ONE-POT SYNTHESIS OF PYRANO[2,3-*c*]PYRAZOLES USING LEMON PEEL POWDER AS A GREEN AND NATURAL CATALYST

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Keywords: Pyranopyrazoles; lemon peel powder; one-pot synthesis; natural catalyst

A simple one-pot four-component synthesis of pyrano[2,3-*c*]pyrazoles has been achieved by the condensation of aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate using lemon peel powder as a natural catalyst in ethanol under reflux condition. The advantages of this reaction are less reaction time, high yield, easy availability of the catalyst and green nature of the protocol.

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INTRODUCTION

Pyranopyrazole derivatives are an interesting class of nitrogen and oxygen-containing heterocyclic compounds.[1] Multi-component reactions are known to be selective, effective, atom-economical, time-saving and easy to perform.[2] Pyranopyrazole based heterocyclic compounds have attracted a significant attention due to their pharmaceutical and biological activities.[3] Pyranopyrazoles are the fused heterocyclic compounds which show various biological activities such as fungicidal,[4] anti-inflammatory, [5] anticancer, [6] antimicrobial,[7] antioxidant[8] and bactericidal.[9] Considering the importance of pyranopyrazoles, researchers have reported several methods for their synthesis by using different catalysts such as nano-ZnO,[10] triethanolamine,[11] sodium benzoate,[12] L-tyrosine,[13] NMPyTs,[14] phenylboronic acid,[15] etc.

In continuation of our efforts to the clean synthetic protocol for the synthesis of heterocyclic compounds; herein we wish to report one-pot four-component synthesis of pyranopyrazoles by the reaction of aromatic aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate using lemon peel powder as a catalyst under reflux condition.

EXPERIMENTAL

All the reagents and chemicals were used without further purification. Melting points were recorded in open capillaries and were uncorrected. Progress of the reaction was monitored by TLC plates using ethyl acetate:n-hexane (7:3). FTIR spectra were recorded on a Shimadzu IR Affinity-1S spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrophotometer and chemical shifts were expressed in δ ppm relative to Me_4Si as the internal standard.

General procedure for the synthesis of substituted pyranopyrazoles

In a 25 mL round bottom flask aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), ethyl acetoacetate (1 mmol) and lemon peel powder (10 wt%) was taken in 5 mL ethanol solvent. The resulting reaction mixture was refluxed for a period as indicated in Table 1. The progress of reaction was monitored by using TLC plates in ethyl acetate / n-hexane (7:3). After completion of reaction, the reaction mass was diluted with hot ethanol and filtered off to separate lemon peel powder catalyst as the residue. The residue was washed with hot ethanol (3 x 5 mL), the combined filtrates were concentrated and recrystallized from ethanol to afford the corresponding pure product. All the products were confirmed by comparison of their melting points with the literature values and analysis of IR, ^{1}H NMR and mass spectral data.

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

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.74 (s, 3H, CH_3), 4.75 (s, 1H, CH), 7.30 (d, 1H, Ar-H), 7.31 (d, 1H, Ar-H), 7.65 (s, 2H, NH_2), 7.79 (d, 2H, Ar-H), 11.04 (s, 1H, NH); ESI-MS: 298.06 $(M+1)^+$.

6-Amino-3-methyl-4-(4-hydroxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.75 (s, 3H, CH_3), 4.45 (s, 1H, CH), 6.52 (d, 1H, Ar-H), 6.53 (dd, 1H, Ar-H), 6.54 (dd, 1H, Ar-H), 6.62 (d, 1H, Ar-H), 7.50 (s, 2H, NH_2), 13.4 (s, 1H, NH); ESI-MS: 269 $(M+1)^+$.

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

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.31 (s, 2H, NH_2) 2.89 (s, 3H, CH_3), 4.76 (s, 1H, CH), 7.01 (d, 2H, Ar-H), 7.15 (d, 2H, Ar-H), 12.03 (s, 1H, NH); ESI-MS: 287 $(M+1)^+$.

6-Amino-3-methyl-4-(4-flurophenyl)-1, 4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.10 (s, 2H, NH_2), 2.73 (s, 3H, CH_3), 4.74 (s, 1H, CH), 6.75 (d, 2H, Ar-H), 7.01 (d, 2H, Ar-H), 11.07 (s, 1H, NH); ESI-MS: 271.09 $(M+1)^+$.

