

Synthesis and Isomerization of 3-Pyrroline Enamines

A. Gilbert Cook*, Karen A. Switek, Kenneth A. Cutler and Allison M. Witt

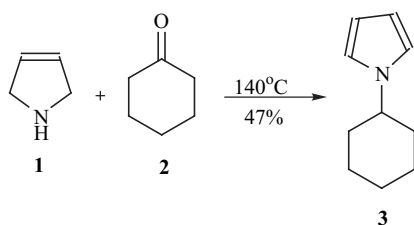
Department of Chemistry, Valparaiso University, Valparaiso, IN 46383, USA

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Abstract: 3-Pyrroline reacts with cyclic ketones to form enamines as kinetically controlled products. Under more vigorous conditions, pyrroles are formed as thermodynamically controlled products by way of a 1,3-hydride shift.

Keywords: Enamine, pyrrole, isomerization, pyrroline.

The reaction of 3-pyrroline (**1**) with cyclohexanone (**2**) in refluxing xylene results in the formation of 1-cyclohexylpyrrole (**3**) [1] in a 47% yield (**Equation 1**) via a 1,3-hydride shift.



Equation 1.

The presence of a pyrrole ring in this product was demonstrated by ^{13}C NMR with δ 107.2 and 118.2 ppm due to pyrrole ring carbons and by ^1H NMR with δ 6.12 and

6.71 ppm due to pyrrole ring hydrogens [2]. Similar reactions take place when 3-pyrroline is allowed to react with 2-substituted cyclohexanones and cyclopentanones (**Table 1**).

When the reactions were allowed to take place at room temperature with molecular sieves present, the major products were the corresponding enamines. For example, when 2-methylcyclohexanone (**4**) is allowed to react at room temperature with 3-pyrroline (**1**), most of the product is enamine **5** with a small amount of pyrroles **6** (*cis* isomer) and **7** (*trans* isomer) (**Equation 2**). But when this reaction is run in refluxing toluene, only pyrroles **6** and **7** are obtained.

It is obvious from these results that the enamine is initially formed as the kinetically controlled product, and then isomerization of the enamine via a 1,3-hydride shift

Table 1. Product Distribution and Reaction Conditions for Reactions of 3-Pyrroline With Cyclic Ketones^a

Ketone	Temperature ($^{\circ}\text{C}$)	Total Yield (%)	Distribution (%)	
			Enamine	Pyrrole
2-Methylcyclohexanone	25	17	91 ^b	9
2-Methylcyclohexanone	110	36	0	85 <i>cis</i> ^c , 15 <i>trans</i>
Cyclopentanone	25	72	93	7
Cyclopentanone	110	36	80	20
2-Methylcyclopentanone	25	43	99 ^d	1
2-Methylcyclopentanone	110	22	0	36 <i>cis</i> ^c , 64 <i>trans</i>
2-Acetylcyclopentanone	110	58	100 ^e	0

^aThe relative amounts of isomers were determined by integration of ^{13}C NMR signals obtained in CDCl_3 solvent using a 30-second relaxation delay in combination with integration of GC-MS spectra.

^bIt is 100% trisubstituted.

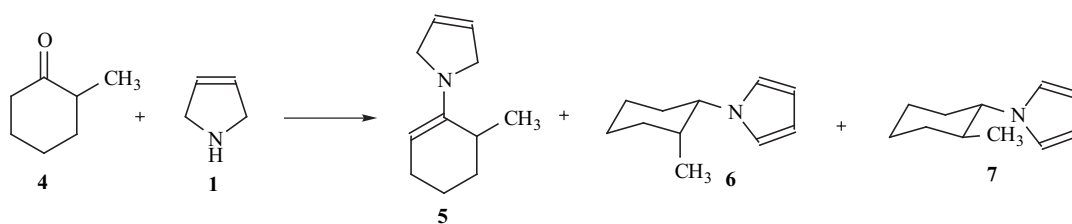
^cThe *cis/trans* distribution was determined using the fact that the ^{13}C NMR chemical shift for the methyl group in the *trans* isomer (equatorial methyl) is shifted further downfield than in the *cis* isomer (axial methyl). See Breitmaier, E.; Voelter, E.; *Carbon-13 NMR Spectroscopy*, 3rd ed., VCH, New York 1987, pages 186-189. Also the retention time on a Crosslinked 5% Ph Me Silicon 30 m capillary column is longer for the *cis* isomer than for the *trans* isomer.

