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Recent advances in synthesis of organic nitrogen–oxygen systems for medicine and materials science

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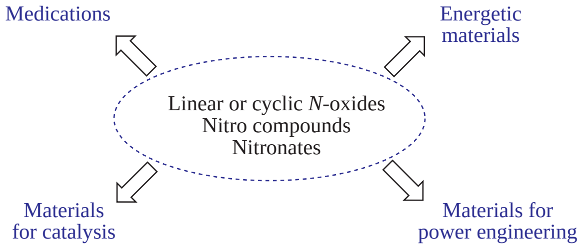
Current trends and characteristic examples of recent advances in syntheses of practically important compounds bearing semi-polar nitrogen–oxygen bonds (NO-systems) are considered. Their applications for the preparation of pharmaceutically relevant molecules, energetic materials and some other useful products are briefly discussed with a focus on original reports published in the period 2015–2017.



1. Introduction

A global trend in modern organic chemistry and materials science is directed toward the construction of molecular frameworks with various degrees of complexity in view of creating practical technologies while keeping their development sustainable.[1] Organic compounds bearing semi-polar $N^+–O^-$ bonds, which are commonly designated as nitrogen–oxygen systems (NO-systems), represent an important integral part of these frameworks. Many useful medications capable of releasing *in vivo* nitric oxide, a ubiquitous and crucial regulator for cellular metabolism,[2] fall to this category. Compounds containing several properly located N–O bonds along with a balanced elemental composition may instantly release under initiation conditions significant amount of accumulated chemical energy *via* highly exothermic intra- or intermolecular redox reactions. This unique property makes them potential components of energetic materials for industrial and military applications.[3] Moreover, nitro compounds, which belong to most important N–O systems, are extensively used in organic synthesis for the preparation of complex molecular scaffolds, in particular those presenting in natural compounds and active pharmaceutical ingredients.[4] Versatile reactivity and excellent transformability of the nitro group are effectively utilized in this type of chemistry.

Two years ago, we analyzed prospective approaches to linear and cyclic organic *N*-oxides (1,2,3,4-tetrazine 1,3-dioxides, 1-alkoxy-triazene 2-oxides and 1,2,5-oxadiazole 2-oxides), aliphatic nitro compounds and their synthetically useful derivatives (nitronates).[5] In this focus article (which is not a comprehensive review) we are giving an overview of current trends and recent achievements in synthesis of practically important nitrogen–oxygen systems and their application for the preparation of pharmaceutically relevant molecules, energetic materials and some other useful compounds. A significant part of considered papers have been published in the period 2015–2017.

2. Pharmacology-oriented nitrogen-oxygen systems

The molecular hybridization approach[6] has become a powerful tool in drug design, leading to the creation of novel drug candidates with improved pharmacological properties. In recent years, significant efforts have been directed toward the construction of hybrid pharmaceuticals containing prospective NO-releasing fragments, first of all 1,2,5-oxadiazole 2-oxide (furoxan) and methylenebis-(1-oxy-1-triazene 2-oxides) units decorated with suitable nitrogen heterocycles and/or functional groups.

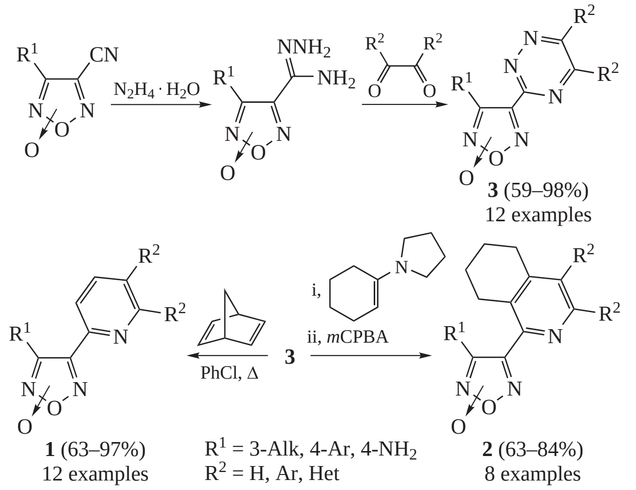
2.1. N-*Oxide-based pharmacology-oriented molecules*

Among the variety of nitrogen–oxygen organic motifs capable of releasing NO under physiological conditions, the furoxan (1,2,5-oxadiazole 2-oxide) scaffold has attracted considerable attention due to its high stability under ambient conditions and the absence of nitrate tolerance under continuous therapy.[7]

A convenient one-pot protocols were recently developed for highly effective synthesis of novel polyheterocyclic ensembles **1** and **2** in which furoxan and pyridine (dihydroisoquinoline, indenopyridine or terpyridine) rings are attached to each other *via* a C–C bond in good to excellent yields.[8] The methods are based on the tandem inverse-electron-demand hetero-Diels–Alder/retro-Diels–Alder reactions of the tailor-made (1,2,4-triazin-3-yl)-furoxans **3** with norbornadiene or 1-(pyrrolidino)cyclohexene accompanied by spontaneous elimination of N_2 from the 1,2,4-triazine ring (Scheme 1).

Hardly accessible (1*H*-1,2,3-triazolyl)furoxans **4** were readily obtained from corresponding nitro- or aminofuroxans. The developed approaches are based on the nucleophilic substitution/[3+2] cycloaddition tandem reactions[9] and Lewis acid-catalyzed Wolf-type cyclocondensation of aminofuroxans with diazo-β-dicarbonyl compounds[10] (Scheme 2).

A facile regio- and diastereoselective synthesis of isoxazolyl-, isoxazolinyl- and (1,2,4-oxadiazolyl)furoxans **5**–**7** from available



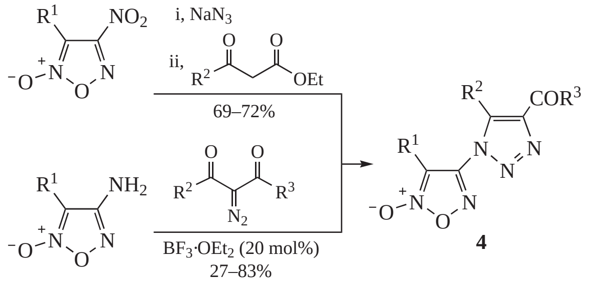
3 (59–98%)
12 examples

1 (63–97%)
12 examples

R^1 = 3-Alk, 4-Ar, 4-NH_2
R^2 = H, Ar, Het

2 (63–84%)
8 examples

Scheme 1 Synthesis of polyheterocyclic systems **1** and **2** bearing the furoxanylpyridine core.

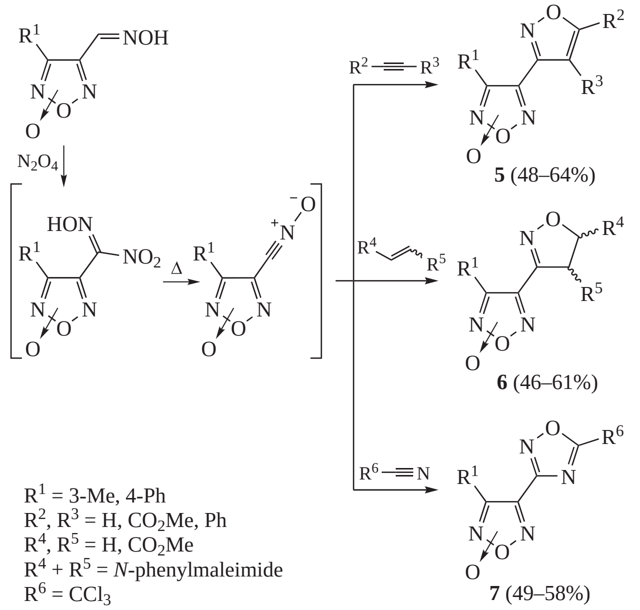


R^1 = Ph, Me, CO_2Me, Ac
R^2, R^3 = Me, OEt

Scheme 2 Synthesis of (1,2,3-triazolyl)furoxans **4**.

oximinofuroxans has been developed. The method is based on *in situ* generation of corresponding furoxancarbonitrile oxides *via* a cascade sequence of nitration and thermolysis reactions followed by their [3 + 2] cycloaddition to various dipolarophiles: alkynes, olefins, or activated nitriles (Scheme 3).[11]

With the same goal, novel of 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]-thiadiazines **8** bearing 6-furoxanyl and 6-furazanyl units have been designed using facile condensation of corresponding α-haloketones with thiocarbohydrazide followed by one-pot nitrosation and tautomerisation reactions (Scheme 4).[12]



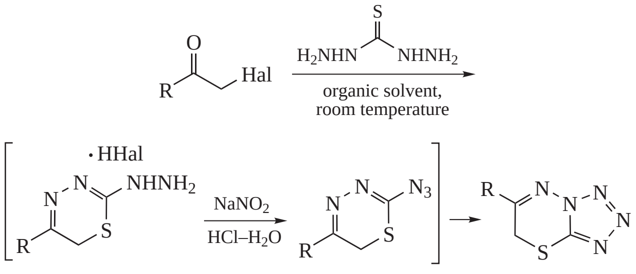
5 (48–64%)

6 (46–61%)

7 (49–58%)

R^1 = 3-Me, 4-Ph
R^2, R^3 = H, CO_2Me, Ph
R^4, R^5 = H, CO_2Me
R^4 + R^5 = *N*-phenylmaleimide
R^6 = CCl_3

Scheme 3 Synthesis of isoxazolyl-, isoxazolinyl- and (1,2,4-oxadiazolyl)-furoxans **5**–**7**.

