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Scalable preparation, characterization, and application of alkali-treated starch as a new organic base catalyst

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Graphical Abstract

Scalable preparation, characterization, and application of alkali-treated starch as a new organic base catalyst

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Abstract: Preparation, characterization, and application of alkali starch (AS) given by dry cogrinding of starch and alkali is described in this work. Grinding using a mortar (agate) and pestle or, more conveniently, a ball mill has been found to be satisfactory for the preparation of the AS. The AS products were characterized by scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) and x-ray fluorescence (XRF) analyses. The base capacities of ASs were 4.25-4.45 mmol/g, respectively. AS is a low cost and easy to handle base catalyst that showed promising catalytic performance in the synthesis of a dihydroquinazolinebased antibacterial drug that involves tandem hydration or decarboxylative amidation, imination, and Aza-Michael reactions.

Keywords: Alkaline starch; Anionic polymer; Base catalyst; Antibacterial drug.

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1. Introduction

Natural carbohydrates are among the best alternatives for the manmade polymeric materials, because of their biocompatibility, simple reproduction, and extra active sites.¹⁻³ Starch is the second most abundant polysaccharide composed of cross-linked amylopectin and linear polymers of amylose that helically solubilize in water.⁴ Amylose and amylopectin are different in their chain length, degree of cross-linking, and branching,⁵ so the percent of these polymers are different in various starches.⁶ The amylose/amylopectin ratio determines the average molecular weight (AMW) of starches, so the AMW of amylopectin ($>10^7$ g/mol) is greater than amyloseenriched starches.^{7,8} The granules of starch have amylopectin short chains in their semicrystalline parts and mixture of branched amylopectin and amylose in their amorphous parts.9 Although glycoside linkages in starch is predominantly α -C₁-C₄, amylopectin contains shorter chains of linked α -C₁-C₄ glucoses that joined to each other by α -C₁-C₆ glycoside bonds after each 25-30 glucose units.¹⁰ However, the physical and chemical properties of starch including AMW, particle size, morphology, viscosity, and adhesion are dependent to the ratio of amylose/amylopectin.¹¹ Due to the susceptibility of starch to enzymatic, chemical, and physical treatments, oxidation, etherification, alkalization, esterification, dextrination, cross-linking, grafting, or partial hydrolysis improves the properties of this natural biopolymer.¹²⁻¹⁶ Alkalitreated starch (AS), obtained from the reaction of starch with alcoholic solutions of sodium or potassium hydroxide, is a kind of anionic starch that used as thickener, stabilizer, and binder of feed products.¹⁷⁻¹⁹ The main problems associated with preparation of AS in aqueous alkaline solutions are gelatinization of starch, consumption of a large amount of volatile alcohols, and fewer interaction of NaOH with starch in these hydrogen-bonded solutions. Despite the recognized features of the value-added AS in food industries, this organic base has not yet been

considered as an anionic catalyst in chemical processes. To overcome the above shortcomings, development of more efficient methods for preparation of AS and use of this biocompatible alkali catalyst in green organic transformations has been established in our laboratory.

Grinding²⁰ by mortar-pestle or ball milling²¹ provide dual chemo-mechanical mixing of starting materials together with local heating and large area of contact between the solids. Cogrinding of solids by pestle or ball milling is an efficient way to synthesis of supra-molecular materials that have advantages of short reaction times, high yields, and easy workup of the product.²²

Due to the antibacterial properties of 2-phenyl-2,3-dihydroquinazoline-4(1*H*)-one (1),²³⁻²⁶ we have recently prepared this pharmaceutical and its derivatives using Amberlyst A26-OH as catalyst.²⁵ The objective of this work was easier access to AS by simple grinding or ball milling of starch with NaOH in the absence of organic solvents, characterization of AS, and examination of the catalytic proficiency of this anionic carbohydrate polymer in the large scale synthesis of antibacterial drug 1^{26} (Scheme 1)



Scheme 1. Preparation of alkaline starch and its catalytic use in synthesis of antibacterial compound 1.

2. Experimental

2.1. Materials

Corn starch with approximately 20.7% amylose and 79.3% amylopectin ($M_W = 10^5 - 10^7$) was purchased from Mahshad Co-operation (Yazd, Iran). The water content was determined by drying the corn starch in a vacuum oven at 50 °C until constant weight and was found to be 11.1%. Sodium hydroxide, Hammet indicators, isatoic anhydride, ammonium acetate, and benzaldehyde were all purchased from Merck (Darmstadt, Germany).

