Radical Reactions

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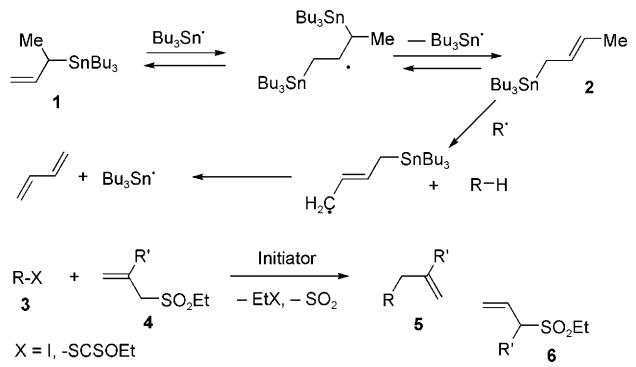
Radical Allylation with α-Branched Allyl Sulfones**

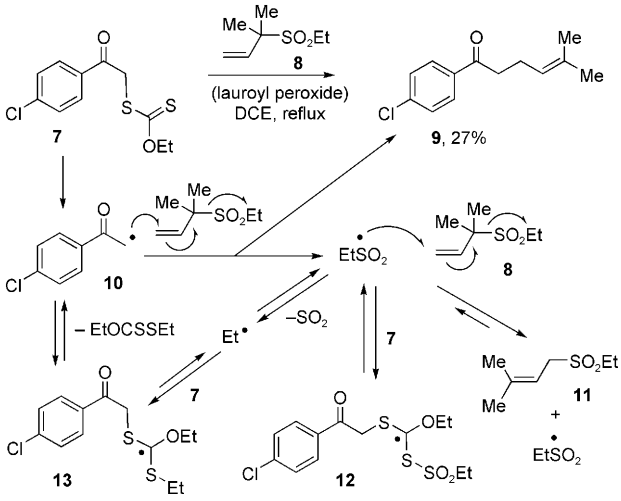
*Nicolas Charrier and Samir Z. Zard**

Radical allylations, especially using allylstannanes, have emerged as powerful synthetic tools as evident by the numerous synthetic applications on a wide range of substrates.[1,2] One of the chief limitations of this technology is with respect to the substitution pattern around the allyl group. α-Substituted allylstannanes, such as **1**, rapidly rearrange under the reaction conditions into their more stable γ-substituted isomers (e.g. **2**), and these were found to react mostly through abstraction of the allylic hydrogen atom rather than by the desired addition–fragmentation process (Scheme 1).[2e,3,4] Other approaches using allylcobalt,[5] allylgallium,[6] allylhalogen,[7] or allylsulfur[8] derivatives have been explored in an attempt to overcome these shortcomings, but most still require a stoichiometric amount of a tin-based promoter[9] (or other metal-based reagents) and have usually been applied to the introduction of simple allyl moieties.[10] A combination of radical and ionic sequence have also been devised.[11]



Scheme 1. Side reactions during allylation with α-substituted allyl triorganotin reagents.

We recently described a tin-free allylation of iodides and xanthates **3** based on the use of allyl ethyl sulfones of general structure **4** and leading to terminal alkenes **5** (Scheme 1).[12] Unfortunately, when we tried to expand its scope to encompass α-substituted allyl sulfones **6**, we encountered the same problems of undesired isomerization. Thus, lauroyl-peroxide-mediated reaction of xanthate **7** with α,α-dimethylallyl ethyl sulfone **8** in 1,2-dichloroethane (DCE) at reflux was sluggish, requiring 70 mol% peroxide and giving only 27% of the desired product **9** (Scheme 2). Considerable quantities of the unwanted rearranged sulfone **11** were formed by addition–fragmentation of the intermediate ethylsulfonyl radicals with α,α-dimethylallyl ethyl sulfone **8**. Unlike the case of β-substituted allyl sulfones **4**, which can not be isomerized by reaction with ethylsulfonyl radicals (because the addition–fragmentation is degenerate), the persistence of the ethylsulfonyl radicals in the medium in the case of α-substituted allyl sulfones such as **8** (and more generally **6**) turns out to be a serious problem. Ethylsulfonyl radicals can not be removed through reaction with xanthate **7**, as the addition to the thiocarbonyl leads to an intermediate **12** with a quite weak SO_2–S bond. This intermediate forms readily but only collapses back to the starting components and does not therefore propagate the chain. The result is a poor yield of product **9** and the need for a relatively large amount of initiator in addition to an excess of the allylating agent **8**, as much of it is wasted through isomerization into γ,γ-dimethylallyl ethyl sulfone **11**.



Scheme 2. Allylation with α-substituted allyl sulfone reagents.

