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A Synthetically Useful Source of Propargyl Radicals.

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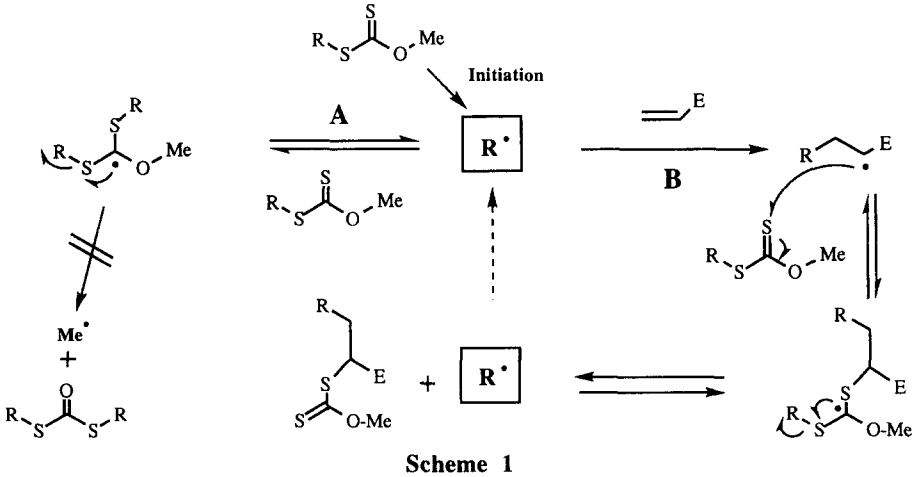
Abstract : S-propargyl xanthates constitute a convenient source of propargyl radicals that can be captured in an inter- or intra-molecular fashion. Copyright © 1996 Published by Elsevier Science Ltd

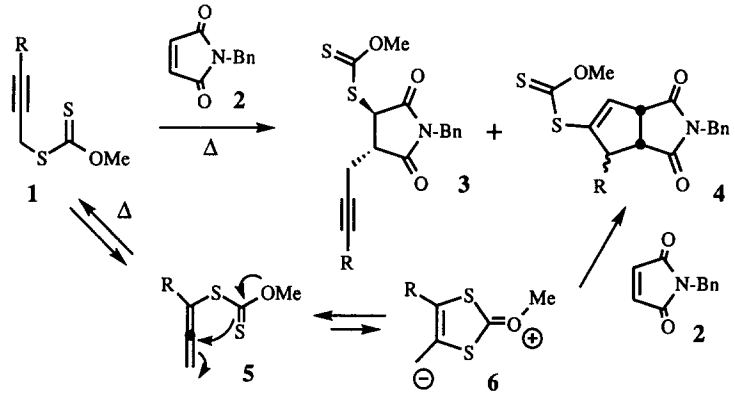
Propargylic radicals have hardly been applied to organic synthesis, despite the recent and still growing popularity of radical based synthetic methods.[1] The underlying causes for such a neglect may be traced to the relatively unreactive nature of such species[2] and to the lack of convenient methods for generating them. Yet, the advantages accruing from introducing an alkyne group by such a process are quite significant in view of the importance and immense richness of acetylene chemistry.[3] In this Letter, we wish to describe a simple and fairly general method for generating and capturing propargyl radicals.



Scheme 1

Over the past few years, we have shown that xanthates constitute a general source of radicals of various types such as alkyl, acyl, alkoxycarbonyl, alkoxythiocarbonyl, and even stannyl radicals.[4] The reaction manifold in Scheme 1 outlines the general case where the radicals thus produced are captured by an external olefin (an O-methyl xanthate is shown for clarity but other xanthates with a primary group on the oxygen such as O-ethyl or O-neopentyl xanthates can equally be used). The major property of this system is that the starting xanthate does not compete with the trap for radical R• since the reaction of this xanthate with

$R^{\bullet}$ is degenerate (path A in Scheme 1). The effective lifetime of the radical species is thus increased, allowing the use of relatively unreactive traps or the manipulation of "lazy" radicals such as benzyl, allyl, or, as we now demonstrate, propargyl radicals through path B in the same Scheme.



