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Synthesis of Selective β-Lactam Derivatives

بناء بعض مركبات البيتا لاكتام

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Abstract

In this work, the mild conditions of Mitsunobu reaction were used to convert the hydroxyl group of 6-triphenylmethylaminopenicillanyl alcohol to amines by using different nuleophiles such as phthalimide, di-*tert*-butyliminodicarboxylate and potassium cyanate. The existence of the β-lactam carbonyl group increased the instability towards nucleophilic attack of refluxing methanol and the four-membered ring was opened. Treating 3-Di-*tert*-Butoxycarbonylaminomethyl-6-triphenylmethylamino - penicillanate with 50% trifluoroacetic acid in dichloromethane, resulted in the cleavage of triphenylmethyl group and one *tert*-butyl group. While the removal of both triphenylmethyl groups as well as di-*tert*-butylamino carbonyl group occurred when 75% trifluoroacetic acid was used. The significance of this study is to synthesize β-lactam derivatives that might to be more resistant to degradation by β-lactamase and hence, therapeutically more effective.

Key words: Synthesis, β-Lactams, Antibiotics, Penicillin, Mitsunobu Reaction, Alcohol.

ملخص

في هذا البحث تم استخدام ظروف تفاعل معتدلة باستخدام تفاعلات متسونوبو لتحويل مجموعة الهيدروكسيل من مركب 6-triphenylmethylaminopenicillanyl alcohol لمجموعة الامين باستخدام نيكليوفيلات مختلفة مثل phthalimide، di-tert-butyliminodicarboxylate وpotassium cyanate. بينت هذه الدراسة أن وجود مجموعة الكاربونيل على حلقة البيتا لاكتام ادى الى عدم استقرار الحلقة نحو الهجوم النيوكليوفيلي من الميثانول ونتج عن ذلك فتح الحلقة الرباعية. تفاعل المركب -Di-tert-Butoxycarbonylaminomethyl-6-triphenylmethylamino-penicillanate٣ مع حمض trifluoroacetic بتركيز ٥٠% باستخدام محلول ثنائي كلورو ميثان، أدى إلى انشقاق مجموعة منtriphenylmethyl ومجموعة من tert-butyl. في حين تمت إزالة كلاً من مجموعتيtriphenylmethyl و di-tert-butylamino carbonyl group عندما تم إستخدام حامض trifluoroacetic بتركيز ٧٥%. خلاصة هذه الدراسة هو امكانية تحضير مشتقات من مركبات تحتوي على حلقة البيتا لاكتام التي يمكن أن تكون أكثر مقاومة للتحلل من قبل البيتا لاكتاميز، وبالتالي من الممكن أن يصبح لها فعالية علاجية أكبر.

Introduction

The synthesis of amino compound from alcohol under mild conditions has received much attention, and many methods for this synthesis have been devised. For achieving this, the hydroxyl group of the alcohol must first be converted to halide or nosyl derivative before the amine can be produced. On the other hand, Mitsunobu reaction allows the conversion of primary and secondary alcohols to esters or amines.

The beta lactam antibiotics that are currently available feature the reactive β-lactam ring system, a highly strained and reactive cyclic amide (Block & Beale 2004). The reactive nature of the β-lactam ring system makes penicillins and related compounds susceptible to a variety of degradative processes (Block & Beale 2004).

The main cause of the deterioration of penicillin is the reactivity of the strained β-lactam ring, particularly to hydrolysis (Block & Beale 2004). The course of hydrolysis and the nature of the degradation products are pH dependent (Hou & Poole 1971, Blaha et al 1976).

The β-lactam carbonyl group undergoes nucleophilic attack by water or hydroxide ion to form the inactive penicilloic acid [2], which is reasonably stable in neutral to alkaline solutions but readily undergoes decarboxylation and further hydrolysis reactions in acidic solution to form penicilloic acid [2] (Lemke et al 2008). In strongly acidic solutions (pH<3) the reaction is more complex (Lemke et al 2008).

