through the bromo-substituted imidazoles. Thus, the bromination of imidazole with bromine gave 2,4,5-tribromoimidazole (**71)**, which was reduced to 4(5)-bromoimidazole (**72)** by Na_2SO_3. Chlorination of the product with NaOCl gave an 81% yield of 4(5)-bromo-5(4)-chloroimidazole **73**, the reduction of which with Na_2SO_3 led to chloroimidazole **68** (yield 79%). The same product was obtained with a yield of about 90% by treating bromoimidazole **72** with conc. HCl at 150°C, but in this case it contained about 8% of the initial compound **72** as impurity [33].



Trichloroimidazole **70** was also obtained with yields of 35-69% by heating tribromoimidazole **71** and 2-bromo-4,5-dichloroimidazole (**74**) with conc. HCl [33].

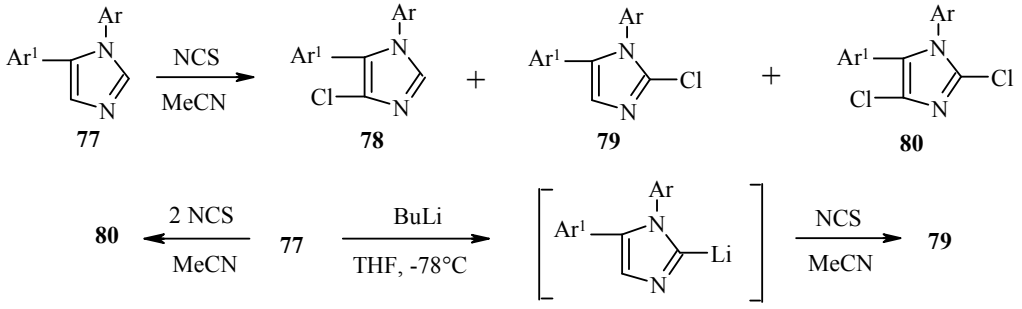


The chlorination of 2-substituted imidazoles **75** by the action of PCl_5 [34], chlorine [35], NaOCl [33, 36, 37], and N-chlorosuccinimide (NCS) [38] leads to the corresponding 4,5-dichloroimidazoles **76** (yields 18-93%).



R = Alk, COOH, $CH(OEt)_2$, 3-pyridyl

The chlorination of 1,5-diarylimidazoles **77** with N-chlorosuccinimide gave mixtures of 4-chloro-, 2-chloro-, and 2,4-dichloroimidazoles **78**, **79**, and **80** (yields 60-84, ~2, and ~5% respectively). If two moles of NCS are used to one mol of diarylimidazole **77** the main products are the dichlorides **80** (yields ~80%). The 2-chloroimidazoles **79** were synthesized by the treatment of compounds **77** with butyllithium and chlorination of the obtained 2-lithio derivatives with NCS (yields 37-80%) [39].



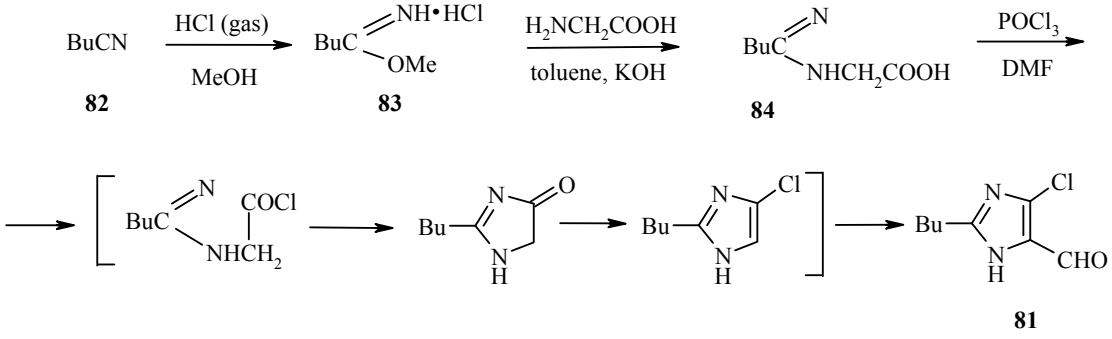
Ar = C_6H_4R-*p* (R = F, SMe, SO_2Me); Ar^1 = $C_6H_4R^1$-*o* (R^1 = Cl, F); $C_6H_4R^1$-*m* (R^1 = Me, OMe); $C_6H_4R^1$-*p* (R^1 = Alk, OAlk, SMe, SO_2Me, NH_2, NEt_2); $C_6H_3(OEt)_2$-*m*,*m*'; $C_6H_3R^1{}_2$-*m*,*p* (R^1 = Cl, F); $C_6H_2Cl_2$-*m*,*m*', OMe-*p*

1,5-Diaryl-4-chloro-2-methyl(hydroxymethyl)imidazoles were synthesized by an analogous method from 1,5-diaryl-2-methyl(hydroxymethyl)imidazoles (yields 60-80%) [39, 40].

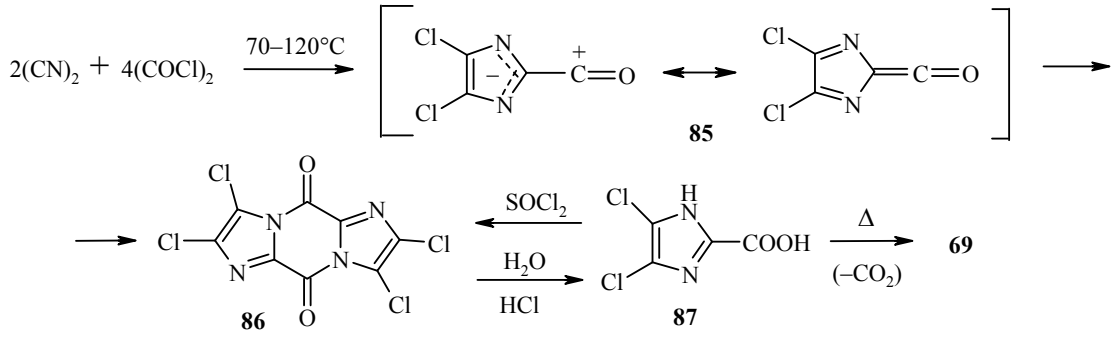
2.2.2. Production from Aliphatic Compounds

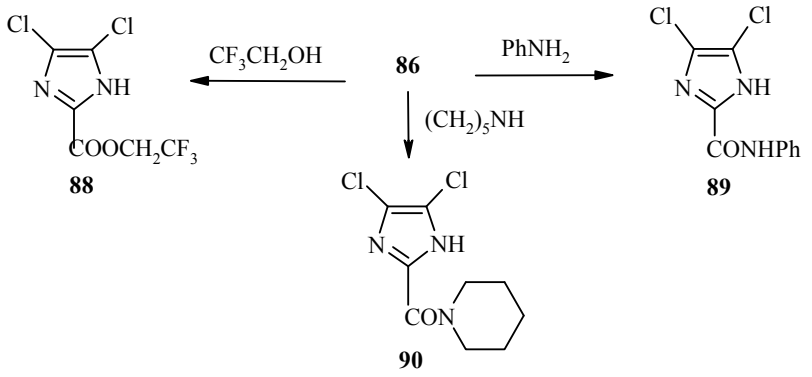
2.2.2.1. From the Nitriles of Carboxylic Acids

The synthesis of 2-butyl-5(4)-chloro-4(5)-formylimidazole (**81**) from butyronitrile **82** through the imino ester **83** and the amino acid **84** has been described. Cyclization of the latter by the action of $POCl_3$ in DMF led to compound **81** with a yield of 54% on the nitrile **82** [41].



