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Modification of Starch via the Biginelli Multicomponent Reaction

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An efficient and straightforward modification of starch using renewable and commercially available aromatic aldehydes (benzaldehyde, vanillin, and *p*-anisaldehyde) and urea via the Biginelli multicomponent reaction is reported in this work. First, starch acetoacetate (SAA) with a degree of substitution ranging from 1.4 to 2.5, depending on the reaction time or the molar ratio of reactants, is prepared. SAA is then modified with different aromatic aldehydes and urea via the Biginelli reaction. The modified products are characterized by ATR-IR, NMR, and gel permeation chromatography (GPC). The processability of the products is also investigated using a hot press instrument, revealing that glycerol is a suitable and renewable plasticizer for the Biginelli products.

Starch, one of the most important and abundant renewable polymers, receives enormous interest both in polymer chemistry and material science due to its outstanding features (e.g., renewability, biocompatibility, high thermal stability, and low cost).[1] Nevertheless, bottlenecks such as low solubility in organic solvents, high hydrophilicity, and brittleness reduce the feasibility of processing for potential future applications. Whereas various chemical modifications like esterification, etherification, crosslinking, etc. have been developed to overcome the above-mentioned issues, most of these methods face limitations such as low yield, inefficiency, or side product formation.[2–6]

Quite recently, multicomponent reactions (MCRs) emerged as a powerful tool to prepare tailor-made, multi-functionalized (bio)polymer architectures, offering high atom efficiency and molecular diversity in a one-pot synthesis under considerably mild and sustainable conditions.[7–11] Despite these advantages, multicomponent reactions on carbohydrates have not been investigated comprehensively. In 2018, the modification of cellulose by the Passerini 3 component reaction (P-3CR) and Ugi 4-CR, which are two well-known isocyanide-based examples for MCRs, have been reported.[12] Yet, the utilization of isocyanides is still one of the drawbacks in terms of sustainability of these approaches, particularly because of their handling, multiple step synthesis associated with large amounts of waste, as well as potential toxicity. A non-isocyanide based alternative, the Biginelli multicomponent reaction, has been recognized as another benchmark MCR.[13–15] Explicitly, this reaction facilitates the synthesis of heterocyclic compounds, the so-called 3,4-dihydropyrimidin-2(1H)-ones (DHPMs), via condensation of an aromatic aldehyde, a *β*-keto ester, and urea (or thiourea) in the presence of a Lewis or Brønsted acid catalyst.[16–18] In fact, these DHPMs are well known for their pharmacological application possibilities due to their antibacterial, antiviral, or antitumor activity.[19,20]

Very recently, Sui et al. have introduced a Biginelli-type modification of cellulose acetoacetate.[21] Based on this related approach, we extend it transferring it to starch and by providing a detailed molecular analysis as well as thermal and processability data of the obtained products. Glycerol, a commonly applied and renewable plasticizer for starch, was used in order to improve the processability of the modified products.[22–24] Furthermore, we focus on the use of only renewable components.

In this study, we investigate the synthesis and characterization of modified starch products by first synthesizing starch acetoacetate **(SAA)** and subsequently modifying it with different renewable components (such as benzaldehyde, vanillin, and *p*-anisaldehyde) in a sustainable fashion by applying the Biginelli multicomponent reaction (**Scheme 1**).

SAA was prepared via a straightforward procedure. Native starch was dissolved in DMSO at 90 °C for 30 min at ambient atmosphere. After the complete dissolution, *tert*-butyl acetoacetate (*t*-BAA) was added dropwise at 120 °C for 2 h under air flow. The purified products were characterized by ATR-IR and NMR spectroscopy (see Supporting Information for detailed experimental procedure). The acetoacetylation of starch was confirmed by the appearance of two significant bands in the respective IR spectra at 1710 and 1743 cm^{-1}, which belong to the carbonyl stretching vibrations of the acetoacetate moiety. Moreover, the intensity of the O–H stretching vibrations of the starch backbone around 3300 cm^{-1} was significantly reduced due to the substitution reaction (**Figure 1**). The ^{1}H NMR spectrum showed two significant magnetic resonances arising

