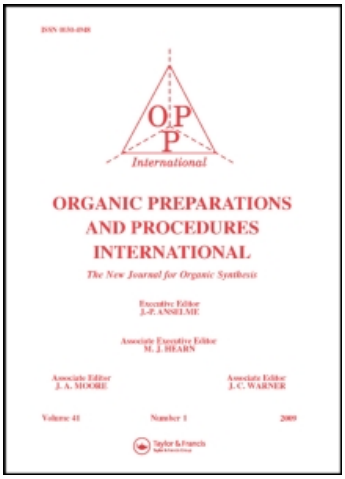

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SYNTHESIS AND SYNTHETIC UTILITY OF 3-ISOXAZOLOLS

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INTRODUCTION

3-Hydroxyisoxazoles (3-isoxazolols) are planar five-membered aromatic heterocycles existing in two tautomeric forms, the 3-hydroxyisoxazole (**1**) and the isoxazolin-3-one (**2**) form. The former tautomeric form is the predominant one as determined from ultraviolet and infrared spectral data,[1,2] and supported by theoretical calculations.[3] Unlike oxazoles, isoxazoles contain a weak N-O bond

1 **2**

Fig. 1

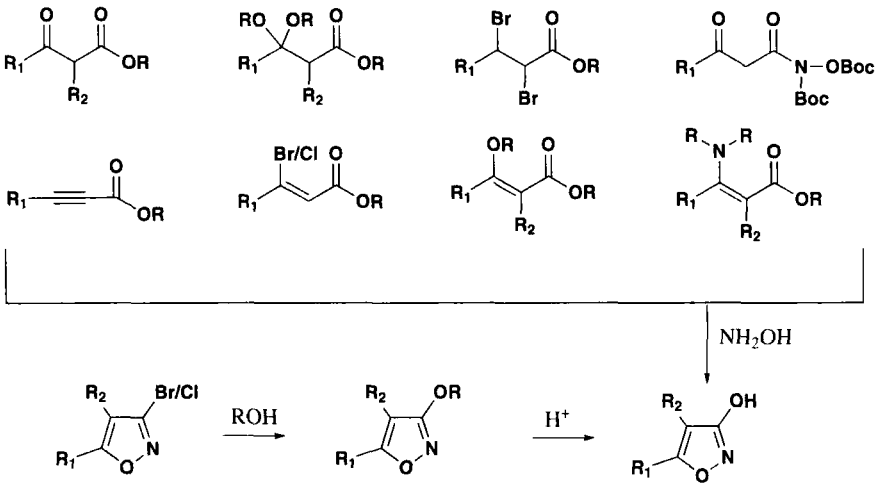
making the ring susceptible to ring-cleaving reactions. An important property of the 3-isoxazolols is the relatively high acidity of the 3-hydroxy group, a property which has made this heterocyclic unit a widely used carboxyl group bioisoster in medicinal chemistry.[4] The pK_a of the simplest compound in this class, 3-isoxazolol (**3**), has been determined by ^{13}C-NMR titration to be 5.85, compared to 7.54 for the sulfur analog 3-isothiazolol (**4**).[4] This difference in acidity is likely to be one of the major factors determining the different biological actions observed for these two structurally related heterocycles.[4]

3 **4**

Fig. 2

The discovery in the mid-nineteen sixties of the naturally occurring 3-isoxazolols muscimol (**5**) and ibotenic acid (**6**) (*Fig. 3*) possessing unique biological activities greatly accelerated the interest in 3-isoxazolols and their use in medicinal chemistry, and consequently the search for versatile

methods for their preparation. The 3-isoxazolol unit is typically incorporated into chemical structures using readily available building blocks containing suitable functional groups in the 4- or 5-positions of this heterocyclic moiety. In this review, we will, however, not focus on the chemistry and reactivity of the various 3-isoxazolol derivatives, but rather focus on the formation of this core heterocycle and, furthermore, on synthetic methods for the introduction of appropriate substituents in the 4- and 5-positions. A number of reactions leading to 3-isoxazolols have been developed, of which the most extensively explored and used are outlined in *Scheme 1*. These reactions include cyclization of β-keto esters and a number of derivatives thereof, as well as the cleavage of 3-alkoxyisoxazoles.



Scheme 1

Although some handbooks on heterocyclic chemistry have briefly dealt with the subject, the formation of monocyclic[5,6] 3-isoxazolols as well as the annulated analogs[5,7] has, to our knowledge, not previously been reviewed. Therefore, our goal is to give an exhaustive coverage of this subject, although we have chosen not to cover the patent literature. In the field of medicinal chemistry, 3-isoxazolols have been quite extensively used, and have been incorporated into a range of more or less complex structures, notably in the design and synthesis of compounds acting at subsets of neurotransmitter receptors in the central nervous system (CNS). Since the discovery of the naturally occurring neuroactive 3-isoxazolols muscimol (**5**) and ibotenic acid (**6**),[8] a wide variety of compounds has been developed using these structures as leads. Thus, muscimol (**5**), which is a nonselective 4-aminobutyric acid (GABA) receptor agonist,[9] has been used as lead for the synthesis of 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol (THIP, **7**), a specific[10] and clinically active[11] $GABA_A$ receptor agonist, and 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol (THPO, **8**), a specific inhibitor of GABA uptake (*Fig. 3*).[12] Whereas ibotenic acid (**6**) interacts nonselectively with all types of (*S*)-glutamate receptors in the CNS,[13] the structural analog (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid [(*S*)-AMPA, **9**][14] acts selectively at the AMPA subtype of ionotropic receptors. Compound **9** has also been

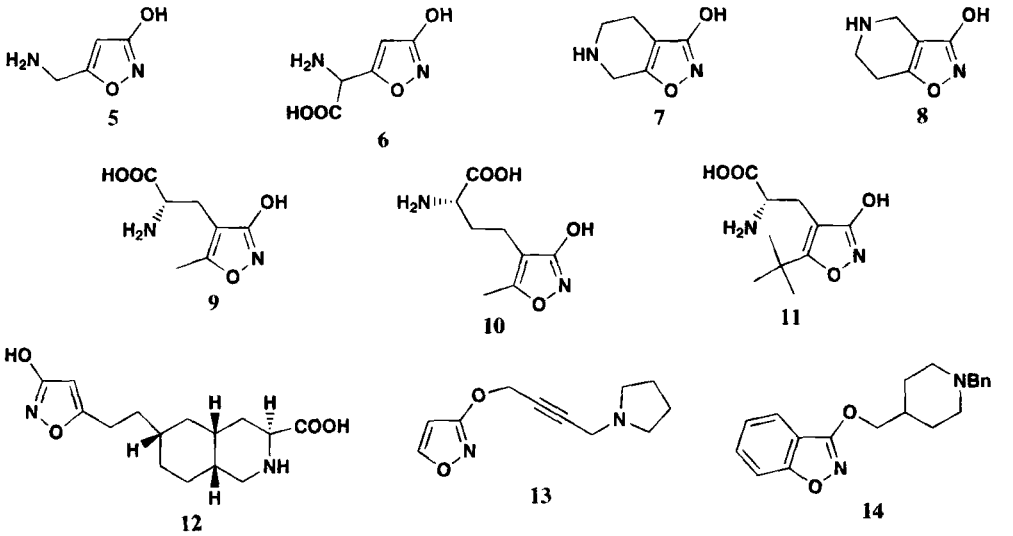


Fig. 3

an important lead compound, resulting in *e.g.* (*S*)-2-amino-4-(3-hydroxy-5-methyl-4-isoxazolyl)butyric acid [(*S*)-homo-AMPA, **10**],[15] a specific metabotropic glutamate receptor ligand, and (*S*)-2-amino-3-(5-*tert*-butyl-3-hydroxy-4-isoxazolyl)propionic acid [(*S*)-ATPA, **11**][16-18] which is a systemically active[19,20] compound with selectivity for the kainic acid receptor GluR5. Examples of neuroactive compounds belonging to other structural classes, but still containing a 3-oxygenated isoxazole moiety, are compounds **12-14**. The decahydroisoquinoline **12** is an AMPA receptor antagonist,[21] **13** is a functionally selective M_3 muscarinic receptor agonist,[22] and the 1,2-benzisoxazole **14** displays activity as an acetylcholinesterase inhibitor.[23]

3-Isoxazolols actually have been incorporated as core structures of compounds in almost all fields of the medicinal chemistry, including the search for novel antibiotics,[24-30] antianaphylactics,[31] anthelmintics,[32] plasma glucose-lowering agents,[33] compounds affecting platelet aggregation,[34-37]

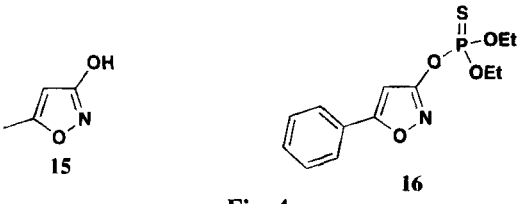
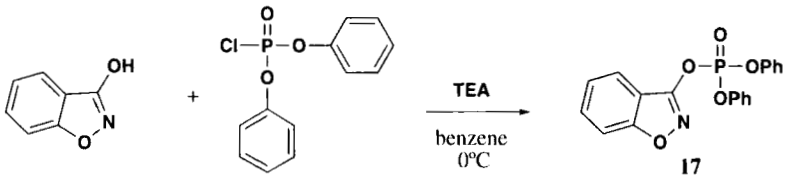


Fig. 4

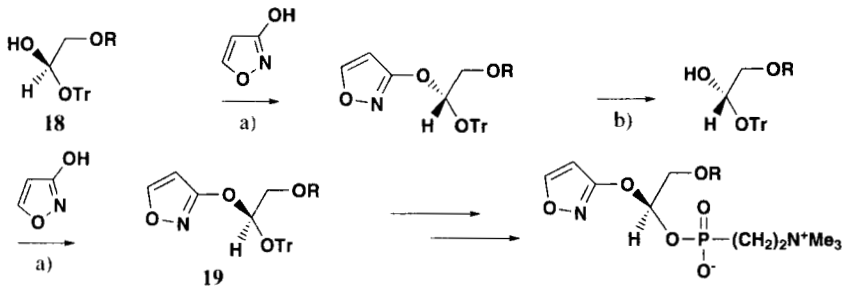
compounds with antihypertensive effect,[38] HIV protease inhibitors,[39] antimalarial agents,[40,41] antiviral agents,[42-44] cholecystokinin antagonists,[45] and compounds for the treatment of asthma.[46,47] An area in which there has been a substantial interest in 3-isoxazolols and other 3-oxygenated isoxazoles is agro-

chemicals.[48-53] Examples of two compounds which have been developed into commercial products are 5-methyl-3-isoxazolol (Tachigaren®, **15**)[52a] and the phosphorothioate isoxathion (Karphos®, **16**),[52b] a soil fungicide and a broadspectrum insecticide, respectively. From a synthetic point of view, an interesting use of the 3-isoxazolol ring is presented by Ueda *et al.*, who developed the peptide coupling activating agent **17** from 1,2-benzisoxazol-3-ol and diphenyl phosphorochloridate (*Scheme 2*).[54,55] Compound **17** activates carboxylic acids efficiently by forming a reactive carboxylic-phosphoric anhydride intermediate in the synthesis of amide and ester bonds.



Scheme 2

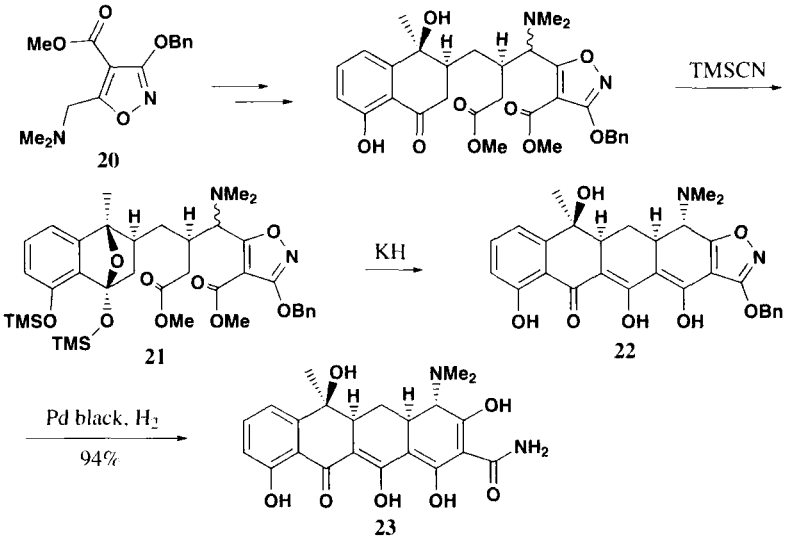
The lability of 3-isoxazolols towards catalytic hydrogenation was utilized by Nakamura *et al.* for the formation of a hydroxyl protecting group (*Scheme 3*). The 3-oxygenated isoxazole moiety was incorporated in **18** via a Mitsunobu reaction inverting the stereochemistry, and after deprotection and



a) PPh_3, dimethyl azodicarboxylate b) H_2, 10% Pd-C, EtOH.

Scheme 3

reintroduction of the isoxazole unit, compound **19** possessing the desired stereochemistry was obtained.[37] These particular properties of isoxazoles were utilized by Stork *et al.* in a different way in the synthesis of tetracyclines.[56,57] Thus, isoxazole **20** constituted one of the rings used to generate **21**, which was cyclized to give the pentacyclic structure **22** (*Scheme 4*). Subsequent hydrogenolysis and debenzylation of the isoxazole part of the molecule then unmasked the β-keto amide function of (±)-12a-deoxytetracycline **23**.[56]

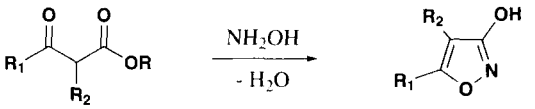


Scheme 4

I. SYNTHESIS OF 3-ISOXAZOLOLS

1. Cyclization of β-Keto Esters

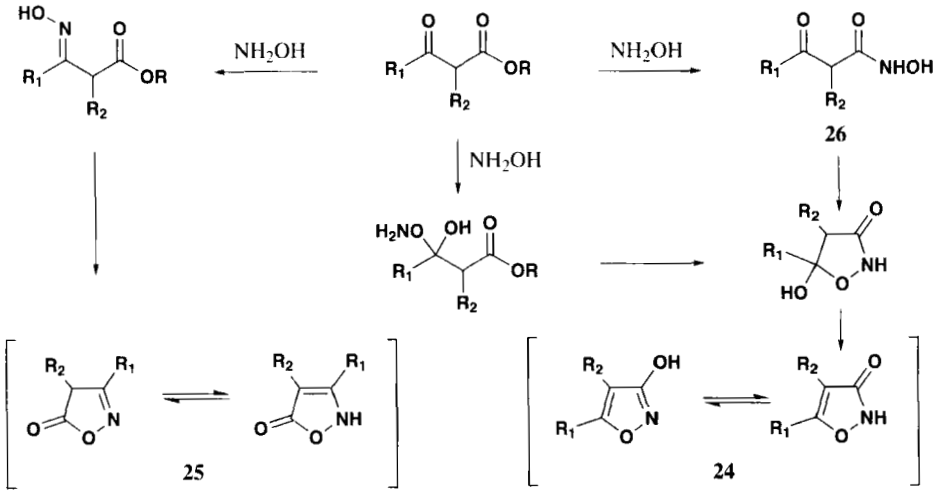
In analogy to the formation of isoxazoles from 1,3-diketones, as first described by Claisen at the end of the nineteenth century,[58,59] isoxazoles containing a 3-hydroxy group can be synthesized by cyclization of β-keto esters with hydroxylamine (*Scheme 5*).[51,60-67] Appropriate substitution of the β-keto ester makes it possible to introduce substituents in the 4-position and/or the 5-position of the ring.



