Tetrahedron Vol. 45, No. 10, pp. 3203 to 3216, 1989
Printed in Great Britain.

0040–4020/89 $3.00+.00

CYCLOPROPANONE EQUIVALENTS FROM 3-CHLOROPROPIONIC ACID. USE OF 1-PIPERIDINO-1-TRIMETHYLSILYLOXYCYCLOPROPANE IN SYNTHETIC APPLICATIONS

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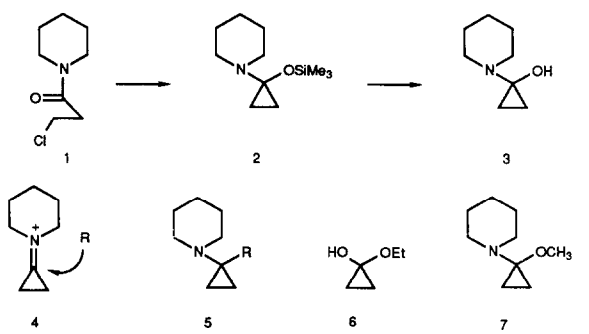
(*Received in Belgium* 26 *August* 1988)

Abstract: 1-Piperidino-1-trimethylsilyloxycyclopropane and the corresponding 1-hydroxy-1-piperidinocyclopropane, conveniently prepared from the piperidide of 3-chloropropionic acid, react as cyclopropanone equivalents with various nucleophiles. Use of these derivatives in the formation of pyrroles, pyrrolines and pyrrolizidines is described. The rearrangement of dicyclopropyl ketimines is explored.

Because cyclopropanones are generally labile and difficult to isolate, the chemistry of this class of ketones has been explored largely through derivatives which may act as precursors of the parent ketone. Among such precursors have been the addition products of alcohols, acids, amines and thiols.[1,2,3] In this paper we will report on the reactions of one such cyclopropanone addition product, 1-piperidinocyclopropanol (3).

In early communications on the formation of (3), we employed the diazomethane-ketene route.[1b] This method is inconvenient and hazardous, especially for larger-scale reactions, and we therefore sought an alternative preparative method. We now report details of the use of the Ruhlmann procedure,[4a] previously employed[4b] in the formation of the hemiketal (6), as a convenient synthetic route to the carbinol amine (3) and its silyl ether (2). Both of these derivatives may be used for the ready generation of functionalized cyclopropane residues of type (5) when combined with suitable nucleophilic reagents.

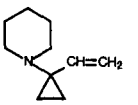
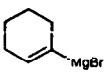
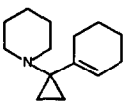
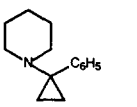
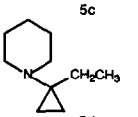
The silyl ether (2) was prepared in one step starting from the piperidide of 3-chloropropionic acid (1).[5] Reductive cyclization using sodium sand in ether in the presence of trimethylchlorosilane[4] generated (2) in high yield. Conversion of this silyl ether to the known carbinol amine (3)[1b] took place in methanolic tetrabutylammonium fluoride. Both (2)



1 2 3 4 5 6 7

and (3) may be used for the ready generation of cyclopropane derivatives corresponding to (5). Thus, the silyl ether (2) can be reacted directly with Grignard reagents to provide cyclopropanated addition products as summarized in Table 1.[6]

Table 1

RMgBr	Product (yield, %)
$H_2C{=}CH{-}MgBr$	 (67)
	 (95)
C_6H_5MgBr	 (79)
H_3CCH_2MgBr	 (92)

5a

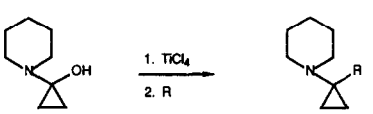
5b

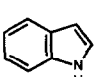
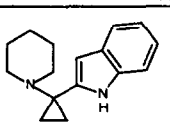
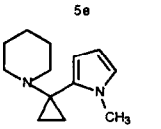
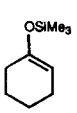
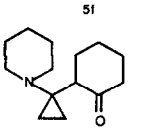
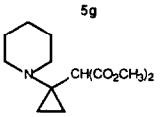
5c

5d

Alternatively, treatment of the carbinol amine (3) with titanium tetrachloride in methylene chloride[7] provides another method for the addition of donor reagents such as indole, N-methylpyrrole, silyl enol ethers and species containing active methylene groups. Following the $TiCl_4$-promoted addition to (3) the reaction mixture was stirred overnight and worked up by the addition of water as noted in our earlier work[1b] and in the studies of de Boer.[2] These results are summarized in Table 2. Under the conditions noted above, the reactions of nucleophilic reagents with (2) and (3) appear to take place by addition to intermediate iminium ions. For example, the iminium salt (4) is most probably involved in the facile conversion of (2) to the methyl ether (7) by the action of methanol and acid.

Table 2



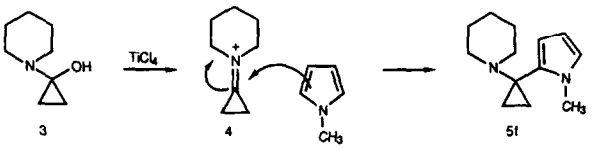
R	Product (yield, %)
	 (84)
	 (65)
	 (63)
$(CH_3O_2C)_2CH_2$	 (55)