Hydrolysis of the β-lactam can be shown through kinetic analysis to involve participation of the side amide chain; the rate of this reaction differs widely depending on the nature of the side chain, leading to a variety of inactive degradation products (Blaha et al 1976, Lemke et al 2008). Substitution of an electron withdrawing group in the α-position of penicillin G has been shown to stabilize the penicillin to acid-catalyzed hydrolysis (Doyle et al 1961).

After the isolation of the first penicillins, no real improvements were made until the isolation of 6-aminopenicillanic acid [4] (Nayler 1991, Batchelor et al 1959). This compound can be converted to hundreds of synthetic and semisynthetic penicillins by acylation of the 6-amino group.

Sheehan (Sheehan & Ferris 1959) provided another route to synthetic penicillins by converting a natural penicillin such as, Penicillin G, to an intermediate from which the acyl side chain has been removed, which then can be treated to form biologically active penicillins with a variety of new side chains.

Perron (Perron et al 1964) has reported the synthesis of derivatives of 6-aminopenicillanyl alcohol, such as 6-triphenylmethylaminopenicillanyl alcohol and 6-phenylacetamidopenicillanyl alcohol which were used as starting materials in the current study to prepare β-Lactam derivatives.

Mitsunobu reaction provides a route to prepare protected amines (Mitsunobu et al 1972, Hughes 1992, Hughes 1996). This mild reaction converts the hydroxyl group into a good leaving group that is able to be displaced by a wide range of nucleophiles (Mitsunobu 1981, Mitsunobu 1967).

Experimental procedures

Melting points (uncorrected) were determined on a Kofler hot-stage apparatus. NMR spectra were recorded on a Bruker WM360 (360 MHz) Fourier Transform Instrument. NMR data are reported as parts per million (δ) and are referenced to TMS as internal standard. Infra-red spectra were recorded on a Perkin Elmer 1720 Fourier Transform Instrument. Mass spectra were recorded on Kratos MS80 and MS25. UV spectra were recorded on a Philips PU8720 spectrophotometer.

Optical rotations were measured on a Perkin Elmer PE241 polarimeter using a 1 dm path length micro cell. Thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} pre-coated silica gel plates of thickness 0.2 mm. Column chromatography was performed using Merck Kieselgel 60 (230-400 mesh). Diethyl ether, and tetrahydrofuran were dried over lithium aluminum hydride. Dichloromethane and triethylamine were dried over calcium hydride. Petroleum ether (60-80°C) was dried over calcium chloride. All other reagents were obtained from commercial suppliers, and were used without further purification.

Preparation of 6-Triphenylmethylaminopenicillanic acid [5]

Compound 5 has been prepared according to the method of Sheehan and Ferris (Sheehan & Ferris 1959).

Preparation of Triethylammonium 6-Triphenylmethylaminopenicillanate [6]

6-Triphenylmethylaminopenicillanic acid [5] (40 g, 90 mmol) was suspended in dichloromethane (200 mL) and triethylamine (18.20 g, 180 mmol, 25 mL) was added drop wise while stirring at room temperature. When the reaction mixture became homogenous after two hours of stirring, it was washed with water (2×100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford yellow foam.

Yield 44.1 g, 90%; **I.R. ($CHCl_3$) ν_{max} (cm^{-1})** 1775 (C=O, β-lactam ring); **^{1}H-nmr ($CDCl_3$) δ:** 7.50 (m, 15H, $(C_6\underline{H}_5)_3C$), 4.51 (d, 1H,

$J_{5,6}$=3.7 Hz, C-5 H), 4.41 (dd, 1H, $J_{6,5}$=3.7 Hz, $J_{6,NH}$=11.28 Hz, C-6 H), 4.22 (s, 1H, C-3 H), 3.26 (d, 1H, $J_{NH,6}$=11.28 Hz, NH), 2.87 (q, 6H, J=8 Hz, (CH_2CH_3)$_3$), 1.56 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.20 (t, 9H, J=8 Hz, (CH_2CH_3)$_3$).