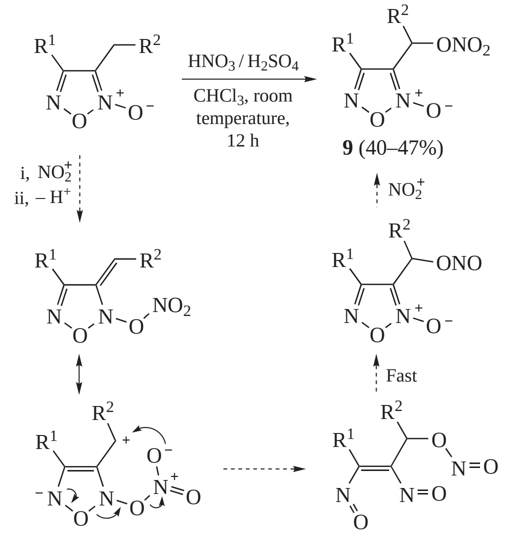


Hal = Br, Cl
R = Me, furoxanyl, furazanyl, nitrofuranyl, aryl

8 (61–88%)
10 examples

Scheme 4 Synthesis of 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **8**.

It might be expected that furoxan derivatives containing the nitroxy group, which is also capable of releasing nitrogen oxide (nitroglycerine is a well known example), would possess an enhanced NO-releasing ability. A convenient synthesis of 3-(2-nitroxyalkyl)furoxans **9** (though, in moderate yields) by the nitration of corresponding 3-alkylfuroxans with mixed acids was recently developed (Scheme 5).[13] The structure of products was proved by 2D HMBC NMR. The proposed reaction scheme includes addition of the nitronium cation to the external oxygen of the furoxan ring, followed by a Grob-type fragmentation, fast ring closure and oxidation (ONO to ONO_2) reactions.



9 (40–47%)

R^1 = Me, EtO, Et, Pr, Bu, Bu^i, *n*-C_5H_{11}
R^2 = H, Me, Et, Pr, Pr^i, Bu

Scheme 5 Synthesis of 3-(2-nitroxyalkyl)furoxans **9**.

Cytotoxic activity of novel and reported hetarylfuroxans (36 compounds) against five human cancer cell lines: A549 (lung adenocarcinoma), HCT116 (colon cancer), HeLa (servical cancer), MCF7 (breast carcinoma), RD (rhabdomyosarcoma) was evaluated. 4-(2-Methylpyridin-5-yloxy)-3-phenylfuroxan, bis-(1,2,4-oxadiazolyl)furoxan, 4-amino-3-(indenotriazin-3-yl)furoxan and nitrobifuroxans exhibited promising cytotoxicity towards all studied cell lines and could be considered as perspective structural scaffolds for further optimization. Furthermore, phenylnitro- and phenylcyanofuroxans proved to be effective inhibitors of platelets agglutination induced by adenosine diphosphate and adrenaline (Figure 1).[14] The NO-releasing capacity of the furoxan-based compounds was measured by quantitative spectrophotometric determination of nitrite anions generated *via* the Griess

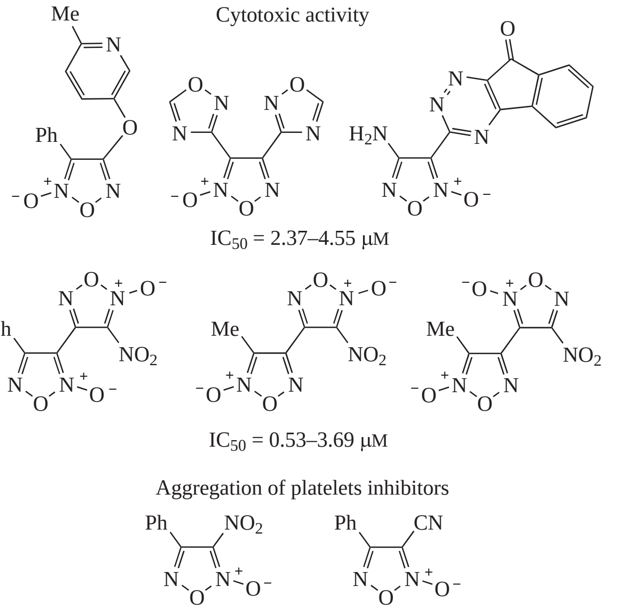
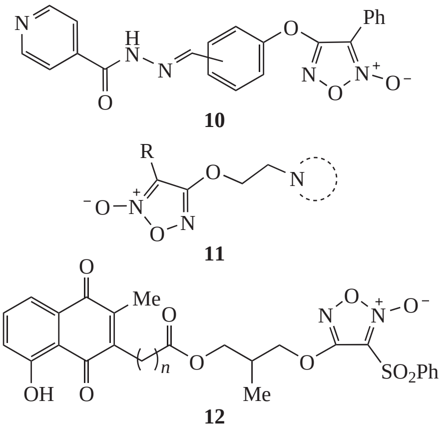


Figure 1 Hetarylfuroxans exhibiting promising cytotoxic and agglutination activities.

reaction. Interestingly, the obtained data strongly correlated with cytotoxic activity of studied compounds.[9]

Hybrid furoxan derivatives **10–12**, in which less rigid structural fragments were attached to the furoxan ring *via* the oxygen atom, also exhibited useful biological activities (Figure 2). Compound **10** appeared highly active *in vitro* against *Mycobacterium tuberculosis* H37Rv.[15] Furoxan derivatives **11** proved to be useful for efficient treatment of ocular hypertension (IOP-lowering activity).[16] Furoxan-naphthoquinone hybrid **12** displayed promising activity against breast cancer (MDA-MB-231) and hepatocellular (HepG2) or lung (A549) carcinoma cells.[17]



10

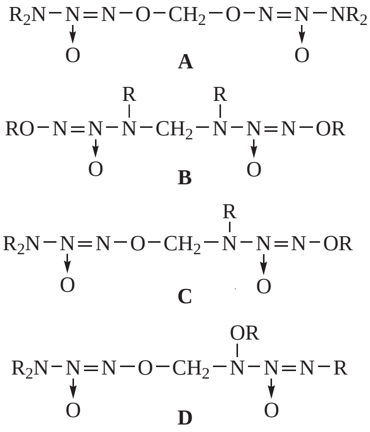
11

12

Figure 2 Novel pharmacology-relevant furoxan-based hybrids.

Available information on chemoselective syntheses,[18] pharmacological activity and NO-donor properties[19] of furoxan-based hybrids was summarized in very recent reviews. On the whole, the hybridization of the NO-donor furoxan scaffold with structural fragments present in currently used medications is considered as a promising approach to novel multifunctional drugs which may overcome the multidrug resistance problem. Furoxan-based hybrids often reveal useful biological activities superior to or different from those of the parent medications and furoxan precursors. The search for novel furoxan-derived hybrid structures with a view to their clinical potential opens up opportunities for the creation of more powerful multifunctional furoxan-based medications.

Another prospective class of NO-donor compounds is 1-hydroxytriazene 2-oxide derivatives. Among them, methylenebis(1-oxy-1-triazene 2-oxides) (MBOTO) **A** and their isomeric analogues **B–D** attract considerable attention (Figure 3). Compounds of this type are capable of releasing NO *in vivo* thus being promising for treatment of several types of disorders.[20] Over the past two years, researches in this area were mainly focused on selective synthesis and various transformations of *N*-β-hydroxyethyl- and *N*-β-haloethyl-substituted MBOTO. The functionalized MBOTO derivatives are of interest themselves as reliable NO-donors. Furthermore, they are considered as convenient building blocks for rational design of other NO-releasing hybrid molecules.



$$R_2N-\underset{\substack{\downarrow\\ O}}{N}=N-O-CH_2-O-N=\underset{\substack{\downarrow\\ O}}{N}-NR_2 \quad \textbf{A}$$

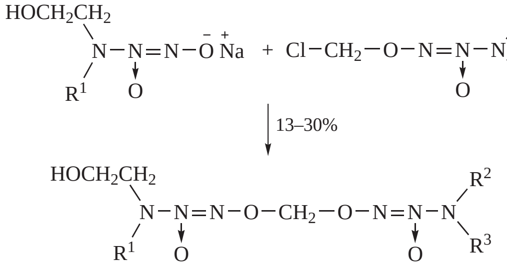
$$RO-N=\underset{\substack{\downarrow\\ O}}{N}-\overset{\substack{R\\ |}}{N}-CH_2-\overset{\substack{R\\ |}}{N}-\underset{\substack{\downarrow\\ O}}{N}=N-OR \quad \textbf{B}$$

$$R_2N-\underset{\substack{\downarrow\\ O}}{N}=N-O-CH_2-\overset{\substack{R\\ |}}{N}-\underset{\substack{\downarrow\\ O}}{N}=N-OR \quad \textbf{C}$$

$$R_2N-\underset{\substack{\downarrow\\ O}}{N}=N-O-CH_2-\overset{\substack{OR\\ |}}{N}-\underset{\substack{\downarrow\\ O}}{N}=N-R \quad \textbf{D}$$

Figure 3 The MBOTO of types **A**–**D**.

