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RESEARCH ARTICLE

A Facile One Post Synthesis of Pyrano[2,3-*c*] Pyrazoles with Implement of Various Basic Catalysts and its Biological Evaluation

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ABSTRACT

A series of pyrano[2,3-c]pyrazoles, was efficiently synthesized via one-pot, multi component reaction(MCRs) of 3-amino-1H-pyrazol-5(4H)-one, aromatic aldehydes and malononitrile in the presence of various basic catalyst. The key advantages of this process are high yields, shorter reaction times, easy work-up, and purification of products by non-chromatographic method.

KEYWORDS

Pyrano[2,3-c]Pyrazoles, Multi Component Reaction, Non-Chromatographic Method

INTRODUCTION

Multi component reactions (MCRs) have more importance, great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity[1,2]. MCRs comply with the principles of green chemistry in terms of economy of steps as well as many of the rigid criteria of an ideal organic synthesis. These reactions are effective in construction highly functionalized small organic molecules from readily available starting materials in a single step with natural flexibility for creating molecular complexity and diversity coupled with minimization of time, labor, cost and waste production[3-6]. The pyranopyrazole nucleus is a fertile source of biologically important molecules. Compounds containing this moiety have many pharmacological properties and play important roles in biochemical processes.

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They are reported to possess a multiplicity of pharmacological properties including anticancer[7], antimicrobial[8], anti-inflammatory[9], insecticidal, and molluscicidal activities[10,11]. They are also potential inhibitors of human Chk1 kinase[12]. They also find applications as pharmaceutical ingredients and biodegradable agrochemicals[13]. In a view of great importance of pyranopyrazoles various methods for synthesis of 6-amino-5-cyanodihydro-pyrano-[2,3-c]pyrazoles has been reported. During the last few years, some methods were introduced for the synthesis of these compounds. Pyranopyrazoles were first obtained in 1973 by reaction between 3-methyl-1 phenylpyrazolin-5-one and tetracyanoethylene[14]. After this Otto had proposed the synthesis of the dihydropyrano[2,3-c] pyrazoles in 1974, via the base catalyzed cycloaddition of 4-aryliden-5-pyrazolone[15]. Sharanin and research group have developed a three-component reaction between pyrazolone, an aldehyde and malononitrile in ethanol using triethylamine as the catalyst[16]. Kappusami and co-workers have developed solvent-free multicomponent synthesis of

pyranopyrazoles using per-6-amino-β-cyclodextrin as a catalyst[17]. More recently Myrboh et al. reported the synthesis of pyranopyrazoles using L-proline and γ-alumina as catalyst[18]. As a part of ongoing program on the development of novel methods in organic synthesis, we report herein a simple, rapid and high yielding one pot three component reaction protocol for the synthesis of pyranopyrazole derivatives employing environmentally friendly wide range of basic catalyst.

EXPERIMENTAL

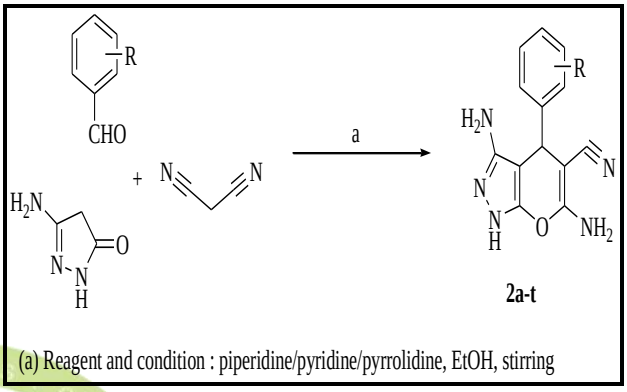
All research chemicals were purchased from Sigma–Aldrich and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates from E-Merck Co and compounds visualized either by exposure to UV. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on SHIMADZU- FTIR-8400 spectrophotometer using KBr pellet method. ^{1}H spectra were recorded on Bruker 400-MHz NMR spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectrum was recorded on JOEL SX 102/DA-600-Mass spectrometer and elemental analysis was carried out using Heraus C, H, N rapid analyzer.

Synthesis of Synthesis of 3-amino-1H-pyrazol-5(4H)-one [1]

3-amino-1H-pyrazol-5(4H)-one was prepared by known literature method.[19] Synthesis of Pyrazolon **[1]** was accomplished by condensing ethylcyano acetate with hydrazine hydrate (99%) in stirring without solvent at room temperature for 15 minutes. After this solid was falls out filter it and washed with diethyl ether and stored at low temperature.

