CHEMCOMM Communication
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A new synthesis of 1-chloroalkynes

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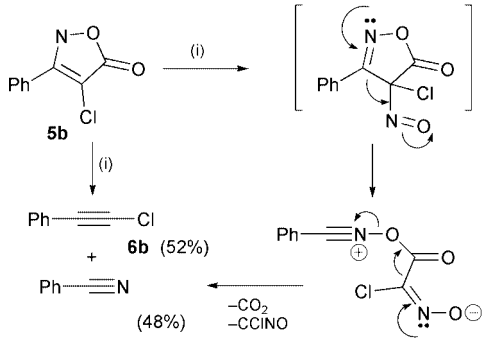
Received (in Cambridge, UK) 24th July 2001, Accepted 9th August 2001
First published as an Advance Article on the web 4th September 2001

4-Unsubstitued isoxazolinones derived from the corresponding β-ketoesters can be chlorinated and converted into 1-chloroalkynes upon treatment with sodium nitrite and ferrous sulfate in aqueous acetic acid.

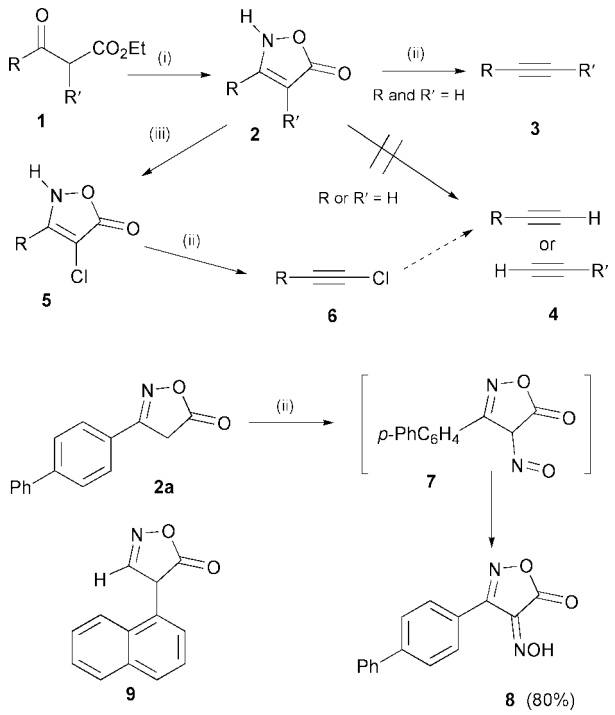
We reported a few years ago a new, practical, and versatile synthesis of alkynes based on the nitrosative cleavage of isoxazolinones using a combination of sodium nitrite, aqueous acetic acid and ferrous sulfate (Scheme 1; only one tautomeric form of the isoxazolinone is drawn).[1] Ferrous sulfate is needed to generate nitric oxide *in situ* in order to suppress an unwanted radical side reaction leading to the dimerisation of the isoxazolinone. The main limitation of this reaction is that it does not, so far, allow access to terminal alkynes: neither R nor R′ in the starting isoxazolinone **2** can be a hydrogen atom, for the reaction pathway of such substrates does not follow the desired course upon nitrosation. For instance, isoxazolinone **2a** gives a good yield of oxime **8** following tautomerism of the *C*-nitroso intermediate **7**, whereas isoxazolinone **9** leads to a complex mixture under the same reaction conditions.[2] We have now developed a simple solution to this difficulty hinging on the elaboration of 1-chloroalkynes. Not only can these act as surrogates for terminal alkynes[3] but they also have a very rich chemistry of their own.[4] Noteworthy in this respect are the numerous transition metal based couplings involving 1-haloalkynes in general.[5]

In a preliminary experiment, we prepared chloroisoxazolinone **5b** in 72% yield by treatment of commercially available 3-phenylisoxazolin-5(4*H*)-one **2b** with sulfuryl chloride.[6] However, upon exposure of **5b** to a mixture of sodium nitrite, aqueous acetic acid and ferrous sulfate at room temperature under an inert atmosphere, a nearly 1 : 1 mixture of the desired 1-chlorophenylacetylene **6b** and benzonitrile was obtained (Scheme 2). Benzonitrile is presumably formed through the thermal fragmentation of the corresponding *C*-nitroso intermediate as outlined in Scheme 2.

