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Radical addition to strained olefins: a flexible access to small ring derivatives

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Abstract

Intermolecular radical additions to various strained olefins such as cyclopropenes, cyclobutenes, azetines and methylenecyclopropanes can be accomplished in useful yield using the xanthate transfer method; the adducts may undergo further cyclisation to give polycyclic structures. © 2000 Published by Elsevier Science Ltd.

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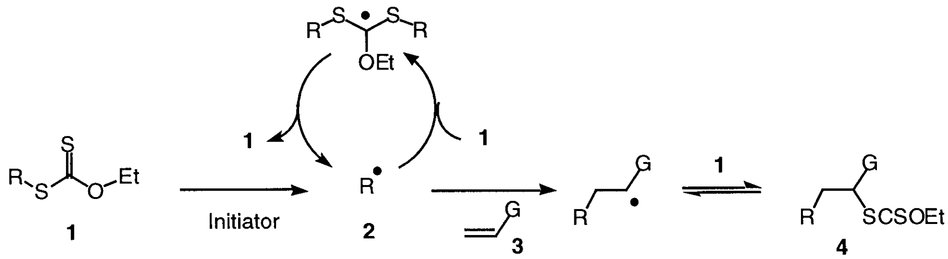
Xanthates (dithiocarbonates) have emerged as valuable radical precursors for inter- or intramolecular additions onto olefins.[1] As a member of the general class of group transfer reactions,[2] additions of xanthates exhibit several attractive features inherent in the mechanism, the most important aspect being, perhaps, derived from the degeneracy of the reaction of intermediate radical **2** with its precursor **1** (Scheme 1). As a consequence, radical **2** acquires a relatively long effective lifetime, enabling intermolecular addition to non-activated olefins (e.g. **3**). This is generally difficult to perform with alternative methodologies such as those based on



Scheme 1. The radical xanthate transfer process

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stannanes. Furthermore, the final product **4** is also a xanthate, allowing in principle subsequent radical transformations as well as access to the exceptionally rich chemistry of sulfur. Absence of heavy metals,[3] ease of scale-up, simple access to starting material[4] and cheapness are also additional assets.

Few radical additions on strained cycloalkenes have been reported in the literature.[5] We were thus curious to see whether xanthates could provide a more general access to substituted cyclopropanes and cyclobutanes. A concomitant work, just published by Saicic et al.,[6] prompts us to report our own results.

We first examined the case of cyclobutenes. Olefin **3a** is easily accessible from commercial 1,1-cyclobutane dicarboxylic acid.[7] Addition of various xanthates (**1a**–**e**) was effected in acceptable yields to give the desired adducts (**5a**–**e**).[8] The radical chain was triggered using lauroyl peroxide as the initiator and 1,2-dichloroethane as the solvent. In this respect, our study differs from that of Saicic et al. who, surprisingly, found that chemical initiation failed and had to employ photochemical initiation. The radical added regioselectively at the less hindered end of the double bond, leading to a mixture of diastereoisomers with the *trans* isomer dominating (Fig. 1). In the case of the *t*-butyl xanthate **1b**, the greater steric bulk resulted in the exclusive formation of the *trans* isomer **5b** (yields in brackets in Figs. 1–4 are based on recovered starting material). Finally, we found that the aromatic derivatives **5d** and **5e** could be further converted into the corresponding tetralones **6** and **7** in 45 and 40% yield, respectively, upon heating with stoichiometric amounts of peroxides.[9] Such complex, polycyclic tetralones would be very difficult to obtain by classical methods.

