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A Facile Synthesis of Cephem Side Chains by Palladium Catalyzed Cross-Coupling of 3-Substituted-Δ^3-Cephems with Dialkylzinc or Vinyltributyltin.

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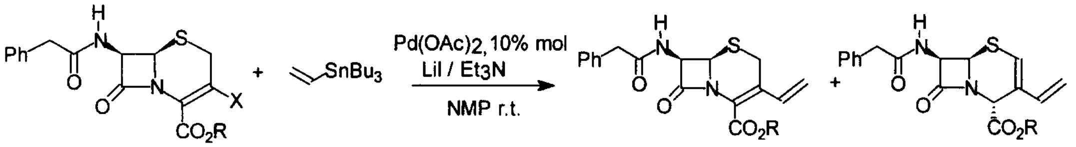
Abstract. Synthesis of 3-vinyl- and 3-alkyl-Δ^3-cephems was performed in a regioselective manner by palladium acetate catalyzed reaction of 3-sulfonato- or 3-bromo-Δ^3-cephems with dialkylzinc or vinyltributyltin. A new access to 3-alkyl-Δ^3-cephems is opened, starting from the allenyl compound **10**.

The chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of synthetic chemists, since they present a variety of synthetic challenges. In recent years, considerable interest has been found in the modification of the C(3) position of cephems to obtain 3-alkenyl substituted cephems, orally administered cephalosporin antibiotics with a broad spectrum of antibacterial activity and enhanced biological properties.[2]

Recently, Farina[3] and Torii[4] have developed methodologies to obtain 3-vinyl-cephems through the reaction of organocuprates[5,6] or alkenyltributyltin with allenylazetidinones,[7] starting from the readily available penicillin V sulfoxide diphenylmethyl ester. Moreover, palladium-catalyzed coupling reactions of organotin compounds with 3-(triflioxy)cephems, leading to the synthesis of 3-substituted cephems under mild conditions, has been described.[8] In contrast, very little is known about the use of the inexpensive and commercially available alkenylsulfonate or halogen derivatives in cross-coupling reactions with alkenyltin reagents.[9]

We wish now to report our success in the coupling of 3-sulfonato- and 3-bromo-cephems with vinylstannane in the presence of palladium acetate as a catalyst instead of other more expensive palladium complexes (Scheme 1).

Scheme 1



1 a X = OSO_2CF_3, R = $CHPh_2$
b X = OSO_2CF_3, R = PNB
2 a X = Br, R = $CHPh_2$
b X = Br, R = PNB
3 a X = OSO_2CH_3, R = $CHPh_2$
b X = OSO_2CH_3, R = PNB

PNB = p-nitrobenzyl

4 a-b

5 a-b

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The reaction is performed under mild conditions, at room temperature in anhydrous *N*-methylpyrrolidone (NMP), simply by treating the 3-substituted cephem **1-2-3** with vinyltributyltin and $Pd(OAc)_2$ (10% mol) in the presence of LiI and Et_3N (Table 1).

Table 1. Reaction of 3-substituted cephem **1-3** with vinyltributyltin and $Pd(OAc)_2$ as catalyst[a].

Entry	substrate	LiI	Et_3N	t (h)	**4 / 5** (Δ^3/Δ^2)[b]	Overall yield[c] %
1	**1a**	-	-	10	100 / 0	92
2	**1a**	-	0.1 eq.	5	100 / 0	93
3	**1b**	-	-	4	100 / 0	93
4	**2a**	2 eq	-	72	70 / 30	90
5	**2b**	-	-	6	100 / 0	88
6	**2b**	2 eq	-	3	100 / 0	85
7	**2b**	2 eq	0.1 eq	3	65 / 35	86
8	**3a**	-	-	72	-	-
9	**3a**	2 eq.	-	72	100 / 0	85
10	**3a**	2 eq.	0.1 eq.	4	20 / 80	87
11	**3b**	2 eq.	-	24	5 / 95	85

[a]For experimental conditions see ref. 10. [b]ratio is determined by H^{1}NMR analysis. [c]Isolated yield

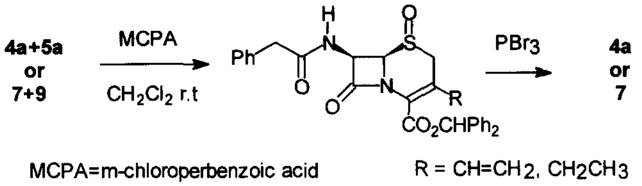
As shown in Table 1, the reaction yields are very high in all cases examined, the remaining isolated material being starting material. Several reactions were run with final times ranging between 3 h and 72 h but they are generally complete in 6 h at room temperature. The reaction of triflates **1a** and **1b** with vinyltributyltin, as already well known for the cross-coupling reaction, has proved to be extremely general affording the 3-vinylcephem **4a-b** in excellent yields as a single isomer (entries 1-3) whereas mesylates **3a-b** lead to the products only in the presence of LiI (entries 8-11). In the case of the bromides **2a-b** the effect of LiI is to increase the reaction rate (entries 5, 6). Another remarkable aspect of this reaction is that the *p*-nitrobenzyl esters react faster than the diphenylmethanyl ones, probably due to steric effects.

