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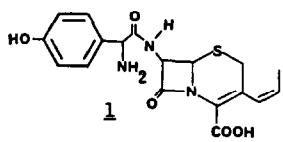
PALLADIUM CATALYSIS IN CEPHALOSPORIN CHEMISTRY: A VERSATILE NEW APPROACH TO 3-SUBSTITUTED CEPHEMS

Vittorio Farina*[1], Stephen R. Baker and Chester Sapino, Jr.

Pharmaceutical Research and Development Division
Bristol-Myers Company
P.O. Box 4755
Syracuse, New York 13221-4755

SUMMARY: The coupling of 3-triflyloxycephems with unsaturated stannanes proceeds under mild conditions with the use of a palladium (0) catalyst based on the new ligand tri(2-furyl)phosphine.

In connection with our synthetic work aimed at an efficient synthesis of the broad-spectrum oral antibiotic BMY-28100, 1[2], we have considered several approaches to the stereorational construction of the Z-propenyl side chain at C(3) of the cephem nucleus.



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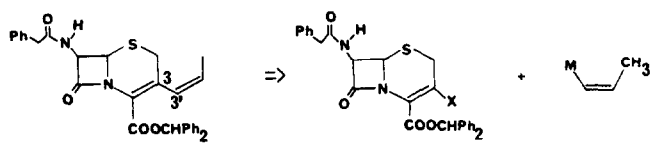
A stereospecific approach involving direct formation of the C(3)-C(3') bond appeared especially interesting, in view of its novelty[3] and possible generality (Eq. 1).

(1)



2 3 4

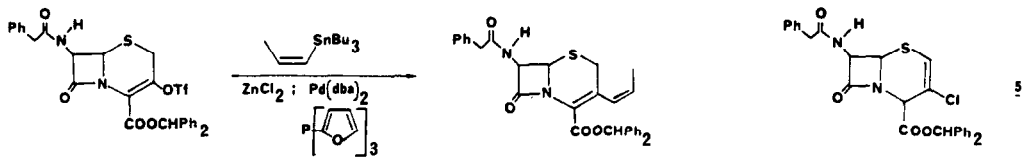
a) X = OSO_2CF_3 a) M = $SnBu_3$
b) X = Cl b) M = Li
c) X = OSO_2CH_3
d) X = $OP(O)(O\Phi)_2$
e) X = OH

Since 3-hydroxycephems, i.e. 3e, are readily available[4], we explored the palladium-catalyzed coupling of suitably functionalized cephems (3a-d) with Z-propenyltributyl stannane[5], according to Stille's methodology[6].

We found that coupling between triflate 3a[7] and olefinic stannanes is unsatisfactory when carried out according to the literature conditions[6]. The use of $Pd(P\phi_3)_4$ - LiCl in THF led largely to the 3-chloro cephem 3b, which readily isomerized to the Δ^2-cephem 5 and gave only traces of the desired product 2. Use of zinc chloride[8] as the halide source gave no 5, but conversion to 2 was so slow in refluxing THF that extensive decomposition of the sensitive 3a took place and 2 was obtained in very poor yield.

After some experimentation, we found that the desired coupling could be induced in satisfactory yield with complete stereospecificity (>99%) by carrying out the reaction at room temperature in N-methylpyrrolidinone, in the presence of $ZnCl_2$[9], and using a catalytic system obtained by combining 2% moles of bis(dibenzylideneacetonyl)palladium (0) [$Pd(dba)_2$] with 4% moles tri(2-furyl)phosphine (Eq. 2).

(2)



3a 2 5

N-Methylpyrrolidinone as a solvent offered enhanced rates over THF or CH_3CN; in addition, the reaction showed first order kinetics[6] over at least three half-lives, and proceeded readily to completion, while in most other solvents the reaction slowed down dramatically after one half-life.

The substitution of tri(2-furyl)phosphine[10] for triphenylphosphine was alone responsible for a rate enhancement[11] of ca. 17; the coupling yield also increased from 20-25% to 65% due to the much milder conditions employed.

