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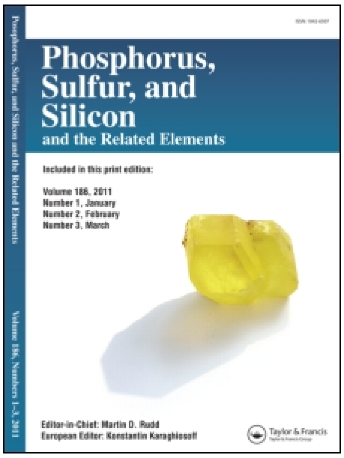

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Some New Radical Reactions for Organic Synthesis

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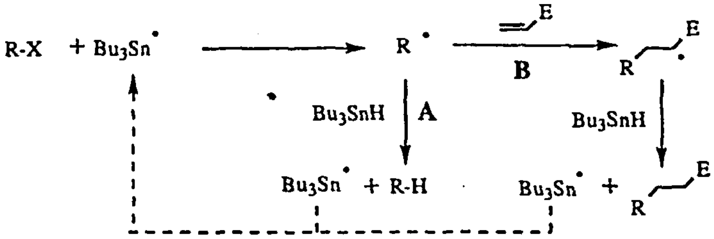
Xanthates are convenient precursors of a variety of radicals that can be captured in an inter-or intramolecular fashion. Overall, the process involves rupture of the sulfide C-S bond and addition of the elements of the xanthate to the olefinic trap. The xanthate in the product can be used in another radical sequence or ionically modified in a grear variety of ways. S-Propargyl xanthates exihibit a special but interesting behaviour which involves a sigmatropic rearrangement to the corresponding allene and ring closure to a novel betaine.

Keywords: Radical reactions; xanthates; allylation; sulfones

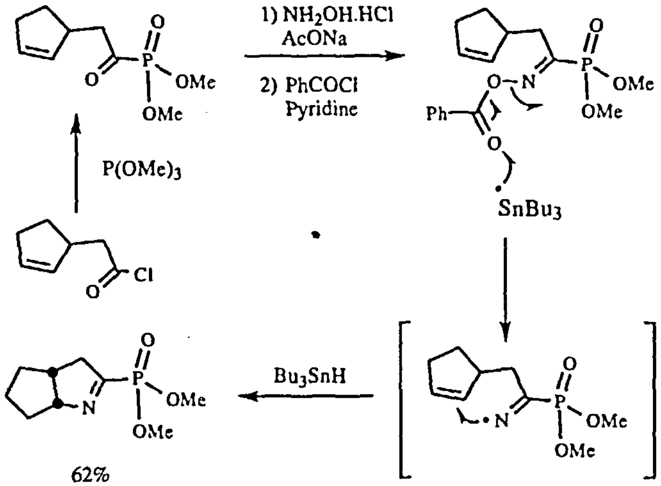
Radical reactions offer many of the properties desired by synthetic organic chemists in terms of mildness, variety, and potential for C-C bond formation as well as for functional group interchange.[1] As a consequence, the use of free radical processes in organic synthesis has witnessed an extraordinary development over the past twenty years or so. There is however one main difficulty with radicals in comparison with the more common ionic processes: Radicals usually interact with themselves (dimerisation, disproportionation) with extremely fast rates that are practically diffusion controlled. It is therefore essential that the desired reaction sequence be made of very fast steps in order to keep the steady-state concentration of radical species very low. This notion is illustrated by the typical and now extremely popular chain process based on tributylstannane where the propagating steps are quite fast, as in scheme 1 below:



X = Cl, Br, I, -OCSSMe, -NC, -NO$_2$, -SR', -SeR' etc...

