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Oxims as reagents

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Contents

I.	Introduction	797
II.	Acidity of oximes	798
III.	N- and O-nucleophilicity of the oxime function	801
IV.	Nucleophilic attack on the C=N bond of oximes	808
V.	Dehydration	816
VI.	The Beckmann rearrangement	817
VII.	Reaction of oximes involving substituents	818
VIII.	Conclusion	819

Abstract. **Data on the chemical properties of oximes and their derivatives widely used in the synthesis of different nitrogen-containing acyclic and heterocyclic compounds are systematised and analysed. The polyfunctional nature of oximes is emphasised and their uniqueness as the reagents for directed organic synthesis in the presence of bases is shown. The bibliography includes 332 references.**

I. Introduction

Oximes have found their application in organic synthesis back in the 19th century [1] and as analytical reagents, in the beginning of the 20th century.[2,3] At present, oximes surpass carbonyl compounds and alcohols in both the diversity of reactions and the extent of their application in synthetic chemistry. The oxime function can rather easily be introduced into an organic molecule. This may involve oximation of a carbonyl group with hydroxylamine, nitrosation of hydrocarbons, reduction of nitro compounds, oxidation of amines, oxidative ammonolysis, *etc*. At the same time, the oxime function is readily transformed into such important groups as carbonyl, amino, nitro and cyano groups and can also serve as a convenient protective group.

All compounds that contain the oxime fragment, which represents a pharmacophore group, exhibit diverse biological activities.[4–11] For example, oximes of the furan and thiophene series and their ethers possess vasorelaxant, antispasmodic, sedative, antidepressant, tranquillising, anticonvulsive, analgesic, anti-inflammatory, cytotoxic, anticancer, antiviral and bactericidal properties.[4] These derivatives are also recommended as insecticides, fungicides, pesticides, herbicides, protozoacides and plant growth regulators.[4] A wide spectrum of biological activity was revealed for oximes of the pyridine,[5] indole, isatin,[6] pyrrole [7] and quinoline series.[11] Oximes of α,β-unsaturated ketones are known as insecticides,[8] vasorelaxants [9] and antimicrobial agents.[10]

A recently published series of comprehensive reviews [4–7,11] devoted to the chemistry and biological activity of oximes of heterocyclic ketones generalises the latest achievements in this field. They provide information on the development of most typical, classical reactions of oximes and the discovery and elaboration of novel or specific transformations characteristic of certain classes of compounds. The present review does not discuss the papers cited in this series; however, it cannot be considered as an exhaustive supplement to this series. The purpose of our survey is to generalise (using typical examples) and systematise new information on the most typical chemical reactions of oximes, based on the structural peculiarities of the oxime group and its nearest environment. Attention is paid to the reactions that proceed in the presence of bases. In the analysis of the published material, this aspect seems to be important, because it focuses attention on the multifacet nature of reactivity of oximes and oximate anions. Traditionally, these compounds are considered as the objects of the Beckmann rearrangement that takes place in the presence of acids.

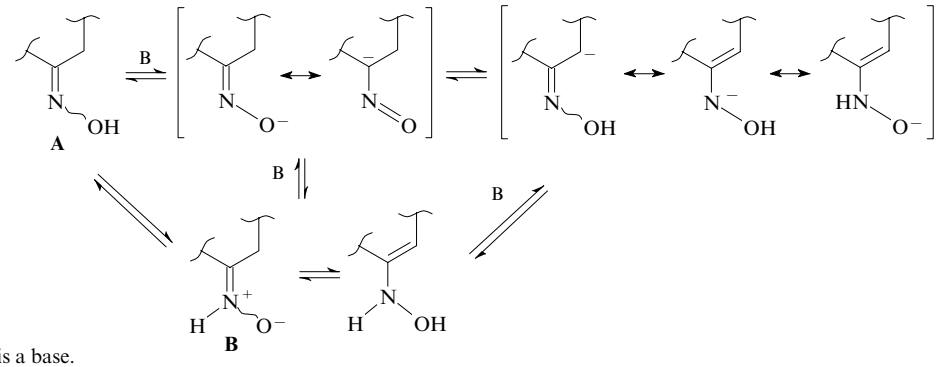
Oximes (**A**) and their tautomers, NH-nitrones (**B**) and the corresponding anions can exist in various tautomeric and resonance forms (Scheme 1), which allows one to call them 'chemical chameleons'. The following properties of oximes in the presence of bases can be mentioned: (1) OH- and CH-acidity; (2) O- and N-nucleophilicity; (3) the possibility of the nucleophilic attack on the C=N bond; (4) dehydration; (5) various transformations of substituents (including their migration).

To make systematisation and analysis of base-promoted reactions of oximes easier, it seemed reasonable to assign them to one of the types listed. However, such an assignment is not always unambiguous, because many reactions of oximes simultaneously manifest several sides of their multifacet reactivity.

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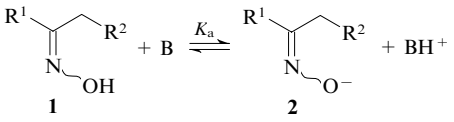
Scheme 1



B is a base.

II. Acidity of oximes

On treatment with bases, oximes (**1**) undergo deprotonation to give oximate anions (**2**).



R^1, R^2 = H, Alk, Ar, Het.

Oximes that contain hydrogen atoms in the α-position relative to the oxime function exhibit sufficiently high CH-acidity together with OH-acidity. Moreover, coordination of a transition metal with an oxime group results in activation of the β-C−H bond.

1. OH-Acidity

Studies of acid–base properties of mono- and dioximes of diketones are associated with their wide use in analytical chemistry. OH-Acidity of oximes and its correlation with their configuration was the subject of several studies.[12–27]

Table 1. Acidity constants of certain oximes.

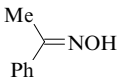
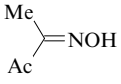
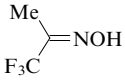
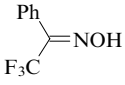
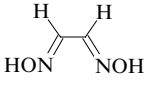
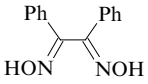
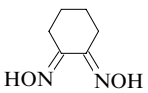
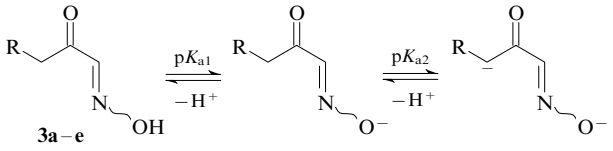
Oxime	pK_a	Ref.
	11.48	13
	9.38	13
	9.76	14
	9.05	12
	9.94, 11.49	26
	10.29, 11.91	27
	10.68, 11.92	26

Table 1 shows the data on the acidity of certain oximes. The pK_a values depend on the effect of substituents at the oxime function.

The values of the acidity constants of dioximes of α-diketones are in the ranges of 10.4–10.8 (for the first hydroxyl group) and 11.9–12.4 (for the second hydroxyl group).[16–21]

A substantial increase in the oxime acidity is observed for α-oxo aldoximes **3a**–**e**.[22] For these compounds, pK_{a1} changes from 8.30 (for oxime **3a**) to 6.54 (for **3e**), the latter oxime being among the most acidic oximes known.



R = H (**a**), MeS (**b**), MeSO (**c**), $MeSO_2$ (**d**), Me_2S^+ (**e**).

It should be noted that the acidity of poly(acrolein oximes) is independent of their molecular mass and the content of oxime units; moreover, the pK_a (9.8)[28] value is lower than that of the monomer, acrolein oxime (10.61).[29]

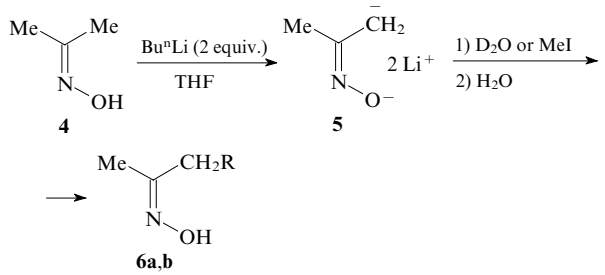
2. CH-Acidity

a. α-CH-Acidity (reactions of oxime carbanions)

The above-mentioned α-oxo aldoximes **3** exhibit sufficiently high CH-acidity, namely, pK_{a2} = 12.23 (for compound **3c**), 11.10 (**3d**), 10.55 (**3e**).[22] In the general case, the electron-acceptor nature of the C=N−OH function enhances the mobility of the α-hydrogen atoms, which makes it possible to synthesise the corresponding C-anions of oximes (or of their esters) under the action of organometallic compounds.[30–32] This reaction is widely used in organic synthesis for the formation of new C−C bonds.

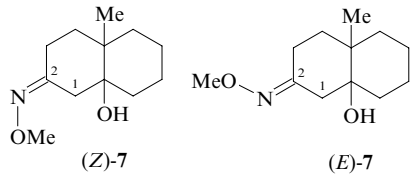
Generation of C-anions often faces a problem of low solubility of dimetallated oximes, which can be solved by different methods. Thus Ensley and Lohr[33] proposed to carry out aldol condensation with lithiated *O*-tetrahydropyranyloximes as carbanions, which can be prepared using only one equivalent of lithium diisopropylamide (LDA). Gawley *et al.*[34] employed cuprates of oxime ethers for 1,4-addition to cyclohexenone. These reagents are synthesised by treating the corresponding oxime ethers with potassium diisopropylamide followed by their reaction with the $Cu_2Br_2 \cdot Me_2S$ complex. This approach allows one to enhance the efficiency of carbanion generation as compared with LDA.

Stereochemistry of oxime metallation was the subject of several studies.[35–38] Thus, being treated with two equivalents of butyllithium, acetone oxime (**4**) exclusively forms *syn*-dianion **5**, methylation and deuteration of which leads to products **6a**,**b**, respectively.[35]



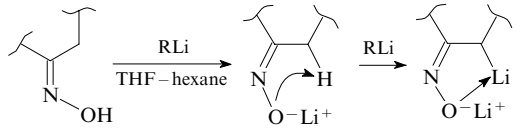
R = Me (**a**, 73%), D (**b**, 100%).

Being treated with NaOH, the *Z*-isomer of *O*-methyloxime of a decalone derivative with a tertiary hydroxyl group **7** undergoes dehydration more readily as compared with the *E*-isomer.[36] This is explained by the higher rate of anion formation from compound (*Z*)-**7** upon proton abstraction from position 1. In this case, the ratio of *syn*- and *anti*-anions in the deprotonation product is 95 : 5.



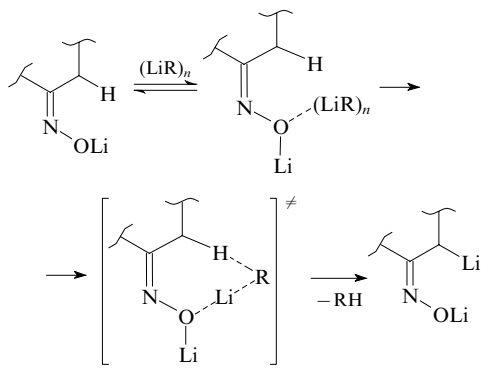
The assumption of the higher mobility of the *syn*-hydrogen atoms as compared with the *anti*-hydrogen atoms was confirmed also for deuteration (D_2O, −60 °C) of a metallation product of *O*-methyl dibenzyl ketoxime with lithium isopropylcyclohexylamide in ether.[36]

Ketoxime dianions with lithium cations can exist in the free state at 20 °C for several hours; moreover, neither the equilibrium between *syn*-and *anti*-forms nor the isomerisation of dianions are observed even at elevated temperatures.[38] This is associated with the enhanced stability of *syn*-dianions due to the formation of chelate structures with an alkali metal. It is assumed that the formation of dilithio derivatives occurs stepwise, namely, the lithium salt is converted into a soluble dilithio derivative under the action of the second equivalent of butyllithium.



R = Bu^n, Bu^s.

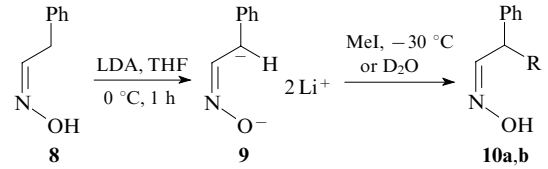
However, systematic studies of metallated compounds that contain heteroatoms capable of forming complexes with lithium made it possible to assume a different mechanism of selective *syn*-lithiation.[39] An organolithium compound is preliminarily coordinated by the oxygen atom of the oxime function, which is followed by the transfer of lithium to the α-carbon atom. Thus, selective



syn-metallation is due to the combined effect of kinetic and thermodynamic factors.

Stabilisation of *syn*-anions is also explained[35] by their partly aromatic nature. It is assumed that in a system containing six π-electrons, attractive interaction arises between the α-carbanionic site and the oxygen atom, which selectively stabilises the *syn*-form.

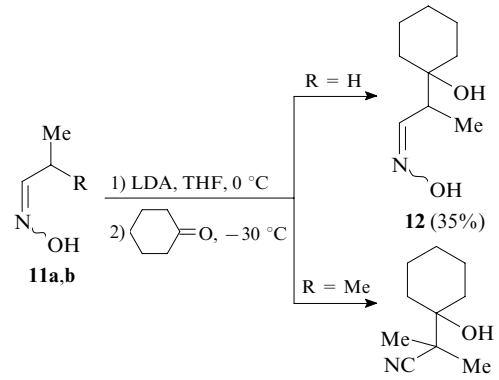
LDA was used as a base for the generation of a *syn*-dianion of aldoxime **8**.[39]



R = Me (**a**, 86%), D (**b**, 100%).

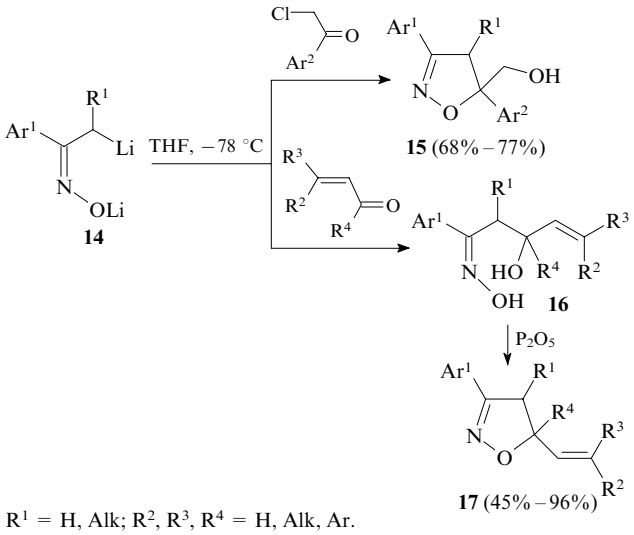
Z-Configuration of the starting oxime, which is not isomerised under mild conditions of lithiation, favours the formation of *syn*-dianion **9**. This is confirmed by high yields of methylation (**10a**) and deuteration (**10b**) products.[39]

Propanal oxime carbanion (**11a**) was used as a methylene component in the condensation with cyclohexanone to yield aldol **12**. However, in the case of isobutyraldehyde oxime (**11b**), condensation together with dehydration of the oxime led to nitrile **13**.[39]



R = H (**a**), Me (**b**).

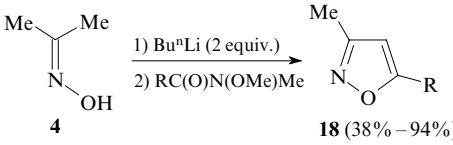
Oxime C-anions react with different electrophiles including carbonyl compounds. As the result of intramolecular dehydration of the adducts of these reactions, namely, alcohols, they are heterocyclised into isoxazole derivatives. Thus, when treated with α-chloroacetophenones under very mild conditions, dilithio derivatives of alkyl aryl ketoximes **14** form isoxazolines **15**.



R^1 = H, Alk; R^2, R^3, R^4 = H, Alk, Ar.

However, their reactions with α,β-unsaturated aldehydes and ketones lead to acyclic 1,2-adducts **16**. The latter are cyclised into 5-vinylisoxazolines **17** under the action of P_2O_5.[40]

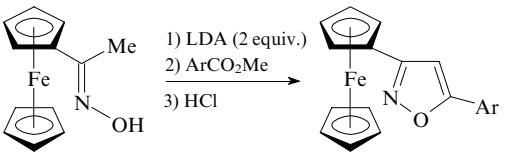
Numerous of 5-alkyl-3-methylisoxazoles **18** were synthesised from the dilithio derivative of acetone oxime (**4**) and *N*-methoxy-*N*-methylamides of carboxylic acids (the Weinreb amides).[41]



4 **18** (38% – 94%)

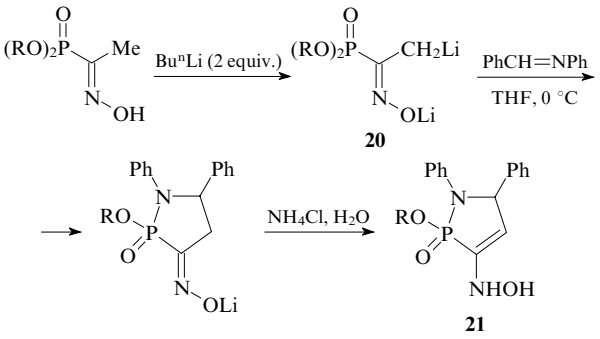
R = Alk, cyclo-Alk, Ar.

Reactions of dilithiated acetylferrocene oxime with methyl benzoates afford (5-arylisoxazole-3-yl)ferrocenes **19**.[42]



19 (20% – 76%)

A Schiff base was used as the electrophile in reactions with oxime dianions. Thus starting from α-oxophosphonate derivatives **20** and benzylideneaniline, 2-alkoxy-3-hydroxyamino-2-oxo-1,5-diphenyl-1,2-azaphosphol-3-enes **21** were synthesised (yields 10% – 30%).[43]



20 **21**

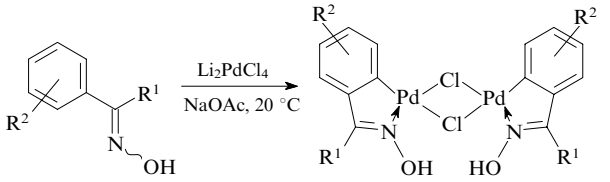
R = Et, Pr^n, Bu^n.