^d It is 83% trisubstituted and 17% tetrasubstituted.

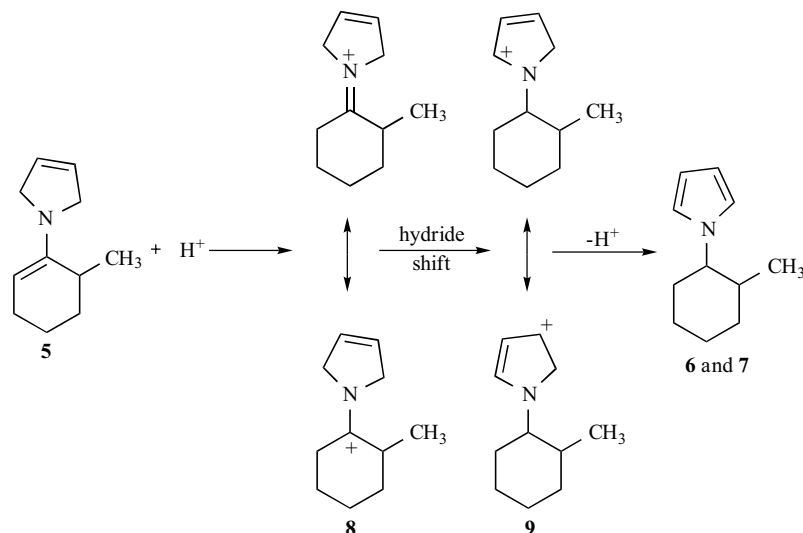
^e It is 100% tetrasubstituted.

*Address correspondence to this author at the Department of Chemistry, Valparaiso University, Valparaiso, IN 46383, USA; E-mail: Gil.Cook@valpo.edu

takes place to form the thermodynamically controlled pyrrole product. *Ab initio* calculations using the hybrid density functional B3LYP/6-31* model were run on these enamine



Equation 2.



Scheme 1.

Table 2. Enamines and Pyrroles Calculated Energies*

Ketone	Enamine		Pyrrole	
	Trisubstituted	Tetrasubstituted	Cis	Trans
Cyclohexanone	-444.807617		-444.846780	
2-Methylcyclohexanone	-484.119288	-484.116053	-484.155744	-484.161461
Cyclopentanone	-405.489889		-405.521562	
2-Methylcyclopentanone	-444.803656	-444.802334	-444.834998	-444.839150
2-Acetylcyclopentanone	-558.130306	-558.141435	-558.163215	-558.165034

* The calculations used hybrid density functional B3LYP/6-31G* model. The energy is in hartrees.

Table 3. Iminium Ions, Transitions States and Activation Energies*

Ketone	Iminium Ion	Transition State		Activation Energy	
		Cis	Trans	Cis	Trans
2-Methylcyclohexanone	-484.530197	-484.428712	-484.426357	0.101485	0.103840
2-Methylcyclopentanone	-445.211421	-445.105740	-445.179012	0.105681	0.032409

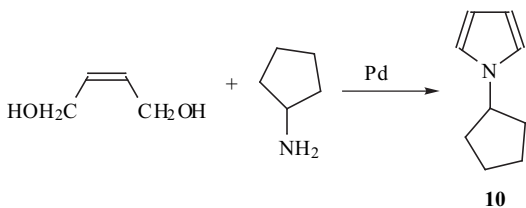
The calculations used hybrid density functional B3LYP/6-31G model. The transition state Hessians yielded only one imaginary frequency, and the normal coordinates correspond to the imaginary frequency connecting reactants and products in this isodesmic reaction. The energy is reported in hartrees.