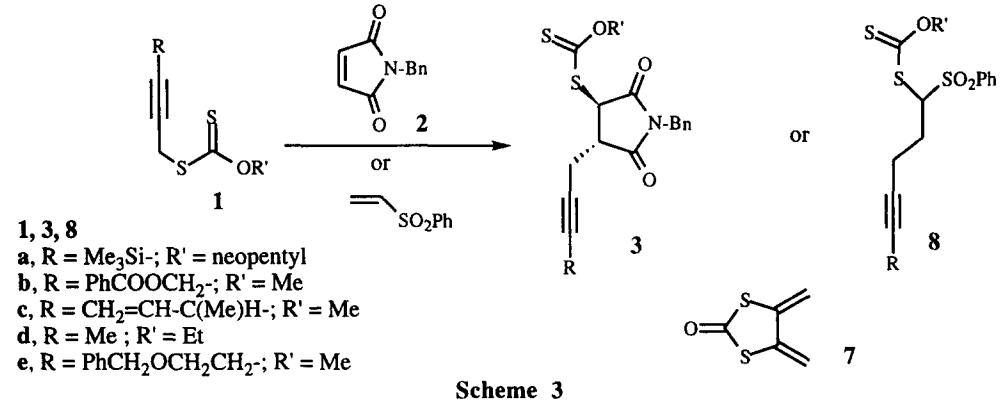
Scheme 2

When we first attempted, in accord with this mechanistic reasoning, to generate and capture the simplest propargyl radical starting from xanthate **1** (R = H), we found that the radical pathway leading to adduct **3** (R = H) was very minor compared with an unexpected, formal cycloaddition to a cyclopentene derivative **4** (scheme 2).[5] The latter transformation proceeds by an initial rearrangement of the propargyl xanthate into its allenic isomer **5**, either by a [3,3] sigmatropic rearrangement or possibly by a radical chain process.[6] The allene appears to be in a favourable equilibrium with a reactive betain **6** of a new type, possessing its own interesting chemistry. However, for our present purposes, its was necessary to suppress the formation of the allene in order to reveal the radical chemistry of the propagyl xanthate.

Both the sigmatropic rearrangement and the radical chain process causing the isomerisation into the allene would be expected to be sensitive to steric hindrance at the acetylenic terminus. It seemed therefore that in the case of substituted propargylic xanthates (**1**, R ≠ H), the formation of the corresponding allene might become sufficiently slow at 80°C to allow the radical chain process outlined in scheme 1 to take place. Indeed, when a mixture of **1a**, containing a bulky trimethylsilyl group, and N-benzyl maleimide were heated in refluxing cyclohexane in the presence of a small amount of di-lauroyl peroxide (DLP), a clean reaction ensued to give the radical adduct **3a** in 85% yield. None of the unwanted cyclopentene derivative of type **4** could be found.

The trimethylsilyl substituent may be replaced by other groups as illustrated by the reaction of xanthates **1b** with N-benzyl maleimide to give **3b** in 58% yield. We had earlier shown that xanthate **1b** is converted upon heating into the highly reactive diene **7** (captured *in situ* with various dienophiles).[7] Fortunately, this rearrangement, which also proceeds through the corresponding allene isomer and betain according to the mechanism in Scheme 2, is too slow at 80°C to compete with the present radical process. In the case of **1c**, the presence of the terminal olefin and a relatively labile tertiary hydrogen which is both allylic and propargylic, does not seem to affect the outcome of the reaction which gives the expected product **3c** in 60% yield. Finally, it seems that even a methyl group is sufficient to allow a distinction between these two

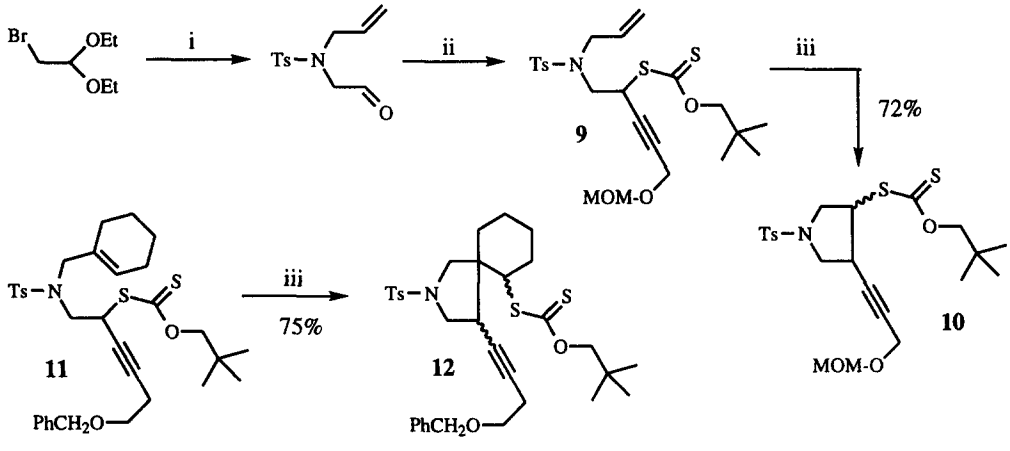
very different aspects of S-propargyl xanthate chemistry, as shown by the obtention of **3d** from xanthate **1d** and the same maleimide trap in 72% yield. In this case a small amount of the cis isomer was detected (cis: trans ratio 1:10).



