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Palladium-Promoted Derivatizations of Novel C-Fused Penem Ring Systems

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Key Words: palladium catalysis, esterification, carboxylation, β-lactams, penems

Abstract: *Palladium-catalyzed coupling reactions and carboxylations are reported for the functionalization of bicyclic beta-lactam ring systems related to the penem family of antibiotics.* © 1997 Elsevier Science Ltd.

The effectiveness of the beta-lactam antibiotics has been on a steady decline due to the emergence of drug-resistant microorganisms. It is now apparent that the development of new antibacterial drugs for battling infections caused by these pathogenic agents is both necessary and urgent.[1] Over the last thirty years, a wide diversity of new beta-lactam ring systems have been introduced and investigated for antibiotic properties.[2] Our laboratory has become interested in studies on non-conventional beta-lactam rings related to the penicillins, penems, or clavulanic acids in which the position of the lactam functionality within the four-membered ring has been altered.[3] We recently reported the synthesis of C-fused beta-lactam core structures corresponding to the penem[4] class of compounds whose lactam group is removed from the centers of the ring fusion (see Figure I).[3b] In this paper, we describe means by which the vinyl halide group X within these structures can be efficiently exchanged for functionalities in order to enable suitable compounds to be prepared for biological studies.

Figure 1. Structures of N-Fused and C-Fused Penems

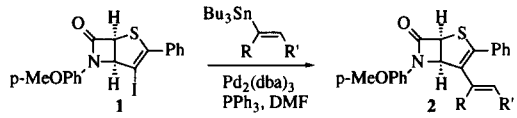
N-fused penems C-fused penems

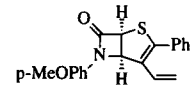
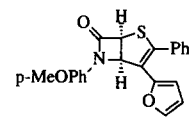
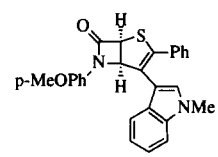
The positioning of the vinyl halide in these C-fused penems beta to a potent (sulfur) leaving group presented a difficult challenge in attempting to replace the halogen (X=I) for other functionality. Our initial attempts to carry out low temperature metallation (tBuLi or Mg°) and subsequent alkylation or aldol reaction, or radical generation (Bu_3SnH/AIBN or $(Bu_3Sn)_2$) in the presence of various radical trapping agents, led only to products derived from opening of the dihydrothiophene or beta-lactam rings. We therefore centered our attention on palladium-catalyzed processes, recognizing the success and mild nature of Stille cross-coupling reactions[5] and related CO insertion[6] processes involving unsaturated halides or triflates. However, only a very limited number of examples of Pd(0)-promoted reactions on beta-lactams or functionality related to our systems have been reported.[7]

We first examined the Stille cross-coupling of substrate **1**[3b] with organotin reagents using 3 mol% of palladium bis(dibenzylideneacetone) ($Pd_2(dba)_3$) in the presence of 6 mol% of triphenylphosphine (Table I). Reaction of **1** with tributylvinyltin provided a high yield of adduct **2a**[8], which upon ozonolysis gave the

corresponding aldehyde derivative. Likewise, heteroaromatic rings can be introduced onto the bicyclic core of **1**, as evidenced by the formation of furan adduct **2b** and indole[9] adduct **2c**. These examples demonstrate that the sulfur and beta-lactam moieties in **1** do not interfere with the alkylation reaction, and suggest that other palladium-promoted processes might also prove successful.

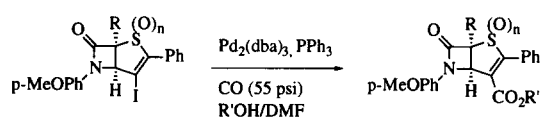
Table I. Palladium-Promoted Cross Coupling Reactions of Beta-Lactam 1 with Organostannanes



Organostannane	Adduct **2** (isolated % yield)
Bu_3Sn	 (**2a**, 80%)
Bu_3Sn O	 (**2b**, 80%)
Bu_3Sn NMe	 (**2c**, 74%)

This latter possibility was demonstrated upon examination of CO insertion reactions of **1** using catalytic $Pd_2(dba)_3$ in a mixed alcohol-dimethylformamide solvent under an atmosphere of carbon monoxide, to produce the desired esters **5** and **6** in good yield (Table II).[6] Similarly, α-ethylthio beta-lactam derivative **3** and bis-sulfone **4** provided esters **7** and **8**, respectively. While these insertion reactions proceed smoothly at room temperature, it was generally advantageous to run them at the slightly elevated temperature of 50°C.

