American Journal of Current Organic Chemistry

http://www.ivyunion.org/index.php/ajcoc

Research Article

Synthesis and Characterization of Novel Oxoazetidine Containing Phenyl Imidazole Carbamates

V. Esther Rani*

Department of Chemistry, Sri Krishnadevaraya University, India

Abstract

The pharmacological important of nitrogen containing heterocyclic of novel Oxoazetidine containing Phenyl Imidazole Carbamates 8(a-d) which are synthesize from reaction between aldehyde, aniline and monochloro acetyl chloride via Schiff base intermediate which on under goes with reaction of acid, azide and alcohols. The Oxoazetidines were established by IR, ^{1}H NMR, ^{13}CNMR and mass spectral analysis.

Keywords: Imidazole; Oxoazetidine and Schiff base

Academic Editor: Taihong Shi, PhD, PhD, Sun Yat-sen University, China

Received: December 31, 2015; **Accepted**: March 18, 2016; **Published**: June 15, 2016

Competing Interests: The authors have declared that no competing interests exist.

***Correspondence to**: V. Esther Rani, Department of Chemistry, Sri Krishnadevaraya University, India

Email: vesther9@gmail.com

Introduction

Oxoazetidine is of great pharmacological importance of nitrogen containing heterocycles. β-lactam derivatives of oxoazetidine as antibacterial agents. Since the discovery in 1945 that the structure of penicillin contains a β-lactam function, a vast amount of effort has been devoted to producing other β-lactam antibiotics [1]. The synthesis of these compounds most commercial β-lactam antibiotics are made by the synthetic method.

Oxoazetidine containing Phenyl Imidazole Carbamates of oxoazetidine skeleton is well established as the pharmacophore of β-lactam antibiotics. The antibiotics are the most widely employed nitrogen containing heterocycle class of antibiotics [2]. The important of biologically active oxoazetidine antibiotics to development of many novel methods for the construction of appropriately substituted oxoazetidines. Oxoazetidine derivatives are reported to show wide variety of antitubercular [3], anticonvulsant [4], antimicrobial [5-7], anti-inflammatory [8] and cardiovascular activities [9].

Experimental

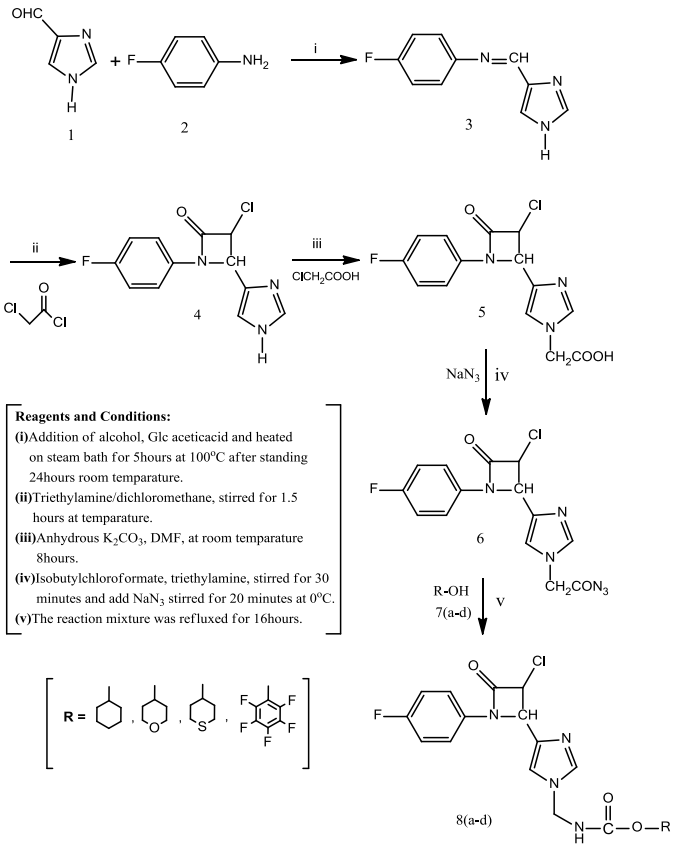
1. Materials and methods

All the chemicals used in the present investigation were purchased from Sigma-Aldrich chemical company, Inc.USA. And used without further purification.