The reaction of the dinitrile of oxalic acid (dicyanogen) with oxalyl chloride takes place through the intermediate ketene **85**, which is converted straight away into the dimer **86** (yield 60%) [42]. The latter was also obtained by treatment of the acid **87** with thionyl chloride (yield 68-72%) [36].

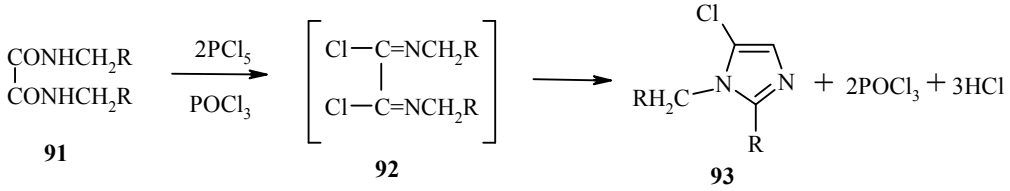




The dimer **86** is a highly reactive compound. During hydrolysis it is converted into the acid **87** (yield 91%), the decarboxylation of which gives dichloroimidazole **69** (yield 60%) [37, 42]. The ester **88** (yield 78%) [42] and the amides **89** and **90** (yields 70-98%) [36, 42] were synthesized by the reaction of the dimer **86** with trifluoroethanol and amines respectively.

2.2.2.2. From the Amides of Oxalic Acid

The exothermic reaction of N,N'-dialkyl(diaralkyl)oxamides **91** with PCl_3 [3], discovered by O. Wallach, takes place smoothly in $POCl_3$ as solvent [43] and leads to the intermediate N,N'-dialkyl-(diaralkyl)oxalimidoyl chlorides **92** [44]. The latter readily undergo cyclization under analogous conditions with the formation of 5-chloroimidazoles **93** (yields 50-92%) [43-45].

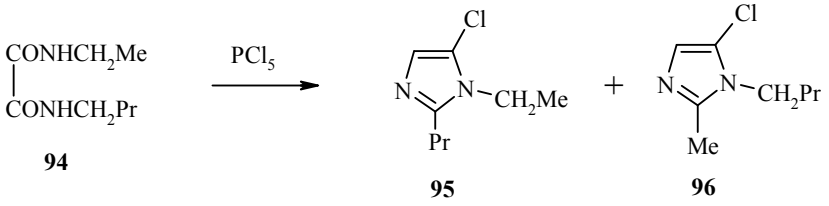


R = H, Alk, Ph

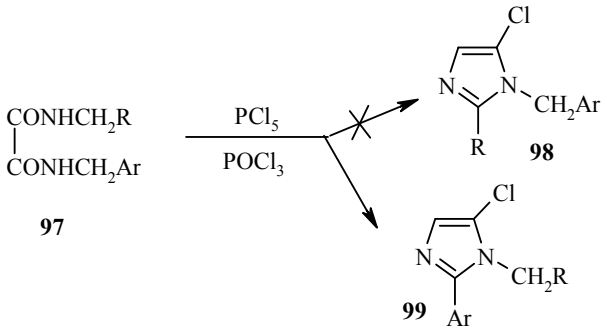
The intermediate dichlorodiimide **92** (R = Et) was isolated, its structure was established, and the conditions for transformation to the corresponding chloroimidazole **93** were determined [44].

The reaction of the amides **91** with PCl_5 is regiospecific; as confirmed by chromatography the obtained 5-chloroimidazoles **93** do not contain the 4-chloro isomers as impurities [44, 45].

The reaction of N-butyl-N'-ethyloxamide **94** with PCl_5 leads to a mixture of isomeric 5-chloro-imidazoles **95** and **96** with a total yield of 76% [46].

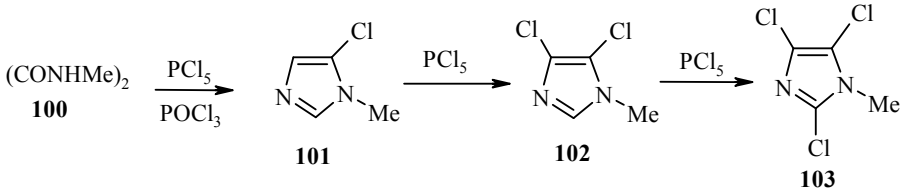


During the cyclization of N-alkyl-N'-arylmethyloxamides **97** by the action of PCl_5 of the two theoretically possible isomers **98** and **99** only the 1-alkyl-2-aryl-5-chloroimidazoles **99** were isolated (yields 39-81%), indicating higher reactivity for the CH_2Ar group compared with the CH_2Alk group [47].

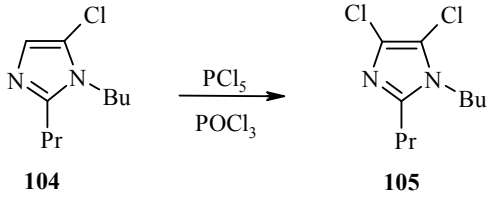


R = H, $(CH_2)_3OMe$; Ar = Ph, C_6H_4Cl-*o*, C_6H_4Cl-*p*, 3-pyridyl

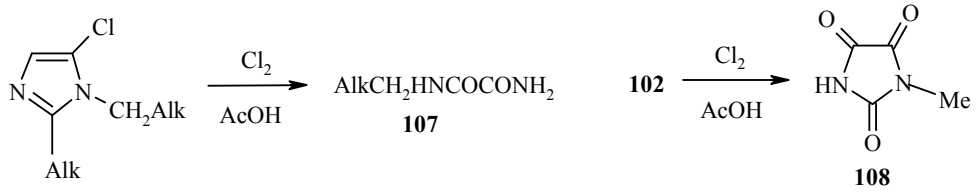
A detailed study of the reaction of N,N'-dimethyloxamide **100** with PCl_5 made it possible to isolate also small amounts (2-4%) of 4,5-dichloro-1-methyl- and 2,4,5-trichloro-1-methylimidazoles (**102**) and (**103**) respectively in addition to the main product 5-chloro-1-methylimidazole (**101**) (yield 51-56%) [48]. Compounds **102** and **103** result from further chlorination of the chloroimidazole **101** by the action of PCl_5 at position 4 and then at position 2 of the imidazole ring [34, 48, 49].



The chlorination product **105** was obtained similarly with a yield of 97% from the dialkyl-substituted chloroimidazole **104** [34, 49].



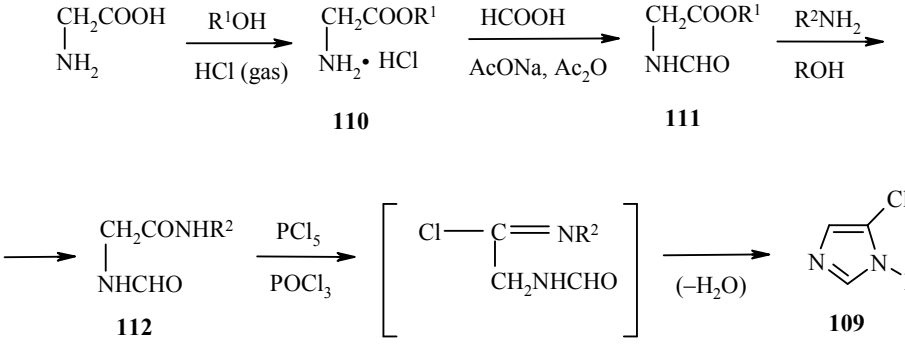
In the reaction of compounds **101** and **102** with chlorine in $POCl_3$ the yields of the di- and trichloroimidazoles **102** and **103** respectively are very low. Attempts at chlorination with chlorine in glacial acetic acid led to oxidation of the initial 5-chloroimidazoles **106** to N-alkyloxamides **107** and of the dichloroimidazole **102** to 1-methylparabanic acid **108** [50].



