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Generation and Intermolecular Capture of Cyclopropylacyl Radicals

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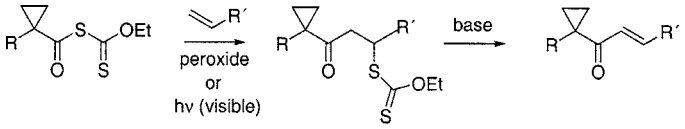
ABSTRACT



Cyclopropylacyl radicals derived from *S*-cyclopropylacyl xanthates (dithiocarbonates) undergo intermolecular additions to olefins without loss of CO or ring opening. In the presence of a phenyl ring on carbon C-1 of the cyclopropane ring, loss can be made to occur in the absence of an olefinic trap. The adducts from the cyclopropylacyl radical additions are easily converted into enones by base-induced *β*-elimination of the xanthate group.

As an illustration of the synthetic potential of the radical transfer of xanthates and related groups,[1] we contemplated the possibility of constructing ϵ-lactam **1**, the core structure of various vasopeptidase inhibitors of some recent importance,[2] by the addition of xanthate **3** to protected allyl glycine **4** as outlined in Scheme 1. The acyl radical **5** arising from **3** would be expected to rapidly lose carbon monoxide to give the stabilized tertiary radical **6**, which would then undergo the desired addition to the olefinic trap to give ultimately adduct **8**.[3] This compound has two differentially protected amines and all the elements necessary to constitute an immediate precursor to the target molecule **1**. The synthesis of the requisite xanthate **3** was straightforward from the known acid chloride **2**,[4] and conditions were found to induce its addition to simple olefins such as allyl acetate and vinyl pivalate, affording adducts **9** and **10** in 76 and 94% yields, respectively (Scheme 1). However, the addition proceeded quite poorly with protected allyl glycine **4**. Only a low yield (<10%) of desired adduct **8** could be secured by heating at 60 °C in 1,2-dichloroethane in the presence of lauroyl peroxide as an initiator.

The main problem was the tendency of xanthate **11**, which is in equilibrium with radical **6**, to undergo elimination of xanthic acid **12** to give olefin **13**.[5] The xanthic acid released in this process acts as an inhibitor for the radical chain. This unimolecular elimination is favored by an increase in temperature, hence the need to operate below 60 °C, in contrast to the usual radical additions we have routinely performed over the years in temperature ranges of 80−130 °C.

To limit this problem, we examined the use of the cyclopropyl analogue **15**, where thermal elimination of the xanthate group would be expected to be difficult due to the strain inherent in the resulting olefin. At the same time, this would allow access to perhaps even more interesting vaso-

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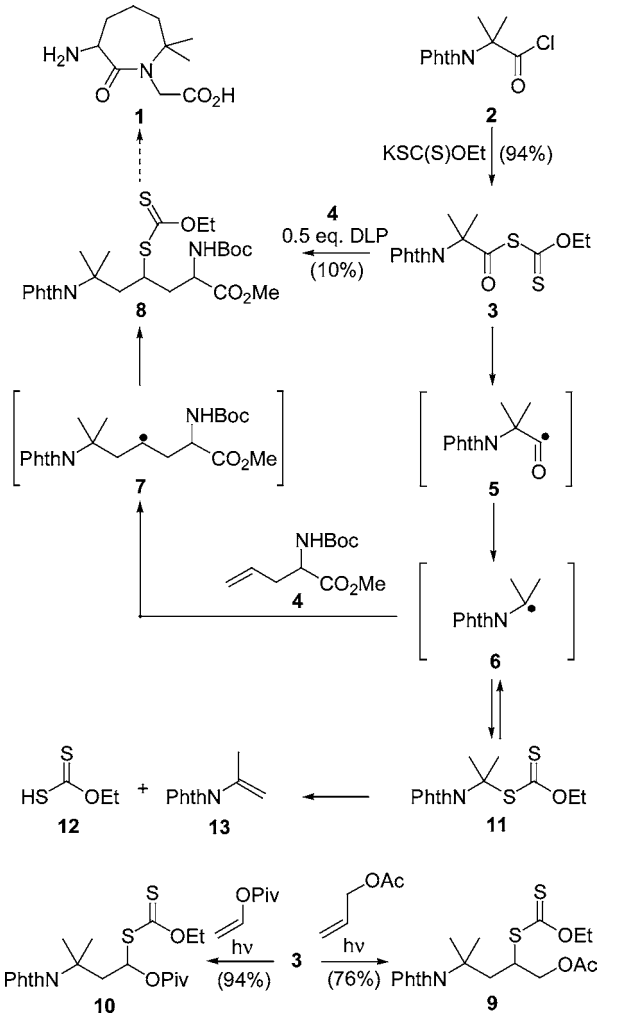
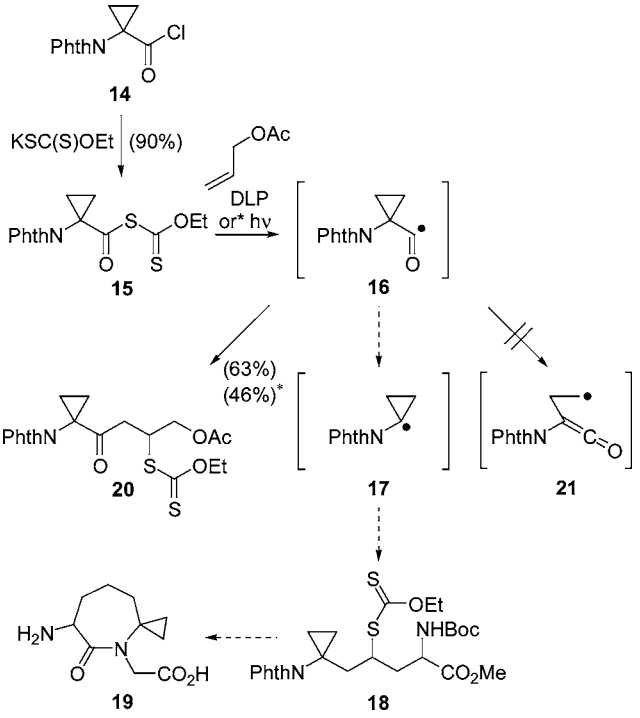
Scheme 1



