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On the viability of 5-*endo*-dig cyclisations of *O*-propargylic hydroxylamine derivatives, leading to 2,5-dihydroisoxazoles (3-isoxazolines)

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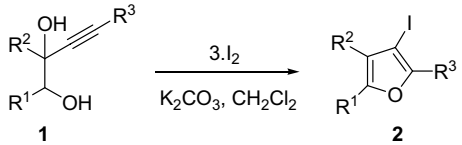
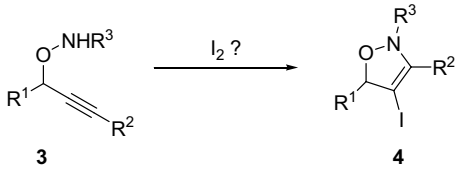
Abstract—*O*-Propargylic hydroxylamines undergo smooth 5-*endo*-dig cyclisations upon exposure to 3 equiv of molecular iodine to give respectable yields of the corresponding 4-iodo-2,5-dihydroisoxazoles, which should find a number of applications as intermediates for syntheses amongst this useful class of heterocycles.

Despite being a favoured process according to Baldwin's rules,[1] the 5-*endo*-dig cyclisation mode has only enjoyed the prominence afforded to related annulation reactions relatively recently. Some time ago, encouraged by a scattering of isolated examples in the older Russian literature,[2] we discovered that such cyclisations could be used to a great effect in the synthesis of 3-iodofurans **2** from 3-alkyne-1,2-diols **1** by treatment with 3 equiv of iodine in the presence of anhydrous potassium carbonate (Scheme 1).[3] Subsequently, we have shown that similar cyclisations can be highly effective in the synthesis of β-halopyrrole derivatives.[4] Furthermore, many other halide-induced cyclisations, both 5-*endo*-dig and other modes, in which nucleophilic centres are induced to bond to acetylenic carbons, have been used to elaborate an impressive range of heterocycles[5] and even carbocycles.[6]



Scheme 1.

Of course, such chemistry offers a double advantage as it is effective both in forming a particular heterocyclic system but also leaves the latter endowed with a halide atom, which is usually ideally set up for the incorporation of an additional substituent by using one of the plethora of palladium-catalysed coupling reactions now available. The presence of such halide atoms can also give the option of selective carbonylation reactions leading to ester formation, along with the potential for the generation of useful metallated intermediates by halogen–metal exchange and homologation by radical formation. It occurred to us that such cyclisation methodology might be extended to include examples of alkynyl hydroxylamine derivatives **3** (Scheme 2).



Scheme 2.

If successful, this would lead to halo-isoxazoline derivatives **4** and, subsequently perhaps, various other oxidation states of these useful heterocycles, along with open-chain 1,3-amino alcohol derivatives, following cleavage of the relatively weak N–O bond.[7] In addition, this approach could provide a useful complementarity to the ubiquitous [1,3]-dipolar cycloaddition chemistry, which is most often deployed to obtain this type of heterocycle.[7,8] Initially, we wondered whether such

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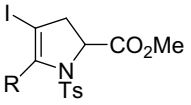
cyclisations would be viable because of the weakness of the N–O bond. However, we were reassured that this might well not be a problem by the recent reports of the successful 5-*exo* cyclisation of various unsaturated hydroxylamine derivatives.[9] Our isolation of iodo-dihydropyrroles **5**[4] also indicated both that such 5-*endo*-dig cyclisations were viable when a sulphonamide acted as the nucleophile and that dehydration resulting in aromatisation (as shown in Scheme 1) was not necessary to drive the cyclisation to completion. Herein, we report on a successful model study, which does indeed demonstrate the viability of the proposed cyclisation shown in Scheme 2.



