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Synthesis of 1-(5-(3-aminophenyl)-3-phenyl-4, 5-dihydro-1-H-pyrazole-1-yl) ethanone Derivatives using Acid Chloride

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Abstract: ***Pyrazoline class of compounds work as better moieties for many treatments, they have many pharmacological properties such as antibacterial, antifungal, antiinflammatory, antipyretic, diuretic, cardiovascular activities. So many endeavour are made to synthesize pyrazolines. In this work pyrazoline derivatives were efficiently synthesized in excellent yields and in less reaction time using ethanol and hydrazine hydrate. Different reagents were used to synthesize the derivatives of parent molecules by using 'nucleophilic addition reaction' way of synthesis. All the synthesized compounds were confirmed by 1HNMR and Mass spectral data.***

Keywords: ***Hydrazine hydrate, Pyrazolines, Nucleophilic addition reaction***

I. INTRODUCTION

Nitrogen containing heterocyclic compounds and their fused analogues represent an important class of heterocyclic compounds. They exist in numerous natural products, presenting a wide range of biological and pharmaceutical activities. Pyrazoles have occupied a distinctive position in the design and synthesis of novel biologically active agents that exhibit considerable medicinal activities.[1] Pyrazolines are well known nitrogen containing five membered heterocyclic compounds.[2] In their structure, two nitrogen atoms are present in five-membered ring. Pyrazoline derivatives have been found in natural products in the form of vitamins, alkaloids and pigments.[3] In the last few years, attention has been paid on the pyrazoline derivatives owing to their molecular structure with simplicity of preparation and wide application in pharmaceutical field.[4] Pyrazoles have been studied for over a decades as an important class of heterocyclic compounds and still continue to attract considerable attention due to the broad range of biological activities they possess, including antimicrobial, antihistaminic,[5] antifungal,[6] anticancerous,[7] antioxidant,[8] anticonvulsant,[9] antiamoebic,[10] cytotoxic,[11] molluscicidal,[12] antiInflammatory and Analgesic,[13] etc. Vijayvergiya et al., synthesized 3,5- diaryl-1-phenyl/isonicotinoyl-2- pyrazolines and evaluated their antibacterial activity against gram+ve bacteria S. aureus, S. albus, S. pyogenes , S. viridans and gram –ve bacteria E. coli and S. typhosa.[14]. Reddy et al. synthesized a series of novel 1- (4-sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines and screened there in vitro anti- inflammatory activity. [15] In addition, pyrazoles are attractive building blocks for pharmaceutical and agricultural research, since they are present in the structures of a variety of leading drugs and pesticides, including Celebrex,[16] Viagra,[17] Zometapine[18] Fenpyroximate,[19] etc.
Pyrazoles are generally synthesized by (i) the reaction of 1,3-dicarbonyl compounds with hydrazines,[20] (ii) the reaction of R,β-unsaturated or doubly unsaturated aldehydes or ketones with hydrazines,[21] and (iii) 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes or alkynes.[22]

