Review

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Synthesis and reactivity of heterocyclic hydroxylamine-*O*-sulfonates

Abstract: The heterocyclic hydroxylamine-*O*-sulfonates constitute a novel family of formal *O*-substituted hydroxyguanidines and hydroxyamidines that serve as functional precursors to a variety of fused heterocyclic ring systems incorporating N-N, N-O, N-S, or N-N^+ moiety. They are readily accessible from the reaction of 2-chloroazoles, 2-chloroazines, and 2-chlorodiazines with hydroxylamine-*O*-sulfonic acid. They have a rich chemistry exemplified by tandem reactions, such as nucleophilic addition-electrophilic amination, nucleophilic addition-electrophilic 5-*endo-trig* cyclization or fluorogenic Mannich-electrophilic amination reaction. The heterocyclic hydroxylamine-*O*-sulfonates have significant potential for use in synthesis of anticancer, antiviral, and antimicrobial agents. The newly discovered fluorogenic reaction and fluorescent dyes (Safirinium-P and Safirinium-Q) have found applications in fluorescent detection and labeling.

Keywords: electrophilic amination; fluorescent labeling; fluorogenic reaction; heterocyclic hydroxylamine-*O*-sulfonate; Mannich reaction; tandem reaction.

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Introduction

O-Substituted hydroxylamine derivatives have been extensively reviewed [1–3] and compounds with N-O linkage constitute a vital group of chemical reagents, which incorporate either the nucleophilic or electrophilic nitrogen atom. Thus, the *O*-substituted nitrogen atom may retain its natural nucleophilic amine reactivity ($^{\sigma-}$NH-O-R$^{\sigma+}$), and such compounds are used for the synthesis of *N*-hydroxyamides [4], *N*-hydroxypeptides [5], *N*-hydroxy β-lactams [6], hydroxamic acids [7], *N*-hydroxyimides [8], oximes [9], nitrones [10], isoxazoles [11], nitriles [12], amides [13], and can be applied to α-acyloxylation of aldehydes and ketones [14]. By contrast, when the hydroxylamine nitrogen atom is substituted with oxygen atom integrated into an electron-withdrawing group, the polarity inversion ('umpolung') of the molecule induces the electrophilic character of the nitrogen atom ($^{\sigma+}$NH-O-EWG$^{\sigma-}$).

The chemical process in which a nucleophile (Nu^-) attacks an electrophilic nitrogen atom of $^{\sigma+}$NH-O-EWG$^{\sigma-}$ and leads to the Nu-NH_2 product with simultaneous liberation of the O-EWG^- leaving group is usually named electrophilic amination [15–17]. The examples of reagents that comprise the electrophilic nitrogen atom and a good leaving group include: hydroxylamine-*O*-sulfonic acid (HOSA) [18], *O*-alkyl- [19], *O*-aryl- [20], *O*-acyl- [21], *O*-phosphinyl- [22], *O*-silyl- [23], *O*-sulfonyl-hydroxylamines [24], their oximes, and oxaziridines [25] (compounds **A**, **B**, and **C** in Figure 1).

Although the chemical literature pertaining to the electrophilic amination reactions is fairly extensive, the examples of intramolecular transformations that give access to heterocyclic compounds are rather rare. Worth mentioning are the Narasaka-Heck cyclizations (formerly aza-Heck reactions) that furnish heterocyclic C-N bonds [26–28], base-mediated 1,3-elimination of sulfuric acid from *N*-hydroxyguanidine-*O*-sulfonic acids leading to (alkylimino)diaziridines [29] and synthesis of pyrrolidines via intramolecular substitution on nitrogen atom [30].

Hydroxylamine-*O*-sulfonic acid (HOSA) behaves as either a nucleophile (δ^-NH_2 synthon) or electrophile (δ^+NH_2 synthon) depending on substrates used and reaction conditions. These attributes make HOSA a versatile chemical reagent, especially in the area of organic functional group transformations and heterocyclic chemistry. Among these applications of special interest is the conversion of carbonyl compounds into oxime sulfonates, which can be

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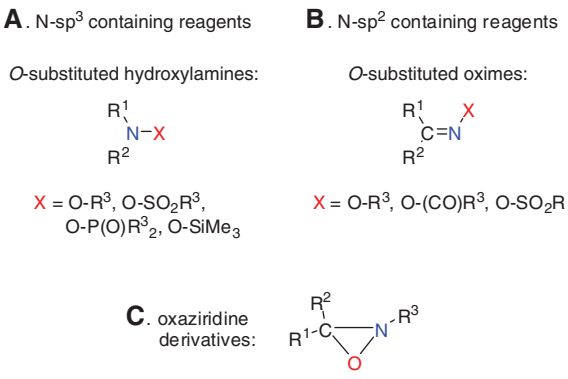


Figure 1 Hydroxylamine derivatives used for electrophilic amination reactions.

further transformed to oxime-*O*-sulfonic salts, nitriles, oximes, diaziridines, oxaziridines, and amides through the Beckmann rearrangement [3].

Recently, HOSA has been used for the synthesis of *O*-substituted heterocyclic hydroxylamines **D** and **E** (Figure 2) which, in turn, find applications in the synthesis of structurally diverse heterocyclic compounds with potential biological activities.

The general concept of this approach is based on ambiguous chemical properties of *O*-substituted hydroxylamines of types **D** and **E**. Typically, the construction of a nitrogen-containing heterocyclic ring system is based on tandem nucleophilic addition-electrophilic amination processes which take advantage of both the nucleophilic and electrophilic properties of these reagents. The tandem reactions of the heterocyclic hydroxylamine-*O*-sulfonates **D** and **E** with heterocumulenes or carbonyl compounds yield bicyclic heterocyclic compounds incorporating O-N, S-N, N-N, and N-N$^+$ bonds (Scheme 1).

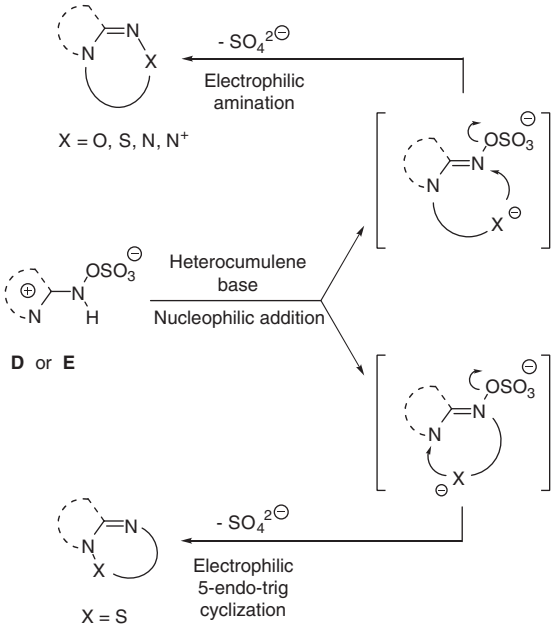
Synthesis of heterocyclic hydroxylamine-*O*-sulfonates

The nucleophilic properties of HOSA are particularly useful for its reactions with activated heterocyclic halides.

D
O-sulfonic hydroxylamines of 2-imidazoline

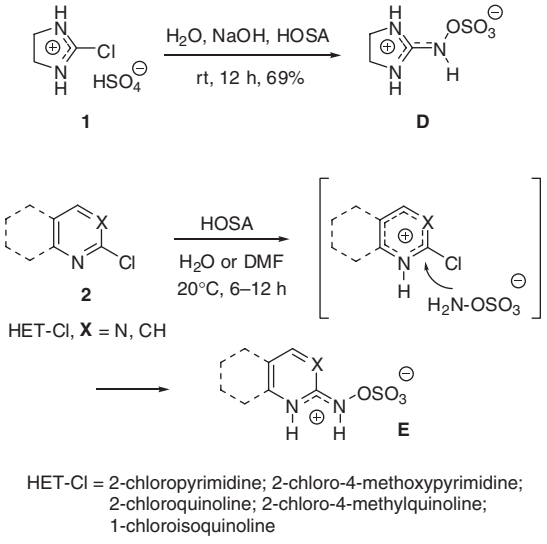
E
O-sulfonic hydroxylamines of azines i diazines
X = CH or N

Figure 2 *O*-Substituted heterocyclic hydroxylamines.



