A Platinum Open Access Journal for Organic Chemistry

Review

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Recent advances in direct catalytic applications of alginates and alginic acid in organic synthesis

Siamand Ilkhanizadeh*, Amrah Nouri, and Jabbar Khalafy

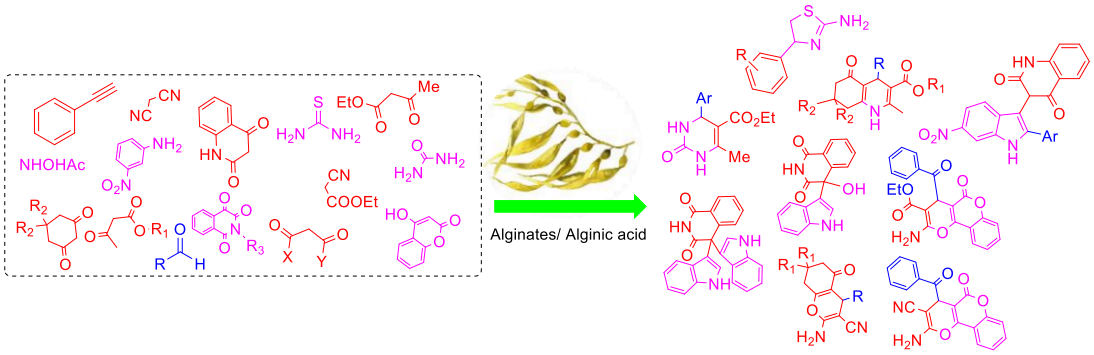
Department of Organic Chemistry, Faculty of Chemistry, Urmia University, Urmia, 11 km Sero road, Iran 5756151818, PO Box 165

Email: siamandelkhanizade@gmail.com

Received 12-19-2022 **Accepted** 03-14-2023 **Published on line** 03-22-2023

Abstract

The application of biopolymers in organic chemistry, especially in catalysis, has been an active research area in recent years. Alginates are constituents of brown algae cell walls; they are naturally occurring polysaccharides. Renewability, high surface area, low cost, availability, chemical stability and the abundance of functional groups in their structure make them promising alternatives for oil-derived or hazardous metallic components in catalytic systems. The present review provides an overview of the studies on using alginates in catalytic systems and more profoundly focuses on the reported studies concerning the direct catalytic applications of alginic acid and sodium alginate in organic synthesis.



Keywords: Biopolymers, alginates, organic synthesis, green chemistry

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1. Introduction

1.1 Green chemistry

Catalysts are the pillars of green chemistry according to Paul Anastas and John Warner who developed the green chemistry definition in the 1990s.[1] The definition is comprised of twelve rules which have been designed to decrease the adverse impacts of chemical processes on environmental and human health.[2] Rule number nine focuses on catalysts and their efficiency in chemical reactions, apparently, a properly catalyzed reaction would be highly accelerated, so save time and energy, produce the desired products selectively or dominantly with the least possible waste or unexpected products, catalyzed reactions could be operated under milder conditions, including lower temperatures and pressures, and in the environmentally friendly solvents,[1] so, the waste reduction, atom economy, energy efficiency, and reduced toxicity which are some other goals of green chemistry, may be partially achieved by selecting an efficient catalyst.[1-4] On the other hand, another fundamental rule of green chemistry emphasizes the use of renewable feedstocks in chemical processes. Thus, the possibility of using renewable feedstocks as catalysts in organic chemistry would be an outstanding achievement in line with green chemistry goals.[1-4] Biopolymers have received significant attention and have recently been examined as alternatives to synthetic organic polymers. Naturally abundant polysaccharides such as starch and cellulose, lignin, chitosan, collagen, wool, and alginates have been successfully used as catalyst support or absorbents in catalytic systmes.[5-9] More importantly are reports on using these polysaccharides directly as efficient catalysts in organic synthesis.[9] Herein, we wish to highlight the recent achievements in using alginates and alginic acid in catalytic systems with the focus on their direct application as heterogenous catalyst.

1.2 An introduction to alginates

In the late 1880s, the British chemist E.C.C. Stanford discovered and patented the extraction of sodium alginate from Kelp, large brown algae seaweeds.[10] Although they are found in some species of bacteria, like *genus Pseudomonas* and *Azotobacter*, the primary source of alginates is still algae, specifically brown algae, sodium alginate is widely distributed in matrix and cell walls of *Ascophyllum nodosum, Laminaria spp., Lessonia nigrescens, Sargassum turbinarioides, Cystoseira barbata*, and many other large brown seaweeds.[11,12]

In brown seaweed, alginate is mainly present as the calcium salt of alginic acid, although magnesium, potassium, and sodium salts may also be present. Since only the sodium and potassium salts of alginic acid are soluble in water, the first step in the extraction process is to convert the insoluble calcium and magnesium

salts into soluble sodium alginate. For this purpose, the seaweed can be treated with alkali, and then an ion exchange is necessary to replace Ca^{2+} ions with Na^{+} ions. However, many authors believe that a more efficient extraction method is the first treating of the seaweed with a dilute mineral acid; the calcium alginate is converted to alginic acid, which is more readily extracted with alkali than the original calcium alginate.[13]

Since their discovery in the late 1880s, alginates have attracted immense attention and found a wide range of utilization in different industries, from the manufacturing of welding rocks to cosmetic, food and drug products.[14] Sodium alginate forms a highly viscous colloid when dissolved in water; it can expand at least ten times its volume and has thickening, suspending, emulsifying, stabilizing, and gel-forming characteristics.[15-16] in 1983, the Food and Drug Administration (FDA) of the United States approved the direct use of sodium alginate as a component of the food, since then, a long history of utilization in the food and packaging industry has been made.[17] Thickening, gelling, and film-forming are the three main properties that are responsible for the wide use of alginates in food industry.[17,18]

In the cosmetic industry, alginates can be used as moisturizing, anti-aging, and thickening agents.[19] Recent pharmacological studies show that alginic acid has immunomodulatory,[20] antioxidant,[21] and antiinflammatory activities.[22]

2. Chemical Structure and Catalytic Capability of Alginates

Alginates are linear copolymers composed of two uronic acid monomers: β-D-mannuronic acid (M) and α-L-guluronic acid (G) linked through 1-4 glycosidic bonds, M units (M-blocks), G units (G-blocks), and alternate mixed M and G units (MG-blocks) constitute the sequences of various lengths (Figure 1). The ratio of G and M units in the structure which considerably vary with the algal source, strongly affects the basic properties of alginates, where high contents of G units produce more viscosity in gels, alginates with more MG/GM blocks are soluble at low pH, whereas alginates rich in MM or GG blocks are insoluble.[23]

As illustrated in Figure 1, alginates have plenty of exposed hydroxyl and carboxylate functional groups on their structure, this an advantage when they are used as support for active species such as metal cations, organometallic species, or metal nanoparticles, since the functional groups act as both a reductant and a stabilizer; High surface area and chemical stability are the other advantages of alginates as catalyst support.[24]

Alginates in different forms, such as wet or dry gels, can be used as support for active species, including organometallic or metallic catalysts. Metal nanoparticles can also be embedded in the alginate structure successfully, the hydroxyl and carboxylate functional groups can interact with the metal nanoparticles to form composite particles.[25]

Three main characteristics are responsible for catalytic capability of sodium alginate and alginic acid when they are used directly as heterogenous catalysts in organic reactions: their remarkably high functional group density (5.6 mmol per gram), their strong water absorbance capability, and finally, their stability in most organic solvents. On the other hand, alginic acid possesses a mildly acidic character (pKa 3.5) which makes it an ideal Bronsted acid heterogenous biopolymeric catalyst.[26]