Information on oxime 1,4-dianions and their cyclisation can also be found in Refs 44 – 46.

b. β-CH-Acidity (cyclopalladation)

Mono- and dioximes capable of chelation are good ligands for complexes with transition metal cations. This property forms the basis for the wide use of oximes as analytical reagents for different metals, namely, nickel, copper, cobalt, iron, palladium, platinum, manganese, rhodium, rhenium, molybdenum, *etc*.[47] In contrast to 'hard' lithium cations, transition metal cations coordinate preferentially to the nitrogen atom of the oxime group. Such an interaction is most likely a result of donating of electrons from the occupied d-orbitals of the metal to the lowest unoccupied molecular orbitals (LUMO) of the C=N bond, which leads to π-binding and additional stabilisation of the complex as a whole.

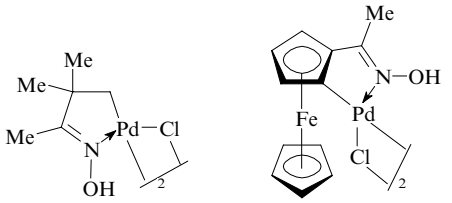
Coordination of a palladium atom to the oxime nitrogen atom favours the activation of the β-C – H bond. Thus cyclopalladation of oximes of aromatic ketones in the presence of bases results in the formation of bis(palladazole) system **22**, which is surprisingly stable in air and in aqueous medium.[48 – 54] This process is usually carried out at room temperature by treating an oxime with lithium tetrachloropalladate (Li_2PdCl_4) in methanol in the presence of sodium acetate as the base.



22

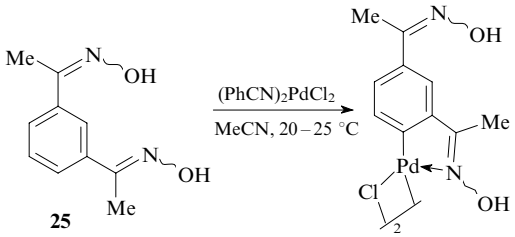
R^1 = Alk, Ar; R^2 = Ar.

Analogously, pinacolone and acetylferrocene oximes yielded palladium complexes **23** and **24**.[54]



23 **24**

It should be mentioned that in the absence of a base in the reaction of 1,3-diacetylbenzene dioxime (**25**) with palladium(II) bis(benzonitrile) dichloride in acetonitrile cyclopalladation occurs, which involves only one oxime group to yield a dimeric complex **26**.[54]

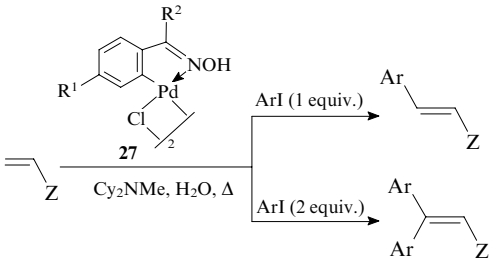


25 **26**

The CH-acidity of *syn*-α-methyl (or methylene) groups is not manifested in cyclopalladation, in contrast to lithiation reactions.

At present, complexes of the type **22** are actively studied as the catalysts of different cross-coupling processes[55] (including the Heck,[56,57] Suzuki,[58 – 60] Stille,[56] Ullmann,[58] Sonogashira[61,62] and Glaser[62] reactions). They are effective in both organic[54,56,58,61,62] and aqueous[57,59,60] media. Palladium and rhenium oxime complexes are also used as catalysts in the aza-Heck reaction.[63] In addition, terminal alkynes have recently been acylated with acid chlorides in the presence of such systems.[64]

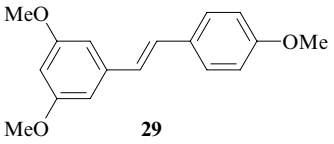
Controlled mono- and diarylation of α,β-unsaturated carbonyl compounds by aryl iodides was carried out using cyclopalladated 4-hydroxyacetophenone oxime (**27**) as the catalyst.[57] The yields of the reaction products were high (up to 98%).



27

R^1 = OH, R^2 = Me (**27**); Z = CO_2Bu^t, $C(O)NMe_2$, CN, C(O)Me; Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$.

Palladacycles **27** and **28** (R^1 = Cl, R^2 = 4-ClC_6H_4) proved to be efficient catalysts in the synthesis of methylated resveratrol (**29**) and its analogues,[65] which exhibit high antineoplastic activity.



29

Cross-coupling of the corresponding styrene with *p*-iodomethoxybenzene is carried out in the presence of methylcyclohexylamine and tetrabutylammonium bromide in aqueous dimethylamine (or in water) at 120 °C in air or under microwave irradiation. The reaction is highly regiospecific, *viz*., stilbene **29** and its analogues are obtained in virtually quantitative yields.

Thus, under the action of strong bases, oximes acquire α-CH-acidity, while in the presence of palladium cations aryl ketoximes acquire β-CH-acidity of the aryl substituent. This allowed the development of a convenient method of synthesis of *ortho*-substituted aromatic compounds based on the catalytic version of cyclopalladation.

III. N- and O-nucleophilicity of the oxime function

Nucleophilicity of oximes is their most important chemical property that manifests itself most clearly in basic media. The oxime function contains three nucleophilic reaction sites, *viz*., N, O and C atoms. The neutral molecule usually plays the role of an N-nucleophile, while an anion (oximate) plays the role of a strong O-nucleophile (due to the α-effect [12, 13, 66–68]). Nucleophilicity of the carbon atom is determined by the contribution of a nitroso tautomer into the equilibrium.

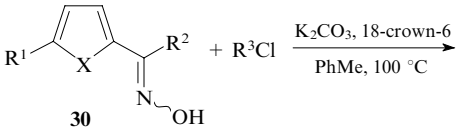
1. Reactions with electrophiles in the presence of bases

The N–O-selectivity of reactions of oximes with electrophiles depends on their structural features, the reagent nature and the reaction conditions. As a rule, the implementation of one or another reaction pathway can be rationalised within the framework of the theory of hard and soft acids and bases. The material of this section is arranged according to the type of the electrophilic agent. Reactions of oximes with alkyl halides, oxirane, bifunctional electrophiles, acylating agents and organoelement halides, which occur under different conditions, are considered.

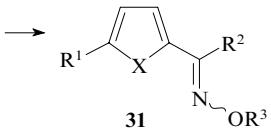
Substitution of oximate ions for a halogen atom was studied in sufficient detail for various classes of organic substances. Having no intention to comprehensively survey the literature on this issue, we merely show the most typical examples of such reactions.

O-Alkyl(aryl)oximes can be obtained from the corresponding oximes and organyl halides in alkaline medium.[69, 70] Alkylation of oxime salts (oximates) with alkyl halides often involves not only the oxygen atom but also the nitrogen atom (the manifestation of N-nucleophilicity). The direction of the reaction depends on the structure of substituents in the reagents and the solvent polarity. The nature of the alkali metal cation and the halogen (*e.g*., in benzyl halides [69, 70]) affects little the ratio of the substitution products. The dependence of the direction of alkylation on the oxime configuration was the subject of several studies.[71–74] It was shown [71] that the reaction of (*E*)-benzaldoxime with alkyl halides preferentially yields the O-alkylation products, while *Z*-isomer gives the N-alkylation products (nitrones).

Regioselectivity of O-alkylation of oximes can be increased by carrying out the reaction in a two-phase system. Under conditions of phase-transfer catalysis in the presence of K_2CO_3, furyl and thienyl ketoximes **30** were alkylated at the oxygen atom; the yields of products **31** were 15%–83%.[75]



30

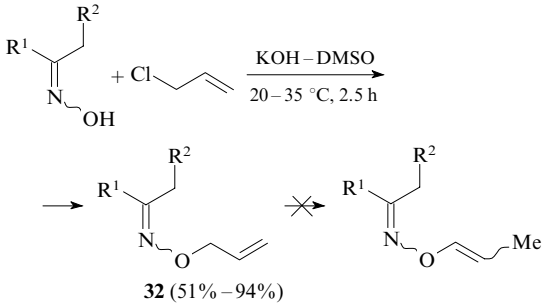


31

X = O, S; R^1 = H, Me; R^2 = Me, Pr^i; R^3 = Bu^n, $(CH_2)_3Si(Me)$.

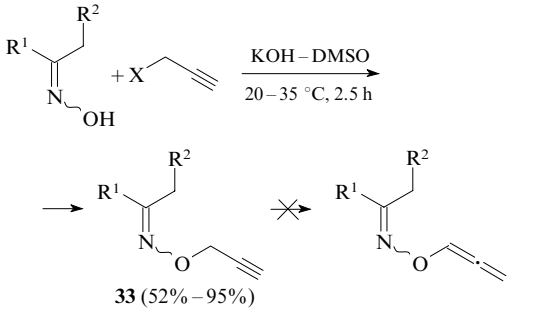
O-Butyl-, *O*-allyl-, *O*-(2-chloroethyl)oximes and *O*,*O*′-methylenedioximes were prepared from the corresponding halides and oximes in a two-phase system (NaOH, Bu^n_4NBr).[76] The alkylation of *E*,*E*-dioximes of 1,2-diketones, such as dimethylglyoxime, with dichloromethane under the conditions of phase-transfer catalysis (K_2CO_3, 18-crown-6), results in methylene dioximes and 21-membered heteromacrocycles, the oxime fragments in which are sequentially linked by methylene bridges.[77, 78]

Oximate anions generated in the KOH–DMSO system substitute readily a halogen atom in allyl and propargyl halides to form the corresponding *O*-allyl- (**32**) and *O*-propargylketoximes (**33**).[79]



32 (51%–94%)

R^1 = Me, Pr^n, Bu^n, n-C_6H_{13}; R^2 = Me, Et, Pr^n, Bu^n, Ph, 4-MeC_6H_4, 2-thienyl; R^1–R^2 = $(CH_2)_5$.



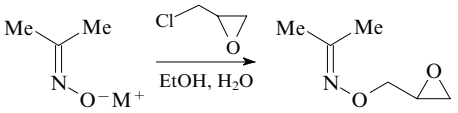
33 (52%–95%)

R^1 = Me, Pr^n, Pr^i, Bu^n; R^2 = Me, Et, Pr^n, Pr^i, Bu^t, Ph, 4-ClC_6H_4, 2-thienyl, 2-furyl; R^1–R^2 = $(CH_2)_n$ (n = 4–7, 11); X = Cl, Br.

It should be noted that no expected shift of the multiple bond to the oxygen atom to form prop-1-enyl and allenyl ethers was observed (for acid–base rearrangements of *O*-propargylketoximes in *N*-alkenylacrylamides, see Section IV.1). The fundamental reasons for the inertness of *O*-allyloximes as regards prototropic isomerisation were analysed by quantum-chemical methods.[80]

Earlier, *O*-allylketoximes were obtained [81] in a reaction of ketoximes with allyl halides in the presence of alkali metal hydroxides in polar aprotic solvents (*N*-methylpyrrolidone, dimethylacetamide, DMF).

Condensation of sodium or potassium salts of acetone oxime (**4**) with epichlorohydrin in aqueous ethanol produced *O*-glycidyloxime **34**.[82]

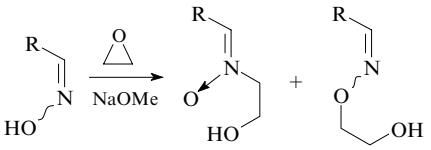


34

M = Na, K.

Cyclisation of γ-chloroximes[83,84] and γ-sulfonyloximes[85] into 1,2-oxazines in the presence of bases proceeds as an intramolecular nucleophilic substitution with involvement of oximate anions as the *O*-centred nucleophiles.

As in the reactions with alkyl halides, the direction of oxime reactions with oxirane depends first of all on the oxime configuration. Thus alkylation of the *E*-isomer of benzaldoxime **35a** with oxirane yields the N- (**36a**) and O-substitution (**37a**) products in a ratio of 1 : 5.[72,73] *Z*-Isomers of oximes of benzaldehyde (**35a**) and furfural (**35b**) give preferectially nitrones **36a**,**b** (**36a** : **37a** = 6 : 5, **36b** : **37b** = 10 : 1).[74]

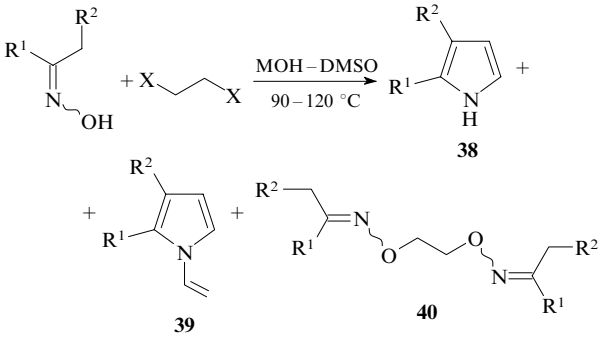


35a,**b** **36a**,**b** **37a**,**b**

R = Ph (**a**), 2-furyl (**b**).

Alkylation of acetone oxime (**4**) with oxirane leads to the O-alkylation product, namely, acetone O-(2-hydroxyethyl)oxime in quantitative yield,[72] whereas *Z*-oxime of 2-acetylpyridine is not alkylated with this reagent even under drastic conditions.[74] *O*-(2-Hydroxyalkyl)oximes are also prepared under the action of oxiranes in the presence of secondary amines.[86,87]

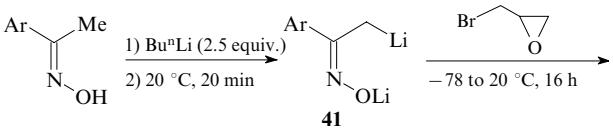
The one-pot synthesis of pyrroles **38** and **39** by the Trofimov reaction[88–90] (see Section IV.2.b) from ketoximes and dihaloethanes (synthetic equivalents of acetylene) in superbasic media leads in certain cases to the substitution of oximate anions for a halogen atom. As a result of this process, side products, namely, ethylene glycol diethers of ketoximes **40** (*E*,*E*-, *E*,*Z*- and *Z*,*Z*-isomers) are formed; their content in the mixture can reach 47%.



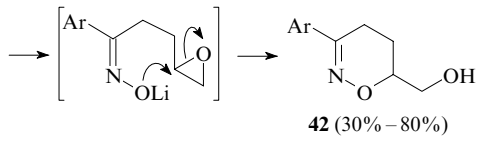
38 **39** **40**

R^1 = Me, Et, Pr^n; R^2 = H, Me, Et, Pr^n, Pr^i; R^1–R^2 = $(CH_2)_5$;
X = Cl, Br; M = Li, Na, K.

A regiospecific reaction of dilithiated oximes **41** with epibromohydrin produces 6-hydroxymethyl-5,6-dihydro-4*H*-1,2-oxazines **42**.[91]



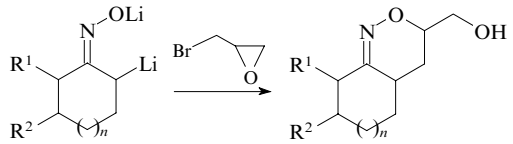
41



42 (30%–80%)

Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 1-naphthyl, 2-naphthyl.

Under similar conditions, epibromohydrin reacts with dilithio derivatives of cycloalkanone and tetralone oximes to afford the corresponding bicyclic 1,2-oxazines **43** and their condensed tricyclic analogues **44**.[91]

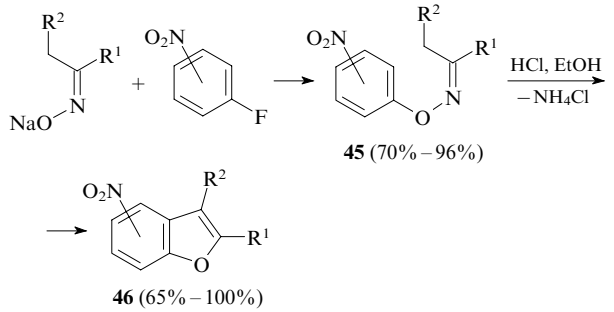


43, **44**

43: R^1 = R^2 = H: *n* = 1 (38%), 2 (51%), 3 (49%), 7 (52%);
44: R^1–R^2 = benzo, *n* = 1 (48%).

It should be noted that the acyl group in *O*-acyloximes is easily replaced by an *O*-alkyl group upon treatment of the substrate in a phase-transfer system alkyl halide–KOH–18-crown-6–benzene.[92]

Substitution of a fluorine atom in an aromatic ring under the action of sodium oximates is described.[93] *O*-Aryloximes **45** formed are converted into benzofurans **46** upon refluxing with HCl in anhydrous ethanol.

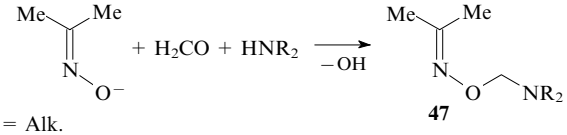


45 (70%–96%)

46 (65%–100%)

R^1, R^2 = Alk.

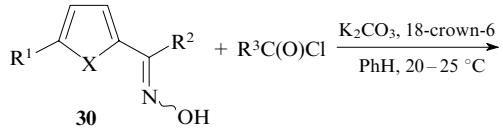
O-Aminomethyloximes **47** were synthesised[94] by the Mannich condensation.† The same products are formed upon alkylation of oximes with aminomethyl halides.



47

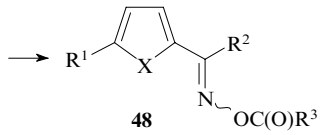
R = Alk.

