VERSATILE SYNTHESIS OF AN INTERMEDIATE FOR THE 1β-METHYLCARBAPENEM SYNTHESIS

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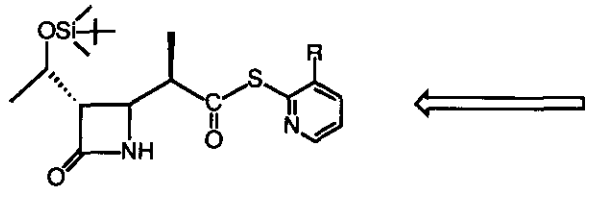
Abstract- A 1β-Methylcarboxylate (1) which is a requisite intermediate for the synthesis of the 1β-methylcarbapenem was obtained in an efficient manner by the coupling reaction of a Z(O)-pyridylthiosilyl enol ether and a 4-acetoxyazetidinone derivative in the presence of $ZnCl_2$ in CH_2Cl_2. The reactive silyl enol ether was prepared by the *reverse addition* method in high yield.

On the basis of molecular structure alone, the carbapenem antibiotics, *i.e.* thienamycin has allured considerable interest from several laboratories towards the synthesis of this interesting molecule.[1] Furthermore a recent report about the stability of the 1β-methylcarbapenem molecule toward DHP-1 has prompted these laboratories to synthesize the more complicated , 1β-carbapenem molecule.[2]

The study on the carbapenem project in our laboratories successfully developed a method for the construction of the carbapenem skeleton by a trialkylphosphite coupling method using oxalyl amide derivative.[3] In the light of this accomplishment we have chosen compound (1) as a suitable candidate for the synthesis of 1β-methylcarbapenem antibiotics. There are several methods of utilizing boron[4] or tin[5] enolate to achieve a highly diastereoselective aldol reaction but we opted to adhere to the conventional way of using a silyl enol ether coupling method as the synthetic strategy.

Scheme 1.



4-Acetoxyazetidinone derivative

•

Pyridylthiosilyl enol ether derivative

1 a: R=H, b: R=CH_3

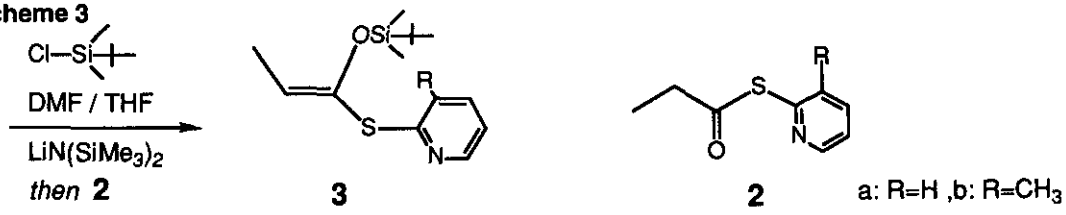
In 1988 a Bristol-Myers group reported on the 1β-methylcarbapenem intermediate synthesis by the coupling method using silyl enol ether of pyridylmethylthiol ester of propionic acid.[6] Their method based on the chelation effect incited us to prepare the reactive pyridylthiosilyl enol ether by employing a modified synthetic method, however what sort of modification would be required remained to be the problem. Indeed the conventional method to prepare our desired pyridylthiosilyl enol ether gave a very low yield along with other side products due to the inherent propensity of the pyridylthio moiety to behave as a leaving group as depicted in Scheme 2.

