

Construction of cephem framework *via* sequential reductive 1,2-elimination–hydride addition in a tributyltin hydride–copper(I) chloride–NMP system: synthesis of 3-norcephalosporin

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A sequential reductive 1,2-elimination and hydride addition process for 3,4-disubstituted butenoates derived from penicillin is successfully performed with the aid of a combination of tributyltin hydride and copper(I) chloride in *N*-methyl-2-pyrrolidinone (NMP) to afford 3-norcephalosporin.

Since Morin's pioneering work,¹ penicillin to cephalosporin conversion has been intensively investigated and various synthetic approaches to useful cephalosporin antibiotics have emerged.² In previous papers, we disclosed a conceptually new strategy for the conversion of penicillin to cephalosporin involving a sequential addition–cyclization reaction of allenecarboxylate **1** derived from penicillin **Pc**, leading to 3-substituted cepheims **3** (Scheme 1).³ Independently, Kant and Farina reported an analogous access to the 3-substituted cepheims **3**.⁴ In the procedures explored thus far, nucleophiles (Nu[−]) attack the centre carbon atom of the allene moiety of **1**, leading to the adducts **2**, and are finally introduced at the C(3)-position of the cephem framework **3**. The procedures are, however, not necessarily amenable to practical use because the key intermediates **1** are not always easy to handle owing to their lability.[†]

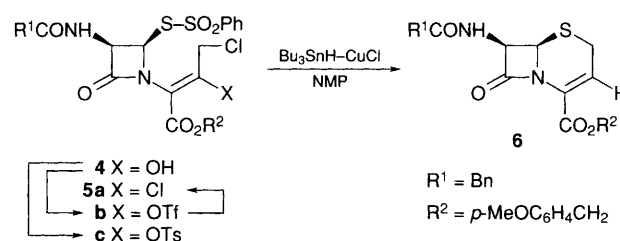
We sought a synthetic equivalent to the allenecarboxylate **1**, which is readily available and stable under ambient conditions and can undergo a similar addition–cyclization leading to the cephem framework **3**. Consequently, we found that 3,4-disubstituted 2-[4-(phenylsulfonylthio)-2-oxoazetidin-1-yl]but-2-enoates **5** (X = Cl, OTf and OTs) derived from penicillin **Pc** could play a role as an alternative source of the allenecarboxylate **1** to offer a new methodology for the construction of the cephem framework. Herein, we describe a sequential reductive 1,2-elimination, hydride addition and cyclization of the 3,4-disubstituted butenoates **5** leading to 3-norcephalosporin **6** *via* a newly devised tributyltin hydride, copper(I) chloride and NMP combination.

The 3,4-disubstituted but-2-enoates **5** (X = Cl, OTf and OTs) were easily prepared from penicillin **Pc**; thus the reaction of

enol **4** derived from penicillin **Pc** according to the reported procedure⁵ with trifluoromethanesulfonic anhydride and triethylamine (1.5 equiv. each) in CH₂Cl₂ at −78 °C for 1 h afforded the corresponding trifluoromethanesulfonate **5b** (95%) which was, in turn, treated with lithium chloride (10 equiv.) in NMP containing aluminum chloride (3 equiv.) at room temperature for 4 h to give the 3,4-dichlorobut-2-enoate **5a** (83%). The toluene-*p*-sulfonate **5c** (89%) was similarly prepared by treatment of **4** with tosyl chloride (1.5 equiv.) and sodium carbonate (3 equiv.) in CH₂Cl₂ at 0 °C for 2 h. All of the 3,4-disubstituted but-2-enoates **5** obtained thus far are stable enough to survive under ambient conditions for several weeks without appreciable change.

The reaction of the 3,4-dichlorobut-2-enoate **5a** with tributyltin hydride and copper(I) chloride in NMP was carried out under ambient conditions (Table 1). To a mixture of **5a** and copper(I) chloride (2.0 equiv.) in NMP was added tributyltin hydride (2.2 equiv.) at once and the mixture was stirred for 4 h to give the 3-norcephalosporin **6** (36%) together with recovered **5a** (34%) (entry 1). A considerable amount of **5a** was recovered, even with an even greater excess of tributyltin hydride (entry 2). Completion of the reaction could be achieved successfully by portionwise addition of tributyltin hydride, in four separate batches at 30 min intervals, affording the desired product **6** in 80–81% yield (entries 3 and 4). In a similar manner, the transformation of **5b** and **5c** into the 3-norcephalosporin **6** was performed in 70–79% yield (Table 2).