Scheme 1

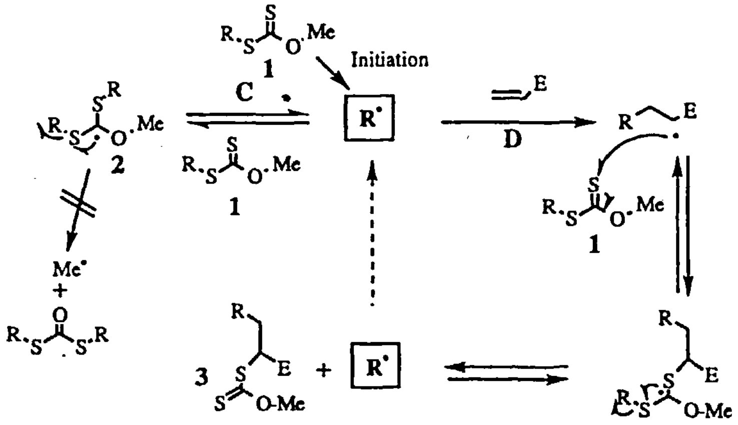
A serious competition problem arises however when several steps have to be performed in a given order in the same pot. In the scheme above, it is more challenging to proceed cleanly through the synthetically much richer path **B** than to accomplish merely a reduction (i. e. only R-X ----> R-H via path A). It is because of the tough competition between paths **A** and **B** that most applications involve intramolecular processes (e. g. cyclisations) where the importance of path A can be effectively curtailed by the use of high dilution, syringe pump addition of the stannane etc.[1]. Despite this limitation, the synthetic potential of stannane based chemistry is enormous. We have for example exploited the weakness of the N-O bond in oximes to generate and capture nitrogen centered radicals.[2] One example, displayed in Scheme 2 and involving 5-exo-trig ring closure of an iminyl radical, will suffice as an illustration.[3] In this case, the rate of cyclisation is reasonably fast and no difficulties are encountered with premature reduction.



Scheme 2

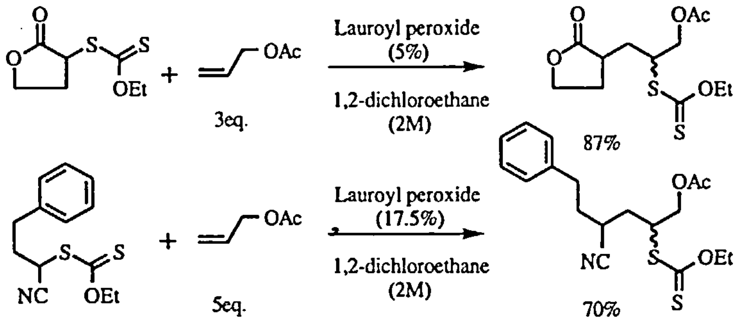
But there is another way to control a complex situation of fast elementary steps, and that is to design a radical process where redundant or degenerate loops force the radical in the desired direction. We have devised several such systems based on sulfur chemistry, which do not involve the use of heavy metals such as tin or mercury, and which allow not only functional group inter conversions but also the creation of new inter- or intramolecular carbon-carbon bonds under mild conditions.

The most general system involves xanthates **1** or related thiocarbonyl derivatives.[4] The mechanistic manifold underlying our approach is set out in Scheme 3 (ref. 2). Following a chemical or photochemical initiation step, a radical **R•** thus generated has the choice of either reacting with the starting xanthate (path **C**) or with a given trap, say an olefin, placed in the medium (path **D**). The former possibility leads to an adduct **2** where β-scission of the strong carbon-oxygen is very unfavourable since it would produce the thermodynamically less stable methyl radical (in comparison to **R•**). Rupture of either of the carbon-sulfur bonds on the other hand leads back to the **R•** and the starting xanthate **1**. The same will apply if the methyl group on the oxygen is replaced by another group, as long as the corresponding radical is of comparable, but preferably of lower stability with respect to **R•** (in most applications a primary substituent is sufficient). The properties of this radical generating method are thus analogous to those of atom transfer processes, also known as Kharasch reactions.[1]