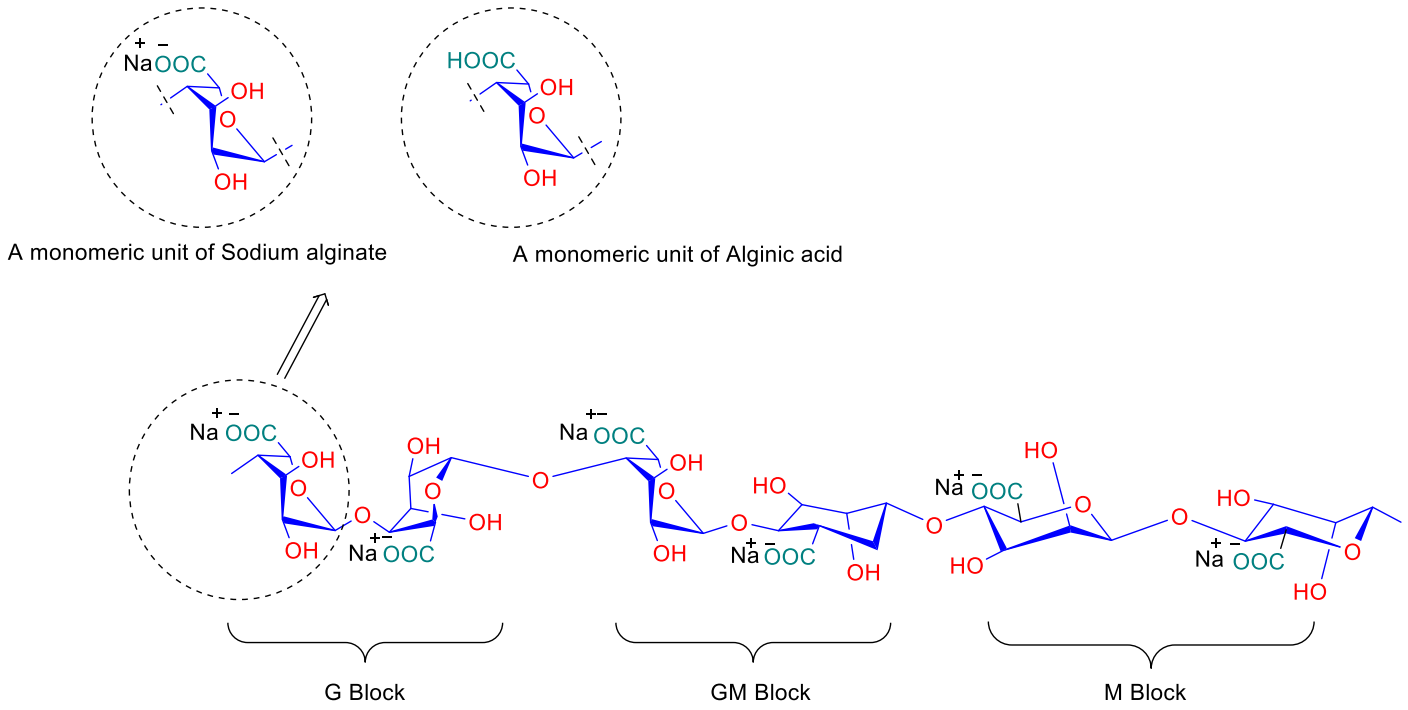


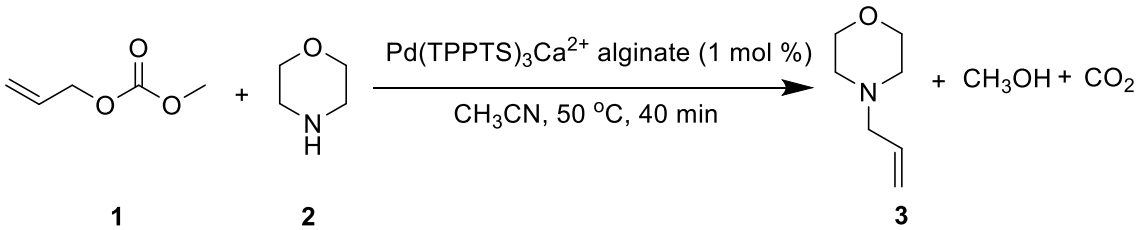
Figure 1 Chemical structure of sodium alginate biopolymer.

3. Alginates in Organic Synthesis

3.1 Alginates as support for metal ions, organometallic species, and metal nanoparticles

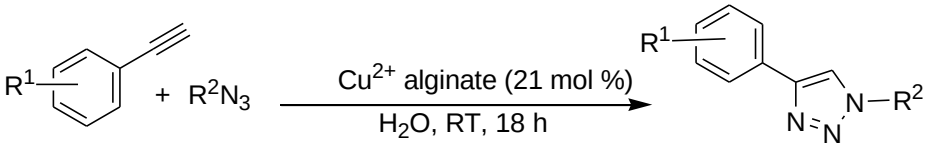
The first reported application of alginates for catalysis was in 2005, where alginate beads were used in an organometallic catalytic system. Alginate beads were utilized as support for the hydrosoluble trisulfonated triphenylphosphine palladium(0) complex, $Pd(TPPTS)_3$, to be employed in the heterogeneous allylic substitution of methyl allyl carbonate (**1**) with morpholine (**2**) (Scheme 1).[24] The catalyst was prepared by impregnation of both alcogel and aerogel Ca^{2+}-alginate beads with an aqueous solution of $Pd(TPPTS)_3$. The prepared gels demonstrated an acceptable catalytic activity in that transformation so that an excellent yield of the desired product **3** was achieved in a few minutes with both aerogel and alcogel catalysts. The only considerable difference of the two formulations was upon recycling, when the catalyst was prepared from the aerogel formulation, a higher stability was demonstrated.[24]

Investigations suggest that in the dried material, the catalytic sites are not accessible, while in the presence of water, due to swelling of the catalyst support, they became more accessible, and the catalyst became activated.



Scheme 1 Allylic substitution of methyl-allylcarbonate (1) with morpholine in the presence of $Pd(TPPTS)_3Ca^{2+}$alginate.

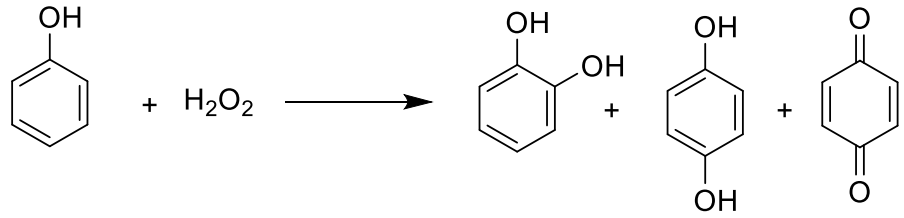
Interaction of a Cu^{2+} salt with sodium alginate, leads to the formation of Cu^{2+}-alginate gel beads, which was an example of a catalytic system based on alginate supported metal ions, it was used for 1,3-dipolar cycloadditions of alkynes **4** with azides **5** in water (Scheme 2).[27] The catalyst was prepared by dropwise addition of viscous sodium alginate solution (3% w/v) into an aqueous solution of copper acetate monohydrate (20 % w/v). The desired products, e.g., 1,4-disubstituted 1,2,3-triazoles **6**, were obtained in good to excellent yields. In the same report, Cu^{2+}-alginate hydrogel beads have also been employed in the oxidative coupling of phenols and 2-naphthols in water, affording the desired products in high yields. In both cases, the catalyst was recovered by simple filtration and reused several times without significant loss of activity.[27]



4 **5** **6**

Scheme 2 Synthesis of 1,4-disubstituted 1,2,3-triazoles in the presence of Cu (II)-alginate biopolymer supported catalyst.

Different forms of Cu-Alginate were used for hydroxylation of phenols (**7**) with hydrogen peroxide (Scheme 3), the results were reported by Fengwei Shi and coworkers in 2012.[28] They prepared the Cu-alginate dry beads and powder using different concentrations of copper chloride dehydrate and sodium alginate. Their investigations suggest that in the absence of the catalyst, H_2O_2 alone was unable to oxidize phenol quantitatively (only 5.3%). By adding Cu-alginate, whether in dry beads or powder form, a significant increase in conversion was observed; the conversion increased as the Cu(II) content increases, so the activity of Cu-alginate catalyst depends on the immobilized content of Cu(II) ions. They also found that the powder form carried more Cu (II) and showed higher catalytic activity than the dry beads, 62.5 % conversion in the presence of powder was obtained compared to 52.9 % in the presence of the dry beads, and catechol (**8**) to hydroquinone (**9**) ratio was 3 :2.