106, **107** Alk = Et, Pr

2.2.2.3. Synthesis from Glycine

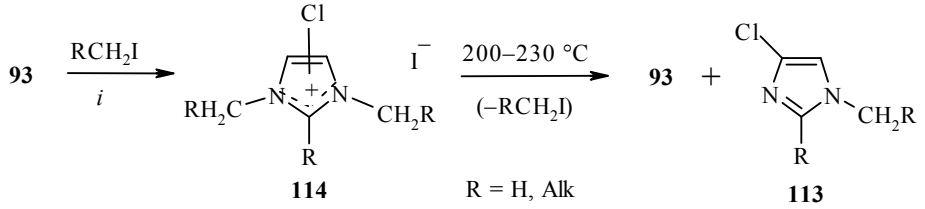
It is possible to synthesize 1-alkyl(aryl, aralkyl)-5-chloroimidazoles **109** starting from glycine, and the alkyl substituent can be fairly long and branched. Thus, the formylation of glycine methyl or ethyl ester **110** with formic acid in the presence of acetic anhydride gives the corresponding esters of N-formylglycine **111** (yields ~80%) [51]. Treatment of the latter with primary amines leads to the amides **112** (yields 40-96%) [51, 52]. 5-Chloroimidazoles **109** were synthesized by cyclization of the amides **112** and also of N-formylglycine anilide (obtained by the method in [53]) by the action of PCl_5 (yields 26-52%) [54, 55].



R^1 = Me, Et; R^2 = Alk, $PhCH_2$, Ph

2.2.3. Synthesis of 1-Alkyl(1,2-dialkyl)-4-chloroimidazoles

1-Alkyl(1,2-dialkyl)-4-chloroimidazoles **113**, unobtainable by direct chlorination, are obtained in two stages from the similarly substituted 5-chloroimidazoles of type **93**. Quaternization of the latter with alkyl iodides leads to the quaternary salts **114** (yields 60-92%), which undergo thermal cleavage with the formation of a mixture of 5-chloro- and 4-chloroimidazoles. The desired 4-chloroimidazoles **113** (yields 35-60%) and also the initial 5-chloroimidazoles **93** (yields 5-10%) were isolated from the mixture by fractional distillation [56-58].

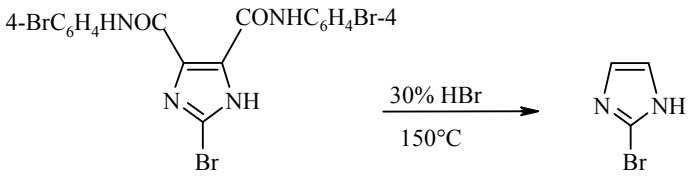


i = acetone (benzene)

3. SYNTHESIS OF BROMOIMIDAZOLES

3.1. Synthesis of 2-Bromoimidazoles

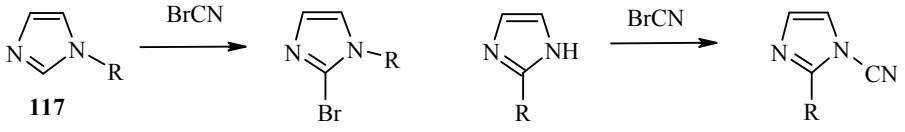
2-Bromoimidazole (**115)** was obtained with a 52% yield by treating 2-bromoimidazole-4,5-dicarboxamide **116** with 30% HBr at 150°C [59].



116 **115**

1-Aralkyl-substituted derivatives were obtained from the bromide **115** by alkylation (see Section 4.1).

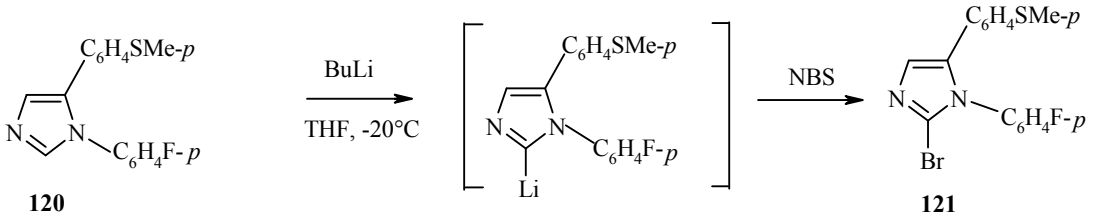
The reaction of 1-alkyl(benzyl)imidazoles **117** with BrCN leads to the corresponding 2-bromoimidazoles **118** (yields 24-64%). Under these conditions the 2-alkylimidazoles **75** form 2-alkyl-1-cyanoimidazoles **119** [60].



117 **118** **75** **119**

117, **118** R = Alk, $PhCH_2$; **75**, **119** R = Alk

The reaction of 1,5-diarylimidazole **120** with BuLi followed by bromination of the intermediate lithium derivative with N-bromosuccinimide leads to the 1,5-diaryl-2-bromoimidazole **121** [39].



120 **121**

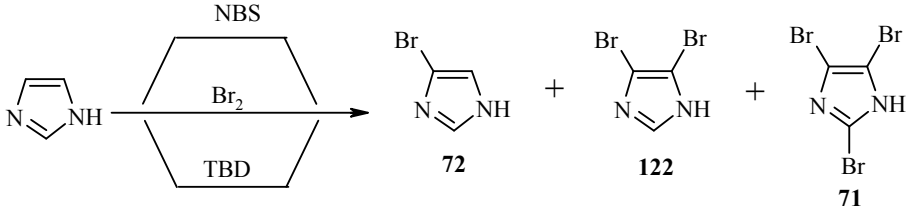
The synthesis of 2-bromo-1-methylimidazole **7b** [16] was mentioned above (Section 1.1).

3.2. Synthesis of 4(5)-Bromo-, 4,5-Dibromo-, and 2,4,5-Tribromoimidazoles

3.2.1. By Bromination of Imidazoles

The bromination of imidazole by bromine [33, 61-63], NBS [61, 64], and 2,4,4,6-tetrabromohexa-2,5-diene (TBD) [65] leads to various mixtures of 4(5)-bromo- **72**, 4,5-dibromo- **122**, and 2,4,5-tribromoimidazole **71**. The yield of the tribromide **71** during the bromination of imidazole with bromine in glacial acetic acid in the presence of AcONa amounts to 78-80% [62].

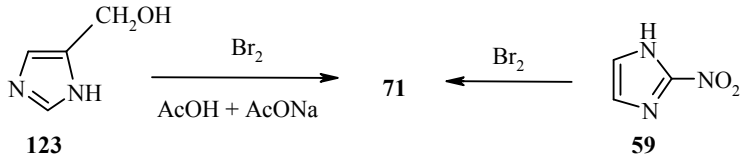
The bromination of imidazole with NBS also leads to a mixture of compounds **72**, **122**, and **71** with yields of 41, 38, and 3% [64] or 41, 28, and 27% respectively [63].



