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Synthesis and characterization of pyrrole-pyrimidine biheterocycles

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ABSTRACT

In the present work we have utilized cyanovinyl ester group of ethyl α-cyano 2-Pyrrole acrylate for the synthesis of Pyrrole- pyrimidine biheterocycles.The reaction of ethyl α-cyano 2-Pyrrole acrylate have been carried with semicarbazone derivatives and reactions result in the formation of biheterocyclic molecules presenting important synthesis for medicinal chemists.

KEYWORDS

Pyrrole;
Hydrazinecarboxamide;
Cyanovinyl;
Alcohols;
Chemotherapeutic.

INTRODUCTION

Biheterocycles are compounds containing two heterocycles which are linked by a single bond between two heterocycle rings. The preparation and utilization of biheterocyclic systems is a demanding goal[1], seeing that they are interesting compounds with numerous potential fields of applications as electrical or electronic materials[2a-c], as monomers for the synthesis of conductive polymers[3], with rich photophysical and photochemical properties[4], and as luminescent molecular sensors[5]. Incorporation of biheteroaryls into macropolycyclic structures leads to very interesting ligands to form photoactive cryptates of interest as novel luminescent material[6]. The formation of helicates, helices incorporating metal ions, as versatile supramolecular complexes[7] is another important potentiality of biheterocycles. Biheterocycles have provided a wide range of finely tuned chelating ligands in coordination and organometallic chemistry.

In this investigation work was undertaken with objective to utilize ethyl α-cyano 2-pyrrole acrylate and hydrazinecarboxamide derivatives (semicarbazones) for the synthetic utilities.

EXPERIMENTAL

Reagents and solvents

The solvents were procured from E.Meck, Ranbaxy, S.D.Fine, Himedia and Qualigens. They were used after purification and drying by conventional methods[8]. The commercially available chemicals of analar grade of B.D.H., guaranteed reagent of Merck and analytical reagents or equivalent grade of others were used as such.

Ethyl α-cyano 2-pyrrole acrylate was prepared as per following procedure[9]

A solution of pyrrole-2-aldehyde (2.0 gm, 0.0210 mole), ethylcyanoacetate (3.3684 gm, 0.0297 mole) and diethylamine (0.1473 gm, 0.0020 mole) in toluene 60 ml was refluxed for 1 hr. After cooling, the crystals were collected, washed with light petroleum and air-dried. Yield: 3.41 gm (85%). m.p.130-132°C observed

(135°-138°C reported).

Acetone semicarbazone

In a 50 ml round bottomed flask, 1.0 g (0.0089 mole) of semicarbazide hydrochloride and 1.5 g (0.010 mole) of crystallized sodium acetate was dissolved in 10ml of water. 0.789 g (1.0ml, 0.013 mole) of the acetone was added with shaking. Compound is crystalline solid, soluble in water and alcohol. Yield: 0.300 g (29.07%). m .p.190°C.

Methyl ethyl ketone semicarbazone

In a 50 ml round bottomed flask, 1.0 g (0.0089 mole) of semicarbazide hydrochloride and 1.5 g (0.01102 mole) of crystallized sodium acetate was dissolved in 10ml of water. 1.0 g (1.24 ml, 0.0138 mole) of methyl ethyl ketone was added. White coloured precipitate obtained, the precipitate was filtered, washed with a 15 ml of water and recrystallised from aqueous alcohol. Crystalline solid is soluble in water and alcohol. Yield: 0.350 g (30.43%). m.p. 140°C.

Acetophenone semicarbazone

In a 50 ml round bottomed flask, 2.5 g (0.0224 mole) of semicarbazide hydrochloride was dissolved in 2.5 ml of water. Another solution prepared by mixing 10 ml of cold pyridine in 5.125 g (5.0 ml, 0.0426 mole) of acetophenone. Precipitate was filtered and recrystallised from aqueous alcohol (95% alcohol). Crystalline solid is soluble in alcohol. Yield: 2.021g (80.9%). m .p:195°C observed (198°C reported).

Salicylaldehyde semicarbazone

In a 50 ml round bottomed flask, 1.0 g (0.0089 mole) of semicarbazide hydrochloride and 1.5 g (0.01102 mole) of crystallized sodium acetate was dissolved in 10ml of water. 1.0g (0.872 ml, 0.0081 mole) of salicylaldehyde was added. White colored precipitate was obtained. Recrystallised from aqueous alcohol. Yield: 0.600 g (37.38). m .p. 231°C .

