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Short Communication

High selective autocatalytic esterification of glutamic acid by benzyl alcohol with $CuCl_2$ promoting

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ABSTRACT

We found that the esterification of L-glutamic acid by benzyl alcohol is greatly promoted by $CuCl_2$ even in H_2O solvent, and the selectivity and yield of γ-benzyl ester of L-glutamic acid achieved 100% and 95.31%. Metal cation coordination to the amino acids via neighboring amino and carbonyl groups increased α position carboxyl acidity which initiates the esterification reaction to selectively take place on γ position carboxyl group. In this autocatalytic process H_2O has no effect on esterification.

1. Introduction

The esterification of glutamic acid and benzyl alcohol for the preparation of γ-benzyl ester of glutamic acid in the presence of an acid has been described [1–10], and the γ-benzyl ester of glutamic acid and its derivatives are very useful compounds in the preparation of products which were used in medicine [11–15], agriculture [16], peptides [17] and polymerizations [18–24]. In many cases, γ-benzyl ester of glutamic acid, α-benzyl ester of glutamic acid and diester dibenzyl 2-aminopentanedioate are formed simultaneously, which results in the low yield of γ-benzyl ester of glutamic acid. Normally, γ-benzyl ester of glutamic acid often contains numerous impurities which render it unusable without subsequent purification treatments. Furthermore, racemization frequently occurs and the desired L or D derivatives are not obtained [9].

Herein, we present a new strategy to selectively convert L-glutamic acid into γ-benzyl ester of L-glutamic acid. This study shows that Cu^{2+}, Fe^{3+} and Zn^{2+} metal cation coordination to the amino acids via neighboring amino and carbonyl groups increased α position carboxyl acidity which initiates the esterification reaction to selectively take place in γ position carboxyl group. Most importantly, in this autocatalytic process H_2O has no effect on esterification.

2. Experimental

2.1. Materials

Benzyl alcohol (99.0%) was purchased from Kermel (China). L-glutamic acid (Bio-reagent) was supplied by AMRESCO. $CuCl_2$ and other chemical reagents were purchased from Tianjin Chemical Reagent Factory (AR). All reagents were used as received, without further purification.

2.2. The process of esterification of glutamic acid with benzyl alcohol

The reaction takes place via typical condition, that is 6.8 mmol L-glutamic acid, 10.2 mmol benzyl alcohol (L-glutamic acid/benzyl alcohol molar ratio = 1:1.5) and 0.68 mmol $CuCl_2$ are loaded into a 50 ml single-port reaction flask, and the mixture is stirred at 60 °C for 2 h. After the reaction, the reaction mixture was cooled to be analyzed.

2.3. Characterization

All products were analyzed by the high performance liquid chromatograph (Beijing Purkinje General Instrument L6 equipped with UV and a 996 photodiode array detector, Microsorb-MV 100-5 C18 250 × 4.6 mm, volume ratio of methanol/water/acetic acid/acetonitrile = 39.9:39.9:0.2:20, 1 ml/min, 35 °C). Products were quantified according to the calibration curves. Retention times of γ-benzyl ester of glutamic acid, α-benzyl ester of glutamic acid and benzyl alcohol were 2.4 min, 3.1 min and 5.2 min, respectively.

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3. Results and discussion

3.1. Esterification of glutamic acid by benzyl alcohol promoted by different catalysts

In the present study, we used metal chloride, homogeneous organic acid and solid acids as catalyst to catalyze the synthesis of benzyl ester of L-glutamic acid. Results were shown in Fig. 1. When homogeneous CH_3SO_3H was used as catalyst, L-glutamic acid conversion can achieve 76.88%, but the yield and selectivity of γ-benzyl ester of L-glutamic acid only reached 44.44% and 57.81%. It is well known that CH_3SO_3H is capable of achieving selective and efficient esterification of L-glutamic acid in γ position, but the performance of CH_3SO_3H in this transformation is out of our expectation, which was attributed to the much less CH_3SO_3H usage. In CH_3SO_3H catalytic process, the necessary amount of alkanesulfonic acid to be added is at least 1 mol per mole of glutamic acid because the amine functional group needs to be neutralized [9], however, the amount of CH_3SO_3H used in this catalytic tests was only 10 mol% of glutamic acid amount. Importantly, benzyl alcohol undergoes benzaldehyde easily in the presence of strong organic acid, and α-benzyl ester of glutamic acid and diester diester dibenzyl 2-aminopentanedioate appeared simultaneously. In addition, racemization also occurs to give L or D derivatives at the same time [9].

