A Facile Synthesis of 1β-Methylcarbapenem Skeleton Utilizing Cyclization of α,β-Unsaturated Ester with Methanesulfenyl Chloride

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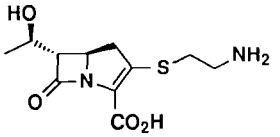
A facile synthetic route to 1β-methylcarbapenem skeleton is described utilizing cyclization of α,β-unsaturated ester with methanesulfenyl chloride.

Since the discovery of thienamycin **1** in 1976, carbapenems have received considerable attention among the β-lactam antibiotics due to high antibacterial activity.[1] Thienamycin is, however, biologically unstable and metabolized by renal dehydropeptidase I.[1] On the other hand, 1β-methylcarbapenem **2** possesses chemical and metabolic stability,[1] and therefore, since the first report by Shih and co-workers of Merck group in 1984, the synthesis of 1β-methylcarbapenem derivatives has attracted the interest of synthetic chemists due to the difficulty of constructing the highly strained bicyclic structure as well as controlling the stereochemistry.[1,2] The 1β-methylcarbapenem skeleton having a bicyclic ring system has been constructed based on the Rh(II) catalyzed carbene insertion,[3] the intramolecular Witting reaction,[4] the Dieckmann reaction,[5] and so on.



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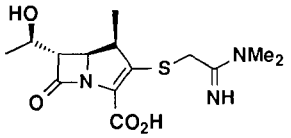

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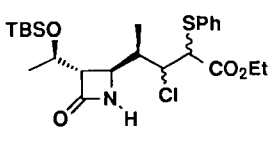
Although these methods have been widely used for the synthesis of 1β-methylcarbapenem, many other procedures have been reported, involving the ketenedithioacetal-terminated cyclization,[6] NBS-promoted cyclization,[7] the Eschenmoser sulfide contraction,[8] and cyclization of hypervalent iodonium ylides.[9] These strategies offer considerable advantages in further study of carbapenem antibiotics.

We have already reported a straightforward synthetic method of a 1β-methylcarbapenem intermediate, α,β-unsaturated ester derivative **5**, starting from the chiral β-lactam.[10,11] In this letter, we wish to report a new facile synthesis of 1β-methylcarbapenem skeleton utilizing cyclization of the α,β-unsaturated ester **5** with methanesulfenyl chloride and subsequent olefination. It has been previously reported by Ihara *et al.*, that in thienamycin synthesis cyclization of α,β-unsaturated ester derivative with benzenesulfenyl chloride gave the corresponding bicyclic products in poor yield in a three-step procedure.[12] We also attempted the cyclization of α,β-unsaturated ester **5** with benzenesulfenyl chloride, and obtained the adduct **3** in 25% yield.



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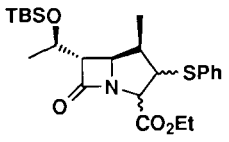

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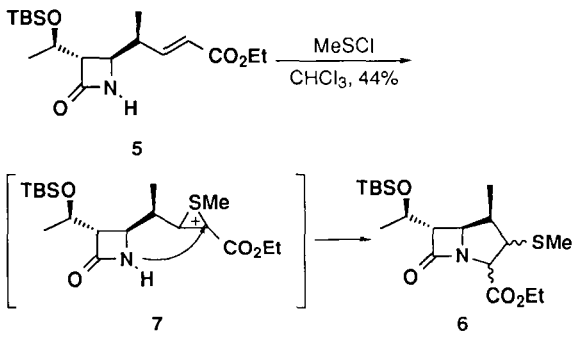
Subsequent cyclization of **3** gave the bicyclic compound **4** in only 10% yield.

The low yield of the bicyclic compound **4** may be due to the low reactivity of benzenesulfenyl chloride, and therefore, more reactive alkanesulfenyl halides were investigated. Among the sulfenyl halides used, methanesulfenyl chloride effected the cyclization of α,β-unsaturated ester **5** most effectively to give 1β-methylcarbapenam derivative **6**[13] in moderate yield in only a single-step. We next screened the effects of solvent and reaction temperature, and found that the use of 6 equiv. of methanesulfenyl chloride in $CHCl_3$ at ambient temperature gave the 1β-methylcarbapenam derivative **6** in 44% yield (Scheme 1).[14]

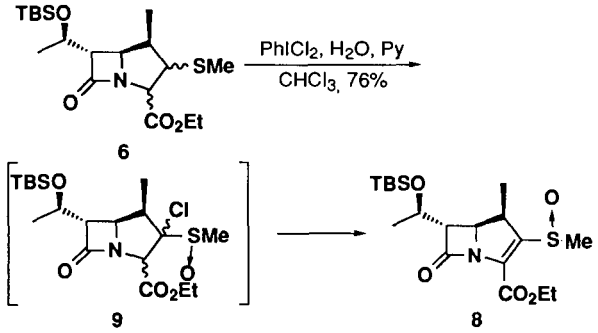


Scheme 1.

