Synthesis and Biological Activity of 3-Chloro-1-(4-perimidine methylcarbonyl amino)-4-phenyl-azetidin-2-one

DINESH R. PANCHASARA and SUBHASH PANDE*

Department of Chemistry,
Govt. Geetanjali P.G. Girls College, Bhopal, India.
dinesh_patel81@yahoo.com

Received 17 February 2009; Accepted 15 April 2009

Abstract: Perimidine-1-acetic acid hydrazide (**1**) undergoes facile condensation with aromatic aldehydes to afford the corresponding azomethine (*i.e.* Schiff base) derivatives (**2a-h**) in good yield. Cyclocondensation of compounds (**2a-h**) with chloro acetyl chloride affords 3-chloro-1-(4-perimidine methylcarbonylamino)-4-phenyl-azetidin-2-ones (**3a-h**). The structures of these compounds were established on the basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: Perimidine-1-acetic acid hydrazide, Azetidinone, Antibacterial activity.

Introduction

Perimidine derivatives are of wide interest because of their diverse biological activities and chemical application. Several classical synthetic methods have been reported for synthesis of perimidine derivatives. The most widely used method for preparation of perimidine is the cyclocondensation reaction of 1, 8-diaminonaphthalene with carboxylic acids under reflux condition microwave irradiation¹⁻¹⁴. These heterocyclic systems find wide use in medicine, agriculture and industry. A large number of azetidinones containing β -lactam rings¹⁷⁻²⁰ are known to exhibit various biological activities like antibacterial, antifungal²¹ and antibiotic²² activities. More particularly and recently these types of compounds have been found in the treatment of T.B. and other chemotherapeutic diseases. Hence, it was thought of interest in merging of both azetidinone and perimidine-1-acetic acid hydrazide moieties may enhance the drug activity of compounds up to some extent or might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of perimidine-1-acetic acid hydrazide containing an azetidinone moiety. Hence the present communication comprises the synthesis of 3-chloro-1-(4-perimidine methylcarbonylamino)-4-phenyl-azetidin-2-one. The research work is scanned in Scheme 1.

Scheme 1

Where, R = (a) C_6H_5 , (b) $4\text{-OH-C}_6\text{H}_4$, (c) $2\text{-OH-C}_6\text{H}_4$, (d) $4\text{-OCH}_3\text{-C}_6\text{H}_4$,
 (e) $4\text{-OH-3-OCH}_3\text{-C}_6\text{H}_3$, (f) $4\text{-Cl-C}_6\text{H}_4$, (g) $2\text{-NO}_2\text{-C}_6\text{H}_4$, (h) $5\text{-Br-2-OH-C}_6\text{H}_3$

Experimental

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^1H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Materials

2-Methyl perimidine (**1**) was prepared by reported method¹⁵ and other materials were used as AR grade.

Preparation of perimidine-1-acetic acid hydrazide

Equimolar solution of 2-methyl perimidine (0.1 mole) in the dry acetone (60 mL) and ethyl chloroacetate (0.1 mole) in the presence of anhydrous K_2CO_3 (5 g) was refluxed for 8 h, cooled and the solid thus obtained was filtered, dried and crystallized from ethanol to furnish **1**, yield is about 70%. m.p. 150°C . and this compound (0.05 mole) and hydrazine hydrate (0.05 mole) in 1,4-dioxane (35 mL) was refluxed on heating coil for 5 h. the excess of solvent was removed and the product crystallized from methanol to give **1**, yield is about 80%, m.p. 122°C ¹⁶.

Preparation of azomethyl derivatives (2a-h)

An equimolecular mixture of perimidine-1-acetic acid hydrazide (0.01 mole) and the aromatic aldehyde (**a-h**) in ethanol (15 mL) and conc. H_2SO_4 (0.4 mL) was refluxed on a water bath for 1-2 h. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table 1.