Scheme 2

2

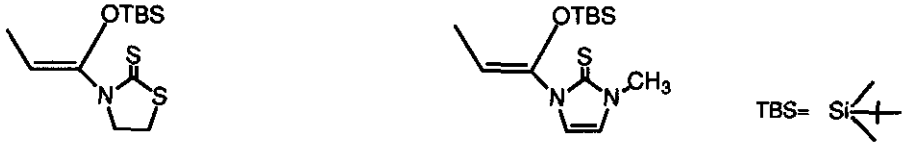
To prevent this side reaction we performed this silyl enol ether formation reaction by the *reverse addition*[7] as follows: To a stirring solution of hexamethyldisilazane(7.5 ml) in THF(50 ml) was added 22.5 ml(1.2 *eq.*) of *n*-butyllithium, 1.6 M solution in hexane at room temperature and after 30 min the solution was cooled to -78 °C . To this cooled solution was added (1.2~2 *eq.*) of DMF, 8.37 ml(2 *eq.*) of triethylamine , 9.01 g(2 *eq.*) of *t*-butyldimethylsilyl chloride (TBSCl) followed by 5 g of 2-pyridylthiopropiolate (**2a**) in 10 ml THF solution. After stirring for 10~20 min (tlc monitored) ethyl acetate was added and the organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent the residue was purified by rapid elution through a silica gel column or by distillation (*bp* 130°C/0.1 mmHg for **3 a**) to give 8.6 g of the desired silyl enol ether. 270 MHz ^{1}H-nmr revealed approximately a 20:1 mixture of Z(O) and E(O) silyl enol ether. The ^{1}H-nmr of the main Z(O) isomer(**3a**) in $CDCl_3$ gave δ: 0.09(6H,s), 0.88(9H,s),1.73 (3H, d, J=6.6Hz), 5.45 (1H, q, J=6.6 Hz), 6.97~7.02(1H), 7.32(1H, d, J=8.6 Hz) 7.51~7.57(1H), 8.42(1H, d, J=4 Hz) (Scheme 3).

Scheme 3



By the same procedure the 3-methylpyridylthio analogue (**3b**) was obtained in the same ratio and yield.[8] The adequate levels of purity can be attained by simply removing the solvent under reduced pressure without resorting to distillation. In this reaction 1~2 *eq.* of DMF is necessary to promote the reaction cleanly and efficiently. The present method is applicable to the syntheses of the active silyl enol ethers such as **4** and **5** from the corresponding amides in high yields (Scheme 4).[9]

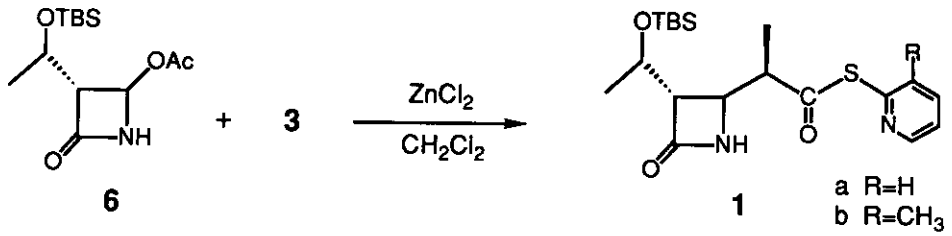
Scheme 4



Now with the requisite silyl enol ethers (**3a,b**) at our disposal, we proceeded to the crucial coupling reaction. Thus into a solution of 171 mg of acetoxyazetidinone derivative (**6**) and 337 mg (2 *eq.*) of

silyl enol ether(**3a**) in dry methylene chloride (15 ml) was added 163 mg(2 *eq.*) of $ZnCl_2$ (freshly fused) and the suspension was stirred at 12°C~15°C for 15 h. Methylene chloride was added and the organic layer was washed with brine three times and dried over $MgSO_4$. After removal of the solvent the crude residue was rapidly chromatographed on silica gel (c-Hex:AcOEt=1:1) to afford 170 mg (72%) of the exclusively β-methylcarboxylate derivative (**1a**) in >50:2 (β:α) ratio, mp 109°C.

