The Preparation of 2-Isoxazolines from *O*-Propargylic Hydroxylamines via a Tandem Rearrangement–Cyclisation Reaction

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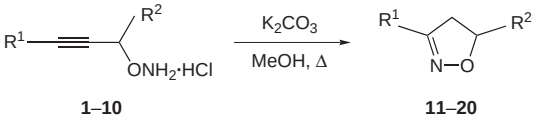
Abstract: A method for the conversion of *O*-propargylic hydroxylamines into 2-isoxazolines in 60–84% yield is described. For 3-alkylpropargyl or 3-arylpropargyl hydroxylamines this was achieved by heating a methanolic solution of the hydrochloride salt in the presence of K_2CO_3. In the case of the 3-unsubstituted compounds, the hydrochloride salts were first converted to the free bases, which rearranged upon heating in methanol. In one case, the methodology was extended to enable the direct transformation of a *O*-propargyl phthalimide into a 2-isoxazoline in 65% yield by treatment with methyl hydrazine at room temperature over 19 hours.

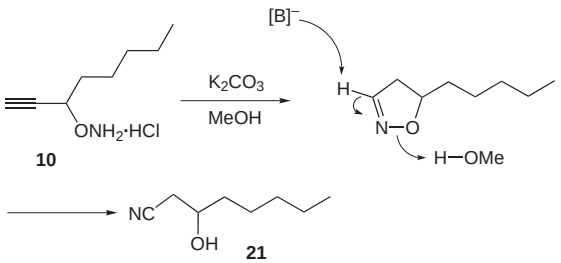
Key words: isoxazoline synthesis, *O*-propargylic hydroxylamine, sigmatropic rearrangement

The 2-isoxazoline ring is an important constituent of a number of biologically active molecules including the antitumour drug Acivicin[1] and the antithrombotic agent DMP 802.[2] In addition, due to their ability to undergo facile reductive ring-opening reactions they are of interest as synthetic intermediates.[3] As a consequence, many synthetic methods have been developed to produce 2-isoxazolines of which the reaction of α,β-unsaturated ketones with hydroxylamine and the cycloaddition of nitrile oxides to alkenes are the most important.[3,4] The 1,3-dipolar cycloaddition route is especially versatile[5] but has some disadvantages due to the tendency of nitrile oxides to dimerise to furoxans.[4] To compensate for dimerisation losses it is common to use an excess of the dipolarophile,[6] or in some cases of nitrile oxide.[7] However, this can complicate the final purification and isolation of the product and wastes potentially valuable intermediates. Consequently, new synthetic methods are of interest and in this communication we report a simple procedure for the synthesis of 2-isoxazolines by intramolecular rearrangement of *O*-propargylic hydroxylamines (Scheme 1). A search of the literature has revealed a single prior example of this rearrangement but the conditions were relatively severe (18 equiv NaOH, MeOH, reflux, 3 h) and the scope of the reaction was not explored.[8] The conditions reported herein are considerably milder and the method has been generalised to yield a wide range of mono- and disubstituted 2-isoxazolines.



Scheme 1

O-Propargylic hydroxylamine hydrochloride salts **1**–**10** were synthesised using a literature method[9] for use in a project connected with the preparation of insecticidal muscarinic acetyl choline receptor agonists.[10] While normally the salts **1**–**10** were found to be stable upon even prolonged storage, during the course of our work we discovered that they could be induced to undergo intramolecular rearrangement to give the 2-isoxazolines **11**–**20** in good yields. The best general conditions involved heating a 0.3 M solution of the hydroxylamine hydrochloride and K_2CO_3 (1 equiv) in dry methanol at reflux for 7.5 hours. Under these conditions, 3-aryl substituted *O*-propargylic hydroxylamines were converted cleanly to the corresponding 2-isoxazolines, which were isolated in 71–84% yield after chromatography (Table 1, compounds **11**, **12**, **13**, **14**, **17** and **18**).[11] 3-Alkyl substituted hydroxylamines were also smoothly converted but the yields were slightly lower, 60–74% (Table 1, compounds **15** and **16**). In contrast, 3-unsubstituted propargylic hydroxylamines gave none of the expected isoxazoline using these standard conditions. In the case of the *n*-pentyl substituted compound **10**, the β-hydroxynitrile **21** was isolated in 79% from this reaction, presumably due to a base-catalysed opening of the isoxazoline ring (Scheme 2). In order to try and prevent this undesired side reaction the procedure was repeated using the free hydroxylamine bases and without addition of the K_2CO_3. Under these modified conditions the desired isoxazolines **19** and **20** were isolated in 63% and 61% yield, respectively (Table 1).[11]



