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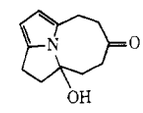

i

following spectral data: NMR ($CDCl_3$) τ 4.2 (AB q, 2 H, J = 3.1 Hz), 7.5 (m, 13 H); IR (KBr) 3280 (OH), 1690 cm^{-1} (C=O); MS *m/e* 205 (M^+), 204, 106, 92.
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Synthesis of Bicyclo[2.2.2]octenes and Bicyclo[3.2.2]nonenes by π-Cyclization

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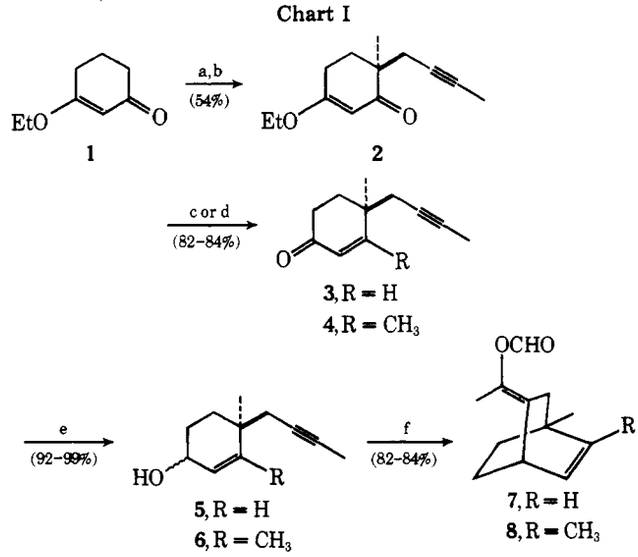
The (2-butynyl)cyclohexenols **5**, **6**, and **12** undergo cyclization to bicyclic enol formates **7**, **8**, and **13**, respectively, upon treatment with formic acid at room temperature. The trimethylsilylpropynyl analogue **17** cyclizes in the alternative sense to yield, after hydrolysis and protodesilylation, the bicyclo[3.2.2]nonenone **18**.

π-Cyclization (the interaction of a carbon–carbon multiple bond with a neighboring cationic center) has become an important method for the creation of carbocycles. The most extensive and definitive work in the area is that of Johnson and co-workers and concerns mainly the application of π-cyclization to the synthesis of steroids.[1,2] We have now found that π-cyclization provides a convenient synthesis of bicyclo[2.2.2]octenes and bicyclo[3.2.2]nonenes.

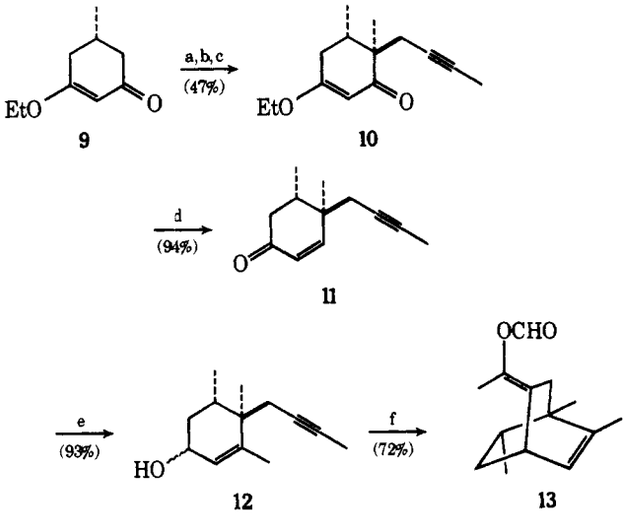
The method is typified by the synthesis of enol formates **7** and **8** (Chart I). Successive alkylation of enol ether **1**[3] by methyl iodide and 1-bromo-2-butyne[4] affords enol ether **2**, which may be reduced or treated with methyllithium to yield, after acid workup, enones **3** or **4**. Reduction of these materials affords allylic alcohols **5** and **6**. When these allylic alcohols are dissolved in 98% formic acid and kept at room temperature for 2 h, bicyclic enol formates **7** and **8** are produced in good yield (33–38% overall from enone **1**). The structures assigned are consistent with elemental compositions, infrared spectra, and both proton and carbon nuclear magnetic resonance spectra of the two compounds. Only one stereoisomer is produced in each case. Although the geometry of the double bond is unknown, it is probably *E*, as depicted in Chart I (anti addition).