Oxytriazene *N*-oxides **13** (type **A**) bearing one *N*-β-hydroxyethyl substituent could generally be accessed in 10–30% yield by the reaction of 3-alkyl-3-hydroxyethyl-1-hydroxy-1-triazene 2-oxide salts with different chloromethoxy substituted 3,3-dialkyl-1-hydroxy-1-triazene 2-oxides (Scheme 6).[21] Structurally related unsymmetrical bifunctional compounds **14** and **15** bearing one *N*-β-hydroxyethyl fragment were obtained with reagents containing 3-β-chloro-, 3-β-bromo-, and acetoxyethyl groups.

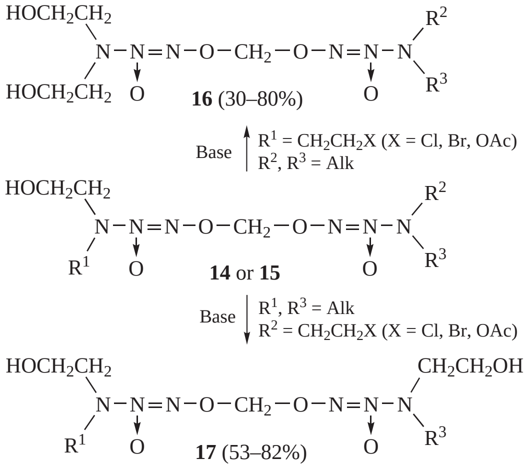


13 R^1, R^2, R^3 = Alk
14 R^1, R^3 = Alk, $R^2 = CH_2CH_2X$ (X = Cl, Br, OAc)
15 $R^1 = CH_2CH_2X$ (X = Cl, Br, OAc), R^2, R^3 = Alk

Scheme 6 Synthesis of oxytriazene *N*-oxides **13**–**15**.

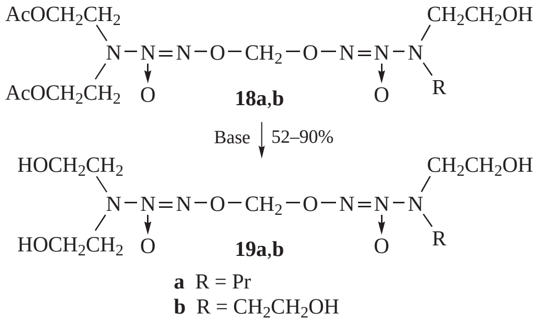
Compounds **16** and **17** containing two *N*-β-hydroxyethyl moieties could be generated in aforementioned way with only miserable yield (2–4%). A more rational approach to their synthesis is based on treatment of the corresponding *N*-chloro-, *N*-bromo- and acetoxyethyl-*N*(*N*′)-hydroxyethyl derivatives **14** or **15** with a base (Scheme 7).[22]

The tris- and tetrakis-*N*-β-hydroxyethyl MBOTO analogues are also available by the developed procedure. Thus, treatment of 3,3-bis(2-acetoxyethyl)-3′-(2-hydroxyethyl)-3′-propylmethylenebis(1-oxy-1-triazene 2-oxide) **18a** with sodium hydroxide gave 3,3,3′-tris(2-hydroxyethyl)-3′-propylmethylenebis(1-oxy-1-triazene 2-oxide) **19a** in 90% yield.[23] Similarly, *N*-tetrakis(β-hydroxy-



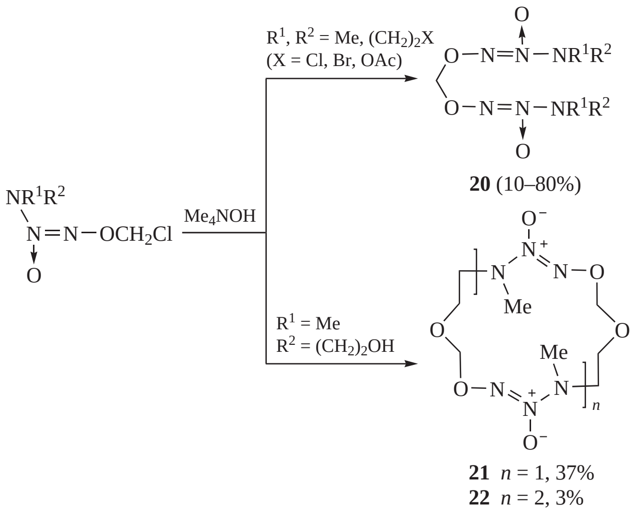
Scheme 7 Synthesis of oxytriazene *N*-oxides **16** and **17**.

ethyl)methylenebis(1-oxy-1-triazene 2-oxide) **19b** was obtained in 52% yield from *N*,*N*′-tetraacetoxyethyl precursor **18b** and sodium hydrocarbonate (Scheme 8).[24]



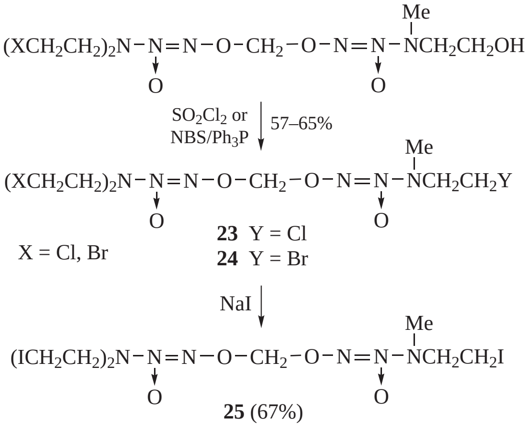
Scheme 8 Synthesis of tris- and tetrakis-*N*-β-hydroxyethyl MBOTOs **19a**,**b**.

1-(Chloromethoxy)triazene *N*-oxides, which do not contain hydroxyethyl group, reacted with Me_4NOH affording symmetrical linear MBOTO **20** in up to 80% yield (Scheme 9). This reaction tolerated 3,3-dialkyl-substituted oxytriazene *N*-oxides and some of their functionalized derivatives bearing Cl and Br atoms and acetoxy group in the β-position of the ethyl groups.[25] Unexpectedly, similar reaction of the 3-hydroxyethyl analogue proceeded in another direction to afford so far unknown cyclic ethers of alkyleneoxytriazene oxides **21** and **22** in 37 and 3% yield, respectively. Crystal structure of the major product, dimeric compound **21**, was confirmed by X-ray diffraction analysis.



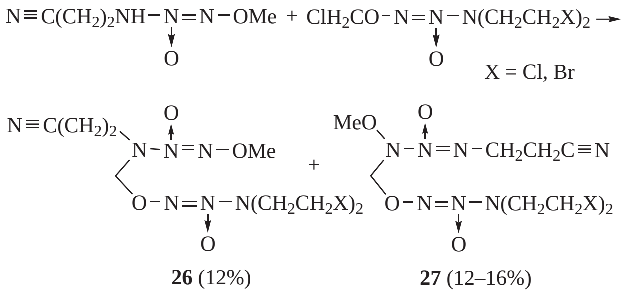
Scheme 9 Synthesis of symmetrical linear and cyclic MBOTO **20**–**22**.

Along with *N*-β-hydroxyethyl substituted MBOTOs, corresponding *N*-β-haloethyl (chloro-, bromo- and iodoethyl) MBOTO derivatives containing up to three chemically active halogen atoms in different combinations were a subject of extensive studies over the past two years. A general synthetic approach towards *N*,*N*- and *N*,*N*′-bis-β-haloethyl MBOTOs was developed which is based on replacement of the hydroxyl groups in β-hydroxyethyl, bis-β-haloethyl and β-hydroxyethyl-β(β′)-haloethyl derivatives with chlorine or bromine atoms and on haloid exchange reactions.[26] For example, *N*,*N*-bis-β-chloro(bromo)ethyl MBOTOs bearing β-hydroxyethyl groups at the N′ atom were converted to the corresponding tris-halo derivatives **23** or **24** under the action of thionyl chloride or NBS/Ph_3P. Subsequent reactions of **23** and **24** with NaI afforded *N*,*N*,*N*′-tris-iodoethyl substituted MBOTO **25** (Scheme 10).[27]



Scheme 10 Synthesis of *N*-β-haloethyl derivatives of MBOTO.