1, 3, 8
a, R = Me_3Si-; R' = neopentyl
b, R = $PhCOOCH_2$-; R' = Me
c, R = CH_2=CH-C(Me)H-; R' = Me
d, R = Me ; R' = Et
e, R = $PhCH_2OCH_2CH_2$-; R' = Me

Scheme 3

Other electrophilic olefins can be used as trap for the intermediate propargylic radical. Thus, under the same conditions, replacing **2** with phenyl vinyl sulfone gave the corresponding addition products **8a** and **8e** starting from **1a** and **1e** in 53% and 56% yield respectively (or 82 and 64% respectively based on recovered phenyl vinyl sulfone). It is perhaps worth pointing out that compounds such as **8** contain a sulfone and a xanthate in a geminal disposition representing in fact a masked thioaldehyde group, an aspect which we have not yet examined.



Conditions: (i) Allylamine (4eq), $NaHCO_3$ (2eq),, 60°C, 12hrs; TsCl, NaOH, Ether; CF_3CO_2H, H_2O, $CHCl_3$, 0°C (38%). (ii) $HCCCH_2OMOM$, BuLi, THF, -78°C then MsCl (37%); Sodium O-neopentyl xanthate (1.2eq), acetone (72%). (iii) Dilauroyl peroxide (6%), cyclohexane, reflux, 6hrs.

Scheme 4

The propargylic can also be effectively captured by a suitably located internal olefin. The starting materials for such a process are easily prepared from the corresponding unsaturated aldehydes as shown by

the sequences in Scheme 4. Propargylic xanthate **9** was thus prepared from 2-diethoxy-1-bromoethane using standard chemistry. Initiation in the same way as above resulted in a smooth reaction to give xanthate **10**, the product expected from a 5-exo cyclisation, as an approximately 1:1 cis: trans mixture of isomers in 72% combined yield. Analogue **11** was made in the same way except that 1-cyclohexenyl methylamine was used instead of allylamine in the first step and 1-benzyloxy-3-butyne was the the alkyne partner. In this case, cyclisation provided a spiro derivative in 75% yield, this time as a mixture of all four possible diastereomers. One isomer could be obtained pure and completely characterised, except for its relative stereochemistry which has not yet been defined with certainty.

As far as we can tell, these preliminary results represent the first high yielding inter- or intramolecular additions of propargylic radicals.[8] In addition to introducing an alkyne unit in an unusual manner, the last propagation step of the chain reaction involves transfer of the equally useful xanthate group. Complex and heavily functionalised structures are thus cleanly and rapidly assembled under very mild conditions.[9] The scope and synthetic applications of this new methodology are currently under study.

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3. See for example: (a) Hudrlik, P. F.; Hudrlik, A. M. in *The Chemistry of the Carbon-Carbon Triple Bond;* Patai, S., Ed.; John Wiley & Sons: Chichester, 1978; chap. 7, pp 199-273. (b) Corey, E. J.; Cheng, X.-M. The Logic of Chemical Synthesis; J. Wiley & Sons: New York, 1989; many of the total syntheses discussed by Corey and Cheng involve acetylene chemistry.
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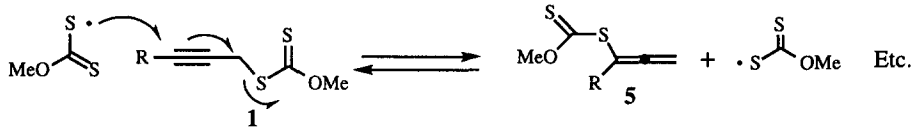
5. Boivin, J.; Tailhan, C.; Zard, S. Z. *J. Am. Chem. Soc.* **1991**, *113*, 5874-5876.
6. The radical chain path for formation of allene **5** can be pictured as follows:



7. Boivin, J.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 7853-7856.
8. Following our initial work on S-propargyl xanthates (ref. 5), one report appeared concerning the formation of an allene by cyclisation of a propargyl radical generated using tributylstannane: F.-H. Wartenberg; H. Junga; Blechert, S. *Tetrahedron Lett.* **1993**, *34*, 5251-4252. For another very recent example using sulfone chemistry, see: Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209-1210.
9. Typical experimental procedure: A solution of the xanthate (2 mmoles) and olefinic trap (1 mmol) in degassed cyclohexane (4 ml) is heated to reflux under argon with periodical addition od dilauroyl peroxide (2% every 1.5-2 hrs) until consumption of the starting material. The solvent is distilled off under reduced pressure, and the residue purified by column chromatography on silica gel.

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