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On the diverse outcomes of base-induced cyclisations of 2-alkynylphenylhydroxamic acids

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Abstract—Base-induced cyclisations of 2-alkynylphenylhydroxamic acids occur by attack of nitrogen onto the alkyne group in either *exo* or *endo* fashions to give the corresponding isoindol-1(2*H*)-ones or 1(2*H*)-isoquinolinones depending upon the alkyne substituent.

Since the original observations of Stephens and Castro on the facile cyclisation of 2-alkynylbenzoic acids **1** to the ylidenephthalides **2**,[1] this has been expanded into a useful heterocyclic synthesis, especially by modification of the carboxylic acid into the corresponding amides[2] or hydrazides.[3] There is however a potential drawback associated with this methodology: in many versions, the isomeric isochromenones **3** are formed, sometimes as mixtures along with the phthalides **2** (Fig. 1).[1]

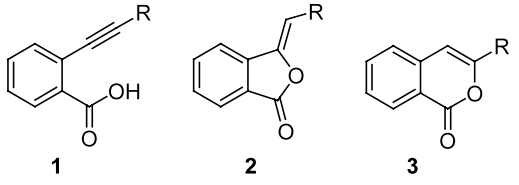

Figure 1.

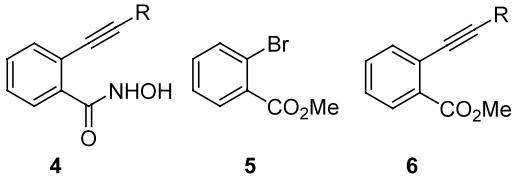

Figure 2.

Our combined interests both in this area and also in the reverse Cope elimination of unsaturated hydroxylamines[4] led us to speculate that it might be possible to carry out such cyclisations but using 2-alkynylphenyl hydroxamic acids **4**. At the outset, the viability of such cyclisations was far from clear as was the nature of the products, as these could in principle proceed via three different nucleophilic centres, the carbonyl or hydroxylamine oxygens or the nitrogen in either an *endo* or an *exo* fashion. Herein, we report on a surprising diversity of outcomes to what turned out to be extremely viable and selective.

The necessary starting materials were all prepared from methyl 2-bromobenzoate **5** by Sonogashira coupling[5] with the appropriate 1-alkyne (Fig. 2). Under relatively standard conditions [$(Ph_3P)_4Pd$, CuI (cat.) in degassed 1:3 THF–Et_2NH, reflux 3 h], couplings of ester **5** with 1-alkynes provided 82-95% isolated yields of the expected 2-alkynylbenzoates **6**. Attempts to generate the key hydroxamic acids **4** by similar couplings but using 2-bromophenylhydroxamic acid were, perhaps not surprisingly, unsuccessful.

A straightforward method for the conversion of such benzoate esters **6** into the corresponding hydroxamic acids involves heating the ester with hydroxylamine. Starting with the hexynyl derivative **7**, we heated this with excess hydroxylamine in methanol until transformation to what appeared to be a single product was complete (Scheme 1).[6] Typically this took around three hours. This first experiment gave a single product, m.p.

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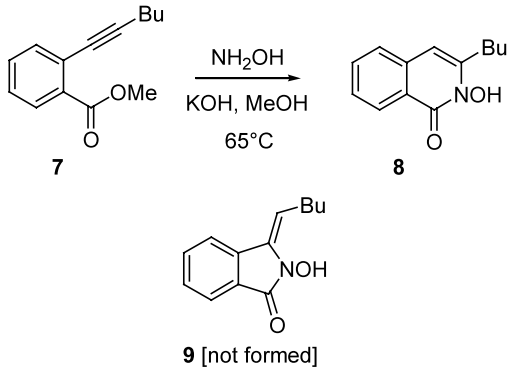
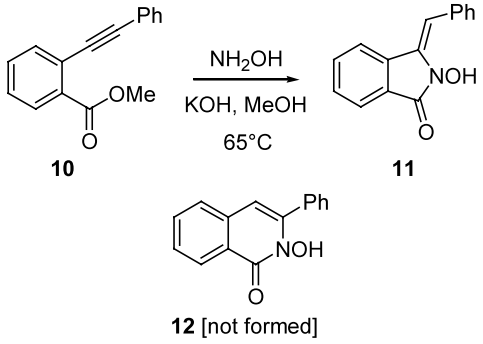