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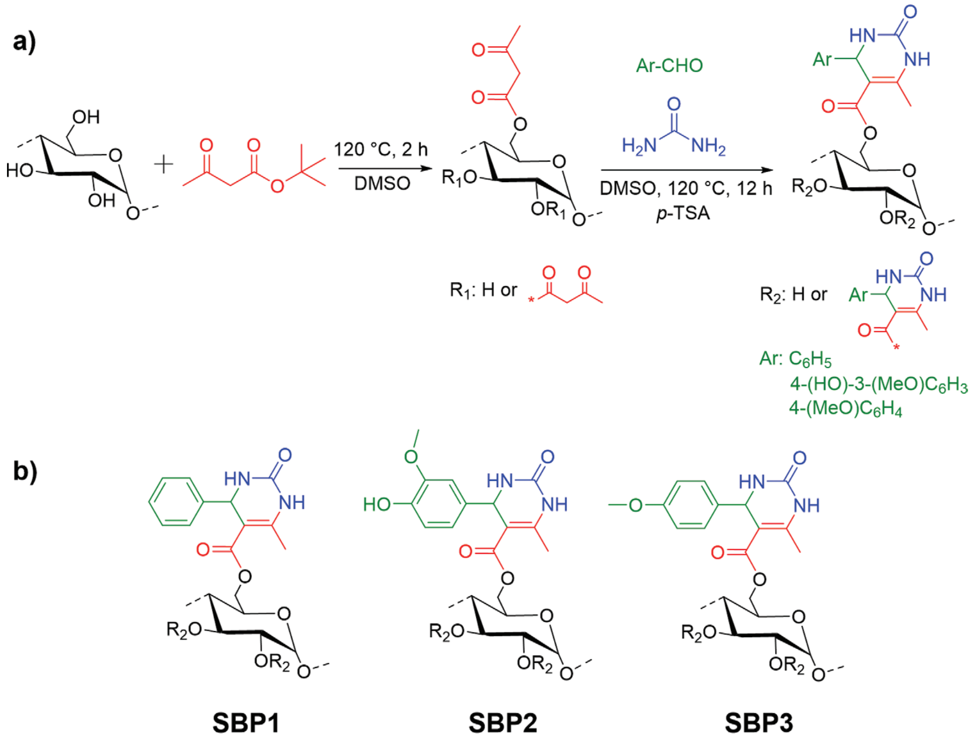

Scheme 1. a) Scheme of the Biginelli modification of starch. b) Isolated starch Biginelli polymers (**SBPs**).

from the methyl group of the acetoacetate at 2.18 ppm and the methylene group at 3.61 ppm, respectively. The peaks between 3.10 and 5.78 ppm were attributed to the protons of the anhydroglucose unit (AGU) of starch (**Figure 2**). Ultimately, the degree of substitution (DS) of the **SAA** products was determined via ^{31}P NMR. The unreacted hydroxyl groups were thus

