New Regiospecific Catalytic Approaches to 4,5-Dihydroisoxazoles and 2,5-Dihydroisoxazoles from *O*-Propargylic Hydroxylamines

David W. Knight,*[a] Anthony J. Proctor,[a] John M. Clough[b]

[a] School of Chemistry, Cardiff University, Main College, Park Place, Cardiff, CF10 3AT, UK
Fax +44(2920)874030; E-mail: knightdw@cf.ac.uk

[b] Syngenta, Research Chemistry, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK

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Dedicated with all best wishes and gratitude for all the training and advice to Professor Gerry Pattenden on the occasion of his 70th birthday from two of his young apprentices, DWK and JMC.

Abstract: Unprotected *O*-propargylic hydroxylamines undergo generally essentially quantitative cyclisations when exposed briefly to silver nitrate adsorbed onto silica gel to give 4,5-dihydroisoxazoles [2-isoxazolines], while N-protected derivatives give the corresponding 2,5-dihydroisoxazoles [3-isoxazolines] in similarly excellent yields, given that an appropriate functionality on nitrogen is used.

Key words: 4,5- and 2,5-dihydroisoxazoles, *O*-propargylic hydroxylamines, cyclisations, silver nitrate on silica gel

The three isomeric dihydroisoxazoles,[1] of which two (**1** and **2**, Figure 1) form the subject of this paper, are significant chemical entities for a number of reasons. Firstly, some display biological activities in their own right[2] and secondly they can act as precursors to heteroaromatic isoxazoles.[1] However, perhaps equally important roles are offered by their decomposition chemistry: for example, relatively facile reductive cleavage of the weak N–O bond of 4,5-dihydroisoxazoles **1** leads to either β-hydroxy ketones (aldols) or γ-amino alcohols, depending upon the exact conditions used.[1,3] Clearly, this is a most useful additional feature associated with these heterocycles as it offers completely different tactics for the synthesis of these valuable compound types.

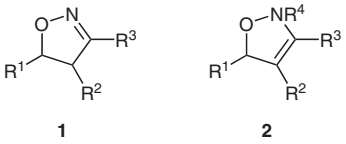

Figure 1

In terms of their synthesis, there are a few classical methods for the elaboration of these structural types,[1] one of the most useful being the synthesis of 4,5-dihydroisoxazoles **1** using [1,3]-dipolar cycloadditions between nitrile oxides and alkenes.[4,5] Well-established protocols are available for carrying out this methodology, and current interest is very much centred on the development of asymmetric versions, especially because of their potential to contribute to the asymmetric synthesis of the valuable degradation products mentioned above.[6] An entirely different strategy features various intramolecular cyclisations, the simplest of which are base-induced cyclisations of allylic oximes[7] or, in a reverse sense, of propargylic hydroxylamines to give 4,5-dihydroisoxazoles.[8] Other methods have been adapted for inducing cyclisations of allylic oximes including palladium-catalysed alkene carbonylation[9] and an application of bromoetherification.[10] A dual iron–gold catalyst has been found to be capable of both introducing a hydroxylamine function at a propargylic alcohol site by hydroxy displacement and of inducing subsequent cyclisation to similar 4,5-dihydroisoxazoles.[11] In related studies, cationic gold(I) complexes have been shown capable of causing cyclisations of *O*-allenylmethyl hydroxylamines to give such heterocycles in a stereocontrolled fashion,[12] which can also be obtained starting with enones by sequential Michael addition of thiophenol, oximation, *S*-methylation, and internal displacement of sulfur.[13] Examples of *spiro*-substituted derivatives have been prepared by thermal rearrangements of various *N*-nitroso-4,5-dihydropyrazoles.[14]

Isomeric 2,5-dihydroisoxazoles **2** can likewise be obtained usually in decent yields from intramolecular cyclisations of *O*-propargylic hydroxylamines, given the use of a suitable protecting group (Boc) on nitrogen, by employing a mixed Au/Ag catalyst system[15] as well as by 5-*endo*-dig iodocyclisations[16] of similar precursors, generally protected at nitrogen by a sulfonyl group.[17] This type of heterocycle can also be obtained in a so far limited way by selenoetherifications of *O*-allyl oximes followed by borohydride reductions of the resulting iminium species.[18] A particularly good way to make examples of the third member of this group, the 2,3-dihydroisoxazoles, is by zinc(II)-catalysed 5-*endo*-dig cyclisations of the corresponding acetylenic hydroxylamines;[19] such heterocycles are useful as precursors of both β-amino ketones and γ-amino alcohols.[20]

