SYNTHESES OF CARBACEPHAM AND CARBACEPHEM RING SYSTEM BY EMPLOYING RADICAL CYCLIZATION

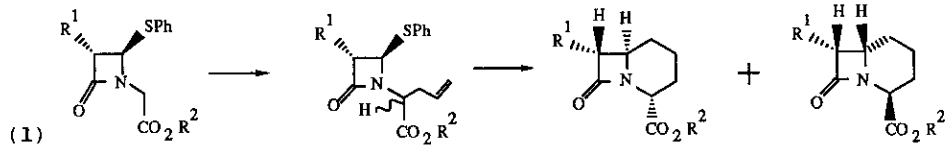
Tetsuji Kametani,* Shih-Der Chu, Akira Itoh, Sayuri Maeda, and Toshio Honda
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract —— Radical cyclization reaction was successfully applied to the construction of carbacepham and carbacephem ring system.

In 1982, we have reported[1] the synthesis of carbacepham ring system by using a radical cyclization reaction. Here, we would like to report a further application of this strategy to the synthesis of 7-substituted carbacephams in addition to the synthesis of carbacephems. 3-Substituted 4-phenylthio-azetidinones (**1a** - **c**) were converted to the corresponding allyl derivatives (**2a** - **c**) in moderate yields. Radical cyclization of (**2a** - **c**) using tri-n-butyltin hydride in the presence of a catalytic amount of AIBN in refluxing benzene afforded the expected carbacephams (**3a** - **c** and **4a** - **c**) in a ratio of ca. 2 : 1 in 50 - 60% yields, where the formation of 1-methylcarbapenam, namely an another possible cyclization product could not be observed. The stereochemistry of the products was determined based on their nmr spectra.[2] Since a phenylselenyl group was also recognized as a good progenitor to generate a radical center, we therefore examined the radical cyclization reaction of 4-phenylselenoazetidinone derivative (**7**), easily derived from (**5**) via (**6**) by two steps.[3] Treatment of (**7**) with tri-n-butyltin hydride in the presence of AIBN in refluxing benzene furnished the carbacepham (**8**), identical with an authentic specimen,[1] in 59% yield. Its conversion yield was clearly superior to those of the corresponding 4-phenylthio derivative, the radical cyclization of which afforded (**8**) in 40 - 45% yield. In order to synthesize a carbacephem skeleton, a propargyl group was introduced into 1-methoxycarbonylmethyl-4-

phenylthio-2-azetidinone to give (**9**), whose radical cyclization under the similar reaction condition as above afforded the carbacephems (**10** and **11**) as an inseparable oil in 10.3% yield, in the ratio of ca. 5 : 1.

Thus, we could disclose a construction of carbacepham and carbacephem ring system by employing a radical cyclization reaction as a key step.



(**1**)

a R^1 = Et, R^2 = Me

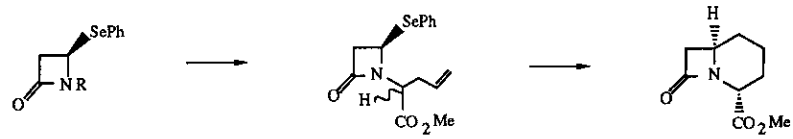
(**2**)

(**3**)

(**4**)

b R^1 =  , R^2 = Me

c R^1 =  , R^2 = CH_2Ph

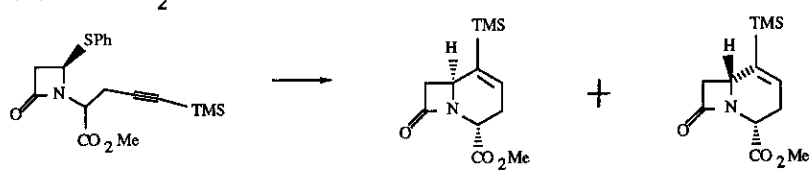


(**5**) R = H

(**6**) R = CO_2Me

(**7**)

(**8**)



(**9**)

(**10**)

(**11**)

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