This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Alginic acid: a highly efficient renewable and heterogeneous bio-polymeric catalyst for one-pot synthesis of the Hantzsch 1,4-dihydropyridines

Mohammad G. Dekamin,*a Siamand Ilkhanizadeh,a Zahra Latifidoost,a Hamed Daemi,b Zahra Karimi,a and Mehdi Barikani b

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Alginic acid, a naturally occurring polysaccharide, in its granular form and without any post-modification was found to be an efficient environmentally benign, easily recoverable and low-cost catalyst for the clean and rapid synthesis of 1,4-dihydropyridine derivatives (DHPs) just based on its polysaccharide architecture. The Hantzsch pseudo-four-component reaction of ethyl or methyl acetoacetate, ammonium acetate and different aldehydes is catalyzed by alginic acid efficiently under mild conditions to afford desired products in high to quantitative yields and clean reaction profiles. Avoiding the use of any transition-metal, the use of a one-pot and multi-component procedure for the synthesis of DHPs, reusability of the catalyst and operational simplicity are important features of this methodology.

Designing and application of new eco-friendly chemicals and processes have almost been mandatory to keep and increase human health standards due to growing environmental pollution arising from industrial activities and their intensive impact on living systems as well as economic point of view. Therefore, science and technology has shifted toward green processes nowadays. Consequently, developing chemical processes using more environmentally acceptable catalysts, chemicals and atom efficient procedures have been emerged as subjects of innovation in green chemistry. For instance, the terrible impact of non-biodegradable wastes is still an open challenge in either developed or developing countries. In this regard, great efforts have been performed to use different bio-based feedstocks such as chitosan,4 chitin,5 starch,6 cellulose,7 gelatin,8 wool and alginates9 as biopolymeric support in the transition metal-based heterogeneous catalytic systems. However, complete replacement of transition metal-based heterogeneous catalytic systems by the metal-free biopolymeric analogues is of significant importance because of both toxicity and difficulty in separation of metal catalysts from the final products, especially in the pharmaceutical industry.10

Alginic acid, also called algin or alginate, is a naturally occurring anionic polysaccharide distributed widely in the cell walls of brown algae. It can also be produced by a microbial fermentation using special bacteria including Azotobacter and Pseudomonas. Alginic acid is an acidic form of alginate and has a plenty of both exposed carboxylic acid and hydroxyl groups inside its backbone. Alginic acid and its salts are linear copolymer with homopolymeric blocks of (1→4)-linked α-L-guluronic acid (G) and β-D-mannuronic acid (M) residues (Fig. 1).12 Therefore, it can activate the reaction components by not only Bronsted acid centers but also hydrogen bonding, as a heterogeneous organocatalyst.13 The catalytic activity of alginic acid can also be intensified by the hydrophilic/hygrosopic nature of these polymers when organic reactions produce water as their byproducts. It is noteworthy that alginic acid is capable of absorbing 200-300 times its own weight in water.14 These requirements are fully met in the multicomponent reaction (MCR) for synthesis of the Hantzsch 1,4-dihydropyridines (1,4-DHPs).

Fig. 1. Chemical structure of alginic acid (1).

