

Synthetic Reactivity Of Substituted 2,4,7,8-Tetraazabicyclo[4,2,0]-Oct-1(6)Ene-3-Thione Towards The Synthesis of Novel Heterocycles

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Abstract:

The synthon 8-benzoyl -5-(4'-methoxy phenyl)-2,4,7,8-tetraazabicyclo[4.2.0]-oct-1(6)-ene-3-thione is synthesis by the action of 4(E)-2-benzoyl-4-(4'-methoxy benzylidene)-1,2-diazetid-3-one with thiourea in Alc. KOH, which in turn is synthesis by the condensation of 3- benzoyl-1,2-diazetid-3-one with anisaldehyde in presence of fused sodium acetate, acetic acid and catalytic amount of acetic anhydride

The thione so obtained is treated with chloro acetic acid to get substituted thiazolo (3,2-a) pyrimidine-6(2H)-one, which on condensation with benzaldehyde in presence of fused sodium acetate ,acetic acid and a catalytic amount of acetic anhydride gives 2-benzoyl-5-benzylidene-8-(4'-methoxy phenyl)-3,8-dihydro-1H-[1,2]diazeto[3,4-a][1,3]thiazolo[3,2-a]pyrimidine-6-(5H)-one which consist of exocyclic double bond adjacent to carbonyl group serve as an intermediate in the synthesis of poly heterocyclic ring by the action with carbonyl reagents such as hydrazine hydrate, phenyl hydrazine , hydroxyl amine hydrochloride, and thiourea

Introduction:

Literature survey reveals that various 2-azetid-3-one derivatives have attracted considerable attention as they showed wide range of pharmacological activities^{1,3}

The biological activity of β lactam antibiotic is generally believed to be associated with the chemical reactivity of their β lactam ring which in turn is thought to be dependent on the tail end i.e. amide side chain as well as on the head of antibiotic molecule⁴

Initially most of the research work was concern with the modification of tail end, which leads to the introduction of clinically useful cepham and penam derivatives⁵.

Subsequently special attention was focused on modification of head of antibiotic molecule. Replacement of sulphur atom of these bicyclic compounds by carbon^{6,7} nitrogen⁸, or oxygen^{9,10} were carried out in order to enhance reactivity of azetid-3-one carbon function and consequently the antibacterial activity. Various ring homologues¹¹ have also been reported with similar objectives. A recent report¹² describe the synthesis of novel biologically active compound by introduction of third hetero atom in place of C₃ of cepha[osporin]. More recently some workers in this field got

interest in the synthesis of compounds containing more than one β lactam ring^{13,18}. The versatile role of β lactams in bacterial chemotherapy needs no introduction in recent years to focus considerable interest in the synthesis and modification of penam and cepham nucleus in order to obtained compounds with enhanced activity.

Encouraged by the recent work on azetid-3-one nucleus in heterocyclic system and its importance in the biological system an attempt was made here to synthesise poly heterocyclyl pyrimidines incorporate with diazetidin moiety

Experimental:

All the melting points were determined in open capillary tube and may be uncorrected. The purity of the compounds were checked by TLC on silica gel coated glass plate. Infrared spectra were monitored in Nujol. /KBr plate using IR spectrophotometer. 1H NMR were obtained using 200 Mz spectrophotometer

Experiment No. 1

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

A mixture of 2-benzoyl-1, 2-diazetid-3-one (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 (1) in 70% yield. The product was crystallised from aqueous alcohol.

PROPERTIES AND CONSTITUTION OF COMPOUND (1) M. P. 220-221°C.

1. TLC studies indicated RF value 0.69 in ethanol as eluent.
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 $C_{17}H_{14}N_2O_3$.
4. IR : [IR Plate No. 1] 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.
PMR : [PMR Plate No. 1] 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.

Analysis:

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

Calculated for, $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.76; N, 9.52.

On the basis of analytical and spectral data compound (1) was assigned the structure as 4(E)-2-benzoyl-4-(4^l-methoxy benzyldiene) -1,2 - diazetidin-3-one.

Experiment No. 2

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

A mixture of 4(E)-2-benzoyl-4-[4^l-methoxy benzyldiene)-1, 2-diazetid-3-one (1) (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 over night. 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 (2) in 90% yield.