General procedure for the synthesis of 3,6-diamino-1,4-dihydro-4-subarylpyrano[2,3-c]pyrazole-5-carbonitrile 2(a-t)

At first, substituted benzaldehyde (0.01 mol), malononitrile (0.01 mol) and piperidine/pyridine/pyrrolidine as a catalyst (1 drop) and ethanol as solvent was stirred for 2 min, then 3-amino-1H-pyrazole-5(4H)-one (0.01 mol) was added to this mixture and stirred at room temperature for 15-60 min. The reaction was monitored by TLC. The solid was falls out which indicates completion of reaction. Solids was filtered out and washed by cold ethanol and after that was crystallized from hot ethanol to afford the pure products. Some derivatives have good crystalline property while most of were fluffy in nature.



Scheme 1: Synthesis of 3,6-diamino-1,4-dihydro-4-subarylpyrano[2,3-c]pyrazole-5-carbonitrile

Table 1: Physical parameters of substituted pyranopyrazole derivatives

Code	R	M.F.	M.W.	M.P. °C	R_f
2a	4-H	$C_{13}H_{11}N_5O$	253	168-171	0.55
2b	4-CH_3	$C_{14}H_{13}N_5O$	267	188-190	0.51
2c	4-OCH_3	$C_{14}H_{14}N_5O_2$	283	184-186	0.61
2d	2,5-OCH_3	$C_{15}H_{15}N_5O_3$	313	188-190	0.57
2e	3,4-OCH_3	$C_{15}H_{15}N_5O_3$	313	180-182	0.48
2f	3,4,5-OCH_3	$C_{16}H_{17}N_5O_4$	343	173-175	0.60
2g	4-Cl	$C_{13}H_{10}Cl$	28	189-	0.52

		N_5O	7	191	
2h	3-Cl	$C_{13}H_{10}ClN_5O$	287	218-220	0.62
2i	2-Cl	$C_{13}H_{10}ClN_5O$	287	148-150	0.50
2j	2,4-Cl	$C_{13}H_{10}Cl_2N_5O$	322	198-200	0.56
2k	2,6-Cl	$C_{13}H_9Cl_2N_5O$	322	208-210	0.49
2l	4-Br	$C_{13}H_{10}BrN_5O$	332	220-222	0.47
2m	3-Br	$C_{13}H_{10}BrN_5O$	332	194-196	0.52
2n	2-Br	$C_{13}H_{10}BrN_5O$	332	230-232	0.50
2o	4-F	$C_{13}H_{10}FN_5O$	271	270-273	0.58
2p	4-OH	$C_{13}H_{11}N_5O_2$	269	138-140	0.61
2q	2-OH	$C_{13}H_{11}N_5O_2$	269	185-187	0.56
2r	4-NO_2	$C_{13}H_{10}N_6O_3$	298	188-190	0.49
2s	3-NO_2	$C_{13}H_{10}N_6O_3$	298	183-185	0.53
2t	2-NO_2	$C_{13}H_{10}N_6O_3$	298	181-183	0.59

TLC Solvent system: Hexane: Ethyl acetate - 6:4.

3,6-diamino-1,4-dihydro-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (2a)

Mp 168-171ºC; IR (cm^{-1}): 3412 (N-H stretching of free primary amine), 3220 (N-H stretching of pyrazole ring), 3121 (C-H stretching of aromatic ring), 2181 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazole ring), 1612 (N-H deformation pyrazole ring), 1178 (N-N deformation of pyrazole ring), 1049 (C-H in plane bending of aromatic ring), 725 (C-H out of plane bending for monosubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.50 (s, 1H, -CH), 5.32 (s, 2H, -NH_2), 6.22 (s, 2H, -NH_2), 6.68-6.72 (m, 5H, Ar-H), 11.12 (s, 1H, -NH); MS: *m/z* 253; Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65; O. Found: C, 61.63; H, 4.39; N, 27.64%.