2.2. Characterization of catalysts and products

The base capacity of the prepared ASs was determined by either acid-base titration or Hammet indicators. FT-IR spectra were carried out on a Brucker instrument (Brucker, Karlsrohe, Germany). The XRF (Brucker, S4 Explorer, Germany) analysis were recorded at room temperature. The surface morphology of ASs was examined by SEM (Vega3 Tescan, Czech). The viscosity of corn starch and ASs were measured by viscometer (Ford cup, Biuged, China). The melting point of AS was determined by a Büchi B-540 apparatus (Germany). The drug prepared using AS was characterized by FT-IR, ¹H NMR, ¹³C NMR, and melting point (Supporting file).

2.3. Preparation of AS

AS was prepared by finely grinding of corn starch (100 g) with NaOH (38 g) in either an agate mortar (AS1) or ball milling (AS2) at 25 minutes. To remove the unreacted NaOH from the prepared AS, it was washed four times with EtOH, until to pH 7 for output EtOH. The given pale yellowish solid was then dried in a vacuum oven at 70 °C for 2 h.

2.4. Evaluation of the catalytic activities of ASs in synthesis of 1

To check the catalytic efficiencies of the given ASs in the synthesis of **1**, three individual experiments were performed for each of AS1 and AS2. In the first experiments, a mixture of AS1 or AS2 (0.5 g), isatoic anhydride (50 mmol), NH₄OAc (75 mmol), and benzaldehyde (50 mmol) was magnetically stirred at 80 °C for 30 min. In the second experiments, a mixture of AS1 or AS2 (0.5 g), 2-aminobenzamide (50 mmol), and benzaldehyde (50 mmol) was stirred at 80 °C for 20 minutes. Alternatively, a mixture of AS1 or AS2 (1 g), benzonitrile (50 mmol), water (25 mL), and benzaldehyde (50 mmol) was stirred at 80 °C for 1 h.

In each case, after the completion of the reaction (thin layer chromatography monitoring with hexane:EtOAc (70:30)), 50 mL of EtOAc was added, the catalyst was filtered, and the product

was isolated by evaporation of the solvent. The above three reactions with AS2 yielded product **1** in 96%, 97%, and 93%, respectively. The yields of similar reactions with AS1 were 93, 91, and 87%. The purity of the given **1** from AS2-catalyzed reactions was so high that the analytical data confirmed its structure without further purification.

3. Results and discussion

3.1. Preparation of AS by mortar-pestle or ball milling grinding methods

The alkaline starches AS1 and AS2 were respectively prepared by grinding of corn starch with NaOH using mortar-pestle and ball milling, four times washing of the pale yellowish solids with EtOH, and drying in vacuum oven. Color changes from white to pale yellow besides to pH changes from 7 to 12.5 and 12.6 in these processes support the alkoxidiation of some of 2,3,6-hydroxyl groups of starch and breaking of some of glycoside bonds to give the AS1 and AS2. These anionic polymers were characterized by acid-base titration, chemical composition, surface morphology, and FT-IR spectral data.

3.2. Acid-base analysis of ASs

While corn starch is neutral (pH = 7), the prepared alkaline starches by simple grinding or ball milling showed pHs of 12.5 and 12.6, respectively. The base capacities of these alkaline starches were determined by titration of the solution of 1 g AS1 or AS2 in 100 mL of water with 0.1 N standard solution of HCl. The volume of titrant used for neutralization of the given solutions from AS1 and AS2 were 42.5 and 44.5 mL, respectively. According to $M_1V_1 = M_2V_2$ at neutralization point, the molarity of solutions of AS1 and AS2 were 0.0425 and 0.0445 mol/Li (mmol/mL) and the base capacity or mmols of OH⁻ in solution of 1 g AS1/100 mL is 4.25 mmol/g, whereas 1 g of AS2 is equal to 4.45 mmol/g of OH⁻.

Alternatively, the base strengths $(H-)^{27}$ of the prepared ASs were determined by shaking of a 50 mg of AS1 and AS2 sample in methanol solution of various Hammet indicators and left to equilibrate for 2 h after which no color changes was observed. Nitroaniline (H- = 18.4), 2,4-dinitroaniline (H- = 15.0), and phenolphthalein (H- = 9.8) are the Hammet indicators used in this work and the base strengths of both of ASs were found to be H- > 18.4. The acid-base titrations, pH values of 12.5 and 12.6 as well as H- > 18.4 for ASs confirmed the alkalization of starch to ASs.

3.3. FT-IR spectral analysis of ASs

As FT-IR spectra of ASs show (Fig 1.), broadening of O-H stretching at 2000-3500 cm⁻¹ and CH₂ stretching at ~2930 cm⁻¹ are significant, although the C-O stretching for AS1 and AS2 appears sharper than neutral starch at 1021 cm⁻¹. A similar sharpening of CH₂ bending at 1456 cm⁻¹ for ASs supports much polarity and freedom of their CH₂ groups by breaking of some of H-O-CH₂ bonds. The expansion of O-H stretching bands of ASs is also due to the salt formation as C-O⁻Na⁺, all these changes are evident from Fig. 1.