5e

5f

5g

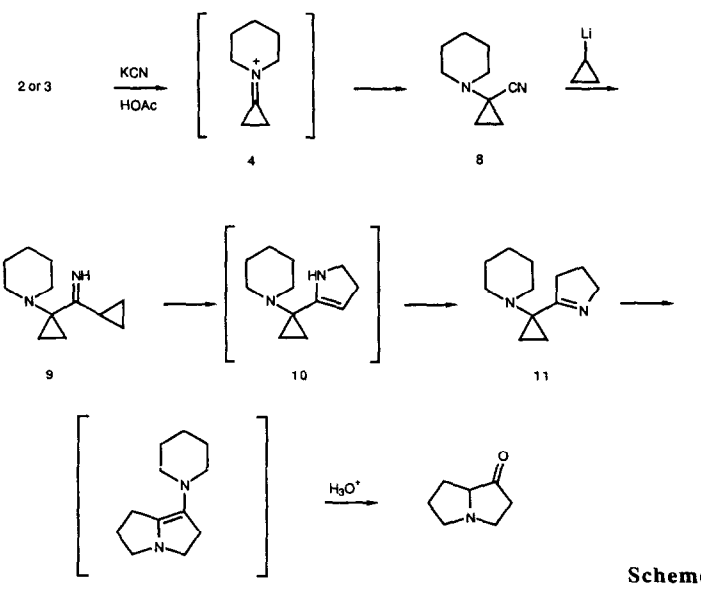
5h



Pyrrolizidine Formation

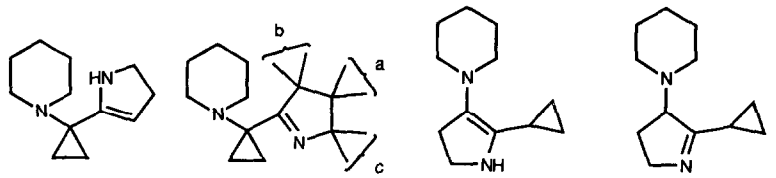
The cyclopropanone equivalent (3) could be utilized for the formation of pyrrolizidines by successive cyclopropyl imine rearrangements as described in the following: Treatment of (2) or (3) with KCN in the presence of aqueous acetic acid gave the nitrile (8), most probably by addition of cyanide to the iminium salt (4).[8] The yield of addition product (8) was somewhat better with the carbinol amine (3) (73%) than with the silyloxy derivative (2) (62%). The nitrile was then allowed to react with cyclopropyllithium in ether at -78°C followed by warming to 0° for 1 h, and the reaction mixture worked up with an aqueous solution of Na_2SO_4.

The resulting imine (9) was taken up directly into xylene and heated for 4 h, whereupon it underwent transformation exclusively to the pyrroline (11) (78%). The conversion of (9) to (11) most probably involves a cyclopropyl imine rearrangement to the enamine (10) followed by isomerization to the cyclic imine tautomer (11). Although the rearrangement appeared to take place without addition of acid catalyst, the Kugelrohr-distilled ketimine (9) was completely unreactive when the xylene solution was heated to reflux in a reaction vessel which had previously been carefully washed with base. These results and the work reported below confirm Stevens' earlier conclusions regarding the requirement for acid catalysis in the thermal rearrangement of cyclopropyl ketimines.



Scheme 1

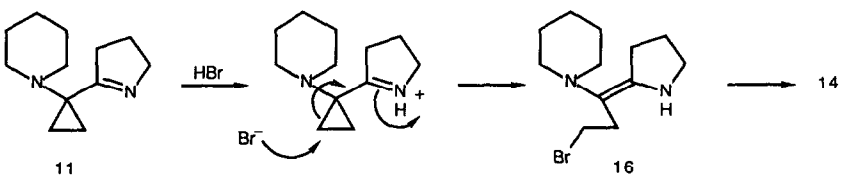
Proof of structure of (11) and unambiguous exclusion of the isomeric possibilities (10), (12) and (13), was provided by IR and NMR spectroscopy. In particular, the 500 MHz ^1H spectrum displays complex but discrete groups of resonances for methylene protons at positions b and c centered at δ 2.40 and 3.80, and a quintuplet at 1.82 corresponding to the protons at a. Irradiation of the 1.82 signal (a) yields singlets at 2.40 and 3.80; irradiation of the 2.40 signal (b) yields triplets at 3.80 and 1.83, while irradiation of the 3.80 resonance (c) yields triplets at 1.82 and 2.40. All of the above evidence clearly establishes (11) as the structure of the rearrangement product.



10 11 12 13

Prolonged heating of the pyrroline (11) in xylene did not lead to further ring expansion, but when it was converted to the hydrobromide salt with anhydrous HBr and then heated, neat, at 140° for 10 min under nitrogen, a second cyclopropyl imine rearrangement took place (Scheme 1). The product was the pyrrolizidinone (15)[9] (51%). We assume that the intermediate (14) underwent hydrolysis to (15) during dilute acid workup. It was possible to convert the nitrile (8) directly to the pyrrolizidinone (15) as follows: After addition of (8) to cyclopropyllithium, and workup with $Na_2SO_4 \cdot OH_2O$, the resulting imine was treated *in situ* with anhydrous HBr, the solvent removed, and the salt heated under N_2 at 150° for 5 min. Hydrolysis of the reaction mixture yielded (15) (30% from 8).

The direct conversion of the imine (9) to the pyrrolizidinone (15) as well as the rearrangement of the pyrroline (11) to (15) may involve ring-opening of the cylopropane ring by HBr, forming the intermediates (16) and (14) as shown (Scheme 2).[10] While the individual steps in the formation of (15) have precedent in the work of Stevens[10] and Pinnick,[11] the *bis*-ring expansion process is novel.



