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Green approach: A simple one-pot synthesis of pyranopyrazoles scaffold

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The past decade has witnessed significant progress in synthesizing structurally diverse and biologically relevant pyrano[2,3-c]pyrazole derivatives through the integration of green methodologies. A straightforward and environmentally friendly one-step method has been developed to synthesize divergent pyranopyrazoles in good yields with the aid of zinc acetate as a Lewis acid catalyst in toluene as solvent under reflux conditions.

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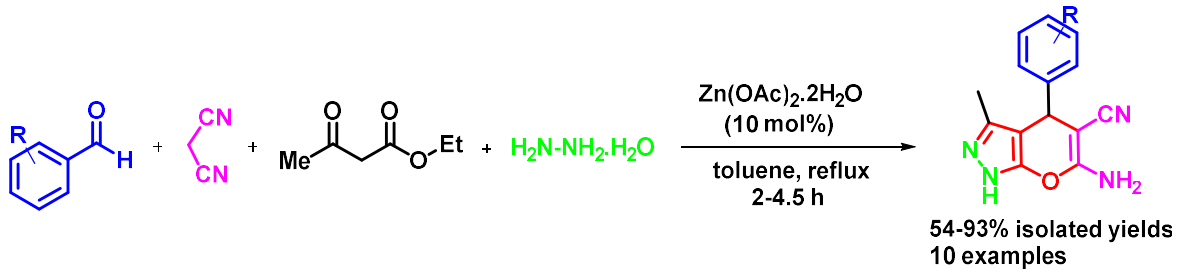

Graphical Abstract

1. Introduction

The first multicomponent reaction, credited to Strecker and dating to 1850, served as the catalyst for a string of reactions that have been documented in literature.[1] Multicomponent reactions (MCRs) are a unique class of synthetically useful organic reactions in which one or more different starting ingredients are combined in one pot to form a final product.[2-4] These reactions have been carefully used in a number of synthetic transformations, where traditional techniques typically demand for a lengthy process with numerous phases. High yields, atom-/step economy, shortened reaction times, environmental friendliness, and a useful tool for building a library of novel chemical entities (NCEs) are all benefits of the MCR technique, which is particularly useful in the drug development process.[5-9] In heterocyclic chemistry, the creation of highly convergent syntheses has been a constant since heterocyclic scaffolds frequently consist of more than two building

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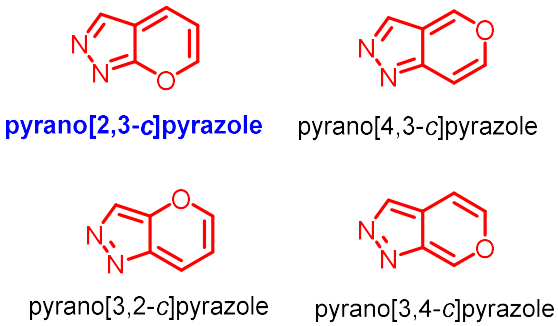
units.[10] Heterocycles' triumphant journey toward functional molecules has been closely linked to their synthesis by multicomponent reactions (MCRs) from the early days of organic chemistry.

As a subgroup of heterocycles, pyranopyrazoles have attracted a lot of interest because of their various structural roles and biological activity.[11-14] The four different isomer configurations of these compounds-pyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]pyrazole, pyrano[3,4-*c*]pyrazole, and pyrano[4,3-*c*]pyrazole-are made up of fused pyran and pyrazole rings (**Fig. 1**).



