Iranian Journal of Organic Chemistry Vol. 10, No. 4 (2018) 2489-2494

Synthesis of 3,4-dihydropyrimidinones by the reaction between β-ketoesters, aromatic aldehydes and urea in the presence of pectin as a hetero polysaccharide catalyst

Khatereh Khandan-barani*

Department of Chemistry, Zahedan Branch, Islamic Azad University, Zahedan, Iran

Received: September 2018; Revised: September 2018; Accepted: December 2018

Abstract: Pectin is a high-molecular-weight carbohydrate polymer which is present in virtually all plants where it contributes to the cell structure. Use of green and biodegradable catalyst in organic synthesis is undeniable. Easy access, inexpensive, natural and green catalysts are valuable. Herein, pectin was applied as a natural and hetero polysaccharide catalyst for the synthesis of 3,4-dihydropyrimidinone derivatives under suitable conditions. The most advantages of this research are: use of natural, green and biodegradable catalyst, easy work-up and high yields.

Keywords: Hetero polysaccharide, 3,4-Dihydropyrimidinone, Pectin, β-Ketoester

Introduction

Pectin is a gelatin-like carbohydrate in the cell walls of plants. Pectin acts like a gel, sometimes referred to as a "fragile solid" in cooking. Pectin is semisoluble in liquids, which means that it is able to take up some liquid. This is especially important in cooking fruits and vegetables because it allows them to soften when cooked. Pectin is extracted from apples and citrus fruits. Soluble pectin is capable of forming a gel once the correct concentrations of acid and sugar are reached. This is helpful to thicken syrups, such as those used to make jams and jellies. [1–3] The family of pectin products is made up of a variety of hydrocolloids, all of which contain d-galacturonic acid in the sodium salt form as the basic building block. All contain some percentage of the uronic acid units in the form of a methyl ester (-$COOCH_3$); so while all pectin preparations are somewhat anionic, the degree to which they are anionic varies [4-6] (Figure **1**).

*Corresponding author. Tel: (+98) 5433443600, Fax: (+98) 5433441099, E-mail: kh_khandan_barani@yahoo.com

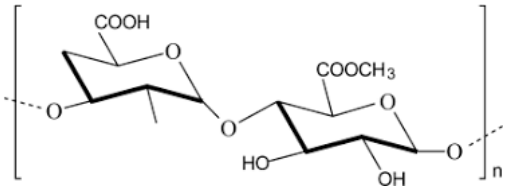
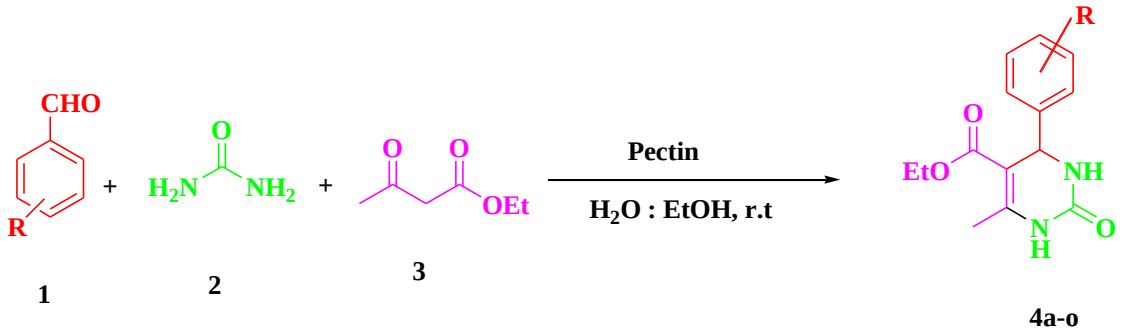


Figure 1: The structure of pectin

Research interest in 3,4-dihydropyrimidin-2-(1H)-ones (Biginelli compounds', DHPMs), has surged rapidly, owing to the pharmacological properties [7–9] associated with many derivatives of this privileged hetero-cyclic core. The biological activity [7] of these Biginelli compounds includes antiviral, antitumor, antibacterial and anti-inflammatory properties. Out of the five major bases in nucleic acids, three (i.e. cytosine, uracil, and thymine) are pyrimidine derivatives, which are found in DNA and RNA [10, 11]. In an attempt to prepare DHPMs, different types of acidic catalysts such as H_2SO_4 [12], BF_3-

EtOH/CuCl [13], $LaCl_3$-7H2O with catalytic amount of concentrated HCl [14], $CeCl_3$-$7H_2O$ [15], $InCl_3$ [16], $Cu(OTf)_2$ [17], $LiClO_4$ [18], $InBr_3$ [19], $FeCl_3$-$6H_2O$/HCl [20], Iron(III) tosylate [21], TMSI [22], have been used. However, in spite of their potential utility many of the existing methods suffer from some drawbacks, such as the use of strong acidic conditions, long reaction times, tedious workup procedures, environmental disposal difficulties, and low yields of the products. According to mentioned reasons and in continue of our research on multi-component reactions[23-26] we herein report green synthesis of 3,4-dihydropyrimidinone derivatives the presence of hetero polysaccharide pectin as a natural and cheap and easily available catalyst via the reaction between aryl aldehydes, urea and ethylacetoacetate (scheme**1**). The process is remarkably simple, high yielding, highly efficient, time and energy saving.



