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Construction of five- and six-membered nitrogen heterocycles based on reactions of cross-conjugated trimethylsilyl-substituted enynones and enones with amino compounds

1.4.3. Organic Chemistry

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Introduction

Relevance of the field of research and degree of its development

Nitrogen-containing heterocycles are one of the most important classes of organic compounds, widely represented among natural compounds and substances with a variety of useful properties, that are used in medicine, agriculture, dye production and optoelectronics. Since the variety and possibilities of complicating the structures of organic compounds, in particular heterocyclic ones, are limitless, the search for new methods of their synthesis is a task that never loses its relevance. Among the strategies that have proven themselves well in the construction of heterocyclic systems, approaches using compounds with several reaction centers can be distinguished, which allows for the effective synthesis of complex molecules in a minimum number of stages. Such structures include enynones, unsaturated ketones containing a linear or cross-conjugated system of three fragments: a carbonyl group, double and triple carbon-carbon bonds. The reactions of enynones with nucleophiles are successfully used to produce a variety of carbocyclic, *N*-, *O*-, *S*-heterocyclic structures. The relative location of reaction centers affects the availability and activity of enynones, as well as determines the possible directions of further transformations, and, given the polyelectrophilic nature of such structures, the question of selectivity is particularly acute. Whithin this work, a new type of cross-conjugated enynones – 5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones is proposed. The presence of the ethoxy group determines the high reactivity of the β-carbon atom of the double bond and, as a result, the regioselectivity of the addition of nucleophiles as a whole, and the trimethylsilylethynyl fragment preserved in the reaction product provides ample opportunities for further modification of such compounds. For example, in the presence of an aryl substituent in an adjacent position, cycloisomerization of *ortho*-aryl(ethynyl)heterocycle into a polyfused structure can be realized. This is a process well studied on carbocycles and much less on heterocyclic substrates. Therefore, in the course of this work, not only the reactions of previously unknown enynones with nitrogen-containing nucleophiles were studied, which make it possible to design mono- and bicyclic structures, including ethynyl-substituted ones, but also options for switching from them to more complex systems.

Another option for applying the synthetic potential of unsaturated compounds in the synthesis of various heterocycles containing nitrogen atom(s) is the use of a double carbon–carbon bond to create an energy-rich aziridine ring and implement its further transformations. To accomplish this task, *N*-phthalimidoaziridines are of particular interest as compounds with a potentially leaving group on the nitrogen atom. The thermal transformations of *N*-phthalimidoaziridines, during which reactive 1,3-dipoles – azomethine ylides should be

formed, have been very poorly studied. Several examples of such reactions were described in the 70s of the XX century, but a systematic study of the behavior of *N*-phthalimidoaziridines under heating was initiated only in the group of Prof. M.A. Kuznetsov. Thermal transformations of *N*-phthalimidoazomethine ylides can proceed in several competing directions, which is largely due to the presence of potentially leaving electron-withdrawing phthalimide group on the nitrogen atom, and in principle a transformation to several classes of compounds (pyrrolines, pyrrolidines, oxazoles, imines) can be carried out. The preferred course of the reaction along one pathway should be determined in each case by the nature of the substitution of the aziridine and the activity of the dipolarophile, and most of this work is devoted to the study of this fundamental dependence. In addition, a wide range of unsaturated substrates for the preparation of *N*-phthalimidoaziridines by oxidative aminoaziridination was studied, including five-membered heterocycles with one heteroatom and their vinyl derivatives, and the conditions under which the processes accompanying 1,3-dipolar cycloaddition can be realized as the dominant ones.

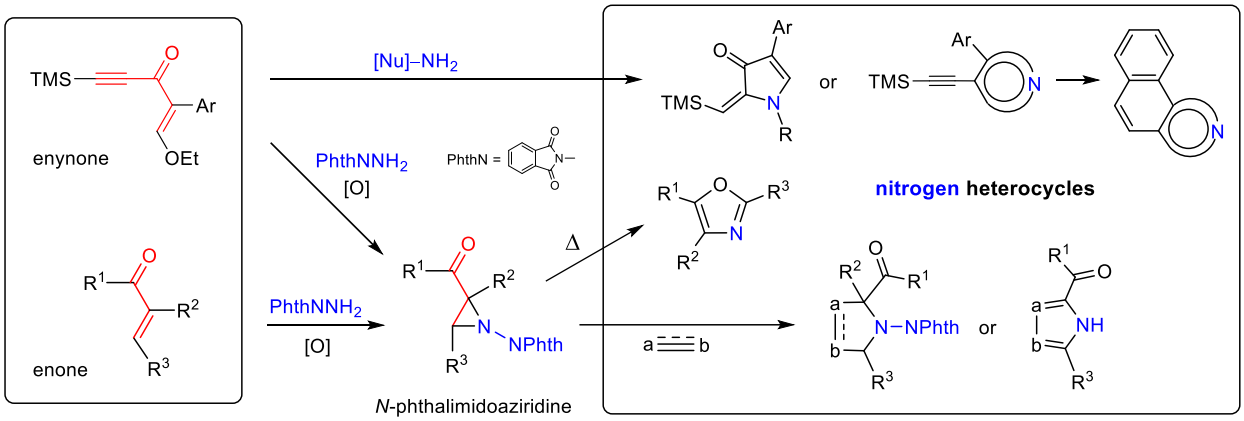
Thus, the results of this dissertation expand knowledge about the chemistry of functionalized unsaturated compounds, demonstrating the applicability of cross-conjugated trimethylsilyl-substituted enynones and *N*-phthalimidoaziridines as effective building blocks in the directed synthesis of nitrogen-containing heterocycles.

Goals and objectives

The goal of the work is the development of effective methods for the synthesis of five- and six-membered nitrogen-containing heterocyclic compounds based on the reactions of α,β-unsaturated carbonyl compounds (conjugated enynones and enones). The introduction of a nitrogen atom(s) during construction of a heterocycle is supposed to be carried out by using nitrogen nucleophiles, taking into account the electrophilic properties of substrates, and during oxidative aminoaziridination of their double carbon-carbon bond in order to realize the synthetic potential of the resulting *N*-phthalimidoaziridines. This leads to the formulation of the following objectives:

- to elaborate methods for the synthesis of cross-conjugated trimethylsilyl-substituted enynones and *N*-phthalimidoaziridines of various structures, to study the possibility of varying substituents of unsaturated substrates,
- to investigate the interaction of enynones with nitrogen-containing mono- and binucleophiles, to determine the selectivity of reactions, the influence of electronic and steric factors, the limits of applicability,

- to study the possibility of cycloisomerization for the resulting *ortho*-aryl(ethynyl)heterocycles under conditions of electrophilic activation and transition metal catalysis,
- to investigate the reactions of inter- and intramolecular 1,3-dipolar cycloaddition of *N*-phthalimidoaziridines, to determine the stereochemical features of their course, the influence of the number and nature of substituents,
- to study the concomitant thermal transformations of *N*-phthalimidoaziridines, in particular the formation of oxazoles, and the possibility of their preferential realization.



Scientific novelty

- New methods have been proposed for the selective construction of five- and six-membered nitrogen-containing heterocyclic compounds with an ethynyl or methylidene substituent in the side chain based on reactions of previously unknown cross-conjugated enynones with nucleophiles,
- the effect of a triple bond substituent on the choice of a catalytic system for the cyclization of *ortho*-aryl(ethynyl)heteroarenes has been demonstrated for the first time,
- the possibility of *ipso*-cyclization of *ortho*-(4-halophenyl)(arylethynyl)heteroarenes under conditions of electrophilic activation has been discovered and the mechanism of this transformation has been clarified,
- the *push-pull* effect of the cleavage of *N*-phthalimidoaziridines at the C–C bond has been discovered – facilitating the thermal generation of azomethine ylides by a combination of substituents of various electronic nature on neighboring carbon atoms,
- the conditions under which the transformation of *N*-phthalimidoaziridines into oxazoles is realized as the dominant process among other thermal transformations have been determined, and the relative activity of various carbonyl-containing groups in this process has been established for the first time,

- for the first time, the possibility of intramolecular cycloaddition of azomethine ylides thermally generated from aziridines to inactive multiple bonds in the side chain has been shown,
- the structural features of *N*-phthalimidoaziridines, determining the possibility, probability and selectivity of their thermal isomerization into imines with a 1,2-shift of the phthalimide group, have been established for the first time,
- the first examples of tricyclic bisaziridines – derivatives of 3,7-diazatricyclo[4.1.0.$0^{2,4}$]heptane have been synthesized,
- for the first time, the chemo- and regioselectivity of oxidative aminoaziridination of 2-vinylfuran derivatives at the endocyclic C=C bond has been demonstrated.

Theoretical and practical importance

The practical significance of the work consists in the development of new synthetic methods and obtaining examples of heterocycles of various classes, including

- monocyclic five-membered: 5-ethynyl- and 3-ethynylpyrazoles, 2-(trimethylsilylmethylidene)pyrrol-3-ones, *N*-phthalimidopyrroles, pyrrolines and pyrrolidines, 2-thiophenyloxazoles, 5-ethynyloxazoles,
- monocyclic six-membered: 5-aryl-4-ethynylpyrimidines, 5-aryl-2-(trimethylsilyl)pyran-4-ones,
- fused bi- and tricyclic: 7-ethynylpyrazolo[1,5-*a*]pyrimidines, benzo[*h*]quinolines, benzo[*f*]quinazolines, chromeno[4,3-*b*]pyrrolidines and pyrrolines, pyrrolo[3,4-*c*]pyrrole-1,3-diones,
- spirocyclic: spiro[indene-2,2'-pyrrolidine]-1,3-diones, spiro[cyclohexa-2,5-diene-1,5'-cyclopenta[*d*]pyrimidin]-4-ones.

The proposed synthetic strategies are characterized by the availability of starting compounds, a small number (1-3) of steps during the transformation from an acyclic precursor to a heterocyclic product, a high degree of chemo-, regio- and stereoselectivity, and simplicity of experimental implementation. The accomplished studies have determined the limits of applicability of the techniques for varying the structure of reagents, optimal conditions for carrying out the reactions and ranges of achieved yields. All previously unknown compounds are fully described, and their physical and chemical characteristics can be used to assign structures of new derivatives. For a number of compounds (4-aryl-2-(trimethylsilylmethylidene)pyrrol-3-ones, 6-aryl-7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines, 6-aryl-3-phenylbenzo[*f*]-quinazolines, 2-thiophenyloxazoles) fluorescence in the UV range was detected and described, and the data obtained can be used in the search and design of new fluorescent materials.

The theoretical significance of the work consists in the accumulation of knowledge about the reactivity of enynones and *N*-phthalimidoaziridines, the patterns of reactions with their participation and the possibilities of synthetic application of such and similar structures. As a result of studying the reactions of enynones with nucleophiles, information on the factors determining the relative activity of the reaction centers of polyelectrophilic unsaturated compounds and the selectivity of their interaction with nucleophiles of various structures was obtained. Study of cycloisomerization of *ortho*-aryl(ethynyl)heterocycles allowed us to identify structural features that affect the conditions and direction of cyclization. In the course of studying the thermal transformations of *N*-phthalimidoaziridines, the features of the behavior of such aziridines in contrast to *N*-alkyl(aryl)-substituted ones were determined: the possibility of aromatization into oxazoles during 1,5-electrocyclization of azomethine ylides; preferred isomerization of 2,3-diarylaziridines with migration of the phthalimide group; facilitation of generating azomethine ylides by separating donor and acceptor substituents on neighboring carbon atoms. In addition, data on the possibilities of oxidative aminoaziridination of five-membered aromatic heterocycles with one heteroatom and their vinyl derivatives have been expanded.

Research methodology and methods

The research methodology is based on the collection and analysis of literary data highlighting the relevance and degree of (not)studied research tasks, the selection of specific objects and determining the range of their variation (the choice of substituents in the structures is justified by the study of electronic and spatial factors determining the reaction course and the result, as well as the generality and limits of applicability of synthetic techniques), optimization of the conditions of target reactions, establishment of the structure and description of the properties of reaction products, collection and analysis of the experimental data obtained, their theoretical interpretation and generalization of the research results.

The work uses methods of fine organic synthesis for implementing reactions, analyzing and separating reaction mixtures, isolating products and purifying them. The composition and structure of all compounds obtained in the work were established using instrumental analysis methods: nuclear magnetic resonance (NMR) spectroscopy (on ^{1}H, ^{13}C, ^{15}N nuclei, including various two-dimensional correlation techniques), mass-spectrometry, elemental analysis. Compounds with fluorescence were characterized by spectroscopy data in the UV and visible regions. The structure of the compounds for which monocrystals of proper quality were obtained was described using X-ray diffraction analysis (XRD).

NMR, HRMS, UV and XRD analyses were performed at the SPbU Magnetic Resonance Research Centre, Chemical Analysis and Materials Research Centre, Centre for Optical and Laser Materials Research, and Research Centre for X-Ray Diffraction Studies, respectively.

Degree of reliability and approbation of the results

Experimental data were obtained using proven chemical equipment and modern informative instrumental research methods. The limits of applicability of the proposed methods and reproducibility of the results are confirmed by a sufficient number of consistent examples. The analysis of the results and theoretical reasoning were carried out taking into account the known literature data. This determines the quality and high degree of reliability of the work done.

The results of the research were presented by the author personally in the form of oral reports at national and international conferences: All-Russian congress on heterocyclic chemistry «KOST-2021» (Sochi, 12-16.10.2021), VI International symposium “The chemistry of diazocompounds and related systems” (St. Petersburg, 6-10.09.2021), WSOC 2019. Scientific conference «Markovnikov readings. Organic chemistry form Markovnikov to the present day» (Krasnovidovo, 18-21.01.2019), XV International Congress of Young Chemists “YoungChem 2017” (Lublin, Poland, 11-15.10.2017), Anatolian conference on synthetic organic chemistry (Antalya, Turkey, 16-19.03.2015), XI International Congress of Young Chemists “YoungChem 2013” (Poznan, Poland, 9-13.10.2013), and also co-authored several oral presentations presented by M.A. Kuznetsov and P.R. Golubev, and many poster presentations at more than 30 conferences of various levels.

The main content of the work is presented in 23 articles (references [1-23] in reverse chronological order; including 4 reviews on the topic of the dissertation [3, 5, 7, 10]) in scientific journals reviewed by Scopus and Web of Science databases, of which 16 articles are in journals of Q1 and Q2 quartiles.[1] Experimental data, a description of synthetic techniques, and characteristics of the compounds obtained are included in these articles.

Personal contribution

The author personally participated in determining research directions, planning and formulation of specific tasks, conducting the bulk of experimental work, analyzing and interpreting data, summarizing results and preparing publications. Under the guidance of the author, 8 final qualification papers on the topic of this work have been prepared and defended.

[1] According to the Scimago Journal & Country Rank for the year of publication: https://www.scimagojr.com/

The author took an active part in the preparation of PhD theses of P.R. Golubev (2015 г.), A.N. Shestakov (2017 г.), and A. Yu. Stukalov (2018 г). A part of work was funded by Russian Foundation for Basic Research (grant no. 16-33-00171), The Council for Grants of the President of the Russian Federation (grant МК-5965.2016.3) and Russian Science Foundation (grant no. 18-73-00089), under guidance of the author of the dissertation, and grants of SPbU (grant no. 12.38.16.2011) and Russian Science Foundation (grant no. 14-13-00126), in which the author of the dissertation was the main performer.

Main findings of the dissertation to be defended

- A new type of cross-conjugated enynones, which substitution pattern allows the selective construction of five- and six-membered heterocycles with an ethynyl or methylidene substituent in the side chain as a result of interaction with nitrogen mono- and binucleophiles,
- regioselectivity of cyclization of *ortho*-aryl(ethynyl)heterocycles and selective activity with respect to various catalysts determined by substituents in the substrate,
- methods of stereoselective construction of monocyclic and polycyclic fused and spirolinked heterocycles based on a combination of oxidative aminoaziridination of enones and their analogues followed by thermal generation of azomethine ylides from *N*-phthalimidoaziridines and their inter- and intramolecular 1,3-dipolar cycloaddition,
- design of the structure of *N*-phthalimidoaziridines capable of preferential conversion to oxazoles as a result of 1,5-electrocyclization of thermally generated azomethine ylides.

Main scientific results

Below is a short list of the main scientific results, provided with links to the numbers of publications in the list of references, where the relevant material is presented, indicating the numbers of sections of the dissertation, where a more detailed description is given.

1. Synthetic approach to 2-aryl-5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones (Section 1.2) [3, 15, 17].
2. Synthetic approach to 5-(trimethylsilylethynyl)pyrazoles (Section 1.5) [3, 17].
3. Synthetic approach to 4-ethynylpyrimidines (Section 1.6) [3, 15].
4. Synthetic approach to 7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines (Sections 1.7, 4.2) [3, 9].
5. Synthetic approach to 2-(trimethylsilylmethylidene)pyrrol-3-ones (Sections 1.4, 4.1) [4, 13].
6. Synthetic approach to 2-(trimethylsilyl)-4*H*-pyran-4-ones (Section 1.3) [1].

7. Synthetic approach to benzo[*f*]quinazolines, benzo[*h*]quinolines and benzo[*c*]acridines (Sections 2.2, 2.3, 4.3) [5, 6, 8].
8. Synthetic approach to 2-thiophenyloxazoles (Sections 3.3.2, 4.4) [2].
9. Synthetic approach to 5-ethynyloxazoles (Section 3.3.1) [7, 14].
10. Synthetic approach to *N*-phthalimidopyrrolidines (Section 3.4.1.1) [21, 23].
11. Synthetic approach to derivatives of spiro[indene-2,2'-pyrrolidine]-1,3-dione (Section 3.4.1.3) [7, 16].
12. First examples of intramolecular 1,3-dipolar cycloaddition of *N*-phthalimidoaziridines (Section 3.4.2) [20].
13. First examples of 5-thia(seleno)-3,7-diazatricyclo[4.1.0.$0^{2,4}$]heptane system (Section 3.2.2.1) [10, 19].
14. Synthetic approach to monohydrazones of hexa-2,5-diene-1,4-dione (Section 3.2.2.2) [10, 11].
15. Study of reaction between *N*-phthalimidoaziridines and dimethyl acetylenedicarboxylate (Section 3.4.1.2) [22].
16. Study of isomerization *N*-phthalimidoaziridines into imines (Section 3.4.3.1) [10, 12, 18].

Chapter 1. Cross-conjugated trimethylsilyl-substituted enynones

1.1. Introduction

In general, enynones are compounds containing directly linked double and triple bonds and a carbonyl group (ketone or aldehyde fragment) in various combinations. Four types of such structures can be depicted: linear pent-2-en-4-yn-1-one (**A**) and pent-4-en-2-yn-1-one (**B**), as well as cross-conjugated pent-1-en-4-yn-3-one (**C**) and 2-methylidenebut-3-in-1-one (**D**) (Fig. 1.1).

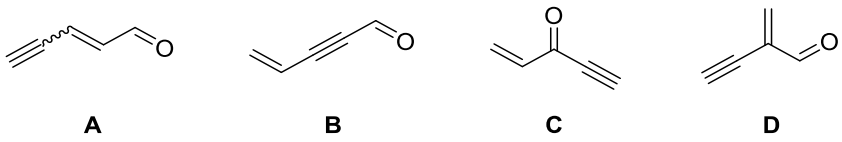


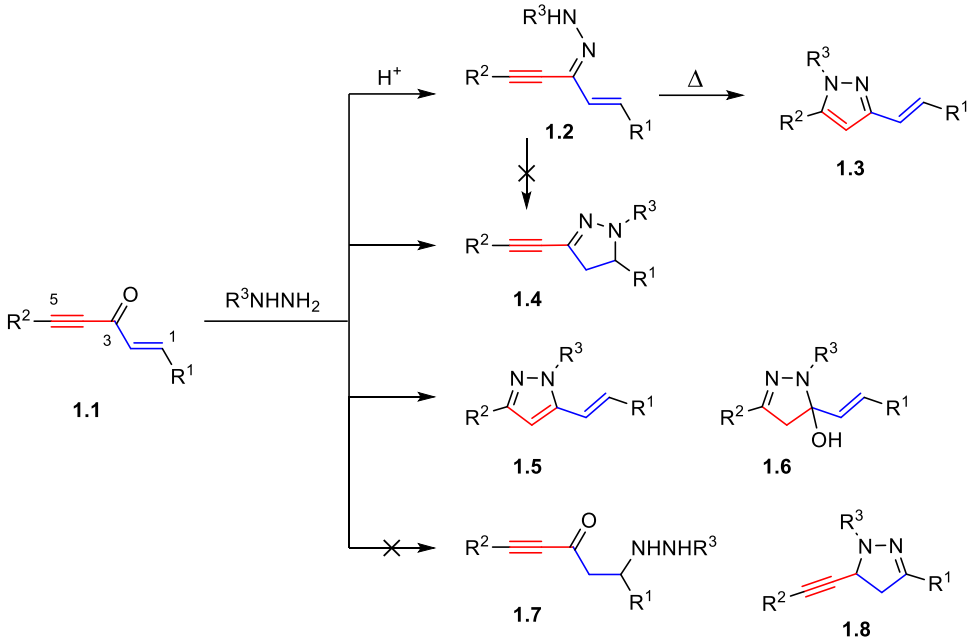
Fig. 1.1. Types of enynones

The definition "enynones" does not specify a type of skeleton, but is widely used in modern Russian and English-language literature to abbreviate one or more types, depending on the context. Due to the presence of three multiple bonds, such compounds are actively used to build various carbo- and heterocyclic systems, allowing for highly efficient synthesis of complex objects in a minimum number of steps, which, in particular, finds application in medical chemistry [24, 25]. For example, being polyelectrophilic compounds, enynones are easily involved in reactions with mono- and binucleophiles (recent achievements in this field are highlighted in reviews by A.A. Golovanov [26, 27]). Due to electrophilic activation, transformations of cross-conjugated enynones into heterocyclic systems, described by us in the review [3], are possible. On the other hand, as extended π-systems, enynones are susceptible to transition metal catalysis, which makes it possible to carry out cyclizations [28–30], generate metallocarbenoids and carry out their further transformations [31–32].

The availability and reactivity of each type of enynones depends on the relative location of key structural elements, while the largest number of synthetic options (according to SciFinder^n) is known for linear pent-2-en-4-yn-1-ones (**A**) (Fig. 1.1). Cross-conjugated pent-1-en-4-yn-3-ones (**C**) differ from other enynones by the central location of the carbonyl group relative to multiple bonds and, consequently, by its similar effect on the displacement of the electron density and the reactivity of double and triple bonds. A superposition of enone and ynone with a common carbonyl group is created in such enynones. As a result, three electrophilic centers are found in the pent-1-en-4-yn-3-one molecule: C^1, C^3 and C^5 atoms, and therefore, the formation of various products can be expected after interaction with nucleophiles. For example, symmetrically substituted pent-1-en-4-yn-3-ones **1.1** (Scheme 1.1), having the same groups on

C^1 and C^5 atoms, in reaction with monosubstituted hydrazines can give either 3-ethynylpyrazolines (4,5-dihydro-1*H*-pyrazoles) **1.4** [33-38], if the fragment –C=C–C=O involved, or 3-vinylpyrazoles **1.3** [36, 39], if the addition proceeds along the fragment –C≡C–C=O, although in some cases the reaction stops at hydrazones **1.2** – as a result of the addition of hydrazine to the carbonyl group [35–37] (Scheme 1.1).

Scheme 1.1 (literature data [33–39, 43, 44])



In the simplest case of the reaction of 1,5-diphenylpent-1-en-4-yn-3-one (**1.1**, $R^1 = R^2 =$ Ph, Scheme 1.1) with phenyl hydrazine ($R^3 =$ Ph), according to quantum chemical calculations [37], it is thermodynamically advantageous to form exactly such a hydrazone (**1.2**, R^1–$R^3 =$ Ph), and not the addition to any of the two β-positions of multiple bonds, which corresponds to the known selectivity of the interaction of α,β-unsaturated ketones with hydrazines [40, 41]. Again, according to calculations, further cyclization of arylhydrazone by a triple bond is thermodynamically more advantageous than by a double bond [36]. In practice, it turns out that in the presence of acid in the reaction mixture (boiling in ethanol with 2-3 drops of HCl for 20 min), a hydrazone **1.2** is easy formed (R^1–$R^3 =$ Ph, Scheme 1.1), which is clearly facilitated by protonation of the carbonyl oxygen atom of enynone [36]. Under more severe conditions (boiling in DMF), such a hydrazone cyclizes along the acetylene fragment into pyrazole **1.3** [36]. When conducting a reaction between 1.5-diphenylpent-1-en-4-yn-3-one (**1.1**, $R^1 = R^2 =$ Ph) and phenyl hydrazine ($R^3 =$ Ph) in boiling ethanol in the absence of acid, only 1,5-diphenyl-3-(phenylethynyl)-4,5-dihydro-1*H*-pyrazole is obtained (**1.4**, R^1–$R^3 =$ Ph, Scheme 1.1) [37]. In general, this confirms the previously known [42] assumption that the formation of hydrazone **1.2** and pyrazoline **1.4** are independent parallel processes in the interaction of hydrazine with the

fragment –C=C–C=O. Interestingly, the aza-Michael addition of hydrazines to the double bond of pent-1-en-4-yn-3-ones (hydrazines **1.7**, Scheme 1.1), as well as the formation of the corresponding pyrazolines **1.8**, is not observed even if this bond is terminal (**1.1**, R^1 = H); pyrazolines **1.4** are obtained instead [36, 38, 43].

The introduction of various substituents to the C^1 and C^5 atoms of pent-1-en-4-yn-3-one is a possible tool to control the selectivity of the reaction. For example, if there is an electron-rich heterocyclic substituent at the end of the double bond of 5-phenylpent-1-en-4-yn-3-one (**1.1**, R^1 = furan-2-yl, pyrrol-2-yl, thiophen-2-yl, R^2 = Ph, Scheme 1.1) or when using electron-poor arylhydrazines (R^3 = pyridin-2-yl, 4-$O_2NC_6H_4$, 4-BrC_6H_4), the initial addition of hydrazine proceeds along the β-position of the triple bond (aza-Michael addition) followed by cyclization along the carbonyl group into pyrazoles of type **1.5** [37]. One example of the formation of 5-hydroxy-4,5-dihydro-1*H*-pyrazole **1.6** (R^1 = R^2 = Ph, R^3 = Ac) is also described in the reaction of 1,5-diphenylpent-1-en-4-yn-3-one with acetic acid hydrazide [44].

In general, using the example of Scheme 1.1, it is obvious that the selectivity of the interaction of pent-1-en-4-yn-3-ones with nucleophiles is ambiguous and depends on the reaction conditions, the nature of the nucleophile (the examples shown in Scheme 1.1 are valid, strictly speaking, only for monoarylhydrazines having sharply different nucleophilicity of nitrogen atoms) and, most importantly, on the substituents of enynone. The study of factors, including structural ones, determining the selectivity of such reactions, is an interesting task. Oddly enough, it is a little-studied task until recently, especially considering that the range of possible nucleophiles is not limited only to hydrazines, and based on these transformations, new methods for the effective synthesis of functionalized heterocyclic compounds can be developed.

The cross-conjugated enynones **1.9** proposed by us for the first time, the chemistry of which forms the basis of this chapter, have a unique set of substituents that expands the synthetic potential of the basic pent-1-en-4-yn-3-one: the ethoxy group at the double bond and the trimethylsilyl group at the triple bond (Fig. 1.2).

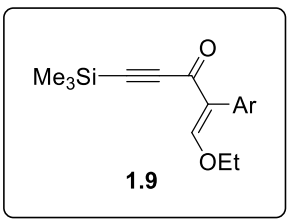


Fig. 1.2. Objects of dissertation research – 2-aryl-5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones

Preliminary assessment of the electrophilic potential of enynones **1.9** is possible using the calculation of electrophilicity indexes [45]. Figure 1.3 shows for comparison the index values for

enynone **1.9a**[2] and 1,5-diphenylpent-1-en-4-yn-3-one (**1.1a**) [37], whose selectivity with hydrazines was described above.

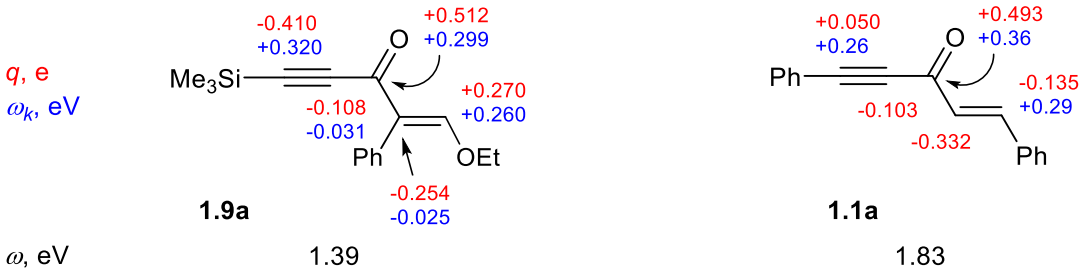


Fig. 1.3. Charges (marked in red) and local electrophilicity indexes (marked in blue) of the atoms of enynone **1.9a** and 1,5-diphenylpent-1-en-4-yn-3-one (**1.1a**) [37]. The values of the total electrophilicity index are shown below.

According to the value of the total electrophilicity index, enynones **1.9** can be classified as medium-strength electrophiles [37, 45]. The distribution of local electrophilicity indexes corresponds to the expected large values for the β-positions of multiple bonds relative to the carbonyl group – the C^1 and C^5 atoms. the highest value for the trimethylsilyl-substituted C^5 atom theoretically indicates the preferred site of attack by the nucleophile. At the same time, it is known that the steric effect of a sufficiently bulky Me_3Si group is not so great due to the relatively long Si–C bond (24% longer than the C–C bond in the *tert*–butyl group) [46], and it does not completely block the electrophilic activity of the triple bond in enynones. Examples of addition of nucleophiles to the β-atom of the R_3Si–C≡C–C=O fragment are known: *ortho*-aminothiophenol [47], thiocarbamates [48], amines [49].

However, the value of the electrophilicity index is not an absolute criterion, and the thermodynamic parameters of the addition of a nucleophile to the electrophilic centers of a molecule can greatly change the relative probability of a process. Obviously, there is a possibility for nucleophilic attack onto a carbonyl group in the center of the C≡C–C(O)–C=C fragment: formation of imines [50], hydrazones [36, 51], tertiary alcohols [52, 53]. The presence of an ethoxy group at a double bond conjugated to a carbonyl group makes it possible to formally replace it with a nucleophile, and, indeed, α,β-unsaturated ketones with an alkoxy group at a double bond easily attach mono- and binucleophiles [54-57].

We expected that the presence of the EtO–CH= fragment would determine the selectivity of the reaction between the 2-aryl-5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones **1.9** and nucleophiles, but the polyelectrophilic nature of enynones and the lack of literature data on the

[2] DFT quantum chemical calculations at the M06-2X/6-31G(d,p) level of theory with full geometry optimization were performed by N.V. Rostovskii and T.N. Zakharov, SPbU.

behavior of such compounds left open the question of regioselectivity, This is what we have been studying in this work. We expected that the presence of the EtO–CH= fragment would determine the selectivity of the interaction of the proposed 2-aryl-5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones **1.9** with nucleophiles, but the polyelectrophilic nature of enynones and the lack of literature data on the behavior of such compounds left open the question of regioselectivity. This is what we have been studying in this work.

Prior to our publications, only two examples of pent-1-en-4-yn-3-ones with a single substituent on the C^1 atom – the RO group (R = H, Alk) can be found in the literature: 5-phenyl-1-ethoxypent-1-en-4-yn-3-one, which was obtained in 1981 by carbonylation of 1-bromo-2-ethoxyethylene in the presence of phenylacetylene [58], and an intermediate compound in the synthesis of the diterpenoid ottensinin [59]. When replacing the hydrogen atom at the C^1 atom with any group, the number of examples increases significantly, which is primarily due to the ease of obtaining such compounds by adding alcohols to diacetylene ketones [60, 61] and condensation of methyl ketones and derivatives of propargylic acids [62–65].

The literature describes only a few examples of the construction of heterocycles based on reactions of 1-RO-pent-1-en-4-yn-3-ones (R = H, Ph) with nucleophiles, and they were published before 2000 [66, 67]. The use of 5-silyl-substituted pent-1-en-4-yn-3-ones in heterocyclic synthesis is presented in the works of A.A. Golovanov [36, 51], published after the main part of our work, considered here. And in general, our work has made a significant contribution to the development of the chemistry of pent-1-en-4-yn-3-ones [27].

It is important that the trimethylsilyl group can be easily removed from the triple bond (such desilylation has been known since 1967 [68], the most commonly used reagents are Bu_4NF/THF [69] and K_2CO_3/MeOH [70]), therefore, with the preservation of the acetylene fragment in the products, the possibility of their further modifications is created. At the same time, such creation of an alkynyl–substituted heterocycle can be considered as an advantageous alternative to the Sonogashira reaction, which is certainly a very effective and popular method of introducing an ethynyl fragment into the side chain of cyclic compounds, however, requiring the presence of a leaving group, which is not always easy to introduce into the substrate molecule [71, 72].

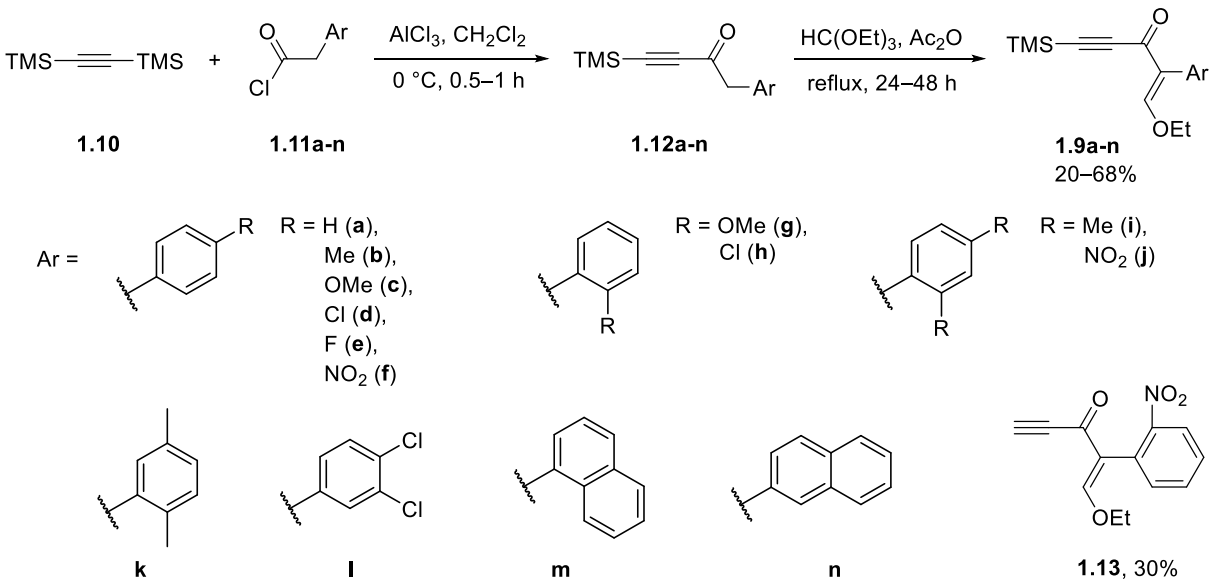
Thus, this chapter of the dissertation is devoted to the study of the synthetic potential of 2-aryl-5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones in the design of heterocyclic systems. The presented material is presented in order of increasing complexity of nucleophiles used as partners for enynones, and the final part is devoted to possible transformations of synthesized compounds.

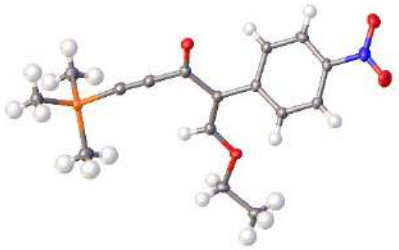
1.2. Preparation of enynones

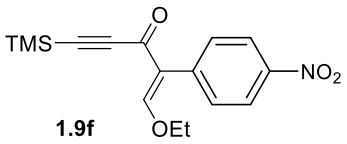
The content of the section is based on the articles [1, 15, 17].

2-Aryl-5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones **1.9** were obtained by the introduction of an ethoxymethylene fragment to the methylene group of 1-aryl-4-(trimethylsilyl)but-3-yn-2-ones **1.12**, readily available, in turn, by acylation of bis(trimethylsilyl)acetylene **1.10** (Scheme 1.2) [73, 74]. The activity of the methylene group of ketones **1.12** in interaction with triethyl orthoformate was quite expected to be noticeably lower than that of 1,3-dicarbonyl compounds [75], and therefore the reaction required harsh conditions, especially in comparison with standard methods of introduction of the ethoxymethylene group [76, 77]. In some cases, the heating time required for the conversion of the substrate at 130–140 °C reached 48 hours, which inevitably led to tarring and decrease in product yield. The best results were observed for electron-deficient ketones **1.9d,e,f,j** (Scheme 1.2, R = NO_2, F, Cl, yields 50–68%), but in general, enynones with aromatic substituents of various electronic nature and with different steric demands can be obtained in this way. The trimethylsilyl group was preserved in all enynones except compound **1.13** with a 2-nitrophenyl substituent. In all cases, the reaction proceeded stereoselectively, and the (*E*)-configuration of the enynone double bond was confirmed by the X-ray diffraction data for compound **1.9f** (Fig. 1.4).