Figu. 1. Isomers of pyranopyrazoles

But because this isomer has biological importance, pyrano[2,3-*c*]pyrazoles are the ones that have been studied the most. These substances have demonstrated encouraging antiviral, antibacterial, anticancer, and anti-inflammatory qualities. Furthermore, they demonstrate the capacity to conceivably suppress the function of the human Chk1 kinase enzyme (**Figure 2**).[15-16] Because of their structural variety, it is possible to alter different parts of the molecule to affect their activity, which creates opportunities for research on the link between structure and activity. In the one-pot multicomponent reaction of pyranopyrazoles, the overall reaction scheme usually consists of an aldehyde, malononitrile, hydrazine hydrate, β-ketoester/ethyl acetoacetate, and a suitable catalyst or promoter. Condensation, cyclization, and subsequent rearrangement are some of the sequential transformations that the reaction goes through to produce the pyranopyrazole product. Undoubtedly, a great deal of study has gone into the synthesis of pyrano[2,3-*c*]pyrazole, leading to the discovery of a variety of techniques and synthetic pathways. Pyranopyrazole synthesis has been approached from different angles using catalysts like $PhCO_2Na$, thiamine hydrochloride, taurine, Fe/Cu nanocomposites, ethylene glycol (E-G), Fe3O4@chitosan-tannic acid bionanocomposite, piperidine, $SnCl_2$, dodecylbenzene sulfonic acid (DBSA), PTSA, ionic liquids, citric acid, β-cyclodextrin, NH_4Cl, ZrO_2-NPs, PS-PTSA, nano-eggshell/Ti(IV), thiamine hydrochloride, heteropolyacid, $PhCO_2Na$, chitosan hydrogel, taurine, Fe/Cu nanocomposites, ethylene glycol (E-G), Fe_3O_4@chitosan-tannic acid bionanocomposite, etc.[17-46] However, the majority of the material now in publication concentrates on attaining high yields and product diversity, frequently overshadowing the crucial significance of sustainability.

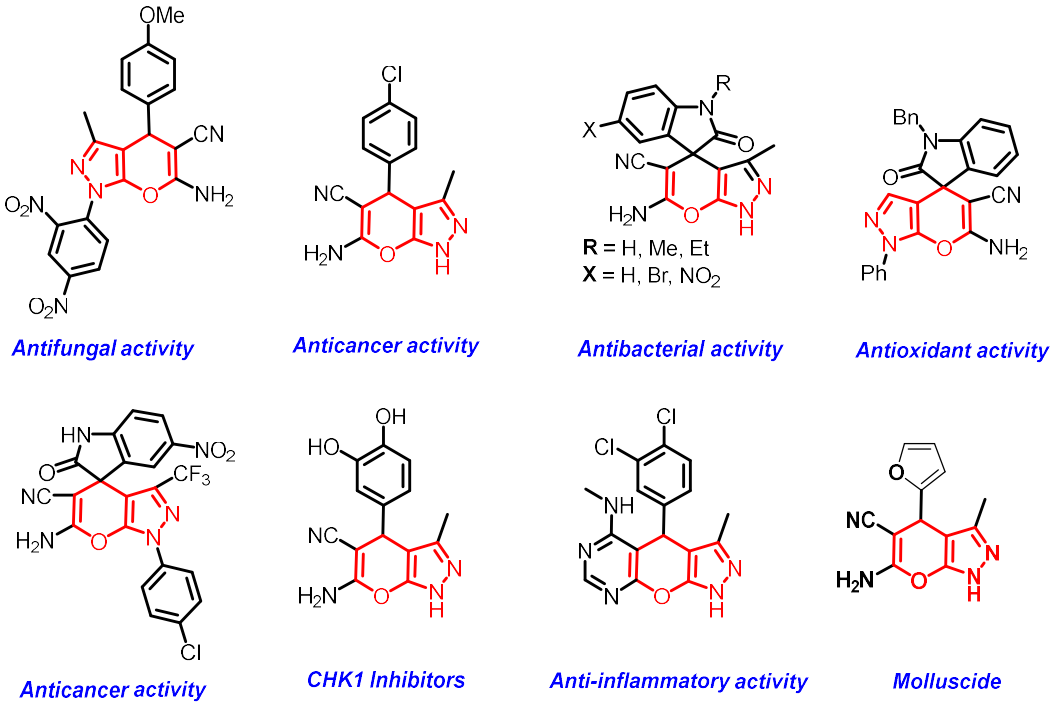


Fig. 2. Some biologically active pyrano[2,3-c]pyrazoles

Of the several zinc salts that are available, zinc acetate is one of the inexpensive, more easily obtained, and less toxic Lewis acids. Because of its peculiar physical and chemical characteristics, which show that it can be helpful in enabling a broad range of synthetic transformations in both organic synthesis and catalysis, it is known as a multifunctional catalyst.[47-54] Zinc acetate is affordable, easy to produce, and stable in the presence of oxygen and moisture when used in laboratory conditions. As a follow-up to earlier studies and a current addition to green synthetic methods, we report a one-pot multicomponent synthesis of pyranopyrazole. Following a comprehensive analysis of all pertinent published data, we came to the conclusion that $Zn(OAc)_2•2H_2O$ was not involved in the relevant reaction.

