Russian Chemical Reviews **84** (4) 335 – 377 (2015) © 2015 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4503

Recent advances in isoxazole chemistry

A V Galenko, A F Khlebnikov, M S Novikov, V V Pakalnis, N V Rostovskii

Institute of Chemistry, Saint Petersburg State University
Universitetskii prosp. 26, Peterhof, 198504 Saint Petersburg, Russian Federation

The preparation methods and reactions of isoxazoles are described and systematized on the basis of analysis of the literature published from 2005 to present. In the discussion of synthesis, major attention is focused on the most efficient approaches: condensation of hydroxylamine with 1,3-dielectrophiles and reactions of nitrile oxides with alkenes and alkynes. Five-membered ring opening reactions leading to acyclic functionalized or other heterocyclic compounds are considered. The transformations of isoxazole derivatives that occur without ring cleavage to form fused heterocyclic systems, as well as reactions that lead to the introduction of C-substituents into isoxazoles, are considered. Data on the biological activity of some isoxazole derivatives are reported.
The bibliography includes 439 references.

Contents

I. Introduction 335
II. Synthesis of isoxazoles 335
III. Reactions of isoxazoles 355

I. Introduction

Isoxazoles exhibit a wide spectrum of biological activity and show some unique physicochemical properties, which is responsible for their use in medicine [1–3] and agriculture,[4] as well as in technology.[5,6] Equally important is the use of these compounds as various building blocks in organic synthesis. This is, first of all, due to the fact that isoxazoles, being aromatic heterocycles and, hence, relatively stable compounds, have a weak oxygen – nitrogen bond. These structural features of isoxazoles enable their modification without five-membered heterocyclic ring opening. Nevertheless, the cyclic structure can be converted in some cases into an acyclic functionalized compound.

Different aspects of isoxazole chemistry have been addressed in early reviews.[2,3,7,8] However, almost 10 years have passed from publication of the last comprehensive review [7] covering the literature on the synthesis and chemistry of isoxazoles from 1992 to 2004. In the present review, we survey more recent studies on the chemistry of this important class of heterocycles published from 2005 to present.

A V Galenko Candidate of Chemical Sciences, Postdoctoral Research Associate at the Institute of Chemistry SPSU.
Telephone: +7(812)428 – 9384, e-mail: st009724@spbu.ru
Current research interests: synthesis of heterocyclic compounds, mechanisms of organic reactions.
A F Khlebnikov Doctor of Chemical Sciences, Professor at the same Institute.
Telephone: +7(812)428 – 9384, e-mail: a.khlebnikov@spbu.ru
M S Novikov Doctor of Chemical Sciences, Professor at the same Institute.
Telephone: +7(812)428 – 9384, e-mail: m.s.novikov@chem.spbu.ru
Current research interests of authors: synthesis and application of strained small rings, the chemistry of heterocyclic compounds, quantum chemical calculations, mechanisms of organic reactions.
V V Pakalnis Candidate of Chemical Sciences, Senior Teaching Assistant at the same Institute.
Telephone: +7(812)428 – 9384, e-mail: viktoriapakalnis@mail.ru
Current research interests: synthesis of heterocyclic compounds, mechanisms of organic reactions.
N V Rostovskii Candidate of Chemical Sciences, Teaching Assistant at the same Institute.
Telephone: +7(812)428 – 9384, e-mail: n.rostovskiy@spbu.ru
Current research interests: synthesis of heterocyclic compounds, mechanisms of organic reactions, quantum-chemical calculations, photochromism and thermochromism.

Received 17 September 2014
Uspekhi Khimii **84** (4) 335 – 377 (2015); translated by G A Kirakosyan

II. Synthesis of isoxazoles

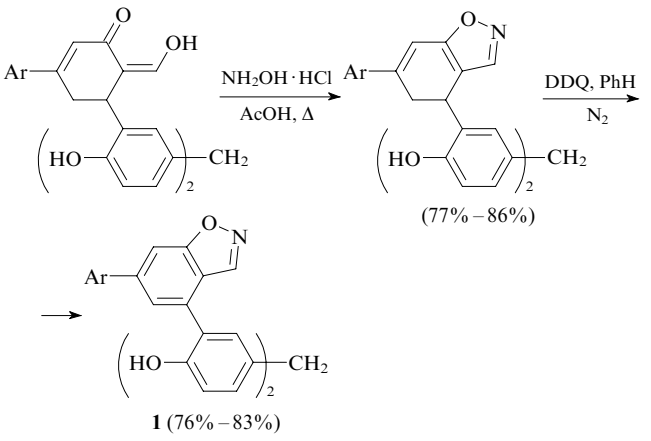
II.1. Condensation of hydroxylamine with 1,3-dielectrophiles

One of the most popular methods of synthesis of isoxazoles is condensation of hydroxylamine with different 1,3-dielectrophiles — 1,3-ketoaldehydes, 1,3-diketones, 1,3-ketoesters, 1,3-ketonitriles, 4-acetyl-2,3-dihydrofurans, ketoenamines, α-acyl ketene dithioacetals and 1-aryl-3,4,4-trichloro-3-buten-1-ones. A major challenge for using this approach is to choose proper conditions that will selectively direct the reaction with hydroxylamine at one of the two electrophilic centres.

1,3-Ketoaldehydes in an acid medium react with hydroxylamine, as a rule, at the formyl group,[9] whereas in the presence of pyridine, the reaction occurs at the ketone group. For example, methylenebis(4,6-diarylbenzo[*d*]isoxa-

zoles) **1** have been synthesized by condensation of appropriate 1,3-ketoaldehydes with hydroxylamine in an acid medium followed by the oxidation of intermediate products with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 1).[10]

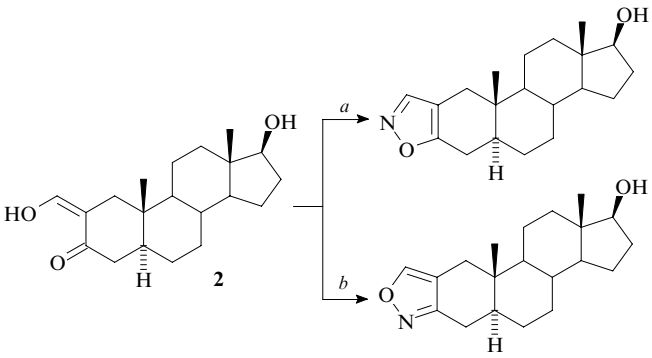
Scheme 1



Ar = Ph, 4-BrC_6H_4, 4-$H_2NC_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-Fu, 2-Py, 1,3-thiazol-5-yl, pyrazin-2-yl; Fu is furyl, Py is pyridyl

The reactions of steroid 1,3-ketoaldehydes **2** with hydroxylamine hydrochloride in an aqueous alcohol solution and in the presence of pyridine proceed through different paths to give isomeric 17β-hydroxyandrostanoisoxazoles (Scheme 2).[11]

Scheme 2



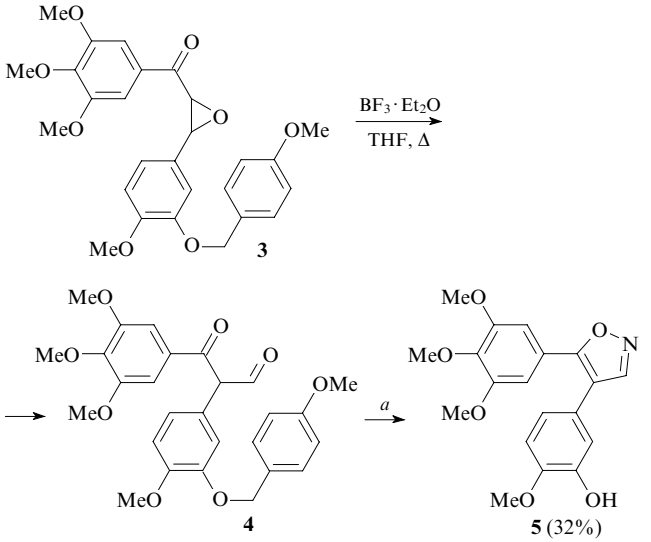
(*a*) EtOH, H_2O, $NH_2OH \cdot HCl$; (*b*) $NH_2OH \cdot HCl$, PyH

At the same time, epoxide **3** synthesized by the reaction of the corresponding substituted chalcone with an excess of boron trifluoride diethyl etherate has been rearranged into 2,3-diaryl-3-oxopropanal **4**.[12] The latter reacts with hydroxylamine hydrochloride in the presence of pyridine to form 4,5-diarylisoxazole **5** (Scheme 3).

For symmetric 1,3-diketones, the challenge of regioselective condensation is removed. In particular, the condensation of hydroxylamine with symmetric (*E*,*E*)-1,7-bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione in an acetic acid solution leads to the only product in 59% yield, 4,4′-[(*E*,*E*)-isoxazole-3,5-diylbis(ethene-2,1-diyl)]diphenol exhibiting acaricidal activity.[13]

The cyclocondensation of 3-(1*H*-[1,2,4]triazol-3-ylsulfanyl)pentane-2,4-dione with hydroxylamine gives 3-(3,5-dimethylisoxazol-4-ylsulfanyl)-1*H*-[1,2,4]triazole, which reacts with azine salts to form a polyheterocyclic system tested as a plant growth stimulator.[14]

Scheme 3

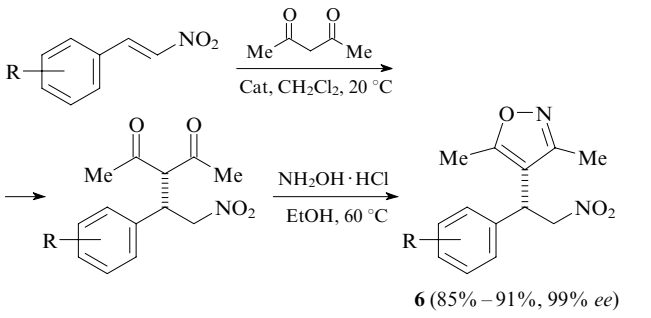


(*a*) $NH_2OH \cdot HCl$, PyH

Copper porphyrin complexes with the 2-(1-acetyl-2-oxopropyl) substituent can be easily converted into the corresponding isoxazole derivatives through the condensation of the acetylacetonyl moiety with hydroxylamine.[15]

A method of enantioselective addition of 1,3-dicarbonyl compounds to nitroalkenes has been developed.[16] The reaction products have been subjected to condensation with hydroxylamine, which gives 3,4,5-trisubstituted isoxazoles **6** with high enantiomeric excess (*ee*) (Scheme 4).†

Scheme 4



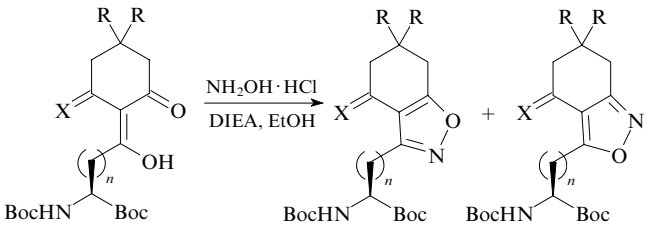
R = H, 4-Me, 4-OMe, 3-OMe, 4-CF_3, 4-F; Cat is chiral catalyst

If a 1,3-diketone lacks functional groups that control the reaction direction, isomeric products can form. In particular, condensation of acyl-substituted cyclohexanones with hydroxylamine sometimes occurs at both the endo- and exocyclic carbonyl functionality to give 1,2- (**7**) and 2,1-benzisoxazoles (**8**) (Scheme 5).[17]

Stereoselective synthesis of isoxazole **9** with an *E*-alkenyl moiety in the 5-position has been accomplished through a three-component reaction involving PhSeLi, 1-(1-alkynyl)-cyclopropyl ketone and 4-bromobenzaldehyde. First, 1,3-diketone is formed, which then reacts with NH_2OH with subsequent oxidative elimination of the PhSe group (Scheme 6).[18]

† Hereinafter, the yields given in multistage synthesis schemes refer to a particular stage, unless otherwise is indicated.

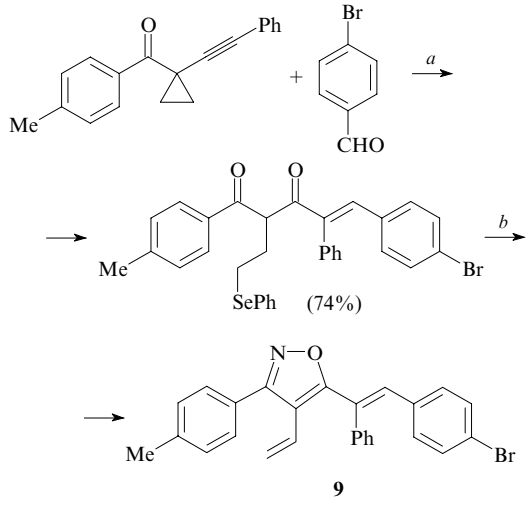
Scheme 5



Boc = C(O)OBu^t, DIEA = Pr^i_2NEt

n	R	X	Products	Yield (%)
1	H	2H	**7** + **8**	86
1 or 2	Me	O	**7**	75–100

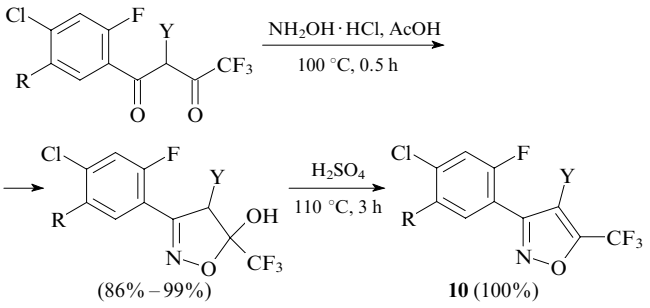
Scheme 6



(*a*) PhSeLi, 1,4-dioxane, N_2, 20 °C, 20 h; (*b*) 1) $NH_2OH \cdot HCl$, AcOH, EtOH, Δ, 6 h (62% yield), 2) H_2O_2, THF, 20 °C, 2 h (89%)

The condensation of 1-aryl-4,4,4-trifluorobutane-1,3-diones with hydroxylamine at the aroyl carbonyl group followed by cyclization and acid dehydration afforded 3-aryl-5-(trifluoromethyl)isoxazoles **10** in high yield (Scheme 7).[19]

Scheme 7

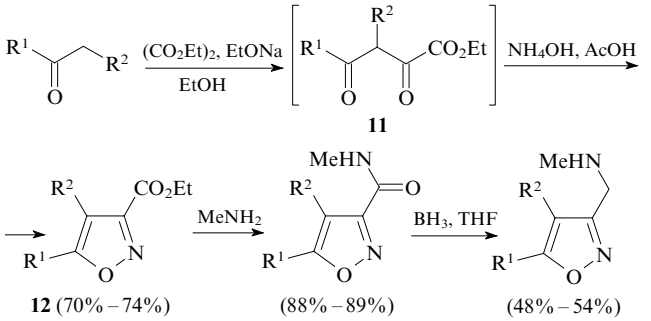


Y = H, Cl; R = OMe, OH, Me

Examples of reactions of hydroxylamine with both symmetric 1,3-dicarbonyl compounds (pentane-2,4-dione and 3-methylpentane-2,4-dione) and asymmetric compounds (1-phenylbutane-1,3-dione) have been described.[20] The authors have developed a method of synthesis of 3,5-disubstituted and 3,4,5-trisubstituted isoxazoles under microwave (MW) radiation in a continuous-flow capillary microreactor.

The reactions of 2,4-dioxobutanoates **11** with hydroxylamine are regioselective involving the α-carbonyl group to give 3-alkoxycarbonylisoxazoles **12**, which can be easily converted into 3-carboxy-,[21] 3-hydroxymethyl-[22] and 3-aminomethylisoxazoles[23] (Scheme 8).

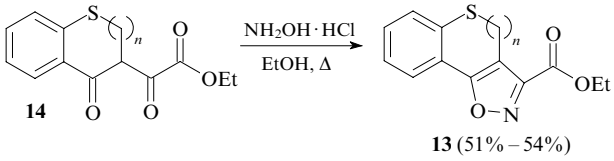
Scheme 8



R^1 = Ph, R^2 = H; R^1–R^2 = $(CH_2)_4$

Only one isomer of fused alkoxycarbonylisoxazoles **13** is afforded upon condensation of hydroxylamine with cyclic derivatives of 2,4-dioxobutanoates **14** (Scheme 9).[24]

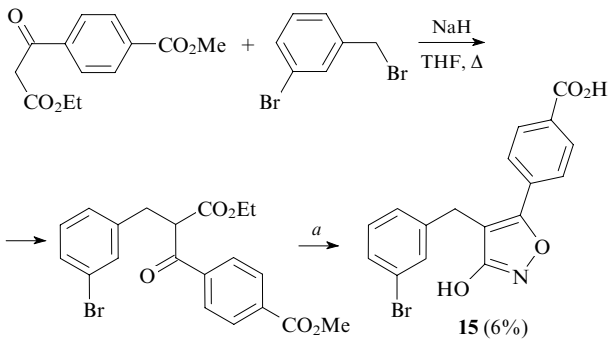
Scheme 9



n = 1, 2

4-[4-(3-Bromophenylmethyl)-3-hydroxyisoxazol-5-yl]benzoic acid (**15**), obtained in low yield by condensation of hydroxylamine with 1,3-ketoester at the ester group at low temperatures (Scheme 10), is a potential glutamate carboxypeptidase II inhibitor. The reaction in a refluxing neutral solution leads to isomeric 5-hydroxyisoxazole as the major product.[25]

Scheme 10



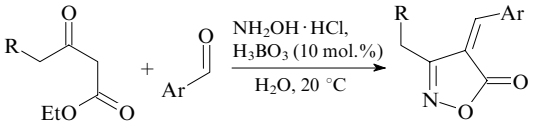
(*a*) 1) $NH_2OH \cdot HCl$, NaOH, MeOH, H_2O, pH 10, −35 °C; 2) NaOH, THF, H_2O

A three-component one-pot synthesis of 4-arylmethylidene-substituted isoxazolones from acetoacetic ester, hydroxylamine and aromatic aldehydes in an aqueous ethanol solution in the presence of sodium acetate has been described.[26] The authors have revealed that, on exposure to visible light, the reaction completes in 15 min to give

nearly pure target 4-arylmethylidene-3-methylisoxazol-5(4*H*)-ones in 56%–89% yields. At the same time, on refluxing the reaction mixture in the dark, the yields and purity of the products are considerably lower. No reaction occurs with substituted aromatic and aliphatic aldehydes with electron-withdrawing groups.

An analogous reaction of 3-ketoesters in an aqueous medium catalyzed by boric acid has been studied.[27] The authors have developed a protocol that affords analytically pure isoxazoles **16** in high yield at room temperature within 1–2 h (Scheme 11). Aromatic aldehydes with electron-withdrawing substituents do not enter into this reaction as well.

Scheme 11



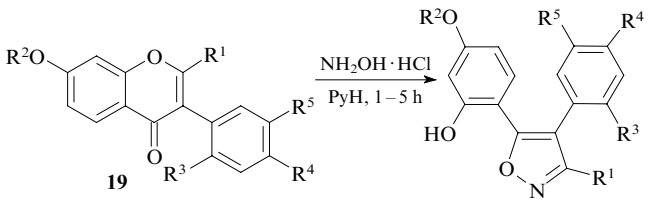
16 (82%–95%)

R = H, Cl, Ph; Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-(3 or 4)-HOC_6H_4, 4-$Me_2NC_6H_4$, 2-Fu, 2-Th; Th is thienyl

The reaction of 3-acyl-substituted chromones with hydroxylamine mainly occurs through the pyran ring opening and subsequent recyclization to give chromeno[3,4-*d*]isoxazole derivatives **17**; transformations of the latter enable the introduction of CN and $C(O)NH_2$ groups into the 3-position of polyfluoro- and polychloroalkylchromones. In some cases, the reaction of 3-(polyfluoroacyl)chromones with hydroxylamine leads to 4-salicyloylisoxazole derivatives **18a–e** (Scheme 12).[28, 29]

2-Unsubstituted and 2-methyl- and 2-trifluoromethylchromones **19** react regioselectively with NH_2OH to give corresponding isoxazoles **20** (Scheme 13).[30, 31]

Scheme 13

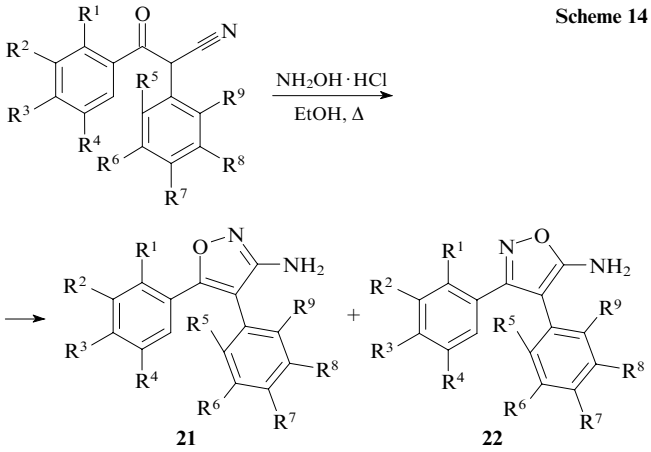


19 **20** (54%–87%)

R^1 = H, Me, CF_3; R^2 = H, Me, Et, $CH_2{=}C(Me)CH_2$, 4-$FC_6H_4CH_2$, CH_2CH_2–N(CH$_2$CH$_2$)NMe, CH_2CH_2–N(CH$_2$CH$_2$)NEt, CH_2CH_2–N(CH$_2$CH$_2$)O, CH_2CH_2–N(CH$_2$CH$_2$); R^3, R^4, R^5 = H, OMe

In addition to 1,3-dicarbonyl compounds, β-ketonitriles have been used as 1,3-dielectrophiles in synthesis of isoxazoles. In most cases, the reaction of ketonitriles and

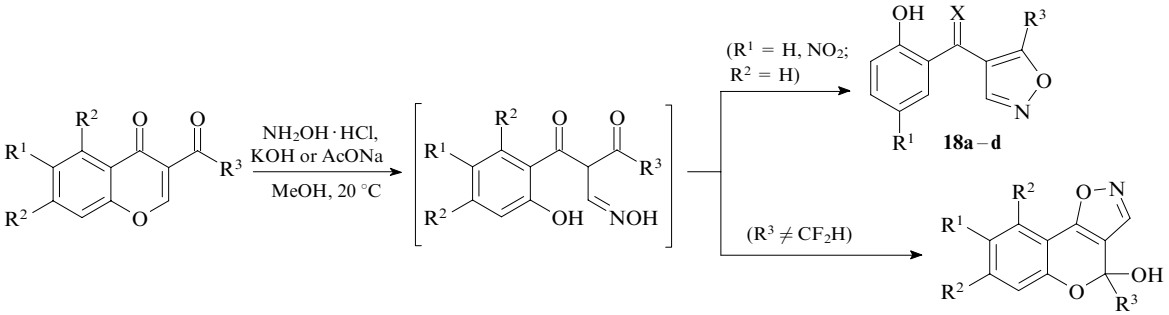
Scheme 14



21 **22**

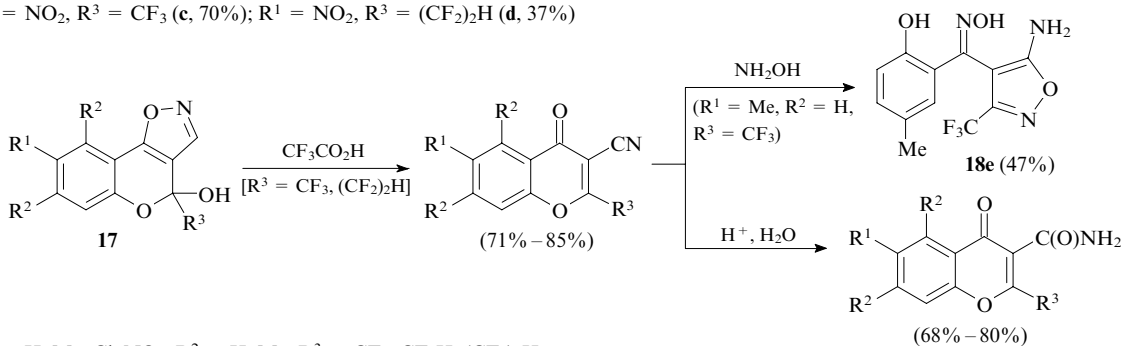
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 = H, OMe; R^2–R^3, R^3–R^4, R^7–R^8 = OCH_2O, $O(CH_2)_2O$

Scheme 12



18a–d **17** (10%–72%)

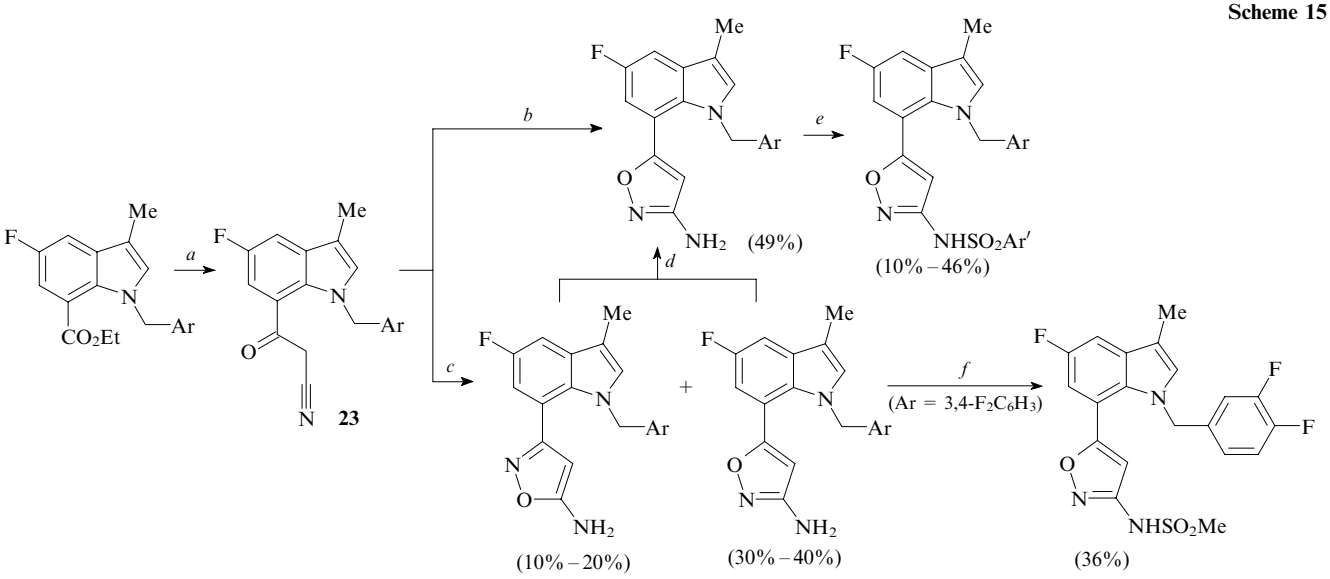
18: X = O: R^1 = H, R^3 = CF_2H (**a**, 55%); X = NOH: R^1 = H, R^3 = CF_2H (**b**, 20%); R^1 = NO_2, R^3 = CF_3 (**c**, 70%); R^1 = NO_2, R^3 = $(CF_2)_2H$ (**d**, 37%)



17 (71%–85%) **18e** (47%) (68%–80%)

R^1 = H, Me, Cl, NO_2; R^2 = H, Me; R^3 = CF_3, CF_2H, $(CF_2)_2H$

Scheme 15



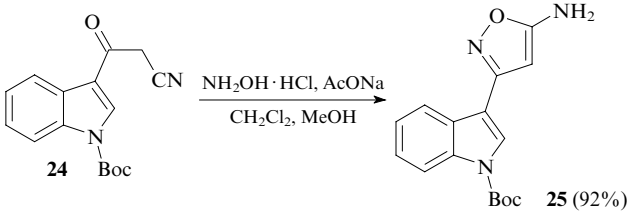
(*a*) Bu^{n}Li, MeCN,THF, $-78 \rightarrow 20$ °C, 1 h; (*b*) 1) $NH_2OH \cdot HX$, NaOH, H_2O, EtOH, Δ, 17 h; 2) 36% aqueous HCl, 90 °C, 2 h; (*c*) $NH_2OH \cdot HX$, NaOH, H_2O, EtOH, Δ; (*d*) 36% aqueous HCl, Δ, 2 h; (*e*) $Ar'SO_2Cl$, PyH; (*f*) $MeSO_2Cl$; Ar = 3,4-$F_2C_6H_3$, 3-$MeOC_6H_4$, 2,3-dihydrobenzo[1,4]dioxan-6-yl, 2-Naph; Ar′ = 4,5-$Cl_2C_4H_3$, 3,4-$F_2C_6H_3$, 2,4,5-$F_3C_6H_2$, 3,4-$Cl_2C_6H_3$; X = Cl, HSO_4; Naph is naphthyl

hydroxylamine proceeds nonselectively to form both 3-amino- and 5-aminoisoxazoles. In particular, condensation of α-cyanodeoxybenzoins with hydroxylamine in boiling ethanol in the presence of sodium acetate leads to a mixture of isomeric aminoisoxazoles **21** and **22** in 25%–60% overall yield and with an isomer ratio from 1 : 1 to 1.5 : 1 (Scheme 14).[32]

The reactions of indolyl-substituted β-ketonitriles **23**, synthesized from 7-ethoxycarbonyl-substituted indoles, are analogous (Scheme 15).[33] The authors have only sometimes isolated regioisomeric 5-amino-3-(indol-7-yl)isoxazole forming in insignificant amounts. They have suggested that 5-aminoisoxazoles unstable toward acids are hydrolyzed upon treatment of the reaction mixture with concentrated hydrochloric acid and that the hydrolysis products are cyclized again to form 3-aminoisoxazoles.

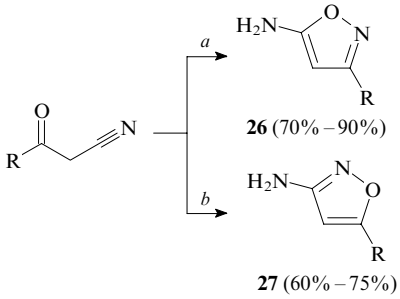
At the same time, it has been reported[34] that β-ketonitrile **24** reacts with hydroxylamine hydrochloride to form only one of the two possible isomers in high yield, namely, 5-aminoisoxazole **25** (Scheme 16).

Scheme 16



There are several examples where the regioselectivity of the condensation of 1,3-ketonitriles with hydroxylamine has been improved. In particular, under strict control of pH and temperature, condensation of 3-alkyl-3-oxopropionitriles containing small alkyl substituents can selectively give either 3-alkyl-5-aminoisoxazoles **26** or 5-alkyl-3-aminoisoxazoles **27** (Scheme 17).[35]

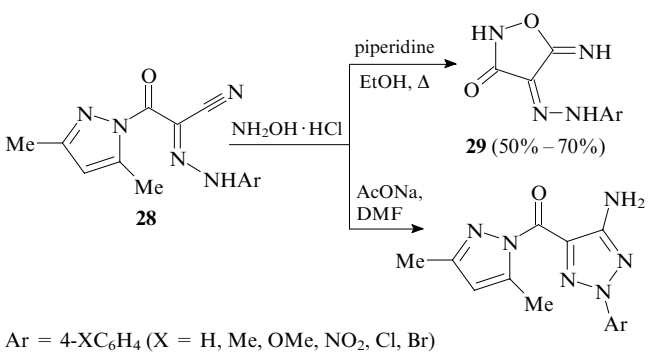
Scheme 17



(*a*) 1) $(NH_2OH)_2 H_2SO_4$ (1.1 equiv.), NaOH, pH > 8, 100 °C, 1,5 h; 2) HCl (1 equiv.), 100 °C, 15 min; (*b*) 1) $(NH_2OH)_2H_2SO_4$ (1.1 equiv.), NaOH, 7 < pH < 8, 45 °C, 72 h; 2) HCl (1.6 equiv.), 50 °C, 2.5 h; R = Pr^i, cyclo-C_3H_5, cyclo-C_4H_7, 1-Me-cyclo-C_3H_4, 1-F-cyclo-C_3H_4

When studying the reactions of (3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropionitrile with dinucleophiles, El Rady[36] has shown that the reaction of hydrazone **28** with hydroxylamine in ethanol in the presence of piperidine leads to isoxazoles **29** (Scheme 18). It should be noted that the

Scheme 18

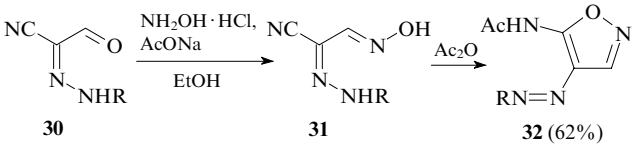


Ar = 4-XC_6H_4 (X = H, Me, OMe, NO_2, Cl, Br)

same reactants react in dimethylformamide in the presence of sodium acetate to give 1,2,3-triazole derivatives.

In reactions with α-formylnitriles, regioselectivity challenges are also absent. For example, nitrile **30** reacts with hydroxylamine in boiling ethanol to give oxime **31**, which is cyclized in boiling acetic anhydride into isoxazole **32** (Scheme 19).[37]

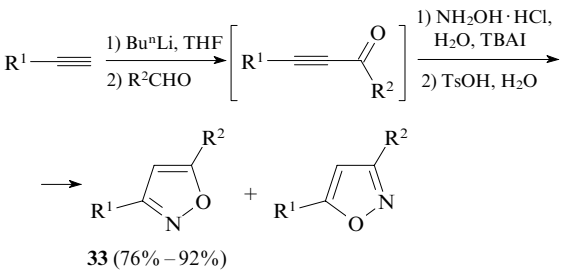
Scheme 19



Formation of the isoxazole ring with the use of 2,3-dihydrofuran as a 1,3-dielectrophile has been described.[38]

Synthesis of isoxazoles **33** based on terminal acetylenes, which are converted into alkynyl ketones, has been reported by Harigae *et al.*,[39] who achieved good preparative yields of the products and high regioselectivity at the stage of condensation with NH_2OH (Scheme 20).

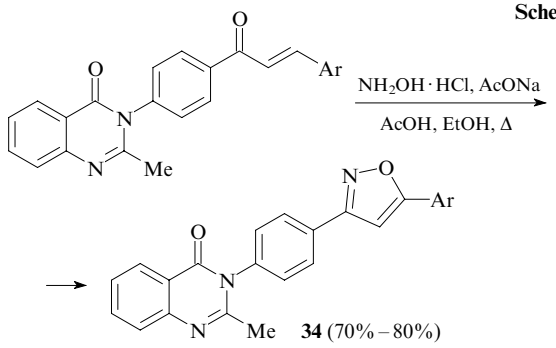
Scheme 20



R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$F_3CC_6H_4$, 4-ClC_6H_4, 2-$MeOC_6H_4$, 3-MeC_6H_4, 1-Naph, 2-Th, 2-Fu, Et, Bu^t, Cy;
R^2 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 2-Py, n-C_6H_{13};
TBAI = Bu^n_4NI, Ts = 4-$MeC_6H_4SO_2$, Cy = cyclo-C_6H_{11}

The condensation of 1-(indol-2-yl)-3-phenyl-2-propyn-1-ones with hydroxylamine in ethanol in the presence of pyridine has been shown to lead in some cases only to substituted 3-(indol-2-yl)-5-phenylisoxazoles and, in other cases, to a mixture of isomeric isoxazoles in low to moderate yield.[40] Unfortunately, no correlation between the structure of initial alkynyl ketones and condensation regioselectivity has been found.

Scheme 21

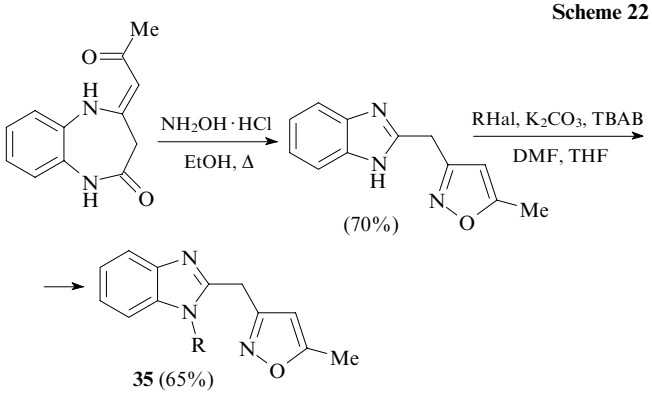


Ar = 4-$MeOC_6H_4$, 4-$H_2NC_6H_4$, 4-HOC_6H_4, 4-$O_2NC_6H_4$, 4-$F_3CC_6H_4$, 4-ClC_6H_4, 3-$MeOC_6H_4$, 3-$H_2NC_6H_4$, 3-HOC_6H_4, 3-$O_2NC_6H_4$, 3-$F_3CC_6H_4$, 3-ClC_6H_4

Isoxazoles **34**, containing the quinazoline ring, have been synthesized through condensation of alkenyl ketones with hydroxylamine.[41] No details how 4,5-dihydroisoxazole, which must form in condensation of alkenyl ketone with hydroxylamine, is converted into isoxazole have been presented. This is likely a result of oxidation with air oxygen during long-term refluxing in ethanol (Scheme 21).

The enaminoketone moiety of molecules can also serve as a 1,3-dielectrophile in synthesis of isoxazoles.[42–47] In particular, the reaction yielding 2-[(5-methylisoxazol-3-yl)methyl]benzimidazoles **35** has been described (Scheme 22).[48]

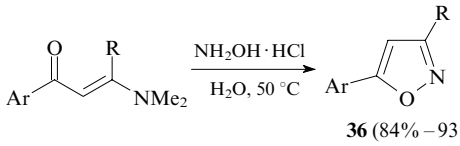
Scheme 22



R = Bn, All, HC≡CCH_2; All is allyl; TBAB = Bu^n_4NBr

A protocol of condensation of aromatic enamino ketones with hydroxylamine hydrochloride in water affording isoxazoles **36** in high yield has been reported.[49] After isolation of the products from the reaction mixture by means of usual filtration, they do not require additional purification (Scheme 23).

