Molbank **2007**, M542 http://www.mdpi.org/molbank/

Synthesis and Physical Characterization of (E)-1-(3-morpholinopropyl)-3-phenoxy-4-styrylazetidine-2-one as the First β-lactam Bearing a Morpholino Moiety

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Received: 3 January 2007 / Accepted: 27 February 2007 / Published: 31 May 2007

Keyword: Azetidine-2-one, N-morpholinopropyl monocyclic β-lactam, Staudinger reaction, AM1

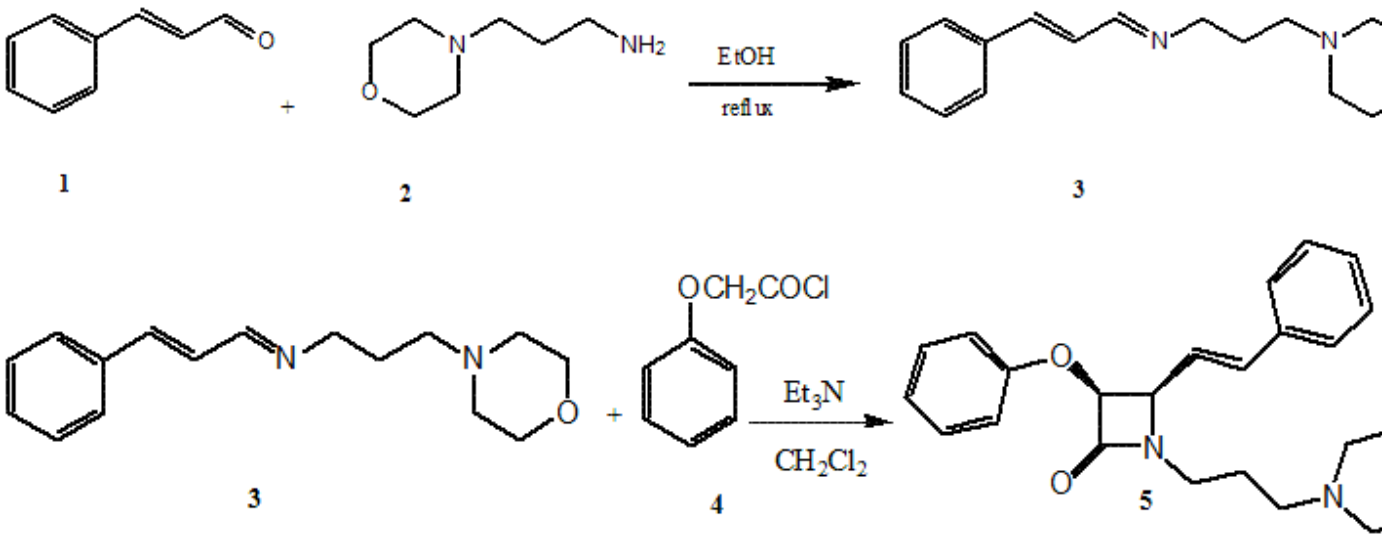
Abstract: In this paper we propose the synthesis of (E)-1-(3-morpholinopropyl)-3-phenoxy-4-styryl azetidine-2-one as a new monocyclic β-lactam. Its structure has been confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic data. In addition to its synthesis we present AM1 calculation to characterize the physical properties of the molecule.

Introduction

The synthesis of monocyclic *β*-lactams has received considerable attention in recent years due to their potential antibacterial activity. Several synthetic entries toward monocyclic *β*-lactams have been developed, the most important routes being (1) the ester enolate-imine condensation, (2) cyclization of β-amino carboxylic acids and esters, (3) cyclocondensation of ketenes, ketenimines, and keteniminium salts with imines, (4) cycloaddition of chromium-carbene complexes with imines, (5) cyclizationof *β*-functionalized amides, imidates, and hydroxamates,and (6) oxidation of azetidines [1]. The reaction between ketenes and imines (Staudinger) is one of the most convenient forms to obtain 2-azetidinones (*β*-lactams) in a convergent and stereocontrolled manner. The importance of this reaction stems from the utility of β-lactams in medicinal chemistry and from the utility of the obtained cycloadducts in the synthesis of compounds of biological interest. In addition, the reaction is very versatile and therefore can be used in combinatorial chemistry [2]. Morpholine is a simple heterocyclic compound with a great industrial importance. It is used as anticorrosive agent and as chemical intermediate catalyst, solvent, antioxi-dant in the production of various pharmaceuticals and pesticides [3]. Therefore we decided to synthesize some new monocyclic β-lactams bearing a morpholino moiety and one of them is reported here.

