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Improved synthesis of 3-methoxy-4-hydroxymandelic acid by glyoxalic acid method

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ABSTRACT

The most important industrial process for the synthesis of vanillin is performed in two steps involving an condensation reaction of glyoxalic acid with guaiacol followed by an oxidative decarboxylation of the intermediary 3-methoxy-4-hydroxymandelic acid (MHPA) formed, thereby producing not only vanillin, but also byproducts, which have to be eliminated. In the present study, we focused our efforts on the first step of vanillin synthesis, namely, the condensation reaction governing the yield of vanillin. The factors influencing the stability of glyoxalic acid were preliminarily evaluated to provide significant referential value for suppressing the dismutation of glyoxalic acid in the condensation reaction, and the results indicate that the stability of glyoxalic acid largely depends on the pH, temperature, and holding time of the feed solution. Then the process of the condensation reaction was optimized under the factors affecting the stability of glyoxalic acid, as well as the molar ratio of guaiacol to glyoxalic acid. Under the optimized conditions, the maximum yield of the condensation reaction can reach to 88%.

1. Introduction

The exceptionally wide application of vanillin in the food, cosmetic, pharmaceutical, nutrition, and fine chemical industries makes vanillin one of the most important aromatic compounds and justifies the very large number of researches to improve its production processes.[1] Vanillin can be prepared by a few methods from different starting materials, such as guaiacol,[2] *p*-hydroxybenzaldehyde,[3] cresol,[4] isoeugenol,[5] or lignin,[6] etc. Among those methods, the guaiacol–glyoxalic acid route, which consists of two successive steps involving a condensation reaction followed by an oxidation decarboxylation (Fig. 1), has become one of the most promising technology in vanillin synthesis due to its advantages in high efficiency, short process, and simple equipments.

Currently, the primary drawback of the guaiacol–glyoxalic acid route is the low yield of vanillin. This disadvantage has seriously restricted the wider application of that method in industry. Due to the low yield of the condensation reaction compared with that of the following oxidation decarboxylation,[7] how to improve the condensation reaction becomes a key for increasing the overall yield. Generally, the condensation reaction between guaiacol and glyoxalic acid according to reported procedures is carried out at room temperature or even higher temperature, which not only contributes to the unsatisfied yield of MHPA (<80%, based on glyoxalic acid), but also resulted in the poor product purity, as the product is with dark color and requires further purification.[8] It has been clear that the condensation step also suffered from two side reactions. One major issue is the tendency of glyoxalic acid to undergo Cannizzaro dismutation reaction, giving rise to glycolic acid and oxalic acid (Fig. 2). Another problem encountered in the condensation reaction is that the hydrogens on the *ortho*-position, or both the *ortho*-position and *para*-position of guaiacol can be substituted by glyoxalic acid to form 2-hydroxy-3-methoxylmandelic acid and 4-hydroxyl-5-methoxyl-1,3-benzenediglycolic acid, respectively. Obviously, there is still room and need to further optimize the first condensation step in terms of yield and product purity.

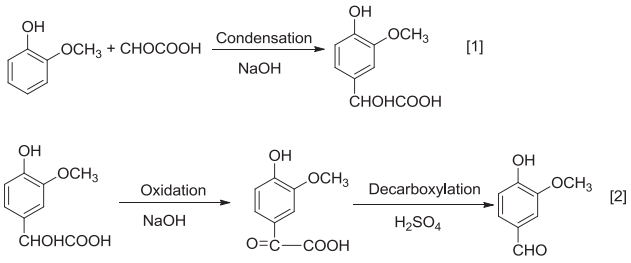

Fig. 1. Synthesis of vanillin by the guaiacol–glyoxalic acid route.