Scheme 23

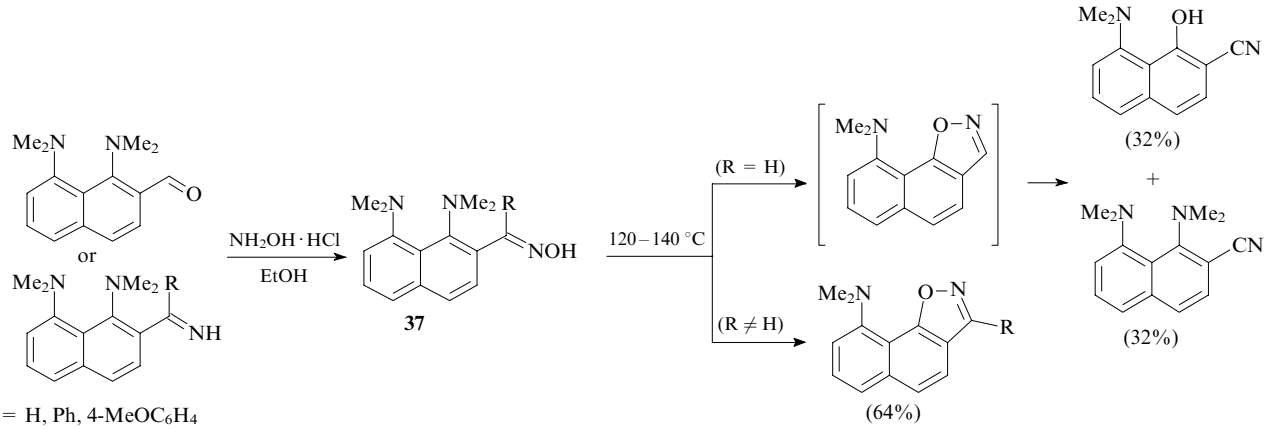


Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeO_2CC_6H_4$, 4-$BocNHC_6H_4$, 2-Naph, 2-Th; R = H, Me

Heterocyclization of 1,8-bis(dimethylamino)naphthalene-2-carbaldehyde at the carbonyl group has been described.[50] One of the dimethylamino groups, which is usually a poor nucleofuge, is subjected to intramolecular nucleophilic substitution. In the case of oximes **37** (R ≠ H), the reaction affords 3-substituted *N*,*N*-dimethylnaphtho[2,1-*d*]isoxazole-9-amines. In the absence of a substituent in the 3-position of oxime **37** (R = H), the product is unstable under reaction conditions and is cleaved at the N–O bond concurrently with dehydration of the initial oxime to give the cyano group (Scheme 24).

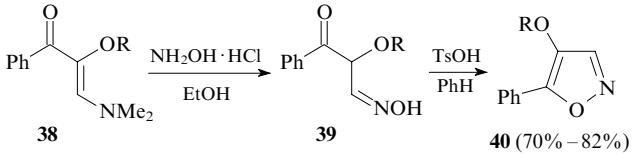
2-(Fluoroalkoxy)enaminones **38** have been synthesized in almost quantitative yield by treating α-fluoroalkoxyacetophenones with dimethylformamide dimethylacetal.[51] Refluxing of compounds **38** in ethanol with hydroxylamine hydrochloride leads to acyclic products of substitution of hydroxylamine for the dimethylamino group in high yields. Oximes **39** are converted into isoxazoles **40** only on refluxing in benzene in the presence of *p*-toluenesulfonic acid with azeotropic removal of water (Scheme 25).

Scheme 24



R = H, Ph, 4-$MeOC_6H_4$

Scheme 25



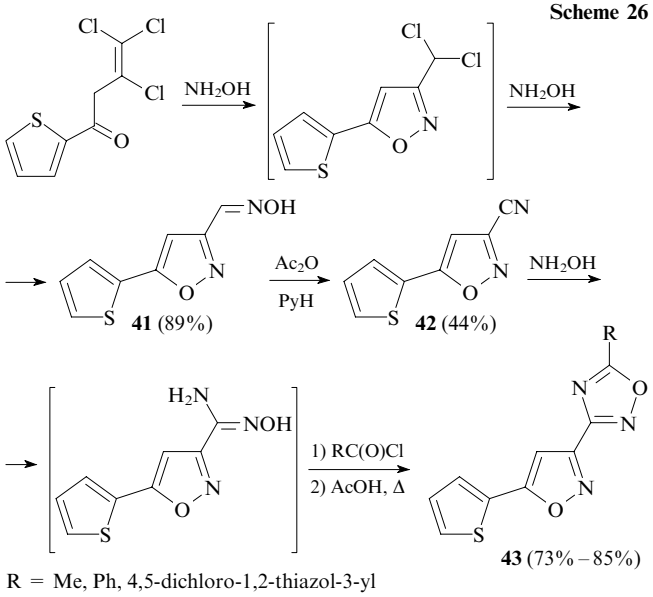
R = CF_2CHF_2, CF_2CHClF

At the same time, the enamine synthesized from ethyl 3-(3-chlorophenyl)-3-oxopropionate and dimethylformamide dimethylacetal reacts with hydroxylamine hydrochloride in methanol to form ethyl 5-(3-chlorophenyl)isoxazole-4-carboxylate in 78% yield without addition of any dehydrating agents.[46]

Alkyl-, sulfo- and carbamoyl-substituted isoxazoles have been synthesized through the condensation of α-acylketene dithioacetals with hydroxylamine hydrochloride followed by the oxidation of the sulfide to sulfone with sodium perborate in water. Advantages of this reaction are high yields, low temperature and the use of water as a solvent.[52]

The reaction of 1-(2-thienyl)-3,4,4-trichloro-3-buten-1-one with hydroxylamine yields isoxazole **41**, which is converted into nitrile **42** under the action of acetic anhydride in pyridine. Compound **42** reacts with NH_2OH to give the corresponding amidoxime; O-acyl derivatives of the latter are heterocyclized in acetic acid to give 5-substituted 3-[5-(thien-2-yl)isoxazol-3-yl]-1,2,4-oxadiazoles **43** in good yields (Scheme 26).[53]

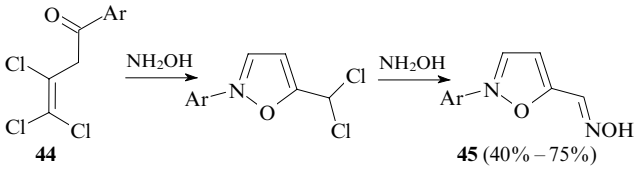
Scheme 26



R = Me, Ph, 4,5-dichloro-1,2-thiazol-3-yl

A regioselective reaction of hydroxylamine with 3,4,4-trichloro-3-buten-1-ones has been described.[54] The condensation of compounds **44** with hydroxylamine leads to isoxazole derivatives **45** (Scheme 27).

Scheme 27



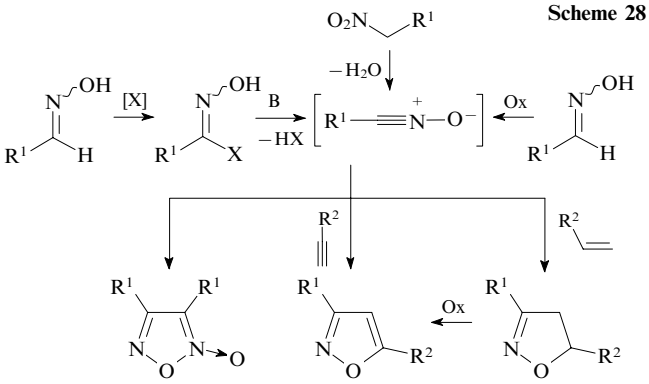
Ar = Ph, 4-MeC_6H_4, 2,5-$Me_2C_6H_3$

II.2. Reactions of nitrile oxides with alkenes and alkynes

Reactions of nitrile oxides with alkenes (with subsequent spontaneous or oxidative aromatization), as well as with alkynes, afford 3,4,5-trisubstituted and 3,5-disubstituted isoxazoles. In addition to the target reaction of cycloaddition to a dipolarophile, nitrile oxides are also able to dimerize into furoxans. The proportion between these two processes is determined by the reactivity of the dipolarophile and steric factors.[55] Nitrile oxides are usually generated *in situ* by one of the following methods: dehydrohalogenation of *N*-hydroximidoyl halides in the presence of bases, oxidation of aldoximes or dehydration of primary nitroalkanes (Scheme 28).

The data presented in this Section are systematized according to the method of nitrile oxide generation. However, we have not completely succeeded in our effort since many research teams dealing with 1,3-dipolar cycloaddition of nitrile oxides to dipolarophiles simultaneously use different methods of dipole generation. At the same time, it is not always possible to clearly differentiate methods. For example, the reaction of aldoximes with hypochlorites or chloramine T, which is formally an oxidation reaction, proceeds through the intermediate formation of *N*-hydroximidoyl chlorides, which immediately lose HCl because of the alkaline medium inherent in both the hypochlorite salts

Scheme 28



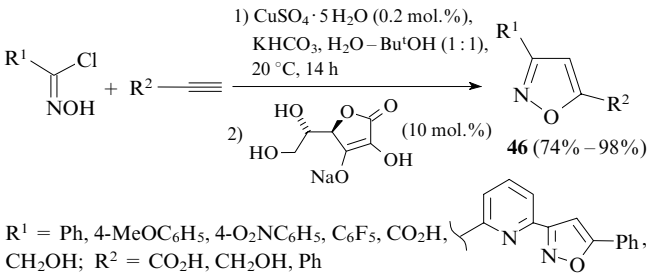
[X] is halogenating agent, X is halogen atom, Ox is oxidant, B is base

and *N*-chlorotoluenesulfonamide sodium salt (see Scheme 28).

One of the earliest and best developed methods for generation of nitrile oxides is dehydrohalogenation of *N*-hydroximidoyl halides under the action of different bases. Imidoyl halides can be obtained by different methods: by the reaction of aldoximes with *N*-halosuccinimides, free halogens, hydrogen halides in the presence of oxidants, *etc*. Below, we consider sequences of reactions leading to isoxazoles through the stage of formation of nitrile oxides and their 1,3-dipolar cycloaddition to alkenes and alkynes.

Cycloaddition of nitrile oxides, generated through dehydrohalogenation of *N*-hydroximidoyl chlorides (much more rarely, bromides) under the action of bases, to terminal alkynes is, in most cases, highly regioselective and leads to 3,5-disubstituted isoxazoles (see Scheme 28).[56–113] For the preferential formation of precisely 3,5-disubstituted isoxazoles, the reaction is often carried out in the presence of catalytic amounts of copper compounds. For example, 1,3-dipolar cycloaddition of copper(I) acetylenides to nitrile oxides gives 3,5-disubstituted isoxazoles **46** (Scheme 29).[56] Quantum chemical calculations have shown that the process is nonconcerted and involves the formation of metallacyclic intermediates. Sodium ascorbate is used for reducing copper(II) to copper(I). It has been demonstrated that nitrile oxides with electron-withdrawing substituents react more slowly than those with electron-donating groups. This method of generation of nitrile oxides have been used for synthesis of isoxazoles.[114–119]

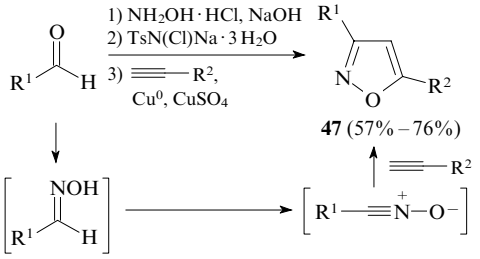
Scheme 29



R^1 = Ph, 4-$MeOC_6H_5$, 4-$O_2NC_6H_5$, C_6F_5, CO_2H, CH_2OH; R^2 = CO_2H, CH_2OH, Ph

An analogous approach has been described.[120] 3,5-Disubstituted isoxazoles **47** have been synthesized through the cycloaddition of nitrile oxides to copper(I) acetylenides. Nitrile oxides have been generated from both aliphatic and (hetero)aromatic aldoximes under the action of chloramine T in the presence of a base. Acetylenides have been synthesized *in situ* from terminal acetylenes and a stoichiometric mixture of copper(II) sulfate and copper chips (Scheme 30).

Scheme 30



R^1 = CH=CHPh, Et, Bu^n, Bu^t, Cy, Bn, Ar, 2-Fu;
R^2 = Ar, CH_2Ar, CH_2Bu^n, CO_2H, CH_2OH

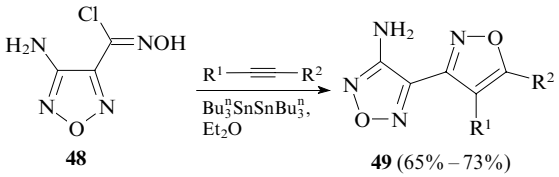
This protocol has also been used later;[121–126] in particular, ultrasonication of the reaction mixture has been reported.[126] In the latter case, it has been demonstrated that the yields of isoxazoles increase if only copper chips are used as the copper source.

It has been found[127] that the cycloaddition of nitrile oxides (generated by dehydrohalogenation of *N*-hydroximidoyl chlorides) to terminal acetylenes in the presence of catalytic amounts of copper on iron bimetallic system gives β-aminoenones, rather than isoxazoles, in moderate to high yields. The latter are a result of iron-catalyzed N–O bond cleavage in intermediate isoxazoles and reduction with hydrogen evolved in the reaction of iron with HCl eliminated from imidoyl chloride. The introduction of a base binding HCl prevents the conversion of isoxazoles into aminoenones.

Cycloaddition of nitrile oxides synthesized from *N*-hydroximidoyl chlorides to terminal alkynes in the presence of copper(I) oxide nanocrystals as a catalyst has been studied.[128] Under these conditions, isoxazoles are produced in 76%–95% yields. Copper(I) acetylenides are also most likely the intermediates in the transformation underlying a one-pot synthesis of 3,5-disubstituted isoxazoles. The reaction of aromatic aldehydes, hydroxylamine hydrochloride, *N*-chlorosuccinimide and various terminal acetylenes containing aromatic or aliphatic groups is catalyzed by a specifically prepared clay with copper(I and II) ions.[129]

Cycloaddition of furazanyl-substituted nitrile oxides, formed by the reaction of $Bu^n_3SnSnBu^n_3$ with 3-aminofurazan **48**, to different acetylenes, including disubstituted, gives isoxazoles **49** in good yields (Scheme 31).[130]

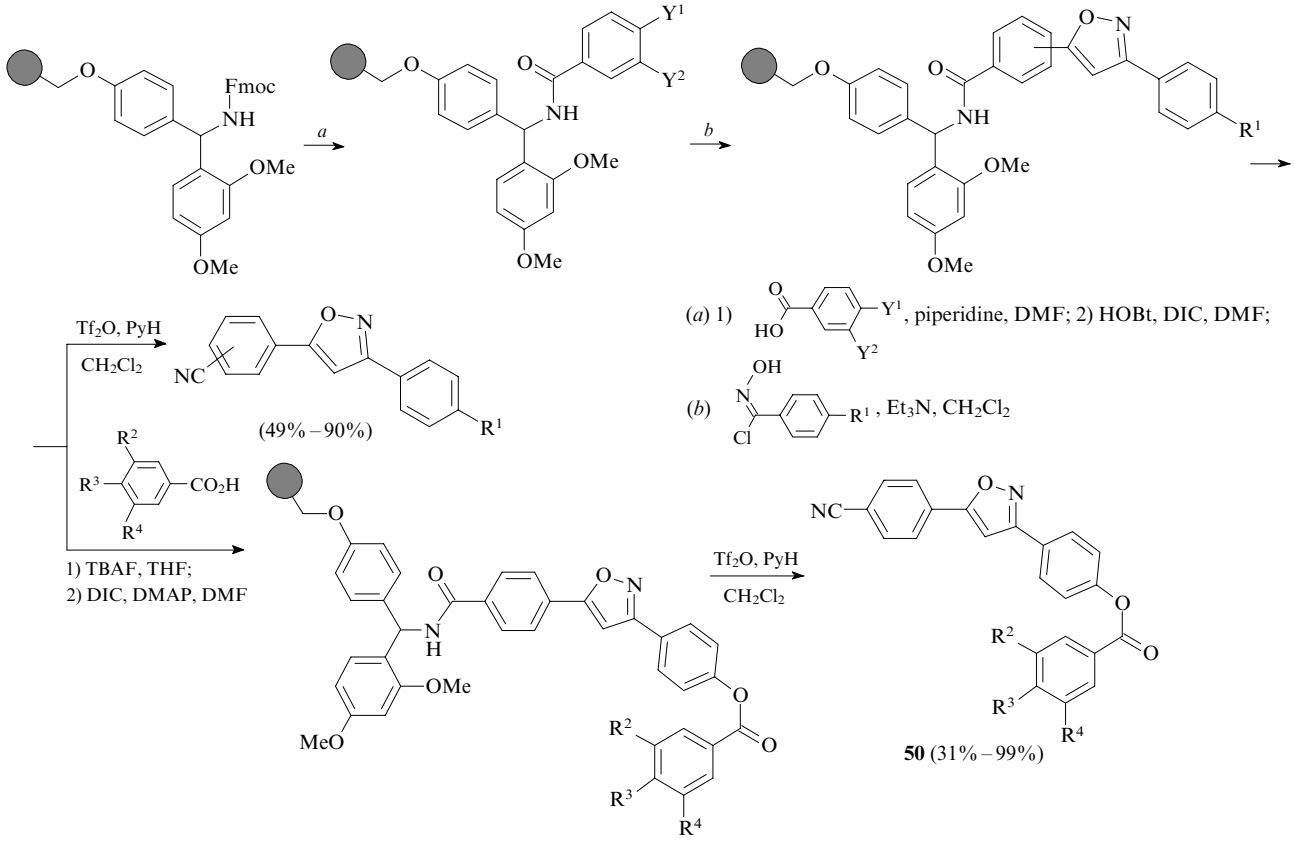
Scheme 31



R^1 = H, CH_2OH; R^2 = CH_2OH, Bu^t, CH_2Br

3,5-Diarylisoxazoles **50** with long-chain alkoxyl substituents have been synthesized through the addition of alkoxy-substituted benzonitrile oxides, generated *in situ* from the corresponding imidoyl chlorides, to terminal arylacetylenes tethered through a linker to a polymeric matrix with subsequent elimination of the products from the polymer.[131] It has been suggested by the authors that

Scheme 32



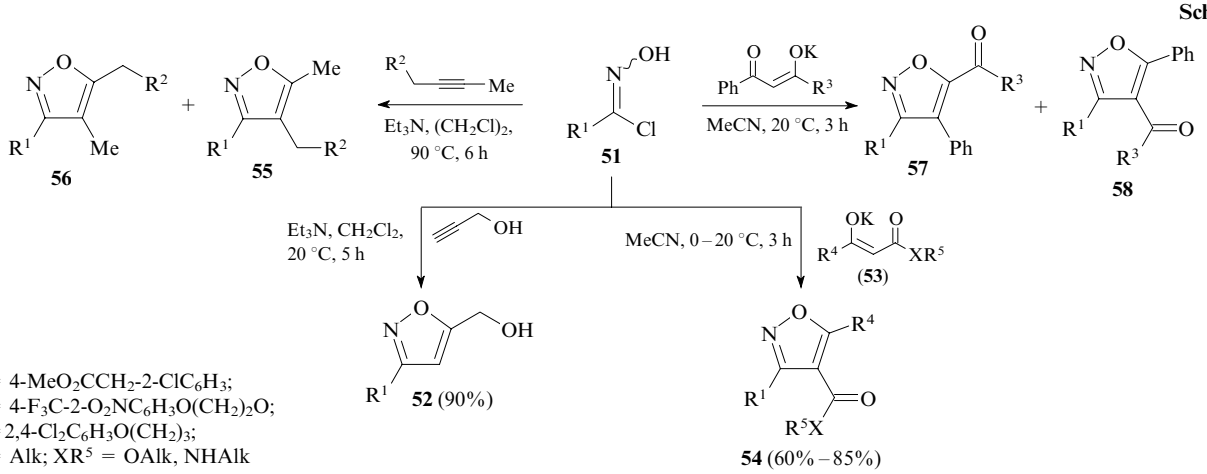
is polymeric matrix; Y^1 = H, Y^2 = C≡CH; Y^1 = C≡CH, Y^2 = H; R^1, R^2, R^3, R^4 = H, OC_nH_{2n+1} (n = 1–10); isomers: *meta*, *para*; Fmoc is (fluoren-9-yl)methoxycarbonyl, HOBt is 2-hydroxybenzotriazole, DIC is *N*,*N*′-diisopropylcarbodiimide, TBAF = Bu^n_4NF, Tf is trifluoromethylsulfonyl, DMAP is 4-(dimethylamino)pyridine

such isoxazoles can exhibit liquid-crystalline properties (Scheme 32, the yields are given based on the initial immobilized amide).

It has been underscored by researchers dealing with large-scale synthesis in industry [132] that generation of nitrile oxides from aldoximes using *N*-chlorosuccinimide with subsequent dehydrohalogenation has a disadvantage that prevents safe scale-up — the reaction is highly exothermic and has an irreproducible induction period. It has been demonstrated that, when concentrated aqueous hydrochloric acid is added to the reaction mixture, the reaction begins immediately after mixing the reactants, and the experimenter can better control heat removal.

Dimethyl 3-chloromethylisoxazole-4,5-dicarboxylate has been synthesized from dimethyl acetylenedicarboxylate and chloroacetonitrile oxide in high yield.[133, 134] The addition of nitrile oxide, obtained from *N*-hydroxy-4-fluorobenzimidoyl chloride in a solution of aqueous *tert*-butyl alcohol in the presence of K_2CO_3, to tetramethyl acetylenediphosphonate has been reported to give tetramethyl [3-(4-

Scheme 33

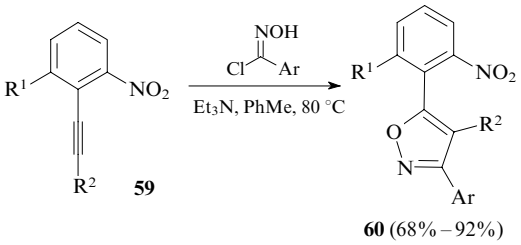


R^1 = 4-MeO_2CCH_2-2-ClC_6H_3;
R^2 = 4-F_3C-2-$O_2NC_6H_3O(CH_2)_2O$;
R^3 = 2,4-$Cl_2C_6H_3O(CH_2)_3$;
R^4 = Alk; XR^5 = OAlk, NHAlk

fluorophenyl)isoxazole-4,5-diyl]bis(phosphonate) in 80% yield.[135] It has been shown[136] that, for asymmetric C,C-dipolarophiles, cycloaddition of nitrile oxides is expected to be highly regioselective and to give the target products in good yields only when the carbon atoms of the dipolarophiles noticeably differ in reactivity, which is achieved by introducing different substituents. Reactions of nitrile oxide, prepared through dehydrohalogenation of imidoyl chloride **51**, with propargyl alcohol and β-ketoester enol lead to only one isomeric isoxazole **52**. Analogously, amide **53** leads to isoxazoles **54**, whereas dialkyl-substituted acetylenes and 1,3-diketone enols give a mixture of regioisomers **55** and **56** (60% yield) and **57** and **58** (75% yield, 7 : 1), respectively (Scheme 33).

It has been demonstrated that the presence of the nitro group in the *ortho* position of substituted phenylacetylenes **59** (both terminal and internal) considerably facilitates the cycloaddition reaction and drives it toward 5-(2-nitrophenyl)isoxazoles **60** (Scheme 34).[137]

Scheme 34

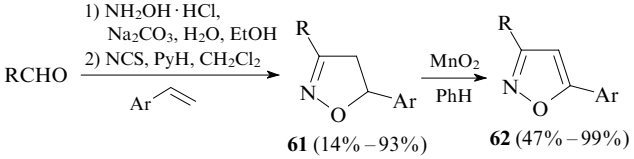


R^1 = H, Cl, Me; R^2 = H, Me, CO_2Me, Br, Cl

When reactions of nitrile oxides with asymmetric disubstituted alkynes lead to a mixture of regioisomeric 3,4,5-trisubstituted isoxazoles while terminal acetylenes give mixtures of 3,5- and 3,4-disubstituted isoxazoles, the presence of catalytic amounts of N-heterocyclic carbenes in the reaction mixture not only promotes the reaction and increases the yields but also enhances the regioselectivity of the process.[138]

In synthesis of isoxazoles through the cycloaddition of nitrile oxides to alkenes, it is necessary to oxidize intermediate isoxazolines.[139–145] For example, the reaction of nitrile oxides, produced from aromatic aldehydes, with styrenes leads regioselectively to isoxazolines **61**, which are oxidized with MnO_2 to give 3,5-diarylisoxazoles **62** (Scheme 35).[142] 3,5-Disubstituted isoxazolines synthesized by addition of nitrile oxide (generated by the reaction of benzofuran- and benzothiophene-5-carbaldehyde oximes with chloramine T) to styrene are readily oxidized by dichlorodicyanobenzoquinone to give the corresponding isoxazoles in high overall yields.[146]

Scheme 35



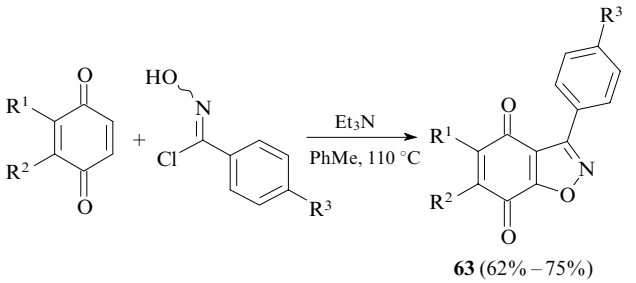
Ar = 4-XC_6H_4 (X = Br, Cl, Me, OBu^t);
R = 4-YC_6H_4 (Y = OC_7H_{15}-n, OC_8H_{17}-n, OC_9H_{19}-n, $OC_{10}H_{21}$-n, Br, NO_2); NCS is *N*-chlorosuccinimide

Examples are known when oxidation of 5-alkyl-3-aryl-4,5-dihydroisoxazoles (synthesized through the cycloaddition of arylnitrile oxides to 1-heptene) to isoxazole occurs in two steps: first, isoxazoline is brominated with *N*-bromosuccinimide, and the intermediate mixture of 4-bromo- and 5-bromoisoxazolines undergoes dehydrohalogenation when treated with a base.[147]

The cyclocondensation of arylnitrile oxides, synthesized by dehydrohalogenation of the corresponding imidoyl chlorides, with chalcones gives 5-aroyl-3,4-diarylisoxazoles in ~60% yield.[148] When the reaction is carried out in dichloromethane in presence of triethylamine at room temperature, spontaneous oxidation of the expected 4,5-dihydroisoxazoles is of low probability in view of the fact that other reasearchers[149] have needed to specifically oxidize isoxazolines formed under analogous conditions with chloramine T.

When the double bond involved in cycloaddition to benzoyl nitrile oxide is the quinone C=C bond, the intermediate isoxazoline is spontaneously oxidized to corresponding isoxazole **63**, presumably, with air oxygen (Scheme 36).[150] The same scheme of synthesis of isoxazoles has been used in Ref. 151, with the only difference that nitrile oxide has been obtained *in situ* by oxidation of both (hetero)aromatic and aliphatic aldoximes with sodium hypochlorite, while substituted naphthoquinones have been used as dipolarophiles.

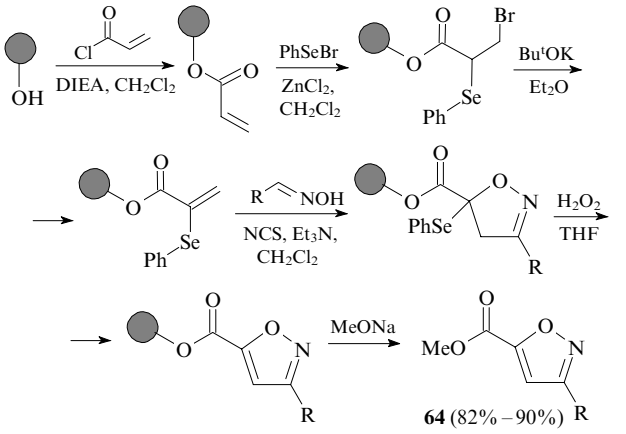
Scheme 36



R^2 = H: R^1 = H, Ph; R^1–R^2 = $(CH)_4$; R^3 = H, Me, OMe

A protocol for synthesis of 3-substituted methyl isoxazole-5-carboxylates based on the cycloaddition of nitrile oxide (obtained *in situ* from aldoxime, *N*-chlorosuccinimide and a base) to a polymer-bound acrylate residue has been developed (Scheme 37).[152] Using simple operations, such as mixing, washing with a solvent and filtration, the authors

Scheme 37

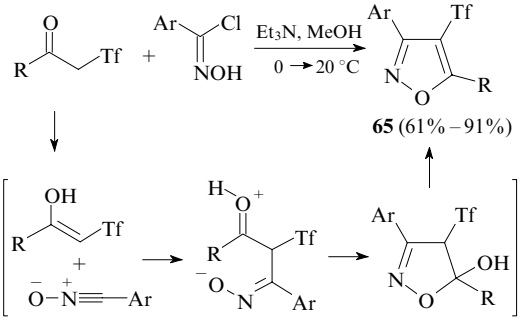


R = Pr^i, Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2,6-$Cl_2C_6H_3$, 1-Naph, 2-Fu

have succeeded in obtaining target isoxazoles **64** in high yields and with purity close to analytical.[152]

In synthesis of isoxazoles *via* 1,3-dipolar cycloaddition, enol forms of 1,3-dicarbonyl compounds are often used as dipolarophiles.[109, 136, 153–163] For example, 4-triflylisoxazoles **65** have been synthesized for the first time from α-triflyl ketones and imidoyl chlorides in the presence of Et_3N (Scheme 38).[164]

Scheme 38



65 (61%–91%)

R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, PhCH=CH, Me, 2-Fu, 2-Naph; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 2-Naph

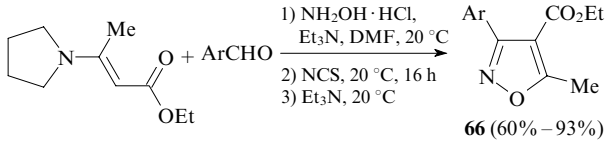
The cycloaddition of nitrile oxides to Meldrum's acid affords 3-substituted 5-hydroxyisoxazoles.[85] Examples of cycloaddition of nitrile oxides to the enol forms of α-methylene ketones are also known.[165, 166] The reaction of enol forms of aroylnitromethanes with arylnitrile oxides generated *in situ* from *N*-hydroximidoyl chlorides under the action of triethylamine leads to 3,5-diaryl-4-nitroisoxazoles.[167]

Yet another family of dipolarophiles is represented by ketoenamines.[168–170] Their application can be exemplified by an efficient method of production of ethyl 3-aryl-5-methylisoxazole-4-carboxylates **66** from aromatic aldehydes (Scheme 39).[171] An analogous approach has been successfully used when aliphatic aldoximes are introduced into the reaction.[172]

The cycloaddition of nitrile oxides to enamines has given 3,4-disubstituted isoxazoles **67** in 60%–67% yields, and recrystallization turns out to be sufficient for their purification (Scheme 40).[173]

Isoxazoles have also been synthesized through cycloaddition of nitrile oxides to *O*-trimethylsilyl derivatives of carbonyl compounds,[174] enol ethers,[98] α-bromo(pentafluorophenyl)vinylsulfonate,[175] as well as to cyano- and

Scheme 39



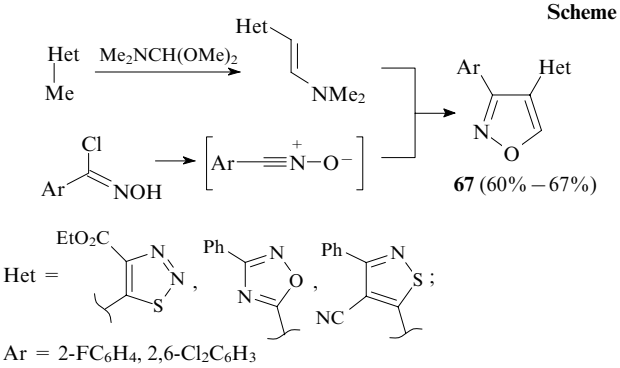
66 (60%–93%)

Ar = 2-$MeOC_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, 2-MeO-3-BrC_6H_3, 3-NC-4-FC_6H_3, 2,5-$(MeO)_2C_6H_3$, 2-Cl-4-FC_6H_3, 3-Br-2-pyridyl

chloro-substituted alkenes.[176–178] In these transformations, an intermediate isoxazoline produced by cycloaddition becomes aromatic due to the elimination of one of the labile substituents in the ring. Analogously, an intermediate product of cycloaddition of benzoylnitrile oxide, generated from aldoxime through oxidation with hypochlorite, to 1-nitro-1,2-diphenylethene spontaneously loses a nitrous acid molecule to give 3,4,5-triphenylisoxazole.[179]

A high potential of organolithium derivatives of phenyl-

Scheme 40



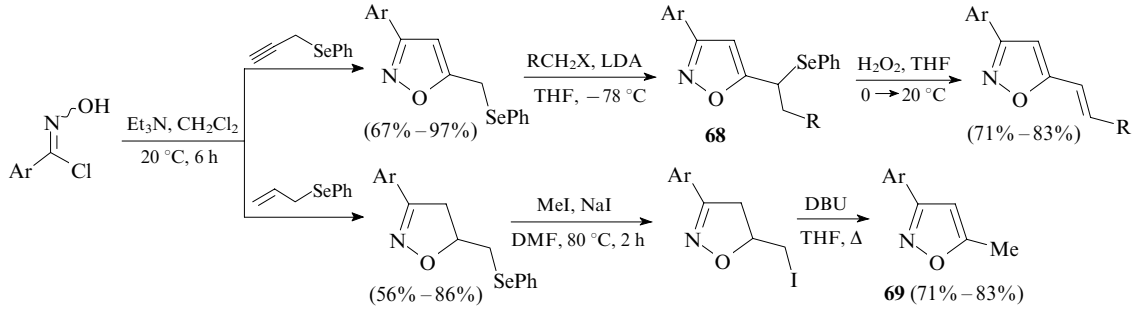
67 (60%–67%)

Ar = 2-FC_6H_4, 2,6-$Cl_2C_6H_3$

selenomethylisoxazoles as nucleophiles for generation of new carbon–carbon bonds has been reported.[180] Phenylselenomethylisoxazoles **68** are obtained through the addition of arylnitrile oxides to phenyl propargyl selenide. Substitution of an iodine atom for the phenyl selenide residue in the addition products and subsequent iodine elimination lead to 5-methylisoxazoles **69** in high yields (Scheme 41).

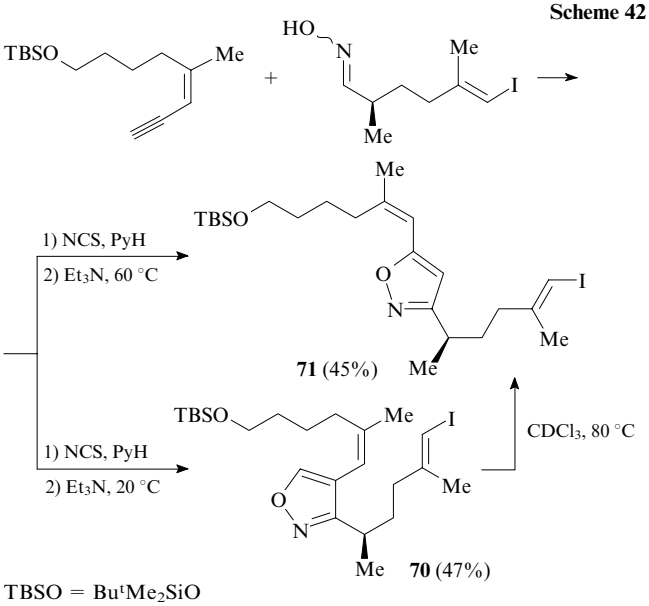
It has been revealed[181] that the regioselectivity of the reaction of an aliphatic nitrile oxide with a terminal alkyne is a function of temperature, which is associated with isomerization of 3,4-disubstituted isoxazole **70** into 3,5-disubstituted isomer **71** (Scheme 42).

Scheme 41



Ar = Ph, 4-BrC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$; R = Me, CH=CH_2, C(Me)=CH_2, CO_2Me, Ph; LDA is lithium diisopropylamide, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

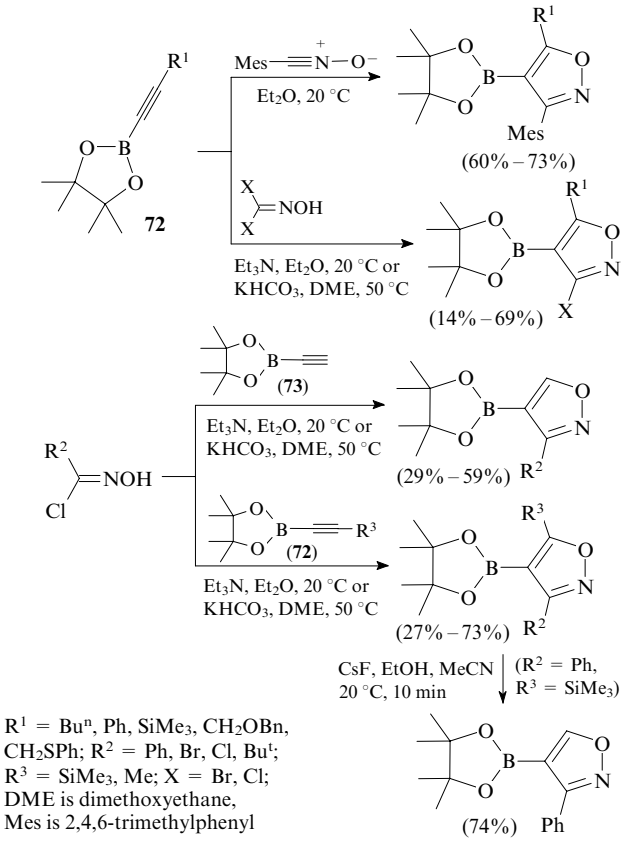
Scheme 42



TBSO = Bu^tMe_2SiO

The thermal reaction of cycloaddition of alkynyl iodides to nitrile oxides is highly regioselective due to steric factors and leads to 4-iodoisoxazoles — starting compounds for the Suzuki reaction.[182] Cycloaddition of nitrile oxides to alkynyl boronates **72** and **73** is a direct route to 3,4,5-trisubstituted, as well as to 3,5- and 3,4-disubstituted isoxazoles. It is noteworthy that desilylation of 5-trimethylsilylisoxazoles can occur even in the presence of the bulky boronate substituent at the C(4) atom, which can be used for producing 3,4-disubstituted isoxazoles (Scheme 43).[183]

Scheme 43

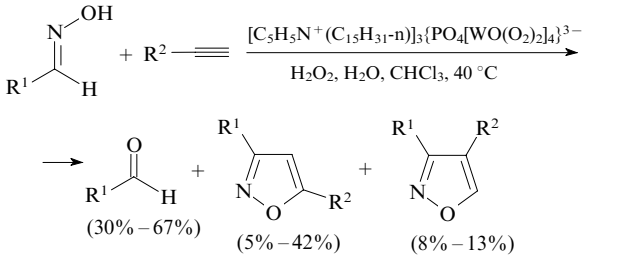


R^1 = Bu^n, Ph, $SiMe_3$, CH_2OBn, CH_2SPh; R^2 = Ph, Br, Cl, Bu^t; R^3 = $SiMe_3$, Me; X = Br, Cl; DME is dimethoxyethane, Mes is 2,4,6-trimethylphenyl

Below, we consider the reactions in which nitrile oxides, involved in [3 + 2]-cycloaddition to multiple bonds to give isoxazole derivatives, are generated through aldoxime oxidation.

For conversion of aldoximes into nitrile oxides reacting with alkenes and alkynes, hydrogen peroxide and a tungsten(VI) complex have been used.[184] However, under these conditions, the cycloaddition reaction is not always regiospecific and is often accompanied by partial hydrolysis of aldoximes to aldehydes (Scheme 44).