Scheme 5

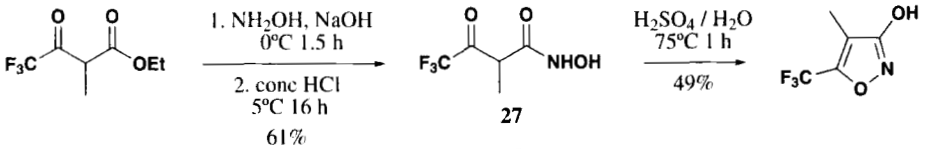
The synthesis of 3-isoxazolols from β-keto esters is the most important and widely used route, although it has one major disadvantage. Thus, due to the several possible ways of attack by hydroxylamine on the β-keto ester this cyclization reaction, in addition to generating the 3-isoxazolol **24**, leads to the formation of substantial amounts of an undesired by-product, the 5-isoxazolone **25** (*Scheme 6*), existing predominantly in this tautomeric form.[68] Furthermore, the distinction between the two isomeric cyclization products has in some cases caused problems, which is reflected in some of the early literature. Since the first reports of cyclization of this type, leading almost exclusively to 5-isoxazolones,[69] great efforts have been made to improve the yields of the 3-isoxazolol isomer. This has been accomplished mainly by varying the reaction conditions or by modifying the structure of the

reacting β-keto ester in a way that directs the attack of hydroxylamine thereby favoring the desired product. The reaction is typically carried out in two consecutive steps. Initial formation of the hydroxamic acid under basic conditions followed by acidification to bring about cyclization and dehydration. The mechanism of the formation of these cyclization products has been studied by ^{13}C NMR,[67] confirming that a β-ketohydroxamic acid **26** (*Scheme 6*) is most likely the intermediate leading to the



Scheme 6

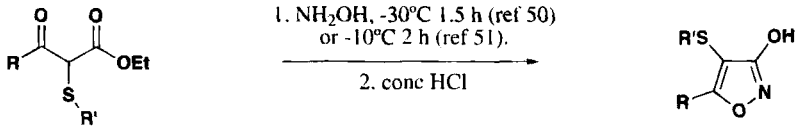
3-isoxazolol. Such hydroxamic acids have in fact been isolated and characterized. This has been the case for the cyclic intermediate **42**[70] (see *Scheme 14*) and the hydroxamic acid **27** which, quite surprisingly, did not cyclize during the treatment with concentrated hydrochloric acid (*Scheme 7*).[71] Furthermore, the following section describes how β-keto esters have been ketalized and subsequently converted into their hydroxamic acids which, after isolation, were cyclized to the 3-isoxazolols.



Scheme 7

A contribution to the understanding of the mechanism was provided by Jacobsen *et al.* who studied the influence of pH in the first step of the reaction.[66] Thus, when the pH was kept at 9-10 before the acidification, the highest yields of 3-isoxazolols were obtained. Moreover, cyclization of methyl acetoacetate at pH 9-10 gave 5-methyl-3-isoxazolol (**15**) in 70% yield (see *Scheme 15*),

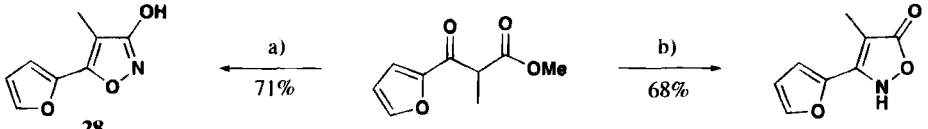
whereas the yields decreased to below 40% and 50% at pH 8 and pH 11, respectively. The authors argued that a pH of 9-10 predominantly generates hydroxylamine in its neutral form, in which the nitrogen atom preferentially attacks the ester carbonyl leading to the β-ketohydroxamic acid. The hydroxy group of hydroxylamine has a pK_a of 13.7,[72] and increasing pH above 10 gradually increases the portion of the more nucleophilic oxide, and, consequently, the amount of product formed by reaction of this oxygen species on *e.g.* the ester carbonyl. The influence of reaction temperature was studied by Sato *et al.* who found that good yields of 3-isoxazolols could be obtained when the hydroxamic acid formation was carried out at low temperature.[51] They greatly improved the outcome of the reaction of *e.g.* ethyl acetoacetate with hydroxylamine from only trace amounts of 5-methyl-3-isoxazolol (**15**) to 72% by lowering the temperature from 0°C to –30°C. A more recent paper, nevertheless, reports a 24% yield of **15** from ethyl acetoacetate, when this step is carried out at 0°C.[73] However, the versatility of the method using low temperature in the initial step was confirmed on a series of substituted β-keto esters, and this report,[51] as well as a very recent study,[50] showed that this procedure can also be used to obtain good yields of 3-isoxazolols with alkylthio substituents at the 4-position (*Scheme 8*). Interestingly, an attempt to cyclize the furyl keto ester **29** using the method[66] based on



Ref 50: R and R' = alkyl (32-72%). R = Me; R' = $MeOCH_2CH_2$ (42%), $HC{\equiv}CCH_2$ (33%), or 2,4-$Cl_2C_6H_3CH_2$ (23%). Ref 51: R = Me; R' = alkyl (yield 39-68%) or Ph (17%).

Scheme 8

constant pH gave the 5-isoxazolone **30** exclusively, whereas the procedure keeping the reaction mixture at –30°C before acidification afforded the desired product **28** in good yield (*Scheme 9*).[74] A



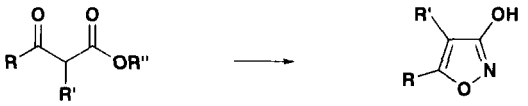
28 **29** **30**

a) 1. NH_2OH, NaOH, $MeOH/H_2O$, -30°C 3 h and 5°C 30 min 2. conc HCl, 5°C 20 h.
b) 1. NH_2OH, aq NaOH, pH 10 ±0.2, rt 2 h 2. conc HCl, 5°C 20 h.

Scheme 9

similar observation was made in the cyclization of ethyl 2-benzoylacetate into 5-phenyl-3-isoxazolol, as the latter method gave an 80% yield of the desired 3-isoxazolol,[51] as compared to 47% obtained at constant pH (see *Table 1*).[75]

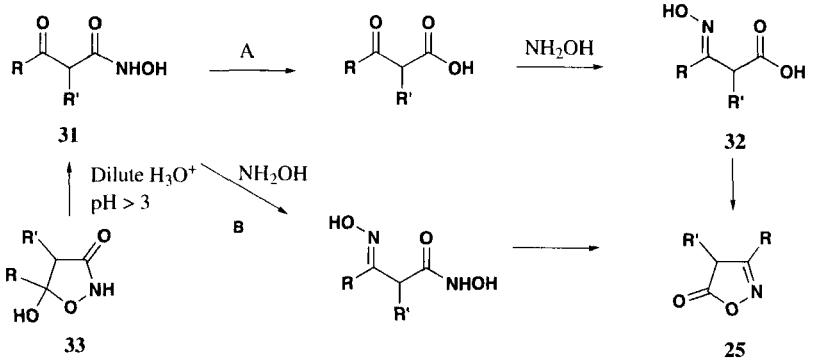
Table 1



R	R'	R''	Yield (%)	Ref
Me	phenyl	Et	5[a]	62
phenyl	H	Me	49	66
phenyl	H	Et	80, 47[b]	51, 75
phenyl	Me	Et	88, 5	51, 62
2-MeO-phenyl	Me	Me	57	78
3-MeO-phenyl	Me	Me	57	78
4-MeO-phenyl	Me	Me	41	78
2-furyl	Me	Me	68	74

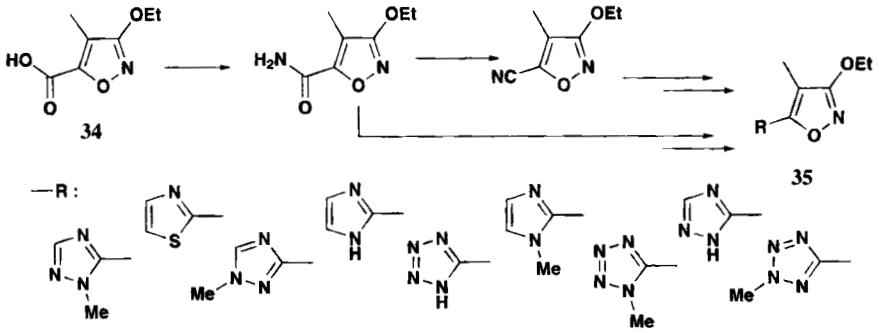
a) 80% 5-isoxazolone. b) In earlier reports only the 5-isoxazolone (ref 62 and 66).

The most important factor determining the outcome of the reaction appears to be the procedure used for the subsequent acidification and ring closure. It thus seems to be crucial, in order to maximize the yield of 3-isoxazolol, that theF reaction mixture is quenched by rapid addition to strong acid rather than a slower acidification. An illustration of this point is the isolation of a 70% yield of 5-methyl-3-isoxazolol (**15**) from methyl acetoacetate and hydroxylamine, by rapid pouring of the reaction mixture into concentrated hydrochloric acid in contrast to only 1% yield after dropwise addition of acid.[66] It has been argued that the hydroxamic acid intermediate, which leads to 3-isoxazolol, can otherwise be converted into the corresponding 5-isoxazolone. Two mechanisms for such a conversion have been suggested (*Scheme 10*).[66,67] One route (A) involves the hydrolysis of the hydroxamic acid **31** to the β-keto acid and subsequent attack by hydroxylamine to form oxime **32**, which cyclizes to 5-isoxazolone **25**.[66] An alternative proposal (route B) suggests that the cyclic intermediate **33**, present before acidification, is hydrolyzed to the β-ketohydroxamic acid **31**, and subsequently attacked by another molecule of hydroxylamine to form a hydroxamic acid oxime, which then cyclizes to **25**.[67] The former proposed mechanism is supported by the observation that hydroxamic acids can be hydrolyzed under acidic conditions,[76,77] whereas the latter theory was supported by ^{13}C NMR spectral evidence of some of the intermediates.[67]



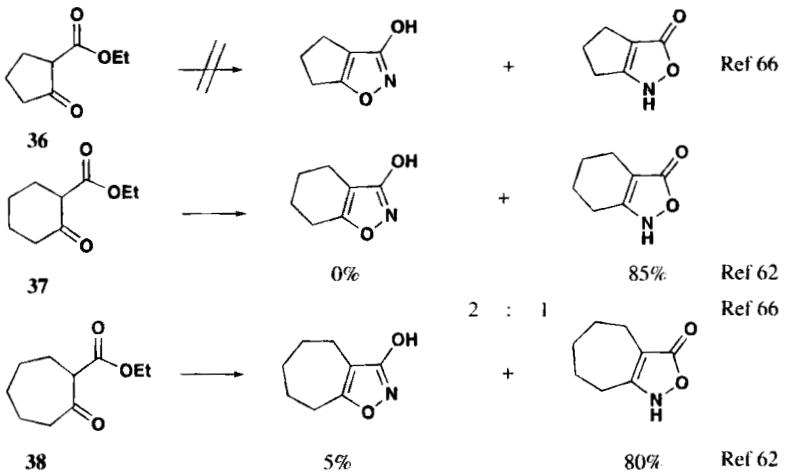
Scheme 10

As mentioned earlier, cyclization of β-keto esters remains the most important method leading to 3-isoxazolols and has been widely used to synthesize compounds with various substituents at the 4-position and/or the 5-position of the ring. However, in the reaction of β-keto esters containing aromatic substituents at the 3-position, the control of regioselectivity has been particularly difficult, and the formation of 3-isoxazolols containing aromatic substituents directly connected to the ring continues to be a major challenge. As can be seen from *Table 1*, analogs containing mainly phenyl groups have so far been synthesized albeit often with limited success. A number of compounds of this type have, however, been prepared by direct cyclization of 2,3-dibromo esters as described in section 7. In a recent report, Bang-Andersen *et al.* avoid the use of direct cyclization of β-keto esters and instead describe the synthesis of a considerable number of isoxazoles **35** containing five-membered heterocyclic 5-substituents by modifying the carboxylic function of the common building block **34** (*Scheme 11*).[79] The isoxazolols **35** were subsequently converted into a series of pharmacologically



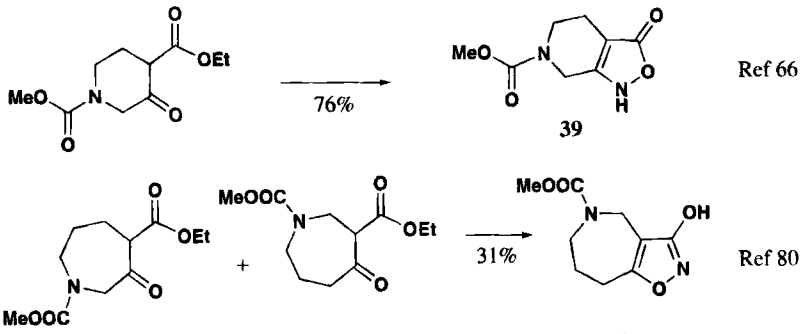
Scheme 11

important analogs of the neuroactive amino acid AMPA (**9**) by a standard multi-step sequence. The formation of bicyclic 3-isoxazolols starting from cyclic β-keto esters has been attempted but, so far, success has been limited (*Scheme 12*). Thus, 2-(ethoxycarbonyl)cyclopentanone **36** does not give any detectable amounts of cyclization product and only cyclopentanone oxime was isolated.[66] An early