11 16

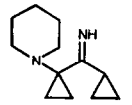
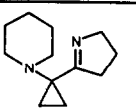
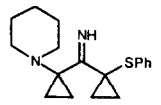
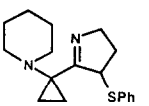
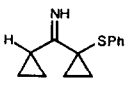
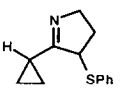
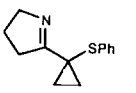
Scheme 2

Substituent Effects in Cyclopropane Ring-Opening

A noteworthy feature of the formation of (11) from (9) is the exclusive participation of the less substituted cyclopropane ring in the formation of the pyrroline. This result is unexpected in the light of earlier findings of other investigators[12,13,14,15,16] on substituent effects in the thermal conversion of vinylcyclopropanes to cyclopentenes. While it seems reasonable that cleavage of the more substituted ring in (9) would be favored by the enhanced stabilization of a carbonium ion intermediate, steric effects may play a dominant role in a process analogous to the cyclopropane ring opening in the conversion of 11 to 16, pictured above.[17]

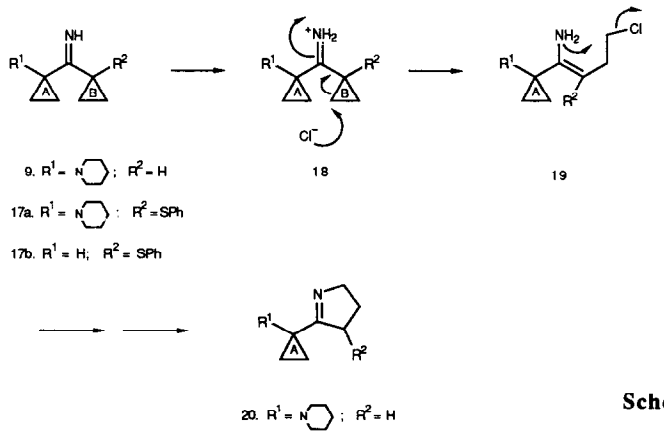
In further studies on this acid-catalyzed thermolysis, we have examined the effects of substituents in determining the preferred opening (A vs. B) of the cyclopropyl rings in the presence of both nucleophilic and non-nucleophilic counterions. Table 3 summarizes the results obtained with ammonium chloride. The thermolyses were all carried out in refluxing xylene at 140° for 1.5-5 h. No reaction took place in the absence of NH_4Cl (or other acid) as shown by the recovery of the starting ketimine from reaction vessels which were previously washed with base.

Table 3

dicyclopropylketimine	pyrroline	yield, %
 9	 11	78
 17a	 20	69
 17b	 21	28
	 22	22

The findings in Table 3 are in accord with the mechanism proposed earlier[10] by Stevens for related rearrangements of monocyclopropyl ketimines.[10,11,18] Thus (Scheme 3), attack of halide ion on the protonated ketimine derived from (9) appears to take place via (18) at the less-substituted cyclopropane ring (B), leading, through intermediate (18) to pyrroline (20) as shown. In the case of (17a), containing a thiophenyl group, attack on ring (B) (yielding 21) is again favored, most probably by the participation of the sulfur atom in stabilizing the negative charge developing in the transition state. With substrate (17b), it might be expected that the combination of steric and electronic factors operating at stage (18) would yield a mixture of products, (21) and (22) as is, in fact, observed.

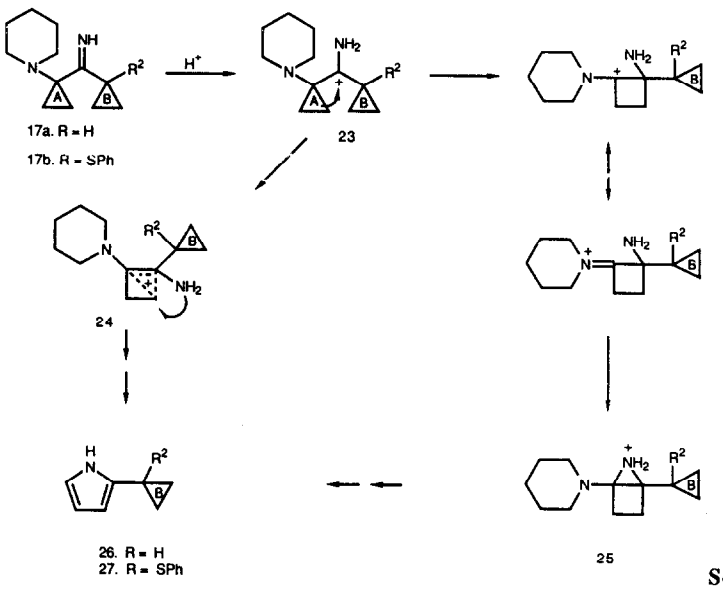
A completely different result was obtained when the dicyclopropyl ketimines were subjected to acid-catalyzed thermolyses in the presence of a non-nucleophilic counterion.



Scheme 3

On heating (9) and (17a) in xylene with the dimethyl ether complex of fluoroboric acid, both substrates underwent rearrangement to pyrrole derivatives (26) (32%) and (27) (42%).[19] In these instances, the only products isolated[20] resulted from ring-opening of the cyclopropyl ring (A) (containing the electron-releasing piperidino group). These findings are in

disagreement with previous reports in which it is proposed that a cyclopropyl ketimine rearrangement *does not occur* in the presence of an acid with a non-nucleophilic counterion.[10,18] One may now conclude that, even without the attack of a nucleophile, *cyclopropyl ketimines will, in fact, undergo acid-catalyzed rearrangement if there can be sufficient stabilization of the positive charge formed during the ring-opening process.*



Scheme 4

Formation of the pyrrole derivative by expansion of ring (A) may occur by initial protonation of the imine to form the *bis*-cyclopropyl carbinyl cation (23).[21] Ring-expansion of (23) to a 5-membered ring could then take place either through the bridged ion (24) or the bicyclic intermediate (25).[22] Scheme 4 outlines two possible pathways for this transformation.[22,23,24]

The application of this rearrangement to the synthesis of α-substituted pyrroles is under investigation. We will report separately on the mechanism of the ring-expansion.

Acknowledgments: This work was supported in part by N.I.H. Grant GM-07874. The authors express appreciation to Dr. Roger Frechette and Mr. Chi Vu for help in the preparation of this manuscript.