Physico-chemical techniques

TLC was routinely used to check the formation and status of products on silica Gel-G or alumina. Ambassador® melting point apparatus based on electrically controlled heating device was used for melting point determination using capillary tubes open on one side and are uncorrected. Ambassador® melting point apparatus provided a temperature range from room temperature to 360°C. The infrared spectra of products were recorded (4000-500 cm^{-1}) in KBr disc, using a Schimadzu 8201 PCFT IR spectrometer in Regional Sophisticated Instrumentation Centre, at Central Drug Research Institute, Lucknow. Proton nuclear magnetic Resonance (^1H NMR spectrum) was recorded on Bruker DRX-300 spectrometer (300 MHz FT NMR) instrument using tetramethylsilane as an internal reference. The ^1H NMR spectra were taken in $CDCl_3$, MeOD, unless otherwise stated. The chemical shift values are expressed in δ-scale.

Syntheses and characterization of pyrrole pyrimidine biheterocycles

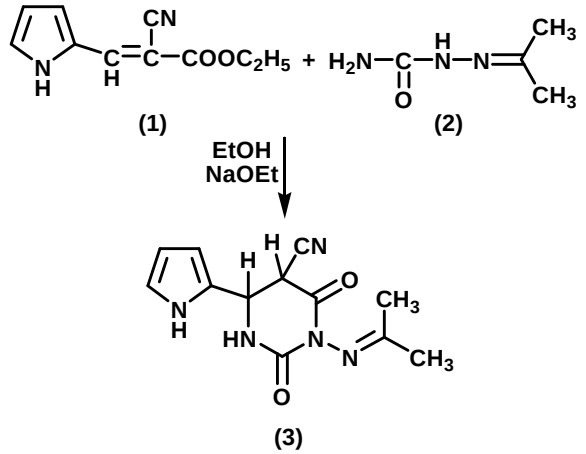
(a) Synthesis of 5-cyano 3, 4, 5-trihydro 1N-(propyl 2-imino) 4-(pyrrolyl) 2, 6-dioxopyrimidine (3)

0.0190 g (0.001 mole) of ethyl α-cyano-2 pyrrole acrylate was dissolved in 20 ml and 0.1031g (0.001mole) of acetone semicarbazone[10] in 20ml of absolute ethyl alcohol. Mixed both the solutions and equimolar solution of sodium ethoxide was added to above solution. Reaction mixture was then refluxed for 40 hrs; the precipitate formed was filtered off, washed with ethanol and air dried. Yield: 30 mg (11.57 %). m.p.: At 240°C vapors start accumulating in upper portion of capillary. After 250°C further no change was noticed up to 290°C.

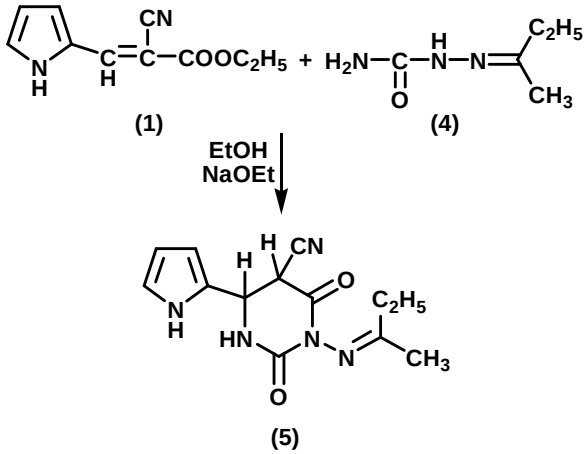
IR (KBr): 3278.8 cm^{-1} (br, NH, pyrr), 1619.7 cm^{-1} (C=O), 1579.1 cm^{-1} (C=N), 2213.0 cm^{-1} (C≡N). ^1H NMR (MeOD): δ 7.885 (1H, pyrr), δ 1.279 (s,CH_3), δ 2.112 (s, CH_3), δ 7.208 (s, 1H, C3, pyrr), δ 6.335 (s, 1H,C4, pyrr), δ 7.075 (s, 1H,C5,pyrr) δ 6.315 (s, 1H, C4 Het.) δ 7.197 (s, 1H, C5 Het.).