The time course of the cyclization of the dichloride **5a** to the 3-norcephalosporin **6** was monitored by HPLC (Fig. 1),



Scheme 2

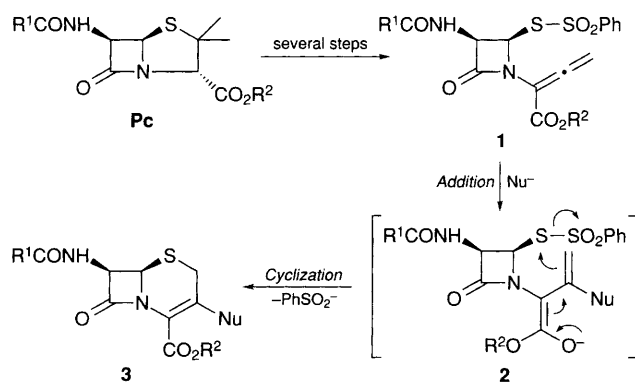
Table 1 Reaction of 3,4-dichlorobutenoate **5a** with Bu₃SnH and CuCl^a

Entry	Bu ₃ SnH			<i>t</i> /h	Products (%) ^b	
	Equiv.	No. of additions	Equiv. CuCl		6	Recovered 5a
1	2.2	1	2.0	4	36	34
2	4.4	1	3.0	6	40	34
3	1.0	4 ^c	2.0	2	80	0
4	1.0	4 ^c	4.0	2	81	0

^a Carried out with substrate **5a** (0.15 mmol) in NMP (3 ml) at room temp.

^b Isolated yields after column chromatography (SiO₂; PhMe–AcOEt, 2 : 1).

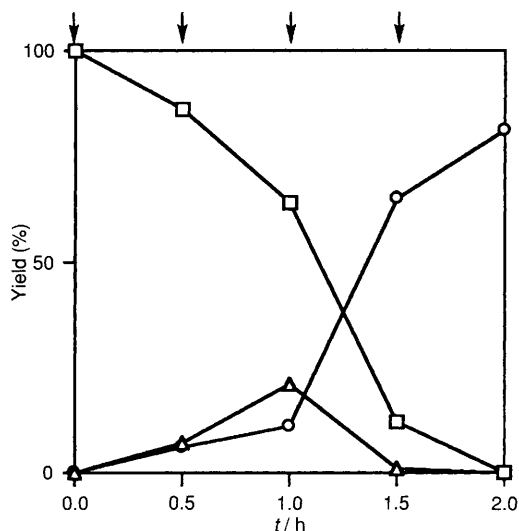
^c Portions of Bu₃SnH added at intervals of 30 min.



Scheme 1

Table 2 Reaction of 3,4-disubstituted butenoates **5** with Bu₃SnH and CuCl^a

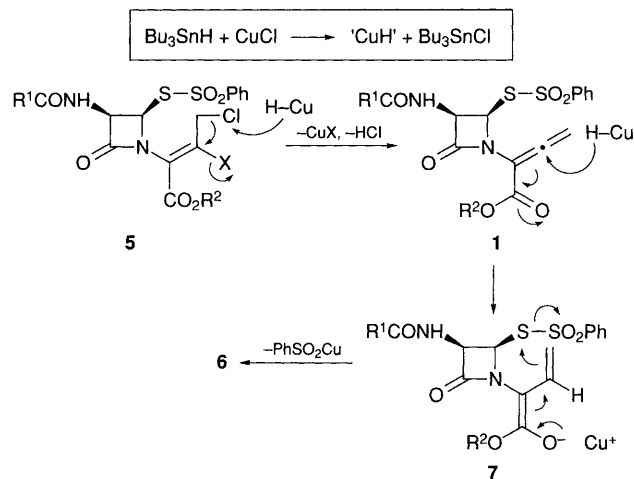
Entry	Substrate	Bu ₃ SnH		Equiv. CuCl	t/h	Products (%) ^b	
		Equiv.	No. of additions			6	Recovered 5
1	5a	1.0	4 ^c	4.0	2	81	0
2	5b	1.0	4 ^c	2.0	2	70	17
3	5b	1.0	5 ^c	4.0	2.5	79	0
4	5c	1.0	4 ^c	4.0	2	76	0

^a Carried out with substrates **5** (0.15 mmol) in NMP (3 ml) at room temp.^b Isolated yields after column chromatography (SiO₂; PhMe–AcOEt, 2 : 1).^c Portions of Bu₃SnH added at intervals of 30 min.**Fig. 1** Time course of the reaction of 3,4-dichlorobutenate **5a** with Bu₃SnH and CuCl as described in Table 1, entry 4; (□) = dichloroazetidinone, (Δ) = allenecarboxylate, (○) = 3-norcephalosporin and (↓) = addition of Bu₃SnH (1 equiv.)

showing that during the course of the reaction, the allenecarboxylate **1** was formed and finally disappeared. This fact suggests that reductive 1,2-elimination of the vicinal dichloro group of **5a** leading to **1** and subsequent hydride addition to afford the 3-norcephalosporin **6** via the adduct **7** (Scheme 3). It is likely that copper(I) hydride generated from the reaction of tributyltin hydride with copper(I) chloride⁶ functions both as the reducing agent for the 1,2-elimination and as a hydride source of the latter addition–cyclization stage.

Further mechanistic and synthetic studies on the *in situ* generated copper(I) hydride species are in progress and the details will be reported in due course.

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**Scheme 3**

try of Education, Science, and Culture of Japan. The SC-NMR Laboratory of Okayama University is thanked for obtaining NMR spectra.

Footnote

† The allenecarboxylates **1** can be stored in a refrigerator for several days without appreciable change but are gradually decomposed under ambient conditions, particularly in the presence of a trace amount of acid or base.

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