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RESEARCH ARTICLE

Synthesis and Characterization of Some New Pyrazole Derivatives

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Abstract

This work contain many steps starting from esterification of isophthalic acid to yield diester compound [I] which was converted to their acid hydrazide [II], then the later compound reacted with ethylacetoacetate to yield pyrazol-5-one compound [III]. Afterword added acetyl chloride to give the compound [IV], the reaction of this compound with theiosemicarbazide led to produce a new carbothioamide compound [V], which was reacted with ethyl chloro acetate to yield the thioxoimidazolidin compound [VI]. The condensation reactions of this compound with different substituted aldehyde give new alkene derivatives [VII] a-d. The synthesized compounds were characterized by melting points, FT-IR, 1H-NMR and Mass spectroscopy.

Keywords: *Pyrazole, Heterocyclic, Isophthalic acid, Acid hydrazide, Alkene derivatives.*

Introduction

Pyrazole is important class in synthesis organic compounds [1] the structures of Pyrazole have five heteroring with two nitrogen atoms. The molecules that containing pyrazole unit can used in many applications for example technology and pharmacology as anticancer [2], antioxidant also in antiviral agents [3, 4].In recent years pyrazoles unites have very important types of structures for this found many methods to synthesis this compounds.

Many routes used to modification synthesis of pyrazole unite, the first of this via the Knorr [5]. In nowadays routes for synthesis substituted pyrazoles as [(1)] Cyclo condensation reaction the hydrazine and carbonyl compounds, many workers used this method to synthesized subsitituted pyrazoles such as: reported the reaction [6] phenyl hydrazine and 1, 3- diketone derivatives this lead synthesized substituted pyrazole in good yield. Also, Girish et al [7].

Synthesized of compounds have pyrazole rings via reaction the phenyl hydrazine, ethyl acetoacetate and nano- ZnO catalyzed. In addition pyrazole was synthesized from dipolar cyclo addition reaction [8-10]. In this work we adopted the first methods to synthesis new subsitituted pyrazoles and their derivatives.

Materials

The all compounds were providing via Merck, Fluka and Aldrich chemicals companies.

