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Facile and Multicomponent Synthesis of Amino Pyrazole employed by Mg $(NO_3)_2$ As Catalyst

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ABSTRACT:

The right path of investigation in the present study, an efficient and cost-effective method for the preparation of derivatives of 5-Amino-1, 3-diaryl-1 H-pyrazole-4-carbonitriles using Phenyl hydrazine, substituted aromatic aldehyde, and malononitrile in acetonitrile as a solvent employing $Mg(NO_3)_2$ as a catalyst under solvent condition. The chemical structures of the titled compounds were confirmed by ^{1}H-NMR &^{13}CNMR, Mass spectral and Elemental analysis. Antimicrobial activities of the titled compounds were also examined by various strains and exhibited mild to moderate anti-bacterial activities.

KEYWORDS:

Aromatic aldehyde, Phenyl hydrazine, malononitrile, Amino Pyrazole, $Mg(NO_3)_2$, anti-bacterial activities

INTRODUCTION:

Heterocyclic compounds containing nitrogen linkage have received considerable attention in recent times due to their wide applications. The cyclization reaction of suitable linear compounds is one of the most common and popular methods for preparing these heterocyclic compounds [1,2]. Between these azacontaining heterocyclic compounds, pyrazoles have a long history of application in various agrochemical and pharmaceutical industries [3]. These compounds are known to display anti-tumor [4] , anti-bacterial [5], anti-microbial [6], anti-fungal [7] , anti-inflammatory [8], analgesic [9] , anti-depressant [10], antimalarial [11], anti-tumor [12] , and anti-viral activities [13]. It is well-known that the study of pyrazole derivatives is significant in pesticide chemistry, because of their herbicidal [14], and insecticidal activities [15]. A previous investigation revealed that 5- amino-4-cyanopyrazole derivatives have anti-bacterial activity16. The pyrazole moiety makes the core structure of blockbuster drugs such as Celebrex(R) [17] and Viagra(R) [18] that act as PDE-5 inhibitors.

A survey of the literature shows that the majority of the strategies involve multistep sequences or expensive catalysts, inert atmosphere, anhydrous conditions, lengthy reaction times, and laborious workup. It is well-known that nitriles are widely used as intermediates for a large number of heterocyclic compounds23. In continuation of our research interest in the synthesis of biologically important heterocyclic compounds, we have synthesized a series of newpyrazole derivatives by simple grinding of aromatic aldehydes, malononitrile, and phenyl hydrazine (scheme-1).

2.MATERIAL AND METHODS:

All chemicals, reagents and solvent were purchased from Merck Chemical Companies and they were used as accepted. The ^{1}H NMR (400MHz, $CDCl_3$) and ^{13} C NMR ($CDCl_3$, 100 MHz) spectra were measured on a Bruker Avance DPX-250, FT-NM

spectrometer (δ in ppm). Tetramethylsilane (TMS) was used as internal standard. The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

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

Phenyl hydrazine, (1.10 mol) aromatic aldehyde (1.12mol), and malononitrile (1.10 mmol) were dissolved in acetonitrile in the 50mL RBF and Mg $(NO_3)_2$ is added above the mixture and the reaction was continued for three hours. The reaction mixture was identified with help of TLC and. The product was isolated by adding ethyl acetate and was separated. The ethyl acetate layer was distilled off and get final product

.Representative spectral data of the products:

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

White solid; Yield-84 %, M.P = 168 − 170◦C, ^{1}HNMR ($CDCl_3$, 400 MHz)δppm ; 6.954 (t, J = 7.2 Hz, 1H), 7.174(d, J = 8.4 Hz, 2H), 7.285– 7.385 (m, 3H), 7.421 (t, J = 8.0 Hz, 2H),7.564 (s, 1H), 7.770 (d, J = 7.6 Hz, 2H), 7.872 (s, 1H). 13CNMR ($CDCl_3$, 100MHz) δppm: 111.80, 114.26, 121.58, 126.74, 128.49, 129.09, 129.67, 135.54, 137.80, 145.12, 150.64, 156.47; LCMS (m/z): 260.65(M+). Anal. Calcd for: $C_{16}H_{12}N_4$: C- 73.83; H-4.65; N, 21.52. Found: C- 73.48; H, 4.86; N, 21.72%

2.3.5-Amino-3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4- carbonitrile (4b) :

Yellow powder ; Yield-84 %, M.P = 158 − 160◦C ; 1H NMR (CDCl3, 400 MHz) δppm : 6.774 (t, J = 7.0 Hz, 1H), 6.875–6.957 (m, 2H), 7.047 (d, J = 7.6Hz, 2H), 7.141 (m, 1H), 7.240 (d d, J = 7.6 Hz and J = 8.8 Hz, 2H), 7.544 (d d, J = 1.7 Hz and J = 7.0 Hz, 1H), 8.174 (s, 1H), 10.318(s, 1H), 10.654 (s, 1H); 13CNMR(CDCl3,100 MHz)δ ppm : 113.60, 117.81, 119.08, 120.55, 122.32, 125.46, 128.17, 130.54, 131.15, 137.13, 146.62, 151.55, 153.30, 157.51.Anal.Calcd forC16H12N4 O : C- 69.55; H- 4.38; N- 20.28. Found: C- 69.48 , H-4.46; N, 20.35.

