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Synthetic routes toward 2-substituted 2-imidazolines

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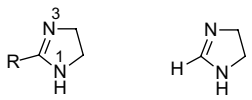
1. Introduction

2-Substituted 2-imidazolines **1** have attracted considerable attention in recent years in the development of compounds with pharmacologically useful properties. 2-Imidazoline is the term typically used to describe 4,5-dihydroimidazole **2**.[1] The numbering system for the heterocyclic ring is based on imidazole with the nitrogen atom connected to two carbon atoms via single bonds as atom number 1 and the second nitrogen atom is atom number 3.[1] Thus, 2-substituted 2-imidazolines bear substituents other than hydrogen at C-2 (Scheme 1).[1]



2-alkyl-2-imidazoline, **1** 2*H*-2-imidazoline, **2**

Scheme 1.

Examples of pharmacologically-active 2-substituted 2-imidazolines are many and include investigational compounds[2–5] as well as those currently in clinical use (Scheme 2). Much of the interest in these compounds is centered on their adrenergic activity. Phentolamine **3**[2,3] is a nonselective α adrenergic antagonist while cirazoline **4**[3] is an α_1 agonist but an α_2 antagonist. Clonidine **5** is a selective α_2 agonist.[6] Several 2-substituted 2-imidazolines such as tetrahydrozoline **6** and oxymetazoline **7** are the active ingredients in over-the-counter formulations with adrenergic activity as vasoconstrictors being their mode of action.[6]

Imidazoline receptors[7] have been proposed in an effort to explain some of the biological activity of clonidine **5**, which cannot be fully explained by its action at α_2 receptors.[8] Currently, three imidazoline receptors—I_1, I_2 and I_3—have been identified.[7] The challenge in characterizing these receptors has been designing ligands that are specific to imidazoline receptors while lacking activity at adrenergic receptors. Several 2-substituted 2-imidazolines with such activity have been discovered. For example, although cirazoline **3** exhibits both α_1 agonist activity and binding to imidazoline receptors, removal of the cyclopropyl group and replacement of the oxygen atom with a methylene group yielded **8**, which exhibit high affinity for I_2 receptors but no α_1 agonist activity.[9,10] It is worth noting that,

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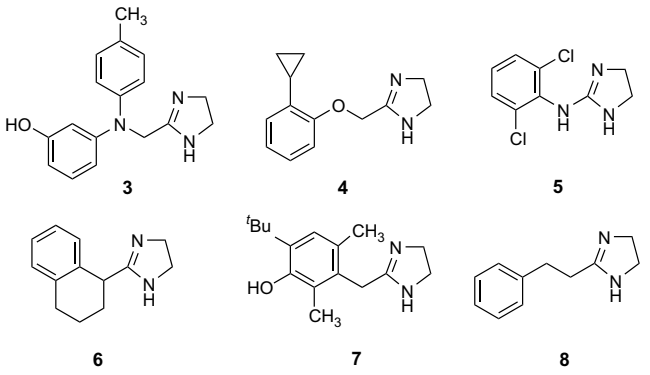


Scheme 2.

despite their name, imidazoline receptors also bind compounds that do not contain the 2-imidazoline ring system.[7]

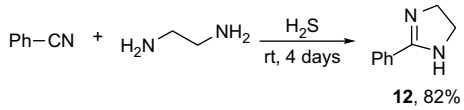
The 'Nutlins' (**9**–**11**) are a class of highly substituted 2-imidazolines, which exhibit antitumor activity by blocking the binding of the p53 tumor suppressing gene and a protein, MDM2 (Scheme 3).[11] Nutlins displace p53 from the MDM2 protein and, thus, may serve as potential anti-cancer therapies.[11] In every instance, substitution at C-2 of the imidazoline ring system was required for antitumor activity.[12]

Other activity observed for 2-substituted 2-imidazolines includes anti-diabetic[13,14] and antiparasitic[15,16] activity as well as selective inhibition of monoamine oxidase[17] and radioprotective properties.[18] With such a wide range of potential uses, 2-substituted 2-imidazolines are an important class of compounds drawing increased synthetic interest. This review is intended to be a resource for organic chemists, providing a summary of more established as well as recently developed methods for the preparation of 2-substituted 2-imidazolines. Although 2*H*-2-imidazolines are useful as precursors to *N*-heterocyclic carbenes,[19,20] the preparation of these compounds will not be considered in this review. But their use in nucleophilic additions to form 2-substituted 2-imidazolines will be included. Since the last review[1] on this topic is more than 50 years old, some discussion of methods included in that review is also presented.

2. Synthesis from nitriles

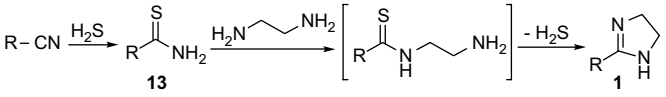
Alkyl and aryl nitriles react with salts of 1,2-ethanediamine at high temperatures to form 2-substituted 2-imidazolines.[1,21] Sulfonate salts of 1,2-ethanediamine form homogenous reaction mixtures and are preferred in these reactions over hydrochloride salts, which form mixtures that are initially heterogeneous and slower to react.[21]

As noted in a previous review,[1] the direct reaction of nitriles with 1,2-ethanediamine is too slow to be synthetically useful. However, the addition of H_2S to these reactions was shown to improve the utility of the reaction of diamines with nitriles.[22,23] Thus, benzonitrile was mixed with a 3-fold excess of 1,2-ethanediamine and the mixture was saturated with H_2S at 0 °C and, after *4 days* at room temperature, 2-phenyl-2-imidazoline **12** was obtained in 82% yield (Scheme 4).[22]



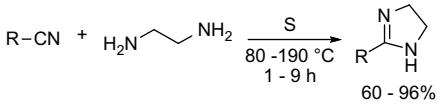
Scheme 4.

The obvious drawback to this method is the lengthy reaction time. However, the mechanism would be crucial to the development of more rapid reactions. H_2S reacts with the nitrile to form a thioamide **13**, which has been observed to react with diamines more rapidly than the corresponding amide (Scheme 5).[22]

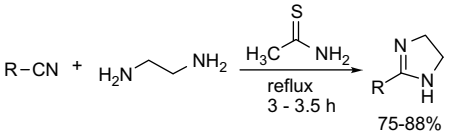


Scheme 5.

