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ZIRCONIUM-PROMOTED BICYCLIZATION OF ENYNES. EFFECTS OF ENYNE STRUCTURE[1]

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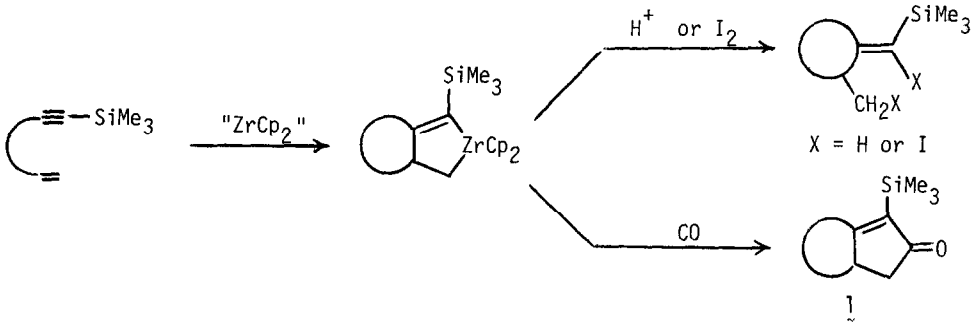
SUMMARY: The bicyclization reaction of enynes of the $XC{\equiv}CCH_2YCH_2CH{=}CH_2$ type promoted by 2 *n*-BuLi-Cl_2ZrCp_2 proceeds in high yields in cases where X is alkyl, aryl, alkenyl, Me_3Si, or Me_3Sn and Y is CH_2 or NCH_2Ph.

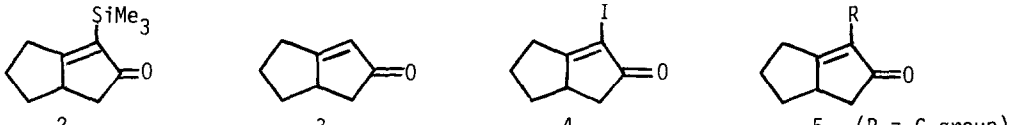
We have recently reported a Zr-promoted bicyclization reaction of trimethylsilylalkynes containing an ω-alkenyl group[3] (eq 1).



(1)

1

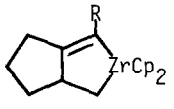
Unfortunately, all our attempts to induce the corresponding reaction of terminal enynes have resulted in mixtures of unidentified products, none of which was dominant. Similarly frustrating were our attempts to replace the Me_3Si group of the bicyclization-carbonylation product 1 with various electrophiles. Thus, for example, treatment of 2 with (a) *n*-Bu_4NF in THF, (b) HI in refluxing benzene, and (c) NaOH-MeOH in Et_2O[4] gave 3 only in 45, 45, and 20% yields, respectively,[5] and all attempts to replace Me_3Si with I or a carbon group have thus far failed to produce 4 or 5 in significant yields.



2 3 4 5 (R = C group)

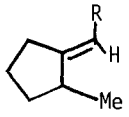
It was evident that, if this reaction were to be of some synthetic value, it should be able to accommodate various carbon and hetero atom groups either as substituents or as part of the ring moieties. We now report (i) that the Zr-promoted bicyclization reaction of test substrates $XC{\equiv}C(CH_2)_3CH{=}CH_2$ to produce 6, that are readily convertible to

7 on protonolysis, proceeds in high yields in cases where X is Me,[6] $(CH_2)_2CH=CH_2$, Ph, $CH=CHC_6H_{13}$-*n*, $CH=CHCH(OSiMe_2Bu\text{-}t)C_5H_{11}$-*n*, or $SnMe_3$, (ii) that, unlike 2, the carbonylation product of 6f, i.e., 8, can be readily convertible into 3 and 4 in high yields (eq 2), and (iii) that treatment of $Me_3SiC{\equiv}CCH_2N(CH_2Ph)CH_2CR^1{=}CHR^2$ (9) with 2 *n*-BuLi-Cl_2ZrCp_2 produces the corresponding pyrrolidine derivatives 10, readily hydrolyzable to 11, in high yields (eq 3). Unlike the Pauson-Khand reaction of enynes[7] which, under normal conditions, leads directly to the formation of cyclopentenones, the Zr-promoted enyne bicyclization reaction can be used to produce either cyclopentenones or monocycles containing an exocyclic alkene. Some other transition metal-promoted reactions of diynes[3b,8] and enynes[9] to produce stereodefined exocyclic dienes have recently been developed. However, there has been only one other isolated example of stereoselective conversion of an enyne into an exocyclic monoene promoted by a Ti reagent.[8]



6

6a (93%)
6b (80%)
6c (90%)
6d (90%)
6e (88%)
6f (92%)



