Tetrahedron Letters No. 6, pp 527 - 530, 1974. Pergamon Press. Printed in Great Britain.

STUDIES ON THE ACID-CATALYZED OPENING OF NON-RIGID ACYLCYCLOPROPANES: A DRAMATIC SOLVENT EFFECT. A ROUTE TO THE BICYCLO[2.2.1]HEPTANE RING SYSTEM

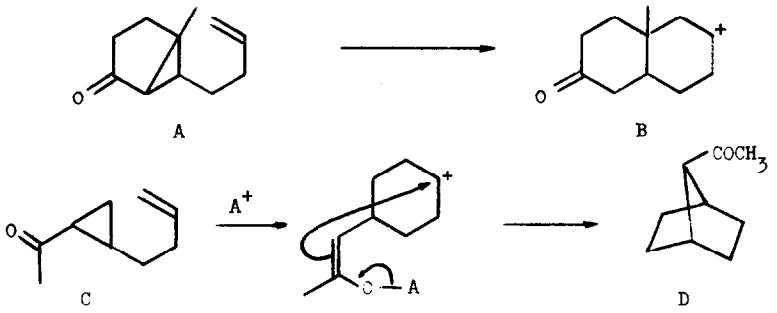
Paul A. Grieco* and Robert S. Finkelhor

Department of Chemistry, University of Pittsburgh

Pittsburgh, Pennsylvania 15260

(Received in USA 4 December 1973; received in UK for publication 4 January 1974)

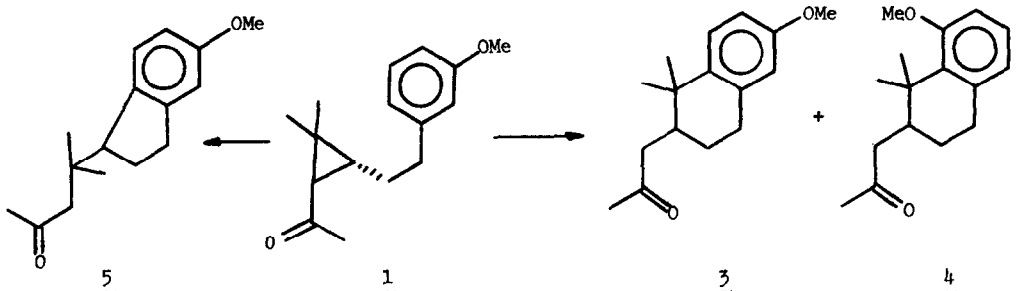
The possibility of initiating a cationic biogenetic-like olefin cyclization via the acid-catalyzed opening of a rigid cyclopropyl ketone with participation of a suitably disposed olefinic center has been demonstrated (cf. A→B).[1,2] We became intrigued with the idea of utilizing such a cationic cyclization for construction of bicyclic monoterpenes possessing the bicyclo[2.2.1]heptane ring system (C→D). Although the familiar bridged bicyclic system of fenchane and related terpenes is not derived naturally by such a cyclization pathway, we explored the possibility of forming such structural types from non-rigid cyclopropyl ketones possessing a suitably oriented double bond.



Previous attempts to construct bicyclo[2.2.1]heptane derivatives by solvolysis of Δ^3-cyclohexenyl carbinyl systems have resulted in very low yields or have failed.[3] Similarly, other attempts involving the cyclization of epoxy olefins have failed.[4] A recent report,[5] however, has demonstrated that the enol acetate of dihydrocarvone upon treatment with boron trifluoride results

in the formation of camphor.

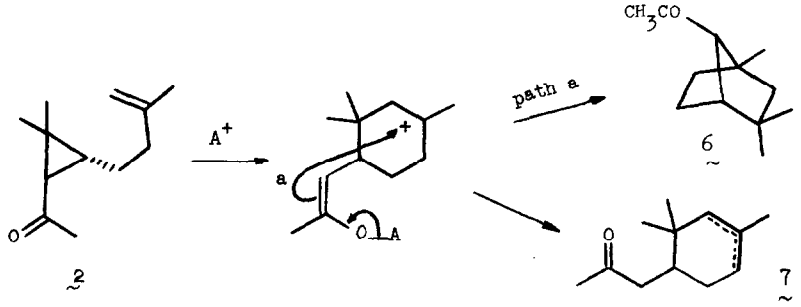
We wish to report results concerning the acid-catalyzed reactions of non-rigid acylcyclopropanes 1 and 2, and a remarkable influence of solvent[6] on the nature of the cyclization products obtained from cyclopropylketone 2. In view of previous work on rigid suitably constituted aryl cyclopropyl ketones,[1b] one might anticipate that ketone 1 would undergo cyclization to a mixture of ketones 3 and 4. However, the possibility remained that cyclization could



5 1 3 4

conceivably lead to 5. The conversion of 1→3 is of extreme importance if there is to be a chance for bicyclo[2.2.1]heptane ring formation via cyclization of 2. m-Anisyl cyclopropyl ketone 1 [prepared from the corresponding m-anisyl cyclopropyl ester[7] by hydrolysis to the acid followed by treatment with lithium hydride/methyllithium[8]] upon treatment with stannic chloride in benzene gave an 85% yield of crystalline ketone 3,[9] mp 90-91°. NMR analysis (250 MHz)[10] indicated that isomer 4 was absent; furthermore, there was no indication that compound 5 was formed.

