Synthesis of 4-(2-Methoxyethyl)-2-azetidinone

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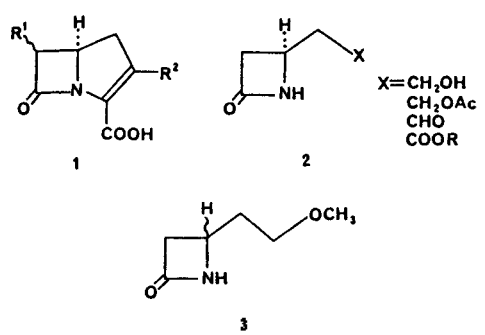
A potential carbapenem template, 4-(2-methoxyethyl)-2-azetidinone (**3**), was prepared in seven steps from 5,6-dihydro-2H-pyran-2-one (**5**).

Introduction

The recent discovery of naturally occurring carbapenem antibiotics **1** has provided impetus for the considerable synthetic activity[1] due to their structural diversity and significant antibacterial properties. The most attractive and versatile intermediates for the synthesis of such bicyclic carbapenemes could be 4-substituted-2-azetidinones (**2**). These monocyclic β-lactams have so far been prepared from 1-acetoxybutadiene[2], L-aspartic acid[3], dialkyl acetonedicarboxylates,[4] D-glyceraldehyde acetonide,[5] and chiral γ-butyrolactone.[6] In this paper we wish to report another approach to 4-(2-methoxyethyl)-2-azetidinone (**3**) from 5,6-dihydro-2H-pyran-2-one (**5**).



Results and Discussion

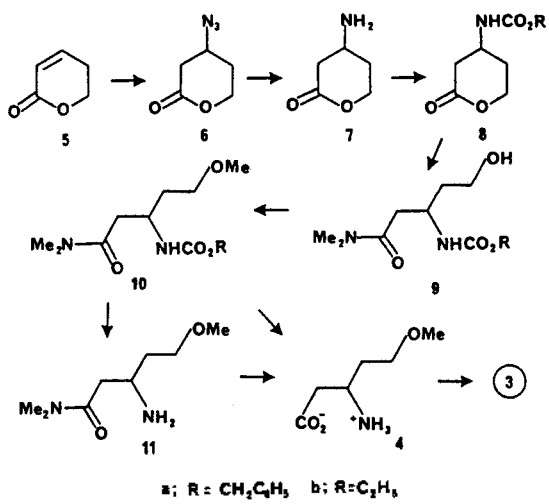
One of the most appropriate templates for the synthesis of 2-azetidinone derivatives is functionalized β-amino acids and the β-amino acid that can directly afford 4-(2-methoxyethyl)-2-azetidinone (**3**) is 3-amino-5-methoxypentanoic acid (**4**). This β-amino acid **4** was synthesized in six steps from 5,6-dihydro-2H-pyran-2-one (**5**).

5,6-Dihydro-2H-pyran-2-one (**5**) was prepared from 3-butenoic acid and paraformaldehyde[7] and this α,β-unsaturated lactone was subjected to the Michael-type addition reaction. Treatment of the α,β-unsaturated lactone **5** with hydrogen azide[8] in the presence of catalytic amount of triethylaluminum produced β-azido-δ-valerolactone (**6**) in 83 % yield.[9] Attempted Michael addition of hydrogen azide alone, sodium azide- Lewis acids, or potassium phthalimide to the lactone **5** in various reaction conditions was not successful.

Reductive hydrogenolysis of the azido moiety of the β-azidolactone **6** and subsequent protection of the resulting amino group with benzyloxycarbonyl or ethoxycarbonyl afforded β-benzyloxycarboxamido- or β-ethoxycarboxamido-δ-valerolactone (**8a** or **8b**) in moderate yields. Ring opening reaction of the protected lactones **8** with dimethylamine produced N,N-dimethyl-3-benzyloxycarboxamido-5-hydroxypentanamide (**9a**), and N,N-dimethyl-3-ethoxycarboxamido-5-hydroxypentanamide (**9b**),respectively. Protection of the hydroxyl group of the amides **9** by etherification with methyl iodide and silver oxide in acetonitrile[10] then gave the fully protected β-amino acids **10**.