(b) Synthesis of 5-cyano 3,4,5-trihydro 1N-(butyl 2-imino) 4-(pyrrolyl) 2,6-dioxopyrimidine (5)

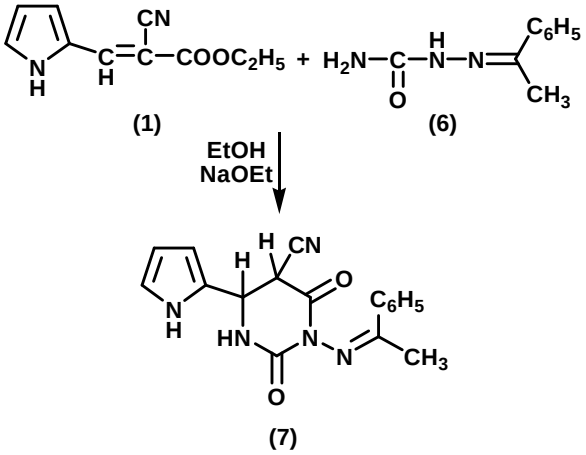
0.0190 g (0.001 mole) of ethyl α-cyano-2 pyrrole acrylate was dissolved in 20 ml and 0.1219 g (0.001 of mole) of methyl ethyl semicarbazone[10] in 40 ml absolute ethyl alcohol. Mixed both the solutions and equimolar solution of sodium ethoxide was added to above solution. Reaction mixture was then refluxed; the precipitate formed was filtered off, washed with ethanol and dried. Yield: 40 mg (14.63 %). m.p.: near 270°C



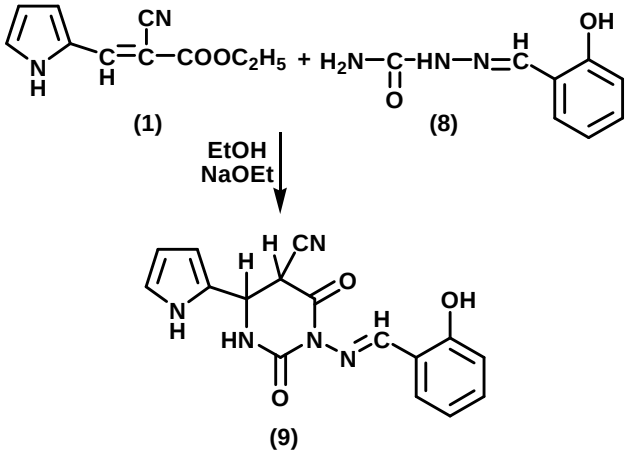
Scheme 1 : Synthesis of 5-cyano 3, 4, 5-trihydro 1N-(propyl 2-imino) 4-(pyrrolyl) 2, 6-dioxopyrimidine (3)



Scheme 2 : Synthesis of 5-cyano 3,4,5-trihydro 1N-(butyl 2-imino) 4-(pyrrolyl) 2,6-dioxopyrimidine (5)



Scheme 3 : Synthesis of 5-cyano 3,4,5-trihydro 1N-(methyl phenyl imino) 4-(pyrrolyl) 2,6-dioxopyrimidine (7)



Scheme 4 : Synthesis of 5-cyano 3,4,5-trihydro 1N-(o-hydroxybenzaldimino) 4-(pyrrolyl) 2,6-dioxopyrimidine (9)

vapor in the middle of capillary appears with slight melting.

IR (KBr): 3300.1 cm^{-1} (NH, pyrr), 1694.6 cm^{-1}(C=O), 1580.9 cm^{-1} (C=N), 2209.7 cm^{-1} (C≡N), 3458.9 cm^{-1} (NH, Het). ^{1}H NMR (MeOD): δ 7.887 (s, 1H, pyrr), δ 1.279 (s, CH_3), δ 1.938 (s, CH_3), δ 7.201 (s, 1H, C3, pyrr), δ 6.336 (s, 1H, C4, pyrr), δ 7.084 (s, 1H, C5, Pyrr), δ 6.315 (s, 1H, C4 Het.) δ 7.197 (s, 1H, C5 Het.).