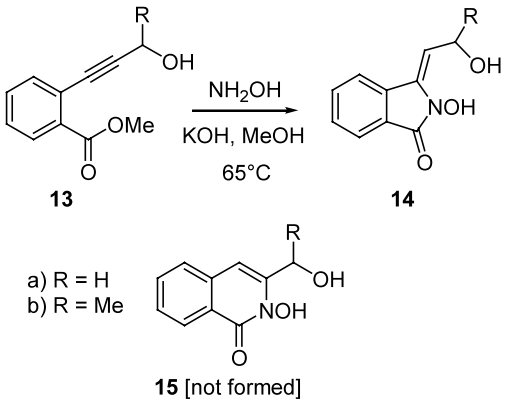
Scheme 1.

108–110°C, in 86% isolated yield. This was tentatively identified as the isoquinolinone **8** from its ^{1}H NMR data which featured a singlet at δ_H 6.45 and a triplet ($J=7$Hz) centred at δ_H 2.88. An alternative structure, formation of which could reasonably be expected in the light of some of the foregoing results,[1–3] the ylideneisoindolone **9** which would arise from *exo*-cyclisation was ruled out in the light of these data. The latter would be expected to display an olefinic proton as a triplet together with an allylic methylene with a double triplet or apparent quartet splitting pattern. This conclusion was confirmed by comparison with literature data (lit.[7] m.p. 108–109°C) and also by an X-ray crystallographic determination.[8]

Thinking that we had discovered a new isoquinolinone synthesis, we treated the phenylalkyne derivative **10** with hydroxylamine under the same conditions[6] and isolated a single crystalline product; m.p. 172°C, in 81% yield (Scheme 2). However, this was proven to be the isoindolone **11** instead, rather than the isomeric isoquinolinone **12**. While spectroscopic data did not provide completely unambiguous proof of structure **11**, the lower melting point (137–138°C)[7] of isoquinolinone **12** indicated this was not the structure of the product. Moreover, an NOE enhancement between the new olefinic proton singlet at δ_H 6.90 and an aromatic doublet at δ_H 7.80 indicated the (*Z*)-stereochemistry shown. Any lingering uncertainty was removed when an X-ray crystallographic determination proved the correctness of structure **11**.[8]



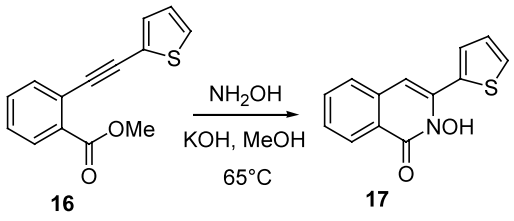
Scheme 2.



Scheme 3.

Similar *exo*-cyclisations occurred when the propargylic alcohol derivatives **13** were exposed to excess hydroxylamine in hot methanol:[6] only the (*Z*)-isoindolones **14a** (m.p. 94°C) and **14b** (m.p. 96°C) were isolated in 65% and 60% yields respectively (Scheme 3). In both cases, ^{1}H NMR data unambiguously distinguished these structures from those of the isomeric isoquinolinones **15**.[9] Both ^{1}H and especially ^{13}C data showed both products to be single geometric isomers, again identified as having (*Z*)-stereochemistry from NOE enhancements of 4-5% between the alkene protons and aromatic doublets. These data clearly exclude the alternative formulation as isoquinolinones **15**.

