PAPER

Progress in the chemistry of nitrogen-, oxygen- and sulfur-containing heterocyclic systems

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The review is devoted to modern trends in the chemistry of nitrogen-, oxygen- and sulfur-containing monocyclic, polynuclear and benzo(hetero)annulated heterocyclic compounds. Methods for the synthesis and chemical reactivity of furazan, furoxan, thiazole, thiadiazole, dithiazole, thiophene, glycoluril, imidazotriazine, diaziridine and other heterocycles are discussed. Characteristic features of reactions depending on the structure of the starting compounds, intermediates and reaction medium (organic solvents, ionic liquids) and mechanistic aspects of the most interesting transformations are considered. Data on the biological activities and prospects for practical applications of the indicated heterocyclic systems are presented. The bibliography includes 383 references.

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1. Introduction

The chemistry of heterocyclic compounds is an important field of modern organic chemistry. Heterocyclic compounds widely occur in living nature and play a key role in the metabolism of living organisms. For example, pyrimidine and purine bases are parts of nucleic acids; many amino acids contain heterocyclic moieties (proline, histidine, tryptophan); a heterocyclic core is present in chlorophyll and haemoglobin, some hormones (serotonin, histamine), vitamins (B_{12}, group vitamins E), *etc*. Heterocyclic compounds play an important role in medicinal chemistry: they form the basis of most pharmaceuticals, including natural products, *e.g.*, antibiotics (penicillin and cephalosporin) or

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alkaloids (morphine and reserpine). However, a large portion of widely used medications are synthetic derivatives of various heterocycles, first of all, this refers to anticancer, analeptical, analgesic or cardiovascular drugs. Many pesticides, herbicides and insecticides are also based on heterocycles.

Heterocyclic compounds are equally important in various areas of applied chemistry. Indeed, they are parts of dyes, photosensitive materials, antioxidants, rubber vulcanizing agents, *etc*. Heterocycles are utilized as precursors or intermediates in the synthesis of a broad range of functional derivatives and acyclic products.

Studies of the methods of synthesis and the reactivity of heterocyclic compounds has been a key research area of the N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences (ZIOC RAS) throughout the period of its existence. The first laboratory of heterocyclic compounds was organized at the Institute in 1938 on the basis of Laboratory for Analysis and Synthesis (LASYN) of Plant and Animal Products at the Commission for Studying Natural Productive Forces at the USSR Academy of Sciences, which was founded in 1922 by A.E.Chichibabin, an outstanding Russian chemist, the initiator of pyridine chemistry. Professor Ya.L.Goldfarb, who also was a research employee of this Laboratory, together with other researchers, moved in 1938 to ZIOC RAS where he worked throughout the rest of his life up to 1985 (since 1946 he headed the laboratory, which was named the Laboratory of Heterocyclic Compounds). Initially, the research carried out at the Laboratory was focused on the chemistry of pyridine derivatives,[1–3] some of which were found to be analeptics, anaesthetics, antihelminthics, *etc*. However, the reputation of Ya.L.Goldfarb and his colleagues was mainly due to their studies in thiophene chemistry.[4–8] This area of chemistry was of particular interest for the country accommodating abundant raw materials (sour crude oils) for the production of thiophene, its homologues and fused systems containing a thiophene ring.

In 1962, the Department of Organic Synthesis (DOS), with Doctor of Chemical Sciences S.S.Novikov (since 1974, Corresponding Member of the USSR Academy of Sciences) at the head, was founded at the ZIOC RAS; the main goal of the Department was to perform research in the chemistry of energetic compounds, first of all, nitro compounds. The first studies of this Department were devoted to nitroaromatic compounds (hexanitrobenzene, nonanitromesitylene). In a short while (1968 – 1969), S.S.Novikov proposed the program 'Chemistry of Polynitrogen Compounds' and since then, new-generation energetic compounds have been mainly developed on the basis of polynitrogen and nitrogen – oxygen heterocycles (pyrazoles, triazoles, tetrazoles, furazans, furoxans) in various combinations. Switching to energetic compounds based on heterocycles was caused by their high enthalpy of formation and higher density compared with aromatic compounds and also more environmentally benign combustion products, as nitrogen is formed

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Translation: Z.P.Svitanko

as a major product instead of carbon monoxide or dioxide. This line of research was supervised by Academician V.A.Tartakovsky and Professors A.A.Fainzil'berg, L.I.Khmel'nitskii, S.A.Shevelev and O.A.Luk'yanov. Combinations of these heterocycles with explosophoric groups (nitro, nitramino, azido, azo and azoxy groups) resulted in the synthesis of unique highly energetic structures. The results of these studies, which were ahead of similar studies abroad, were recently summarized in dedicated reviews.[9, 10]

However, in the mid-1980s, it became evident that the research cannot be confined to only fundamental studies of thiophene chemistry or synthesis of only energetic structures and that it is necessary to pursue other practical goals, in the framework of which fundamental studies could also be developed. Therefore, new research trends appeared on the basis of synthesis of key heterocycles. In particular, apart from the synthesis of furazan- and furoxan-derived energetic compounds, researchers of the Laboratory of Nitrogen-Containing Compounds headed by Prof. L.I.Khmel'nitskii (since 1995, by Professor N.N.Makhova) paid considerable attention to the preparation of pharmacologically oriented hybrid structures combining an NO donor furoxan ring and a pharmacophoric heterocycle. Simultaneously, they developed the chemistry of saturated heterocycles — glycolurils and diaziridines — as neurotropically active compounds. In addition, a separate research division called the Laboratory of Polysulfur Nitrogen Heterocycles (headed by Professor O.A.Rakitin) was separated from this Laboratory in 1995; the new division was mainly concerned with the chemistry of sulfur-and-nitrogen heterocycles as potential structures for pharmaceutics and agrochemistry and materials with magnetic properties and electrical conductivity for electronics. In the early period, these studies were carried out in cooperation with Prof. Ch. Rees (Imperial College London, UK). In recent years, the Laboratory of Nitro Aromatic Compounds (headed by Prof. S.A.Shevelev and since 2014 by Dr. Sci. I.L.Dalinger) has pursued a new line of research, namely, the synthesis of fused polyheterocyclic structures as potential pharmacologically active compounds. These products are prepared from available precursors such as trinitrotoluene (the studies were a part of the Arms Conversion Programme), nitro benzofuroxan derivatives or other benzannulated heterocycles (superelectrophiles). The researchers of the Laboratory of Heterocyclic Compounds (headed by Prof. Ya.L.Gol'dfarb, since 1985 by Prof. M.M.Krayushkin) have concentrated on the synthesis of photoactive and biologically active compounds, addressing, first of all, thiophene derivatives and other sulfur-containing molecules. The search for biologically active compounds was mainly based on the preparation of organosulfur derivatives of oxalic acid — monothiooxamides, oxamic acid hydrazides, *etc*. Data about these compounds were presented in recent publications and patents.[11 – 16] Lately, the attention has been focused on photocyclization processes as convenient, environmentally benign methods for the design of fused arenes and heterocycles and on the search for photoactive compounds, which are of interest as optical data storage elements.

This review presents analysis of the modern trends in development of the chemistry of nitrogen-, oxygen- and sulfur-containing monocyclic, polynuclear and benzo(hetero)-annulated heterocyclic compounds derived from furazan, furoxan, thiazole, thiadiazole, dithiazole, thiophene, glycoluril, diaziridine and other heterocycles.

The following abbreviations are used:
Anthr — 9-anthryl
bmim — 1-n-butyl-3-methylimidazolium,
Boc — *tert*-butyloxycarbonyl,
CAN — cerium ammonium nitrate,
CDI — carbonyl-1,1′-diimidazole,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
DAC — donor – acceptor cyclopropanes,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCC — dicyclohexylcarbodiimide,
DCM — dichloromethane,
DEAD — diethyl acetylenedicarboxylate,
DHI — 4,5-dihydroxyimidazolidin-2-one,
DHIT — 4,5-dihydroxyimidazolidin-2-thione,
DIPEA — diisopropylethylamine (Hünig's base),
DMAD — dimethyl acetylenedicarboxylate,
DMAP — 4-dimethylaminopyridine,
DME — dimethoxyethane (glyme),
dr — diastereomeric ratio,
emim — 1-ethyl-3-methylimidazolium,
EWG — electron withdrawing group,
Fc — ferrocenyl,
FRET — fluorescence resonance energy transfer,
Fu — furyl,
GED — gas-phase electron diffraction
HASA — hydroxylamine-*O*-sulfonic acid,
IL — ionic liquid,
Ind — indol-3-yl,
LA — Lewis acid,
LDA — lithium diisopropylamide,
LP — lone pair,
m-CPBA — *m*-chloroperoxybenzoic acid,
MS — molecular sieves,
Naph — naphthyl,
NCS — *N*-chlorosuccinimide,
NMP — *N*-methylpyrrolidone,
Nu — nucleophile,
PMP — *p*-methoxyphenyl,
Py — pyridyl,
rt — room temperature,
TEA — triethylamine,
Tf — trifluoromethanesulfonyl (triflyl),
TFA — trifluoroacetic acid,
TFAA — trifluoroacetic anhydride,
Th — thienyl,
TMS — trimethylsilyl,
TNT — 2,4,6-trinitrotoluene,
Ts — *p*-toluenesulfonyl (tosyl).

2. New synthetic strategies and reactivity of nitrogen- and oxygen-containing heterocycles

2.1. New trends in the chemistry of 1,2,5-oxadiazoles

In recent years, derivatives of 1,2,5-oxadiazoles (furazans) and their N-oxides (furoxans) have attracted particular attention because of their potential applicability in the so-called dual-use technologies: as pharmacologically active compounds and as components of energetic formulations. Compounds incorporating a furazan ring are promising antimicrobial[17] and antiproliferative agents.[18, 19] Furoxan derivatives are nitric oxide donors, which determines the broad spectrum of their pharmacological activities as vasodilating, antiplatelet, antiparasitic and antitumor agents.[20] On the other hand, furazans and furoxans contain reactive oxygen atoms and have positive enthalpies of formation; in

combination with high density, this makes these compounds suitable for the synthesis of quite a few highly energetic materials for various purposes.[21,22] Recent reviews give a systematic account of the chemical properties and practical applications of 1,2,5-oxadiazoles. Among them are publications covering approaches to the preparation of non-annulated heterocyclic systems incorporating the 1,2,5-oxadiazole ring,[23] methods for the targeted synthesis and functionalization of furoxans[24] and the main classes of NO donor prodrugs based on furoxans.[25,26] The present Section summarizes the most recent results concerning some aspects of the design of energetic materials and pharmacologically oriented compounds based on 1,2,5-oxadiazoles and describes new synthetic strategies developed for the synthesis and transformations of these heterocyclic systems.

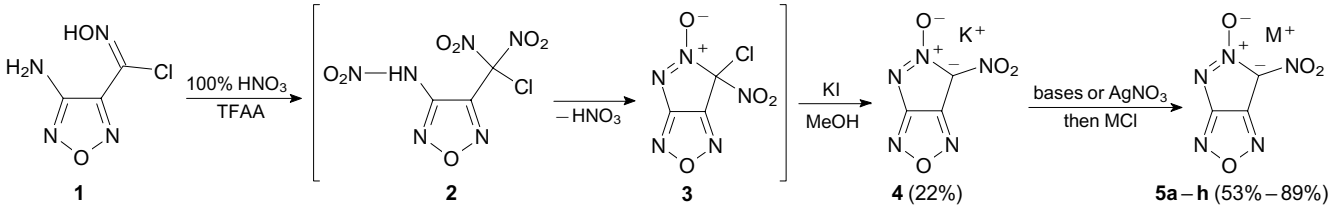
Recently, an unusual transformation of 4-amino-*N*-hydroxyfurazan-3-carbimidoyl chloride (**1**) under nitration conditions was discovered. On treatment with concentrated nitric acid in the presence of trifluoroacetic anhydride (TFAA), simultaneous nitration of the amino and oxime groups of the starting chloro oxime **1** takes place. The resulting nitramine **2** undergoes (one-pot) intramolecular cyclization to give bicyclic pyrazolo[3,4-*c*]furazan 5-oxide **3**, in which the C–Cl bond is reduced with KI to afford high-energy potassium salt **4** (Scheme 1). The subsequent replacement of the potassium cation by various polynitrogen cations opens up the way to a series of energetic organic salts **5a**–**h** possessing a moderate sensitivity to mechanical impact and excellent detonation performance comparable with those of RDX and HMX.[27]

The replacement of two chlorine atoms in the bicyclic furazano[3,4-*b*]pyrazine system **6** under the action of (dinitrofluoromethyl)- and (trinitromethyl)tetrazolium salts **7a**,**b** in an ionic liquid, 1-n-butyl-3-methylpyrrolidinium triflylamide ([bmpyrr]NTf_2), serves as an environmentally benign route to high-energy tetracyclic systems **8a**,**b** — potential low-sensitive components of various energetic formulations. The reaction mechanism includes the initial formation of ditetrazole derivatives **9a**,**b**, which undergo fast elimination of molecular nitrogen from both tetrazole rings to generate dinitrilimines **10a**,**b**. Cyclization of the latter furnishes the final furazano[3,4-*e*]di(1,2,4-triazolo)[4,3-*a*:3′,4′-*c*]pyrazines **8a**,**b** (Scheme 2).[28] The furazano[3,4-*b*]pyrazine moiety is a building block for the design of a variety of energetic materials.[29,30]

The proneness of a tetrazole ring attached to the electron-withdrawing furazan moiety to cycloreversion was used as a key step of the synthesis of bicyclic 4*H*-furazano[3,4-*e*]-1,3,4-oxadiazine system **11**. Nitrofurazan **12** reacts with the sodium salt of phenyltetrazole **13** with intermediate formation of tetrazolylfurazan **14**, which releases a nitrogen molecule, thus generating nitrilimine **15**. Intermediate **15** reacts with a second molecule of the starting nitrofurazan **12** to be converted to carbocation **16**, in which one nitro group undergoes the nitro–nitrite rearrangement. The final step comprises oxadiazine ring closure in intermediate **17** with simultaneous elimination of an NOF molecule, which affords the target product **11** (Scheme 3).[31]

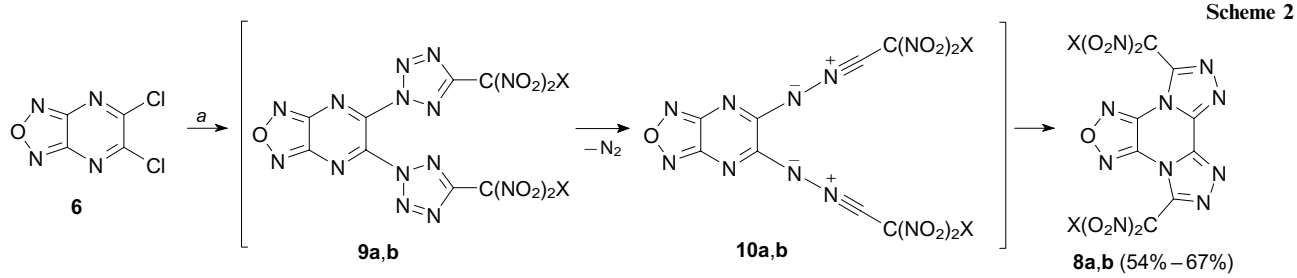
Among the synthetic routes to energetic compounds based on 1,2,5-oxadiazoles, mention should be made of the recently developed approaches to high-energy tetrazolylfuroxan salts **18a**–**h** containing explosophoric azide and azo groups.[32,33] The synthesis is based on [3 + 2]-cycloaddition of the azide anion to readily accessible cyanofuroxans **19a**,**b** followed by double metathesis of ammonium cations and various polynitrogen cations (Scheme 4). It is noteworthy that, regarding the set of physicochemical characteristics and calculated detonation parameters, the synthesized ammonium salts **18a**,**b** can be considered as an environmentally friendly alternative to the initiating explosives

Scheme 1



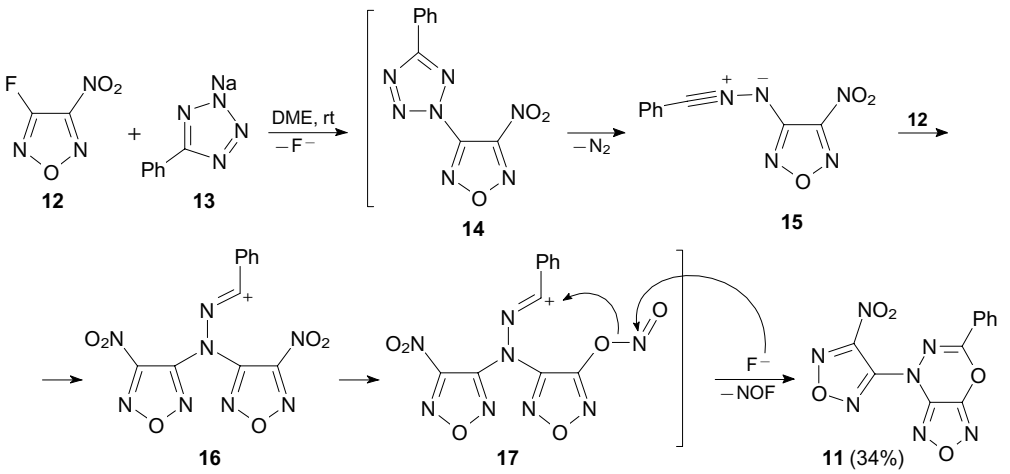
5: M^+ = NH_4 (**a**), NH_3OH (**b**), (**c**), (**d**), (**e**), (**f**), (**g**), (**h**)

Scheme 2



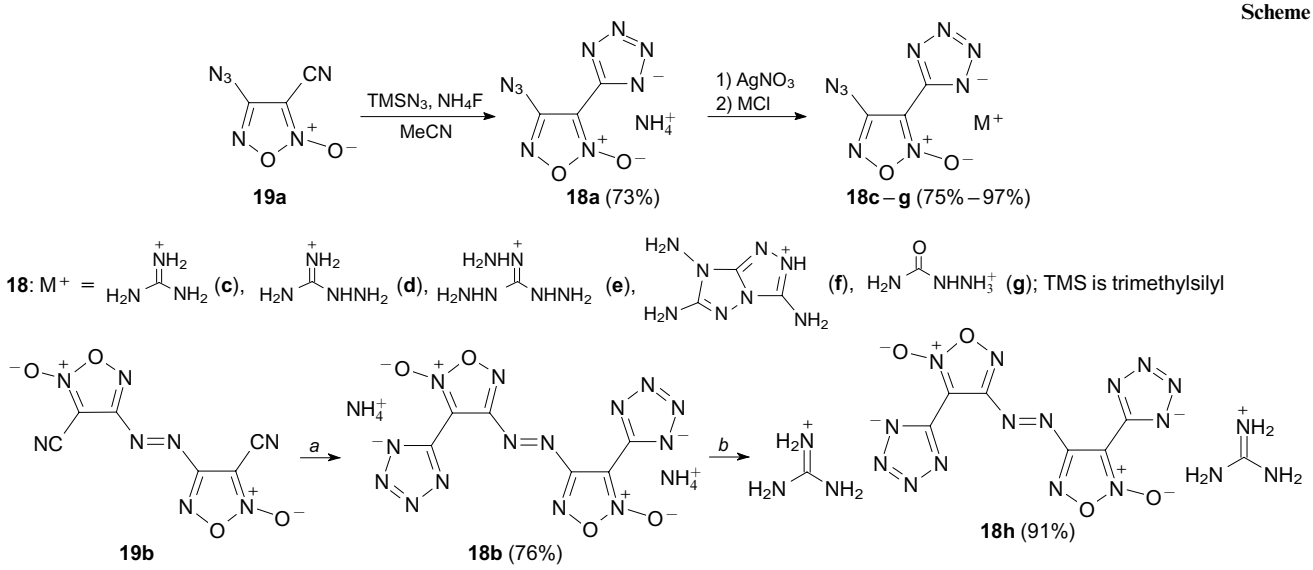
(*a*) M^+ $C(NO_2)_2X$ (**7a**,**b**), [bmpyrr]NTf_2, 40 °C; M = Na, X = F (**a**); M = Bu^n_4N, X = NO_2 (**b**)

Scheme 3



DME is dimethoxyethane (glyme), rt is room temperature

Scheme 4



(*a*) $TMSN_3$, NH_4F, MeCN; (*b*) 1) $AgNO_3$, 2) MCl

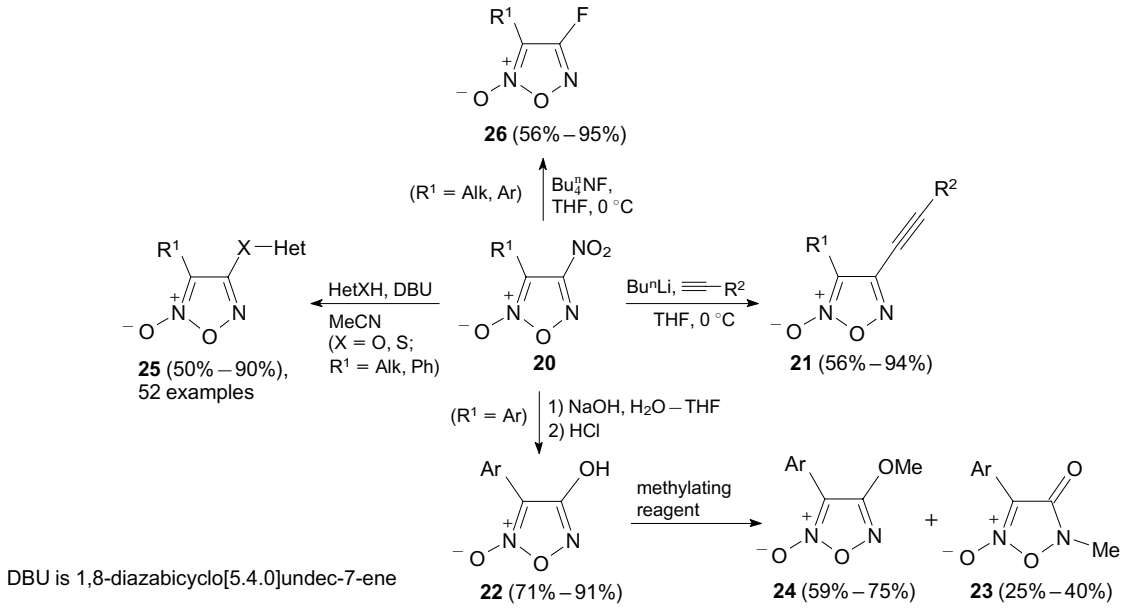
based on lead compounds, whereas guanidinium salts **18c**,**h** possess very low sensitivity to mechanical impact, which enables their use as energetic compounds.[33]

The key methods for the synthesis of nitrofurazans and nitrofuroxans[34 – 39] including (nitropyrazolyl)furazans[40 – 42] as promising components of energetic formulations are summarized in a recent review.[10] Therefore, below we consider the modern aspects of application of nitro-1,2,5-oxadiazole only for the preparation of pharmacologically active compounds.

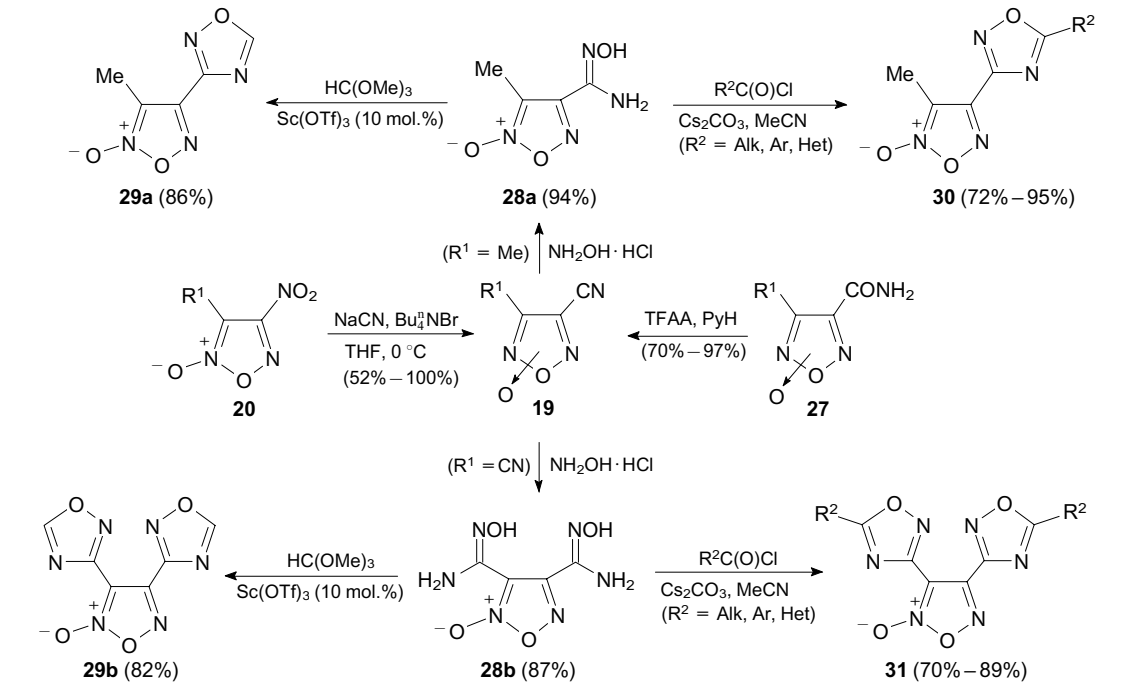
Owing to the strong electron-withdrawing nature of the 1,2,5-oxadiazole ring, the nitro group in nitrofurazans and nitrofuroxans tends to undergo nucleophilic substitution on treatment with various nucleophiles.[43] In particular, the nitro group in nitrofuroxans **20** is displaced under mild conditions with fluoride,[44] hydroxyl,[45] hetaryloxy and hetarylsulfanyl anions.[46, 47] Recently, a series of alkynylfuroxans **21** were synthesized using this approach, representing a rather rare case where the C – C bond is formed directly to the furoxan ring.[48] In addition, the proneness of the furoxan ring to prototropic tautomerism was detected for the first time in the methylation reaction of hydroxyfuroxans **22**. This reaction gave rise to a new heterocyclic system — 3-aryl-5-methyl-1,2,5-oxadiazol-4(5*H*)-one 2-oxide **23** (formed apart from the major product **24**). The reactions of nitrofuroxans **20** with heterocyclic alcohols and their thio analogues produce compounds **25** (Scheme 5).[45] 4-Fluorofuroxans **26** obtained by substitution of the nitro group are photoinduced NO donors, promising as potential pharmacologically active prodrugs.[44, 49]

The nitro group of 4-nitrofuroxans **20** can also be substituted on treatment with cyanide anion to give the corresponding furoxancarbonitriles **19** (Scheme 6).[50] This approach can serve for the synthesis of 3-aryl-4-cyanofuroxans in high yields. Meanwhile, the method based on dehydration of accessible furoxancarboxamides **27** proved to be more appropriate for the synthesis of cyanofuroxans with various functional groups.[32] Cyanofuroxans are valuable substrates for the design of diverse hetarylfuroxans. In particular, the addition of hydroxylamine to the nitrile group of cyanofuroxans followed by cyclocondensation of amidoximes **28** thus formed with ortho esters or carboxylic

Scheme 5



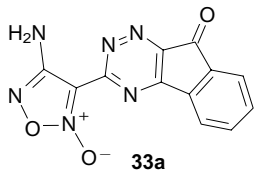
Scheme 6



acid chlorides opens up the route to an extensive series of (1,2,4-oxadiazolyl)furoxans **29**–**31** (see Scheme 6).[51] Bis(1,2,4-oxadiazolyl)furoxan **29b** is a typical example of implementing a dual-use technology. This compound has high cytotoxic activity against some tumour cell lines, on the one hand,[52] and is considered as a promising ingredient of eutectic melt-castable explosives instead of TNT, on the other hand.[53]

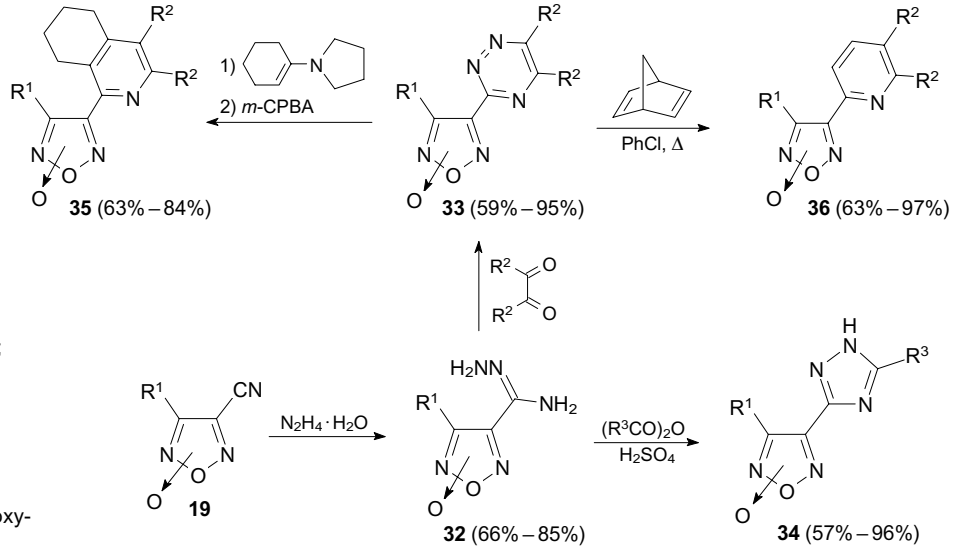
The addition of hydrazine to the nitrile group of cyanofuroxans **19** smoothly proceeds to give amidrazones **32**, which condense with α-dicarbonyl compounds and carboxylic acid anhydrides to yield (1,2,4-triazinyl)- (Ref. 54) and (1,2,4-triazolyl)furoxans[55] **33** and **34**, respectively. Owing to the strong electron-withdrawing effect of the furoxan ring, (1,2,4-triazinyl)furoxans **33** undergo a hetero- and retro-Diels–Alder reaction sequence with 1-(pyrrolidino)cyclohexene and norbornadiene to give tetrahydroisoquinolines **35** and pyridines **36** (Scheme 7).[54] It was also found that 4-amino-3-(indenotriazin-3-yl)furoxan (**33a**) is a promising apoptosis-inducing agent against chronic myeloid leukaemia K562 cells.[52]

Structure 33a



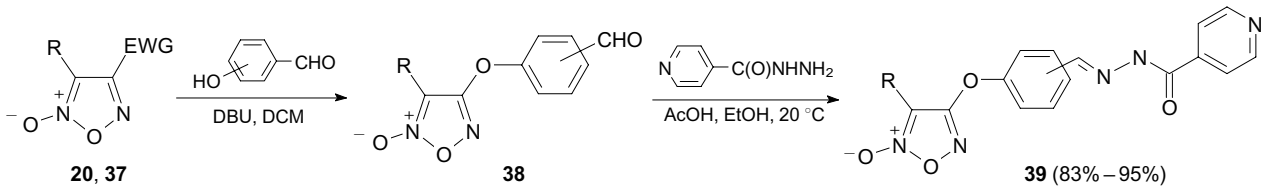
33a

Scheme 7



R^1 = 3-Me, 4-Ph, 4-NH_2;
R^2 = H, Ph, 2-Py;
$R^2 – R^2$ = ;
R^3 = Me, CF_3;
m-CPBA is *m*-chloroperoxybenzoic acid

Scheme 8



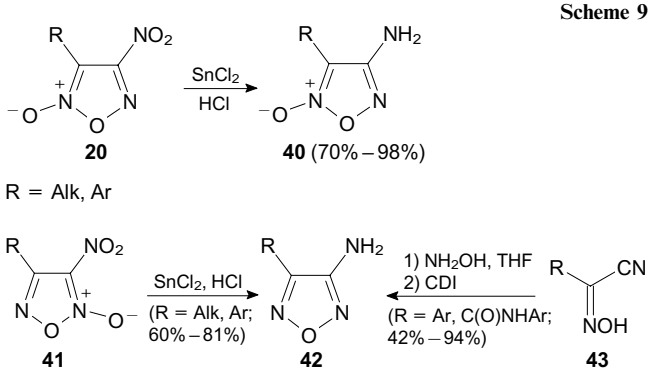
R = Me, Ph, SO_2Ph; EWG = NO_2 (**20**), SO_2Ph (**37**); EWG is electron withdrawing group, DCM is dichloromethane

Nucleophilic substitution reaction of the nitro or phenylsulfonyl group of furoxan functional derivatives **20** and **37** on treatment with isomeric hydroxybenzaldehydes furnished aryloxyfuroxans **38** (Scheme 8). The condensation of compounds **38** at the aldehyde group with isonicotinic acid hydrazide resulted in the formation of hydrazones **39**, which exhibit high antituberculosis activity.[56]

Recently, it was shown that the nitro group of 4-nitrofuroxans **20** can be chemoselectively reduced with $SnCl_2$ in concentrated hydrochloric acid, which affords 4-aminofuroxans **40**. The reaction proceeds under mild conditions to give 3-alkyl- and 3-aryl-4-aminofuroxans in high yields. It is noteworthy that reduction of 3-nitro isomers **41** under analogous conditions affects the N-oxide moiety of the ring and selectively leads to aminofurazans **42** (Scheme 9).[57, 58] Recently, a convenient method was developed for the synthesis of aminofurazans **42** based on the one-pot tandem reaction comprising the addition of hydroxylamine to cyanoximes **43** and the subsequent dehydration of the intermediate aminoglyoximes with carbonyl-1,1′-diimidazole (CDI) under mild conditions.[59]

Aminofurazans **42** and aminofuroxans **40** are weakly basic amines because of the strong electron-withdrawing effect of the 1,2,5-oxadiazole ring; this markedly restricts the synthetic potential of these compounds. In particular, diazotization of amino-1,2,5-oxadiazoles is usually conducted with nitrosylsulfuric acid in a mixture of concentrated sulfuric and phosphoric acids.[60] However, recently a conceptually new method was developed for diazotization of aminofurazans **42** and aminofuroxans **40** under very mild conditions on treatment with $NOBF_4$ in trifluoroacetic acid

Scheme 9

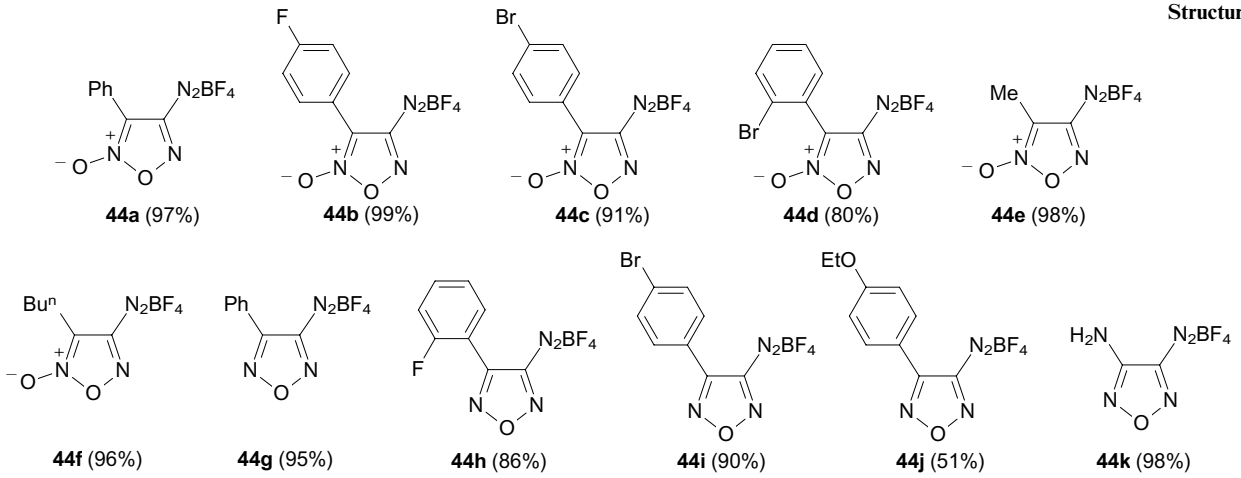


R = Alk, Ar

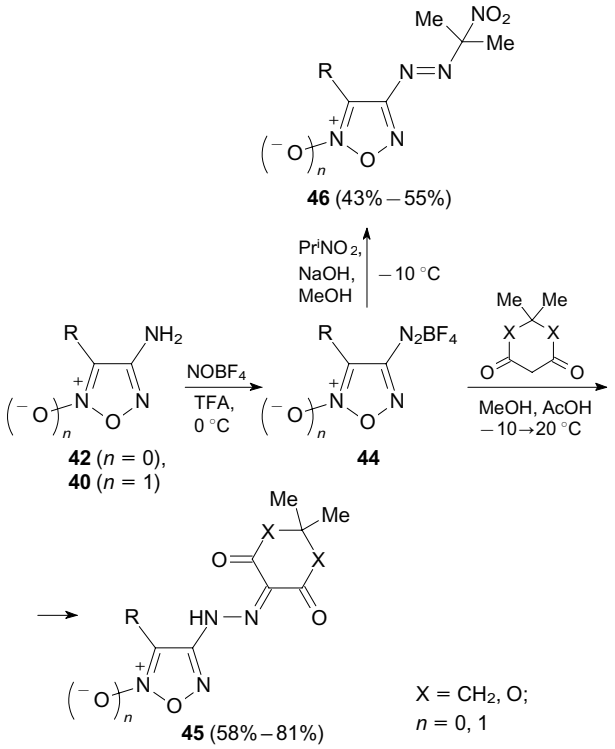
(TFA). A considerable benefit of this approach is the possibility to isolate the corresponding furazanyl- and furoxanyldiazonium salts **44a** – **k** in a pure state in high yields. Subsequently, a series of hydrazones **45** and azo compounds **46** were prepared by azo coupling of salts **44** with methylene active compounds (Scheme 10).[61]

Despite the low basicity, aminofuroxans can be oxidized to azofuroxans **47** under relatively mild conditions. In particular, a recent environmentally friendly method for the synthesis of azo compounds **47** includes oxidation of aminofuroxans **40** with hypohalites, which are electrochemically generated from NaCl or NaBr. It is noteworthy that during the reaction the furoxan ring may partially isomerize, and the subsequent oxidative coupling with the starting amine **40** affords isomeric azofuroxans **48** (Scheme 11).[62]

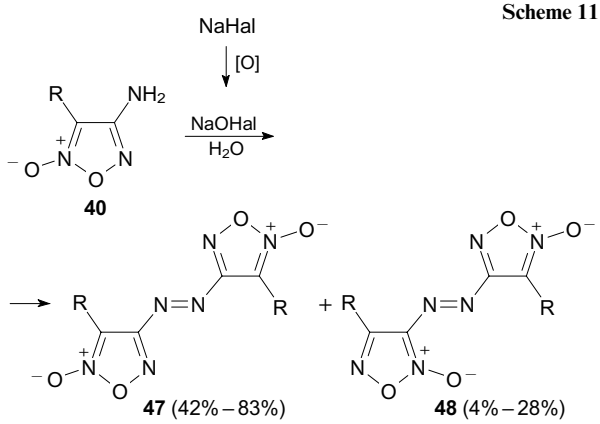
Structures 44



Scheme 10



Scheme 11



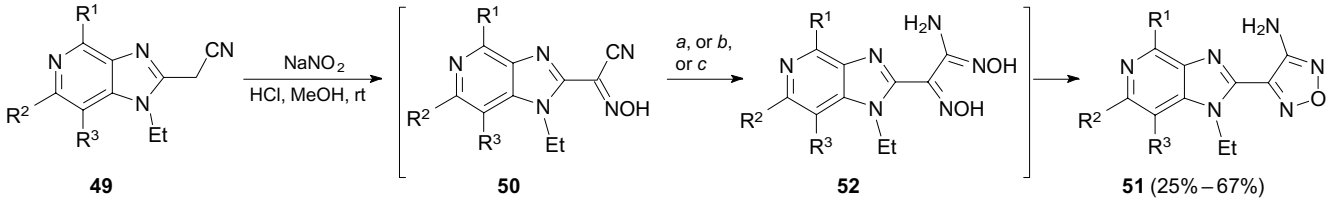
Aminofurazans containing a benzimidazole or azabenzimidazole substituent are promising cytotoxic agents.[63] The synthesis of this type of structures is depicted in Scheme 12. The nitrosation of the active methylene group in functionalized azabenzimidazole derivatives **49** affords geminal cyanoximes **50**, which react with hydroxylamine in a basic medium to give the target aminofurazans **51** through cyclodehydration of the *in situ* generated aminoglyoximes **52**.[63–68] The synthesis of benzimidazolylfurazans **53** is based on the condensation of imidate **54** with *o*-phenylenediamine derivatives (see Scheme 12).[69,70] Aminofurazanylazabenzimidazole derivatives **51** proved to be efficient as a new class of inhibitors of mitogen-activated protein kinase 1 (MSK-1) responsible for the degradation of hippocampal neurons and inducing cerebrovascular ischemia.[64,65] Furthermore, compounds **51** are able to inhibit the protein kinase B family (including the AKT1, AKT2 and AKT3 genes), which can be used in the cancer therapy.[67,68]

Recently a new intramolecular rearrangement of heterocyclic N-oxides was found considering 3-aminofuroxans **55**. The condensation of the initial amines with trimethyl orthoformate yields imino ethers **56**, which rearrange to furazanylcarbamates **57** under the action of sub-stoichiometric amounts of potassium cyanide. The putative mechanism of this reaction includes the addition of the cyanide anion to the C=N bond of the imino ether followed by 5-*exo*-*tet*-cyclization of intermediate **58** to bicyclic structure **59**. Cleavage of the 1,2,4-oxadiazoline ring in intermediate **59** results in the formation of final furazanylcarbamates **57** (Scheme 13). This rearrangement successfully proceeds also for six-membered heterocyclic (pyridine and pyrimidine) N-oxides with Lewis acid catalysts.[71]

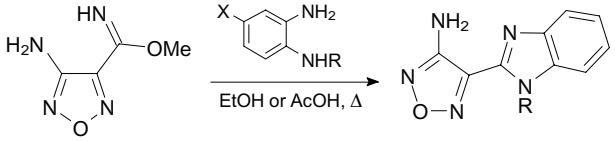
The reactions of diaroylfuroxans **60** with aqueous ammonia afford aminofurazans **61** *via* the furoxan ring opening step.[72] The authors assumed that the reaction starts with the addition of an ammonia molecule to one of the carbonyl groups of diaroylfuroxan **60**. Then intermediate **62** eliminates a carboxamide molecule, thus generating unstable furoxan anion **63**, which is cleaved to give α-oximinoacetonitrile oxide **64**. The addition of one more ammonia molecule to the nitrile oxide group yields aminoglyoxime **65**, which is dehydrated, thus completing the process by the formation of aminofurazans **61** (Scheme 14).

