Thermal Ring-Expansion of *N*-Acyl Cyclopropyl Imines

Pei-Lin Wu* and Wen-Shan Wang

Department of Chemistry, National Cheng Kung University, Tainan, Taiwan 70101, R.O.C.

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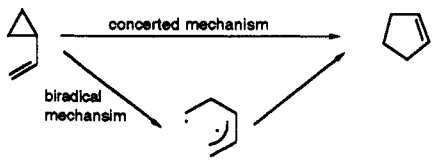
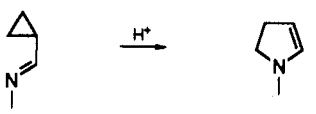
The FVT of *N*-acyl cyclopropyl imines with methyl, phenyl, and acyl substituents at C-1 or C-2 of the cyclopropyl ring has been studied. The parent *N*-acyl cyclopropyl imine and *N*-acyl methylcyclopropyl imines gave no ring-expansion products but ring-opened mixtures, decomposed fragments, and polymerization tars after FVT, whereas *N*-acyl phenylcyclopropyl imines and *N*-acyl acylcyclopropyl imines generated ring-expansion products, 2-pyrrolines. It demonstrates the first study on the thermal rearrangement of *N*-acyl cyclopropyl imines.

Cyclopropane possesses the largest amount of strain per methylene of any monocycloalkane (29 kcal/mol total).[1] Furthermore, the acute bond angles (60°) lead to a considerable amount of π-character in the ring bonds, which imbues this functional group with some of the characteristics of double bond.[2] These two factors are often cited to rationalize the high reactivity of the cyclopropyl group, including the well-known thermal conversion of vinylcyclopropanes to cyclopentenes.[3] The parent reaction is a unimolecular process with an activation energy of 49.7 kcal/mol.[4] Although in several cases a concerted mechanism has been proposed for this rearrangement,[5] the majority of these reactions involve biradical intermediates.[6]



The aza analog reaction of the rearrangement of cyclopropyl imines to 2- or 1-pyrrolines, has also been studied.[7] However, unlike the all-carbon examples, this reaction seems to require acid catalysis. In 1967, Edmonson reported that cyclopropyl imine was recovered unchanged after being heated to 560 °C in the gas phase.[8] More recently, Wasserman observed that no reaction takes place in the absence of NH_4Cl (or other acid) in the thermolysis of cyclopropyl imine.[9]



There are two primary explanations which account for the unfavorability of the thermal rearrangement of cyclopropyl imines. First, the transformation is a 1,3-sigmatropic shift which is thermally forbidden.[10] This results in the high activation energy and the biradical nature of the all-carbon rearrangement. Second, the carbon–nitrogen π-bond is much stronger (>10 kcal/mol) than the carbon–carbon π-bond;[11] so imines are comparatively reluctant to participate in thermal reactions in which the π-bond is lost.[12] In order to promote the thermal (i.e., not acid catalyzed) ring expansion reaction of cyclopropyl imines, a structural change in the reactant is needed. To the best of our knowledge, an *N*-acyl function has very little interaction with an imine, whereas there is 20 kcal/mol resonance stabilization for an amide.[13] Therefore, if a carbonyl group were present on the nitrogen atom of the imine, the developing amide stabilization, during the course of the reaction, would more than compensate for the loss of the C=N π-bond. There are many examples, such as the 1-aza-Diels–Alder,[14] 1-aza-ene,[15] and 1-aza-Cope reactions,[16] which succeeded when an acyl group was present on the nitrogen atom.

Since *N*-acyl imines are unstable,[17] they are best made from *N*,*O*-bis(methoxycarbonyl)hydroxylamine derivatives by thermal elimination of carbon dioxide and

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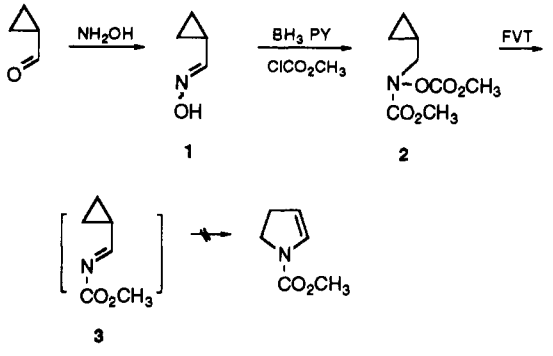
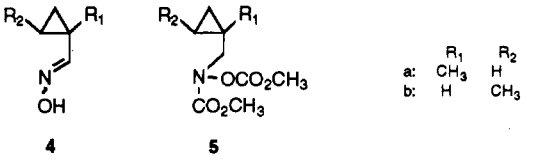
methanol. As a result, flash vacuum thermolysis (FVT)[18] is a method which can be used as a method for producing the *N*-acyl imine as well as inducing the subsequent thermal rearrangement. Our apparatus for FVT has three main components: a flask for the reactant, a thermolysis tube with a temperature controller, and a receiver to trap the products. A typical procedure begins with freezing the reactant in order to prevent it from evaporating too early. Then the apparatus is evacuated to 10^{-1}–10^{-2} Torr, and the tube is heated to the desired temperature. With the receiver immersed in liquid nitrogen, the sample is gently heated to distill it through the hot tube, after which it condenses in the receiver.