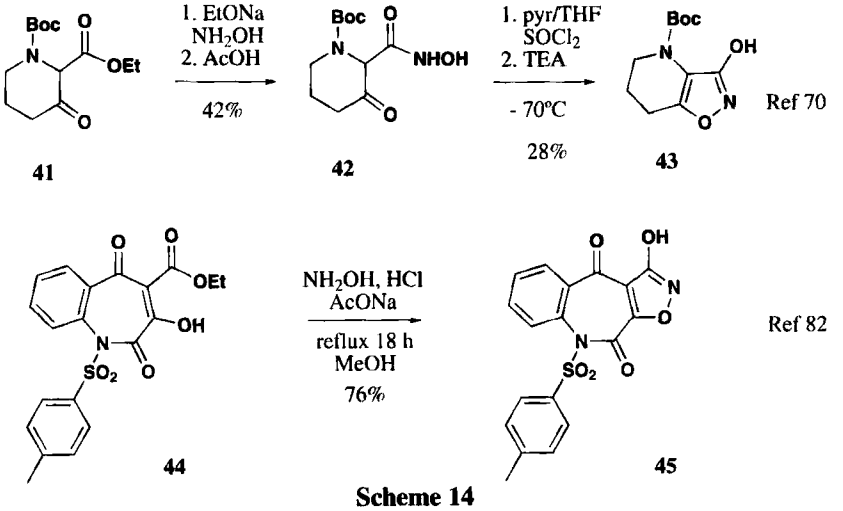
Scheme 12

paper by Jacquier *et al.* indicated that neither 2-(ethoxycarbonyl)cyclohexanone **37** nor 2-(ethoxycarbonyl)cycloheptanone **38** could be transformed into the respective bicyclic 3-isoxazolols,[62] but the use of an improved procedure, keeping pH at 10, **37** gave a 2:1 ratio of 3-isoxazolol to 5-isoxazolone.[66] However, the same method could not be used starting from a six-membered heterocyclic β-keto ester giving a 76% yield of the 5-isoxazolone **39** and only trace amounts of the desired 3-isoxazolol (*Scheme 13*).[66] An illustration of the often unpredictable outcome of these cyclization reactions is the fact that under identical reaction conditions, a mixture of two similar seven-membered β-keto esters



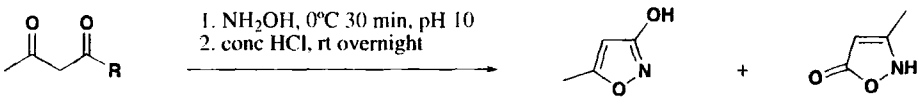
Scheme 13

gave the expected four products, of which 3-isoxazolol **40** was isolated in 31% yield.[80] A rather unusual route was followed to synthesize a related bicyclic compound **43** from β-keto ester **41** (*Scheme 14*).[70] In this case, the hydroxamic acid **42** was isolated and the bicyclic ring system was formed by treating **42** with thionyl chloride at –70°C, a procedure originally developed for the formation of 1,2-benzisoxazolols from salicylic hydroxamic acids (see *Section 10*).[81] In contrast to the synthetic problems discussed above, Waly *et al.* report the synthesis of benzazepine **45** in 76% yield, by simply refluxing the β-keto ester analog **44** with hydroxylamine.[82] Finally, it is interesting to note



Scheme 14

that the reaction of ethyl thiolacetoacetate (**46**) with hydroxylamine gave only 15% of 5-methyl-3-isoxazolol (**15**) together with 40% of the 5-isoxazolone (*Scheme 15*).[66] This represents, to our knowledge, the only example of the use of a β-keto thiol ester as starting material for the synthesis of 3-isoxazolols. For comparison, the same authors obtained a 70% and 61% yield of 3-isoxazolol products under identical conditions for the cyclization of methyl acetoacetate and ethyl acetoacetate, respectively.[66]

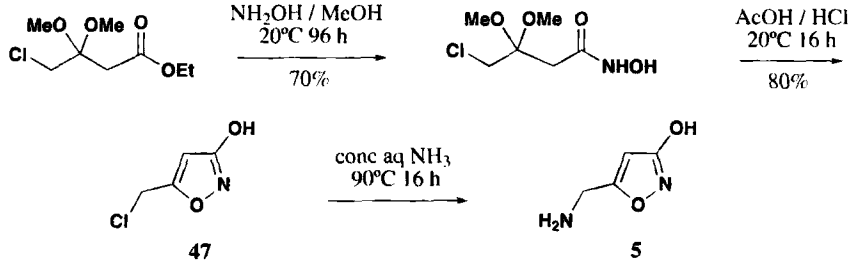


R = SEt, **46**	15%	40%
R = OMe	70%	-
R = OEt	61%	-

Scheme 15

2. Cyclization of β-Ketalized Keto Esters

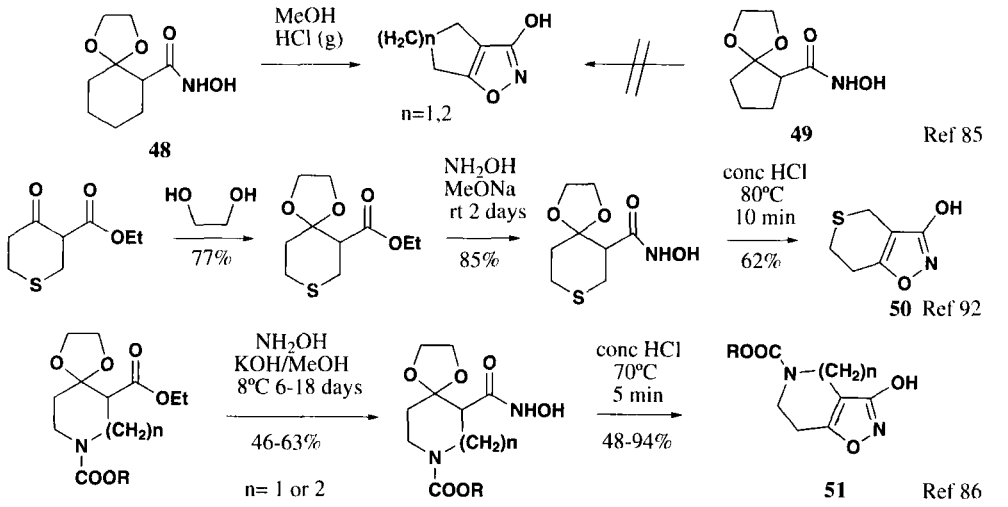
One solution to the problem of controlling regioselectivity of the reaction between β-keto esters and hydroxylamine has been to protect the β-keto functionality as a ketal, thereby directing attack by hydroxylamine to the ester moiety.[50,83-93] 3-Isoxazolol synthesis from these ketalized β-keto esters are carried out in two steps, often involving the isolation and characterization of the corresponding hydroxamic acids; these can be subsequently cyclized by heating in strong acid. This strategy involving ketalization was originally developed for the synthesis of muscimol (**5**) as shown in *Scheme 16*.[83] Interestingly enough, when Konda *et al.* later repeated this sequence, only 24% of the chloromethylisoxazolol **47** was obtained when the cyclization step was performed at 60-80°C for 30



Scheme 16

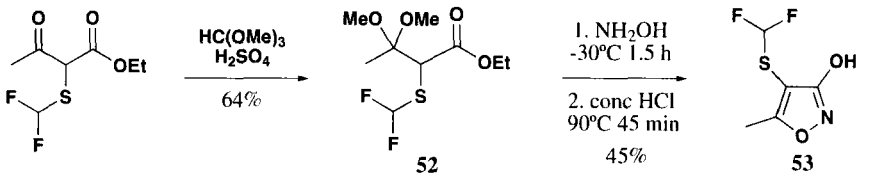
hours,[91] as compared to the 80% yield originally isolated under much less drastic conditions (20°C for 16 hours).[83] Jacquier *et al.* extended the use of ketalization to a series of β-keto esters ketalized with ethylene glycol and containing various substituents at the β-carbon (alkyl, cycloalkyl, or phenyl) and the α-carbon (hydrogen, methyl, or ethyl).[85] The cyclizations were carried out using concentrated hydrochloric acid or either methanol or acetic acid saturated with HCl gas, affording in all cases the 3-isoxazolols in good yield (80-95%). Although the authors failed in their attempts to cyclize hydrox-

amic acid **49** (*Scheme 17*), the reaction was successful in the conversion of the six-membered analog **48**[94] to the corresponding bicyclic 3-isoxazolol in more than 80% yield.[85] Later, our group took advantage of this procedure in the synthesis of some bicyclic structures,[86,89,92] such as compounds **50** and **51**



Scheme 17

as intermediates for the synthesis of muscarinic acetylcholine receptor agonists[92] and bicyclic analogs of GABA, respectively.[86] In a recent report, 3-isoxazolol **53**, containing a 4-difluoromethylthio substituent, could not be synthesized by direct cyclization of the respective β-keto ester, but was successfully prepared from the dimethyl acetal **52** (*Scheme 18*).[50]

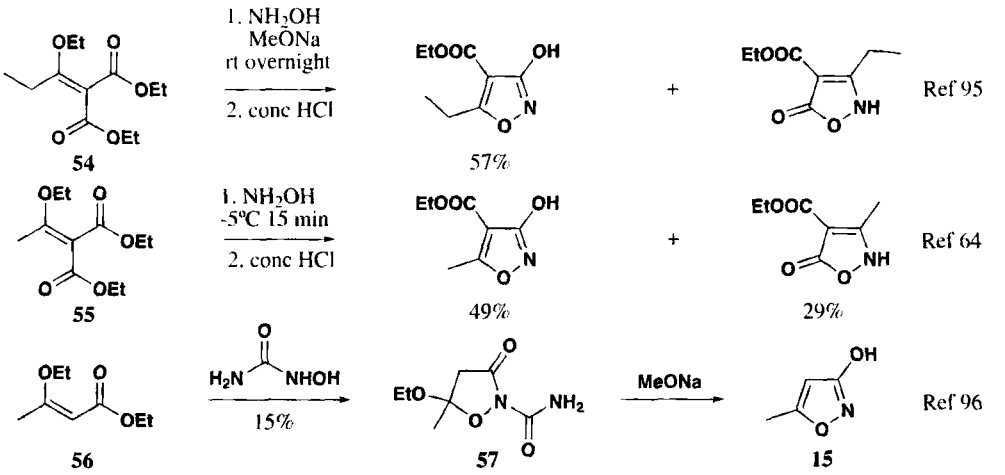


Scheme 18

Despite the great advantage of minimizing or avoiding formation of the 5-isoxazolone isomer, the strategy based on ketalization of the β-keto ester has, so far, not been widely exploited. It has been argued that difficulties in forming ketals of β-keto esters substituted at the α-carbon make the method inapplicable to the synthesis of certain 4-substituted 3-isoxazolols.[51,64] This obstacle is, however, not obvious from the original study by Jacquier *et al.*, who achieved equally good yields from the 4-substituted as well as the unsubstituted β-keto esters.[85] On the other hand, this study reported generally much lower yields for the α-substituted analogs in the step following ketalization, namely the hydroxamic acid formation (10-20% as compared to 20-65% when unsubstituted), perhaps an indication of instability of ketals of this particular type of β-keto esters.

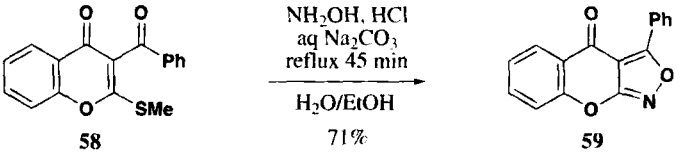
3. Cyclization of β-Enol and β-Enamine Esters

Transformation of the β-keto functionality into enol ethers or enamines with the goal of suppressing formation of the 5-isoxazolone isomer has been attempted, but, so far, only a few examples have been reported with limited success. Enol ethers **54** and **55** have been treated with hydroxylamine, leading to mixtures of 3-isoxazolol and 5-isoxazolone products (*Scheme 19*). Thus, 29% of this latter undesired by-product was obtained from **55**,[64] whereas in the case of **54** the 5-isoxazolone isomer was detected



Scheme 19

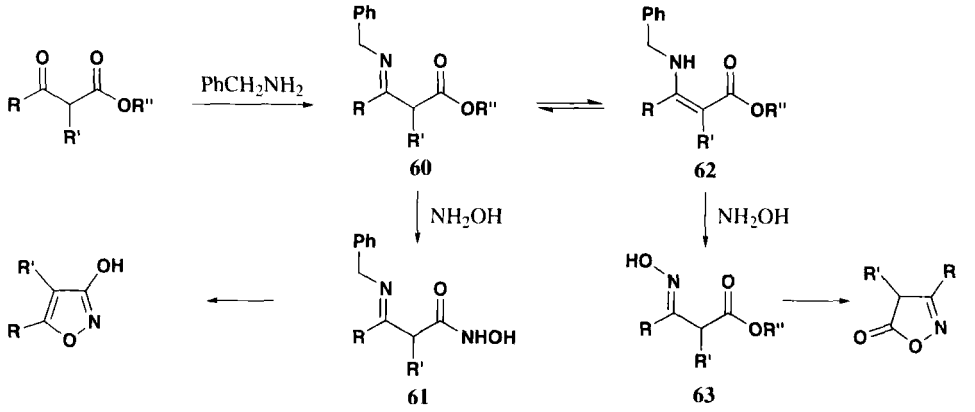
but not isolated.[95] Upon cyclization of **56** with *N*-hydroxyurea, the isolated product turned out to be isoxazoline **57** in poor yield.[96] Elimination of the 5-ethoxy group by treatment of **57** with strong base gave the 3-isoxazole **15** (yield not reported for this step). In analogy with the reaction of enol ethers, the 2-methylthiochromone **58** (*Scheme 20*) reacted with various amines by replacement of the mercapto group.[97] With bidentate reagents such as hydrazine and hydroxylamine, tricyclic compounds



58 59

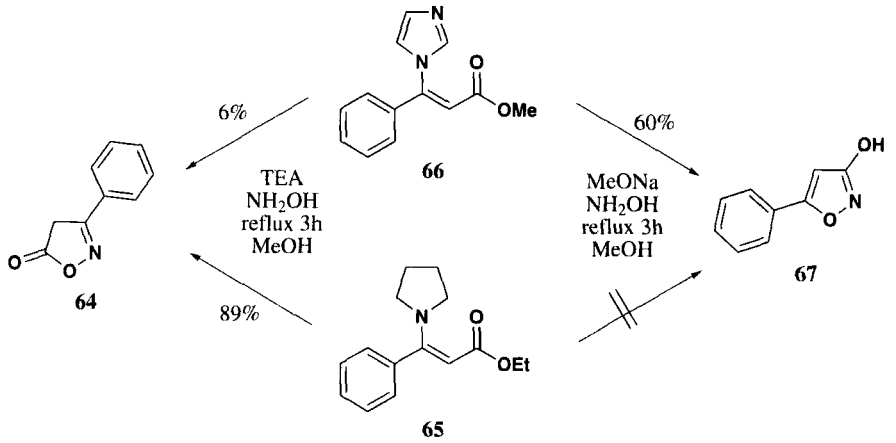
Scheme 20

were formed, and in the latter case the product was the 3-oxygenated isoxazole derivative **59**. Bowden *et al.* in an early study introduced the use of imine protection of the keto group into the field of β-keto ester based 3-isoxazolol synthesis.[64] Upon reaction of β-keto esters with benzylamine, they claimed the isolation of the imines **60** and the ring closure of these intermediates *via* **61** to give 3-isoxazolols (*Scheme 21*). It was, however, later shown that the intermediate product was in fact the enamine **62**, which when treated with hydroxylamine did not give the hydroxamic acid but the oxime **63** instead.[65]



