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MULTICOMPONENT SYNTHESIS OF AMINO PYRAZOLE PROMOTED BY PH_3P 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 Ph_3P 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, Ph_3P and Anti-microbial activity.

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INTRODUCTON

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 Triphenylphosphine catalyst (Scheme No.1).

MATRIAL AND METHODS

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.

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

Phenyl hydrazine, (1mmol) aromatic aldehyde (1mmol) and malononitrile (1mmol) 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 Ph_3P. The reaction was continued at 70^oC until 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.

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

White powder; Yeild-86%, M.P-160 -162^oC, IR (KBr, cm^{-1}): 3485, 3341, 3083, 2359, 1599, 1412, 1253, 1126, 1100, 1075cm−1. 1HNMR (400MHz, $CDCl_3$) δppm: 6.954 (t, J = 7.6 Hz, 1H), 7.116 (d, J = 7.8 Hz, 2H, Ar-H), 7.295-7.356 (m, 3H, Ar-H), 7.442 (t, J = 8.4 Hz, 2H, Ar-H), 7.684 (s, 1H, Ar-H), 7.760 (d, J=8.0Hz, 2H, Ar-H), 7.814 (s, 1H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 112.45, 113.78, 121.52, 126.09, 128.49, 129.15, 129.84, 135.66, 137.94, 145.09, 150.41, 156.50. LCMS (m/z): 260.54 (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.

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

Yellow powder; Yeild-90%, M.P. = 175–177^oC, IR (KBr, cm^{-1}): 3580, 3415, 3355, 3124, 2324, 2184, 1605, 1415, 1224, 1191, 1106, 1052 cm−1. ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.824 (t, J = 6.8 Hz, 1H, Ar-H), 6.856–6.940 (m, 2H,Ar-H), 6.968 (d, J = 7.6Hz, 2H Ar-H), 7.114-7.118 (m, 1H Ar-H), 7.241 (d, J = 7.6 Hz , 2H Ar-H), 7.544 (d, J = 7.2 Hz , 1H

Ar-H), 8.114 (s, 1H Ar-H), 9.386(s, 1H,-OH), ^{13}CNMR (100MHz, $CDCl_3$) δppm: 112.77, 117.54, 119.85, 120.87, 122.43, 126.88, 128.55, 129.05, 130.65, 138.88, 146.60, 150.05, 153.36, and 156.50: 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.

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

Pale Pink solid; Yield- 86%, M.P.-187–189^{o}C, IR (KBr, cm^{-1}): 3480, 3325, 3058, 2965, 2312, 1597, 1416, 1250, 1122, 1110 and 1055. ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 2.154 (s, 3H,CH_3), 6.915 (d, J = 6.8 Hz, 1H, Ar-H), 7.150 (d, J = 7.6 Hz, 2H, Ar-H), 7.226 (d, J= 7.6 Hz, 2H, Ar-H), 7.295-7.335 (m, 2H, Ar-H), 7.554 (d, J = 8.8Hz, 2H, Ar-H), 7.774 (s, 2H, Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 20.77, 105.87, 114.77, 121.58, 127.06, 128.27, 129.33, 131.35, 138.04, 140.47, 146.20, 149.82 and 154.20. 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.

5-Amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4d)

White solid; Yield- 89%, M.P.- 189–191^{o}C, IR (KBr, cm^{-1}): 3446, 3317, 3058, 2328, 1594, 1417, 1290, 1251, 1131, 1078. ^{1}HNMR (400MHz, $CDCl_3$) δppm: 6.887 (t, J =9.2Hz, 1H, Ar-H), 7.154 (d, J = 7.6 Hz, 2H, Ar-H), 7.287–7.324 (m, 2H, Ar-H), 7.386 (d, J= 8.0 Hz, 2H,Ar-H), 7.622 (d, J = 8.8 Hz, 2H,Ar-H), 7.671 (s, 2H, NH_2). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 112.68, 114.57, 121.87, 128.07, 128.78, 129.45, 132.28, 134.17, 137.87, 145.88, 151.55, 156.87. 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.

