One Pot Multicomponent Synthesis of Amino Pyrazole Promoted by Imidazole and Bioevluation

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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 Imidazole in ethanol 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

KEYWORDS:

Phenyl hydrazine, aromatic aldehydes, and malononitrile, 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile , imidazole , 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 represents 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 malanonitrile (3) in the presence of imidazole 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 1HMR and 13CNMR (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, (1 mmol) aromatic aldehyde (1 mmol), and malononitrile (1 mmol) 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 Imidazole. 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). 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 powder; Yeild-84 %, M.P-154 -156^{0}C,. 1HNMR (400MHz,$CDCl_3$) δ ppm: 7.052 (t, J = 7.2 Hz, 1H), 7.128 (d, J = 7.6 Hz, 2H,Ar-H), 7.231– 7.386 (m, 3H,Ar-H), 7.458 (t, J = 8.0 Hz,2H,Ar-H),7.697(s,1H,Ar-H),7.772(d,J=8.8Hz,2H,Ar-H),7.914(s,1H,Ar-H);^{13}CNMR(100 MHz, $CDCl_3$) δppm: 112.22, 114.07, 120.84, 127.12,128.56, 129.45, 129.92, 136.66, 138.94, 146.09, 151.41, 157.50. 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):

Pal yellow powder; Yeild-94 %, M.P-164–166°C, ^{1}HNMR (400MHz,$CDCl_3$) δ ppm : 6.810 (t, J = 6.4 Hz, 1H,Ar-H), 6.864–6.974 (m, 2H,Ar-H), 6.982 (d, J = 7.2Hz, 2H Ar-H), 7.154 (s, 1H Ar-H), 7.346 (d, J = 7.0 Hz ,2H Ar-H), 7.548 (d, J = 5.4 Hz , 1H Ar-H), 8.157 (s, 1H Ar-H), 9.486(s, 1H,-OH), ^{13}CNMR (100MHz, $CDCl_3$) δ ppm: 114.77, 118.54, 119.81, 121.87, 123.43, 127.88, 128.65, 129.12, 130.06, 139.88, 146.74, 151.58, 154.36, and 157.78: 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.

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

Pal yellow powder solid; Yield- 90%, M.P.-158–160 °C, ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 2.247 (s, 3H,CH_3),7.091(d, J = 6.4 Hz, 1H,Ar-H), 7.187 (d, J = 7.2 Hz,2H,Ar-H), 7.246 (d, J= 8.6 Hz, 2H,Ar-H), 7.296–7.345 (m, 2H ,Ar-H), 7.564 (d, J = 8.2Hz, 2H, Ar-H), 7.775 (s, 2H,Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 21.58, 106.81, 115.65, 120.58, 127.47, 128.69, 129.12, 132.36, 139.47, 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 (4d):

Pal yellow powder solid; Yield- 87%, M.P.- 171–173°C, ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.887 (t, J =9.4Hz, 1H,Ar-H), 7.184 (d, J = 7.4 Hz, 2H, Ar-H), 7.297–7.358 (m, 2H,Ar-H), 7.396 (d, J= 8.8 Hz, 2H,Ar-H), 7.677 (d, J = 8.4 Hz, 2H,Ar-H), 7.871 (s, 2H,NH_2). ^{13}CNMR (100MHz, $CDCl_3$)δ ppm: 111.68, 115.57, 122.87,128.04, 128.68, 129.41, 131.28, 134.04, 137.83, 145.86, 151.57 ,155.87. 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 (4e):

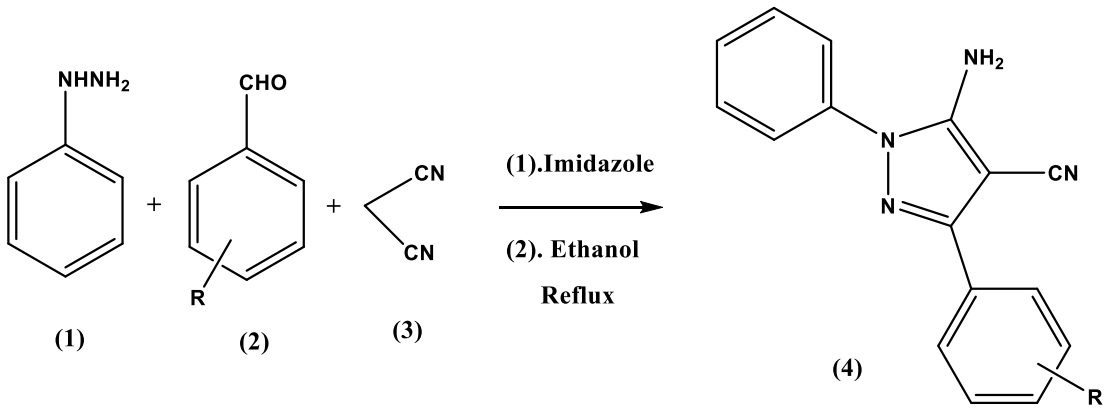
Yellow compound; Yield- 85 %, M.P. - 166–168°C, ^{1}HNMR (400MHz,$CDCl_3$) δ ppm: 6.158 (s, 2H,.NH_2) 7.184 (d, J = 6.4 Hz, 2H,Ar-H), 7.307–7.367 (m, 2H, Ar-H), 7.750–.790 (m, 3H,Ar-H), 8.175 (s, 1H,Ar-H), 8.256 (d,J=8.4 Hz, 2H,Ar-H) ; LCMS (m/z):306.03 (M+H). Molecular formulae: $C_{16}H_{11}N_5O_2$: Analysis of Elements: C-62.95; H-3.63; N-22.94. Obtained: C- 62.88; H- 3.61; N- 23.06