II. EXPERIMENTAL PROTOCOLS

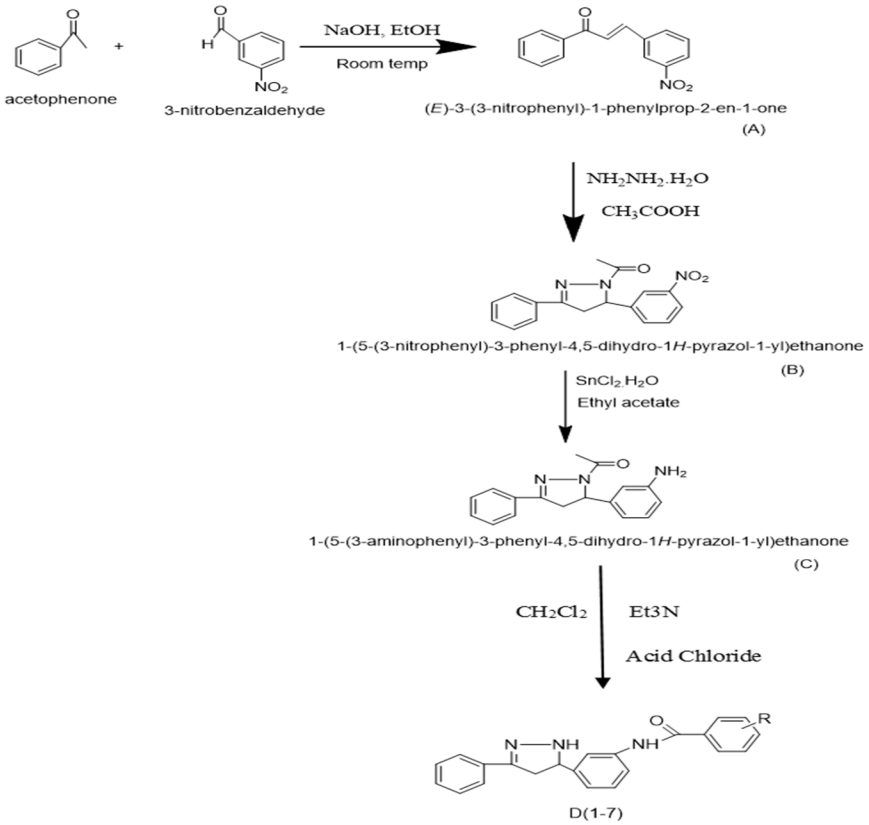
A. *Materials and Methods*

All reagents were purchased from commercial sources and used without purification. Melting points of compounds were taken on melting apparatus .The 1H NMR spectra of compounds were recorded in CDCl3 on Bruker AVANCE II 400 MHz spectrometer, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ ppm.

1) *Synthesis of 1-(5-(3-aminophenyl)-3phenyl-4, 5-dihydro-1H-pyrazole-1-yl) ethenone derivatives*
2) *Synthesis of (E)-3-(3-nitrophenyl)-1-phenyl prop-2-en-1-one (A):* To a solution of acetophenone (1eq) and meta-nitrobenzaldehyde (1eq) in ethanol (10 vol), aq NaOH (1.2eq) was added slowly at 5-10^{o}C and stirred at room temperature for 30 min. Progress of reaction was monitored by TLC in ethyl acetate-petroleum ether mixture (2:8). The precipitated solid was filtered, washed with water, dried and purified by recrystallisation using ethanol to afford a little compound of yellow solid. Then the Product was confirmed by using spectral technique such as IR, ^{1}HNMR and ^{13}CNMR.

3) *Synthesis of 1-(5-(-3-nitrophenyl)-3-phenyl-4,5-dihydro-1-H-P-pyrazole-1-yl)ethenone(B):* (E)-3-(3-nitrophenyl)-3-phenylprop-2-en-1-one (A) (1eq) and hydrazine hydrate (2eq) were taken in acetic acid (10Vol) as solvent and stirred at 120^0C For 30 min in microwave. Progress of reaction was monitored by TLC in ethyl acetate – petroleum ether mixture (3:7). Resulting reaction mixture was poured into crushed ice with strring. The solid obtained was filtered, washed with water, dried and purified by silica gel (100-200#) column chromatography in 10% ethyl acetate petroleum ether as eluent to obtain a title compound as yellow solid. Then the Product was confirmed by using spectral technique such as IR, ^{1}HNMR and ^{13}CNMR.
4) *Synthesis of 1-(5-(3-aminophenyl)-3-phenyl-4, 5-dihydro-1-H-pyrazole-1-yl) ethanone (C):* A solution of 1-(5-(-3-nitrophenyl)-3-phenyl-4, 5-dihydro-1-H-pyrazole-1-yl) ethanone (B) (1eq) and $SnCl_2$ (1.5eq) in ethyl acetate (20 vol.) was stirred at room temperature for 12 hour. Progress of reaction was monitored by TLC in ethyl acetate-petroleum ether mixture (4:6). Resulting reaction mixture was poured in ice cold water and neutralised by K_2CO_3.Organic layer washed by water and brine, dried on Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by silica gel (100-200#) coloum chromatography in 20% ethyl acetate petroleum ether as eluent to obtain a title compound as reddish solid. Then the Product was confirmed by using spectral technique such as IR, ^{1}HNMR and ^{13}CNMR.
5) *Synthesis of 1-(5-(3-aminophenyl)-3-phenyl-4,5-dihydro-1-H-pyrazole-1-yl)ethanone derivatives using acid chloride (D1-D7):* A solution of 1-(5-(3-aminophenyl)-3-phenyl-4,5-dihydro-1-H-pyrazole-1-yl)ethanone(C) (1eq), different substituted acid chloride(1.2eq) and triethylamine (1.2eq) in DCM(10Vol) was stirred at room temperature for 1-2 hour. Progress of reaction was monitored by TLC in ethyl acetate-petroleum ether mixture (3:7). Resulting reaction mixture was diluted with DCM and water added. Separated organic layer washed by water and brine, dried on Na_2SO_4 and concentrated under reduced pressure to afford crude product, which was purified by silica gel (100-200#) flash column chromatography in 30% ethyl acetate-petroleum ether as eluent to obtain a title compound. Then the Product was confirmed by using spectral technique such as IR, ^{1}HNMR and ^{13}CNMR.