3,6-diamino-1,4-dihydro-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile (2b)

Mp 188-190ºC; IR (cm^{-1}): 3473 (N-H stretching of free primary amine), 3227 (N-H stretching of pyrazole ring), 3117 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1635 (C=N stretching of pyrazole ring), 1600 (N-H deformation pyrazole ring), 1188 (N-N deformation of pyrazole ring), 1053 (C-H in plane bending of aromatic ring), 806 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.30 (s, 3H, -CH_3), 4.50 (s, 1H, -CH), 5.20 (s, 2H, -NH_2), 6.40 (s, 2H, -NH_2), 7.01-709 (m, 4H, Ar-H, *J* = 16.92 Hz), 11.88 (s, 1H, -NH); MS: *m/z* 267; Anal. Calcd. for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.92; H, 4.92; N, 26.19%.

3,6-diamino-1,4-dihydro-4-(4-methoxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2c)

Mp 184-186ºC; IR (cm^{-1}): 3487 (N-H stretching of free primary amine), 3234 (N-H stretching of pyrazole ring), 3057 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazole ring), 1604 (N-H deformation pyrazole ring), 1287 (C-O stretching of methoxy group), 1182 (N-N deformation of pyrazole ring), 1049 (C-H in plane bending of aromatic ring), 826 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 3.76 (s, 3H, -OCH_3), 4.50 (s, 1H, -CH), 5.14 (s, 2H, -NH_2), 6.22 (s, 2H, -NH_2), 6.80-6.82 (dd, 2H, Ar-H), 7.07-7.09 (dd, 2H, Ar-H), 11.84 (s, 1H, -NH); MS: *m/z* 283; Anal. Calcd. for $C_{14}H_{13}N_5O_2$: C,

59.36; H, 4.63; N, 24.72. Found: C, 59.36; H, 4.64; N, 24.75%.

3,6-diamino-1,4-dihydro-4-(2,5-dimethoxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2d)

Mp 188-190ºC; IR (cm^{-1}): 3470 (N-H stretching of free primary amine), 3211 (N-H stretching of pyrazole ring), 3107 (C-H stretching of aromatic ring), 2190 (C≡N stretching of the nitrile group), 1625 (C=N stretching of pyrazole ring), 1605 (N-H deformation pyrazole ring), 1274 (C-O stretching of methoxy group), 1180 (N-N deformation of pyrazole ring), 1050 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 3.72 (s, 3H, -OCH_3), 3.94 (s, 3H, -OCH_3), 4.59 (s, 1H, -CH), 5.09 (s, 2H, -NH_2), 6.43 (s, 2H, -NH_2), 6.71-6.77 (m, 3H, Ar-H), 11.32 (s, 1H, -NH); MS: *m/z* 313; Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.51; H, 4.82; N, 22.38%.

3,6-diamino-1,4-dihydro-4-(3,4-dimethoxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2e)

Mp 180-182ºC; IR (cm^{-1}): 3465 (N-H stretching of free primary amine), 3215 (N-H stretching of pyrazole ring), 3122 (C-H stretching of aromatic ring), 2187 (C≡N stretching of the nitrile group), 1641 (C=N stretching of pyrazole ring), 1612 (N-H deformation pyrazole ring), 1280 (C-O stretching of methoxy group), 1175 (N-N deformation of pyrazole ring), 1048 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 3.65 (s, 3H, -OCH_3), 3.85 (s, 3H, -OCH_3), 4.23 (s, 1H, -CH), 5.26 (s, 2H, -NH_2), 6.21 (s, 2H, -NH_2), 7.01-709 (m, 3H, Ar-H), 11.19 (s, 1H, -NH); MS: *m/z* 313; Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.49; H, 4.80; N, 22.33%.

3,6-diamino-1,4-dihydro-4-(3,4,5-trimethoxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2f)

Mp 173-175ºC; IR (cm^{-1}): 3462 (N-H stretching of free primary amine), 3214 (N-H stretching of pyrazole ring), 3126 (C-H stretching of aromatic ring), 2180 (C≡N stretching of the nitrile group), 1628 (C=N stretching of pyrazole ring), 1591 (N-H deformation pyrazole ring), 1271 (C-O stretching of methoxy group), 1182 (N-N deformation of pyrazole ring), 1059 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 3.81 (s, 9H, -OCH_3), 4.61 (s, 1H, -CH), 5.24 (s, 2H, -NH_2), 6.47 (s, 2H, -NH_2), 7.11-7.19 (s, 2H, Ar-H), 11.56 (s, 1H, -NH); MS: *m/z* 343; Anal. Calcd. for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40. Found: C, 55.98; H, 4.96; N, 20.42%.