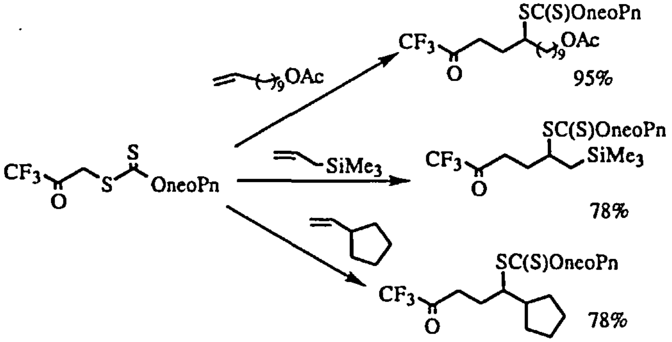
Scheme 3

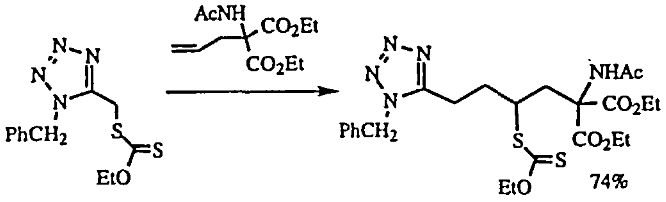
In other words, paths C and D are not in competition with each other, unlike the situation prevailing with tributylstannane shown in Scheme 1. Because R• is not irreversibly quenched by its precursor, its effective lifetime in the medium becomes longer; it is therefore possible to use relatively unreactive traps that cannot normally be employed with other radical generating systems or to work with "lazy" radicals such as benzyl, allyl, or even propargyl radicals. Another, non negligible practical advantage is that the reactions can be run in a quite concentrated medium since the kinetic constraints imposing high dilution no longer apply. Overall, following two reversible steps, another xanthate 3 is finally produced whereby a new carbon-carbon bond and a new carbon-sulfur bond have been formed. The possibility of adding radicals to unactivated olefins is illustrated by the two examples in scheme 4. This must be contrasted with the failure of similar radicals generated using tributyltin hydride to add to a simple terminal olefin in an intermolecular fashion, even using syringe pump techniques;[5] mostly reduction occurred in this case. It is important to note that the reactions with the xanthates were run at the quite high concentration of 2M.



Scheme 4

A variety of radicals, some hitherto inaccessible, can be created by the xanthate method, and their interception by unactivated olefins provides an expedient, convergent entry to a great diversity structures. Trifluoroacetonyl[6] or tetrazolymethyl[7] radicals are two species which had not been examined before and which readily participate in the present process as demonstrated by the examples in Scheme 5. Many functional groups are tolerated and, since the adducts themselves contain a xanthate moiety, a great number of further ionic or radical based transformations become possible.

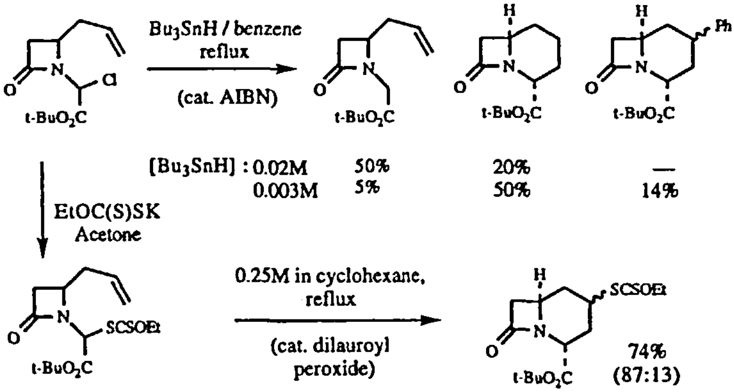




Conditions: dilauroyl peroxide(cat.)
Cyclohexane, reflux.

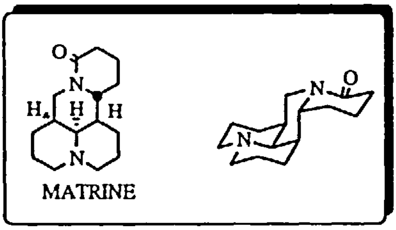
Scheme 5

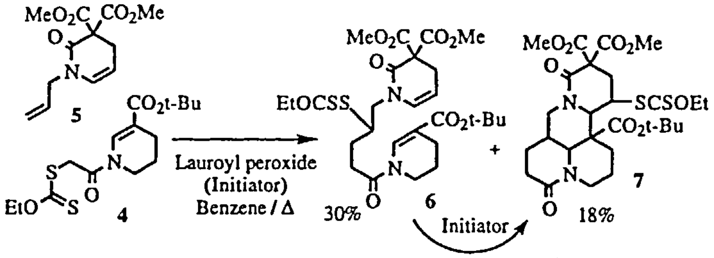
Intramolecular reactions are of course generally easier to perform and many highly functionalised mono or polycyclic systems can be readily constructed. The cyclisation of the β–lactam depicted in Scheme 6 is an interesting example. In a pioneering study performed more than ten years ago, Bachi and his co-workers[8] found that the radical derived from the chloride using tributylstanne underwent a *6-endo-trig* ring closure but this process was relatively sluggish and high dilution (0.003M) was necessary in order to attain a 50% yield. At higher concentrations mostly premature reduction occurred. By substituting the chloride with a xanthate, a similar bicyclic product could be obtained through the radical transfer reaction in good yield and at a much greater concentration.[9] The presence of the xanthate in the product is an added bonus.