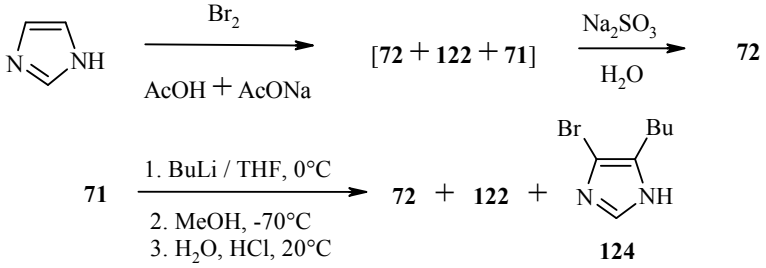
72 **122** **71**

A mixture of the same products **72**, **122**, and **71** (yields 78, 13, and <1% respectively) is obtained during the bromination of imidazole *p*-toluenesulfonate [63].

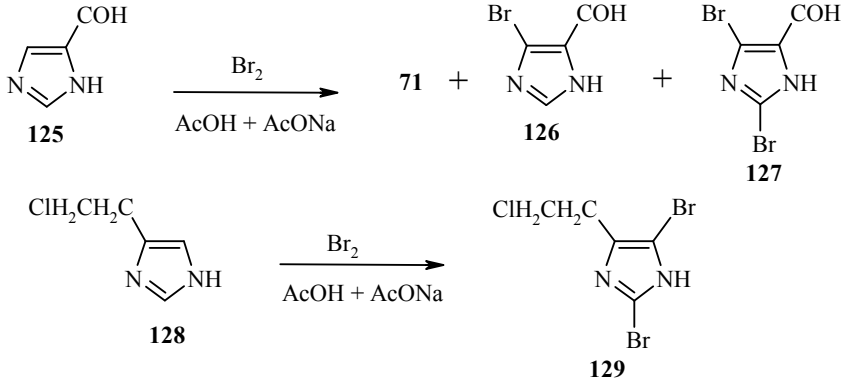
The tribromide **71** was also synthesized with a yield of 23-30% by the bromination of 4(5)-hydroxymethylimidazole (**123**) [62] and 2-nitroimidazole **59** [66].

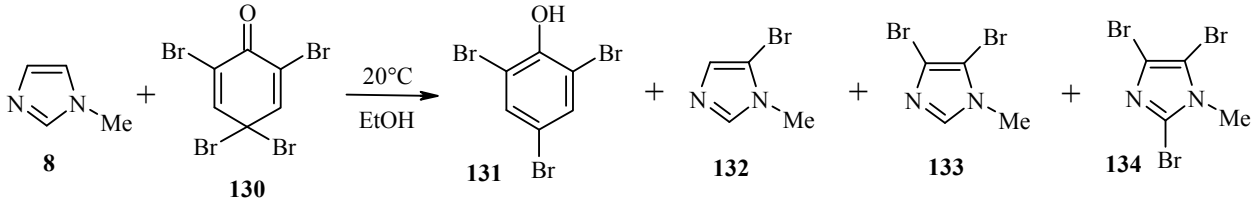


The simplest preparative method for the production of bromoindazole **72** (yield 62% on the imidazole) is reduction of the technical mixture of bromoimidazoles formed during the bromination of imidazole with bromine by the action of Na_2SO_3 [62]. The reduction of the tribromide **71** with butyllithium gives an increased yield of the bromoimidazole **72** of 83%, but in this case the product contains the dibromide **122** and 4(5)-bromo-5(4)-butylimidazole (**124**) as impurities [62].



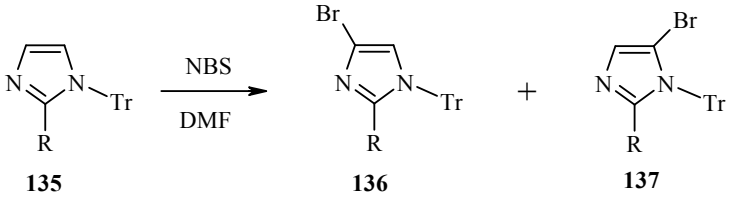
The bromination of 4(5)-substituted imidazoles with bromine leads to mixtures of products. Thus, in the case of 4(5)-formylimidazole (**125**), the tribromoimidazole **71**, the bromoaldehyde **126**, and the dibromoaldehyde **127** are formed with yields of 14, 32, and 2% respectively. The 2,4(5)-dibromo product **129** was obtained from 4(5)-(2-chloroethyl)imidazole under the same conditions with a yield of 76% [62].





As a result of the bromination of 1-methylimidazole **8** with TBD **130** a mixture of 2,4,6-tribromophenol **131** and bromoimidazoles **132**-**134**, containing 66% of the monobromide, is formed. If the amount of TBD is doubled the main product of the reaction is the dibromide **133** (yield 65%) [65].

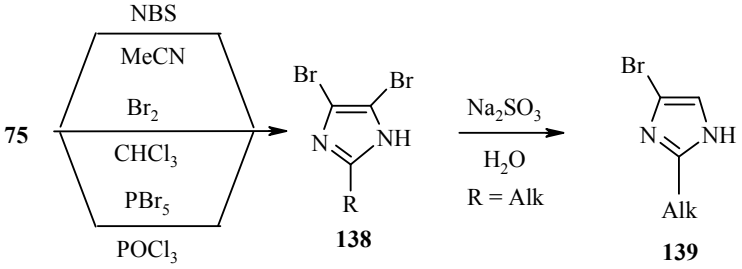
The reaction of 1-tritylimidazoles **135** with NBS leads to mixtures of the corresponding substituted derivatives of 4-bromoimidazole **136** (yields 64-75%) and 5-bromoimidazole **137** (yield <10%) [64].



135 **136** **137**

R = H, Me; Tr = CPh_3

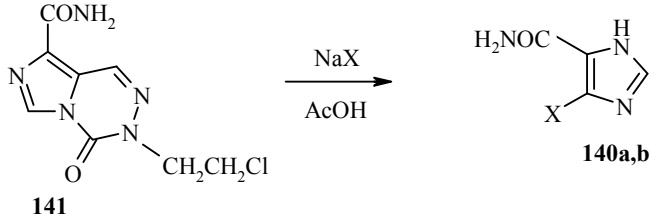
The 4,5-dibromoimidazoles **138** were synthesized with yields of 52-92% by bromination of the 2-substituted imidazoles **75** with bromine [33, 36, 67], NBS [38, 64], and PBr_5 [34, 49]. Reduction of the products (with R = Alk) by Na_2SO_3 gave 2-84% yields of the 2-alkyl-4(5)-bromoimidazoles **139** [67].



138 **139**

R = Alk, COOH, COOEt, $CONHC_6H_4Br$-*p*, 3-pyridyl, NO_2

Cleavage of the bicyclic compound **141** by heating with NaBr or NaI in acetic acid led to the 4(5)-bromoimidazole-5(4)-carboxamide **140a** or the iodide **140b** respectively (yields 22-31%) [68].

