were appropriate dried prior to use.

General Procedure. To a magnetically stirred solution of α,β-unsaturated aldehyde (1.7 mmol) in 1.5 mL of dry solvent, in a round-bottomed flask equipped with an Ar inlet and $CaSO_4$ drying tube, was added ylide **5**[3,11] (1.7 mmol) all at once. Stirring was continued for 18 h at room temperature. The solution was concentrated under reduced pressure to give the formylcyclopropanecarboxylates as crude oils, which were purified by distillation under reduced pressure or by column chromatography.

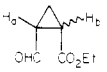
Ethyl 2-Methyl-2-formylcyclopropanecarboxylates (1 and 2). To 5.4 g (77 mmol) of **6** in 50 mL of acetone was added 11.4 g (77 mmol) of ylide **5**. Workup as above afforded 10.9 g of crude **1/2** as an oil. Short-path vacuum distillation afforded 10.0 g (83%) of **1/2** as a clear oil: bp 51-53 °C (0.3 mmHg) [lit.[3] bp 45 °C (<1 mmHg)]; TLC (hexanes/EtOAc 3:1) R_f 0.35; IR 2990, 1721 (br) cm^{-1}; UV (95% EtOH) λ_{max} 210 nm (ϵ 1828), 280 nm (ϵ 56).

The two isomers were separated by HPLC (Zorbax-Sil; CH_2Cl_2/hexane, 52:48) to give *cis*-**1** [t_R 22.5 min; NMR ($CDCl_3$) δ 1.26 (s, 3, CH_3), 1.27 (t, 3, CH_2CH_3, J = 7.5 Hz), 1.41 (m, 1, H_c), 2.08 (br s, 1, H_b), 2.10 (m, 1, H_a), 4.17 (q, 2, $COCH_2$, J = 7.5 Hz), 9.37 (s, 1, CHO)] and *trans*-**2** [t_R 17.5 min; NMR ($CDCl_3$) δ 1.40 (s, 3, CH_3), 1.30 (t, 3, CH_2CH_3, J = 7.5 Hz), 1.50-1.58 (m, 2, H_b and H_c), 2.24 (s, 1, H_a), 4.20 (q, 2, $COCH_2$, J = 7.5 Hz), 8.87 (s, 1, CHO)].

A sample of *trans*-**2** was readily air-oxidized in dilute $CHCl_3$ solution to cleanly give the trans acid ester which was hydrolyzed (1 N HCl) to provide crude *trans*-1-methyl-1,2-cyclopropanedicarboxylic acid. Two crystallizations from CH_3CN afforded clean diacid: mp 169-171 °C (lit.[9] mp 168 °C).

Ethyl 2-Formylcyclopropanecarboxylates (3 and 4). To 95 mg (1.7 mmol) of **7** in 1.5 mL of acetone was added 250 mg (1.7 mmol) of ylide **5**. Workup as above provided crude **3/4** as a viscous red oil. Column chromatography with $CHCl_3$/MeOH (99:1) elution afforded 155 mg (65%) of **3/4** as a clear oil: TLC ($CHCl_3$/MeOH 10:1) R_f 0.72; IR 2994, 1720 (br) cm^{-1}; UV (hexane) λ_{max} 203 nm (ϵ 1126), 284 (ϵ 27).

The two isomers were separated by HPLC (Zorbax-Sil; CH_2Cl_2/hexane, 41:59) to give *cis*-**3** [t_R 22 min; NMR ($CDCl_3$) δ 1.28 (t, 3, CH_3, J = 7.5 Hz), 1.54 (m, 2, CH_2), 1.94 (m, 1, H_b), 2.06 (m, 1, H_a), 4.28 (q, 2, $COCH_2$, J = 7.5 Hz), 9.35 (d, 1, CHO, J = 4 Hz)] and *trans*-**4**: [t_R 19 min; NMR ($CDCl_3$) δ 1.29 (t, 3, CH_3, J = 7.5 Hz), 1.53 (m, 2, CH_2), 2.26 (m, 1, H_b), 2.45 (m, 1, H_a), 4.29 (q, 2, $COCH_2$, J = 7.5 Hz), 9.31 (d, 1, CHO, J = 3.5 Hz).



Kinetic Studies. In an Ar-flushed 178 mm × 5 mm o.d. NMR tube was dissolved 16 mg (0.23 mmol) of **6** in 0.5 mL of benzene-d_6 or acetone-d_6. Base-line spectra were recorded by FT-NMR at 270 MHz, then 36 mg (0.24 mmol) of ylide **5** in 0.5 mL of the appropriate d_6 solvent was added. Spectra were collected for 25 s at appropriate intervals, and the relative amounts of **6** and product (**1/2**) were determined by integration of the aldehydic proton region where there was no overlap of resonances for the three species in either solvent.

Acknowledgment. We thank the National Cancer Institute for the financial support of R.W.C., Jr., in the form of a fellowship. Helpful discussions on ^1H NMR interpretations with Dr. Brad Helmer are acknowledged. We also express our gratitude to Ms. Pat Mings for the preparation of this manuscript.

Registry No. *cis*-**1**, 13950-14-6; *trans*-**2**, 13949-97-8; *cis*-**3**, 13950-12-4; *trans*-**4**, 13949-93-4; **5**, 7380-81-6; **6**, 78-85-3; **7**, 107-02-8; *trans*-1-methyl-1,2-cyclopropanedicarboxylic acid, 697-49-4.

(11) The sulfur ylide was prepared in high yield according to Payne[3] and was found to be stable for 2-4 weeks under Ar at -20 °C while protected from light. However, this compound was rapidly destroyed when exposed to short-wavelength UV light.

