Tetrahedron Letters,Vol.24,No.23,pp 2347--2350,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

REACTION OF METHYLENECYCLOPROPYLCARBINOLS WITH FORMIC ACID

Edward W. Thomas
Diabetes and Atherosclerosis Research,
The Upjohn Company, Kalamazoo, MI 49001

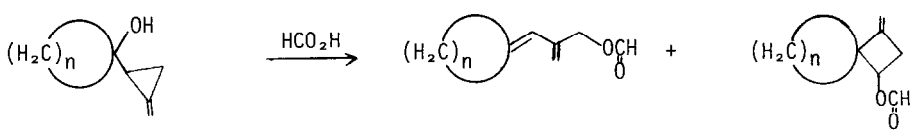
ABSTRACT: 1-(2-Methylenecyclopropyl)-cyclohexanol reacted with formic acid to yield 2-(cyclohexylidene-methyl)-2-propenyl formate and 3-methylenespiro-[3.5]-nonyl formate; similar alcohols reacted with formic acid to afford the corresponding cyclobutyl formates and dienes in varying ratios.

Previously, we had synthesized a series of methylenecyclopropylcarbinols and found they were quite stable except when exposed to acid, Scheme I.[1]

Scheme I

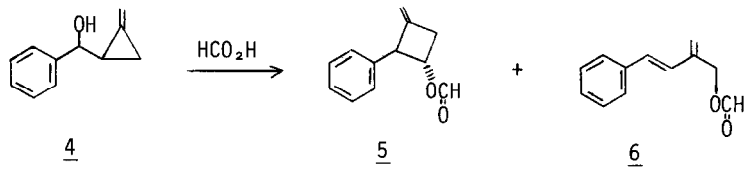
For example: R = H, R¹ = nC_7H_{15}, Ph and R,R¹ = $-(CH_2)_5-$

We now wish to report the novel rearrangement of these methylenecyclopropylcarbinols to dienes. Reaction of 1-(2-methylenecyclopropyl)-cyclohexanol (1a) with formic acid produced diene 2a (61%) as the main product accompanied by a small amount of cyclobutyl formate 3a (5.5%). Additional examples of this general reaction include the rearrangement of alcohol 1b to diene 2b (70%) and cyclobutyl formate 3b (9%), and the rearrangement of the more stable diastereomer 4 to 5 and 6 in 50% yield, as a 1:1 mixture. Others have explored the rearrangement of similar systems, synthesized in a different manner, and found cyclobutanols were the major products, Scheme II.[2] No evidence for the formation of dienes was reported.



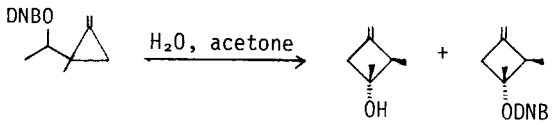
1 2 3

a, n = 5; b, n = 11



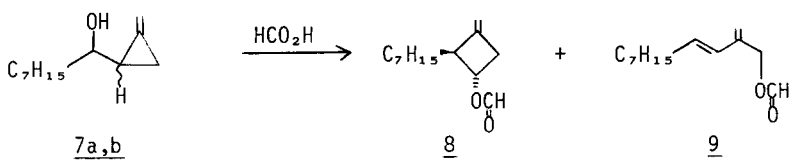
4 5 6

Scheme II

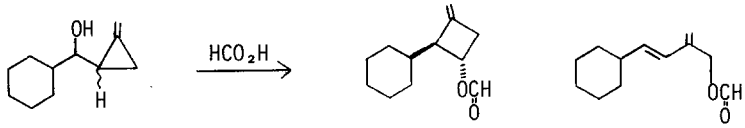


This diene synthesis is a modification of Julia's method of olefin synthesis,[3] where the cyclopropyl group has been replaced by a methylenecyclopropyl group. Although Julia has reported the formation of dienes from cyclopropylcarbinols,[4] to my knowledge this is the first report of methylenecyclopropylcarbinols affording dienes.

The following secondary alcohols did not yield dienes as major products under acidic conditions, but behaved as did similar alcohols reported in the literature,[2] in that the vinyl group migrated affording methylenecyclobutyl derivatives. Alcohol 7a when stirred with formic acid for 0.5 hours predominately rearranged to the cyclobutyl formate 8 (66%)[5] and a minor amount of diene 9 (1.4%) was also isolated. The other diastereomer 7b, in formic acid, also rearranged to only one major product, 8. Similarly, both diastereomers 10a and 10b, when taken separately, reacted with formic acid to form 11 (65%), accompanied by a small amount of 12 (1.2%).