Chart I



a, lithium diisopropylamide (LDA), THF, −78 °C, CH_3I; b, LDA, THF, −78 °C, $CH_3C{\equiv}CCH_2Br$; c, $LiAlH_4$, ether, H_3O^+; d, CH_3Li, H_3O^+; e, $LiAlH_4$; f, HCO_2H, 25 °C

Chart II

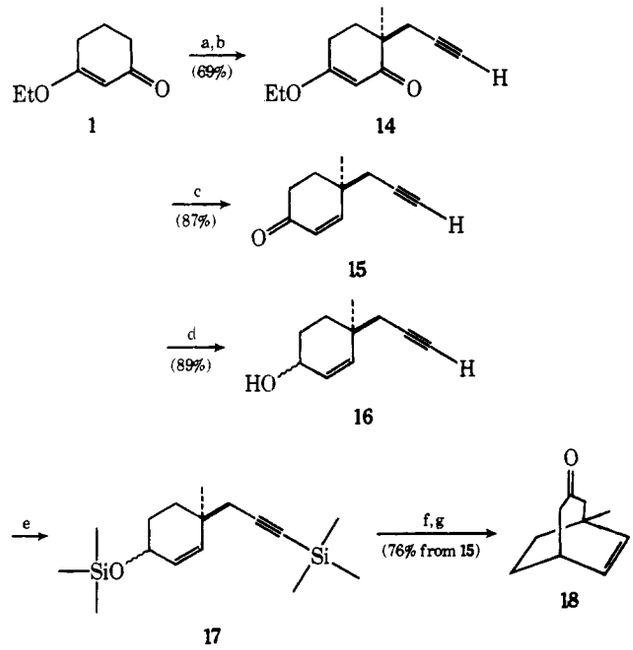


a, LDA, THF, −78°C, CH_3I; b, LDA, THF, −78°C, $CH_3C{\equiv}CCH_2Br$; c, recrystallize; d, CH_3Li; e, $LiAlH_4$; f, HCO_2H, 25 °C

To further explore the scope of this method of forming bicyclo[2.2.2]octenes, we have converted the methylated enol ether 9[5] into compound 13 (Chart II). Successive alkylations of 9 yield a mixture of stereoisomers in which isomer 10 predominates and may be obtained in a pure state by recrystallization.

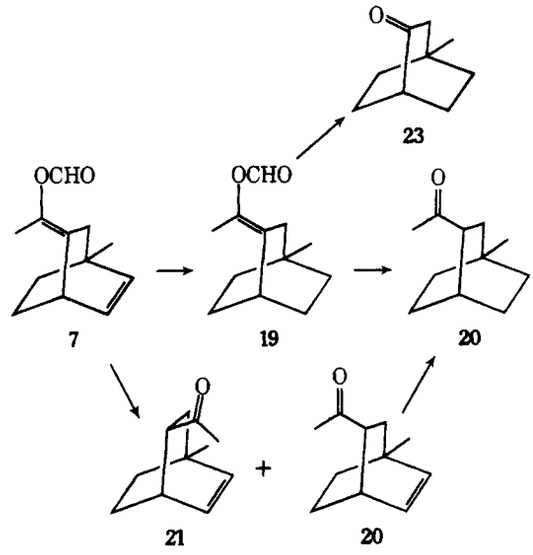
By a simple modification, the method provides a synthesis of the bicyclo[3.2.2]nonenone 18 in 41% overall yield (Chart III). In this case, cyclization of the allylic cation probably occurs at the terminus of the propargyl chain so as to avoid placing a positive charge adjacent to the electropositive silicon atom.

Chart III



a, LDA, THF, −78°C, CH_3I; b, LDA, THF, −78°C, $HC{\equiv}CCH_2Br$; c, $LiAlH_4$, H_3O^+; d, $LiAlH_4$; e, *n*-BuLi, $(CH_3)_3SiCl$; f, HCO_2H, 25 °C; g, KOH, CH_3OH, H_2O

The difunctional compounds produced in these reactions may have synthetic utility. For example, catalytic hydrogenation of 7 (10% Pd/C in C_2H_5OH) affords enol formate 19. The enol formate double bond is quite resistant to reduction. Hydrolysis of 19 yields methyl ketone 20. The same methyl ketone is produced by reversing the order of the two operations. Hydrolysis of 7 affords a 3:1 mixture of two unsaturated ketones (21 and 22). Hydrogenation of this mixture yields 20. Ozonization of enol formate 19 yields bicyclo[2.2.2]octanone 23.