The oxidation of 1,4-dioximes **66** with nitric acid forms the 1,2,5-oxadiazolo[3,4-*d*]pyridazine 1,5,6-trioxide bicyclic system (Scheme 15). Compounds **67** are of interest as efficient NO donors.[73]

Scheme 12

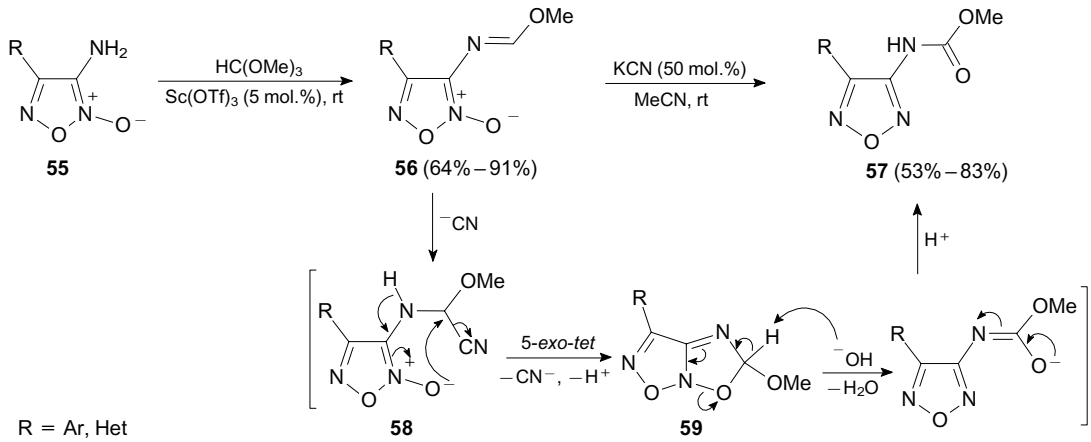


R^1 = H, Cl; R^2 = H, Br, MeO, PhO, TsO, 3-AcNHC$_6$H$_4$O, 4-AcNHC$_6$H$_4$O; R^3 = H, Br;
(*a*) NH_2OH, NaOH, H_2O, 90 °C; (*b*) NH_2OH, TEA, THF, Δ; then TEA, THF, Δ; (*c*) NH_2OH, TEA, THF, H_2O, 90 °C; then TEA, dioxane, 150 °C (sealed tube); TEA is triethylamine, Ts is *p*-toluenesulfonyl (tosyl)

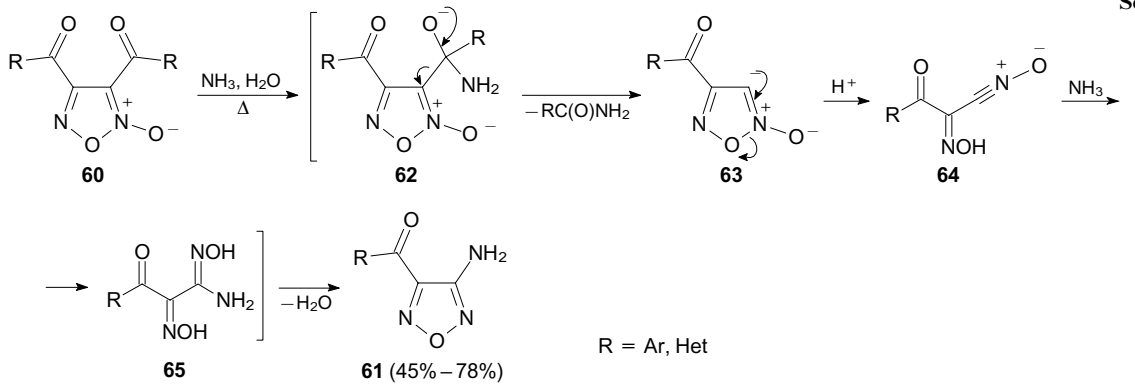


X = H, OH, NH_2; R = H, Alk, Ar

Scheme 13

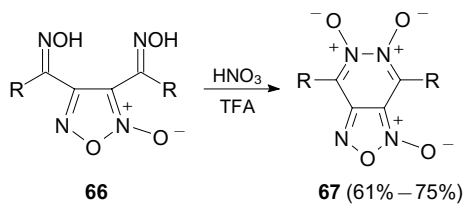


Scheme 14



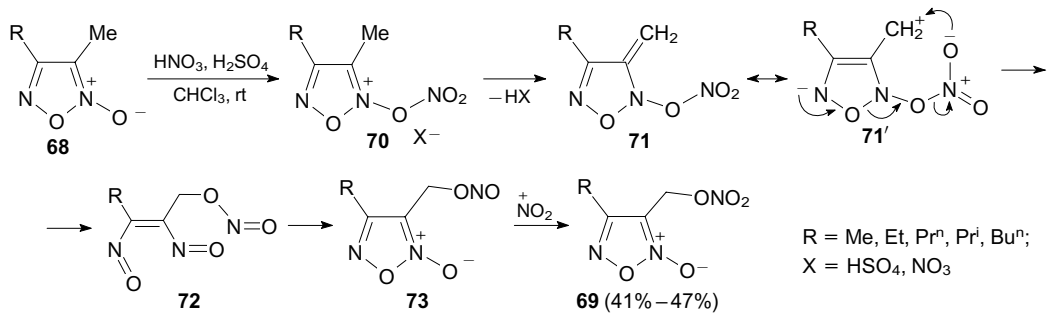
Treatment of 3-methyl-4-alkylfuroxans **68** with a sulfuric and nitric acid mixture gives nitroxymethylfuroxans **69** in moderate yields. The reaction mechanism probably includes the initial addition of the nitronium cation to the N-oxide group at the furoxan ring giving salt **70**, which dissociates to afford intermediate **71**. Then tautomer **71′** undergoes Grob fragmentation to be converted to dinitrosoethylene **72**, which rapidly cyclizes to furoxan **73**. The oxidation of the nitrite group completes the formation of nitroxymethylfuroxans **69** (Scheme 16).[74]

Scheme 15

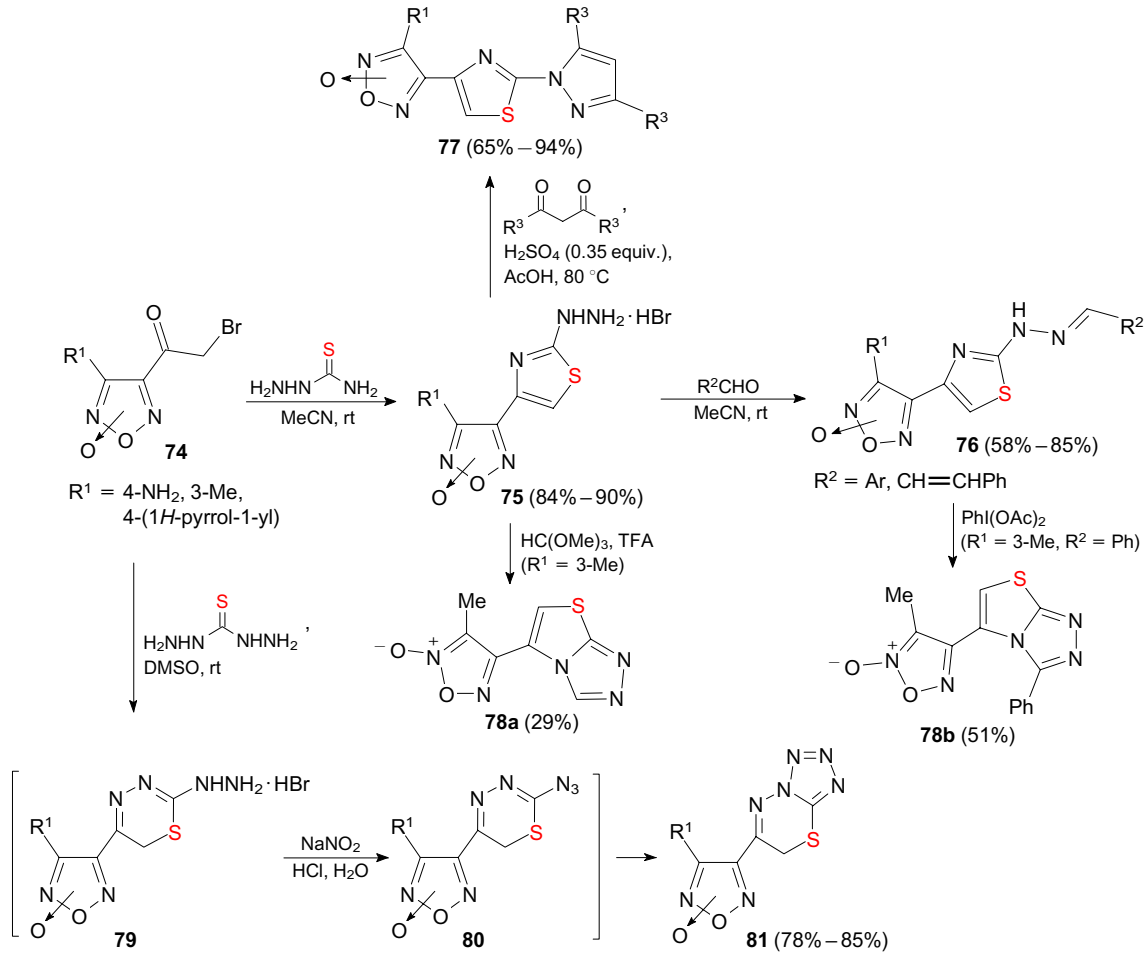


R = H, Me, Ar, Cl, NO_2

Scheme 16



Scheme 17

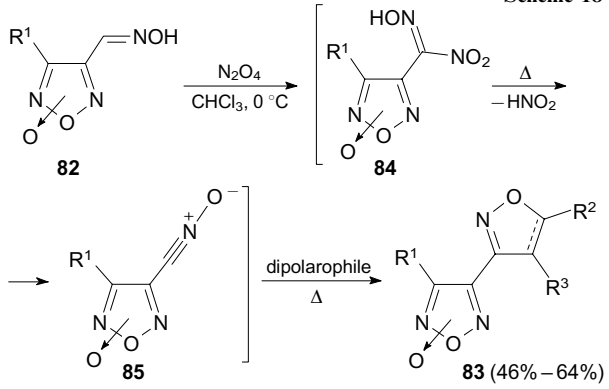


Bromoacetylfuroxans **74** serve as convenient precursors for the synthesis of sulfur-containing hetarylfuroxans. In particular, the condensation of substrates **74** with thiosemicarbazide proceeds regioselectively and affords hydrazinylthiazoles **75**, which successfully react with aldehydes or 1,3-dicarbonyl compounds at the hydrazine group giving hydrazones **76** or pyrazoles **77**, respectively.[75,76] Hydrazones **76** can also be directly prepared from bromoacetylfuroxans **74** *via* a one-pot process almost without decrease in the product yield.[75] In addition, using some particular examples, it was demonstrated that the thiazolo[2,3-*c*]-1,2,4-triazole system can be fabricated as a substituent at the furoxan ring (structures **78a**,**b**) using condensation of hydrazinylthiazole **75** with ortho ester or oxidation of hydrazone **76** with $PhI(OAc)_2$.[75] The reaction of bromoacetylfuroxans **74** with thiocarbohydrazide results in the regioselective formation of hydrazinyl-1,3,4-thiadiazines **79**, which tend to rapidly decompose during isolation. The one-pot nitrosation of compounds **79** afforded azides **80**, which cyclized to furoxanyl-7*H*-tetrazolo[5,1-*b*]-1,3,4-thiadiazines **81** as a result of azide–tetrazole tautomerization (Scheme 17).[77]

Cascade reactions of furoxanylaldoximes **82** formed the basis of a regioselective synthesis of isoxazolyl- and isoxazolinylfuroxans **83**. This approach includes radical nitration of the starting oximes **82** with N_2O_4. Thermolysis of the resulting nitrolic acids **84** leads to generation of nitrile oxides **85**, which are trapped by appropriate dipolarophiles to give target hetarylfuroxans **83** (Scheme 18).[78]

Recently, more convenient methods were proposed for the synthesis of (1,2,4-triazolyl)furazans **86** and **87**; the new methods have considerable advantages over the known thermal cyclodehydration of N-acylamidrazones.[79] One method is based on tandem condensation of furazanylami-

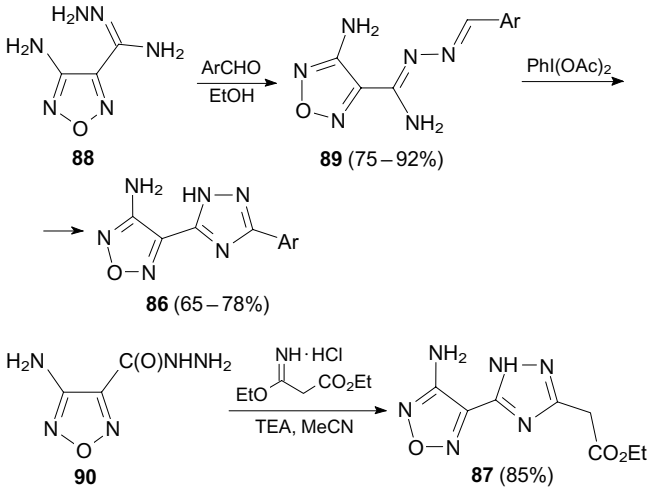
Scheme 18



R^1 = 3-Me, 4-Ph, CH=NOH; R^2, R^3 = H, CO_2Me, CO_2Et;
$R^2 – R^3$ = (O)CN(Ph)C(O)

drazones **88** with aromatic aldehydes and subsequent oxidation of compounds **89** with $PhI(OAc)_2$.[80] The other method is the base-promoted condensation of aminofurazancarboxylic acid hydrazide **90** with ethoxycarbonylacetimidate (Scheme 19).[81] Both approaches are characterized by mild conditions and high yields of the target products.

Scheme 19



The recently synthesized Pt complexes of the furazan series exhibit high antitumour activities against human cancer cells, while causing less adverse effects than the known drug cisplatin.[82, 83] Promising compounds possessing anticoagulant activity were obtained among furoxan derivatives (Fig. 1).[84 – 86] A distinctive feature of furoxans as antiplatelet agents is the selective mechanism of action: they inhibit the platelet aggregation induced by adrenaline or adenosine diphosphate, which are responsible for thrombus formation in the human body in the vast majority of cases.

Thus, the development of new and upgrading of the existing synthetic strategies in the furazan and furoxan chemistry not only expanded the libraries of nitrogen heterocyclic systems and gave rise to new design methods, but also provided quite a few compounds with useful properties. A number of new regio- and chemoselective approaches to the construction of polyheterocyclic systems with a 1,2,5-oxadiazole ring were found. New transformations of furazans and furoxans based on intramolecular rearrangements and cyclizations were discovered. The developed synthetic strategies can serve as a reliable foundation for the design of dual-use technologies for creation of both new generation energetic materials and pharmacologically active compounds with a wide range of action.

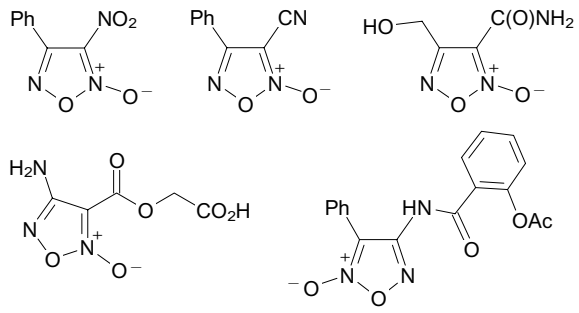


Figure 1. Structures of furoxan derivatives possessing antiplatelet activities.

2.2. Synthesis of polynuclear N-heterocyclic systems based on nitro(het)arenes

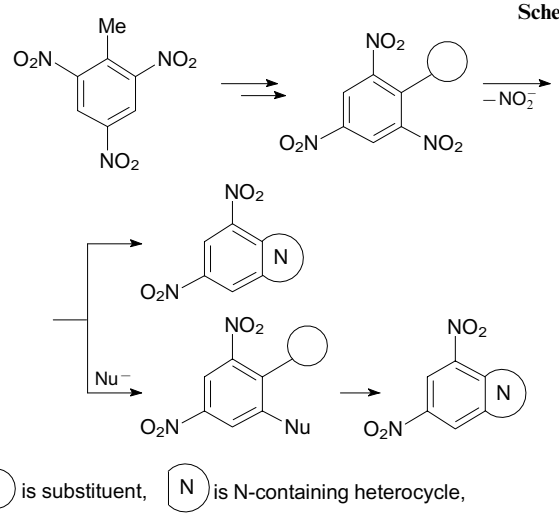
Many biologically active compounds, including alkaloids and therapeutic agents (antibiotics, muscle relaxants, antipsychotics, *etc.*), are based on fused polyheterocyclic systems. They are parts of dyes and are widely used in agrochemistry and some other fields. Despite great advances in the synthesis of various polyheterocyclic systems, development of facile and convenient methods for synthesizing new structures and the search for new approaches to the already known classes of polyheterocycles are relevant problems for organic chemistry. They can be solved only with a strategy based on available starting compounds possessing high and diverse reactivity. These conditions are met for nitro(het)arenes, which have high synthetic potential and are readily available — some aromatic nitro compounds are manufactured on an industrial scale. One of the most readily available and promising precursors for a broad range of fused heterocycles is 2,4,6-trinitrotoluene (TNT).

A systematic study of the chemistry of TNT resulted in the development of a synthetic strategy towards five-membered aromatic benzannulated heterocycles. The strategy is based on the transformation of the methyl group of TNT followed by intramolecular displacement of the *ortho*-nitro group, resulting in the formation of the heterocycle, or intermolecular selective nucleophilic displacement of the *ortho*-nitro group followed by cyclization (Scheme 20).

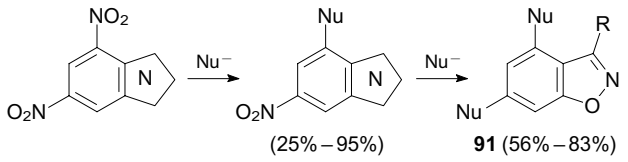
This strategy was employed to synthesize various 4,6-dinitro-substituted benzoheterocycles including benzothiophenes, benzo[*d*]isothiazoles, benzo[*d*]isoxazoles, indoles, indazoles, 2,3-dihydrobenzofurans and so on. (The synthesis and characteristics of these bicyclic systems are summarized in a review.[87]) For most of these systems, the 4-NO_2 group was found to be selectively substituted on treatment with anionic nucleophiles[88 – 92] Most often, the substitution proceeds under mild conditions and in the case of the most π-deficient benzo[*d*]isoxazoles **91**, both nitro groups can be successive substituted[93] (Scheme 21).

Six-membered benzannulated heterocycles containing two *meta*-nitro groups in the benzene ring behave in a similar way. For example, reactions of 8-R-5,7-dinitroqui-

Scheme 20



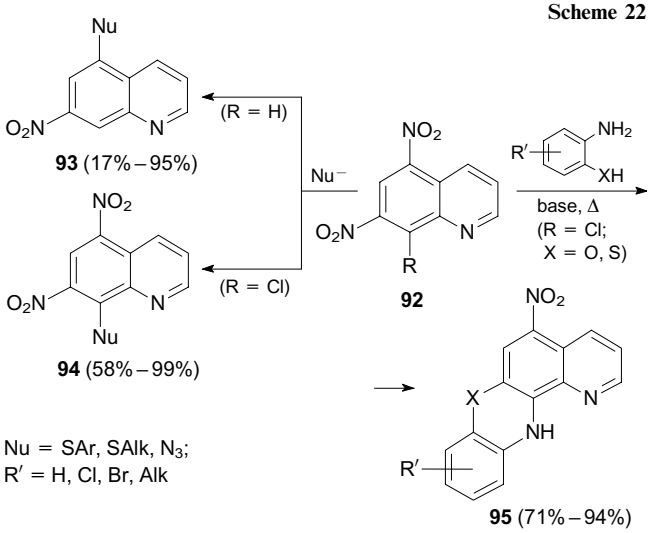
Scheme 21



nolines **92** with anionic nucleophiles give selective substitution products of the 5-NO_2 group (for R = H)[94] or the 8-Cl atom (for R = Cl)[95] — compounds **93** and **94**, respectively. When dinitroquinolines **92** (R = Cl) react with dinucleophiles (*o*-aminophenols and their thio analogues), the chlorine atom and the nitro group were displaced successively[96] to give pyrido[2,3-*a*]phenoxazines and -phenothiazines **95**. In the case of aminobenzenethiols, Smiles rearrangement products were isolated (Scheme 22).

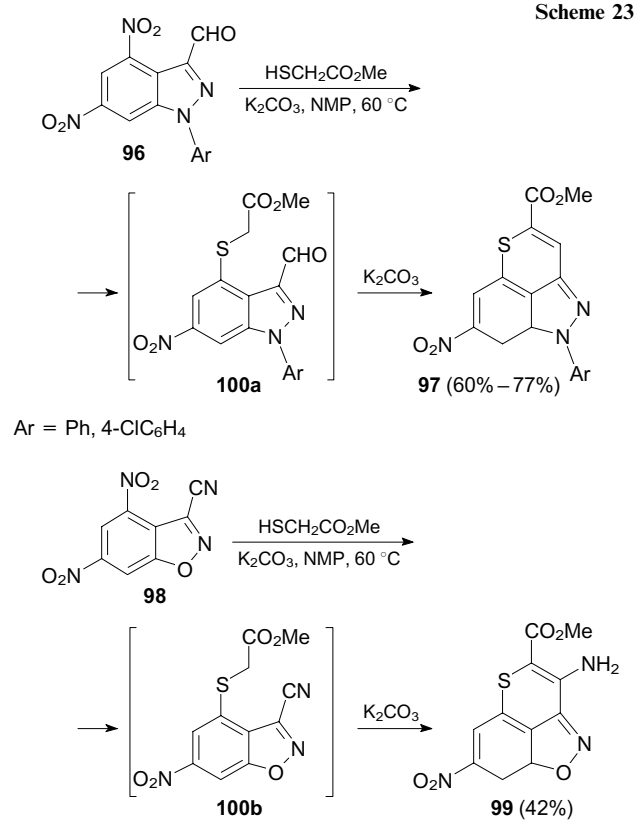
The high mobility of the nitro group in position 4 and the presence of a substituent in position 3 in 4,6-dinitrobenzazoles **96** were utilized for the construction of *peri*-annulated polycyclic systems. It was found[97] that the

Scheme 22



reaction of compound **96** with thioglycolic acid ester in *N*-methylpyrrolidone (NMP) affords tricyclic structures **97**, while nitrile **98** is converted to amino thiopyrano[4,3,2-*cd*]-benzo[*d*]isoxazole derivative **99**. The reaction includes nucleophilic substitution of the 4-nitro group with thioglycolate and subsequent intramolecular cyclization of the resulting intermediates **100a**,**b** (Scheme 23). *peri*-Annulated 14π-electron heteroaromatic systems consisting of two six-membered and one five-membered rings represent a rather rare type of heterocycles, while structures of type **99** have previously been unknown.

Scheme 23



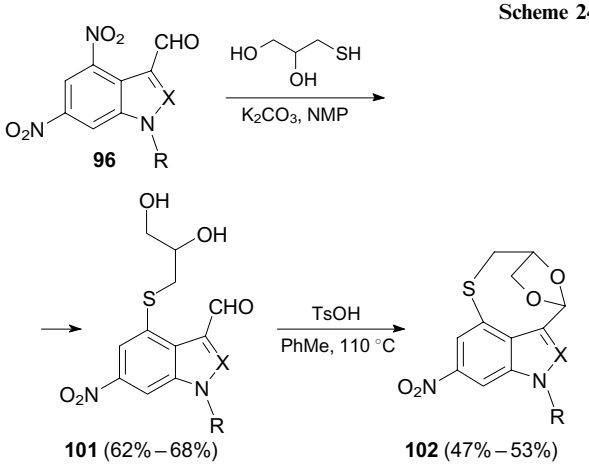
When thioglycerol is used as the nucleophilic agent, nucleophilic substitution products **101** formed from dinitrobenzazoles **96** are converted to polycyclic acetals **102** under acidic conditions (Scheme 24).[98]

Heating of indazoles **103** in *N*-methylpyrrolidone in the presence of potassium carbonate gives rise to pyrazolocinnolines **104**, a previously unknown heterocyclic system, resulting from intramolecular displacement of the nitro group.[99] Meanwhile, benzisoxazoles **105** react in a different way: intramolecular ring transformation takes place to give aryltriazoles **106** (Scheme 25).[100]

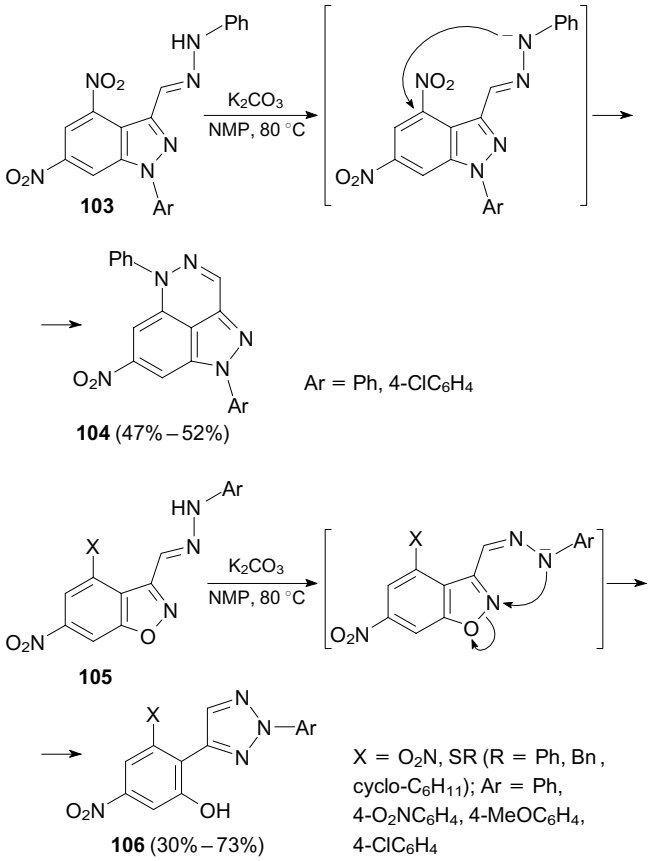
In the last decade, a new trend has been actively developed in the chemistry, namely, their dearomatization of nitroarenes in [3 + 2]- and [4 + 2]-cycloaddition reactions. The C=C–NO_2 moieties present in π-deficient nitroarenes can participate in pericyclic reactions as both dienophiles and heterodienes. They can also add to some dipoles, giving rise to five-membered heterocycles. Many examples of the indicated reactions have been considered in a review.[101, 102]

Recently, Shevelev and co-workers[103, 104] reported the first [3 + 2]-cycloaddition reactions of unstabilized azomethine ylides to nitroarenes. It should be emphasized that the

Scheme 24

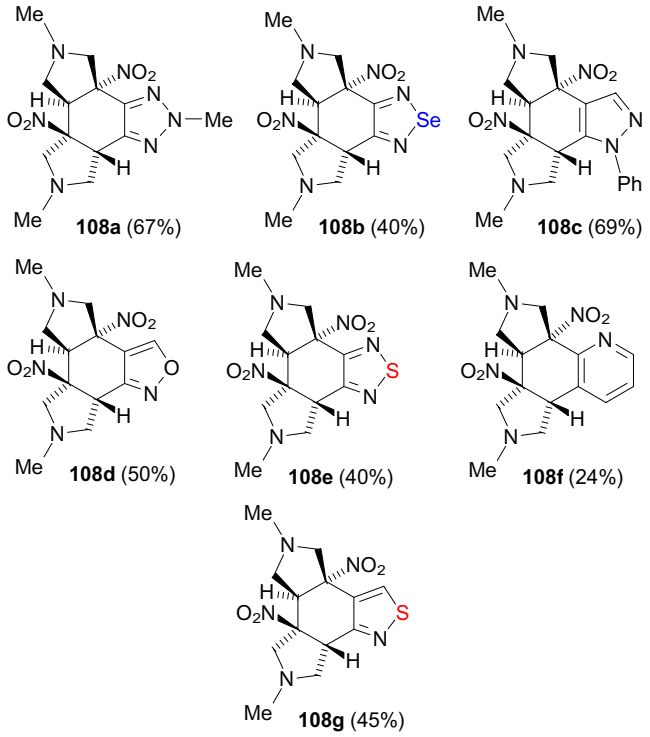


Scheme 25

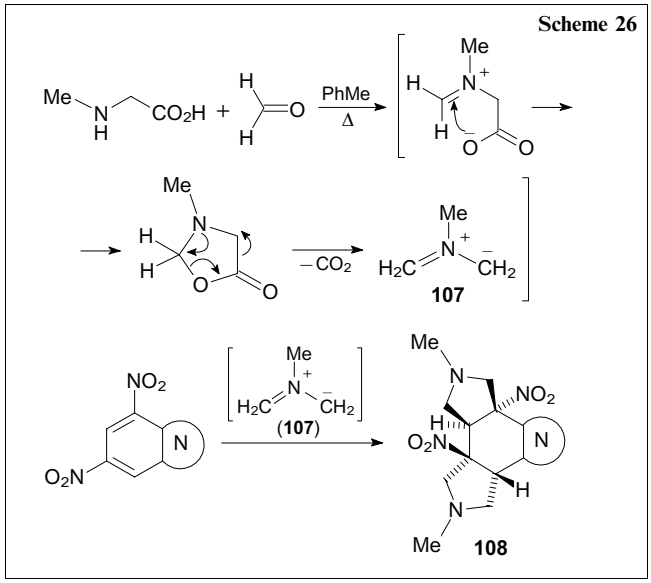


participation of aromatic carbocycles as 2π-components in pericyclic reactions is very rarely encountered, and the addition of dipoles to nitroarenes has not been systematically studied previously. It was found that *m*-dinitrobenzenes fused to various azoles or azines easily undergo 1,3-dipolar cycloaddition reaction with *N*-methylazomethine ylide (**107**) formed *in situ* from sarcosine and paraformaldehyde. The addition of two equivalents of the dipole to both C=C–NO_2 moieties furnishes new polycyclic systems **108** incorporating two annulated pyrrolidine rings (Scheme 26). The reactions proceed diastereoselectively and afford *anti*-bis-adducts as a result of equally probable

Structures 108



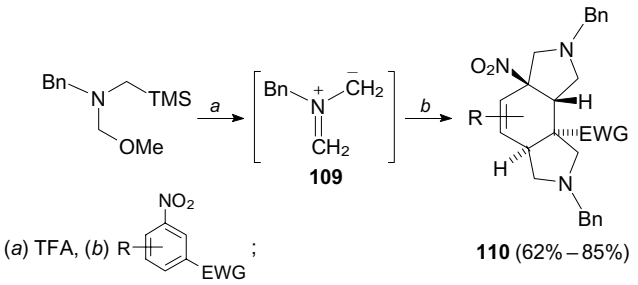
Scheme 26



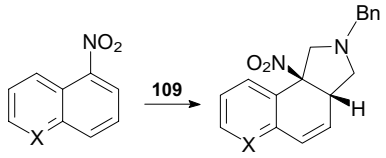
addition of azomethine ylide **107** from opposite sides relative to the dipolarophile plane.

Later, Lee *et al.*[105,106] reported reactions of the same type for mono- and dinitro benzene, naphthalene and quinoline derivatives with *N*-benzylazomethine ylide (**109**). In particular, *o*- and *m*-dinitrobenzenes produced bis-adducts **110**, while naphthalene derivatives were converted to monoadducts **111** at 20 °C. The authors demonstrated that this reaction proceeds smoothly if a nitro group and some electron-withdrawing substituent are present in the benzene ring, while in the case of naphthalene and quinoline derivatives, the presence of only a nitro group is sufficient (Scheme 27). In the case of bis-cycloaddition, the second equivalent of azomethine ylide **109** adds on the opposite side with respect to the first one. The authors

Scheme 27



EWG = NO_2, CO_2Me, CF_3, Cl; R = H, F, Cl, CF_3

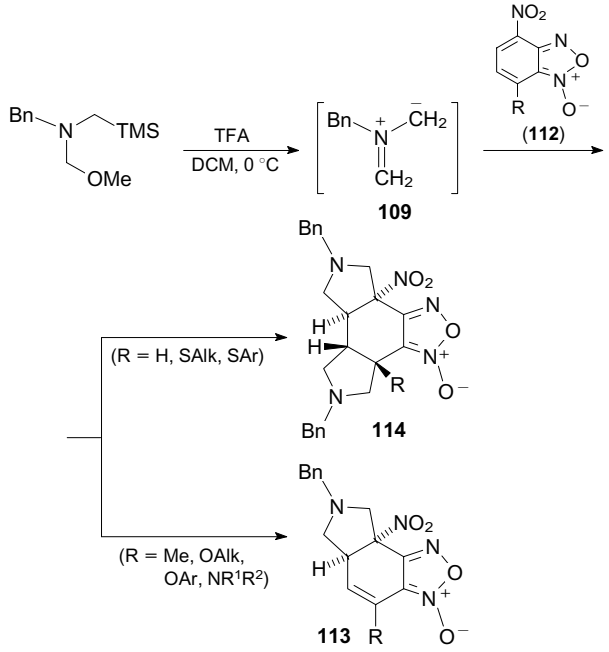


suggest a concerted mechanism of dipole addition relying on the results of quantum chemical calculations.

At the same time, 7-R-4-nitrobenzofuroxans **112** react with dipole **109** to yield mono- (**113**) or bis-adducts (**114**) depending on the nature of the substituent R (Scheme 28).[107]

The reactions presented in Schemes 26–28 are typical examples of MBFT (multiple bond forming transformations) strategy,[108–113] which allows the formation of several C–C or C–heteroatom bonds in one step. This is an attractive tool for increasing the molecular complexity and functional diversity of organic compounds, which is in high demand for the design of new pharmaceutical agents and other biologically active products.

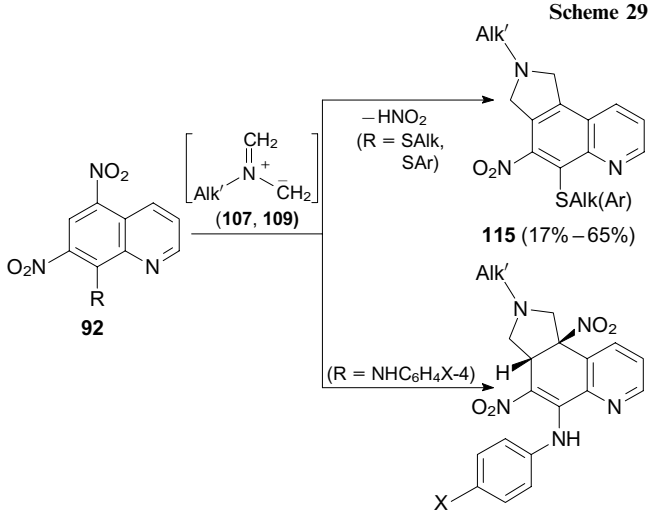
Scheme 28



113: R = Me (70%), OMe (70%), OPh (76%), NHPh (64%), N(Me)Ph (67%), morpholino (65%);
114: R = H (45%), SPh (64%), SC_6H_{11}-cyclo (89%), SCH_2Fu-2 (91%); Fu is furyl

The outcome of reactions of 8-R-substituted dinitroquinolines **92** with *N*-methyl- (**107**) and *N*-benzylazomethine ylides (**109**) depends on the nature of the substituent R. When R = SAlk or SAr, isoindolines **115** are formed irrespective of the dipole used or the temperature. The cycloaddition is regioselective, involves the C(5)–C(6) bond and is accompanied by benzene ring rearomatization with elimination of HNO_2.[95, 114] The reactions of 8-arylamino-substituted dinitroquinolines (**92**, R = NHAr) with azomethine ylides **107** and **109** afford fused pyrrolidines **116**, formed as dearomatization products in good yields. Unlike the transformations of 8-thio-substituted quinolines, in this case, no HNO_2 elimination takes place (Scheme 29).[95, 114]

Scheme 29



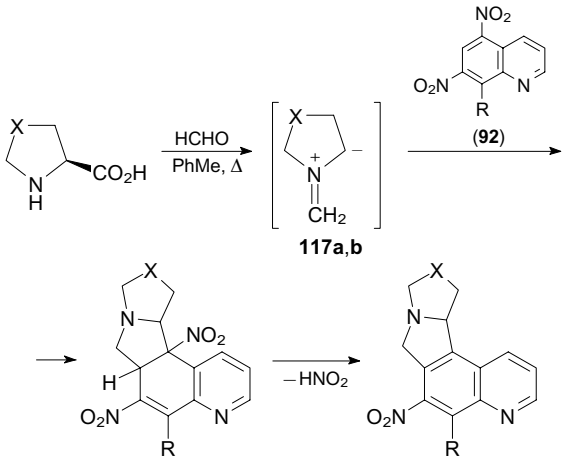
The use of cyclic azomethine ylides **117a**,**b** in this type of reactions opens up the way to polyfused derivatives **118**, the reaction being accompanied by nitrous acid elimination[114] (Scheme 30).

The reactions of monocyclic nitroarenes with *N*-alkylazomethine ylides underlay the development of a new simple synthetic route to nitroisoindoles.[115] 1,3,5-Trinitrobenzene and some its derivatives react with dipole **107** to give isoindoles **119a–d**. Unlike analogous reactions of nitrobenzazoles, in this case, the addition of the dipole is accompanied by elimination of HNO_2 and subsequent oxidation. The addition is selective, involves only positions 2 and 3 with respect to the substituent R and affords stable nitro isoindole derivatives **119** (Scheme 31).

The use of cyclic amino acids instead of sarcosine for the synthesis of azomethine ylides **117a**,**b** can give rise to isoindoles **120a–d** and **121a**,**b** fused onto one more heterocycle (Scheme 32).[115]

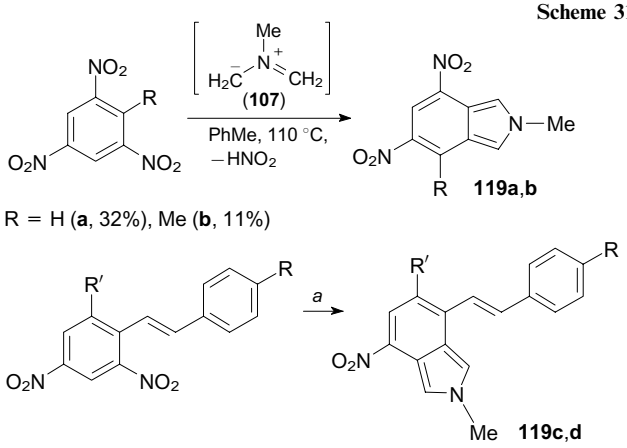
Yet another efficient one-step method for annulation of a pyrrole ring onto nitroarenes includes the reaction between nitrobenzazoles and a related type of dipoles — mesoionic 1,3-oxazolium-5-olates (or munchnones) **122**, which contain a moiety analogous to azomethine ylide in the molecule.[116] Unsymmetrical munchnone **122a** reacts with nitrobenzazoles **123a**,**b** to give mixtures of isomeric isoindoles **124** and **125** (50%–88% total yield); each of the

Scheme 30



117: X = CH_2 (**a**), S (**b**);
R = SAlk, SAr, NHAr, $NAlk_2$

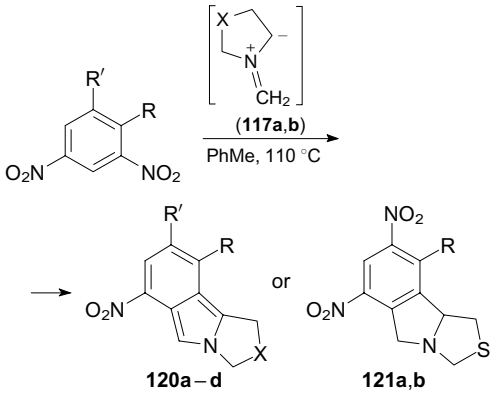
Scheme 31



R = H (**a**, 32%), Me (**b**, 11%)

(*a*) **107**, PhMe, 110 °C, $-HNO_2$;
R′ = NO_2, R = H (**c**, 49%); R′ = SO_2Bu^i, R = Cl (**d**, 44%)

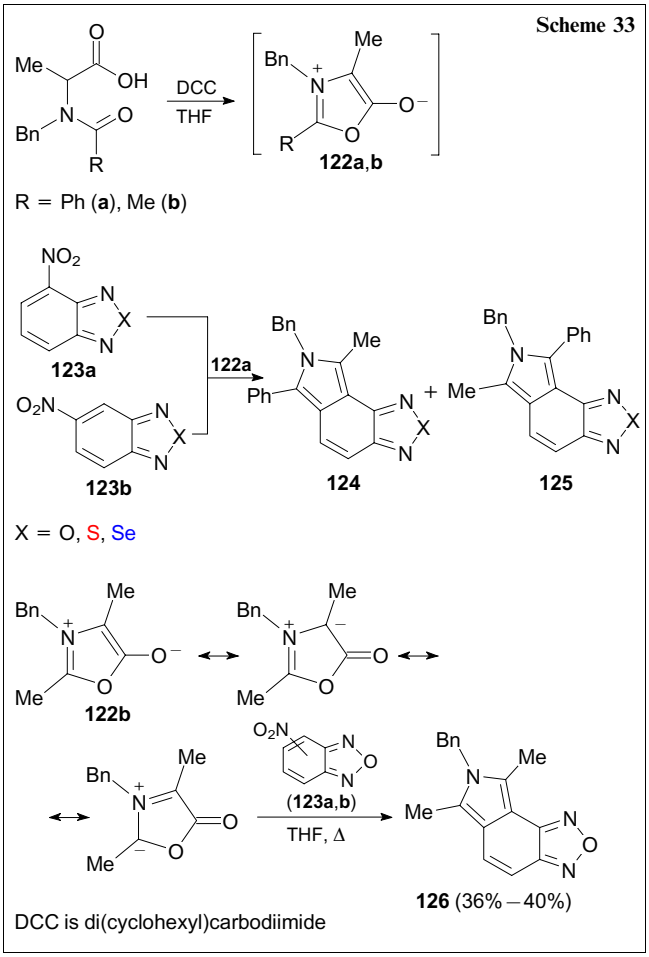
Scheme 32



120: R′ = NO_2, R = CH═CHPh (**a**, 38%); R′ = SO_2Bu^i,
R = CH═CH(C_6H_4Cl-4) (**b**, 58%); R′ = NO_2: R = Me (**c**, 11%),
CH═CHPh (**d**, 35%);
121: R = Me (**a**, 36%), CH═CHPh (**b**, 34%);
X = CH_2, S

products was isolated in a pure state. In the case of symmetrical dimethylmunchnone **122b**, the reactions with isomeric nitrobenzofurazans **123a**,**b** (X = O) give the same isoindole **126** (Scheme 33).

Scheme 33

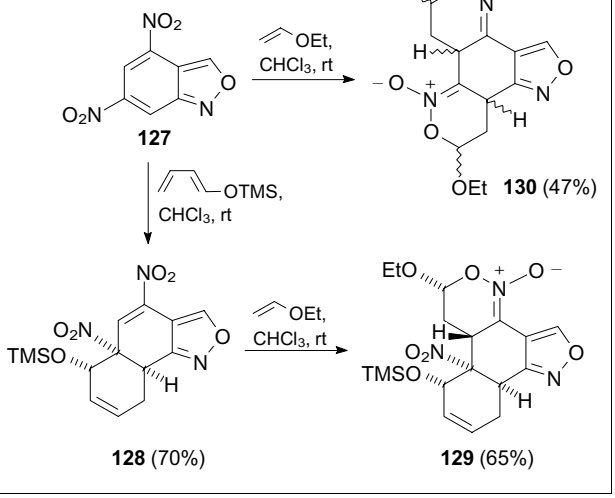


One more feature of highly electrophilic polynitroarenes is the ability to undergo normal or inverse electron demand [4 + 2]-cycloaddition (Diels – Alder reaction). Electron-withdrawing substituents and annulated electron-deficient heterocycles reduce the system aromaticity; as a result, the C═C – NO_2 moieties of nitroarenes resemble conjugated nitroalkenes in the chemical reactivity.

For example, 4,6-dinitrobenzo[*c*]isoxazole (dinitroanthranil)[117] **127** undergoes the Diels – Alder reaction with 1-(trimethylsilyloxy)buta-1,3-diene at room temperature in $CHCl_3$.[118] The normal electron demand reaction involves the C(6) – C(7) bond and has high regio- and diastereoselectivity, giving a good yield of adduct **128**, which then reacts with ethyl vinyl ether as a heterodiene to be converted to derivative **129** (Scheme 34). The reaction of anthranil **127** with ethyl vinyl ether affords bis-adduct **130** as a mixture of diastereomers in 9 : 1 ratio. In the reaction with ethyl vinyl ether, both nitroalkene moieties of compound **127** act as heterodienes with respect to the nucleophilic dienophile (see Scheme 34).

Compounds **131**, which are representatives of another type of nitroarenes able to undergo the Diels – Alder reaction, are structural analogues of nitrobenzodifuroxan, *i.e.*, the products of formal replacement of one furoxan ring by another electron-deficient ring. The superelectrophilic properties of these nitroarenes are retained. The general route to

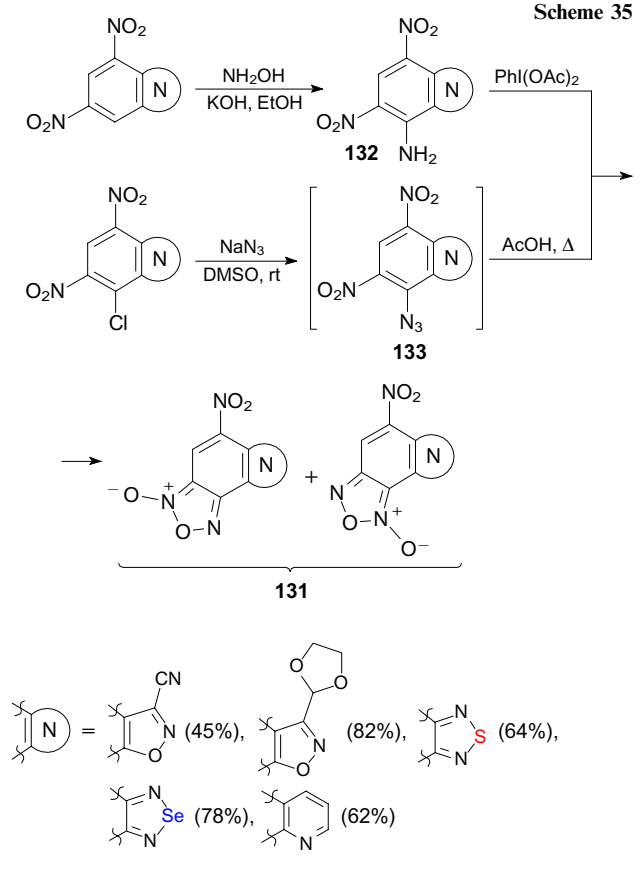
Scheme 34



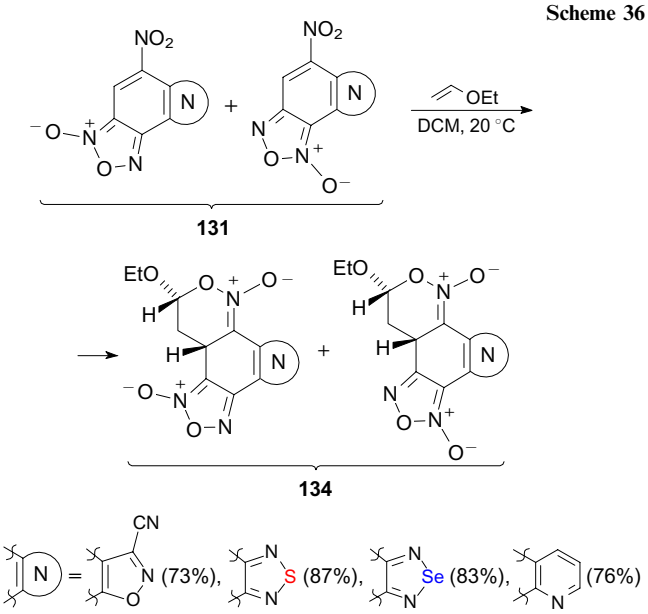
compounds of this type includes the amination of dinitrobenzo derivatives of heterocycles *via* vicarious or oxidative substitution of hydrogen followed by oxidative cyclization of dinitroanilines **132** or preparation and subsequent thermolysis of dinitroazides **133** (Scheme 35). As a rule, tricyclic systems **131** are formed as inseparable 5 : 1 to 3 : 2 mixtures of isomers differing in the position of the exocyclic furoxan oxygen atom.

