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Nitroazoles: Synthesis, Structure and Applications

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Preface

The present monograph is devoted to the chemistry of nitroazoles, one of the most interesting series of heteroaromatic compounds. The azoles hold a special position in the chemistry of heterocycles. Their unique properties and specific biological activity attract much attention of research chemists all over the world. During the last years the interest in the chemistry of nitroazoles has increasing. The nitro derivatives of azoles have found a wide application in various fields of industrial chemistry, agriculture, and medicine. Medical products developed by nitroazoles incluce azomycin, metronidazole, misonidazole, tinidazole, nitazole, etc., ionic liquids, high-energy materials, synthons for nanocompounds, universal bases in peptide nucleic acids, plant growth regulators, and intermediates for organic synthesis.

The investigations in the field of energetic compounds have received enormous interest in recent years. Energetic materials on the base nitroazoles – explosives, propellants, and pyrotechnics – are widely used for both civilian and military applications. Nitroazoles, especially polynitroazoles, possess higher heat of formation, density, and oxygen balance than their carbocyclic analogs. A number of ongoing research programs worldwide are aimed for the development of new explosives and propellants with higher performance characteristics or enhanced insensitivity to thermal or shock insults and pyrotechnics with reduced smoke. The preparation of nitroazoles demonstrates its great synthetic potential. At the same time, feasibility and availability of the starting molecules make this strategy a powerful method for high-energy material construction. The introduction of electron-withdrawing nitro groups into azole cycle tends to produce energetic materials with high density, low sensitivity, and good thermal stability. Synthesis, molecular design, and explosive characteristics of new energetic compounds based on nitroazole have been studied in the famous Lawrence Livermore National Laboratory (USA). The investigations of research teams of A. Katritzky, A. Pozharskii, J. Elguero, S. Shevelev, V. Semenov, A. Sheremetev and so on, unveil the wide synthetic possibility of producing nitroazoles.

We consider azoles as five-membered heteroaromatic compounds and their annelated derivatives containing at least two endocyclic heteroatoms, one of which is nitrogen (pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, thiazole, selenazoles, tetrazole, indazole, benzimidazole, benzoxazole, benzothiazole, benzoselenazoles, benzotriazole, etc.).

A large body of information on the methods of synthesis, application, structure, and properties of all known five-membered nitroazoles – pyrazoles, imidazoles, triazoles, tetrazoles, oxazoles, isoxazoles, oxadiazoles, thiazoles, isothiazoles, thiadiazoles, selenazoles, selenadiazoles, and their benzo analogs – indazoles, benzimidazoles, benzoxazoles, benzisoxazoles, benzoxadiazoles, benzothiazoles, benzoisothiazoles, benzothiadiazoles, benzotriazoles, benzoselenazoles, and benzoselenadiazoles has been systematized, summarized, and critically discussed in this monograph.

Chapters 1 and 2 give comprehensive data on the preparation methods of all known *C*- and *N*-nitroderivatives of five-membered azoles and their condensed analogs. This book focuses on the nitration reaction, one of the main synthetic routes to nitroazoles. General information on the theory of nitration is given prior to the chapter covering synthetic methods. A separate section in the monograph is given to the special class of nitroazoles – polynitroazoles.

The critical evaluation of a large body of the information on the study of nitroazoles by physical/chemical methods (NMR, NQR, ESR, UV, IR- spectroscopy, X-ray, mass spectrometry, polarography, dipole moments, and other methods) is presented in Chap. 3.

Chapter 4 is devoted to the application of nitroazoles, many of which are important building blocks in drug discovery, well-known medicines, and hypoxic cell radiosensitizers.

Special attention is paid to those nitroimidazole derivatives among which are medicines with a vividly expressed therapeutical activity (azomycine, metronidazole, ipronidazole, carnidazole, dimetridazole, secnidazole, and many others) and to nitrotriazoles, nitrotetrazoles, and polynitroazoles used as high-energy compounds.

Our extensive investigations of the tautomerism, reactivity, electrochemistry, and structure of nitro derivatives of azoles are also included. Enormous number of facts are covered in the book.

This treatise constitutes the first complete collection of information on the chemistry of azoles containing a nitro group in the cycle. The monograph of Prof. Boyer (1986) on nitroazoles deals with only the *C*-nitro derivatives of *N*- and *N*,*O*-containing five-membered heterocycles, whereas the *N*-nitro derivatives presenting a new class of the oxide nitrogen generators (in particular, *N*-nitropyrazoles), as well as also thia- and selenazoles and all benzazoles remained unheeded. Prof. J.H. Boyer has noted that "that 'rapid development' of the chemistry of the nitroazoles in the Soviet Union began about 1960 and has provided more journal publications of research in the area than were found for any other country" and "the Russian emphasis on investigating" nitroazoles "has been outstanding."

This monograph provides comprehensive systematization of data on *C*- and *N*-nitroazole chemistry with in-depth information on structure and preparation, that is, nitration reactions and heterocyclization.

The monograph is mainly addressed to research professionals, research scientists (chemists, physicists, pharmaceutics, biochemists, chemical technologists), engineers, and "physicians—especially those dealing with oncology". This book can

be used as a textbook for postdoctorals and graduate students in chemistry, biochemistry, medical pharmacology, agricultural bioapplications, and for all who want to get acquainted with the chemistry and structure of nitroazoles.

The book may be of interest for the specialists dealing with the production of high-energy compounds (gas generators for air-bags, explosives, propellants, and pyrotechnics), nanomaterials, polymers, fibers, superelectrophiles, nonlinear optical materials, dyes (including fluorescent and cyanine dyes), and inhibitors of metal corrosion. It is also useful for people working in pharmaceutical industry.

We hope that it will be an invaluable reference for professionals in the field of heterocyclic chemistry, and that this book will initiate new investigations in this area.

The recent nature of the material and a large number of references (~2,200) make the book interesting for a wide range of specialists.

The authors would greatly appreciate receiving from readers any suggestions, comments, and recommendations.

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Contents

Introduction

Vigorous development of the chemistry of nitro compounds can be explained in terms of the practical and theoretical significance of these compounds. It can be said with assurance that the chemistry of nitro compounds has transformed into an independent area of organic chemistry. Many nitro compounds are used as explosives, ignition mixtures, and rocket fuels. Nitro aromatics serve as initial compounds for numerous dyers and pharmaceutical preparations. Nitro group-containing substances are constituents of many medicines. There are known nitro-containing pesticides and anticorrosion additives, technical solvents, etc.

From the theoretical viewpoint, compounds containing the nitro group are of interest due to their peculiar reactivity. They are very convenient in the investigation of structure–composition relationships. The reaction of electrophilic nitration is one of the most important and popular directions in organic chemistry.

Nitro compounds were the objective of much research. Certain aspects of this field of organic chemistry are discussed in many monographs and reviews. Well known treatise is a monograph on the chemistry of nitro and nitroso groups edited by Feuer [1]. The chemistry and technology of aromatic nitro compounds is considered in monographs [2–4]. Much attention has been given to unsaturated [5], aliphatic and alicyclic nitro compounds [6].