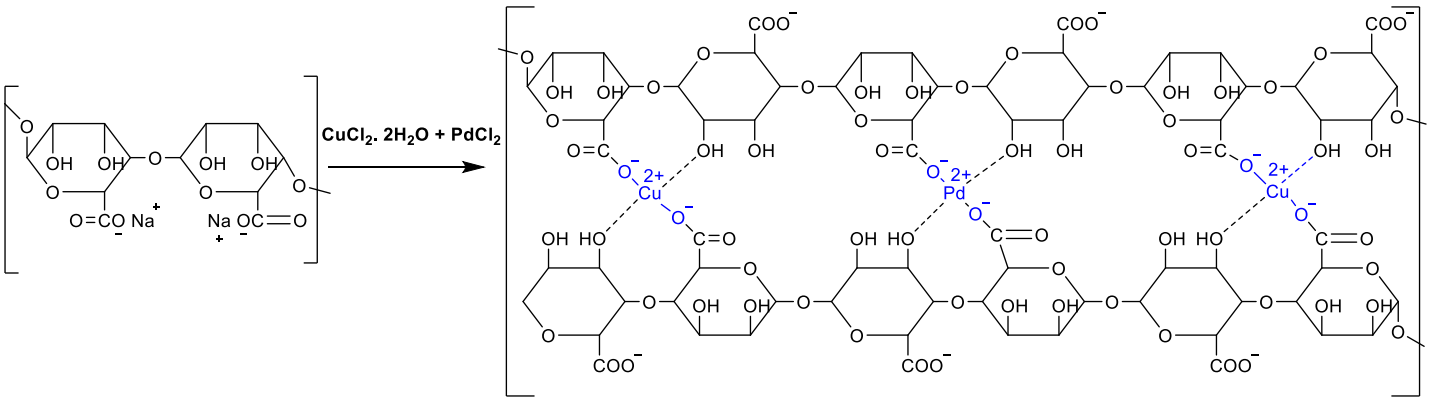
7 **8** **9** **10**

Scheme 3. Phenol hydroxylation reaction in the presence of Cu (II)-alginate dry beads.

Another study by the same authors in 2015 assessed the effect of employing a Cu-Pd-alginate binary catalyst system.[29] This binary system has been prepared by dripping sodium alginate in $CuCl_2$ and $PdCl_2$ solutions of different concentrations containing both the crosslinking ions (Scheme 4), with molar Cu/Pd ratios comprised between 4:1 and 30:1. The Cu^{2+} and Pd^{2+} contents of the beads before and after phenol hydroxylation were determined by Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICPAES).

According to the investigations, the binary Cu–Pd–ALG dry bead catalysts have better catalytic activities than Cu–ALG catalyst reported previously.

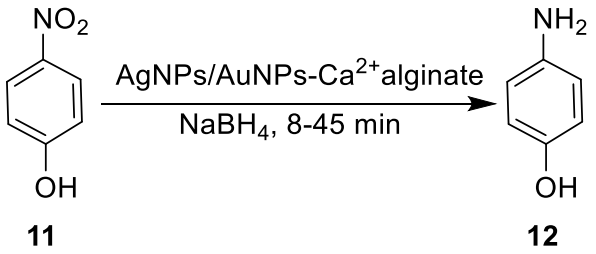
An interesting finding is that the introduction of Pd can greatly reduce the formation of byproducts. Given on a tar-free basis, the selectivity to benzoquinone (BQ) (**10**) decreased to less than 0.5%. When, the content of Pd^{2+} in catalyst increased, the selectivity to BQ decreased. The Cu-Pd-alginate was found to be active in the model reaction up to three reaction cycles, the conversion of phenol decreased from 53.9% to 50.7% in the presence of the reused catalyst; however the CAT/HQ ratio showed very little change, which illustrated excellent stability of the catalyst.[29]



Scheme 4 The synthesis of Cu–Pd–ALG dry beads catalyst.

The catalytic activity of Cu/polyacrylamide/graphene oxide (GO) alginate aerogel for the phenol hydroxylation reaction with H_2O_2 (Scheme 3) was evaluated by Cong Shan and coworkers in 2017.[30] In their proposed system, the polyacrylamide (PAAm) acted as a double network crosslinking agent, and GO served as a mechanical reinforcement. The catalysts were prepared by the addition of solutions composed of sodium alginate, PAAm, and GO with different ratios in aqueous solutions of $CuCl_2$. After the spontaneous formation of hydrogel beads and maturation, the beads were dried by freeze-drying method in order to obtain aerogels beads. An outstanding catalytic activity was observed, where Cu/PAAm/GO alginate aerogel showed 78.5% conversion of phenol with 95.9% selectivity (hydroquinone plus catechol). Cu/PAAm alginate catalysts gave less than 50% conversion, so it can be concluded that the GO improved the mechanical properties as well as the catalytic activity of the alginate-based materials. The excellent catalytic activity of Cu/PAAm/GO alginate was attributed to the fact that both GO and Cu ions decompose H_2O_2 and generate hydroxyl radicals.

Silver (Ag) and gold (Au) nanoparticles were grown on calcium alginate hydrogel beads to prepare a Ca-alginate-stabilized Ag and Au nanoparticles catalytic system for the first time in 2010. The prepared catalysts were used for the catalytic reduction of 4-nitrophenol (**11**) (Scheme 5).[31] Ag and Au were embedded by immersing calcium alginate hydrogel beads in solutions containing the desired metal in the form of salt, to allow ion exchange. The nanoparticles were then prepared by a photochemical approach (irradiation using a UV light source). The catalytic activity of Ag and Au NPs supported on Ca-alginate beads was confirmed in the model 4-nitrophenol reduction in the presence of sodium borohydride as a reductant. Although both catalysts showed a high catalytic activity, but the reaction proceeded much faster in the presence of Ag/CA compared to that of Au/CA that may be attributed to better catalytic activity of Ag, or the difference in surface coverage. Both catalysts were recyclable up to three cycles.



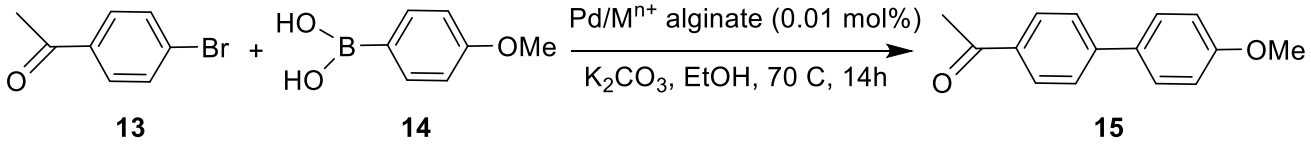
Scheme 5 The Catalytic reduction of 4-nitrophenol in the presence of AgNPs/AuNPs-Ca^{2+}-alginate.

An improvement of the previously-mentioned reduction method was reported by Lunhong Ai and Jing Jiang in 2013.[32] They proposed an alternative preparations of Ag nanoparticles embedded in alginate under simulated solar light irradiation. Different methods were employed to obtain the complexation of alginate with Ag^{+} cations, sodium alginate was directly dripped into an aqueous solution containing Ba^{2+} and Ag^{+} ions. Then Ag-containing beads were irradiated with a 500W Xe arc lamp for a short time to form the nanoparticles. The resulting beads were then characterized by SEM and EDX mapping, both confirming the uniform distribution of the nanoparticles. Ba^{2+} ions act as an ionic cross-linking agent to prepare alginate-based hydrogels, an experiment revealed that in the absence of Ba^{2+} ions, the prepared hydrogel beads collapse in a very short time when they are used in the catalytic reduction of 4-nitrophenol, so the structural stability of the system is highly dependant to the use of Ba^{2+} ions.

A heterogenous catalyst based on palladium nanoparticles chelated in the framework of alginate biopolymer was reported in 2009, and its catalytic activity was confirmed in the Suzuki reaction.[33] The electrostatic interactions between the carboxylate groups of the alginate matrix and Pd^{2+}, which complex and stabilize the metal in the form of alginate hydrogel beads, help to stabilize the catalytic system. The alginate gel in the presence of a calcium salt was first prepared, the calcium was exchanged by palladium at different loadings. The beads were dehydrated by consecutive washings with increasing amounts of ethanol that led to a spontaneous reduction of the Pd^{2+} cations to Pd^{0} nanoparticles (PdNPs), without the need of costly and environmentally dangerous reducing agents. Finally, the prepared materials were, dried under supercritical conditions to obtain the corresponding aerogel catalyst with increased surface areas. With this procedure, the metals were a homogeneously distributed in the gel beads. The possibility to control the amount of Pd in the final solid also led to tailor nanoparticle sizes by selecting the optimal amount of palladium to avoid significant formation of palladium clusters and aggregation of nanoparticles. The catalytic activity of this system depends on the size of the particles and on the nature of the halobenzene **13** (Scheme 6).