Deprotonated monosubstituted 1-alkoxy-1-triazene 2-oxides reacted with chloromethoxy substituted oxytriazene *N*-oxides giving complex mixtures of isomeric alkylation products **A**–**D** (see Figure 3) in poor yields. Nevertheless, this approach provided an access to β-cyanoethyl substituted compounds **26** and **27** which may be used as substrates for further functionalization of 1-alkoxy-1-triazene 2-oxide backbone. The molecular diversity is needed for *in vitro* evaluation of the MBOTO structure–NO-donor activity relationship (Scheme 11).[28]



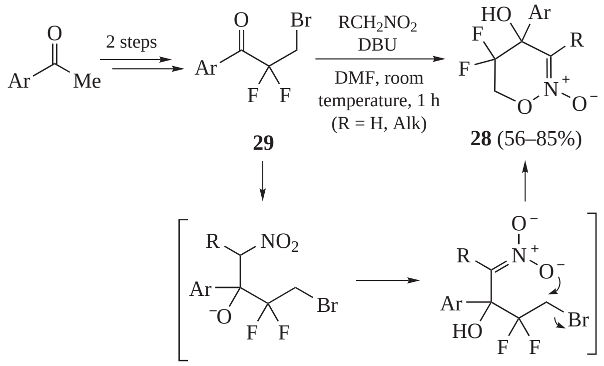
Scheme 11 Synthesis of β-cyanoethyl substituted compounds **26** and **27**.

2.2. Nitro compound derived pharmacology-oriented molecules

Nitroalkanes, nitroolefins and, in some cases, nitroarenes are considered as convenient and readily available intermediates in organic synthesis, including total synthesis of natural products and active pharmaceutical ingredients.[29] A strong activating effect of the nitro group in carbon–carbon and carbon–heteroatom bond forming reactions (Henry, aza-Henry, Michael, cycloaddition, *etc*.) along with its amazing transformability to a number of other functional groups make nitro compounds reagents of choice for organic chemists. In particular, reduction of nitro compounds (especially, enantiomerically and/or diastereomerically enriched ones) provides an expedient access to various bioactive amine scaffolds, which are presently in high demand by pharmaceutical industry and R&D.[30]

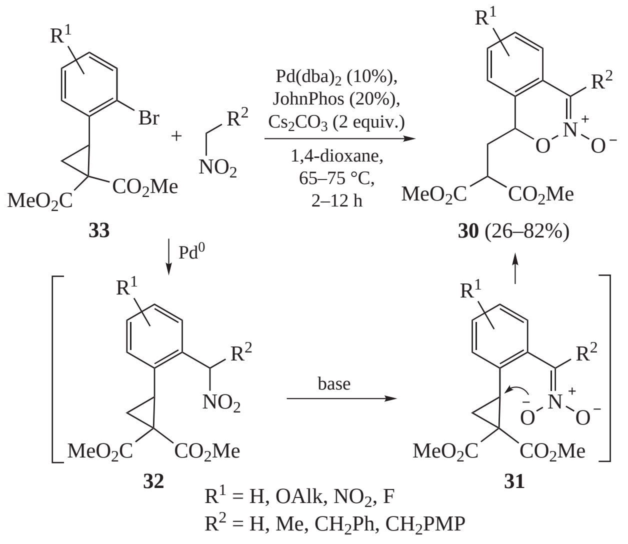
Nitronates are among most synthetically useful derivatives of aliphatic nitro compounds.[31] Over the past decade, numerous approaches to five-membered cyclic *O*-alkyl nitronates based on modern [3 + 2][32] and [4 + 1]-annulation[33] processes have been developed. In contrast, the synthesis of 6-membered cyclic nitronates (1,2-oxazine-*N*-oxides), which are traditionally prepared by an inverse-electron demand [4 + 2] cycloaddition, have received much less attention.[34] Currently, elaboration of novel synthetic routes to 6-membered cyclic nitronates is a challenging area.

An efficient synthesis of previously unknown fluorine substituted nitronates **28** by condensation of nitroalkanes with bielectrophilic 2-bromo-1,1-difluoroethylketones **29** has been recently developed[35] (Scheme 12). The condensation process is promoted by DBU and affords various nitronates **28** in high yields, including highly reactive C-3 unsubstituted derivatives (R = H). The mechanism is likely to involve the initial attack of the nitronate anion on the carbonyl group followed by an intramolecular substitution of bromine atom. Starting 2-bromo-1,1-difluoroethylketones **29** are easily attainable from substituted acetophenones.



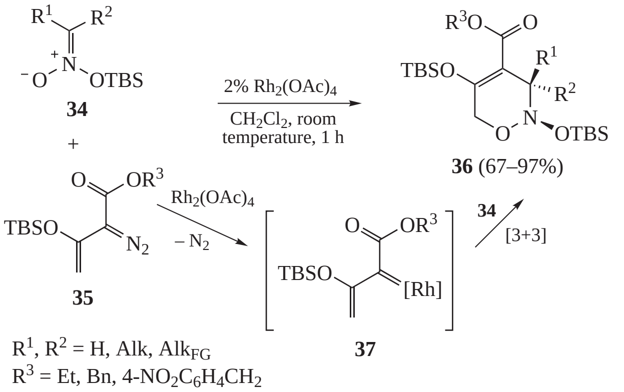
Scheme 12 Synthesis of fluorinated nitronates **28**.

Another [3 + 3]-type approach to hitherto unknown [4,5]-benzoannulated 1,2-oxazine-*N*-oxides **30** involves the intramolecular ring opening of donor–acceptor cyclopropane with a nitronate anion in intermediate **31** as a key process.[36] The required cyclopropane substituted nitro compounds **32** were generated *in situ* by the palladium / JohnPhos-catalyzed C,C-coupling of nitroalkanes with *o*-bromoaryl substituted cyclopropanes **33** (Scheme 13).



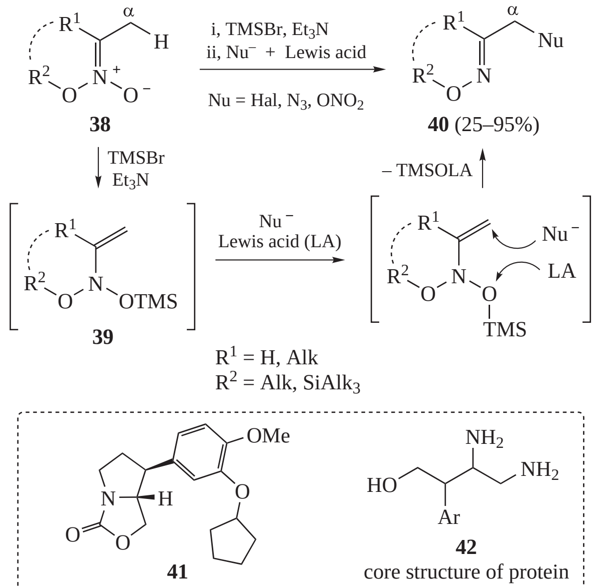
Scheme 13 Pd-catalyzed [3 + 3] assembly of [4,5]-benzoannulated nitronates **30**.

In some cases, nitronates may act themselves as convenient counterparts in [3 + 3]-annulations with donor–acceptor cyclopropanes.[37] Very recently, a rhodium-catalyzed [3+3]-annulation of nitronates **34** with silylated enol diazoacetates **35** leading to 3,6-dihydro-2*H*-1,2-oxazines **36** was developed[38] (Scheme 14). The process is likely to involve a rhodium-carbene intermediate **37** (generated from diazo compound **35** and rhodium acetate), which enters a stepwise [3 + 3]-annulation process with nitronate **34** to give adduct **36** with the recovery of metal catalyst. Importantly, moderate asymmetric induction could be achieved by the use of a rhodium catalyst bearing chiral ligands derived from alanine.



Scheme 14 [3 + 3]-Annulation of nitronates **34** with silylated enol diazoacetates **35**.

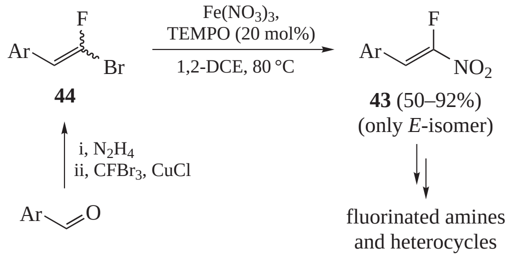
High oxidative potential of *N*-oxide unit in nitronates was exploited to achieve C–H functionalization of the α-position. For this goal, nitronates **38** were transformed to *N*-silyloxyenamines **39**, in which former α-carbon atom is activated towards addition reactions. The resulting compound **39** reacted with nucleophiles in the presence of Lewis acids (cobalt, zinc, chromium salts) to give α-functionalized oximes **40**. The overall result of the process was oxidation of the α-C–H bond and reduction of the *N*-oxide in initial nitronate **38** (Scheme 15). This strategy allows one to accomplish a facile synthesis of halide,[39] nitroxy[40] and azido derivatives[41] of nitronates **38**. Synthetic utility of α-functionalized oximes **40** was demonstrated by the stereoselective synthesis of



Scheme 15 Convenient strategy for α-C–H functionalization of nitronates **38**.

a potent PDE 4B inhibitor **41** and a core structure of known protein kinase B$_\alpha$ inhibitors **42**.

