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# Geminal oxygen – nitrogen – halogen systems. *N*-Halohydroxylamine derivatives

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**Abstract. Published data on the synthesis and properties of *N*-halohydroxylamine derivatives are described systematically and analysed. The bibliography includes 123 references**.

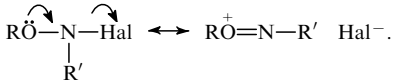
## I. Introduction

The development of the chemistry of *N*-halohydroxylamine derivatives started relatively recently, although the first representative of this class, *N*-chloro-*N*-methoxy-*p*-toluenesulfonamine, was described as early as 1953.[1] *N*-Halo-*N*,*O*-dialkylhydroxylamines are the nitrogen analogues of α-halo ethers, which are widely used in organic synthesis as highly reactive alkylating reagents.[2] It is this formal analogy that attracted our attention about 20 years ago. This analogy has worked perfectly, and this permitted the synthesis of new classes of organic compounds by simple nucleophilic substitution of chlorine in *N*-chlorohydroxylamine derivatives. In particular, *N*-alkoxy-*N*-*tert*-alkyl-*O*-alkylhydroxylamines (nitrosoacetals),[3,4] *N*,*N*-dialkoxy-*O*-alkylhydroxylamines (trialkoxyamines, orthonitrites),[5] and *N*-alkoxy-*O*-alkylhydroxylamines (NH-dialkoxyamines, orthoethers of nitrosyl hydride)[6] have been synthesised in this way, and oxidation of the latter compounds gave stable dialkoxyaminyl radicals[7] and their dimers (tetraalkoxyhydrazines).[7,8] The vast synthetic potential of *N*-halohydroxylamine derivatives is also due to the possibility of converting them into highly reactive intermediates such as *N*-alkoxynitrenes,[9] *N*-substituted *N*-alkoxyaminyl radicals,[7,10] and *N*-alkoxynitrenium ions.[5,11] Thus intramolecular cyclisation of *N*-chloro-*O*-alkylhydroxamates involving an aromatic substituent present in the acyl or alkoxyl fragment of their molecules, which occurs *via* intermediate *N*-acyl-*N*-alkoxynitrenium ions, is a general method for the synthesis of a large number of nitrogen-containing heterocycles.[12–18]

*N*-Halohydroxylamine derivatives are also of interest from the stereochemical viewpoint, since the two σ-electron-withdrawing substituents attached to the nitrogen atom markedly increase its configurational stability.[4,19–26] This made it possible to prepare optically active derivatives of 2-chloro-1,2-oxazolidine[19,20] and 2-chloroxaziridine[24,25] with an asymmetric nitrogen atom. The non-symmetrically substituted *N*-alkoxy-*N*-*tert*-alkyl-*O*-alkylhydroxylamines synthesised from *N*-chloro-*N*-*tert*-alkyl-*O*-alkylhydroxylamines were partially resolved into optical antipodes, which were the first chiral compounds with asymmetric nitrogen atoms in an open chain.[4]

Some aspects of the chemical behaviour of O – N – Cl systems have been considered in a number of reviews.[12,27–29] In the present review, we have attempted to survey all the currently available data on the synthesis, properties, and stereochemistry of *N*-halohydroxylamine derivatives.

The stereochemistry and chemical properties of geminal oxygen – nitrogen – halogen systems are mostly determined by the stabilising interaction between the non-bonding ($n_\pi$) orbital of the oxygen atom and the antibonding σ* orbital of the N – Hal bond, which is described in terms of the concept of valence bonds as hyperconjugation.



According to the theory of molecular orbital perturbation, the energy of $n-\sigma^*$ stabilisation is approximately proportional to the overlap of the interacting orbitals and is inversely proportional to the difference between their energies.[30,31] The $n-\sigma^*$ interaction results in kinetic destabilisation of the N – Hal bond, *i.e.* in an increase in its tendency to dissociate (kinetic anomeric effect[32])† yielding a nitrenium ion stabilised due to the π-overlap between the vacant $2p_z$ orbital of the N atom and the occupied $2p_z$ orbital of the neighbouring O atom (Fig. 1).[4,13–15,33,34]

*N*-Alkoxynitrenium (nitrenium-oxonium ions) are ambident cations. They react with nucleophiles according to two competing pathways.[5,10,35,36]

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† The structural consequences of the $n-\sigma^*$ interaction are considered in Section VII.

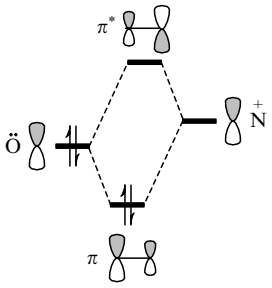
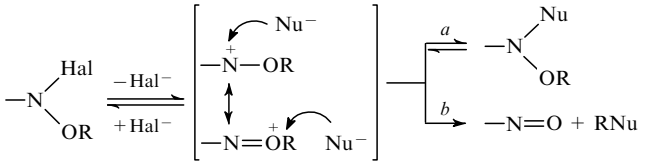


**Figure 1.** Interaction of the $2p_z$ orbitals of nitrogen and oxygen in alkoxynitrenium ions.

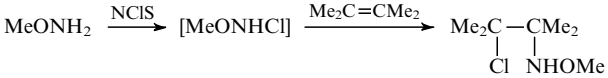


The addition of nucleophiles to the nitrenium centre [pathway (*a*)] is a reversible orbitally controlled reaction, which occurs in the case of 'soft' nucleophiles with high-lying highest occupied molecular orbitals (HOMO). Conversely, dealkylation of the oxonium site [pathway (*b*)] is an irreversible charge-controlled reaction occurring in the case of 'hard' nucleophiles having low-lying HOMO.

The thermal stability and the reactivity of *N*-halohydroxylamine derivatives depend appreciably on the type of the halogen. The former decreases,[13,37] whereas the latter increases with an increase in the electron-withdrawing ability of the N–Hal bond. The above-mentioned properties of *N*-halohydroxylamine derivatives also depend substantially on the type of the third substituent at the nitrogen atom. Electron-releasing substituents, which favour ionisation of the N–Hal bond to even a greater extent, diminish the thermal stability and increase the reactivity of these compounds. For instance, whereas *N*-chloro-*N*-*tert*-alkyl-*O*-alkylhydroxylamines[4] are stable distillable liquids, *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines[5] cannot be detected by $^1$H NMR spectroscopy even at $-30$ °C. Conversely, electron-withdrawing substituents decrease the polarisation of the N–Hal bond, and in some cases, they even change the direction of polarisation; this, for example, occurs in the case of *N*-halo-*N*-alkoxy-substituted sulfonamides[1,38] and phosphamides.[38]

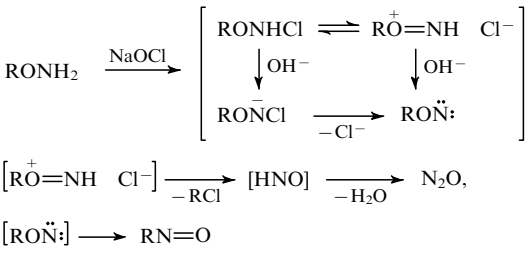
## II. *N*-Halo-*O*-alkylhydroxylamines

*N*-Halo-*O*-alkylhydroxylamines are unstable and have not been isolated in a pure state. Nevertheless, *N*-chloro-*O*-methylhydroxylamine, generated by treatment of *O*-methylhydroxylamine with *N*-chlorosuccinimide, has been involved *in situ* in the addition to tetramethylethylene.[39]



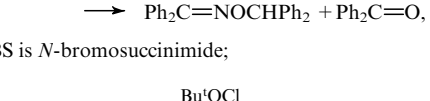
NCS is *N*-chlorosuccinimide.

Two routes of transformation of *N*-chloro-*O*-*tert*-alkylhydroxylamines have been discovered; in weakly alkaline solutions, they form $N_2O$, while in strongly alkaline media (6 N or 8 N NaOH), they are converted into nitrosoalkanes.[40] Dinitrogen monoxide was assumed to result from decomposition of nitrosyl hydride formed upon dealkylation of the intermediate nitrenium-oxonium ions. Nitroso-derivatives result from 1,2-rearrangement of the alkoxynitrenes,[41,42] which can be generated from *N*-chloro-*O*-alkylhydroxylamines *via* 1,1-elimination[40] or deprotonation of *N*-alkoxynitrenium ions.[35]

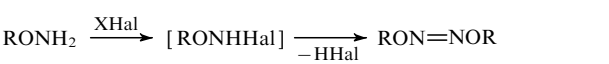


R = Bu$^t$, $Me_2EtC$.

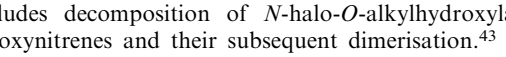
It has been assumed that the products of monohalogenation of *O*-diphenylmethylhydroxylamine[43] and 1,2-bis(aminooxy)-ethane[44] are mostly formed *via* decomposition of intermediate hyponitrites yielding $N_2$ and alkoxy radicals, which, in turn, disproportionate to give an aldehyde (or ketone) and an alcohol.



NBS is *N*-bromosuccinimide;

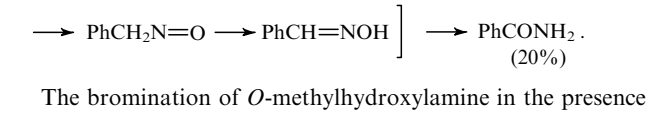


In some cases, hyponitrites are the final products of monohalogenation of *O*-alkylhydroxylamines.[45,46]



R = Et, Bu$^t$; XHal = $Br_2$, NaOCl, chloramine T.

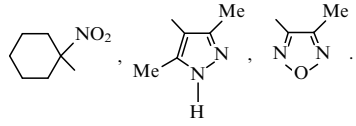
One of the possible pathways to hyponitrites in this reaction includes decomposition of *N*-halo-*O*-alkylhydroxylamines to alkoxynitrenes and their subsequent dimerisation.[43] The intermediate formation of benzyloxynitrene has also been assumed[4] for the chlorination of *O*-benzylhydroxylamine.[47]



The bromination of *O*-methylhydroxylamine in the presence of *C*-nitroso-derivatives affords diazene oxides in 5%–20% yields.[9]



XBr = $Br_2$, NBS;
R = $Me_2(NO_2)C$, $MeO_2CCMe_2$, Ph, 2,4-$(NO_2)_2C_6H_3$,



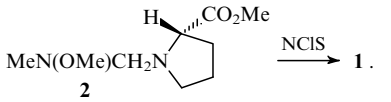
## III. *N*-Halo-*N*,*O*-dialkylhydroxylamines

This type of compound has been studied most comprehensively. Methods for synthesis of acyclic and cyclic *N*-chloro-, *N*-bromo-, and *N*-fluoro-derivatives have been developed; chemical properties of these derivatives have been studied.

