

Synthetic Reactivity of 2-Benzoyl-1, 2-Diazetidone Towards The Synthesis of Novel Heterocyclic Compounds

Suhas Anirudha Morkhade
Associate Prof.

Abstract:

2-benzoyl-1,2-diazetidone was synthesized by the action of chloroacetic acid with benzohydrazide, which on condensation with benzaldehyde gives 4(E)-2-benzoyl-4-benzylidene-1,2-diazetidone. The compound so formed consists of exocyclic double bond adjacent to carbonyl group possess wide synthetic applicability toward the synthesis of novel heterocyclic compound by the action with carbonyl reagents such as hydrazine hydrate, phenyl hydrazine, hydroxyl amine hydrochloride and thiourea.

Introduction:

β Lactam ring possess biological activity and their activity is regarded to be associated with tail end of amide side chain and head end of antibiotic molecule. Many investigators explored the research on tail end that is amide side chain of β -lactam ring¹. Wolf² et al synthesized aza analogue of cepham. Prompted with this work Bose³ and workers attempted the synthesis of 1-azadethiapenam derivatives from Phenyl imidazoline with azido acetyl chloride in presence of tri ethyl amine, but they were unsuccessful in getting desired product by blocking the participation through amidification of imidazoline derivative.

Thus prompted with earlier work an attempt was made to synthesize diazetidine moiety from simple hydrazide and chloro acetic acid followed by its condensation with substituted Aromatic aldehyde, so obtained 4(E)-1-benzoyl-4-arylidene-1,2-diazetidone consists of exocyclic double bond conjugated with carbonyl group served as good synthon for the synthesis of fused tri and Tetra azabicyclo [3,2,0] hept-1-ene derivatives, 3-oxa-2,6,7-triazabicyclo[3,2,0] hept-1-ene and thiazolo pyrimidine derivatives

Experimental:

All the melting points were determined in open capillary tube and may be uncorrected. The purity of compounds were checked by TLC on silica gel coated glass plate. Infrared spectra were monitored in Nujol/KBr plates and recorded on Bomem 104 FT infrared spectrophotometer. ¹H NMR spectra were recorded on a Germani 200 Mz

spectrophotometer. Elemental analysis was carried on CHNO rapid analyser.

Experiment No. 1

Synthesis of Benzoyl hydrazide.

A mixture of methyl benzoate (0.01M, 13.6g), hydrazine hydrate (0.01 M, 5 g) in ethanol 25 ml was refluxed for one hour. The resulting mixture was concentrated and allowed to cool to get fine needle shaped colourless, crystalline solid. It was crystallised from dilute alcohol to get benzoyl hydrazide in 90% yield.

PROPERTIES AND CONSTITUTION OF COMPOUND (1) m. p. 115 - 116°C.

1. TLC studies indicate R_f value 0.75 in ethanol as solvent.
2. The compound is colourless crystalline solid m. p. 115 - 116°C.
3. Analytical results indicated molecular formula of the compound to be C₇H₈N₂O.
4. IR: [IR plate No. 1] 3299 - 3223 cm⁻¹ NH₂ str.; 3020.7 cm⁻¹ Ar-CH str.; 2278.9 cm⁻¹ N-C=O str.; 1660.6-1618.9 cm⁻¹ C=O str.
5. PMR: [PMR plate No. 1] δ 9.02, s, 1H, NH; δ 7.35 - 7.45, m, 5H, Ar-H; δ 4.18, s, 2H, NH₂.

On the basis of analytical and spectral data compound (1) was assigned the structure as benzoyl hydrazide.

Analysis:

Found; C, 62.01; H, 5.67; N, 19.99.

Calculated for, C₇H₈N₂O; C, 61.76; H, 5.88; N, 20.58.

This section deals with the synthesis of 1-benzoyl-1, 2-diazetidone (2).

Different workers have synthesized¹⁻³ 2-azetidones by the action of chloroacetyl chloride

on exocyclic C=C conjugated with >C=O group in different molecules in presence of triethyl amine using different solvents such as 1:4 dioxane, ethanol etc.

Sharma³⁷ et al attempted the synthesis of 2-azetidiones by the reaction between imines with lithium enolate of ethyl isobutyrate.

Bhawal³⁸ et al have reported the synthesis azetidin-2- ones by the cycloaddition reaction of acids and imines in presence of tri ethyl phosphite hexachloro acetone & tri ethylamine.

Desai³⁹ et al have reported the synthesis of 2-oxo azetidin due to their close association with various types of biological activities such as hypnotic, anaesthetic, analgesic, sedative, antifungal, anticonvulsant, etc. by the action of chloro acetyl chloride in triethyl amine using 1:4 dioxane as a solvent on 2-[2,2¹-aza-2-(4- nitro phenyl carbonyl amino) vinyl] phenoxy acetate.