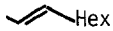
7

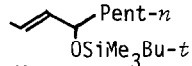
7a (65%)
7b (55%)
7c (70%)
7d (69%)
7e (70%)
7f (60%)

a: R = Me

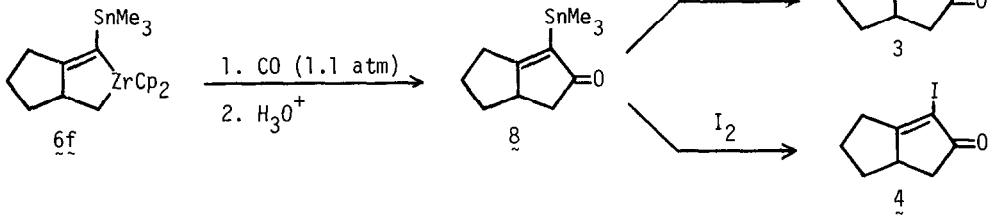
b: R = 

c: R = Ph

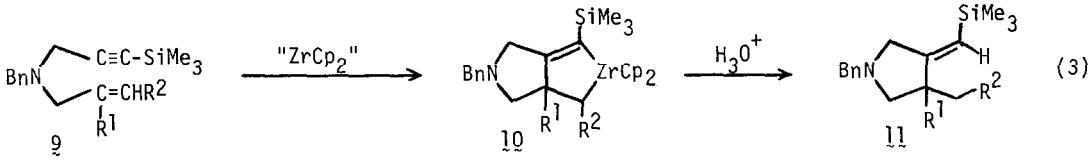
d: R = 

e: R = 

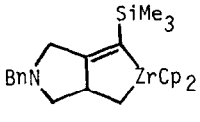
f: R = $SnMe_3$



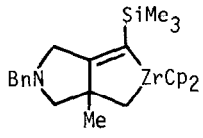
(2)



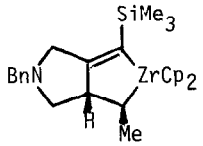
(3)



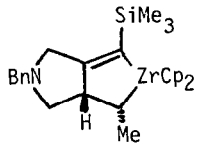
10a (85%)



10b (95%)



10c (92%)

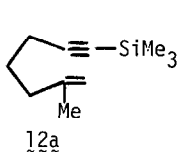


10d (86%)

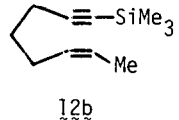
The following procedure for the preparation of 11a (R^1=R^2=H) is representative. To a solution of Cl_2ZrCp_2 (321 mg, 1.1 mmol) in 5 mL of THF at -78°C under nitrogen was added 1.6 M *n*-BuLi in hexane (1.45 mL, 2.32 mmol). After 1 h at -78°C, 257 mg (1.0 mmol) of 9a (R^1=R^2=H) in 2 mL of THF was added. The reaction mixture was warmed to 22°C, stirred for 3 h, and quenched with 3 N HCl (0°C). The resultant mixture was treated with $NaHCO_3$ and extracted with ether. The organic layers were washed with brine, dried over $MgSO_4$, concentrated, and Kugelrohr distilled to give 179 mg (69%) of 11a:[10] ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.08 (s, 9 H), 1.08 (d, J = 7 Hz, 3 H), 1.95-2.15 (m, 1 H), 2.4-3.5 (m, 4 H), 3.67 (s, 2 H), 5.2-5.4 (m, 1 H), 7.38 (s, 5 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 0.48, 17.44, 40.38, 59.38, 60.75, 61.31, 116.75, 126.92, 128.22, 128.79, 138.92, 162.84.

All protonolysis products of 6, i.e., 7, and 10 except 7b are isomerically ≥98% pure, as judged by ^{1}H and ^{13}C NMR as well as GLC. Although 7b appears homogeneous by GLC and ^{1}H NMR, its ^{13}C NMR spectrum reveals the presence of an unidentified compound[11] to the extent of ca. 10%. The ^{1}H NMR Cp signals for 6a, 6b, 6d, 6f, 10a, and 10c appear as partially resolved two singlets at δ 6.00-6.10 ppm. On the other hand, those for 6c (5.95 and 6.19), 6e (5.65 and 6.05), 10b (6.03 and 6.18), and 10d (5.70 and 5.82) are well resolved, and their chemical shifts are indicated above in parentheses.