A great number of publications deal with the reaction of nitration [7–20]. At the same time, volumes literature on nitro heterocycles has not been systematized until the present time. Direct nitration of some five-membered heterocycles such as pyrroles, furans, thiophenes, pyrazoles, imidazoles, and thiazoles has been discussed by Katritzky [21, 22]. Some synthetic routes to nitrated six-membered nitrogen-containing aromatic heterocycles [23], as well as the nitration of oxo-pyrimidines and -imidazoles [24], and quantum-chemical studies of the nitration of benzazoles [25] have been reported.

The present monograph is devoted to the chemistry of a fascinating class of heterocyclic compounds, that of nitroazoles. The presence of the nitro group in the heterocyclic ring containing two or more hetero atoms points to a unique character of this cycle.

Some little data on the nitroazoles have been published in monographs and reviews dealing with the derivatives of pyrazole [26, 27], oxazole [28], thiazole [29], 1,2,4-triazole [30], 1,2,3-triazole [31], tetrazoles [32], benzimidazole [33], and benzotriazole [34]. Some representatives of nitroazoles are described in a comprehensive and

excellent book on heterocycles by Katritzky and Pozharskii [35] and in reviews on five-membered ring systems with two and more heteroatoms [36–39]. Recently Elguero and colleagues have surveyed some problems on tautomerism investigation of azoles [40]. Special monographs and reviews are dedicated to the chemistry, biological properties, and clinical application of nitroimidazoles [41–43]. In a monograph devoted to nitroazoles [44], only five-membered heterocycles with *N*- and *N*,*O*-endocyclic heteroatoms have been considered, whereas thia- and selenazoles, *N*-nitroazoles (a new class of the oxide nitrogen generator [45]), and all the nitrobenzoazoles were ignored. We have published some reviews on the synthesis of five-membered nitroazoles [46, 47] and their fused analogs [48, 49], on NMR spectroscopy [50] and mass spectrometry of nitroazoles [51], and on electronic substituent effects in five-membered, nitrogen-containing aromatic heterocycles [52].

Thus, azoles represent five-membered heteroaromatic compounds and they're benzanalogs with two or more heteroatoms of which at least one is nitrogen. According to Albert's classification subdividing all heteroaromatic compounds into π-rich and π-deficient ones, the azoles occupy an intermediate position, as they do not show clearly expressed π-donating or π-deficient properties [53]. It should be noted that this classification reflects the π-electron density distribution in the ground state of a molecule. Though reactivity is determined by the difference in energy of the ground and the transition state of the reaction, in practice a correlation of π-sufficiency change and the facility of electrophilic substitution is frequently observed. Really, as the number of "pyridine" nitrogen atoms increases the π-donating properties of azoles decrease and thus their reactivity in electrophilic substitution reactions is reduced [54]. However, this is not the case sometimes. Thus, 1*H*-imidazo[1,2]benzimidazole, for example, is less active than its 9*H*-isomer in the reactions of this type, though the donating ability of the latter is lower [55].

Nitroazoles possess a very broad array of practical applications. They can be used as anticancer preparations, antiseptics, radiosensitizers, herbicides, fungicides, dyes, ionic liquids, etc. The significant number of applications of nitroazoles makes them rather promising for research and requires deep understanding of their peculiar electronic structure, spectral properties, and chemical and tautomeric transformations [56, 57].

All this provoked us to write a monograph considering from unified positions all the literature available and our own data concerning the methods of synthesis, structure, properties, and application of *C*- and *N*-nitroderivatives of azoles and their condensed analogs.

An extensive volume of literature related to the question under consideration made us exclude a number of references to earlier publications and patents cited in the aforementioned monographs and reviews as well as in later publications.

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Synthesis of Five-Membered Nitroazoles

Abstract Synthesis methods of various *C*- and *N*-nitroderivatives of five-membered azoles – pyrazoles, imidazoles, 1,2,3-triazoles, 1,2,4-triazoles, oxazoles, oxadiazoles, isoxazoles, thiazoles, thiadiazoles, isothiazoles, selenazoles and tetrazoles – are summarized and critically discussed. The special attention focuses on the nitration reaction of azoles with nitric acid or sulfuric–nitric acid mixture, one of the main synthetic routes to nitroazoles. The nitration reactions with such nitrating agents as acetylnitrate, nitric acid/trifluoroacetic anhydride, nitrogen dioxide, nitrogen tetroxide, nitronium tetrafluoroborate, *N*-nitropicolinium tetrafluoroborate are reported. General information on the theory of electrophilic nitration of aromatic compounds is included in the chapter covering synthetic methods. The kinetics and mechanisms of nitration of five-membered azoles are considered. The nitroazole preparation from different cyclic systems or from aminoazoles or based on heterocyclization is the subject of wide speculation. The particular section is devoted to the chemistry of extraordinary class of nitroazoles – polynitroazoles. Vicarious nucleophilic substitution (VNS) reaction in nitroazoles is reviewed in detail.

Electrophilic Nitration of Azoles

The most widespread method of introducing nitro group in aromatic compounds, i.e., electrophilic substitution, is mainly used for the preparation of nitrodiazoles and benzazoles. The accumulation of "pyridine" nitrogen atoms in the cycle reduces the electrophilic substitution ability of compounds. Therefore, some indirect methods of introducing the nitro group are employed for the synthesis of triazole and tetrazole nitro derivatives.

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The ability of azoles to electrophilic substitution reactions is determined by the activity of reagents, the basicity of substrates, and the acidity of media. This caused some uncertainty in the interpretation of results and complicated a comparison of the reactivity of various azoles. The situation has changed after Katritzky and Johnson [1] have reported the criteria allowing, with a sufficient degree of reliance, the establishment in what form (base or conjugative acid) the compound reacts. The information on the mechanism of nitration of azoles was basically borrowed from the extensive literature on the nitration of aromatic hydrocarbons [2–8]; therefore, we have found expedient to discuss briefly some works in this field.

Nitration of aromatic compounds is an immensely important industrial process. The nitroaromatic compounds so produced are themselves widely utilized and act as chemical feedstocks for a great range of useful materials such as dyes, pharmaceuticals, perfumes, and plastics [6, 7].

Electrophilic Nitration Mechanism

As commonly accepted, the nitration of aromatic compounds is a typical reaction of electrophilic substitution, with the NO_2^+ nitronium ion serving as a directly attacking moiety. On nitration by only nitric acid, the nitronium cation is formed via autoprotolysis according to Scheme 1:

$$HNO_3 + HNO_3 \overset{\text{fast}}{\rightleftharpoons} H_2NO_3^+ + NO_3^-$$

$$H_2NO_3^+ \xrightarrow{\text{slowly}} H_2O + NO_2^+$$

$$H_2O + HNO_3 \xrightarrow{\text{fast}} H_3O^+ + NO_3^-$$

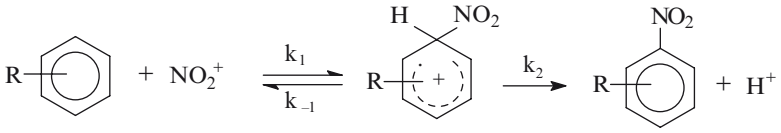
$$3\,HNO_3 \rightleftharpoons NO_2^+ + 2\,NO_3^- + H_3O^+$$

Scheme 1

In a sulfuric–nitric mixture the protonation of nitric acid occurs at the expense of a stronger sulfuric acid.