Scheme 1 The course of the tandem reactions with use of substrates **D** and **E**.

Thus, 2-chloro-4,5-dihydroimidazole (**1**) undergoes a reaction with an excess of HOSA in aqueous solution at room temperature to yield 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate **D** [31], analogously to the reactions of **1** with *O*-methyl- and *O*-benzyl-hydroxylamines [32, 33]. As shown in Scheme 2, HOSA can also be used as an efficient nucleophilic aminating reagent for 2-chloropyrimidines, 2-chloroquinolines, and 1-chloroisoquinolines (**2**), giving



Scheme 2 The reactions of activated heterocyclic halides **1** and **2** with HOSA.

rise to the formation of heteroaromatic hydroxylamine-*O*-sulfonates **E**, which in solid state and in solution exist in the form of betaines [34, 35]. Importantly, the competitive N-amination reaction of a heterocyclic ring has not been perceived. The observed nucleophilic aromatic substitution (S_NAr) requires an excess of HOSA, and the reaction may be suppressed by triethylamine, which suggests that this reaction is acid-catalyzed. Thus, HOSA protonates the azine nitrogen atom, which activates the C-2 carbon atom and makes it susceptible to the attack of a weak nucleophile $H_2N\text{-}OSO_3^-$. Under acidic conditions, concurrent N-amination reaction of azines does not take place, as it usually requires a rather strong basic environment.

The structures of compounds **D** and **E** were confirmed by single crystal X-ray diffraction analyses proving that in the solid state they exist in zwitterionic form. Betaines of types **D** and **E** upon treatment with bases such as NaOH or triethylamine are converted into the corresponding sulfonate salts **D′** and **E′** (Scheme 3), and these salts are used for further transformations including a variety of tandem nucleophilic addition-electrophilic amination reactions.

According to chemical intuition, the endocyclic nitrogen atoms (N) in *O*-substituted heterocyclic hydroxylamine **D′** and its oxime tautomer **D″** should react as nucleophiles, whereas the exocyclic nitrogen atom (N) should demonstrate electrophilic properties. The justification of the above assumption is based on chemical knowledge, results of quantum-chemical calculations, molecular modeling, and studies of annular tautomerism within the heterocyclic ring system (Figure 3).

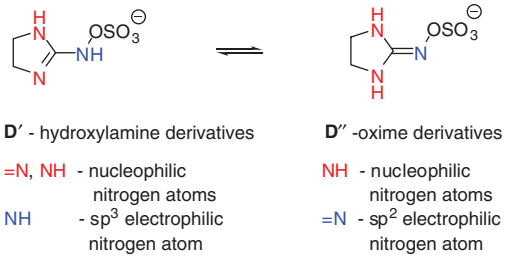


Figure 3 Tautomeric structures of 4,5-dihydroimidazole derivatives (**D′** and **D″**).

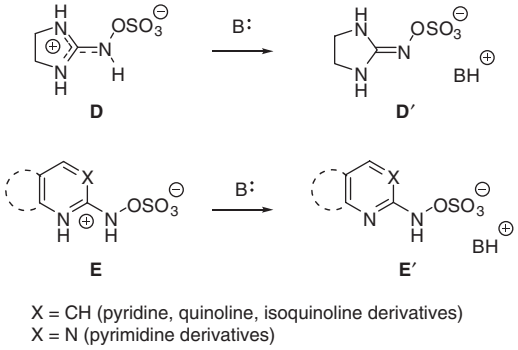
Structure and reactivity of heterocyclic hydroxylamine-*O*-sulfonates

The results of molecular modeling [36] for the tautomeric structures **D′** and **D″** indicate that in DMF solution the oxime **D″** is thermodynamically more stable, whereas in vacuum the hydroxylamine **D′** prevails, owing to a strong intramolecular hydrogen bond formation between the proton of the exocyclic NH group and the negatively ionized oxygen atom of the sulfate group (Figure 4). The results of molecular modeling studies for tautomeric structures **D′** and **D″** are presented in Figure 5.

In both cases (**D′** and **D″**), the HOMO orbital density [ν(e/au³)] mapped on isodensity surface (0.002 e/au³), corresponding to the molecular size and shape, is greater at the vicinity of the exocyclic N2 nitrogen atom than at the endocyclic N1 and N3 atoms, which indicates that the frontier orbital controlled reactions should involve the exocyclic nitrogen atom. By contrast, the relatively higher negative charges at the endocyclic N1 and N3 nitrogen atoms imply their involvement in the charge-controlled reactions.

Analogous calculations performed for heteroaromatic tautomeric **E′** and **E″** (Figure 6) show that hydroxylamine **E′** tautomer of the pyrimidine derivative prevails in vacuum and in DMF solution, whereas in cases of quinoline and isoquinoline both tautomeric forms **E′** (hydroxylamine) and **E″** (oxime) are present in DMF solution.

The results of the quantum chemical calculations presented in Figure 7 indicate that the hydroxyguanidine tautomeric forms **E′** and **E″** are not much different in terms of electronic structure from the tautomers **D′** and **D″** described



Scheme 3

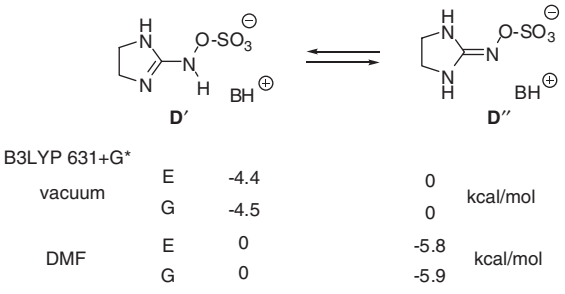


Figure 4 The relative stability of the hydroxylamine (**D′**) and oxime (**D″**) derivatives.

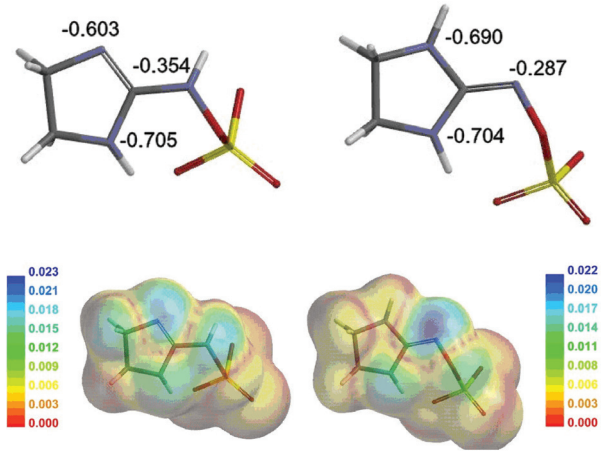


Figure 5 Natural charges [e] (top) and the HOMO absolute values [V(e/au³)] (bottom) mapped on the isodensity surface (0.002 e/au³) calculated with the B3LYP density functional method using the 6-31+G* basis set [36].

earlier. Thus, the HOMO orbital densities are greater in the proximity of exocyclic N2 nitrogen atoms, whereas the greatest natural charge values are located at the endocyclic