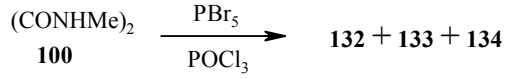


141 **140a,b**

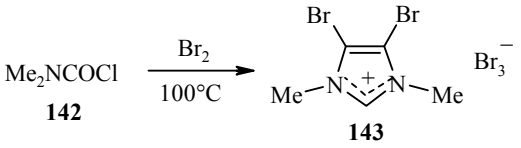
a X = Br, **b** X = I

3.2.2. Production from Aliphatic Compounds

The reaction of N,N'-dimethyloxamide **100** with PBr_5 in $POCl_3$ takes place similarly to the reaction with PCl_5 and leads to a mixture of 5-bromo- (**132**), 4,5-dibromo- (**133**), and 2,4,5-tribromo-N-methylimidazoles, **134** with yields of 25-30%. The formation of the di- and tribromide **133** and **134** respectively is explained by the successive bromination of the initially formed 5-bromo-1-methylimidazole **132** [48, 49].



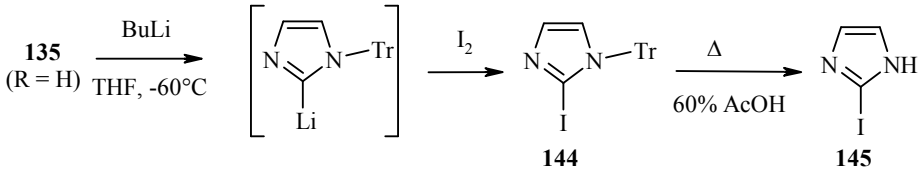
Bromination of the carbamoyl chloride **142** with bromine gives a 16% yield of 4,5-dibromo-1,3-dimethylimidazolium perbromide **143** [69].



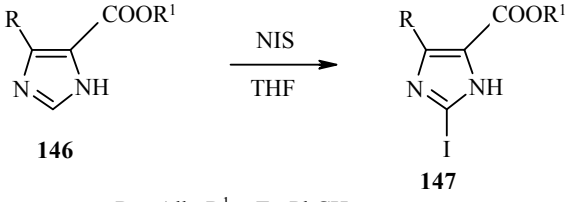
4. SYNTHESIS OF IODOIMIDAZOLES

4.1. Synthesis of 2-Iodoimidazoles

The general method for the synthesis of 2-haloimidazoles **7a-d** by the action of butyllithium followed by a halogen reagent on 1-methylimidazole **8** has already been described above (Section 1.1). The analogous treatment of 1-tritylimidazole **135** (R = H) with butyllithium and iodine leads to an 88% yield of 2-iodo-1-tritylimidazole **144**, the hydrolysis of which in 60% acetic acid gives 2-iodoimidazole **145** [70, 71].

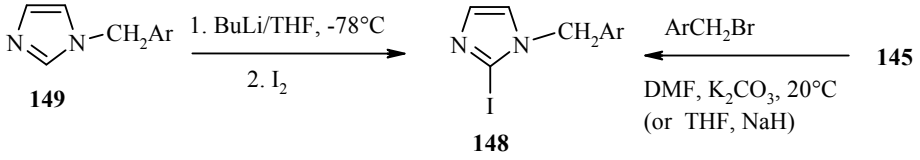


2-Iodoimidazoles **147** were obtained by the iodination of 4,5-disubstituted imidazoles **146** with N-iodosuccinimide (yields 60-88%) [72].



R = Alk; R^1 = Et, $PhCH_2$

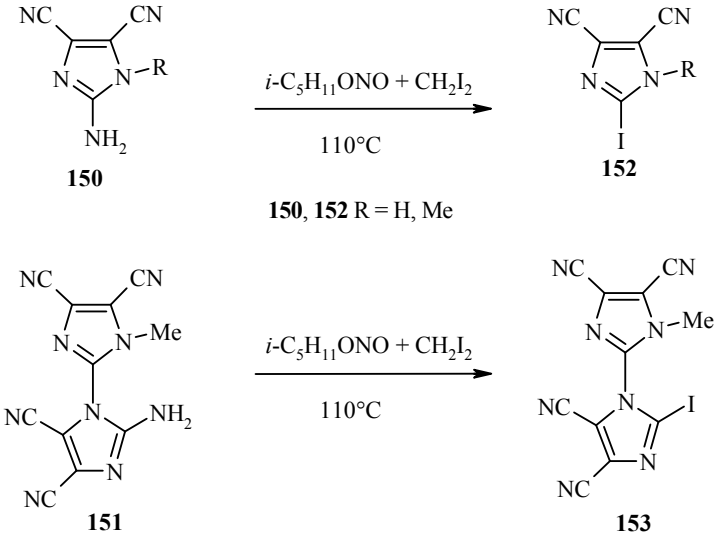
1-Aralkyl-2-iodoimidazoles **148** were synthesized in two ways: Iodination of 1-aralkylimidazoles **149** (yields 22-71%) [71] and alkylation of 2-iodoimidazole **145** (yields 58-93%) [71, 73, 74].



Ar = Ph, C_6H_4OMe-*o*,-*m*,-*p*, C_6H_4CN-o,-*m*,-*p*, C_6H_4Cl-*o*,-*m*,-*p*, $C_6H_4CF_3$-*o*,-*m*,-*p*, $C_6H_3(OMe)_2$-*m*,-*m*'

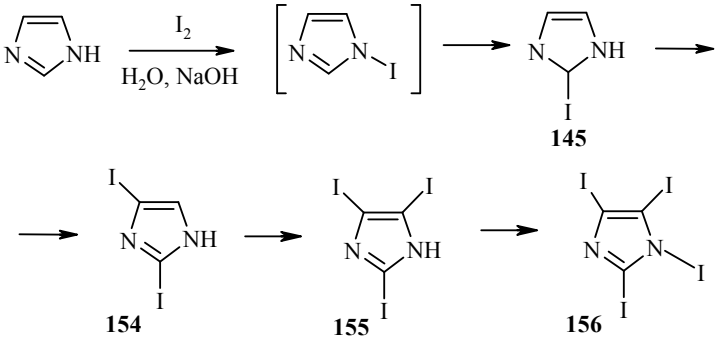
The corresponding 1-aralkyl-2-chloro(bromo)imidazoles were obtained similarly by the alkylation of 2-chloro- (**57**) and 2-bromoimidazoles **115** in THF in the presence of NaH (yields 59-93%) [74].

The reaction of 2-aminoimidazoles **150** and **151** with isoamyl nitrite and diiodomethane at 110°C leads to substitution of the NH_2 group by an iodine atom and the formation of the 2-iodo-substituted products **152** (yields 33-40%) and **153** (yield 71%) respectively [15].



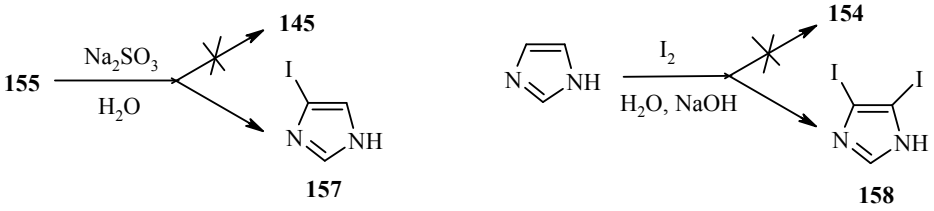
4.2. Synthesis of 4(5)-Iodo-, 4,5-Diodo-, 2,4,5-Triiodo-, and 1,2,4,5-Tetraiodoimidazoles

H. Pauly and co-authors, who first obtained iodoimidazoles at the beginning of the twentieth century [75-77], considered that the iodination of imidazole with iodine in a aqueous solution of NaOH took place by the successive formation of the 2-iodo (**145**), 2,4(5)-diiodo (**154**), 2,4,5-triiodo (**155**), and 1,2,4,5-tetraiodo (**156**) derivatives of imidazole. This iodination scheme was presented in the monograph [3]. The structure of the triiodide **155** was adopted by analogy with the structure of its tribromo-substituted analog **71**. According to data in [76, 77], the same authors considered that they had obtained the 2-iodo-substituted product **145** during the reduction of di- and triiodoimidazoles with Na_2SO_3.