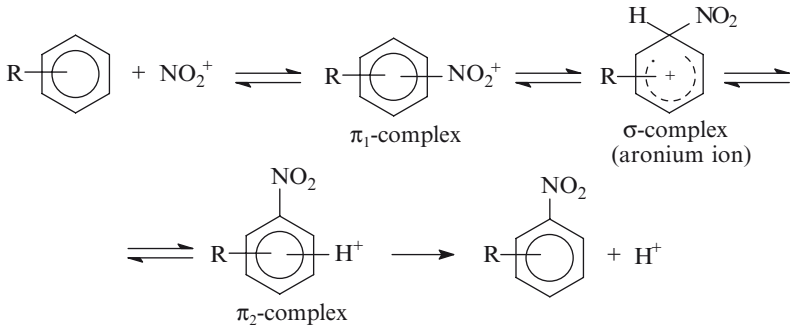
$$HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$$

There are many kinetic evidences for the fact that the nitronium cation and the aromatic substrate are involved in a reversible bimolecular reaction to form a σ-complex, which, being a strong acid, undergoes fast deprotonation (Scheme 2).



Scheme 2

The nitration pathway of this type was mainly supported by the data reported by Ingold [2]. Later this Scheme has been slightly modified by introducing one more stage, that of the formation of π-complex between the reagent and the substrate (Scheme 3).



Scheme 3

Numerous kinetic investigations of the formation of π-complexes carried out on model compounds have shown a high reaction rate and a low energy of activation of these interactions [3, 9]. As seen from the X-ray available data, the residue of aromatic substrate in π-complexes is structurally similar to the initial compound. All this has allowed a suggestion that in most cases elementary stages with participation of π-complexes do not play an essential role in electrophilic substitution [10]. The limiting stage of the process is the formation of σ-complex that is confirmed, in particular, by correlation of the arene basicity determining the stability of σ-complexes and the reaction rate [9–11]. The energy profile of the reaction is presented in Fig. 1, where ΔE^* is the total energy of activation.

Except for nitric acid and the nitrated mixture, the nitration of aromatic compounds can be carried out with nitronium salts as well [12].

$NO_2^+ \chi^-$, Where $\chi^- = BF_4^-$, ClO_4^- and *etc*

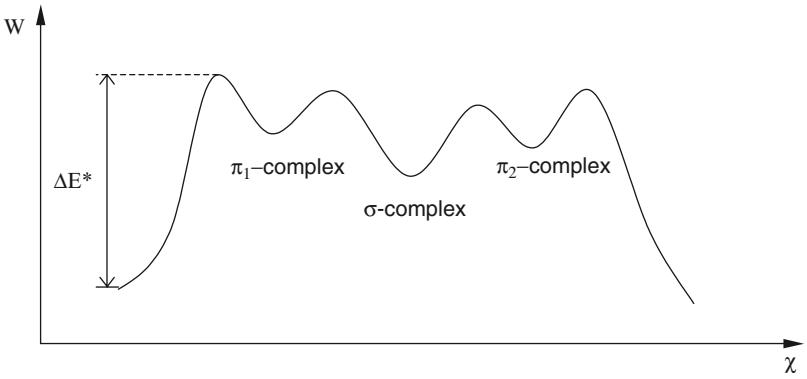


Fig. 1 The energy profile of the reaction of electrophilic substitution: *W* is energy, χ denotes the reaction coordinate

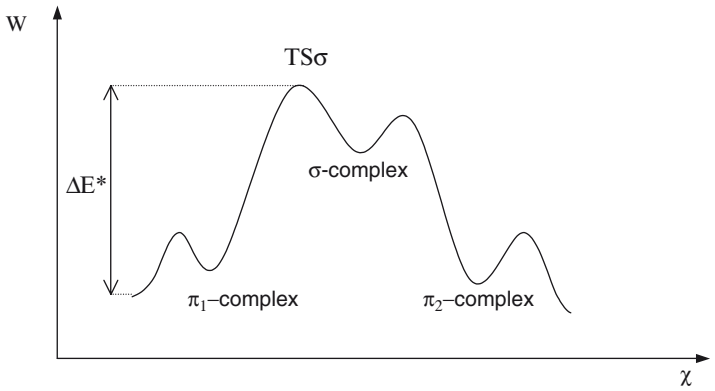
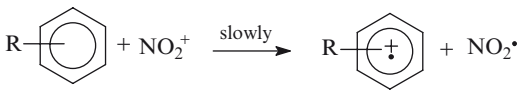


Fig. 2 The energy profile of nitration with nitronium salts: *W* is energy, χ stands for the reaction coordinate, and ΔE^* denotes the total energy of activation

Olah et al. have found out that the reaction rates on the nitration with nitronium salts are in good agreement with the stability of π-complexes [6, 13–16]. On this basis the authors have assumed that the nitronium salts serve as the nitrating agent; the stage limiting the reaction rate is the formation of π-complex (Fig. 2) that is rather uncommon in aromatic substitution.

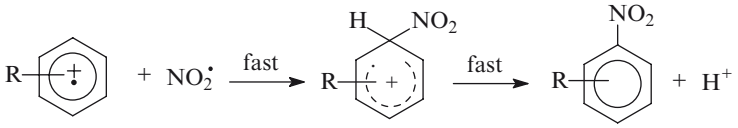
These works have caused intensive polemic discussed in detail in a review [12] and a monograph [24].

Another nitration mechanism has been offered by Perrin for arenes oxidized more easily than toluene [17]. In his opinion, a one-electron transfer from the aromatic substrate to the nitronium cation takes place (Scheme 4).



Scheme 4

The resultant radical cation of aromatic compound reacts with a nitrogen dioxide radical (Scheme 5).



Scheme 5

Ross et al. have reported some discrepancy between the experimental data and generally accepted mechanism of nitration [18–20]. The authors paid special attention to the participation of the radical cation of the aromatic substrate during nitration. It has been shown [20] that in the gas phase the nitronium cation does not act as a nitrating

agent and generates, by means of one-electron transfer, the aromatic radical cations, which react with $NO_2^{\cdot}$ to form nitroaromatic products. Thus, a serious experimental support for the participation of aromatic radical cations in the process of nitration has been provided. The formation of the aromatic radical cation on the initial step of nitration has been considered in a special review by Morkovnikov [21].

Without going into further discussion on the role of one-electron transfer in the mechanism of nitration of aromatic compounds, it should be noted that the nitration mechanism, which seemed to be strictly proved and clear after Ingold's studies [2], now again attracts steadfast attention. The research in this direction is worth further development.

