Radical cyclization reactions of 4-bromo vinylogous-esters, vinylogous-amides and enones

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Radicals generated from 4-bromo vinylogous-esters, vinylogous-amides and enones cyclize to a tethered acetylene side-chain preferentially at the γ-position; theoretical calculations of the spin density of the radicals and the relative stability of the radical intermediates are performed to rationalize the experimental observations.

Radical reactions have emerged as one of the most useful synthetic methodologies in the formation of carbon–carbon bonds.[1] Previously we have described intramolecular cyclization reactions of α-ketone[2] and α-enone[3] radicals. As an extension to our work in this area, we investigated the intramolecular cyclization reactions of allylic enone radicals **2**, Scheme 1. Both from theoretical and experimental points of view, it is of special interest to discover whether radicals **2**, generated from 4-bromo cycloalkenones **1**, would cyclize at the α- or γ-position due to delocalization of the radical. Here we report the preliminary results of this investigation.

Vinylogous-esters **5** and **8** and vinylogous-amides **11**, **14** and **17** were prepared by literature methods.[4] Thus, 3-trimethylsilylprop-2-yn-1-ol[5] was condensed with cyclohexane-1,3-dione and cyclopentane-1,3-dione to afford vinylogous-esters **5** and **8**. Condensation of 3-trimethylsilylpropynylamine[6] with the corresponding cycloalkane-1,3-diones, followed by reaction with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine gave *tert*-butoxycarbonyl (Boc) protected vinylogous-amides **11**, **14** and **17**. Enones **21** and **24** were synthesized by treatment of the corresponding 3-ethoxycycloalkenones with 4-trimethylsilylbut-3-ynylmagnesium bromide followed by treatment with dilute HCl.[7] Bromination of **5**, **8**, **11**, **14**, **17**, **21** and **24** with *N*-bromosuccinimide (NBS) and AIBN in refluxing CCl$_4$ afforded the corresponding 4-bromo compounds **6**, **9**, **12**, **15**, **18**, **22** and **25**. Radical cyclizations were then carried out using tin hydride,[2] the results of which are summarized in Table 1. 4-Bromo vinylogous-esters and vinylogous-amides cyclized in acceptable yields. 4-Bromo enone **22** underwent radical cyclization with some difficulty to give both the cyclized product **23** and the reduction product **21** in equal amounts. 4-Bromo enone **25** did not cyclize to **26** but gave only the reduction product **24**. In general, radicals generated from 4-bromo cyclohexenones **6**, **12** and **22** were found to cyclize in better yields than the radicals generated from 4-bromo cyclopentenones **9**, **15** and **25**. However, it is interesting to note that most of radical cyclizations occurred at the γ-carbon. Only in entry 5, the radical generated from compound **18** with a highly hindered γ-position cyclized both at the γ- and α-positions to give **19** and **20** (1 : 2.5). Exocyclic double bonds formed after cyclization were isomerised into conjugated systems under the reaction condition (entries 1, 2 and 4, Table 1). In entry 6, the enone double bond was deconjugated after cyclization to give **23**.

To understand this unusual regioselectivity of radical cyclization at the γ-carbon, we performed PM3 calculations[8] on model radical systems **27** and **28**. Spin densities at the α- and γ-positions, expressed as the square of atomic orbital coefficients in SOMO, are 0.34 and 0.49 for **27**, and 0.33 and 0.53 for **28**. For the reaction under kinetic control, these coefficients are in accordance with the experimental observations. It is noteworthy that HOMO electron densities at the α- and γ-positions of the corresponding anionic species **29** are 0.47 and 0.32, which are opposite to the radical species. It is well known that reactions of anion **29** usually occur at the α-position.[9] We also calculated the relative stability of intermediates **30** and **31** which were formed *via* the α- or γ-cyclization (pathway *a* or *b* in Scheme 1). We found that **31** is 4.5 kcal mol^{-1} (1 cal = 4.184 J) more stable than **30**. This probably reflects that cyclization at the γ-position, maintaining the conjugate enone π system in the transition state, is the pathway having the lower activation energy.

