Indian Journal of Chemistry
Vol. 61, April 2022, pp. 405-410

Pectin as a natural biopolymer catalyst promoted green synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives in aqueous ethanol media

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Received 19 July 2020; accepted (revised) 22 December 2021

A green and one-pot protocol for the facile synthesis of biologically important dihydropyrano[2,3-*c*]pyrazole derivatives has been developed. In this method pectin has been utilized as a natural biopolymer catalyst to get quick access to the dihydropyrano[2,3-*c*]pyrazole derivatives in aqueous ethanol media and short reaction times. The main advantages of this method are the operational simplicity, reduced reaction time, high yield of the products, avoidance of any hazardous organic solvent, toxic catalyst, tedious purification step, convenient work up procedure and employment of natural, highly efficient and readily available catalyst. All these factors make the present method economical, green and sustainable.

Keywords: Pectin, natural biopolymer catalyst, dihydropyrano[2,3-*c*]pyrazoles, green protocol, aqueous ethanol media, four-component condensation

Most of the biologically active potential drugs used currently are synthetic organic molecules that often contain a heterocyclic ring[1]. Despite recent advances in drug-designing molecular biology and combinatorial synthetic methodology, the range of easily accessible and suitable functionalized heterocyclic motifs towards the synthesis of structurally diverse compounds is rather limited[2]. Dihydropyrano[2,3-c]pyrazole derivatives are a promising class of heterocyclic compounds and a structural unit of a variety of therapeutic agents[3]. The synthesis of dihydropyrano[2,3-c]pyrazole derivatives is receiving great attention among synthetic chemists due to their diverse bioactivity profiles with various medicinal activities including potential inhibitor of the human Chk1 kinase[4], anticancer[5a], analgesic[5b], molluscicidal[6] and antimicrobial[7].

Because of the above mentioned applications, many methods using different types of catalysts are reported for the preparation of these compounds. Some of these catalyst are: ZrO_2 NPs (Ref. 8), choline chloride/Urea deep[9], isonicotinic[10], molecular sieves[11], meglumine[12], CAPB[13], L-proline/KF-alumina[14], CTACl[15], lipase[16], Bovine Serum Albumin[17], β-cyclodextrin[18], morpholine triflate[19], TPSPPTNM,[20] [Dabco-H][AcO],[21] Na_2 eosin Y[22] and caffeine[23]. However, many of these methods suffer from disadvantages such as low yields, long reaction times, harsh reaction conditions, tedious work-up and requirement of excess amounts of reagents or catalysts. Therefore, it is important to find green, mild and convenient methods for the synthesis of these types of compounds.

Pectin, a biopolymer is a complex plant polysaccharide present in the primary cell wall, is a form of soluble fiber. Pectin has an important role in plant growth, morphology, development, cell adhesion and plant defense and also works as an emulsifier, gelling and stabilizing agent in diverse food and specialty products and also reveals defense mechanisms against plant pathogens and wounding. Scientific research has revealed a number of health benefits and multiple biomedical uses of pectin[24].

As part of our program aimed at developing synthetic procedures with readily available and highly efficient catalyzed[25-28] using of multi-component reactions[29-34], preparation of various biologically active dihydropyrano[2,3-*c*]pyrazole derivatives are of considerable interest and we report herein a natural, biopolymer and mild pectin-catalyzed procedure for synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives *via* four-component cyclocondensation reaction of ethyl acetoacetate, hydrazine hydrate, aryl aldehyde derivatives and malononitrile which might solve some cost problems in industry.

Experimental Section

Melting points all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ^{1}H NMR spectra were

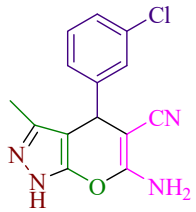
recorded on a Bruker DRX-400 Avance instrument with DMSO-d_6 as solvent. In this article, all reagents and solvents were purchased from Merck, Fluka and Acros chemical companies were used without further purification. Pectin was purchased from Sigma-Aldrich (CAS No. 9000-69-5).

General procedure for preparation of dihydropyrano[2,3-c]pyrazole derivatives, 5a-q

Pectin (Sigma-Aldrich) (20 mol%) was added to a mixture of ethyl acetoacetate (**1**, 1 mmol), hydrazine hydrate (**2**, 1 mmol), aryl aldehyde derivatives (**3**, 1 mmol) and malononitrile (**4**, 1 mmol) in H_2O/EtOH (3 mL,1:1) at 50°C. After completion of the reaction (by Thin layer chromatography TLC) the mixture was cooled to rt, the precipitated product was filtered and washed with aqueous ethanol. The crude product was purified by recrystallization from ethanol to afford the desired product (**5a-q**).