3,6-diamino-4-(4-chlorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2g)

Mp 189-191ºC; IR (cm^{-1}): 3465 (N-H stretching of free primary amine), 3231 (N-H stretching of pyrazole ring), 3121 (C-H stretching of aromatic ring), 2190 (C≡N stretching of the nitrile group), 1628 (C=N stretching of pyrazole ring), 1610 (N-H deformation pyrazole ring), 1180 (N-N deformation of pyrazole ring), 1049 (C-H in plane bending of aromatic ring), 845 (C-Cl stretching), 811 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.56 (s, 1H, -CH), 5.11 (s, 2H, -NH_2), 6.26 (s, 2H, -NH_2), 6.56-6.63 (dd, 2H, Ar-H), 6.89-6.96 (dd, 2H, Ar-H), 11.10 (s, 1H, -NH); MS: *m/z* 287; Anal. Calcd. for $C_{13}H_{10}ClN_5O$: C, 54.27; H, 3.50; N, 24.34. Found: C, 54.25; H, 3.52; N, 24.36%.

3,6-diamino-4-(3-chlorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2h)

Mp 218-220ºC; IR (cm^{-1}): 3471 (N-H stretching of free primary amine), 3212 (N-H stretching of pyrazole ring), 3125 (C-H stretching of aromatic ring), 2188 (C≡N stretching of the nitrile group), 1614 (C=N stretching of pyrazole ring), 1590 (N-H deformation pyrazole ring), 1178 (N-N deformation of pyrazole ring), 1061 (C-H in plane bending of aromatic ring), 829 (C-Cl stretching), 760 (C-H out of plane bending for 1,3-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.65 (s, 1H, -CH), 5.12 (s, 2H, -NH_2), 6.32 (s, 2H, -NH_2), 6.91-6.99 (m, 4H, Ar-H), 11.22 (s, 1H, -NH); MS: *m/z* 287; Anal. Calcd. for $C_{13}H_{10}ClN_5O$: C, 54.27; H,

3.50; N, 24.34. Found: C, 54.28; H, 3.51; N, 24.33%.

3,6-diamino-4-(2-chlorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2i)

Mp 148-150ºC; IR (cm^{-1}): 3462 (N-H stretching of free primary amine), 3220 (N-H stretching of pyrazole ring), 3120 (C-H stretching of aromatic ring), 2197 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazole ring), 1611 (N-H deformation pyrazole ring), 1181 (N-N deformation of pyrazole ring), 1066 (C-H in plane bending of aromatic ring), 851 (C-Cl stretching), 742 (C-H out of plane bending for 1,2-disubstituted aromatic ring); ^{1}H NMR (DMSO-*d*$_6$) δ ppm: 4.55 (s, 1H, -CH), 5.28 (s, 2H, -NH_2), 6.36 (s, 2H, -NH_2), 6.74-6.82 (m, 4H, Ar-H), 11.05 (s, 1H, -NH); MS: *m/z* 287; Anal. Calcd. for $C_{13}H_{10}ClN_5O$: C, 54.27; H, 3.50; N, 24.34. Found: C, 54.25; H, 3.52; N, 24.36%.

3,6-diamino-4-(2,4-dichlorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2j)

Mp 198-200ºC; IR (cm^{-1}): 3472 (N-H stretching of free primary amine), 3230 (N-H stretching of pyrazole ring), 3112 (C-H stretching of aromatic ring), 2189 (C≡N stretching of the nitrile group), 1628 (C=N stretching of pyrazole ring), 1610 (N-H deformation pyrazole ring), 1175 (N-N deformation of pyrazole ring), 1041 (C-H in plane bending of aromatic ring), 812 (C-Cl stretching); ^{1}H NMR (DMSO-*d*$_6$) δ ppm: 2.30 (s, 3H, -CH_3), 4.50 (s, 1H, -CH), 5.20 (s, 2H, -NH_2), 6.40 (s, 2H, -NH_2), 7.01-709 (m, 4H, Ar-H, *J* = 16.92 Hz), 11.88 (s, 1H, -NH); MS: *m/z* 322; Anal. Calcd. for $C_{13}H_9Cl_2N_5O$: C, 48.47; H, 2.82; N, 21.74. Found: C, 48.48; H, 2.80; N, 21.76%.