Preparation of 3-chloro-1-(4-perimidine methylcarbonylamino)-4-phenyl-azetidin-2-one (3a-h)

A mixture of perimidine-1-acetic acid hydrazide (**2a-h**) (0.001 mole) and triethylamine (TEA) (0.003 mole) was dissolved in 1,4-dioxane (25 mL) cooled and stirred. To this well stirred cooled

solution chloroacetyl chloride (0.0012 mole) was added drop wise. The reaction mixture was stirred for 14 h at room temperature. Excess of solvent was removed by distillation. The residue was poured over crushed ice and then air dried. The product thus obtained was purified by column chromatography over silica gel using 30% ethyl acetate: 70% benzene as eluent. Recrystallization from ether/n-hexane gave white powdered 3-chloro-1-(4-perimidine methylcarbonylamino)-4-phenyl-azetidin-2-one (**3a-h**) which was obtained in 45-67% yield. All the compounds were characterized by analytical and spectral data (Table 2) of the compounds is assigned in Scheme 1.

Results and Discussion

It was observed that Perimidine-1-acetic acid hydrazide (**1**) on condensation with aromatic aldehydes to yield azomethyl derivatives (**2a-h**). The structures of (**2a-h**) were confirmed by elemental analysis and IR spectra showing absorption band at 1620-1640(C=N). The C,H,N analysis and ¹H NMR data of all compounds are presented in Table 1.

The cyclocondensation of (**2a-h**) with chloroacetyl chloride resulted in formation of 2-azetidinones (**3a-h**). The structures assigned to (**3a-h**) were supported by the elemental analysis and IR spectra showing absorption bands at 1620-1640(C=N of- perimidine) and 1740-1750(C=O of monocyclic β-lactam). The C, H, N analysis and ¹H-NMR data of all compounds are presented in Table 2.

The examination of data reveals that the elemental contents are consistence with the predicted structure shown in scheme1. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS data of selected samples. The LC-MS of samples **3c** and **3f** give the molecular ion peak (*m/z*) at 440 and 457 respectively. These values are corresponds to their molecular weight.

Biological screening

Antibacterial activities

Antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus subtilis* and *staphylococcus aureus*) and gram-negative bacteria (*E coli*, *Salmonella typhi* and *Klebsiella promioe*) at a concentration of 50 µg/mL by agar cup plate method. Methanol system was used as control in this method. Under similar condition using tetracycline as a standard for comparison carried out control experiment. The area of inhibition of zone measured in cm. Compound **3d**, **3f** and **3g** were found more active against the above microbes. Other compounds found to be less or moderate active than tetracycline (Table 3).

Antifungal activities

The fungicidal activity of all the compounds was studied *in vitro* at 1000 ppm concentration. Plant pathogenic organisms used were *aspergillus*, *Nigrospora sp.*, *Fusarium oxysporium*, *Botrydepladia thiobromine* and *Albicans*. The antifungal activity of all the compounds (**3a-h**) was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 g, dextrose 20 g, agar 20 g and water one liter. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120 °C for 15 min. at 15 atm.pressure. These medium were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\text{Percentage of inhibition} = 100(X-Y) / X$$

Where, X = Area of colony in control plate
Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (**3a-h**) is shown in Table 4.

Table 1. Analytical and spectral data of compounds (**2a-h**).