The above results demonstrate that the aryl group undergoes at least 85% participation in non-rigid systems. Cyclization studies involving cyclopropyl ketone 2 indicate that the double bond undergoes 90% olefin participation generating a cyclohexyl cation which can experience simple proton loss or can be trapped by the enol generated via the acylcyclopropane opening (Scheme I).

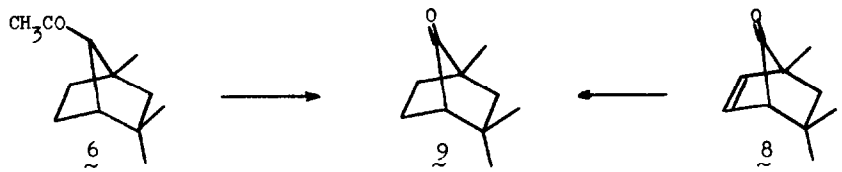


2 6 7

Scheme I

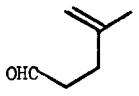
We had previously demonstrated that olefin participation in the acid-catalyzed opening of rigid cyclopropyl ketones can lead to a geometry in which the enol generated is in a position to trap the resulting carbonium ion.[1c,d] In the present non-rigid case, a favorable geometry for carbon-carbon bond formation via the enol is lacking.

Treatment of 2 with stannic chloride in benzene resulted in a greater than 90% yield of an 80:20 mixture of 7 and 6 respectively. Despite the low yield of 6 (ca. 18%), it was evident that the geometry required for formation of the bicyclo[2.2.1]heptane system can be achieved. Cyclization of ketone 2 at 25°C as a 0.1 M solution in nitromethane containing 10 mol-equiv of stannic chloride was complete in 30 min. Surprisingly, analysis of the reaction mixture (glc) revealed an 80:20 mixture of 6 and 7 respectively. Preparative glc afforded a pure sample of ketone 6 which had properties in agreement with the assigned structure: λ (film) 5.86μ; δ 0.98 (s, 3H), 1.07 (s, 3H), 1.13 (s, 3H), 2.03 (s, 3H), 2.57 (broad singlet, 1H), no olefinic protons; molecular ion m/e 180. Further proof of structure was obtained by degradation (Baeyer-Villiger oxidation, hydrolysis, Jones oxidation) to 1,3,3-trimethylbicyclo[2.2.1]heptan-7-one 9, which was shown to be identical (glc, mass spec) with a sample of 9 prepared by catalytic hydrogenation of 1,5,5-trimethylbicyclo[2.2.1]hept-2-ene-7-one 8.[11]

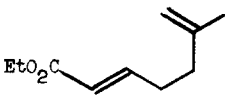


6 9 8

Cyclopropyl ketone 2 was synthesized as follows. Condensation of ethyl diethylphosphonoacetate with aldehyde 10 gave (83% yield) the trans-α,β-unsaturated ester 11. Construction of the gem-dimethylcyclopropane unit was achieved in 65% yield employing triphenylphosphonium isopropylide.[7] Acid 12 (R=H), obtained by hydrolysis of the corresponding ethyl ester 12 (R=Et), was converted into 2 by treatment with lithium hydride followed by methyllithium (95% yield).[8]



10



11

12

References

1. a) G. Stork and M. Marx, J. Amer. Chem. Soc., 91, 2371 (1969);
   b) G. Stork and M. Gregson, ibid., 91, 2373 (1969);
   c) G. Stork and P. A. Grieco, ibid., 91, 2407 (1969);
   d) G. Stork and P. A. Grieco, Tetrahedron Lett., 1807 (1971).
2. The use of cation-olefin cyclizations initiated by protonation of cyclopropyl ketones has recently been employed in the synthesis of (±)-cedrene and (±)-cedrol [E. J. Corey and R. D. Balanson, Tetrahedron Lett., 3153 (1973)].
3. C. F. Wilcox and S. S. Chibber, J. Org. Chem., 27, 2332 (1962); W. Rittersdorf, Angew. Chem. Internat. Edition, 4, 444 (1965); F. Cramer and W. Rittersdorf, Tetrahedron, 23, 301 (1967).
4. J. C. Fairlie, G. L. Hodgson and T. Money, Chem. Comm., 1196 (1969).
5. D. J. Goldsmith and R. C. Joines, J. Org. Chem., 35, 3573 (1970); D. J. Goldsmith and C. J. Cheer, ibid., 30, 2264 (1965).
6. A similar solvent effect has been observed in the nonenzymic, biogenetic-like cyclization studies of Johnson [G. D. Abrams, W. R. Bartlett, V. A. Fung and W. S. Johnson, Bioorg. Chem., 1, 243 (1971)].
7. P. A. Grieco and R. S. Finkelhor, Tetrahedron Lett., 3781 (1972).
8. T. M. Bare and H. O. House, Org. Syn., 49, 81 (1967).
9. All compounds exhibited satisfactory spectral and analytical data.
10. NMR spectra were obtained at the National Institutes of Health NMR facility for biomedical studies (Mellon Institute).
11. We are grateful to Professor G. H. Whitham (University of Oxford) for a generous gift of 1,5,5-trimethylbicyclo[2.2.1]hept-2-ene-7-one [J. J. Hurst and G. H. Whitham, J. Chem. Soc., 710 (1963)]. We thank Mr. John Woods for making the glc comparison for us.