The overall conversion would be synthetically useful because the starting materials are readily prepared and the acyl function provides a convenient, reactive group for further elaboration (or removal) in the product. Furthermore, the 2-pyrroline skeleton is valuable in the synthesis of natural alkaloids[19] and is more easily isolated and handled than is the typical enamine.

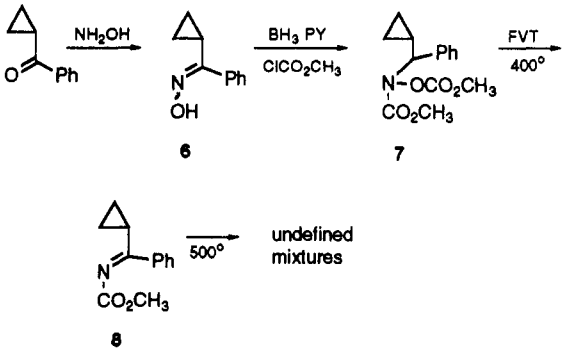
The simplest candidate molecule to explore the ring-expansion reaction was *N*-methoxycarbonyl cyclopropyl imine **3**. The precursor, *N*,*O*-bis(methoxycarbonyl)-*N*-(cyclopropylmethyl)hydroxylamine (**2**) was readily synthesized *via* oximation, reduction, and acylation of cyclopropanecarboxaldehyde. Compound **2** was quite thermally stable; it was almost quantitatively recovered after evaporation through a thermolysis tube at 350 °C. By ^{1}H NMR analysis of the crude pyrolysate, thermal reactions set in at 400 °C, and the starting material was completely consumed by FVT at 500 °C. Careful examination of the products after thermolysis of **2** at 500 °C disclosed none of the desired ring-expansion product, Rather, there was a complex mixture of ring-opened dienes, decomposition fragments, and tars.[20] The identification of these products was not pursued because the objective was to make 2-pyrrolines.



The same results (failure to provide 2-pyrrolines) were recorded for the thermolysis of **5a** and **5b** with methyl substituents present at C-1 and C-2; these were made from **4a** and **4b**, respectively. Reports on the all-carbon rearrangement show that methyl substitution has no effect on those reactions either.[21] Although the desired products were not obtained in any of these reactions, it was interesting to note that the cyclopropyl group ring-opened under the influence of the *N*-acyl function, in contrast to earlier (nonacylated) precedent discussed above.



In order to further explore the possibility of a cyclopropyl *N*-acyl imine to 2-pyrroline conversion, compound **7** with a phenyl group on the imine carbon was prepared from oxime **6**. Thermolysis of **7** at 400 °C resulted in the isolation of the *N*-acyl imine (46% yield) accompanied by the corresponding phenyl cyclopropyl ketone, which presumably derives from hydrolysis of **8** during workup. Raising the thermolysis temperature to 500 °C resulted in an undefined mixture that lacked the desired 2-pyrroline derivative.



Isolation of *N*-acyl imine **8** is interesting because such compounds are usually too reactive to be purified. The stability of **8** may be due, at least in part, to conjugation with the phenyl ring deactivating the carbon–nitrogen π-bond. This may impede the desired rearrangement as well. Moreover, substitution at this position in the all-carbon reaction is usually found to inhibit the reaction, possibly for steric reasons.[22] Such a substituent is not well placed to help stabilize radicaloid intermediates in this reaction. Taken together, these considerations may explain a low propensity for molecule **8** to undergo the desired rearrangement.

Work in other laboratories has demonstrated that substituents can have an effect on the vinylcyclopropane rearrangement. The reported effects vary with the nature and location of the substituents.[23] Following that work, we focused on phenyl and carbonyl substitution at C-1 and C-2 of **3**.

Following the standard method, compounds **10** (with a phenyl group on the three-membered ring) were prepared. With evaporation of **10a** through the oven at 500 °C, the desired 2-pyrroline **11a** was isolated in 38% yield. The balance of crude product is a complex mixture of decomposition products and polymers which could not be