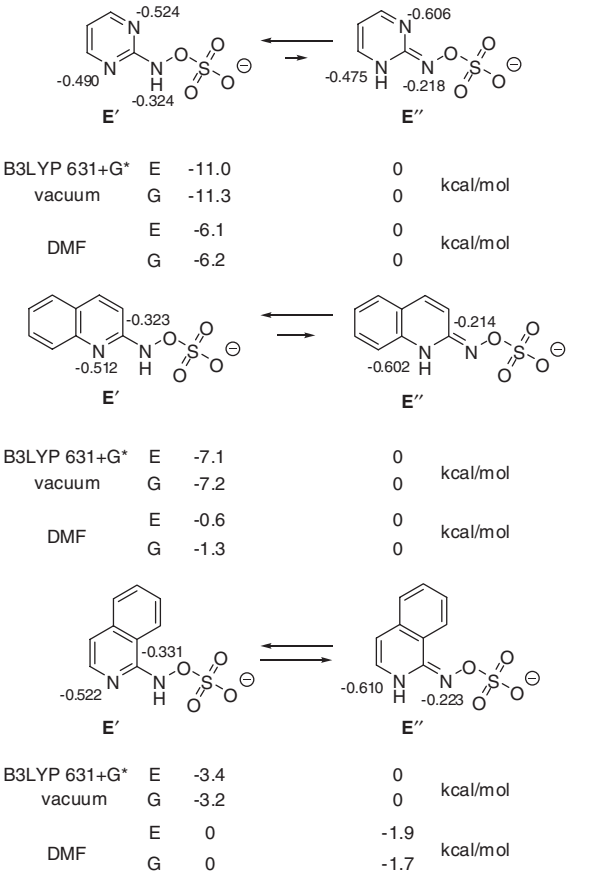


Figure 6 Relative stability of hydroxylamine (**E′**) and oxime (**E″**) derivatives and natural charges [e] calculated with the B3LYP density functional method using the 6-31+G* basis set [36].

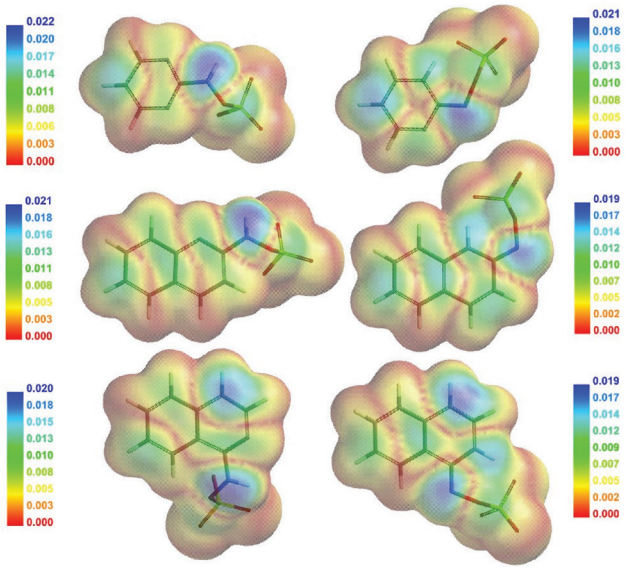
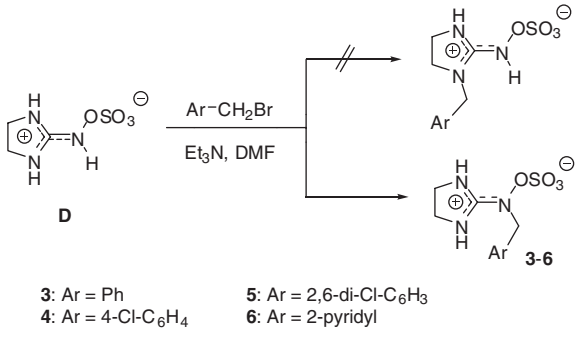


Figure 7 The HOMO absolute values [V(e/au³)] mapped on the isodensity surface (0.002 e/au³) for derivatives **E′** (left) and **E″** (right) calculated with the B3LYP density functional method using the 6-31+G* basis set [36].

N1 nitrogen atoms. These findings suggest ambident reactivity of heterocyclic hydroxylamine-*O*-sulfonates **D** and **E**, that is, electrostatically controlled reactions should involve endocyclic N1 nitrogen atoms and the reactions controlled by frontier orbitals should take place at exocyclic N2 atoms.

Alkylation and acylation of heterocyclic hydroxylamine-*O*-sulfonates

The benzylation reaction of 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate **D** exclusively proceeds at the exocyclic nitrogen atom leading to the products **3**–**6** [37]. Regioselectivity of this reaction suggests that it proceeds under frontier orbital control (Scheme 4). This result is not



Scheme 4 Regioselective alkylation of 2-hydroxyliminoimidazolidine-*O*-sulfonate.

accidental, because subsequent studies have proven that analogous benzylation of 2-benzyloxyiminoimidazolidine assumes a similar course [38].

The results of our quantum chemical calculations suggest that the benzylation reaction of **D** proceeds under frontier orbital control. Although the mechanism of this reaction was not investigated, taking into consideration that the product substituted at the exocyclic nitrogen atom is energetically favored by 2.5 kcal/mol over its N1-substituted counterpart [37], it could be inferred that the N2-substituted products **3**–**6** are both kinetically and thermodynamically favored.

It is pertinent to note that in the case of amidine derivatives of type **F**, described by Beak et al. as 'protomeric ambident nucleophiles' [39], heterocyclic amidines of type **G** called 1,3-dinucleophiles [40] and 2-aryliminoimidazolidines **H** [41, 42], which directly refer to the structure of the heterocyclic hydroxylamine **D**, the electrophilic attack at the less basic sp^2 hybridized exocyclic nitrogen atom is also favored (Figure 8). Such a reaction course has been rationalized using the Curtin-Hammett principle [43, 44], hard and soft acids and bases (HSAB) [45], or just steric hindrance [40].

Interestingly, the reaction of 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate **D** with benzoyl chloride under Schotten-Baumann reaction conditions leads to the formation of 1,3-dibenzoylimidazolidin-2-one (**7**) (Scheme 5), whereas the expected *N*-benzoylated imidazoline derivative has not been observed in the reaction mixture [46]. However, analogous reaction of **D** with two equivalents of milder benzoylating reagent, that is, benzoyl cyanide affords 2-benzoyloxy-iminoimidazolidine (**8**) in 12% yield through retro-ene transformation of

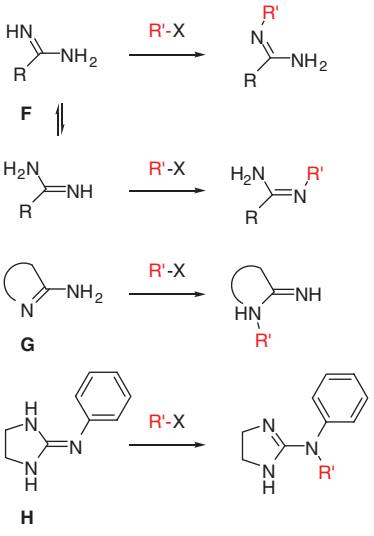
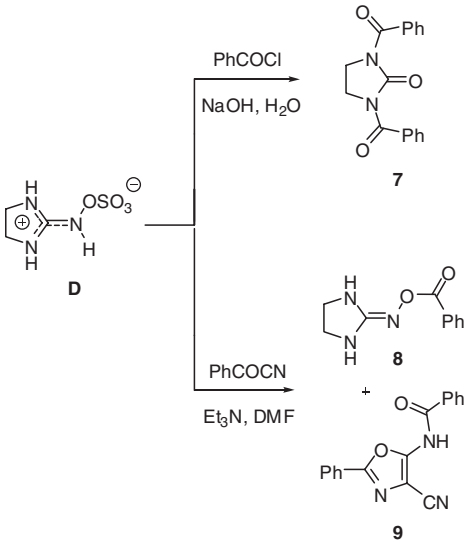


Figure 8 Regioselective alkylation of ambident amidine and guanidine nucleophiles **F**, **G**, and **H**.