Spectra data of selected and known products are represented below:

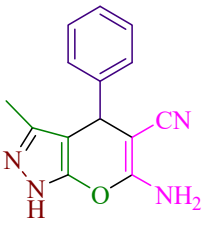
6-Amino-4-(3-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, 5b



5b

Yield 74%. m.p.229-231°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77 (3H, s, CH_3), 5.08 (1H, s, CHAr), 7.19–7.45 (6H, m, ArH and NH_2), 12.15 (1H, s, NH).

6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, 5f



5f

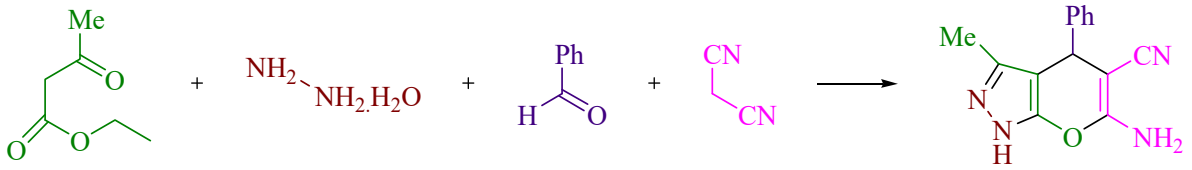
Yield 87%. m.p.245-247°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (3H, s, CH_3), 4.61 (1H, s, CHAr), 6.89 (2H, s, NH_2), 7.18 (2H, d, J = 9.2 Hz, ArH), 7.21-7.26 (1H, m, ArH), 7.31-7.36 (2H, m, ArH), 12.11 (1H, s, NH).

Results and Discussion

At the beginning, the optimal conditions for this reaction were investigated. Conducting reaction between ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) in the presence of the pectin as catalyst were selected as model. A variation of the amount of the pectin from 5 to 10, 15 and 20 mol% led to 33%, 47%, 62% and 87%, of yields, respectively (Table I, entries 3-6). When 5 mol% of catalyst was used, the reaction needed more time to furnish, and yield also decreased. The amount of pectin required for this transformation in a range of different temperatures (rt and 50 °C) was also evaluated. These results indicated that, 20 mol% pectin at 50°C gives a high yield of the product in duration of the reaction. The use of different solvents such as H_2O/EtOH, EtOH, H_2O, MeOH, CH_3CN, CH_2Cl_2 and $CHCl_3$ was investigated and among all these solvents, H_2O/EtOH (1:1) was found to be the best in terms of the yield of the product and time of completion in comparison with other solvents (Table I, entry 6). The best result was obtained with 20 mol % of the pectin as catalyst at 50 °C in H_2O/EtOH (1:1) and afforded 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5f**) in 20 min with 87 % of yield (Table I, entry 6). After optimizing the conditions, the extension of this process was studied by the reaction of ethyl acetoacetate (**1**, 1 mmol), hydrazine hydrate (**2**, 1 mmol), aryl aldehyde derivatives (**3**, 1 mmol) and malononitrile (**4**, 1 mmol) in the presence of 20 mol% pectin in H_2O/EtOH (1:1) at 50°C (Scheme I). The results of this study are presented in Table II. The reaction was clean, and no chromatographic separation was performed because no impurities were observed. After completion of the reaction, the solid product was collected by simple filtration.

Also, the proposed mechanism for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives are shown in the Scheme II. On the basis of the above results and previous studies, a plausible mechanism can reasonably proposed for the synthesis of pyranopyrazole **5** from aryl aldehyde derivatives, hydrazine hydrate, malononitrile and ethyl acetoacetate

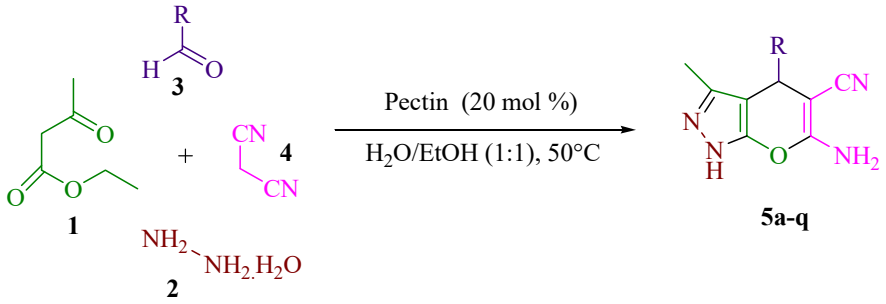
Table I — Optimization of the reaction condition on the synthesis of **5f**[a]



