

SYNTHESIS OF 3-AZABICYCLO[3.3.1]NONANE-6,9-DIONES

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Abstract- A one pot synthesis of 3-azabicyclo[3.3.1]nonane-6,9-diones is described *via* the addition of acryloyl chloride to enamines of *N*-carboxy-4-piperidones. Yields of bicycle were highest when additions were made to vigorously boiling solutions of morpholine enamines. X-Ray analysis of an azabicyclic system revealed a chair-chair structure to be the preferred conformation. Hydrolysis of 3-azabicyclo[3.3.1]nonane-6,9-diones (**IIa**) and (**IIb**) yielded the monocyclic carboxylic acids (**IIIa**) and (**IIIb**).

INTRODUCTION

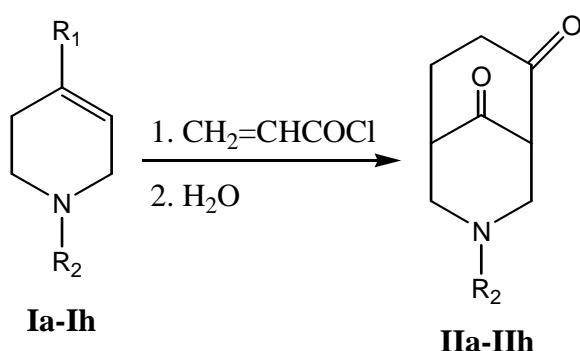
Substituted 3-azabicyclo[3.3.1]nonanes are a structurally fascinating and practically significant class of compound that has attracted attention for their pharmacological properties, use in syntheses and as models for more complex natural molecules. The 3-azabicyclo[3.3.1]nonane system is used for molecular recognition at specific binding sites on proteins and as such is an integral component of more complex alkaloids.¹ Asymmetric cleavage of azabicyclo[3.3.1]nonanes has been utilized in order to achieve stereoselective synthesis of alkaloids including 7-demethyltecomanine, a compound known to display a powerful hypoglycemic activity.² Functionalized azaadamantanes, providing a source of conformationally restricted amines, have been employed as receptor antagonists and have been synthesized from 3-azabicyclo[3.3.1]nonane derivatives.³ Structural studies of substituted 3-azabicyclo[3.3.1]nonanes have been performed to establish conformational regularities⁴⁻⁷ and specific azabicycles have been modeled for

a variety of pharmacological interests including assessment of potential effectiveness as muscarinic agents and serotonin (5-HT) receptor ligands.⁴

An established synthetic strategy for the synthesis of bicyclo[3.3.1]nonanes structures involves the reaction of cycloalkanone enamines with bis electrophiles.⁸ This method has seen some application towards the formation of azabicyclic structures. For example, azabicyclo[3.3.1]nonanes have been synthesized by cyclization reactions of enamines with bis electrophilic reagents such as acrolein,⁹ 2-bromomethacrylates,¹⁰ ethyl β,β' -dibromoisobutyrate¹¹ and 2-benzoyl-1,3-dichloropropane.¹¹ However, as a synthetic approach for the synthesis of azabicyclic nonanes, reactions of biselectrophiles with enamines remains essentially under utilized. This paper describes a single vessel synthesis of 3-azabicyclo[3.3.1]nonane-6,9-diones from reactions of acryloyl chloride with enamines of *N*-carboxy-4-piperidones.

RESULTS AND DISCUSSION

Solutions containing 0.0292 moles of enamine I in 250 mL of benzene were heated to a vigorous reflux under a nitrogen atmosphere and neat acryloyl chloride was added dropwise over a 30 min period. The reaction mixtures were maintained at reflux for 18 h followed by hydrolysis and work up yielding the 3-azabicyclo[3.3.1]nonane-6,9-diones (**II**). Azabicyclicdiones (**IIa**) and (**IIb**) were formed from enamines (**Ia**) and (**Ib**) with purified yields ranging from 80 to 85%.



