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SYNTHESIS AND CHARACTERIZATION OF 2' CHLOROSPIRO[CYCLOHEXANE/ CYCLOPENTANE/CYCLO BUTANE-1,5'-PYRROLO[2,3-D]PYRIMIDIN]-6'(7'H)-ONE

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Keywords:

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ABSTRACT

A Novel and efficient synthetic sequence for the preparation of 3,3 di substituted oxi indoles was developed from Pyrimidine hydrazines and α-branched aldehydes via Fisher Indole synthesis followed by imine oxidation.

INTRODUCTION

Fused and spirocyclic ring systems are the key structural elements of numerous important organic molecules, including many natural products and marketed drugs. Many synthetic efforts in heterocyclic chemistry have been directed towards the synthesis of hetero aromatic ring systems; apart from certain cases such as steroid-like molecules and some other natural products, fused and spirocyclic heteroaliphatic frameworks have received less attention. The situation has since changed and recent trends in medicinal chemistry have shifted towards three-dimensional scaffolds as the central cores of potential drugs[1]. Conformationally restricted templates, including spirocyclic ones, have advantages for drug discovery, since, due to their pre-organisation, they have increased chance of potent and selective binding with their Biologicaltargets.Itisnotsurprisingtherefore,thatspirocyclicheteroaliphatic molecules have attracted significant attention from synthetic and medicinal chemists[2] Furthermore, special attention has been paid to oxygen-enriched molecules since it was shown that many compound collections have less oxygen content compared to natural products and marketed drugs.[3] Therefore, fused and spirocyclic ring systems based on saturated oxygen heterocycles are of particular interest.

Spirocyclic compounds isolated from plant and animal origin has important applications in medicinal chemistry. The tetrahedral nature of the spirolinked carbon rendered it important conformational features and structural implications for biological systems. Spiro heterocycles have been found to play fundamental roles in biological processes and have exhibited diversified biological activity and pharmacological and therapeutical properties.

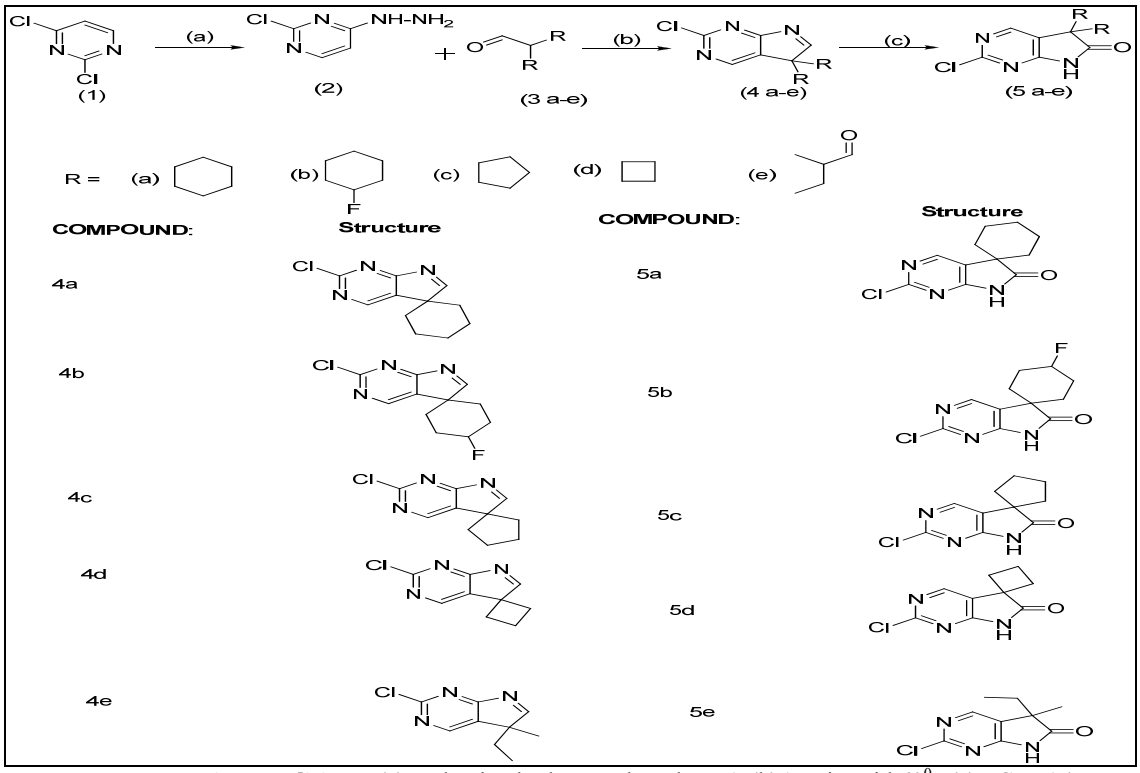
Spirocyclic compounds have fascinated chemists for more than a century. In 1900, Bayer created the first spiran which was described as a bicyclic hydrocarbon connected by a single carbon. Due to the tetrahedral nature of the spirolinked carbon, the ring planes are nearly perpendicular to each other[4]. Spirocyclic compounds have important conformational features and structural implications for biological systems. A number of review surveys regarding synthetic approaches to spiro compounds have been published.[5-10] Much attention has been focused on methods of preparing spiroheterocycles which have been studied extensively for their biological activity.[11-12].