Scheme 44

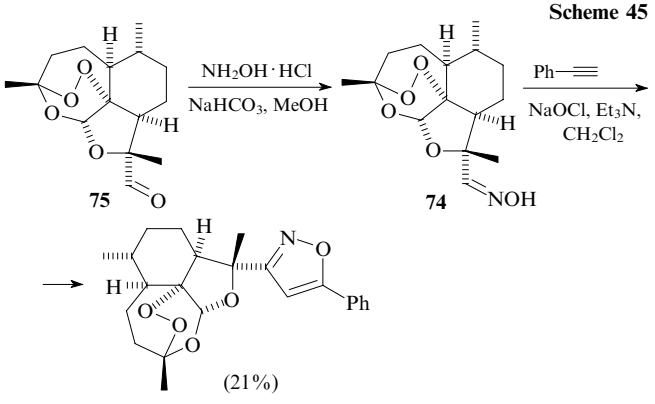


R^1 = Ph, Bu^s; R^2 = Ph, n-C_6H_{13}, CO_2Me

A protocol using chromium(IV) oxide (trademark Magtrieve™) for direct oxidation of aldoximes to nitrile oxides that enter into cycloaddition reactions with alkenes and alkynes to give isoxazolines and isoxazoles in high yields has been described.[185, 186]

A method for synthesis of nitrile oxides with the use of sodium hypochlorite (bleaching method) has two modifications: homogeneous (a hypochlorite solution is added to a solution of aldoxime and a nitrogenous base in alcohols or tetrahydrofuran) and heterogeneous (the oxidant and the reactants are in different phases: the oxidant is in an aqueous solution, while the reactants are in chloroalkanes, aromatic hydrocarbons or diethyl ether). Oxidation of aromatic and aliphatic aldoximes with hypochlorite generates nitrile oxides that react with terminal acetylenes (propargyl alcohol and its esters, propargyl halides, protected propargylamine, substituted arylacetylenes) to give 3,5-disubstituted isoxazoles in good to quantitative yields.[67, 70, 84, 91, 113, 187–200] In reactions with phenylacetylenes containing bulky substituents in the aromatic ring, the yields of isoxazoles have decreased.[12, 201–203] The yields of the products of cycloaddition of nitrile oxides to hetaryl-substituted acetylenes can vary from low to good.[40] The homogeneous variant of the method using hypochlorite as the oxidant affords nucleosides with isoxazole substituents, as a rule, in fair yields.[204] However, in some cases, the yields

Scheme 45

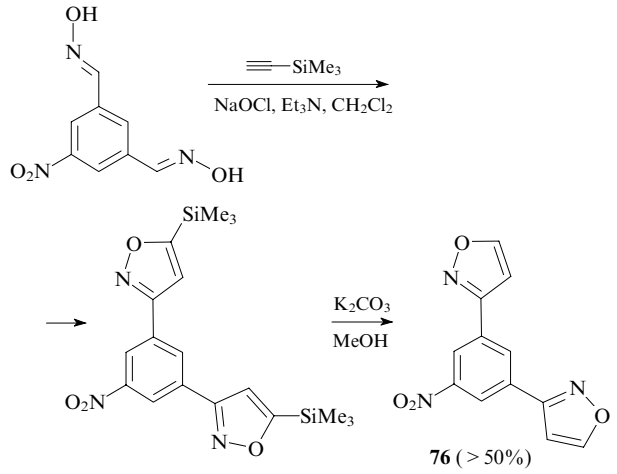


of such products are low; for example, this is the case for carbaldehyde oxime **74** — an artemisinin derivative (**75**) (Scheme 45).[205]

The cycloaddition of nitrile oxide, generated *in situ* through the treatment of chloroacetaldehyde oxime with a sodium hypochlorite solution, to ethyl propiolate has been used to synthesize ethyl 3-(chloromethyl)isoxazole-5-carboxylate.[92] In this case, the target product turns out to be contaminated with 68% of regioisomeric ethyl 3-(chloromethyl)isoxazole-4-carboxylate.

Treatment of a mixture of arylenedi(aldoxime) and trimethylsilylacetylene with sodium hypochlorite enables the synthesis of trimethylsilyl-substituted *m*-bis(isoxazol-3-yl)benzene, which reacts with K_2CO_3 in methanol to give compound **76** (Scheme 46).[206]

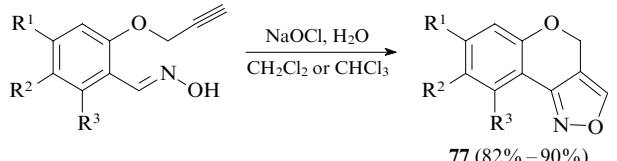
Scheme 46



N-Propargylisatin enters into the 1,3-dipolar cycloaddition reaction with 4-methoxybenzonitrile oxide at two reaction centres; the C≡C and C=O bonds in the 3-position act as dipolarophiles.[207]

A protocol for synthesis of substituted 4*H*-chromeno[4,3-*c*]isoxazoles **77** through intramolecular cycloaddition of nitrile oxide to the triple bond has been reported.[208] The reaction is characterized by unusual regioselectivity caused by only one possible mutual orientation of the reacting moieties (Scheme 47).

Scheme 47

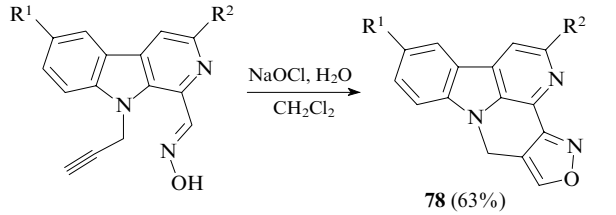


R^1, R^2, R^3 = H, Me, OMe; R^2–R^3 is benzo

Analogous regioselectivity has been observed earlier by Vaidya *et al.*,[209] as well as in synthesis of 7*H*-indolo[3,2,1-*i*,*j*]-isoxazolo[4,3-*c*][1,5]naphthyridines **78** (Scheme 48).[210]

The reaction of *N*-*tert*-butoxycarbonyl-3-(prop-2-yn-1-ylamino)propanal with chloramine T also gives one regioisomer — 5-*tert*-butoxycarbonyl-4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridine.[211] Treatment of substituted malonaldehyde dioximes with sodium hypochlorite leads to diastereomeric spiro-fused isoxazoles **79**, **80** and **81**, **82**,

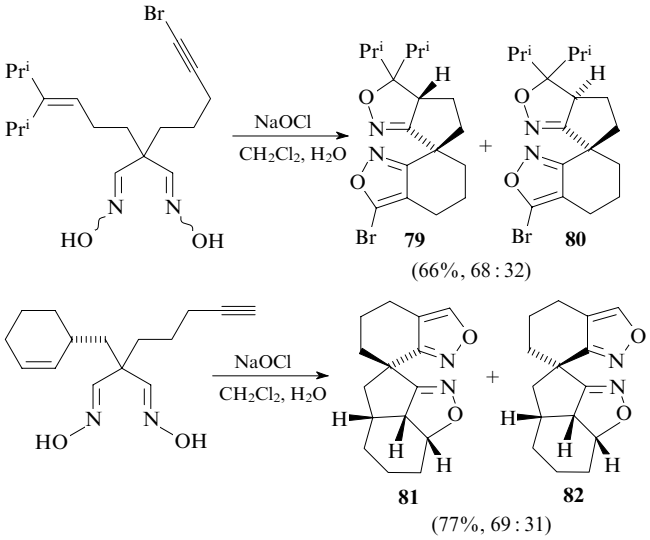
Scheme 48



R^1 = H, F; R^2 = H, CO_2Me

which can be easily separated by usual chromatographic methods (Scheme 49).[212–214]

Scheme 49



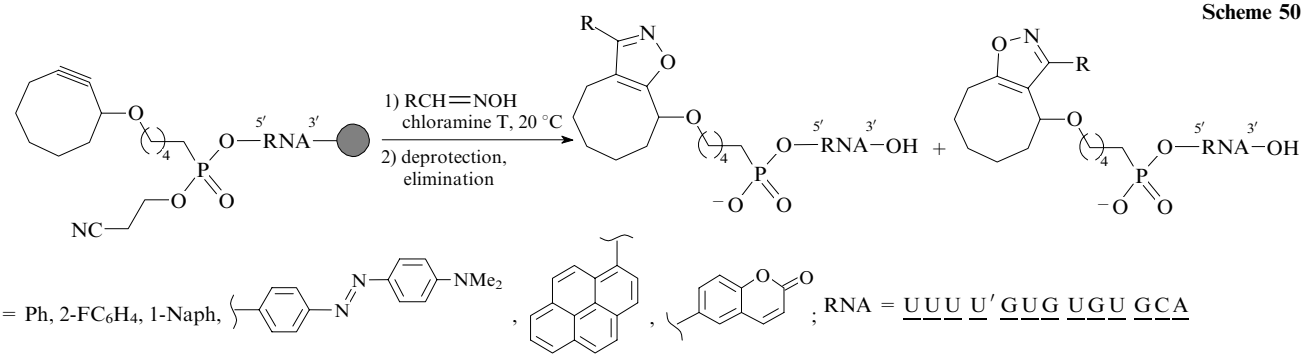
Chloramine T has also been used for producing cyclic derivatives of carbohydrates (substituted 4,6-dihydrofuro[3,4-*c*]isoxazoles and 4,6,7,8-tetrahydrooxepino[4,3-*c*]isoxazoles) through intramolecular [3 + 2]-cycloaddition of nitrile oxide to *O*-propargyl carbohydrates.[215] In particular, the reaction of 2-[2-(phenylethynyl)phenyl]acetaldehyde oxime with sodium hypochlorite gives 8*H*-indeno[2,1-*c*]isoxazole in good yield.[216]

Nitrile oxides generated from aromatic aldoximes treated with chloramine T react with terminal acetylenes to give 3,5-disubstituted isoxazoles.[217–219] Mild conditions of aldoxime oxidation (water–ethanol or DMF–ethanol solutions, room temperature) make it possible to apply this method for labelling DNA strands (Scheme 50).[220, 221]

The regioselective formation of 3-aryl-5-benzoyl-4-phenylisoxazoles through the reaction of 1,3-diphenylprop-2-yn-1-one with alkoxy-substituted benzonitrile oxides generated *in situ* by oxidation of aromatic aldoximes with chloramine T in boiling ethanol has been observed.[222] Analogously, treatment of aldoximes and acetylenes (both terminal and internal) with chloramine T in methanol gives definite regioisomers of 3,5-disubstituted and 3,4,5-trisubstituted isoxazoles.[223] *tert*-Butyl hypoiodite, generated directly in the reaction mixture from *tert*-butyl hypochlorite and potassium iodide, has been used as the oxidant for oximes.[224] The reaction occurs with both aliphatic and aromatic aldoximes, as well as with different alkenes and acetylenes, the yields of 3,5-disubstituted and 3,4,5-trisubstituted isoxazolines and isoxazoles being rather high.

Nitrile oxides synthesized by oxidation of a wide range of aromatic aldoximes with hypoiodite, generated *in situ*

Scheme 50

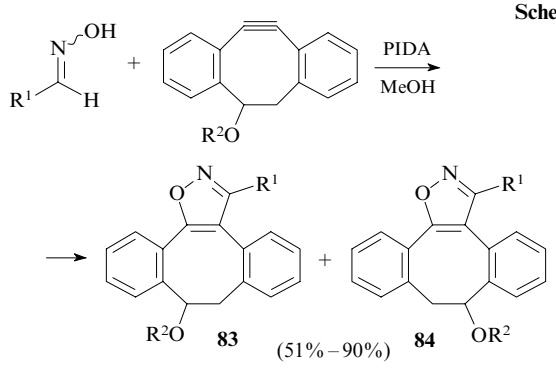


from potassium iodide and oxone ($2\,KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in an aqueous methanol solution, have been introduced into the cycloaddition reaction with terminal aliphatic alkenes and styrenes. The reaction leads to 3,5-disubstituted isoxazolines in good yields. Aliphatic aldoximes, as well as phenylacetylene, have shown unsatisfactory results under these conditions, while 3,5-diphenylisoxazole has been obtained only in low yield.[225] The same reaction, with the difference that potassium chloride rather than iodide was used so that the oxidant of aldoximes was hypochlorite formed in the reaction mixture, gave the target products in fair yields even for terminal alkynes.[226]

Protocols for oxidation of oximes to nitrile oxides by hypervalent iodine compounds and reactions of the resulting nitrile oxides have been summarized.[227] In particular, aldoximes are oxidized by phenyliodonium diacetate (PIDA) to nitrile oxides, which react with alkenes and phenylacetylenes to give, respectively, 3,5-disubstituted 4,5-dihydroisoxazoles and 3,5-diphenylisoxazole.[228] The latter is formed only in 50% yield, which is significantly lower that the yields of isoxazolines — the products of cyclocondensation with alkenes.

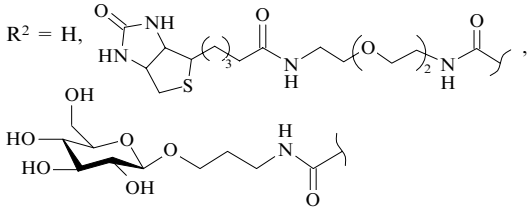
As a rule, generation of nitrile oxides from aldoximes through the oxidation with hypervalent iodine compounds in the presence of terminal alkynes is much worse than in the presence of alkenes. This is believed to be due to side reactions of active hypervalent iodine compounds with the terminal alkyne itself.[227] The situation is noticeably better in the case of disubstituted acetylenes, which is supported by available data [229, 230] (Scheme 51). The cycloaddition of nitrile oxide is also promoted by strain of the cyclooctyne moiety; however, the process can be accompanied by the formation of both regioisomers, for example, compounds **83** and **84**.

Scheme 51



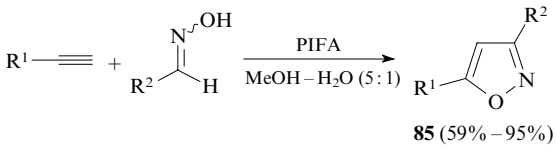
R^1 = Ph, 2-MeC_6H_4, $Ph(CH_2)_2$, 4-$[N_3(CH_2)_2(OCH_2CH_2)_3O]C_6H_4$;

R^2 = H,



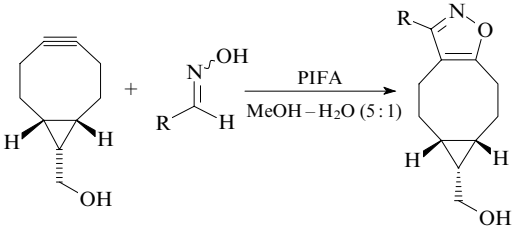
Pnenyliodonium bis(trifuoroacetate) (PIFA) has been used as the oxidant, and the resulting nitrile oxide has been made to react with alkynes (Scheme 52).[230]

Scheme 52



85 (59%–95%)

R^1 = Ph, 4-$MeOC_6H_4$, $(CH_2)_4OH$, 2-Py; R^2 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$O_2NC_6H_4$, PhCH=CH, Cy, C_6F_5, Pr^n



86 (84%–95%)

R = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, Pr^n, PhCH=CH, C_6F_5

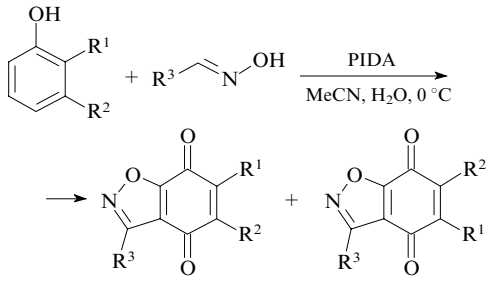
The reaction leads to 3,5-disubstituted (**85**) and 3,4,5-trisubstituted (**86**) isoxazoles in good yields under very mild conditions. The same oxidant,[231] as well as a milder reagent (PIDA),[232] has been used for developing a protocol for synthesis of ^{18}F-labelled compounds intended for positron emission tomography.

The use of [hydroxy(tosyloxy)iodo]benzene for oxidation of aldoximes under mild conditions in an aqueous medium with subsequent cyclization of the resulting nitrile oxides into isoxazolines and isoxazoles has been described.[233] This oxidant has been suggested to be suitable for synthesis of asymmetric 3,5-disubstituted and 3,4,5-trisubstituted isoxazoles.[234] The developed method involving the treatment of an aromatic aldoxime with an oxidant followed by the reaction with acetylene in boiling acetonitrile gives isoxazoles in moderate to good yields. However, the presence of electron-donating substituents in the aromatic ring of oximes sharply decreases the yields of the products.

The above syntheses of isoxazolines and isoxazoles require oxidation of initial aldoximes with stoichiometric amounts of hypervalent iodine compounds, which are rather expensive and sometimes difficultly available reagents. A mixture of inexpensive and poorly available oxone with a catalytic amount of iodoarene has been used as the oxidant.[235] The mixture generates active hypervalent iodine species that convert aldoximes into nitrile oxides. In this case, 3,5-disubstituted isoxazoles have been synthesized in 27%–75% yields.

Phenyliodonium diacetate has been used not only for conversion of aldoximes into nitrile oxides but also for parallel oxidation of different phenols to *p*-quinones, which act as dipolarophiles in the cycloaddition reaction giving target benzisoxazoles **87** and **88** in an overall yield of 19%–95% (Scheme 53).[236]

Scheme 53

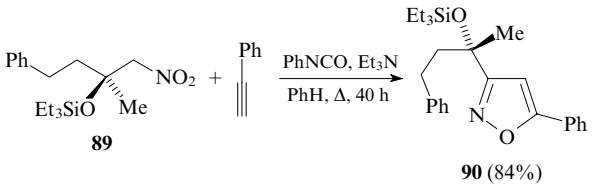


R^1 = H, Me, Bu^t; R^2 = H, Me, $HO_2C(CH_2)_2$, Bu^t; R^1–R^2 = $(CH_2)_4$; R^3 = Ph, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2,4,6-$(MeO)_3C_6H_2$, 3,4,5-$(MeO)_3C_6H_2$, 4-$BnOC_6H_4$, 4-ClC_6H_4, 3-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-FC_6H_4, 3-FC_6H_4, 4-Pr^iC_6H_4, 4-$AcNHC_6H_4$, 4-HOC_6H_4, 2-Naph, 4-Py, 2-Py, imidazol-2-yl, $Ph(CH_2)_2$, EtO_2C

A synthesis of 3,5-disubstituted isoxazoles from *N*-propargylsaccharin, aromatic aldoximes and *N*-chlorosuccinimide on alumina under solvent-free microwave irradiation has been described.[237] Comparison of this protocol with the classical method of synthesis of isoxazoles from the same reactants with the use of sodium hypochlorite in the dichloromethane–water system has shown that the new procedure leads to higher, nearly quantitative, yields in shorter times. Analogously, the reaction of 2-butynoate, benzaldoxime and *N*-chlorosuccinimide gave ethyl 5-methyl-3-phenylisoxazole-4-carboxylate but only in 43% yield.[238]

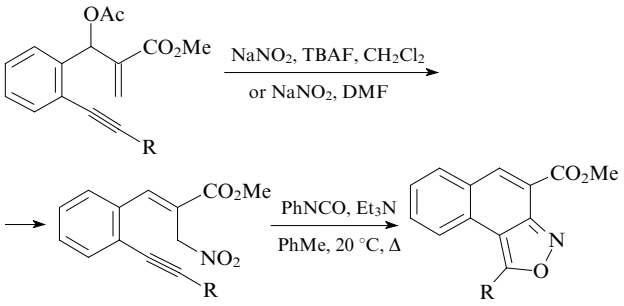
Reactions of dehydration of primary nitroalkanes are also used for generating nitrile oxides. Sometimes, water-removing acylating reagents, high temperatures in the presence of strong acids or highly basic reaction media are used for this purpose. A classical method of dehydration of primary nitroalkanes, which goes back to the discovery, by Mukaiyama and Hoshino,[239] that they can be converted into nitrile oxides, consists in the reaction of a nitro derivative with isocyanates in the presence of catalytic amounts of tertiary amines. This well-proven method is still successfully used. For example, refluxing a mixture of nitroalkane **89**, phenylacetylene, phenyl isocyanate and triethylamine in benzene gives 3-alkyl-5-phenylisoxazole **90** in high yield (Scheme 54).[240, 241] *N*-Propargylmorpholine and 2-(2-nitroethoxy)tetrahydro-2*H*-pyran react with the same reagents to give tetrahydropyranyl-protected [5-(morpholinomethyl)isoxazol-3-yl]methanol.[242]

Scheme 54



Intramolecular cycloaddition of nitrile oxides obtained from Baylis–Hillman adducts leads to naphtho[2,1-*c*]isoxazoles **91** (Scheme 55).[243]

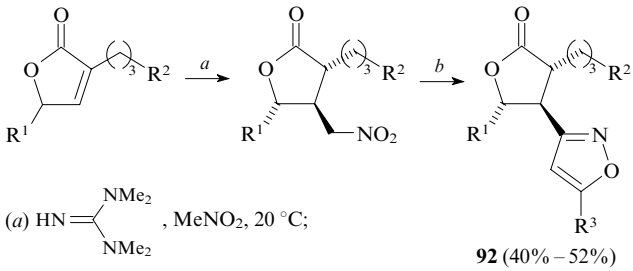
Scheme 55



R = H, Ph, Bu^n, CH_2OMe

Cycloaddition of nitrile oxides, generated from nitro derivatives, to terminal acetylenes is employed to synthesize heterocyclic analogues of prostaglandins **92**, and mild conditions of formation of the isoxazole ring make it possible to retain the configuration of several chiral centres (Scheme 56).[244]

Scheme 56

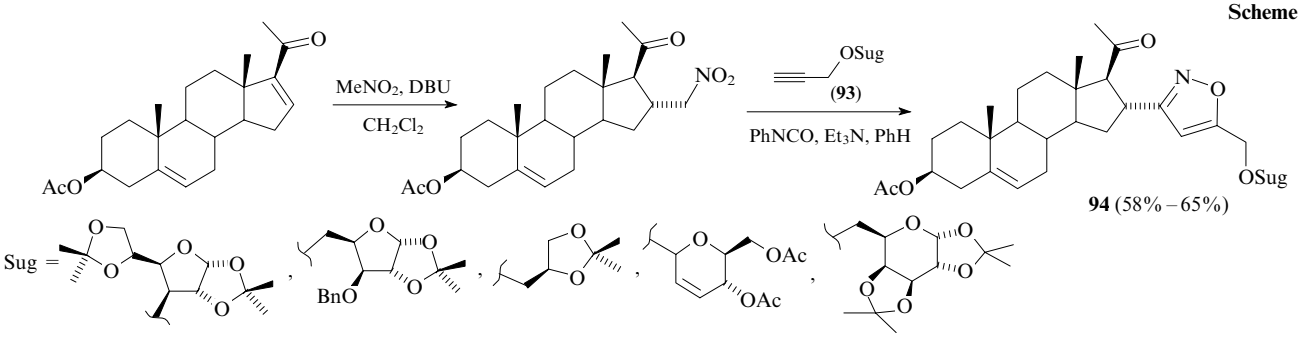


(*b*) ≡—R^3, PhNCO, Et_3N, PhH, 20 °C;
R^1 = H, Me; R^2 = 3-$MeOC_6H_4$, 4-$MeO_2CC_6H_4$, $MeO_2C(CH_2)_3$;
R^3 = n-C_5H_{11}, $EtO_2C(CH_2)_2$

On the basis of addition of nitrile oxides generated from nitroalkanes to acetylenes **93**, a simple route to synthesis of steroid–carbohydrate conjugates **94** has been suggested (Scheme 57).[245] The Mukaiyama reaction afforded 2-(5-arylisoxazol-3-yl)cyclopentanecarboxamides, which were used for studying voltage-gated sodium channels responsible for pain sensation.[246]

Nitroethane and terminal acetylenes react in the presence of phenyl isocyanate and triethylamine to give 8-methyl-7-(3-methylisoxazol-5-yl)methyl-5-(4-nitrophenyl)-8,9-dihydro-7*H*-1,3-dioxo[4,5-*h*][2,3]benzodiazepine (Ref. 71) and 3-benzyloxy-9,9-dimethyl-8-[(3-methylisoxazol-5-yl)methyl]-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrazino[1,2-*a*]pyrimidine-2-carboxamide.[247] The reactions of 3-pyridylacetylenes with aliphatic nitroalkanes in the presence of phenyl isocyanate and triethylamine give 3-alkyl-5-(3-pyridyl)isoxazoles in moderate to high yields.[248, 249] The reaction of phenylacety-

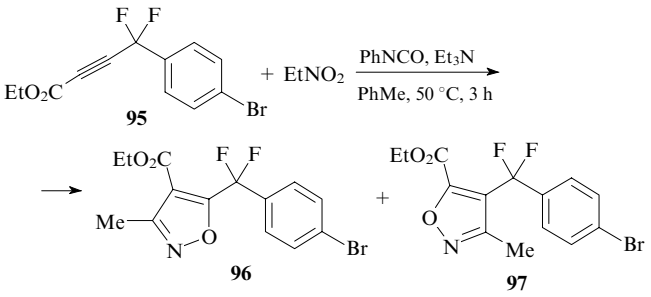
Scheme 57



lene and 3-nitropropionamide afforded, although in low yield, *N*,*N*-di-n-pentyl(5-phenylisoxazol-3-yl)acetamide.[193] Heating nitroethane and methyl 3-arylpropiolate with phenyl isocyanate and triethylamine in toluene leads to 5-aryl-3-methylisoxazole-4-carboxylates in high yields.[250]

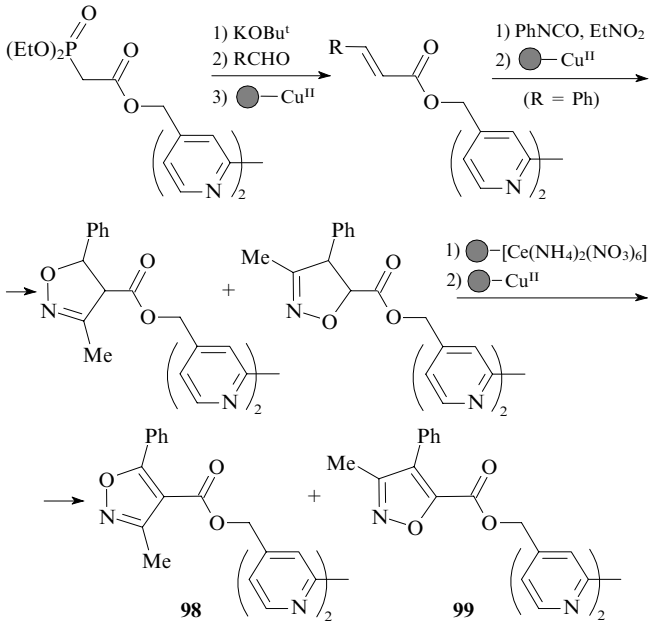
The reactions of nitrile oxides prepared from nitroethane by Mukaiyama's procedure with enantiomerically enriched ethyl-4-fluoro-2-pentynoate and 1-phenyl-4-fluoro-2-pentyn-1-one afforded a 92 : 8 mixture of isomers: ethyl 3-methyl-5-(1-fluoroethyl)isoxazole-4-carboxylate and ethyl 3-methyl-4-(1-fluoroethyl)isoxazole-5-carboxylate (71% overall yield) or a 91 : 9 mixture of isomers: 4-benzoyl-3-methyl-5-(1-fluoroethyl)isoxazole and 5-benzoyl-3-methyl-4-(1-fluoroethyl)-isoxazole (83% overall yield).[251] In these reactions, the configuration of chiral centres is completely retained. Under analogous conditions, nitroethane and ethyl 4-(4-bromophenyl)-4,4-difluoro-2-butynoate (**95**) react to give a mixture of isoxazoles **96** and **97** in 97% overall yield and with a considerably higher content of the minor isomer (2 : 1) (Scheme 58).[252]

Scheme 58



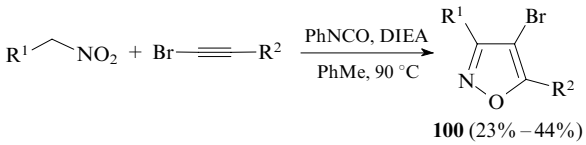
Various heterocyclic systems have been synthesized by a template method.[253] First, 2-(diethoxyphosphoryl)acetate groups are introduced as substituents into the central 2,2′-bipyridine moiety. These substituents then enter into the Horner–Emmons reaction with aldehydes, and the resulting ester is introduced into further reactions involving the C=C bond or the ester group. An advantage of this method is that, at any stage, the product containing the central bipyridine moiety can be isolated from the reaction mixture by means of resin-bound copper(II) species due to the formation of strong chelates, which are then decomposed by tetramethylenediamine (TMEDA). The peripheral moieties can be eliminated from the bipyridine nucleus. Using only washing and filtering operations, the authors have managed to obtain the products in high yield and close to analytical purity. One of the reactions (Scheme 59) demonstrating the wide scope of the method is the cycloaddition of nitrile oxide generated from nitroethane to the phenyl acrylate bound to the bipyridine nucleus. Subsequent oxidation of intermediate 4,5-dihydroisoxazole with ammonium cerium(IV) nitrate produces a mixture of 3-methyl-5-phenylisoxazole-4-carboxylate (**98**) and 3-methyl-4-phenylisoxazole-5-carboxylate (**99**) in 95% overall yield.

Scheme 59



The use of arylbromoalkynes as dipolarophiles afforded 3-alkyl-5-aryl-4-bromoisoxazoles **100**, although in low yield (Scheme 60).[254] The halogen atom in the 4-position of the isoxazole ring can be replaced by an aryl group under Suzuki reaction conditions.

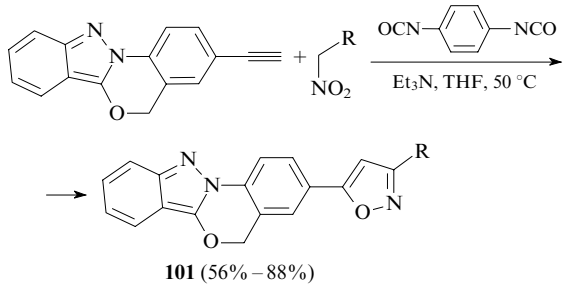
Scheme 60



R^1 = CO_2Me, Me, CH_2OTHP; R^2 = Ar, 3-Py, 3-Fu;
THP is tetrahydropyran-2-yl

A modified version of the classical Mukaiyama method consists in using 1,4-phenylene diisocyanate as the dehydrating agent. This facilitates the purification of the product since diisocyanate is converted into polymeric urea, which is readily removed from the reaction mixture by filtration. This method has afforded isoxazoles **101** in high yield (Scheme 61)[255] and has been employed as one of the ways to synthesize 1-(3-alkylisoxazol-5-yl)methyl-5-aryl-1*H*-pyr-

Scheme 61



101 (56%–88%)

R = Me, Et, Pr^n

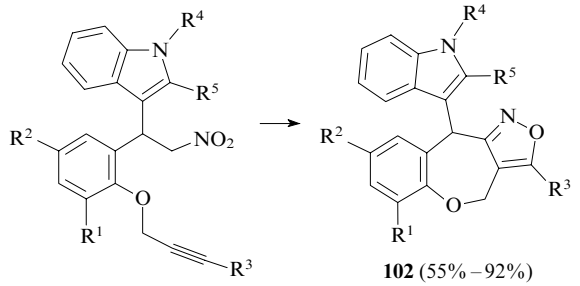
azole-3-carboxylates and 1-(3-alkylisoxazol-5-yl)methyl-3-aryl-1*H*-pyrazole-5-carboxylates.[256] The same strategy has enabled the synthesis of 5-(silyloxymethyl)isoxazole-3-carboxylate from silylated propargyl alcohol and nitroacetic ester,[257] and 9-(3-propylisoxazol-5-yl)nonanoic acid from 1-nitrobutane and 10-undecynoic acid.[258] Phenylene diisocyanate has been successfully used for multikilogram syntheses: *N*-[(3-isopropylisoxazol-5-yl)methyl]-*N*-(4,6-dichloropyrimidin-2-yl)acetamide has been prepared in amounts of ~22 kg from *N*-(4,6-dichloropyrimidin-2-yl)-*N*-(prop-2-ynyl)acetamide and 2-methyl-1-nitropropane.[259]

[3 + 2]-Cycloaddition of alkynyldimethylsilyl ethers to alkyl(aryl)-substituted nitrile oxides, synthesized by the Mukaiyama method or by dehydrohalogenation of *N*-hydroximidoyl chlorides,[260] gives a mixture of regioisomeric trisubstituted isoxazoles. However, subsequent acid hydrolysis leads to isolation of only 4-silyl-substituted isoxazoles since 5-silyl derivatives are hydrolyzed. Cross-coupling of 4-substituted regioisomers with aryl iodides gives 3,4,5-trisubstituted isoxazoles.

Nitrile oxides, generated *in situ* using both the Mukaiyama method and dehydrohalogenation, have been introduced into cycloaddition to terminal acetylenes to synthesize a wide range of isoxazole–glycoside assemblies.[64] The synthesis of 5-{[(benzo[*b*][1,4]dioxan-2-yl)methoxy]methyl}isoxazoles containing various substituents in the 3-position with the use of the Mukaiyama method, dehydrohalogenation of *N*-hydroximidoyl chlorides and oxidation of oximes with sodium hypochlorite has been reported.[70] Different 5-aryl-3-(hetarylmethyl)- and 3-aryl-5-(hetarylmethyl)isoxazoles have been synthesized using various methods, including those employing phenyl isocyanate.[113]

Other acylating agents are also often used as dehydrating compounds. For example, 10-(indol-3-yl)-4,10-dihydrobenzo[6,7]oxepino[4,3-*c*]isoxazoles **102** have been synthesized using different combinations of the acylating agent (PhNCO, EtO_2CCl, Boc_2O), solvent (CH_2Cl_2, THF, PhMe, MeCN) and base (Et_3N, DMAP).[261] The di-*tert*-butyl dicarbonate–4-*N*,*N*-dimethylaminopyridine system in toluene appears to be most efficient (Scheme 62). An analogous procedure has been employed to synthesize oxepinoisoxazoles.[262] It has been demonstrated that, in synthesis of oxepinoisoxazoles from enantiomerically enriched starting compounds, the configuration of chiral centres is retained.[263]

Scheme 62

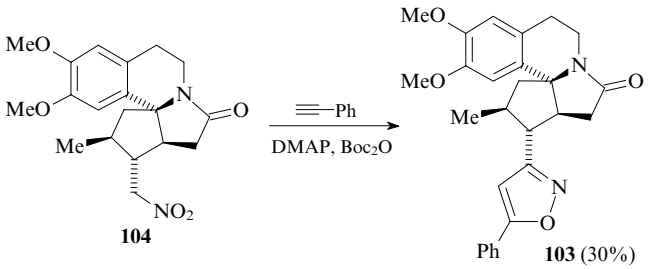


102 (55%–92%)

R^1 = H, OEt; R^2 = H, Br; R^3 = H, Et;
R^4 = H, Me, Et, Bn, 4-$BrC_6H_4CH_2$; R^5 = H, Me

Di-*tert*-butyl dicarbonate, in the presence of dimethylaminopyridine, converts optically active 2-aryl-1-nitropropanes into nitrile oxides under mild conditions; the latter react with ethyl propiolate to give 3-alkylisoxazole-5-carboxylates in high yield and with complete retention of the chiral centre configuration.[264] Goff[265] has managed to synthesize 5-phenylisoxazole **103**, containing an alkaloid substituent in the 3-position, by treating compound **104** with di-*tert*-butyl dicarbonate in the presence of phenylacetylene and dimethylaminopyridine (Scheme 63).

Scheme 63

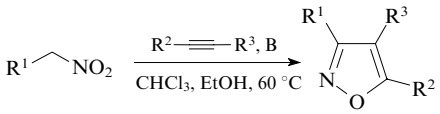


104 **103** (30%)

Novel 3,5-disubstituted isoxazoles attached through the C(3) atom of the ring to the 3-position of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose have been synthesized *via* intermediate nitrile oxides generated from nitro compounds in the reaction with ethyl chloroformate and triethylamine.[266] 3-Substituted isoxazole-4,5-dicarboxylates have been synthesized in a similar way from dimethyl acetylenedicarboxylate and 2-(indol-3-yl)-2-(tetrahydrofurodioxol-5-yl)nitroethane.[267]

It has been reported[268] that the synthesis of 3-substituted 5-phenylisoxazoles, which are formally the products of 1,3-dipolar cycloaddition, to phenylacetylene, of nitrile oxides generated from nitroalkanes with an electron-withdrawing substituent in the α-position to the nitro group, is achieved in the presence of bases, such as 1,4-diazabicyclo[2.2.2]octane, tetramethylenediamine or *N*-methylimidazole. It has been suggested that the reaction can also occur without intermediate formation of nitrile oxide, through an intermediate nitronate–dipolarophile adduct, since only some of the starting nitro compounds give nitrile oxide dimerization products under reaction conditions in the

Scheme 64



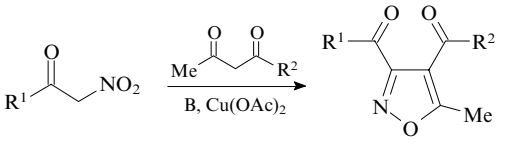
(20%–99%)

R^1 = Ac, Bz, EtO_2C, $PhSO_2$, MeNHC(O), PhNHC(O), Ph;
R^2 = Ph, $HOCH_2$; R_3 = H, $HOCH_2$; B = DABCO, TMEDA, DMAP, NMI *etc.*; DABCO is 1,4-diazabicyclo[2.2.2]octane, NMI is 1-methylimidazole

absence of a dipolarophile. In some cases, the fact that nitrile oxides are reaction intermediates has been proven by the presence of products of their side reactions.[269] Later, the same team has comprehensively studied this reaction for a wide range of nitro compounds and dipolarophiles in the presence of different organic bases and has suggested the reaction mechanism (Scheme 64).[270]

It has been demonstrated that the presence of catalytic amounts of copper(II) compounds in the reaction mixture facilitates the generation of nitrile oxides even from inactive nitro compounds.[271] Additions of copper(II) compounds have afforded isoxazoles **105** from nitroalkanes and enol forms of 1,3-dicarbonyl compounds (Scheme 65).

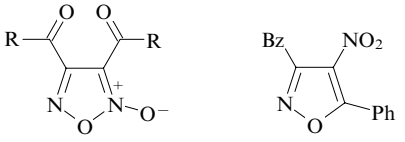
Scheme 65



R^1 = Ph, OMe, OEt, NHMe; R^2 = Me, Ph, OMe;
B = DABCO, NMPi, NMI, Et_3N; NMPi is *N*-methylpiperidine

In some reactions, furoxans **106** (nitrile oxide dimerization products) are formed, and in the case of benzoylnitromethane, self-condensation product **107** is identified.