Results and Discussion

Treatment of cinnamaldehyde **1** with morpholinopropyl amine **2** in ethanol under reflux condition afforded the new Schiff base **3** as a dark-red liquid. The [2+2] cycloaddition of this imine with the ketene (Staudinger reaction) generated *in situ* from phenoxyacetyl chloride in the presence of triethylamine in dry dichloromethane afforded 1-(3-morpholinopropyl)-3-phenoxy-4-styryl azetidine-2-one **5** . The coupling constants for H_3 and H_4 were 4.25 Hz which is consistent with the *cis* of geometry. The *cis* geometric isomer of the product was also confirmed by theoretical calculations. Then the optimized structure of the molecule was calculated.



Scheme 1

All calculations in this work were carried out with the AM1 level of theory using the GAUSSIAN 03 suite of programs [4]. More information about these methods is available elsewhere [5]. Figure 1 presents the optimized structure of the molecule with bond lengths and bond angles shown.

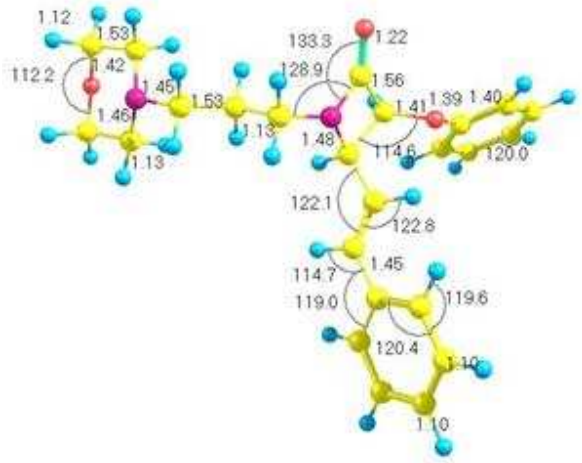


Figure 1. AM1 optimized geometry and with all bond lengths shown in angstroms (Å), and bond angles in degrees (°). In the figure, yellow spheres are carbon, blue spheres are hydrogen atoms, purple spheres are nitrogen, and red spheres are oxygen atoms.

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) [6].

Table.1 Thermodynamic properties of the molecules 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 [5] 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 [6-8].

	Fitted Thermodynamic Equation (T/1000=t)

Cp	$-184.26382*t +2484.37019*t^2 -1617.80676*t^3 +382.29145*t^{-2}$
S	$96.58246*\ln(t) + 2068.27*t -1006.92872*t^2/2 +109.15444 *t^3/3 -0.34424/(2*t^2) -11.32637$
ΔH	$403.63999*t +594.57262*t^2/2-1.27691*t^3 /3+166.61048*t^4/4 +7.63003/t -108.27816$

Experimental

General

All required chemicals were purchased from Merck and Fluka chemical companies. Dichloromethane and triethylamine were dried by distillation over CaH_2 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 $CDCl_3$ or DMSO-d_6 using a Bruker Avance DPX instrument (operating at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts were reported in ppm (δ) downfield from TMS. All of the coupling constants (*J*) are in Hertz. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnegan 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 60 Merck (230-270 mesh).

Synthesis of 3-morpholino-N-((E)-3-phenylallylidene) propan-1-amine

A mixture of cinnamaldehyde (2.00 g, 15.00 mmol) and 3-morpholinopropan-1-amine (2.16 g, 15.00 mmol) was refluxed in ethanol for 6 hours. Then the solvent was evaporated under reduced pressure.The croud product was obtained as a dark-red oil.