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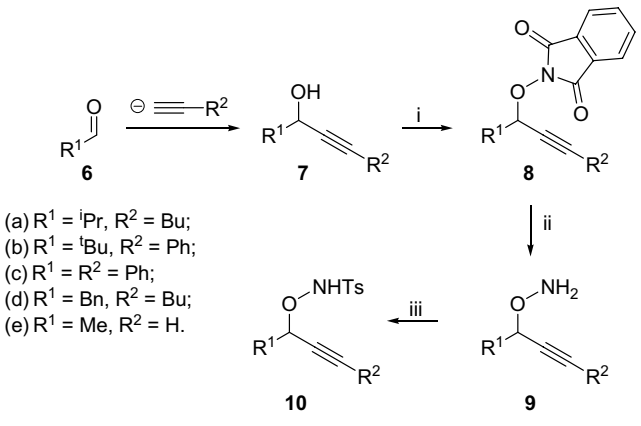
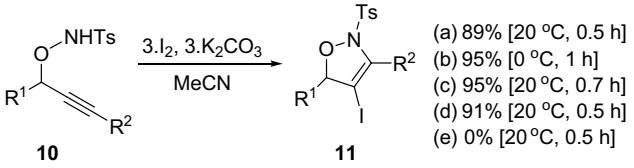
The required precursors **3** were synthesised using the four step sequence shown in Scheme 3 which, after some optimisation, turned out to be highly efficient. Firstly, an aldehyde, R^1CHO **6** was condensed with either an alkynyl lithium or an alkynyl Grignard reagent to give excellent yields of propargylic alcohols **7**. These were then subjected to a Mitsunobu reaction with *N*-hydroxy phthalimide using a standard set of reagents, DEAD or DIAD and Ph_3P.[10] Initially, this was a very poor step when carried out in solvents such as ethyl acetate or dichloromethane or mixed systems, delivering yields which were usually much less than 50%. It was only when we employed anhydrous tetrahydrofuran as the solvent that viable yields, usually around 85–90%, were obtained.[10] However, to secure these, the usual relatively demanding level of column chromatographic separation was required. This necessity is such a drawback to an otherwise extremely useful reaction that many derivatives of the reagents or sophisticated solvent systems have been developed in efforts to alleviate this and render the method 'chromatography-free'.[11] Unfortunately, these modified reagents are generally not commercially available. This encouraged us to develop the first chromatography-free Mitsunobu work-up method which employs the more commonplace reagents, DEAD or DIAD, and triphenylphosphine.[12] When using this new procedure, yields of at least 90% of O-alkylated hydroxyphthalimides **8** were routinely secured. While removal of the phthalimide protecting group could be effected reasonably efficiently using the classical Ing–Manske procedure (hydrazine),[13] a much milder method[14] consisted of exposure to aqueous methylamine in ether at ambient temperature (1–4 h) followed simply by filtration through celite, to remove highly insoluble *N*,*N*′-dimethylphthalic diamide, and evaporation. The resulting *O*-alkyl hydroxylamines **9** were then directly N-tosylated to give the required sulfonamides **10** in reasonable yields.[15]



Scheme 3. Reagents and conditions: (i) Ph_3P (1.2 equiv), THF, 0 °C, add DIAD (1.1 equiv), 0.25 h, add alcohol **7** (1 equiv), 20 min, add *N*-hydroxy phthalimide (1.1 equiv), 16 h, 20 °C, >90% [Ref. 12]; (ii) aq $MeNH_2$, Et_2O, 20 °C, 3 h; (iii) TsCl (1.1 equiv), py, DMAP (cat.), CH_2Cl_2, 0 °C, 16 h, 60–70%.

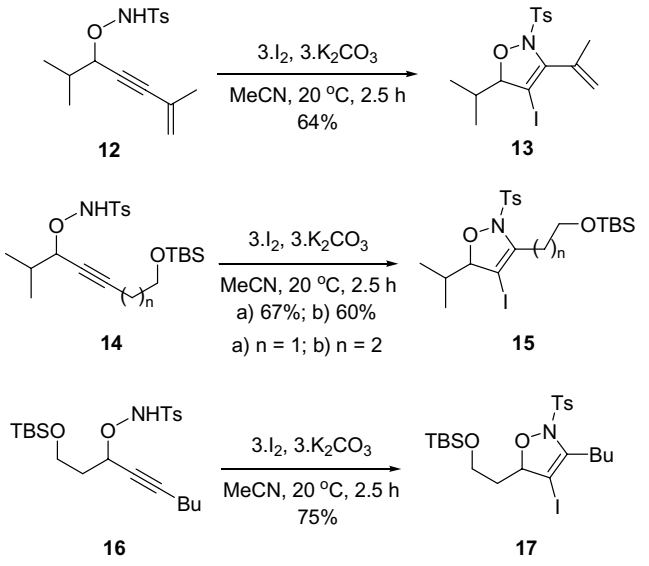
We were delighted to find that these precursors **10** responded well to a typical set of conditions for carrying out 5-*endo* iodocyclisations, amongst other types of ring generation, and gave the desired iodo-oxazolines **11** in excellent isolated yields (Scheme 4).[16] An exception was the l-alkyne derivative **10e**, which failed to give any of the 3-unsubstituted derivative [**11e**; $R^2 = H$], but instead an unidentified mixture of products.



Scheme 4.

