

Synthesis of some 5-methyl-4-(diazo-4-(heteroaryl) phenyl)-pyrazolone derivatives

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ABSTRACT

A group of α , β unsaturated carbonyl compounds, as intermediates were prepared by diazotization of para amino acetophenone, coupling followed by cyclization with hydrazine derivatives. The hetero aryl methyl ketones upon reaction with aromatic aldehydes under basic condition, furnished the corresponding α , β unsaturated carbonyl compounds. These intermediates were allowed to cyclize with hydrazine derivatives, hydroxyl amine and thiourea to form pyrazole, isoxazole and thiopyrimidine derivatives respectively. The structures of synthesized compounds were confirmed by IR, UV, (¹H, ¹³C) –NMR and MS.

Keywords: α , β unsaturated carbonyl compounds, pyrazole, isoxazole, thiopyrimidine derivatives.

INTRODUCTION

α , β unsaturated carbonyl compounds can be prepared by condensing arylketones with aromatic aldehydes in presence of condensing agents. They are associated with a wide range of biological activities such as anti-inflammatory, antimicrobial, antifungal, antioxidant, cytotoxic, antitumor and anticancer activities (Kalirajan et al., 2009). These compounds were known to undergo a variety of chemical reactions in synthesis of variety of heterocyclic compounds (Pande&Saxena.,1987), pyrazole derivatives(Fedele et al., 2005), Isoxazole derivatives (Tang et al,2009, Jiang et al,2009) and pyrimidine derivatives (Gilchrist et al.,1997, Manish et al., 1998, Bhujan et al.,2011, Baddy et al., 1944, Hayamh et al.,2010, Ekhllass et al.,2010,Nielsen et al., 1995). These derivatives were possess biological properties (Anness et al., 2010, Ahmedet al.,2005,(Onyilagna et al.,1997, Fischeret al.,2003, Brown et al., 1994, Vishal et al.,2012, Zoltewicz et al., 1978,Vijay et al., 2010). The present work aim to synthesize certain derivatives that were designed to possess a two side nitrogen hetero cycles separate by di azo phenyl linkage in order to be evaluate for possible anti-cancer activity.

MATERIALS AND METHODS

Melting points were uncorrected and were recorded on melting point apparatus (Gallenkmp, England) by using open capillary tube. IR spectra were record on FTIR spectrometer (Perkin Elmer model 8400s) using KBr disc method, NMR(¹H, ¹³C) spectra were record on (Brucker AMX 400 MHZ) spectrometer in DMSO as solvent and TMS as internal standard. Splitting patterns were designated as follows s: singlet, d: doublet m: multiplet. Mass spectra were record on a Shimadzu GC.M.QP 1000 mass spectrometer at 70 eV.

Preparation of 3-diazo- (p- acetylphenyl)–ethyl acetoacetate I.

A solution of p- amino acetophenone(0.338g, 0.01mole) in 5ml conc. HCl was diazotized with sodium nitrite (0.01mole, 0.18g) at 0-5°C.

The diazotized solution gradually was added to ethyl acetoacetate (0.01mole, 1.30g) in 20ml ethanol and (0.02mole 1.8g) sodium acetate while the temperature was kept at 0-5°C. The reaction mixture was stirred for 2-3 hrs. at 5-10°C. The precipitated product was filtered and air dried.

Yield 64.4%, m.p 132-133°C, IR 1694cm⁻¹, 1601cm⁻¹, 1631cm⁻¹, 1513cm⁻¹.

Preparation of 4-diazo-(p-acetylphenyl)-5-methyl-1-substitued) pyrazole-3-ones II, III

Phenylhydrazinium hydrochloride or hydrazine sulfate (0.01mole) was added to 3-di azo-(acetyl phenyl)-ethyl acetoacetate (I) in 25ml ethanol and refluxed for 12-13hours. The mixture was cooled and poured into crush ice, filtered washed with water, air dried. Recrystallized from ethanol.

