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New Access to Fused Vinylcyclopropanes by Radical Cyclization.

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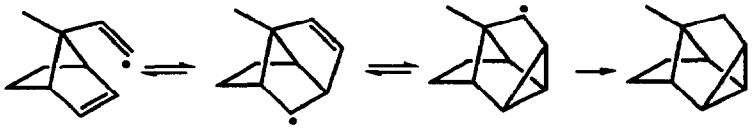
ABSTRACT: **A new methodology allowing to assemble fused vinylcyclopropanes by cyclization of vinyl radicals is herein reported. This methodology is based on the trapping of the cyclopropylcarbinyl radical intermediate by β-phenylthiyl elimination which provides the vinylcyclopropane. Preliminary results on a few model compounds illustrate the feasibility and usefulness of the method.**

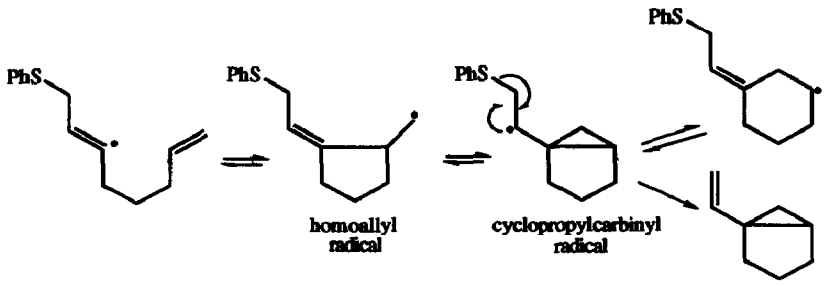
In a recent publication, we reported on the structural factors affecting cyclopropanation in the cyclization of vinyl radicals by the tin hydride method.[1] It was found that only dienyl models having an intrinsically large amount of strain with a well constrained geometry successfully give cyclopropanation (Scheme 1). The reason for this is that, generally, the equilibrium constant between the open homoallyl radical and the closed cyclopropylcarbinyl radical favors the former. These results were in agreement with previous literature observations on homoallyl radical ring closure.[2]

Scheme 1.



In an attempt to circumvent those limitations and develop a viable cyclopropanation method based on vinyl radical cyclization, we chose a new strategy inspired by the work of Cekovic.[3] In this strategy, the cyclopropylcarbinyl radical generated during the course of vinyl radical cyclization is exposed to a β-phenylthiyl elimination which is fast enough to compete efficiently with the reversible ring opening usually observed to give the 6-ENDO trig cyclization product.[4] A second element of the strategy is to use bistributyltin as radical generator[5] in order to ensure that β-phenylthiyl elimination becomes virtually irreversible because of the formation of a strong tin-sulfur bond; these precautions should then allow the efficient capture of vinylcyclopropane from the cyclopropylcarbinyl radical intermediate (Scheme 2). Finally, a third element of this endeavor is to develop the new cyclopropanation methodology as reagent- or synthon-based.

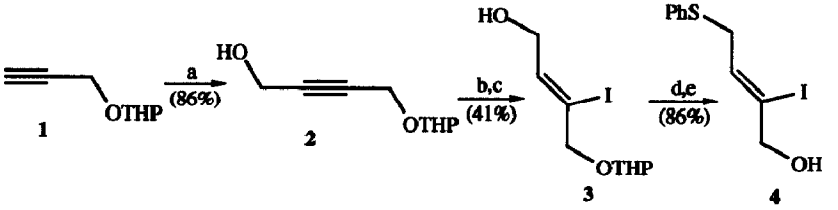
Scheme 2.



While this work was in progress, related papers by Dowd[6], Luh[7] and Malacria[8] appeared reporting the trapping of the cyclopropylcarbinyl intermediate in the vinyl radical cyclization of appropriately substituted models. In the first case, stabilization of the radical center was effected by overlap with a neighboring ketonic carbonyl group. In the second case, stabilization was effected by allylic conjugation with a vinyl silane group and in the third case, it was attributed to allylic conjugation where one of the contributing canonical forms is a double bond which is tetrasubstituted and endocyclic to a five membered ring. While the above cited references report successful radical cyclopropanations, our endeavor, as indicated, is aimed at developing a reagent for the rapid assembly of the vinylcyclopropane appendage on a variety of different substrates.

