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Synthesis Of Novel Pyrimidine Derivatives Derived From Synthon Benzohydrazide.

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Abstract:

Benzo hydrazide on cyclisation with methyl acetoacetate followed by condensation with aromatic aldehyde in presence of fused Sodium acetate and acetic acid gives (4Z)- 2- benzoyl- 4- benzylidene- 5- methyl - 2,4- dihydro-3H- pyrazolo -3-one, this on treatment with thiourea in Alc KOH gives pyrazolo [3, 4-a] pyrimidine- 6 - thione, which on fused with chloro acetic acid followed by condensation with aromatic aldehyde i.e. benzaldehyde gives a potential 1 - benzoyl -5- phenyl- 7- benzylidene- 3 - methyl-1,4- dihydro pyrazolo [4, 3-c][1,3] thiazolo (3,2-a) pyrimidine-8(7H)-one.

This 7- benzylidene pyrazolo [4,3-c][1,3]thiazolo (3,2-a) Pyrimidine 8(7H) - one consists of exocyclic double bond adjacent to carbonyl group open up the synthetic route to the synthesis of different derivatives such as pyrazoles, isoxazoles and thione derivatives of pyrazolo thiazolo pyrimidines, by action with hydrazine, phenyl hydrazine, hydroxyl amine hydrochloride and thiourea.

Introduction:-

Different investigators have reported therapeutic applicability of pyrazolone and their derivatives. [1,2] Certain halogenated and non halogenated pyrazoles have been reported as fungisides [3,4]. Some of the workers [5,6] exploited importance of C=O group directly attached with pyrazole as a pesticides.
some workers [7] have reported the synthesis and anticancer activity of pyrimidine and thiazolo pyrimidine derivatives. Dave [8s] et al synthesised pyrrolo [2.3-d] pyrimidine as a potential antibacterial, analgesic. anti-inflammatory, and antihistalmic agent. Shraddha Singh et al synthesised pyrimidine dione which is evaluated for their cardiovascular activity

Thus keeping in mind the therapeutic importance of thiazolo pyrimidine, an attempt was made to synthesise important heterocycles by using synthon 7- benzylidene- 4- dihydro pyrazolo [4,3-c][1,3] thiazolo (3,2-a) pyrimidine -8(7H)-one.
This synthon consists of exocyclic double bond adjacent to carbonyl group which is useful to react with carbonyl reagent such as hydrazine hydrate, phenyl hydrazine, hydroxyl amine hydrochloride and thiourea

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 monitered in Nujol. /KBr plate using IR spectrophotometer. 1H NMR were obtained using using 200 Mz spectrophotometer

Experiment No. 1

Synthesis of (4z)-2-benzoyl-4-benzylidene-5-methyl-2, 4-dihydro-3H- pyrazolo-3-one (2). The synthesis involved two steps.

Step I: Synthesis of 2-benzoyl-5-methyl-2,4-dihydro-3H-pyrazolo-3-one (1).

The benzoyl hydrazide (0.1M) was heated with methyl acetoacetate (0.1M) for 4 hrs and the resulting solid was isolated from aqueous alcohol to get (1) in 78% yield m.p. 229 to 230°C.

Step II :

The compound (1) (20.2g, 0.1M) was dissolved in glacial acetic acid (50 ml) and to this fused sodium acetate (12.3g, 0.15M) and benzaldehyde (10.6g, 0.1M) was added and the mixture was refluxed for 3 hrs. It was then cooled and poured over crushed ice. The resulting solid was washed and crystallised from aqueous ethanol to get (2) in 85% yield m.p. 220 - 221°C.

Yield 85% m.p. 220-221°c; RF value 0.82 in acetone as eluant.

The spectral analysis of compound is as follows.
IR : [IR plate No. 1] 3005.9 cm^{-1} aromatic compound, 2836.7 CH_3 str., 1666.4 – 1632.9 cm^{-1} > C = O, 689.4 cm^{-1} C = C bending out of plane.
PMR : [PMR plate No.1] □ 10.42, s, 1H, CH=, □ 7.41 - 7.98, m, 10H, Ar-H, □ 3.32, s, 3H, CH_3.
Analysis:
found; C, 74.53; H, 4.77; N, 9.59; S, 11.12.

Calculated for, $C_{18}H_{14}N_2O_2$; C, 74.48; H, 4.82; N, 9.65; S, 11.03.