The reactions of compounds **131** as heterodienes with ethyl vinyl ether produce complex polycyclic systems **134** as a result of formation of the oxazine N-oxide ring (Scheme 36). The reactions are diastereoselective, but the

Scheme 35



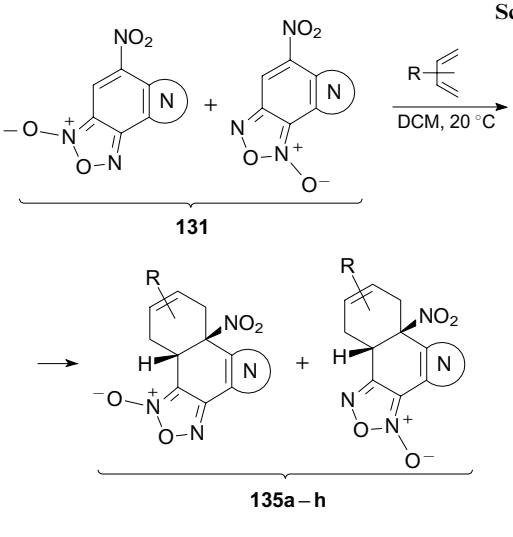
Scheme 36



ratio of regioisomers in the products changes with respect to that for the starting compounds.[114, 116, 119–121]

Furoxans **131** undergo the normal electron demand Diels–Alder reaction with donor dienes. Like in reactions with ethyl vinyl ether, the process is diastereoselective and the products are mixtures of furoxan regioisomers **135a–h** in different ratios (Scheme 37).[114, 119–122]

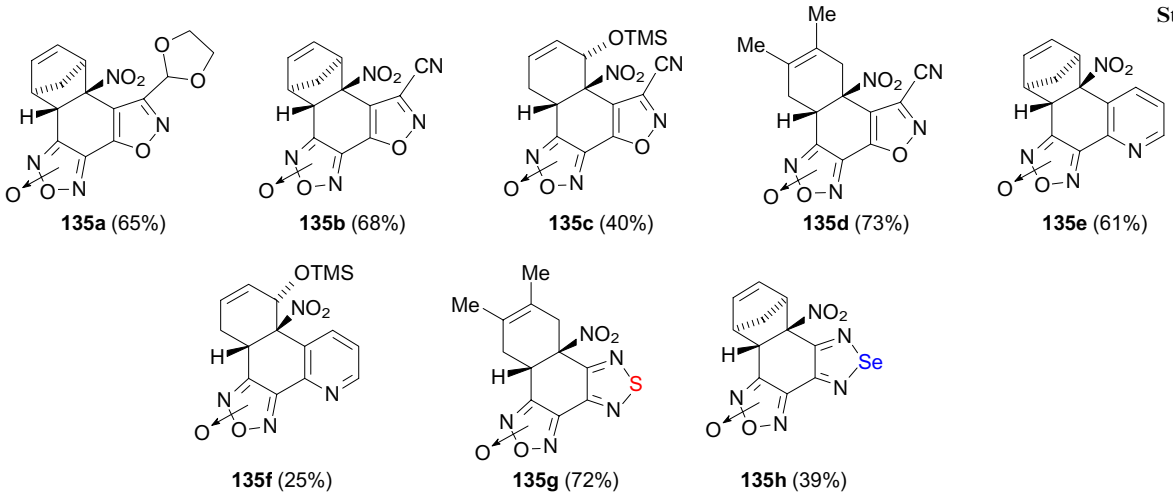
Scheme 37



The synthetic strategy towards fused nitrogen heterocycles based on nitroarenes was extended to nitrohetarenes, in particular, nitropyridines. The reactions of 2-chloro-3,5-dinitropyridine (**136**) with various *o*-aminophenols **137** give rise to (dinitropyridyl)aminophenols **138**, which are converted to 10*H*-pyrido[3,2-*b*][1,4]benzoxazines or 10*H*-dipyrido[2,3-*e*:3′,2′-*b*][1,4]oxazines **139** upon intramolecular displacement of the nitro group induced by heating in DMF at 100 °C in the presence of TEA (Scheme 38).[123] Compounds of these classes are analogues of anti-neurodegenerative drugs.[124, 125]

An approach to polycyclic systems incorporating one or two pyrrolidine rings was developed on the basis of 1,3-dipolar cycloaddition of 2-R-3,5-dinitropyridines **140**

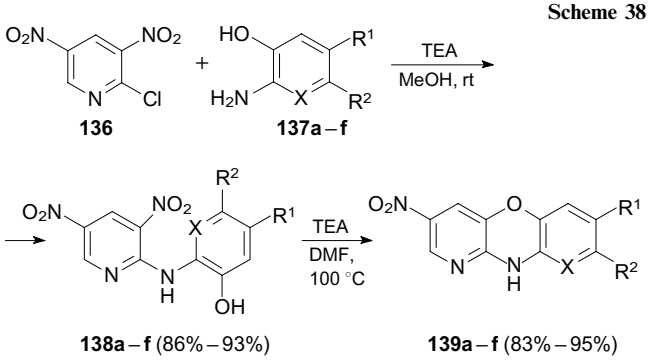
Structures 135



135a (65%) **135b** (68%) **135c** (40%) **135d** (73%) **135e** (61%)

135f (25%) **135g** (72%) **135h** (39%)

Scheme 38



136 **137a – f**

138a – f (86% – 93%) **139a – f** (83% – 95%)

X = CH: $R^1 = R^2 = H$ (**a**); R^1 = Me, R^2 = H (**b**); R^1 = H: R^2 = Me (**c**), Cl (**d**), Br (**e**); X = N: $R^1 = R^2 = H$ (**f**)

to *N*-methylazomethine ylide (**107**).[126, 127] The dipole was found to add only to the C=C–NO_2 moieties of the starting pyridine. The reaction outcome is affected by the nature of substituent in position 2, in particular, 2-aryloxy and 2-thio derivatives give bis-adducts **141**, whereas in the case of 2-amino-substituted 3,5-dinitropyridines, the formation of expected bis-adducts **142** was accompanied by the formation of compounds **143** resulting from the addition of one equivalent of the dipole followed by rearomatization (Scheme 39). Decahydrodipyrrolo[3,4-*b*:3′,4′-*d*]pyridines **142**, which are derivatives of a new heterocyclic system containing a combination of two 3-nitropyrrolidine moieties annulated onto a tetrahydropyridine ring, may be of interest as potential NO donors, according to published data.[128]

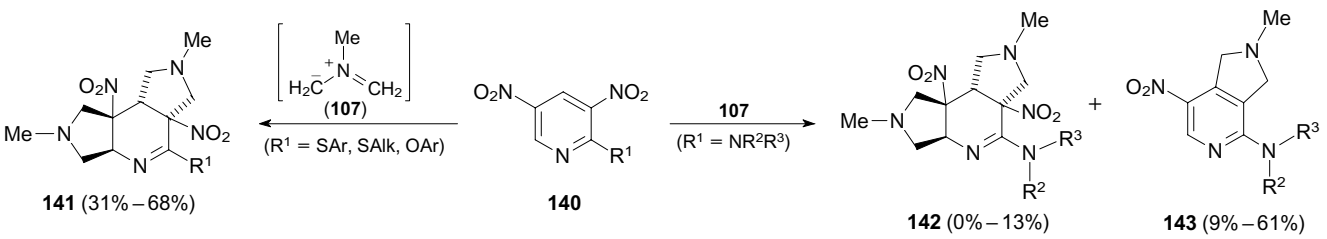
Recently,[129] facile and convenient methods have been developed for the synthesis of 2-R-6,8-dinitro-1,2,4-triazolo[1,5-*a*]pyridines **144**. The reactions of 2-choro-3,5-dinitropyridine (**136**) with carboxylic acid hydrazides, or the reaction of 2-hydrazinopyridine **145** with appropriate acid chlorides and subsequent cyclization of hydrazides **146** on refluxing in $POCl_3$ result in the formation of triazolopyridine derivatives **147**. The latter undergo the Dimroth rearrangement under the reaction conditions to give isomeric triazolopyridines **144a – f** in moderate to nearly quantitative yields (Scheme 40).

The oxidation of 3,5-dinitropyridylhydrazones of aldehydes **148**, which were prepared by condensation of hydrazine **145** with various aldehydes, is yet another approach to dinitrotriazolopyridines **144**.[129] Refluxing of hydrazones **148** with an equimolar amount of lead tetraacetate in AcOH furnishes triazolo[1,5-*a*]pyridines **144b,g – k**. Since the oxidation of hydrazones **148** is expected to result in only triazolo[4,3-*a*]pyridines **147**, we conclude that in this case, too, the Dimroth rearrangement takes place (Scheme 41).

The bicyclic structures containing two nitro groups thus obtained may be useful not only because of their high synthetic potential, but also as precursors of highly energetic compounds.

One more line of research of fused nitropyridines is the synthesis of highly electrophilic azolopyridines and study of their reactions with neutral C-nucleophiles. In particular, aminopyridine **149** was used as the starting compound to develop synthetic routes to 4-aza-6-nitrobenzofuroxan **150** and 4-aza-6-nitrobenzoselenadiazole **151**. Compound **150** was prepared by oxidative cyclization of 2-amino-3,5-dinitropyridine (**149**) in the presence of $PhI(OAc)_2$,[130] while

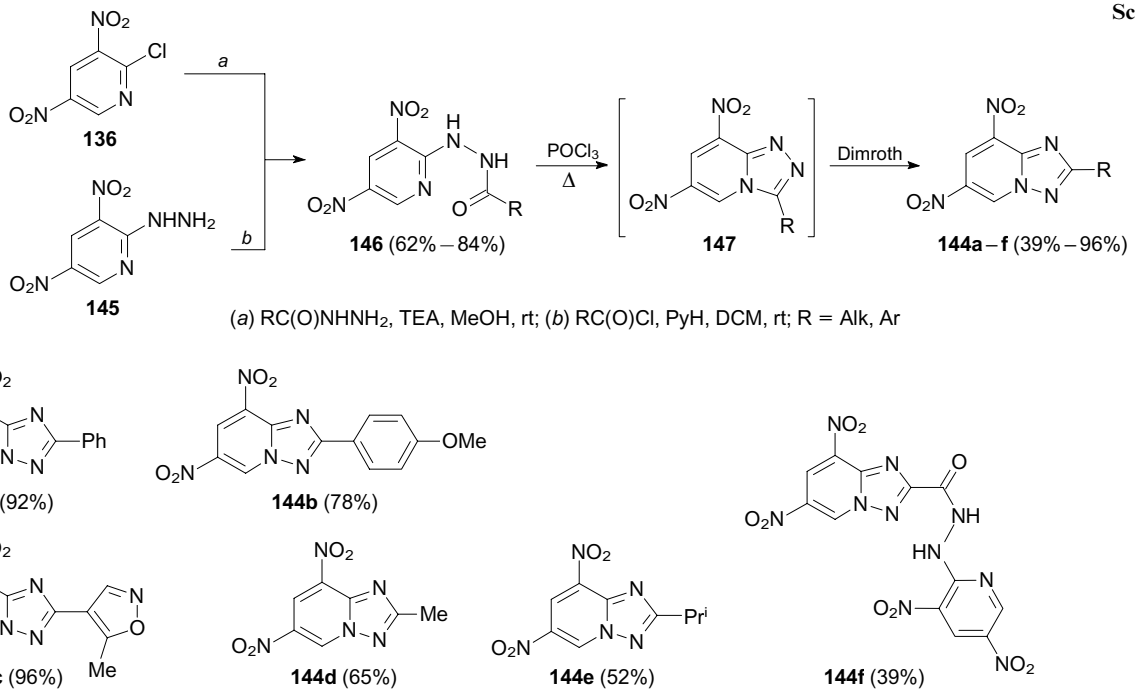
Scheme 39



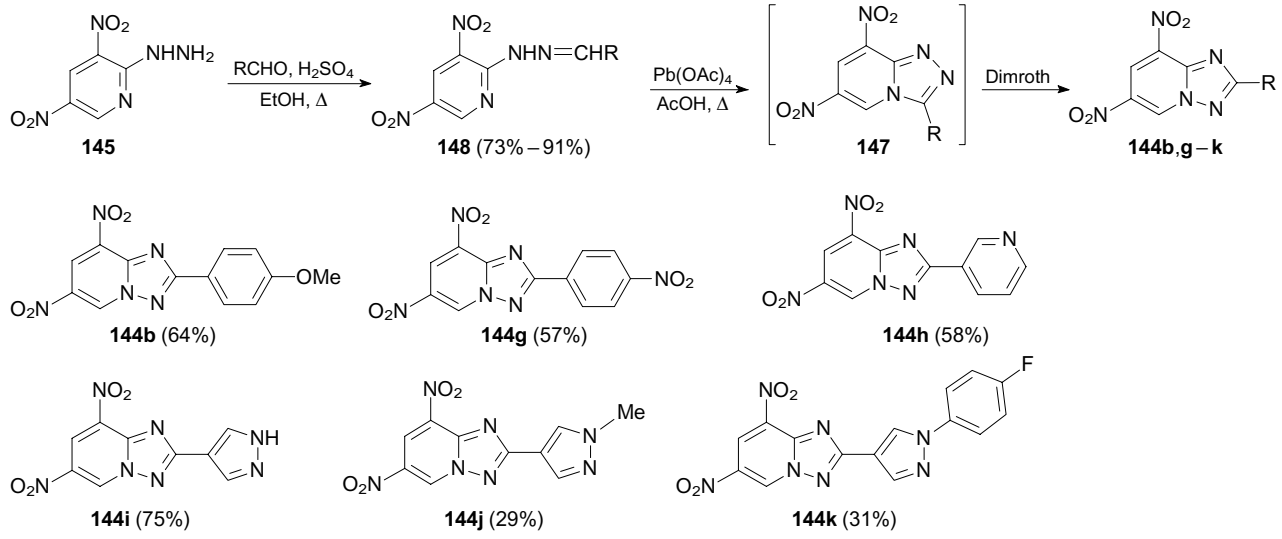
141 (31% – 68%) **140** **142** (0% – 13%) **143** (9% – 61%)

R^1 = SAr, SAlk, OAr, NR^2R^3; $R^2 = R^3$ = Alk; R^2 = Me, R^3 = Ph

Scheme 40



Scheme 41

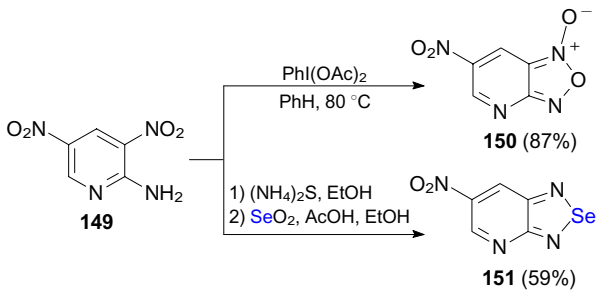


bicyclic compound **151** was obtained by selective reduction of the 3-nitro group with ammonium sulfide followed by the reaction of intermediate *o*-diamine with SeO_2 (Scheme 42).[131]

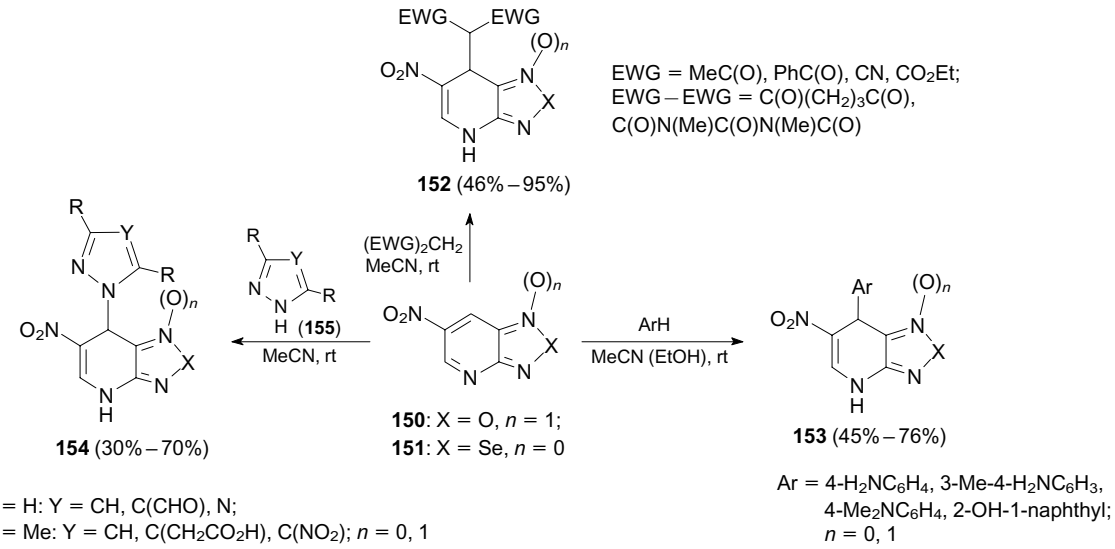
It was shown that compounds **150** and **151** readily react with CH-acids, for example, 1,3-dicarbonyl compounds, and with π-excessive arenes and azoles to give C–C- and C–N-bound adducts, 1,4-dihydropyridines **152**–**154** fused to a furoxan or selenadiazole ring (nucleophilic dearomatization) (Scheme 43). In most cases, the reactions proceed without bases, which attests to higher electrophilicity of fused nitropyridines. It turned out, however, that in polar solvents (DMSO, TFA, *etc.*) azole adducts **155** containing electron-withdrawing substituents partially or completely degrade to give the starting compounds.[130, 131]

Thus, approaches to the synthesis of a broad range of fused polynuclear nitrogen-containing heterocyclic systems based on nitro arene and hetarene derivatives were developed. The discovered ability of nitro(het)arenes to undergo aromatic nucleophilic substitution reactions with displacement of the nitro group (S_N^{Ar}) and the hydrogen atom (S_N^H) and to undergo [3+2]- and [4+2]-cycloaddition reactions opens up synthetic routes to previously unknown or diffi-

Scheme 42



Scheme 43



cult-to-obtain fused polyheterocyclic systems. The molecules of these compounds contain a variety of pharmacophoric moieties, the combinations of which makes these products promising as precursors for the synthesis of pharmacologically oriented heterocyclic structures.

3. Progress in the chemistry of sulfur – nitrogen heterocycles

3.1. New strategy towards complex sulfur – nitrogen heterocycles

The interest of specialists working in various fields of chemical science, medicine and technology in sulfur – nitrogen heterocycles not only persists, but has been increasing during the last decades. The presence of several heteroatoms with lone pairs and the electronegativity difference between the heteroatoms and carbon account for the unique properties of these compounds and makes them promising for practical purposes in pharmaceutical industry, agrochemistry and also in electronics — as materials possessing magnetic properties and electrical conductivity. However, until recently, these heterocycles were prepared by multistep processes that required expensive reagents.

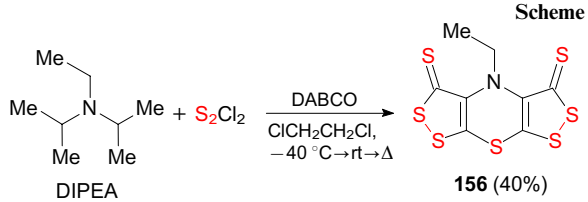
More than 25 years ago researchers of the ZIOC RAS headed by Prof. O.A.Rakitin, in cooperation with Prof. Charles Rees (Imperial College London, UK) put forward a new strategy for the synthesis of new sulfur-nitrogen heterocycles from simple (often commercially available) chemicals and sulfur monochloride (S_2Cl_2). This strategy is based on the complex and diverse reactivity of sulfur monochloride.[132, 133] Sulfur monochloride is a potent chlorinating agent, but it is rarely used for this purpose. The most important feature of S_2Cl_2 is sulfurating ability, which is used, in particular, for heterocyclization of organic compounds. Sulfur monochloride also has oxidative and dehydrating properties. The reactions involving sulfur monochloride usually end in products of complex multistep transformations, including chlorination, dehydrochlorination and sulfurization. Unfortunately, the diverse types of sulfur monochloride reactivity is manifested simultaneously, which gives mixtures that are difficult to separate and necessitates careful choice of reaction conditions for selective formation of a particular product.

Using sulfur monochloride, it is possible to obtain diverse sulfur-containing heterocyclic systems. Considering the structure of S_2Cl_2, it would be reasonable to expect the formation of heterocycles with two sulfur atoms, and sometimes this is actually the case. However, it was shown that sulfur monochloride can also introduce one, three, four, five and even ten sulfur atoms, both bound and not bound to one another. The formation of each class of such heterocycles is considered separately in this Section.

3.1.1. Synthesis of 1,2-dithiols

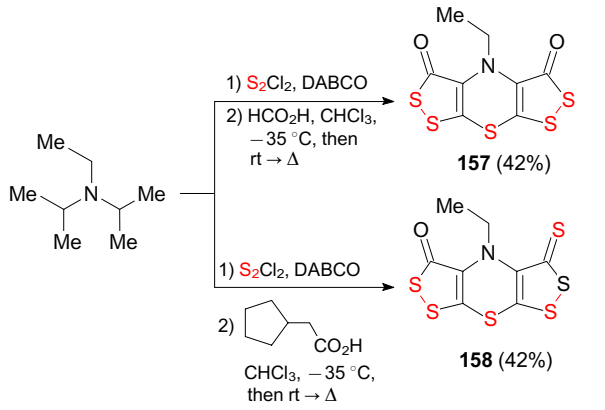
The transformation of the N-isopropyl group to the dithiole ring discovered about 20 years ago was studied in most detail. It was shown that diisopropylethylamine (DIPEA, Hünig's base) reacts with sulfur monochloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) to give an unexpected heterocyclic system — tricyclic bis(1,2-dithiolothiazine) **156**.[134] In this reaction, tricyclic compound **156** is formed upon the replacement of 14 isopropyl C – H bonds of Hünig's base by 10 C – S bonds and two C = C double bonds, which proceeds under mild conditions on mixing of three commercially available and cheap reagents (Scheme 44).

Scheme 44



The addition of formic and cyclopentaneacetic acids as oxygen donors at the final step gives rise to bis(1,2-dithiolothiazine) oxo derivatives **157** and **158** (Scheme 45).[135] The reaction was found to be general: several other substituted and unsubstituted bis(1,2-dithiolothiazines) were prepared in this way in high to moderate yields.[136 – 142] It is noteworthy that substituted bis(1,2-dithiolothiazines) exhibited high activity against feline immunodeficiency virus (FIV), which is the closest biological model of the human immunodeficiency virus.[139] In all cases (Schemes 46 and 47), the reactions with S_2Cl_2 and DABCO are conducted in chloro-

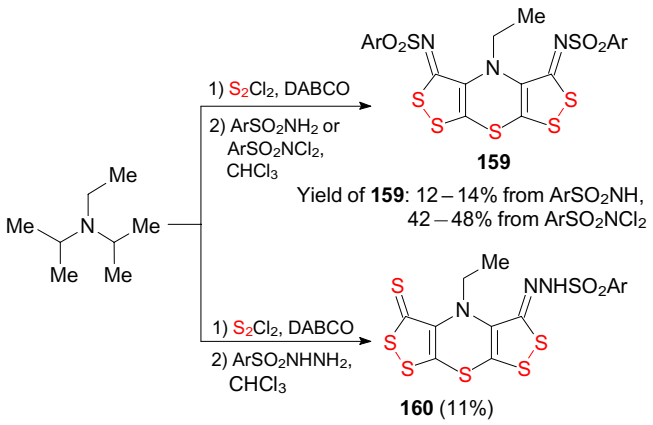
Scheme 45



form at reduced temperature (−35 °C) with subsequent heating of the reaction mixture (see Scheme 45).

Bis(arylsulfonylimino) (**159**) and monohydrazide (**160**) bis(dithiolo)thiazine derivatives are formed in moderate to low yields in the reaction of DIPEA, S_2Cl_2 and DABCO followed by treatment with arylsulfonamides or their N,N-dichloro derivatives in the former case or with arenesulfonic acid hydrazide in the latter case (Scheme 46).[140]

Scheme 46



When sulfur monochloride is taken in excess with respect to DABCO, the reaction does not give the tricyclic products, but stops after the formation of 1,2-dithiole rings from both isopropyl groups. In this case, *N*,*N*-bis(5-chloro-3-oxo-1,2-dithiol-4-yl)amines **161** can be isolated in low yields after treatment of the reaction mixture with formic acid (Scheme 47).[141]

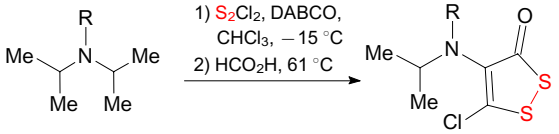
In all of the reactions described above, both isopropyl groups in *N*-alkyldiisopropylamines react with S_2Cl_2, which affords 1,2-dithiole rings. However, there are temperature conditions (−15 °C) under which one isopropyl group reacts. 5-Chlorodithiol-3-ones **162** generated upon treatment of the reaction mixture with formic acid were isolated in high yields (Scheme 48).[142]

2-Methylindoles **163** can be considered as structural analogues of the N-isopropyl group. In a study of the reaction of *N*-alkyl- and *N*-benzyl-2-methylindoles with S_2Cl_2 and DABCO, the addition of triethylamine at the final step was found to generate previously unknown dithioloindoles **164** in high yields (Scheme 49).[143, 144] Note that the reaction of isomeric 1,3-dimethylindole **165** with

Scheme 47

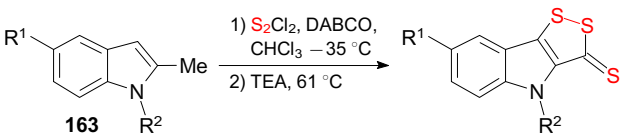
R = Et, Bn, CH_2CH_2Cl, CH_2CH_2SPh, *etc.*

Scheme 48



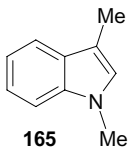
R = Bn, CH_2CH_2Phth, CH_2CH_2Cl, $CH_2CH_2N_3$, CH_2CH_2CN, *etc.*; Phth is phthalimido

Scheme 49



R^1 = H, F; R^2 = H, Me, Et, Pr^i, Bn, CH_2Ar, *etc.*

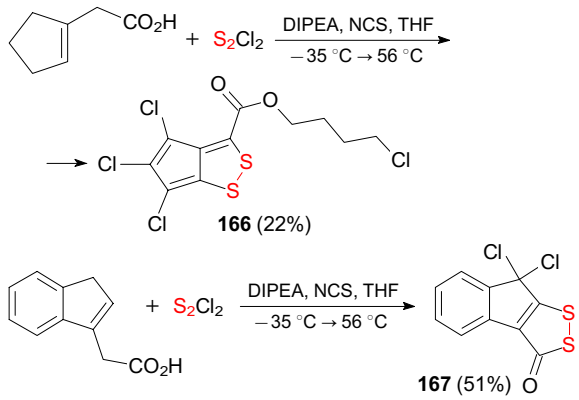
Structure 165



sulfur monochloride does not give the expected dithioloindole, but affords only the products of chlorination of the pyrrole and benzene rings.

In some cases, it was shown that a latent isopropyl group attached to a carbon atom can also participate in the formation of a 1,2-dithiole ring.[145, 146] Treatment of cyclopentenylacetic and indenylacetic acids with a mixture of sulfur monochloride, Hünig's base and *N*-chlorosuccinimide (NCS) in tetrahydrofuran yields 1,2-dithiole deriva-

Scheme 50

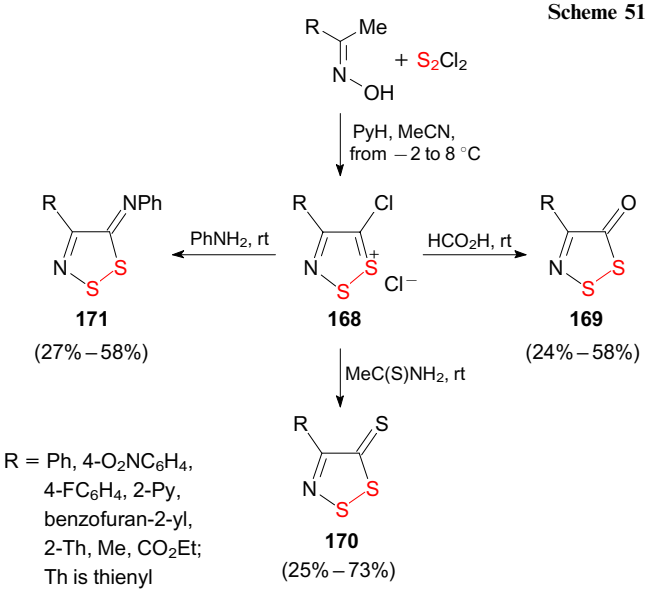


tives **166** and **167**. The formation of these products is accompanied by exhaustive chlorination of the carbocycle, while in the case of compound **166**, also by oxidation of the cyclopentane moiety and acid esterification with chlorobutanol. The latter is formed upon opening of the tetrahydrofuran ring when treated with HCl under the reaction conditions (Scheme 50).

3.1.2. Synthesis and reactions of 1,2,3-dithiazoles

1,2,3-Dithiazoles occupy an important place among five-membered sulfur–nitrogen heterocycles owing to their interesting physical and biological properties and diversified chemistry of their derivatives. The most recent comprehensive review on the synthesis and reactivity of 1,2,3-dithiazoles was published by O.A.Rakitin and L.S.Konstantinova [147] in 2008. The diversity of chemistry of the monocyclic 1,2,3-dithiazoles is due to ready availability and high reactivity of 4,5-dichloro-1,2,3-dithiazolium chloride **168** (R = Cl), so-called Appel's salt. However, before the studies carried out at the ZIOC RAS, other 4-substituted 1,2,3-dithiazolium chlorides **168** were scarcely investigated. These studies demonstrated that 5-oxo- (**169**), 5-thioxo- (**170**) and 5-phenylimino-1,2,3-dithiazoles (**171**) can be selectively synthesized by reactions of readily available ethanone oximes with sulfur monochloride and pyridine in acetonitrile with addition of formic acid, thioacetamide or aniline, respectively, at the final step.[148] It is evident that 1,2,3-dithiazolium chlorides **168** are formed as the key intermediates in this synthesis. Unlike Appel's salt, these compounds are unstable during isolation;[149] however, they readily form derivatives **169**–**171** when react *in situ* with the corresponding nucleophiles (Scheme 51).

Scheme 51

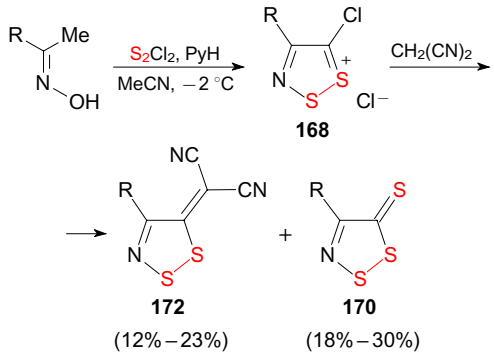


R = Ph, 4-$O_2NC_6H_4$, 4-FC_6H_4, 2-Py, benzofuran-2-yl, 2-Th, Me, CO_2Et; Th is thienyl

The synthesis of C-substituted 1,2,3-dithiazoles turned out to be more challenging. 4-Substituted 1,2,3-dithiazole salts **168** obtained from ethanone oximes and sulfur monochloride react with malonodinitrile less selectively.[150] Along with 4-substituted 5*H*-1,2,3-dithiazol-5-ylidenes **172**, the corresponding thiones **170** were also isolated from the reaction mixture, moreover, in higher yields (Scheme 52).

5,5′-Bis(1,2,3-dithiazoles) **173** are of interest as precursors of stable radical cations possessing magnetic susceptibility and electrical conductivity. A facile and convenient

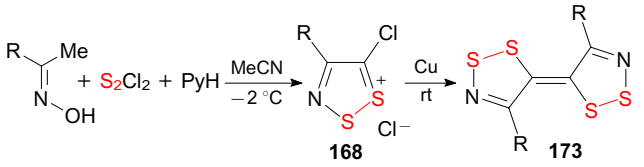
Scheme 52



R = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 2-Th, Me

method was developed for the synthesis of these compounds, consisting in the reaction of ethanone oximes with sulfur monochloride and pyridine in acetonitrile followed by treatment of the reaction mixture with a reducing agent. Among a variety of organic and inorganic reducing agents, the best result was attained in the reaction with copper powder at room temperature.[151] The method proved so efficient that dimer **173** (R = Cl) was obtained in a nearly quantitative yield from Appel's salt taken in a pure state (Scheme 53).

Scheme 53

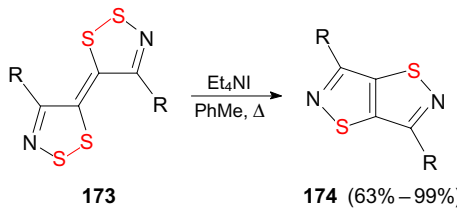


R = Ph (64%), 4-FC_6H_4 (71%), 2-Th (35%), 4-$MeOC_6H_4$ (81%)

The synthesized 5,5′-bis(1,2,3-dithiazoles) **173** are thermally and photochemically unstable compounds, being converted to isothiazolo[5,4-*d*]isothiazoles.[152] It was found that the conversion of di(het)arylbi(1,2,3-dithiazoles) **173** to di(het)arylisothiazolo[5,4-*d*]isothiazoles **174** can proceed under milder conditions by the ANRORC (Addition of the Nucleophile, Ring Opening and Ring Closure) mechanism with Et_4NI used as the nucleophile (Scheme 54). This reaction represents a new convenient pathway to 3,6-di(2-thienyl)isothiazolo[5,4-*d*]isothiazoles **174** (R = 2-Th), which can be employed in the synthesis of components of molecular electronic materials.

No convenient general synthetic route to fused 1,2,3-dithiazoles was reported in the literature; only procedures for the preparation of particular single compounds

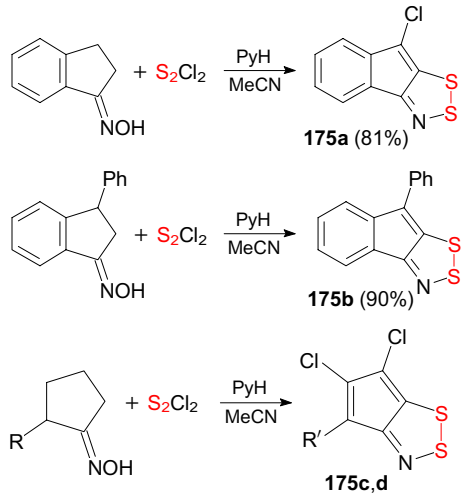
Scheme 54



R = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 2-Th

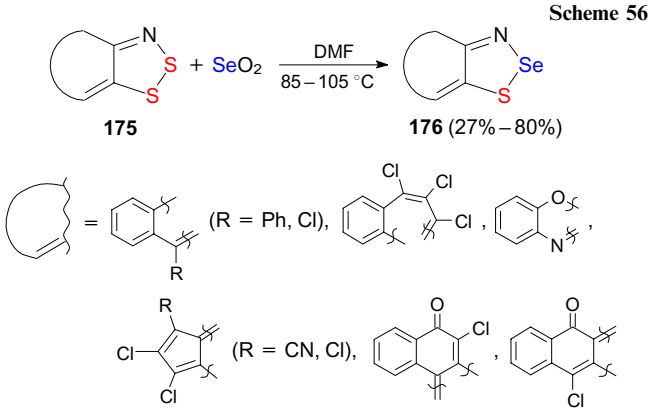
were available.[153] In a detailed investigation of the reaction of cyclic oximes with sulfur monochloride in the presence of organic bases, the best results can be obtained with pyridine in acetonitrile.[154] Furthermore, the completion of the reaction does not require long-term keeping of the reaction mixture and the selectively formed fused dithiazoles **175a–g** are isolated in high yields without column chromatography. The reaction starts at −25 °C and then the mixture of reactants is refluxed in acetonitrile (Scheme 55).

Scheme 55



1,2,3-Thiaselenazoles **176** are poorly studied compounds since they are difficult to obtain; meanwhile, they are of interest as precursors for the preparation of the corresponding radical cations possessing magnetic properties and electrical conductivity.[153] It was found that the S(2) atom of 1,2,3-dithiazoles is selectively replaced by selenium *via* the reaction of fused 1,2,3-dithiazoles **175** with selenium dioxide in DMF.[155] The reaction mechanism was studied by quantum chemical calculations, which demonstrated that the replacement of sulfur by selenium on treatment with SeO_2 is thermodynamically favourable because of the conversion of the SeO_2 molecule to SO_2 (Scheme 56). Quantum

Scheme 56



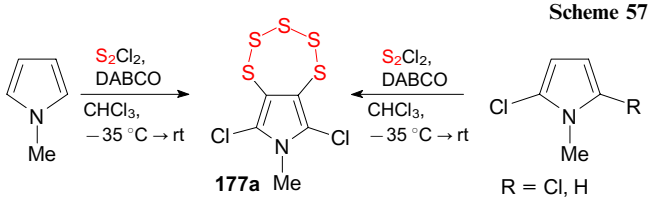
chemical modelling of the reaction revealed two possible pathways, each consisting of three steps.

Biological activity assays showed that 1,2,3-dithiazoles represent a new class of potent reversible melanin synthesis inhibitors with a high potential for further development.[156] It was found that some monocyclic 5-oxo-, 5-thioxo- and 5-phenylimino-1,2,3-dithiazoles (compounds **169–171**) exhibit high activity against FIV.[157] 4-Phenyl-5*H*-1,2,3-dithiazole-5-thione **170** (R = Ph) possesses a good balance between the biological activity and toxicity, which means that its further study holds promise.

3.1.3. Synthesis of fused 1,2,3,4,5-pentathiepins

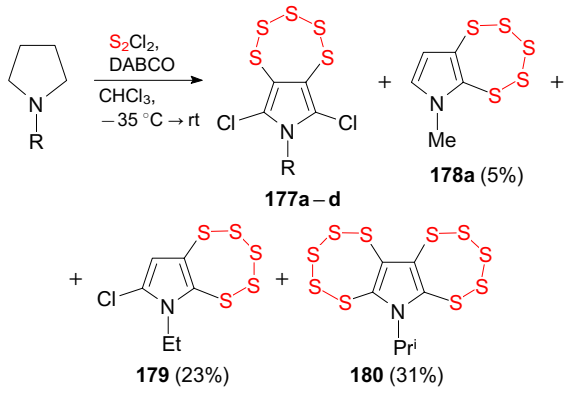
Sulfur monochloride treatment of π-excessive heterocycles such as pyrroles and thiophenes or their tetrahydro derivatives resulted in the unexpected formation of mono- and bis(pentathiepins).[158, 159] Dichloropyrrolopentathiepin **177a** was isolated after the reaction of *N*-methylpyrrole with sulfur monochloride in the presence of DABCO; under optimized conditions the yield of **177a** was 50%.[160] During this reaction, both α-positions of the pyrrole ring are chlorinated and the pentathiepin moiety adds to the β-positions. It is no surprise that 2-chloro- and 2,5-dichloropyrroles form pyrrolopentathiepin **177a** in higher yields (60%–70%) (Scheme 57).

Scheme 57



Sulfur monochloride, which has also oxidative properties, can oxidize the pyrrolidine ring to a pyrrole one. A study of the behaviour of readily available N-alkylpyrrolidine derivatives towards S_2Cl_2 and DABCO demonstrated that *N*-methyl-, *N*-ethyl-, *N*-isopropyl- and *N*-*tert*-butylpyrrolidines form *N*-alkyl-dichloropyrrolopentathiepins **177** in low to moderate yields under these conditions.[161] In addition, a minor amount (5%) of unchlorinated product **178a** with a pentathiepin ring attached to pyrrole positions 2 and 3 was isolated upon the reaction with *N*-methylpyrrolidine. In the case of *N*-ethylpyrrolidine, monochlorinated product **179** is formed, while in the case of *N*-isopropylpyrrolidine, the only and the first currently known bis(pentathiepin),

Scheme 58



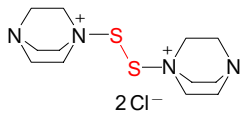
177: R = Me (**a**, 31%), Et (**b**, 29%), Pr^i (**c**, 16%), Bu^t (**d**, 31%)

compound **180**, is obtained as the major product (Scheme 58).

In these reactions, sulfur monochloride acts as both a sulfurating (formation of the pentathiepin ring) and a chlorinating (pyrrole ring chlorination) reagent. It could be expected that reagent **181**, obtained from two equivalents of DABCO and one equivalent of sulfur monochloride in $CHCl_3$, would be more potent as a sulfurating agent than as a chlorinating agent.[162]

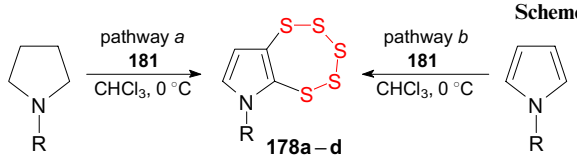
Study of the reactions of *N*-alkylpyrrolidines with reagent **181** (pathway *a*) showed that in all cases, only non-chlorinated products, *N*-alkylpentathiepinopyrroles **178**, are formed in moderate yields. The same products were obtained under similar conditions from the corresponding *N*-alkylpyrroles (pathway *b*), but *N*-isopropylpyrrole was selectively converted to bis(pentathiepin) **180** (Scheme 59).

Structure 181

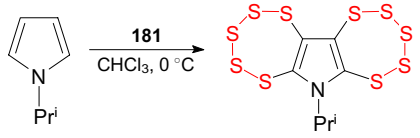


181

Scheme 59



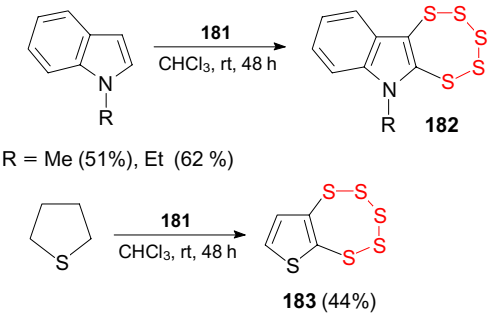
pathway *a*: R = Me (**a**, 29%), Et (**b**, 31%), Pr^i (**c**, 30%), Bu^t (**d**, 61%)
pathway *b*: R = Me (**a**, 33%), Bu^t (**d**, 44%)



180 (33%)

This reaction was extended to other heterocycles. In particular, it was found that *N*-alkylindoles react similarly to pyrroles to give pentathiepins **182** in good yields.[161] The reaction of compound **181** with tetrahydrothiophene also affords pentathiepin **183** in a reasonable yield (Scheme 60). Unfortunately, other aromatic heterocycles such as thiophene, benzothiophene or furan do not react with **181**.

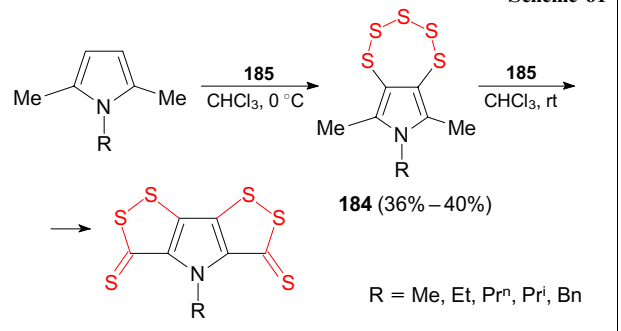
Scheme 60



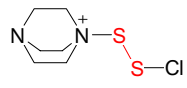
If both α-positions of pyrrole are substituted by, *e.g.*, methyl groups, the pentathiepin moiety is formed at the γ-bond of the pyrrole ring, resulting in moderate yields of pentathiepinopyrroles **184**. Further study of the synthesis of pentathiepinopyrroles **184** from 2,5-dimethylpyrroles demonstrated that the optimal result is attained with reagent **185** (the adduct of equimolar amounts of S_2Cl_2 and DABCO) at low temperature (0 °C).[163]

Unexpectedly, pentathiepins **184** isolated in a pure state were found to further react with compound **185** at room temperature to give bis(1,2-dithiolo)pyrroles **186** in high yields (Scheme 61). The pentathiepin ring and methyl group are usually inert to mixtures of sulfur monochloride and DABCO; however, in this case, reagent **185** presumably behaves as an electrophile with respect to the methyl groups of compounds **184**, which results in the formation of bis(1,2-dithiolo)pyrroles **186** *via* a complex cascade of reactions.

Scheme 61



Structure 185

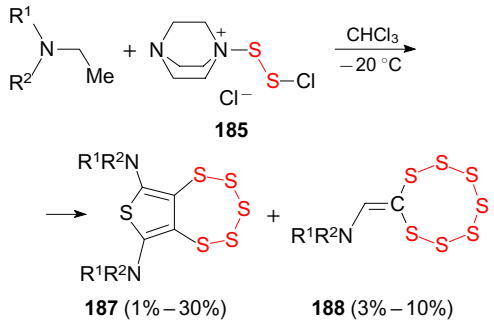


185 Cl^-

Even more unexpected results were obtained when **185** was allowed to react with triethylamine, which is often used in various transformations as an inert base.[164] This reaction afforded thienopentathiepin **187** ($R^1 = R^2$ = Et, 30%) and heptathiocane **188** ($R^1 = R^2$ = Et, 10%). The thiophene ring in compound **187** is constructed with the participation of two ethyl groups of two triethylamine molecules, with the C–C bond being formed from two formally non-activated

methyl groups, while the pentathiepin ring is formed, most likely, as in the above examples. The reaction proved to be fairly general for other tertiary *N*-ethylamines, although the final products were isolated in low yields. However, this unusual transformation furnishes unique thienopentathiepins **187** and heptathiocanes **188** in one step from cheap or readily available starting compounds (Scheme 62).

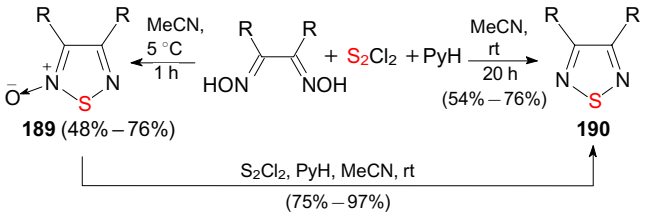
Scheme 62



R^1 = Et: R^2 = Et, Pr^n, Bn; R^1 = R^2 = Pr^i, Bn; $R^1–R^2$ = $(CH_2)_4$

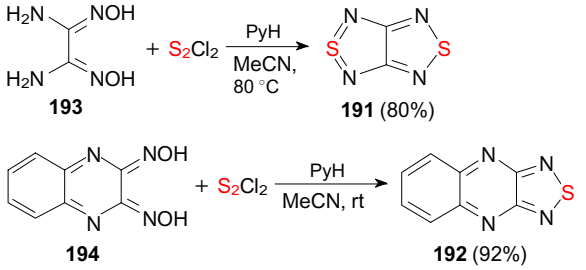
The pentathiepins thus synthesized, like other heterocycles containing S–S bonds, showed activity against FIV when present in nanomolar concentrations, along with low toxicity, in a cell culture *in vitro*.[165]

Scheme 63



189: R = Me, Ph, morpholino, R–R = $(CH_2)_4$, benzo;
190: R = Me, Ph, morpholino CN, Cl, NMe_2; R–R = $(CH_2)_4$, benzo,

Scheme 64



3.1.4. Synthesis and reactions of 1,2,5-thiadiazoles

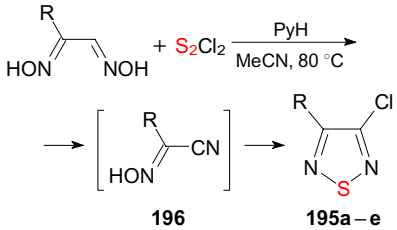
1,2,5-Thiadiazoles, both monocyclic ones or those fused to benzene or heterocyclic rings, possess diverse useful chemical and physical properties and find use in various fields of medicine, agriculture, organic electronics and spintronics.[153,166–168] Study of the reactivity of sulfur monochloride demonstrated that using S_2Cl_2, it is possible to obtain 1,2,5-thiadiazoles from various starting alicyclic or heterocyclic compounds — vicinal diamines and glyoximes, *ortho*-amino-nitro derivatives or 1,2,5-oxa- and 1,2,5-selenadiazoles. Whereas the first two transformations had been known before (although the yields of the final products were often relatively low), the last three transformations were discovered for the first time.

In order to develop the general method for the synthesis of 1,2,5-thiadiazoles, the reaction of vicinal glyoximes with sulfur monochloride was studied in detail.[169] Unexpectedly, it turned out that this reaction with the S_2Cl_2–PyH system in acetonitrile at 5 °C selectively gives 1,2,5-thiadiazole *N*-oxides **189** in moderate yields. The resulting N-oxides **189** can be converted to 1,2,5-thiadiazoles **190** in a nearly quantitative yield *via* the reaction with the same reagent at 20 °C. Thiadiazoles **190** are also formed directly from vicinal glyoximes when a similar reaction is carried out at room temperature (Scheme 63).

Previously, several methods for the preparation of thiadiazolothiadiazole **191** and thiadiazoloquinoxaline **192** have been proposed.[153,166] On the basis of the developed general synthetic route to 1,2,5-thiadiazoles from vicinal glyoximes,[169] efficient one-step procedures were elaborated for the synthesis of heterocyclic systems **191** and **192** from diaminoglyoxime **193** and 1,4-dihydroquinoxaline-2,3-dione dioxime (**194**), respectively (Scheme 64).[169] It is clear that in both cases, the two reactions involving sulfur monochloride proceed simultaneously, that is, thiadiazole ring closure from the dioxime moiety and the formation of the thiadiazole and pyrazine rings from diamine and piperazine moieties. Studies revealed that both heterocyclic systems can serve as precursors for the synthesis of charge transfer complexes and radical anion molecules, which behave as magnetic and electrically conductive materials.[170–173]

It was found that monosubstituted glyoximes react with sulfur monochloride and pyridine in acetonitrile to give 4-substituted 3-chloro-1,2,5-thiadiazoles **195**.[174] Monosubstituted thiadiazoles could not be isolated in any of the examples; evidently, in this case, the reaction follows a mechanism differing from that of the previous reactions and involves the intermediate formation of cyanoxime **196**, as it was proved by Kryschenko *et al.*[174] (Scheme 65).