The Oxime Rearrangement Cyclization. Synthesis of Alkylidene-Δ^1-pyrrolines

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Appropriately functionalized alkenyl oximes cyclize to Δ^1-pyrrolines when treated with trimethylsilyl polyphosphate (PPSE) in refluxing CCl_4. The reaction is stereospecific, and the reaction conditions do not cause oxime isomerization at a rate comparable to rearrangement cyclization. Terminators found to be compatible with PPSE are trisubstituted olefins and styryl groups; some vinyl chlorides may be used under more forcing conditions (P_2O_5/CCl_4/reflux). Alkenyl amides also cyclize under the stated conditions via a nitrilium ion transition state.

Introduction

The field of cationic cyclizations as a tool for organic synthesis has blossomed in recent years largely due to the pioneering work of the Johnson group. Johnson has concluded that the only two good initiators for cationic cyclizations in the carbocycle series are stabilized ions derived from acetals and allylic alcohols. Thus, much of the work in recent years has been in the development of efficient cyclization terminators.[1] These studies have had several objectives in common, among which are assistance (i.e., rate enhancement) in the cyclization, minimization of product multiplicity arising from carbonium ion rearrangements, random deprotonations, etc., and manipulation of ring size. Both olefinic[2] and acetylenic/allenic[3] terminators have

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(2) Other than unfunctionalized alkenes, the following sp^2-hybridized nucleophiles have been shown to be efficient cationic cyclization terminators. **Enol ethers**: (a) Felkin, H.; Lion, C. *Tetrahedron* **1971**, *27*, 1387-1401, 1403-1408; *Chem. Commun.* **1968**, 60-61. **Chloro olefins**: (b) Lansbury, P. T. *Acc. Chem. Res.* **1972**, *5*, 311-320. **Fluoro olefins**: (c) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800-7802. **Allylsilanes**: (d) Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*, 513-518. (e) Fleming, I.; Pearce, A.; Snowden, R. L. *J. Chem. Soc., Chem. Commun.* **1976**, 182-183. (f) Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 251-255. **Vinylsilanes**: (g) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851-1853. (h) Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297-5300. **Styrenes**: (i) Johnson, W. S.; Hughes, L. R.; Carlson, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1281-1282. (j) Closson, W. D.; Roman, S. A. *Tetrahedron Lett.* **1966**, 6015-6020. (k) Garst, M. E., Cheung, Y.-F.; Johnson, W. S. *J. Am. Chem. Soc.* **1979**, *101*, 4404-4406.

0022-3263/84/1949-1946$01.50/0

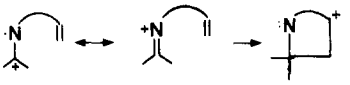
Table I. Rearrangement Cyclization Yield Study for Oxime 1[a]

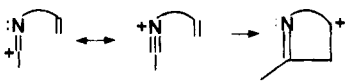
Lewis acid	PCl_5	P_2O_5	$AlCl_3$	$SnCl_4$	$ZnBr_2$	PPSE[b]
toluene	33	67	<1	1	3	
glyme	41	69	2	0	NR	
ether	16	46	NR	4	9	
acetonitrile	29	25	0	6		
nitromethane	9	48	12	11	9	
carbon tetrachloride	4	73	11	30	7	74
ethylene chloride	20	64	6	6	0	

[a] Reactions were run on an E/Z mixture of isomers (thermodynamic) at reflux using an excess of acid and worked up by partitioning between 10% HCl and ether. Neutralization of the aqueous acid fraction and extraction with $CHCl_3$ afforded the product in the yields shown. In several cases, a mixture of products was produced; the yields shown reflect a GC analysis of the product mixture. Thus, a 0% yield means that products other than 1 were formed, while NR indicates recovery of starting material. [b] Trimethylsilyl polyphosphate (PPSE) was reported as a reagent for the Beckmann rearrangement subsequent to completion of this yield study but is included here for comparison purposes. See text and ref 18.

been utilized.

Our interest in this area centers around the utilization of nitrogen-stabilized cations as initiators as a means to form heterocycles. Two oxidation states may be envisioned for the nitrogen-stabilized cation: an iminium or a nitrilium ion, as illustrated in eq 1 and 2, respectively. There


[1]


[2]

are advantages and disadvantages to each approach, but a critical feature that we find intriguing is the obtention of an *imine* vs. an *amine* as a cyclization product in the latter case. The utility of an imine as a functional group that might direct further reactivity (e.g., by alkylation) or functional group modification (e.g., reduction, transamination) might well serve a useful purpose during the course of a natural product synthesis, for example.

Iminium ion cyclizations have been well-studied by Speckamp[4] and others[2g,5] to the extent that the use of iminium ion cyclizations in synthesis is now routine. Nitrilium ion cyclizations, on the other hand, have not been developed as fully, chiefly because mild methods for the generation of a given nitrilium ion have not been available. Alkylation of nitriles (the Ritter reaction[6]) has been used to generate a wide variety of heterocycles by cationic cyclization.[7] Olefinic nitriles were tested as cationic cyclization substrates in the carbocycle series using Meerwein salt as a catalyst, but the products were obtained in only modest yield.[8]

Oximes have been used as nitrilium ion sources for carbocycle synthesis,[9] a process that occurs by a Beckmann fragmentation[10] mechanism, but the reported yields were low. Nitrilium ions produced by Beckmann rearrangement[11] of oximes are used as the key step in the synthesis of several isoquinolines,[12] a process viewed as a variant of the Bischler–Napieralski reaction.[13] For aliphatic cationic cyclizations, oximes appear to be particularly inviting for the construction of cyclization substrates because of their facility for regiospecific deprotonations and alkylations.[14] When this fact is coupled with the well-known stereospecificity of the Beckmann rearrangement, it becomes obvious that a method is available for the preparation of a number of nitrilium ion precursors under conditions amenable to other synthetic manipulations. It remains only to find a suitable set of conditions for a Beckmann rearrangement–cyclization sequence that (a) does not catalyze the rate of oxime E/Z isomerization at a significant rate, (b) affords a single cyclization product in predominance over others, and (c) is compatible with other functional groups. We now report the details of the initial phase of our investigation of this process, including a search for a mild set of reaction conditions and the testing of several different terminators.[15,16]