## 1. Synthesis

The simplest representative of acyclic *N*-chloro-*N,O*-dialkylhydroxylamines, namely *N*-chloro-*N,O*-dimethylhydroxylamine **1**, has been prepared by chlorination of *N,O*-dimethylhydroxylamine [48] and by cleavage of aminal **2** upon treatment with *N*-chlorosuccinimide.[4]

$$MeNHOMe \xrightarrow[-10\ ^\circ C]{Bu^tOCl} \underset{\mathbf{1}\ (5\%)}{MeN(Cl)OMe},$$

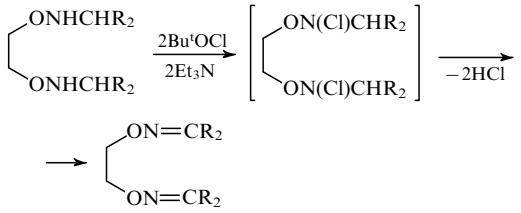



**2**

Compound **1** withstands vacuum distillation (b.p. 35 °C at 200 mm Hg). It was characterised by spectroscopic methods.[4, 48, 49] However, the attempts to synthesise other *N*-chloro-*N,O*-dialkylhydroxylamines containing an α-hydrogen atom in the *N*-substituent failed.[50, 51] These compounds are thermally unstable and are readily dehydrochlorinated to *O*-ethers of oximes.

$$R^1R^2CHNHOR^3 \cdot HCl \xrightarrow{NaOCl} [R^1R^2CHN(Cl)OR^3] \xrightarrow[-HCl]{} R^1R^2C{=}NOR^3$$

$R^1$ = Me, Et; $R^2$ = H, Et; $R^3$ = Et, Me.




R = H, Me.

Conversely, *N*-chloro-*O*-alkyl-*N*-*tert*-alkylhydroxylamines **3a**–**g** for which this dehydrochlorination is impossible are thermally stable under ambient conditions. They have been prepared by chlorination of the corresponding hydroxylamines [4, 48, 52–57] and by cleavage of *N*-*tert*-alkyl-*N*-methoxy-*O*-methylhydroxylamine **4** upon treatment with acyl chlorides or chlorotrimethylsilane.[58, 59]

$$R^1NHOR^2 \xrightarrow{Bu^tOCl} \underset{\mathbf{3a-g}}{R^1N(Cl)OR^2}$$

$R^1 = MeO_2CCMe_2$: $R^2$ = Me (**a**), Pr$^i$ (**b**);
$R^1 = MeO_2CCH_2CMe_2$: $R^2$ = Me (**c**), Pr$^i$ (**d**), $PhCH_2$ (**e**);
$R^1 = MeO_2CC(CF_3)Me$: $R^2$ = Me (**f**);
$R^1 = (EtO_2C)_2CHCMe_2$: $R^2$ = Me (**g**).

$$\underset{\mathbf{4}}{MeO_2CCMe_2N(OMe)_2} \xrightarrow{XCl} \underset{\mathbf{3a}}{MeO_2CCMe_2N(Cl)OMe}$$

XCl = AcCl, $CF_3COCl$, $SOCl_2$, $Me_3SiCl$.

The compound **3a** in a pure state decomposes over a period of 12 h at 20 °C,[4] whereas **3c** can be distilled *in vacuo* and remains unchanged in solution ($CCl_4$) for at least a month.[4]

The only known acyclic *N*-bromo-*N,O*-dialkylhydroxylamine **6** was synthesised by bromination of the oxime *O*-ether **5** in the presence of CsF.[60]

$$\underset{\mathbf{5}}{CF_2{=}NOCF_2CF_3} \xrightarrow{Br_2,\ CsF} \underset{\mathbf{6}\ (99\%)}{CF_3N(Br)OCF_2CF_3}.$$

The attempt to prepare *N*-bromo-*N*-*tert*-alkyl-*O*-methylhydroxylamine **7** was unsuccessful; this compound is unstable and undergoes further transformations under the reaction conditions.[59]

$$MeO_2CCMe_2N(OMe)_2 \xrightarrow[-AcOMe]{AcBr} \underset{\mathbf{7}}{[MeO_2CCMe_2N(Br)OMe]} \xrightarrow{AcBr}$$

$$\longrightarrow MeO_2CCMe_2N(Ac)OMe + MeO_2CNHOMe + MeO_2CCMe_2N(O){=}NCMe_2CO_2Me.$$

Acyclic fluorinated *N*-fluoro-*N,O*-dialkylhydroxylamines have been reported. These derivatives have been synthesised by fluorination of the corresponding NH-hydroxylamines,[61] oxime *O*-ethers,[60] and trifluoronitrosomethane [62] and by photochemical reaction of *N,N*-difluoroamines with trifluoromethyl peroxide.[63]

$$CF_3NHOC_2F_5 \xrightarrow{F_2} \underset{(98\%)}{CF_3N(F)OC_2F_5};$$

$$CF_2{=}NOCFXCF_3 \xrightarrow{F_2} CF_3N(F)OCFXCF_3$$

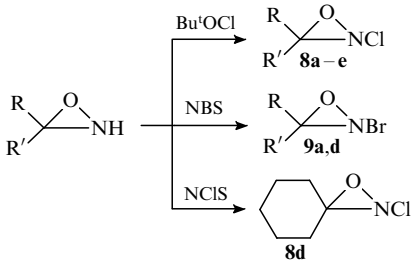
X = H (87%), Cl (62%);

$$CF_3N{=}O \xrightarrow{F_2} CF_3N(F)OCF_3 + CF_3ON(CF_3)_2 + CF_3ONF_2;$$

$$R_FNF_2 + (CF_3O)_2 \xrightarrow{h\nu} \underset{(5\%-17\%)}{R_FN(F)OCF_3} + \underset{(1\%-5\%)}{R_FN(OCF_3)_2}$$

$R_F = CF_3, C_3F_7$.

Apart from the acyclic *N*-halo-*N,O*-dialkylhydroxylamines described above, a number of cyclic analogues have also been described. 2-Haloxaziridines **8a**–**e** and **9a**,**d** have been obtained in two ways: by halogenation of the corresponding NH-oxaziridines and by oxidation of *N*-chlorimine **10**.[24, 25, 64, 65]




R = R′ = Me (**a**); R = Me, R′ = Et (**b**); R = R′ = Bu$^t$ (**c**);
R,R′ = $(CH_2)_5$ (**d**); R,R′ = $CH_2CH(Me)(CH_2)_3$ (**e**);

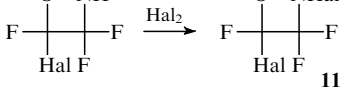



**10**

MCPBA is *m*-chloroperbenzoic acid;
MNPA is monoperphthalic acid.

The chloroxaziridines **8a**–**e** can be distilled *in vacuo* without decomposition; in a pure state, they can be kept unchanged for 1 month at 0 °C, while as solutions in $CDCl_3$, they are stable for 1 h at 100 °C in sealed tubes. The 2-bromoxaziridines **9a**,**d** are stable for 1 weak at 0 °C in inert solvents; neat compounds can be stored at −78 °C but vigorously decompose to give the corresponding ketone at temperatures above 0 °C.[65]

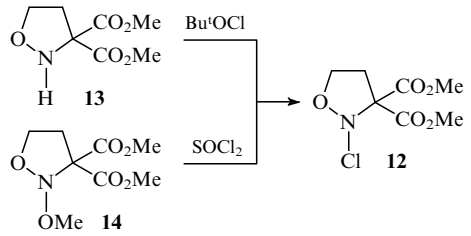
Thermally stable 2-chloro- and 2-fluoro-perhalo-1,2-oxazetidines **11** have been prepared by halogenation of the corresponding 1,2-oxazetidines.[23, 66]




**11**

Hal = Cl, F.

Dimethyl 2-chloro-1,2-oxazolidine-3,3-dicarboxylate **12** has been synthesised by the chlorination of 1,2-oxazolidine **13** [20] and by the reaction of the methoxy-derivative **14** with $SOCl_2$.[20, 58]

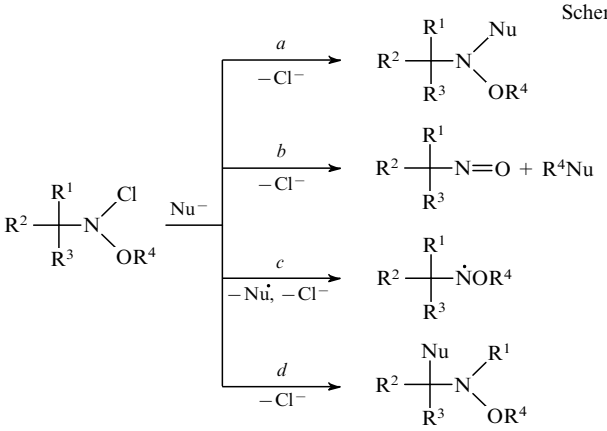


## 2. Reactions with nucleophiles

The chemical properties of acyclic *N*-chloro-*O*-alkyl-*N*-*tert*-alkylhydroxylamines, 2-haloxaziridines, and 2-chloro-1,2-oxazolidine **12** have been studied. For these compounds, reactions with nucleophilic reagents are most typical.

The transformations of *N*-chloro-*O*-alkyl-*N*-*tert*-alkylhydroxylamines under the action of nucleophilic reagents follow, as a rule, one of the four pathways shown in Scheme 1: (*a*) nucleophilic substitution of chlorine, (*b*) formation of *C*-nitroso-derivatives, (*c*) redox reactions, (*d*) 1,2-rearrangements.

Scheme 1



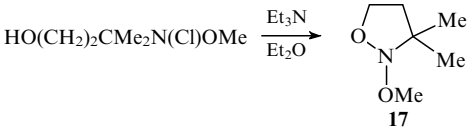
### a. Nucleophilic substitution of chlorine

*N*-Chloro-*O*-alkyl-*N*-*tert*-alkylhydroxylamines **3a**–**g** react smoothly with alcohols and glycols in the presence of bases to give *N*-alkoxy-*N*-*tert*-alkyl-*O*-alkylhydroxylamines **15** in 20%–85% yields.[4,48,53–58,67–69] In the case of secondary and tertiary alcohols, the reaction also affords diazene oxides **16** resulting from a competing redox reaction [pathway (*c*)]. In some cases, the compounds **16** are the only reaction products.[4,59]

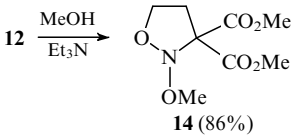
$$\underset{\mathbf{3a-g}}{R^1N(Cl)OR^2} \xrightarrow{R^3OH,\ B} \underset{\mathbf{15}}{R^1N(OR^3)OR^2} + \underset{\mathbf{16}}{R^1N(O)=NR^1}$$

$R^3$ = Me, Et, Pr$^i$, Bu$^t$, $PhCH_2$, $CF_3CH_2$, $HO(CH_2)_2$, $HO(CH_2)_3$;
B = $Et_3N$, $R^3ONa$.

The intramolecular version of this reaction has been used to synthesise *N*-methoxy-1,2-oxazolidine **17**; the product was obtained in 45% yield.[4,52]



Methanolysis of 2-chloro-1,2-oxazolidine **12** also proceeds smoothly.[20,58]

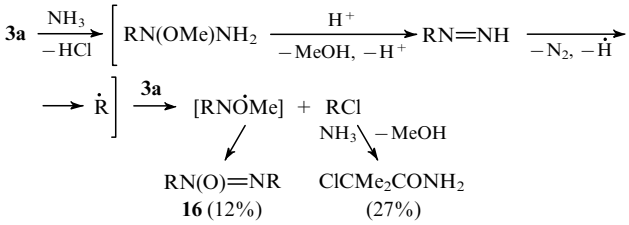


The products of nucleophilic substitution of chlorine were obtained in reactions of the compounds **3a**,**c** with sodium acetate, thiocyanate, and cyanide and also with a Grignard reagent.[10]

$$\underset{\mathbf{3a,c}}{RN(Cl)OMe} \xrightarrow[-Cl^-]{Nu^-} RN(Nu)OMe$$

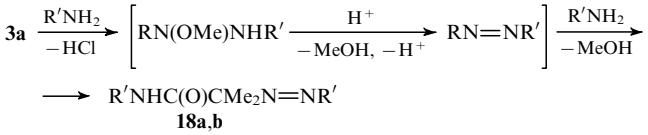
R = $MeO_2C(CH_2)_nCMe_2$: $n$ = 0, 1; Nu = AcO, NCS, CN, Et.