The solid acids, such as phosphomolybdic acid, phosphotungstic acid and H_2SO_4/Al_2O_3, were used as catalysts, and the selectivity of γ-benzyl ester of L-glutamic acid came up to 100%, but low glutamic acid conversion was obtained. Among $FeCl_3$, $ZnCl_2$, $CoCl_2$, $CuCl_2$, $CrCl_3$, $BiCl_3$ and $SnCl_4$, $CuCl_2$ shows the best performance despite much less $CuCl_2$ was used, and the selectivity and yield of γ-benzyl ester of L-glutamic acid achieved 100% and 95.31%. The esterification activity of metal chloride catalysts is in the following order: $CuCl_2 > FeCl_3 > ZnCl_2 > CoCl_2 > BiCl_3 > SnCl_4 > CrCl_3$. When $CuCl_2$ and $FeCl_3$ were used as catalysts, benzyl alcohol does not undergo any side reactions.

3.2. Effect of temperature and solvent on esterification

Temperature plays a key role on esterification (see Fig. 2A). A better yield of γ-benzyl ester of glutamic acid achieved 77.58% even at 37 °C. This result is markedly improved if the choice is made to maintain the temperature at 60 °C which are not excessively high and low. High temperature deteriorates the yield and selectivity of γ-benzyl ester of glutamic acid.

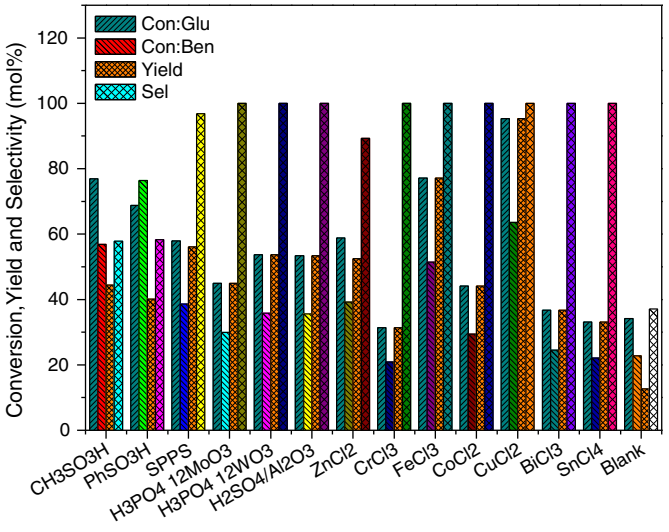


Fig. 1. Results of the esterification of benzyl alcohol and L-glutamic acid over different catalysts at 60 °C. (6.8 mmol L-glutamic acid, L-glutamic acid/benzyl alcohol molar ratio = 1:1.5, 2 h, solid catalyst 0.1 g, others 0.68 mmol, racemization was not detected).

