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A Convergent Approach to Functionalised Alkynes

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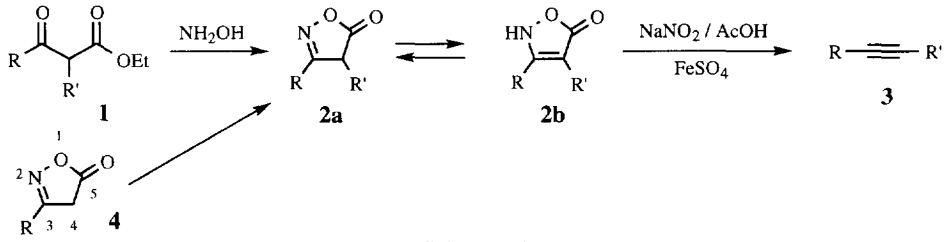
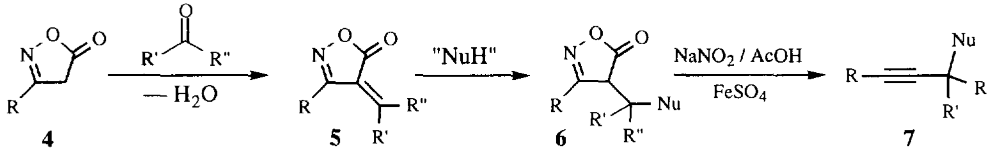
Abstract : Knoevenagel type condensation of 4-unsubstituted isoxazolinones with ketones or aldehydes followed by Michael addition of a nucleophile — hydride, cyanide, or phosphite— and exposure of the adduct to sodium nitrite / aqueous acetic acid and ferrous sulfate gives variously functionalised alkynes.

Recently, we described a new reaction[1] for converting a β-ketoester **1** into an alkyne **3** by nitrosation of the corresponding isoxazolin-5-one **2** in the presence of ferrous sulfate (Scheme 1). The latter reagent is needed to suppress the formation of dimers of the isoxazolinone by generating nitric oxide *in situ*. The utility of this transformation stems from the rich array of existing methods for constructing the starting β-ketoesters with the desired substitution pattern.[2] In one illustration of this aspect, we developed a convenient route to large ring acetylenes hinging on the ring expansion of cycloalkanones with ethyl diazoacetate.[3] We now wish to report that by using the little explored chemistry of the isoxazolinone itself, a variety of functionalised alkynes can be assembled in a straightforward, convergent manner. This alternative approach delivers alkynes that are not easily accessible otherwise and thus complements the chemistry of β-ketoesters.



