ONE POT THREE COMPONENT SYNTHESIS OF PYRANOPYRAZOLE BY AMMONIUM CHLORIDE

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Abstract:

A simple and green one pot protocol for the synthesis of various pyranopyrazoles derivatives catalyzed by ammonium chloride has been developed. Operational simplicity and environment-friendly green approach are the advantages of this method.

Keywords: pyranopyrazoles; one pot reaction; catalysis; ultrasound waves; aqueous medium

1. INTRODUCTION:

A multicomponent reaction (MCR) is a process in which three or more reactants are combined in a single reaction vessel to produce a product that incorporates substantial portions of all the components. 1. Reactions where three or more different components are combined in one reaction vessel, leading to the formation of a single product are summarized under multi-components reaction. MCRs cover topics such as sustainability, atom economy and eco-efficiency, high convergence (process efficiency), and reduce the intermediate steps or functional group manipulations, thus reducing time and energy, known as step efficiency. Significantly broadened scopes, new techniques more environmentally benign methods and entirely novel Multi-components reactions reflect the increasingly incentive paths that synthetic chemist follow in this field.(Bienaymé, Hulme, Oddon, & Schmitt, 2000) The first multicomponent reaction was described in 1850 by Strecker, and later many such reactions have been reported in the literature.

One of the main causes of environmental pollution which can harm to our planet is the use of conventional energy sources and use of toxic and hazardous chemicals in production processes.(Ghorani-Azam, Riahi-Zanjani, & Balali-Mood, 2016) For the welfare of human, polluting technologies must be

replaced by benign alternatives. Green chemistry offers more eco-friendly and green alternatives to conventional chemistry practices such as energy efficient energy sources, reduction or elimination of the use of toxic and hazardous chemicals in production processes. Microwave irradiation dramatically accelerates organic reactions, improves yield, selectivity and Microwave-assisted organic synthesis (MAOS) is considered as green approach towards organic synthesis as it offers simple, clean, fast, efficient and economic technique for synthesis.

Heterocyclic are among the various biologically significant compounds those proved to be useful for mankind and emerged as powerful and bond forming efficient tools in organic, combinatorial and medicinal chemistry.(Martins et al., 2015)

Pyranopyrazole are fused heterocyclic compounds having significant biological activities such as anticancer activity(Wang et al., 2000), analgesic(Hayata, 2002) & antimicrobial(Ambethkar, Padmini, & Bhuvanesh, 2015), anti-inflammatory(Faidallah & Rostom, 2017), anticoagulant, spasmolytic, hypnotic(M Khandare et al., 2017), diuretic activities.

Here we report one pot four component synthesis of pyranopyrazoles by the reaction of aromatic aldehyde, malononitrile, ethyl acetoacetate, hydrazine hydrate using ammonium chloride(Pagore, Rupnar, Tekale, & Pawar, 2015) as a catalyst in aqueous medium under ultrasound irradiation method in short time.