The Hantzsch pseudo-four-component reaction is the oldest and most general known method for the synthesis of 1,4-DHPs and their derivatives which are medicinally and pharmacologically very important molecules. Indeed, commercial drugs such as nifedipine, amlodipine, nicardipine and felodipine constitute a major class of ligands for L-type Ca2+ channels (LTCC) blockers that are widely used to treat conditions such as hypertension and angina (Fig. 2).15 Therefore, the attempts to modify the conditions of the Hantzsch reaction are still of growing importance.
Literature survey shows that several modified methods for Hantzsch reaction have been reported using different catalysts mostly consisting of Bronsted or Lewis acids in recent years. For example, homogeneous catalytic systems such as p-TSA, 3,4,5-trifuorobenzencarboxylic acid in ionic liquid or InCl₃, Cd(NO₃)₂·4H₂O, Yb(OTf)₃, Sc(OTf)₃ hafnium (IV) bis(perfluoroalkanesulfonyl)imide complex [Hf(NPf₃)(4) and Zn[(L)proline]₂] have been reported. On the other hand, organic Lewis bases such as sulfonic acid supported 12-tungstophosphoric acid, preyssler heteropolyacids, Ce(SO₄)₂·SiO₂, self-assembled tinphosphonate nanoparticles, Zn-VCO₃ hydrotalcite, and hydromagnesite have also been reported. Furthermore, enzymes such as candida antarctica lipase B or baker’s yeast, ionic liquids, and non-ionic surfactant Triton X-100 have demonstrated catalytic activity for DHP synthesis. In spite of their merits, most of these methods suffer from the use of hazardous or expensive catalysts or solvents, long reaction times, high temperature and complicated workup. Although some heterogeneous catalysts such as sulfonic acid supported γ-Fe₂O₃ or cellulose, silica supported 12-tungstophosphoric acid, preyssler heteropolyacids, Ce(SO₄)₂·SiO₂, self-assembled tinphosphonate nanoparticles, Zn-VCO₃ hydrotalcite, and hydromagnesite have been introduced in the recent years but there is still room to improve the reaction conditions in terms of the use of renewable biopolymeric and transition metal-free heterogeneous catalysts under mild conditions. In continuation of our interest to explore application of biopolymers in different fields, especially their catalytic activity without any post-modification as well as MCRs, we wish herein to report the first catalytic activity of alginic acid (1) as a mild, highly effective and convenient bifunctional heterogeneous biopolymeric catalyst for the one-pot synthesis of 1,4-dihydropyridines via Hantzsch reaction in EtOH (Scheme 1).

Scheme 1. Pseudo-four-component reaction of different aldehydes 2, β-ketoesters 3, and nitrogen sources 4 catalysed by alginic acid (1) in EtOH under reflux conditions.

To evaluate the catalytic activity of alginic acid (1) for the synthesis of 1,4-DHPS, first the reaction of 4-chlorobenzaldehyde (2a), ethyl acetoacetate (3a), and ammonium acetate (4a) (2:1:1.2 mole ratio) was investigated as the model reaction in EtOH. The results are summarized in Table 1. In the absence of any catalyst, only a poor yield of the corresponding 1,4-DHP 5a was obtained after 4 h (entry 1). Interestingly, the yield of the desired product 5a was significantly improved in shorter reaction times when catalytic amounts of 1 were added to the reaction mixture in EtOH (entries 2-5). The model reaction was also studied in other solvents such as 50% aqueous EtOH (v/v), H₂O and EtOAc using alginic acid (1) loading of 10 mol% (entries 6-8). The obtained yield of the desired product 5a in H₂O was significantly less than compared to EtOH under similar catalyst loading and reflux conditions (entries 3 and 6). This may be attributed to both lower solubility of the reactants and rendering the established equilibrium between the reactants and reaction intermediates or desired product 5a to the left side in H₂O compared to EtOH (Scheme 4). Finally, the effect of temperature on the obtained yield and required reaction time was also examined (entries 9, 10). The obtained results demonstrated higher yields in shorter reaction times can be obtained in EtOH under reflux conditions.

Table 1 Optimization of the Hantzsch pseudo-four-component reaction for the synthesis of 5a catalyzed by alginic acid (1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>EtOH</td>
<td>Reflux</td>
<td>4 h</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>EtOH</td>
<td>Reflux</td>
<td>40</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>EtOH</td>
<td>Reflux</td>
<td>40</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>EtOH</td>
<td>Reflux</td>
<td>50</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>EtOH</td>
<td>Reflux</td>
<td>2 h</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>H₂O</td>
<td>Reflux</td>
<td>3 h</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>3.5</td>
<td>Aqueous</td>
<td>Reflux</td>
<td>2 h</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>EtOAc</td>
<td>Reflux</td>
<td>5 h</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>4.5</td>
<td>EtOH</td>
<td>25</td>
<td>3.5 h</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>EtOH</td>
<td>50</td>
<td>2 h</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>5.5</td>
<td>EtOH</td>
<td>Reflux</td>
<td>60</td>
<td>92</td>
</tr>
</tbody>
</table>

* Reaction conditions: 4-Chlorobenzaldehyde (2a, 1 mmol), ethyl acetoacetate (3a, 2 mmol), ammonium acetate (4a, 1.2 mmol). * Isolated yields. * 50% v/v. * The scale up of model reaction using 4-chlorobenzaldehyde (2a, 10 mmol), ethyl acetoacetate (3a, 20 mmol), and ammonium acetate (4a, 11 mmol).