3-Amino-5-methoxypentanoic acid (**4**) was prepared from the fully protected amides **10** in two different routes. Hydrogenolysis of the benzyloxycarbonyl group of the amide **10a** produced N,N-dimethyl-3-amino-5-methoxypentanamide (**11**) in 90 % yield and subsequent hydrolysis of the amino-amide **11** afforded the β-amino acid **4** in 82 % yield. Direct hydrolysis of the fully protected **10b** with aqueous sodium hydroxide also produced the β-amino acid **4** in 86 % yield.

Dehydrative cyclization of the β-amino acid **4** with 2-bromo-1-methylpyridinium iodide and triethylamine in acetonitrile[11] then furnished in 64 % yield racemic 4-(2-methoxyethyl)-2-azetidinone (**3**) (see Scheme 1).



Scheme 1

Experimental

General. Infrared spectra were obtained by using a Perkin-Elmer 170B spectrophotometer and ^{1}H-NMR spectra were recorded on Varian EM 360A instrument, with TMS in deuteriochloroform or DSS in deuterium oxide as internal standard. Column chromatography was performed on silica gel 60 (Merck). All the chemicals used were reagent grade and purified prior to use if necessary.

5,6-Dihydro-2H-pyran-2-one (5) was prepared in 25 % yield from 3-butenoic acid and paraformaldehyde by following literature procedure[7]. IR ($CHCl_3$): ν= 1720 cm^{-1} (carbonyl); ^{1}H-NMR ($CDCl_3$): δ=2.30-2.60 (m, 2H, -CH_2CH=), 4.40 (t, J=6 Hz, 2H, -CH_2O-). 5.92 (dt, J=10 and 1.5 Hz, 1H, =CHCH$_2$-), 6.92 ppm (dt, J=10 and 4 Hz, 1H, =CHC=O).

β-Azido-δ-valerolactone (6). A mixture of 2.0 m*l* (3.8 mmol) of 25 % triethylaluminum in toluene and 40 m*l* (40 mmol) of 1.0 M hydrogen azide in chloroform was stirred at −78° C for 20 min under nitrogen atmosphere and 3.0g (30 mmol) of 5,6-dihydro-2H-pyran-2-one **(5)** was added. The solution was stirred at rt for 48 hrs and washed with aqueous sodium bicarbonate solution. Usual work-up and column chromatography (EtOAc/$CHCl_3$ = 1/3) afforded 3.57 g (87 % yield) of **6** as a colorless oil. IR ($CHCl_3$): ν = 2135 (azido), 1750 cm^{-1} (carbonyl); ^{1}H-NMR ($CDCl_3$): δ = 1.80–2.25 (m, 2H, $-CH_2-$), 2.60 (dd, J = 6 Hz, 2H, $-CH_2C=O$), 3.80–4.37 ppm (m, 3H, –NCH– and $-CH_2O-$).

β-Amino-δ-valerolactone (7). To a solution of 2.6g (18 mmol) of the azido compound **6** in 20 m*l* of absolute methanol was added 1 g of 5 % Pd-C and the mixture was hydrogenolyzed at the hydrogen pressure of 3 atm at rt for 24 hrs. Filtration, evaporation, treatment with choloroform, filtration and evaporation afforded 1.93 g (91 % yield) of **7** as a yellowish oil, which was directly used for the next step without further purification. IR (neat): ν = 3430 (brd, $-NH_2$), 1745 cm^{-1} (carbonyl); ^{1}H-NMR (D_2O): δ = 1.76–2.10 (m, 2H, $-CH_2-$), 2.90 (dd, J = 6 and 1.5 Hz, 2H, $-CH_2C=O$), 3.50–3.92 ppm (m, 3H, – NCH– and $-CH_2O-$).