Fig 1. The FT-IR spectra of corn starch and ASs.

3.3. XRF analysis of ASs

The comparative chemical compositions of AS1 and AS2 with corn starch in Table 1 shows large differences in %C, %O, %Na, C/O, and Na/O that all support the conversion of starch to AS (Table 1).

Table 1

The chemical composition of corn starch and ASs

Composition	Starch	AS1	AS2
Na (%)	0.14	16	17.7
Cl (%)	0.114	0.131	0.128
C (%)	27.1	21	20.8
O (%)	25.3	43.6	44.5
C/O	1.07	0.48	0.47
Na/O	0.005	0.37	0.40

The Na/O ratio is a good quantity to support the formation and anionic structure of AS. The 74 and 80 times larger amount of Na/O for AS1 and AS2 than starch confirmed the formation of sodium salt by converting of some OH groups to O⁻Na⁺. Similarly, ~5 times reduced C/O of ASs is due to increase in their oxygen quantities that maybe due to the cleavage of some of glycoside bonds to two OH groups.

3.5. SEM analysis of AS1, AS2, and starch

The compared SEM images of starch, AS1, and AS2 in 5 μ m and 100 μ m dimensions (Fig. 2.) showed difference in regular size distribution, morphologies, and porosities of ASs than native starch. These changes are results of the conversion of some OH groups to O⁻Na⁺ and alkaline hydrolysis of some glycoside bonds. The similarity in surface morphologies and repeated sights in SEM images of Ass can be attributed to the small differences in mortar-pestle grinding and ball milling mechanical techniques applied for their preparation. No better uniformity was obtained by change in the applied conditions for preparation of ASs or extra washing of them by EtOH.



Fig. 2. SEM images in 5 µm (left): starch (A1), AS1 (B1), AS2 (C1) and 100 µm (right): starch (A1), AS1 (B2),

AS2 (C2).

While the fine SEM analysis of particle size for AS2 show the irregular particles with dimension of $< 2 \mu m$ (Fig. 3), the histogram of size distributions, derived from SEM images of AS1 and AS2, reveals particles with average diameters of 2-15 μm (Fig. 4).



Fig. 3. SEM micrograph of AS2 in 50 µm dimension.



Fig. 4. Histogram of particle size distribution for ASs.

3.6. Viscosity test of AS and starch

Change in viscosity is demonstrative for structural changes of carbohydrate polymers. Thus, viscosities of ASs were determined by stirring of the homogeneous solutions of 2 g of each sample in 75 mL of distilled water at 25 °C for 20 min at controlled pH and temperature. A similar measurement was applied for starch's slurry solution, while difference in conditions was neglected due to the filtering of slurries. The viscosity of the prepared AS1 and AS2 were 5.1% and 6.5% higher than that initial corn starch.

3.7. Nitrogen adsorption isotherms of ASs

Based on the results obtained from the nitrogen adsorption isotherms, the surface area of AS2 is slightly higher than AS1 and the surface areas of ASs are significantly larger than starch (Fig. 5).



Fig. 5. Nitrogen adsorption of ASs at 25 °C.

3.8. Decomposition point of ASs

The decomposition point of AS1 and AS2 originated with color changes were 221-227 °C and 225-230, both lower than that of corn starch (254-260 °C). This trends that is attributed to the lower intermolecular hydrogen-bonding interactions of O⁻Na⁺ in ASs show the critical role of hydrogen bonding in OHs of starch.

3.9. Catalytic activity of ASs in the synthesis of antibacterial compound 1

To check the activity of ASs in organic transformations, AS-catalyzed synthesis of antibacterial drug of 2-phenyl-2,3-dihydroquinazoline-4(1H)-one $(1)^{26}$ was considered. Thus, various ASs were initially prepared by solvent-free ball milling of 10 g of starch with 0.1 mmol of inorganic bases. To check the effect of base on the catalytic activity of the given ASs in synthesis of **1**, the three-component model reaction of isatoic anhydride (50 mmol), benzaldehyde (50 mmol), and ammonium acetate (75 mmol) at 80 °C was screened with 0.5 g of

these ASs for 30 minutes (Fig. 6). The yield of reactions were calculated after extraction of product with EtOAc, filtering the remained solid catalyst, and evaporation of solvent.



Fig. 6. Effect of inorganic base on the yield of 1 using AS's catalysts.

According to the results, higher yields of compound **1** were obtained from AS-catalysts made by NaOH or KOH, which due to the cheapness of NaOH it was used in further experiments.