Furthermore, the catalytic activity of the alginic acid (1) was examined in the next step to prove its feasibility as a heterogeneous biopolymeric catalyst for scale up of the Hantzsch reaction (entry 11). Interestingly, the alginic acid was found to be an efficient catalyst for performing of the Hantzsch reaction at higher scales. Therefore, alginic acid (1) higher scales. Therefore, alginic acid (1) was significantly improved in shorter reaction times when catalytic amounts of 1 were added to the reaction mixture in EtOH (entries 2-5). The model reaction was also studied in other solvents such as 50% aqueous EtOH (v/v), H₂O and EtOAc using alginic acid (1) loading of 10 mol% (entries 6-8). The obtained yield of the desired product 5a in H₂O was significantly less than compared to EtOH under similar catalyst loading and reflux conditions (entries 3 and 6). This may be attributed to both lower solubility of the reactants and rendering the established equilibrium between the reactants and reaction intermediates or desired product 5a to the left side in H₂O compared to EtOH (Scheme 4). Finally, the effect of temperature on the obtained yield and required reaction time was also examined (entries 9, 10). The obtained results demonstrated higher yields in shorter reaction times can be obtained in EtOH under reflux conditions.
Fig. 3. Different aldehydes (2a-p) and ammonia derivatives (4a-c) examined in the Hantzsch MCR catalysed by alginic acid (1).

To our delight, the diludine (5b), a substance with noteworthy pharmaceutical and food applications as well as organic reductive agent, was prepared in short reaction time and excellent yield (See also ESI). Moreover, all the aromatic aldehydes having either electron-withdrawing substitutes (2c-2h) or electron-donating ones (2j-2o) reacted smoothly to provide the corresponding Hantzsch esters (5c-5o) in good to excellent isolated yields. However, the aldehydes carrying nitro groups (2d, 2e) afforded lower yields compared to those having other electron-withdrawing substituents rather than nitro group or even electron-donating ones. Lower yields obtained for aldehydes having meta- and para-nitro substituents (2d, 2e) may be attributed to the competitive formation of less reactive corresponding imines. The obtained yields in these cases were improved somewhat by late addition of aldehydes 2d or 2e to the reaction mixture (89% and 84%, respectively). On the other hand, the effect of nitrogen source in the Hantzsch reaction catalysed by alginic acid (1) was also examined. It has been reported that ammonium salts of carbonate or bicarbonate show somewhat higher efficiency than the acetate salt in hot water. However, it should be noted that those former salts produce CO$_2$ on their decomposition as reaction proceeds (Scheme 4). The greenhouse effect of CO$_2$ is well known. Therefore, ammonium acetate is one of the best choice as ammonia source in the Hantzsch reaction. Furthermore, aliphatic or aromatic amines including benzyl amine (4b) and p-toluidine (4c) were also examined. Lower yields of the desired DHPs (5q and 5r, respectively) can be attributed to the more steric hindrance and stronger resonance effect of these amines compared to ammonium acetate.

\[\text{Scheme 2. Pseudo-four-component synthesis of different diethyl 1,4-DHP-3,5-dicarboxylate (5a-r) catalysed by alginic acid (1) in EtOH under reflux conditions.}\]

