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THE USE OF KETENE THIOACETALS AS INITIATORS IN BIOMIMETIC CYCLIZATIONS

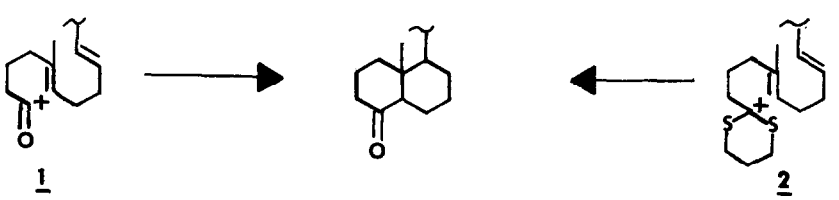
R. S. BRINKMEYER[1]
Department of Chemistry, Stanford University,
Stanford, California 94305 USA

A considerable effort in the area of biomimetic polyolefin cyclization has been made to uncover functional groups which will generate cyclizable cationic centers. Of prime importance to our investigation was that these new cyclization initiators promote the cyclization of at least two rings and provide a product with suitable functionality for further elaboration, if desired.

Although a number of cyclization initiators exist they have, for the most part, been found to be used in forming only a single ring. For example, the cyclization of acylium[3a] (1) or nitrilium[3b] ions have been reported to form a single ring. Our attempts to expand their use as initiators for the cyclization to two or four rings have thus far been unsuccessful. We therefore became interested in developing an acylium ion equivalent suitable in the cyclization to two or more rings .

Previous publications have reported that under acidic conditions, a ketene thioacetal (or vinyl sulfide) can form cations like 2 (Scheme 1), which can be considered as synthetic equivalents to acylium ions, and these cations can be trapped with either an external[4] or internal[5] nucleophile. In addition, during the early stages of our investigations, Andersen and coworkers[6] found that the cation from a ketene thioacetal can be trapped intramolecularly with a double bond to form a single 6-membered ring in good yield. We thus have been involved in the study of the cyclization of substrates 6 and 10, to determine if ketene thioacetal can be used to initiate a cyclization to two or more rings.

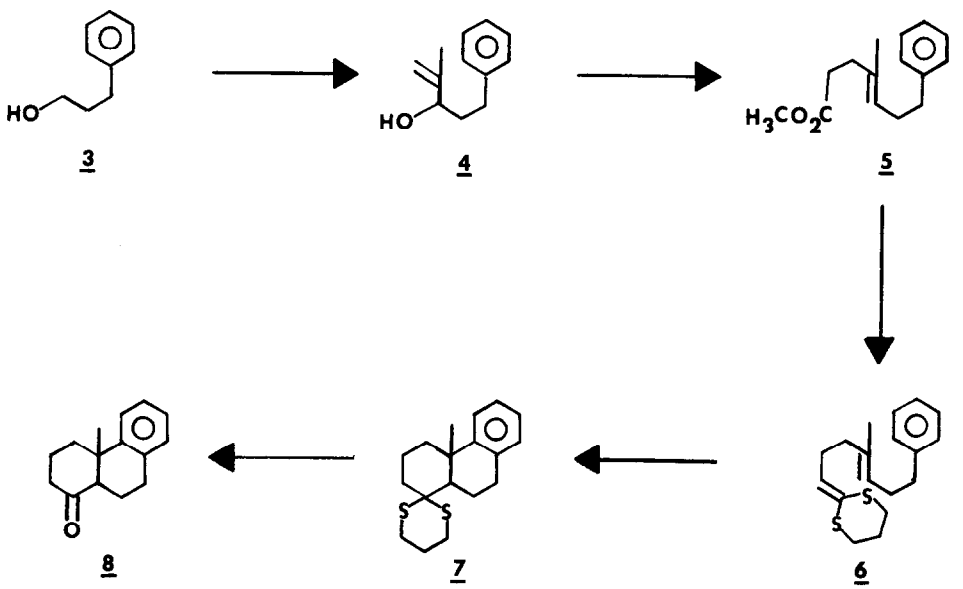
SCHEME 1



1 2

Cyclization substrate 6 was synthesized (Scheme 2) starting from commercially available 3-phenyl-1-propanol by oxidation[7] (CrO_3,py,HCl, CH_2Cl_2, 20°) followed by reaction with 2-propenyl magnesium bromide to give alcohol 4 in 90% distilled yield [bp 80-82° (1.0 mm); lit[7] bp 126-7° (9 mm)]. Ortho-ester Claisen rearrangement[9] [$CH_3C(OMe)_3$, $EtCO_2H$, 110°] provided ester 5[10] in 79% yield after column chromatography (silica gel). Reduction of 5 (LAH, Et_2O), followed by a modified Collins oxidation[11] (CrO_3, py, CH_2Cl_2, 25°) gave the aldehyde[10] in 95%

