

Synthetic Exploration of 2-Furoyl-1, 2-Diazetidone-3-One towards synthesis of novel heterocycles:

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Abstract:

Synthon used is 2-furoyl-1, 2-diazetidone-3-one which is synthesis from furoic hydrazide on cyclisation with chloroacetic acid. Furoic hydrazide is in turn synthesis from furoic acid. Furoic acid was converted to furoyl chloride by the action with thionyl chloride which on treatment with hydrazine hydrate, gives the synthon 2-furoyl-1, 2-diazetidone-3-one. This on treatment with benzaldehyde in presence of fused sodium acetate, acetic acid and a catalytic amount of acetic anhydride gives 2-furoyl-1,2-diazetidone-4-benzylidene -3-one 2-furoyl-1,2-diazetidone-4-benzylidene -3-one consist of exocyclic double bond adjacent to carbonyl group opens a new synthetic route towards synthesis of novel heterocycles by the action with carbonyl reagents such as hydrazine hydrate, phenyl hydrazine, hydroxyl amine hydrochloride and thiourea.

Introduction:

Biological activity of β lactam ring is generally associated with the presence of amide side chain at the tail as well as head of antibiotic molecule. Wolf² and workers have reported the synthesis aza analogue of cepham. Prompted with this Bose³ et al have synthesis 1-azetidinopenam derivative by the action of phenyl imidazoline with azidoacetyl chloride in presence of triethyl amine, but they did not get success, however their synthetic discrepancy was overcome by sharma⁴ and coworkers.

They synthesis the above penam analogue by blocking the participation through amidification of imidazoline derivatives.

Prompted by the earlier work on azetidone heterocycles an attempted have been made to synthesis diazetidine moiety by treating simple hydrazide with chloro acetic acid, followed by its condensation with substituted aromatic aldehyde

The so obtained 2-furoyl-4-benzylidene-1, 2-diazetidone-3-one consist of exocyclic double bond adjacent to carbonyl group opens up a route for synthesis of novel heterocycles

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 2-furoic hydrazide:

A mixture of furoic acid (0.1 M, 129 g) and thionyl chloride (0.2M, 24g) was stirred several hours using magnetic stirrer. The oily layer so separated was removed using separating funnel to get furoyl chloride.

Furoyl chloride (0.1M, 13 g) with hydrazine hydrate (0.1M, 3.2 g) in ethanol 25ml was refluxed for 2 hr. The resulting mixture was concentrated to half and allow to cool. Fine crystals of Furoic hydrazide gets separated as a white crystalline solid, it was crystallized from alcohol yield 90 % melting point 77-79°C. Molecular formula C₅H₆N₂O₂.

Spectral data

IR [IR plate No.1] 3450-3442 cm⁻¹ [NH str, 2325 cm⁻¹ N-C=O str, 1657-1700 cm⁻¹ C=O str.

PMR [PMR plate No 1] δ 10.65, S, 1H, NH proton δ 7.62-7.57 m, 3H, furoyl moiety δ 4.21-3.89. 2H, NH₂ proton.

Analysis

Found C, 47.58; H, 4.79; N, 22.17; O, 25.42. Calculated for C₅H₆N₂O₂: C, 47.61; H, 4.76; N, 22.22; O, 25.39.

On the basis of analytical and spectral data compound (1) was assign the structure as-2-furoyl hydrazide

Experiment No. 2

Synthesis of 2-furoyl-1, 2-diazetidone-3-one

A mixture of 2-furoic hydrazide (0.1M, 12.6g), chloroacetic acid (1M, 94g) was heated under water bath for an hour. The resulting mixture was

kept overnight and the product is isolated by using ice cold water. The product so obtain was washed several times with water to remove unreacted acid, filtered to get the product with 90% yield, melting point-136°C.

Properties and constitution of the compound (2) m.p.136°C

1. TLC studies indicate RF value 0.86 in acetone as eluant.
2. The compound is white crystalline solid crystallised from dil alcohol with m.p. 136°C.
3. Analytical results indicate molecular formula of the compound $C_7H_6N_2O_3$.
4. IR [IR Plate No. 2] $3450-3437\text{ cm}^{-1}$ NH str, 2352 cm^{-1} $>N-C=O$ str, $1700-1692\text{ cm}^{-1}$ $>C=O$ str.
5. PMR [PMR Plate No. 2] δ 10.15, S, 1H, NH proton δ 7.62-7.55 m, 3H, furoyl moiety δ 3.86-3.61 2H azetidine ring proton..