2. Instruments

Thin Layer Chromatography was performed on aluminum sheet of silica gel 60F254, E-Merk, Germany using iodine as visualizing agent. Melting points were determined in open capillary tubes on Mel-Temp apparatus and are uncorrected. IR spectra were measured using Nexus, 470-670-760 spectrophotometer FT IR, spectrometer spectrum 8400 s, using KBr pellets for solid compounds and neat liquid compounds between KBr plates. NMR spectra were measured at 24^{o}C on a Jeol 400 MHz spectrometer using deuterium locking $^{13}C(^{1}H)$-NMR observation frequency 75 MHz, ^{1}H-NMR,observation frequencies, 400 MHz.

3. Experimental Procedures



Scheme 1: Synthesis of Oxoazetidine containing Phenyl Imidazole Carbamates 8(a-d)

3.1 General method for Preparation of Schiff Bases (3)

The reaction mixture of 1H-imidazole-4-carbaldehyde **(1)** (1.00 mmol) and 4-fluoroaniline **(2)** (1.00 mmol) were refluxed in ethanol (15 ml) for 1-4 hours. After cooling, the products of Schiff base **(3)** were dissolved by adding water and the crude product **(3)** was precipitated after the reaction mixture was neutralized with potassium carbonate. The precipitate was filtered, washed with water and recrystallised from aqueous alcohol and dried under vacuum over night. The Schiff base of **3** 71% yield, mp 172°C.

3.2 General method for Synthesis of 3-chloro-1-(4-fluorophenyl)-4-(1H-imidazol-4-yl) azetidin-2-one (4)

The mixture of corresponding N-((1H-imidazol-4-yl) methylene)-4-fluoroaniline **3** (2.5mol) with appropriate monochloroacetyl chloride (2 mol) in presence of Et_3N (1.5 mol) in dichloromethane (20 ml) at room temperature. The reaction mixture was boiled under reflux with stirring for 1.5 hours and left at room temperature. At the end of the reaction was neutralized with excess of sodiumbicarbonate. The collected product of **4** was washed with water, dried in vacuum, purified by thin layer chromatography using cyclohexane and ethyl acetate (9:1) solvent mixture as a

mobile phase. Pour the content on crushed ice. The dried product was 3-chloro-1-(4-fluorophenyl)-4-(1H-imidazol-4-yl) azetidine-2-one **4** recrystallized with absolute alcohol 66% yield, mp 151^{o}C.

3.3 General method for Synthesis of 2-(4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidine-2-yl)-1H-imidazol-1-yl) acetic acid (5)

A mixture of 3-chloro-1-(4-fluorophenyl)-4-(1H-imidazol-4-yl) azetidine-2-one **4** (2mol), anhydrous K_2CO_3 (1.5mol), chloroacetic acid (2 mol) and dimethyl formamide (DMF) (2 mmol) was stirred at room temperature for 8 hours. The progress of the reaction was monitored by thin layer chromatography using cyclohexane and ethylacetate (9:1) solvent mixture as an elutent. The reaction mixture was diluted with ice cold water. The separated solid was identified as **5**. This was collected by filtration and recrystallized from ethanol, m p 164^{o}C, yield 72%.

3.4 General method for Synthesis of 2-(4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidine-2-yl)-1H-imidazol-1-yl) acetyl azide (6)

To a solution of acetic acid **5** (2mol), in isobutyl chloroformate was added triethyl amine (3mol) and stirred for 30 minutes. To the reaction mixture aqueous NaN_3 (1mol) was added and stirred for 20 minutes at 0^{0}C. After completion, reaction mixture was poured in ice cold water (20ml), extracted with diethyl ether (10 ml). The organic layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give crude product. The crude product was purified by column chromatography (60-120 mesh silica gel, eluent: 10 % EtoAc-pet ether), to give pure acid azide **6**. This was collected by filtration and recrystallized from ethanol, m p 112^{o}C, yield 70%.