The first resolution of this difficulty was to increase the temperature of the reaction. The unimolecular extrusion of sulfur dioxide from the ethylsulfonyl radical has a high positive entropy component and is consequently much more sensitive to temperature than the bimolecular addition to α,α-dimethylallyl ethyl sulfone **8a**, the first step in the unwanted isomerization sequence. The faster loss of sulfur dioxide would generate highly reactive ethyl radicals, and these

[*] N. Charrier, Prof. S. Z. Zard
Laboratoire de Synthèse Organique associé au CNRS
Ecole Polytechnique
91128 Palaiseau Cedex (France)
Fax: (+33) 169335972
E-mail: zard@poly.polytechnique.fr

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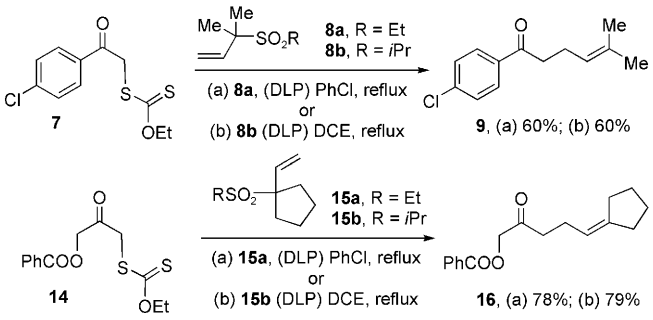
should preferentially attack the more radicophilic thiocarbonyl group of xanthate **7** to give key intermediate **13**. Collapse of the latter can now proceed in the desired direction and propagate the chain through the formation of starting carbon radical **10**. Indeed, when the reaction was performed in refluxing chlorobenzene, the yield of **9** increased to 60% and required only 30 mol% of lauroyl peroxide (Scheme 3).

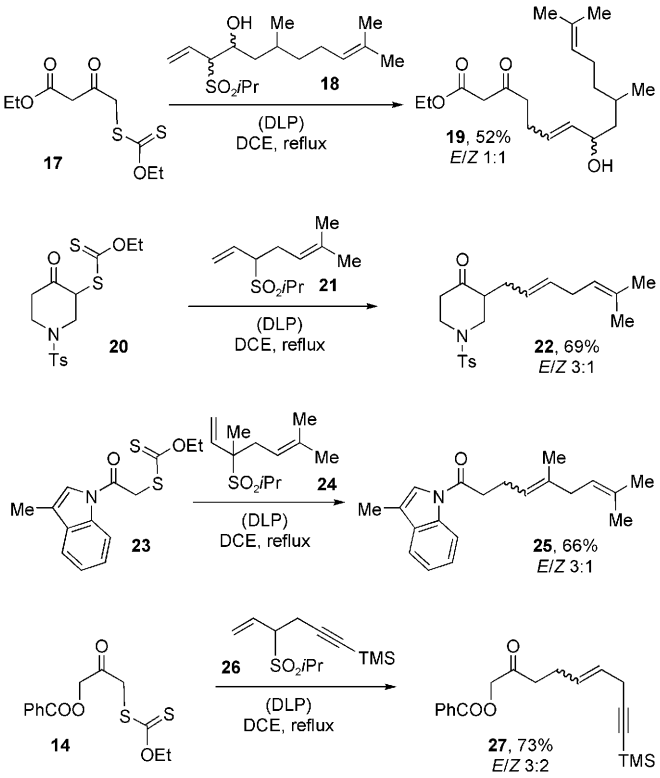


Scheme 3. Resolutions of premature allyl sulfone isomerization. DLP = dilauroyl peroxide.

Only little of isomerized sulfone **11** was produced. In the same manner, xanthate **14** was converted into **16** in 78% yield using sulfone **15a** as the allylating agent (Scheme 3). This simple expedient opened the route to the introduction of more substituted allyl side chains, at least in the case of robust substrates able to withstand the relatively high temperature.

For more complex or fragile structures, a milder and more general procedure was required. To avoid the problematic isomerization of the allyl sulfone, we postulated that replacing the ethyl group by an isopropyl group would lead to the formation of isopropylsulfonyl radicals, and these should extrude sulfur dioxide at a significantly faster rate as compared with ethylsulfonyl congeners. Even though no kinetic measurements for the extrusion process were available, we hoped that the enhancement in the rate of fragmentation would be sufficient for our purposes, allowing us to operate at a much lower temperature and without the problem of isomerization of the allyl sulfone reagent.

Indeed, using isopropyl sulfones **8b** and **15b** as the allylating agent, the same allylated products **9** and **16** were obtained from xanthates **7** and **14**, respectively, in almost identical yield and at the much lower temperature of DCE at reflux. The mildness of the reaction conditions permits the introduction of more functionalized side chains, as illustrated by the examples in Scheme 4. Thus, citronellal-derived sulfone **18** reacted with acetoacetyl xanthate **17** to furnish diene **19** in 52% yield, without the need to protect the allylic alcohol. The synthesis of the delicate skipped dienes **22** and **25** was accomplished in 69% and 66% yield starting from xanthates **20** and **23**, and sulfones **21** and **24**, respectively. The fact that there is little interference from the easily abstractable doubly allylic hydrogen atoms is quite remarkable. Finally, the possibility of accessing the even more interesting skipped enynes is highlighted by the clean formation of