Scheme 2



peptidase inhibitors derived from **19**, where the geminal dimethyl group has been replaced by a metabolically more robust cyclopropane (Scheme 2).[2b] The desired acyl xanthate **15** was readily prepared by reaction of potassium *O*-ethyl xanthate with the corresponding acid chloride **14**.[6] When this new xanthate was irradiated in the presence of allyl acetate in refluxing 1,2-dichloroethane, we were surprised to find that adduct **20**, isolated in 46% yield, still retained the carbonyl group. An improved yield (63%) was obtained when initiation was conducted with 10 mol % lauroyl peroxide instead of visible light.

Clearly, the cyclopropylacyl radical intermediate **16** did not readily undergo decarbonylation to give **17**, in contrast to the dimethyl analogue. Cyclopropyl radicals resemble to a certain extent vinyl radicals.[7] They are less stable than their aliphatic counterparts, and this is apparently sufficient to slow considerably the extrusion of carbon monoxide.[8] Nor does the lone pair of the nitrogen seem to counterbalance the destabilizing effect of the cyclopropyl ring. Indeed, irradiation of xanthate **15** in refluxing 1,2-dichloroethane for several hours did not cause any decomposition and the starting material was recovered essentially unchanged in >95% yield. In the absence of the olefinic trap and with no possibility of losing carbon monoxide, the cyclopropylacyl radical **16** is condemned to evolve back into the starting material by reacting with its precursor, xanthate **15**.

The addition to allyl acetate described above appears to be the first case where a cyclopropylacyl radical is generated and captured in an *intermolecular* fashion. We are aware of only one example reported by Pattenden and co-workers,[8d] where a cyclopropylacyl radical was intercepted by an internal olefin. Interestingly, the cyclopropylacyl radical does not undergo ring opening to ketene **21** in the present case. Scission to the ketene was observed earlier by Pattenden's group,[8d] but only when the ensuing radical was stabilized by conjugation to a carbonyl group.

As shown by the transformations depicted in Scheme 3, additions to various olefins could be accomplished in synthetically useful yields. Except for vinyl pivalate, the use of peroxide proved to be more efficient than photochemical initiation.[9] We also found it beneficial to add most of the peroxide at the beginning in order to favor the radical chain addition over the slow decomposition of the starting xanthate.

