Scientia Iranica C (2014) 21(6), 2076–2081

SCIENTIA
IRANICA

Sharif University of Technology
Scientia Iranica
Transactions C: Chemistry and Chemical Engineering
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Research Note

Sodium alginate: A renewable and very effective biopolymer catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones

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Received 22 May 2013; received in revised form 28 October 2013; accepted 4 January 2014

KEYWORDS
Alginate;
3,4-Dihydropyrimidin-2(1H)-ones;
One-pot synthesis;
Catalyst;
Biopolymer.

Abstract. A convenient and mild methodology is described for the preparation of 3,4-dihydropyrimidin-2(1H)-ones in the presence of sodium alginate as the biopolymer catalyst. The sodium alginate was found as a novel, very mild, recyclable, efficient, eco-friendly and very noteworthy biopolymer catalyst.

1. Introduction

Multi-Component Reactions (MCRs) have attracted more synthetic attention during recent years. MCRs play an important role in combinatorial chemistry because of their significant ability to synthesize several compounds, for example small drug-like molecules [1-3]. The 3,4-dihydropyrimidin-2(1H)-ones are well-known compounds with different applications in medical industries because of their pharmacological and therapeutic properties [4]. Many synthetic methods have been developed to modify Biginelli reaction by microwave [5,6], ultrasound irradiation [7,8], ionic liquids [9] and using different catalysts for example $FeCl_3$/tetracthyl orthosilicate [10], chiral ytterbium complexes [11], α-zirconium sulfophenylphosphonate [12], ruthenium hydroxide [13], triflates [14], binol-based phosphoric acids [15], Amberlyst-70 [16] and polymeric catalysts like polyoxometalate [17], polystyrene-poly(ethylene glycol)-bound sulfonic acid (PS–PEG–SO_3H) [18], and polyvinylsulfonic acid [19].

Natural polysaccharides have been attracted as biopolymers because of their unique structures and properties during recent years [20-24]. Alginic acid and its carboxylic salts are important biopolymers with interesting features such as biocompatibility, biodegradability and the ability of gelation with multivalent cations [25,26]. These polymers can be obtained by two different sources of bacteria and brown algae [27]. The chemical structure of alginate is shown in Scheme 1 [28].

Recently, cellulose sulfuric acid has emerged as a promising recyclable biopolymer catalyst for acid-catalyzed reactions, such as the synthesis of α-amino nitriles [29-32]. In addition, Dekamin et al. illustrated that some organic compounds, for example α-amino nitriles and imines; can be synthesized under mild conditions by using the chitosan as a biopolymer catalyst [33].

As a part of our continuing efforts on the develop-

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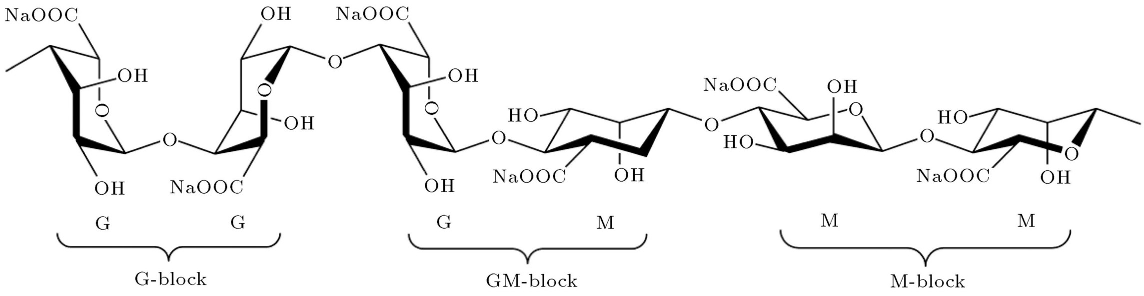
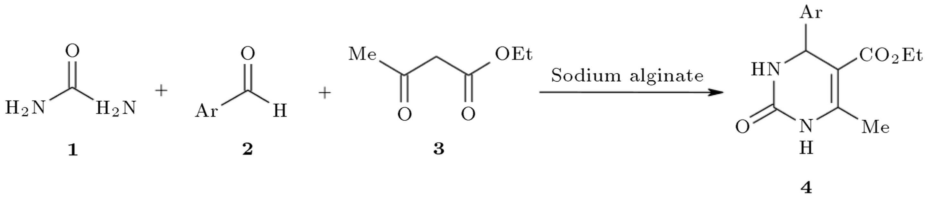


Scheme 1. Chemical structure of sodium alginate.



Scheme 2. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones in the presence of sodium alginate.

ment of new applications for the alginates [34-39], we examined one of the novel aspects of this biopolymer as a media and catalyst for the organic reactions. To the best of our knowledge, there is no report in open literature regarding the application of alginates as the catalyst or solvent for the organic reactions. Therefore, we selected a multi-component reaction for proving the catalytic activity of these biopolymers. Herein, we report a novel, very mild, efficient, recyclable, eco-friendly, biocompatible, biodegradable and very noteworthy polymeric media for the preparation of 3,4-dihydropyrimidin-2(1H)-ones via 3CR Biginelli reaction (Scheme 2).

