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Syntheses and characterization of pyrrole pyrazoline heterocycles

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ABSTRACT

Over a past few years, functionalized cyanovinylpyrroles started attracting attention as molecular optical switches, in particular as ultrafast ones, for design of many medicinally impotant pyrrole heterocycles. Cyanovinylpyrroles are attracting attention as starting material for synthesis of biheterocyclic molecules. In the present work we have utilized ethyl α-cyano 2-pyrrole acrylate for the synthesis of pyrrole pyrazoline heterocycles. The reaction of ethyl α-cyano 2-pyrrole acrylate have been carried with hydrazides and hydrazine derivatives and reactions result in the formation of heterocyclic molecules presenting important synthesis for medicinal chemists. The structure of synthesized compounds was confirmed by spectral (IR, ^{1}H NMR) data.

KEYWORDS

Cyanovinylpyrrole;
Anticholinergic;
Isoniazide;
Antispasmodic;
Antiphlogistic.

INTRODUCTION

Cyanovinylpyrroles have rich and broad synthetic capabilities, especially high affinity to intramolecules cyclizations with participation of functional groups on the double bond, these compounds have been and are being extensively used in organic synthesis as convenient building blocks for the construction of complex pyrrole systems. Therefore, growing interest in the development of synthetic methods for the preparation of Cyanovinylpyrroles and understanding their reactivity seems quite obvious and explicable.. In working with various pyrazolone derivatives, in order to have an ideal one for the treatment of rheumatoid arthritis, many newer observations have been made, and an interesting one to record is the development of anticholinergic activity in compounds obtained by introducing a 4-pyperidinomethyl group in the pyrazolone ring[1]. The product is 2-phenyl-5-methyl-4-piperidinomethyl-3-pyrazolone, m.p.224.5°C. The compound has been found to show antispasmodic action and antiphlogistic activity[2]. The most antiarthritic successful drug1, 2-diphenyl-4-n-3, 5-pyrazolidinedioneis found to reduce[3] eosinophil count, to enhance excretion of urate salts in the urine[4], and to exert other biological activity[5].

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[6]. 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. Hydrazine hydrate, 2,4-dinitrophenylhydrazine, Isoniazide and phenylhydrazine was purchased commercially and used as such or after purification.

Ethyl α-cyano 2-pyrrole acrylate[7,10]

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 hour; using a Dean Stark apparatus. 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).

Salicyl hydrazide[8]

A mixture of 15.215g (8.45ml, 0.1mole) of methyl salicylate and 7.509g (7.29ml, 0.15mole) of 100% hydrazine hydrate in 100ml of absolute ethyl alcohol was refluxed for 10 hrs. The solution was concentrated and refrigerate for 16 hrs. White coloured precipitate obtained was filtered and recrystallised from alcohol. Yield: 6.12g (40%), m.p: 140°C-146°C.

p-nitrophenylhydrazine[9]

p-nitroaniline 5.0g (0.0356 mole) was dissolved in concentrated HCl, 10.5g (17.9ml, 0.2868 mole) in 1ml of water and cooled quickly to a 0ºC in a freezing mixture so as to obtained the hydrochloride of the base in a fine state of division. The diazotization was affected in usual way by the gradual addition of the sodium nitrite 3.0 g (0.0434 mole) in 5ml of water, cooled to 0°C. The mixture was being vigorously stirred. The stirring is continued for few minutes after the addition of nitrite solution. The solution filtered quickly and then added from a dropping funnel to the ice cold solution of sodium sulfite 20.5g (0.1621mole) in 5ml of water containing sodium hydroxide 2.0g (0.050mole).

The addition required 5 minutes then acidified to 35ml of concentrated HCl and warmed on water bath at 55°C for 3 minutes. It is left overnight, when a mass of yellow needles separated.

They are filtered, drained and the crystals heated on water bath for 7 minutes with 10ml of concentrated HCl. The color changed to orange, crystals remaining undissolved. After cooling for a time, the sodium salt and the nitrophenyl hydrazine hydrochloride are dissolved in water and 3.5 g (0.025 mole) of a cold saturated solution of sodium acetate added when the base separated. Compound was recrystalised from alcohol. Yield: 2.10g (38.4%), m.p: 155-156°C (157°C reported).