3,6-diamino-4-(2,6-dichlorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2k)

Mp 208-210ºC; IR (cm-1): 3450 (N-H stretching of free primary amine), 3088 (C-H stretching of aromatic ring), 2198 (C≡N stretching of the nitrile group), 1662 (C=N stretching of pyrazole ring), 1134 (N-N deformation of pyrazole ring), 1068 (C-H in plane bending of aromatic ring), 820 (C-Cl stretching); 1H NMR (DMSO-*d6*) δ ppm: 5.63 (s, 1H, -CH), 6.31 (s, 2H, -NH_2), 6.60 (s, 2H, -NH_2), 7.21-7.28 (m, 2H, Ar-H), 7.41-7.43 (dd, 1H, Ar-H, *J* = 7.68 Hz), 11.91 (s, 1H, -NH); MS: *m/z* 322; Anal. Calcd. for $C_{13}H_9Cl_2N_5O$: C, 48.47; H, 2.82; N, 21.74. Found: C, 48.48; H, 2.81; N, 21.76%.

3,6-diamino-4-(4-bromophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2l)

Mp 220-222ºC; IR (cm^{-1}): 3466 (N-H stretching of free primary amine), 3230 (N-H stretching of pyrazole ring), 3101 (C-H stretching of aromatic ring), 2215 (C≡N stretching of the nitrile group), 1630 (C=N stretching of pyrazole ring), 1606 (N-H deformation pyrazole ring), 1180 (N-N deformation of pyrazole ring), 1058 (C-H in plane bending of aromatic ring), 806 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-*d*$_6$) δ ppm: 4.47 (s, 1H, -CH), 5.14 (s, 2H, -NH_2), 6.38 (s, 2H, -NH_2), 6.52-6.54 (dd, 2H, Ar-H), 7.01-7.09 (dd, 2H, Ar-H), 11.35 (s, 1H, -NH); MS: *m/z* 332; Anal. Calcd. for $C_{13}H_{10}BrN_5O$: C, 47.01; H, 3.03; N, 21.08. Found: C, 47.03; H, 3.04; N, 21.11%.

3,6-diamino-4-(3-bromophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2m)

Mp 194-196ºC; IR (cm^{-1}): 3484 (N-H stretching of free primary amine), 3222 (N-H stretching of pyrazole ring), 3134 (C-H stretching of aromatic ring), 2190 (C≡N stretching of the nitrile group), 1622 (C=N stretching of pyrazole ring), 1610 (N-H deformation pyrazole ring), 1185 (N-N deformation of pyrazole ring), 1049 (C-H in plane bending of aromatic ring), 778 (C-H out of plane bending for 1,3-disubstituted aromatic ring); ^{1}H NMR (DMSO-*d*$_6$) δ ppm: 4.39 (s, 1H, -CH), 5.28 (s, 2H, -NH_2), 6.41 (s, 2H, -NH_2), 6.67-6.73 (m, 4H, Ar-H), 11.27 (s, 1H, -NH); MS: *m/z* 332; Anal. Calcd. for $C_{13}H_{10}BrN_5O$: C, 47.01; H, 3.03; N, 21.08. Found: C, 47.03; H, 3.04; N, 21.11%.

3,6-diamino-4-(2-bromophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2n)

Mp 230-232ºC; IR (cm^{-1}): 3463 (N-H stretching of free primary amine), 3201 (N-H stretching of pyrazole ring), 3121 (C-H stretching of aromatic ring), 2231 (C≡N stretching of the nitrile group), 1640 (C=N stretching of pyrazole ring), 1615 (N-H deformation pyrazole ring), 1177 (N-N deformation of pyrazole ring), 1034 (C-H in plane bending of aromatic ring), 722 (C-H out of plane bending for 1,2-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.57 (s, 1H, -CH), 5.26 (s, 2H, -NH_2), 6.45 (s, 2H, -NH_2), 6.64-6.70 (m, 4H, Ar-H), 11.61 (s, 1H, -NH); MS: *m/z* 332; Anal. Calcd. for $C_{13}H_{10}BrN_5O$: C, 47.01; H, 3.03; N, 21.08. Found: C, 47.03; H, 3.04; N, 21.11%.