The same research group extended the previous procedure to the preparation of PdNPs supported on numerous alginate/ M^{n+} gels by means of different gelling metals and studied the effects a second metal on the catalytic capability of PdNP-alginate to promote the Suzuki-Miyaura reaction.[34] A library of different M^{n+}/PdNP supported on alginate (M¼Mn, Ni, Zn, Co, Ca, Ba, Ce, Cu) was prepared according to the previously-described ion exchange procedure, with different M/Pd ratios. The surface area and nanoparticle size distribution of the obtained materials was influenced by the gelling cations employed. All gelling metals, except for Co^{2+}, had a positive effect on the catalytic efficiencies of the alginate-supported catalysts. This effect is remarkable in the case of Cu^{2+}, which leads to both the higher surface area and the narrower distribution of nanoparticle sizes. This is also reflected on the reactivity and recyclability of the alginate/$Cu^{2+/}$PdNP catalysts with respect to the other gelling cations. The palladium nanoparticles supported on copper-alginate aerogels showed a superior catalytic performance compared to other materials. This

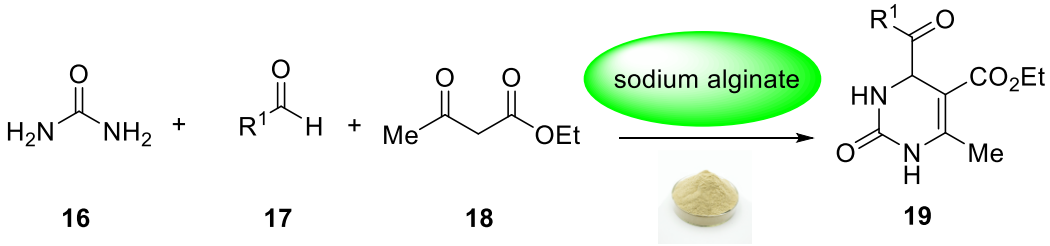
higher catalytic activity is reflected in its TOF value of 10^{-1} and a TON value close to 10^{6}. An exciting aspect of this study is that it can be extended to gold and platinum nanoparticles.



Scheme 6. The Suzuki reaction catalyzed by PdNPs-Cu^{2+}-alginate.

3.2 Direct catalytic utilization of alginates and alginic acid in the synthesis

The idea of using alginates directly as a catalyst in an organic transformation was first examined time in 2013 when Daemi and his co-workers suggested a novel, eco-friendly methodology for the construction of a series of 3,4-dihydropyrimidin-2(1 *H*)-one derivatives **19** via multicomponent concentration reaction of urea (**16**), ethyl acetoacetate (**18**), and Aromatic aldehydes **17** in the presence of sodium alginate (Scheme 7).[26] They indicated that biopolymeric sodium alginate could efficiently catalyze the mentioned Biginelli reaction under mild conditions with excellent yields of the desired products (75%-95%). More importantly, the catalyst was recyclable for four consecutive runs without significant loss of its activity. The great catalytic activity of sodium alginate is attributed to its chemical structure; two polar hydroxyl and carboxylate groups are present on each monomeric unit of alginate (Figure 1). The active protons in the chemical structure of the alginate chains can interact with the polar functional groups of the starting materials and reaction intermediates. Hydroxyl groups of sodium alginate may help to accelerate the reaction through the hydrogen bonding between the hydrogen donor and acceptor molecules and intermediates, while the carboxylate parts can activate the nucleophilic sites of the reaction by interacting with the active acidic protons at the same time. The water-absorbing capacity of alginates is another factor that can improve the reaction speed in case water is a byproduct of the reaction.

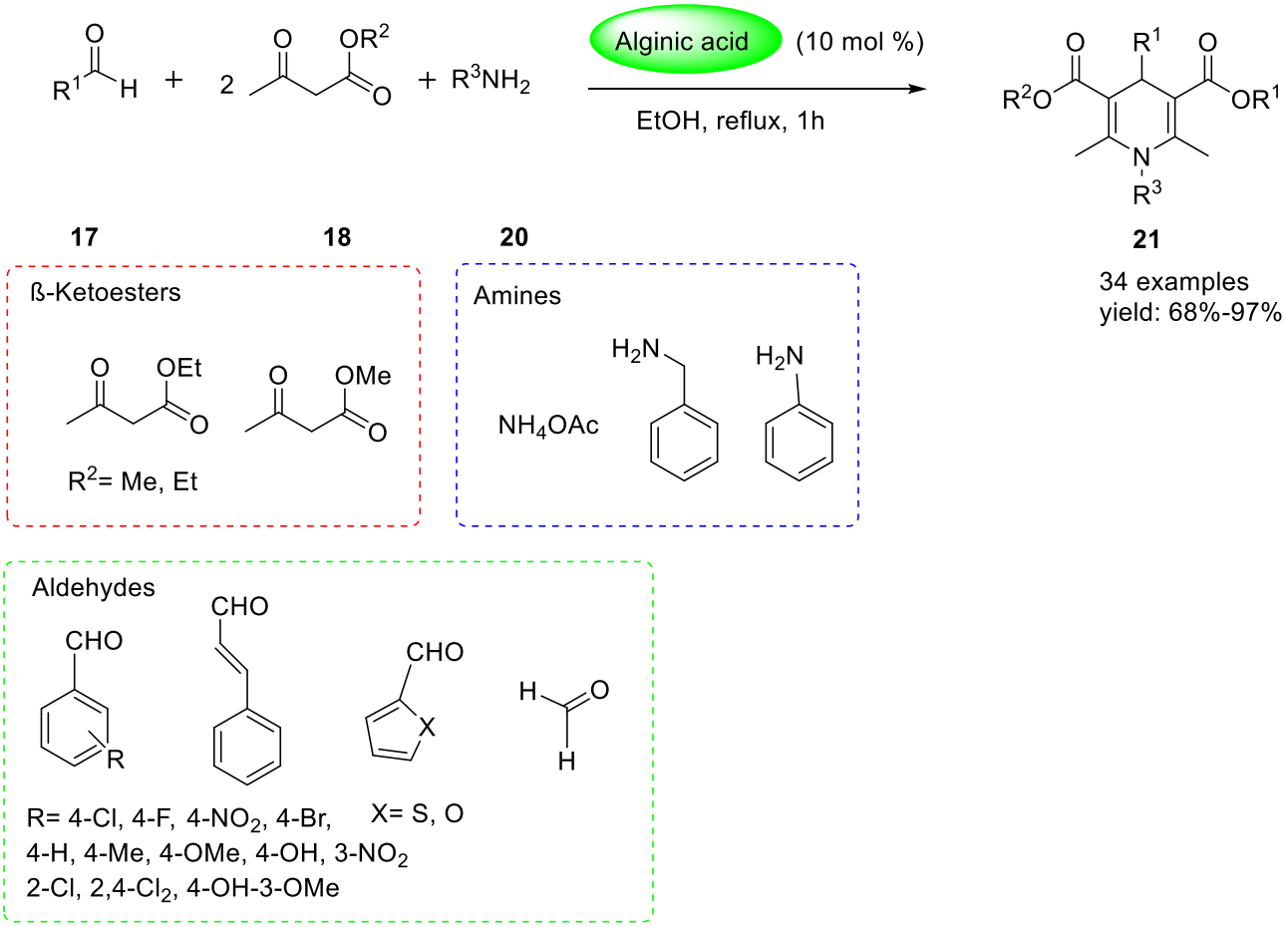


R^1=C_6H_5, 4-$OMeC_6H_4$, 4-ClC_6H_4,4-MeC_6H_4, 4-$NO_2C_6H_4$, 2-BrC_6H_4, C_4H_3O, 3-$NO_2C_6H_4$, 2-OHC_6H_4, 4-OHC_6H_4, 2-ClC_6H_4

Scheme 7 One-pot multicomponent synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one derivatives in the presence of sodium alginate.