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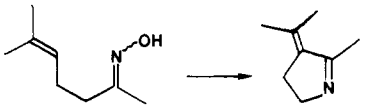
Results

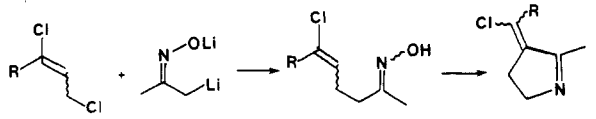
The oxime of 6-methylhept-5-en-2-one, **1**, was treated with a series of Lewis acids, all of which are either reported to effect the Beckmann rearrangement or are used in other cationic cyclizations, under anhydrous conditions, in an effort to maximize the yield of 3-isopropylidene-2-methyl-Δ^1-pyrroline, **2**.[17] The results are shown in Table



1 **2**

I. Trimethylsilyl polyphosphate, PPSE, was reported recently[18] as a useful reagent for the Beckmann rearrangement and was shown to be an excellent reagent for the rearrangement cyclization, albeit subsequent to the completion of the rest of the yield study. Whereas our preliminary account recommends P_2O_5 in refluxing toluene, carbon tetrachloride, ethylene chloride, or glyme as the optimal conditions (time needed 10–20 h), we now recommend PPSE as the reagent of choice. The reactions are cleaner and faster, and PPSE is compatible with sensitive functionality, such as esters.[18] All of the reactions reported herein (except **7** → **9**) were accomplished on a mixture of oxime geometric isomers, the ratio of which was that of the thermodynamically equilibrated starting materials.[19]

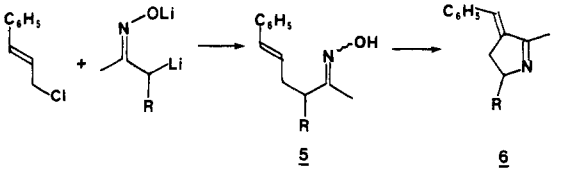
Two other terminators were tested: the vinyl chloride[2b] and styryl[2i,j,k] groups. Condensation of acetone oxime dianion with 1,3-dichloro-2-butene and 1,3-dichloropropene afforded (*Z*)-**3a** and (*Z*)-**3b**, which were equilibrated to their thermodynamic C=N stereoisomer ratios (ca. 70% *E*) during the course of purification by column chromatography or vacuum distillation. Treatment of **3a** with P_2O_5 in refluxing toluene afforded **4a** as a mixture of *E* and *Z* isomers (ca. 1:1) in 50% yield. Treatment of **3b** with P_2O_5 in refluxing CCl_4 and treatment of either **3a** or **3b** with PPSE in refluxing CCl_4 failed to produce significant yields of **4a** or **4b**, even after refluxing overnight.



3 **4**

(a) R=CH$_3$ (b) R=H

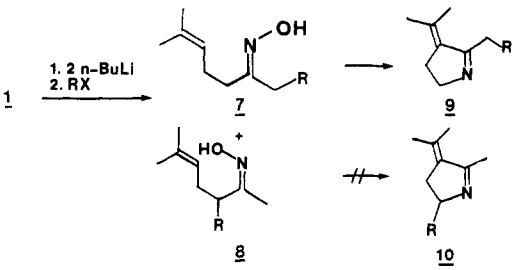
To test the utility of the styryl group, oxime **5a** was prepared by alkylation of acetone oxime dianion with *trans*-cinnamyl chloride. Treatment of the thermodynamic mixture of oxime stereoisomers (ca. 70% *E*) with P_2O_5 afforded **6a** in 50% yield; similar treatment with PPSE gave **6a** in 59% yield. Moreover, (*Z*)-2-butanone oxime dianion[14c] was alkylated with *trans*-cinnamyl chloride to yield **5b**, which equilibrated to the thermodynamic mixture of oxime stereoisomers during the course of silica gel chromatography. Rearrangement cyclization with P_2O_5 in refluxing CCl_4 afforded pyrroline **6b** in 82% yield.



5 **6**

(a) R=H (b) R=CH$_3$

The dianion of oxime **1** was alkylated with methyl iodide to give a 4:1 mixture (GC analysis) of **7a** and **8a**, which was treated immediately with P_2O_5 in refluxing CCl_4, affording pyrroline **9a** in 44% yield after chromatography. No pyrroline resulting from rearrangement cyclization of **8** (i.e., **10**) was detected. The same dianion was alkylated with 2-methoxyethyl iodide and ethyl bromoacetate, affording **7b**/**8b** and **7c**/**8c** in 74% and 68% yield, respectively. Rearrangement cyclization of **7b**/**8b** with P_2O_5 in refluxing CCl_4 afforded **9b** with no trace of **10b**; while treatment of **7c**/**8c** with PPSE in refluxing CCl_4 afforded **9c** with no trace of **10c**. The yields for the preparation of **9b** and **9c** after chromatography were less than 10%.