Most of the methods that were developed since the publication of a mechanism for this reaction seem to involve the preparation of thioamide **13** as a key intermediate with the primary differences among the methods being the means of introducing sulfur into the reaction. Elemental sulfur was used to catalyze the conversion of nitriles in the presence of an equimolar quantity of diamine to 2-substituted 2-imidazolines in good yield (Scheme 6).[24] And, thioacetamide was used in less than stoichiometric quantities to convert nitriles to 2-substituted 2-imidazolines using a 10-fold excess of diamine (Scheme 7).[25] In this instance, diamine reacts with the thioacetamide to release H_2S, which then catalyzes the subsequent reaction of nitrile and diamine.[25]

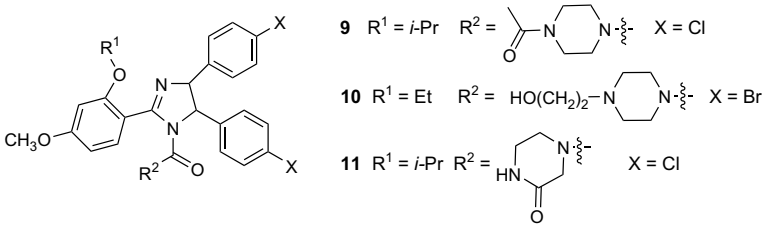


Scheme 6.



Scheme 7.

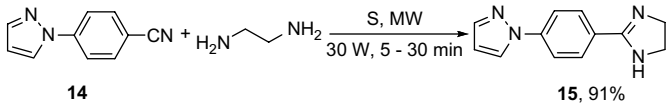
2-Substituted 2-imidazolines have also been prepared by treating nitriles with $(NH_4)_2S$ in a mixture of water, triethylamine, and pyridine at reflux *prior to* the addition of diamine.[26] Again, the



Scheme 3.

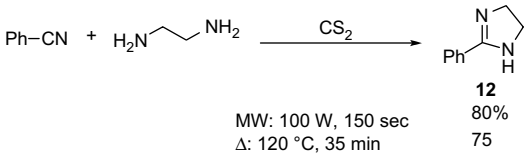
key intermediate in this reaction was the thioamide formed from the nitrile and aqueous $(NH_4)_2S$.

Microwave technology has been successfully applied to accelerating the rate of formation of 2-imidazolines from nitriles and diamines. Arylnitrile **14**, 1,2-ethanediamine, and sulfur were combined and irradiated at 30 W for 15 min to yield 2-aryl-2-imidazoline **15** in 91% yield.[27] The internal temperature of the reaction mixture reached 110 °C. But analogous reactions using an oil bath as the heat source produced lower yields. Typical reaction times in microwave-mediated reactions ranged from 5 to 30 min to achieve synthetically useful yields (Scheme 8).[27]



Scheme 8.

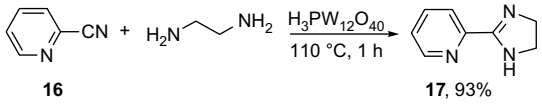
Other reagents that introduce sulfur have been employed in connection with the application of microwave technology. Substoichiometric amounts of CS_2 have been used with nitriles and diamines to form 2-substituted 2-imidazolines under microwave conditions.[28] For example, benzonitrile was mixed with 4 equiv of 1,2-ethanediamine and 10 mol% CS_2 and irradiated at 100 W for 150 s to produce 2-phenyl-2-imidazoline **12** in 80% yield.[28] By contrast, heating this mixture to 120 °C in an oil bath for 35 min produced a 75% of 2-imidazoline **12** (Scheme 9).[28] Similar yields from conventional heating at 120 °C for 6 h had been previously reported.[29]



Scheme 9.

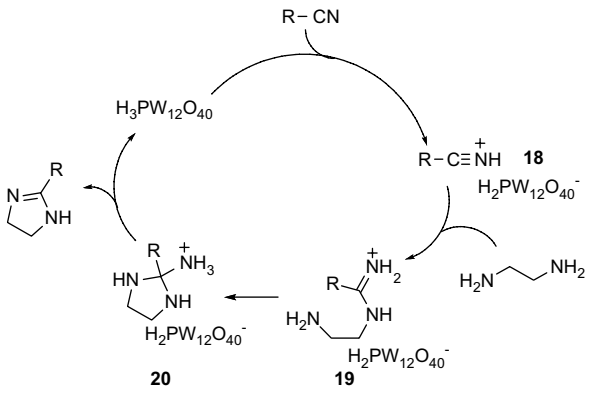
Microwave irradiation was also used to convert nitriles and diamines into 2-substituted 2-imidazolines using catalytic P_2S_5.[30] Microwave power of 720 W was used and reactions were complete in 75 s to 20 min with yields of 2-imidazoline ranging from 86 to 98%. Interestingly, the use of ultrasound produced comparable yields, although reaction times were 10–20 min.[30] In a similar fashion, ultrasound has been used to convert nitriles and diamines into 2-substituted 2-imidazolines using catalytic sulfur.[31]

Catalytic tungstophosphoric acid ($H_3PW_{12}O_{40}$) has been used to catalyze the formation of 2-substituted 2-imidazolines from nitriles and diamines under solvent-free conditions.[32] For example, 2-cyanopyridine **16** was combined with 4 equiv of 1,2-ethanediamine and 1 mol% $H_3PW_{12}O_{40}$ and heated for 1 h at 110 °C to yield 2-imidazoline **17** in 93% yield (Scheme 10).[32]



Scheme 10.

A catalytic cycle has been proposed to explain this reaction with $H_3PW_{12}O_{40}$ serving to protonate the nitrile, allowing attack of the amine and subsequent ring closure (Scheme 11).[32]

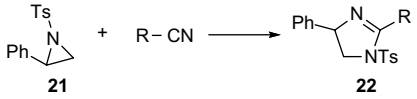


Scheme 11.