4-diazo-(p-acetylphenyl)-5-methyl-1-phenyl) pyrazole-3-one II

Yield 67%, m.p 143-144°C, Rf value 0.43, mobile phase ratio ethyl acetate 1: 1 petroleum ether. IR 1638cm⁻¹, 1504cm⁻¹, 1380 cm⁻¹, 1603 cm⁻¹, 1116cm⁻¹, 2958 cm⁻¹, 2200 cm⁻¹, ¹H-NMR 2.20-3.36ppm (s, 3H CH₃), 7.38, 7.87 ppm (m, 11Ar-H), ¹³C-NMR, 194.16ppm, 196.40ppm, 132ppm, 147ppm, 24.91ppm, 39.98 ppm, 114.06, 196ppm.

4-diazo-(p-acetylphenyl)-5-methyl-1-H) pyrazol-3-one III

Yield 57%, m.p 198-199°C, Rf value 0.89, mobile phase ratio ethyl acetate 3: 7 petroleum ether. IR 1674cm⁻¹, 3001cm⁻¹, 2864cm⁻¹, 1654cm⁻¹, 1056cm⁻¹, 2245cm⁻¹, 1319cm⁻¹.

General synthesis of 4-diazo-(p-(aryl)-alken-1-on)phenyl)-5-methyl-pyrazol-3-ones IV, V

Benzaldehyde derivatives (0.01mol) in 30ml ethanol 10ml sodium hydroxyl were added to 4-diazo-(p-acetyl phenyl)-5-methyl-1-substitued pyrazole-3-ones. The reaction mixture was stirred for 24 hours. Then was poured into ice -water contained small amount of concentrated hydrochloric acid, filtered, washed by water and dried, recrystallized from ethanol.

4-diazo-(p-(5-phenyl-pent-2, 4-dien-1-on)-phenyl) -5-methyl-1-phenyl-pyrazol-3-one IV

Yield 74%, m.p 144-145°C, Rf 0.84, mobile phase ratio petroleum ether 7: 3 ethyl acetate, IR 1696cm⁻¹, 1679 cm⁻¹, 1569cm⁻¹, 2233cm⁻¹, 1053cm⁻¹, 1322cm⁻¹, 1648 cm⁻¹. ¹H-NMR 7.80-7.90 ppm (m, 14Ar-H), 1.10ppm (d, 2H, CH=CH), 3.70ppm (s, 3HCH₃). ¹³C-NMR 162.61ppm, 167.18ppm, 115ppm, 119ppm, 39.12ppm.

4-diazo-(p-(3-(p-N, N-dimethyl amino phenyl)-propen-1-on) phenyl)-5-methyl-pyrazol-3-one V

Yield 52%, m.p 215-216°C, Rf 0.80, mobile phase ratio petroleum ether 7: 3 ethyl acetate. IR 1678 cm⁻¹, 1641 cm⁻¹, 1564 cm⁻¹, 2245cm⁻¹, 1054 cm⁻¹, 1329 cm⁻¹, 1630 cm⁻¹, 3284 cm⁻¹, ¹H-NMR 7.60-7.80ppm (m, 13Ar-H), 2.00-ppm (d, 2H, CH=CH), 2.40-ppm (s, 3H CH₃), 3.10ppm (6H, 2CH₃). ¹³C-NMR 162ppm, 113.66ppm, 131.78ppm, 4.23ppm, 4.73ppm, 4.23ppm, 4.73ppm, 26.29ppm, 49.66ppm.

General Synthesize of 4-diazo-(p-(5-(substitued phenyl)-pyrazol-2-phenyl-3-yl)-phenyl)-5-methyl-substued pyrazole-3-one VI, VII

A mixture of compounds (IV and V) 0.01 mole and phenyl hydrazinium hydro chloride 0.01mole in 25ml ethanol were reflux 13-16 hours. The mixture was cooled, poured into crushed ice -water washed, filtered, air dried. Recrystallized from ethanol.