β-Benzyloxycarboxamido-δ-valerolactone (8a). To a mixture of 3.5 g (20 mmol) of the amino compound **7** and 2.54 g (24 mmol) of sodium carbonate in 20 ml of water was added 4.26 ml (30 mmol) of benzyl chloroformate and the mixture was stirred at rt for 16 hrs. Extraction with chloroform, usual work-up and column chromatography (EtOAc/$CHCl_3$ = 1/1) produced 3.05 g (63 % yield) of **8a** as a colorless oil. IR ($CHCl_3$): ν = 3440 (–NH–), 1740 cm^{-1} (carbonyl); ^{1}H-NMR ($CDCl_3$): δ = 1.66–1.95 (m, 2H, $-CH_2-$), 2.55 (t, J = 8 Hz, 2H, $-CH_2C=O$), 3.75–4.26 (m, 3H, –NCH– and $-CH_2O-$), 5.00 (s, 2H, $-CH_2Ph$), 6.07 (brd, 1H, –NH–), 7.20 ppm (s, 5H, phenyl).

β-Ethoxycarboxamido-δ-valerolactone (8b) was prepared in 64 % yield as a colorless oil from the amino compound **7** and ethyl chloroformate, by following exactly the same procedure employed for the synthesis of **8a**. IR (neat): ν = 3450 (–NH–), 1740 cm^{-1} (carbonyl); ^{1}H-NMR ($CDCl_3$): δ = 1.23 (t, J = 7 Hz, 3H, $-CH_3$), 1.60–1.98 (m, 2H, $-CH_2-$), 2.30–2.60 (m, 2H, $-CH_2C=O$), 3.50–3.85 (m, 2H, $-CH_2O-$), 4.20 ppm (brd q, 3H, –NCH– and $-OCH_2CH_3$).

N,N-Dimethyl-3-benzyloxycarboxamido-5-hydroxypentanamide (9a). To a solution of 2.49 g (10 mmol) of **8a** in 20 ml of chloroform was added 10 ml of 50 % aqueous dimethylamine and the mixture was stirred at rt for 4 hrs. Separation of the chloroform layer and usual work-up gave in quantitative yield the hydroxy compound **9a** as a yellowish oil. IR (neat): ν = 3460 (brd, –OH and –NH), 1630 cm^{-1} (carbonyl); ^{1}H-NMR (D_2O): δ = 1.36–1.80 (m, 2H, $-CH_2-$), 2.17–2.46 (m, 2H, $-CH_2C=O$). 2.57, 2.62 (each s, 6H, N-Me_2), 3.43 (t, J = 6 Hz, 2H, $-CH_2O-$), 3.85–4.13 (m, 1H, –NCH–), 4.83 (s, 2H, $-CH_2Ph$), 6.15 (brd, 1H, –NH–), 7.05 ppm (s, 5H, phenyl).

N,N-Dimethyl-3-ethoxycarboxamido-5-hydroxypentanamide (9b) was prepared in quantitative yield from **8b** and dimethylamine as a yellowish oil by following exactly the same procedure employed for the synthesis of **9a**. IR (neat): ν = 3450 (brd, –OH and –NH–), 1630 cm^{-1} (carbonyl); ^{1}H-NMR ($CDCl_3$): δ = 1.25 (t, J = 7 Hz, 3H, $-CH_3$), 1.70–2.05 (m, 2H, $-CH_2-$), 2.60–2.80 (m, 2H, $-CH_2C=O$), 2.90, 3.02 (each s, 6H, N-Me_2), 3.60–3.92 (m, 3H, –NCH– and $-CH_2O-$), 4.15 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 6.36 ppm (brd, 1H, –NH–).