On the basis of elemental and spectral analysis compound (2) was assigned the structure as (4z)-2-benzoyl-4 benzylidene-5-methyl-2, 4-dihydro-3H-pyrazolo-3-one.

Experiment No. 2

Synthesis of 1-benzoyl-3-methyl-4-phenyl-1, 4, 5, 7- tetrahydro - 6H -pyrazolo [3, 4-a] pyrimidine-6-thione (3).

(4z)-2- Benzoyl -4- benzylidene -5-methyl-2, 4-dihydro-3H- pyrazolo-3-one (2) (0.04 M, 11.6 g), thiourea (0.04 M, 3.04 g) and KOH (0.04 M) in ethanol (25 ml) was heated under reflux for 4 hr. The resulting mixture was concentrated to half of its volume, allowed to cool, diluted with water and acidified with dilute acetic acid to get (3) in 80% yield .

Yield 80% m.p. 194-195°c; RF value 0.79 in acetone as eluant.
The spectral analysis of compound is as follows.
IR : [IR plate No. 2] 3760.1 cm^{-1} NH str., 3058.3 cm^{-1} aromatic, 2277.6 cm^{-1} -C = S str.; 1640.4 cm^{-1} > C=O str.
PMR : [PMR plate No.2] □ 11.82, s, 1H, NH; □ 10.47, s, 1H, NH; □ 7.41 - 8.43 m, 10H, Ar-H; □ 3.31, s, 3H, CH_3; □ 2.45, s, 1H, CH proton.
Desulphurization test is -ve : with alkaline plumbite solution, this may be due to tautomerization.
Analysis:

Found; C, 66.01; H, 4.49; N, 15.97; S, 9.21.

Calculated for, $C_{19}H_{16}N_4SO$; C, 65.51; H, 4.59; N, 16.09; S, 9.19.

On the basis of elemental and spectral analysis compound (3) was assigned the structure as 1-benzoyl-3-methyl-4 phenyl-1, 4, 5, 7-tetrahydro-6H-pyrazolo (3, 4-a) pyrimidine-6-thione

Experiment No. 3.

Synthesis of 1-benzoyl-3-methyl-4-phenyl-1,4-dihydro pyrazolo [4, 3-e] [1, 3] thiazolo [3, 2-a] pyrimidine-8(7H)-one (4).

Chloroacetic acid (9 g, 0.096 M) was melted on waterbath and 1-benzoyl-3-methyl-4-phenyl-1,4,5,7-tetrahydro-6H-pyrazolo [3,4- a] pyrimidine - 6 - thione (3) (3.132 g, 0.009 M) was added to it portion wise to maintain its homogeneity. The homogenous melt was further heated on a water bath for 30 min and kept overnight. The solid thus obtained, was washed with water until neutral and crystallised from ethanol to get (4) in 82% yield.

Yield 82%; m.p. 189-190°c; RF Value 0.71 in benzene as an eluant.

With alkaline plumbite solution it does not undergo desulphurization indicating no free sulphur.
The spectral analysis of compound is as follows.
IR : [IR plate No. 3] 3206.3 cm^{-1} OH str.; 3058.0 cm^{-1} aromatic; 2279.3 cm^{-1} N-C=O str.; 1639.2 cm^{-1} PH - C = O str.
PMR : [PMR plate No.3] □ 11.5, s, 1H, CH proton; □ 10.24, S, 1H, OH; □ 8.45 s, 1H, Ph-CH; □ 7.95-7.38, m, 10H, Ar-H; □ 3.02, s, 3H, CH_3
Analysis:
found; C, 74.53; H, 4.77; N, 9.59; S, 11.12.
Calculated for, $C_{18}H_{14}N_2O_2$; C, 74.48; H, 4.82; N, 9.65; S, 11.03.

On the basis of elemental and spectral analysis compound (4) was assigned the structure as 1-benzoyl-3-methyl-4-phenyl-1, 4- dihydro pyrazolo [4, 3-e] [1, 3] thiazolo [3, 2-a] pyrimidine- 8 (7H)-one.

Experiment No. 4

Synthesis of (7z)-1-benzoyl-5-phenyl-7-benzylidene-3-methyl-1, 4-dihydro poyrazolo (4,3-e) (1, 3) thiazolo (3,2-a) pyrimidine-8 (7H)-one (5).