Scheme 5

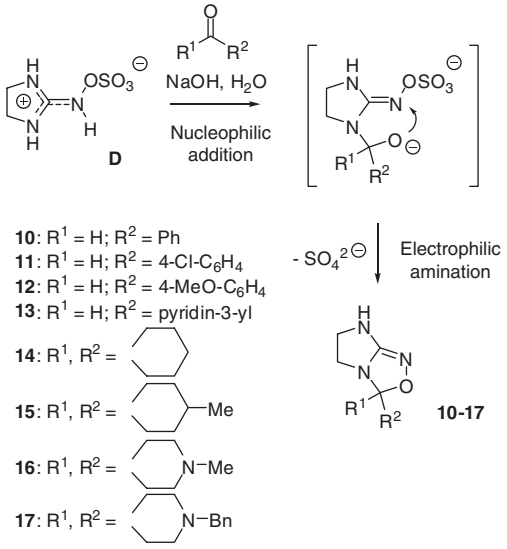
transient anhydride. The main product **8** is accompanied by *N*-(4-cyano-2-phenyloxazol-5-yl)benzamide (**9**) resulting from trimerization of benzoyl isocyanide.

Tandem reactions of heterocyclic hydroxylamine-*O*-sulfonates

Reactions with carbonyl and thiocarbonyl compounds

Treatment of **D** with aromatic aldehydes in aqueous NaOH solution gives the 3-substituted 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]oxadiazoles **10**–**13** and analogous reaction with cyclic ketones enables preparation of spiro compounds **14**–**17** (Scheme 6). The yields of these processes are moderate (23–35%), except for benzaldehyde, which gives the product **10** in 74% yield [30]. Mechanistically, the reaction comprises initial nucleophilic addition of the imidazoline NH group to the carbonyl group and subsequent abstraction of the proton from the hydroxyl group followed by intramolecular electrophilic amination of the anionic oxygen atom with simultaneous extrusion of the sulfate group (tandem nucleophilic addition-electrophilic amination reaction).

It should be pointed out that previously the reaction of aromatic oxime-*O*-sulfonates with phenolate anion already installed at the *ortho* position of the phenyl ring was applied for the transformation of salicyl aldehyde [47] and 2-hydroxyacetophenone [48] into benzo[*d*]isoxazoles and 3-methylbenzo[*d*]isoxazoles, respectively.



Scheme 6 Reaction of hydroxylamine-*O*-sulfonate **D** with aldehydes and ketones.

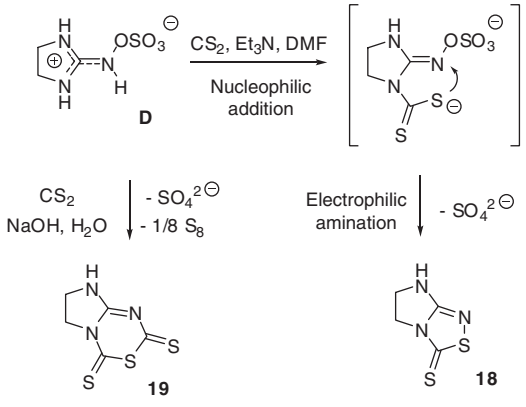
Moreover, the treatment of 1,3-diketones with HOSA provided isoxazoles and 5,6-dihydro-4*H*-cyclopenta[*c*]isoxazoles [48] and similar reactions of enaminones gave 4,5,6,7-tetrahydrobenzo[*c*]isoxazoles and 4,5,6,7-tetrahydrobenzo[*d*]isoxazoles in high yields [49].

Reactions with heterocumulenes

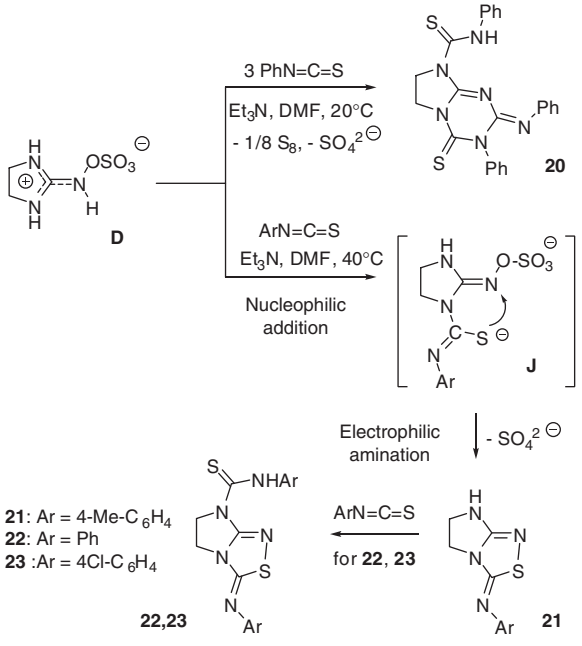
The reaction of hydroxylamine-*O*-sulfonate **D** with carbon disulfide takes two different courses, depending on a base-solvent combination [31]. As shown in Scheme 7, the reaction of **D** with CS_2 carried out in DMF in the presence of triethylamine gives 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione (**18**) in good yield as a result of the tandem nucleophilic addition-electrophilic amination reaction, which is mechanistically related to the formation of oxadiazoles **10**–**17** described above. By contrast, compound **D** in aqueous NaOH solution, which is more effective than DMF at solvating atoms with partial negative charges, undergoes a reaction with two molecules of carbon disulfide that, after desulfurization, gives 7,8-dihydroimidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithione (**19**).

The reaction of hydroxylamine-*O*-sulfonate **D** with aryl isothiocyanates is strongly dependent on stoichiometry of the reagents and temperature (Scheme 8). Thus, at room temperature compound **D** undergoes a reaction with three molar equivalents of phenyl isothiocyanate that, following desulfurization, affords 3-phenyl-2-phenylimino-2,6,7,8-tetrahydroimidazo[1,2-*a*][1,3,5]triazine-4(3*H*)-thione (**20**) as the sole product [31]. However, a tandem nucleophilic addition-electrophilic amination reaction takes place when **D** is treated with aryl isothiocyanates at 40°C; 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole (**21**) is formed in case of 4-methylphenyl isothiocyanate, and 7-substituted derivatives **22** and **23** are obtained in the case of more reactive phenyl and *p*-chlorophenyl isocyanates [35].

Conceptually similar approaches to the syntheses of compounds containing an S-N bond include one-pot transformations of thioenaminones [49], amidines [50], or α-acetylenic aldehydes and ketones [51] into isothiazoles and 1,2,4-thiadiazoles by means of the



Scheme 7 Reactions of hydroxylamine-*O*-sulfonate **D** with carbon disulfide.

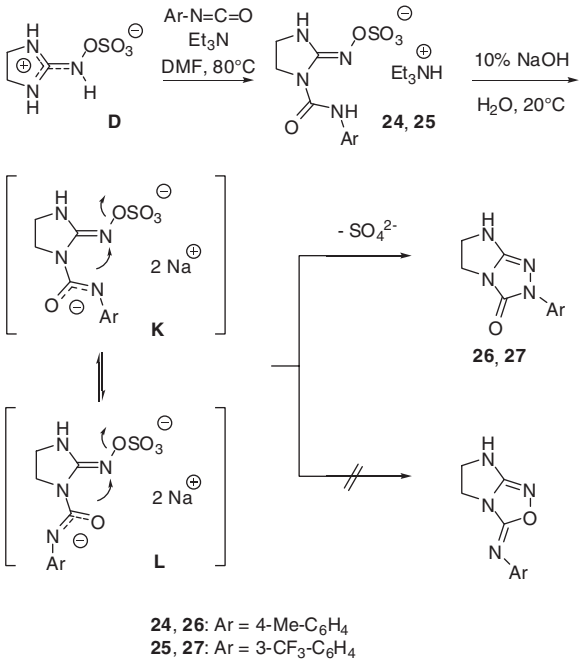


Scheme 8 Reaction of hydroxylamine-*O*-sulfonate **D** with aromatic isothiocyanates.