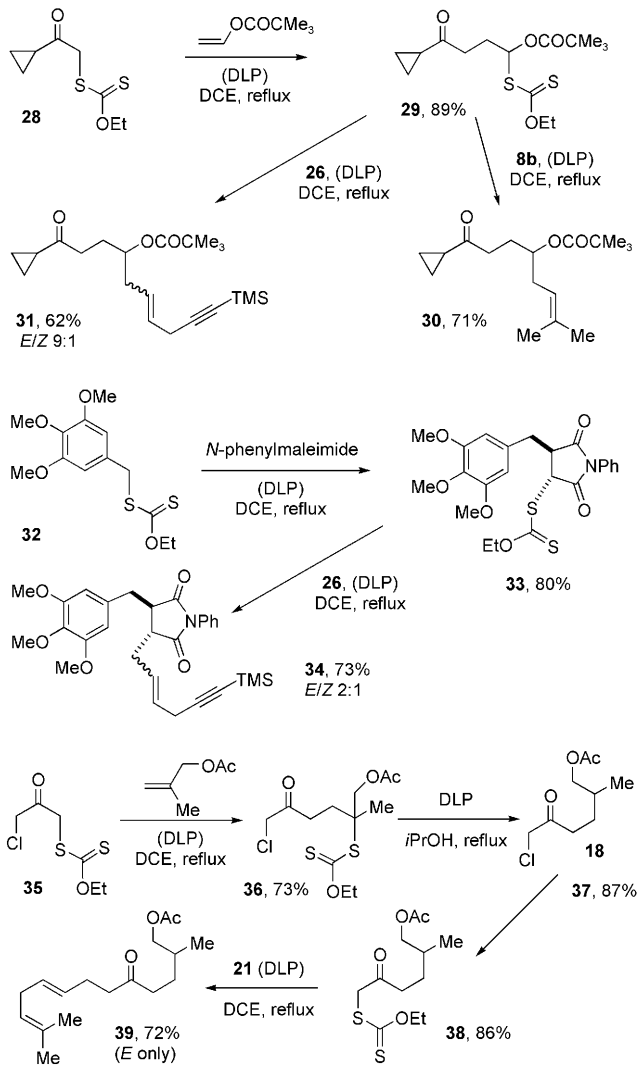


Scheme 4. Radical additions on functionalized allyl sulfones. TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

compound **27** in 73% yield from xanthate **14** and sulfone **26**.

Although access to the series of allylated derivatives displayed in Scheme 3 would be beyond most of the previous radical allylation reactions, the fact that the precursors are xanthates provides a concise and modular route to considerably more complex structures, by combining the now well-established xanthate transfer technology[13] with the present allylation process. This approach is exemplified by the transformations in Scheme 5.

Addition of cyclopropylacetonyl xanthate **28** to vinyl pivalate provides adduct **29** in 89% yield. Allylation with sulfones **8b** and **26** under the usual reaction conditions furnishes allylated compounds **30** and **31** in 71% and 62% yield, respectively. The reaction of trimethoxybenzyl xanthate **32** with *N*-phenylmaleimide gives a high yield of the *trans* adduct **33**, and the xanthate group in the latter can be replaced efficiently by an enyne side chain through a radical addition–fragmentation process to allyl sulfone **26**. The yield of the resulting product **34** is 73% and, as would be expected, the C–C bond formation takes place from the opposite side to the trimethoxybenzyl side chain with net overall retention of configuration. Another variation is illustrated by the last sequence starting with chloroketone xanthate **35**. This highly versatile xanthate[14] undergoes reaction with methallyl acetate to give **36**, from which the xanthate group can be reductively removed by further reaction with lauroyl peroxide in isopropyl alcohol. Displacement of the chloride in **37** now gives rise to another xanthate **38**, which can be allylated in



Scheme 5. Modular approach to complex structures.

good yield by reaction with allyl sulfone **8b**. Thus, the two sides of the initial ketone can be elongated by two different radical reactions.

In conclusion, by a simple modification of the substituent on the sulfone group, and guided by kinetic considerations, we have succeeded in expanding considerably the scope of the tin-free radical allylation of xanthates. This method complements the route based on allyl diphenylphosphine oxide we recently devised,[15] with the added advantage that the starting branched allyl sulfones are generally more readily available by reaction of the anion derived from the parent allyl isopropyl sulfone with various electrophiles such as aldehydes and alkylating agents.[16] The xanthate partners can be accessed by various routes, including the radical xanthate transfer onto activated or nonactivated olefins. A broad variety of structures can therefore be assembled by this simple, yet powerful, convergent, and flexible approach.

Experimental Section

Typical procedure for the radical allylation: Lauroyl peroxide (0.1 mmol) was added every hour to a solution of the xanthate (1.0 mmol) and allyl sulfone (2.0 mmol) in degassed DCE at reflux (1.0 mL) under a nitrogen atmosphere, until complete consumption of the starting xanthate. The reaction mixture was then cooled to room temperature, concentrated in vacuo, and purified by flash column chromatography.

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