When *N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamines **3a**,**c** react with ammonia or amines, the corresponding *N*-methoxyhydrazine derivatives formed initially upon nucleophilic substitution of chlorine are unstable and decompose with elimination of MeOH. Thus the reaction of **3a** with $NH_3$ gave α-chloroisobutyramide and diazene oxide **16**.[70] This outcome can be explained by assuming that the intermediate *N*-methoxyhydrazine derivative decomposes to give NH-diazene, which undergoes homolytic cleavage yielding a *tert*-alkyl radical. The reaction of the latter with the initial compound **3a** followed by ammonolysis gives the final products.



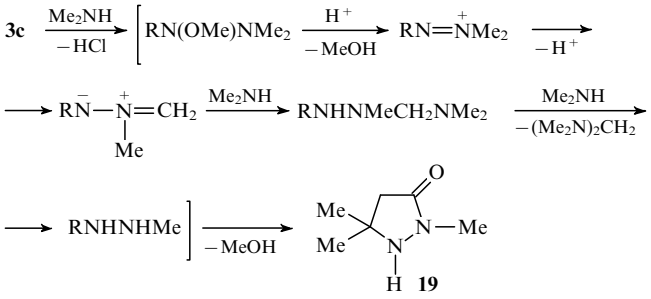
R = $MeO_2CCMe_2$.

In conformity with this scheme, the reactions of **3a** with primary amines give rise to non-symmetrical diazenes **18a**,**b**.[70]



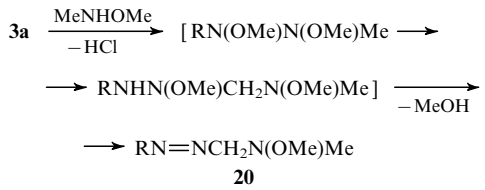
R = $MeO_2CCMe_2$; R′ = Me [**18a** (99%)], Et [**18b** (93%)].

Pyrazolidone **19** was obtained in 68% yield by the reaction of the compound **3c** with dimethylamine.[70] The formation of this product was explained in terms of a scheme including decomposition of the intermediate *N*-methoxyhydrazine derivative giving a diazenium salt, which then undergoes a typical cleavage with abstraction of the α-proton and generation of a zwitter-ion. This ion adds dimethylamine giving rise to a non-symmetrical aminal, which disproportionates yielding bis(dimethylamino)methane and the corresponding hydrazine; cyclisation of the latter affords the final reaction product.



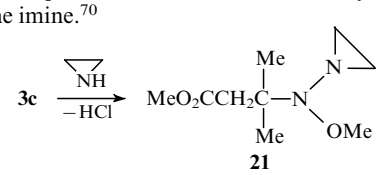
R = $MeO_2CCH_2CMe_2$.

When the compound **3a** reacts with a less basic *N*,*O*-dimethylhydroxylamine, the aminal formed by a similar scheme does not disproportionate; instead, it eliminates MeOH, which results in the formation of diazene **20** in 42% yield.[70]



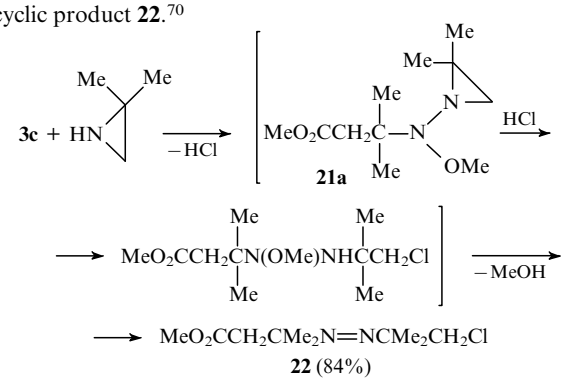
R = $MeO_2CCMe_2$.

Stable aziridine derivative **21** containing an *N*-methoxyhydrazine moiety was synthesised in 70% yield as the product of nucleophilic substitution of chlorine by reaction of **3c** with ethylene imine.[70]



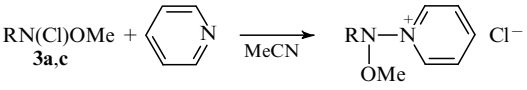
The instability of *N*-methoxyhydrazine derivatives [70] is due to the easy rupture of the N–O bond, caused by the vicinal $n_{N(1)}-\sigma^*_{N-O}$ orbital interaction. In the aziridine **21**, this interaction is weak, because the positive mesomeric effect of the ethylene imine nitrogen atom is low. This accounts for the stability of this compound.

Nevertheless, the reaction of the compound **3c** with 2,2-dimethylethylene imine under the same conditions affords the acyclic product **22**.[70]



It was assumed that, due the fact that 2,2-dimethylethylene imine is more basic than ethylene imine, the aziridine ring in the chlorine substitution product **21a** formed initially is cleaved under the action of HCl according to an $S_N2$ mechanism.

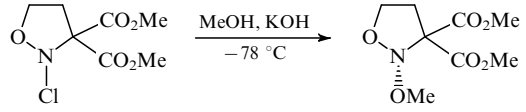
The reactions of **3a**,**c** with pyridine also occur as nucleophilic substitution of chlorine.[70]



R = $MeO_2CCMe_2$, $MeO_2CCH_2CMe_2$.

Based on kinetic studies, it was concluded that this reaction occurs by the $S_N2$ mechanism.[20]

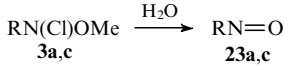
It was shown that methanolysis of optically active *N*-chloro-1,2-oxazolidine (+)-**12** (its synthesis is described in Section VIII) occurs with retention of the optical activity and affords *N*-methoxy-1,2-oxazolidine *R*-(−)-**14** with an optical purity of about 3%.[19,20] However, since the optical purity and the absolute configuration of the starting (+)-**12** are unknown, no reliable conclusions about the mechanism of this reaction can be drawn.



(+)-**12** (*R*)-(−)-**14**

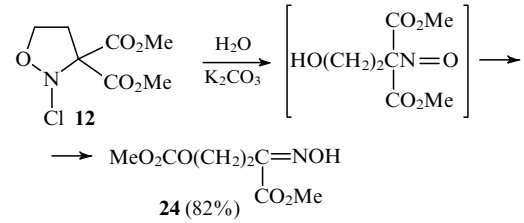
**b. Formation of *C*-nitroso-derivatives**

*C*-Nitroso-derivatives **23a**,**b** have been prepared by hydrolysis of *N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamines **3a**,**c** in the presence of $K_2CO_3$ [10,71] or $SbCl_5$.[71]

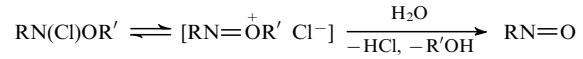


R = $MeO_2CCMe_2$ [**23a** (88%)], $MeO_2CCH_2CMe_2$ [**23c** (91%)].

Hydrolysis of *N*-chloro-1,2-oxazolidine **12** also gives rise to a nitrosoalkane. However, this product is unstable and rearranges to oxime **24** as a result of migration of the methoxycarbonyl group from the C atom to the O atom.[57]

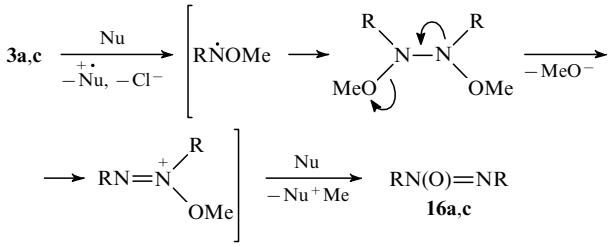


These reactions proceed presumably *via* intermediate nitrenium-oxonium ions. Water is a hard nucleophile; therefore, in conformity with the general principles outlined in Section I, it reacts with these ions with dealkylation of the oxonium centre.[10]



**c. Redox reactions**

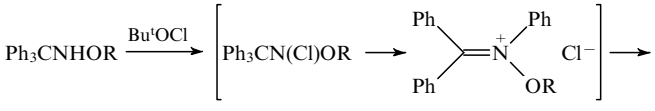
When *N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamines **3a**,**c** react with sterically hindered alcohols in the presence of $Et_3N$,[4] sterically hindered amines ($Et_3N$, $Et_2NH$),[10] Grignard reagents,[10] triphenylphosphine,[10] or sodium ethanethiolate,[10] nucleophilic substitution of chlorine is suppressed completely or partially by the competing redox reaction. This reaction affords *N*-substituted-*N*-methoxyaminyl radicals, dimerisation of which results in the formation of unstable 1,2-dimethoxyhydrazine derivatives. Decomposition of these compounds yields the final products, diazene oxides **16a**,**c**.

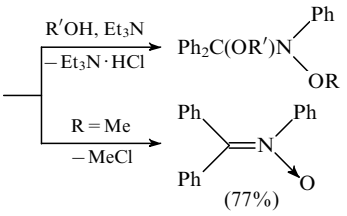


R = $MeO_2CCMe_2$ (**a**), $MeO_2CCH_2CMe_2$ (**c**).

**d. 1,2-Rearrangements**

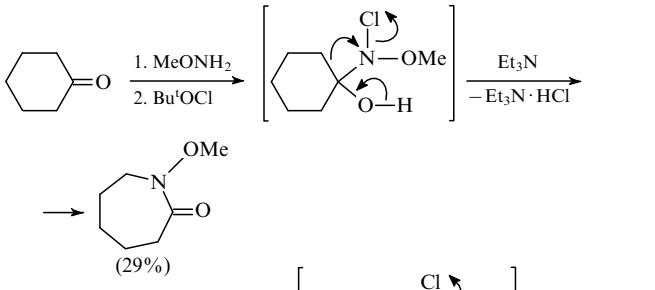
1,2-Rearrangement with migration of the phenyl group to the electron-deficient nitrogen atom is the predominant route of transformation of *N*-chloro-*O*-alkyl-*N*-triphenylmethylhydroxylamines under conditions of alcoholysis. This rearrangement occurs spontaneously even in the absence of an external nucleophile.[11]

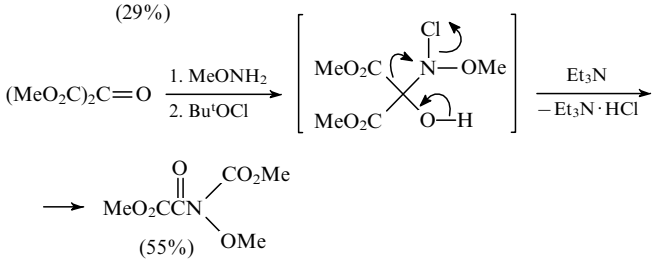





R = Me, $MeO_2CCMe_2$; R′ = Me, Et.

