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A NEW PRACTICAL METHOD FOR THE SYNTHESIS OF ACETYLENES .

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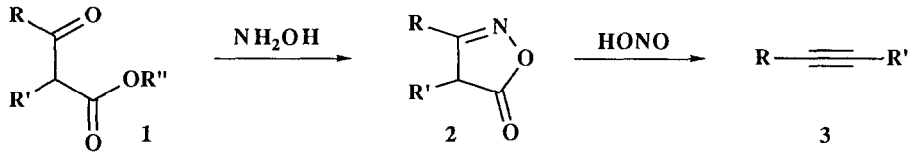
Summary : The reaction of isoxazol-5-ones derived from ß-keto esters and hydroxylamine with sodium nitrite and ferrous sulphate in aqueous acetic acid affords the corresponding acetylenes in moderate to good yield

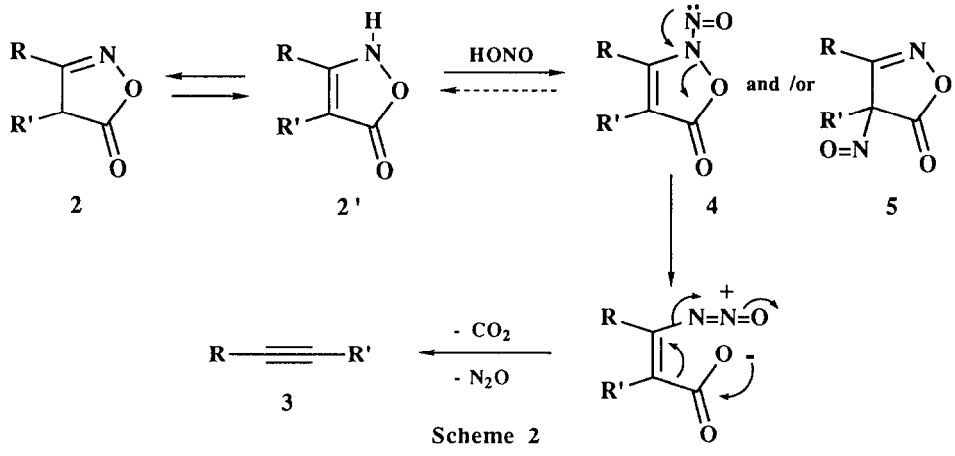
Acetylenes possess an extraordinarily rich and varied chemistry and, over the years, a large number of methods have been developed for introducing the acetylenic fragment[1]. Nevertheless, in view of the central role played by this family of compounds in organic synthesis, new reactions leading to the formation of the carbon-carbon triple bond are still needed. In this Letter, we wish to report a new process for converting ß-keto esters into acetylenes. Because the former compounds are so readily available, we believe this novel method to be a useful addition to the existing arsenal of the organic chemist.

Our approach consists in converting first the ß-keto-ester **1** into the corresponding isoxazol-5-one[2] **2** by reaction with hydroxylamine followed by ring cleavage and concomitant acetylene formation through nitrosation with sodium nitrite and acetic acid as shown in scheme 1.



Scheme 1

The mechanistic basis of this conception is outlined in scheme 2 below. Thus nitrosation of the nitrogen atom of the isoxazolone would lead to the N-nitroso compound **4** which could undergo ring scission and loss of carbon dioxide and nitrous oxide to give the desired acetylene. Isoxazolones are known to exist in tautomeric equilibrium[2] where form **2'** dominates when R' ≠ H. Moreover, although nitrosation could also occur on C-4 to yield **5**, it was hoped that this would be a reversible process if R'≠ H.