2. Material and methods

2.1. Materials

All chemicals were purchased from Aldrich or Merck and used as received. The Sodium Alginate (SA) with number-averaged molecular weight 12,000-40,000 was obtained from Sigma and used without any post-modification.

2.2. General procedure for synthesis of 3,4-dihydropyrimidin-2(1H)-ones in the presence of sodium alginate

All derivatives of 3,4-dihydropyrimidin-2(1H)-ones were synthesized as follows: A mixture of aldehyde (1 mmol), urea (1 mmol) and ethyl acetoacetate (1 mmol) were mixed in aqueous alginate solution (1 mL) and stirred at 20°C for a proper time. Then, ethanol as a nonsolvent was added (3 × 3 mL) to the reaction mixture, and products were separated from alginate solution and dried over $MgSO_4$. The solvent was removed and the crude product was recrystallized from ethanol to give pure dihydropyrimidone. All the reactions were carried out at 15-30°C and completed within 2-4 h (Table 1). The characterizations of all the products were performed by comparison of their melting points and their spectral data with those of authentic samples.

2.3. Measurements

Melting points were determined using an electrothermal apparatus. The FTIR spectra were performed with a Bruker-Equinox 55 IR spectrometer (Ettlingen, Germany) which was equipped by H.ATR accessories with a ZnSe crystal. The ^{1}H NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO)-d_6 solution using a Bruker Avance 400 MHz Spectrometer (Germany). Analytical TLC was carried out using Merck 0.2 mm silica gel 60 F-254 Al-plates.

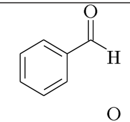
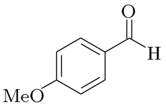
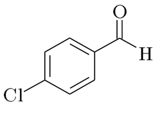
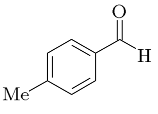
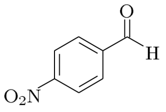
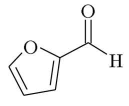
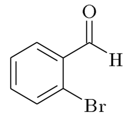
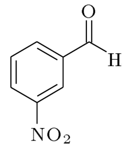
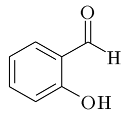
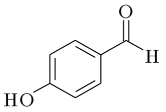
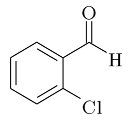
3. Results and discussion

The 3,4-dihydropyrimidin-2(1H)-ones were synthesized by condensation of an aldehyde, urea and ethyl acetoacetate in solution of sodium alginate in 75-95% yields.

The reusability of the alginate as the catalyst was also investigated. After each run, ethanol (3 × 3 mL) was added to the reaction mixture to separate the products and the unreacted starting materials. After washing, the recycled alginate was dissolved in water and used for further runs. No decrease in activity was observed even after four runs (Table 1, entry 10). This shows that aqueous alginate solution is an effective and recyclable media for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones.

The excellent yields and significant lower temperatures of the reaction in the alginate solution compared to previous reports are probably related to the specific structure of the alginate. The structure of the alginate

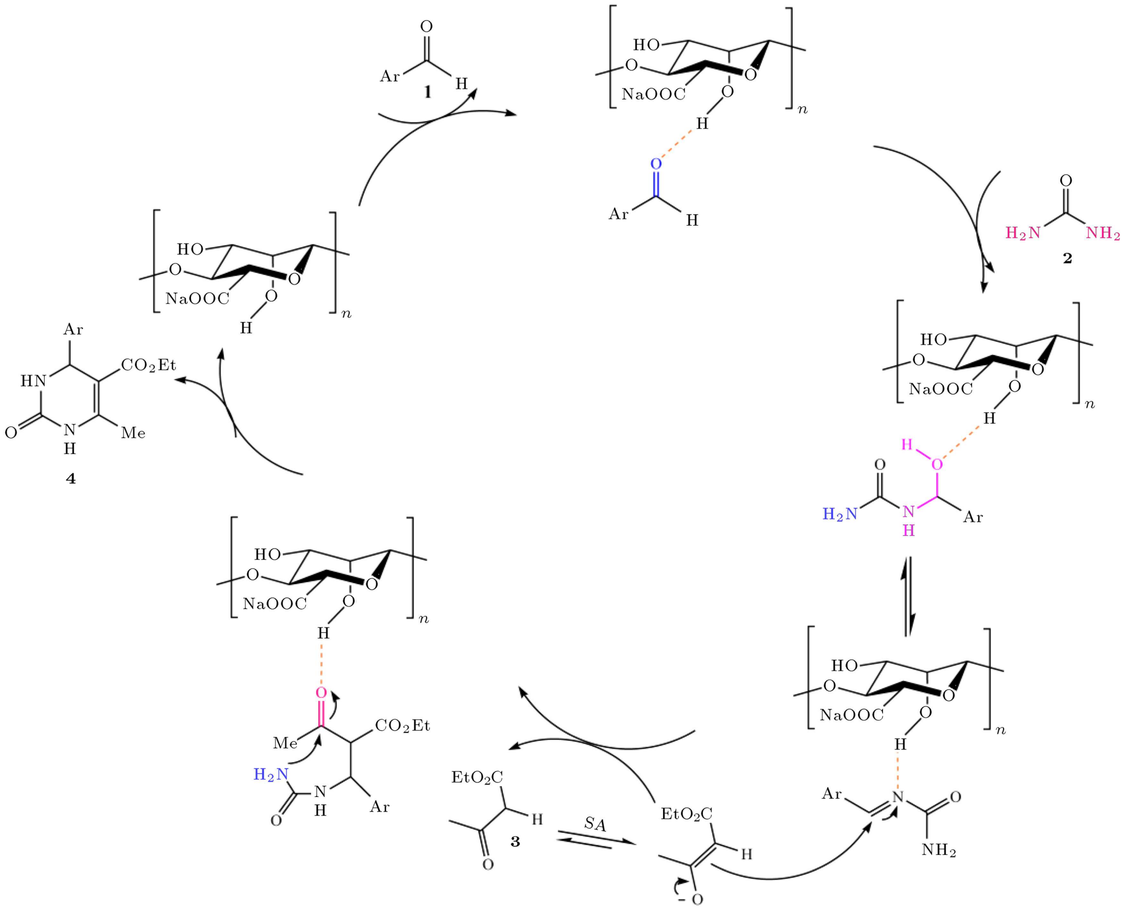
Table 1. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones **4**.