Structures 106, 107



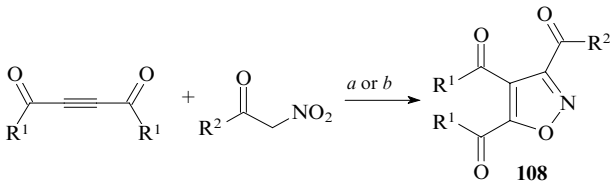
R = OMe (68%), OEt (43%)

In addition to the above reactions, a rather large number of reactions of cycloaddition of nitrile oxides (or their analogues) to alkenes leading to 4,5-dihydroisoxazoles have been studied. In the reactions of nitroacetate with fumarates or maleates as dipolarophiles, the resulting isoxazoline-3,4,5-tricarboxylates have been oxidized to the corresponding isoxazoles.[272]

5-Substituted isoxazole-3-carboxylates are obtained in good preparative yields by the reaction of nitroacetate and terminal acetylenes (phenylacetylene and propargyl alcohol) catalyzed with bases in an aqueous medium.[273] *N*-Methyl-2-nitroacetamide reacts with propiolic acid and methyl propiolate in an aqueous solution in the presence of sodium alkali to give a mixture of isoxazole-3,5- and -3,4-carboxylic acid derivatives.[274]

Similar results have been reported:[275] the reaction of symmetric acetylenes and nitromethanes with electron-withdrawing substituents in the α-positions catalyzed by nitrogen-containing heterocycles yields trisubstituted isoxazoles **108** (Scheme 66, conditions *a*). Earlier, the same authors have carried out this reaction under different conditions, namely, by long-term refluxing of the reactants in toluene in the presence of triphenylphosphine (conditions *b*).[276]

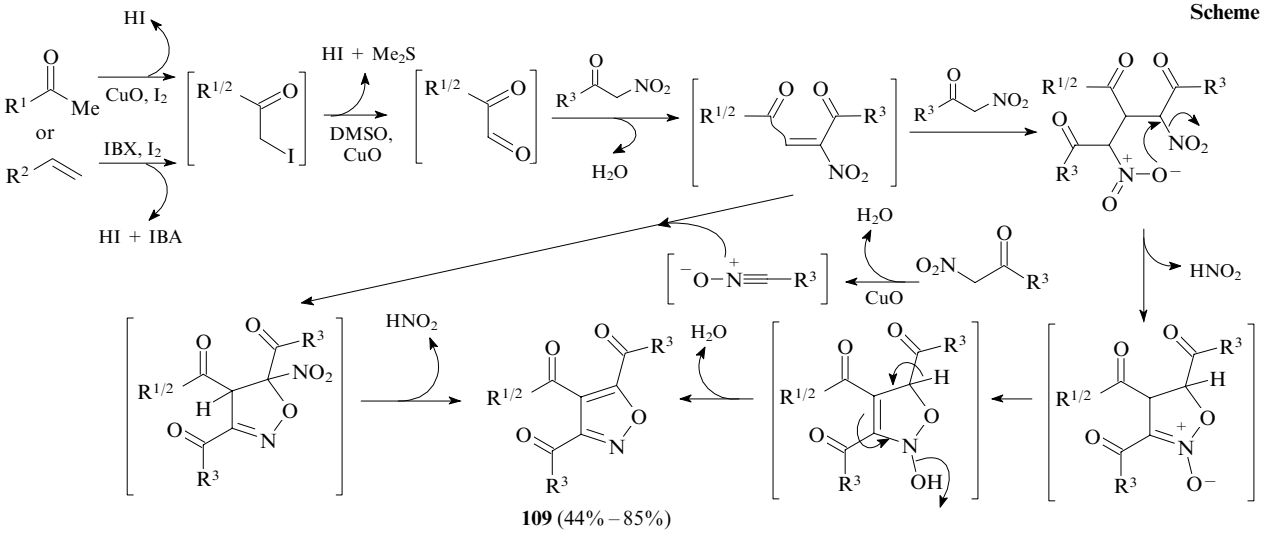
Scheme 66



(*a*) pyridine or NMI, H_2O–MeCN (5 : 1), 20 °C (65% – 85% yield);
(*b*) PPh_3, PhMe, Δ (70% – 90% yield);
R^1 = OMe, OEt, OBu^t, Ph; R^2 = OMe, OEt, Ph

The reaction of activated nitro compounds (nitroacetates, benzoylnitromethane, phenylsulfonylnitromethane) with 2,3-dichloro- and 2-bromo-1,4-naphthoquinones in the presence of bases has been studied with the aim to synthesize naphtho[2,3-*d*]isoxazole-4,9-diones with an electron-withdrawing substituent in the 3-position.[277] The target compounds have been obtained in low yield, and the reaction has yielded large amounts of side products.

Scheme 67



R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-Th, 2-Fu, 1-Naph, 2-Naph, benzofuran-2-yl, PhCH=CH, 4-$MeOC_6H_4CH$=CH, 4-$O_2NC_6H_4CH$=CH, $Ph(CH=CH)_2$; R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-Naph; R^3 = EtO, Pr^i, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4; IBX is iodoxybenzoic acid (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide), IBA is 1-hydroxy-1,2-benziodoxol-3(1*H*)-one

Study of dehydration of benzoylnitromethane by strong acids in boiling toluene with subsequent cycloaddition of the generated nitrile oxide to alkynes has demonstrated that, in the presence of polyphosphoric acid on silica gel, the reaction affords products in good to quantitative yields. The acid taken in catalytic amounts can be recovered and repeatedly used.[278] As in Refs 92 and 274, the reaction with propiolates gives small amounts of regioisomeric 3-benzoylisoxazole-4-carboxylate. The reaction with nitroacetate leads to products in noticeably lower yields and occurs at higher temperature in another solvent (*o*-dichlorobenzene instead of toluene). This is consistent with the conclusion that aroylnitrometanes that are more prone to enolization than nitroacetates or amides undergo dehydration much more easily than these compounds.[268]

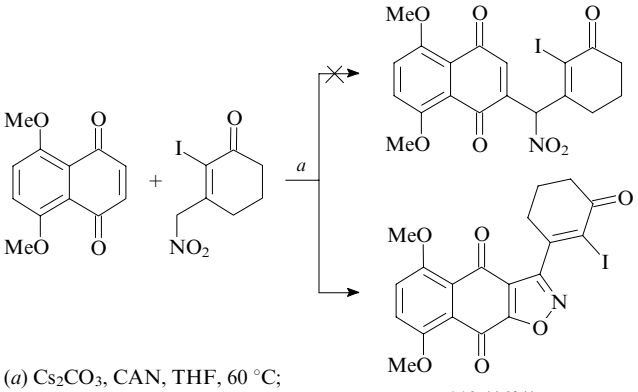
It has been shown that polyethylene glycol promotes the generation of nitrile oxides from activated nitro compounds, such as nitroacetates and aroylnitromethanes.[279] For example, these nitro compounds react with terminal acetylenes in the polyethylene glycol (PEG) 400 — water system at 90 °C for 4–6 h to give 3,5-disubstituted isoxazoles in high yields.

A one-pot protocol involving several reactions has been developed to synthesize trisubstituted isoxazoles.[280] The iodination and Kornblum oxidation convert acetophenones or arylalkenes into unstable ketoaldehydes, which are then subjected to condensation with activated nitroalkanes to give 2-nitro-2-butene-1,4-diones. The latter react with the second molecule of activated nitroalkane to form isoxazoles **109** (Scheme 67).

The authors believe that the final transformation is the Michael addition. However, taking into account the ease of generation of nitrile oxides from activated α-acceptor-substituted nitromethanes, it cannot be ruled out that this stage is a 1,3-dipolar cycloaddition.

In addition to specially developed methods for synthesis of isoxazoles through 1,3-dipolar cycloaddition, examples are available where isoxazoles have been isolated in reactions that were expected to give quite different products. In particular, fused isoxazole **110** has been obtained through the oxidative Michael addition of nitromethyl-substituted enones to quinones.[281] Isoxazole **110** is the product of dehydration of the isoxazoline adduct of [3 + 2]-cycloaddition of the nitrile oxide to alkene (Scheme 68).

Scheme 68

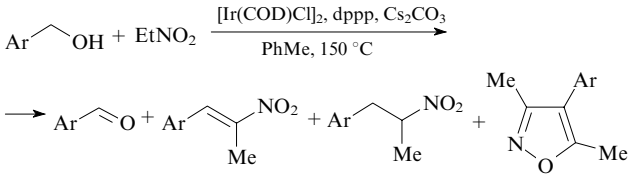


(*a*) Cs_2CO_3, CAN, THF, 60 °C;
CAN is ammonium cerium(IV) nitrate

110 (46%)

The cross coupling of benzyl alcohols with different CH-acids has been studied.[282] The reaction with nitroethane gives isoxazoles **111** as side products, sometimes in rather high yields (Scheme 69).

Scheme 69



111 (9%–60%)

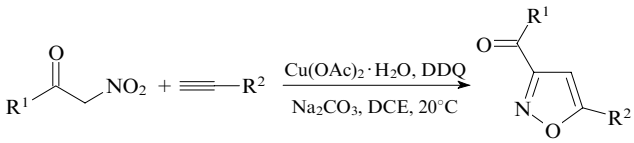
Ar = Ph, 4-HOC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3-$H_2NC_6H_4$, indol-3-yl;
COD is 1,5-cyclooctadiene, dppp is 1,3-bis(diphenylphosphino)propane

II.3. Other methods of synthesis

The methods of synthesis of isoxazoles reviewed in this Section are considerably less significant and are not as versatile as the above-described approaches. Nevertheless, sometimes such reactions are simplest and most efficient.

A one-pot synthesis of 3,5-disubstituted isoxazoles **112** from terminal alkynes and activated nitro compounds catalyzed by copper salt $Cu(OAc)_2 \cdot H_2O$ in the presence of stoichiometric amounts of DDQ has been reported.[283] This method affords isoxazoles with carbonyl and ester groups in the 3-position of the heterocycle (Scheme 70).

Scheme 70

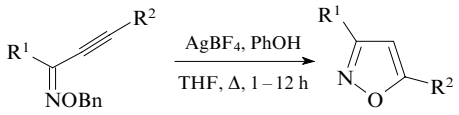


112 (28%–75%)

R^1 = OMe, Ph, Bu^n; R^2 = Ph, $SiMe_3$, n-C_6H_{13}, $(CH_2)_3Cl$, 2-Th, 3-Th;
DCE is 1,2-dichloroethane

Intramolecular cyclocondensations can also lead to 3,5-di- and 3,4,5-trisubstituted isoxazoles. For example, a facile and practical synthesis of isoxazoles **113** from alkynyl ketone oxime ethers *via* a silver-catalyzed cyclization and subsequent protonation of phenols has been developed (Scheme 71).[284]

Scheme 71

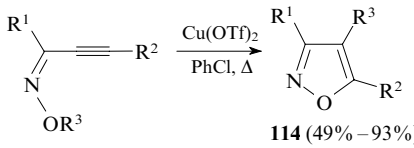


113 (59%–86%)

R^1 = H, CO_2Me, Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 2-Fu;
R^2 = Bu^n, CH_2OMe, CH_2OAc, CH_2OH, CO_2Et, Ph

It should be noted that when the process is catalyzed by copper(II) triflate, the formation of the isoxazole ring is followed by migration of the *O*-arylmethyl substituent to the 4-position of forming heterocycle **114** (Scheme 72).[285]

Scheme 72

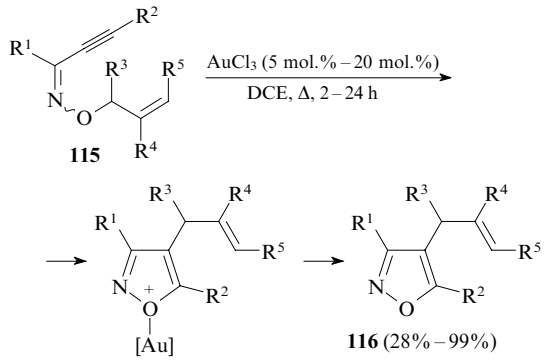


114 (49%–93%)

R^1 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, Cy, CO_2Me; R^2 = H, Ph, Bu^n, Cy, CH_2OTBS; R^3 = $CH_2C_6H_4OMe$-4, $CH_2C_6H_4NMe_2$-4, $CH_2C_6H_4OMe$-2, C_6H_4OTBS-4, $CH(Me)C_6H_4OMe$-4, $CHPh_2$, CH_2-Naph-2

Gold-catalyzed transformations of alkynyl oxime ethers **115** occur in a similar way. These transformations through the domino reaction involving the cyclization and Claisen rearrangement of an intermediate cationic complex regioselectively lead to trisubstituted isoxazoles **116** (Scheme 73).[286]

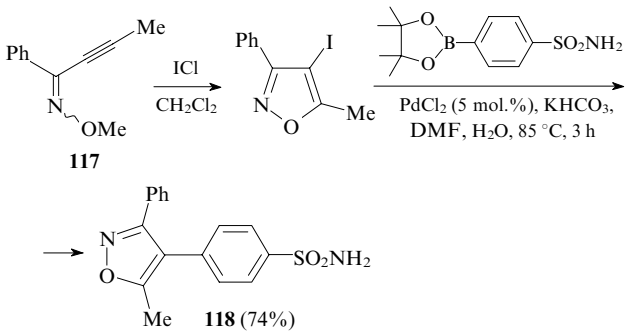
Scheme 73



R^1 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 2-Fu, CO_2Me, Cy;
R^2 = Cy, Bu^n, Ph, 2-BrC_6H_4, All, CH_2OTBS, CH_2OH;
R^3 = H, Me, All; R^4 = H, Me, CH_2OTBS; R^5 = H, Me, CO_2Et

Numerous functionally substituted 2-alkyn-1-one *O*-methyl oximes (for example, compound **117**) are cyclized under mild conditions in the presence of iodine chloride to give the corresponding 4-iodoisoxazoles. The latter are of special interest since they enter into Pd-catalyzed coupling to give 3,4,5-trisubstituted isoxazoles. This approach is one of the methods of synthesis of valdecoxib (**118**) (Scheme 74).[238, 287]

Scheme 74

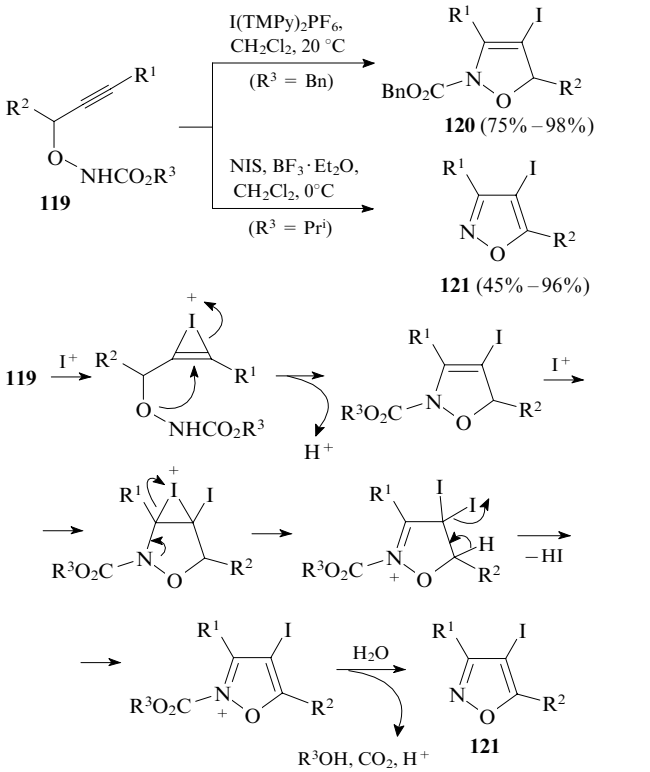


The cyclization of *N*-alkoxycarbonyl *O*-propargylic hydroxylamines **119** based on oxidative aromatization leads to 4-iodo-2,5-dihydroisoxazoles **120** and 3,5-disubstituted 4-iodoisoxazoles **121**. In this reaction, the iodonium cation acts as both the iodination agent and the oxidant (Scheme 75).[288] A putative scheme of the reaction has been reported.

Benzo-fused isoxazoles **122** can be synthesized from *ortho*-azido-substituted aryl ketones in the presence of $FeBr_2$ as the catalyst (Scheme 76).[289]

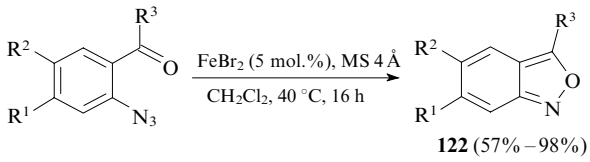
An original method of synthesis of 3-substituted isoxazole-4-carbaldehydes **123** through the reaction of corresponding nitro compounds and oxetan-3-one has been developed (Scheme 77).[290] Although the mechanism of this cascade transformation is unclear, the ease of the reaction and high yields of the products, which are difficult to synthesize by other methods, make this method a valuable tool of the synthetic chemist.

Scheme 75



R^1 = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, Bu^n, 1-Naph, 2-Th;
R^2 = H, Me; R^3 = Pr^i, Bn; TMPy is 2,4,6-trimethylpyridine;
NIS is *N*-iodosuccinimide

Scheme 76



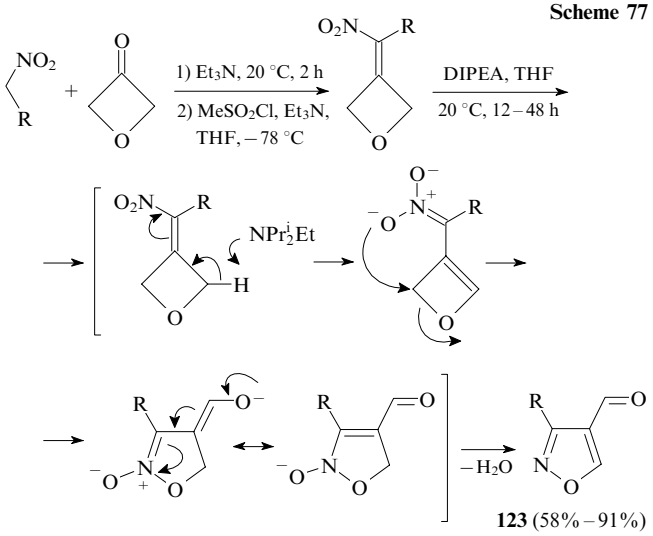
R^1 = H, Me, OMe; R^2 = H, Cl;
R^3 = H, Me, Pr^i, Cy, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4;
MS is molecular sieves

gem-Dichloroarylcyclopropanes containing acceptor substituents in the benzene ring react with the $NOCl \cdot 2\,SO_3$ complex to chemo- and regioselectively transform into 3-aryl-5-chloroisoxazoles **124** in high yields (Scheme 78).[291] If the benzene ring has donor substituents, the yields of isoxazoles decrease because side reactions occur.

An efficient and simple method has been suggested for synthesis of 3-chloromethyl-1,2-benzisoxazoles **125** through the modified Boekelheide rearrangement under the action of $POCl_3$ (Scheme 79).[292] This method leads to target products **125** in moderate to high yields.

Yet another method of synthesis of isoxazoles, described for the synthesis of novel furobenzisoxazole derivatives, involves the Posner reaction of 5-hydroxy-3-methylfuro[3,2-*g*]chromen-7-one (**126**) with hydroxylamine hydrochloride to give (5-methylfuro[2′,3′:4,5]benzo[1,2-*d*]-isoxazol-3-yl)acetic acid (**127**) (Scheme 80).[293]

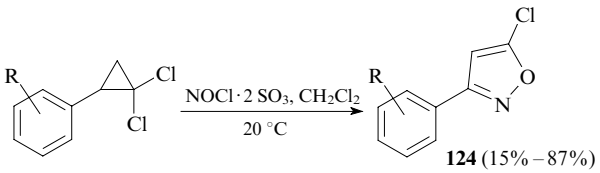
Scheme 77



123 (58%–91%)

R = Bn, $CH_2C_6F_5$, CH_2(3-Py), $CH_2C_6H_4CF_3$-4, $CH_2C_6H_4NO_2$-4, CH_2(3-Ind), CH_2Cy, piperonyl, $(CH_2)_2CO_2Me$, CH_2CO_2Et, $(CH_2)_3OAc$, $(CH_2)_2CH{=}CH_2$, $(CH_2)_2NHBoc$, CH_2OTBS, Ph, 4-Bu^{t}C$_6$H$_4$; IND is indolyl

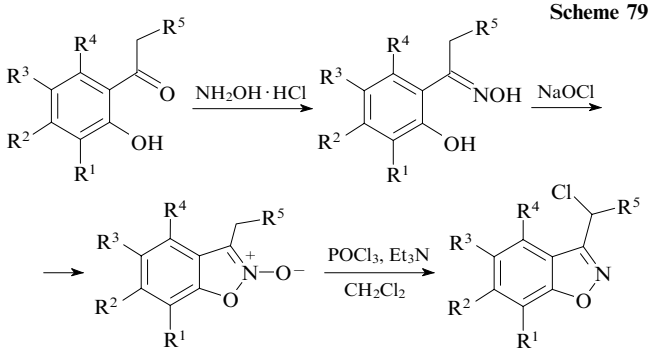
Scheme 78



124 (15%–87%)

R = H, 3-Cl, 4-Cl, 3-Br, 4-Br, 2-NO_2, 3-NO_2, 4-NO_2

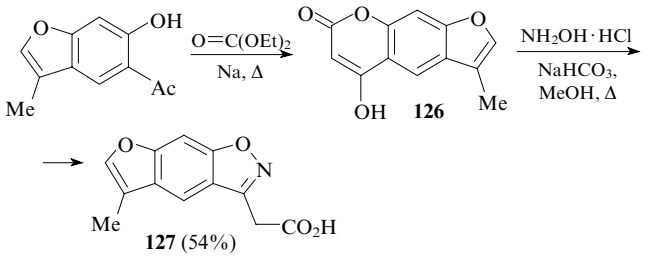
Scheme 79



125 (30%–65%)

R^1 = H, Me, NO_2; R^2 = H, Me, OMe; R^3 = H, Me, Et, Ph, Cl, Br, NO_2; R^4 = H, Me; R^5 = H, Me, Et, Pr^i, Ph

Scheme 80



126

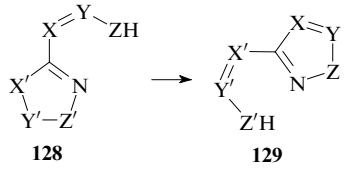
127 (54%)

III. Reactions of isoxazoles

III.1. Isoxazole reactions involving ring opening

One of important rearrangements actively used in synthesis of heterocycles is the Boulton–Katritzky rearrangement.[294,295] This process involves the transformation of azole **128**, which has a triatomic unsaturated side chain, into other azole **129**; the side chain is involved in formation of a new ring through bonding to the nitrogen atom of the starting compound (Scheme 81).

Scheme 81



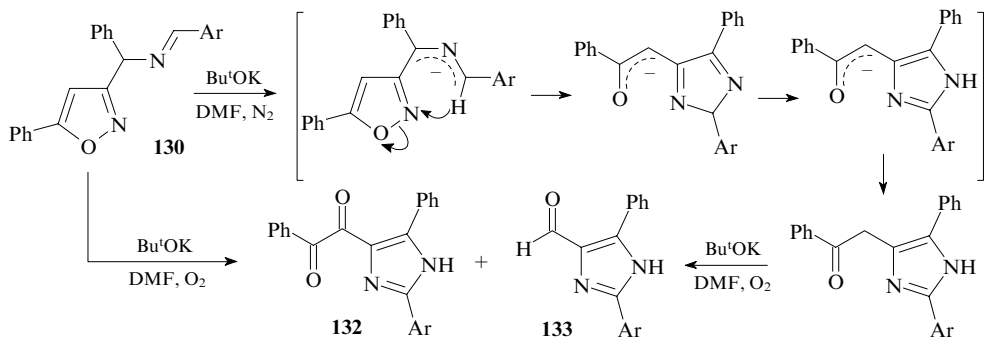
128 **129**

Recently, this recyclization has been used for transforming isoxazole derivatives into imidazole derivatives. In particular, the Boulton–Katritzky rearrangement of 3-[(*N*-arylmethylideneamino)methyl]-substituted isoxazoles **130** leads to imidazoles **131** (Scheme 82).[296,297] An important condition for the synthesis of compounds **131** is that the reaction should be carried under an inert gas atmosphere. In the presence of air, only oxidation products **132** and **133** are isolated.

The Boulton–Katritzky rearrangement of *N*-(isoxazol-3-yl)thioureas **134** leads to 1,2,4-thiadiazoles **135**. The starting compounds are synthesized either from 3-aminoisoxazoles and isothiocyanates,[298–300] or from 3-isothiocyanatoisoxazoles and amines.[301,302] Isoxazol-3-ylthioureas **134** are unstable and, in some cases, spontaneously rearrange to 1,2,4-thiadiazoles **135** (Scheme 83).

Experimental and quantum chemical (density functional theory (DFT) calculations) study of the base-catalyzed rearrangement of 3-amido-5-methylisoxazole **136** has

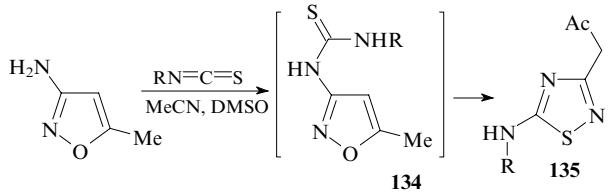
Scheme 82



130 **132** **133** **131** (80%–98%)

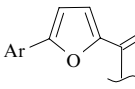
Ar = RC_6H_4 (R = H, 2-Me, 3-Me, 4-Me, 4-OMe, 4-CF_3, 4-F, 4-Cl, 4-Br, 4-NMe_2)

Scheme 83

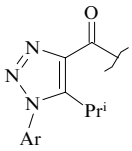


134 **135**

R = OMe, OEt, OBn, Me, Pr^n, Ph, 2-ClC$_6$H$_4$ (50%–76% yields);



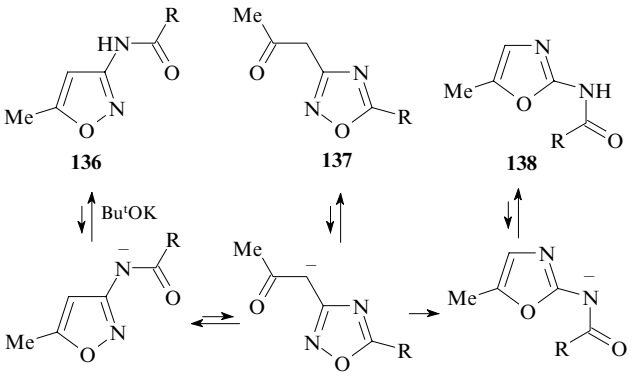
(Ar = 3-O$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 2-Cl-4-O$_2$NC$_6$H$_3$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2,5-Cl$_2$C$_6$H$_3$, 3,4-Cl$_2$C$_6$H$_3$, 2-F$_3$CC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$) (78%–89%);



(Ar = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 4-MeOC$_6$H$_4$) (76%–97%)

shown that this process is a cascade reaction involving the Boulton–Katritzky rearrangement to less stable 1,2,4-oxadiazole **137**.[303] On heating, the latter transforms into more stable oxazole **138** (Scheme 84).

Scheme 84



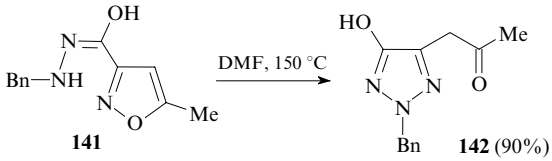
136 **137** **138**

R = Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, Pr^i

Similar cascade processes have been described for isoxazolocoumarins. For example, 3-aminoisoxazolo[4,5-*c*]coumarins **139** react with carboxylic acid anhydrides or chlorides to form corresponding amides, and their heating in DMSO is accompanied by the Boulton–Katritzky rearrangement to 2-acetamido-, 2-benzoylamido- or 2-aminooxazoles **140** depending on the nature of the acylating agent (Scheme 85).[304, 305]

Isocarboxazid (**141**) rearranges on heating to 5-acetonyl-2-benzyl-4-hydroxy-1,2,3-triazole **142** in DMF, ionic liquids or as a melt. This is the first reported example of the Boulton–Katritzky rearrangement of an acyl hydrazide (Scheme 86).[306]

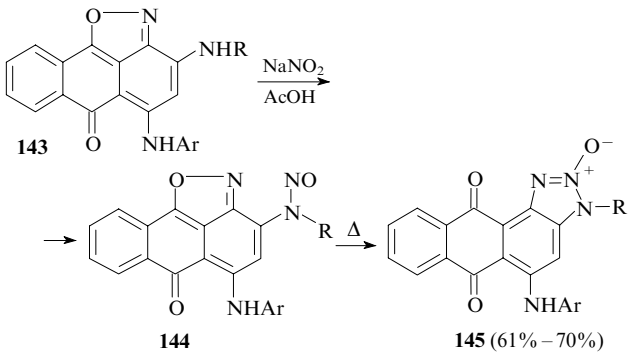
Scheme 86



141 **142** (90%)

Nitrosylation of 3-alkylamino-5-arylamino-6*H*-anthra[1,9-*c*,*d*]isoxazol-6-ones **143** with sodium nitrite gives unstable *N*-nitroso derivatives **144**, which undergo on heating the Boulton–Katritzky rearrangement to 3-alkyl-5-arylamino-6,11-dioxo-3*H*-6,11-dihydroanthra[1,2-*d*][1,2,3]-triazole 2-oxides **145** (Scheme 87).[307]

Scheme 87

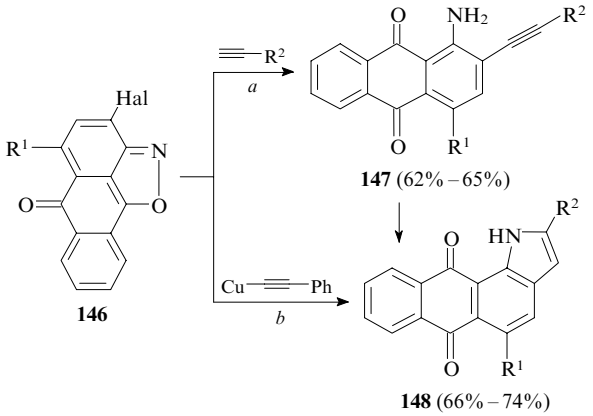


143 **144** **145** (61%–70%)

R = Et, Bu^n, Bu^i; Ar = Ph, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$

It has been shown[308] that the Cu-catalyzed reductive isoxazole ring opening in compounds **146** under Sonogashira conditions occurs at lower temperatures than the

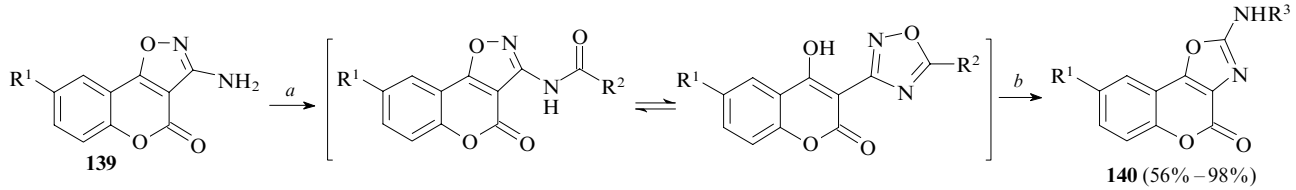
Scheme 88



146 **147** (62%–65%) **148** (66%–74%)

(*a*) Pd(PPh$_3$)$_2$Cl$_2$, PPh$_3$, CuI, Et$_3$N, PhH, 45–50 °C; (*b*) PyH, 115 °C (for Hal = I, R^1 = 4-MeC$_6$H$_4$NH 92% yield); Hal = I, Br; R^1 = 3-MeC$_6$H$_4$NH, 4-MeC$_6$H$_4$NH; R^2 = Ph, SiMe$_3$, CH$_2$OPh

Scheme 85



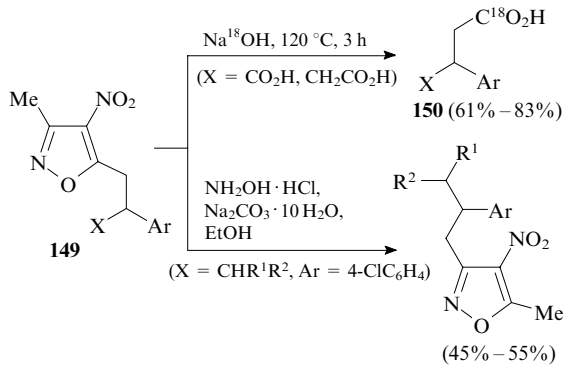
139 **140** (56%–98%)

(*a*) (R^{2}CO)$_2$O or R^{2}C(O)Cl; (*b*) DMSO, 90 °C; R^1 = H, Me; R^2 = Me, Ph, CF$_3$; R^3 = Ac, Bz, H

5-*endo-dig*-recyclization of aminoacetylenes **147** to indoles **148**. This makes it possible to stop the cascade reaction at the stage of formation of compounds **147** (Scheme 88).

4-Nitroisoxazoles **149** can be used for selective labelling of the carboxyl group of acids **150** through the decomposition of the isoxazole ring by ^{18}O-labelled alkali.[309] The reaction of 5-alkyl-3-methyl-4-nitroisoxazoles **149** with hydroxylamine is accompanied by a rearrangement leading to the interchange of nitrogen and oxygen atoms in the five-membered ring (Scheme 89).[310]

Scheme 89

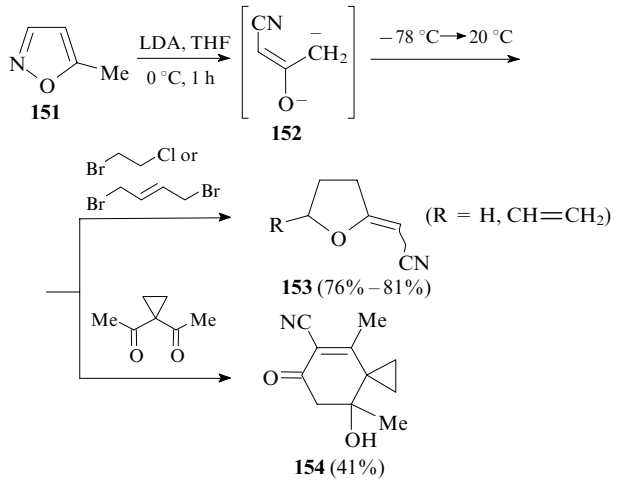


Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$O_2NC_6H_4$;
X = CO_2H, CH_2CO_2H, CHR^1R^2 (R^1 = CO_2Et, CO_2Bu^t, H;
R^2 = CO_2Et, CO_2Bu^t, NO_2, CO_2H)

Reductive isoxazole ring opening under the action of $Mo(CO)_6$, H_2/Ni-Ra (Ni-Ra is Raney nickel), SmI_2 and other reducing systems leads to enaminones, which are widely used as starting compounds in synthesis of various heterocycles.[311–317]

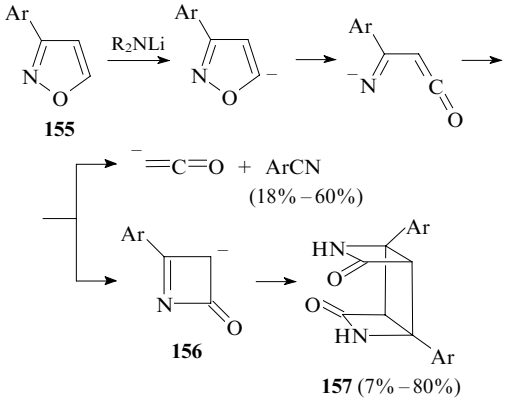
Ring opening in 5-methylisoxazole **151** under the action of LDA leads to cyanoacetone dianion **152**, which reacts with dihaloalkanes and dihaloalkenes to give 2-cyanomethylidenetetrahydrofurans **153**[318] and with 1,1-diacetylcyclopropane to form spirocyclic compound **154** (Scheme 90).[319]

Scheme 90



3-Arylisoxazoles **155** react with sterically hindered lithium dialkylamides. Stereoselective dimerization of intermediate azetine anion **156** affords *syn*-2,6-diaryl-3,7-diazatetracyclo[4.2.0.0^{2,5}]octane-4,8-diones **157**. This reaction can be competed with by the fragmentation of intermediate noncyclic anions leading to arylnitriles (Scheme 91).[320, 321]

Scheme 91

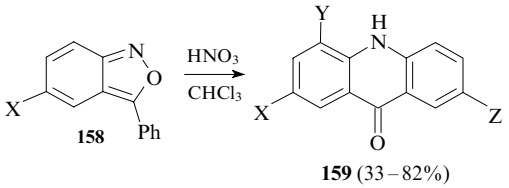


Ar = Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 4-$F_3CC_6H_4$, 2-$F_3CC_6H_4$

The product of the reaction of 3-phenylisoxazole with alkyllithium, which occurs through the formation of the anion at the C(5) atom, depends on the size of the reagent alkyl group. In particular, the reaction with *tert*-butyllithium is mainly accompanied by fragmentation to benzonitrile, while the reaction with smaller reagents (MeLi, EtLi, Bu^nLi) additionally yields enaminones. In the case of EtLi and MeLi, 2-alkyl-4,6-diphenylpyrimidines are also produced.[322]

The reaction of 5-halo-3-phenylbenzo[*c*]isoxazoles **158** with concentrated nitric acid in chloroform leads in one stage to acridinone nitro derivatives **159** (Scheme 92).[323]

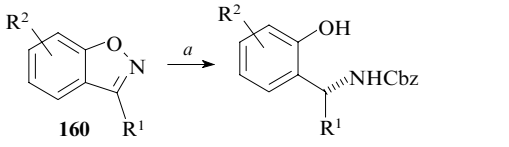
Scheme 92



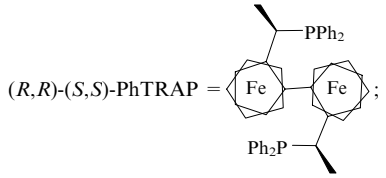
X = Br, Y = NO_2, Z = H; X = I, Y = H, Z = NO_2;
Y = Z = NO_2: X = Br, I

The isoxazole ring in 3-substituted 1,2-benzisoxazoles **160** undergoes reductive opening on a chiral ruthenium

Scheme 93



R^1 = Me, Pr^i, CH_2CH_2Ph, Ph; R^2 = H, 6-OMe, 5-OMe, 4-OMe, 5-Me, 6-Me, 5-F, 6-F; CbzOsu is *N*-(benzyloxycarbonyloxy)succinimide;

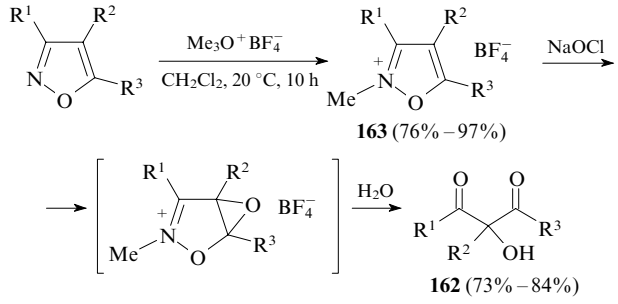


(*a*) {Ru(*p*-cymol)[(*R*,*R*)-(*S*,*S*)-PhTRAP]}Cl (2.5 mol.%), CbzOSu, H_2 (50 atm), THF, 80 °C, 4 h

catalyst to give, in the presence of an acylating agent, α-substituted chiral *o*-hydroxybenzylamines **161** with low enantiomeric excesses (Scheme 93).[324]

α-Hydroxy-β-diketones **162** have been synthesized by N-methylation and hydroxylation of isoxazoles through the intermediate formation of corresponding isoxazolium salts **163** (Scheme 94).[325]

Scheme 94



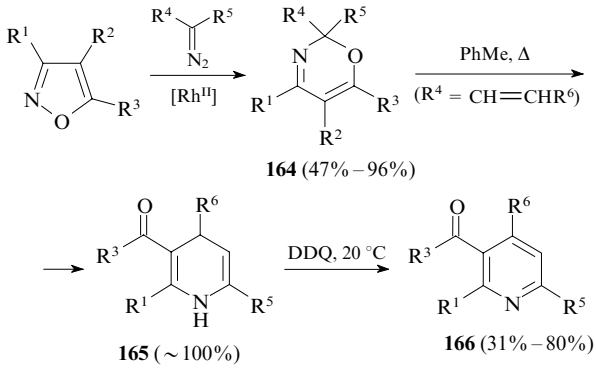
163 (76%–97%)

162 (73%–84%)

R^1 = Ph, Bu^t; R^2 = H, Me, CO_2Et, Ph; R^3 = Me, Bu^t, Ph

The formal insertion of carbenoids, generated from diazo compounds in the presence of a rhodium catalyst, into the N–O bond of isoxazole leads to 2*H*-1,3-oxazines **164**.[326, 327] Oxazines **164** with substituent R^4 containing a vinyl moiety can be transformed to functionalized 1,4-dihydropyridines **165** and then to pyridines **166** (Scheme 95).

