Chinese Chemical Letters Vol. 15, No. 4, pp 411-412, 2004
http://www.imm.ac.cn/journal/ccl.html

Preparation of D-Phenylalanine by Asymmetric Transformation

Ben Mei WEI, Li Jian JIANG*, Ying Ping ZHENG, Hai Qing XU

Department of Chemistry and Chemical Industry, Southeast University, Nanjing 210096

Abstract: The method of preparing D-phenylalanine by asymmetric transformation is reported. D-phenylalanine was prepared from DL-phenylalanine by two-step reaction. D-phenylalanine (2S, 3S)-tartrate was prepared by heating DL-phenylalanine, salicylaldehyde, and (2S, 3S)-tartaric acid in propionic acid; the obtained D-phenylalanine (2S, 3S)-tartrate was treated with triethylamine in ethanol giving D-phenylalanine with 98% optical purity in 69% yield.

Keywords: D-Phenylalanine, DL-phenylalanine, asymmetric transformation.

D-Phenylalanine has been widely applied in the pharmaceutical field such as an analgesic[1], an antistress agent[2] *etc*. It can also be used for treatment of melancholia and diabetes[3].

There are a few reports on preparation of D-phenylalanine. For example, biological processes such as the enzymic hydrolysis of benzylhydantoins[4], biological synthesis in a multienzyme system[5] using phenylpyruvic acid as starting material, the microbial degradation of DL-phenylalanine[6] or N–acyl-DL-phenylalanine[7], the stereocontrolled synthesis[8] and the chemical resolution of DL-phenylalanine[9] have been studied. However, the total yield of these methods is lower than 40%. Therefore, it is necessary to study the method of preparing D-phenylalanine to increase the yield.

A new method, so-called asymmetric transformation was utilized in the preparation of optical active amino acids. By this new method both optical purity and yield of the amino acids are high. Shiraiwa *et al.* have reported the preparation of D-histidine[10] and D-proline[11] by asymmetric transformation, the yields of D-histidine and D-proline are 95% and 85% respectively, and the optical purity is about 100%. Maryanoff[12] *et al.* have reported a second order asymmetric transformation of racemic 4-chlorophenyl- alanine methyl ester *via* salt formation with (2S, 3S)-tartaric acid in the presence of salicylaldehyde, the yield of 4-chlorophenylalanine methyl ester is 68%, and the optical purity is 98%. But so far as we know, there is no report on the preparation of D-phenylalanine by asymmetric transformation method.

On the base of the solubility and the racemization of L-phenylalanine[13], we studied possibility of the preparation of D-phenylalanine by asymmetric transformation method and have optimized the condition of asymmetric transformation from DL-phenylalanine to D-phenylalanine in the presence of (2S, 3S)-tartaric acid and salicylaldehyde in propionic

* E-mail:ljjiang@jlonline.com

acid.

A mixture of DL-phenylalanine (6.60 g, 0.04 mol), (2S, 3S)-tartaric acid (6.00 g, 0.04 mol), and 0.001 mol salicylaldehyde in 100 mL propionic acid was stirred at 80°C for 8 h. After that, and the mixture were cooled to 10°C in an ice bath and filtrated, washed thoroughly with diethyl ether or acetone and dried. D-Phenylalanine (2S, 3S)-tartrate (10.88 g, 86.3%) was obtained. m.p. 158-160°C, Anal. Calcd. for $C_{13}H_{17}NO_8$: C 49.52, H 5.44, N 4.46%. Found: C 49.36, H 5.72, N 4.29%. IR (KBr, cm^{-1}): 3411.5(O-H), 3066.3(C-H), 1724.1(COOH), 1695.6(COOH), 1629.6(NH), 1595.1(COO^-), 1310.0. ^1H NMR δ(D_2O, ppm), 3.01 (dd, 1H, J=7.8, 14.5Hz), 3.17 (dd, 1H, J=5.3, 14.5Hz), 4.02 (dd, 1H, J=5.3, 7.8Hz), 4.61 (s, 2H), 7.34-7.25 (m, 5H).

Mixture of D-phenylalanine (2S, 3S)-tartrate (12.6 g, 0.04 mol) and triethylamine (11.1 mL, 0.08 mol) in ethanol was stirred at room temperature for 1 h. After being filtrated, washed with ethanol and dried, D-phenylalanine was obtained (5.29 g, 80.1%). m.p. 280-283°C, $[\alpha]_D^{25}$+33.8(c 1.0, H_2O) ($[\alpha]_D^{25}$+34.5, lit.[14]). IR (KBr, cm^{-1}): 3066.3(C-H), 1619.9(NH), 1589.1(COO^-), 1035.6, 852.4, 698.1.

The yield of D-phenylalanine on the basis of DL-phenylalanine is 69%.

References

1. S. Ehrenpreis, R. C. Balagot, J. Greenberg, S. Myles, F. Ellyin, *Degrad. Endog. Opioids: Its Relevance Hum. Pathol. Ther.*, **1983**, 117.
2. R. Irmgard, O. Peter, G. Renate, B. Sylvia, G. Erhard, W. Arthur, Germany(East) Patent 229931(1985), *Chem. Abstr.*, **1986**, *105*, 108512u.
3. N. Shimura, Japanese Patent 02131422(1990), *Chem. Abstr.*, **1990**, *113*, 109345u.
4. K. Yokozeki, K. Kubota, *Agric. Biol. Chem.*, **1987**, *51*(3), 721.
5. H. S. Bae, S. G. Lee, S. P. Hong *et al*., *J. Mol. Catal. B: Enzym.*, **1999**, *6*, 241.
6. O. Ikumasa, Y. Kenzo, Japanese Patent 2001 224395(2001), *Chem. Abstr.*, **2001**, *135*, 151713s.
7. M. Shoichiro, N. Kazunari, N. Kiyoteru, M. Toru, Japanese Patent 6391097(1988), *Chem. Abstr.*, **1989**, *110*, 37788d.
8. Y. Z. Jiang, G. L. Liu, C. Y. Zhou *et al.*, *Synth. Commun.*, **1991**, *21*(8-9), 1087.
9. W. Hans, T. H. Wolter, European Patent 180276(1986), *Chem. Abstr*., **1986**, *105*, 134150u.
10. T. Shiraiwa, K. Shinjo, Y. Masui *et al.*, *Bull. Chem. Soc. Jpn.*, **1991**, *64*, 3741.
11. T. Shiraiwa, K. Shinjo, H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **1991**, *64*(11), 3251.
12. C. A. Maryanoff, L. Scott, R. D. Shah, F. J. Villani Jr., *Tetrahedron: Asymmetry*, **1998**, *9*, 3247.
13. S. Yamada, C. Hongo, R. Yoshika, I. Chibata, *J. Org. Chem.*, **1983,** *48*, 843.
14. J. Buckingham *et al.*, *Dictionary of Organic compounds-5 th ed.*, **1982**, 4592.

Received 30 June, 2003