Conjugated nitroolefins are another synthetically important class of nitro compounds. Due to the ease of preparation (usually by condensation of nitroalkanes with aldehydes) and versatile reactivity, α-nitroolefins have become highly valuable intermediates in the target-oriented synthesis of useful nitrogen-containing products.[42] However, fluorinated nitroalkenes, which are in demand by modern medicinal chemistry as precursors to bioactive fluorinated amines and heterocycles, remain hard-to-prepare compounds. An efficient synthesis of α-fluorinated nitrostyrenes **43** has been recently reported which is based on the radical nitration–debromination of β-fluoro-β-bromostyrenes **44** (Scheme 16) readily available from aromatic aldehydes and $CFBr_3$.[43] In the developed procedure, mild oxidative nitration of C–Br bond was achieved by the action of iron(III) nitrate in the presence of TEMPO. This scheme represents the most straightforward approach to α-fluorinated nitrostyrenes of type **43** developed to date.

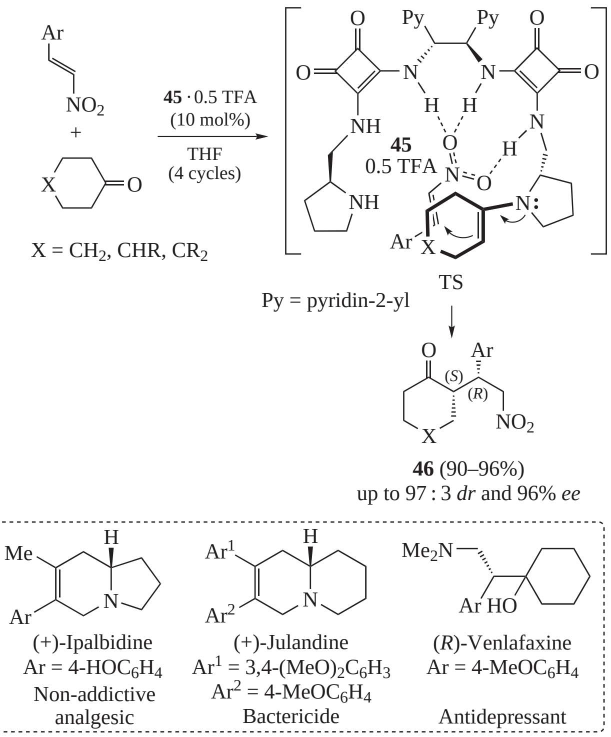


Scheme 16 Synthesis of β-fluoro-β-nitrostyrenes *via* radical nitration–debromination reactions.

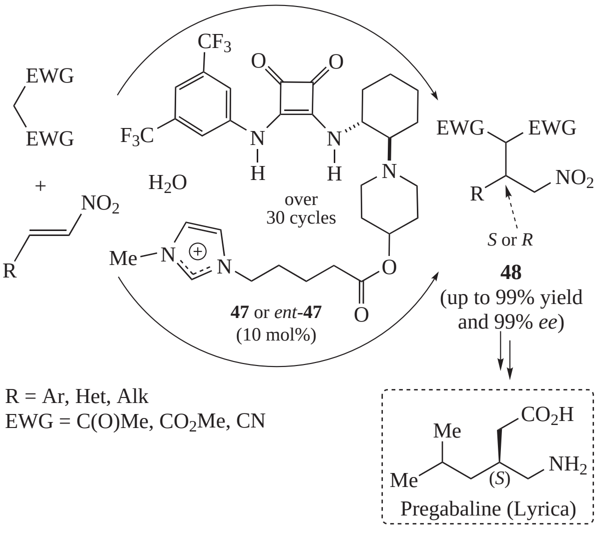
α-Nitroolefins are highly suitable substrates for stereo- and enantioselective Michael reactions with carbo- and heteronucleophiles promoted by metal-free organocatalysts which serve both as activators and sources of chirality.[44] Over the past decade, asymmetric organocatalysis has become a powerful strategy for enantioselective synthesis of natural and man-maid bioactive compounds.[45] Commonly, careful selection between known catalysts or elaboration of novel original catalyst are needed for attaining maximal productivity and stereoinduction in organocatalytic reactions.[46] A few recent applications of this state-of-art catalytic methodology to pharmacology-oriented transformations of α-nitroolefins are summarized below.

Original C_2-symmetrical pyrrolidine-based squaramide **45** bearing chiral 1,2-bis(pyridin-2-yl)ethane spacer group appeared highly efficient catalyst of asymmetric Michael reactions of 6-membered cyclic ketones with various β-nitrostyrenes to afford corresponding adducts **46** in high yield with excellent diastereo- (up to 97 : 3) and enantioselectivity (up to 96% *ee*) (Scheme 17).[47] The high level of stereocontrol was secured here by multi-centered hydrogen bonds between squaramide units in catalyst **45** and the nitro group of a β-nitrostyrene substrate in the transition state of the catalytic reaction. Valuable precursors to alkaloids (+)-ipalbidine and (+)-julandine, which exhibit potent analgesic and antimicrobial activities, and to a next-generation antidepressant drug (–)-venlafaxine (marketed by Pfizer as a racemate with the trade-name of EffexorXR®) have been prepared by the developed procedure. The reactions are readily scalable and recyclable.

Very recently, novel ionic liquid supported bifunctional tertiary amines **47** and *ent*-**47** containing squaramide structural units have been designed for sustainable non-covalent catalysis of asymmetric Michael reactions between β-dicarbonyl compounds and α-nitroolefins under ‘on water’ conditions. Corresponding adducts **48** were generated in these reactions in nearly quantitative yield with enantioselectivity up to 99% *ee* (Scheme 18).[48] Unexpectedly efficient stereoinduction in this case may be attributed to the amphiphilic contact ion pair (composed of the PF_6^- anion and the imidazolium cation) tagged to catalyst **47** that protects the latter from unfavorable influence of water *via* Coulombic and hydrophobic (created by the alkyl spacer group) interactions. The amphiphilic catalyst could be readily separated from products and over 30 times reused in the process. The prepared compounds **48** are close precursors to pharmacologically important non-natural β-amino acids and the most active (*S*)-enantiomer of anticonvulsant pregabalin (trademark Lyrica™).

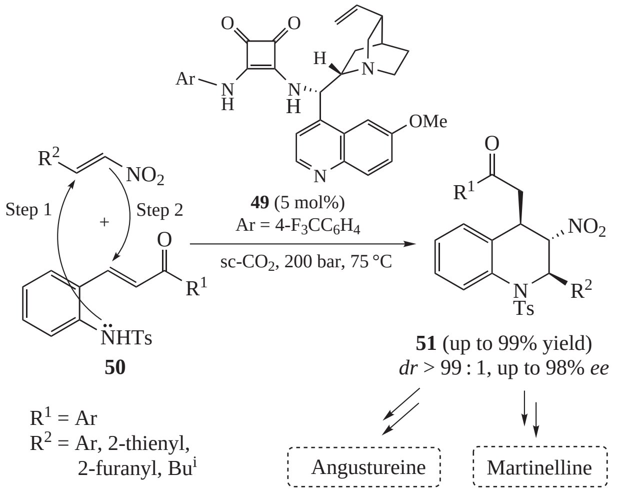


Scheme 17 Catalytic asymmetric addition of cyclic ketones to β-nitrostyrenes.



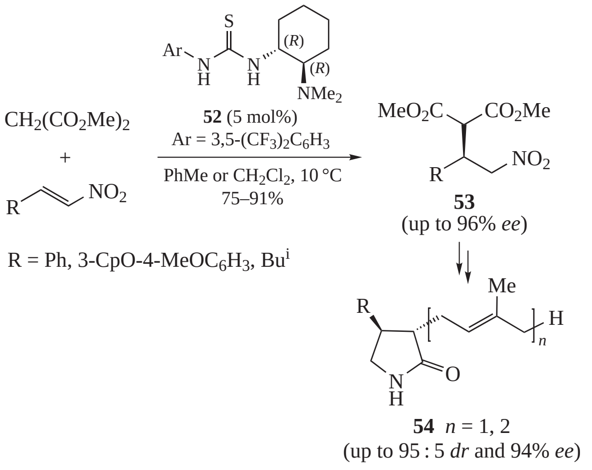
Scheme 18 Asymmetric ‘on-water’ reactions of β-dicarbonyls with α-nitroolefins catalyzed by compound **47**.

