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Synthetic equivalents of alkynyl and propargyl radicals

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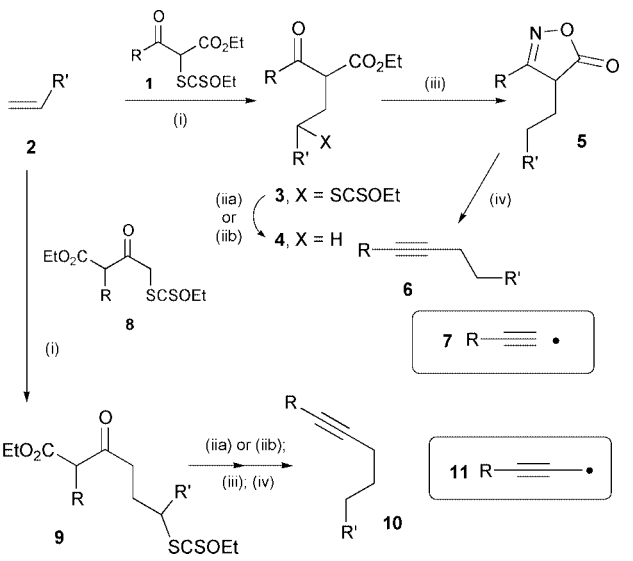
Radicals derived from β-ketoesters can, depending on the position of the unpaired electron, represent synthetic equivalents to the high energy and elusive alkynyl radicals or to the stabilised and relatively unreactive propargyl radicals by application of the xanthate transfer reaction followed by nitrosative cleavage of the corresponding isoxazolinones.

Retrosynthetic disconnections of acetylenic targets and intermediates almost never encompass the possibility of using synthons equivalent to propargyl or alkynyl radicals. Synthetic plans rely mostly on the corresponding hypothetical anionic or cationic species and on organometallic coupling or methathesis reactions.[1] Propargylic radicals are stabilised species and are relatively unreactive: although they do undergo ring-closure to non-activated olefins, *intermolecular* additions require activated olefins for success.[2] Alkynyl radicals, in contrast, are highly energetic species, accessible only with great difficulty[3] and, as far as we know, have very rarely been used in synthesis. One notable example is the photochemical generation of phenylethynyl radical from phenyliodoacetylene and its capture by aromatic compounds.[4] The instability of alkynyl radicals is reflected in the strength of the corresponding C–H bond, estimated to be around 130 kcal mol^{-1}, nearly 20 kcal mol^{-1} higher than that of an alkene C–H bond.[3] In view of the central role played by acetylenes in organic chemistry, it seemed worthwhile developing a route which would be an overall synthetic equivalent to either alkynyl or propargyl radicals.

Our approach is based on combining two reactions we have developed in recent times: the nitrous acid mediated cleavage of isoxazolinones[5] with the intermolecular radical addition of xanthates.[6] As shown in the top sequence in Scheme 1, addition of a radical located in position 2 of a β-ketoester and derived from the corresponding xanthate **1** to olefin **2** gives an adduct **3**, where a new C–C bond has been formed in an intermolecular manner. Reductive removal of the xanthate, formation of the isoxazolinone **5** (only one tautomeric form is drawn),[7] and cleavage with nitrous acid finally provides the desired alkyne **6**. This compound corresponds formally to the addition of the inaccessible alkynyl radical **7** to the starting olefin **2**. If the initial radical is located at position 4 of the β-ketoester (*i.e.* starting with xanthate **8**), the overall sequence leading to acetylene **10** is equivalent to the addition of a propargyl radical **11** to the olefin. This approach, involving an electron attracting α-acetonyl radical, complements the use of the propargyl radical itself which, as was stated above, has a rather nucleophilic character and therefore requires an olefin activated by an electrophilic group as partner.

The examples collected in Table 1 give an idea of the scope of the sequence corresponding to the overall addition of an alkynyl radical. Both the radical addition and the nitrosative cleavage occur under mild conditions and are tolerant of various functional groups commonly encountered in organic synthesis. In the case of the isoxazoline **5e** derived from *N*-tosylallylamine **2e** (entry 5), *N*-nitrosation occurred to give **6′e** (**6**, R′ = $-CH_2N(NO)Ts$) in 46% yield, in addition to the 'normal' alkyne **6e**, itself formed in 20% yield. The *N*-nitroso group in **6′e** could be removed by warming with triethylamine in aqueous THF, thus bringing the overall yield of alkyne **6e** to 47%.[8]

For convenience, the xanthate group in the adduct was reductively removed either by treatment with a stoichiometric quantity of lauroyl peroxide in isopropanol (yields with an asterisk in Table 1)[9] or, more conventionally, with tributylstannane; its presence, however, allows the insertion of another radical transformation, namely cyclisation onto an aromatic ring.[10] This is illustrated by the synthesis of the 3-alkynyl indoline pictured in Scheme 2. Thus, addition of xanthate **1c** to *N*-allyl-*N*-mesyl-*p*-bromoaniline **2e** gave the expected adduct **12** in a reasonable yield (43%, along with 28% of recovered xanthate). Exposure of this adduct to stoichiometric amounts of lauroyl peroxide (added portion-wise over several hours) in refluxing 1,2-dichloroethane resulted in ring-closure to indoline **13** (86%). Finally, conversion into the corresponding isox-



Scheme 1 *Reagents and conditions*: (i) lauroyl peroxide (5–20 mol%), 1,2-dichloroethane, reflux; (iia) lauroyl peroxide (100–110%), isopropanol, reflux; (iib) Bu_3SnH (AIBN), cyclohexane, reflux; (iii) $NH_2OH{\cdot}HCl$, AcONa, EtOH, reflux; (iv) $NaNO_2$, $FeSO_4$, AcOH, H_2O, RT.