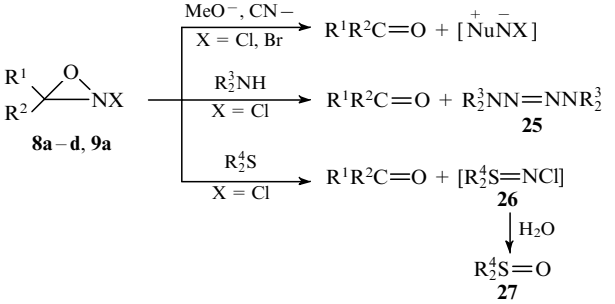
A 1,2-rearrangement with migration of the alkyl or methoxycarbonyl group from the carbon atom to the nitrogen atom was found in the chlorination of the adducts of $MeONH_2$ with cyclohexanone or dimethyl mesoxalate. The rearrangement products were isolated after treatment with $Et_3N$.[11]



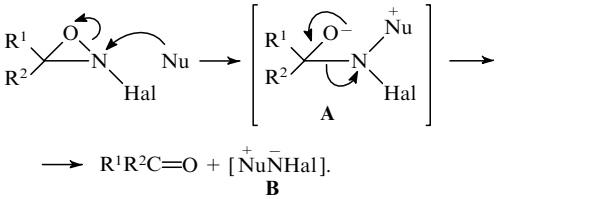




The mechanism of these rearrangements has not been studied; however, they are believed to involve the formation of intermediate nitrenium ions.

2-Haloxaziridines **8** and **9**, unlike *N*-chloro-*N*,*O*-dialkylhydroxylamines, possess relatively low reactivity with respect to nucleophiles. In addition, the reactions of these compounds with some nucleophiles, for example, $MeO^-$, $Me_2NH$, morpholine, dimethyl sulfide, and diisopropyl sulfide, occur as substitution of oxygen rather than chlorine, *i.e.* when the nucleophile attacks the nitrogen atom, an oxygen-containing anion becomes the leaving group.[65]



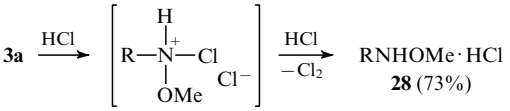

$R^1 = R^2 = Me$ (**a**); $R^1 = Me$, $R^2 = Et$ (**b**); $R^1 = R^2 = Bu^t$ (**c**); $R^1$, $R^2 = (CH_2)_5$ (**d**); $R^3_2 = Me_2$, $(CH_2)_2O(CH_2)_2$; $R^4 = Me$, $Pr^i$.



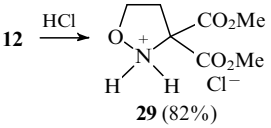

The intermediate **A** thus formed decomposes yielding the corresponding ketone and a substituted *N*-haloamine **B**. The latter reacts with amines giving rise to tetrazene **25** (apparently, *via* diazenium salt and *N*-aminonitrene) or reacts with dialkyl sulfides with formation of *N*-chlorosulfimines **26**. The formation of sulfoxides **27** in the reactions of **8a**,**d** with dialkyl sulfides was explained by hydrolysis of *N*-chlorosulfimines **26**.

## 3. Other reactions

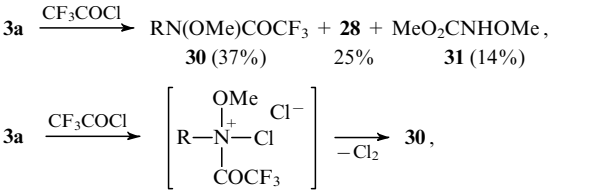
*N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamine **3a** [59] and oxazolidine **12** [20] react with gaseous HCl to give the corresponding hydrochlorides **28** and **29**.



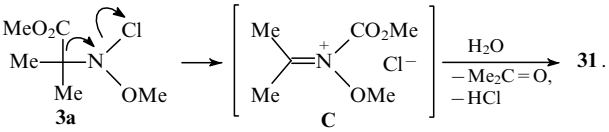

R = $MeO_2CCMe_2$.




The reaction of the compound **3a** with $CF_3COCl$ affords *N*-methoxytrifluoroacetamide **30**, the hydrochloride **28**, and methyl *N*-methoxycarbamate **31**.[59]



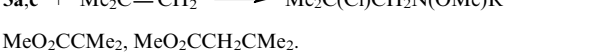

R = $MeO_2CCMe_2$.




Presumably, the trifluoroacetamide **30** is formed upon decomposition of the *N*-chloro-*N*-methoxy-*N*-trifluoroacetylammonium salt formed intermediately. *N*-Methoxcarbamate **31** results from 1,2-rearrangement of the compound **3a**, accompanied by migration of the methoxycarbonyl group, and subsequent hydrolysis of the resulting intermediate **C** by traces of water. The HCl evolved during this process reacts with the initial compound **3a** according to the scheme described above to give the hydrochloride **28**.

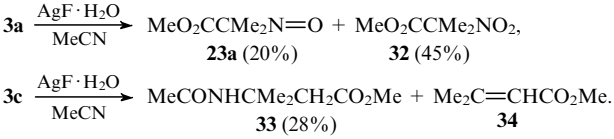
Treatment of **3a** with reagents facilitating ionisation or heterolytic rupture of the N–Cl bond, for example, $SO_2$ or $BF_3 \cdot Et_2O$, also results in 1,2-rearrangement.[59]

This is why $SO_2$ initiates the addition of *N*-chloro-*N*,*O*-dialkylhydroxylamines **3a**,**c** to isobutene.[55]

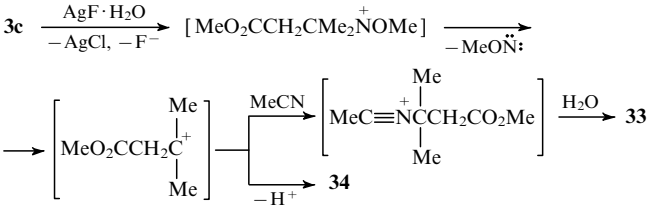



R = $MeO_2CCMe_2$, $MeO_2CCH_2CMe_2$.

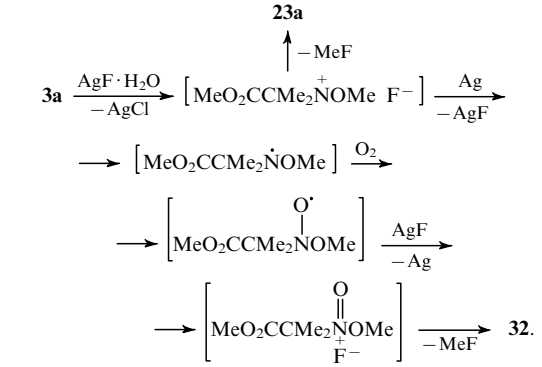
The reactions of **3a** and **3c** with $AgF \cdot H_2O$ in MeCN can follow different pathways depending on the nature of the alkyl substituent at the nitrogen atom.[10]



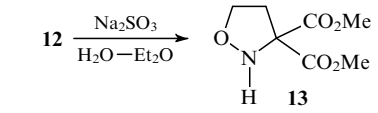
In the case of **3c**, this reaction was assumed to occur *via* elimination of methoxynitrene from the intermediate nitrenium ion to give a *tert*-alkyl cation, which is stabilised through the Ritter reaction with acetonitrile or deprotonation.[10]



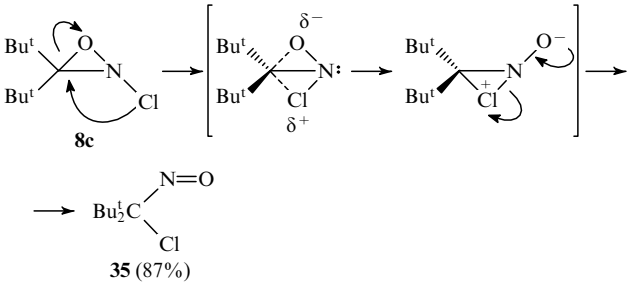
The same transformation of **3a** does not occur, because the corresponding *tert*-alkyl cation is less stable; therefore in this case, redox process predominates.[10]



*N*-Chloroxazolidine **12** is reduced by $Na_2SO_3$ to give 1,2-oxazolidine **13** in 67% yield.[20]



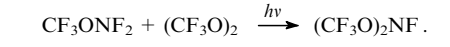
It was found that the sterically hindered 2-chloroxaziridine **8c**, unlike non-hindered **8a**,**b**,**d**, rearranges to α-chloronitrosoalkane **35**. The rearrangement of pure **8c** at 0 °C proceeds slowly, whereas that in $CDCl_3$ at 60 °C occurs over 15–20 min.[64,65] It was assumed[65] that this rearrangement occurs as intramolecular attack by chlorine on the carbon atom of the oxaziridine ring.



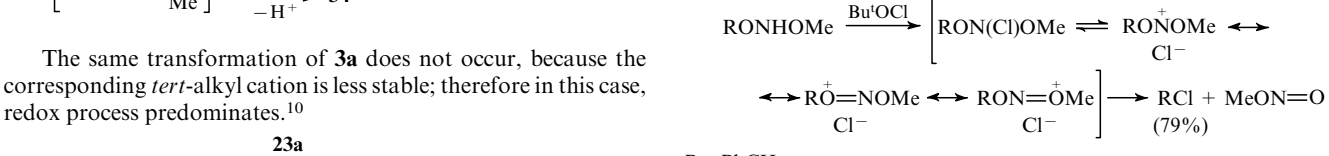
During photolysis of 2-chloroxaziridine **8c**, the corresponding oxaziridinyl radical was detected by EPR spectroscopy.[72]

## IV. *N*-Halo-*N*-alkoxy-*O*-alkylhydroxylamines

The only fluorine-containing compound of this type was prepared in 3% yield by photochemical reaction of *N*,*N*-difluoro-*O*-trifluoromethylhydroxylamine with trifluoromethyl peroxide.[63]



*N*-Bromo- and *N*-iodo-derivatives of *N*-alkoxy-*O*-hydroxylamines are unknown. *N*-chloro-derivatives are thermally unstable, due to the easy heterolysis of the N–Cl bond yielding dialkoxynitrenium ions stabilised by resonance; these ions undergo irreversible dealkylation through the action of the internal nucleophile, *i.e.* the chlorine atom. For instance, chlorination of *N*-benzyloxy-*O*-methylhydroxylamine by Bu$^t$OCl gives benzyl chloride and methyl nitrite resulting from decomposition of the intermediate *N*-chloro-*N*-benzyloxy-*O*-methylhydroxylamine, which could not be detected by $^1$H NMR spectroscopy even at −30 °C.[5]



R = $PhCH_2$.

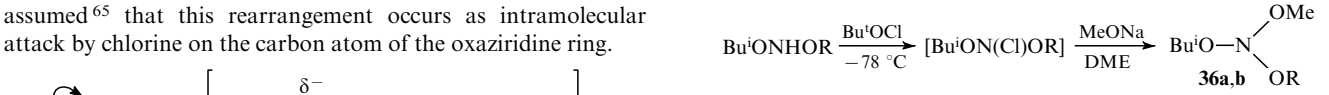
Nevertheless, *N*-chloro-*N*-methoxy-*O*-methylhydroxylamine was *in situ* involved in several reactions. It was found that in reactions with $Me_3N$ and pyridine, this compound, unlike *N*-chloro-*N*,*O*-dialkylhydroxylamines (Section III), acts as a methylating rather than an aminating reagent.[5]



Nu = $Me_3N$, Py.

