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Cascade Radical Reactions of Methylenecyclopropane Derivatives

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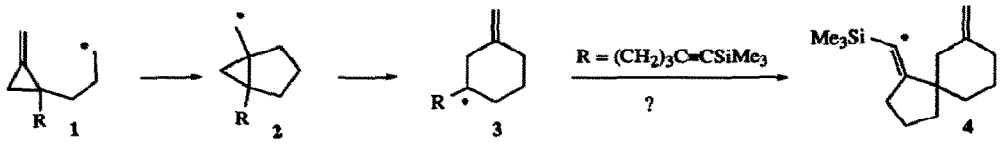
Abstract - Radicals derived from methylenecyclopropane derivatives **8**,**9** and **17** underwent a sequence of radical cyclisations and fragmentation to give tricyclic products.

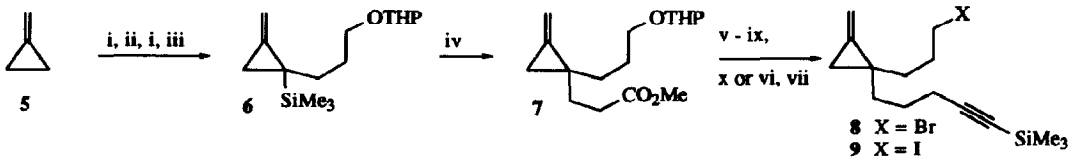
We have been investigating radical cyclisations of methylenecyclopropane derivatives. In our preliminary studies[1] we found that (methylenecyclopropyl)propyl radicals **1** (R=H, $SiMe_3$) underwent initial 5-*exo* cyclisation, leading to intermediate cyclopropylmethyl radicals **2**, which then opened to give methylenecyclohexyl radicals **3** (Scheme 1).



SCHEME 1

In principle an additional alkene or alkyne functionality, tethered to the methylene cyclopropane (eg. **1**, R=$(CH_2)_3C{\equiv}CSiMe_3$), could be used to trap the resulting methylenecyclohexyl radical **3**, leading to spirocycles **4**.[2] We have now investigated such a possibility and describe the results in this paper.

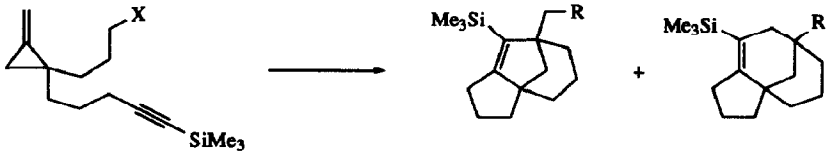
Initially radical precursors **8** and **9** were prepared as outlined in Scheme 2. Thus methylenecyclopropane **5** was sequentially deprotonated, silylated, deprotonated and alkylated to give **6** in a one pot procedure, as already described.[3] Treatment of **6** with catalytic TBAF in DMF/HMPA,[4] in the presence of methylacrylate, gave ester **7** which, after standard functional group manipulations, gave bromide **8** and iodide **9**.



Reagents: i, BuLi, THF, -78°C; ii, Me_3SiCl; iii, $Br(CH_2)_3OTHP$, 63% over four steps; iv, methylacrylate, cat. TBAF, 1 eq. HMPA, DMF, 90°C, 47%; v, $LiAlH_4$, THF, 0°C; vi, $MeSO_2Cl$, Et_3N, CH_2Cl_2, r.t.; vii, NaI, acetone, reflux, 95% over three steps; viii, $Me_3SiC{\equiv}CLi$, HMPA, THF, -78 → 0° C, 69%; ix, Amberlite IR-120, MeOH; x, CBr_4, Ph_3P, CH_2Cl_2, 85% over two steps.

SCHEME 2

Syringe pump addition of Bu_3SnH and catalytic AIBN to bromide **8** in refluxing toluene gave an inseparable mixture of **10** and **11** in 69% yield (ration **10**:**11**, 1:3) (Scheme 3).[5] Under atom transfer conditions[6] (using one equivalent of hexabutylditin), iodide **9** could be converted in low yield to iodides **12** and **13**, which could be separated by column chromatography. Reduction of **13**, using $NaBH_3CN$ and catalytic Bu_3SnCl,[7] gave **11** as a single compound.



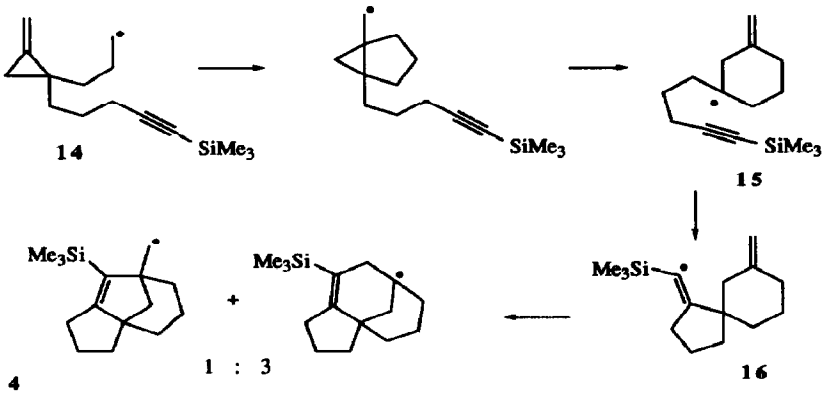
8 X = Br — Bu_3SnH, AIBN, syringe pump addition — **10** (R = H) : **11** (R = H) 1 : 3 (69%)