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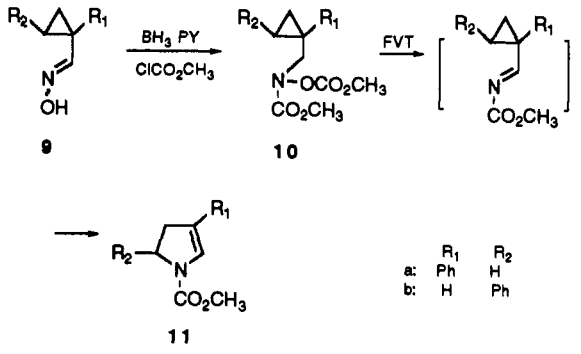
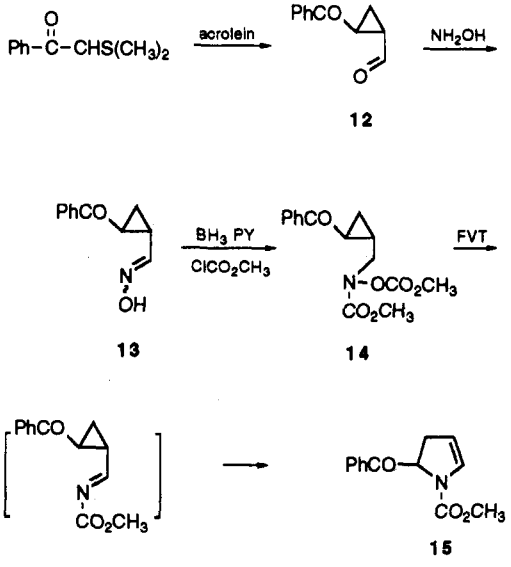
identified. Compound **10b** furnished a 37% yield of pyrroline **11b** under the same conditions. Thus, a phenyl substituent does make the ring-expansion more competitive with simple ring-opening.

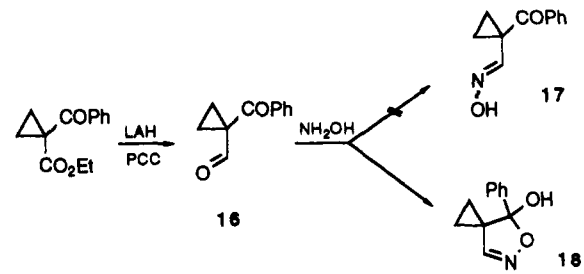


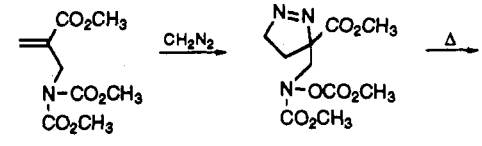
With the encouraging results from phenyl substitution on the ring, we decided to explore the effect of carbonyl substitution on the ring. The reaction of sulfur ylide with acrolein readily afforded *trans* aldehyde **12** with a benzoyl group at C-2. Reaction with hydroxylamine produced oxime **13**. Thermolysis of **14** provided a 21% yield of 2-pyrroline **15**. Apparently the carbonyl group is not quite as effective as the phenyl group at C-2.

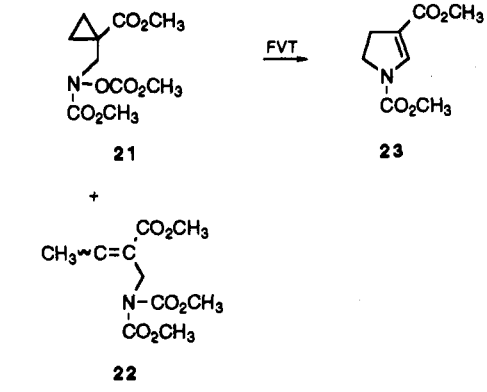


In order to examine the effect of a carbonyl group at the C-1 position, we attempted to make the oxime **17** from aldehyde **16**. However, the only product of the reaction was the cyclized isoxazole **18**. The alternative preparation by way of **19** and diazomethane afforded 1-pyrrazoline **20**. Pyrolysis of **20** at 120 °C gave an inseparable mixture of the desired precursor **21** and its isomers **22**. This mixture (28% by ^{1}H NMR) was submitted to FVT at 500 °C and yielded 35% of 2-pyrroline **23** (based on pure **21**).

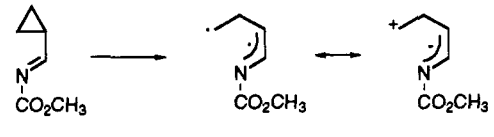
The thermolysis reactions were followed by ^{1}H NMR analysis and thin layer chromatography over a temperature range of 350–550 °C. The starting material began to disappear, and the 2-pyrroline appeared, at 400 °C. Remaining starting material gradually decreased to zero, and the 2-pyrroline yield was at a maximum at 500 °C. Above 500 °C, the yield of the product dropped rapidly. Thus, the maximum yield of the ring-expansion products occurred at the temperature at which loss of carbon dioxide and methanol was complete. The implication of this is







that the activation energy for the ring expansion is less than or equal to that for the initiated elimination reaction. Acceleration of the ring expansion reaction by phenyl and acyl substituents, and not methyl substituents, is notable. Bearing in mind that substituents can alter a reaction mechanism, the observed effects are most consistent with biradical intermediate **24a**. However, the polar resonance structure **24b** should make a significant contribution in the reaction.



In summary, this paper presents the first study on the thermal rearrangement of *N*-acyl cyclopropyl imines forming 2-pyrrolines. Phenyl and acyl substitution at C-1 or C-2 of the cyclopropyl ring is critical to the reaction; unsubstituted and methyl substituted cyclopropanes do not give the desired reaction. Presumably, the electronic effects of the phenyl and acyl substituents lower the activation energy for the process. The 2-pyrroline products are valuable skeletons for the preparation of natural alkaloid.