The first catalytic application of alginic acid was reported for the oldest and the most general method for the synthesis of 1,4-dihydropyridines **21**, the Hantzsch pseudo-four-component reaction, in 2014, Dekamin, Ilkhaniizadeh, and co-workers used alginic acid in its granular form, without any post-modifications for the synthesis of medically valuable 1,4 DHP derivatives from the reaction of methyl or ethyl acetoacetate (**18**), (hetero)aromatic and α,β-unsaturated aldehydes, formaldehyde (**17**) and ammonia surrogates such as primary aliphatic and aromatic amines, and ammonium acetate (**20**) (Scheme 8).[35] A vast library of 1,4 DHPs were synthesized in the presence of a catalytic amount of alginic acid (10 mol %) under environmentally benign

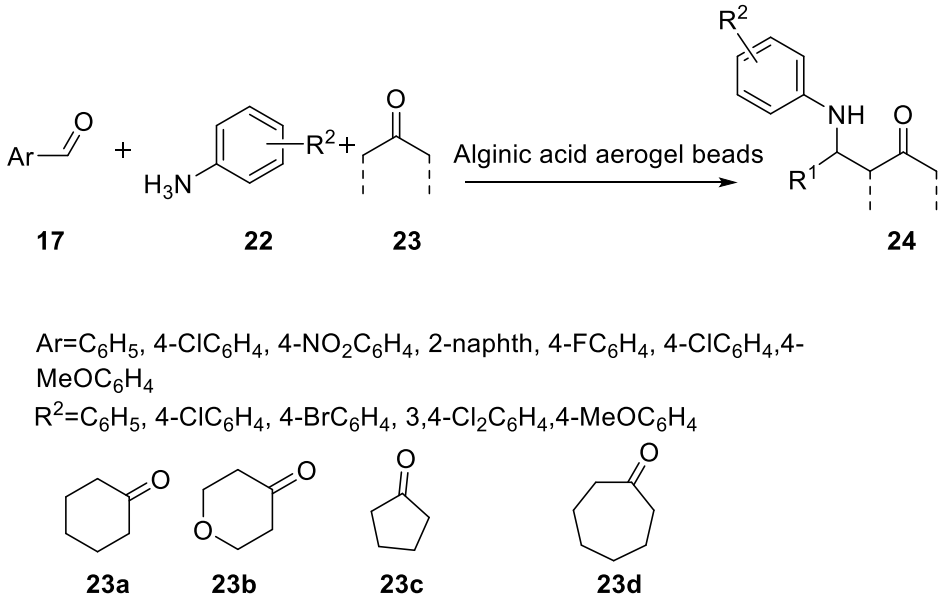
conditions in ethanol solvent under reflux condition. According to that report, all the aliphatic and aromatic aldehydes having either electron-withdrawing substitutes or electron-donating ones and those with steric hindrance in meta and para positions reacted smoothly to provide the corresponding Hantzsch esters in good to excellent isolated yields (96%-98%). Although the primary ammonia surrogate used in the reactions was ammonium acetate (**20a**), benzylamine (**20b**) or para-toluidine (**20c**) were also examined in the model reaction as the ammonia surrogate, the lower yields of the desired products (68-75%) while using benzylamine and para-toluidine could be attributed to the more steric hindrance and stronger resonance effect of those amines compared to ammonium acetate (**20a**). The recyclability of alginic acid was also examined in five consecutive runs of the model reaction; after washing with ethyl acetate and drying at 60 °C, the solid alginic acid recovered from the reaction by simple filtration, it could be reused in subsequent reactions with slight loss of activity. It is supposed that alginic acid starts catalyzing the reaction by activating the carbonyl functional group of aldehyde for a Knoevenagel addition of enol form of the β-ketoesters **18** (methyl or ethyl acetoacetate); another enol form of the β-ketoester then adds through a Michael addition followed by the addition of the nitrogen source **20**, which finally lead to the desired product, during all stages of the reaction, alginic acid plays its role by protonating and activating the ingredients and the intermediates, more details of the mechanism are included in the original paper.[35] Four equivalents of water per 1,4-dihydropyridine product is produced in this reaction, hence, the water-absorbing ability of alginate plays a critical role in the progress of the reaction by absorbing the water and driving the reaction to the right according to Le Chatelier's principle.



Scheme 8 Pseudo-four-component reaction of different aldehydes β-ketoesters, and nitrogen sources catalyzed by alginic acid in ethanol under reflux conditions.

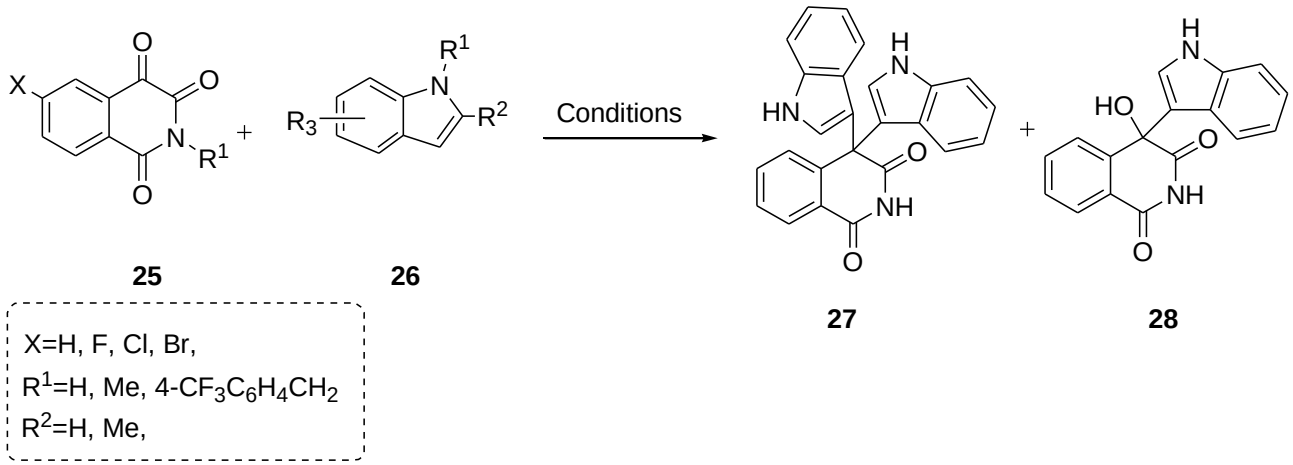
The Mannich reaction is a fundamental transformation in organic chemistry; its 3C direct version provides very straightforward access to structurally diverse b-amino carbonyl compounds. In 2015, using alginic acid as a promoter for the three-component Mannich reaction was reported by Pettignano *et al*.[36] they used highly dispersed alginic acid aerogel beads to catalyze the reaction between aldehydes **17**, anilines **22**, and ketons **23** (Scheme 9). In that research work, the capability of alginic acid as a mild, renewable, and recyclable heterogeneous Brønsted acid catalyst in CH_3CN-H_2O (8:2) solvent has been demonstrated, and the corresponding Mannich products **24** have been prepared in high yields (57-95%) and purity.

Another research paper was published in 2015 in which Anvitia Srivastava and his co-workers suggested alginic acid for the Friedel-Crafts reaction of indoles **26** with a variety of isoquinoline-1,3,4-triones **25** leading to 4-hydroxy-4-indolylisoquinoline-1,4-dione derivatives **27**, **28**.[25] Interestingly, by performing the reaction in pure water at room temperature, alginic acid catalyzed the reaction selectively and the desired monoindolyl adduct **24** was obtained in a high chemical yield of 75% in the model reaction (Scheme 10). The recyclability of alginic acid was examined again in that research work. It was found that it can be recycled and reused for five consecutive runs without significant loss of activity. The suggested methodology seems to have all features of a green, environmentally friendly, and straightforward methodology.[37]



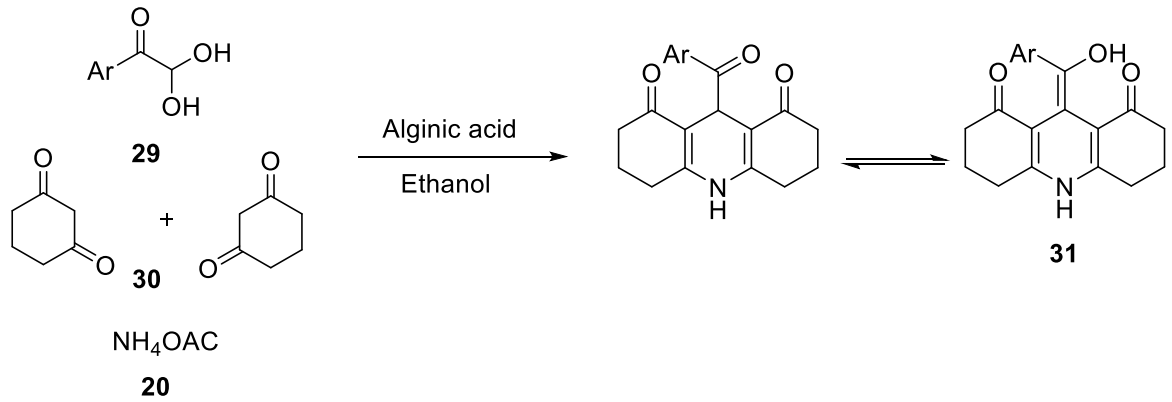
Scheme 9. Alginic acid catalyzed Mannich reaction of aldehydes, anilines and ketons.