Despite the numerous studies reported about this process, there has been no systematic study undertaken concerning the condensation reaction between guaiacol and glyoxalic acid. Attempting to efficiently prevent the undesired reactions from occurring in the

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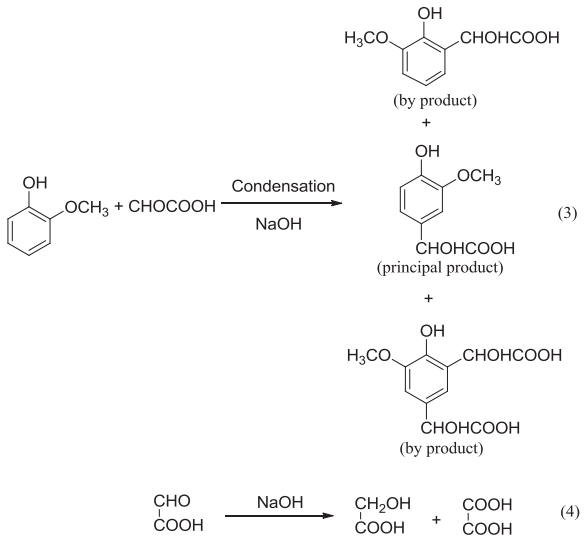

Fig. 2. Possible pathways of the condensation reaction between guaiacol and glyoxalic acid in alkaline solution.

condensation reaction, we present here a systematic study of this reaction from two aspects. First, the stability of glyoxalic acid in alkaline solution was investigated with the aim at more effectively avoiding the undesired dismutation reaction of glyoxalic acid; second, the factors affecting the yield of MHPA were optimized one by one in order to get a better understanding of how to control the reaction selectivity.

2. Results and discussion

2.1. Stability of glyoxalic acid

It may take several hours for the condensation reaction between guaiacol and glyoxalic acid to complete. Thus, if either the pH, or temperature of the reaction medium is not well controlled in the process, the dismutation reaction of glyoxalic acid will be promoted, which is not beneficial to improve the yield of MHPA. Therefore, the stability of glyoxalic acid under different pH, temperature, and holding time was studied to provide valuable guides for better utilizing glyoxalic acid starting material in the condensation reaction.

2.1.1. Effect of pH on the stability of glyoxalic acid. Industrial grade glyoxalic acid of 20 g (37 wt %) was firstly diluted with water to the concentration of 1.0 mol L^{-1} at room temperature, then 30% NaOH was added in a dropwise fashion into the glyoxalic acid solution under stirring to adjust the pH to 3, 5, 7, 9, 11, 13, respectively, the volume of glyoxalic acid solution was recorded under the different pH. In case that glyoxalic acid is too stable to undergo dismutation reaction or other side reactions under different pH, the theoretical values of the glyoxalic acid concentration can be calculated. Meanwhile, the corresponding measured values of the glyoxalic acid concentration were determined by the sodium sulfite method.[9]

Fig. 3 showed that the measured value of the glyoxalic acid concentration was nearly equal to its corresponding theoretical value in the case of pH≦5, indicating that the dismutation reaction of glyoxalic acid did not happen in such conditions. It also indicated that the measured concentration of glyoxalic acid was lower than the corresponding theoretical value when the pH is higher than 5, and the gap was getting bigger as the pH increased. When the pH of the solution rose to 7 and 9, the measured value deviating from the theoretical value was 4% and 7%, respectively. Furthermore, the measured value of the glyoxalic acid concentration decreased significantly when pH increased to 13, and that measured value was 18% lower than the corresponding theoretical value. From that observation, a conclusion can be drawn: the stability of glyoxalic acid strongly depends on the pH of the glyoxalic acid solution, and the dismutation reaction of glyoxalic acid can readily take place in the case of pH above 11.

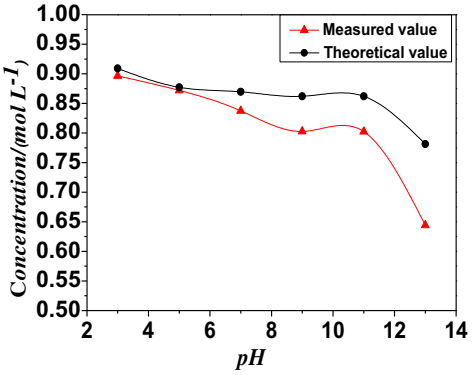

Fig. 3. Loss of glyoxalic acid at different pH.