The tertiary amine, squaramide bifunctional chiral organocatalysts allow a facile synthesis of enantiomerically enriched complex molecules to be performed *via* pot and atom economy domino reactions.[49] These reactions become especially attractive for pharmaceutical industry when inflammable, non-toxic and easy-to-evaporate dense gases in liquid or supercritical (sc) state are used as the reaction media.[50] Recently, the first asymmetric organocatalytic domino reaction in an sc-CO_2 was reported. In the presence of bifunctional quinine-derived squaramide **49**, *o*-(*N*-tosylamino)- phenyl α,β-enones **50** reacted with α-nitroolefins affording intermediate Michael adducts (step 1) which underwent spontaneous diastereoselective intramolecular cyclization (step 2) to tetrahydroquinolines **51** in excellent overall yield with very high diastereo- and enantioselectivity in the sc-CO_2 medium (Scheme 19).[51] The tetrahydroquinoline fragment is present in many bioactive compounds, particularly, in angustureine exhibiting anti-mycobacterial and anti-malarial activities and martinelline which is a potent antagonist of bradykinin receptors and is used as an eye medicine for conjunctivitis.



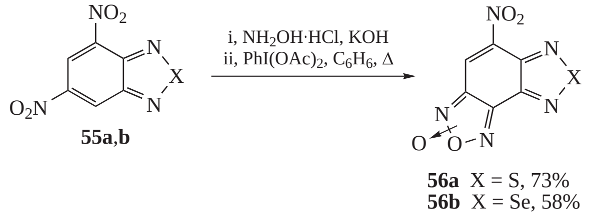
Scheme 19 Organocatalytic domino synthesis of tetrahydroquinolines **51** in sc-CO_2.

Chiral tertiaty amine-derived thiourea **52** efficiently catalyzes asymmetric Michael reactions between malonates and nitroolefines to furnish corresponding γ-nitro esters **53** with enantioselectivity up to 91% *ee* (Scheme 20). Products **53** were diastereoselectively converted to pharmacology-relevant prenyl- or geranyl-substituted pyrrolidin-2-ones **54** in several conventional synthetic steps.[52] A favorable combination of privileged pharmacophoric fragments (pyrrolidin-2-one unit, aryl and/or branched alkenyl groups) and proper configuration of key stereocenters allow one to consider them as prospective candidates to further biological studies.



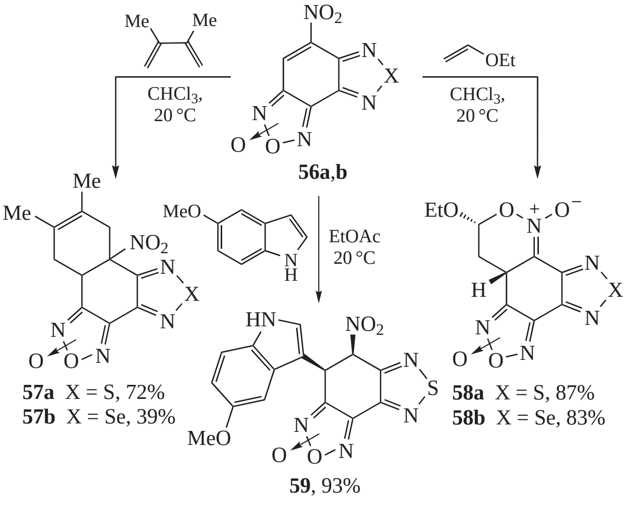
Scheme 20 Asymmetric synthesis of prenyl- and geranyl-substituted pyrrolidin-2-ones **54**.

In some cases, π-deficient polynitroarenes (hetarenes) formally containing the α-nitroolefin fragments may act as 1,3-dipoles or dipolarophiles in cycloaddition reactions which result in dearomatization of starting compounds.[53] The dearomatization strategies are currently considered as a prospective facile approach to pharmacologically relevant polycyclic compounds and complex natural products.[54] To obtain suitable active substrates, dinitrobenzoazoles **55a**,**b** were converted to corresponding fused benzofuroxans **56a**,**b** *via* the amination / oxidative cyclization reactions (Scheme 21).[55] Products **56** exist as mixtures of two isomers with different location of the exocyclic oxygen atom.



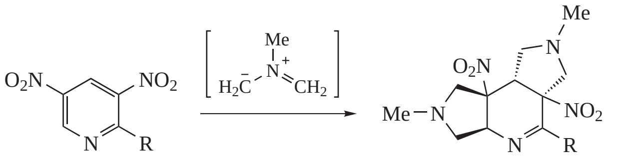
Scheme 21 Synthesis of fused benzofuroxans **56**.

Compounds **56a**,**b**, which incorporate electron-deficient nitrovinyl moiety, may act as either dienophiles or heterodienes in the Diels–Alder reactions. The reactions with 2,3-dimethyl-1,3-butadiene resulted in the formation of tetracycles **57a**,**b**, whereas corresponding reactions with ethyl vinyl ether gave fused dihydrooxazine-*N*-oxides **58a**,**b** in high yields.[56] Furthermore, the activated nitrovinyl group in compounds **56** readily behaved even as Michael acceptor. This unusual reaction pathway was illustrated by the synthesis of adduct **59** from **56a** and 5-methoxyindole (Scheme 22). The obtained compounds containing two or three useful pharmacophore fragments (NO-donor furoxan ring along with another azole and indole units) may be considered as prospective platforms for the design of pharmacology-oriented nitrogen–oxygen systems.



Scheme 22 Cycloaddition and Michael addition reactions of fused benzofuroxans **56**.

Another cycloaddition process, namely 1,3-dipolar cycloaddition, has been recently suggested for the construction of polynuclear nitrogen heterocycles. An efficient and convenient one-step synthesis of novel polycyclic system, 1,2,3,3a,5a,6,7,8,8a,8b-decahydropyrrolo[3,4-*b*:3′,4′-*d*]pyridine derivatives **61** was developed on the basis of 1,3-dipolar cycloaddition of unstabilized *N*-methyl azomethine ylide to 2-substituted 3,5-dinitropyridines **60** (Scheme 23).[57] According to X-ray diffraction data, the addition of the dipole to compounds **60** occurs stereoselectively from the opposite sides of the pyridine ring at two C=C bonds that are activated by the nitro groups. The obtained novel heterocyclic system contains 3-nitropyrrolidine fragments fused with



R= SPh, S-c-C_6H_{11}, OPh, S-Bu^i, SCH_2-furyl-2

Scheme 23 The 1,3-dipolar cycloaddition of azomethine ylide to 3,5-dinitropyridines **60**.

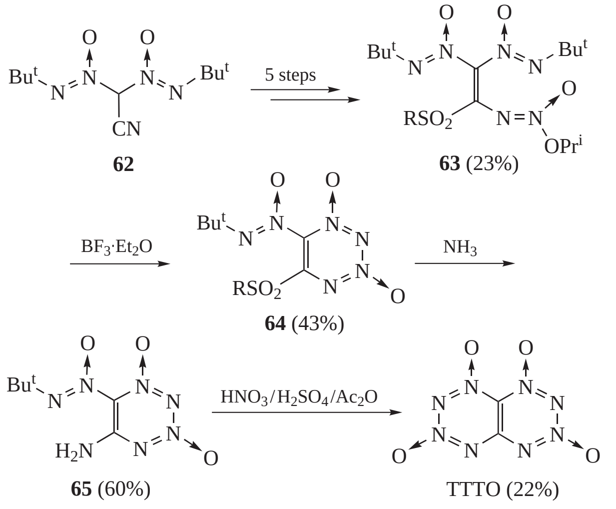
partially saturated pyridine ring and can be considered as potential nitric oxide donor.[58] Furthermore, hydrogenated pyrrolo[3,4-*c*]pyridine core is an important to pharmacology scaffold since compounds of this type possess antibacterial, anticancer and cognition activating properties.[59]

3. Energetic nitrogen–oxygen systems

Properly composed nitrogen–oxygen systems, which contain a significant store of accumulated chemical energy, may have other, different from pharmacology, practical applications, first of all, as ingredients of energetic materials. Promising recent results in this important area are mainly associated with the first synthesis of [1,2,3,4]tetrazino[5,6-*e*][1,2,3,4]tetrazine 1,3,6,8-tetraoxide (TTTO), facile preparation of novel stable nitramino- and nitrofuroxan derivatives with balanced elemental content, and the development of safe and efficient syntheses of energetic *N*- and *O*-nitro compounds in liquid 1,1,1,2-tetrafluoroethane medium.

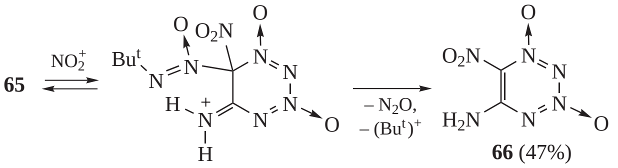
Cyclic high-nitrogen systems with *N*-oxide oxygen atoms are of significant interest as a new generation of high energy density materials (HEDM).[60] One of the most promising compounds of this type is TTTO.[61] This compound has gained much attention in the scientific community due to its high energetic characteristics. A number of theoretical studies on TTTO have been published.[62] By these data, the TTTO heat of formation is about 206 kcal mol^{-1}, density 1.98 g cm^{-3}, estimated detonation velocity 9.71 km s^{-1}, and detonation pressure 432 kbar, which puts it on a par with the most powerful explosives known.

