



Pergamon

Tetrahedron Letters 41 (2000) 2995–2998

TETRAHEDRON  
LETTERS

## Preparation and reactivity of carbapenem-2-stannane

Jeremy D. Hinks,\* Eric Hunt and Andrew K. Takle

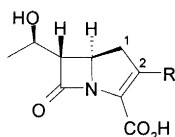
SmithKline Beecham Pharmaceuticals, Department of Medicinal Chemistry, New Frontiers Science Park, Third Avenue,  
Harlow, Essex, CM19 5AW, UK

Received 14 January 2000; accepted 14 February 2000

### Abstract

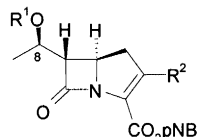
A carbapenem-2-stannane derivative was prepared via cross coupling of a carbapenem-2-triflate with hexamethylditin. A study of the reactions of the carbapenem-2-stannane with aryl halides, vinyl triflates and hydroxamoyl chlorides is described. © 2000 Elsevier Science Ltd. All rights reserved.

One of the areas of research in the field of carbapenem antibacterials has been the preparation of synthetic analogues **1** of thienamycin **2**,<sup>1</sup> with aryl and, to a lesser extent, heteroaryl groups attached directly to the C-2 position. One method for preparing this class of compounds is the Stille cross coupling procedure,<sup>2</sup> using the carbapenem triflate **3** and aryl stannanes.<sup>3</sup>



**1** R = aryl or heteroaryl

**2** R = SCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>



**3** R<sup>1</sup> = SiMe<sub>2</sub><sup>t</sup>Bu, R<sup>2</sup> = OSO<sub>2</sub>CF<sub>3</sub>

**4** R<sup>1</sup> = H, R<sup>2</sup> = OSO<sub>2</sub>CF<sub>3</sub>

**5** R<sup>1</sup> = SiMe<sub>2</sub><sup>t</sup>Bu, R<sup>2</sup> = SnMe<sub>3</sub>

**6** R<sup>1</sup> = H, R<sup>2</sup> = SnMe<sub>3</sub>

For the preparation of novel carbapenem derivatives, this methodology is limited by the synthetic availability of suitable substituted stannanes. For instance, many heterocyclic stannanes are difficult to prepare if the heteroaromatic nucleus is unstable under anionic reaction conditions. Switching the reactive groups such that the vinyl stannane is part of the carbapenem nucleus increases the potential diversity of the reaction, by virtue of the fact that the coupling partners can now be halides or pseudohalides, which in the case of many heterocycles are more accessible. A further advantage is that acid chlorides, benzyl

\* Corresponding author. Current Address: University of Southampton, Department of Chemistry, Highfield, Southampton SO17 1BJ.

halides, and vinyl triflates are also viable partners in the coupling reaction.<sup>4</sup> Thus, efforts were directed towards preparing carbapenem-2-stannanes **5** and **6**.

Three approaches were investigated. Radical introduction of tin by displacement of a C-2 thioalkyl group has been shown to be effective in the formation of 2-stannylpenems;<sup>5</sup> however, under these conditions 2-thioethylcarbapenem failed to react with tri-*n*-butyltin hydride. The other approaches utilised the triflate **3** as the substrate. Attempts to displace the triflate group with tri-*n*-butyltin zincates were uniformly unsuccessful, with or without Pd(0) catalysis. However, treatment with hexamethylditin in a palladium(0) catalysed displacement reaction did show some promise. Initial experiments on triflate **3** are summarised in Table 1.