Scheme 95



164 (47%–96%)

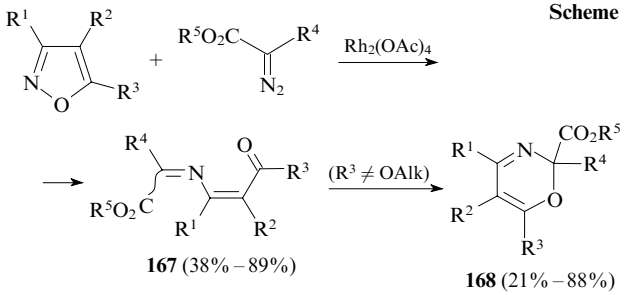
165 (~100%)

166 (31%–80%)

R^1 = Me, CH_2Cl; R^2 = H, Br; R^3 = Me, CH_2CO_2Me, $(CH_2)_2OTBS$; R^4 = H, CO_2Me; R^5 = CO_2Me, CO_2Et; R^6 = Ar, Het, CO_2Me

It has been recently demonstrated that the reaction of isoxazoles with diazo compounds occurs through the intermediate formation of (3*Z*)-1-oxa-5-azahexa-1,3,5-trienes **167**, which then undergo 6π-cyclization to give 2*H*-1,3-oxazines **168**. Theoretical and experimental evidence shows that 2*H*-1,3-oxazines **168** are, as a rule, thermodynamically more stable than corresponding (3*Z*)-1-oxa-5-azahexa-1,3,5-trienes **167**. Exceptions are oxazahexatrienes forming from 5-alkoxyisoxazoles, which makes such a reaction with diazo esters a good approach to the synthesis of 1,4-di(alkoxycarbonyl)-2-aza-1,3-butadienes (Scheme 96).[328]

Scheme 96



167 (38%–89%)

168 (21%–88%)

R^1 = Me, Ph; R^2 = Ph, Cl, Br, I; R^3 = Me, Ph, OMe, OBu^t; R^4 = H, Ph, CO_2Me, CF_3; R^5 = Me, Et

The behaviour of isoxazoles in photolysis[329–331] and thermolysis[332] has been studied. It has been suggested that isoxazoles undergo photoinduced isomerization to oxazoles through the rearrangement of an azirine intermediate.

III.2. Isoxazole reactions leading to formation of fused heterocyclic systems

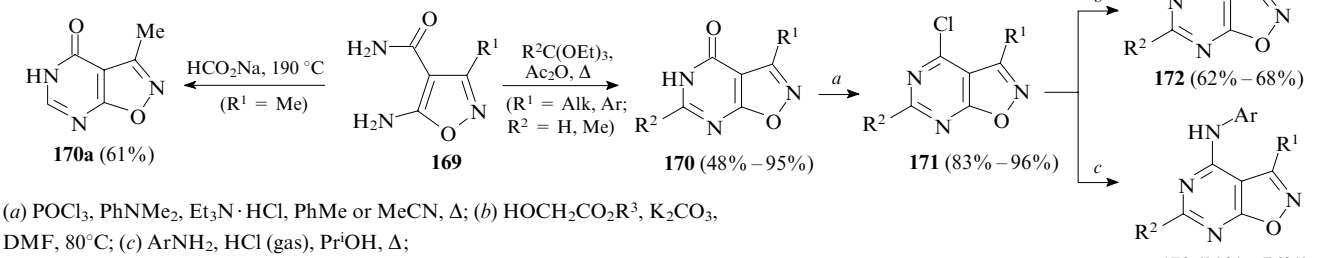
Formation of fused systems from isoxazoles is possible if the molecule contains two nucleophilic centres, one electrophilic and one nucleophilic centres or two nucleophilic centres. Below, we consider examples of annulation according to this classification of initial systems.

III.2.a. Reactions of isoxazoles containing two nucleophilic centres

Reactions of 5-aminoisoxazole-4-carboxamides **169** with triethyl orthoformate, triethyl orthoacetate[333, 334] or sodium formate[335] lead to isoxazolo[5,4-*d*]pyrimidin-4-(5*H*)-ones **170**. Derivatives of these systems obtained through the stage of formation of chloride **171** — isoxazolo[5,4-*d*]pyrimidines **172**[333] and **173**[334] — are novel correctors of the mutant protein ΔF508-CFTR (Scheme 97).

Analogously, 5-aminoisoxazole-4-carbonitrile **174a** can be used for synthesis of isoxazolo[5,4-*d*]pyrimidine **175**.[336] Chloro-substituted isoxazolo[5,4-*d*]pyrimidine **176** has

Scheme 97



170a (61%)

169

170 (48%–95%)

171 (83%–96%)

172 (62%–68%)

173 (30%–76%)

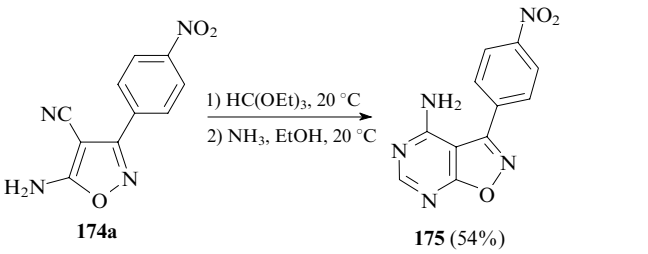
(*a*) $POCl_3$, $PhNMe_2$, $Et_3N \cdot HCl$, PhMe or MeCN, Δ; (*b*) $HOCH_2CO_2R^3$, K_2CO_3, DMF, 80°C; (*c*) $ArNH_2$, HCl (gas), Pr^{i}OH, Δ;

172: R^1 = Me, Et, Ph, 4-FC_6H_4, 4-MeC_6H_4, 3-ClC_6H_4, 3-FC_6H_4, 4-$MeOC_6H_4$; R^2 = H, Me; R^3 = Me, Et;

173: Ar = 2,3-$Me_2C_6H_3$, 3-$MeOC_6H_4$, 2-MeC_6H_4, 3-MeC_6H_4, 3,4-$(OCH_2O)C_6H_3$; R^1 = 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-$MeOC_6H_4$; R^2 = H, Me

been obtained in one-pot synthesis from 5-aminoisoxazole-4-carbonitrile **174b** and *N*,*N*-dimethyldichloromethyleneiminium chloride.[337] Subsequent nucleophilic substitution of the chlorine atom in compound **176** by an amino, methoxy or sulfanyl group has opened the way to new 6-dimethylamino-substituted isoxazolo[5,4-*d*]pyrimidines **177** (Scheme 98).

Scheme 98

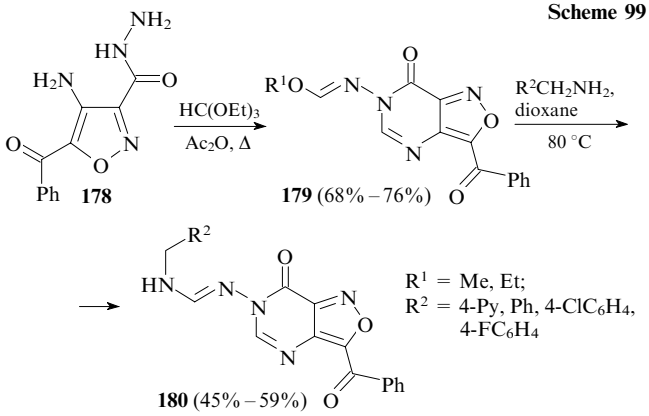


(*a*) 1) $[Cl_2C{=}NMe_2]^+Cl^-$, DCE, Δ; 2) HCl (gas), DCE, 20 °C;
(*b*) amine, or NaOMe, or NaSH;

R = NHBn, NMe_2, $NHPr^n$,  (X = CH_2, CHMe, O, S, NC_6H_4Ac-4, $NCH_2C_6H_3(OCH_2O)$-3,4), OMe, SH

Condensation of 4-amino-5-benzoylisoxazole-3-carboxylic acid hydrazide (**178**) with triethyl orthoformate gives compounds **179**, which then readily react with amines to form 3-benzoyl-7-oxo-7*H*-isoxazolo[4,3-*d*]pyrimidin-6-ylideneformamidines **180** (Scheme 99).[338]

Scheme 99

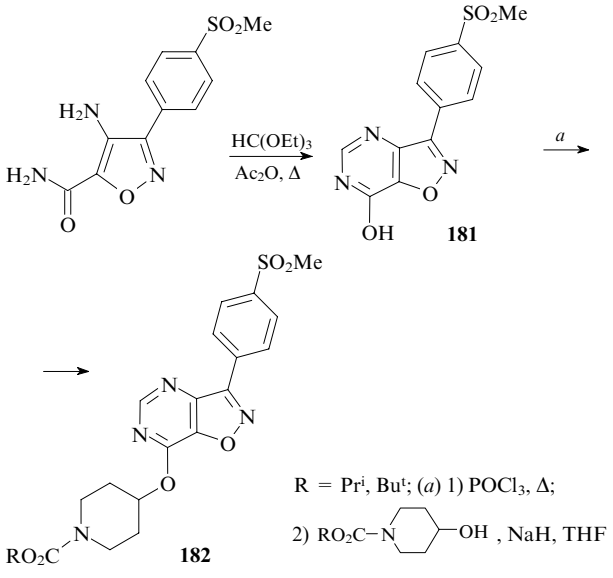


An analogous procedure leads to isoxazolo[4,5-*d*]pyrimidines, for example, compound **181**, which is an intermediate in the synthesis of more complex isoxazolo[4,5-*d*]pyrimidines **182** modified at the hydroxyl group (Scheme 100).[339]

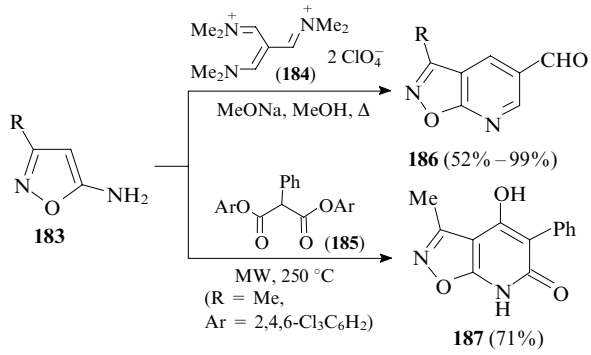
Reactions of 5-aminoisoxazoles **183** with 2-dimethylaminomethylene-1,3-bis(dimethylamino)propane diperchlorate (**184**) and activated malonate **185** are new methods of synthesis of isoxazolo[5,4-*b*]pyridines **186**[340] and **187**[341] (Scheme 101).

Reactions of 5-amino-3-methylisoxazole (**183a**) with a large number of α,β-unsaturated carbonyl compounds have been described.[342] In all cases, isoxazolo[5,4-*b*]pyridine derivatives **188** have been obtained in good yields (Scheme 102).

Scheme 100

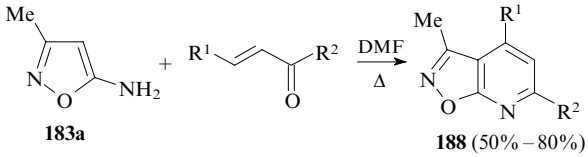


Scheme 101



R = Me, Pri, But, 4-MeC_6H_4

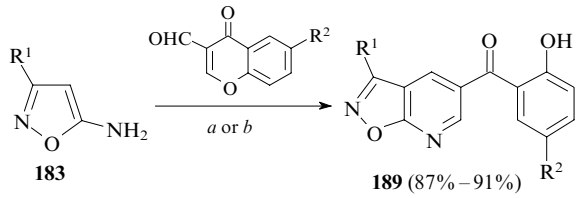
Scheme 102



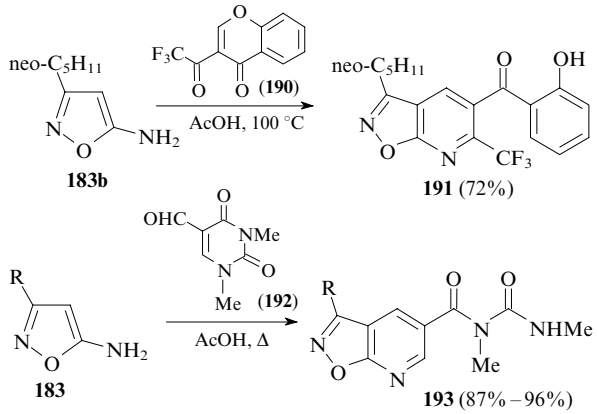
R^1 = Ph, 4-$MeOC_6H_4$; R^2 = Ph, CO_2H, CH=CHPh

Reactions of 5-aminoisoxazoles with 3-formyl- or 3-acylchromones are widely reported in the literature. This reaction is a simple and efficient method for synthesis of 5-(2-hydroxybenzoyl)isoxazolo[5,4-*b*]pyridines **189** (R^2 = H,[343] Me[344]). It is worth noting that the reaction of 5-amino-3-neopentylisoxazole (**183b**) with 3-trifluoroacetylchromone (**190**) gives, as the major product, regioisomer **191** containing the trifluoromethyl group at the C(6) atom.[345] The reaction of recyclization of 5-formyl-1,3-dimethyluracil (**192**) with 5-aminoisoxazoles **183** occurs analogously to give isoxazolo[5,4-*b*]pyridines **193** containing the nicotinamide moiety in high yields (Scheme 103).[346]

Scheme 103



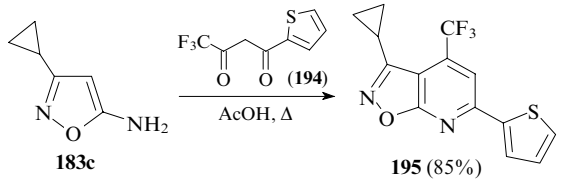
(*a*) 1) Me_3SiCl, DMF, 100 °C; 2) H_2O, UST, 20 °C (for R^2 = H);
(*b*) TsOH, EtOH, 90 °C (for R^2 = Me);
R^1 = Me, Pr^i, Ph; R^2 = H, Me; UST is ultrasonic treatment



R = Me, Pr^i, 4-MeC_6H_4

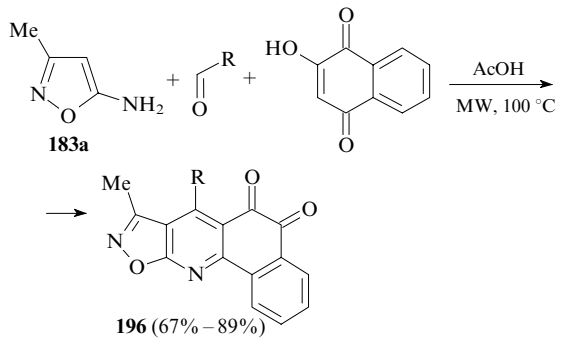
Condensation of 5-aminoisoxazole **183c** with 1,3-dicarbonyl compounds is also observed. In particular, the reaction with 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione (**194**) in acetic acid is regioselective to give isoxazolo[5,4-*b*]pyridine **195** (Scheme 104).[347]

Scheme 104



A new domino reaction based on 5-aminoisoxazole **183a** has been recently suggested for regioselective synthesis of highly functionalized benzo[*h*]isoxazolo[5,4-*b*]quinolones **196** in high yields (Scheme 105).[348]

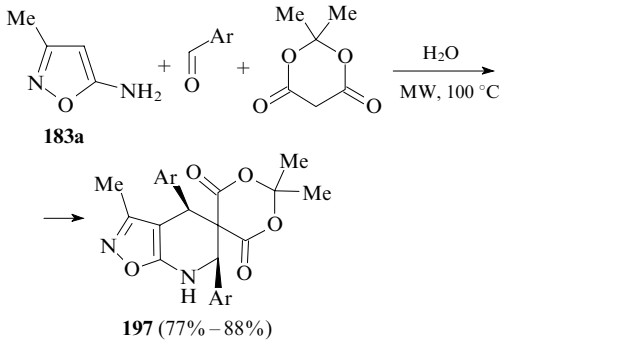
Scheme 105



R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-MeC_6H_4, 4-$Me_2NC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 2-Th

A multicomponent reaction of 5-amino-3-methylisoxazole (**183a**), an aromatic aldehyde and Meldrum's acid gives spiro(isoxazolo[1,3]dioxanopyridine)-4,6-diones **197** (Scheme 106).[349]

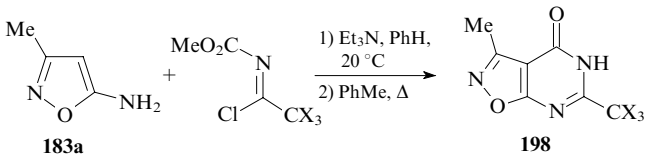
Scheme 106



Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-ClC_6H_4, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-Th

The reaction of 5-amino-3-methylisoxazole (**183a**) with methyl *N*-(1-chloro-2,2,2-trihaloethylidene)carbamates gives isoxazolo[5,4-*d*]pyrimidinones **198** in high yield (Scheme 107).[350]

Scheme 107



X = F (69%), Cl (73%)

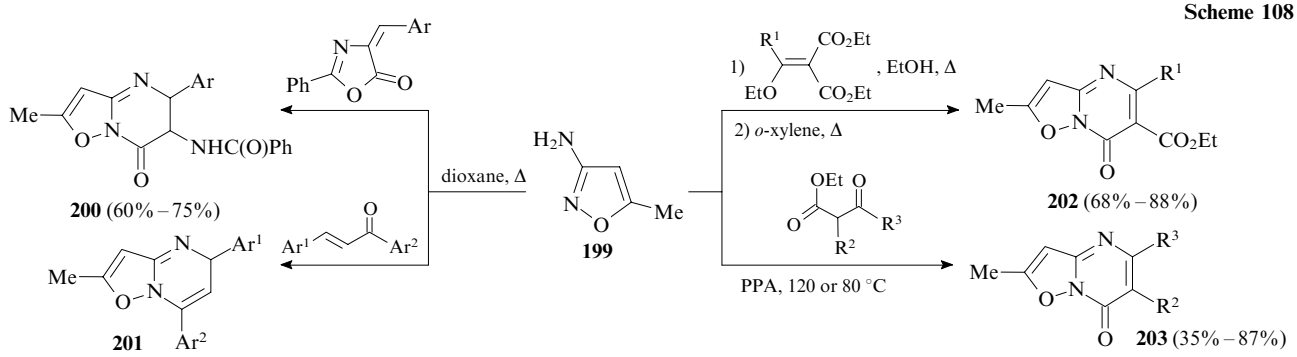
3-Aminoisoxazoles containing two nucleophilic nitrogen atoms are convenient initial compounds for synthesis of different isoxazoles fused across the N=C bond. In particular, reactions of 3-aminoisoxazole **199** with α,β-unsaturated carbonyl compounds,[351] ethoxymethylene derivatives of 1,3-dicarbonyl compounds[352] or with 1,3-dicarbonyl compounds afford isoxazolo[2,3-*a*]pyrimidines **200**–**203** in good yields (Scheme 108).[353, 354]

The condensation of 3-aminoisoxazole **199** with γ-ketoesters catalyzed by polyphosphoric acid (PPA) underlies the method of synthesis of isoxazolo[2,3-*a*][1,3]diazepin-8-ones **204** (Scheme 109).[353]

Yet another method of synthesis of isoxazolo[2,3-*a*]pyrimidine derivatives is the L-proline-catalyzed three-component Diels–Alder reaction of imines, generated *in situ* from 3-aminoisoxazole **199** and aromatic aldehydes, with nitrostyrylisoxazoles **205**.[355] Isoxazolo[2,3-*a*]pyrimidines form even at room temperature as a (6–9):1 mixture of diastereomers *trans*-**206** and *cis*-**206** in 84%–90% overall yields (Scheme 110).

In addition to isoxazolo[2,3-*a*]pyrimidines, other fused heterocycles can also be obtained from 3-aminoisoxazoles. In particular, 3-amino-5-methylisoxazole (**199**) reacts with aryl isocyanates and aryl isothiocyanates to give, respectively, isoxazolo[2,3-*b*][1,2,4]oxadiazoles **207** (X = O) and isoxazolo[2,3-*b*]-[1,2,4]thiadiazoles **207** (X = S) in high yields.[356] The reaction of 3-amino-5-methylisoxazole with 4-chloro-2-oxo-2*H*-chromene-3-sulfonyl chloride (**208**) gives 9-methyl-7,7-dioxo-7*H*-5,8-dioxa-7λ^6-thia-7a,11-diazacyclopenta[*b*]phenanthren-6-one (**209**),[357] while the reaction with methyl *N*-(1-chloro-2,2,2-trihaloethylidene)carbamates leads to 2-trihalomethyl-4*H*-isoxazolo[2,3-*a*][1,3,5]triazin-4-ones **210** (Scheme 111).[350]

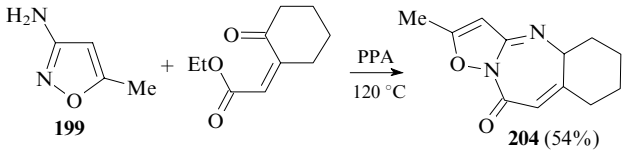
Scheme 108



200 (60%–75%) **201** **199** **202** (68%–88%) **203** (35%–87%)

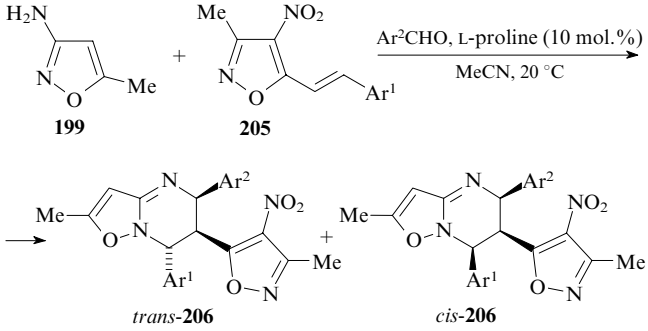
200: Ar = Ph, 2-ClC_6H_4, 2-$MeOC_6H_4$, 2-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2,6-$Cl_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 3-MeO-4-HOC_6H_3;
201: Ar^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4; Ar^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-HOC_6H_4;
202: R^1 = H, Me, Et, Ph; **203**: R^2 = H, R^3 = Me; $R^2–R^3$ = $(CH_2)_3$, $(CH_2)_4$, $CH_2N(Bn)CH_2$, $CH_2CH_2N(Me)CH_2$, $CH_2CH_2N(Bn)CH_2$, $CH_2CH_2N(Pr^i)CH_2$, $CH_2CH_2N(CH_2CH_2Ph)CH_2$

Scheme 109



199 **204** (54%)

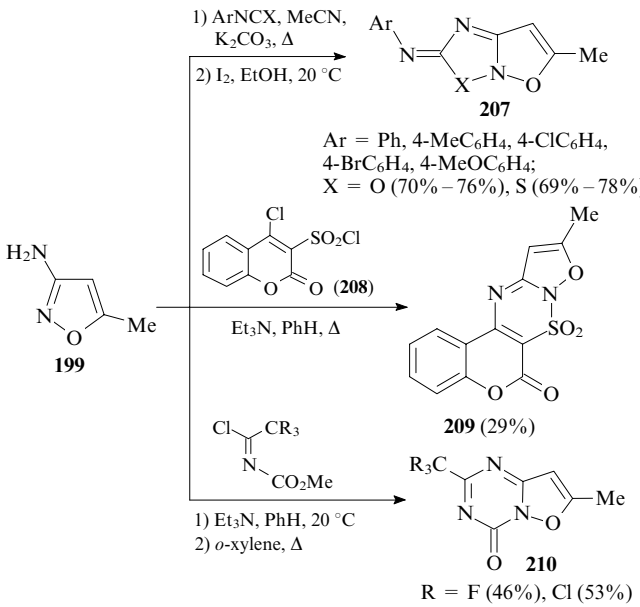
Scheme 110



199 **205** *trans*-**206** *cis*-**206**

Ar^1, Ar^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4

Scheme 111



199 **207** **208** **209** (29%) **210**

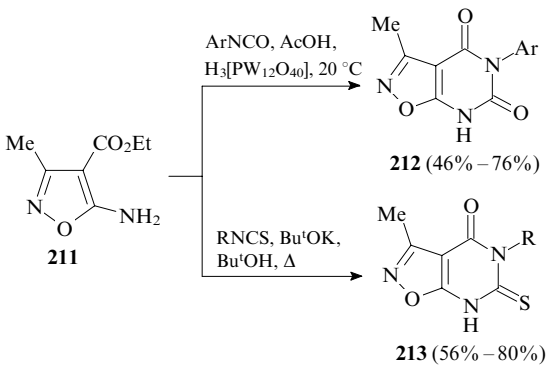
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$;
X = O (70%–76%), S (69%–78%)

R = F (46%), Cl (53%)

III.2.b. Reactions of isoxazoles containing nucleophilic and electrophilic centres

One of the isoxazole derivatives containing both the nucleophilic and electrophilic centres is ethyl-5-amino-3-methylisoxazole-4-carboxylate (**211**), which is used as a starting compound for synthesis of different fused heterocyclic systems. Isoxazolo[5,4-*d*]pyrimidine derivatives **212** have been synthesized through condensation of isoxazole **211** and aryl isocyanates catalyzed by a solid acid catalyst — the $H_3[PW_{12}O_{40}]$ heteropoly acid.[358] The analogous reaction with alkyl or aryl isothiocyanates in the presence of potassium *tert*-butoxide leads to isoxazolo[5,4-*d*]pyrimidines **213** (Scheme 112).[359]

Scheme 112

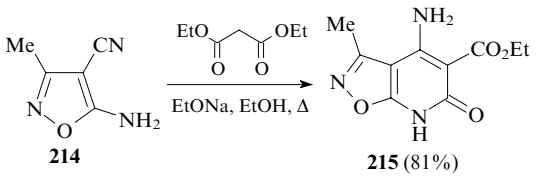


211 **212** (46%–76%) **213** (56%–80%)

212: Ar = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 3-ClC_6H_4, 4-$O_2NC_6H_4$, 3,4-$Cl_2C_6H_3$;
213: R = Et, Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 3-MeC_6H_4, 3-ClC_6H_4

Reactions of heteroaromatic aminonitriles with diethyl malonate under basic conditions have been studied.[360] In particular, the reaction of isoxazole **214** gives isoxazolo[5,4-*b*]pyridine derivative **215** in high yield (Scheme 113).

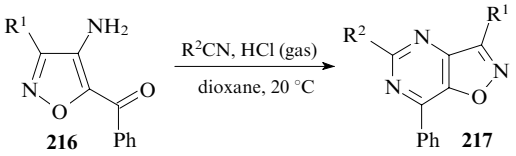
Scheme 113



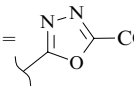
214 **215** (81%)

The reaction of 4-amino-5-benzoylisoxazoles **216** with nitriles in the presence of gaseous HCl has enabled the synthesis of isoxazolo[4,5-*d*]pyrimidines **217** (Scheme 114).[338, 361]

Scheme 114



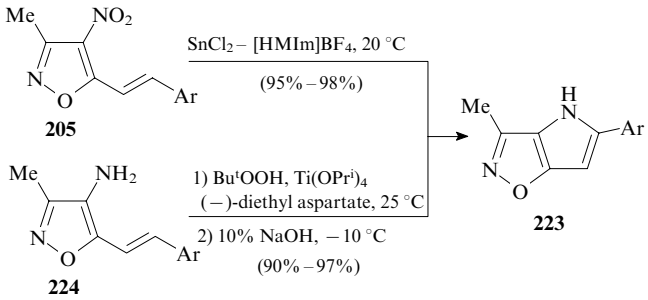
R^1 = C(O)NH_2: R^2 = Me, CH_2Cl (81%–85%);

R^1 =  CO_2Et, R^2 = Me (84%)

An efficient protocol for the synthesis of isoxazolo[4,5-*b*]pyridine *N*-oxides **218**–**220** through the condensation of 3,5-dimethyl-4-nitroisoxazole (**221**) with methyl ketones under the action of piperidine has been developed (Scheme 115).[362–364] The isoxazole : aromatic aldehyde : ketone ratio is 2 : 1 : 2 in the case of substituted acetophenones and 3 : 1 : 1 in the case of acetylacetone. The *N*-oxide oxygen atom in product **220** has been eliminated with the use of phosphorus(V) oxychloride to give isoxazolo[4,5-*b*]pyridines **222**.[365]

Intramolecular cyclization is widely used for constructing fused isoxazoles. For example, the reductive cyclization of 3-methyl-4-nitro-5-styrylisoxazoles **205** under the action of $SnCl_2$ in the ionic liquid [HMIm]BF_4 (HMIm is 1-n-hexyl-3-methylimidazolium), which plays a role of the solvent and catalyst, gives pyrrolo[2,3-*d*]isoxazoles **223** in high yields.[365] Isoxazoles **223** can also be obtained through the Sharpless epoxidation of 4-amino-3-methyl-5-styrylisoxazoles **224** with the subsequent intramolecular opening of the oxirane ring (Scheme 116).[366]

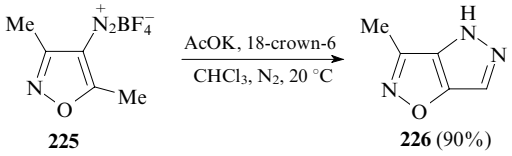
Scheme 116



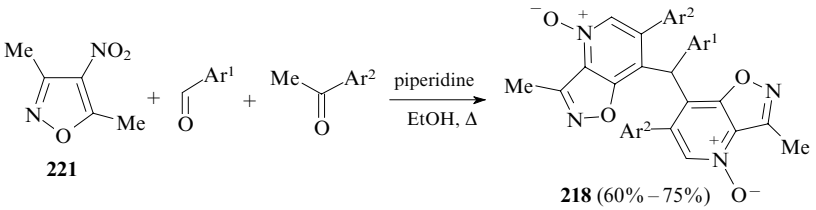
205: Ar = Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 2-HOC_6H_4, 3-MeO-4-HOC_6H_3;
224: Ar = Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-$Me_2NC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$

Yet another example of intramolecular cyclization is the reaction of 3,5-dimethylisoxazol-4-yldiazonium tetrafluoroborate (**225**) with potassium acetate in the presence of 18-crown-6 leading to 3-methyl-4*H*-pyrazolo[3,4-*d*]isoxazole **226** (Scheme 117).[367]

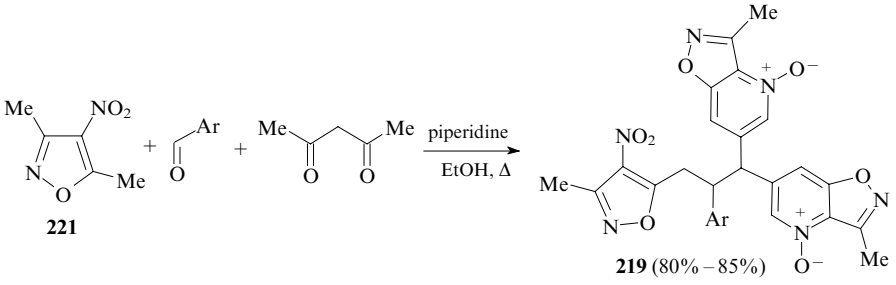
Scheme 117



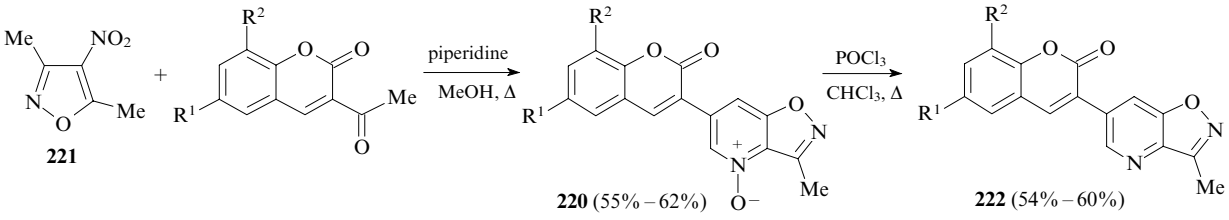
Scheme 115



Ar^1 = Ph, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$;
Ar^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-HOC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$

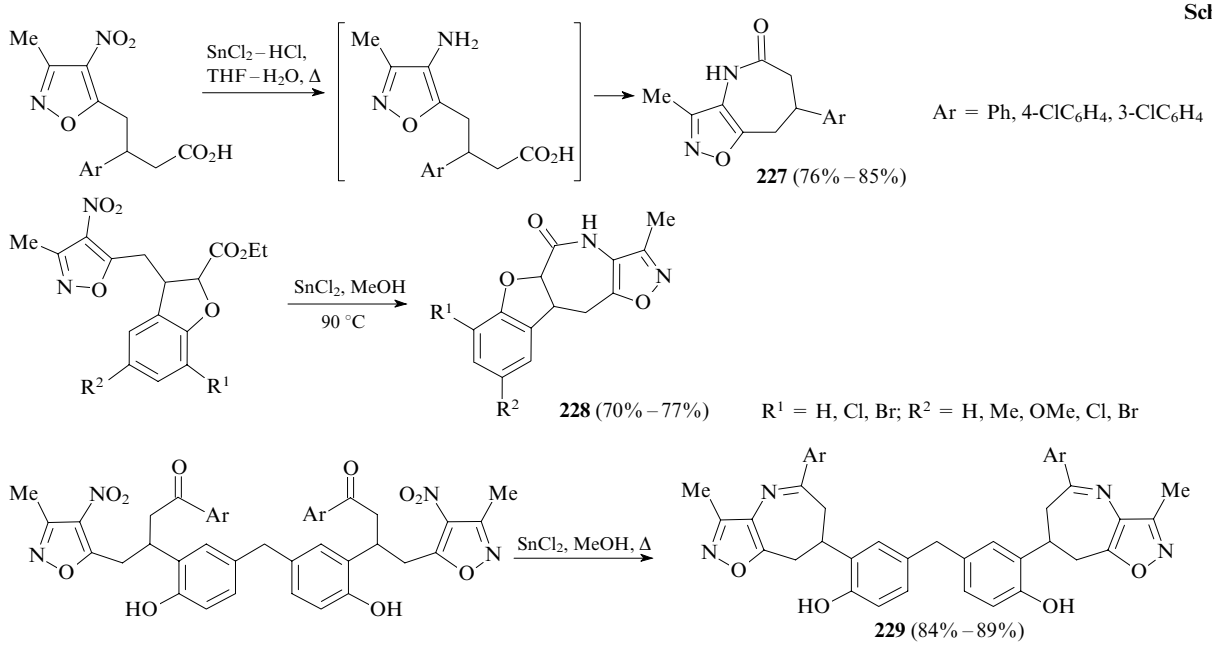


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 2-MeC_6H_4, 4-$Me_2NC_6H_4$, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$



R^2 = H: R^1 = H, Br, Cl; R^1 = H, R^2 = OMe; R^1 = R^2 = Br, Cl

Scheme 118

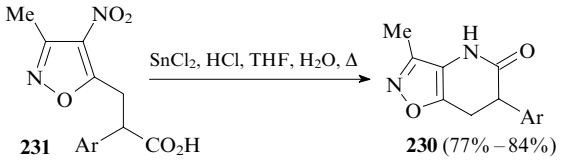


Ar = Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-HOC_6H_4, 2-Fu, 2-Th

The reduction of the nitro group at the C(4) atom in corresponding isoxazoles to the amino group with the subsequent intramolecular cyclization at the ester or keto group leads to isoxazolo[4,5-*b*]azepine derivatives **227**–**229** in high yields (Scheme 118).[368–370]

The same sequence of reactions has been successfully used to synthesize 6,7-dihydroisoxazolo[4,5-*b*]pyridin-5(4*H*)-ones **230** from 2-aryl-3-(3-methyl-4-nitroisoxazol-5-yl)propanoic acid **231** (Scheme 119).[371]

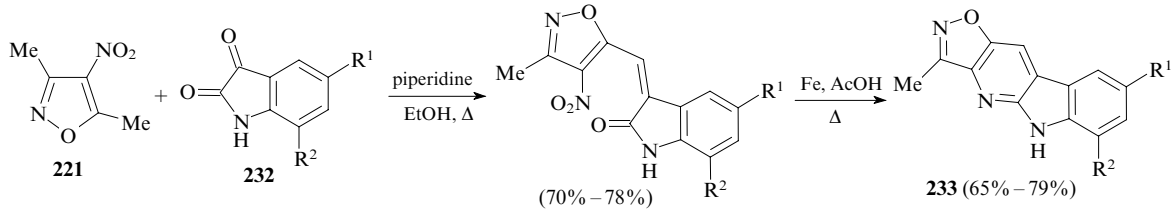
Scheme 119



Ar = Ph, 4-ClC_6H_4, 3-$MeOC_6H_4$

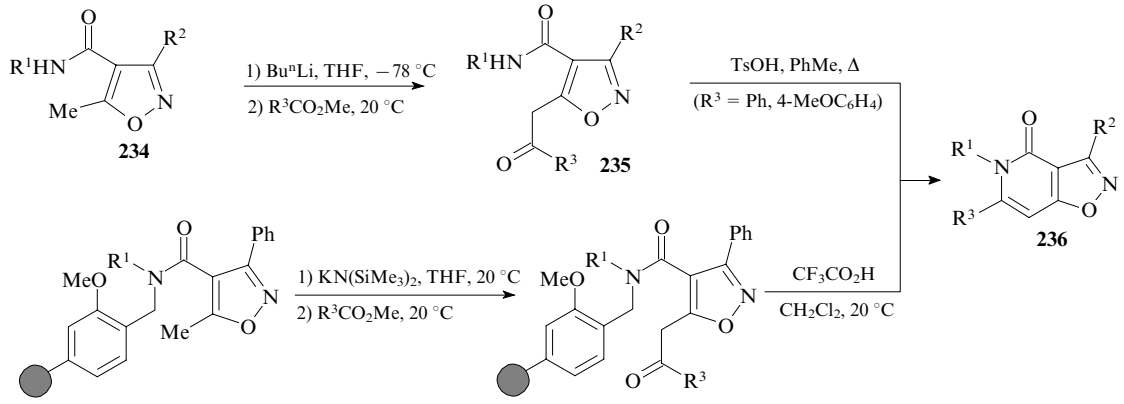
The reactions of 3,5-dimethyl-4-nitroisoxazole (**221**) with isatins **232** have been used to synthesize new isoxazolo[5′,4′ : 5,6]pyrido[2,3-*b*]indoles **233**. The process consists of

Scheme 120



R^1 = H, Br, Cl, F, Me, OMe; R^2 = H, Me, Cl

Scheme 121



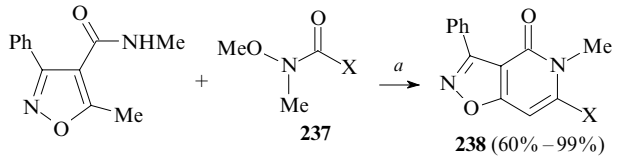
R^1 = Me, Et, Pr^i; R^2 = Ph, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2-Py, 3-Py, 4-Py; R^3 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 4-$Me_2NC_6H_4$, 4-$Pr^iOC_6H_4$, 4-$Pr^nC_6H_4$, 3-$Me_2NC_6H_4$, 3-$F_3CC_6H_4$, 3,4-$(OCH_2O)C_6H_3$, 3-F-4-$MeOC_6H_3$, 3-Br-4-$MeOC_6H_3$

two stages: the Knoevenagel condensation and the reduction of the nitro group with subsequent intramolecular cyclization.[372] Compounds **233** exhibit antitumour activity comparable with the activity of cisplatin (Scheme 120).

