Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2589-2592, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00377-2

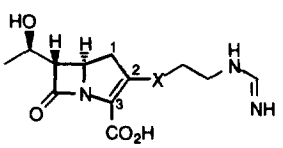
Facile Synthesis of 2-Alkyl Substituted Carbapenems *via* Palladium-Catalyzed Cross-Coupling Reaction

Yukitoshi Narukawa*, Koichi Nishi, and Hiroshi Onoue

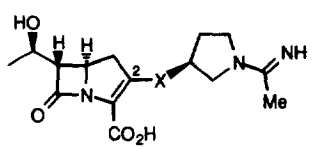
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Abstract: A direct synthesis of highly functionalized 2-alkylcarbapenems *via* a palladium-catalyzed cross-coupling reaction of alkylboranes with carbapenem-2-yl triflates is described. An advantage of this procedure is the introduction of C-2 alkyl side chain at the later stage of the synthesis, thus allowing the syntheses of a wide variety of functionalized 2-alkylcarbapenems more accessible.

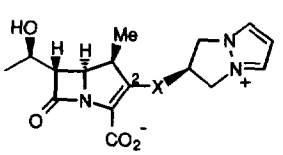
Since the discovery of thienamycin, carbapenems have been recognized as one of the most important class of β-lactam antibiotics. Most of the novel carbapenems synthesized so far belong to the thienamycin-like carbapenems, those with side-chain connected to the C-2 position by sulfur atom (e.g., X=S, **1a-4a**)[1]. During our investigation in this field, we were interested in synthesizing 2-alkylcarbapenems, *i.e.*, carbon analogs of thienamycin-like carbapenems in which C-2 side-chain is linked by carbon atom instead of sulfur (X=CH_2, **1b-4b**). While thienamycin-like carbapenems have been prepared from a well-known intermediate, carbapenem-2-yl phosphate and appropriate thiols, the synthesis of 2-alkylcarbapenems required introduction of alkyl side-chain *before* construction of the carbapenem skeleton[2], which would not be appropriate for the syntheses of a wide variety of 2-alkyl derivatives, especially highly functionalized ones. Herein we report Suzuki coupling reaction[3] of alkylboranes with carbapenem-2-yl triflates and its application to the syntheses of functionalized 2-alkylcarbapenems **1b-4b**[4], carbon analogs of clinically important compounds **1a-4a**.



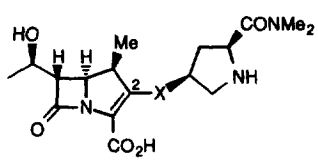
1a: X = S (imipenem)
1b: X = CH_2,



2a: X = S (panipenem)
2b: X = CH_2

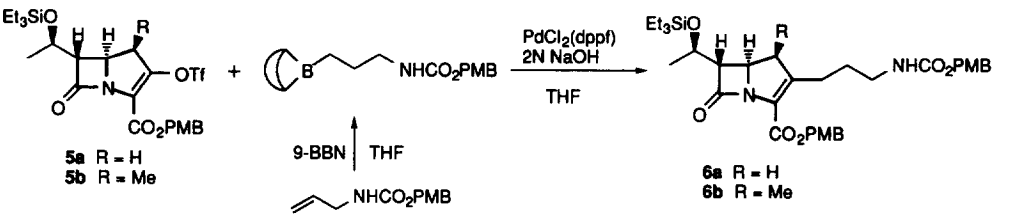


3a: X = S (biapenem)
3b: X = CH_2



4a: X = S (meropenem)
4b: X = CH_2

The requisite substrates for this reaction, carbapenem-2-yl triflates **5a,b** were prepared according to the established procedure from diazo derivatives[5]. The alkylboranes were prepared by hydroboration of the corresponding olefinic compounds with 9-BBN and used without further purification. The coupling reactions of triflate **5** with alkylboranes proceeded readily in THF at 60°C in the presence of 5 mol% of $PdCl_2$(dppf) and one equivalent of 2N NaOH (see the Table). A representative procedure is as follows: To an ice-cooled solution of 4-methoxybenzyl N-allylcarbamate (600 mg, 2.71 mmol) in THF (3 ml) was added a solution of 9-BBN in THF (0.5M, 8.1 ml, 4.1 mmol). Stirring was continued at r.t. for 2 h and cooled in an ice-bath. A solution of freshly prepared enol triflate **5a** (4.1 mmol) in THF (8 ml) was added to this, followed by $PdCl_2$(dppf) (99 mg, 0.14 mmol) and 2N aq NaOH (1.36 ml, 2.7 mmol) successively. After stirring with ice-cooling for 1 h, the reaction mixture was heated to 60°C for 2 h. The mixture was poured into water, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. Purification of the residue by silica gel chromatography gave coupling product **6a** (1.50 g, 85% yield) as a colorless oil.