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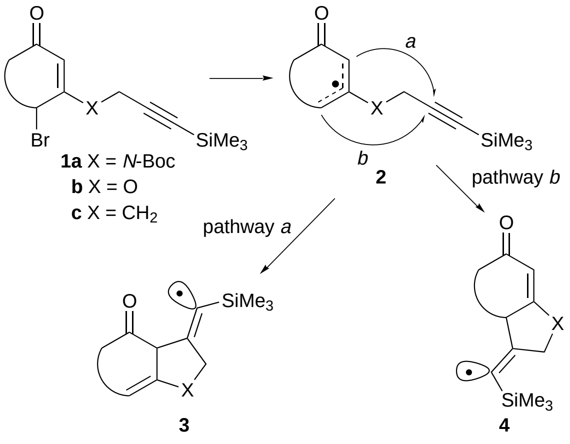
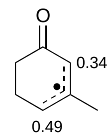


Scheme 1



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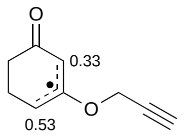

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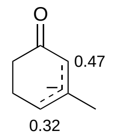

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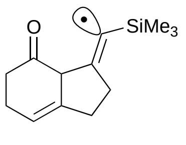

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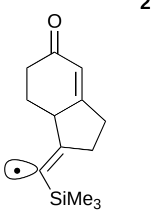

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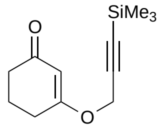
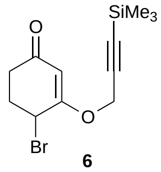
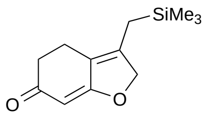
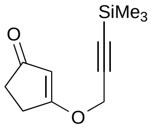
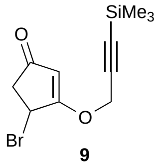
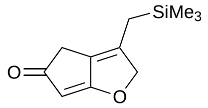
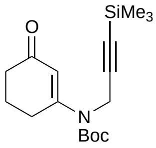
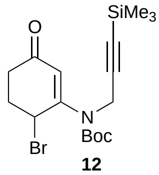
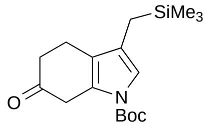
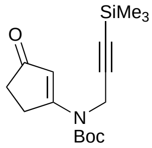
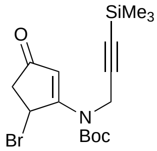
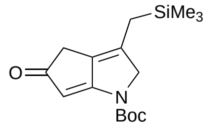
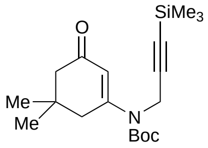
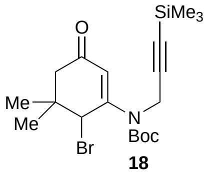
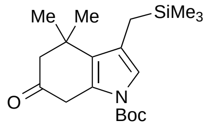
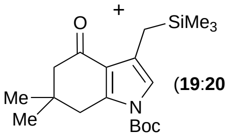
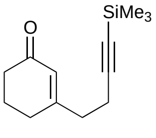
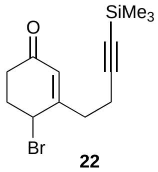
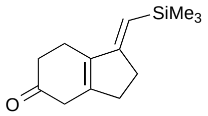
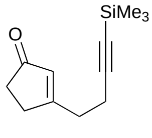
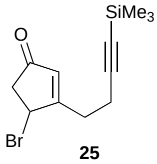
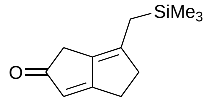
Table 1 Radical cyclization of 4-bromo vinylogous-amides, vinylogous-esters and enones

Entry	Starting material	4-Bromo compound (%)	Cyclized product (%)	Reduction (%)
1	 **5**	 **6** 63[a]	 **7** 68[c]	—
2	 **8**	 **9** 27[b]	 **10** 42[c]	52
3	 **11**	 **12** 81	 **13** 70[d]	—
4	 **14**	 **15** 60	 **16** 51[e]	23
5	 **17**	 **18** 81	 **19** +  **20** (**19**:**20** = 1:2.5) 50[d]	—
6	 **21**	 **22** 83	 **23**[f] 31	31
7	 **24**	 **25** 63	 **26** 0	85

[a] Yield based on 67% conversion; 33% of **5** was recovered. [b] Yield based on 73% conversion; 27% of **8** was recovered. [c] The reaction was carried out in refluxing toluene. [d] The unstable crude cyclization product was treated with I_2 and DBU to give the pyrrolo compound which was isolated by flash column chromatography (florisil, 6 : 1 hexane–ethyl acetate). [e] The reaction was carried out in refluxing xylene. [f] The geometry of the vinylsilane group in **23** was tentatively assigned *E*.

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