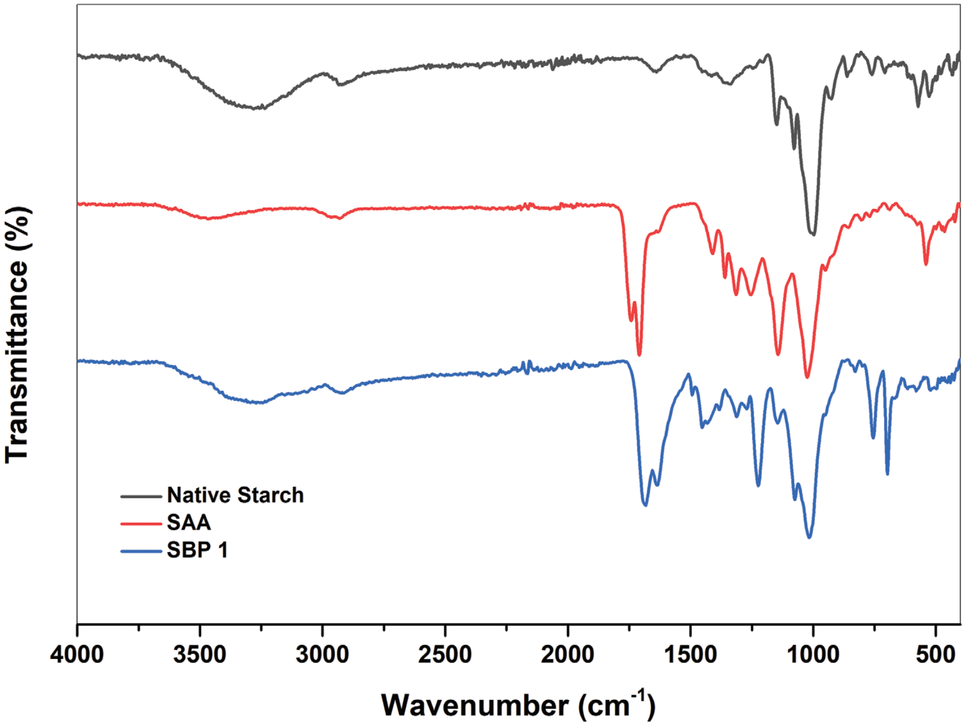

Figure 1. ATR-IR data of native starch, **SAA**, and **SBP1** (spectra were normalized to the intensity of the C—O stretching vibrations of the pyranose units at 1018 cm^{-1}).

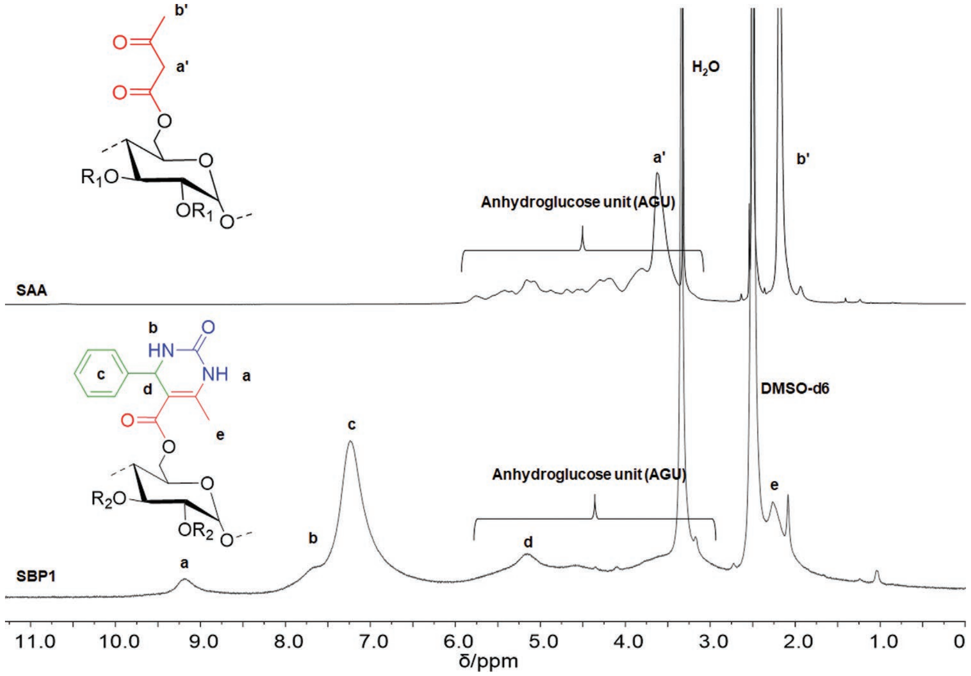

Figure 2. ^{1}H NMR spectra of **SAA** and **SBP1** in DMSO-d_6 at ambient temperature.

reacted with the phosphorylating agent, revealing a broad peak between $\delta = 143–150$ ppm, which is attributed to phosphorylated hydroxyl group of the starch. The ratio of integration of the free hydroxyl groups relative to the internal standard was used in the equation that previously reported (Figure S2, Supporting Information).[25] The highest DS was determined as 2.5 and by decreasing the reaction time or the *t*-BAA equivalents, less substituted **SAAs** could be obtained as well.