Scheme-1-Synthesis of 1-(5-(3-aminophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone



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III. RESULTS AND DISCUSSION

A. Characterization of Synthesized Derivatives

1) Synthesis of (E)-3-(3-nitrophenyl)-1-phenyl prop-2-en-1-one (A)

Structure of synthesized derivative and characteristics of the derivatives are shown below

^{1}HNMR -8.31(S,2H),8.17(S,1H),8.14(D,1H),7.99(D,1H),7.89(D,1H),7.84(S,1H),7.64(T,1H),7.73(T,1H),7.66(T,1H)

^{13}C NMR-189.7(S,2C),147.8(S,1C),141.5(D,1C),137.9(S,2C),129.2(,129.5(D,3C),122.7(D,1C)

MASS SPECTRUM-m/z-253.07(100%),254.08 (16.5%),255.08(1.9%)

2) Synthesis of 1-(5-(-3-nitrophenyl)-3-phenyl-4,5-dihydro-1-H-P-pyrazole-1-yl)ethenone(B)

^{1}HNMR-8.18(S,1H),8.08(D,1H),7.66(D,1H),7.68(D,1H),7.52(T,1H),4.9(T,2H),3.94(D,2H),2.04(S,3H)

13CNMR-193.9(S,1C),146.1(D,1C),142.2(D,1C),137.7(S,1C),129.5(D,1C),122.7(D,1C)15.4(q,1C),9.9(q,1C)

MASS SPECTRUM-m/z-309.11(100%), 310.11 (19.5%), 311.12(2.3%)

3) Synthesis of 1-(5-(3-aminophenyl)-3-phenyl-4, 5-dihydro-1-H-pyrazole-1-yl) ethanone (C)

^{1}H NMR-7.67(D,1H),7.52(D,1H),7.15(T,1H),6.61(S,1H),6.65(S,1H),6.45(D,1H),6.27(S,2H),4.9(T,1H),3.94,3.69(D,2H),2.04(S,3H)

^{13}C NMR-

168.5(S,1C),151.7(S,1C),144.3(S,1C),136.4(S,1C),131..0(D,1C),128.8(D,2C),116.9(D,1C),113(D,1C),65.9(D,1C),39.9(T,1C),23.4(Q 1C)

MASS SPECTRUM-m/z-279.14(100%), 280.14(18.6), 281.14(2.0%), 280.13(1.1%)

Structure of synthesized derivatives are shown below and summarized in table 1.

N-(3-(3-phenyl-4,5-dihydro-1-H-pyrazole-5-yl)phenyl)benzamide(D1)

^{1}H NMR-

7.67(D,2H),7.52(T,3H),7.23(T,2H),7.33(T,2H),7.26(T,1H),7.18(T,1H),7.0(T,1H),3.9(S,1H),6.65(D,1H),6.61(D,1H),4.35(D,2H),3.94,3.69(D,2H),4.0(T,1H)

^{13}C NMR-

164.7(S,1C),151.7(S,1C),143.7(S,1C),136.4(S,1C),131.0(D,1C),128.2(D,2C),122.5(D,1C),135.7(D,1C),51.1(D,1C),42.6(T,1C)

MASS SPECTRUM-m/z-341.15(100%), 342.16(21.1%), 343.16(3.0%), 342.15(1.1%)

Table 1. Summary of the synthesized derivatives and substitution (D1-D7)

Entry no-	Structure	Yield (%)	Physical constant(^{0}C)
D1	R-H	80	113
D2	2F	92	106
D3	3F	95	104
D4	4F	93	108
D5	2OMe	79	92
D6	3OMe	78	96
D7	4OMe	76	90

IV. CONCLUSION

We have synthesized the derivatives of pyrazolines with different reagents. The intermediates formed were further reacted with several reagents which results in different derivatives. Purity and functional group of the compounds were analyzed with NMR. The derivatives synthesized were obtained in good yield, not less than 65%.