2. Results and Discussion

2.1 Effect of zinc salts, solvents and temperature

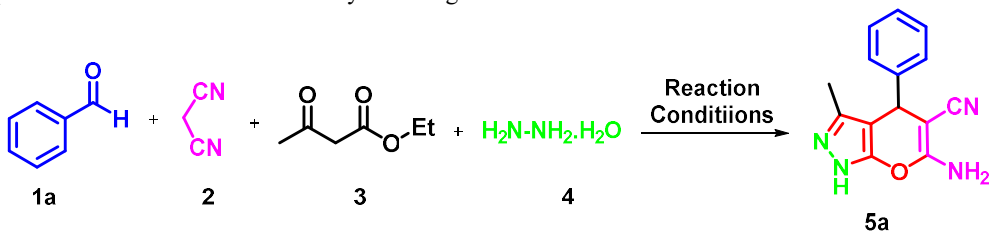
Later, various zinc catalysts were examined under controlled circumstances to determine how well they supported the control reaction on benzaldehyde, hydrazine hydrate, malanonitrile and ethyl acetoacetate (**Table 1**). $Zn(OAc)_2.2H_2O$ (10 mol%) was found to be the most effective catalyst when compared to the other catalysts tested ($ZnCl_2$, ZnO, $Zn(NO_3)_2$, $ZnCO_3$ and $ZnSO_4$) in terms of reaction time and yield at reflux temperature in toluene as solvent. The control reaction was determined to be viable at 110 °C. The related product was produced in minimal or small amounts when the temperature was gradually lowered till ambient temperature. The reaction can produce the best results at 5 mol%, according to studies of catalyst loading (5, 7.5, and 10 mol%). Higher catalyst concentrations (12.5 and 15 mol%) had no effect on the yield either up or down.

Table 1. Effect of available zinc salts tested

Entry	Zinc salt	Reaction time (h)	Isolated yield (%)[a]
1	$ZnCl_2$	4.5	64
2	ZnO	24	7
3	$Zn(NO_3)_2$	48	11
4	$ZnCO_3$	48	NR
5	$ZnSO_4$	24	NR
5	$Zn(OAc)_2.2H_2O$	2	89

Toluene emerged as the superior solvent under reflux conditions proved to be the most effective reaction condition (**Table 2**, Entry 1), surpassing other less efficient solvents (Table 2, entries 2-6). Non polar solvents (entries 1 and 6) proved to be better compared to that of polar solvents (entries 2-5) as evident from Table 2. For this reason, we further prepared derivatives from the above standard reaction condition (**Figure 3**). The results revealed that aldehydes with electron-withdrawing groups or electron-donating groups have similar effect. Important to note is functional group ($-NO_2$) be at *ortho*-, *meta*-, or *para*- position has no steric effect to form the corresponding pyranopyrazoles (**5f**, **5g** and **5h**, Figure 3). Heteroaromatic aldehyde such as furfural gave the product **5i** in good yield. However, aliphatic aldehyde (*n*-butanal) reacted sluggishly to give the corresponding product **5j**.

Table 2. Optimization of the solvent and catalyst loading



1a 2 3 4 5a

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[a,b]
1	$PhCH_3$	Room temperature 110 °C	8 2	23 89
2	CH_3CN	Reflux	6	18
3	EtOAc	Reflux	4	43
4	EtOH	Reflux	8	28
5	$CHCl_3$	Reflux	6	30
6	CCl_4	Reflux	6	78
7	Without Solvent	Room temperature	12	NR

[a]Yields refer to pure isolated product

[b]$Zn(OAc)_2•2H_2O$ as Lewis catalyst loading: (89%, 10 mol%); (82%, 7.5 mol%) and (80%, 5 mol%)

