Tetrahedron Letters,Vol.29,No.8,pp 897-900,1988
Printed in Great Britain

0040-4039/88 $3.00 + .00
Pergamon Journals Ltd.

CYCLOPENTANE SYNTHESIS and ANNULATION: INTRAMOLECULAR RADICAL CYCLIZATION of ACETALS

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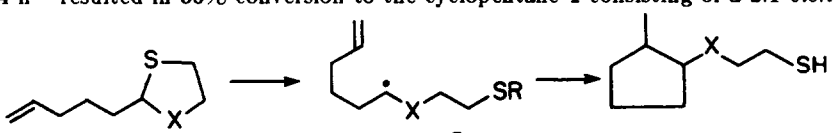
Summary: A general procedure for cyclopentane synthesis based on free-radical cyclization of thioacetals is described. This permits the rapid assembly, by intramolecular annulation, of various ring systems bearing useful functionality for use in total synthesis.

Free-radical reactions have evolved recently to join their counterparts, electrophilic, nucleophilic, and pericyclic processes in the arsenal of the synthetic organic chemist.[1,2] The established preference of 5-hexenyl radicals to form five-membered rings[3] allows the rapid construction of complex systems particularly cyclopentanoid natural products.[4-7] In order to further develop and exploit radical carbon-carbon bond formation diverse radical sources which also incorporate useful substituents are desirable to supplement classical halogen precursors.[8]

Gutierrez and coworkers[9] established that tri-*n*-butyltin hydride plus AIBN (azobis(isobutyronitrile) as initiator was effective for desulfurization of dithioacetals and that this process involved a stepwise radical chain reaction. It appeared likely that quenching of an olefinic intermediate radical such as **3** would be slow relative to cyclization. We wish to report that this is the case and that ring closure is effected with retention of synthetically useful functionality.

Treatment of a 0.02 M benzene solution of **1** with *n*-Bu_3SnH (1.2 equiv.) and AIBN (4%) at reflux (80 °C) for 24 h[10] resulted in 60% conversion to the cyclopentane **4** consisting of a 2:1 *cis:trans* isomer



1 X = S
2 X = O

3 R = $Sn^n Bu_3$

4 X = S
5 X = O

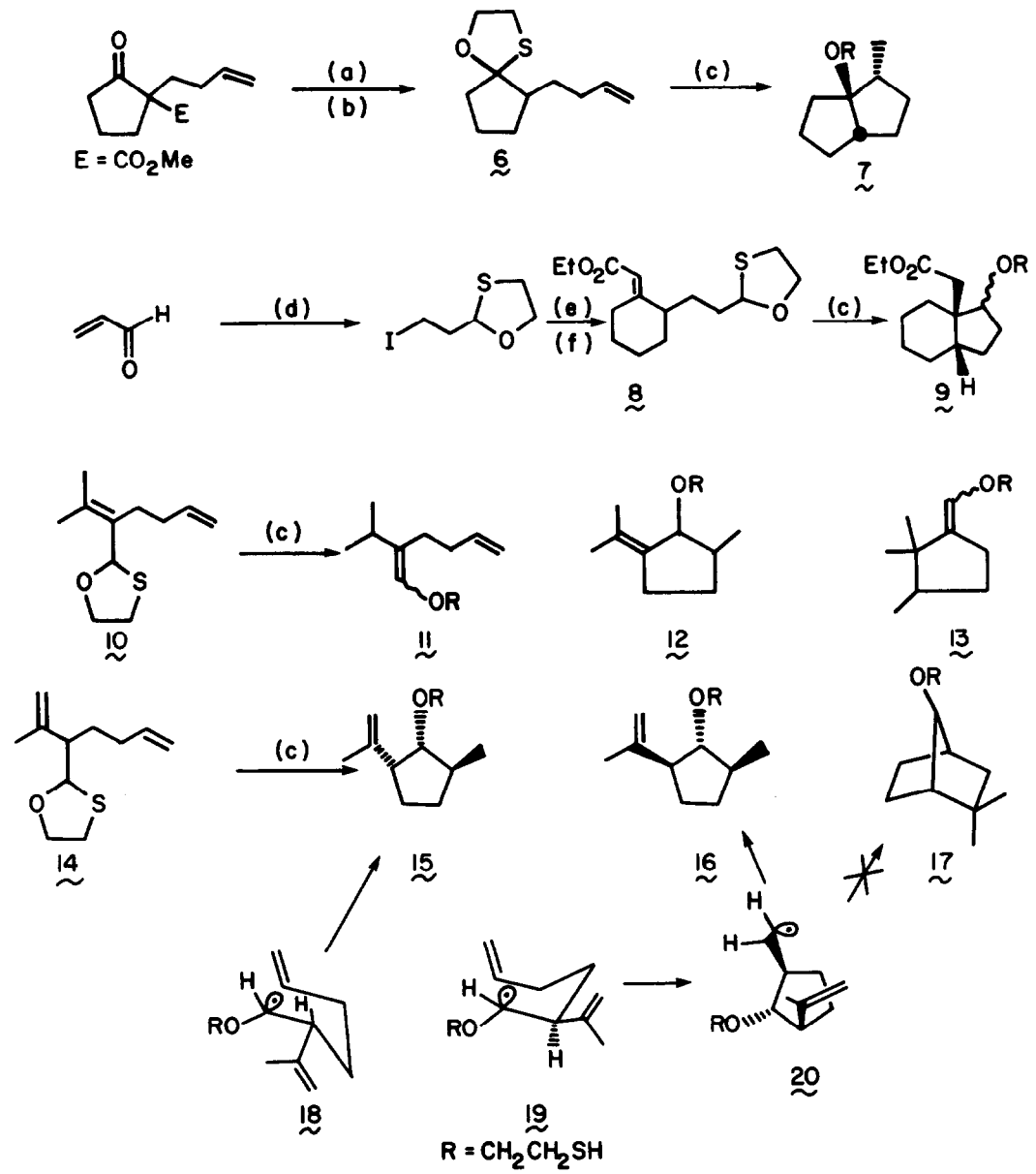
ratio. The major *cis* isomer gave rise to a methyl doublet at δ 1.07 compared to δ 0.98 for the minor compound in ^{1}H nmr spectrum and as expected due to the γ-gauche effect, the relative field positions were reversed in the ^{13}C nmr spectrum δ 15.1 (*cis*) and δ 19.3 (*trans*).[11]