3.5 General method for Synthesis of Cyclohexyl / tetrahydro-2H-pyran-4-yl / tetrahydro-2H-thiopyran / perfluorophenyl ((4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidin-2-yl)-1H-imidazol-1-yl) methyl) Carbamate 8(a-d)

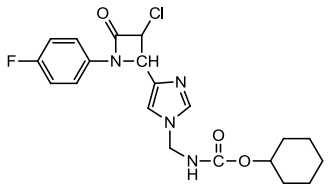
To the solution if acid azide **(6)** (1ml), in Cyclohexanol **(7a)** (10ml) was added and reaction mixture was refluxed for 16 hours. After completion of the reaction, solvent was evaporated under vacuum to give crude residue, which was purified by column chromatography (60-120 mesh silica gel). The reaction was monitored with TLC using cyclohexane and ethylacetate (9:1) as an eluent. Finally the product compound Cyclohexyl ((4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidin-2-yl)-1H-imidazol-1-yl) methyl) Carbamate **(8a)** was purified from aqueous dimethyl formamide. Yield 68%, m p 140-142^{o}C.

The similar experimental procedure was adopted to synthesize **8(b-d)** from acid azide **(6)** and Tetrahydro-2H-pyran-4-ol **(7b),** Tetrahydro-2H-thiopyran-4-ol **(7c)** and 2,3,4,5,6-pentafluorophenol **(7d)**.

4. Spectral data

The structure of these newly synthesized compounds of **8a/b/c and d** were established by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data and microanalytical data.

4.1 Cyclohexyl ((4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidin-2-yl)-1H-imidazol-1-yl) methyl) Carbamate (8a)

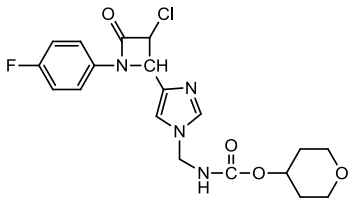


The product was synthesized according to general procedure **3.5** to afford the target compound as a yellow white solid 0.61g (68%), m p 140-142^{o}C. MF: $C_{20}H_{22}ClFN_4O_3$, MW: 420.14, MS: 420.14 for Anal.Found (Cald) C 57.08(56.38); H 5.27(4.77); N 13.31(12.61).
IR (KBr 4000-400 cm^{-1}): 3065 (stretching of Ar-H), 2982 (CH), 1690 (C=O), 1548 (C-N), 1140 (C-O) and 720 cm^{-1}(C-Cl).

^{1}H-NMR (400 MHz, DMSO-d6): δ_{PPM} 1.43-1.80 (m, 10H of Cyclohexyl), 3.91 (m, 1H of Cyclohexyl), 5.16 (d, 1H of azetidine J=7.5), 5.40 (d, 2H of CH_2 J=7.0), 5.44 (d, 1H of azetidine), 6.88 (s, 1H of imidazole), 7.25-7.29 (m, 4H of C_6H_4F J=8.0), 7.83 (s, 1H of imidazole) and 8.03 (s, 1H of NH).

^{13}C-NMR (75 MHz, DMSO-d6): δ_{PPM} 137.18, 118.8, 125.3, 65.1, 61.7, 162.2, 135.1, 123.2, 115.7, 162.9, 115.7, 123.24, 64.3, 156.2, 76.8, 30.8, 24.1, 25.7, 24.1 and 30.8 corresponding to C_1 to C_{20} respectively.

4.2 Tetrahydro-2H-pyran-4-yl ((4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidin-2-yl)-1H-imidazol-1-yl) methyl) Carbamate (8b)

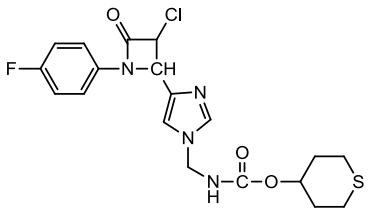


The product was synthesized according to general procedure **3.5** to afford the target compound as a white solid 0.56g (66%), m p 150-152^{o}C. MF: $C_{19}H_{20}ClFN_4O_4$, MW: 422.84, MS: 422.12 for Anal.Found (Cald) C 53.97(53.27); H 4.77(4.07); N 13.25(12.55).
IR (KBr 4000-400 cm^{-1}): 3060 (stretching of Ar-H), 2980 (CH), 1690 (C=O), 1545 (C-N), 1138 (C-O) and 720 cm^{-1}(C-Cl).