A mixture of 1 - benzoyl - 3 - methyl - 4 - phenyl - 1, 4- dihydro poyrazolo (4, 3-e) (1, 3) thiazolo (3, 2-a) pyrimidine-8(7H)-one (4) (0.03 M, 11.64 g), benzaldehyde (0.03 M, 3.18) glacial acetic acid (40 ml), fused sodium acetate (0.03 M, 2.43 g) & catalytic amount of acetic anhydride (5 ml) was heated under reflux for three hours. The resulting mixture was cooled and poured over crushed ice to get (5) in 75% yield. It was crystallizes from aqueous alcohol.

Yield 75% m.p. 233-234°c; Rf value 0.91 in alcohol, acetone mixture as eluant.

The spectral analysis of compound is as follows.

IR : [IR plate No. 4] 3012.1 cm^{-1} aromatic; 2052.7 cm^{-1} N-C=O str.; 1632.2 cm^{-1} PH-C=O str.; 603.6 cm^{-1} C=C bending out of plane.

PMR : [PMR plate No.4] □ 10.32– 10.23, s, 2H, Ph-CH; □ 7.99 -7.42, m, 15H, Ar-H; □ 3.13, s, 3H, CH_3.

Analysis:

Found; C, 70.49; H, 4.23; N, 11.82; S, 6.66.

Calculated for, $C_{28}H_{20}N_4SO_2$; C, 70.58; H, 4.20; N, 11.76; S, 6.72.

On the basis of elemental and spectral analysis compound 5 was assigned the structure as (7z) - 1 - benzoyl - 5 - phenyl - 7 - benzylidene -3-methyl-1, 4-dihydro poyrazolo (4,3-e) (1,3) thiazolo (3,2-a) pyrimidine-8(7H)-one.

Analysis:

Found; C, 70.49; H, 4.23; N, 11.82; S, 6.66.

Calculated for, $C_{28}H_{20}N_4SO_2$; C, 70.58; H, 4.20; N, 11.76; S, 6.72.

Experiment No. 5.

Synthesis of 1-benzoyl-3-methyl-4,7-diphenyl-1,4,7,8-tetrahydro- 6aH-pyrazolo [4, 3-e] pyrazolo [3', 4', 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine (6)

To a (7z)-1-benzoyl-5-phenyl-7-benzylidene -3-methyl-1, 4- dihydro poyrazolo (4, 3-e) (1, 3) thiazolo (3, 2-a) pyrimidine-8(7H)-one (5) (0.003 M, 1.428 g) in ethanol (10 ml), hydrazine hydrate (0.003 M) was added and then the reaction mixture was refluxed for 4-5 hour. The resulting mixture was concentrated, cooled and poured over crushed ice to get the product (6) in 69% yield. It was filtered and crystallised from alcohol.

Yield 69%, m.p. 239 - 240°c; Rf value 0.89 in Benzene as eluant

The spectral analysis of compound is as follows.

IR : [IR plate No. 5] 3005.4 cm^{-1} aromatic; 1633.3 – 1667.9 cm^{-1} PH-CO str.

PMR : [PMR plate No.5] □ 10.34– 10.40, 1H, NH; □ 7.41-7.99, m, 16H, Ar-H and Ar-CH; □ 2.57, s, 3H, CH_3.

Analysis

Found, C, 72.79; H, 4.70; N, 12,11; S, 6.98.

Calculated for, $C_{28}H_{22}N_6SO$; C, 72.72; H, 4.76; N, 12.12; S, 6.92.

On the basis of elemental and spectral analysis compound (6) was assigned the structure as 1-benzoyl-3-methyl-4, 7-diphenyl-1, 4, 7, 8-tetrahydro-6aH-pyrazolo [4, 3-e] pyrazolo [3', 4',4,5] [1, 3] thiazolo [3, 2-a] pyrimidine.

Experiment No. 6

Synthesis of 1-benzoyl - 3 -methyl- 4, 7, 8-triphenyl - 1, 4, 7, 8 - tetrahydro - 6aH - pyrazolo [4, 3 - e] pyrazolo (3', 4', 4, 5] [1, 3] thiazolo [3, 2-a] pyrimidine. (7).

A mixture of 1-benzoyl-5-phenyl-7-benzylidene-3- methyl-1, 4-dihydro pyrazolo (4, 3-e) (1, 3) thiazolo (3, 2-a) pyrimidine-8(7H) -one (5) (.003 M. 1 428 g). phenyl hydrazine (0.003 M, .324 g) and alcohol (10ml) was added. The reaction mixture was heated under reflux for 5 hrs, cooled to room temperature and poured into cold water. The yellow solid thus separated, was filtered washed well with water and crystallised from glacial acetic acid giving yellow needles, m. p. 227-228°C yield 70%

Yield 70%, m.p. 227 - 228°C; Rf value 0.69 in acetone as eluant.