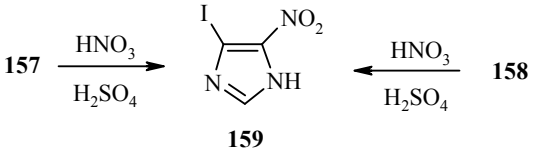


A scheme for the stepwise iodination of imidazoles at position 2 and then at position 4(5) was also suggested by other authors [3, 78-80]. In these papers, as also in Pauly's papers [75-77], the obtained iodoimidazoles, including iodopilocarpine, iodohistidine, etc., were assigned the structure of the respective 2-iodo-substituted derivatives without any structural evidence.

In the sixties to eighties of the twentieth century repeated investigations of previously described iodo and diiodo derivatives of imidazole were undertaken. Thus, in [81, 82] 4(5)-iodoimidazole **157** and not 2-iodoimidazole **145**, as previously considered [77], was obtained by the reduction of the triiodide **155** with Na_2SO_3 according to the method in [77]. It was demonstrated [82] that the 4,5-diiodo derivative **158** and not the 2,4(5)-diiodo derivative **154** was formed during the iodination of imidazole under the previously described conditions [77-79].

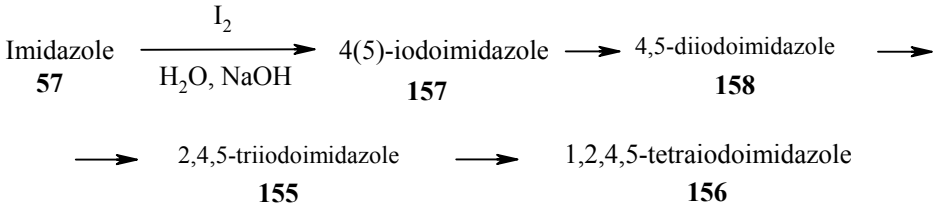


The structure of compounds **157** and **158** was proved rigorously by means of the ^{1}H NMR spectra [81, 82], mass spectra [83], and chemical transformations to 4(5)-iodo-5(4)-nitroimidazole **159** during the nitration of iodoimidazole **157** [84] and *ipso* nitration of diiodoimidazole **158** [85, 86].



4(5)-Iodo-5(4)-methylimidazole [82] and 4(5)-iodohistidine [81, 82, 87] were synthesized again by the iodination of 4(5)-methylimidazole and histidine according to the previously described methods, and their structures were confirmed by modern spectral methods. The previously named compounds were assigned the structures of the corresponding 2-iodo derivatives.

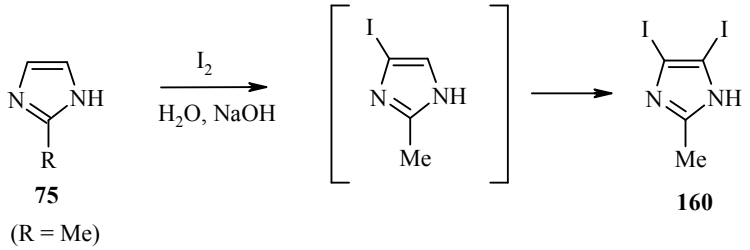
Thus, as a result of the repeated investigations [81-87] it was established that the iodination of imidazole takes place through the same stages as its chlorination and bromination. The only difference lies in the fact that with an excess of iodine the triiodoimidazole **155** also undergoes iodination at position 1 with the formation of the tetraiodoimidazole **156**.



In addition to compound **156**, which was synthesized by iodination of the triiodide **155** [76, 78], other 1-iodosubstituted imidazoles such as 1-iodo-2,4,5-trimethylimidazole, obtained by the iodination of 2,4,5-trimethylimidazole [76], are also known.

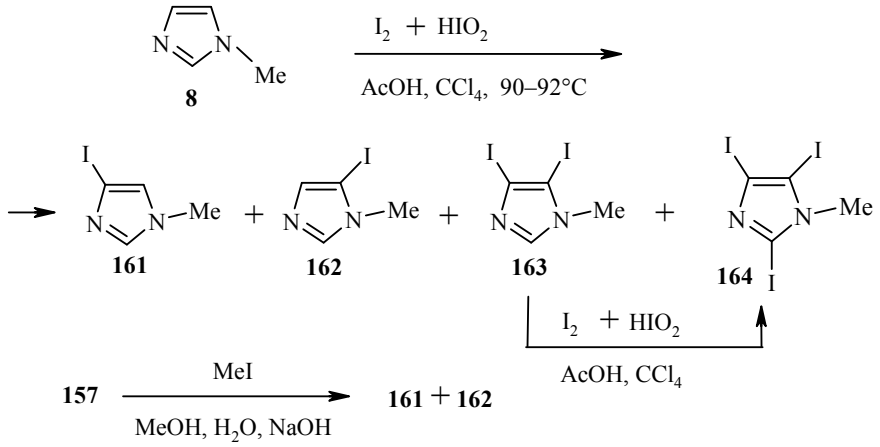
Simplified methods for the production of iodoimidazoles were proposed in a series of papers: The iodide **157** was obtained by reduction of the technical mixture of triiodo- **155** and diiodoimidazoles **158** with Na_2SO_3 [89]; the diiodide **158** was produced by the iodination of imidazole with the calculated amount of iodine in the water–NaOH–hexane system [82]; the triiodide **155** was obtained by the iodination of imidazole with iodine in the water–NaOH–petroleum ether system [90].

The iodination of 2-methylimidazole **75** (R = Me) does not stop at the stage of the monoiodo derivative but goes further with the formation of the 4,5-diiodide **160** [79].

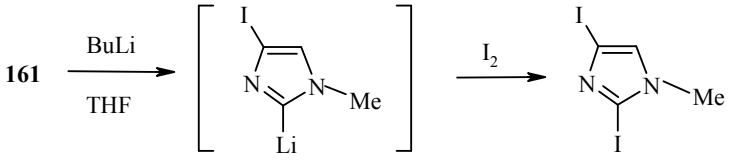


75 (R = Me) **160**

The iodination of 1-methylimidazole **8** with a mixture of I_2 and HIO_3 leads to the formation of the products **161**-**164**: the iodoimidazoles **161** and **162** (yield of 4:1 mixture 14%), the diiodide **163** (yield 33%), and the triiodoimidazole **164** (yield 2%). Compound **164** was also obtained with a 94% yield by the iodination of the diiodoimidazole **163**, while the isomeric iodoimidazoles **161** and **162** were obtained with yields of 38 and 52% respectively by the methylation of 4(5)-iodoimidazole **157** [91].



2,4-Diodo-1-methylimidazole **165** was synthesized with a 39% yield by the lithiation of 4-iodo-1-methylimidazole **161** followed by substitution of the lithium atom by iodine [91].