The palladium-catalyzed reaction of **3a** in the absence of LiI (entry 8) did not work and returned starting material. We suggest that in our system, as already reported by Farina,[8] a mesylate / iodide exchange takes place through conjugate addition followed by elimination.[11]

The small amount of Et_3N added in some cases to the reaction mixture (entries 2, 7, 10), seems to increase the reaction rate favouring elimination of the leaving group at C(3) with subsequent partial Δ^3/Δ^2 isomerization. To confirm this behaviour we added Et_3N in catalytic amounts to **4a** and obtained **4a** / **5a** in a 1 / 1 ratio.

However, the complete isomerization to the more interesting, for antibacterial activity, Δ^3-cephem compound (**4a or 7**) was achieved *via* oxidation of the mixture Δ^3/Δ^2 with MCPA[12] followed by treatment with PBr_3 (Scheme 2).

Scheme 2



In a similar way, we examined the reaction of 3-mesyloxy-cephem with dialkylzinc. When **3a** was reacted with diethylzinc or dimethylzinc in the presence of LiI and $Pd(OAc)_2$, the corresponding 3-alkylcephems **6-8** and **7-9** were isolated as mixtures of Δ^3/Δ^2 isomers (Scheme 3, Table 2).

Scheme 3

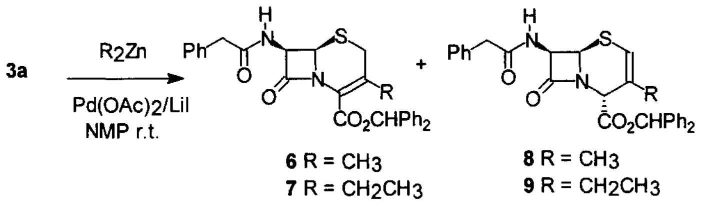


Table 2. Reaction of **3a** with dialkylzinc and Pd $(OAc)_2$ as catalyst.

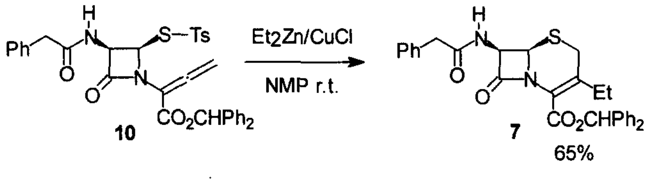
Entry	substrate	reagents[a]	products (Δ^3/Δ^2)[b]	Overall yield[c] %
1	**3a**	LiI/Me_2Zn	**6-8** (25/75)	65
2	**3a**	LiI/Et_2Zn	**7-9** (40/60)	75

[a] reaction performed at room temperature, in anhydrous NMP, treating **3a** with 10% mol $Pd(OAc)_2$, LiI (2 eq.) and R_2Zn (1.5 eq, 1 M in THF). [b] ratio is determined by H^1NMR analysis. [c] Isolated yield.

Even in this case, the Δ^3-cephem **7** was obtained according to the procedure reported in Scheme 2.

Next, we focused our attention on the intramolecular ring closure of the allenylazetidinone **10**, easily obtained from penicillin V sulfoxide,[7] to introduce a variety of carbon based substituents of our choice at the cephem C(3) position.[6] In fact, the reaction of **10** in a 1M solution of anhydrous NMP with CuCl (1 eq.) and diethylzinc (1.3 eq, 1M in THF) afforded **7** in 65% yield, through 1,4-conjugate addition at the central allenic carbon (Scheme 4).

Scheme 4



In conclusion, we have accomplished cross-coupling reactions of **1-2-3** with organometallic reagents under mild conditions to obtain 3-vinyl- and 3-alkyl-Δ^3-cephems in excellent yields. The results disclosed herein considerably extend the scope of the reaction. Moreover, the use of the less expensive and readily available starting materials and catalyst is particularly interesting for industrial applications.

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10. *Typical procedure*: In a flask under N_2 atmosphere, at room temperature, 0.33 mmol (190.7 mg) of **3a** in10 mL of anhydrous NMP are treated with 2 eq. of LiI (0.088g, 0.66 mmol), 0.1 eq. of $Pd(OAc)_2$ (0.007g, 0.033 mmol), 0.1 eq. of Et_3N (4.6 μL, 0.033 mmol) and 1.25 eq. of vinyltributyltin (0.12 mL, 0.41 mL). The reaction is followed by TLC and HPLC analysis and after consumption of the starting material the reaction mixture is diluted with 20 mL of AcOEt and washed with water (3x20 mL). The organic phase is dried, concentrated in *vacuo* and purified on silica gel to furnish (146.7 mg) of products **4a**/**5a** as an amorphous solid in 20/80 ratio and 87% overall yield.
    All compounds gave spectral data identical with those reported in literature.
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