(c) Synthesis of 5-cyano 3,4,5-trihydro 1N-(methyl phenyl imino) 4-(pyrrolyl) 2,6-dioxopyrimidine (7)

0.0190 g (0.001 mole) of ethyl α-cyano-2 pyrrole acrylate was dissolved in 20 ml of absolute ethyl alcohol and 0.1651 g (0.001 mole) of acetophenone semicarbazone[11] in 40 ml. Mixed both the solutions and equimolar solution of sodium ethoxide was added to above solution. Reaction mixture was then refluxed for 48 hrs; the precipitate formed was filtered off, washed with ethanol and dried. Yield: 30 mg (9.33 %). m.p.: around 230°C some vapours in the middle of the capillary appeared with sharp melting. Further no change up to 280°C.

IR (KBr): 3313.7 cm^{-1} (NH, pyrrole), 1698.4 cm^{-1}(C=O), 1583.9 cm^{-1} (C=N), 2208.0 cm^{-1} (C≡N). ^{1}H NMR (MeOD): δ 7.884 (s, 1H, pyrr), δ 2.239 (s,CH_3), δ 7.208 (s, 1H, C3, pyrr), δ 6.335 (s, 1H, C4, pyrr), δ 7.082 (s, 1H, C5, pyrr), δ 6.314 (s, 1H, C4 Het.) δ 7.198 (s, 1H, C5 Het.).

(d) Synthesis of 5-cyano 3,4,5-trihydro 1N-(o-hydroxybenzaldimino) 4-(pyrrolyl) 2,6-dioxopyrimidine (9)

0.0190 g (0.001 mole) of ethyl α-cyano-2 pyrrole acrylate was dissolved in 10 ml of absolute ethyl alcohol and 0.1791g (0.001mole) of salicylaldehyde

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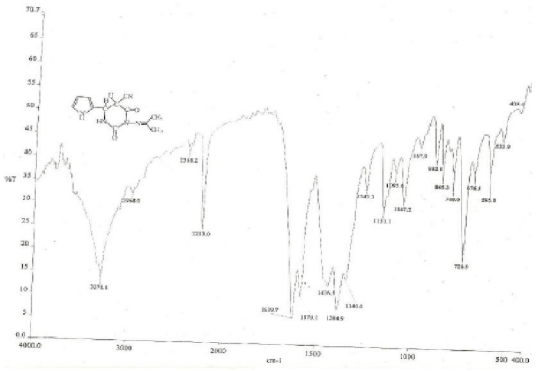

Figure 1 : IR spectrum of compound (3)

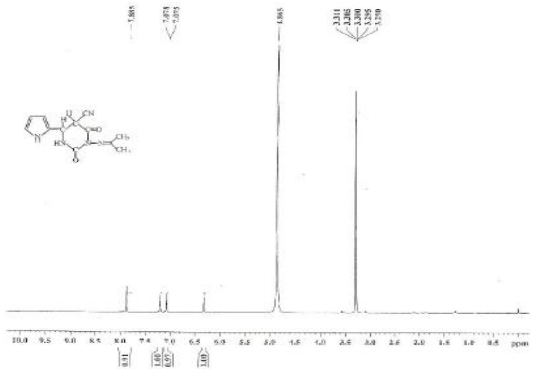

Figure 2a : ^{1}H NMR spectrum of compound (3)

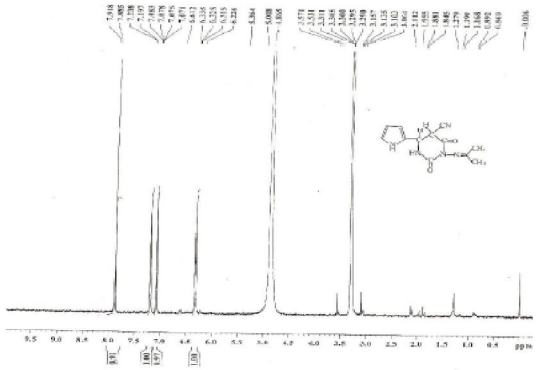

Figure 2b : ^{1}H NMR spectrum of compound (3)

