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CONVERSION OF KETONES HAVING δ,ε-π-FUNCTIONS TO CYCLOPENTANOLS BY ZINC-TRIMETHYLCHLOROSILANE

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Abstract: A new method for five-membered ring annulation is described which involves free radical generation from ketones by zinc-trimethylchlorosilane followed by internal addition to a π-bond.

In 1973 Motherwell reported a novel reaction for the transformation of ketones to olefins (e.g., cyclohexanone → cyclohexene) involving the use of zinc metal-trimethylchlorosilane (TMSCl) as reagent.[1,2] Although this process has been utilized for the synthesis of a number of steroidal olefins,[3] no other applications have appeared. We describe herein a new method for ring formation leading to cyclopentanol systems which depends on the reductive activation of ketones by Zn-TMSCl and subsequent internal addition to a variety of π-unsaturated functions to form the 5-membered ring.

The experimental results suggest that the action of zinc-TMSCl on the unsaturated ketone generates by electron transfer and silylation an α-trimethylsilyloxy radical which adds to the δ,ε-multiple bond to form a 5-membered ring according to the following scheme.

Stabilization of the radical resulting from cyclization, usually by H atom abstraction from solvent, then generates product. The cyclization reactions were generally performed with an excess of zinc powder (ca. 20 equiv) and TMSCl (ca. 6 equiv) in the presence of 2-4 equiv of 2,6-lutidine in tetrahydrofuran (THF) solution (ca. 0.2 M in the ketonic substrate) at reflux for 12-18 hr. The function of 2,6-lutidine is to prevent proton or zinc chloride-catalyzed elimination of the tertiary trimethylsilyloxy group. Products were isolated by an aqueous workup (which effects hydrolysis of the TMS ether) followed by chromatography.

For example, reaction of cis-2-(3-butenyl)-4-t-butylcyclohexanone (1) under the above conditions afforded as major product the cis-fused hydrindanol 1A (66%) together with the minor by-products 1B (7%) and 1C (4%).[4] In the absence of 2,6-lutidine the olefin 1C is obtained as the exclusive cyclization product (71% yield), clearly as a result of acid catalyzed elimination of the tertiary oxygen function in the precursors 1A/1B. The cis ring fusion for 1A is assigned on the basis of previous knowledge of such radical cyclizations,[5] and the orientation of methyl follows from steric considerations for the

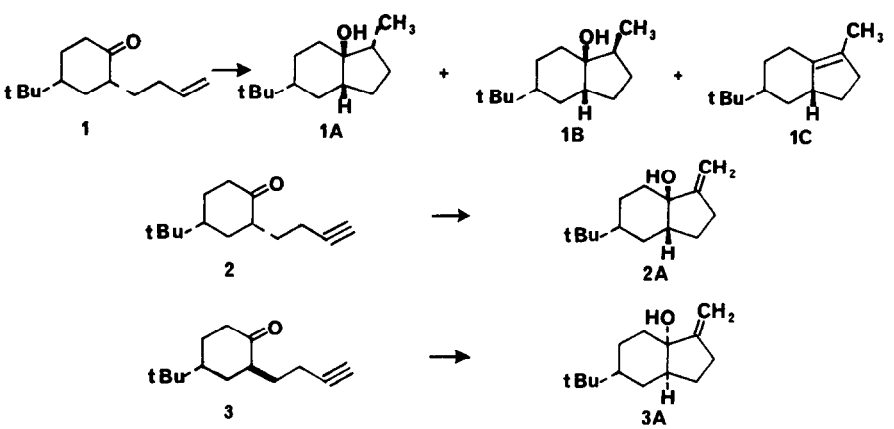
cyclization and the chemical correlation discussed in the following paragraph.[6,7]

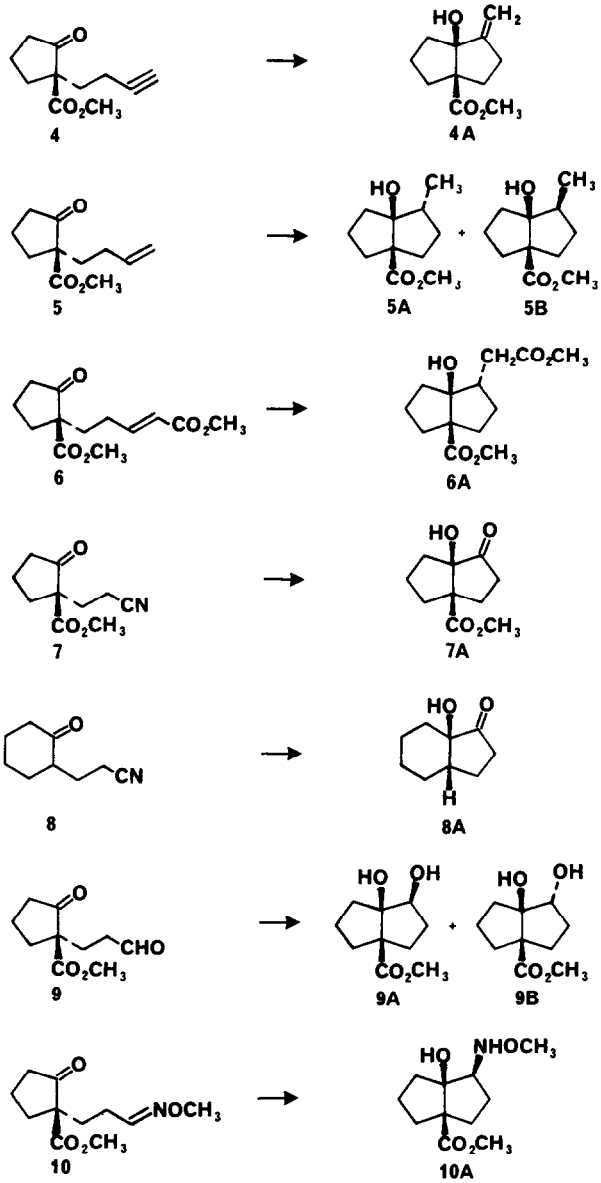
TMSCl-Zn cyclization of the acetylenic ketone (2) corresponding to 1 afforded as the exclusive bicyclic product the allylic alcohol 2A (74% yield), hydrogenation of which (1 atm. H_2, Pd-C) produced 1A and 1B in a ratio of 6:1, respectively, in support of the stereochemical assignment. Hydrogenation of the TMS ether of 2A yielded 1A and 1B in a ratio of 2:1. TMSCl-Zn cyclization of 3, the trans isomer of 2, produced 3A in 68% yield.