Scheme 1.2







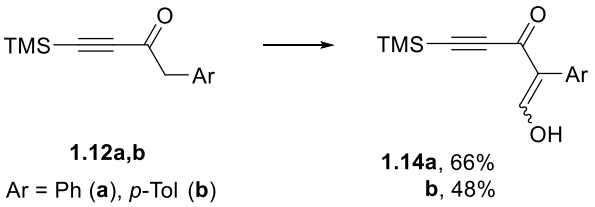
CCDC 885771

Fig. 1.4. Structure of enynone **1.9f** according to the X-ray data, processed by OLEX2 [78]

Unfortunately, within this work, it was not possible to synthesize similar enynones with CO_2Me, CN, COPh groups instead of Ar at the C^2 atom in order to expand the substrate scope. However, this does not mean that it is fundamentally impossible to obtain such structures, and the study of their synthetic potential can clearly become the subject of more than one interesting publication.

Additionally, given the harsh reaction conditions and not always high yields of enynones, we considered the possibility of replacing the ethoxymethylene group with a fragment with similar chemical properties in order to simplify synthesis and increase yields. But, for example, the interaction of ketones **1.12** with dimethyl acetal of dimethylformamide (for the introduction of the =CH–NMe_2 group) led to instant tarring of the reaction mixture.

Scheme 1.3



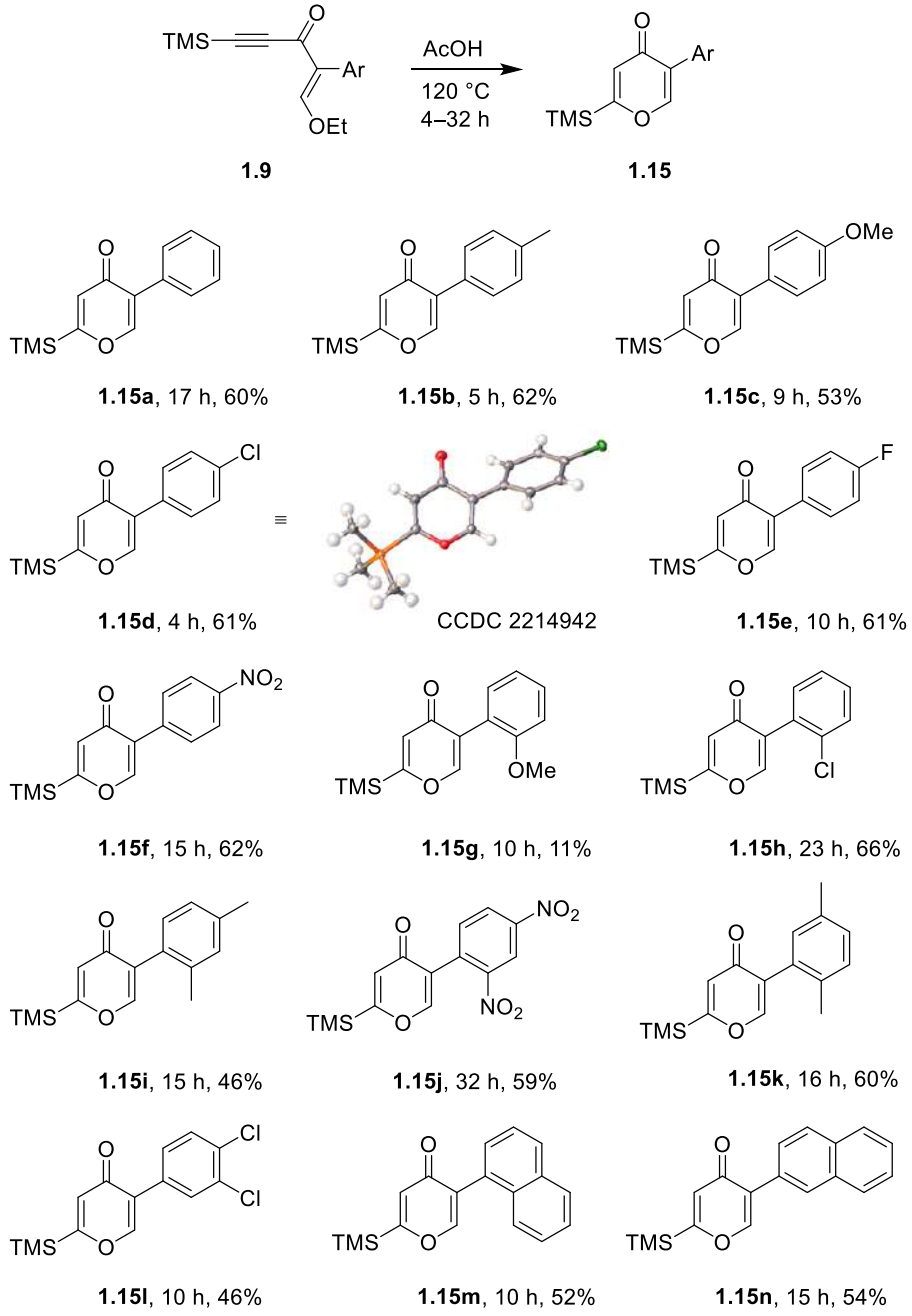
Conditions: 1) BuLi, TMS_2NH, Et_2O, –5 °C, 1 h. 2) $HCO_2CH_2CF_3$, Et_2O, –30 °C to r.t., 12 h. 3) H_2SO_4, –78 °C

Some success has been achieved in formal formylation by condensation of lithium ketone enolate with 2,2,2-trifluoroethyl formate (Scheme 1.3) [59, 79]. The corresponding enols **1.14a,b** (2-aryl-1-hydroxy-5-(trimethylsilyl)pent-1-en-4-yn-3-ones) were obtained with good yields from two ketones (**1.12a** (Ar = Ph), **b** (Ar = *p*-Tol), Scheme 1.3), but it was not possible to adapt the technique similarly for the remaining ketones. The most likely reason is the high reactivity and, consequently, low stability of enols **1.14**: many byproducts were observed in the reaction mixture, enols were destroyed during chromatographic purification on silica gel, and when trying to extract their sodium salts into an aqueous medium, the trimethylsilyl group was instantly removed (the corresponding enol with a terminal triple bond was detemined by NMR spectroscopy). Therefore, at the moment, the reaction of ketones **1.12** with $HC(OEt)_3$ in an acetic anhydride medium (Scheme 1.2) is the main method for obtaining enynones of type **1.9**.

1.3. Intramolecular cyclization. Synthesis of pyranones

The content of the section is based on the article [1].

Scheme 1.4

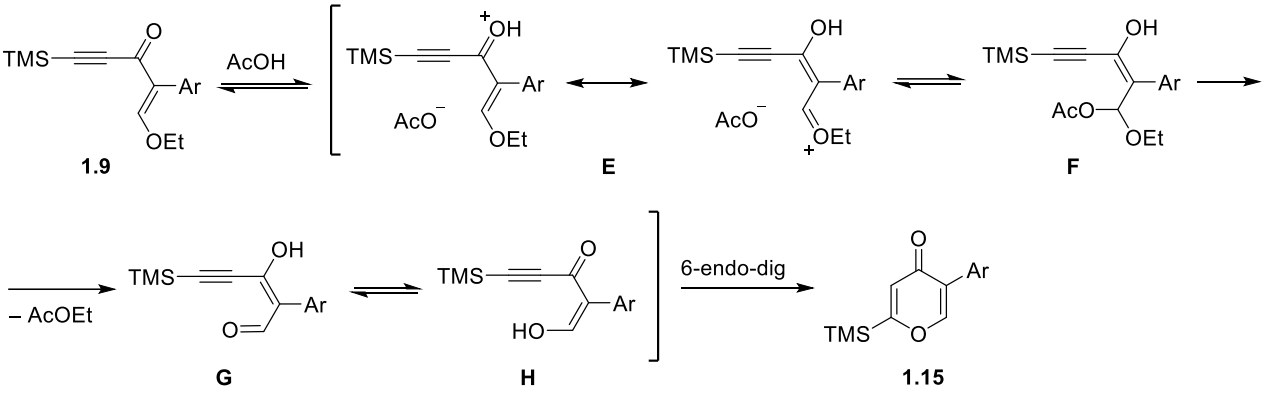


Enynones **1.9** are of interest primarily as polyelectrophilic partners for external mono- and binucleophiles. At the same time, the oxygen atom of the ethoxy group can act as an intramolecular nucleophilic center, and the length of the hydrocarbon chain of enynones allows for the closure of a five- or six-membered ring. Indeed, heating enynones **1.9** in acetic acid leads to the formation of 5-aryl-2-(trimethylsilyl)-4*H*-pyran-4-ones **1.15** (Scheme 1.4). The nature and position of the substituent in the benzene ring have practically no effect on the reaction yield: 46-66% for 13 examples, and only (2-methoxyphenyl)substituted pyranone **1.15g** was obtained in

11% yield. Also, the duration of enynone complete conversion (4-32 h) fluctuated without an obvious dependence on the structure of the substrate.

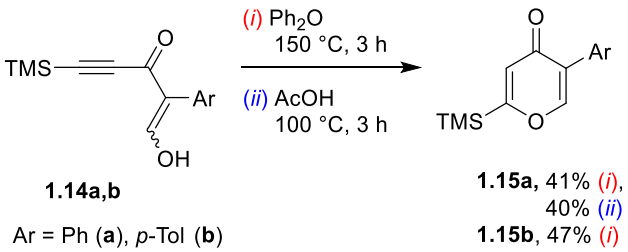
Obviously, for this transformation, it is necessary to replace the ethyl group with a hydrogen atom, and the most likely proton donor in this case is the acetic acid molecule, which participates in the formation of enol **H** according to the proposed reaction mechanism on Scheme 1.5.

Scheme 1.5



An indirect confirmation of this assumption is an experiment with separately obtained enols **1.14a,b** similar to the proposed intermediate **H**. When heated in acetic acid, pyranones **1.15a,b** were formed (Scheme 1.6), which are identical to pyranones obtained from similarly substituted ethoxyenynones **1.9a,b**. The reaction of enols **1.14** proceeded under milder conditions than for enynones **1.9** (100 °C, 3 h vs. 120 °C, ≥5 h), which is consistent with the absence of an elimination of the ethyl acetate molecule during the cyclization of enols. Interestingly, enols **1.14** can also be cyclized in a neutral aprotic medium of diphenyl ether, however at a higher temperature.

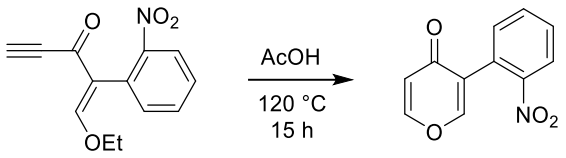
Scheme 1.6



The observed regioselectivity of the cyclization of enynones **1.9** and **1.14** in the 6-endo-dig direction does not correspond to the recently revised Baldwin rules for the nucleophilic cyclization of alkynes [80], according to which products with an exocyclic double bond should preferably be formed. The presence of a trimethylsilyl group at a triple bond is not a determining

factor, since the cyclization of enynone **1.13** with a terminal acetylene fragment proceeds in a similar way into pyranone **1.16**, albeit in a higher yield (Scheme 1.7).

Scheme 1.7



1.13 **1.16a**, 85%

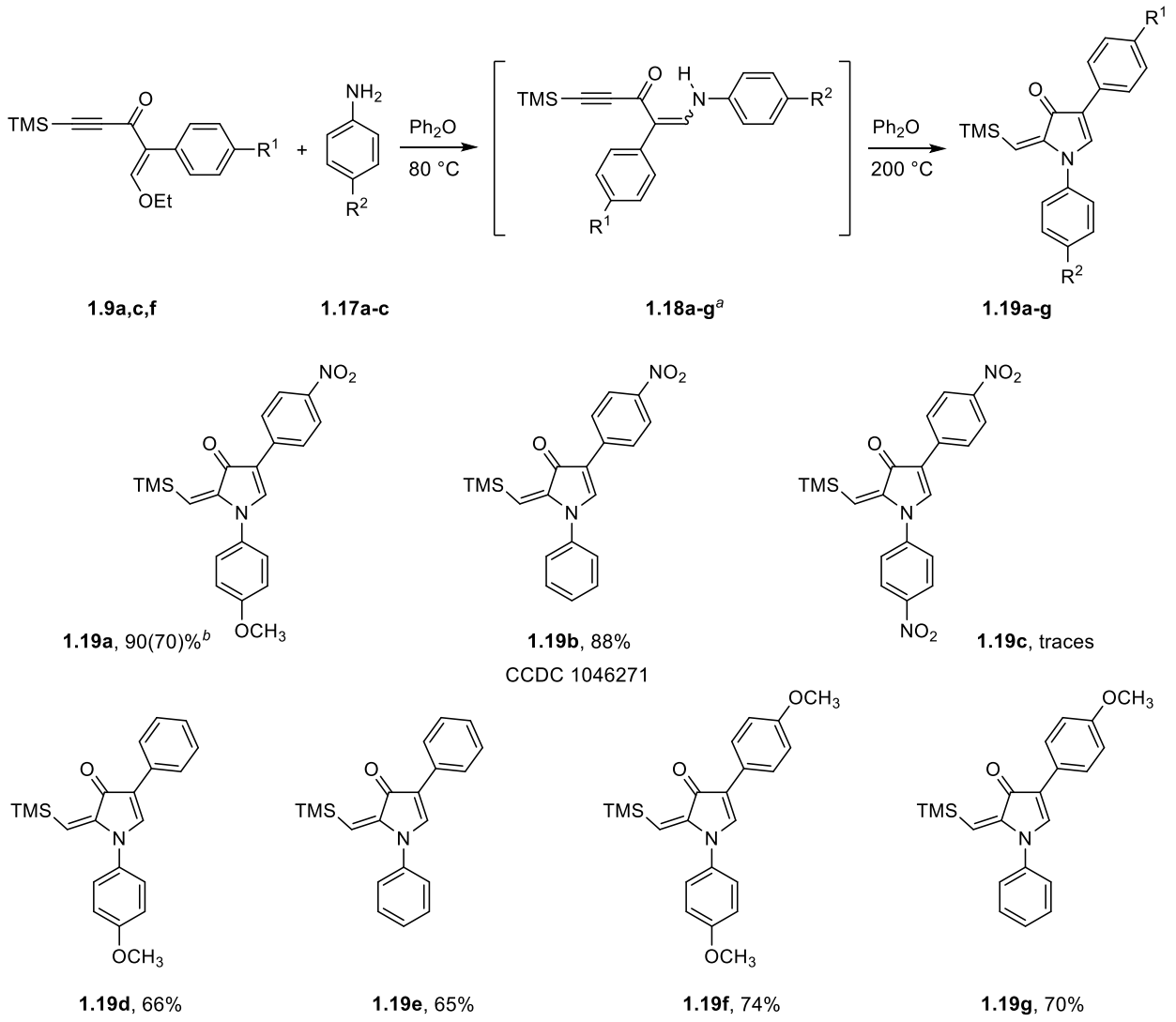
According to literature data, cyclization of 1-[O]-pent-1-en-4-yn-3-ones can lead to both pyranones and 2-methylidenfuran-3-ones, or to a mixture of both isomers [62, 65, 81-86]. Several methods have been proposed for the selective formation of γ-pyrones by hydration of penta-1,4-diyn-3-ones (for example, using Au/TiO_2 nanoparticles [87], TfOH [88], TsOH/MeOH [60]) or penta-2,4-diyn-1-ones using piperidine [89], but only 2,6-disubstituted pyranones are obtained in this way. The only example of the formation of 3-alkylpyran-4-one is given in the previously mentioned work [59]. On the background of known methods, our cyclization of enynones **1.9** represents a selective approach to pyran-4-ones **1.15** with an nontypical substitution pattern: an aromatic substituent at C^5, a free sixth position of the ring, a labile trimethylsilyl group at C^2 (the possibility of desilylation is shown further in Section 1.8.1).

1.4. Reactions with amines. Synthesis of pyrrolones

The content of the section is based on the articles [4, 13].

The interaction of enynones **1.9** with primary amines (anilines) **1.17** begins with the formation of enamines **1.18** – products of the formal substitution of the OEt group at a double bond by the NHR group (Scheme 1.8). The reaction is possible in various solvents (benzene, EtOH, CH_2Cl_2, THF, CH_3CN) already at room temperature, and even in the presence of an excess of amine a single product is formed. This indicates the highest activity of the C^1 atom among all electrophilic centers in the structure of enynones. Unlike the initial (*E*)-enynones **1.9**, enamines **1.18** exist in solution as a mixture of (*E*)/(*Z*)isomers (in crystalline form, according to the XRD, only the (*Z*)-isomer), and the appearance of the (*Z*)-isomer can be explained by its stabilization by an intramolecular hydrogen bonding. However, the configuration change is quite easy, and the ratio of forms depends on the properties of the medium: for compound **1.18a** (R^1 = NO_2, R^2 = OMe), the (*Z*)-isomer ((*E*)/(*Z*) ~1:10, 20-60 °C) prevails in chloroform, whereas in dimethyl sulfoxide, on the contrary, it is an (*E*)-isomer ((*E*)/(*Z*) ~3:1, 25 °C), apparently due to the contribution of intermolecular hydrogen bonds arising in a polar solvent.

Scheme 1.8



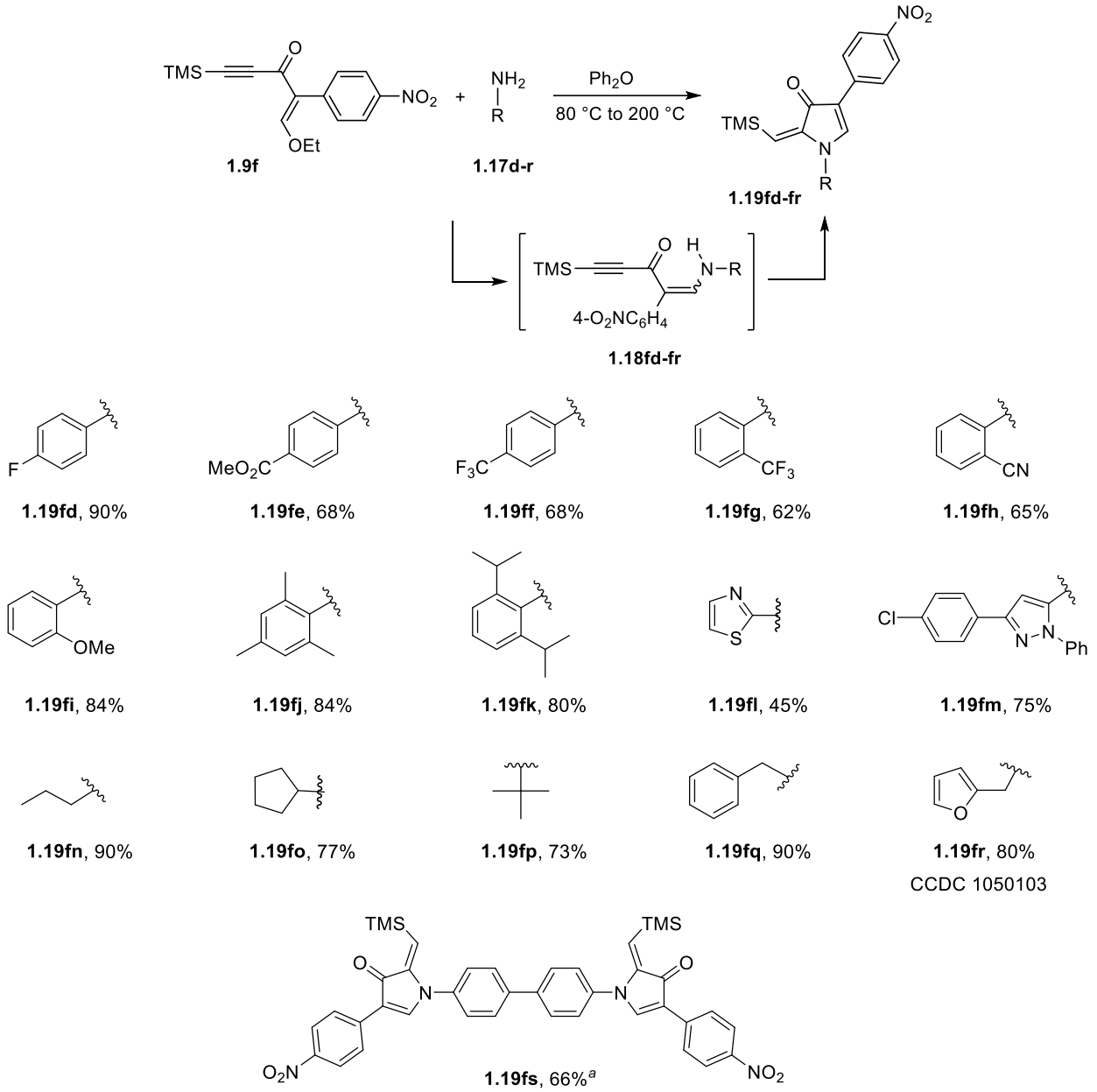
[a] Enamine **1.18a** (R^1 = NO_2, R^2 = OMe; CCDC 1045422) was isolated in 95% yield, other compounds were used without isolation.

[b] The yield for 5 mmol of starting enynone is given in paretheses; other reactions were performed on 0.35 mmol scale.

According to the relative location of nucleophilic and electrophilic centers, enamines **1.18** are analogues of the initial enynones **1.9**, therefore, it would be justified to expect similar products of intramolecular cyclization. But the result of heating the enamines was not pyridones (nitrogen analogues of pyranones **1.15**), but (2*E*)-1,4-diaryl-2-(trimethylsilylmethylidene)-1,2-dihydro-3*H*-pyrrole-3-ones **1.19**, and much more severe conditions were required for their formation compared to the cyclization of enynones **1.9** into pyranones **1.15**: heating in diphenyl ether at 200 ° C for 0.5–1 h (Scheme 1.8). Despite the fact that both steps on the way from enynones **1.9** to pyrrolones **1.19** consist, in fact, in heating compounds in a neutral medium, the low-temperature step of the formation of enamines **1.18** cannot be skipped: heating an equimolar mixture of enynone **1.9f** and *para*-anisidine (**1.17a**) immediately at 200 °C led to noticeable

tarring, which is probably explained by the implementation of low-activity side processes at low temperatures. However, both steps can be carried out in the same solvent without the isolation of enamine in its pure form. This is much more convenient experimentally, and although the first step in diphenyl ether proceeds more slowly than, for example, in tetrahydrofuran, this can be compensated by increasing the temperature to 80 °C while maintaining the same reaction duration (30 min).

Scheme 1.9



[a] Bispyrrolone **1.19fs** was obtained from benzidine and 2 eq. of enynone **1.9f** in two steps: bis-enamine in THF at 60 °C in 92% yield, its cyclization in Ph_2O at 200 °C in 72% yield.

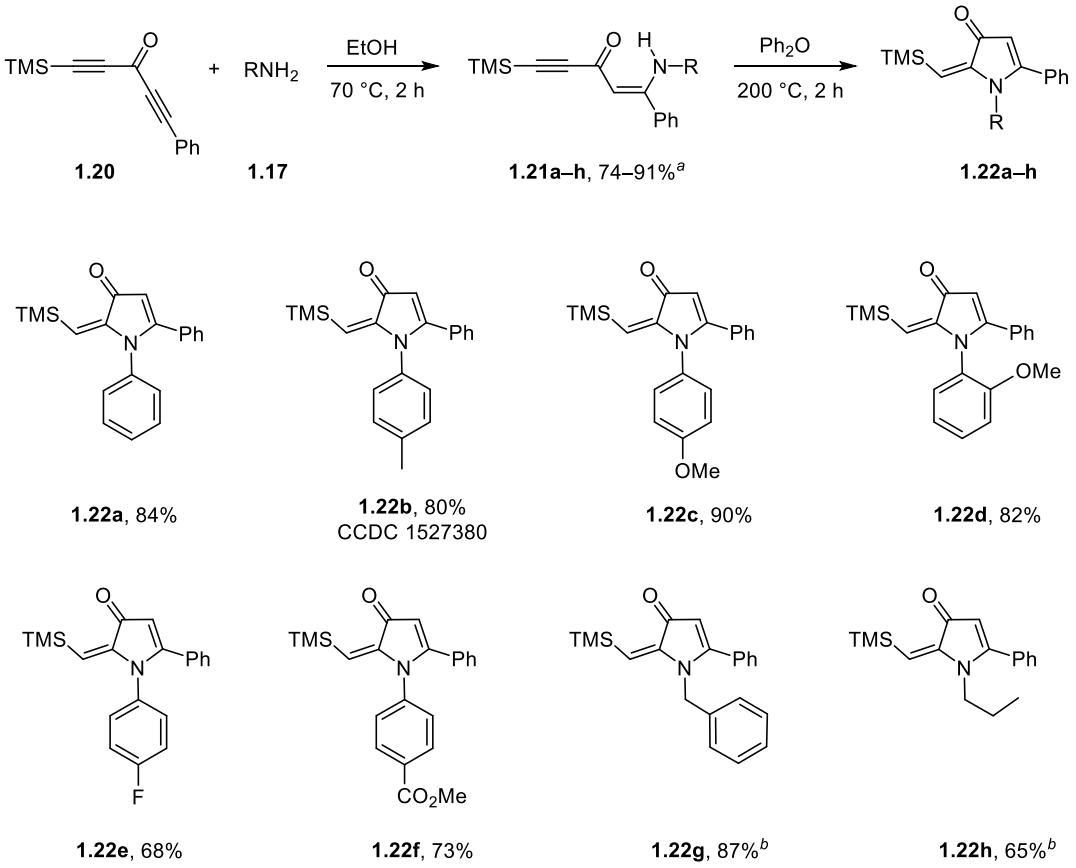
The reaction proceeds smoothly in sufficiently high yields of the only products for a wide range of aromatic and aliphatic amines with substituents of various electronic and steric nature (Scheme 1.9), and therefore can be recommended for obtaining such structures. The ease of

formation of pyrrolones **1.19** correlates with the nucleophilicity of amines: the reaction of enynones with π-deficient amines (*para*-nitroaniline, 2-, 3- and 4-aminopyridines, 2-amino-1,3,4-oxa- and thiadiazoles) was not observed, while when using n-propyl amine, the corresponding enamine was cyclized into pyrrolone **1.19fn** already at 175 °C.

The regioselectivity of cyclization of aminoenynones **1.18** in the 5-exo-dig direction is opposite to the 6-endo-dig variant observed for ethoxyenynones **1.9** (Scheme 1.4) and hydroxyenynones **1.14** (Scheme 1.6), although the substrates differ only by heteroatom with complete skeleton analogy. According to the few literature data, it can be concluded that 1-aminopent-1-en-4-yn-3-ones with an aryl or alkyl group at the triple bond are cyclized into 4-pyridones (upon catalysis by Au/TiO_2 [87] or AgTFA [90], under microwave irradiation [91]). Only one work [60] showed that under the action of *N*-iodosuccinimide (NIS), both 6-endo-dig and 5-exo-dig cyclization of such aminoenynones into doubly iodinated pyridine-4-ones and pyrrole-3-ones, respectively, can occur, and selectivity depends on the presence of Brönsted acid (*p*-TosOH) and the order of addition of NIS, however, convincing explanations for this observation are not provided. Therefore, the formation of pyrrolones **1.19** in our work is a unique example of non-catalyzed thermal 5-exo-dig cyclization of 1-aminopent-1-en-4-yn-3-ones.

Additionally, we showed that aminoenynones **1.21**, which differ from aminoenynones **1.18** in the position of an aryl substituent, are also prone to 5-exo-dig cyclization when heated in diphenyl ether (Scheme 1.10). Compounds **1.21** can be obtained as a result of selective addition of amines to an asymmetrically substituted penta-1,4-diyn-3-one **1.20**: under the specified conditions, only the aryl-substituted triple bond reacts and exclusively (*Z*)-enamines **1.21** are formed. The absence of (*Z*/*E*)-isomerization of enamines **1.21**, observed in enamines **1.18**, can probably be explained by the disadvantage of the (*E*)-configuration due to a change in the position of the aryl substituent. When aminoenynones **1.21** are heated in diphenyl ether, the five-membered ring of (2E)-1-R-2-(trimethylsilylmethylidene)-5-phenyl-1,2-dihydro-3*H*-pyrrole-3-ones **1.22** is formed (Scheme 1.10): both the conditions and the result of the reaction are similar to that observed during the formation of pyrrolones **1.19** (Schemes 1.8, 1.9).

Scheme 1.10



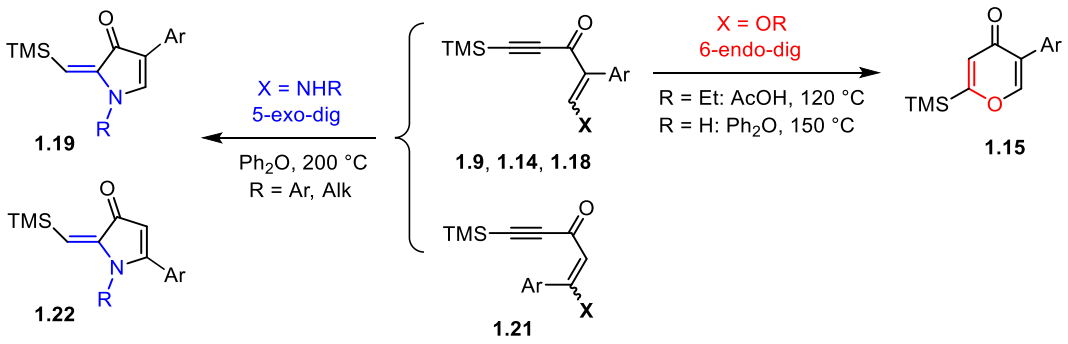
[a] Data of XRD analysis for the structure **1.21c** (R = 4-$MeOC_6H_4$) – CCDC 1911263.

[b] For alkyl amines, the first step was performed in THF at room temperature (0.5-1 h) to avoid desilylation, which was observed in ethanol.

Thus, the cyclization of 1-(R)amino-5-(trimethylsilyl)pent-1-en-4-yn-3-ones (compounds **1.18** and **1.21**), regardless of the position of the aryl substituent (at C^1 or C^2), proceeds along the 5-exo-dig pathway with the formation of pyrrol-3-ones **1.19** and **1.22**. This is a fundamental difference from 6-endo-dig cyclization 1-hydroxy(ethoxy)-5-(trimethylsilyl)pent-1-en-4-yn-3-ones (compounds **1.9** and **1.14**) into pyran-4-ones **1.15** leads to the conclusion that the nature of the heteroatom at a double bond determines the direction of cyclization (Scheme 1.11). In all cases, the reaction is possible in neutral diphenyl ether, but the acidity of enols **1.14** (the formation of which is also assumed on the **1.9**→**1.15** pathway) should be higher than that of enamines, therefore, the participation of a proton in the activation of a triple bond and the influence on the regioselectivity of cyclization can be assumed. We performed trial experiments on the cyclization of aminoenynone **1.18b** (Ar = 4-$O_2NC_6H_4$, R = Ph) in acetic acid and a mixture of diphenyl ether with acetic acid. In the first case, heating at 120 °C for 1 h led only to tarring of the starting compound, and in the second case after 1 h at 200 °C pyrrolone **1.19b** was isolated in a lower yield than in the reaction in pure diphenyl ether (Scheme 1.8). Probably, the much more severe heating conditions ensure the implementation of 5-endo-dig cyclization of

aminoenynones, for which 6-endo-dig closure is not energetically advantageous even in the presence of an acid, and for hydroxyenynones 6-endo-dig cyclization dominates even under milder conditions.

Scheme 1.11



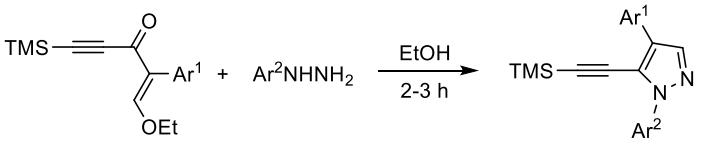
1.5. Reactions with hydrazines. Synthesis of pyrazoles

The content of the section is based on the articles [13, 17].

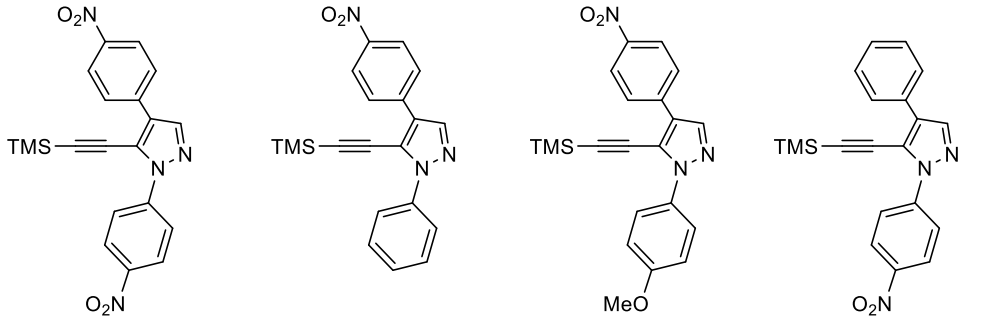
When asymmetric binucleophiles, *i.e.* monosubstituted hydrazines, are introduced into reaction with polyelectrophilic enynones **1.9**, the issue of regioselectivity becomes more complicated due to the different activity of nucleophilic centers and the appearance of a set of possible electrophile-nucleophile combinations. In aliphatic and aromatic monosubstituted hydrazines, the nucleophilicity of nitrogen atoms is not the same and is determined by the nature of the substituent, so it is fair to expect different selectivity when interacting with enynones.

It turned out that enynones **1.9** easily react with monosubstituted hydrazines **1.23** and **1.25**: as a result, pyrazoles **1.24**, **1.26** and **1.27** with a trimethylsilyl-substituted triple bond in the side chain in the third or fifth position of the pyrazole ring are formed in yields of at least 54% (Schemes 1.12 and 1.13). The reaction with aryl hydrazines **1.23** proceeds completely regioselectively with the formation of only 5-alkynylpyrazoles in cases where at least one of the starting compounds contains a nitro group in the aromatic ring (compounds **1.24a-d,g**); in other cases, the selectivity is not lower than 9:1 (Scheme 1.12). For alkylhydrazines **1.25**, the isomer ratio is leveled, and for n-propyl hydrazine **1.25a**, selectivity is even reversed in favor of the corresponding 3-alkynylpyrazole **1.27a** (Table 1.1, line 1). In reaction with free hydrazine, a single product **1.26e** is formed, which exists at room temperature as an equilibrium mixture of two tautomeric forms (~3:1, DMSO-d_6) (Table 1.1, line 5).

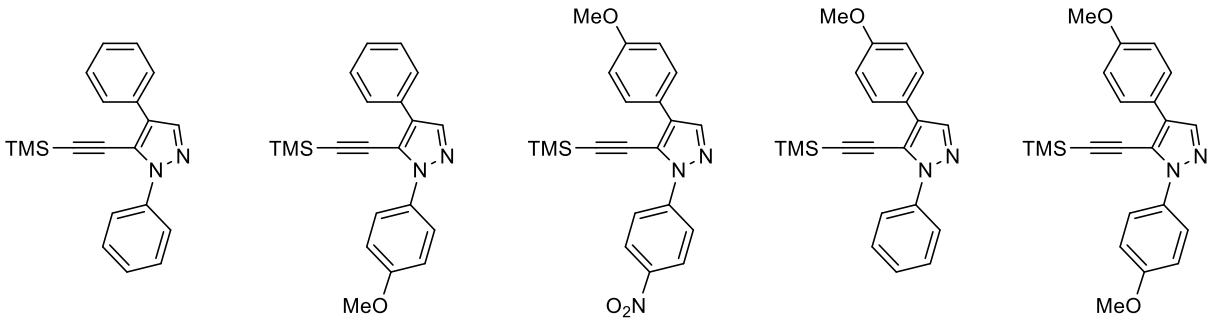
Scheme 1.12



1.9a,c,f **1.23a-c** **1.24a-i**[a]



1.24a, 65%[b] **1.24b**, 84% (1:0) **1.24c**, 94% (1:0)[c] **1.24d**, 48% (1:0)



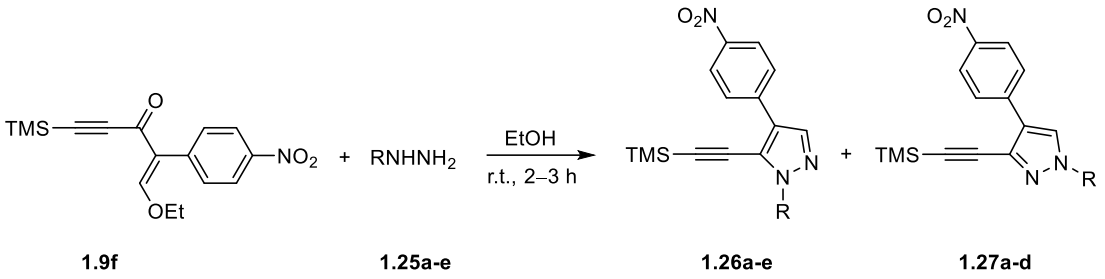
1.24e, 74% (12:1) **1.24f**, 80% (10:1)[c] **1.24g**, 62% (1:0) **1.24h**, 63% (10:1) **1.24i**, 61% (9:1)[c]

[a] Preparative yields are given. The ratios of 5-alkynyl- and the corresponding 3-alkynylpyrazoles according to the ^{1}H NMR spectra of the reaction mixtures are given in parentheses.