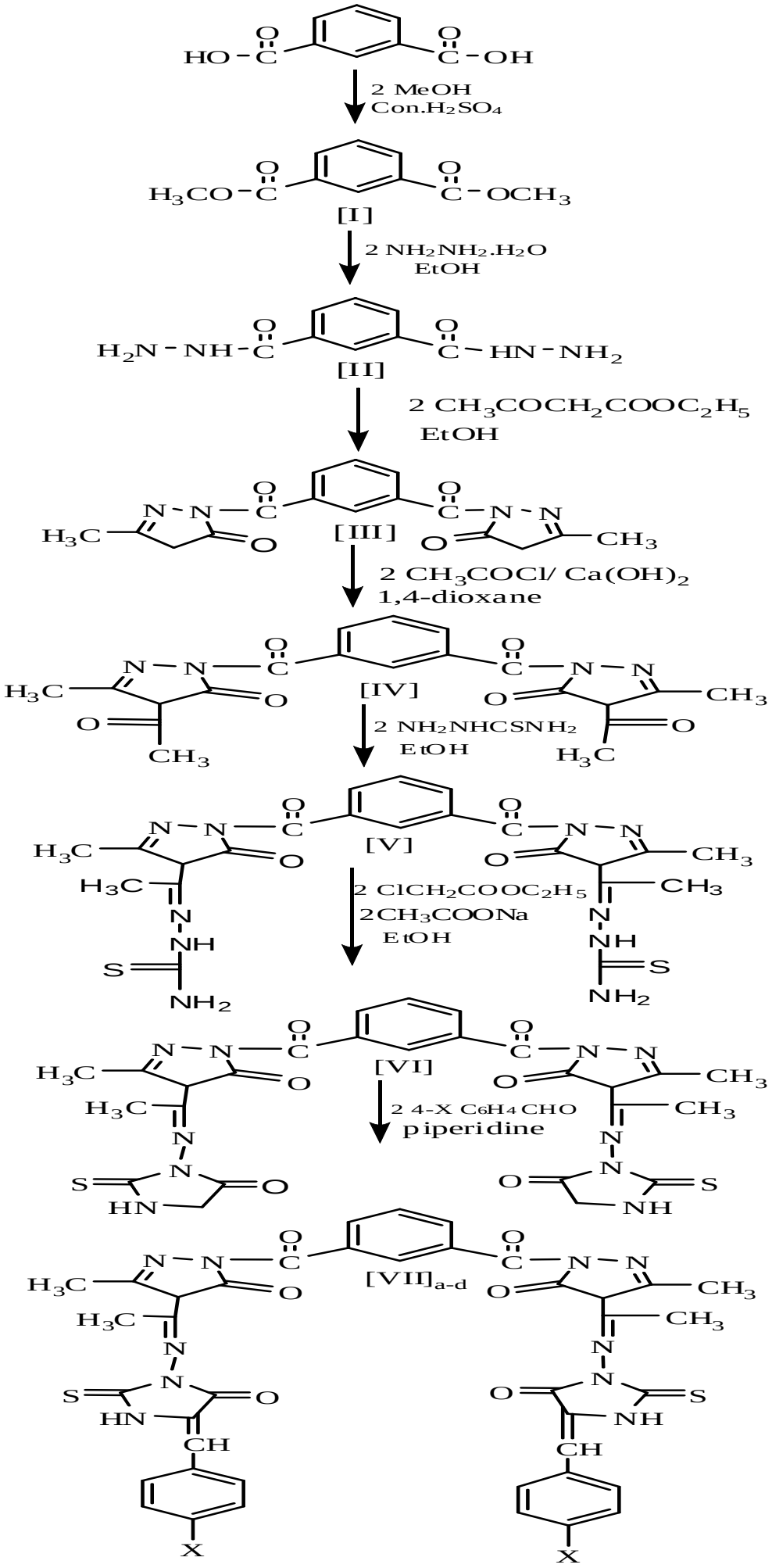
Techniques

The FTIR spectra were measured as KBr disk by a Shimadzu 600 FTIR spectrometer in the range 4000-400 cm^{-1}. The ^{1}H-NMR spectra were acquired in DMSO–$d_6$solutionby a Bruker 400 MHz spectrometer with tetramethylsilane (TMS) as an internal reference.