The spectral analysis of compound is as follows.

IR : [IR plate No. 6] 3008 cm^{-1} aromatic; 1632.6 cm PHCO str.: 691.3 C-C bending out of plane.

PMR : [PMR plate No.6] □ 10.43, 1H, s, ring proton; □ 7.10 - 7.99, m, 20H, Ar-H; □ 2.55, s, 3H, CH_3.

On the basis of analytical and spectral analysis compound (7) was assigned the structure as 1-benzoyl-3-methyl-4, 7, 8- triphenyl -1, 4, 7, 8 - tetrahydro - 6aH - pyrazolo [4, 3-c] pyrazolo (3^1,4',4,5) [1 ,3] thiazolo [3, 2-a) pyrimidine.

Analysis

Found; C, 72.69; H, 4.31; N, 15.01; S, 5.48.

Calculated for, $C_{34}H_{26}N_6SO$; C, 72.08; H, 4.59; N, 14.84; S, 5.65.

Experiment No. 7

Synthesis of 1-benzoyl-3-methyl-4,7-diphenyl-1,4,6a,7-tetrahydro isoxazolo [3', 4', 4, 5] [1, 3] thiazolo [3, 2-a] pyrazolo [4, 3-e] pyrimidine. (8).

A mixture of (7z)-1-benzoyl-5-phenyl-7-benzylidene-3- methyl-1, 4-dihydro pyrazolo (4, 3-e) (1, 3) thiazolo (3, 2-a) pyrimidine 8(7H)-one (5) (0.003 M, 1.428 g), aq solution of hydroxyl amine hydro chloride (0.003 M, 0.21 g), KOH (0.003 M, 0.165 g) in alcohol (15 ml) was heated under reflux for 4 hr. The resulting mixture was cooled, diluted

with ice cold water and acidified with dilute acetic acid to get (8) in 79% yield.

Yield 79%, m.p. 243 - 244°C; Rf value 0.81 in acetone hexane mixture as eluant.

The spectral analysis of compound is as follows.

IR : [IR plate No. 7] 3002.4 cm^{-1} aromatic; 2083.7 cm^{-1} -N-CO str., 1633.6 cm^{-1} pH-CO str.: 599.5 cm^{-1} bending out of plane.

PMR : [PMR plate No.7] □ 10,39, s, 2H, Ar-CH; □ 7.99-7.41 m, 16H, 15 Ar-H and 1H ring proton; □ 2.56, s, 3H, CH_3 proton.

Analysis:

Found; C, 68.47; H, 4.31; N, 14.12; S, 6.48.

Calculated for, $C_{28}H_{21}N_5SO_2$; C, 68.43; H, 4.27; N, 14.25; S, 6.51

On the basis of analytical and spectral analysis compound (8) was assigned the structure as 1-benzoyl-3-methyl-4,7-diphenyl-1,4,6a,7-tetrahydro isoxazolo [3',4'4,5] [1,3] thiazolo [3,2,a] pyrazolo[4,3,e] pyrimidine.

Experiment No, 8

Synthesis of 1-benzoyl -3-methyl-(4,7)-diphenyl -4,7-dihydro pyrimido [3,'4',4,5] [1,3] thiazolo [3,2,a] pyrazolo [4,3-e] pyrimidine (9)

A mixture of (7Z)-1-benzoyl-5-phenyl-7-benzylidine-3-methyl-1,4-dihydro pyrazolo[4,3,e][1,3] thiazolo[3,2,a]pyrimidine-8(7H) one(5) (0.003M,1.428g),tniourea(0.003m,0.228g) and KOH(,003,M)in ethanol(25ml)was heated under reflux for 4 hr. The resulting mixture was concentrated to half of the volume,diluted with ice cold water,then acidify with acetic acid and kept overnight.The solid thus obtained was filtered,washed with water and crystallise from ethanol to get (9).

Yield 85%, m.p.236-237 ^{O}C,Rf value 0.76 in acetone as eluant

Spectral analysis of the compound is as follows

IR: [IR plate No.8] 3002.4 cm^{-1} Ar-CH str;2289 cm^{-1} N-C=O str ;1633.6 Ph C=O str.

PMR [PMR plate No.8] δ 10.41, s, 2H, NH proton, δ 7.42-7.99, m, 17H, 15Ar-H & 2H for Ar-CH: δ 3.27, s, 3H, CH_3 proton.