An excess of n-butyllithium converts 5-methylisoxazole-4-carboxamides **234** to dianions that can be attached to the corresponding benzoate to form ketones **235**. Under acid conditions, these ketones undergo further cyclization to isoxazolo[4,5-*c*]pyridones **236**.[170] In addition, a solid-phase method of synthesis of isoxazolo[4,5-*c*]pyridones **236** has been developed (Scheme 121).

The use of Weinreb amides **237** (X = Ar) instead of benzoates has enabled the synthesis of isoxazolo[4,5-*c*]pyridones **238** (Scheme 122).[373] The cyclization of intermediate ketones is carried out by hydrochloric acid in tetrahydrofuran.

Scheme 122

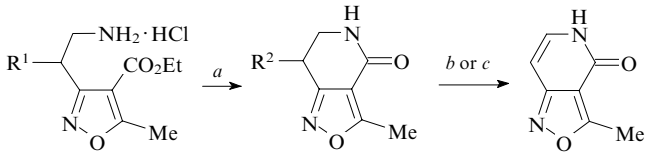


237 **238** (60%–99%)

(*a*) 1) Bu^{n}Li, THF, −70 °C; 2) HCl, THF, 20 °C;
X = $R_nC_6H_{5-n}$ (R_n = 4-MeO, 2,4-$(MeO)_2$, 3,4-(OCH_2O), 4-$CH_2OCH_2CH_2OH$, 4-$CH_2OCH_2CH_2OMe$ (42%), 4-$CH_2OCH_2CH_2OPr^i$, 4-OPh, 4-CH_2NMe_2, 4-(4-methylpiperazinomethyl), 4-Py, Me

The intramolecular cyclization of isoxazoles **239** forms the core of 6,7-dihydroisoxazolo[4,3-*c*]pyridone **240**, and its diazotization gives isoxazolo[4,3-*c*]pyridin-4-one **241**, which mimics the structure of natural 3-acylpyridin-2-ones (Scheme 123).[374]

Scheme 123



239 **240** (80%) **241**

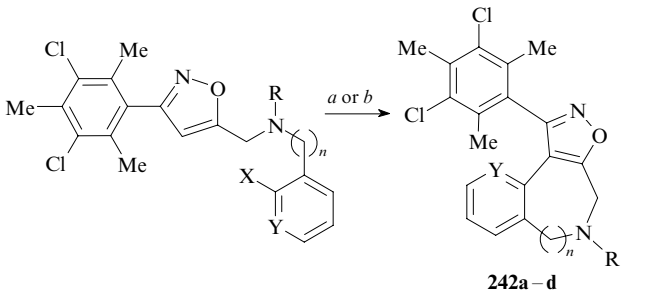
(*a*) Na_2CO_3, H_2O, 20 °C; (*b*) 1) Bu^{t}OCl, MeOH, 0 °C; 2) *hv*, MeOH (R^2 = H, 55%); (*c*) $NaNO_2$, 2 M HCl, 0 °C (R^2 = NH_2, 80%);
R^1 = H, $NH_2 \cdot HCl$; R^2 = H, NH_2

Several new fused systems containing the isoxazole ring can be obtained through cross-coupling reactions. In particular, the palladium-catalyzed intramolecular arylation of isoxazole at the 4-position gives a series of isoxazoles **242a**–**d**, including fused partially hydrogenated pyridine (n = 0), azepine (n = 1) and azocine (n = 2) rings (Scheme 124).[66]

Intramolecular nucleophilic substitution of the halogen atom by an amino group has been used for synthesis of 4,5,6,7-tetrahydroisoxazolo[3,4-*b*]pyridine derivatives **243**[375] and isoxazolo[4,3-*c*]quinolin-4(5*H*)-one derivatives **244** (Scheme 125).[376]

Isoxazoles fused with a hydrocarbon ring have been synthesized. Formation of such heterocyclic systems based on isoxazoles — naphtho[1,2-*c*]isoxazole **245** and 2-oxa-1-azabenzo[*e*]azulenes **246** (Scheme 126) — has been described.[377, 378]

Scheme 124

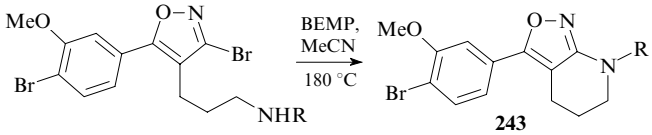


242a–**d**

(*a*) $Pd(OAc)_2$ (2 mol.%), Bu$^n_4$Cl (1 equiv.), AcOK (2 equiv.), DMA, MW, 120 °C; (*b*) $Pd(OAc)_2$ (2 mol.%), Cs_2CO_3 (2 equiv.), PPh_3 (4 mol.%), CuI (2 equiv.), DMA, MW, 150 °C; DMA = $AcNMe_2$

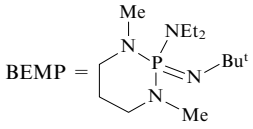
Compound **242**	Conditions	n	R	X	Y
a	*a*	0	Boc	I	CH
b	*a*	0	Boc	Br	N
c	*a*	1	Me	I	CH
d	*b*	2	Boc	Br	CH

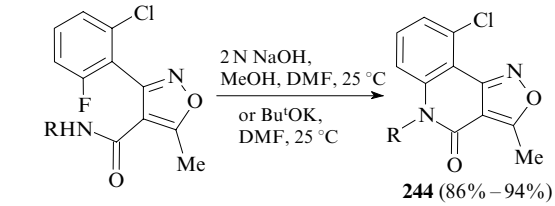
Scheme 125



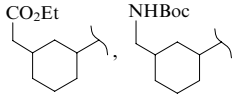
243

R = 4-$FC_6H_4CH_2$, PhCHMe, 4-FC_6H_4CHMe, 3,5-$F_2C_6H_3CH_2$;

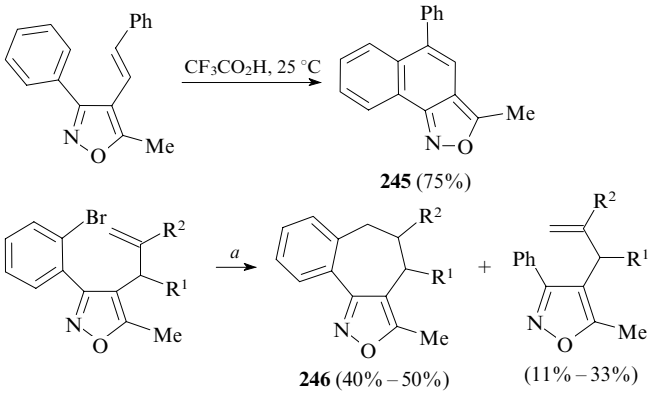




244 (86%–94%)

R = $(CH_2)_4CO_2H$, $(CH_2)_4NHBoc$, 

Scheme 126



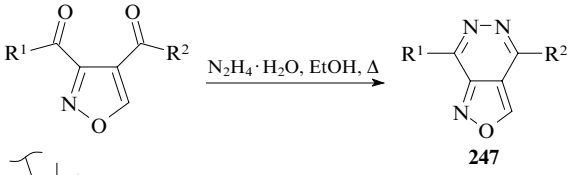
245 (75%) **246** (40%–50%) (11%–33%)

(*a*) Bu$^n_3$SnH, AIBN, PhMe, N_2, Δ; R^1 = H, OH, OAc;
R^2 = CO_2Me, CO_2Et, CN; AIBN is azobis(isobutyronitrile)

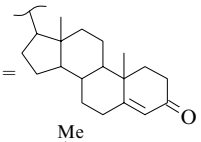
III.2.c. Reactions of isoxazoles containing two electrophilic centres

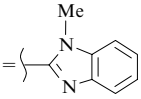
Annelation reactions involving isoxazoles with two electrophilic centres are known. The presence of two carbonyl groups in the 3- and 4-positions of isoxazole makes it possible to obtain isoxazolo[3,4-*d*]pyridazine derivatives **247** by treatment with hydrazine hydrate, which is frequently used in practice (Scheme 127).[169, 379–383]

Scheme 127

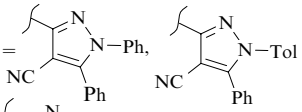


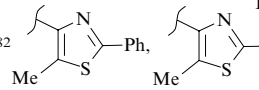
247

R^1 =  : R^2 = Ph, 2-Th (60%–68%);[379]

R^2 =  : R^1 = Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$ (51%–55%);[380]

R^2 = 2-Th: R^1 = Ph, 4-MeC_6H_4, 2-Fu, 2-Th, 1-Naph, 2-Naph (55%–85%);[381] R^2 is benzofuran-2-yl: R^1 = Ph, 2-Naph (89%–94%);[169]

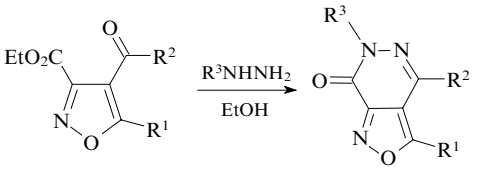
R^1 = Ph, 2-Fu, 2-Th, 2-Naph; R^2 = 

(87%–92%),[382]  Tol (73%–80%);[383]

Tol is *p*-tolyl

Isoxazole containing one keto group and one ester group in the 3- and 4-positions reacts with hydrazine or substituted hydrazines to produce isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones **248** (Scheme 128).[384–389]

Scheme 128

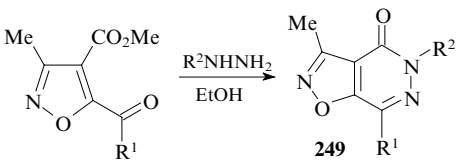


248

R^1 = Me, R^3 = H: R^2 = Me, Et, Pr^i, CH_2OEt (73%), cyclo-C_5H_9 (30%), H (60%); R^1 = R^3 = Me, R^2 = Cy (24%); R^1 = R^2 = Me: R^3 = $X_nC_6H_{5-n}$ [X_n = H, 4-F, 4-CF_3 (28%), 4-NO_2 (96%), 4-Me, 4-OMe, 2,4-F_2, 3,5-Cl_2 (93%), 3,5-$(CF_3)_2$]; R^1 = CH(OH)Me, R^2 = Me, R^3 = 4-ClC_6H_4

Reactions of isoxazoles containing one ester group and one keto or formyl group in the 4- and 5-positions with hydrazine hydrate or substituted hydrazines lead to isoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones **249** (Scheme 129)[390–393]

Scheme 129

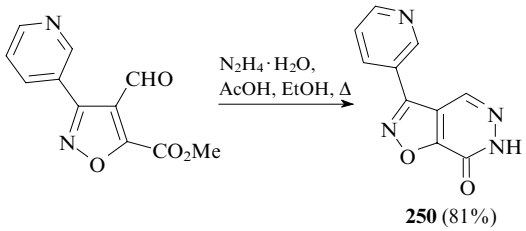


249

R^2 = H: R^1 = Bn, 2-$ClC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 2-$MeC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 2-$O_2NC_6H_4CH_2$, 4-$O_2NC_6H_4CH_2$, 2-$MeOC_6H_4CH_2$, 4-$MeOC_6H_4CH_2$ (31%–91%);[390, 391] R^1 = R^2 = H (53%);[392] R^1 = Me: R^2 = H, 4-$H_2NSO_2C_6H_4$ (82%–88%)[393]

or to isoxazolo[4,5-*d*]pyridazin-7(6*H*)-ones **250** (Scheme 130)[394] depending on the mutual arrangement of the ester and carbonyl groups.

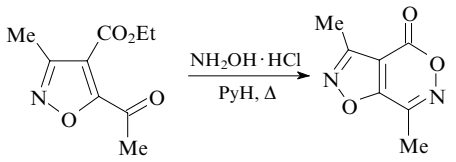
Scheme 130



250 (81%)

If hydroxylamine rather than hydrazine is used in similar reactions, they afford isoxazolo[5,4-*d*][1,2]oxazin-4-ones, for example, compound **251**, in high yield (Scheme 131).[393]

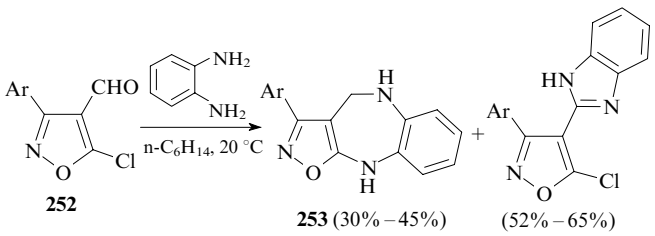
Scheme 131



251 (65%)

The reaction of *o*-phenylenediamine with 3-aryl-4-formyl-5-chloroisoxazoles **252** gives, as one of the products, isoxazolo[5,4-*b*]benzodiazepines **253**, which are isolated from the reaction mixture as side products (Scheme 132).[395]

Scheme 132

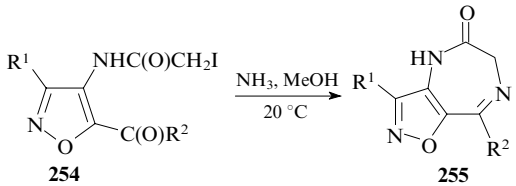


252 **253** (30%–45%) (52%–65%)

Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$

There are heterocyclic systems containing fused isoxazole and diazepine rings. In particular, the reaction of 5-acyl-4-(iodoacetylamino)isoxazoles **254** with a methanol solution of ammonia gives isoxazolo[4,5-*e*][1,4]diazepin-5-ones **255** (Scheme 133).[396]

Scheme 133



254 **255**

R^1 = $C(O)NH_2$, C(O)NHBn, Ph; R^2 = Ph, Me

III.3. Introduction of C-substituents into the isoxazole ring

The vast majority of methods for introducing aryl, hetaryl and alkenyl groups into isoxazoles involve the functionalization of the 4-position of the isoxazole ring. The introduction of a new group in this position is accomplished by replacement of the borate moiety, halogen atom, hydrogen

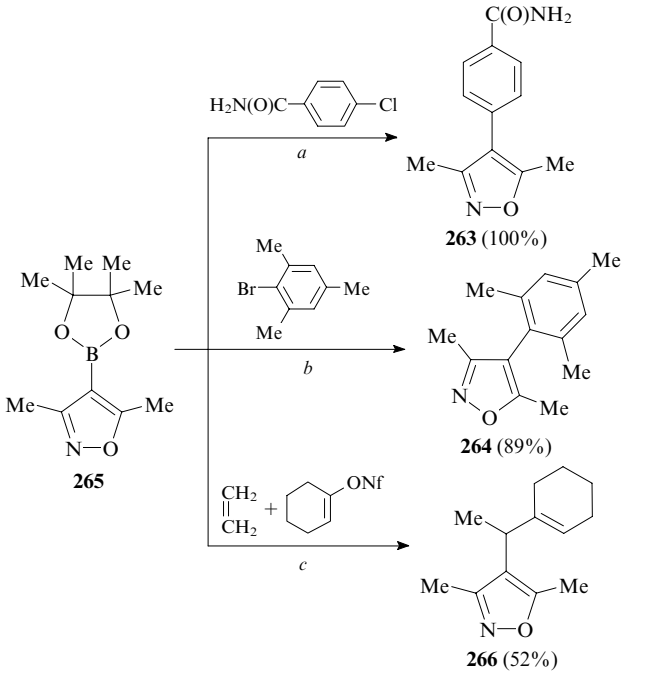
atom or through the stage of metallation. Substrates for such reactions are 4-isoxazolylboronic acids, 4-isoxazolylboronates, 4-bromo- or 4-iodoisoxazoles; the use of potassium isoxazol-4-yltrifluoroborate and lithium isoxazol-4-yltriisopropylborate as substrates has been described.

The Pd-catalyzed reaction of 3,5-dimethylisoxazol-4-ylboronic acid **256** with hetaryl [397–400] and alkenyl halides [401, 402] gives coupling products **257**–**262** (Scheme 134).

Compounds **263** and **264**, the products of the Suzuki cross-coupling reaction of acceptor-substituted [403] and sterically hindered aryl halides [404] with isoxazol-4-ylboronic acid pinacol ester **265**, have been obtained in high yields (Scheme 135). This reagent has also been used for 1,1-difunctionalization of ethylene with the participation of vinyl ethers, which gives the product of alkylation of the isoxazole system at the 4-position. In particular, the three-component palladium-catalyzed reaction of boronate **265**, ethylene and cyclohexen-1-ylnonaflate gives substituted isoxazole **266** in moderate yield (see Scheme 135).[405]

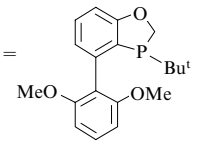
4-Halo-substituted isoxazoles are often used as initial compounds for introduction of an aryl, hetaryl or alkenyl substituent into the isoxazole ring. For example, the Suzuki cross-coupling of 4-bromo-3,5-dimethyl-isoxazole **267a** with 2,6-dimethyl-substituted phenylboronic acids **268** catalyzed by N-heterocyclic palladium carbene complexes leads to arylation products **111** in 67% to 87% yield (Scheme 136).[406–408] Arylation of 5-alkylsulfanyl-4-iodo-3-(4-methylsulfonylphenyl)isoxazoles **269a**,**b** [R^1 = Me (**a**), Et (**b**)] to corresponding 4-arylisoxazoles **270** has been successfully accomplished by *para*-substituted arylboronic acids with the use of the $Pd(PPh_3)_4$ catalyst.[409] Triallyl(aryl)silanes can be used as alternative arylating agents. In particular, cross-coupling product **111a** has been synthesized

Scheme 135

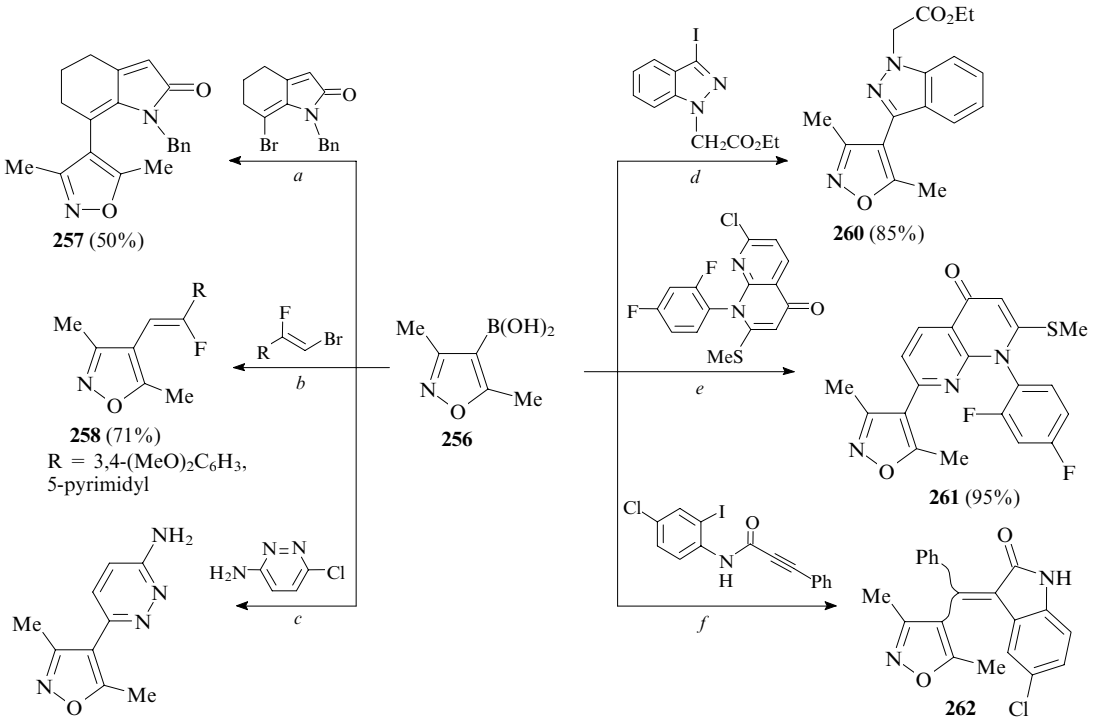


(*a*) Cat (2 mol.%), NaOH, THF, MeOH, 70 °C; [403]
(*b*) $Pd_2(dba)_3$, BI-DIME, K_3PO_4, PhMe, H_2O, 100 °C; [404]
(*c*) $Pd_2(dba)_3$ (5 mol.%), DMA, $NaHCO_3$, dba (15 mol.%), Δ; [405] dba is dibenzylideneacetone, Nf is perfluorobutanesulfonyl;

BI-DIME =



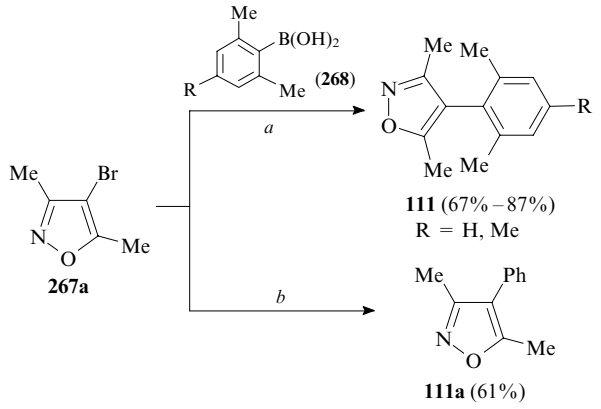
Scheme 134



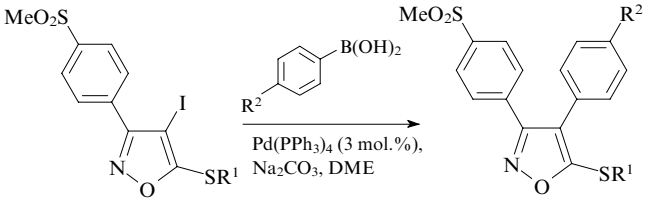
(*a*) $Pd(PPh_3)_2Cl_2$, KF, TBAI, THF, H_2O; [402] (*b*) $Pd(dppf)Cl_2$ (10 mol.%), Cs_2CO_3, THF, 90 °C, 8 h; [401] (*c*) $Pd(PPh_3)_4$ (5 mol.%), K_2CO_3, MW, 120 °C, 10 min; [397] (*d*) $Pd(PPh_3)_4$, $NaHCO_3$, DME, H_2O, 20 °C, 13 h; [399] (*e*) SPhos, $Pd(OAc)_2$, Et_3N, 1,4-dioxane, 20 °C, 5 h; [400]
(*f*) $Pd(PPh_3)_4$, CuTC, THF, 25 °C, 15 h; [398] dppf is 1,1′-bis(diphenylphosphino)ferrocene,
SPhos is 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, CuTC is copper(I) thiophene-2-carboxylate

from bromide **267a** and triallyl(phenyl)silane in 61% yield (see Scheme 136).[410]

Scheme 136



(*a*) Pd-Cat (1 mol.% – 2 mol.%), KOH or Bu^{t}OK, DME or PhMe;
(*b*) All_3SiPh, $TBAF \cdot 3H_2O$, $PdCl_2$ (5 mol.%), PCy_3 (10 mol.%), DMSO, H_2O, 80 °C, 18 h

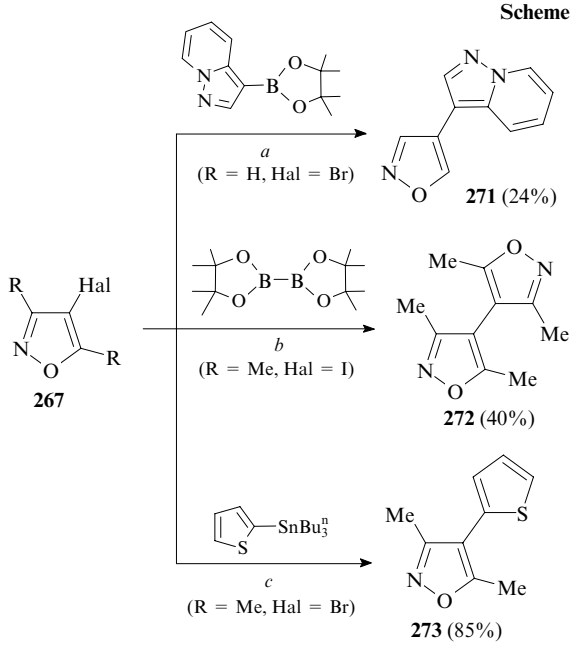


R^1 = Me (**a**), Et (**b**); R^2 = H, F, Br, Me, Et

The Suzuki reaction of 4-haloisoxazoles **267** is also suitable for the synthesis of 4-hetaryl-substituted isoxazoles, for example, compounds **271** and **272**; however, their yields are essentially lower than the yields of arylation products (Scheme 137).[411,412] At the same time, these substrates afford high yields of hetarylation products **273** in the Stille – Migita reaction of **267** with 2-(tributylstannyl)thiophene catalyzed by the new Pd-PEPPSI-IPent system containing a sterically hindered ligand (see Scheme 137).[413]

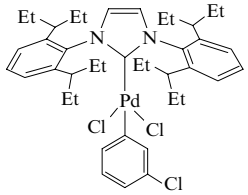
To introduce an alkenyl substituent in the 4-position of the isoxazole ring, the catalytic reaction of 4-iodoisoxazole **267** with vinylsilanes or vinyldisiloxanes is used. Under alkaline conditions, the latter are at equilibrium with vinylsilanolates, which precisely enter into cross-coupling in the presence of $Pd(dba)_2$, as, for example, in the synthesis of isoxazole **274** from iodide **267b** (Scheme 138).[414] The use of vinylsilanes in the synthesis of isoxazoles **275** with the α,β-unsaturated carbonyl moiety has been suggested by Wagner and co-workers.[415] The key reagent in the described synthetic one-pot sequence (Hiyama coupling – Narasaka acylation) is 1,2-disilylethylene **276**. At the first stage, this alkene undergoes Pd-catalyzed coupling with iodoisoxazole **267b** accompanied by the substitution of the methyldi(ethoxy)silyl group, and then, in one-pot mode, the resulting vinylsilane is acylated in the presence of a rhodium catalyst to give compound **275**. The same research group has reported another interesting example of introduction of the alkenyl substituent into the isoxazole ring with the use of an enyne system. This protocol implies that the vinylsilane required for the Hiyama cross-coupling is generated by hydrosilylation of enyne **277** and, without isolation, is subjected to coupling with isoxazole **267b** in the presence of the Pd – Rh catalyst and tetra-n-butylammonium fluoride to

Scheme 137



(*a*) $Pd(Amphos)Cl_2$, Na_2CO_3, DME, N_2, 80 °C;
(*b*) $Pd(dppf)Cl_2$ (4 mol.%), K_2CO_3, DMSO, N_2, 80 °C;
(*c*) Pd-PEPPSI-IPent (4 mol.%), CsF, MS 4 Å, 1,4-dioxane, 80 °C;
$Pd(Amphos)Cl_2$ is bis[di(*tert*- butyl)(4-methylaminophenyl)-phosphino]dichloropalladium(II);

Pd-PEPPSI-IPent =



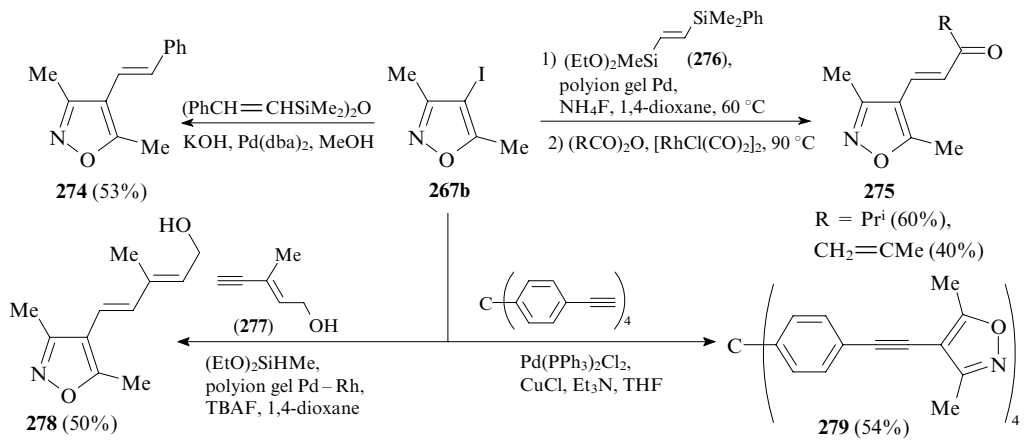
give alkenylation product **278** in moderate yield.[416] It should be noted that all reactions of iodoisoxazole **267b** shown in Scheme 138 occur with high *E*-stereoselectivity.

The only example of formation of 4-alkynyl-substituted isoxazole has been described,[417] where tetrasubstituted methane compound **279** and an analogous 1,3,5,7-tetrasubstituted adamantane compound have been synthesized by the Sonogashira reaction.

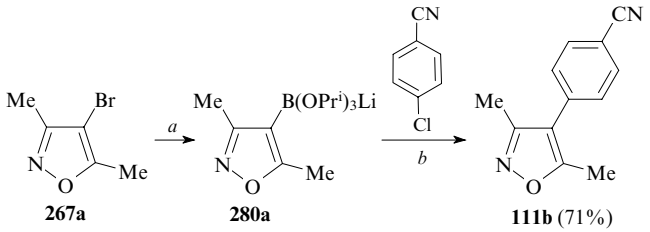
Lithium isoxazolyltriisopropylborate **280a** and potassium isoxazolyltrifluoroborate **280b**, synthesized from, respectively, isoxazolyl bromide **267a** and isoxazolylboronic acid **256**, are another two convenient nucleophilic substrates for the Suzuki reaction, especially for coupling with acceptor-substituted aryl chlorides, which can be successfully used for modifying the substituents in the isoxazole ring resulting in compounds **111b** and **281** (Scheme 139).[418,419] Magnesium isoxazol-4-yltriisopropylborate has also been successfully used for the Suzuki arylation at the 4-position involving ethyl 4-bromobenzoate.[420]

The possibility of direct arylation of the ring based on the Pd-catalyzed activation of the C(4) – H bond has been studied for 3,5-dimethylisoxazole **282** as an example (Scheme 140).[421–428] As a whole, these reactions proceed under more severe conditions, but afford products **111** in good yields. An exception is 2-bromobenzonitrile, which is arylated to give the product in low yield. It is worth noting that the arylating agents are not only aryl bromides and aryl

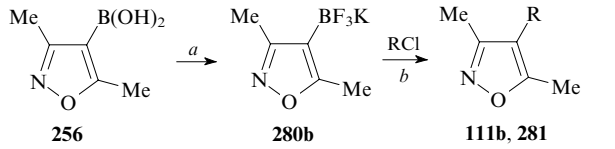
Scheme 138



Scheme 139



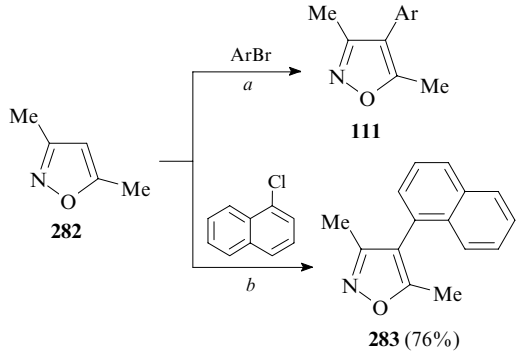
(*a*) 1) Bu^nLi, THF, PhMe; 2) $B(OPr^i)_3$, −78→20 °C;
(*b*) Cat (3 mol.%), K_3PO_4, 40 °C



(*a*) KHF_2, MeOH, H_2O; (*b*) $Pd(OAc)_2$, RuPhos, Na_2CO_3, EtOH;
R = 4-NCC_6H_4 (**111b**, 71%), 2-Py (**281**, 95%);
RuPhos is 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

iodides but also sometimes aryl chlorides, as in the synthesis of compound **283**.[421]

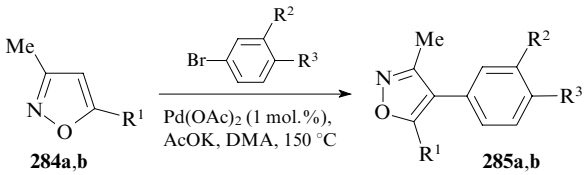
Scheme 140



(*a*) $Pd(C_3H_5)(dppb)Cl_2$, AcOK, 130–150 °C; (*b*) $Pd(OAc)_2$
(5 mol.%), Bu^nAd_2P (5 mol.%), K_3PO_4, NMP, 125 °C;
Ar = 4-NCC_6H_4 (75%), 4-$MeO_2CC_6H_4$ (81%), 4-$O_2NC_6H_4$ (86%),[425]
4-AcC_6H_4 (71%), 2-NCC_6H_4 (23%),[427] 3-$(EtCONHCH_2)C_6H_4$
(73%),[423] 4-H_2N-3-ClC_6H_3 (71%),[424] 5-cyano-3-pyridyl;[426]
Ad is 1-adamantyl, NMP is *N*-methyl-2-pyrrolidone,
dppb is 1,4-bis(diphenylphosphino)butane

Few experiments on the direct arylation of other isoxazoles have shown that the yields can essentially depend on the nature of the substituent at the C(5) atom. For example, 3-methyl-5-phenyl- (**284a**) and 5-hydroxymethyl-3-methylisoxazoles (**284b**) under such conditions give coupling products **285a**,**b** in considerably lower yields than their 3,5-dimethyl analogue (Scheme 141).[422, 424]

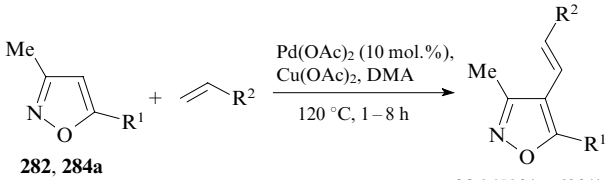
Scheme 141



R^1 = Ph, R^2 = Cl, R^3 = NH_2 (**a**, 53%);[424]
R^1 = CH_2OH, R^2 = H, R^3 = CN (**b**, 38%)[422]

As distinct from direct arylation, direct alkenylation reactions of isoxazoles have been much less studied: only one study[429] is available (Scheme 142). Moderate yields of 4-alkenylisoxazoles **286** have been achieved in the reaction of 3,5-dimethyl- (**282**) and 3-methyl-5-phenylisoxazoles (**284a**) with both styrene and some electron-deficient alkenes.

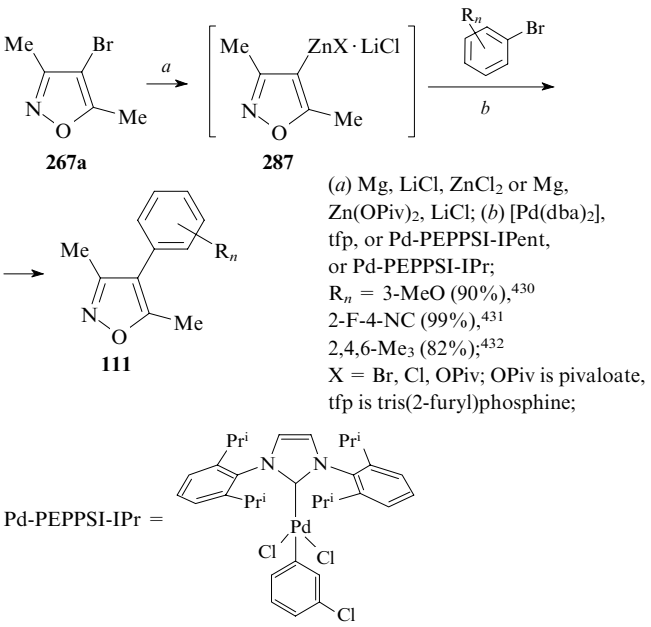
Scheme 142



R^1 = Me, Ph; R^2 = CO_2Bu^n, CO_2Bu^t, Ph, $C(O)NMe_2$

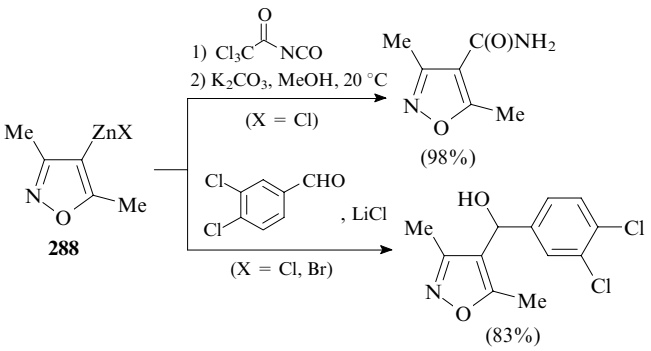
Another way to introduce a C-substituent into the 4-position of the isoxazole ring implies its metallation and subsequent Pd-catalyzed cross-coupling reactions or reactions with electrophilic reagents. For example, Zn derivatives **287**, forming under mild conditions from bromide **267a**, can be smoothly introduced into the Negishi reaction with aryl bromides (Scheme 143).[430, 431] Arylation products **111** are produced in high yield even in the case of *ortho*-substituted aryl bromides.[432]

Scheme 143



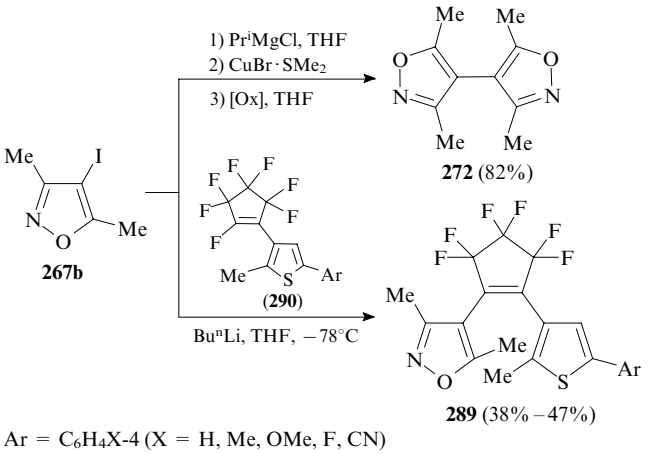
Being rather strong nucleophiles, 4-isoxazolylzinc derivatives **288** readily enter into condensation reactions with isocyanates[433] and aldehydes[434] to form a new C(4)–C bond (Scheme 144).

