Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(6):312-317
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Green and efficient synthesis of pyranopyrazoles catalyzed by ammonium chloride in water

Vijay P. Pagore[a], Balaji D. Rupnar[a], Sunil U. Tekale[b] and Rajendra P. Pawar[a*]

[a]Department of Chemistry, Deogiri College, Station Road, Aurangabad (MS) India
[b]Department of Chemistry, Shri Muktanand college, Gangapur, (MS) India

---

ABSTRACT

We herein report a green and efficient ammonium chloride catalyzed four component condensation of aldehyde, malononitrile, hydrazine hydrate and ethyl acetoacetate in aqueous medium to synthesize pyranopyrazoles. This method follows the principle of green chemistry by using environmentally benign synthetic method along with use of cost effective catalyst and green reaction medium.

Keywords: Green reaction, Pyranopyrazoles, Ammonium chloride, Water, energy efficient

---

INTRODUCTION

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. 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.

Solvents play a key role in chemical reactions to dissolve and bring the reactants in homogeneous phase. Instead of using harmful and hazardous organic solvents water can be used as green solvent due to it's abundant, nontoxic, non-corrosive and non-flammable nature.

Pyranopyrazoles are fused heterocyclic compounds present in biologically important natural products. It is one of the privileged medicinal pharmacophore having significant biological activities such as anticancer activity [1] (figure I), antimicrobial [2], anti-inflammatory [3], insecticidal [4] and molluscicidal activities [5].

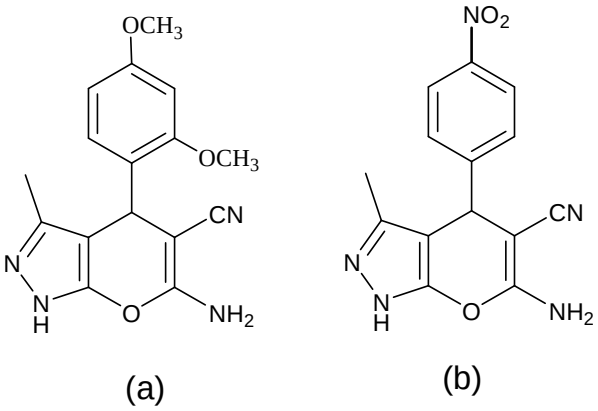
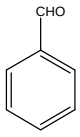
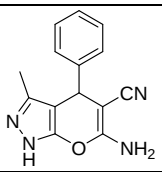
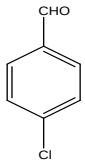
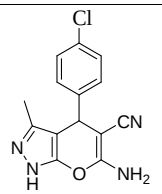
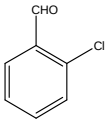
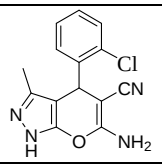
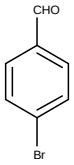
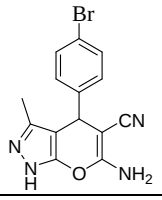


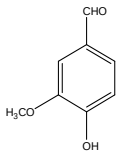
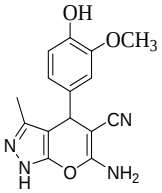
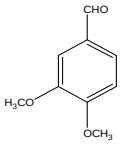
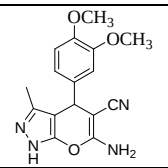
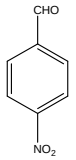
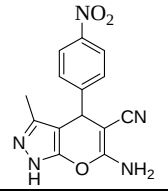
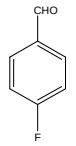
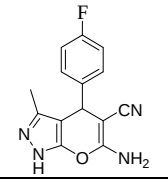
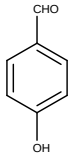
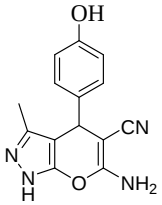
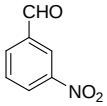
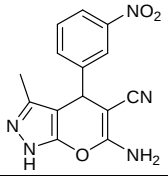
Figure I: Biologically active pyranopyrazole derivatives

Owing to their significant biological properties several synthetic approaches for the synthesis of these compounds were reported. Out of these, the simple approach involves four component condensation of aromatic aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate. Recent reports involve the use of [BMIM]OH [6], nano ZnO [7], L-proline and γ-alumina [8], glycine [9], silica in water [10], $Ba(OH)_2$ in water at reflux [11], cetyl trimethyl ammonium bromide [12] under microwave irradiation [13], citric acid [14].