Experimental Section

1-(3-Chloropropionyl)piperidine (1)

To 150 mL of freshly distilled methylene chloride, piperidine (30.0 mL, 0.30 mol) and N,N-dimethylaniline (70.0 mL, 0.55 mol) were added. The solution was cooled to 0°C under a nitrogen atmosphere, and 3-chloropropionyl chloride (Aldrich (98%), 24.0 mL, 0.246 mol) in 30 mL of methylene chloride was added dropwise at 0° in 30 min. The solution was allowed to warm to 22°C and was stirred for 12 h. The reaction mixture was washed with 2 x 200 mL portions of 1N aqueous hydrochloric acid, water, and saturated aqueous sodium bicarbonate. The aqueous layers were back-extracted with 100 mL of methylene chloride. The organic layers were combined, dried over magnesium sulfate, and sovent was removed *in vacuo* on a rotary evaporator. The resultant green liquid was purified by distillation, yielding the amide (42 g, 97%) bp 99-107°C/0.35 mm Hg, Lit[25] bp 118-119°C/2 mm Hg: IR (neat film) 2940, 2850, 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.54 (6H, br s), 2.70 (2H, t), 3.40 (4H, br s), 3.72 (2H, t).

1-Piperidino-1-trimethylsilyloxycyclopropane (2)

To finely divided sodium, (22.9 g, 996 mmol) in 1500 mL of ether was added 110 mL of trimethylsilyl chloride under a nitrogen atmosphere. To this mixture, the chloroamide (1) (45 g, 260 mmol), in 75 mL of ether was added dropwise with constant vigorous stirring during 5 h. The solution was stirred for 24 h at 22°C and the solvent carefully decanted. The residual solids were washed with 100 mL of ether, the organic layers combined, and excess trimethylsilyl chloride and ether removed by distillation, yielding (2) (47.5 g, 87%, 95% pure) as an orange oil: IR (neat) 3100, 3000, 2950, 2845 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$ δ 0.15 (9H, s), 0.82 (4H, br s), 1.50 (6H, br s), 2.7 (4H, br s); MS m/e(%) 214 (4.5), 213 (24.9), 124 (45.1), 84 (49.7), 73 (100).

Anal. Calcd. for $C_{11}H_{23}NOSi$: C, 61.91; H, 10.86; N, 6.56. Found: C, 61.86; H, 10.68; N, 6.61.

1-Hydroxy-1-piperidinocyclopropane (3)

To 160 mL of 1 N tetra-n-butylammonium fluoride in methanol was added 1-piperidino-1-trimethylsilyloxycyclopropane (32 g, 150 mmol) prepared (undistilled) as described above. The solution was stirred for 1 h at 22°C. The solvent was removed *in vacuo* on a rotary evaporator yielding a viscous orange oil which was partitioned between 750 mL of ether and 750 mL of water. The aqueous layer was washed with 2 x 500 mL portions of ether. The organic layers were combined, and the solvent removed *in vacuo*, yielding an orange crystalline mass (16.4 g). Recrystallization from ether/hexane yielded 6.1 g of 1-hydroxy-1-piperidinocyclopropane, mp 80.5-82°C, lit[1b] 81-82°C. From the mother liquor, an additional 6 g of product could be obtained by evaporation of the solvent and flash chromatography of the residue on silica gel. The combined yield was 57%. This compound was identical in all respects (NMR, IR, MS) to a sample prepared from cyclopropanone and piperidine: IR ($CHCl_3$) 3750, 3600, 3450, 3090, 3000, 2880, 2850, 1460; ^1H NMR (90 MHz, $CDCl_3$) δ 0.72-0.96 (4H, AA'BB'), 1.48 (6H, br s), 2.40-2.88 (5H, m); MS m/e(%) 142(4.0), 141 (45.4), 126 (43.0), 84 (100).

1-Piperidino-1-vinylcyclopropane (5a)

To 25 mL of dry tetrahydrofuran containing 1-piperidino-1-trimethylsilyloxycyclopropane (0.30 g, 1.4 mmol), vinyl magnesium bromide (Aldrich, 4 mL, 1.1 M in tetrahydrofuran) was added at 22°C for 60 h. The excess Grignard reagent was quenched with 2 mL of 10% aqueous sodium hydrogen phosphate. The aqueous mixture was washed with 3 x 60 mL of ether. The organic layers were combined and dried over magnesium sulfate. The mixture was filtered and solvent was removed *in vacuo* on a rotary evaporator at less than 30°C yielding 0.24 g of pale yellow oil. Flash chromatography of the residue on silica gel using 10% ether/pentane as eluent yielded the adduct (0.142 g, 67%) as a colorless liquid: IR (neat film) 3084, 3007, 2939, 2856, 2808, 1451, 1231 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.52-0.68 (4H, m), 1.64 (6H, br s), 2.60-2.74 (4H, m), 4.90 (1H, dd), 5.06 (1H, dd), 6.22 (1H, dd); MS m/e(%) 151 (31), 150 (100), 136 (28.5), 122 (35.0), 108 (25.8), 94 (26.7), 84 (15.4).

Exact mass calcd for $C_{10}H_{17}N$: 151.136. Found: 151.135.

1-(Cyclopenten-1-yl)-1-piperidinocyclopropane (5b)

To 2 mL of anhydrous tetrahydrofuran containing magnesium turnings (53 mg, 2.18 mmol), 2 mL of tetrahydrofuran containing 1-bromocyclopentene (255 mg, 1.73 mmol) was added in several portions. The reaction was stirred at 22°C for 16 h. To this mixture, 1-piperidino-1-trimethylsilyloxycyclopropane (360 mg, 1.7 mmol) was added neat in two portions. The reaction was stirred for 3 h. Work-up in the usual way yielded the cyclopentenyl adduct (48 mg, 15%) as a colorless liquid: IR ($CHCl_3$ solution), 3086, 3006, 2936, 1443 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 5.48 (1H, br t), 2.76-2.48 (4H, m), 2.44-2.08 (4H,

m), 2.00-1.88 (2H, m), 1.80-1.28 (6H, br s), 0.76-0.52 (4H, AA'BB'); MS m/e (%) 192 (60), 19 (37.7), 148 (100).