PROPERTIES AND CONSTITUTION OF COMPOUND (2) m. p. 195 196°C.

1. TLC studies indicated Rf value 0,69 in ethanol as eluent.

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

3. Analytical results indicated molecular formula of compound (2) to be $C_{18}H_{16}N_4SO_2$.

4. IR: [IR Plate No. 2] 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.

PMR : [PMR Plate No. 2] 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, OCH₃ proton; δ 1.25, 1H, s, NH proton.

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

On the basis of all these properties compound (2) 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.

Experiment No. 3

Synthesis of 2-benzoyl-8-(4^l-methoxy phenyl)-2,8-dihydro-1H-[1,2] diazeto [3,4-a] [1,3] thiazolo [3,2-a] pyrimidine-6(5H)-one (3).

Chloroacetic acid (28 g, 0.3 M) was melted on a water bath and 8-benzoyl-5-aryl-2,4,7,8-tetraazabicyclo [4.2.0]-oct-1(6)-ene- 3-thione (2) (0.03M, 10.56g) was added to it in an instalment to maintain its homogeneity. The homogeneous melt was further heated on a water bath for 30 min. and kept over night. The solid thus obtained was washed with water until neutral and crystallised from ethanol to get (3) in 72% yield.

PROPERTIES AND CONSTITUTION OF COMPOUND (3) M. P. 223 - 224°C.

1. TLC studies indicated Rf Value 0.79 in acetone as eluent,

2. The compound is yellow coloured crystalline solid m. p. 223 - 224°C.

3. Analytical results indicated molecular formula of compound to be $C_{20}H_{16}N_4SO_3$

4. IR: [IR Plate No. 3] 3203 cm^{-1} OH str.; 3006 cm^{-1} Ar-CH str.; $1667 - 1632\text{ cm}^{-1}$ C=O str.

PMR : [PMR Plate No. 3] δ 10.42, s, 1H, NH proton; δ 7.99 - 7.33, m, 10H, 9Ar-H, 1H for Ar-

CH; δ 6.02, s, 2H, CH₂ proton; δ 3.62 - 3.40, s, 3H, OCH₃.

Analysis: Found; C, 61.59; H, 3.97; N, 14.52; S, 8.21.

Calculated for, C₂₀H₁₆N₄SO₃; C, 61.22; H, 4.08; N, 14.28; S, 8.16.

On the basis of analytical and spectral data compound (3) was assigned the structure as 2-benzoyl-8-(4^l-methoxy phenyl)-2, 8- dihydro-1H-[1, 2] diazeto [3, 4-a] [1, 3] thiazolo [3, 2-a] pyrimidine-6(5H)-one.

Experiment No. 4

Synthesis of (5z)-2-benzoyl-5-benzylidene-8-(4^l-methoxy phenyl)-2, 8 - dihydro - 1H - [1, 2] diazeto [3, 4 - a] [1, 3] thiazolo [3, 2-a] pyrimidine-6(5H)-one (4).

A mixture of 2 - benzoyl - 8 - (4^l-methoxy phenyl) -2, 8-dihydro-1H-[1, 2] diazeto [3, 4-a] [1, 3] thiazolo [3, 2-a] pyrimidine - 6(5H)-one (3) (0.03 M, 11.76 g), benzaldehyde (0.03 M, 3.18 g) and anhydrous sodium acetate (0.03 M, 2.52 g) in acetic acid (25 ml) and catalytic amount of acetic anhydride (2 ml) was heated under reflux for 3 hr, cooled and poured over crushed ice. The semisolid thus obtained was triturated with cold alcohol to get (24a) in 79% yield.

Detailed examination of compound.

1. Compound 4 is yellow crystalline solid, m. p. 278 - 279°C.
2. TLC studies showed R_f = 0.67 in acetone as eluent.
3. Elemental analysis indicated the molecular formula as C₂₇H₂₀N₄SO₃.
4. The spectral data is as follows:
IR: [IR Plate No. 4] 3250 cm⁻¹ NCO str.; 1670 - 1631 cm⁻¹ CO str.
PMR: [PMR Plate No. 4] δ 10.39, s, 1H, for NH; δ 7.99 - 7.41, m, 16H, 14 Ar-H, 2H for Ar-H; δ 3.60-3.40 s, 3H, OCH₃.