Scheme 2

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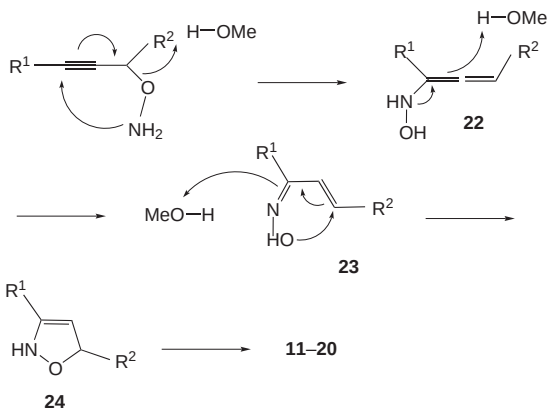
Table 1 The Synthesis of 2-Isoxazolines from *O*-Propargylic Hydroxylamine Hydrochloride Salts[11]

Hydroxylamine hydrochloride	R^1	R^2	2-Isoxazoline	Isolated yield (%)
1	2-ClC_6H_4	H	**11**	74
2	3-$MeOC_6H_4$	H	**12**	78
3	4-ClC_6H_4	H	**13**	71
4	3,5-$(CF_3)_2C_6H_3$	H	**14**	83
5	*n*-Pr	H	**15**	60
6	Et_2NCH_2	H	**16**	74
7	Ph	Me	**17**	84
8	Ph	*i*-Pr	**18**	84
9[a]	H	Ph	**19**	63
10[a]	H	*n*-Pentyl	**20**	61

[a] Rearrangement performed on the free hydroxylamine without K_2CO_3.

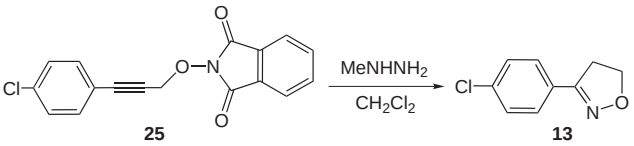
The mechanism for the transformation of *O*-propargylic hydroxylamines to 2-isoxazolines has not been investigated, however, one possibility involves an initial 2,3-sigmatropic rearrangement to give the *N*-allenic hydroxylamines **22** (Scheme 3). These could then rearrange to give the α,β-unsaturated oximes **23** which could undergo a 5-*endo*-trig cyclisation to give the 3-isoxazolines **24**. Finally, isomerisation of the enamine to the more stable imine would give the observed 2-isoxazoline products **11**–**20**. The previously reported rearrangement of *N*-benzyl-*O*-allylic hydroxylamines to give *N*-allylic hydroxylamines provides good precedent for the initial rearrangement step to give allenes **22**.[12]

The propargylic hydroxylamines used in this work were synthesised from the corresponding phthalimide protected



Scheme 3

precursors as described in the literature.[9] The utility of the current transformation would be greatly increased if these precursors could be directly transformed into 2-isoxazolines. Consequently, a 0.3 M solution of the phthalimide **25** and methyl hydrazine (1 equiv) in CH_2Cl_2 were stirred together at room temperature for 19 hours. After workup and chromatography, the 2-isoxazoline **13** was isolated in 65% yield (Scheme 4).[11] Conducting the same experiment under the literature conditions,[9] whereby the reaction was worked up after four hours, yielded the non-rearranged *O*-propargyl hydroxylamine hydrochloride **3** in 80% yield.



