Tetrahedron Letters, Vol. 33, No. 45, pp. 6719-6722, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

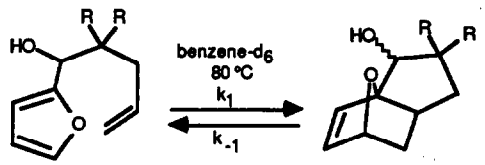
EASY PREPARATION OF A CYCLOBUTANONE KETAL VIA A RADICAL CYCLIZATION. THE *GEM*-DIALKOXY EFFECT

MICHAEL E. JUNG,*,[1] IVAN D. TRIFUNOVICH,[2] AND NATHALIE LENSEN

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Summary: A new method for the facile synthesis of cyclobutanones, the key step of which is a radical cyclization to generate the four-membered ring, is reported. In addition, a comparison of the *gem*-dialkyl and *gem*-dialkoxy effects in radical cyclizations to give cyclobutane systems shows that in this system the *gem*-dialkoxy effect is the larger.

For several years now, we have studied both substituent and solvent effects on the rates and equilibria of various cyclization reactions, including the Diels-Alder reaction, the ene reaction, and radical cyclization.[3] In particular, we have obtained experimental evidence for the greater importance of rotamers effects (higher population of reactive rotamer or selective destabilization of ground state) vs. angle effects (the Thorpe-Ingold effect) in the *gem*-dialkyl effect.[3a] In these studies we observed much larger than average rate accelerations for cyclizations of substrates with an oxygen atom at the substituted carbon (rate increases of up to 10^5 in going from H to Me) than those normally seen in all carbon cases (usually rate increases of 5-10), thereby implying that oxygen substituents might give larger rate increases than carbon substituents. In 1985 Sternbach published an excellent study of the intramolecular Diels-Alder reaction of several *gem*-disubstituted α-(3-butenyl)furan-2-methanols **1** in benzene-d_6 at 80° C and concluded that heteroatom substitution had a greater effect on both the rate and equilibrium constant for the cycloaddition than did carbon substituents, with the relative rates for sulfur and oxygen substituents being 2.5 and 5.2.[4] We now report that

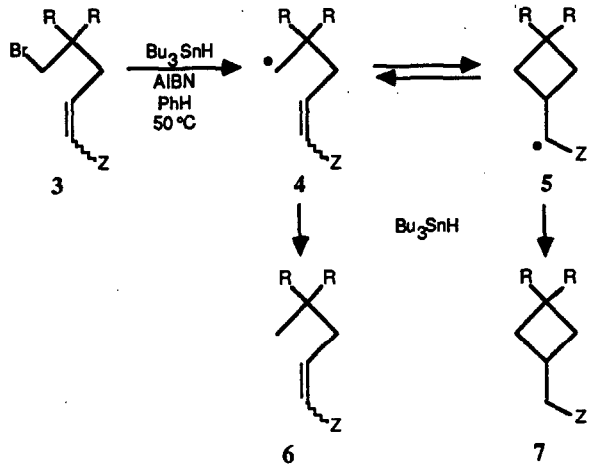


		k_1 (rel)	
1a	R = $CH_2CH_2CH_3$	1	**2a**
1b	R = SCH_2CH_3	2.5	**2b**
1c	R = OCH_2CH_3	5.2	**2c**

this heteroatom effect can be used synthetically to produce cyclobutane rings in high yield by radical cyclization.

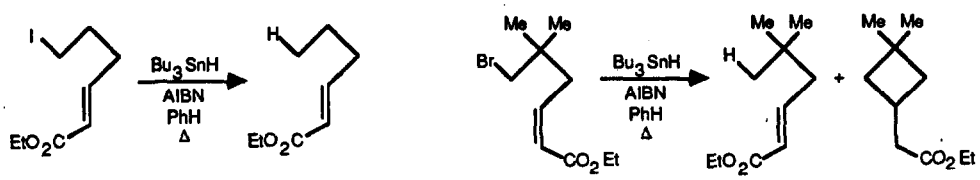
Although radical cyclizations are extremely useful for the synthesis of 5- and 6-membered ring systems,[5] the production of small (3- and 4-membered) rings by radical cyclization is generally not successful, although there are