4-diazo-(p-(5-(2-phenyl ethanol)-pyrazol-2-phenyl-3-yl) -phenyl)-5-methyl-1-phenyl-pyrazol-3-one (VI)

Yield 81%, m.p 116-117°C, R f value 0.93, mobile phase ratio chloroform 9: 1 methanol. IR 1662cm⁻¹, 1595 cm⁻¹, 1105cm⁻¹, 2306 cm⁻¹, 1340 cm⁻¹, 2921cm⁻¹, 2852cm⁻¹. ¹H-NMR 3.31ppm (s, 3H, CH₃), 7.00-7.50ppm (m, 19A-H), 1.23ppm (s, 1H pyrazole).

4-diazo-(p-(5-(p-N, N-dimethyl amino phenyl)-pyrazol-2-phenyl-3-yl)-phenyl)-1-H-pyrazol-3-one (VII)

Yield 88%, m.p 156-157°C, RF value 0.95, and mobile phase ratio ethanol 9: 1chloroform. IR 1602cm⁻¹, 1681cm⁻¹, 1066cm⁻¹, 2370cm⁻¹, 1367 cm⁻¹, 2921cm⁻¹, 2852cm⁻¹, 3346cm⁻¹, UV λ max (nm) 366.41, ¹H-NMR 2.40 ppm (s, 3H CH₃), 3.00ppm (s, 1H N-H), 6.90-8.30ppm (m, 8Ar-H), 3.60ppm (s, 6H NCH₃), 1.68ppm (s, 1H pyrazole).

General Synthesis of 4-diazo-(p-(5-(substitued phenyl)-isoxazol-5-yl)-phenyl)-5-methyl-substued pyrazole-3-one VIII, IX

A mixture of compound (IV and V) 0.01mole and hydroxyl amine hydrochloride 0.01 mole in 25ml ethanol and in basic condition were reflux 13-16 hours, then cooled pour into crush ice, filtered washed with water, air dried. Recrystallized from ethanol.

4-diazo-(p-(5-(2-phenylethenyl)-isoxazol-5-yl)-phenyl)-5-methyl-1-phenyl-pyrazol-3-one (VIII)

Yield 88%, m.p 122-123°C, and RF value 0.91, mobile phase ratio chloroform 9:1 methanol. IR 1596cm^{-1} , 1659cm^{-1} , 1155cm^{-1} , 2360cm^{-1} , 1070cm^{-1} , 2854cm^{-1} , 2933cm^{-1} , UV λ max(nm) 309.28, $^1\text{H-NMR}$ 7.17-7.52ppm(m, 19Ar-H), 1.23ppm(s, 1H 1isoxazole), 2.50-3.30ppm (s, 3H CH_3).

4-diazo-(p-(5-(p-N, N-dimethyl amino phenyl)-isoxazol-5-yl)-phenyl)-5-methyl-1-H-pyrazol-3-one (IX)

Yield 25%, m.p 171-17°C, Rf value 0.82, mobile phase ratio ethanol 9:1 chloroform, UV λ max (nm) 309.28. IR 1596cm^{-1} , 1676cm^{-1} , 1116cm^{-1} , 2360cm^{-1} , 1365cm^{-1} , 1031cm^{-1} , 2921cm^{-1} , 2852cm^{-1} , $^1\text{H-NMR}$ 2.00-2.50ppm(s, 3H CH_3), 6.50-8.51ppm(m, 8 Ar-H), 3.40ppm-4.00ppm(s, 6H NCH_3), 1.23 ppm (s, 1H isoxazole).