Experimental Section[6]

Alkylation of Enones 1 and 9. These compounds were alkylated by the procedure of Danheiser and Stork.[3] After introduction of the first alkyl group, the product was distilled and alkylated again with the second alkyl halide. The following compounds were prepared.

3-Ethoxy-6-(2-butynyl)-6-methylcyclohex-2-enone (2). Enol ether 1 was alkylated first with 1-bromo-2-butyne and then with methyl iodide to provide 2 in 45% yield or in the reverse order to provide 2 in 54% yield. The product is a clear liquid with bp 95–100 °C (0.05–0.08 Torr): ^1H NMR 1.07 (3, s), 1.37 (3, t, J = 7 Hz), 1.77 (3, t, J = 1.5), 3.95 (2, q, J = 7 Hz), 5.13 ppm (1, s).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.55; H, 8.69. HRMS: Found, 206.1311.

3-Ethoxy-6-(2-propynyl)-6-methylcyclohex-2-enone (14). Enol ether 1 was alkylated first with methyl iodide and then with propargyl bromide to provide 14 in 54% yield. The product is a clear liquid with bp 70 °C (0.01 Torr): ^1H NMR 1.11 (3, s), 1.37 (3, t, J = 7 Hz), 3.92 (2, q, J = 7 Hz), 5.12 ppm (1, s).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.44. HRMS: Found, 192.1131.

(5*S*,6*R*)-3-Ethoxy-6-(2-butynyl)-5,6-dimethylcyclohex-2-enone (10).[7] This material was prepared by successive alkylations of enol ether 9 with methyl iodide and 1-bromo-2-butyne.[8] The distilled product [bp 120 °C (0.03 Torr)], obtained in 59% yield, is contaminated by approximately 20% of the diastereomer having trans methyl groups. The pure cis product (mp 76–77 °C) is obtained by recrystallization from light petroleum ether: ^1H NMR (360 MHz, 1% in $CDCl_3$) 0.91 (3, s), 0.97 (3, d, J = 6.4 Hz), 1.32 (3, t, J = 7.2 Hz), 1.70 (3, t, J = 2.4 Hz), 2.06 (1, dq, J = 16.4 and 2.4 Hz), 2.22 (1, ddd, J = 1.5, 10, and 17.5 Hz), 2.37 (1, dd, J = 5 and 17.5 Hz), 2.53 (1, ddq, J = 5, 6.4, and 10 Hz), 2.77 (1, dq, J = 2.4 and 16.4 Hz), 3.86 (2, m, diastereotopic OCH_2CH_3), 5.26 ppm (1, d, J = 1.5 Hz).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.51; H, 9.17. HRMS: Found, 220.1457.

By reversing the order in which the two alkyl groups are introduced, a product consisting of 90% trans isomer and 10% cis isomer (10) is obtained in 44% yield.[9] Recrystallization from *n*-butyl alcohol affords pure trans isomer: mp 85–87 °C; ^1H NMR 1.00 (3, d, J = 6 Hz), 1.17 (3, s), 1.37 (3, t, J = 7 Hz), 1.75 (3, t, J = 2 Hz), 3.88 (2, q, J = 7 Hz), 5.07 ppm (1, s).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.06; H, 9.13.

4-(2-Butynyl)-4-methylcyclohex-2-enone (3). A solution of 15.45 g (75 mmol) of enol ether 2 in 150 mL of ether is cooled to 0 °C in an ice bath and 2.85 g of $LiAlH_4$ is added. After 2 h at 25 °C, the reaction is worked up by successive additions of 3 mL of water, 3 mL of 15% aqueous NaOH, and 9 mL of water. The ether solution is filtered. After drying and evaporation, the crude enone is obtained as a yellow oil. Distillation of this material gives 9.95 g (82%) of pure enone 3: bp 75 °C (0.1 Torr); IR 1677 cm^{-1}; ^1H NMR 1.23 (3, s), 1.78

(3, t, J = 2 Hz), 5.78 (1, d, J = 10 Hz), 6.70 ppm (1, d, J = 10 Hz).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.15; H, 8.56. HRMS: Found, 162.1035.