Scheme 21

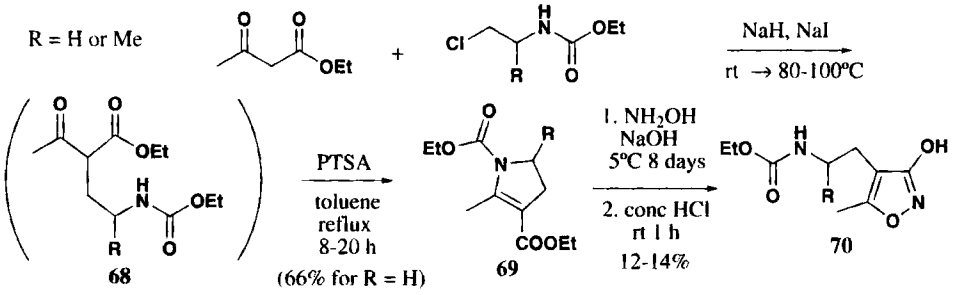
Consequently, acidification afforded exclusively the 5-isoxazolone and not the 3-isoxazolol as claimed earlier.[64] Some interesting information regarding the reactivity of the β-amino-α,β-unsaturated esters can be deduced from a study by Kashima *et al.*, who described the reaction between hydroxylamine and a series of cinnamic esters containing β-enamino groups derived from nitrogen-containing heterocycles (*Scheme 22*).[72] The use of the weak base, triethylamine, led in all cases to the formation of 5-isoxazolone **64** exclusively, the highest yields being obtained from substrate **65** containing the electron-donating 1-pyrrolidinyl group. With the use of a large excess of sodium



Scheme 22

methoxide, hydroxylamine is deprotonated generating a strong oxygen nucleophile. Under these conditions, enamino ester **66**, containing the electron-withdrawing 1-imidazolyl group, gave 3-isoxazolol **67** as the only product. In contrast, when **65** was treated under identical conditions, only 5-isoxazolone **64** was isolated, albeit in very low yield (3%). Additionally, when the above method was

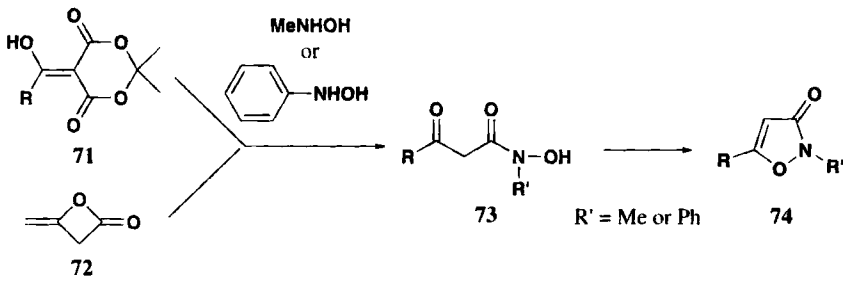
applied to the synthesis of the soil fungicide 5-methyl-3-isoxazolol (**15**) from methyl 3-(1-imidazolyl)crotonate, only a modest 19% yield of the desired compound was obtained.[72] Finally, there is an example of cyclic enamines **69** being transformed into 3-isoxazolols **70** containing an amino group as the 4-substituent (*Scheme 23*).[87] Enamines **69** were initially identified as one of two products following the alkylation of ethyl acetoacetate. The other product was the acyclic compound **68**, and to complete the ring closure into **69**, the product mixture was refluxed in toluene with 4-toluenesulfonic acid. However, the subsequent conversions into isoxazolols **70** were quite unsatisfactory and gave only poor yields.



Scheme 23

4. Cyclization of N,O-Protected Hydroxamic Acids

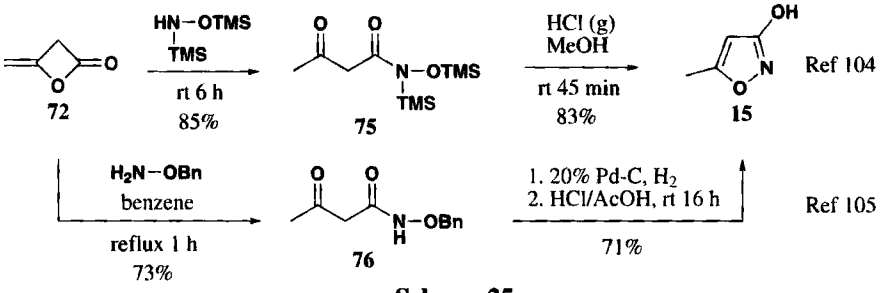
To address the problem of regioselectivity described above, it would be desirable to form an N,O-diprotected β-ketohydroxamic acid, which by deprotection and cyclization would lead exclusively to the formation of the desired 5-substituted 3-isoxazolol. The synthesis of N-methyl and N-phenyl β-ketohydroxamic acids **73** from the reaction of diketene (**72**) or acylated Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione)[98,99] **71** with N-alkylhydroxylamine have been described, as well as their transformation into N-alkyl isoxazolin-3-ones **74** (*Scheme 24*).[100-103] However, due to the



Scheme 24

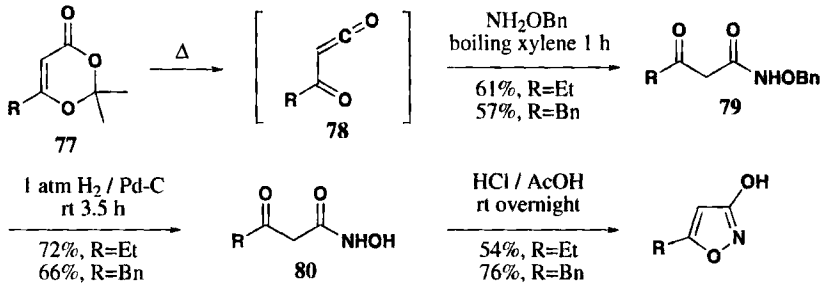
stability of the C-N bond, such heterocyclic products **74** cannot be converted easily into the unprotected 3-isoxazolols. To the best of our knowledge, the only synthesis of a 3-isoxazolol from a N,O-diprotected hydroxamic acid is, until recently, the synthesis of 5-methyl-3-isoxazolol (**15**) by cycliza-

tion of **75** (*Scheme 25*).[104] In this simple and successful sequence, diketene (**72**) was reacted with *N,O-bis*(trimethylsilyl)hydroxylamine to give the N,O-diprotected hydroxamic acid **75** which gave **15**



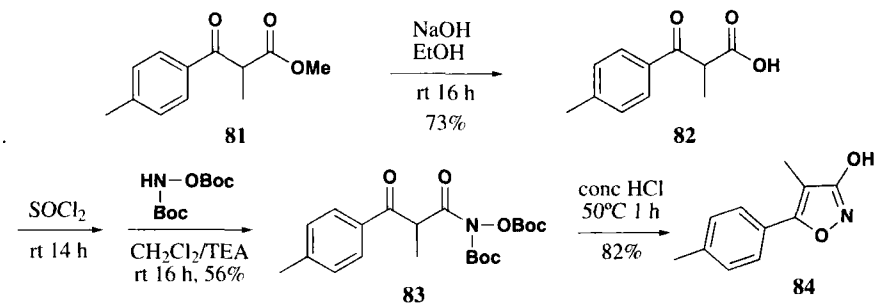
Scheme 25

when treated with methanolic HCl. The similar reaction of **72** with *O*-benzylhydroxylamine gave hydroxamic acid **76**, which after a debenzylation step was cyclized to the 3-isoxazolol.[105] These methods are, however, not generally useful since the lack of analogs of diketene (**72**) has limited it to the synthesis of 3-isoxazolol **15**. Furthermore, it is worth noting that it is not superior to the direct cyclization of **72** with hydroxylamine. Thus, although the 5-isoxazolone was first reported to be the product of this reaction,[105,106] Jacobsen *et al.* in fact succeeded in preparing **15** from diketene (**72**) in 71% yield.[66] Sato *et al.* used acylketene **78**, formed by heating 2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-ones **77**, to acylate *O*-benzylhydroxylamine thereby obtaining the O-benzyl protected hydroxamic acids **79** (*Scheme 26*).[107] After catalytic hydrogenolysis of the benzyl group, the free hydroxamic acids **80** were converted into the 3-isoxazolols by treatment with hydrogen chloride in acetic acid. We recently presented another approach to the diprotected hydroxamic acids in which the β-keto ester **81** was first



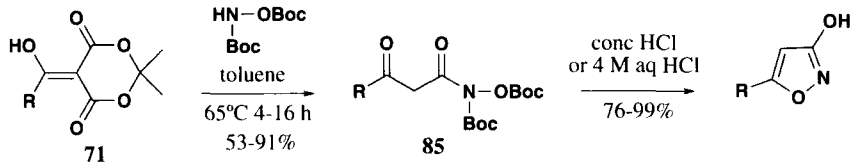
Scheme 26

converted into the β-ketocarboxylic acid **82** by hydrolysis in aqueous NaOH (*Scheme 27*).[108] Formation of the corresponding acid chloride using $SOCl_2$ and subsequent *in situ* reaction with *N,O*-diBoc hydroxylamine[109] gave β-ketohydroxamic acid **83**. Treatment of **83** with concentrated hydrochloric acid afforded the expected 3-isoxazolol **84** as the only product in 82% yield. Attempts to generalize



Scheme 27

this procedure were, however, not successful due to very rapid decarboxylation of the β-keto carboxylic acid, in contrast to **82** which underwent decarboxylation only slowly after several days. Using another strategy, we exploited the high reactivity of acyl Meldrum's acids towards nucleophilic attack. Acyl Meldrum's acids **71** are known to react with alcohols and thereby forming β-keto esters.[98,99,110-112] Similarly, aminolyses with *N,O*-diBoc hydroxylamine resulted in good yields of the corresponding β-ketohydroxamic acids **85** (*Scheme 28*), and subsequent treatment with either 4 M or concentrated hydrochloric acid cleaved both Boc protecting groups and cyclized the hydroxamic acid



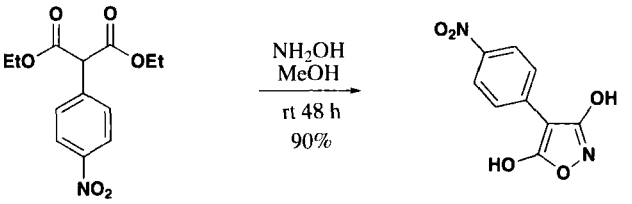
R = alkyl, cycloalkyl, benzyl, or phenyl.

Scheme 28

to give 5-substituted-3-isoxazolols in high yields.[108] Although acyl Meldrum's acids are easily accessible from Meldrum's acid with well-known acylation reagents,[100,110,111,113-117] a problem in relation to the synthesis of 3-isoxazolols is the fact that they are not easily prepared from aromatic carboxylic acids, of which only few examples exist.[100,113,118] Finally, this novel method, so far, does not allow for the introduction of substituents in the 4-position of the 3-isoxazolol ring.

5. Cyclization of Malonic Acid Esters

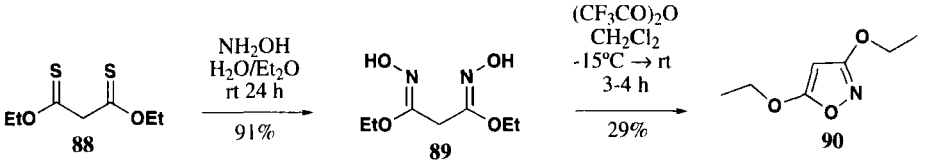
In the case of the reaction of hydroxylamine with malonic acid esters, the problem of regioselectivity is absent, as symmetrical malonates lead only to the 4-substituted 3,5-dihydroxyisoxazoles.[119-123] These compounds have been prepared and studied in detail by Zvilichovsky's group who found them to be very strong organic acids.[121] As an example, 4-(4-nitrophenyl)-3,5-dihydroxyisoxazole (**87**) (*Scheme 29*), formed by the condensation of hydroxylamine with diethyl 2-(4-nitrophenyl)malonate (**86**), is reported to have a very low pK_a value (–0.1).[121] Hartke *et al.* studied the



86 87

Scheme 29

reaction of diethyl dithiomalonate (**88**) with amines and bidentate nitrogen nucleophiles.[124] Compound **88** reacted readily with hydroxylamine to give **89** (*Scheme 30*), from which 3,5-diethoxyisoxazole (**90**) was prepared in a ring closure reaction expedited by the addition of an equimolar amount of trifluoroacetic anhydride.

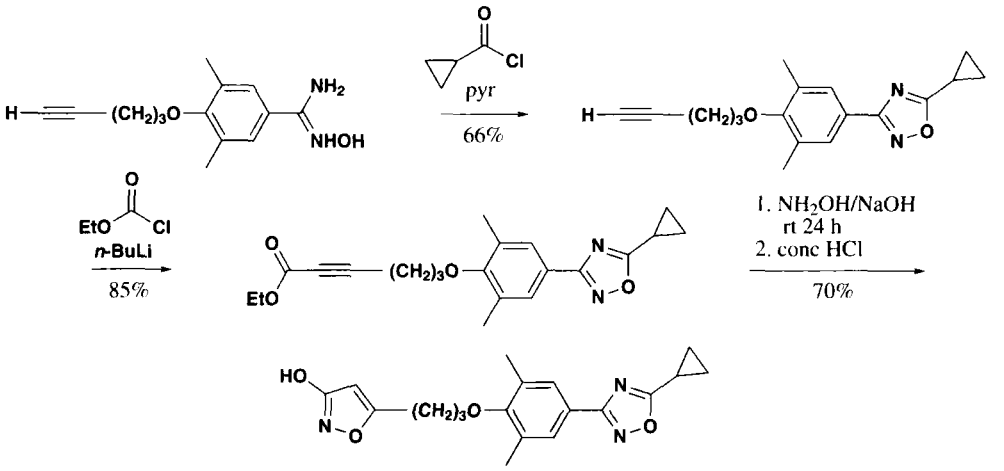


88 89 90

Scheme 30

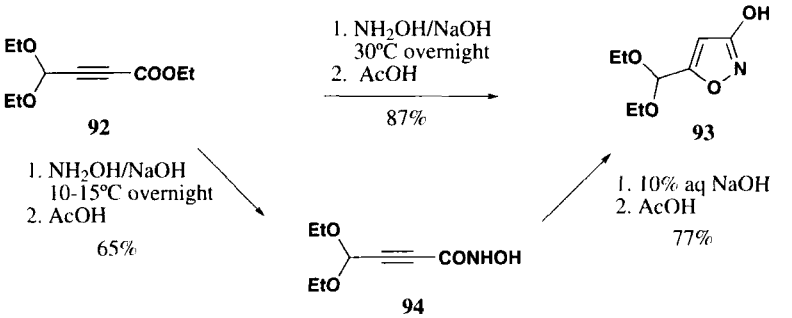
6. Cyclization of Acetylenic Esters

Acetylenic esters are known to be good substrates for 3-isoxazolol synthesis. Hydroxylamine initially attacks these unsaturated esters, and the hydroxamic acid formed subsequently adds to the triple bond leading to ring formation. The reaction is typically carried out using excess sodium hydroxide in alcohol at room temperature followed by acidification with concentrated hydrochloric acid and extraction or precipitation of the product. A recent example of this procedure is the synthesis of compound **91**, an intermediate synthesized in the search for novel antiviral compounds against common cold (*Scheme 31*).[43] This reaction has been applied to acetylenes having both aliphatic and aromatic substituents at the triple bond (*Table 2*). The latter group is exemplified by a number of phenyl analogs, but since other aromatic and heteroaromatic substrates have not yet been included, it remains to be seen whether the use of such acetylene esters can replace the unsuccessful cyclization of the corresponding β-keto esters. Some information about the reactivity of aliphatic acetylenic esters towards hydroxylamine is, however, available. The group of Nakamura showed that it is possible to control the formation of hydroxamic acids and 3-isoxazolols by varying the reaction temperature.[125,128] Thus, treatment of **92** with hydroxylamine under basic conditions overnight at 30°C gave 3-isoxazolol **93**, whereas reaction under the same conditions at 5-10°C unexpectedly resulted in the isolation of the hydroxamic acids **94** (*Scheme 32*).[128] It was therefore concluded, that under