Catalytic SmI_2 has also been used to effect the formation of 2-substituted-2-imidazolines from benzonitrile and 1,2-ethanediamine.[33] $ZrOCl_2 \cdot 8H_2O$ has been used in catalytic quantities to convert aryl nitriles to 2-aryl-2-imidazolines under a variety of conditions including conventional heating at reflux, microwave irradiation, and ultrasonication.[34]

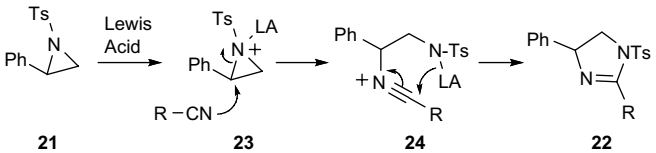
N-Tosylaziridines **21** react with nitriles in the presence of Lewis acids to form 2-substituted 2-imidazolines **22**.[35–40] These methods are summarized in Table 1. In general, an excess of nitrile was used and the yields were generally lower than those obtained following other routes. The newly-formed 2-substituted 2-imidazolines were also substituted at N-1 and at C-4.

Table 1
Summary of 2-imidazoline formation via *N*-tosylaziridines



Entry	Reagents/conditions	Time	Yield (%)	Reference
1	$ZnBr_2$, neat, 80 °C	1 h	61–73	35
2	$BF_3 \cdot OEt_2$, CH_2Cl_2, rt	5 min	49–76	36,39,40
3	Et_3OBF_4, CH_2Cl_2, rt	5 min	49–74	36,39
4	$Cu(OTf)_2$, neat, 65 °C	30 min	62–82	37
5	$Sc(OTf)_3$, neat, rt	15–25 min	51–94	38

The mechanism common to all of these methods appears to involve Lewis acid activation of the aziridine **21** followed by nucleophilic attack by the nitrile to open the activated aziridine **23** (Scheme 12).[35,37,38] Ring closure then occurs via attack of the nitrogen from the aziridine ring on the carbon of intermediate **24**. Experiments rule out the opening of the aziridine ring prior to attack by the nitrile as a possible pathway.[35]



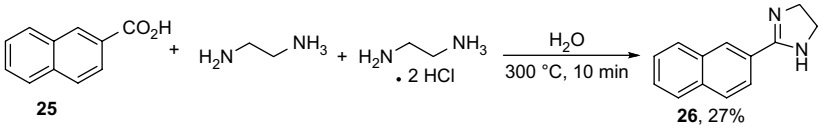
Scheme 12.

3. Synthesis from carboxylic acids and derivatives

In general, the reaction of carboxylic acids and 1,2-diamines results in low isolated yields of the desired 2-substituted 2-imidazoline.[1] Acetic acid reacted with 1,2-ethanediamine to form

2-methyl-2-imidazoline in only 19% yield.[41] Higher molecular weight acids reacted with 1,2-diamines or their salts at temperatures above 230 °C to form 2-substituted 2-imidazolines.[42] Azeotropic removal of water improved yields slightly but most of the desired imidazoline was recovered as a salt.[43] Sodium acetate was reacted with 1,2-ethanediamine to form 2-methyl-2-imidazoline in 8% isolated yield.[44] Mineral acids and other dehydrating reagents such as $AlCl_3$, PCl_3, and P_2O_5 have also been reported to effect the conversion of carboxylic acids into 2-imidazolines.[45]

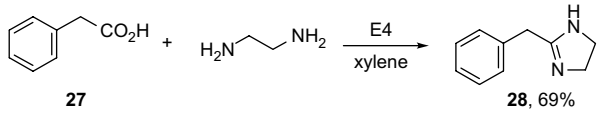
A more recent example illustrates the challenges of starting from carboxylic acids in the synthesis of 2-substituted 2-imidazolines. 2-[^{11}C]-Naphthoic acid **25** was combined with 1,2-ethanediamine and 1,2-ethanediamine dihydrochloride in water and heated to 300 °C for 10 min to yield 2-(2-naphthyl)-2-imidazoline **26** in 27% yield (Scheme 13).[46] This route is, in fact, rarely used and, in this instance, was employed due to the short half-life of the carboxylic acid, which was formed via a Grignard addition to $^{11}CO_2$.[46]



25 **26**, 27%

Scheme 13.

Significant improvement in the yields of reactions of carboxylic acids and 1,2-diamines was achieved using a small-pore zeolite catalyst.[47] When a 1:1 mixture of phenylacetic acid (**27**) and 1,2-ethanediamine in xylene were heated in the presence of Ersorb (E4), the known α-blocker tolazoline **28** was formed in 69% yield (Scheme 14).[47]

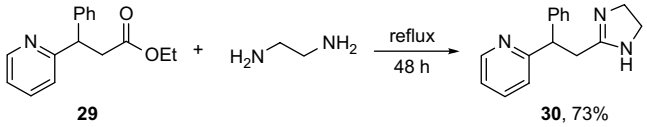


27 **28**, 69%

Scheme 14.

Ersorb is a mildly acidic solid[48] and likely serves the same role as mineral acids and other condensing agents described in earlier syntheses.[1,45] The use of another ion exchange resin to catalyze these reactions has also been reported.[49]

More typically, carboxylic acid derivatives such as esters are used to prepare 2-imidazolines and the yields are generally much higher than when a carboxylic acid is the substrate.[50–53] After heating for 48 h, a mixture of ethyl ester **29** and 1,2-ethanediamine yielded 2-substituted 2-imidazoline **30** in 73% isolated yield (Scheme 15).[52] Yields in the 60–70% range are typical of this reaction.[1] Hydrochloride salts of diamines have also been used in the conversion of esters to 2-imidazolines.[54,55]



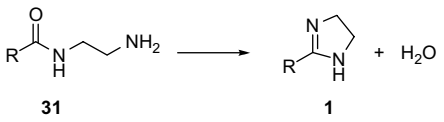
29 **30**, 73%

Scheme 15.

