Multicomponent Synthesis and Invitro study of Amino Pyrazole Employed by Et_3N as a Catalyst

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ABSTRACT:

In the present study and followed by conventional method, an efficient and design synthesis a novel series of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives. These derivatives can be obtained by Phenyl hydrazine, aromatic aldehydes, and malononitrile in presence of base catalyst Et_3N in DCM as a solvent at reflux. All the newly obtained derivatives were evaluated by the advanced spectroscopic analysis such as ^{1}HNMR, ^{13}CNMR and LCMS and structural determination of titled analogous were calculated by elemental analysis. In addition to the newly synthesised compounds were examined by their anti-microbial activity. This environmentally benign and practical method offers many advantages, such as mild reaction conditions, high yields, use of available catalyst, mild reaction conditions and easy workup.

KEYWORDS:

Phenyl hydrazine, aromatic aldehydes, and malononitrile, 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile, Et_3N, anti-microbial activity

INTRODUCTION:

Heterocyclic compounds are a highly valuable and unique class of compounds. These compounds demonstrate a broad spectrum of physical, chemical and bio-logical characteristics [1,2]. In nature, heterocyclic compounds are widely distributed and display an important part in metabolism owing to their structural nucleus occurring in various natural products, including hormones, antibiotics, alkaloids, vitamins and many others [3–5]. Amongst heterocyclic compounds, nitrogen-containing heterocycles are extensively found as a core framework in a huge library of heterocycles and show several employments in natural science and other areas of science. 6 Additionally, nitrogen-containing heterocycles have striking structural features and they are widely observed in natural products, for instance, vitamins, hormones and alkaloids Additionally, nitrogen-containing heterocycles have striking structural features and they are widely observed in natural products, for instance, vitamins, hormones and alkaloids [7,8].

Pyrazoles represent an interesting structural motif found frequently in various bioactive molecules. Pyrazole derivatives exhibit a broad spectrum of biological profiles, for instance, anti-tubercular [9], anti-AIDS [10] anti-malarial, anti-microbial [11] antitumor [12,13] anticancer [14] and antifungal. In addition, pyrazoles have also been found as promising anti-hyperglycaemic, [15] anti-depressant [16], anti-conversant [17], anti-pyretic, [18] anti-anxiety [19,20] and insecticidal agents.

Our attention was on the more recent, undocumented synthesis pathways for these hybrid molecules. We have assessed the newly synthesized compounds' antibacterial studies. Initially, we attempted a pilot reaction using substituted aromatic aldehydes (1), phenyl hydrazine (2) and malononitrile (3) in the presence of Et_3N catalyst (Scheme-1).

2. METHODS AND MATERIALS:

2.1. Experimental Methods:

The first supplies, including reagents, solvents, and chemicals, were bought commercially from Sigma Aldrich PVT Limited and solvents without being purified beforehand. The determination of the melting point of various titled prepared analogous that are uncorrected is done using the Agarwal 535 melting point equipment. The mobile phase used in the thin layer chromatography for the identification of the desired derivative was ethyl acetate and n-hexane (4:6). The compounds were then seen under UV light in the iodine chamber. Spectroscopic data from the novel derivatives, including ^{1}HMR and ^{13}CNMR (400MHz and 100MHz), were recorded with references to TMS The molecular weight of derivative estimated by the use of LCMS. The compound was determined by elemental analysis

2.2. General procedure for the preparation of 5-Amino-1, 3-diaryl-1 H-pyrazole-4-carbonitriles derivatives:

Phenyl hydrazine, (10 mole) aromatic aldehyde (10 mole), and malononitrile (10 mole) were taken in 50mL RBF and the resulting mixture was reflux at room temperature for two hours . After completion of the reaction (as monitored by TLC) the product were isolated by adding ethanol to obtain pure products. Initially the reaction started at RT few minutes and added catalyst such as Et_3N. The reaction was continued at 70^0Cuntil completely consumed all reactants and also identified spot of reaction on the TLC plates as mobile system (Ethyl acetate: n-hexane = 3:7). The catalyst is recovered by filtration after completion of the reaction. The mixture then neutralised with solution of $NaHCO_3$ and added the Ethylacetae, separated the organic layer. This organic layer washed with water in twice, separated the ethyl acetate and distilled and vacuumed. The desired compound was recrystallized from ethanol.

