Molbank **2007**, M538 http://www.mdpi.org/molbank/

Synthesis and Physical Characterization of 4-(anthracen-10-yl)-1-cyclohexyl-3-phenoxyazetidin-2-one as a New *Trans* 2-azetidinone

Aliasghar Jarrahpour [*, a], Mohammad Nazari [a], and Abraham F. Jalbout [b]

a Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran.
b Department of Chemistry, University of Arizona, Tucson, AZ 85721 USA
*Author to whom correspondence should be addressed. Tel: + 98 711 2284822; Fax: +98 711 2280926; E-mail: jarrah@susc.ac.ir

Received: 3 January 2007 / Accepted: 19 January 2007 / Published: 31 May 2007

Keywords: 2-Azetidinone, AM1, polycyclic aromatic imine.

Abstract: In this paper we propose the synthesis of 4-(anthracen-10-yl)-1-cyclohexyl-3-phenoxyazetidin-2-one. In addition to its synthesis AM1 calculations to characterize the physical properties of the molecule is also presented.

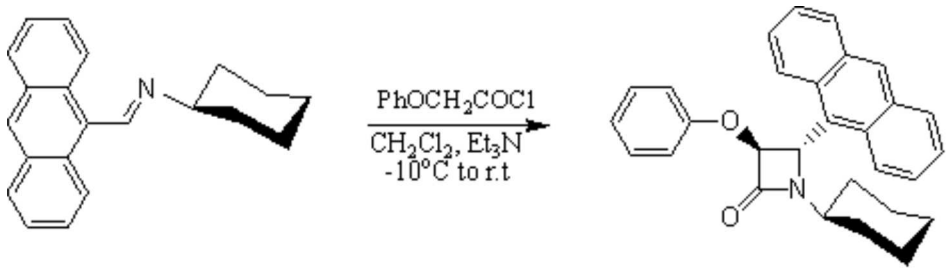
Introduction

β-lactam antibiotics have saved many lives since 1945 [1]. Apart from their clinical use, recent reports on the use of β-lactams for purposes other than antibiotics are gaining attention. This four-membered cyclic amide has been extensively used for the synthesis of several biologically active heterocyclic compounds [2]. It has been established that Taxol can be prepared by a coupling reaction between natural baccatin and suitably substituted hydroxy β-lactam [3]. Banik and his coworkers have been engaged in the synthesis and biological evaluation of compounds in which a polycyclic aromatic ring is present [4]. During the course of this study, we became interested in the synthesis of cyclic amides (for example, β-lactam) also bound to a polyaromatic ring. Although there are many methods known for the construction of the β-lactam rings, the Staudinger reaction is still the most frequently used and is considered to be the most effective. This paper describes for the first time the synthesis of a *trans* β-lactam with polyaromatic imine and identifies a new stereochemical aspect of the Staudinger reaction [5]. The formation of the *cis* and *trans* β-lactams by consideration of a number of factors has been reported. The substituents present in the imines, acid chloride, conditions of reaction, nature of the base, nature of the solvent, order of the addition of the reagents, and temperature of the reactions have shown to affect the formation of the β-lactam ring [6]. To explain the stereoselectivity, some computer- assisted theoretical calculations have also been reported [7].

Results and Discussion

Polyaromatic aldimine **1** was prepared in quantitative yield by condensation of cyclohexylamin and 9-anthraldehyd in refluxing ethanol. The formation of Schiff base **1** was readily established from its spectral data. Treatment of **1** with the ketene derived from phenoxyacetyl chloride in the presence of triethylamine afforded *trans*-2-azetidinone **2** (Scheme 1).

Scheme 1



1 **2**

The presence of this new compound was confirmed by t.l.c. monitoring. Its IR spectrum showed the β-lactam carbonyl at 1778.0 cm^{-1}. The indicated *trans* stereochemistry for this polycyclic β-lactam was deduced from analysis of its ^{1}H-NMR spectrum. The coupling constant of H-3 and H-4 is 1.55 Hz which is consistent with this kind of stereochemistry. In addition, ^{13}C-NMR spectroscopic data of β-lactam **2** definitely showed the β-lactam carbonyl at 167.23. The mass spectrum showed the M and M+1 at 421 and 422 respectively. We next performed theoretical calculations to present a viable structure for the product. All calculations in this work were carried out with the AM1 level of theory using the GAUSSIAN03 suite of programs [8]. More information about these methods is available elsewhere [9]. Figure 1 presents the optimized structure of the molecule with bond lengths and bond angles shown.