3,6-diamino-4-(4-fluorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2o)

Mp 184-186 ºC; IR (cm-1): 3487 (N-H stretching of free primary amine), 3234 (N-H stretching of pyrazole ring), 3057 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazole ring), 1604 (N-H deformation pyrazole ring), 1328 (C-F stretching of substituted aryl ring), 1182 (N-N deformation of pyrazole ring), 1049 (CH in plane bending of aromatic ring), 826 (C-H out of plane bending for 1,4- disubstituted aromatic ring); 1H NMR (DMSO-*d6*) δ ppm: 4.56 (s, 1H, -CH), 5.14 (s, 2H, -NH_2), 6.40 (s, 2H, -NH_2), 6.98-7.03 (t, 2H, Ar-H, *J* = 8.56 Hz), 7.16-7.19 (dd, 2H, Ar-H, *J* = 8.28 Hz), 11.92 (s, 1H, -NH); MS: *m/z* 271; Anal. Calcd. For $C_{13}H_{10}FN_5O$: C, 57.56; H, 3.72; N, 25.82. Found: C, 57.57; H, 3.73; N, 25.85%.

3,6-diamino-1,4-dihydro-4-(4-hydroxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2p)

Mp 138-140ºC; IR (cm^{-1}): 3477 (N-H stretching of free primary amine), 3220 (N-H stretching of pyrazole ring), 3123 (C-H stretching of aromatic ring), 2189 (C≡N stretching of the nitrile group), 1633 (C=N stretching of pyrazole ring), 1601 (N-H deformation pyrazole ring), 1182 (N-N deformation of pyrazole ring), 1052 (C-H in plane bending of aromatic ring), 809 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.54 (s, 1H, -CH), 5.29 (s, 2H, -NH_2), 5.71 (s, 1H, -OH), 6.28 (s, 2H, -NH_2), 6.66-6.70 (dd, 2H, Ar-H), 6.89-6.96 (dd, 2H, Ar-H), 11.32 (s, 1H, -NH); MS: *m/z* 269; Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 57.95; H, 4.10; N, 25.99%.

3,6-diamino-1,4-dihydro-4-(2-hydroxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2q)

Mp 185-187ºC; IR (cm^{-1}): 3469 (N-H stretching of free primary amine), 3224 (N-H stretching of pyrazole ring), 3110 (C-H stretching of aromatic ring), 2213 (C≡N stretching of the nitrile group), 1632 (C=N stretching of pyrazole ring), 1602 (N-H deformation pyrazole ring), 1185 (N-N deformation of pyrazole ring), 1048 (C-H in plane bending of aromatic ring), 732 (C-H out of plane bending for 1,2-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.59 (s, 1H, -CH), 5.34 (s, 2H, -NH_2), 5.89 (s, 1H, -OH), 6.32 (s, 2H, -NH_2), 6.78-6.85 (m, 4H, Ar-H), 11.45 (s, 1H, -NH); MS: *m/z* 269; Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 58.02; H, 4.10; N, 26.02%.

3,6-diamino-1,4-dihydro-4-(4-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2r)

Mp 188-190ºC; IR (cm^{-1}): 3465 (N-H stretching of free primary amine), 3225 (N-H stretching of pyrazole ring), 3113 (C-H stretching of aromatic ring), 2192 (C≡N stretching of the nitrile group), 1645 (C=N stretching of pyrazole ring), 1598 (N-H deformation pyrazole ring), 1188 (N-N deformation of pyrazole ring), 1053 (C-H in plane bending of aromatic ring), 821 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.47 (s, 1H, -CH), 5.31 (s, 2H, -NH_2), 6.64 (s, 2H, -NH_2), 6.45-6.52 (dd, 2H, Ar-H), 6.76-6.81 (dd, 2H, Ar-H), 11.49 (s, 1H, -NH); MS: *m/z* 298; Anal. Calcd. for $C_{13}H_{10}N_6O_3$: C, 52.35; H,

3.38; N, 28.18. Found: C, 52.36; H, 3.39; N, 28.15%.

3,6-diamino-1,4-dihydro-4-(3-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2s)

Mp 183-185ºC; IR (cm^{-1}): 3477 (N-H stretching of free primary amine), 3223 (N-H stretching of pyrazole ring), 3118 (C-H stretching of aromatic ring), 2192 (C≡N stretching of the nitrile group), 1630 (C=N stretching of pyrazole ring), 1617 (N-H deformation pyrazole ring), 1182 (N-N deformation of pyrazole ring), 1051 (C-H in plane bending of aromatic ring), 764 (C-H out of plane bending for 1,3-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.42 (s, 1H, -CH), 5.37 (s, 2H, -NH_2), 6.38 (s, 2H, -NH_2), 6.67-6.73 (m, 4H, Ar-H), 11.68 (s, 1H, -NH); MS: *m/z* 298; Anal. Calcd. For $C_{13}H_{10}N_6O_3$: C, 52.35; H, 3.38; N, 28.18. Found: C, 52.34; H, 3.36; N, 28.18%