Nitration with Nitric Acid or Sulfuric–Nitric Acid Mixture

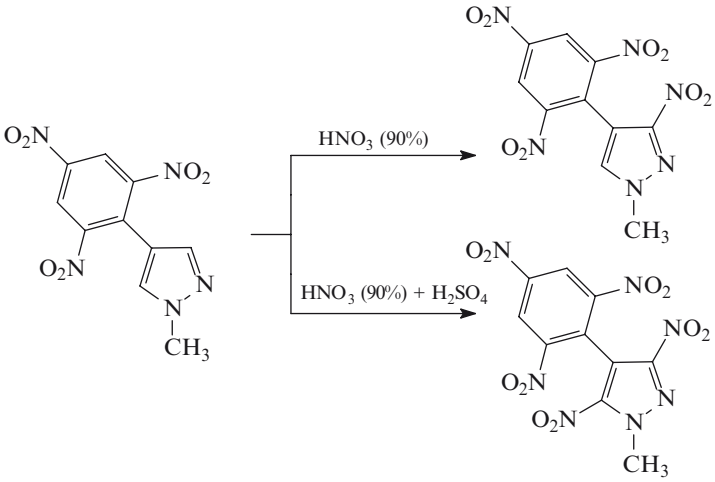
Pyrazoles

In 1893 Büchner and Fritsch [22] obtained 4-nitropyrazole for the first time by heating pyrazole with a mixture of oleum and nitric acid. This method with slight modifications has been used for the synthesis of 4-nitropyrazole up to the present time [23, 24]. During the nitration of substituted pyrazoles the nitro group usually enters at position 4, if it is free [25–53]. Such a process is consistent with the data from quantum-chemical calculations, i.e., the maximum π-electron density at the C-4 atom of the pyrazole ring [54]. The presence of alkyl substituents in the pyrazole ring facilitates the nitration process [25, 26, 39, 51, 52, 55], and here the steric factors are not determining. In fact, the presence of a *tert*-butyl group at position 3 or 5 does not prevent nitration at position 4 [42]. The nitration of 5-chloropyrazoles with a mixture of 100% nitric acid and 65% oleum (or a mixture of 60% nitric acid and polyphosphoric acid) affords substituted 5-chloro-4-nitropyrazoles in 45–91% yield [53].

The nitration of aryl- and thienylpyrazoles leads to the corresponding 4-nitropyrazoles. In this case, however, nitration of the aryl and thienyl substituents also occurs [22, 35, 37, 38, 52]. The nitration of 3-aryl-5-halopyrazoles is accompanied by introduction of a nitro group into the aromatic ring. 4-Chloropyrazoles failed to undergo nitration under these conditions [53]. Thus, 3- and 5-substituted 1-phenylpyrazoles usually form the corresponding 1-(4-nitrophenyl)-4-nitropyrazoles during nitration with a nitrating mixture [35–38]. At the same time nitration with nitric acid or a nitrating mixture under mild conditions leads to the corresponding *para*-nitrophenylpyrazoles [56–61]. 1-(4-Nitropheny)-4-nitropyrazoles are only formed if the concentration of nitric acid in the nitrating mixture is increased (or if the mixture is heated) [33, 34, 61]. 5(3)-Substituted 3(5)-(3-pyridyl)pyrazoles are nitrated at position 4 of the pyrazole ring [27–29]. During the nitration of 3(5)-methylpyrazole [51, 52], 3(5)-trimethylsilylpyrazole [43], 3(5)-halogeno-5(3)-methylpyrazole [44, 48, 49], pyrazole-3-carboxylic acid [30, 62], and 3(5)-nitropyrazole [29, 63] the corresponding 4-nitro derivatives are obtained.

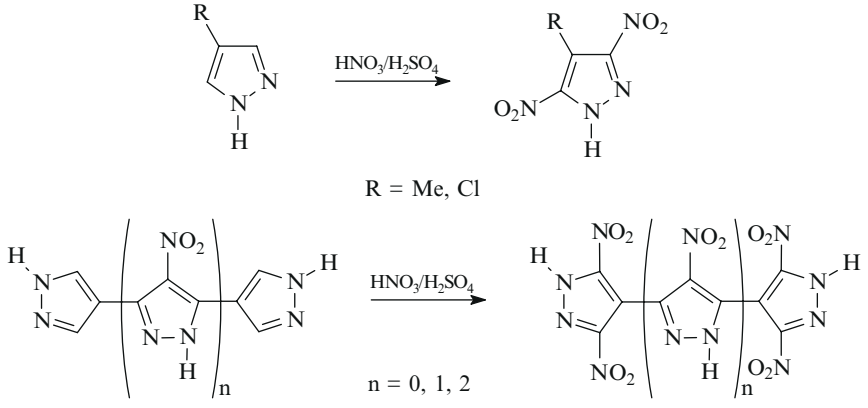
The introduction of such electron-withdrawing groups as 2,4-dinitrophenyl, picryl, or nitroguanidyl at position 1 of pyrazole does not hinder the nitration of pyrazole at position 4 [32, 41, 64].

The nitration of 3-hydroxy- or 5-hydroxypyrazoles (pyrazolones) also takes place at position 4 [65–67]. Although it was considered for a long time that pyrazoles are only nitrated at position 4, in rare cases the nitro group enters at position 3 or 5 [41, 45–47, 63, 68–72]. This usually occurs when position 4 is already occupied. Thus, for example, 1-methyl-3-nitro-4-(2,4,6-trinitrophenyl)pyrazole is formed when 1-methyl-4-(2,4,6-trinitrophenyl)pyrazole is heated in nitric acid (Scheme 6).



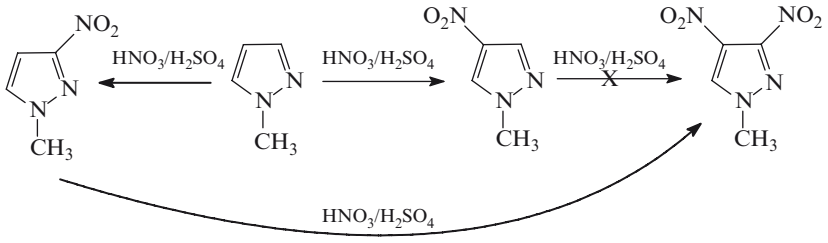
Scheme 6

At the same time the use of a sulfuric–nitric acid mixture leads to the 3,5-dinitro derivative [68]. Analogically dinitro compounds with high yield (70–80%) are observed on the nitration of 4-methyl-, 4-cloropyrazole and polypyrazoles [71, 73] (Scheme 7).



Scheme 7

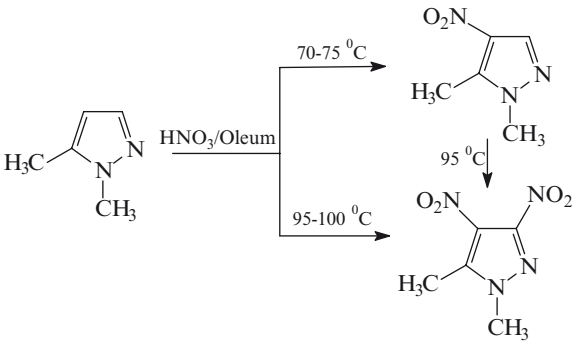
When 1-methylpyrazole is heated for a long time with a sulfuric–nitric acid mixture, 1-methyl-4-nitropyrazole and 1-methyl-3,4-dinitropyrazole are formed in a ratio of 4:1. Here the dinitro derivative is formed as a result of further nitration of 1-methyl-3-nitropyrazole [45] (Scheme 8).