Preparation of 6-Triphenylmethylaminopenicillanyl alcohol [7]

Compound 7 has been prepared according to the method of Perron et al (Perron et al 1964)

Preparation3-Phthalimidomethyl-6-triphenylmethylaminopenicillanate [8].

A solution of 6-triphenylmethylaminopenicillanyl alcohol [7] (1.128 g, 2.52 mmol), triphenylphosphine (0.728 g, 2.78 mmol), and phthalimide (0.41 g, 2.77 mmol) in dry tetrahydrofuran (30 mL), was stirred and cooled to 0°C, diethyl azodicarboxylate (0.5 g, 0.43 mL, 2.77 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred at 0°C for four hours and overnight at room temperature. The solvent was removed *in vacuo* to give orange oil. Diethyl ether (10 mL) was added, the reaction mixture was cooled for 30 min. The precipitated diethyl hydrazinedicarboxylate was filtered off and washed with diethyl ether (10 mL). The solvent was removed from the filtrate *in vacuo* to give orange oil. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to give [8] as a colourless oil.

Yield 0.321 g, 22 %; $[\alpha]_D^{20}$ = +195° (c=0.01, chloroform); **I.R. ($CHCl_3$) ν_{max} (cm^{-1})**: 1780 (C=O, β-lactam ring) and 1747 (C=O, phthalimide); **^{1}H-nmr ($CDCl_3$) δ:** 7.73 (d, 2H, J=8.4 Hz, *ortho* phthaloyl H), 7.61 (d, 2H, J=8.4 Hz, *meta* phthaloyl H), 7.33 (m, 15H, (C_6H_5)$_3$C), 4.44 (d, 1H, $J_{5,6}$ =3.8 Hz, C-5 H), 4.33 (dd, 1H, $J_{6,5}$=3.8 Hz, $J_{6,NH}$=11.4 Hz C-6 H), 4.09 (dd, 1H, $J_{3,2A}$=5.01 Hz, $J_{3,2B=}$10.6 Hz C-3 H), 3.60 (m, 2H, -CH_2N), 3.32 (d, 1H, $J_{NH,6}$=11.4 Hz, NH),1.47 (s, 3H, CH_3),1.42 (s,

3H, C<u>H</u>3); **m.s. EI m/e**: 573[M]$^{+}$, 300 [M-$(C_6H_5)_3$C-]$^{+}$, 277 [M-$(C_6H_5)_3$CNHCHCO+3H]$^{+}$; **$C_{35}H_{31}N_3O_3S$**, (573.2088), requires 573.2086.

Reaction of 3-Phthalimidomethyl-6-triphenylmethylaminopenicillanate [8] with Hydrazine.

A solution of anhydrous hydrazine (0.231 mL, 7 mmol) in dichloromethane (5 mL) was added to a solution of 3-phthalimidomethyl-6-triphenylmethylaminopenicillanate [8] (2 g, 3.5 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for three hours at room temperature. The slurry obtained was filtered and the filtrate was evaporated *in vacuo* to give yellow foam. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to give [11] a white solid which was recrystallized from a mixture of petroleum ether (60-80°C) and ethyl acetate to give [11] a white solid.

Yield 0.66 g, 40 % **$[\alpha]_D^{19}$**= -50° (c=0.02, chloroform); **I.R. ($CHCl_3$) ν_{max} (cm^{-1})**: 1750 (C=O, imide); **^{1}H-nmr ($CDCl_3$) δ:** 7.33 (m, 15H, $(C_6\underline{H}_5)_3C$), 4.07 (d, 1H, $J_{5,6}$=4.6 Hz, C-5 <u>H</u>), 4.33 (dd, 1H, $J_{6,5}$=4.6 Hz, $J_{6,NH}$=7.02 Hz C-6 <u>H</u>), 4.09 (dd, 1H, overlapped $J_{3,2A}$=3.6 Hz, C-3 <u>H</u>), 2.94 (dd, 1H, $J_{2A,3}$=3.6 Hz, $J_{2A,2B}$=11.7 Hz -C<u>H</u>$_A$N), 2.79 (ddd, 1H, $J_{2B,3}$=8.8 Hz, $J_{2B,2A}$=11.7 Hz -C<u>H</u>$_B$N), 2.59 (d, 1H, $J_{NH,6\underline{H}}$= 11.4 Hz, N<u>H</u>), 1.70 (br s, 2H, NH_2), 1.33 (s, 3H, C<u>H</u>3), 1.31 (s, 3H, C<u>H</u>3); **m.s.[+ve FAB (glycerol)] m/e**: 476 [MH], 331 [$(C_6H_5)_3$CNHCHCONHNH$_2$+H]$^{+}$, 145 [M-$(C_6H_5)_3$CNHCHCONHNH$_2$ + H]$^{+}$.