IR (cm^{-1}): 1633.6 ($\nu_{C=N}$)

^{1}H-NMR (250 MHz, $CDCl_3$, ppm) 1.83 (2H, m, C<u>H</u>$_2$-CH$_2$-morpholine ring) 2.16 (2H, s, C<u>H</u>$_2$-morpholine ring), 2.38 (4H, m, C<u>H</u>$_2$-N morpholine ring), 3.53 (2H, t, C<u>H</u>$_2$-N=CH), 3.70 (4H, t, C<u>H</u>$_2$-O morpholine ring), 6.89 (1H, s, C<u>H</u>=CH-Ph), 6.92 (1H, s, CH=C<u>H</u>-Ph), 7.32-7.49 (5H, m, ArH), 8.02 (1H, d, C<u>H</u>=N)

^{13}C-NMR (62.9 MHz, $CDCl_3$, ppm): 162.88 (C=N), 141.48 (Ph-<u>C</u>), 127.18-135.70 (aromatic carbons and Ph-CH=<u>C</u>H), 66.99 (<u>C</u>H$_2$-O morpholine ring), 59.45 (<u>C</u>H$_2$-N morpholine ring), 56.64, 53.69, 27.75 (CH$_2$ carbons). MS (m/e, %): 259 (M+1, 0.9), 258 (M^+, 4.0), 172 (4.1), 144 (85.0), 130 (6.7), 128 (3.4), 116 (12.9), 114 (86.5), 100 (100.0), 77 (13.0).

Synthesis of 1-(3-morpholinopropyl)-3-phenoxy-4-styryl azetidine-2-one

A solution of phenoxyacetyl chloride **4** (0.86 g, 5.00 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of (3-morpholino-N-3-phenylallylidenepropan-1-amine **3** (1.00 g) and distilled triethylamine (2.33 g, 10.00 mmol) in CH_2Cl_2 (20.00 mL) at 0^{o}C.The reaction mixture was then allowed to warm to room temperature and stirred overnight. Then it was washed with saturated sodium bicarbonate solution (20 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the crude product which was then purified by column chromatography over silica gel (eluent EtOAC : EtOH 10 : 3) to afford **5** as a brown solid.

Melting Point: 65-70 ^{o}C. IR (KBr, cm^{-1}) : 1754.1($\nu_{C=O}$). ^{1}H-NMR (250 MHz, $CDCl_3$, ppm) 6.71 (10H, m, ArH), 6.52 (1H, d, CH=C<u>H</u>-Ph, *J* = 15.8), 5.93 (1H, dd, C<u>H</u>=CH-Ph, *J* = 8.75, 16), 5.36 (1H, d, H-3, *J* =

4.25), 4.45 (1H, dd, H-4, *J* = 4.25, 8.75), 3.26 (4H, t, CH_2-O), 3.06 (4H, p, C$\underline{H_2}$-N), 2.91 (2H, m,C$\underline{H_2}$-CH_2-CH_2-morpholine), 2.07 (CH_2-CH_2-C$\underline{H_2}$-morpholine ring), 1.39 (2H, m, -CH_2-C$\underline{H_2}$-CH_2-morpholine ring).

^{13}C-NMR (62.9 MHz, $CDCl_3$, ppm):164.81 (C=O), 114.61-156.74 (aromatic carbons), 126.37 (C$\underline{H}$=CH-Ph), 123.21 (CH=C$\underline{H}$-Ph), 80.83 (C-3), 65.99 ($\underline{C}H_2$-O), 60.13 (C-4), 55.29 (CH_2-CH_2-$\underline{C}H_2$-morpholine ring), 53.06 ($\underline{C}H_2$-N), 39.44 ($\underline{C}H_2$-CH_2-CH_2-morpholine ring), 23.91(CH_2-$\underline{C}H_2$-CH_2-morpholine ring).

MS (m/e, %): 393(M^++1, 0.1), 392(M^+, 0.1), 299 (1.7), 222(0.8), 212 (1.9), 169(0.8), 100(100), 77(7.3), 70 (5.4). Anal.Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44, H, 7.19, N, 7.14 Found: C, 71.88, H, 7.24, N, 7.97.

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