In the similar set of trials, seven AS samples were prepared by ball milling of 10 g of corn starch with various amounts of NaOH. To check the effect of amount of NaOH on the catalytic behaviors of ASs, synthesis of **1** was followed by running of the model reaction with 0.5 g of these AS-catalysts (Fig. 7).



Fig. 7. Effect of NaOH loading on the efficiency of the given AS from 10 g starch.

As results show, the maximum yield of **1** is due to reaction with 0.5 g of AS made from 10 g of starch and 3.8 g or 0.095 mmol of NaOH, although a similar control experiment using 0.5 g of NaOH in place of AS gave 70% yield of **1**. Thus, 3.8 g NaOH was selected as the optimum amount of base for preparation of AS.

Further, AS1 and AS2 were prepared by mortar-pestle grinding or ball milling of 10 g starch and 3.8 g NaOH. Then, various loadings of these ASs were used in the 50 mmol scale model reaction. The results of loading of AS1 and AS2 on the yield of **1** was compared with original starch in Fig. 8.



Fig. 8. Comparison of starch, AS1, and AS2 loadings on the yield of model reaction for synthesis of 1.

The results obviously show the authority of ASs, expressly AS2 in higher yield synthesis of **1**. The higher catalytic performance of AS2 may be due to the higher surface area (Fig. 5) or smaller particle size of AS2 which is obvious in the SEM results (Figures 2-4).

To optimize the conditions for AS2-catalyzed synthesis of **1**, typically the effects of solvent and temperature were also studied on the reaction yield. Thus, three-component model reaction of isatoic anhydride (50 mmol), benzaldehyde (50 mmol), and ammonium acetate (75 mmol) at 80 °C was run with 0.5 g of AS2 in different solvents for 30 minutes (Figure 9).



Fig. 9. Effect of solvent on the yield of 1 using 0.5 g of AS2 in model reaction at 80 °C.

According to the results, the maximum 96% yield of product **1** was obtained from the solventfree experiment in 50 mmol scale with 0.5 g of AS2 at 80 °C and 0.5 h.

The results of screened solvent-free reactions, at temperatures of 40-90 °C in an oil bath, showed that 80 °C is the optimum reaction temperature for giving the maximum yield of product **1** from the model reaction.



Fig. 10. Effect of temperature on the yield of 1 by solvent-free reaction using 0.5 g of AS2.

The recycling of AS2 was also tested. Hence, after the completion of the solvent-free reaction of isatoic anhydride (50 mmol), benzaldehyde (50 mmol), and ammonium acetate (75 mmol) at 80 °C, EtOAc was added and AS2 was separated by filtration. The given solid was washed with EtOH, and dried in an oven at 70 °C for 2 h. The SEM image of the recycled AS2 shows no significant changes in its surface morphology (Fig 11).





This is in agreement with the catalytic activity of the reused AS2 in the second reaction run,

although yield of 1 with four times recycled catalyst was also 94-95% (Fig. 12).







To show the superiority of AS-catalysts in the synthesis of **1**, the results of this work was compared with the previously reported methods (Table 2).

Table 2

The catalytic performance of AS in the synthesis of 1



To examine the versatility of AS2, product **1** was obtained in 97% yield by different reaction of 2-aminobenzamide (50 mmol) and benzaldehyde (50 mmol) using 0.5 g of AS2 at 80 °C and solvent-free conditions. The adaptability of catalyst AS2 was also confirmed by successful

reaction of 2-aminobenzonitrile (50 mmol) with benzaldehyde (50 mmol) and 2.5 mL of H_2O using 1 g of AS2 at 100 °C to give product 1 in 93% yield.

Conclusion

In conclusion, the alkali-treated starch (AS) prepared by either ball milling or simple grinding of corn starch with sodium hydroxide have been characterized by way of base capacity, viscosity, and decomposition point, although XRF, SEM, and FT-IR techniques also support its operational features. The adeptness of this bioorganic base catalyst was demonstrated in the synthesis of antibacterial compound of 2-phenyl-2,3-dihydroquinazoline-4(1H)-one, whereas it was reusable for three cycles without significant loss of activity. The AS is a low cost and easy handle catalyst that its applications in organic synthesis is in due course in our laboratory.

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Highlights

- Grinding by mortar-pestle or ball mill of starch and NaOH gives alkaline starch.
- Solvent-free alkalization helps to much interaction of starch with NaOH.
- The base capacity of alkaline starch (AS) is high to act as an alkali catalyst.
- AS is a handlebar solid, low-cost anionic polymer, and reusable catalyst.
- As shows a talented catalytic performance in synthesis of an antibacterial drug.