Preparation of 3-Di-*tert*-Butoxycarbonylaminomethyl-6-riphenylmethylamino - penicillanate [9].

A solution of 6-triphenylmethylaminopenicillanyl alcohol [7] (2.26 g, 5.10 mmol), triphenylphosphine (1.45 g, 5.56 mmol), and di-*tert*-butyliminodicarboxylate (1.66 g, 7.67 mmol) in dry tetrahydrofuran (60 mL), was stirred and cooled to 0°C. Diethyl azodicarboxylate (1 g, 0.96

mL, 5.54 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for four hours and overnight at room temperature. The solvent was removed *in vacuo* to give orange oil. Diethyl ether (20 mL) was added, and after cooling the reaction mixture for 30 min, the precipitated diethyl hydrazinedicarboxylate was filtered off and washed with diethyl ether (20 mL). The solvent was removed from the filtrate *in vacuo* to give orange oil. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to give [9] as a colorless oil.

Yield 0.83 g, 26 %; $[\alpha]_D^{26}$ = +200 ° (c=0.024, chloroform); **I.R. ($CHCl_3$) ν_{max} (cm^{-1}):** 1770 (C=O, β-lactam ring) and 1736 (C=O, ester); **^{1}H-nmr ($CDCl_3$) δ:** 7.33 (m, 15H, $(C_6\underline{H}_5)_3C$), 4.36 (dd, 1H, $J_{6,5}$= 3.8 Hz, $J_{6,NH}$=11.5 Hz, C-6 $\underline{H}$), 4.10 (d, 1H, $J_{5,6}$=3.8 Hz, C-5 $\underline{H}$), 3.90 (dd, 1H, $J_{3,2A}$=5.20 Hz, $J_{3,2B}$=8.86 Hz, C-3 $\underline{H}$), 3.41 (dd, 1H, $J_{2A,3}$=5.2 Hz, $J_{2A,2B}$=11.48 Hz, -$C\underline{H}_AN$), 3.20 (dd, 1H, $J_{2B,3}$=8.9 Hz, $J_{2B,2A}$=11.48 Hz, -$C\underline{H}_BN$), 3.15 (d, 1H, $J_{NH,6}$= 11.5 Hz, N$\underline{H}$), 1.55-1.40 (24H, 2$C\underline{H}_3$ and 2$(C\underline{H}_3)_3$); **^{13}C-nmr $CDCl_3$):** 175.00 (-$\underline{C}$ON), 172.3 (-$\underline{C}O_2$), 170.0 (-$\underline{C}O_2$), 127 ($(\underline{C}_6H_5)_3C$-), 73.20 ($(C_6H_5)_3\underline{C}$-), 69.14 (-$\underline{C}$-6, -$\underline{C}$-5), 66.51 (-$\underline{C}$-3), 63.50 (-$\underline{C}$-2), 53.0 (-$\underline{C}H_2N$), 43.9 (-$\underline{C}H_3$), 30.0 (-$\underline{C}H_3$), 25.25 (-$\underline{C}H_3$); **m.s. (+ve FAB, m/e:** 400 $[M-(C_6H_5)_3C-]^+$, 243 $[-(C_6H_5)_3C]^+$.