In general, the cyclisations were relatively rapid and very clean. This was particularly fortunate, as products **11** are sensitive to silica gel chromatography over a prolonged period, undergoing variable amounts of elimination of toluenesulfinic acid to give the corresponding isoxazoles, along with other unidentified decomposition products. Rapid filtration through silica using ethyl acetate–petrol mixtures served to secure pure products, which were also unstable when kept in solution but which could be stored below 0 °C for prolonged periods.

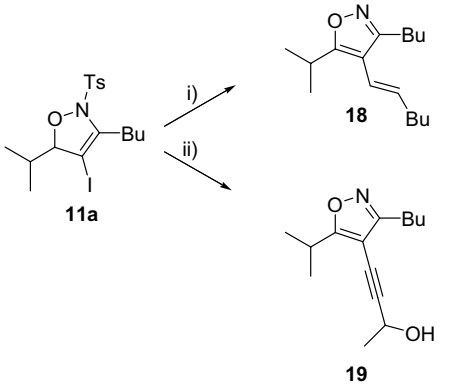
In order to exemplify further these successful cyclisations, we chose to incorporate more reactive functional groups into the isoxazoline side chains, which could potentially compete with the 5-*endo*-dig pathway and which would also offer possibilities for subsequent transformations of the initial products. In all cases, the approach to these precursors was the same as that outlined in Scheme 3. For example, by starting with 3-methylbut-3-en-l-yne, hydroxylamine derivative **12** was prepared in a good overall yield. Subsequent exposure to the usual iodocyclisation conditions for 2.5 h led to the isolation of the expected product **13** in 64% yield (Scheme 5). There was no evidence which suggested the formation of addition products involving the alkene group.



Scheme 5.

Starting with the *O*-TBS derivative of 3-butyn-1-ol, the required precursor [**14a**, $n = 1$] was also obtained in a good yield and subsequently underwent smooth cyclisation to provide the hydroxyethyl isoxazoline **15a** in 67% isolated yield, after a reaction period of 2.5 h at ambient temperature. No products arising from competing 5-*endo* cyclisation by the oxygen atom were observed; the slightly lower yield was due to some loss of the silyl group to give the corresponding alcohol (10–15% isolated). In the same way, homologous hydroxylamine **14b**, derived from 4-pentyn-l-ol, was converted into isoxazoline **15b** in a similar yield and again with some loss of the silyl group. In this case, we did not observe the formation of any products from either 5-*exo* or 6-*endo* cyclisations of the oxygen onto the alkyne function. Finally, precursor **16** was obtained from the corresponding silyl ether of 3-hydroxypropanal and found to also undergo smooth cyclisation to give iodo-isoxazoline **17** without competition from either of these two possible alternative modes involving oxygen as the nucleophile. Hence, the prospects for the incorporation of at least some functionalised side chains look viable.

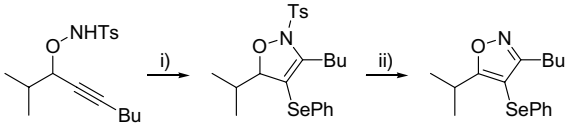
The 4-iodo-isoxazolines reported in this letter, to the best of our knowledge, appear to be a novel class of compounds which, by reason of the presence of an iodine atom bonded to an sp^2-carbon should have some potential in palladium-catalysed coupling chemistry. A very brief survey in the present study showed that the derivatives reported herein are very prone to elimination to give the corresponding isoxazoles. For example, an attempted Suzuki coupling reaction between iodide **11a** and (*E*)-hexenylboronic acid resulted in the isolation of a good yield of vinyl isoxazole **18** (Scheme 6). Similarly, a Sonogashira coupling using the same iodo-isoxazoline gave, in albeit lower yield, alkynyl isoxazole **19**. It is not clear if the elimination of *p*-toluenesulfinic acid to give the corresponding 4-iodo-isoxazoles precedes the coupling step. A few examples of both types of coupling reactions using iodo-isoxazoles are known,[17] although,



Scheme 6. Reagents and conditions: (i) (*E*)-1-hexenylboronic acid, 10 mol % $(Ph_3P)_4Pd$, 2 equiv Na_2CO_3, aq EtOH, reflux, 16 h, 81%; (ii) 2 equiv but-1-yn-3-ol, 5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI, DMF/Et_3N, 60 °C, 16 h, 37%.

perhaps ominously, examples of such couplings do not feature in a recent and extensive treatise on the subject of such couplings involving heteroaromatics.[18]

Finally, we were able to demonstrate that selenocyclisation is also possible in this area. Exposure of hydroxylamine derivative **11a** to phenylselanyl chloride in the presence of potassium carbonate, initially at low temperature, led to an excellent yield of selanyl derivative **20** (Scheme 7). The claimed yield of 95% is based solely on the weight of the product and ^1H NMR analysis which suggested >96% purity. This was because all attempts to fully purify this product, especially using silica gel chromatography, resulted in rapid elimination to give selanyl-isoxazole **21**, which was isolated in a pure state, typically in overall yields of 70–75%.