Scheme 8

The introduction of electron-donating substituents into the pyrazole ring facilitates the nitration process, while the introduction of electron-withdrawing substituents retards it. In fact, 4-nitropyrazole, 1-methyl-4-nitropyrazole, 1,3-dimethyl-4-nitropyrazole, and 1-methyl-4-nitro-5-pyrazole carboxylic acid are not nitrated to the dinitro-substituted compounds [47, 63]. However, when heated with a mixture of nitric acid and oleum, 1,5-dimethyl-4-nitropyrazole changes to the 1,5-dimethyl-3,4-dinitro derivative [47].

The simultaneous introduction of two nitro groups into the pyrazole ring is rarely observed [29, 45–47, 63, 68]. This occurs under considerably more rigorous conditions than mononitration. Thus, 1-alkyl-4-bromo-3,5-dinitropyrazoles are also formed together with 1-alkyl-4-nitropyrazoles (as a result of *ipso*-substitution) during the nitration of l-alkyl-4-bromopyrazoles [46]. Here, it was assumed that the nitro group enters first at position 3. However, it was established more recently that the nitration rate of 4-bromo- and 4-chloro-1-methylpyrazoles with the sulfuric–nitric acid mixture is higher at position 5 than at position 3 [74] (Scheme 9)

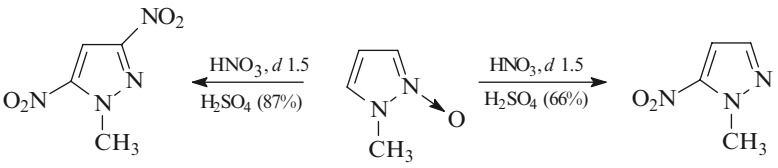


Scheme 9

The "pyrrole" nitrogen atom activates the pyrazole ring toward electrophilic reagents to a greater degree than the "pyridine" nitrogen atom deactivates it. This is confirmed by the higher rate constant for substitution of the hydrogen atom at position 3 of

1,4-dimethylpyrazole than the rate constant for the substitution of hydrogen at the ortho position of toluene [64].

Some examples of the nitration of pyrazole N-oxides are known [75, 76]. The result of nitration is determined by the ratio of the components in the nitrating mixture (Scheme 10).



Scheme 10

In some cases 1-methyl-5-nitro- and 1-methyl-3,5-dinitropyrazole can form as a result of deoxygenation [76]. Nevetheless, the nitration of 2-benzylpyrazole 1-oxide by sulfuric–nitric acid mixture leads to 2-benzyl-3-nitropyrazole 1-oxide in quantitative yield. Further nitration takes place in the phenyl 4-position forming 3-nitro-2-(4-nitrobenzyl)pyrazole 1-oxide and then in the pyrazole 5-position to give 3,5-dinitro-2-(4-nitrobenzyl)pyrazole 1-oxide as the final product [77].

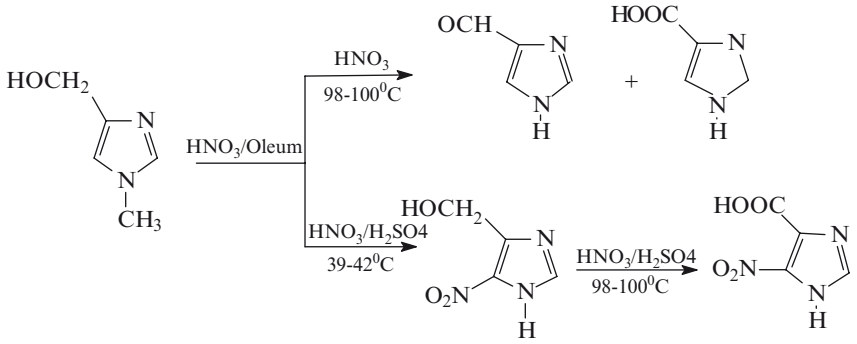
Imidazoles

In spite of extensive investigations into the electrophilic substitution of imidazoles, no rational explanation has yet been found for certain features of the reaction [78]. The nitration of imidazoles takes place exclusively at position 4 or 5. In reaction with the sulfuric–nitric acid mixture imidazole itself forms the 4(5)-nitro derivative [79–85]. A large number of papers have been devoted to the production of 2-methyl-4(5)-nitroimidazole by the nitration of 2-methylimidazole [79, 82, 86–94]. This is due to the fact that 2-methyl-4(5)-nitroimidazole is an important intermediate product in the synthesis of highly effective medical products (metronidazole, tinidazole, dimetridazole, etc.).

The nitration of other 2-alkyl-substituted imidazoles takes place similarly: 2-ethylimidazole [86, 87, 92, 95], 2-propylimidazole [87], 2-isopropylimidazole [87, 89–92, 96], and 2-butylimidazole [87, 89]. During the nitration of 2-phenylimidazole with the sulfuric–nitric acid mixture the nitro group enters first at position 4 of the benzene ring [97, 98], and nitration at position 4(5) of the imidazole ring only takes place under more rigorous conditions [82, 91]. In cases where the aryl group is passivated by electron-withdrawing substituents the nitration takes place exclusively in the imidazole ring [86, 99–102]. The presence of other substituents at position 2 does not change the direction of nitration [88, 93, 103–108].

The presence of a substituent at position 4(5) of the imidazole ring does not prevent entry of the nitro group at position 5(4) [87, 95, 109–121]. The size of the substituent does not play a part (isopropyl, cyclopentyl, and cyclohexyl) [113].

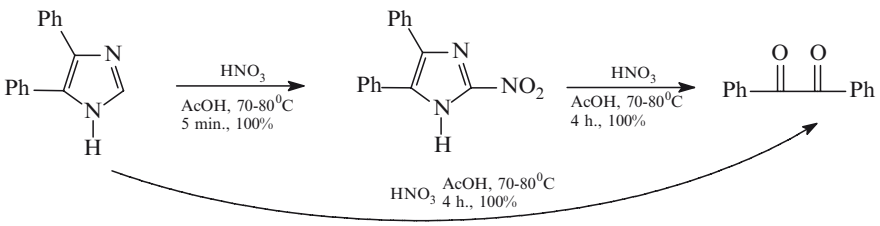
In some cases the nitration is accompanied by oxidation of the side groups [122, 123]. Thus, for example, depending on the conditions, 4(5)-hydroxymethylimidazole is converted by the action of the sulfuric–nitric acid mixture into the corresponding aldehyde [124–126], into 4(5)-imidazolecarboxylic acid [124, 125], or into 4(5)-nitro-5(4)-imidazolecarboxylic acid [122, 123] (Scheme 11).