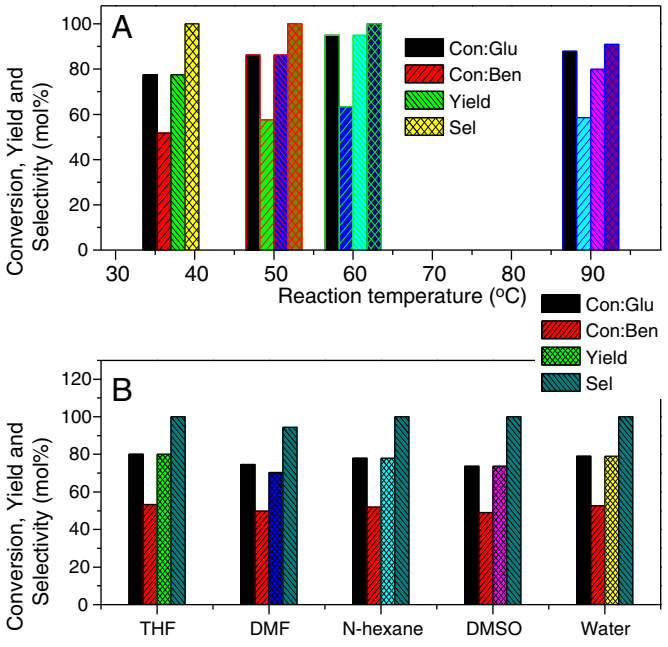


Fig. 2. A: Esterification of benzyl alcohol with L-glutamic acid at different temperatures over $CuCl_2$ catalyst (6.8 mmol L-glutamic acid, L-glutamic acid/benzyl alcohol molar ratio = 1:1.5, 2 h, 0.68 mmol $CuCl_2$, racemization was not detected). B: Esterification of benzyl alcohol and L-glutamic acid with different solvents over $CuCl_2$ at 60 °C (conditions: L-glutamic acid 6.8 mmol, 2 h, $CuCl_2$ 0.68 mmol, solvent 10 ml).

Usually, the solvents, which do not dissolve the γ-benzyl ester of L-glutamic acid, are very suitable, such as benzene, toluene, xylene and chlorobenzene. Herein, THF, DMF, n-hexane, DMSO and H_2O were loaded into the reaction system to allow better stirring of the medium (see Fig. 2B). When THF and n-hexane were used, γ-benzyl ester of L-glutamic acid yields achieved 80.00% and 77.91% under condition with distillation of the solvent/water azeotrope. If the reactions were carried out in DMF, DMSO and H_2O under condition without the removal of by-producing H_2O, γ-benzyl ester of L-glutamic acid yields still reach 70.39%, 73.64% and 78.99%, respectively, which indicated that H_2O has no effect on esterification of glutamic acid by benzyl alcohol in the presence of $CuCl_2$.

3.3. Effect of mole ratio of L-glutamic acid/benzyl alcohol on esterification

As the amount of benzyl alcohol increase, L-glutamic acid conversion and γ-benzyl ester of L-glutamic acid yield increased (see Fig. 3). When

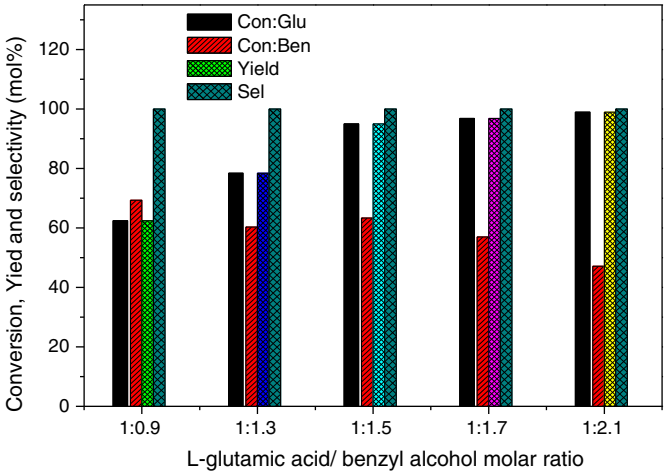


Fig. 3. Esterification of benzyl alcohol and L-glutamic acid at different L-glutamic acid/benzyl alcohol molar ratios (conditions: L-glutamic acid 6.8 mmol, 60 °C, 2 h, $CuCl_2$ 0.68 mmol).

Table 1
Effect of metal chloride on glutamic acid pH and solubility.