1 **2** **3** **4a-o**

Scheme 1: Synthesis of 3,4- dihydropyrimidin-2(*1H*)-ones in the presence of pectin as green and natural catalyst at ambient temperature in aqueous media

Table 1: Synthesis of 3,4-dihydropyrimidinone derivatives.

Entry	R	Product	Time(min)	Yield(%)	M.p (°C)	M.p reported (°C)
1	H	4a	90	85	200-202	201-203 [27]
2	4-CH_3	4b	120	85	215-216	214-215 [28]
3	4-NO_2	4c	60	95	208-210	209-210 [29]
4	4-Cl	4d	65	90	210-212	212-213 [30]
5	4-OH	4e	80	75	199-201	198-200 [31]
6	2-Cl	4f	65	86	219-221	216-218 [32]
7	4-Br	4g	70	88	196-198	197-200 [33]
8	4-OMe	4h	100	80	203-205	202-204 [34]
9	4-F	4i	60	93	182-183	183-185 [35]
10	2-NO_2	4j	65	90	208-210	206-208 [30]
11	3-Br	4k	70	85	185-186	185-186 [36]
12	4-NMe_2	4l	150	80	252-254	255-256 [37]
13	3-NO_2	4m	90	90	225-227	227-229 [38]
14	3-Cl	4n	75	92	189-190	191-193 [39]
15	3,4-$(OMe)_2$	4o	130	70	178-179	175-177 [40]

Results and discussion

The reaction conditions were optimized for the synthesis of 3,4-dihydropyrimidinone derivatives. The reaction between benzaldehyde, urea and ethylacetoacetate was chosen as a model reaction (Scheme **1**). The reaction was performed with different amount of solvent and catalyst. The results are summarized in table **2** and **3**.

Table 2: Effect of amount of catalyst for the synthesis of 3,4- dihydropyrimidin-2(1*H*)-ones

Entry	Catalyst loading (g)	Time (min)	Yield (%)
1	0.02	150	50
2	0.03	110	60
3	0.04	100	65
4	**0.05**	**90**	**85**
5	0.06	90	85

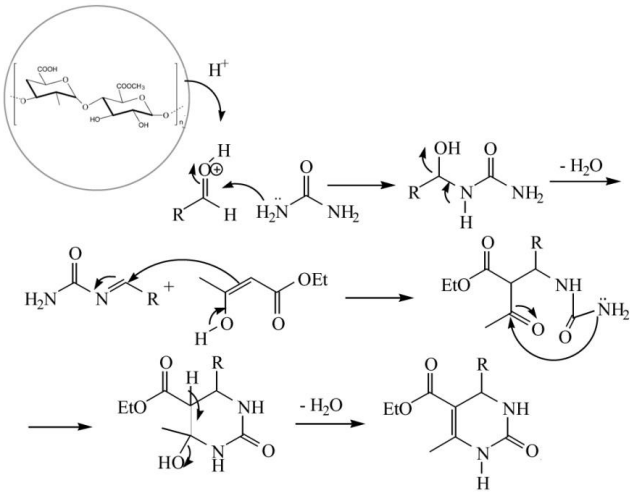
Table 3: Influence of different solvents for the synthesis of 3,4- dihydropyrimidin-2(1H)-ones in the presence of pectin (0.05 g) at ambient temperature

Entry	Solvent	Yield(%)
1	H_2O	50
2	H_2O:EtOH(1:1)	70
3	**H_2O:EtOH(1:2)**	**85**
4	H_2O:EtOH(1:3)	85
5	H_2O:EtOH(1:4)	80
6	EtOH	80

Next the reaction conditions were optimized for the synthesis of 3,4-dihydropyrimidinones, the best results was found at ambient temperature with (0.05 g) of pectin in H_2O:EtOH (1:2).

The scope and efficiency of these procedures were explored for the synthesis of a wide variety of substituted 3,4-dihydropyrimidinones. A series of aromatic aldehydes were investigated (Table **1**).