Recently ammonium chloride has emerged as effective, efficient and inexpensive catalyst because of its mild and environmentally benign character. It was employed for the synthesis of pyrrolo[3,4-b]pyridines [15], imidazo[1,2-a]pyridines [16], diindolylmethanes [17], spirochromenes and spiroacridines compounds [18], 3,4-dihydropyrimidinones [19] etc.

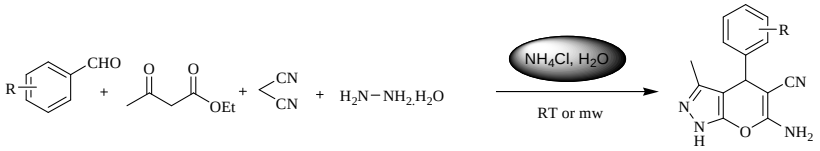
Table 1: Ammonium chloride catalyzed synthesis of pyranopyrazoles in aqueous medium

Entry	Aldehydes	Products	Time in min RT	Time in min Mw	Yield in % RT	Yield in % Mw	m.p. found	m.p. reported
1			180	3	84	86	226-228	228-230[11]
2			165	2:30	90	91	230-232	233-234 [6]
3			190	3	90	85	244-245	246-247 [6]
4			200	2:30	88	90	179-180	179-180 [7]

5			220	3:30	86	85	233-234	234-236 [7]
6			240	4	85	82	161-162	160-162[19]
7			180	2:30	91	88	248-250	251-252 [6]
8			180	2:30	88	86	242-244	244-246[20]
9			200	3	86	81	220-222	224-226 [6]
10			210	3:30	88	84	212-214	214-216 [6]

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. Microwave irradiation dramatically accelerates organic reactions, improves yield, selectivity etc.

As a part of ongoing program in search of novel methods in organic synthesis, we explore room temperature stirring as well as simple, rapid and high yielding microwave assisted one-pot four-component reaction protocol for the synthesis of pyranopyrazole derivatives employing water as an eco-friendly reaction medium and ammonium chloride as a cost effective catalyst.



Scheme 1

MATERIALS AND METHODS

Chemical reagents were purchased from SD Fine or spectrochem chemical company in high purity and 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 an 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 power output of 140-700 W. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography).

General procedure for synthesis pyranopyrazoles using NH_4Cl in water

I) By Stiring at room temperature

Ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol), aldehyde (1 mmol), malononitrile (1 mmol) and ammonium chloride (0.5 mmol) in 5 mL water was stirred at room temperature until the completion of reaction (monitored by TLC, ethyl acetate: hexane 4:1). After completion of reaction, the reaction mixture was poured onto ice-cold water and filtered off. The residue was dried and recrystallized from ethanol followed by washing with 30% ethyl acetate. The products were confirmed by comparison with authentic samples, IR, ^{1}H NMR and melting points.

II) Under mw irradiations

Ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol), aldehyde (1 mmol), malononitrile (1 mmol) and ammonium chloride (0.5 mmol) in 5 mL water was exposed in a microwave oven at the power of 210 W and irradiated for a period of 30 sec at a time. After each irradiation the reaction mixture was removed from the microwave oven for shaking. The total period of microwave irradiation was 2-4 min (**Table 1**). The progress of reaction was monitored by TLC (ethyl acetate: hexane 4:1). After completion of reaction, the reaction mixture was cooled to room temperature, poured onto ice-cold water and filtered. The residue was dried and recrystallized from ethanol to get the corresponding pyranopyrazoles followed by washing with a mixture of EA: hexane (3:7).