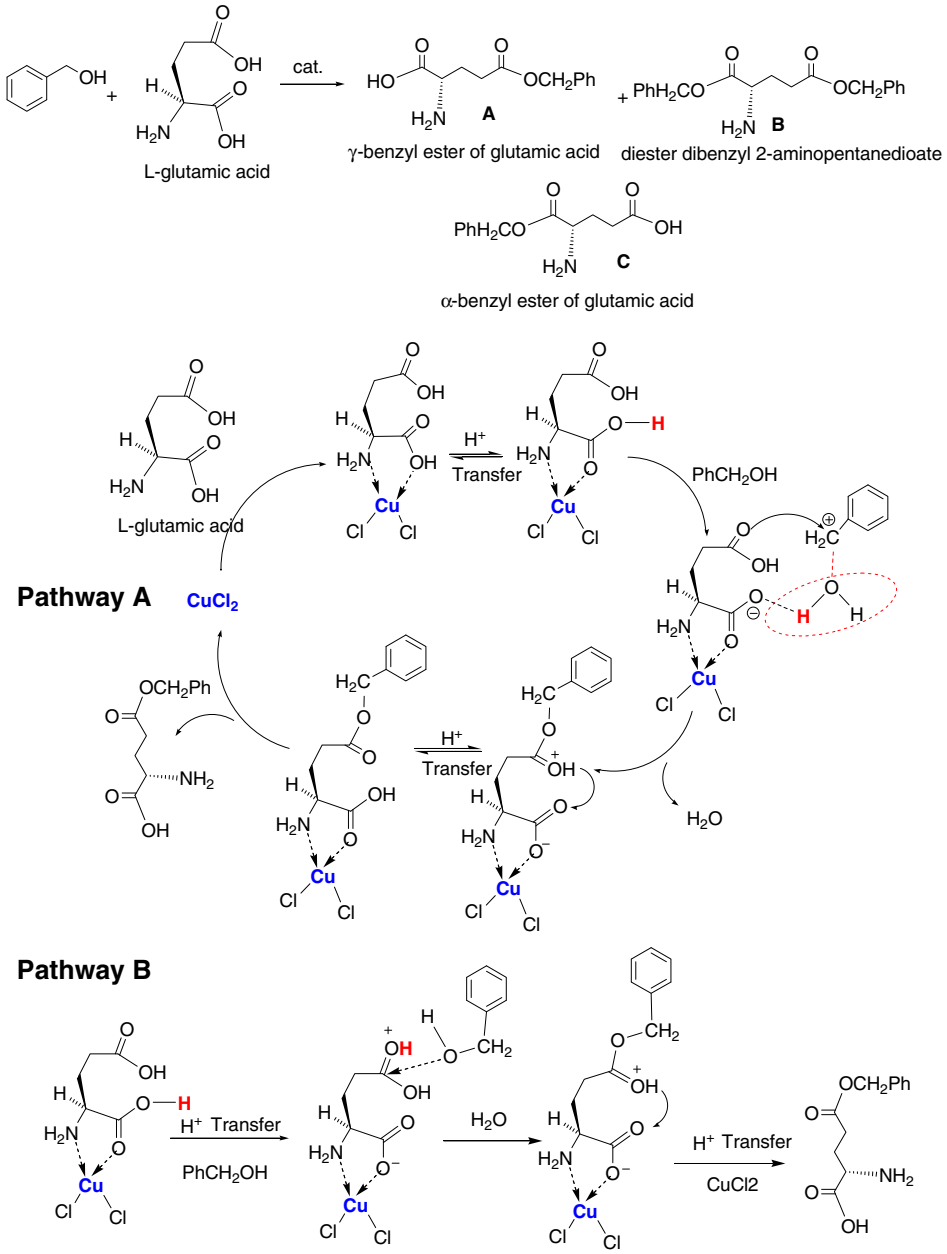
Sub.	Glu/H_2O	Glu/H_2O/$CuCl_2$	H_2O/$CuCl_2$	Glu/H_2O/$FeCl_3$	H_2O/$FeCl_3$	Glu/H_2O/$ZnCl_2$	H_2O/$ZnCl_2$
pH	3.23	2.1	3.8	1.64	1.55	2.9	4.23
Solubility	Precipitate	Dissolve	Dissolve	Dissolve	Dissolve	Precipitate	Dissolve

Condition: 6.8 mmol L-glutamic acid, 10 ml H_2O, metal chloride 1.15 mmol; effect of metal chloride on glutamic acid solubility property: 3.4 mmol L-glutamic acid, 45 ml H_2O, metal chloride 3.4 mmol.