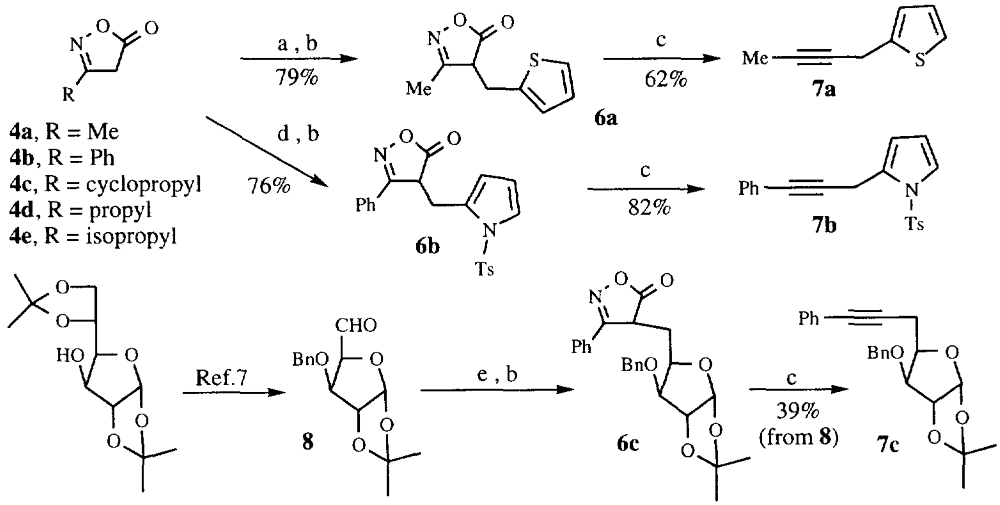
Scheme 1

Isoxazolinones such as **2** or **4** possess a remarkably high acidity that is comparable to that of acetic acid, with pKa's in the range of 4-6.[4] The conjugate base has in fact aromatic character and benefits therefore from extra stabilisation. Isoxazolinones **4**, unsubstituted in the 4 position, belong hence to the "active methylene" class of compounds and can undergo Knoevenagel type condensations with aldehydes and ketones.[5] The highly electrophilic 4-alkylidene isoxazolin-5-ones **5** thus produced would be expected to behave as effective Michael acceptors, leading to adducts **6** that are now suitable alkyne precursors, as outlined in scheme 2 (for convenience and clarity only one tautomeric form of the isoxazolinone—cf **2a** & **2b**— is drawn). This sequence represents an overall alkylation of an oxazolinone such as **4**, and should allow the introduction of a great variety of substituents. In view of the stability and ambident character of the conjugate anion, direct alkylations are in general not only problematic (polyalkylation) and unselective (Cversus N- alkylation) but also limited in terms of suitable alkylating agents.[4]



Scheme 2

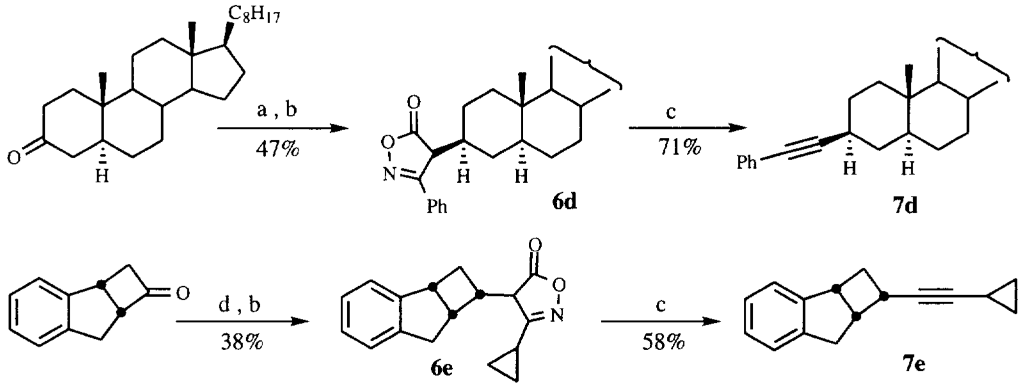
Marchesini and co-workers[6] reported for example that 4-alkylidene isoxazolinones of structure **5** can be cleanly reduced with sodium borohydride to the saturated derivatives (**6**, Nu = H) through a formal conjugate hydride addition. In our case, the utility of such a combination of steps is illustrated by the following examples. Condensation of methyl isoxazolinone **4a** with 2-thiophenecarboxaldehyde, merely by heating the two in ethanol-choloroform, followed by treatment with sodium borohydride in ethanol furnished **6a** in high yield (79%). Exposure of this compound to sodium nitrite and iron sulfate in aqueous acetic acid afforded the desired acetylene **7a** in 62% yield (scheme 3). The same sequence was applied starting from N-tosyl-2-pyrrolecarboxaldehyde and 3-phenyl isoxazolinone **4b**, providing acetylene **7b** in good overall yield. It is necessary to have an electron withdrawing group on the nitrogen of the pyrrole; in its absence, the pyrrole ring does not survive the nitrosating conditions and a complex mixture is observed. Alkynes of much greater complexity can be elaborated, as shown by the condensation-reduction-nitrosation operation on the known[7] carbohydrate aldehyde **8** which produced alkyne **7c** in 39% overall yield for the three steps without purification of the intermediates.



(a) 2-Thiophenecarboxaldehyde, ethanol. (b) $NaBH_4$, ethanol. (c) $NaNO_2$ / $FeSO_4$ / AcOH / H_2O.
(d) N-Tosyl-2-pyrrolecarboxaldehyde. (e) **4b** / cat. piperidine / ethanol.