Synthesis of 2-benzoyl-1, 2-diazetid-3-one was reported in this section, which involves reaction of benzoyl hydrazide with chloroacetic acid in absolute alcohol as a solvent and a drop or two of piperidine as a condensing agent.

Experiment No. 2

Synthesis of 2-benzoyl-1, 2-diazetid-3-one (2).

A mixture of benzoyl hydrazide (1) (0.1 M, 13.6 g), chloroacetic acid (0.1 M, 9.4 g) in dry alcohol and a drop or two of piperidine was refluxed for 2 hr. Then the resulting mixture was concentrated to half and allowed to cool in ice bath. The white coloured crystals of 2-benzoyl- 1, 2-diazetid-3-one, which separated were filtered and recrystallised from aqueous ethanol to get the product (2) in 60% yield.

PROPERTIES AND CONSTITUTION OF COMPOUND (2) m. p. 157 - 158°C.

1. TLC studies indicated R_f value 0.71 by using acetone as eluant.
2. The compound is white coloured crystalline solid m. p. 157 - 158°C.
3. Analytical results indicated the molecular formula of the compound to be C₉H₈N₂O₂.
4. IR: [IR Plate No. 2] 3251 cm⁻¹ OH str. due to intramolecular hydrogen bonding; 2368 cm⁻¹ NC=O str.; 1685 - 1641 cm⁻¹ >C=O str
5. PMR: [PMR Plate No. 2] δ 10.19, s, 1H, NH proton; δ 7.93 - 7.43, m, 5H, Ar-H; δ 4.23 - 4.04 s, 1H, CH; δ 2.82, s, 1H, azetidine ring proton.

On the basis of analytical and spectral data compound (2) was assigned the structure as 2-benzoyl-1, 2-diazetid-3-one.

Analysis:

Found; C, 60.98; H, 5.01; N, 16.07.

Calculated for, C₉H₈N₂O₂; C, 61.36; H, 4.54; N, 15.

This section is devoted for the synthesis of benzylidene derivative of 2 - benzoyl- 1, 2 - diazetidin -3 - one which involved condensation of 2 - benzoyl - 1,2-diazetid - 3-one with substituted aromatic aldehyde in presence of fused sodium acetate, acetic acid by heating under reflux for 3-4 hrs. The aldehydes used is anisaldehyde Synthon 4(E)-2-benzoyl - 4 - (4¹ methoxy benzylidene)- 1,2 - diazetidin- 3 - one possess wide applicability due to presence of additive property of exocyclic C=C conjugated with carbonyl group towards the synthesis of novel heterocyclic compounds

Experiment No. 3

Synthesis of 4 (E)-2-benzoyl - 4 - (4¹-methoxy benzylidene)-1, 2- diazetidin-3-one (3).

A mixture of 2-benzoyl-1, 2-diazetid-3-one (2) (0.1M, 7.6g) anisaldehyde (0.1M, 13.6g), fused sodium acetate (0.1M. 8.2g) in acetic acid (50 ml) and a catalytic amount of acetic anhydride (2ml) was refluxed for 4 hr. The resulting mixture was cooled and poured over crushed ice. The semisolid thus obtained, was triturated with cold alcohol to get (3) in 70% yield. The product was crystallised from aqueous alcohol.

PROPERTIES AND CONSTITUTION OF COMPOUND (21a) m. p. 220 - 221°C.

1. TLC studies indicated RF value 0.69 in ethanol as eluant.
2. It is a pale yellow coloured crystalline solid m. p. 220 - 221°C.
3. Elemental analysis and molecular weight determination shows that molecular formula of compound is C₁₇H₁₄N₂O₃.
4. IR: [IR Plate No. 3] 3195 cm⁻¹ OH str.; 3001 cm⁻¹, Ar-H; 2361.5 cm⁻¹ N-C=O str.; 1636 cm⁻¹ >C=O str.; 1539 cm⁻¹ C=C str.
5. PMR: [PMR Plate No. 3] δ 10.37, s, 1H, NH; δ 8.45 - 7.40, m, 10H Ar-H & 1H, Ar-CH; δ 3.24, s, 3H, OCH₃ proton.

On the basis of analytical and spectral data compound (3) was assigned the structure as 4(E)-2-benzoyl-4-(4¹-methoxy benzylidene) -1, 2-diazetid-3-one.

Analysis:

Found: C, 70.12; H, 4.92; N, 9.31.