Acylation of oximes can be effected under different conditions. For example, in benzene in the presence of solid K_2CO_3 and 18-crown-6, O-acylated derivatives **48** are formed from 2-furyl and 2-thienyl ketoximes **30**; this involves no Beckmann rearrangement.[96]



30

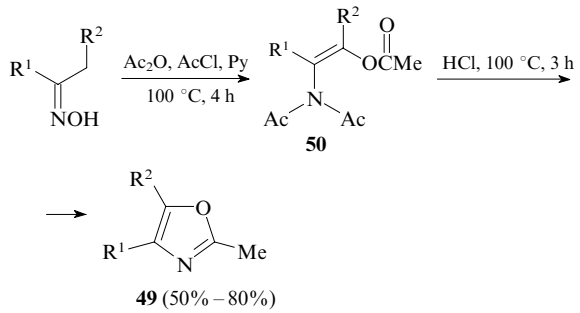
† The Mannich reaction with aldoximes is known[95] to involve the α-carbon atom.



48

X = O, S; R^1 = H, Br; R^2 = Me, Et, Pr^i; R^3 = Me, Et, Bu^t, Ph.

If the acylation agent represents a mixture of Ac_2O and AcCl, then ketoximes are converted into oxazoles **49** in the presence of pyridine. The reaction proceeds *via* β-acetoxy enamides **50**.[97]

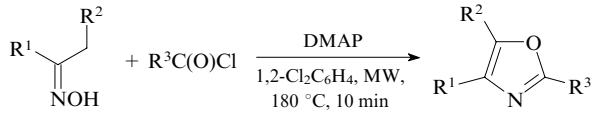


50

49 (50% – 80%)

R^1 = Me, Bn, Ph; R^2 = Me, Ph; $R^1 – R^2$ = $(CH_2)_4$, $(CH_2)_2CHMeCH_2$.

Recently, it has been shown [98] that the acylation of ketoximes with carboxylic acid chlorides in the presence of organic bases under conditions of microwave activation (150 W) also affords oxazoles **49**.

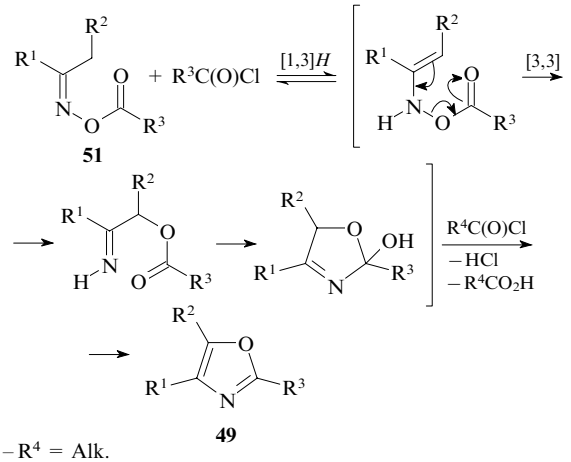


49 (25% – 62%)

R^1 = Me, Et, Pr^i, Ph, 4-BrC_6H_4; R^2 = Me, Ph; $R^1 – R^2$ = $(CH_2)_4$;
R^3 = Bu^t, Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, $BnOCH_2$, PhCH=CH;
DMAP is dimethylaminopyridine.

This process also occurs in the absence of microwave irradiation; however, the yields of oxazoles are substantially lower. For example, the yield of oxazole **49** (R^1 = Me, R^2 = Ph, R^3 = 4-$CF_3C_6H_4$) is 43% *versus* 62% with microwave activation.[98]

The cyclisation mechanism was not discussed in Ref. 98. However, since no intermediates of the type **50** were detected, the transient formation of *O*-acylketoximes **51** seems to be the most likely. The consecutive 1,3-prototropic shift and [3,3]-sigmatropic rearrangement are similar to the mechanism of pyrrole synthesis *via* *O*-vinyloximes by the Trofimov reaction (see Section III. 2.b).

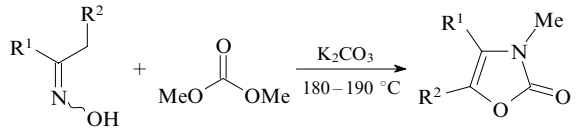


51

49

$R^1 – R^4$ = Alk.

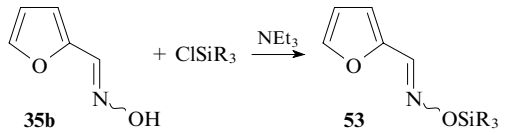
The reaction of aliphatic and aromatic ketoximes containing α-methylene groups with dimethyl carbonate in the presence of K_2CO_3 leads to 4,5-disubstituted 3-methyloxazolin-2-ones **52**.[99] Presumably, the reaction involves the [3,3]-sigmatropic rearrangement and the role of dimethyl carbonate is the initial N-methylation of oximes.



52 (22% – 48%)

R^1 = Me, Et, Pr^n, Ph; R^2 = Me, Et, Ph; $R^1 – R^2$ = $(CH_2)_n$ (n = 4, 5).

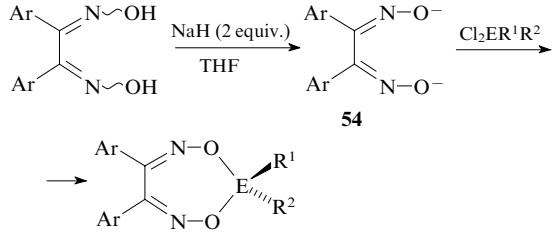
In the presence of tertiary amines, furfural oxime **35b** reacts with trialkylchlorosilanes to give *O*-silyl ethers **53**.[100] This is a typical example of nucleophilic substitution at the silicon atom where oximes play the role of O-centred nucleophiles.



35b **53**

R = Alk.

Recently,[101] O,O′-centred dianions of vicinal dioximes **54** have been used for the synthesis of 7-membered silicon- (**55**) and tin-containing (**56**) heterocycles. The reaction occurs as the nucleophilic substitution of chlorine atoms in the corresponding dichlorides.

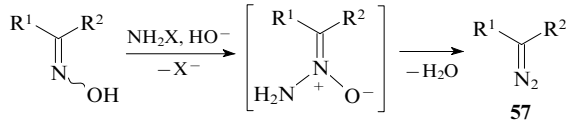


54

55, **56** (60% – 77%)

Ar = 4-XC_6H_4 (X = H, Me, Cl, MeO);
E = Si (**55**): R^1 = Me, Bu^n, Ph; R^2 = Me, Bu^n, Ph, Cl;
E = Sn (**56**): R^1 = R^2 = Me, Bu^n, Ph.

In this Section, it is appropriate to mention the conversion of oximes into diazoalkanes **57** under the action of N-electrophiles, namely, chloroamine or hydroxylaminosulfonic acid (the Forster reaction).[102, 103] In the first stage of this reaction, oximes act as N-nucleophiles.



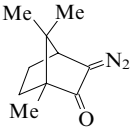
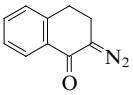
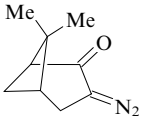
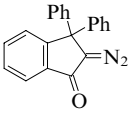
57

R^1, R^2 = H, Alk, Ar; X = Cl, OSO_3H.

Various diazo compounds were synthesised by this method.[103 – 108] Table 2 shows the most interesting of them (including diazomethane).

Thus, using the substitution reactions involving oximes as O- and N-nucleophiles, it is possible to synthesise various *O*-organyloximes, nitrones and diazo compounds, which are valuable intermediates in organic synthesis. The selectivity of these reactions can be controlled by varying the substituents in oximes and electrophilic agents and changing the oxime configurations and experimental conditions.

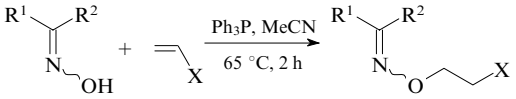
Table 2. Oximes in the Forster reaction.[102]

Oxime	Diazo compounds	Yield (%)
Formaldoxime	$H_2C{=}N_2$	75
3-Hydroxyiminocamphor		70
2-Hydroxyimino-1-tetralone		57
α-Hydroxyiminonopinone		85
2-Hydroxyimino-3,3-diphenyl-1-indanone		65

2. Nucleophilic addition of oximes to unsaturated systems

a. Reactions with alkenes

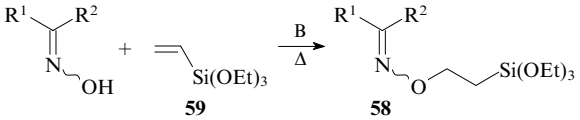
Bases catalyse the addition of oximes to electron-deficient alkenes. The catalysts are usually represented by alkali metal hydroxides [109,110] and alkoxides,[111] quaternary ammonium salts.[110] However, the reaction proceeds most smoothly in the presence of triphenylphosphine:[112] in some cases, adducts **58** were obtained in quantitative yield.



58

R^1	R^2	X	Yield (%)
Bu^t	H	SO_2Ph	89
Cy	H	SO_2Ph	88
Styryl	H	SO_2Ph	90
4-$NO_2C_6H_4$	H	CO_2Et	85
3-$NO_2C_6H_4$	H	CO_2Et	80
	H	CN	80
	H	SO_2Ph	95
3-HSC_6H_4	H	SO_2Ph	92
3-Py	H	SO_2Ph	88
Et	Me	SO_2Ph	84
Ph	Me	SO_2Ph	87
4-$MeSO_3C_6H_4$	H	SO_2Ph	96
	Me	CO_2Et	30
	Me	SO_2Ph	84

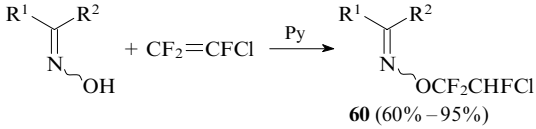
Under the action of bases, oximes add to trialkoxy(vinyl)silanes **59** to form the corresponding *O*-alkylated derivatives **58** [X = $Si(OEt)_3$].[113]



59 **58**

R^1 = Alk; R^2 = H, Alk; B = AlkONa, AlkSNa, $NaNH_2$, *etc*.

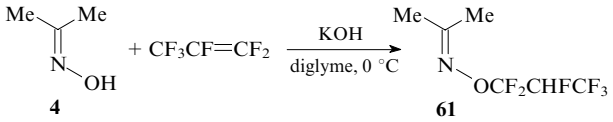
Different nitrogen bases were used as the catalysts in the reactions of oximes with polyfluoroalkenes. Thus *O*-chlorofluoroethyloximes **60** were synthesised in high yields from chlorotrifluoroethylene in the presence of pyridine.[114]



60 (60% – 95%)

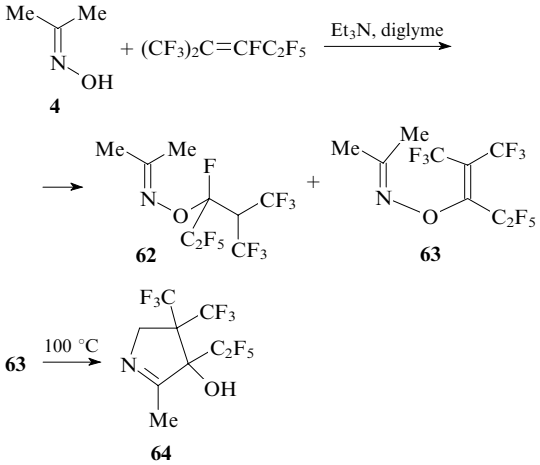
R^1, R^2 = Alk, Ar.

Acetone oxime (**4**) reacts with perfluoropropylene to form acetone *O*-hexafluoropropyl oxime (**61**).[115]



4 **61**

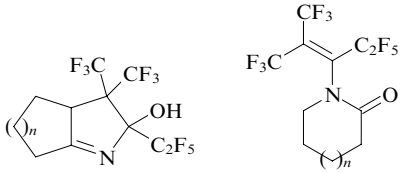
However, the reaction of acetone oxime (**4**) with perfluoro-2-methylpent-2-ene (dimer of perfluoropropylene) in the presence of triethylamine proceeds in a more complicated fashion. In addition to adduct **62**, the reaction gives the product of formal replacement of one of fluorine atoms, namely, compound **63**, which is rearranged upon heating into 4-hydroxy-2-methyl-5,5-bis(trifluoromethyl)-4-pentafluoroethyl-1-pyrroline (**64**).[115]



4 **62** **63** **64**

It should be mentioned that this rearrangement exactly corresponds to a proved stage of the Trofimov reaction, *viz*., the [3,3]-sigmatropic shift in *O*-vinyloximes, which leads to the formation of, first, hydroxypyrrolines and, then, pyrroles.

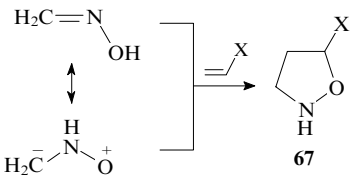
The addition of oximes to alkenes can also occur in the absence of bases upon heating of the reactants. Thus thermolysis of a mixture of perfluoro-2-methylpent-2-ene and cycloalkanone oximes produced pyrrolines **65** and the Beckmann – Chapman rearrangement products, namely, *N*-perfluoroalkenyllactams **66**.[116]



65a,**b** **66a**,**b**

n = 1 (**a**), 2 (**b**).

1,3-Dipolar cycloaddition of formaldoxime with electron-deficient alkenes is shown [117] to afford 5-substituted isoxazolidines **67**. This reaction pathway is attributed to the fact that it is the mesomeric form of formaldoxime, *i.e*., betaine, with a positive charge on the oxygen atom and a negative charge on the carbon atom that is involved in cyclisation.

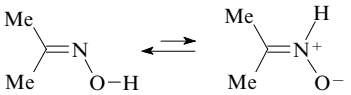


67

X = CN, CO_2Me.

This transformation is an unusual example of [2 + 3]-cycloaddition of nitrones with the change in polarity ('Umpolung').

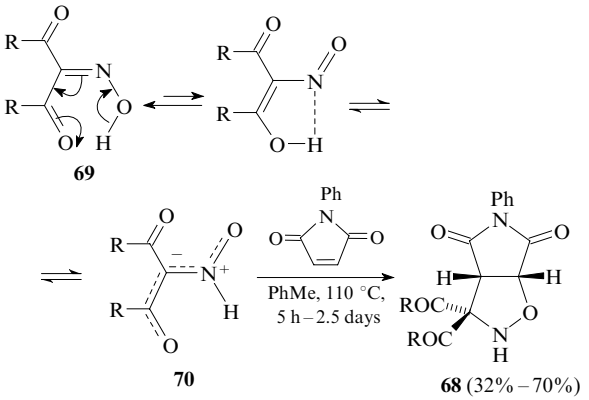
It is known [118–121] that oximes can be thermally isomerised into nitrones as a result of the 1,2-prototropic shift.



4

The fact that oximes react with alkenes in the form of NH-nitrones is also confirmed by the synthesis of isoxazolidines **67**. The mechanism of addition can be either intermolecular (as in the above example) or intramolecular.[122–136]

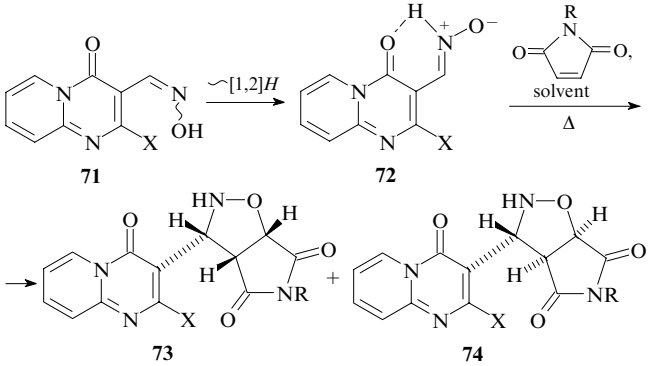
Up up to recently, information on the use of oximes in the NH-nitrone form in the intermolecular addition to dipolarophiles was limited to a few studies.[117,120] Thus it was reported [120] that cycloadduct **68** is formed in the reaction of oxime **69** (or, more exactly, its NH-nitrone tautomer **70**) with *N*-phenylmaleimide.



69 **70** **68** (32% – 70%)

R = OMe, OEt; R – R = $CH_2CMe_2CH_2$.

The prospects of studying the isomerisation of oximes into NH-nitrones with the aim of generating NH-1,3-dipoles and their synthetic application are evident. Recently, it has been reported [137] on a successful addition of oximes of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehydes **71** in their nitrone form **72** to the activated double bond of *N*-substituted maleimides. The yields of diastereomeric isoxazolidines **73** and **74** depend on the structure of the reactants and the reaction conditions and amount to 66% – 82%.



71 **72** **73** **74**

X = pyrrolidin-1-yl, morpholin-1-yl, NBn_2, OEt;

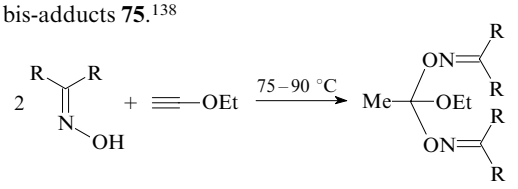
R = Me, Ph; solvent is PhH, EtOH, MeCN.

Thus, in the synthesis *O*-organyloximes, the nucleophilic addition of oximes to electron-deficient alkenes is an alternative to the nucleophilic substitution involving oximate anions. This reaction can follow a synchronous mechanism (like cycloaddition), which opens up an easy way to the synthesis of pyrrolines and isoxazolidines that contain reactive functional groups. These hydrogenated azoles are promising building blocks in organic synthesis. It should be stressed that, in the latter case, the reaction takes place in the absence of a base, *i.e.*, oximes play the role of non-ionised nucleophilic reagents.

b. Reactions with alkynes

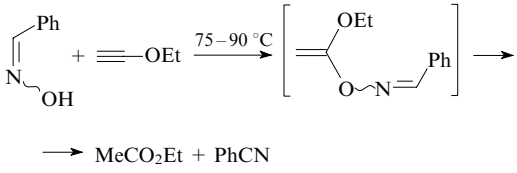
Like other electrophilic reagents, alkynes can attack an oxime molecule at both oxygen and nitrogen atoms. However, the fate of intermediates differs in many aspects and depends on various factors. Reactions of nucleophilic addition of acetylene derivatives to oximes usually lead to *O*-vinyl ethers. However, examples of heterocyclisation of intermediates formed as a result of the alkyne attack on the N-nucleophilic site are also documented.