2.1.2. Effect of holding time on the stability of glyoxalic acid. The glyoxalic acid solution prepared as described above was kept in nitrogen atmosphere for different holding periods ranging from 1 to 24 h. All the study about holding time was conducted at room temperature.

As shown in Fig. 4, the glyoxalic acid concentration was kept almost constant for the holding time of 24 h in the range of pH 3–9. It can be observed that the glyoxalic acid concentration decreased by 7% at pH 11 after 12 h, and then remained almost unchanged, indicating that a small amount of glyoxalic acid had been converted to glycolic acid and oxalic acid. Whereas the glyoxalic acid concentration declined by 14% at pH 12 after 24 h, and its descending rate was two times as fast of that at pH 11. It should be pointed out that almost 93% of glyoxalic acid initially presented in the solution was consumed after 24 h at pH 13. The results show that the dismutation reaction of glyoxalic acid can be effectively suppressed at pH≤11 even if the holding time is up to 24 h. Otherwise, the glyoxalic acid concentration will decrease sharply with increasing the holding time at pH above 11.

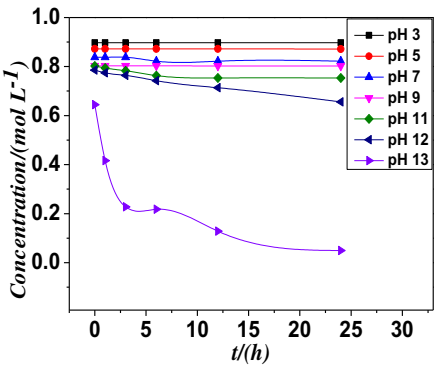

Fig. 4. Concentration change of glyoxalic acid with holding time at different pH.

2.1.3. Effect of temperature on the stability of glyoxalic acid. Taking into account that the condensation reaction between guaiacol and glyoxalic acid was generally carried out at pH of 11–13, we selected the solution with pH as 11 to study the temperature influence on the stability of glyoxalic acid. The results were presented in Fig. 5.

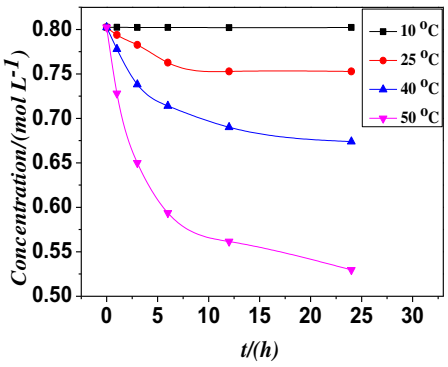

Fig. 5. Concentration change of glyoxalic acid with holding time at different temperatures at pH=11.

It can be observed that the glyoxalic acid concentration was almost unaffected with the increasing holding time at 10 °C. A 7% decrease in the glyoxalic acid concentration was found at 25 °C after 24 h. When the temperature rose to 40 °C, the glyoxalic acid concentration decreased dramatically by 16% for the same period of holding time. With the temperature further increasing to 50 °C, almost 34% of glyoxalic acid was consumed in the dismutation reaction throughout the holding period. The results here obtained suggest that temperature is shown to be a significant factor in the undesired dismutation reaction of glyoxalic acid and that side reaction can be effectively restrained in low temperature.

2.2. Condensation reaction

The results of previous experiments have proved that the stability of glyoxalic acid strongly depends on the pH of the feed solution and the temperature. Additionally, it can be presumed that reasonable control on the molar ratio of reactants is important to restrain the undesired substitution reactions of guaiacol with glyoxalic acid. Consequently, we focused our efforts on the impact of pH, temperature, and molar ratio of the reactants to improve the yield of the condensation reaction between guaiacol and glyoxalic acid.