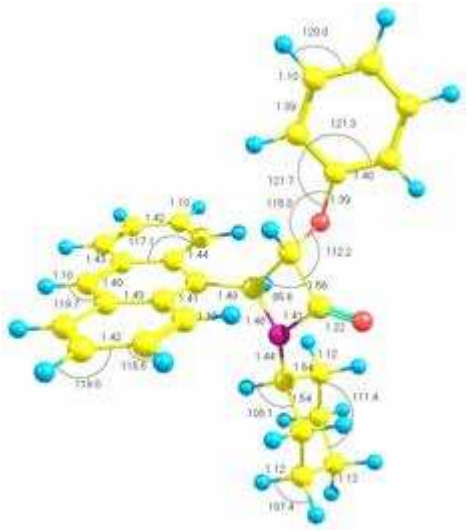


Figure 1. AM1 optimized geometry and with all bond lengths shown in angstroms (Å), and bond angles in degrees (°).). In the figure, yellow spheres are carbon, blue spheres are hydrogen atoms, purple spheres are nitrogen, green spheres are chlorine and red spheres are oxygen atoms.

Table 1 shows the thermodynamic properties for the structure in figure 1 where T (temperature in K), S (entropy in J mol^{-1} K^{-1}), C_p (heat capacity at constant pressure in kJ mol^{-1} K^{-1}), and $\Delta H = H° - H°_{298.15}$ (enthalpy content, in kJ mol^{-1}), T_1=100 K, T_2=298.15 K, and T_3=1000 K calculated AM1 frequencies. The fits were performed according to the equations implemented by the National Institute of Standards and Technology (NIST) [10].

Table 1. Thermodynamic properties of the molecule in Figure 1, calculated at the AM1 level of theory, where C_p is the heat capacity in J mol^{-1} K^{-1}, S is the entropy in J mol^{-1} K^{-1}, and DH is the standard enthalpy kJ mol^{-1}. These where the fitted results to the Shomate equations [10] which are implemented by the JANAF tables of the NIST databases. These equations converged to an R^2 value of 0.999 on average. These equations have been very good at predicting physical properties of various molecules, as we have tested in the past [11-13].

1	Fitted Thermodynamic Equation (T/1000 = t)

C_p	-102.6425+2015.93089 *t -834.19359*t^2 -0.899*t^3 +0.81049 *t^{-2}
S	-146.41593*ln(t) + 2119.35904*t -789.63261*t^2/2 -137.09185 *t^3/3 -1.52784/(2*t^2) -0.32924
ΔH	-208.75034*t +2516.84737*t^2/2-1598.5675*t^3 /+368.81851*t^4/4 -1.95655/t +39.549

Experimental

All required chemicals were purchased from Merck and Fluka chemical companies. Dichloromethane and triethylamine were dried by distillation over CaH2 and then stored over 4Å molecular sieves. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a Bruker Avance DPX instrument (operating at 250 MHz for 1H and 62.9 MHz for 13C). Chemical shifts were reported in ppm (δ) downfield from TMS. The coupling constant (*J*) is in Hertz. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography (t.l.c.) was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kieselgel (230-270 mesh).

Synthesis of (E)-N-(antheracen-10-ylmethylene) cyclohexanamine (1):

A mixture of cyclohexylamine (0.24 g, 2.40 mmol) and 9-anthraldehyde (0.50 g, 2.40 mmol) was refluxed in ethanol for 4 hours. After cooling the solution the precipitate formed was filtered off and washed with ethanol to give Schiff base **1** as a yellow solid and then was recrystalized from ethanol (95%). IR (KBr, cm^{-1}): 1630 (C=N). ^{1}H-NMR (250 MHz, $CDCl_3$, ppm): 1.11-1.98 (m, 10H, cyclohexyl), 3.47 (m, 1H, C<u>H</u>-N, cyclohexyl), 7.24-8.01 (m, 9H, Aromatic), 9.02 (s, 1H, C<u>H</u>=N). ^{13}C-NMR δ (ppm): 24.84-34.75 (cyclohexyl), 71.66 (<u>C</u>-N, cyclohexyl), 124.00-131.00 (aromatic carbons), 157.64 (<u>C</u>=N). MS (m/z): 287 (M^+), 288 (M+1), 57, 69, 73, 83, 95, 97, 110, 129, 149, 177, 204,