Calculated for, C₁₇H₁₄N₂O₃; C, 69.38; H, 4.76; N, 9.52.

The synthon reported is. 4(E)-2-benzoyl-4-(4^l-methoxy benzylidene)-1, 2-diazetid-3-one possessed wide applicability due to the presence of additive property of exocyclic double bond conjugated with carbonyl group which prompted us to investigate their behaviour towards the action of hydrazine hydrate, phenyl hydrazine, hydroxyl amine hydrochloride and thiourea

Experiment No. 4

Synthesis of 3-acetyl-7-benzoyl-4-(4^l-methoxy phenyl)-2, 3, 6, 7- tetraazabicyclo [3.2.0]-1-ene (4).

A mixture of 4(E)-2-benzoyl-4-(4^l-methoxy benzylidene)-1, 2 -diazetid-3-one (3) (0.01 M, 2.94 g), hydrazine hydrate (0.02 M, 1 g) in acetic acid (10 ml) and alcohol (10 ml) was heated under reflux for 3 hr. The resulting mixture was concentrated cooled and poured over crushed ice to get (4) in 72% yield. The product was filtered, dried and crystallised from alcohol.

DETAILED EXAMINATION OF COMPOUND (4)

1. Compound (4) is colourless crystalline solid m. p. 218-220^c.
2. TLC studies indicated R_f = 0.78 in acetone as eluant.
3. Analytical result indicated molecular formula of the compound to be C₁₉H₁₈N₄O₃
4. Spectral data is as follows:
IR: [IR Plate No. 4] 3200 cm⁻¹ OH str.; 3002 cm⁻¹ aromatic; 2364.3 cm⁻¹ N-C=O str.; 1634 cm⁻¹ > C=O str.
PMR: [PMR Plate No. 4] δ 10.33, s, 1H, NH; δ 7.99 - 7.42, m, 11H, 9Ar-H & 2H for CH ring proton; δ 3.16, s, 3H, OCH₃; δ 2.58, s, 3H, CH₃ proton.

On the basis of all these properties compound (4) was assigned the structure as 3-acetyl-7-benzoyl-4-(4^l-methoxy phenyl)-2, 3, 6, 7-tetraazabicyclo [3.2.0]-1-ene.

Analysis:

Found; C, 64.92; H, 5.19; N, 16.12.

Calculated for, C₁₈H₁₆N₄O₂: C, 65.14; H, 5.14; N, 16.

Experiment No. 5

Synthesis of 7-benzoyl-3-phenyl-4-(4^l-methoxy phenyl)-2, 3, 6, 7- tetraazabicyclo [3.2.0] hept-1-ene (5).

A mixture of (4E)-2-benzoyl-4-(4^l-methoxy benzylidene)-1, 2 -diazetid-3-one (3) (0.01 M, 2.94 g), phenyl hydrazine (0.02 M, 2.16g alcohol (20 ml) was heated under reflux for 4 hr. The resulting mixture was cooled and poured over crushed ice to get (5) in 80% yield. The product was crystallised from aqueous alcohol.

DETAILED EXAMINATION OF COMPOUND (5)

1. Compound (5) is yellow coloured crystalline solid m. p. 205-206^c.
2. TLC studies indicated R_f = 0.87 in benzene as eluant.
3. Analytical result indicated molecular formula of the compound to be C₂₃H₂₀N₄O₂.
4. Spectral data is as follows:
IR: [IR Plate No. 5] 3205 cm⁻¹ OH str. 3008 cm⁻¹ aromatic; 2368.2 cm⁻¹ N-C=O str.; 1632 cm⁻¹ > C=O str.; 535 cm⁻¹: C=C str.
PMR: [PMR Plate No. 5] δ 10.48, s, 1H, NH; δ 7.98 - 7.34 m, 16H, 14Ar-H & 2H for CH ring proton; δ 3.40, s, 3H, OCH₃.

On the basis of all these properties compound (5) was assigned the structure as 7-benzoyl-3-phenyl-4-(4^l methoxy phenyl)-2,3,6,7-tetraazabicyclo [3.2.0] hept-1-ene.

Analysis:

Found; C, 72.01; H, 5.12; N, 14.56.

Calculated for, C₂₃H₂₀N₄O₂: C, 71.87; H, 5.20; N, 14.58.

Experiment No. 6

Synthesis of 7- benzoyl – 4- (4^l- methoxy phenyl) - 3-oxa-2, 6, 7- triazabicyclo [3.2.0] hept-1-ene (6).