The 1,8-acridinediones, as a member of acridinediones family are a group of nitrogen-containing heterocyclic compounds exhibiting a broad range of biological and pharmaceutical properties. In 2016 Poursatar, *et al* reported an efficient route for the synthesis of a series of novel acridinediones **31** from the reaction of 1,3-cyclohexanedione (**30**), arylglyoxals **19** and ammonium acetate (**5**) in the presence of alginic acid in EtOH solvent, in short times with excellent isolated yields of the desired products (79%-98%) (Scheme 11).[3]



25 **26** **27** **28**

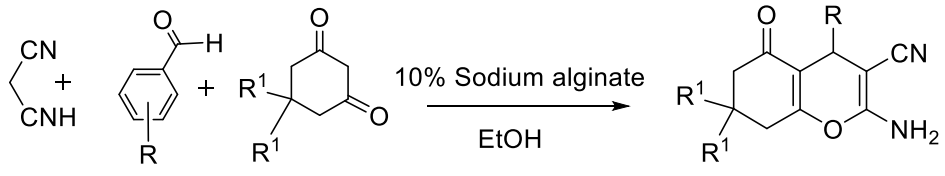
Scheme 10 The Friedel-Crafts reaction of Indoles with a variety of isoquinoline-1,3,4-triones leading to 4-hydroxy-4-indolylisoquinoline-1,4-dionederivatives in the presence of alginic acid.



29 **30** **31** **20**

Ar= C_6H_5, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

Scheme 11 The Reaction between cyclohexane dione and arylgloxals for the synthesis of 1,8-acridinedione derivatives catalyzed by sodium alginate.



33 **17** **32** **34**

R= H, 4-Cl, 2-Cl, 4-Br, 2-NO_2, 3-NO_2, 4-NO_2, 4-Me, 4-OMe, 4-OH, 3-OH, 4-CN, 3-OMe-4-OH, 3,4-$(OMe)_2$

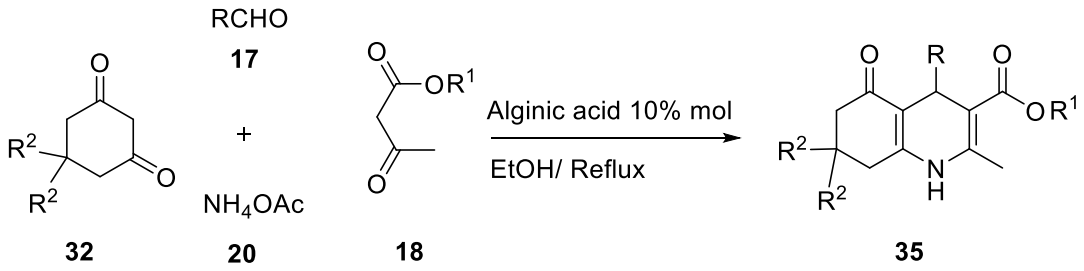
R^1= H, Me

Scheme 12 Synthesis of 2-amino-4H-pyran derivatives from the three-component reaction of malononitrile, aldehydes and 1,3-dicarbonyl compounds.

Dekamin, Peyman, and coworkers in 2016 used sodium alginate to catalyze the synthesis of various 2-amino-3-cyano-4*H*-pyran annulated derivatives **34** through three-component condensation reaction of

different aldehydes **17**, malononitrile (**33**), and diverse 1,3-dicarbonyl compounds **31** (Scheme 12)[39]. It is reported that the corresponding 4*H*-pyran derivatives **22** were obtained in high to excellent yields (80%-96%) after 25-150 min stirring in EtOH under reflux conditions in the presence of 10 mol % of sodium alginate.

In 2018, a straightforward method for the synthesis of polyhydroquinolines through the Hantzsch reaction of ethyl acetoacetate (**18**), different aldehydes **17**, ammonium acetate (**20**), and cyclic 1,3-diones **18** was reported by Dekamin and coworkers (Scheme 13).[40] According to their investigations, in the presence of catalytic amount of alginic acid (10 mol%), the corresponding polyhydroquinolines **35** can be obtained in short times by refluxing in ethanol in yields of 75-97%. They also compared the catalytic potency of alginic acid and sodium alginate for the Hantzsch reaction. They found out that alginic acid can perform better by giving a higher yield of the desired product (95%), while in the presence of sodium alginate, a slightly lower yield (80%) in the model reaction is obtained. These findings highlight the critical role of carboxylic acid moiety in the structure of alginic acid to promote the Hantzsch reaction. Although solvent-free conditions seem to be ideal for condensation reactions, according to the investigations, performing the model reaction under solvent-free and mechanochemical (ball milling) conditions affords a moderate yield of the desired PHQ. Performing the model reaction in water under similar catalyst loading afforded a lower yield of the desired products that may be attributed to the lower solubility of the starting materials in water compared to EtOH and the possibility of backward reactions of intermediates and products in water according to Le Chatelier's principle because some extra water is also produced as a by-product of the condensation reaction. It is also noteworthy that in the aqueous medium, swellable gel-like structures of alginic acid are formed; it seems that the hygroscopic nature of alginic acid decreases substantially in its swellable form. Therefore, its catalytic activity would be reduced for reactions that one of their by-products is water.



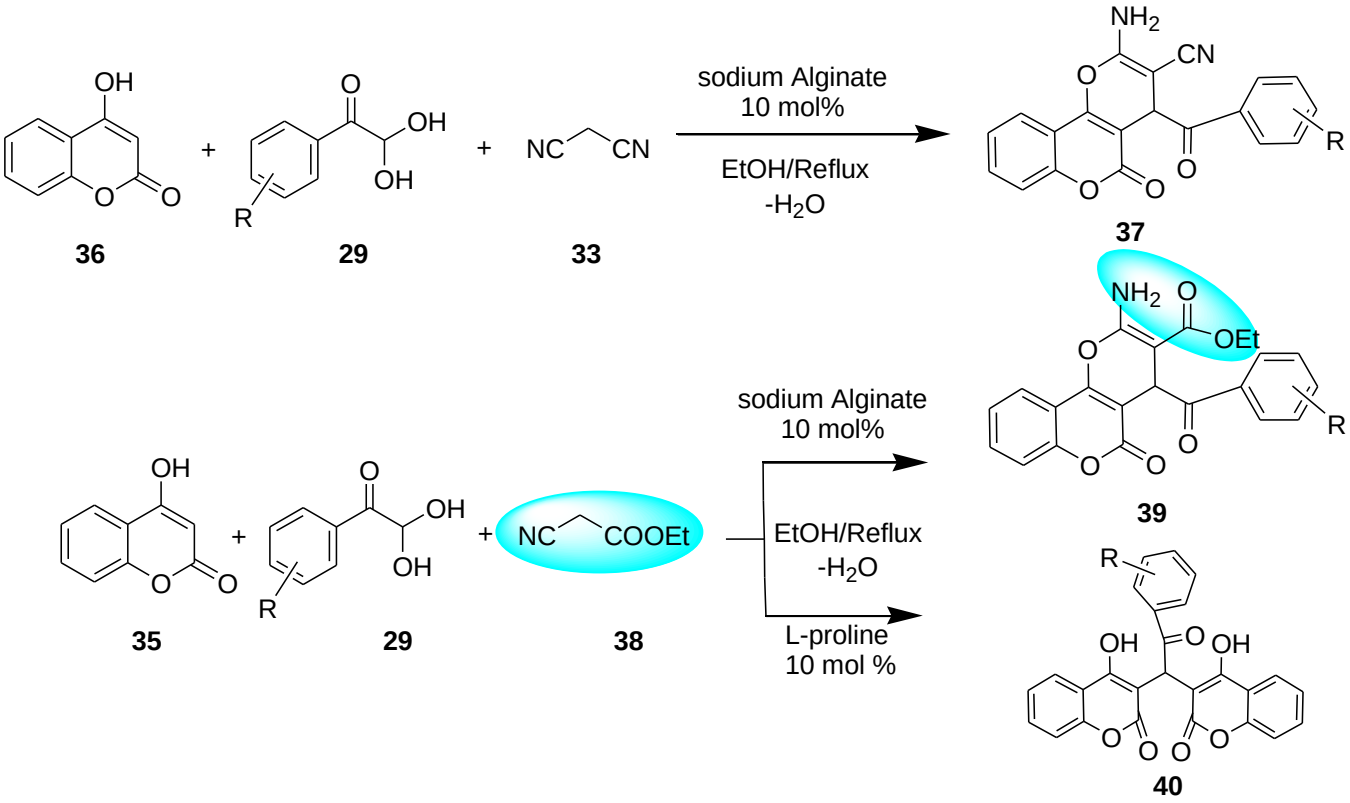
R=H, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$,4-BrC_6H_4O, 2-ClC_6H_4O, 2,4-$Cl_2C_6H_3$, C_6H_5, 4-MeC_6H_4O, 4-$MeOC_6H_4$, 4-OHC_6H_4, (4-OH,3-MeO)C_6H_3,C_4H_3O, C_4H_3S