Recently, the first synthesis of TTTO has been reported.[63] The synthetic strategy was based on the sequential closure of two 1,2,3,4-tetrazine-1,3-dioxide (TDO) rings by the generation of intermediate oxodiazonium ions and their intramolecular coupling with *tert*-butyl-*NNO*-azoxy groups (Scheme 24). The synthesis started with nitrile **62**, a pathway to which had been recently discovered.[64] It was converted in 5 steps to compound **63** and then by reaction with $Et_2O{\cdot}BF_3$ to TDO **64**. Treatment of the latter with NH_3 resulted in the $MeSO_2$ group substitution to afford TDO **65** which was converted to TTTO with the help of a $HNO_3/H_2SO_4/Ac_2O$ system of reagents. The structure of TTTO was confirmed by X-ray diffraction analysis of its molecular complex with benzene.



Scheme 24 Synthesis of TTTO.

An attempt to prepare TTTO by treatment of TDO **65** with nitronium tetrafluoroborate was also made taking into account that similar reaction with corresponding benzene derivatives produced benzotetrazine-1,3-dioxides in good yields.[65] However, in case of TDO **65**, novel energetic compound **66** was obtained in 47% yield instead of expected TTTO.[66] A plausible mechanism of this reaction involves electrophilic substitution resulting in the replacement of the *tert*-butyl-*NNO*-azoxy group by the nitro group (Scheme 25).



Scheme 25 Synthesis of TDO **66**.

Hypothetic TDOs **67**–**69** (Figure 4) annulated with tetraazapentalene systems belong to so far unknown class of heterocycles. They could possess enhanced stability along with excellent energetic properties. Theoretical studies carried out by Chinese researchers demonstrated that some of these compounds should have high explosion velocity and detonation pressure and once experimentally synthesized, would be an ideal explosives which combine high store of accumulated energy with low sensitivity to shock and friction.[67] Precursors of TDOs **67**–**69** could be corresponding 1- and 2-substituted [1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine-4,6-dioxides (TT) **70** and **71**.

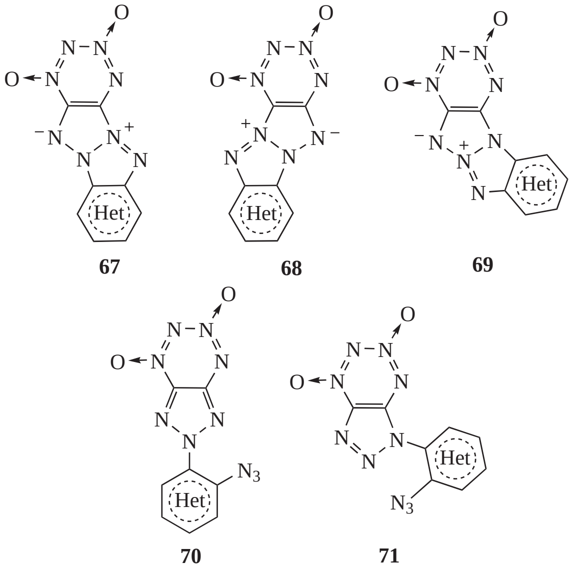
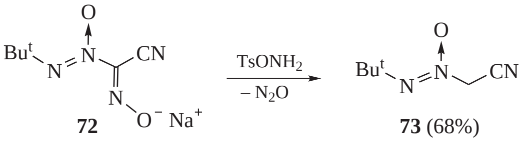


Figure 4 Hypothetic TDOs **67**–**69** annulated with tetraazapentalene systems and their precursors.

Heterocycles of type **70** or **71** are challenging compounds. In fact, a synthetic route to TTs, in which TDO cycles were annulated with the 1,2,3-triazole ring bearing 2-alkyl groups, was recently developed.[68] However, this route cannot be used for the synthesis of appropriate aryl- or heteroaryl substituted compounds. Very recently, a prospective approach to such compounds has been proposed, which is based on the use of (*tert*-butyl-*NNO*-azoxy)acetonitrile **73** bearing active methylene group. This new precursor was readily obtained by treating Na-salt **72** with $TsONH_2$ (Scheme 26).[69] It is the first case of single-stage reduction of an oxime group to a methylene unit. Nitrile **73** has been applied as active substrate for the synthesis of model compounds with phenyl substituents[70] and will become a key starting material for further synthesis of TT **70** and **71**.



Scheme 26 Synthesis of (*tert*-butyl-*NNO*-azoxy)acetonitrile **73**.

Furoxan derivatives have remained very attractive building blocks for the synthesis of hybrid energetic materials over the past two years. A favorable combination of high total O + N content (69.7%), relatively high density and positive heat of formation of furoxan unit make it particularly promising as an integral component in the construction of new high-energy-dense materials. In particular, high-energetic salts of nitraminofuroxans **74a–c** and bis(dinitromethyl)furoxan **75** were recently synthesized by Shreeve's group[71] (Figure 5). Salts **74** were prepared by nitration of corresponding aminofuroxans followed by metathesis of cations. Synthesis of compounds **75** included replacement of chlorine atoms in bis(chlorodinitromethyl)furoxan with potassium cations under the action of KI. Furoxan salts **74** and **75** are characterized by promising density, a key parameter which exerts a significant impact on detonation performance of energetic compounds.

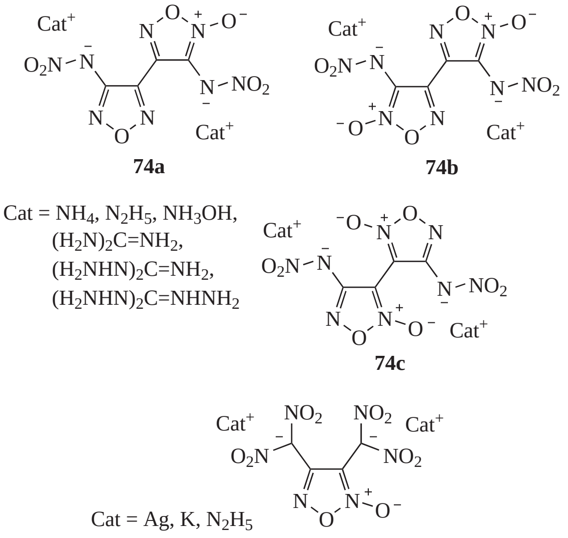
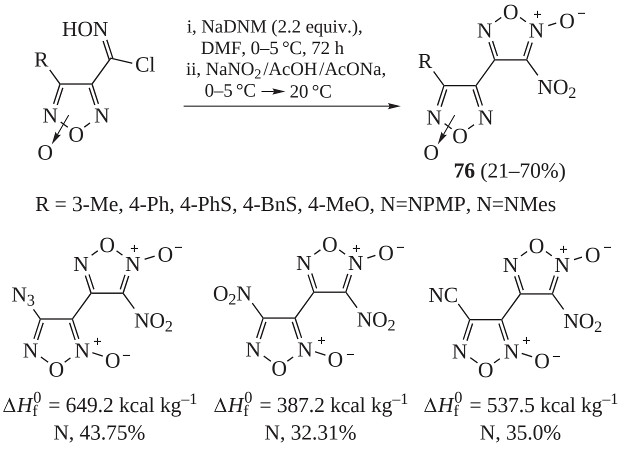


Figure 5 Energetic salts of nitraminofuroxans and bis(dinitromethyl)-furoxan.

Novel energetic nitro bifuroxans **76** were prepared from corresponding furoxanylhydroxamic acid chlorides.[72] The one-pot method included treatment of the latter with dinitromethane sodium salt and nitrosation of *in situ* generated acylation products with $NaNO_2/AcOH/AcONa$ followed by intramolecular cyclization of resulting nitroso compounds to afford compounds **76** (Scheme 27). Some of the obtained nitro bifuroxans are characterized by high enthalpies of formation and enhanced nitrogen content.

Among other recent achievements in this area are novel synthesis of energy-rich 3,4-bis(trinitroethylaminofurazanyl)-furoxan,[73] preparation of 3,4-bis(nitrofurazanyl)furoxan (DNTF)–trinitroazetidine (TNAZ) eutectic mixture for potential application in melt cast explosives[74] and important results of theoretical study on the mechanism of dinitrofuroxan formation *via* oxidation of dinitroglyoxime.[75]

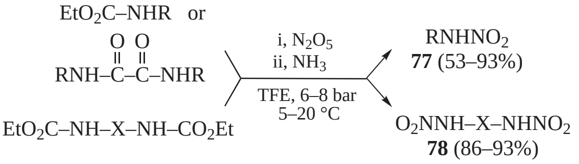


Scheme 27 Synthesis of energetic bifuroxanyl nitro derivatives **76**.