Reaction of 3-di-*tert*-Butoxycarbonylaminomethyl-6-triphenylmethylaminopenicillanate [9] with 50% trifluroacetic acid.

3-di-*tert*-Butoxycarbonylaminomethyl-6-triphenylmethylaminopenicillanate [9] (0.2 g, 0.311 mmol) was dissolved in 10 mL 50% TFA and dichloromethane. The reaction mixture was stirred at room temperature for 15 minutes. The solvent was removed *in vacuo* to give colorless oil. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to give *tert*-butylaminoxy 6-aminopenicillanate [12] as colorless oil.

Yield 0.12 g, 54 %; $[\alpha]_D^{22}$ =+110° (c=0.05, chloroform); **I.R. ($CHCl_3$) ν_{max} (cm^{-1})**: 3200 (NH_2), 1760 (C=O, β-lactam ring) and 1736 (C=O, ester); **^{1}H-nmr ($CDCl_3$) δ:** 5.38 (d, 1H, $J_{6,5}$=3.9 Hz, C-6 H), 5. 00 (br, 1H, NH_2), 4.88 (d, 1H, $J_{5,6}$=3.8 Hz, C-5 H), 4.03 (dd, 1H, $J_{3,2A}$=5.00 Hz, $J_{3,2B}$=8.40 Hz, C-3 H), 3.56 (dd, 1H, $J_{2A,3}$=5.0 Hz, $J_{2A,2B}$=11.70 Hz, -CH_AN), 3.44 (dd, 1H, $J_{2B,3}$=8.40 Hz, $J_{2B,2A}$=11.70 Hz, -CH_BN), 1.3-1.5 (15H, 2 CH_3 and $(CH_3)_3$).

Reaction of 3-di-*tert*-Butoxycarbonylaminomethyl-6-triphenylmethylaminopenicillanate [9] with 75% trifluroacetic acid.

3-di-*tert*-Butoxycarbonylaminomethyl-6-triphenylmethylaminopenicillanate [9] (0.1 g, 0.155 mmol) was dissolved in 10 mL 75 % TFA in dichloromethane. The reaction mixture was stirred at room temperature for 15 min. The solvent was removed *in vacuo* to give an oil. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to give 3-aminomethyl-2,2-dimethyl-6-aminopenam [13] as a colorless oil.

Yield 0.03 g, 14 %; $[\alpha]_D^{25}$ =+143 ° (c=0.05, chloroform); **I.R. ($CHCl_3$) ν_{max} (cm^{-1})** 3200 (NH_2), 1760 (C=O, β-lactam ring) and 1736 (C=O, ester); **^{1}H-nmr ($CDCl_3$) δ:** 5.38 (d, 1H, $J_{6,5}$=3.9 Hz, C-6 H), 4.88 (d, 1H, $J_{5,6}$=3.8 Hz, C-5 H), 4.03 (dd, 1H, $J_{3,2A}$=5.00 Hz, $J_{3,2B}$=8.40 Hz, C-3 H), 3.56 (dd, 1H, $J_{2A,3}$=5.0 Hz, $J_{2A,2B}$=11.70 Hz, -CH_AN), 3.44 (dd, 1H, $J_{2B,3}$=8.40 Hz, $J_{2B,2A}$=11.70 Hz, -CH_BN), 1.50 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

Reaction of 6-Triphenylmethylaminopenicillanyl Alcohol [7] with Potassium Cyanate.

A solution of 6-triphenylmethylaminopenicillanyl alcohol [7] (2.26 g, 5.10 mmol), triphenylphosphine (1.45 g, 5.56 mmol), and potassium cyanate (1.5 g, 5.10 mmol) in dry tetrahydrofuran (60 mL), was stirred at

-10°C. Diethyl azodicarboxylate (1 g, 0.96 mL, 5.54 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for four hours and overnight at room temperature. The solvent was removed *in vacuo* to give on orange oil. Diethyl ether (20 mL) was added, and after cooling the reaction mixture for 30 min, the precipitated diethyl hydrazinedicarboxylate was filtered off and washed with diethyl ether (20 mL). The solvent was removed from the filtrate *in vacuo* to give orange oil. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to give [10] as a colorless oil.