9 X = I — 1 eq. $(Bu_3Sn)_2$, hv, toluene, 110 °C, 20 hrs — **12** (R = I) 6%; **13** (R = I) 18% (+ 41% starting iodide **9**)

Bu_3SnCl, $NaCNBH_3$, AIBN, ^tBuOH, reflux, >90%

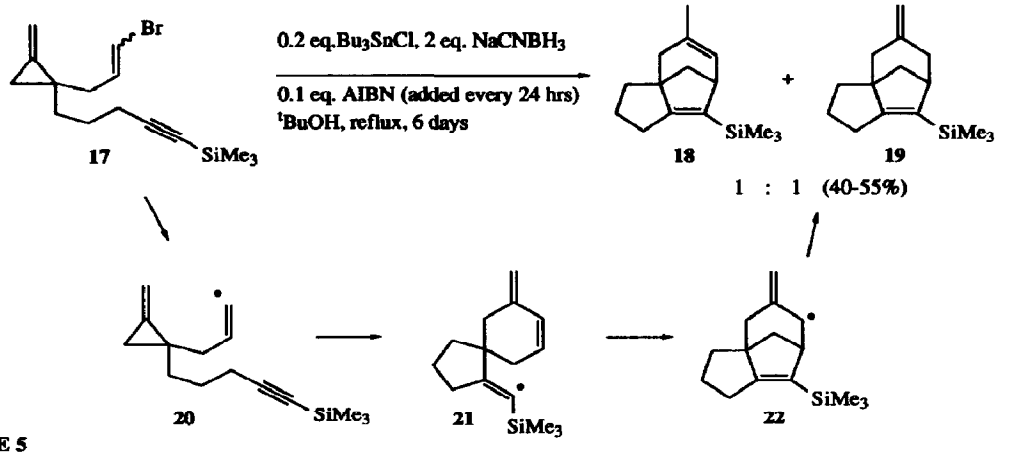
SCHEME 3

The formation of tricyclic products in the above reactions was unexpected, but is readily understood. Thus, the first formed radical **14** (Scheme 4) cyclises onto the methylenecyclopropane and then rearranges to the methylene cyclohexane radical **15**. Intramolecular cyclisation of radical **15** onto the tethered alkyne gives the reactive vinyl radical **16** which can then cyclise onto the methylenecyclohexane with the observed 3:1 regioselectivity.



SCHEME 4

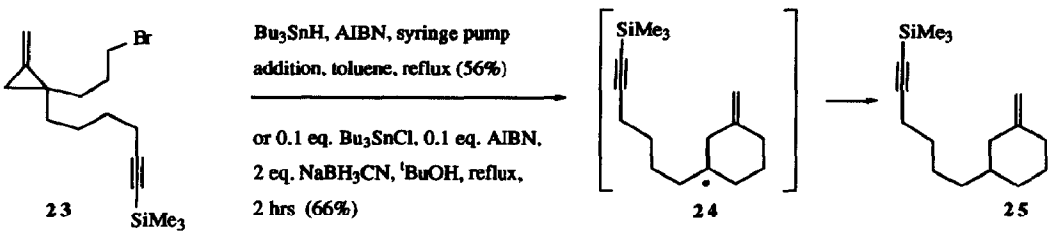
Intrigued by the outcome of these cyclisations, we next prepared vinyl bromide **17**, using an analogous route to that used for the preparation of **8** (Scheme 2). Treatment of **17** with $NaBH_3CN$ and catalytic Bu_3SnCl[7] then gave a mixture of double bond regioisomers **18** and **19**,[5] although the reaction was very slow and required addition of catalytic AIBN at 24 hourly intervals over 6 days. Isolated yields of 40-55% of the mixture of **18** and **19** were obtained, along with some recovered starting bromide **17**. Presumably the vinyl radical **20** initially produced, leads to the intermediate vinyl radical **21** which cyclises onto the cyclohexene to give the allyl radical **22**, and this is finally reduced non-selectively (Scheme 5).



SCHEME 5

We also examined the cyclisation of bromide **23** with an additional methylene in the alkyne tether. Thus, bromide **23** was treated with $NaBH_3CN$ and Bu_3SnCl, but gave only the substituted methylenecyclohexane

25 (Scheme 6), indicating that the formation of a spiro[5.5]undecane can not compete with reduction of the intermediate radical **24**, under the conditions used here.



SCHEME 6

In conclusion we have found that cascade radical reactions of suitably substituted methylenecyclopropanes can lead to complex tricyclic products. Further studies to explore the scope of these reactions are underway.

Acknowledgements.

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3. See refs 1b and 1c. For original work on the alkylation of methylenecyclopropane see a) Sternberg, E.; Binger, P. *Tetrahedron Lett.*, **1985**, *26*, 301; b) Thomas, E. W. *Tetrahedron Lett.*, **1983**, *24*, 1467.
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