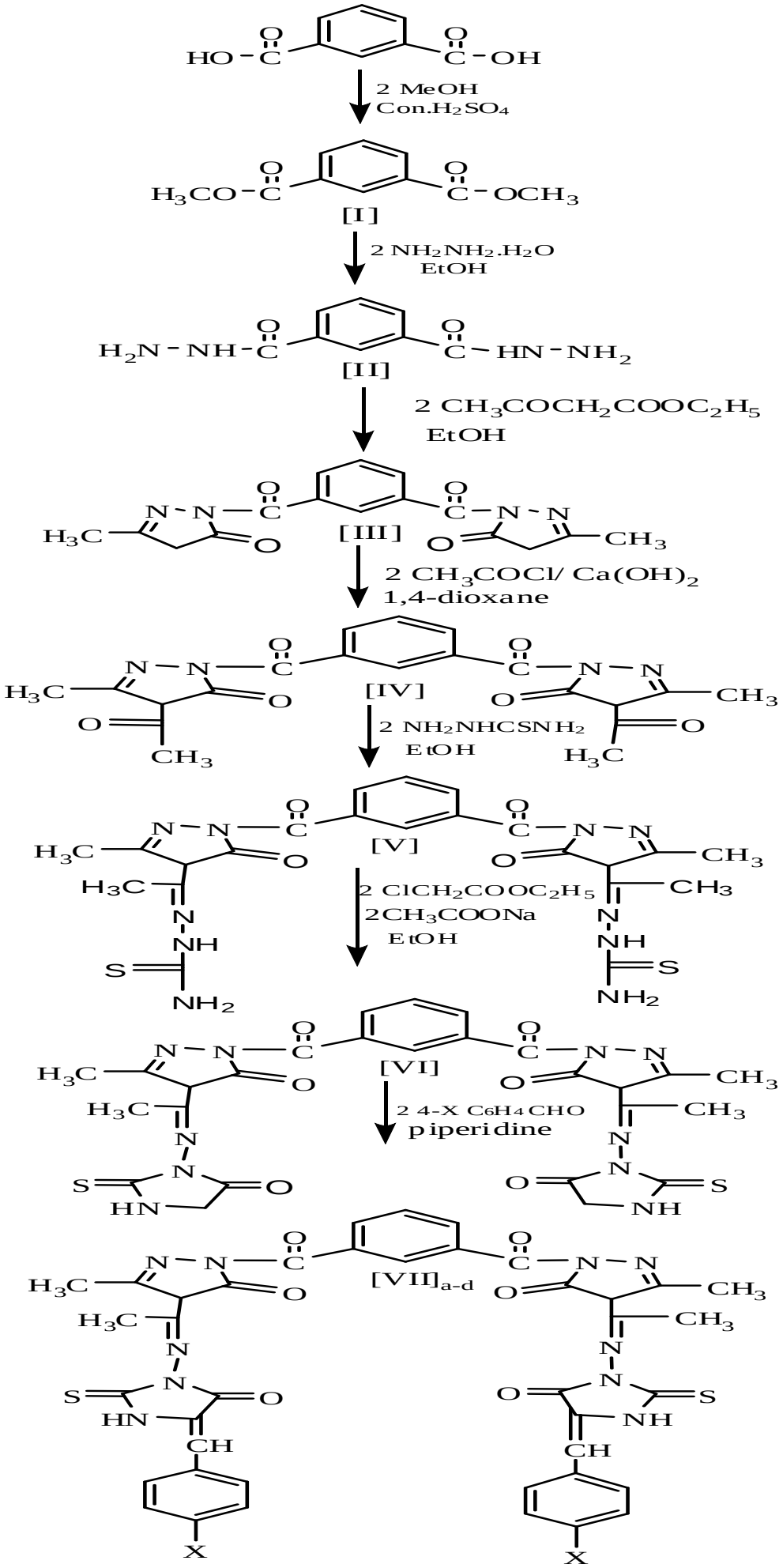
Mass spectra of compounds were measured by Electron Impact (EI) 70eVmass using a MS Model: 5975C VL MSD with Tripe-Axis Detector spectrometer .The melting points measured via Hot-Stage, Gallen Kamp.

Synthesis

The routes for synthesis new compounds as according to the Scheme1.



X=H,CH_3,OCH_3,NO_2



X=H,CH3,OCH3,NO2

Scheme 1:

Preparation of Dimethylisophthalate [I]

A mixture of isophthalic acid (40.846 gm, 0.246 mol), in absolute methanol (200mL) and H_2SO_4 (5.4 mL) then refluxed (6 hrs). After cooling washed the mixture with sodium bicarbonate solution, then washed with water several times [11], dried then used ethanol to recrystallize. The color white powder, yield 71%, m.p. = 67-69 °C.

FTIR (ν /cm^{-1}): 1714(C=O), 1190(C-O).

Preparation of Isophthalic Acid Hydrazide [II]

A mixture of ester compound [I](0.006 mol) and 80% hydrazine hydrate 3mL in absolute ethanol 5mL was refluxed for (3 hrs). The mixture was cooled at room temperature, solvent was evaporated[12] and the solid formed collected then used ethanol to recrystllized, off white powder, yield 89%, m.p. = 220-222°C,FTIR (ν /cm^{-1}): 3280-3188 (NH_2,NH),1654(C=O amide).