Scheme 11

The oxidation of the hydroxymethyl group probably takes place more readily than nitration of the ring [124–127]. However, the entry of a nitro group into the imidazole ring without oxidation of the hydroxymethyl group has been reported [107, 110]. Imidazolecarboxylic acids are not nitrated, and their nitro derivatives are therefore obtained by different methods. Nevertheless, the 4- and 5-mononitro-substituted compounds were isolated with the 4,5-dinitro derivative as impurity during the nitration of ethyl 1-methylimidazole-2-carboxylate with a mixture of 100% nitric and sulfuric acids at 95°C [128].

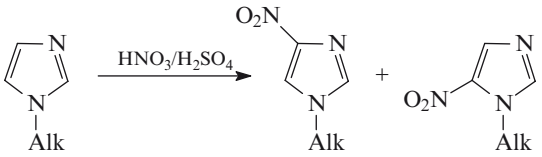
The imidazole ring has high resistance to the destructive action of various oxidizing agents, including nitric acid. It is not possible to introduce the nitro group into the position 2 of imidazole ring, but the reaction 4,5-diphenylimidazole in HNO_3 (1–2 moles) and AcOH with quantitive yield leads to 2-nitro-4,5-diphenylimidazole [129] (Scheme 12).



Scheme 12

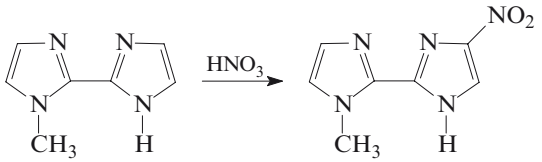
However *N*-acetyl-4,5-diphenylimidazole obtained by boiling in acetic anhydride does not react with excess HNO_3 (1–6 moles) during 4 h [129].

The action of the nitrating mixture on 1-alkylimidazoles gives the 4-and 5-nitro derivatives with a preference for the former [130–132]. The sizes of the substituent have practically no effect on the ratio of the isomers [132]. At the same time this effect is quite noticeable in the series of carbocyclic substrates (Scheme 13).



Scheme 13

The introduction of a substituent at position 1 of the imidazole ring hinders nitration, and most nitro-*N*-methylimidazoles have been prepared by the *N*-methylation of the corresponding nitroimidazoles. Thus, of the two possible nitration products only 1-methyl-2-(4-nitro-2-imidazolyl)imidazole is formed by the action of one equivalent of nitric acid on 1-methyl-2-(2-imidazolyl)imidazole [133] (Scheme 14).



Scheme 14

In this case, probably, nitration takes place through the monocation, and the nitro group attacks the less basic fragment of the molecule.

The nitration of 1,2-disubstituted imidazoles also leads to a mixture of 4-nitro and 5-nitro derivatives [128, 134–139]. The nature of the substituents in the imidazole ring has an effect on the ratio of the isomers. However, specific investigations in this direction have not yet been undertaken. During the nitration of 1,2-disubstituted imidazoles only the 4-nitro [140–143] or the 5-nitro [144–148] derivatives were isolated. It is not impossible that a mixture of isomers was obtained here.

The nitration of 1-methyl-2-(2-furyl)- and 1-methyl-2-(2-thienyl)imidazoles in polyphosphoric acid was described [149, 150]. At room temperature the nitro group enters at position 5 both of the furan and of the thiophene rings. Nitration of the furan derivative by 2 moles of nitric acid leads mainly to the dinitro derivative 1-methyl-2-(5-nitro-2-furyl)-5-nitroimidazole [149]. The introduction of a second nitro group into the thienyl derivative requires more rigorous conditions (80°C, 2 moles of nitric acid). Its position in the imidazole ring was not established [150].

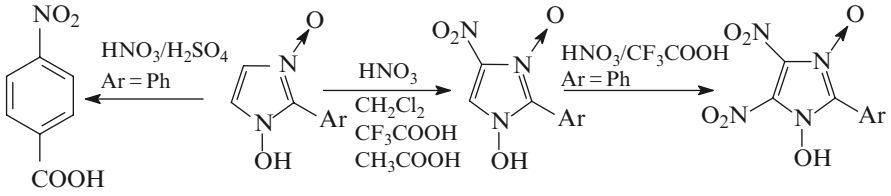
As in the 1,2,4-trisubsrituted derivatives, during the nitration of 1,4-disubstituted imidazoles the nitro group only enters at position 5 [151–154]. If the substituents contain double bonds or hydroxyl groups, a transformation of the side chain can

occur in addition to nitration [152]. On the other hand, during the nitration of 1,5-di- and 1,2,5-trisubstituted imidazoles the nitro group enters at the free position 4 [151, 155–157].

The nitration of 1-alkyl- and 1,2-dialkyl-5-halogenoimidazoles [151, 155, 158], which are used as intermediates in the pharmaceutical chemistry industry, has been investigated in greatest detail. For instance, the immunodepressant azathioprine ("imuran") was obtained from 1-methyl-4-nitro-5-chloroimidazole [158].

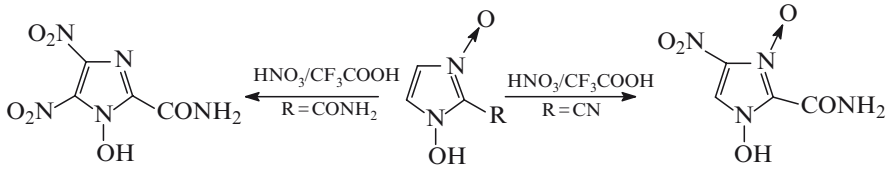
For many years it was not possible to introduce two nitro groups into the imidazole ring [159]. By the use of a somewhat unusual nitration condition (by heating the substrate first with nitric acid and then with the sulfuric–nitric acid mixture) it was possible to obtain 4,5-dinitroimidazole [79]. The method has now also been used for the production of 4,5-dinitroimidazoles [84, 93, 160]. It was also shown that *C*-polynitrobisimidazoles [79] and not *N*-nitroimidazoles, as considered earlier [161], are formed during the nitration of 2,2′-bisimidazole and its bromine derivatives. As already mentioned earlier, during the nitration of ethyl l-methylimidazole-2-carboxylate the 4,5-dinitro derivative was also isolated together with the other nitration products [128]. Increase in the reaction time increases the amount of the dinitro derivative.

The nitration of 1,4,5-trimethylimidazole 3-oxide with the sulfuric–nitric acid mixture leads to the 2-nitro derivative [76, 162]. Both this compound and 1-methylpyrazole 2-oxide enter into reaction in the form of the free base [76]. The nitration of 2-aryl-1-hydroxyimidazole 3-oxides leads either to cleavage of the imidazole ring or to the formation of the 4-nitro or 4,5-dinitro derivatives, depending on the reaction conditions [162] (Scheme 15).



Scheme 15

1-Hydroxyimidazole 3-oxide, which does not have substituents at position 2, is unstable under the conditions of nitration. Uncommon nitration of 1-hydroxy-2-cyanoimidazole 3-oxide and 1-hydroxy-2-carbamoylimidazole 3-oxide was observed in [162] (Scheme 16).