Analysis:

Found; C, 64.98; H, 4.09; N, 16.09; S, 11.78.

Calculated for, $C_{29}H_{22}N_6S_2O$; C, 65.16; H, 4.11; N, 15.73; S, 11.98

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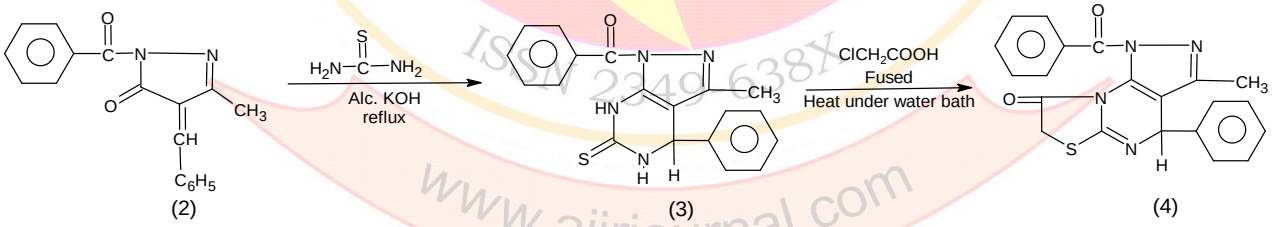

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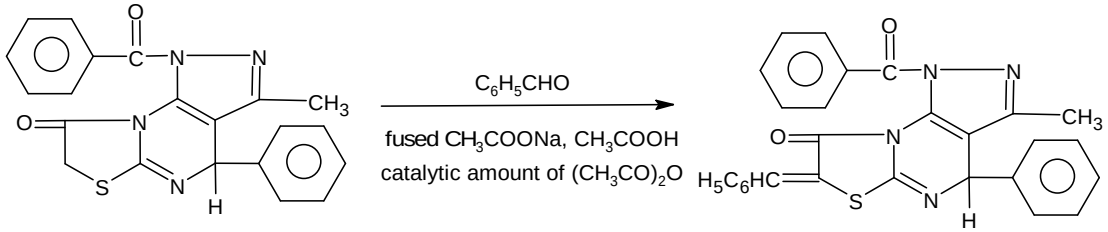

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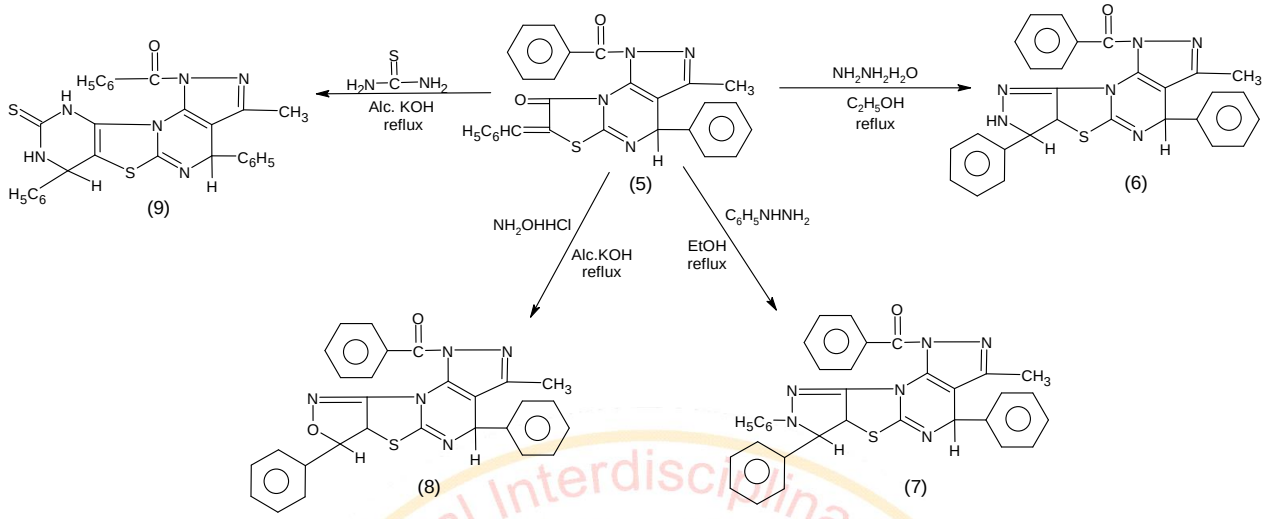

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