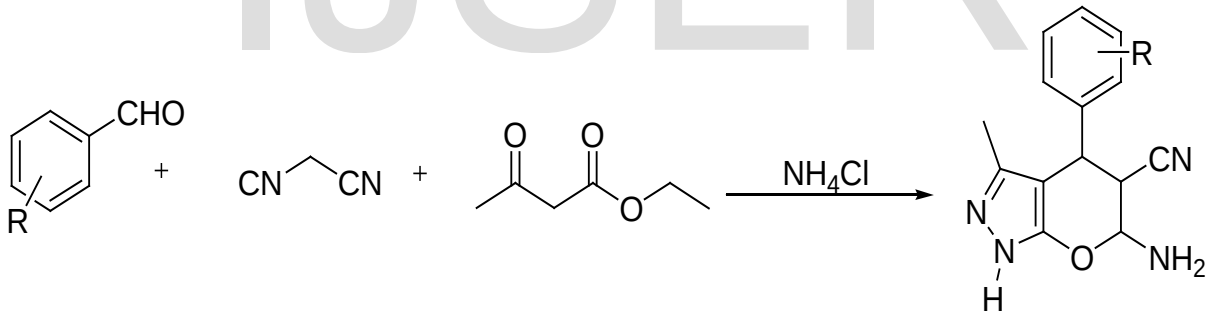


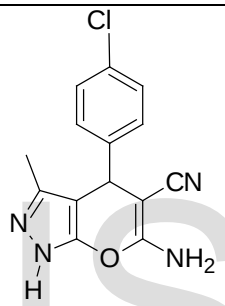
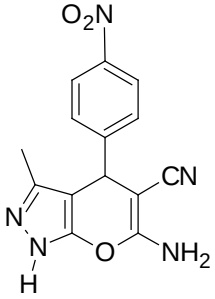
Fig 1: General Scheme

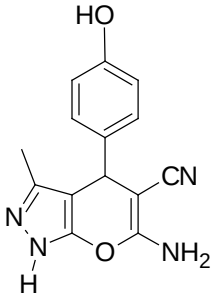
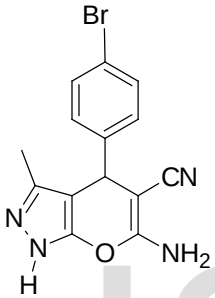
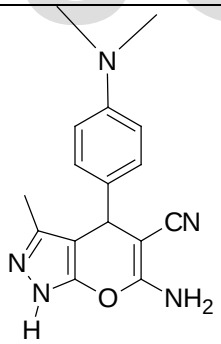
2. RESULTS AND DISCUSSION

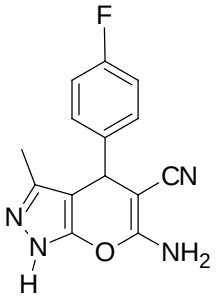
To optimize the reaction conditions, we have carried out the model reaction of 4-hydroxybenzaldehyde, ethyl acetoacetate, hydrazine hydrate, and Aluminum chloride as a catalyst by using water or ethanol as a solvent or without solvent, at room temperature, reflux and by using ultrasound irradiations. Results obtained are presented in Table 1. High yields were obtained by using ultrasonication method and utilizing water as a green solvent in short time. Effect of various solvent on synthesis of compound are listed in table 2. In order to understand amount of catalyst to obtain maximum yield we have carried out

model reaction with different amount of catalyst (Table 3) and found that 10 mol % of catalyst is sufficient, further increasing the amount of catalyst does not affect the yield.

Table 1: various derivatives and their yields

Sr.No.	Compound No.	Name of Compound	Reaction Time	Boiling/Melting Point ^{0}C	%Yield
1.	**3a**	 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile	**30**	**Mp;174**	**78**
2.	**3b**	 6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile	**30**	**194**	**87**

3.	**3c**	 6-amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile	**45**	**222**	**94.23**
4.	**3d**	 6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile	**30**	**178**	**72**
5.	**3e**	 6-amino-4-[4-(dimethylamino)phenyl]-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile	**45**	**224**	**76.20**

6.	**3f**	 6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile	**30**	**170**	**83.58**

Spectral data of compound 3b.

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

Brown solid. IR (KBr): ν 3373.50, 3450.32, 2191.13, 1932.67, 854.47, 1H NMR: (200 MHz, CDCl3) δ 8.27 (s, 1H, NH), 7.43-7.47 (dd, 2H, arom), 8.17 (s, 2H, NH2), 8.21 (s, 2H, NH2), 1.56 (s, 3H, CH3), 7.55 (s, 3H, arom).

Table 2: Effect of various solvent on synthesis of compound 3.