[b] It was not possible to register the spectrum of the reaction mixture due to the low solubility of the components.

[c] 4-Methoxyphenylhydrazine was used as its hydrochloride, and the reactions were carried out in the presence of an equimolar amount of triethyl amine.

Scheme 1.13



1.9f **1.25a-e** **1.26a-e** **1.27a-d**

Table 1.1

№	Hydrazine **1.25**	R	**1.26**, %	**1.27**, %	**1.26** : **1.27**[a]
1	**a**	*n*-Pr	29	45[b]	0.6:1
2	**b**	Bn	46	33	1.4:1
3	**c**	*i*-Pr	60	15	4:1
4	**d**	*t*-Bu	54	0	1:0
5	**e**	H	74		

[a] According to the ^{1}H NMR spectrum of the reaction mixture
[b] CCDC 885772

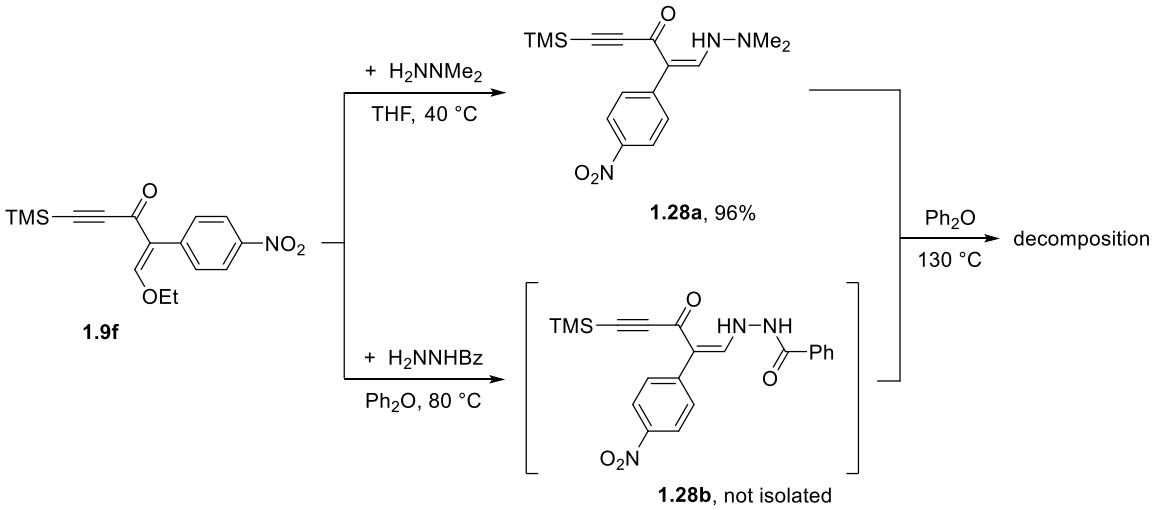
The observed selectivity of the reaction of enynones **1.9** with hydrazines and the above results with amines (Section 1.4) allow us to conclude about the greatest electrophilicity of the C^1 atom in the fragment >CH=OEt of the enynone molecule. It is possible to confidently assume the initial addition of hydrazine precisely to the C^1 enynone atom, therefore, the result of the reaction with hydrazine is determined by the ratio of the nucleophilicity of its nitrogen atoms. In monoaryl hydrazines, the aromatic substituent lowers the nucleophilicity of the neighboring nitrogen atom, whereas in monoalkyl hydrazines, the donor alkyl substituent increases the nucleophilicity of the substituted atom compared with the terminal one, but simultaneously reduces its steric accessibility. As a result, the difference in the nucleophilicity of nitrogen atoms is more pronounced in monoaryl hydrazines **1.23** than in monoalkyl hydrazines **1.25**, which is clearly confirmed by experimental data on the selectivity of the formation of 5- or 3-alkynylpyrazoles (this difference reaches a maximum in 4-nitrophenyl hydrazine, which explains the complete selectivity of the reaction in cases **1.24a,d,g**).

Interestingly, when using 4-methoxyphenylhydrazine hydrochloride in the absence of a base, the selectivity of the reaction decreased sharply: pyrazole **1.24f** and its isomer with an alkynyl substituent in the third position of the ring were formed in comparable quantities (~2:1). Here we can assume a twofold effect of free hydrogen chloride appearing in the reaction mixture: firstly, protonation of the carbonyl oxygen atom of enynone, as a result of which the electrophilic properties of the C^3 atom increase and the difference in activity between C^3 and C^1

decreases, and secondly, the nucleophilicity of nitrogen atoms in 4-methoxyphenyl hydrazine correlates with basicity, therefore the initial addition to enynone by a substituted nitrogen atom becomes more likely. In any case, the selectivity of the reaction decreases, and it is obvious that in the synthesis of pyrazoles, preference should be given to the free form of hydrazine or use a sufficiently strong base to trap the acid from its salt.

The reaction of enynones **1.9** with *N*,*N*-substituted hydrazines obviously cannot lead to the formation of pyrazoles, but *N*-substituted pyrrolones in this case could not be obtained also (Scheme 1.14). We tested *N*,*N*-dimethyl hydrazine and benzhydrazide in reaction with enynone **1.9f**, but the enhydrazines **1.28**, formed on the first step, completely decomposed upon further heating at a higher temperature. Therefore, these reactions can only be considered as another confirmation of the highest activity of the ethoxymethylene group among all electrophilic centers in the structure of enynone.

Scheme 1.14

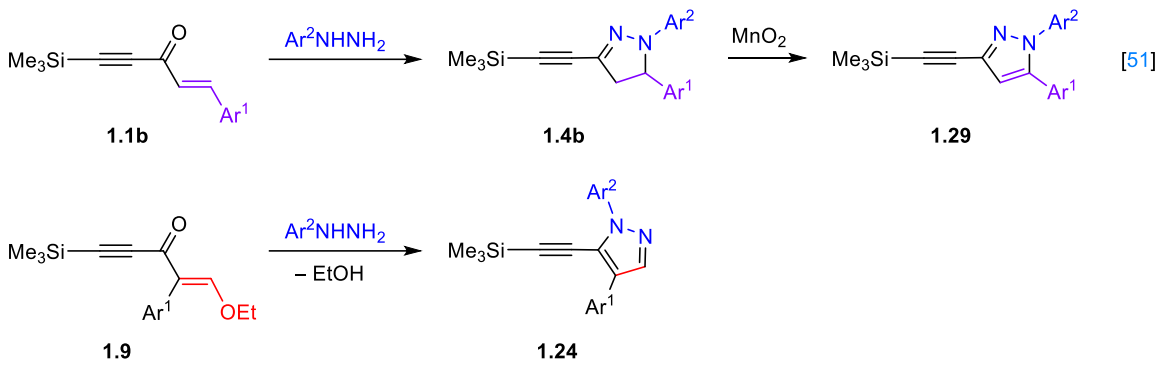


Despite the previously mentioned ease of removing the trimethylsilyl group from the triple bond under the action of a base in a proton solvent (see Section 1.1), the TMS–C≡C fragment remains unaffected in all the reactions with hydrazines described above, even when heated in an alcoholic solution.

In general, the reaction of enynones **1.9** with monosubstituted hydrazines, especially aromatic ones, is a convenient method for the selective synthesis of 5-(trimethylsilylethynyl)pyrazoles. And the selectivity of this reaction fundamentally distinguishes it from both the above described variants of the interaction of pent-1-en-4-yn-3-ones **1.1** with hydrazines (Scheme 1.1, Section 1.1), and, for example, from the reaction of 1-aryl-5-(trimethylsilyl)pent-1-en-4-yn-3-ones **1.1b** with arylhydrazines, where 3-(trimethylsilylethynyl)pyrazolines **1.4b** are formed, and the initial addition of hydrazine occurs

on the carbonyl group (Scheme 1.15, top line) [51]. In our enynones **1.9**, on the contrary, the addition of hydrazine begins precisely on the β-atom of the C=C bond, which leads to the formation of 5-ethynylpyrazole (Scheme 1.15, bottom line).In addition, the presence of the leaving ethoxy group in substrates **1.9** provides a free third position of the pyrazole ring and the absence of the oxidation step necessary to achieve aromaticity, as in the case of **1.4b→1.29** [51].

Scheme 1.15 (literature data [51] – upper line)

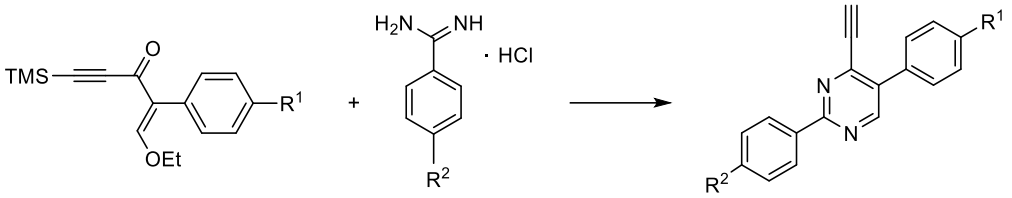


1.6. Reactions with amidines. Synthesis of pyrimidines

The content of the section is based on the article [15].

The reaction of enynones **1.9** with amidines is more predictable than with hydrazines, since amidines are symmetric binucleophiles. Indeed, the only products of the interaction of enynones **1.9** with amidines **1.30** are 2,5-diaryl-4-ethynylpyrimidines **1.31**, they were obtained in 43-85% yields (Scheme 1.16). This reaction can be noted as one of experimentally the easiest within this work, since pyrimidines **1.31** are poorly soluble in alcohol and precipitate during the reaction, which greatly facilitates their isolation from the reaction mixture. The symmetry of the nucleophilic centers of amidine does not allow us to draw conclusions about the place of initial attachment to the enynone molecule, but it is likely that, as in previous cases, it is the C^1 atom in the ethoxymethylene group, and then the addition to the carbonyl carbon atom occurs. In all the experiments carried out, the reaction took place at room temperature for no more than 2 h (with the exception of the least active 4-nitrobenzamidine), which, when compared with hydrazines, indicates the expected greater nucleophilicity of amidines. They also have a higher basicity (for example, the pKa value of phenylhydrazine 5.27 [92], benzamidine 11.6 [93]), which is sufficient for desilylation of the triple bond in an alcoholic solution. All pyrimidines **1.31** obtained have a terminal triple bond in the side chain, and the trimethylsilyl group can be preserved in pyrimidines **1.32** only if the reaction is carried out in an aprotic solvent, for example dichloromethane (Scheme 1.17).

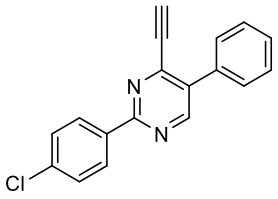
Scheme 1.16



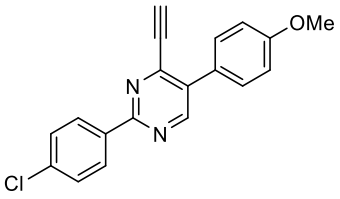
1.9a-d,f **1.30a-e** **1.31a-y**, 43–85%
25 examples

R^1, R^2 = NO_2, Cl, H, Me, OMe

Conditions: NaOMe, MeOH, r.t., 0.5-2 h (R^2 = H, Me, OMe, Cl) or $NaHCO_3$, EtOH, r.t., 12 h (R^2 = NO_2)

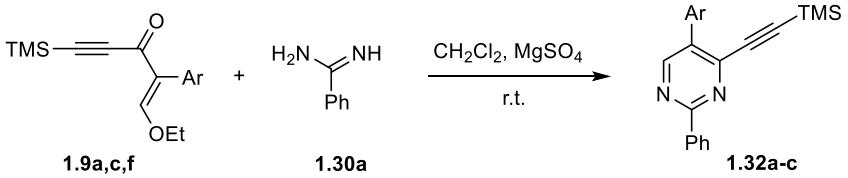


CCDC 972361



CCDC 954795

Scheme 1.17



1.9a,c,f **1.30a** **1.32a-c**

Ar = Ph (**a**)
4-$MeOC_6H_4$ (**c**)
4-$O_2NC_6H_4$ (**f**)

61% (**a**)
75% (**b**)
15% (**c**)

The reaction of nitrosubstituted enynone **1.9f** with free benzamidine **1.30a** deserves a special comment, since here the yield of silylated pyrimidine **1.32c** unexpectedly decreased to only 15% (Scheme 1.17), whereas the desilylated analogue was isolated in 73% yield (for comparison, the yields of the other two desilylated pyrimidines (analogues of **1.32a,b**) are even lower: 48% and 55%, respectively). The main product in 50% yield turned out to be the ethyl ester of 4-nitrophenylacetic acid, and this transformation of enynone **1.9f** was also observed in the presence of other bases, for example *i*-Bu_2NEt in a solution of CH_2Cl_2 in an argon atmosphere, but we did not establish the mechanism of this unusual transformation.

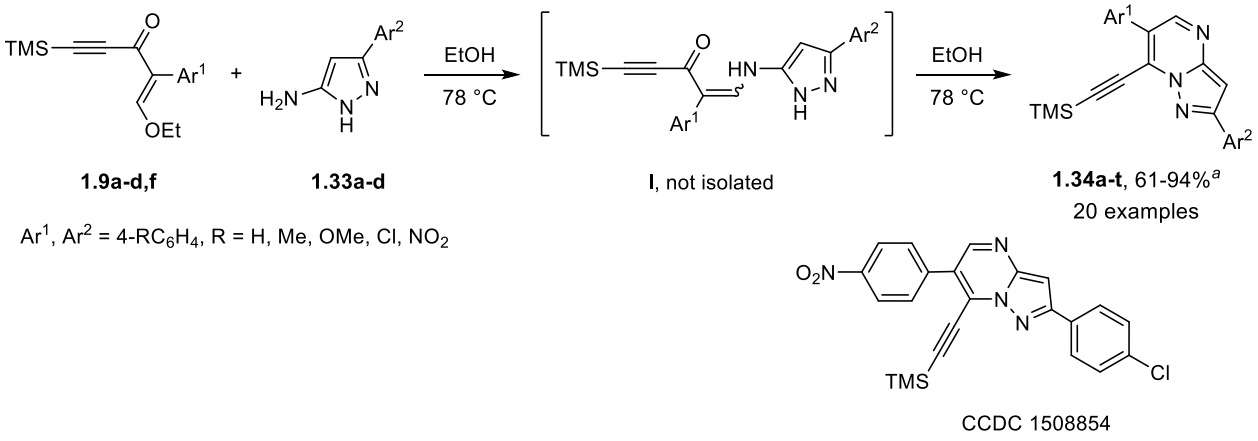
Elimination of the ethoxy group of enynone **1.9** during the reaction provides a free sixth position of 4-alkynylpyrimidines **1.31** and **1.32** – according to literature data, there are very few examples of pyrimidines with this type of substitution, and the Sonogashira reaction is used to introduce a triple bond in these cases [94-97]. Our strategy can be recommended as a new effective and convenient alternative approach to such structures.

1.7. Reaction with pyrazolamines. Synthesis of pyrazolo[1,5-*a*]pyrimidines

The content of the section is based on the article [9].

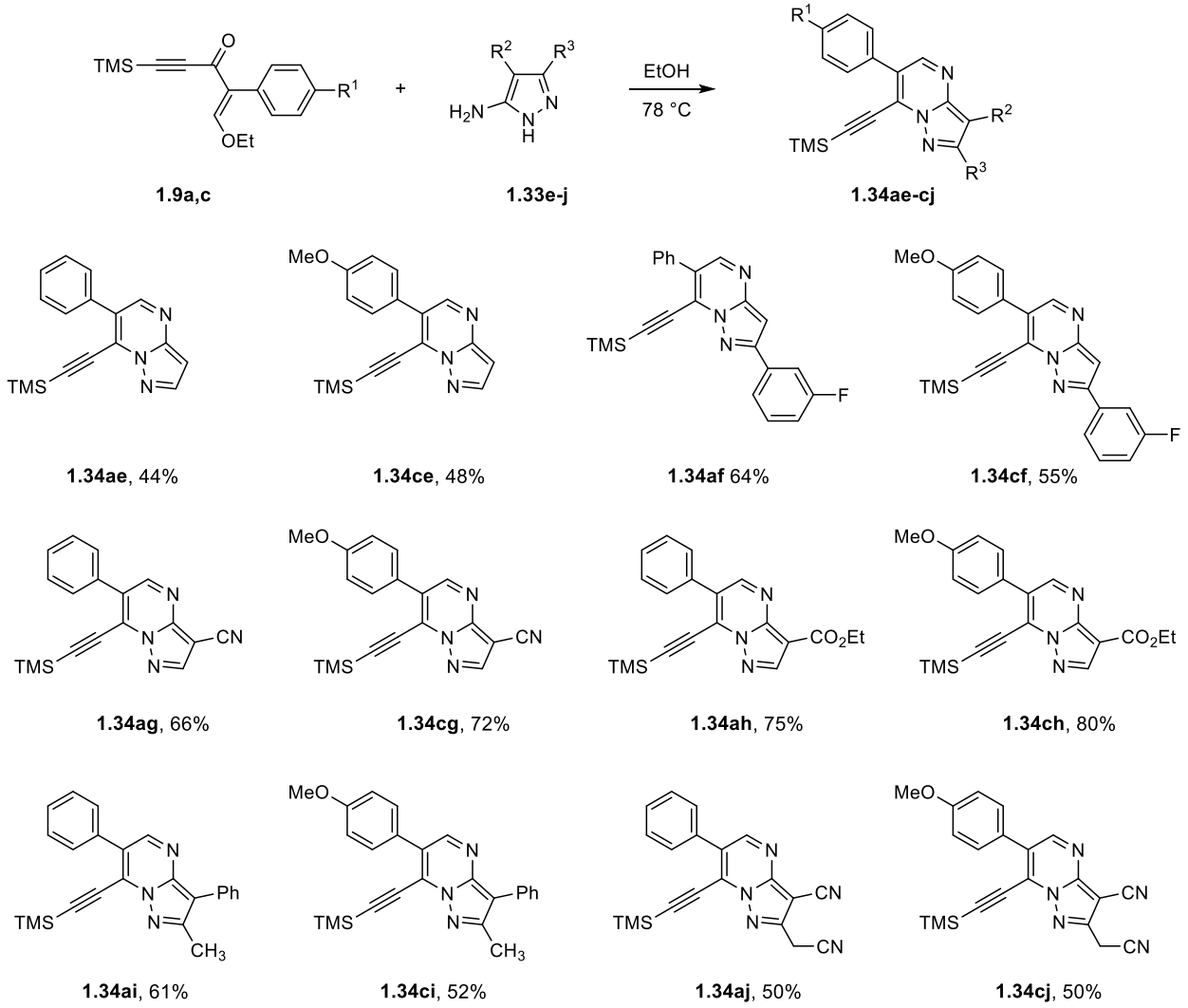
1*H*-Pyrazol-5(3)-amines are asymmetric binucleophiles, and there are contradictory data in the literature on the relative activity of their exo- and endocyclic nitrogen atoms [98-100]. On the one hand, pyrazolamines contain a primary amino group, and, as with amines, in reaction with enynones **1.9**, the formation of corresponding pyrrolones of type **1.19** can be expected, and on the other hand, they can be considered as heterocyclic analogues of amidines and can lead to the formation of pyrazolopyrimidines. It turned out that the reaction proceeds unambiguously along the second pathway, and the corresponding 7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines **1.34** can be obtained in high yields (Scheme 1.18). The reaction is quite general, we have demonstrated its applicability for a wide range of variously substituted pyrazolamines **1.33** (Schemes 1.18, 1.19). Given the ease of experimental implementation (refluxing the reaction mixture in ethanol for 12-20 h), it can be recommended as an approach to such compounds. Our results show that the basicity of pyrazolamines is lower than that of amidines (the pKa value of 1*H*-pyrazole-3-amine is 4.30 [101]), and is insufficient for desilylation of the triple bond of the resulting pyrazolopyrimidines **1.34** even when heated in an alcoholic solution.

Scheme 1.18



[a] Yield of pyrazolopyrimidine **1.34a** (Ar^1 = Ar^2 = Ph) was 85% for 1.65 mmol of enynone; other reactions were performed on 0.33 mmol scale.

Scheme 1.19



Even if, in general, pyrazolamines **1.33** in reaction with enynones **1.9** act as analogues of amidines, the ambiguous relative activity of their exo- and endocyclic nitrogen atoms suggests the possibility of formation of both the 7-ethynylpyrazolo[1,5-*a*]pyrimidines shown in the scheme, and isomeric compounds with an ethynyl substituent in the fifth position of the core. According to the ^{1}H and ^{13}C one-dimensional NMR spectra, as well as 2D NOESY, it is impossible to make a clear choice between these structures, but the modern variety of two-dimensional NMR spectroscopy techniques allows us to solve complex structural problems. In this case, using the HSQMBC ^{1}H-^{15}N experiment, the N–H spin-spin coupling constants were determined, and by comparing their values with the literature data for pyridine and pyrrole, we determined the exact position of the ethynyl substituent in the core of the molecule. The XRD data obtained later only confirmed our conclusions (Scheme 1.18). Thus, in the reaction of enynones **1.9** with pyrazolamines **1.33**, the formal substitution of the ethoxy group with the amino group of pyrazole occurs first, probably with the formation of enamine I (Scheme 1.18),

and then the cycle closes with the participation of the carbonyl group and the endocyclic nitrogen atom of pyrazole.

It is worth noting that very few examples of ethynyl-substituted pyrazolo[1,5-*a*]pyrimidines can be found in the literature, and all of them were obtained using the Sonogashira reaction [102-104]. Moreover, the compounds **1.34** obtained by us are the first examples of the class of 7-ethynylpyrazolo[1,5-*a*]pyrimidines.

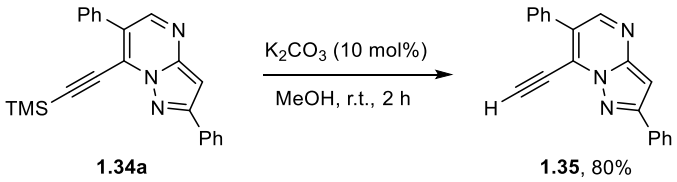
1.8. Several examples of further modification

1.8.1. Desilylation and thiation

The content of the section is based on the articles [1, 9].

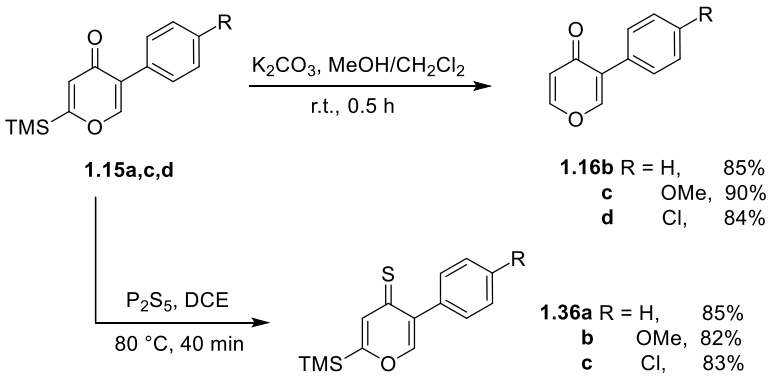
The absolute majority of the heterocyclic compounds described above, formed in the reactions of enynones **1.9** with nucleophiles, have a trimethylsilyl-substituted triple bond in the side chain. The ease of removing the $SiMe_3$ group from the triple bond is well known from the literature data [68-70], therefore we demonstrated only the fundamental possibility of its removal using one example of pyrazolo[1,5-*a*]pyrimidine **1.34a** (Scheme 1.20).

Scheme 1.20



Interestingly, the desilylation of 2-(trimethylsilyl)pyranones **1.15** can be carried out in a similar way: the reaction proceeds smoothly, without ring cleavage (the same result can be obtained using an ammonia solution in ethanol instead of the K_2CO_3/MeOH system) (Scheme 1.21). A similar pyranone **1.16a** was obtained by cyclization of desilylated (2-nitrophenyl)-substituted enynone **1.13** (Section 1.3, Scheme 1.7).

Scheme 1.21

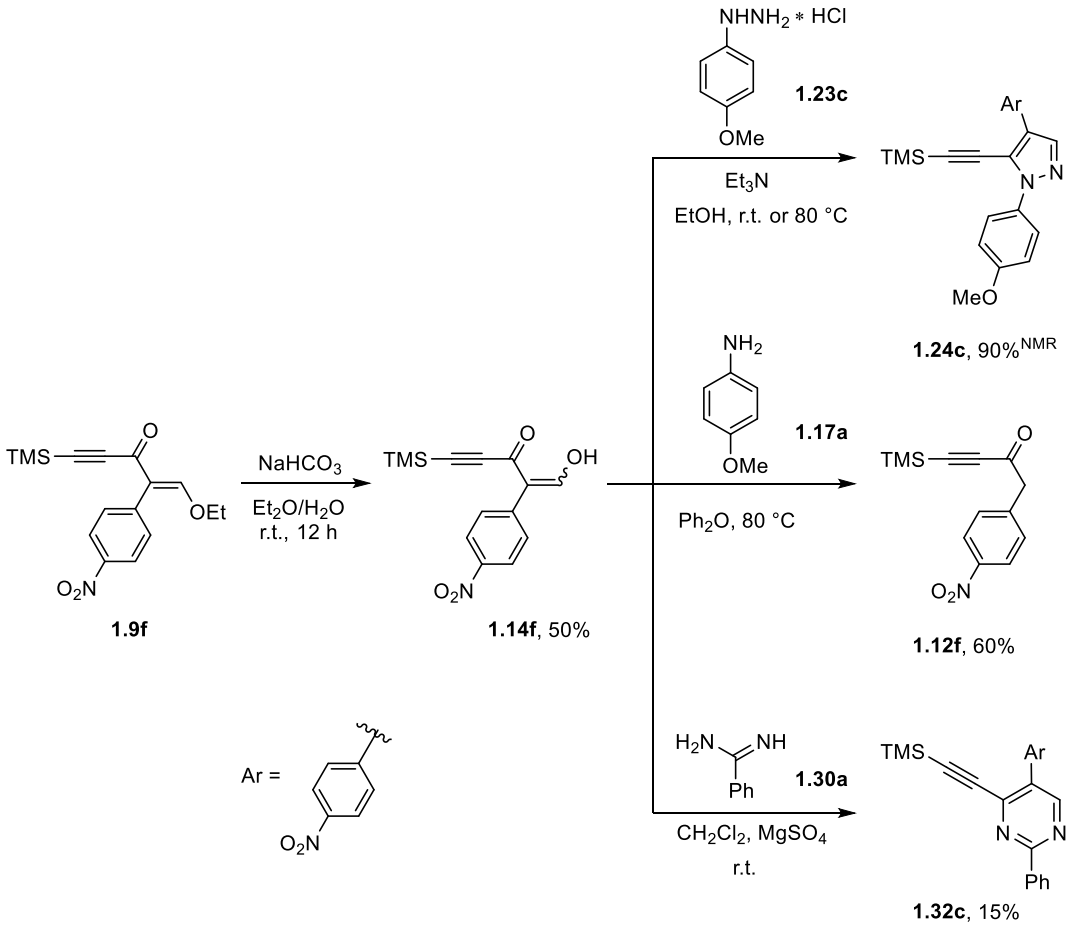


Using the example of the same pyranones **1.15**, the possibility for thiation of the carbonyl group using P_2S_5 was shown (Scheme 1.21). The resulting pyranthions **1.36** have a bright red or orange color, are stable in dry form, but are quite easily hydrolyzed back to pyranones in a wet solution (in a solution of initially pure pyrantion **1.36a** in $CDCl_3$ after 3 days at room temperature, its mixture with pyranone **1.15a** was observed in the ratio *ca*. 1:0.35).

1.8.2. Reactions of hydroxyenynones with nucleophiles

Section 1.2 (Scheme 1.3) describes our attempt to develop a method for formylation of ketones **1.12** to obtain hydroxyenynones **1.14** as analogues of ethoxyenynones **1.9**. Interestingly, the most active (4-nitrophenyl)substituted enynone **1.9f** is hydrolyzed to the corresponding enol **1.14f** when treated with $NaHCO_3$ in a water/diethyl ether mixture (Scheme 1.22). We used this compound to compare the reactivity of hydroxy- and ethoxyenynones in reactions with nucleophiles (an analogy in intramolecular cyclization into pyranones was shown in Section 1.3).

Scheme 1.22



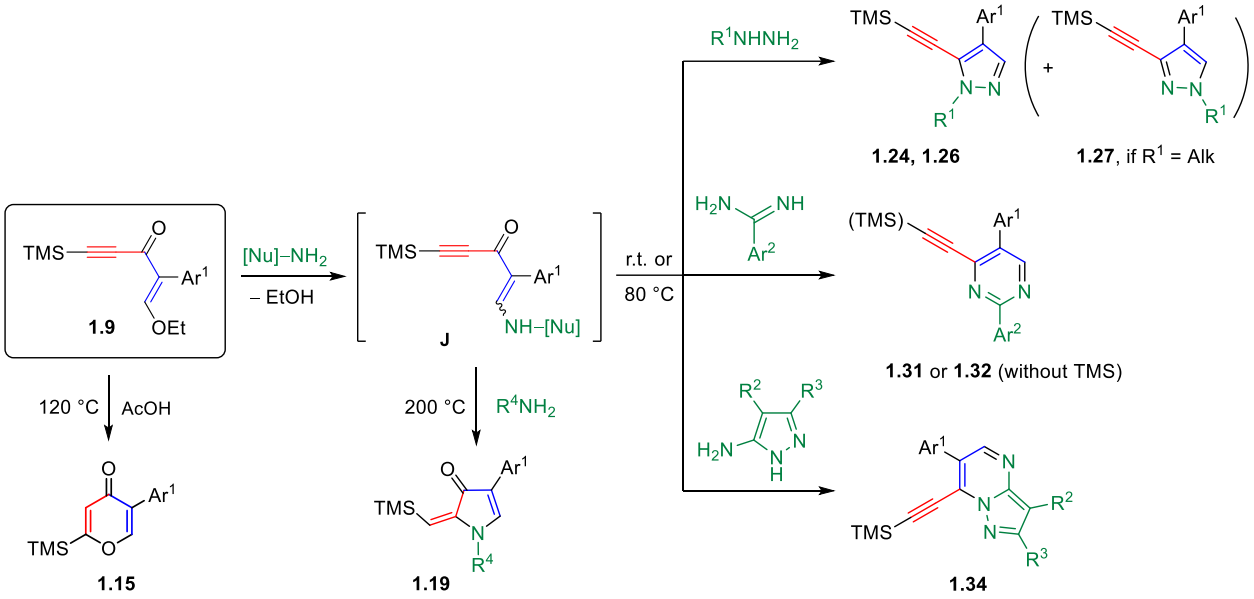
Whereas the reaction of hydroxyenynone **1.14f** with 4-methoxyphenylhydrazine (**1.23c**) resulted to the previously obtained pyrazole **1.24c** in excellent yield under the same conditions as for nitrosubstituted ethoxyenynone **1.9f** (Scheme 1.12), the reaction with 4-methoxyaniline

(**1.17a**), failed to give the expected aminoenynone **1.18a**. The only product of this reaction was ketone **1.12f**, the result of the deformylation of the initial enol **1.14f** (Scheme 1.22). In reaction with benzamidine (**1.30a**), the expected pyrimidine **1.32c** was obtained, but in the same low 15% yield as from ethoxyenynone **1.9f** (Scheme 1.17), although no other products were found in the reaction mixture, including ethyl 4-nitrophenylacetate formed from ethoxyenynone **1.9f**, and the low yield of the target compound was due to strong tarring. These examples illustrate the broader synthetic potential of ethoxyenynones **1.9** than hydroxyketones of type **1.14**, therefore, the development of synthetic schemes based on enynones **1.9** seems more reasonable.

1.9. Conclusion

The reactions described in Chapter 1 are combined in one Scheme 1.23, illustrating the synthetic potential of 2-aryl-5-(trimethylsilylethynyl)-1-ethoxypent-1-en-4-yn-3-ones **1.9** presented by us. All the considered variants of their interaction with nitrogen nucleophiles are characterized by high, often 100% chemoselectivity. The reactions begin with the formal substitution of the ethoxy group of enynone by the amino group of the nucleophile with the formation of an intermediate of the general type J, which indicates the dominant activity of the C^1 atom among the electrophilic centers of enynone. If the length of the atom chain allows, a five- or six-membered rinf is formed with the involvement of a carbonyl group, which is observed in reactions with hydrazines, amidines and pyrazolamines. These reactions take place under mild conditions (heating to 80 °C), and the trimethylsilyl-substituted triple bond is retained in the side chain of the products. In reaction with amines, the transformation of aminoenynone **J** occurs only upon heating to 200 °C, with participation of the triple bond (5-exo-dig cyclization), and the resulting pyrrolone contains a trimethylsilylmethylidene substituent. Enynones **1.9**, however, tend to intramolecular 6-endo-dig cyclization into pyranones, and the change in selectivity is probably associated with a change in the nucleophilic heteroatom and the participation of acid in the cyclization process. In general, it is fundamentally possible to use all electrophilic centers of enynones **1.9**, but in each case a certain selectivity of the construction of a heterocyclic core is realized.

Scheme 1.23



The resulting heterocyclic compounds have a substitution pattern, which is atypical for representatives of their classes (due to the presence of a leaving ethoxy group at a double bond of enynones); the methods of their preparation are operationally simple and give good yields of the target products. The main advantage of the proposed strategy is the embedding of an ethynyl substituent directly during the selective assembling of the central heterocyclic core, which is an alternative to the Sonogashira reaction, generally used to introduce an ethynyl substituent into an already prepared heterocycle. At the same time, the set of substituents and vacant positions of the target compounds make them a convenient platform for further modification and construction of more complex structures.

Chapter 2. Cyclizations of *ortho*-aryl(ethynyl)heterocycles

2.1. Introduction

Many of the heterocyclic compounds synthesized by us from trimethylsilyl-substituted cross-conjugated enynones have an interesting structural feature – the *ortho*-arrangement of ethynyl and aromatic substituents in the heterocyclic core of the molecule. This creates conditions for cyclization, in fact, isomerization, of *ortho*-alkynylbiaryl, and opens up the fundamental possibility of constructing polycyclic fused arenes. This transformation gained fame and popularity after the publication of A. Fürstner's work in 2002 [105]. In general, cyclization can proceed in the 6-endo or 5-exo direction (for example, for 2-ethynylbiphenyl to form phenanthrene or 9-methylidenefluorene, respectively), which depends on the structure of the substrate and the catalyst used. On the topic of hydroarylation of alkynes (in another way, the introduction of alkynes into the C_{Ar}–H bond of arenes), of which the cyclization in question is a special case, many reviews have been written, but they mainly concern intermolecular reactions and cases where there is still some kind of connecting link between the aromatic ring and the triple bond [106-111 and references in [5]]. Therefore, in 2019, we wrote a large review on the cyclization of *ortho*-ethynylbiaryls, aiming to systematize the rapidly growing amount of information on this topic (257 references) [5]. The literature data are divided in sections depending on the type of cyclization activation, and although the leading place belongs to transition metal catalysis, variants of electrophilic activation, radical induction, basic catalysis and historically the first pyrolytic method are described. In following years, interest in such reactions did not fade, but on the contrary, the number of publications continues to grow rapidly now. For example, works on the π-activation of alkynes using γ-Al_2O_3 [112], cyclization with simultaneous introduction of a cyano group (a variant of electrophilic activation using $[CN]^+$) [113], selective formation of 9-methylidenefluorenes in Pd^0-catalyzed cyclization [114] are interesting; some other examples can be found in articles [115-126].

A special place among the cyclizations of *ortho*-ethynylbiaryls is occupied by reactions of compounds having a central heterocyclic core, since the result of cyclization can be influenced by the ring size, number, type and position of heteroatoms. This effect is much stronger than in situations where the heterocycle acts as an aromatic substituent that "accepts" the triple bond. Research in this area has begun quite recently, and at the time of publication, our work on the cyclization of the *ortho*-(aryl)ethynylpyrimidines [8] was the first example of the reaction of substrates with this heterocyclic core.

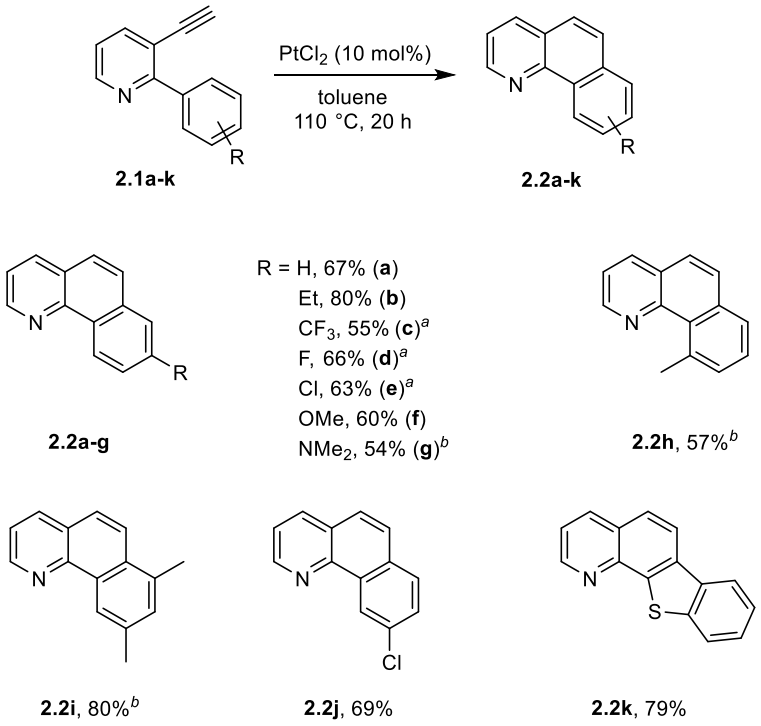
We decided to start by studying *ortho*-(aryl)ethynylpyridines, on the one hand, for testing reaction conditions on simpler objects, and on the other, for the possibility of comparing substrates with different heterocyclic rings in similar transformations.