Analysis: Found; C, 68.15; H, 4.01; N, 11.56; S, 6.76.

Calculated for, C₂₇H₂₀N₄SO₃; C, 67.5; H, 4.16; N, 11.66; S, 6.66.

On the basis of these properties the compound (4) was assigned the structure as (5z)-2-

benzoyl-5-benzylidene-8-(4^l-methoxy phenyl)-2, 8-dihydro-1H-[1, 2] diazeto [3, 4-a] [1, 3] thiazolo [3, 2-a] pyrimidine-6(5H)-one.

Experiment No. 5

Synthesis of 2-benzoyl-5-phenyl-9-(4^l-methoxy phenyl)-2, 5, 6, 9 - tetrahydro-1H, 4aH-[1, 2] diazeto [3, 4-0] pyrazolo [3^l, 4^l, 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine (5).

A mixture of (5z)-1-benzyl-5-benzylidene-8-(4^l-methoxy phenyl)-2, 8-dihydro-1H-[1, 2] diazeto [3, 4-a] [1, 3] thiazolo [3, 2-a] pyrimidine-6(5H)-one (4) (0.003 M, 1.44 g), hydrazine hydrate (0.006 M, 0.3 g) in ethanol (20 ml) was refluxed for 3 hr, then concentrated, cooled in ice bath to get (5) in 60% yield.

DETAILED EXAMINATION OF COMPOUND

1. Compound 5 is pale yellow coloured crystalline solid. m. p. 173 - 174°C.
2. TLC studies showed R_f = 0.71 in alcohol as eluent.
3. The spectral data is as follows:
IR: [IR Plate No. 5] 3759 cm⁻¹ NH str.; 3186 cm⁻¹ OH str.; 2211 cm⁻¹ N-C=O str.; 1643cm⁻¹ C=O str.
PMR: [PMR Plate No. 5] δ 11.52, s, 1H, NH proton; δ 8.45 - 7.88, m, 17H, 14 Ar-H, 2H for ArCH & 1H for ring proton; δ 3.50 s, 3H, OCH₃ δ 1.25, s, 1H, NH proton.

Analysis: Found; C, 65.76; H, 4.57; N, 16.97; S, 6.51.

Calculated for, C₂₇H₂₂N₆SO₂; C, 65.58; H, 4.45; N, 17.01; S, 6.47.

On the basis of all these properties the compound (5) was assigned the structure as 2-benzoyl-5-phenyl-9-(4^l-methoxy phenyl)-2, 5, 6, 9-tetrahydro-1H, 4aH-[1, 2 diazeto [3, 4-0] pyrazolo [3^l, 4^l, 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine.

Experiment No. 6

Synthesis of 2-benzoyl-5,6-diphenyl-9-(4^l-methoxy phenyl)-2,5,6, 9-tetrahydro-1H, 4aH-[1, 2] diazeto [3, 4-0] pyrazolo [3^l, 4^l, 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine (6).

A mixture of (5z)-2-benzoyl-5-benzylidene-8-(4^l-methoxy phenyl)-2, 8 -dihydro - 1H-[1, 2] diazeto [3, 4-a] [1,3] thiazolo [3,2-a]

pyrimidine-6(5H)-one (4)(0.003 M, 1.44 g), phenyl hydrazine (0.003M, 0.324 g) and absolute alcohol (10ml) was heated under reflux for 5 hrs, cooled to room temperature and poured into cold water. The pale yellow solid separated was washed with water and crystallised from aqueous alcohol m. p. 217 - 219°C yield, 68%.

Detailed examination of compound (6).

1. Compound 6 is pale yellow coloured crystalline solid. m. p. 217-219°C.

2. TLC studies showed Rf = 0.78 in dioxane as eluent. Analytical results indicated the molecular formula of the compound to be C₃₃H₂₆N₆SO₂,

The spectral data is as follows:

IR: [IR Plate No. 6] 3206 cm⁻¹ OH str.; 1665 - 1632 cm⁻¹ CO str.

