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Green and Efficient Synthesis of Pyranopyrazoles.

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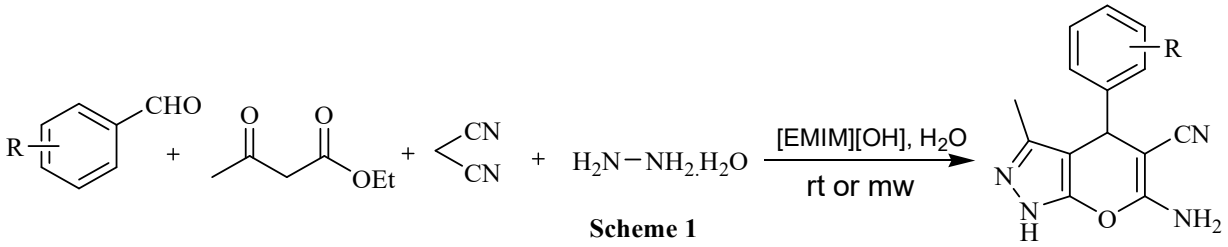
ABSTRACT
A green and efficient process is reported for synthesis of biologically significant pyranopyrazoles derivatives by the multicomponent reaction of aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate using ionic liquid under microwave irradiation. The process used is clean, simple and easily approachable for the synthesis of pyranopyrazoles. Ionic liquid in water is used as green alternatives to organic solvents. The reactions are efficiently completed by microwave irradiations which is a good alternative for conventional procedures. An advantage of process; it is a cost-effectiveness and carried by non-conventional way.

KEYWORDS
Green reaction, Pyranopyrazoles, Ionic liquid, Water, Microwave irradiation.

1. INTRODUCTION

Pyranopyrazole is an important class of heterocyclic compounds as they are having significant biological activities such as insecticidal [1],antibacterial [2], vasodilatory [3], bactericidal [4], anticancer [5].Due to their significant biological properties, several researchers reported the synthesis of pyranopyrazoles. Various catalysts used to synthesize pyranopyrazoles are citric acid [6], borax [7], Bronsted-acidic ionic liquid[$(CH_2)_4SO_3HMIM][HSO_4$] [8], triethylamine [9] and nano zinc oxide [10].

Green chemistry aims to find out more eco-friendly alternatives to conventional chemistry practices. Thus environmentally benign methods of synthesis are getting more importance. Keeping the green approach in mind we use ionic liquid as a catalyst in water as a reaction medium for the synthesis of pyranopyrazoles.



Scheme 1

Scheme 1. General scheme for the synthesis of pyranopyrazoles.

2. MATERIALS AND METHODS

Chemical and reagents were purchased from SD Fine Chemical companies and Spectrochem chemical companies in high purity, used without further purification. All the materials were of commercial-grade reagent. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus. Infrared (IR) spectra in KBr were recorded using a Perkin-Elmer FT-IR spectrometer 65. ^{1}H NMR spectra were recorded on 400 MHz FT-NMR spectrometer in DMSO-d_6 as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. The microwave irradiation was carried out in a scientific microwave oven (CATA-4R-Model No. QW-99, India makes), 2450 MHz Frequency, with a power output of 140-700 W. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography).

2.1. General procedure for synthesis pyranopyrazoles using [EMIM][OH] in water

2.1.1. By stirring at room temperature

Aldehyde (1mmol), malononitrile (1mmol), ethyl acetoacetate (1mmol) and hydrazine hydrate (1.5mmol) with 0.2 mmol of [EMIM][OH] in 5ml water was stirred at room temperature. The progress of the reaction is monitored by TLC (ethyl acetate: hexane 4:1). After completion of the reaction, the reaction mixture was filtered and washed with water. The residue was dried and

recrystallized from ethanol followed by washing with 30% ethyl acetate. The products were confirmed by comparisons with authentic samples, IR, ^{1}H NMR, and melting points.

2.1.2. Under MW irradiation

Ethyl acetoacetate (1mmol), hydrazine hydrate (1.5mmol), aldehyde (1mmol), malononitrile (1mmol), and catalytic amount [EMIM][OH] (0.20 mmol) in 5ml water was irradiated in microwaves at the power of 210W. The progress of the reaction was monitored by TLC (ethyl acetate: hexane 4:1). The total period of microwave irradiation was 2-4 min (Table 1). After completion of the reaction, the reaction mixture was cooled to room temperature, filtered and washed with water. The residue was dried and recrystallized from ethanol to get the corresponding pyranopyrazoles followed by washing with a mixture of EA: hexane (3:7).