91

Scheme 31



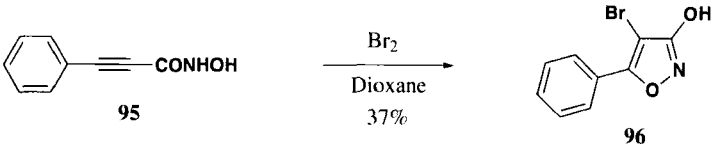
Scheme 32

basic conditions hydroxylamine addition to the triple bond is less favorable than hydroxamic acid formation. McCarry *et al.* reported that isolation of the hydroxamic acid depends on the pH of the reaction mixture.[127] After treatment of ethyl 4-chlorotetrolate with hydroxylamine in basic methanol for 15 min at –35°C, quenching with 6M hydrochloric acid led to the corresponding hydroxamic acid whereas adjustment of the pH to 8.5-9 and stirring at room temperature for 10 hours gave the 3-isoxazolol in 41% yield (see *Table 2*). They further studied the pH dependence of the cyclization of this particular hydroxamic acid, and found the optimal yield of the 3-isoxazolol occurs at pH 8.5 to 9 and no product formation at a pH above 10.5 or below 6.5.[127] Ten years earlier, a report had actually argued that formation of 3-isoxazolol (**3**) from ethyl propiolate is favored at high pH (> 11), whereas a lower pH yields the corresponding 5-isoxazolone.[130]

Table 2

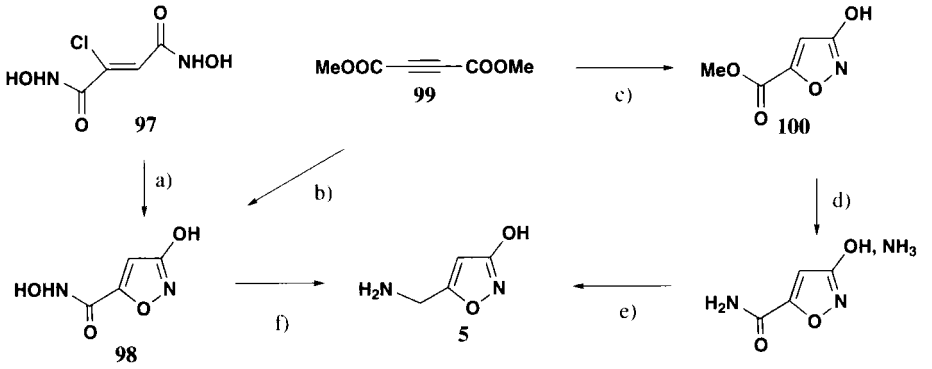
R	R'	Yield (%)	Ref
H	Et	59	125
Me	Me	92	125
cyclopropyl	Et	70	126
$ClCH_2$	Et	41	127
$(EtO)_2CH$	Et	87	128
phenyl	Et	87, 88	125,129
2-Cl-phenyl	Me	83	129
4-Cl-phenyl	Et	52	125
2,6-diCl-phenyl	Et	85	129
4-MeO-phenyl	Et	48	125
$4\text{-}NO_2$-phenyl	Et	77	125

Another way to cyclize acetylenic hydroxamic acids was reported by Zborovskii *et al.*, who accomplished the cyclization of compound **95** in the presence of bromine.[131] Under these conditions, bromine was introduced into the 4-position to give 4-bromo-5-phenyl-3-isoxazolol (**96**) rather than the otherwise expected cyclization product (*Scheme 33*). An alternative to the use of hydroxylamine is *N*-hydroxyurea which in contrast to the former reagent apparently reacts exclusively at the hydroxy



Scheme 33

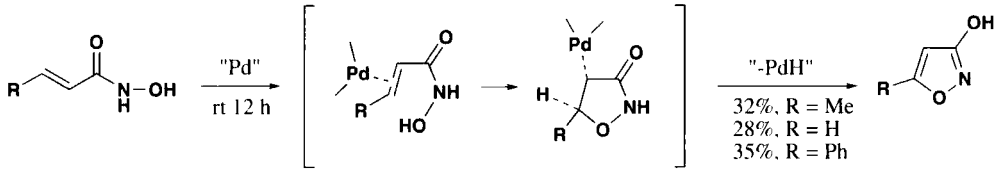
group. It can thus be considered as an N-protected hydroxylamine derivative and has as such been utilized in the synthesis of 3-isoxazolols from acetylenic esters.[132-136] Dimethyl acetylenedicarboxylate (**99**) has been reacted with either reagent, yielding the isoxazolols **98** (51-55%)[134,137] and **100** (60-72%)[135,136] upon treatment with hydroxylamine (two equivalents) and hydroxyurea, respectively (*Scheme 34*). A comparable yield of **98** (56%) was obtained when the chlorofumardihydroxamic acid **97** was cyclized under basic reaction conditions.[137] Jäger *et al.* considered the hydroxamic acid **98** a



a) aq NaOH, rt overnight (56%, ref 137). b) NH_2OH/NaOH, rt overnight (51-55%, ref 134, 137).
c) *N*-hydroxyurea, 5 eq TEA, rt 1h (60%, ref 135) / *N*-hydroxyurea, 1.1 eq DBU (72% ref 136).
d) conc NH_3 2h (quantitative yield, ref 135). e) 8.6 eq borane-dimethylsulfide, reflux 8h (51%, ref 135).
f) 8.6 eq borane-dimethylsulfide, reflux 22h (32%, ref 134).

Scheme 34

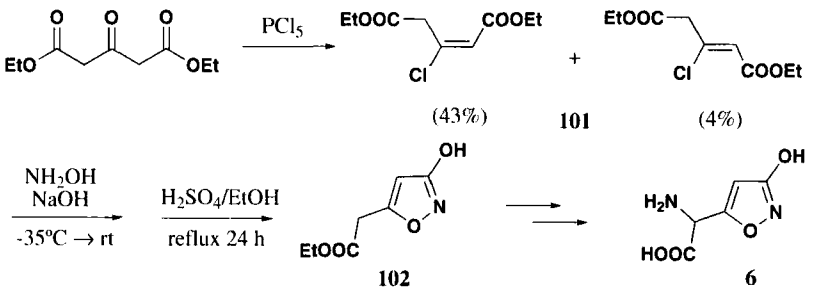
potential precursor for muscimol (**5**) by reduction of the hydroxamic acid group to amine, but were unable to reproduce the previously reported synthesis of **98** from dimethyl acetylenedicarboxylate (**99**) and hydroxylamine. Instead, they succeeded in synthesizing **5** from the ester **100** by reaction with ammonia and subsequent reduction of the amide upon treatment with borane dimethylsulfide complex.[135] Subsequently, Welch *et al.* reported that it was indeed possible to reduce **98** using borane dimethyl sulfide complex, and obtained muscimol (**5**) in an overall 17% yield from dimethyl acetylenedicarboxylate (**99**).[134] The synthesis of **100** was improved to 72% by replacing triethylamine with the stronger base 1,8-diazabicyclo[5.4.0]undecene-7 (DBU).[136] Furthermore, these authors treated **100** with either methylamine, isopropylamine, pyrrolidine, or morpholine to give the respective muscimol (**5**) analogs.[136] Finally, it should be noted that a brief communication has described the cyclization of an olefinic hydroxamic acid by treatment with lithium chloropalladite and triethylamine (*Scheme 35*).[138] In contrast to the direct cyclization product, which would be the partially saturated isoxazoline, 5-substituted 3-isoxazolols were isolated.



Scheme 35

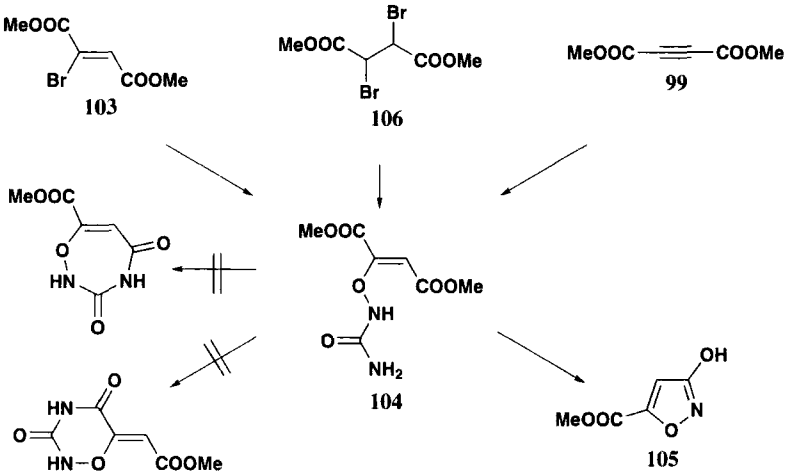
7. Cyclization of β-Halo-α,β-unsaturated Esters and 2,3-Dibromo Esters

In a synthesis of the naturally occurring neuroactive compound ibotenic acid (**6**), intermediate **102** was formed by cyclization of diethyl 3-chloroglutaconate **101** (*Scheme 36*).[139] The *cis*- and *trans*-isomers of **101** were reacted separately with hydroxylamine in the presence of excess sodium



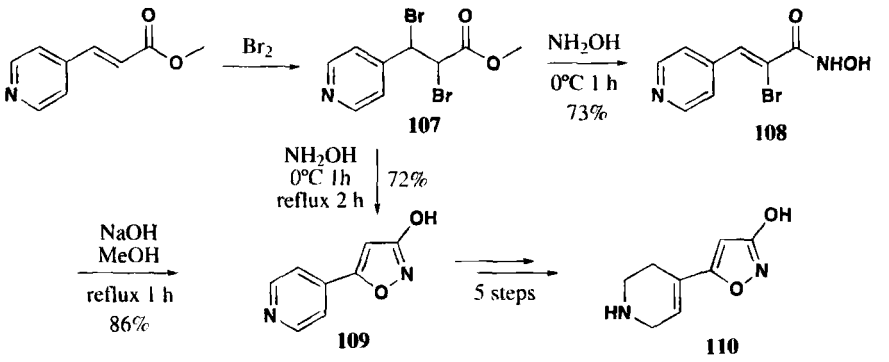
Scheme 36

hydroxide to form the isoxazole ring. Subsequent esterification with ethanol gave **102** in overall yields of 60% and 53%, respectively. In a similar fashion, dimethyl 2-bromofumarate (**103**) provided isoxazole **105** upon treatment with *N*-hydroxyurea (*Scheme 37*).[132] In all reactions between *N*-hydroxyurea and either dimethyl acetylenedicarboxylate (**99**), 2,3-dibromosuccinate (**106**), or dimethyl 2-bromofumarate (**103**), the acyclic product **104** was isolated. Although other possible cyclization products were



Scheme 37

suggested from this common intermediate, isoxazole **105** was nevertheless the only cyclic product detected.[132] A recent example of the use of a 2,3-dibromo ester as starting material is the synthesis of analogs of the $GABA_A$ receptor agonist 5-(4-piperidyl)-3-isoxazolol (4-PIOL) such as **110** (*Scheme 38*).[140] For 3-isoxazolols bearing heteroaromatic 5-substituents, cyclization of β-keto esters has proven particularly troublesome, and attempts to prepare isoxazole **109** directly using that methodology failed



Scheme 38

and yielded only the 5-isoxazolone isomer. Instead, **109** was successfully synthesized from the dibromo ester **107** in good yield.[140] Furthermore, when the reaction mixture was neutralized with concentrated hydrogen bromide after keeping it at 0°C, the intermediate hydroxamic acid **108** could be isolated and characterized, indicating that under basic conditions, the reaction proceeds *via* an initial dehydrobromination. Intermediate **108** was subsequently cyclized to give **109** in 86% yield. It is evident that dibromo esters represent a suitable alternative to β-keto esters as substrates for 3-isoxazolols. This has been particularly useful when aromatic 5-substituents are desired, as can be seen from *Table 3*. The only major disadvantage of this methodology is the requirement of many synthetic steps, and also that it has not provided a method for the introduction of 4-substituents into the isoxazole ring.