EXPERIMENTAL SECTION

Material and Methods: Melting points were determined using an electro thermal digital apparatus and are uncorrected. Purity of the compound was checked by thin layer chromatography (TLC). IR spectra were prepared on a FT-IR spectrophotometer using KBr

discs. ^{1}H PMR spectra were recorded on Bruker spectrophotometer (300 MHz) in DMSO-d6 or CDCl3 using TMS as an internal standard. All the reagents and solvents were reagent grade and were used without further purification unless otherwise specified. Microwave reactions were conducted using a focused single mode microwave unit. The machine consists of a continuous focused microwave power delivery system with operator selectable power output. The reactions were performed either in a Round-bottomed flask equipped with condenser, or in a glass tube sealed with a septum under the pressure set at 100 psi. The reported reaction temperature was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The reaction mixture was magnetically stirred. Reactions were monitored by TLC using aluminum plates pre-coated with a 0.25 mm layer of silica gel containing a fluorescent indicator (Merck Art. 5544). Kieselgel 60 (40–63 µm) was used for column chromatography. Melting points are uncorrected. Chemical shifts (δ) are given in parts per million (ppm) relative to δH 7.24 / δC 77.0 (central line of t) for CHCl3/CDCl3, δH 3.31 /δC 49.0 CH3OD/CD3OD, and δH 2.49 (m) / δC 39.5 (m) for (CH3)2SO/(CD3)2SO. The splitting patterns are reported as s (singlet), d (doublet), t (triplet) q (quartet), m (multiplet) and br (broad).Coupling constants (J) are given in Hz.

Scheme:



Reagents & Reaction conditions: (a)Hydrazine hydrate, Ethanol, TEA (b)Acetic acid,60^{0}c (c)mCPBA(meta chloro per benzoic acid),DCM,RT,3-4 hrs

The title compounds) were synthesised in three sequential steps using different reagents and reaction conditions the 5(a-d) were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

Preparation of 2-chloro-4-hydrazinylpyrimidine (2):

A mixture of 2,4 di chloro Pyrimidine(1) (0.01mol) in methanol was taken and cooled to 0-5^{0} c in an ice bath,tri ethyl amine(0.01 mol)was added to the cold reaction mixture and then hydrazine hydrate (0.012 mol) was added slowly at 5-10^{0} c. The reaction mass was allowed to stir at room temperature for 1 hr.The solid thus obtained was filtered ,washed with chilled water and dried to afford compound(2),pale yellow solid. Melting point 140^{0}c-142^{0}c

Preparation of 2'-chlorospiro[cyclohexane/-1,5'-pyrrolo[2,3-d]Pyrimidine(4a), 2'-chloro-4-fluorospiro[cyclohexane-1,5'-pyrrolo[2,3-d]Pyrimidine](4b), 2'-chlorospiro[cyclopentane-1,5'-pyrrolo[2,3-d]pyrimidine](4c), 2'-chlorospiro[cyclobutane-1,5'-pyrrolo[2,3-d]Pyrimidine(4d): 2-chloro-5-ethyl-5-methyl-5H-pyrrolo[2,3-d]pyrimidine (4e);

To a solution of the aldehyde(3 a-e) (2.0 mmol) in acetic acid (20 mL) was added the 2-chloro-4-hydrazinylpyrimidine (2.0 mmol). The mixture was heated at 60^{0} C for 0.5-2 h, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL), and washed with ice-cold saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, and concentrated. The residue was subjected to column chromatography on silica gel, using ethyl acetate/petroleum ether (1:20 to 1:5) as eluent, to give a title compounds(4a-e).