General Synthesize of 4-diazo-(p-(5-(substituted phenyl)-2-thiopyrimidine-6-yl)-5-methyl substituted pyrazole-3-one (X, XI)

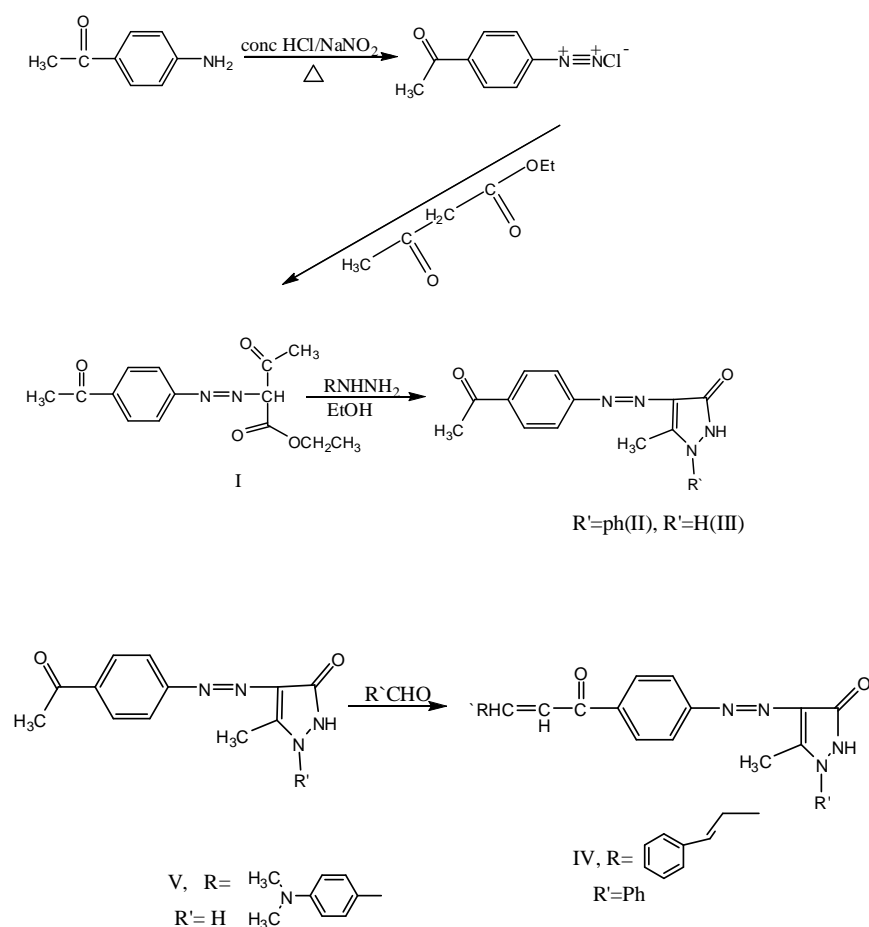
A mixture of compound (IV and V) 0.01 mole and thio urea 0.01mole in 25 ml ethanol under basic condition, reflux upon 12 hours, poured into crush ice, filtered, dried. Recrystallized from ethanol.

4-diazo-(p-(5-(2-phenylethenyl)-2-thiopyrimidine-6-yl)-phenyl)-5-methyl-1-phenyl pyrazol-3-one (X)