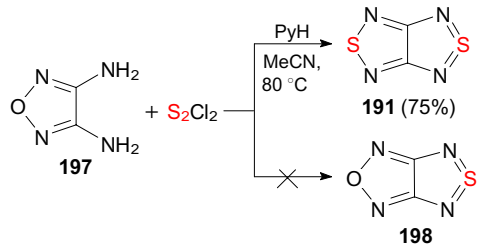
Scheme 65



R = Ph (**a**, 65%), Me (**b**, 20%), SPh (**c**, 33%), piperidino (**d**, 30%), morpholino (**e**, 32%)

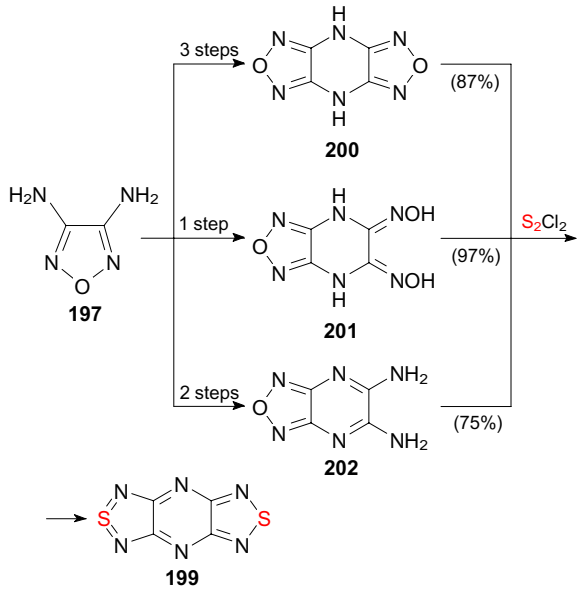
The reaction of 3,4-diamino-1,2,5-oxadiazole (diaminofurazan, **197**) with sulfur monochloride carried out with the goal to obtain oxadiazolothiadiazole **198** unexpectedly gave thiadiazolothiadiazole **191** in a good yield.[170] The key feature of this transformation is the previously undescribed direct substitution of a sulfur atom for the oxygen atom in the 1,2,5-oxadiazole ring (Scheme 66).

Scheme 66



Konstantinova *et al.*,[175] who continued studying this reaction, ascertained that bis(thiadiazolo)pyrazine **199** can be prepared from compounds **200**–**202** containing the 1,2,5-oxadiazole ring. These compounds, in turn, are formed in several steps from 3,4-diamino-1,2,5-oxadiazole (**197**). The reactions are carried out in acetonitrile using various reactant ratios and different temperatures. As in some other transformations, in this case, the replacement of the oxygen atom in the oxadiazole ring by sulfur is accompanied by simultaneous oxidation of the piperazine ring to the pyrazine ring and formation of the second thiadiazole ring from the *ortho*-diamine or *ortho*-dioxime moiety (Scheme 67).

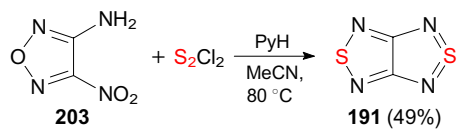
Scheme 67



The reaction of 3-amino-4-nitro-1,2,5-oxadiazole (**203**) with sulfur monochloride and pyridine in acetonitrile follows an even more unexpected pathway, which results in the formation of thiadiazolothiadiazole **191**.[176] In this case, too, two transformations take place in parallel: the sulfur substitution for oxygen in the oxadiazole ring and the formation of the second thiadiazole ring from the *ortho*-aminonitro moiety (Scheme 68).

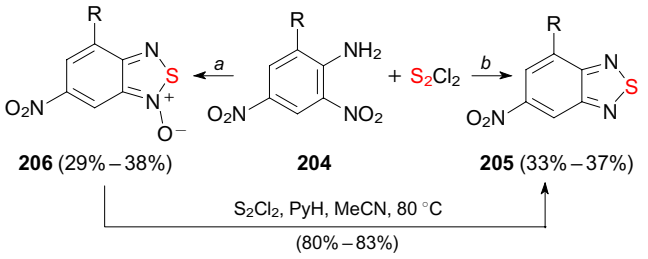
Since the basicity of the aminonitrooxadiazole **203** is similar to that of *o*-nitroanilines, it was of interest to study

Scheme 68



the behaviour of the latter under similar conditions. It was found that commercially available 2,4-dinitroaniline and 2,4,6-trinitroaniline (**204**), which can be easily synthesized, react with sulfur monochloride and pyridine in acetonitrile to afford benzothiadiazoles **205**.[176] Further investigation of this reaction demonstrated that the use of DABCO as a base and chloroform as a solvent makes it possible to isolate benzothiadiazole *N*-oxides **206**, which can be converted to benzothiadiazoles in high yields by the reaction with sulfur monochloride and pyridine in acetonitrile. Moreover, using the Griess assay, it was established that 6-nitro-2,1,3-benzothiadiazole 1-oxide **205** (R = H) is capable of *in vitro* exogenous nitric oxide release in high yield (69%), which attests to good prospects for these compounds as NO donors (Scheme 69).[177]

Scheme 69



(*a*) DABCO, $CHCl_3$; (*b*) PyH, MeCN, 80 °C; R = H, NO_2

In the subsequent investigation of the replacement of oxadiazole oxygen by sulfur, oxadiazoloselenadiazolopiperazine **207** was introduced in the reaction with sulfur monochloride in DMF. It turned out that in this case, oxadiazolothiadiazole **208** is formed initially in a high yield, which indicates that the previously unknown reaction of sulfur substitution for another chalcogen, selenium, takes place in 1,2,5-chalcogenadiazoles.[175] The use of excess sulfur monochloride in the reaction with tricyclic structure **207** results in the formation of bis(thiadiazole) **209**, indicating simultaneous replacement of two different chalcogens (selenium and oxygen) in the oxadiazole and selenadiazole rings of the initial molecule by sulfur. It was found that other selenium-containing tricyclic structures **210** and **211** can also react with sulfur monochloride in a similar way (Scheme 70).

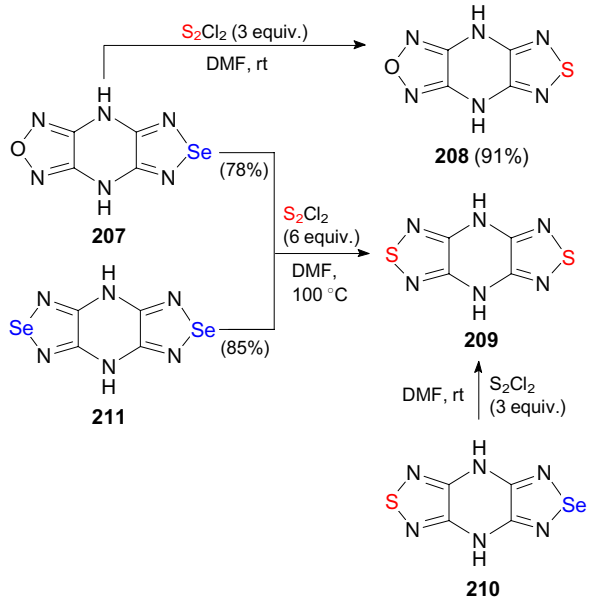
This reaction was extended to a number of fused selenadiazoles: it was found that 1,2,5-selenadiazoles **212a**,**b** and **213a**–**c** fused onto electron-withdrawing rings react with sulfur monochloride in DMF giving mono- and bis(thiadiazoles) **191**, **192**, **214a**,**b** in high yields (Scheme 71).[175]

An attempted synthesis of thiadiazoloselenadiazole **215** from 3,4-diaminothiadiazole **216** unexpectedly resulted in the formation of selenadiazoloselenadiazole **217** upon the reaction of **216** with selenium dioxide in DMF.

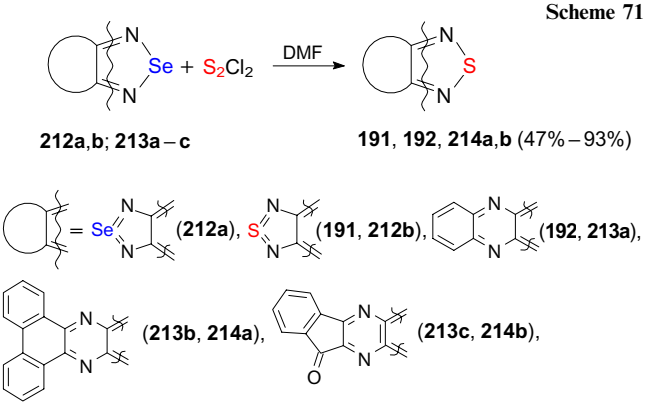
Thus, the authors discovered one more reaction resulting in replacement of one chalcogen atom in 1,2,5-chalcogenadiazoles with another one (Scheme 72).[178]

The reactions of selenium dioxide with 1,2,5-thiadiazoles fused onto electron-withdrawing heterocycles **191**, **192** and **215** in DMF give the corresponding 1,2,5-selenadiazoles **212b**, **213** and **217** in good yields (Scheme 73). The driving force for the reaction is the release of gaseous sulfur(IV) dioxide, which is thermodynamically more

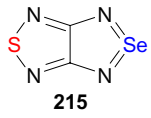
Scheme 70



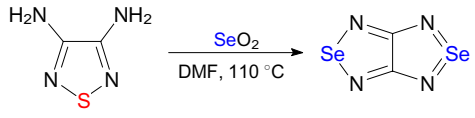
Scheme 71



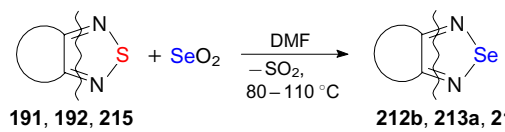
Structure 215



Scheme 72



Scheme 73



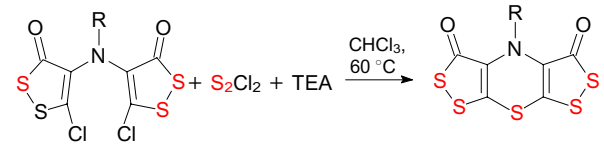
favourable than the selenium dioxide molecule. Monocyclic and benzene ring-fused 1,2,5-thiadiazoles do not react even under drastic conditions.[178]

3.1.5. Synthesis of other heterocycles with one sulfur atom

The formation of heterocyclic molecules with one sulfur atom *via* reactions with sulfur monochloride implies elimination of a sulfur dichloride (SCl_2) molecule or a sulfur atom from the intermediate compound; this is accompanied by ring contraction to a more stable (most often, heteroaromatic) system. Below we present several recent examples of reactions of this type.

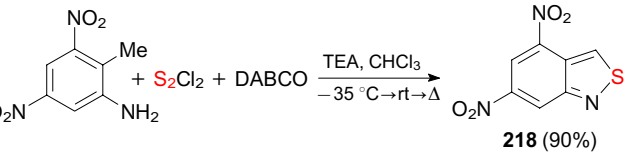
Treatment of *N*,*N*-bis(5-chloro-3-oxo-1,2-dithiol-4-yl)amines **161** with a mixture of S_2Cl_2 and triethylamine in chloroform furnishes bis(dithiolo)thiazines **157** in high yields.[179] The novelty of this type of 1,4-thiazine ring closure is in the unusual substitution of sulfur for chlorine atoms in reactions with electrophilic sulfur monochloride and its mixtures with tertiary amines. The possible key steps of insertion of sulfur atoms are the addition of S_2Cl_2 followed by elimination of an SCl_2 molecule from intermediate compounds (Scheme 74).

Scheme 74



The reaction of 2-methyl-3,5-dinitroaniline with sulfur monochloride and DABCO in chloroform followed by the addition of triethylamine affords fused 4,6-dinitrobenzo[*c*]-isothiazole **218** in a high yield (Scheme 75).[104] It is noteworthy that despite the wide variation of substituents in the benzene ring of *o*-methylanilines, the authors failed to find other examples of isothiazole ring formation. Thus, the reaction requires the presence of several strong electron-withdrawing groups in the *ortho*- and *para*-positions to the methyl group.

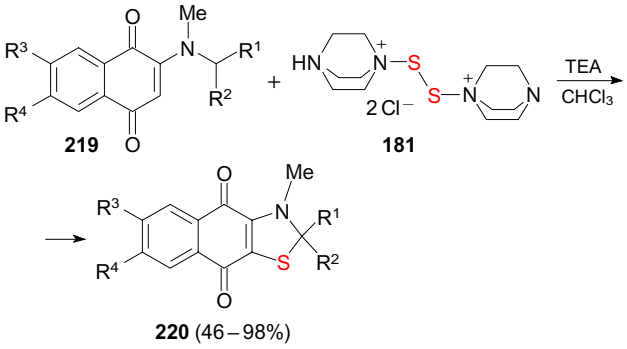
Scheme 75



The reaction of N-substituted 2-(methylamino)naphthoquinones and anthracene-1,4-diones **219** with sulfur monochloride and DABCO in chlorobenzene followed by treatment with triethylamine gives the corresponding 2,3-dihydronaphtho[2,3-*d*]-1,3-thiazole-4,9-diones and 2,3-dihydroanthra[2,3-*d*]-1,3-thiazole-4,11-diones **220** in moderate to high yields (Scheme 76).[180]

Thus, the reactions of sulfur monochloride with aliphatic and heterocyclic compounds can furnish heterocyclic systems with different numbers of sulfur atoms. Special mention should be made of the discovered possibility of direct replacement of one chalcogen atom by another in various chalcogen–nitrogen heterocycles. The approaches

Scheme 76



219 **181** **220** (46–98%)

R^1 = H, Me; R^2 = H, Me, Pr^n, Ph, CH_2NBn_2; R^3 = R^4 = H, R^3–R^4 is benzo

to sulfur–nitrogen heterocycles with the use of sulfur monochloride developed at the ZIOC RAS became a potent tool for the preparation of compounds with a specified structure. The synthesized compounds showed a unique diversity of properties promising for applications not only in chemistry, but also in the materials science and especially in biomedicine.

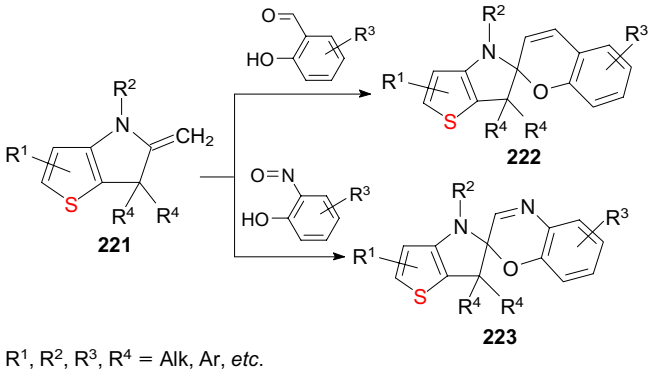
3.2. Photoactive compounds

3.2.1. Thermally reversible photochromes based on thiophene and thienopyrrole merocyanine dyes

As noted in the Introduction, in recent years, fundamental studies in thiophene chemistry have switched to the synthesis and properties of photoactive compounds to develop promising new materials for photonics and material chemistry. Molecules of this type may be of interest as molecular switches, transistor elements, 3D optical memory systems, *etc*. The attention of researchers was focused on extending the range of thermally reversible photochromes (spiropyrans and spirooxazines) and on investigating a unique class of photochromes, thermally irreversible dihetarylethenes, which appeared in the 1990s.[181] The interest in these classes of compounds stemmed, not least of all, from the fact that they contain thienyl moieties and the experience accumulated in thiophene chemistry could thus be implemented in full measure.

Initially, the studies at the ZIOC RAS were pursued along two lines: synthesis of photochromic spiro compounds and synthesis of thienopyrrole-based merocyanine dyes. Photochromic spiro compounds were first obtained by V.Z.Shirinyan *et al.*[182–184] The synthesis was performed by condensation of thiophene analogues of the Fischer base **221** with various *o*-hydroxybenzaldehydes, which gave spiropyrans **222**, and with *o*-hydroxynitrosoarenes to obtain spirooxazines **223** (Scheme 77).[182–184]

Scheme 77



221 **222** **223**

R^1, R^2, R^3, R^4 = Alk, Ar, *etc*.

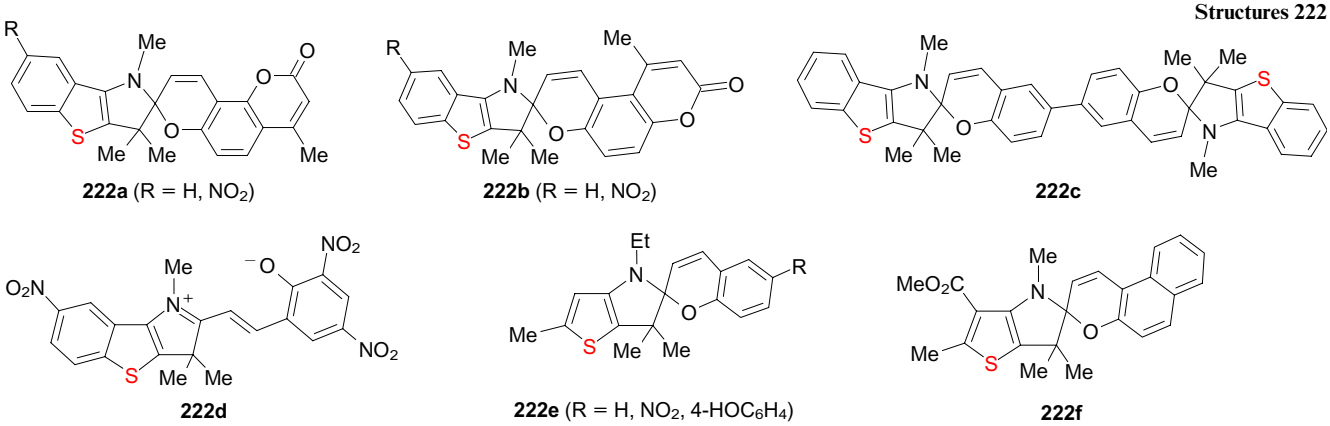
The starting compounds **221** were prepared using two approaches. The key step of the first approach (pathway *a*) was the construction of the 4,6-dihydrothieno[3.2-*b*]pyrrol-5-one system **224** (X = O) by the Stolle reaction involving arylaminothiophene **225** (Scheme 78).[185–187] The second approach (pathway *b*), which proved to be more efficient, was based on the Fisher reaction (rarely applied previously for thiophene derivatives) involving thienylhydrazine **226** as the starting compound.[188] In this case, the reaction proceeded *via* the formation of annulated thienopyrroles **227**, **228**. The starting thiophene derivatives **225** and **226** were obtained from available hydroxythiophenes **229** (see Scheme 78).

The alkylation of benzothienopyrrolenines **230** with alkyl triflate gave good yields of salts **231**, which were subjected to condensation with various *o*-hydroxyaldehydes according to the conventional route to give benzothienopyrrole spiropyrans **222a–f** (Scheme 79).[189–191]

An efficient approach based on the condensation of thienopyrrole Fischer base analogues **221a** with *o*-hydroxynitrosoarenes was proposed for the synthesis of thienopyrrole spirooxazines **223**. The target photochromes **223a–c** were formed with a high degree of purity (Scheme 80).[190, 192]

Thienopyrrole-based merocyanine dyes **232–234** were prepared by condensation of thienopyrrolium salts **235** with heterocyclic analogues of salicylaldehydes or dimethylaminomethylidene derivatives of heterocycles (Scheme 81).[193]

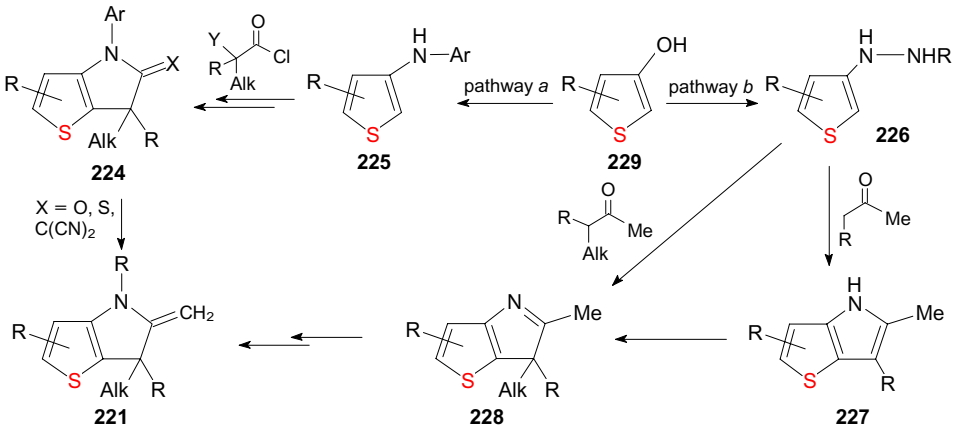
Structures 222



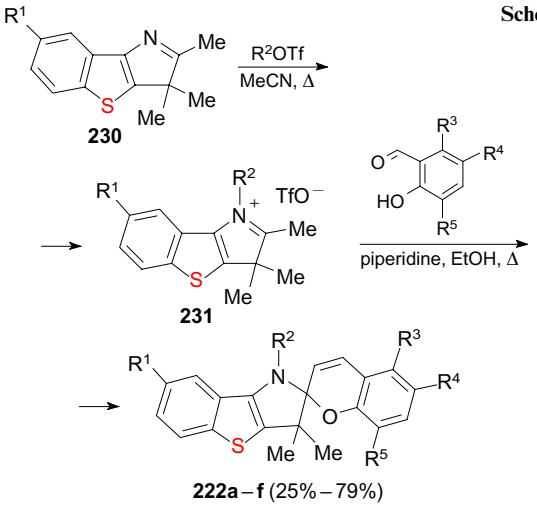
222a (R = H, NO_2) **222b** (R = H, NO_2) **222c**

222d **222e** (R = H, NO_2, 4-HOC_6H_4) **222f**

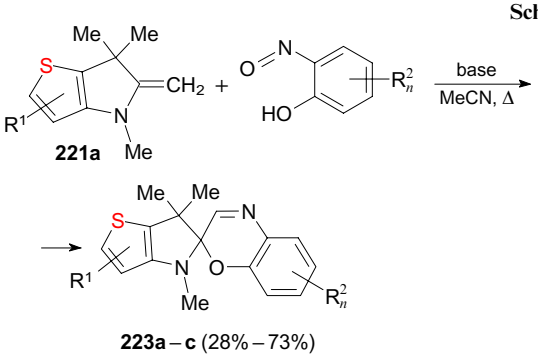
Scheme 78



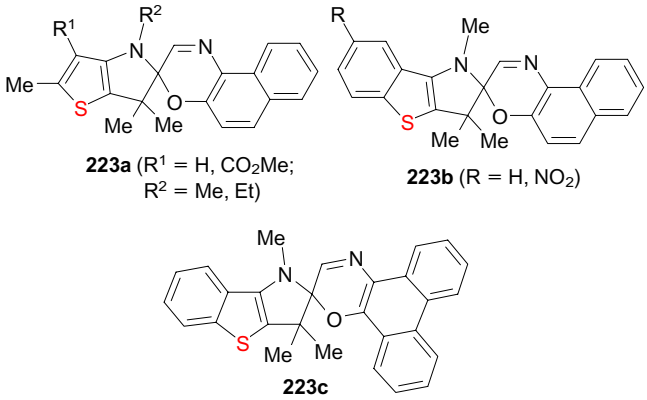
Scheme 79



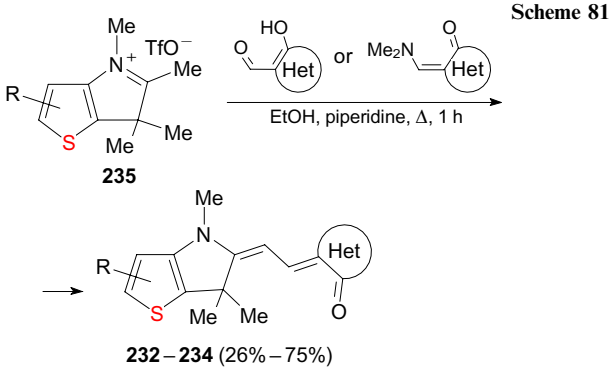
Scheme 80



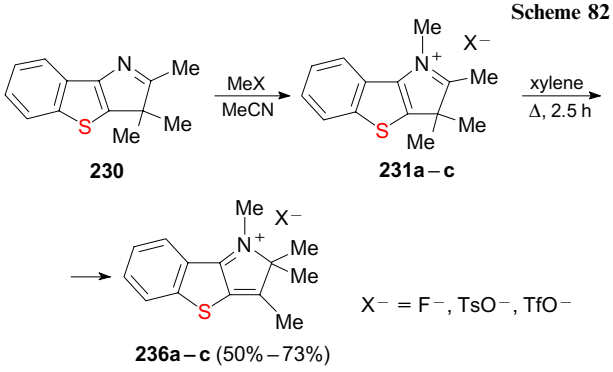
Structures 223



Scheme 81



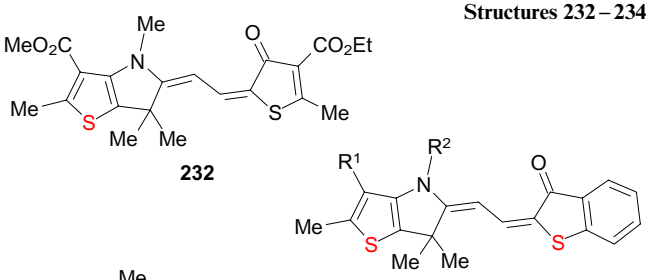
Scheme 82



Salts **231a–c** formed upon alkylation of thienopyrrolenine derivatives **230** were found to undergo thermal rearrangement (1,5-shift) to give salts **236a–c**. The driving force for the rearrangement is apparently high stability of the 2*H*-benzothienopyrrole system, which may be due to positive charge stabilization with the participation of the sulfur atom.[193] The reactions of salts **236a–c** with heterocyclic salicylaldehyde analogues also afford merocyanine dyes **237a–c** (Scheme 82).

It is worth noting that merocyanines **237a–c** tend to show red spectral shifts by more than 110 nm in comparison with the spectra of isomeric dyes **232–234**, which is caused

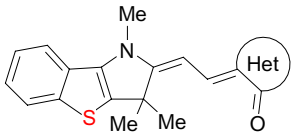
Structures 232 – 234



232

233

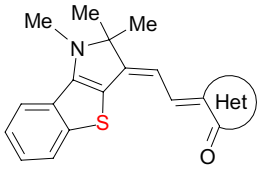
(R^1 = H, CO_2Me; R^2 = Me, Et)



234

Het is 4-methoxy-5-methylcarbonylthiophen-3-one, 1-(4-chlorophenyl)-3-phenylpyrazole, chroman-2,4-dione

Structures 237



237a – c

Het is 4-methoxy-5-methylcarbonylthiophen-3-one (**a**), 1-(4-chlorophenyl)-3-phenylpyrazole (**b**), chroman-2,4-dione (**c**)

by the presence of an additional double bond between the nitrogen atom and the carbonyl group.

Thus, investigation of the reactions between thiophene analogues of the Fischer base resulted in the synthesis of previously unknown photochromic spiro compounds and merocyanine dyes based on thienopyrroline. The spectral kinetic characteristics of these photochromes and merocyanines were investigated and useful correlations between the structure and physicochemical characteristics of the compounds were established.

3.2.2. Thermally irreversible photochromic dihetarylethenes

Thermally irreversible, photochromic dihetarylethenes with high photo-switching cyclability (photostability) are considered as promising precursors for the design of photosensitive and photocontrolled materials for various practical purposes, in particular, multilayer rewritable optical discs. In addition, these compounds are of increasing interest for biological and medical applications as efficient tools for the spatial and temporal control of biological systems.

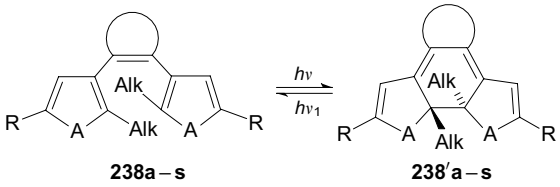
Photochromic di(het)arylethenes with on carbo- and heterocyclic ethene linkers comprising thienyl, benzothienyl, oxazole, imidazole and other substituents as aryl moieties have been studied for more than 15 years at the Laboratory of Heterocyclic Compounds, ZIOC RAS (Scheme 83, A is heteroatom). In the beginning of the 21st century, this laboratory became a world leader in the synthesis of new dihetarylethenes **238a – s** and **238′a – s**.[194 – 197] Particular attention was paid to the synthesis of bridged photochromes **238a – f**, as these compounds provide the highest photo-switching cyclability.

Photochromic dihetarylethenes **239** based on cyclobutenediones were synthesized for the first time.[198 – 200] They were prepared by reactions of various thiophenes with squaric acid dichloride (**240**) (Scheme 84).

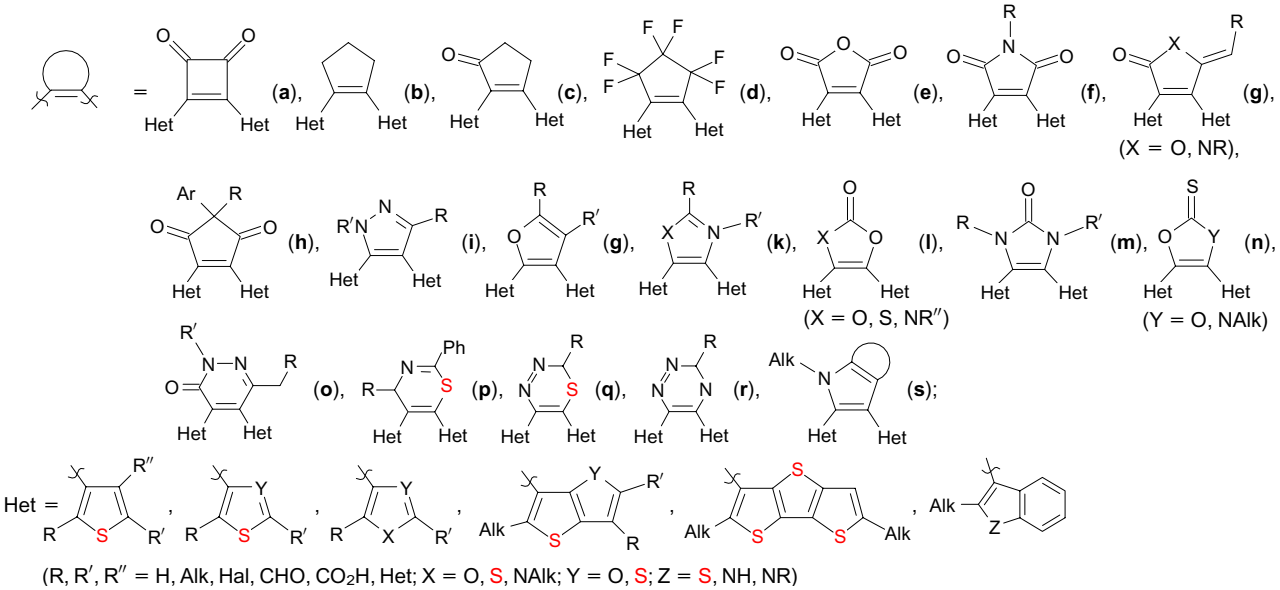
In turn, dihetarylcyclobutenediones **239** were used to synthesize promising, previously unknown photochromic dihetarylethenes with diarylfurandione (**241**) and maleimide (**242**) bridges. For this purpose, compounds **239** were oxidized with hydrogen peroxide and the products were reacted with aromatic amines (Scheme 85).[201 – 204]

An alternative approach to the synthesis of maleimide dihetarylethenes is cross-coupling of 2-methyl-3-benzothienylboronic acid (**243**) with 3,4-dibromo-*N*-butylmaleimide **244**, which gives maleimide **245**. The reaction takes place on

Scheme 83

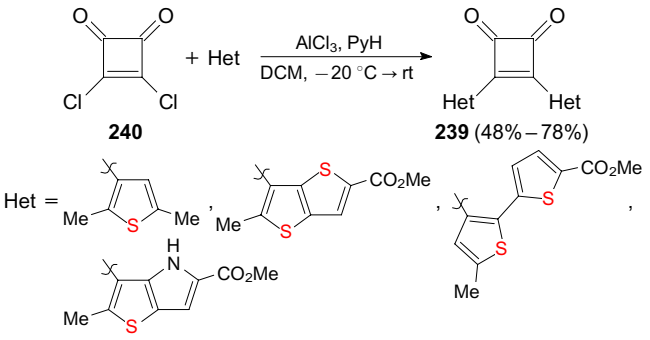


238a – s **238′a – s**

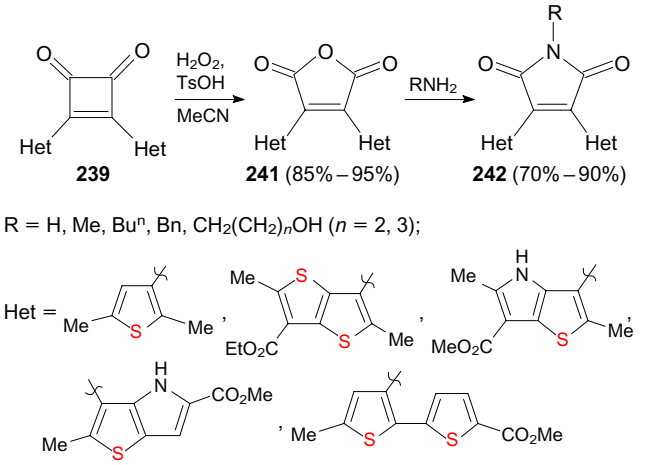


(R, R′, R″ = H, Alk, Hal, CHO, CO_2H, Het; X = O, S, NAlk; Y = O, S; Z = S, NH, NR)

Scheme 84



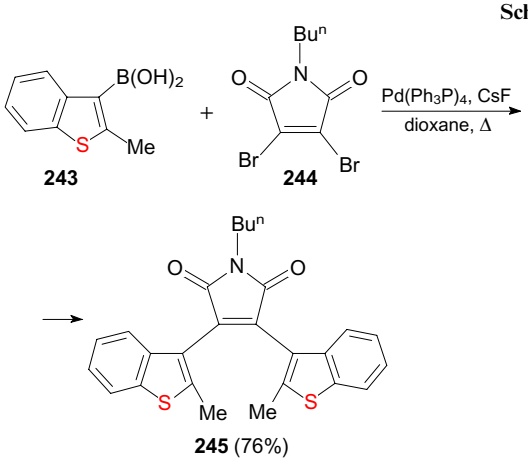
Scheme 85



refluxing of reactants in dioxane in the presence of $Pd(Ph_3P)_4$ and CsF.[205] Later, the method was successfully extended to other heterocyclic and aromatic boronic acids (Scheme 86).

An unusual synthesis of dithienylmaleimides in which the maleimide moiety is attached to position 2 of the thiophene ring is depicted in Scheme 87. The reaction of dichloromaleimide **246** with hydroxythiophene **229a** proceeds in good yields[206] and can give both mono **247** and dithienylethenes **248**, depending on the ratio of reactants and reaction conditions. The alkylation of the hydroxyl group in **248** yields alkylated analogues **249** (see Scheme 87). Unlike dithienylmaleimides **242** and **245** in which the thiophene ring is attached to position 3,

Scheme 86



2-thienylmaleimides **247**–**249** do not exhibit photochromism, but have fluorescence properties.

The development of photochromes based on perfluorocyclopentene **250** is described in a considerable number of papers, which are covered in reviews.[196, 197, 207] Therefore, the present review presents only the general approach to these reactions. In particular, Scheme 88 shows the most typical example of the design of perfluorocyclopentene photochromes **251** and **252** *via* reactions of the lithium salts of heterocycles **253** with perfluorocyclopentene **250**.[208]

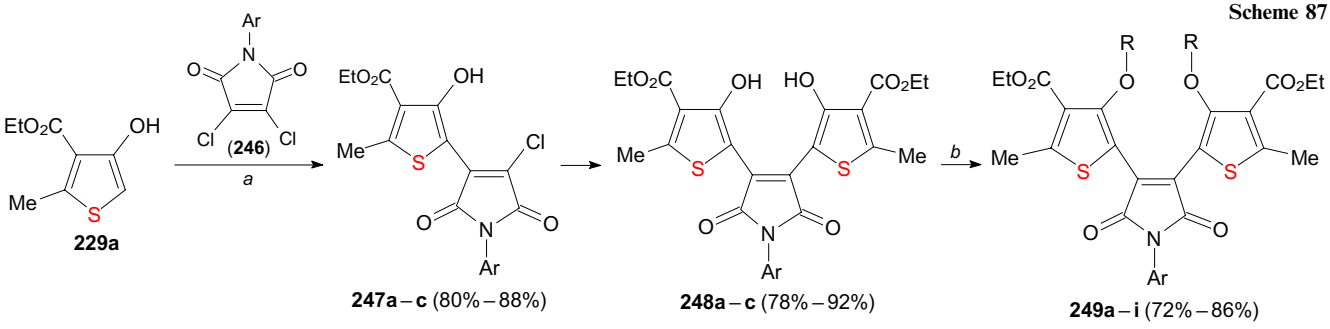
The same authors synthesized[209] product **254**, one of the most promising compounds by that time, possessing cyclability of more than 2000 (Scheme 89).

The structures of both this dihetarylethene and its cyclic form were established by X-ray diffraction. It was found that in the starting compound **254a** (R′ = CF_3), the planes of the thienothienyl rings are rotated relative to each other by 65.8°, whereas the heterocycles of photoproduct **254′a** are arranged in one plane, thus forming a potent system of conjugation, which accounts for the considerable red shift of the absorption band of the product (Fig. 2).

Most often, functionalization of perfluorocyclopentene photochromes does not affect fluorine atoms and can be used to introduce the Br atom and the SO_2Et, CO_2H, CO_2Me and C(O)NHAr substituents into thiophene rings of the basic structure **254b** (to give compounds **255**–**259**, Scheme 90; the character F inside the ring means perfluorination).[208]

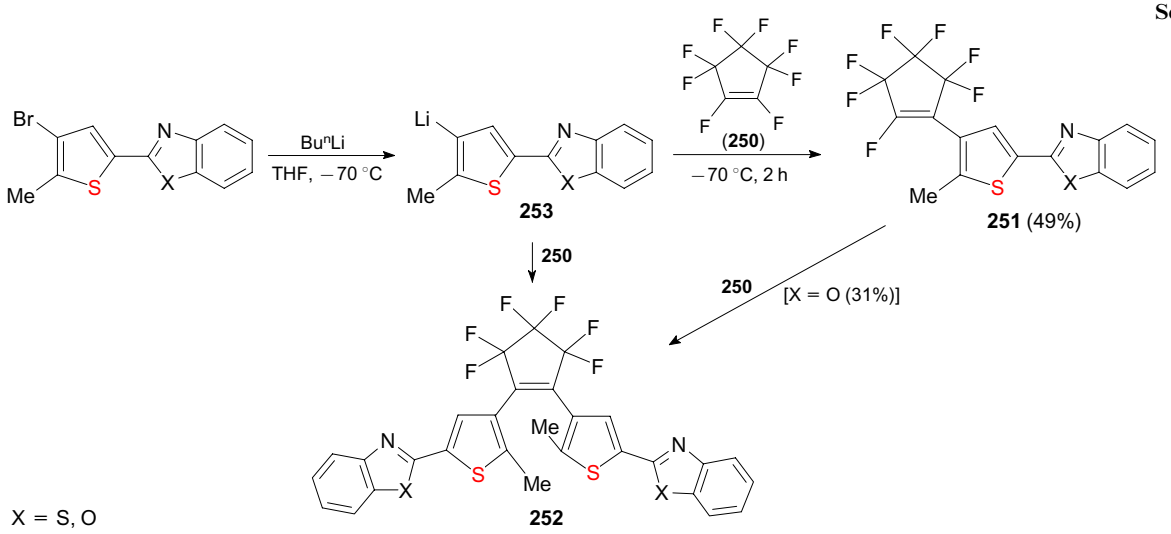
Benzothiophene analogues **260** were first iodinated into the aromatic ring and, after that, compounds **261** were introduced into Pd-catalyzed Suzuki–Miyaura cross-coupling with various boronic acids. Depending on the reaction

Scheme 87

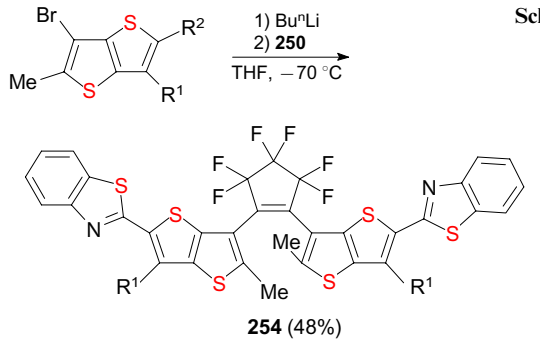


(*a*) Na, PhH, Δ; (*b*) RX, K_2CO_3, DMF, rt; Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**); R = Alk, X = Hal

Scheme 88



Scheme 89



conditions and the molar ratio of boronic acid to diiodo derivative **261**, the reactions gave a broad range of products **262** – **264**, which are of interest for applications in photonics and molecular electronics.[210] Under the Friedel – Crafts reaction conditions, acylation products **265a**,**b** were formed (Scheme 91).[211]

Bromoacetyl derivatives **265a**,**b** were found to be efficient precursors of symmetrical and unsymmetrical structures **266a**,**b** and **267a**,**b** exhibiting fluorescence, which can be considered as promising optical data storage elements (Scheme 92). The starting compounds **268a**,**b** were obtained by three-component condensation of imidazolidin-2-one or thiazolidin-2-one with aldehydes and 5-aminopyrazole (51% – 57% yield).[212, 213]

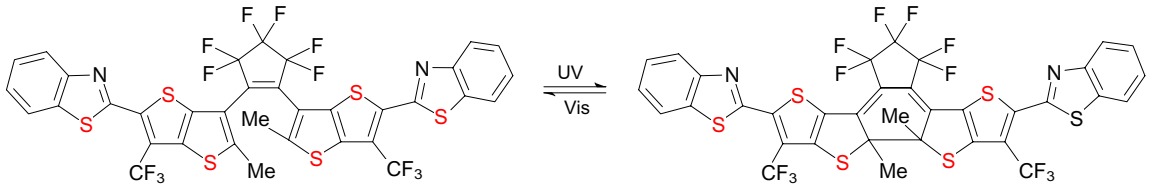
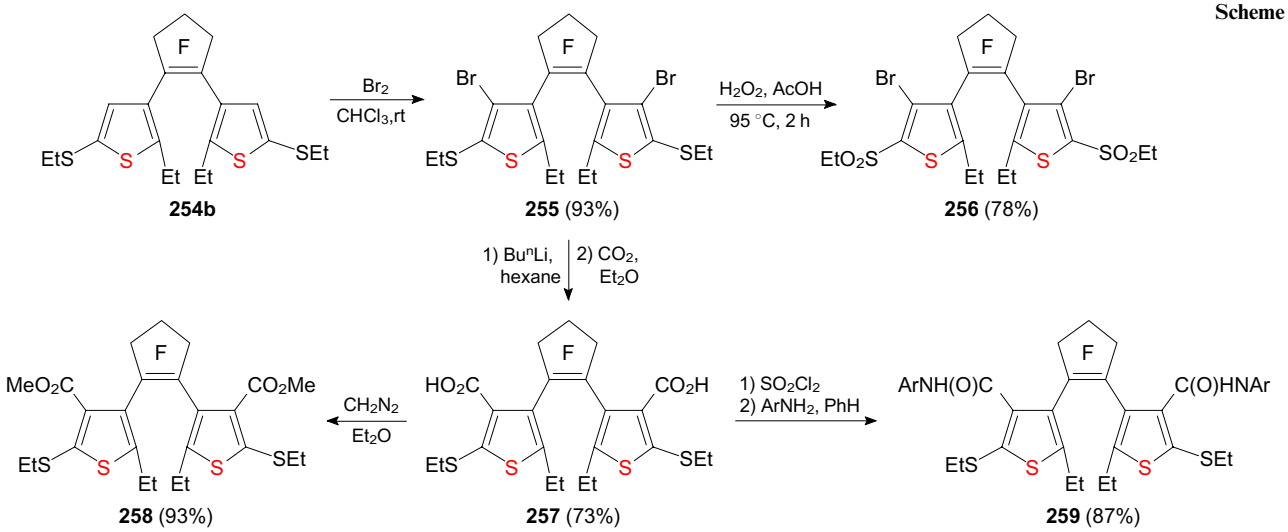
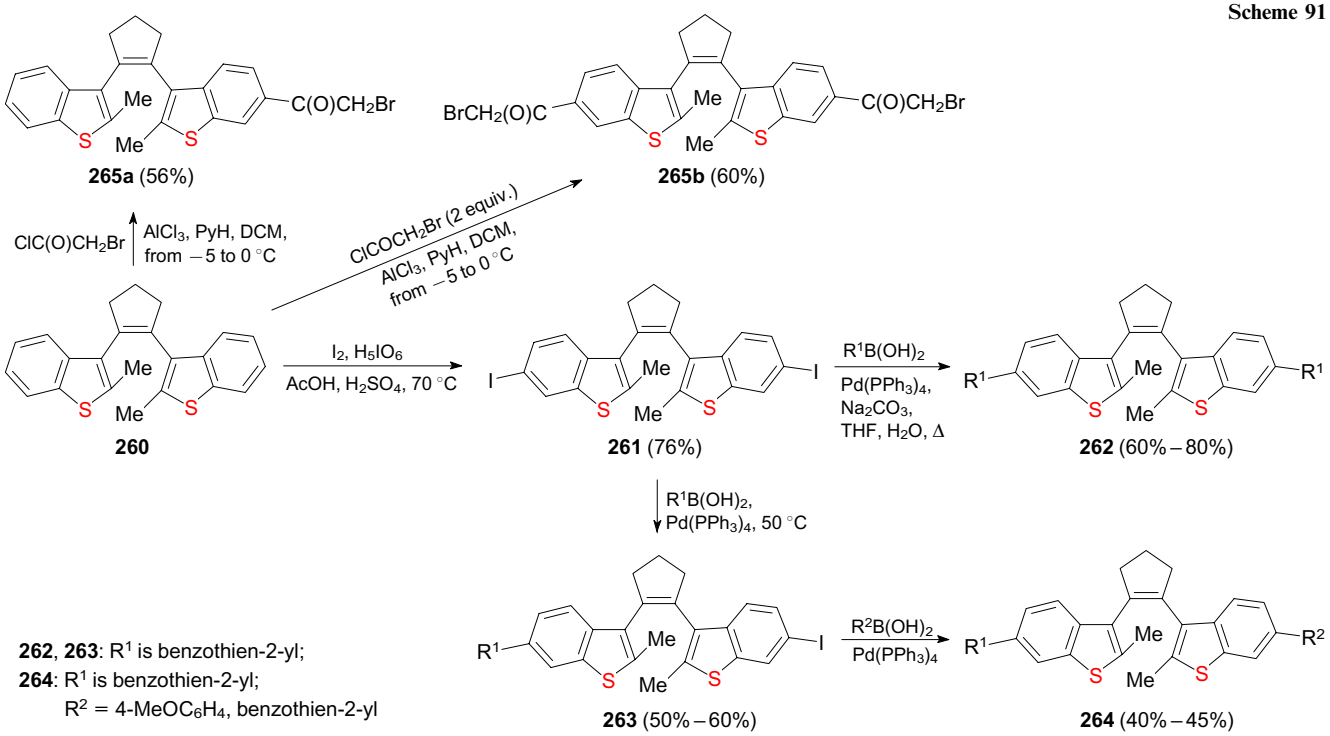


Figure 2. Structures of dihetarylethene **254a** and photoproduct **254′a**.

