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PREPARATION OF 3-PYRROLIDONE AND 4-PERHYDROAZEPINONE

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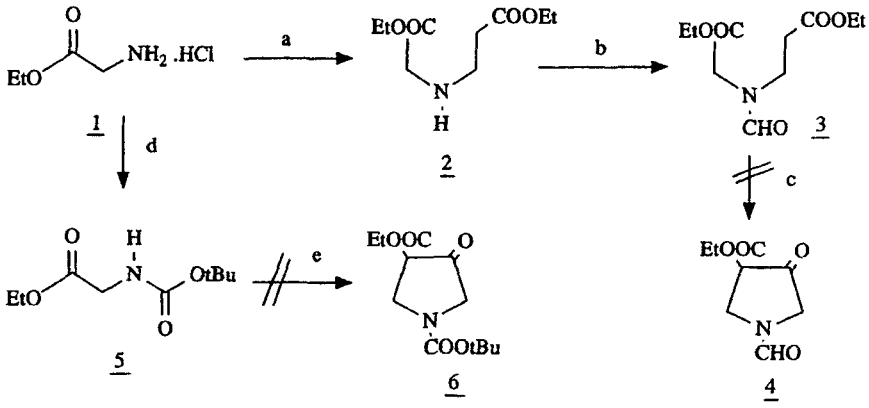
ABSTRACT.- Efficient multigram preparations of 3-pyrrolidone by sequential Michael addition and Dieckmann condensation, and of 4-perhydroazepinone by ring expansion have been achieved.

INTRODUCTION

In the course of a synthetic project we required multigram amounts of both 3-pyrrolidinone, **12**, and 4-perhydroazepinone, **16**. The availability of these ketoamines is in sharp contrast with that of their commercially available congener 4-piperidone, **13**, and those of their isomers 2-pyrrolidone and ε-caprolactam. In fact, at the best of our knowledge, the preparation of the seven-membered ketoamine **16** has been reported in the patent literature.[1] This preparation involves Dieckmann cyclization of ethyl N-

SCHEME 1



a- i)NaOH/H_2O, ii)H_2C=CHCOOEt; b- HCOOH; c- HNa/benzene;

d- $HNaCO_3/(BOC)_2O$; e- i)HNa/benzene, ii)H_2C=CHCOOEt.

ethoxycarbonylethyl-N-benzyl-4-aminobutirate followed by palladium-catalyzed hydrogenolysis of the N-benzyl group. On the other hand, only two preparations of **12** can be found.[2,3] One of these preparations reports the cyclization of diethyl 2-formyl-2-azabutane-1,4-dicarboxylate, **3**, (Scheme 1) with "a solution of 0.135 mole of sodium ethoxide in 300 ml of benzene"[2] to obtain intermediate **4**. The second reference reports the hydrogenolysis of 4-carbethoxy-N-phenyl-3-pyrrolidone as the method of choice.[3]

We want to present alternative syntheses for both **12** and 16.

RESULTS

Michael addition of ethyl glycinate to ethyl acrylate gives diethyl 2-azabutane-1,4-dicarboxylate, **2**, (Scheme 1) which is

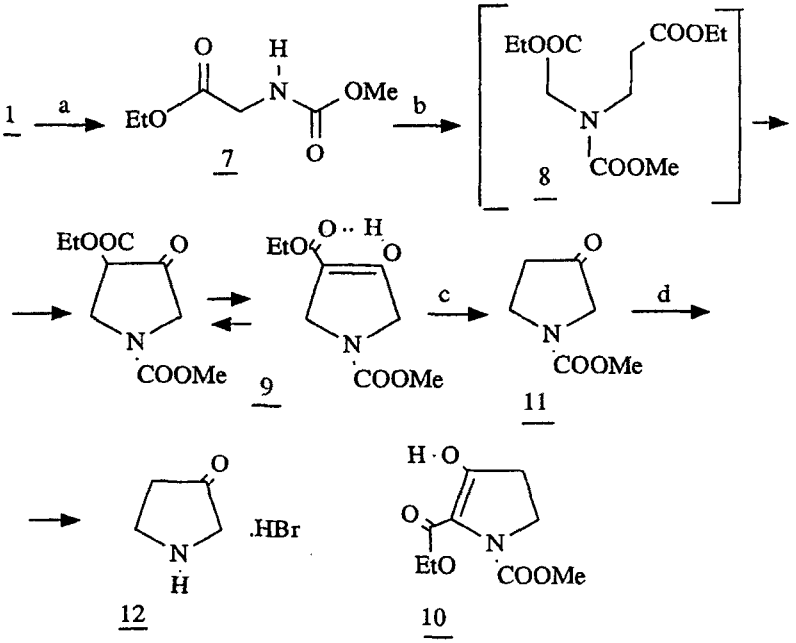
converted into the formyl derivative **3** as previously described.[2] The complexity of the pmr spectrum of **3** suggests the rotation around the N-CHO bond is slow. The presence of two singlets at 8.05 and 8.20 integrating for one proton is particularly informative. All attempts to transform **3** into **4** (sodium ethoxide in benzene[2] and sodium hydride in benzene) were unsuccessful.

