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Intermolecular additions of cyclobutanone derived radicals. A convergent, highly efficient access to polycyclic cyclobutane containing structures

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Abstract—α-Xanthyl cyclobutanones undergo intermolecular radical additions to olefins bearing various functional groups. Adducts containing a phosphonate can be made to cyclise by an internal Wittig–Horner–Emmons reaction to give cyclohexene and cycloheptene rings fused to the cyclobutane.

Cyclobutane derivatives play an important role in organic synthesis, both as synthetic targets, since a sizeable number of natural products and especially terpenes contain a cyclobutane subunit, and as synthetic intermediates, in view of the variety of useful and sometimes specific transformations undergone by the strained 4-membered carbocycle.[1] In this second context, cyclobutanones are of special prominence. Their chemistry is amazingly rich[2] and they are readily accessible through the powerful and highly flexible [2+2] cycloaddition of ketenes and ketene iminium salts.[3] The latter approach is particularly well suited for enantioselective syntheses.[4] However, in contrast to larger cycloalkanones, alkylation of enolates derived from cyclobutanones is complicated by self-condensation and by the possibility for the enolate to undergo a thermal electrocyclic opening. This imposes quite severe constraints on the nature of the alkylating agents and the experimental conditions that can be used. The very few examples described in the literature concern only highly reactive alkylating agents such as methyl iodide and allyl and propargyl halides.[5] In one example, a less reactive alkyl bromide could be introduced in modest yield by using the magnesium salt of the derived cyclobutanone cyclohexylimine.[5d] It is not surprising, therefore, that the introduction of side chains onto a cyclobutanone usually necessitates an indirect approach such as a sequence of aldol reaction, dehydration, and reduction. We have now found that the xanthate transfer radical addition reaction we uncovered a few years ago[6] nicely complements existing methods and allows entry into cyclobutane structures hitherto unavailable or accessible only with difficulty.

Bromide **2** was easily prepared from cyclobutanone **1** by the reaction with bromine in chloroform or by treatment of the corresponding enol silyl ether with NBS.[7] We found the latter procedure more general. Displacement of the bromide to give the desired xanthate **3** was accomplished in good yield by the action of potassium *O*-ethyl xanthate in acetone (Scheme 1). The analogous substitution of the less reactive but more readily accessible chloride (by partial reduction of the dichloroketene adduct) could not be achieved in satisfactory yield. We were pleased to find that refluxing a solution of **3** with allyl acetate in 1,2-dichloroethane in the presence of a small amount of lauroyl peroxide resulted in a smooth radical addition to give compound **4** in 67% isolated yield as a mixture of diastereoisomers. It must be noted that the stereochemistry of the xanthate precursor is of no consequence since both epimers lead to the same radical. Reductive removal of the xanthate group with tributyl stannane gave a 9:1 mixture of epimers **5** (87%). The same reductive dexanthylation could be accomplished in 78% yield under tin-free conditions using stoichiometric amounts of lauroyl peroxide in 2-propanol.[8] The *trans* epimer dominates since the radical addition to the olefin occurs from the least hindered side opposite to the butyl group. The utility of this sequence leading to branched cyclobutanones is highlighted by the conversion of **5**