Physico-chemical techniques

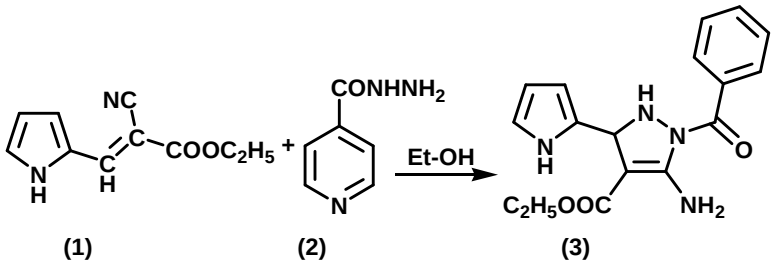
TLC was routinely used to check the formation and status of products on silica Gel-G or alumina. Ambassador® melting point apparatus based on electrically controlled heating device was used for melting point determination using capillary tubes open on one side and are uncorrected. Ambassador® melting 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.

Synthesis and characterization of pyrrole-pyrazoline derivatives

Synthesis of 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(isonicotinoyl) pyrazoline (3) (Scheme 1)

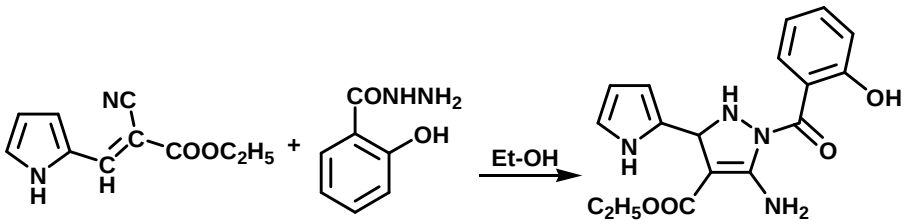
0.0190g (0.001mole) of ethyl α-cyano 2-pyrrole acrylate was dissolved in 20ml of absolute ethyl alcohol and 0.137g (0.001mole) of Isoniazide was dissolved in 20ml of ethyl alcohol.At room temperature, there was dropwise addition of solution of acid hydrazide to solution of pyrrole with stirring.No change in colour the mixture of solutions. Reflux the solution mixture for 19 days. Major portion of the compound was separated through column chromatography.

Yield: 60 mg (18.32%), m.p.: At 159ºC rises up in capillary with melting and vapours in the middle of the capillary. IR (KBr) cm^{-1}: 3270.5 (NH, pyrr), 1658.9 (C=O), 3452.8 (NH_2), 1613.7 (C=N) 2963.4



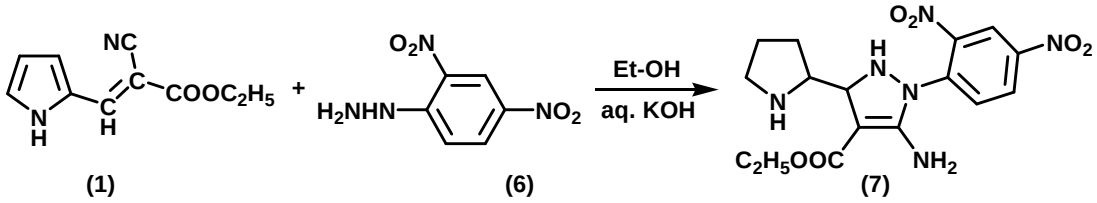
(1) (2) (3)

Scheme 1



(1) (4) (5)

Scheme 2



(1) (6) (7)

Scheme 3

(CH_3), 2858.2 (CH_2). ^{1}H NMR ($CDCl_3$) δ in ppm: 9.713 (br, 1H, pyrr), 6.274 (br s, NH), 6.982 (s, 1H, C_3, pyrr), 6.543 (s, 1H, C_4, pyrr), 6.909 (s, 1H,C_5, pyrr), 7.606 (s, 1H, C_5 Het.) 8.093 (s, 2H, NH_2), 7.668 (d, 2H, pyridine C_3-H and C_5-H), 8.788 (d, 2H, pyridine C_2-H and C_6-H), 0.901 (t, 3H, CH_3), 4.314 (q, 2H, CH_2).