and pyrrole products (Table 2). These calculations show that all the pyrrole products are thermodynamically more stable than the enamine products. A possible mechanism for this acid catalyzed isomerization is given in Scheme 1 using enamine 5 as the example. It involves the hydride shift in

the iminium ion (8) from the 2-position of the heterocyclic amine to the 1-position of the cyclohexyl moiety. Then a proton is lost from the pyrrolinium ion (9) to give the final pyrrole product. The major product in the reaction of enamine 5 is the *cis* pyrrole (6) in a *cis:trans* ratio of 85:15

(Table 1) even though *ab initio* calculations show the *trans* product (7) to be more stable than the *cis* product (6) (Table 2). The reason for this is seen in the relative energies of the transition states with the activation energy leading to the *cis* isomer being smaller than that leading to the *trans* isomer (Table 3). So the *cis* isomer is the kinetically controlled isomerization product and the *trans* isomer is the thermodynamically controlled isomerization product. In the case of 2-methylcyclopentanone, the major pyrrole product is the *trans* isomer (Table 1). *Ab initio* calculations show that the transition state leading to the *trans* isomer is lower in energy than that leading to the *cis* isomer. So the *trans* isomer is both the kinetically controlled and thermodynamically favored isomer (Table 3). Three of the four activation energies are surprisingly large in these calculations, and this may be due either to solvent effects or to an different, lower energy reaction mechanism.

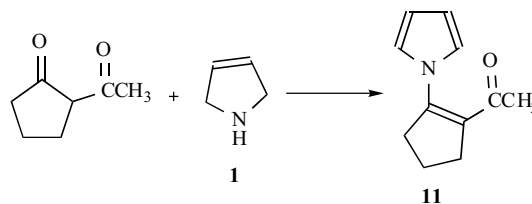
The trisubstituted enamine 5 is the only enamine isomer produced as contrasted with a 90:10, trisubstituted to tetrasubstituted enamine isomeric ratio when pyrrolidine is the secondary amine used [3]. The amount of trisubstituted isomer present in the product mixture is indicative of the importance of $n-\pi$ resonance between the amine moiety and the alkene [4]. So it appears that the 3-pyrroline has even greater $n-\pi$ resonance interaction than pyrrolidine. This observation corresponds to the fact that 1-methyl-3-pyrroline has a lower IP_1 than the corresponding saturated 1-methylpyrrolidine due to homoconjugative interaction between the nitrogen lone-pair electrons and the non-adjacent π -electrons [5]. The lower the IP_1 the greater the $n-\pi$ resonance interaction [4]. On the other hand, this does not appear to be an important factor in five-member rings, since the 83:17 trisubstituted to tetrasubstituted ratio for the 3-pyrroline enamine derived from 2-methylcyclopentanone (see Table 1) is almost identical to the 85:15 ratio found for the corresponding pyrrolidine enamine. In fact, we have found that the trisubstituted to tetrasubstituted ratios for 2-methylcyclopentanone derived enamines are not very sensitive to the amine moieties involved [6].



Equation 3.

The identity of the 1-cyclopentylpyrrole (10) obtained as one of the products from the reaction of 3-pyrroline with cyclopentanone was substantiated by comparing its spectral properties with those of an authentic sample obtained by an independent pathway. The synthetic pathway used was the method reported by Murahashi [7] (Equation 3).

When the methyl group is replaced by an acetyl group in the 2-position of cyclopentanone and allowed to react with 3-pyrroline (1), only the tetrasubstituted enamine (11) is obtained in a 58% yield (Equation 4). No trisubstituted enamine or pyrrole products are obtained even though the reaction is heated for 3 hours at 110° with an acid catalyst. *Ab initio* calculations show the tetrasubstituted enamine to be more stable than the trisubstituted isomer (see Table 2).