Yield 0.16 g, 58 %; **I.R. ($CHCl_3$) ν_{max} (cm^{-1})**: 1779 (C=O, β-lactam ring) and 2251 (C=N=O); **^{1}H-nmr ($CDCl_3$) δ:** 7.33 (m, 15H, $(C_6\underline{H}_5)_3C$), 4.44 (dd, 1H, $J_{6,5}$ =3.8 Hz, $J_{6,NH}$ =11.5 Hz, C-6 $\underline{H}$), 4.10 (d, 1H, $J_{5,6}$ =3.8 Hz, C-5 $\underline{H}$), 3.90 (dd, 1H, $J^{3,2A}$=5.10 Hz, $J_{3,2B}$=8.90 Hz, C-3 $\underline{H}$), 3.43 (dd, 1H, $J_{2A,3}$=5.10 Hz, $J_{2A,2B}$=11.50 Hz, -C$\underline{H}_A$N), 3.23 (dd, 1H, $J_{2B,3}$=8.90 Hz, $J_{2B,2A}$=11.50 Hz, -C$\underline{H}_B$N), 3.17 (d, 1H, $J_{NH,6}$= 11.5 Hz, N$\underline{H}$), 1.43 (s, 3H, C$\underline{H}_3$), 1.30 (s, 3H, C$\underline{H}_3$).

Discussion

Using phthalimide as nucleophile for Mitsunobu reaction

Mitsunobu reported the formation of amines from alcohol via the use of phthalimide (pKa=8.3) as the acidic component and subsequent reduction with hydrazine (Mitsunobu 1972). Walker (Varasi et al 1987) revised the mechanism of Mitsunobu reaction and showed that the order of mixing the reagents can have a profound effect on the reaction pathway and demonstrated that the true mechanism of the reaction was more complex than previous studies have suggested.

A solution of alcohol [7], triphenylphosphine, phthalimide and diethyl azodicarboxylate were stirred in dry tetrahydrofuran at 0°C to prepare 3-phthalimido methyl 6-triphenylaminopenicillinate [8] as a colorless oil in 22% yield.

The general procedure for deprotection of the phthalimide group is the use of hydrazine hydrate in boiling ethanol (Landini and Rolla 1976) and the free amine is obtained in high yield. However, the existence of the β-lactam carbonyl group would increase the instability towards nucleophilic attack of refluxing ethanol (Lemke et al 2008).

To avoid the hydrolysis effect of refluxing ethanol with hydrazine, the cleavage of a phthalimido substituent without affecting the β-lactam ring was attempted by treating the protected amine [8] with anhydrous hydrazine in less polar solvent such as dichloromethane at room temperature. However, nucleophilic attack occurred and the four membered ring was opened as confirmed by the infra-red spectrum which showed disappearance of the β-lactam carbonyl absorption at 1780 cm^{-1}.

Using di-*tert*-butyliminodicarboxylate as nucleophile for Mitsunobu reaction.

Following the standard Mitsunobu reaction, the expected 3-di-*tert*-butoxycarbonyl aminomethyl-6-triphenylmethylaminopenicillanate [9] was obtained as colorless oil in 26% yield on purification by column chromatography. The low yield of the product might be attributed to the difficulty of the isolation and purification of the pure compound from the triphenylphosphine oxide and diethyl hydrazinedicarboxylate byproducts (Camp 1988), and to the low acidity of di-*tert* butyliminodicarboxylate compared to the phthalimide, and several groups have found that the reaction yield depends on the acidity of the acidic component (Edwards et al 1990, Wada and Mitsunobu 1972).

Different solvent systems were used in attempts to optimize the yield of compound [9] such as, (tetrahydrofuran, 10% hexamethylphosphorotriamide), (tetrahydrofuran, 50% hexamethylphosphorotriamide) and (100% hexamethylphosphorotriamide) gave 30%, 36%, and 32% yield, respectively.