Experimental Section

General. Infrared spectra were recorded on a spectrometer (Hitachi 260-30) as either thin films or KBr solid dispersions. Nuclear magnetic resonance spectra were recorded on Bruker

WP-100, AC-200, and AMX-400 FT-NMR spectrometers; all chemical shifts are reported in ppm from tetramethylsilane as an internal standard. Mass spectra were recorded on a VG 70-250S spectrometer. Column chromatography was carried out using 70–230-mesh silica gel (E. Merck). All reactions were carried out under an atmosphere of nitrogen.

Cyclopropanecarbaldoxime (1). Sodium carbonate (0.80 g, 7.5 mmol) was added to a solution of hydroxylamine hydrochloride (1.04 g, 15 mmol) in a minimum amount of water. The cyclopropanecarboxaldehyde (0.70 g, 10 mmol) in 3 mL of 95% ethyl alcohol was added to the aqueous solution and stirred at room temperature for 2 h. The resulting mixture was extracted with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Pure product 1 (0.84 g, 99% yield) was recrystallized from hexane as white needle crystal. Generally this procedure produced an isomeric mixture of *syn* and *anti* oximes. This *syn* and *anti* mixture was not separated and was used for further reaction: mp 80–81 °C; IR (KBr) 3200, 2880, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.6–0.7 and 0.8–1.0 (m, 4H, $2CH_2$), 1.5–1.7 and 2.2–2.4 (m, 1H, CH), 6.02 and 6.93 (d, 1H, CH=N, J = 9 Hz and 8 Hz), 8.1–9.2 (b, 1H, NOH); MS m/z (relative intensity) 85 (74, M^+), 68 (100); HRMS m/e 85.0525 (C_4H_7NO requires 85.0528).

***N,O*-Bis(methoxycarbonyl)-*N*-(cyclopropylmethyl)hydroxylamine (2).** A mixture of oxime 1 (0.43 g, 5 mmol) and pyridine–borane (0.56 g, 6 mmol) in 4 mL of 95% ethanol was kept at 0 °C. Then 7.5 mL of a 10% HCl solution was added over a 20-min period with vigorous mixing, and the mixture was stirred for 20 min at room temperature. The solution was cooled to 0 °C again, and NaOH pellets were added cautiously until the pH was in the range of 8–10.[24] The mixture was extracted with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to a volume of 50 mL. Triethylamine (0.38 g, 4 mmol) was added to the diethyl ether solution, then methyl chloroformate (0.40 g, 4 mmol) was added dropwise at 0 °C. After being stirred stirring at room temperature for 2 h, the solution was acidified with 10% HCl solution. The ether layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting product was purified by column chromatography to give monoacylated hydroxylamine which always contains a pyridine derivative. The product was acylated again. Triethylamine (0.38 g, 4 mmol) and methyl chloroformate (0.40 g, 4 mmol) were added to a diethyl ether solution of this monoacylated hydroxylamine. The solution was stirred at room temperature for 2 h and then filtered and concentrated *in vacuo*. Pure diacylated product 2 (0.42 g, 41% yield) was finally obtained by column chromatography as a colorless liquid: IR (film) 3010, 2960, 1790, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.2–0.3 and 0.5–0.6 (m, 4H, $2CH_2$), 1.0–1.2 (m, 1H, CH), 3.50 (d, 2H, CH_2N, J = 7 Hz), 3.78 (s, 3H, NCO_2CH_3), 3.91 (s, 3H, OCO_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 3.04, 8.36, 53.45, 55.23, 55.93, 154.78, 156.07; MS m/z (relative intensity) 203 (11, M^+), 68 (24), 59 (90) 55 (100); HRMS m/e 203.0793 ($C_8H_{13}NO_5$ requires 203.0794).

1-Methylcyclopropanecarbaldoxime (4a). Pyridinium chlorochromate (3.23 g, 15 mmol) was suspended in 15 mL of methylene chloride at room temperature. 1-Methylcyclopropanemethol (0.86 g, 10 mmol) dissolved in 5 mL of methylene chloride was quickly added. The reaction mixture was stirred for 1.5 h. Diethyl ether was added and the dark solution was filtered through a short column of Florisil. Additional ether was used to wash the residue and the column.[25] The solution was concentrated in vacuo to give 1-methylcyclopropanecarboxaldehyde. Owing to the easy oxidation of this aldehyde, further oximation using the procedure for the preparation of oxime 1 was conducted. Pure **4a** (0.86 g, 87% yield) was obtained by column chromatography as a single isomer: mp 32–33 °C; IR (KBr) 3280, 2950, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.6–0.8 (m, 4H, $2CH_2$), 1.23 (s, 3H, CH_3), 6.93 (s, 1H, CH=N), 8.5–8.7 (b, 1H, NOH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.62, 16.71, 19.39, 157.57; MS m/z (relative intensity) 99 (85, M^+), 82 (100), 67 (48).