The reactions of oximes with ethoxyacetylene on moderate heating in the absence of catalyst result in regiospecific formation of bis-adducts **75**.[138]

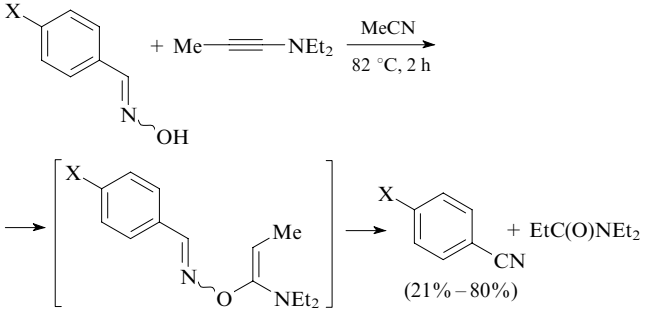


R = H, Me, Et, Ph. **75** (30% – 63%)

Under similar conditions, aromatic aldoximes (both *syn*- and *anti*-isomers) sometimes give dehydration products, *viz*., nitriles and ethyl acetate, together with the addition products.[138] For example, *syn*- and *anti*-benzaldoximes form bezonitrile in the reaction with ethoxyacetylene. This reaction route was explained [138] by decomposition of intermediate monoadducts, which, however, could not be isolated.



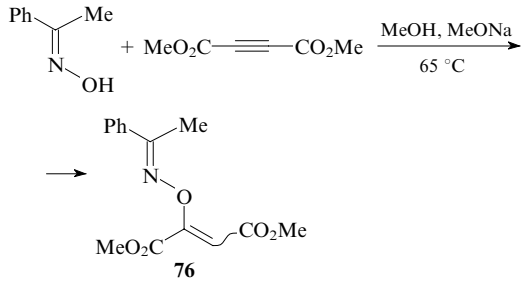
Substituted benzonitriles were also prepared in the reaction of benzaldoximes with 1-(*N,N*-diethylamino)propyne.[139]



X = H, Cl, NO_2, OMe.

The yields of products depend on the configuration of the starting oxime. The low yield of benzonitrile (X = H, 21%) in the case of *Z*-benzaldoxime is probably due to steric factors.

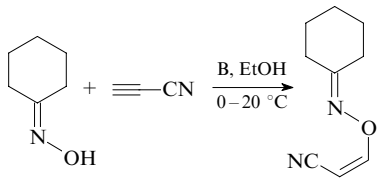
The reaction of acetophenone oxime with dimethyl acetylenedicarboxylate in the presence of sodium methoxide leads to *O*-adduct **76** in quantitative yield.[140]



76

Compound **76** was obtained as a mixture of *cis*- and *trans*-isomers (1 : 2, according to the ^{1}H NMR data).

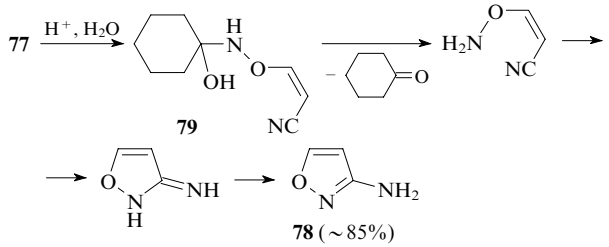
Cyanoacetylene adds to cyclohexanone oxime in a mixture of ethanol and *N*-methylmorpholine (5 : 2 by volume) at 0 – 20 °C to yield β-cyclohexylideneiminooxyacrylonitrile (**77**).[141]



77

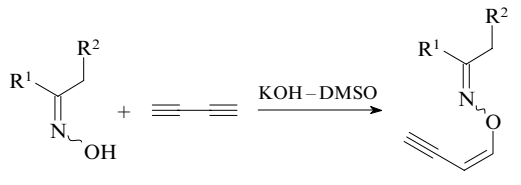
B is *N*-methylmorpholine.

Mild acid hydrolysis of the synthesised compound **77** converts it into 3-aminoisoxazole **78** and regenerates the ketone.[141] This suggests high susceptibility of such *O*-vinyloximes to the electrophilic addition of water to the C=N bond to form intermediates **79**.



79 **78** (~85%)

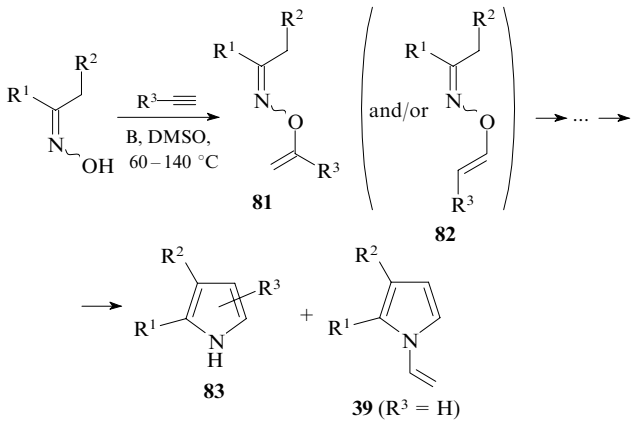
Oximes react with diacetylene in DMSO in the presence of catalytic amounts of KOH at temperature not exceeding 60 °C, which leads to the (*Z*)-*O*-ethynylvinyl derivatives **80**.[142, 143]



80 (36% – 41%)

R^1, R^2 = Alk.

Whereas oxime adducts to activated alkynes are formed even in the presence of weak bases (*e.g.*, triphenylphosphine-catalysed reaction of oximes with ethyl propiolate[144]), the vinylation of oximes with acetylene occurs only in superbasic media (*e.g.*, in the KOH – DMSO system), which enhance the nucleophilicity of oximate anions. Under such conditions, oximes add to acetylene and its alkyl and aryl derivatives to form *O*-vinyloximes **81** or **82**. This process represents the first stage of the Trofimov reaction,[88, 145 – 156] which leads to pyrroles **83** and *N*-vinylpyrroles **39** (the latter are formed in the excess of acetylene).



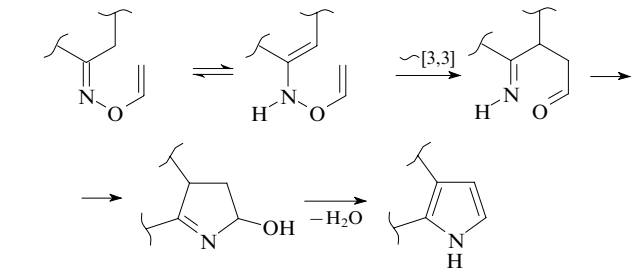
81 **82** **83** **39** (R^3 = H)

R^1, R^2 = Alk, Ar, Het; R^3 = H, Alk, Ar;
B are alkali metal hydroxides or alkoxides.

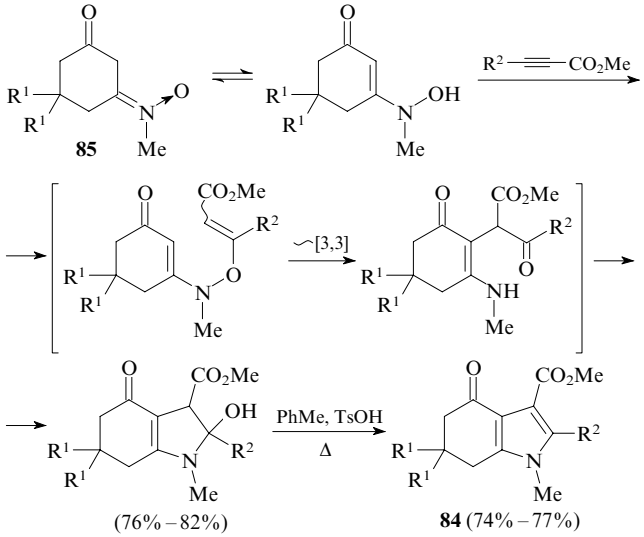
The yields of pyrroles depend on the structure of starting ketones and usually amount to 50% – 70%; in certain cases, they can be nearly quantitative. The prerequisite for this reaction is that a ketoxime had an α-methyl or methylene group relative to the oxime function. If an oxime has both groups, then the methylene group is involved, as a rule, in the pyrrole ring formation.[88, 147, 149, 156 – 170]

In the absence of α-methylene groups in the oxime molecule [*e.g.*, in methyl (het)aryl, methyl *iso*(*tert*)alkyl, diaryl, aryl hetaryl ketoximes], intermediate *O*-vinyl ketoximes can be isolated.[88, 147, 149, 156 – 169, 171, 172] Isopropyl (het)aryl ketoximes were used for the synthesis of 3*H*-pyrroles, which are difficult to synthesise.[173]

O-Vinyloximes **81** and **82** easily rearrange into pyrroles upon heating in the KOH – DMSO system[88, 147, 149, 167] or in pure DMSO.[174, 175]



Recently, a similar reaction scheme was used for the synthesis of 4-oxo-4,5,6,7-tetrahydroindoles **84** from nitrone **85**.[176]

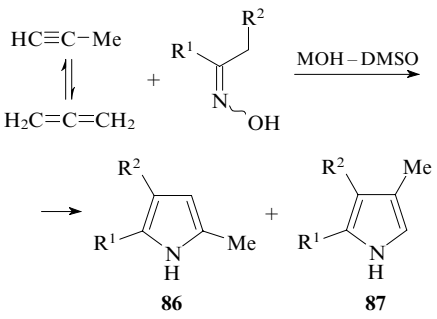


85 (76% – 82%) **84** (74% – 77%)

R^1 = H, Me; R^2 = H, CO_2Me.

It should be noted that *O*-vinylamidoximes synthesised by the addition of amidoximes to acetylene in superbasic media do not undergo the [3,3]-sigmatropic rearrangement that would lead to the formation of the desired imidazoles.[177]

The reaction of ketoximes with the simplest homologue of acetylene, *i.e.*, propyne, its isomer allene and their mixture was studied[178] in the MOH – DMSO system. In all the cases (at ordinary and elevated pressures, at different temperatures and reaction times), 5- (**86**) and 4-methylpyrroles **87** are formed.

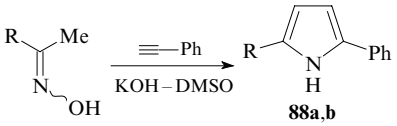


86 **87**

R^1 = Me, Pr^i, Bu^t, Ph, 2-furyl, 2-thienyl; R^2 = H, Me;
$R^1 - R^2 = (CH_2)_4$; M = K, Cs.

Under these conditions, easy prototropic isomerisation of propyne to allene and *vice versa* occurs. The result of the reaction depends substantially on the ketoxime structure, being determined not only by electronic factors, but also by steric factors. Thus the more branched is the substituent at the oxime function, the larger the fraction of 4-substituted pyrrole **87**. This synthesis of pyrroles, which involves the use of a propyne – allene mixture, *i.e.*, a large-scale waste of pyrolysis of hydrocarbons into acetylene, extends significantly the scope of this reaction for the synthesis of 4- and 5-methylpyrroles with various substituents in positions 2 and 3 accessible.

The reaction of oximes of acetone and acetophenone with phenylacetylene carried out under conditions of the Trofimov reaction produced 2-phenylpyrroles **88a**,**b**.[179]

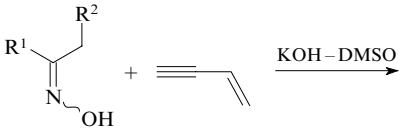


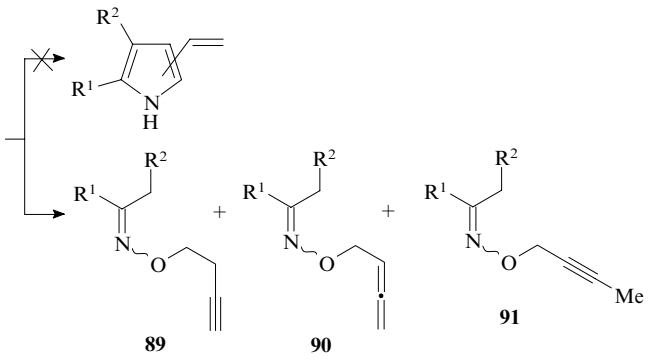
88a,**b**

R = Me (**a**), Ph (**b**).

Thus, the reaction of ketoximes with acetylene allows one to easily obtain pyrroles with alkyl, aryl and hetaryl substituents as well as different systems annelated with the pyrrole ring. This reaction makes an almost unlimited series of *N*-vinylpyrroles available. These compounds, on the one hand, contain a convenient protective *N*-vinyl group which can easily be removed[180,181] and, on the other hand, represent good building blocks for the synthesis of pyrrole derivatives and monomers with wide synthetic potentials.

As in the case of reactions with diacetylene (see above), no pyrroles are formed in the reaction of ketoximes with vinylacetylene in systems MOH – DMSO (M = K or Li). This reaction produces only mixtures of *O*-butynyl and *O*-butadienyl ketoximes **89** – **91** (yield < 50%).[182]

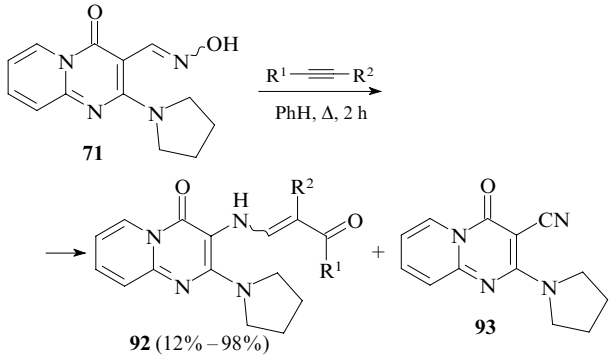




89 **90** **91**

R^1 = Me, R^2 = H, $R^1 - R^2 = (CH_2)_4$.

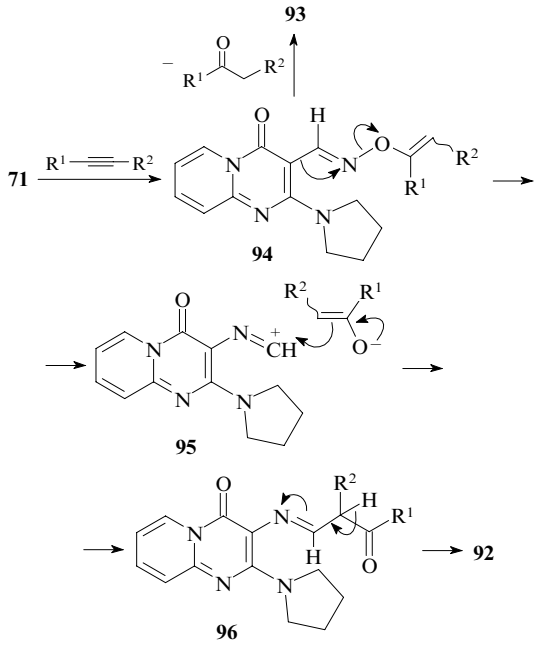
Recently, information on the nucleophilic addition of heterocyclic oxime **71** to dimethyl acetylenedicarboxylate, dibenzoylacetylene and methyl propiolate has appeared.[137]. The reaction proceeds on refluxing the reactants in benzene for 2 h. In place of expected O- or N-adducts, enamines **92** and traces of nitriles **93** were isolated.



71 **92** (12% – 98%) **93**

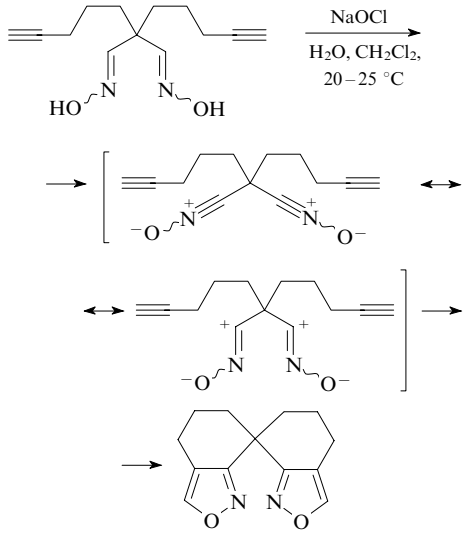
$R^1 = R^2 = CO_2Me$, C(O)Ph; R^1 = H, $R^2 = CO_2Me$.

The formation of enamines **92** is explained by the O-nucleophilic attack of oxime **71** on the triple bond. *O*-Vinyloxime **94** formed undergoes decomposition along the Beckmann rearrangement path to give carbocation **95** and an enolate; these react to afford imine **96**. Rearrangement of the latter leads to enamine **92**, while nitrile **93** is formed as a result of elimination of the ketone from *O*-vinyloxime **94**.



94 **95** **96**

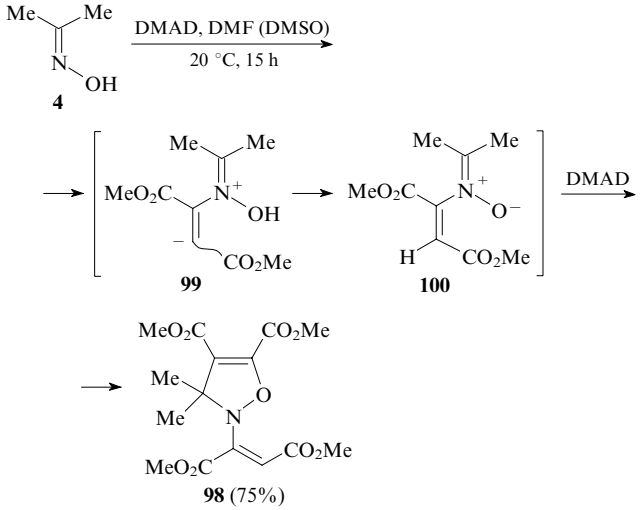
Synthesis of the first spirocyclic bis(isoxazole) **97** as a racemate is described.[183] This cyclic bis(*O*-vinyloxime) represents a C_2-symmetric chiral ligand used in enantioselective catalysis. Intramolecular cyclisation of diacetylenic dialdoxime occurs under the action of 5% aqueous NaOCl. According to the researchers cited, the reaction yields bis(nitrile oxide). However, another possible mechanism includes the primary O-nucleophilic attack of the oxime function on the triple bond followed by oxidation of intermediates. Resolution of this racemate into optical isomers was accomplished by column chromatography on a chiral stationary phase.