The mechanism that has been proposed for the reaction of diamines and esters involves the formation of an amide followed by cyclization to form the imidazoline ring system.[50] Support of this mechanism was provided by a study that showed that *N*-acyl-1,2-ethanediamine **31** (formed from the reaction of 1,2-ethanediamine and an ester) underwent cyclization to yield 2-substituted 2-imidazolines **1**.[56] This mechanism could be applied to the reaction of diamines and carboxylic acids and, given the difficulty of forming an amide from these reactants, explains the low yields. Indeed, this mechanism can be used to explain the formation of 2-imidazolines from the reaction of all of the derivatives of carboxylic acids and diamines that follow (Scheme 16).[50]

N-Aroyl-1,2-ethanediamines could not be isolated, apparently undergoing facile cyclization during attempted isolation via distillation.[56] But aliphatic analogs are more robust, requiring the presence of a base such as CaO to induce cyclization of the imidazoline ring.[50,56] A concise summary of the conditions favoring facile cyclization and those requiring the use of a condensing agent or elevated temperatures has been reported.[57]

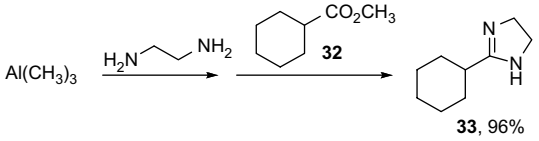
More recent developments have allowed the formation of 2-substituted 2-imidazolines from esters under milder reaction



31 **1**

Scheme 16.

conditions. When added to trimethylaluminum, 1,2-ethanediamine forms an organoaluminum intermediate that reacts with esters to form 2-imidazolines in high yield and at low temperature.[58] Thus, methyl cyclohexanecarboxylate **32** was converted into 2-cyclohexyl-2-imidazoline **33** in 96% yield (Scheme 17).[58]

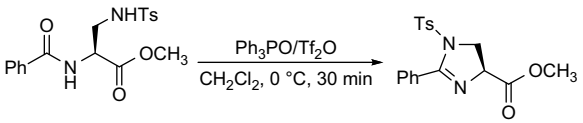


33, 96%

Scheme 17.

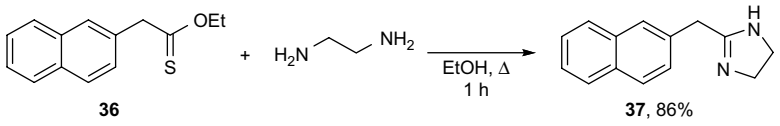
Amides also react with 1,2-ethanediamine to form 2-imidazolines.[1] In a different fashion, amides bearing a pendant tosyl-protected amine were cyclized to form 2-substituted 2-imidazolines with bis-(triphenyl)oxophosphonium trifluorosulfonate.[59] For example, amide **34** was treated with triphenylphosphine oxide and triflic anhydride at 0 °C to form 2-imidazoline **35** in 96% yield (Scheme 18).[59]

O-Alkyl thioesters can also be converted into 2-imidazolines with diamines. *O*-Ethyl thioester **36** reacted with 1,2-ethanediamine (as the sulfonate salt) in alcohol at reflux to yield 2-(2-naphthylmethyl)-2-imidazoline **37** (Scheme 19).[60]



34 **35**, 96%

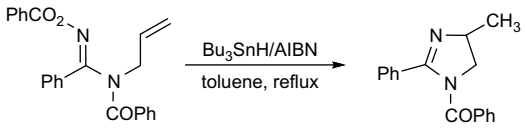
Scheme 18.



36 **37**, 86%

Scheme 19.

Amidines have also been converted into 2-imidazolines by nucleophilic substitution on 1,2-dibromoethane or 1,2-dichloroethane.[61] But amidines have also been converted into 2-imidazolines using radical processes.[62] *N*-Allyl-substituted amidine **38** cyclized to form 2-imidazoline **39** in 88% yield upon heating in the presence of Bu_3SnH and AIBN (Scheme 20).[62]



38 **39**, 88%

Scheme 20.

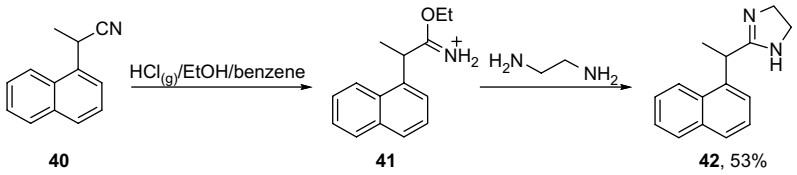
Also known as imino ethers,[1] imidates, formed from the reaction of nitriles, gaseous HCl, and alcohols, have been shown to react with diamines to form 2-substituted 2-imidazolines.[63–65] When 1-naphthylpropionitrile **40** was treated with gaseous HCl and ethanol, protonated imidate **41** was formed and, without purification, treated with 1,2-ethanediamine to yield 2-[1-(1-naphthyl)ethyl]-2-imidazoline **42** in 53% yield (Scheme 21).[63,64]

The hydrochloride salts of imidates also undergo cyclization with the hydrochloride salts of 1,2-diamines to form 2-substituted 2-imidazolines.[69]

2-Imidazolines with substitution at N-1 and C-4 can be accessed through the condensation of acid chlorides with 2-aminoalcohols followed by sequential treatment with $SOCl_2$ and an alkylamine.[70,71] For example, upon treatment with benzoyl chloride, valinol **48** was converted into amide **49**, which formed imidoyl chloride **50** after treatment with $SOCl_2$. Addition of **50** to a solution of NH_3 in $CHCl_3$ and subsequent washing with aqueous NaOH yielded 4-isopropyl-2-phenyl-2-imidazoline (**52**) in 79% yield (Scheme 23).[70]

4. Synthesis from aldehydes

Recent reports of the use of aldehydes as a starting material for the synthesis of 2-substituted-2-imidazolines represent a significance advance in the field. Generally, aldehydes reacted with diamines in the presence of an oxidizing agent to yield the desired 2-substituted-2-imidazoline.[72–76] Some of the methods used to prepare 2-phenyl-2-imidazoline **12** from benzaldehyde and 1,2-ethanediamine are compared in Table 2.



40 **41** **42**, 53%

Scheme 21.