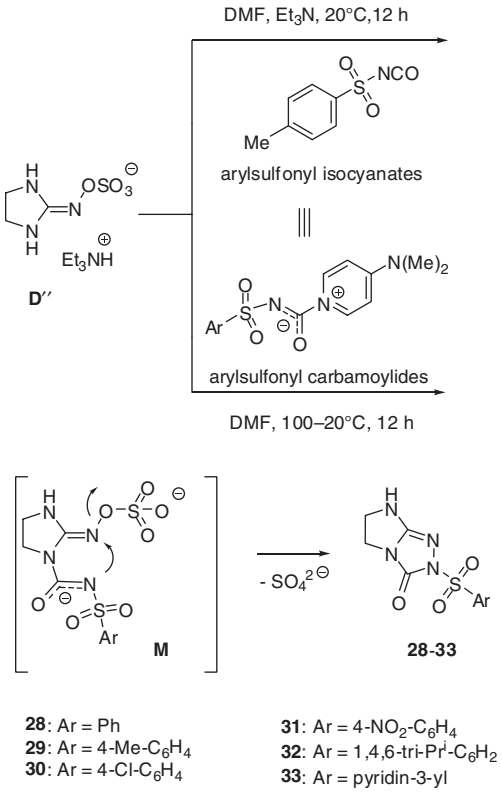
intramolecular *S*-amination in the transiently formed oxime-*O*-sulfonates.

As shown in Scheme 9, reaction **D** with aryl isocyanates carried out in the presence of triethylamine leads to the formation of ureas **24** and **25**, that is, the products of nucleophilic addition which can be separated from the reaction mixture in pure form [35]. To induce an intramolecular electrophilic amination reaction, ureas **24** and **25** have to be treated with a strong base, which is able to generate the ambident ureate anion **K**. Hence, upon treatment with 10% NaOH in aqueous solution, an instantaneous N-N bond-forming reaction takes place furnishing 6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones **26** and **27** in high yields. It should be noted that the alternative *O*-amination reaction of the ambident anion **L**, leading to the formation of oxadiazoles, is not observed (Scheme 9).

Hydroxylamine-*O*-sulfonate **D** can also react with arylsulfonyl isocyanates and their safe and stable analogs such as the 4-dimethylaminopyridinium arylsulfonyl carbamoylides [52–54]. As depicted in Scheme 10, treatment of **D″** with *p*-tolylsulfonyl isocyanate at room temperature or heating at 80°C with corresponding arylsulfonyl carbamoylides furnishes 2-(arylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones **28**–**33** in 23–69% of isolated yield [35]. Apparently, the initially formed sulfonylureas are stronger NH acids than the corresponding ureas **24** and **25** (Scheme 8), and suffer deprotonation in the presence of triethylamine and DMAP to give ambident anions **M**, which undergo spontaneous regioselective *N*-amination to give the final bicyclic products **28**–**33**.



Scheme 9 Reaction of hydroxylamine-*O*-sulfonate **D** with aryl isocyanates.



Scheme 10 Reaction of salt **D″** with arylsulfonyl isocyanates and arylsulfonyl carbamoylides.

It is worth noting that the pyridine or isoquinoline formimidates and formamidines react with HOSA in the presence of pyridine to give [1,2,4]triazolo[1,5-*a*]pyridine or [1,2,4]triazolo[5,1-*a*]isoquinoline, respectively [55], via the tandem nucleophilic substitution-electrophilic amination reaction. Another variant of N-N bond formation consists of the treatment of 4-aminopyrimidine-5-carbaldehydes with HOSA. The initially formed oxime-*O*-sulfonates undergo intramolecular electrophilic amination to give the expected *N*-aryl[3,4-*d*]pyrazolopyrimidines [56].

To some extent, the electrophilic amination reactions of anions **J** (Scheme 8), **K** (Scheme 9), and **M** (Scheme 10) presented above resemble the previously investigated S_N2 reactions at sp^2-hybridized carbon [57–63] or nitrogen [64] atoms, as well as the Boulton-Katritzky rearrangement [65, 66]. Thus, the substitution of the sulfate leaving group by an amidate or thioamidate anion may proceed according to either the $S_N2\pi$ mechanism (out-of-plane nucleophilic attack) by interacting with the π orbital of the

imino group, or $S_N2\sigma$ mechanism (in-plane attack) where a nucleophile interacts with the σ orbital of the imino nitrogen atom (Figure 9).

Theoretical studies of the transition states for the examined processes with use of the density functional B3LYP/6–31+G* method are consistent with the favored *N*-amination reactions of the amidate anions **K** and **M** and *S*-amination reaction of the thioamide **J** through the planar in-plane $S_N2\sigma$ transition states **TS-K**, **TS-M**, and **TS-J** with low activation energies $\Delta G^{\ddagger}$ of 11.1, 23.7, and 15.3 kcal/mol, respectively (Figure 10). The displacement of the sulfate anion by nitrogen or sulfur atom occurs in a nearly linear manner as the corresponding N-N2-O and S-N2-O bond angles are equal to 169.8°, 170.7° and 163.9°. The *p*(π)-atomic orbitals of the exocyclic C=N2 bond perpendicular to the imidazoline ring are not involved in bond-building or bond-breaking processes of σ-bonds. The 'looseness' of these transition states correlates with the activation barriers, that is, the higher barrier for the concerted S_N2 reaction, the larger stretching of the N2-O bond in the transition structures. All the investigated reactions are exothermic by ΔG ranging from -19.6 kcal/mol to -59.5 kcal/mol. The reaction of aryl amidate anion **K** has a lowest barrier (11.1 kcal/mol) and is considerably more exothermic (59.5 kcal/mol) than the corresponding reaction of aryl thioamidate **J** (36.8 kcal/mol) and especially arylsulfonyl amidate anion **M** (19.6 kcal/mol).

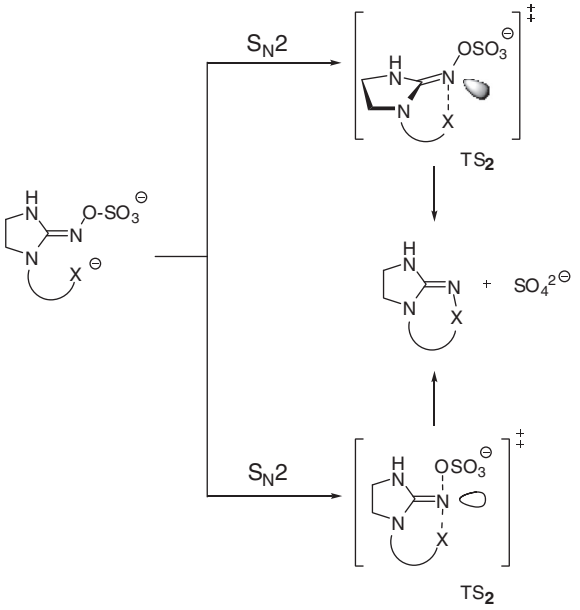


Figure 9 $S_N2\pi$ and $S_N2\sigma$ mechanisms of intramolecular nucleophilic substitution.