Scheme 6

We have exploited the possibility of making C-C bond in a intermolecular as well as the possibility of constructing 6-membered rings in order to accomplish the total synthesis of matrine, a tetracyclic alkaloid extracted from *Sophora flavenscens* Ait.[10] As shown in Scheme 7, reaction of xanthate 4 with olefin 5 gives directly the desired skeleton 7 by a radical cascade. The major isomer as far as the relative stereochemistry of the ring junctions is concerned (3:1 ratio) corresponds to that of matrine itself whereas the minor isomer has the stereochemistry of allomatrine. What is perhaps worth pointing out is that the reaction also yields an open chain intermediate 6 where xanthate transfer occurred before the first ring closure but this is of no consequence to the efficacy of the process because the radical can be regenerated and the cyclisation completed in 80-90% yield simply by exposing intermediate 6 to the action of the peroxide initiator under the same experimental conditions.

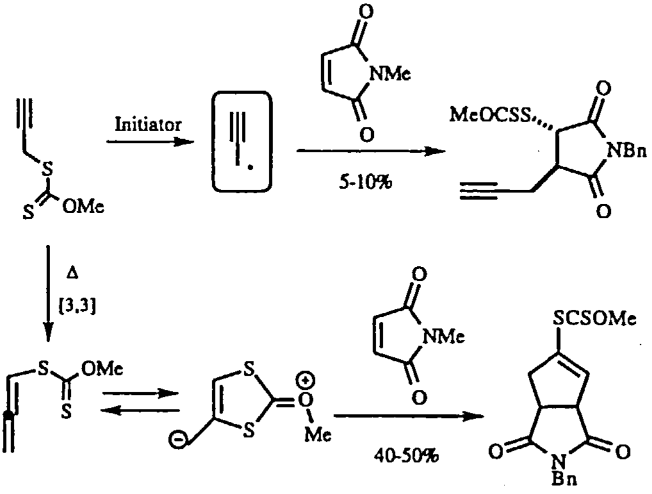




Scheme 7

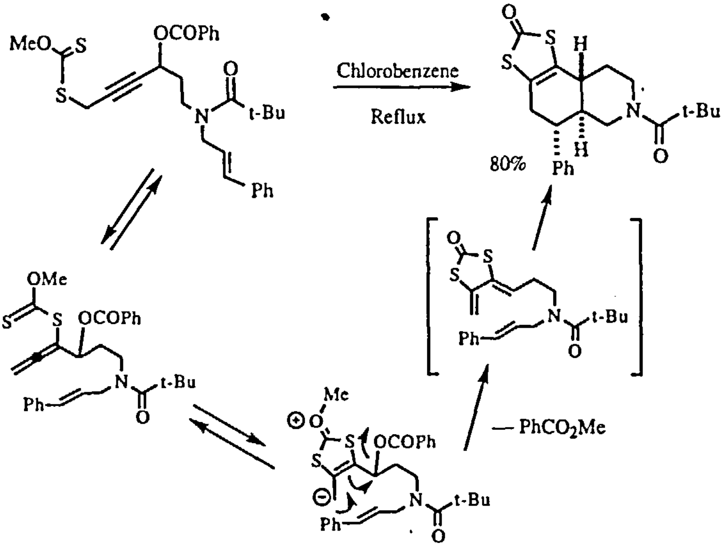
Conversion to matrine involved classical functional group manipultions: reductive removal of the xanthate group using a combination of lauroyl peroxide and isopropanol (see below); selective cleavage of the t-butyl ester and Barton decarboxylation; selective reduction of the less hindered lactam with borane, and finally hydrolysis and spontaneous double decarboxylation of the malonate unit.

