ORGANIC LETTERS
1999
Vol. 1, No. 3
363−365

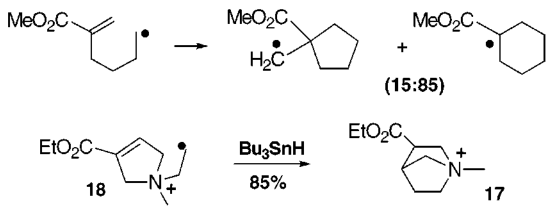
Regioselective 6-*Endo* Cyclization of 5-Carbomethoxy-5-hexenyl Radicals: A Convenient Synthesis of Derivatives of the 1-Azabicyclo[2.2.1]heptyl System

Ernest W. Della,* Chris Kostakis, and Paul A. Smith

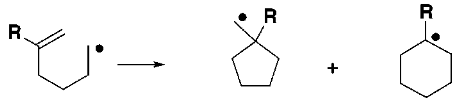
Department of Chemistry, Flinders University, Bedford Park, South Australia 5042
ern.della@flinders.edu.au

Received April 5, 1999

ABSTRACT



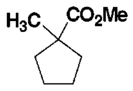
Ring closure of the 5-carbomethoxy-5-hexenyl radical is governed largely by the polar effect, and as predicted by frontier molecular orbital considerations, *endo* cyclization predominates, leading to cyclohexyl rather than cyclopentyl-based products. In cyclization of the corresponding β-ammonio species 18, stereoelectronic effects do not distinquish between attack of the radical center at C3 or C4, each of which represents a 5-*exo* ring closure. The radical 18 is found to cyclize with great rapidity and with high stereoselectivity to give bicyclo[2.2.1]heptane products in accordance with expectation based on polar effects; this transformation represents an excellent entry to the physiologically important bicyclic ester 17.



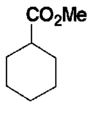
1, R = H
4, R = CH_3
7, R = CO_2Me

2, R = H
5, R = CH_3
8, R = CO_2Me

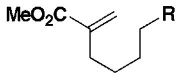
3, R = H
6, R = CH_3
9, R = CO_2Me



10



11



12, R = COOH
13, R = $COONC_5H_4S$
14, R = H

Intensive investigations over many years have placed the understanding of the factors which influence the regiochemistry of ring closure of the 5-hexenyl radical **1** on a firm foundation.[1] It is generally accepted that this reaction has an early transition state and is under kinetic control.[1d] The overwhelming preference for 5-*exo* cyclization to give the cyclopentylmethyl radical **2** over 6-*endo* ring closure, which gives **3**, is a consequence of the interplay of three main factors, the stereoelectronic, polar, and steric effects. All three effects favor production of **2**. The regiochemistry of cyclization of substituted 5-hexenyl radicals provides a striking example in which additional steric effects are thought to assume a much more prominent role in controlling the mode of ring closure.[1e,2] Rearrangement of the 5-methyl-5-hexenyl radical **4**, for example, is observed to afford a 40:60 ratio of the radicals **5**:**6**. This reversal of regioselectivity has been ascribed to a decrease in the rate of 5-*exo* cyclization; the rate of formation of **6** has been shown to be essentially unaffected by the attached methyl group.

---

(1) For leading references, see: (a) Beckwith, A. L. *J. Chem. Soc. Rev.* **1993**, 143. (b) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (d) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. (e) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. (e) Giese, B. Radicals. In *Organic Synthesis: Formation of Carbon Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon: New York, 1986.

(2) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472.

10.1021/ol990557n CCC: $18.00 © 1999 American Chemical Society
Published on Web 07/15/1999

We wish to report our observations on the behavior of the 5-carbomethoxy-5-hexenyl radical **7**. A priori, stereoelectronic factors predict C5 to be the preferred site of attack by the radical center in ring closure of **7**. In terms of steric effects, it seems reasonable to assume, on the basis of the conformational energies of the ester and methyl groups in cyclohexane, that the less bulky ester group would have a smaller influence on the regiochemistry. The expectation is, therefore, that the combined effect of these two factors on ring closure of **7** should lead to an approximately equal mixture of **8** and **9**. The polar effect, however, is seen to predict a high preference for the 6-*endo* product **9**. Consideration of the appropriate frontier orbitals of the reactants,[1d] viz., the (nucleophilic) radical SOMO and the alkene LUMO, reveals that the most favorable interaction occurs between C1 and C6 because of the greater magnitude of the orbital coefficient and hence greater concentration of spin on C6 compared to that on C5.