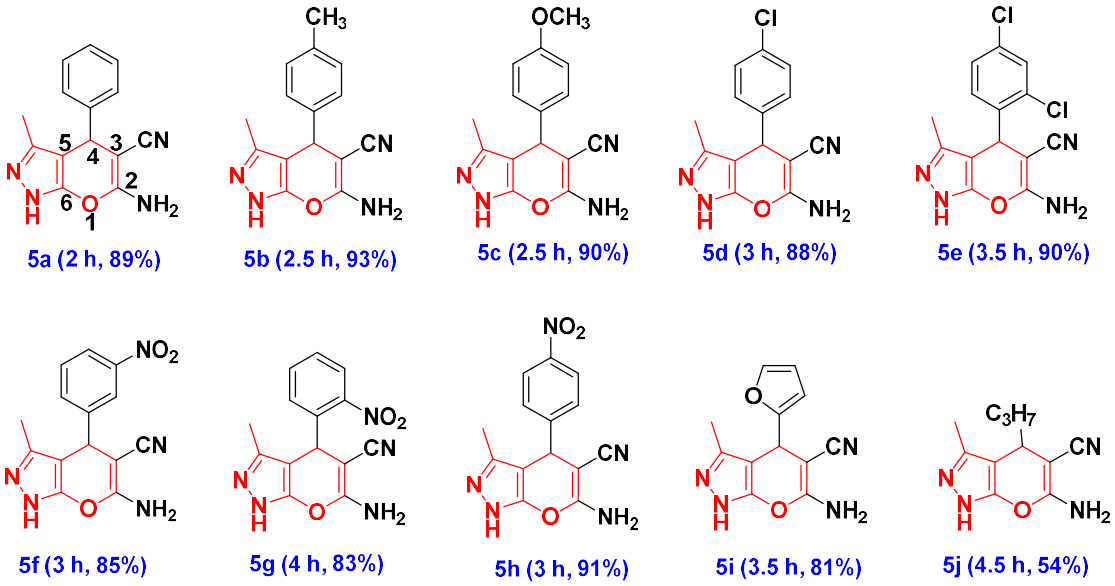


Fig. 3. Synthesized dihydropyrano[2,3-*c*]pyrazoles

3. Experimental

3.1 Material and Methods

All reagents and chemicals were of analytical grade and used without further purification. The progress of the reaction was monitored on TLC. All the products were confirmed by comparing their melting points, IR, and ^{1}H NMR data with literature data.

General procedure for the synthesis of substituted pyranopyrazole (5a-j)

To a round bottom flask substituted aromatic aldehyde (1mmol), malononitrile (1mmol), ethyl acetoacetate (1mmol), and hydrazine hydrate (1 mmol) in toluene under reflux conditions for the time as specified in **Figure 3**. The advancement of the reaction was tracked through TLC (10% ethyl acetate: *n*-hexane). The resulting product was combined with water and ethyl acetate (1:4). The combined solvent extracts underwent vacuum concentration. Subsequently, the compounds underwent recrystallization in ethanol to yield the purified product (**5a-j**).

Spectral data of synthesized compounds

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano [2,3-*c*] pyrazole-5-carbonitrile (5a):

Yellow crystalline solid. **m.p.** 210-212 ^{0}C. **IR (KBr) cm^{-1}-** 3477 and 3231 (NH_2), 3121 (NH), 2191 (CN), 1639, 1559. **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.00 (1H, s, NH), 7.30 (2H, t, *J* = 7.56), 7.22 (3H, m, *J*= 7.28 and 11.24), 6.71 (2H, s, -NH_2), 4.50 (1H, s, C-4), 1.79 (3H, s, CH_3). **^{13}C NMR- (100 MHz, DMSO *d6*)** – 161.35, 155.26, 144.93, 136.04, 128.91, 127.94, 127.20, 121.24, 98.13, 57.71, 36.73, 10.20. **MS (EI):** *m/z* Calcd. for $C_{14}H_{12}N_4O$= 252.10, Found= 253.15 [M^+ + 1].