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

Red compound; Yield- 84%, M.P. - 169–171^{o}C, IR (KBr, cm^{-1}): 3464, 3352, 3105, 2354, 1602, 1418, 1459, 1342, 1250, 1121, 1108, 1091; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.258 (s, 2H, .NH_2) 7.188 (d, J = 6.8 Hz, 2H, Ar-H), 7.295–7.344 (m, 2H, Ar-H), 7.753–.794 (m, 3H, Ar-H), 8.110 (s, 1H, Ar-H), 8.254 (d, J=8.4 Hz, 2H, Ar-H); LCMS (m/z): 306.38 (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

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

Orange solid; Yield- 83%, M.P- 158–160^{o}C, IR (KBr, cm^{-1}): 3450, 3322, 3108, 2329, 1590, 1475, 1444, 1342, 1330, 1264, 1145, 1102 and 1092. ^{1}HNMR (400MHz, CDCl3) δppm : 6.158 (s, 2H, NH_2), 7.118 (d, J =8.4 Hz, 2H, Ar-H), 7.366 (t, J=8.8 Hz, 2H, Ar-H), 7.586 (t, J =7.2 Hz, 1H, Ar-H), 7.778 (s, 1H, Ar-H), 7.829 (s, 1H, Ar-H), 8.024 (d, J =8.0 Hz, 1H, Ar-H), 8.144 (d, J =8.0 Hz, 1H), 8.488 (s, 1H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 112.66, 115.04, 120.95, 121.38, 123.55, 128.58, 129.74, 131.08, 135.12, 138.77, 145.22, 149.66, 156.58. LCMS (m/z): 305.65 (M+). Molecular formulae: $C_{16}H_{11}N_5O_2$: C, Analysis of Elements: Calculated: C-62.95; H- 3.63; N- 22.94; Obtained: C- 62.78; H- 3.77; N- 22.90.

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

Yellow powder; Yield- 84%, M.P. = 174–176^{o}C; IR (KBr, cm^{-1}): 3435, 3329, 3066, 2319, 1601, 1475, 1296, 1261, 1136, and 1065. 1HNMR (400MHz, $CDCl_3$) δppm: 6.258 (s, 2H, NH_2), 7.066(d, J = 6.8 Hz, 1H), 7.152 (d, J =8.4 Hz, 2H), 7.345 (dd, J = 5.4 Hz and J = 11.8Hz, 3H), 7.568 (s, 1H, Ar-H), 7.854 (s, 1H, Ar-H). 13CNMR (100MHz, CDCl3) δppm: 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

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 No.1).

To observed that the optimized the reaction conditions, we initially a catalyst evaluated exercise employing substituted aryl aldehyde (1mmol),

malononitrile (1mmol), and phenyl hydrazine (1mmol) 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.

The amount of catalyst is very most significant role play during in this reaction; 1mmole amount of the catalyst was utilized in starting, acquired traces amount of product and gradually developing upto 5mmol amount of the catalyst during the reaction. Hence, maximum amount yield obtained (90). Further, amount of the catalyst increased up to entry "5" and get no improvement as shown Table No.2.

The above catalyst play a significant role play during the reaction process, we maintained to the examination of solvent effects by using a various types of solvents, including H_2O, CH_3CN, EtOH, MeOH and MDC. The observations are found that the 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 No.3).

In order to investigate the catalytic function of Ph_3P, 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 developed 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 No.4). We were able to attain 93% 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 thiazole group of desired compounds appeared at 156-155. ^{1}HNMR values different protons shown at 8.488 δppm of pyrazine molecules, 6.258 δppm of NH_2 protons. The hydroxyl proton appear at9.386 δppm.