2.2.1. pH. It has been previously confirmed that pH of the feed solution is imperative for restraining the dismutation reaction of glyoxalic acid. Hence, the effect of pH on the yield of MHPA was firstly studied at the conditions of the reaction temperature of 10 °C, reaction time of 32 h, and molar ratio of guaiacol to glyoxalic acid of 1.5. The results were shown in Fig. 6. It can be observed that due to the negligible solubility of guaiacol in the reaction medium at pH 9, the condensation reaction of guaiacol with glyoxalic acid hardly occurred, leading to the MHPA yield of only 12%. Whereas guaiacol could completely react with sodium hydroxide to generate its water-soluble sodium salt at pH 11, obtaining a transparent solution with light blue colour. The conversion of guaiacol to its water-soluble sodium salt markedly promoted the condensation reaction between guaiacol and glyoxalic acid, bringing the yield of MHPA to the maximum value of 88%. Further increasing pH of the reaction medium had little influence on the solubility of guaiacol, but would accelerate the dismutation reaction of glyoxalic acid. As a result, the yield of MHPA decreased to 83% and 51% at pH 12 and 13, respectively. The results here obtained show that the effect of pH on the yield of MHPA is highly significant and that it is necessary to maintain the pH at 11 so that the condensation reaction is optimized to obtain the maximum yield of MHPA.

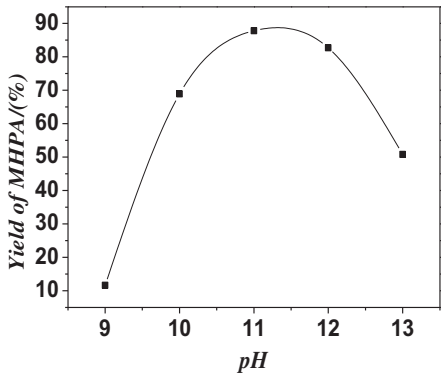

Fig. 6. The effect of pH on the yield of MHPA.

2.2.2. Temperature. It should be remarked that the elevated temperature will be undoubtedly helpful to speed up the condensation reaction, but higher temperature will also accelerate the side reactions, decrease the utilization ratio of glyoxalic acid in the condensation reaction. The results obtained about the temperature influence on the yield of MHPA were depicted in Fig. 7. The following condensation reaction was performed at the conditions of pH 11 and 1.5 molar ratio of guaiacol to glyoxalic acid.

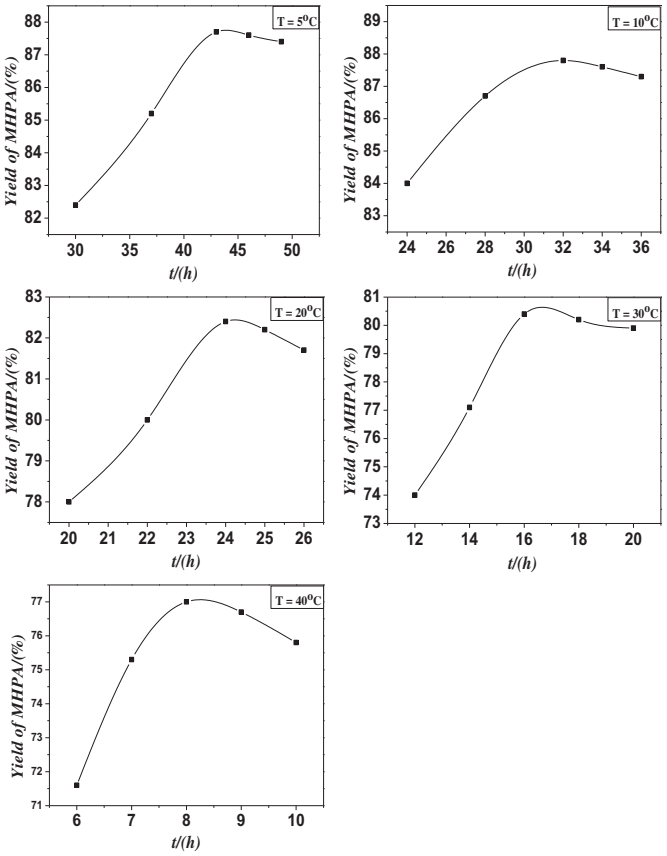

Fig. 7. The effect of temperature on the yield of MHPA.