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.62; H, 9.00; N, 14.06.

***trans*-2-Methylcyclopropanecarbaldoxime (4b).** The analogous procedure for the preparation of **4a** was used. 2-Methylcyclopropanemethanol (0.84 g, 10 mmol) gave **4b** (0.84 g, 85% yield) as *syn* and *anti* isomers: IR (film) 3270, 2960, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.7–0.8 (m, 2H, CH_2), 0.9-1.1 (m, 1H, $CHCH_3$), 1.13 (d, 3H, CH_3, J = 5 Hz), 1.9–2.1 (m, 1H, CHC=N), 6.03 (d,1H, CH=N, J = 9 Hz), 9.2–9.7 (b, 1H, NOH); MS m/z (relative intensity) 99 (27, M^+), 82 (100), 67 (65), 55 (83).

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.49; H, 9.05; N, 14.10.

***N,O*-Bis(methoxycarbonyl)-*N*-((1-methylcyclopropyl)methyl)hydroxylamine (5a).** The analogous procedure for the preparation of **2** was used. Oxime **4a** (0.50 g, 5 mmol) gave **5a** (0.56 g, 51% yield) as a colorless liquid: IR (film) 3000, 2960, 1800, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.3–0.4 (m, 4H, $2CH_2$), 1.13 (s, 3H, CH_3), 3.50 (s, 2H, CH_2N), 3.79 (s, 3H, NCO_2CH_3), 3.91 (s, 3H, OCO_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.96, 13.96, 20.96, 53.46, 55.92, 58.85, 154.64, 156.13; MS m/z (relative intensity) 217 (5, M^+), 69 (98), 59 (100); HRMS m/e 217.0948 ($C_9H_{15}NO_5$ requires 217.0950).

***N,O*-Bis(methoxycarbonyl-*N*-((2-methylcyclopropyl)methyl)hydroxylamine (5b).** The analogous procedure for the preparation of **2** was used. Oxime **4b** (0.50 g, 5 mmol) gave **5a** (0.58 g, 53% yield) as a colorless liquid: IR (film) 3000, 2960, 1800, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.15–0.25 and 0.3–0.4 (m, 2H, CH_2), 0.55–0.65 (m, 1H, $CHCH_3$), 0.65–0.75 (m, 1H, $CHCH_2N$), 0.95 (d, 3H, CH_3, J = 6 Hz), 3.34 and 3.52 (dd, 2H, CH_2N, J = 8, 15 Hz and 7, 15 Hz), 3.71 (s, 3H, NCO_2CH_3), 3.84 (s, 3H, OCO_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.26, 11.72, 16.77, 18.10, 53.48, 54.81, 55.96, 154.85, 156.16; MS m/z (relative intensity) 217 (14, M^+), 69 (100), 59 (98); HRMS m/e 217.0951 ($C_9H_{15}NO_5$ requires 217.0950).

Cyclopropyl Phenyl Ketoxime (6). Hydroxylamine hydrochloride (1.04 g, 15 mmol) was dissolved in 5 mL of pyridine, followed by the cyclopropyl phenyl ketone (1.46 g, 10 mmol). The solution was heated at 85–90 °C for 14 h. After the solution was cooled to room temperature, 30 mL of ethyl acetate was added. The solution was washed with a 10% HCl solution several times to remove excess pyridine. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Pure white crystals of **6** were obtained by recrystallization from hexane as *syn* and *anti* isomers: mp 78–79 °C; IR (KBr) 3160, 3050, 2870, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.6–1.0 (m, 4H, $2CH_2$), 1.7–1.9 and 2.2–2.4 (m, 1H, CH) 7.2-7.5 (m, 5H, C_6H_5), 8.7–9.6 (b, 1H, NOH); MS m/z (relative intensity) 161 (100, M^+), 91 (46), 77 (74); HRMS m/e 161.0834 ($C_{10}H_{11}NO$ requires 161.0841).

***N,O*-Bis(methoxycarbonyl)-*N*-((1-cyclopropyl)benzyl)hydroxylamine (7).** The analogous procedure for the preparation of **2** was used. Oxime **6** (0.81 g, 5 mmol) gave **7** (0.27 g, 19% yield) as colorless liquid: IR (film) 3070, 2960, 1800, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.4–0.9 (m, 4H, $2CH_2$), 1.3–1.7 (b, 1H, CH), 3.78 (bs, 6H, NCO_2CH_3 and OCO_2CH_3), 4.46 (bd, 1H, CHN, J = 10 Hz), 7.3–7.6 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 4.44, 4.89, 12.64, 53.68, 55.95, 68.87, 127.77, 128.30, 138.36, 154.58, 156.51; MS m/z (relative intensity) 279 (3, M^+), 131 (100), 77 (13), 59 (11); HRMS m/e 279.1111 ($C_{14}H_{17}NO_5$ requires 279.1107).