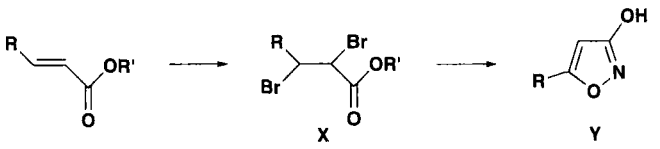
8. 3-Isoxazolols from 3-Alkoxyisoxazoles

3-Alkoxyisoxazoles have been reported to provide 3-isoxazolols by acid cleavage of the alkoxy groups in numerous cases. Such alkoxy derivatives are synthesized primarily from 3-halo substituted isoxazoles or by alkylating the hydroxy group of 3-isoxazolols. Since the preparation of 3-isoxazolols from 3-alkoxyisoxazols has been of great importance, the following sections will, in addition to this subject, address the formation of 3-alkoxyisoxazoles from 3-haloisoxazoles as well as the synthesis of this latter group of compounds.

a) Hydrolysis of 3-Alkoxyisoxazoles

Although 3-alkoxyisoxazoles continues to be an important source of 3-isoxazolols, very few methods for their cleavage have been developed. Hydrolysis using strong acids has been nearly the exclusive method of choice, and the generally harsh reaction conditions require great stability of the functional groups present. Aqueous hydrochloric acid has been used in a number of cases,[15,79,95,140,144,145] but the reagent most frequently applied is hydrogen bromide. Depending on the substrate, slightly different procedures have been used, and a few examples of these are given in *Scheme 39*. There are, however, alternatives to cleavage by strong acids. Thus, it was discovered that hydrolysis took place under mild basic conditions in a mixture of ammonia and tin(IV)chloride

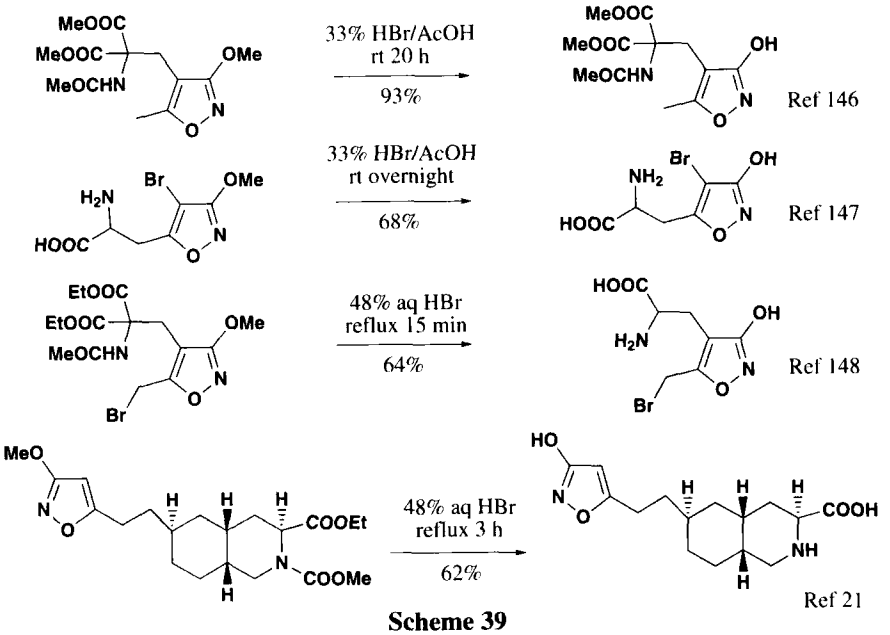
Table 3



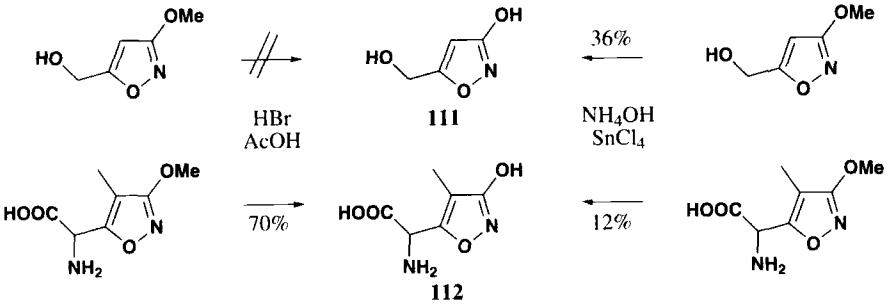
Entry	R	R'	X Yield (%)	Y Yield (%)	Ref
1		Et	28	57	141[a]
2		Me	91	63	74[b]
3		Me	87	56	74[b]
4		Me	90	72	140[c]
5		Me	94	58	74[b]
6		Me	94	43	74[b]
7		Me	91	75	142[d]
8		Me	68	49	142[d]
9		Me	84	73	142[d]
10		Me	95[e]	61	142[f]

a) 1. Br_2 /AcOH, rt 18h. 2. Hydroxyurea/NaOH, rt → reflux. 3. conc HCl. b) 1. HBr/Br_2 /AcOH, 60°C 4h → rt overnight. 2. NH_2OH/NaOH, 0°C 1h → reflux 2h. 3. conc HCl. c) 1. HBr/Br_2 /AcOH, rt 30 min → 60°C 3h. 2. NH_2OH/NaOH, 0°C 1h → reflux 2h. 3. conc HCl. d) 1. Br_2 /CCl_4, rt overnight. 2. NH_2OH/NaOH, 0°C 1h → reflux 6h. 3. 4M HCl, 0°C 30 min. e) Br_2 , $CHCl_3$, rt overnight (ref 143). f) 1. Hydroxyurea/NaOH, rt 6h → reflux 20h. 2. conc HCl.

(Scheme 40).[149] An example is compound **111** which could not be obtained from 5-hydroxymethyl-3-methoxyisoxazole using hydrogen bromide in glacial acetic acid, whereas it was isolated in 36% yield after heating at 105°C for 2-3 days in aqueous ammonia and $SnCl_4$. In contrast, the final step in the synthesis of 4-methyl ibotenic acid (**112**) from the corresponding O-methyl derivative was far more effectively accomplished using acid deprotection rather than aqueous ammonia and $SnCl_4$.[149] It should be noted that O-benzyl groups have been cleaved by use of catalytic hydrogenation[150-152] or, alternatively, hydrogen bromide[153] or hydrogen chloride[140,154] in different solvents.



Scheme 39

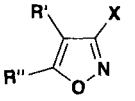


Scheme 40

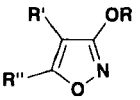
b) Synthesis of 3-Alkoxyisoxazoles

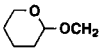
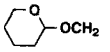
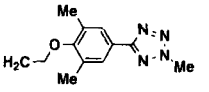
3-Alkoxyisoxazoles are quite readily formed from 3-haloisoxazoles by substitution of the halogen atom with the desired alkoxy group upon treatment with the appropriate alcohol under strongly basic conditions. As exemplified by the synthesis of the 2,5-diisoxazolyltetrahydrofuran **114** from 3-bromoisoxazole **113** (*Scheme 41*),[155] this transformation is typically carried out upon refluxing the isoxazole with the required alcohol in aqueous KOH. Several compounds containing various functional groups including base-stable protecting groups such as THPO and Boc group have been synthesized using this methodology (*Table 4*). To prepare monocyclic alkoxyisoxazoles, the corresponding bromo derivatives are most frequently chosen. However, for the synthesis of bicyclic benzisoxazoles

Table 4

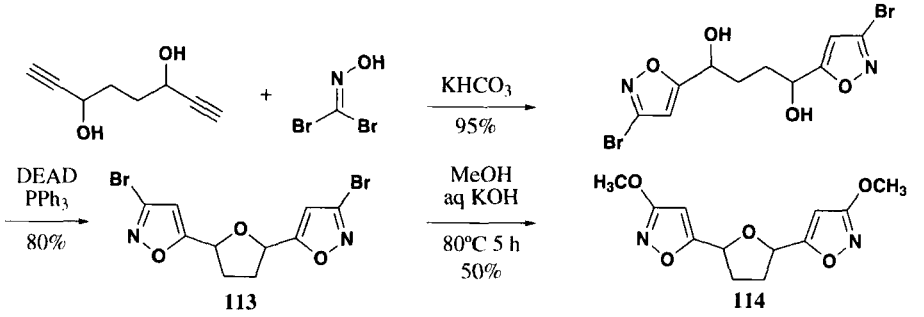


ROH
KOH, reflux



Entry	X	R'	R''	R	Reaction Time (h)	Yield (%)	Ref
1	Br	Me	CH_2OH	Me	12	58	162
2	Br	CH_2OH	Me	Me	12	89	163,162
3	Br	COOH	Me	Me	96	61	164
4	Br	H	Me	Me	24	57[a]	64
5	Br	H	Ph	Me	4	95	165
6	Br	H	Ph	Et	4	90	165
7	Br	H	COOH	Me	4	79	21
8	Cl	H	COOH	Me	4	82	64
9	Br	H	CH_2NH_2	Me	48	66-68	166,167
10	Br	H	COOH	Bn	2	45	153
11	Br	H		Me	2	60	28
12	Br	H		$(CH_2)_2OH$	4[b]	45	28
13	Br	H		Me[c]	6	81	42

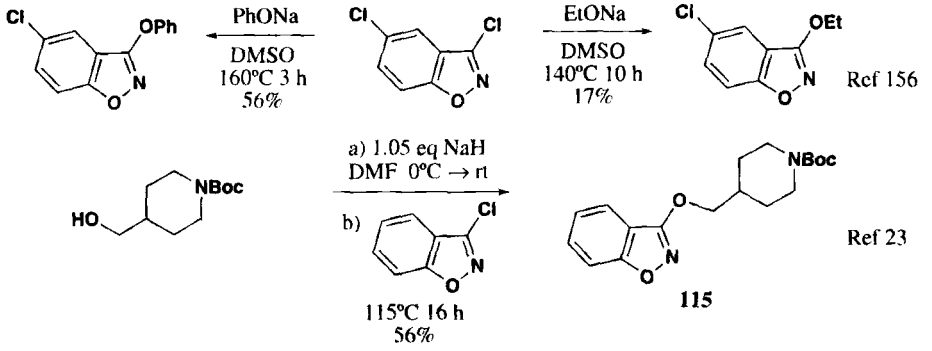
a) Calculated yield of crude product. b) 80°C. c) Substitution using ethanol and *n*-propanol was also reported.



113 114

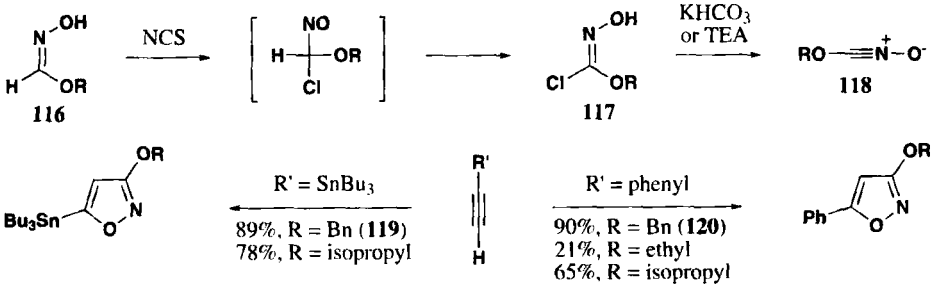
Scheme 41

the 3-chloro compounds have been treated with sodium alkoxides in aprotic solvents such as DMSO and DMF (*Scheme 42*).[23,156,157] This is exemplified for compound **115**, which was found to be a suitable bioisoster for the benzoyl functionality in a particular class of acetylcholinesterase inhibitors.[23] In this connection, it should be noted that 3-halobenzisoxazoles have not only been reacted with alcohols to form 3-alkoxyisoxazoles, but also with other nucleophiles such as amines, azide, and hydroxide to provide the respective substitution products.[23,158-161]



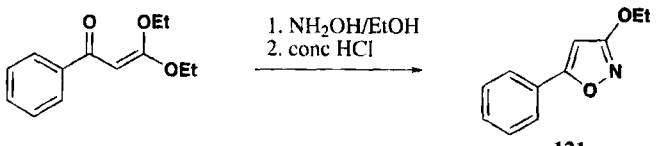
Scheme 42

Alternative procedures for the preparation of 3-alkoxyisoxazoles have been described. Thus, the use of alkoxynitrile oxides in cycloaddition reactions with either olefins or acetylenes has been reported to yield 3-alkoxyisoxazolines and 3-alkoxyisoxazoles, respectively.[168] Alkoxynitrile oxides **118** are dipolar compounds formed by chlorination of alkyl formhydroximates **116** with *N*-chlorosuccinimide (NCS) followed by dehydrochlorination of the chlorinated oxime **117** in the presence of base as for example potassium bicarbonate or triethylamine (*Scheme 43*).[168] A one-pot reaction was developed in which formhydroximate **116**, NCS, base, and the acetylenic substrate were heated in ethyl



Scheme 43

acetate at 48°C for 34-48 hours (*Scheme 43*). Monosubstituted substrates gave the 5-substituted isoxazoles predominantly, but in other cases mixtures of regioisomers were obtained. Of particular interest in the context of 3-isoxazolols are the two compounds **119** and **120**, having a 3-benzyloxy substituent, since compounds of this type are generally easy to debenzylate to give the free 3-isoxazolols. In analogy to the formation of 5-amino-3-isoxazolols from cyanoketene acetals (*Section 9*), benzoylketene acetal has been reported by Stachel to afford 3-ethoxy-5-phenylisoxazole (**121**) upon treatment with hydroxylamine (*Scheme 44*).[169]

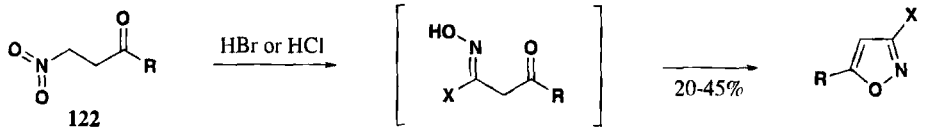


121

Scheme 44

c) Synthesis of 3-Haloisoxazoles

The initial approach to 3-bromoisoxazoles and 3-chloroisoxazoles proceeded *via* cyclization of β-nitroketones **122** by heating in hydrobromic acid or hydrochloric acid, respectively (*Scheme 45*).[170]

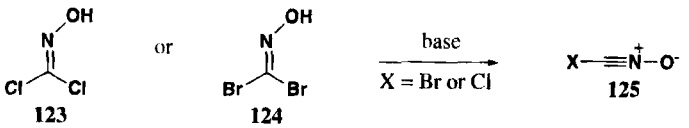


122

R = Me, Et, or Ph; X = Br or Cl

Scheme 45

The yields obtained using this methodology are generally low,[32,170-172] and it has therefore not been recognized as a general synthetic route. In contrast, the most important and widely used procedure for the synthesis of 3-haloisoxazoles is based on 1,3-dipolar cycloaddition of a halonitrile oxide **125** with acetylenes in a reaction analogous to that described for the synthesis of isoxazolidines from alkenes. In the first reports, acetylenic Grignard reagents were the substrates,[2,165] generating exclusively 4-unsubstituted 3-haloisoxazoles, but its extensive use on terminal as well as disubstituted alkynes has

