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New method for preparation of D-valine

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Abstract: A method for preparing D-valine from L-valine by racemization and chemical resolution is presented. The resolving reagent, D-2, 3-dibenzoyl tartaric acid was obtained by hydrolyzation of D-2, 3-dibenzoyl tartaric anhydride prepared by reaction of benzoyl chloride with D-tartaric acid. DL-valine was prepared by racemization of L-valine in the presence of aldehyde in a medium of acetic acid at 100 to 110 ℃ for 3 h. In the presence of mineral acid, reaction of D-2, 3-dibenzoyl tartaric acid with DL-valine formed diastreroisomeric salts at 84 to 95 ℃. Salt composed of D-2, 3-dibenzoyl tartaric acid and D-valine precipitated when the diastreroisomeric salts mixtures were cooled to 15 ℃. The salt was reacted with base giving D-valine with yield of 70% to 80% and optical purity of over 98%.

Key words: L-valine; racemization; chemical resolution; D-valine

D-valine is a significant chiral compound and has been widely used as an intermediate in the syntheses of drugs and agricultural pesticides including antitumor drugs, the compounds of diarylborinic amino acid[1] and novel pesticides of pyrethroidesters[2]. Its diiodophthaloyl derivatives have antimicrobial activities[3], and its derivatives of penicillamine are drugs for the treatment of immune-deficiency diseases, especially for AIDS[4].

Some studies about the preparation of D-valine have been reported, including induced crystallization[5], chemical resolution[6,7], microbial asymmetric conversion[8] and stereo asymmetric synthesis[9]. The induced crystallization is not adaptable to industrial production of D-valine because the production cycle is too long and the optical purity and yield of the product are low. Chiral auxiliary are too costly in stereo asymmetric synthesis. The microbial asymmetric conversion is carried out in a multienzyme system produced from microbes. In the system, DL-5-isopropylhydantoin can be converted directly to D-valine. In this method, fatal hydrocyanic acid is needed to prepare the starting material DL-5-isopropylhydantoin, and also yield of DL-5-isopropylhydantoin is not high. Chemical resolution is an important method of preparation of D-amino acids and other chiral compounds. There are a few reports on the preparation of D-valine by the method. In 1934, Holmes[6] let L-menthoxyacetyl chloride react with DL-valine to form the diastereoisomeric amide. By fractional crystallization, the two pure diastereoisomers were obtained. D- and L-valine were obtained by hydrolysis of the two pure diastereoisomers in aqueous alcohol with hydrobromic acid, respectively. The resolving process was complex and the yield and optical purity of the product were not reported. In 1984, Shiraiwa[7] described a process of resolving DL-valine via formation of adduct with L-phenylalanine. When an alkaline solution containing L-phenylalanine and DL-valine was adjusted to pH 5.5 with hydrochloric acid, the adduct of L-phenylalanine and D-valine precipitated selectively. Aqueous solution of the adduct was treated with active carbon to remove L-phenylalanine and gave D-valine with optical purity of 84.5% to 100% and yield of 24.5% to 31.5% on the base of DL-valine. Therefore, searching for new resolution reagents in resolving DL-valine is valuable.

We investigated the process of preparing D-valine by racemizing L-valine and resolving the racemate with new resolving reagent. First, racemization of L-valine and preparation of the resolving reagent were studied and optimized. Then, the possibility of resolving DL-valine by the resolving reagent was studied and the resolving condition was optimized. In order for the salts of D- and L-valine to form more easily with the resolving reagent crystallize, D-2, 3-dibenzoyl tartaric acid (D-DBTA) was selected as the resolving reagent. The results show that D-DBTA can form diastereoisomeric salts with D-valine and L-valine, respectively. The solubility of the diastereoisomeric salts formed from D- and L-valine is remarkably different in aqueous solution, and they can be separated easily by filtration. D-valine can be obtained by reaction of the diastereoisomeric salt with alkali. To our knowledge, this is the first report on preparation of D-valine by resolving DL-valine with D-DBTA up to the present.

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1 Experimental

1.1 Synthesis of D-DBTA

15 g of D-tartaric acid and 45 g of benzoyl chloride were placed in a three-necked flask equipped with a reflux condenser, mechanical stirrer and a long-stem thermometer. The mixture was stirred at 140 to 150 ℃ for 2 h. To the mixture, 100 mL of benzene was added and then stirred for 15 min. Then, the mixture was cooled, filtered, washed with benzene and dried. The obtained solid was dissolved in 65% aqueous acetone. The mixture was boiled under reflex for 2 h, and then evaporated to dryness *in vacuo*. The residue was taken up with 1 mol/L hydrochloric acid and stirred for a few minutes. 29.5 g of D-DBTA was obtained after being filtered and washed with water. The yield is 82.4% on the basis of D-tartaric acid (m.p. 86 to 88 ℃, $[\alpha]_D^{25} = +87.5$ (c = 1, alcohol)).

1.2 Racemization of L-valine

Four drops of salicylic aldehyde were added to a solution of 4 g of L-valine in 20 mL of acetic acid. The mixture was stirred at 100 to 110 ℃ for 3 h and then evaporated to dryness *in vacuo*. The residue was dissolved in 30 mL of aqueous ethanol and the solution was stirred for a few minutes. 3.23 g of the white powder was obtained after being filtered, washed with ethanol and dried. The yield of product was 80.8% (m.p.295 to 297 ℃, $[\alpha]_D^{25} = 0$ (c = 1, 6 mol/L HCl)).