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The results of the numerous investigations described in this review demonstrate the great diversity of the methods for the synthesis of haloimidazoles (about 20). This is explained both by the ease of halogenation of the imidazoles with halogens (with the exception of fluorine) and with the various halogen-containing reagents (NaOCl, PBr_5, N-halosuccinimides, etc.) and by the chemical nature of the inserted halogen atom. We have examined both general and special methods for the synthesis of haloimidazoles. A general method for the production of chloro-, bromo-, and iodoimidazoles is halogenation by the action of NaOCl, Br_2, and I_2, leading

to the formation of mixtures of mono-, di-, and trihaloimidazoles, which require separation. The lithiation of imidazoles with BuLi followed by substitution of the lithium atom by halogen is used for the synthesis of 2-haloimidazoles. Owing to the impossibility of inserting a fluorine atom by the direct fluorination of imidazoles the synthesis of fluoroimidazoles is based on the diazotization of aminoimidazoles in aqueous HBF_4 followed by photochemical decomposition of the intermediate imidazolediazonium fluoroborates.

At the preparative level special methods for the production of individual groups of imidazole derivatives are useful: 2-Iodoimidazoles by the action of isoamyl nitrite and diiodomethane on 2-aminoimidazoles; 2-chloro-imidazoles by the treatment of imidazol-2-ones with $POCl_3$ or $POCl_5$; 1-alkyl(aralkyl)-2-bromoimidazoles by the bromination of the initial imidazoles with BrCN; 4(5)-chloro-, 4(5)-bromo-, and 4(5)-iodoimidazoles by the reduction of 4(5)-bromo-5(4)-chloroimidazole and 4,5-dibromo(diiodo)- and 2,4,5-tri-bromo(triiodo)imidazoles with Na_2SO_3; 1-alkyl(1,2-dialkyl)-5-chloroimidazoles from N,N'-dialkylimidazoles and the amides of N-formylglycine by reaction with PCl_5; 1-alkyl(1,2-dialkyl)-4-chloroimidazoles by thermal decomposition of the iodides of 1,3-bis(1,2,3-trialkyl)-4(5)-chloroimidazoles; 1,5-diaryl-4-fluoroimidazoles by the cyclization of 1,2-diaryl-3-di(fluoromethyl)amidines by the action of $SnCl_2$.

REFERENCES

1. M. D. Mashkovskii, *Drugs* [in Russian], Novaya Volna, Moscow (2005), p. 444.
2. M. Ogawa and A. Nishimura, Eur. Pat. Application No. 1417887, *Ref. Zh. Khim.*, 04.18-190.271P (2004).
3. K. Hofmann, *Imidazole and its Derivatives*. Interscience, New York, Interscience, London (1953), Pt. I.
4. E. Schipper and A. Day, in: R. Elderfield (editor), *Heterocyclic Compounds* [Russian translation], Izd. Inostr. Lit., Moscow (1962), Vol. 5, p. 161.
5. P. Bouchet, C. Coquelet, and J. Elguego, *Bull. Soc. Chim. Fr.*, 171 (1977).
6. B. Iddon, *Heterocycles*, **23**, 417 (1985).
7. R. C. Patterson, A. DiMaggio, A. L. Hebert, T. J. Haley, J. P. Mikitka, and I. M. Sarkar, *J. Org. Chem.*, **36**, 631 (1971).
8. J. Kraupa, *Chem. Listy*, **67**, 1035 (1973).
9. K. L. Kirk and L. A. Cohen, *J. Am. Chem. Soc.*, **93**, 3060 (1971).
10. K. L. Kirk and L. A. Cohen, *J. Am. Chem. Soc.*, **95**, 4619 (1973).
11. F. Farba, C. Gálvez, A. González, P. Viladoms, and J. Vilarrasa, *J. Heterocycl. Chem.*, **15**, 1227 (1978).
12. J. Vilarrasa, C. Galvez, and M. Callaffel, *Anal. Quim.*, **71**, 631 (1975); *Chem. Abstr.*, **83**, 178919 (1975).
13. Y. Takeuchi, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **44**, 4240 (1979).
14. Y. Takeuchi, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **43**, 3570 (1978).
15. M. E. Borai, A. N. Moustafa, M. Anwar, and F. I. Abdel Hay, *Pol. J. Chem.*, **55**, 1659 (1981).
16. N. S. Mani, J. A. Jablonowski, and T. K. Jones, *J. Org. Chem.*, **69**, 8115 (2004).
17. K. L. Kirk, W. Nagai, and L. A. Cohen, *J. Am. Chem. Soc.*, **95**, 8389 (1973).
18. W. A. Sheppard and O. W. Webster, *J. Am. Chem. Soc.*, **95**, 2695 (1973).
19. O. W. Webster, Ger. Pat. Appl. 2317453; *Chem. Abstr.*, **83**, 14926 (1974).
20. E. C. Coard, Liu Hui, and P. G. Rasmussen, *Tetrahedron*, **55**, 2811 (1999).
21. K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **38**, 3647 (1973).
22. T. Chandra, X. Zou, E. J. Valente, and K. L. Brown, *J. Org. Chem.*, **71**, 5000 (2006).
23. K. Burger, R. Ottinger, H. Goth, and J. Firl, *Chem. Ber.*, **115**, 2494 (1982).
24. B. Dolensky, Y. Takeuchi, L. A. Cohen, and K. L. Kirk, *J. Fluor. Chem.*, **107**, 147 (2001).

