ONE POT SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRANOPYRAZOLES IN AQUEOUS MEDIUM

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A simple and green one pot protocol for the synthesis of pyranopyrazoles using ultrasonication waves in aqueous medium has been developed. Advantages of this method are it provides operational simplicity and environment-friendly green approach.

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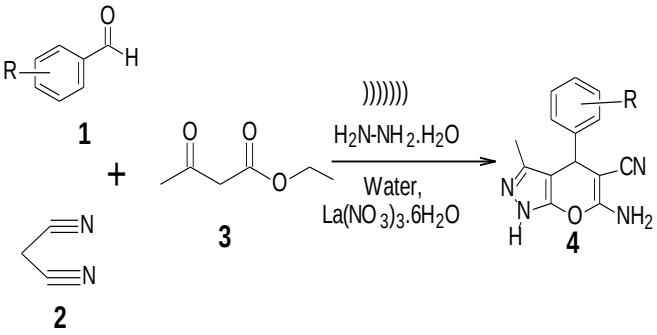
Introduction

Multicomponent reactions (MCRs) are known as efficient tools for the generation of complex heterocyclic bioactive compounds useful in organic and medicinal chemistry, in which three or more reactants react to give final product in a one-pot procedure.[1] The first multicomponent reaction was described in 1850 by Strecker, and later many such reactions have been reported in the literature.[2] This attracted attention of industrial and academic researchers.[3]

Water is the safest and abundant substance in nature, and almost all compounds are sparingly soluble in water. Hence it is referred as a benign 'Universal Solvent'.[4] The search for alternative reaction media to replace volatile, flammable and often toxic organic solvents is an important objective in the development of the green chemical process.[5] Hence organic synthesis in an aqueous medium is preferred from environmental as well as from the economical point of view.

Pyrano pyrazole is a fused heterocyclic compound, which adds functional diversity to the molecule and provides fruitful area to study the bioactivity. Pyranopyrazoles were first obtained in 1973 by the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyano ethylene.[6] Pyranopyrazole scaffold has shown bioactivity such as anticoagulant, spasmolytic, hypnotic, diuretic,[7] insecticidal,[8] anti-inflammatory,[9] anticancer,[10] antibacterial and antifungal[11], as well as antimicrobial.[12] Owing to the biological importance, scientists have developed several methodologies for the synthesis of pyranopyrazoles by using different catalysts such as piperidene,[13] DBSA,[14] PTSA,[15] [Sipim]HSO_4,[16] citric acid,[17] β-cyclodextrin,[18] NH_4Cl,[19] ZrO_2-NPs,[20] PS-PTSA,[21] thiamine hydrochloride.[4] But still, these methods have certain limitations like use of harsh reaction conditions, low yield of products, use of volatile organic solvents, etc. Recently ultrasound irradiation has been used in organic synthesis.

In continuation of our efforts to the ecofriendly synthetic approach towards synthesis of bioactive heterocyclic compounds, herein we wish to report one pot four component synthesis of pyranopyrazoles by the reaction of aromatic aldehyde, malononitrile, ethyl acetoacetate, hydrazine hydrate using lanthanum (III) nitrate as a catalyst[22] in aqueous medium under ultrasound irradiation method in short time.



Scheme 1. General synthetic route to prepare compounds 4.