It was against this background that we speculated that the exceptionally efficient furan synthesis that we have recently developed could perhaps also be used to form these useful types of heterocycles in a very clean and simple manner.[21] This methodology (Scheme 1) employs as the catalyst silver(I) nitrate adsorbed on silica gel, a material

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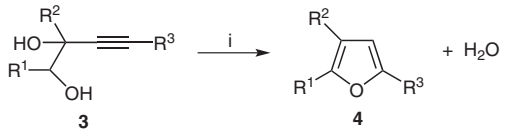
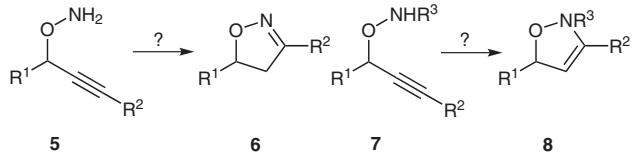
more usually associated with use as a stationary phase for alkene isomer separation. The precursor 3-alkyne-1,2-diols **3** are converted into the furans **4** in essentially quantitative yields under virtually neutral conditions and at ambient temperature in a matter of a few hours. The method is also amenable to adaption to flow methodology, and the catalyst, being heterogeneous, can readily be recovered and recycled. However, there was certainly an element of doubt in this present idea as Dalla and Pale have shown that hydroxy groups positioned adjacent to an alkyne group greatly facilitate the binding of silver(I) ions to the acetylenic function.[22]



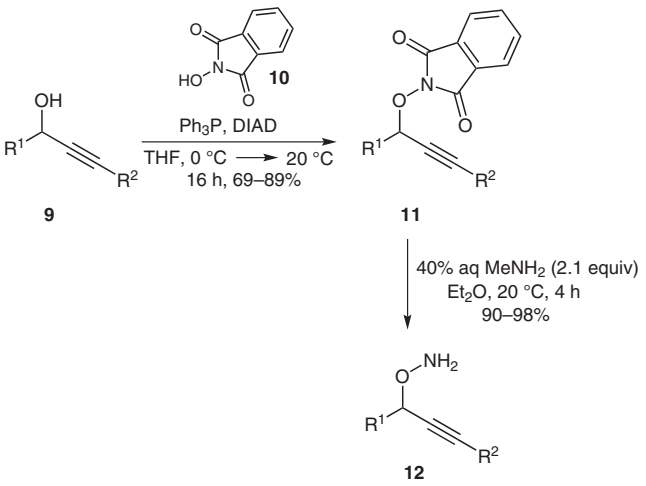
Scheme 1 *Reagents and conditions*: i) 10% w/w $AgNO_3$–SiO_2 (10 mol%), CH_2Cl_2, 20 °C, ca. 3 h, >97%.

Of course, this is exactly the set up in the case of the furan precursors **3**, but would not be the case in the projected precursors **5** and **7** which we hoped could be converted into the corresponding dihydroisoxazole isomers **6** and **8** (Scheme 2) in much the same manner. Herein, we report that both types of cyclisations are indeed viable but, in the latter case, only with a limited range of nitrogen protecting groups.



Scheme 2

The synthesis of suitable precursors proved to be relatively straightforward, but did stimulate the development of a new, chromatography-free method for working up a Mitsunobu reaction.[23] A series of secondary propargylic alcohols **9**, generated by condensations of aldehydes with lithio acetylides, were subjected to a Mitsunobu displacement with *N*-hydroxyphthalimide **10** (Scheme 3).[24] These all proceeded to give respectable yields of the expected phthalimides **11** without the need for conventional column chromatography; for a full description of this method, see reference 23 and for definitions of the nature of the R^1 and R^2 substituents, see Table 1 below. The only exception was the diphenyl example [**11**; $R^1 = R^2 = Ph$], in which case the product was exceptionally sensitive to elimination and decomposition, presumably by reason of the facile generation of a highly stabilised secondary benzylic and propargylic carbenium ion when exposed to any type of acid. Only when the Mitsunobu reagents were added sequentially without any intermediate periods of stirring[23] could a 41% yield be realised. The phthalimide group was then removed from all such products by exposure to aqueous methylamine in diethyl ether and the desired products **12** isolated by cooling the resulting mixture to 0 °C, filtering off the precipitated phthalic diamide and solvent evaporation.