2.2.1.5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (4a):

Colourless solid; Yeild-84 %, M.P-184 -186^0C, 1HNMR (400MHz,$CDCl_3$) δ ppm: 7.092 (t, J = 8.0 Hz, 1H), 7.178 (d, J = 7.2 Hz, 2H,Ar-H), 7.237– 7.376 (m, 3H,Ar-H), 7.468 (t, J = 8.4 Hz,2H,Ar), 7.647 (s, 1H, Ar), 7.777(d, J=8.4Hz, 2H, Ar), 7.954 (s, 1H, Ar-H); ^{13}CNMR (100 MHz, $CDCl_3$) δppm : 114.74, 115.17, 121.84, 128.12,128.76, 129.12, 129.66, 136.71, 139.94, 145.09, 152.41, 158.50. LCMS (m/z): 260.24 (M+). Molecular formulae: $C_{16}H_{12}N_4$: Analysis of Elements: Calculated: C-73.83; H-4.65; N- 21.52. Obtained: C- 73.48; H-, 4.86; N- 21.72.

2.2.2.5-Amino-3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4b):

Pale-yellow compound; Yeild-93 %, M.P-168–170°C, ^{1}HNMR (400MHz,$CDCl_3$) δ ppm : 6.820 (t, J = 6.5 Hz, 1H,Ar-H), 6.874–6.984 (m, 2H,Ar-H), 7.025 (d, J = 7.2Hz, 2H Ar-H), 7.174 (s, 1H Ar-H), 7.356 (d, J = 7.0 Hz ,2H Ar-H), 7.648 (d, J = 5.4 Hz , 1H Ar-H), 8.257 (s, 1H Ar-H), 9.586(s, 1H,-OH), ^{13}CNMR (100MHz, $CDCl_3$) δ ppm: 114.72, 118.50, 119.80, 122.87, 124.43, 127.45, 128.75, 129.04, 132.06, 138.88, 145.74, 152.58, 156.36, and 160.78: LCMS (m/z): 275.33 (M+H). Molecular formulae: $C_{16}H_{12}N_4$ O; Analysis of Elements: Calculated: C- 69.55; H- 4.38; N-20.28. Obtained: C- 69.47; H-4.37; N- 20.34.

2.2.2.5-Amino-3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4c):

Brown solid; Yeild-90 %, M.P-175–177°C, ^{1}HNMR (400MHz,$CDCl_3$) δ ppm : 6.920 (t, J = 7.5 Hz, 1H,Ar-H), 6.974–7.184 (m, 2H,Ar-H), 7.240 (d, J = 7.6Hz, 2H,Ph), 7.325 (s, 1H Ar-H), 7.456 (d, J = 7.2 Hz ,2H,C_6H_5), 7.744 (d, J = 6.4 Hz , 1H Ar-H), 8.157 (s, 1H,C_6H_5), 9.614 (s, 1H,-OH), ^{13}CNMR (100MHz, $CDCl_3$) δ ppm: 115.72, 118.45, 120.80, 123.87, 125.43, 127.77, 128.58, 129.14, 131.06, 140.28, 146.74, 150.58, 155.36, and 161.78: LCMS (m/z): 287.47 (M+H). Molecular formulae: $C_{17}H_{12}N_4$ O; Analysis of Elements: Calculated: C- 69.55; H- 4.38; N-20.28. Obtained: C- 69.47; H-4.37; N- 20.34

2.2.3.5-Amino-1-phenyl-3-p-tolyl-1H-pyrazole-4-carbonitrile (4d):

Yellow solid; Yield- 91%, M.P.-188–190 °C, ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 2.225 (s, 3H,CH_3), 7.074 (d, J = 6.8 Hz, 1H,Ar-H), 7.177 (d, J = 7.6 Hz,2H,Ar-H), 7.286 (d, J= 8.2 Hz, 2H,Ar-H), 7.292–7.348 (m, 2H ,Ar-H), 7.560 (d, J = 8 .0Hz, 2H, Ar-H), 7.784 (s, 2H,Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 22.58, 108.81, 116.65, 121.58, 128.47, 128.74, 129.55, 133.36, 138.47, 142.47, 146.74, 148.81, and 154.25. LCMS (m/z):274.05 (M+). Molecular formulae: $C_{17}H_{14}N_4$: Analysis of Elements: Calculated: C-74.43; H-5.14; N- 20.42. Obtained: C-74.38; H-5.12; N- 20.47

2.2.4.5-Amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4e):

Pal brown solid; Yield- 87%, M.P.- 192–194°C, ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.787 (t, J =9.0Hz, 1H,Ar-H), 7.154 (d, J = 7.6 Hz, 2H, Ar-H), 7.298–7.378 (m, 2H,Ar-H), 7.401 (d, J= 8.0 Hz, 2H,Ar-H), 7.687 (d, J = 8.0 Hz, 2H,Ar-H), 7.881 (s, 2H,NH_2). ^{13}CNMR (100MHz, $CDCl_3$) δ ppm: 112.68, 116.57, 124.87,128.25, 128.74, 129.25, 132.28, 135.14, 137.80, 145.80, 151.55 ,157.87. LCMS (m/z):296.54 (M+H). Molecular formulae: $C_{16}H_{11}ClN_4$: Analysis of Elements: Calculated: C-65.20; H-3.76; N-19.01; Obtained: C-65.13; H- 3.75; N-19.10.