The comparatively long lifetime of radicals generated by the present method can be used to force inherently "lazy" radicals to react. Propargyl radicals belong to such a class of relatively stabilised and little studied species. However, when, in a preliminary study,[11] we attempted to generate the simplest member in the presence of N-methyl maleimide as the olefinic trap, we were surprised by the formation of a cyclopentene derivative, as shown in Scheme 8. Initially, we thought that this was a radical process but further experiments did not corroborate our hypothesis and another route had to be envisaged. It seems that the propargyl xanthate undergoes a sigmatropic rearrangement to the allenyl isomer which then cyclises to a new type of betain, and this intermediate is capable of reacting with the electrophilic olefin to give the cyclopentene adduct.



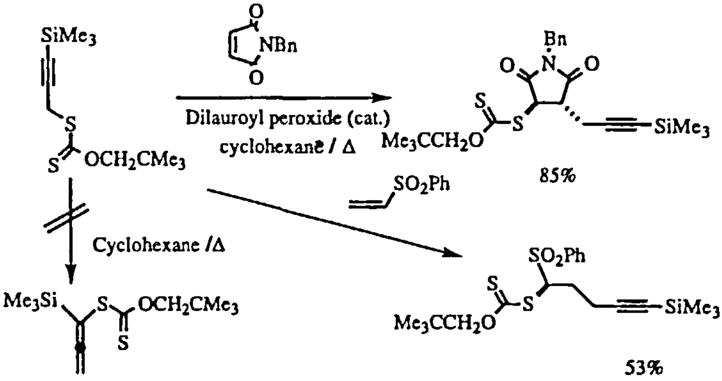
Scheme 8

This betain intermediate has an intriguing reactivity which we have only partially explored.[4] The negatively charged allylic part is sufficiently nucleophilic to participate in Michael additions to electrophilic olefins; it can also be protonated by a carboxylic acid or a substance of a similar acidity (e.g. a tetrazole) and this may be used as a method for the synthesis of esters or for the alkylation of acidic substances in general. But perhaps the most interesting aspect is the formation of rigid,highly reactive cisoid dienes by placing a leaving group such as a benzoate next to the acetylene bond. This is illustrated by the the expeditous construction of the tricyclic system shown in Scheme 9.[12]



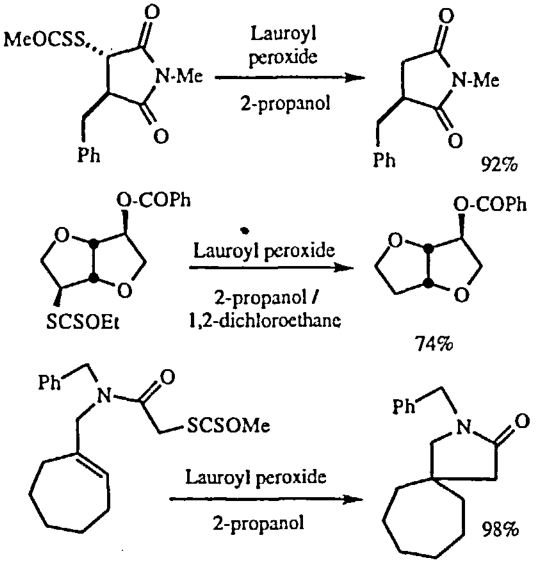
Scheme 9

Our first attempts at generating propargyl radicals thus foundered because of the unanticipated ionic behaviour of S-propargyl xanthates. It turns out that only the simplest member rearranges to the allene at temperatures around 80°C: as soon as a substituent is placed at the acetylenic terminus, much higher temperatures (e. g. refluxing chlorobenzene) are needed to accomplish the [3,3] sigmatropic shift. Since the radical reactions are usually carried out in refluxing cyclohexane, benzene, or 1,2-dichloroethane, then it should be possible to avoid the ionic pathway by hindering the triple bond. This is indeed the case: as shown in scheme 10, a trimethylsilyl group (or even a methyl group) is enough. This represents, as far as we know, the first high yielding instances of inter-or intramolecular capture of a propargylic radical to give otherwise inaccessible, complex alkynes.[13]



