

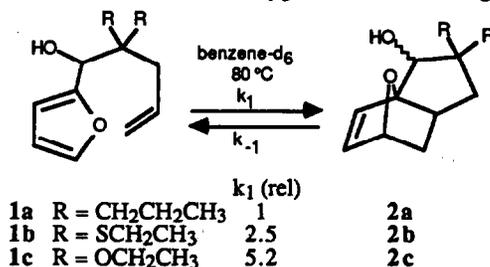
EASY PREPARATION OF A CYCLOBUTANONE KETAL VIA A RADICAL CYCLIZATION. THE *GEM*-DIALKOXY EFFECT

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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.

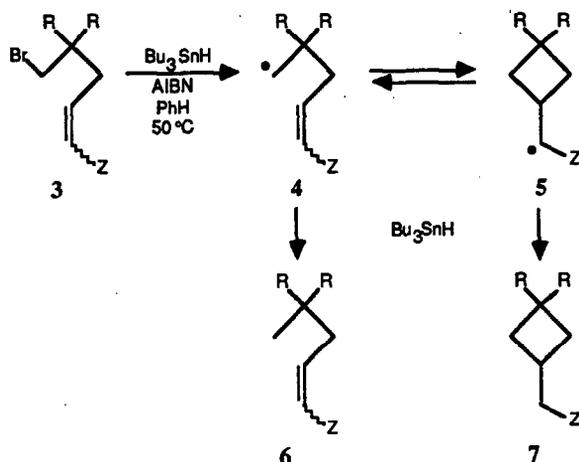
For several years now, we have studied both substituent and solvent effects on the rates and equilibria of various cyclization reactions, including the Diels-Alder reaction, the ene reaction, and radical cyclization.³ In particular, we have obtained experimental evidence for the greater importance of 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



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

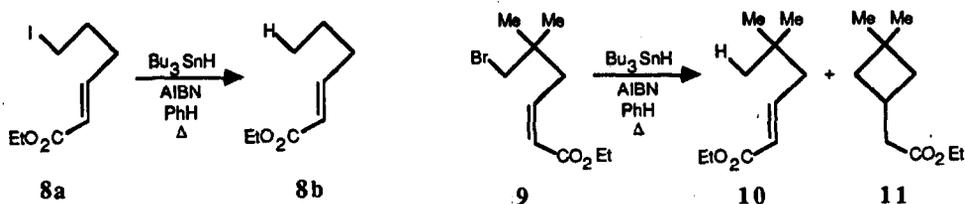
Although radical cyclizations are extremely useful for the synthesis of 5- and 6-membered ring systems,⁵ the production of small (3- and 4-membered) rings by radical cyclization is generally not successful, although there are

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 cyclobutylcarbiny 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

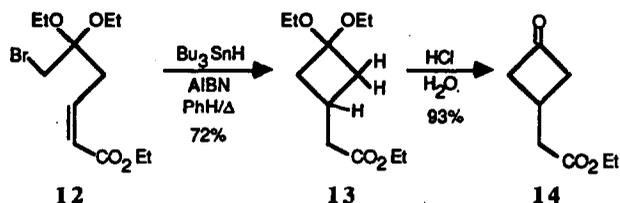


conditions (e.g., a reasonably high concentration of tributyltin hydride) gave a 2:1 ratio of acyclic to cyclic products (**6** and **7**, $\text{R}=\text{Me}$ $\text{Z}=\text{CN}$) while the use of catalytic hydride (Bu_3SnCl , excess NaCNBH_3) gave an approximately 1:1 mixture of **6** and **7**.⁸ 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 $^1J_{\text{CH}}$ coupling constants as seen in the uncoupled ^{13}C NMR spectrum. The $^1J_{\text{CH}}$ 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.



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.

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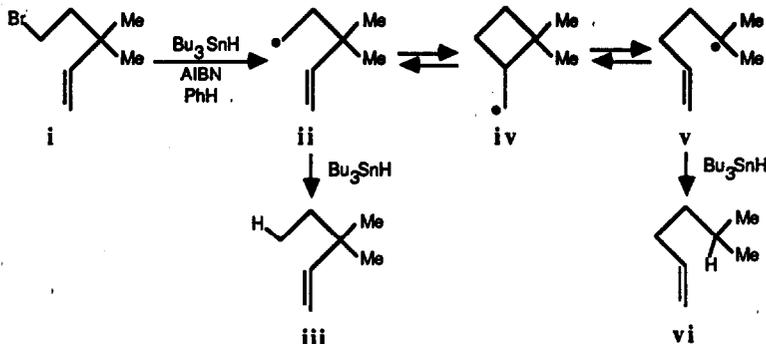
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8. The cyano group is necessary for cyclization since Beckwith showed earlier that no vinyl transfer is seen when the bromoalkene **i** is treated with the stannane, namely the only product isolated is **iii**. If the radical **ii** had cyclized to **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 ^1H 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.

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14. There is another possible argument to explain this result, based on inductive effects and not rotamer populations. Since the radical **4** ($\text{R}=\text{OEt}$, $\text{Z}=\text{CO}_2\text{Et}$) 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** ($\text{R}=\text{OEt}$, $\text{Z}=\text{CO}_2\text{Et}$) in which this inductive destabilization is greatly diminished. We are currently investigating systems to test this inductive destabilization hypothesis.

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