4-Methyl-4-(2-propynyl)cyclohex-2-enone (15). Enone **15** is prepared from enol ether **14** by the same procedure as that used for the preparation of enone **3**: IR 3300, 2120, 1678 cm^{-1}; ^1H NMR 1.27 (3, s), 5.83 (1, d, J = 10 Hz), 6.73 ppm (1, d, J = 10 Hz).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.79; H, 8.08. HRMS: Found, 148.0869.

4-(2-Butynyl)-3,4-dimethylcyclohex-2-enone (4). To a solution of 2.06 g (10 mmol) of enol ether **2** in 50 mL of dry ether at −10 °C is added 10 mL of 2 M methyllithium in ether. The solution is allowed to warm to room temperature over a 1.5-h period and is then washed with 100 mL of 15% aqueous HCl. After a normal workup, 1.48 g of enone **4** is obtained as a pale yellow liquid (84%): IR 1672, 1618 cm^{-1}; ^1H NMR 1.20 (3, s), 1.77 (3, t, J = 2 Hz), 1.92 (3, d, J = 1.2 Hz), 5.70 ppm (1, broad s). This compound was not further purified, but was directly converted into enol formate **8**.

(4*R*,5*S*)-4-(2-Butynyl)-3,4,5-trimethylcyclohex-2-enone (11).[7] Enone **11** is prepared from enol ether **10** by the same procedure as that used for the preparation of enone **4**. The material is obtained as an analytically pure off-white solid, mp 77–80 °C, in 98% yield: ^1H NMR 0.97 (3, d, J = 7 Hz), 1.00 (3, s), 1.73 (3, t, J = 2 Hz), 1.83 (3, d, J = 1 Hz), 5.73 ppm (1, broad s).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.88; H, 9.43. HRMS: Found, 190.1403.

Conversion of Enones 3, 4, and 11 into Bicyclo[2.2.2]octenes. The first step of this two-stage conversion is reduction of the enone with lithium aluminum hydride in ether. The enone to be reduced (8 mmol) is dissolved in 30 mL of dry ether, cooled to −10 °C, and 8 mmol of $LiAlH_4$ is added. The solution is stirred magnetically and allowed to warm to room temperature over a 1-h period. After being worked up in the normal manner (see procedure for preparation of compound **3**), the allylic alcohol is obtained, usually as a clear or pale yellow oil. ^1H NMR analysis reveals that all of the allylic alcohols are diastereomeric mixtures. In general, these materials were not subjected to combustion analysis or mass spectroscopy, but were used in crude form for subsequent cyclization.

The following cyclization procedure is typical.

(*E*)-5-(1-Formyloxyethylidine)-1-methylbicyclo[2.2.2]oct-2-ene (7). A solution of 8.95 g of allylic alcohol **5** in 200 mL of 97% formic acid is stirred at room temperature for 2 h. The solution is carefully poured into 250 mL of ice-cold 50% aqueous NaOH. The resulting mixture is extracted with ether and the resulting ether solution dried and evaporated to obtain bicyclic enol formate **7** as a dark oil. Kugelrohr distillation affords 8.68 g of **7** as a clear liquid (82%).

The enol formate produced by this workup procedure is typically contaminated with 5–15% of a 1:1 mixture of methyl ketones **21** and **22**, which are formed by base-catalyzed hydrolysis of **7**. This problem may be minimized by using anhydrous formic acid and evaporating the solvent after cyclization. However, even this modification still yields a product which is contaminated by a few percent of hydrolyzed material, perhaps as a result of the equivalent of water which is produced in the reaction. For example, a solution of 250 mg of allylic alcohol **5** in 5 mL of light petroleum ether is diluted with 25 mL of anhydrous formic acid (distilled from boric anhydride) and kept at room temperature for 2 h. The solvent is removed by evaporation at 0.5 Torr to afford 270 mg (93%) of nearly pure enol formate **7**, which is purified by distillation [bp 60–65 °C (0.01 Torr)]: IR 1733, 1149 cm^{-1}; ^1H NMR 1.16 (3, s), 1.87 (3, t, J = 1.5 Hz), 3.23 (1, broad d, J = 6.5 Hz), 5.97 (1, dd, J = 1.5 and 8.5 Hz), 6.23 (1, dd, J = 6.5 and 8.5 Hz), 7.92 ppm (1, s); ^{13}C NMR 15.57, 24.50, 26.73, 32.22, 33.94, 34.77, 39.03, 128.45, 131.23, 134.95, 139.32, 158.78 ppm.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.27; H, 8.53. HRMS: Found, 192.1153.