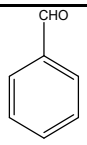
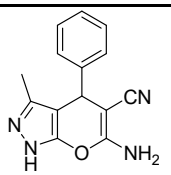
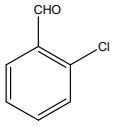
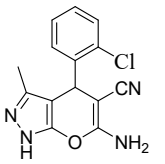
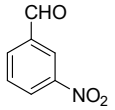
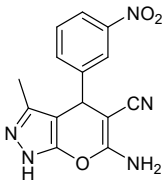
2.2. Spectral data for representative pyranopyrazoles.

6-Amino-3-methyl-4-(4-nitro-phenyl)-2, 4, dihydro-pyrano-[2, 3-c] pyrazole-5-carbonitrile:

IR (KBr): IR (KBr): ν 3396, 3231, 3181, 2189, 1641, 1597, 1489, 1398, 1072, 1010, 810, 745 cm^{-1}; ^{1}H NMR (300, CDCl3): δ 1.81 (s, 3H), 4.59 (s, 1H), 6.80 (s, 2H), 7.88 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.20-7.53 (m, 2H), 12.06 (s, 1H);

6-Amino-3-methyl-4-(4-chloro-phenyl)-2, 4, dihydro-pyrano-[2, 3-c] pyrazole-5-carbonitrile: IR (KBr): ν 3408, 3234, 3178, 2190, 1642, 1597, 1508, 1490, 1401, 1264, 1091, 1014, 806, 745; ^{1}H NMR (300, $CDCl_3$): δ 1.82 (s, 3H), 4.59 (s, 1H), 6.80 (s, 2H), 7.88 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.20-7.53 (m, 2H), 12.06 (s, 1H);

Table 1. [EMIM][OH] catalyzed the synthesis of pyranoprazoles in aqueous medium.

Entry	Aldehydes	Products	Time in min		Yield (%)		m.p. Found	m.p. Reported
			RT	MW	RT	MW		
1			160	2:40	86	88	225-226	228-230 [12]
2			155	2:20	90	92	244-245	246-247 [11]
3			150	2: 30	88	86	213-215	214-216 [11]

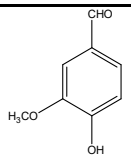
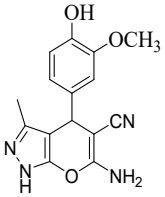
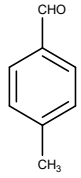
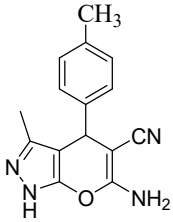
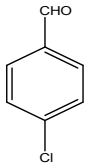
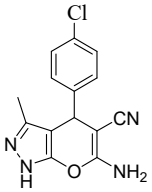
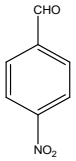
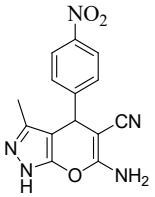
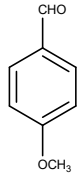
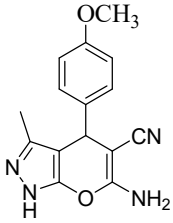
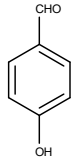
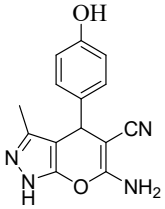
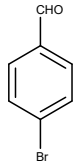
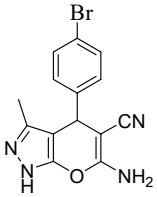
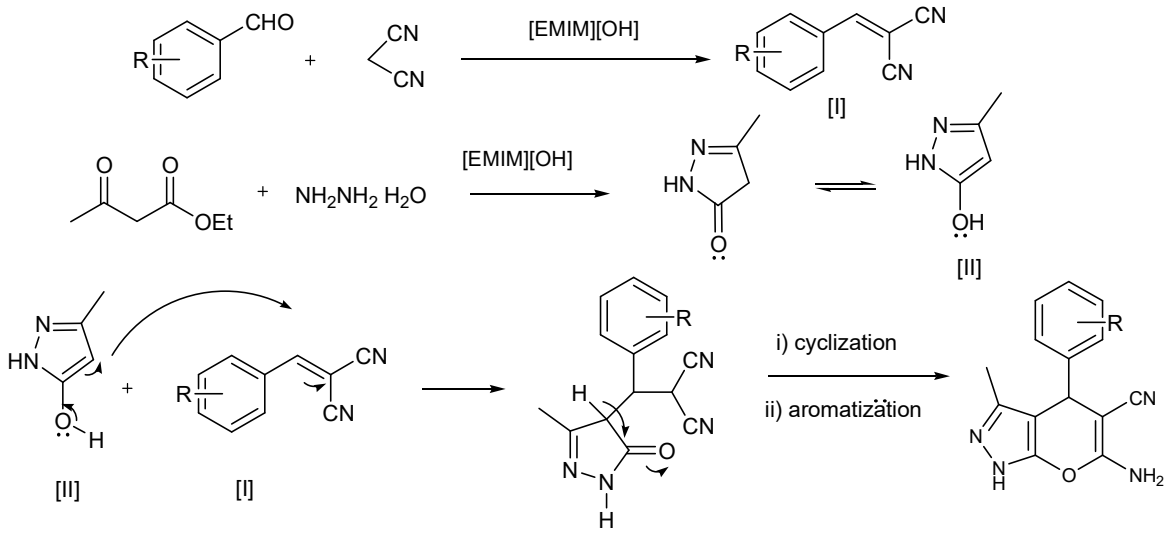
4			180	2:30	89	92	232-233	234-236 [10]
5			200	3:00	88	87	205-206	206-207 [10]
6			210	2:10	84	86	232-233	233-234 [11]
7			180	2:00	91	89	248-249	251-252 [11]
8			180	2:40	90	87	236-238	240-242 [10]
9			200	2:30	88	83	221-222	224-226 [11]
10			210	2:20	88	84	178-180	179-180 [10]