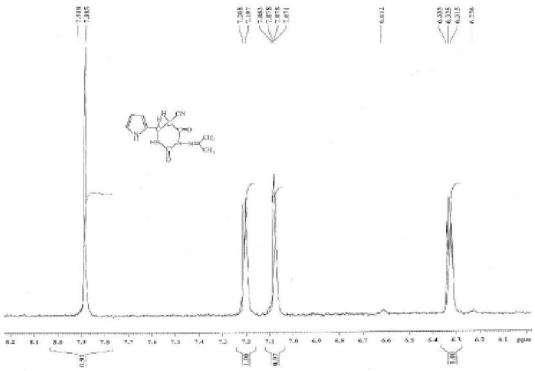

Figure 2c : ^{1}H NMR spectrum of compound (3)

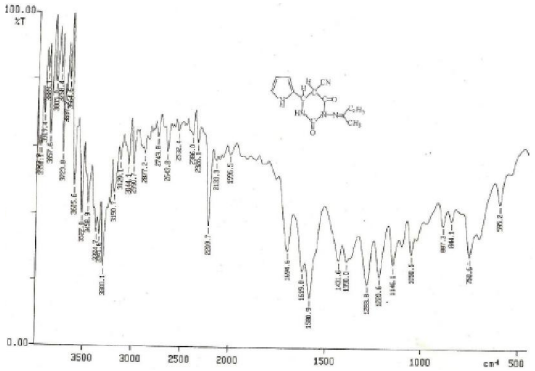

Figure 3 : IR spectrum of compound (5)

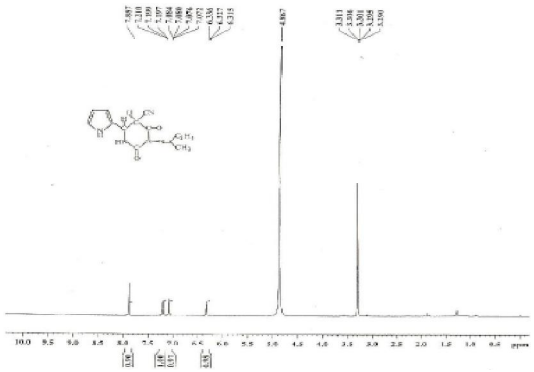

Figure 4a : ^{1}H NMR spectrum of compound (5)

semicarbazone[11] in 50 ml. Mixed both the solutions and equimolar solution of sodium ethoxide was added to above solution. Reaction mixture was then refluxed for 60 hrs; the precipitate formed was filtered off, washed with ethanol and dried. Yield: 25 mg. (10.23 %). m.p.: around 210°C vapors appeared in the middle of capillary. Further no visible change up to 290°C.

IR (KBr): 3312.2 cm^{-1}(NH, pyrr), 1695.9 cm^{-1} (C=O), 1583.7 cm^{-1} (C=N), 2208.5 cm^{-1} (C≡N). ^{1}H NMR (MeOD): δ 7.893 (s, 1H, pyrr), δ 7.201 (s, 1H, C3, pyrr), δ 6.341 (s, 1H, C4, pyrr), δ 7.086 (s, 1H, C5, pyrr), δ 6.331 (s, 1H, C4, Het) δ 7.198 (s, 1H, C5, Het.). δ 4.825 (s, 1H, Hydroxy).

RESULTS AND DISCUSSION

The structure of the formed compound **(3)**, **(5)**, **(7)** and **(9)** are given on the basis of their spectral analysis. The IR spectrum of the 5-cyano 3,4,5-trihydro 1N-(propyl 2-imino) 4-(pyrrolyl) 2,6-dioxopyrimidine **(3)** shows a broad band at 3278.8 cm^{-1} indicating the presence of pyrrolic NH as well as heterocyclic NH. A band at 2213.0 Cm^{-1} shows nitrile stretching confirming the presence of nitrile group in heterocyclic moiety. The C=O stretching shows a band at 1619.7 cm^{-1} and C=N stretching appears at 1579.1 cm^{-1}.