Scheme 5



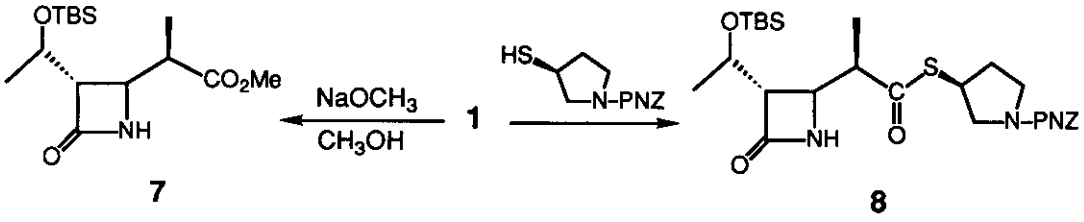
Ir(KBr)cm^{-1}:1757,1718, 1696,1564, 3181, 3099. ^{1}H-Nmr($CDCl_3$) δ:0.07(6H, s),0.87(9H, s),1.19 (3H, d, J=5.9 Hz), 1.35(3H, d, J=7.2 Hz), 3.00~3.05(2H, m), 3.99(1H, dd, J=2.0 and 5.3 Hz), 4.19 ~4.23(1H, m), 5.90(1H, NH), 7.30~7.32(1H, m), 7.60(1H, d, J=7.9 Hz), 7.73~7.93(1H, m), 8.63(1H, d, J=3.9 Hz).

By almost the same way at 18°C the β-methyl-3-methylpyridylthiocarboxylate derivative (**1b**) was obtained in 78% yield , mp 120~122°C. Nmr($CDCl_3$) δ:0.07(6H, s), 0.87(9H, s), 1.20(3H, d, J=6.0 Hz), 1.35(3H, d, J=7.0 Hz), 2.36(3H, s), 3.02~3.13(2H, m), 4.00(1H, dd, J=4.0 and 2.0 Hz), 4.20 (1H, m), 5.89(1H, br), 7.28(1H, dd, J=8.0 and 5.0 Hz), 7.64(1H, dd, J=8.0 and 1.0 Hz), 8.50 (1H, dd, J=5.0 and 1.0 Hz).

In this aldol coupling reaction the α:β ratio has a critical dependence on the reaction temperature and from the experiment it was evidenced that during a 5 h reaction period maintaining the temperature at 18°C is the ideal reaction temperature (β CH_3:α CH_3 = > 50:1).[10]

Both the pyridylthio esters (**1a** and **1b**) thus obtained were transformed into any other type of thiol esters by treating them with the appropriate thiol (RSH) in the basic medium (Et_3N/CH_2Cl_2). A representative example is illustrated in the Scheme 6. The thiolester (**8**) shown in Scheme 6 was transformed into the oxalyl amide derivative which has also been converted into the carbapenem derivative by the triethylphosphite method developed in our laboratories.[3]

Scheme 6



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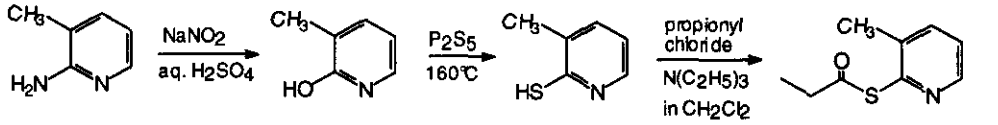
8. The 3-methylpyridylthio propiolate (**2b**) was prepared from 3-methyl-2-aminopyridine by the following sequence.



mp 137-139°C mp 163-165°C bp 108℃/0.05 mmHg

2b

Nmr (270 MHz,CDCl3) of the silyl enol ether (**3b**), δ : 0.04 (6H, s), 0.85 (9H, s),1.75 (3H, d, J= 7.3 Hz), 2.24 (3H, s), 5.33(1H, q, J=6.6 Hz), 6.93~8.38(3H, m)

9. The structure of the compound (**5**) (mp 87°C) was determined unambiguously by X-ray crystallography by Dr. T. Hata of Sankyo Research Laboratories. Both compounds(**4**) and (**5**) are inactive as a coupling partner with 4-acetoxyazetidinone derivative (**6**).
10. Performing the reaction at higher temperature (*e.g.* 30°C) gave correspondingly lower ratio of β-Me to α–Me product (10:1) . The reaction of **2b** with TBSOTf/Et3N gave 1:1 (E(O):Z(O)) mixture of the silyl enol ether. From this mixture the E(O) isomer of **3b** was obtained by the 6 times repeating tlc separation (c- Hex:AcOEt = 10:1), and the coupling reaction with **6** gave **1b** in a ratio of 2:1(α:β).

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