3,6-diamino-1,4-dihydro-4-(2-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (2t)

Mp 181-183ºC; IR (cm^{-1}): 3478 (N-H stretching of free primary amine), 3222 (N-H stretching of pyrazole ring), 3123 (C-H stretching of aromatic ring), 2180 (C≡N stretching of the nitrile group), 1629 (C=N stretching of pyrazole ring), 1610 (N-H deformation pyrazole ring), 1190 (N-N deformation of pyrazole ring), 1052 (C-H in plane bending of aromatic ring), 726 (C-H out of plane bending for 1,2-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 4.58 (s, 1H, -CH), 5.31 (s, 2H, -NH_2), 6.25 (s, 2H, -NH_2), 6.67-6.73 (m, 4H, Ar-H), 11.23 (s, 1H, -NH); MS: *m/z* 298; Anal. Calcd. for $C_{13}H_{10}N_6O_3$: C, 52.35; H, 3.38; N, 28.18. Found: C, 52.38; H, 3.37; N, 28.19%

RESULT AND DISCUSSION

Several methods are used in the synthesis of these dihydropyrano[2,3-c]pyrazole derivatives.

The synthesis of these heterocycles has been usually carried out in polar protic organic solvents such as water, methanol and polar aprotic organic solvents such as acetonitrile, DMF and DMSO. The choice of a solvent is a crucial factor for multicomponent reactions. So at the first step we looked into the solvent selection for this reaction.

We had selected protic solvent ethanol for this reaction. Apart from the solvent, the efficiency of the multicomponent reactions is mainly affected by the catalyst and the reaction time. Here we employed variety of basic catalyst (piperidine/pyrrolidine/pyridine) and observed time for completion of reaction.

Basicity of catalyst effect on the rate of reaction. More basic catalyst completed reaction fast than other. So, here when reaction is carried out using piperidine as catalyst reaction takes less time for completion, while for pyrrolidine and pyridine take more time for completion.

Table 2: Effects of different catalysts on the reaction productivity

Code	Piperidine		Pyrrolidine		Pyridine	
	Yield %	Time (minute)	Yield %	Time (minute)	Yield %	Time (minute)
2a	89	15	82	25	74	30
2b	87	15	82	25	71	30
2c	89	15	80	25	77	30
2d	90	15	84	25	75	30
2e	84	15	81	25	72	30
2f	85	15	81	25	74	30
2g	88	15	82	25	72	30
2h	87	15	82	25	71	30
2i	86	15	80	25	74	30
2j	85	15	78	25	73	30
2k	88	15	80	25	70	30

2l	87	15	77	25	74	30
2m	89	15	82	25	75	30
2n	90	15	83	25	71	30
2o	91	15	81	25	75	30
2p	87	15	80	25	72	30
2q	85	15	80	25	71	30
2r	80	22	75	30	65	40
2s	81	22	75	35	64	38
2t	81	25	75	35	65	40

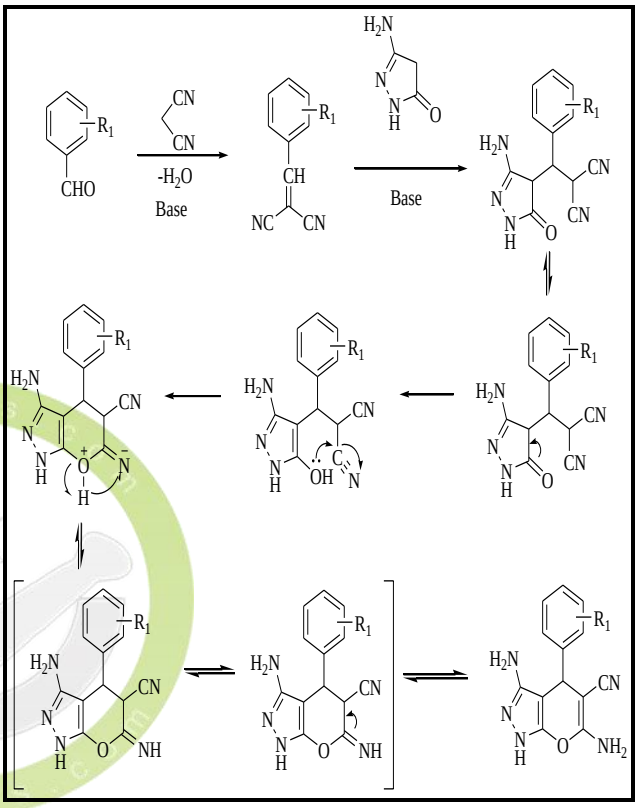
Possible mechanism for the base catalyzed synthesis of substituted pyranopyrazoles has been proposed in Scheme 2. In summary, this paper describes a convenient and efficient process for the synthesis of substituted pyranopyrazoles through the three components coupling of aldehydes, pyrazolone and malononitrile using variety of base as a catalyst.