Synthesis of 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(o-hydroxybenzoyl) pyrazoline (5) (Scheme 2)

0.190 g (0.001 mole) of ethyl α-cyano 2-pyrrole acrylate was dissolved in 15 ml of absolute ethyl alcohol and 0.1521 g (0.001 mole) of salicylhydrazide in 15 ml. At room temperature, salicylhydrazide solution was added pyrrole with stiring. No change in colour of the mixture of solutions was noticed. Solution was refluxed for 35 days. Compound constituting major portion was separated through column chromatography.

Yield 62 mg (18.54 %), m.p.: At 145ºC color changes from bluish green to brown. At 180ºC move upward with melting. IR (KBr) cm^{-1}: 3288.9 (NH, pyrr), 1620.2 (C=O), 3432.0 (NH_2), 2966.6 (CH_3), 2926.6 (CH_2). ^{1}H NMR ($CDCl_3$) δ in ppm: 9.729 (br, 1H, pyrrole), 7.476 (s, -NH), 7.449 (s, 1H, C- 3, pyrr), 6.992 (dd, 1H, C-4, pyrr), 7.059 (d, 1H, C-5, pyrr), 7.346 (s 1H, C- 5 Het.) 8.010 (s, 2H, NH_2), δ 0.900 (t, 3H, CH_3), 2.409 (q, CH_2), 11.793 (br, s, 1H, OH).

Synthesis of 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(2, 4- dinitrophenyl) pyrazoline (7) (Scheme 3)

0.0951 g (0.0005 mole) of ethyl α-cyano 2-pyrrole acrylate was dissolved in 20 ml of absolute ethyl alcohol and 0.0990 g (0.0005 mole) of 2,4-dinitrophenylhydrazine in 100 ml. Both the solutions were mixed. In above solution 1.0 ml 1N KOH solution was mixed with stirring. Quick change in color from yellowish brown to dark brown was observed. Stirring was continued and after 3 days, dark brown black colored precipitate obtained. Precipitate was filtered, washed with 5 ml of water and dried in air.

Yield: 30 mg (7.72%), m.p.: At 180ºC vapor observed in the middle of the capillary followed with brown ring. Further no change up to 290ºC. IR (KBr) cm^{-1}:

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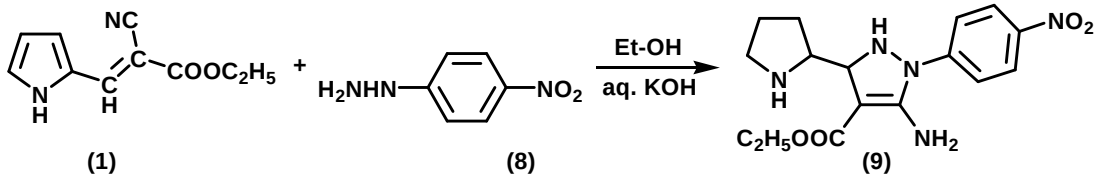
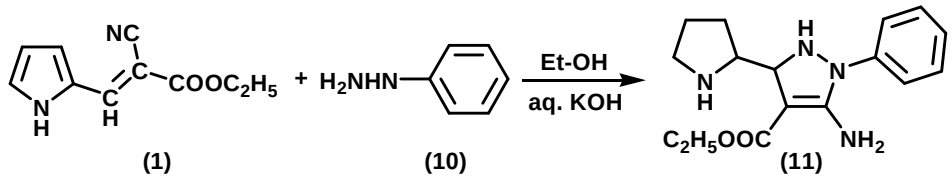


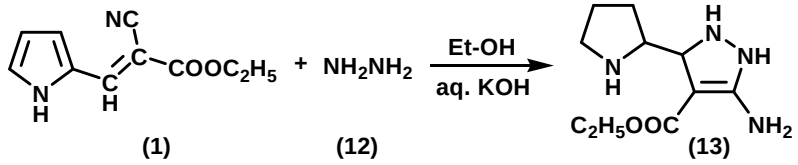
(1) (8) (9)

Scheme 4



(1) (10) (11)

Scheme 5



(1) (12) (13)

Scheme 6

3451.9 (NH, pyrr), 1654.0 (C=O), 1401.0 (NO_2 & NH_2).