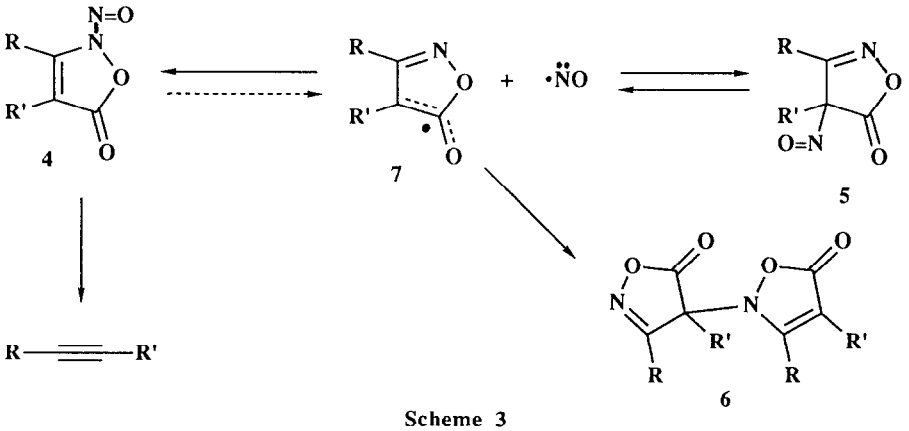


2 2' 4 5

3

Scheme 2

In the event, treatment of isoxazolone **2a** derived from ß-keto ester **1a** with sodium nitrite in aqueous acetic acid gave indeed acetylene **3a** but only in low yield (20%). The other major product turned out unexpectedly to be the dimer **6a**, isolated in 40 % yield. The formation of such dimers upon treatment of isoxazol-5-ones with a number of oxidants have been reported[3]. Indeed, Marchesini and co-workers [3a] have stated that oxidation of isoxazol-5-ones with sodium nitrite in acetic acid leads to such dimers but, surprisingly, not to acetylenes Dimer **6a** arises almost certainly from the coupling of radical **7a** which in turn could be formed either directly from the starting isoxazolone by a one electron oxidation or, perhaps more likely under our conditions, by the dissociation of the tertiary nitroso derivative **5a** (and maybe even **4a**) (scheme 3). Such a dissociation is favoured by the stability of the radicals produced: nitric oxide and the resonance stabilised tertiary radical **7a**, which may also has some aromatic character through spin delocalisation onto the carbonyl group. As the gaseous nitric oxide eventually escapes from the medium, radical **7** couples to give dimer **6**.



4 7 5

6

Scheme 3

If such a dissociation is indeed taking place in the medium, then by loading the system with nitric oxide, dimer formation would be suppressed[4], but the tertiary C-nitroso derivative would still be in equilibrium with the N-nitroso isomer via its constituent radicals as depicted in scheme 3. Irreversible formation of the acetylene would eventually drain this equilibrium towards the desired product.

We were quite pleased to find that the simple expedient of adding an excess of ferrous sulphate at the beginning of the experiment followed by simultaneous addition of the isoxazolone **2a** and the remaining sodium nitrite caused the yield of acetylene **3a** to jump to 47% at the expense of the dimer which was now barely detectable[5]. Ferrous sulphate and sodium nitrite react to give nitric oxide[6] which is thus continuously produced in the medium. An external source of nitric oxide would presumably have the same beneficial effect although this has not yet been ascertained.

Table

Entry	Substituents in compounds **1-7**	Yield of acetylenes **3** from isoxazolones **2**
1	**a**, R = Me ; R'= 1-naphthylmethyl-	47%
2	**b**, R = Me ; R'= $PhCH_2$-	59%
3	**c**, R = CH_2=$CH(CH_2)_7$- ; R'= CH_2=$CH(CH_2)_8$-	62%
4	**d**, R = $MeO_2C(CH_2)_4$- ; R'= $MeO_2C(CH_2)_3$-	63%
5	**e**, R = Ph- ; R'= $PhCH_2$-	70%
6	**f**, R = Ph- ; R'= CH_2=$CHCH_2$-	72%
7	**g**, R, R'= -$(CH_2)_{10}$-	61%
8	**h**, R = Ph- , R'= $MeO_2C(CH_2)_2$-	55%

A variety of acetylenes were prepared in reasonable yields by this simple procedure as shown by the examples collected in the table. Skipped enynes in particular seem to be accessible by this method as illustrated by example **3f** (entry 6). One further interesting application concerns the synthesis of cyclododecyne (entry 7) free from the isomeric allene Most of the earlier methods[7] afford an unseparable mixture of both. Another aspect is that now the starting ß-keto-esters or the isoxazolones derived thereof become latent acetylenes. Their rich chemistry can therefore be exploited to obtain acetylenes hitherto not easily available. This is illustrated by example **3h**, where precursor **1h** was prepared by a Michael addition of ethyl benzoylacetate to methyl acrylate. Direct introduction of the acetylenic fragment by conjugate addition of acetylides is often problematic[8].

Only a few synthetically useful methods for making acetylenes from a heterocyclic ring exist[1,9]. The novel reaction described here uses readily available starting materials and cheap reagents. The yields have not been optimised and there is still room for improvement. These practical considerations as well as a more thourough examination of the various intriguing mechanistic aspects are currently under study

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4. For a theoretical treatment of the control of the selectivity through internal suppression of fast modes, see: Fischer, H. *J. Am. Chem. Soc* **1986**, *108*, 3925.

5. A typical experimental procedure is as follows: To a suspension of ferrous sulphate (3.9g) in degassed acetic acid (30ml) is added half of a degassed solution of sodium nitrite (2.4g) in water (14ml). After 10 min. at room temperature, a degassed solution of the isoxazolone (3.5 mmol) in acetic acid is added dropwise simultaneously with the remainder of the sodium nitrite solution over about 30 min. After a further 30 min., the mixture is diluted with water and worked up in the usual manner. The crude product is then purified by flash chromatography on silica.

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