2.2.5.5-Amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4- carbonitrile (4f):

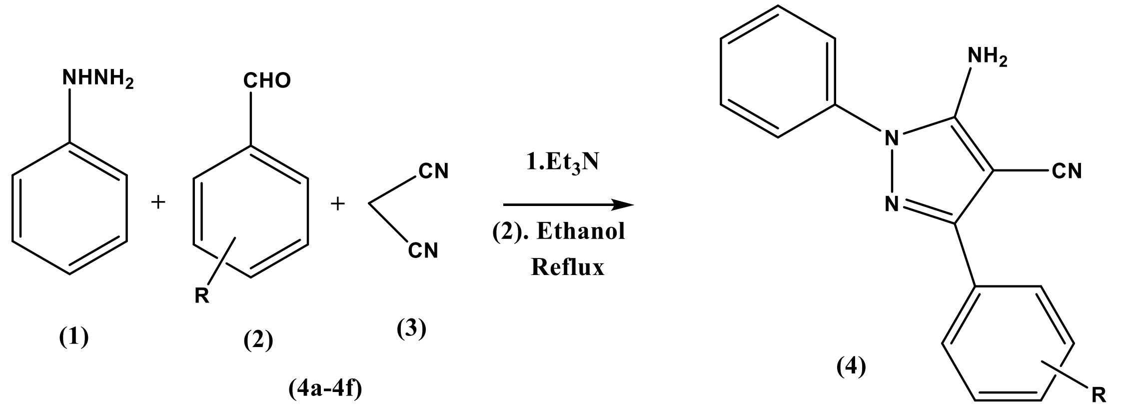
Yellow powder; Yield- 84 %, M.P. - 179–181°C, ^{1}HNMR (400MHz,$CDCl_3$) δ ppm: 6.188 (s, 2H,.NH_2) 7.144 (d, J = 6.8 Hz, 2H,Ar-H), 7.317–7.387 (m, 2H, Ar-H), 7.745–7.992 (m, 3H,Ar-H), 8.195 (s, 1H, Ar-H), 8.246 (d, J=8.5 Hz, 2H,Ar-H) ; ^{13}CNMR (100MHz, $CDCl_3$) δ ppm: 114.74, 117.58, 125.80, 128.28, 128.95, 129.79, 131.02, 136.74, 137.89, 146.75, 152.25 , 157.88 ; LCMS (m/z) : 307.46 (M+2) ; Molecular formulae : $C_{16}H_{11}N_5O_2$: Analysis of Elements : C-62.94; H-3.62; N-22.93. Obtained: C- 62.86; H- 3.60; N- 23.05

2.2.7.5-Amino-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole-4- carbonitrile (4g):

Yellow solid; Yield- 80 %, M.P. = 156–158°C; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.214 (s, 2H, NH_2), 7.084(d, J = 7.0 Hz, 1H), 7.189 (d, J =8.0 Hz, 2H), 7.375 (d, J = 6.5 Hz), 7.548 (s,1H, Ar-H), 7.876 (s, 1H, Ar-H). 13CNMR (100MHz, $CDCl_3$) δppm: 113.29,117.58, 121.06, 124.87, 127.44, 128.19, 128.77, 129.27, 130.78,141.58, 146.75, 158.87. LCMS (m/z):267.68 (M+H). Molecular formulae: $C_{14}H_{10}N_4S$: Calculated: C- 63.14; H-3.78; N-21.04. Obtained: C, 63.04, H, 3.76; N, 21.12

3. RESULTS AND DISCUSSION:

Initially, the study of the desired analogous can be prepared from Phenyl hydrazine, aromatic aldehydes, and malononitrile in presence of strong base catalyst Et_3N in ethanol as a solvent at reflux as shown in (Scheme-1).



R = H, 4-OH, 4-CH_3, 4-Cl, 4-NO_2, Thiophene

(Scheme-1)

The catalyst was first assessed for using substituted aromatic aldehyde (10mole), malononitrile (10 mole), and phenyl hydrazine (10 mole) in the presence of various types of base catalysts, including Ph_3N, Et_3N, DABCO, DBU, and K_2CO_3 at reflux, in order to observe the optimization of the reaction conditions. The type of the catalyst had no discernible impact on the yield of Pyrazole, according to the admiration of the reaction conditions. Therefore, this three-component coupling cyclisation reaction proceeded smoothly in the absence of any base catalyst, generating the required 5-amino-4-cyano 1, 3 biphenyl Pyrazoles in excellent yield after 150 minutes using a straightforward reflux technique

Table –1: Effect of the various catalyst synthesis of desired compound (4b):

Entry	Catalyst	Time (min)	Yield (%)
1	DBU	150	55
2	DABCO	150	46
3	Imidazole	150	59
4	Ph_3N	150	72
5	Et_3N,	150	93

The amount of catalyst is very most important role play during this reaction; 1mole amount of the catalyst was applied in starting, acquired traces amount of product and gradually developing up to 5 mmol amount of the catalyst during the reaction. Hence, maximum amount yield obtained (92). Further, amount of the catalyst increased up to entry “5” and get no improvement as shown Table-2.