Exact mass calcd for $C_{13}H_{21}N$: 191.167. Found: 191.166.

1-Phenyl-1-piperidinocyclopropane (5c)

To 25 mL of dry tetrahydrofuran under nitrogen containing magnesium turnings (0.175 g, 7.2 mmol) and a crystal of iodine, bromobenzene (0.63 mL, 6.0 mmol) was added dropwise during 15 min. The reaction was stirred for 1 h, and neat 1-piperidino-1-trimethylsilyloxycyclopropane (0.50 g, 2.3 mmol) was added in one portion. The mixture was stirred for 4 h at 22°C, then worked up in the usual manner, yielding 1-phenyl-1-piperidinocyclopropane (0.364 g, 79%) as a colorless liquid: IR (neat film) 3075, 3020, 2940, 2875, 2820, 1490 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.72-1.00 (4H, AA'BB'), 1.08-1.64 (6H, m), 2.48 (4H, br t), 7.32 (5H, br s); MS m/e(%) 201 (17.9), 200 (100), 117 (23.7), 1.04 (37.7), 91 (14.4), 84 (20.8), 77 (13.9).

Exact mass calcd for $C_{14}H_{19}N$: 201.152. Found: 201.149.

1-Ethyl-1-piperidinocyclopropane (5d)

To 50 mL of dry tetrahydrofuran under a nitrogen atmosphere containing ethyl magnesium bromide (Aldrich, 5.6 mL, 3N in ether, 16.8 mmol), neat 1-piperidino-1-trimethylsilyloxycyclopropane (1.2 g, 5.6 mmol) was added dropwise during 35 min. The reaction mixture was stirred for 22 h at 22°C. Work-up in the usual manner gave the desired ethyl adduct (0.79 g, 92%) as a colorless liquid: IR (neat film) 3060, 2970, 2890, 1450, 1265, 1000 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.40 (4H, br s), 0.76 (3H, t, J=9 Hz), 40 (6H, br s), 1.52 (2H, q, J=9 Hz), 2.6 (4H, br t); MS m/e(%) 154 (2), 153 (16.9), 138 (100), 124 (12.2), 84 (28). 56 (69).

Exact mass calcd for $C_{10}H_{19}N$: 153.152. Found: 153.151.

1-(Indol-3-yl)-1-piperidinocyclopropane (5e)

To 125 mL of dry methylene chloride, 1-hydroxy-1-piperidinocyclopropane (0.50 g, 3.5 mmol) was added. The solution was cooled to -78°C under a nitrogen atmosphere, and titanium (IV) tetrachloride (0.20 mL, 1.8 mmol) was added neat in one portion. The resulting yellow suspension was stirred at -78°C for 30 min. Indole (1.25 g, 10.7 mmol) was added in one portion. The mixture was allowed to warm to 22°C. The solids dissolved and the reaction was stirred for 16 h at 22°C. Dilute aqueous sodium bicarbonate (100 mL) was added and the solvents were removed by decantation. The remaining residue was hydrolyzed with 10 mL of saturated sodium bicarbonate. The aqueous layers were combined and dried over magnesium sulfate. Solvent was removed *in vacuo* on a rotary evaporator yielding 1.8 g of yellow oily solid. This material was purified by flash chromatography using 50% ether/hexane as eluent yielding the desired adduct (0.706 g, 85%) as a while solid, mp (decomposition) 206-207°C: IR ($CHCl_3$ solution) 3477, 3008, 2938, 2857, 2811, 1453, 1240 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.72-1.04 (4H, AA'BB'), 1.16-1.76 (6H, m), 2.64 (4H, br t), 7.00-7.48 (4H, m), 7.72-7.92 (1H, m), 8.64 (1H, br s); ^{13}C NMR (67.88 MHz, $CDCl_3$) δ 135.5 (s), 128.9 (s), 125.4 (d), 121.6 (d), 120.2 (d), 119.4 (d), 113.5 (s), 110.9 (d), 51.3 (t), 41.0 (s), 26.1 (t), 24.2 (t), 14.5 (t); MS m/e(%) 241 (14.2), 240 (84.1), 225 (100).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.70; H, 8.22; N, 11.49.

1-(N-methylpyrrol-2-yl)-1-piperidinocyclopropane (5f)

To 50 mL of methylene chloride, 1-hydroxy-1-piperidinocyclopropane (0.396 g, 2.8 mmol) was added. The solution was cooled to -78°C under a nitrogen atmosphere and titanium (IV) tetrachloride (0.34 mL, 3.1 mmol) was added neat in one portion. The resulting yellow suspension was stirred for 120 min at -78°C. Neat N-methylpyrrole (0.46

mL, 8.4 mmol) was added in one portion. The mixture was allowed to warm to 22°C. The solids dissolved and the pale yellow solution was stirred at 22°C for 19 h. The reaction was quenched by the addition of 10 mL of water. The aqueous layer was washed with 4 x 40 mL of methylene chloride. The organic layers were combined, and washed with 20 mL of brine. Solvent was removed *in vacuo* on a rotary evaporator yielding 0.85 g of colorless oil. This material was purified by flash chromatography using 50% ether/pentane as eluent yielding the desired adduct (0.30 g, 65%) as a colorless liquid: IR (neat film) 3100, 3010, 2940, 2850, 1480, 1240 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.84-0.96 (4H, AA'BB'), 1.44 (6H, br m), 2.52 (4H, br t), 3.64 (3H, s), 6.04 (2H, m), 6.52 (1H, t); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 130.3 (s), 121.6 (d), 111.2 (d), 106.1 (d), 51.2 (t), 40.9 (s), 34.6 (a), 2.2 (t), 24.1 (t), 14.9 (t); MS m/e(%) 205 (13), 204 (100), 203 (85), 120 (96.8), 106 (79.7), 84 (25.3).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.18; H, 9.81; N, 14.01.