Table 1  
Preparation of carbapenem-2-stannane **5**

Pd(0)	(mol%)	Ligand	(mol%)	Yield	(conditions)
Pd(PPh <sub>3</sub> ) <sub>4</sub>	5	-	-	4%*	(4h at reflux)
Pd <sub>2</sub> (dba) <sub>3</sub>	5		20	8%	(1h at reflux)
Pd <sub>2</sub> (dba) <sub>3</sub>	5	AsPh <sub>3</sub>	20	11%	(1h at RT)
Pd <sub>2</sub> (dba) <sub>3</sub>	5	AsPh <sub>3</sub>	10	37%	(0.5h at RT)
Pd <sub>2</sub> (dba) <sub>3</sub>	10	AsPh <sub>3</sub>	40	33%	(0.5h at RT)

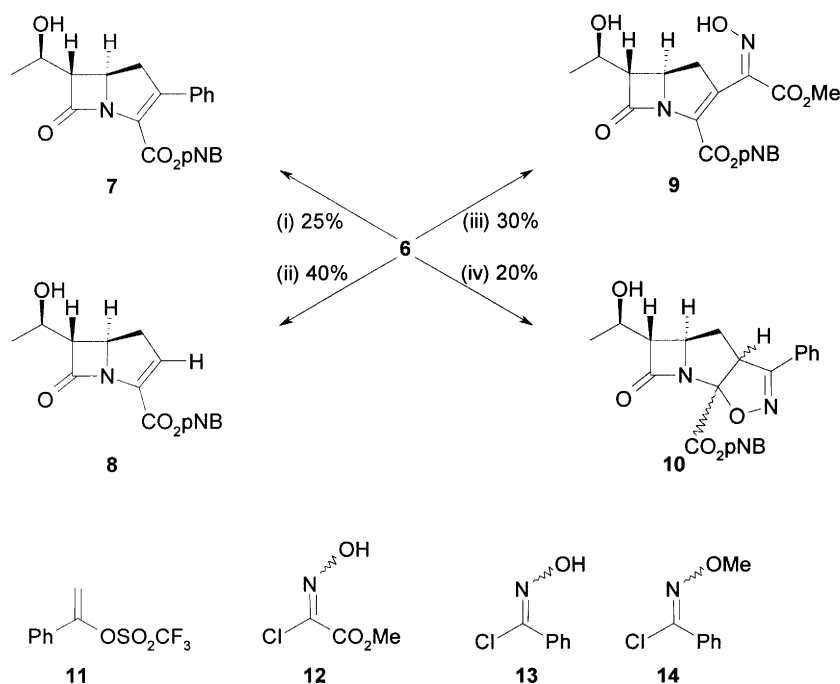
\* Major product was carbapenem-2-chloride (25%)

The most effective ligand was found to be triphenylarsine, in keeping with the work of Farina et al.<sup>6</sup> The optimal conditions were found to be 5 mol% Pd(0) with triphenylarsine in a ratio of 1:2 (Table 1). However, the best yields for this transformation were obtained using a substrate without 8-hydroxyl protection, and under the conditions described above, triflate **4** was converted into stannane **6** in 45% yield.<sup>7</sup> The reaction was equally effective on *p*-nitrobenzyl and *p*-methoxybenzyl esters. Attempts to utilise hexabutyliditin, however, resulted in substantially reduced yields.

A preliminary survey into the synthetic utility of **6** (Scheme 1) has yielded the following results. Coupling of **6** with iodobenzene was studied under a variety of conditions: (a) Pd<sub>2</sub>(dba)<sub>3</sub>/AsPh<sub>3</sub>; (b) BzPdCl(PPh<sub>3</sub>)<sub>2</sub>; (c) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>; (d) Pd(PPh<sub>3</sub>)<sub>4</sub>. Only catalyst (c) demonstrated any utility in the coupling reaction. The yield was enhanced slightly (to 25%) by employing a zinc cocatalyst.<sup>8</sup> Curiously, 2-methylcarbapenem was also detected under these conditions; the mechanism by which this is formed is unknown.

Reaction of **6** with the vinyl triflate **11** produced only the 2*H*-carbapenem **8** (this transformation was also obtained using the 8-TBDMS protected stannane **5**). This finding suggests that the required oxidative addition between the triflate and Pd(0) catalyst occurs successfully, however, this species must then undergo a β-elimination process producing phenylacetylene and a H-Pd-OSO<sub>2</sub>CF<sub>3</sub> (or Cl) complex before the rate determining transmetalation from tin to Pd(II) can occur. Transmetalation to the above Pd(II) complex followed by reductive elimination gives the 2-*H* carbapenem **8**.

