Chinese Chemical Letters Vol. 13, No. 2, pp 117 – 118, 2002
http://www.imm.ac.cn/journal/ccl.html

Efficient Synthesis of 3-N-Phthaloyl Homophenylalanine Lactone

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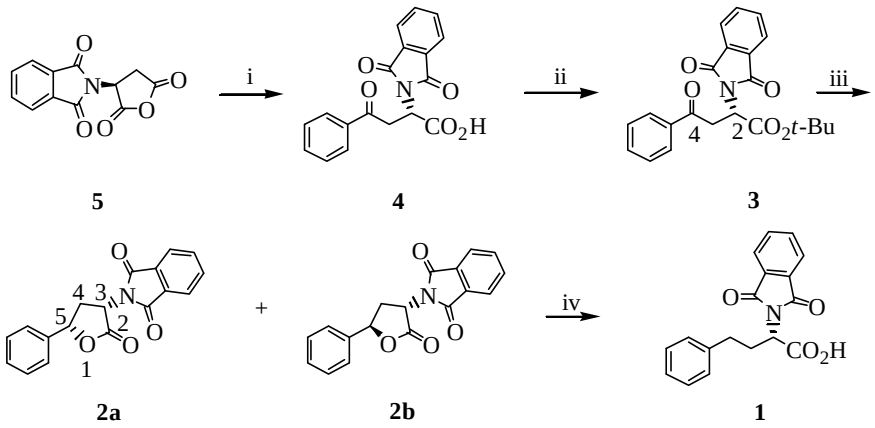
Abstract: A new method for the synthesis of 3-N-phthaloyl homophenylalanine lactone has been developed and its mechanism was proposed

Keywords: Homophenylalanine, diastereomeric, stereochemical hindrance.

-Amino acids take an important role in biology because many of them are the precursors for a variety of biological active compounds[1,2]. Among them L-(+)-homophenylalanine [L-(+)-HPA] has received great attention due to its pharmaceutical interest as a component of angiotension converting enzyme (ACE) inhibitors. During the synthesis of L-(-)-HPA[3], we need to hydrogenolyze compound **3** to prepare **1** with Pd/C and hydrochloric acid in tetrohydrofuran. However, we obtain compound **2a** and **2b**[4] with high yield. After a more detailed study, we found that this reaction can be a general and efficient way for synthesis of 5-phenyl lactone. Herein we report this useful reaction.

Scheme 1



Reagents and conditions: i) $AlCl_3$, Benzene, 50°C; ii) DCC, *t*-BuOH, CH_2Cl_2; iii) and iv) Pd/C, H_2, hydrochloric acid, THF.

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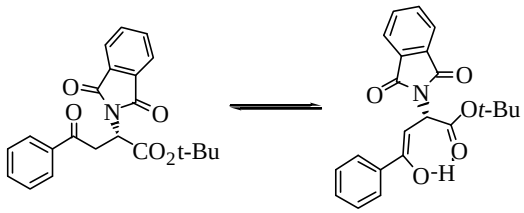
The synthetic route for compound **1** is summerized in **Scheme 1**. We used N-phthaloyl-(L)-aspartic anhydride **5** as starting material which was prepared according to literature[5]. Friedel-Crafts acylation of **5** afforded compound **4** in 80% yield. Treatment of **4** with DCC and *t*-BuOH in CH_2Cl_2 afforded compound **3**. Hydrogenation of **3** with Pd/C in THF and HCl afforded a pair of diastereomeric products **2a** (3S, 5S) and **2b** (3S, 5R) over 90% yield (de: 23.6%, **2a** > **2b**, ^{1}H-NMR). The stereochemistry of C-5 in **2a** and **2b** was determined by ^{1}H-NMR. The chemical shift of C-5 proton in **2b** is 5.90 ppm, which shifts to down field, comparing with that in **2a** (5.47 ppm). The reason is that H-5 in **2b** is desheilded by N-phthlyol group. When hydrogenation of methyl ester of **4** in the same condition as above, only 4-oxo converted into 4-ol in 90% yield, no cyclic ester was found, subsequent hydrogenation of this alcohol afforded methyl ester of compound **1**. From above results we can conclud that hydrogenation of the -carbonyl group of aromatic ring forms benzyl alcohol firstly, then the benzyl alcohol is dehydronated by catalytic hydrogenation. In the acid solution, *t*-butyl ester is unstable and more favorable to form five-membered cyclic ester, in contrast, the methyl ester is stable and difficult to convert into lactone.

The stereochemistry of C-5 may be explained by the mechanism, shown in **Scheme 2**. In the presence of acid, **3** existed in enolized form **6**. The formation of hydrogen bonding between the OH group and carbonyl group made **6** in ring form conformation. Owing to the stereochemical hindrance of bulky N-phthaloyl group, hydrogen atom is more favored to attack from the top of the ring to form **2a**.

Scheme 2



3 **6**

References and Notes

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3. Q. Y. Xu, G. Wang, X. C. Wang, T. X. Wu, X. F. Pan, *Tetra. Asy.*, **2000**, *11*, 2309.
4. **2a** ^{1}H-NMR (200MHz, $CDCl_3$), δ ppm: 2.65-3.14 (m, 2H, H-4), 5.27 (dd, 1H, *J* = 11.8 Hz, 9.2 Hz, H-3), 5.47 (dd, 1H, *J* = 10.4 Hz, 6.4 Hz, H-5), 7.27 - 7.53 (m, 5H, Ar-H), 7.74 - 7.91 (m, 4H, Ar-H). **2b** 2.65 - 3.14 (m, 2H, H-4), 5.12 (t, 1H, *J* = 9.6Hz, H-3), 5.90 (dd, 1H, *J* = 11.8 Hz, 8.4 Hz, H-5), 7.27 - 7.53 (m, 5H, Ar-H), 7.74 - 7.91 (m, 4H, Ar-H). **2a**+**2b** MS (HS): *m*/*z* 307, 245, 174, 148, 116. **2a**+**2b** IR (KBr, cm^{-1}): 3065, 1776, 1714, 1498, 1461, 1396.
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Received 4 June, 2001