A Cyclopropenone Route to New Pyrrolizidine Derivatives

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New pyrrolizidine derivatives **6** and **7** were prepared from the 1,5-dihydro-2*H*-pyrrol-2-one **3a** *via* an acidic intramolecular aldol condensation in 16% and 42% yields, respectively. Compound **6** was obtained by dehydration of **7** with *p*-toluenessulfonic acid in 67% yield.

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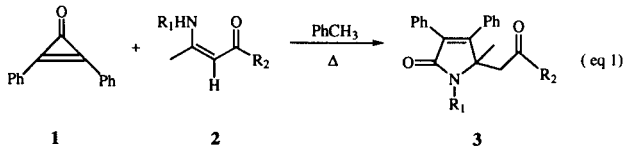
Over the years, cyclopropenone chemistry has furnished a wealth of new carbocyclic and heterocyclic systems [1]. Our interest in expanding the frontiers involving applications of cyclopropenone derivatives in synthesis has prompted us to seek more complex target nuclei. Some years ago, we reported the formation of 1,5-dihydro-2*H*-pyrrol-2-ones **3** from the reaction of diphenylcyclopropenone **1** with simple enaminones **2** (eq 1) [2]. It occurred to us that the presence of an activated methylene in the C5 substituent of (**3**) might permit construction of a second ring through intramolecular aldol condensation involving an appropriately situated carbonyl group in the *N*-substituent.



(eq 1)

1 **2** **3**

We began our study preparing the enaminone **2a**, obtained quantitatively by the reaction of the aminoacetal **4** with acetylacetone. The reaction of **2a** with diphenylcyclopropenone (**1**) afforded derivative **3a** in 71% yield (Scheme 2).

Our first attempt to hydrolyze the acetal group of (**3a**) was with trifluoroacetic acid [3]. Under these conditions the aldehyde **5** was formed quantitatively but no bicyclic compound was observed. Attempts at cyclization of **5** under more drastic conditions, reflux with trifluoroacetic acid or reaction with concentrated hydrochloric acid at room temperature [4], were unsuccessful and a complex mixture of products was observed as a result.

By using concentrated hydrochloric acid, the hydrolysis of **3a** afforded compounds **6** and **7** (obtained as a 1:1 mixture of C6 epimers) in 16% and 42% yield, respectively. Evidence for the structural assignments was obtained from the spectral data: for **6** the ir spectrum showed absorptions at 1700 and 1680 cm^{-1}. The ^1H nmr spectrum of **6** contained signals at δ 4.30 (2H, split AB quartet, J = 18, J = 2 Hz) and 6.60 (broad singlet, 1H); for **7** the ir spectrum showed absorptions at 3400 (OH) and 1710 cm^{-1}. The ^1H nmr spectrum of **7** (as a mixture of C6 epimers) contained signals at 3.9-6.0 (m, 8H), corresponding to C5, C6 methine and C7 methylene hydrogens.

The difference in behavior between **3a** and **5** under concentrated hydrochloric acid conditions may mean that **5** is not an intermediate in the formation of **6** and **7** from **3a** or that high concentrations of **5** favor intermolecular condensations.

As previously mentioned, the hydrolysis of **3a** with trifluoroacetic acid did not afford compounds **6** and **7**. We observed the quantitative formation of the aldehyde **5**, even though there is a ketone group in **3a** susceptible to an intramolecular aldol condensation. This is an interesting result that can be explored in synthetic strategies if one needs to hydrolyze an acetal group and avoid an intramolecular reaction with an enolizable ketone. This result, to the best of our knowledge, has never been reported [5].

Compounds **6** and **7** contain the nucleus present in the pyrrolizidine alkaloids [6]. Many pyrrolizidine derivatives are known [7,8] but few with a carbonyl group in the 2 position of the rings as in **6** and **7** have been documented [9].

The results of the present study demonstrate once again the potential of cyclopropenone chemistry in the area of heterocycle synthesis.

EXPERIMENTAL

The melting points are uncorrected. The spectra disks unless otherwise indicated were measured with a Perkin Elmer 399 B spectrophotometer, ^1H nmr spectra (unless otherwise stated) with a Brucker AW-80 instrument with an internal standard, mass spectra with a Varian MAT 311 A spectrometer.