2.2. Transition metal catalyzed cyclization

The content of the section is based on the articles [6, 8].

2-Aryl-3-ethynylpyridines **2.1** with a terminal triple bond turned out to be inert with respect to electrophilic activation under acidic conditions (in CF_3COOH, TfOH), but under the action of Lewis acid, a new ring of benzo[*h*]quinolines **2.2** was formed (Scheme 2.1). Among several tested catalysts ($InCl_3$, $GaCl_3$ и $Yb(OTf)_3$) $PtCl_2$ (10 mol%) turned out to be the most active. Its tolerance to substituents in the substrate allows to obtain a number of variously substituted benzo[*h*]quinolines **2.2** in good yields. More severe conditions (temperature increase by 20 °C) were required for sterically hindered compounds **2.2h,i** and dimethylamino-substituted compound **2.2g**.

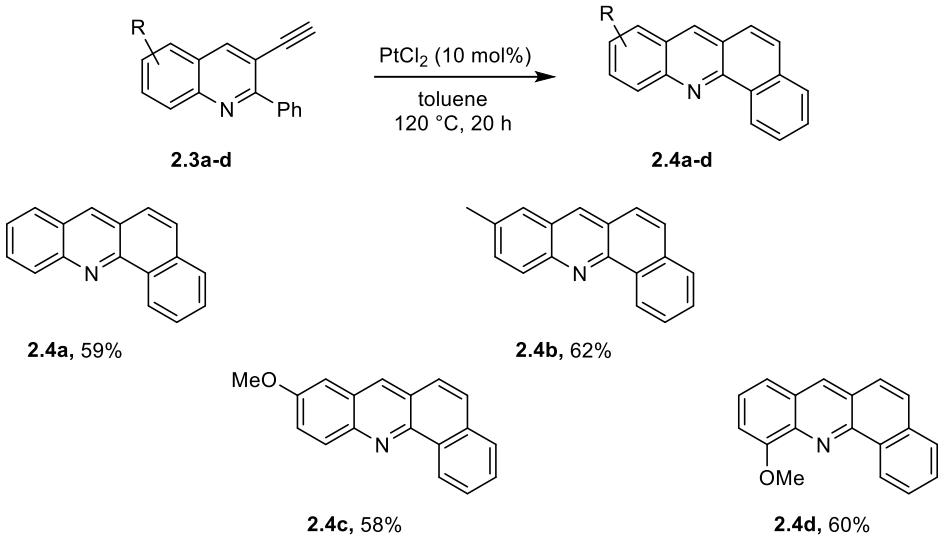
Scheme 2.1



[a] For 48 h.
[b] At 130 °C in chlorobenzene.

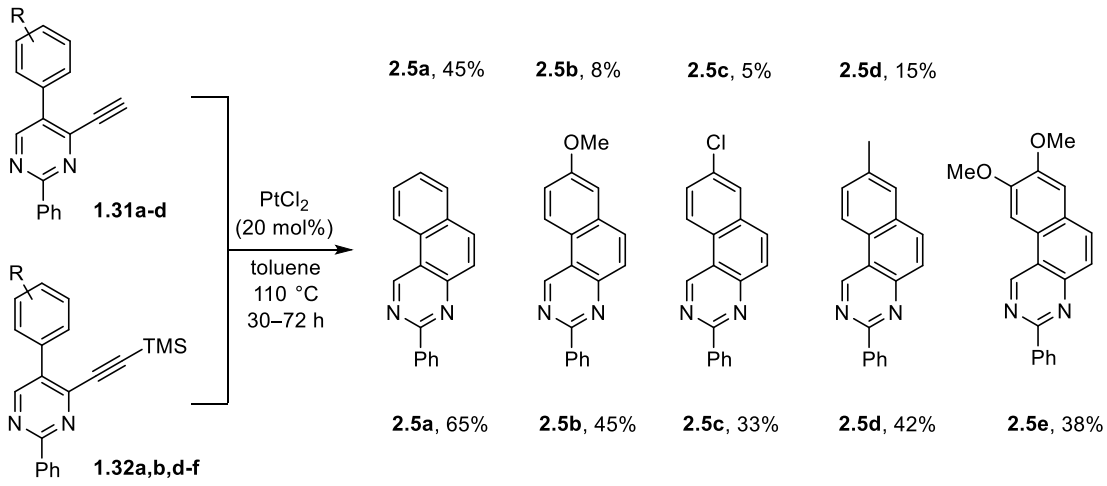
The expansion of the heterocyclic ring to quinoline in compounds **2.3** had practically no effect on the course of cyclization: only a slight increase in temperature to 120 °C was required to complete the conversion (Scheme 2.2). The corresponding benzo[*c*]acridines **2.4** were obtained in *ca.* 60% yields independently of substituents in the substrates.

Scheme 2.2



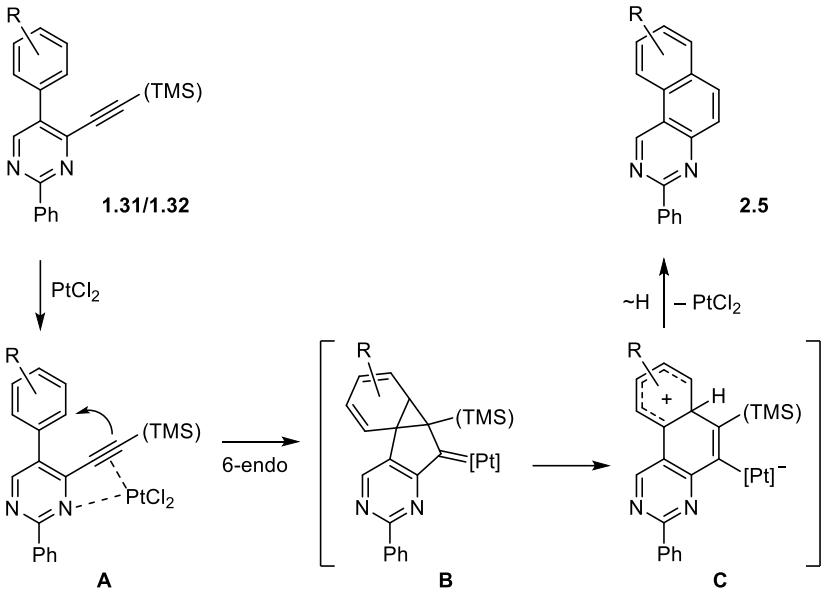
But the transition from pyridines **2.1** to pyrimidines **1.31** (see Section 1.6) has become more dramatic. Cyclization of pyrimidines **1.31** using $PtCl_2$ turned out to be fundamentally possible, although it proceeded in low yields of final benzo[*f*]quinazolines **2.5** (Scheme 2.3, top line of values) despite the variation in time, reaction conditions and catalyst loading, which eventually required twice as much as in the reactions of pyridines and quinolines. An acceptable 45% yield was achieved only for the product **2.5a**. Interestingly, pyrimidines **1.32** with a trimethylsilyl group on a triple bond showed themselves to be more active under the same conditions, and the yields of cyclization products were noticeably higher (Scheme 2.3, bottom line of values). In this case, the reaction was accompanied by desilylation, and exactly the same benzo[*f*]quinazolines **2.5** were formed as before from the corresponding pyrimidines **1.31** unsubstituted at triple bond. Cyclization with simultaneous removal of the trimethylsilyl group was previously described on several examples [127-130], and the authors of [127] associate this with trace amounts of hydrochloric acid in platinum chloride. However, desilylation during cyclization is not the rule, and the $SiMe_3$ group can be preserved in the product [131-133], and may even block the activity of a triple bond in a metal-catalyzed reaction [134].

Scheme 2.3



When comparing two series of reactions (Schemes 2.1 and 2.3), it becomes obvious that the metal-catalyzed cyclization of *ortho*-aryl(ethynyl)pyrimidines is more difficult than that for pyridines. There are several reasons for this. Firstly, the appearance of a second nitrogen atom in pyrimidines increases the probability of a platinum-heteroatom coordination, and also leads to an increase in the electron deficiency of the heterocyclic core, due to which the electron density on the triple bond decreases and its coordination with platinum worsens. But no less, if not more significant, is the different relative arrangement of structural fragments: heteroatom, triple bond and aromatic substituent – in pyridines and pyrimidines. The electron-withdrawing effect of the heterocyclic nitrogen atom on the triple bond is clearly more pronounced for their "*ortho*" arrangement, as in pyrimidines, than for the "*meta*" position in pyridines. Moreover, the close proximity of the nitrogen atom and the ethynyl substituent in pyrimidines **1.31**, **1.32** creates conditions for double coordination of platinum (structure **A**, Scheme 2.4) (examples of four-coordinated complexes of platinum(II) are known [135]) and for a decrease in its catalytic activity. But in general, the mechanism of this cyclization should fit perfectly into the scheme proposed on the basis of quantum chemical calculations in [136] (Scheme 2.4).

Scheme 2.4



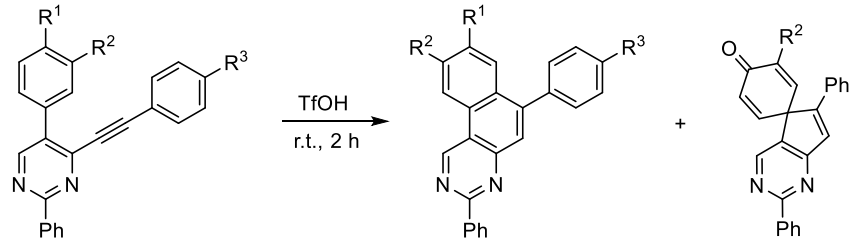
2.3. Electrophilic cyclization

The content of the section is based on the articles [6, 8].

Pyrimidines **2.6**, modified by an aromatic substituent at a triple bond, turned out to be inert to $PtCl_2$, but very capable of electrophilic cyclization. At the same time, in trifluoroacetic acid, which is actively used for carbocyclic analogues [5], the cyclization of pyrimidines **2.6** does not occur even when heated to 80 °C, apparently due to the π-deficient nature of the heterocycle. But in stronger acids: sulfuric acid, trifluoromethanesulfonic acid, polyphosphoric acid – the reaction proceeds with almost quantitative yield. We chose TfOH because it avoids side processes (see below), and obtained a number of benzo[*f*]quinazolines **2.7** (Scheme 2.5).

The electronic properties of substituents in benzene rings, both at pyrimidine and at a triple bond, significantly affect the reaction. The most electron-withdrawing nitro group sharply reduces the activity of substrates, and the effect is stronger for conjugation with a triple bond: pyrimidine **2.6c** did not react even under prolonged heating (Table 2.1, line 3), and pyrimidine **2.6h** gave only 20% of the cyclization product (at 50 °C for 24 h; Table 2.1, line 11). Probably, the protonation process of the triple bond is more sensitive, than the subsequent electrophilic substitution in the ring, to the electron density deficit created by the nitro group.

Scheme 2.5



2.6a-h **2.7a,b,d,e,g,h** **2.8a,b**

Table 2.1

№	Pyrimidine **2.6**	R^1	R^2	R^3	Benzo[*f*]quinazoline, yield (%)	Cyclohexadienone, yield (%)
1	**a**	H	H	H	**2.7a** (97)	0
2	**b**	H	H	OMe	**2.7b** (95)	0
3	**c**	H	H	NO_2	0	0
4	**d**	Me	H	H	**2.7d** (98)	0
5	**e**	Cl	H	H	**2.7e** (97)	0
6	**e**	Cl	H	H	0	**2.8a** (82)[a,b]
7	**e**	Cl	H	H	**2.7e** + **2.8a**, 1:0.9 (89)[c]	
8	**f**	OMe	H	H	0	**2.8a** (98)
9	**g**	OMe	OMe	H	**2.7g** (32)	**2.8b** (65)
10	**g**	OMe	OMe	H	**2.7g** (87)[d]	0
11	**h**	NO_2	H	H	**2.7h** (20)[e]	0

[a] CCDC 1490103.
[b] In conc. H_2SO_4 at 20 °C for 20 h.
[c] In TfOH with ~10% f water.
[d] At 0 °C.
[e] At 50 °C for 24 h.

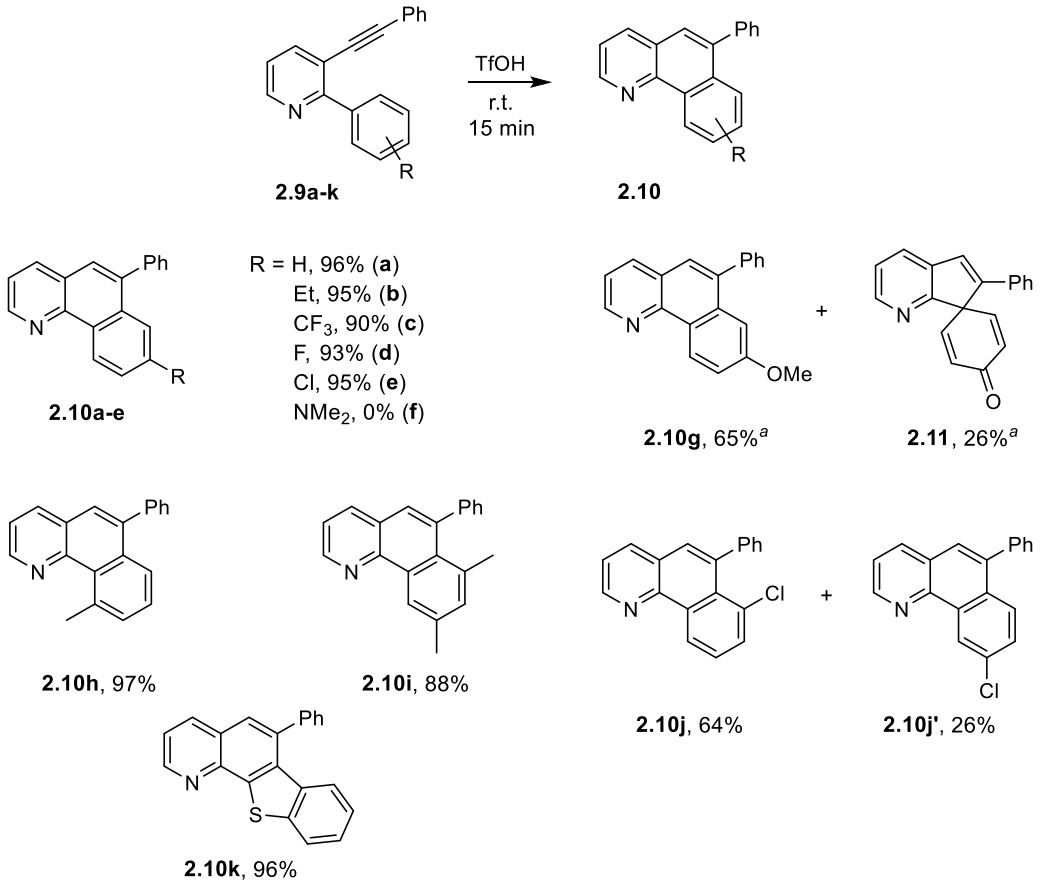
On the other hand, the donor methoxy group facilitates cyclization, although being in the *para*-position of the phenyl substituent at the pyrimidine ring (R^1 = OMe), it changes the direction of the reaction: instead of isomerization, cyclization occurs with the formation of a spirocyclohexadienone **2.8** (Scheme 2.5). This is the only process for the 4-methoxysubstituted substrate **2.6f** (product **2.8a**, Table. 2.1, line 8), and for the substrate**2.6g**, where the effect of two methoxy groups is inconsistent, the formation of both products **2.7g** and **2.8b** in a ratio of ≈1:2 is observed (cycloisomerization is regioselective) (Table 2.1, line 9), but when the temperature drops to 0 °C, only benzo[*f*]quinazoline **2.7g** is obtained in 87% yield (Table 2.1, line 10).

It turned out that the formation of the spirocyclic system **2.8** is possible not only from methoxysubstituted substrates, but also from those having a halogen atom in the same position. For example, this happens if wet trifluoromethane sulfonic acid or concentrated sulfuric acid is

used for the cyclization of chloro-substituted pyrimidine **2.6e** (Table 2.1, lines 6.7), and in sulfuric acid, spirobicycle **2.8a** is the only product.

Pyridines **2.9**, like pyrimidines **2.6**, proved to be inert to the action of trifluoroacetic acid even when heated. But trifluoromethane sulfonic acid also showed excellent results here – practically quantitative conversion to the target product in just 15 minutes at room temperature (Scheme 2.6). High yields of benzo[*h*]quinolines **2.10** were achieved for variously substituted substrates, only dimethylaminosubstituted pyridine **2.9f** gave a mixture of unidentified products without traces of benzoquinoline, probably due to the strong electron-withdrawing character of the protonated amino group, which reduces the probability of cyclization.

Scheme 2.6

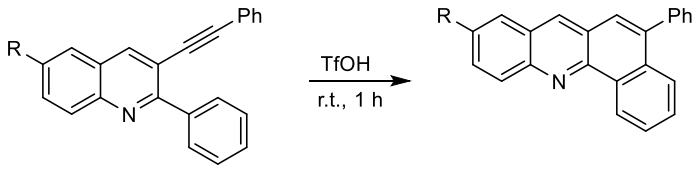


[a] At 0 °C only compound **2.11** in 93% yield.

Most notable when compared with (4-methoxyphenyl)substituted pyrimidine **2.6f**, which turned exclusively into spirobicycle **2.8a**, is the fact that similarly substituted pyridine **2.9g** gave a mixture of benzo[*h*]quinoline **2.10g** and spirobicycle **2.11** with the predominance of the former. Spirocompound **2.11** became the only product only when the temperature dropped to 0 °C. Thus, the possibility of *ipso*-cyclization is influenced by the type of heterocyclic core (see below).

Cyclization of *ortho*-aryl(ethynyl)quinolines **2.12** was demonstrated on a couple of examples: it proceeds smoothly, requires a little more time than for pyridines (Scheme 2.7).

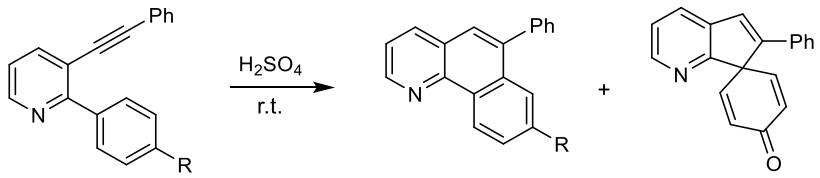
Scheme 2.7



2.12a,b **2.13a** (R = H), 94%
b (R = Me), 96%

For halogenated pyridines, *ipso*-cyclization turned out to be less characteristic than for pyrimidines, although it is also possible in principle (Scheme 2.8). In concentrated sulfuric acid, spirobicycle **2.11** is formed only from fluorinated pyridine **2.9d** as a minor component in a mixture with benzo[*h*]quinoline **2.10d**, and from chlorinated pyridine **2.9e**, unlike pyrimidine **2.6e**, it failed: here the only product is the result of conventional cyclization – benzo[*h*]quinoline **2.10e**.

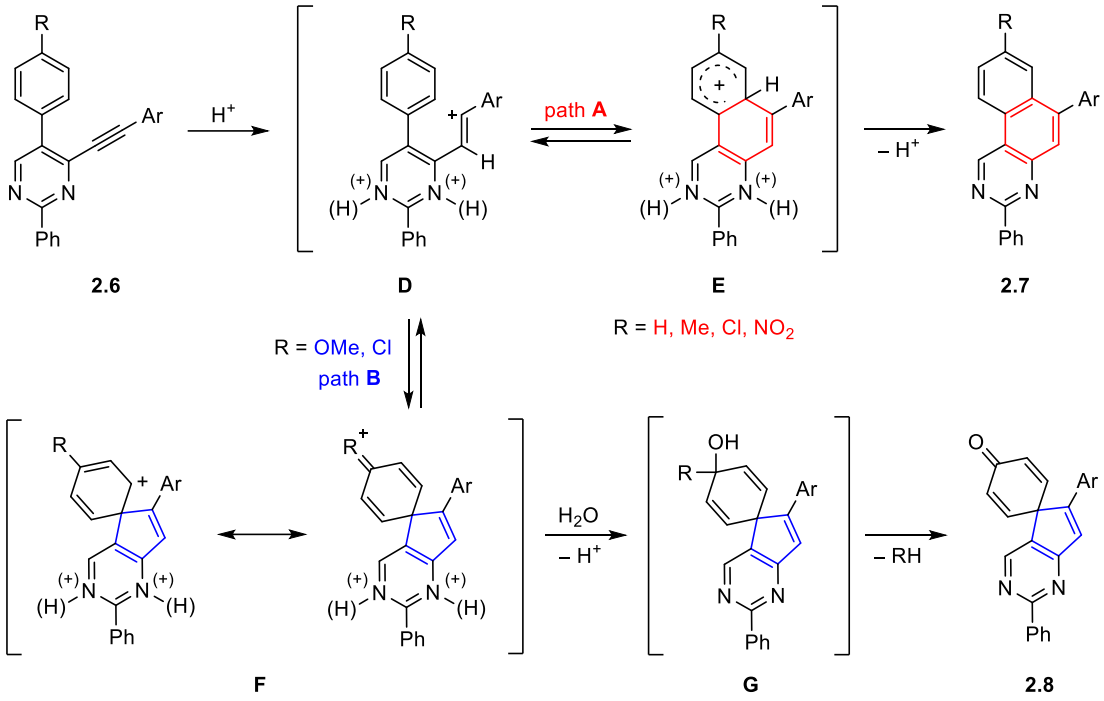
Scheme 2.8



2.9d,e R = F 12 h **2.10d**, 52% **2.11**, 21%
R = Cl 0.5 h **2.10e**, 88% –

Based on the results obtained, we propose mechanisms for both cyclization pathways, shown by the example of pyrimidines **2.6** (Scheme 2.9), including the initial protonation of the triple bond and/or nitrogen atoms of the ring, leading to a vinyl cation **D** stabilized by conjugation with an aryl substituent (if it does not have an acceptor group). Further, either electrophilic substitution in the *ortho*-position of the aromatic ring is possible, followed by the formation of a conjugated fused tricyclic system of benzo[*f*]quinazoline (pathway A), or an attack at the *ipso*-position with the formation of a spirobicyclic cyclohexadienone system in the presence of water in the reaction medium or during its treatment with water (pathway B). The choice between two directions is determined by the substituent R in the benzene ring at the C^5 atom of the pyrimidine core.

Scheme 2.9



The described mechanisms were confirmed by NMR spectroscopic data of cations formed from pyrimidines **2.6e** (R = Cl, Ar = Ph) and **2.6f** (R = OMe, Ar =Ph) in TfOH. In the first case, the benzo[*f*]quinazoline cation **2.7e**, twice protonated by both nitrogen atoms, was recorded, and in the second case, a spirocation of structure **F** with a methyl group on the oxygen atom, protonated by the N^1 atom, was identified. In addition, quantum chemical calculations[3] have shown that the *ipso*-cyclization of vinyl cation **D** from methoxysubstituted pyrimidine **2.6f** into spirocation **F** is a barrier-free process and proceeds with an energy gain of 14.4 kcal/mol. For chloro-substituted pyrimidine **2.6e**, *ipso*-cyclization **D→F** turned out to be a kinetically controlled process, and *ortho*–isomerization **D→E** turned out to be a thermodynamically controlled process (the difference in activation barriers is ≈2 kcal/mol, the difference in the energy of the cations **E** and **F** is ≈15 kcal/mol). Therefore the first reaction is realized with the possibility of instantaneous irreversible hydrolysis (sulfuric acid, wet trifluoromethanesulfonic acid), and the second – in an anhydrous medium.

For pyridines **2.9**, the ratio of the two directions of cyclization is shifted towards the formation of a more thermodynamically stable conjugated fused system of benzo[*h*]quinoline **2.10**. *ipso*-Cyclization of methoxysubstituted pyridine **2.9g** is obviously a kinetically controlled process, as indicated by the exceptional formation of spiroproduct **2.11** at low temperature (Scheme 2.6). The influence of the nature of the halogen is consistent with the mechanism

[3] DFT quantum chemical calculations at the B3LYP/6-31+g(d,p) level of theory with full geometry optimization were performed by Prof. A.F. Khlebnikov, SPbU.

described above: the fluorine atom has a stronger +M effect compared to the chlorine atom, contributing to the stabilization of the positive charge during *ipso*-cyclization, and is also more easily subjected to nucleophilic substitution, which contributes to the formation of a spirobicycle.

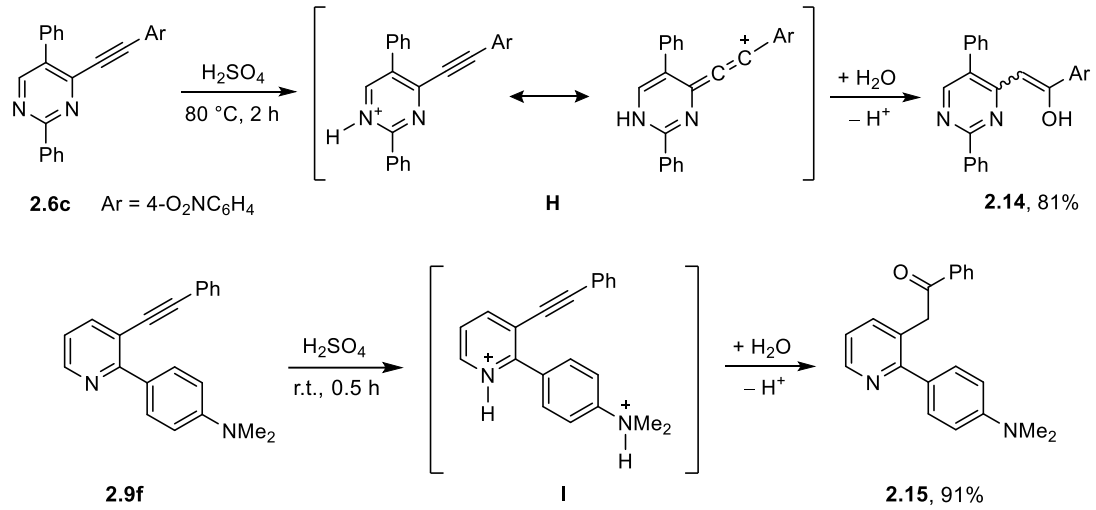
In general, *ipso*-cyclization is easier for pyrimidines than for pyridines, although the former have a more electron-deficient heterocyclic core. Therefore, here, as in metal-catalyzed cyclization (see Section 2.2), the mutual arrangement of the heteroatom(s), ethynyl and aryl substituents seems to play an important role. In pyridines **2.9**, the nitrogen atom is located in close proximity to the *ipso*-carbon atom of the benzene ring, which is subjected to electrophilic attack, and in pyrimidines **2.6**, both nitrogen atoms are equally more distant from a similar carbon atom.

Several examples of similar *ipso*-cyclizations of only RO-substituted *ortho*-ethynylbiaryls upon transition metal catalysis are described in the literature (R = H, CH_2OMe, C(O)*t*-Bu, cat. $PtCl_2$, $InCl_3$ [137], R = H, cat. $Ph_3PAuCl/AgOMs$ [138], R = Me, cat. $BrettPhosAuNTf_2$ [139]) and upon electrophilic activation by [I^+] (R = Me [140–143]). Moreover, even among the variety of other *ipso*-cyclizations leading to the formation of spirocyclohexadienone derivatives [144], variants with halogenated substrates (a halogen atom instead of an RO group in the *para*-position of an aryl substituent) are very few [145-149]. At the same time, the participation of halogenated pyridines and pyrimidines in *ipso*-cyclization along with methoxysubstituted analogues is of fundamental importance for the interpretation of the mechanism of this transformation. The mechanism of *ipso*-cyclization of methoxysubstituted substrates under the action of I^+ is described in the literature, similar to ours, but different in the last step: the transfer of a methyl cation from an oxygen atom to an external nucleophile [143, 150]. In our case, it is obvious that there is a "substitution" not of the methyl group on the oxygen atom, but of the methoxy group (or the halogen atom) entirely, that is, the oxygen atom of the carbonyl group of spirobicycle **2.8**/**2.11** "comes" into the structure from the water molecule.

At last, two reactions demonstrating the difference between sulfuric acid and trifluoromethanesulfonic acid as a medium for substrates not prone to cyclization are worth mentioning (Scheme 2.10). Pyrimidine **2.6c**, inert in TfOH, and pyridine **2.9f**, which gave a complex mixture of products in TfOH, underwent regioselective triple bond hydration in sulfuric acid to form enol **2.14** and ketone **2.15**, respectively. The position of the hydroxy (oxo) group indicates the same localization of the positive charge in the intermediates as during cyclization, which, however, did not occur. For pyrimidine **2.6c**, the initial protonation of the nitrogen atom of the ring with the formation of an allene type cation **H** can be assumed; this cation is incapable

of cyclization, and addition of a water molecule occurs. For pyridine **2.9f**, such an electron density transfer is impossible, therefore, protonation of the nitrogen atom of the ring and of the amino group (structure **I**) creates the strong electron-withdrawing effect, deactivating the benzene ring to an electrophilic attack.

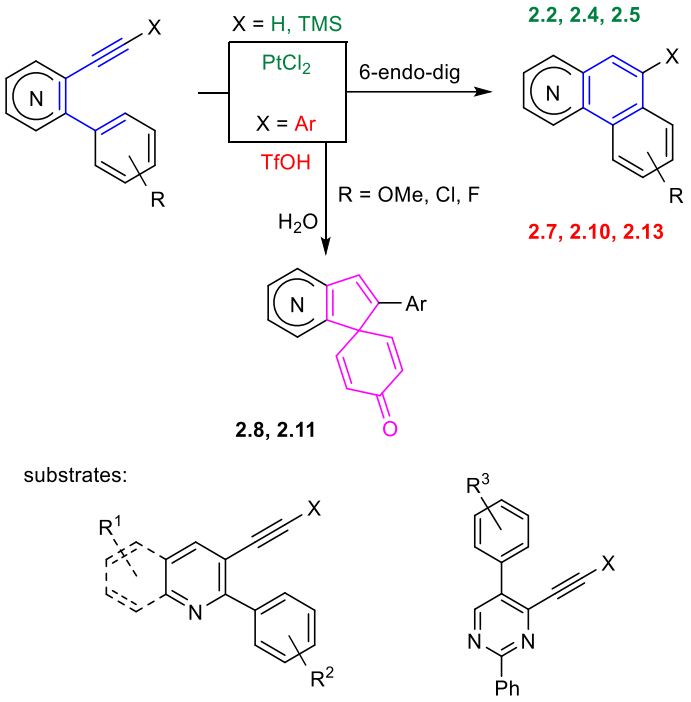
Scheme 2.10



2.4. Conclusion

Based on the results of the material presented in Chapter 2, several conclusions can be drawn. Cyclization of *ortho*-aryl(ethynyl)heterocycles (pyridines and pyrimidines) can be used as an effective method for the synthesis of polyfused heterocyclic compounds. The cyclization conditions are determined by a substituent on a triple bond: for compounds with a terminal triple bond (or with a trimethylsilyl group on it), it is appropriate to use $PtCl_2$ catalysis, while for (arylethynyl)substituted ones – electrophilic activation by strong acids (trifluoromethanesulfonic, sulfuric) (Scheme 2.11). In any case, cycloisomerization proceeds in the 6-endo-dig fashion, although under conditions of electrophilic activation, in the presence of a methoxy group or a halogen atom in the *para*-position of an aryl substituent involved in cyclization, competing *ipso*-cyclization may occur with the formation of a spiro(cyclopenta)cyclohexadienone derivative. The ratio of *ortho*- and *ipso*-cyclization products depends on the type of heterocycle, temperature and, in the case of halogen-containing substrates, the presence of water in the reaction mixture. In this case, during the reaction, a formal substitution of the halogen atom or the entire methoxy group occurs.

Scheme 2.11



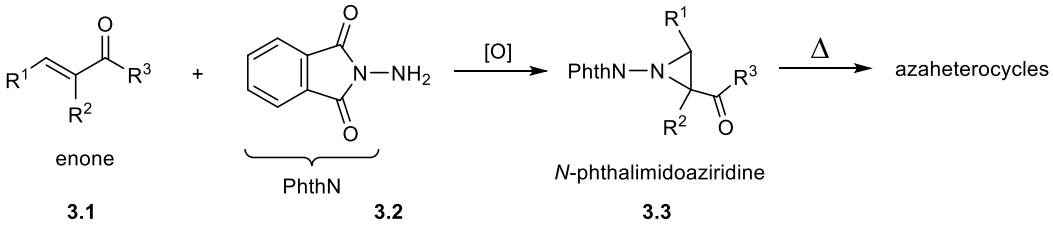
In general, pyridines turned out to be more prone to cyclization than pyrimidines, but the relative activity of *ortho*-aryl(ethynyl)heterocycles in any cyclization is determined by the mutual arrangement of the main fragments in the core of the molecule: heteroatom(s), aryl and ethynyl substituents.

Chapter 3. Synthesis of heterocycles from enones through *N*-phthalimidoaziridines

3.1. Introduction

Among the hydrazines, several representatives of which we have successfully used as binucleophiles in reactions with enynones to produce pyrazoles (Section 1.5), a special place is occupied by *N*-aminophthalimide (PhthNNH$_2$, **3.2**), being a synthon of unsubstituted hydrazine with a phthaloyl protective group on the nitrogen atom. It is known to be a rather weak nucleophile and interacts mainly with aldehydes and much worse with ketones [150, 151]. PhthNNH$_2$ is much more widely used in the synthesis of *N*-phthalimidoaziridines when interacting with alkenes under oxidative conditions (Scheme 3.1). We became interested in the possibility of using the synthetic potential of the energy-rich strained aziridine ring to construct nitrogen-containing heterocyclic compounds. The sequence of oxidative aminoaziridination of the double carbon-carbon bond and the subsequent transformation of the aziridine ring represents an effective synthetic approach to five- and six-membered azaheterocycles from acyclic conjugated enones.

Scheme 3.1

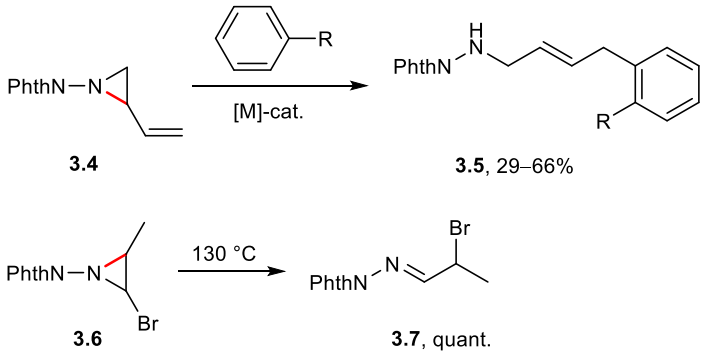


The first mention of *N*-phthalimidoaziridines dates back to 1969 [153, 154], to the beginning of a period of rapid development of the chemistry of aminonitrenes, the addition of which to C=C bonds is one of the main methods of synthesis of aminoaziridines [155]. New approaches to *N*-phthalimidoaziridines are still being developed [156-158], which clearly indicates an interest in these compounds and their synthetic potential. On the one hand, *N*-phthalimidoaziridines can be considered as compounds with a protected amino group on the nitrogen atom, and, given that phthaloyl protection can be removed by treatment with hydrazine [159-162], *N*-aminocompounds can be obtained in reactions with their participation, which are difficult to access by other methods. On the other hand, under certain conditions, one can expect a break of the N–N bond with the elimination of the phthalimide molecule, which can cause transformations not characteristic of other aziridines (in some cases, the removal of the phthalimide group from the nitrogen atom is carried out purposefully [156, 163-165]). Finally,

the phthalimide group is an electron-withdrawing substituent, therefore, the behavior of such aziridines may differ markedly from the "usual" *N*-alkyl- and *N*-aryl-substituted ones.

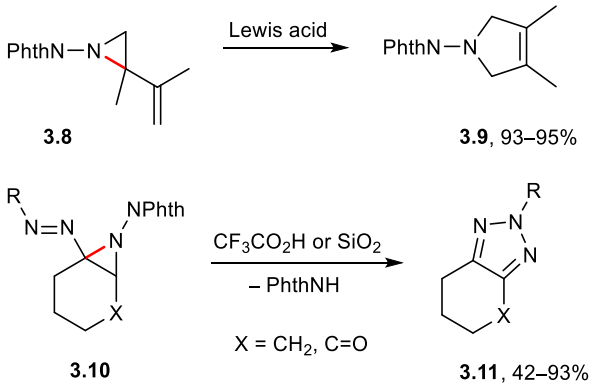
According to the literature data, the most studied reactions of *N*-phthalimidoaziridines are the ones accompanied by the ring opening via the breaking of the C–N bond [166, 167], and the phthalimide group on the nitrogen atom contributes to this process. For example, in 2-vinylazyridines, the phthalimide group, along with the tosyl group, provides selective breaking of the C–N bond during the addition of boronic acids [168], phosphine oxides [169], during the allylation of arenes (for example, **3.4**→**3.5**, Scheme 3.2) [170-172]. Other examples of the C–N bond cleavage of *N*-phthalimidoaziridines to form hydrazones are also known (for example, **3.6**→**3.7**, Scheme 3.2) [173, 174] and hydrazines [175-178].