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

Pink solid; Yield-87 %, M.P = 154 − 156°C ;^{1}H NMR ($CDCl_3$, 400 MHz)δppm: 2.145 (s, 3H), 7.048 (d d, J = 3.8 Hz and J = 7.2 Hz, 1H), 7.175 (d, J = 7.6 Hz,2H), 7.242 (d, J= 9.4 Hz, 2H), 7.289 –7.373 (m, 2H), 7.624 (d, J = 7.0Hz, 2H), 7.740 (s, 2H).^{13} C NMR ($CDCl_3$, 100 MHz) δ ppm: 21.90, 104.65, 113.22, 120.44, 126.62, 129.71, 129.77, 132.95, 138.14, 138.97, 145.20, 148.82, 153.20. Anal. Calcd for: $C_{17}H_{14}N_4$: C- 74.43; H- 5.14; N- 20.42. Found: C-74.88; H-5.18; N- 20.12.

2.4.5-Amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4- carbonitrile (4d):

Red powder; Yield-84 %, M.P = 162 − 164°C. 1H NMR ($CDCl_3$, 400 MHz) δppm : 6.984 (s, 1H) 7.187 (d, J = 7.6 Hz, 2H), 7.289–7.324 (m, 2H), 7.743–7.904 (m, 3H), 8.124 (s, 1H), 8.424 (d, J = 7.6 Hz, 2H) ; ^{13}CNMR ($CDCl_3$,100 MHz) δ ppm: 111.44, 114.42, 121.10,121.38, 122.98, 129.85, 129.94, 131.80, 134.30, 137.72,144.27,149.16, 156.41 ; LCMS (m/z):305 (M+). Anal. Calcd for $C_{16}H_{11}N_5O_2$: C- 62.95; H- 3.63; N-22.94. Found: C, 62.87; H- 3.60; N, 23.04.

2.5.5-Amino-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole-4- carbonitrile (4e):

Orange powder ; Yield-83 %, M.P = 160 − 161°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δppm : 6.970 (t, J =7.8 Hz, 1H), 7.158 (d, J =8.0 Hz, 2H), 7.321(t, J=7.6 Hz, 2H), 7.556 (t, J =9.2 Hz, 1H), 7.764 (s, 1H), 7.859 (s, 1H),8.051 (d, J =7.4 Hz, 1H), 8.154 (d, J =8.4 Hz, 1H), 8.148 (s, 1H). 13 C NMR (CDCl3, 100 MHz) δ ppm: 112.44, 113.42, 121.10, 121.38, 122.98, 129.85, 129.94, 131.80, 134.30, 137.72,144.27,149.16, 156.41. Anal.Calcd for $C_{16}H_{11}N_5O_2$: C- 62.95; H-3.63; N- 22.94. Found: C- 62.78; H, 3.61; N, 22.99.

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

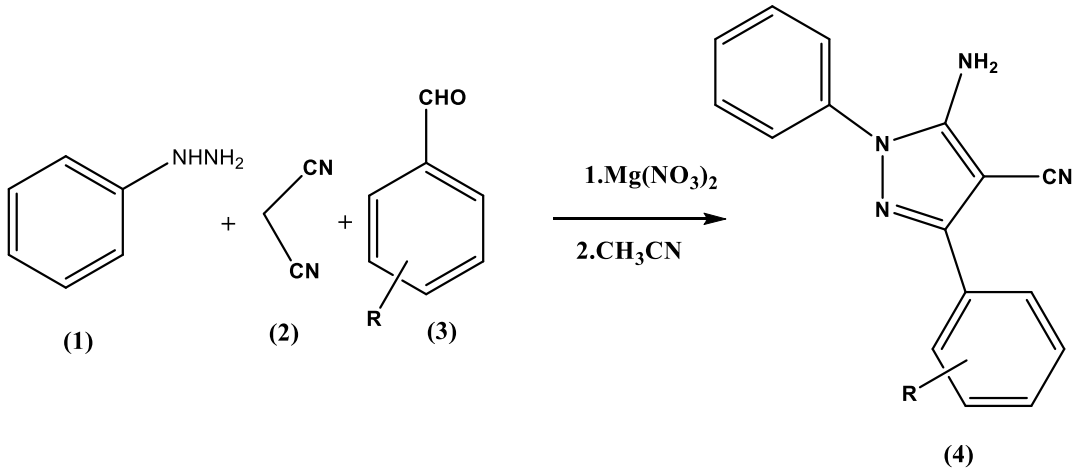
Yellow solid; Yield-84 %, M.P = 161 – 163 ; ^{1}H NMR ($CDCl_3$, 400 MHz) δppm : 6.944(t, J =7.0 Hz, 1H), 7.075 (d d, J = 3.4 Hz and J = 5.8 Hz, 1H), 7.212 (d, J =7.6 Hz, 3H), 7.326 (d d, J = 5.2 Hz and J = 14.8Hz, 3H), 7.546 (s,1H), 7.874 (s, 1H). ^{13} C NMR ($CDCl_3$, 100 MHz) δ ppm 112.24, 114.44, 121.64, 123.44, 125.93, 126.81, 127.74, 129.75, 132.71,141.90, 145.86, 155.15. Anal. Calcd for $C_{14}H_{10}N_4S$: C- 63.14;H- 3.78; N- 21.04. Found: C, 63.04; H- 3.77; N, 21.12.