Therefore, we studied other amine protecting groups. Ethyl N-tert-butoxycarbonylglycinate, **5**, was prepared by a known method.[4] However, attempts of Michael addition with ethyl acrylate (sodium hydride, refluxing benzene) were inconclusive. The idea was to prepare either **6** or compounds from its Dieckmann condensations.

However, the target was accomplished using the methoxycarbonyl protection (Scheme 2). Thus, N-methoxycarbonyl-3-pyrrolidone, **11**, was prepared as previously described[5] by a sequence involving protection of the ethyl glycinate amine group and one pot Michael and Dieckmann reactions to afford 4-ethoxycarbonyl-N-methoxycarbonyl-3-pyrrolidone, **9**, which upon decarboxylative acid hydrolysis gives N-methoxycarbonyl-3-pyrrolidone, **11**. The pmr spectrum of purified **9** presents a triplet of low intensity at δ 2.7 which can not be accommodated neither by the keto nor by the enol form of **9**. However, it can be attributed to the protons at C4 of isomer **10**, produced by an alternative Dieckmann cyclization. This was not further studied since both **9** and **10** afford the same **11** upon hydrolysis and decarboxylation.

Finally, treatment of **11** with 1N hydrobromic acid in acetic acid at 100ºC affords the required 3-pyrrolidone hydrobromide in

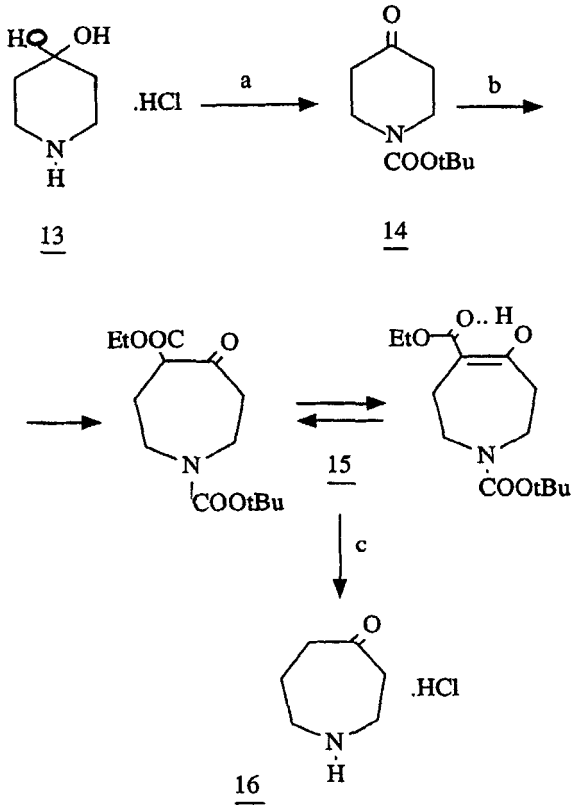
SCHEME 2



a- NaOH/ClCOOMe; b- i)HNa/benzene, ii)H_2C=CHCOOEt;
c- HCl/H_2O; d- HBr/AcOH.

84% yield. This compound exists in water in equilibrium with its hydrate (addition of water to the carbonyl group) as evidenced by pmr and cmr spectra. Thus, the pmr spectrum (in deuterium oxide) shows signals of **12** at δ 2.60 (t, J = 8.2Hz, 2H), 3.70 (s, 2H) and 3.75 (t, J = 8.2Hz, 2H). Additional signals assignable to the hydrate appear at higher fields: δ 2.10 (t, J = 6.9, 2H), 3.20 (s, 2H) and 3.40 (t, J = 6.9Hz, 2H). The ratio **12**/hydrate was 78:22. It should be noted that the six-membered ring **13** is commercially available as hydrate hydrochloride.