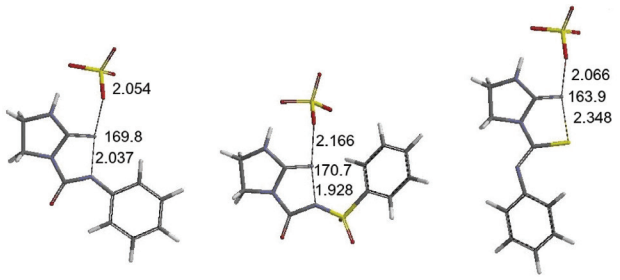
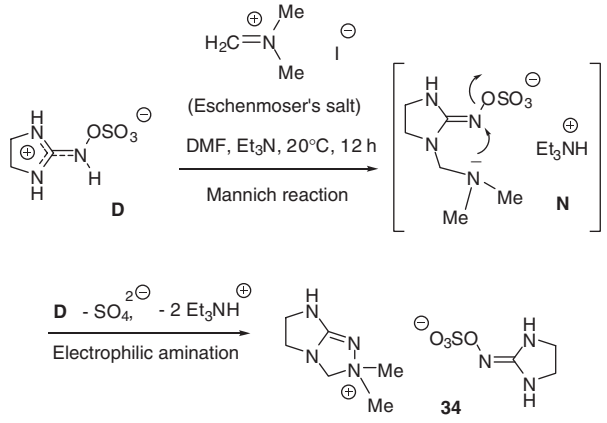


Figure 10 N-N, S-N, and N-O atom distances [Å] and N-N-O i S-N-O bond angles [°] calculated for $S_N2\sigma$ transition states **TS-K** (left), **TS-M** (middle), and **TS-J** (right).

The results presented above prompted us to develop a new synthetic method for the preparation of bicyclic imidazo[2,1-*c*][1,2,4]triazole derivatives incorporating the N-N⁺ bond. We found that the reaction of hydroxylamine-*O*-sulfonate **D** with Eschenmoser's salt in a 2:1 molar ratio carried out in anhydrous DMF in the presence of triethylamine gives rise to the formation of 2,2-dimethyl-3,5,6,7-tetrahydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-2-ium 2-hydroxylimino-imidazolidine-*O*-sulfonate (**34**) in 64% yield (Scheme 11) [67]. The reaction proceeds via an initial Mannich-type reaction between the Eschenmoser's salt and the endocyclic nitrogen atom affording the aminal (**N**), followed by intramolecular electrophilic amination of the tertiary amine group, which yields the product **34** incorporating the N-N⁺ bond. All attempts to isolate the intermediary formed Mannich base (**N**) were unsuccessful, suggesting that this aminal is very susceptible to intramolecular electrophilic amination.

An alternative approach to the imidazo[2,1-*c*][1,2,4]triazol-2-ium salts involves the application of the well-known benzotriazole aminals, which serve as Eschenmoser's salt precursors [68]. Apparently, the iminium



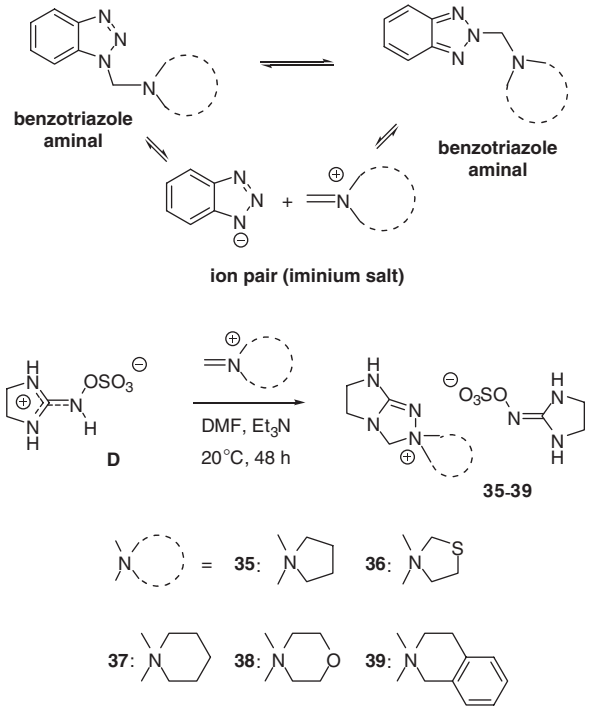
Scheme 11 Tandem Mannich-electrophilic amination reaction.

cations generated in solution from benzotriazole aminals react with hydroxylamine-*O*-sulfonate **D** to form Mannich-type bases which, in turn, undergo spontaneous intramolecular electrophilic amination reaction that gives rise to the formation of the spiro-fused triazolium salts **35**–**39** in 44–68% yield (Scheme 12).

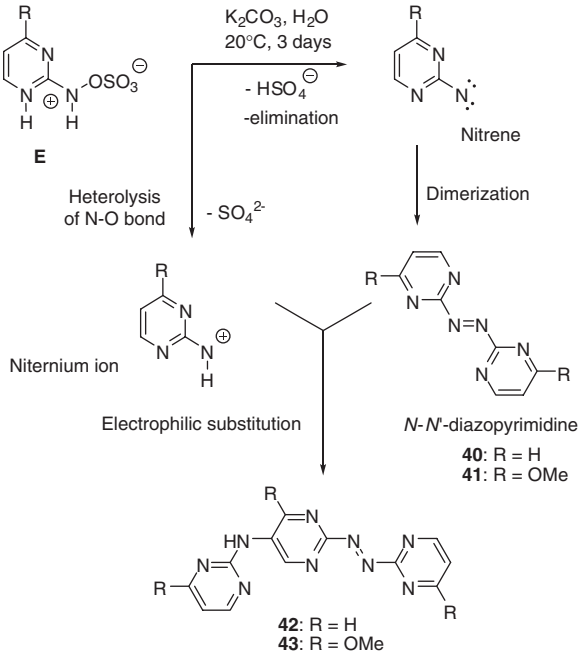
The azaaromatic hydroxylamine-*O*-sulfonates **E** may serve as the precursors of nitrene species generated by α-elimination of HSO_4^- (homolysis of N-O bond) or nitrenium ions formed by N-O bond heterolysis (Scheme 13). Thus, the treatment of pyrimidine derivatives **E** (**X** = N, Scheme 2) with aqueous K_2CO_3 solution at room temperature affords two types of products: *N*,*N*′-diazopyrimidines (**40**, **41**), derived from dimerization of the corresponding nitrenes and the products (**42**, **43**) of heteroarylation of nitrenium ions.

Previously, Takeuchi and Watanabe generated analogous 2-pyrimidylnitrenium ion from tetrazolo[1,5-*a*] pyrimidine in the presence of trifluoroacetic acid [69], and computational studies of heteroarylnitrenium ions were performed by the Cramer, Falvey, and Di Stefano groups [70–74].

The *O*-substituted heterocyclic hydroxylamines **E** upon treatment with acyl isothiocyanates in the presence of triethylamine are transformed into compounds **44**–**57** in moderate yield, as a result of tandem nucleophilic addition-electrophilic 5-*endo-trig* cyclization (Scheme 14).