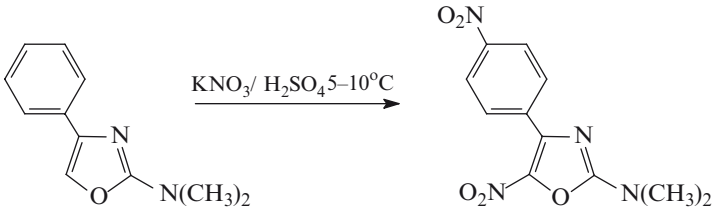


Scheme 16

During the nitration of the cyano derivative the nitrile group is transformed into an amide group, simultaneously with the introduction of the nitro group at position 4, and 1-hydroxy-2-carbamoyl-4-nitroimidazole 3-oxide is formed. During nitration of the corresponding carbamoyl derivative two nitro groups enter the molecule with simultaneous deoxygenation, resulting in the formation of 1-hydroxy-4,5-dinitroimidazole.

Oxazoles and Isoxazoles

The direct entry of a nitro group into the oxazole ring (1,3-oxazole) (exclusively at position 5) has only been reported twice [163, 164]. Thus, 2-dimethylamino-4-(4-nitrophenyl)-5-nitrooxazole was isolated when 2-dimethylamino-4-phenyloxazole was heated [163] (Scheme 17).



Scheme 17

The nitro group probably enters first at the *para*-position of the phenyl ring, after which the oxazole ring is nitrated. The action of nitric acid on 2-phenyloxazole in boiling dichloroethane gives 5-nitro-2-phenyloxazole with a yield of 15% together with the products from nitration of the benzene ring [164]. The nitration of the same compound under certain conditions excluding protonation by the action of *N*-nitropicolinium fluoroborate in acetonitrile gives a 90% yield of 5-nitro-2-phenyloxazole [164].

The isoxazoles (1,2-oxazoles) are nitrated exclusively at position 4. Isoxazole itself is nitrated with difficulty, and the yield of the nitro derivative does not exceed 3.5% [165, 166]. With nitronium tetrafluoroborate as nitrating agent it is possible to increase the yield of 4-nitroisoxazole to 35% [167].

The introduction of electron-donating substituents into the isoxazole ring facilitates the nitration process. Thus, the nitration of 3,5-dialkylisoxazoles [168–171] or bis(3-methylisoxazolyl-5) [172] gave the corresponding 4-nitro derivatives Under the same conditions, however, 3-methyl-5-(2-methoxy-2-phenylethyl)isoxazole was only nitrated in the phenyl ring [173]. Conversely, even at room temperature the nitration of 3-methyl-5-dichloromethyl- and 3-dichloromethyl-5-methylisoxazole gives the corresponding 4-nitro derivatives [174]. The nitration of 3-bromo-5-methylisoxazole is similar [175].

Only the benzene ring is nitrated during the action of the sulfuric–nitric acid mixture on 3-phenylisoxazole. At the same time a mixture of nitric and acetic acids converts it into 3-phenyl-4-nitroisoxazole [176]. Earlier Musante [177] isolated a

compound melting at 174–177°C during the nitration of 3-phenylisoxazole and assigned it the structure of 3-(4-nitrophenyl)isoxazole. More recently, however, it was shown [178] that this compound was 5-(4-nitrophenyl)isoxazole. The latter is formed during the nitration of 5-phenylisoxazole present in the initial reagent as impurity. The fact is that the 3- and 5-phenylisoxazoles have very similar melting points, and the 3- and 5-substituted isomers are formed in the selected method for the synthesis of the initial phenylisoxazole. This explains the error in the interpretation of the results from the nitration of 5-phenylisoxazole [179]. It was considered that a mixture of 5-(4-nitrophenyl)isoxazole (45%) and 4-nitro-5-phenylisoxazole (30%) was formed here. In fact, however, the latter was 4-nitro-3-phenylisoxazole formed as a result of nitration of the other isomer [178].

The contradictory data on the direction of nitration have been checked many times [178, 180–182]. It was shown that small amounts of 5-(3-nitrophenyl)isoxazoles and 4-nitro-5-(4-nitrophenyl)isoxazoles were formed together with the 5-(4-nitrophenyl)isoxazole [178, 180]. The structure of 4-nitro-5-(4-nitrophenyl) isoxazole was demonstrated by the nitration of 5-(4-nitrophenyl)isoxazole [178, 181]. During a more thorough investigation of this process it was found that an equimolar mixture of 5-(2-nitrophenyl)-, 5-(3-nitrophenyl)-, and 5-(4-nitrophenyl) isoxazoles is formed as a result of the reaction [182]. They are accompanied by a small amount of a mixture of difficultly separated 4-nitro-5-(4-nitrophenyl)- and 5-(3-nitrophenyl)isoxazoles.

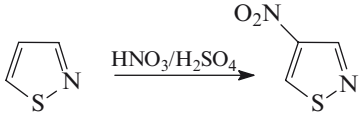
The kinetics of the nitration of 3-methyl-5-phenyl- and 5-methyl-3-phenylisoxazoles [183] and 5,5-dimethylisoxazole [184] were studied. During the nitration of 3,5-diphenylisoxazole by the sulfuric–nitric acid mixture only the phenyl group enters into the reaction [177, 185]. In acetic anhydride, however, the main nitration product is 3,5-diphenyl-4-nitroisoxazole [185].

Initially it was considered that 3-phenylamino-5-phenylisoxazole and 3-phenylamino-5-phenylpyrazole were nitrated exclusively in the phenyl ring [186]. More recently, however, it was shown that the nitro group also enters at position 4 of the heterocycle [187, 188].

Thiazoles and Isothiazoles

The nitration of the isothiazole (1,2-thiazole) ring takes place exclusively at position 4. The 4-substituted isothiazoles are either not nitrated at all [189, 190] or, as in the case of 4-phenylisothiazole, are nitrated in the benzene ring [191].

The action of the sulfuric–nitric acid mixture on isothiazole gives a high yield of the corresponding 4-nitro derivative [190, 192, 193] (Scheme 18).



Scheme 18

Table 1 The relative nitration rates (F) of thiazoles and isothiazoles

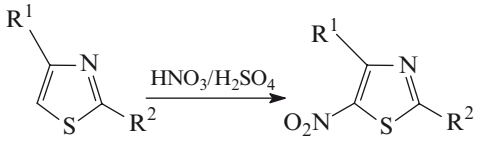
Thiazoles		Isothiazoles	
R	F	R	F
2,4-Me_2	1	3,5-Me_2	0.16
2,5-Me	0.5	5-Me	0.0094
4-Me	0.066	3-Me	0.0055
5-Me	0.04	H	0.0024

The nitration of 3-alkylisothiazoles [190, 193, 194], 5-alkylisothiazoles [190, 193], and other derivatives of isothiazole containing halogen atoms or electron-donating substituents at positions 3 and 5 [183, 193–197] takes place similarly.

Thiazole itself is not nitrated even under fairly rigorous conditions [198, 199]. However, many of its derivatives containing electron-donating substituents are nitrated smoothly.