- a, R₁ = morpholine, R₂ = CO₂CH₂CH₃
 b, R₁ = morpholine, R₂ = CO₂C(CH₃)₃
 c, R₁ = morpholine, R₂ = CH₂CH₂CH₃
 d, R₁ = morpholine, R₂ = CH₂C₆H₅
 e, R₁ = pyrrolidine, R₂ = CO₂CH₂CH₃
 f, R₁ = pyrrolidine, R₂ = CO₂C(CH₃)₃
 g, R₁ = piperidine, R₂ = CO₂CH₂CH₃
 h, R₁ = piperidine, R₂ = CO₂C(CH₃)₃

Trial	Enamine I	Solvent	Time, h	Temp °C	Yield % of II
1	Ia, Ib	Benzene	18	80	80-85
2	Ia, Ib	Benzene	26	25	35-40
3	Ia	Benzene	46	10	23
4	Ic, Id	Benzene	18	80	10-15
5	Ie, If	Benzene	18	80	75-80
6	Ig, Ih	Benzene	18	80	70-75
7	Ia	Toluene	18	110	5-10

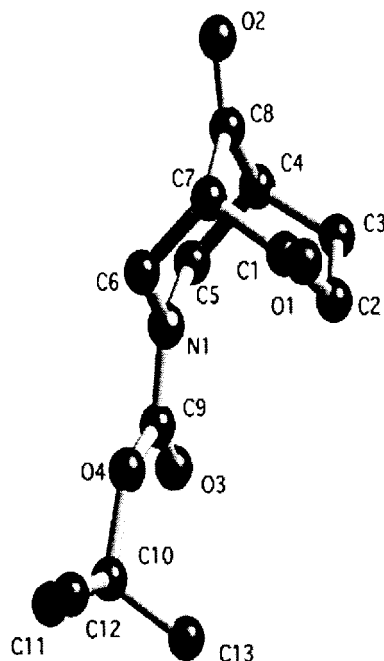
Efforts to affect cyclizations of acryloyl chloride with enamines (**Ic**) and (**Id**) resulted in minor amounts of azabicycles (**IIc**) and (**IIId**). Preliminary analysis of the crude product mixtures suggests that competition between the enamine and the nitrogen transannular to the enamine for the acryloyl chloride carbonyl to be a probable cause of the low yields for **IIc** and **IIId**. The fact that this problem does not occur with **Ia** and **Ib** is consistent with resonance stabilization of the lone pair electrons on the nitrogen with the adjoining carbonyl.

Attempts at the formation of **IIa** and **IIb** using enamines of pyrrolidine and piperidine were successful but with slightly lower yields for both trials. Rates of addition and concentration variations of the acryloyl chloride appeared less critical than the reaction temperature and solvent. There was little change in yields when the acryloyl chloride was added neat, as a benzene solution or added over varied intervals. Yields were highest when the addition was carried out into a vigorously refluxing benzene solution containing the enamine and decreased as the temperature of the receiving solution decreased. An attempt to increase reaction temperatures further by substituting toluene for benzene as the solvent resulted in a dramatic decrease in yield.

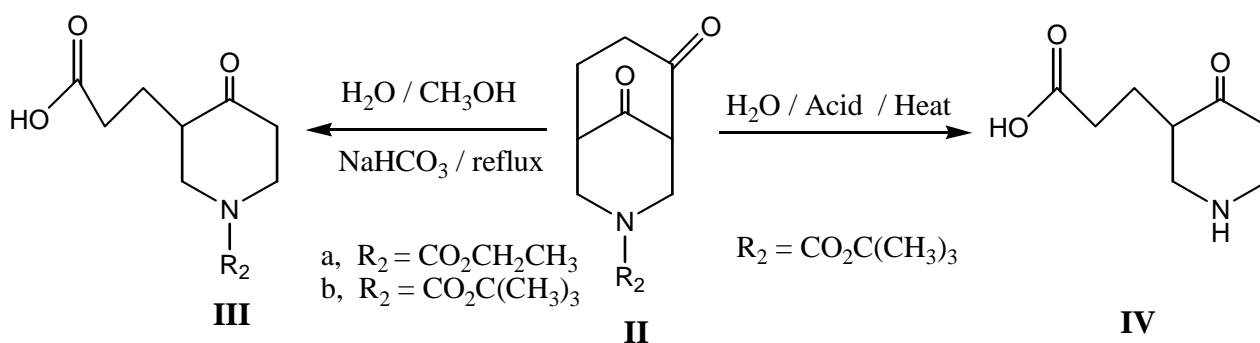
A proposed cyclization mechanism for this reaction involves N-acylation of the enamine with subsequent [3,3] sigmatropic rearrangement yielding a ketene intermediate followed by cyclization.¹² More recently, a competing reaction pathway was invoked involving C-acylation of the enamine followed by intramolecular Michael alkylation.¹³ Analysis of the regio- and stereochemical features of bicyclic products clearly shows that the reaction pathway is directed by the nature of the reactant substituents. The azabicyclic diketones being reported here were formed from unsubstituted enamine and acid chloride reactants and therefore both mechanistic routes for these products remain viable.