Synthesis of 4-(anthracen-10-yl)-1-cyclohexyl-3-phenoxy-2- azetidinone (2):

A solution of phenoxyacetyl chloride (0.22 g, 1.30 mmol) in dry CH2Cl2 (10 mL) was slowly added to a solution of (E)-N-(antheracen-10-ylmethylene) cyclohexanamine 1 (0.29 g, 1.00 mmol) and triethylamine (0.26 g, 2.60 mmol) in CH_2Cl_2 (15 mL) at –10 ^{o}C. The reaction mixture was then allowed to warm to room temperature, stirred overnight and then it was washed with saturated sodium bicarbonate solution (20 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated to give the crude product as a white solid which was then purified by recrystalization from ethyl acetate (Yield 78 %). m.p. 177-180 ^{o}C. IR (KBr, cm^{-1}): 1778.0 (CO β-lactam). ^{1}H-NMR (250 MHz, $CDCl_3$, ppm): 0.88-2.11 (m, 10H cyclohexyl protons), 3.50 (m, CH-N, cyclohexyl), 5.21(H_4, d, 1H, *J* = 1.55), 5.78 (H3, d, 1H, J = 1.55), 6.53-7.97 (ArH, m, 14H). ^{13}C-NMR δ (ppm): 24.74-30.31 (cyclohexyl), 57.10 (CN, cyclohexyl), 115.37-129.89 (aromatic carbons), 157.73 (Ph-O-C_3), 167.23 (β-lactam C=O).MS (m/z): 421 (M), 422 (M+1), 328, 296, 239, 204, 134, 77. Anal. Calcd for $C_{29}H_{27}NO_2$: C, 82.63; H, 6.46; N, 3.32 Found: C, 82.60; H, 6.48; N, 3.29.

Acknowledgment

AAJ and MN thank the Shiraz University Research Council for financial support (Grant No.85-GR-SC-23). AFJ would like to thank the University of Arizona supercomputer center for these calculations.

References

1. a) Banik, B. K.; Becker, F. F. *Tetrahedron Lett*. **2000**, *41*, 6551-6554. b) Bose, A. K.; Manhas, M. S.; Banik, B. K.; Srirajan, V. In *The Amide Linkage: Selected Structural Aspects in Chemistry Biochemistry, and Material Science*; Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds; Wiley- Interscience: *New York*, 2000; Chapter 7, p. 157 (β-lactams: Cyclic Amides of Distinction).
2. (a) Bose, A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S. *Tetrahedron: Symposium-in-Print 80* **2000**, *56*, 5603-5619. (b) Banik, B. K.; Ghatak, A.; Becker, F. F. *J. Chem. Soc., Perkin Trans*. **2000**, *1*, 2179.
3. Suffness, M. In *Taxol Science and Applications*; CRC Press, 1995.
4. Becker, F. F.; Banik, B. K. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2877.
5. Staudinger, H. *Liebigs Ann. Chem*. **1907**, *356*, 51.
6. For an elegant contribution, see: Georg, G. I.; Ravikumar, V. T. *In The Organic Chemistry of _ β-lactams*; Georg, G. I., Ed.; VCH publishers: *New York,* 1992; p. 295.
7. For examples, see: (a) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc*. **1993**, *115*, 995. (b) Arrieta, A.; Lecea, B.; Cossio, F. P. *J. Org. Chem*. **1998**, *63*, 5869, and references cited therein.
8. Frisch, M. J., et.al., GAUSSIAN03, Revision A.1, M. J. Frisch, et. Al., Gaussian, Inc., Pittsburgh PA, 2003.
9. Foresman, J. B., Æ Frisch, Exploring Chemistry with Electronic Structure Methods, 2nd edition Gaussian, INC, Pittsburgh, PA, 1996.
10. Linstrom, P. J., Mallard, W.G., Eds., NIST Chemistry WebBook, NIST Standard Reference Database Number 69, July 2001, National Institute of Standards and Technology, Gaithersburg, MD 20899.
11. Jalbout, A. F , Solimannejad, M., Labonowski, J.K. *Chem. Phys. Letts*. **2003**, 379, 503.
12. Jalbout, A. F., Jiang, Quasri, A., Jeghnou, H., Rhandour, A. *Vib. Spect*. **2006**, in press.
13. Jalbout, A. F., Nazara, F., Turker, L. *J. Mol. Struct. (THEOCHEM)* **2004**, *627*, 1. (Invited Review).