Scheme 3.2 (literature data [170–172, 174])



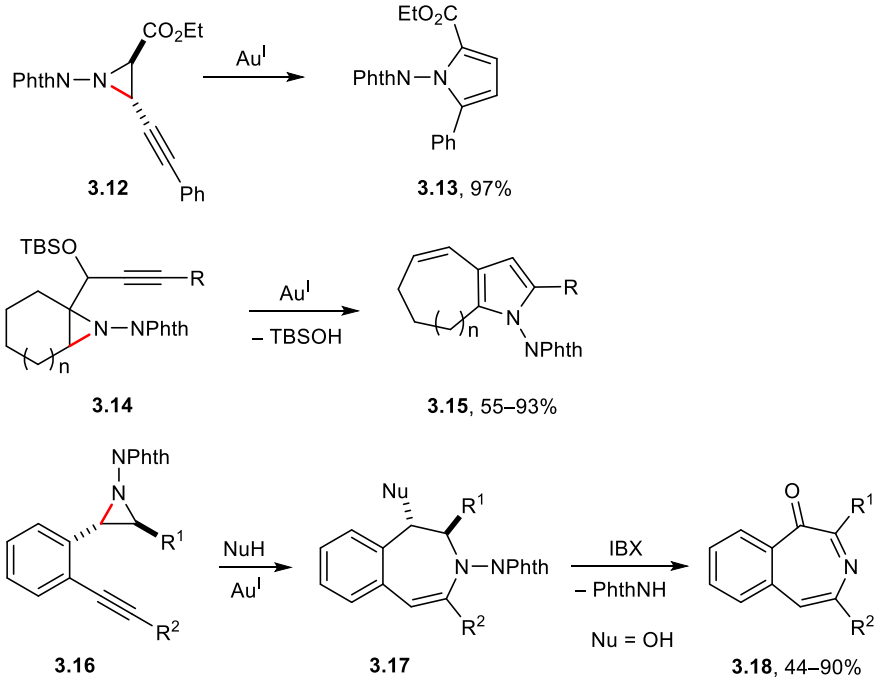
The presence of a multiple bond in the side chain at the carbon atom makes it possible to expand the aziridine ring, which is easily opened by the C–N bond [179]. For example, for 2-vinyl-1-phthalimidoaziridines, a Lewis acid catalyzed rearrangement with the formation of 3-pyrrolines is possible (for example, **3.8**→**3.9**, Scheme 3.3) [180-182], similar to the thermal transformation of vinyl cyclopropane→cyclopentene [183]. 2-Azosubstituted aziridines behave in a similar way, but the reaction is accompanied by the elimination of the phthalimide molecule, which leads to the formation of an aromatic triazole system (for example, **3.10**→**3.11**, Scheme 3.3) [184].

Scheme 3.3 (literature data [180, 181, 184])



For *N*-phthalimidoaziridines having a triple bond in the side chain, various metal-catalyzed transformations are realized, which are equally determined by the initial coordination of the metal along the C≡C fragment. Thus, *N*-phthalimidopyrroles can be obtained from 2-ethynyl- (by catalysis with gold(I) (for example, **3.12**→**3.13**, Scheme 3.4) [185] or copper(II) [186]) or 2-propargylaziridines (as a result of a cascade of several reactions, for example, **3.14**→**3.15**, scheme 3.4 [187]). (*ortho*-Alkynylphenyl)aziridines are capable of Au(I)-catalyzed cyclization into 3-benzazepines under the action of a nucleophile (aniline or water), and during oxidation, a phthalimide molecule may be eliminated, providing the formation of 1*H*-benzo[*d*]azepin-1-one (for example, **3.16**→**3.17**→**3.18**, Scheme 3.4) [188].

Scheme 3.4 (literature data [185, 187, 188])

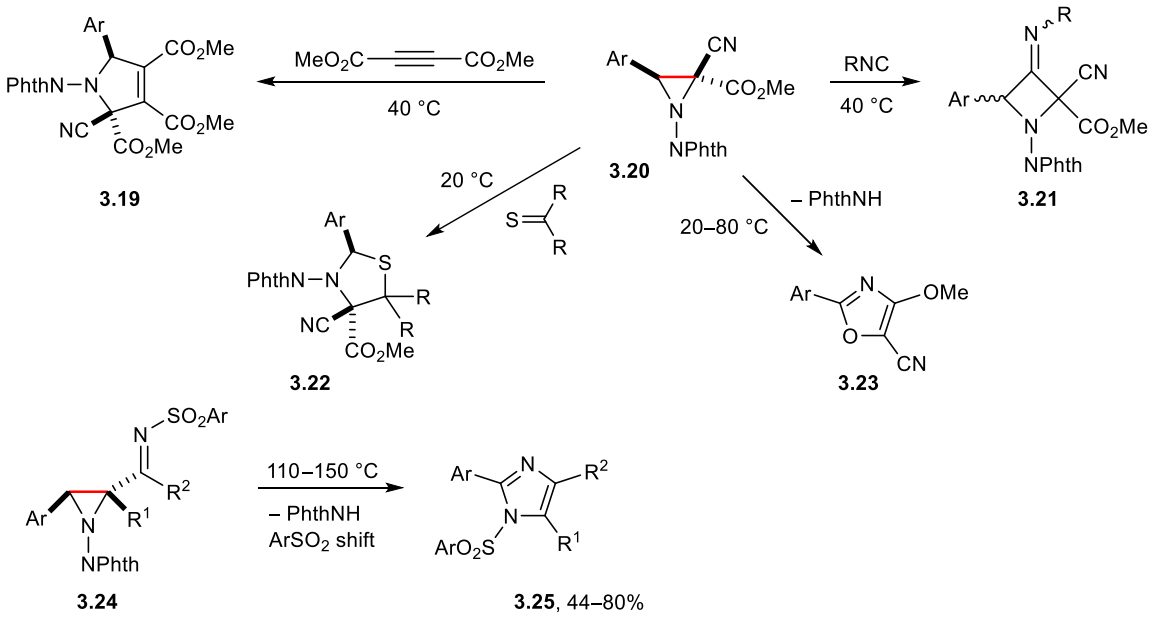


Thus, in the reactions described above, the opening of the aziridine ring by the C–N bond occurs either as a result of a nucleophilic attack on a carbon atom, or an electrophilic attack on a nitrogen atom. However, when heated or irradiated, the aziridine ring can be cleaved by the C–C bond. It is an electrocyclic process that proceeds in a stereocontrolled manner in accordance with the rules for orbital symmetry preservation for coordinated reactions with the formation of octetstabilized 1,3-dipoles – azomethine ylides [189]. The chemistry of azomethine ylides is diverse [190], but it is mainly based on 1,3-dipolar cycloaddition reactions to unsaturated compounds, since in this way it is possible to obtain the widest set of heterocyclic structures, including those with a certain configuration of stereocenters [189, 191, 192].

Prior to the start of our work described in this chapter, the possibility of generating azomethine ylides from *N*-aminoaziridine derivatives had been studied extremely sparingly. In the only series of works by a group of French researchers, it was shown that some tri- and

tetrasubstituted *N*-phthalimidoaziridines, when interacting with dimethyl acetylenedicarboxylate (DMAD) [193, 194] and isonitriles [195, 196], already under low heating (and even at room temperature), actually give products whose formation can be interpreted as a result of transformations of the corresponding *N*-phthalimidoazomethine ylides (for example, **3.20**→**3.19** and **3.20**→**3.21**, Scheme 3.5). Later in the works of A.V. Ushkov [197, 198] some of these results were clarified and even refuted, and also thioketones were tested as dipolarophiles (**3.20**→**3.22**, Scheme 3.5). It turned out that the relative orientation of substituents in aziridine of type **3.20** is preserved in adducts, which does not correspond to the Woodward-Hoffman rules mentioned above and may be a consequence of isomerization of a dipole or its uncoordinated addition to a dipolarophile. The cyclization of *N*-phthalimidoazomethine ylides into oxazoles was also shown for the first time in the work of A. Foucault (**3.20**→**3.23**, Scheme 3.5) [193], but the systematic study of this reaction as a synthesis method was started in the thesis of E.V. Beletsky [199]. And more recently, the possibility of obtaining *N*-sulfonylimidazoles **3.25** in a similar way with the thermal opening of 2 sulfonylimidoyl-1-phthalimidoaziridines **3.24** (scheme 3.5) has been demonstrated [200].

Scheme 3.5 (literature data [193–198])



Thus, it was obvious that *N*-phthalimidoaziridines are fundamentally capable of entering into transformations starting with the breaking of the C–C bond. The resulting azomethine ylides can give adducts of 1,3-dipolar cycloaddition or turn into oxazoles, and the preferred course of the reaction in one of the competing directions, in theory, should be determined for each substrate by the nature of substitution of the aziridine ring and the activity of dipolarophile, but no systematic study of these processes has been conducted. The study of the synthetic potential of thermal transformations of *N*-phthalimidoaziridines as a platform for the construction of

nitrogen-containing heterocyclic compounds from conjugated enones and their analogues became the basis of the work presented in this chapter of the dissertation.

The synthetic approach to aziridines by oxidation of *N*-aminophthalimide in the presence of unsaturated compounds is well known, but we applied it to a fairly wide range of substrates not previously studied in this reaction, and Section 3.2 is devoted to the description of the results obtained. Effective synthesis of oxazoles with a non-trivial substitution pattern by transformation of *C*-acyl-substituted *N*-phthalimidoaziridines is demonstrated in Section 3.3. Then, information on the reactions of inter- and intramolecular cycloaddition of aziridines to multiple bonds, opening access to nitrogen heterocycles with a certain configuration of stereocenters (Section 3.4). Most of the aziridines synthesized by us have different substituents at carbon atoms,[4] which allows us to trace the influence of electronic factors on the possibility and ease of ring opening and the formation of 1,3-dipoles. Since the cleavage of the aziridine ring by the C–C bond must obey the rules for orbital symmetry preservation, but the literature data described above indicated the opposite (Scheme 3.5), we paid close attention to establishing the structure of the products and the stereochemical result of all reactions. It is worth noting that the reactions of intramolecular cycloaddition of azomethine ylides [201], which have generally been studied much less than intermolecular ones, for *N*-aminoaziridine derivatives were unknown before our work. Other possible thermal transformations of some *N*-phthalimidoaziridines are described in Section 3.4.3.

3.2. Synthesis and properties of *N*-phthalimidoaziridines

3.2.1. Oxidative aminoaziridination of substituted alkenes

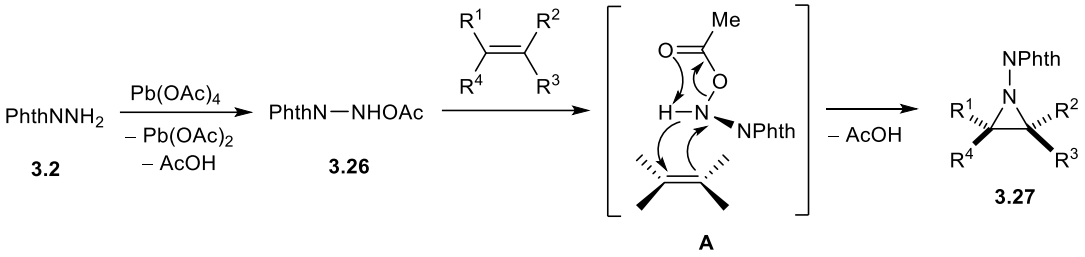
The content of the section is based on the articles [2, 11, 12, 14, 16, 18, 20–23].

The *N*-phthalimidoaziridines obtained in this work were synthesized by oxidative aminoaziridination of compounds with C=C bond (Scheme 3.6). This method has been known for more than half a century, and our review of the literature on this topic [10] confirmed that it still remains the most convenient and effective way to synthesize *N*-aminoaziridine derivatives of type **3.27**, providing tolerance to many functional groups and stereospecific addition while maintaining the relative orientation of substituents at a double bond [202]. We obtained *N*-aminophthalimide (**3.2**) ourselves using well-known methods [203, 204], and commercially

[4] In this chapter, the concepts of "disubstituted" and "trisubstituted" aziridines are used in relation to the number of substituents at the carbon atoms of the aziridine ring. They are not correct according to the nomenclature of organic compounds, since they do not take into account the substituent on the nitrogen atom, but since the phthalimide group is invariably present in all substrates, we use these names as more illustrative when describing and comparing various *N*-phthalimidoaziridines.

available lead tetraacetate ($Pb(OAc)_4$) was used as an oxidant. In the work of R. Atkinson [205, 206], it was found that during oxidation, *N*-acetoxyderivative **3.26** is formed and then involved in reaction with an alkene by analogy with epoxidation by peracids, and nitrene like PhthN–N̈: does not participate in the reaction.

Scheme 3.6 (literature data [205, 206])



Lead tetraacetate is historically the first oxidant used in aziridination, but it is far from the only possible one (the search for new oxidants was largely caused by the toxicity of lead compounds). Hypervalent iodine-based oxidants are deservedly popular, in particular (diacetoxyiodo)benzene ($PhI(OAc)_2$) [207, 208]. However, the mechanism of its interaction with amino compounds is different (ligand exchange to form aminodiodane PhI(OAc)(NHNPhth), which directly reacts with the double bond of the alkene) [207], and, as a rule, a longer time is required for complete conversion of the substrate, especially for the electron-deficient alkene.

We were satisfied with the results achieved with $Pb(OAc)_4$ throughout the work, including with electron-deficient substrates, despite the electrophilic nature of *N*-acetoxyaminophthalimide **3.26** formed using $Pb(OAc)_4$ [207, 209]. In several cases, we tried to use $PhI(OAc)_2$, as shown in Scheme 3.7, Table 3.1 (see Section 3.2.2.2 below) and Scheme 3.8, Table 3.2 (see Section 3.3.2 below), but the initial choice proved to be correct. $Pb(OAc)_4$ provides higher and faster conversion of substrates at lower temperature than $PhI(OAc)_2$.

Scheme 3.7

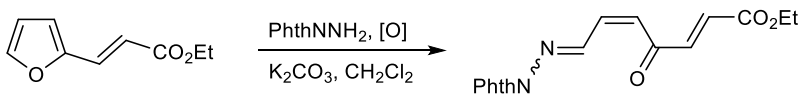
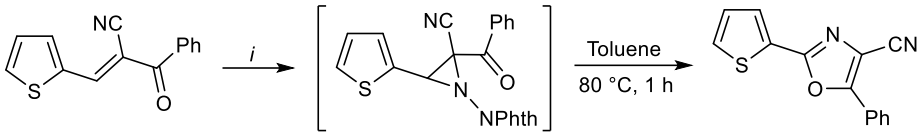


Table 3.1

№	Oxidant	Temperature, °C	Yield, %
1	$Pb(OAc)_4$	13	4
2	$Pb(OAc)_4$	0	28
3	$Pb(OAc)_4$	–20	55
4	$PhI(OAc)_2$	13	23
5	$PhI(OAc)_2$	0	38
6	$PhI(OAc)_2$	–20	17

Scheme 3.8



i: PhthNNH$_2$ (1.5 eq.), oxidant (1.5 eq., see Table), K_2CO_3 (6 eq.), CH_2Cl_2

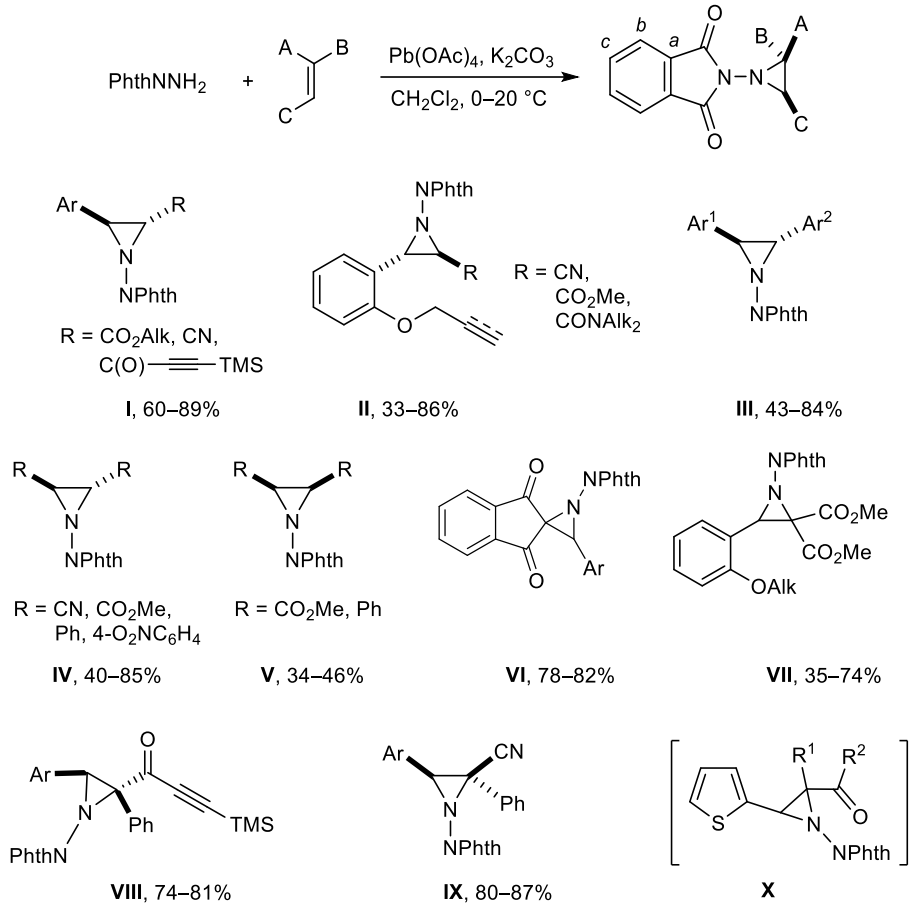
Table 3.2

№	Oxidant	Temperature, duration of aziridination step	Yield, %
1	$Pb(OAc)_4$	0 °C, 30 min	71
2	$PhI(OAc)_2$	0 °C, 1 h	22
3	$PhI(OAc)_2$	25 °C, 1 h	12
4	$PhI(OAc)_2$	0–25 °C, 24 h	traces
5	*t*-BuOCl	0 °C, 1 h	0
6	*t*-BuOCl	25 °C, 1 h	0

In addition, $Pb(OAc)_4$ is highly soluble in dichloromethane, and the $Pb(OAc)_2$ formed during reduction, on the contrary, is very poorly and easily removed from the reaction mixture during filtration (and can be disposed of). Thus, the effectiveness of Pb(OAc)4 in our work is high, and the method of conducting asiridination is simple, convenient, fast and minimizes possible risks.

In our work, we obtained a wide range of *N*-phthalimidoaziridines in 33-89% yields (Scheme 3.9). The absolute majority of synthesized aziridines were not described earlier. Usually this reaction is carried out at a reduced temperature (0 °C and below), but for some di- and tri-substituted compounds significantly higher yields were obtained at 13-20 °C. Due to the low activity of triple and non-conjugated terminal double bonds in the oxidative aminoaziridination [210], the addition of *N*-aminophthalimide to the corresponding compounds occurred chemoselectively, affecting only the substituted C=C bonds (structures **I**, **II** and **VIII**, Scheme 3.9).

Scheme 3.9[5]



Almost all disubstituted *N*-phthalimidoaziridines are colorless or yellow crystalline substances stable under normal conditions. Among the trisubstituted aziridines, there are many compounds unstable at room temperature (in particular, some compounds of series **VI**, **IX** and **X**, Scheme 3.9); their formation was detected by thin-layer chromatography (TLC) of the reaction mixtures and confirmed by the structures of the products obtained in the subsequent reactions. It is worth noting that the phthalimide group has very characteristic signals of hydrogen and carbon atoms in the corresponding ^{1}H and ^{13}C NMR spectra: δ 7.65–8.00 ppm (H^{b,c}); 164–165 (CON), 129–130 (C^{a}), 123–124 (C^{b}), 134–135 (C^{c}) ppm, however, the form of signals depends on orientation and number of all the other substitutents. In some cases, the phthalimide group in the ^{1}H NMR spectra appears as two wide signals of different heights, which is due to its slow rotation along the N–N bond (the AA'XX' proton system turns into ABXY in this case). For the same reason, the signals of the C^{a} and CON atoms of the phthalimide group in the ^{13}C NMR spectrum can be broadened and not even visible.

[5] For a more convenient presentation of the material in this scheme, here the aziridines are numbered in Roman numerals, and in the following sections – in Arabic.

A characteristic feature of *N*-aminoaziridine derivatives is the slow inversion of the endocyclic nitrogen atom in the NMR time scale [202, 211, 212]. According to ^{1}H NMR spectra, aziridines **I** and **II** with substituents of different relative volume exist at room temperature as a mixture of two invertomers with a significant predominance of one of them (ratio 1: ≤0.07), and for aziridines **III** with two aryl substituents of similar size, the content of the minor invertomer increases markedly, and at 25 °C mixture of two invertomers is observed in the ratio 1 : (0.23–0.85).

As a rule, for compounds **I** and **II**, the doublets of the AX system of aziridine protons of the main invertomer are located in stronger fields than the minor one (the total range δ 3.5–5.5 ppm). In the ^{1}H NMR spectra, the downfield signal of the proton of the main invertomer is slightly lower and wider than the upfield signal, due to long-range interaction with aryl *ortho*-protons. Therefore, a downfield signal can be assigned to a proton at a carbon atom with an aryl group, a upfield signal can be assigned to a proton at another carbon atom. Considering that the phthalimide substituent deshields the syn-located proton of the aziridine ring [202, 212], the major invertomer of aziridines **I** and **II** is a sterically more advantageous form with an *anti*-arrangement of the phthalimide and aryl groups.

In symmetric *trans*-disubstituted aziridines **IV**, the inversion of the nitrogen atom is degenerate, and two doublets of aziridine protons of a single form are present in the ^{1}H NMR spectra. Symmetric *cis*-disubstituted aziridines **V** and trisubstituted aziridines **VI-IX** exist as one thermodynamically more advantageous invertomer (or the amount of the second one is too small for identification by NMR), and one singlet of aziridine protons is visible in their ^{1}H NMR spectra.

The preservation of the (*E*)-configuration of the double bond of the initial unsaturated compounds during oxidative aminoaziridination is confirmed by small values of the vicinal spin-spin coupling constant of aziridine protons (~5.0–6.0 Hz) (in *cis*-aziridines ^{3}J = 6-8 Hz [202, 212]), and its value for an invertomer with *anti*-orientation of phthalimide and aryl groups is usually lower than that for the *syn*-invertomer.

3.2.2. Oxidative aminoaziridination of five-membered heterocycles

In addition to the aziridination of acyclic unsaturated substrates, the oxidation of *N*-aminophthalimide in the presence of five-membered aromatic heterocycles with one heteroatom is of certain interest. Their lower aromatic stabilization energy than that of benzene, but at the same time the π-excessive nature of the aromatic system, allows us to hope for the possibility of obtaining unusual bicyclic aziridines or other structures. There are known examples of participation in the aziridination reaction of donor-substituted arenes: 1,3-dimethoxybenzene and

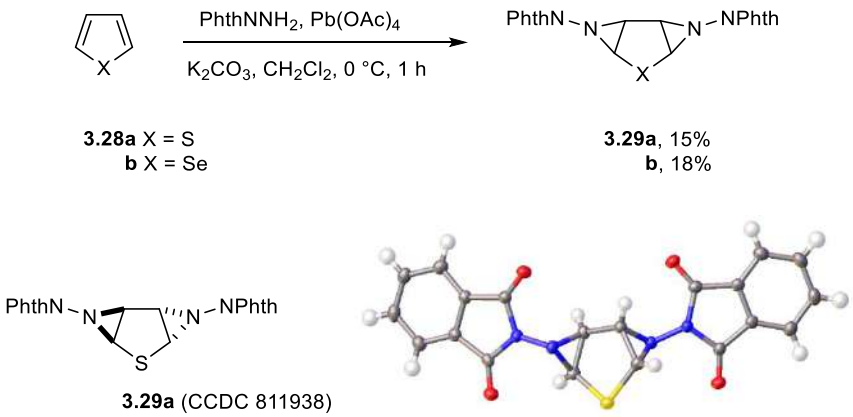
N,*N*-dimethylaniline – with the formation of 3*H*-azepines due to the rearrangement of the original aziridines [213]. Examples of successful synthesis of phthalimidoaziridines at the C=C bond of the five-membered ring of benzo[*b*]furans [214-216] and indoles [217, 218] are also described, although in reaction with benzo[*b*]thiophene, not an analogous aziridine was obtained, but a product of insertion into the β-C–H bond of the thiophene ring [215]. At the same time, the aziridination of monocyclic alkyl and arylfuranes yields only heterocycle disclosure products [219], and information on the aziridination of monocyclic pyrrole and thiophene derivatives, according to our information, is missing.

3.2.2.1. Thiophene and selenophene

The content of the section is based on the article [19].

As a result of oxidation of *N*-aminophthalimide by lead tetraacetate in the presence of thiophene (**3.28a**), we managed to obtain tricyclic bisaziridine **3.29a**; a similar product **3.29b** was isolated from the reaction with selenophene (**3.28b**) (Scheme 3.10).

Scheme 3.10



According to X-ray diffraction analysis, bisaziridine **2.27a** has a *trans*-orientation of three-membered rings relative to the central five-membered one and an *anti*-*anti*-orientation of the phthalimide fragments of the main invertomer. A small amount of the second invertomer appears in the solution at room temperature (≥10:1).

The low yield of bisaziridines and the absence of monoaziridines even during the reaction with an equimolar ratio of *N*-aminophthalimide and heterocycle, apparently, indicates the instability of monoadducts. The addition of the second equivalent of *N*-acetoxyaminophthalimide should clearly be easier, because after the first aziridination the aromaticity of the system is disrupted and a C=C bond, conjugated with an unshared pair of electrons of a sulfur or selenium atom, is formed. However, the original monoadduct probably enters into other transformations, leading to the disintegration of the molecule.

Nevertheless, in this way we showed the fundamental possibility of oxidative aminoaziridination of thiophene and selenophene and obtained the first representatives of unusual tricyclic bisaziridines – derivatives of 5-tia(seleno)-3,7-diazatricyclo[4.1.0.$0^{2,4}$]heptane.

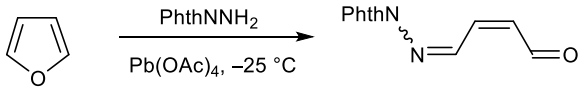
During oxidative aminoaziridination of 2-vinylthiophene derivatives, the reaction proceeds exclusively via an exocyclic double bond, as shown in Section 3.3.2, and the thiophene ring remains unaffected.

3.2.2.2. Furan and its 2-vinyl derivatives

The content of the section is based on the article [11].

As mentioned above, the oxidation of *N*-aminophthalimide in the presence of alkyl- and aryl-substituted furans, as well as benzo[*c*]furan and its derivatives, leads to the opening of a five-membered ring with the formation of phthaloyl hydrazones of unsaturated dicarbonyl compounds [219]. A similar transformation was observed when 2-methylfuran was treated with tosyliminophenyliodide (TsN=IPh) as a source of nitrene [220]. We managed to carry out this transformation for the unsubstituted furan (**3.30**) (Scheme 3.11), although the work of D.V. Jones reported a failure in this case. The resulting single (2*Z*,4*Z*)-isomer of 4-(phthaloylhydrazono)but-2-enal **3.31** is easily isomerized by the C=N bond, and after 4 h a mixture of two forms was observed in $CDCl_3$ solution in the ratio 0.5:1 (4*Z*/4*E*).

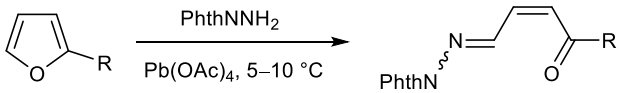
Scheme 3.11



3.30 **3.31**, 29%

An attempt to reduce the activity of the substrate and prevent the ring cleavage by introducing electron-withdrawing substituents into the furan ring was unsuccessful: the reaction with both 2-acetylfuran (**3.32a**) and furan-2-carbonitrile (**3.32b**) gave the same result, although it required a higher temperature than for unsubstituted furan (Scheme 3.12).

Scheme 3.12



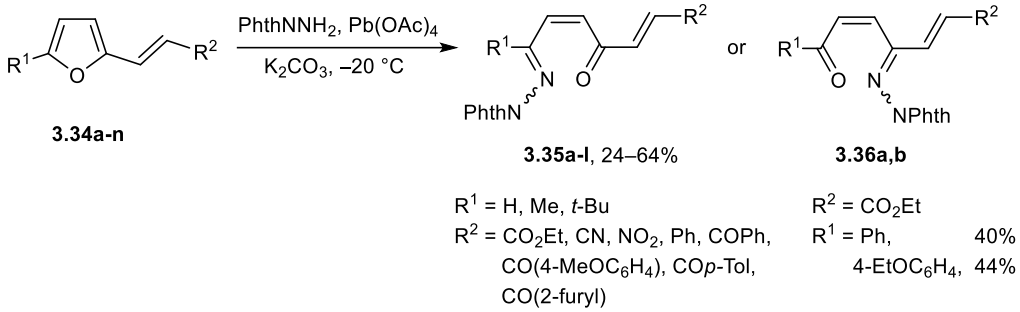
3.32a,b R = COMe (**a**), CN (**b**)[a] **3.33a,b**[b]

[a] Product **3.33b** contains 20% of the isomer of the C=C bond.
[b] Hydrazones were not isolated because of their instability.

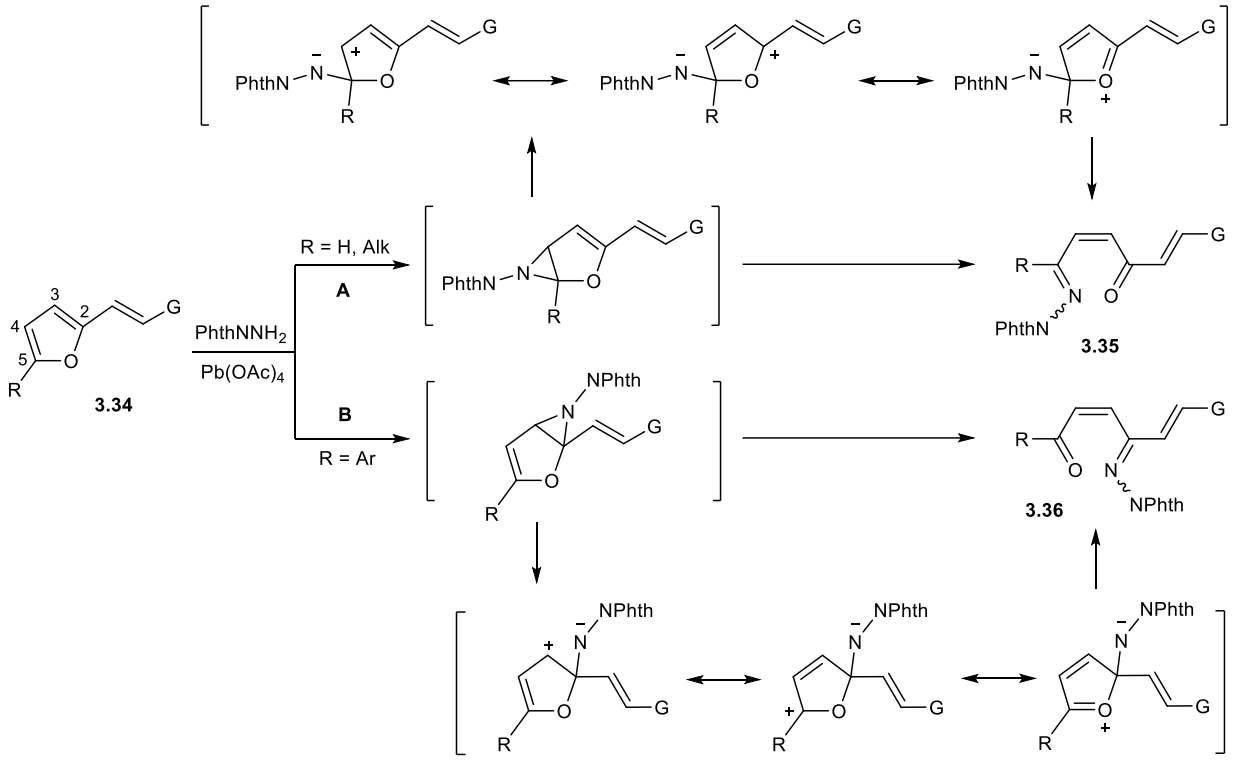
Hoping for easier aziridination of the exocyclic double bond of 2-vinylfuran, we synthesized a number of its derivatives **3.34**, but were only convinced of the opposite (Scheme 3.13). Conversion to hydrazones **3.35** or **3.36** was observed in all cases, and it occurred chemo-

(only the endocyclic bond C=C participated in the reaction), regio- (the hydrazone fragment was formed either at the C^2 atom or at the C^5 atom of the former furan ring) and stereoselectively (in all compounds (*Z*)-C=C bond, one isomer of the C=N bond).

Scheme 3.13



Scheme 3.14

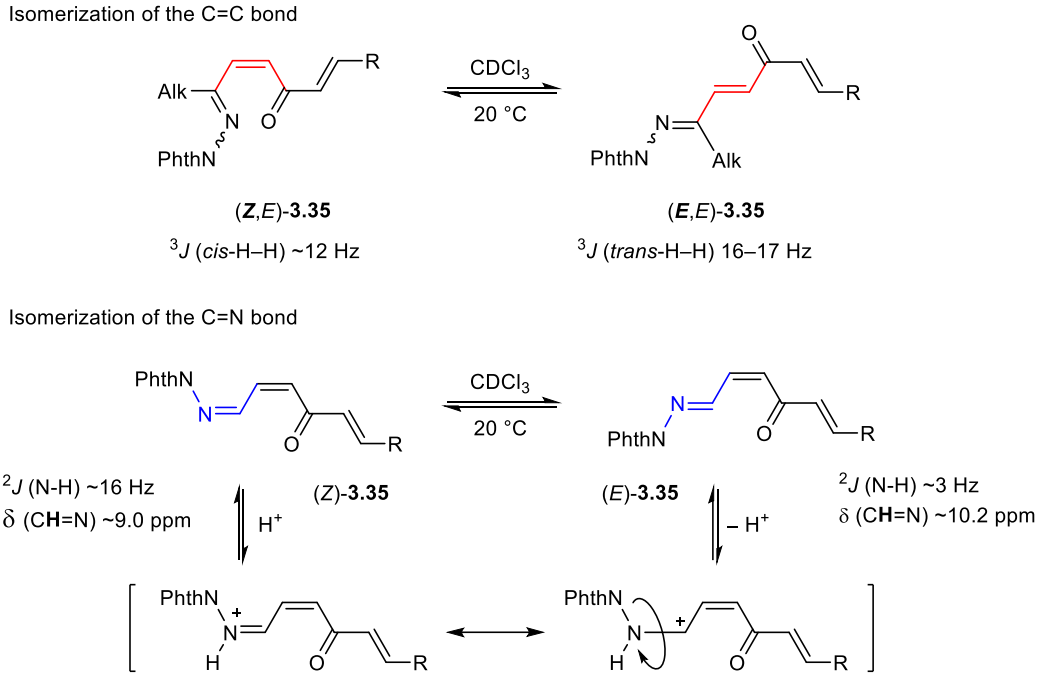


This is in accordance with the mechanism involving the initial addition of *N*-acetoxyaminophthalimide to the double bond of the furan ring with subsequent rearrangement of an unstable bicyclic intermediate (Scheme 3.14) [219]. The regioselectivity of the addition is determined by a substituent at the C^5 position of furan: at R^1 = H, Alk, the reaction proceeds along the C^4=C^5 bond (path A), at R^1 = Ar – on the contrary, at the C^2= C^3 bond (path B). Considering that the bulk *tert*-butyl group does not interfere with the attack on the adjacent bond (Scheme 3.13, compound **3.35**, R^1 = *t*-Bu, Scheme 3.14, path A), we assume that not the steric factor is the main one, but the minimization of the loss of resonance stabilization, since the

effective conjugation of the aromatic substituent at C^5 atom with an adjacent π-system is preserved on the path B.

