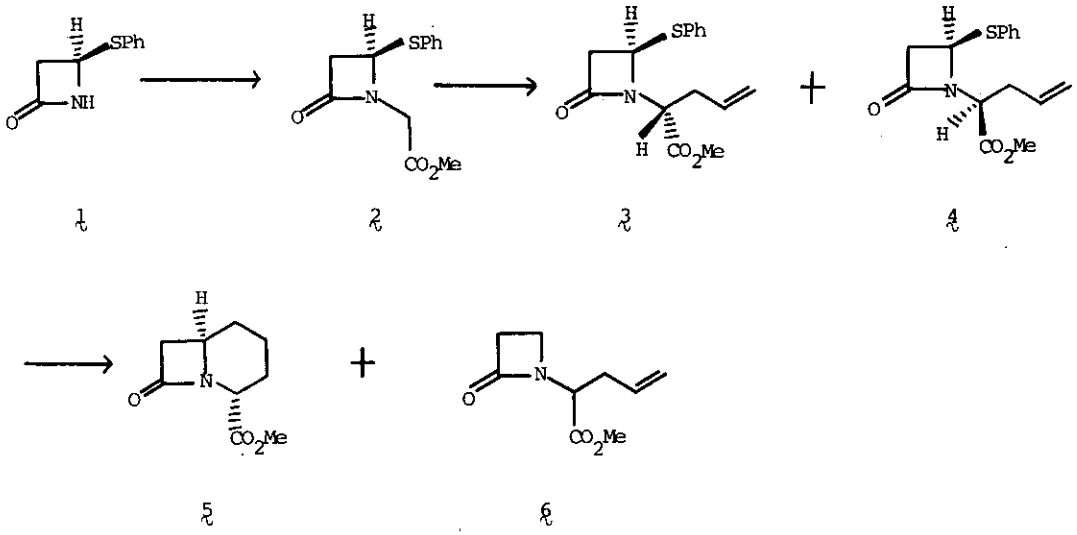
A FORMATION OF CARBACEPHAM RING SYSTEM BY 1,6-BOND COUPLING THROUGH A RADICAL CYCLIZATION REACTION

Tetsuji Kametani* and Toshio Honda
Institute of Medicinal Chemistry, Hoshi University, Ebara-2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract ——— A facile formation of carbacepham ring system was achieved by 1,6-bond formation of 3, employing a radical cyclization as a key reaction.

Introduction of functionalized carbon units at the C_4-position of β-lactams becomes an increasingly interesting reaction[1-17] with regard to the synthesis of carbapenem and carbacephem antibiotics. We have recently reported[5] the new carbon-introducing reactions at the C_4-position of β-lactams, and the application of this reaction has led to the facile synthesis of an antibiotic PS-5[18]. In continuation of our work on the synthesis of non-classical β-lactam antibiotics employing the above strategy, we have investigated the radical cyclization reaction of 4-phenylthioazetidinone (3) with tri-n-butyltin hydride[19]. We here wish to report a simple synthesis of a carbacepham ring system by 1,6-bond formation.

4-Phenylthioazetidin-2-one (1) was alkylated with methyl bromoacetate in dry tetrahydrofuran in the presence of lithium hexamethyldisilazide to afford N-methoxycarbonylmetyl-4-phenylthioazetidin-2-one (2), in 91 % yield, whose treatment with allyl bromide in the presence of lithium hexamethyldisilazide in dry tetrahydrofuran at -78°C gave rise to the allyl derivatives[20] 3 and 4, in 79 % yield, as an inseparable mixture of diastereoisomers.



Radical cyclization of 3 and 4 with tri-n-butyltin hydride and α,α´-azobis-isobutyronitrile was carried out in refluxing dry benzene for 18 h to afford the carbacepham derivative 5 in 43 % yield (66 % yield based on consumed starting material), together with a trace amount of the desulfurized compound 6, whereas formation of a carbapenam derivative which might be another possible cyclization product could not be observed under these reaction condition. Interestingly, the recovered starting material was only 4. The structure of the cyclized product was determined based on its spectral data[21]. Thus, a facile construction of carbacepham ring system by 1,6-bond formation was achieved employing a radical cyclization reaction as a key step, and the application of this reaction for various types of β-lactam analogues is under investigation.

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20 NMR δ($CDCl_3$) 4.08 (0.5H, t, J = 7.5 Hz, $NC\underline{H}CO_2Me$ for 4) and 4.27 (0.5H, t, J = 7.5 Hz, $NC\underline{H}CO_2Me$ for 3).

21 IR $\nu_{max.}$ ($CDCl_3$) : 1760 (sh), 1740 cm^{-1}; NMR δ($CDCl_3$) 3.73 (3H, s, OMe), 4.50 (1H, br d, J = 6.5 Hz, C_4-H); MS m/e 183(M^+); a relative configuration of the methoxycarbonyl group for 5 was tentatively assigned to be α, based on its chemical shift : see L. D. Cama and B. G. Christensen, Tetrahedron Letters, 1978, 4233; and the treatment of 5 with base showed no change in its NMR spectrum.

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