The following compounds were also prepared.

(*E*)-5-(1-Formyloxyethylidine)-1,2-dimethylbicyclo[2.2.2]-oct-2-ene (8). The product as obtained is contaminated with varying amounts of hydrolyzed material (vide supra). An analytical specimen was obtained by preparative GLC (5 ft × 0.25 in. Carbowax at 170 °C, He flow 30 mL min^{-1}, retention time 7.0 min): ^1H NMR 1.13 (3, s), 1.73 (3, d, J = 1.5 Hz), 1.87 (3, t, J = 1.5 Hz), 3.13 (1, m), 5.87 (1, broad d, J = 6 Hz), 7.87 ppm (1, s); ^{13}C NMR 15.46, 17.02, 22.22, 26.61, 32.45, 34.23, 37.16, 39.07, 124.93, 128.63, 134.42, 144.66, 158.94 ppm.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.39; H, 8.58. HRMS: Found, 206.1339.

(*E*)-(1*R*,7*S*)-5-(1-Formyloxyethylidine)-1,2,7-trimethylbicyclo[2.2.2]oct-2-ene (13).[7] The analytical sample was obtained by preparative GLC (5 ft × 0.25 in. Carbowax at 170 °C, He flow 30 mL min^{-1}, retention time 7.8 min): ^1H NMR 0.97 (3, d, J = 7 Hz), 1.12 (3, s), 7.90 ppm (1, s).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.70; H, 8.96. HRMS: Found, 220.1441.

1-Methylbicyclo[3.2.2]non-6-en-2-one (18). Enone **15** is reduced by the same method as that outlined previously for the reduction of enones **3, 4,** and **11**; allylic alcohol **16** is isolated in 87% yield. A solution of 2.67 g (17.8 mmol) of this material in 150 mL of dry ether is cooled to −70 °C and treated with 25 mL (50 mmol) of 2 M *n*-butyllithium. The resulting heterogeneous mixture is allowed to warm to room temperature over a 2-h period. Trimethylsilyl chloride (6.85 g, 63 mmol) is added and the mixture is kept at room temperature overnight. The mixture is filtered through a fine filter paper (Whatman 40) and evaporated to obtain 4.16 g (80%) of compound **17**. This material is dissolved in a mixture of 150 mL of 97% formic acid and 15 mL of ether, then kept at room temperature for 5 h. After a normal workup, 2.45 g of dark oil is obtained. ^1H NMR analysis shows that this material is an enol formate and contains trimethylsilyl resonances. It is dissolved in 100 mL of methanol and 50 mL of 1 M aqueous KOH is added. After 5 h at room temperature, the solution is evaporated to a gummy semisolid which is partitioned between 10% HCl and ether. After drying and evaporation, the ether layer affords 1.66 g (76%) of enone **18** as a dark liquid. GLC analysis (0.25 in. × 5 ft OV-101 at 130 °C) reveals that the product is homogeneous. An analytical specimen was obtained by preparative GLC: IR 1704 cm^{-1}; ^1H NMR 1.14 (3, s), 6.00 (1, d, J = 9 Hz), 6.30 ppm (1, dd, J = 7 and 9 Hz).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.10; H, 9.41. HRMS: Found, 150.1082 (49.22% relative to *m/e* 93).

(*E*)-3-(1-Formyloxyethylidine)-1-methylbicyclo[2.2.2]octane (19). To a solution of 0.5 g of bicyclic enol formate **7** in 30 mL of ethanol is added 50 mg of 10% palladium on carbon. The mixture is stirred at atmospheric pressure with hydrogen gas for 2 h. The catalyst is removed by filtration to obtain 440 mg (87%) of enol formate **19** as a clear liquid. The analytical sample was obtained by preparative GLC (5 ft × 0.25 in. Carbowax): ^1H NMR 0.87 (3, s), 1.72 (3, s), 2.37 ppm (1, broad t).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.91; H, 9.13. HRMS: Found, 194.1320.