Key energetic components of explosives, powders, and solid propellants contain nitro groups.[3] In industry, corresponding nitration reactions are commonly carried out with a large excess of mixed acids (*e.g.* HNO_3/H_2SO_4), which act as both nitrating agent and media.[76] These processes are explosion-risky and harmful for the environment, as huge amount of acidic wastes are produced, which require expensive and energy-consuming disposal. A promising approach to address the environmental issues is based on the use of sulfuric acid-free dinitrogen pentoxide (DNP)/liquefied gases nitrating system.[77] The DNP is highly active and selective nitrating agent that produces readily utilizable nitric acid as by-product. On the other hand, some industrially available gases (carbon dioxide or freons) in either liquid or supercritical state provide advantages of safe and inert solvent with added capability of being readily separated from the reaction products by simple decompression.

Recently, a safe and efficient one-pot synthesis of primary *N*-nitramines **77** and **78** from available *N*-alkylcarbamates or *N,N'*-dialkyloxalamides by a sequence of nitration (DNP)/ammonolysis reactions in liquid 1,1,1,2-tetrafluoroethane (TFE) has been developed (Scheme 28).[78] The chemically stable and nontoxic for humans TFE can be readily liquefied due to remarkably low equilibrium vapor pressure (5.7 bar at 20 °C). Just 10% molar excess of N_2O_5 was enough to attend excellent overall yields of products **77** and **78**. The procedure is safer than known methods as there is no need here for isolation (purification) of sensitive to shock and friction intermediate *N*-alkylcarbamate or *N,N'*-dialkyloxalamide nitro derivatives. Furthermore, it is environment-friendly, because the only by-products are ammonium nitrate and ethyl carbamate or oxamide, which may have further chemical or agricultural application (*e.g.*, as fertilizers). The TFE can be readily re-compressed (as it is in freezing units) and recycled into the reaction that should significantly reduce production cost.

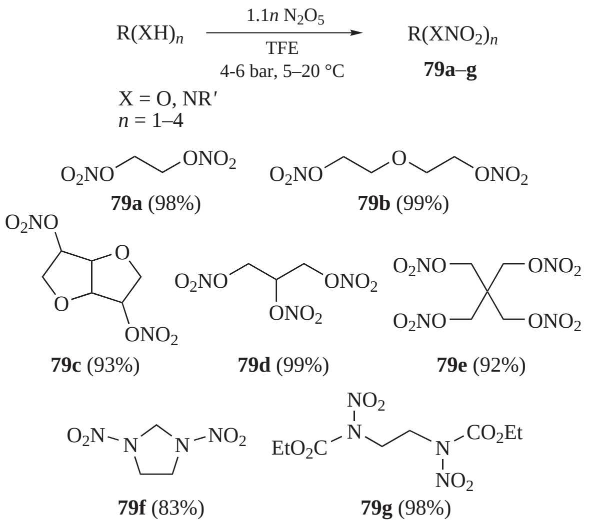
Liquid DNP/TFE nitrating system appeared suitable for efficient synthesis of various *O*- and *N*-nitro compounds (Scheme 29).



R = Alk
X = $(CH_2)_2$, $(CH_2)_3$, *trans*-cyclohexane-1,2-diyl

Scheme 28 One-pot synthesis of primary *N*-nitramines in liquid TFE.

The method significantly reduces fire and explosion risks (nitration in an extinguisher), which are associated with known nitration procedures, and affords target molecules **79** in high yield under mild reaction conditions.[79] From the practical viewpoint, the method provides an industrially applicable pathway to produce organic nitrate and nitramine-based high energy materials.

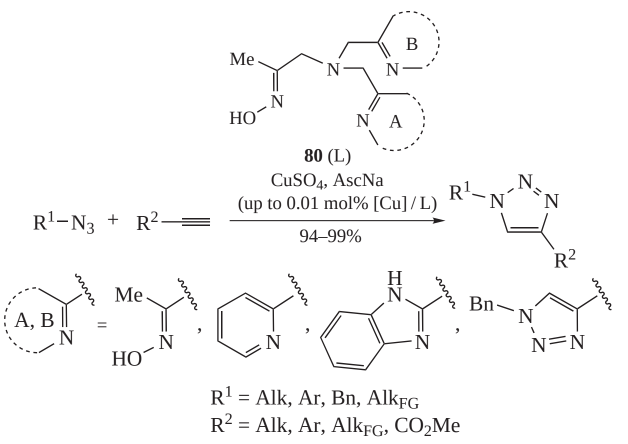


Scheme 29 The O- and N-nitration reactions in the PNP/TFE nitrating system.

4. Nitrogen-oxygen systems for other useful applications

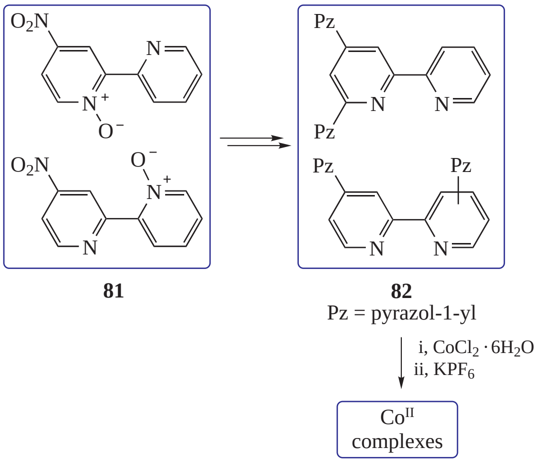
Being extensively explored in the fields of medicinal chemistry and energetic materials, N–O-systems may be also applied as precursors to useful materials for catalysis and power engineering.

A recent example is the use of functionalized oximes, derived from nitroalkanes, as ligands in copper-catalyzed azide–acetylene cycloaddition (‘click reaction’) (Scheme 30).[80] The most active catalysts proved to be tripodal structures **80** bearing one or two oxime arms in combination with donor heterocyclic fragments. Intriguingly, a synergistic effect was found in these hybrid systems that resulted in a significant enhancement of catalytic activity for ‘mixed’ oxime–heterocycle ligands **80**. Using these ligands, one can reduce catalyst loadings in ‘click reaction’ up to 0.01 mol% without a notable decrease in conversion of starting materials. Ligands **80** were prepared in a modular manner from available nitroalkanes.



Scheme 30 Oximes **80** as ligands for Cu-assisted azide–acetylene cycloaddition.

Nitrogen heterocycles incorporating the nitro and the *N*-oxide groups can be transformed to hybrid molecules with practically useful properties. Efficient synthesis of novel di- and tetra(pyrazolyl) bipyridine ligands **82** from available bipyridine *N*-oxide nitro derivatives **81** *via* conventional chlorination ($POCl_3$) and pyrazolation reactions has been recently developed (Scheme 31).[81] The ligands were readily converted to the corresponding homoleptic octahedral cobalt(II) complexes with PF_6^- anions, which are of interest as potential redox components for electrochemical applications, in particular, in dye-sensitized solar cells.



Scheme 31 *N*-Oxide-based synthesis of homoleptic octahedral cobalt(II) complexes.

5. Conclusions

Significant achievements have been attained over the past two years in synthesis of organic nitrogen–oxygen systems and their application as pharmaceuticals or their precursors, energetic compounds and intermediates for other useful materials. Original syntheses of prospective hybrid molecules containing NO-releasing 1,2,5-oxadiazole 2-oxide (furoxan) and methylenebis(1-oxy-1-triazene 2-oxides) fragments decorated with suitable nitrogen heterocycles and/or functional groups have been developed. Some of the prepared compounds exhibited useful biological activities (NO-donor, anti-cancer, anti-tuberculosis, *etc.*) *in vitro*. Novel stereo- and enantioselective reactions of nitroalkane derivatives (nitronates), nitroolefins and nitroarenes have been elaborated which allowed a facile synthesis of close precursors to natural product analogues, active pharmaceutical ingredients and other useful materials to be accomplished. Promising results have been attained in an important area related to energetic nitrogen–oxygen systems. These results include the first synthesis of unique high-energy compound [1,2,3,4]tetrazino[5,6-*e*][1,2,3,4]tetrazine 1,3,6,8-tetraoxide (TTTO), a simple preparation of novel nitramino- and nitrofuroxan derivatives with balanced elemental composition, and the development of facile green protocols for efficient syntheses of energetic *N*- and *O*-nitro (polynitro) compounds in liquid 1,1,1,2-tetrafluoroethane medium.

It is expected that biological testing of pharmacology-relevant *N*-oxide molecules will provide reliable identification of pro-drug NO-releasing molecules and leaders for efficient treatment of damaging diseases. The development of highly selective and applicable to pharmaceutical industry catalytic methodologies for multi-scale production of important medications, in particular those derived from the nitro compounds, may also be envisioned.

Future researches in the field of energetic nitrogen–oxygen systems are expected to be targeted to the synthesis of 1,2,3,4-tetrazine 1,3-dioxide derivatives annulated with high-enthalpy heterocyclic, in particular tetraazapentalene, systems which could exhibit, according to theoretical predictions, enhanced stability along with excellent energetic properties. Studies aimed at the elaboration of novel furoxan-derived explosives and propellant ingredients will also be a priority of energetic community. Application of green chemistry methods for industrial preparation and processing of basic energetic materials will certainly become an important area of research in coming years.

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