7 **8** **9** **10**

(a) R=CH$_3$ (b) R=CH$_2$CH$_2$OCH$_3$ (c) R=CH$_2$CO$_2$C$_2$H$_5$

Discussion

In the search for a reagent that would effect the rearrangement cyclization smoothly, we chose a substrate, **1**, whose terminator (a trisubstituted olefin) is not among those considered to be exceedingly efficient. The rationale for this approach lies in the expectation that success with a "poor" terminator would portend success with more efficient terminators.[2,3] Although numerous products were obtained in several of the cases studied, we chose to maximize the yield of pyrroline **2** on the basis of Meyers' early observation of similar products from his Ritter reaction nitrilium ion cyclizations.[7] Subsequent to our work, Yamamoto observed similar predominance of deprotonation as a major reaction pathway in nitrilium ion cyclizations.[15] Within the error limits of NMR integration,[23] the thermodynamic *E*/*Z* ratio for oxime **1** is 70/30. Table I indicates several experiments where yields in the 70% range are obtained. Since the reaction is stereospecific (vide infra), we can infer nearly quantitative conversion of the *E* isomer to the pyrroline product in these cases.

While the present studies were conducted with the thermodynamic mixture of *E* and *Z* stereoisomers, it was

(16) Portions of this work are taken from the dissertation of E.J.T., University of Miami, 1981, and were presented at the 181st National Meeting of the American Chemical Society, Atlanta, GA, March 29, 1981; ORGN 12. A preliminary account of this work has appeared: Gawley, R. E.; Termine, E. J. *Tetrahedron Lett.* **1982**, *23*, 307–308.

(17) The structure of this product was confirmed by X-ray crystal analysis: Gawley, R. E.; Termine, E. J.; Onan, K. D. *J. Chem. Soc., Chem. Comun.* **1981**, 568–569. We presume that this imine is identical with that obtained earlier by Wallach (identified as 2,3,3-trimethyl-3,6-dihydropyridine: see Wallach, O. *Justus Liebigs Ann. Chem.* **1901**, *319*, 77) and Wagner-Jauregg (not identified by other than its empirical formula: see Wagner-Jauregg, T.; Roth, M. *Helv. Chim. Acta* **1962**, *45*, 771–774).

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(19) Yamamoto has reported that oxime isomers may be separated chromatographically.[15] In our hands, the technique of short column chromatography,[20] which uses TLC grade silica gel, has proven useful on occasion, but attempts to do large-scale separations (≥1.5 g) have met with limited success. Attempts to utilize chromatographic methods that use larger size silica particles (e.g., flash[21] or medium-pressure[22] chromatography) resulted in the destruction of the oxime on the column.

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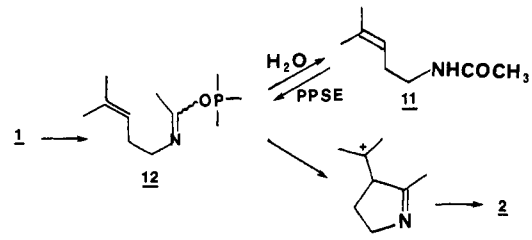
of interest to know whether the reagent used for the rearrangement cyclization was capable of isomerizing the oxime stereoisomers at a comparable rate, since the desired stereoisomer might not always be the thermodynamically favored one. Unfortunately, geometrically pure *E*-oxime stereoisomers are not conveniently available in quantities that we consider preparatively useful.[19] Nevertheless, the absence of pyrrolines **10a–c**, which would have arisen via (*Z*)-**8a–c** → (*E*)-**8a–c** → **10a–c**, affirms the stereospecificity of the reaction.

During the course of the yield study, the Beckmann rearrangement product, amide **11**, was obtained on several occasions. It was found that subjecting **11** to the cyclization conditions afforded pyrroline **2** in high yield. Premature quenching of the reaction affords mixtures of **1**, **2**, and **11**, but resubmission to the reaction conditions ultimately yields only **2**. Similar results were also obtained in the cyclization of styrene oxime **5a**; PPSE treatment of vinyl chloride oximes **3a–b** afforded only the Beckmann amide, which could not be cyclized with PPSE. These experiments suggest that perhaps the cyclization does not proceed via a free nitrilium ion but instead via an intermediate (i.e., **12**) similar to that postulated in the Ritter reaction, the so-called "Ritter intermediate".[6] This imino ester then cyclizes in a concerted manner with the *assistance*[24] of the double bond, as follows:



The styryl group may be utilized as an efficient terminator, but vinyl chlorides appear to work only under forcing conditions. Johnson et al. have reported that vinyl chlorides fail to participate in a polyene cyclization.[2c]

The conversion of (*Z*)-2-butanone oxime into pyrroline **6b** and oxime **1** into **9a–c** illustrates the principle of substituent incorporation prior to cyclization. The reasons for low yield in the cyclization of **7b** and **7c** are not clear, but we believe that the functionalized side chains may be interfering with the formation or cyclization of the postulated imino–ester intermediate.[25]

Summary

The oxime rearrangment cyclization is a stereospecific reaction that produces alkylidene-Δ^1-pyrrolines in high yield. Mild conditions have been identified that do not effect oxime isomerization at a rate that is competitive with rearrangement cyclization. The reagent of choice is trimethylsilyl polyphosphate, PPSE. Terminators that have proven feasible are trisubstituted olefins and styryl groups. Vinyl chloride terminators may be used under the more forcing conditions of P_2O_5 in refluxing toluene. The "nitrilium ion" cyclization substrate may be accessed via rearrangement of the appropriate oxime or via the amide that would be the Beckmann rearrangement product from the oxime. Applications of "nitrilium ion" cyclizations are the subject of ongoing work in our laboratories, and will be reported in due course.