4-Methylbicyclo[2.2.2]octan-2-one (23). A solution of 0.5 g of enol formate **19** dissolved in 15 mL of methanol and 15 mL of methylene chloride is cooled to −78 °C and ozone (generated with a Welshbach Ozonator) is passed through until the solution turns blue. After adding 2 mL of dimethyl sulfide, the solution is warmed to room temperature and stirred for 1 h. The mixture is concentrated on a rotary evaporator and the residue partitioned between pentane and water. Evaporation of the dried pentane layer affords 340 mg (96%) of ketone **23** as a light yellow liquid: IR 1724 cm^{-1}; ^1H NMR 0.98 (3, s), 2.00 (2, s), 2.17 ppm (1, broad t).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.17; H, 9.81. HRMS: Found, 138.1029.

3-Acetyl-1-methylbicyclo[2.2.2]octane (20). Enol formate **19** (1.65 g) is added to 25 mL of 0.35 M KOH in methanol. After 2 h, the mixture is neutralized with concentrated HCl. The mixture is concentrated under reduced pressure to a yellow oil which is taken up in ether, dried over $MgSO_4$, and filtered. Removal of the ether affords 1.46 g of ketone **20** as a pale yellow liquid: IR 1709 cm^{-1}; ^1H NMR 0.80 (3, s), 1.87 ppm.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.53; H, 10.84. Found: C, 79.43; H, 10.69. HRMS: Found, 166.1386.

(4*S*,5*S*)-5-Acetyl-1-methylbicyclo[2.2.2]oct-2-ene (21) and (4*S*,5*R*)-5-Acetyl-1-methylbicyclo[2.2.2]oct-2-ene (22).[7] Hydrolysis of enol formate **7**, by essentially the same procedure as that given above for the hydrolysis of **19**, affords a 3:1 mixture of ketones **21** and **22** in 95% yield. The two isomers have retention times on GLC (6 ft × 0.25 in. Carbowax at 120 °C) of 2.7 and 3.4 min, respectively. The major product (retention time 3.4 min) was collected by preparative GLC for analysis: IR 1710 cm^{-1}; ^1H NMR 1.17 (3, s), 2.00 (3, s), 6.00 ppm (2, m).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.35; H, 9.75. HRMS: Found, 164.1200.

The minor component (retention time 2.7 min) was not isolated in a pure state. From the mixture of **21** and **22**, it may be deduced that the minor isomer has ^1H NMR signals at 1.17 (3, s) and 2.10 ppm (3, s). Atmospheric hydrogenation of the mixture over 10% Pd/C in ethanol affords ketone **20**, identical spectrally with the material prepared previously.

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onance Laboratory for instructing us in the use of the HX-360 spectrometer.

Registry No.—1, 5323-87-5; 2, 61484-02-4; 3, 61484-03-5; 4, 61484-04-6; *cis*-5, 61484-05-7; *trans*-5, 61484-06-8; *cis*-6, 61484-07-9; *trans*-6, 61505-79-1; 7, 61484-08-0; 8, 61484-09-1; 9, 61484-10-4; *cis*-10, 61484-11-5; *trans*-10, 61484-12-6; 11, 61484-13-7; 12 isomer A, 61505-42-8; 12 isomer B, 61484-14-8; 13, 61484-15-9; 14, 61484-16-0; 15, 61484-17-1; *cis*-16, 61484-18-2; *trans*-16, 61484-19-3; *cis*-17, 61484-20-6; *trans*-17, 61484-21-7; 18, 61484-22-8; 19, 61484-23-9; 20, 61484-24-0; 21, 61484-25-1; 22, 61521-26-4; 23, 40291-46-1; 1-bromo-2-butyne, 3355-28-0; methyl iodide, 74-88-4; propargyl bromide, 106-96-7; formic acid, 64-18-6; trimethylsilyl chloride, 75-77-4; ozone, 10028-15-6.