This difference between the behaviour of *N*-chloro-*N*,*O*-dialkylhydroxylamines and *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines in the above reactions was explained[5] by the fact that the nitrogen electrophilic centre in the latter is 'harder' and, hence, the orbitally controlled addition of nucleophiles to the nitrenium centre becomes possible only for very 'soft' nucleophiles containing high-lying HOMO. A similar difference in the properties has also been noted for monoalkoxy- and dialkoxycarbenium cations.[73]

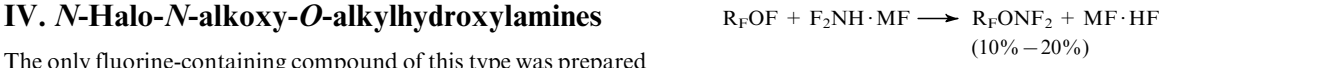
In accordance with the foregoing, nucleophilic substitution of chlorine in *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines occurs under the action of sodium methoxide and yields trialkoxyamines **36a**,**b** .[5,74]



R = Me [**36a** (64%)], Et [**36b** (50%)]; DME is dimethoxyethane.

## V. Derivatives of *N*,*N*-dihalohydroxylamines

The only known compounds of this type are *N*,*N*-difluorohydroxylamine derivatives. The data on the synthesis and properties of compounds of the general formula $XONF_2$, where X = $CF_3$, $C_2F_5$, $Cl(CF_2)_2$, $FOCH_2$, $F_2NOCH_2$, $(CF_3)_2N$, $FCO_2$, $FSO_2$, $SF_5$, published before 1976 have been surveyed in reviews.[27,28] Later, a method for the synthesis of *N*,*N*-difluoro-*O*-perfluoroalkylhydroxylamines by reaction of perfluroalkyl hypofluorites with difluoroamine–alkali metal fluoride complexes has been developed.[75]



$R_F$ = $CF_3$, iso-$C_3F_7$, $FOCF_2$; MF = KF, RbF, KF–NaF.

*N*,*N*-Difluorohydroxylamine derivatives have also been synthesised by reactions of trifluoroamine oxide with fluoroalkenes in the presence of Lewis acids ($BF_3$, $AsF_5$, $SbF_5$).[76,77]

$$RCF{=}CF_2 + F_3NO \xrightarrow{Cat.} RCF_2CF_2ONF_2$$

R = F, Cl, Br, $C_2F_5O$, $C_3F_7OCF(CF_3)CF_2O$;

$$RCF{=}CF_2 + F_3NO \xrightarrow{Cat.} RFC(CF_3)ONF_2$$

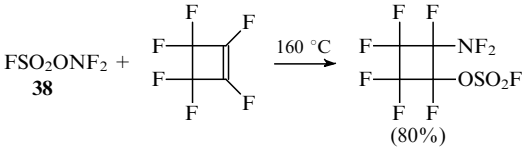
R = $CF_3$, $C_5F_{11}$, $SF_5$, FCO.

*N*,*N*-Difluorohydroxylamines **37** are cleaved by $AsF_5$ to give FNO, which is formed as a nitrosonium salt.[78]

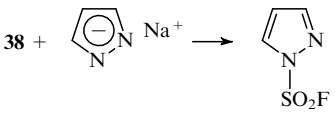
$$\underset{\mathbf{37}}{RONF_2} \xrightarrow{AsF_5} RF + NO^+AsF_6^-$$

R = $CF_3$, $SF_5$.

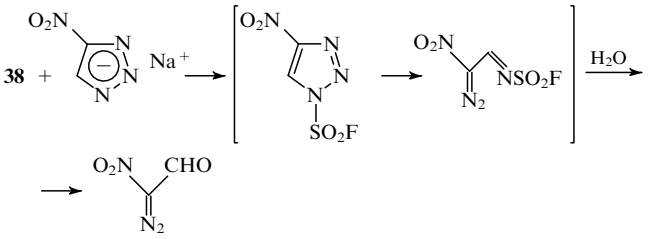
In reaction with perfluorocyclobutene, *O*-fluorosulfonyl-*N*,*N*-difluorohydroxylamine **38** acts as a pseudohalogen.[79]



The reactions of **38** with ethylnitramine, ethylenedinitramine, and salts of azoles (imidazoles, pyrazoles, triazoles) lead to *N*-fluorosulfonylation products.[80] The reaction of **38** with the sodium salt of pyrazole was reported to be an example.[80]



The reaction of the sodium salt of 4-nitrotriazole with the compound **38** is accompanied by ring opening. Subsequent hydrolysis affords formylnitrodiazomethane in 36% yield.[80]



## VI. *N*-Halo-*N*-alkoxyamides

As noted above, a typical feature of systems containing the O–N–Hal triad is polarisation of the N–Hal bond towards the halogen, which accounts for its anionic mobility. When the nitrogen atom carries an electron-withdrawing substituent, polarisation of the N–Hal bond decreases or even changes its direction, which has a substantial influence on the properties of these systems.

### 1. *N*-Halo-*N*-alkoxyphosphamides

*N*-Halo-*N*-alkoxyphosphamides **39**,[81] **40**,[38] and **41**[82] have been prepared by halogenation of the corresponding NH amides.

$$\underset{\mathbf{39a-d}}{(EtO)_2P(O)N(Cl)OR} \quad \underset{\mathbf{40a,b}}{(Me_2N)_2P(O)N(Cl)OR} \quad \underset{\mathbf{41}}{(EtO)_2P(O)N(Br)OBu^t}$$

R = Me (**a**), $PhCH_2$ (**b**), Bu (**c**), Et (**d**).

The compounds **39a–d** are stable in a benzene solution (withstand refluxing for several hours); however, in a pure state they decompose over a period of 2 days at 0–5 °C. They give the typical 'positive chlorine' reaction.[81] The addition of **39c** to styrene occurs by a radical mechanism and is not regiospecific yielding adducts **42** and **43** and some other products.[81]

$$\mathbf{39c} \xrightarrow{PhCH{=}CH_2} \underset{\mathbf{42}}{(EtO)_2P(O)N(OBu)CH_2CH(Cl)Ph} +$$

$$+ \underset{\mathbf{43}}{(EtO)_2P(O)N(OBu)CHPhCH_2Cl} + (EtO)_2P(O)OBu +$$

$$+ PhCH(Cl)CH_2Cl + ClCH_2CH(Ph)CH(Ph)CH_2Cl.$$

The attempts to carry out nucleophilic substitution of the chlorine atom in *N*-chloro-*N*-alkoxyphosphamides **39a** and **40a** failed. The reaction with MeONa in MeOH involves the phosphoryl group and is accompanied by elimination of the pseudohalogen fragment N(Cl)OMe.[38] The compound **39a** reacts with MeOH in the presence of $Et_3N$ giving rise to amide **44**.[38]

$$\mathbf{39a} \xrightarrow{MeOH,\ Et_3N} \underset{\mathbf{44}\ (71\%)}{(EtO)_2P(O)NHOMe}.$$

Photolysis of a solution of *N*-bromo-*N*-*tert*-butoxyphosphamide **41** in cyclopropane at −100 °C gave radical **45**, which was detected by EPR spectroscopy.[82]

### 2. *N*-Halo-*N*-alkoxysulfonamides

*N*-Halo-*N*-alkoxysulfonamides **46a–e**[1,38,83] and **47**[84,85] have been described.

$$\underset{\mathbf{46a-e}}{RSO_2N(Cl)OR'} \qquad \underset{\mathbf{47}}{RSO_2N(Br)OR'}$$

R = Me, R′ = Me (**a**), $MeSO_2$ (**b**);
R = 4-$MeC_6H_4$, R′ = Me (**c**);
R = $Me_2N$, R′ = $PhCH_2$ (**d**);
R = 2,6-$Me_2$-4-$Bu^tC_6H_2$, R′ = $Bu^t$ (**e**).

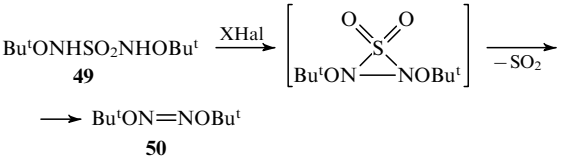
R = Me, $Me_2N$, 4-$O_2NC_6H_4$,
R′ = $Bu^t$; R = 4-$MeC_6H_4$,
R′ = Me, Et, $Pr^i$, $Bu^t$, $PhCH_2$;
R = 2,6-$Me_2$-4-$Bu^tC_6H_2$,
R′ = Me, $Bu^t$, $PhCH_2$.

The attempt to prepare the *N*-Br analogue of the compound **46a** resulted in the formation of 1,2-dimethoxyhydrazine derivative **48**.[83]

$$MeSO_2NHOMe \xrightarrow{NBS} [MeSO_2N(Br)OMe] \longrightarrow$$

$$\longrightarrow \underset{\mathbf{48}}{MeSO_2(MeO)N{-}N(OMe)SO_2Me}.$$

Halogenation of compound **49** yields hyponitrite **50**, apparently *via* the intermediate thiadiaziridine dioxide.[46,86]



XHal = NaOCl, NaOBr, chloramine T.

*N*-Halo-*N*-alkoxysulfonamides **46a**,**b**,**d** act as chlorinating reagents with respect to $H_2O$ and MeOH, being thus converted into the corresponding NH amides.[38,83] Thus compound **46c** chlorinates aniline into the aromatic ring.[1]

$$\mathbf{46c} + PhNH_2 \xrightarrow{EtOH-AcOH}$$

$$\longrightarrow 4\text{-}MeC_6H_4SO_2NHOMe + 4\text{-}ClC_6H_4NH_2.$$

Photolysis of solutions of *N*-bromo-*N*-alkoxysulfonamides **47** in $CFCl_3$ or in a mixture of $CFCl_3$ with $CH_2Cl_2$ at −30 to −60 °C is accompanied by the generation of the corresponding *N*-alkoxysulfonamidyl radicals, which have been detected by EPR spectroscopy.[84,85]

### 3. *N*-Halo-*N*-alkoxycarbamates

The only known compound of this type, methyl *N*-chloro-*N*-methoxycarbamate **52**, was synthesised by chlorination of the *N*-methoxycarbamate **51**. It can be distilled *in vacuo* without decomposition; upon treatment with MeOH and $Et_3N$ it is converted into the initial *N*-methoxycarbamate **51** and hydrazine derivative **53**.[87,88]

$$MeO_2CNHOMe \xrightarrow{Bu^tOCl} \underset{\mathbf{52}}{MeO_2CN(Cl)OMe} \xrightarrow[-Et_3\overset{+\cdot}{N},\ -Cl^-]{MeOH,\ Et_3N} [\,MeO_2C\dot{N}OMe\,] \longrightarrow \underset{(30\%)}{\mathbf{51}} + \underset{\mathbf{53}\ (36\%)}{MeO_2C(MeO)N{-}N(OMe)CO_2Me}$$

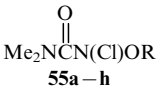
### 4. *N*-Chloro-*N*-alkoxyureas

*N*-Chloro-*N*-alkoxyureas **54**,[89,90] **55a–h**,[38,91,92] **56**,[8,93,94] and **57a–i**[95] have been prepared by chlorination of the corresponding NH ureas with $Bu^tOCl$.