97 (67%)

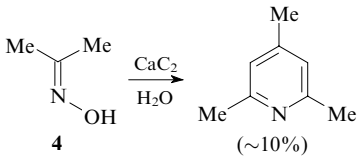
Summarising, we show several examples of reactions of oximes with acetylene derivatives that involve an electrophilic attack on the nitrogen atom.

Thus acetone oxime (**4**) adds to dimethyl acetylenedicarboxylate (DMAD) to form a cyclic product, namely, functionalised 4,5-isoxazoline **98**.[184–186]

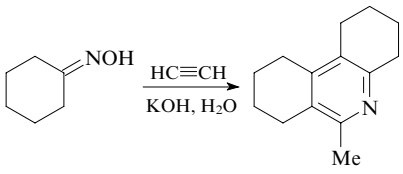


Presumably, the addition of oxime to the C≡C bond produces a zwitterionic intermediate **99**, *i.e.*, the oxime plays the role of an uncharged nucleophile. Intramolecular transfer of a proton in the intermediate **99** results in the formation of nitrone **100**. The latter enters 1,3-dipolar addition with the second molecule of dimethyl acetylenedicarboxylate to yield isoxazoline **98**, which is the 1 : 2 adduct.

It should be noted that in some cases the data on the reactions of oximes with acetylenes conflict with one another. For instance, the results of a publication[187] describing synthesis of simplest *O*-vinyloximes by vinylation of oximes with calcium carbide in an aqueous medium at 200–220 °C were checked in another study[188] and were not confirmed. Under these conditions, instead of *O*-vinyloximes, pyridines were obtained in low yields.[88,189]

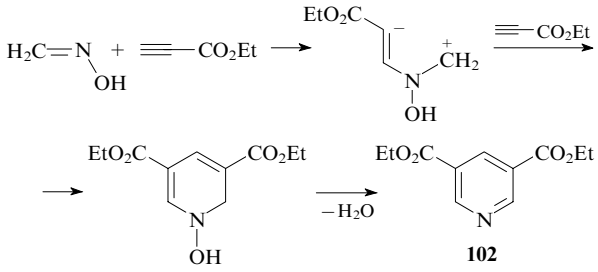


In the presence of KOH, cyclohexanone oxime reacts with unsubstituted acetylene to form 6-methyl-1,2,3,4,7,8,9,10-octahydrophenanthridine (**101**) in a yield of up to 30%.[88] However, the conditions of this reaction were not optimised by the authors.



101 (20%–30%)

3,5-Diethoxycarbonylpyridine **102** was synthesised in a reaction of formaldoxime with ethyl propiolate.[117] Here, the hydroxyl group of oxime remains inert with respect to the triple bond and the nitrogen atom plays the role of a nucleophilic centre. The reaction proceeds on refluxing the reactants in 50% aqueous methanol; no intermediate adduct was isolated.

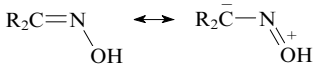


Reactions of α-chlorooximes[190,191] and α-amidooximes[192,193] with acetylenes are also documented. However, since these compounds may be considered as the derivatives of hydroxamic acids (acid chlorides and amides), their reactions are beyond the scope of our survey.

IV. Nucleophilic attack on the C=N bond of oximes

Being treated with bases, oximes not only undergo deprotonation, which enhances their nucleophilicity, but are also subjected themselves (especially, oxime ethers) to a nucleophilic attack on the nitrogen atom. Thus, competition often exists between the roles that an oxime plays as the nucleophilic regent and as the object of a nucleophilic attack.

The presence of an oxygen atom adjacent to the C=N double bond that can exert both negative inductive and positive mesomeric effects reduces the basicity of the nitrogen atom as compared with imines and decreases the positive charge on the carbon atom, making the latter less susceptible to the nucleophilic attack. For instance, the higher resistance of oximes against hydrolysis as compared with imines is explained[194] by the participation of the oxygen atom in charge delocalisation.



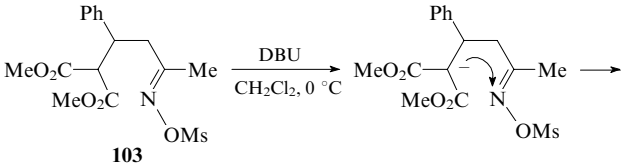
On the other hand, the electronegative nature of the oxygen atom favours nucleophilic substitution at the nitrogen atom of the oxime function.

1. Intramolecular nucleophilic substitution at the nitrogen atom

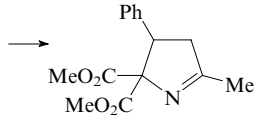
a. Heterocyclisation of oxime derivatives into azoles

Oximes with a nucleophilic site in the side chain and the N–O bond activated by the introduction of an acceptor substituent at the oxygen atom undergo intramolecular nucleophilic substitution to afford 5-membered nitrogen-containing heterocycles.‡

Thus *O*-mesyloxime **103**, which has an activated methine group in the γ-position with respect to the oxime function, is converted quantitatively into pyrroline **104** upon its treatment with a strong organic base, namely, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[196, 197]

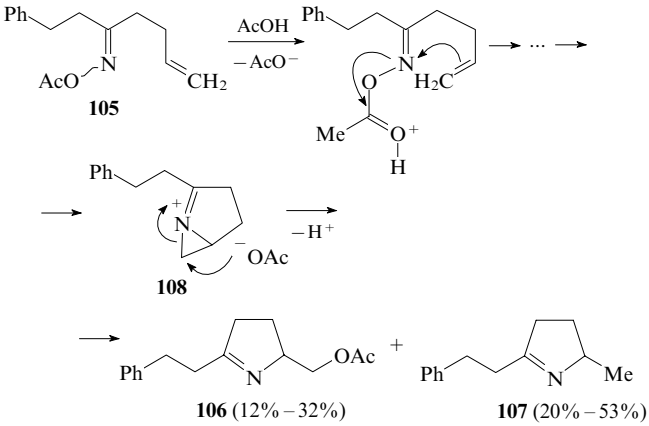


103



104 (99%)

Heating of *O*-acetyloxime of γ,δ-unsaturated ketone **105** (the ratio of *Z*- and *E*-isomers is ~1 : 1) in an acidic medium in the presence of hydrogen donors (AcOH, cyclohexa-1,4-diene, dioxane) under reflux for 6 h leads to a mixture of 2-acetoxymethyl-3,4-dihydro-2*H*-pyrrole **106** and 2-methyl-3,4-dihydro-2*H*-pyrrole **107**, which are formed by different mechanisms.[198] The reaction was assumed to proceed *via* a cationic intermediate **108**.



105

108

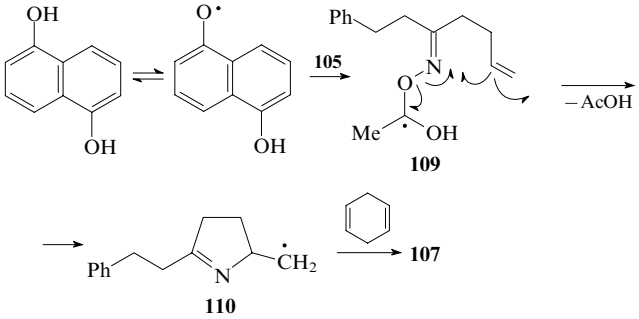
106 (12%–32%) **107** (20%–53%)

However, since 2-methylpyrroline **107** could not be formed according to a nucleophilic substitution mechanism, it was assumed[198] that an additional pathway of radical cyclisation exists.§

‡ During preparation of this review for publication, one more review[195] appeared, which is devoted to the use of intramolecular nucleophilic substitution at the oxime nitrogen atom for the synthesis of various nitrogen heterocycles and contains partially the material presented in this section.

§ Although homolytic reactions of oximes are not considered in a special Section, it seemed reasonable to present the scheme of the radical mechanism. Studies of the synthesis of pyrrolines by photochemical cyclisation of *O*-acetyl- and *O*-methyloximes of γ,δ-unsaturated ketones were continued in a recent publication.[199]

The possible mechanism was confirmed in experiments carried out in toluene-d_8 in the presence of free-radical traps such as hydroquinone and naphthalene-1,5-diol. The sequence of transformations that involve naphthalene-1,5-diol is as follows:[198]

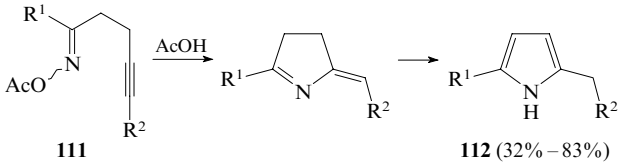


109

110

The transfer of an electron from naphthalene-1,5-diol to oxime **105** leads to the formation of radical **109**, which cyclises to form pyrroline radical **110**. The latter splits a hydrogen atom from cyclohexa1,4-diene to form pyrroline **107**.

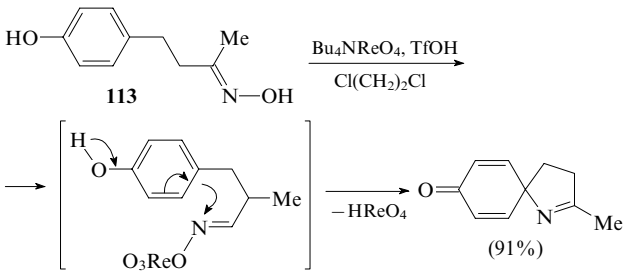
Under similar conditions (AcOH, hydroquinone, cyclohexa-1,4-diene, dioxane, reflux, 6–24 h), *O*-acetyloximes **111**, which contain alkyl substituents, cyclise to pyrroles **112**.[198]



111 **112** (32%–83%)

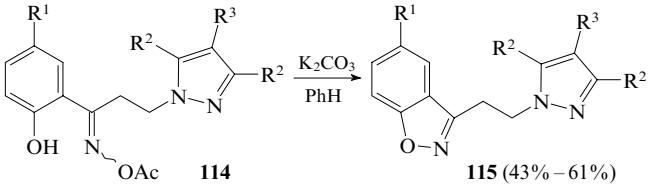
R^1 = Me, Ph, $(CH_2)_2Ph$; R^2 = H, Ph, CO_2Et.

The direction of heterocyclisation of phenols depends on the mutual arrangement of the hydroxyl group and the side-chain oxime fragment. Intramolecular nucleophilic substitution of the S_N2 type at the nitrogen atom is observed in the reaction of ketoxime **113** with tetrabutylammonium perrhenate in the presence of trifluoromethanesulfonic acid (TfOH). Here, the phenolic substituent plays the role of a nucleophile.[200]



113

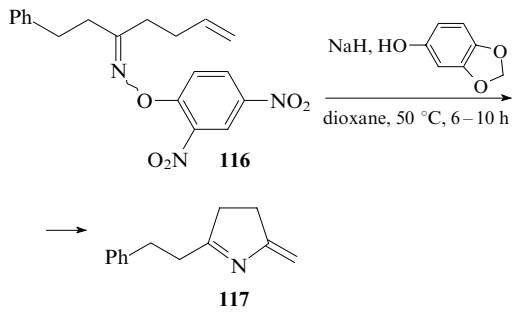
Examples of an intramolecular nucleophilic attack of a phenoxide ion on the nitrogen atom in an acetylated oxime function are known[201]. Thus the treatment of *O*-acetyloximes **114** with potassium carbonate in benzene leads to benzoisoxazoles **115**.



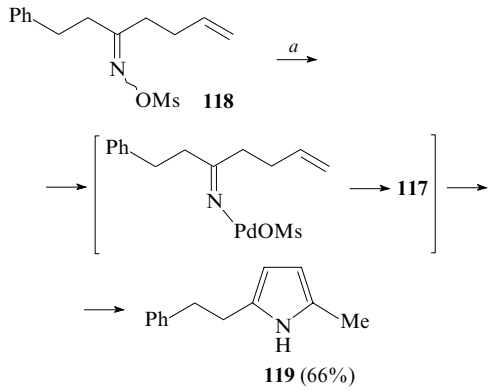
114 **115** (43%–61%)

R^1, R^2, R^3 = H, Alk.

Reduction of *O*-2,4-(dinitrophenyl)oximes of γ,δ-unsaturated ketones **116** in the presence of a radical trap (3,4-methylenedioxyphenol) leads to cyclisation to pyrrolines **117**.[202]

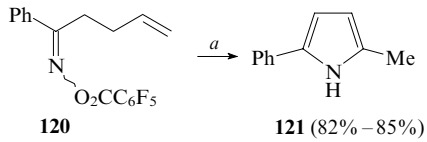


As a result of the aza-Heck intramolecular reaction, *O*-methylsulfonyloxime **118** is converted into pyrrole **119**, the yield of the expected Beckmann rearrangement products being 10% (see below, Section VI).[203]



(*a*) $Pd(OAc)_2$ (10 mol.%), $P(o\text{-}Tol)_3$ (30 mol.%), Et_3N, DMF, 80 °C, 0.5 h.

The use of *O*-acyloximes increases the regioselectivity of the process. Thus, irrespective of its configuration, *O*-pentafluorobenzoyloxime **120** undergoes Pd(0)-catalysed cyclisation to pyrrole **121**. The high yield of the product was explained by the absence of side Beckmann rearrangement.[203]



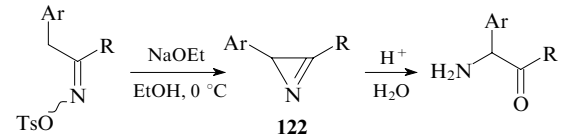
(*a*) (1) $Pd(PPh_3)_4$ (3 mol.% – 10 mol.%), Et_3N, DMF, 80 °C, 1 h; (2) Me_3SiCl, CH_2Cl_2, 20 °C, 0.5 h.

This version of the aza-Heck reaction is a simple approach to the synthesis of 2,5-disubstituted pyrroles provided oximes of the types **118** and **120** are available. Surveys [195, 204] show several more examples of such cyclisation and also discuss relevant publications [205 – 211] describing intramolecular nucleophilic substitution reactions at the oxime nitrogen atom that involve unsaturated substituents and proceed under the action of, *e.g.*, Ni(0) [210] and copper salts.[211 – 217] Similar reactions that lead to quinoxalines and 2*H*-dihydropyrroles were considered.[218]

b. The Neber rearrangement

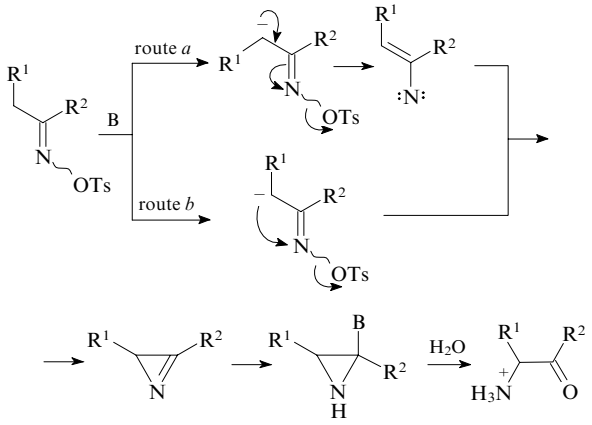
THe mechanisms of the Neber and the Hoch – Campbell reactions (see Section IV.1.c) assume the formation of intermediate azirines as the key stage. Intramolecular nucleophilic substitution of the groups at the oxime nitrogen atom is realised by a carbanion, which is generated as a result of the abstraction of an α-proton under the effect of bases. It thus seems reasonable to discuss these reactions in the Section devoted to the nucleophilic attack on the C=N bond.

The Neber rearrangement [84, 219 – 229] represents a transformation of ketoxime sulfonates into α-amino ketones in the presence of bases. In certain cases, intermediate azirines **122** were isolated from the reaction mixtures.[226 – 229]



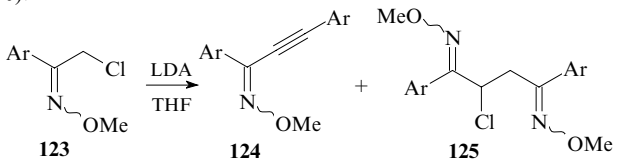
R = Ar, CH_2Ar.

Two possible mechanisms of the rearrangement were proposed,[227, 230] namely, the nitrene mechanism (route *a*) and the anionic mechanism (route *b*).



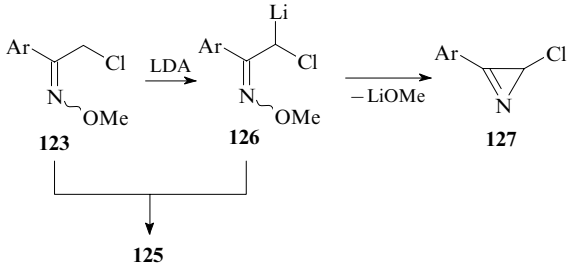
The mechanism of the Neber rearrangement was also considered in other studies.[231, 232] The use of chiral quaternary ammonium salts as the phase-transfer catalysts allowed preparation of optically active amino ketones (*ee* reaches 70%).[232] This suggests that the reaction follows the anionic route *b*, because the route *via* nitrenes should lead to the loss of stereochemical information transferred in the deprotonation of oxime upon the action of a chiral base.

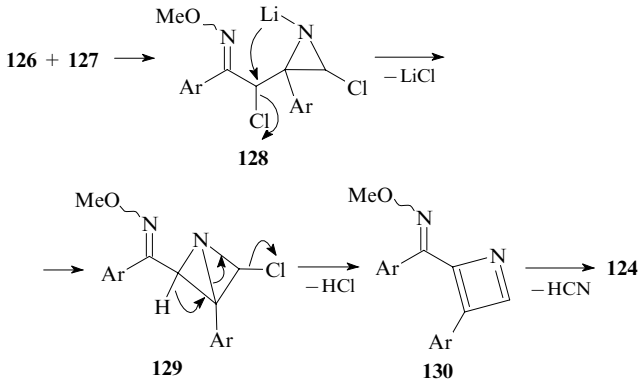
The reaction of *O*-methyloximes of substituted α-chloro acetophenones **123** with LDA leads to *O*-methyloximes of 1,3-diarylpropyn-1-ones **124** and bis(*O*-methyloximes) of 1,4-diketones **125** (in certain cases, *e.g.*, for Ar = Ph, their yield reaches 38%).[233]



Ar = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 2-naphthyl.

