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Cyclization of Methyl-Substituted 6-Heptenyl Radicals

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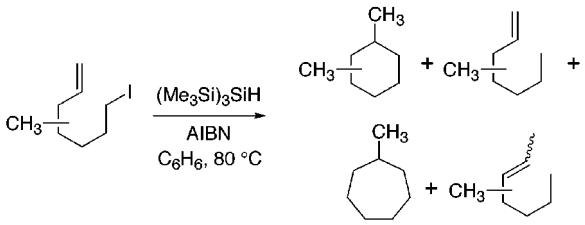
ABSTRACT



The behavior of a series of methyl-substituted 6-heptenyl radicals, generated from the corresponding iodides ($(Me_3Si)_3SiH$, AIBN in benzene at 80 °C), has been investigated. The stereoselectivity of the 6-exo cyclizations, affording dimethylcyclohexanes, is low, and sizable quantities of methylcycloheptane, generated via 7-endo cyclization, are also produced.

Seminal studies of substituted 5-hexenyl radicals by Beckwith's group in the mid-1970s[1,2] demonstrated that these reactive intermediates cyclize rapidly, generally in a highly regioselective 5-exo fashion, to give the corresponding cyclopentylmethyl radicals with a high degree of stereocontrol that is predictable by analysis of the steric interactions present in the chairlike transition state for the ring closure.[3] Subsequently, it was soon recognized that 5-exo cyclization of functionalized 5-hexenyl radicals provides a convenient route to a variety of cyclopentyl-containing materials, and the substantial primary literature detailing the use of this chemistry has been extensively reviewed.[4]

The behavior of substituted 6-heptenyl radicals has received considerably less attention.[1,4] This state of affairs is most likely attributable to the poorer prospects for synthetic utility of this higher homologue of the 5-hexenyl radical. The rate of cyclization of the parent 6-heptenyl radical is approximately an order of magnitude slower that of the 5-hexenyl radical,[1,5] its ring closure is considerably less regioselective ($k_{exo}/k_{endo} \sim 6$ for the 6-heptenyl radical[1] vs $k_{exo}/k_{endo} \sim 50$ for the 5-hexenyl radical),[4] and the 6-heptenyl radical is prone to rearrangement, via [1,5]-hydrogen atom transfer, to give a 1-butylallyl radical.[1] The presence of an electron-withdrawing group at the terminal vinyl position of the 6-heptenyl radical significantly improves both the rate of cyclization and the regioselectivity of the ring closure,[4] and Hanessian's group has reported that these rearrangements proceed in a highly regioselective 6-exo fashion with moderate stereoselectivity via a transition state resembling a chairlike arrangement of the radical.[6] Indeed, the 6-exo cyclization of substituted 6-heptenyl radicals has been exploited in organic synthesis and many such isomerizations are known to proceed with substantial diastereoselectivity.[7] Nonetheless, each of the systems examined to date include additional structural features that may well have contributed to the observed stereoselectivities.

In connection with a study of the cycloisomerization of methyl-substituted 6-heptenyllithiums, we were interested in

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

(2) (a) Beckwith, A. L. J.; Blair, I. A.; Phillipou *Tetrahedron Lett.* **1974**, 2251. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (c) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484.

(3) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(4) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Essay 4. (b) Beckwith, A. L. J. Tetrahedron **1981**, *37*, 3073. (c) Surzur, J. M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, Chapter 3. (d) Hart, D. J. *Science* **1984**, *223*, 883. (e) Giese, B. *Radicals in Organic Synthesis*; Pergamon: New York, 1986. (f) Curran, D. P. *Synthesis* **1988**, 417 and 489. (g) Giese, B. *Angew., Chem. Int. Ed. Engl.* **1989**, *28*, 969. (h) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1995.

(5) (a) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

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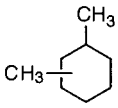
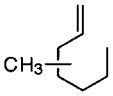
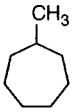
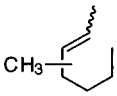
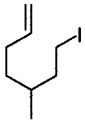
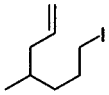
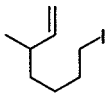
Table 1. Cyclization of Substituted 6-Heptenyl Radicals[a]

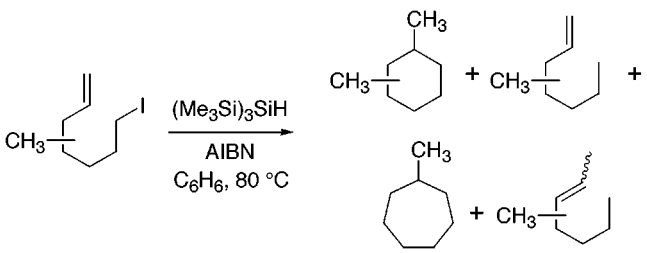
entry	iodide	products,[b] % yield				
			cis:trans[c]			
1		51.0	53:47	37.9	6.1	5.0
2		52.8	48:52	25.3	9.7	12.2
3		70.2	55:45	12.2	17.6	<1
4		47.9	42:58	33.8	14.5	3.8

[a] A 0.05 M solution of the organoiodide in benzene was heated at reflux under an atmosphere of nitrogen and 1.1 molar equiv of a 0.1 M solution of $(Me_3Si)_3SiH$ in benzene containing approximately 15 mg of AIBN was added via syringe pump at a rate of 0.5 mL/h. [b] Relative yields of C_8H_{16} products determined by capillary GC analysis of reaction mixtures. [c] Isomeric ratio of dimethylcyclohexanes.

the stereochemistry of the ring closure of methyl-substituted 6-heptenyl radicals. A review of the literature revealed, somewhat surprisingly, that these simple systems have apparently not been investigated. Herein we report the result of a study of the behavior of a series of methyl-substituted 6-heptenyl radicals detailing the regioselectivity and stereoselectivity of the cyclizations.