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

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.50 (s, 2H, NH_2), 2.69 (s, 3H, CH_3), 4.71 (s, 1H, CH), 6.92 (d, 2H, Ar-H), 7.21 (d, 2H, Ar-H), 10.21 (s, 1H, NH); ESI-MS: 331.02 $(M+1)^+$.

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

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.80 (s, 3H, CH_3), 3.85 (s, 6H, CH_3), 4.55 (s, 1H, CH), 6.56 (s, 1H, CH), 6.61 (d, 1H, CH), 6.65 (d, 1H, CH), 7.60 (s, 2H, NH_2), 13.2(s, 1H, NH); ESI-MS: 313 $(M+1)^+$.

6-Amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (7)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.00 (s, 2H, NH_2), 2.70 (s, 3H, CH_3), 4.54 (s, 1H, CH), 6.65 (d, 1H, Ar-H), 6.66 (dd, 1H, Ar-H), 6.67(dd, 1H, Ar-H), 6.75 (d, 1H, Ar-H), 13.7 (s, 1H, NH); ESI-MS: 287 $(M+1)^+$.

6-Amino-4-(2-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (8)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.75 (s, 3H, CH_3), 4.45 (s, 1H, CH), 6.52 (d, 1H, Ar-H), 6.53 (dd, 1H, Ar-H), 6.54 (dd, 1H, Ar-H), 6.62(d, 1H, Ar-H), 7.50 (s, 2H, NH_2), 12.04 (s, 1H, NH); ESI-MS: 269 $(M+1)^+$.

6-Amino-4-furan-2-yl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (9)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.40 (s, 2H, NH_2), 2.67 (s, 3H, CH_3), 4.94 (s, 1H, CH), 5.77 (d, 1H, Ar-H), 6.01 (dd, 1H, CH), 7.10 (d, 1H, Ar-H), 13.01 (s, 1H, NH); ESI-MS: 243.05 $(M+1)^+$.

6-Amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (10)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.97 (s, 3H, CH_3), 4.05 (s, 1H, NH), 6.23 (s, 2H, NH_2), 6.67-6.87 (m, 2H, Ar-H), 7.19 (t, 1H, CH), 7.30 (d, 1H, Ar-H), 11.38 (s, 1H, NH); ESI-MS: 299.23 $(M+2)^+$.

6-Amino-4-(4-dimethylaminophenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (11)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.50 (s, 2H, NH_2), 2.74 (s, 3H, Ar-H), 2.89 (s, 6H, CH_3), 4.45 (s, 1H, CH), 6.43 (d, 2H, Ar-H), 6.84 (d, 2H, Ar-H), 12.40 (s, 1H, NH); ESI-MS: 296.12 $(M+1)^+$.

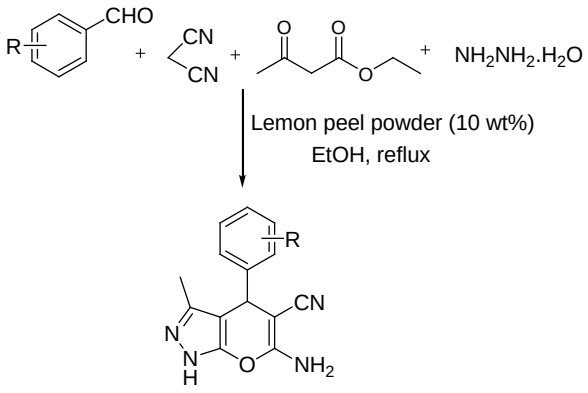
RESULT AND DISCUSSION

In the present work, we have synthesized pyranopyrazole derivatives using variously substituted aromatic aldehydes. A model four component condensation reaction was performed on 4-hydroxybenzaldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate using lemon peel powder as a catalyst in water solvent or without water or ethanol solvents at room temperature, reflux condition and by using ultrasound irradiation.

To follow the principles of green chemistry, initially a model reaction was carried on 4-hydroxybenzaldehyde in the absence of solvent or without solvent at room temperature, reflux condition and ultrasonic irradiation. But the corresponding product was obtained in a less amount (52 %, 45 %). Then we carried out the same reaction in the presence of water, ethanol solvent under room temperature, reflux condition and ultrasonic irradiation. We observed that the reaction required a long reaction time in water with lesser yield as compared to ethanol. Excellent yield was obtained in ethanol solvent under reflux conditions as compared to room temperature and ultrasonic irradiation. The results obtained are presented in Table 2.