Scheme 12

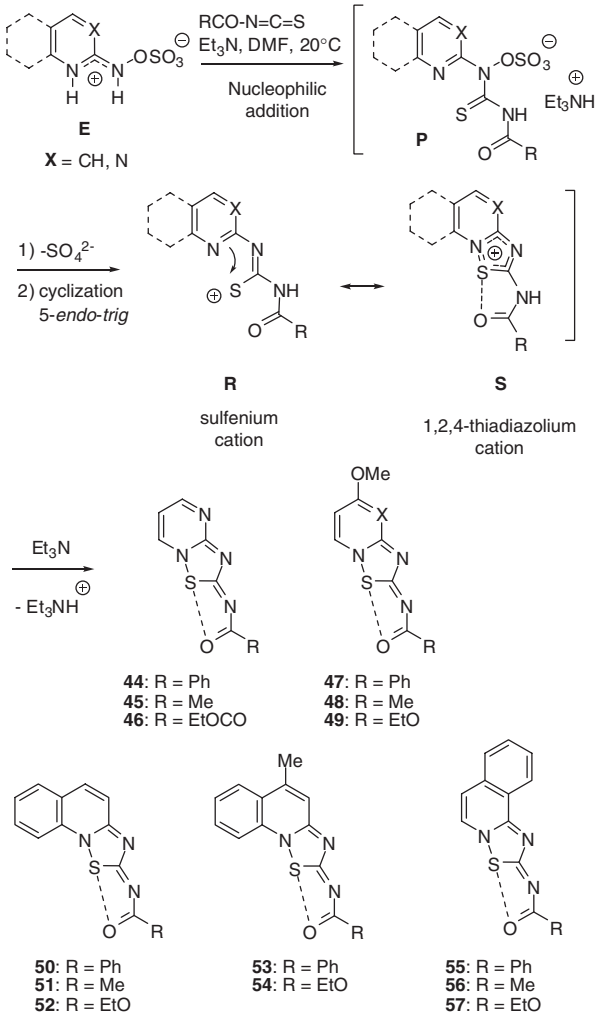


Scheme 13 Hydroxylamine-*O*-sulfonates **E** as the precursors of nitrene and nitrenium ions.

Apparently, the initially formed anions **P**, which are the products of the frontier orbital-controlled addition of the NH group to the heterocumulenes, are transformed into the sulfenium ions **R** as a result of N-O bond heterolysis. The subsequent electrophilic 5-*endo-trig* cyclization gives rise to the formation of the resonance stabilized 1,2,4-thiadiazolium cations **S**, which upon treatment with a second molar equivalent of triethylamine give rise to the deprotonated [1,2,4]thiadiazole derivatives **42**–**55**.

The electronic structure of the sulfenium cation **R**, which participates in the electrophilic 5-*endo-trig* cyclization, was studied using quantum chemical calculations with the long-range and dispersion-corrected ωB97X-D/6-31+G* function [36]. The results are consistent with the suggestion that the disintegration of nitrenium ion may lead to a highly electrophilic sulfenium ion **R**. Both, the N-O bond heterolysis and the proton abstraction from the resonance-stabilized 1,2,4-thiadiazolium cation **S** are exothermic with the heats of these processes in DMF estimated to be 15.2 and 35.9 kcal/mol, respectively (Figure 11).

To ensure that no alternative nucleophilic 5-*endo-trig* cyclization was taking place, DFT calculations of a concerted S_N2' reaction were carried out. Thus, the species of type **P** could suffer a base-promoted abstraction of the proton from the thiourea moiety to give the dianion



Scheme 14 The tandem nucleophilic addition-electrophilic 5-*endo-trig* cyclization.

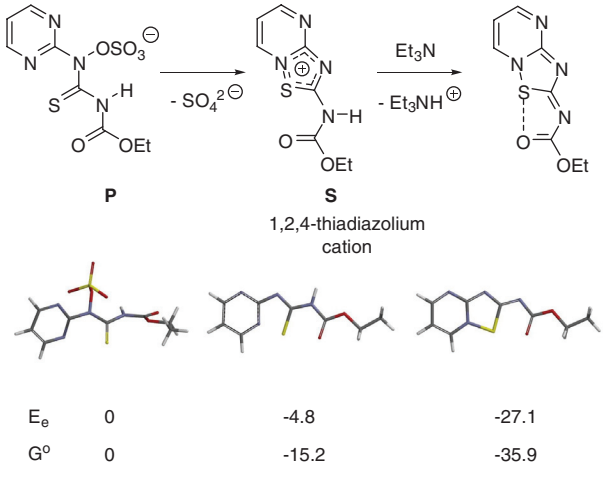
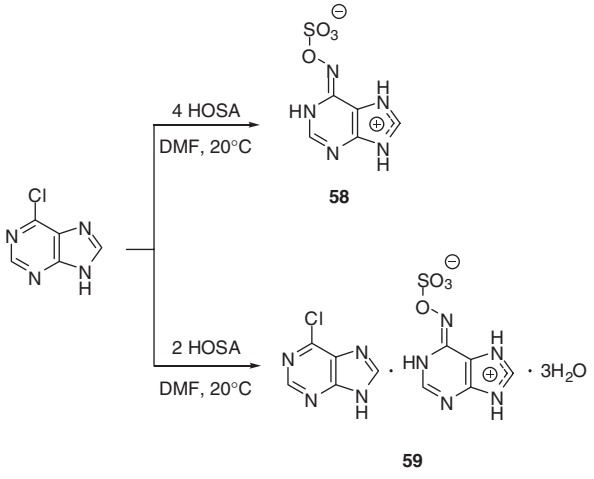


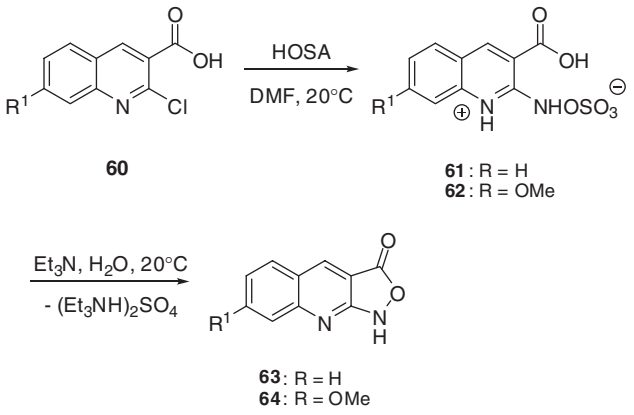
Figure 11 The relative electronic energy (ΔE) and Gibbs free energy (ΔG) profiles (298.15 K, kcal/mol) for sulfenium-driven 5-*endo-trig* cyclization calculated with the long-range and dispersion-corrected ωB97X-D/6-31+G* functional method using the SM8 solvation model [36].

which bears a nucleophilic sulfur at the homoallylic position suitable for 5-*endo-trig* cyclization via intramolecular concerted S_N2' reaction with loss of the SO_4^{2}-dianion. Although the transition state for this process has been suggested, it is rather prohibited by a high energy barrier of 58.3 kcal/mol and, therefore, should not contribute to the observed mild cyclization that furnishes products **44**–**57**. Analogous 2-acylimino-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine compounds were prepared elsewhere by oxidation of N^1-(2-pyrimidyl)-N^2-benzoyl-thioureas with bromine [75–77].

2-Aminoazine derivatives are widely present in drugs, natural products, as well as various cooking and pyrolysis products from proteinaceous food [78, 79]. It has been well documented that metabolic transformation of aminoaza-heterocyclic drugs may be a prelude of their elimination from the host or may produce reactive or toxic intermediates and metabolites. Although the sulfation of aromatic and heteroaromatic hydroxylamines by the sulfotransferase family of enzymes has been investigated in various biological systems [80–83], a possible product of the sulfate conjugation in adenine metabolism has not been revealed. The 1*H*-purin-6-ylideneaminooxysulfonic acid (**58**), which could be formed in mammals' system by *O*-sulfation of the well-known ultimate carcinogen 6-hydroxylaminopurine (6-HAP) [84], can be obtained by subjecting 6-chloropurine to the reaction with HOSA. As shown in Scheme 15, the reaction carried out in DMF at room temperature in the presence of fourfold excess of HOSA gives the desired product **58** in pure form [85]. Interestingly enough, when twofold excess of HOSA is used, the reaction is not complete and upon crystallization of crude product



Scheme 15 Synthesis of (Z) 1*H*-purin-6-ylideneaminooxysulfonic acid (**58**) and its complex with 6-chloropurine (**59**).