Synthesis of di (3-methyl)-1H-pyrazol-5(4H)-one) isophthalo [III]

A mixture of acid hydrazide [II] (0.54g, 0.0028 mole), ethyl -acetoacetate (0.728 g, 0.0056 mole) in absolute ethanol (20 mL) refluxed for (3hrs.).The cured product was allowed cool and be formed precipitate on cooling filtered and recrystallized by ethanol, pal yellow powder, yield 91% , m.p. =129-131°CFTIR (ν /cm^{-1}): 2981-2893 (C-H aliph.), 1682(C=O lactam), 1645(C=O amide), 1639 (C=N), 1604 (C=C). ^{1}H NMR (400 MHz, DMSO-d6): δ/ppm =8.73-7.57 (m, 4H, Ar-H), 3.31 (s, 2H, at C4 of pyrazole ring), 1.96 (s, 3H, CH_3 at C3 of pyrazole ring).

Synthesis of di (4-acetyl-3-methyl-1H-pyrazol-5 (4H)-one) isophthalo [IV]

1, 4-Dioxanesolution (25 mL) of compound [III] (4.23g, 0.013 mole) and acetyl chloride (2.05 g, 0.026 mole) refluxed 4 hrs. in oil bath with calcium hydroxide (2.8 g, 0.38 mole) then cooled. After that the resulted was added to the dilute hydrochloric acid (4.5 mL of concentrated HCl in water 20 mL). The crude product was collected by filtrations and washed several times with water.

Recrystallized by ethanol, brown powder, yield 69% , m.p. =102-104 °C,FTIR (ν /cm^{-1}): 2983-2873 C-H aliph.),1704(C=O ketone), 1695(C=O lactam), 1647(C=O amide), 1610 (C=N), 1600 (C=C),^{1}H NMR (400 MHz ,DMSO-d6): δ/ppm =8.46-7.02 (m, 4H, Ar-H), 3.81 (s, 1H, at C4 opyrazolef ring), 2.98 (s ,3H, $COCH_3$), 1.91 (s, 3H, CH_3 at C3 of pyrazole ring).

Synthesis of di (2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4 yl)ethylidene) hydrazine carbothioamide) isophthalo [V]

The iosemicarbazide (1.82 g, 0.02 mol) was added to compound [IV] (4.1g, 0.01 mol) with EtOH (20 mL) and three drops of GAA. The mixture then was refluxed 3hrs. The product cooled after that filtered the product.

Recrystallized by ethanol, brown powder , yield 73% , m.p. =138-140°C, FTIR (ν /cm^{-1}): 3452-3178(NH_2,NH), 2981-2854(C-H aliph..),1689(C=O lactam), 1643 (C=O amide), 1620 (C=N), 1595 (C=C), 1249 (C=S),^{1}H NMR (400 MHz ,DMSO-d6): δ/ppm = 9.10(s,1H,NH), 8.60-6.94 (m, 4H, Ar-H), 4.12(s,2H,NH_2), 3.43 (s, 1H, at C4 of pyrazole ring), 2.56(s, 3H, CH_3 at C3 of pyrazole ring),1.88 (s ,3H, CH_3C=N).

Synthesis of di (3-methyl-4-(1-(5-oxo-2-thioxoimidazolidin-1-ylimino) ethyl)-1H-pyrazol-5(4H)-one) isophthalo [VI]

A mixture of compound [V] (0.55g, 0.001 mole), ethyl chloro acetate (0.25g, 0.002 mole) and fused sodium acetate (0.49g, 0.006mole) in ethanol then refluxed 4 hrs. After that cooled then poured onto water. The product was filtered, washed via water, dried.

Recrystallized from ethanol, the color is yellow, yield 65%, m.p. =160-162 dec· °C. FTIR (ν /cm^{-1}): 3250(NH),2985-2882(C-H aliph.),1710(C=O lactam), 1646(C=O amide), 1625 (C=N), 1600 (C=C), 1254 (C=S),^{1}H NMR (400 MHz ,DMSO-d6): δ/ppm =9.79(s,1H,NH), 8.34-6.83 (m, 4H, Ar-H), 3.98(s, 1H, at C4 of pyrazole ring), 3.65 (s,2H ,CH_2 at C4 of imidazolidinone ring),2.43(s, 3H, CH_3 at C3 of pyrazole ring), 1.76(s ,3H, CH_3C=N-).

