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A Facile Synthesis of 3-(1,3-butadienyl)cephalosporins

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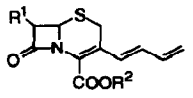
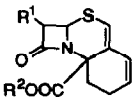
Abstract: *3-(1,3-Butadienyl)cephalosporins* ***1*** *were prepared in high yields from readily available* ***3*** *via phosphates* ***(E)-6****.*

Tremendous work has been done in the field of cephem antibiotics searching for new and effective drugs[1], including the semisynthetic approach by chemical modifications at the C-3 and C-7 side chains. Although the 1,3-butadiene moiety is an attractive group in synthetic organic chemistry[2] and suitable for its chemical modifications, cephalosporins **1** bearing this substituent at the 3-position have been hitherto unknown. One of the reasons is that the reaction of cephalosporin 3-triphenylphosphonium ylide with acrolein, leads to the tricyclic compound **2**, presumably via an initial Michael addition at C-4 followed by the intramolecular Wittig reaction[3].



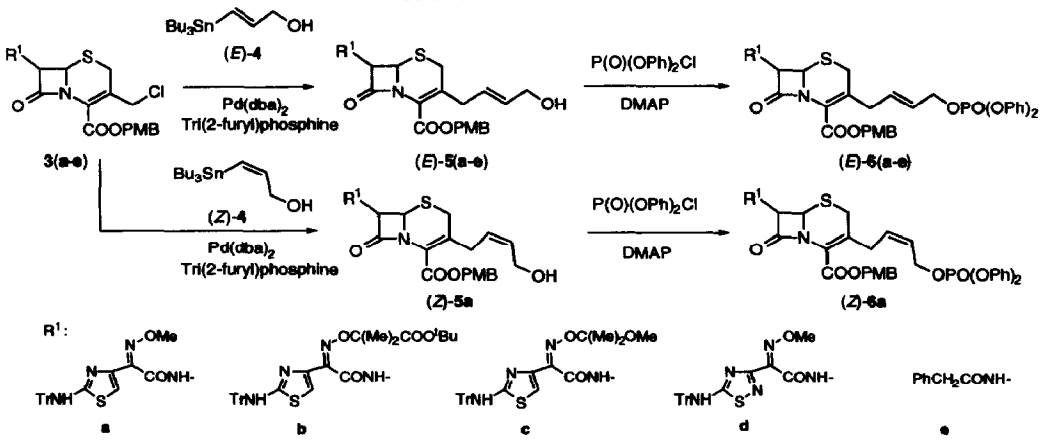
1



2

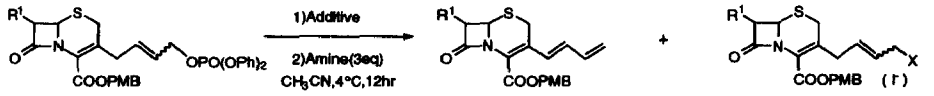
However, in the course of our study of substitution reactions of phosphates **6**, which are readily available from 3-chloromethylcephems **3**, we found that compounds **1** were obtained in excellent yields. Thus, **3(a-e)**

Scheme



were allowed to react with (*E*)-3-tributylstannyl-2-propen-1-ol, (*E*)-**4**[4] under Pd(0)-catalyzed cross-coupling conditions(73-97% yields)[5]. The resulting (*E*)-**5**(**a-e**) were converted to (*E*)-**6**(**a-e**) using diphenyl chlorophosphate(72-99% yields). (*Z*)-**6a** was similarly prepared utilizing (*Z*)-**4** (Scheme).

(*E*)- and (*Z*)-**6a** reacted with pyridine to give the substituted products, (*E*)- and (*Z*)-**7**(X=Pyr$^+$) (Entries 1 and 2). Similarly (*Z*)-**6a** reacted with *N*-ethyl-*N*-methylcarbamoylmethylamine to give the substituted product, (*Z*)-**7**(X=N$^+$MeEtCH$_2$CONH$_2$), while (*E*)-**6a** did not afford (*E*)-**7**(X=N$^+$MeEtCH$_2$CONH$_2$) but **1a** in 63% yield(Entries 3 and 4). The use of diisopropylethylamine, a hindered base, improved the yield of **1a** to 94%(Entry 5). In the case of **1a**, the total yield from **3a** was 86%. Under all the attempted conditions, (*Z*)-**6a** did not give the elimination product(Entries 2,4 and 6). Some examples of other 7-acylamino derivatives, **1**(**b-e**), are also exhibited in the following table.



Entry	Substrate	Amine	Additive	Product(%)[a]	
				1	(*E*)/(*Z*)-**7**
1	(*E*)-**6a**	Pyr	NaI	(0)	(*E*)X=Pyr$^+$(32)
2	(*Z*)-**6a**	Pyr	NaI	(0)	(*Z*)X=Pyr$^+$(28)
3	(*E*)-**6a**	MeEtNCH$_2$CONH$_2$	NaI	(63)	(0)
4	(*Z*)-**6a**	MeEtNCH$_2$CONH$_2$	NaI	(0)	(*Z*)X=N$^+$MeEtCH$_2$CONH$_2$(73)
5	(*E*)-**6a**	iPr$_2$NEt	-	(94)	(0)
6	(*Z*)-**6a**	iPr$_2$NEt	-	(0)	(0)[b]
7	(*E*)-**6b**	iPr$_2$NEt	-	(96)	(0)
8	(*E*)-**6c**	iPr$_2$NEt	-	(83)	(0)
9	(*E*)-**6d**	iPr$_2$NEt	-	(90)	(0)
10	(*E*)-**6e**	iPr$_2$NEt	-	(74)	(0)

[a] Isolated yield. [b](*Z*)-**6a** was recovered intact.

The reactions(*e.g.* Diels-Alder and 1,3-dipolar cycloaddition reactions) and biological activities of **1** and their related compounds will be reported in further articles.

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