Chinese Chemical Letters Vol. 15, No. 12, pp 1395-1396, 2004
http://www.imm.ac.cn/journal/ccl.html

Study on the Stereoselective Synthesis of Carbapenem Sidechain (2S,4S)-4-Acetylsulphanyl-2- [(S)-1-phenylethylcarbamoyl]–pyrrolidine-1-carboxylic Acid 4-Nitrobenzyl Ester

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Abstract: A stereoselective and economic synthesis of the carbapenem sidechain (2S, 4S)-4-ace-tylsulphanyl-2- [(S) 1-phenylethyl-carbamoyl] pyrrolidine-1-carboxylic acid 4-nitrobenzyl ester was developed. Due to the effect of spatial hindrance, only the (2S,4S) diastereomer **3** was obtained by coupling **1** and the inexpensive racemic **2** catalyzed by EEDQ.

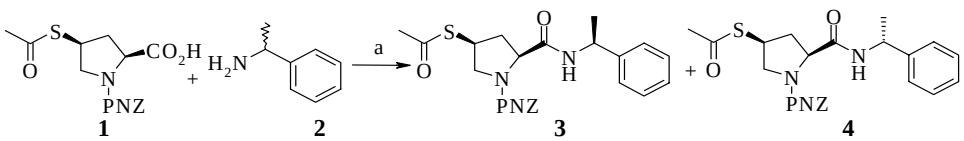
Keywords: Stereoselective synthesis, carbapenem sidechain, acylation.

Since the first 1ß-methylcarbapenem thienamycin was found by a research group at Merck as a synthetic carbapenem antibiotic, which shows increased chemical and metabolic stability in addition to excellent antibacterial activity and broad antibacterial spectrum[1], much work has been devoted on the synthesis of (2S,4S)-2-substituted 4-mercaptopyrrolidine derivatives employed as important sidechains of carbapenems.

As shown in **Scheme 1**, we report here the stereoselective synthesis of (2S,4S)-4-acetylsulphanyl-2-[1-phenyl-(1'S) ethylcarbamoyl] pyrrolidine-1-carboxylic acid 4-nitrobenzylester **3**. In theory, coupling of **1**[2] and **2** can afford two compounds **3**[3] and **4** catalyzed by N-carbethoxy-2-ethoxy-1, 2-dihydroquinoline(EEDQ). In fact, we accomplished the reaction in yield 41% based on **1** and the ^{1}H-NMR data showed that only one diastereomer was got from the reaction.

In order to understand the reaction mechanism and determine the configuration of the diastereomer, two reactions were designed: compound **1** reacted with optically pure compound **5** and **6** to afford **3** and **4,** respectively (in **Scheme 2**). As a result, it was found that under the same reaction condition, compound **3** was obtained in yield 84%

Scheme 1



1 **2** **3** **4**

Reagents and conditions: a. EEDQ, toluene, r.t. 41%.

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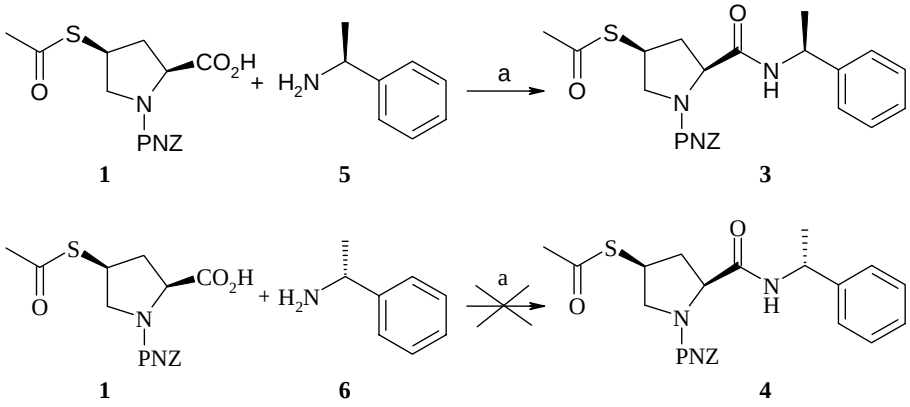
while compound **4** was not obtained. The electronic effect of compounds **5** and **6** in the reactions is the same, the only influence factor is the different spatial hindrance of **5** and **6** in this reaction. From the three reactions, we concluded that in the **Scheme 1** the only one product should be compound **3**, namely (2S, 4S)-4-acetylsulphanyl-2-[1-phenyl-(1'S)-ethylcarbamoyl]–pyrrolidine-1-carboxylic acid 4-nitrobenzyl ester. Therefore, **3** could be obtained from **1** and racemic **2** in one step without resolution.

In summary, we developed a simple way to synthesize the optically pure compound **3**.

Scheme 2



Reagents and conditions: a. EEDQ, toluene, r.t.

References and Notes

1. D. H.Shih, F.Baker, L.Cama *et al*., *Heterocycles*, **1984**, *21*, 29.
2. S. Makoto, M. Haruki, I. Takaaki *et al*., US5122604, 1990-05-21.
3. Data of compound **3**: ^{1}H NMR (300MHz, DMSO-d_6, δ ppm): 1.33-1.36(d, 3H, J=7.2Hz), 1.68-1.75(m, 1H), 2.30(s, 3H), 2.63-2.71(m, 1H), 3.17-3.30(m, 1H), 3.87-4.03(m, 2H), 4.25-4.40(m, 1H), 4.86-4.92(q, 1H, J=7.2Hz), 5.16-5.22(m, 2H), 7.16-7.28(m, 5H), 7.55-8.19(m, 4H). MS (FAB, *m/z*): 472(M+H$^+$), 293(9), 247(12), 105(100).

Received 28 October, 2003