

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

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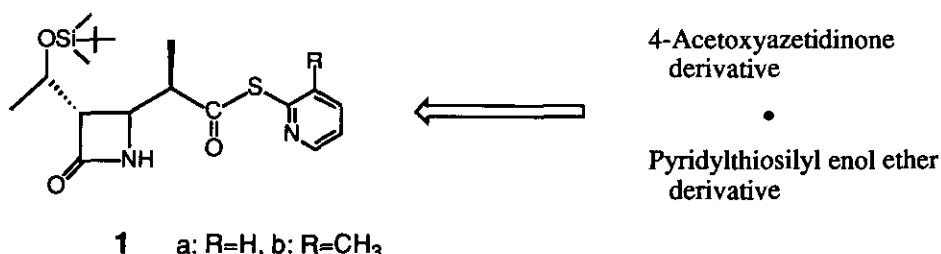
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Abstract- A 1 β -Methylcarboxylate (1) which is a requisite intermediate for the synthesis of the 1 β -methylcarbapenem was obtained in an efficient manner by the coupling reaction of a Z(O)-pyridylthiosilyl enol ether and a 4-acetoxyzetidinone derivative in the presence of ZnCl₂ in CH₂Cl₂. 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 1 β -methylcarbapenem molecule toward DHP-1 has prompted these laboratories to synthesize the more complicated, 1 β -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 1 β -methylcarbapenem antibiotics. There are several methods of utilizing boron⁴ or tin⁵ 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.



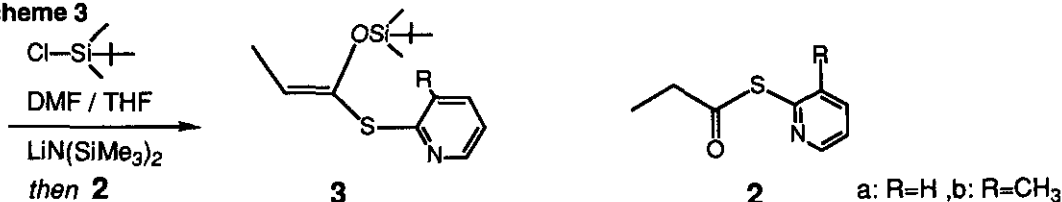
In 1988 a Bristol-Myers group reported on the 1 β -methylcarbapenem intermediate synthesis by the coupling method using silyl enol ether of pyridylmethylthiol ester of propionic acid.⁶ Their method based on the chelation effect incited us to prepare the reactive pyridylthiosilyl enol ether by employing 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



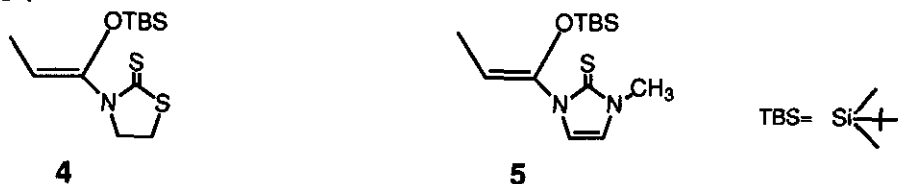
To prevent this side reaction we performed this silyl enol ether formation reaction by the reverse addition⁷ as follows: To a stirring solution of hexamethyldisilazane (7.5 ml) in THF (50 ml) was added 22.5 ml (1.2 eq.) of *n*-butyllithium, 1.6 M solution in hexane at room temperature and after 30 min 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-pyridylthiopropionate (**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 MgSO₄. 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 **3a**) to give 8.6 g of the desired silyl enol ether. 270 MHz ¹H-nmr revealed approximately a 20:1 mixture of Z(O) and E(O) silyl enol ether. The ¹H-nmr of the main Z(O) isomer (**3a**) in CDCl₃ gave δ : 0.09(6H, s), 0.88(9H, s), 1.73 (3H, d, *J*=6.6 Hz), 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

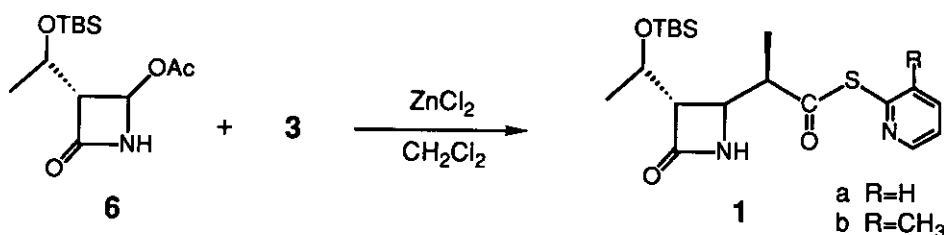
Scheme 4



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



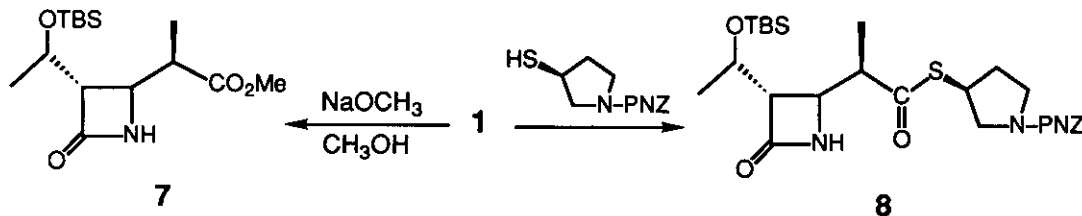
$\text{Ir}(\text{KBr})\text{cm}^{-1}$: 1757, 1718, 1696, 1564, 3181, 3099. $^1\text{H-Nmr}(\text{CDCl}_3)$ δ : 0.07(6H, s), 0.87(9H, s), 1.19(3H, d, $J=5.9$ Hz), 1.35(3H, d, $J=7.2$ Hz), 3.00–3.05(2H, m), 3.99(1H, dd, $J=2.0$ and 5.3 Hz), 4.19–4.23(1H, m), 5.90(1H, NH), 7.30–7.32(1H, m), 7.60(1H, d, $J=7.9$ 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 . $\text{Nmr}(\text{CDCl}_3)$ 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

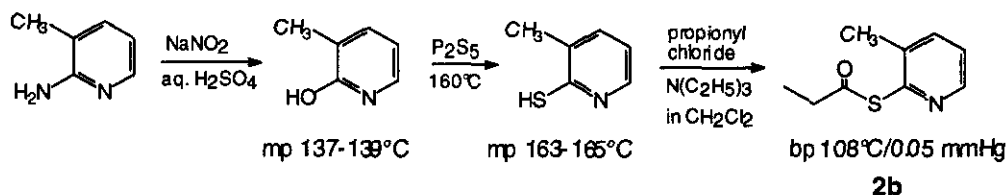
Both the pyridylthio esters (**1a** and **1b**) thus obtained were transformed into any other type of thiol esters by treating them with the appropriate thiol (RSH) in the basic medium ($\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$). A representative example is illustrated in the Scheme 6. The thiolester (**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.



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-acetoxiazetidinone 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).

Received, 20th October, 1993