Scheme 3

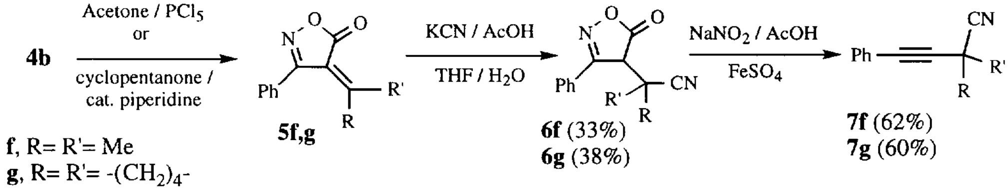
Branched alkynes may be obtained if ketones are employed in the condensation step. For instance, reaction of **4b** with cholestanone in the presence of a small amount of piperidine, followed by sodium borohydride reduction afforded isoxazolinone **6d** in 47% for the two steps. As expected, introduction of the hydride occured from the least hindered α-face. Finally, nitrosation under the usual conditions gave 3β–(phenylethynyl)-cholestane **7d** in 71% yield (Scheme 4). A more interesting case is shown by the synthesis of alkyne **7e**, substituted by a cyclopropane ring on one end and a cyclobutane on the other. Such a compound would be quite tedious to make by conventional routes but is easily accessible by the present approach: condensation of cyclobutanone **9**[8] with cyclopropylisoxazolinone **4c**, stereoselective reduction to **6e** (38% overall) and nitrosation to give **7e** in 58% yield.



(a) **4b** / cat. piperidine / ethanol. (b) $NaBH_4$ / ethanol. (c) $NaNO_2$ / $FeSO_4$ / AcOH / H_2O. (d) / **4c** / cat. piperidine / ethanol.

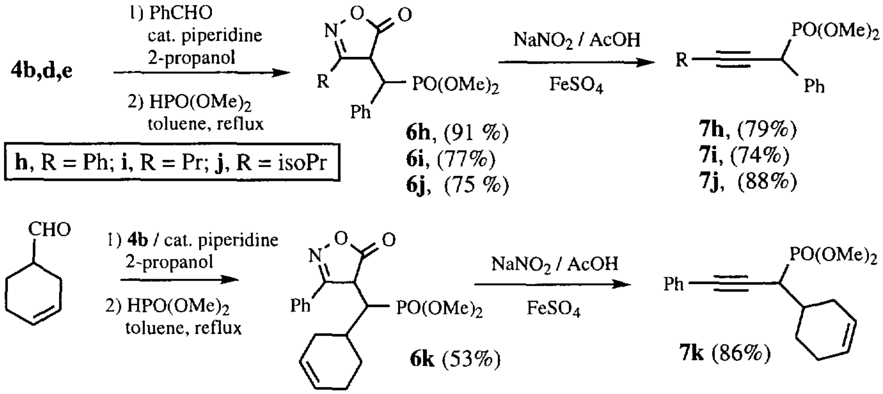
Scheme 4

The reduction step in the above sequence may be replaced by addition of hydrogen cyanide (Scheme 5). The two following examples illustrate this variant: addition of potassium cyanide and acetic acid to an ice-cooled isopropanol solution of **5f** and **5g**[5] gave isoxazolinones **6f** and **6g** in 33% and 38% yield respectively; subsequent nitrosative cleavage delivered cyanoalkynes **7f** (62%) and **7g** (60%). Even though the yields are only moderate in these examples, it is worth pointing out that a functionalised quaternary center has been introduced next to the acetylenic moiety in a straightforward manner.



Scheme 5

Another class of alkynes that would be accessible with difficulty by existing routes are propargylic phosphonates. Simple members have been prepared by the reaction of phosphites with propargyl halides and related derivatives.[9] This synthetically limited approach is further complicated by the easy base catalysed isomerisation to the allene derivative.[9b] We found that heating the condensation products with dimethyl phosphite in toluene in the absence of added base resulted in a clean Michael addition to give the corresponding phosphonates **6h-k**, and these were cleanly converted into the respective alkynes **7h-k** without contamination with the allene isomers, as summarized in scheme 6.



Scheme 6

These varied examples demonstrate the scope of this versatile and convergent approach to functionalised acetylenes which complements existing methods.[10] In most cases, the yields were satisfactory, even though unoptimised. In addition of its tolerance for a number of important functional groups, the cheapness of the reagents, the ready availability of the starting materials, and the simplicity of the experimental procedure[1,3] are further noteworthy features.

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