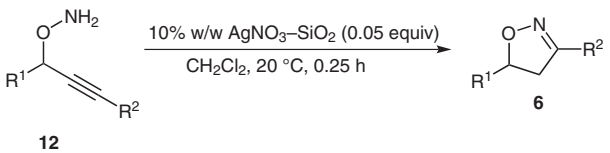
Scheme 3

The unprotected *O*-propargylic hydroxylamines **12** turned out to be relatively sensitive but, fortunately, were isolated in a sufficiently pure state as to be suitable for attempting the key step in this sequence. We were delighted to find that 10% w/w silver nitrate–silica gel was indeed capable of catalysing their conversion into the corresponding 4,5-dihydroisoxazoles **6** under very mild conditions, despite the absence of a propargylic hydroxy group as discussed above. After some optimisation, we found the best conditions for most substrates involved simply stirring a suspension of 0.05 equivalents of the catalyst with the precursor **12** in dry dichloromethane for fifteen minutes. Filtration through a plug of either Celite or silica gel, washing the solid with fresh dichloromethane and evaporation of the combined filtrates left the essentially pure dihydroisoxazoles **6** in excellent yields (Table 1).

The only detectable impurities were very small traces of the corresponding isoxazole oxidation products, the amount of which increased if more silver nitrate was used. Under the optimised conditions, levels of these oxidation products were usually around 2–3%. Subsequent ongoing studies have indicated that such byproducts may well not arise by simple oxidation of the dihydroisoxazoles **6**.[25] Notable features of this chemistry are that both benzyl and especially silyl protecting groups survive unmolested (entries 3 and 4) and that a highly hindered example (entry 6) works equally well, as did the diphenyl derivative (entry 7), which was more difficult to prepare (see above). Examples of terminal alkynes (entries 8 and 9) proved slower to react but, by using twice as much catalyst, equivalent yields were obtained after reaction times of one hour. A final example (entry 10) demonstrated, perhaps surprisingly, that electron-poor alkynes react just as easily.

We presume that such cyclisations proceed via the corresponding enamines (2,5-dihydroisoxazoles), although at-

Table 1 Synthesis of 4,5-Dihydroisoxazoles **6** from Hydroxylamines **12**



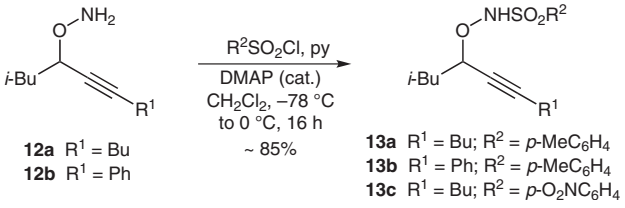
12

Entry	**12**	R^1	R^2	Yield (%)[a]
1	**a**	*i*-Bu	Bu	96
2	**b**	*i*-Bu	Ph	90
3	**c**	*i*-Bu	CH_2OBn	92
4	**d**	*i*-Bu	$(CH_2)_2OTBS$	91
5	**e**	*i*-Bu	4-$MeOC_6H_4$	91
6	**f**	*i*-Bu	*t*-Bu	96
7	**g**	Ph	Ph	89
8	**h**	*i*-Bu	H	96[b]
9	**i**	Ph	H	96[b]
10[c]	**j**	*i*-Bu	4-$O_2NC_6H_4$	88

[a] Overall yields from the phthalimides **11**.
[b] Terminal alkynes required exposure to 0.1 equiv of Ag(I) for 1 h for complete reaction.
[c] The starting material was obtained by a Sonogashira coupling between the precursor alkyne in entry 8 and 4-iodonitrobenzene.