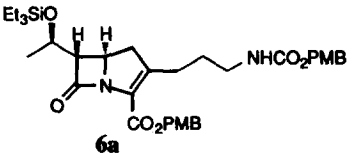
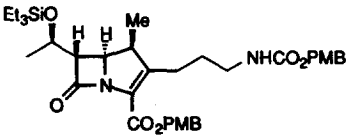
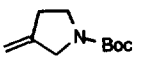
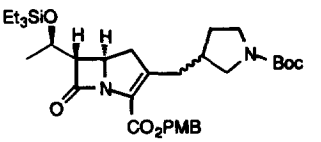
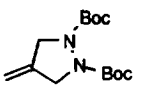
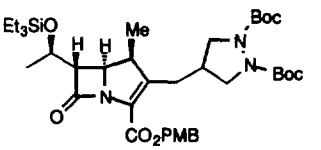
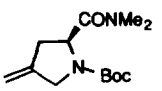
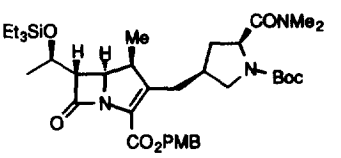


In entry 5 we could obtain the desired *cis*-pyrrolidine derivative[7] *via* hydroboration of 9-BBN, which is the preferred stereochemistry for excellent antibacterial activity[1d]. The coupling reaction also occurred effectively in DMF or in dioxane. As a catalyst, $PdCl_2$(dppf) was found to be most effective and the use of $Pd(OAc)_2$ or $Pd(Ph_3P)_4$ resulted in lower yields. The reaction was also possible even at r.t. in a moderate yield (5 mol% $PdCl_2$(dppf), 3h, 49% yield). These results indicate that this cross-coupling reaction has wide applicability for the synthesis of highly functionalized 2-alkylcarbapenems.

Highly efficient methodology in our hand, we turned our attention to synthesize the 2-alkylcarbapenems **1b-4b**, carbon analogs of clinically important agents. Simple deprotection of these coupling products **6a, 10-12** using $AlCl_3$-anisole method[8] followed by functionalization of the resultant amino group according to the literature[1a-d] gave desired 2-alkylcarbapenems **1b-4b** in good yields (yields of deprotection and N-functionalization: **1b**, 52%; **2b**[9], 40%; **3b**, 32%; **4b**, 47%)[10].

In summary, we have synthesized 2-alkyl substituted carbapenems by the direct formation of a carbon-carbon bond at the C-2 position *via* palladium-mediated cross-coupling reaction of alkylboranes with carbapenem-2-yl triflates. This method allows the introduction of a wide variety of alkyl substituents at the C-2 position *after* construction of the carbapenem skeleton. Utility of this reaction has been demonstrated by the synthesis of carbon analogs of clinically important carbapenems .

Table Palladium-Catalyzed Cross-Coupling Reaction of Alkylboranes with Enol Triflates

Entry	Enol Triflate	Olefin	Product	Yield(%)
1	**5a**		 **6a**	85
2	**5b**		 **6b**	66
3	**5a**	 **7**	 **10**	71*
4	**5b**	 **8**	 **11**	66
5	**5b**	 **9**	 **12**	64

* as a mixture of 1:1 isomers[9]

Acknowledgement: The authors thank Dr. Y. Terui for NMR measurement, Dr. Y. Ikenishi for mass spectroscopy analysis, and Dr. S. Sakaki for antimicrobial assay.

References and Notes

1. (a) imipenem: Leanza, W. J.; Wildonger, K. J.; Miller, T. W.; Christensen, B. G. *J. Med. Chem.* **1979**, *22*, 1435. (b) panipenem: Miyadera, T.; Sugimura, Y.; Hashimoto, T.; Tanaka, T.; Iino, K.; Shibata, T.; Sugawara, S. *J. Antibiot.* **1983**, *36*, 1034. (c) biapenem: Nagao, Y.; Nagase, Y.; Kumagai, T.;

Matsunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.* **1992**, *57*, 4243. (d) meropenem: Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519.