Entry	**ArCHO 1**	**Time (h)**	**Temperature (°C)**	**4, %Yield**[a]	**m.p. (°C)**
1		2.5	20	4a, 90	202-203 [41]
2	MeO	2	15	4b, 95	208-210 [41]
3	Cl	3	20	4c, 93	213-214 [41]
4	Me	2.5	20	4d, 92	215-218 [41]
5	O_2N	3.5	30	4e, 75	207-208 [41]
6		3	25	4f, 76	203-205 [17]
7	Br	3	20	4g, 85	206-208 [42]
8	NO_2	4	30	4h, 78	232-234 [17]
9	OH	2.5	20	4i, 90	199-201[17]
10	HO	2	15	4j, 93,92,92,91	228-230 [17]
11	Cl	3	25	4k, 87	215-216 [17]

[a] Isolated yield.

is formed by two polar hydroxyl and carboxylate functional groups and saccharide moieties. On the other hand, all of the reactants in these 3CRs have two polar functional groups and nonpolar hydrocarbon parts. It seems the reactants migrate from the polar medium (water) to the surface of polymeric alginate because of their nonpolar parts [40]. It can be assumed that the reactants can accumulate better on surface of alginate than water. Therefore, the reaction is performed under mild conditions.

Another reason for completion of the reaction is the presence of active protons in the chemical structure of the alginate chains and their interactions with the polar functional groups of the starting materials and reaction intermediates. Hydroxyl groups of alginate can accelerate this reaction through the hydrogen bonding between the hydrogen donor and acceptor molecules and intermediates. A mechanistic rationalization for this reaction is provided, which involve a multistep sequence of events (Scheme 3).



Scheme 3. Plausible mechanism for preparation of 3,4-dihydropyrimidin-2(1H)-ones in the presence of polymeric alginate.

4. Conclusion

In summary, we introduced a new and remarkable biopolymer catalyst for the preparation of 3,4-dihydropyrimidin-2(1H)-ones via a one-pot, three-component condensation reaction between urea, ethyl acetoacetate and benzaldehydes. Sodium alginate was found as a reusable and novel eco-friendly catalyst for the Biginelli reaction.

Acknowledgments

The authors would like to thank the Research Council of the University of Tehran and Iran Polymer and Petrochemical Institute, Tehran, I.R. Iran for funding this project.

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Biographies

Hamed Daemi is currently a PhD candidate at Iran Polymer & Petrochemical Institute in Polymer Engineering field. His research interests are the synthesis of different advanced chemicals, for example polyurethanes, heterocycles and biopolymer nanoparticles. Recently, He has focused on investigation of catalytic activity of both synthetic and natural polymers in organic reactions. He has published more than 25 papers and patents in recent two years.

Reza Rezaieyeh Rad received his postgraduate degree in organic chemistry at university of Tehran. Title of his thesis was trapping of huisogen zwitter ion by electron-deficient alkenes: synthesis of highly substituted cyclopentadienyl anions. Recently, he has studied eco-friendly polymer catalysts for organic chemistry synthesis.

Mehdi Adib has received his PhD in organic chemistry from Tarbiat Modarres University (2002). He has focused on the development of new routes for the preparation of biologically active heterocyclic compounds and new methods for the synthesis of organic compounds. He has published more than 100 papers about different organic chemicals during recent years.

Mehdi Barikani received his PhD in Polymer Technology from Loughborough University of Technology, Loughborough, Leicestershire, UK (1986). He deals with all subjects of polyurethane and related compounds (elastomers, adhesives, foams and thickeners), thermally stable polymers including polyimides and polyurethane imides, polymers in drug delivery system, polyolefin foams, synthesis of new polymers, conductive polymers, biodegradable and green nanopolymers. He has published over 200 papers, 30 patents and 8 books in his field.