Experimental Section

General Procedures. Chlorinated solvents were reagent grade and were used without purification. Tetrahydrofuran was distilled immediately prior to use from sodium benzophenone ketyl. All other reagents obtained from commercial sources were used without further purification. All reactions were run under an inert atmopshere of nitrogen or argon. Short column chromatography refers to the procedure of Hunt and Rigby;[20] flash chromatography refers to the procedure of Still;[21] medium-pressure chromatography refers to the procedure of Meyers.[22] Gas chromatography (GC) was performed on a Varian 2440-10 chromatograph equipped with flame ionization detectors and 2 m × $^1/_8$ in. stainless steel columns packed with 10% Carbowax 20M + 5% KOH on Chromosorb WAW, 80–100 mesh. Analytical samples of all new compounds were homogeneous by TLC (10–20% acetone in petroleum ether) and/or GC. Spectra were recorded as follows: ^{1}H NMR spectra in $CDCl_3$ (unless otherwise noted) on a Hitachi Perkin-Elmer R-600 spectrometer; ^{13}C NMR spectra in $CDCl_3$ on a Varian FT-80A spectrometer (unless otherwise noted); chemical shift data are in ppm downfield from internal tetramethylsilane. In some cases, hydroxylic protons do not appear between 0 and 10 ppm or are exchanging and are not included in the NMR data summary. IR spectra were recorded as a neat film or as a CCl_4 solution on a Perkin-Elmer 599 spectrometer; peaks are reported in reciprocal centimeters. Temperatures are reported in degrees Celsius and are uncorrected. High-resolution mass spectra were obtained via the Research Triangle Center for Mass Spectrometry, Research Triangle Park, NC.

Preparation of Oximes. 6-Methylhept-5-en-2-one oxime (1) was prepared by oximation of the corresponding ketone[27] by standard procedures[28] and purified by distillation: bp 110–115 °C (8 mm); ^{1}H NMR δ 1.60 (3 H, br s), 1.67 (3 H, br s), 2.27 (3 H, t, J = 1.8 Hz), 2.0–2.5 (4 H, m), 4.9–5.3 (1 H, br m), 9.3–9.6 (1 H, br s); IR 3250, 1665, 1360, 1340 cm^{-1}.

All other oximes were prepared by alkylation of the dianion of either acetone oxime or **1** in tetraydrofuran, using Jung's procedure.[14c] The preparation of **3a** is typical.

6-Chlorohept-5-en-2-one Oxime (3a). To a solution of 1.485 g of acetone oxime (20.3 mmol) in 75 mL of THF at −78 °C was added (via syringe) 27.5 mL of a 1.6 M solution of *n*-butyllithium in hexane over the course of 30 min. The solution was stirred for 20 min at 0 °C and then recooled to −78 °C and treated with 2.80 g of 1,3-dichloro-2-butene.[29] After the solution was stirred for 5 min, the bath was removed, and the reaction was allowed to warm to room temperature for 1 h. The mixture was poured into water and extracted with ether. The combined ether layers were dried with $MgSO_4$ and condensed in vacuo to afford 2.91 g of **3a** (89%). The crude *Z* oxime may be purified either by short column chromatography eluting with 15% acetone in petroleum ether or by vacuum distillation: bp 110 °C (0.6 mm); calcd for $C_7H_{12}ClNO$, M^+ = 161.0607, found 161.0606; ^{1}H NMR δ 1.87 (3 H, s), 2.07 and 2.08 (3 H, s, *E* and *Z* isomers at C-7), 2.2–2.5 (4 H, m), 5.3–5.7 (1 H, m), 7.8–8.3 (1 H, br s); IR 3610, 3280, 1670, 1370 cm^{-1}.

6-Chlorohex-5-en-2-one oxime (3b) was obtained from acetone oxime and 1,3-dichloropropene,[27] crude yield 85–94%, and purified by either short column chromatography eluting with 8% acetone in petroleum ether or by vacuum distillation: bp 79 °C (0.43 mm); calcd for $C_6H_{10}ClNO$, M^+ = 147.0451, found 147.0451; ^{1}H NMR δ 1.59, 1.65, 1.67, 1.72 (3 H, 4 singlets, geometric isomers at C=C and C=N), 1.8–2.4 (4 H, m), 5.2–5.9 (2 H, m) , 9.4–9.8 (1 H, br); IR 3250, 3020, 1665, 1632, 1445, 1370 cm^{-1}.

6-Phenylhex-5-en-2-one oxime (5a) was obtained from acetone oxime and cinnamyl chloride,[27] crude yield 68%, and purified

(24) We use the word assistance in the transitive sense in this instance; by was of contrast, participation is derived from an intransitive verb.

(25) It is also possible that the rate of oxime isomerization has been altered appreciably in these compounds. Work in progress indicates that the rate of oxime isomerization is somewhat substitutent dependent. For example, aldoximes isomerize roughly 100 times faster than oximes of methyl ketones: Garcia-Pons, T., unpublished results.

(26) Partial ^{13}C spectra of some of the pyrrolines reported here have been detailed elsewhere: Gawley, R. E.; Termine, E. J.; Goicoechea-Pappas, M. *Org. Magn. Reson.* **1983**, *21*, 177–178.

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(29) K & K Laboratories, Inc., ICN Pharmaceuticals, Inc.

either by short column chromatography eluting with 15% acetone in petroleum ether or by vacuum distillation: bp 115 °C (0.05 mm) and 124 °C (0.06 mm); calcd for $C_{12}H_{15}NO$, M^+ = 189.1153, found 189.1152; ^1H NMR δ 1.88 (3 H, s), 2.2–2.7 (4 H, m), 6.0–6.4 (2 H, br m), 7.27 (5 H, m); IR 3610, 3400, 1650, 1600 cm^{-1}.

3-Methyl-6-phenylhex-5-en-2-one oxime (5b) was obtained from (*Z*)-2-butanone oxime[14c] and cinnamyl chloride,[27] crude yield 90%, and purified by short column chromatography eluting with 10% ethyl ether in petroleum ether: calcd for $C_{13}H_{17}NO$, M^+ = 203.1309, found 203.1311; ^1H NMR (C_6D_6) δ 0.90 (3 H, d, J = 7.2 Hz), 1.66 (3 H, s), 1.9–2.7 (2 H, br m), 3.4–3.9 (1 H, br m), 5.5–6.3 (2 H, m), 7.1 (5 H, br); IR 3620, 3400, 1645, 1600 cm^{-1}.