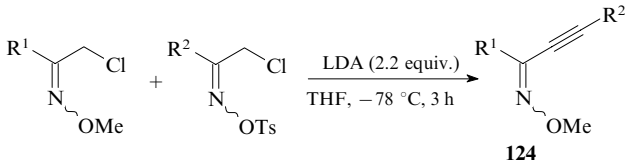
Bisoximes **125** are formed in the reaction of the starting substrate with its lithiation product **126**, while alkynyloximes **124** are formed as a result of several rearrangements *via* chloroazirines **127**.





It was assumed [233] that, first, aziridine **128** is formed from chloroazirine **127** and its lithium derivative **126**, which is followed by a two-step fragmentation of the intermediate 1-aza-2-chlorobicyclo[1.1.0]butane **129**. Its dehydrochlorination with ring-opening yields unstable azacyclobutadiene **130**, which decomposes into alkynyloxime **124** and HCN. In certain experiments (*e.g.*, for Ar = 4-ClC_6H_4), the addition of $MgBr_2$ to the reaction mixture substantially increases the yield of alkynyloximes **124** (from 19% to 70%), which at best reaches 81%.

In reactions of two different α-chlorooximes one of which has a good leaving group (TsO, $EtCO_2$) at the nitrogen atom, cross-coupling occurs.[233] As a result, alkynyloximes **124** with different substituents are formed. If an oxime has no bulky groups (*e.g.*, *tert*-butyl), the reaction proceeds stereoselectively.



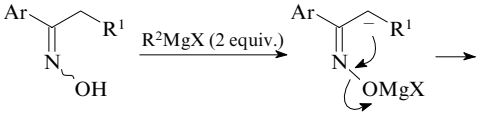
R^1	R^2	Yields of compounds **124** (%)	Ratio *Z* : *E*
Me	Ph	57	> 95 : 5
Bu^t	Ph	63	62 : 38
cyclo-C_5H_9	Ph	73	> 95 : 5
n-C_8H_{17}	Ph	69	> 95 : 5
Ph	4-ClC_6H_4	73	94 : 6
4-$MeOC_6H_4$	Ph	68	> 95 : 5
4-ClC_6H_4	Ph	65	> 95 : 5

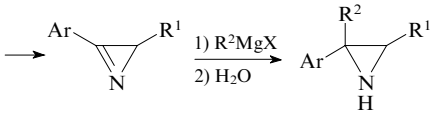
The Neber rearrangement was used for the synthesis of compounds that can influence the cardiovascular system,[234, 235] exhibit antipsychotic activity [236] and are potential histamine antagonists (H_2).[237]

c. The Hoch – Campbell reaction

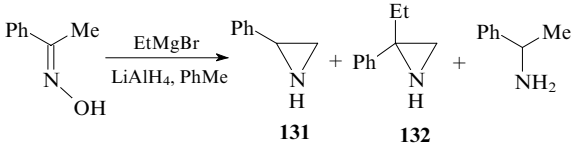
Hoch [238] and Campbell [239 – 242] have independently discovered that, when treated with Grignard reagents, ketoximes afford aziridines in the yields varying from low to moderate. Later, this reaction was used in the synthesis of various compounds of this class.[101, 108, 243 – 248] Upon hydrolysis, the aziridine ring opens to yield amino alcohols.[239]

Formally, the Hoch – Campbell reaction is similar to the Neber rearrangement, because it involves a nucleophilic attack of a carbanionic centre on the oxime nitrogen atom.[219]

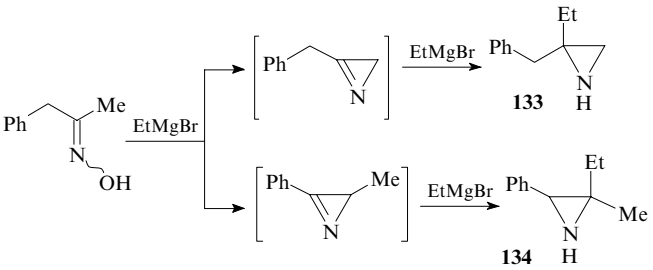




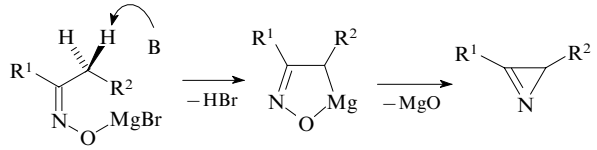
A mixture of aziridines **131** and **132** with α-phenylethylamine in the 64 : 1 : 35 ratio was isolated upon the reaction of acetophenone oxime with EtMgBr in the presence of $LiAlH_4$. The formation of aziridine **131** confirms the role of azirines as the intermediates in this reaction.[249]



By the example of benzyl methyl ketoxime, it was shown [244] that the formation of an azirine ring is stereospecific in toluene. This reaction preferentially involves a substituent in the *syn*-position with respect to the hydroxyl group of the oxime function and produces aziridine **133**. However, in THF both possible isomers, *viz.*, compounds **133** and **134**, are formed.



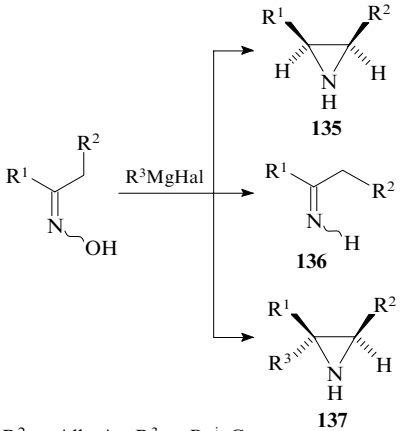
It was assumed [101] that the cationoid Mg atom favours the proton abstraction from the *syn*-methylene group due to the intramolecular stabilisation of the carbanionic centre formed.



B = AlkMgBr.

The preferential involvement of *syn*-methylene groups in the formation of aziridines was also observed in the reaction of *O*-alkylketoximes with the Grignard reagents.[36] The steric effect of substituents in the azirine ring determines the stereoselectivity of the addition of an organomagnesium compound to the intermediate azirine.[244]

Three types of compounds, namely, aziridine **135**, ketimine **136** and a product of the Hoch – Campbell reaction **137**, were

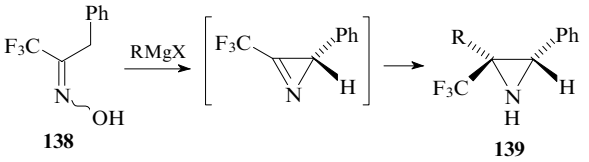


R^1, R^2 = Alk, Ar; R^3 = Bu^i, Cy.

obtained in a reaction of a series of aliphatic and aromatic ketoximes with organomagnesium derivatives.[250]

The result of this reaction depends strongly on the nature of both the oxime and the Grignard reagent used. Thus cyclohexanone oxime is converted exclusively into the Hoch–Campbell reaction products **137** [$R^1-R^2=(CH_2)_4$], whereas benzophenone oxime and camphor oxime form only ketimines **136**. Among all organomagnesium compounds used, isobutylmagnesium bromide showed the best results in the reductive formation of aziridine, whereas in the case of phenethyl- and 2,2-diphenylethylmagnesium bromides the reaction did not follow this pathway.

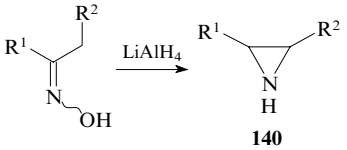
Trifluoromethylaziridines **139** were synthesised in reactions of trifluoromethyl ketoxime **138** with Grignard reagents.[251,252]



138 **139**

R = Alk, All.

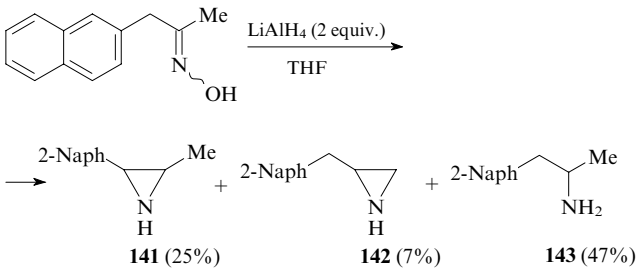
Substituted aziridines **140** are formed together with amines in reactions of oximes with lithium aluminium hydride.[253,254] It is evident that this kind of transformation can be considered as an analogue of the Hoch–Campbell reaction.



140

R^1, R^2 = H, Alk, Ar.

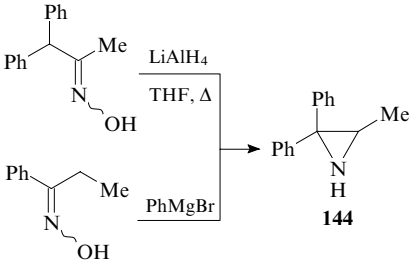
Reflux of a mixture of *syn*- and *anti*-isomers (1 : 4) of β-naphthylpropan-2-one oxime with 2 equivalents of $LiAlH_4$ in THF yields *cis*-3-methyl-2-(β-naphthyl)aziridine **141**, 2-(β-naphthylmethyl)aziridine **142** and a primary amine **143**.[254]



141 (25%) **142** (7%) **143** (47%)

Naph = naphthyl.

Reduction of 1,1-diphenylpropan-2-one oxime with lithium aluminium hydride in boiling THF produces 3-methyl-2,2-diphenylaziridine **144** in 41% yield.[253] Its structure was also confirmed by an independent synthesis according to the Campbell method from ethyl phenyl ketoxime and PhMgBr.[241]



144

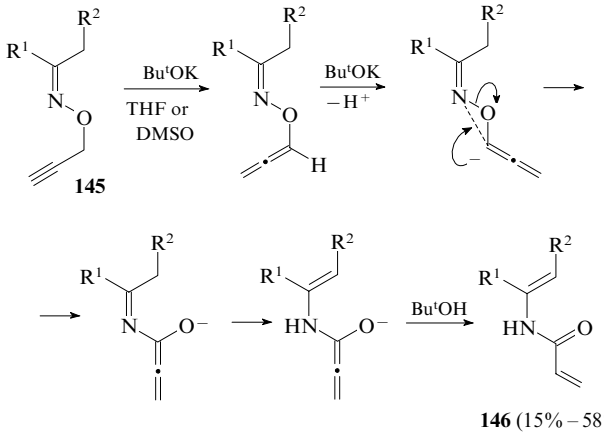
It was noted[253] that the methyl group is involved in the formation of an aziridine ring upon the reduction of 1-alkyl-1-phenylpropan-2-ones with $LiAlH_4$. Thus the reactions of 1-methyl-1-phenyl- and 1-ethyl-1-phenylpropan-2-ones produced, in addition to primary amines, 2-(1-phenylethyl)- and 2-(1-phenylpropyl)aziridines in 38% and 31% yields, respectively. Under similar conditions, aldoximes also form aziridines in 38% yield, whereas the attempts to obtain aziridines from *O*-tosylaldoximes by the Neber reaction failed.[219]

Reduction of di(*p*-methylbenzyl) ketone oxime and its acyl derivatives with $LiAlH_4$ in THF proceeds stereopecifically to give *cis*-aziridines (yields >80%).[255] Complex hydride $NaAlH_2(OC_2H_4OMe)_2$ exhibits higher selectivity, it reduces ketoximes and their ethers into substituted aziridines in high yield with only trace amounts of amines.[255]

Thus, the conversion of oximes into aziridines under the action of $LiAlH_4$ and related hydrides resembles the reactions with organomagnesium compounds: in both cases azirines are the intermediates which are formed in an intramolecular nucleophilic attack of the α-carbanionic centre on the oxime nitrogen atom.[256]

d. Miscellaneous reactions

In closing this Section, we consider two examples of the nucleophilic attack on the C=N bond. Thus it is assumed that the intramolecular nucleophic substitution at the oxime nitrogen atom is the key stage of the mechanism of strong-base-induced rearrangement of *O*-propargylketoximes **145** into *N*-1-alkenylacrylamides **146**.[257]

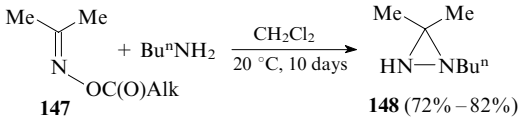


145

146 (15%–58%)

R^1 = Alk, Ar; R^2 = H, Alk; $R^1-R^2=(CH_2)_n$; n = 3, 4.

Carbon and nitrogen atoms in the C=N bond manifest simultaneously their electrophilic properties in the reaction of acetone oxime esters **147** with butylamine to give diaziridine **148**.[258]



147 **148** (72%–82%)

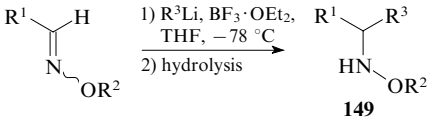
For similar acetaldoxime derivatives, the yield of diaziridine is only 16% due to the concomitant elimination of the acid $AlkCO_2H$.

2. Addition of organometallic compounds to the C=N bond

The reaction of organometallic compounds with oximes or their ethers is of interest for the synthesis of hydroxylamines. Addition of alkyl- or phenyllithium to unprotected oximes requires a substantial excess of the organolithium compound.[259] Moreover, the presence of active α-hydrogen atoms relative to the oxime function substantially reduces the yield of the adduct.

Lewis acids favour the reaction of organometallic compounds with the oxime group probably due to the coordination to nitrogen and oxygen atoms, which increases the positive charge on the carbon atom. Thus in the presence of 1 equivalent of $BF_3\cdot OEt_2$,

(het)aryllithium compounds add to aldoxime ethers to form *O*-alkylhydroxylamines **149** (in yields up to 64%).[260]

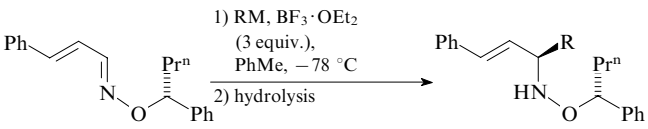


149

R^1 = Me, Pr^i; R^2 = Me, Bu^n; R^3 = Ar, Het.

In this case, the oxime group configuration has a strong effect on the yield of the reaction product, which is substantially higher for *Z*-isomers.[260]

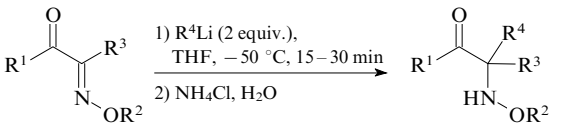
The addition of organolithium and organomagnesium compounds to (*R*)-*O*-(1-phenylbutyl)cinnamaldoxime **150** was used as the key stage in asymmetric synthesis of α-amino acids.[261] The highest yields of adducts **151** were achieved in reactions with alkyl(or aryl)lithium.



150 **151** (76% – 95%, 71% – 93% *de*)

R = Alk, Ar; M = Li, MgBr.

The reaction of organolithium compounds with oximes of α-oxo carboxylic acids, their esters and amides **152** produces derivatives of *N*-hydroxy amino acids **153**.[262]

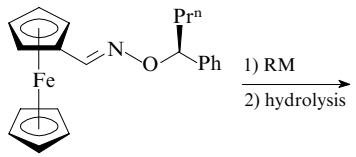


152 **153** (63% – 80%)

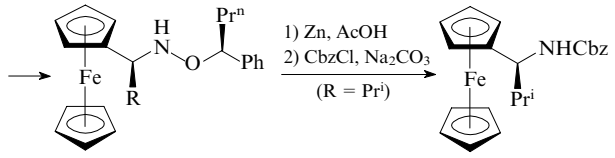
R^1 = OH, OMe, OBu^t, NMePh; R^2 = Bn, PhCHMe; THP;
R^3 = H, Me; R^4 = Me, Bu^n, Bu^s, Bu^t, Ph;
THP is tetrahydropyran-2-yl.

High yields of products of this reaction were explained by the activating effect of the acceptor substituent at the oxime function. However, organomagnesium and organozinc compounds do not react with oximes **152** under these conditions.[262]

A series of chiral ferrocenylalkylamines (*e.g.*, compound **154**) were synthesised by diastereoselective 1,2-addition of organometallic reagents to ethers of ferrocenecarbaldelyde oxime **155** containing a chiral substituent, which was followed by reduction of hydroxylamines **156** formed.[263]



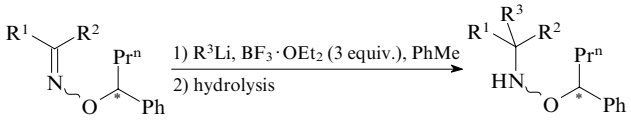
155



156 **154** (62%)

156: R = Pr^i (85%), Bu^n (81%), All (70%);
M = Li, MgHal; Cbz is benzyloxycarbonyl.

Recently, an asymmetric synthesis of α-amino acids, which is based on diastereoselective addition of organolithium compounds (2-furyllithium, phenyllithium, vinyllithium) to (*R*)- and (*S*)-*O*-(1-phenylbutyl)oximes **157** was carried out.[264] The corresponding hydroxylamines **158** were obtained with high diastereoselectivity (the configuration of the new chiral centre is given first).