A mixture of (4E)-2-benzoyl-4-(4^l-methoxy benzylidene)-1, 2-diazetid-3-one (3) (0.01 M, 2.94 g), aqueous solution of hydroxyl amine hydrochloride (0.02 M, 1.4 g) potassium hydroxide (0.02 M, 1.10 g) in (20 ml) alcohol was heated under reflux for 4 hr. The resulting mixture was concentrated, cooled acidified with acetic acid and poured over crushed ice to get (6) in 74% yield. The product was crystallised from aqueous alcohol.

DETAILED EXAMINATION OF COMPOUND (6)

1. Compound (6) is colourless crystalline solid m. p. 235-236^c.
2. TLC studies indicated R_f= 0.87 in dioxane as eluant.

3. Elemental analysis indicated molecular formula of the compound to be $C_{17}H_{15}N_3O_3$.

4. Spectral data is as follows:

IR: [IR Plate No. 6] 3202 cm^{-1} OH str.; 3004 cm^{-1} aromatic; 1633 cm^{-1} $>C=O$ str.; 1535 cm^{-1} $C=C$ str.

PMR: [PMR Plate No. 6] δ 10.45, s, 1H, NH; δ 8.05 - 7.43, m, 10H, 9Ar-H & 1H for Ar-CH δ 3.34, s, 3H, OCH_3 ; δ 2.54, s, 1H, ring proton.

On the basis of elemental and spectral analysis, compound (6) was assigned the structure as 7-benzoyl-4-(4^l-methoxy phenyl)-3-oxa-2, 6, 7-triazabicyclo [3.2.0] hept-1-ene.

Analysis:

Found; C, 65.98; H, 4.97; N, 13.62.

Calculated for, $C_{17}H_{15}N_3O_3$; C, 66.01; H, 4.85; N, 13.59.

Experiment No. 7

Synthesis of 8 - benzoyl -5- (4^l- methoxy phenyl) - 2, 4, 7, 8- tetraazabicyclo [4.2.0]-oct-1(6)-ene-3- thione (7).

A mixture of 4(E)-2-benzoyl-4-(4-methoxy benzylidene)-1, 2 -diazetid-3-one (3) (0.04 M, 11.76 g) thiourea (0.04 M, 3.04 g) and potassium hydroxide (0.04 M, 2.2 g) in ethanol (50 ml) was heated under reflux for 4 hr. The reaction mixture was concentrated to half of its volume, diluted with water, then acidified with dil acetic acid & kept overnight. The solid thus obtained was filtered,

washed with water and crystallised from ethanol to get 8-benzoyl-5-(4^l-methoxy phenyl)-2, 4, 7, 8 - tetraazabicyclo [4.2.0]-oct-1(6)-ene-3-thione (7) in 90% yield.

PROPERTIES AND CONSTITUTION OF COMPOUND (7) m. p. 195. 196°C.

1.TLC studies indicated R_f value 0.69 in ethanol as eluant.

2.The compound is pale yellow coloured crystalline solid m. p. 195 - 196°C.

3.Analytical results indicated molecular formula of compound (22a) to be $C_{18}H_{16}N_4SO_2$

4. IR: [IR Plate No. 7] 3205 cm^{-1} OH str.; 3006 cm^{-1} Ar-H; 2247.7 cm^{-1} $N-C=O$ str.; 1632 cm^{-1} CO str.; 2534 cm^{-1} $C=C$ str.

5. PMR: [PMR Plate No. 7] δ 10.34, s, 2H, NH proton; δ 8.04 - 7.33, m, 10H, 9Ar-H & 1H, Ar-CH; δ 3.61-3.45, s, 3H, OCH_3 proton; δ 1.25, s, 2H, , NH proton.