In the following step, the **SAA** product with the highest DS (2.5) was reacted with an aromatic aldehyde, urea, and a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) to produce starch Biginelli polymers **(SBPs)**. First, benzaldehyde was chosen as a model compound in order to optimize the reaction conditions. After dissolution of the **SAA** in DMSO at ambient temperature, benzaldehyde, urea (1.75 equivalents each, with respect to the acetoacetate unit), and *p*-TSA (10 mol% of acetoacetate unit) were added to the reaction mixture. Reactions were performed at 120 °C for 12 h. Afterward, vanillin and *p*-anisaldehyde were used with the same reaction conditions to expand the diversity of the final products (see Supporting Information for detailed experimental procedures) and to produce fully renewable **SBPs**. After purification, the successful transformations were confirmed by ATR-IR and ^{1}H NMR. The formation of the 3,4-dihydropyrimidin-2(1H)-one structures was validated by the disappearance of the initial carbonyl vibrations at 1710 and 1743 cm^{-1} along the new prominent vibrations at 1634 and 1683 cm^{-1}. Furthermore, an aromatic vibration at 1450 cm^{-1} became visible due to the use of aromatic aldehydes (Figure 1). The ^{1}H NMR spectrum also revealed the characteristic signals of the DHPM structure: the CONH moieties at 7.7 and 9.2 ppm, in addition to the aromatic signal at 7.2 ppm and the CH peak of heteroatomic ring at 5.2 ppm confirm the success of the modification. Furthermore, the methylene peak of **SAA** at 3.61 ppm vanished, thus proving the full conversion of **SAA** to **SBPs** (Figure 2). Unfortunately, the DS of the **SBPs** could not be validated by ^{31}P NMR as it was performed for **SAA**, because the **SBPs** precipitated during the phosphorylation step of the sample preparation. Nevertheless, due to the full conversion of **SAA** to **SBPs**, their DS values were considered the same (within experimental error of ^{1}H NMR) as the **SAA** used for the Biginelli reaction. A detailed characterization of all **SBPs** can be found in the Supporting Information.

As the solubility of (modified) carbohydrates is often limited, hexafluoroisopropanol **(HFIP)** +0.1 wt% potassium trifluoroacetate had to be selected as a common solvent and eluent for the gel permeation chromatography (GPC) in order to be able to compare all the results (**Table 1**). Interestingly, the respective GPC analysis revealed that **SAA** (DS: 2.5) shows an M_n of 262 kDa with $Đ = 2.3$, whereas **SBPs** show lower M_n (110–143 kDa with $Đ = 2.8–3.6$), which might be explained by their different (smaller) hydrodynamic volumes in the chosen solvent due to the presence of strong hydrogen bonding in the Biginelli products or by the exclusion limit of the GPC columns. Since the exclusion limit was around 3.7 mL (elution volume), molecules with higher molecular weight than the exclusion limit might be detected at higher retention times (**Figure 3**). In order to investigate a possible degradation of the starch backbone under the Biginelli reaction conditions, a control reaction was performed with **SAA** in DMSO/*p*-TSA at 120 °C. However, very fine insoluble fibers were obtained, probably because of an aldol condensation of the β-keto-ester, therefore GPC analysis was not possible afterwards. A possible degradation thus cannot be ruled out (see also below), but the results show that the Biginelli reaction proceeds preferred compared to this side-reaction and that in any case, high molecular weight modified starches could be confirmed (see Table 1).

Table 1. Molecular and thermal characterization data of the modified starch samples.

Sample	M_n [kDa][a)]	M_w [kDa][a)]	$Đ$[a)]	Yield[b)] [%]	T_g [°C]	$T_{d,5\%}$ [°C]
SAA	262	612	2.3	88	93	185
SBP1	110	400	3.6	64	–[c)]	275
SBP2	143	406	2.8	60	–[c)]	277
SBP3	124	452	3.6	61	–[c)]	280

[a)] GPC in HFIP using PMMA standards for calibration; [b)] yields were determined based on DS; [c)] not observed.

In order to better understand the Biginelli modification, samples were taken from the reaction mixture at different time intervals. The taken samples were first precipitated, then purified using a general procedure (see Supporting Information), and analyzed by ATR-IR and GPC. The samples taken after 1 and 2 h were not soluble in **HFIP**, thus GPC analysis was not possible. For the following samples, a lower molecular weight compared to **SAA** was observed, but the molecular weight increased until 12 h reaction time, whereas a slight decrease was dominant for the longer reaction time, reasonably because of some degradation (low molecular weight species of ≈1 kDa were observed by GPC). The ATR-IR results showed a similar trend (Figure S11, Supporting Information). More importantly, already after 1 h, C = O vibrations of **SAA** disappeared quantitively, confirming the efficiency of the modification. Additionally, the intensity of the carbonyl peak arising from the Biginelli products continuously increased up to 12 h and then started to diminish slightly because of some minor degradation. A degradation after too long reaction times was also indicated by decreasing yields.

