

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

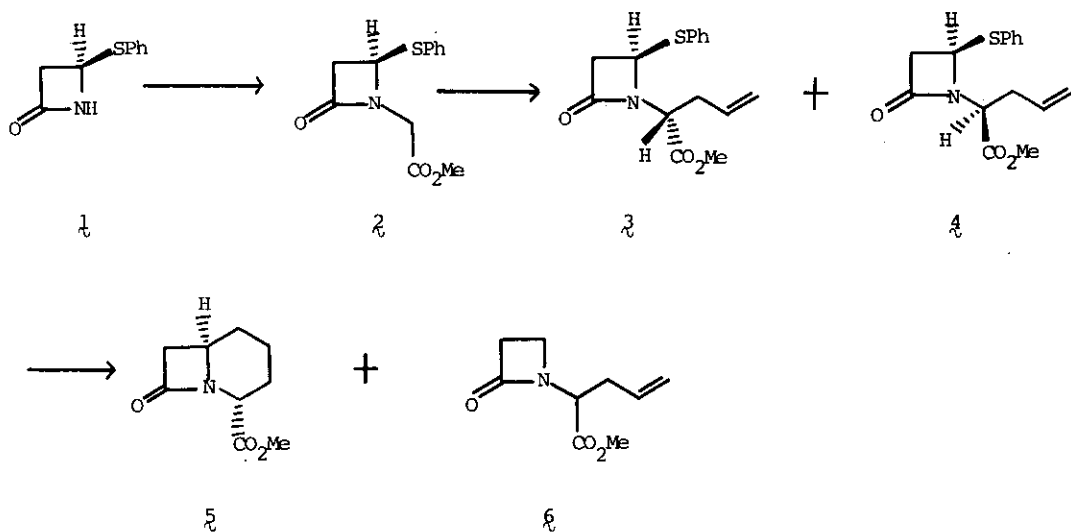
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Abstract ——— A facile formation of carbacepham ring system was achieved by 1,6-bond formation of **3**, employing a radical cyclization as a key reaction.

Introduction of functionalized carbon units at the C<sub>4</sub>-position of β-lactams becomes an increasingly interesting reaction<sup>1-17</sup> with regard to the synthesis of carbapenem and carbacephem antibiotics. We have recently reported<sup>5</sup> the new carbon-introducing reactions at the C<sub>4</sub>-position of β-lactams, and the application of this reaction has led to the facile synthesis of an antibiotic PS-5<sup>18</sup>. 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<sup>19</sup>. We here wish to report a simple synthesis of a carbacephem 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-methoxycarbonylmethyl-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<sup>20</sup> **3** and **4**, in 79 % yield, as an inseparable mixture of diastereoisomers.



Radical cyclization of **3** and **4** with tri-*n*-butyltin hydride and  $\alpha, \alpha'$ -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<sup>21</sup>. 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  $\beta$ -lactam analogues is under investigation.

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- 20 NMR  $\delta$ (CDCl<sub>3</sub>) 4.08 (0.5H, t, J = 7.5 Hz, NCHCO<sub>2</sub>Me for 4) and 4.27 (0.5H, t, J = 7.5 Hz, NCHCO<sub>2</sub>Me for 3).
- 21 IR  $\nu_{\text{max}}$  (CDCl<sub>3</sub>) : 1760 (sh), 1740 cm<sup>-1</sup>; NMR  $\delta$ (CDCl<sub>3</sub>) 3.73 (3H, s, OMe), 4.50 (1H, br d, J = 6.5 Hz, C<sub>4</sub>-H); MS m/e 183(M<sup>+</sup>); a relative configuration of the methoxycarbonyl group for 5 was tentatively assigned to be  $\alpha$ , 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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