A number of cis-pentalane derivatives were also obtained stereospecifically and in good yield by reductive cyclization using the TMSCl-Zn-lutidine procedure. Acetylenic keto ester 4 afforded 4A exclusively (77% yield),and the olefinic analog 5 gave in 82% yield a mixture of 5A and 5B[7] (ratio 5:1).[8] Cyclization of the unsaturated keto ester 6 produced a single isomer 6A (76%), the stereochemistry of which follows from the above analogies and also its resistance to lactone formation under either acidic or basic conditions. The ketonitrile 7 was reductively cyclized to the hydroxy ketone 7A cleanly (82%) and similarly 8 gave 8A (78%).

Ketoaldehyde 9 was converted by Zn-TMSCl-lutidine to a mixture of diols 9A (less polar, 56%) and 9B (more polar, 19%). Reduction of 7A with sodium borohydride in ethanol at -20° afforded only trans diol 9B, consistent with the stereochemical assignment. Cyclization of keto methoxime 10 produced the bicyclic hydroxylamine 10A (84%) which was converted to keto ester 7A by the sequence: (1) O-trimethylsilylation (TMSCl-Et_3N); (2) oxidation with peracetic acid in ethyl acetate at 25° in the presence of sodium carbonate to the keto ester methoxime; and (3) methoxime hydrolysis with acidic aqeous acetone containing formaldehyde at 25°.

The results described above demonstrate considerable generality for the TMSCl-Zn induced cyclization of unsaturated ketones. The process is attractive for the annulation of 5-membered rings for other reasons including (a) stereoselectivity, (b) tolerance of numerous functional groups, and (c) ready availability of suitable substrates by alkylation. As might be expected the corresponding cyclizations with substrates capable of forming 6- but not 5-membered rings is not as facile and is also stereochemically non selective. The cyclization reported here is obviously related to the sodium-ammonia and lithium napth-




O
CO2CH3
4
HO
CH2
CO2CH3
4A
CH3
5
5A
5B
CO2CH3
6
CH2CO2CH3
6A
CN
7
7A
8
8A
H
CHO
9
OH
9A
9B
NOCH3
10
NHOCH3
10A

alenide reactions of keto acetylenes originally reported by Stork[9] and investigated in detail by Pradhan.[10] New methodology for the generation of 5-membered rings by internal addition of carbon radicals to π-bonds has recently been reported from a number of laboratories.[5,11,12]

References and Notes

1. W. B. Motherwell, Chem. Comm., 935 (1973).

2. The same reagent has been used to convert benzaldehyde to a phenyl carbenoid species by C. L. Smith, J. Arnett, and J. Ezike, ibid., 653 (1980).

3. P. Hodge and M. N. Khan, J. Chem. Soc. Perkin I, 809 (1975).

4. All cyclizations were conducted under an inert atmosphere (argon or nitrogen). Structural assignments are supported by infrared, mass spectral, ^{13}C NMR, and 270 MHz pmr data as well as by the interconversions indicated in the text. Product mixtures were analyzed by gas liquid chromatography or by preparative tlc separation.

5. A. L. J. Beckwith, Tetrahedron, 37, 3073 (1981).

6. All starting materials and products were racemates.

7. In general, the relative polarities of isomeric cyclopentanols on silica gel plates were as expected from the stereochemical assignments with the major (A) isomer being more polar than the minor (B) isomer.

8. Hydrogenation (1 atm. Pd-C) of 4A produced 5A and 5B in a ratio of 1:1, but hydrogenation of the bulky triisopropylsilyl ether of 4A afforded 5B exclusively confirming the stereochemical assignment.

9. G. Stork, S. Malhotra, H. Thompson, and G. Uchibayashi, J. Am. Chem. Soc., 87, 1148 (1965).

10. S. K. Pradhan, S. R. Kadam, J. N. Kolhe, T. V. Radhakrishnan, S. V. Sohani, and V. B. Thaker, J. Org. Chem., 46, 2622 (1981).

11. For example, (a) M. Okabe, M. Abe and M. Tada, J. Org. Chem., 47, 1775 (1982) and refs. cited therein; (b) S. Danishefsky, S. Chackalamannil and B-J. Uang, J. Org. Chem., 47, 2231 (1982); (c) G. Stork, "Current Trends in Organic Synthesis," Pergamon Press, 1983, p. 359; (d) M. Julia, Pure and Applied Chem., 40, 553 (1974).

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