Compd.	Mol formula, (Mol.wt).	Yield	M.P.* °C	Elemental Analysis						¹ H NMR (δ, ppm)			
				%C		% H		%N		Ar-H	-CH=N	-OH	-OCH ₃
				Found	Calcd.	Found	Calcd.	Found	Calcd.				
2a	C ₂₁ H ₁₈ N ₄ O (342)	90	224	73.63	73.68	5.21	5.26	16.35	16.37	7.5-7.7(m, 5H)	9.5-9.7(t)	-	-
2b	C ₂₁ H ₁₈ N ₄ O ₂ (358)	80	202	70.30	70.39	5.00	5.02	15.60	15.64	7.5-7.8(m, 4H)	9.5-10.2(t)	5.1(s)	-
2c	C ₂₁ H ₁₈ N ₄ O ₂ (358)	85	221	70.30	70.39	5.00	5.02	15.61	15.64	7.5-7.8(m, 4H)	9.5-10.2(t)	5.3(s)	-
2d	C ₂₁ H ₂₀ N ₄ O ₂ (360)	88	198	70.70	70.00	5.51	5.55	15.50	15.56	7.5-7.8(m, 4H)	9.5-9.8(t)	-	3.9(s)
2e	C ₂₂ H ₂₀ N ₄ O ₃ (388)	79	211	68.00	68.04	5.12	5.15	14.40	14.43	7.5-7.7(t, 3H)	9.5-9.7(t)	5.2(s)	3.7(s)
2f	C ₂₁ H ₁₇ N ₄ ClO (376)	80	188	66.89	66.93	4.48	4.51	14.85	14.87	7.5-7.8(m, 4H)	9.5-9.9(t)	-	-
2g	C ₂₁ H ₁₇ N ₅ O ₃ (387)	75	216	65.09	65.12	4.36	4.39	18.05	18.09	7.5-7.8(m, 4H)	9.5-9.85(t)	-	-
2h	C ₂₁ H ₁₇ N ₄ O ₂ Br (436.90)	76	210	57.65	57.68	3.85	3.89	12.80	12.82	7.5-7.8(t, 3H)	9.5-9.75(t)	5.2(s)	-

* Uncorrected

Table 2. Analytical and Spectral Data of Compounds (**3a-h**).

Compd.	Mol formula (Mol.wt).	Yield	M.P. °C	Elemental Analysis						¹ H NMR (δ, ppm)					
				%C		% H		%N		C ₄ -H	C ₃ -H	Ar-H	- CH ₂	- OH	- OCH ₃
				Found	Calcd.	Found	Calcd.	Found	Calcd.						
3a	C ₂₃ H ₁₉ N ₄ O ₂ Cl(418.50)	70	187	65.92	65.95	4.52	4.54	13.36	13.40	2.9(d,1H)	4.3(d,1H)	7.5-7.7(m, 5H)	3.95	-	-
3b	C ₂₃ H ₁₉ N ₄ O ₃ Cl(434.50)	67	183	63.49	63.52	4.35	4.37	12.86	12.89	3.2(d,1H)	4.0(d,1H)	7.5-7.8(m, 4H)	3.95	5.1(s)	-
3c	C ₂₃ H ₁₉ N ₄ O ₃ Cl(434.50)	60	168	63.48	63.52	4.35	4.37	12.86	12.89	3.1(d,1H)	4.1(d,1H)	7.5-7.8(m, 4H)	3.95	5.3(s)	-
3d	C ₂₄ H ₂₁ N ₄ O ₃ Cl(448.50)	59	177	64.18	64.21	4.65	4.68	12.46	12.49	3.2(d,1H)	4.0(d,1H)	7.5-7.7(m, 4H)	3.95	-	3.9(s)
3e	C ₂₄ H ₂₁ N ₄ O ₄ Cl(464.50)	55	191	61.95	62.00	4.48	4.52	12.04	12.06	2.8(d,1H)	4.18(d,1H)	7.5-7.8(t, 3H)	3.95	5.2(s)	3.7(s)
3f	C ₂₃ H ₁₈ N ₄ O ₂ Cl ₂ (453)	52	189	60.90	60.93	3.94	3.97	12.34	12.36	3.1(d,1H)	4.1(d,1H)	7.5-7.8(m, 4H)	3.95	-	-
3g	C ₂₃ H ₁₈ N ₅ O ₄ Cl(463.50)	56	154	59.50	59.55	3.85	3.88	15.07	15.10	3.1(d,1H)	4.1(d,1H)	7.5-7.8(m, 4H)	3.95	-	-
3h	²³ H ₁₈ N ₄ O ₃ BrCl(513.40)	58	186	53.73	53.76	3.48	3.50	10.89	10.91	2.8(d,1H)	3.8(d,1H)	7.5-7.7(t, 3H)	3.95	-	-

Table 3. Antibacterial activity of compounds (**3a-h**).