R^1=Et R^2=H or Me

Scheme 13 a straightforward method for the synthesis of polyhydroquinolines through the Hantzsch reaction of ethyl acetoacetate, different aldehydes, ammonium acetate, and cyclic 1,3-diones in the presence of alginic acid.

Ilkhanizadeh, Khalafy, and Dekamin continued their recent investigations on using sodium alginate and alginic acid in organic synthesis, in 2019, they reported the reaction of 4-hydroxycoumarin, different arylglyoxals **29**, and malononitrile (**33**) or ethylcyanoacetate (**38**) catalyzed by sodium alginate without post modification to obtain some known and novel 4-aroyl-pyrano[3,2-c]chromenes (Scheme 14) under environmentally benign conditions in ethanol in high to excellent yields (80-91 %).[41] An important aspect of the mentioned reaction is the use of ethyl cyanoacetate (**38**), which has a lower reactivity compared to malononitrile (**33**), its reaction with 4-hydroxycoumarin (**36**), and different arylglyoxals **29** leads to a library of

novel pyrano[3,2-c]chromene derivatives (**27**), it is observed that by performing the reaction in the presence of p-toluenesulfonic acid (*p*-TSA), triethylamine (TEA), tetrabutylammonium bromide (TBAB) and sulfamic acid in EtOH under reflux condition, a dark mixture of inseparable products was obtained (entries 1-4). In the presence of L-proline, a biscoumarin product **40**was the major product, and ethyl cyanoacetate (**38**) did not involve entirely in the reaction, so sodium alginate was the only catalyst that could selectively catalyze the reaction and provide the desired novel products (Table 1).



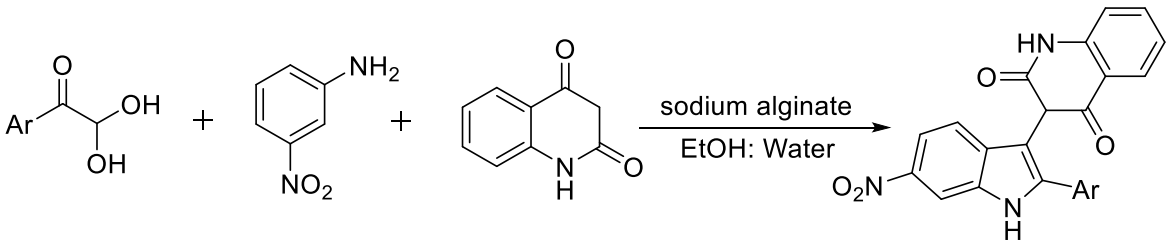
Scheme 14 Multicomponent synthesis of known and novel pyrano[3,2-c]chromene derivatives catalyzed by sodium alginate**.**

Table 1 Effect of different catalysts on the synthesis of **27**

Entry	Catalyst	Yield[a] (%)	
		27	**28**
1	Sodium Alginate	80	-
2	*p*-TSA	-	-
3	TEA	-	-
4	TBAB	-	-
5	Sulfamic acid	-	-
6	L-proline	15	65

In 2020, Nouri, Marjani and coworkers, used sodium alginate as a biopolymeric catalyst for the synthesis of novel 3-(2-aryl-6 nitro-*1H*-indol-3-yl) quinoline-2,4(1*H*,3*H*)-diones **31**. 3-nitroaniline (**29**), 4-

hydroxyqulinoline-2(1*H*)-one (**30**) and arylglyoxal monohydrate derivatives **19** reacted in the presence of a catalytic amount of sodium alginate in ethanol: water (1:1) solvent under mild conditions[42] (Scheme 15). The synthesized products may possess significant pharmaceutical effects because of their unique structures; some known and frequently used drugs, such as indomethacin as an anti-inflammatory drug, and arbidol with anti-viral activity, have similar core structures to the synthesized molecules.[42] Some noteworthy features of this work are mild reaction conditions, using a reusable, affordable catalyst, easy isolation and separation of the products, and high to excellent yields (63–82%).

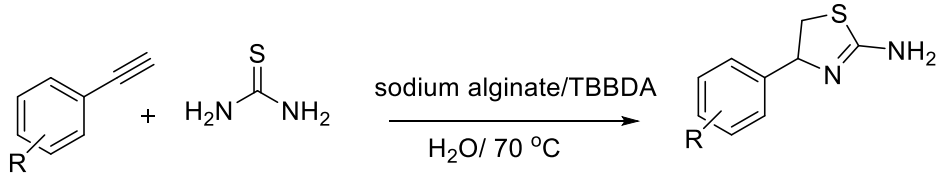


29 **41** **42** **43**

Ar= Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3-$OMeC_6H_4$, 4-MeC_6H_4, 3,4-$(MeO)_2C_6H_3$, 4-$NO_2C_6H_4$

Scheme 15 Synthesis of 3-(2-aryl-6 nitro-1H-indol-3-yl) quinoline-2,4-(1H,3H)diones through the reaction of arylgloxal monohydrate derivatives, 3-nitroaniline and 4-hydroxyquinolin-2(1H)one in the presence of sodium alginate.

Thiazole is indisputably one of the most important heterocyclic scaffolds; It can be found in many biologically active compounds and drug-like molecules. Many drugs, such as anti-HIVs, antifungal agents, and anti-neoplastic agents, contain thiazole structures.[43] With these in mind, designing efficient, environmentally acceptable methodologies for synthesizing the thiazole derivatives would be of great importance. 2-amino-4-arylthiazole derivatives **46** were synthesized in an aqueous medium from the reaction of substituted phenylacetylene (**44**) and thiourea (**45**) in the presence of sodium alginate granular form without any modifications (10 mol%) along with TBBDA (N,N,N',N'-tetrabromobenzene-1,3-disulfonamide) (Scheme 16).



44 **45** **46**

R: H, 4-Me, 4-OH, 4-OMe, 3-pyridine, 4-Cl, 4-NO_2, 4-Br, 4-NH_2, 3-NO_2

Scheme 16 Synthetic route to 2 amino-4-arylthiazole derivatives from the reaction of phenyl acetylene and thiourea in the presence of sodium alginate and TBBDA.

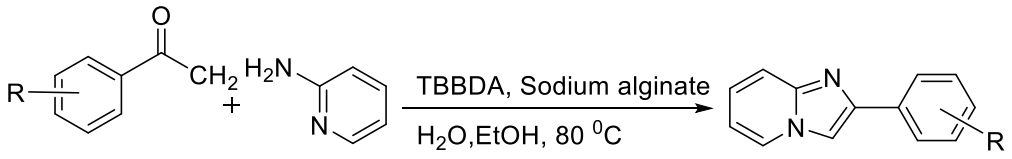
Gorji and coworkers in 2021 proposed this eco-friendly method to synthesize biologically interesting thiazole derivatives and thoroughly investigated sodium alginate's catalytic capability.[31] They compared the catalytic potency of sodium alginate with other natural well-known biopolymers such as starch and chitosan as

indicated in Table 2. According to their investigations, by using a catalytic amount of sodium alginate (0.05 g) along with TBBDA (0.25 mmol), a high yield (87%) of the desired product can be obtained in short reaction time (Table 2, entry 3). In contrast, in the presence of starch and chitosan under the same conditions, traces or low yields of the desired product was obtained even after long reaction times (Table 2, entries 10 and 11).