2.7.5-Amino-3-(5-methylthiophen-2-yl)-1-phenyl-1H-pyrazole-4-carbonitrile (4g):

Yellow solid; Yield-88 %, M.P = 188 − 190°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δppm: 2.211 (s, 3H), 6.774 (m, 1H), 6.895–6.974 (m, 2H), 7.146 (d, J = 7.6 Hz, 2H), 7.278–7.322 (m, 2H), 7.446 (s, 1H), 7.876 (s, 1H).^{13} CNMR ($CDCl_3$, 100 MHz) δ ppm: 17.55, 114.21, 116.03, 121.42, 125.21, 126.44, 128.06, 129.47, 134.48, 139.66, 142.67, 146.07, 156.74 and Anal. Calcd for $C_{15}H_{12}N_4S$: C- 64.26; H- 4.31; N-19.98; Found: C- 64.37; H- 4.25; N-20.05

RESULTS AND DISCUSSION

To observed to optimize the reaction conditions, we recognized a catalyst evaluation of exercise and employing substituted benzaldehyde (1.125mol), malononitrile 1(.10mol), and phenyl hydrazine (1.10mol) in the presence of Mg $(NO_3)_2$ in acetonitrile and the various base catalysts such as DABCO, Et_3N, DBU and K_2CO_3 at room temperature. The evaluation of the reaction conditions constructed that the nature of the catalyst had no significant effect on the yield of pyrazole. Surprising, there no any base catalyst, this three-component one pot coupling cyclization reaction continued smoothly to scaffold the target 5-amino-4-cyano 1, 3 diphenyl pyrazole in excellent yield after 3hours by simple refluxing condition . Hence, the phenyl hydrazine itself is acting as both a Bronsted base catalyst in this reaction and as a nucleophile due to the bases had no effect on the reaction product and these optimized conditions in hand, this three component reaction can be readily diversified through a combination of a range of aryl aldehydes, malononitrile, and phenyl hydrazine.



(1) (2) (3) (4)

R = H, 4-CH_3, 2-OH, 4=NO_2, 4-NO_2, thiophene, 5-CH_3-thiophene

(Scheme-1)

We represented that the reaction of Phenyl hydrazine, (1.10 mol) aromatic aldehyde (1.12mol), and malononitrile (1.10 mmol) were dissolved in acetonitrile in the 50mL RBF and Mg(NO3)2 is added was investigated to optimize the model of the reaction conditions with respect to molar ratio of catalyst to the substrate and strong base as catalyst. It was observed that 75 mol% of catalyst was sufficient to obtain the titled derivatives in 85-90% yield within 20 min in CH_3CN as solvent at reflux. The encouragement of these successful results, different substituted aldehydes was investigated under optimized conditions to

understand the scope and generality of this procedure (Table- 1). The scope and impact of the catalyst can be applied during this reaction and also various catalyst such as transition metal catalyst and transition metal catalyst were used in the reaction. The effect of the catalyst is $Mg(NO_3)_2$, this catalyst is played a significant role until the completion of the reaction as compared with other catalyst viz; TiO_2, $ZnCl_2$ and $FeCl_3$ and it is also highly impact performance during the reaction . The effect of the product as well as time of reaction was shown as given below Table – I.