7-Methyloct-6-en-3-one oxime (7a) and 3,6-dimethylhept-5-en-2-one oxime (8a) were obtained from 1 and methyl iodide, crude yield 98%. For the purpose of the rearrangement cyclization, this mixture was not purified further. Analysis by GC (175 °C) indicated a 4:1 ratio of **7a**/**8a**, with some unreacted **1**. Analytical samples of each were obtained by short column chromatography of the mixture, eluting with 10% acetone in petroleum ether. **7a**: calcd for $C_9H_{17}NO$, M^+ = 155.1309, found 155.1311; ^1H NMR (C_6D_6) δ 0.98 (3 H, t, J = 7.8 Hz), 1.51 (3 H, br s), 1.62 (3 H, br s), 2.0–2.2 (4 H, br), 2.33 (2 H, q, J = 7.8 Hz), 5.1 (1 H, br), 10.0 (1 H, br); IR 3600, 3280, 1650, 1370 cm^{-1}. **8a**: calcd for $C_9H_{17}NO$, M^+ = 155.1309, found 155.1311; ^1H NMR (C_6D_6) δ 0.91 (3 H, d, J = 6.7 Hz), 1.52 (3 H, br s), 1.61 (3 H, br s), 1.66 (3 H, s), 2.0–2.1 (2 H, m), 3.6 (1 H, m), 5.12 (1 H, br t); IR 3590, 3250, 1650, 1610, 1350 cm^{-1}.

1-Methoxy-8-methylnon-7-en-4-one oxime (7b) and 6-methyl-3-(2-methoxyethyl)hept-5-en-2-one oxime (8b) were obtained from 1 and 2-methoxyethyl iodide, prepared as follows. A mixture of 2-methoxyethyl bromide[30] (6.8 g, 48.7 mmol), sodium iodide (8.42 g, 56.1 mmol), and 75 mL of acetone were refluxed for 2 h, cooled, filtered, and condensed in vacuo. The residue was dissolved in ether, washed with dilute sodium thiosulfate, dried with magnesium sulfate, and condensed. The product was not characterized; crude yield of alkylation, 74%. For the rearrangement cyclization, this mixture was used directly. Analytical samples of each were obtained by short column chromatography, eluting with 10% acetone in petroleum ether. **7b**: calcd for $C_{12}H_{21}NO_2$, M^+ = 199.1571, found 199.1574; ^1H NMR (C_6D_6) δ 1.53 (3 H, s), 1.63 (3 H, s), 1.6–2.0 (2 H, m), 2.1–2.65 (6 H, m), 3.13 (3 H, s), 3.23 (2 H, t, J = 6.2 Hz), 5.14 (1 H, br); IR 3330, 3110, 1655, 1453, 1390, 1380, 1125 cm^{-1}. **8b**: calcd for $C_{12}H_{21}NO_2$, M^+ = 199.1571, found 199.1574; ^1H NMR (C_6D_6) δ 1.53 (3 H, br s), 1.60 (3 H, br s), 1.70 (3 H, s), 1.2–2.5 (5 H, br), 3.12 (3 H, s), 3.2–3.9 (2 H, m), 5.2 (1 H, br t, J = 6.6 Hz); IR 3300, 3120, 1652, 1450, 1380, 1127 cm^{-1}.

Ethyl 4-oxo-8-methylnon-7-enoate 4-oxime (7c) and 6-methyl-3-[(ethoxycarbonyl)methyl]hept-5-en-2-one oxime (8c) were obtained from 1 and ethyl bromoacetate,[27] crude yield 68%. Analytical samples were not prepared from this mixture, which was used directly.

General Procedures for Rearrangement Cyclizations. Method A (P_2O_5). A mixture of 300–500 mg of oxime (as a mixture of *E* and *Z* stereoisomers) and 2–3 equiv of P_2O_5 in 50 mL of solvent (CCl_4 or $C_6H_5CH_3$) was stirred at reflux overnight. After cooling, the solvent was decanted and the residue was *completely dissolved* in one or two 15–20-mL portions of 10% HCl. The organic supernatant was washed twice with 10% HCl and discarded. The combined aqueous layers were cooled in an ice bath and brought to pH 9 with 50% NaOH solution. Chloroform extraction, drying with $MgSO_4$, and evaporation in vacuo afforded the crude pyrrolines in 50–75% yield.

Method B (PPSE). A mixture of 1.5 g of P_2O_5, 3 mL of hexamethyldisiloxane,[27] and 7 mL of CCl_4[31] was refluxed for 1.5 h. To the resulting colorless solution of PPSE (cooled to 20 °C) was added 1 mmol of oxime (as a mixture of *E* and *Z* stereoisomers). The solution was refluxed from 1.5 to 5 h and cooled. A successful cyclization is indicated by a gummy precipitate on the walls of the flask. The reaction was quenched with 5 mL of water and transferred to a separatory funnel. The gummy precipitate was dissolved in two successive 5-mL water rinses and added to the contents of the separatory funnel. The layers were separated, and the organic layer was washed with 5 mL of 10% HCl. The combined aqueous layers were cooled to 0 °C and brought to pH 9 with 50% NaOH solution (ca. 1.5 mL). The aqueous phase was then extracted with 3 × 10 mL portions of $CHCl_3$, which were combined, dried with $MgSO_4$, and condensed in vacuo.