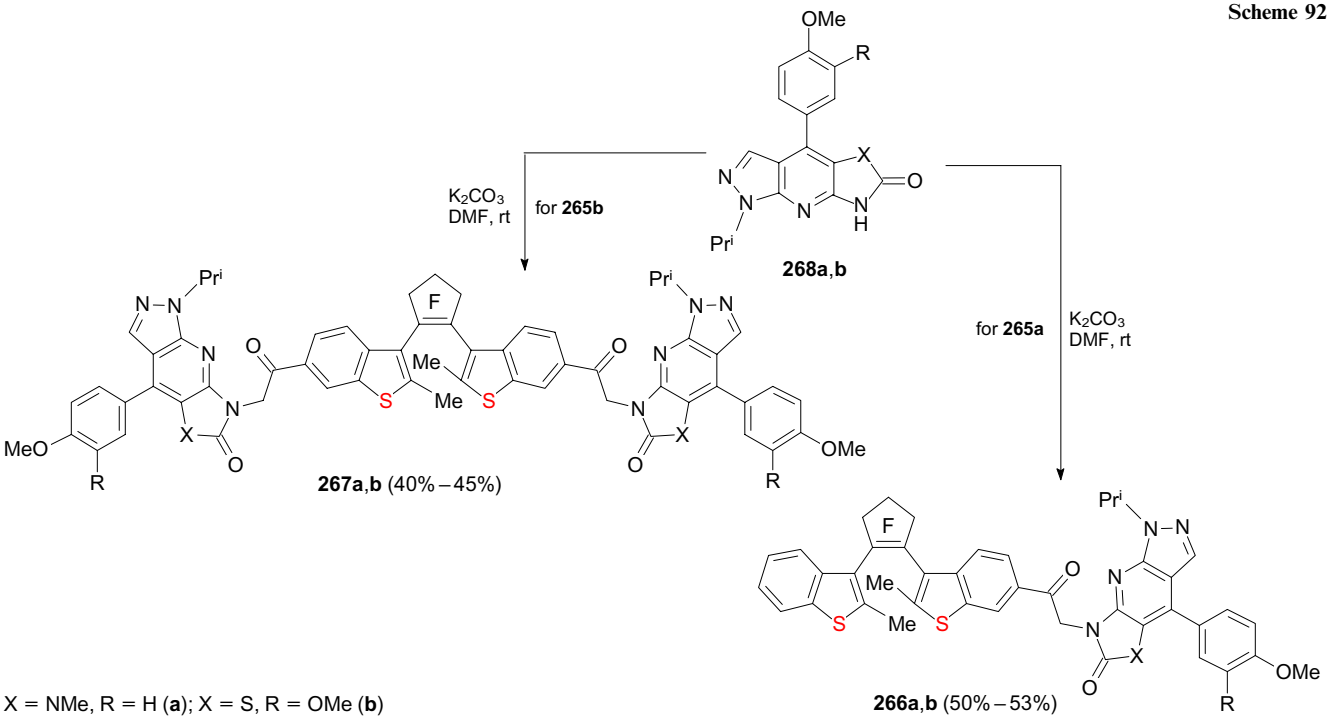
Scheme 90



Scheme 91



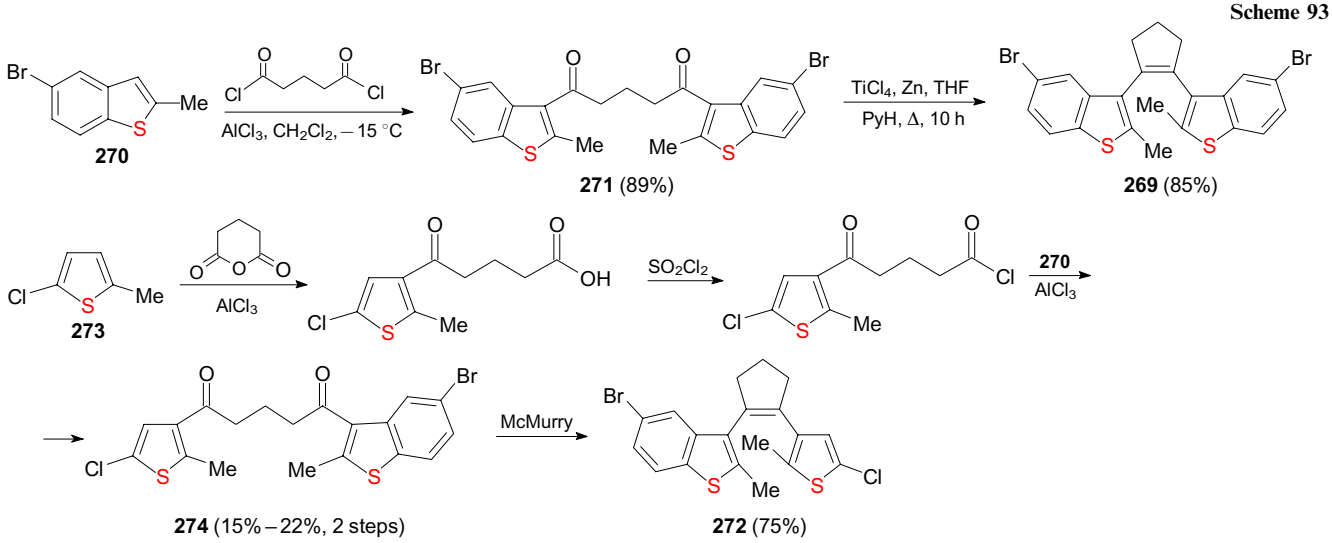
Scheme 92



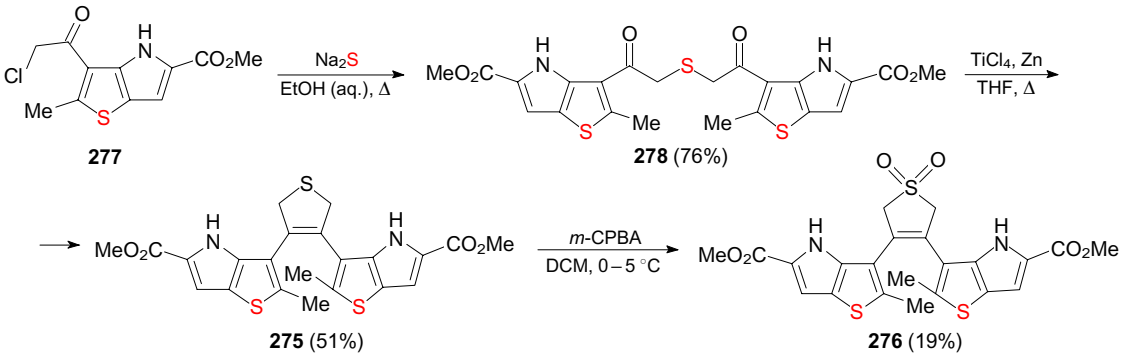
Generally, perfluorocyclopentene-based dihetarylethene photochromes can be considered to be accessible. However, the relatively high cost of perfluorocyclopentene and certain inconvenience of handling caused by its high volatility (T_b = 26–28 °C) and also relatively low yields of products stimulated the search for approaches to photochromes with more convenient bridges, *e.g.*, cyclopentene.

The McMurry reaction using relatively accessible glutaric acid derivatives (chloride or anhydride) as the starting compounds and giving symmetrical and unsymmetrical dihetarylethenes proved to be most efficient.[214,215] This approach is exemplified by the synthesis of symmetrical structures **269** *via* the Friedel–Crafts acylation of bromomethylthiophene **270** with glutaric acid dichloride followed by the McMurry reaction of the resulting diketone **271**.[216] Unsymmetrical structure **272** is obtained in a similar way: chloro(methyl)thiophene **273** is acylated with glutaric anhydride and the resulting diketone **274** is subjected to McMurry cyclization (Scheme 93). A study of the photochromic properties of the synthesized cyclopentene dihetarylethenes showed good reason for further search for photochromes among these structures.

Scheme 93



Scheme 94

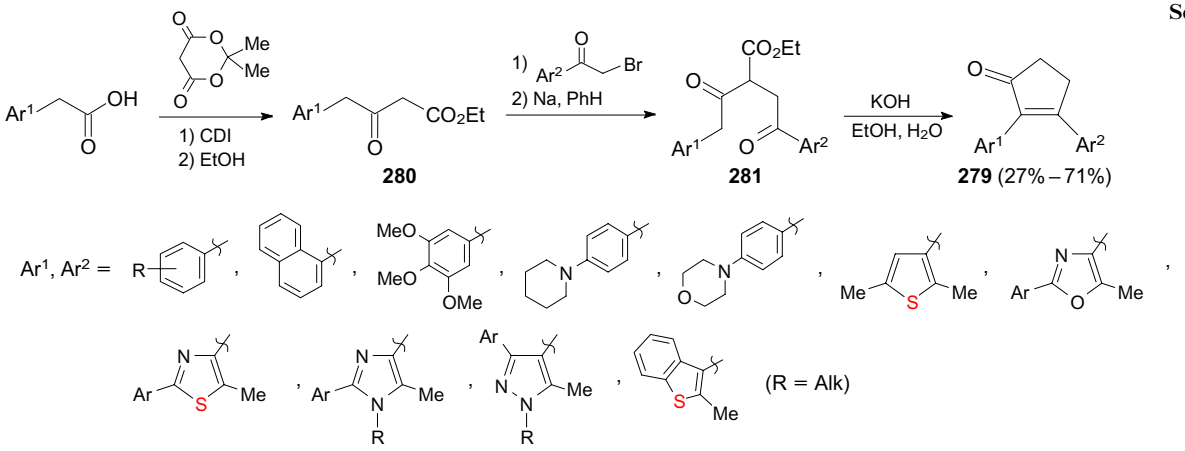


This reaction was successfully used to obtain a dichlorinated analogue of compound **269** [217] and photochromes **275** and **276** with a heteroatom in the bridge.[218] In the latter case, chloromethyl ketone **277** was converted to diketone **278** by the reaction with sodium sulfide followed by McMurry cyclization to give photochrome **275**, which was oxidized to sulfone **276** in the presence of *m*-chloroperbenzoic acid (Scheme 94).

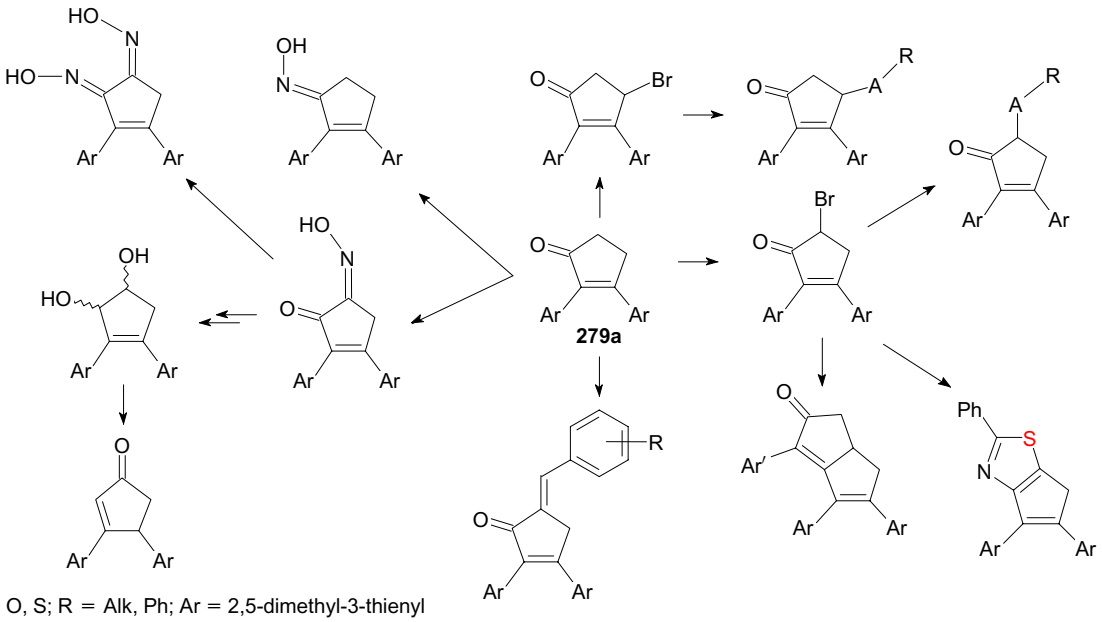
Apart from perfluorocyclopentene- and cyclopentene-bridged dihetarylethenes considered above, previously unknown photochromic cyclopentenone-based diarylethenes **279** were synthesized and studied in detail. A convenient method was proposed for the synthesis of these products from available compounds.[219–221] This method is based on condensation of phenacyl bromides with ethyl (het)aryl-3-oxobutanoate **280** in anhydrous benzene in the presence of sodium metal. In turn, keto ester **280** is prepared by C-acylation of Meldrum's acid with carbonyldiimidazole. The resulting diketone **281** cyclizes to the target **279** in the presence of 7% KOH in aqueous ethanol (Scheme 95).

This method was utilized to prepare a broad range of new photochromic diarylethenes **279** with various aromatic and heteroaromatic substituents, and the products were used to study modifications of the cyclopentenone moiety. The approaches to functionalization of the ethene bridge are depicted in Scheme 96 in relation to 2,3-bis(2,5-di-

Scheme 95

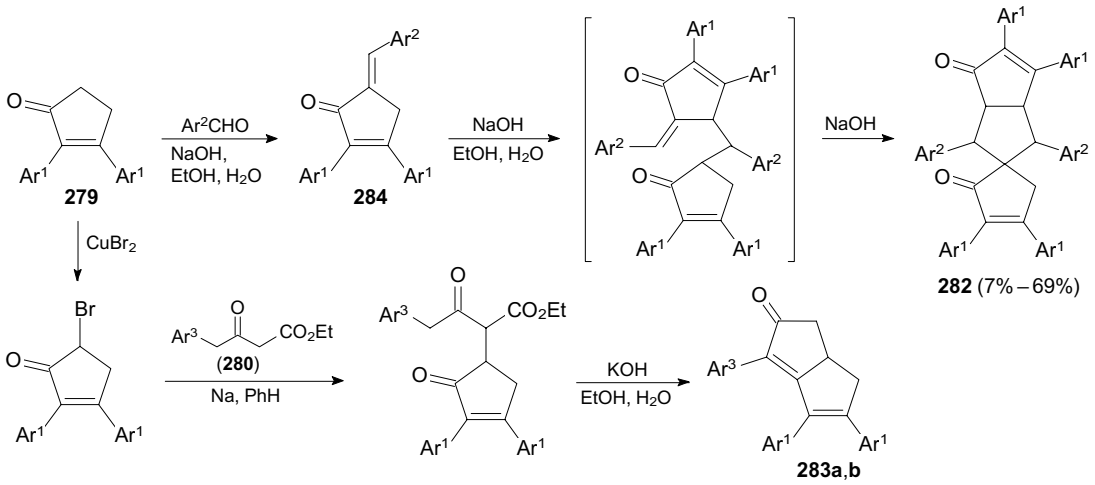


Scheme 96



A = NAlk, O, S; R = Alk, Ph; Ar = 2,5-dimethyl-3-thienyl

Scheme 97



Ar^1 is 2,5-dimethyl-3-thienyl; Ar^2 = Fc, 2-Py, 3-Py, anthracen-9-yl; **283**: Ar^3 = 1-Naph (**a**, 13%), 2,5-dimethyl-3-thienyl (**b**, 32%); Fc is ferrocenyl, Naph is naphthyl

methyl-3-thienyl)cyclopent-2-en-1-one (**279a**). Further modification of the five-membered ring in symmetrical and unsymmetrical 2,3-diarylcyclopent-2-en-1-ones **279** with various aryl groups has been reported.[219, 222]

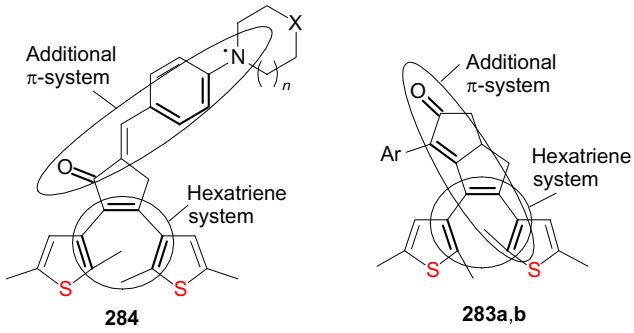
Photochromic diarylethenes **282** and **283** with a spiro system and an elongated chain of conjugation in the ethene bridge were first prepared by condensation of 2,3-diarylcyclopent-2-en-1-ones **279** with aromatic aldehydes followed by functionalization of both the starting compound and condensation products **284** (Scheme 97).[223 – 225]

3.2.3. Spectral kinetic properties of cyclopentenone-based diarylethenes

The fluorescence properties of diarylethenes were studied for the design of promising smart materials including materials for 3D optical data storage. In these materials, fluorescence properties can be used for non-destructive readout for both single compounds and according to the FRET (fluorescence resonance energy transfer) approach.[226, 227]

The fluorescence diarylcyclopentenones can be conventionally divided into two types (Fig. 3). In one type of compounds, additional π-systems are introduced into the hexa-1,3,5-triene moiety responsible for photoswitching (*e.g.*, compounds **284** and **283a**,**b**), while in the second type, the introduced fluorophore and the photochromic moiety of the molecule are linked through either a 'flexible' (O atom) (compounds **285** – **287**) or a 'rigid' (C=C bond) (compound **288**) spacer. In all cases, fluorescence is inherent only in acyclic forms. A general trend for all fluorescent diarylcyclopentenones, except compounds with a flexible spacer, is a considerable decrease in the quantum yields of the forward and reverse photoswitching reactions.

The structure – property relationship was established by studying the effect of various structural factors on the spectral properties of unsymmetrical dihetarylethenes **289** – **294** (Table 1). As can be seen from the Table, the

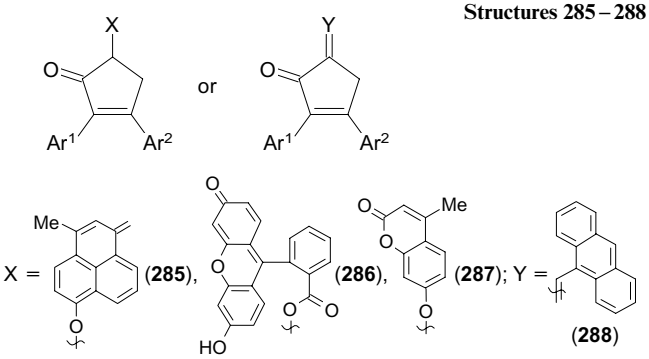


284 **283a,b**

X = O, CH_2

Figure 3. Fluorescent diarylcyclopentenes.

Structures 285 – 288



Ar^1 is 2,5-dimethyl-3-thienyl: Ar^2 = 1-Naph, 2,5-dimethyl-3-thienyl

pairs of unsymmetrical dihetarylethenes based on thiophene, oxazole and thiazole have different spectral properties. For example, the absorption maxima of the initial and closed-ring forms of compounds **289** and **291** differ by 225 and 158 nm, respectively, and the absorption coefficients also differ considerably. A similar trend holds for the pair of compounds **292** and **294** (see Table 1).[228]

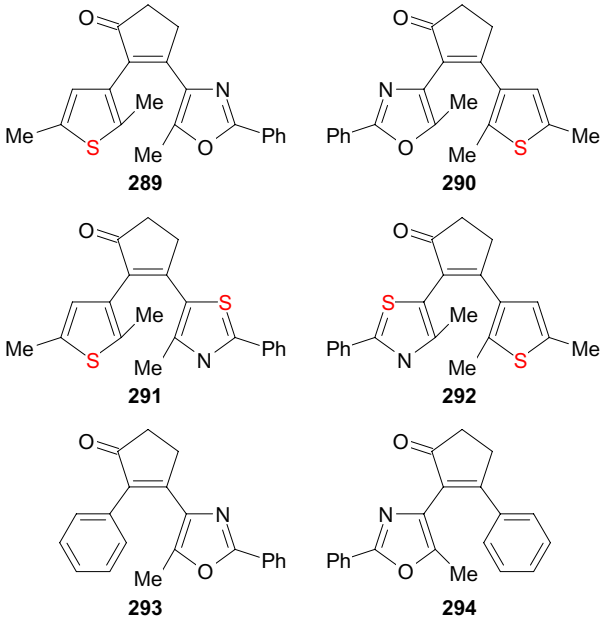
The variation of the azole (Az) nature in a series of 2,3-diarylcyclopent-2-en-1-ones affords dihetarylethenes with a broad range of absorption maxima (from 501 to 579 nm) of the photoinduced forms (Fig. 4).

Table 1. Spectral characteristics of the initial dihetarylethenes and the closed-ring forms (in acetonitrile).

Compound	Open-ring form		Closed-ring form	
	λ_{max} /nm	ε [a]	λ_{max} /nm	ε [a]
289	298	26 000	523	7600
290	284	24 300	549	6000
291	343	22 000	501	4300
292	313	19 700	490	3000
293	297	23 000	–	–
294	279	27 800	540	540

[a] In L mol^{-1} cm^{-1}.

Structures 289 – 294



The reduction of the carbonyl group induces blue shift of the absorption maxima of photoinduced forms: 1,2-diarylcyclopentenes have absorption maxima of the photoinduced forms in the 420 – 500 nm range. The use of cyclopentenone-bridged dihetarylethenes in organic field effect

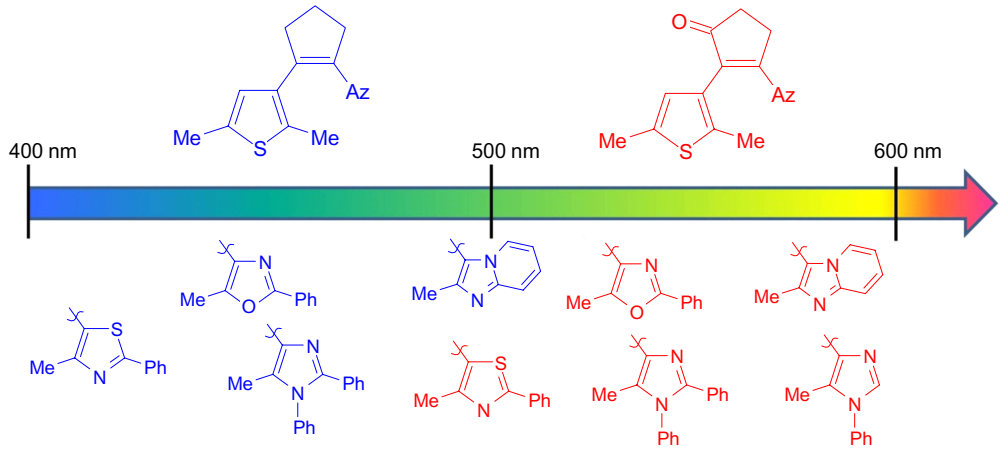


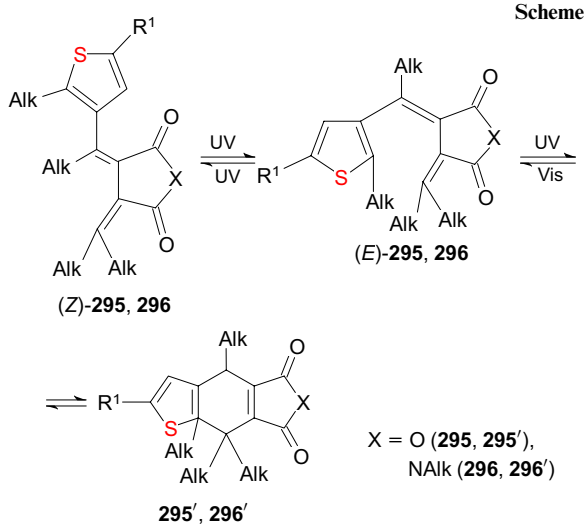
Figure 4. Absorption maxima of photoinduced (closed-ring) foms of dihetarylethenes.

transistors considerably increases their efficiency. These devices demonstrate high programming rate, record high switching coefficients at low operating voltages and write–erase cycling stability.[229] The authors also demonstrated that even minor changes in the structure of dihetarylethene bridges induce considerable changes in the parameters of field effect transistors, which can be used to control characteristics of the devices.[230]

3.2.4. Thermally irreversible photochromic fulgides and fulgimides

Fulgides **295** (X = O) and fulgimides **296** (X = N–Alk) also exhibit photochromic properties, similar to those of dihetarylethenes. These compounds undergo thermally irreversible, but photoreversible interconversions between the open- (*Z*- and *E*-isomers) and closed-ring forms **295′**, **296′** (*C*-isomer) (Scheme 98).

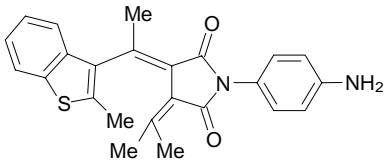
Scheme 98



As a rule, fulgimides are obtained by reactions of organic amines with fulgides, their close analogues derived from maleic anhydride. Scheme 99 demonstrates the synthesis of thiophene-based bis(fulgimide) system **297**, in which the photochromic moieties are linked by aromatic diamine bridges, from fulgide **298**. The key step is the reaction of 3-acetyl-2,5-dimethylthiophene with diethyl isopropylidenesuccinate in the presence of a base. The condensation of the resulting diacid **299** induced by carbonyldiimidazole gives fulgide **298**.[231]

The condensation of fulgide **298** with Boc-substituted (Boc is *tert*-butyloxycarbonyl) hydrazine gives aminofulgimide **300**, which is of interest for its synthetic potential; the overall yield (after hydrolysis of Boc-protected product **301**) is 70%.[232] A similar sequence of transformations, resulting in approximately the same product yield, was applied to prepare fulgimide **302**.[233] Both amines were allowed to react with aldehydes, which gave photochromic hybrids (*e.g.*, compounds **303**) in almost quantitative yields (Scheme 100).[233–235]

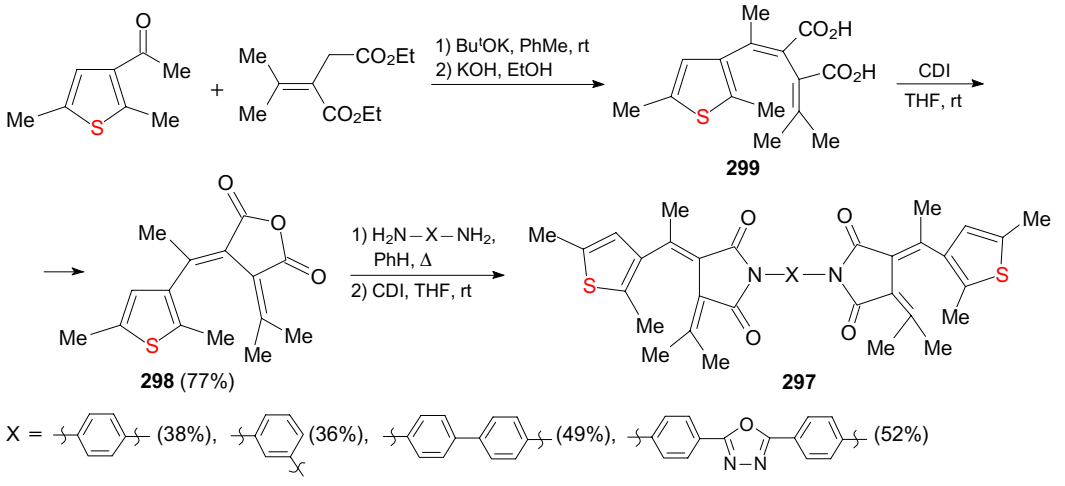
Structure 302



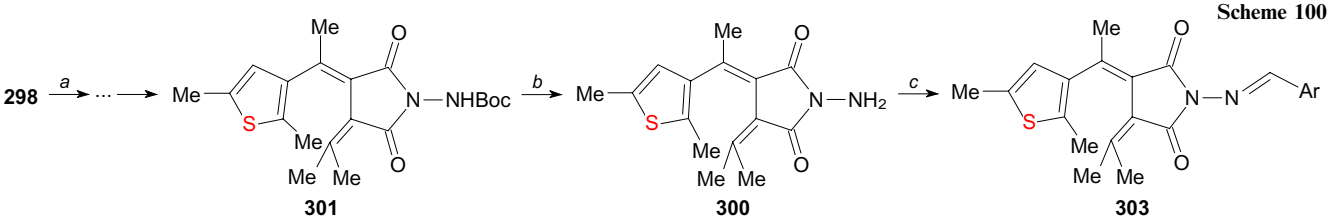
302

The prepared thermally irreversible photochromes were converted to photochromic polymer systems containing photochrome–fluorophore pairs, which were found acceptable for the design of recording media allowing non-destructive fluorescence readout for 3D optical random access (rewritable) memory.[236] In addition, it was demon-

Scheme 99



Scheme 100



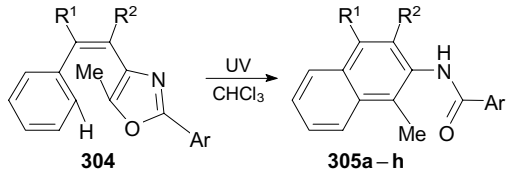
(*a*) $H_2NNHBoc$, PhH, Δ; (*b*) HCl, MeOH, rt; (*c*) ArCHO, TsOH, EtOH, rt

strated that photochromic fulgimides are successfully immobilized on a polyacrylate film, which is important for adjusting the technology of manufacturing multilayer discs.[237]

3.2.5. Irreversible photoreactions of dihetarylethenes

Studies of hybrid compounds, arylhetarylethenes **304**, demonstrated that they are devoid of photochromic properties and on exposure to ultraviolet light, they undergo an irreversible phototransformation being converted to naphthalene derivatives **305a – h** (Scheme 101).[238]

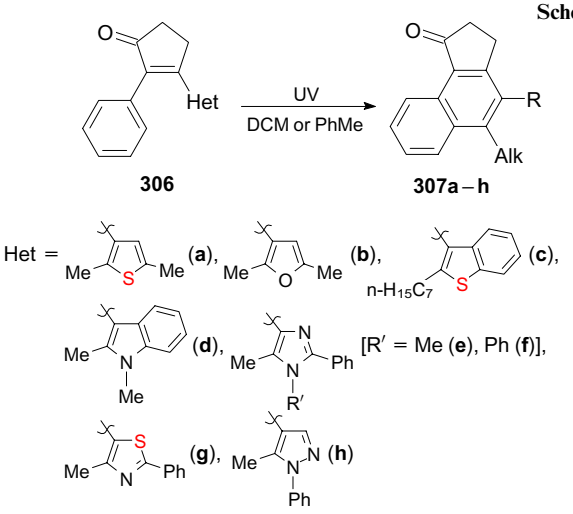
Scheme 101



304 **305a – h**

Ultraviolet irradiation of 3-hetaryl-2-phenylcyclopent-2-enones **306** containing fragments of five-membered heterocycles such as furan, thiophene, thiazole, benzothiophene, indole, imidazole and pyrazole as hetaryl substituents induces a photorearrangement giving naphthalenes **307** in good yields. These products retain the functional groups present in the initial heterocycle (Scheme 102).[239]

Scheme 102

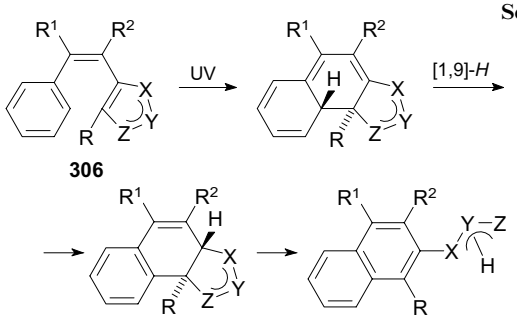


306 **307a – h**

The mechanism of this reaction corresponds to the photocyclization – [1,*n*]-H-shift – ring transformation cascade process, which, unlike the classical Mallory reaction, affords naphthalene derivatives or their isosteric analogues. Thus, in the case of compound **306a**, apart from the usual product **308**, the reaction may give phenanthrene isostere **309**, formed *via* elimination of methane (Schemes 103, 104).[240 – 243]

Thus, investigation of the photocyclization of cyclopentenone derivatives sheds light on the nature of interaction between light and matter, and this reaction by itself is an efficient route to functionally substituted fused compounds.

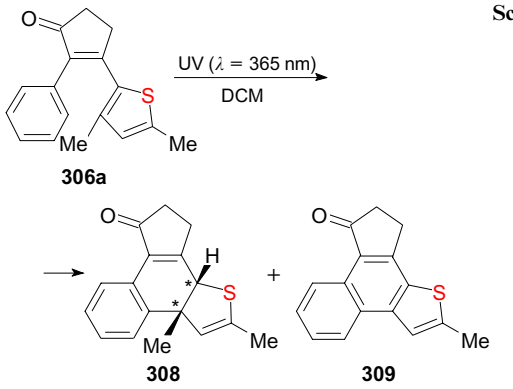
Scheme 103



306

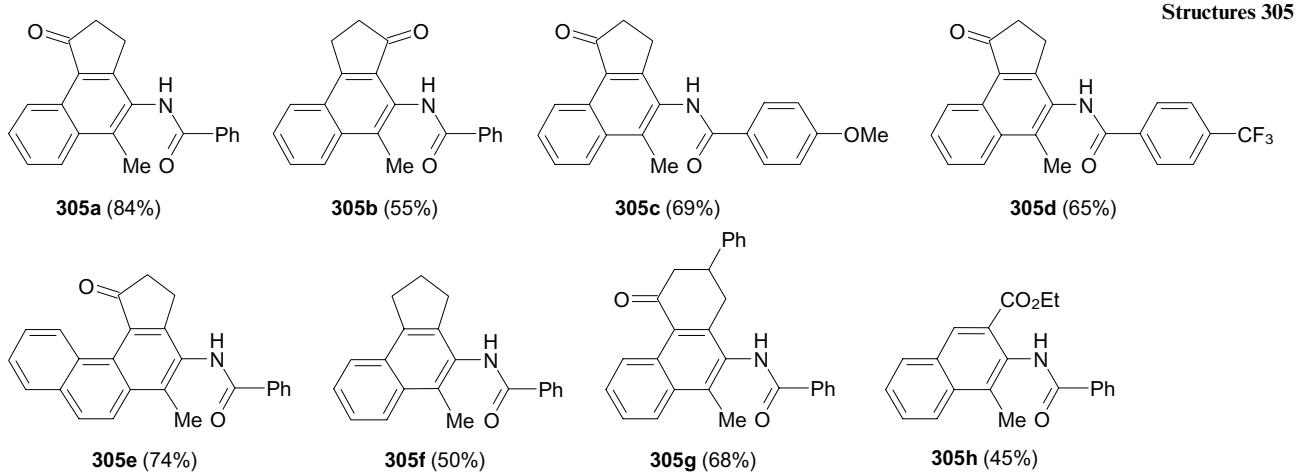
R^1, R^2 = Alk; X, Y, Z are heteroatoms

Scheme 104



306a **308** **309**

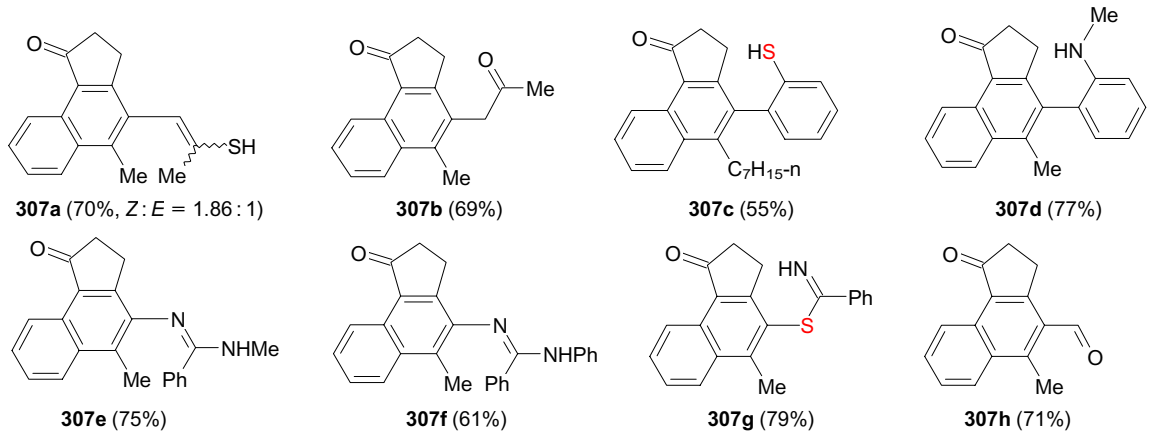
Structures 305



305a (84%) **305b** (55%) **305c** (69%) **305d** (65%)

305e (74%) **305f** (50%) **305g** (68%) **305h** (45%)

Structures 307



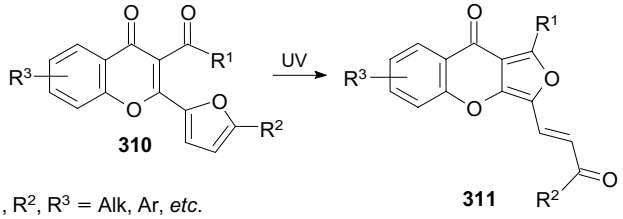
307a (70%, *Z* : *E* = 1.86 : 1) **307b** (69%) **307c** (55%) **307d** (77%)

307e (75%) **307f** (61%) **307g** (79%) **307h** (71%)

3.2.6. Compounds for archival optical data storage. Acylchromones and their structural analogues

An important goal is to design elements for multilayer archival (*i.e.*, non-rewritable) transparent optical discs. In these devices, for example, photomaterials can undergo irreversible transformations on exposure to UV light to be converted to stable fluorophores, which are applicable for non-destructive luminescence data readout. At the Laboratory of Heterocyclic Compounds, ZIOC RAS, 3-acyl-2-hetarylchromones **310** and their structural analogues were considered initially as such light-rresponsive components. These compounds do not exhibit fluorescence properties; however, on UV irradiation, they are irreversibly converted to fluorescent products **311** (Scheme 105).

Scheme 105



310

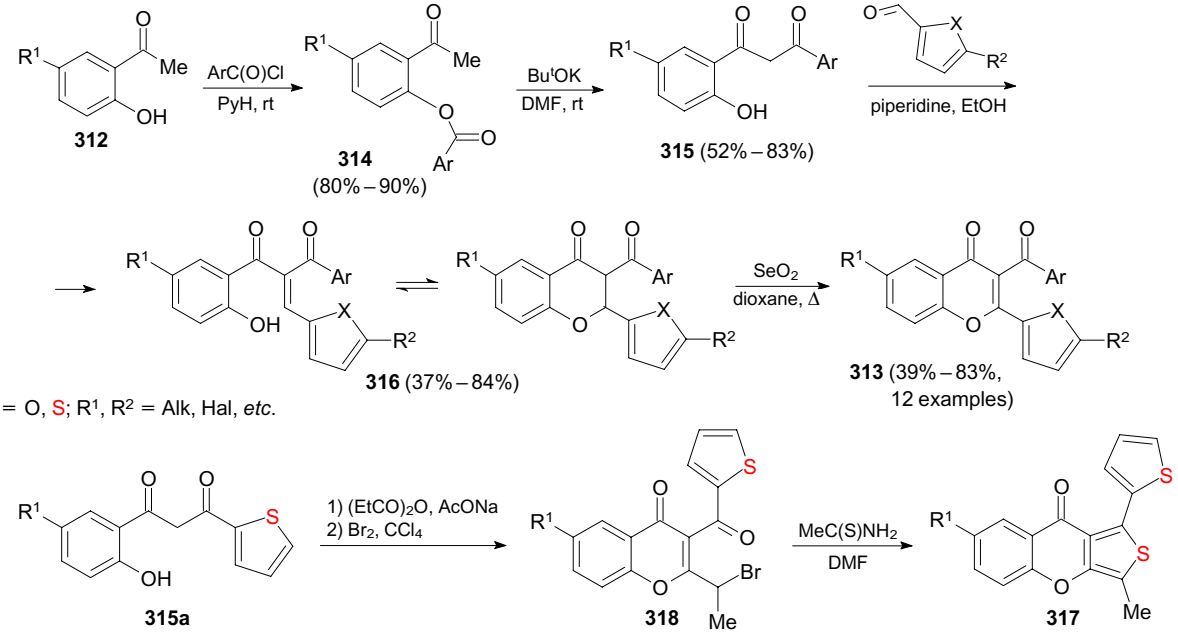
R^1, R^2, R^3 = Alk, Ar, *etc.*

311

Within the framework of implementing this idea, hydroxyacetophenones **312** were subjected to consecutive transformations, as generally shown in Scheme 106, which resulted in the synthesis of previously unknown 3-acyl-2-hetarylchromones **313** (X = O, S) containing various heterocyclic moieties and functional groups.[244, 245] First, condensation of the initial compounds **312** with aromatic carboxylic acid chlorides in pyridine was carried out. The resulting esters **314** were converted to diketones **315**, which reacted with heterocyclic aldehydes to give an equilibrium mixture of crotonic condensation products **316**. On treatment with SeO_2, these products were oxidized to give the target chromones **313**, with their yield being independent of the ratio of isomers **316** (see Scheme 106).

Compounds **314a** (Ar = 2-Th) can be easily converted to 1-thienyl-9*H*-thieno[3,4-*b*]chromones **317** *via* cyclization induced by propionic acid anhydride followed by bromination and condensation of intermediate **318** with thioacetamide (see Scheme 106).[246] Study of the photochemical properties of compounds **313** demonstrated that they are of interest as components of recording media for multilayer

Scheme 106



312 **314** (80%–90%) **315** (52%–83%)

316 (37%–84%) **313** (39%–83%, 12 examples)

X = O, S; R^1, R^2 = Alk, Hal, *etc.*

315a **318** **317**

archival optical discs, which is indicative of good prospects of this line of research and good reason for the synthesis of structural analogues of these chromones. The photoproducts formed upon irradiation of these compounds are characterized by high luminescence intensity.[236]

Analysis of the published data and the own studies of the authors showed that the photoactive core of these compounds is a moiety (marked by crimson colour in Fig. 5) containing a double bond with a vicinal acyl (or aroyl) substituent and a furan ring. This fact determined the direction of further studies of the target structures, namely, design of new heterocyclic compounds containing the 3-(furan-2-yl)propenone system, study of their behaviour on exposure to UV light and elucidation of the physicochemical properties of both the initial compounds and phototransformation products.

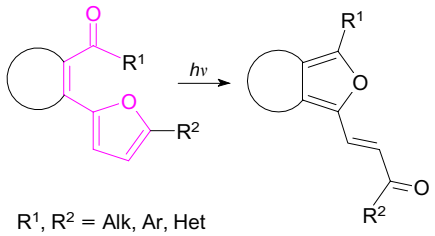


Figure 5. Result of photoirradiation of molecules containing 3-(furan-2-yl)propenone moiety.

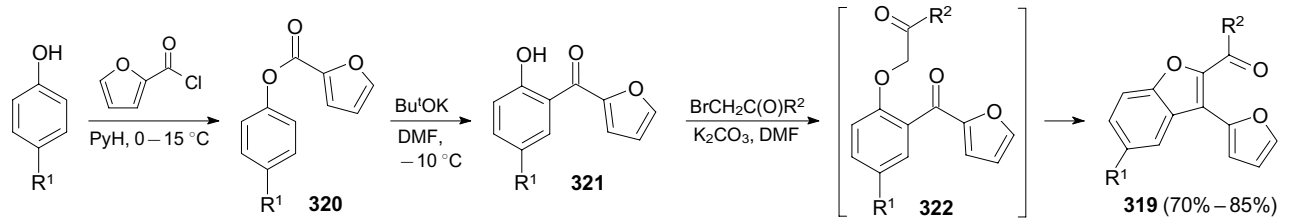
For this purpose, 2-benzolyl-3-(furan-2-yl)benzofuran derivatives **319** were prepared.[247] This was done by acylation of *para*-substituted phenols with furancarboxylic acid, and the resulting ester **320** was subjected to Baker–Venkataraman rearrangement. The alkylation of the hydroxy group of hydroxy ketone **321** with bromoacetophenones afforded target compounds **319** *via* intermediate **322** (Scheme 107).

According to photochemical studies, benzofurans **319** form photoinduced fluorescent photoproducts. Continuation of these studies resulted in the synthesis of previously unknown 3-aroyl-2-furylthiochromones **323** and their sulfoxides **324**. They were prepared by analogy with the above compounds *via* diketone **325** (Scheme 108).[248]

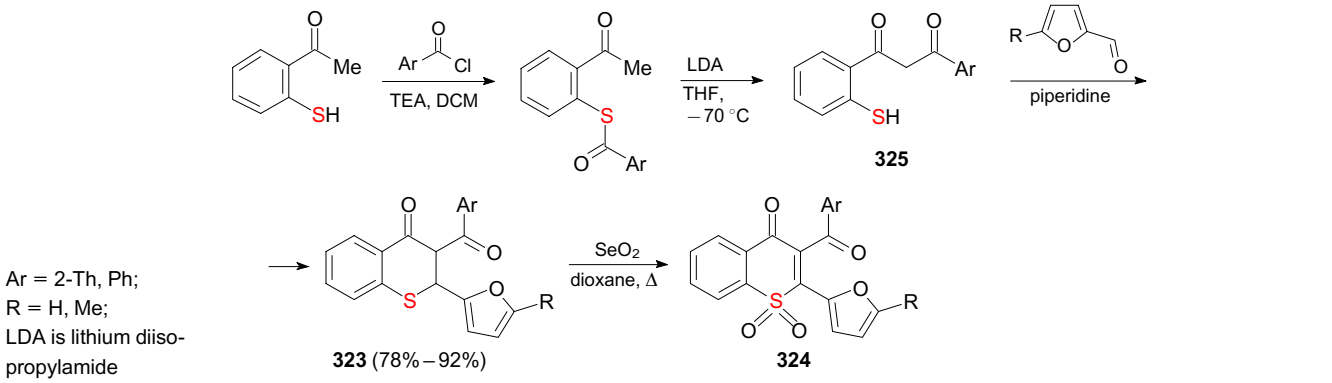
It should be noted that even in the case of successful photocyclization, the yields of fluorescent products were low, which complicated determination of their structure. The situation changed for the study of ring closure of cyclopentane derivatives **326** to give fluorescent products **327** (Scheme 109).[249] Compound **327** (R = NO_2) was isolated in the crystalline state and characterized by X-ray diffraction.

Compounds **326** were prepared by treating 1,2-dibromocyclopentene with isopropylmagnesium bromide and LiCl with subsequent addition of, first, a solution of $ZnCl_2$

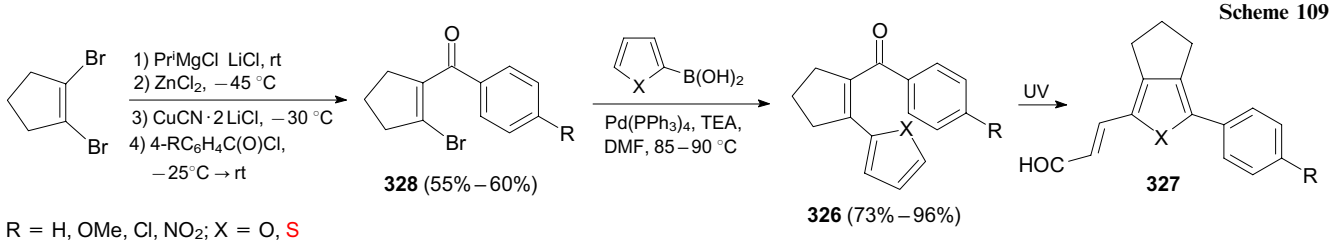
Scheme 107



Scheme 108



Scheme 109



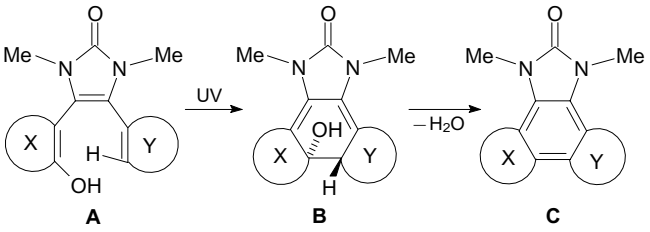
in THF at −45 °C and, second, a solution of CuCN·2 LiCl in THF at −30 °C. At the final step of this sequence, benzoyl chloride was added, which yielded monobromide **328**. The target compounds **326** were obtained by Pd-catalyzed Suzuki cross-coupling of the monobromide with furanyl- or thienylboronic acid (see Scheme 109).