Table-2: Impact of the catalyst (Et_3N) for synthesis of derivatives (4b):

Entry	Catalyst (mmol)	Time (min)	Yield (%)
1	1.0	150	traces
2	2.5	150	40
3	5.0	150	92
4	10	150	92
5	15	150	92

The catalyst was played a significant role play during the reaction method, we maintained to the examination of solvent effects by using a type of solvents, including H_2O, CH_3CN, EtOH, MeOH, and MDC. The observations are identified that excellent reaction conditions are those if without the use of solvents and also the completion of the reaction as well as for the yield of the desired product compared than those obtained in any of the solvents investigated (Table-3).

Table-3: The comparison of the solvent for synthesis of compound (4b):

Entry	Catalyst (mmol)	Time (min)	Yield (%)
1	H_2O	150	15
2	MeOH	150	54
3	EtOH	150	47
4	CH_3CN	150	64
5	MDC	150	92

In order to investigate the catalytic function of imidazole, substituted aryl aldehydes were first chosen for the reaction with 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile. Even though at higher temperatures, the reaction conditions were enhanced to synthesis titled compounds and an efficiently in a solvent-free situation with a catalytic quantity of Ph_3P. As a result, we introduced reaction catalyst to a range of solvents and conducted reactions at varying temperatures (Table-3). We were able to attain 92% of the product yield in the ethanol system through experiments.

CHARACTERISATION:

The structure of the desired derivatives was constructed by the evidence of spectral analysis such as IR, ^{1}HNMR, ^{13}CNMR, LCMS and elemental analysis. In this study, proton NMR of titled derivatives evaluated by various values of respective groups such as hydroxyl proton, methoxy protons, pyrazine protons, methyl protons, as well as aromatic protons appeared at various range of values.^{13}CNMR of these derivatives appeared at different values. The thiazides group of desired compounds appeared at 162-154. ^{1}HNMR values different protons shown at 8.288 δppm of pyrazine molecules, 6.558 δppm of NH_2 protons. The hydroxyl proton appears at 9.586 δ ppm.

4. BIOLOGICAL ACTIVITY:

Table-4: Antimicrobial activity screening activity synthesized scaffold:

Entry	***Zone of inhibition in (mm)**					
	Bacteria				**Fungi**	
	S. aureus	**E. coli**	**S. typhi**	**B. substills**	**A. Niger**	**C. albicans**
4a	**07**	**06**	**07**	**10**	**06**	**05**
4b	**16**	**17**	**17**	**18**	**11**	**12**
4c	**17**	**18**	**20**	**20**	**13**	**14**
4d	**21**	**21**	**19**	**20**	**17**	**16**
4e	**20**	**22**	**20**	**19**	**12**	**10**
4f	**11**	**12**	**10**	**12**	**10**	**09**
4g	**14**	**14**	**12**	**10**	**07**	**07**
streptomycin	**25**	**25**	**22**	**22**	**NA**	**NA**
fluconazole	**NA**	**NA**	**NA**	**NA**	**20**	**20**
DMSO	**---**	**----**	**---**	**---**	**---**	**---**

The results of the above table-4 exhibited that the anti-bacterial activity of compound 4b,4c mostly electron donating group of compounds viz; these derivatives showed good active potent while electron withdrawing group of compounds “4d” exhibited an excellent potent active. The compound 4e and 4f showed moderate active potential due to electron withdrawing group groups present in the compound. We also identified the antifungal activity of compound (4a-4g) showed different activity compound 4d showed good activity and rate of the compound showed low to moderate activity.

5. CONCLUSION

In conclusion, this investigation of desired compound has disclosed a novel and convenient one-pot synthesis of Polysubstituted amino pyrazole analogues via multi-component reactions. This triethylamine is a base catalyst reaction proceeded smoothly in good to excellent yields and offered different other advantages including short reaction time, simple experimental workup procedures, and no toxic by-products. The approach to pyrazole systems presented herein avoids the use of catalyst, toxic organic solvent. This protocol represents a promising green route for the synthesis of this class of compounds

6. AKOWNLDEMENT:

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