References and Notes

(1) See W. S. Johnson, K. Wiedhaup, S. F. Brady, and G. L. Olson, *J. Am. Chem. Soc.*, **96**, 3979 (1974), and previous papers in the series.
(2) For applications of π-cyclization to the synthesis of other types of systems, see, inter alia, (a) R. A. Volkmann, G. C. Andrews, and W. S. Johnson, *J. Am. Chem. Soc.*, **97**, 4777 (1975); (b) S. Murayama, D. Chan, and M. Brown, *Tetrahedron Lett.*, 3715 (1968); (c) J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968).
(3) R. L. Danheiser and G. Stork, *J. Org. Chem.*, **38**, 1775 (1973).
(4) L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, 1971, p 158.
(5) J. P. Blanchard and H. L. Goering, *J. Am. Chem. Soc.*, **73**, 5863 (1951).
(6) Infrared spectra (IR) were measured as neat films on a Perkin-Elmer 137 infrared spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were measured in CCl_4 on a Varian T-60 or a Bruker HX-360 nuclear magnetic resonance spectrometer. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ) and are followed in parentheses by the integrated area, multiplicity, and coupling constant in hertz. Carbon magnetic resonance spectra (^{13}C NMR) were measured in $CDCl_3$ on a Nicolet TT-23 nuclear magnetic resonance spectrometer operating at 25.14 MHz. Chemical shifts are referenced to $CDCl_3$ and are reported in parts per million downfield from tetramethylsilane (central peak of $CDCl_3$ triplet = 1936 Hz).
(7) These products are racemic. The name given is that of the enantiomer depicted in the text.
(8) This experiment was first carried out by Phillip Nies.
(9) This experiment was first carried out by Mario Curzi.

Intramolecular 1,3-Dipolar Cycloadditions of Nitrile Imines Bearing an Alkenyl Substituent

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Two series of nitrile imines bearing an alkenyl substituent were generated in situ from the corresponding 1-chlorohydrazones by treatment with triethylamine in aromatic hydrocarbon solvents. The intramolecular 1,3-dipolar cycloaddition, leading to fused ring 2-pyrazolines, was the exclusive or the predominant reaction with few exceptions. Retention of stereochemistry was observed in the case of 1,2-disubstituted ethylenic functions.

1,3-Dipolar cycloadditions are well known for their utility in heterocyclic syntheses as well as for the interesting mechanistic questions which they raise. In recent years, intramolecular examples have been reported to give fused or bridged ring heterocycles.[2] In these cases, observations have often been in contrast with the usual intermolecular patterns, particularly regarding orientation.

In this context, we now report an extensive study on the behavior of nitrile imines containing a carbon–carbon double bond potentially able to behave as a dipolarophile. In order to investigate electronic and steric effects on these intramolecular reactions, the nitrile imines **4a–e** and **10a–c** were studied (Charts I and II).

Chart I

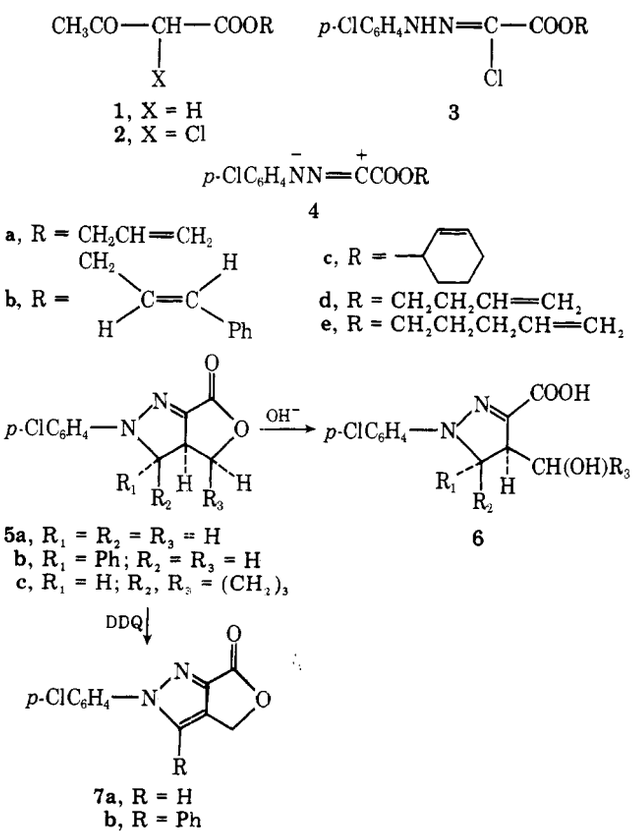

Chart II