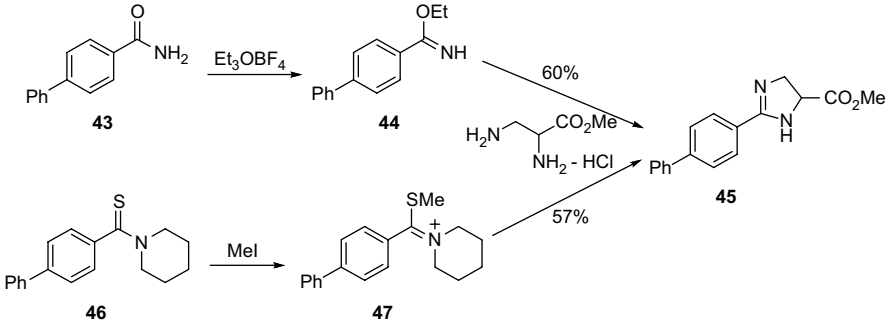
Another route that employs imidates has also been described.[66] 4-Biphenylamide **43** was converted to ethyl imidate **44** with Et_3OBF_4, which was then treated with the hydrochloride salt of methyl 2,3-diaminopropionate in ethanol at reflux to yield 2-imidazoline **45** in 60% yield (Scheme 22).[66] This approach has also been applied to the preparation of bis(imidazolines).[67]

Thioimidates also react with 1,2-diamines to form 2-imidazolines.[65,66,68] For example, thioamide **46** was converted into thioimidate **47**, which, upon treatment with the hydrochloride salt of methyl 2,3-diaminopropionate, yielded 2-imidazoline **45** in slightly lower yields than the imidate pathway (Scheme 22).[66]

Pyridinium hydrobromide perbromide has been used as an oxidizing agent in a similar method to those summarized in Table 2.[76]

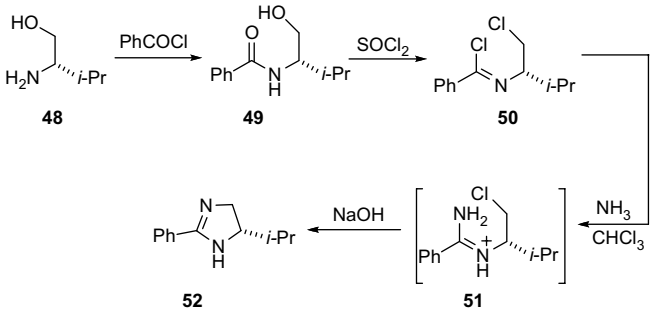
These reactions appear to occur via a common mechanism. The aldehyde and diamine form an imine **53** with a pendant NH_2 group, which cyclizes to form an *N*,*N*,-acetal **54**. Subsequent N-halogenation gives haloamine **55**, which undergoes elimination to form 2-substituted 2-imidazoline **1**.[72,75] This mechanism is supported by ^1H NMR data showing the presence of intermediate **54** in solution (Scheme 24).[72,75]

Despite the similarities in the likely mechanisms, some differences in reactivity are evident. The use of I_2 without KI results in



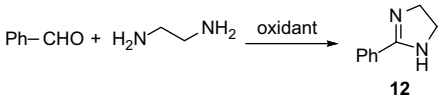
43 **44** **45** **46** **47**

Scheme 22.

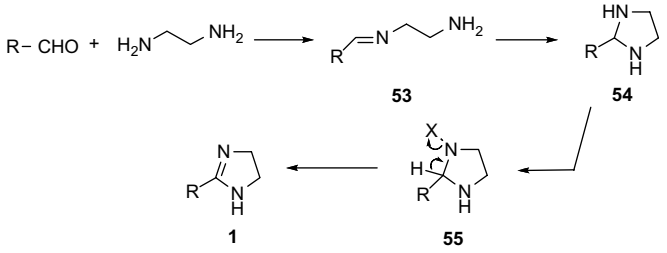


Scheme 23.

Table 2
Methods for synthesis of 2-phenyl-2-imidazoline from benzaldehyde



Entry	Oxidant	Solvent	Conditions	Yield (%)	Reference
1	NBS	CH_2Cl_2	0 °C, 20 min then rt, overnight	99	[72]
2	*t*-BuOCl	*t*-BuOH	50 °C, 2 h	100	[73]
3	$I_2/KI/K_2CO_3$	H_2O	90 °C, 30 min	90	[74]
4	I_2/K_2CO_3	*t*-BuOH	70 °C, 3 h	100	[75]



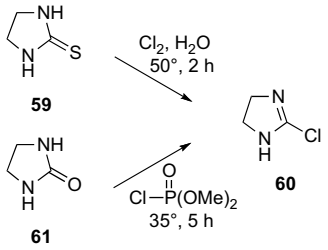
Scheme 24.

much lower yields when the substrate is an aliphatic aldehyde.[75] The use of I_2[75] or pyridinium hydrobromide perbromide[76] require greater than 2-fold excess of reagent to accomplish 2-imidazoline formation. And, although NBS-mediated reactions required some of the longest reaction times,[72] this method can also accommodate NCS and NIS and has been applied to the total synthesis of (−)-spongotine.[77] It is also noteworthy that when NBS was used in conjunction with 1,3-diamines, 2-substituted 2-tetrahydropyrimidines were isolated in good to excellent yield.[78]

Benzaldehyde was also converted into a trisubstituted 2-imidazoline via formation of bis-imine **56**, which thermally rearranged into 2,4,5-triphenyl-2,5-dihydroimidazole **57**.[79] Subsequent treatment with base yielded 2,4,5-triphenyl-2-imidazoline **58** (Scheme 25).[79]

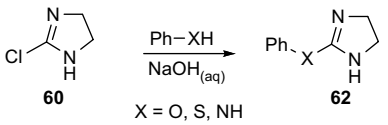
5. Synthesis via substitution at C-2 of an existing 2-imidazoline

Imidazoline rings can be prepared from readily available starting materials that allow substitution at C-2, resulting in 2-substituted 2-imidazolines without *de novo* synthesis of the imidazoline ring system. Typically, 2-imidazolidinethione (or *N*,*N*′-ethylene thiourea) **59** was mixed with aqueous Cl_2 to form 2-chloro-2-imidazoline **60**.[80] 2-Imidazolidinone (or *N*,*N*′-ethylene urea) **61** is another potential starting material, undergoing a reaction with dimethyl chlorophosphate to form 2-chloro-2-imidazoline **60** (Scheme 26).[80,81]



Scheme 26.