It has been observed that when the temperature increased from 5 to 10 °C, the completion time of the condensation reaction was shortened by 11 h, but the yields of MHPA essentially remained the same standing at 88% after the condensation reaction reached equilibrium. That observation is in accordance with the previous result that the dismutation reaction of glyoxalic acid can be effectively inhibited at temperature below 10 °C. Besides, it also showed that when the temperature rose from 10 to 40 °C, the completion time of the condensation reaction was reduced from 32 to 8 h, while the yield of the condensation reaction decreased from 88% to 77%. The lower yield at elevated temperature was attributed to the aggravation of side reactions. The results indicate that the condensation reaction between guaiacol and glyoxalic acid is suitable to perform at low temperature, even it means longer reaction time.

2.2.3. Molar ratio of guaiacol to glyoxalic acid. Attempting to restrain the undesired substitution reactions of guaiacol with glyoxalic acid, we also studied the effect of the molar ratio of guaiacol to glyoxalic acid on the yield of MHPA. Fig. 8 showed that the equimolar reaction of guaiacol with glyoxalic acid gave MHPA in 72% yield. When the molar ratio of guaiacol to glyoxalic acid increased to 1.2, the yield of MHPA rose rapidly to 80%. It was found that the maximum yield of MHPA 88% could be achieved at a 1.5 molar ratio of guaiacol and glyoxalic acid. With the molar ratio of guaiacol to glyoxalic acid further increasing, it not only had no significant influence on the improvement of the product yield, but would also increase the cost to recycle the unreacted guaiacol. The results reveal that guaiacol/glyoxalic acid molar ratio of 1.5 is adequate.

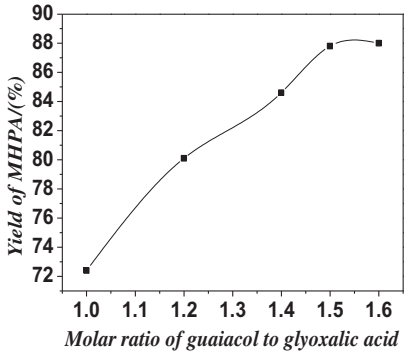

Fig. 8. The effect of molar ratio of guaiacol to glyoxalic acid on the yield of MHPA.

3. Conclusions

We reported for the first time a systematic study on the condensation reaction between guaiacol and glyoxalic acid from two aspects. The study on the stability of glyoxalic acid reveals that the three main parameters of pH, temperature, and holding time have significant influence on the undesired dismutation reaction of glyoxalic acid, and that side reaction can be effectively suppressed within 24 h at the conditions of pH≤11 and temperature ≤25 °C. Based on the prevenient research, the condensation reaction between guaiacol and glyoxalic acid was performed under optimized condition to afford MHPA with the maximum yield of 88%. This study will bring valuable advantages to the industrial synthesis of vanillin by the guaiacol–glyoxalic acid route.

4. Experimental section

4.1. General

The commercially available products were used without further purification. The theoretical value of glyoxalic acid was calculated without consideration of loss of glyoxalic acid at different pH. The measured value of glyoxalic acid was determined by the sodium sulfite method in consideration of loss of glyoxalic acid resulted from dismutation reaction. The condensation reaction between guaiacol and glyoxalic acid was carried out under atmospheric pressure of nitrogen. Initially, guaiacol (0.15 mol) and water (230 g) were added into a 500 ml four-neck bottom reactor, which was fitted with an overhead stirrer. NaOH (30 wt %) was gradually added under stirring to adjust the pH of the guaiacol solution to 11. The reaction temperature was kept at 10 °C by a water bath. The solution of sodium glyoxylate (0.1 mol) with pH 4–5 was subsequently added dropwise into the guaiacol solution within 1 h under stirring. The resulting mixture was stirred for another 1 h, and kept in a resting state for 32 h to give MHPA in 88% yield. During the reaction, samples were withdrawn and analyzed by HPLC at fixed times. The unreacted guaiacol was recovered by extraction with toluene after the pH of the condensation solution was adjusted to 4.5. ^{1}H NMR spectral data of the product were compared to those of authentic samples.

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