Table 1 Yield (%) of compounds **3**–**6** (Piv = pivalate)

R	1	R′	2	3	4	5	6
Ph	**1a**	$-CH_2SiMe_3$	**2a**	**3a** (86)	**4a** (75)	**5a** (80)	**6a** (76)
Ph	**1a**	$-CH_2PO(OEt)_2$	**2b**	**3b** (78)	**4b** (85)	**5b** (74)	**6b** (80)
c-C_3H_5-	**1b**	$-(CH_2)_9OPiv$	**2c**	**3c** (74)	**4c** (75)*	**5c** (83)	**6c** (75)
c-C_3H_5-	**1b**	$-CH_2PO(OEt)_2$	**2b**	**3d** (68)	**4d** (84)*	**5d** (90)	**6d** (67)
c-C_3H_5-	**1b**	$-CH_2NHTs$	**2d**	**3e** (65)	**4e** (92)	**5e** (89)	**6e** (20)
Me	**1c**	$-(CH_2)_9OPiv$	**2c**	**3f** (75)	**4f** (72)*	**5f** (81)	**6f** (60)

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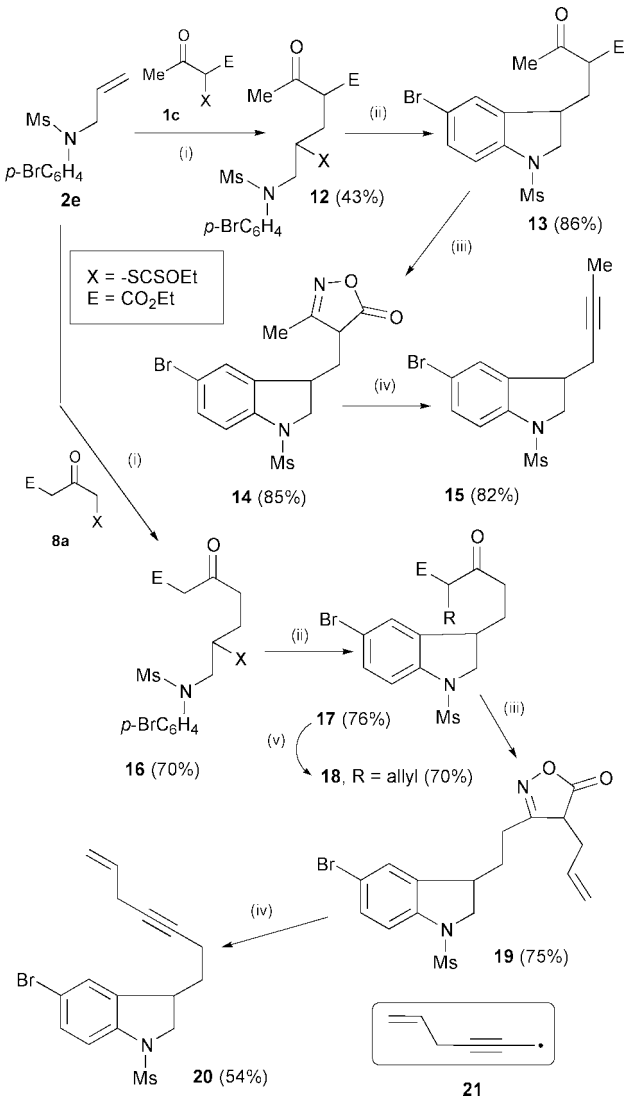

Scheme 2 *Reagents and conditions*: (i) lauroyl peroxide (5–30 mol%), 1,2-dichloroethane, reflux; (ii) lauroyl peroxide (100–110%), 1,2-dichloroethane, reflux; (iii) $NH_2OH.HCl$, AcONa, EtOH, reflux; (iv) $NaNO_2$, $FeSO_4$, AcOH, H_2O, RT; (v) allyl bromide, K_2CO_3, acetone, reflux.

azolinone and nitrosation furnished the desired alkyne **15** in 70% yield for the two steps.

A similar sequence can be used to illustrate the case of a propargyl radical equivalent. As shown in the bottom part of Scheme 2, radical addition of xanthate **8a** to the same olefin **2e** and similar ring closure provided indoline **17** in 42% overall yield. Allylation of the ketoester with allyl bromide, formation of the isoxazolinone, and nitrosative cleavage gave compound **20** containing the delicate, skipped enyne motif. This sequence corresponds to effecting the addition of stabilised and unreactive propargylic radical **21** to the unactivated olefin present in **2e**. Incidentally, the elaboration of a β-ketoester in the 4-position under neutral conditions *via* xanthate **8a** is worth underlining. Usually, it is necessary to resort to the highly basic di-anion[10] or to the bis-silylenol ether under Lewis acid catalysis[11] in order to functionalise position 4 without affecting the much more acidic position 2 of the ketoester.

In summary, the present approach complements existing methods by allowing the rapid assembly of a variety of otherwise inaccessible alkynes. It also brings a practical solution to the longstanding problem of finding synthetically useful and tame surrogates for the unavailable and unruly alkynyl radicals.

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