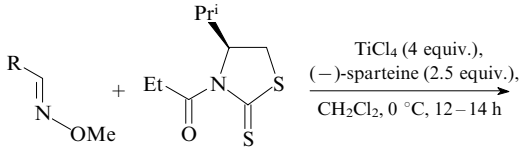


157 **158**

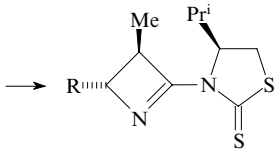
R^1	R^2	R^3	Yield (%)	*de* (%) (configuration)
Pr^i	Me	2-furyl	31	52 (*R*,*S*)
4-BrC_6H_4	Me	2-furyl	14	> 95 (*R*,*S*)
4-$BrC_6H_4CH_2$	H	2-furyl	40	83 (*S*,*R*)
Pr^i	H	Ph	38	95 (*R*,*S*)
Bu^t	H	Ph	31	> 98 (*R*,*S*)
$EtMe_2C$	H	Ph	32	> 98 (*R*,*S*)
Pr^n	H	H_2C=CH	87	84 (*R*,*S*)
Pr^i	Me	H_2C=CH	54	> 95 (*S*,*R*)
H_2C=$CH(CH_2)_2$	H	H_2C=CH	77	94 (*R*,*S*)
Cy	H	H_2C=CH	74	92 (*S*,*S*)
Ph	H	H_2C=CH	46	98 (*S*,*S*)

Reductive cleavage of the N – O bond in hyroxylamines **158**, followed by a series of successive transformations produces *N*-substituted amino acids and their esters.[264]

O-Methyloximes add chlorotitanium enolate of *N*-propionylthiazolidine-2-thione **159** to form azetine **160**.[265]



159



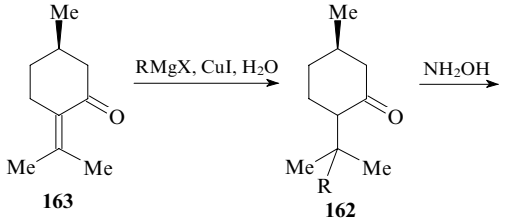
160

R = Cy, Ph, styryl, 1-naphthyl, 2-thienyl.

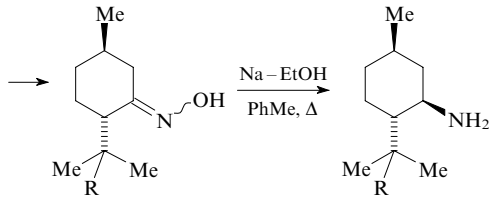
3. Reduction of oximes

Depending on the reagent nature, the reduction of oximes may produce amines, hydroxylamines or alcohols. As a rule, alkali metals or complex metal hydrides are used as the reducing agents. The key stage of this reaction is the transfer of a hydride ion or an electron to the antibonding orbital of the C=N bond to form an N-anion or a radical anion. Below, different types of reagents used in the oxime reduction are considered.

Oximes are smoothly reduced with sodium in liquid ammonia to form amines.[266] Optically pure menthylamine (**161a**), (−)-8-methylmenthylamine (**161b**) and (−)-8-phenylmenthylamine (**161c**) were prepared from the available menthone (**162**, R = H) and (+)-pulegone (**163**) by reduction of the corresponding oximes with the Na – ethanol system in refluxing toluene.[267]



163 **162**

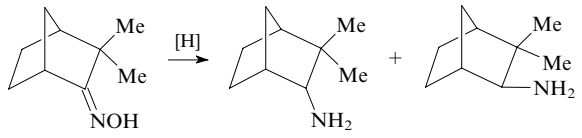


161a–c

R = H (**a**, 59%), Me (**b**, 67%), Ph (**c**, 93%).

Refluxing of ketoximes in THF in the presence of $LiAlH_4$ usually leads to aziridines in addition to amines (yields up to 47%).[253,255] $TiCl_4$ or $FeCl_3$ additives to lithium aluminium hydride make the process more selective in the case of oximes of chroman-4-one, acetophenone and benzophenone. The corresponding amines were obtained in 60% – 70% yields.[268]

A search for reagents for the reduction of camphenylone oxime **164** was carried out[269] with the aim of preparing *endo*-2-camphenylamine **165**.

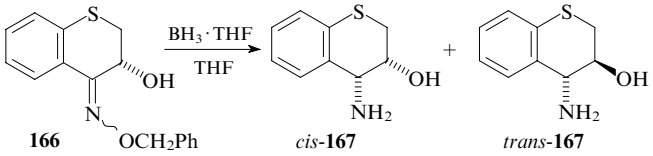


164 *endo*-**165** *exo*-**165**

Systems $LiAlH_4$ – THF (product **165** is formed in 72% yield, the ratio *endo* : *exo* = 5 : 3), $NaBH_4$ – $TiCl_4$ – glyme (76%, 100 : 0) and Na – Pr^nOH (78%, 100 : 0) have proved to be effective.

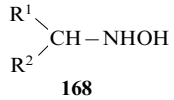
In the presence of chiral additives, the asymmetric reduction of oximes is possible. Thus a complex of lithium aluminium hydride with 3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose reduces different aliphatic and aromatic ketoximes and their methyl and tetrahydropyranyl ethers to chiral amines in low or moderate optical yields.[270] The best enantioselectivity (56% *ee*) was achieved in the reduction of methyl cyclohexyl ketoxime.

Borane and its complexes are widely used for the reduction of various oximes. For example, the possibility of stereoselective reduction of cyclic α-hydroxy *O*-benzylketoxime **166** with borane to form 1,2-aminoalcohol **167** was demonstrated.[271] The yields were in the range 68% – 86%, the mixture preferentially contained the *cis*-isomer (68% – 92% *de*).



166 *cis*-**167** *trans*-**167**

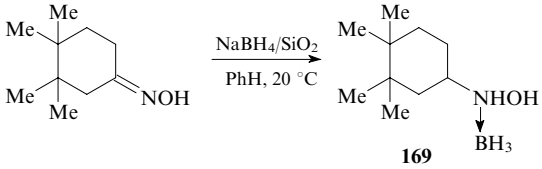
Pyridine – borane is a selective reductive system. Upon the action of this reagent, oximes are converted into substituted hydroxylamines in high yields; other functional groups (ester, nitrile, nitro groups) remaining unaffected.[272] Thus the pyridine – borane complex prepared by reaction of pyridine hydrochloride with sodium borohydride reduces oximes of aliphatic and aromatic ketones and of aromatic aldehydes to the corresponding hydroxylamines **168** in 74% – 92% yields.[273] This method can also be applied for the efficient reduction of *O*-acyl- and *O*-methyloximes.[274]



168

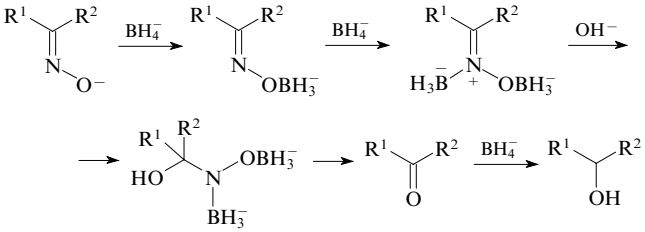
R^1 = H: R^2 = Ph, 3-$NO_2C_6H_4$, 4-CNC_6H_4, 4-ClC_6H_4; R^1 = Me, R^2 = $PhCH_2CH_2$; R^1 = Pr^n: R^2 = Pr^n, Ph.

Sodium borohydride is also an efficient reducing agent under various conditions. For example, silica gel-supported $NaBH_4$ reacts with oximes at room temperature in benzene to form borane complexes of hydroxylamines **169**.[275]



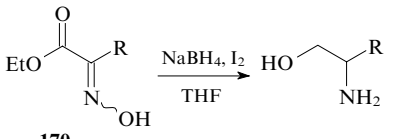
169

Refluxing of oximes with sodium borohydride in aqueous alkali affords alcohols formed upon reduction of the corresponding ketones.[276]



R^1, R^2 = Alk.

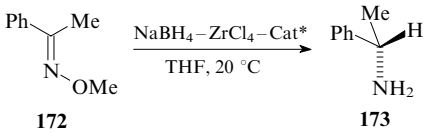
Oximes of α-oxo esters **170** are reduced with sodium borohydride in THF in the presence of I_2, AcOH, $TiCl_4$, $ZrCl_4$, $CoCl_2$, H_2SO_4 and Me_3SiCl to the corresponding amino alcohols **171**.[277]



170 **171** (60% – 85%)

R = Me, Et, Pr^i, Bu^n, Ph.

The reduction of *O*-alkylketoximes with a system $NaBH_4$ – $ZrCl_4$ modified with chiral amino alcohols was studied.[278] For example, reduction of acetophenone *O*-methyloxime **172** afforded (*S*)-1-phenylethylamine **173** in 89% – 96% yield and optical purity of 42% – 95% *ee*.



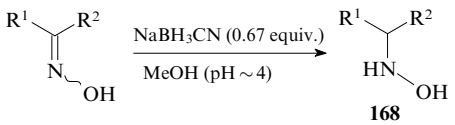
172 **173**

Cat* is (*S*)-valinol, 1,1-diphenyl-(*S*)-valinol, (*S*)-leucinol, (*S*)-isoleucinol.

Among amino alcohols studied, (*S*)-valinol and 1,1-diphenyl-(*S*)-valinol exhibit the highest enantioselectivity.

Sodium cyanoborohydride is often used as the reducing agent. Thus cyclisation of oxime ethers of 2-(3-hydroxylphenyl)ethyl ketones into the corresponding quinolines under the action of $NaBH_3CN$ is accompanied by the formation of hydrogenated derivatives.[273]

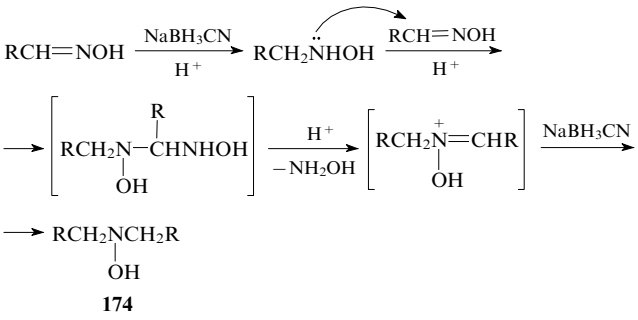
Ketone oximes are smoothly reduced with sodium cyanoborohydride in weakly acidic media (pH ~4) to form the corresponding *N*-alkylhydroxylamines **168**.[279]



168

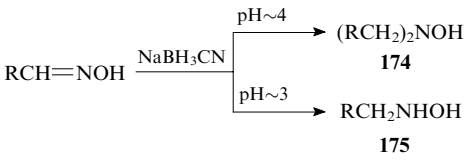
R^1	R^2	Time /h	Yield (%)
Me	Et	3	73
Me	Ph	1	75
$(CH_2)_4$		3	77
$(CH_2)_5$		3	66

Under these conditions, aldoximes undergo reductive *N*-alkylation to form bisalkylated hydroxylamines **174**.[272] These products may have been formed as a result of the following sequence of reactions:



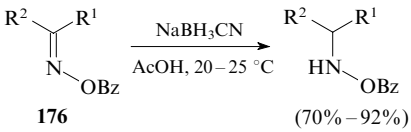
174

A decrease in the pH of the medium (down to ~3) allows one to substantially diminish the contribution of this process and synthesise monoalkyl derivatives **175**. The change in the reaction pathway is explained [272] by the acceleration of the oxime group reduction.



Compound	R	Time /h	Yield (%)
174	n-C_6H_{13}	3	57
	Ph	4	60
175	n-C_6H_{13}	1	33
	Ph	1	79

Sodium cyanoborohydride in acetic acid reduces *O*-benzoyloximes of aliphatic ketones **176** to the corresponding *O*-benzoylhydroxylamines.[274]



176 (70%–92%)

R^1–R^2 = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2CH(Bu^t)(CH_2)_2$, $(CH_2)_{11}$;
R^1 = Bn, R^2 = Me.

The reduction of ethers of oximes of aromatic aldehydes and ketones proceeds much more slowly than the decomposition of sodium cyanoborohydride under the action of acetic acid. For this reason, the reduction of the C=N bond in these compounds is ineffective under these conditions.

Triethylsilane in trifluoroacetic acid is a good alternative to sodium cyanoborohydride. This system makes it possible to reduce the above-mentioned benzoyloximes **176** (yields 73%–95%) and ethers of oximes of aromatic aldehydes to hydroxylamines.[274]

The hydrazine–Raney Ni system in aqueous or aqueous ethanolic solutions easily reduces ketoximes to the corresponding amines; under these conditions, aldoximes do not react.[280]

4. Deoximation

Deoximation is a method of conversion of oximes into carbonyl compounds. In the general case, this reaction assumes a primary attack of an O-centred nucleophile (H_2O or OH^-) on the carbon atom of the C=N bond. Apparently, the rate of the process will increase with an increase in the electrophilicity of the carbon atom of the C=N bond or the nucleophilicity of the O-nucleophile. The formation of complexes with Lewis acids (or protonation) and the oxidation of the oxime group should enhance the former parameter, while the use of superbasic media (such as KOH–DMSO) should enhance the latter parameter. The examples shown below agree well with these assumptions.

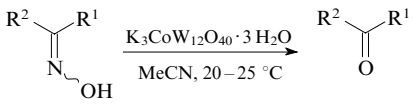
The deoximation reaction is widely used in organic synthesis and analysis, for example, in purification and identification of carbonyl derivatives.[281] Deoximation of oximes synthesised by nitrosation of active methylene groups in different organic compounds and also by condensation of nitroalkenes with aldehydes,[282] is the key stage in the synthesis of certain carbonyl compounds.[281] The oxime group can play a protective role and also selectively activate α-methylene groups;[283] hence, the studies aimed at the conversion of oxime groups into carbonyl ones are topical. Deoximation in basic media is a less common and less efficient reaction as compared with the acid-catalysed process. However, it is of interest, first of all, as a method for synthesising carbonyl compounds from oximes that contain groups unstable in the presence of acids.[281] Oxidation of alkali metal ketoximates with, *e.g.*, fluorochlorate, is often used for regeneration of ketones.[284]

Deoximation of sodium aldoximates and ketoximates with $CuCl_2 \cdot H_2O$ in acetonitrile proceeds much faster and, in certain cases, leads to higher yields of carbonyl compounds as compared with deoximation of neutral oximes.[285] This is explained [285] by the greater susceptibility of oximates to oxidation due to the higher energy of the highest occupied molecular orbital (HOMO) and larger negative charge of the oximate anion, which favour the interaction with the electrophilic centre of the oxidant.

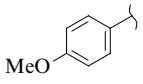
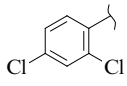
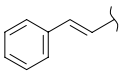
Deoximation is sometimes a side process, *e.g.*, in the synthesis of pyrroles from ketoximes and acetylenes in superbasic media by to the Trofimov reaction.[88, 145–156]

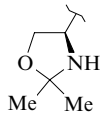
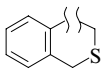
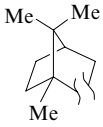
At present, deoximation methods are being actively studied.[286–300] In the past two years, several new efficient methods were developed for the removal of the oxime protection under mild conditions.[296, 301–305]

One of modern methods of deoximation is based on the use of potassium salt of cobalt-tungstic heteropolyacid $K_2CoW_{12}O_{40} \cdot 3\,H_2O$, which is an inexpensive and easily recoverable heterogeneous catalyst.[296] The reaction proceeds in acetonitrile at room temperature, the products are formed in good yields. This method allowed the conversion of various aldoximes and ketoximes, *e.g.*, compounds **177a–g**, into carbonyl compounds.



177a–g

Compound **177**	R^1	R^2	Time /min	Yield (%)
a		H	60	95
b		H	45	90
c		H	30	93

Compound **177**	R^1	R^2	Time /min	Yield (%)
d		H	45	86
e		Me	90	92
f			90	90
g			60	85

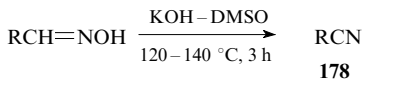
The fact that in this case the removal of the oxime protection is not accompanied by the oxidation of the liberated aldehyde function (in contrast to other reactions of oxidative hydrolysis) is an important advantage of the proposed method. Even sterically hindered camphor oxime **177g** is successfully converted under these conditions into camphor with high yield, while the oxime of α,β-unsaturated aldehyde **177c** undergoes chemoselective deoximation with the retention of the double bond and its configuration. It should be noted that deoximation of optically active oxazolidine **177d** containing an aldoxime function in the α-position with respect to the asymmetric carbon atom did not affect the chiral centre configuration.[296]

Among other recently developed deoximation methods, cleavage of oximes with antimony pentachloride (CH_2Cl_2, 0 °C – room temperature, the carbonyl compound is formed in 75% – 92% yields),[301] hydrolysis of oximes in the presence of iodobenzoic acid and β-cyclodextrin (room temperature, yields 82% – 96%) [302] and oxidative hydrolytic cleavage of oximes with *N*-bromosaccharin under microwave irradiation (acetone, H_2O, 2 – 3 min, yields 88% – 97%) [303] deserve mention.

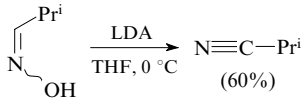
V. Dehydration

Dehydration of aldoximes, like deoximation, is usually carried out with acidic reagents.[306] However, when aldoximes contain groups sensitive to acids, the conversion of aldehydes into nitriles by elimination of water from the oxime group can be accomplished in basic media, *i.e.*, *via* oximate anions.

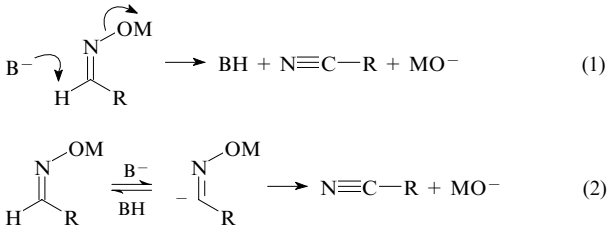
An effective synthesis of nitriles **178** by dehydration of aldoximes on heating in a superbasic system (KOH – DMSO) is described.[88, 307]



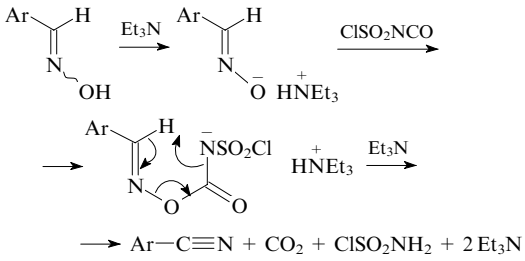
Elimination of water from aldoximes can occur under the action of such a base as LDA.[39]



Most probably, the aforementioned elimination processes follow the E2 [reaction (1)] and/or E1cB [reaction (2)] mechanisms.



