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A Facile Synthesis of C(3)-Alkenyl Substituted Cephems through Addition-Cyclization of Allenecarboxylates derived from Penicillin[1]

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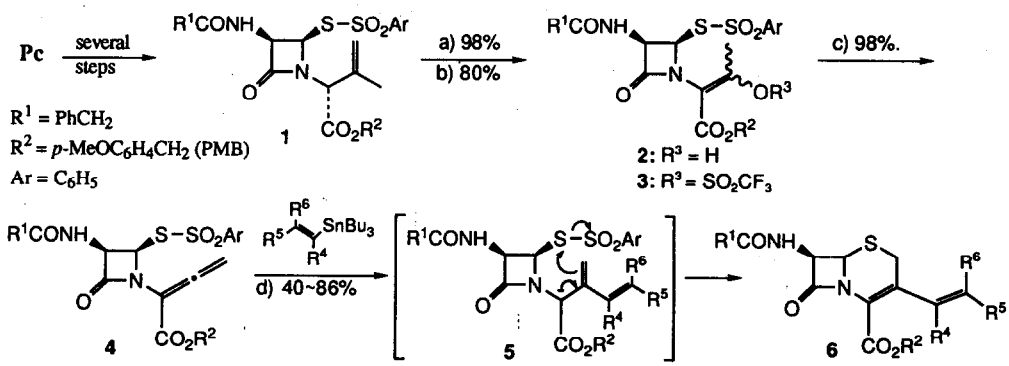
Key words: *3-Alkenylcephems; Allenecarboxylates; Penicillin-cephalosporin Conversion*

Summary: A short-cut route to cephalosporins bearing alkenyl substituents on the C(3)-position through copper(I) chloride-promoted Michael-type addition of alkenyltributyltins to allenecarboxylates, derived from penicillin, is described.

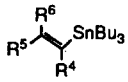
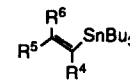
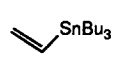
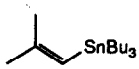
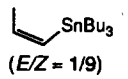
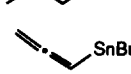
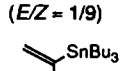
C(3)-Alkenyl substituted cephems **6** are an important class of orally active β-lactam antibiotics.[2] Much effort has been made to develop an efficient methodology for introduction of the alkenyl moieties at the C(3)-position of the cephem framework. Hitherto explored procedures for this purpose mainly rely on the Wittig reactions and/or reactions of 3-trifluoromethylsulfonyloxy- and 3-fluorosulfonyloxy-cephems with alkenyltin compounds or alkenylcuprates.[3] In a previous paper,[4] we disclosed a new methodology for penicillin-cephalosporin conversion involving addition of heteroatom nucleophiles to allenecarboxylates **4** derived from penicillin **Pc** and subsequent cyclization leading to C(3)-heteroatom substituted cephems. Recently, Kant and Farina reported a conceptually analogous route to the C(3)-alkenyl substituted cephems **6** ($R^4 = R^5 = H$, $R^6 = CH_3$) through Michael addition of (Z)-(1-propenyl)$_2$CuMgBr to allenecarboxylates **4** (Ar = $CH_3C_6H_4$) at -100 ℃ and subsequent cyclization.[5] This prompts us to report herein that a newly deviced copper(I) chloride-promoted addition of alkenyltin compounds to the allenecarboxylates **4** can effect a similar transformation (**4** → **6**; Ar = C_6H_5) at ambient conditions (Scheme 1).



Scheme 1

The allenecarboxylate **4** was prepared from penicillin as outlined in Scheme 1 (**Pc** → **4**).[4] The conversion of **4** into the C(3)-alkenylcephems **6** was performed by treatment of **4** with alkenyltributyltins (1.5 equiv.) in *N*-methylpyrrolidinone (NMP) in the presence of copper(I) chloride (1.2 equiv.) at ambient temperature. The reaction completed in 1 h to afford the corresponding C(3)-alkenylcephems **6** in 56~86% yields (Table 1, entries 1~4). The presence of copper(I) chloride is indispensable since lack of copper(I) chloride provides no appreciable amounts of **6**.[6] Notably, the reactions of **4** with allenyl- and phenyltributyltins proceeded in a similar fashion to afford 3-allenyl- and 3-phenylcephems **6**, respectively (entries 5 and 6).

Table 1. Reaction of Allenecarboxylate with Alkenyltributyltins[a)]

Entry		Yield (%)[b)]	Entry		Yield (%)[b)]
1		70	4		56
2	 (*E*/*Z* = 1/9)	66 (*E*/*Z* = 1/9)	5		40
3		86	6	$PhSnBu_3$	42

a) Carried out with **4** (0.17 mmol), alkenyltributyltin (0.25 mmol) and CuCl (0.21 mmol) in NMP (1 ml).
b) Isolated yield.

References and Notes

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2) Webber, J. A.; Ott, J. L.; Vasileff, R. T. *J. Med. Chem.*, **1975**, *18*, 986; Yamanaka, H.; Chiba, T.; Kawabata, K.; Takasugi, H.; Masugi, T.; Takaya, T. *J. Antibiot.*, **1985**, *38*, 1738; Naito, T.; Hoshi, H.; Aburaki, S.; Abe, Y.; Okumura, J.; Tomatsu, K.; Kawaguchi, H. *J. Antibiot.*, **1987**, *40*, 991.

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5) Kanto, J.; Farina, V. *Tetrahedron Lett.*, **1992**, *33*, 3563.

6) Copper(I) chloride is the best choice among so far examined metal salts. The yields of **6** ($R^4 = R^5 = R^6 =$ H) decreased in the following order: CuCl (70%) > CuBr (43) > $PdCl_2$ (16) > $CuCl_2$, $NiCl_2$, $AgNO_3$ (0).

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