2-Methyl-3-isopropylidene-Δ^1-pyrroline (2): crude yield via method A in toluene, 81% (83% pure by GC); via method B in CCl_4, 74% (no impurities visible by NMR). **2** was purified by short column chromatography, eluting with 10% acetone in petroleum ether, or by vacuum distillation in a Kugelrohr oven:[32] bp 80–90 °C (8 mm);[17] calcd for $C_8H_{13}N$, M^+ = 123.1047, found 123.1046; ^1H NMR (400 MHz[33]) δ 1.79 (3 H, s), 1.99 (3 H, s) 2.27 (3 H, t, ^5J = 1.8 Hz), 2.52–2.56 (2 H, br m), 3.73–3.74 (2 H, br m); ^{13}C NMR (100 MHz[33]) δ 20.7 (q), 21.8 (q), 24.9 (q), 30.9 (t), 56.1 (t), 130.2 (s), 136.9 (s), 170.8 (s); IR 1655, 1385 (d) cm^{-1}.

(*E*)- and (*Z*)-2-Methyl-3-(1-chloroethylidene)-Δ^1-pyrroline (4a): crude yield via method A, 50%. **4a** was purified as a mixture by short column chromatography, eluting with 10% acetone in petroleum ether: calcd for $C_7H_{10}ClNO$, M^+ = 143.0502, found 143.0505; ^1H NMR δ 2.19 and 2.27 (3 H, t, ^5J = 1.8 Hz), 2.37 and 2.41 (3 H, s), 2.4–2.9 (2 H, br m), 3.5–4.0 (2 H, br m); ^{13}C NMR δ 20.8 and 21.2 (q), 23.1 and 26.1 (q), 33.5 and 33.7 (t), 55.9 and 56.6 (t), 124.0 and 130.2 (s), 137.6 and 140.0 (s) 167.4 and 169.8 (s); IR 1645, 1390 cm^{-1}.

2-Methyl-3-benzylidene-Δ^1-pyrroline (6a): crude yield via method A, 50%; via method B, 59%. **6a** was purified by short column chromatography, eluting with 10% acetone in petroleum ether: calcd for $C_{12}H_{13}NO$, M^+ = 171.1047, found 171.1045; ^1H NMR δ 2.19 (3 H, t, ^5J = 2.0 Hz), 2.6–2.9 (2 H, br m), 3.7–4.1 (2 H, br m), 6.67 (1 H, t, ^4J = 2.7 Hz), 7.1–7.5 (5 H, m); ^{13}C NMR δ 15.4 (q), 28.9 (t), 58.2 (t), 123.9 (d), 127.0 (d), 127.8 (d), 128.0 (d), 136.2 (s), 142.2 (s), 171.8 (s); IR 1645, 1603, 1390, 700 cm^{-1}.

2,5-Dimethyl-3-benzylidene-Δ^1-pyrroline (6b): crude yield via method A, 82%. **6b** was purified by short column chromatography, eluting with 15% acetone in petroleum ether: calcd for $C_{13}H_{15}N$, M^+ = 185.1204, found 185.1208; ^1H NMR δ 1.31 (3 H, d, J = 7.2 Hz), 2.19 (3 H, d, ^5J = 1.8 Hz), 3.9–4.4 (1 H, m), 2.8–3.3 (2 H, m), 6.67 (1 H, t, ^4J = 3.0 Hz), 7.1–7.5 (5 H, m); ^{13}C NMR δ 19.9 (q), 26.3 (q), 41.5 (t), 69.2 (d), 128.7 (d), 131.5 (d), 132.4 (d), 132.5 (d), 140.8 (s), 150.0 (s), 174.8 (s); IR 1635, 1595, 1385, 690 cm^{-1}.

2-Ethyl-3-isopropylidene-Δ^1-pyrroline (9a): crude yield via method A, 72%. **9a** was purified by short column chromatography, eluting with 10% acetone in petroleum ether: calcd for $C_9H_{15}N$, M^+ = 137.1204, found 137.1201; ^1H NMR δ 1.20 (3 H, t, J = 7.4 Hz), 1.79 (3 H, s), 1.98 (3 H, s), 2.1–2.9 (4 H, br m), 3.5–4.0 (2 H, br m); ^{13}C NMR δ 11.5 (q), 21.0 (q), 25.4 (q), 27.9 (t), 31.5 (t), 56.3 (t), 129.4 (s), 136.8 (s), 175.0 (s); IR 1675, 1645, 1375 cm^{-1}.

2-(3-Methoxypropyl)-3-isopropylidene-Δ^1-pyrroline (9b): crude yield via method A (a multicomponent mixture by GC, 200 °C), 58%. An analytical sample was prepared by medium-pressure chromatography, eluting with 25% acetone in hexane: calcd for $C_{11}H_{19}NO$, M^+ = 181.1466, found 181.1463; ^1H NMR δ 1.78 (3 H, s), 1.98 (3 H, s), 1.9–2.2 (2 H, br m), 2.3–2.9 (4 H, br m), 3.32 (3 H, s), 3.45 (2 H, t, J = 6.2 Hz), 3.5–4.0 (2 H, br t, J = 5.9 Hz); ^{13}C NMR δ 21.1 (q), 25.4 (q), 27.0 (t), 31.1 (t), 31.3 (t), 56.1 (t), 58.5 (q), 72.3 (t), 129.9 (s), 136.6 (s), 173.7 (s); IR 1650, 1590, 1450, 1380, 920 cm^{-1}.

2-[2-(Ethoxycarbonyl)ethyl]-3-isopropylidene-Δ^1-pyrroline (9c): crude yield via method B, 48%. **9c** was purified by flash chromatography, eluting with 33% acetone in petroleum ether: calcd for $C_{12}H_{19}NO_2$, M^+ = 209.1415, found 209.1417; ^1H NMR δ 1.24 (3 H, t, J = 7.0 Hz), 1.79 (3 H, br s), 2.01 (3 H, br s), 2.2–3.1 (6 H, br m), 3.5–3.9 (2 H, br m), 4.14 (2 H, q, J = 7.0 Hz); ^{13}C NMR δ 14, 21, 25, 30, 31 (2 C's), 56, 60, 130, 137, 172, 173; IR 1742, 1660, 1600, 1450, 1380, 1180, 1045, 760 cm^{-1}.