In the next stage, the size effect of the alkyl group of ester moiety in the β-ketoester 3 on the yield of the expected 1,4-DHPs was also investigated using methyl acetoacetate (3b) instead of ethyl acetoacetate (3a). Corresponding 1,4-DHPs 6a-p were obtained in good to excellent yields (Scheme 3, See also ESI). In all of studied cases, similar trend of reactivity were observed compared to ethyl acetoacetate (3a).
proposed for the synthesis of 1,4-DHPs 5-6 through MCR of aldehydes 2, β-ketoesters 3, and nitrogen sources 4 catalysed by alginic acid (I) (Scheme 4). First, alginic acid (I) activates the carbonyl functional group of aldehyde 2 for the next addition of enol form of β-ketoesters 3 on it to form the corresponding Kenovenagle intermediate (II). This intermediate is also protonated by alginic acid (I) to be activated for the next Michael addition of enol form of β-ketoesters 3. Then, one of the keto functional groups in the intermediate (IV) is activated through proton transfer from alginic acid (I) to react with the nitrogen source 4 and give imine intermediate (V). This later intermediate is also activated through proton transfer from alginic acid (I) to facilitate its subsequent tautomerisation to the corresponding enamine (VI). In the next step, alginic acid (I) activates the remaining keto functional group for ring closure by amino group of the enamine moiety. Finally, elimination of third H₂O molecule is catalysed by alginic acid (I) to afford the desired 1,4-DHP 5-6. Furthermore, all the above steps can be competitively catalysed through hydrogen bonding rather than proton transfer with weaker interactions. On the other hand, ring closure may take place from position 4- of 1,4-DHP rather than its 1-position, alternatively. This means that enamine formation and condensation with the second molecule of β-ketoesters 3 can take place prior to Michael addition in the above proposed mechanism.

On the other hand, the reusability of alginic acid (1) was also investigated for at least 6 runs. The results are summarised in Fig. 4. The obtained results demonstrated that alginic acid (I) is reusable for the practical applications in the Hantzsch 1,4-DHPs synthesis.

According to obtained results, the following mechanism can be

**Scheme 3.** Pseudo-four-component synthesis of different dimethyl 1,4-DHP-3,5-dicarboxylate (6a-p) catalysed by alginic acid (I) in EtOH under reflux conditions.

---

**Fig. 4.** Reusability of alginic acid catalyst (I) for the Hantzsch MCR to afford 5a.

In conclusion, a new, renewable and readily recoverable biopolymeric catalyst for the MCR Hantzsch reaction has been described which displays particularly high efficiency just based on polysaccharide architecture of alginic acid. Avoiding the use of any transition-metal, clean reaction profiles, the use of a one-pot and multi-component procedure for the synthesis of DHPs, reusability of the catalyst and operational simplicity are the important features of this methodology. Further development of this methodology to bicyclic and tricyclic derivatives of DHPs are currently underway and will be presented in due course.
Scheme 4. Plausible mechanism for the Hantzsch pseudo-four-component reaction of different aldehydes 2, β-ketoesters 3, and nitrogen sources 4 catalysed by alginic acid (1).

Notes and references

a Pharmaceutical and Biologically-Active Compounds Research Laboratory, Department of Chemistry, Iran University of Science and Technology, Tehran 16846-13114, Iran, Fax: (+98) 21 77491204, E-mail: mdekamin@iust.ac.ir

b Polyurethane Department, Iran Polymer and Petrochemical Institute, P.O. Box 14965-115, Tehran, Iran.

† Electronic Supplementary Information (ESI) available: [Experimental procedure, characterization data, IR and 1H NMR spectra of products, and IR spectra and TGA of catalyst]. See DOI: 10.1039/b000000x/15

‡ This research was supported by The Research Council of Iran University of Science and Technology (IUST), Tehran, Iran (grant no. 160/1085) and Iran Polymer and Petrochemical Institute, Tehran, Iran.


Page 6 of 7
Graphical Abstract

Alginic acid: a highly efficient renewable and heterogeneous bio-polymeric catalyst for one-pot synthesis of the Hantzsch 1,4-dihydropyridines

Mohammad G. Dekamin, Siamand Ilkhanizadeh, Zahra Latifidoost, Hamed Daemi, Zahra Karimi and Mehdi Barikani

Alginic acid was found to be an efficient, environmentally benign, easily recoverable and low-cost catalyst for clean synthesis of 1,4-dihydropiridine derivatives (DHPs).