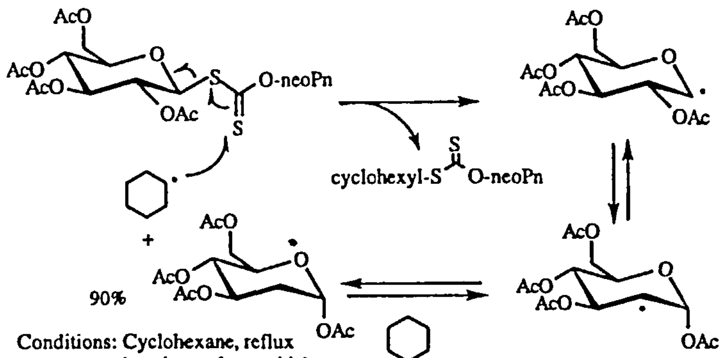
Scheme 10

The presence of the xanthate group in the end product may be considered as a synthetic asset, but many targets do not contain sulfur and it is necessary sometimes to perform a reductive cleavage with tributylstannane or with Raney nickel or nickel boride. It seemed however that the very degeneracy of the reaction of a radical with its xanthate precursor (path C in Scheme 2) may in fact be exploited to accomplish the replacement of the xanthate group with a hydrogen atom abstracted from isopropanol. The process is not a chain reaction any more and consists in the portion-wise addition of stoichiometric amounts of lauroyl peroxide to a refluxing solution of the xanthate in isopropanol alone or in mixture with another solvent. This generally high yielding transformation is limited in practice to secondary cases (Scheme 11) but these are synthetically the most interesting; moreover, a cyclisation step can be incorporated as shown by the third example in the same scheme.[14]



Scheme 11

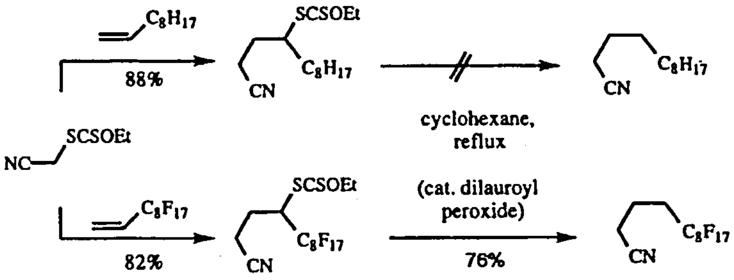
We accidentally found that if the radical that is produced is electrophilic in character but not stabilised, the hydrogen abstraction can occur from cyclohexane and the reduction becomes "catalytic" in peroxide because the cyclohexyl radical, unlike that derived from isopropanol, is capable of propagating the chain.[15] Radicals possessing such properties can be derived from carbohydrates, and we have exploited this polar effect to prepare 2-deoxy sugars in a very economical way, by incorporating a 1,2-acetyloxy shift into the sequence. This is illustrated by the example in Scheme 12. The yield is very high (in the 90% range) and the starting xanthate in this case is readily made from commercially available acetobromoglucose; moreover, the co-product is cyclohexyl xanthate which is non polar and can easily be separated from the desired product. The reaction can be extended to the corresponding benzoate which also undergoes migration to the anomeric carbon. If the xanthate group is on another secondary position in the sugar, then simple reduction without any migration occurs.



Conditions: Cyclohexane, reflux
(cat. lauroyl peroxide)

Scheme 12

That an unstabilised radical with electrophilic character is necessary for hydrogen abstraction from cyclohexane to occur under the reaction conditions was shown by a competion experiment, summarised in scheme 13. Thus, two xanthates were prepared by addition of the cyanomethyl radical to 1-decene on one hand and to 1-heptadecafluorodecene on the other, and exposed in the same flask, to the action of lauroyl peroxide in cyclohexane. Only the fluorinated substrate was reduced; the non-fluorinated xanthate was recovered largely unscathed.[15] The tremendous inductive effect of the fluorine atoms renders the radical quite electrophilic without stabilising it: the hydrogen abstraction from cyclohexane is in consequence speeded up to a synthetically useful level.



Scheme 13

One very important advantage of xanthates is that a variety of carbon centered (and even tin centered) radicals can be readily generated and captured. By employing the appropriate precursor, many highly functionalised structures thus become readily accessible. We have for example used acyl xanthates to access a new generation of anti-inflammatory steroids which appear promising for the treatment of asthma and which possess the general structure depicted in Figure 1. The delicate thioacetal motif adorning ring D is difficult to construct using conventional ionic chemistry.