Similar treatment of **2** afforded (after chromatography) a 60% isolated yield of **5** as a single isomer (δ 0.99; 18.8). Ether cleavage was effected with BCl_3 (CH_2Cl_2, -78 to 21 °C, 1.5 h) to provide *trans*-2-methylcyclopentanol whose structure was confirmed by comparison with an authentic sample. Stereochemical assignments are often difficult in cyclopentanols compared to cyclohexanols and thus *cis*-2-methylcyclopentanol was also prepared. Their key spectral features provide useful data for related assignments (^{1}H nmr: *trans* δ 0.98, 3.70; *cis* δ 1.02, 4.06; ^{13}C nmr: *trans* δ 18.0, 80.1; *cis* δ 13.5, 76.0). In view of the improved yield and stereoselectivity with the oxathiolane, plus the fact that oxygen is often a more useful synthetic substituent, a number of other substrates were examined in order to delineate the utility of this procedure.

The substituted cyclopentane ketal **6** prepared by alkylation, decarboxylation, and ketalization cyclized to the single diquinane isomer **7** (66% yield, 75% conversion, δ 0.96, 14.4) as illustrated. The parent *tertiary* alcohol displayed a methyl doublet at δ 0.97 and a ^{13}C nmr signal at δ 13.3. (In bicyclo[3.3.0] octanes a C2 *endo*-methyl group absorbs at $\sim\delta$ 15 compared to its *exo*-epimer $\sim\delta$ 19).[11] Under the same standard conditions intramolecular Michael addition proceeded to give the *cis*-hydrindane **9** in 30% isolated yield (2:1, *trans:cis*) accompanied by 60% recovered starting material. The diene **10** will give rise to an allylic radical after C-S bond cleavage. In principle two cyclopentane systems **12** and **13** could be formed. In practice, the intermediate was insufficiently reactive and cyclization was not effected in synthetically useful yields. Instead the major product was the enol ether **11**. This method for the generation of protected enols from conjugated acetals under neutral conditions should have further utility.

The range of tandem radical cyclizations that may be profitably employed in synthesis is still uncertain. Acetal **14** possesses an internal stereochemical trap and it was of interest to determine if, in addition to the initial ring closure products, further *exo* cyclization to the norbornane skeleton **17** could be achieved as a minor pathway from the appropriate *cis* isomer. (*Endo* closure to a bicyclo[3.2.1]octane is also a possibility.)

Guided by the Beckwith[3,12,13] and Houk[14] stereochemical models and the results above, the expected major product **15** (δ 0.98, 14.3, 86.1) arose from an *exo* chair transition state **18** which was incapable of cyclizing further due to the *trans* orientation of the carbon side chains. This material was accompanied by a minor isomer tentatively assigned structure **16** (δ 1.01, 13.7, 88.8, ratio of **15:16**, 65:35) from the related intermediate **19**. These tentative stereochemical assignments were facilitated by comparison with an



(a) NaI, HMPA, 160 °, 5 h, 50%
(b) $HOCH_2CH_2SH$, $ZnCl_2$, Na_2SO_4, dioxane, 21 °, 24 h, 80%
(c) nBu_3SnH, AIBN, C_6H_6, 80 °, 24 h
(d) *i.* NaI, TMSCl, CH_3CN, 10 min; *ii.* $HOCH_2CH_2SH$, 21 °, 10 min, 72%
(e) Cyclohexanone, KH, THF, 1% DMSO, 10 min, 0 °, 1.5 h 0 → 21 °, 60%
(f) $(EtO)_2POCH_2CO_2Et$, NaH, THF, HMPA, 0-21 °, 48 h, 90%

authentic sample of *trans*-2-ethenylcyclopentanol (δ 3.87, 78.1) and suggest that the hydroxylcarbon will be at lowest field when the alkyl groups are both *trans* to the alcohol and *cis* to each other as in **16**. Bicyclic products were not detected and apparently intermediate **20** does not cyclize further before being quenched by the tin hydride. However, this example is quite demanding and as suggested by a referee cyclization may be strongly retarded due to the vinyl methyl group.[15] Thus, for a synthetically useful selective trapping strategy of this type to succeed it will likely be necessary to employ less substituted systems and more highly stablized intermediates in which the initial cyclization is reversible.[16,17]

In conclusion, thioacetals particularly 1,3-oxathiolanes are useful precursors of radical intermediates for intramolecular ring closure to cyclopentane systems. Cyclization effected by selective ring cleavage provides cyclic compounds with a reasonable level of stereocontrol that retain useful functionality for subsequent synthetic manipulations. These features should facilitate the extended use of these methods in synthesis.

Acknowledgements We are grateful to Memorial University of Newfoundland and the Natural Sciences and Engineering Research Council of Canada for financial support of this research, B. Gregory for high resolution mass spectra and a referee for constructive comments.

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(Received in USA 7 September 1987)