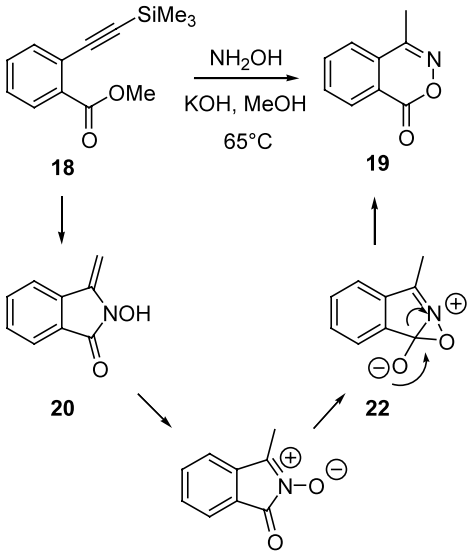
However, such a structure **17** was obtained as a single isomer in 72% isolated yield when the thiophenyl derivative **16** was heated with hydroxylamine (Scheme 4).



Scheme 4.

A final example produced some more complex chemistry: when the silylated alkyne derivative **18** was treated similarly,[6] the only product isolated was the benzoazinone **19**, m.p. 163–164°C, in 64% yield (Scheme 5). This was identified by comparison with authentic material derived from 2-acetylbenzoic acid.[10] A possible mechanism for formation of this unexpected product involves the assumed ester to hydroxamic acid conversion followed by *exo*-cyclisation to give the methylideneisoindolone **20**, during which desilylation also takes place. Tautomerism would then lead to the more stable nitrone **21** which could rearrange to the observed product **19** via the oxaziridine alkoxide **22**.

In summary, we have defined new and straightforward syntheses of some isoquinolinones and isoindolones



Scheme 5.

which, while clearly limited to a particular substituent, are remarkable for their selectivity in favour of either *endo* or *exo*-cyclisation. In each case, examination of crude material did not reveal the presence of the alternative product. At present we can only speculate on the origins of this very high selectivity which may be associated with the fact that all isoindolones are formed when the alkyne is substituted with an electron-withdrawing group, albeit not a powerful one, while the isoquinolinones **8** and **17** have electron-donating substituents. However, these relatively weak influences of such substituents does not seem entirely sufficient to account for such a high level of regioselectivity. Hopefully further studies along with theoretical calculations will provide a better insight.[11]

Acknowledgements

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4. Hanrahan, J.; Knight, D. W.; Salter, R. *Synlett* **2001**, 1587.
5. Sonogashira, K.; Tohda, Y.; Hagihara, N. A. *Tetrahedron Lett.* **1975**, 4467.
6. General method: Warm solutions of hydroxylamine hydrochloride (6 eq.) in methanol (0.5 ml $mmol^{-1}$) and potassium hydroxide (9 eq.) in methanol (0.25 ml $mmol^{-1}$) were mixed and the resulting solution cooled to below 40°C when potassium chloride precipitated. This was filtered off and a methyl 2-alkynylbenzoate (1 equiv.) was added. The resulting mixture was then refluxed until the reaction appeared to be complete according to TLC (ca. 3 h). The cooled mixture was then evaporated. Excess ice-cold 2 M hydrochloric acid was added to the residue and the product extracted into dichloromethane. The combined organic extracts were washed with water and brine then dried, filtered and evaporated. Crystallization of the resulting residue, usually from ethyl acetate or ethyl acetate-petrol mixtures then secured the pure products in the yields quoted.
7. Moriconi, E. J.; Creegan, F. J. *J. Org. Chem.* **1966**, *31*, 2090.
8. These data have been deposited on the Cambridge Crystallographic Database: Compound **8** [CCDC No. 193931], compound **11** [CCDC No. 193932].
9. Isoindolinone **14a** showed δ_H ($CDC1_3$) 4.70 (1H, d, *J* 6.3) and 5.91 (t, *J* 6.3) while the related protons in analogue **14b** resonated at 4.58 and 5.83.
10. (a) Gabriel, S. *Ber.* **1883**, *16*, 1995; (b) Kampschmidt, L. W; Wibaut, J. P. *Rec. Trav. Chem.* **1954**, *73*, 431; (c) Sudoh, Y; Jin, Z.-T; Matsamura, H. *J. Heterocycl. Chem.* **1982**, *19*, 525.
11. Full analytical and spectroscopic data consistent with the proposed structures have been obtained for all compounds reported herein.