A desire to prepare carbapenem derivatives with an oxime substituent attached via C-2<sup>9</sup> led us to investigate the reaction of hydroxamoyl chloride **12**<sup>10</sup> with **6**. Surprisingly, the reaction produced the C-2 oxyimino derivative **9** as a single isomer. The structure was confirmed as the (*E*)-isomer by



Scheme 1. Reactions of carbapenem-2-stannane **6**. Reagents and conditions: (i)  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $\text{ZnCl}_2$ , PhI, THF (ii)  $\text{Pd}_2(\text{dba})_3$  (5 mol%)/ $\text{AsPh}_3$  (10 mol%), LiCl, THF (iii) **12**,  $\text{BzPdCl}(\text{PPh}_3)_2$ , THF (iv) **13**,  $\text{Pd}_2(\text{dba})_3$  (5 mol%)/ $\text{AsPh}_3$  (10 mol%), THF

NOE experiments which showed a positive NOE between the carbapenem C-1 protons and the oxime proton ( $\text{CDCl}_3$ : 7.2 ppm, exchange in  $\text{D}_2\text{O}$ ). There are no literature examples of this reaction and, therefore, further oxime analogues were investigated under the same conditions. When the unstable derivative **13** was submitted to the coupling conditions the only detectable product was the isoxazoline **10**, presumably arising by cycloaddition of the nitrile oxide (derived through elimination of HCl from the hydroxamoyl chloride) across the carbapenem 2,3-double bond. The cycloaddition could only occur if prior destannylation had taken place under the acidic reaction conditions. Reaction with methoxime **14**, which cannot eliminate HCl, gave no coupling or cycloaddition product. These latter results suggest that sequential loss of HCl from **12**, destannylation, cycloaddition and ring opening of the isoxazoline represent a more plausible mechanism for the production of oxime **9**.

In conclusion, the carbapenem-2-stannanes **5** and **6** have been prepared by the Pd(0) catalysed reaction of hexamethylditin with **3** and **4**, respectively, and a preliminary investigation has been made into the reactions of **6** with aryl halides, vinyl triflates, and hydroxamoyl chlorides.

## References

- Albers-Schonberg, G.; Arison, B. H.; Hensens, O. T.; Hirschfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491–6499.
- Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 508–524.
- Rano, T. A.; Greenlee, M. L.; DiNinno, F. P. *Tetrahedron Lett.* **1990**, *31*, 2853–2856.
- Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth & Co., **1987**; pp. 185–242.
- Armitage, M. A.; Lathbury, D. C.; Sweeney, J. B. *Tetrahedron Lett.* **1995**, *36*, 775–776.
- Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

7. The best conditions for the preparation of **6** were as follows: A solution of tris(dibenzylideneacetone) dipalladium(0) (26 mg, 5 mol%) in dry THF (4 ml) was treated with triphenylarsine (17 mg, 10 mol%) and lithium chloride (96 mg, 2.3 mmol) and the mixture stirred at rt. This solution was added to triflate **4** (0.57 mmol) which was stirred in THF (4 ml) at  $-78^{\circ}\text{C}$  followed immediately by hexamethylditin (205 mg, 0.63 mmol). The reaction was allowed to warm to rt and then heated to  $50^{\circ}\text{C}$  for 15 min. After cooling the crude residue from the reaction was chromatographed over silica gel eluting with 30% ethyl acetate in hexane. The product was isolated as a foam (45%). The compound was characterised by NMR, IR and mass spectroscopy.
8. Zinc cocatalysts have been shown to improve the yields in many Pd(0) catalysed couplings of vinyl stannanes; see: Negishi, E.-I.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256.
9. Clear, N. J. C.; Davis, J. S.; Eglinton, A. J. E.; Fell, S. C. M.; Hinks, J. D.; Hird, N. W.; Hunt, E.; Moss, S. F.; Pearson, M. *J. J. Antibiotic.* **1997**, *50*, 237–245
10. Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366.