Table 2 Optimization of the reaction condition, catalyst loading and comparing the catalytic activity of sodium alginate with starch and chitosan along with TBBDA.

Entry	Conditions	Time (h)	Yield (%)[b]
1	TBBDA (0.25 mmol), water, 70 ^{0}C, Alginate (0)	8	N.R
2	TBBDA (0.2 mmol), water, 70 ^{0}C, Alginate (0.05 g)	4	75
3	**TBBDA (0.25 mmol), water, 70 ^{0}C, Alginate (0.05 g)**	**2**	**87**
4	TBBDA (0.25 mmol), water/EtOH, 70 ^{0}C, Alginate (0.05 g)	2	72
5	TBBDA (0.25 mmol), water/MeCN, 70 ^{0}C, Alginate (0.05 g)	2	63
6	TBBDA (0.25 mmol), water, RT, Alginate (0.05 g)	4	44
7	TBBDA (0.25 mmol), water, Reflux, Alginate (0.05 g)	2	87
8	TBBDA (0.25 mmol), water, 70 ^{0}C, Alginate (0.025 g)	2	80
9	TBBDA (0.25 mmol), water, 70 ^{0}C, Alginate (0.1 g)	2	88
10	TBBDA (0.25 mmol), water, 70 ^{0}C, Chitosan (0.1 g)	5	40
11	TBBDA (0.25 mmol), water, 70 ^{0}C, Starch (0.1 g)	24	Trace
12	NBS (0.25 mmol), water, 70 ^{0}C, Alginate (0.1 g)	24	50
13	HBr, water, 70 ^{0}C, Alginate (0.1 g)	24	N.R

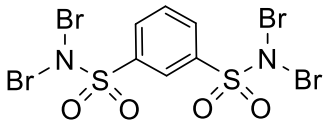
Imidazopyridine derivatives are amongst highly important nitrogenous heterocycles, due to their extensive pharmacological applications. A green, intelligent approach to the synthesis of phenylimidazo[1,2-a] pyridine derivatives **49** was reported by Zafari and her co-workers in 2021; they used the reaction of acetophenone derivatives **47**, and 2-aminopyridine (**48**) in the presence of sodium alginate as a catalyst in H_2O:EtOH mixtures at 80°C, (Scheme 17). The pure product was obtained from recrystallization of the crude product in EtOH. N,N,N′,N′-tetrabromobenzene-1,3-disulfonamide (TBBDA) was used as brominating agent in that reaction (Figure 2).[44]



47 **48** **49**

R: H, 3-Cl, 3-NO_2, 4-Br, 4-Cl, 4-NO_2, 4-CH_3, 4-OMe, 4-OH, Ph, N-(4-acetylphenyl)-4-methylbenzenesulfonamide, N-(4-acetylphenyl)-2-chlorobenzamide

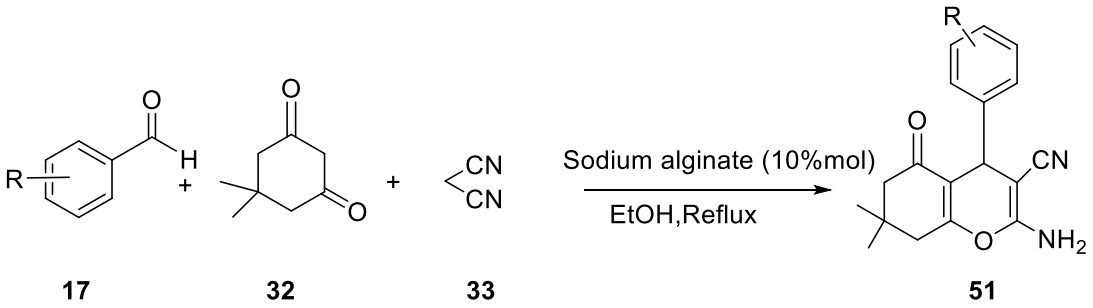
Scheme 17 synthesis of phenylimidazo[1,2-a] pyridine derivatives in the presence of sodium alginate.



50

Figure 2 Chemical structure of TBBDA.

In 2022, Farzaneh Mohamadpour reported a straightforward, metal free approach for one- pot synthesis of Tetrahydrobenzo[b]pyrans **51** in the presence of catalytic amount of sodium alginate as a reusable bifunctional biopolymeric catalyst.[45] The reaction of aromatic aldehydes **17**, dimedone (**32**), and malononitrile (**33**), in the presence of sodium alginate (10% mol) was operated in ethanol solvent under reflux conditions. The corresponding products **51** were synthesized and purified in excellent yields (81-96%) with no chromatographic purification (scheme 18). According to this report, by performing the reaction in the absence of catalyst in EtOH under reflux condition, only 18% of the desired product is obtained; adding 10 mol% of sodium alginate dramatically increases the isolated yield of the desired product to 93%.



17 **32** **33** **51**

R: H, 3,4-$(OMe)_2$, 4-F, 4-Br, 4-OMe, 3-Me, 2-Cl, 2-OMe,3-NO_2, 3-Br, 2,3-$(OMe)_2$, 2-NO_2 3-OH, 3-F, 4-Me, 3-Cl, 4-OH, 4-NO_2

Scheme 18 one pot synthesis of Tetrahydrobenzo[b]pyrans catalyzed by sodium alginate.

4. Conclusions

In summary, the present review highlights the recent applications of alginates and alginic acid as catalyst support and especially their direct catalytic applications in the synthesis of organic heterocyclic molecules. It has been demonstrated that by using a catalytic amount of these natural macromolecules, even with no modifications, a variety of organic reactions can be efficiently catalyzed to produce libraries of chemical compounds with pharmaceutically important backbones. Using natural renewable feedstocks in catalysis is a promising approach toward safer chemical processes. Alginic acid and sodium alginate are natural, biodegradable, reusable, and abundant compounds that show acceptable catalytic activity; these characteristics make them ideal catalysts to be used in more chemical reactions in the future.

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Authors' Biographies

Siamand Ilkhanizadeh was born in Bookan, Iran, in 1989. He received his B.Sc. degree in applied chemistry from Kurdistan University, Sanandaj, Iran, in 2012; His M.Sc. degree in organic chemistry from Iran University of Science and Technology (IUST), Tehran, Iran, under the supervision of Professor Mohammad Ghorban Dekamin in 2014, and His Ph.D. degree from Urmia University, Urmia, Iran, under the supervision of professor Jabbar Khalafy in 2019. His research interests include biopolymers, the synthesis of heterocyclic compounds, organocatalysts, synthetic methodology, extraction, and the synthesis of natural products.

Amrah Nouri was born in Urmia, Iran, in 1989. He received his B.Sc. degree in applied chemistry from Ardabil Azad University, Ardabil, Iran, in 2013, His M.Sc. degree in phytochemistry from the Pharmaceutical branch of Azad University, Tehran, Iran, in 2015 and his Ph.D. degree in organic chemistry from Urmia University, Urmia, Iran, under the supervision of Professor Jabbar Khalafy in 2019. His research interests include organic

synthesis, heterocyclic synthesis, asymmetric synthesis, natural product synthesis and applications of various catalysts in multicomponent reactions.

Jabbar Khalafy was born in Marand, Iran, in 1952. He received his B.Sc. degree in chemistry from Tabriz University, Tabriz, Iran, in 1975, his M.Sc. degree in organic chemistry from Manchester University, Manchester, England, in 1977 and his PhD degree in organic chemistry from Manchester University, Manchester, England, under the supervision of Professor J. M. Bruce, in 1979. He is Full Professor in the faculty of Chemistry at Urmia University, Urmia, Iran. His research interests include organic synthesis, heterocyclic synthesis, asymmetric synthesis, natural product synthesis, FVP, synthetic methodology and applications of various catalysts in multicomponent reactions.