Crystallography data for bicycle (**IIb**) reveals a chair-chair configuration which is consistent with reports on the relative stabilities of chair-chair and chair-boat conformations of bicyclo[3.3.1]nonane systems.¹⁴ Additional studies of this reaction with substituted acyl chlorides and ketones may provide information about parameters that affect the reaction course and the influence of the nitrogen in directing the cyclization.

Molecular Structure of **IIb**: Bond Lengths (Å) and angle (°)



Bicycles (**IIa**) and (**IIb**) were hydrolyzed in a basic methanol / water solution to yield compounds (**IIIa**) and (**IIIb**) respectively. Efforts to induce ring opening of the bicycle by acid catalyzed hydrolysis were also successful. However, for compound (**IIb**), these conditions also caused decarboxylation of the *t*-BOC group resulting in structure (**IV**).



Removal of the *t*-BOC group from (**IIb**) while retaining the integrity of the bicyclic system would free the nitrogen for derivatization reactions such as alkylations (or acylations) and thereby open the possibility for synthesis of a variety of 3-azabicyclo[3.3.1]nonanes. Initial attempts to remove the *t*-BOC group from (**IIb**) were unsuccessful. Acid catalyzed decarboxylations using trifluoroacetic acid resulted in a myriad of unidentified products as did thermally induced decarboxylations in either DMSO or DMF.

EXPERIMENTAL

Ketones, acryloyl chloride, *p*-toluenesulfonic acid, and amines were obtained from commercial sources. The ketones and tosic acid were used without purification and the acryloyl chloride and amines were distilled immediately before use. Solvents were dried by standard methods and distilled. Melting points were determined in a capillary tube on a Thomas Hoover MP apparatus. IR spectra were recorded on a Mattson Instruments Polaris Spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Varian EM360L CW 60MHz spectrometer upgraded with an Anasazi Instruments, Inc. EFT FT NMR upgrade with Carbon-13 accessory. Carbon type assignments were made from ^{13}C NMR DEPT data. Quantitative Technologies Inc. Whitehouse, NJ performed analyses. HRMS were performed at Montana State University Dept. of Chemistry and Biochemistry.

General Procedure for the Synthesis of Bicycles (**IIa-IIIh**)

The enamines (**Ia-Ih**) were formed in a 500 mL round bottom flask by reaction of the 4-oxo-1-piperidinecarboxylates (0.029 mol) with freshly distilled amine (0.032 mol) and a catalytic amount of *p*-toluenesulfonic acid in benzene (250 mL). The reaction vessel was equipped with a Dean-Stark trap and a reflux condenser and the mixture was maintained at reflux under nitrogen as the water was removed by a water-benzene azeotrope. After 24 h of heating, the enamine formation was determined to be more than 95% complete by GC/MS. While maintaining reflux, freshly distilled acryloyl chloride (0.035mol) was added drop wise over a 30 min period through the reflux condenser. During the addition a solid, tan colored imminium salt formed and coated the sides of the reaction vessel. The mixture was maintained at reflux and under nitrogen for 18 h after which time the reaction was cooled in an ice bath. The solid imminium salt was collected using a Buchner funnel and vacuum filtration and subsequently washed with several portions of cold hexane. The imminium salt was placed in a 500 mL round bottom flask with 100 mL of an ice/water slush and 100 mL of benzene. The reaction slowly warmed to rt and was stirred for 24 h. The reaction mixture was placed in a separatory funnel and the benzene layer was removed. The water was extracted with four additional 50 mL portions of benzene and the benzene extracts were combined. The volume of benzene was reduced to about 75 mL by rotary evaporation and magnesium sulfate and decolorizing charcoal were added. The solution was then vacuum filtered through a fritted glass funnel containing silica gel and flushed with benzene. Removal of the benzene by rotary evaporation resulted in isolation of bicycles (**IIa-IIIh**) generally as white solids.