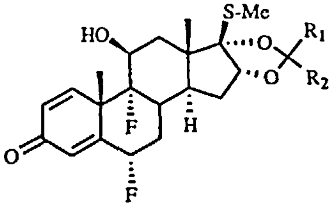
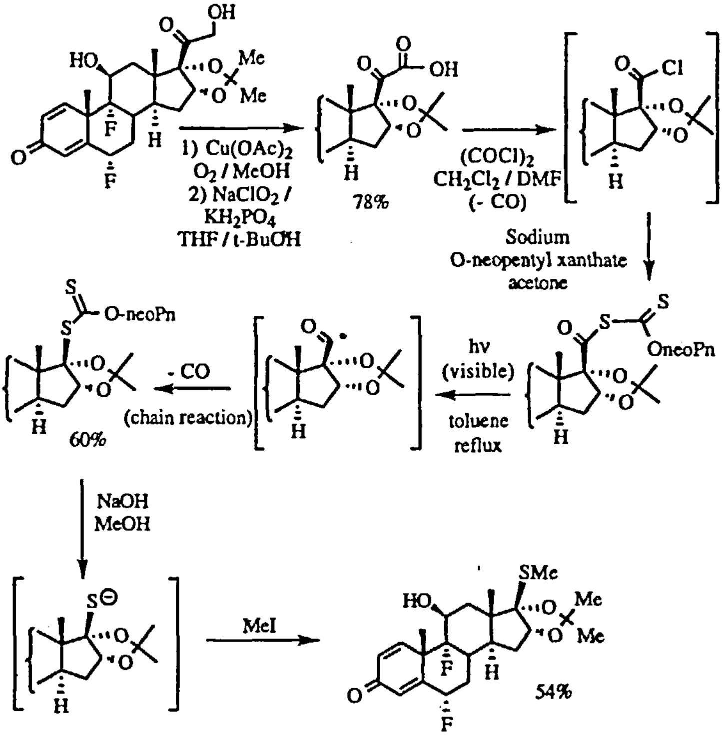


Figure 1

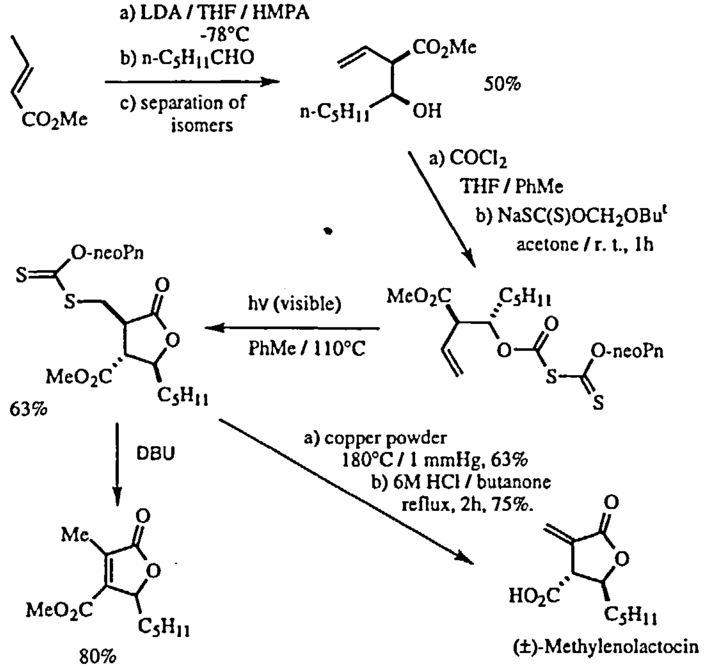
The route, outlined in scheme 14, involves a degradation of the corticosteroid side chain of the commercially available fluocinolone acetonide.[16] On carbon is lost as carbon monoxide during the formation of the acid chloride from the α-ketoacid and the second is extruded from the acyl radical, also as carbon monoxide. Sponification of the xanthate followed by alkylation of the thiolate with methyl iodide finally delivers the thioketal structure with the correct stereochemistry. It is worth pointing out that radical reaction involving S-acyl xanthates can be triggered using visible light, an observation first made by the late Sir Derek Barton and his colleagues nearly fourty years ago.[17] One advantage of this approach is that a variety of analogues can be made simply by using different alkylating agents in the last step.