We have employed the Barton ester **13** of the half ester **12**[3] as precursor to the radical **7**. A solution of tributyltin hydride (1.05 equiv) in benzene containing a catalytic amount of AIBN was added over 15 min to a solution of the ester **13** in benzene maintained at 80 °C and illuminated by a tungsten lamp (300 W). After being allowed to stand for a further hour under these conditions, the mixture was quenched and worked up. Analysis of the product by GC revealed the presence of a 15:85 mixture of the cyclic esters **10** and **11**. The product of reduction, **14**, was not detected. This observation is strongly indicative of a more dominant role exerted by the polar effect in directing the mode of ring closure of the radical **7**.

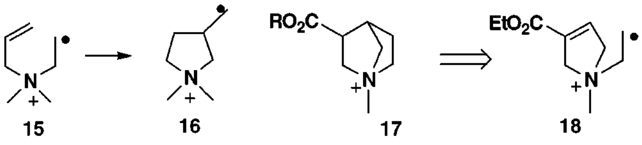
We also undertook a kinetic study of the rate of cyclization of **7**, the results of which are collated in Table 1; included for comparison are the corresponding data for the 5-hexenyl and 5-methyl-5-hexenyl radicals **1** and **4**. Inspection of the data displayed in Table 1 reveals a number of intriguing phenomena. First, the rate of *endo* cyclization of **7** is ca. seven times faster than that for the *exo* mode. This provides strong support for the predictions presented above for the regiochemistry of ring closure of **7** and demonstrates the dominance of the polar effect in its cyclization. Second, the presence of the ester substituent is seen to have a spectacular effect on the kinetics of cyclization. Thus, comparison of the rates of *endo* ring closure for the three species **1**, **4**, and **7** shows that reaction of **7** occurs several orders of magnitude faster than that of **1** or **4**. Third, it is noteworthy that, unlike the retarding influence of the methyl group on the rate of *exo* ring closure in the radical **4**, there is no apparent attenuation in rate as a result of a steric effect of the COOMe group in the rate of *exo* cyclization of the radical **7**; indeed, this mode of ring closure occurs more rapidly in **7** than in the parent radical **1**.

Table 1. Experimental Kinetic Data for Cyclization of the 5-Hexenyl Radicals **1**, **4**, and **7**

radical	*exo*:*endo*[a]	$k(exo)^b$ (s^{-1})	$k(endo)^b$ (s^{-1})	ref
1	97:3	2.3×10^5	4.1×10^3	4
4	40:60	5.3×10^3	9.0×10^3	2
7	15:85	2.9×10^5	2.2×10^6	*c*

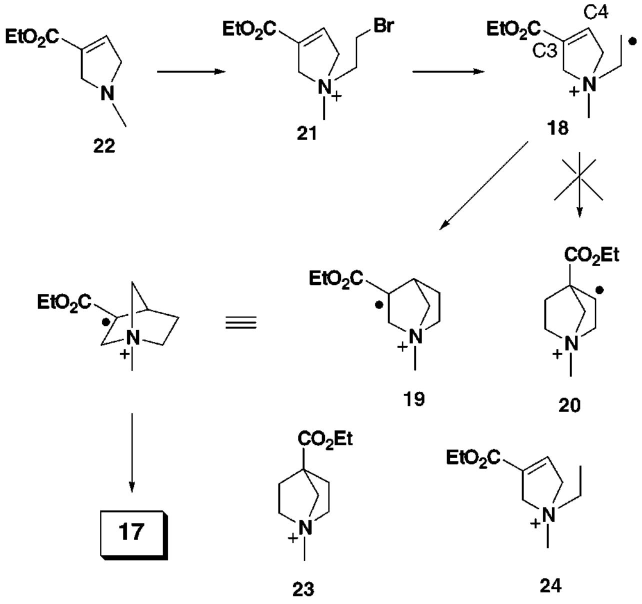
[a] 80 °C. [b] 25 °C. [c] This work.