SCHEME 2



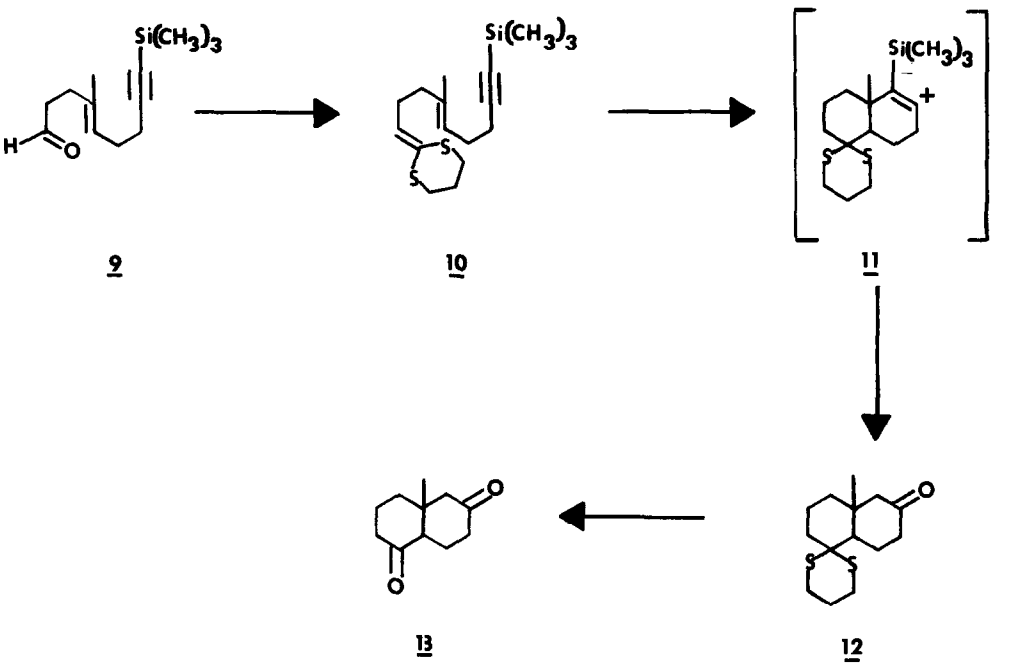
yield after column chromatography (neutral alumina, activity grade III). Treatment of this aldehyde with 2-lithio-2-trimethylsilyl-1,3-dithiane[4] (-60°, THF) provided ketene thioacetal 6[10] in 79% yield after column chromatography (neutral alumina). The best results found for cyclizing 6 were trifluoroacetic acid in trifluoroethanol (1:10 respectively) at 0°. This provided compound 7 which upon immediate hydrolysis[12] ($HgCl_2$, $CaCO_3$, aq MeCN) gave the known[10,13] ketone 8 as a mixture of cis and trans isomers in a 1:2 ratio in 55% yield after distillation [bp 110-112° (0.1 mm); lit[13] bp 150-155° (0.5 mm)]; ir (film) 1705, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.03 and 1.35 (s, 3H), 1.5-3.1 (m, HH), 7.1 m (4H); m/e 214 for both cis and trans isomers[17].

The ketene thioacetal 10 was synthesized as outlined in Scheme 1 starting with the known[14] aldehyde 9. Treatment of 9 with 2-trimethylsilyl-2-lithio-1,3-dithiane[4] (THF, -50°) gave ketene thioacetal[10] 10 in 68% yield after column chromatography (neutral alumina).

Cyclization of 10 to 12[10] was effected with trifluoroacetic acid in trifluoroethanol in 76%

yield after chromatography. The cyclization proceeded so as to form cation 11,[14,15] thus providing decalone 12. Hydrolysis[12] of the dithiane in 12 with mercuric chloride (Ca_2CO_3, aq CH_3CN) gave the known[10,16] dione 13 in 89% yield after chromatography and sublimation (mp 82-83°, lit[16] mp 84-85°); ir ($CHCl_3$) 1710, 1378 cm^{-1}; nmr ($CDCl_3$) δ 0.78 (s, 3H) 1.5-2.82 (m, 13H); and m/e 180, 165, 137, and 120.

SCHEME 3



9 10 11 12 13

Thus, the cyclization of a ketene thioacetal as an acylium ion equivalent proceeded smoothly to two rings compared to attempted cyclizations of other acylium ion precursors (e.g., acid chloride). Also, this initiator provides a carbonyl at C-4 (steroid numbering) allowing further elaboration of the product if desired. Future plans are to use this initiator in promoting a cyclization to four rings.

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References and Notes

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