Equation 4.

EXPERIMENTAL SECTION

Both ^1H and ^{13}C NMR spectra along with DEPT, COSY and HETCOR 2D NMR spectra were recorded on a Bruker Model AC-200 FT-NMR spectrometer. Infrared spectra were obtained with a Bomem Michelson 120 FT-infrared spectrophotometer. The low resolution mass spectra were determined on a Hewlett Packard BCD Plus GC-MS system. The high resolution mass spectra were determined on a Finnigan MAT XL95 mass spectrometer under the auspices of Dr. Karl Wood, Department of Chemistry, Purdue University. The molecular modeling calculations were obtained using the Spartan '02 Windows program Wavefunction, Inc., Irvine, CA. The identifications of the compounds were made using DEPT, COSY and HETCOR 2-D NMR techniques along with IR and GC-MS. The analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, NY, and the University of Illinois Microanalysis Laboratory, Urbana, IL. Mixtures of tri- and tetrasubstituted enamines as well as mixtures of *cis* and *trans* pyrroles were usually not isolated as individual isomers. The relative amount of each isomer in a mixture was determined using GC/MS spectrometry in conjunction with ^{13}C NMR integrated signals using a 30-second relaxation delay. The enamines are quite unstable in the presence of air.

Reaction of 3-Pyrroline with Cyclohexanone

A stirred solution of 3-pyrroline (1.59 g, 23 mmol), cyclohexanone (1.79 g, 18.3 mmol), and 25 mL of xylene was refluxed for one hour with the water being removed with a Dean-Stark trap. The xylene solvent was removed, and 1.3 g (47%) of a colorless liquid was obtained upon distillation of the residual oil from CaH_2 , bp 120-124° C (17 mm). This product was identified as the known 1-cyclohexylpyrrole [8] from its spectroscopic properties: ^1H NMR (CDCl_3 , 200 MHz) δ (ppm) 6.71 (t, $J=2.1$, 2H, A_2X_2 type triplet [9]), 6.12 (t, $J=2.1$, 2H, A_2X_2 type triplet), 3.75 (m, 1H), 2.2-1.2 (m, 10H); ^{13}C NMR (CDCl_3 , 50 MHz) δ (ppm) 118.21, 107.17, 58.46, 34.50, 25.56, 25.33; MS (70 eV, EI) m/z (rel intensity) 149 (M^+ , 80), 148 (16), 120 (22), 106 (22), 94 (24), 81 (13), 68 (60), 67 (100), 55 (17), 41 (18).

Reaction of 3-Pyrroline with 2-Methylcyclohexanone

(a) Room Temperature

A mixture of 3-pyrroline (1.0 g, 14.5 mmol), 2-methylcyclohexanone (1.63 g, 14.5 mmol) and some molecular sieves (3A) were allowed to stand at room temperature for 66 hours. A GC analysis of the final solution showed 33% 1-(6-methylcyclohex-1-enyl)-3-

pyrroline (**5**) and 4% **1-(2-methylcyclohexyl)pyrrole** in the reaction mixture. The **1-(6-methylcyclohex-1-enyl)-3-pyrroline (5)** was isolated by distillation, bp 75-77°C (0.4 mm). Anal. Calcd. for C₁₁H₁₇N: C, 80.92; H, 10.50; N, 8.58. Found: C, 79.93; H, 10.63; N, 8.31. The spectroscopic properties are as follows: IR ν_{\max} (film) 1643 (s, N=C=C) and 1620 (w) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 5.62 (s, 2H), 5.60 (s, 1H), 3.49 (s, 4H), 2.13-1.40 (m, 7H), 0.77 (d, J=6.6, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 145.7, 127.7, 90.9, 53.1, 35.4, 28.9, 27.1, 24.4, 13.8; MS (70 eV, EI) m/z (rel intensity) 163 (M⁺, 83), 148 (100), 134 (36), 120 (49), 106 (21), 95 (21), 80 (16), 68 (38), 53 (18), 41 (21). Its GC and spectroscopic properties showed it to be 100% the trisubstituted isomer.