Table-I: The effect of catalyst for preparation of titled derivatives (4b):

Entry	Catalyst	Time (hrs.)	Yield (%)
1	TiO_2	3	45
2	$ZnCl_2$	3	89
3	$FeCl_3$	3	76
4	$Mg(NO_3)_2$	3	70

To determine the appropriate concentration of the catalyst is pph_3, we investigated the model of the reaction at various moles of catalyst, i.e., 1.0, 2.0, 3.0, 4.0, 5.0 mol%. The product yielded from the various derivatives was 64%, 71%, 78%, 83%, 90% and 90% respectively. It was observed that the product of derivatives constant at 90% when concentration of the catalyst was increased from 1.0 to1 mol%. This indicates that 4.0 mol% of Mg $(NO_3)_2$ is sufficient for the excellent result considering the reaction time and yield of product. The results are summarized in (Table-II).

Table-II: Optimization of catalyst at different concentrations (catalyst %) for the Preparation of (4b).

Entry	**Catalyst**	**No.of moles(%)**	**Reaction Time(min)**	**Yield (%)**
1	$Mg(NO_3)_2$	1.0	180	65
2	$Mg(NO_3)_2$	2.0	180	72
3	$Mg(NO_3)_2$	3.0	180	81
4	$Mg(NO_3)_2$	4.0	180	90
5	$Mg(NO_3)_2$	5.0	180	90

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The different solvents were used during the reaction and the percentage of product as well as the reaction time was altered. It is revealed that aqueous medium as well as base such as $Mg(NO_3)_2$ are used, the time of reaction is more as well as percentage of yield is poor where as other solvents such as polar a protic solvent DMF and THF are used in this reaction, time of the reaction minimized and percentage of the reaction improved .During the reaction, CH_3CN is used as solvents, the reaction time and product percentage was improved compared with remaining solvents before used as shown in Table-III.

Table-III : Optimization of different solvents for the synthesis of derivative"4bi"

Entry	**Catalyst**	**Solvent**	**Time(hrs)**	**Yield (%)**
1	$Mg(NO_3)_2$	H_2O	10	65
2	$Mg(NO_3)_2$	EtOH	08	54
3	$Mg(NO_3)_2$	DMF	05	47
4	$Mg(NO_3)_2$	THF	08	70
5	$Mg(NO_3)_2$	CH_3CN	03	90

The reaction reveals that the catalyst was effectively performed for the synthesis of target analogous from substituted benzaldehyde (1.125mol), malononitrile 1(.10mol), and phenyl hydrazine (1.10mol) (Scheme-1). The reaction of 2 equivalents of indole with 1.0 equivalent substituted aromatic aldehydes followed successfully to scaffold 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile(4) with an excellent yield. The chemical structures of (4**a**–4**g**) were confirmed by ^{1}H, ^{13}C NMR and LCMS mass spectral data.

4.2. BIO EVALUATION:

4.2.1. Antibacterial activity:

The newly titled derivatives and well characterized compounds **(4a-4g)** were screened for ***in vitro*** antibacterial activity against Gram(+Ve) bacteria, Gram(-Ve) bacteria using agar well diffusion assay and zones of inhibition of the test compounds were expressed in mm as shown in Table-IVI

4.2.2. Antibacterial activity:

The ***invitro*** antibacterial activity of the target compounds **(4a-4g)** was compared with standard references **" streptomycin''** as collected in (Table-III)..As identified in Table-III most of the newly synthesized derivatives generally evaluated activity against all the tested bacterial strains. The compound" 4b,4f **"** showed excellent antibacterial activity against gram(+Ve)bacterial strains viz; E.coli, P.aeruginosa and gram(-Ve) bacterial strains viz; Subtilis, and S. aureus respectively due to such compounds possesses halogen atoms. The derivatives 4c, 4d and 4g showed moderate to good potent activity against bacterial strains. The compounds**"4a** and 4e**"**showed poor activity against bacterial strains due to compounds having more electron withdrawing groups. These results represented that the compounds bearing electron donating groups exhibited moderate to good activity than the compounds containing electron withdrawing groups. The compounds bearing halogen atoms showed excellent active potential against antibacterial strains.

Table-IV : Antibacterial activity of the newly synthesized compounds (4a-4g):

Compound	Anti-Bacterial Activity			
	Gram(+ve) bacteria		Gram(-ve) bacteria	
	Escherichia coli	Pseudomonas aeruginosa	Bacillus subtilis	Staphylococcus aureus
4a	06	05	07	08
4b	22	21	21	20
4c	18	17	19	20
4d	07	09	08	10
4e	10	12	11	09
4f	20	21	22	20
4g	17	19	18	20
Streptomycin	25	25	25	25
DMSO				

Streptomycin was used as standard. a 100 lg/mL of compound in each well.
Values are average of three readings

5. CONCLUSION:

In conclusion, we have disclosed a novel and convenient one-pot synthesis of substituted amino pyrazole analogues via one pot multi-component reactions. This catalyst-free reaction proceeded smoothly in good to excellent yields and offered several 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 excellent model reaction for the synthesis of this class of compounds and in addition to study of the antibacterial potent activity of the target derivatives.

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