Synthesis of 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(4-nitrophenyl) pyrazoline (9) (Scheme 4)

0.1902 g (0.001 mole) of ethyl α-cyano 2-pyrrole acrylate was dissolved in 20 ml of absolute ethyl alcohol and 0.1531g (0.001mole) of p-nitrophenylhydrazine in 20 ml. Both the solutions were mixed. 1.0 ml 1N KOH solution was added in above solution with stirring. Quick change in color from yellowish brown to dark brown was observed. Stirring was maintained and after 3 days black colored precipitate obtained. The precipitate was filtered and washed with 10 ml of water and dried in air.

Yield: 150 mg (43.68%), m.p.: At 120ºC some vapour was seen in the middle portion of capillary. Further no change up to 280ºC. IR (KBr) cm^{-1}: 3286.0 (NH, pyrr), 3345.2 (NH_2), 2913.6 (CH_3), 2853.1 (CH_2), 1648.3 (C=O), 1490.9 (NO_2), 3009.8 (C_6H_6).

Synthesis of 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(phenyl) pyrazoline (11) (Scheme 5)

In a 50 ml round bottomed flask, 0.0190 g (0.001 mole) of ethyl α-cyano 2-pyrrole acrylate was dissolved in 15 ml of absolute ethyl alcohol and 0.108 g (0.098 ml, 0.001 mole) of phenyl hydrazine was mixed. I above solution mixture 1.0 ml of 1N KOH solution was added. On mixing color changed from light brown to dark greenish. After 49 hrs, black colored precipitate obtained. Filtered the precipitate and washed with a 5 ml of ethyl alcohol and dried in air.

Yield: 30 mg (7.72%), m.p.: At 120ºC some vapours observed in the middle portion of capillary. Further no change up to 290ºC. IR (KBr) cm^{-1}: 3412.0 (br,NH, pyrr), 1630.0 (C=O), 2918.6 (CH_3), 2853.1 (CH_2).

Synthesis of 3-amino 4-carbethoxy 5-(2-pyrrolyl) pyrazoline (13) (Scheme 6)

In a 50 ml round bottomed flask, 0.0190 g (0.001 mole) of ethyl α-cyano 2-pyrrole acrylate was dissolved in 15 ml of absolute ethyl alcohol and 0.050 g (0.04 ml, 0.001mole) of 100% hydrazine hydrate was mixed with the solution. 1.0 ml 1N KOH solution was added in above solution with stirring. Quick change in color from light brown to golden brown was observed. Vigorous stirring maintained all the while. After, 21 hrs precipitate appeared. Solution was further stirred for 48 hrs. Precipitate was filtered and washed with 5 ml of ethyl alcohol and dried in air.

Yield: 20 mg (8.99 %), m.p.: At 200ºC vapors observed in the middle of the capillary. Further no change up to 280ºC. IR (KBr) cm^{-1}: 3416.4 (NH, pyrr), 1630.8

(C=O) 2802.3 (CH_3), 2629.4 (CH_2).

RESULT AND DISCUSSION

The structure of the formed compound **(3)**, **(5)**, **(7)**, **(9)**, **(11)** and **(13)** are given on the basis of their spectral analysis. The IR spectrum of the compound 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(isonicotinoyl) pyrazoline **(3)** shows pyrrolic NH stretching at 3270.5 cm^{-1}. The carbonyl stretching shows a band at 1658.9 cm^{-1}. A band at 1613.7 Cm^{-1} shows the presence of (C=N) stretching. The band at 3452.8 Cm^{-1} indicated the presence of (NH_2) stretching. Methyl group show a stretching band at 2963.4 cm^{-1}.

^{1}H NMR spectra of the compound shows a broad absorption at δ 9.713 of pyrrolic NH.A broad peak at δ 6.274 indicated the presence of the proton of heterocyclic NH. Three singlet peaks at δ 6.982, δ 6.543 and δ 6.909 shows protons of pyrrolic C-3, C-4, and C-5. Two singlet peaks at δ 7.606 and δ 8.093 show the presence of heterocyclic proton and proton of amino groups. The band at δ 7.668 and at δ 8.788 shows the presence of protons of pyridine. A peak at δ 0.901 shows the proton of methyl group. Above information gives the structure of the compound as **(3)**.