Treatment of compound [9] with 50% trifluoroacetic acid in dichloromethane, removed the triphenylmethyl group and at the same time, one *tert*-butyl group was cleaved to give compound [12] in 54 % yield.

When compound [9] was treated with 75% trifluoroacetic in dichloromethane, compound [13] was obtained in 14% yield. The removal of both the triphenylmethyl group as well as di-*tert*-butylaminocarbonyl group was confirmed by ^{1}H-nmr. The removal of both groups could be attributed to the acidic sensitivity of both groups.

Preparation of an isocyanate derivative by means of Mitsunobu reaction.

Following Mitsunobu reaction, treatment of the alcohol [7] with potassium cyanate, triphenyl phosphine and diethyl azodicarboxylate in acidic medium, the isocyanate [10] was isolated in 58% yield after purification by silica gel column chromatography. The structure was confirmed by Infra red spectroscopy which showed a sharp peak at 2251 corresponds to (N=C=O).

Conclusion

In the present work, the synthesis of β-lactams with an amino group at C-3 was achieved following Mitsunobu reactions. The efficacy of these new β-lactam compounds as antibacterial compounds should be evaluated against bacteria who have developed antibiotic-resistance. Therefore, further biological studies are required.

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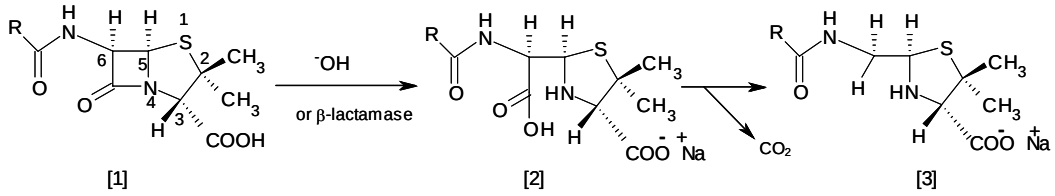
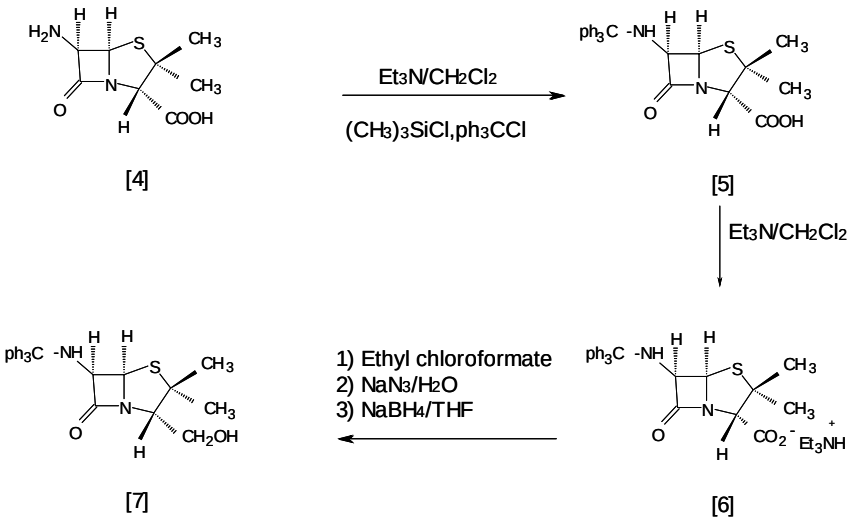
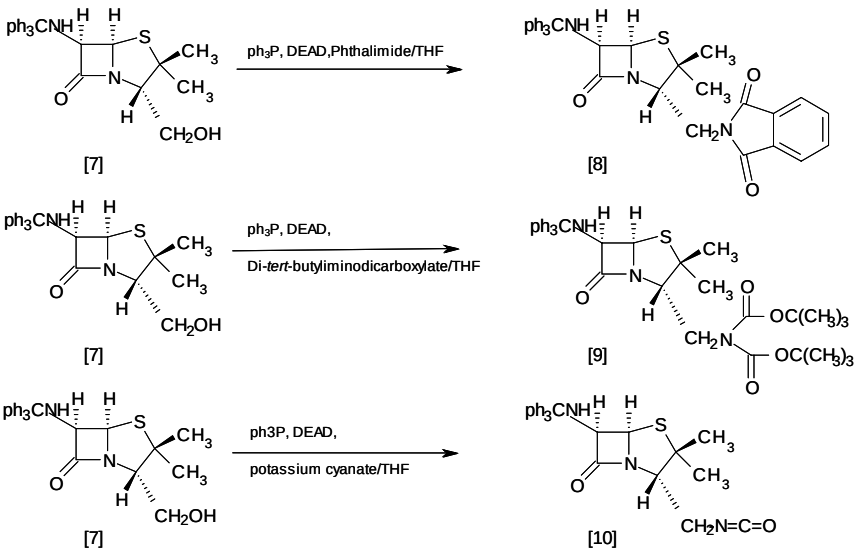
Scheme (1): Hydrolysis of β-lactam carbonyl group to form the inactive penicilloic acid.