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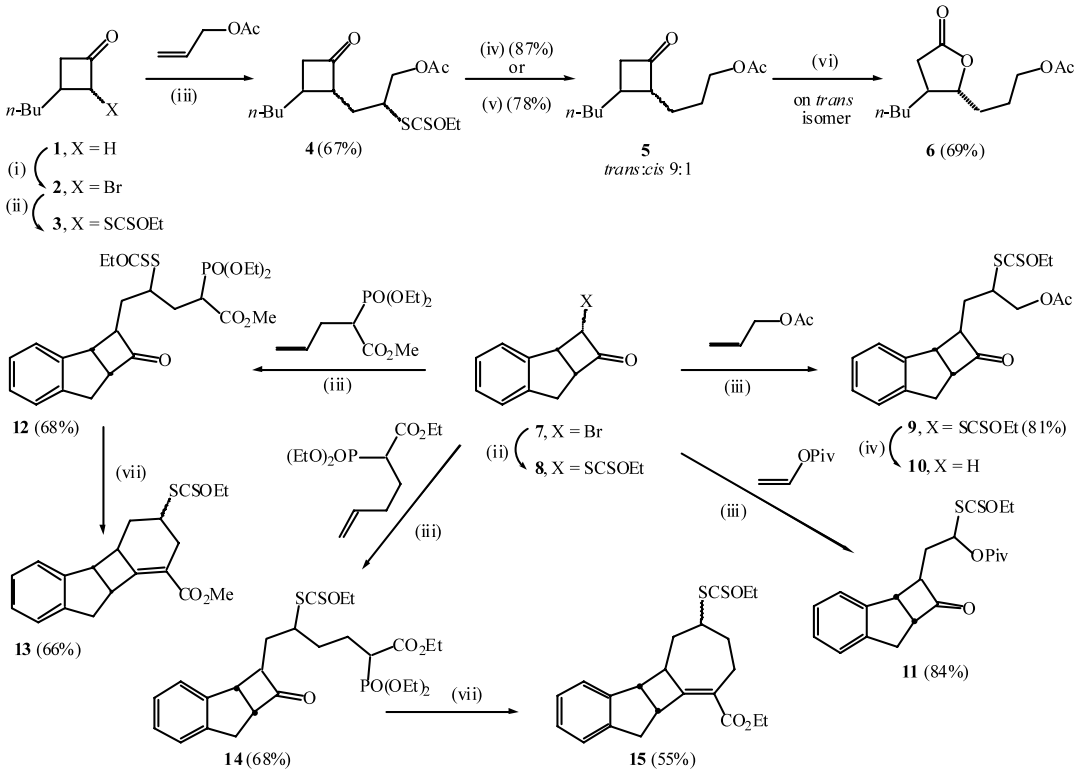
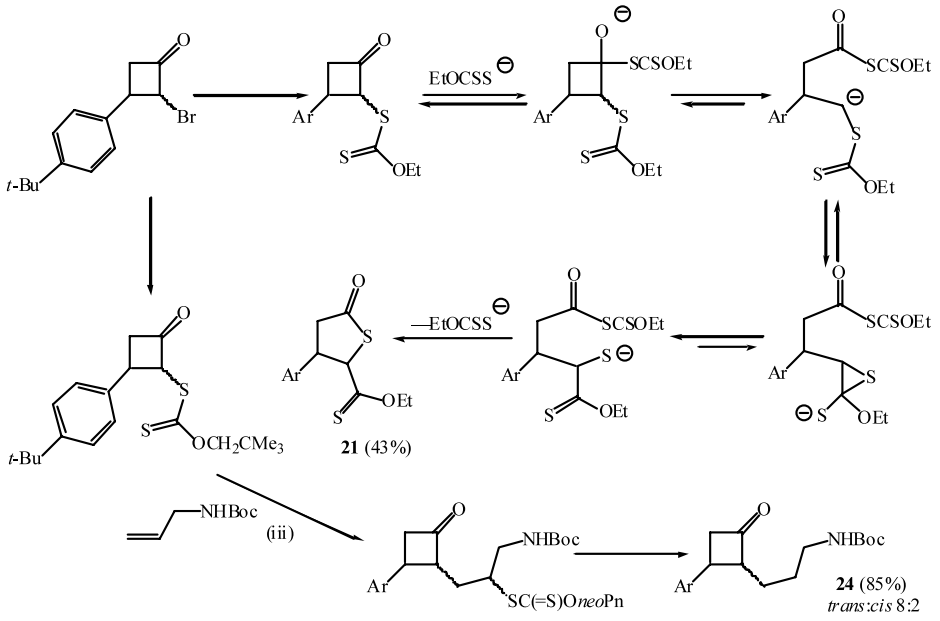


Scheme 1. *Reagents and conditions*: (i) $Br_2/CHCl_3$ or TBSOTf, Et_3N, CH_2Cl_2; −78°C then NBS, THF, 0°C; (ii) EtOCSSK/acetone, rt; (iii) lauroyl peroxide (5–20 mol%), 1,2-CH_2ClCH_2Cl, reflux; (iv) *n*-Bu_3SnH (AlBN), benzene, reflux; (v) lauroyl peroxide (140 mol%), 2-propanol, reflux; (vi) *m*-CPBA, CH_2Cl_2, rt; (vii) NaH, THF, rt.

into lactone **6** in 69% yield by the regio- and stereoselective Bayer–Villiger reaction.