Compd	Zone of Inhibition				
	Gram +ve		Gram -ve		
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Klebsiella promioe</i>	<i>Salmonella typhi</i>	<i>E.coli</i>
3a	57	53	48	44	67
3b	55	58	62	57	56
3c	60	62	60	54	59
3d	71	75	80	77	82
3e	50	54	42	55	58
3f	83	80	70	78	84
3g	74	82	79	72	70
3h	60	67	69	62	58
Tetracycline	80	57	83	74	72

Table 4. Antifungal activity of compounds (**3a-h**).

Compd	Zone of Inhibition at 1000 ppm, %				
	<i>Aspergillus niger</i>	<i>Nigrospora Sp.</i>	<i>Fusarium oxyporium</i>	<i>Botrydepladia Thiobromine</i>	<i>Albicans</i>
3a	70	59	66	58	51
3b	62	68	65	50	68
3c	73	71	78	72	61
3d	72	67	64	79	69
3e	60	62	66	62	75
3f	50	63	68	71	62
3g	65	74	70	60	66
3h	69	78	69	74	73

Acknowledgement

The authors are thankful to Dr. (Mrs.) Nayantara, principal of the college for providing laboratory facilities.

References

1. Caliendo G, Carlo R, Meli R and Perissutti E, *J Med Chem.*, 1993, **28**, 969.
2. X. Bu, Deady L W, Finaly G J, Baguley B C and Denny W A, *J Med Chem.*, 2001, **44**, 2004.
3. Di-martino J L, Jacquault P, Bazureau J P and Hamelin J, *Bull Soc Chim Fr.* 1996, **133**, 587.
4. Hendrickson J B and Hussoin M S, *J Org Chem.*, 1987, **52**, 4137.
5. Morita N, Dickstein J I and Miller S I, *J Chem Soc., Perkin Trans.*, 1979, **1**, 2103
6. Deady L.W and Rodemann T, *J Heterocycl Chem.*, 1998, **35**, 1417.
7. Caddick S, *Tetrahedron*, 1993, **51**, 1403.
8. Foroughifar N, Mobinikhaledi A and Fathinejad Jirandehi H, *Sulfur and Silicon and the Related Elements*, 2003, **178**, 1241.
9. Langa F, de la Cruz P, de la Hoz A, Diaz-Ortiz A and Diez-Barra E, *Contemporary Org Synth.*, 1997, **4**, 373.
10. Varma R.S, *Green Chem.*, 1999, **1**, 43.

11. Foroughifar N, Mobinikhaledi A, Fathinejad Jirandehi H and Memar S, *Sulfur and Silicon and the Related Elements*, 2003, **178**, 1269.
12. Bose A.K, Banik B.K, Lavlinskaia N, Jayaraman M and Manhas M.S, *Chemtech.*, 1997, **27**, 18.
13. Foroughifar N and Mobinnikhaledi A, *Asian J Chem.*, 2002, **14**, 614.
14. Mobinikhaledi A and Foroughifar N, Phosphorus, *Sulfur and Silicon and the Related Elements*, 2004, **179**, 1175-1180.
15. Mobinikhaledi A, Amrollahi M.A, Foroughifar N and Fathinejad jirandehi H, *Asian J Chem.*, 2005, **17(4)** 2411.
16. Bhatt A.K, Karadiya H.G, Shah P.R and Patel H.D, *Orient J Chem.*, 2003, **19(3)** 704-706.
17. Clarke H. T, Johnson J. R and Robinson R, *The chemistry of penicillin*, Princeton University Press, Princeton, New Jersey, 1949.
18. Patel H S, Mistry H J and Desai H D, *Oriental J Chem.*, 2003, **19(1)**, 187-192.
19. Patel H. S and Patel V. K, *Indian J heterocycl Chem.*, 2003, **12**, 253-256.
20. Desai K R, and Bhanvesh Naik, *Indian J Chem.*, 2006, **45(B)**, 267-271.
21. Mulwad V V and Choudhari B P, *Indian J heterocycl Chem.*, 2003, **12**, 197-200.
22. Akiba K and Wada M, *Chem Abstr.*, 1989, **111**, 96964b.