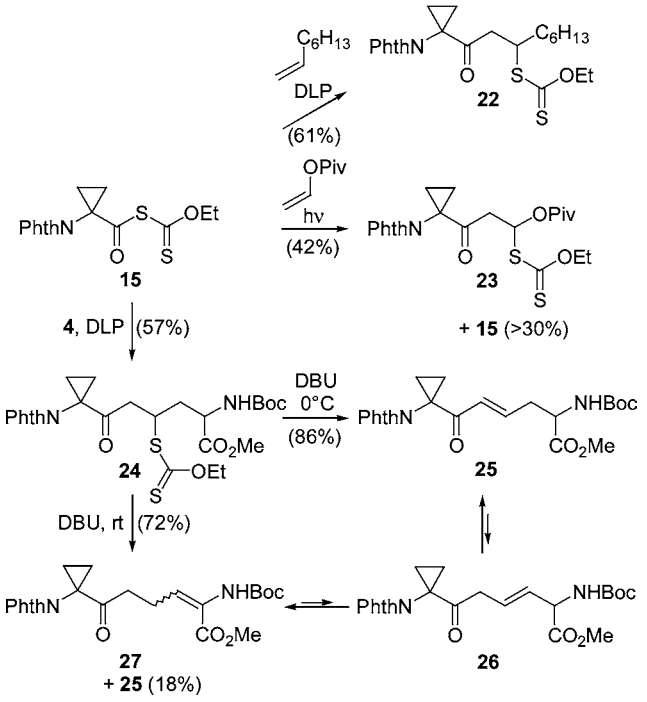
(6) For preparation of acid chloride **14**, see: Haddow, J.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1297−1304 (modified procedure).

(7) For a review of cyclopropyl radicals, see: Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625−1651.

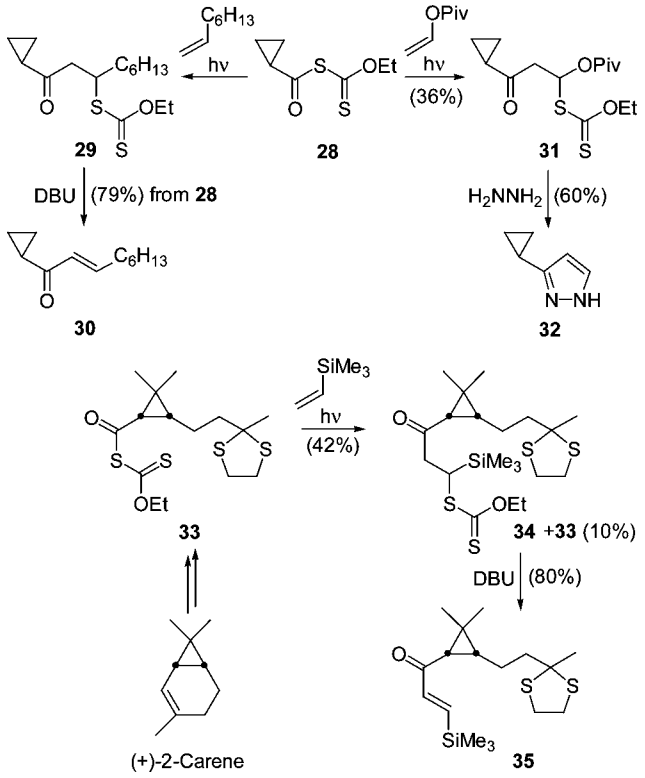
(8) Stability of cyclopropylacyl radicals: (a) Kerr, J. A.; Smith, A.; Trotman-Dickenson, A. F. *J. Chem. Soc. A* **1969**, 1400−1403. (b) Blum, P. M.; Davies, A. G.; Sutcliffe, R. *J. Chem. Soc., Chem. Commun.* **1979**, 217−218. (c) Davies, A. G.; Sutcliffe, R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1483−1488. (d) De Boeck, B.; Herbert, N.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 6971−6974.

(9) Initiation with DLP led to polymerization of vinyl pivalate. A similar result was obtained when a solution of **15** in vinyl pivalate was irradiated.