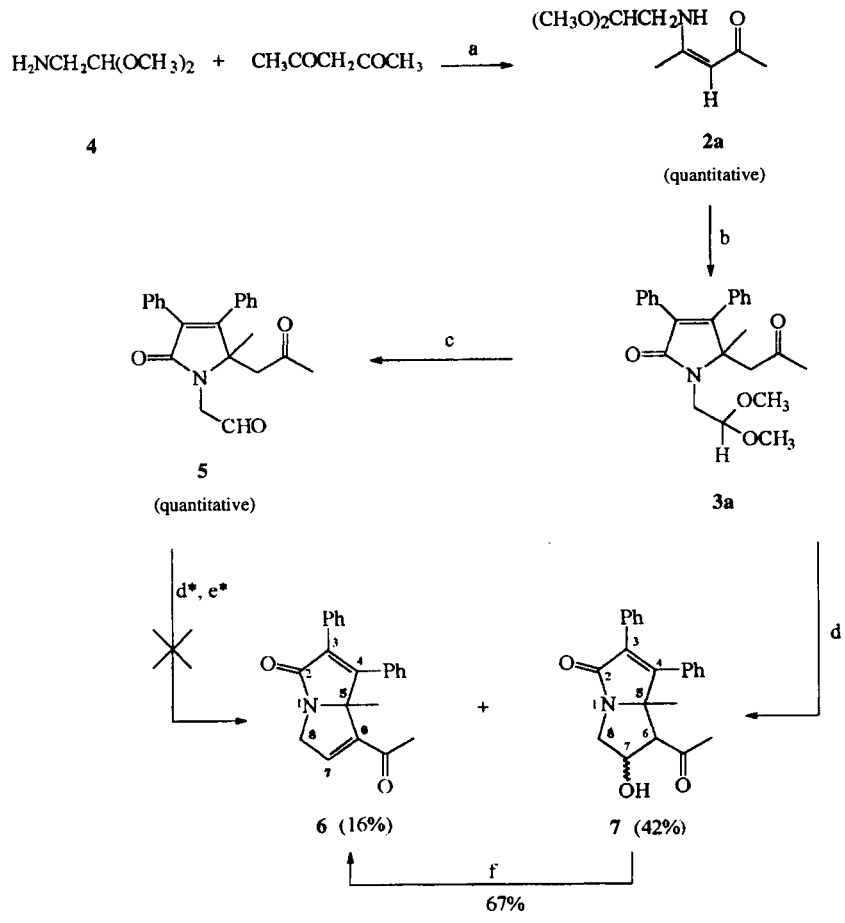
Enaminones **2a** [10] and diphenylcyclopropenone (**1**) [11] were prepared according to known procedures.

4-(2,2-Dimethoxyethylamine)-3-penten-2-one (**2a**).

The physical properties of **2a** are ^1H nmr (carbon tetrachloride): δ 1.80 (s, 6H), 3.5 (m, 2H), 3.35 (s, 6H), 4.30 (t, 1H), 4.80 (s, 1H), 11.2 (br s, 1H); ir: 1595, 1555 cm^{-1}.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.51; H, 9.12; N, 7.42.

Scheme 2



* complex mixture of products was observed

a) rt, 15 h; b) toluene, diphenylcyclopropenone (**1**), 6 days, Δ; c) CF_3COOH, 1 h; d) conc HCl, 2 h, rt; e) CF_3COOH, Δ; f) TsOH, benzene, Dean-Stark, reflux, 23 h.

1-(2,2-Dimethoxyethyl)-1,5-dihydro-2*H*-pyrrol-2-one (**3a**).

A solution of 2 mmoles of diphenylcyclopropenone (**1**) and 2 mmoles of **2a** in toluene (10 ml) was heated under reflux for 6 days after which time the solvent was removed by rotatory evaporation. The residue was triturated with ethyl ether and afforded **3a** (559 mg, 71% yield) mp 98.0-100.0°; ^1H nmr (carbon tetrachloride): δ 1.33 (s, 3H), 1.90 (s, 3H), 2.65 (AB, 2H, J = 18), 3.1-3.6 (m, 2H), 3.28 (s, 3H), 3.40 (s, 3H), 4.60 (dd, 1H, J = 6, J = 2), 7.0-7.4 (m, l0H); ir 1720, 1670 cm^{-1}.