Synthesis of Compounds [VII] a-d

A mixture of compound [VI] (6.36g, 0.01 mole) and different aromatic aldehyde (0.02 mole) was refluxed in presence of piperidine (0.5Ml) for 3 hrs. After that cooled the product then poured onto cold water. Filtered the solid, washed, dried then recrystallized from acetone.

Data of the Compound [VII]$_a$

The color yellow, yield 50%, m.p. =188-190 dec. °C, FTIR (ν /cm^{-1}): 3396(NH), 2931-2856(C-H aliph.), 1710(C=O lactam), 1656(C=O amide), 1625(C=N), 1600(C=C), 1259 (C=S).

Data of the Compound [VII] $_b$

The color yellow, yield 45% , m.p.=218-220 dec.°C, FTIR (ν /cm^{-1}): 3320(NH),2935-2860(C-H aliph.),1702(C=O lactam), 1642(C=O amide), 1622 (C=N), 1605 (C=C),1263(C=S), ^{1}H NMR (400 MHz ,DMSO-d6): δ/ppm =13.03 (S, 1H, NH), 8.51-7.64 (m, 12H,Ar-H),7.03(s,1H,-CH=C-), 3.99(s,1H,at C4 of pyrazole ring), 2.22(s, 3H, CH_3 at C3 of pyrazole ring),1.86(s,3H,CH_3 at phenyl ring), 1.19(s,3H,CH_3C=N-).

Data of the Compound [VII]$_c$

The color yellow, yield 68%, m.p. gummy, FTIR (ν /cm^{-1}): 3269(NH), 2931-2823(C-H aliph.), 1695(C=O lactam), 1658(C=O amide), 1620 (C=N), 1593 (C=C), 1261(C=S).

Data of the Compound [VII]$_d$

The color red, yield 71%, m.p. gummy, FTIR (ν /cm^{-1}): 3369(NH), 2931-2856(C-H aliph.), 1696(C=O lactam), 1663(C=O amide), 1625 (C=N), 1600 (C=C), 1517(NO_2), 1253(C=S).

Results and Discussion

The synthetic routes of new compounds [VII]$_{a-d}$ is outlined in Scheme 1. The reaction of isophthalic acid with absolute methanol in presence of sulfuric acid resulted the ester compound [I]. The FTIR spectrum for compound [I]a display absence absorption stretching bands O-H and C=O groups (carboxylic moiety) for compounds reaction together presents of new bands at (1714) cm^{-1}and (1190) cm^{-1}assigned to C=O and C-O groups of ester moiety, respectively.

Subsequently, the reaction of compound [I] with with80% hydrazine hydrate in ethanol gave isophthalic acid hydrazide compound [II]. FTIR spectrum of compound [II]$_a$ display stretching vibration asymmetry and symmetry of NH_2 and NH groups in the region (3280-3188)cm^{-1} as well as stretching absorption at (1654) cm^{-1}for υ C=O (amide) with disappearance of absorption stretching bands due to ester group. When the reacted acid hydrazide with ethylacetoacetate in absolute ethanol, pyrazole compound [III] was formation. FTIR spectrum for compound[III] display absence of bands of NH_2 and NH groups with appearance of new stretching bands in (2981-2893) cm^{-1} for (C-H aliph.) groups in addition to display absorption band (C=O lactam) group in (1682 cm^{-1}), stretching band at 1645 cm^{-1} for (C=O amide) groups, stretching band in 1639 cm^{-1} for (C=N) groups also band in 1604 cm^{-1} for (C=C) group.