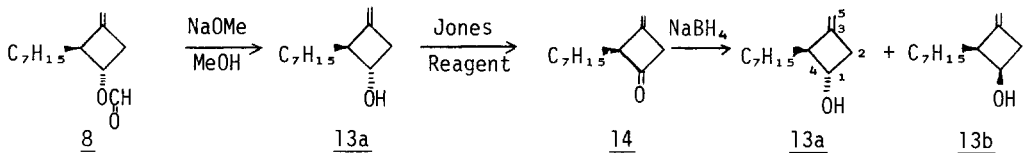


7a,b 8 9



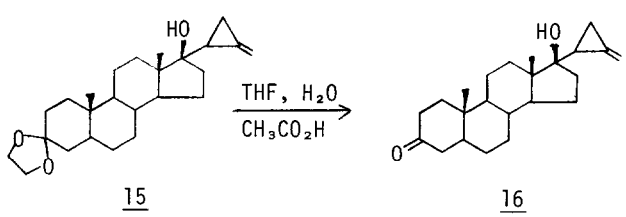
10a,b 11 12

The stereochemistry on the ring of 8 was not easily ascertainable, since in the reaction the other diastereomer was not formed. We obtained the other diastereomer by the following sequence. Formate 8 was cleaved to alcohol 13a,[6] followed by Jones oxidation to ketone 14. Because the ketone was too unstable to isolate, it was converted directly to a 1:1 mixture of alcohol diastereomers. One alcohol was identical with 13a by NMR and HPLC analysis. The other diastereomer 13b[7] was similar to 13a but different enough that we could assign stereochemistry.[8]



8 13a 14 13a 13b

In the presence of acetic acid for 24 hours at room temperature, alcohol 1b was inert. We used this selectivity of acids toward methylenecyclopropylcarbinols to cleave the ketal of steroid 15 to ketone 16 (66%).[11]



15 16

Acknowledgment. The author wishes to thank The Upjohn Company's Physical and Analytical Chemistry Department for elemental analyses, mass spectra, and IR spectroscopy. The author is also grateful to S.A. Mizsak for his discussion of the NMR data.

References and Notes

1. E. W. Thomas, Tetrahedron Lett., in press.

2. H. Monti and M. Bertrand, Tetrahedron Lett., 3007-3010 (1972).

3. (a) M. Julia, C. Descoins, and C. Risse, Tetrahedron Suppl., 8, 443-462 (1966); (b) M. Julia, S. Julia, and R. Guegan, Bull. Soc. Chim. Fr., 1072-1079 (1960).

4. M. Julia, S. Julia, B. Stalla-Bourdillon and C. Descoins, Bull. Soc. Chim. Fr., 2533-2541 (1964).

5. Compound 8: ^{1}H-NMR ($CDCl_3$)δ 0.7-1.0(m,3H,CH_3), 1.05-1.80(m,12H,CH_2), 2.40-3.20(m,3H,=C-CH,=C-CH_2), 4.78(t,1H,CH-O,J=7.0Hz), 4.80-5.00(m,2H,=CH_2), 8.02(s,1H,O_2CH); ^{13}C-NMR($CDCl_3$)ppm 14.1, 22.7,26.9,29.3,29.7,31.3,31.9,38.4,52.2,70.3,105.8,144.9,160.4; IR(neat) 2925,2850,1725,1169,880 cm^{-1}.

6. Compound 13a: ^{1}H-NMR($CDCl_3$)δ 0.73-1.01(m,3H,CH_3), 1.10-1.65(m,12H,CH_2), 2.20(d,1H,J=6.0Hz,OH), 2.30-3.05(m,3H,=C-CH,=C-CH_2), 3.90 (qt,1H,J=6.0Hz,CH-O), 4.78-4.92(m,2H,=CH_2); ^{13}C-NMR($CDCl_3$)ppm 14.1,22.7,27.2,29.3,29.9,31.6,31.9,41.0,55.6,69.8,104.7,145.5; IR(neat) 3321,2957,2924,2856,1678,1467,1079,877 cm^{-1}.

7. Compound 13b: ^{1}H-NMR($CDCl_3$)δ 0.70-1.01(m,3H,CH_3), 1.02-1.70(m,12H,CH_2), 2.73(s,1H,OH), 2.40-3.15(m,3H,=C-CH_2,=C-CH), 4.42(q,1H,J=6.0Hz,CH-O), 4.80-4.95(m,2H,=CH_2); ^{13}C-NMR($CDCl_3$)ppm 14.1,22.7,27.4,27.7,29.4,29.8,32.0,41.1,50.5,65.4,106.5,148.1; IR(neat) 3331,2956,2929,2856,1675,1467,1099,878 cm^{-1}.

8. In the ^{1}H-NMR the proton on the alcohol carbon of 13a(3.90δ) is shifted upfield in relation to the same proton in 13b(4.42δ). As one would expect[9] a proton cis to a C_7H_{15} group would be shifted upfield relative to a proton cis to another proton. The ^{13}C-NMR also favors this assignment.[10] The 6C of 13b is shifted upfield (27.7ppm) due to the cis hydroxyl group. The 6C of 13a is shifted downfield (31.6ppm) as the hydroxyl group is trans to C6 and exerts less of a shielding effect than on 13b.

9. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; (International series of Monographs in Organic Chemistry; Vol. 5) Pergamon Press: Oxford, 1969; p. 219-237.

10. S. A. Mizsak and G. Slomp, Prostaglandins, 10, 807-812 (1975).

11. All new compounds gave satisfactory NMR, ^{13}C-NMR, IR and mass spectra. Combustion analyses were in agreement with theoretical values.

(Received in USA 13 December 1983)