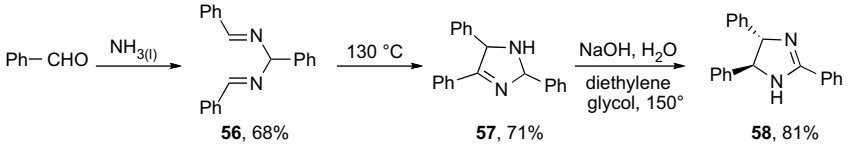
Once formed, 2-chloro-2-imidazoline **60** has been shown to undergo substitution with a variety of nucleophiles, including amines,[80–84] phenols,[80] and thiophenols,[80] to form 2-substituted 2-imidazolines with heteroatom substituents at C-2 (**62**). The yields of substitution products via this path were, however, rather low when phenols and thiophenols were used (Scheme 27).[80]



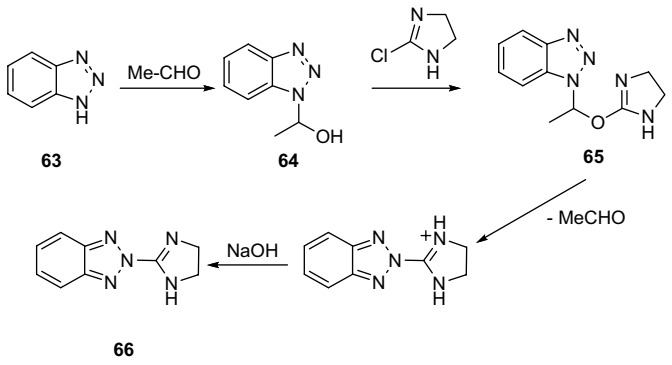
Scheme 27.

An unusual reaction of azoles with 2-chloro-2-imidazoline **60** has been reported. Attempts to use triazoles as nucleophiles failed under mild conditions and, at elevated temperatures, 2-chloro-2-imidazoline **60** tended to self condense via the reaction of the nucleophilic N-3 of one ring on the electrophilic C-2 of the other.[85] However, benzotriazole **63** reacted with acetaldehyde to form a hemiaminal **64**, which attacked C-2 of the 2-chloro-2-imidazoline **60** to form an intermediate **65**. Extrusion of acetaldehyde and concomitant rearrangement led to the desired 1-(4,5-dihydro-1*H*-imidazol-2-yl)benzotriazole **66** in 85% yield (Scheme 28).[85]

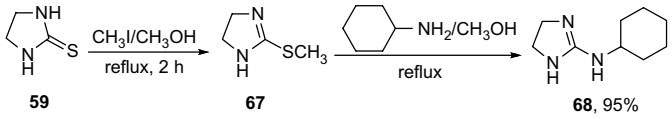
Another useful route to 2-alkylamino-2-imidazolines via substitution at C-2 is the use of 2-methylmercapto-2-imidazoline **67** as the electrophile in reactions with amines.[86–88] Imidazoline **67** was easily prepared by the reaction of 2-imidazolidinethione **59** with CH_3I in methanol.[86] After isolation as the hydroiodide salt, **67** underwent substitution at C-2 with 1° and 2° amines. For example, treatment of 2-methylmercapto-2-imidazoline **67** with cyclohexylamine in refluxing methanol resulted in a 95% yield of 2-cyclohexylamino-2-imidazoline **68** in 95% yield (Scheme 29).[86]



Scheme 25.

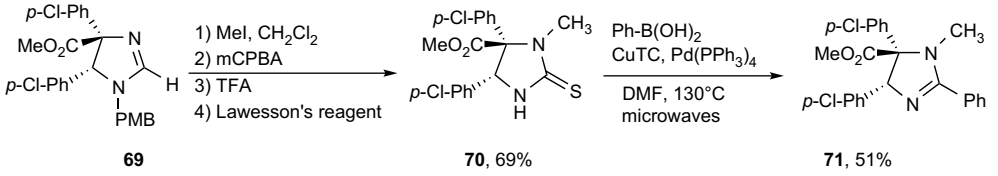


Scheme 28.



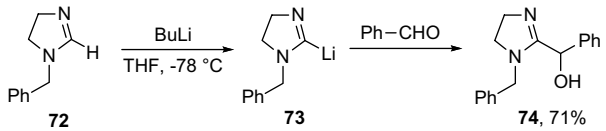
Scheme 29.

Functionalization at C-2 of polysubstituted 2*H*-2-imidazolidine **69** has been achieved via conversion to the corresponding 2-imidazolidinethione **70**[12] followed by a variation[89] of the Liebeskind–Skrogl arylation[90,91] to yield 2-aryl-2-imidazoline **71** (Scheme 30).[12]



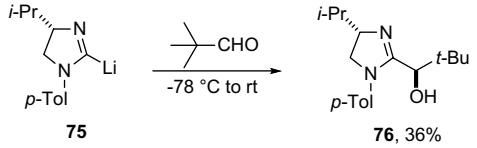
Scheme 30.

2-Imidazolines lacking a substituent at C-2 can be formed via several methods[67,70,71] and then metalated at C-2 to allow reaction with an electrophile,[67,71] with metalation using *n*-BuLi being preferable to *t*-BuLi.[67] For example, 1-benzyl-2-imidazoline **72** reacted with *n*-BuLi resulting in the formation of 2-lithio-2-imidazoline **73**, which then added to benzaldehyde to yield 1-benzyl-2-(1-hydroxyalkyl)-2-imidazoline **74** in 71% yield (Scheme 31).[92]



Scheme 31.

The introduction of chirality at C-4 of 2-lithio-2-imidazoline **75** with *i*-Pr or *t*-Bu groups allowed condensation with pivaldehyde to yield enantiopure 2-(1-hydroxyalkyl)-2-imidazolines **76**, which proved to be a useful ligand in the addition of diethylzinc to aldehydes (Scheme 32).[71]



Scheme 32.