Scheme 144



In recent years, few new examples of alkenylation and arylation of isoxazoles through the formation of their organometallic derivatives have been reported. In particular, new asymmetric photochromic bishetarylethenes **289**

Scheme 145

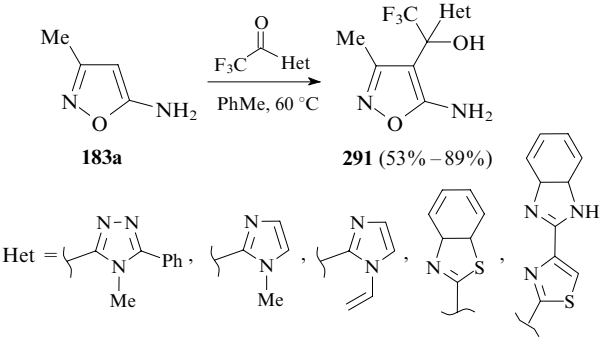


Ar = C_6H_4X-4 (X = H, Me, OMe, F, CN)

have been synthesized through lithiation of iodoisoxazole **267b** with subsequent coupling with fluoride **290** (Scheme 145).[435] The oxidative homocoupling of the cuprate reagent prepared from the same isoxazole **267b** has enabled the synthesis of bis(isoxazole) **272** in 82% yield, which is essentially higher than the yield achieved in the Suzuki reaction (see Scheme 137).[436]

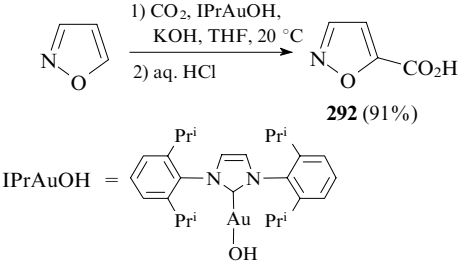
Some electrophilic 2-trifluoroacetylazoles revealed high activity in the reaction of C-hydroxyalkylation of different five-membered nitrogen-containing heterocycles, including 5-amino-3-methylisoxazole (**183a**). The latter has been converted into hydroxy derivatives **291** in moderate to high yields (Scheme 146).[437]

Scheme 146



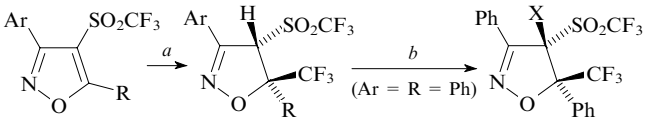
A new catalytic method suggested by Boogaerts and Nolan[438] for carboxylation of arenes, as well as of a rather large number of N-heterocycles, including isoxazole, is one of a few recently published examples of introduction of a C(5)-substituent into the isoxazole system (Scheme 147). The carboxylation of unsubstituted isoxazole by this method is catalyzed by the NHC gold(I) hydroxide complex. The reaction occurs with high regioselectivity at the most acidic C–H bond to give isoxazole-5-carboxylic acid (**292**) in 91% yield.

Scheme 147



Recently, an efficient protocol has been developed for the introduction of the trifluoromethyl group into the 5-position of isoxazol-4-yl(trifluoromethyl)sulfones **293** through additive trifluoromethylation in the Me_3SiCF_3–AcOK system (Scheme 148).[439] The reaction is highly diastereoselective and afford oxazolines **294** in high yields. Some decrease in the yield of the addition product (to 64%) is observed for the 5-methyl-substituted substrate. Oxazolines **294** formed in this reaction are convenient synthons for further ring functionalization. In particular, their fluorination with Selectfluor®, as well as bromination and chlorination with corresponding *N*-halosuccinimides, gives completely functionalized isoxazoline derivatives **295**–**297** in high yield with good diastereoselectivity.

Scheme 148



293 **294** (64% – 98%) (93 : 7 – 100 : 0 *dr*) **295**: X = F (89%, 80 : 20 *dr*); **296**: X = Br (96%, 95 : 5 *dr*); **297**: X = Cl (84%, 85 : 15 *dr*)

(*a*) 1) Me_3SiCF_3, AcOK, DMSO; 2) 1 N HCl;

(*b*) Selectfluor, or NBS, or NCS, MeCN;

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 2-Naph; R = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 2-Naph

* * *

As can be seen from the above material, the chemistry of isoxazole continues to attract attention of synthetic chemists, which results in the successful development of both the methods for synthesis of isoxazole derivatives and their synthetic applications. The necessity to develop synthetic methods opening the way to novel derivatives of this heterocyclic series is dictated primarily by the needs of pharmaceutical chemistry in efficient drugs. A huge variety of transformations of isoxazoles due to the weak N–O bond and easy introduction of functional groups into the heterocyclic ring, as well as due to the possibility of activation of the C–H bonds of the ring, determines a very wide range of their applications in organic synthesis. It involves functionalization reactions of acyclic compounds, the synthesis of nitrogen-containing heterocycles through recyclization reactions, the introduction of isotopic labels, *etc*. It is evident that the synthetic potential of isoxazoles is far from being exhausted by the processes considered in this review. In the coming years, we should expect to see the development of new synthetically significant reactions with their participation, in particular, reactions with highly reactive intermediates, as well as reactions catalyzed by transition metal compounds.

The review was prepared with financial support of the Russian Foundation for Basic Research (Project No. 14-03-00187) and St Petersburg State University (Grants 12.50.1565.2013, 12.38.239.2014 and 12.38.217.2015).

References

1. D Greenwood *Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph* (New York: Oxford University Press, 2008)
2. D Giomi, F M Cordero, F Machetti, in *Comprehensive Heterocyclic Chemistry III* Vol. 4 (Eds A R Katritzky, C A Ramsden, E F V Scriven, R J K Taylor) (Oxford: Elsevier, 2008) p. 365
3. P Grünanger, P Vita-Finzi, in *The Chemistry of Heterocyclic Compounds* Vol. 49 (Ed. E C Taylor) (New York: Wiley-Interscience, 1991) Pt. 1
4. H Ahrens, G Lange, T Müller, C Rosinger, L Willms, A van Almsick *Angew. Chem., Int. Ed.* **52** 9388 (2013)
5. P J van Koningsbruggen *Top. Curr. Chem.* **233** 123 (2004)
6. J Han, H Guo, X-G Wang, M-L Pang, J-B Meng *Chin. J. Chem.* **25** 129 (2007)
7. T M V D Pinho e Melo *Curr. Org. Chem.* **9** 925 (2005)
8. P G Baraldi, A Barco, S Benetti, G P Pollini, D Simoni *Synthesis* 857 (1987)
9. T Honda, H Yoshizawa, C Sundararajan, E David, M J Lajoie, F G Favaloro Jr, T Janosik, X Su, Y Honda, B D Roebuck, G W Gribble *J. Med. Chem.* **54** 1762 (2011)
10. A Srinivas, A Nagaraj, Ch S Reddy *J. Heterocycl. Chem.* **46** 497 (2009)
11. M K Parr, M Gütschow, J Daniels, G Opfermann, M Thevis, W Schinzer *Steroids* **74** 322 (2009)
12. J Kaffy, R Pontikis, D Carrez, A Croisy, C Monneret, J-C Florent *Bioorg. Med. Chem.* **14** 4067 (2006)
13. J Luo, W Ding, Y Zhang, Z Yang, Y Li, L Ding *J. Pestic. Sci.* **38** 214 (2013)
14. K A Eliazyan, L V Shahbazyan, V A Pivazyan, A P Yengoyan *J. Heterocycl. Chem.* **48** 188 (2011)
15. F Giuntini, M A F Faustino, M G P M S Neves, A C Tomé, A M S Silva, J A S Cavaleiro *Tetrahedron* **61** 10454 (2005)
16. B Liu, X Han, Z Dong, H Lv, H-B Zhou, C Dong *Tetrahedron: Asymmetry* **24** 1276 (2013)
17. R J Middleton, S L Mellor, S R Chhabra, B W Bycroft, W C Chan *Tetrahedron Lett.* **45** 1237 (2004)
18. J Xu, L Wu, X Huang *J. Org. Chem.* **76** 5598 (2011)
19. Y Zhou, Y Chen, W Miao, J Qu *J. Heterocycl. Chem.* **47** 1310 (2010)
20. A M Rodriguez, A Juan, M V Gómez, A Moreno, A de la Hoz *Synthesis* **44** 2527 (2012)
21. L P Tan, H Wu, P-Y Yang, K A Kalesh, X Zhang, M Hu, R Srinivasan, S Q Yao *Org. Lett.* **11** 5102 (2009)
22. G Lopopolo, F Fiorella, M de Candia, O Nicolotti, S Martel, P-A Carrupt, C Altomare *Eur. J. Pharm. Sci.* **42** 180 (2011)
23. D M Musatov, E V Starodubtseva, A K Rakishev, O V Turova, M G Vinogradov *Russ. J. Org. Chem.* **47** 1199 (2011) [*Zh. Org. Khim.* **47** 1181 (2011)]
24. P Palanisamy, S J Jenniefer, P T Muthiah, S Kumaresan *RSC Adv.* **3** 19300 (2013)
25. M Teus, A Jirgensons, M Dambrova, R Mezhapuke *Chem. Heterocycl. Compd.* **43** 1440 (2007) [*Khim. Geterotsikl. Soedinen.* 1693 (2007)]
26. F Saikh, J Das, S Ghosh *Tetrahedron Lett.* **54** 4679 (2013)
27. H Kiyani, F Ghorbani *Res. Chem. Intermed.* (2013); DOI: 10.1007/s11164-013-1411-x
28. V Ya Sosnovskikh, V S Moshkin, R A Irgashev *Tetrahedron Lett.* **47** 8543 (2006)
29. V Ya Sosnovskikh, V S Moshkin, M I Kodess *Tetrahedron* **64** 7877 (2008)
30. S P Bondarenko, M S Frasinyuk, V P Khilya *Chem. Nat. Compd.* **43** 402 (2007) [*Khim.Pprirod. Soedin.* 332 (2007)]
31. S P Bondarenko, O N Miroshnikov, M S Frasinyuk, V P Khilya *Chem. Nat. Compd.* **49** 826 (2013) [*Khim. Pprirod. Soedin.* 712 (2013)]
32. D V Tsyganov, V N Khrustalev, L D Konyushkin, M M Raihstat, S I Firgang, R V Semenov, A S Kiselyov, M N Semenova, V V Semenov *Eur. J. Med. Chem.* **73** 112 (2014)
33. A M Polozov, G Hategan, H Cao, A S Kiselyov, W Zeller, J Singh *Tetrahedron Lett.* **51** 575 (2010)
34. J Slätt, T Janosik, N Wahlström, J Bergman *J. Heterocycl. Chem.* **42** 141 (2005)
35. L Johnson, J Powers, F Ma, K Jendza, B Wang, E Meredith, N Mainolfi *Synthesis* **45** 171 (2013)
36. E A El Rady *Heterocycl. Commun.* **18** 215 (2012)
37. S O Abdallah, N H Metwally, H F Anwar, M H Elnagdi *J. Heterocycl. Chem.* **42** 781 (2005)
38. A M Maharramov, N D Sadikhova, I G Mammadov, M A Allahverdiyev *Chem. Heterocycl. Compd.* **45** 400 (2009) [*Khim. Geterotsikl. Soedin.* 514 (2009)]

39. R Harigae, K Moriyama, H Togo *J. Org. Chem.* **79** 2049 (2014)
40. S F Tohid, N I Ziedan, F Stefanelli, S Fogli, A D Westwell *Eur. J. Med. Chem.* **56** 263 (2012)
41. G Saravanan, V Alagarsamy, P Dineshkumar *Arch. Pharm. Res.* (2013); DOI: 10.1007/s12272-013-0262-8
42. S Chimichi, M Boccalini, M M M Hassan, G Viola, F Dall Acquab, M Curini *Tetrahedron* **62** 90 (2006)
43. E Rajanarendar, P Ramesh, M Srinivas, K Ramu, G Mohan *Synth. Commun.* **36** 665 (2006)
44. A I Moskalenko, A V Boeva, V I Boev *Russ. J. Gen. Chem.* **81** 529 (2011) [*Zh. Obshch. Khim.* **81** 433 (2011)]
45. S Lee, J N Kim, J H Min, K S Yoon, K D Shin, B-M Kwon, D C Han *Bull. Korean Chem. Soc.* **31** 3800 (2010)
46. E J Hanan, A van Abbema, K Barrett, W S Blair, J Blaney, C Chang, C Eigenbrot, S Flynn, P Gibbons, C A Hurley, J R Kenny, J Kulagowski, L Lee, S R Magnuson, C Morris, J Murray, R M Pastor, T Rawson, M Siu, M Ultsch, A Zhou, D Sampath, J P Lyssikatos *J. Med. Chem.* **55** 10090 (2012)
47. M M Al-Sanea, I M El-Deeb, S H Lee *Bull. Korean Chem. Soc.* **34** 437 (2013)
48. B El Azzaoui, B Rachid, M L Doumbia, El M Essassi, H Gornitzka, J Bellan *Tetrahedron Lett.* **47** 8807 (2006)
49. G Dou, P Xu, Q Li, Y Xi, Z Huang, D Shi *Molecules* **18** 13645 (2013)
50. M A Povalyakhina, A S Antonov, O V Dyablo, V A Ozeryanskii, A F Pozharskii *J. Org. Chem.* **76** 7157 (2011)
51. Yu A Davydova, T M Sokolenko, Yu L Yagupolskii *J. Fluorine Chem.* **157** 58 (2014)
52. M M Savant, A M Pansuriya, C V Bhuva, N Kapuriya, A S Patel, V B Audichya, P V Pipaliya, Y T Naliapara *J. Comb. Chem.* **12** 176 (2010)
53. V I Potkin, S K Petkevich, P V Kurman *Russ. J. Org. Chem.* **47** 928 (2011) [*Zh. Org. Khim.* **47** 911 (2011)]
54. S K Petkevich, V I Potkin, R V Kaberdin *Russ. J. Org. Chem.* **40** 1146 (2004) [*Zh. Org. Khim.* **40** 1194 (2004)]
55. C Grundmann, P Grunanger, in *The Nitrile Oxides: Versatile Tools of Theoretical and Preparative Chemistry* (Eds H Bredereck, K Hafner, E Müller) (Berlin, Heidelberg, New York: Springer-Verlag, 1971) p. 86
56. F Himo, T Lovell, R Hilgraf, V V Rostovtsev, L Noodleman, K B Sharpless, V V Fokin *J. Am. Chem. Soc.* **127** 210 (2005)
57. G P Savage, G T Wernert *Aust. J. Chem.* **58** 882 (2005)
58. M Hocek, P Nauš, R Pohl, I Votruba, P A Furman, P M Tharnish, M J Otto *J. Med. Chem.* **48** 5869 (2005)
59. D V Vorobyeva, N M Karimova, I L Odinets, G-V Rëoschenthaler, S N Osipov *Org. Biomol. Chem.* **9** 7335 (2011)
60. A Dondoni, P P Giovannini, A Massi *Org. Lett.* **6** 2929 (2004)
61. A K Parhi, R W Franck *Org. Lett.* **6** 3063 (2004)
62. D Kovács, Z Kádár, G Mótyán, G Schneider, J Wölfling, I Zupkó, É Frank *Steroids* **77** 1075 (2012)
63. T Haino, Y Ueda, T Hirao, T Ikeda, M Tanaka *Chem. Lett.* **43** 414 (2014)
64. F Pérez-Balderas, F Hernández-Mateo, F Santoyo-González *Tetrahedron* **61** 9338 (2005)
65. S Su, J R Giguere, S E Schaus, J A Porco Jr *Tetrahedron* **60** 8645 (2004)
66. L Basolo, E M Beccalli, E Borsini, G Broggini, S Pellegrino *Tetrahedron* **64** 8182 (2008)
67. E Coutouli-Argyropoulou, P Lianis, M Mitakou, A Giannoulisa, J Nowak *Tetrahedron* **62** 1494 (2006)
68. M J Choi, D W Oh, J W Jang, Y S Cho, S H Seo, K S Jeong, S Y Ko, A N Pae *Bull. Korean Chem. Soc.* **32** 2015 (2011)
69. K S Lee, Y K Kang, K H Yoo, D C Kim, K J Shin, Y-S Paik, D J Kim *Bioorg. Med. Chem. Lett.* **15** 231 (2005)
70. V V Vaidya, K S Wankhede, S J Nara, M M Salunkhe, G K Trivedi *Synth. Commun.* **39** 3856 (2009)
71. M Kertész, I Pallagi, S Sólyom *J. Heterocycl. Chem.* **44** 431 (2007)
72. C M Scorzo, M L Fascio, N B D'Accorso, M G Cabrera, L A Saavedra *J. Braz. Chem. Soc.* **21** 43 (2010)
73. D Giguère, R Patnam, M-A Bellefleur, C St-Pierre, S Sato, R Roy *Chem. Commun.* 2379 (2006)
74. J Ge, H Wub, S Q Yao *Chem. Commun.* **46** 2980 (2010)
75. B Kónya, T Docsa, P Gergely, L Somsák *Carbohydr. Res.* **351** 56 (2012)
76. V V Vaidya, K S Wankhede, M M Salunkhe, G K Trivedi *Can. J. Chem.* **86** 138 (2008)
77. M Tanaka, T Ikeda, J Mack, N Kobayashi, T Haino *J. Org. Chem.* **76** 5082 (2011)
78. E McClendon, A O Omollo, E J Valente, A T Hamme II *Tetrahedron Lett.* **50** 533 (2009)
79. Y-J Shang, J-W Wu, C-L Fan, J-S Hu, B-Y Lu *J. Organomet. Chem.* **693** 2963 (2008)
80. F Jourdan, C Bubert, M P Leese, A Smith, E Ferrandis, S Regis-Lydi, S P Newman, A Purohit, M J Reed, B V L Potter *Org. Biomol. Chem.* **6** 4108 (2008)
81. A Mores, M Matziari, F Beau, P Cuniasse, A Yiotakis, V Dive *J. Med. Chem.* **51** 2216 (2008)
82. W Zhou, L Zhang, N Jiao *Angew. Chem., Int. Ed.* **48** 7094 (2009)
83. M Gucma, W M Golebiewski *Monatsh. Chem.* **141** 461 (2010)
84. Y Liu, Z Cui, B Liu, B Cai, Y Li, Q Wang *J. Agric. Food Chem.* **58** 2685 (2010)
85. J E Gómez-Galeno, Q Dang, T H Nguyen, S H Boyer, M P Grote, Z Sun, M Chen, W A Craigo, P D van Poelje, D A MacKenna, E E Cable, P A Rolzin, P D Finn, B Chi, D L Linemeyer, S J Hecker, M D Erion *ACS Med. Chem. Lett.* **1** 478 (2010)
86. S André, D Giguère, T K Dam, F Brewer, H-J Gabius, R Roy *New J. Chem.* **34** 2229 (2010)
87. B Lee, J-H Kwak, S-W Huang, J-Y Jang, S Lim, Y-S Kwak, K Lee, H S Kim, S-B Han, J-T Hong, H Lee, S Song, S-Y Seo, J-K Jung *Bioorg. Med. Chem.* **20** 2860 (2012)
88. S Shafi, S Singh, S Haider, D M Reddy, M S Alam, G N Swamy, H M S Kumar *J. Heterocycl. Chem.* **50** 361 (2013)
89. S C Bottorff, B B Kasten, J Stojakovic, A L Moore, L R MacGillivray, P D Benny *Inorg. Chem.* **53** 1943 (2014)
90. D A Patrick, S A Bakunova, S M Bakunova, T Wenzler, R Brun, R R Tidwell *Bioorg. Med. Chem.* **22** 559 (2014)
91. K R Reddy, P S Rao, G J Dev, Y Poornachandra, C G Kumar, P S Rao, B Narsaiah *Bioorg. Med. Chem. Lett.* **24** 1661 (2014)
92. A Lilienkampf, J Mao, B Wan, Y Wang, S G Franzblau, A P Kozikowski *J. Med. Chem.* **52** 2109 (2009)
93. N Jullien, A Makritis, D Georgiadis, F Beau, A Yiotakis, V Dive *J. Med. Chem.* **53** 208 (2010)
94. G Muncipinto, T Kaya, J A Wilson, N Kumagai, P A Clemons, S L Schreiber *Org. Lett.* **12** 5230 (2010)
95. D Zhang, J Jia, L Meng, W Xu, L Tang, J Wang *Arch. Pharm. Res.* **33** 831 (2010)
96. K P Landge, J S Oh, A N Pae, W K Park, J Y Gong, H Y Koh, S H Jung *Bull. Korean Chem. Soc.* **32** 2449 (2011)
97. P Ratcliffe, L Abernethy, N Ansari, K Cameron, T Clarkson, M Dempster, D Dunn, A-M Easson, D Edwards, K Everett, H Feilden, K-K Ho, S Kultgen, P Littlewood, J Maclean, D McArthur, D McGregor, H McLuskey, I Neagu, O Nimz, L-A Nisbet, M Ohlmeyer, R Palin, Q Pham, Y Rong, A Roughton, M Sammons, R Swanson, H Tracey, G Walker *Bioorg. Med. Chem. Lett.* **21** 4652 (2011)
98. J A Spicer, K M Huttunen, C K Miller, W A Denny, A Ciccone, K A Browne, J A Trapani *Bioorg. Med. Chem.* **20** 1319 (2012)
99. Y N Oh, J Kwak, H Y Koh, S H Jung *Bull. Korean Chem. Soc.* **33** 4227 (2012)

100. C Bryant, I D Kerr, M Debnath, K K H Ang, J Ratnam, R S Ferreira, P Jaishankar, D M Zhao, M R Arkin, J H McKerrow, L S Brinen, A R Renslo *Bioorg. Med. Chem. Lett.* **19** 6218 (2009)
101. O Corminboeuf, O Bezencon, L Remeň, C Grisostomi, S Richard-Bildstein, D Bur, L Prade, P Strickner, P Hess, W Fischli, B Steiner, A Treiber *Bioorg. Med. Chem. Lett.* **20** 6291 (2010)
102. J-P Leclerc, J-P Falgueyret, M Girardin, J Guay, S Guiral, Z Huang, C S Li, R Oballa, Y K Ramtohul, K Skorey, P Tawa, H Wang, L Zhang *Bioorg. Med. Chem. Lett.* **21** 6505 (2011)
103. R D Jadhav, K S Kadam, S Kandre, T Guha, M M K Reddy, M K Brahma, N J Deshmukh, A Dixit, L Doshi, N Potdar, A A Enose, R A Vishwakarma, H Sivaramakrishnan, S Srinivasan, K V S Nemmani, A Gupte, A K Gangopadhyay, R Sharma *Eur. J. Med. Chem.* **54** 324 (2012)
104. M Asano, T Nakamura, Y Sekiguchi, Y Mizuno, T Yamaguchi, K Tamaki, T Shimozato, H Doi-Komuro, T Kagari, W Tomisato, R Inoue, H Yuita, K Oguchi-Oshima, R Kaneko, F Nara, Y Kawase, N Masubuchi, S Nakayama, T Koga, E Namba, H Nasu, T Nishi *Bioorg. Med. Chem. Lett.* **22** 3083 (2012)
105. J Qin, P Dhondi, X Huang, R Aslanian, J Fossetta, F Tian, D Lundell, A Palani *ACS Med. Chem. Lett.* **3** 100 (2012)
106. M Y Cha, K-O Lee, S-J Kang, Y H Jung, J Y Song, K J Choi, J Y Byun, H-J Lee, G S Lee, S B Park, M S Kim *J. Med. Chem.* **55** 2846 (2012)
107. M J Mitton-Fry, J T Arcari, R Barham, J Casavant, B S Gerstenberger, S Han, J R Hardink, T M Harris, T Hoang, M D Huband, M S Lall, M M Lemmon, C Li, J Lin, S P McCurdy, E McElroy, C McPherson, E S Marr, J P Mueller, L Mullins, A A Nikitenko, M C Noe, J Penzien, M S Plummer, B P Schuff, V Shanmugasundaram, J T Starr, J Sun, A Tomaras, J A Young, R P Zaniewski, M F Brown *J. Med. Chem.* **56** 5541 (2013)
108. M J Mitton-Fry, J T Arcari, J M Casavant, S M Finegan, M E Flanagan, H Gao, D M George, B S Gerstenberger, S Han, J R Hardink, T M Harris, T Hoang, M D Huband, R Irvine, M S Lall, M M Lemmon, C Li, J Lin, S P McCurdy, J P Mueller, L Mullins, M Niosi, M C Noe, D Pattavina, J Penzien, M S Plummer, H Risley, B P Schuff, V Shanmugasundaram, J T Starr, J Sun, J Winton, J A Young, M F Brown *Bioorg. Med. Chem. Lett.* **22** 5989 (2012)
109. K C Coffman, T A Palazzo, T P Hartley, J C Fettinger, D J Tantillo, M J Kurth *Org. Lett.* **15** 2062 (2013)
110. M J Choi, E S No, D A Thorat, J W Jang, H Yang, J Lee, H Choo, S J Kim, C S Lee, S Y Ko, J Lee, G S Nam, A N Pae *J. Med. Chem.* **56** 9008 (2013)
111. R K Bowman, A D Brown, J H Cobb, J F Eaddy, M A Hatcher, M R Leivers, J F Miller, M B Mitchell, D E Patterson, M A Toczko, S Xie *J. Org. Chem.* **78** 11680 (2013)
112. M D Ascenzio, S Carradori, C De Monte, D Secci, M Ceruso, C T Supuran *Bioorg. Med. Chem.* **22** 1821 (2014)
113. M Leivers, J F Miller, S A Chan, R Lauchli, S Liehr, W Mo, T Ton, E M Turner, M Youngman, J G Falls, S Long, A Mathis, J Walker *J. Med. Chem.* **57** 1964 (2014)
114. X-Z Wang, J Jia, Y Zhang, W-R Xu, W Liu, F-N Shi, J-W Wang *J. Chin. Chem. Soc.* **54** 643 (2007)
115. L Yin, J Jia, G L Zhao, W R Xu, L D Tang, J W Wang *Indian J. Chem., Sect. B* **50** 695 (2011)
116. K Sastraruji, T Sastraruji, A T Ung, R Griffith, A Jatisatienr, S G Pyne *Tetrahedron* **68** 7103 (2012)
117. D C B da Silva-Alves, J V dos Anjos, N N M Cavalcante, G K N Santos, D M A F Navarro, R M Srivastava *Bioorg. Med. Chem.* **21** 940 (2013)
118. J Stec, A Fomovska, G A Afanador, S P Muench, Y Zhou, B-S Lai, K El Bissati, M R Hickman, P J Lee, S E Leed, J M Auschwitz, C Sommervile, S Woods, C W Roberts, D Rice, S T Prigge, R McLeod, A P Kozikowski *ChemMedChem* **8** 1138 (2013)
119. S P Muench, J Stec, Y Zhou, G A Afanador, M J McPhillie, M R Hickman, P J Lee, S E Leed, J M Auschwitz, S T Prigge, D W Rice, R McLeod *Bioorg. Med. Chem. Lett.* **23** 3551 (2013)
120. T V Hansen, P Wu, V V Fokin *J. Org. Chem.* **70** 7761 (2005)
121. B J D Wright, J Hartung, F Peng, R Van de Water, H Liu, Q-H Tan, T-C Chou, S J Danishefsky *J. Am. Chem. Soc.* **130** 16786 (2008)
122. M Koufaki, E Theodorou, X Alexi, M N Alexis *Bioorg. Med. Chem.* **18** 3898 (2010)
123. G Chennakrishnareddy, B Vasantha, N Narendra, V V Sureshbabu *Int. J. Pept. Res. Ther.* **17** 185 (2011)
124. M Koufaki, A Tsatsaroni, X Alexi, H Guerrand, S Zerva, M N Alexis *Bioorg. Med. Chem.* **19** 4841 (2011)
125. M V Yermolina, J Wang, M Caffrey, L L Rong, D J Wardrop *J. Med. Chem.* **54** 765 (2011)
126. M Koufaki, T Fotopoulou, G A Heropoulos *Ultrason. Sonochem.* **21** 35 (2014)
127. S Kovács, Z Novák *Tetrahedron* **69** 8987 (2013)
128. K Chanda, S Rej, M H Huang *Nanoscale* **5** 12494 (2013)
129. S B Bharate, A K Padala, B A Dar, R R Yadav, B Singh, R A Vishwakarma *Tetrahedron Lett.* **54** 3558 (2013)
130. Y Luo, B Wang, G Zhang, Y Zhou, P Lian *J. Heterocycl. Chem.* **50** 381 (2013)
131. M Tanaka, T Haino, K Ideta, K Kubo, A Mori, Y Fukazawa *Tetrahedron* **63** 652 (2007)
132. E C Hansen, M Levent, T J Connolly *Org. Process Res. Dev.* **14** 574 (2010)
133. L I Robins, J C Fettinger, D S Tinti, M J Kurth *J. Comb. Chem.* **9** 139 (2007)
134. G J Yu, S Iwamoto, L I Robins, J C Fettinger, T C Sparks, B A Lorsbach M J Kurth *J. Agric. Food Chem.* **57** 7422 (2009)
135. Ya A Vereshchagina, A Z Alimova, E V Sharova, O I Artyushin, D V Chachkov, E A Ishmaeva *Russ. J. Org. Chem.* **49** 1369 (2013) [*Zh. Org. Khim.* **49** 1384 (2013)]
136. R Epple, R Russo, M Azimioara, C Cow, Y Xie, X Wang, J Wityak, D Karanewsky, A Gerken, M Iskandar, E Saez, H M Seidel, S-S Tian *Bioorg. Med. Chem. Lett.* **16** 4376 (2006)
137. M L McIntosh, M R Naffziger, B O Ashburn, L N Zakharov, R G Carter *Org. Biomol. Chem.* **10** 9204 (2012)
138. S Kankala, R Vadde, C S Vasam *Org. Biomol. Chem.* **9** 7869 (2011)
139. D Simoni, G Grisolia, G Giannini, M Roberti, R Rondanin, L Piccagli, R Baruchello, M Rossi, R Romagnoli, F P Invidiata, S Grimaudo, M K Jung, E Hamel, N Gebbia, L Crosta, V Abbadessa, A Di Cristina, L Dusonchet, M Meli, M Tolomeo *J. Med. Chem.* **48** 723 (2005)
140. L I Robins, R D Carpenter, J C Fettinger, M J Haddadin, D S Tinti, M J Kurth *J. Org. Chem.* **71** 2480 (2006)
141. M Girardin, S J Dolman, S Lauzon, S G Ouellet, G Hughes, P Fernandez, G Zhou, P D O'Shea *Org. Process Res. Dev.* **15** 1073 (2011)
142. G D Vilela, R R da Rosa, P H Schneider, I H Bechtold, J Eccher, A A Merlo *Tetrahedron Lett.* **52** 6569 (2011)
143. A Takada, Y Hashimoto, H Takikawa, K Hikita, K Suzuki *Angew. Chem., Int. Ed.* **50** 2297 (2011)
144. A Rescifina, M G Varrica, C Carnovale, G Romeo, U Chiacchio *Eur. J. Med. Chem.* **51** 163 (2012)
145. G Lavanya, L M Reddy, V Padmavathi, A Padmaja *Eur. J. Med. Chem.* **73** 187 (2014)
146. P P Yadav, G Ahmad, R Maurya *Tetrahedron Lett.* **46** 5621 (2005)

147. V N Kovganko, N N Kovganko *Russ. J. Org. Chem.* **42** 430 (2006) [*Zh. Org. Khim.* **42** 442 (2006)]
148. M Shailaja, A Manjula, B V Rao *Indian J. Chem., Sect. B* **50** 214 (2011)
149. V Padmavathi, R P Sumathi, K V Reddy, A S Reddy, D B Reddy *Synth. Commun.* **30** 4007 (2000)
150. N Ben Hamadi, M Msaddek *Heterocycl. Commun.* **12** 457 (2006)
151. A Bargiotti, L Musso, L Merlini, G Gallo, A Ciacci, G Giannini, W Cabri, S Penco, L Vesci, M Castorina, F M Milazzo, M L Cervoni, M Barbarino, C Pisano, C Giommarelli, V Zuco, M De Cesare, F Zunino, S Dallavalle *Eur. J. Med. Chem.* **53** 64 (2012)
152. N Tang, S-R Sheng, Q-S Hu, H-E Qu, M-Z Cai *Synth. Commun.* **42** 3279 (2012)
153. Y Koyama, R Yamaguchi, K Suzuki *Angew. Chem., Int. Ed.* **47** 1084 (2008)
154. G Enderlin, C Taillefumier, C Didierjean, Y Chapleur *Tetrahedron: Asymmetry* **16** 2459 (2005)
155. M A Schmidt, K Katipally, A Ramirez, O Soltani, X Hou, H Zhang, B-C Chen, X Qian, R P Deshpande *Tetrahedron Lett.* **53** 3994 (2012)
156. J D Butler, K C Coffman, K T Ziebart, M D Toney, M J Kurth *Chem. – Eur. J.* **16** 9002 (2010)
157. R Epple, M Azimioara, R Russo, Y Xie, X Wang, C Cow, J Wityak, D Karanewsky, B Bursulaya, A Kreusch, T Tuntland, A Gerken, M Iskandar, E Saez, H M Seidel, S-S Tian *Bioorg. Med. Chem. Lett.* **16** 5488 (2006)
158. M Kainuma, M Makishima, Y Hashimoto, H Miyachi *Bioorg. Med. Chem.* **15** 2587 (2007)
159. K C Coffman, T P Hartley, J L Dallas, M J Kurth *ACS Comb. Sci.* **14** 280 (2012)
160. P V Ramana, A R Reddy *J. Heterocycl. Chem.* **49** 621 (2012)
161. T Misawa, H Hayashi, Y Sugiyama, Y Hashimoto *Bioorg. Med. Chem.* **20** 2940 (2012)
162. Y Yang, M Zhang, Y Zhu, L Zhang, Q Xie, L Song, H Deng *Chin. J. Chem.* **31** 950 (2013)
163. Y Yamashita, Y Hirano, A Takada, H Takikawa, K Suzuki *Angew. Chem., Int. Ed.* **52** 6658 (2013)
164. H Kawai, Y Sugita, E Tokunaga, N Shibata *Eur. J. Org. Chem.* 1295 (2012)
165. C Peifer, K Kinkel, M Abadleh, D Schollmeyer, S Laufer *J. Med. Chem.* **50** 1213 (2007)
166. J-J Wang, J-Z Li, Y-W Li, J Jakus, Y K Shim *J. Porphyrins Phthalocyanines* **14** 859 (2010)
167. H Kawai, K Tachi, E Tokunaga, M Shiro, N Shibata *Angew. Chem., Int. Ed.* **50** 7803 (2011)
168. A R Reddy, G Goverdhan, A Sampath, K Mukkanti, P P Reddy, R Bandichhor *Synth. Commun.* **42** 639 (2012)
169. A O Abdelhamid *J. Heterocycl. Chem.* **46** 680 (2009)
170. M Nakamura, H Kurihara, G Suzuki, M Mitsuya, M Ohkubo, H Ohta *Bioorg. Med. Chem. Lett.* **20** 726 (2010)
171. S Zhu, S Shi, S W Gerritz *Tetrahedron Lett.* **52** 4001 (2011)
172. R C F Jones, J P Bullous, C C M Law, M R J Elsegood *Chem. Commun.* **50** 1588 (2014)
173. V A Bakulev, I V Efimov, N A Belyaev, S S Zhidovinov, Yu A Rozin, N N Volkova, A A Khabarova, O S El'tsov *Chem. Heterocycl. Compd.* **48** 1880 (2013) [*Khim. Geterotsikl. Soedin.* 2002 (2012)]
174. D C Schmitt, L Lam, J S Johnson *Org. Lett.* **13** 5136 (2011)
175. C C Lee, R J Fitzmaurice, S Caddick *Org. Biomol. Chem.* **7** 4349 (2009)
176. J Lasri, S Mukhopadhyay, M A J Charmier *J. Heterocycl. Chem.* **45** 1385 (2008)
177. F Micheli, G Bonanomi, F E Blaney, S Braggio, A M Capelli, A Checchia, O Curcuruto, F Damiani, R Di Fabio, D Donati, G Gentile, A Gribble, D Hamprecht, G Tedesco, S Terreni, L Tarsi, A Lightfoot, G Stemp, G MacDonald, A Smith, M Pecoraro, M Petrone, O Perini, J Piner, T Rossi, A Worby, M Pilla, E Valerio, C Griffante, M Mugnaini, M Wood, C Scott, M Andreoli, L Lacroix, A Schwarz, A Gozzi, A Bifone, C R Ashby Jr, J J Hagan, C Heidbreder *J. Med. Chem.* **50** 5076 (2007)
178. F Ren, G Deng, H Wang, L Luan, Q Meng, Q Xu, H Xu, X Xu, H Zhang, B Zhao, C Li, T B Guo, J Yang, W Zhang, Y Zhao, Q Jia, H Lu, J-N Xiang, J D Elliott, X Lin *J. Med. Chem.* **55** 4286 (2012)
179. M Ganesh, I N N Namboothiri *Tetrahedron* **63** 11973 (2007)
180. W M Xu, E Tang, X Huang *Tetrahedron* **61** 501 (2005)
181. T M Kaiser, J Huang, J Yang *J. Org. Chem.* **78** 6297 (2013)
182. J A Crossley, D L Brown *J. Org. Chem.* **75** 5414 (2010)
183. J E Moore, M W Davies, K M Goodenough, R A J Wybrow, M York, C N Johnson, J P A Harrity *Tetrahedron* **61** 6707 (2005)
184. F P Ballistreri, U Chiacchio, A Rescifina, G Tomaselli, R M Toscano *Molecules* **13** 1230 (2008)
185. S Bhosale, S Kurhade, U V Prasad, V P Palle, D Bhuniya *Tetrahedron Lett.* **50** 3948 (2009)
186. S Bhosale, S Kurhade, S Vyas, V P Palle, D Bhuniya *Tetrahedron* **66** 9582 (2010)
187. N E H Mustaphi, S Ferfra, E M Essassi, B Garrigues *Phosphorus, Sulfur, Silicon Relat. Elem.* **180** 2193 (2005)
188. L Edjlali *J. Chin. Chem. Soc.* **55** 1322 (2008)
189. Y-G Suh, N-J Kim, B-W Koo, K-O Lee, S-H Moon, D-H Shin, J-W Jung, S-M Paek, D-J Chang, F Li, H-J Kang, T V T Le, Y N Chae, C Y Shin, M-K Kim, J I Lim, J-S Ryu, H-J Park *J. Med. Chem.* **51** 6318 (2008)
190. P P Shao, F Ye, A E Weber, X Li, K A Lyons, W H Parsons, M L Garcia, B T Priest, McH M Smith, J P Felix, B S Williams, G J Kaczorowski, E McGowan, C Abbadie, W J Martin, D R McMasters, Y-D Gao *Bioorg. Med. Chem. Lett.* **19** 5329 (2009)
191. Y R Mirzaei, L Edjlali *J. Iran. Chem. Soc.* **7** 685 (2010)
192. S Al-Busafi, M Al-Belushi, K Al-Muqbali *Synth. Commun.* **40** 1088 (2010)
193. B Cosimelli, F Simorini, S Taliani, C La Motta, F Da Settimo, E Severi, G Greco, E Novellino, B Costa, E Da Pozzo, S Bendinelli, C Martini *Eur. J. Med. Chem.* **46** 4506 (2011)
194. M Flipo, M Desroses, N Lecat-Guillet, B Villemagne, N Blondiaux, F Leroux, C Piveteau, V Mathys, M-P Flament, J Siepmann, V Villeret, A Wohlkönig, R Wintjens, S H Soror, T Christophe, H K Jeon, C Locht, P Brodin, B Déprez, A R Baulard, N Willand *J. Med. Chem.* **55** 68 (2012)
195. P R Kumar, M Behera, K Raghavulu, A J Shree, S Yennam *Tetrahedron Lett.* **53** 4108 (2012)
196. J H Frederich, J K Matsui, R O Chang, P G Harran *Tetrahedron Lett.* **54** 2645 (2013)
197. R M Kumbhare, U B Kosurkar, M J Ramaiah, T L Dadmal, S N C V L Pushpavalli, M Pal-Bhadra *Bioorg. Med. Chem. Lett.* **22** 5424 (2012)
198. P S Rao, C Kurumurthy, B Veeraswamy, Y Poornachandra, C G Kumar, B Narsaiah *Bioorg. Med. Chem. Lett.* **24** 1349 (2014)
199. I Gaamoussi, I Fichtali, A B Tama, E M El Hadrami, D Armentano, G De Munno, M Julve, S-E Stiriba *J. Mol. Struct.* **1048** 130 (2013)
200. J I Montgomery, J A Abramite, U Reilly, M F Brown, J M Chen, R A Barham, Y Che, S W Chung, C A Menard, M Mitton-Fry, L M Mullins, M C Noe, J P O'Donnell, R M Oliver III, J B Penzien, M Plummer, L M Price, V Shanmugasundaram, A P Tomaras, D P Uccello, L A McAllister *Bioorg. Med. Chem. Lett.* **22** 6832 (2012)