**54**

R = Me, R′ = Me, $PhCH_2$;
R = Et, R′ = Me.



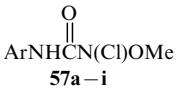
**55a–h**

R = Me (**a**), $Bu^i$ (**b**), $CH_2{=}CHCH_2$ (**c**), $PhCH_2$ (**d**), $MeO_2CCH_2$ (**e**), $MeO_2CCH_2CH_2$ (**f**), $MeO_2CCMe_2$ (**g**), $HOCH_2CMe_2$ (**h**).



**56**

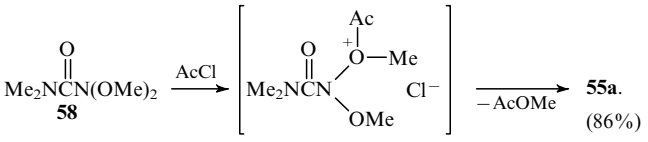
*n* = 0, 2, 3.



**57a–i**

Ar = Ph (**a**), 4-$ClC_6H_4$ (**b**), 4-$O_2NC_6H_4$ (**c**), 4-$MeC_6H_4$ (**d**), 4-$CNC_6H_4$ (**e**), 4-$MeSO_2C_6H_4$ (**f**), 3-$F_3CC_6H_4$ (**g**), 3,4-$Cl_2C_6H_3$ (**h**), 2,6-$Me_2C_6H_3$ (**i**).

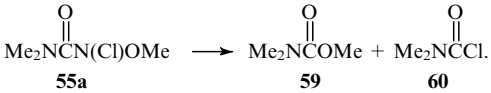
The compound **55a** was also obtained by cleavage of *N*,*N*-dimethoxyurea **58** upon treatment with acetyl chloride.[96]



**58**

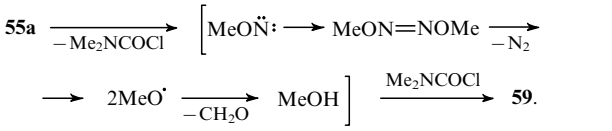
**55a**. (86%)

*N*-Chloro-*N*-alkoxyureas **54**, **55a–h**, **56**, and **57a–i** are non-distillable liquids or crystalline solids stable under ambient conditions. At room temperature in a $CCl_4$ solution, **55a** completely decomposes over a period of 25 days to give methyl *N*,*N*-dimethylcarbamate **59** and *N*,*N*-dimethylcarbamoyl chloride **60** in 1 : 1 ratio.[38]

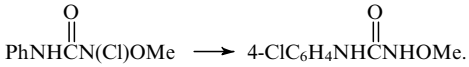


**55a** **59** **60**

The carbamoyl chloride **60** results presumably from a concerted rearrangement with migration of chlorine to the carbonyl group and ejection of methoxynitrene (HERON rearrangement).[97] The driving force of this migration is the orbital $n_o - \sigma^*_{N-Cl}$ interaction in the O – N – Cl structural fragment. The *N*,*N*-dimethylcarbamate **59** is formed in this process upon interaction of *N*,*N*-dimethylcarbamoyl chloride with the MeOH produced among the products of decomposition of the intermediate methoxynitrene;[38] this process is shown below:

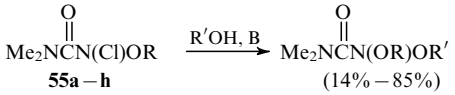


Among *N*-chloro-*N*-methoxyureas **57a–i**, only those which contain electron-withdrawing substituents in the aryl group are thermally stable under ambient conditions. The compound **57a** isomerises at room temperature giving *N*-(4-chlorophenyl)-*N*′-methoxyurea.[95]



**57a**

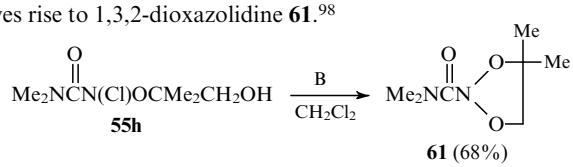
*N*-Chloro-*N*-alkoxyureas readily undergo nucleophilic substitution of chlorine atoms, because the carbamoyl group does not have any significant effect on the polarisation of the N – Cl bond. This also accounts for the similarity of chemical properties of *N*-chloro-*N*-alkoxyureas and *N*-chloro-*N*,*O*-dialkylhydroxylamines (see Section III). Thus *N*-chloro-*N*-alkoxyureas **54–56** react with alcohols and glycols in the presence of bases affording *N*,*N*-dialkoxyureas.[8,38,89–94] For instance, these reactions have been described for **55a–h**.[38]



**55a–h** (14% – 85%)

B = R′ONa, collidine, NaOAc;
R′ = Me, Et, $Bu^i$, $CH_2{=}CHCH_2$, $CF_3CH_2$, $HO(CH_2)_2$.

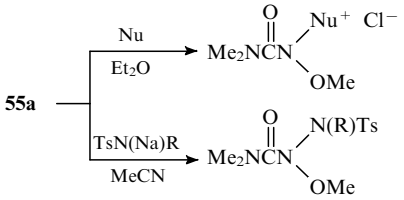
Intramolecular cyclisation of *N*-chloro-*N*-alkoxyurea **55h** gives rise to 1,3,2-dioxazolidine **61**.[98]



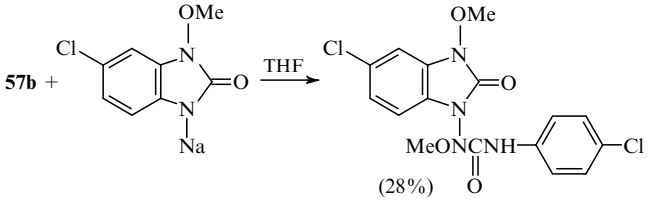
**55h** **61** (68%)

B is collidine.

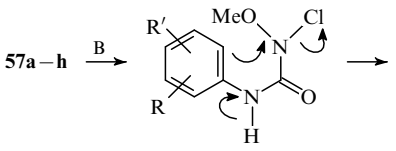
Products of nucleophilic substitution of chlorine in *N*-chloro-*N*-methoxyureas **55a** and **57b** were also obtained with other nucleophilic reagents.[95,99]

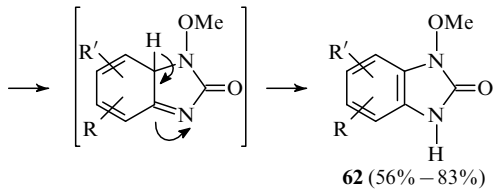


Nu = $Me_3N$, Py; R = Me, Ph.



On treatment with bases, *N*-chloro-*N*-methoxyureas **57a–h** cyclise to give 1-methoxy-2-benzimidazolinones **62**.[95]

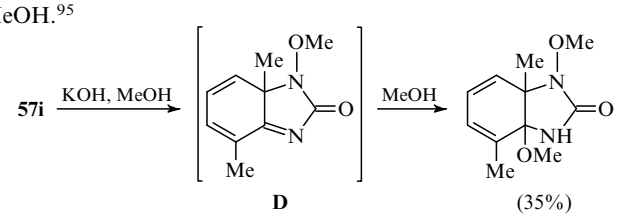




**62** (56% – 83%)

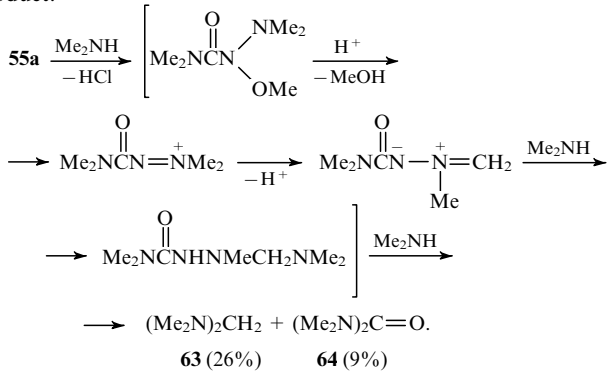
B = Bu$^t$OK, NaH.

The formation of non-aromatic intermediate **D** during the cyclisation of **57i** was proved by isolation of its adduct with MeOH.[95]



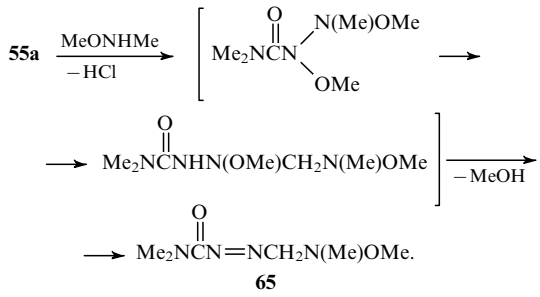
**D** (35%)

The reaction of *N*-chloro-*N*-methoxyurea **55a** with $Me_2NH$ affords bis(dimethylamino)methane **63** and the urea **64**;[99] these products are formed *via* a scheme similar to that considered in Section III for the reaction of *N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamine **3c** with $Me_2NH$. Dimethylurea **64** results apparently from carbamoylation of $Me_2NH$ by an intermediate product.



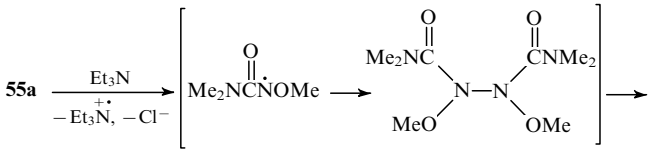
**63** (26%) **64** (9%)

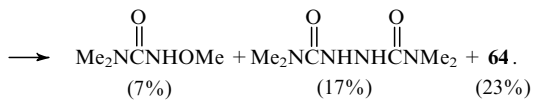
The reaction of *N*-chloro-*N*-methoxyurea **55a** with *N*,*O*-dimethylhydroxylamine affords diazene **65** in 38% yield.[99] This reaction proceeds presumably according to a similar scheme except that the intermediate aminal does not disproportionate, but instead, it eliminates MeOH yielding the product **65**.



**65**

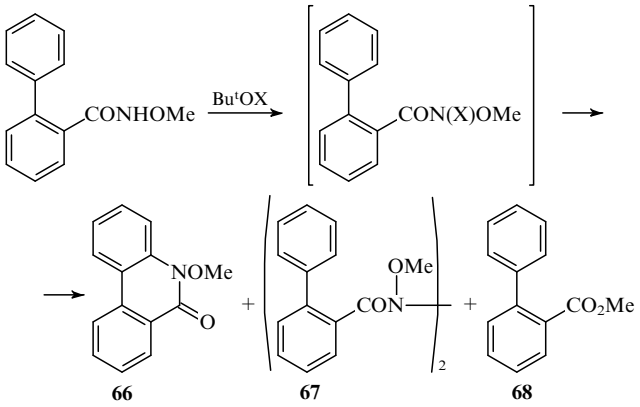
In the reaction of *N*-chloro-*N*-methoxyurea **55a** with $Et_3N$, nucleophilic substitution of chlorine is hampered for steric reasons. Therefore, a redox reaction occurs, the final products of which are formed upon transformations of the *N*-methoxycarbamidyl radical and substituted 1,2-dimethoxyhydrazine formed as intermediates.[99]





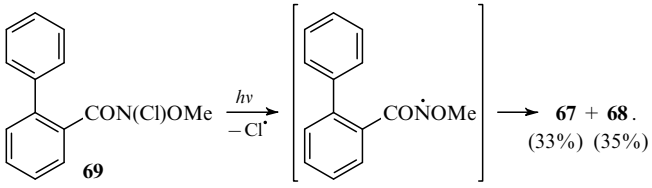
## 5. *N*-Halo-*O*-alkylhydroxamates

Among compounds of this type, only *N*-chloro-derivatives are known; they are synthesised by the chlorination of the corresponding NH hydroxamates with Bu$^t$OCl. The attempts to iodinate and brominate *N*-methoxyamide of biphenyl-2-carboxylic acid resulted in the formation of *N*-methoxy-phenathridone **66**, hydrazine derivative **67**, and the product of its decomposition **68**.[13,37]

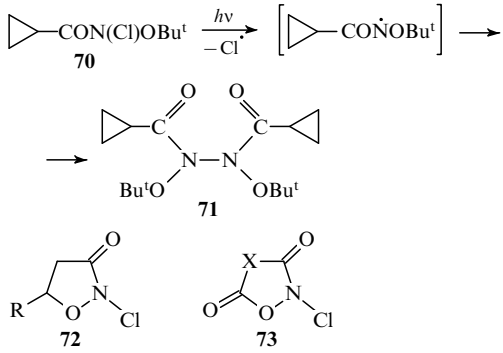


X = Br, I.