In a similar fashion, 2-lithio-2-imidazolines added to dialkyl or diaryl haloboranes to form boron-bridged bis(imidazolines).[67] A pair of bismacrocyclic imidazolinium salts were prepared and deprotonated using KO^{t}Bu, allowing condensation with CS_2 to yield a 2-dithiocarboxylated-2-imidazolinium salt.[93]

6. Synthesis via multicomponent coupling approaches

Several methods have been reported in which multiple components were coupled together to ultimately form 2-substituted 2-imidazolines. An early method employed alcoholic Cl_2 to couple an alkene, a nitrile, and an alkylamine, leading to the formation of a highly substituted 2-alkyl-2-imidazolines.[94] For example, propionitrile and 2-methyl-2-butene reacted in the presence of Cl_2 to form chloroimine **77**. Treatment with *tert*-butylamine formed intermediate **78**, which underwent cyclization in the presence of sodium methoxide to yield 2-imidazoline **79** in 38% overall yield (Scheme 33).[94]

A multicomponent coupling approach that follows a 1,3-dipolar cycloaddition pathway has recently been described.[95–97] When a mixture of benzylamine, benzaldehyde, and oxazolone **80** were heated in the presence of TMS-Cl, imidazoline **81** was isolated in 75% yield and with high diastereoselectivity.[96] The mechanism that has been invoked involves TMS-Cl mediated conversion of oxazolone **80** into münchnone intermediate **82** and formation of imine **83** from benzaldehyde and benzylamine. Subsequent 1,3-dipolar cycloaddition produced bicyclic intermediate **84**, which rearranged to form imidazoline **81** (Scheme 34).[96] Diastereoselectivity seems to arise from steric interaction of the silyl group and the benzaldehyde derived phenyl group on the imine.[96,98] Of particular note, this methodology allows for the diastereoselective synthesis of 2-substituted 2-imidazolines[97] with up to four points of substituent diversity.[98]

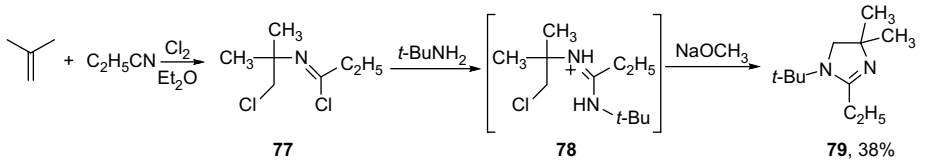
A münchnone intermediate has also been invoked to explain the Pd-mediated three-component coupling of an imine **85**, benzoyl chloride, and CO to form similar polysubstituted 2-substituted 2-imidazolines **86** (Scheme 35).[99]

Yet another example of a three-component coupling reaction leading to 2-substituted 2-imidazolines is a two-step sequence involving the iodide-mediated rearrangement of the product of the coupling of an aziridine, a terminal alkyne, and tosyl azide.[100] Aziridine **87** reacted with phenylacetylene and tosyl azide in the presence of CuCl and triethylamine to form *N*-sulfonylated aziridine **88**. Subsequent treatment of **88** with NaI in acetone led to the formation of polysubstituted 2-imidazoline **89** in 61% overall yield (Scheme 36).[100] A similar reaction involves the methyl thiocyanate induced rearrangement of a *N*-methylated version of aziridine **87**.[101]

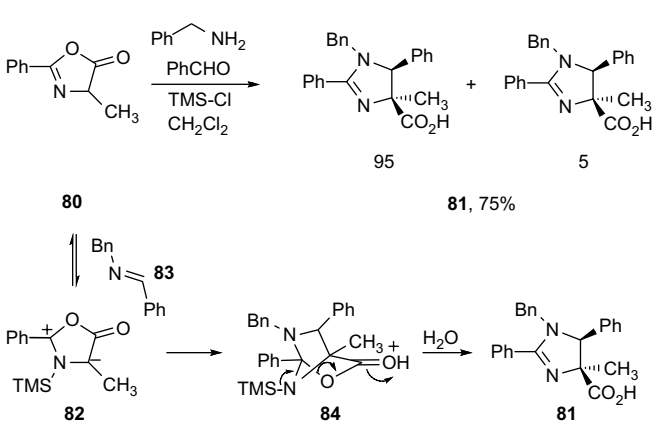
A major advantage of these methods is that highly substituted 2-imidazolines are formed quickly and, for library development, multiple points of diversity are easily introduced using combinatorial techniques.[95,97]

7. Synthesis via miscellaneous reactions

Alkylation of the α-carbon of 2-methyl-2-imidazoline has been used to lengthen the alkyl chain at C-2 and to prepare

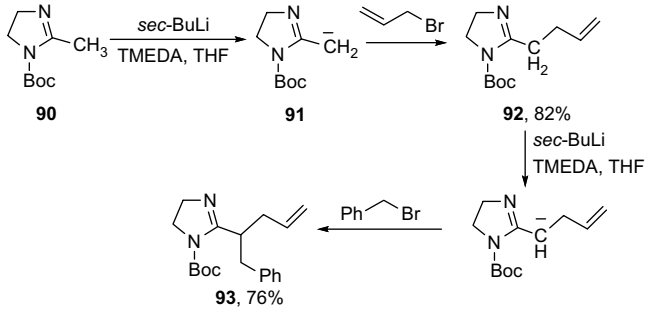


Scheme 33.

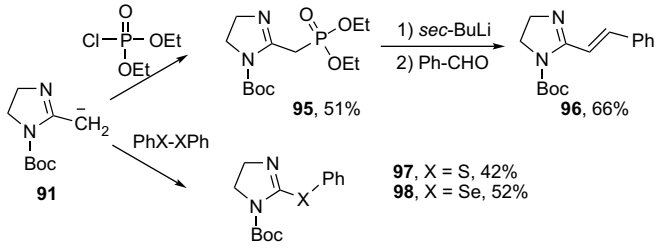


Scheme 34.

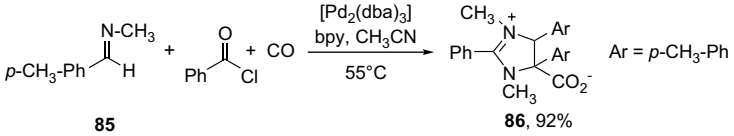
2-alkyl-2-imidazolines with branched alkyl groups.[102] For example, Boc-protected 2-methyl-2-imidazoline **90** was deprotonated with *sec*-BuLi in TMEDA/THF and the resultant anion **91** was alkylated using allyl bromide to yield 2-(but-3-enyl)-1-*tert*-butoxycarbonyl-2-imidazoline **92**.[102] Imidazoline **92** underwent a second deprotonation and alkylation benzyl bromide to yield protected imidazoline **93** (Scheme 37).[102]



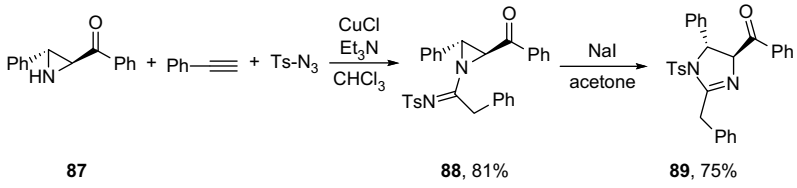
Scheme 37.