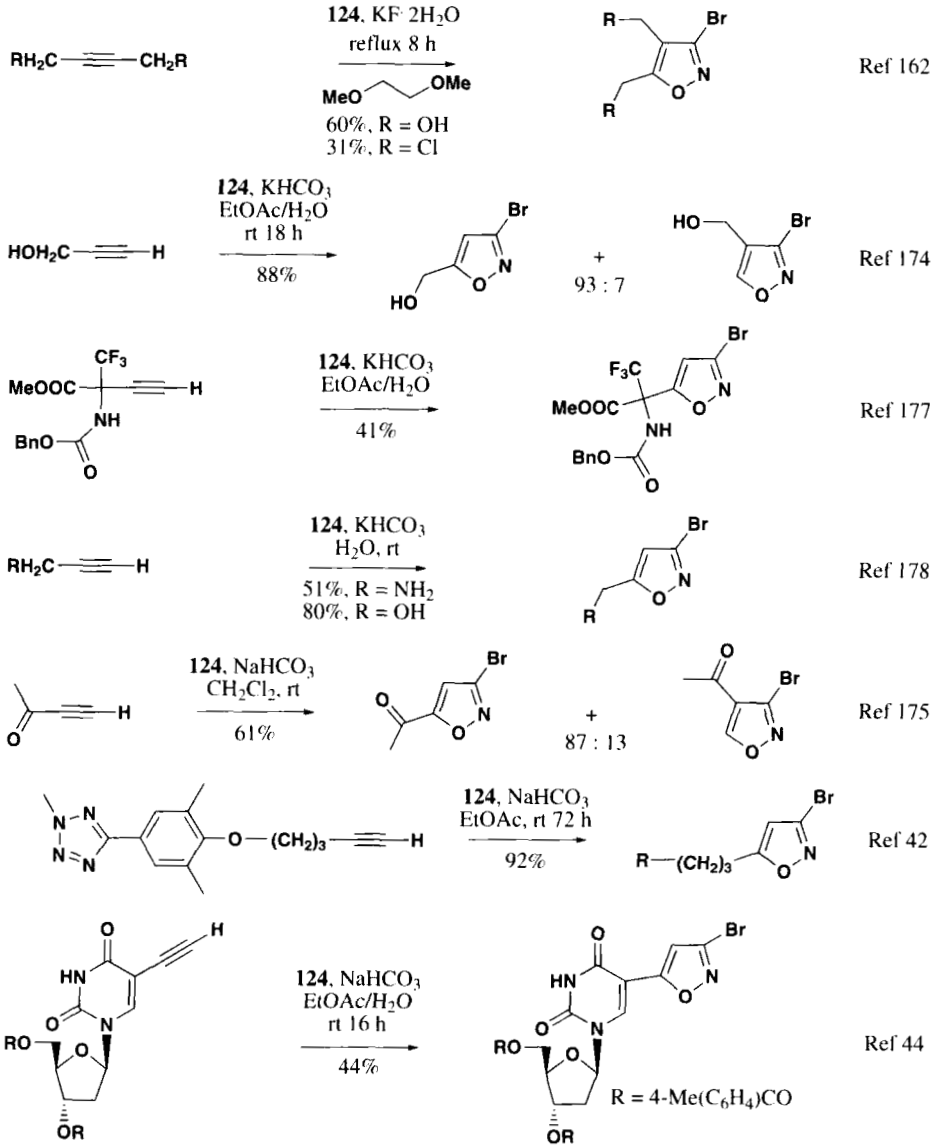


123 124 125

Scheme 46

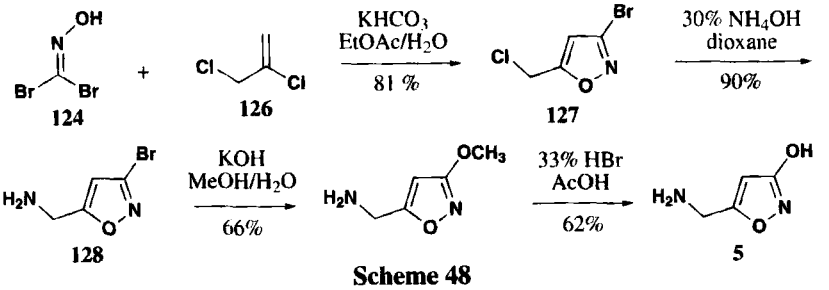
demonstrated its value as a general method to the formation of 3-haloisoxazoles. The reactive species, a halonitrile oxide **125**, typically is formed *in situ* from the dihaloformoxime by reaction with a weak base. Both dichloroformoxime **123** and dibromoformoxime **124** are used to generate the nitrile oxide, yielding 3-chloroisoxazoles[64,173] and 3-bromoisoxazoles,[42,44,155,162,164,167,174-182] respectively. Chloronitroacetyl chloride has also been suggested as a source of chloronitrile oxide when treated with sodium bicarbonate in dichloromethane.[183] Nevertheless, dibromoformoxime **124** is the most commonly used reagent, one reason being the higher toxicity of dichloroform oxime. As illustrated in *Scheme 47*, the reaction is compatible with a number of functional groups, and may be carried out in mixed organic-aqueous solvent systems as well as under anhydrous conditions. The limitation of this method is that it is not as useful for nonactivated disubstituted alkynes. A method has, however, been described in

which potassium fluoride dihydrate is used as a hydrohalide scavenger keeping the reaction mixture acidic thereby improving the reactivity of the formed nitrile oxide according to the authors.[162] The yields achieved are moderate to good, but when the acetylene used is unsymmetrical a mixture of the two possible regioisomers is typically obtained. However, terminal acetylenes react with the nitrile oxides in high regioselectivity, practically generating only the 5-substituted 3-haloisoxazoles.[174] An alternative to the reaction on acetylenes is the use of olefins containing substituents on the double



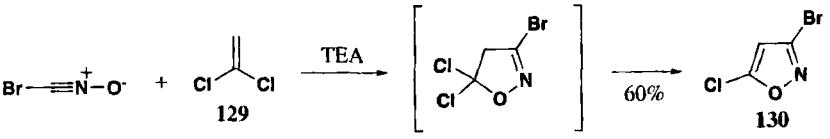
Scheme 47

bond which can be easily eliminated, thereby yielding the isoxazole and not the otherwise expected isoxazoline. As shown in *Scheme 48*, the chloro substituted olefin **126** led to 3-chloro-5-chloromethylisoxazole (**127**) by 1,3-dipolar cycloaddition with bromonitrile oxide followed by dehydrochlorination. Compound **127** was reacted with ammonia to give **128**, which after refluxing 24 hours in methanolic potassium hydroxide and treatment of the intermediate 3-methoxyisoxazole with hydrobromic acid led to muscimol (**5**) in an overall yield of 30% (*Scheme 48*).[166] An identical cycloaddition and elimination mechanism was used for the synthesis of 3-bromo-5-chloroisoxazole



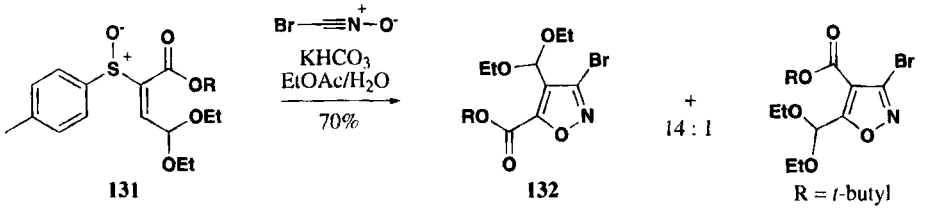
Scheme 48

(**130**) from 1,1-dichloroethylene (**129**).[184] In a recent report, the tolylsulfinyl group of **131** gave enhanced dipolarophile reactivity as well as high regioselectivity. The isoxazoline intermediate could



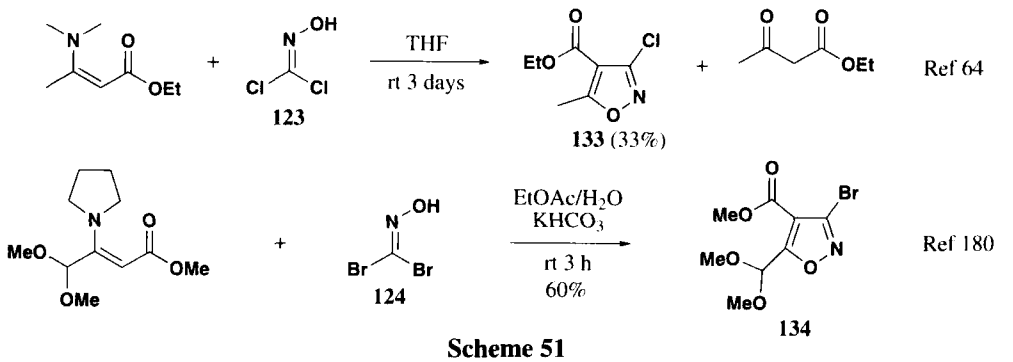
Scheme 49

not be detected and compound **132** was isolated in 70% yield (*Scheme 50*). In two cases, enamines have been substrate in dipolar cycloaddition reactions which after elimination of the amino moieties

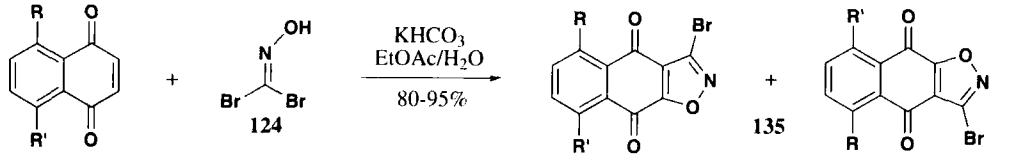


Scheme 50

gave isoxazoles **133** and **134** (*Scheme 51*).[64,180] Finally, bromonitrile oxide was reacted with naphthoquinones to give the corresponding naphthoisoxazoles **135** as mixtures of the two possible regioisomers or, when symmetrically substituted naphtoquinones were used, as single products (*Scheme 52*).[181]



Scheme 51



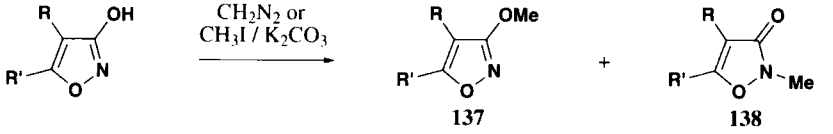
Scheme 52

N-Methyl-4-isoxazolin-3-ones have been used as starting materials for the synthesis of 3-chloroisoxazoles.[185,186] Thus, it was found that heating of **136** with phosphorus oxychloride converted these compounds into the corresponding 3-chloroisoxazoles (*Scheme 53*) by an unknown mechanism.[185] Acceptable yields of 3-chloroisoxazoles were obtained, except for a bicyclic and a 5-ethoxycarbonylmethyl substituted analog, for which yields of only 18% and 5%, respectively were isolated.

R = H, Me, COOEt; R' = Me, COOMe, $(CH_2)_2$COOMe, CH=CHCOOMe.

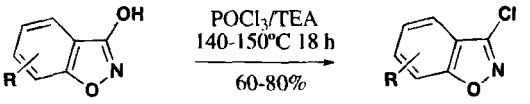
Scheme 53

The transformation into 3-chloroisoxazoles has relevance in light of the difficulties related to the introduction of protection groups at the 3-hydroxy group of 3-isoxazolols. Thus, alkylation or acylation of this hydroxy function result in mixtures of 3-O- (**137**) and 2-N-alkylated (**138**) or, analogously, acylated compounds (*Scheme 54*).[73,151] As the 2-N-alkylated isoxazoles are inherently difficult to



Scheme 54

deprotect, the conversion into 3-chloroisoxazoles represent a potential use of these often useless by-products. A procedure for the direct synthesis of 3-chloroisoxazole by chlorination and oxidation of isoxazoline by refluxing with $CuCl_2$ in DMSO has been described, but no yield for the transformation was given.[187] Finally, if desired, it is possible to proceed in the opposite direction from 3-hydroxyisoxazole to 3-haloisoxazole,[157-159,188-190] as demonstrated by Böshagen, who converted a series of 1,2-benzisoxazoles **139** into the corresponding 3-chloroisoxazoles **140** by heating in a mixture of phosphorous oxychloride and triethylamine (*Scheme 55*).[156] A later study demonstrated an increase of the

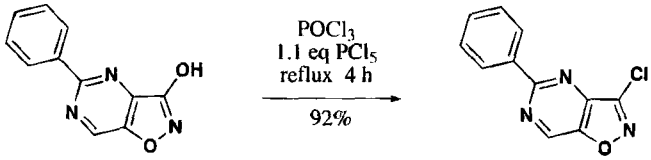


139 **140**

R = Cl, I, NO_2, MeO, Me, $MeSO_2$, MeCOO.

Scheme 55

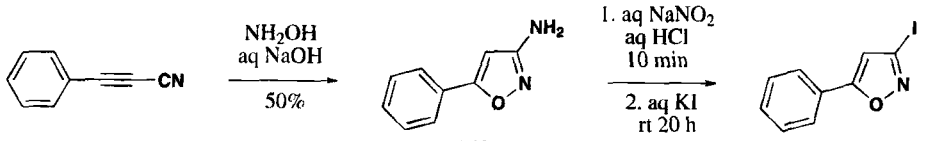
yield of 3-chloroisoxazole by using pyridine hydrochloride and phosphoric acid.[189] Furthermore, a mixture of phosphorus pentaoxide and phosphorus chloride was used for the conversion of isoxazolopyrimidine **141** into **142** in 92% yield (*Scheme 56*).[190] To complete the discussion of 3-haloisoxazoles, there is a single report on the synthesis of a 3-iodoisoxazole, 3-iodo-5-phenylisoxazole (**144**),



141 **142**

Scheme 56

by diazotization of the 3-amino derivative **143**,[125] and subsequent treatment with potassium iodide (*Scheme 57*).[32]

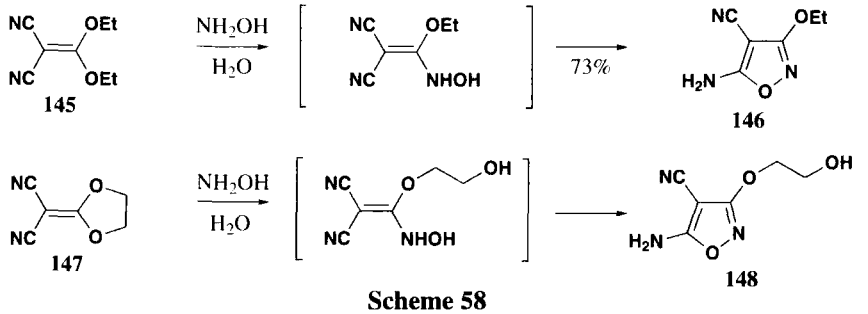


143 **144**

Scheme 57

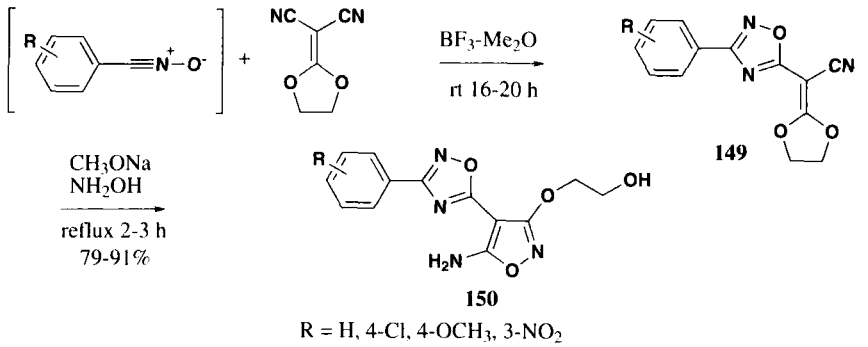
9. Synthesis of 5-Amino-3-isoxazolols

In an early study, Middleton *et al.* focused on the reaction of dicyanoketene acetals with amines, and found that upon reaction with bases such as hydrazine, amidines, and hydroxylamine, they gave pyrazoles, pyrimidines, and 3-alkoxyisoxazoles, respectively (*Scheme 58*).[191] Thus, the



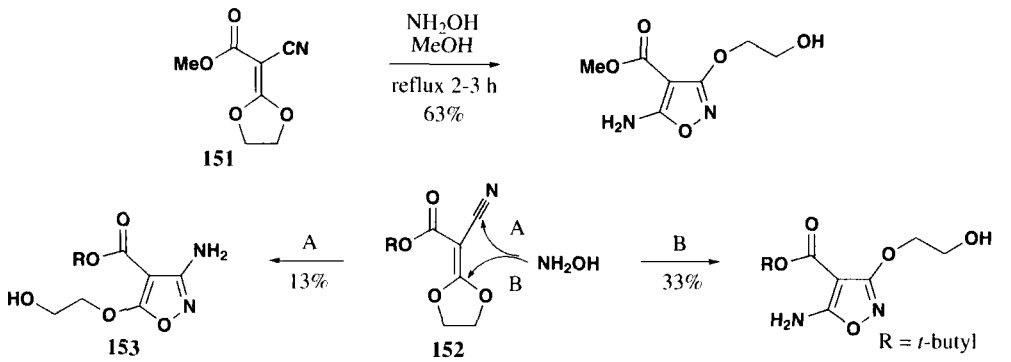
Scheme 58

diethyl acetal **145** gave an exothermic reaction with hydroxylamine, and 5-amino-4-cyano-3-isoxazole (**146**) was reported to be the main product. Similarly, the ethylene acetal **147** gave the 3-(2-hydroxyethoxy)isoxazole **148** (yield not given). More recently, the same methodology was applied to the substituted cyanoketene ethylene acetal **149** (*Scheme 59*). The 1,2,4-oxadiazole nucleus of **149** is formed in the first step in which the nitrile oxide attacks the cyano group of dicyanoketene ethylene acetal, leaving the acetal group intact until the reaction with hydroxylamine to afford good overall



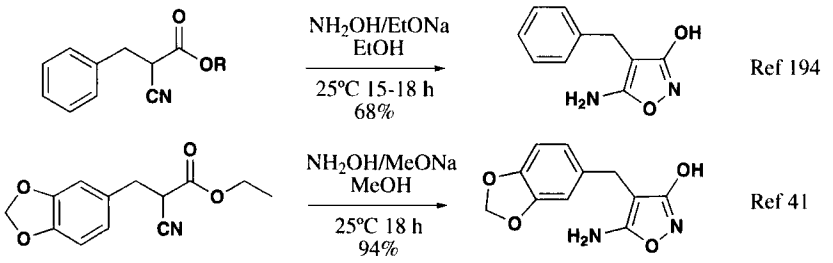
Scheme 59

yields of the 5-amino 3-isoxazolols **150**. Similar results were obtained by Neidlein *et al.* from the reaction of compound **151** (*Scheme 60*).[192] However, when using the *tert*-butyl ester **152** as substrate, they obtained a mixture of two products; the formation of **153** was explained to be the result of reaction of hydroxylamine with the cyano group.