PMR: [PMR Plate No. 6] δ 10.16, s, 1H, NH; δ 9.25, s, 1H, ArCH; δ 7.95-6.78 m, 20H, 19Ar-H & 1H for Ar-CH; δ 3.50, s, 3H, OCH₃; δ 1.25, s, 1H, pyrazole ring proton.

Analysis: Found; C, 70.01; H, 4.47; N, 14.94; S, 5.42.

Calculated for, C₃₃H₂₆N₆SO₂; C, 69.47; H, 4.56; N, 14.73; S, 5.6

On the basis of all these properties the compound (6) was assigned the structure as 2-benzoyl-5, 6-diphenyl-9-(4^l-methoxy phenyl)-2, 5, 6, 9-tetrahydro-1H, 4aH-[1, 2] diazeto [3, 4-O] pyrazolo [3^l, 4^l, 4, 5] [1, 3] thiazolo (3, 2-a) pyrimidine.

Experiment No. 7

Synthesis of 2-benzoyl-5-phenyl-9-(4^l-methoxy phenyl)-2,4a,5,9 - tetrahydro-1H-[1, 2] diazeto [3, 4^l-a] isoxazolo [3^l, 4^l, 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine (7).

A mixture of (5z)-1-benzoyl-5-benzylidene-8-(4^l-methoxy phenyl)-2, 8-dihydro-1H-[1, 2] diazeto [3, 4-a] [1, 3] thiazolo [3, 2-a] pyrimidine-6(5H)-one (4) (0.003 M, 1.44 g), aqueous solution of hydroxyl amine hydrochloride (0.006 M, 0.42 g) and KOH (0.006 M, 0.33g) in ethanol (20 ml) was heated under reflux for 4 hrs. Then cooled, poured over crushed ice and acidified with dilute acetic acid to get (7) in 72% yield.

PROPERTIES AND CONSTITUTION OF COMPOUND (7) M. P. 179 180°C.

1. TLC studies indicated Rf 0.81 in acetone as eluent.

2. The compound is pale yellow coloured crystalline solid m. p. 179- 180°C.

3. Analytical results indicated molecular formula of compound (7) to be C₂₇H₂₁N₅SO₃,

IR: [IR Plate No. 7] 3205 cm⁻¹ OH str.; 1633 cm⁻¹ C=O str.

PMR : [PMR Plate No. 7] δ 10.42, s, 1H, NH; δ 7.99 - 7.42 m, 17H, 14 Ar-H, 2H for ArCH & 1H for ring proton; δ 3.57 - 3.54, s, 3H, OCH₃.

Analysis: Found; C, 65.89, H, 4.44; N, 14.04; S, 6.59.

Calculated for, C₂₇H₂₁N₅SO₃: C, 65.45; H, 4.24; N, 14.14; S, 6.46.

On the basis of all these properties compound (7) was assigned the structure as 2-benzoyl-5-phenyl-9-(4^l-methoxy phenyl)-2, 4, 5, 9-tetrahydro-1H, 4aH-1, 2 diazeto [3, 4^l-a] isoxazolo [3^l, 4^l, 4, 5][1,3] thiazolo [3, 2-a] pyrimidine.

Experiment No. 8

Synthesis of 2-benzoyl-5-phenyl-10-(4^l-methoxy phenyl)- 2, 5, 8, 10-tetrahydro-1H-[1,2] diazeto [3, 4-O] pyrimido [4^l, 5^l, 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine 7(6H)-thione (8).

A mixture of (5z)-1-benzoyl-5-benzylidene-8-(4^l-methoxy phenyl)-2, 8-dihydro-1H-[1, 2] diazeto [3, 4-a] [1, 3] thiazolo [3, 2-a] pyrimidine-6(5H)-one (4) (0.003 M, 1.44 g), thiourea (0.006 M, 0.456 g) and potassium hydroxide (0.006 M, 0.33 g) in alcohol (20 ml) was heated under reflux for 4 hrs. The resulting mixture was concentrated to half, diluted with water and then acidified with dilute acetic acid to get (8) in 75% yield.

Detailed examination of compound (8).