SCHEME 3



a- i)$HNaCO_3/H_2O$, ii)$(BOC)_2O$;
b- $N_2CHCOOEt/BF_3.Et_2O$; c- 4N HCl.

Solid **12** hydrobromide exists as pure anhydrous form (Ir(KBr): 1762 cm^{-1} and correct elemental analysis).

The seven-membered ketoamine **16** was better prepared by the sequence of Scheme 3. The six-membered ring of N-tert-butoxycarbonyl-4-piperidone, **14**,[6] was expanded by treatment with

ethyl diazoacetate and boron trifluoride to give N-tert-butoxycarbonyl-5-ethoxycarbonyl-4-perhydroazepinone, **15**. This expansion method has been successfully applied by others in a related case.[7] Decarboxylative hydrolysis of crude **15** affords 4-perhydroazepinone hydrochloride, **16**, in 67% overall yield from **13**.

EXPERIMENTAL

The pmr and cmr spectra were recorded at 80MHz and 20MHz, respectively, unless otherwise specified. Bp's refer to oven temperature. Mp's are uncorrected.

Diethyl 2-azabutane-1,4-dicarboxylate, **2**. A 4.7M aqueous solution of NaOH (75 ml, 0.36 mole) was added into a stirred, ice-cooled, solution of ethyl glycinate hydrochloride (50.0 g, 0.36 mole) in water (75 ml). Then, ethyl acrylate (35.8 g, 0.36 mole) was added and the mixture stirred at room temperature for 19 hours (glc monitoring), after which it was partitioned with dichloromethane (3 x 125 ml). The organic layer was dried with anhydrous sodium sulfate, filtered and evaporated. The residue was distilled (bp 85-87ºC/0.5mmHg) to afford **2** (49.2 g, 68%) (Lit.[2] bp 98-99ºC/1.0mmHg); ir (film): 3339, 1736 cm^{-1}; pmr (deuteriochloroform): δ 1.20 (t, J = 7.2Hz, 3H), 1.25 (t, J = 7.2Hz, 3H), 1.80 (s, 1H), 2.40 (t, J = 7.2Hz, 2H), 2.80 (t, J = 7.2Hz, 2H), 3.40 (s, 2H), 4.10 (q, J = 7.2Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H).

Diethyl 2-formyl-2-azabutane-1,4-dicarboxylate, **3**. It was prepared from **2** in 68% yield according to reference 2: bp 155-160ºC/0.1mmHg; ir (film): 1734, 1674 cm^{-1};

pmr(deuteriochloroform): δ 1.30 (three t, 6H), 2.60 (m, 2H), 3.60 (m, 2H), 4.00 (s, 2H), 4.10 (m, 4H), 8.05 and 8.20 (two s, 1H).

Ethyl N-tert-butoxycarbonylglycinate, **5**. It was prepared from **1** in 81% yield according to reference 4: bp 78-81ºC/0.15mmHg; ir(film): 3376, 1753, 1717 cm^{-1}; pmr(deuteriochloroform): δ 1.35 (t, J = 6.6Hz, 3H), 1.50 (s, 9H), 3.90 (d, 2H), 4.25 (q, J = 6.6Hz, 2H), 5.1 (broad s, 1H).

Ethyl N-methoxycarbonylglycinate, **7**. It was prepared from **1** in 71% yield according to reference 5: bp 134-135ºC/16mmHg; ir(film): 3353, 1711 cm^{-1}; pmr(deuteriochloroform): δ 1.30 (t, J = 7.3Hz, 3H), 3.70 (s, 3H), 3.90 (d, J = 4.4Hz, 2H), 4.20 (q, J = 7.3Hz, 2H), 5.15 (broad s, 1H).

4-Ethoxycarbonyl-N-methoxycarbonyl-3-pyrrolidone, **9**. It was prepared from **7** in 46% yield according to reference 5: bp 114-116ºC/0.5mmHg; ir(film): 1772, 1720, 1706, 1640 cm^{-1}; pmr(deuteriochloroform): keto-enol mixture δ 1.25 (broad t, 3H), 2.70 (low intensity t, see Results Section), 3.20-4.50 (m, 6-7H), 3.65 (broad s, 3H), 9.9 (broad absortion, 0-1H); cmr(deuteriochloroform): δ 13.8, 13.9, 14.0, 45.9, 48.5, 50.1, 51.2, 52.1, 52.4, 52.6, 53.4, 60.3, 61.8, 97.1, 155.0, 166.3, 167.4, 203.1.