Entry	Pectin (mol %)	Solvent/Conditions	Time (min)	Isolated Yield (%)
1	Catalyst free	H_2O/EtOH, RT	240	trace
2	Catalyst free	H_2O/EtOH, 50°C	240	trace
3	5	H_2O/EtOH, 50°C	75	33
4	10	H_2O/EtOH, 50°C	50	47
5	15	H_2O/EtOH, 50°C	35	62
6	20	H_2O/EtOH, 50°C	20	87
7	20	H_2O/EtOH, RT	30	56
8	20	Solvent free, 50°C	85	28
9	20	EtOH, 50°C	25	54
10	20	EtOH, RT	45	42
11	20	H_2O, RT	70	31
12	20	MeOH,50°C	40	46
13	20	MeOH, RT	65	34
14	20	CH_3CN, RT	60	37
15	20	CH_2Cl_2, RT	95	24
16	20	$CHCl_3$, RT	95	19
17	25	H_2O/EtOH, 50°C	20	87

[a] Reaction conditions: Benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1 mmol) and ethyl acetoacetate (1 mmol) and catalyst in various solvents and temperatures.

Table II — Pectin catalyzed synthesis of dihydropyrano[2,3-c]pyrazole derivatives

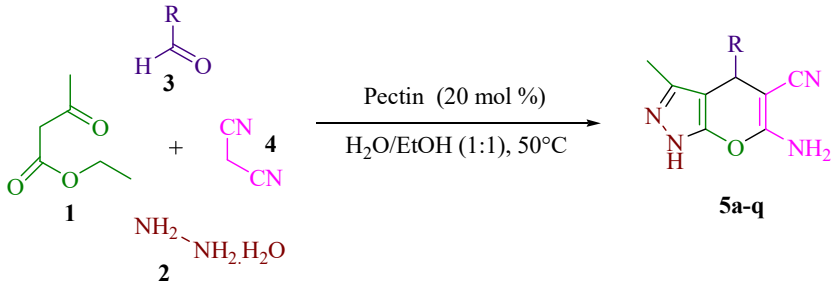


5a-q

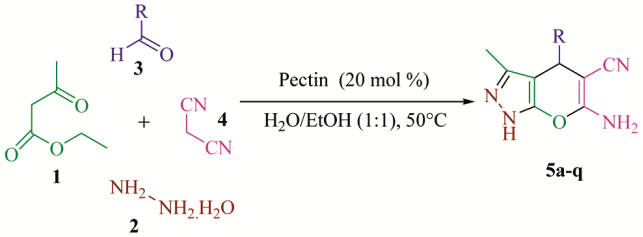
Entry	R	Product	Time (min)	Isolated Yields (%)	m.p. (°C)	Lit. m.p. (°C)
1	4-OMe- C_6H_4	**5a**	20	87	212-214	210-212 (Ref. 12)
2	3-Cl- C_6H_4	**5b**	30	74	229-231	230-231 (Ref. 12)
3	3-O_2N-C_6H_4	**5c**	20	89	191-193	190-193 (Ref. 13)
4	4-Br- C_6H_4	**5d**	30	72	179-181	180-181 (Ref. 8)
5	4-Me-C_6H_4	**5e**	15	89	203-205	205-208 (Ref. 13)
6	C_6H_5	**5f**	20	87	245-247	244-246 (Ref. 13)
7	3-F- C_6H_4	**5g**	15	88	240-242	242-243 (Ref. 12)
8	4-OH- C_6H_4	**5h**	30	75	222-224	220-223 (Ref. 11)
9	2-Cl- C_6H_4	**5i**	20	84	244-246	245-246 (Ref. 12)

(*Contd.*)