General Method for FVT. The reactant (10–300 mg) was first frozen in a liquid nitrogen bath, and a vacuum was applied. Once the vacuum (10^{-1}–10^{-2} Torr) had been established, the heater was turned on. The temperature of the hot tube was regulated by a temperature controller. When the set temperature was reached, the receiver was placed in a liquid nitrogen bath, and the reactant was thawed by heating and evaporated through the hot tube. The product was condensed and collected in the receiver at liquid nitrogen temperature and washed out with diethyl ether. After removal of the solvent, the crude product was purified by column chromatography.

Cyclopropyl Phenyl *N*-(Methoxycarbonyl)ketimine (8). By the general method for FVT, **7** (174 mg, 0.62 mmol) gave **8** (59 mg, 46% yield) as a colorless liquid: IR (film) 3060, 2950, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0-1.2 (m, 4H, $2CH_2$), 1.9–2.1 (m, 1H, CH), 3.67 (s, 3H, NCO_2CH_3), 7.3–7.7 (m,

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5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.63, 18.07, 52.94, 126.78, 128.40, 130.50, 137.70, 163.27, 176.78; MS *m/z* (relative intensity) 203 (79, M^+), 144 (73), 118 (100), 77 (87), 59 (33); HRMS *m/e* 203.0946 ($C_{12}H_{13}NO_2$ requires 203.0947).

1-Phenylcyclopropanecarbaldoxime (9a). The analogous procedure for the preparation of **1** was used. 1-Phenylcyclopropanecarboxaldehyde[27] (1.46 g, 10 mmol) gave **9a** (1.46 g, 91% yield) as a single isomer: mp 82–83 °C; IR (KBr) 3250, 3050, 2920, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19 (s, 4H, $2CH_2$), 7.23 (s, 1H, CH=N), 7.2–7.4 (m, 5H, C_6H_5), 7.5–7.9 (b, 1H, NOH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.46, 26.30, 126.91, 128.22, 129.35, 140.03, 155.82; MS *m/z* (relative intensity) 161 (16, M^+), 144 (100); HRMS *m/e* 161.0841 ($C_{10}H_{11}NO$ requires 161.0841).

***trans*-2-Phenylcyclopropanecarbaldoxime (9b).** The analogous procedure for the preparation of **1** was used. 2-Phenylcyclopropanecarboxaldehyde[26] (1.46 g, 10 mmol) gave **9b** (1.48 g, 92% yield) as *syn* and *anti* isomers: mp 59–60 °C; IR (KBr) 3240, 3030, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2–1.5 (m, 2H, CH_2), 1.8–1.9, 2.1–2.3, and 2.5–2.7 (m, 2H, 2CH), 6.22 (d, 1H, CH=N of *syn* isomer, J = 8 Hz), 7.0–7.4 (m, 6H, C_6H_5, and NOH, 1H, CH=N of *anti* isomer); MS *m/z* (relative intensity) 161 (58, M^+), 144 (100), 115 (81); HRMS *m/e* 161.0841 ($C_{10}H_{11}NO$ requires 161.0841).

***N,O*-Bis(methoxycarbonyl)-*N*-((1-phenylcyclopropy)-methyl)hydroxylamine (10a).** The analogous procedure for the preparation of **2** was used. Oxime **9a** (0.81 g, 5 mmol) gave **10a** (0.67 g, 49% yield) as a colorless liquid: IR (film) 3060, 2960, 1800, 1730, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.8–1.0 (m, 4H, $2CH_2$), 3.53 (s, 3H, OCH_3), 3.85 (s, 5H, OCH_3 and CH_2N), 7.2–7.5 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.23, 23.96, 53.35, 55.97, 59.34, 126.59, 128.08, 129.40, 142.14, 154.52, 155.87; MS *m/z* (relative intensity) 279 (7, M^+), 204 (51), 130 (100), 91 (49), 77 (21), 59 (40); HRMS *m/e* 279.1106 ($C_{14}H_{17}NO_5$ requires 279.1107).

***N,O*-Bis(methoxycarbonyl)-*N*-((*trans*-2-phenylcyclopropyl)methyl)hydroxylamine (10b).** The analogous procedure for the preparation of **2** was used. Oxime 9b (0.81 g, 5 mmol) gave 10b (0.80 g, 57% yield) as a colorless liquid: IR (film) 3030, 2960, 1790, 1730, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.9–1.0 (m, 2H, CH_2), 1.4–1.5 and 1.8–1.9 (m, 2H, 2CH), 3.54 and 3.82 (dd, 2H, CH_2N, J = 8, 15 Hz and 6, 15 Hz), 3.75 and 3.79 (s, 6H, $2OCH_3$), 7.0–7.3 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.58, 19.88, 21.94, 53.52, 54.37, 55.82, 125.64 (2C), 128.10, 141.67, 154.60, 156.00; MS *m/z* (relative intensity) 279 (12, M^+), 130 (100), 91 (74), 77 (17), 59 (45); HRMS *m/e* 279.1107 ($C_{14}H_{17}NO_5$ requires 279.1107).

