Novel Construction of Penems and Carbapenems. Further Evidence of a Carbene Intermediate for the Oxalimide Cyclization Reaction

Tetsuji Kametani,* Shih-Der Chu, Akira Itoh, Tzu-Chueh Wang, Atsushi Nakayama, and Toshio Honda

Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

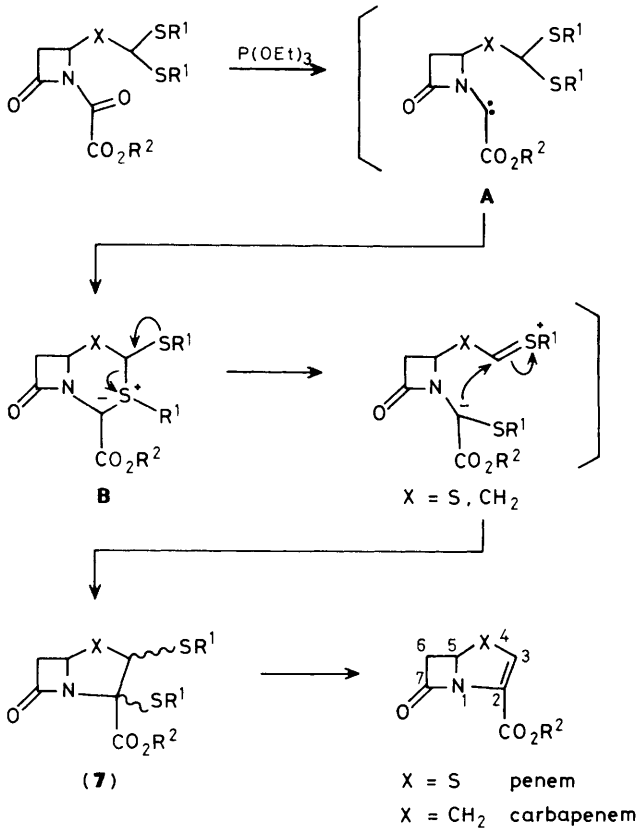
A novel construction of penem and carbapenem ring systems has been achieved by employing an oxalimide cyclization as a key step.

Penems and carbapenems have attracted great interest[1] from both a biological and a synthetic viewpoint, owing to their recognition as potent antimicrobial agents. Among the methods for the synthesis of these important compounds, an intramolecular Wittig reaction forming a 2,3-double bond, as developed by Woodward[2] and co-workers has been widely used.

In 1982, the Schering group demonstrated[3] a new synthesis of penems by employing the oxalimide cyclization reaction, and this remarkable reaction was considered to proceed through a carbene intermediate. Recently we have been involved[4] in the development of a new carbon–carbon bond forming reaction *via* the rearrangement of sulphur ylide intermediates[5] which were easily prepared by the preferential interaction of a carbene or carbenoid with divalent sulphur.

In this communication, we report a novel construction of the penem and carbapenem ring system by the application of the above strategy as shown in Scheme 1. Silylation of the ester (**1**)[2b] with t-butyldimethylsilyl chloride gave the *N*-silylated derivative (**2**), which on ozonolysis (O_3, CH_2Cl_2, −78 °C, then Me_2S) yielded the aldehyde (**3**) in 86% yield from (**1**). Treatment of (**3**) with benzenethiol (2.1 equiv.) in the presence of $BF_3{\cdot}OEt_2$ (3 equiv.)[6] in acetonitrile at 0 °C for 3 h furnished the dithioacetals (**4**) and (**5**) in the ratio of 6 : 1. The former oily compound (**4**) was easily transformed to the latter (**5**), m.p. 100 °C (CH_2Cl_2–n-hexane), on exposure to 10% aqueous hydrochloric acid in tetrahydrofuran (thf). Thus, the dithioacetal (**5**) was isolated in 91.8% combined yield from (**3**). Oxalimide formation[3] of (**5**) with $ClC(:O)CO_2Me$ (1.2 equiv.) in dichloromethane in the presence of Et_3N gave the ester (**6**) in 96% yield. Cyclization of (**6**) in refluxing chloroform (0.02 M solution) using triethyl phosphite (2.5 equiv.) as a carbene generating agent[3] for 5 h provided the penam (**7**) in 92% yield, all four possible stereoisomers being produced in the ratio of *ca.* 1 : 2 : 2 : 4.† The observed

† The four diastereoisomers can be partially separated by careful chromatography; the ratio however was determined on the basis of the n.m.r. spectrum of the mixture, and the stereochemistry of these diastereoisomers could not be determined at this stage. All compounds are racemic, and fully characterized by spectroscopy and elemental analyses.