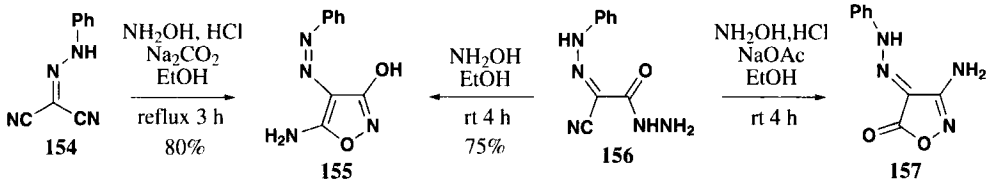
Scheme 60

When treated with hydroxylamine under basic reaction conditions, α-cyanoacetates give the corresponding 5-amino-3-isoxazolols as exemplified in *Scheme 61*.[41,193-196] Finally, there have been



Scheme 61

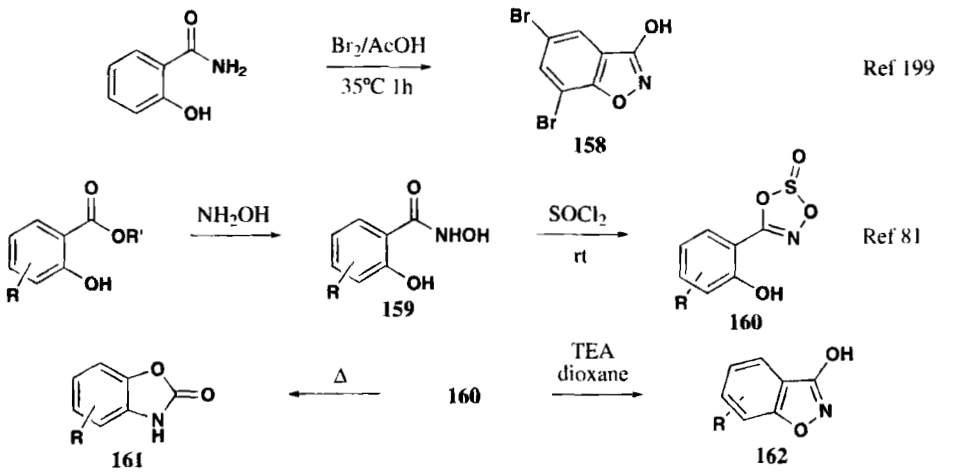
two reports describing the synthesis of the 4-substituted 5-amino-3-isoxazolol **155** from α-cyanophenylhydrazones (*Scheme 62*).[197,198] Cyclization of **156** with either neutral hydroxylamine or hydroxylamine hydrochloride in the presence of sodium acetate was reported to give the 3-isoxazolol **155** and the 5-isoxazolone **157**, respectively.[197] The same group also suggested isoxazolol **155** as the product of refluxing **154** and equimolar amounts of hydroxylamine hydrochloride and sodium carbonate.[198] It should, however, be noted that none of the products were unambiguously characterized.



Scheme 62

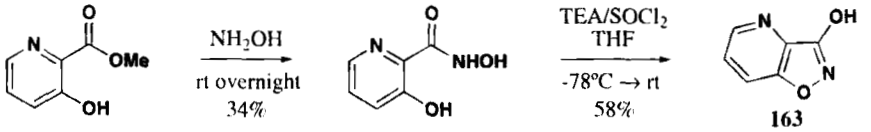
10. Synthesis of 1,2-Benzisoxazol-3-ols

In an early report by Freiser *et al.* on the synthesis of 1,2-benzisoxazol-3-ols,[199] salicylamide was subjected to bromination and the product isolated was characterized as the dibromobenzisoxazol-3-ol **158** (*Scheme 63*). Later, Böshagen described the cyclization of salicylhydroxamic acids.[81] Thus, upon treatment of **159** with neat thionyl chloride a crystalline product was isolated. The structure of this product was determined to be **160**, which upon heating in organic solvent released sulfur dioxide to give the rearranged product **161** (*Scheme 63*). However, when compounds **160** were treated with



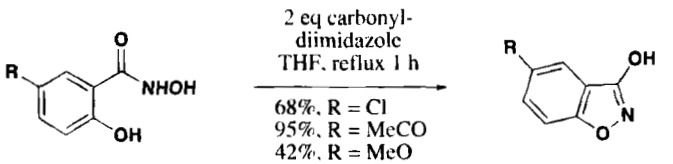
Scheme 63

triethylamine at room temperature, they cyclized to 1,2-benzisoxazol-3-ols **162** exclusively. This reaction was developed into a one-pot procedure, which provided a series of variably substituted 1,2-benzisoxazol-3-ols in 70-90% yields.[81] Although modifications have later been made to this general methodology, it remains an important route to 1,2-benzisoxazol-3-ols,[70,200,201] which has also been utilized for the cyclization of a pyridine hydroxamic acid to afford the isoxazolopyridine-3-ol **163** (*Scheme 64*).[70] An alternative route for cyclization of salicylhydroxamic acids was developed by



Scheme 64

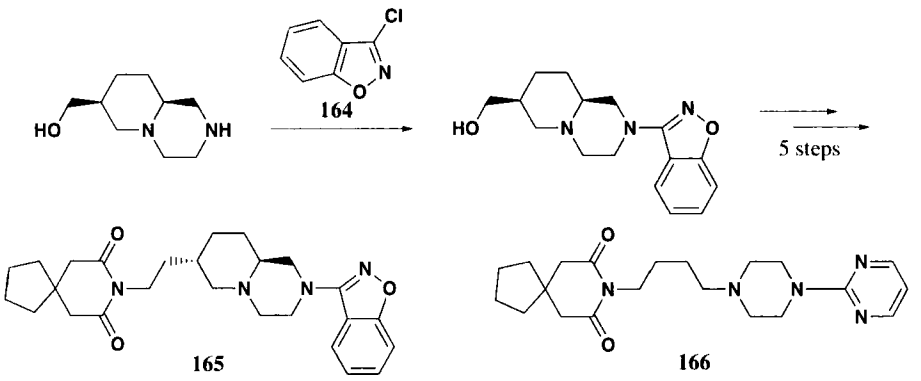
Friary and Sunday, who replaced thionyl chloride with carbonyldiimizazole and obtained efficient conversion into the corresponding benzisoxazol-3-ols (*Scheme 65*).[202] Interestingly, the analog



Scheme 65

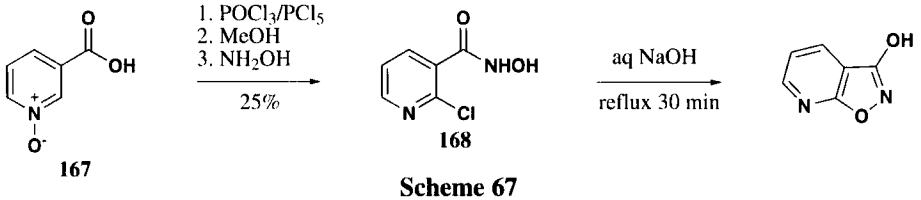
containing an acetyl substituent in the 5-position could not be prepared by use of thionyl chloride, whereas replacing this reagent with carbonyldiimidazole led to the desired product in 95% yield. This procedure was later used to synthesize analogs of the serotonergic anxiolytic buspirone (**166**) (*Scheme*

66).[159,188] Thus, Urban *et al.* prepared 1,2-benxisoxazol-3-ol in 76% yield,[188] and this compound was treated with phosphorous oxychloride to give **164**, a precursor for the synthesis of the optically active buspirone analog **165**.



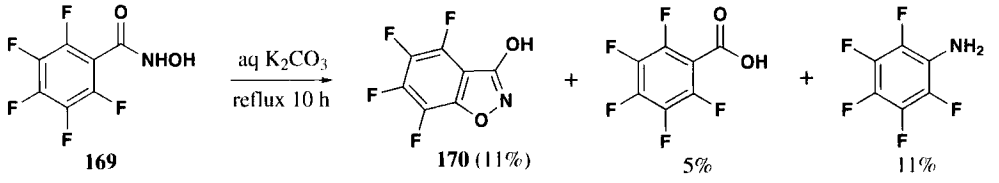
Scheme 66

It is possible to obtain intramolecular cyclization of 2-halo substituted hydroxamic acids, provided that the 2-position is sufficiently activated for aromatic nucleophilic substitution. An early report described the conversion of the N-oxide **167** into hydroxamic acid **168** and subsequent ring closure to the corresponding 3-isoxazolol in aqueous sodium hydroxide (*Scheme 67*).[64] In this case,



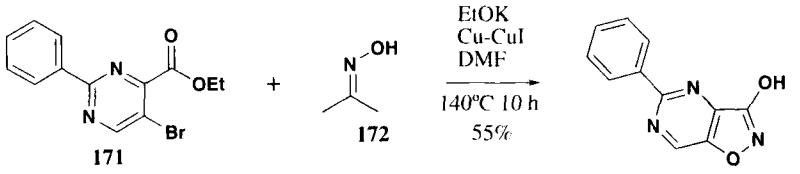
Scheme 67

the ring formation *via* an addition-elimination mechanism is facilitated by the relatively high reactivity of 2-chloropyridines towards nucleophilic substitution. In a similar manner, tetrafluorobenzisoxazol-3-ol (**170**) was isolated upon treatment of **169** with base, though in poor yield and with concomitant formation of the substituted benzoic acid and aniline side-products (*Scheme 68*).[203] Attempts to avoid hydrolysis of hydroxamic acid **169** by carrying out the reaction in anhydrous DMF, DMSO, or pyridine only gave trace amounts of **170**.



Scheme 68

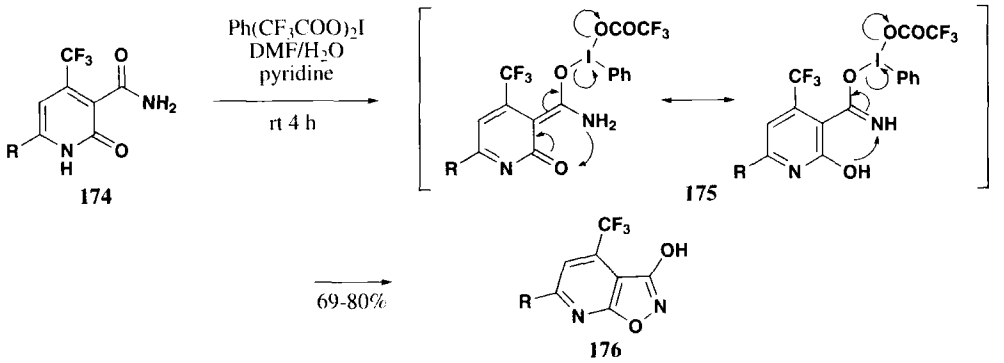
New procedures for the preparation of 3-isoxazolols fused with six-membered heterocycles have recently been reported (*Scheme 69*). One such reaction is the synthesis of isoxazolopyrimidine **173** from the carboxylic ester **171**. The best yield was obtained when acetoxime (**172**) was used as



171 172 173

Scheme 69

nitrogen-oxygen source reacting on the ester, as compared to a route *via* the corresponding hydroxamic acid.[190] In another report, the hypervalent iodine reagent phenyliodine(III) *bis*(trifluoroacetate) reacted with 3-carboxamide-2-oxopyridines **174** to provide 3-isoxazolols **176** *via* a mechanism suggested to involve an intramolecular cyclization of intermediate **175** (*Scheme 70*).[204] Finally, 5-amino-3-isoxazolol **177** gave, upon condensation with acetylacetone, the isoxazolopyridine **178** (*Scheme 71*).[205]



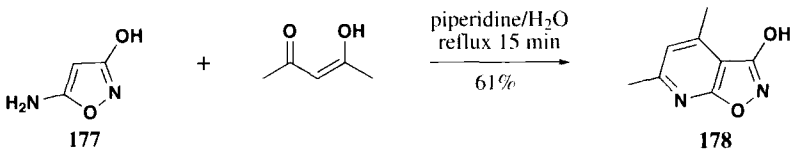
174 175 176

R = Me, Et, Ph, 4-tolyl, 4-Cl-Ph.

Scheme 70

II. CONCLUSIONS

The naturally occurring neuroactive amino acid ibotenic acid (**6**) and its decarboxylated product muscimol (**5**) contain the 3-isoxazolol unit as a carboxyl group bioisoster. This discovery prompted the synthesis of a large number of 3-isoxazolol containing zwitterionic compounds, which



177 178

Scheme 71

have played a major role in the pharmacological characterization of the central glutamate and GABA receptors. Parallel with these medicinal chemistry approaches, the 3-isoxazolol unit and other 3-oxygenated isoxazole groups have been incorporated into a variety of compounds of pharmacological interest.

The synthesis of 3-isoxazolols and the chemical transformation of these compounds are frequently complicated by problems related to regioselectivity of reactions. In general, a number of synthetic problems in the 3-isoxazolol field remain to be solved, although several selective and effective synthetic methods and chemical reactions have been reported in recent years.

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