Biological activity

The results of the above Table No.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 active potent. The compound 4e and 4f exhibited moderate active potential due to Nitro groups present in the compound. We also observed the Antifungal Activity of compound (4a-4g) exhibited different activity compound 4d showed good activity and rate of the compound showed low to moderate activity.

Table No.1: Comparison among the various catalyst synthesis of titled compound (4b)

Entry	Catalyst	Time (min)	Yield (%)
1	DBU	120	58
2	DABCO	120	46
3	K_2CO_{32}	120	62
4	Ph3N	120	92
5	Et3N,	120	65

Table No.2: Optimization amount of the catalyst (Ph_3P) for synthesis of derivatives (4b)

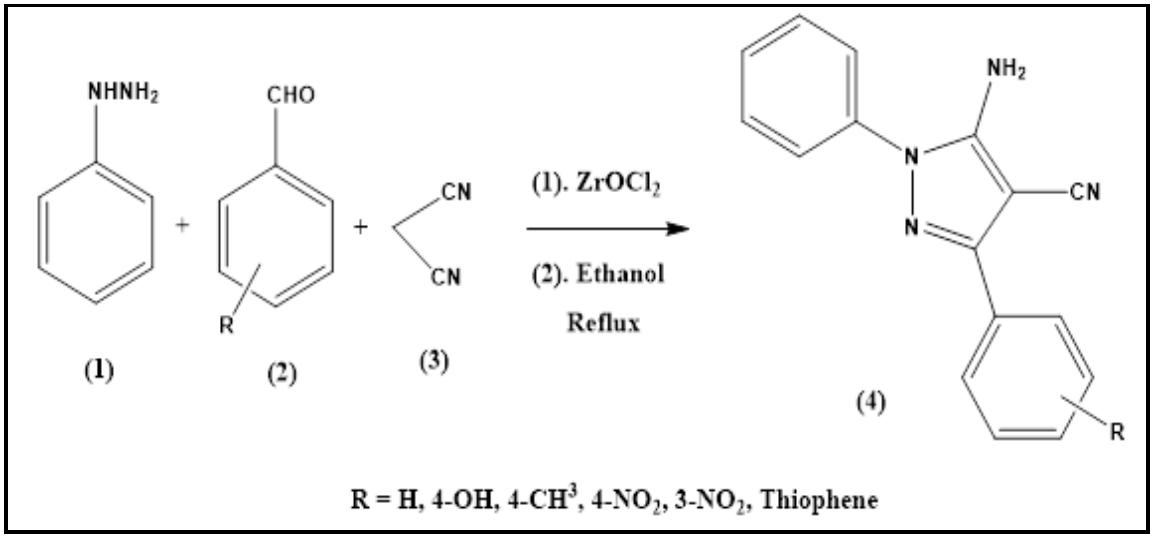
Entry	Catalyst (mmol)	Time (min)	Yield (%)
1	1.0	120	traces
2	2.5	120	40
3	5.0	120	90
4	10	120	90
5	15	120	90

Table No.3: The comparison of the solvent for synthesis of compound (4b)

Entry	Catalyst (mmol)	Time (min)	Yield (%)
1	H_2O	120	10
2	MeOH	120	48
3	EtOH	120	90
4	DMF	120	56
5	MDC	120	68

Table No.4: Antimicrobial activity screening activity synthesized scaffold

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S.aureus	*E.coli*	*S. typhi*	*B.substills*	*A. niger*	*C. albicans*
1	4a	05	05	07	06	04	05
2	4b	15	16	16	17	10	11
3	4c	18	19	18	18	12	14
4	4d	21	21	19	20	17	16
5	4e	10	12	15	14	12	10
6	4f	12	10	10	12	10	09
7	4g	12	10	11	09	07	07
8	Streptomycin	25	25	22	22	NA	NA
9	Fluconazole	NA	NA	NA	NA	20	20
10	DMSO	---	----	---	---	---	---



Scheme No.1

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 Ph_3P 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.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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