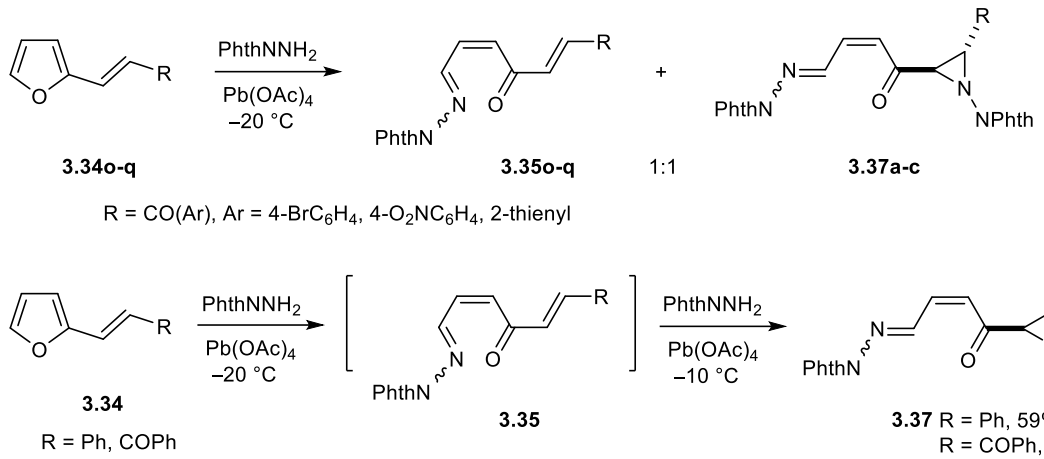
Hydrazones **3.35** and **3.36** were obtained as a single (*Z*)-isomer of the C=C bond and a single isomer of the C=N bond (only in two cases **3.35** (R^1 = H, R^2 = CN, CO(2-furyl)) mixtures of isomers of the C=N bond in a ratio of 1:0.6–0.7). (*Z*)-Configuration of the former furan C^3–C^4 bond is determined by the structure of the substrate, and we observed prototropic isomerization of this bond of ketohydrazones **3.35** (R^1 = Me, *t*-Bu, R^2 = CN, CO_2Et, NO_2) in $CDCl_3$ solution or upon prolonged contact with silica (Scheme 3.15). The isomerization of the C=N bond occurred under similar conditions in all hydrazones **3.35** and **3.36** noticeably faster, and it was possible to stabilize the single form only in a dry and distilled solvent (Scheme 3.15).

Scheme 3.15



The exocyclic bond of 2-vinylfuran derivatives **3.34a-n** remained untouched in all hydrazones **3.35a-l** and **3.36a,b** (Scheme 3.13), but mixtures of hydrazones **3.35o-q** and aziridines **3.37a-c** with a hydrazone fragment in the side chain in the ratio ~1:1 were obtained for three similar substrates **3.34o-q** (Scheme 3.16, top line). We have separately demonstrated by the example of two compounds **3.34** (R = Ph, COPh) (Scheme 3.16, bottom line) that the "second" aziridination proceeds under more severe conditions. Aziridines at the (*E*)-C=C bond were formed only at a higher temperature and after aziridination and the ring opening of the furan. Interestingly, the (*Z*)-C=C bond remained unaffected, and such selectivity was observed earlier [221], although the reasons are not obvious.

Scheme 3.16

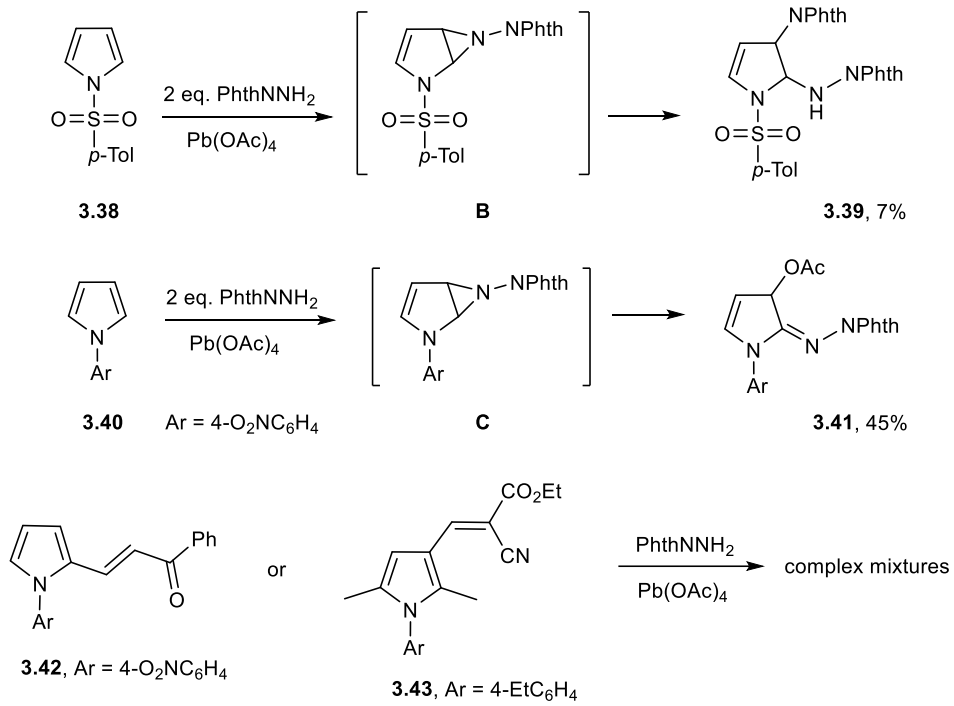


Given the ease of oxidation of furan derivatives to 1,4-dicarbonyl compounds by many oxidants [222-224], including $Pb(OAc)_4$ [225], it can be assumed that the opening of the five-membered ring of compounds **3.34** occurs before interaction with *N*-aminophthalimide. However, we have shown (using the example of ethyl 3-(furan-2-yl)acrylate), that in the absence of *N*-aminophthalimide, substrate conversion is not observed at -20 °C or even 20 °C, and therefore, in the reaction under discussion, the key step is precisely the interaction of *N*-acetoxyaminophthalimide with the endocyclic furan bond. In general, this is a rare example of the aziridination of a bond included in the aromatic system in the presence of a "conventional" double carbon-carbon bond. The resulting hydrazones, derivatives of (2*Z*)-hexa-2,5-dien-1,4-dione, are quite labile and difficult to access by other methods [226]. They are of interest as fragments of some natural compounds [227], and the reaction described in this section, in principle, can be used for their directed synthesis.

3.2.2.3. Pyrrole derivatives

Oxidation of *N*-aminophthalimide in the presence of *N*-acceptor-substituted pyrroles **3.38** and **3.40** did not lead to the formation of stable aziridines (Scheme 3.17). Products **3.39** and **3.41** can be interpreted as the result of the ring opening of aziridines **B** and **C**, initially formed at the C^2=C^3 bond of the pyrrole ring. The introduction of vinylpyrroles **3.42** and **3.43** into the reaction led only to the tarring and formation of a complex mixture of compounds, probably due to the low stability and high reactivity of the intermediate products of aziridination. Apparently, only the inclusion of pyrrole in the conjugation system (as in indole [217, 218]) can provide the necessary balance of activity and stability in this reaction.

Scheme 3.17



3.3. Synthesis of oxazoles

The first report on the conversion of 2-acylazyridines to oxazoles was published in 1968 [228]: in the evaporative element of a gas chromatograph at 220 °C, the quantitative formation of corresponding oxazoles from 2-aroyl-3-phenyl-1-R-aziridines (R = t-Bu, Bn, Me, c-Hex) occurred with the elimination of a substituent on the nitrogen atom. The first work on the conversion of several phthalimidoaziridines into oxazoles under much milder conditions (20-78 °C) appeared a little later [194], but this reaction and the influence of the nature of substituents began to be studied in more detail in our group by E.V. Beletsky in 2009 [199]. Our review of the literature data on the reactions of 2-acylazyridines [7] showed that this area has not received sufficient attention. Although the conversion of α,β-unsaturated carbonyl compounds into aziridines with a suitable leaving group on the nitrogen atom (for example, phthalimide) in combination with subsequent thermolysis can become a common two–step method for the synthesis of oxazoles, possessing a number of valuable properties [229-232]. This idea is demonstrated by the examples described below.

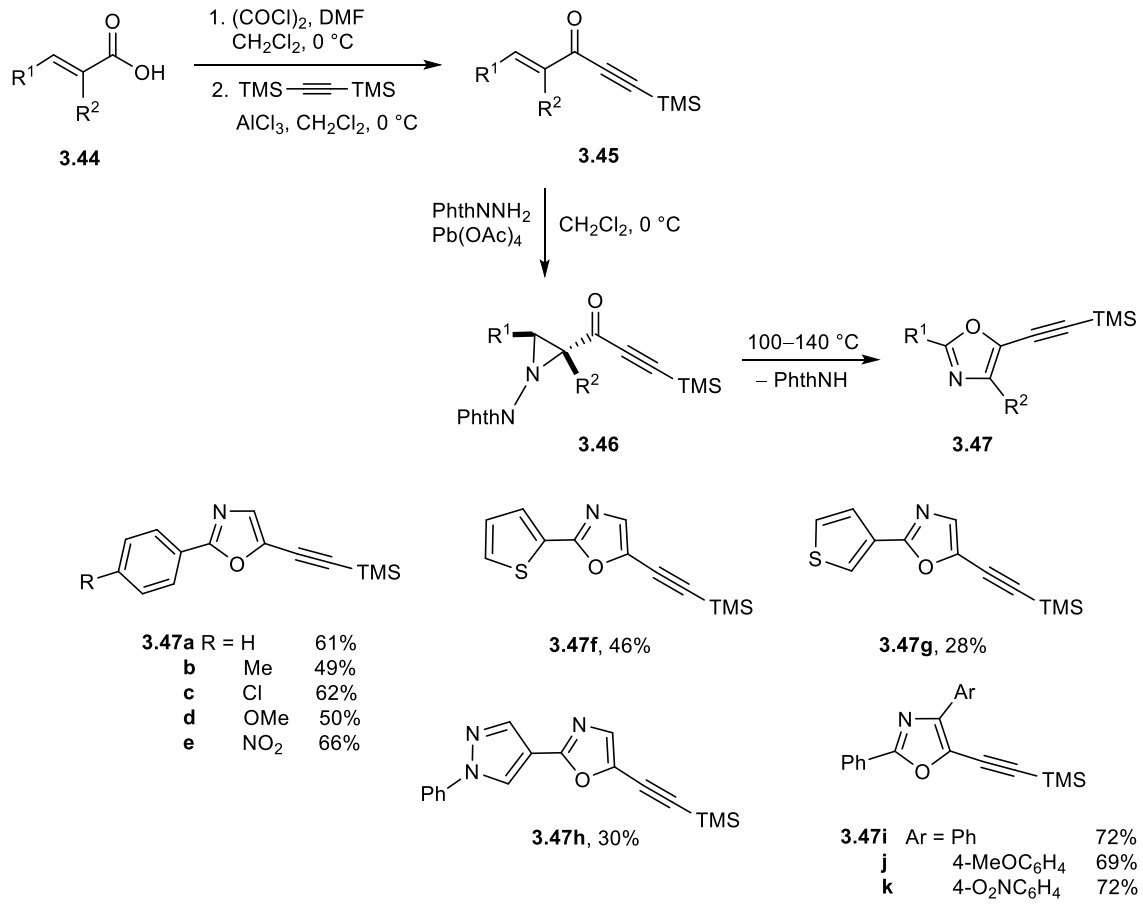
3.3.1. 5-Ethynyloxazoles

The content of the section is based on the article [14].

We proposed a synthetic strategy towards oxazoles with trimethylsilylethynyl substituent from cross-conjugated enynones, using the construction and subsequent cleavage of the aziridine ring as a key transformation (Scheme 3.18). Chloroanhydrides of unsaturated acids **3.44** were

used for the acylation of bis(trimethylsilyl)acetylene by analogy with the synthesis of enynones 1.9 (see Section 1.2), and the resulting ketones **3.45** were subjected to oxidative aminoaziridination (see Section 3.2.1). The final *N*-phthalimidoaziridines **3.46** turned out to be quite stable compounds, and the opening of the three-membered ring was observed only when heated above 100 °C. The corresponding oxazoles **3.47** were obtained in 28-72% yields, and in all cases the triple bond with the $SiMe_3$ group was preserved in the reaction product. The cyclization of trisubstituted aziridines into oxazoles **3.47i-k** occurred under milder conditions, as well as for disubstituted compounds with an electron–donating aromatic substituent R^1 (**3.47b,d,f**) (Scheme 3.18). Thus, (as will be seen further for other aziridines), the breakage of the C–C bond is facilitated while increasing the number of substituents at the aziridine carbon atoms and when substituents of different electronic effects are located at the opposite terminal carbon atoms of the resulting azomethine ylide.

Scheme 3.18



Our proposed method for the production of 5-ethynyloxazoles can be considered as a convenient and effective alternative to known methods for the synthesis of such structures. The leading position among those described in the literature is occupied by synthetic sequences based on the introduction of an ethynyl substituent by the Sonogashira reaction in the presence of a

suitable leaving group (Hal or OTf) at the C^5 oxazole atom [233-239]. Ir^{III}-catalyzed alkynylation of oxazole at the unsubstituted fifth position is also possible, but only in the presence of a carbonyl substituent at C^4 atom [240]. An example of the transformation of an acetyl group at C^5 atom into an ethynyl fragment upon treatment with a mixture of polyaminophosphazene (P_2-base) and nonafluorobutanesulfonylfluoride is described [241]. Common to all these methods is the need for not always easy and fast prior assembly of the oxazole ring with a certain substituent at C^5 atom. Direct alkynylation at the unsubstituted fifth position is known so far only by the example of the Pd^0-catalyzed reaction of (4-methoxyphenyl)acetylene and 2-phenyloxazole [242]. On the other hand, 5-alkynyloxazoles can be obtained by the van Leysen method [243] by reaction between tosylmethylisocyanide with acetylene carbonyl compounds [244, 245], but in the case of substrates with a trimethylsilyl group at a triple bond, yields do not exceed 40% [245]. 2-(Isoquinoline-1-yl)oxazoles with phenylethynyl or propyn-1-yl substituent in the fifth position can be obtained by the reaction of Reissert salts with corresponding acetylene aldehydes in no more than 39% yields [246]. Other variants of the synthesis of 5-alkynyloxazoles by constructive reactions of acetylene substrates are presented by single examples [247-249].

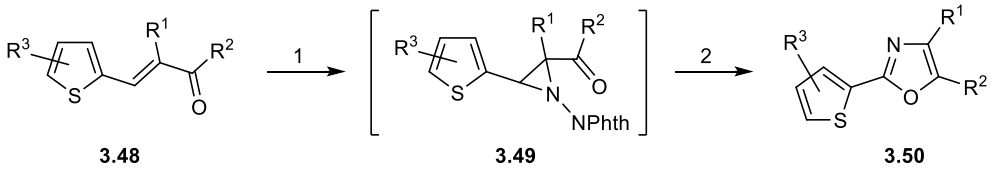
On the general background, our method is characterized by simplicity and accessibility of substrates and reagents, a small number of steps (without transition metal catalysis) with a good overall yield and the possibility of obtaining oxazoles with an easily modifiable trimethylsilylethynyl substituent.

3.3.2. 2-Thiophenyloxazoles

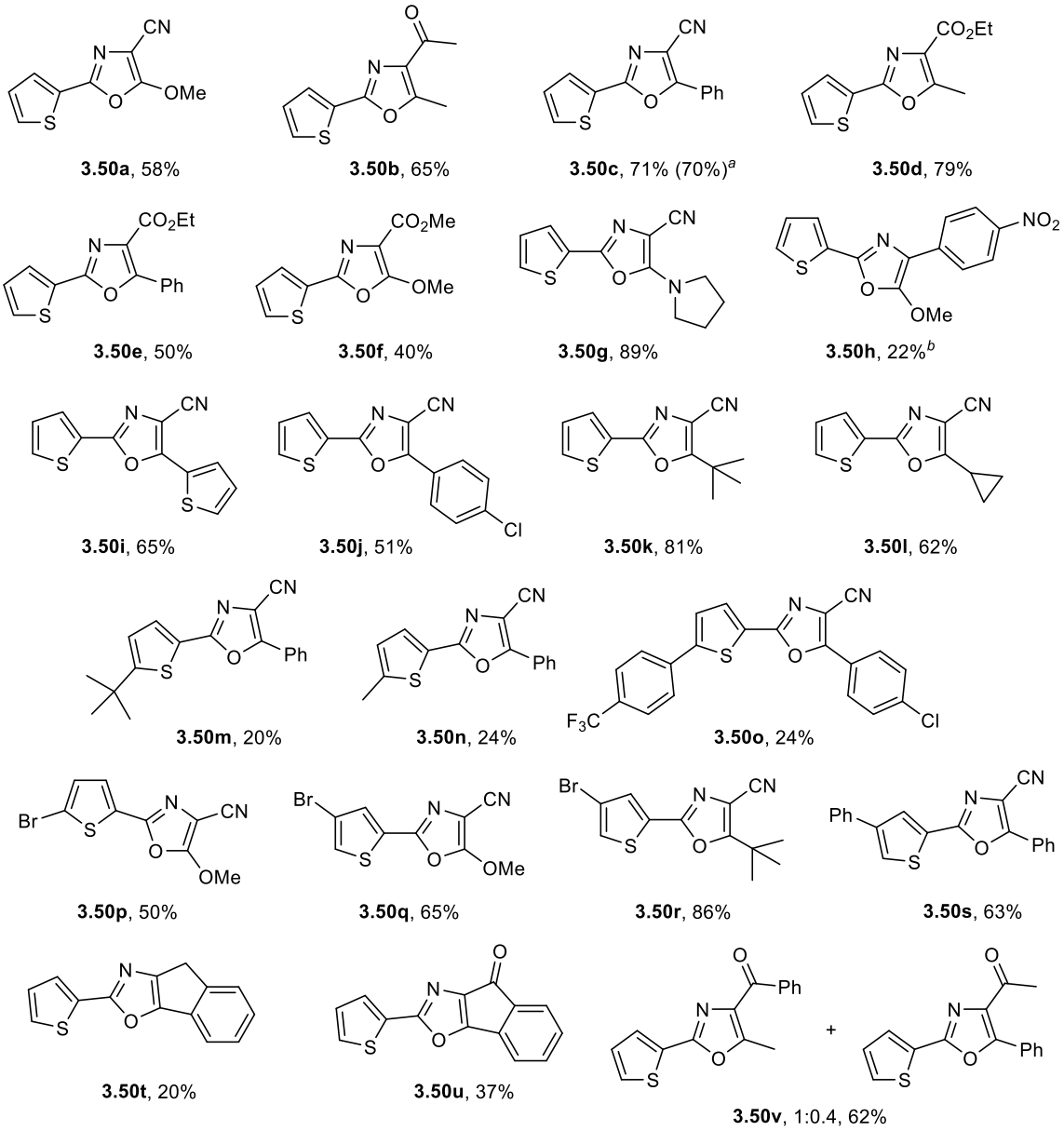
The content of the section is based on the article [2].

As mentioned in Section 3.2.2.1, the aziridination of 2-vinylthiophene derivatives proceeds exclusively via an exocyclic double bond. Upon oxidative aminoaziridination of conjugated enones **3.48** with a thiophenyl substituent at the β-carbon atom, trisubstituted aziridines of the type **3.49** should be formed. These compounds turned out to be unstable and it was not possible to isolate them individually (Scheme 3.19). At the same time, low stability may indicate the ease of aziridine ring opening, and indeed, such aziridines can be easily transformed into oxazoles **3.50**.

Scheme 3.19



1. $PhthNNH_2$, $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, 0 °C, 0.5 h. 2. CH_2Cl_2, 40°C, 1 h or toluene, 80 °C, 1 h



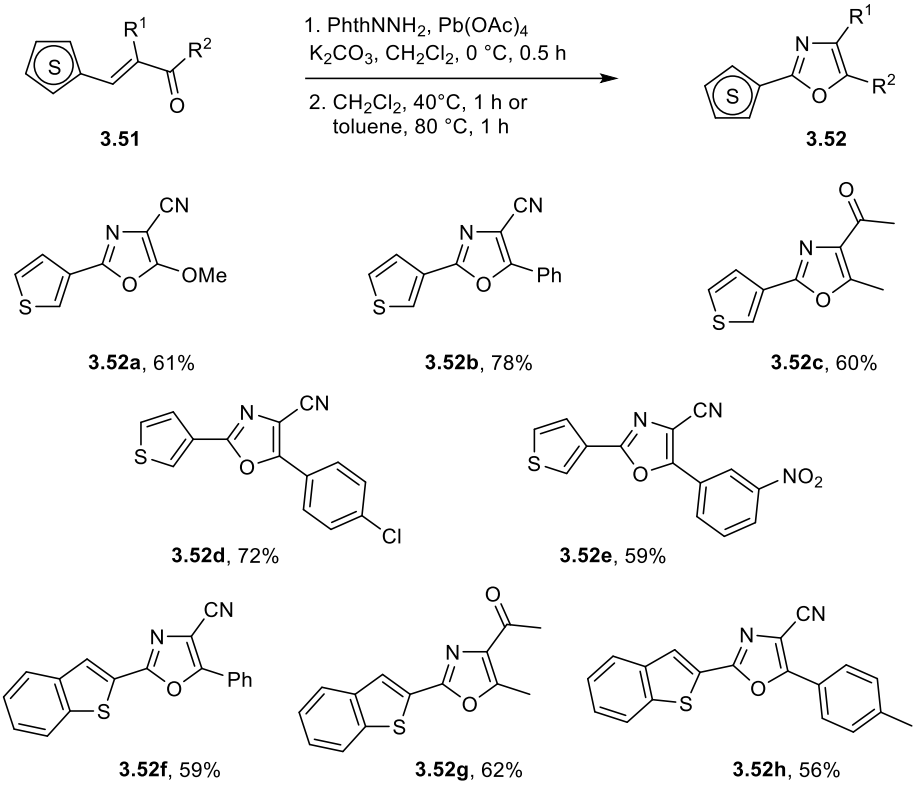
[a] Yield of oxazole **3.50c** from 1.0 g of substrate **3.48c**.

[b] The product of isomerization of aziridine (imine) was obtained in 60% yield, see Scheme 3.27.

The mild and, most importantly, fast treatment of the reaction mixture after aziridination makes it possible to obtain a solution of aziridine in dichloromethane, in which, upon subsequent heating, conversion to oxazole occurs. The boiling point of dichloromethane (40 °C) is sufficient for the conversion of the most active aziridines into the corresponding oxazoles **3.50a,b,g,p,q** in half an hour. In other cases, the solvent was replaced by toluene to provide a higher temperature

(80 °C) necessary to complete the reaction in about 1 h. And only to obtain the indenone derivative **3.50t**, heating at 160 °C was required for 1.5 h, therefore we assumed that the corresponding aziridine should be quite stable and, indeed, isolated and fully characterized the compound **3.49t**, thereby confirming the intermediate formation of aziridines during this transformation (Scheme 3.19). Interestingly, when heating the solution obtained after aziridination of methyl (*E*)-2-cyano-3-(thiophen-2-yl)acrylate (**3.48a**), the appearance and subsequent disappearance of a bright crimson color was observed, which can be interpreted as the generation and cyclization of azomethine ylide, respectively.

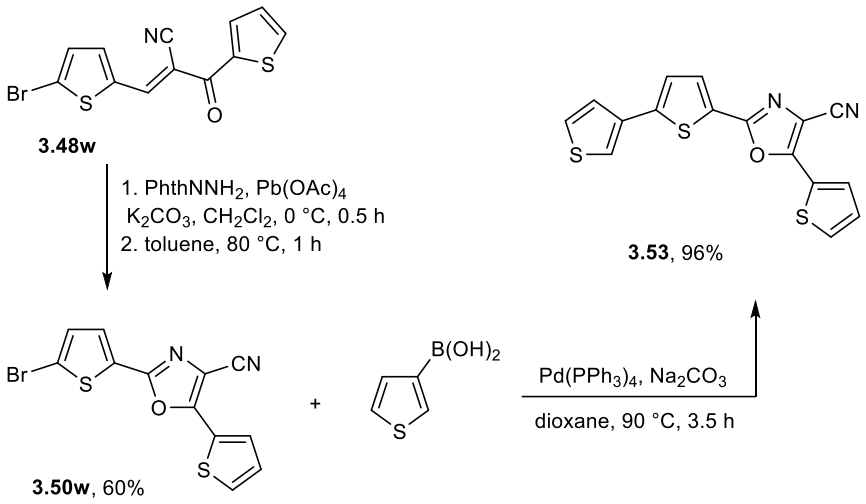
Scheme 3.20



A wide range of substrates was introduced into this transformation: thiophen-2-yl- **3.48**, thiophen-3-yl- and benzo[*b*]thiophen-2-yl derivatives **3.51** with various substituents, and the corresponding oxazoles **3.50** and **3.52** were obtained in 20-89% yields (Schemes 3.19 and 3.20). Variation of the substituent in the fifth position of the oxazole ring demonstrates the possibility of involvment of a carbonyl group from both a ketone and an ester and amide fragment. In the presence of two different carbonyl fragments at one aziridine carbon atom, cyclization proceeds chemoselectively, which can be seen on the example of compounds **3.50d,e,v**, and the activity of the groups decreases in the row $CH_3C{=}O$ > PhC=O > EtOC=O (Scheme 3.19). The substituent at the C^4 atom of oxazole, as a rule, is represented by a functional group (CN, CO_2Alk, Ac, PhCO), but it can also be aromatic. Surprisingly, a distant substituent in the fifth position of the thiophene ring has a negative effect on the result (see the lowest yields of oxazoles **3.50m-p**,

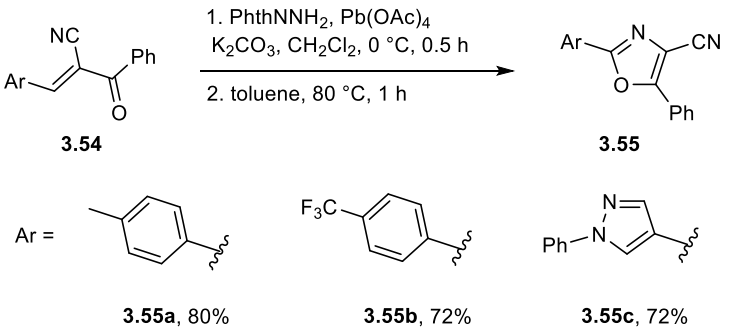
Scheme 3.19), whereas the introduction of a thiophene substituent to the C^4 atom does not give such an effect (compounds **3.50q-s**). Despite this, we were able to synthesize oxazole **3.53**, included in the chain of thiophene units, using the aziridination of 5-bromothiophene-2-yl derivative **3.48w** (Scheme 3.21).

Scheme 3.21



We have demonstrated the versatility of the proposed method on several compounds without a thiophene fragment (**3.54**→**3.55**, Scheme 3.22), and we can recommend this technique as an effective method for the synthesis of not only thiophenyl-, but also aryl-substituted oxazoles in general.

Scheme 3.22



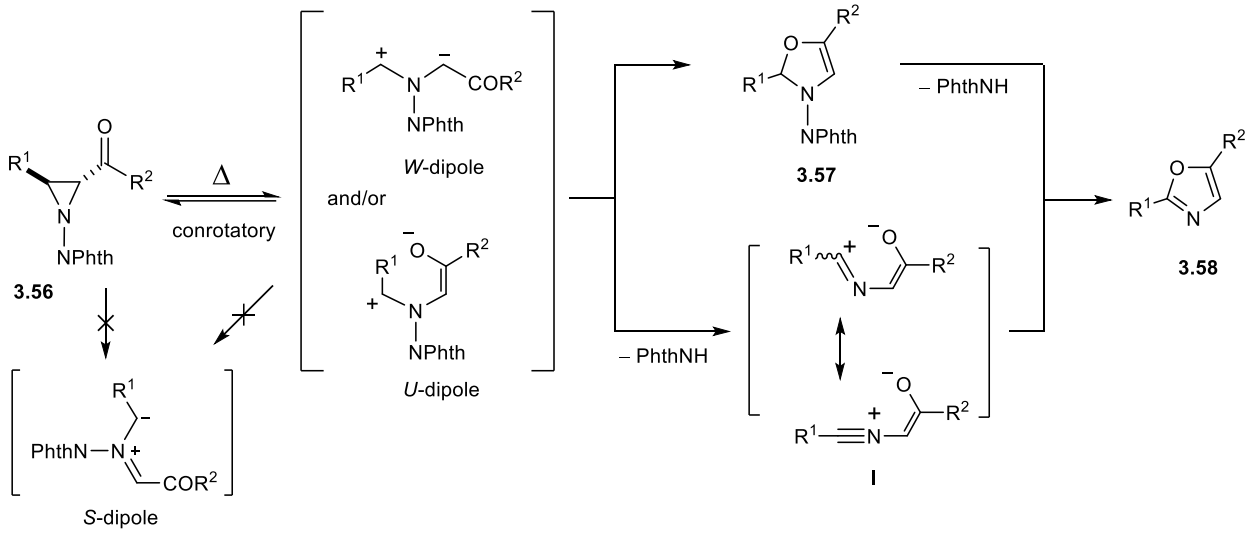
Thiophenyl-substituted oxazoles are of interest as structures combining two directly related valuable heterocyclic fragments. In addition to the known biological activity exhibited by oxazole derivatives [229-231], thiophene compounds are of practical value as active components of organic electronic devices [250-253]. The search for new luminophores with the thiophene-oxazole dyad was carried out among several 5-aryl-2-(2-thienyl)oxazoles [254, 255], and we decided to study the spectral characteristics of the compounds we obtained. It turned out that some thiophenyloxazoles exhibit fairly well-defined fluorescence, which is described in detail in Section 4.4.

3.3.3. Mechanism of transformation of aziridines into oxazoles

The content of the section is based on the articles [2, 14].

The conversion of 2-acyl-1-phthalimidoaziridines into oxazoles is consistent with the mechanism of 1,5-electrocyclization of thermally generated azomethine ylides in accordance with Scheme 3.23. According to the rules for orbital symmetry preservation, the relative position of substituents in azomethine ylide should correspond to the conrotatory cleavage of the aziridine C–C bond. During the formation of oxazoles, this stereochemical information is lost, but there is no reason to believe that the C–C bond is broken in any other way. In cases where the formation of oxazole is a process concomitant with 1,3-dipolar cycloaddition (see Section 3.4 below) [16, 20, 21, 256], the configuration of the adducts corresponds to the stereospecific formation and addition of azomethine ylides.

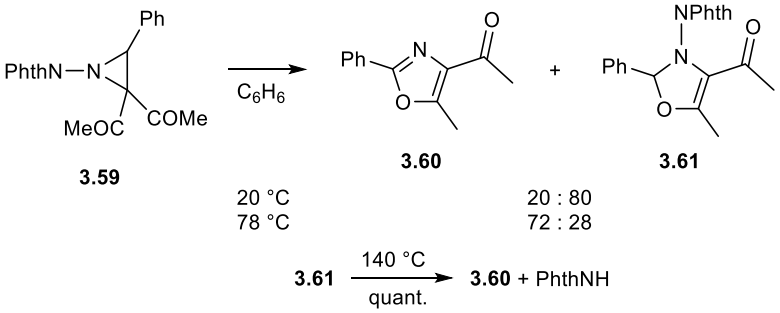
Scheme 3.23



Thus, upon heating an initial *trans*-disubstituted aziridine **3.56**, *U*- or *W*-type dipoles can be formed (Scheme 3.23). The *W*-dipole most likely enters into intermolecular reactions, for example, 1,3-dipolar cycloaddition, since a sterically uncomplicated exo-approach to dipolarophile is possible for it, whereas the closure of the oxazole ring is more probably in the *U*-form of azomethine ylide due to the spatial proximity of the atoms forming the new bond. As a result of such cyclization, *N*-phthalimidooxazoline **3.57** should be formed, from which the phthalimide molecule is further eliminated. In our reactions described above, such oxazolines were not deteceted, but in the already mentioned work of E.V. Beletsky [199], during thermolysis of *N*-phthalimidoaziridine obtained from benzylideneacetone, an oxazoline of presumably such a structure was isolated in a yield of 3% (with an oxazole yield of 60%). In 1976, a paper [194] reported the parallel formation of oxazolines and oxazoles from several

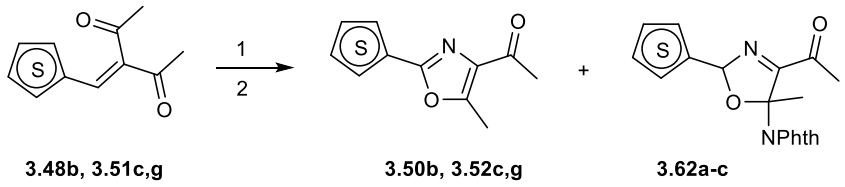
trisubstituted *N*-phthalimidoaziridines. Using the example of aziridine **3.59**, it can be seen (Scheme 3.24) that at a higher temperature the content of oxazole **3.60** increases, although the elimination of phthalimide from the isolated oxazoline **3.61** occurs only under much more severe conditions.

Scheme 3.24 (literature data [194])



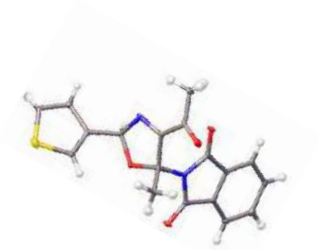
In our work [2] oxazolines were obtained in reactions of thiophenyl-substituted aziridines (Scheme 3.25), and only for substrates with two geminal acetyl groups **3.48b**, **3.51c,g**, and an almost identical ratio of oxazole and oxazoline **3.62** was observed regardless of the thiophene fragment (Table 3.4).

Scheme 3.25



3.48b, 3.51c,g **3.50b, 3.52c,g** **3.62a-c**

1. $PhthNNH_2$, $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, 0 °C, 0.5 h. 2. Heating - see Table.



3.62b

Table 3.4

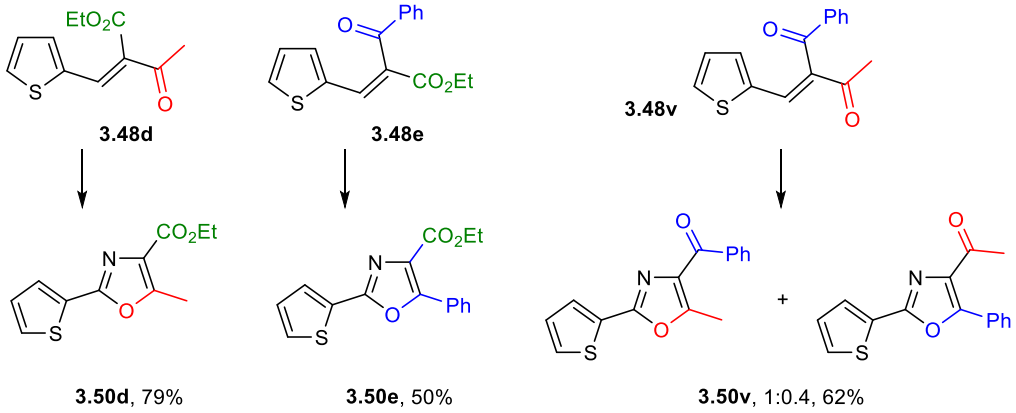
Substrate	Heating conditions	Oxazoline, yield (%)	Oxazole:oxazoline
Thiophen-2-yl (**3.48b**)	CH_2Cl_2, 40 °C, 1 h	**3.62a**, 21	3.1:1
Thiophen-3-yl (**3.51c**)	toluene, 80 °C, 1 h	**3.62b**, 22	2.7:1
Benzo[*b*]thiophen-2-yl (**3.51g**)	toluene, 80 °C, 1 h	**3.62c**, 18	3.4:1

Independent heating of oxazolines **3.62** (2 h at 80 °C, 2 h at 100 °C) did not lead to the formation of oxazoles, which suggests different ways of formation of these compounds. Surprisingly, the structure of oxazoline **3.62** turned out to be not the same as expected during the cyclization of azomethine ylide: the phthalimide group is located not on the nitrogen atom, but on the C^5 atom (the carbon atom of the former C=O bond that took part in the cyclization). We have proved this structure of oxazoline by NMR spectroscopy (^1H, ^{13}C, DEPT, ^1H-^{13}C HSQC, ^1H-^{13}C HMBC and ^1H-^{15}N HMBC) and XRD data.

In the work cited [194, 199], the proof of the structure of oxazolines is not mentioned, and, given the similar substitution pattern of compounds in Schemes 3.24 and 3.25, it can be assumed that oxazolines obtained from aziridines **3.59** also have a structure of type **3.62**, and not **3.61**. Elimination of the phthalimide molecule from oxazolines **3.62** should be difficult, that is confirmed by experimental data. It remains unclear when the migration of the phthalimide group occurs, but it is obvious that such oxazolines are not intermediates on the aziridine→oxazole pathway. However, this does not negate the possibility of intermediate formation of oxazolines of type **3.57** and **3.61** with a phthalimide group on the nitrogen atom and further elimination of phthalimide leading to oxazole, as in Scheme 3.23.