N,N-Dimethyl-3-benzyloxycarboxamido-5-methoxypentanamide (10a). To an ice-cooled solution of 1.18 g (4 mmol) of the hydroxy compound **9a** in 10 ml of acetonitrile was added 5 m*l* of methyl iodide followed by 0.93 g (8 mmol) of silver oxide, and the mixture was stirred at rt for 26 hrs. Removal of silver iodide, evaporation and column chromatography (EtOAc/MeOH = 9/1) gave 1.07 g (87 % yield) of **10a** as a colorless oil. IR (neat): ν = 1640 cm^{-1} (carbonyl); ^{1}H-NMR ($CDCl_3$): δ = 1.56–1.90 (m, 2H, $-CH_2-$), 2.42–2.66 (m, 2H, $-CH_2O-$), 2.80, 2.90 (each s, 6H, N-Me_2), 3.48 (t, J = 6 Hz, 2H, $-CH_2O-$), 3.58 (s, 3H, $-OCH_3$), 4.34–4.57 (m, 1H, –NCH–), 5.03 (s, 2H, $-CH_2Ph$), 6.05 (brd, 1H, –NH–), 7.27 ppm (s, 5H, phenyl).

N,N-Dimethyl-3-ethoxycarboxamido-5-methoxypentanamide (10b) was prepared in 85 % yield as a colorless oil from the hydroxy compound **9b**, by following exactly the same procedure employed for the synthesis of **10a**. IR (neat): ν = 1640 cm^{-1} (carbonyl); ^{1}H-NMR ($CDCl_3$): δ = 1.27 (t, J = 6 Hz, 3H, $-CH_2CH_3$), 1.60–2.00 (m, 2H, $-CH_2-$), 2.45–2.70 (m, 2H, $-CH_2C=O$), 2.92, 3.03 (each s, 6H, N-Me_2), 3.33 (s, 3H, $-OCH_3$), 3.60 (brd t, J = 6 Hz, 2H, $-OCH_2-$), 4.13(q, J = 6Hz, 2H, $-OCH_2CH_3$), 4.50–4.80(m, 1H, –NCH–), 6.15 ppm (brd, 1H, –NH–).

N,N-Dimethyl-3-amino-5-methoxypentanamide (11). To a solution of 0.92 g (3 mmol) of **10a** in absolute ethanol was added 1 g of 5 % Pd-C and the mixture was hydrogenolyzed at the hydrogen pressure of 3 atm at rt for 19 hrs. Filtration, work-up and short column chromatography (methanol) afforded 0.47 g (90 % yield) of **11** as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 1.60–1.92 (m, 2H, $-CH_2-$), 2.18–2.53 (m, 3H, $-CH_2C=O$ and –NCH–), 2.35 (s, 2H, $-NH_2$), 2.90 , 2.95 (each s, 6H, $-NMe_2$), 3.25 (s, 3H, $-OCH_3$), 3.45 ppm (t, J = 6 Hz, 2H, $-OCH_2-$).

3-Amino-5-methoxypentanoic acid (4) was prepared from **10b**, and **11** respectively. **From 10b:** To a suspension of 2.46 g (10 mmol) of **10b** in 50 ml of water was added 2.5 g of sodium hydroxide and the mixture was refluxed for 10 hrs. Washing with chloroform, acidification with dilute hydrochloric acid to pH 6.7 and evaporation gave a sticky solid which was treated with absolute ethanol to precipitate out sodium chloride. Short column chromatography (mehtanol) then produced 1.25 g (86 % yield) of **4** as an oil. **From 11:** By following the above procedure, **4** was also obtained in 82 % yield as an oil. IR (neat): ν = 3450 (brd, carboxylate), 1660, 1560, 1420 cm^{-1}; ^{1}H-NMR (D_2O): δ = 1.65–2.18 (m, 2H, $-CH_2-$), 2.40–2.75 (m, 3H, $-CH_2C=O$ and –NCH–), 3.33 (s, 3H, $-OCH_3$), 3.55 ppm (t, J = 6 Hz, 2H, $-OCH_2-$).