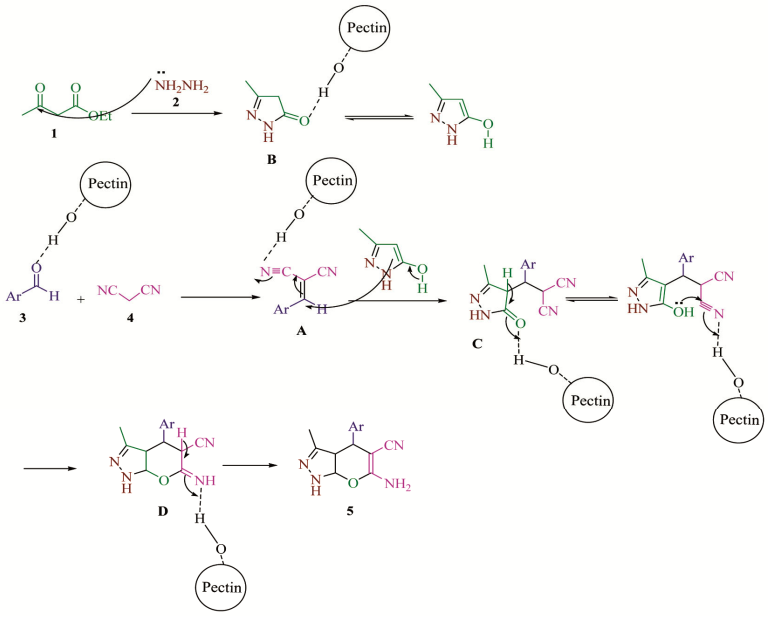
Table II — Pectin catalyzed synthesis of dihydropyrano[2,3-c]pyrazole derivatives (*Contd.*)



Entry	R	Product	Time (min)	Isolated Yields (%)	m.p. (°C)	Lit. m.p. (°C)
10	3-Br- C_6H_4	**5j**	25	73	223-225	223-224 (Ref. 13)
11	2-O_2N-C_6H_4	**5k**	15	88	242-244	243-244 (Ref. 12)
12	2-OMe- C_6H_4	**5l**	15	89	250-252	249-250 (Ref. 12)
13	4-Cl- C_6H_4	**5m**	30	76	233-235	234-235 (Ref. 12)
14	3-OH- C_6H_4	**5n**	25	82	225-227	225-228 (Ref. 13)
15	4-O_2N-C_6H_4	**5o**	20	85	249-251	248-249 (Ref. 12)
16	2,4-$(Cl)_2$- C_6H_3	**5p**	30	72	228-230	229-230 (Ref. 12)
17	3,4-$(OMe)_2$-C_6H_3	**5q**	20	86	186-188	188-191 (Ref. 11)



Scheme I — Synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives



Scheme II — Proposed mechanism for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives

Table III — Comparison of catalytic ability some of catalysts reported in the literature for synthesis of dihydropyrano[2,3-c]pyrazole derivatives [a]

Entry	Catalyst	Conditions	Time/Yield (%)	Reference No.
1	ZrO_2 NPs	Etoh/H_2o, RT	5 min/95	8
2	Choline chloride	Urea Deep, 80°C	10 min/95	9
3	Isonicotinic acid	Solvent-free, 85°C	30 min/90	10
4	Molecular sieves	EtOH, Reflux	1 h/84	11
5	Meglumine	EtOH/H_2O, RT	15 min/95	12
6	CAPB	H_2O,50-60°C	4 min/96	13
7	L-proline	H_2O, Reflux	10 min/87	14
8	KF-alumina	EtOH, Reflux	12 min/80	14
9	CTACl	H_2O,90°C	240 min/89	15
10	Lipase	EtOH, 30°C	1h/90	16
	Pectin	H_2O/EtOH, 50°C	20 min/87	This work

[a] Based on the four-component reaction of benzaldehyde, hydrazine hydrate, malononitrile and ethyl acetoacetate.

(Scheme II). At first, the pectin is a major role in the formation of arylidenemalononitrile (**A**) from Knoevenagel condensation of benzaldehyde **3** and malononitrile **4**. The 3-methyl-1*H*-pyrazol-5(4*H*)-one **B** was formed from the condensation of ethyl acetoacetate (**1**) and hydrazine hydrate **2**, which would be converted to its corresponding enol in the presence of the pectin. Subsequent Michael-type addition of a corresponding enol to the intermediate **A** to produce intermediate **C**, which underwent intramolecular cyclization by the nucleophilic addition of enol oxygen to nitrile group to generate intermediate **D**. Finally, the tautomerization of intermediate **D** gave dihydropyrano[2,3-*c*]pyrazoles **5**.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives are shown in Table III. This study reveals that pectin has shown its extraordinary potential to be an alternative green, natural biopolymer, mild, readily available and highly efficient catalyst for synthesis of these biologically active heterocyclic compounds, in addition to the use of high yields and short reaction times in the reactions are the notable advantages this present methodology.

Conclusion

In conclusion, we have explored the use of pectin as a natural biopolymer catalyst for the green and one-pot synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives in aqueous ethanol media with easily separation of products with no column chromatographic separation. The use of an environmentally friendly, mild and readily available catalyst, along with simplicity of operation, high yields and short reaction times, provides a good example of a competitive alternative synthetic methodology for these compounds.

Acknowledgements

The author gratefully acknowledges financial support from the Research Council of the Apadana Institute of Higher Education.

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