Scheme 14

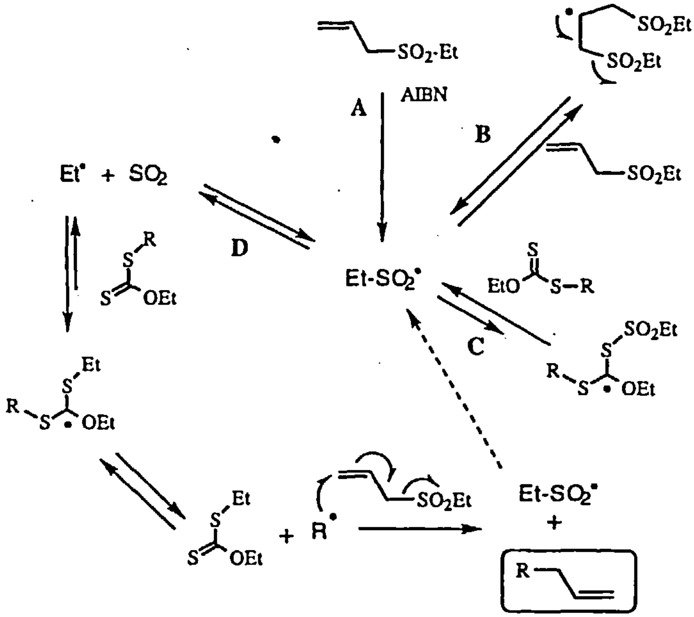
The formation of lactones by interception of an alkoxycarbonyl radical derived from an S-alkoxycarbonyl xanthate is exemplified by the short synthesis of (±) methylenolactocin[18] outlined in Scheme 15.

The xanthate group in the adduct is in the β–position with respect to the carbonyl group and is easily eliminated. In this case, however, this must be done by heating with copper powder since the use of a base such as DBU results in the migration of the double bond to give the undesirable isomer.



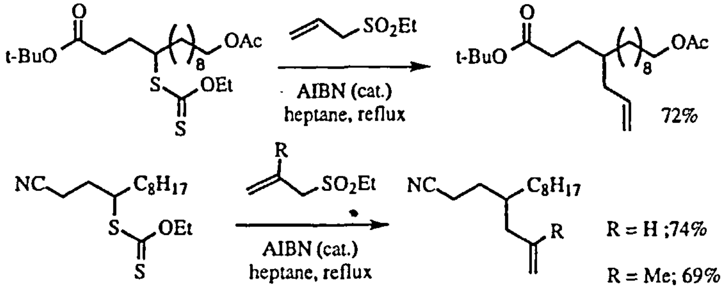
Scheme 15

The degeneracy principle can be used to replace the xanthate functionality by an allyl unit through a radical manifold where the unwanted side reactions are minimised.[19] The principle is delineated in Scheme 16. Radicals derived from the initiator (e.g. AIBN) react with ethyl allylsulfone to produce ethylsulfonyl radicals (path A). The reaction of ethylsulfonyl radicals with ethyl allylsulfone (path B) is degenerate whereas their addition to the thiocarbonyl group (path C) is highly reversible, the reverse process being strongly favoured by the weakness of the -SO_2—S- bond. The only alternative that remains is extrusion of sulfur dioxide (path D) which now leads to ethyl radicals. Although these reactive species can (and certainly do occasionally) add to ethyl allylsulfone, their reaction with the xanthate is much faster due to the greater radicophilicity of the thiocarbonyl group in comparison with an unactivated olefin. Expulsion of R$^\bullet$ now is favored and, since its interaction with its xanthate precursor is degenerate, this radical must now add to ethyl allylsulfone to give the deired allylation product.



Scheme 16

The feasibility of this new system is demonstrated by the examples in Scheme 17. A simple, economical radical allylation is now in hand which, again, does not involve heavy metals. Substituted allyl derivative can be used and the yields are quite respectable.



Scheme 17

In summary, this work on xanthates and allylsulfones has opened access to a variety of transformations which were hitherto difficult to accomplish. The possibility of creating C-C bonds in an intermolecular fashion on unactivated olefins starting with a variety of radical species is especially noteworthy.

Acknowledgement:

We wish to thank our co-workers whose names are mentioned in the references and who have participated skillfully and enthusiastically in this work. We also would like to acknowledge financial support from Hoechst Marion Roussel, the CNRS, and the Ministère de l'Education.

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