Scheme 4

In summary, *O*-propargyl hydroxylamine hydrochlorides **1**–**10** have been smoothly transformed into substituted 2-isoxazolines **11**–**20** in isolated yields of 60–84%.[11] In one case, the methodology has been extended to enable the direct transformation on an *O*-propargyl phthalimide into the 2-isoxazoline **13** in 65% yield. Since the phthalimide **25** is readily synthesised from the corresponding propargylic alcohol,[9] the methodology formally represents a two-step route for converting propargylic alcohols into 2-isoxazolines.

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(11) **Preparation of 3-(2-Chlorophenyl)-2-isoxazoline (11).** A mixture of the *O*-propargylic hydroxylamine hydrochloride salt **1** (275 mg, 1.26 mmol), K_2CO_3 (175 mg, 1.27 mmol) and dry MeOH (5 mL) was heated at reflux under a nitrogen atmosphere for 7.5 h. The solution was then concentrated in vacuo at 40 °C, H_2O (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo at 40 °C. The crude product was purified by flash chromatography (gradient elution; EtOAc–heptane) to give the isoxazoline **11** as an oil (169 mg, 0.93 mmol, 74%). IR: ν_{max} = 3066 (w), 2954 (m), 2887 (m), 1584 (m), 1476 (m), 1434 (s), 1342 (s), 1037 (m), 934 (m), 880 (s), 643 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.48 (2 H, t, *J* = 8.7 Hz, C4-H_2), 4.51 (2 H, t, *J* = 8.7 Hz, C5-H_2), 7.26–7.38 (2 H, m, Ph), 7.43 (1 H, dd, *J* = 0.7, 6.3 Hz, Ph), 7.64 (1 H, dd, *J* = 0.8, 7.9 Hz, Ph). MS (EI): *m/z* (%) 183 (33) [M^+], 181 (100) [M^+], 155 (20), 153 (79), 151 (87), 137 (65), 113 (20), 111 (53), 75 (74). Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.60; H, 4.46; N, 7.79%. Compounds **12**, **13**,[13] **14**, **15**,[14] **16**, **17**[13] and **18**[15] were prepared using an analogous procedure.

Preparation of 5-Phenyl-2-isoxazoline (19). The *O*-propargylic hydroxylamine hydrochloride salt **9** (1.84 g, 10.0 mmol) was dissolved in CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo at 40 °C to give the free hydroxylamine (1.44 g, 9.8 mmol). A portion of this material (300 mg, 2.04 mmol) was dissolved in dry MeOH (5 mL) and heated at reflux under a nitrogen atmosphere for 8 h. The solution was then concentrated in vacuo at 40 °C and the crude product purified by flash chromatography (gradient elution; EtOAc–heptane) to give the isoxazoline **19** as an oil (188 mg, 1.28 mmol, 63%). IR and ^1H NMR spectra as previously reported.[16] Compound **20** was prepared using an analogous procedure.

Preparation of 3-(4-Chlorophenyl)-2-isoxazoline (13). Methyl hydrazine (0.15 g, 3.3 mmol) was instilled into a cooled solution (0 °C) of the phthalimide (**25**) (1.00 g, 3.2 mmol) in CH_2Cl_2 (10 mL) under a nitrogen atmosphere. The mixture was stirred at r.t. for 19 h, after which time the precipitated 2-methyl-2,3-dihydrophthalazine-1,4-dione was removed by filtration and discarded. The filtrate was diluted with Et_2O (50 mL), cooled to 0 °C and anhyd $HCl_{(g)}$ was bubbled through for approximately 5 min to give a small amount of brown precipitate which was filtered off and discarded. The filtrate was then concentrated in vacuo at 40 °C and the crude product purified by flash chromatography (gradient elution; EtOAc–heptane) to give the isoxazole **13** as a crystalline solid (380 mg, 2.1 mmol, 65%); mp 114–116 °C (lit.[13] 116–117 °C). IR and ^1H NMR spectra as previously reported.[13]

Compounds **17**–**20** were isolated as racemic mixtures.

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