The cyclization proceeded most probably *via* episulfonium intermediate **7**, followed by the attack of the nitrogen nucleophile to give the 1β-methylcarbapenam derivative **6**. Although the cyclization product **6** contained a mixture of C-2 and C-3 diastereomers, and actually four isomers were detected by 270 MHz ^{1}H-NMR, the transformation into 1β-methylcarbapenem skeleton did not appear to be influenced by the stereochemistry at C-2 and C-3.

Next, we investigated the olefination of C-2 - C-3 bond. The method of introduction of the double bond at C-2 - C-3 has been reported for the synthesis of PS-5,[15] in which iodobenzene dichloride was successfully used. The same reagent was used for the present derivative **6** in dichloromethane containing pyridine and water. Unlike in the case of PS-5, the concomitant formation of an intermediary 2-chloro derivative **9** was observed. After careful examination into the reaction conditions, the best result was achieved using 8 equiv. of water and 4 equiv. of iodobenzene dichloride in $CHCl_3$-pyridine (8:1) at 30 °C for 8 h to give the 1β-methylcarbapenem derivative **8**[16] in 76% yield without any detection of 2-chloro derivative **9** (Scheme 2).[17]

The observed facile transformation into the vinyl sulfoxide **8** may be explained as follows: The initial oxidation of sulfide **6** into sulfoxide was followed by chlorination to give α-chloro sulfide, which was further oxidized to form the 2-chlorosulfoxide



Scheme 2.

9. This kind of chlorination has a precedent in carbapenem synthesis.[15] The subsequent elimination into the vinyl sulfoxide **8** was effected by pyridine, which acted as a mild base. It has been reported that replacement of the sulfoxide at the C-2 side chain of carbapenem with various thiols proceeded readily to give 1β-methylcarbapenems.[18]

In summary, we have developed a facile synthetic method for 1β-methylcarbapenem derivative employing the cyclization with methanesulfenyl chloride and the olefination utilizing iodobenzene dichloride. In contrast to the procedures previously reported,[7] the present strategy allows direct use of an electron deficient olefin possessing a necessary carboxylate moiety as a precursor, which underwent an efficient cyclization followed by a single-step transformation into **8**. This process offers a new approach to 1β-methylcarbapenem antibiotics.

References and Notes

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13 **6**, ^{1}H-NMR(270 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.80 (s, 6H), 0.81 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.23-1.54 (m, 7H), 2.05 (s, 3H), 2.50-2.55 (m, 1H), 2.82-2.84 (m, 1H), 3.42 (d, J = 11.7 Hz, 1H), 3.74-3.76 (m, 1H), 4.17 (q, J = 7.26 Hz, 2H), 4.29 (m, 1H); IR (neat) 2870, 1750, 1460, 1370, 1250, 1160, 830, 780 cm^{-1}

14 A representative procedure is as follows: To a solution of **5** (30 mg, 0.084 mmol) in $CHCl_3$ (1.8 ml) was added methansulfenyl chloride (0.22 M solution in CH_2Cl_2, 2.29 ml, 0.504 mmol) at ambient temperature under an argon atmosphere. After the mixture was stirred for 43 h, it was concentrated in vacuo. Purification of the residue on buffered silica-gel TLC gave the 1β-methylcarbapenam derivative **6** (14.9 mg, 44%).

15 a) J. H. Bateson, R. I. Hickling, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, **1980**, 1084. b) T. Yoshioka, A. Watanabe, K. Issiki, Y. Fukagawa, and T. Ishikura, *Tetrahedron Lett.*, **27**, 4335 (1986).

16 **8**, ^{1}H-NMR(270 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.79 (s, 3H), 0.80 (s, 6H), 1.08 (d, J = 6.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.27 (d, J = 4.6 Hz, 3H), 2.20-2.40 (m, 1H), 2.89 (s, 3H), 3.50-3.70 (m, 1H), 4.11-4.23(m, 3H); IR (neat) 2900, 2850, 1750, 1700, 1420, 1370, 1000, 850 cm^{-1}

17 Oxidation was carried out as follows: To a solution of **6** (6 mg, 0.014 mmol) in $CHCl_3$ (0.6 ml) was added iodobenzene dichloride (16.4 mg, 0.056 mmol) and H_2O (2.1 μl, 0.028 mmol) and pyridine (70 μl, 1.04 mmol) at 0 °C under an argon atmosphere, and the reaction mixture was stirred for 8 h at 30 °C. After concentration in vacuo, purification of the residue on buffered silica-gel TLC gave the 1β-methylcarbapenem derivative **8** (4.5 mg, 76%).

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