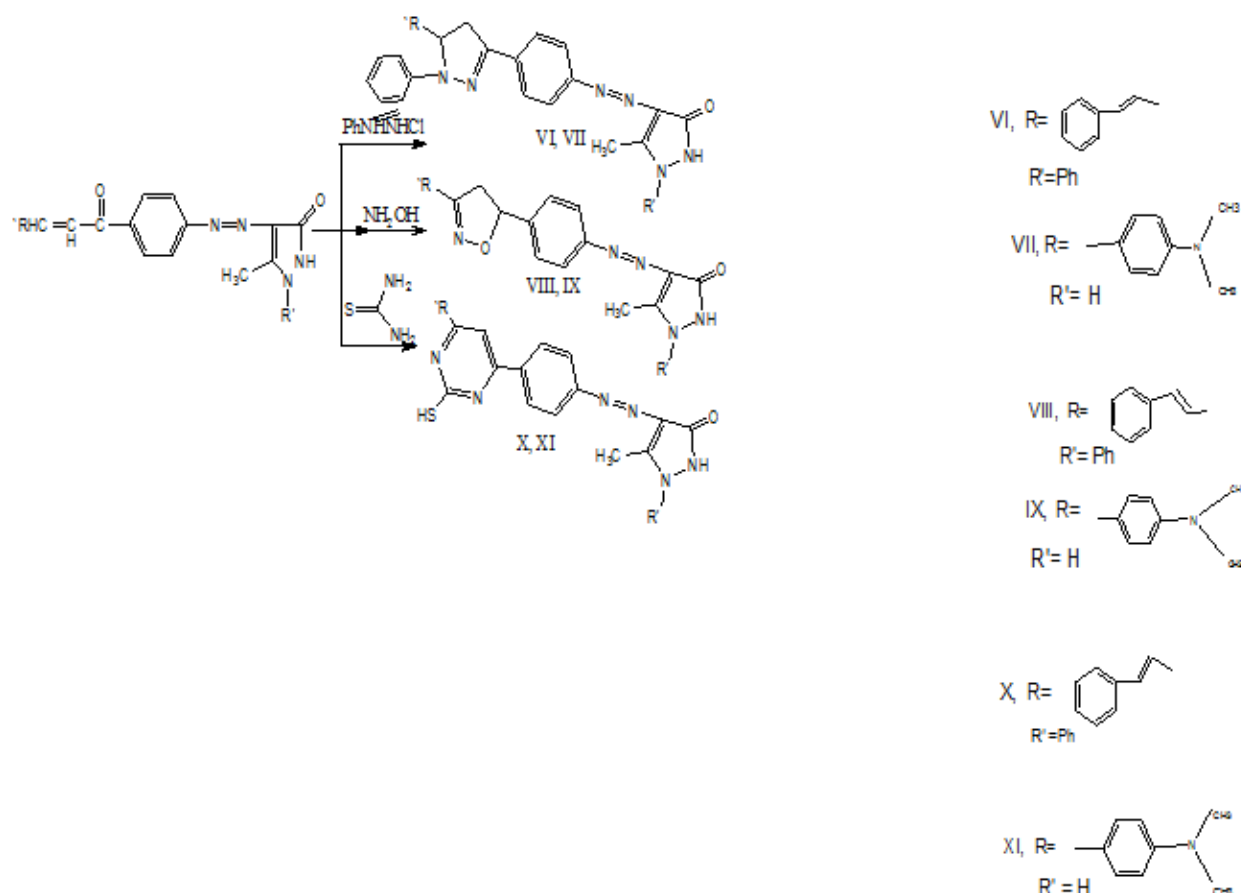
Yield 56%, m.p 163-164°C, Rf value 0.82, mobile phase ratio chloroform 7:3 methanol IR 1662cm^{-1} , 1596cm^{-1} , 1164cm^{-1} , 1369cm^{-1} , $756(\text{C-S})$, $2850(\text{S-H})$, $2918(\text{C-H})$. $^1\text{H-NMR}$ 3.13-3.33ppm(s, 3H CH_3), 1.96ppm (s, 1H pyrimidine), 4.48ppm (s, 1H SH) 7.50-7.60ppm (m, 19Ar-H).

4-diazo-(p-(5-(p-N, N-dimethyl amino phenyl)-2-thio pyrimidine-6-yl)-phenyl)-5-methyl-1-pyrazol-3-one (XI)

Yield 60%, Rf value 0.77, mobile phase ratio ethanol 9:1 chloroform, m.p 130-131°C, IR 1664cm^{-1} , 1598cm^{-1} , 1166cm^{-1} , 2340cm^{-1} , 1359cm^{-1} , 649cm^{-1} , 2855cm^{-1} , 2923cm^{-1} , 344cm^{-1} , UV λ max (nm) 296. $^1\text{H-NMR}$ 2.60ppm (s, 3H CH_3), 3.31ppm (s, 1HNH), 6.90-8.30 ppm (m, 8Ar-H), 3.90ppm (s, 6HN CH_3), 1.35ppm (s, 1Hpyrimidine), 4.30ppm (s, 1HSH).