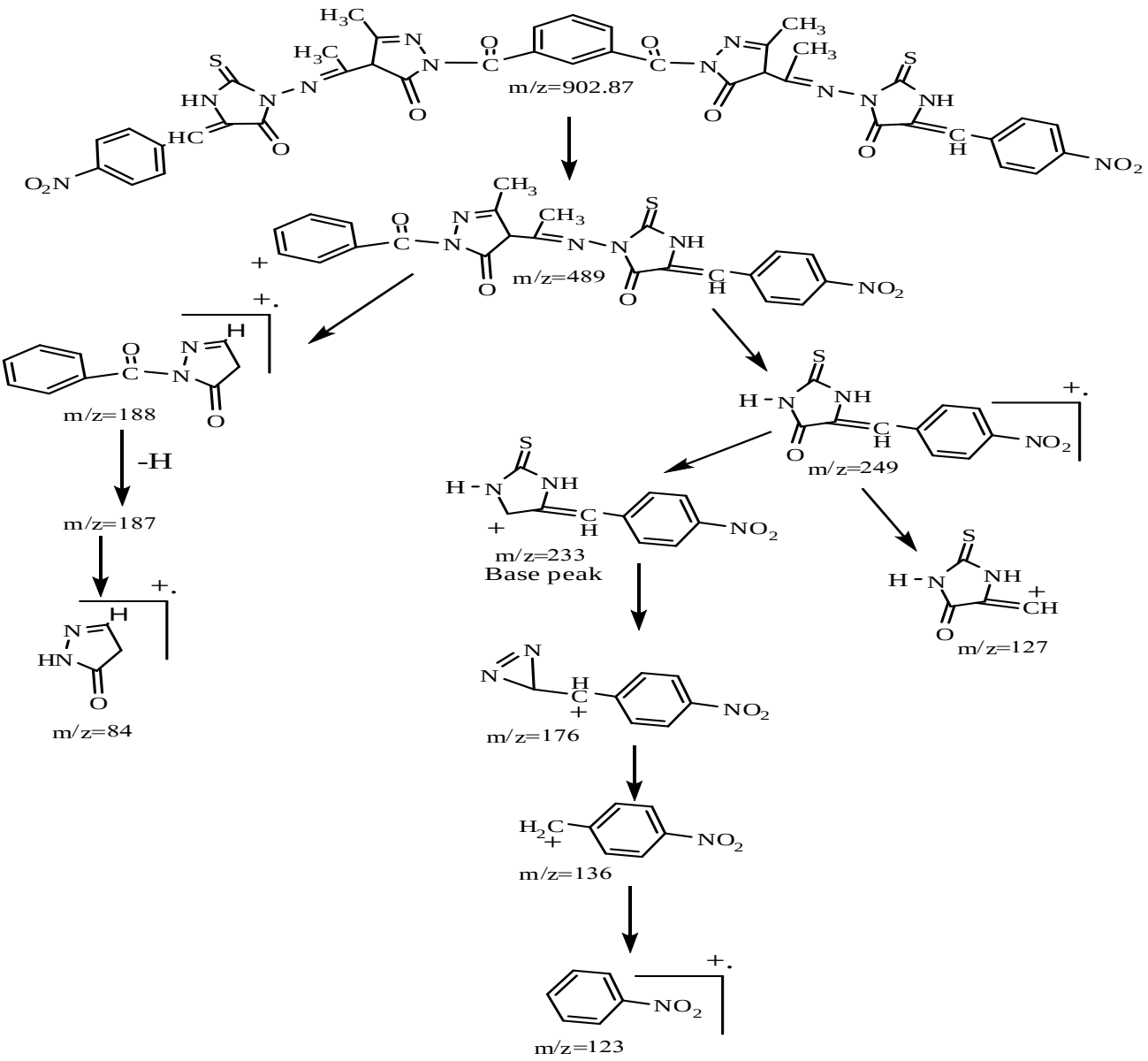
The synthesis of di (4-acetyl-3-methyl-1H-pyrazol-5 (4H)-one) isophthalo [IV] was achieved by heating at reflux compound [III] with acetyl chloride and calcium hydroxide in 1,4-Dioxane medium. The FTIR spectrum for compound [IV] showed appearance of new stretching band at 1704 of (C=O) ketone group. After that the compound [IV] reacted with theiosemicarbazide and few drops of GAA to product compound [V].