1. Compound 8 is colourless crystalline solid, m. p. 238 - 239°C.

2. TLC studies showed Rf 0.73 in dioxane as eluent

3. Elemental analysis indicated the molecular formula as C₂₈H₂₂N₆S₂O₂

The spectral data is as follows:

IR: [IR Plate No. 9] 3879 cm^{-1} NH str. 3199 cm^{-1} OH str.; 1640 cm^{-1} CO str.

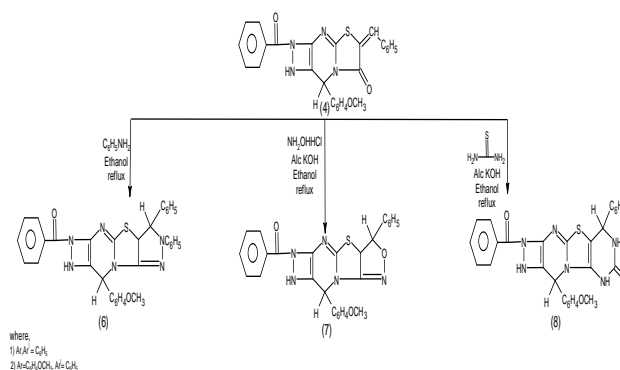
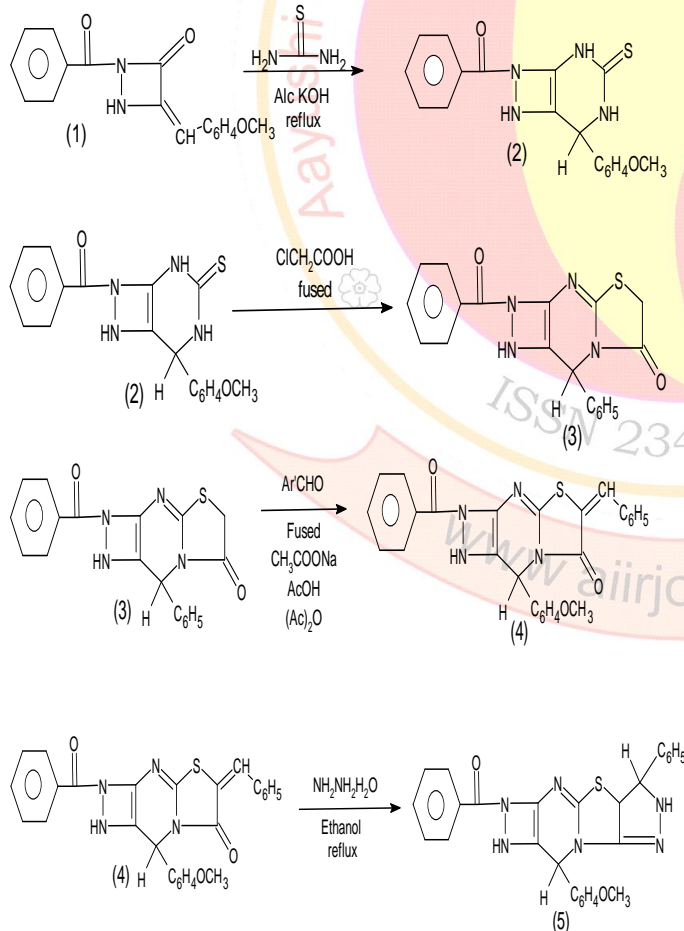
PMR : [PMR Plate No. 9] δ 11.64, s, 1H, NH; δ 10.31, s, 1H, NH; δ 8.46 – 7.38 m, 16H, 14 Ar-H, 2H for ArCH; δ 3.56, s, 3H, OCH₃; δ 1.25, s, 1H, NH proton.

Analysis: Found; C, 62.92; H, 3.92; N, 15.81; S, 12.01.

Calculated for, C₂₈H₂₂N₆S₂O₂; C, 62.45, H, 4.08; N, 15.61; S, 11.89

On the basis of all these properties compound (8) was assigned the structure as 2-benzoyl-5-phenyl-10-(4^l-methoxy phenyl)-2, 5, 8, 10-tetrahydro-1H-[1, 2] diazeto [3, 4-0] pyrimido [3', 4', 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine 7(6H)-thione,

Scheme



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