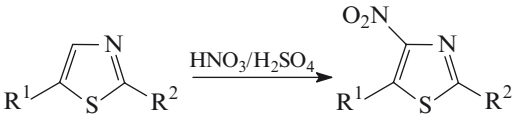
Table 1 gives the relative rate constants for the nitration of thiazoles and isothiazoles. They demonstrate the higher reactivity of the thiazoles during nitration [190, 200]. Such high regioselectivity is not observed during the nitration of thiazoles, as during the nitration of isothiazoles.

Electron-donating substituents at position 2 or positions 2,4 of the thiazole ring direct the entering nitro group toward position 5 of the ring [201–218] (Scheme 19).



Scheme 19

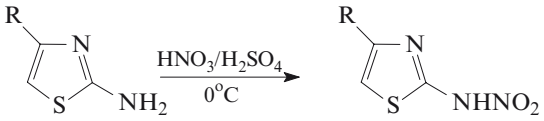
If, however, this position is occupied, e.g., in the case of 5-substituted or 2,5-disubstituted thiazoles, the 4-nitro derivative is formed [201, 202, 205, 207, 208, 210, 211, 219, 220] (Scheme 20).



Scheme 20

Only one example of the nitration of thiazoles at position 2 has been described; the action of the sulfuric–nitric acid mixture on 4,5-dimethylthiazole gave 4,5-dimethyl-2-nitrothiazole [199].

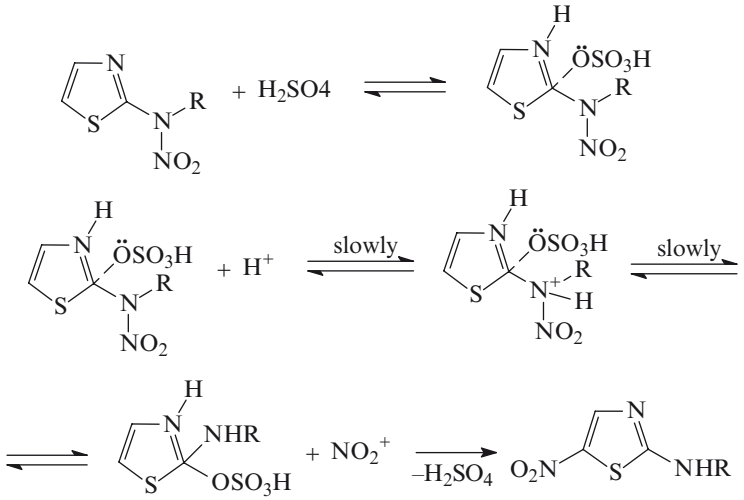
The nitration of 2-amino- and 2-acetamidothiazoles has been studied particularly widely [202–205, 220–226]. This is explained by the wide range of biological activity in the respective nitro derivatives. Here, nitroamines can also form in addition to nitration of the thiazole ring [203, 204, 225] (Scheme 21).



Scheme 21

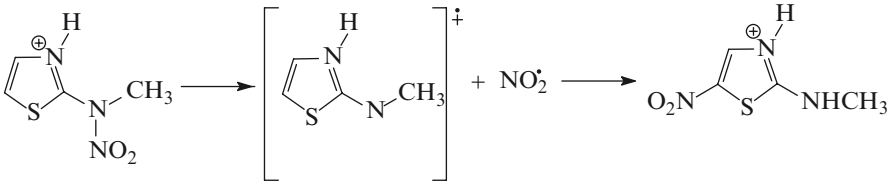
The conditions required for the isolation of such nitroamines have been described [204]. In concentrated sulfuric acid they readily rearrange to 2-amino-5-nitrothiazoles. The isomerization rate depends strongly on the sulfuric acid concentration [204]. Thus, the formation of 2-amino-5-nitrothiazoles may be the result both of direct electrophilic substitution in the thiazole ring and of the aforementioned rearrangement.

A study of the kinetics of isomerization of nitroaminothiazoles [227–229] showed that both intramolecular and intermolecular migration of the nitro group occur [228]. The following reaction mechanism was proposed (Scheme 22).



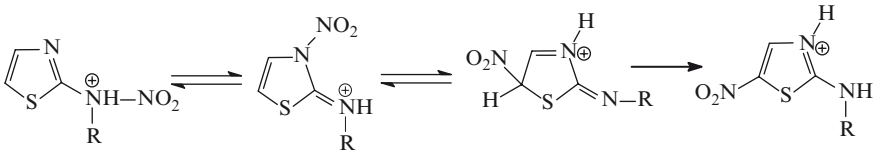
Scheme 22

This gave rise to some objection concerning, in particular, the structure of the intermediates ([230], part 2, p. 73). It would be more logical to suppose the intermediate formation of radical cations according to the following Scheme ([230], part 2, p. 83) (Scheme 23).



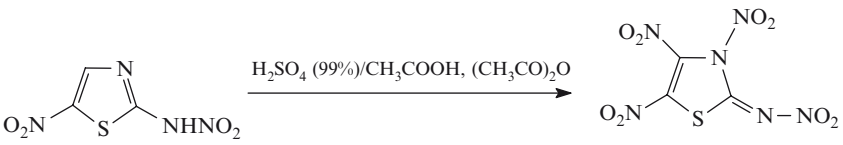
Scheme 23

However, the formation of free radicals in the rearrangement process was denied [231], and this makes it possible to introduce certain corrections into the previously proposed mechanism (Scheme 24).



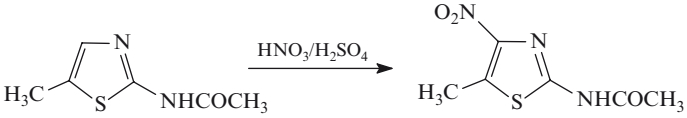
Scheme 24

It would probably be useful to carry out a more detailed investigation of these reactions using ESR and CIDNP techniques. Further nitration of 2-nitroamino-5-nitrothiazole leads to 2-nitroimino-3,4,5-trinitro-3*H*-thiazoline [203] (Scheme 25).



Scheme 25

When position 5 is occupied as, for example, in the case of 2-acetamido-5-methylthiazole, the 4-nitro derivative is formed with a small yield [223] (Scheme 26).



Scheme 26

2-Acetamido-4-phenylthiazole is nitrated at position 5 of the thiazole ring [232], in contrast to 2-amino-4-phenylthiazole, which is nitrated in the phenyl ring [233]. This agrees with existing data on the reactivity of thiazoles during electrophilic substitution. N-(2-Thiazolyl)-2-aminopyridine is nitrated exclusively in the thiazole ring [222].

The nitration of 2-, 4- and 5-phenylthiazole with 1 mole of HNO_3 in concentrated H_2SO_4 occurs at *para*-position of the phenyl ring, but not to thiazole cycle [203, 247]. It can be explained then that these compounds react in so-called conjugated acid form (protonated form), but not in base form. Analogically, 2-substituted 4-(2-furyl)thiazole is nitrated into furyl cycle 5 position; however, further nitration with two moles HNO_3 leads to 2-substituted 5-nitro-4-(5-nitro-2-furyl)-thiazoles along with other products [234] (Scheme 27).