A proposed mechanism for the formation of **4a** is shown in scheme **2**. Pectin has many free carboxyl group that can active carbonyl group.



Scheme 2: Proposed mechanism for the synthesis of 3,4- dihydropyrimidin-2(1H)-ones in the presence of pectin.

Conclusion

In summary, a green procedure by using pectin as a green and natural catalyst for the one-pot synthesis of 3,4- dihydropyrimidin-2(1*H*)-ones has been developed. We report an eco-friendly and straightforward one-pot condensation for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in the presence of pectin as a highly effective, green, natural and biodegradable catalyst. Pectin is inexpensive, clean, safe, nontoxic, and easy access. Moreover, this method has several other advantages such as, high yields, operational simplicity, clean and neutral reaction conditions, which makes it a useful and attractive process for the synthesis of a wide variety of biologically active compounds.

Experimental

IR spectra were obtained on a JASCO FT/IR-460 plusspectrometer. Melting points were taken on an Electrothermal 9100 apparatus. The ^{1}H NMR spectra were obtained on Bruker DRX-400 Avance instruments with DMSO as a solvent. Chemicals were purchased from Merck (Darmastadt, Germany), Fluka (Buchs, Switzerland), and used without further purification.

General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (4a):

A mixture of aromatic aldehyde **1** (1 mmol), urea **2** (1 mmol) ethyl acetoacetate **3** (1 mmol), and pectin (0.05 g) in H_2O:EtOH (1:2) was stirred at ambient temperature for appropriate time. After completion of the reaction (monitored by TLC), the precipitate was filtered off and washed with ethanol (3× 2 mL) to give the pure product **4a**.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a):

FT–IR (KBr, ν_{max}/cm^{-1}): 3330 (NH), 3321(NH), 1698 (2C=O).^{1}HNMR (400.1 MHz, DMSO-d_6): δ=1.08 (t, *J*= 7.1 Hz, 3H), 2.23 (s, 3H), 3.96 (q, *J* = 7.1 Hz, 2H), 5.12 (s, 1H), 7.22-7.31 (m, 5H), 7.78 (s, 1H), 9.25 (s,1H).

5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4c):

FT–IR (KBr, ν_{max}/cm^{-1}): 3243 (NH), 3112(NH), 1705 and 1648 (2C=O).^{1}HNMR (400.1 MHz, DMSO-d_6): δ=1.12 (t, *J* =7.0 Hz, 3H), 2.31 (s, 3H), 4.05 (q, *J* = 7.1 Hz, 2H), 5.66 (d, *J* = 2.4 Hz, 1H,), 7.47 (d, *J* = 9.2 Hz, 2H), 7.58 (s, 1H), 8.23 (d, *J* = 9.2 Hz, 2H), 9.11(s, 1H).

5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4d):

FT–IR (KBr, ν_{max}/cm^{-1}): 3330 (NH), 3217 (NH), 1669 (2C=O).^{1}HNMR (400.1 MHz, DMSO-d_6): δ=1.12 (t, *J* =7.1 Hz, 3H), 2.29 (s, 3H), 3.97 (q, *J* = 7.1 Hz, 2H), 5.37 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 9.1, 2H), 7.63 (s, 1H), 7.78 (d, *J* = 9.1, 2H), 9.14 (s, 1H).

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4h):

FT–IR (KBr, ν_{max}/cm^{-1}): 3241(NH), 3115(NH), 1713 and 1649 (2C=O).^{1}HNMR (400.1 MHz,DMSO-d_6): δ=1.17 (t, *J* = 6.8 Hz, 3H), 2.29 (s, 3H), 3.68 (s, 3H), 3.73 (q, *J* = 6.8 Hz, 2H), 5.08 (s, 1H), 6.79-7.12 (m, 4H), 7.59 (s, 1H), 9.22 (s, 1H).

5-(Ethoxycarbonyl)-4-(3-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4k):

FT–IR (KBr, ν_{max}/cm^{-1}): 3335 (NH), 3147(NH), 1672 (2C=O).^{1}HNMR (400.1 MHz, DMSO-d_6):δ=1.14 (t, *J* =7.2 Hz, 3H), 2.29 (s, 3H), 4.01 (q, *J* = 7.2 Hz, 2H), 5.16 (s, 1H), 7.22-7.50 (m, 4H), 9.66 (s, 1H), 10.38 (s, 1H).

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the Zahedan Branch, Islamic Azad University.