Spectral data for representative Pyranopyrazoles.

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

IR (KBr): cm^{-1} 3473, 3224, 3117, 2195, 1652, 1525, 1491, 1400, 1349, 805, 733 cm^{-1}; ^{1}H NMR (300, $CDCl_3$): δ 1.82 (s, 3H), 4.82 (s,1H), 6.92 (s, 2H), 7.59-7.81 (m, 2H), 8.01 (s, 1H), 8.09(d, J = 8.4 Hz, 1H), 12.13 (s, 1H).

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

IR (KBr) cm^{-1} 3397, 2923, 2853, 2189, 1644, 1599, 1515, 1490, 1401, 1019, 874; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (s, 3H, CH_3), 4.57 (s, 1H, CH), 6.79 (s, br, 2H, NH_2), 7.32 (d, 2H, *J* = 8.4 Hz, ArH), 7.45 (d, 2H, *J* = 8.6 Hz, ArH), 12.06 (s, 1H, NH).

RESULTS AND DISCUSSION

Ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol), aldehyde (1 mmol), malononitrile (1 mmol) and ammonium chloride (0.5 mmol) in 5 mL water was stirred at room temperature or irradiated with microwaves to obtain pyranopyrazoles (**Table 1**). For optimizing the various reaction parameters the reaction of hydrazine hydrate, ethyl acetoacetate (EAA), malononitrile, and p-chlorobenzaldehyde was chosen as a model reaction. Keeping in mind the green chemistry principles we decided to test the reaction in water and ammonium chloride as catalyst at room temperature stirring and under microwave irradiation.

Initially, the reaction was optimized by varying molar ratios of catalyst (**Table 2**). The reaction shows good results in terms of yield and rate of reaction with 0.5 mmol of catalyst. Further increase in amount of catalyst did not affect the time or yield of the reaction. For complete conversion it takes 2.5 to 4 hours at room temperature stirring and 2 to 4 minutes under microwave irradiation. The major difficulty with using water as a solvent at room temperature is the less solubility of reactants hence it takes 2.5 to 4 hours stirring to form product. But under microwave irradiation, the reaction is very fast due to combined effect of microwave and water. Since water is polar solvent it absorbs microwaves and converts them into heat energy, consequently at higher temperature its dielectric constant decreases and the ionic product increases, water behaves similar to that of ethanol or acetone.

Hence for complete conversion it takes only 2 to 4 minutes under microwave irradiation. After completion of reaction the residue is filtered off. As ammonium chloride is soluble in water it goes along with filtrate. 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 the aldehydes gives good to excellent yield of the corresponding products. In Spectral data, the IR spectrum exhibited sharp bands at 3410 cm^{-1}, 3356 cm^{-1} (NH_2), 2190 cm^{-1} (CN), supporting the formation of products. A plausible reaction mechanism for this reaction is shown in Scheme 2.

Table 2: Optimization of catalyst for synthesis of pyranopyrazoles

Entry	Catalyst (mmol)	Time in min		Yield in %	
		Mw	RT	MW	RT
1	0.1	5	300	45	45
2	0.25	3:30	240	70	65
3	0.50	2:30	165	92	90
4	0.75	2:30	165	92	90

Plausible reaction mechanism for the synthesis of pyranopyrozole:

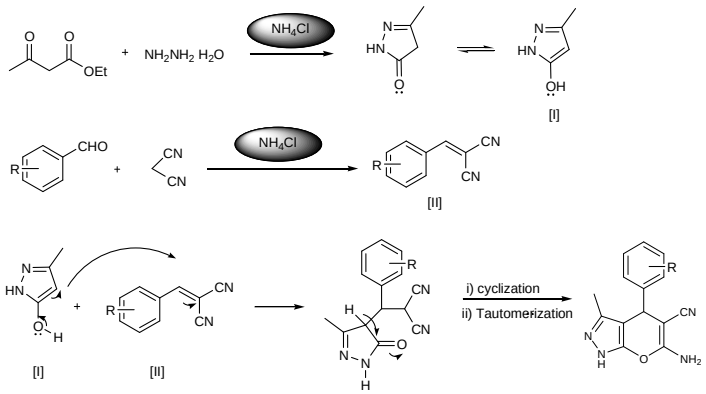


Figure 2

CONCLUSION

We report an atom-economical multicomponent reaction using energy-efficient microwave irradiation or room temperature stirring in presence of ammonium chloride as mild, cost effective and 'green' catalyst along with water as the eco-friendly green solvent to synthesize pyranopyrazoles.

Acknowledgement
The authors are thankful to the principal Dr. M. L. Jadhav, Deogiri College, Aurangabad for providing laboratory facilities and for his encouragement during the said work.

REFERENCES

[1] H. Adibi, L. Hosseinzadeh, S. Farhadi, F. Ahmadi, *J. Reports Pharma Sci.*, **2013**, 2, 116.
[2] E. S. El-Tamany, F. A. El-Shahed, B. H. Mohamed, *J. Serb. Chem. Soc.*, **1999**, 64, 9.

[3] M. E. A. Zaki, H. A. Saliman, O. A. Hiekal, A. E. Z. Rashad, *Naturforsch., C: Biosci.*, **2006**, 61, 1.
[4] E. S. El-Tamany, F. A. El-Shahed, B. H. Mohamed, *J. Serb. Chem. Soc.*, **1999,** 64, 9.
[5] F. M. Abdelrazek, P. Metz, N. H. Metwally, S. F. El-Mahrouky, *Arch. Pharm.*, **2006**, 339, 456.
[6] J. M. Khurana, A. Chaudhary, *Green Chem. Lett. Rev.*, **2012**, 5, 633.
[7] S. U. Tekale, S. S. Kauthale, K. M. Jadhav, R. P. Pawar, *Journal of Chemistry*, **2013**, Article ID 840954.
[8] H. Mecadon, M. R. Rohman, I. Kharbangar, B. M. Laloo, I. Kharkongor, M. Rajbangshi, B. Myrboh, *Tetrahedron Lett*., **2011**, 52, 3228.
[9] M. B. M. Reddy, V. P. Jayashankara, M. A. Pasha, *Synth. Commun*., **2010**, 40, 2930.
[10] P. V. Shinde, J. B. Gujar, B. B. Shingate, M. S. Shingare, *Bull. Korean Chem. Soc*., **2012**, 33, 1345.
[11] S. H. S. Azzam, M. A. Pasha, *Tetrahedron Lett*., **2012**, 53, 6834.
[12] A. S. Nagarajan, B. S. R. Reddy, *Synlet*, **2009**, 2002.
[13] J. F. Zhou, S. J. Tu, H. Q. Zhu, S. J. Zhi, *Synth. Commun*., **2002**, 32, 3363.
[14] P. B. Pawar, S. D. Jadhav, B. M. Patil, R. V. Shejwal and Suresh Patil, Archives of Applied Science Research, **2014,** 6, 150-158.
[15] P. Janvier, X. Sun, H. Bienayme, J. Zhu, *J. Am. Chem. Soc.*, **2002**, 124, 2560.
[16] A. Shaabani, F. Rezazadeh, E. Soleimani, *Monatsh Chem***., 2008**, 139, 931.
[17] J. Azizian, F. Teimouri, M. R. Mohammadizadeh, *Catal. Commun.*, **2007**, 8, 1117.
[18] M. Dabiri, M. Bahramnejad, M. Baghbanzadeh, *Tetrahedron* **2009**, 65, 9443.
[19] A. Shaabani, A. Bazgir, F. Teimouri, *Tetrahedron Lett*. **2003**, 44, 857.
[20] Harshita Sachdeva and Rekha Saroj, *The ScientificWorld Journal*, **2013**, Article ID 680671.