N-Methoxycarbonyl-3-pyrrolidone, **11**. It was prepared from **9** in 56% yield according to reference 5: mp 61-63ºC (Lit.[5] mp 62-64ºC); ir(KBr): 1757, 1701 cm^{-1}; pmr(deuteriochloroform): δ 2.60 (t, J = 8.0Hz, 2H), 3.75 (s, 3H), 3.80 (s, 2H), 3.85 (t, J = 8.0Hz, 2H).

3-Pyrrolidone hydrobromide, **12**. A solution of **11** (4.6 g, 32.4 mmole) in 130 ml of 1N hydrobromic acid in acetic acid was heated

at 100ºC for 4 hours (ir monitoring). The cooled solution was poured into anhydrous diethyl ether (230 ml) and the mixture was ice-cooled. The formed precipitate (4.5 g, 84%) was filtered off: mp 123-125ºC; ir(KBr): 3500, 3430, 3033, 1762 cm^{-1}; pmr(deuterium oxide): free ketoamine hydrobromide: δ 2.60 (t, J = 8.2Hz, 2H), 3.70 (s, 2H), 3.75 (t, J = 8.2Hz, 2H), hydrate: δ 2.10 (t, J = 6.9Hz, 2H), 3.20 (s, 2H), 3.40 (t, J = 6.9Hz, 2H); cmr(deuterium oxide): free ketoamine hydrobromide δ 35.5, 44.4, 50.8, 210.9, hydrate: 37.3, 45.3, 54.8.

Anal. Calcd. for C_4H_8BrNO: C, 28.94; H, 4.86; N, 8.44; Br, 48.13. Found: C, 29.08; H, 4.81; N, 8.30; Br, 47.70.

N-tert-Butoxycarbonyl-4-piperidone, **14.** It was prepared from **13** in 89% yield according to reference 6: mp 72-74ºC (Lit.[6] mp 70-72ºC); ir(KBr): 1719, 1688 cm^{-1}; pmr(deuteriochloroform): δ 1.5 (s, 9H), 2.4 (t, J = 6.0Hz, 4H), 3.7 (t, J = 6.0Hz, 4H).

N-tert-butoxycarbonyl-5-ethoxycarbonyl-4-perhydroazepinone, **15.** Ethyl diazoacetate (5.31 g, 46.5 mmole) and the complex boron trifluoride-diethyl ether (5.21 g, 36.7 mmole) were simultaneously but independently added during 90 minutes over a stirred solution of **14** (7.0 g, 35.2 mmole) in anhydrous diethyl ether (30 ml). The ethereal solution was under argon atmosphere and cooled at -25ºC (isopropanol-dry ice bath). The mixture was stirred for an additional hour (glc monitoring). Then, aqueous potassium carbonate was dropwise added to the stirred mixture until gaseous evolution ceased. The organic layer was separated, dried with anhydrous sodium sulfate, filtered and evaporated to afford 9.0 g (90%) of crude **15** that was used without further purification:

pmr(deuteriochloroform): keto-enol mixture: δ 1.3 (triplets, 3H), 1.5 (s, 9H), 1.9-2.2 (m, 2H), 2.5-2.9 (m, 2H), 3.1-3.9 (m, 4H), 4.2 (quadruplets, 2H).

4-Perhydroazepinone hydrochloride, **16.** A mixture of crude **15** (9.0 g, 31.6 mmole) and 4N hydrochloric acid (150 ml) was refluxed for 6 hours. The solution was evaporated to dryness to afford 3.97 g (84%) of a brown solid. A sample recrystallized from hot ethanol gave mp 161-163ºC; ir(KBr): 3410-2400 (broad), 1707 cm^{-1}; pmr(deuterium oxide-dioxane), 400 MHz: δ 1.90 (m, 2H), 2.60 (t, J = 5.5Hz, 2H), 2.75 (t, 5.3Hz, 2H), 3.20 (t, J = 5.3Hz, 2H), 3.30 (t, J = 5.5Hz, 2H); cmr(deuterium oxide): δ 21.3, 40.8, 42.9, 43.0, 49.7, 215.4; ms (m/e): 113(M^+ free base, 10), 57(56), 56(45), 43(74), 42(100).

Anal. Calcd. for $C_6H_{12}ClNO$: C, 48.17; H, 8.08; N, 9.36. Found: C, 47.99; H, 8.00; N, 9.24.

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