60

61: R = H
62: R = OMe

63: R = H
64: R = OMe

Scheme 16 Synthesis of isoxazolo[3,4-*b*]quinolin-3(1*H*)-ones **63** and **64**.

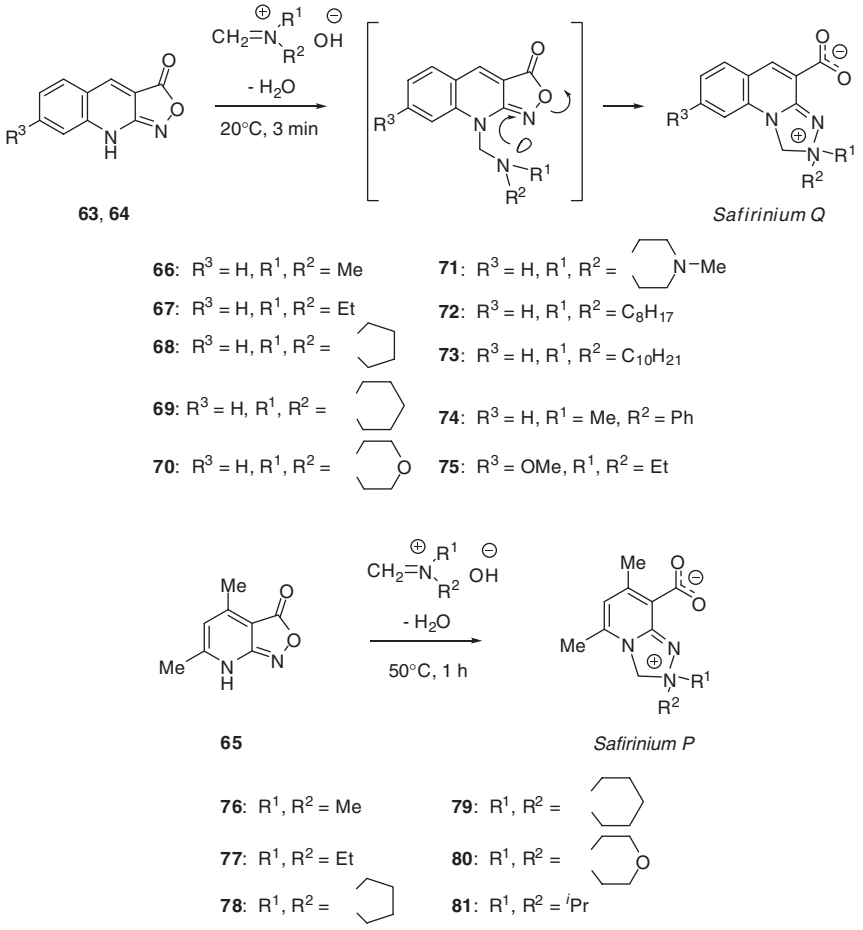
the complex **59** composed of 6-chloropurine, sulfonic acid **58**, and three water molecules is formed.

The synthesis of aza-aromatic hydroxylamine-*O*-sulfonates of type **E** described above marked the starting point for the reactions of 2-chloroquinoline-3-carboxylic acids (**60**) with HOSA [86]. As expected, the nucleophilic substitution reactions produce hydroxylamine derivatives **61** and **62**, which upon treatment with triethylamine provide the desired isoxazolo[3,4-*b*]quinolin-3(1*H*)-ones **63** and **64** (Scheme 16).

In the chemical literature, there is just one publication referring to the synthesis of an analogous compound, 4,6-dimethylisoxazolo[3,4-*b*]pyridin-3(1*H*)-one (**65**), which can be obtained by the cyclocondensation of *N*-hydroxy-3-(hydroxyamino)-3-iminopropanamide with acetylacetone in the presence of piperidine [87].

It was assumed that the carboxylate group incorporated into the fused isoxazolone ring system would behave as a leaving group in the electrophilic amination reactions of the N1 nitrogen atom. The Mannich reactions of **63** with formaldehyde and secondary amines leads to the formation of zwitterionic 1,2,4-triazolo[4,3-*a*]quinoline **66**–**75** derivatives. A similar reaction with pyridine-containing substrate **65** affords 1,2,4-triazolo[4,3-*a*]pyridines **76**–**81** (Scheme 17).

The multicomponent fluorogenic reaction of isoxazolo[3,4-*b*]quinolin-3(1*H*)-ones **63** proceeds



63, **64**

Safirinium Q

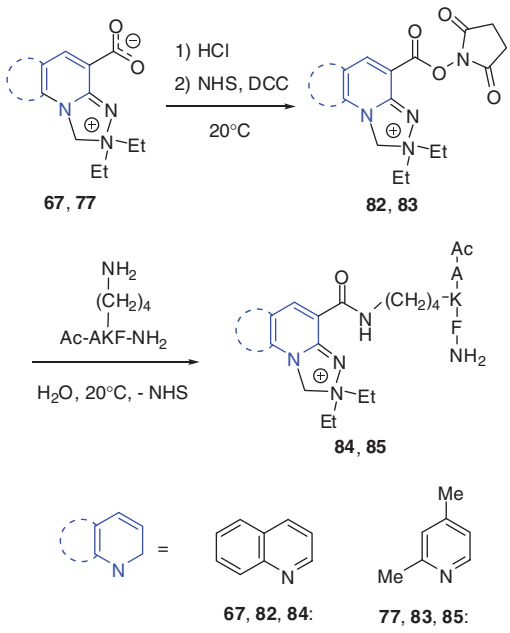
66: R^3 = H, R^1, R^2 = Me
67: R^3 = H, R^1, R^2 = Et
68: R^3 = H, R^1, R^2 =
69: R^3 = H, R^1, R^2 =
70: R^3 = H, R^1, R^2 =
71: R^3 = H, R^1, R^2 =
72: R^3 = H, R^1, R^2 = C_8H_{17}
73: R^3 = H, R^1, R^2 = $C_{10}H_{21}$
74: R^3 = H, R^1 = Me, R^2 = Ph
75: R^3 = OMe, R^1, R^2 = Et

65

Safirinium P

76: R^1, R^2 = Me
77: R^1, R^2 = Et
78: R^1, R^2 =
79: R^1, R^2 =
80: R^1, R^2 =
81: R^1, R^2 = ^{i}Pr

Scheme 17 The tandem Mannich-electrophilic amination reaction.



Scheme 18 Synthesis of amine-reactive fluorescent dyes **82** and **83** and their use for labeling of the lysine-containing tripeptide Ac-AKF-NH_2.

quantitatively and is completed at room temperature within 3 min. Therefore, it can serve in environmental monitoring of either formaldehyde or secondary amines [86].

The betaines **67** (Safirinium Q) and **77** (Safirinium P) upon treatment with *N*-hydroxysuccinimide (NHS) and dicyclohexylcarbodiimide (DCC) were converted into the fluorescent, water-soluble, and photo-stable probes **82** and **83**, which were further used for fluorescent labeling of the lysine-containing tripeptide Ac-AKF-NH_2 (formation of conjugates **84** and **85**, respectively) (Scheme 18). It can be envisaged that the amine-reactive dyes of types **82** and **83** will find applications for fluorescent labeling of peptides, proteins, amino sugars, modified oligonucleotides, and drugs. What is important is that they have already been used for fluorescent staining of *Bacillus subtilis* spores in aqueous solution at room temperature [86].

Conclusion

We have highlighted recent advantages in the preparation and applications of heterocyclic hydroxylamine-*O*-sulfonates to various tandem reactions useful for efficient N-O, N-S, N-N, and $N\text{-}N^+$ bond formation. These methods are valuable for the synthesis of novel heterocyclic ring systems, that is, new chemotypes relevant to medicinal and pharmaceutical chemistry. The synthetic methods presented in this review can also be used for development of novel fluorescent probes with broad applications in biomedical and environmental sciences.

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