***N*-(Methoxycarbonyl)-3-phenyl-2-pyrroline (11a).** By the general method for FVT, **10a** (210 mg, 0.75 mmol) gave **11a** (56 mg, 38% yield) as a colorless liquid: IR (film) 3060, 2950, 1720, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) for two rotomers δ 2.9–3.1 (m, 2H, CH_2), 3.78 (s, 3H, NCO_2CH_3), 3.8–4.0 (m, 2H, CH_2N), 7.0–7.2 (m, 1H, C=CHN), 7.2–7.4 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.66, 45.63, 52.68, 121.57, 124.27, 125.05, 126.40, 128.47, 134.46, 152.68; MS *m/z* (relative intensity) 203 (100, M^+), 188 (82), 144 (84), 77 (15), 59 (32); HRMS *m/e* 203.0947 ($C_{12}H_{13}NO_2$ requires 203.0946).

***N*-(Methoxycarbonyl)-5-phenyl-2-pyrroline (11b).** By the general method for FVT, **10b** (241 mg, 0.86 mmol) gave **11b** (67 mg, 37% yield) as a colorless liquid: IR (film) 3030, 2950, 1710, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) for two rotomers δ 2.4–2.6 and 3.2–3.4 (m, 2H, CH_2), 3.56 and 3.69 (bs, 3H, NCO_2CH_3), 5.0–5.2 (m, 2H, CH and CH=CN), 6.67 and 6.82 (bs, 1H, C=CHN), 7.1–7.4 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.93, 52.35, 60.25, 106.58, 125.28, 127.10, 128.47, 129.67, 143.53, 152.00; MS *m/z* (relative intensity) 203 (100, M^+), 144 (16), 77 (24), 59 (21); HRMS *m/e* 203.0947 ($C_{12}H_{13}NO_2$ requires 203.0946).

***trans*-2-Benzoylcyclopropane-1-carboxaldehyde (12).** A solution of bromoacetophenone (4.98 g, 25 mmol) and dimethyl sulfide (1.86 g, 30 mmol) in 30 mL of acetone was stored in a water bath for 2 h.[28] Filtration gave sulfonium bromide as a white solid. This sulfonium bromide was added slowly into a suspension solution of NaH (01.5 g, 60% in oil, 37.5 mmol) in 50 mL of tetrahydrofuran. The solution was stirred at room temperature for 2 h.[29] A sulfur ylide was generated after filtration and concentration. Acrolein (1.40 g, 25 mmol) was added to a solution of the sulfur ylide in 50 mL of tetrahydrofuran. The mixture was heated at 60 °C for 30 min and then concentrated *in vacuo*.[28] Pure aldehyde **12** (2.95 g, 68% yield) was obtained by column chromatography as white crystals: mp 52–53 °C; IR (KBr) 3060, 2850, 2760, 1700, 1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.6–1.9 (m, 2H, CH_2), 2.6–2.7 and 3.2–3.4 (m, 2H, 2CH), 7.4–8.1 (m, 5H, C_6H_5), 9.50 (d, 1H, CHO, J = 3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.34, 25.70, 32.74, 128.07, 128.58, 133.40, 136.61, 195.98, 198.62; MS *m/z* (relative intensity) 174 (11, M^+), 105 (100), 77 (95); HRMS *m/e* 174.0681 ($C_{11}H_{10}NO_2$ requires 174.0681).

***trans*-2-Benzoylcyclopropane-1-carbaldoxime (13).** The analogous procedure for the preparation of **1** was used. Aldehyde **12** (1.74 g, 10 mmol) gave **13** (1.47 g, 78% yield) as *syn* and *anti* isomers: mp 126–127 °C; IR (KBr) 3290, 3030, 1660 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 1.3–1.6 (m, 2H, CH_2), 2.2–2.3 and 2.8–2.9 (m, 1H CH), 3.1–3.2 (m, 1H, CHCO), 6.32 and 7.18 (d, 1H, CH=N, J = 8 Hz and 8 Hz), 7.5–8.2 (m, 5H, C_6H_5), 7.5–7.9 (b, 1H, NOH); MS *m/z* (relative intensity) 189 (3, M^+), 172 (10), 105 (100), 84 (53), 77 (97); HRMS *m/e* 189.0790 ($C_{11}H_{11}NO_2$ requires 189.0790).

***N,O*-Bis(methoxycarbonyl)-*N*-((trans-2-benzoylcyclopropyl)methyl)hydroxylamine (14).** The analogous procedure for the preparation of **2** was used. Oxime **13** (0.95 g, 5 mmol) gave **14** (0.86 g, 56% yield) as a colorless liquid: IR (film) 3010, 2960, 1790, 1730, 1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0–1.1 and 1.4–1.6 (m, 2H, CH_2), 1.9–2.0 and 2.6–2.7 (m, 2H, 2CH), 3.54 and 3.91 (dd, 2H, CH_2N, J = 8, 15 Hz and 6, 15 Hz), 3.76 and 3.78 (s, 6H, $2OCH_3$), 7.4–8.1 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.82, 22.66, 23.19, 53.28, 53.71, 55.98, 127.97, 128.39, 132.81, 137.41, 154.52, 155.97, 198.59; MS *m/z* (relative intensity) 307 (6, M^+), 105 (100), 77 (64), 59 (42); HRMS *m/e* 307.1055 ($C_{15}H_{17}NO_6$ requires 307.1056).