Preparation of 2'-chlorospiro[cyclohexane-1,5'-pyrrolo[2,3-d]pyrimidin]-6'(7'H)-one(5a),2'-chloro-4-fluorospiro[cyclohexane-1,5'-pyrrolo[2,3-d]pyrimidin]-6'(7'H)-one(5b),2'-chlorospiro[cyclopentane-1,5'-pyrrolo[2,3-d]pyrimidin]-6'(7'H)-one(5c), 2'-chlorospiro[cyclobutane-1,5'-pyrrolo[2,3-d]pyrimidin]-6'(7'H)-one(5d),2-chloro-5-ethyl-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one(5e):

Compound 4(a-e) (0.02 m mol) dissolved in CH_2Cl_2 and mCPBA (0.80 m mol) was added at 0^{0}c.The reaction mixture was stirred at RT for 1 hr and concentrated. The Residue was re dissolved in ethyl acetate, washed with sodium bisulfite, Na2CO3 and brine. The organic layer was dried over Na2SO4, Concentrated and purified by chromatography with ethyl acetate in CH_2Cl_2 to provide Oxi Indole product.

Analytical data of synthesized compounds:

Compound 2:

^{1}H NMR(DMSO-d6,ppm):

δ 7.5(1H,d,j=8HZ),6(1H,d,J=8HZ),2(2H,S,broad),3.9(1H,S,broad)

IR (KBr, cm-1):

700(C-Cl),3450(-NH),3350 and 3400(Two peaks indicates-NH_2),

1080(C-N),1600(N-H bending),3100(aromatic C-H),1500(aromatic C=C)

^{13}C NMR(DMSO-d6,ppm):

155,160,105,170(4 aromatic carbons)

Compound 4a:

3100(Aromatic –CH stret),1500(aromatic C=C stret),750(C-Cl stret),1150(C-N stret),2900(C-H stret),1400(-CH bending)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s),7.5(1H,d,J=7HZ), 1.5-1.9(10H,m)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(N=**C** carbon),39,34,20,25(6aliphatic carbons)

Compound 4b:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret),1200(C-F stret), 2950(C-H stret),1450(-CH bending)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s),7.5(1H,d,J=7HZ), 1.5-1.9(8H,m), 3.3(1H,m,-C**H**-F)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(N=**C** carbon),39,27,29, (5 aliphatic carbons),90(**C**-F)

Compound 4c:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret), 2900(C-H stret),1400(-CH bending)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s),7.5(1H,d,J=7HZ), 1.5-1.9(8H,m)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(N=**C** carbon),37,40,25 (5 aliphatic carbons)

Compound 4d:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret), 2920(C-H stret),1410(-CH bending)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s),7.5(1H,d,J=7HZ), 2-2.4(6H,m)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(N=**C** carbon),39,32,16 (4 aliphatic carbons)

Compound 4e:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret), 2920(C-H stret),1410(-CH bending)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s),7.5(1H,d,J=7HZ), 1.5(3H,S),1.4(2H,q,J=7HZ),0.9(3H,t,J=7HZ)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(N=**C** carbon),25,35,10 (3 aliphatic carbons)

Compound 5a:

3100(Aromatic –CH stret),1500(aromatic C=C stret),750(C-Cl stret),1150(C-N stret),2900(C-H stret),1400(-CH bending),1745(C=O stretching)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s),8(1H,S,-NH), 1.5-1.9(10H,m)

^{13}C NMR(DMSO-d6,ppm):

155,160,165,125(Pyrimidine ring carbons),180(C=O),55(Spiro carbon),33,20,25(5aliphatic carbons)

MS (EI): m/z = 237.2 [M^{+}], Elemental Analysis for Chemical Formula $C_{11}H_{12}ClN_3O$ Calculated: C, 55.59; H, 5.09; N, 17.68 found: C, 55.59; H, 5.07; N, 17.68,