1.3 Preparation of D-valine by resolution

3.76 g of D-DBTA was added to a solution of 2.34 g of DL-valine in 20 mL of hydrochloric acid. The mixture was stirred at 95 ℃ for 50 min, and then cooled to 15 ℃ and filtered. The obtained precipitate was dissolved in 30 mL of ethanol and 2 equimolar amounts of triethylamine. The mixture was stirred at room temperature for 1 h. The formed precipitate was filtered and washed with ethanol. 0.94 g of D-valine was obtained. Resolving yield (on the basis of D-valine in DL-valine): 80.3%, $[\alpha]_D^{20} = -28.75$ (c = 1, 5 mol/L HCl) ($[\alpha]_D^{20} = -28.8$ (c = 1, 5 mol/L HCl)[10]). The resolving mother liquor was concentrated and adjusted to pH 5.5 with triethylamine. The formed precipitate was collected by filtration and washed with ethanol. 0.83 g of L-valine was obtained in 71.0% of yield (on the basis of L-valine in DL-valine). $[\alpha]_D^{20} = +27.5$ (c = 1, 6 mol/L HCl) ($[\alpha]_D^{20} = +27.6$ (c = 1, 6 mol/L HCl)[10]).

2 Results and Discussions

2.1 Synthesis of D-DBTA

Synthesis of D-DBTA is carried out by two steps. First, reaction of benzoyl chloride with D-tartaric acid forms D-2, 3-dibenzoyl tartaric anhydride. Then, the anhydride is hydrolyzed giving D-DBTA. Reaction temperature is very important for the preparation of D-2, 3-dibenzoyl tartaric anhydride. If the temperature is lower than 140 ℃, D-tartaric acid cannot entirely convert into D-2, 3-dibenzoyl tartaric anhydride. If the temperature is over 150 ℃, some by-products form and carbonization of the compounds occurs.

2.2 Racemization of L-valine

The influence of temperature, catalyst and solvent on the racemization was studied. It showed that the racemization rate was markedly promoted by temperature when the temperature is at 90 to 110 ℃. When reaction temperature is over 110 ℃, yield of DL-valine falls due to decomposition of the valine. Salicylaldehyde, benzaldehyde and *n*-butanal can catalyze the racemization of L-valine. The rate of racemization of L-valine in the presence of salicylaldehyde is higher than the other two catalysts. Formic acid, acetic acid and propionic acid can be used as a solvent for racemization. The racemization rate may depend on the protonation and proton abstraction of the Schiff base formed by valine and aldehydes. From the dissociation constants of the aliphatic acids, the order of protonation should be formic acid > acetic acid > propionic acid while the order of proton abstraction is propionic acid > acetic acid > formic acid. The overall reaction rate may be the highest in acetic acid[11]. This is in accordance with the experimental result. Furthermore, when propionic acid served as the solvent, L-valine could not be dissolved completely, the degree of racemization was lower than with the other two solvents.

2.3 Preparation of D-valine by resolution

D-DBTA and L-DBTA can be used for resolving of DL-valine. When D-DBTA was used as a resolving reagent, the salt D-valine D-2, 3-dibenzoyl tartrate first precipitated from the solution because of its lower solubility in the cold acidic aqueous solution. The salt was neutralized with a base, and D-valine was obtained. The mother liquor of the resolution was concentrated and adjusted to pH 5.5 with the base,

and L-valine was obtained. The yield and optical purity of D-valine were 80% and 98%, respectively. Those of L-valine were 70% and 98%.

Solvents and temperature can affect the resolving result. The effect of the solvent on the resolution of DL-valine shows that water is a better resolving solvent than others. The effect of temperature is shown in Tab.1. From Tab.1, it can be seen that the optical purity of D-valine increases and reaches its maximum with the increase of temperature at 84 to 90 ℃. When the temperature is higher than 90 ℃, the yield of D-valine reduces slowly due to hydrolysis of D-DBTA.

Tab.1 Effect of temperature on the resolution of DL-valine

Reaction temperature/℃	Reaction time/min	Specific rotation	Optical purity*/%	Yield/%
84	50	−22.50	78.13	82.05
86	50	−22.50	78.13	82.05
88	50	−25.00	86.81	78.63
90	50	−28.75	99.83	80.34
92	40	−28.75	99.83	76.07
95	40	−28.75	99.83	71.79

Note: * The optical purity of the obtained D-valine was estimated on the basis of the specific rotation ($[\alpha]_D^{20} = -28.8$, $c = 1.5$ mol/L HCl)[10].

3 Conclusion

The above results indicate that the method of preparing D-valine by racemization of L-valine and chemical resolution of DL-valine using D-DBTA as the resolving reagent is accessible. The method can be potentially employed in commercial production.

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一种制备 D-缬氨酸的新方法

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摘要: 介绍了 L-缬氨酸经消旋化及化学拆分制备 D-缬氨酸的方法. 苯甲酰氯和 D-酒石酸反应生成 D-2, 3-二苯甲酰酒石酸酐, 后者于丙酮水溶液中水解得到拆分剂 D-2, 3-二苯甲酰酒石酸. 在醛的催化下, L-缬氨酸于 100 ~ 110 ℃ 消旋化 3 h 得到 DL-缬氨酸. DL-缬氨酸在无机酸存在下与 D-2, 3-二苯甲酰酒石酸于 84 ~ 95 ℃反应生成非对映体盐. 当温度降低至 15℃, D-2, 3-二苯甲酰酒石酸和 D-缬氨酸形成的盐沉淀出来, 用碱处理该盐后得到 D-缬氨酸, 收率为 70% ~ 80%, 光学纯度达到 98% 以上.

关键词: L-缬氨酸; 消旋化; 化学拆分; D-缬氨酸

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