Analysis

Found: C, 50.37; H, 3.51; N, 16.35; O, 29.01.

Calculated for $C_7H_6N_2O_3$: C; 50.16, H; 3.61, N; 16.86, O; 28.91

On the basis of analytical and spectral data compound (2) was assign the structure as-2-furoyl-1, 2-diazetidene-3-one

Experiment No. 3

Synthesis of 2-furoyl-1, 2-diazetidene-4-benzylidene-3-one (3)

A mixture of 2-furoyl-1, 2-diazetidene-3-one (0.1M, 16.6g), benzaldehyde (0.1M, 10.6g), fused sodium acetate (0.1M, 8.2g) in acetic acid 30 ml and a catalytic amount of acetic anhydride 2 ml was refluxed for 3 hr. The resulting mixture was cooled and poured over crush ice to get (3) with 90% yield m.p. 171°C.

Properties and constitution of compound (3) m.p. 171°C

1. TLC studies indicates Rf value 0.79 in ethanol as eluant.
2. The compound is white crystalline solid with m.p. 171°C.
3. Analytical results indicate molecular formula of the compound is $C_{14}H_{10}N_2O_3$.
4. IR [IR Plate No.3] $3450-3437\text{ cm}^{-1}$ NH str, δ 2290 cm^{-1} $>N-C=O$ str, $1689-1656\text{ cm}^{-1}$ $>C=O$ str.
5. PMR [PMR Plate No.3] δ 10.44 S, 1H, N-H proton, δ 7.55-7.37 m, 8H Aromatic H, δ 3.25, 1H, S, Ar-CH proton.

Analysis

Found: C; 65.67 ; H; 3.97; N, 10.99; O; 18.93.

Calculated for $C_{14}H_{10}N_2O_3$: C, 66.14 ; H, 3.93 ; N; 11.02 ; O, 18.89.

On the basis of analytical and spectral data compound (3) was assign the structure as 2-furoyl-1, 2-diazetidene-4-arylidene-3-one (3).

Experiment No. 4

Synthesis of 3-acetyl-7-furoyl-4-phenyl-2, 3, 6, 7-tetraazabicyclo [3, 2, 0]-1-ene (4).

A mixture of 2-furoyl-1, 2-diazetidene-4-arylidene-3-one (0.01 M, 2.54g), hydrazine hydrate (0.02M, 1g) in acetic acid (10 ml) was heated under reflux for 3 hr. The resulting mixture was concentrated cooled and poured over crushed ice to get (4) in 75% yield. The product was filtered, dried and crystallised from alcohol.

Detail examination of compound (4)

1. Compound (4) is a colourless crystalline solid with m.p. 125°C.
2. TLC studies indicate RF value 0.72 in acetone as eluant.
3. Analytical result indicated molecular formula of the compound to be $C_{16}H_{14}N_4O_3$.
4. Spectral data is as follows:
IR [IR Plate No.4] 3205 cm^{-1} -OH str, 3008 cm^{-1} aromatic, 2308.2 cm^{-1} $>N-C=O$ str, 1632 cm^{-1} $>C=O$ str, 535 cm^{-1} $C=C$ str,
PMR [PMR Plate No 4] δ 10.48, S, 1H, NH, δ 7.98-7.34, m, 8H, δ 3.40, S, 3H, CH_3 proton.

Analysis

Found: C, 62.01; H, 4.49; N, 18.49; O,15.01.

Calculated for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.51; N, 18.06; O, 15.48.

On the basis of analytical and spectral date compound (4) was assigned the structure as 3-acetyl-7 furoyl-4-phenyl-2, 3, 6, 7-tetraazabicyclo [3, 2, 0]-1-ene

Experiment No. 5

Synthesis of 7-furoyl-3, 4-diphenyl-2, 3, 6, 7-tetraazabicyclo [3, 2, 0] hept-1-ene(5).

A mixture of 2-furoyl-1, 2-diazetidene-4-benzylidene-3-one (0.01M, 2.54g), phenyl hydrazine (0.02 M, 2.16 g) and alcohol (20 ml) was heated under reflux for 4 hr. The resulting mixture was cool processed and worked up as described in experiment

no (4) to get (5) in 85% yield. The product was crystallised from alcohol m.p. 217-220°C.