Generally, it can be stated that, among the studied types of compounds, the products of photocyclization of benzopyrans, benzothiopyrans and cyclopentene derivatives deserve most attention as regards the set of their properties. These derivatives show rather large Stokes shifts, have high light sensitivity, photostability and intense fluorescence, which makes them applicable for optical data storage devices. The properties of these compounds make it possible to prepare samples of light-sensitive polymer layers with non-destructive optical data readout for 3D archival optical storage. Efficient technologies for the fabrication of multilayer recording media with waveguide fluorescence optical data readout were developed and multilayer optical discs based on them were manufactured.

3.2.7. Photocyclization with water elimination

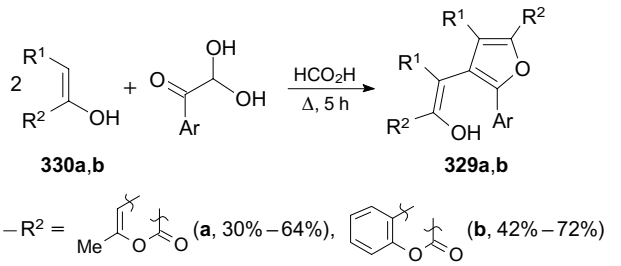
A bottleneck of the studies associated with photocyclization of chromones and their structural analogues are low yields of the reaction products. Further search for compounds generating fluorescent products on exposure to ultraviolet light revealed imidazole derivatives **A**, which undergo photoinduced 6π-electrocyclization to give derivatives **B**, which spontaneously eliminate water to yield products **C** (Scheme 110). Methods for the synthesis of initial imidazol-2-ones were elaborated, their behaviour on UV irradiation was investigated, and the fused cyclization products were identified and studied for photochemical properties in order to find efficient fluorescent compounds among them.

Scheme 110



A convenient method for the synthesis of pyran-4-one (**329a**) or chromen-4-one (**329b**) derivatives with hydroxyl groups at the reaction centres includes the condensation of arylglyoxals with two equivalents of 4-hydroxy-6-methylpyran-2-one (**330a**) or 4-hydroxycoumarin (**330b**) in formic acid (Scheme 111).[250]

Scheme 111



Further studies resulted in the development of a synthetic route to previously unknown substituted benzofurans **331** and **332** based on the reaction of 3,4-methylenedioxyphenol **333** and 2-naphthol (**334**) with pyridinium salts **335**. The latter are formed upon multicomponent condensation of arylglyoxals with carbo- or heterocyclic enols **330a**,**c**,**d** in the presence of 4-dimethylaminopyridine (Scheme 112).[251]

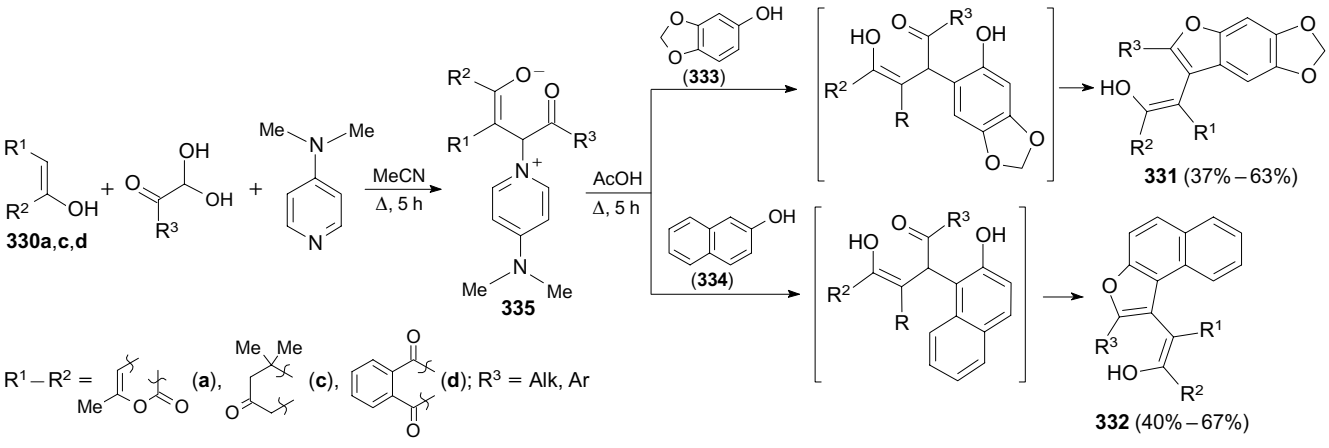
In essence, this is a new, general and rather simple approach to the synthesis of substituted benzofurans by reactions of various phenols with pre-synthesized pyridinium salts, which are allowed to react without isolation (in a one-pot version).

This research cycle was continued by studying the introduction of substituents at position 2 of the pyran ring using the reactions of 5-hydroxy-2-methyl-4*H*-pyran-4-one (**336**) with arylglyoxals, which resulted in a convenient method for the preparation of 1,2-diketones **337a**–**j**. These reactions were also carried out in the presence of dimethylaminopyridine, with air oxygen acting as the oxidant for alcohols **338** (Scheme 113).[252]

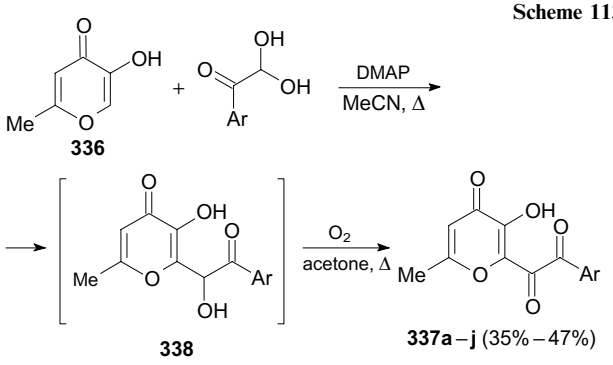
1,2-Diketones **337a**,**c**,**f** thus formed are convenient synthons for the subsequent reactions. For example, they were converted to quinoxalines **339a**,**c**,**f** *via* condensation with *o*-phenylenediamine (Scheme 114).[252]

A similar approach, that is, the reaction of 1,2-diketones **337** with aldehydes in acetic acid in the presence of ammo-

Scheme 112

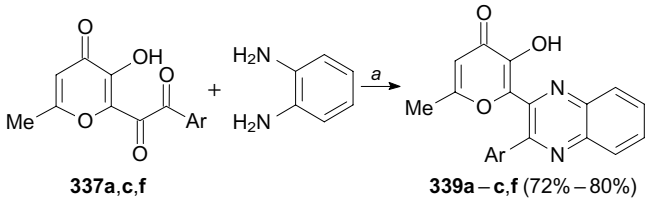


Scheme 113



Ar = 4-ClC$_6$H$_4$ (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-BrC$_6$H$_4$ (**c**), 3,4-(OCH$_2$O)C$_6$H$_3$ (**d**), 4-FC$_6$H$_4$ (**e**), 2-Th (**f**), 2,4-Me$_2$C$_6$H$_3$ (**g**), 4-MeC$_6$H$_4$ (**h**), 4-HO-3-MeOC$_6$H$_3$ (**i**); 3-MeOC$_6$H$_4$

Scheme 114

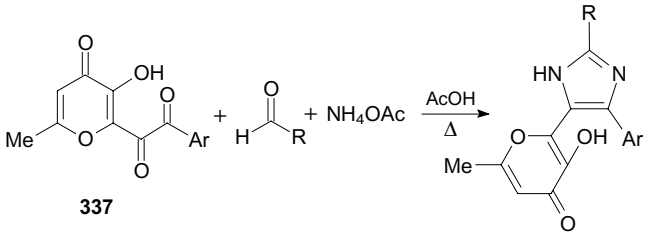


(*a*) AcOH, Δ; 4-ClC$_6$H$_4$ (**a**), 4-BrC$_6$H$_4$ (**c**), 2-Th (**f**)

nium acetate, underlay the synthesis of imidazole derivatives **340** (Scheme 115).[253]

Scheme 116 depicts the pathways to several 2,3-substituted indoles **341** – **344** based on three-component condensation of aromatic amines with arylglyoxals and enols in the presence of catalytic amounts (5 mol.%) of *p*-toluenesulfonic acid, conducted by refluxing the reactants in ethanol for 2.5 h.[254] The enol components used include pyranone, coumarin, cyclohexanedione and cyclopentanedione. In

Scheme 115



Ar = 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-Th; R = 2,3,4-(MeO)$_3$C$_4$H$_2$, 2-Th

order to avoid the formation of regioisomeric mixtures upon the subsequent photocyclization, the authors used only the *para*-substituted arylglyoxals in this reaction.

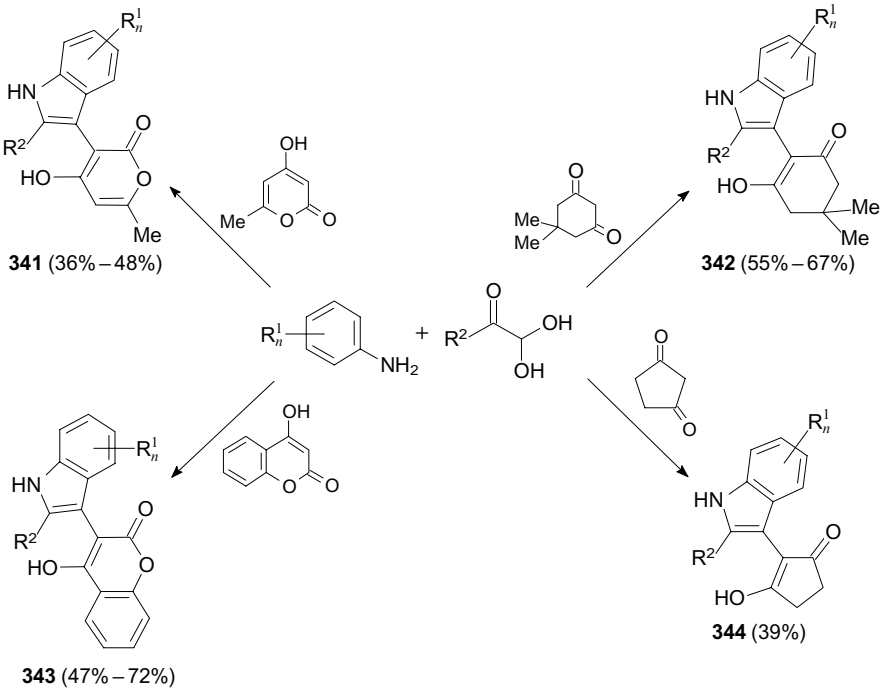
This method was successfully extended to the synthesis of imidazol-2-ones **345a** – **f** and **346a** – **g** (Scheme 117).[255]

An important distinction of the above hydroxyl-containing dihetarylethenes from typical 1,2-diarylethenes (stilbenes), the photochemical behaviour of which was studied in considerable detail, is the replacement of one aryl substituent at the cyclic ethene bridge by a β-dicarbonyl moiety, which exists almost entirely in the enol form.

Solutions of imidazoles containing hydroxyl groups at the reaction centres, compounds **331**, **332** and **338** – **346**, were UV irradiated for several hours using a Vilber Lourmat VL-6.LM lamp at 365 nm wavelength in conventional glass test tubes or even in open Petri dishes. Dimethyl sulfoxide or *N*-methylpyrrolidone was used as the solvent. It is significant that no inert atmosphere or special quartz glassware was required for the photocyclization to take place.

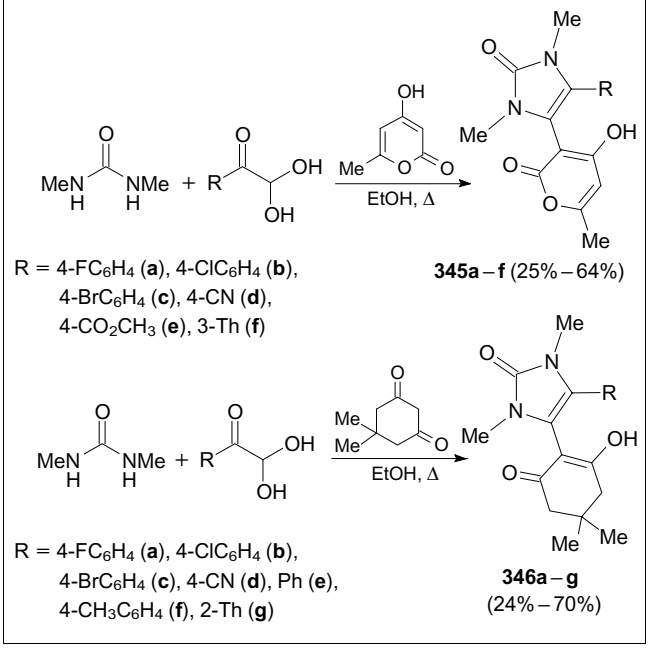
In most cases, the process ends with the expected cyclization of the reactants. For example, ultraviolet irradiation (λ = 365 nm) of indoles **341** – **344** in *N*-methylpyrrolidone at room temperature for 25 h furnishes fused

Scheme 116

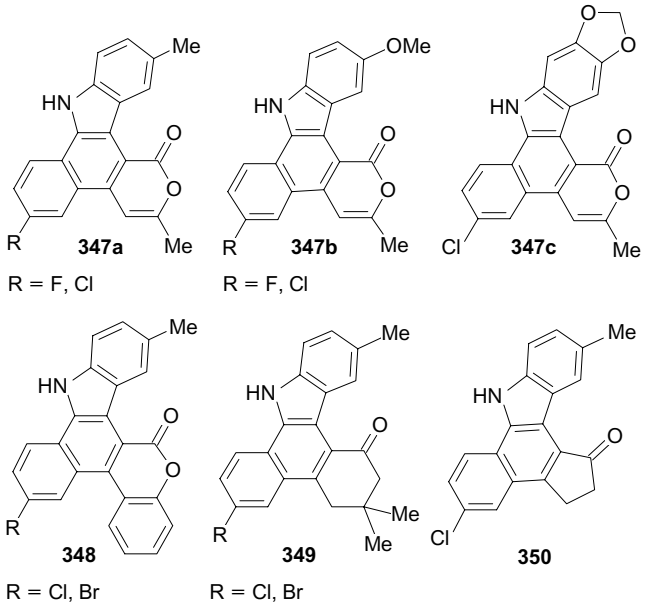


R^1_n = 4-Me, 4-OMe, 3,4-(OCH$_2$O);
R^2 = 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-Pr^{i}C$_6$H$_4$

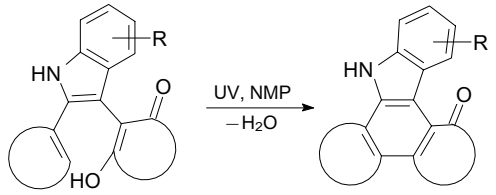
Scheme 117



Structures 347 – 350



Scheme 118

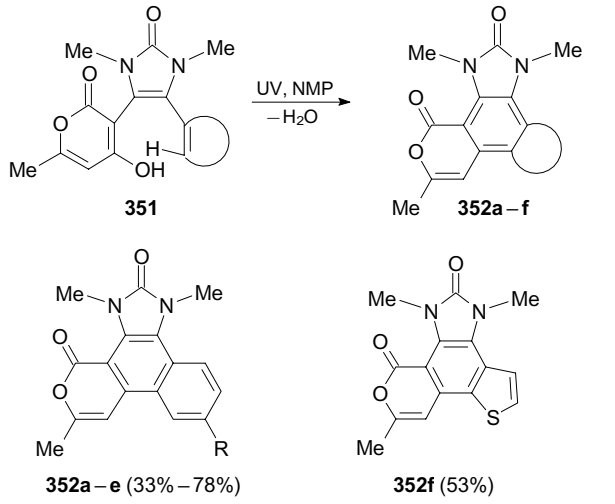


photoproducts **347 – 350** in 33% – 52% yields (Scheme 118).[255]

It should be emphasized that the proposed approach successfully solves the problem of synthesis of compounds used as optical data storage elements. Whereas the initial hydroxyl-containing dihetarylethenes **351** do not show fluorescence, the products of 6 – 15-h photocyclization **352a – f** exhibit efficient fluorescence in the 497 – 503 nm range (Scheme 119).[255]

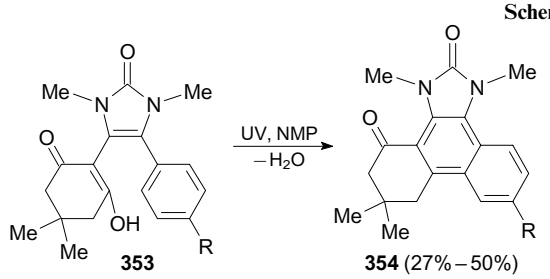
Apart from the above-mentioned compounds, photoirradiation was also studied for imidazolones **353**, which contain only aromatic substituents. In this case, the reaction gave polyfused structures **354**, which also possess intense fluorescence in the region of 500 – 525 nm (Scheme 120).

Scheme 119



352: R = F (**a**), Cl (**b**), Br (**c**), CN (**d**), CO_2Me (**e**)

Scheme 120



354: R = Me, F, Cl, Br, CN

Generally, photoirradiation of dihetarylethenes containing hydroxyl groups at the reaction centre is a facile and efficient method for the synthesis of fused four-membered heterocyclic systems possessing fluorescent properties.

Thus, while concluding the Section of the review devoted to the synthesis and properties of photoactive compounds, we can state that this research area proved to be highly successful. This resulted in the synthesis of a broad range of photochromic thermally irreversible dihetarylethenes and fulgimides and also new chromone or similar-type organic fluorophores. These compounds served for the design of recording media allowing non-destructive fluorescence data readout to be used in random access and archival data storage devices, which made it possible to develop the scientific grounds of fabrication of multilayer optical discs. Samples meant for archival data storage were fabricated using pilot plant facilities; the results of testing of the functional properties of the samples attest to the possibility

of manufacturing standard size optical disks with 2.6 TB data capacity.

4. New approaches to the synthesis and transformations of glycolurils and diaziridines

4.1. Glycolurils, their analogues and precursors

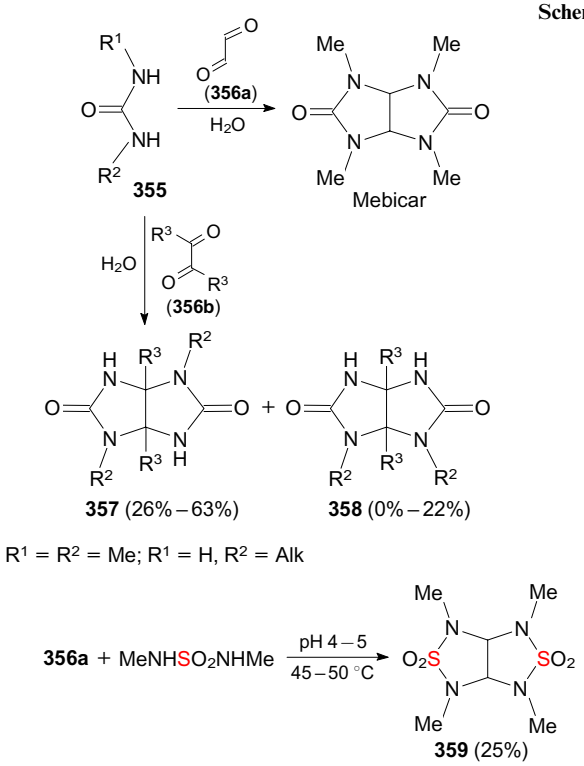
The chemistry of glycolurils {tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones} has been developed for more than 100 years. The interest in these compounds is associated with a wide range of their practical applications in various fields of science and technology. They are used in agriculture as fertilizers and in supramolecuar chemistry as building blocks; they serve as precursors of pharmacologically active (antibacterial, nootropic and neuroprotective) agents and highly energetic compounds. When a new efficient daytime anxiolytic, mebicar (tetramethylglycoluril, mebix, adaptol), developed at the Laboratory of Nitrogen-Containing Compounds of the ZIOC RAS,[256] was introduced into medical practice in 1979, the studies of compounds of this class, their precursors [imidazolidin-2-one(thione) derivatives], heteroanalogues (imidazooxazoline, imidazothiazoline and imidazotriazine derivatives) and polyheterocyclic compounds based on them have been continued. This Section covers the most interesting recent results obtained at the ZIOC RAS on the synthesis, reactions and properties of glycolurils, their precursors and analogues. A Subsection is devoted to the synthesis and reactivity of imidazotriazines, close analogues of glycolurils, which were converted to thioglycoluril, imidazothiazolotriazine and pharmacologically active spiro(pyrrolidine-oxindole) derivatives.

4.1.1. New approaches to the synthesis of glycolurils, their precursors and heteroanalogues

The derivatives of glycolurils and their heteroanalogues are prepared using two main approaches. According to one approach, the key reagents are ureas or their analogues and α-dicarbonyl compounds, and also 1,4-disubstituted 1,4-diaza-1,3-dienes and isocyanic and/or isothiocyanic acid or isocyanates. The other approach involves annulation of imidazolidine, oxazoline and thiazoline rings to imidazolidin-2-one(thione) derivatives and their bicyclic analogues.

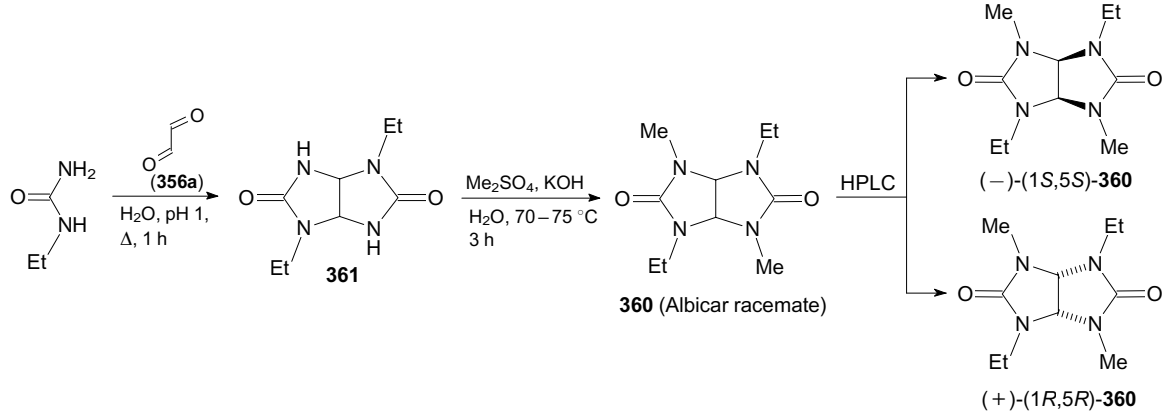
The former approach was actively developed in the 20th century. Hundreds of glycolurils, both C- and N-substituted and unsubstituted, were prepared by condensation of ureas and their analogues **355** with α-dicarbonyl compounds **356** and by condensation of 1,4-disubstituted 1,4-diaza-1,3-dienes with isocyanic and/or isothiocyanic acid or isocyanates. These methods were summarized in a recent review[257] and, therefore, they will be considered only briefly. The reactions of glyoxal (1,2-dioxoethane, **356a**) and benzil (1,2-dioxo-1,2-diphenylethane, **356b**) with 1-substituted ureas underlay the development of regioselective syntheses of 1,4- (**357**) and 1,6-dialkyl(carboxyalkyl, aminoalkyl)glycolurils (**358**) (Scheme 121).[258,259] The sulfur analogue of tetramethylglycoluril (mebicar) **359** was prepared by the reaction of glyoxal with 1,3-dimethylsulfamide (see Scheme 121).[260]

Scheme 121



Along with mebicar, which has no elements of chirality, racemic albicar (1,4-dimethyl-3,6-diethylglycoluril, **360**) is one more promising glycoluril, which has passed preclinical trials and was recommended for clinical trials.[261] It is prepared by the reaction of glyoxal with ethylurea followed by methylation of the intermediate 1,4-diethylglycoluril **361** (Scheme 122).[262] Since the use of enantiopure agents is an important issue for medical practice, albicar racemate was

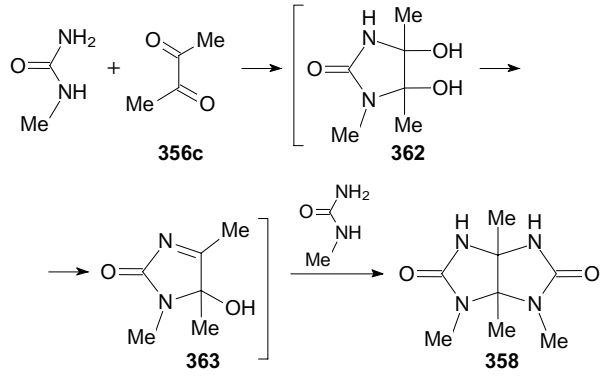
Scheme 122



recently resolved into (−)-(1*S*,5*S*)- and (+)-(1*R*,5*R*)-enantiomers by preparative chiral phase HPLC and the pharmacological action was evaluated for both enantiomers. It was shown that (−)-(1*S*,5*S*)-**360** has a stimulating effect on the central nervous system, which is associated with activation of the serotonergic system, while (+)-(1*R*,5*R*)-**360** has a depressant effect.[262]

The condensation of ureas and their analogues with α-dicarbonyl compounds is closely related to the second approach to glycoluril synthesis, as imidazolidin-2-one derivatives — 4,5-dihydroxyimidazolidin-2-ones (DHI) **362** and 5-hydroxy-1*H*-imidazol-2(5*H*)-ones (imidazolones) **363** — are formed as intermediates along the pathway to 1,6-disubstituted glycolurils **358** (Scheme 123).[263] However, compounds **362** and **363** were not isolated in the reaction shown in this scheme.

Scheme 123

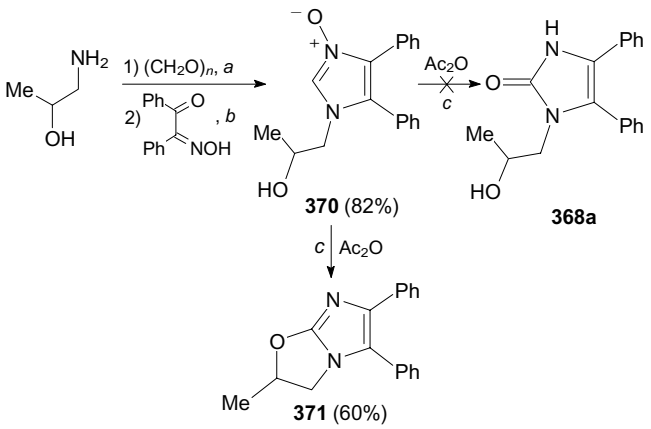


The greatest contribution to the chemistry of glycolurils and their heteroanalogues was made by the systematic studies carried out at the Laboratory of Nitrogen-Containing Compounds, ZIOC RAS, on the synthesis of glycoluril precursors. These compounds include derivatives of imidazolidin-2-one(thione), DHI (**362**), imidazolone (**363**) and 4,5-dihydroxyimidazolidine-2-thione (DHIT, **364**), and also bicyclic analogues of imidazolones: 7,7a-diphenylimidazooxazolone (**365**), 8,8a-diphenylimidazooxazinone (**366**) and 9,9a-diphenylimidazoazepinone (**367**) derivatives. Then imidazolidine, oxazoline, thiazoline and triazine rings were annulated onto these precursors using various ureas, KSCN in the presence of acids, (thio)semicarbazide or aminoguanidine.

Before these works, only a few representatives of 1-substituted 5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones **363**,[264] DHI and DHIT (**362** and **364**) [265] were reported in the literature, while their bicyclic analogues were unknown. In order to develop a general route towards these compounds, the oxidation reactions of 1-substituted 4,5-diphenyl-1*H*-imidazol-2(3*H*)-ones (imidazolinones) **368** with concentrated HNO_3 were studied in detail;[266 – 268] these reactions were employed to prepare compounds that were previously inaccessible, in particular, imidazolones **363** (8 examples),[266] imidazooxazolone **365a**,[267] imidazooxazinones **365b** (Ar = Ph, *n* = 2),[267] **366** [Ar is *p*-methoxyphenyl (PMP), *n* = 2] [258] and imidazooxazepinones **367**.[268] In addition, (3a*R**,10a*S**)-3,3a,10,10a-tetrakis-(4-methoxyphenyl)-5,6,12,13-tetrahydrodiimidazo[5,1-*b*:5′,1′-*g*]-1,6,3,8-dioxadiazecine-1,8(3a*H*,10a*H*)-dione (**369**) was unexpectedly obtained (Scheme 124).[268]

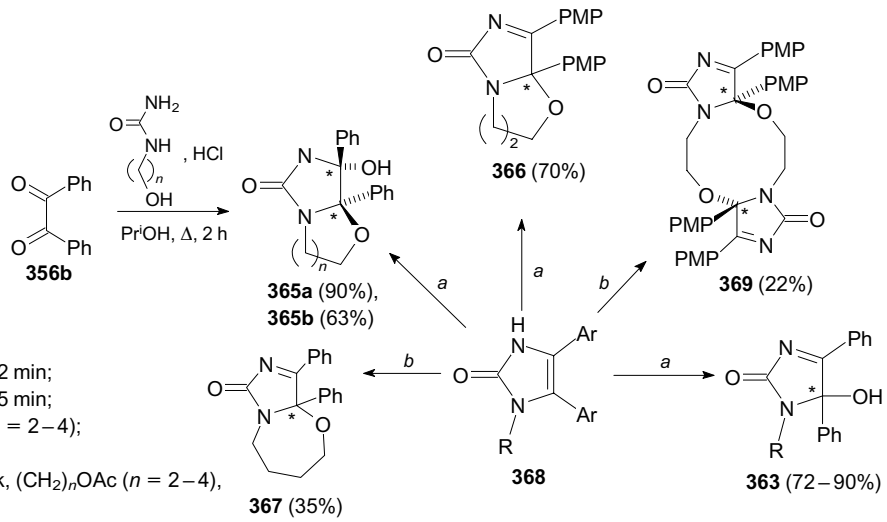
An attempted synthesis of imidazolone **368a** [R = $CH_2CH(Me)OH$] resulted in a transformation that had no published prototypes: the intermediate N-oxide **370** did not rearrange to imidazolone **368a**, but formed instead an intramolecular cyclization product, 2-methyl-5,6-diphenyl-2,3-dihydroimidazo[2,1-*b*]oxazole (**371**) (Scheme 125).[269]

Scheme 125



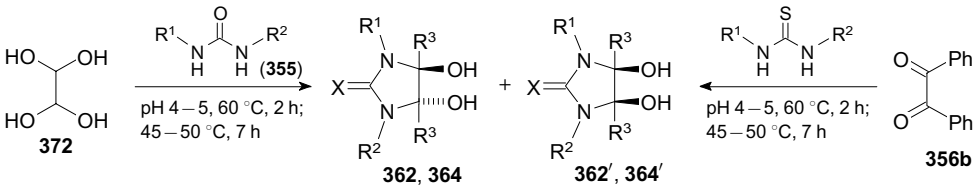
(*a*) MeOH, rt, 24 h; (*b*) MeOH, Δ, 3 h; (*c*) $CHCl_3$, rt, 24 h

Scheme 124



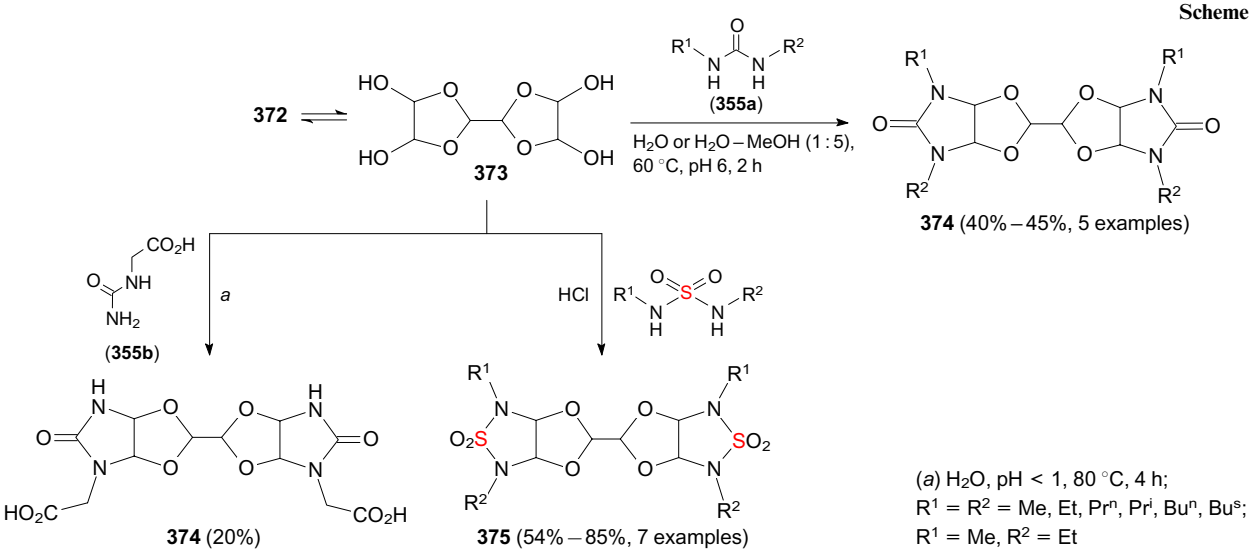
(*a*) HNO_3 (65%), MeCN, rt, 2 min;
(*b*) HNO_3 (65%), MeCN, rt, 5 min;
363: R = Alk, $(CH_2)_nOAc$ (*n* = 2 – 4);
365: *n* = 1 (**a**), 2 (**b**);
368: Ar = Ph, PMP; R = Alk, $(CH_2)_nOAc$ (*n* = 2 – 4), $(CH_2)_mOH$ (*m* = 2, 3)

Scheme 126



362, **362′**: X = O; R^1, R^2 = H, Alk; R^3 = H, Ph (10–98%, 8 examples);
364, **364′**: X = S, R^1 = H, Alk; R^2 = H, Alk, Ph; R^3 = H, Ph (37–97%, 7 examples)

Scheme 127

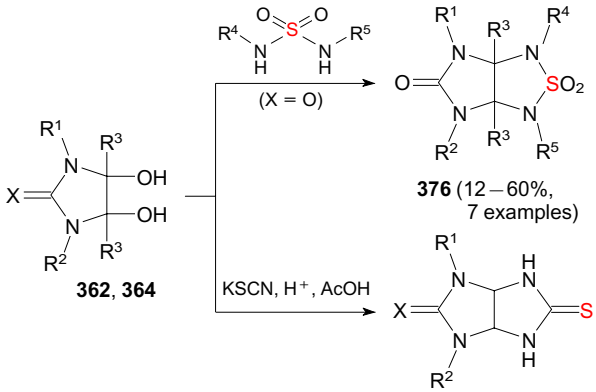


In order to elaborate effective synthetic protocols towards the building blocks such as DHI (**362**) and DHIT (**364**), urea or thiourea cyclocondensation with glyoxal (**356a**), including its hydrated forms (**372** and **373**), and with benzil (**356b**) were investigated in detail (Scheme 126).[270–274] The reactions of urea and thiourea derivatives with bis-*gem*-diol **372** and benzil **356b** were found to give DHI and DHIT with high diastereoselectivity, namely, one racemate **362**, **364** or **362′**, **364′** predominated in the products with different diastereomeric ratios. Often, the DHI and DHIT racemates could not be separated and, hence, the compounds were used for further studies as diastereomeric mixtures (**362** + **362′**, **364** + **364′**) (see Scheme 126).

Unexpectedly, the reactions between glyoxal in the bis-dioxolane form **373** with 1,3-dialkylureas **355a** (R^1 = R^2 = Me, Et; R^1 = Me: R^2 = Bu^t, cyclo-C_6H_{11}) and *N*-carbamoylglycine **355b** (R^1 = H, R^2 = CH_2CO_2H) gave rise to compounds **374**, representing a new bis-bicyclic system — bis(dioxolanoimidazolidine).[274] Similarly, 1,3-dialkylsulfamides react with trimer dihydrate **373** to give bis-bicyclic bis(dioxolanothiadiazolidines) **375** (Scheme 127).[275]

In the last decade, condensations of DHI and DHIT with various ureas have been used to prepare a wide range of glycolurils and semithioglycolurils (X = O, S) with various types of substitution at nitrogen and bridging carbon atoms.[257, 258, 276] The reaction of 1,3-dialkylsulfamides with DHI (**362**) affords sulfonic analogues of N-substituted glycolurils — compounds **376**.[277] The condensation of DHI or DHIT with KSCN in the presence of hydrochloric

Scheme 128

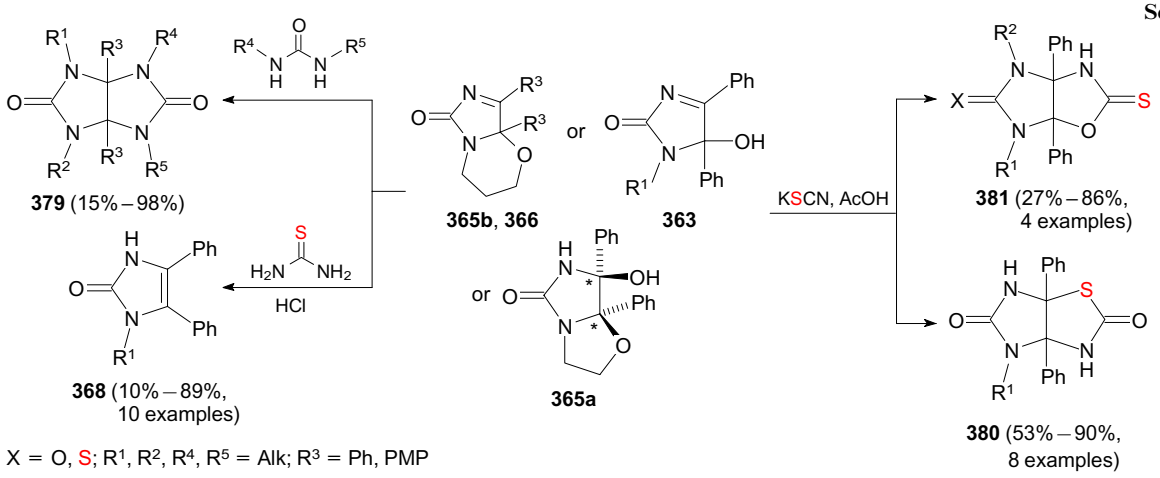


X = O (**362**, **377**), S (**364**, **378**);
R^1, R^2, R^4, R^5 = H, Alk; R^3 = H, Ph

and acetic acids yielded a large set of semithio- (**377**) and dithioglycolurils **378** (Scheme 128).[278, 279]

Imidazolones **363** and their bicyclic analogues **365**, **366** (like DHI and DHIT) proved to be efficient starting compounds for the synthesis of glycolurils. When they react with urea or 1-alkyl(hydroxyalkyl)ureas, the reactions give 1-substituted,[280] 1-alkyl-6-(hydroxyalkyl)- (Refs 268, 281) and 1,6-(dihydroxyalkyl)-substituted[267] 3a,6a-diphenylglycolurils **379** (Scheme 129). Furthermore, the use of these precursors provided the preparation of molecules that cannot be obtained with DHI or DHIT. Unexpectedly, thiourea behaved as a reducing agent towards imidazolones **363** and bicyclic compounds **365a**,**b**, which resulted in the

Scheme 129



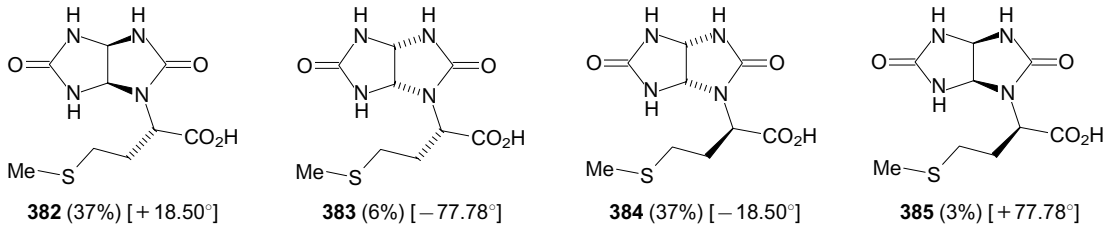
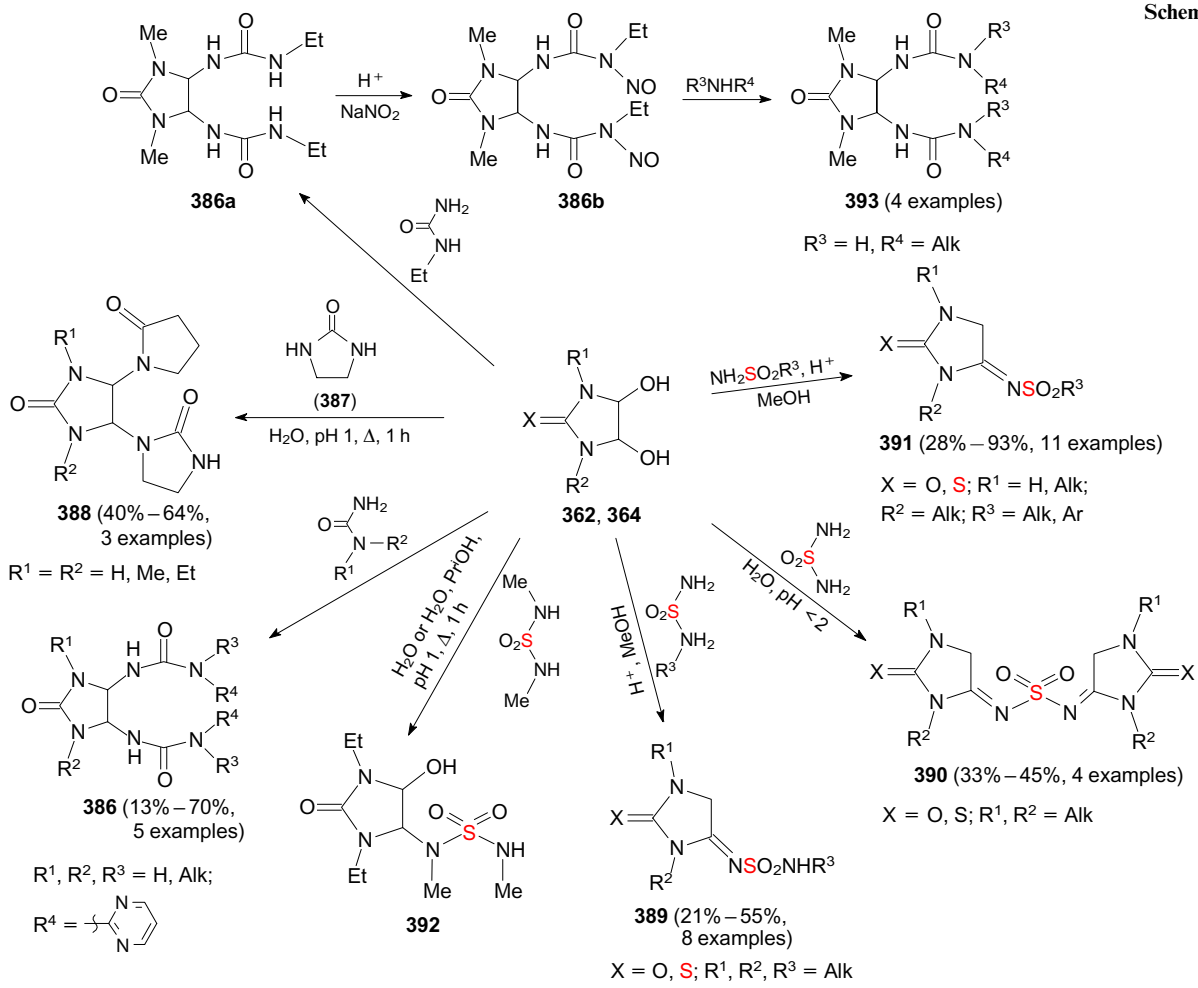


Figure 6. Enantiomerically pure glycolurils with the (*S*)- and (*R*)-methionine moiety and $[\alpha]_D^{20}$ values measured in 1 M NaOH at a concentration of 2 mg mL^{-1} (in brackets).

Scheme 130



formation of imidazolinones **368** instead of expected thioglycolurils.[282] The condensation of imidazolones **363** with KSCN in AcOH gave imidazothiazole derivatives **380**,[266] while the reaction of bicyclic compounds **365a**,**b** with the same reagents afforded (thio)imidazooxazoles **381** (Ref 283) (see Scheme 129).

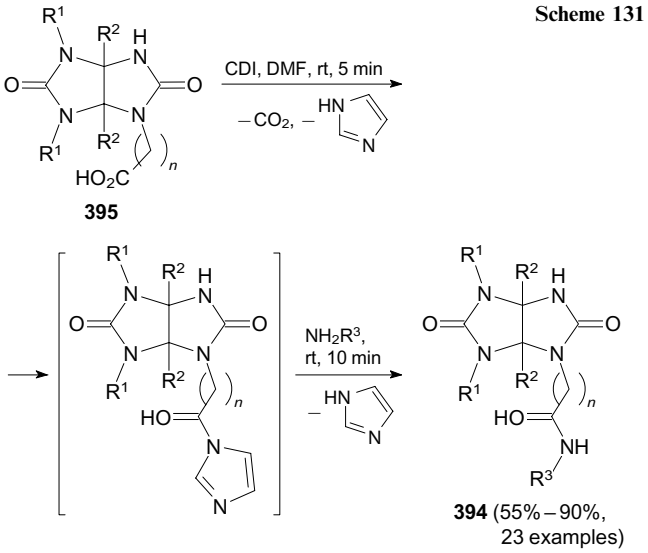
However, the most readily available DHI and DHIT still remain the main precursors of glycolurils. Of special note are highly diastereoselective reactions of enantiopure (*S* or *R*)-*N*-carbamoyl-α-amino acids with DHI (**362**) discovered by Kravchenko *et al.*,[284] which allowed the synthesis of enantiomerically pure glycolurils **382**–**385** (see, for example, Fig. 6). Note that (+)-(*S*)-2-[(3a*S*,6a*R*)-(2,5-dioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl]-4-(methylthio)butanoic acid (**382**) showed neuroprotective properties.