Scheme 3 shows the preparation of reagent **4** from which all of our reported models can be prepared. A vinyl iodide has been chosen as the vinyl radical precursor to prevent any competition with a possible cleavage of the carbon-sulfur bond.[9] Starting from the commercially available protected propargyl alcohol **1**, the monoprotected butynediol **2** was obtained by the reaction of paraformaldehyde on the acetylenic anion of **1**. This newly introduced alcohol function then served as a directing group for the regiospecific *Z* reductive addition of aluminum.[10] Iodination of the vinylaluminum intermediate followed by transformation of the unprotected alcohol into the corresponding phenylthioether[11] and deprotection of the remaining hydroxyl group led to the desired "reagent" **4**.

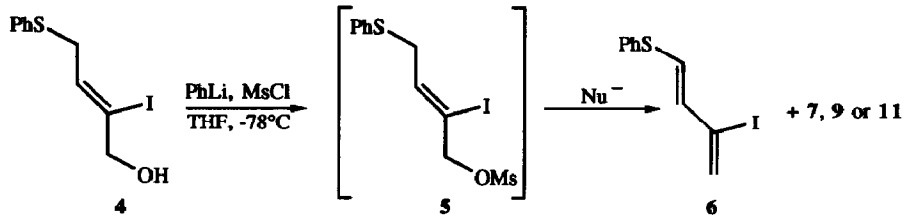
Scheme 3.[a]



[a] Yields are not optimized; (a) BuLi, THF, -78°C, $(CH_2O)_n$; (b) Red-Al, 0°C, ether; (c) I_2, CH_2Cl_2, -78°C; (d) Bu_3P, PhSSPh, THF, rt; (e) p-TsOH, MeOH, rt

Mesylate **5** of the "reagent" was generated *in situ* using PhLi and mesyl chloride at -78°C then treated immediately with the anion of branched malonates to give models **7, 9** and **11** with unoptimized low to acceptable yields varying from 29% to 42% (Table 1). The low yields are mostly caused by an undesirable competing elimination giving diene **6** as a major side product along with the desired substitution product **7**, **9**, or **11** (Scheme 4).

Scheme 4.