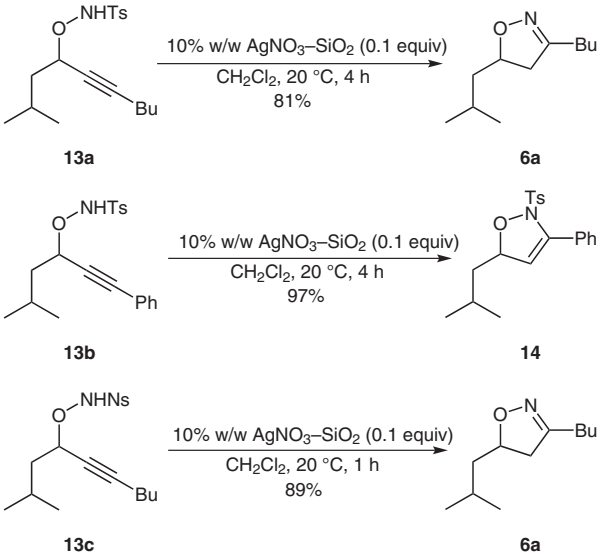
tempts to observe such species by ^{1}H NMR proved fruitless. We therefore turned to a study of how to make such isomeric heterocycles by adding a suitable protecting group to the amine nucleophile in the hydroxylamines **12**. In view of the very mild nature of the cyclisations, it seemed highly likely that this would be an easily achieved aim but, as so often happens, this turned out to be an erroneous assumption.

We chose to use sulfonamide derivatives first of all as these, especially the *N*-tosyl derivatives, were expected to be very stable. Three examples **13a–c** were prepared, but under carefully controlled conditions in order to avoid bis-sulfonylation of the rather nucleophilic nitrogen. This was achieved in good yields (Scheme 4) using strictly one equivalent of the sulfonyl chloride and mixing the reactants at low temperature prior to warming to ambient.



Scheme 4

In view of the usual stability of tosylamides, we were very surprised to find that exposure of the tosyl derivative **13a** to 0.1 equivalents of 10% w/w silver nitrate–silica gel resulted in a relatively slow conversion but into the 4,5-dihydroisoxazole **6a** (Scheme 5)! By contrast, the corresponding phenyl derivative **13b** was converted very efficiently into the expected 2,5-dihydro-isomer **14**. The related 4-nitrophenylsulfonyl (nosyl) derivative **13c**, also having two alkyl substituents, was similarly but more rapidly converted, with loss of the sulfonyl group, into the same 4,5-dihydroisoxazole **6a**. These surprisingly facile hydrolyses suggest that there may be more than meets the eye to these types of cyclisation, especially in view of the very contrasting result obtained from the phenyl-substituted derivative **13b**. Some related and also unexplained limitations have been observed in related gold-catalysed cyclisations involving sulfonamides.[15]

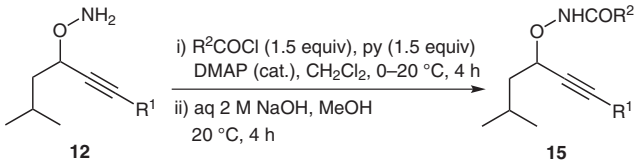


Scheme 5

This spelled the end to our work on sulfonamide derivatives as we turned to various *N*-acyl analogues with a view to achieving more predictable and general success in such cyclisations leading to the 2,5-dihydro-isomers; we chose to start with carbamate-like derivatives (Table 2). Once again, the synthesis of these suffered from overreaction with the acylating reagent, meaning that all of the initial products were contaminated with the corresponding bis-acyl analogues. This was, however, easily solved in all cases except one by a simple ambient temperature hydrolysis of one of two such groups.

Our first observation was that the 'methoxycarbonyl' derivative **15a** seemed to be a rather unstable moiety, the $ONHCO_2Me$ group, reflected both by the very poor yield obtained in making it and also by its unexpected and complete decomposition when exposed to silver nitrate–silica gel. By contrast, the corresponding '*N*-Boc' derivative **15b** was much more stable but unfortunately resistant to silver-catalysed cyclisation. Hence, such 'carbamate' derivatives did not seem well suited to this type of cyclisation, in contrast to the related gold-catalysed chemistry.[15] Similarly, the *N*-trifluoromethyl derivative **15c** also failed