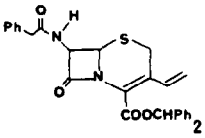
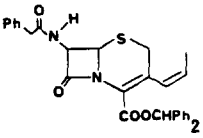
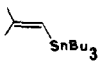
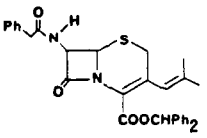
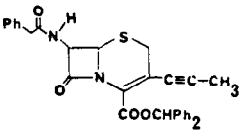
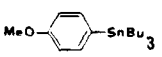
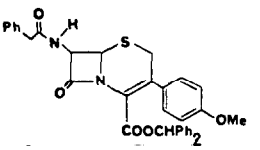
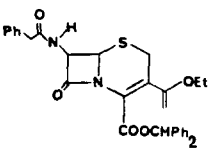
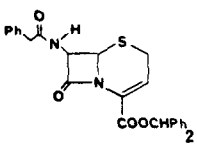
Tri(2-furyl)phosphine has not previously been used as a ligand in catalytic Pd(0) chemistry[12]. We postulate that this new phosphine facilitates the transmetalation step, usually the slow one in stannane couplings[6], by reducing electron density at palladium[13]. Our method[14] served to introduce alkenyl, aryl and alkynyl groups at C(3) (see Table).

Reduction with tin hydride was also successful. Allyl stannanes did not react satisfactorily under the above conditions. Cephems 3b, 3c and 3d, on the other hand, failed to undergo coupling with vinyl stannanes under conditions that worked well for 3a; decomposition resulted at higher temperatures.

The present method seems versatile enough to provide an entry into a variety of new classes of semisynthetic cephalosporins. We are currently exploring these and other possibilities.

TABLE

Palladium-Catalyzed Coupling of 3a with Stannanes.

Entry	Stannane	Product		Temperature (Time)	% Yield (Isolated)
1			6	25°C, 1 h	79
2			2	25°C, 16 h	65 [a]
3			7	25°C, 72 h	66
4			8	50°C, 1 h	50
5			9	50°C, 6 h	57
6			10	25°C, 16 h	52
7			11	65°C, 1 h	68 [b]

[a] 98% Z-Stannane gave 97% Z product.

[b] THF was used as a solvent, with 5 equivalents of tin hydride.

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7. Triflate 3a was prepared in 90% yield from 3e with 1 eq. triflic anhydride and diisopropylamine in CH_2Cl_2 at -78°C.
8. Godschalx, J.; Stille, J.K. Tetrahedron Lett. 1980, 2599.
9. Use of LiBr or LiI led to the rapid formation of the Δ-2 3-halocephems analogous to compound 5. This reaction was not catalyzed by palladium. Our coupling took place at appreciable rate (although rather slowly) even without any halide source. Full details will appear in due course.
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11. Rates for a number of ligands were determined by a quantitative reverse-phase (C-18) HPLC method.
12. Trost, B.M.; Verhoeven, T.R. in "Comprehensive Organometallic Chemistry"; Wilkinson, G.; Stone, F.G.A.; Abel, E.W. Eds.; Pergamon Press: New York; Vol. 8, 799.
13. We have observed an even more substantial rate enhancement in a related study: Farina, V.; Baker, S.R.; Bengini, D.A.; Sapino, C., submitted for publication.
14. A typical procedure follows: Triflate 3a (107 mg, 0.169 mmol) in dry N-methylpyrrolidinone (3 mL) was treated with the appropriate stannane (0.20 mmol). Zinc chloride (52 mg, 0.38 mmol), $Pd(dba)_2$ (2.45 mg, 0.0042 mmol) and tri(2-furyl)phosphine (2.0 mg, 0.0085 mmol) were then added. The dark solution was stirred under Argon at 25-50°C for the required time (see Table). The products were isolated by flash chromatography on SiO_2. All new compounds were characterized by elemental analysis, NMR and mass spectroscopy.

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