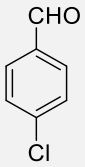
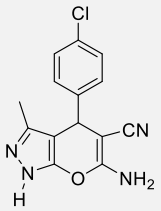
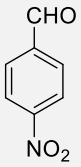
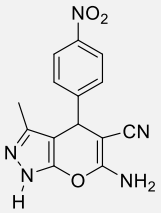
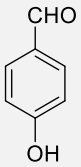
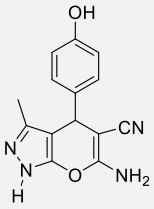
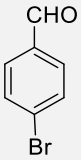
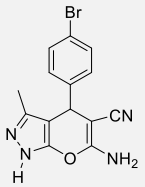
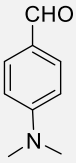
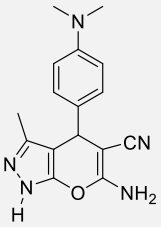
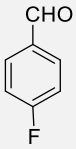
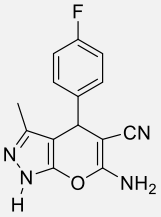
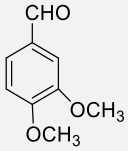
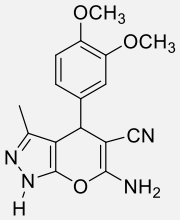
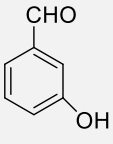
Experimental

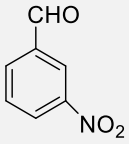
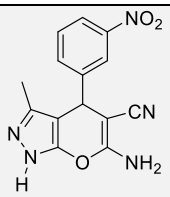
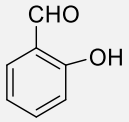
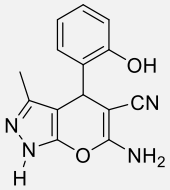
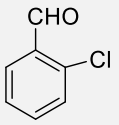
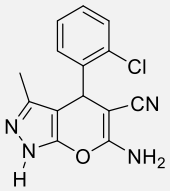
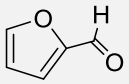
All reagents and chemicals were of analytical grade and used without further purification. Sonication was performed in ultrasonic cleaner with a frequency of 25 KHz and nominal power 250 W. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

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 $La(NO_3)_3.6H_2O$ (10 % mol) were taken in 20 mL water as a green solvent.

Table 1. Synthesis of pyranopyrazole derivatives

Sr. No.	Benzaldehyde	Product	Time, min	Yield, %	M.P., °C, found	M.P., °C lit.(ref.)
1			30	77.13	174	175[9]
2			30	85.41	193	195[9]
3			45	94.22	220-222	222-224[10]
4			30	70.61	178	177[9]
5			45	75.37	224-225	225-227[10]
6			30	83.58	169-170	169-171[10]
7			40	57.05	190-191	188-190[10]
8			30	67.46		-

9			45	73.41	190-192	190-192[10]
10			30	64.72	208-210	208-210[10]
11			40	65.75	144-146	144-146[10]
12			45	62.82	174-176	176-178 [10]

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 ^{1}H NMR data with literature data.

Spectral data of compound 8.

6-Amino-3-methyl-4-(4-nitrophenyl)-2, 4-dihydropyrano [2,3-c] pyrazole-5-carbonitrile (2). Brown solid. IR (KBr): v 3373.50, 3450.32, 2191.13, 1932.67, 854.47, ^{1}H NMR : (200 MHz, $CDCl_3$) δ 8.27 (s, 1H, NH), 7.43-7.47 (dd, 2H, arom), 8.17 (s, 2H, NH_2), 8.21 (s, 2H, NH_2), 1.56 (s, 3H, CH_3), 7.55 (s, 3H, arom).

Results and discussion

To optimize the reaction conditions, we have carried out the model reaction of 4-hydroxybenzaldehyde, ethyl acetoacetate, hydrazine hydrate, and lanthanum (III) nitrate 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 2. High yields were obtained by using ultrasonication method and utilizing water as a green solvent in short time.

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 2. Effect of various solvent on synthesis of compound **3.**

Entry	Solvent	Temperature, ^{0}C/)))))))	Time, min	Yield, %
1	H_2O	r.t.	360	85
2	H_2O	Reflux	240	83
3	H_2O	)))))))	45	94
4	EtOH	r.t	378	70
5	EtOH	reflux	300	67
6	EtOH	)))))))	50	80
7	Without Solvent	r.t	420	40
8	Without Solvent	reflux	480	45
9	Without Solvent	)))))))	120	35

Table 3. Effect of catalyst, on the synthesis of pyranopyrazole **3** by ultrasonification

Entry	Amount of $La(NO_3)_3.6H_2O$, mol %	Yield, %
1	No catalyst	8
2	5	40
3	10	94
4	20	94
5	30	92

Mechanism

The possible mechanism for this reaction is, malononitrile and benzaldehyde through Knoevenagel condensation produces ylidene malononitrile and hydrazine on reaction with ethyl acetoacetate produces pyrazolone. These ylidenemalononitrile and pyrazolone together produce our desired product through Michael addition.