Detail examination of compound (5).

1. Compound (5) is a pale yellow coloured crystalline solid with m.p. 217-219°C.
 2. TLC studies indicate RF value 0.69 using alcohol as eluant.
 3. Analytical results indicate molecular formula of the compound C₂₀H₁₆N₄O₂.
 4. IR [IR Plate No.5] 3202 cm⁻¹ OH str, 2310 cm⁻¹ > N-C=O str, 1680 to 1700 cm⁻¹ C=O str.
- PMR [PMR Plate No.5] : δ 10.02, S, 1H, NH proton, δ 7.22-6.5 m, 13H Ar-H, δ 3.19, 1H, CH proton.

Analysis

Found: C, 70; H, 4.59; N, 16.32; O, 9.27.

Calculated for C₂₀H₁₆N₄O₂: C, 69.76; H, 4.65; N, 16.27; O, 9.30.

On the basis of analytical and spectral data compound (5) was assigned the structure 7- furoyl 3, 4-diphenyl-2, 3, 6, 7 tetraazabicyclo [3, 2, 0] hept-1-ene.

Experiment No. 6

Synthesis of 7-furoyl-4-phenyl-3-oxa-2, 6, 7 triazabicyclo [3, 2, 0] hept-1-ene (6).

A mixture of 2-furoyl-1, 2-diazetidene-4-arylidene-3-one (0.01M, 2.54g), hydroxyl amine hydrochloride (0.02M, 1.4g), potassium hydroxide (0.02M, 1.10g) in ethanol (20 ml) was heated under reflux for 4 hr. The resulting mixture was concentrated cooled and acidified with acetic acid to get the product (6). The compound was crystallised using ethanol, melting point of crystalised sample 222 to 225°C.

Detail examination of compound (6)

1. Compound (6) is a colourless crystalline solid with m.p. 222-225°C.
2. TLC studies indicate RF 0.81 using alcohol as eluant.
3. Elemental analysis and molecular weight determination indicate molecular formula of the compound C₁₄H₁₁N₃O₃.
4. IR[IR Plate No.6] 3202 cm⁻¹ OH str, 1633 cm⁻¹ C = O str

PMR [PMR plate No. 6] δ 10.45, S, 1H, NH proton, δ 8.05 - 7.43, m, 10H, Ar-H, δ 2.54, S, 1H ring proton

Analysis:

Found: C, 62.22; H, 4; N, 15.63; O, 17.91.

Calculated for C₁₄ H₁₁N₃O₃: C, 62.45; H, 4.08; N, 15.61; O, 17.84.

On the basis of elemental and spectral analysis compound (6) was assigned the structure as 7-furoyl - 4- phenyl - 3 -oxa - 2,6,7, triazabicyclo [3,2,0] hept -1- ene.

Experiment No. 7

Synthesis of 8 - furoyl - 5 phenyl - 2, 4, 7, 8 - tetraazabicyclo [4, 2, 0] - oct-1(6) ene - 3- thione (7). A mixture of 2 - furoyl - 1, 2 - diazetidene - 4-benzylidene - 3 - one (0.01 M, 2.54 g), thiourea (0.04 M, 3.04 g) and potassium hydroxide(0.04 M, 2.2g) in ethanol (50ml) 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 product (7) with 90% yield.

Properties and constitution of compounds (7) m. p. 205 - 207° C.

1. TLC studies indicate Rf value 0.67 using acetone as eluant
 2. The compound is pale yellow coloured crystalline solid m. p. 207-208°C
 3. Analytical results indicated molecular formula of the compound C₁₅H₁₂N₄SO₂
 4. IR [IR plate No. 7] 3205 cm⁻¹ OH str, 3006 cm⁻¹ Ar -C H, 2247.7 cm⁻¹ > N-C =O str, 1632 cm⁻¹ > C = O str, 2534 cm⁻¹ C = C str.
- PMR [pmr plate No. 7] δ 10.34, S, 2H, NH proton, δ 8.04 - 7.33, m, 10 H, 9 Ar-H & 1 H for Ar - CH, δ 1.25, 1 H, S, NH proton

Analysis:

Found C, 64.32; H, 4.30; N, 19.95; O, 11.5.