In a similar fashion, xanthate **8** was prepared from the indene-derived bromide **7** and made to react with allyl acetate. The adduct, **9**, obtained in 81% yield, was a mixture of only two isomers, which gave the same reduced derivative **10** upon exposure to tributylstannane. Clearly in this case, the radical addition occured exclusively from the least hindered *exo* face. Allyl acetate can be replaced by other olefins. For example, in the presence of vinyl pivalate, a good yield of adduct **11** is obtained containing a geminal xanthate and pivaloxy representing in fact a masked aldehyde function. We have used such adducts recently in a flexible synthesis of pyrroles and of various carbocycles.[9] Perhaps more interestingly, radical addition to methyl 2-(diethylphosphono)-4-pentenoate furnished xanthate **12** in 68% yield and this compound underwent a smooth ring closure upon treatment with sodium hydride in THF to give tetracyclic derivative **13** in 66% yield.[10] The seven-membered ring homologue **15** could be constructed by simply incorporating one more carbon into the olefinic trap, as illustrated by the synthesis of adduct **14** and its ring closure by the intramolecular Horner–Emmons reaction in 68% and 55% yield respectively.

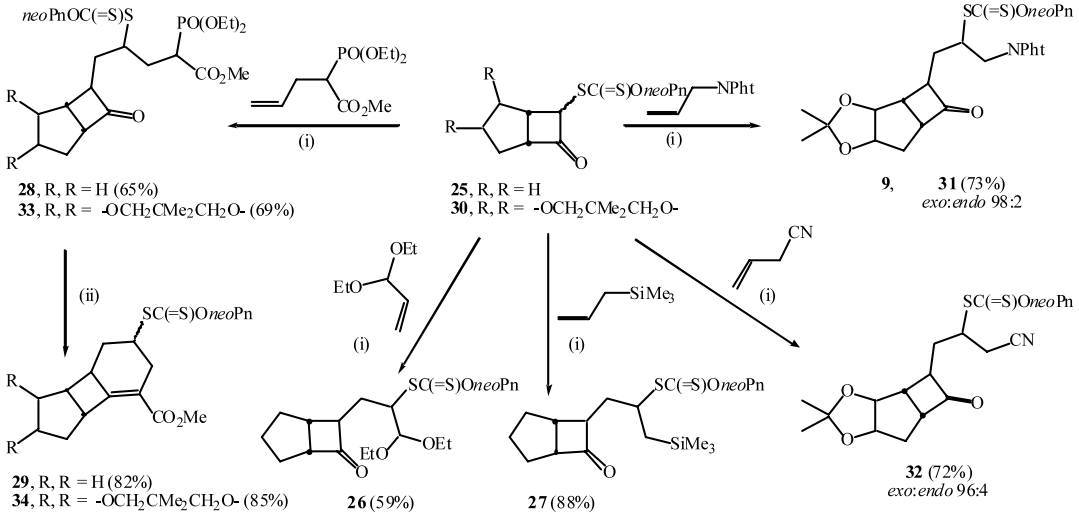
We found the radical next to the carbonyl group in a cyclobutanone to be noticeably more reactive towards ordinary olefins than the analogous radical in a cyclohexanone. This may be due to a diminished stabilisation by resonance in the cyclobutenoxyl canonical structure because of increased strain, in comparison with the essentially strain-free cyclohexenoxyl mesomeric form. A further, stark reminder of the special nature of cyclobutanones arose when we attempted to prepare xanthate **17**. The reaction of bromide **16** with potassium *O*-ethyl xanthate at room temperature was more sluggish and somewhat less clean than with the analogous case of bromide **2**, presumably a consequence of increased hindrance from the bulkier substituent. We therefore repeated the reaction in refluxing acetone in the hope of accelerating the reaction and isolated a compound in 43% yield, which had the correct molecular weight by mass spectrometry, a pattern of signals in the NMR spectrum roughly compatible with the expected structure **17**, but the IR did not show the carbonyl absorption typical of a cyclobutanone. The prominent band in the carbonyl region appeared at 1713 cm^{-1}. The ^{13}C spectrum showed two signals at 216.1 and 69.0 ppm, hinting at the presence of a thiocarbonyl group. This was confirmed by an IR band at 1051 cm^{-1}. These data are in accord with structure **21**, resulting from further reaction of the desired xanthate under the harsher experimental conditions. Thus, reversible addition of the xanthate salt to the reactive carbonyl group of the cyclobutanone gives intermediate **18** which collapses by opening of the strained ring to give transient anion **19**, which undergoes rearrangement to the more stabilised thiolate **20** and then ring-closure to the observed derivative **21**, as outlined in Scheme 2.