Racemic 4-(2-methoxyethyl)-2-azetidinone (3). To a solution of 0.75 g (5 mmol) of 3-amino-5-methoxypentanoic acid **(4)** in 350 ml of acetonitrile was added 1.8 g (6 mmol) of 2-bromo-1-methylpyridinium iodide and 1.4 ml (10 mmol) of triethylamine, and the solution was refluxed for 36 hrs under nitrogen atmosphere. Evaporation and column chromatography (EtOAc/MeOH = 9/1) afforded 0.37 g (64 % yield) of **3** as a colorless oil. IR (neat): ν = 3350 (–NH–), 1755 cm^{-1} (β-lactam carbonyl); ^{1}H-NMR ($CDCl_3$): δ = 1.88 (q, J = 6 Hz, 2H, $-CH_2-$), 2.52, 2.68 (each dd, J = 2 and 1 Hz; ratio = 4:7). 3.02, 3.17 (each dd, J = 5 and 2 Hz, ratio = 7:4) (1H each, total 2H, $-CH_2C=O$), 3.32 (s, 3H, $-OCH_3$), 3.46 (t, J = 6 Hz, 2H, $-OCH_2-$), 3.60–3.82 (m, 1H, –NCH–), 6.70 ppm (brd, 1H, –NH–).

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Dicyanoanthracene and Biphenyl Co-sensitized Photooxygenation of 1,1-Diphenyl-2-vinylcyclopropane

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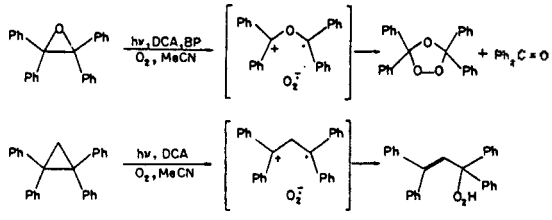
Co-sensitized photooxygenation of 1,1-diphenyl-2-vinylcyclopropane (VCP-DPh) with 9,10-dicyanoanthracene and biphenyl in oxygen-saturated acetonitrile solution produced 3,3-diphenyl-5-vinyl-1,2-dioxolane as the major product. The same photoproduct was obtained by acetone sensitized photooxygenation in oxygen-saturated acetone solution. However, VCP-DPh remained intact when directly irradiated with DCA or irradiated with Rose Bengal to generate singlet oxygen. A mechanism involving a cosensitizer radical cation and sensitizer radical anion is proposed.

Introduction

Photooxygenation of olefins sensitized by cyano-substituted aromatic hydrocarbons such as 9,10-dicyanoanthracene(DCA) has been shown to proceed by an electron-transfer mechanisms by initial formation of the radical anion of the sensitizer and radical cation of the olefins even though singlet oxygen is definitely involved in certain olefins.[1] Subsequent reaction of O_2^- with the radical cation affords the oxygenated product. Recently, Schaap and co-workers showed that the photooxygenation of epoxides to yield the corresponding ozonides could be co-sensitized by the non-light-absorbing, chemically unreactive aromatic hydrocarbon, biphenyl (BP), in conjunction with DCA.[2] They reported that a dramatic enhancement of the rate of photooxygenation of epoxides was observed in the presence of biphenyl. The photooxygenation of aryl-substituted cyclopropanes in the presence of DCA and acetonitrile also gives rise to the hydroperoxide and dioxolanes.[3]



Vinylcyclopropane compounds which exhibit bifunctionality show much enhanced chemical reactivities compared to simple cyclopropanes itself, and show extended conjugation of the unsaturated double bond and cyclopropane ring. By introduction of polar substituents to the cyclopropane ring, the vinylcyclopropanes undergo various addition reactions more readily with facile opening of the cyclopropane ring.[4] In contrast with the extensive studies of photochemical and theoretical aspects of cyclopropane chemistry, the electron-transfer photooxygenation of cyclopropane compounds are only known in limited cases. Our interest has been around electron-transfer photooxygenation of substituted vinylcyclopropanes by cyanoaromatic-sensitization in oxygen saturated polar solvents.

Experimental

Instruments. UV-VIS absorption spectra were recorded on a Cary 17 spectrophotometer. Proton and carbon-13 magnetic resonance spectra were recorded with a Varian FT-80A spectrometer in chloroform-d. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer using potassium bromide pellets or a sodium chloride cell. Mass spectra were determined with a Hewlett Packard 5985A GC/MS system. Fluorescence spectra were recorded on a Aminco-Bowman spectrofluorometer with an Aminco-XY