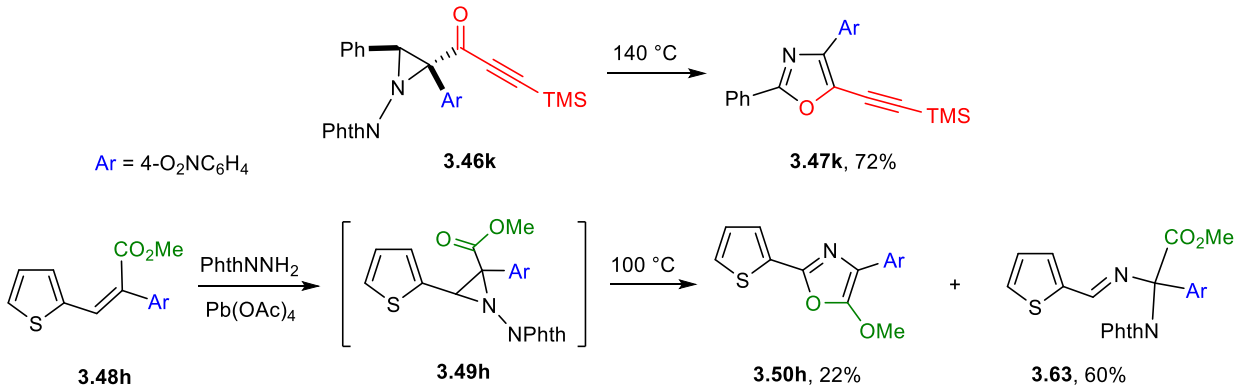
It is possible that the formation of oxazole **3.58** proceeds through nitrile ylide **I** (Scheme 3.23), resulting from the elimination of phthalimide from the initial azomethine ylide [194]. The electrocyclization of nitrile ylide should be easier, taking into account the lower steric hindrance and the greater electrophilicity of the carbon atom carrying a partial positive charge. The fact of chemoselective formation of oxazoles from trisubstituted aziridines with various carbonyl substituents at one carbon atom testifies in favor of the pathway through nitrile ylide (Scheme 3.26). The different configuration of the double bond in substrates **3.48d,e,v** determines the different relative spatial arrangement of substituents in the corresponding aziridines and azomethine ylides. However, exactly the acyl C=O bond participates in the cyclization, and not the alkoxycarbonyl group in the cases of **3.48d,e**, and a mixture of products is formed in the presence of two acyl groups (acetyl and benzoyl) at **3.48v**. The convergence of the oxygen atom of one or another carbonyl group with the terminal carbon atom of the dipole can be achieved by an equilibrium between *U*- and *W*-azomethine ylides through the closure of the aziridine ring (Scheme 3.23) (isomerization of dipoles by rotation around the C–N bond looks unlikely, since the *S*-dipole formed in this case would enter into a 1,3-dipolar cycloaddition to give adducts with the appropriate orientation of the substituents, which we did not observe (see below)). In nitrile ylide **I**, free rotation around the C–N bond can be assumed, and therefore this reaction pathway provides the possibility of choosing a more favorable direction of cyclization and the observed selectivity.

Scheme 3.26



The mentioned difference in the activity of carbonyl groups ($CH_3C{=}O$ > $PhC{=}O$ > $EtOC{=}O$) can also be traced when comparing the thermolysis products of aziridines **3.46k** and **3.49h** (Scheme 3.27). With a similar substitution pattern, the presence of a less active methoxycarbonyl group at the C^2 atom in aziridine **3.49h** causes a low yield of 5-methoxyoxazole **3.50h** and the implementation of the isomerization process into imine **3.63** (see Section 3.4.3.1 below), whereas in the reaction of aziridine **3.46k** with the TMS–C≡C–C(O) group at the C^2 atom no imines were detected, and the yield of oxazole **3.47k** is much higher.

Scheme 3.27



In any case, this reaction is general for 2-acylazyridines, and the presence of a phthalimide group on the nitrogen atom causes a relatively easy elimination of the phthalimide molecule and aromatization of the resulting cycle. Therefore, the combination of oxidative aminoaziridination of α,β-unsaturated carbonyl compounds and thermal transformation of the resulting *N*-phthalimidoaziridines can serve as an affordable and effective method for the synthesis of oxazoles from conjugated enones.

3.4. Syntheses based on 1,3-dipolar cycloaddition

3.4.1. Intermolecular reactions

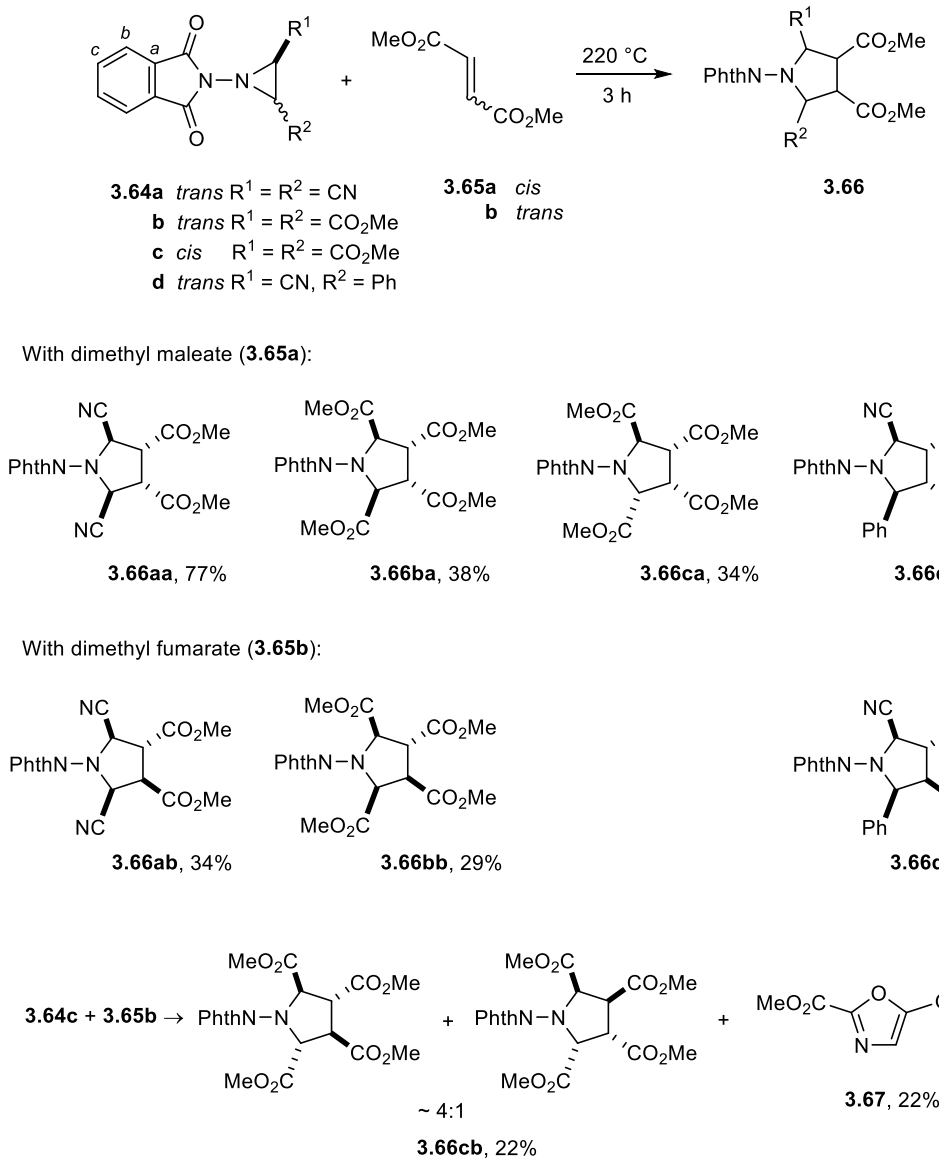
3.4.1.1. Reactions with C=C dipolarophiles

The content of the section is based on the articles [21, 23].

Assuming the formation of azomethine ylides at the second step of the enone→aziridine→oxazole sequence, we became interested in the possibility of developing methods for the synthesis of nitrogen-containing heterocyclic compounds based on 1,3-dipolar cycloaddition reactions of *N*-phthalimidoazomethine ylides. It turned out that in the only series of studies on the participation of *N*-phthalimidoaziridines in 1,3-dipolar cycloaddition reactions, only the reactions of several tri- and tetrasubstituted aziridines with DMAD and isonitriles were described [193-196]. The spatial structure of the few adducts was not reliably established, therefore, the stereochemical patterns of the process and the possibility of selective synthesis of *N*-aminoazole derivatives remained unclear. We selected disubstituted aziridines with groups of various electronic character as model objects, and the set of dipolarophiles consisted of the most studied and often used compounds with electron-deficient double carbon-carbon bonds as "traps": *N*-phenylmaleimide, dimethyl maleate, dimethyl fumarate. In our opinion, this combination of cycloaddition partners makes it possible to investigate the spatial course of the entire sequence of transformations and the influence of electronic factors on the ease of breaking the C–C bond and generating azomethine ylides.

N-Phthalimidoaziridines **3.64a-d** were introduced in reaction with dimethyl maleate (**3.65a**) and dimethyl fumarate (**3.65b**) (Scheme 3.28). To begin the interaction, heating of a mixture of aziridine and dipolarophile to 220 °C was required, which was achieved by conducting synthesis in a solution of benzene or chlorobenzene in a sealed ampoule or a thick-walled glass jar with a screw cap. At this temperature, the complete conversion of the substrate occurred in 3-4 h. As a result, the corresponding products of 1,3-dipolar cycloaddition were obtained – previously unknown derivatives of *N*-phthalimidopyrrolidine **3.66**, and in all cases, except one, in the form of a single stereoisomer.

Scheme 3.28



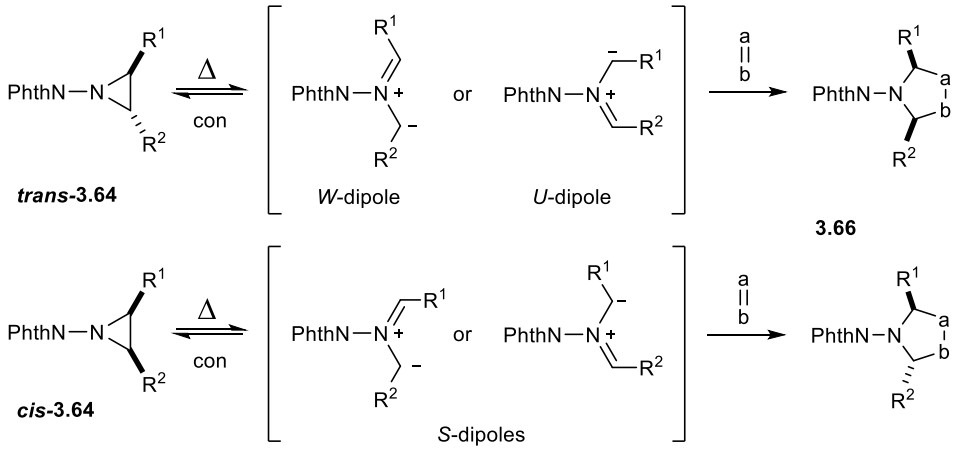
Establishing their structure was a very interesting non-trivial task, since it is impossible to draw an unambiguous conclusion about the configuration of each isomer from one-dimensional NMR spectra. In five-membered heterocycles, the ranges of values of the vicinal spin-spin coupling constants for *cis*- and *trans*-located protons strongly overlap, and therefore their values are not a reliable criterion for configuration [257]. A striking example of this is the adduct **3.66ab** of aziridine **3.64a** with dimethyl fumarate (**3.65b**), in which all the vicinal constants in the ring are almost the same ($J_{2,3}$ = $J_{4,5}$ = 9.1 Hz, $J_{3,4}$ = 9.8 Hz). It was possible to solve the problem of establishing the structure using two–dimensional NOESY spectroscopy, recording ^{13}C NMR spectra at low temperature (as a result, the already difficult rotation of the phthalimide group along the N-N bond slows down, and signals of nonequivalent carbon atoms of the halves of the phthalimide group become visible in the absence of axial symmetry of the pyrrolidine cycle) and general considerations about the nature of symmetry in each case and the conclusions

about the possible form of signals of a five-membered ring. Our reasoning is supported by the XRD data of the adduct **3.66aa** [21].

The reaction of *cis*-aziridine **3.64c** with dimethyl maleate (**3.65a**) gave the expected one isomer of pyrrolidine **3.66ca**, and only in reaction with dimethyl fumarate (**3.65b**) a mixture of diastereomers **3.66cb** and oxazole **3.67** was formed. At the same time, in the presence of more active dipolarophiles (*N*-phenylmaleimide or DMAD, see below), oxazole formation was also not detected.

The results obtained completely fit into a two-step mechanism (Scheme 3.29), according to which the beginning of the process is the conrotatory cleavage of 2,3-disubstituted-1-phthalimidoaziridines **3.64** into the corresponding azomethine ylides, possibly reversible, allowed during thermolysis by the rules for orbital symmetry preservation. Then there is a coordinated addition of these 1,3-dipoles to multiple bonds of dipolarophiles, and both steps are completely stereospecific, and cycloaddition is stereoselective. Even with the formation of two isomers comparable in stability, as in the case of *cis*-aziridine **3.64c** with dimethyl fumarate (**3.65b**), the less sterically hindered adduct prevails in the mixture **3.66cb** (we did not observe the formation of the most sterically hindered all-*cis* adduct in any case) (Scheme 3.28).

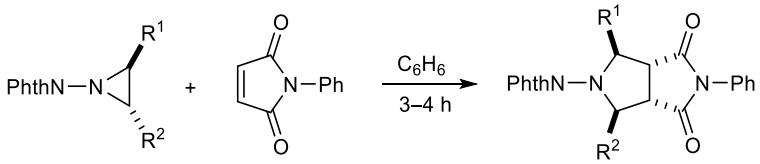
Scheme 3.29



The limiting step of the whole process is probably the cleavage of the aziridine ring at the C–C bond, whose rate should depend on the substituents at carbon atoms. According to the literature data [194], the CN group, which exhibits pronounced acceptor properties, facilitates the cleavage of the aziridine ring into azomethine ylide as much as possible, however, our results show that the CO_2Me group has a similar effect: in both cases, the "opening temperature" of the aziridine ring is equally high. In any case, it is obvious that the formation of azomethine ylides from substituted aziridines **3.64** is much more difficult than from trisubstituted ones **3.20**, which open already at room temperature (Scheme 3.5).

In order to clarify the electronic factors determining the ease of breaking the C–C bond in *N*-phthalimidoaziridines, we compared *trans*-disubstituted substrates **3.64** having various combinations of acceptor and donor substituents at carbon atoms in reaction with one dipolarophile – *N*-phenylmaleimide (**3.68**) (Scheme 3.30), whose activity as "trap" of dipoles, in particular azomethine ylides, is well known [258, 259]. In each case, the temperature was selected in such a way that all reactions were completed in about the same time (3-4 h) (Table 3.3). The corresponding 1,3-dipolar cycloaddition adducts – previously unknown derivatives of *N*-phthalimidopyrrolidine **3.69** (tetrahydropyrrolo[3,4-c]pyrrole-1,3-diones) – turned out to be the only products in all reactions. It confirms the above mentioned stereospecificity and stereoselectivity of the transformation (it is worth noting that in the reaction with *N*-phenylmaleimide, the question of stereoselectivity of addition is practically not important, since the *trans*-conjection of two five-membered cycles, as well as the formation of all-*cis*-substituted pyrrolidine, are very unlikely).

Scheme 3.30



3.64 **3.68** **3.69**

Table 3.3

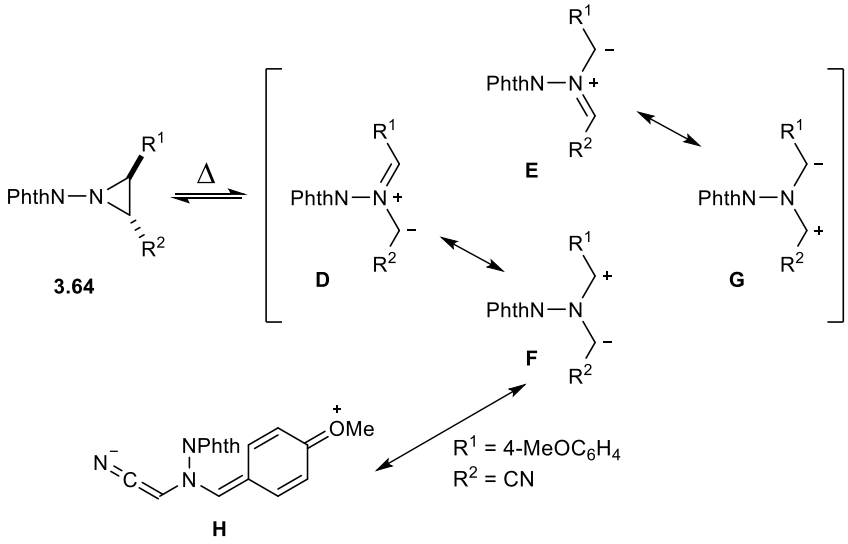
Aziridine **3.64**	R^1	R^2	T, °C	Yield, %
a	CN	CN	220	58
b	CO_2Me	CO_2Me	220	88
d	CN	Ph	120	82
e	CO_2Et	Ph	150	69
f	CN	4-$O_2NC_6H_4$	135	89
g	CN	4-$MeOC_6H_4$	115	69
h	Ph	Ph	120	–[a]

[a] Adduct did not form. See in detail in Section 3.4.3.1.

Based on the results, it can be concluded that the replacement of one acceptor group in symmetric aziridines **3.64a** and **3.64b** by a phenyl group in aziridines **3.64d** and **3.64e**, respectively, leads to a noticeable decrease in temperature. The benzene ring is able to effectively delocalize the charge of any sign, but when a donor methoxy group is introduced into its *para*-position (aziridine **3.64g**), there is a decrease in temperature, albeit not so significant, but still compared with the introduction of an acceptor nitro group (aziridine **3.64f**). On the other hand, with the preservation of the phenyl group at one carbon atom and the introduction of an ethoxycarbonyl group instead of a cyano group at another atom (aziridines **3.64d** vs. **3.64e**), a

tightening of reaction conditions is observed. In general, the stronger the donor properties of the substituent at one carbon atom of the aziridine ring and the acceptor properties at the other, that is, the higher the polarization of the C–C bond, the easier its cleavage occurs.

Scheme 3.31



An explanation of the observed patterns can be seen when comparing the resonance structures of the resulting 1,3-dipoles (Scheme 3.31). For azomethine ylides, octet stabilization of the positive charge is possible due to an unshared electron pair of the nitrogen atom, which is realized in structures **D** and **E**, while carbon atoms possess a partial negative charge. Such resonance structures make the greatest contribution to the stability of azomethine ylides formed from aziridines with two acceptor substituents at carbon atoms. However, with substituents of various electronic nature, the contribution of structures **F** and **G** increases significantly, since effective stabilization of both negative and positive charges is possible (see the example of the resonant structure **H**, Scheme 3.31). It seems that this option is preferable for *N*-phthalimidoazomethine ylides, where the positive charge of the dipole is localized further from the acceptor phthalimide group. Thus, the formation of azomethine ylide from *N*-acceptor-substituted aziridine proceeds under milder conditions if there are substituents of an opposite electronic nature on the carbon atoms.

3.4.1.2. Reactions with DMAD

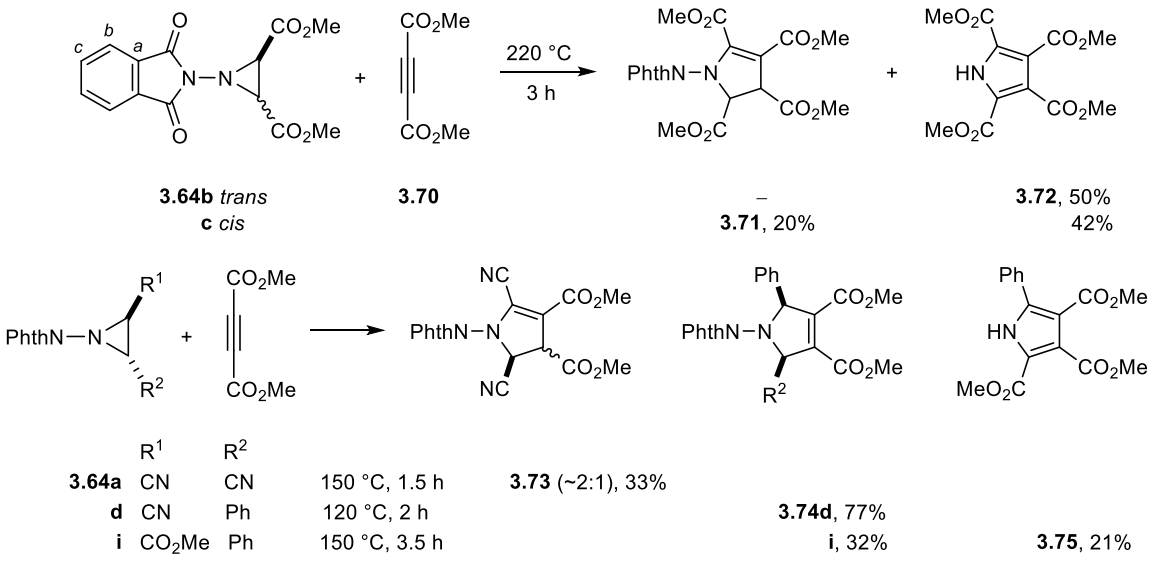
The content of the section is based on the article [22].

Dimethyl acetylenedicarboxylate (DMAD) is one of the most well-known and active dipolarophiles with a triple bond [260, 261]. As already mentioned, several tri- and tetrasubstituted *N*-phthalimidoaziridines were previously introduced into the reaction with it [193-196], but the results obtained were contradictory, and the spatial structure of the

compounds was not established. Subsequent verification showed [197] that the main product of these transformations is 3-pyrroline, and the reaction proceeds with the preservation of the relative location of the aziridine substituents, and not with the reversal that we observed for disubstituted *N*-phthalimidoaziridines and dipolarophiles with a double carbon–carbon bond (Schemes 3.28, 3.30). Therefore, the stereochemical result of the reaction between DMAD and disubstituted *N*-phthalimidoaziridines was all the more interesting.

It turned out that aziridines **3.64a-d,i** react with DMAD (**3.70**) with the formation of a surprisingly wide range of products: 2-pyrrolines **3.71**, **3.73**, 3-pyrrolines **3.74** and pyrroles **3.72** and **3.75** (Scheme 3.32), and spatial structures **3.74** can be interpreted as the result of a concerted 1,3-dipolar cycloaddition of thermally generated *cis*-azomethine ylides to the triple bond of DMAD. Formally, the formation of 2-pyrrolines corresponds to proton migration in the theoretically initial 3-pyrroline, and the formation of pyrroles corresponds to the elimination of the phthalimide molecule from 3-pyrroline, but isolated 3-pyrroline **3.74i** is stable when heated at 150 °C for 5 h. Most likely, the formation of pyrroles **3.72** and **3.75** is the result of the addition of a dipole formed during the elimination of phthalimide from the original azomethine ylide to DMAD. The ratio of the rates of cycloaddition and modification of the ylide, apparently, determines the ratio of the reaction products. It is noteworthy that double bond migration is observed only in products of symmetric aziridines **3.64a,c**.

Scheme 3.32



The temperature and duration of heating required to complete the reaction of each aziridine turned out to be almost the same as in experiments with *N*-phenylmaleimide (Scheme 3.30), with the exception of aziridine **3.64a**, where the reaction ended in 1.5 h at 150 °C instead of 3 h at 220 °C (Table 3.3). The most likely is the participation of DMAD in the cleavage of the aziridine **3.64a**, which is additionally confirmed by the formation of isomeric mixture **3.73** only

in this case. In general, the conclusions drawn above about the rate-determining character of the azomethine ylide generation step and the influence of the nature of substituents on the ease of cleavage of disubstituted *N*-phthalimidoaziridines are valid for the reactions described here.

N-Phthalimidopyrrolines, like almost all other cycloaddition products in this work, are characterized by slow rotation in the NMR time scale along the N–N bond, which can be seen in a distortion of the symmetry of the phthalimide proton multiplet in the ^{1}H NMR spectra. In the ^{13}C NMR spectra of 3-pyrrolines **3.74**, there is a broadening of the signals of the $C^{a,b}$ atoms and the disappearance of the signals of the imide carbon atoms, and for 2-pyrrolines **3.71**, **3.73**, there is a doubling of the signals of the carbon atoms of the phthalimide group. Thus, in the α-position to the endocyclic nitrogen atom, a smaller substituent at sp^2-hybridized carbon atom, being in the "plane" of the five-membered ring, creates greater obstacles to the rotation of the phthalimide group than a larger substituent at sp^3-hybridized atom.

The ambiguous spectral characteristics of 3-pyrrolines **3.74**, which made difficult to establish their structure, are worth special noting. These are large values of the long-range spin–spin coupling constants $J(H^2–H^5)$ = 4.6 (**3.74i**) and 5.1 Hz (**3.74d**) (usually the values of the fourth and homoallyl fifth constants are in the range 0.1-3.0 Hz [262]), a large difference (~20 ppm) in the chemical shifts of the signals of carbon atoms of the double bond, weak NOE between pyrroline protons in the 2D NOESY spectrum. Therefore the spatial structure of 3-pyrrolines **3.74** was proved by the XRD data [263], and it corresponds to a concerted cycloaddition of *cis*-azomethine ylides formed under thermal conditions in accordance with the rules for orbital symmetry preservation to the triple bond.

3.4.1.3. Spirocyclic aziridines

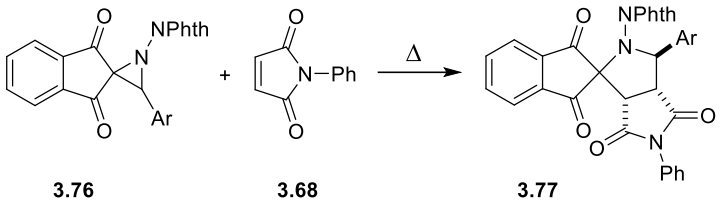
The content of the section is based on the article [16].

Spirocyclic aziridines are interesting as potential sources of unusual azomethine ylides, having one of the carbon atoms as a part of the ring. We intended using transformations of spirocyclic aziridines, in particular 1,3-dipolar cycloaddition to compounds with multiple bonds, as an approach to obtaining spirocyclic pyrrolidine derivatives. Considering that spirocyclic structures are part of various approved medicines and drug candidates [264-266], are widely distributed in natural compounds [267, 268], and are used in optoelectronics [269, 270] and other fields [271], the development of methods for their synthesis is an interesting and urgent task [272-277].

Heating spiroaziridines **3.76** in the presence of *N*-phenylmaleimide (**3.68**) can serve as a convenient way to synthesize spiro-linked pyrrolidines **3.77** (spiro[indene-2,1'-pyrrolo[3,4-*c*]pyrroles]), since they are formed in this reaction in high yield as the only product (Scheme

3.33). The result of the reaction can be interpreted as the result of stereoselective 1,3-dipolar cycloaddition of thermally generated azomethine ylide to the maleimide double bond, and a deviation from full selectivity was observed only in two cases, but even there the minor all-*cis* isomer was obtained in insignificant amounts (no more than 4% of the main isomer).

Scheme 3.33



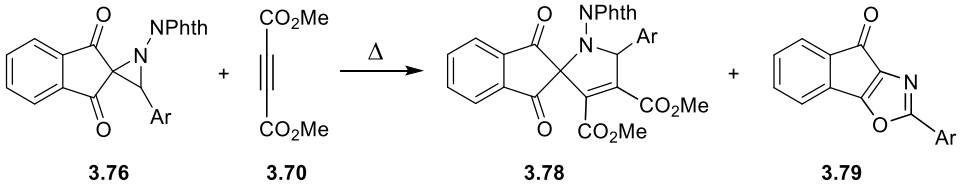
3.76 **3.68** **3.77**

Ar =	R = Me,	25 °C	34%
	Cl	55 °C	95%
	NO_2	75 °C	87%
	CO_2Me		71%[a]
	CN		78%[b]
	CF_3		88%
Ar = 3-pyridyl		75 °C	75% (CCDC 968896)

[a] The product contains 3% of *all-cis*-isomer.
[b] The product contains 4% of *all-cis*-isomer.

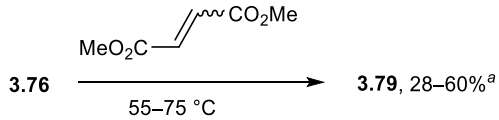
Using DMAD (**3.70**) as a "trap", spiro[inden-2,2'-pyrroles] **3.78** can be obtained from aziridines **3.76** (Scheme 3.34). Byproducts in both cases were the corresponding indeno[2,1-*d*][1,3]oxazol-4-ones **3.79**. In reactions with dimethyl maleate and dimethyl fumarate, oxazoles **3.79** were predominant or even the only products.

Scheme 3.34



3.76 **3.70** **3.78** **3.79**

Ar = 4-ClC_6H_4	55 °C	77%	14%
4-$O_2NC_6H_4$	75 °C	66%	5%



3.76 → **3.79**, 28–60%[a]

[a] Adduct of 1,3-dipolar cycloaddition was obtained in 25% yield in the reaction between aziridine **3.76** (Ar = 4-$O_2NC_6H_4$) and dimethyl maleate.

When comparing the reaction conditions of spiroaziridines **3.76**, it is obvious that decrease of the electron-withdrawing character of the substituent in the *para*-position of the phenyl ring at the third carbon atom causes a noticeable decrease in the optimal reaction temperature up to room temperature at R = CH_3 (Scheme 3.33). Methyl-substituted aziridine

3.76 is so unstable that the only isolable product was obtained in the reaction with maleimide (adduct **3.77**, Scheme 3.33), and it was not possible to isolate individual substances from reactions with other dipolarophiles mentioned here.

In general, the reaction conditions for spiroaziridines **3.76** are much milder than for disubstituted aziridines **3.64** described in Section 3.4.1.1. Increasing the number of dipole-stabilizing substituents favors the ring opening. Aziridines **3.76** are also included in the spirosystem, where two substituents are rigidly linked to each other, and the so-called "spiroactivation" effect has to be mentioned. It consists in a much easier course of ring opening reactions of spiro-1,1-diacylcyclopropanes than their monocyclic analogues [278, 279]. Probably, this phenomenon causes the low resistance of spiroaziridines **3.76** due to high vulnerability, *i.e.* to nucleophilic attack.

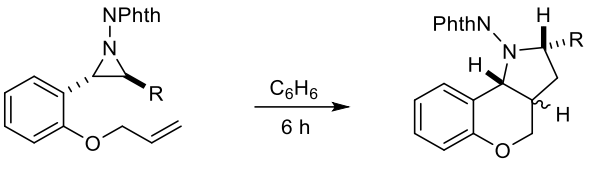
The general dependence of the ease of ring opening of the aziridine on the nature of substitution is fully consistent with the results of heating disubstituted compounds in the presence of dipolarophiles (Section 3.4.1.1). That is, indeed, for *N*-phthalimidoaziridines with substituents of various electronic nature at neighboring carbon atoms (*push-pull* aziridines), the formation of azomethine ylides is easier compared with exclusively acceptor-substituted compounds. This phenomenon is known and is used to activate donor-acceptor cyclopropanes in cycloaddition reactions [280, 281], but according to our data, it has not been previously described for aziridines.

3.4.2. Intramolecular cycloaddition

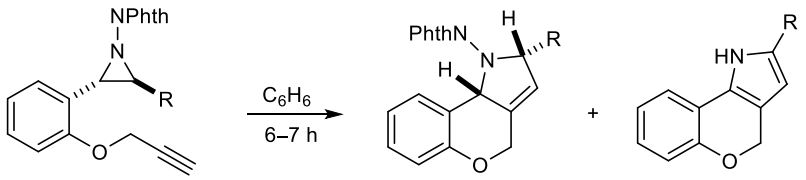
The content of the section is based on the article [20].

Intramolecular transformations of aziridines occurring with the ring opening are of particular interest due to the possibility of creating polycyclic structures via the most atom-economical strategy. We suggested previously unknown aziridines **3.80** and **3.82** (Scheme 3.35), as objects of study of intramolecular cycloaddition. Their design, firstly, takes into account the ease of opening of donor-acceptor *N*-phthalimidoaziridines mentioned before: a benzene ring at one carbon atom and a CN/CO_2Me/$CONR_2$ group at another. Secondly, the total length of the aziridine side chain suggests the possibility of closing a five- or six-membered cycle, and the spatial proximity of the reacting fragments allows using multiple bonds not activated by acceptor substituents as an internal dipolarophile [282].

Scheme 3.35



3.80a	R = CO_2Me	150 °C	**3.81a,** 10% *cis* : *trans* = 2.3:1
b	R = CN	120 °C	**b,** 50% *cis* : *trans* = 2.2:1
c-h	R = $CONAlk_2$	150 °C	–



3.82a CO_2Me	150 °C	**3.83a**, 53%	**3.84a**, 9%
b CN	120 °C	**b**, 91%	–
c $CONMe_2$	150 °C	**c**, 12%	**c**, 5%
d $CONEt_2$	150 °C	**d**, 11%	**d**,11%
e $CON(CH_2)_5$	180 °C (2 h)	**e**, 28%	**e**, 22%

Indeed, such aziridines upon heating turn into tricyclic structures – derivatives of chromeno[4,3-*b*]pyrrole **3.81**, **3.83**, **3.84** (Scheme 3.35), which can be interpreted as the result of thermally induced conrotatory opening of the aziridine at the C–C bond and subsequent concerted 1,3-dipolar cycloaddition of the resulting azomethine ylide to a multiple bond in the side chain. In the case of aziridines with a double bond **3.80a,b**, mixtures of diastereomeric adducts **3.81** were formed, which, apparently, is a consequence of the different mutual orientation of the dipole and the allyl group during cyclization. At the same time, the relative location of the former aziridine substituents indicates the stereospecific formation of azomethine ylides and strict preservation of the configuration during the addition process. Higher yields of adducts **3.83** (pyrroles **3.84** correspond to the loss of a phthalimide molecule during the reaction) were obtained for compounds with a triple bond **3.82** (Scheme 3.35), which, in principle, is consistent with the greater activity of alkynes as "traps", but can also be explained by steric factors. In cycloaddition, coplanarity of the planes of the π-systems of the ylide and the dipole is necessary; it is achieved with any orientation of an axially symmetric triple bond, unlike a double bond with a plane of symmetry.

Allyloxysubstituted aziridines with amide groups **3.80c-h** do not give the expected adducts of cycloaddition, but here the reaction proceeds in an unusual way, which is discussed in more detail in Section 3.4.3.2.

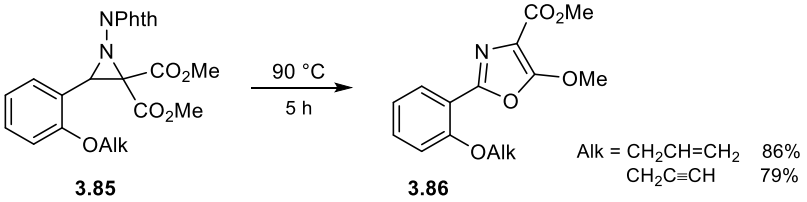
A comparison of the conditions of intramolecular transformation of aziridines **3.80**, **3.82** and intermolecular reactions of similarly substituted aziridines **3.64** (Section 3.4.1.1) reveals the same tendency to tighten the ring opening conditions when replacing the CN group (120 °C) by

CO_2Me (150 °C) regardless of the dipolarophile. Thus, the conclusions repeatedly drawn above about the influence of the electronic nature of substituents on the ease of the aziridine ring opening are valid for intramolecular reactions as well.

In general, despite the moderate yields of products, these reactions can be recommended for the production of chromeno[4,3-*b*]pyrrolidine and pyrroline derivatives, which are of interest as fragments of some natural compounds [283, 284] and substances with biological activity [285, 286]. It is worth noting that the idea of intramolecular cycloaddition of azomethine ylides to multiple bonds in the side chain is implemented to build a framework of chromeno[4,3-*b*]pyrrolidine [284, 287-289] and pyrrolo[3,2-*c*]quinoline [290, 291]. However, the use of aziridines to generate azomethine ylides in this transformation was previously mentioned in one example [292], but after our work this was successfully expanded to a number of *N*-benzylazyridines [293].

Interestingly, after heating similar trisubstituted aziridines **3.85** with two ester groups at the C^2 atom (Scheme 3.36), instead of the products of intramolecular 1,3-dipolar cycloaddition, only 5-methoxyoxazoles **3.86** were isolated in good yields in both cases (double and triple bonds in the side chain).

Scheme 3.36



3.85 **3.86**

Consequently, the conversion of 2-acylaziridines into oxazoles becomes dominant in the presence of low-active dipolarophiles and with the inevitable proximity of one of the two carbonyl groups to the positively charged end of the dipole (*cf.* with spirocyclic aziridines **3.76**). This is consistent with the fact that the dipolarophile structure affects the value of the cycloaddition activation barrier, whereas the possibility of an intramolecular process is determined only by aziridine substituents. Therefore, for the low-active "traps", 1,5-electrocyclization of the intermediate azomethine ylide into oxazole becomes preferable.

3.4.3. Other thermal transformations of *N*-phthalimidoaziridines

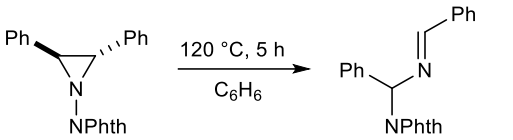
For some of the aziridines obtained by us, other thermal transformations were observed, accompanying or even dominating over the 1,3-dipolar cycloaddition and conversion to oxazoles. These processes turned out to be characteristic for a certain type of substitution of the aziridine ring, and this section is devoted to a more detailed description of them.

3.4.3.1. Rearrangement into imines

The content of the section is based on the article [2, 12, 18].