6-Amino-1,4-dihydro-3-methyl-4-*p*-tolylpyrano[2,3-*c*]pyrazole-5-carbonitrile (5b):

White crystalline solid. **m.p.** 207-208 ^{0}C. **IR (KBr) cm^{-1}-** 3406 and 3315 (NH_2), 3188 (NH), 2191 (CN), 1646 (C=N), 1600 (C=C). **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.19 (1H, s, NH), 8.21 (2H, m, *J* = 8.8 Hz, Ar), 7.47 (2H, m, *J* = 8.8 Hz, Ar), 7.03 (2H, s, -NH_2), 4.82 (1H, s, C-4), 3.73 (s, 3H, OCH_3), 1.78 (3H, s, CH_3). **^{13}C NMR- (100 MHz, DMSO *d*$_6$)** - δ ppm 161.06, 154.58, 152.02, 146.30, 135.84, 128.51, 128.77, 123.83, 120.45, 96.48, 55.80, 35.80, 9.66. **MS:** *m/z* Calcd. for $C_{15}H_{14}N_4O$= 266.12, Found= 267.14 [M^+ + 1].

6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile (5c):

Light yellow crystalline solid. **m.p.** 209-210 ^{0}C. **IR (KBr) cm^{-1}-** 3483 and 3249 (NH_2), 3122 (NH), 2190 (CN), 1643 (C=N), 1600 (C=C). **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.08 (1H, s, NH), 7.10 (2H, m, *J* = 8 Hz, Ar), 6.89 (2H, m, *J* = 4 Hz, Ar), 6.82 (2H, s, -NH_2), 4.55 (1H, s, C-4), 3.74 (3H, s, OCH_3), 1.80 (3H, s, CH_3). **^{13}C NMR- (100 MHz, DMSO *d*$_6$)** - δ ppm 161.16, 158.45, 155.24, 136.96, 136.02, 128.96, 121.28, 114.25, 98.37, 58.15, 55.48, 35.93, 10.21. **MS:** *m/z* Calcd. for $C_{15}H_{14}N_4O_2$= 282.12, Found= 283.16 [M^+ + 1].

6-Amino-4-(4-chlorophenyl)-1,4-dihydro-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile (5d):

Yellow crystalline solid. **m.p.** 228-230 ^{0}C. **IR (KBr) cm^{-1}-** 3373 and 3311 (NH_2), 3171 (NH), 2193 (CN), 1627, 1581, 1372, 1255, 879. **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.12 (1H, s, NH), 7.38 (2H, m, *J* = 11.2 Hz, Ar), 7.21 (2H, m, *J* = 11.2 Hz, Ar), 6.90 (2H, s, NH_2), 4.63 (1H, s, C-4), 1.79 (3H, s, CH_3). **^{13}C NMR-(100 MHz, DMSO *d*$_6$)** - δ ppm 160.84, 154.61, 143.38, 135.68, 132.49, 131.19, 129.96, 128.39, 120.62, 97.12, 56.68, 18.45, 9.66. **MS:** *m/z* Calcd. for $C_{14}H_{11}ClN_4O$= 286.06, Found= 287.10 [M^+ + 1].

6-Amino-4-(2,4-dichlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5e):
White crystalline solid. **m.p.** 223-225 °C; **IR (KBr) cm^{-1}-** 3478 and 3246 (NH_2),3117 (NH), 2190 (CN), 1640, 1504, 1408, 1100, 1052, 866, 741. **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 11.87 (s, 1H, NH), 7.70 (d, 2H, *J* = 8.4 Hz, ArH), 7.62 (d, 2H, *J* = 8.4 Hz, ArH), 7.13 (s, 2H, NH_2), 7.02 (s, 1H, ArH), 4.58 (s, 1H, C-4), 1.74 (s, 3H, CH_3). **^{13}C NMR- (100 MHz, DMSO *d*$_6$)** - δ ppm 161.8, 155.4, 140.6, 135.9, 133.3, 132.6, 129.3, 128.5, 120.7, 96.8, 55.7, 33.6, 10.0. **MS:** Exact mass: (M^+): calcd. 320.0232; found 320.0236.

6-Amino-1,4-dihydro-3-methyl-4-(3-nitrophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (5f):

Brown crystalline solid. **m.p.** 214-215 ^{0}C. **IR (KBr) cm^{-1}-** 3433 and 3334 (NH_2), 3202 (NH), 2189 (CN), 1668, 1529, 1419, 1358. **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.19 (1H, s, NH), 8.13 (1H, m, *J* = 10.4 Hz, Ar), 8.02 (1H, m, *J* = 1.2 Hz, Ar), 7.63 (2H, s, Ar), 7.03 (1H, s, NH_2), 4.87 (1H, s, C-4), 1.80 (3H, s, CH_3). **^{13}C NMR- (100 MHz, DMSO *d*$_6$)** - δ ppm 161.07, 154.61, 147.80, 146.74, 135.88, 134.34, 130.19, 121.94, 121.77, 120.49, 96.59, 56.04, 35.55, 9.68. **MS:** *m/z* Calcd. for $C_{14}H_{11}N_5O_3$= 297.09, Found= 298.13 [M^+ + 1].