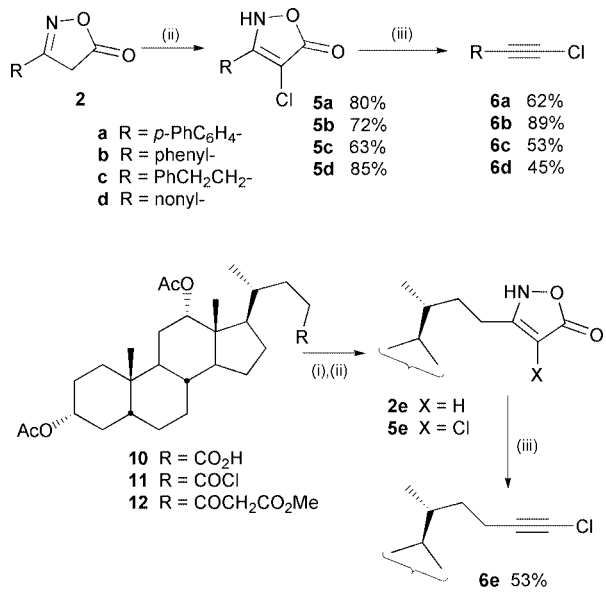


Scheme 2 *Reagents*: (i) $NaNO_2$, $FeSO_4$, AcOH, H_2O.

This undesired pathway could be almost totally eliminated by the simple expedient of lowering the reaction temperature to 0–5 °C. The yield of **6b** under these slightly modified conditions increased to 89%. A number of chloroisoxazolinones were prepared using well established routes to ketoester precursors and subjected to the nitrosative cleavage (Scheme 3). In most instances, the yield of the chloroalkynes was quite acceptable. The synthesis of chloroalkyne **6e** derived from 3,12-diacetoxycholanic acid **10** is typical. Treatment of the corresponding acid chloride **11** with Meldrum's acid[7] followed by heating with methanol provided ketoester **12**, which was cleanly converted

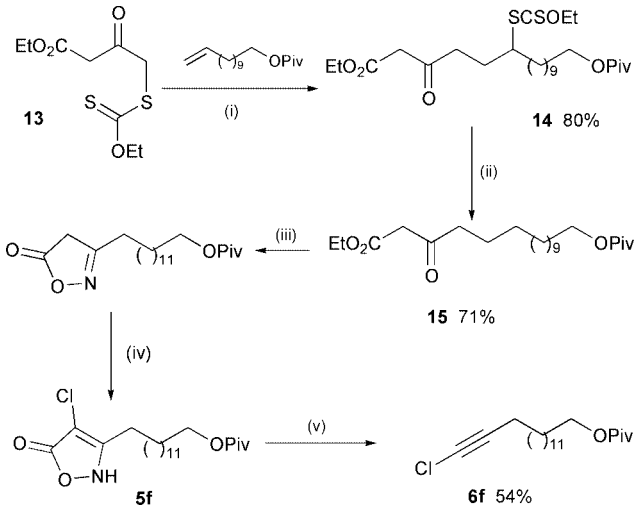


Scheme 1 *Reagents*: (i) NH_2OH; (ii) $NaNO_2$, $FeSO_4$, AcOH, H_2O; (iii) chlorinating agent.



Scheme 3 *Reagents*: (i) NH_2OH·HCl, AcONa, EtOH, reflux; (ii) TMSCl, Bu_4NBr (Cat.), DMSO, THF; (iii) $NaNO_2$, $FeSO_4$, AcOH, H_2O, 5 °C.

 DOI: 10.1039/b106657a



Scheme 4 *Reagents*: (i) lauroyl peroxide (5–20 mol%), 1,2-dichloroethane, reflux; (ii) lauroyl peroxide (80 mol%), propan-2-ol, reflux; (iii) $NH_2OH{\cdot}HCl$, AcONa, MeOH, reflux; (iv) TMSCl, Bu_4NBr (Cat.), DMSO, THF; (iii) $NaNO_2$, $FeSO_4$, AcOH, H_2O, 5 °C.

into isoxazolinone **2e** with hydroxylamine. Chlorination was accomplished by a combination of trimethylchlorosilane, DMSO and a catalytic amount of Bu_4NBr. This reagent system, reported by Fraser and Kong,[8] turned out to be superior in general to sulfuryl chloride for the chlorination of the isoxazolinones. Finally, nitrosation of **5e** furnished the desired chloroalkyne **6e** in 53% yield.

As shown by the sequence in Scheme 4, we were able to combine this approach to chloroalkynes with a powerful process for the creation of carbon–carbon bonds based on the radical chemistry of xanthates.[9,10] Thus, addition of xanthate **13** derived from commercially available ethyl 4-chloroacetoacetate to 10-undecyl pivalate gave the expected adduct **14** in 81% yield. Reductive removal of the xanthate group was achieved by portion-wise addition of stoichiometric amounts of lauroyl peroxide to a refluxing solution of **14** in isopropyl alcohol.[11] The resulting ketoester **15** was converted into the chloroisoxazolinone **5f** in the same way as above and subjected to the nitrosative cleavage to give the desired chloroalkyne **6f** in 54% overall yield for the last three steps.

This approach to 1-chloroalkynes allies simplicity with the use of readily available substrates and cheap, ecologically acceptable, reagents. None of the yields has been optimised and room for improvement certainly exists; nevertheless, in combination with the numerous routes to ketoester precurors, it provides a flexible and rapid route to otherwise inaccessible acetylenes.

Notes and references

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Typeset and printed by Black Bear Press Limited, Cambridge, England