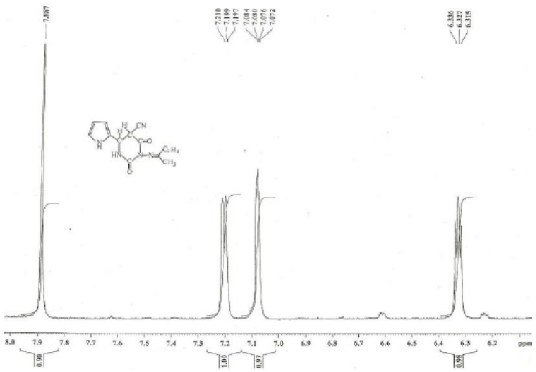

Figure 4b : [1]H NMR spectrum of compound (5)

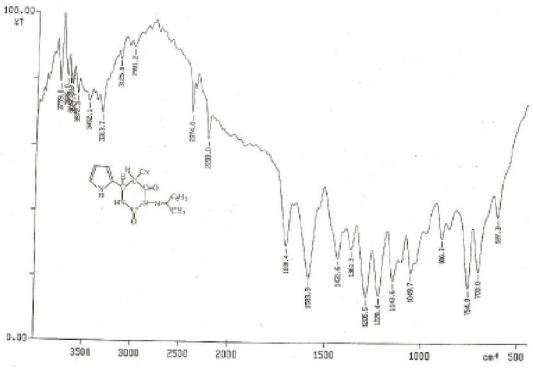

Figure 5 : IR spectrum of compound (7)

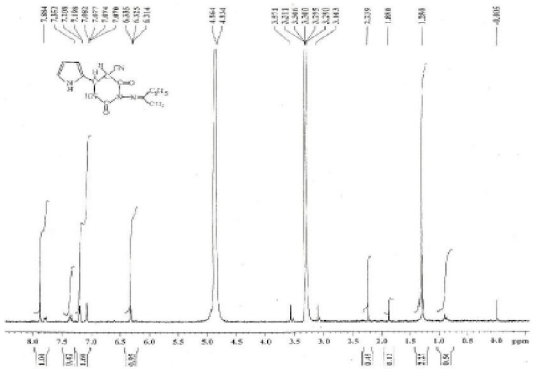

Figure 6a : [1]H NMR spectrum of compound (7)

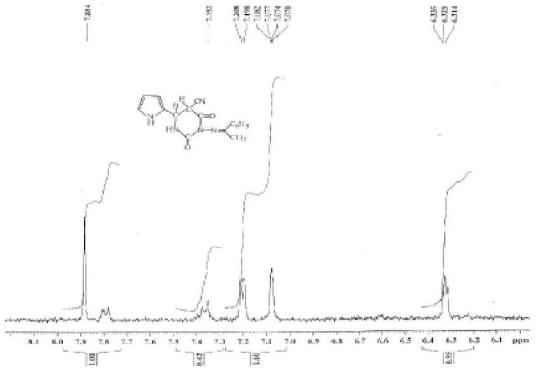

Figure 6b : [1]H NMR spectrum of compound (7)

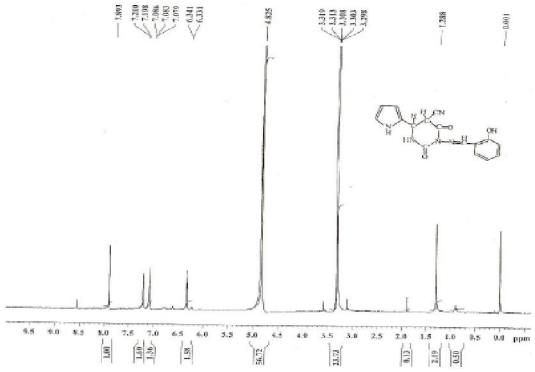

Figure 7a : [1]H NMR spectrum of compound (9)

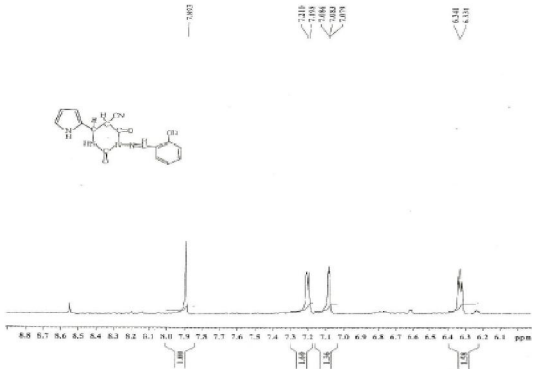

Figure 7b : [1]H NMR spectrum of compound (9)

[1]H NMR spectra of the compound **(3)** shows a singlet peak at δ 7.885 which is of one proton present on nitrogen atom of pyrrole . The pyrrole protons C-3 shows a singlet peak at δ 7.208, C-4 at δ 6.335 and C-5 at δ 7.075. Peaks at δ 1.279 and δ 2.112 indicate the presence of two methyl protons. Singlet peak at δ 6.315 and δ 7.197 shows the presence of heterocyclic protons.

