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Letter

Catalytic reductive amination of α -ketocarboxylic acids as a useful route to amino acids

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Abstract

The reductive amination of α -ketocarboxylic acids using Raney nickel catalyst gave the desired amino acids in essentially quantitative yields. Both ammonia gas and aqueous ammonia as the aminating agents gave similarly high yields.

Keywords: Amino acid; Reductive amination; α -Ketocarboxylic acid; Phenylalanine, Raney nickel

1. Introduction

Amino acids are an important class of ingredients for the production of biologically active materials such as food additives and pharmaceuticals. Currently most amino acids are produced via three major routes [1]: (1) extraction from biological sources such as protein hydrolysates; (2) manufactured through fermentation [2]; (3) production from chemical processes such as the Strecker synthesis [3].

Since most amino acids are used as supplements in animal feedstock or for human consumption, there is always concern about the residue cyanide in the Strecker synthesis. Besides, handling HCN is also a hazardous operation which is not popular among chemical workers. From a practical standpoint, it is desirable to develop safer and economically more attractive processes for the production of amino acids.

In the development of commercially useful technologies, very frequently great success comes from the development of effective technologies to take advantage

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of new and/or economical feedstocks. In the late 1970's and early 1980's, there was a strong interest in the study of catalytic biscarbonylation of organic halides which gave α -ketocarboxylic acids in high yields [4,5].

The advancement of the catalytic biscarbonylation technology has created an opportunity for the production of the valuable α -ketocarboxylic acids at low cost. However, the technology was not commercially exploited because the demand for this type of material was not very high. In our opinion, if there is a simple method to convert the α -ketocarboxylic acids to high value, large volume chemicals such as amino acids, the economic potential of the combined technologies will be very high. To this end we initiated a study of the catalytic reductive amination of α -ketocarboxylic acids as an economical route to amino acids.

The reductive amination of α -ketocarboxylic acids with dihydrogen and ammonia has been previously studied by Fuenten and Schrage [6] and a 91% yield of phenylalanine lithium salt in the reductive amination of β -phenylpyruvic acid lithium salt using a palladium-on-carbon catalyst has been reported.

Phenylalanine is an important ingredient in the production of the popular artificial sweetener aspartame. In recent years, Toyo Soda in Japan and DSM in the Netherlands have joined forces to produce aspartame from DL-phenylalanine [7]. Therefore, an economical method for the production of DL-phenylalanine is of high commercial interest.

In this study we explored the possibility of developing an effective Raney nickel catalyst system for this type of reaction for the following reasons: (1) nickel-based catalysts are much more economical than noble metal catalysts (the cost of nickel is about 500 times lower than that of palladium); (2) the modification of Raney nickel catalysts with chiral materials such as tartaric acid has been reported to give effective asymmetric hydrogenation catalysts [8]. If the reductive amination of α -ketocarboxylic acid is successful, there is a possibility to further modify the system to achieve our ultimate goal of asymmetric reductive amination.

2. Experimental

2.1. General materials and procedures

Except as noted, all purchased materials were of reagent grade and were used as received. All standard operations were carried out in the absence of air. All solvents were freshly distilled under nitrogen atmosphere before use.

Reductive amination of β -phenylpyruvate with ammonia gas

A 100 ml stainless steel autoclave was charged with 0.2 g of a 50% aqueous slurry of Raney nickel, 2.5 g sodium β -phenylpyruvate monohydrate, 60 ml methanol, and about 10 g of ammonia. The mixture was stirred at 50°C under 200 psig H_2 for 24 h. Upon completion of the reaction, the gas was vented and the solution was decanted. The catalyst was washed with three portions of 50 ml of methanol. The filtrate and the washing were combined and the solvent was evaporated in a rotary evaporator. 1H and ^{13}C nuclear magnetic resonance (NMR) analyses of the residue indicated a quantitative yield of phenylalanine sodium salt.