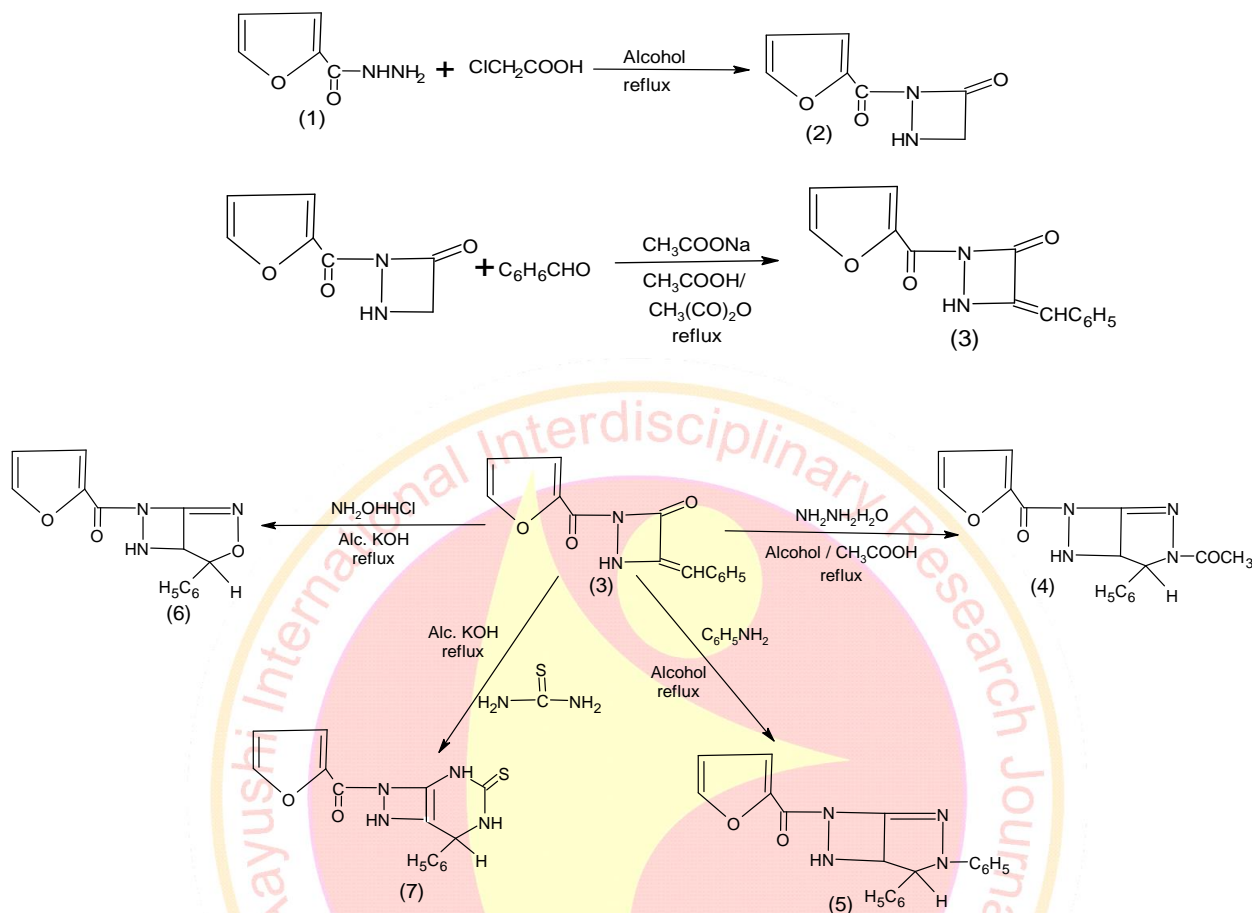
Calculated for C₁₅H₁₂N₄ O₂: C, 64.28; H, 4.28; O, 11.42; N, 20.

On the basis of analytical and spectral data compound (7) was assigned the structure 8 - furoyl - 5 phenyl - 2, 4, 7, 8 - tetraazabicyclo [4, 2, 0] - oct-1(6) ene - 3- thione (7).

Result and discussion:

1. Spectral investigation revealed that the reactions goes in right path as expected
2. From the spectral studies it is noted that the carbonyl group is tautomeric with -NH of diazetidene moiety
3. Sulphur of thiopyrimidine is also in tautomerism with -NH of thiopyrimidine nucleus as desulphurisation test is -ve with alkaline plumbite solution indicate no free sulphur

Scheme:



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