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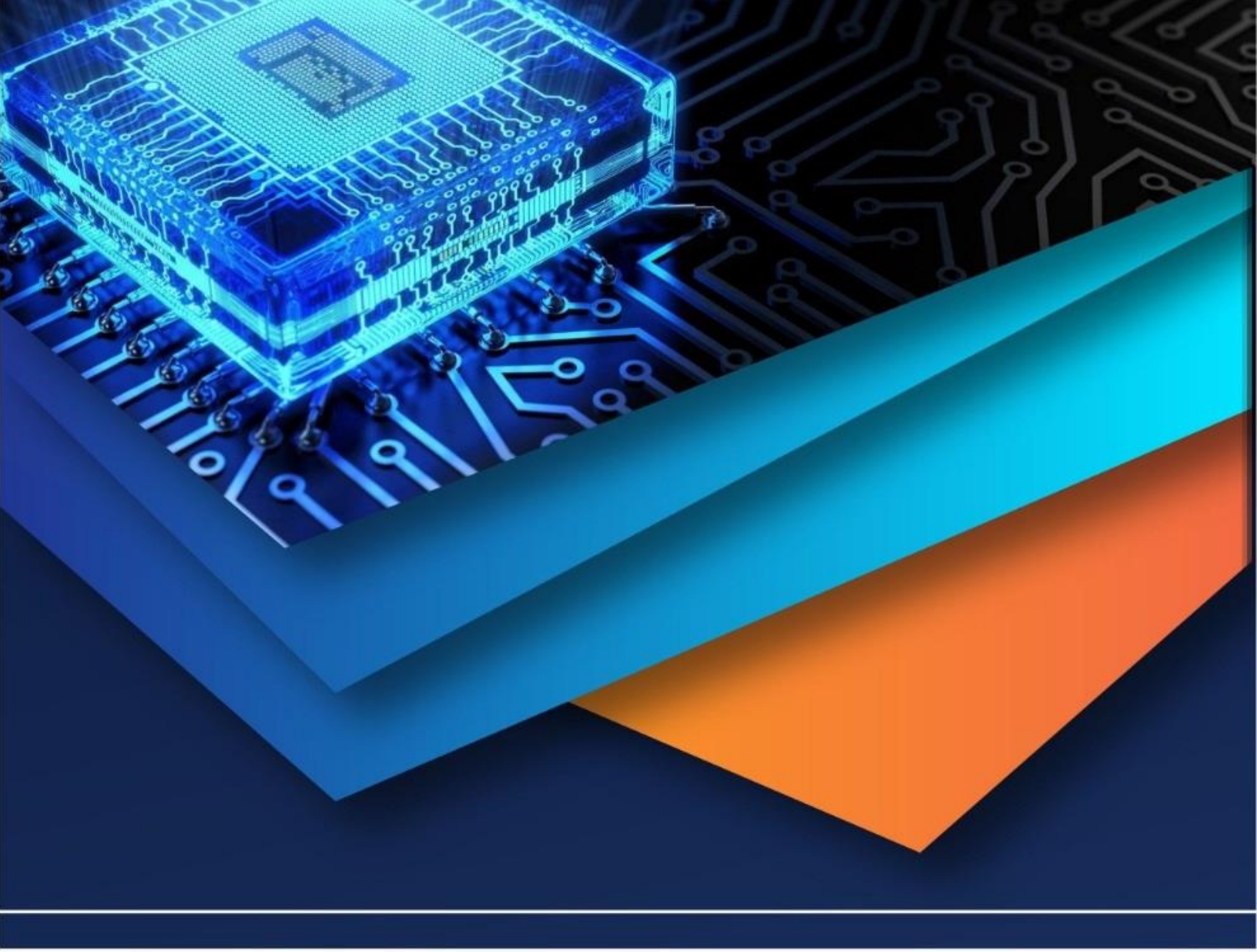

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