Anal. Calcd. for $C_{24}H_{27}O_4N$: C, 73.25; H, 6.92; N, 3.56. Found: C, 73.13; H, 6.90; N, 3.51.

1-(2-Oxoethyl)-l,5-dihydro-2*H*-pyrrol-2-one (**5**).

A solution of 0.203 g (0.52 mmole) of **3a** in 2.0 ml of trifluoroacetic acid (0.03 mole) was kept under room temperature for 1 hour. A solution of sodium bicarbonate was added at 0° until a neutral *p*H. The mixture was extracted with methylene chloride (5 x 30 ml) and the combined extracts were washed with water (4 x 20 ml) and dried (magnesium sulfate). The solvent was removed by rotatory evaporation leading in quantitative yield to **5** as a yellowish oil; ^1H nmr (carbon tetrachloride): δ 1.35 (s, 3H), 1.90 (s, 3H), 2.63 (s, 2H), 4.15 (s, 2H), 6.9-7.4 (m, lOH), 9.48 (s, 1H); ir: 1735, 1720, 1670 cm^{-1}.

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.30; H, 6.11; N, 4.09.

Reaction of 1-(2,2-Dimethoxyethyl)-1,5-dihydro-2*H*-pyrrol-2-one (**3a**) with Concentrated Hydrochloric Acid.

A solution of 0.500 g (1.27 mmoles) of **3a** in concentrated hydrochloric acid (3.0 ml) was stirred for 2 hours. The resulting suspension was cooled to 0° and neutralized with a saturated sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride (5 x 30 ml) and the combined extracts were washed with water (4 x 20 ml) and dried (magnesium sulfate). The solvent was removed by rotatory evaporation leading to a yellowish oil. Trituration with benzene afforded **7** (181 mg, 42% yield).

1-Aza-3,4-diphenyl-5-methyl-6-(1-oxoethyl)-7-hydroxybicyclo-[3.3.0]octan-2-one (**7**).

This compound had mp 239-242°; ^1H nmr (trifluoroacetic acid) (a 1:1 mixture of C6-epimers, as indicated by integration): δ 1.70 (s, 3H), 2.00 (s, 3H), 2.55 (s, 3H), 2.60 (s, 3H), 3.9-6.0 (m, 8H), 7.0-7.6 (m, 20H), ir: 3400, 1710, 1670 cm^{-1}.

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.80; H, 6.07; N, 3.99.

The solvent of the supernatant was removed by rotatory evaporation. Chromatography of the residue on Florisil afforded **6** (65 mg, 16% yield, elution with 10-20% ethyl ether-benzene) provided **6**.

1-Aza-3,4-diphenyl-5-methyl-6-(1-oxoethyl)bicyclo[3.3.0]oct-6-en-2-one (**6**).

This compound had mp 82.0-83.0°; ^{1}H nmr (carbon tetrachloride): δ 1.70 (s, 3H), 2.15 (s, 3H), 4.30 (2H, split qAB, 1 = 18, J = 2), 6.60 (br s, 1H), 6.9-7.5 (m, 10H); ir: 1700, 1680, 1440 cm^{-1}; ms: m/z (relative intensity) 329 (100), 271 (50), 178 (84).

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.90; H, 5.79; N, 4.30.

Reaction of 1-Aza-3,4-diphenyl-5-methyl-6-(1-oxoethyl)bicyclo[3.3.0]oct-6-en-2-one (**6**) with *p*-Toluenessulfonic Acid.

A mixture of 0.200 g (0.55 mmole) of **7** and 0.17 g (0.89 mmole) of *p*-toluenessulfonic acid in benzene (130 ml) was refluxed for 23 hours in Dean-Stark equipment. The dark yellow solution was cooled and neutralized with a saturated sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride (5 x 30 ml) and the combined extracts were washed with water (4 x 20 ml) and dried (magnesium sulfate). The solvent was removed by rotatory evaporation leading to a yellowish oil. Extraction with hot hexane and removal of the solvent by rotatory evaporation leads to **6** (121 mg, 67% yield) as a yellowish solid, mp 82.0-83.0°.

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