Scheme 1. Unsaturated carbonyl aryl diazopyrazolone



Scheme 2. Hetero aryl pyrazolone

RESULTS AND DISCUSSION

All the synthesized compounds were characterized by TLC, melting point, IR, UV, NMR (^1H , ^{13}C) and mass spectroscopy. Coupling reaction with diazotized para acetophenone and ethyl acetoacetate lead to formation of the corresponding 3-acetylphenyl-diazenyl-4-ethyl acetoacetate (I), coupling with phenyl hydrazinium hydrochloride and hydrazine sulfate in ethanol under reflux condition form crossconjugated 4-diazo-(p-acetyl phenyl)-5-methyl-1-(p-(5-substituted phenyl)-5-methyl-1-substituted pyrazole-3-one) (II, III), which lead to formation α , β unsaturated compounds, the crossconjugated 4-diazo-(p-(5-substituted phenyl)-5-methyl-1-substituted pyrazole-3-one) (IV, V), when treated with derivatives benzaldehyde in ethanolic sodium hydroxide. Compounds IV, V upon cyclization with phenyl hydrazinium hydrochloride, hydroxylamine hydrochloride and thiourea in presence basic condition and ethanol lead to formation of the corresponding 4-diazo-(p-(5-(substituted phenyl) pyrazol-2-phenyl-3-yl)-phenyl)-5-methyl-1-substituted pyrazole-3-one (VI, VII), 4-diazo-(p-(5-(substituted phenyl)-isoxazol-5-yl)-phenyl)-5-methyl-1-substituted pyrazole-3-one (VIII, IX), 4-diazo-(p-(5-(substituted phenyl)-2-thio pyrimidin-6-yl)-phenyl)-5-methyl-1-substituted pyrazole-3-one (X, XI) respectively. The purity of these synthesized compounds was checked by melting point, thin layer chromatography. Further their structure was confirmed by infrared spectrum, ^1H -NMR spectra and mass spectroscopy. ^1H -NMR spectra of pyrazole derivatives showed the 19-H aromatic protons as a multiplet in region of δ 7.00-7.50 ppm, compound (VI), 8-H aromatic protons as a multiplet in region of 6.90-8.30 ppm, and a one proton of pyrazole ring at 1.23 ppm, 1.68 ppm showed as a singlet of two compounds. Isoxazole derivatives compounds showed 19-H aromatic protons as a multiplet at range 7.17-7.52 ppm of compound (VII), and 8-H aromatic protons as a multiplet in region 6.50-8.51 ppm of compound (IX), one proton showed as singlet 1.23 ppm due to one proton of isoxazole ring compounds (VI, VII). The pyrimidine derivatives showed multiplet at range 7.06-7.97 ppm due to 19-H aromatic protons as multiplet of compound (X), and 6.90-7.30 ppm due to 8-H aromatic protons multiplet for compound (XI), one proton showed singlet at 1.35 ppm, 1.96 ppm, due to proton of pyrimidine ring of compounds (X, XI), at region 4.48 ppm due to one proton of SH showed as singlet signal compound (X), at 4.30 ppm a signal showed as singlet signal due to one proton of SH of compound (XI).

CONCLUSION

In conclusion, a variety of synthesized α , β unsaturated carbonyl compounds derivatives were prepared in good yield by base catalysis include azo coupling reaction with para acetophenediazonium salt with ethyl acetoacetate, then lead to cyclisation reaction when treated with phenyl hydrazinium hydrochloride in ethanol, the reaction shown to be high facile upon reaction with phenyl hydrazinium hydrochloride, hydroxide amine hydrochloride, thio urea under condensation conditions lead to formation of pyrazole, Isoxazole, and the pyrimidine derivatives.

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