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

Yellow powder; Yield- 84 %, M.P. = 174–176°C; 1HNMR (400MHz, $CDCl_3$) δ ppm: 6.125 (s, 2H, NH_2), 7.067(d, J = 6.4 Hz, 1H), 7.156 (d, J =8.0 Hz, 2H), 7.345 (d, J = 5.0 Hz and J = 11.8Hz, 3H), 7.568 (s,1H ,Ar-H), 7.854 (s, 1H,Ar-H). 13CNMR (100MHz, CDCl3)δ ppm : 114.29,116.58, 120.06, 123.87, 126.44, 126.95, 128.65, 129.17, 130.71,140.15, 145.75, 156.87. 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 titled derivatives can be synthesized from Phenyl hydrazine, aromatic aldehydes, and malononitrile in presence of base catalyst Ph3P 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)

To observed that the optimized the reaction conditions, we initially a catalyst evaluated exercise employing substituted aryl aldehyde (10 mmol), malononitrile (10 mmol), and phenyl hydrazine (10 mmol) in the presence of different base catalysts such as Ph_3N, Et_3N, DABCO, DBU and K_2CO_3 at room temperature. The examination of the reaction conditions was established that the nature of the catalyst had no significant effect on the yield of pyrazole. Interestingly, in the absence of any base catalyst, this three-component coupling cyclization reaction proceeded

smoothly to afford the desired 5-amino-4-cyano 1, 3 biphenyl pyrazole in excellent yield after 25-30 min by simple reflux method.

Table –1: Comparison among the various catalyst synthesis of titled compound (4b):

Entry	Catalyst	Time (min)	Yield (%)
1	DBU	180	55
2	DABCO	180	45
3	Imidazole	180	92
4	Ph_3N	180	71
5	Et_3N,	180	62

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 upto 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: Optimization amount of the catalyst (Ph_3P) for synthesis of derivatives (4b):

Entry	Catalyst (mmol)	Time (min)	Yield (%)
1	1.0	120	traces
2	2.5	120	40
3	5.0	120	92
4	10	120	92
5	15	120	92

The catalyst was played a significant role play during the reaction method , we maintained to the examination of solvent effects by using a types of solvents, including H_2O, CH_3CN, EtOH, MeOH, and MDC. The observations are identified that an 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	120	15
2	MeOH	120	54
3	EtOH	120	89
4	CH_3CN	120	92
5	MDC	120	37

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-4). We were able to attain 92% of the product yield in the ethanol system through experiments.

Characterisation:

The structure of the titled analogous was established by the support of spectral analysis such as 1HNMR, ^{13}CNMR, LCMS and elemental analysis. In this study, proton NMR of titled derivatives evaluated by different values of respective groups such as hydroxyl proton, methoxy protons, pyrazine protons, methyl protons, as well as aromatic protons appeared at different range of values.^{13}CNMR of these derivatives appeared at various values . The thiazole group of desired compounds appeared at 158-154. ^{1}HNMR values different protons shown at 8.488 δppm of pyrazine molecules, 6.258 δppm of NH_2 protons. The hydroxyl proton appears at 9.486 δ ppm.

4. BIOLOGICAL ACTIVITY:

Table-4: Antimicrobial activity screening activity synthesized scaffold:

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
4a	05	05	07	06	04	05
4b	15	16	16	17	10	11
4c	18	19	18	18	12	14
4d	21	21	19	20	17	16
4e	10	12	15	14	12	10
4f	12	10	10	12	10	09
4g	12	10	11	09	07	07
streptomycin	25	25	22	22	NA	NA
fluconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

The results of the above table-4 showed that the anti-bacterial activity of compound 4b,4c mostly electron donating group of compound viz; these derivatives exhibited 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 imidazole 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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