Entry	**Solvent Time,**	**Temperature, 0C/)))))))**	**min**	**Yield, %**
1.	H2O	r.t.	360	86
2.	H2O	Reflux	240	84
3.	H2O	)))))))	45	95
4.	EtOH	r.t.	378	70
5.	EtOH	Reflux	300	65
6.	EtOH	)))))))	50	80
7.	No Solvent	r.t.	420	40
8.	No Solvent	Reflux	480	45
9.	No Solvent	)))))))	120	34

Table 3: Optimization of catalyst for synthesis of pyranopyrazoles

Serial no	**Amount of Ammonium Chloride , mol %**	**Percent yield**
1.	**No catalyst**	**10**
2.	**5**	**52**

3.	**10**	**95**
4.	**20**	**95**
5.	**30**	**92**

Antifungal activity:

Antifungal activity of synthesized compounds has been screened against fungal species *A. niger* and *Phytophthora* using drug streptomycin as a standard. Agar well diffusion method is used for screening purpose. Observations were recorded after 72 h, and the zone of inhibition was measured in mm. The antifungal activity is comparable with Streptomycin against *A. niger* and *Phytophthora megasperma* at a concentration of 10 mg/ml of DMF solvent.

It was observed that all the synthesized compounds showed good antifungal activity against fungal species *A. niger* and *Phytophthora megasperma* as compared to standard drug streptomycin.

Table 4. Zone of inhibition in mm of synthesized pyranopyrazole derivatives

Compounds	***A. Niger***	***P. megasperma***
1.	25	29
2.	17	25
3.	16	29
4.	19	31
5.	16	32
6.	21	28
Standard	14	23

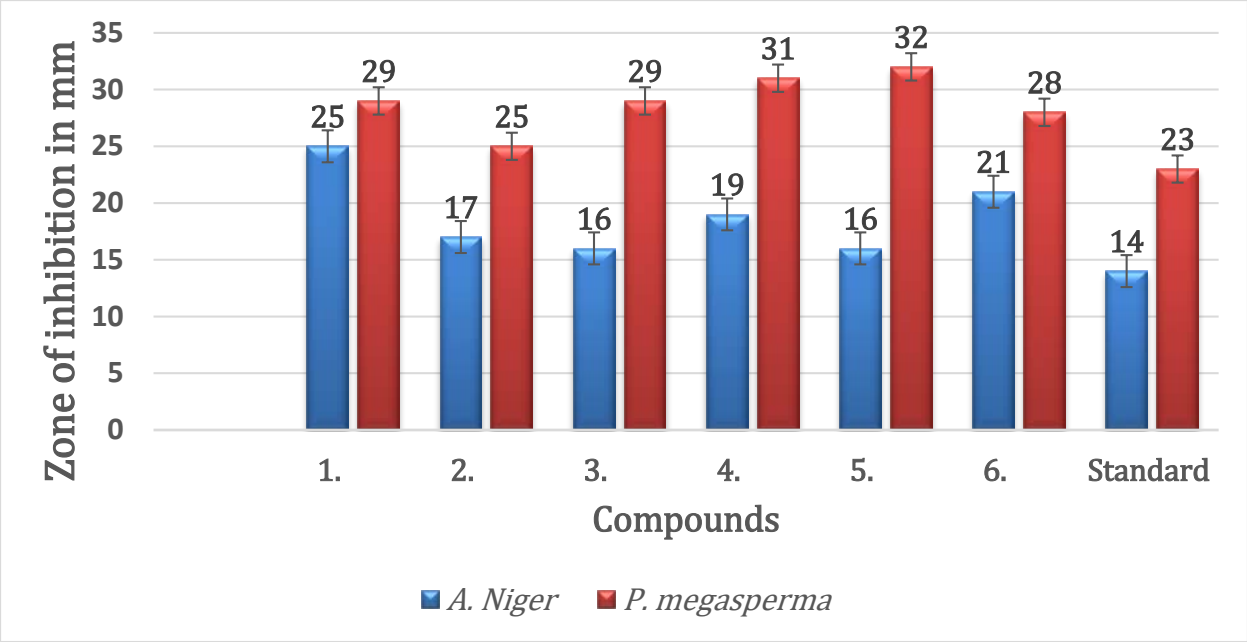


Fig 2: Graphical Zone of inhibition in mm of synthesized pyranopyrazole derivatives

Compounds 1, 2,4, 6, shown excellent activity against *A. niger* whereas compounds 1, 3, 4, 5, 6 have shown excellent activity against *Phytophthora species*, Other compound also showed good to moderate biological activity.