201. Y-S Lee, S M Park, H M Kim, S-K Park, K Lee, C W Lee, B H Kim *Bioorg. Med. Chem. Lett.* **19** 4688 (2009)
202. A Kamal, J S Reddy, M J Ramaiah, D Dastagiri, E V Bharathi, M A Azhar, F Sultana, S N C V L Pushpavalli, M Pal-Bhadra, A Juvekar, S Sen, S Zingde *Eur. J. Med. Chem.* **45** 3924 (2010)
203. A Kamal, E V Bharathi, J S Reddy, M J Ramaiah, D Dastagiri, M K Reddy, A Viswanath, T L Reddy, T B Shaik, S N C V L Pushpavalli, M Pal-Bhadra *Eur. J. Med. Chem.* **46** 691 (2011)
204. Y-S Lee, S M Park, B H Kim *Bioorg. Med. Chem. Lett.* **19** 1126 (2009)
205. T Van Neck, S Van Mierloo, W Dehaen *Molecules* **12** 395 (2007)
206. J B Santella III, D S Gardner, W Yao, C Shi, P Reddy, A J Tebben, G V DeLucca, D A Wacker, P S Watson, K Welch, E A Wadman, P Davies, K A Solomon, D M Graden, S Yeleswaram, S Mandlekar, I Kariv, C P Decicco, S S Ko, P H Carter, J V Duncia *Bioorg. Med. Chem. Lett.* **18** 576 (2008)
207. R Bouhfid, N Joly, E M Essassi, V Lequart, M Massoui, P Martin *Synth. Commun.* **41** 2096 (2011)
208. B Roy, R N De *Monatsh. Chem.* **141** 763 (2010)
209. V V Vaidya, K S Wankhede, M M Salunkhe, G K Trivedi *Synth. Commun.* **38** 2392 (2008)
210. V Singh, S Hutait, S Biswas, S Batra *Eur. J. Org. Chem.* 531 (2010)
211. M Würdemann, J Christoffers *Eur. J. Org. Chem.* 7421 (2013)
212. P S Koranne, T Tsujihara, M A Arai, G B Bajracharya, T Suzuki, K Onitsuka, H Sasai *Tetrahedron: Asymmetry* **18** 919 (2007)
213. K Takenaka, S Nakatsuka, T Tsujihara, P S Koranne, H Sasai *Tetrahedron: Asymmetry* **19** 2492 (2008)
214. K Takenaka, T Nagano, S Takizawa, H Sasai *Tetrahedron: Asymmetry* **21** 379 (2010)
215. S Ghorai, R Mukhopadhyay, A P Kundu, A Bhattacharjya *Tetahedron* **61** 2999 (2005)
216. S Cai, S Zhang, Y Zhao, D Z Wang *Org. Lett.* **15** 2660 (2013)
217. C Freeman, A N Cheallaigh, F Heaney *Tetrahedron* **67** 7860 (2011)
218. I Singh, J S Vyle, F Heaney *Chem. Commun.* 3276 (2009)
219. V Algay, I Singh, F Heaney *Org. Biomol. Chem.* **8** 391 (2010)
220. I Singh, C Freeman, A Madder, J S Vyle, F Heaney *Org. Biomol. Chem.* **10** 6633 (2012)
221. C Freeman, J S Vyle, F Heaney *RSC Adv.* **3** 1652 (2013)
222. K A Kumar, M Govindaraju, G V Kumar *Indian J. Heterocycl. Chem.* **20** 183 (2010)
223. P-A Fournier, M Arbour, E Cauchon, A Chen, A Chefson, Y Ducharme, J-P Falgueyret, S Gagné, E Grimm, Y Han, R Houle, P Lacombe, J-F Lévesque, D MacDonald, B Mackay, D McKay, M D Percival, Y Ramtohul, R St-Jacques, S Toulmond *Bioorg. Med. Chem. Lett.* **22** 2670 (2012)
224. S Minakata, S Okumura, T Nagamachi, Y Takeda *Org. Lett.* **13** 2966 (2011)
225. A Yoshimura, C Zhu, K R Middleton, A D Todora, B J Kastern, A V Maskaev, V V Zhdankin *Chem. Commun.* **49** 4800 (2013)
226. L Han, B Zhang, M Zhu, J Yan *Tetrahedron Lett.* **55** 2308 (2014)
227. C D Turner, M A Ciufolini *ARKIVOC* (i) 410 (2011)
228. B A Mendelsohn, S Lee, S Kim, F Teyssier, V S Aulakh, M A Ciufolini *Org. Lett.* **11** 1539 (2009)
229. B C Sanders, F Friscourt, P A Ledin, N E Mbua, S Arumugam, J Guo, T J Boltje, V V Popik, G-J Boons *J. Am. Chem. Soc.* **133** 949 (2011)
230. A M Jawalekar, E Reubsaet, F P J T Rutjes, F L van Delft *Chem. Commun.* **47** 3198 (2011)
231. B D Zlatopolskiy, R Kandler, D Kobus, F M Mottaghy, B Neumaier *Chem. Commun.* **48** 7134 (2012)
232. T-F Niu, M-F Lv, L Wang, W-B Yi, C Cai *Org. Biomol. Chem.* **11** 1040 (2013)
233. M J Raihan, V Kavala, C-W Kuo, B R Rajua, C-F Yao *Green Chem.* **12** 1090 (2010)
234. R D Jadhav, H D Mistry, H Motiwala, K S Kadam, S Kandre, A Gupte, A K Gangopadhyay, R Sharma *J. Heterocycl. Chem.* **50** 774 (2013)
235. A Yoshimura, K R Middleton, A D Todora, B J Kastern, S R Koski, A V Maskaev, V V Zhdankin *Org. Lett.* **15** 4010 (2013)
236. Y Hou, S Lu, G Liu *J. Org. Chem.* **78** 8386 (2013)
237. M Mabrour, K Bougrin, R Benhida, A Loupy, M Soufiaoui *Tetrahedron Lett.* **48** 443 (2007)
238. J H Kalin, H Zhang, S Gaudrel-Grosay, G Vistoli, A P Kozikowski *ChemMedChem* **7** 425 (2012)
239. T Mukaiyama, T Hoshino *J. Am. Chem. Soc.* **82** 5339 (1960)
240. S-Y Tosaki, K Hara, V Gnanadesikan, H Morimoto, S Harada, M Sugita, N Yamagiwa, S Matsunaga, M Shibasaki *J. Am. Chem. Soc.* **128** 11776 (2006)
241. K Hara, S-Y Tosaki, V Gnanadesikan, H Morimoto, S Harada, M Sugita, N Yamagiwa, S Matsunaga, M Shibasaki *Tetrahedron* **65** 5030 (2009)
242. A van den Hoogenband, J H van Maarseveen, A C McCreary, A T Mulder, G J M van Scharrenburg, H H van Stuivenberg, T J J Zethof, B Zijta, W I I Bakker *Bioorg. Med. Chem. Lett.* **16** 1045 (2006)
243. S-H Ji, W P Hong, S H Ko, K-J Lee *J. Heterocycl. Chem.* **43** 799 (2006)
244. F S Pashkovskii, Ya M Katok, E M Shchukina, E V Koroleva, F A Lakhvich *Russ. J. Org. Chem.* **42** 230 (2006) [*Zh. Org. Khim.* **42** 246 (2006)]
245. K S Wankhede, V V Vaidya, P S Sarang, M M Salunkhe, G K Trivedi *Tetrahedron Lett.* **49** 2069 (2008)
246. P P Shao, F Ye, A E Weber, X Li, K A Lyons, W H Parsons, M L Garcia, B T Priest, McH M Smith, J P Felix, B S Williams, G J Kaczorowski, E McGowan, C Abbadie, W J Martin, D R McMasters, Y-D Gao *Bioorg. Med. Chem. Lett.* **19** 5334 (2009)
247. A Petrocchi, P Jones, M Rowley, F Fiore, V Summa *Bioorg. Med. Chem. Lett.* **19** 4245 (2009)
248. J Liu, L-F Yu, J B Eaton, B Caldarone, K Cavino, C Ruiz, M Terry, A Fedolak, D Wang, A Ghavami, D A Lowe, D Brunner, R J Lukas, A P Kozikowski *J. Med. Chem.* **54** 7280 (2011)
249. L-F Yu, J B Eaton, A Fedolak, H-K Zhang, T Hanania, D Brunner, R J Lukas, A P Kozikowski *J. Med. Chem.* **55** 9998 (2012)
250. T Sato, K Sugimoto, A Inoue, S Okudaira, J Aoki, H Tokuyama *Bioorg. Med. Chem. Lett.* **22** 4323 (2012)
251. D Grée, R Grée *Tetrahedron Lett.* **48** 5435 (2007)
252. A Khalaf, D Grée, H Abdallah, N Jaber, A Hachem, R Grée *Tetrahedron* **67** 3881 (2011)
253. J Siu, I R Baxendale, R A Lewthwaite, S V Ley *Org. Biomol. Chem.* **3** 3140 (2005)
254. J J Letourneau, C Riviello, M H J Ohlmeyer *Tetrahedron Lett.* **48** 1739 (2007)
255. J D Butler, D M Solano, L I Robins, M J Haddadin, M J Kurth *J. Org. Chem.* **73** 234 (2008)
256. L Meng, B A Lorsbach, T C Sparks, J C Fettinger, M J Kurth *J. Comb. Chem.* **12** 129 (2010)
257. J S Warmus, C L Quinn, C Taylor, S T Murphy, T A Johnson, C Limberakis, D Ortwine, J Bronstein, P Pagano, J D Knafels, S Lightle, I Mochalkin, R Brideau, T Podoll *Bioorg. Med. Chem. Lett.* **22** 2536 (2012)
258. Aim Ahmad, An Ahmad, H Varshney, A Rauf, M Rehan, N Subbarao, A U Khan *Eur. J. Med. Chem.* **70** 887 (2013)

259. N R Guz, H Leuser, E Goldman *Org. Process Res. Dev.* **17** 1066 (2013)
260. S E Denmark, J M Kallemeyn *J. Org. Chem.* **70** 2839 (2005)
261. K Ramachandiran, K Karthikeyan, D Muralidharan, P T Perumal *Tetrahedron Lett.* **51** 3006 (2010)
262. R Rohlmann, C-G Daniliuc, O G Mancheno *Chem. Commun.* **49** 11665 (2013)
263. J Peng, D-M Du *Eur. J. Org. Chem.* 4042 (2012)
264. M Zagozda, J Plenkiewicz *Tetrahedron: Asymmetry* **18** 1457 (2007)
265. D A Goff *Tetrahedron* **69** 242 (2013)
266. J Lugitina, V Rjabovs, S Belyakov, M Turks *Tetrahedron Lett.* **54** 5328 (2013)
267. C Praveen, K Karthikeyan, P T Perumal *Tetrahedron* **65** 9244 (2009)
268. L Cecchi, F De Sarlo, F Machetti *Eur. J. Org. Chem.* 4852 (2006)
269. L Cecchi, F De Sarlo, C Faggi, F Machetti *Eur. J. Org. Chem.* 3016 (2006)
270. F Machetti, L Cecchi, E Trogu, F De Sarlo *Eur. J. Org. Chem.* 4352 (2007)
271. E Trogu, L Cecchi, F De Sarlo, L Guideri, F Ponticelli, F Machetti *Eur. J. Org. Chem.* 5971 (2009)
272. E Trogu, F De Sarlo, F Machetti *Chem. – Eur. J.* **15** 7940 (2009)
273. E Trogu, C Vinattieri, F De Sarlo, F Machetti *Chem. – Eur. J.* **18** 2081 (2012)
274. L Guideri, F De Sarlo, F Machetti *Chem. – Eur. J.* **19** 665 (2013)
275. I Yavari, M Piltan, L Moradi *Tetrahedron* **65** 2067 (2009)
276. I Yavari, L Moradi *Tetrahedron Lett.* **47** 1627 (2006)
277. M M M Santos, N Faria, J Iley, S J Coles, M B Hursthouse, M L Martins, R Moreira *Bioorg. Med. Chem. Lett.* **20** 193 (2010)
278. K-I Itoh, T Aoyama, H Satoh, Y Fujii, H Sakamaki, T Takido, M Kodomari *Tetrahedron Lett.* **52** 6892 (2011)
279. R G Chary, G R Reddy, Y S S Ganesh, K V Prasad, A Raghunadh, T Krishna, S Mukherjee, M Pal *Adv. Synth. Catal.* **356** 160 (2014)
280. Y Yang, M Gao, C Deng, D-X Zhang, L-M Wu, W-M Shu, A-X Wu *Tetrahedron* **68** 6257 (2012)
281. A Baranczak, G A Sulikowski *Org. Lett.* **14** 1027 (2012)
282. P J Black, G Cami-Kobeci, M G Edwards, P A Slatford, M K Whittlesey, J M J Williams *Org. Biomol. Chem.* **4** 116 (2006)
283. L Lin, J Zhang, R Wang *Asian J. Org. Chem.* **1** 222 (2012)
284. M Ueda, Y Ikeda, A Sato, Y Ito, M Kakiuchi, H Shono, T Miyoshi, T Naito, O Miyata *Tetrahedron* **67** 4612 (2011)
285. M Ueda, S Sugita, A Sato, T Miyoshi, O Miyata *J. Org. Chem.* **77** 9344 (2012)
286. M Ueda, A Sato, Y Ikeda, T Miyoshi, T Naito, O Miyata *Org. Lett.* **12** 2594 (2010)
287. J P Waldo, R C Larock *J. Org. Chem.* **72** 9643 (2007)
288. T Okitsu, K Sato, T M Potewar, A Wada *J. Org. Chem.* **76** 3438 (2011)
289. B J Stokes, C V Vogel, L K Urnezis, M Pan, T G Driver *Org. Lett.* **12** 2884 (2010)
290. J A Burkhard, B H Tchitchanov, E M Carreira *Angew. Chem., Int. Ed.* **50** 5379 (2011)
291. O B Bondarenko, A Yu Gavrilova, D S Murodov, N S Zefirov, N V Zyk *Russ. J. Org. Chem.* **49** 186 (2013) [*Zh. Org. Khim.* **49** 198 (2013)]
292. V Reddy Avara, L Gorentla, U B Rao Siripalli, P Kumar Dubey *Indian J. Chem., Sect. B* **50** 119 (2011)
293. J M Patel, S S Soman *Chem. Heterocycl. Compd.* **45** 1081 (2009) [*Khim. Geterotsikl. Soedin.* 1352 (2009)]
294. A J Boulton, A R Katritzky, A M Hamid *J. Chem. Soc. C* 2005 (1967)
295. A S Afridi, A R Katritzky, C A Ramsden *J. Chem. Soc., Perkin Trans. 1* 315 (1976)
296. A Martorana, A P Piccionello, S Buscemi, G Giorgic, A Pace *Org. Biomol. Chem.* **9** 491 (2011)
297. A Martorana, A Pace, S Buscemi, A P Piccionello *Org. Lett.* **14** 3240 (2012)
298. Yu I Gorak, N D Obushak, V S Matiichuk, R Z Lytvyn *Russ. J. Org. Chem.* **45** 541 (2009) [*Zh. Org. Khim.* **45** 555 (2009)]
299. N T Pokhodylo, V S Matiychuk *Phosphorus, Sulfur, Silicon Relat. Elem.* **186** 1895 (2011)
300. W Zhong, W Zhang, Y Chen, Y Liu, Y Yao *Org. Process Res. Dev.* **15** 698 (2011)
301. G L Perlovich, A N Proshin, T V Volkova, L N Petrova, S O Bachurin *Mol. Pharmaceutics* **9** 2156 (2012)
302. I V Serkov, A N Proshin, L N Petrova, S O Bachurin *Dokl. Chem.* **435** 311 (2010) [*Dokl. Akad. Nauk* **435** 479 (2010)]
303. A Pace, P Pierro, S Buscemi, N Vivona, G Barone *J. Org. Chem.* **74** 351 (2009)
304. V Ya Sosnovskikh, V S Moshkin, M Yu Kornev, M I Kodess *Mendeleev Commun.* **21** 110 (2011)
305. V Ya Sosnovskikh, V S Moshkin, M I Kodess *Mendeleev Commun.* **20** 209 (2010)
306. S D Van Arnum, H J Niemczyk *J. Heterocycl. Chem.* **46** 909 (2009)
307. L M Gornostaev, L V Dolgushina, N G Titova, E V Arnold, T I Lavrikova *Russ. J. Org. Chem.* **42** 1364 (2006) [*Zh. Org. Khim.* **42** 1380 (2006)]
308. S F Vasilevsky, L M Gornostaev, A A Stepanov, E V Arnold, I V Alabugin *Tetrahedron Lett.* **48** 1867 (2007)
309. M F A Adamo, P Sarti-Fantoni, S Chimichi, A Sandrelli *Tetrahedron Lett.* **51** 6310 (2010)
310. M F A Adamo, D Donati, P Sarti-Fantoni, A Buccioni *Tetrahedron Lett.* **49** 941 (2008)
311. D Donati, S Ferrini, S Fusi, F Ponticelli *J. Heterocycl. Chem.* **41** 761 (2004)
312. M Calle, L A Calvo, A Gonzalez-Ortega, A M Gonzalez-Nogal *Tetrahedron* **62** 611 (2006)
313. S I Sviridov, A A Vasil'ev, S V Shorshnev *Tetrahedron* **63** 12195 (2007)
314. T Sasada, Y Aoki, R Ikeda, N Sakai, T Konakahara *Chem. – Eur. J.* **17** 9385 (2011)
315. V Singh, R Saxena, S Batra *J. Org. Chem.* **70** 353 (2005)
316. X Fan, X Zhang, Y Zhang *Heteroat. Chem.* **16** 637 (2005)
317. A Senthilvelan, M-T Tsai, K-C Chang, W-S Chung *Tetrahedron Lett.* **47** 9077 (2006)
318. N Rasool, M A Rashid, H Reinke, C Fischer, P Langer *Tetrahedron* **63** 11626 (2007)
319. N Rasool, M A Rashid, H Reinke, C Fischer, P Langer *Tetrahedron* **64** 3246 (2008)
320. L Di Nunno, P Vitale, A Scilimati *Tetrahedron* **64** 11198 (2008)
321. L Di Nunno, P Vitale, A Scilimati, L Simone, F Capitelli *Tetrahedron* **63** 12388 (2007)
322. L Di Nunno, A Scilimati, P Vitale *Tetrahedron* **61** 2623 (2005)
323. V Yu Orlov, V V Ganzha, A D Kotov, V G Sokolov *Russ. J. Org. Chem.* **43** 1502 (2007) [*Zh. Org. Khim.* **43** 1509 (2007)]
324. R Ikeda, R Kuwano *Molecules* **17** 6901 (2012)
325. H Takikawa, A Takada, K Hikita, K Suzuki *Angew. Chem., Int. Ed.* **47** 7446 (2008)
326. J R Manning, H M L Davies *J. Am. Chem. Soc.* **130** 8602 (2008)
327. J R Manning, H M L Davies *Tetrahedron* **64** 6901 (2008)
328. A F Khlebnikov, M S Novikov, Yu G Gorbunova, E E Galenko, K I Mikhailov, V V Pakalnis, M S Avdontceva *Beilstein J. Org. Chem.* **10** 1896 (2014)
329. J W Pavlik, H S Martin, K A Lambert, J A Lowell, V M Tsefrikas, C K Eddins, N Kebede *J. Heterocycl. Chem.* **42** 273 (2005)

330. S Lopes, C M Nunes, A Gomez-Zavaglia, T M V D Pinho e Melo, R Fausto *J. Phys. Chem. A* **115** 1199 (2011)
331. S M Fonseca, H D Burrows, C M Nunes, T M V D Pinho e Melo *Chem. Phys. Lett.* **474** 84 (2009)
332. C M Nunes, I Reva, T M V D Pinho e Melo, R Fausto, T Solomek, T Bally *J. Am. Chem. Soc.* **133** 18911 (2011)
333. S B Alyabiev, D V Kravchenko, A V Ivachtchenko *Mendeleev Commun.* **18** 144 (2008)
334. G J Yu, B Yang, A S Verkman, M J Kurth *Synlett* 1063 (2010)
335. J Z Ho, K R Van Arsdale, M P Braun *Helv. Chim. Acta* **91** 958 (2008)
336. Z Ji, A A Ahmed, D H Albert, J J Bouska, P F Bousquet, G A Cunha, K B Glaser, J Guo, J Li, P A Marcotte, M D Moskey, L J Pease, K D Stewart, M Yates, S K Davidsena, M R Michaelides *Bioorg. Med. Chem. Lett.* **16** 4326 (2006)
337. J M Quintela, C Peinador, M J Moreira, R Toba, M Chas *Heterocycles* **68** 933 (2006)
338. E Wagner, K Al-Kadasi, L Becan, W Sawka-Dobrowolska *J. Heterocycl. Chem.* **47** 677 (2010)
339. G Semple, A Ren, B Fioravanti, G Pereira, I Calderon, K Choi, Y Xiong, Y-J Shin, T Gharbaoui, C R Sage, M Morgan, C Xing, Z-L Chu, J N Leonard, A J Grottick, H Al-Shamma, Y Liang, K T Demarest, R M Jones *Bioorg. Med. Chem. Lett.* **21** 3134 (2011)
340. A P Mityuk, S E Kolodych, S A Mytnyk, Yu V Dmytriv, D M Volochnyuk, P K Mykhailiuk, A A Tolmachev *Synthesis* 2767 (2010)
341. A Rivkin, B Adams *Tetrahedron Lett.* **47** 2395 (2006)
342. W S Hamama, M E Ibrahim, H H Zoorob *Arch. Pharm.* **345** 468 (2012)
343. S B Bharate, T R Mahajan, Y R Gole, M Nambiar, T T Matan, A Kulkarni-Almeida, S Balachandran, H Junjappa, A Balakrishnan, R A Vishwakarma *Bioorg. Med. Chem.* **16** 7167 (2008)
344. S V Ryabukhin, A S Plaskon, D M Volochnyuk, A A Tolmachev *Synthesis* 1861 (2007)
345. A Kotljarov, V O Iaroshenko, D M Volochnyuk, R A Irgashev, V Ya Sosnovskikh *Synthesis* 3869 (2009)
346. A P Mityuk, D M Volochnyuk, S V Ryabukhin, A S Plaskon, A Shivanyuk, A A Tolmachev *Synthesis* 1858 (2009)
347. V A Petrosyan, S V Neverov, V L Sigacheva *Russ. Chem. Bull., Int. Ed.* **56** 2184 (2007) [*Izv. Akad. Nauk, Ser. Khim.* 2110 (2007)]
348. B Jiang, G Zhang, N Ma, F Shi, S-J Tu, P Kaur, G Li *Org. Biomol. Chem.* **9** 3834 (2011)
349. N Ma, B Jiang, G Zhang, S-J Tu, W Wever, G Li *Green Chem.* **12** 1357 (2010)
350. M V Vovk, A V Bolbut, V I Dorokhov *Chem. Heterocycl. Compd.* **40** 496 (2004) [*Khim. Geterotsikl. Soedin.* 592 (2004)]
351. E Rajanarendar, S Raju, M Nagy Reddy, K Rama Murthy *Indian J. Chem., Sect. B* **49** 1422 (2010)
352. A Khalfallah, M T Khaddachi *South Afr. J. Chem.* **63** 62 (2010)
353. H S Hilal, M S Ali-Shtayeh, R Arafat, T Al-Tel, W Voelter, A Baraka *Eur. J. Med. Chem.* **41** 1017 (2006)
354. L G Voskressensky, T N Borisova, M V Ovcharov, L N Kulikova, E A Sorokina, R S Borisov, A V Varlamov *Chem. Heterocycl. Compd.* **44** 1510 (2008) [*Khim. Geterotsikl. Soedin.* 1861 (2008)]
355. E Rajanarendar, M Nagi Reddy, K Govardhan Reddy, S Rama Krishna *Tetrahedron Lett.* **53** 2909 (2012)
356. R Eligeti, R Saini, N Dharavath *J. Sulfur Chem.* **33** 427 (2012)
357. M Daci-Ajvazi, S Govori, S Omeragiq *e-J. Chem.* **8** 1522 (2011)
358. F F Bamoharram, M Roshani, M M Heravi, M Mahdavi, A Javid, J S Emampour *Chin. J. Chem.* **28** 974 (2010)
359. A Davoodnia, M Bakavoli, N Pooryaghoobi, M Roshani *Heterocycl. Commun.* **13** 323 (2007)
360. G Spalluto, B Cacciari *Synth. Commun.* **36** 1177 (2006)
361. E Wagner, K Al-Kadasi, M Zimecki, W Sawka-Dobrowolska *Eur. J. Med. Chem.* **43** 2498 (2008)
362. E Rajanarendar, S Raju, M Nagi Reddy, S Rama Krishna, L Hari Kiran, A Ram Narasimha Reddy, Y Narasimha Reddy *Eur. J. Med. Chem.* **50** 274 (2012)
363. E Rajanarendar, M Nagi Reddy, K Rama Murthy *Chin. Chem. Lett.* **21** 927 (2010)
364. E Rajanarendar, D Karunakar, P Ramesh, E Kalyan Rao *Heterocycl. Commun.* **12** 355 (2006)
365. E Rajanarendar, S Raju, A Siva Rami Reddy, K Govardhan Reddy, M Nagi Reddy *Chem. Pharm. Bull.* **58** 833 (2010)
366. E Rajanarendar, G Mohan, P Ramesh, D Karunakar *Tetrahedron Lett.* **47** 4957 (2006)
367. E Rajanarendar, G Mohan, P Ramesh, M Srinivas *J. Heterocycl. Chem.* **44** 215 (2007)
368. M F A Adamo, E F Duffy, D Donati, P Sarti-Fantoni *Tetrahedron* **63** 2684 (2007)
369. E Rajanarendar, K Govardhan Reddy, S Rama Krishna, B Shireesha, Y N Reddy, M V Rajam *Med. Chem. Res.* **22** 6143 (2013)
370. E Rajanarendar, M Nagi Reddy, S Rama Krishna, K Govardhan Reddy, Y N Reddy, M V Rajam *Eur. J. Med. Chem.* **50** 344 (2012)
371. M F A Adamo, E F Duffy, D Donati, P Sarti-Fantoni *Tetrahedron* **63** 2047 (2007)
372. E Rajanarendar, K Govardhan Reddy, S Ramakrishna, M Nagi Reddy, B Shireesha, G Durgaiah, Y N Reddy *Bioorg. Med. Chem. Lett.* **22** 6677 (2012)
373. S Hintermann, M Chiesi, U von Krosigk, D Mathe, R Felber, B Hengerer *Bioorg. Med. Chem. Lett.* **17** 193 (2007)
374. R C F Jones, A K Choudhury, J N Iley, G Loizou, C Lumley, V McKee *Synlett* 654 (2010)
375. J Qin, P Dhondi, X Huang, M Mandal, Z Zhao, D Pissarnitski, W Zhou, R Aslanian, Z Zhu, W Greenlee, J Clader, L Zhang, M Cohen-Williams, N Jones, L Hyde, A Palani *Bioorg. Med. Chem. Lett.* **21** 664 (2011)
376. B H Norman, P A Lander, J M Gruber, J S Kroin, J D Cohen, L N Jungheim, J J Starling, K L Law, T D Self, L B Tabas, D C Williams, D C Paul, A H Dantzig *Bioorg. Med. Chem. Lett.* **15** 5526 (2005)
377. A Li, T M Gilbert, D A Klumpp *J. Org. Chem.* **73** 3654 (2008)
378. V Singh, S Batra *Tetrahedron Lett.* **47** 7043 (2006)
379. A O Abdelhamid, M M Abdelhalim, G A Elmegeed *J. Heterocycl. Chem.* **44** 7 (2007)
380. M R Shaaban, T S Saleh, F H Osman, A M Farag *J. Heterocycl. Chem.* **44** 177 (2007)
381. A O Abdelhamid, A A Al-Atoom *Synth. Commun.* **36** 97 (2006)
382. A O Abdelhamid, A A Fahmi, K N M Halim *Synth. Commun.* **43** 1101 (2013)
383. A O Abdelhamid, A H Elghandour, S A Ahmed, Y H Zaki *J. Heterocycl. Chem.* **43** 249 (2006)
384. J Feixas, M P Giovannoni, C Vergelli, A Gavalda, N Cesari, A Graziano, V Dal Piaz *Bioorg. Med. Chem. Lett.* **15** 2381 (2005)
385. M P Giovannoni, C Vergelli, C Biancalani, N Cesari, A Graziano, P Biagini, J Gracia, A Gavalda, V Dal Piaz *J. Med. Chem.* **49** 5363 (2006)
386. C Biancalani, M P Giovannoni, S Pieretti, N Cesari, A Graziano, C Vergelli, A Cilibrizzi, A Di Gianuario, M Colucci, G Mangano, B Garrone, L Polenzani, V Dal Piaz *J. Med. Chem.* **52** 7397 (2009)

387. M P Giovannoni, N Cesari, C Vergelli, A Graziano, C Biancalani, P Biagini, C Ghelardini, E Vivoli, V Dal Piaz *J. Med. Chem.* **50** 3945 (2007)
388. S A Patel, T Rajale, E O'Brien, D J Burkhart, J K Nelson, B Twamley, A Blumenfeld, M I Szabon-Watola, J M Gerdes, R J Bridges, N R Natale *Bioorg. Med. Chem.* **18** 202 (2010)
389. J K Nelson, B Twamley, T J Villalobos, N R Natale *Tetrahedron Lett.* **49** 5957 (2008)
390. O Ünsal-Tan, K Öqzden, A Rauk, A Balkan *Eur. J. Med. Chem.* **45** 2345 (2010)
391. O Ünsal-Tan, K Özadali, Ö Yesilyurt, H Kayir, T Uzbay, A Balkan *Turk. J. Chem.* **35** 121 (2011)
392. N Cesari, C Biancalani, C Vergelli, V Dal Piaz, A Graziano, P Biagini, C Ghelardini, N Galeotti, M P Giovannoni *J. Med. Chem.* **49** 7826 (2006)
393. H M Faidallah, K A Khan, M S I Makki *J. Chin. Chem. Soc.* **58** 191 (2011)
394. J L García Ruano, C Fajardo, M R Martin *Tetrahedron* **61** 4363 (2005)
395. P Sarita Rajender, G Sridevi, K Kondal Reddy *Synth. Commun.* **42** 2191 (2012)
396. V P Kislyi, E B Danilova, V V Semenov *Mendeleev Commun.* **22** 85 (2012)
397. N Gavande, G A R Johnston, J R Hanrahan, M Chebib *Org. Biomol. Chem.* **8** 4131 (2010)
398. W S Cheung, R J Patch, M R Player *J. Org. Chem.* **70** 3741 (2005)
399. A Fraile, M R Martín, J-L García Ruano, J-A Díaz, E Arranz *Tetrahedron* **67** 100 (2011)
400. K-i Awasaguchi, H Hayashi, H Kawai, H Tominaga, Y Sato, K Hayashi, Y Todo *Synlett* **23** 448 (2012)
401. D R Williams, M W Fultz, T E Christos, J S Carter *Tetrahedron Lett.* **51** 121 (2010)
402. W K Goh, D StC Black, N Kumar *Tetrahedron Lett.* **48** 9008 (2007)
403. G-R Peh, E A B Kantchev, J-C Er, J Y Ying *Chem. – Eur. J.* **16** 4010 (2010)
404. W Tang, A G Capacci, X Wei, W Li, A White, N D Patel, J Savoie, J J Gao, S Rodriguez, B Qu, N Haddad, B Z Lu, D Krishnamurthy, N K Yee, C H Senanayake *Angew. Chem., Int. Ed.* **49** 5879 (2010)
405. V Saini, M S Sigman *J. Am. Chem. Soc.* **134** 11372 (2012)
406. A Chartoire, M Lesieur, L Falivene, A M Z Slawin, L Cavallo, C S J Cazin, S P Nolan *Chem. – Eur. J.* **18** 4517 (2012)
407. L Wu, E Drinkel, F Gaggia, S Capolicchio, A Linden, L Falivene, L Cavallo, R Dorta *Chem. – Eur. J.* **17** 12886 (2011)
408. M G Organ, S Çalimsiz, M Sayah, K H Hoi, A J Lough *Angew. Chem., Int. Ed.* **48** 2383 (2009)
409. R Eskandari, L Navidpour, M Amini, H Shafaroodi, A Shafiee *J. Heterocycl. Chem.* **44** 449 (2007)
410. A K Sahoo, T Oda, Y Nakao, T Hiyama *Adv. Synth. Catal.* **346** 1715 (2004)
411. P A Bethel, A D Campbell, F W Goldberg, P D Kemmitt, G M Lamon, A Suleman *Tetrahedron* **68** 5434 (2012)
412. C F Nising, U K Schmid, M Nieger, S Bräse *J. Org. Chem.* **69** 6830 (2004)
413. M Dowlut, D Mallik, M G Organ *Chem. – Eur. J.* **16** 4279 (2010)
414. H F Sore, C M Boehner, S J F MacDonald, D Norton, D J Fox, D R Spring *Org. Biomol. Chem.* **7** 1068 (2009)
415. C Thiot, C Mioskowski, A Wagner *Eur. J. Org. Chem.* 3219 (2009)
416. C Thiot, M Schmutz, A Wagner, C Mioskowski *Chem. – Eur. J.* **13** 8971 (2007)
417. C I Schilling, O Plietzsch, M Nieger, T Muller, S Bräse *Eur. J. Org. Chem.* 1743 (2011)
418. M A Oberli, S L Buchwald *Org. Lett.* **14** 4606 (2012)
419. G A Molander, B Canturk, L E Kennedy *J. Org. Chem.* **74** 973 (2009)
420. B A Haag, C Sämann, A Jana, P Knochel *Angew. Chem., Int. Ed.* **50** 7290 (2011)
421. H A Chiong, O Daugulis *Org. Lett.* **9** 1449 (2007)
422. J Roger, F Požgan, H Doucet *Adv. Synth. Catal.* **352** 696 (2010)
423. N Laidaoui, A Miloudi, D El Abed, H Doucet *Synthesis* 2553 (2010)
424. A Beladhria, K Beydoun, H B Ammar, R B Salem, H Doucet *Synthesis* **44** 2264 (2012)
425. S Bensaid, H Doucet *ChemSusChem* **5** 1559 (2012)
426. S Bensaid, H Doucet *Tetrahedron* **68** 7655 (2012)
427. J J Dong, J Roger, C Verrier, T Martin, R Le Goff, C Hoarau, H Doucet *Green Chem.* **12** 2053 (2010)
428. Y Fall, C Reynaud, H Doucet, M Santelli *Eur. J. Org. Chem.* 4041 (2009)
429. B Chappell, N Dedman, S Wheeler *Tetrahedron Lett.* **52** 3223 (2011)
430. F M Piller, A Metzger, M A Schade, B A Haag, A Gavryushin, P Knochel *Chem. – Eur. J.* **15** 7192 (2009)
431. S Bernhardt, G Manolikakes, T Kunz, P Knochel *Angew. Chem., Int. Ed.* **50** 9205 (2011)
432. S Calimsi, M Sayah, D Mallik, M G Organ *Angew. Chem., Int. Ed.* **49** 2014 (2010)
433. M A Schade, G Manolikakes, P Knochel *Org. Lett.* **12** 3648 (2010)
434. A Metzger, S Bernhardt, G Manolikakes, P Knochel *Angew. Chem., Int. Ed.* **49** 4665 (2010)
435. S Pu, H Li, G Liu, W Liu, S Cui, C Fan *Tetrahedron* **67** 1438 (2011)
436. D S Surry, X Su, D J Fox, V Franckevicius, S J F Macdonald, D R Spring *Angew. Chem., Int. Ed.* **44** 1870 (2005)
437. P V Khodakovskiy, P K Mykhailiuk, D M Volochnyuk, A A Tolmachev *Synthesis* 979 (2010)
438. I I F Boogaerts, S P Nolan *J. Am. Chem. Soc.* **132** 8858 (2010)
439. H Kawai, Y Sugita, E Tokunaga, H Sato, M Shiro, N Shibata *Chem. Open* **3** 14 (2014)