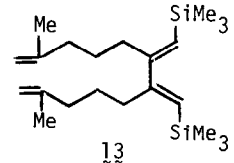
The bicyclization reaction of 9 reveals an unexpected but favorable effect of the amino group. Our earlier attempts to effect the Zr-promoted bicyclization of methylsubstituted enynes 12a and 12b[12] were unsuccessful. For example, treatment of 12a with "$ZrCp_2$" generated from 1 equiv of Cl_2ZrCp_2 and 2 equiv of *n*-BuLi followed by protonolysis only produced 0.32 equiv (64%) of 13 most probably via 14. On the other hand, the presence of a Me group either as R^1 or R^2 in 9 does not prevent the formation of 10b-10d in high yields. Furthermore, the Zr-promoted bicyclization promises to be highly stereospecific, judging from the high stereospecificity (>98% by ^{1}H and ^{13}C NMR) in the formation of 10c[13] and 10d.[14] The striking difference between the reaction of 9 and that of 12 must be attributable to the amino group of 9, but its precise role remains unexplained. Unfortunately, addition of NEt_3, PMe_3, or $PMePh_2$ to "$ZrCp_2$" inhibited the formation of 13 without inducing the desired bicyclization of 12a. It is nonetheless important to note that disubstituted alkene groups are sufficiently reactive so that they can readily participate in the Zr-promoted bicyclization so long as this process is faster than the Zr-promoted alkyne dimerization.



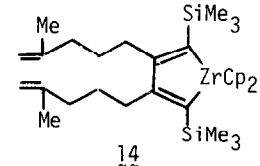
12a



12b



13



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REFERENCES AND NOTES

(1) Metal-Promoted Cyclization. 15. Part 14: Takahashi, T.; Swanson, D. R.; Negishi, E. submitted for publication.

(2) (a) John Simon Guggenheim Fellow (1986-1987). (b) David Ross Predoctoral Fellow (1985-1986). (c) Department of Industrial Chemistry, Faculty of Engineering, University of Tokyo, Tokyo, Japan.

(3) (a) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* 1985, *107*, 2568. (b) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* 1986, *27*, 2829. (c) For a related study of Zr-promoted enyne bicyclization reactions, see also Nugent, W. A.; RajanBabu, T. V.; Thorn, D. L. 192nd ACS National Meeting, Anaheim, September 7-12, 1986, ORGN 78.

(4) See, for example, Colvin, E.; "Silicon in Organic Synthesis," Butterworths, London, 1981, Chap. 7.

(5) These results were obtained by J. M. Tour of our laboratories.

(6) This experiment was initially performed by J. A. Kawas of our laboratories.

(7) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. I* 1973, 977. (b) Khand, I. U.; Pauson, P. L. *J. Chem. Res.* 1977, *8*, 9. (c) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* 1981, *46*, 5436. (d) Croudace, M. C.; Schore, N. E. *J. Org. Chem.* 1981, *46*, 5436. (e) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* 1983, *105*, 2477.

(8) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* 1984, *106*, 6422.

(9) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* 1985, *107*, 1781. (c) Trost, B. M.; Chung, Y. L. *J. Am. Chem. Soc.* 1985, *107*, 4586. (c) Trost, B. M.; Chen, S. F. *J. Am. Chem. Soc.* 1986, *108*, 6053.

(10) All new cyclic organic products have yielded satisfactory high resolution MS or elemental analytical data.

(11) Its spectral data are consistent with 1-(5'-hexenylidene)-2-methylcyclobutane.

(12) This experiment was performed by S. J. Holmes of our laboratories.

(13) 10c: ^{1}H NMR (benzene-d_6, benzene) δ 0.19 (s, 9 H), 1.37 (d, J = 7 Hz, 3 H), 1.54 (dq, J = 11 and 7 Hz, 1 H), 1.77 (dd, J = 10 and 8 Hz, 1 H), 2.10 (dddd, J = 11, 10, 6 and 3 Hz, 1 H), 2.78 (dd, J = 14 and 3 Hz, 1 H), 3.5-3.75 (m, 3 H), 3.93 (d, J = 14 Hz, 1 H), 5.81 (s, 5 H), 5.85 (s, 5 H), 7.1-7.6 (m, 5 H); ^{13}C NMR (benzene-d_6) δ 1.44, 23.10, 40.86, 51.08, 60.60, 63.95, 65.28, 109.57, 110.45, 127.12, 128.49, 128.94, 140.32, 148.10.

(14) 10d: ^{1}H NMR (benzene-d_6, benzene) δ 0.25 (s, 9 H), 1.53 (d, J = 7 Hz, 3 H), 1.79 (q, J = 7 Hz, 1 H), 2.35-2.45 (m, 1 H), 2.73 (d, J = 14 Hz, 1 H), 3.23 (s, 1 H), 3.4-3.8 (m, 3 H), 3.92 (d, J = 14 Hz, 1 H), 5.73 (s, 5 H), 5.85 (s, 5 H), 7.1-7.6 (m, 5 H); ^{13}C NMR (benzene-d_6) δ 1.47, 22.95, 31.28, 38.46, 60.72, 64.86, 109.17, 110.54, 111.00, 128.30, 128.49, 128.97, 140.35, 143.48.

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