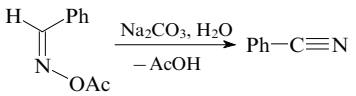
The following mechanism was proposed [308] for the dehydration of aromatic aldoximes to nitriles with chlorosulfonyl isocyanate in triethylamine (yields 74% – 87%):

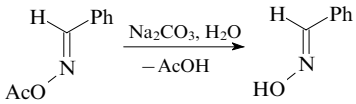


In the presence of triethylamine, the elimination of water from aldoximes also occurs under the action of SCl_2, S_2Cl_2, Cl_3CSCl, PhSCl, PhSeCl, PhSe(O)Cl (in Et_2O or $CHCl_3$) [309] or succinimidylsulfonium (in triethylamine).[310]

The rate of elimination of water or alcohols (in the case of oxime ethers) depends on the configuration of the aldoxime function. Thus upon dehydration in the system $(CF_3CO)_2O$ – pyridine (ratio 1 : 4, 3 h, room temperature), (*E*)-benzaldoxime is transformed into benzonitrile in 38% yield, whereas for its *Z*-isomer the yield is 90%.[311] For *E*-isomers, the yields increase in the presence of excess of pyridine or with triethylamine and with an increase in the reaction temperature. At high temperatures, the nitrile yield is independent of the configuration of the original oxime due to easier *E* – *Z*-isomerisation of the oxime.

Unstable (*Z*)-benzaldoxime acetate **179** obtained on treatment of the corresponding oxime with acetic anhydride readily loses acetic acid even upon slight heating in a sodium carbonate solution. At the same time, under similar conditions, the *E*-form is converted into the original oxime rather than nitrile.[312]

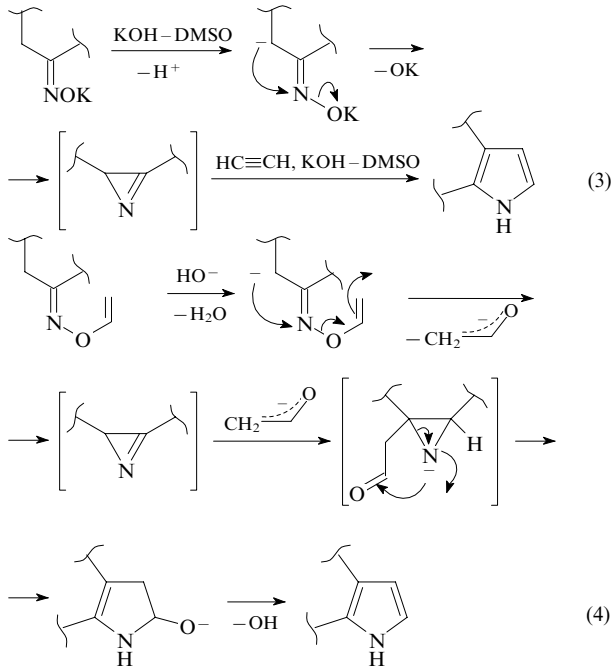




In the water – dioxane system (4 : 1, 25 °C), the base-catalysed elimination of alcohols (phenols) from substituted *O*-alkyl(aryl)-benzaldoximes takes place to afford the corresponding substituted benzonitriles.[313] Under these conditions, the elimination rate is higher by a factor of several tens for *Z*-oximes as compared with *E*-isomers. In the case of *E*-isomers, the rate of *syn*-elimination increases when electron-withdrawing groups are present in the leaving group and/or in the aromatic substituent at the oxime function. The elimination of phenols from (*E*)-*O*-arylbenzaldoximes [Ar = Ph, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$] proceeds smoothly in 60% aqueous DMSO under the action of hydroxide anions. As a result, benzonitriles are formed in quantitative yields.[314] The examples shown above suggest that the reaction

proceeds predominantly by the E2 mechanism, which is characterised by easier *anti*-elimination.

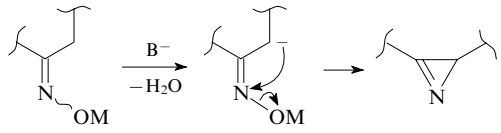
Earlier, it was assumed [88, 157] that the synthesis of pyrroles from ketoximes and acetylene by the Trofimov reaction includes the stage of azirine formation. In this case, either 1,3-dehydration of the ketoxime, which is followed by the reaction of azirine formed with acetylene [reaction (3)], or elimination of vinyl alcohol (as acetaldehyde) from the intermediate *O*-vinyloxime followed by the addition of acetaldehyde as the enolate anion to azirine [reaction (4)] are possible. Both pathways lead to the formation of the pyrrole ring.



(3)

(4)

Although another mechanism is currently accepted, namely, a [3,3]-sigmatropic rearrangement of *O*-vinyloximes, [88, 145–156] it is possible that the above-mentioned pathways are also realised in certain cases (or in parallel). This is confirmed by the fact that, being treated with strong bases, ketoximes undergo 1,3-dehydration and cyclise to azirines (the Hoch–Campbell reaction, see Section IV.1.c). [239, 315, 316]

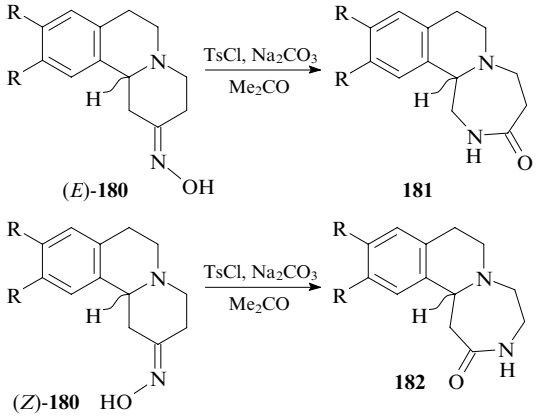


B = RMgX, $LiAlH_4$; M = MgX, AlH_4.

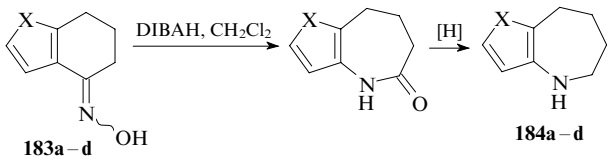
VI. The Beckmann rearrangement

The Beckmann rearrangement, *viz*., the conversion of oximes into the corresponding amides, is traditionally considered as an acid-catalysed process. [108] The examples where it occurs in the presence of bases are less common; however, this is of particular preparative value for oximes with functions unstable in acidic media.

For example, the Beckmann rearrangement of *E*- and *Z*-oximes of benzoquinolizidones **180** into isomeric diazepinoisoquinolines **181**, **182** under the action of *p*-toluenesulfonyl chloride (TsCl) in the presence of Na_2CO_3 occurs with no side skeleton rearrangements typical of reactions in acidic media (yields 45% – 50%). [317]

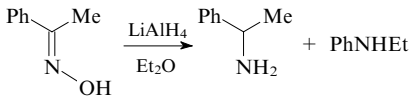


Ring expansion of the cyclohexanone oxime fragment fused to heterocycles in oximes **183a–d** under the action of diisobutyl aluminium hydride (DIBAH) results in tetrahydrofuro- (**184a**), -thieno- (**184b**) and -pyrrolo-[3,2-*b*]azepines (**184c**,**d**). [318] It is evident that the reaction proceeds through the reduction of an intermediate amine, namely, the Beckmann rearrangement product.

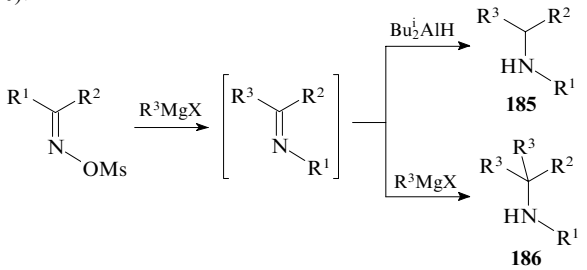


X = O (**a**), S (**b**), NH (**c**), NMe (**d**).

The reaction of acetophenone oxime with $LiAlH_4$ in ether produces, in addition to the expected α-phenethylamine, *N*-ethylaniline, a reduction product of the Beckmann rearrangement. [319]

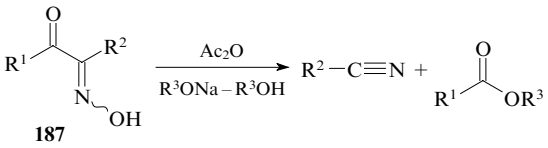


The action of organomagnesium compounds on methanesulfonates of cycloalkanone and acetophenone oximes results in the Beckmann rearrangement to give intermediate imines, which are reduced (with DIBAH) or converted (by the reaction with R^3MgX) into amines **185** or **186**, respectively (yields up to 79%). [320]



R^1 = Alk, Ar; R^2 = Alk; R^3 = Alk, HC≡C, CH_2=$CHCH_2$, HC≡CCH_2; X = Cl, Br, I.

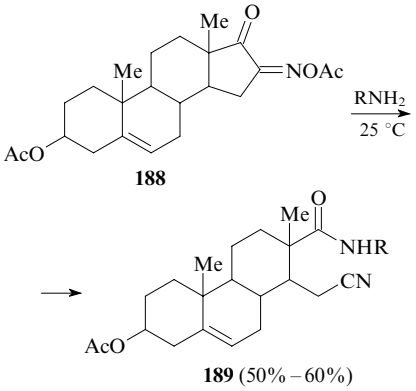
The second order Beckmann rearrangement can also proceed in the presence of bases. For example, under the action of acylating agents, monooximes of α-diketones **187** form nitriles in aqueous solutions of strong bases with elimination of carboxylic acids, [321] whereas in the presence of alcohols, the latter can form the corresponding esters. [322]



187

R^1 = Ph, Bn, CH=CHPh; R^2 = H, Me, Ph; R^3 = H, Me, Et.

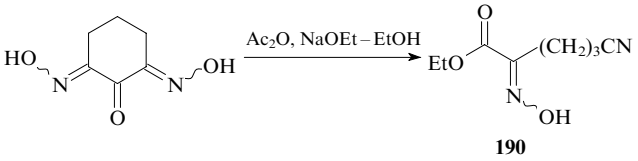
Treatment of steroidal α-acetoxyimino ketone **188** with primary amines at 25 °C brings about the Beckmann rearrangement to give the corresponding amidonitrile **189**.[323]



188 **189** (50% – 60%)

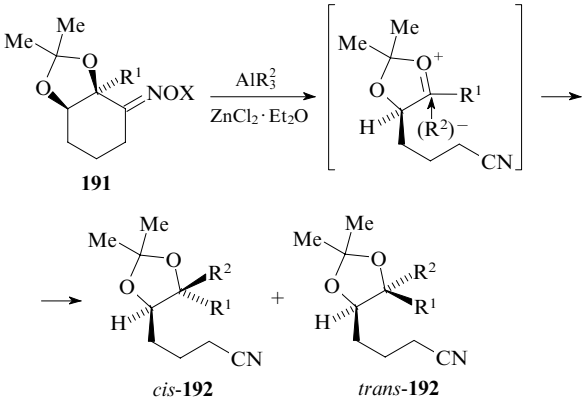
R = Pr^n, Bu^n, Bn, $(CH_2)_nOH$ (n = 2, 3).

Treatment of cyclohexane-1,2,3-trione-1,3-dioxime with acetic anhydride in the NaOEt – EtOH system yields ethyl 2-hydroxyimino-5-cyanopentanoate (**190**).[324]



190

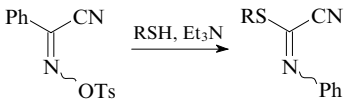
Being treated with organoaluminium compounds in the presence of $ZnCl_2$, esters of oximes of 2-alkyl-2,3-isopropylidenedioxycyclohexanones **191** undergo the Beckmann fragmentation with simultaneous formation of a new carbon – carbon bond to form nitriles **192**. The latter exist as a mixture of geometrical isomers, the overall yield reaches 83%.[325]



191 *cis*-**192** *trans*-**192**

X = Ac, 2,6-$Cl_2C_6H_3C(O)$; R^1 = H, Alk; R^2 = Alk, CH≡C.

In the presence of thiols and trimethylamine, oxime *p*-toluenesulfonate **193** is rearranged into imines **194a**,**b**. This transformation is similar to the Beckmann rearrangement.[326]



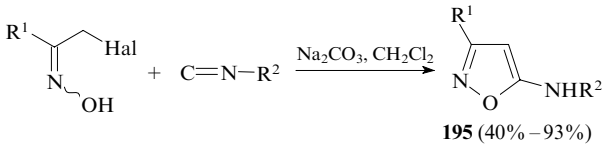
193 **194a**,**b**

R = Et (**a**), Bn (**b**).

VII. Reaction of oximes involving substituents

Many reactions of oximes in the presence of bases occur with simultaneous involvement of both the oxime function and the reaction centres of peripheral functional groups to give heterocyclic compounds. Below, we show several typical examples.

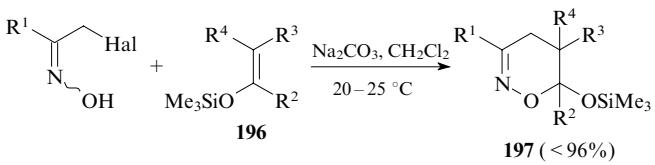
Oximes of α-halo ketones react with isocyanides in the presence of sodium carbonate to form 5-aminoisoxazoles **195**.[327]



195 (40% – 93%)

R^1, R^2 = Alk, Ar; Hal = Cl, Br.

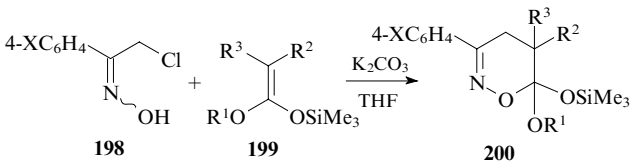
Nitrosoalkenes are the intermediates in this reaction, which are converted into 5,6-dihydro-4*H*-oxazines in the presence of alkenes according to a mechanism of [4 + 2]-cycloaddition.[328] For example, α-halo ketoximes react with trimethylsilyloxy alkenes **196** in the presence of Na_2CO_3 to form oxazines **197** (as a mixture of *cis*- and *trans*-isomers).[329]



196 **197** (< 96%)

R^1 = Ph, CO_2Et; R^2, R^3, R^4 = H, Alk, $OSiMe_3$.

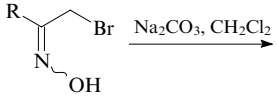
In a similar way, the reaction of oximes of substituted α-chloroacetophenones **198** with ketene silyl acetals **199** in the presence of K_2CO_3 in THF produces 6-alkoxy-3-aryl-6-trimethylsilyloxy-5,6-dihydro-4*H*-1,2-oxazines **200** in moderate yields.[330]

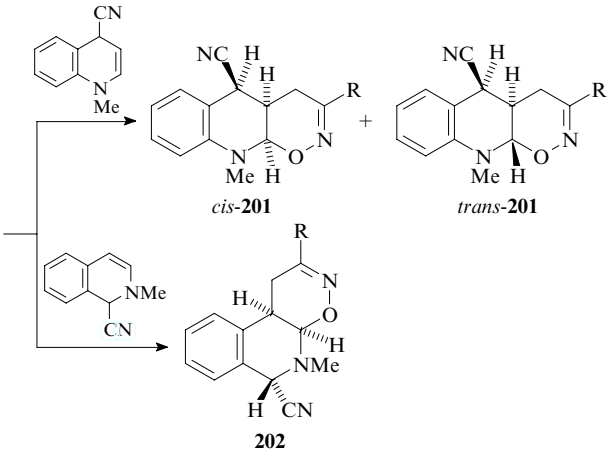


198 **199** **200**

R^1 = H, Alk; R^2 = Alk, Ar; R^3 = Alk; X = H, Cl, Me, OMe.

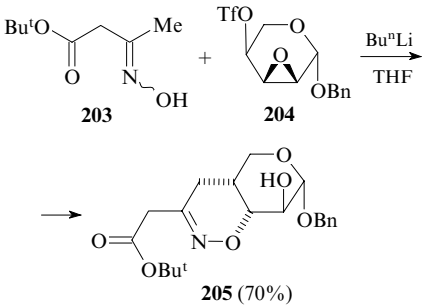
Substituted nitrosoalkenes obtained *in situ* from α-bromooximes add to dihydro(iso)quinolines to form fused oxazines **201** and **202**.[331]





R = Ph, 4-$NO_2C_6H_4$, CO_2Et.

The reaction of β-keto ester oxime **203** with epoxypyranoside **204** under the action of butyllithium in THF produces oxazines **205** enantiospecifically.[332]



VIII. Conclusion

As is seen from the material shown above, oximes and their derivatives are widely used for the synthesis of amines, hydroxylamines, nitriles, amides, ketones, amino ketones, diazo compounds and various heterocycles (isoxazoles, isoxazolidines, benzofurans, pyrroles, pyrrolines, imidazoles, pyridines, oxazines, azirines, aziridines, diaziridines, palladacycles). In the presence of bases and competitive nucleophiles, oximes behave as real 'chemical chameleons'. Depending on substituents, reagents used and reaction conditions, they can play the role of N-, O- and C-nucleophiles, 1,3-dipoles (in the NH-nitrone form), electrophiles (the objects of the nucleophilic attack on the C=N bond), selective ligands for transition metal cations and also the components of highly efficient palladium catalysts. Oximes can undergo dehydration, the Beckmann and Neber rearrangements, Hoch–Campbell and Trofimov reactions, recover aldehydes and ketones, be reduced and add organometallic compounds, *etc*. Such an astonishing chemical plasticity of oximes in the presence of bases makes them versatile synthons in directed organic synthesis.

We believe that systematisation and analysis of chemical properties of oximes as multifunctional nucleophilic agents, which are presented in this review, will help further unravelling of their synthetic potential.

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