^{1}H-NMR (400 MHz, DMSO-d6): δ_{PPM} 1.72-1.97 (m, 4H, $(CH_2)_2$ of pyran), 3.55-3.65 (t, 4H, $(CH_2)_2$ of pyran J=8.5), 4.07 (m, 1H of pyran), 5.16 (d, 1H of azetidine J=7.5), 5.40 (d, 2H of CH_2 J=7.0), 5.44 (d, 1H of azetidine), 6.88 (s, 1H of imidazole), 7.25-7.29 (m, 4H of C_6H_4F J=8.0), 7.83 (s, 1H of imidazole) and 8.03 (s, 1H of NH).

^{13}C-NMR (75 MHz, DMSO-d6): δ_{PPM} 137.18, 118.8, 125.3, 65.1, 61.7, 162.2, 135.1, 123.2, 115.7, 162.9, 115.7, 123.24, 64.3, 156.2, 72.5, 33.4, 63.2, 63.2 and 33.4 corresponding to C_1 to C_{19} respectively.

4.3 Tetrahydro-2H-thiopyran-4-yl ((4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidin-2-yl)-1H-imidazol-1-yl) methyl) Carbamate (8c)

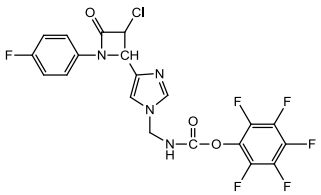


The product was synthesized according to general procedure **3.5** to afford the target compound as a yellow solid 0.65g (65%), m p 161-163^{o}C. MF: $C_{19}H_{20}ClFN_4O_3S$, MW: 438.90, MS: 430.09 for Anal.Found (Cald) C 51.99(51.29); H 4.59(4.09); N 12.77(12.07).
IR (KBr 4000-400 cm^{-1}): 3056 (stretching of Ar-H), 2899 (CH), 1690 (C=O), 1542 (C-N), 1130 (C-O) and 720 cm^{-1}(C-Cl).

^{1}H-NMR (400 MHz, DMSO-d6): δ_{PPM} 1.81-2.06 (m, 4H, $(CH_2)_2$ of thiopyran), 2.47-2.57 (t, 4H, $(CH_2)_2$ of thiopyran J=8.5), 4.17 (m, 1H of thiopyran), 5.16 (d, 1H of azetidine J=7.5), 5.40 (d, 2H of CH_2 J=7.0), 5.44 (d, 1H of azetidine), 6.88 (s, 1H of imidazole), 7.25-7.29 (m, 4H of C_6H_4F J=8.0), 7.83 (s, 1H of imidazole) and 8.03 (s, 1H of NH).

^{13}C-NMR (75 MHz, DMSO-d6): δ_{PPM} 137.18, 118.8, 125.3, 65.1, 61.7, 162.2, 135.1, 123.2, 115.7, 162.9, 115.7, 123.24, 64.3, 156.2, 69.6, 32.2, 25.5, 25.5 and 32.2 corresponding to C_1 to C_{19} respectively.

4.4 Perfluorophenyl ((4-(3-chloro-1-(4-fluorophenyl)-4-oxoazetidin-2-yl)-1H-imidazol-1-yl) methyl) Carbamate (8d)



The product was synthesized according to general procedure **3.5** to afford the target compound as a brownish oily layer 0.64g (68%), m p 169-1721C. MF: $C_{20}H_{11}ClF_6N_4O_3$, MW: 504.77, MS: 504.04 for Anal.Found (Cald) C 47.59(46.89); H 2.20(1.70); N 11.10(10.40).
IR (KBr 4000-400 cm^{-1}): 3054 (stretching of Ar-H), 2992 (CH), 1690 (C=O), 1542 (C-N), 1139 (C-O) and 720 cm^{-1}(C-Cl).