Acknowledgment. It is a pleasure to acknowledge financial support in the form of starter grants from the Research Corporation, the University of Miami Research

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(33) Spectrum recorded at the South Carolina regional NMR center, supported by NSF Grant No. 78-18723.

Council, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. Continuing support is generously provided by a grant from the National Science Foundation. The FT-80A NMR used in these studies was purchased with the aid of a Special Grant from the Camille and Henry Dreyfus Foundation.

Registry No. 1 (isomer 1), 52167-27-8; 1 (isomer 2), 89849-44-5; **2**, 5194-85-4; **3a** (isomer 1), 89849-45-6; **3a** (isomer 2), 89849-46-7; **3a** (isomer 3), 89849-47-8; **3a** (isomer 4), 89849-48-9; **3b** (isomer 1), 89849-49-0; **3b** (isomer 2), 89849-50-3; **3b** (isomer 3), 89849-51-4; **3b** (isomer 4), 89849-52-5; (*E*)-**4a**, 82194-08-9; (*Z*)-**4a**, 82194-09-0; **5a** (isomer 1), 89849-53-6; **5a** (isomer 2), 89849-54-7; **5b** (isomer 1), 89849-55-8; **5b** (isomer 2), 89849-56-9; (*E*)-**6** (R = H), 82194-10-3; (*E*)-**6** (R = Me), 89849-57-0; **7a**, 59222-87-6; **7b**, 89849-58-1; **7c**, 89849-59-2; **8a**, 82194-07-8; **8b**, 89849-60-5; **8c**, 89849-61-6; **9a**, 82194-12-5; **9b**, 85687-68-9; **9c**, 89849-62-7; $(CH_3)_2C{=}CH(CH_2)_2C(O)CH_3$, 110-93-0; MeI, 74-88-4; $MeO(CH_2)_2I$, 4296-15-5; $MeO(CH_2)_2Br$, 6482-24-2; $BrCH_2C(O)OEt$, 105-36-2; acetone oxime, 127-06-0; 1,3-dichloro-2-butene, 926-57-8; 1,3-dichloropropene, 542-75-6; *trans*-cinnamyl chloride, 21087-29-6; (*Z*)-2-butanone oxime, 10341-59-0.

Photochemistry of Diazonium Salts. 5. Syntheses of 2,4-Difluoroimidazole-5-carboxylic Acid and Related Compounds[1f]

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Catalytic hydrogenolysis, effective for the synthesis of 2-aminoimidazoles from 2-(arylazo)imidazoles, cannot be used to prepare 2-amino-4-fluoroimidazoles because the fluorine atom is lost simultaneously; formamidinesulfinic acid, however, achieves the required conversion in good yield. Ethyl 2,4-difluoroimidazole-5-carboxylate is obtained by photolysis of ethyl 2-diazonio-4-fluoroimidazole-5-carboxylate in fluoroboric acid. The ester is saponified to the acid in 1 N base (without loss of fluorine) but is stable in 0.05 N base; the ester also resists ammonolysis to the carboxamide or hydride reduction to the carbinol. Ammonolysis of ethyl 2-amino-4-fluoroimidazole-5-carboxylate is successful, however, and the resulting carboxamide is converted, via diazotization and photolysis, into 2,4-difluoroimidazole-5-carboxamide. *N*-Alkyl derivatives of the difluoro ester undergo facile hydride reduction of the ester function, but only with prior reductive loss of fluorine at C-2. The difluoro acid is stable to diborane reduction over 1 month. These examples of resistance to normal carboxyl modification are ascribed to the facile generation of the imidazolate ion in basic media and a resulting large increase in electron density at the carbonyl carbon by resonance overlap.

The discovery and development of the photochemical Schiemann reaction,[1] in this laboratory, led to the synthesis and biological investigation of a variety of ring-fluorinated imidazoles; for example: 4-fluoroimidazole-5-carboxamide riboside, a broad-spectrum antiviral agent;[2] 2-fluorourocanic acid, a potent inhibitor of urocanase;[3] and 4-fluoroimidazole-TRH, an analogue of thyrotropin-releasing hormone (TRH) that is inactive in pituitary functions but shows strong cardiovascular and central nervous system activities.[4] The 2-fluoro analogue of L-histidine shows bacteriostatic,[1e,5] antiviral,[6] antiparasitic,[7] and antileukemic[8] properties; furthermore, it can partially substitute for histidine in protein biosynthesis in both bacterial[5] and mammalian[9] systems. In contrast, 4-fluoro-L-histidine shows none of these properties.[1e,5-9]

Fluorine at C-2 of the imidazole ring is readily displaced by nucleophiles if a ring nitrogen is first protonated.[1c,7,10] We had hoped to utilize this property as a basis for affinity labeling of histamine and histidine recognition sites in proteins; to date, however, we have found no clear case of irreversible binding. Although 4-fluoroimidazoles show no reactivity toward nucleophiles, one of the fluorine atoms in 4-5-difluoroimidazole is subject to facile displacement;[11] we anticipated, therefore, that a second fluorine atom would also enhance the reactivity of a 2-fluoroimidazole.

In addition, we hoped that biological studies with difluorohistidine might help explain the striking differences in biological activity between 2- and 4-fluorohistidine. Differentiation based on steric effects seems improbable, in view of the very small size of the substituent.[1e] Basicity of the imidazole ring should not be a factor since both compounds are very weak bases (pK 1-2) and show little difference in basicity.[12] On the other hand, 2-fluoroimidazoles are somewhat more acidic than the 4-fluoro isomers[12] and we could not ignore the possibility that the 2-fluoroimidazolate ion is the active species in biological

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