1-(2-Oxocyclohexyl)-1-piperidinocyclopropane (5g)

To 10 mL of dry methylene chloride, 1-hydroxy-1-piperidinocyclopropane (0.187 g, 1.3 mmol) was added. The solution was cooled to -78°C under a nitrogen atmosphere, and titanium (IV) tetrachloride (0.190 mL, 1.70 mmol) was added in one portion. The resulting yellow suspension was stirred at -78°C for 20 min. Neat 1-trimethylsilyloxycyclohexene (0.60 g, 3.9 mmol) was added in one portion. The mixture was allowed to warm to 22°C. The solids dissolved and the solution was stirred for 2 h. The reaction was quenched with 5 mL of water. Aqueous 15% sodium hydroxide was added until the aqueous layer was basic. The aqueous layer was extracted with 3 x 25 mL of methylene chloride. The organic layers were combined and solvent was removed *in vacuo* on a rotary evaporator yielding 0.210 g of the aminoketone as a pale yellow oil. The liquid product was purified by flash chromatography using 15% ether/pentane as eluent yielding the aminoketone (0.167 g, 58%) as a colorless liquid: IR ($CHCl_3$ solution) 1935, 1709 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.40-1.0 (4H, m), 1.10-1.90 (15H, m), 2.10-2.60 (4H, m); ^{13}C NMR (67.88 MHz, $CDCl_3$) δ 210.5 (s), 50.9 (d), 50.4 (t), 43.5 (s), 41.7 (t), 31.8 (t), 26.3 (t), 25.9 (t), 24.2 (t), 23.9 (t), 10.8 (t), 9.6 (t); MS m/e(%) 222 (1.8), 221 (11.1), 193 (9.7), 150 (100), 124 (17.1), 84 (25.5).

Exact mass calcd. for $C_{14}H_{23}NO$: 221.178. Found: 221.177.

Dimethyl 2-(1-piperidinocycloprop-1-yl) Malonate (5h)

To 10 mL of dry methylene chloride, 1-hydroxy-1-piperidinocyclopropane (0.110 g, 0.78 mmol) was added. Titanium (IV) tetrachloride (0.095 mL, 0.86 mmol) was added at -78°C under nitrogen. The resulting suspension was stirred at -78°C for 20 min. and dimethylmalonate (0.135 mL, 1.56 mmol) was added in one portion. The mixture was allowed to warm to 22°C. The solids dissolved and the solution was stirred for 90 h at 22°C. The reaction was quenched with 3 mL of aqueous saturated sodium bicarbonate. The solution was stirred 15 min. The aqueous layer was extracted with 2 x 50 mL of methylene chloride. The organic layers were combined, and the solvent was removed *in vacuo* on a rotary evaporator. The resulting orange residue was purified by flash chromatography utilizing 25% ether/pentane as eluent. The pure adduct was obtained as a colorless liquid (0.107 g, 53%): IR (neat film) 3450, 3020, 2950, 2860, 2800, 1770, 1740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.74 (4H, br s), 1.40 (6H, br s), 2.52 (4H, br s), 3.72 (6H, br s), 3.96 (1H, br s); MS m/e(%) 255 (5.8), 240 (6.0), 196 (100), 164 (53), 124 (25.8), 84 (25.0).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.20; H, 8.30; N, 5.27.

1-Cyano-1-piperidinocyclopropane (8)

To 40 mL of water containing acetic acid (1.3 mL, 22.7 mmol) and 1-piperidyl-1-cyclopropanol (2.1 g, 14.9 mmol) cooled to 0°C, potassium cyanide (0.98 g, 15.1 mmol) in 20 mL of water was added during 3 min. The mixture was allowed to warm to 22°C, and was stirred for 10 h. The aqueous mixture was extracted with 4 x 200 mL of ether. The ether

layers were combined, washed with 100 mL of saturated aqueous sodium chloride and dried over magnesium sulfate. Solvent was removed at less than 30°C *in vacuo* on a rotary evaporator yielding 2.4 g of yellow oil. This material was purified by flash chromatography on silica gel using 10% ether/pentane as eluent. The cyanide (1.6 g, 72%) was obtained as a colorless liquid: IR (neat film) 3075, 3000, 2920, 2830, 2790, 2200 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.90-1.24 (4H, AA'BB), 1.32-1.68 (6H, m), 2.64 (4H, br t); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 118.1 (s), 51.1 (t), 35.3 (s), 25.1 (t), 23.4 (t), 15.1 (m); MS m/e(%) 151 (2.4), 150 (25.5), 135 (100).

Exact mass calcd for $C_9H_{14}N_2$: 150.116. Found: 150.114.

Cyclopropyl 1-Piperidinocycloprop-1-yl Ketimine (9)

To 250 mL of anhydrous ether under a nitrogen atmosphere, cyclopropyl bromide (Aldrich, 2.0 mL, 24.1 mmol) was added. The solution was cooled to -78°C and *tert*-butyllithium (11.5 mL, 2.1 M in pentane, 24.15 mmol) was added in 5 min. The solution was stirred at -78°C for 1.75 h. A solution of 1-cyano-1-piperidinocyclopropane (1.8 g, 12.0 mmol) in 10 mL of ether was added in one portion. The reaction mixture was allowed to warm to 0°C and was stirred for 1 h. The reaction was quenched by the addition of sodium sulfate decahydrate (1.5 g, 4.6 mmol). The mixture was warmed to 22°C and stirred for 1 h. The solids were removed by filtration, and volatiles were removed *in vacuo* on a rotary evaporator. The resultant yellow oil was bulb-to-bulb distilled (180°C/0.1 mm Hg) yielding the ketimine (2.3 g, 99%): IR (neat film) 3191, 1618 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.60-1.04 (9H, m), 1.48 (7H, br m), 2.40 (4H, br t).

Exact mass calcd for $C_{12}H_{20}N_2$: 192.163. Found: 192.161.