(b) Higher Temperature

A stirred mixture of 3-pyrroline (1.0 g, 15 mmol), 2-methylcyclohexanone (1.4 g, 12 mmol), 50 mL of toluene and a catalytic amount of p-toluenesulfonic acid was refluxed for 5 days under nitrogen with water being removed with a Dean-Stark trap. The solvent was removed and the residual oil distilled to give **1-(2-methylcyclohexyl)pyrrole** (0.7 g, 4.3 mmol) in a 36% yield, bp 54-55°C (0.2 mm). It was determined from integration of ¹³C NMR spectra (30 sec relaxation delay) as well as GC/MS data that this is a mixture of 85% *cis* isomer and 15% *trans* isomer. The isomers were not isolated individually. Anal. Calcd. for C₁₁H₁₇N: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.99; H, 10.15; N, 8.44. The spectroscopic data for the *cis* (**6**) isomer is as follows: ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 6.64 (A₂X₂ type triplet, J=2.2, 2H), 6.09 (A₂X₂ type triplet, J=2.2, 2H), 4.03-3.93 (m, 1H), 2.18 (m, 1H), 1.84 (m, 4H), 1.59 (m, 2H), 1.42 (m, 2H), 0.665 (d, J=7.1, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 119.0, 107.1, 60.6, 35.5, 31.5, 25.9, 25.8, 20.1, 12.2; MS (70 eV, EI) m/z (rel intensity) 163 (M⁺, 63), 148 (8), 134 (14), 120 (26), 106 (24), 94 (23), 81 (29), 68 (67), 67 (100), 55 (38), 41 (23). The spectroscopic data for the *trans* (**7**) isomer is as follows: ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 6.64 (A₂X₂ type triplet, J=2.2, 2H), 6.09 (A₂X₂ type triplet, J=2.2, 2H), 4.03-3.93 (m, 1H), 2.18 (m, 1H), 1.84 (m, 4H), 1.59 (m, 2H), 1.42 (m, 2H), 0.686 (d, J=7.0, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 118.8, 107.2, 65.5, 39.4, 34.9, 34.8, 26.2, 26.0, 18.9; MS (70 eV, EI) m/z (rel intensity) 163 (M⁺, 61), 148 (6), 134 (11), 120 (19), 106 (19), 94 (17), 81 (27), 68 (100), 67 (96), 55 (34), 41 (22).

Reaction of 3-Pyrroline with Other Cyclic Ketones

The same room temperature and higher temperature procedures as that used for 2-methylcyclohexanone were used for the reaction of 3-pyrroline with cyclopentanone, 2-methylcyclopentanone and 2-acetylcyclopentanone, respectively. The properties of the products are as follows:

1-Cyclopent-1-enyl-3-pyrroline

bp 107-108°C (18 mm); IR ν_{\max} (film) 1639 cm⁻¹ (s, N=C=C); ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 5.8 (s, 2H), 3.93 (s, 4H), 2.38 (m, 4H), 1.89 (m, 2H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 147.9, 126.3, 90.1, 55.2, 32.3, 30.5, 22.8; MS (70 eV, EI) m/z (rel intensity) 135 (M⁺, 63), 134 (100), 106 (11), 94 (14), 79 (12), 68 (18), 67 (11),

54 (12), 53 (13), 41 (18), 39 (20); HRMS calcd. For C₉H₁₄N: MH⁺, 136.1126. Found MH⁺, 136.1123.

1-Cyclopentylpyrrole

bp 112-114°C (46 mm); IR ν_{\max} (film) 3150 cm⁻¹ (w, C=C-H) and 1493 cm⁻¹ (s, pyrrole ring); ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 6.69 (t, A₂X₂ type triplet, J=2.2, 2H), 6.13 (t, A₂X₂ type triplet, J=2.2, 2H), 4.26 (m, 1H), 2.03-1.60 (m, 8H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 118.8, 107.7, 60.3, 33.9, 24.1; MS (70 eV, EI) m/z (rel intensity) 135 (M⁺, 60), 106 (19), 68 (56), 67 (100), 41 (25).