Conversely, *N*-chloro-*N*-methoxyamide **69** is stable under ordinary conditions; its photolysis is accompanied by rupture of the N–Cl bond and gives the hydrazine **67**, resulting from dimerisation of the intermediate *N*-methoxyamidyl radical, and compound **68**.[13,37]

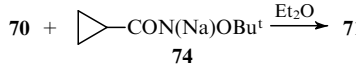


*N*-Alkoxyamidyl radicals have been detected by EPR spectroscopy during the photolysis of *N*-chloro-*O*-alkylhydroxamates **70**,[100] **72**, and **73**.[101]

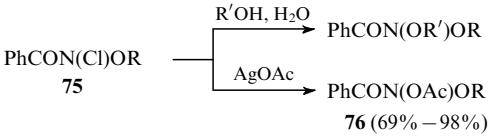


R = H, Ph; X = $Et_2C$, PhN, MeN.

Similarly to *N*-chloro-*N*-alkoxyureas, *N*-chloro-*O*-alkylhydroxamates are able to undergo nucleophilic substitution of chlorine. Thus reaction of the compound **70** with sodium salt **74** gives hydrazine derivative **71** in a quantitative yield.[100]

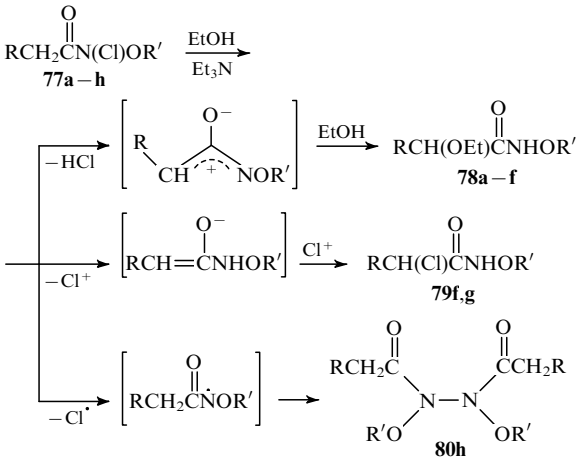


Two other reactions of *N*-chloro-*N*-alkoxybenzamides **75** — alcoholysis[102, 103] and transformation into *N*-acetoxy-*N*-alkoxybenzamides **76** on treatment with silver acetate in ether — also proceed smoothly.[102, 104]



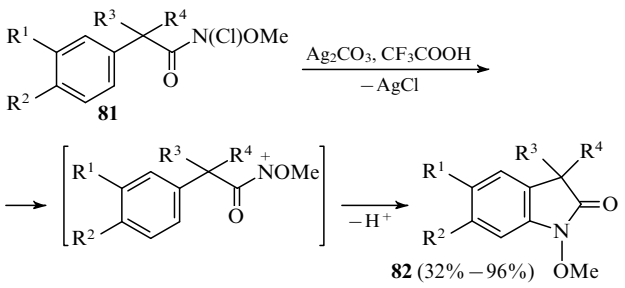

R = Et, Bu, $C_8H_{17}$, $PhCH_2$.

However, alcoholysis of *N*-chloro-*N*-alkoxyarylacetamides **77a – h** does not result in nucleophilic substitution of chlorine.[105] Depending on the nature of the substituent R, these reactions give mostly compounds **78 – 80**.




R = Ph, R′ = Me (**a**), $PhCH_2$ (**b**), Bu$^t$ (**c**); R = 4-$MeOC_6H_4$, R′ = Me (**d**); R = 2-naphthyl, R′ = Me (**e**); R = 4-$O_2NC_6H_4$, R′ = Me (**f**); R = PhCO, R′ = $PhCH_2$ (**g**); R = $PhCH_2$, R′ = Me (**h**).

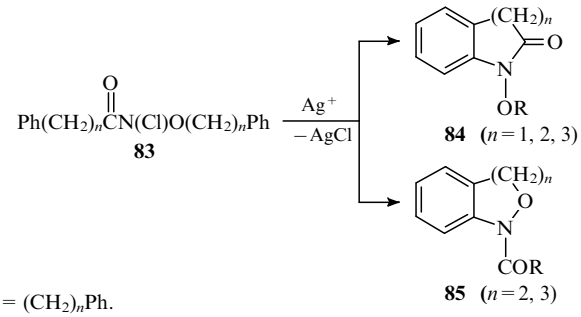
An important characteristic feature of *N*-chloro-*O*-alkylhydroxamates is their ability to be converted on treatment with Lewis acids into highly reactive intermediates, *N*-acyl-*N*-alkoxynitrenium ions,[12 – 18, 33] which tend to undergo inter- and intramolecular electrophilic aromatic substitution. As a rule, these reactions occur at room temperature in the presence of metal ions ($Ag^+$, $Zn^{2+}$, $Pd^{2+}$, $Fe^{2+}$, $Hg^{2+}$). The best results were achieved by using $AgBF_4$ – THF, $Ag_2CO_3$ – $CF_3COOH$, and $Zn(OAc)_2$ – $MeNO_2$ systems. For instance, cyclisation of *N*-chloro-*N*-methoxyarylacetamides **81** is an efficient method for the synthesis of 2-hydroxy-1-methoxyindoles **82**.[12, 14, 16 – 18]




$R^1 = R^3 = R^4 = H$, $R^2$ = Cl, Br, Me, MeCONH, $NO_2$; $R^1 = R^2$ = MeO, $R^3 = R^4 = H$; $R^1 = R^3 = R^4 = H$, $R^2 = NO_2$; $R^1 = R^4 = H$, $R^2$ = MeO, $R^3$ = Me; $R^1 = H$, $R^2$ = MeO, $R^3 = R^4$ = Me.

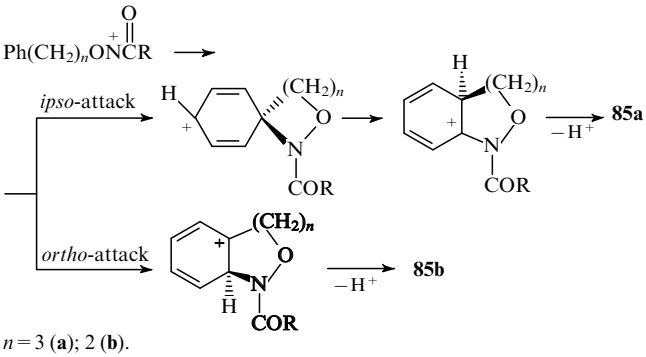
In principle, the electrophilic attack by the intermediate nitrenium ion is directed at one of three positions in the aromatic ring, C(1), C(2), or C(6).[18] When the aromatic ring contains an *ortho*-substituent, the nitrenium ions attack C(2) and C(6).

Cyclisation of *N*-chloro-*O*-alkylhydroxamates **83** can involve the aromatic ring of both arylacyl and arylalkoxyl substituents.[14, 15]



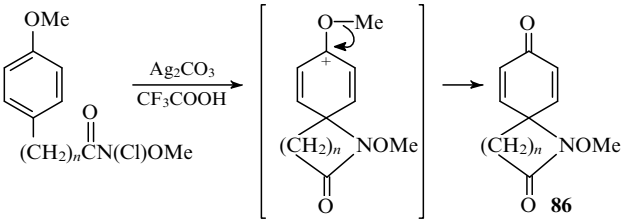

R = $(CH_2)_n$Ph.

In the former case, the reaction yields γ, δ, and ε-*N*-alkoxylactams **84**, while in the latter case, it gives 2,1-benzoxazepines and 2,1-benzoxazines but not benzoxazoles. It was shown experimentally[15] that benzoxazepines result from the *ipso*-attack of the intermediate nitrenium ion on the aromatic nucleus followed by 1,2-migration of the alkyl group, while benzoxazines are formed upon the *ortho*-attack.

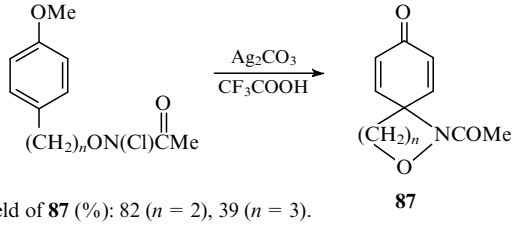



*n* = 3 (**a**); 2 (**b**).

The cyclisation of *N*-chloro-*O*-alkylhydroxamates containing an *ortho*- or *para*-methoxy-substituted aryl group occurs through the *ipso*-attack of the intermediate nitrenium ion on the aromatic ring and affords spirodienones.[14, 18] For example, compounds **86** and **87** have been prepared in this way.[18]

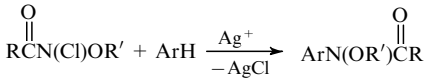



Yield of **86** (%): 71 (*n* = 1), 83 (*n* = 2), 83 (*n* = 3);




Yield of **87** (%): 82 (*n* = 2), 39 (*n* = 3).

*N*-Chloro-*O*-alkylhydroxamates are able to accomplish electrophilic amination of aromatic compounds in the presence of silver salts to give *N*-alkoxy-*N*-arylamides in 20% – 93% yields.[12 – 14, 16, 18]




ArH = $C_6H_6$, PhMe, *p*-$MeC_6H_4$, PhOMe, $C_{10}H_8$, PhCOOMe.

## VII. Structure and stereochemistry

The stereoisomerism of molecules with a tricoordinated nitrogen atom is due to its pyramidal configuration. However, usual

*N*-alkylamines possess low configuration stabilities; the barriers to their pyramidal inversion ($\Delta G^{\neq}$) amount to 20–30 kJ mol$^{-1}$.[106–108] An electronegative substituent at the nitrogen atom increases the inversion barriers by inducing rehybridisation of the bonding orbitals of the N atom accompanied by an increase in the *p*-character of the N–X σ-bond and, correspondingly, by an increase in the *s*-character of the nitrogen lone pair orbital.[106–108] In addition, the planar transition state of the inversion is destabilised by the four-electron interaction between the lone pairs of the two linked heteroatoms. Both effects act in the same direction increasing the pyramidal stability. Indeed, the barriers to inversion in *N*,*N*,*O*-trialkylhydroxylamines[109] and in *N*-chloro-[110,111] and *N*-fluoroamines[111] are as high as 40–50, 38, and 63 kJ mol$^{-1}$, respectively. The presence of two heteroatoms at the nitrogen atom in the O–N–Hal system accounts for the substantially increased configurational stability of the corresponding derivatives. In this case, the orbital $n_O-\sigma^*_{N-Hal}$ interaction also contributes to the stabilisation of the pyramidal configuration of the N atom.[29,34,112,113] The inversion barriers in the *N*-chloro-*N*,*O*-dialkylhydroxylamines **3a**,**c**,**g** are 79–83 kJ mol$^{-1}$.[4] The inversion barrier predicted[4] for *N*-fluoro-*N*,*O*-dialkylhydroxylamines is 113 kJ mol$^{-1}$.