1-(3,4-Dihydro-2H-pyrrol-5-yl)-1-piperidinocyclopropane (11)

To 5 mL of anhydrous p-xylene, ketimine (9) (0.422 g, 2.2 mmol) was added. The solution was heated at reflux under a nitrogen atmosphere for 4.5 h. The solvent was removed by distillation at atmospheric pressure. The resultant red oil was purified by flash chromatography using 25% ether/pentane as eluent. The pyrroline was obtained as a slightly yellow liquid (0.333 g, 77%) which darkened quickly upon standing: IR (neat film) 3100, 3000, 2920, 2840, 1624 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87-0.96 (4H, AA'BB'), 1.40 (6H, br m), 1.82 (2H, m), 2.40 (2H, m), 2.82 (4H, br t), 3.80 (2H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 178.9 (s), 60.3 (t), 50.6 (t), 46.7 (s), 37.0 (t), 26.8 (t), 24.6 (t), 22.3 (t), 15.8 (t); MS m/e(%) 193 (12), 192 (92.7), 141 (100).

Anal. Calcd for $C_{12}H_{20}N_2$: 192.163. Found: 192.162.

1-Pyrrolizidinone (15)

To 125 mL of anhydrous ether the ketimine (9) (0.300 g, 2.38 mmol) was added. Anhydrous hydrogen bromide generated from the admixture of sodium bromide and concentrated sulfuric acid was bubbled through the solution for 2 min. The solvent was removed *in vacuo* on a rotary evaporator. The resultant yellow solid was pyrolyzed neat in a 250 mL round bottom flask under nitrogen at 153°C for 5 min. To this mixture, 50 mL of 1 N aqueous hydrochloric acid was added. The solution was stirred for 1 h at 22°C. The mixture was made basic to pH 13 by the addition of 15% aqueous sodium hydroxide, then extracted with 4 x 50 mL of chloroform. The organic layers were combined and solvent was removed *in vacuo* on a rotary evaporator. The resultant brown oil was purified by flash chromatography using 10% methanol/chloroform as eluent. The 1-azabicyclo[3.3.0]octane (0.063 g, 32%) was obtained as a pale yellow liquid which decomposed upon standing: IR ($CHCl_3$ solution) 2950, 2880, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.73-1.91 (3H, m), 1.95-2.18 (1H, m), 2.27-2.57 (2H, m), 2.60-2.85 (1H, m), 2.90-3.17 (2H, m), 3.30-3.55 (2H, m); MS m/e(%) 126 (1.1), 125 (16.0), 97 (100), 96 (44.9), 69 (84.1).

1-Pyrrolizidinone (15)

To 50 mL of anhydrous ether, pyrroline (11) (0.110 g, 0.57 mmol) was added. Anhydrous hydrogen bromide generated from the admixture of sodium bromide and concentrated sulfuric acid was bubbled through the solution for 2 min. The solvent was removed *in vacuo* on a rotary evaporator. The resultant white solid was pyrolized neat in a 100 mL round bottom flask under nitrogen at 143°C for 5 min. To this mixture, 10 mL of 1 N aqueous hydrochloric acid was added. The solution was stirred for 1 h at 22°C. The mixture was made basic to pH 13 by the addition of 15 mL of aqueous sodium hydroxide, then extracted with 4 x 25 mL of chloroform. The organic layers were combined and solvent was removed *in vacuo* on a rotary evaporator. The resultant brown oil was purified by flash chromatography using 5% methanol/chloroform as eluent, yielding 2-pyrrolizidinone (0.037 g, 51%) as an off-white liquid which decomposed upon standing: IR ($CHCl_3$ solution 2950, 2860, 1745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.70-3.60 (11H, m); MS m/e(%) 126 (1.0), 125 (12.7), 97 (100), 96 (47.9), 69 (81.4).

1-Piperidinocycloprop-1-yl 1-Thiophenylcycloprop-1-yl Ketimine (17a)

To 100 mL of anhydrous tetrahydrofuran, thiophenyl chloropropane (3.0 g, 20 mmol) was added. The solution was cooled to 0°C under a nitrogen atmosphere and n-butyllithium (12.9 mL, 1.55 M in hexane, 20 mmol) was added quickly. The solution was stirred at 0°C for 2 h. Neat 1-cyano-1-piperidinocyclopropane was added in one portion. The mixture was allowed to warm to 22°C and was stirred for 15 h. Sodium sulfate decahydrate (1.4 g, 4.3 mmol) was added and the mixture was stirred for 1 h. The solids were removed by filtration and the solvent was removed from the supernatant *in vacuo* on a rotary evaporator The resultant orange liquid was purified by flash chromatography using 25% ether/pentane as eluent. The desired ketimine (2.1 g, 85%) was obtained as a colorless liquid: IR (neat film) 3300, 3080, 3020, 2940, 1680, 1600, 1590 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.80-1.02 (4H, m), 1.10-1.80 (10H, m), 2.42 (4H, br t), 7.20 (5H, m); MS m/e (%) 301 (2.8), 300 (10.8), 215 (11.1), 191 (100), 151 (10.7), 124 (12.2), 110 (26.6), 109 (6.9), 84 (21.6).

Exact mass calcd for $C_{18}H_{13}SN$: 300.166. Found: 300.165.

Cyclopropyl 1-Thiophenylcycloprop-1-yl Ketimine (17b)

To 50 mL of anhydrous ether under a nitrogen atmosphere, cyclopropyl bromide (Aldrich, 0.48 mL, 5.8 mmol) was added. The solution was cooled to -78°C, and *tert*-butyllithium (2.9 mL, 2.0 M in pentane, 4.8 mmol) was added in 2 min. The solution was stirred at -78°C for 1 h. A solution of 1-cyano-1-thiophenyl cyclopropane (0.50 g, 2.9 mmol) in 1 mL of ether was added in one portion. The reaction was allowed to warm to 22°C and was stirred for 1.5 h. Work-up in the usual way, followed by bulb-to-bulb distillation (173°C/0.2 mm Hg) yielded the ketimine (0.56 g, 91%) as a colorless liquid: IR (neat film) 3350, 2930, 2860, 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$), δ 0.66-1.80 (10H, m), 7.08-7.30 (5H, m); MS m/e(%) 219 (5.9), 218 (17), 217 (100), 149 (12.2), 109 (442), 77 (56.2).