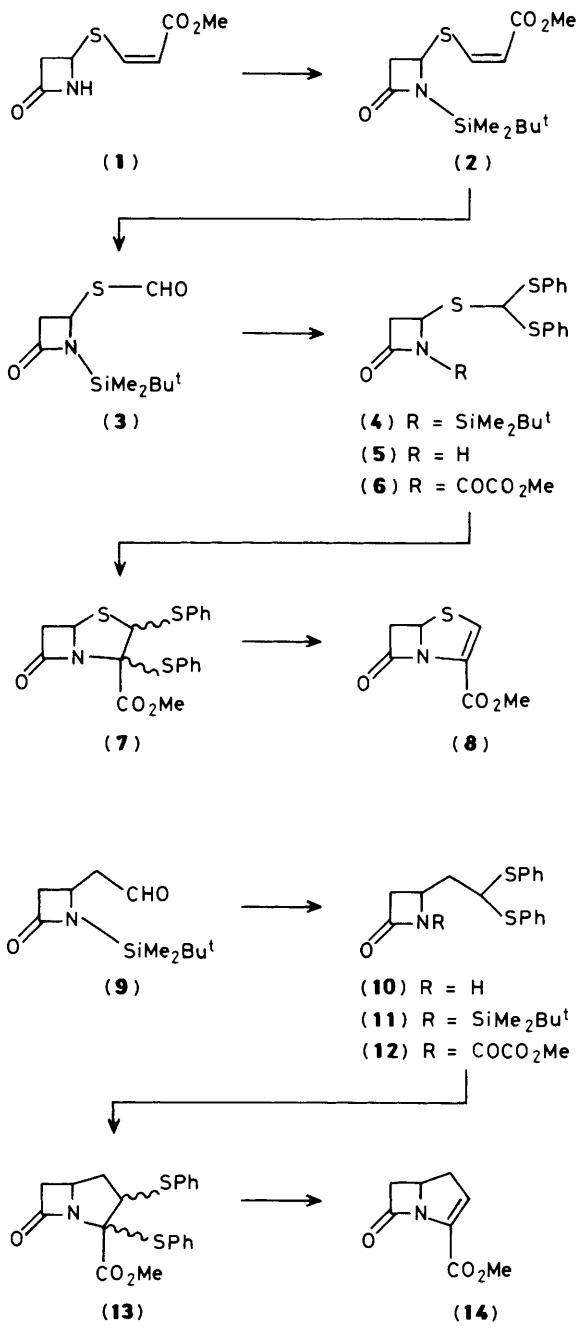


Scheme 1

transposition of a phenylthio group in the product could be rationalized by assuming that this reaction proceeded through the carbene species (**A**), which then formed the sulphur ylide (**B**) and finally its rearrangement provided the desired penam (**7**) as shown in Scheme 1.

The penam (**7**) was successfully converted to the penem (**8**),‡ m.p. 93 °C (diethyl ether–n-hexane), by reductive elimination of the phenylthio group on treatment with tri-n-butyltin hydride (1.2 equiv.) in refluxing benzene in the presence of a catalytic amount of azoisobutyronitrile (AIBN) for 15 min, in 78% yield. Interestingly this alkene synthesis from a β-bis-sulphide with tri-n-butyltin hydride has not hitherto been reported. This method provides a new entry to alkene synthesis, although similar preparations of alkenes starting from bis-dithiocarbonates,[7] and xanthate esters of β-hydroxy sulphides[8] or β-hydroxy sulphones[8] are well known.

Since the oxalimide cyclization was utilized for the synthesis of carbapenems,[9] we extended our synthesis to the construction of a carbapenem. The readily available aldehyde (**9**)[10] was treated with benzenethiol (2.1 equiv.) and $BF_3{\cdot}OEt_2$ (3 equiv.) in acetonitrile at 0 °C for 1 h to give a mixture of the dithioacetals (**10**) and (**11**), which without isolation was exposed to 10% hydrochloric acid in tetrahydrofuran at 0 °C to afford the dithioacetal (**10**), m.p. 113 °C (ether) as the sole product in 86% yield. The oxalimide (**12**) was prepared as described above (ClCOCOMe, Et_3N, CH_2Cl_2, −25 to −10 °C, 15 min) in quantitative yield. Generation of the carbene by treatment of (**12**) with triethyl phosphite (2.5 equiv.) in refluxing chloroform (0.02 M solution) for 20 h furnished the carbapenam (**13**) as a mixture of the possible four diastereoisomers in a similar ratio as in the case of penam synthesis (83% yield). The carbapenam (**13**) was again treated with tri-n-butyltin hydride (1.2 equiv.) and AIBN in refluxing benzene for 15 min to provide the carbapenem (**14**), in 69.2% yield, whose melting point and spectroscopic data were identical with those reported.[11]



Scheme 2

Thus, we report a novel construction of penem and carbapenem ring systems, and this result supports the mechanistic proposal for the Schering penem synthesis involving a

‡ *Selected spectroscopic data* for (**8**): i.r. ($CHCl_3$): 1785, 1715 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 400 MHz): δ 3.57 (1 H, ddd, *J* 0.85, 1.96, and 16.70 Hz, 6-H), 3.82 (3 H, s, OMe), 3.86 (1 H, ddd, *J* 0.80, 3.90 and 16.70 Hz, 6-H), 5.79 (1 H, dd, *J* 1.96 and 3.90 Hz, 5-H), 7.26 (1 H, dd, *J* 0.80 and 0.85 Hz, 3-H).

carbene species. We are currently applying this strategy to the synthesis of biologically active antimicrobial agents bearing 6-hydroxyethyl and 6-amido-functional groups.

Received, 21st December 1987; Com. 1822

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