When the N atom is incorporated in a ring, its pyramidal stability further increases, because in this situation, the change of the nitrogen hybridisation to $sp^2$ in the planar transition state to inversion increases ring strain. Naturally, this effect is more pronounced in rigid bicyclic systems and in small rings. For instance, the inversion barrier in 2-chloro-1,2-oxazolidine **12** ($\Delta G^{\neq}$ = 87 kJ mol$^{-1}$)[19,20] is, on the average, 7 kJ mol$^{-1}$ higher than that in its acyclic analogues **3**.[4] The nitrogen inversion in 2-chloro- and 2-fluoro-substituted perhalo-1,2-oxazetidines **11** is also hindered under normal conditions,[22] and the corresponding 4-monochloro-derivatives have been obtained as stable invertomers.[23] The record-holding height of the barrier to the pyramidal inversion of nitrogen *via* a planar transition state ($\Delta H^{\neq}$ = 184.8 kJ mol$^{-1}$) was predicted for non-substituted 2-chloroxaziridine by *ab initio* calculations in the 3–21G basis set.[26] However, the barrier for 2-chloroxaziridine found experimentally based on the kinetics of racemisation was almost three times lower ($\Delta H^{\neq}$ = 63.9 kJ mol$^{-1}$, $\Delta S^{\neq}$ = 43.5 e.u., and $\Delta G^{\neq}$ = 132 kJ mol$^{-1}$ at 100 °C in *n*-heptane), and, besides, the rate of inversion increased by an order of magnitude on going to a polar solvent (*n*-butanol).[26] This was explained by assuming that in this case, inversion occurs by a dissociative mechanism, because inversion *via* a planar transition state is characterised by low $\Delta S^{\neq}$ values and slows down in polar solvents due to the more efficient solvation of the ground state, which is more polar (the calculation for 2-chloroxaziridine in the same basis set predicts the values $\mu$ = 2.7 and 3.6 D for the transition and ground states, respectively). The transition state to the dissociative inversion is represented by a contact ion pair, because ionic mobility of chlorine is not manifested in reactions of 2-chloroxaziridines **8a**–**d** and **9a**.[65] The driving force of ionisation is the orbital $n_O-\sigma^*_{N-Cl}$ interaction, which results, according to the 2-chloroxaziridine structure optimised in the 6–31G* basis set, in a substantially lengthened N–Cl bond.[25]

The introduction of a π-electron-withdrawing substituent to the nitrogen atom sharply decreases the barrier to its inversion, because π-conjugation is most efficient in the planar transition state.[106,107] In fact, the calculated inversion barrier for *N*-chloro-*N*-formyl-*O*-methylhydroxylamine is only 10.5 kJ mol$^{-1}$.[34] For this compound, two other hindered processes can be expected, namely, amide rotation and rotation around the N–O bond with the maximum barriers of 47 and 55 kJ mol$^{-1}$, respectively.[34] The latter is ~10 kJ mol$^{-1}$ higher than the barriers to rotation around the N–O bond in *N*,*N*,*O*-trialkylhydroxylamines.[109] This increase in the barrier to the rotation around the N–O bond in *N*-chloro-*N*-formyl-*O*-methylhydroxylamine is due to the orbital $n_O-\sigma^*_{N-Cl}$ interaction, which makes the N–O bond 'more double'.[34] The height of this barrier is in good agreement with the experimental $\Delta G^{\neq}_{N-O}$ value, equal to 58 kJ mol$^{-1}$, which was determined for *N*-chloro-*N*-alkoxyurea **55g** by dynamic NMR.[114] In *N*-chloro-*N*-alkoxyureas **55a**,**e**,**g**, hindered rotation around the $Me_2N$–C amide bond is also observed, the corresponding barriers being 60–67 kJ mol$^{-1}$.[114]

There are no experimental data about the structures of *N*-halohydroxylamines. The results of semiempirical and non-empirical calculations for 2-chloroxaziridine,[25,65,115] *N*-chlorohydroxylamine,[33] *N*-chloro-*N*-methylhydroxylamine,[65] *N*-chloro-*N*-formylhydroxylamine,[33] *N*-chloro-*N*-formyl-*O*-methylhydroxylamine,[34] *N*-fluorohydroxylamine,[116–121] *N*,*N*-difluorohydroxylamine,[119,121] *N*,*O*-difluorohydroxylamine,[119–121] trifluorohydroxylamine,[119,121] and *N*,*N*-difluoro-*O*-fluorosulfonylhydroxylamine[122] demonstrate that their geometry is affected by the anomeric $n_O-\sigma^*_{N-Hal}$ interaction, which is manifested as elongation of the N–Hal bonds and shortening of the N–O bonds in these compounds. In addition, it was shown that the energetically preferred conformation for *N*-chloro-[33] and *N*-fluorohydroxylamines[116–121] as well as for *N*-chloro-*N*-formylhydroxylamine[33] and *N*-chloro-*N*-formyl-*O*-methylhydroxylamine[34] is that in which the H–O (or C–O) and N–Hal bonds are nearly perpendicular to each other and, hence, the anomeric $n_O-\sigma^*_{N-Hal}$ interaction is the maximum (Fig. 2, conformation **A**).

In the case of di- and trifluorohydroxylamines, conformation

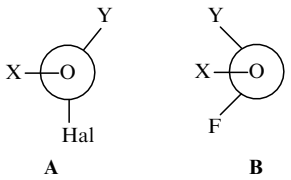
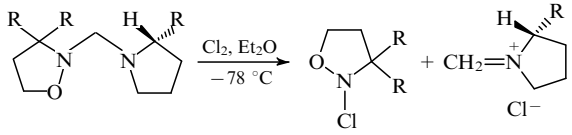



**Figure 2.** Newman projections along the O–N bond for N-halohydroxylamine derivatives XON(Y)Hal. **A**: X = Y = H, Hal = Cl, F; X = H, Y = HCO, Hal = Cl; X = Me, Y = HCO, Hal = Cl; **B**: X = H, Y = F; X = F, Y = H; X = Y = F.

**B** (Fig. 2) has been predicted to be more stable; this conformation is stabilised by the $n_N-\sigma^*_{O-F}$ interaction, which is the most efficient in *O*-fluorohydroxylamine.

## VIII. Optically active cyclic *N*-chlorohydroxylamines

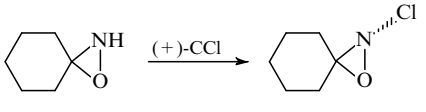
The first optically active compound of this type, (+)-2-chloro-1,2-oxazolidine (+)-**12**, in which only the nitrogen atom was chiral, was prepared in a quantitative yield by cleavage of aminal (*S*)-(−)-**88** by chlorine at −78 °C.[19,20]




(*S*)-(−)-**88** (+)-**12**

R = $MeO_2C$.

However, the time needed for its half-racemisation at 13 °C is only 8 min. The high configurational stability of 2-chloroxaziridines, the half-racemisation time of which at 20 °C is 833 years, made it possible to synthesise them in optically active forms by asymmetric chlorination and kinetic resolution.[24,25]




(2*S*)-(−)-**8d**

CCl is *N*-chlorocamphorimide;

**8d** $\xrightarrow{\text{1-Eph}}$ (2*R*)-(+)-**8d**,

**8e** $\xrightarrow{\text{1-Eph}}$ (5*S*)-(+)-**8e**

1-Eph is 1-ephedrine.

The absolute configurations of **8d** and **8e** were determined by NMR and CD methods.[25] The compound (5*S*)-(+)-**8e** was prepared as a mixture of two diastereoisomers in a ratio of 1.5 : 1, the absolute configuration of the predominant isomer being (2*R*,3*S*,5*S*). The sign of the Cotton effect of the long-wave band in the CD spectrum of optically active 2-chloroxaziridines was shown to be mostly determined by the absolute configuration of the N atom and to depend only slightly on the configurations of the carbon chiral centres.[25]

## IX. Conclusion

Analysis of the published data demonstrates that during the four decades of studies on the chemistry of *N*-halohydroxylamine derivatives, substantial progress has been achieved in this field. All main types of these compounds have been synthesised, namely, acyclic and cyclic *N*-halo-*N*,*O*-dialkylhydroxylamines, *N*-fluoro-*N*-alkoxy-*O*-alkylhydroxylamines, derivatives of *N*,*N*-difluorohydroxylamine, and *N*-halo-*N*-alkoxyamides. It was found that *N*-halo-*O*-alkylhydroxylamines and *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines are thermally unstable under ambient conditions; nevertheless, they can be involved *in situ* in various chemical reactions.

The halogen atom in most of the systems containing the O – N – Hal triad can be easily removed as the anion, which is due to the hyperconjugation $n_O - \sigma^*_{N-Hal}$. Hence, *N*-chloro-*N*-*tert*-alkyl- and *N*-chloro-*N*-alkoxy-*O*-alkyl-hydroxylamines are powerful alkoxyaminating reagents.

A fundamentally important result obtained along this line is the discovered possibility of nucleophilic substitution of chlorine in '*N*-chloramides': *N*-chloro-*N*-alkoxyureas and *N*-chloro-*O*-alkylhydroxamates the chlorine atom of which, unlike that in their *N*-alkyl analogues, possesses anionic mobility. Under the action of Lewis acids, *N*-chloro-*O*-alkylhydroxamates form highly reactive intermediates, *N*-acyl-*N*-alkoxynitrenium ions, capable of reacting with aromatic compounds in intermolecular and intramolecular processes of elecrophilic aromatic substitution.

Compounds containing O – N – Hal fragments belong to one of the few types of derivatives characterised by high pyramidal stability of the nitrogen atom. As a result, 2-chloroxaziridines and 2-chloro-1,2-oxazolidine derivatives have been partially resolved into optical antipodes with an asymmetric N atom.

The orbital $n_O - \sigma^*_{N-Hal}$ interaction in O – N – Hal systems accounts for the predominant existence of the conformation with nearly *anti*-periplanar *p*-orbital of the oxygen atom in relation to the N – Hal bond.

*N*-Amino-substituted derivatives of *N*-halo-*O*-alkylhydroxylamines remained beyond the scope of this review, because, similarly to *N*-halohydrazines, they exist entirely as alkoxydiazenium salts $R_2N^+ = NOR\ Hal^-$.[123] These compounds act as aminoaminating reagents and undergo *O*-dealkylation upon treatment with nucleophiles [see Scheme 1, pathways (*a*) and (*b*)].

The vicinal orbital interaction considered for the O – N – Hal system and related anomeric effects are typical properties of many other geminal systems, for example, N – E – Hal and O – E – Hal, where E = C, N, O, P, S.

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