Compound 5b:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret),1200(C-F stret), 2950(C-H stret),1450(-CH bending),1740(C=O stretching)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s), 8(1H,S,-NH), 1.5-1.9(8H,m), 3.3(1H,m,-C**H**-F)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(C=O carbon),55(spiro carbon), 27 (4 aliphatic carbons),90(**C**-F),55(Spiro carbon)

MS (EI): m/z = 255.2 **[M**+], Elemental Analysis for Chemical Formula $C_{11}H_{11}ClFN_3O$ Calculated: C, 51.67; H, 4.34; N16.43 found: C, 51.64; H4.32; N, 16.46

Compound 5c:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret), 2900(C-H stret),1400(-CH bending), 1745(C=O stretching)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s), 8(1H,S,-NH), 1.5-2.2(8H,m)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(C=O carbon),64(Spiro carbon),37,25 (4 aliphatic carbons)

MS (EI): m/z = 223.66 **[M^{+}]**, Elemental Analysis for Chemical Formula $C_{10}H_{10}ClN_3O$

Calculated: C, 53.70; H, 4.51**;** N, 18.79 found C, 53.68; H, 4.50**;** N, 18.76

Compound 5d:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret), 2920(C-H stret),1410(-CH bending), 1740(C=O stretching)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s), 8(1H,S,-NH), 2-2.6(6H,m)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons175(C=O carbon), 55(Spiro carbon), 31, 15(3 aliphatic carbons)

MS (EI): m/z = 209.63 **[M^{+}]**, Elemental Analysis for Chemical Formula $C_9H_8ClN_3O$

Calculated: C**,** 51.56; H, 3.85**;** N, 20.04,found C, C**,** 51.54; H, 3.83**;** N, 20.02

Compound 5e:

3100(Aromatic –CH stret),1550(aromatic C=C stret),755(C-Cl stret),1170(C-N stret), 2920(C-H stret),1410(-CH bending), 1745(C=O stretching)

^{1}H NMR(DMSO-d6,ppm):

δ8.5(1H,s), 8(1H,S,-NH), 1.5(3H,S),1.8(2H,q,J=7HZ),0.9(3H,t,J=7HZ)

^{13}C NMR(DMSO-d6,ppm):

160,177,125,160(Pyrimidine ring carbons),175(C=O carbon),55(Spiro carbon),21,35,10(3 aliphatic carbons)

MS (EI): m/z = 211.65 **[M^{+}]**, Elemental Analysis for Chemical Formula $C_9H_{10}ClN_3O$

Calculated: C, 51.07; H, 4.76; N, 19.85, found C**,** 51.05; H, 4.75**;** N, 19.82

RESULTS AND DISCUSSION

Spectral studies:

2-chloro-4-hydrazinylpyrimidine(2) was synthesized according to the reported procedure [13]. The reaction of 2-chloro-4-hydrazinylpyrimidine with α branched aldehydes as per the reported procedure[14] to afford 2'-chlorospiro[cyclohexane/-1,5'-pyrrolo[2,3-d]Pyrimidine(4a), 2'-chloro-4-fluorospiro[cyclohexane-1,5'-pyrrolo[2,3-d]Pyrimidine](4b),2'-

chlorospiro[cyclopentane-1,5'-pyrrolo[2,3-d]pyrimidine](4c),2'-chlorospiro[cyclobutane-1,5'-pyrrolo[2,3-d]Pyrimidine(4d),2-chloro-5-ethyl-5-methyl-5H-pyrrolo[2,3-d]pyrimidine (4e); which was reacted with mCPBA to afford corresponding oxi indoles as per the reported procedure[14].

Readily available starting materials and simple synthesizing procedures make this method is very attractive and convenient for the synthesis of various Pyrimidines with oxi indoles. Formation of products was confirmed by recording their Elemental analysis, ^{1}H NMR, FT-IR and mass spectra. The ^{1}H NMR spectra of 4a,4b,4c,4d,5a,5b,5c,5d showed singlet in the region of δ8.5 Pyrimidine ring and 7.5(**H**C=N),respectively.The ^{13}C NMR Spectra of 5a,5b,5c,5d showed 175(**C**=O in oxi indole ring). The Elemental analysis data showed good agreement between the experimentally determined values and the theoretically calculated values with in ±0.3%.

CONCLUSION

In conclusion a series of new 2-chloro-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one 5(a-e) were synthesized in good yield, characterization by different spectral studies.

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