Reductive amination of benzoylformic acid with aqueous ammonia

A 100 ml stainless steel autoclave was charged with 0.2 g of a 50% aqueous slurry of Raney nickel, 2.5 g benzoylformic acid, 60 ml methanol, and 20 ml of 37% aqueous ammonia. The mixture was stirred at 50°C under 200 psig H_2 for 24 h. Upon completion of the reaction, the gas was vented and the solution was decanted. The catalyst was washed with three portions of 50 ml of methanol. The filtrate and the washing were combined and the solvent was evaporated in a rotary evaporator. 1H and ^{13}C NMR analyses of the residue indicated a quantitative yield of phenylglycine.

3. Results and discussion

In our initial study we focused our attention on the reductive amination of β -phenylpyruvic acid because the phenylalanine product is of substantial commercial interest.

When a 50% water slurry of Raney nickel was used as catalyst, the reaction of β -phenylpyruvic acid with liquid ammonia and dihydrogen in methanol solvent was found to be very smooth. At 50°C and 200 psig operating pressure, an essentially quantitative yield of phenylalanine was obtained. The high yield in this reaction was somewhat surprising in light of the fact that β -phenylpyruvic acid itself is not a very stable compound. The decomposition of β -phenylpyruvic acid under relatively mild conditions to give benzaldehyde has been previously observed [9]. The high yield in the Raney nickel-catalyzed reductive amination was probably due to the rapid trapping of the β -phenylpyruvic acid by ammonia which alleviated the problem of the decomposition of the keto acid. This finding was extremely encouraging since both the cost of the catalyst and the operating conditions are easily manageable in an industrial setting. Under more severe conditions (90°C, 850 psig H_2), some of the β -phenylpyruvic acid (starting material) was hydrogenated to give β -phenyllactic acid (Table 1).

The reductive amination of β -phenylpyruvic acid was also achieved by using aqueous ammonia instead of ammonia gas. Equally high (essentially quantitative) yields of the phenylalanine product were obtained under similar conditions (50°C,

Table 1

Raney nickel-catalyzed reductive amination of sodium β -phenylpyruvate^{a,b}

Raney Ni ^c (g slurry)	NaPPA (g)	Temp (°C)	P_{H_2} (psig)	Time (h)	Conv. (%)	Selectivity (%)
0.2	2.5	50	200	1.5	70	> 98
0.2	2.5	50	200	20	100	> 98
2.5	5.0	90	850	3	100	70 ^d

^a The reactions were carried out in about 60 ml methanol.^b About 10 g of liquid ammonia was used in each experiment.^c The Raney nickel was purchased from Aldrich as a 50% aqueous slurry and was used as received.^d The byproduct in this reaction was sodium β -phenyllactate.

Table 2

Raney nickel-catalyzed reductive amination of α -keto acids

α -Keto acid	Source of NH ₃	Conversion (%)	Selectivity (%)
NaPPA	37% NH ₄ OH	100	> 98
<i>p</i> -HO-PPA	37% NH ₄ OH	100	> 98
Pyruvic acid	37% NH ₄ OH	100	97
Benzoylformic acid	37% NH ₄ OH	100	> 98

Reaction conditions: 0.2 g 50% aqueous slurry of Raney nickel; 2.5 g substrate; 60 ml methanol (solvent); 15 g 37% aqueous ammonia; 200 psig H₂; 50°C; 20 h.

200 psig H₂). The simplification of the experiment by using aqueous ammonia has made this method more appealing to most synthetic chemists and consequently the synthesis should be of wider application.

After our success in the reductive amination of β -phenylpyruvic acid, it became clear to us that the synthetic method may be of wider use and a variety of high value amino acids may be produced via this simple and economical route. To test the scope of this chemistry, we also carried out the reductive amination of a wide range of keto acids including β -4-hydroxyphenylpyruvic acid, benzoylformic acid, pyruvic acid, etc. All of these reactions have been demonstrated to be highly efficient, indicating the wide applicability of this synthetic methodology. Details of the results are summarized in Table 2.

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