Exact mass calcd for $C_{13}H_{15}NS$: 217.0925. Found: 217.0913.

1-(3,4-Dihydro-4-thiophenyl-2H-pyrrol-5-yl)-1-piperidinocyclopropane (20)

To 10 mL of anhydrous p-xylene, ketimine (17a) (0.55g, 1.8 mmol) and ammonium chloride (0.05 g, 0.9 mmol) were added. The mixture was heated at reflux under a nitrogen atmosphere for 4 h. Solvent was removed by distillation and the red residue was purified by flash chromatography on silica gel using 25% ether/pentane as eluent. The cyclic imine (0.38 g, 69%) was obtained as a pale yellow liquid: IR (neat film) 3060, 2940, 2860, 1618, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ0.72-1.56 (10H, m), 1.88-2.46 (2H, m), 2.48-2.86 (4H, m), 3.36-4.10 (2H, m), 4.22-4.40 (1H, m), 7.05-7.60 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) 178.0 (s), 135.2 (s), 131.2 (d), 128.7 (d), 126.8 (d), 58.5 (t), 54.3 (d), 50.7 (t), 45.9 (s), 32.5

(t), 26.5 (t), 24.3 (t), 16.5 (t), 12.5 (t).

Exact mass calcd for $C_{18}H_{13}N_2S$: 300.1660. Found: 300.1649.

(3,4-Dihydro-4-thiophenyl-2H-pyrrole-5-yl)cyclopropane (22) and 1-(3,4-Dihydro-2H-pyrrol-5-yl)-1-thiophenylcyclopropane (21)

To 8 mL of anhydrous xylene, ketimine (17b) (0.58 g, 2.7 mmol) was added. The mixture was heated at reflux under a nitrogen atmosphere for 1.5 h. Solvent was removed by distillation and the yellow residue was purified by flash chromatography on silica gel utilizing 20% ether/pentane as eluent. The cyclic imines (22) (0.12 g, 20%) and (21) (0.16 g, 28%) were obtained as colorless liquids. (22): IR (neat film) 3050, 2960, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (2H, dd), 1.69 (2H, dd), 1.87 (2H, quintet), 2.73 (2H, tt), 3.83 (2H, tt), 7.25-7.31 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) 179.4 (s), 137.5 (s), 128.7 (d), 126.3 (d), 125.0 (d), 60.9 (t), 36.4 (t), 25.8 (s), 24.1 (t), 18.8 (t), MS m/e(%) 219 (5.8), 218 (16), 217 (100), 216 (6), 77 (30.2).

Exact mass calcd for $C_{13}H_{15}NS$: 217.093. Found: 217.094.

(21): IR ($CHCl_3$ solution) 3060, 2950, 1625 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.62-1.05 (4H, m), 1.48-2.54 (3H, m), 2.98-3,90 (2H, m), 3.91-4.14 (1H, m), 6.88-7.64 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 177.5 (s), 133.8 (s), 132.5 (d), 129.0 (d), 127.6 (d), 58.5 (t), 55.7 (d), 31.8 (t), 11.6 (d), 9.8 (t), 9.5 (t); MS m/e(%) 219 (2.5), 218 (7.2) (36.6), 117 (100), 109 (37.5), 77 (35.6).

Exact mass calcd for $C_{13}H_{15}NS$: 217.093. Found: 217.0929.

2-Cyclopropylpyrrole (26)

To 2 mL of anhydrous xylene under a nitrogen atmosphere, ketimine (9) (100 mg, 0.52 mmol) and the dimethyl ether complex of fluoroboric acid (50 μl, 0.51 mmol) were added at 22°C. The mixture was heated at reflux for 30 min, then cooled and flash chromatographed. The xylene was eluted with pentane and the product with 5% ether/pentane. The desired pyrrole (17 mg, 31%) was obtained as a colorless liquid: IR (CCl_4 solution) 3560, 3380, 3080, 2990, 1565 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.4-7.6 (1H, br s), 6.72-6.54 (1H, m), 6.25-6.04 (1H, m), 5.92-6.78 (1H, m), 2.04-1.66 (1H, m), 1.00-0.50 (4H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 134.3 (s), 116.1 (d), 108.0 (d), 103.7 (d), 8.0 (d), 6.4 (t); MS m/e(%) 108 (8.5), 107 (100), 80 (79.7), 79 (41.5).

Exact mass calcd for C_7H_9N: 107.0735. Found: 107.0735.

2-(1-Thiophenylcycloprop-1-yl)-pyrrole (27)

To 20 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere, ketimine (17b) (100 mg, 0.33 mmol) and the dimethyl ether complex of fluoroboric acid (31 μl, 0.32 mmol) were added at 22°C. The mixture was heated at reflux for 4 h. Solvent was removed *in vacuo* on a rotary evaporator and the resultant red oil was flash chromatographed using 5% ether/pentane as eluent. The desired pyrrole (31 mg, 42%) was obtained as a colorless liquid: IR (CCl_4) 3460, 3080, 2990, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.5-8.3 (1H, br), 7.4-7.2 (5H, m), 6.5-6.4 (1H, m), 7.0-6.9 (1H, m), 5.75-5.60 (1H, m), 1.48-1.30 (4H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.6 (s), 134.1 (s), 128.7 (d), 128.2 (d), 125.8 (d), 116.9 (d), 108.4 (d), 103.4 (d), 22.8 (s), 18.8 (t); MS m/e(%): 217 (1.9), 216 (4.7), 215 (22.6), 109 (17.5), 77 (47.8), 40 (100).

Exact mass calcd for $C_{13}H_{13}NS$: 215.0769. Found: 215.0759.

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