Scheme 7. Reagents and conditions: (i) 1.05 equiv PhSeCl, 1.1 equiv K_2CO_3, CH_2Cl_2, −78 °C to +20 °C, 2.5 h, ca. 95%; (ii) SiO_2, EtOAc–petrol, ~75%.

Acknowledgements

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References and notes

1. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736, and 739–741.
2. Fabrycy, A.; Kubala, J. *Zh. Obshch. Khim.* **1961**, *31*, 476–479; Fabrycy, A.; Wichert, Z. *Zh. Obshch. Khim.* **1979**, *49*, 2499–2504.

3. Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007–1008; For alternative approaches to the precursors **1**, see: El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2000**, *41*, 5945–5948.
4. Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874–2883; Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622–628.
5. Rao, M. S.; Esho, N.; Sergeant, C.; Dembinski, R. *J. Org. Chem.* **2003**, *68*, 6788–6790; Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769–1772; Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292–10296; Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651–654; van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791–1795; Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957–2960; Knight, D. W.; Sharland, C. M. *Synlett* **2003**, 2258–2260; Knight, D. W.; Sharland, C. M. *Synlett* **2004**, 119–121; Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037–1040; Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2006**, *47*, 2825–2828; Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500–10501, For a comprehensive listing, see Yao et al. cited in Ref. 6.
6. Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1546; Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; Gonzalez, J. M. *Chem. Commun.* **2005**, 2008–2010; Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511–3517.
7. For recent applications, see: Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376–5383; Buhrlage, S. J.; Brennan, B. B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 12456–12457, and references therein.
8. For recent applications of nitrile oxide chemistry, see: Lohse-Fraefel, N.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 2011–2014, and references therein.
9. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L. *J. Chem. Soc., Chem. Commun.* **1995**, 235–236; Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331–2333; Bates, R. W.; Sa-Ei, K. *Org. Lett.* **2002**, *4*, 4225–4227; Janza, B.; Studer, A. *Synthesis* **2002**, 2117–2123; Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203–5205.
10. For reviews, see: Mitsunobu, O. *Synthesis* **1981**, 1–28; Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164; Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.
11. These methods have been highlighted in a recent review: Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772.
12. Proctor, A. J.; Beautement, K.; Clough, J. M.; Knight, D. W.; Li, Y.-F. *Tetrahedron Lett.* **2006**, *47*, 5151–5154.
13. Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2348–2351.
14. Wolfe, S.; Hasan, S. K. *Can. J. Chem.* **1970**, *48*, 3572–3576.
15. The main loss of material under the conditions shown in Scheme 3 appeared to be due to the formation of bis-tosyl derivatives. Subsequent experiments, performed after completion of the present project, have indicated that a superior method is to mix the reactants at −78 °C in dichloromethane and then allow the reaction mixture to slowly warm to ambient temperature during 3 h—Proctor, A. J., unpublished observations.
16. Full analytical and spectroscopic data consistent with the proposed structures have been obtained for all compounds reported herein.
17. For some Stille and Suzuki couplings of iodo-isoxazoles, see: Labadie, S. S. *Synth. Commun.* **1994**, *24*, 709–719; For various Heck and Sonogashira couplings of similar substrates, see: Yamanaka, H.; Shiraiwa, M.; Yamamoto, E.; Sakamoto, T. *Chem. Pharm. Bull.* **1981**, *29*, 3543–3547; For palladium-catalysed couplings with phenylsulfonylacetonitrile, see: Sakamoto, T.; Kondo, Y.; Suginome, T.; Ohba, S.; Yamanaka, H. *Synthesis* **1992**, 552–554; For condensations of metallated derivatives with cyclic ketones, see: Antequera, T.; Ramos, V.; Vincente, T. *Heterocycles* **1986**, *24*, 3203–3211; Polo, C.; Ramos, V.; Torroba, T.; Rodriguez, M. L.; Bossio, R.; Marcaccini, S.; Pepino, R. *Heterocycles* **1991**, *32*, 1757–1764.
18. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*. Tetrahedron Organic Chemistry Series; Pergamon Press: Oxford, 2000; Vol. 20.