25. J. Garcia and J. Vilarrasa, *Heterocycles*, **27**, 1803 (1988).
26. N. R. Jena, P. S. Kushwaha, and P. S. Mishra, *J. Comput. Chem.*, **29**, 98 (2008).
27. R. K. Shukla and P. C. Mishra, *J. Phys. Chem. B*, **112**, 7925 (2008).
28. J. L. Imbach, R. Jacquier, and A. Romane, *J. Heterocycl. Chem.*, **4**, 451 (1967).
29. G. N. Tyurenkova, and N. P. Bednyagina, in: *Methods for the Production of Chemical Reagents and Preparations* [in Russian], IREA, Moscow (1967), No. 15, p. 173.
30. C. P. Whittle, *Aust. J. Chem.*, **33**, 1545 (1980).
31. N. P. Bednyagina, G. N. Tyurenkova, and I. V. Panov, *Zh. Obshch. Khim.*, **34**, 1575 (1964).
32. H. Rutz, K. Gubler, South African Pat. 6802643; *Chem. Abstr.*, **71**, 38964 (1969).
33. A. W. Lutz, S. Delorenzo, *J. Heterocycl. Chem.*, **4**, 399 (1967).
34. P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 398 (1965). [*Chem. Heterocycl. Comp.*, **1**, 265 (1965)].
35. P. M. Kochergin and M. A. Klykov, USSR Inventor's Certificate 232270; *Byul. Izobr.*, No. 1, 28 (1969).
36. J. P. Dirlam, R. B. James, and E. V. Shoop, *J. Heterocycl. Chem.*, **17**, 409 (1980).
37. J. P. Dirlam, R. B. James, and E. V. Shoop, *J. Org. Chem.*, **47**, 2196 (1982).
38. J. J. Baldwin, R. K. Lumma, F. C. Novello, G. S. Ponticello, J. M. Spraque, and D. E. Duggan, *J. Med. Chem.*, **20**, 1189 (1977).
39. C. Almansa, J. Alfón, A. F. de Arriba, F. L. Cavalcanti, I. Escamilla, L. A. Gómez, A. Miralles, R. Soliva, J. Bartrolí, E. Carceller, M. Merlos, and J. García-Rafanell, *J. Med. Chem.*, **46**, 3463 (2003).
40. C. Almansa, J. Bartroli, J. Billoc, F. L. Cavalcanti, R. Ferrando, L. A. Gomez, I. Ramis, E. Carieller, M. Merlos, and J. Garcia-Rafanell, *J. Med. Chem.*, **47**, 5579 (2004).
41. K. Srinivas, N. C. K. Snehalatha, S. Ramesh, and M. Pardhasatadhi, *Synthesis*, 506 (2004).
42. J. Sundermeger and H. W. Roesky, *Angew. Chem.*, **100**, 1417 (1988).
43. P. M. Kochergin, *Zh. Obshch. Khim.*, **34**, 2735 (1964).
44. P. M. Kochergin and R. M. Palei, *Zh. Obshch. Khim.*, **38**, 1132 (1968).
45. G. E. Trout and P. R. Levy, *Rec. Trav. Chim. Pays-Bas*, **85**, 765 (1966).
46. G. E. Trout and P. R. Levy, *Rec. Trav. Chim. Pays-Bas*, **84**, 1257 (1965).
47. E. F. Godefroi, C. A. M. van der Eycken, and P. A. J. Janssen, *J. Org. Chem.*, **32**, 1259 (1967).
48. P. M. Kochergin, *Zh. Obshch. Khim.*, **34**, 3402 (1964).
49. P. M. Kochergin, *Author's Abstract of Thesis for Doc. Chem. Sci.* [in Russian], Moscow (1968).
50. P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 402 (1965). [*Chem. Heterocycl. Comp.*, **1**, 268 (1965)].
51. V. S. Korsunskii, P. M. Kochergin, and V. S. Shlikhunova, *Zh. Org. Khim.*, **26**, 82 (1990).
52. V. S. Korsunskii, P. M. Kochergin, and V. S. Shlikhunova, USSR Inventor's Certificate 445649; *Byul. Izobr.*, No. 37, 61 (1974).
53. F. King, J. Clark-Lewis, D. Ridd, and G. Smith, *J. Chem. Soc.*, 1039 (1954).
54. V. S. Korsunskii, P. M. Kochergin, and V. S. Shlikhunova, USSR Inventor's Certificate 437765; *Byul. Izobr.*, No. 28, 53 (1974).
55. V. S. Korsunskii, P. M. Kochergin, and V. S. Shlikhunova, *Khim.-Farm. Zh.*, **24**, No. 5, 56 (1990).
56. P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 754 (1965). [*Chem. Heterocycl. Comp.*, **1**, 511 (1965)].
57. K. Shimada, *J. Pharm. Soc. Jpn.*, **91**, 221 (1971).
58. D. S. Noyce and G. T. Stowe, *J. Org. Chem.*, **38**, 3762 (1973).
59. G. B. Barlin, *J. Chem. Soc.* (*B*), 641 (1967).
60. P. B. W. McCallum, M. R. Grimmett, A. G. Blackman, and R. T. Weavers, *Aust. J. Chem.*, **52**, 159 (1999); *Ref. Zh. Khim.*, 00.07-19Zh.240 (2000).
61. G. L. Schmir and L. A. Cohen, *Biochemistry*, **4**, 533 (1965).
62. K. E. Stensio, K. Wahlberg, and R. Wahren, *Acta Chem. Scand.*, **27**, 2179 (1973).

63. T. J. Benson and B. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 211 (1992).
64. B. D. Palmer and W. A. Denny, *J. Chem. Soc., Perkin Trans. 1*, 95 (1989).
65. V. Calo, L. Lopez, F. Naso, and P. E. Todeseo, *J. Chem. Soc., Perkin Trans. 1*, 2567 (1972).
66. G. C. Lancini, N. Maggi, and P. Sensi, *Farmaco, Ed. Sci.*, **18**, 390 (1963).
67. P. M. Kochergin, A. M. Tsyganova, L. M. Viktorova, and E. M. Peresleni, *Khim. Geterotsikl. Soedin.*, Coll. 1, *Nitrogen-Containing Heterocycles* [in Russian] (1967), p. 126.
68. G. U. Baig and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 665 (1987).
69. A. L. Kanibolotskii, V. A. Mikhailov, and V. A. Savelova, *Zh. Org. Khim.*, **32**, 1589 (1996).
70. K. L. Kirk, *J. Org. Chem.*, **43**, 4381 (1978).
71. R. M. de Figueiredo, S. Thoret, C. Huet, and J. Dubois, *Synthesis*, 529 (2007).
72. W. E. Allen, Ch. J. Fowler, V. M. Lynch, and L. L. Sessler, *Chem. Eur. J.*, **7**, 721 (2001).
73. M. Moreno-Manas, J. Bassa, N. Liado, and R. J. Pleixtats, *J. Heterocycl. Chem.*, **27**, 673 (1990).
74. M. A. Clyne and F. Aldabbagh, *Org. Biomol. Chem.*, **4**, 268 (2006).
75. H. Pauly and K. Gundermann, *Ber.*, **41**, 3999 (1908).
76. H. Pauly and K. Gundermann, *Ber.*, **43**, 2243 (1910).
77. H. Pauly and E. Aranner, *J. prakt. Chem.* [2], **118** , 33 (1928).
78. J. H. Ridd, *J. Chem. Soc.*, 1238 (1955).
79. M. Hoffer, V. Toome, and A. Brossi, *J. Heterocycl. Chem.*, **3**, 454 (1966).
80. E. Winkelman, W. Raether, U. Gebert, and A. Sinharay, *Arzneim.-Forsch.*, **27** (II), 2251 (1977).
81. H. B. Bensusan and M. S. R. Naidu, *Biochemistry*, **6**, 12 (1967).
82. M. S. R. Naidu, and H. B. Bensusan, *J. Org. Chem.*, **33**, 1307 (1968).
83. N. J. Hasking, G. C. Ford, K. A. Waddell, J. P. Dickens, R. L. Dyer, R. J. Hamill, and T. A. Harrow, *Biomed. Mass. Spectrometry*, **8**, 351 (1981).
84. J. P. Dickens, R. L. Dyer, R. J. Hamill, and T. A. Harrow, *J. Chem. Soc., Chem. Commun.*, 523 (1979).
85. J. P. Dickens, R. L. Dyer, R. J. Hamill, T. A. Harrow, R. H. Bible, P. M. Finnegan, K. Henrick, and P. G. Owston, *J. Org. Soc.*, **46**, 1781 (1981).
86. V. Sudarsuman, K. Nagarajan, T. George, S. J. Shenoy, V. V. Iyer, and A. P. Kaulgud, *Ind. J. Chem.*, **21B**, 1022 (1982).
87. C. T. Holloway, R. P. M. Bond, J. G. Knight, and R. B. Beechey, *Biochemistry*, **6**, 19 (1967).
88. S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, L. V. Epishina, and V. V. Sevast'yanova, *Khim. Geterotsikl. Soedin.*, 664 (1970). [*Chem. Heterocycl. Comp.*, **6**, 614 (1970)].
89. K. L. Kirk, *J. Heterocycl. Chem.*, **22**, 57 (1985).
90. P. J. Garegg, R. Johanson, C. Ortega, and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 681 (1982).
91. M. S. Shvartsberg, L. N. Bizhan, A. N. Sinyakov, and N. R. Myasnikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1563 (1979).