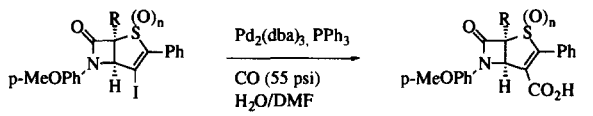
Table II. Palladium-Catalyzed Esterifications of Beta-Lactams



Substrate	R'OH	Adduct (isolated % yield)
1 R=H, n=0	MeOH	**5** R=H, R'=Me, n=0 (75%)
	CH_2=$CHCH_2OH$	**6** R=H, R'=CH_2CH=CH_2, n=0 (73%)
3 R=SEt, n=0	MeOH	**7** R=SEt, R'=Me, n=0 (90%)
4 R=SO_2Et, n=2	MeOH	**8** R=SO_2Et, R'=Me, n=2 (73%)

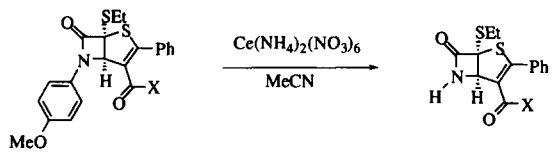
Given the ease and efficiency in which these palladium-promoted reactions occur, we considered the possibility of carrying out the CO insertions in aqueous media to prepare *carboxylic acid* derivatives directly from the iodides. Palladium-assisted carboxylations of this type are rare, and rather limited in scope.[10] Moreover, we are unaware of any reports of palladium-catalyzed carboxylation reactions involving beta-lactam ring systems or vinyl halides. Despite our concern that the beta-lactam might not survive the hydrolytic conditions of the reaction, substrates **1**, **3**, and **4** were found to readily produce carboxylic acids **9**-**11**, respectively, in hydrous dimethylformamide media (Table III). Optimal conditions for this reaction require that only a minimal amount of water (<1%) be present and that the reactions be run at room temperature. Despite the long reaction times (3-5 days), the beta-lactam ring is not opened under these conditions, and the carboxylic acids can be obtained in 65-75% isolated yield after purification by flash chromatography.[11]

Table III. Palladium-Catalyzed Carboxylations of Beta-Lactams



Substrate	Adduct (isolated % yield)
1 R=H, n=0	**9** R=H, n=0 (65%)
3 R=SEt, n=0	**10** R=SEt, n=0 (75%)
4 $R=SO_2Et$, n=2	**11** $R=SO_2Et$, n=2 (72%)

The p-methoxyphenyl N-protecting group can be easily cleaved from these functionalized derivatives using ceric ammonium nitrate in acetonitrile. Thus, upon oxidative deprotection, compounds **10** and **12**[11] cleanly afforded the N-unsubstituted beta-lactams **13** and **14**.



10 X = OH
12 X = SEt

13 X = OH (74%)
14 X = SEt (75%)

In summary, noteworthy features of this methodology include the use of palladium(0) as a catalyst for vinyl halide substitutions on especially sensitive beta-lactam ring systems, and the direct conversion of vinyl iodides to carboxylic acid derivatives. We are presently utilizing these procedures to prepare additional C-fused beta-lactam derivatives for biological testing.

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References and Notes

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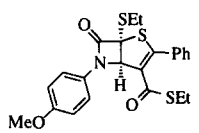
11. In the carboxylation of beta-lactam **3**, a small amount (5-10%) of thioester **12** is also obtained through a yet unidentified pathway.



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