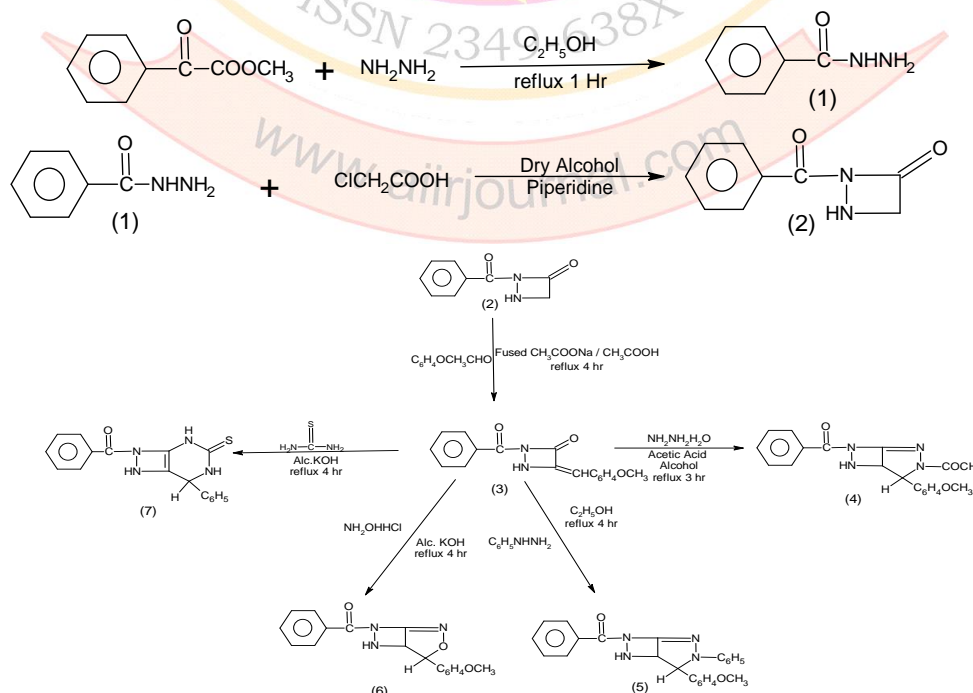
On the basis of all these properties compound 22a was assigned the structure as 8-benzoyl-5-(4^l-methoxy phenyl)-2, 4, 7, 8 - tetraazabicyclo [4.2.0]-oct-1(6)-ene-3-thione.

Analysis:

Found; C, 61.98; H, 4.32; N, 15.99; S, 8.92.

Calculated for, $C_{18}H_{16}N_4SO_2$, C, 61.36; H, 4.54; N, 15.90; S, 9.09.

SCHEME



Result and Discussion:

Spectral investigation result are

- 1)The nmr spectral result observe for the cyclisation of benzohydazide and chloro acetic acid to get the cyclic product 2-benzoyl -1,2- diazetidin -3-one are in good agreement suggesting stability of four membered ring throughout the schematic flow.
- 2)The oxygen of carbonyl group is in tautomerisation with NH of diazetidin moiety this can be indicated on the basis of $-OH$ str at 3200 cm^{-1} to 3251 cm^{-1} throughout the scheme.

Reference:

1. Manhas M S & Bose A K, "Beta Lactams; Natural and synthetic part I, Wiley Interscience, New York, 1971, P 187.
2. Wolfe S, Dueep J, Kannengiesser & Lee W S, Chand. J Chem. 1972, 2902.
3. Bose A K & Kugajevsky 1, Tetrahedron, 1967, 23, 957.
4. Sharma S, Ray J K & Chatterjee B G, J Indian Chem Soc, Vol LIX (4), 1982, 536 – 541.
5. Bose A K, Manhas M S, Kabur J C, Sharma S D, Amine S G, J Med Chem., 17, 1974, 54.
6. Ladva K, Dave U & Parekh H, Indian J Heterocycl Chem, 1 1992, 249.
7. Gujare A S, Bhawsar S B, Shinde D M, Shingare M S, Indian J Chem, 36B, 1997, 449
8. Manhas M S & Bose A K "Beta lactams; Natural & Synthetic Part I, Wiley Interscience, New York, 1971, 198 & 206.
9. Ratcliffe R W, Salzmaan T N & Christen Sen, Tetrahedron lett, 1980, 31.
10. Alain Martin, Doyle T W & Luh B C, J Chem, 1974, 891.
11. Bose A K, Kapur JC & Manhas MS, Synthesis, 1974, 891.
12. Hamashina Y, Kubota T, Ishikura K & Nagta W, Tetrahedron Lett., 1979, 4947.
13. Brown A, Howarth T T, J Chem Soc, Chem Comm., 1976, 266.
14. Scartazzini R, Gosteli J, Bickel H, Woodward, Helv. Chim. Acta. 1972, 55, 2567.
15. Aratani M & Mashimoto M, J Amer Chem Soc, 1980, 102, 395.
16. Chatterjee B G, Nyss N L, Z Naturforsch (b), 1971, 26, 395.
17. Sharma S D, Gupta P K, Bindra J & Sunita, Tetrahedron letter, 1980, 3295.
18. Naoto Hatenaka & I Ojima, J Chem Soc, Chem Comm. 1981, 344.
19. Yamanouchi Pharmaceutical Co Ltd, Chem Abstr, 1980, 93 239394.
20. Merger F, Ger. Patent, 1971, 212 - 216 Chem. Abstr, 1972, 76, 3683.
21. Wolfe S, Dueep J, Kannengiesser G & Lee W S, Cand, J Chem, 1972, 2902.