6-Amino-3-methyl-4-(2-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5g): Light yellow crystalline solid. **m.p.** 214-215 ^{0}C. **IR (KBr) cm^{-1}**- 3420 and 3351 (NH_2), 3167 (NH), 2206 (CN). **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.2 (s, 1H, NH), 7.88 (d, *J* = 8.0 Hz, 1H, HAr), 7.70 (t, *J* = 7.5 Hz, 1H, HAr), 7.53 (t, *J* = 7.0 Hz, 1H, HAr), 7.35 (d, *J* = 8.0 Hz, 1H, HAr), 7.08 (s, 2H, NH_2), 5.12 (s, 1H, C-4), 1.80 (s, 3H, CH_3).

6-Amino-1,4-dihydro-3-methyl-4-(4-nitrophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (5h)

Yellow crystalline solid. **m.p.** 249-250 ^{0}C. **IR (KBr) cm^{-1}**- 3310 and 3165 (NH_2), 2900 (NH), 2185 (CN), 1642, 1596. **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.19 (1H, s, NH), 8.21 (2H, m, *J* = 8.8 Hz, Ar), 7.47 (2H, m, *J* = 8 Hz, Ar), 7.10 (2H, s, NH_2), 4.82 (1H, s, C-4), 1.79 (3H, s, CH_3). **^{13}C NMR- (100 MHz, DMSO *d*$_6$)** - δ ppm 161.06, 154.58, 152.01, 146.30, 135.86, 129.52, 128.77, 124.07, 120.45, 96.48, 55.80, 35.79, 9.66. **MS:** *m/z* Calcd. for $C_{14}H_{11}N_5O_3$= 297.09, Found= 298.14 [M^+ + 1].

6-Amino-4-(furan-2-yl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5i)
Grey solid. **m.p.** 215-216 °C. **IR (KBr) cm^{-1}**- 3470 and 3401 (NH_2), 3120 (NH), 2189 (CN). **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ ppm 12.25 (s, 1H, NH), 7.49 (s, 1H, CH, Ar), 6.33 (s, 1H, CH, Ar), 6.17 (s, 1H, CH), 4.75 (s, 1H, C-4), 1.96 (s, 3H, CH_3) ppm; **^{13}C NMR- (100 MHz, DMSO *d*$_6$)** - δ ppm 162.0, 156.22, 155.32, 142.81, 136.35, 121.35, 110.77, 106.17, 95.62, 54.43, 25.50, 10.11.
6-Amino-4-(4-isopropylphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5j**): White solid, **m.p.** 239-241 °C, **IR (KBr, cm^{-1})**- 3494 and 3233 (NH_2), 2961 (NH), 2196 (CN), 1613, 1597, 1490, 1398, 1053. **^{1}H NMR-(400 MHz, DMSO *d*$_6$)** - δ 12.06 (s, 1H, NH), 7.16 (d, *J* = 7.9 Hz, 2H, Ar), 7.04 (d, *J* = 7.8 Hz, 2H, Ar), 6.83 (s, 2H), 4.52 (s, 1H, C-4), 2.81 (q, *J* = 6.9 Hz, 1H), 1.77 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 6H).

Supporting Information file is available

4. Conclusion

In summary, we successfully implemented a one-pot multicomponent synthesis of pyranopyrazole using an environmentally friendly synthetic approach with inexpensive and less toxic zinc acetate using as a Lewis acid catalyst. Aromatic compounds both with electron donationg and withdrawing functionalities reacted in a similar fashion. Whereas, aliphatic aldehydes proved to be less effective compared to that of reactivity of aromatic compounds. This method utilizes toluene as a solvent and offers benefits such as a shorter reaction duration, straightforward workup, and atom economy. The established protocol is robust and may be used in a variety of organic transformations to reach the desired architecture's complexity in a single pot.

Conflict of Interests

The authors declare that there is no conflict of interest.

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