The IR spectrum of the compound 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(o-hydroxybenzoyl) pyrazoline **(5)** shows pyrrolic NH stretching at 3288.9 cm^{-1} The carbonyl stretching show a band at 1620.2 cm^{-1}. A band at 3432 cm^{-1} shows the presence of NH_2 stretching. Methyl group show a stretching band at 2966.2 cm^{-1}. A band at 2926.6 cm^{-1} shows the presence of methylene group.

^{1}H NMR spectra of the compound shows a broad absorption at δ 9.729 of pyrrolic NH. A broad peak at δ 7.476 indicated the presence of the proton of heterocyclic NH. Three singlet peaks at δ 7.449, δ 6.992 and δ 7.059 shows protons of pyrrolic C-3, C-4, and C-5. Two singlet peaks at δ 7.346 and δ 8.010 shows the presence of heterocyclic proton and proton of amino group. A peak at δ 0.900 shows the proton of methyl group. A broad peak at δ 11.793 shows the proton of OH group. Above information gives the structure of the compound as **(5)**.

The IR spectrum of the compound 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(2, 4- dinitrophenyl) pyrazoline **(7)** shows a broad band at 3451.9 cm^{-1} indicating the presence of pyrrolic NH stretching as well as heterocyclic NH stretching. A band at 1401.0 cm^{-1} indicates the presence of NO group. A band at 1654.0 cm^{-1} indicates the carbonyl group. Above information gives the structure of the compound as **(7)**.

The IR spectrum of the compound 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(4-nitrophenyl) pyrazoline **(9)** shows a band at 3286.0 cm^{-1} indicate the presence of pyrrolic NH stretching. A band at 3345.2 cm^{-1} shows the presence of amino group. Two bands at 2913.6 cm^{-1} and at 2853.1 cm^{-1} shows the presence of methyl and methylene group stretching. A band at 3.009.8 cm^{-1} shows the stretching of aromatic CH. A band at 1648.3 cm^{-1} shows the carbonyl stretching. The band at 1490.9 cm^{-1}indicates the presence of nitro group. Above information gives the structure of the compound as **(9)**.

The IR spectrum of the compound 3-amino 4-carbethoxy 5-(2-pyrrolyl) 2N-(phenyl) pyrazoline **(11)** shows a broad band at 3412.0 cm^{-1} indicating the presence of pyrrolic NH as well as NH stretching of the heterocyclic NH. A band at 1630 cm^{-1} shows the presence of carbonyl group. Above information gives the structure of the compound as **(11)**.

The IR spectrum of the compound 3-amino 4-carbethoxy 5-(2-pyrrolyl) pyrazoline **(13)** shows a broad band at 3416.4 cm^{-1} indicate the presence of pyrrolic NH stretching as well as NH stretching of heterocyclic ring. A band at 2802.3 cm^{-1} and at 2629.4 cm^{-1} shows the presence of methyl and methylene groups. A band at 1630.8 cm^{-1} shows the presence of carbonyl group. Above information gives the structure of the compound as **(13)**.

CONCLUSION

Over the past few years, functionalized C-Vinylpyrroles are attracting attention as starting material for synthesis of biheterocyclic molecules. Structural elements A, B, have been extensively studied as building blocks for the synthesis of various representatives of the pyrrole family, especially condensed heterocycles genetically related to pyrrole, (Scheme 7).

Our research group first utilized the Ethyl α-cyano 2-pyrrole acrylate for synthesis of biheterocycles con-

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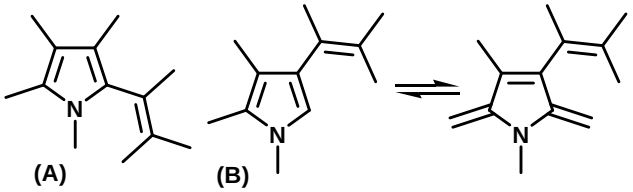

Scheme 7

taining pyrrole. Few reactions of Ethyl α-cyano 2-pyrrole acrylate were designed and carried out with hydrazine, aromatic hydrazines and hydrazides. The formed products have been characterized and are being presented in this paper.

ABBREVIATIONS

br = broad
hrs = hours
s = singlet
t= triplet
q = quartet
pyrr = pyrrolic
Het = hetrocyclic
EtOH = Ethanol
MeOD = Deuterated methanol
$CDCl_3$ = Deuterated chloroform
KOH = Potasium hydroxide

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