The reactions of 1,3-dimethyl-substituted DHI **362** ($R^1 = R^2 = Me$) with some alkylureas were found to give 4,5-diureido-substituted imidazolidin-2-ones **386**.[285] This stimulated the studies of two-step α-ureidoalkylation reactions of ureas with bulky substituents, 1,1-dialkylureas, imidazolidin-2-one (ethyleneurea) **387**, 1-alkyl(1,3-dialkyl)-sulfamides and sulfonic acid amides on treatment with DHI (**362**) or DHIT (**364**). The reactions gave 4,5-disubstituted imidazolidin-2-one derivatives **386** and **388** and sulfimides **389**–**391** (Scheme 130).[285–288] In relation to 1,3-dimethylsulfamide, the effect of high pressure on the outcome of the reaction with DHI was investigated. It was found that under these conditions, the reaction gives product **392**, in which one DHI hydroxyl group is replaced by a sulfamide moiety (see Scheme 130).[289] Furthermore, a different approach was developed for the synthesis of new 4,5-diureido derivatives **393**, which is based on modification of substituents in the ureide moieties by nitrosation of compound **386a** followed by the reaction of nitroso derivative **386b** with amines (see Scheme 130).[290]

Owing to the successfully developed methods for the synthesis of numerous glycolurils and their heteroanalogues, the next stage of development of the chemistry of these compounds was their functionalization at the NH and CO_2H groups and at the NHC(S) moiety. The reactivity of the carboxyl group in glycoluril carboxylic acids was studied by considering the two-step one-pot synthesis of amides **394** *via* the condensation of glycoluril carboxylic acids **395** with a variety of amines (n-propyl-, isopropyl- and n-butylamines, *o*-aminophenol and β-phenylethylamine) induced by excess carbonyldiimidazole (Scheme 131).[291] In this reaction, the formation of two-component gels composed of glycoluril carboxylic acid amides **394** [$n = 2$, $R^1 = R^2 = H$, $R^3 = Pr^n$, Bu^n, $(CH_2)_2Ph$; $n = 3$, $R^1 = R^2 = H$, $R^3 = Pr^n$] and imidazole in 1 : 2.5 ratio in DMF was unexpectedly observed. The gels were found to be thermally reversible, which gave rise to gel–sol and sol–gel transitions. The sample morphology was studied by scanning electron microscopy (SEM). This gelation is of obvious interest, because such behaviour of organic compounds is important for the design of new materials.[292]

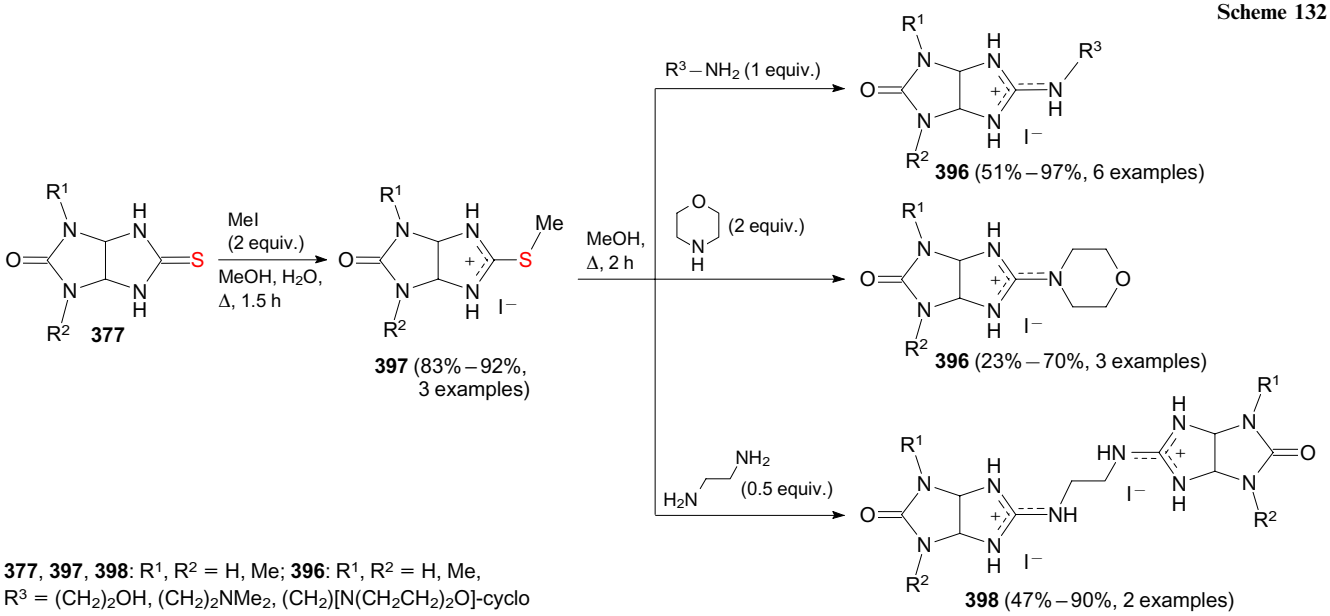
While studying the properties of the NHC(S) moiety in thioglycolurils **377**, researchers found a facile and efficient two-step method for the synthesis of previously inaccessible 1,3-unsubstituted 2-imino-5-oxooctahydroimidazo[4,5-*d*]-imidazol-1-ium iodides **396**. The first step is the condensa-

Scheme 131



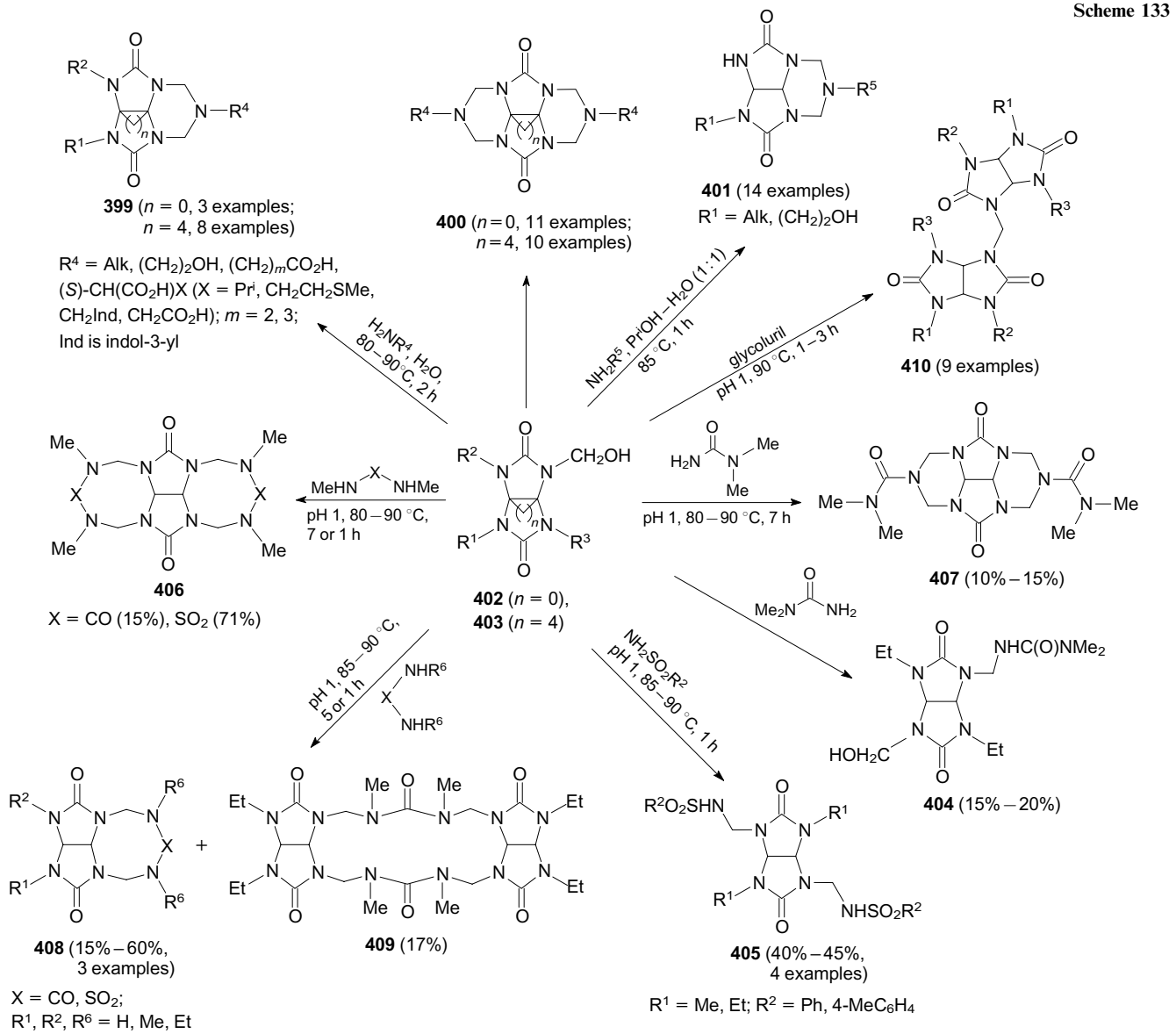
R^1 = H, Me; R^2 = H, Ph; R^3 = Alk, 2-HOC_6H_4, n = 1–3

Scheme 132



377, **397**, **398**: R^1, R^2 = H, Me; **396**: R^1, R^2 = H, Me, R^3 = $(CH_2)_2OH$, $(CH_2)_2NMe_2$, $(CH_2)[N(CH_2CH_2)_2O]$-cyclo

Scheme 133



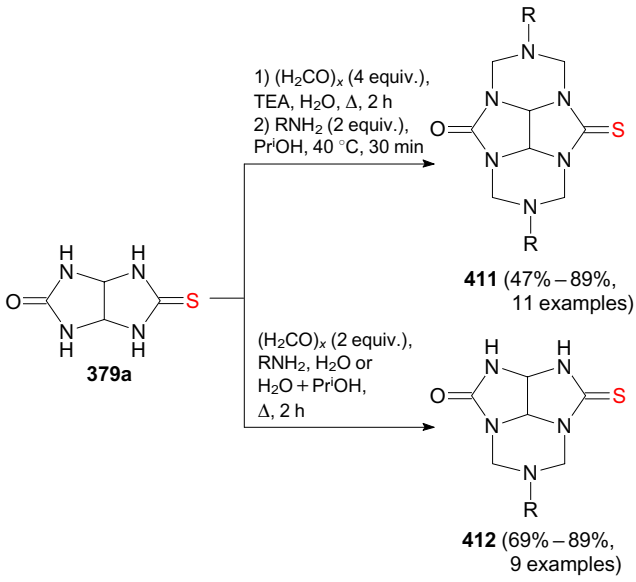
tion of thioglycolurils **377** with MeI, while the second step is the reaction of the resulting thiouronium salts **397** with various primary amines or morpholine. Similar reactions with the use of ethylenediamine give ethylenebis(iminoglycolurils) **398** (Scheme 132).[293]

A wide range of tri-, tetra- and pentacyclic fused heterocyclic compounds **399**–**401** was prepared by condensation of *N*-(hydroxymethyl)glycolurils **402** and **403** with formaldehyde and various amines [including amino acids, particularly (*S*)-α-amino acids, as potassium salts] (Scheme 133).[294–296] Bicyclic compounds containing urea and sulfamide moieties, apart from the glycoluril moiety, as N-substituents (**404**, **405**), and polyheterocyclic fused structures **406**–**409** were synthesized using α-ureidoalkylation of ureas and sulfamides with di- and 1,3,4,6-tetrakis(hydroxymethyl)glycolurils.[297,298] 1,3,4-Trialkyl-6-(hydroxymethyl)-glycolurils **402** (R^1-R^3 = Me, Et) were also used for the α-ureidoalkylation of glycolurils to give *N*,*N*′-methylenebis(glycolurils) **410** (see Scheme 133).[299] The potential of this efficient strategy was tested in the reactions of ureas, formaldehyde and (thio)barbituric acids.[300]

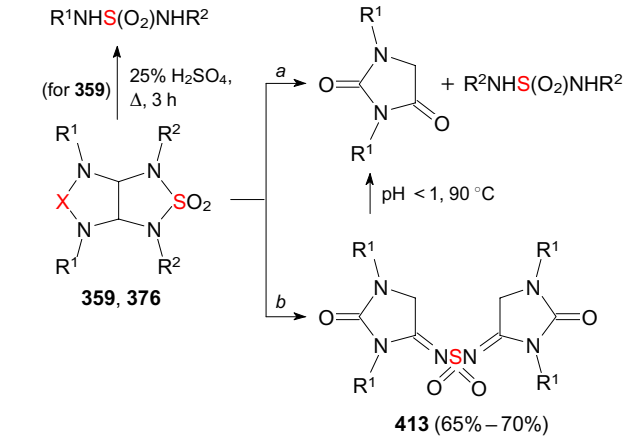
Multicomponent condensations of semithioglycoluril (**379a**), formaldehyde and primary amines were performed for the first time, which resulted in the synthesis of tetra- (**411**)[301] and tricyclic systems **412**.[302] In the synthesis of tetracyclic structures **411**, the effect of the nature of the starting amines on the yields of products was elucidated, while the formation of tricyclic systems **412** was highly regioselective (Scheme 134). Data on analogous reactions of glycolurils were surveyed in a recent review.[303]

The sulfur analogues of glycolurils **359** and **376**, synthesized by reactions of DHI (**362**) or glyoxal (**356a**) with sulfonamides, prove to be insufficiently stable when heated with acids. For example, on heating in a H_2SO_4 solution, these compounds are hydrolyzed with elimination of the sulfonamide moiety. In the presence of hydrochloric or trifluoroacetic acid at pH 1, compounds **376** are converted to diimides **413**. An increase in the acidity of the medium, reaction temperature or reaction time leads to decomposition of this diimide to 1,3-dialkylhydantoin and sulfonamide. The kinetics of **376** → **413** transformations was studied and it was shown that at a constant concentration

Scheme 134



Scheme 135



(*a*) 25% H_2SO_4, Δ, 0.2 – 5 h (for **376**); (*b*) H_2O, pH 1, 60 °C [for **376** (R^2 = H)]; **359**: X = SO_2, R^1 = R^2 = Me; **376**: X = CO; R^1 = Me, Et; R^2 = H, Me, Et

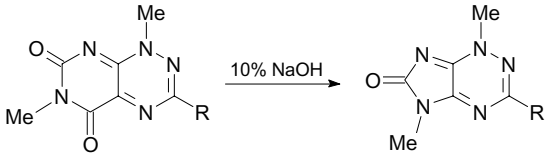
of protons, the reaction has the pseudo-first order (Scheme 135).[304]

4.1.2. Synthesis and reactivity of imidazotriazines

Further development of the most popular synthesis of glycolurils and their analogues based on condensation of 4,5-dihydroxyimidazolidin-2-ones(thiones) DHI and DHIT with N,N′-dinucleophiles initiated a new trend in the chemistry of fused dihydroimidazol-2(1*H*)-one derivatives — imidazotriazines: 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones(thiones), tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*]-1,2,4-triazine-2,7-diones and tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*]-1,2,4-triazine-2,8-diones.

Previously, the synthesis of a number of imidazotriazine derivatives, 6-azapurines (imidazo[4,5-*e*]-1,2,4-triazin-6-ones, **414**), was reported in the literature; the synthesis was performed by rearrangement of 7-azapteridines **415** on treatment with NaOH followed by decarboxylation and oxidation with air oxygen (Scheme 136).[305]

Scheme 136



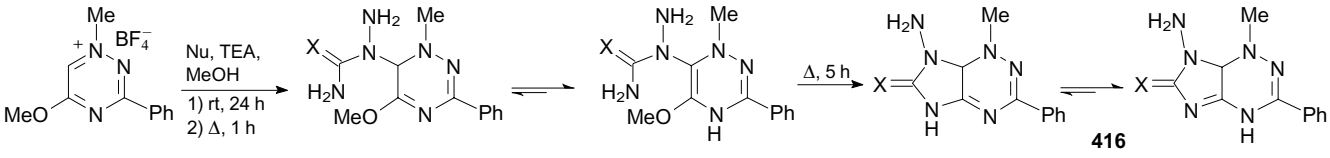
Academician O.N.Chupakhin and co-workers[306] synthesized imidazo[4,5-*e*]-1,2,4-triazin-6-one (**416a**) and its thio analogue (**416b**) in 48% and 14% yields, respectively. Compounds **416** are formed *via* the $A_N-S_N^{ipso}$ tandem process comprising nucleophilic addition and displacement of a good leaving (methoxy) group, which takes place in the reaction of semicarbazide or thiosemicarbazide with π-deficient 5-methoxy-1-methyl-3-phenyltriazinium tetrafluoroborate (Scheme 137).

Among transformations of imidazotriazines, only decomposition of compounds **414** to 1,2,4-triazine-5,6(1*H*,4*H*)-diones and methylurea proceeding in an ethanol solution of NaOH was known previously.[305]

In order to develop an efficient method for the synthesis of perhydroimidazo[4,5-*e*]-1,2,4-triazines **417**, the condensations of diols **362** and **364** with thiosemicarbazides, semicarbazide and aminoguanidine were studied at the Laboratory of Nitrogen-Containing Compounds, ZIOC RAS. It was shown that diols **362** and **364** can form adducts with either one or two nucleophile molecules. Thorough selection of the reaction conditions (refluxing in a 100 : 10 : 1 EtOH, H_2O and HCl mixture or heating in water in the presence or in the absence of propan-2-ol at pH 1 and 70 – 80 °C) and the order of addition of thiosemicarbazide or its analogues (gradually in portions or simultaneously with the diols) furnished a number of imidazotriazines **417** and 4,5-disubstituted imidazolidin-2-ones(thiones) **418** in moderate to high yields (Schemes 138 and 139).[307 – 314]

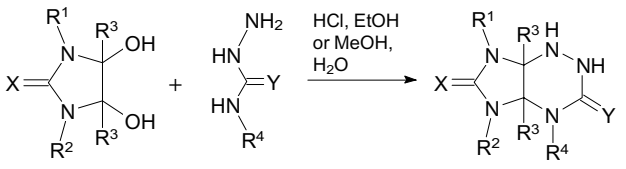
The presence of phenyl substituents in the diol molecule was found to be the factor promoting the regioselective formation of imidazotriazines **417** (see Scheme 138).[307 – 310] The use of 4-substituted thiosemicarbazide and simultaneous addition of reactants resulted in the predom-

Scheme 137



Nu = $H_2NNHC(O)NH_2$, $H_2NNHC(S)NH_2$; X = O (**a**), S (**b**)

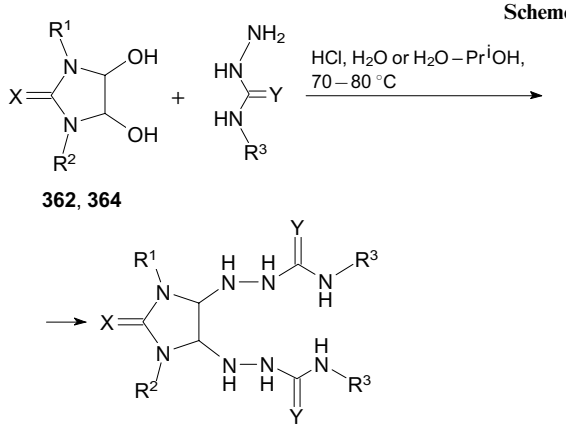
Scheme 138



362, **364** → **417** (21%–96%, 14 examples)

X = O, S; Y = O, S, NH·HCl; R^1 = Me, Et, Bu^t; R^2 = Me, Et, Ph; R^3 = H, Ph; R^4 = H, Me

Scheme 139



362, **364** → **418** (50%–83%, 25 examples)

X = O, S; Y = S, NH·HCl; R^1, R^2 = H, Me, Et; R^3 = H, Me, Et, Bu^i, Ph

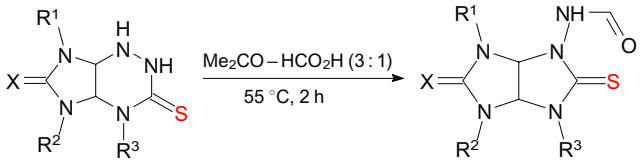
inant formation of monocyclic products **418** (see Scheme 139).[311–314]

The appearance of the general synthetic route to imidazotriazinethiones **417** gave a powerful impetus to studying their chemical reactivity, in particular, reactions with electrophilic agents.[310,315–329] The tandem process including the hydrazone formation and triazine ring contraction in the reaction of imidazotriazines **417** with aromatic and heteroaromatic aldehydes and with phenyl- and furylacrolein derivatives was used to develop a general method for the synthesis of monothio analogues of 4-aminoglycoluril (**419**–**421**) (Scheme 140).[315–320]

Some thioglycolurils **419**–**421** exhibited *in vitro* antiproliferative activity against cancer cell lines (melanoma, rhabdomyosarcoma, lung cancer, intestine cancer and leukaemia cells)[318,319] and sedative activity *in vivo* in open field and elevated plus maze tests.[321] Alkylsulfanyl thioglycoluril derivatives **422** and **423** obtained by alkylation of thioglycolurils **419** and **421** with methyl and ethyl halides in methanol in the presence of potassium carbonate exhibited fungicidal activity against phytopathogens: *Rhizoctonia solani*, *Fusarium oxysporum*, *Fusarium moniliforme* and *Bipolaris sorokiniana* (see Scheme 140).[319,320]

The tandem reactions including the formylation of imidazotriazines **417** with formic acid and the subsequent triazine ring contraction resulted in 4-formamidothioglycolurils **424** in up to 70% yields (Scheme 141). A considerable decrease in the product yield (down to 19%) was observed for starting compound **417** substituted at the triazine ring (R^3 = Me).[310]

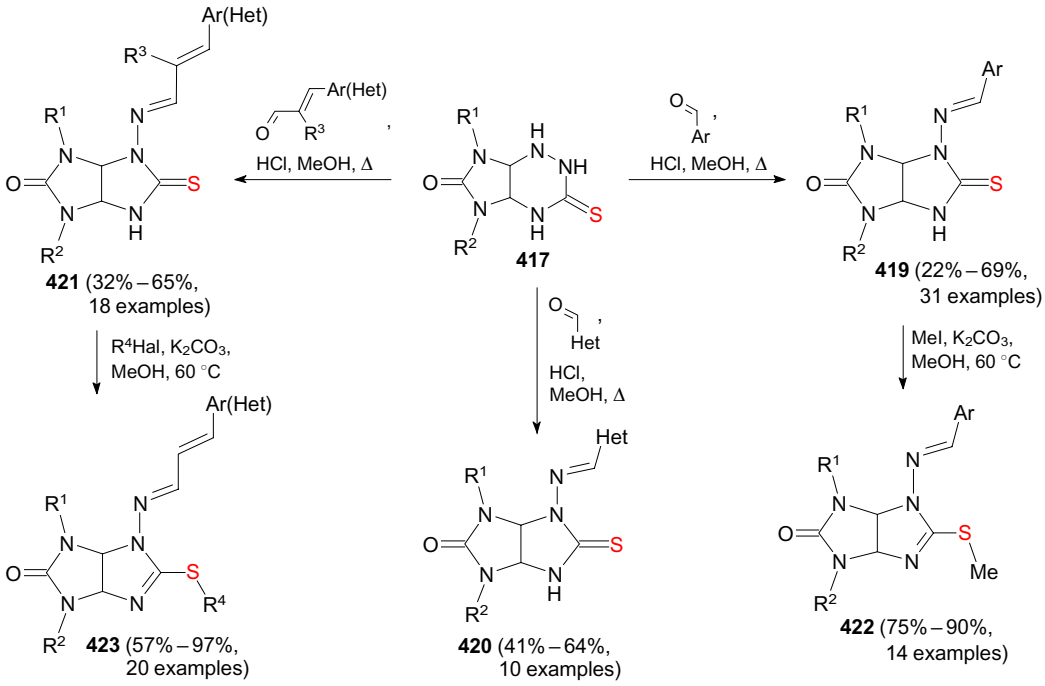
Scheme 141



417 → **424** (19%–70%, 9 examples)

X = O, S; R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Me

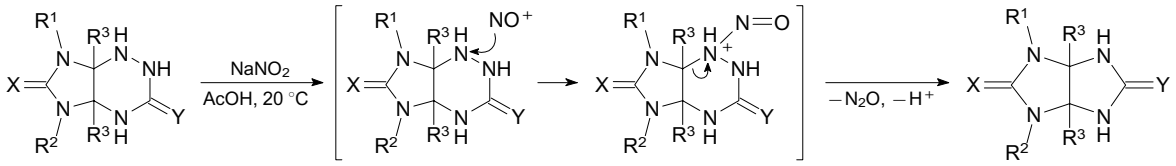
Scheme 140



421 (32%–65%, 18 examples); **417**; **419** (22%–69%, 31 examples); **423** (57%–97%, 20 examples); **420** (41%–64%, 10 examples); **422** (75%–90%, 14 examples)

417: R^1 = Me, Et; R^2 = Me, Et, Ph; **419**–**423**: R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Me; R^4 = Me, Et, 4-$ClC_6H_4CH_2$; Hal = I, Cl

Scheme 142



417 **379**, **425** (31% – 93%)

X = S, O; Y = S, O, NH·HCl; R^1, R^2 = Alk: R^3 = H, Ph

In the above triazine ring contraction reactions, the NH group subjected to the electrophilic attack is retained. The nitrosation of imidazotriazines **417** with sodium nitrite in an acid medium afforded ring contraction products in which this group is lost, namely, 1,3-dialkylglycolurils **379** and their thioxo and imino analogues **425** (Scheme 142).[309, 322]

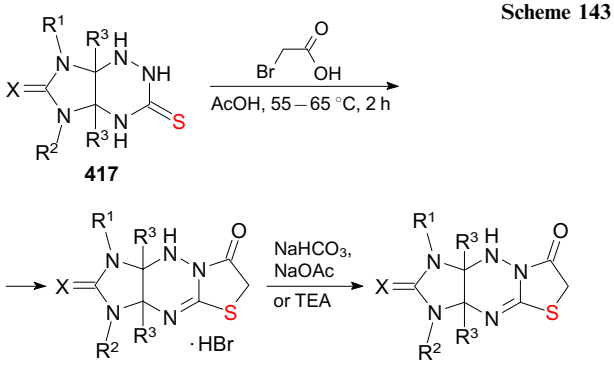
The synthetic value of the reactions of imidazotriazines **417** with aldehydes, formic acid and sodium nitrite in an acid medium is that they form the base for a new synthetic strategy towards thioglycolurils and their analogues.

The alkylation of imidazotriazines with haloacetic acids in an acid medium involves not only S-alkylation, but also cyclodehydration of the intermediate thus formed to give tricyclic structures, imidazo[4,5-*e*]thiazolo[3,2-*b*]triazines **426** or their hydrobromides **427** (Scheme 143).[323 – 325]

Diphenyl-substituted imidazotriazine **417a** was introduced into three-component condensations with bromoacetic acid and various carbonyl compounds.[326 – 329] The condensations with aromatic aldehydes and isatin produced ylidene derivatives of imidazothiazolo[3,2-*b*]triazine **428** and **429a**, respectively,[327, 328] whereas reactions with 3,5-di-*tert*-butyl-1,2-benzoquinone (**430a**) afforded two products: the expected compound **431** and a new heterocyclic system derivative, imidazo[4,5-*e*]thiazolo[2,3-*c*]-1,2,4-triazine **432**. The structure of the latter product was established by X-ray diffraction (Scheme 144).[329]

The product yields in the three-component condensations were, most often, moderate. For this reason, imidazothiazolotriazine derivatives **426** were used in the reactions with carbonyl compounds — *o*-quinones,[329, 330] isatins [325, 328, 331 – 333] and aromatic aldehydes.[327, 334]

Scheme 143



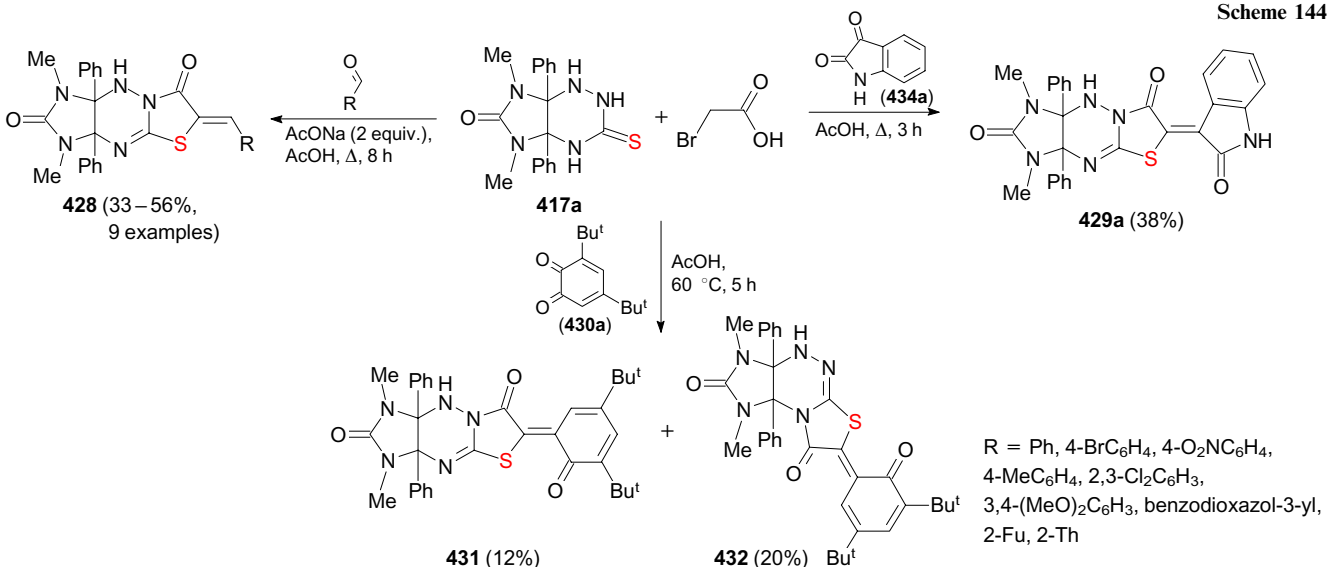
417 **427** (59% – 88%) **426** (60% – 86%, 7 examples)

X = O, S; R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Ph

It is noteworthy that the condensation of imidazothiazolotriazine **426a** with 3,5-di-*tert*-butyl-1,2-benzoquinone also resulted in the formation of isomers **431** and **432** in 35% and 60% yields, respectively. In a control experiment, compound **431** was completely converted to isomer **432** on reflux in acetic acid. This transformation was the first skeletal rearrangement among imidazothiazolotriazines (Scheme 145).[329]

Nitrobenzoquinone **430b** reacts with imidazothiazolotriazine **426a** in acetic acid at room temperature, giving rise to polyheterocyclic compound **433**, the structure of which was established by X-ray diffraction analysis. The latter was

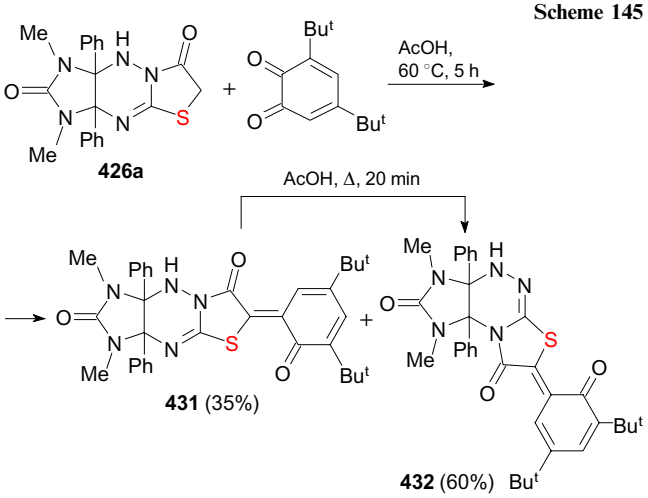
Scheme 144



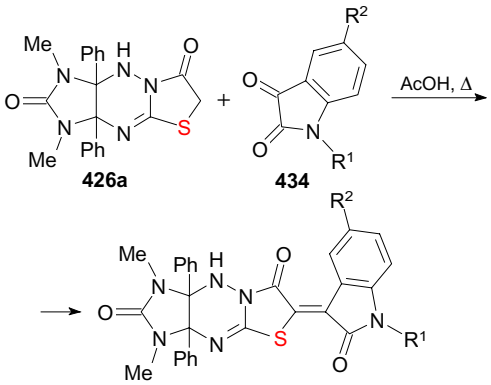
428 (33 – 56%, 9 examples) **417a** **429a** (38%) **(430a)** **431** (12%) **432** (20%)

R = Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-MeC_6H_4, 2,3-$Cl_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, benzodioxazol-3-yl, 2-Fu, 2-Th

Scheme 145

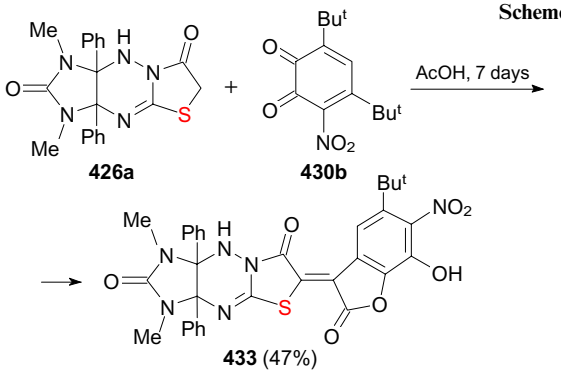


Scheme 147



R^1 = H, Alk; R^2 = H, Br

Scheme 146

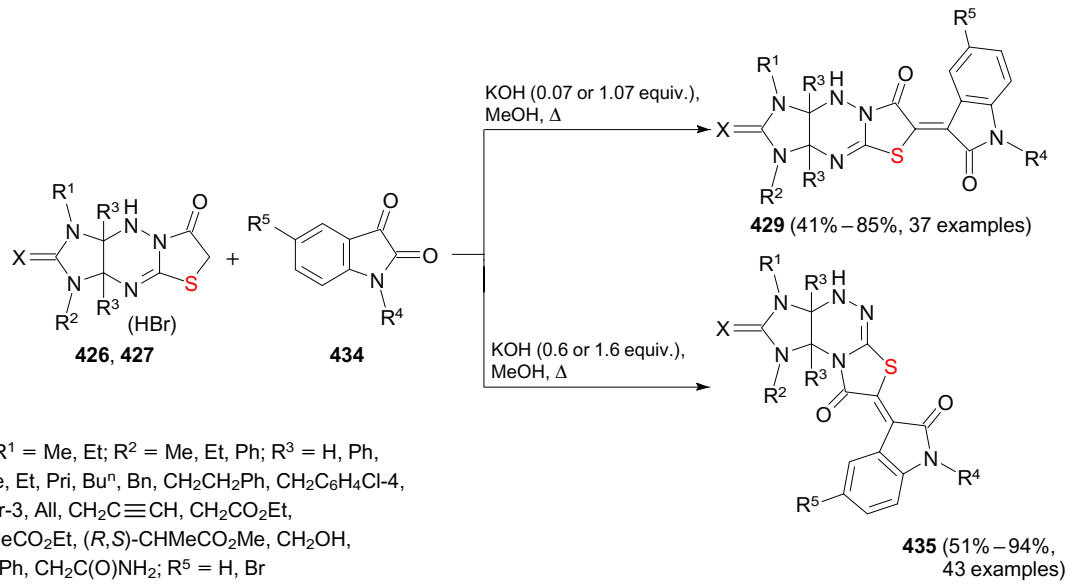


found to contain a benzofuran moiety double-bonded to imidazothiazolotriazine (Scheme 146).[330]

The condensations of compounds **426** and **427** with isatins **434** were conducted in acetic acid and in methanol in the presence of KOH. In acetic acid, high yields of ylidene derivatives of 3a,9a-diphenylimidazothiazolotriazine **429** were attained only in the reaction of compound **426a** with alkylisatins **434** (Scheme 147). When functionally substituted isatins or 3a,9a-unsubstituted compounds **426** and **427** were used, the yields of the reaction products decreased to 10%–20%.[331, 332]

It was found preferable to carry out the process with the KOH catalyst, because in this case, the range of applicable substrates can be markedly extended by functionally substituted isatins and various imidazothiazolotriazines. In addition, the study of the reaction conditions showed that, depending on the amount of KOH, one of two isomeric products is formed, **429** or **435**. The reaction pathway was found to depend also on the nature of substituents at the bridging carbon atoms in **426** and **427**. Imidazothiazolotriazines unsubstituted in positions 3a and 9a smoothly react to give derivatives **429** and their isomers **435**, whereas condensation of 3a,9a-diphenyl derivative **426a** affords mainly products **429**. When the amount of KOH is increased, isomeric derivatives **435** are formed in the early stage of the reaction and then disappear. Only one 3a,9a-diphenyl-substituted compound **435a** (X = O, R^1 = R^2 = Me, R^3 = Ph, R^4 = All, R^5 = H; 55% yield) was isolated in a pure state. Despite some limitations, this reactions opens up wide opportunities for the synthesis of derivatives of the new heterocyclic system — imidazo[4,5-*e*]-thiazolo[2,3-*c*]triazines **435** (Scheme 148).[325, 331–333] Compounds **429** and **435** have antiproliferative action against

Scheme 148

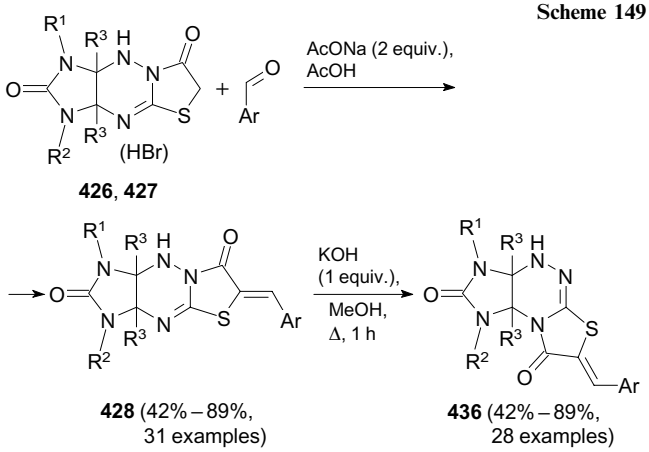


X = O, S; R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Ph, R^4 = H, Me, Et, Pri, Bu^n, Bn, CH_2CH_2Ph, $CH_2C_6H_4Cl$-4, $CH_2C_6H_4Br$-3, All, $CH_2C{\equiv}CH$, CH_2CO_2Et, (*R*,*S*)-$CHMeCO_2Et$, (*R*,*S*)-$CHMeCO_2Me$, CH_2OH, $CH_2OC(O)Ph$, $CH_2C(O)NH_2$; R^5 = H, Br

melanoma, rhabdomyosarcoma, lung cancer, intestine cancer and leukaemia cell lines.[325, 333]

Benzylidene derivatives **428** were synthesized by condensation of imidazothiazolotriazines **426** and **427** with aromatic aldehydes in acetic acid in the presence of 2 equiv. of sodium acetate.[327, 334] The rearrangement of compounds **428** under the action of KOH considerably extended the range of imidazo[4,5-*e*]thiazolo[2,3-*c*]triazines by ylidene derivatives **436**, including 3a,9a-diphenyl derivatives (Scheme 149).[334]

Scheme 149



R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Ph; Ar = Ph, 2-FC_6H_4, 4-FC_6H_4 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2,3-$Cl_2C_6H_3$

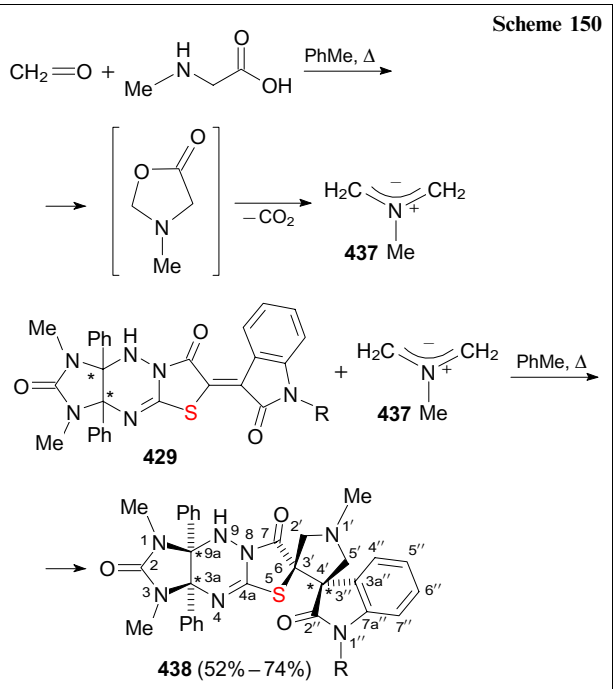
Thus, the condensation of imidazothiazolo[3,2-*b*]triazines with carbonyl compounds — *o*-quinones, isatins and aromatic aldehydes — is a productive research area, which resulted in a discovery of a new acid- or base-catalyzed skeletal rearrangement of the thiazolotriazine moiety to give previously inaccessible isomeric imidazothiazolo[2,3-*c*]triazines and in the synthesis of a library of oxindolylidene(arylmethylidene)imidazo[4,5-*e*]thiazolo[3,2-*b*]- and imidazo[4,5-*e*]thiazolo[2,3-*c*]-1,2,4- triazines.

The presence of an activated double bond in ylidene derivatives opens up the way to quite a few new dispiro polyheterocyclic compounds containing 3,3′- and 2,3′-spiropyrrolidinoxindole and imidazothiazolotriazine moieties.

For the preparation of polynuclear analogues of spiropyrrolidinoxindole, the ylidene imidazothiazolotriazine derivatives were subjected to dipolar cycloaddition reactions with 1,3-dipoles, in particular, with azomethine ylide (**437**) thermally generated *in situ* from sarcosine and formaldehyde. The cycloaddition of ylide **437** to oxindolylidene derivatives of imidazothiazolotriazine **429** resulted in the formation of 3,3′-spiropyrrolidinoxindoles **438** (Scheme 150).[335, 336]

The cycloaddition was conducted by refluxing reactants in toluene for 1 – 10 h using 4 equiv. of sarcosine and paraformaldehyde. Dispiro derivatives **438** were prepared in 52% – 74% yields in the diastereomerically pure form. The stereochemistry of these diastereomers (3a*R**, 3′*R**, 3″*S**, 9a*S** configuration) was determined by X-ray diffraction analysis using compound **438a** (R = Me) as an example. Azomethine ylide has added to dipolarophiles from the side opposite to the direction of phenyl substituents, *i.e.*, the *syn*-side relative to the imidazolidine ring.

Scheme 150

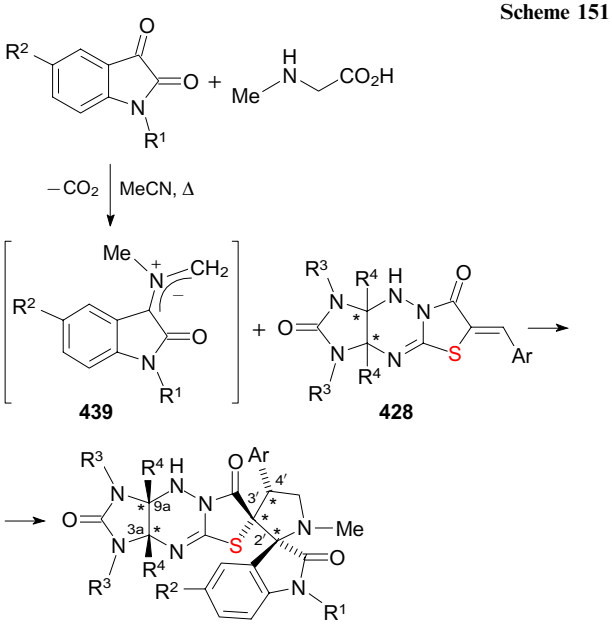


R = H, Me, Et, Bu^n, $CH_2C_6H_4Cl$-4, All, CH_2CO_2Et, $CH(Me)CO_2Et$, CH_2NMe_2

The cycloaddition of arylmethylidene derivatives **428** and azomethine ylides **439** generated from sarcosine and isatins was accomplished by refluxing in acetonitrile or in an acetonitrile – chloroform mixture. This gave a series of dispiro compounds — 2,3′-spiropyrrolidinoxindoles **440** (Scheme 151).[337]

This reaction also gave one diastereomer, which was formed, however, as a result of an *anti-exo*-approach of azomethine ylide to dipolarophile, irrespective of the pres-

Scheme 151



R^1 = H, Me, Et, All; R^2 = H, Br; R^3 = Me, Et; R^4 = H, Ph; Ar = Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 2,4-$Cl_2C_6H_3$

ence or absence of phenyl substituents in positions 3a and 9a. According to X-ray diffraction data, the relative configuration of the stereocentres of compounds **440** is 2′*R**, 3a*S**, 3′*R**, 4′*R**, 9a*R**.[337]

Thus, studies of glycolurils and their close analogues, imidazotriazines, resulted in the development of versatile methods for the synthesis of mono-, bi- and polyheterocyclic compounds (in particular, enantiomerically pure ones): imidazolidin-2-one, glycoluril, thioglycoluril, imidazothiazole and imidazoxazole derivatives, annulated and spiro systems. The syntheses are performed using available reagents (ureas and their analogues, glyoxal, KSCN, $BrCH_2CO_2H$ and isatin derivatives, aldehydes, amines, amino acids) and both traditional and original approaches. New applications were found for Mannich type cycloaminomethylation, aldol crotonic condensation, triazine ring contraction in imidazothiazolotriazines to the imidazolidine ring, 1,3-dipolar cycloaddition of azomethine ylides to ylidene derivatives. Stereoselective syntheses were performed for the first time to prepare enantiomerically pure glycolurils and diastereomerically pure dispiro polyheterocyclic compounds with four or five chiral centres containing 3,3′- and 2,3′-spiropyrrolidinoxindole and imidazothiazolotriazine moieties. New gelators were found among glycoluril acid amides. New approaches to the preparation of (thio)-glycolurils, imidazothiazoles and imidazooxazoles were developed and a amidine skeletal rearrangement of the thiazolotriazine moiety was found. The use of glyoxal in the bis-dioxolane form provided the synthesis of compounds pertaining to a new bis-bicyclic system — bis[dioxolanoimidazo(thiadiazo)lidine].

4.2. Synthesis, structure and reactivity of diaziridines

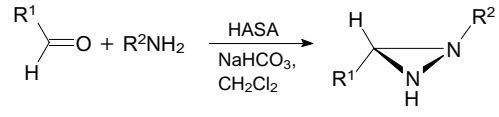
Diaziridines, saturated three-membered heterocycles with two nitrogen atoms (cyclic hydrazines), attract attention of chemists owing to their unique set of properties. First, these compounds, like glycolurils, possess neurotropic activity and, unlike linear hydrazines, they have low toxicity; therefore, they can be used to develop new pharmaceuticals. Second, they contain configurationally stable nitrogen atoms (the inversion barriers are 18–27 kcal mol^{-1}) and are fairly rare objects for studying the stereochemistry of the nitrogen atom. In addition, diaziridines have high positive enthalpy of formation due to the strained nature of the three-membered ring and the presence of a hydrazine moiety, which makes them applicable as potential fuels for liquid rocket propellants instead of toxic hydrazine derivatives. Besides, diaziridines offer the greatest benefits for synthetic organic chemistry, because the diaziridine ring tends to be cleaved at either the C–N or N–N bond on heating or under the action of electrophilic reagents, while the 1,3-dipolar intermediates formed in the reactions can participate in various cycloaddition reactions to give both known and new heterocyclic systems.

Diaziridines were discovered in the mid-20th century by German chemist E. Schmitz, and the early methods for their synthesis and chemical transformations are summarized in a monograph.[338] Studies of the diaziridine chemistry at the Laboratory of Nitrogen-Containing Compounds, ZIOC RAS, were started in 1965 and are now in progress.