Ethyl 3-azabicyclo[3.3.1]nonane-6,9-dione-3-carboxylate (**IIa**): Yield 87%, mp 99 – 102 °C. ¹H NMR (60 MHz, CDCl₃) δ 4.58 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.35 (m, 3H), 2.48 (m, 3H), 2.10 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H). ¹³C NMR (15 MHz, CDCl₃) δ 206.42 (C=O), 206.07 (C=O), 155.09 (C=O), 65.87 (CH), 62.27 (CH₂), 51.23 (CH₂), 50.05 (CH₂), 45.29 (CH), 38.22 (CH₂), 22.60 (CH₂), 14.42 (CH₃). IR (Nujol) 1710, 1660 cm⁻¹ (C=O). HRMS Calc for C₁₁H₁₅NO₄ 225.1001, found 225.1008.

t-Butyl 3-azabicyclo[3.3.1]nonane-6,9-dione-3-carboxylate (**IIb**): Yield 87%, mp 84 – 86 °C. ¹H NMR (60 MHz, CDCl₃) δ 4.64 (m, 2H), 3.34 (m, 3H), 2.78 – 2.06 (m, 5H), 1.49 (s, 9H). ¹³C NMR (15 MHz, CDCl₃) δ 205.89 (2 C=O), 153.29 (C=O), 80.40 (C), 65.54 (CH), 50.31 (CH₂), 49.53 (CH₂), 44.82 (CH), 37.40 (CH₂), 27.46 (3 CH₃), 21.89 (CH₂). IR (Nujol) 1715, 1670 cm⁻¹ (C=O). HRMS Calc for C₁₃H₁₉NO₄ 253.1314, found 253.1312.

Hydrolysis of Bicycles (**IIa-IIb**)

In a 50 mL round bottom flask were added bicycle (**IIa**) or (**IIb**) (4.44 mmol), water (10 mL), methanol (10 mL) and sodium bicarbonate (5.77 mmol) and the reaction was heated at reflux for 12 h. Upon cooling, the reaction mixture was extracted with 10 mL of chloroform. The aqueous layer was brought to a pH of 6.5 by the addition of acetic acid and extracted with three 10 mL portions of chloroform. The chloroform extracts were combined, dried over magnesium sulfate and filtered. Removal of the chloroform by rotary evaporation gave pure product in 60 - 68% yield.

1-Ethoxycarbonyl-3-carboxyethyl-4-oxopiperidine (**IIIa**): Yield 68%, ¹H NMR (60 MHz, CDCl₃) δ 10.04 (br s, 1H), 3.88 (m, 4H), 3.48 – 1.42 (m, 9H), 1.04 (t, J = 7.0 Hz, 3H). ¹³C NMR (15 MHz, CDCl₃) δ 208.67 (C=O), 178.78 (C=O), 155.29 (C=O), 61.82 (CH₂), 48.64 (CH), 47.78 (CH₂), 43.31 (CH₂), 40.27 (CH₂), 30.85 (CH₂), 21.76 (CH₂), 14.24 (CH₃). IR (Neat) 1718, 1694, 1673 cm⁻¹ (C=O).

1-*t*-Butoxycarbonyl-3-carboxyethyl-4-oxopiperidine (**IIIb**): Yield 60%, mp 84 – 87 °C. ¹H NMR (60 MHz, CDCl₃) δ 10.33 (br s, 1H), 3.99 (m, 2H), 3.50 – 1.51 (m, 9H), 1.31 (s, 9H). ¹³C NMR (15 MHz, CDCl₃) δ 209.11 (C=O), 178.10 (C=O), 154.51 (C=O), 80.71 (C), 49.02 (CH), 48.03 (CH₂), 43.59 (CH₂), 40.58 (CH₂), 31.14 (CH₂), 28.21 (3CH₃), 21.97 (CH₂). IR (Neat) 1736, 1716, 1647 cm⁻¹ (C=O).

X-Ray Crystallography of **IIIb**

Colorless, prism. C₁₃H₁₉NO₄. m.w. = 253.29. Triclinic (space group P-1); a = 6.4535(7) Å, b = 10.3245(10) Å, c = 10.4196(11) Å, α = 88.119(2)°, β = 79.724(2)°, γ = 86.800(2)°. V = 681.86(12) Å³. Z =

2. $D_{\text{calc}} = 1.234 \text{ Mg/m}^3$. $T = 293 \text{ K}$. Radiation = 0.71073 \AA . Abs. coeff. = 0.091 mm^{-1} . θ range for data collection = $1.98\text{--}28.28^\circ$. Final R indices; $[I > 2\sigma(I)]$ $R1 = 0.0741$, $wR2 = 0.1715$, R indices (all data) $R1 = 0.1491$, $wR2 = 0.2071$. $R1 = \sum ||F_0| - |F_c|| / \sum |F_0|$. $wR2 = [\sum w(F_0^2 - F_c^2)^2 / \sum w(F_0^2)^2]^{1/2}$

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