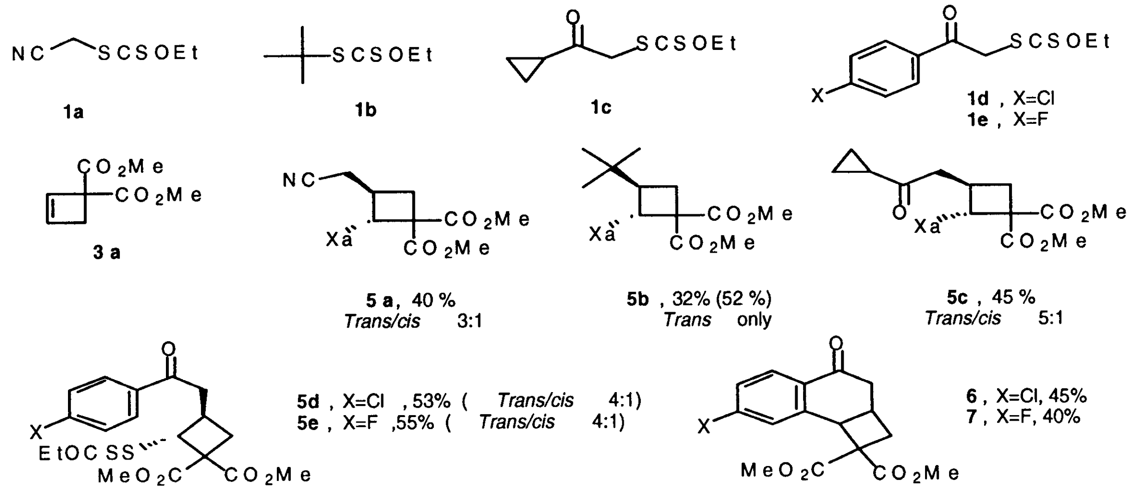


Figure 1. Additions to cyclobutenes

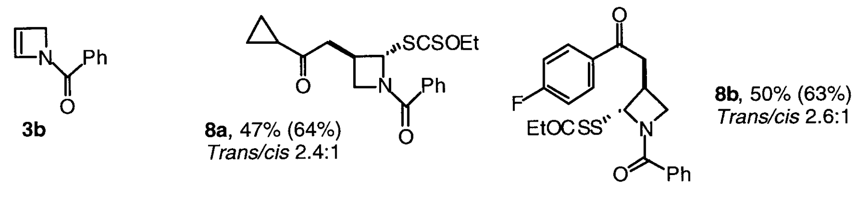
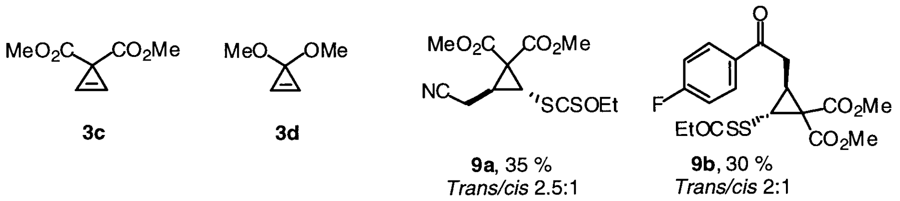
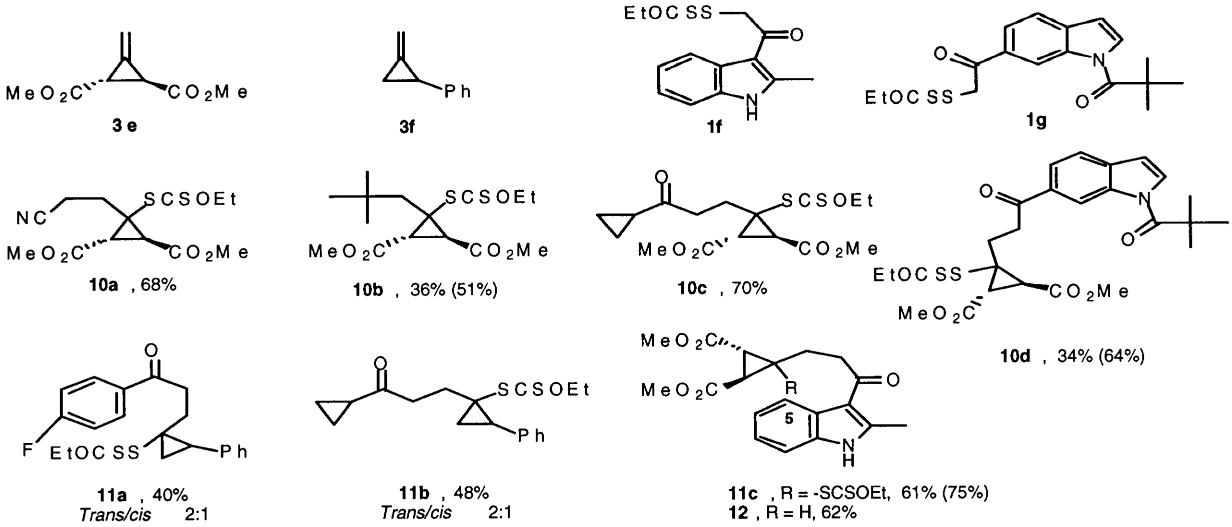