To investigate the properties of the synthesized derivatives, detailed thermal characterization has been conducted via DSC and TGA (Table 1). First, the thermal stability of products was investigated by TGA. In all products, water evaporation was observed between 80 and 175 °C and **SAA** products revealed a relatively high thermal stability ($T_{d,5\%}$ = 185 °C). The thermal stability of the **SBPs** increased 10–15 °C compared to native starch (Figure S13, Supporting Information). DSC analysis of **SAA** samples revealed glass transition temperatures (T_g) between 93 and 131 °C, depending on its DS value, which can be tuned easily by changing the *t*-BAA equivalents during the acetoacetylation reaction (Figure 3). On the other hand, a T_g was not observed for the **SBPs** within the measuring range (–25 to 245 °C), probably since the increase of the inter- and intramolecular hydrogen bonding of the newly introduced DHMP units strongly restricts mobility.

In order to investigate the processability of the obtained products, test specimen were prepared using a hot press instrument. Initially, **SAA** products with various DS values were manipulated above their T_g and under 5 kN force, resulting in the formation of translucent discs. Later, the same method was applied to the **BSPs**, but since these samples did not show a glass transition below their degradation temperature, processing was difficult. After first trails at 145 °C, the appearance of the discs was not homogenous. In order to overcome this situation, glycerol, which is cheap and renewable, was chosen as a possible plasticizer to obtain some initial results on a possible processability of the **SBPs**. Starting from an addition of 20% w/w, the amount of glycerol was increased until translucent discs were obtained. With 20% w/w glycerol, samples were too brittle to be taken as one piece out of the press; however, after increasing the glycerol amount up to 50% w/w, homogenous discs could be obtained in one piece (Figure S14, Supporting Information). The required glycerol amount (50% w/w) was higher than typically used for plasticized (native) starches.[23,24] The obtained discs were cut into 20 mm × 2 mm strips in order to examine their mechanical behavior using a tensile strength instrument. Only the data from the measurements of **SBP2** with 50% w/w glycerol sample was taken, since the others were still too brittle for the tests. The average values of three measurements revealed 16% of elongation at break with a maximum stress value at 5.3 MPa and a Young's modulus (E) of 118 MPa (Figure S15, Supporting Information).

In this work, a Biginelli type modification of starch is reported by first acetoacetylating starch with a high degree of substitution and further reacting it with urea and various renewable and commercially available aldehyde derivatives to demonstrate the versatility of this multicomponent reaction approach. In summary, we demonstrated a straightforward and versatile starch modification under metal-free and considerably mild conditions. Additionally, acetoacetylated starch samples showed thermoplastic behavior with a wide range of T_g values (93–131 °C), depending on the degree of substitution. After the Biginelli modification, products with high molecular weight (M_n of 110–143 kDa) and high thermal stability ($T_{d,5\%}$ = 275–280 °C) were obtained. We could also demonstrate that

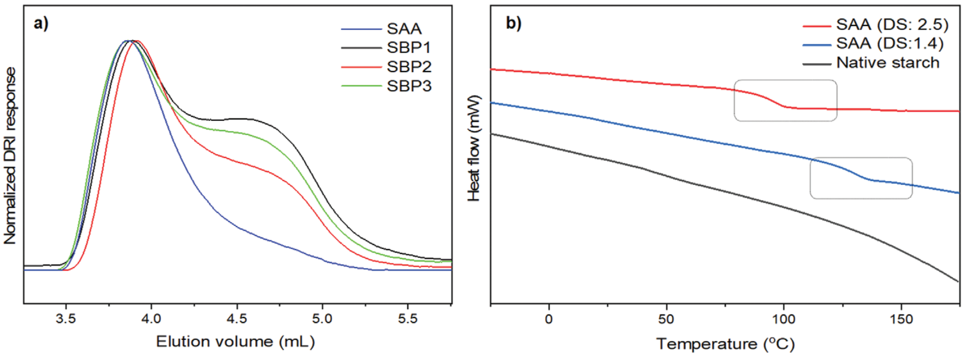

Figure 3. a) GPC traces of the synthesized products, b) DSC graph of native starch and **SAA** with different DS values.

the Biginelli modified starches required glycerol as a plasticizer to be processed.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

Biginelli reaction, multicomponent reactions, renewable resources, starch

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