Table 2. Optimization of catalyst for synthesis of pyranopyrazoles.

Entry	Catalyst(mmole)	Time (min) Mw RT	Yield (%) Mw RT
1	0.05	4	50
		280	45
2	0.10	3:00	72
		200	60
3	0.15	2:00	93
		155	85
4	0.20	2:00	93
		155	85

3. RESULTS AND DISCUSSION

Ethyl acetoacetate (1mmol), hydrazine hydrate (1.5mmol), aldehyde (1mmol), malononitrile (1mmol), and a catalytic amount of [EMIM][OH] (0.20 mmol) in 5ml water was stirred or irradiated with microwave irradiation to obtain pyranopyrazoles (Table 1). Initially, the reaction was optimized for the catalyst by varying molar ratios of catalyst (Table 2). After optimization, we decided to carry out the reaction with 0.2 mmol of [EMIM][OH]. Further increase in the amount of catalyst did not affect the time or yield of the reaction. For complete conversion, it takes 2: 00 to 3.30 hours at room temperature stirring and 2 to 4 minutes under microwave irradiation. At room temperature reactants are partially soluble in water hence it takes more time to form the product. But under microwave irradiation reaction is very fast due to the combined effect of microwave and ionic liquid. Since the ionic liquid is polar it absorbs microwaves and converts them into heat energy, consequently, at a higher temperature, the rate of reaction increases enormously within 1 to 3 minutes. Hence for complete conversion, it takes only 1 to 3 minutes under microwave irradiation. After completion of the reaction, the residue is filtered off and the product obtained is washed with water to ensure the removal of [EMIM][OH]. The residue is recrystallized with ethanol followed by washing with a mixture of 30% ethyl acetate: hexane to afford the pure product. When different aldehydes were investigated to check the feasibility of this protocol, it is found that almost all aldehydes give good to an excellent yield of the corresponding products (Scheme 1). A plausible reaction mechanism for this reaction is shown in Scheme 2.



Scheme 2. Plausible reaction mechanism for the synthesis of pyranopyrazole.

4. CONCLUSION

We report here a clean, simple and easy approach for the synthesis of pyranopyrazoles. We also use the ionic liquid in water as green alternatives to organic solvents and provide energy-efficient microwave irradiations as well as cost-effectiveness and room temperature stirring method for the synthesis of pyranopyrazoles.

5. ACKNOWLEDGMENTS

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6. REFERENCES

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