The IR spectrum of the compound 5-cyano 3,4,5-trihydro 1N-(butyl 2-imino) 4-(pyrrolyl) 2, 6-dioxopyrimidine **(5)** shows pyrrolic NH stretching at 3300.1 cm^{-1} and a band of at 3458.9 cm^{-1}. A band at 2209.7 cm^{-1} shows nitrile stretching confirm the presence of nitrile group in heterocyclic moiety .The C=O stretching shows a band at 1694.6 cm^{-1} and C=N stretching appears at 1580.9 cm^{-1}.

[1]H NMR spectra of the compound **(5)** shows a singlet peak at δ 7.887 which is of one proton present on nitrogen atom of pyrrole. The pyrrole protons C-3 shows a singlet peak at δ 7.201, C-4 singlet peak at δ 6.336 and δ C-5 singlet peak at δ 7.084. Siglet peaks at δ 1.279 and δ 1.938 indicate the presence of two methyl protons. Singlet peak at δ 6.315 and δ 7.197 shows the presence of heterocyclic protons.

The IR spectrum of the compound 5-cyano 3,4,5-trihydro 1N-(methyl phenyl imino) 4-(pyrrolyl) 2, 6-dioxopyrimidine **(7)** shows pyrrolic NH stretching at

3313.7 cm^{-1}. A band at 2208.0 cm^{-1} shows nitrile stretching confirms the presence of nitrile group in heterocyclic moiety. The carbonyl stretching shows a band at 1698.4 cm^{-1} and C=N stretching appears at 1583.9 cm^{-1}.

^{1}H NMR spectra of the compound **(7)** shows a singlet peak at δ 7.884 which is of one proton present on nitrogen atom of pyrrole. The pyrrole proton C-3 shows a singlet peak at δ 7.208, C-4 singlet peak at δ 6.335 and δ C-5 singlet peak at δ 7.082. Singlet peak at δ 6.314 and δ 7.198 shows the presence of heterocyclic protons. A singlet peak at δ 2.239 indicates the presence of methyl proton.

The IR spectrum of the compound 5-cyano 3,4,5-trihydro 1N-(o-hydroxybenzaldimino) 4-(pyrrolyl) 2, 6-dioxopyrimidine **(9)** shows pyrrolic NH stretching at 3312.2 cm^{-1}. A band at 2208.5 cm^{-1} shows nitrile stretching confirms the presence of nitrile group in heterocyclic moiety. The carbonyl stretching shows a band at 1695.9 cm^{-1} and C=N stretching at appears at 1583.7 cm^{-1}.

^{1}H NMR spectra of the compound **(9)** shows a singlet peak at δ 7.893 which is of one proton present on nitrogen atom of pyrrole. The pyrrole proton C-3 shows a singlet peak at δ 7.201, C-4 singlet peak at δ 6.341 and δ C-5 singlet peak at δ 7.086. Singlet peak at δ 6.331 and δ 7.198 shows the presence of heterocyclic protons. A singlet peak of hydroxyl proton appears at δ 4.825.

ABBREVIATIONS

br = broad
hrs = hours
s = singlet
pyrr = pyrrole
Het = hetrocyclic
EtOH-Ethanol
MeOD-Deuterated Methanol
$CDCl_3$-Deuterated Chloroform
NaOEt-Sodium ethoxide

CONCLUSION

Ethyl α-cyano 2-pyrrole acrylate has α,β-unsaturated double bond and electron withdrawing groups both ester and nitrile. Double bond and electron withdrawing groups are set into conjugated system becoming susceptible to nucleophilic attack. Therefore, the formation of above heterocyclic products by reaction of ethyl α-cyano 2-pyrrole acrylate and hydrazine derivatives has been best explained on the basis of initial nucleophilic addition followed by cyclization of intermediate.

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