References

[1] Jacqueline, B. Marcus. *Culinary Nutrition*, Academic Press, **2013**.
[2] O'Neill , M. A.; Ishii, T.; Albersheim, P.; Darvill, A.G.; *Annu Rev Plant Biol.* **2004,** *55*, 109.
[3] Ridley, B. L.; O'Neill, M.A.; Mohnen, D. *Phytochemistry*. **2001**, *57*, 929.
[4] Arendt, E.; Dal Bello, F. *Gluten-Free Cereal Products and Beverages*, Academic Press, **2008.**
[5] Sonia, T. A.; Sharma, C. *Oral Delivery of Insulin*, Woodhead Publishing, **2014.**
[6] Pilnik , W.; Voragen, A. G. J.; Hulme, H. C. (ed). *The biochemistry of fruits and their products*, Academic Press, London, **1970**.
[7] Kappe, C.O. *Tetrahedron*. **1993**, *49*, 6937.
[8] Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Nakeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satoh, F.; Morita, M.; Noguchi, T. *J. Med. Chem.* **1989**, *32*, 2399.
[9] Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem*. **1991**, *34*, 806.
[10] Clark J. H. (Ed.), *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH Publishers, New York, **1994**.
[11] Sheldon, R.A.; VanBekkum, H. *Fine Chemical Through Heterogeneous Catalysis*, Wiely-VCH, Weinheim, Germany, **2002**.
[12] Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc*. **1933**, *55*, 2886.
[13] Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
[14] Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett*. **2000**, *41*, 9075.
[15] Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem*. **2003**, *68*, 587.
[16] Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
[17] Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. Tetrahedron Lett. **2003**, *44*, 3305.
[18] Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T.; *Synthesis*. **2001**, 1341.
[19] Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe. C. *Tetrahedron*, **2002**, *58*, 4801.
[20] Lu, J.; Ma, H. *Synlett*, **2000**, 63.
[21] Starcevich, J. T.; Laughlin, T. J.; Mohan, R. S. *Tetrahedron Lett*. **2013**, *54*, 983.
[22] Sabitha, G.; Reddy, G. S. K.; Reddy, C. S.; Yadav, J. S. *Synlett*. **2003**, 858.
[23] Khandan-Barani, K.; Kangani, M.; Mirbaluchzehi, M.; Siroos, Z.; *Inorganic and Nano-Metal Chem*. **2017,** *5*, 751.
[24] Khandan-Barani, K.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Hazeri, N.; Sajadikhah, S. S. *Arkivoc*. **2011**, *xi*, 22.
[25] Khandan-Barani, K.; Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M. *Iran. J. Org. Chem.* **2012**, 4, 901.
[26] Khandan-Barani, K.; Maghsoodlou, M. T.; Hassanabadi, A.; Hosseini-Tabatabaei, M. R.; Saffari, J.; Kangani, M. *Res Chem Intermed*, **2015**, *41*, 3011.
[27] Raju, C.; Kalaipriya, M.; Uma, R.; Sridhar, R.; Ramakrishna, S. *Curr. Chem. Lett*. **2012**, *1*, 27.
[28] Dadhani, A. B.; Patel, V. K.; Raval, D. K. A. *J. Braz. Chem. Soc*. **2011**, *22*, 511.
[29] Yu, Y.; Liu, D.; Liu, C.; Luo, G. *Bioorganic & Medicinal Chemistry Letters*. **2007**, *17*, 3508.
[30] Khabazzadeh, H.; Saidi, K.; Sheibani, H. *Bioorganic and Medicinal Chemistry Letters*, **2008**, *18*, 278.
[31] Kadre, T.; Jetti, S. R.; Bhatwara, A.; Paliwal, P.; Jain, S. *Arch. Appl. Sci. Res*. **2012**, *4*, 988.
[32] Chandak, S. H.; Lad, N. P.; Upare, P. P. *Heteroatom. Chem*, **2009**, *31*, 469.
[33] Tribhuvannathji, K. V.; Babura, M. D. *Chin. J. Chem*. **2010**, 28, 388.
[34] Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *J. Mol. Catal. A Chem.* **2007**, *271*, 14.

[35] Valizadeh, H.; Shockravi, A. *Heteroatom. Chem*. **2009**, *20*, 284.
[36] Xu, D. Z.; Li, H.; Wang, Y. *Tetrahedron*, **2012**, *68*, 7867.
[37] Lal, J.; Sharma, M.; Gupta, S.; Parashar, P.; Sahu, P.; Agarwal, D. D. *J. Mol. Catal. A: Chem.* **2012**, *352*, 31.
[38] Reddy, Ch.V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N.; *TetrahedronLett*. **2002**, *43*, 2657.
[39] Prabhakar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett*. **2003**, *44*, 3305.
[40] Su, W. K.; Li, J. J.; Zheng, Z. G.; Shen, Y. C. *Tetrahedron Lett.* **2005,** *46*, 6037.