Next, we optimized the amount of catalyst concentration on the same reaction by using 5, 10, 20 and 30 wt.% of the catalyst and observed 50, 90, 90, and 91 % of the product, respectively, in case of the model condensation reaction.

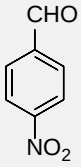
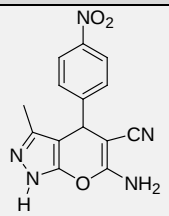
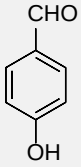
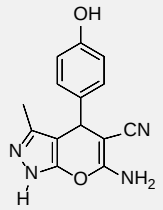
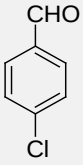
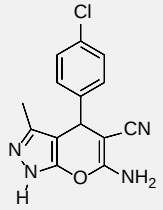
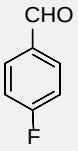
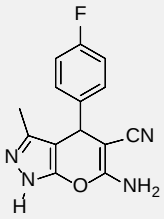
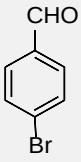
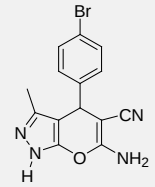
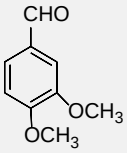
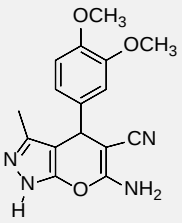
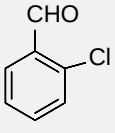
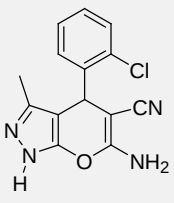
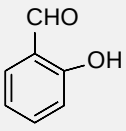
We also carried out the same reaction under solvent-free condition, but the product was obtained in a very less amount (10%). In conclusion, the best result was obtained with 10 wt % of lemon peel powder in ethanol under reflux condition (Table 3). Further increasing the amount of catalyst does not affect yield of the product to a greater extent.



Scheme 1. General reaction for the synthesis of pyranopyrazoles

After completion of reaction, the reaction mass was diluted with hot ethanol and filtered off to separate lemon peel powder catalyst as the residue. The residue catalyst was washed with hot ethanol (3 x 5 mL), combined filtrates were concentrated and recrystallized from ethanol to afford the corresponding pure pyranopyrazole product.

Table 1. Synthesis of pyranopyrazols derivative

Entry	Benzaldehyde	Product	Time, min	Yield, %	M.P., ^{0}C (Found)	M.P. ^{0}C (lit.)
1			120	84	246-248	248-250[17]
2			130	92	222-224	220-222[17]
3			80	80	226	228[16]
4			82	82	240-242	242-244[17]
5			85	71	176-178	178[18]
6			120	58	160-162	161-163[17]
7			120	68	246-247	245[16]
8			130	62	210-212	208-210[18]

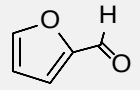
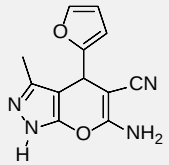
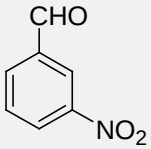
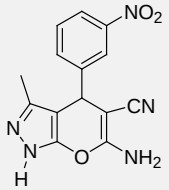
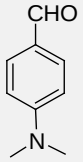
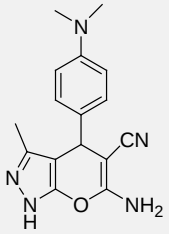
9			80	65	218	219[18]
10			120	74	188-190	190-192[18]
11			90	76	222-224	224-225[18]

Table 2. Effect of various solvent on the model reaction

Entry	Solvent	Temperature	Time, min	Yield, %
1	H_2O	Reflux	180	52
2	Solvent-free	Reflux	300	45
3	Ethanol	Reflux	120	91

Table 3. Effect of catalyst on the synthesis of pyranopyrazoles under reflux condition

Entry	Amount of catalyst, wt%	Yield, %
1	No catalyst	10
2	5	50
3	10	90
4	20	90

CONCLUSION

In conclusion, we report the synthesis of pyranopyrazoles by using one pot four-component procedure with excellent yield. Easy handling, clean method and atom economical transformation are some of the important advantages of the present method.

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