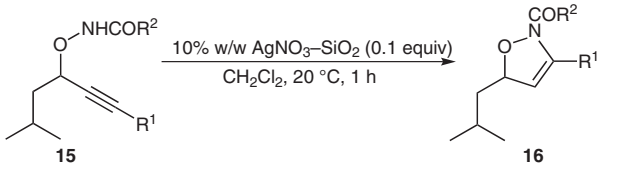
Table 2 Synthesis of *N*-Acyl Derivatives **15**



Entry	12	R^1	R^2	15	Yield over 2 steps (%)
1	**a**	Bu	OMe	**a**	17
2	**a**	Bu	O*t*-Bu	**b**	81
3	**a**	Bu	CF_3	**c**	85
4	**a**	Bu	Me	**d**	92
5	**b**	Ph	Me	**e**	90
6	**h**	H	Me	**f**	88

to undergo cyclisation, perhaps because of the reduced nucleophilicity of the nitrogen. The acetyl derivatives **15d–f** also turned out to be relatively sensitive. For example, hindered rotamer interconversion was apparent from inspection of their room-temperature proton spectra in deuteriochloroform but when attempts were made to secure more informative spectra in warm DMSO-d_6, extensive decomposition set in. However, despite this thermal instability, cyclisations at ambient temperature using the same silver catalyst gave excellent returns of the hoped-for 2,5-dihydroisoxazoles **16**. These and related results are collected in Table 3.

Table 3 Synthesis of 2,5-Dihydroisoxazoles **16** from Acylated Hydroxylamines **15**



Entry	15	R^1	R^2	16	Yield (%)
1	**d**	Bu	Me	**a**	98
2	**e**	Ph	Me	**b**	97
3	**f**	H	Me	**c**	0
4		$(CH_2)_2$OTBS	Ph	**d**	96
5		$(CH_2)_2$OH	Ph	**e**	81

Such cyclisations were a little less rapid than the examples having a free amino group (Table 1), requiring around an hour to reach completion with twice as much catalyst. However, the yields of the 2,5-dihydroisoxazoles **16** were generally excellent, with the exception of the terminal acetylene **15f** which failed to cyclise and which appeared to undergo extensive decomposition instead. The last two examples demonstrate that benzoyl derivatives are equally suitable; it is therefore very likely that a range of other such acyl derivatives could also be used successfully. Furthermore, in the last two examples **16d**,**e**, there was no interference from the pendant silyloxy or hydroxy groups which, potentially, could undergo competing 5-*endo*-dig cyclisations. Overall, it was indeed fortunate that these cyclisations were so clean as the products **16** are quite sensitive to chromatographic purification, which can result in considerable losses. In the present cases, this was not necessary.

We also found it possible to conduct such cyclisations in a flow system, which consisted of an HPLC column packed with 10% w/w silver nitrate on silica gel. A column measuring 15 × 1 cm was capable of cyclising precursors **15d** and **15e** (Table 3; entries 1 and 2) completely to the expected products **16a**,**b** at a flow rate of 0.3 mmol per minute using a 0.1 M solution in dichloromethane. Identical results were obtained using representative examples (entries 1–3) from Table 1, when returns of the corresponding 4,5-dihydroisoxazoles **6** were also essentially quantitative. Hence this could represent a viable tactic for scale-up of these reactions.

Finally, as outlined above, it has been reported that if hydrochloride salts of representative *O*-propargylic hydroxylamines **12** (Scheme 3) are heated with potassium carbonate in methanol or neutralised with sodium hydroxide, then cyclisation to give 4,5-dihydroisoxazoles **6** occurs smoothly.[8] In the present work, we observed that simply heating examples of the 'free' hydroxylamines **12** in methanol failed to produce any of the heterocycles **6**. The reasons behind this remain a mystery.

In summary, this approach represents, overall, a relatively brief and certainly highly efficient route to both 4,5- and 2,5-dihydroisoxazoles. The methodology naturally is regiospecific and hence delivers single isomers of these sensitive heterocycles. The main limitation in synthesising the 2,5-isomers by this method is that the amino group should, in general, be protected as an acyl derivative and not with a sulfonyl or alkoxycarbonyl function. Given that the initial precursors, secondary propargylic alcohols, can be obtained as single enantiomers using a number of approaches, then this chemistry should be amenable to the synthesis of optically pure products of both types.

Acknowledgment

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