***N*-(Methoxycarbonyl)-5-benzoyl-2-pyrroline (15).** By the general method for FVT, **14** (298 mg, 0.97 mmol) gave **15** (47 mg, 21% yield) as a colorless liquid: IR (film) 2950, 1690, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) for two rotomers δ 2.5–2.7 and 3.1–3.4 (m, 2H, CH_2), 3.60 and 3.74 (s, 3H, NCO_2CH_3), 4.9–5.1 (m, 1H, CHN), 5.4–5.6 (m, 1H, CH=CN), 6.6–6.7 and 6.75–6.85 (m, 1H, C=CHN), 7.4-8.0 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.96, 27.68, 60.84, 105.45, 128.65, 128.76, 130.36, 133.45, 133.88, 152.63, 194.91; MS *m/z* (relative intensity) 231 (10, M^+), 126 (100), 105 (46), 77 (82); HRMS *m/e* 231.0898 ($C_{13}CH_{13}NO_3$ requires 231.0895).

5′-Hydroxy-5′-phenyl-4′,5′-dihydrospiro[cyclopropane-1,4′-isoxazole] (18). Lithium aluminum hydride (0.76 g, 20 mmol) was suspended in 50 mL of diethyl ether. The mixture was stirred at room temperature for 30 min. Ethyl 1-benzoylcyclopropanecarboxylate[30] (2.18 g, 10 mmol) in 5 mL of diethyl ether was added slowly and the reaction mixture was heated at 40 °C for 20 h. Excess lithium aluminum hydride was decomposed by the dropwise addition of water followed by a 10% HCl solution. After vigorous stirring for another 20 min, the solution was extracted with ethyl acetate.[31] The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. A pure diol (1.34 g, 75% yield) was obtained by column chromatography as a colorless liquid. The analogous procedure for the preparation of **4a** was used. This diol gave **18** as white crystals: IR (KBr) 3290, 3090, 2900, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.2–0.4, 0.9–1.0, and 1.2–1.4 (m, 4H, $2CH_2$), 3.20 (s, 1H, OH), 6.99 (s, 1H, CH=N), 7.4–7.5 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.20, 13.73, 41.11, 107.38, 127.17, 129.08, 129.47, 140.68, 155.09; MS *m/z* (relative intensity) 189 (19, M^+), 105 (100), 77 (51); HRMS *m/e* 189.0789 ($C_{11}H_{11}NO_2$ requires 189.0790).

***N,O*-Bis(methoxycarbonyl)-*N*-((3-(methoxycarbonyl)-1-**

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pyrazolin-3-yl)methyl)hydroxylamine (20). Alkene 19[32] (1.24 g, 5 mmol) was added into an ice-cooled ether solution of diazomethane, prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (2.14 g, 10 mmol) with KOH (0.60 g) in 1 mL of water and 3.5 mL of diethyl ether.[33] The mixture was allowed to stand for 2 d. Excess diazomethane was destroyed by addition of formic acid and concentrated *in vacuo*.[34] Pure **20** (1.19 g, 82% yield) was obtained by column chromatography as a colorless liquid: IR (film) 2960, 1790, 1730 (bs) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.7–1.8 and 2.0–2.2 (m, 2H, CH_2C), 3.71, 3.74, and 3.83 (s, 9H, $3OCH_3$), 4.3–5.0 (m, 4H, $2CH_2N$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.30, 52.88, 53.47, 54.08, 56.23, 78.89, 97.96, 154.30, 156.24, 168.59; MS *m/z* (relative intensity) 230 (1, $M^+ - CO_2CH_3$), 113 (70), 59 (100); HRMS for 230 *m/e* 230.0777 ($C_8H_{127}N_3O_5$ requires 230.0777).

***N*,4-Bis(methoxycarbonyl)-2-pyrroline (23).** The neat liquid **20**, heated at 120 °C for 30 min, gave **21** along with two stereoisomers **22**. By the general method for FVT, the inseparatable mixture containing 28% of pure **21** (42 mg, 0.16 mmol) gave **23** (10.5 mg, 35% yield) as a colorless liquid: IR (film) 3020, 2960, 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.85 (bt, 2H, CH_2C, J = 9 Hz), 3.72 and 3.78 (s, 6H, $2OCH_3$), 3.90 (bt, 2H, CH_2N, J = 9 Hz), 7.43 and 7.53 (bs, 1H, C=CHN); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7, 46.8, 51.3, 53.2, 113.2, 140.1, 152.4, 165.6; MS *m/z* (relative intensity) 185 (95, M^+), 154 (100), 59 (60); HRMS *m/e* 185.0689 ($C_8H_{11}NO_4$ requires 5.0688).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of all new compounds (**1**, **6**, and **13** have ^1H NMR only) (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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