As mentioned in Section 3.4.1.1, aziridine **3.64h**, obtained from *trans*-stilbene, was inert in the 1,3-dipolar cycloaddition reaction (Scheme 3.30, Table 3.3). Upon heating, its quantitative conversion into imine **3.87** occurs (Scheme 3.37). A similar process dominated when heating aziridine obtained from methyl 2-(4-nitrophenyl)-3-(thiophen-2-yl)acrylate **3.48h**: the formation of the expected oxazole **3.50h** still occurred, but to a lesser extent than isomerization into imine **3.63** (Scheme 3.27). In other reactions described in Sections 3.3, 3.4, similar imines were not detected in appreciable amounts.

Scheme 3.37



3.64h **3.87h**, ~100%

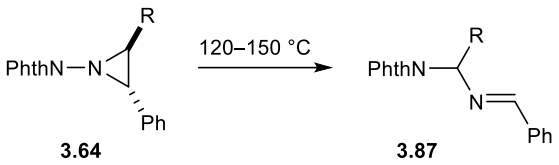
According to the literature, there are examples of "normal" behavior in cycloaddition reactions of 2,3-diphenylaziridines with *N*-alkyl- [294-298], *N*-aryl- [298-300], *N*-aroyl- [301] and *N*-alkoxycarbonyl- [296] substituents. At the same time, migration of the *N*-substituent accompanying the rearrangement into imines has been described for some similar aziridines: *N*-benzyl- [302], *N*-cyclohexyl- [303], *N*-(1,2-di(methoxycarbonyl)vinyl)- [304] and *N*-benzoyl- [305], which proceeds, according to the authors, through the initial generation of azomethine ylides. For *N*-phthalimidoaziridines, a similar rearrangement was reported in the work of Pearson and colleagues [306] for tri- and tetrasubstituted compounds at room temperature (see Scheme 3.40 below). Generalization of the mentioned reactions was not carried out, although in all aziridines undergoing isomerization into mines, there was at least one phenyl substituent at carbon atoms.[6]

We decided to evaluate this process for aryl-substituted phthalimidoaziridines. Upon heating in the absence of dipolarophiles (Scheme 3.38), isomerization to imines **3.87** is possible to a lesser extent for aziridines **3.64d,i,j** obtained from nitrile and esters of cinnamic acid. Therefore, the ring opening with migration of the phthalimide group is a common process for *N*-phthalimidoaziridines having at least one aromatic substituent, but more characteristic for diaryl-substituted structures of type **3.64h** (Scheme 3.37) and **3.49h** (Scheme 3.27).

---

[6] After our work, C^2,C^3-dialkyl-substituted *N*-phthalimidoaziridines were presented as compounds resistant to heating, but 1,2-migration of the phthalimide group with the formation of imine can be induced in such aziridines being included in the polymer under the action of pulsed ultrasound [307].

Scheme 3.38

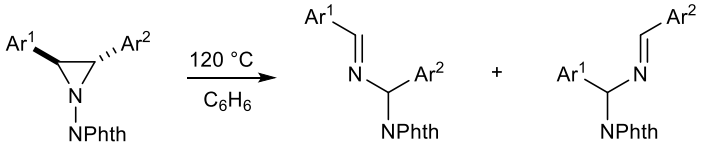


3.64 **3.87**

d	R = CN	23%
i	CO_2All	40%
j	$CO_2CH_2C{\equiv}CH$	41%

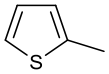
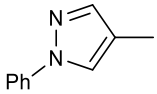
To confirm this hypothesis, we performed thermolysis of a number of 2,3-diaryl-1-phthalimidoaziridines **3.88** (Scheme 3.39, Table 3.5). In all cases, according to the ^{1}H NMR spectra of the reaction mixtures, almost quantitative conversion of aziridine into a mixture of imines **3.89** and **3.90** was observed, except for symmetrical substrates **3.88e,h**, which gave one product. Imines are fairly stable in dry solution, but decompose quickly when crystallization or chromatographic isolation is attempted. An analysis of the structure and ratio of isomeric imines showed that this reaction proceeds regioselectively with a preferred migration of the phthalimide group to a more electron-deficient carbon atom. The same was observed in the rearrangement of asymmetric aziridines **3.49h** (Scheme 3.27) and **3.64d,i,j** (Scheme 3.38).

Scheme 3.39



3.88 **3.89** **3.90**

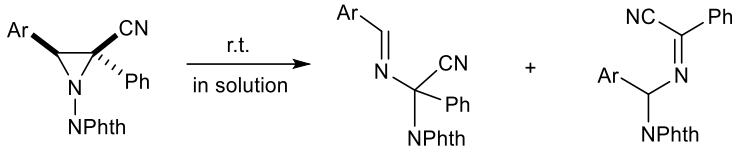
Table 3.5

№	Aziridine **3.88**	Ar^1	Ar^2	Duration, h	Imines	**3.89** : **3.90**[a]
1	**a**	Ph	4-$MeOC_6H_4$	7.5	**3.89a/3.90a**	1:1.5
2	**b**	Ph	4-ClC_6H_4	6.5	**3.89b/3.90b**	1:1
3	**c**	Ph	4-$O_2NC_6H_4$	6	**3.89c/3.90c**	1:0.8
4	**d**	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	5	**3.89d/3.90d**	1:2.5
5	**e**	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	8	**3.89e**	–
6	**f**	Ph		1	**3.89f/3.90f**	1:2
7	**g**	Ph		2	traces[b]	–
8	**h**[c]	Ph	Ph	6	**3.87h**	–

[a] According to ^{1}H NMR spectra of reaction mixtures.
[b] Decomposition of aziridine occurred.
[c] *cis*-2,3-Diphenylaziridine.

However, this conclusion about the reaction selectivity contradicts the one made in Pearson's work [306]. Rearrangement of tri- and tetrasubstituted *N*-phthalimidoaziridines **3.91**, having at least one cyano group as a substituent, was reported to form a mixture of imines **3.92** and **3.93**, where the major isomer **3.93** corresponds to the migration of the phthalimide group to a carbon atom without cyano groups (Scheme 3.40). At the same time, the information on the ratio of isomers looks unreliable, as it contradicts the information previously stated by the same authors in a previous paper [308]. It is possible to find confusion in the assignment of signals and a lack of spectral characteristics of isomers.

Scheme 3.40



3.91 **3.92** **3.93**

Table 3.6

Aziridine **3.91**	Ar	**3.92 : 3.93** (solvent) [306]	**3.92 : 3.93** (yield, solvent)[a]	Isolated yield, %	
				3.92	**3.93**
a	Ph	1:1.08 ($CHCl_3$)	1:0.75 (81%, $CHCl_3$) 1:0.44 (79%, C_6H_6) 1:0.35 (82%, $(CH_3)_2CO$)	63[b]	20[b]
b	4-$MeOC_6H_4$	0:1 (CH_2Cl_2)	1:0.43 (CH_2Cl_2)[c]	51	15
c	4-$NO_2C_6H_4$	–	1:0.77 (81%, $CHCl_3$) 1:0.62 (90%, C_6H_6)	73 (1:0.55)[b]	

[a] According to ^1H NMR spectra of reaction mixtures.
[b] For a reaction in benzene.
[c] Aziridine **3.91b** was not isolated in a pure form.

In order to clarify the unclear issues, we have reproduced several examples from these work. Aziridines **3.91a,c** turned out to be stable substances in solid form, but susceptible to very quick rearrangement in solution already at room temperature. Unlike the diaryl-substituted analogues **3.89**, **3.90**, the resulting imines **3.92**, **3.93** are so stable that it was possible to chromatographically isolate and characterize them in pure form. The ratio of isomers **3.92**/**3.93** established by us, which varies slightly depending on the solvent, in any case does not correspond to the previously published one (Table. 3.6) [306], but confirms our conclusion about the preferred migration of the phthalimide group to a carbon atom having more electron-withdrawing substituents. Such a regioselectivity of the 1,2-shift can be explained by the fact that the nitrogen atom of the phthalimide group should acquire a negative charge stabilized by

two carbonyl groups during heterolytic breakage of the weakened N–N bond (evidence against the radical mechanism is discussed in [306]). Therefore, migration will go mainly to a more electron-deficient carbon atom, which we observed experimentally.

Attempts to carry out 1,3-dipolar cycloaddition reactions with aziridines **3.88c,d** and **3.91a,c** were unsuccessful: in the presence of such active "traps" as DMAD and *N*-phenylmaleimide, the formation of mixtures of imines and only trace amounts of possible adducts was observed. Thus, for such 2,3-diaryl-substituted aziridines, the process of isomerization into imines is more energetically advantageous than cycloaddition. In contrast, aziridine **3.64d**, obtained from cinnamonitrile and having only one aromatic substituent, although it can isomerize to imine **3.87d** (Scheme 3.38), easily gives adducts with dipolarophiles (Schemes 3.28, 3.30, 3.32). On the other hand, 2-acylaziridines **3.46i-k**, although they have two aromatic substituents, do not give imines, but turn into oxazoles **3.47-k** in *ca.* 70% yield (Section 3.3.1, Scheme 3.18).

Consequently, the presence of two vicinal aromatic substituents at aziridine carbon atoms is a necessary, but not the only sufficient factor for the dominant course of isomerization into imines among other possible thermal transformations. The final choice of the reaction pathway depends on the presence and nature of other substituents in the aziridine ring.

The mechanism of the discussed rearrangement has not been precisely established. For aziridines **3.88** and **3.91** with *trans*-orientation of aryl groups, the implementation of the flat configuration of the octet-stabilized dipole is complicated by large steric difficulties created by aromatic substituents and the phthalimide group, both in *W*- and *U*-form (Scheme 3.23). Therefore, in this case the migration of the phthalimide group likely takes place simultaneously with the C–C bond break. For aziridines **3.46i-k** (Scheme 3.18) having *cis*-located aryl substituents, the steric hindrance in azomethine ylide is still less, and, given the possibility of electrocyclization with the participation of a carbonyl group, the phthalimide group splits off leading to nitrile ylide, where spatial difficulties are minimal and closure to oxazole occurs.

In general, the isomerization of 2,3-diaryl-1-phthalimidoaziridines into imines is an inherent process and can significantly reduce the activity of such substrates in "useful" thermal transformations. It must be taken into account when planning synthetic schemes involving such compounds.

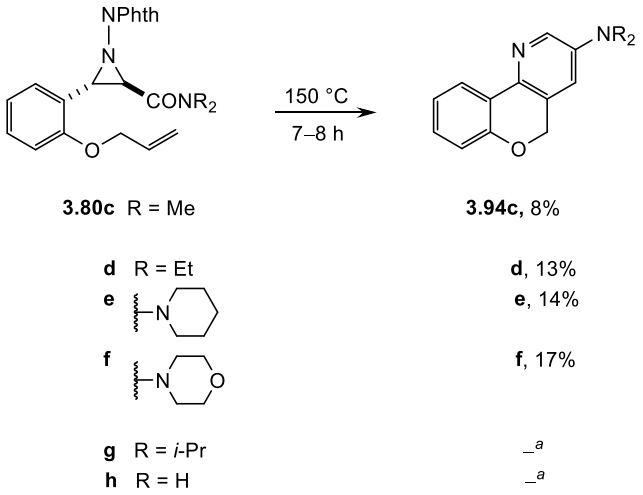
3.4.3.2. Formation of chromenopyridines

The content of the section is based on the papers [20, 309].

An unusual reaction was detected for aziridines **3.80c-h** with a dialkylamide group (Scheme 3.41). Unlike analogues with cyano and methoxycarbonyl groups **3.80a,b**, which gave

products of intramolecular cycloaddition to a double bond in the side chain (Section 3.4.2, Scheme 3.35), after heating of aziridines **3.80c-h**, the corresponding adducts were not obtained. Only 3-aminochromeno[4,3-*b*]pyridines **3.94** were isolated from complex reaction mixtures, although in low yields.

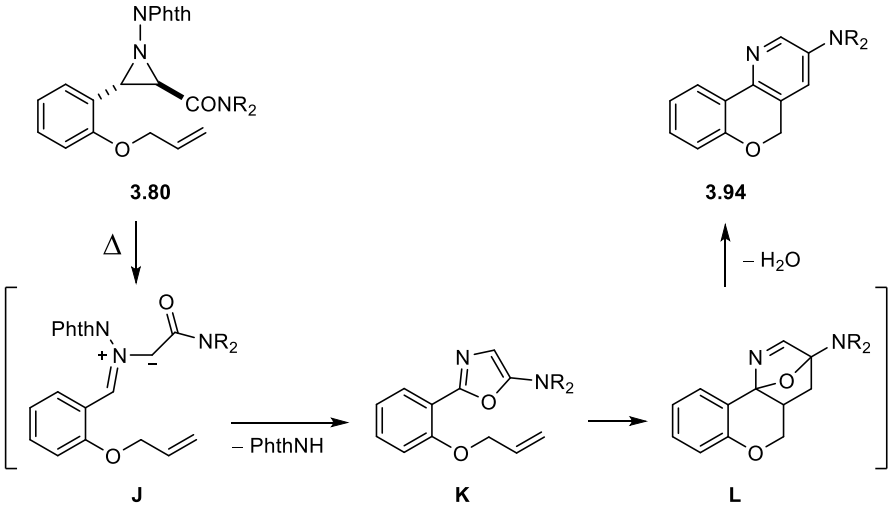
Scheme 3.41



[a] Mixture of unidentified products.

We assume the following sequence of their formation (Scheme 3.42). First, aziridine **3.80** is converted into 5-(dialkylamino)oxazole **K**, followed by an intramolecular Diels-Alder reaction between oxazole and the double bond of the allyl group [310], accompanied by the elimination of a water molecule from the intermediate **L**. The π-donor dialkylamino group, located at the end of the oxazole diene system, clearly facilitate its interaction with an inactive dipolarophile. Although the yield of the reaction is low, this transformation is interesting for its originality, especially since there are no other approaches to obtaining 3-aminochromeno[4,3-*b*]pyridines, according to the literature data.

Scheme 3.42



The formation of oxazole can also occur when heating similar aziridines with a propargyl fragment **3.82c-e** (Scheme 3.35), and the multiplicity of the bond in the side chain should not affect this in any way. Considering that this is an irreversible process, the ratio of reaction paths is determined at the step of the aziridine ring opening: either *N*-phthalimidoazomethine ylide of type **J** joins a multiple bond in the side chain and chromenopyrroline/pyrrol is formed, or its electrocyclization into oxazole occurs, which can then attack tto the same multiple bond. But for the propargyl substrates, despite the high activity of the C≡C bond as a dipolarophile, further formation of the pyridine ring is impossible, and the Diels-Alder adduct apparently decays, therefore we obtain only the adducts of the "usual" 1,3-dipolar cycloaddition **3.83** and **3.84**, but in low yields.

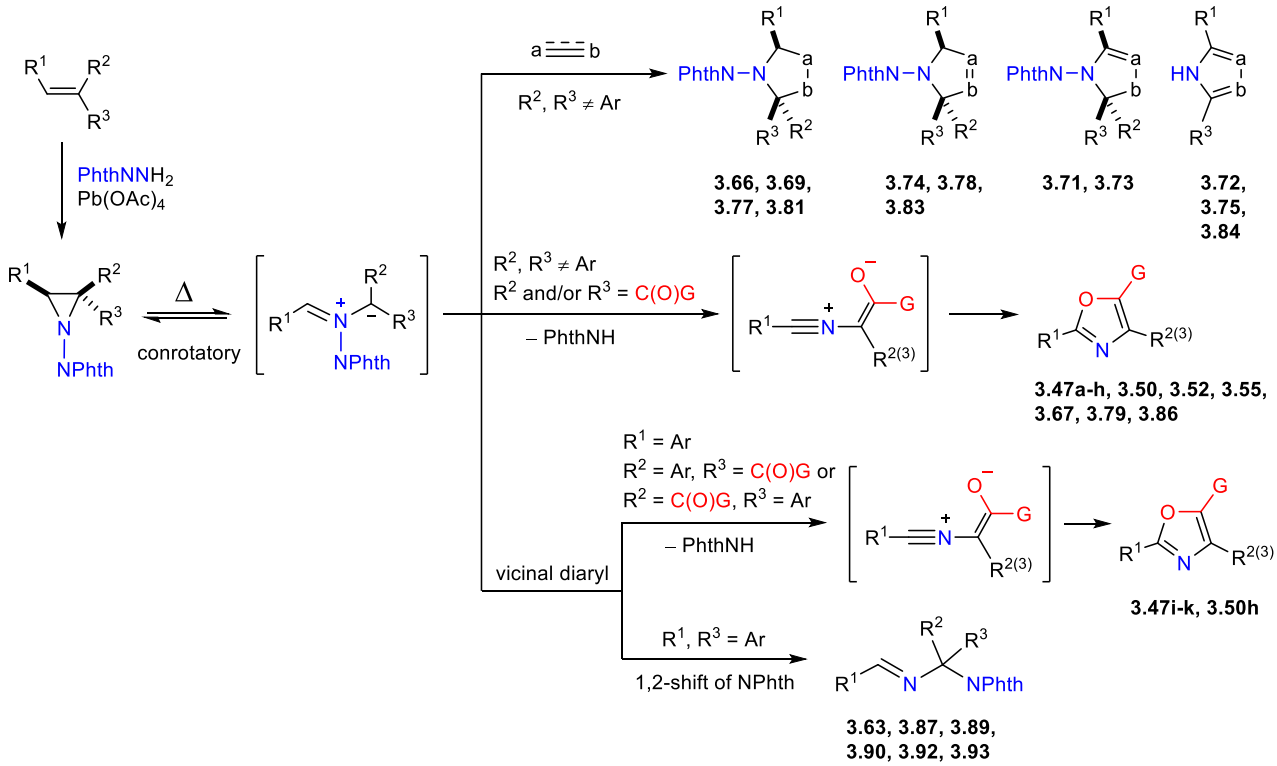
3.5. Conclusion

The results presented in this chapter demonstrate that the construction of *N*-phthalimidoaziridines based on conjugated enones and their analogues is a powerful tool for assembling a wide range of heterocyclic compounds: oxazoles, pyrrolidines, pyrrolines and pyrroles, including bi- and tricyclic ones, with certain substituents and configuration of stereocenters (Scheme 3.43). The proposed methods are characterized by simple implementation, lack of additional reagents and catalysts, good yields of target products.

In addition to the double carbon-carbon bond of substituted alkenes, even double bonds of five-membered aromatic heterocycles with a single heteroatom can be involved in the oxidative aminoaziridination. In vinylfurans, selective aziridination of the endocyclic double bond occurs, followed by rearrangement into monophthaloyl hydrazones of hexa-2,5-dien-1,4-dione. Aziridination of thiophene multiple bonds is possible only in the absence of exocyclic C=C bonds and leads to the formation of tricyclic bisaziridine, whereas in vinylthiophene derivatives the five-membered heterocycle remains unaffected.

Generation of azomethine ylides during the three–membered ring opening at the C-C bond is common to all thermal transformations of *N*-phthalimidoaziridines (Scheme 3.43). The ease of this process is determined by substituents at carbon atoms. An increase in their number favors the formation of azomethine ylides upon heating so much that some trisubstituted aziridines open already at room temperature. At the same time, heating up to 220 °C may be required to break the C–C bond in disubstituted aziridines. With an equal number of substituents, their electronic nature plays a crucial role, and the presence of a phthalimide group on the nitrogen atom causes a donor-acceptor (*push-pull*) effect – the generation of azomethine ylides proceeds under milder conditions if there are substituents of the opposite electronic nature at the carbon atoms: donor at one, acceptor at the other.

Scheme 3.43



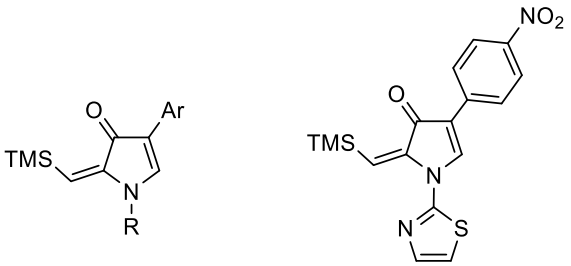
Further transformation of azomethine ylide also depends on the nature of substitution and can occur in three competing directions: 1,3-dipolar cycloaddition, 1,5-electrocyclization and rearrangement into imines (Scheme 3.43). Disubstituted *N*-phthalimidoaziridines are involved in 1,3-dipolar cycloaddition with inversion of the relative orientation of substituents, which corresponds to the conrotatory ring opening and the concerted addition of azomethine ylide to multiple bond of the dipolarophile, and in the intramolecular version, it is possible to use inactive multiple bonds. In case of low-active "traps" or in their absence, intramolecular processes, the rate of which is determined only by substituents of the aziridine, become preferable. Di- and trisubstituted aziridines with vicinal aromatic substituents are prone to rearrangement into imines with a selective 1,2-shift of the phthalimide group, sometimes even in the presence of active dipolarophiles. In the presence of a carbonyl group in the α-position to the aziridine carbon atom, 1,5-electrocyclization of azomethine ylide is realized. The phthalimide group on the nitrogen atom provides the possibility of aromatization of the five-membered ring due to elimination of the phthalimide molecule, resulting in the formation of oxazole. For trisubstituted 2-acylazyridines, the structure of which implies the inevitable spatial proximity of the reacting fragments, cyclization into oxazole becomes the dominant process. And even isomerization into imines of 2,3-diaryl-substituted aziridines is suppressed with the possibility of 1,5-electrocyclization.

In general, taking into account the simplicity, versatility and stereospecificity of *N*-phthalimidoaziridines preparation and the described features of their reactivity, a rational design of the structure of the initial enones is possible and allows for thermal transformations of aziridines in a given direction, thus realizing the targeted synthesis of functionalized heterocyclic compounds.

Chapter 4. Study of photophysical properties

This chapter presents the results of a study of the optical properties of some of the compounds obtained in the work. Due to the presence of a conjugate system that includes several (hetero)aromatic rings, including fused ones, most of our products exhibit fluorescence under a laboratory UV lamp (254/366 nm). For the most promising compounds, we recorded the absorption, emission, and excitation spectra in the UV region and estimated the quantum yield of fluorescence. This information can be useful in the search and development of structures with certain physical properties for further practical application.

4.1. Pyrrolones



1.19 **1.19fl**

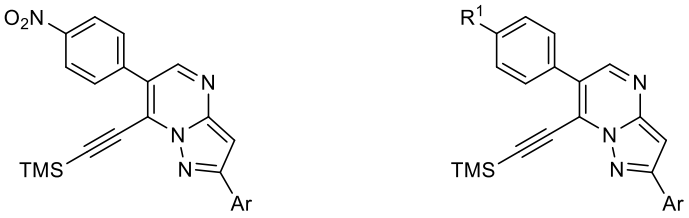
Φ_F = 0.06

Fig. 4.1. 4-Aryl-2-(trimethylsilylmethylidene)-1,2-dihydro-3*H*-pyrrol-3-ones

All pyrrolones **1.19** obtained in [13] (Schemes 1.8, 1.9, Section 1.4) are bright coloured crystalline compounds: from bright orange to dark red (Fig. 4.1). Two or three bands are present in their absorption spectra, and one of them (λ_{max}^{abs} = 432–479 nm, ε ≈·10^4·M^{-1}·cm^{-1}) is characteristic. The maximum wavelength of the emission band is ≈ 550 nm, the values of the Stokes shift lie in the range of ≈ 2700-5000 cm^{-1}. However, it turned out that only pyrrolones containing a *para*-nitrophenyl substituent at the C^4 atom of the pyrrole ring possess fluorescent properties, in other cases emission was either not observed or its intensity was negligible. This is a curious fact, because the nitro group is known as a fluorescence quenching substituent [311, 312].

The substituent at the pyrrolone nitrogen atom also has a strong effect, and the emission intensity increases in the alkyl < aryl < heteroaryl series, moreover, the presence of an electron–donating substituent in the aromatic ring reduces the intensity, and the acceptor one increases. The best result was obtained for pyrrolone **1.19fl** containing a 2-thiazole substituent: the fluorescence quantum yield is 6±1% (relative to the standard 9,10-diphenylanthracene [313]) (Fig. 4.1). Despite the low values, according to our information, this is the first example of fluorescent properties among 2-methylidenepyrrol-3-one derivatives.

4.2. Pyrazolo[1,5-*a*]pyrimidines

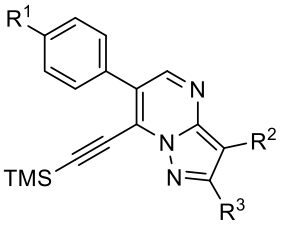


1.34a-d Ar = 4-$R^2C_6H_4$ **1.34e-t**

R^1, R^2 = H, Me, OMe, Cl

Fig. 4.2. 2,6-Diaryl-7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines

7-Ethynylpyrazolo[1,5-*a*]pyrimidines **1.34** are crystalline compounds having a color from bright yellow to beige (Schemes 1.18, 1.19, Section 1.7) [9]. In the absorption spectra of diaryl-substituted compounds (Fig. 4.2) two bands are observed: $\lambda_{max}^{abs} \approx 270$, 330 nm (**1.34a-d**) and $\lambda_{max}^{abs} \approx 290$, 360 nm (**1.34e-t**), which indicates a clear effect of the *para*-nitrophenyl substituent at the C^6 atom of the pyrazolopyrimidine ring on the hypsochromic shift of the absorption bands. Curiously, in the first case, both bands have comparable intensity ($\varepsilon \approx 2.9 \cdot 10^4$ and $1.7 \cdot 10^4$ $M^{-1} \cdot cm^{-1}$), whereas in the second case the shortwave band is noticeably stronger ($\varepsilon \approx 3.5 \cdot 10^4$ and $0.6 \cdot 10^4$ $M^{-1} \cdot cm^{-1}$).The positions of the emission maxima are quite close for all compounds – 500 nm (**1.34a-d**) and 490 nm (**1.34e-t**).



1.34ae-cj

	R^1	R^2	R^3	
ae	H	H	H	
ce	OMe	H	H	
af	H	H	3-FC_6H_4	
cf	OMe	H	3-FC_6H_4	
ag	H	CN	H	
cg	OMe	CN	H	
ah	H	CO_2Et	H	
ch	OMe	CO_2Et	H	
ai	H	Ph	Me	
ci	OMe	Ph	Me	
aj	H	CN	CH_2CN	
cj	OMe	CN	CH_2CN	Φ_F = 0.42

Fig. 4.3. 6-Aryl-7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines

All pyrazolopyrimidines **1.34ae-cj** (Fig. 4.3) have 2-4 bands in the absorption spectrum, except for compounds with 3-fluorophenyl substituent **1.34af** and **1.34cf**, which have only one weak shortwave band ($\lambda_{max}^{abs} \approx 242$ nm, $\varepsilon \approx 1.2 \cdot 10^4$ $M^{-1} \cdot cm^{-1}$). The least substituted compounds **1.34ae** and **1.34ce** also have very weak fluorescence. The spectral characteristics of the remaining pyrazolopyrimidines are quite close: $\lambda_{max}^{em} \approx 460$ nm, Stokes shift ≈ 6040 cm^{-1}. The

quantum yield of fluorescence of the compound **1.34cj** was estimated at 42% (the integrating sphere method).

4.3. Benzo[*f*]quinazolines

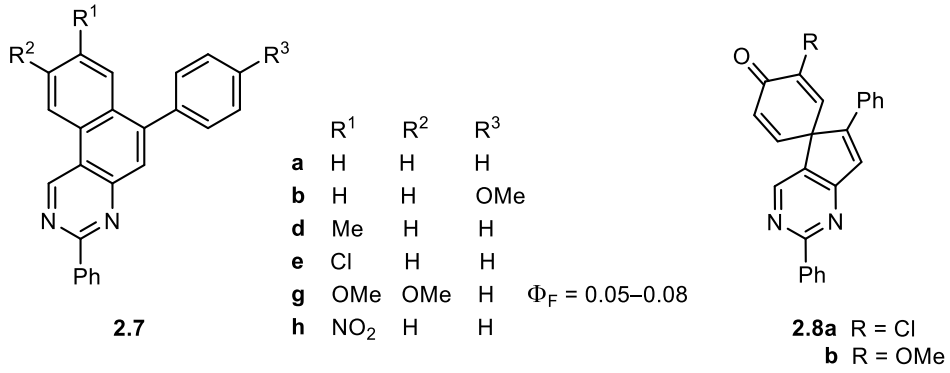


Fig. 4.4. 6-Aryl-3-phenylbenzo[*f*]quinazolines

The absorption maxima of benzo[*f*]quinazolines **2.7** (Scheme 2.5, Section 2.3) [8] are observed in the region of 288-304 nm ($\varepsilon \approx 5 \cdot 10^4$ $M^{-1} \cdot cm^{-1}$), and for spirocompounds **2.8** – $\lambda_{max}^{abs} \approx$ 277 nm ($\varepsilon \approx 3 \cdot 10^4$ $M^{-1} \cdot cm^{-1}$). The emission intensity of spirobicycles is lower, but the band maxima are in the longer wavelength range (λ_{max}^{em} = 409 nm (**2.8a**), 423 nm (**2.8b**)), than that of benzo[*f*]quinazolines **2.7** (λ_{max}^{em} = 373-413 nm), although even for the benzoquinazolines the Stokes shift is ≈ 8300 cm^{-1}. In this case, the nitro group in the benzene ring suppresses fluorescence almost completely, whereas the methoxy group increases the intensity of benzoquinazoline emission. Even for the most active dimethoxysubstituted benzoquinazoline **2.7**, the quantum yield of fluorescence turned out to be low: 8±1% (relative to the standard 9,10-diphenylanthracene [313]) and 5% (the integrating sphere method).

4.4. 2-Thiophenyloxazoles

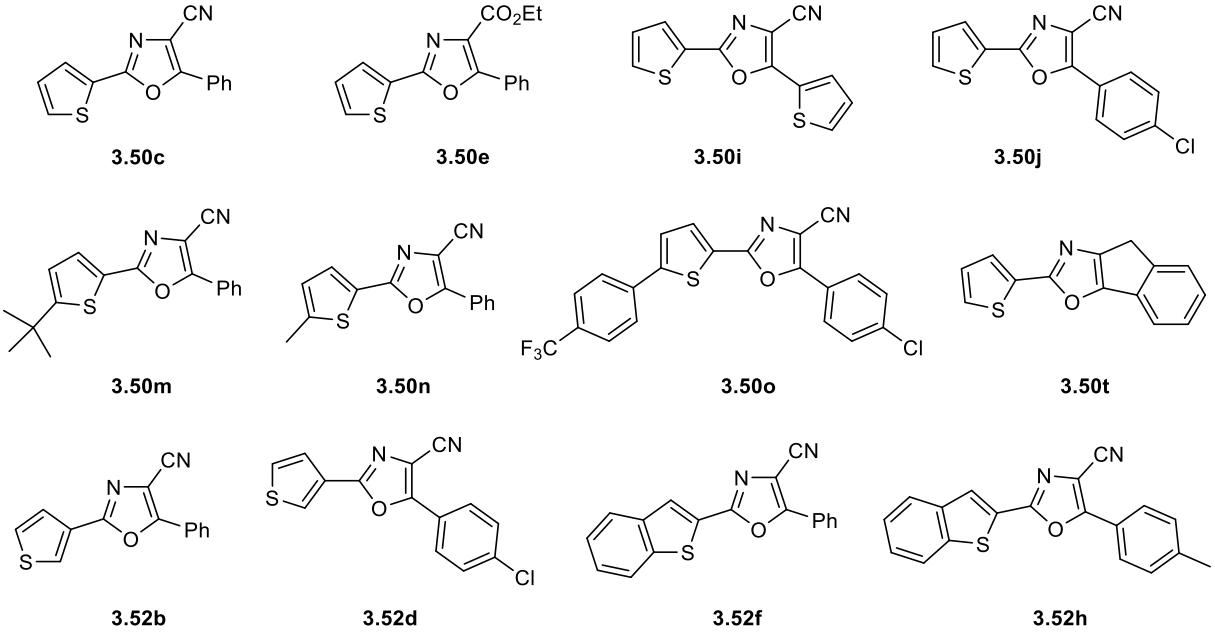


Fig. 4.5. 2-Thiophenyloxazoles

Table 4.1

Oxazol[a]	λ_{max}^{abs}, nm ($\varepsilon \cdot 10^{-4}$, $M^{-1} \cdot cm^{-1}$)	λ_{max}^{em}, nm	$\Delta\nu$, cm^{-1}	Φ_F[b]
3.50c	326 (1.47)	377	4150	0.84
3.50e	315 (2.02)	379	5361	0.71
3.50i	347 (1.48)	401	3881	0.71
3.50j	335 (1.74)	383	3741	0.46
3.50m	336 (1.51)	388	3989	0.46
3.50n	336 (1.48)	386	3855	0.38
3.50o	358 (2.41)	423	4292	0.47
3.50t	344 (2.07)	409	4620	0.03
3.52b	310 (1.47)	361	4557	0.52
3.52d	320 (1.84)	368	4076	0.54
3.52f	340 (2.04)	388	3639	0.39
3.52h	344 (2.91)	393	3624	0.24

[a] For $1 \cdot 10^{-5}$ M solutions in CH_2Cl_2.
[b] Quantum yields are estimated by the integrating sphere method.

Absorption, excitation and emission spectra were recorded for all thiophenyloxazoles **3.50** and **3.52** obtained in [2] (Schemes 3.19, 3.20, Section 3.3.2), and fluorescence quantum yields were estimated for 12 the most active compounds (Fig. 4.5, Table 4.1). The maxima of the

absorption bands lie in the region of 310-358 nm, the emission – 361-423 nm, and as a result, the values of the Stokes shift are 3624-5361 cm^{-1} ($\Delta\lambda$ = 48-65 nm). The alkyl substituent at the C^5 atom of the thiophene ring causes a bathochromic shift of the emission band by 9-11 nm (*cf.* **3.50c** and **3.50m,n**, Table. 4.1), whereas the replacement of the cyano group with an ester group has practically no effect (*cf.* **3.50c** and **3.50e**, Table 4.1). The expansion of the conjugation system in benzothiophene derivatives gives a bathochromic shift (*cf.* **3.50c** and **3.52f**, Table 4.1), and for thiophen-3-yl derivatives the opposite effect is observed relative to thiophen-2-yl analogues (*cf.* **3.52b** and **3.50c**, **3.52d** and **3.50j**, Table 4.1). The fluorescence quantum yields of thiophenyloxazoles are quite high: 24-84% with the exception of compound **3.50t** (Φ_F = 3%), the highest value for oxazole **3.50c**. The relatively high values of the Stokes shift and the quantum yield of fluorescence make thiophenyloxazoles attractive substrates for the construction of fluorescent materials and practical applications in various fields.

Conclusions

1. A new type of cross-conjugated enynones – 2-aryl-5-(trimethylsilyl)-1-ethoxypent-1-en-4-yn-3-ones – can be successfully used for the selective construction of functionalized five- and six-membered nitrogen heterocycles. The polyelectrophilic nature of enynones allows them to react with various nitrogen-containing mono- and binucleophiles. The structural features of such enynones: the ethoxy group at the β-carbon atom of the double bond and the trimethylsilyl group at the β-carbon atom of the triple bond provide high chemoselectivity of interaction with nucleophiles, and, as a rule, the triple bond remains unaffected, resulting in the formation of ethynyl-substituted heterocyclic compounds. In the case of mononucleophiles (amines), the cyclization of the initially formed aminoenynones proceeds only on the α-carbon atom of the triple bond, leading to the formation of 2-methylidenepyrrolones.

2. Cyclization of *ortho*-aryl(ethynyl)heterocycles is an effective way to synthesize polyfused heterocyclic compounds. The type of substituent at a triple bond determines the choice of the optimal catalytic system: for terminal or trimethylsilyl-substituted ethynylheterocycles, it is appropriate to use platinum(II) chloride catalysis, whereas for (arylethynyl)-substituted ones – electrophilic activation by strong acids. The substituent in the aryl fragment of the substrate sets the direction of cyclization under electrophilic conditions: for alkoxy- and halogeno-substituted compounds, *ipso*-cyclization with the formation of spirocyclic products is possible. The direction of cyclization and activity of *ortho*-aryl(ethynyl)heterocycle as a whole depends on the type of heterocyclic core, more precisely on the relative position of the main fragments in it: the heteroatom(s), aryl and ethynyl substituents.

3. Oxidative aminoaziridination of conjugated enones and their derivatives provides an effective tool for constructing heterocyclic structures by thermal transformations of *N*-phthalimidoaziridines. Heating of 2-acyl-substituted *N*-phthalimidoaziridines can be used as a synthetic approach to oxazoles. The inter- and intramolecular 1,3-dipolar cycloaddition of *N*-phthalimidoaziridines to multiple carbon-carbon bonds can serve as a method for the synthesis of monocyclic and polycyclic fused and spirolinked nitrogen heterocycles of determined spatial structure.

4. The general and rate determining step of the reactions of *N*-phthalimidoaziridines upon heating is the opening of a three-membered ring on C-C bond into azomethine ylide, proceeding in accordance with the rules for orbital symmetry preservation. The generation of *N*-phthalimidoazomethine ylides is facilitated by increasing the number of substituents in the

aziridine ring capable of stabilizing the 1,3-dipole, and by combining substituents of various electronic nature at neighboring carbon atoms (*push-pull* effect). The direction of transformation of azomethine ylides is determined by the nature of substituents at carbon atoms and the presence of the potentially leaving phthalimide group on the nitrogen atom – 1,5-dipolar electrocyclization into oxazoles for acyl-substituted aziridines, isomerization into imines for *C,C*-diaryl-substituted aziridines and 1,3-dipolar cycloaddition in the presence of suitable dipolarophiles.

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