Scheme 2. *Reagents and conditions*: (i) EtOCSSK/acetone; (ii) *neo*PnOCSSNa/acetone, rt; (iii) lauroyl peroxide (5–20 mol%), 1,2-CH_2ClCH_2Cl, reflux; (iv) n-Bu_3SnH (AIBN), toluene/cyclohexane, reflux.

We could circumvent this unexpected problem by replacing the potassium *O*-ethyl xanthate with sodium *O*-neopentyl xanthate and keeping the reaction mixture at room temperature. The substitution reaction remained slow but was much cleaner giving the corresponding xanthate **22** in 78% yield after a reaction time of 5 hours. The bulkier neopentyl xanthate is less inclined to attack the carbonyl group of the product **22**, which itself is also sterically more congested.[11] As for the radical addition itself, it proceeded nicely as shown by the efficient addition to Boc-protected allylamine giving adduct **23** in 76% yield. Reductive removal of the xanthate group allowed us to estimate the epimeric ratio as being 80:20 in favour of the *trans* epimer.

The utility of the neopentyl xanthate was further demonstrated by the transformations implemented on the two bicyclic systems portrayed in Scheme 3. Thus, xanthates **25** and **30** derived from the corresponding bromide precursors[12] underwent clean radical additions to various olefins. Addition of **25** to the diethyl acetal of acrolein and to allyl trimethylsilane gave compounds **26** and **27** in 59% and 88% yield respectively, whereas addition to methyl 2-(diethylphosphono)-4-pentenoate provided the Horner–Emmons precursor **28** in 65% yield. The latter was cleanly converted into tricyclic structure **29** by the action of sodium hydride (82%). In the case of xanthate **30**, addition to *N*-allyl phthalimide, allyl cyanide, and methyl 2-(diethylphosphono)-



Scheme 3. *Reagents and conditions*: (i) lauroyl peroxide (5–20 mol%), 1,2-CH_2ClCH_2Cl, reflux; (ii) NaH, THF, rt.

4-pentenoate provided the corresponding adducts **31**, **32**, and **33** in 73%, 72%, and 69% yield, respectively. In all of these examples, the radical addition took place from the more accessible face exclusively or with a very high selectivity. The complete *exo* stereoselectivity in the case of **33** was shown by its cyclisation into **34** (85%) with sodium hydride in THF thus eliminating the asymmetric centre bearing the phosphonate group and simplifying the spectral analysis.

The above examples, involving olefinic traps containing various functional groups, underscore the generality, efficiency, and simplicity of the xanthate transfer radical addition. None of these transformations can be easily accomplished by traditional ionic and organometallic processes or even by other radical based methods. The ability to combine the radical addition with an efficient intramolecular Horner–Emmons olefination and presumably a variety of other ring forming reactions opens access to numerous polycyclic frameworks of some complexity. Finally, the unique chemistry of the cyclobutanone ring itself represents a further tremendous synthetic asset. The strain in the 4-membered ring greatly facilitates a variety of highly selective transformations such as the Bayer–Villiger reaction (as in example **6** above), ring expansions with diazo derivatives,[2,13] the Beckmann and related rearrangements, etc. Further studies along these lines are in progress.

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