4.2.1. New trends of studies on diaziridine synthesis and reactivity

The first stage of research into this class compounds included the development of optimal synthetic routes to mono-, di-, tri- and tetrasubstituted diaziridines and their fused derivatives. The results of these studies are summarized in a review[339] and protected by patents.[340–342] Subsequently, several variations of the developed procedures were reported in foreign literature. The classical approach to the synthesis of diaziridines consisting in mixing of carbonyl compounds, primary aliphatic amines and aminating reagents in the presence of bases was used recently[343] for the diastereoselective synthesis of 1,3-dialkyl- and 1-alkyl-3-aryldiaziridines **441**, with hydroxylamine-*O*-sulfonic acids (HASA) acting as the aminating agent. Under certain conditions, aromatic aldehydes were successfully introduced into the reaction (Scheme 152).

Scheme 152

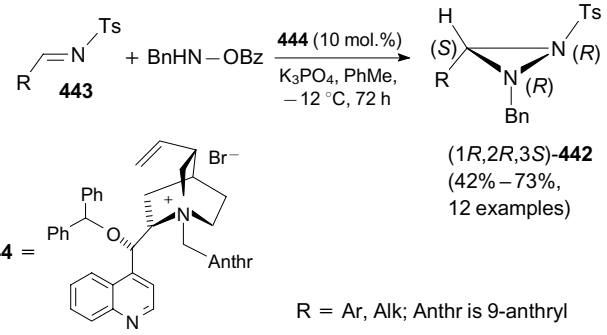


441 (80%–91%, 15 examples)

R^1 = Alk, Ar; R^2 = Alk

Highly diastereoselective syntheses of monocyclic diaziridines and 3,3′-bidiaziridines were performed by reactions of imines and symmetrical (*E*,*s-trans*–*E*)-α-diimines with nosyloxyethylcarbamate as the aminating reagent in the presence of CaO as a base.[344,345] The first catalytic enantio- and diastereoselective synthesis of diaziridines **442** was implemented by the reactions of *N*-tosylaldimines **443** with *N*-benzyl-*O*-benzoylhydroxylamine in the presence of asymmetric phase transfer catalyst **444**. Optically active diaziridines containing two orthogonal N-protected groups are formed as single diastereomers (1*R*,2*R*,3*S*)-**442** with enantiomeric excess (*ee*) of 84%–96% (Scheme 153).[346]

Scheme 153



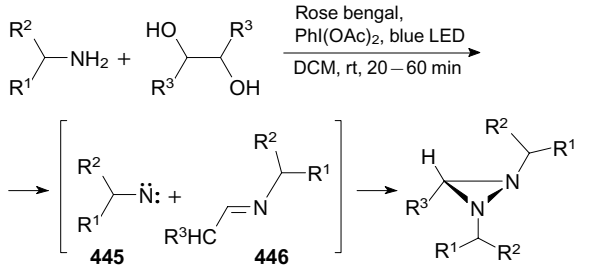
(1*R*,2*R*,3*S*)-**442** (42%–73%, 12 examples)

R = Ar, Alk; Anthr is 9-anthryl

In 2017, researchers from India[347] proposed a basically different approach to the formation of the diaziridine ring, which consists of the photocatalytic generation of nitrenes **445** from primary aliphatic amines and nitrene insertion into the double bond of azomethines **446**. Both reagents were photocatalytically generated in a one-pot process from primary amines and glycols on treatment with $PhI(OAc)_2$ as a Lewis acid and an oxidant under visible light irradiation (λ = 450 nm, blue LED) in the presence of a catalytic amount (1%) of Rose Bengal as a photocatalyst (Scheme 154).

The studies of reactions of diaziridines with electrophilic reagents carried out before 2011 are summarized in a review of Makhova *et al.*[348] However, this line of research continued to develop in recent years. First of all, worthy of note

Scheme 154



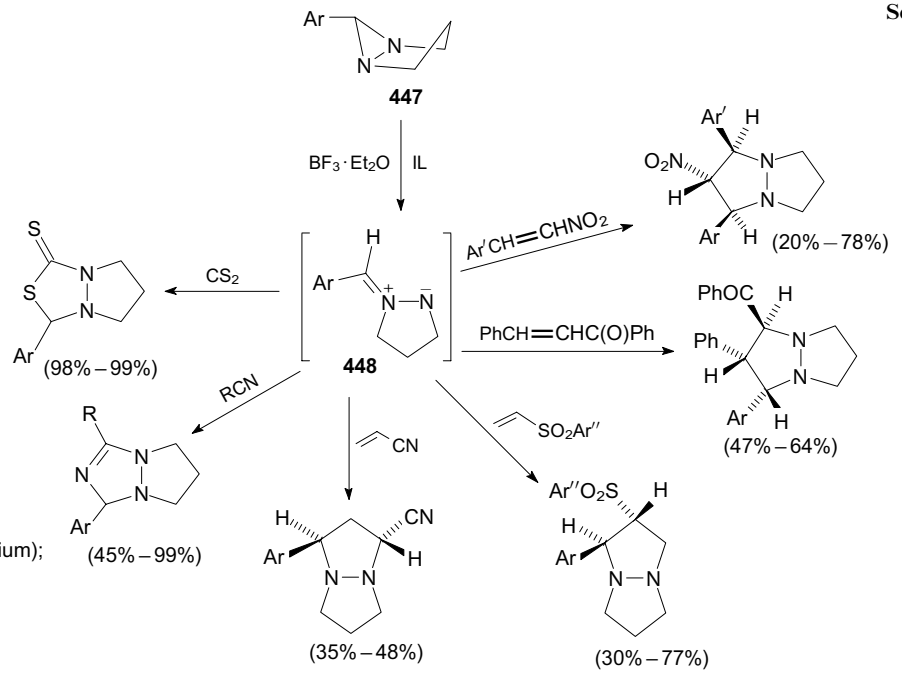
R^1 = Me, Pr^i, Ph, 4-FC_6H_4, 4-MeC_6H_4, 2-$NO_2C_6H_4$, Bn;
R^2 = H, Me, CO_2Et; R^3 = H, Me, Ph, CO_2Et

is the series of studies on diaziridine ring expansion aimed at the development of new facile and environmentally benign synthetic routes to nitrogen-containing heterocyclic systems. The most interesting results were obtained for reactions carried out in ionic liquids (IL), which catalyze and accelerate these processes. These studies used 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **447** as investigation objects. On treatment with a Lewis acid (usually $BF_3 \cdot Et_2O$), the diaziridine rings of these compounds opened to yield azomethine imines **448**. The latter underwent [3 + 2]-cycloaddition, in a one-pot process, with a broad range of dipolarophiles such as activated nitriles,[349] carbon disulfide,[350] terminal alkenes,[351] β-nitrostyrenes [352, 353] and chalcones.[354] This gave a series of cycloaddition products in which the pyrazolidine ring is annulated *via* nitrogen atoms onto the thiadiazolidine, triazoline or pyrazolidine ring bearing various substituents (Scheme 155).

Ionic liquids were used for the [3 + 2]-cycloaddition of azomethine imines **448** to isatins,[355] 4-nitrobenzaldehyde [355] and arylmethylidenemalononitriles **449**.[356, 357] It was found that cycloaddition products (*e.g.*, compounds **450**) undergo cycloreversion (metathesis), thus generating new azomethine imines **448′**. The latter are stabilized either *via* 1,4-*H*-shift to give pyrazolines **451** or by forming new cycloadducts **452** with other dipolarophiles added to the reaction mixture (Scheme 156).

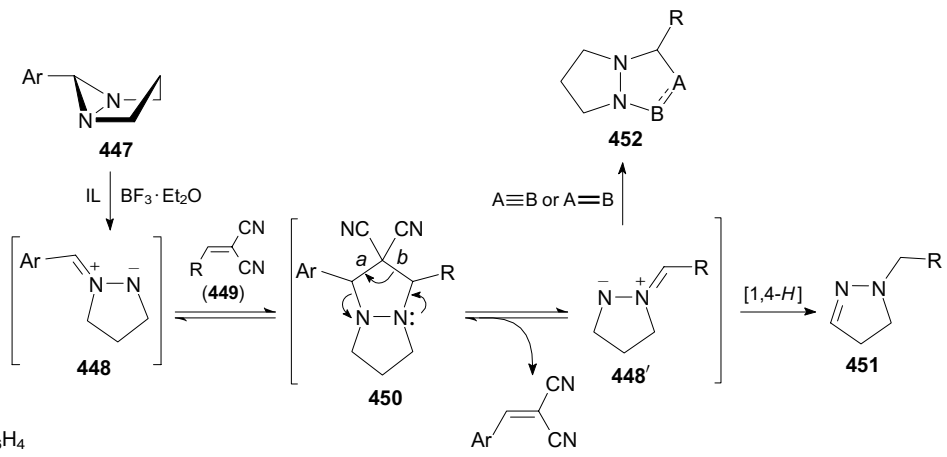
Studies of the metathesis reactions resulted in the development of new, two-step, environmentally benign methods for the synthesis of monosubstituted pyrazolines and pyrazoles and also new fused heterocyclic molecules in which

Scheme 155



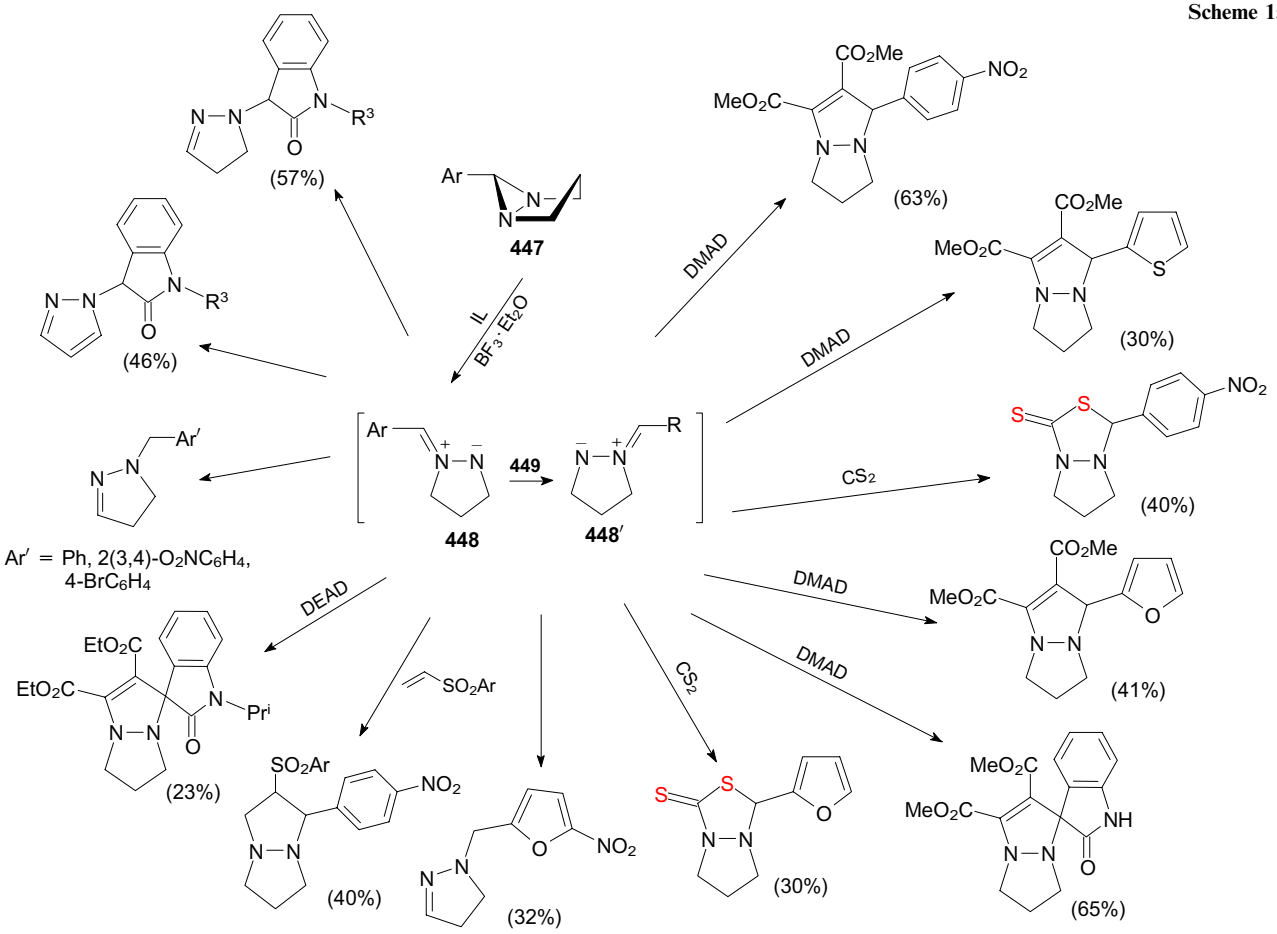
IL = [bmim][BF_4], [bmim][PF_6]
(bmim is 1-n-butyl-3-methylimidazolium);
Ar = 4-$MeOC_6H_4$, 4-$EtOC_6H_4$,
4-Pr^iOC_6H_4, 4-MeC_6H_4;
Ar′ = 4-MeC_6H_4, 3-$O_2NC_6H_4$;
Ar″ = 4-$NO_2C_6H_4$

Scheme 156



Ar = 4-$MeOC_6H_4$,
4-$EtOC_6H_4$, 4-Pr^iOC_6H_4,
4-MeC_6H_4; R = 4-$O_2NC_6H_4$

Scheme 157



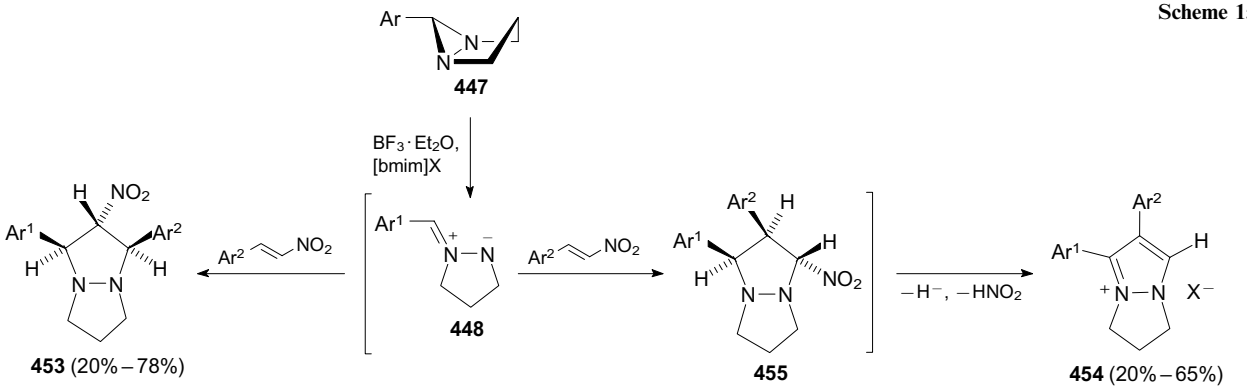
DEAD is diethyl acetylenedicarboxylate, DMAD is dimethyl acetylenedicarboxylate

the pyrazolidine ring is annulated onto pyrazoline, thiadiazolidine or pyrazolidine five-membered rings. The annulated heterocycle can contain functional (CN, SO_2Ar, NO_2) or pharmacophoric heterocyclic substituents (furyl, thienyl, indolyl) (Scheme 157). The ionic liquids used in these reactions are regenerated and reused many times without a considerable decrease in the yields of final products.

When azomethine imines **448** generated from compounds **447** in ionic liquids in the presence of $BF_3 \cdot Et_2O$ react with 3-nitro-β-nitrostyrene, the reaction unexpectedly gives bicyclic cationoid structures **454** with the BF_4^- or PF_6^- anions, along with the expected bicyclic compounds **453**. Compounds **454** are formed as a result of regioisomeric cycloaddition of β-nitrostyrene to azomethine imines **448** and spontaneous aromatization of regioisomeric cycloadducts **455** with elimination of a hydride ion and HNO_2. Evidently, N_2O_3 resulting from acid hydrolysis of HNO_2 acts as the oxidant (Scheme 158).[352]

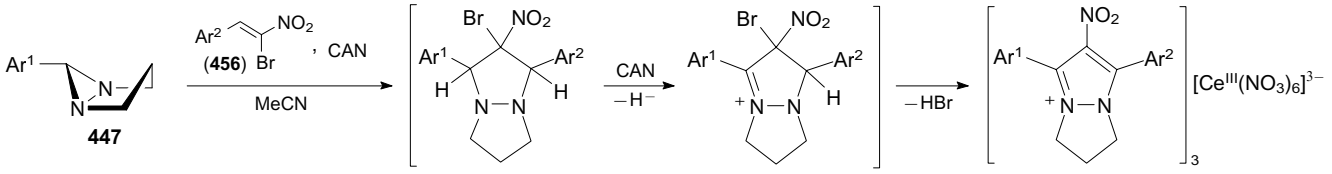
Cationoid structures **454** are of interest as highly conductive plastic organic crystals. In order to prepare analogous salt, cyclocondensation of azomethine imines **448** with (2-bromo-2-nitrovinyl)arenes **456** in the presence of various oxidants was investigated. Cerium(IV) ammonium nitrate (CAN) was found to be the oxidant of choice. This

Scheme 158



Ar^1 = 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-MeC_6H_4; Ar^2 = 3-$O_2NC_6H_4$; X = BF_4, PF_6

Scheme 159

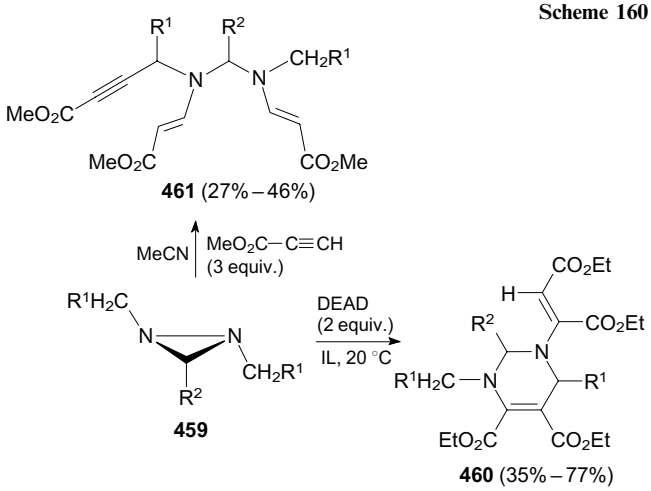


Ar[1], Ar[2] = Ar, Het

approach led to the development of a facile one-pot regioselective method for the preparation of hydrazine-bridged 2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyrazolium cationoid structures **457** with $[Ce^{III}(NO_3)_6]^{3-}$ as the anion (Scheme 159).[358] The reaction smoothly proceeds in MeCN, with CAN being used as the Lewis acid for generation of azomethine imine. Apparently, a hydride ion is first eliminated from the cycloaddition product **458** in the presence of CAN as the oxidant and then the intermediate **458′** thus formed undergoes aromatization *via* elimination of HBr (see Scheme 159).

Alkyl-substituted diaziridines **459** participate in unusual diaziridine ring expansion reactions involving activated acetylenes. When they react with diethyl acetylenedicarboxylate in an ionic liquid, tetrahydropyrimidines **460** (1 : 2 adducts) are formed,[359] while the reactions with methyl propiolate give acyclic structures **461** (1 : 3 adducts)[360] (Scheme 160). These reactions start with the attack by the diaziridine nitrogen atom on the electrophilic carbon atom of the acetylene moiety, resulting in diaziridine ring opening at the N – N bond, which is followed by addition of one or two molecules of the acetylene derivative. In the case of DEAD, this process is accompanied by intramolecular cyclization.

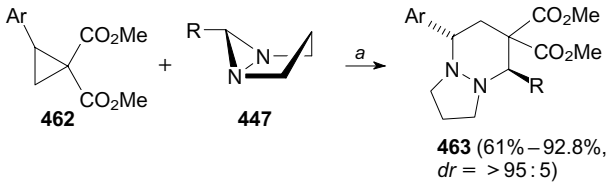
Scheme 160



R[1] = Me, Et, Bu[n]; R[2] = H, Me, Et;
IL = [bmim][BF_4], [bmim][PF_6], [emim][HSO_4];
emim is 1-ethyl-3-methylimidazolium

Recently,[361] researchers of the Laboratory of Nitrogen-Containing Compounds, together with the research group headed by Prof. I.V.Trushkov discovered previously unknown [3 + 3]-cycloaddition reaction of two different three-membered rings — donor – acceptor cyclopropanes (DAC) **462** and diaziridines — to give six-membered heterocyclic compounds, perhydropyridazine derivatives **463**. 6-R-1,5-Diazabicyclo[3.1.0]hexanes **447** were used in the reactions with DAC as the diaziridine substrates. The [3 + 3]-cycloaddition reaction of DAC **462** with diaziridines **447** efficiently proceeds for a broad range of substrates containing both electron-donating and electrically neutral substituents at the aromatic and heteroaromatic rings. Moreover, alkenyl-substituted DAC behaved in this reaction similarly to aromatic analogues. This reaction was successfully carried out for quite a few bicyclic diaziridines **447** containing alkyl, aryl, alkenyl and cyclopropyl substituents at the diaziridine carbon atom and unsubstituted diazabicyclohexanes. The reaction is catalyzed by a soft Lewis acid $[Ni(ClO_4)_2 \cdot 6H_2O]$ and proceeds in high yields and with high diastereoselectivity in DCM on gentle heating (40 °C) (Scheme 161, 20 examples). A similar [3 + 3]-cycloaddition is observed when 7-aryl-1,5-diazabicyclo[4.1.0]heptanes are reacted with DAC under the same conditions.

Scheme 161

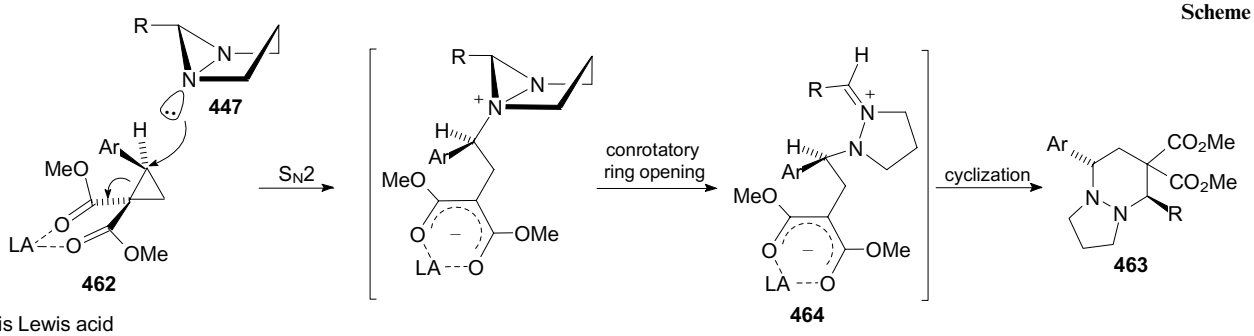


(*a*) $Ni(ClO_4)_2 \cdot 6H_2O$, DCM, MS 4 Å; Ar = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2,4,6-$(MeO)_3C_6H_2$, 3,4,5-$(MeO)_3C_6H_2$, 2-Th; R = H, cyclo-C_3H_5, Ph, 4-$MeOC_6H_2$, 4-ClC_6H_4, 2,4-$(MeO)_2C_6H_3$; MS are molecular sieves, *dr* is diastereomeric ratio

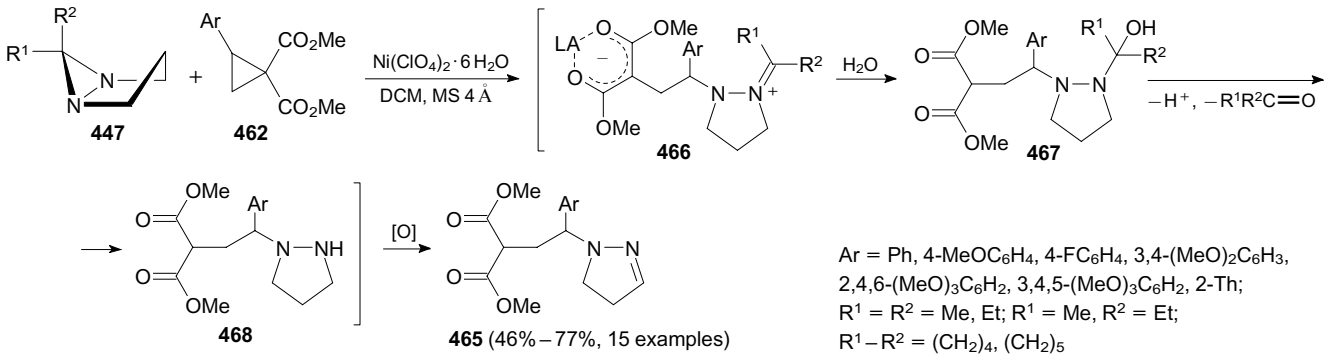
The mechanism of this reaction includes an attack by the diaziridine nitrogen atom of compound **447** on Lewis-acid-activated cyclopropane **462** occurring in such a way that the methine hydrogen atom at the C(2) carbon of DAC points towards the C(3) – C(4) bond of diaziridine. Then the diaziridine ring is opened at the C – N bond and cyclization of intermediate **464** proceeds stereoselectively to give the target perhydropyridazine **463** (Scheme 162).

If the starting bicyclic diaziridines **447** contain bulky substituents at the diaziridine carbon, which prevent the [3 + 3]-cycloaddition to DAC **462**, 1-substituted pyrazolines **465** were isolated as the reaction products. The mechanism of this reaction, like in the case of the synthesis of **463**, includes the alkylation of diaziridine nitrogen by the Lewis acid-activated donor – acceptor cyclopropane **462** as the first step. Then the zwitter-ion intermediate **466** is hydrolyzed to hydroxy derivative **467**, which eliminates a proton and a carbonyl compound, and the resulting pyrazolidine **468** is oxidized by air oxygen to 1-substituted pyrazoline **465** (Scheme 163).[362]

Scheme 162

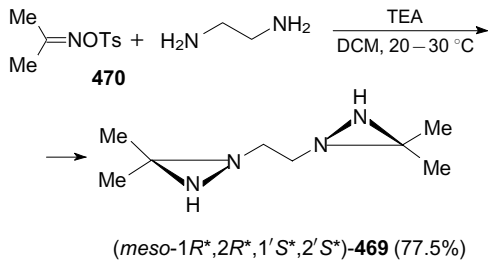


Scheme 163



In recent years, considerable attention has been paid to neurotropic activity of diaziridines; this work resulted in the creation of a new efficient antidepressant drug with post-anxiolytic effect — *N*,*N*′-ethylenebis(3,3-dimethyldiaziridine) (tetramezine, **469**). The antidepressant action of this agent is comparable with the action of known medications (nialamide, imipramine, Prozac, Cipramil), but differs by the fact that its therapeutic effect is observed on the day it is taken, but not 1–2 weeks later as with the known antidepressants. The agent has low acute and chronic toxicity [the half-lethal dose (LD_{50}) is 1140 mg kg^{-1}], causes no adverse effects and can be recommended for senior patients.[363] The synthesis of tetramezine is based on the use of simple and readily available initial compounds and includes the reaction of acetone oxime *p*-toluenesulfonate (**470**) with ethylenediamine in the presence of triethylamine in dichloromethane at 20–30 °C (Scheme 164).[364, 365]

Scheme 164



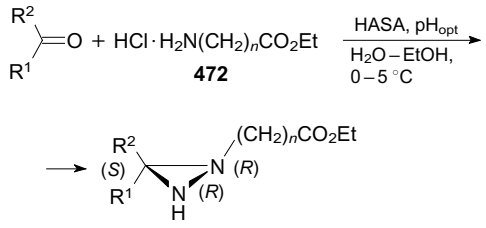
Each diaziridine ring has two stereogenic nitrogen atoms; these centres are stereolabile and, hence, they are prone to interconversion.[366–368] Since substituents at the nitrogen atoms can occupy only *trans*-positions due to the repulsion of nitrogen lone pairs (LPs), both nitrogen atoms are interconverted and, hence, they have the same absolute configuration.[369] Tetramezine (**469**) can exist as only three stereoisomers: an achiral *meso*-form (S_NS_N stereodescriptor in one diaziridine ring and $R_{N'}R_{N'}$ sterodescriptor in the other ring) and two enantiomeric forms in which all nitrogen atoms have *R*- or *S*-configuration; the *meso*-form predominates in the obtained product (the ratio is 3 : 2 according to ^{1}H NMR spectroscopy data). The diastereomers were separated by crystallization from acetone and it was found that the enantiomeric forms can be epimerized almost quantitatively to the *meso*-form on heating in chloroform (the activation barrier is 104.5 kJ mol^{-1} at 37 °C).

The diastereomeric ratio of tetramezine was determined[370] by a set of physicochemical methods including gas-phase electron diffraction (GED), vibrational spectroscopy and quantum chemical calculations. The experimental r_e parameters of the tetramezine diastereomers are in line with the results of B3LYP/cc-pVTZ and MP2/cc-pVTZ calculations, which predict the total energy of the *meso*-form (C_i symmetry group) to be lower (4.7 kJ mol^{-1}) than the total energy of the enantiomeric form (C_2 symmetry group) (6.4 kJ mol^{-1}). The experimentally measured ratio of *meso*- to enantiomeric forms at 360 K is 70% to 30%.

In order to pave the way for the preparation of new neurotropic compounds, methods were developed for the synthesis of hybrid structures containing other active moieties along with the diaziridine ring. Recently, a simple diastereoselective method was developed for the synthesis of 1,3-di- and 1,3,3-trisubstituted diaziridines **471** containing fragments of neurotransmitter amino acids (glycine, β-alanine and γ-aminobutyric acid).[371] It is based on the three-component one-pot condensation of carbonyl compounds, hydrochlorides of amino acid ethyl esters **472** and hydroxylamine-*O*-sulfonic acid. The reaction is carried out under mild conditions under controlled pH of the medium: the optimal values are 8.5 –9.0 for aldehydes and 9.5–10.0 for

ketones. The products based on aldehyds are mixtures of diastereomers with *meso*-form predominating. The epimerization of the minor diastereomer to the predominant one proceeds even during a single distillation of the mixture. This method is general, which enabled the preparation of a library of new type structures **471** containing two neurotropic moieties in the molecule (Scheme 165 shows the *meso*-form for $R^2 = H$).

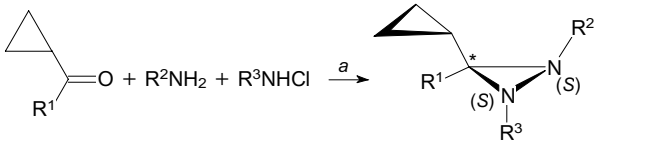
Scheme 165



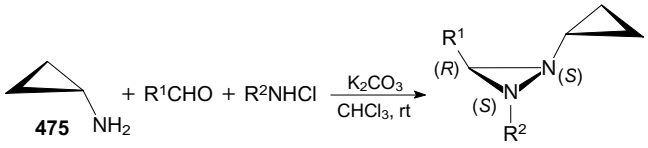
$n = 1-3$; R^1 = Me, Et, Pr^i, Bu^i, Et$_2$CH; R^2 = H, Me;
$R^1 - R^2 = (CH_2)_5$

Recently, a method was developed for the synthesis of hybrid structures containing two three-membered pharmacophoric moieties in one molecule, namely, diaziridine and cyclopropane ones.[372] Depending on the source of the cyclopropane moiety (cyclopropanecarboxaldehyde, methyl cyclopropyl ketone or cyclopropylamine), these rings can be connected by either a C – C (**473**, 13 examples) or C – N (**474**, 5 examples) bond. The synthesis of compounds **473** and **474** is based on one-pot three-component condensation of carbonyl compounds, primary aliphatic amines, including cyclopropylamine **475**, and *N*-chloroalkylamines in an organic solvent in the presence of bases. The resulting products with different substituents at nitrogen atoms are also mixtures of two diastereomers: racemic mixtures of two *meso*-forms and two enantiomeric forms. The authors failed to separate these diastereomers, but each of them was characterized by spectroscopy in the mixture. Scheme 166 shows only the predominant diastereomers — *meso*-forms.

Scheme 166



(*a*) MeOH, 0 – 5 °C or K_2CO_3, $CHCl_3$, rt;
R^1 = H, Me; $R^2 = R^3$ = Me, Et, Pr^n,
$(CH_2)_2Ph$, $(CH_2)_2OH$; $R^2 - R^3 = (CH_2)_3$, $(CH_2)_4$



R^1 = Me, cyclo-C_3H_5; R^2 = Me, Et

4.2.2. Structural features of the diaziridine ring

Since the alkyldiaziridine derivatives are usually liquid, they can be studied by X-ray diffraction only in rare cases. For this reason, in recent years, considerable attention has been given to gas electron diffraction studies of diaziridines in combination with quantum chemical calculations. These studies were carried out by researchers of the ZIOC RAS, together with specialists of the Laboratory of Electron Diffraction Analysis of the Department of Chemistry, M.V.Lomonosov Moscow State University under supervision of D.Sci. I.F.Shishkov.

A GED study of the simplest 1,2-dimethyl- (**476**) and 1,2,3-trimethyldiaziridines (**477**) demonstrated [373, 374] that in both molecules, the methyl groups at the nitrogen atoms have *trans*-positions relative to the ring plane. The 1,2,3-trimethyldiaziridine molecule (**477**) 'chooses' the inevitable *cis*-conformation for the methyl groups at the C – N bond rather than N – N bond, which is a consequence of efficient repulsion of the endocyclic nitrogen LPs (Fig. 7).

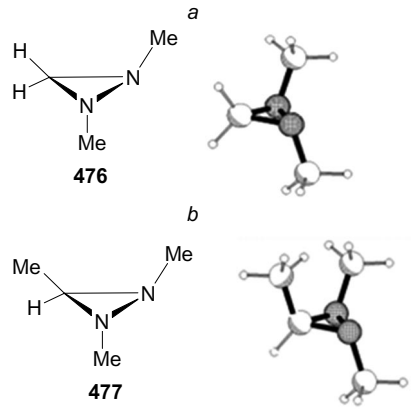


Figure 7. Formulae and molecular structures of 1,2-dimethyl- (*a*) and 1,2,3-trimethyldiaziridines (*b*).

According to GED and B3LYP/cc-pVTZ and MP/cc-pVTZ quantum chemical calculations, the introduction of a cyclopropyl substituent to the carbon atom stabilizes two conformations (*gauche* and *anti*) of the 3-cyclopropyl-1,2-dimethyldiaziridine molecule (**473a**), with the conformation ratio in the gas phase being 1 : 1.5 and the barrier for conformational transition being $\sim 6.0 - 6.7$ kcal mol^{-1} (25 – 28 kJ mol^{-1}) (Fig. 8).[375]

A GED study of the simplest 1,5-diazabicyclo[3.1.0]hexane (**478**) showed that this molecule exists in the flattened boat conformation [376] (Fig. 9). According to calculations, the total energy of the isolated molecule in a boat conformation is 3.4 – 4.2 kcal mol^{-1} lower than the energy in the chair conformation. The boat conformation is stabilized [natural bond orbital (NBO) analysis] by the anomeric effect ari sing upon the interaction of LPs of the N(1) and N(5) atoms with the σ* orbitals of the C(2) – C(3) and C(3) – C(4) bonds, respectively, with its contribution to the charge delocalization being ~ 4.0 kcal mol^{-1}.

The boat conformation was also established for crystalline 6-(4-chlorophenyl)-1,5-diazabicyclo[3.1.0.]hexane by X-ray diffraction analysis [377] and for 6,6′-bis(1,5-diazabicyclo[3.1.0]hexane by both X-ray diffraction analysis [378] and GED.[379] The introduction of methyl substituents to the C(6) carbon atom makes the pyrazolidine moiety of the 6,6-dimethyl-1,5-diazabicyclo[3.1.0.]hexane molecule almost planar.[380] The methyl substituents at the C(3) carbon atom in the 3,3-dimethyl-1,5-diazabicyclo[3.1.0.]hexane molecule give rise to an equilibrium boat – chair mixture of con-

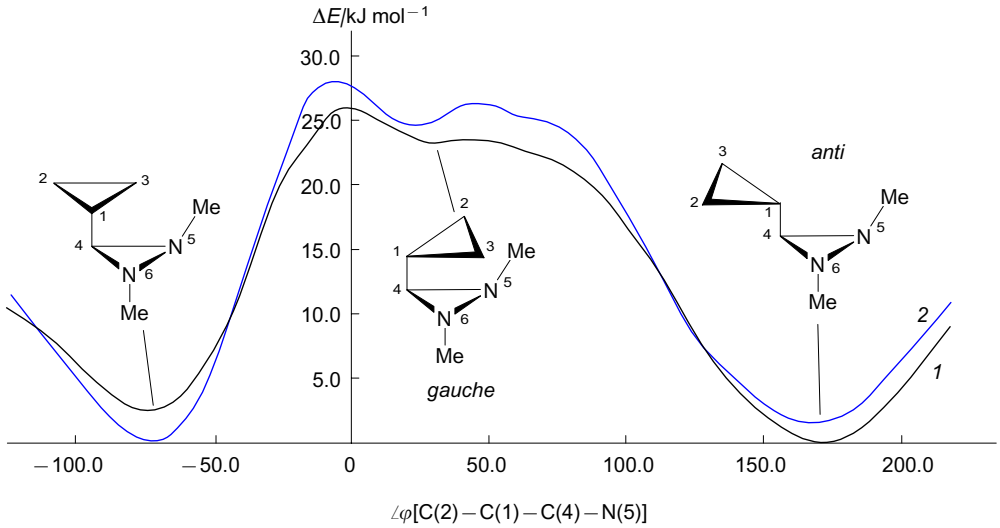


Figure 8. Energy profile of the conformational conversion of the 1,2-dimethyl-3-cyclopropyldiaziridine molecule (**473a**) according to B3LYP/cc-pVTZ (*1*) and MP/cc-pVTZ (*2*) calculations (from Ref. 375).

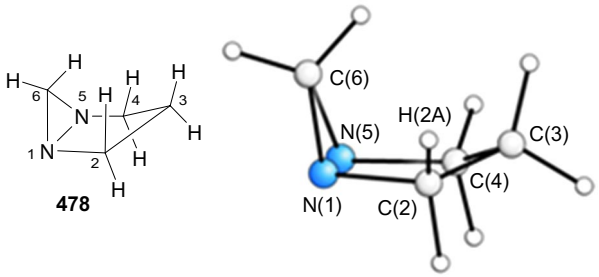


Figure 9. Formula and molecular structure of 1,5-diazabicyclo[3.1.0]hexane (**478**).

formers in 32 : 68 ratio in the gas phase.[380] The structure of 1,6-diazabicyclo[4.1.0.]heptanes was studied by Kuznetsov *et al.*[377] The geometry optimization for the unsubstituted 1,6-diazabicyclo[4.1.0.]heptane molecule (B3LYP/6–31G*) showed that three low-lying conformers with similar energy exist in the isolated state, which hampered the GED examination of this molecule. Using X-ray diffraction study of crystalline 7-phenyl-1,6-diazabicyclo[4.1.0.]heptane (**479**), it was ascertained that the bicyclic seven-membered core of this molecule in the crystal has a chair-like conformation, while the six-membered ring has a boat conformation (Fig. 10).[377]

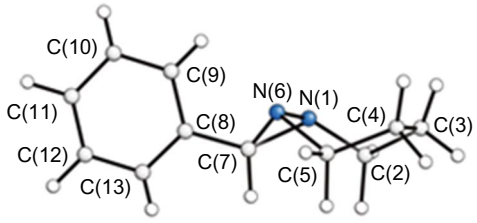


Figure 10. X-Ray diffraction molecular structure of 7-phenyl-1,6-diazabicyclo[4.1.0.]heptane (**479**).

A somewhat unexpected result was obtained in a comparison of the lengths of endocyclic C–N and N–N bonds in diaziridine derivatives and related structures.[381] The N–N interatomic distances in the examined diaziridines (on average 1.512 Å) exceed these values for 1,2-dimethyl-1,2-diazetidine by ~ 0.085 Å (Ref. 382) and exceed those in 1,2-dimethylhydrazine by ~ 0.093 Å,[383] which is attributable to a large contribution of the sp^2 atomic orbitals of nitrogen to antisymmetrical π molecular orbital of the three-membered ring according to the Walsh diagram. The population of this orbital increases the antibonding interaction along the N–N bond and bonding interaction along the C–N bond. Another explanation for the N–N bond elongation in the diaziridine ring is related to efficient repulsion of the LPs of diaziridine nitrogen atoms, resulting in decreasing s-character of the N–N bond in this ring; the increase in the N–N bond lengths on going from acyclic to cyclic molecules is correlated with the increase in the π-nature of the σ_{N-N} bonding orbital. A similar correlation is also observed between the N–N bond length and ellipticity, thus indicating a contribution of the π component to this bond.

Thus, in recent years, new approaches have been developed for diaziridine ring construction and synthesis of hybrid structures containing additional pharmacophoric moieties together with the diaziridine ring. However, especially interesting results were obtained owing to the ability of the diaziridine ring to be cleaved in the presence of electrophilic reagents to give dipolar intermediates. This research culminated in the creation of efficient one- and two-step synthetic procedures for the preparation of a broad range of polyheterocyclic structures that are difficult to prepare by other methods. Structural studies of monocyclic diaziridines by GED and X-ray diffraction methods fully confirmed the *trans*-arrangement of the alkyl substituents at the nitrogen atoms relative to the diaziridine ring plane and revealed the cause for the N–N bond elongation in this heterocycle. It is evident that the potential of available diaziridine derivatives as precursors for paving the way to practically important heterocyclic structures is

far from being exhausted and has prospects for further development.

5. Conclusion

As can be seen from the material covered in the review, the chemistry of nitrogen-, oxygen- and sulfur-containing heterocyclic systems has actively developed at the ZIOC RAS in recent years. The attention was given not only to the methods of synthesis and reactivity of these compounds, but also to the practical applications of the studies. For all classes of compounds, new regio- and chemoselective approaches to the design of both base heterocycles and unique polyheterocyclic systems derived from them were developed.

Indeed, new transformations based on intramolecular rearrangements and cyclizations were found in the studies of furazans and furoxans (Laboratory of Nitrogen-Containing Compounds). These transformations serve for the development of dual-use technologies for the manufacture of both energetic materials and pharmacologically active products. In particular, a series of molecules possessing cytotoxic and anticoagulant activity were obtained among furoxans and compounds with anticancer action were revealed among furazan derivatives. Data on the synthesis of energetic materials based on furazans and furoxans are covered in reviews.[9, 10]

Approaches to the synthesis of a broad range of fused polynuclear nitrogen heterosystems based on the transformations of nitro derivatives of arenes and hetarenes have been elaborated at the Laboratory of Nitro Aromatic Compounds. It is noteworthy that a considerable part of the results have been obtained for the conversion of TNT, an easily available starting compound. Further development of the MBFT (multiple bond-forming transformation) concept appears most promising. It is based on the proneness of nitro(het)arenes to easy aromatization *via* [3 + 2]- and [4 + 2]-cycloaddition, which generates several C – C or C – heteroatom bonds in one step. The development of this strategy, which is a potent tool for increasing the molecular complexity and functional diversity of compounds, may open up fast access to synthetically valuable products, including analogues of natural compounds and pharmacologically oriented heterocyclic molecules.

Researchers of the Laboratory of Polysulfur Nitrogen Heterocycles proposed a new efficient strategy towards the synthesis of complex sulfur – nitrogen heterocycles from simple (often commercially available) reactants and sulfur monochloride (S_2Cl_2). The research culminated in the development of simple and efficient syntheses of 1,2,3-dithiazoles, 1,2,5- thiadiazoles, 1,2,3,4,5-pentathiepins and other sulfur – nitrogen heterocyclic systems, which are of interest for practical applications in pharmaceutical industry, in agrochemistry and in electronics as materials possessing both magnetic properties and electrical conductivity. Great prospects are opened by the recently discovered direct replacement of one chalcogen atom by another in various chalcogen – nitrogen heterocycles.

A large body of research, characterized by a great diversity of synthesized molecules and clear practical goals, was done at the Laboratory of Heterocyclic Compounds. A variety of five-membered heterocyclic compounds, first of all, thiophene derivatives, were used for preparing and studying photoactive compounds: molecular switches, transistor elements, 3D optical data storage devices, *etc*. Methods for the synthesis of spiropyrans and spirooxazines based on thiophene have been developed; the compounds include thermally reversible photochromes, merocyanine dyes, and a quite a number of thermally irreversible photochromes: dihetarylethenes, fulgides and fulgimides that respond only to light stimuli. In these unique molecules, heterocyclic moieties prone to form bonds on exposure to UV light are connected by various bridges. Derivatives of acylchromones, their structural analogues and terarylenes — labile organic compounds that are converted to stable fluorophores on exposure to UV light — were synthesized. These products were employed in the design of recording media for non-destructive fluorescence data readout for optical random access and archival memory devices; this made it possible to elaborate the scientific grounds for the fabrication and functioning of multilayer optical discs and to manufacture pilot samples. These works are at the cutting edge of research in this field and obviously have prospects for practical applications.

Vigorously developing research deals with new methods for the synthesis and studies of reactivity of saturated nitrogen-containing heterocycles, glycolurils and diaziridines, which are new classes of neurotropic compounds (Laboratory of Nitrogen-Containing Compounds). Glycolurils served as the basis for the synthesis of new pharmacologically oriented hybrid molecules, in particular, new bis-bicyclic bis[dioxolanoimidazo(thiadiazo)lidines] and tri- and tetracyclic molecules: products of the Mannich reaction of glycolurils with formaldehyde and primary amines. Enantiopure, practically valuable compounds were obtained among these products. Study of the chemistry of imidazotriazines, glycoluril analogues, gave rise to new synthetic routes to thioglycoluril derivatives, based on triazine ring contraction, and to imidazothiazolotriazines and pharmacologically active spiropyrrolidinoxindoles based on the amidine skeletal rearrangement of the thiazolotriazine moiety discovered by the authors. Some of the synthesized compounds were found to exhibit high sedative, antiproliferative and fungicidal activities.

New approaches to the formation of the diaziridine ring and synthesis of hybrid structures containing additional pharmacophoric moieties along with the diaziridine ring were developed at the Laboratory of Nitrogen-Containing Compounds. Particular emphasis was given to the development of efficient one- and two-step syntheses of polyheterocyclic molecules that were previously unknown or difficult to obtain. These methods made use of the diaziridine ring opening, which gives rise to 1,3-dipoles, prone to undergo dipolar cycloaddition. Apart from [3 + 2]-cycloaddition reactions with various dipolarophiles, bicyclic diaziridines were introduced for the first time into diastereoselective [3 + 3]-cycloaddition with the product of opening of another three-membered ring, that is, a donor – acceptor cyclopropane, with the formation of perhydropyridazine derivatives. These results attest to the extensive opportunities for using diaziridines as building blocks for the preparation of nitrogen-containing heterocycles and polyfunctional compounds of various types, first of all, pharmacologically oriented ones.

Thus, all research areas related to the chemistry of nitrogen-, oxygen- and sulfur-containing heterocycles pursued at the N.D.Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences are characterized by high efficiency and productivity. As regards the practical use of

the results, most success was achieved in the synthesis of photoactive compounds carried out at the Laboratory of Heterocyclic Compounds.

The authors are hoping that the proposed non-traditional ways of solving synthetic challenges, potential applications of new molecules and the analytical presentation of the material given in the review would make this review interesting and useful for a wide circle of readers specializing in the chemistry of heterocyclic compounds and in organic, medicinal and technical chemistry.

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