Figure 2. Radical additions to azetines



3c **3d** **9a**, 35 % *Trans/cis* 2.5:1 **9b**, 30 % *Trans/cis* 2:1

Figure 3. Radical additions to cyclopropenes



3e **3f** **1f** **1g**

10a, 68% **10b**, 36% (51%) **10c**, 70% **10d**, 34% (64%)

11a, 40% *Trans/cis* 2:1 **11b**, 48% *Trans/cis* 2:1 **11c**, R = -SCSOEt, 61% (75%) **12**, R = H, 62%

Figure 4. Radical additions to methylenecyclopropanes

These results encouraged us to examine the behaviour of azetines, a quite unusual substrate for radical additions. Azetines are more fragile than cyclobutenes, but should be more reactive towards an electrophilic radical. Few syntheses of unsubstituted azetines have been reported, the most practical perhaps being that described by Jung.[10] We thus prepared compound **3b** and exposed it to the action of xanthates **1c** and **1e** in the presence of a small amount of lauroyl peroxide. We were pleased to find that a smooth addition occurred to give adducts **8a** and **8b** in 47 and 50% yield (Fig. 2). The *trans* isomer again dominated, but to a lesser extent than with cyclobutene **3a**. Intermolecular radical additions to an azetidine are unprecedented as far as we know.

We next studied additions to cyclopropenes **3c** and **3d**, prepared according to literature methods.[11] Cyclopropene **3c** did participate in the desired radical addition using xanthates **1a** and **1e**, providing adducts **9a** and **9b** in modest yield (Fig. 3). In contrast, we were unable to accomplish a xanthate transfer on cyclopropene **3d**, which proved to be too labile to handle under our conditions. Even at 0°C with triethylborane as initiator, only degraded material was observed.

Additions to *exo*-methylene cyclopropane derivatives would also constitute a route to functionalised cyclopropanes. Thus, starting from readily accessible olefins **3e** and **3f**[12] and xanthates **1a,b,c,e**, as well as xanthates **1f** and **1g**, we prepared adducts **10a–d** and **11a–c** in generally quite reasonable yields, as shown in Fig. 4. We attempted, in the case of **11c**, the construction of a seven-membered ring by a subsequent radical addition onto position 5 of the indole, by analogy with an earlier work.[13] However, upon heating **11c** with equimolar amounts of lauroyl peroxide, the unexpected reduced product **12** was isolated in 62% yield.

In summary, we have shown that the xanthate methodology is applicable to additions to strained olefins such as cyclobutenes, azetines and cyclopropenes. Other similarly strained olefins would certainly be acceptable partners in the process. The yields have not been optimised and room for improvement certainly exists; nevertheless, this approach to mono- and polycyclic molecular architectures containing small rings appears to be quite versatile and synthetically promising.

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