L-glutamic acid/benzyl alcohol molar ratio is 1:2.1, γ-benzyl ester of L-glutamic acid yield achieved 98.93%. It is preferable to carry out the reaction with a slight excess of benzyl alcohol, and the side reactions and the appearance of undesirable by-products are thus avoided.

3.4. Esterification mechanism

In order to study the possible reaction mechanism, the effects of metal chloride on glutamic acid acidity (solution pH) and glutamic acid solubility property were investigated, and results were listed in Table 1. Glutamic acid is not only slightly soluble in water, but it is also soluble in metal chloride solution, such as $CuCl_2$, $FeCl_3$ and $ZnCl_2$. Most importantly, the existence of $CuCl_2$ greatly increased α position carboxyl acidity because of the metal cation coordination to the amino acids via neighboring amino and carbonyl groups [16]. The carboxyl group situated on a carbon in α position is the actual catalyst that initiates the esterification reaction, and the esterification of glutamic acid by benzyl alcohol takes place on γ position carboxyl group (see Scheme 1).



Scheme 1. The esterification of L-glutamic acid and benzyl alcohol, and the possible mechanism of esterification by Lewis acid.

On one hand, the proton transfer from α position carboxyl group to oxygen of benzyl alcohol increases the electrophilicity of the benzyl carbon which is then attacked by the nucleophilic carbonyl oxygen situated on a carbon in γ position to form an oxonium ion (Pathway A). On the other hand, the proton may transfer from α position carboxyl group to carbonyl oxygen in γ position through intramolecular H-bonding, and the nucleophilic addition of benzyl alcohol on the activated carboxylic moiety takes place to form an oxonium ion (Pathway B). After that proton fast transfers from oxonium ion to α position carbonate, and then the formed γ-benzyl ester of L-glutamic acid departs from $CuCl_2$ due to its high steric hindrance. In those processes the esterification reaction occurs without racemization because the chiral center of L-glutamic acid did not take part in the reaction. Most importantly, the esterification of L-glutamic acid by benzyl alcohol mainly undergoes the nucleophilic attack of the carboxylic moiety on the activated benzyl alcohol (Pathway A) rather than the more typical nucleophilic addition of benzyl alcohol on the activated carboxylic moiety (Pathway B) because this reaction only effectively works with benzylic alcohol. When CH_3OH or C_2H_5OH reacted with L-glutamic acid, nearly no γ-ethyl (or methyl) ester of glutamic acid was detected at 37 °C.

The reason for $ZnCl_2$ and $FeCl_3$ having lower activity than $CuCl_2$ was caused by the zero ligand field stabilized energy (LFSE) of Zn^{2+} ($3d^{10}4S^0$) and Fe^{3+} ($3d^5 4S^0$). The t_{2g} and e^*_g of Zn^{2+} and Fe^{3+} were full of and half full of electron, i.e., their LFSE was zero. Zero LFSE made metal cation to produce weaker combination with anions, i.e., Zn^{2+} and Fe^{3+} cannot well increased α position carboxyl acidity [25].

4. Conclusions

In summary, when mineral acids catalyzed the esterification of glutamic acid by benzyl alcohol, the necessary amount of homogeneous acid to be added is more than 1 mol per mole of glutamic acid, however, a little of $CuCl_2$ can promote the esterification of benzyl alcohol by glutamic acid even below 37 °C, and benzyl alcohol does not undergo any side reactions. Importantly, esterification of glutamic acid with benzyl alcohol catalyzed by some metal cation can take place in H_2O solvent, and the existence of H_2O has no effect on esterification.

Most importantly, benzyl alcohol is used in the soap, perfume, paint, lacquer and flavor industries, but it often result in toxic effects including respiratory failure, vasodilation, hypotension, convulsions and paralysis. However, the reasons for benzyl alcohol side effects on organism are undetected up to now. Glutamic acid plays an important role as general acids in enzyme active centers, as well as in maintaining the solubility and ionic character of proteins. Especially, glutamic acid is an important neurotransmitter in neuroscience that plays a key role in long-term potentiation and is important for learning and memory. Herein, we think that the esterification of glutamic acid by benzyl alcohol might take place to result in toxic effects on organism under the promoting of trace element.

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