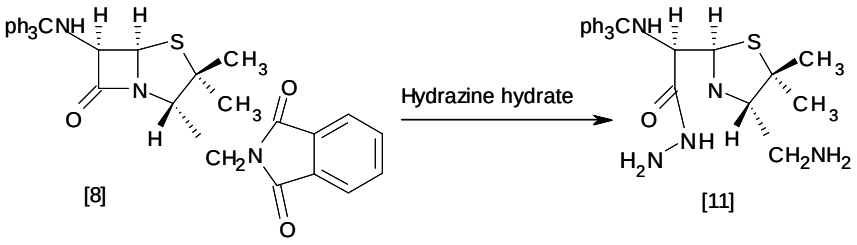
Scheme (2): Synthesis of 6-triphenylmethylaminopenicillanyl alcohol [7].



Scheme (3). Reaction of 6-triphenylmethylaminopenicillanyl alcohol [7] with different nucleophiles for Mitsunobu reaction.

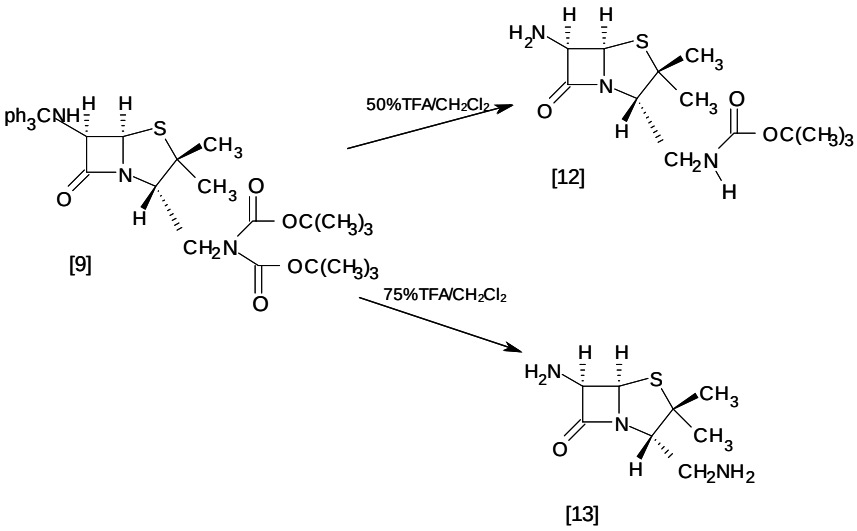


Scheme (4). Reaction of 3-Phthalimidomethyl-6-triphenylmethylaminopenicillanate [8] with Hydrazine Hydrate.



[8] [11]

Scheme (5): Reaction of 3-di-*tert*-Butoxycarbonylaminomethyl-6-triphenylmethylaminopenicillanate [9] with trifluroacetic acid.



[9] [12] [13]