Scheme 38.



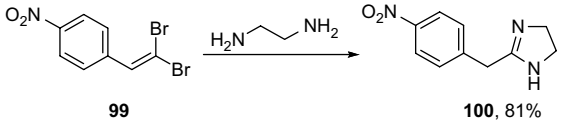
Scheme 35.



Scheme 36.

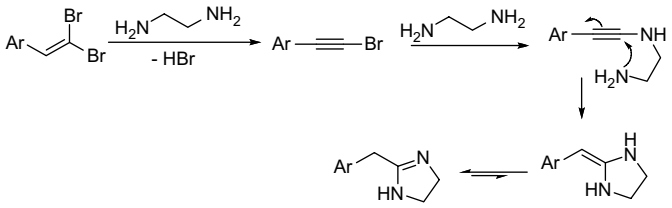
When imidazoline **90** was deprotonated and treated with diethyl chlorophosphate, the resultant phosphonate **95** could be used in Wadsworth–Emmons reactions with aldehydes to yield 2-(1-alkenyl)-2-imidazolines **96**.[102,103] Similarly, addition of diphenyl disulfide or diphenyl diselenide to intermediate **91** resulted in formation of 2-phenylthiomethyl-2-imidazolines **97** and 2-phenylselenomethyl-2-imidazolines **98** (Scheme 38).[102]

Another method that produces 2-substituted 2-imidazolines involves the reaction of 2-aryl-1,1-dibromoethenes with 1,2-ethanediamines. For example, stirring a mixture of 2-(4-nitrophenyl)-1,1-dibromoethene **99** with 1,2-ethanediamine at room temperature for 30 min resulted in the formation of 2-(4-nitrophenylmethyl)-2-imidazoline **100** in 81% yield (Scheme 39).[104]



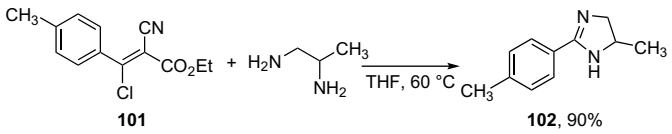
Scheme 39.

A proposed mechanism is shown in Scheme 40.[104]



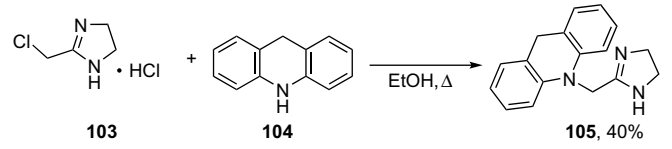
Scheme 40.

2-Aryl-2-imidazolines have also been formed via an interesting double conjugate addition of 1,2-diamines to 3-aryl-3-chloro-2-cyanopropenoates followed by extrusion of ethyl cyanoacetate. Addition of 1,2-propanediamine to cyanopropenoate ester **101** in THF at 60 °C yielded 2-aryl-2-imidazoline **102** in 90% isolated yield.[105] Elevated temperatures are required for cyclization with monosubstitution of amine for chlorine predominating at lower temperatures (Scheme 41).[105]



Scheme 41.

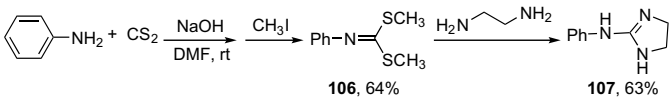
Nucleophilic substitution with amines and amides on 2-chloromethyl-2-imidazoline **103** has been shown to be modestly effective in yielding 2-aminomethyl-2-imidazolines. Reaction of imidazoline **103** with acridan **104** yielded 2-aminomethyl-2-imidazoline **105** in 40% yield.[29] Deprotonated amides proved to be more effective nucleophiles in this reaction, generating higher yields (Scheme 42).[29]



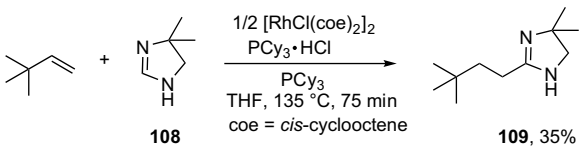
Scheme 42.

A method to prepare 2-arylamino-2-imidazolines from *N*-aryl dithioimidocarbonates has been reported that allows the use of either conventional[106] or microwave heating.[107] Dimethyl *N*-phenyldithioimidocarbonate **106** was prepared in 64% yield by heating CS_2 and aniline in DMF containing aqueous NaOH followed by addition of methyl iodide. When this isolable intermediate was heated with 1,2-ethanediamine at 110 °C for 7.5 h, 2-phenylamino-2-imidazoline **107** was isolated in 63% yield (Scheme 43).[106,107] However, when dithioimidocarbonate **106** was mixed with 1,2-ethanediamine and silica gel and then subjected to microwave irradiation (850 W for 3 min) to achieve a temperature of 140–145 °C, imidazoline **107** was isolated in 82% yield.[107]

Rhodium-catalyzed C–H bond activation has been used to couple 4,4-dimethyl-imidazoline **108** to 3,3-dimethyl-1-butene to yield alkylated 2-imidazoline **109** in modest yield (Scheme 44).[108] Oxazolines, though, have been shown to be better substrates than imidazolines in this reaction.[108]



Scheme 43.



Scheme 44.

8. Summary

2-Imidazolines with substituents at C-2 can be prepared from simple starting materials via well-established methods as well as newer protocols that expand the range of starting materials. For 2-imidazolines bearing additional substituents, a number of new techniques and approaches have been described that can be adapted to library development. Given the growing interest in synthetic targets containing the 2-imidazoline ring system—particularly in the development of new pharmacologically-active compounds—further research in this field is likely.

Acknowledgements

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