The 6-heptenyl radicals were generated from the corresponding iodides as illustrated in Scheme 1.[8] In light of the relatively slow cyclization documented for the parent 6-heptenyl radical,[1] tris(trimethylsilyl)silane, $(Me_3Si)_3SiH$, was used as the hydrogen atom source in these reactions: this silane transfers a hydrogen to a primary radical some four times slower than do trialkyltin hydrides typically used for such reactions.[9] Thus, a 0.05 M solution of each iodide in benzene was heated at reflux under an atmosphere of nitrogen and a 0.1 M solution of 1.1 molar equiv of tris(trimethylsilyl)silane in benzene containing approximately 15 mg of azobis(isobutyronitrile) (AIBN) was added via syringe pump at a rate of 0.5 mL/h. Upon completion of the addition, most of the benzene was removed by careful distillation and the relative yields of C_8H_{16} products were determined by capillary GC and GC/MS.[10] Reaction products were identified by comparison of their GC retention times and mass spectra to those of authentic samples[11] or by comparison of their mass spectra to those previously reported.[12] The results of these experiments are summarized in Table 1.

Scheme 1



Cursory inspection of the data in Table 1 reveals that, as expected,[1,4] cyclization of the substituted 6-heptenyl radicals is not a clean 6-exo process. In addition to sizable quantities of 1-heptenes and lesser amounts of (*E*)- and (*Z*)-2-heptenes,

(6) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859.

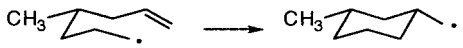
(7) For leading references, see: (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (b) Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9670. (c) Boivin, J.; Crépon, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 199. (d) Contelles, J. M.; Sánchez, B. *J. Org. Chem.* **1993**, *58*, 4293. Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1994**, *59*, 3459. (e) Takahashi, T.; Tomida, S.; Sakamoto, Y.; Yamada, H. *J. Org. Chem.* **1997**, *62*, 1912. (f) Ziegler, F. E.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 7920. (g) Tomida, S.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 2363. (h) Takasu, K.; Kuroyanagi, J.; Katsumata, A.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 6277.

(8) The iodides were prepared via the mesylate (NaI in acetone) from previously reported alcohols: Sumitani, M.; Kanemitsuya, K.; Yasuda, H.; Tani, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1511.

(9) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

product mixtures contained methylcycloheptane, generated by 7-endo cyclization, as a principal component. It is of some interest to note that the relative proportion of 7-endo cyclization increases monotonically as the position of the methyl substituent is varied from C(2) through C(5): $k_{exo}/k_{endo} = 8.4$, 5.4, 4.0, and 3.3 for the 2-methyl-, 3-methyl-, 4-methyl-, and 5-methyl-6-heptenyl radicals, respectively (Table 1, entries 1−4). The origin of this trend in cyclization regioselectivity is obscure, but it is presumably related to subtle conformational changes engendered by the methyl substituents in the various constitutionally isomeric radicals.

In contrast to the substantial stereoselectivities typically observed in the ring closure of substituted 5-hexenyl radicals,[3,4] the stereoselectivity of the 6-exo cyclization of methyl-substituted 6-heptenyl radicals is modest at best. Indeed, the highest selectivity encountered in the ring-closure reactions is a mere 1.4:1 preference for the *trans*-isomer of 1,2-dimethylcyclohexane upon 6-exo cyclization of the 5-methyl-6-heptenyl radical (Table 1, entry 4). Nonetheless, Hanessian's chairlike transition-state model[6] nicely accounts for the formation of the major stereoisomer observed in each of the cyclizations. Thus, for example, 6-exo ring closure of the 4-methyl-6-heptenyl radical via a transition state in which the methyl substituent preferentially occupies a pseudo-equatorial position would be expected to afford *cis*-1,3-dimethylcyclohexane as the major 6-exo product; however, the observed cis/trans preference is only ∼1.2:1 (Table 1, entry 3).



The low regioselectivity and poor stereoselectivities that characterize the cyclization of methyl-substituted 6-heptenyl radicals are perhaps not unexpected given the conformational flexibility inherent in the 6-heptenyl radical. Nonetheless, the results of this model study provide the first quantitative data for the behavior of this class of reactive intermediates.

Acknowledgment. This work was supported by a grant from Procter & Gamble Pharmaceuticals, Mason, OH.

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(10) Analyses were performed on a 25 m × 0.2 mm × 0.33 mm film thickness, cross-linked 5% phenyl-methyl silicone capillary column (50 °C for 30 min and 10 °C/min to 250 °C) which provides base-line separation of the products.

(11) Samples of each of the dimethylcyclohexane products were obtained from Aldrich; the stereoisomeric ratio of the commercial samples was determined by GC analysis and the sructures were confirmed by comparison of the ^{13}C NMR spectra of the mixtures to the ^{13}C chemical shifts reported for each isomer [Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc*. **1967**, *89*, 6612.]. An authentic sample of methylcycloheptane was prepared from 1-methylcycloheptanol [Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M.; Bruce, M. R. *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 92].

(12) National Institute of Standards and Technology Chemistry WebBook; http://webbook.nist.gov/chemistry (accessed April 2001).