scattered reports in the literature for these processes.[6] Presumably cyclization of the radical **4**, generated, for example, from the corresponding halide **3**, to give the cyclobutylcarbinyl radical **5** is a reversible process (due to the strain inherent in the cyclobutane ring) so that further reduction of the radical species **4** and **5** produces a mixture of the acyclic and cyclic products **6** and **7**, respectively, in which the acyclic product usually predominates. Two years ago Park and Newcomb reported an excellent study that showed that a combination of the *gem*-dialkyl effect and a cyano substituent on the alkene allowed cyclization to be a reasonably efficient process.[7] They observed that the normal

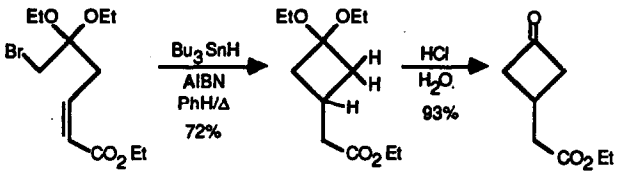


conditions (e.g., a reasonably high concentration of tributyltin hydride) gave a 2:1 ratio of acyclic to cyclic products (**6** and **7**, R=Me Z=CN) while the use of catalytic hydride (Bu_3SnCl, excess $NaCNBH_3$) gave an approximately 1:1 mixture of **6** and **7**.[8] We decided to investigate the *gem*-dialkoxy effect as a method for improving the yield of cyclization in this system.

For completeness, we examined the cyclization of all three classes of unsaturated ester substrates - unsubstituted, *gem*-dialkyl, and *gem*-dialkoxy. Treatment of the unsubstituted substrate, **8a**,[9] with tributyltin hydride in benzene at 80° C afforded only the acyclic product **8b**, as expected. The dimethyl analogue **9**[10] behaved similarly to the analogous cyano compound of Park and Newcomb, giving variable results depending on the exact conditions. Fast addition of a slight excess of hydride produced mostly the acyclic reduced product **10** with some of the cyclobutane **11**, while very slow addition of the hydride via syringe pump to a hot benzene solution of **9** afforded a mixture of **10** and



11 in which the cyclobutane **11** predominated.[11] However, cyclization of the *gem*-diethoxy analogue **12**, prepared in four steps from triethyl orthoacetate,[12] under normal conditions, namely Bu_3SnH in hot benzene for 1h afforded only the cyclic product **13** in 72% purified yield, with no evidence for formation of the simple reduced product. The structure of the product was assigned from the very symmetrical ^1H NMR spectrum and from the $^1J_{CH}$ coupling constants as seen in the undecoupled ^{13}C NMR spectrum. The $^1J_{CH}$ for the methine carbon is 140 Hz while that for the cyclobutyl methylene carbon is 135 Hz, both values indicative of a cyclobutane ring.[13] The structure was confirmed by hydrolysis of the ketal of **13** to give in 93% yield the cyclobutanone **14** which exhibited a carbonyl stretch at 1789 cm^{-1} in the infrared spectrum, as expected for a cyclobutanone.



12 **13** **14**

Therefore, in this system, the *gem*-dialkoxy effect is larger than the *gem*-dialkyl effect and allows for the easy formation of cyclobutanone ketals.[14] We are currently attempting to extend these results to other systems.

Acknowledgement We thank the National Institutes of Health (GM-31349) for generous support.