FTIR spectrum for the compound[V] display absence band (C=O) ketone group with the appearance bands (C=N) group at 1620 cm^{-1} and showed absorption stretching band of asymmetry and symmetry of NH_2 and NH groups in the region (3452-3178)cm^{-1}. The compound [VI] was obtained from reacted the compound [V] with ethyl chloro acetate and fused sodium acetate in ethanol. The FTIR spectrum for compound [VI] showed absorption stretching band NH group in 3250 cm^{-1}and showed stretching band (C=O lactam)[13] in 1710 cm^{-1} also showed absorption band at 1254 cm^{-1}for (C=S) group.

Finally, the compounds [VII]$_{a-d}$ synthesized from reacted the compound [VI] and different aromatic aldehyde in presence of piperidine medium. The FTIR spectra for compounds [VII]$_{a-d}$ display bands NH groups at region (3396-3269)cm^{-1} and bands C=O groups of endo cyclic at region(1710-1695)cm^{-1} while C=O groups for amide showed at region(1663-1642)cm^{-1} also showed absorption stretching bands of C=N groups at region(1625-1620)cm^{-1} . The ^{1}HNMR spectral data of these compounds give good evidence for synthesized these compounds, as follow:

The ^{1}HNMR spectrum of compound [III] display many signals in rang at (8.73-7.57) ppm of four aromatic protons and singlet signal in 3.31 ppm for two protons at C4 of pyrazole ring also showed singlet signal in 1.96 ppm of three protons of CH_3 group at C3 of hetero ring. On the other hand the ^{1}H

NMR of compound [IV] display many signals at rang (8.46-7.02) ppm of four aromatic protons, singlet signal in 3.81 ppm for one proton at C4 of pyrazole ring and singlet signal in 2.98 ppm of three protons for $COCH_3$ group and singlet signal in 1.91 ppm of three protons for CH_3 group at C3 of pyrazole ring. While the ^{1}HNMR of compound [V] display singlet signal in 9.10 ppm of one proton for NH group, many signals at rang (8.60-6.94)ppm of four aromatic protons, singlet signal in 4.12 ppm of two protons for NH_2 group, singlet signal in 3.43ppm of one proton at C4 for pyrazole ring also showed singlet signal at 2.56 ppm of three protons for CH_3 group at C3 of pyrazole ring also singlet signal in 1.88 ppm of three protons for (CH_3C=N-) group [14]. The ^{1}HNMR spectrum of compound [VI] display singlet signal in 9.79 ppm of one proton for NH group[15,16], many signals in region at (8.34-6.83)ppm of four aromatic protons, singlet signal at 3.98 ppm for one proton at C4 of pyrazole ring, singlet signal in 3.65ppm of two protons for CH_2 imidazolidinone ring also showed singlet signal at2.43 ppm of three protons of CH_3 group at C3 of pyrazole ring also singlet signal in 1.76 ppm of three protons for (CH_3C=N-) group. Finally, the ^{1}HNMR spectrum for compound $[VII]_b$ display singlet signal in 13.03ppm of one proton for NH group, many signals at rang (8.51-7.64)ppm of twelve aromatic protons, singlet signal in 7.03ppm of one proton of (-CH=C-) group, also singlet signal in 3.99 ppm of one proton at C4 of pyrazole ring also showed singlet signal in 2.22 ppm of three protons of CH_3 group at C3 of pyrazole ring, singlet signal in 1.86 ppm of three protons of CH_3 group at phenyl ring also singlet signal in 1.19 ppm of three protons for(CH_3C=N-) group. The mass fragment for compound $[VII]_d$ as in Scheme(2).



Scheme2: The mass fragment for compound $[VII]_d$

Conclusions

Pyrazole represent a major class of organic compounds and used some of these derivatives that containing pyrazole unite in therapeutic purposes , therefore modification of the pyrazole structure have allowed using multistep processes to the synthesized of new derivatives may be having a broad spectrum of biological activity.

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