1-(5- and 2-Methylcyclopent-1-enyl)-3-pyrroline

The isomers were not isolated individually. Bp 45-46°C (0.05 mm); HRMS calcd. For C₁₀H₁₅N: M, 149.1204. Found: M, 149.1205. **1-(5-Methylcyclopent-1-enyl)-3-pyrroline**. ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 5.73 (s, 2H), 5.71 (s, 1H), 3.60 (s, 4H), 2.15-1.85 (m, 6H), 0.96 (d, J=6.7, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 152.46, 125.82, 89.72, 53.09, 38.19, 31.07, 19.82, 18.64; MS (70 eV, EI) m/z (rel intensity) 149 (M⁺, 73), 148 (100), 134 (44), 120 (17), 106 (23), 79 (30), 77 (19), 68 (38), 67 (41), 59 (18), 53 (22), 41 (38), 40 (21), 39 (31). **1-(2-Methylcyclopent-1-enyl)-3-pyrroline**. MS (70 eV, EI) m/z (rel intensity) 149 (M⁺, 82), 148 (100), 134 (44), 120 (15), 106 (29), 79 (18), 77 (16), 68 (10), 67 (12), 53 (12), 41 (18), 39 (17).

cis- and trans-1-(2-Methylcyclopentyl)pyrrole

The isomers were not isolated individually. Bp 85-86°C (25 mm). Anal. Calcd. for C₁₀H₁₅N: C, 80.48; H, 10.13; N, 9.39. Found: C, 79.81; H, 10.39; N, 9.45. *cis*-**1-(2-Methylcyclopentyl)pyrrole**: ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 6.62 (t, J=2.2, 2H), 6.11 (t, J=2.2, 2H), 4.31 (q, J=6.6, 1H), 2.17-1.78 (m, 6H), 1.4-1.2 (m, 1H), 0.60 (d, J=6.9, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 120.0, 107.0, 63.3, 39.3, 31.7, 30.5, 22.4, 13.9; MS (70 eV, EI) m/z (rel intensity) 149 (M⁺, 75), 120 (17), 106 (28), 94 (49), 68 (79), 67 (100), 55 (17), 41 (19). *trans*-**1-(2-Methylcyclopentyl)pyrrole**: ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 6.69 (t, J=2.2, 2H), 6.13 (t, J=2.1, 2H), 3.74 (q, J=6.4, 1H), 2.17-1.78 (m, 6H), 1.14-1.2 (m, 1H), 0.96 (d, J=6.2, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 118.6, 107.4, 67.6, 41.6, 33.1, 32.3, 21.8, 17.8; MS (70 eV, EI) m/z (rel intensity) 149 (M⁺, 64), 120 (11), 106 (23), 94 (35), 81 (15), 68 (100), 67 (92), 55 (15), 41 (18).

1-(2-Acetylcyclopent-1-enyl)-3-pyrroline (11)

Bp 148-150°C (0.6 mm). Anal. Calcd. for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.24; H, 8.34; N, 8.15. IR ν_{\max} (film) 3083 (w), 1711 (w), 1626 (s), 1520 (s) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ (ppm) 5.72 (s, 1H), 5.70 (s, 2H), 4.07 (s, 4H), 2.60-2.37 (m, 4H), 1.98 (s, 3H), 1.68 (m, 2H); ¹³C NMR (CDCl₃, 50 MHz) δ (ppm) 190.5, 157.2, 124.5, 104.9, 57.5, 35.4, 32.6, 28.7, 20.3; MS (70 eV, EI) m/z (rel intensity) 177 (M⁺, 77), 162 (23), 136 (44), 134 (100), 120 (20), 106 (24), 95 (36), 67 (42), 43 (48).

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