We have recently been investigating ring closure of α- and *β*-ammonio-substituted 5-hexenyl radicals as a possible entry into heterocyclic compounds.[5] We have observed that the radical **15**, for example, undergoes cyclization with high stereoselectivity, giving **16** exclusively.[5c] One of the major objectives in our ongoing investigation is the synthesis of 3-carb(om)ethoxy-1-azoniabicyclo[2.2.1]heptane bromide (**17**). The methyl ester (**17**, R = CH_3) is of considerable interest because, together with its N-demethylated derivative, it has been shown[6] to possess important physiological properties.



We were particularly interested in exploiting the observed preference for 6-*endo* cyclization in the radical **7** combined with the facility for ring closure of **15** as the basis of a potential synthetic route to the ester **17**. The target radical selected to affect this synthesis was the cyclopentenyl species **18**.

The radical **18** has rather interesting structural ramifications compared to its acyclic analogue **7**. In fact, **18** is uniquely placed because there is no distinction between C3 and C4 as a potential site for 5-*exo* attack of the radical center. According to stereoelectronic considerations, therefore, there is no expected differentiation for ring closure at C3 or C4 in **18**. Furthermore, both steric and polar factors strongly favor formation of **19** over **20** and, as observed above in connection with the acyclic analogue **7**, the polar



factor is particularly effective. On these grounds it was predicted that the bicyclic ester **17** rather than its isomer **23** would be the major product to be derived from treatment of the selected precursor **21** with tributyltin hydride.

To test these hypotheses, synthesis of the precursor **21** was accomplished by treatment of the known[7] amine **22** with 1,2-dibromomethane. Exposure of the derived salt **21**[8] to tributyltin hydride in 2-methyl-2-butanol solution under the conditions referred to above afforded an 85% yield of 3-carbethoxy-1-azoniabicyclo[2.2.1]heptane bromide (**17**, R $= CH_2CH_3$). ^{1}H and ^{13}C NMR spectral analysis of the crude product revealed that it was essentially pure. None of the isomeric species **23**, nor the product of reduction **24**, was detected. The ester **17** (R $= CH_2CH_3$) was obtained as a 10:90 mixture of the *exo* and *endo* isomers. The predominance of the *endo* ester is consistent with the expected *exo* delivery of hydrogen by Bu_3SnH at a C2 trigonal carbon in the norbornyl system **19**.

In conclusion, it is seen that ring closure of the 5-carbomethoxy-5-hexenyl radical **7** is influenced largely by polar effects and *endo* closure predominates. When extended to the 5-carbethoxy radical **18**, it is found that cyclization occurs with high stereoselectivity, in agreement with theoretical predictions. In view of these observations, we suggest that this transformation represents an excellent entry to the important bicyclic ester **17**.

Acknowledgment. We thank the Australian Research Council for financial support.

OL990557N

---

(3) Microanalytical and spectral characterization of the half ester **12** and all intermediate compounds involved in its synthesis from 2-carbomethoxycyclohexanone will be presented in the full paper.

(4) For leading reference, see: Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(5) (a) Della, E. W.; Smith, P. A. *J. Org. Chem.* **1999**, *64*, 2110. (b) Della, E. W.; Knill, A. M.; Smith, P. A, *J. Chem. Soc., Chem Commun.* **1996**, 1637. (c) Della, E. W.; Knill, A. M. *Tetrahedron Lett.* **1996**, *37*, 5805. (d) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996**, *61*, 7529.

(6) For leading reference, see: Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392.

(7) Mattocks, A. R. *J. Chem. Soc., Perkin Trans. 2* **1978**, 896.

(8) Full characterization of **21** and **17** will be presented in the full paper.