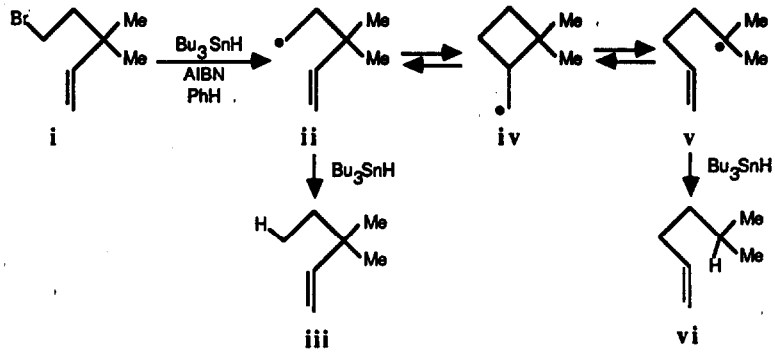
References and Notes

1. UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.
2. UCLA BASF Fellowship Awardee, 1990. Current address: Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ.
3. a) Jung, M. E. Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. b) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1990**, *31*, 4685. c) Jung, M. E. *Synlett* **1990**, 186. d) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469. e) Jung, M. E. Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429.
4. Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *Tetrahedron Letts.* **1985**, *26*, 591.
5. a) Giese, B. "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds," Pergamon Press, Oxford, 1986. b) Curran, D. P. *Synthesis* **1988**, 417, 489.
6. a) Srikrishna, A.; Hemamalini, P.; Sharma, G. V. R. *Tetrahedron Lett.* **1991**, *32*, 6609. b) Fremont, S. L.; Belletire, J. L.; Ho, D. M. *Tetrahedron Lett.* **1991**, *32*, 2335. c) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. d) Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1991**, *32*, 259. e) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1989**, *30*, 3229. f) Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishido, Y. *Tetrahedron Lett.* **1989**, *30*, 2829. g) Piccardi, P.;

Massardo, P.; Modena, M.; Santoro, E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 982. h) Piccardi, P.; Modena, M.; Cavalli, L. *J. Chem. Soc.* (C) **1971**, 3959.

7. Park, S.-U.; Varick, T.R.; Newcomb, M. *Tetrahedron Lett.* **1990**, *31*, 2975.

8. The cyano group is necessary for cyclization since Beckwith showed earlier that no vinyl transfer is seen when the bromoalkene **i** is treated with the stannane, namely the only product isolated is **iii**. If the radical **ii** had cyclized to **iv**, the product **vi** (from the more stable radical **v**) would have been formed (as is the case for the cyclopropyl system). Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.



9. All new compounds exhibited ^{1}H and ^{13}C NMR data and high resolution mass spectral data in accord with their assigned structures.

10. Prepared as follows: propargylation of ethyl isobutyrate (LDA, propargyl bromide, 69%) followed by reduction ($LiAlH_4$, 88%), and tosylation (TsCl, 88%) afforded 2,2-dimethyl-4-pentyn-1-ol tosylate; displacement with bromide and carboethoxylation (LiBr, DMSO, Δ; LDA, $ClCO_2Et$, 73% from tosylate) and hydrogenation (H_2, Lindlar, 95%) furnished **9**.

11. Fast addition gave **10** and **11** in a 2:1 ratio with the doubly reduced product, ethyl 5,5-dimethylhexanoate, being produced in amounts comparable to **11**. Slow addition gave somewhat variable ratios of **10** and **11**, e.g., addition over 3 h gave an approximately 1:1.5 ratio; addition over 8 h gave an approximately 1:9 ratio.

12. Bromination (Br_2, pyr, 58%) followed by propargylation (propargyl bromide, aluminum), carboethoxylation (LDA, $ClCO_2Et$, 77%), and reduction (H_2, Lindlar, 96%) afforded **12** in good overall yield.

13. Foote, C. S. *Tetrahedron Lett.* **1963**, 579.

14. There is another possible argument to explain this result, based on inductive effects and not rotamer populations. Since the radical **4** (R=OEt, Z=CO_2Et) generated from the halide is an electron-deficient species, the effect of the inductively electron-withdrawing β-ethoxy groups would be quite destabilizing and might therefore help cause cyclization to occur to give **5** (R=OEt, Z=CO_2Et) in which this inductive destabilization is greatly diminished. We are currently investigating systems to test this inductive destabilization hypothesis.

(Received in USA 2 July 1992)