3. EXPERIMENTAL

All reagents and chemicals were purchased from SD Fine or spectrochem chemical company, Mumbai, India. All reagents and chemicals were of analytical grade and used without further purification. Sonication was performed in ultrasonic cleaner with a frequency of 25 KHz and nominal power 250 W. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

General procedure for the synthesis of substituted pyranopyrazoles

In 100 mL round bottom flask substituted benzaldehyde (1 mol), malononitrile (1.1 mol), ethyl acetoacetate (1 mol), hydrazine hydrate (1 mol) and NH_4Cl (10 % mol) were taken in 20 mL water as a green solvent.

The resulting reaction mixture was sonicated for a period as indicated in Table 1. The progress of reaction was monitored by using TLC. After completion of reaction, the solid product obtained was filtered, washed with water and recrystallized from ethanol to afford the pure product. All the products were confirmed by comparing their melting points, IR and 1H NMR data with literature data.

Antifungal activity

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4. Conclusion

In conclusion, we have achieved pyranopyrazole synthesis by one pot multicomponent procedure using green synthetic protocol under ultrasound irradiation technique, using water as a green solvent and aluminum chloride as a catalyst. Striking features of this method are short reaction time, easy work up procedure, water solvent, use of ultrasound waves, atom economy.

References:

Ambethkar, S., Padmini, V., & Bhuvanesh, N. (2015). A green and efficient protocol for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives via a one-pot, four component reaction by grinding method. *Journal of Advanced Research*, *6*(6), 975–985. https://doi.org/10.1016/j.jare.2014.11.011

Bienaymé, H., Hulme, C., Oddon, G., & Schmitt, P. (2000). Maximizing synthetic efficiency: Multi-component transformations lead the way. *Chemistry - A European Journal*, *6*(18), 3321–3329. https://doi.org/10.1002/1521-3765(20000915)6:18<3321::AID-CHEM3321>3.0.CO;2-A

Faidallah, H. M., & Rostom, S. A. F. (2017). Synthesis, Anti-Inflammatory Activity, and COX-1/2 Inhibition Profile of Some Novel Non-Acidic Polysubstituted Pyrazoles and Pyrano[2,3-c]pyrazoles. *Archiv Der Pharmazie*, *350*(5). https://doi.org/10.1002/ardp.201700025

Ghorani-Azam, A., Riahi-Zanjani, B., & Balali-Mood, M. (2016). Effects of air pollution on human health and practical measures for prevention in Iran. *Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences*, *21*, 65. https://doi.org/10.4103/1735-1995.189646

Hayata, Y. (2002). NII-Electronic Library Service. *Chemical Pharmaceutical Bulletin*, (43), 2091.

M Khandare, P., D Ingale, R., Taware, A., Shisodia, S., S Pawar, S., Kótai, L., & Pawar, R. (2017). *One Pot Synthesis and Biological Evaluation of Pyranopyrazole in Aqueous Medium*. *European Chemical Bulletin* (Vol. 6). https://doi.org/10.17628/ecb.2017.6.410-414

Martins, P., Jesus, J., Santos, S., Raposo, L. R., Roma-Rodrigues, C., Baptista, P. V., & Fernandes, A. R. (2015). Heterocyclic anticancer compounds: Recent advances and the paradigm shift towards the use of nanomedicine's tool Box. *Molecules*, *20*(9), 16852–16891. https://doi.org/10.3390/molecules200916852

Pagore, V. P., Rupnar, B. D., Tekale, S. U., & Pawar, R. P. (2015). Green and efficient synthesis of pyranopyrazoles catalyzed by ammonium chloride in water. *Der Pharma Chemica*, *7*(6), 312–317.

Reddy, G. M., Garcia, J. R., Zyryanov, G. V., Sravya, G., & Reddy, N. B. (2019). Pyranopyrazoles as efficient antimicrobial agents: Green, one pot and multicomponent approach. *Bioorganic Chemistry*, *82*, 324–331. https://doi.org/10.1016/j.bioorg.2018.09.035

Wang, J., Liu, D., Zhang, Z., Shan, S., Han, X., Srinivasula, S. M., … Huang, Z. (2000). Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells, *97*(13), 2–7.