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.

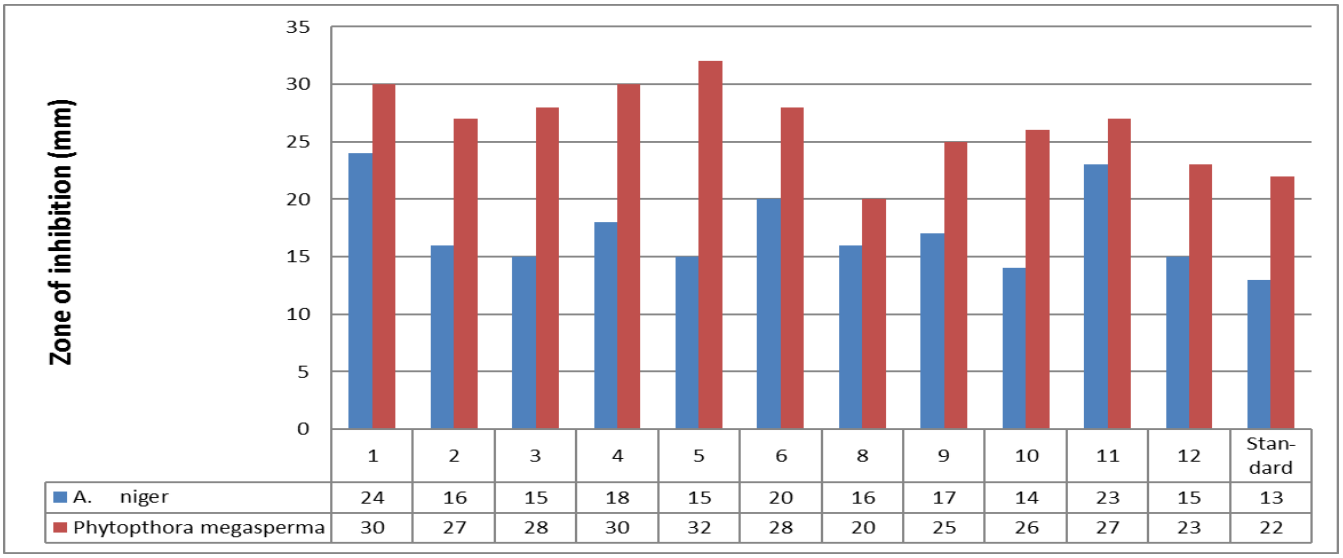
It was observed that all the synthesized compounds showed good antifungal activity against fungal species *A. niger* and *Phytophthora megasperma* as compared to standard drug streptomycin.

Compounds **1**, **4**, **6**, **11** shown excellent activity against *A. niger* whereas compounds **1**, **3**, **4**, **5**, **6,** have shown excellent activity against *Phytophthora* species, Other compound shown good to moderate biological activity.

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

Compound	*A.niger*	*Phytophthora megasperma*
1	24	30
2	16	27
3	15	28
4	18	30
5	15	32
6	20	28
8	16	20
9	17	25
10	14	26
11	23	27
12	15	23
Standard	**13**	**22**

Table 5. Graphical Zone of inhibition in mm of synthesized pyranopyrazole derivatives



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 $La(NO_3)_3.6H_2O$ as a catalyst. Striking features of this method are short reaction time, easy work up procedure, water solvent, use of ultrasound waves, atom economy.

Acknowledgement

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