Pergamon

Tetrahedron Letters, Vol. 37, No. 17, pp. 2987-2988, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00480-7

A Direct and Convenient Approach Toward 2-Alkenylcarbapenems via the Heck Reaction

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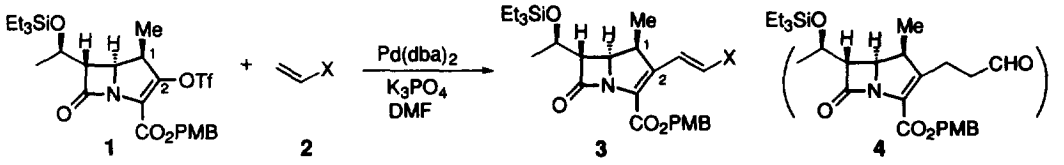
Abstract: Synthesis of 2-alkenylcarbapenems via the Heck reaction of carbapenem-2-yl triflate with mono-substituted alkenes is described. This method enables direct introduction of a variety of functionalized alkenyl substituents into the C-2 position without conversion into alkenylstannanes or alkenylboranes. Copyright © 1996 Elsevier Science Ltd

Carbapenem antibiotics have been of recent interest among β-lactam antibiotics due to their potent and broad-spectrum antibacterial activity[1]. Although many successful syntheses of carbapenems have been known[2], only recently have carbon side chains been directly introduced into the C-2 position of the carbapenem skeleton via carbon-carbon bond formation. 2-Aryl[3a,b], alkenyl[3b,d], and alkylcarbapenems[3c] have been synthesized by palladium-catalyzed cross-coupling reactions of organostannanes or organoboranes with carbapenem-2-yl triflates. These methods allow us to synthesize a wide variety of 2-substituted derivatives from a well-known intermediate, but organostannanes or organoboranes are still necessary in these processes. One reaction which can provide alkenyl-alkenyl coupling from alkenes and alkenyl halides or triflates is the Heck reaction[4] which has been known for more than two decades. Here we report the Heck reaction of carbapenem-2-yl triflate with substituted alkenes and demonstrate its usefulness for the synthesis of 2-alkenylcarbapenems.



a: X = CH_2NHCO_2PMB **d:** X = CH_2OAc **3a** 78% **3d** 57%
b: X = Ph **e:** X = $CH(OEt)_2$ **3b** 91% **3e** 77%
c: X = CO_2Me **f:** X = CH_2OH **3c** 81% **3f** 37%

The reaction of carbapenem-2-yl triflate **1**[3a,b,c] with 4-methoxybenzyl N-allylcarbamate **2a** proceeded readily in the presence of 5 mol% of $Pd(dba)_2$ and K_3PO_4 in DMF at 60°C to give 2-alkenylcarbapenem **3a** in 78% yield. The olefin configuration of the product was determined to be of *E*-geometry by ^1H NMR analysis of the vinylic protons (J = 16.4 Hz). None of the *Z*-olefin product was detected. This reaction could be

carried out using several alkenes having various functional groups, such as ester, acetal, and acetoxy groups. A representative procedure is as follows: To a stirred solution of freshly prepared enol triflate **1** (265 mg, 0.45 mmol)[5] and 4-methoxybenzyl N-allylcarbamate **2a** (198 mg, 0.89 mmol) in DMF (2 ml) were added at r.t. $Pd(dba)_2$ (13 mg, 0.022 mmol, 5 mol%) and potassium phosphate (114 mg, 0.54 mmol). After being stirred at r.t. for 1 h, the reaction mixture was heated to 60°C for 1 h. The mixture was then cooled to r.t., poured into water, and extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. Purification of the residue by silica gel column chromatography gave the cross-coupling product **3a** (231 mg) in 78% yield as a white powder[6].

Screening of various palladium catalysts revealed that this Heck reaction proceeds only when $Pd(dba)_2$ or $Pd(OAc)_2$ is used. Use of $Pd(Ph_3P)_4$, $PdCl_2(Ph_3P)_2$, or $PdCl_2(allyl)_2$ resulted in no desired coupling product or only a trace amount under our reaction conditions. Although most of the coupling reactions gave high yields of desired products, one exception was the reaction with allyl alcohol, which gave aldehyde **4**[7] (21%) as well as the desired coupling product **3f**. One plausible explanation for this result would be the two possible directions of β-hydride elimination during the catalytic cycle.

Acknowledgement: The authors thank Dr. Y. Ikenishi for the mass spectroscopy analysis.

References and Notes

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5. The substrate **1**[3c] was purified by rapid, short column chromatography just before use.
6. Physical data for compound **3a**: IR ($CHCl_3$) ν 3440, 1766, 1710 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.58 (q, *J* = 8.0 Hz, 6 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 1.28 (d, *J* = 5.8 Hz, 3 H), 3.17 (dd, *J* = 6.8 Hz, 2.6 Hz, 1H), 3.16-3.40 (m, 1 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 3.83-3.99 (m, 2 H), 4.09 (dd, *J* = 9.2 Hz, 2.6 Hz, 1 H), 4.20 (quint, *J* = 6.4 Hz, 1 H), 4.78-4.99 (br, 1 H), 5.05 (s, 2 H), 5.20 (s, 2 H), 5.86-6.10 (m, 1 H), 6.87 (d, *J* = 9.0 Hz, 4 H), 7.18 (d, *J* = 16.4 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 2 H), 7.38 (d, *J* = 9.0 Hz, 2 H); HR-MS Calcd for $C_{36}H_{48}N_2O_8SiNa$ $[M+Na]^+$ 687.3074, Found 687.3067; *Anal.* Calcd for $C_{36}H_{48}N_2O_8Si$: C, 65.03; H, 7.28; N, 4.21. Found: C, 64.90; H, 7.24; N, 4.30.
7. Physical data for compound **4**: IR ($CHCl_3$) ν 1769, 1717 cm^{-1}; ^{1}H-NMR(200 MHz, $CDCl_3$) δ 0.59(q, *J* = 8.0 Hz, 6 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 1.12 (d, *J* = 7.4 Hz, 3 H), 1.26 (d, *J* = 6.0 Hz, 3 H), 2.34-2.80 (m, 3 H), 2.91-3.15 (m, 2 H), 3.18 (dd, *J* = 6.6 Hz, 2.8 Hz, 1 H), 3.80 (s, 3 H), 4.09 (dd, *J* = 9.0 Hz, 2.8 Hz, 1 H), 4.20 (quint, *J* = 6.2 Hz, 1 H), 5.17 and 5.23 (ABq, *J* = 12.0 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.37 (d, *J* = 8.6 Hz, 2 H), 9.71 (t, *J* = 1.2 Hz, 1 H); HR-MS Calcd for $C_{27}H_{39}NO_6SiNa$ $[M+Na]^+$ 524.2442, Found 524.2442.
8. All new compounds were analyzed by IR, ^{1}H-NMR, MS and/or ^{13}C-NMR spectroscopies.

(*Received in Japan* 13 *January* 1996; *revised* 29 *February* 1996; *accepted* 7 *March* 1996)