Scheme 3



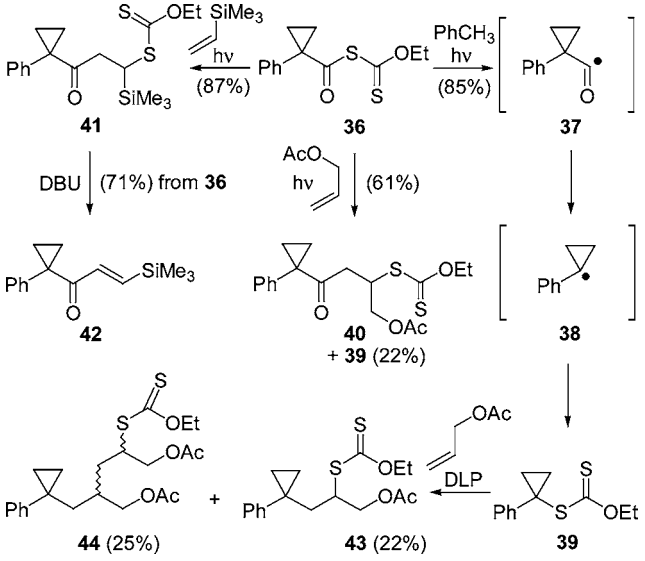
Scheme 4



Acyl xanthates in general are hydrolytically labile,[1] and degradation by this pathway liberates xanthic acid and other sulfur-containing side products that, as was stated above, act as inhibitors. None of the additions presented in Scheme 3 have been optimized, and room for improvement certainly exists. Nevertheless, the process provides access to structures with a dense combination of functionalities that would be very difficult to obtain otherwise. The addition to protected allyl glycine **4** is especially noteworthy since it opens a route to unusual amino acids. The positioning of the xanthate group β- to the carbonyl group in the various adducts allows its elimination with base to produce the unsaturated ketones. In the case of **24**, the resulting olefin can migrate along the chain by a series of prototropic shifts to give ultimately the thermodynamically more stable enamide **27**. Such enamides are very valuable substrates since it is well established that their hydrogenation in the presence of chiral catalysts can give rise to amino acids with high optical purity.[10]

The reaction could be extended to other cyclopropylacyl xanthates (Scheme 4). The simplest derivative, **28**, is less protected by steric hindrance against hydrolysis but nevertheless underwent the desired addition. Addition to octene was immediately followed by treatment with DBU to give directly enone **30** in 79% yield ((*E*)-isomer).[11] In the case of the adduct **31** arising from the reaction with vinyl pivalate, the carbon bearing the xanthate is at the oxidation level of an aldehyde, so that exposure to hydrazine resulted in the formation of 3-cyclopropyl-pyrazole **32** in 60% yield. The volatility of this compound made its isolation on a small scale somewhat inconvenient. The more complex xanthate **33**, a compound readily prepared from (+)-2-carene,[12] also participated in the radical chain addition as illustrated by its addition to trimethylvinylsilane to give adduct **34** in 42% yield. Base-induced elimination of the xanthate group

Scheme 5



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furnished unsaturated ketone **35**, again solely as the (*E*)-isomer. Such vinylsilyl ketones are not trivial to make by other routes.[13] Xanthate **33** is an interesting synthon for the enantioselective synthesis of terpenes containing a geminal dimethylcyclopropyl motif.

To define what group would be needed to induce loss of carbon monoxide, we prepared and examined the phenyl-substituted derivative **36**. In this case, irradiation in refluxing toluene in the absence of a trap resulted in decarbonylation to give xanthate **39** in over 85% yield. Stabilization by the phenyl group thus compensates the untoward effect of the cyclopropyl ring and encourages the expulsion of carbon monoxide from cyclopropylacyl radical **37**. This extrusion nevertheless remains comparatively slow since irradiation in refluxing allyl acetate furnished ketone **40** as the major product (61%) along with xanthate **39**, which was isolated in only 22% yield. With the more reactive and lower boiling vinyltrimethylsilane, the reaction gave almost exclusively the addition product **41** (87%). Treatment with DBU again resulted in clean elimination of the xanthate group to provide the vinylsilyl ketone **42** (71% from **36**). The steric bulk of the phenyl group in **36** protects against hydrolytic degradation and allows efficient additions to be performed photochemically with visible light. We found that xanthate **39**, arising from the decarbonylation process, can be made to add to allyl acetate to give **43** (22%), but this is complicated by further addition leading to **44** (25%, mixture of diastereomers) and presumably smaller amounts of higher oligomers. The ready formation of such side products is again a reflection of the relative instability of radical **38**, despite the presence of the geminal phenyl ring.

The above preliminary results provide insight into the special behavior of cyclopropylacyl radicals. This approach also represents an efficient and flexible route to cyclopropyl ketones. These have proved to be exceptionally useful substrates for organic synthesis.[14]

Acknowledgment. This paper is dedicated with respect to Professor Pierre Potier on the occasion of his 70th birthday. We thank the Fondation Alfred Kastler for generous financial support to M.H. and Prof. Dr. M. Spiteller (University Dortmund) and Dr. W. Spahl (Ludwig Maximilians University Munich) for HRMS analysis.

Supporting Information Available: Experimental procedures and detailed analytical data for compounds **3**, **8**−**10**, **15**, **20**, **22**−**25**, **27**, **28**, **30**−**36**, and **39**−**44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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