Reaction profile is very clean and no side products are formed. All the synthesized pyranopyrazoles have been characterized on the basis of elemental and spectral studies.

Biological Evaluation

The miscellaneous biological activity of pyran and its fused derivatives inspired us to screen the newly synthesized compounds. Nowadays many antimicrobial agents have been applied for treatment; still the medical field needs extensive efforts for the development of new antimicrobial agents to overcome the highly resistant species of microbes.

All the synthesized compounds (2a-t) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two bacterial strains *S. aurues MTCC-96* and *B. subtillitis MTCC-441* and two fungal strains *A. niger MTCC-282* and *C. albicans MTCC-227* taking Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin and Griseofulvin as standard drugs. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMF at the same dilutions as used in the experiments and it was observed that DMF had no effect on the microorganisms in the concentrations studied. The results are depicted in (Table 3).



Scheme 2: Plausible mechanism for the formation of substituted pyranopyrazoles using base as a catalyst

CONCLUSION

In conclusion, we have developed a highly efficient heteropolyacid catalyzed, one pot, three component protocol for the synthesis of pyranopyrazoles via condensation of 3-amino-1H-pyrazol-5(4H)-one, aromatic aldehyde and malononitrile in the presence of base catalyst.

The advantages of this method are clean reaction, short reaction time, high yield, easy purification and economic availability of the catalyst.

The objective of the present study was to synthesize and investigate the anti-microbial activity of new pyranopyrazoles derivatives.

Table 3: Antibacterial and antifungal activity of synthesized compounds 2a-t

Code	Minimal inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	***S. p.***	***E.c.***	***P.a.***	***C. a.***	***A. n.***	***A.c.***
2a	**200**	**100**	**100**	**100**	**250**	1000	250
2b	500	500	250	250	**250**	200	200
2c	500	500	**100**	250	**500**	500	>1000
2d	500	500	250	500	**500**	>1000	1000
2e	**250**	**62.5**	250	500	>1000	>1000	>1000
2f	**100**	200	**62.5**	125	500	>1000	>1000
2g	**250**	250	250	500	1000	500	>1000
2h	**200**	500	**62.5**	500	1000	500	500
2i	**100**	200	500	500	**250**	>1000	>1000
2j	500	500	**100**	250	**250**	1000	250
2k	500	**62.5**	250	250	**250**	200	200
2l	**100**	250	**100**	250	**500**	500	>1000
2m	500	250	250	500	**500**	>1000	1000
2n	500	500	250	500	>1000	>1000	>1000
2o	500	**100**	**100**	125	**500**	>1000	1000
2p	**200**	500	250	500	1000	500	>1000
2q	**250**	500	**62.5**	500	1000	500	500
2r	**250**	500	500	500	**250**	>1000	>1000
2s	500	500	1000	1000	**500**	1000	1000
2t	**200**	**100**	**100**	500	**500**	1000	200
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

Bold letters indicate that synthesized compounds are comparatively active as standard drugs.

DMF used as control and its antibacterial activity is nil or zero.

S.a.- *Staphylococcus aureus MTCC-96* ***S.p.***- *Streptococcus pyogenes MTCC 443*

E.c.- *Escherichia coli MTCC 442* ***P.a.***- *Pseudomonas aeruginosa MTCC 441*

C. a.- *Candida albicans MTCC 227* ***A. n.***- *Aspergillus Niger MTCC 282*

A.c.- *Aspergillus clavatus* MTCC 1323

Results have suggested that pyranopyrazoles derivatives emerge as valuable compounds with great potential to be used as antibacterial agents, and as promising candidates for further efficiency evaluation. Some of the compounds were found to be moderate to low active against fungi, while other compounds are inactive.

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