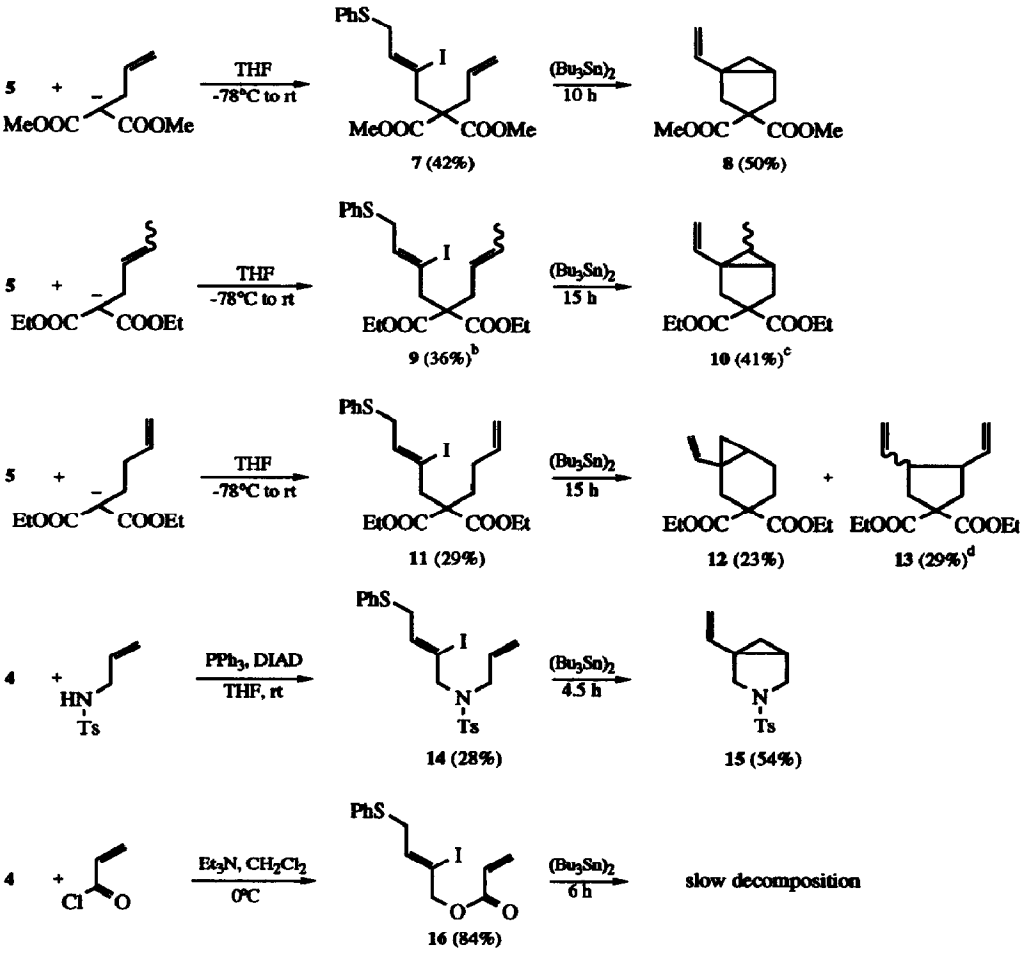


Mitsunobu reaction[12] between **4** and N-tosylated allylamine was used to prepare model **14** in a low 28%

yield. Here again, elimination is a major competing side reaction since the oxytriphenylphosphonium intermediate is also a very good leaving group. Finally, esterification of the "reagent" **4** with acryloyl chloride provided model **16** in 84% yield.

Reaction of the preceding models initiated with bistributyltin gave, in all cases except **16** which did not react usefully, the expected vinylcyclopropane derivatives **8**, **10**, **12** and **15**, by cyclization and trapping of the intermediate cyclopropylcarbinyl radical (Table 1). This demonstrates that the reaction is not only feasible but also quite general. Of all models tested, only **16** did not give cyclopropanation, most probably due to a combination of three adverse factors: a) the reversible addition of the tributyltin radical on the conjugated double bond, b) the

Table 1.[a]



[a] Radical cyclizations were carried out by irradiating approximetaly 10^{-2} M benzene solutions of the model compounds in presence of 1.05 eq. of bistributyltin and a catalytic amount of AIBN, using a 275 W Sylvania sunlamp.
[b] 2.6:1 E/Z ratio. [c] 10:1 exo/endo ratio (NOE). [d] Through [1,5] H shift.

unsuitable *trans* conformation preferably adopted by esters and c) the slowness of the desired 5-EXO trig cyclization in this case because of an unfavorable orbital coefficient in the acrylate LUMO. Model **11** on the other hand gives a lower yield of the expected vinylcyclopropane **12** because of a competing [1,5] hydrogen shift leading to diene **13**. The best results to date are obtained with model **14** which gives a 54% yield of vinylcyclopropanation after a relatively short time of irradiation. The positive influence of heteroatoms such as nitrogen on the rates and yields of radical cyclization reactions is known and has been attributed to shorter C-N bonds and a smaller C-N-C angle in this particulary case.[13] On the other hand, monoalkyl substitution α to the point of attack on the olefin does not appear too detrimental to the yield of the reaction as evidenced by model **9**; furthermore, it appears that cyclization of the homoallyl radical is stereoselective giving rise to a 10:1 *exo-endo* ratio starting from a 2.6:1 E-Z ratio in the olefin which is the site of attack.

Although similar cyclopropanations have recently been reported, as indicated above,[6,7,8] our approach yields cyclopropanation with no 5-EXO trig nor 6-ENDO trig side products and shows good signs of generality. Finally, in view of the broad field of possible chemical transformations provided by vinylcyclopropanes,[14] this new reagent-based methodology should find useful application the organic synthesis. Work is now in progress to optimize yields and extend the scope of the reaction.

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