^{1}H-NMR (400 MHz, DMSO-d6): δ_{PPM} 5.16 (d, 1H of azetidine J=7.5), 5.40 (d, 2H of CH_2 J=7.0), 5.44 (d, 1H of azetidine), 6.88 (s, 1H of imidazole), 7.25-7.29 (m, 4H of C_6H_4F J=8.0), 7.83 (s, 1H of imidazole) and 8.03 (s, 1H of NH).

^{13}C-NMR (75 MHz, DMSO-d6): δ_{PPM} 137.18, 118.8, 125.3, 65.1, 61.7, 162.2, 135.1, 123.2, 115.7, 162.9, 115.7, 123.24, 64.3, 156.2, 142.0, 139.3, 142.4, 140.1, 142.4 and 139.3 corresponding to C_1 to C_{20} respectively.

5. Conclusion

In conclusion, we have demonstrated the synthesis of a series of novel Oxoazetidine containing Phenyl Imidazole Carbamates of **(8a-d)** involving Schiff base intermediate by condensation of aldehyde and 4-fluoroaniline. Some of these compounds may determined by spectral analysis.

Acknowledgements

The author **V.Esther Rani** thanks to U G C – Post Doctoral Fellowship, New Delhi for financial assistance. They are also thankful to IICT Hyderabad and CDRI Lucknow for spectral and analytical data.

References

1. Koppel GA. In small ring Heterocycles, part 2, ed, A. Hassner, Wiley-Interscience, ***Newyork***, 1983, p.219
2. Delpiccolo CML, Fraga MA, Mata EG. An Efficient, Stereoselective Solid-Phase Synthesis of _β-lactams Using Mukaiyama's Salt for the Staudinger Reaction. ***J Comb Chem***. 2003, 5:208-210
3. Patel RB, Desai PS, Desai KR, Chikhalia KH. Synthesis of pyrimidine based thiazolidinones and azetidinones: antimicrobial and antitubercular agents. *Indian J Chem.* 2006, 45B:773-778
4. Siddiqui N, Rana A, Khan SA, Haque SE, Alam MS, Ahsan W, Arshada MF. Anticonvulsant and Toxicity Evaluation of Newly Synthesized 1-2-(3,4-disubstitutedphenyl)-3-chloro-4-oxoazetidin-1-yl-3-(6-substituted-1,3-benzothiazol-2-yl)ureas. ***Acta Chim. Slov***. 2009, 56:462-469

5. Srivastava SK, Dua R, Srivastava SD. Synthesis and antimicrobial activity of [N1-(N-substitutedarylidene- hydrazino)-acetyl]-2-methyl-imidazoles and [N1-(4-substituted aryl-3-chloro-2-oxo-1- azetidinyl-amino)-acetyl]-2-methyl-imidazoles. ***Proc Nat Acad Sci India, Sec. A: Phys. Sci***. 2010, 80:117-121
6. Trivedi PB, Undavia NK, Dave AM, Bhatt KN, Desai NC. Synthesis and antimicrobial activity of 4-oxothiazolidines, 4-oxoazetidines, malonanilic acid hydrazines and pyrazoline derivatives of phenothiazine. ***Indian J Chem***. 1993, *32B* (7):760-765
7. Panwar H, Verma RS, Srivastava VK, Kumar A. Synthesis of some substituted Azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospective antimicrobial agents. ***Indian J Chem***. 2006, *45B*:2099-2104
8. Srivastava, S.K.; Srivastava, S.L.; Srivastava, S.D. Synthesis of new 2-chloro phenothiadiazol-2-oxoazetidines antimicrobial and anti-inflammatory agents. ***Indian J Chem***. 2000, 39B:464-467
9. Kumar A, Gurtu S, Agarwal JC, Sinha JN, Bhargava KP, Shanker K. Synthesis and cardiovascular activity of substituted 4-azetidinones. ***J Indian Chem Soc***. 1983, 60(6):608-610