2. For example, see: Fujimoto, K.; Iwano, Y.; Hirai, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1363. Recently, a new synthesis of 2-alkylcarbapenem was reported: Feigelson, G. B. *Tetrahedron Lett.*, **1995**, *36*, 7407.
3. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
4. Syntheses of 2-arylcarbapenems via Stille coupling-reaction and Suzuki coupling-reaction were reported: (a) Rano, T. A.; Greenlee, M. L.; DiNinno, F. P. *Tetrahedron Lett.* **1990**, *31*, 2853. (b) Yasuda, N.; Xavier, L.; Rieger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U.-H. *Tetrahedron Lett.* **1993**, *34*, 3211.
5. Enol triflate PMB esters **5a,b** were prepared in a similar way as described in literatures: (a) Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936. (b) Fliri, H.; Mak, C.-P. *J. Org. Chem.* **1985**, *50*, 3438. (c) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles*, **1984**, *21*, 29. (d) Uyeo, S.; Itani, H. *Tetrahedron Lett.* **1991**, *32*, 2143. (e) Itani, H.; Uyeo, S. *Synlett* **1995**, 213. These triflates **5** were prepared from diazo compounds just prior to use for the cross-coupling reactions.
6. All new compounds were analyzed by IR, ^{1}H and/or ^{13}C NMR, and MS spectroscopies. Data for **6a**: IR ($CHCl_3$) ν 3442, 1772, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (6 H, q, *J* = 8.0 Hz), 0.94 (9 H, t, *J* = 8.0 Hz), 1.26 (3 H, d, *J* = 6.0 Hz), 1.57-1.74 (2 H, m), 2.58-2.69 (2 H, m), 2.81 (2 H, d, *J* = 9.0 Hz), 3.05 (1 H, dd, *J* = 6.6 Hz, 2.7 Hz), 3.04-3.19 (2 H, m), 3.78 (3 H, s), 3.80 (3 H, s), 4.06 (1 H, dt, *J* = 9.0 Hz, 2.7 Hz), 4.18 (1 H, quint, *J* = 6.3 Hz), 5.03 (2 H, s), 5.00-5.15 (1 H, br), 5.16 and 5.21 (2 H, ABq, *J* = 12.3 Hz), 6.86 (2 H, d, *J* = 8.7 Hz), 6.88 (2 H, d, *J* = 8.7 Hz), 7.31 (2 H, d, *J* = 8.7 Hz), 7.36 (2 H, d, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.92, 6.80, 22.6, 25.4, 27.7, 40.1, 40.3, 52.3, 55.1, 66.2, 66.4, 66.8, 113.8, 127.7, 128.9, 129.8, 129.9, 149.4, 156.6, 159.5, 161.5, 176.5; HRMS calcd for $C_{35}H_{48}N_2O_8SiNa$ $[M+Na]^+$ 675.3075, Found 675.3076.
Data for **1b**: IR (KBr) ν 3373, 1754, 1715, 1578 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 1.27 (3 H, d, *J* = 6.3 Hz), 1.71-1.91 (2 H, m), 2.46-2.75 (2 H, m), 2.87 (2 H, d, *J* = 9.0 Hz), 3.21-3.42 (3 H, m), 4.11 (1 H, dt, *J* = 9.0 Hz, 2.4 Hz), 4.20 (1 H, quint, *J* = 6.3 Hz), 7.75 (1 H, s); UV (H_2O) ν_{max} 267 nm (ε 4500). *Anal.* Calcd for $C_{13}H_{19}N_3O_4 \cdot 2.1H_2O$: C, 48.93; H, 7.33; N, 13.17. Found: C, 48.87; H, 7.03; N, 13.09.
7. *Cis*-stereochemistry of pyrrolidine ring system was confirmed by NOE experiment of the corresponding alcohol obtained by hydroboration of olefin **9** with 9-BBN followed by NaOH-H_2O_2 oxidation. Formation of *trans*-pyrrolidine isomer could not be detected.
8. Ohtani, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1984**, *49*, 5271.
9. The isomers **10** were separated by chromatography (SiO_2, toluene-EtOAc) into less polar (34%) and polar (37%) isomers. Absolute stereochemistry of the pyrrolidine ring was determined by independent synthesis of **10** from chiral *trans*-4-hydroxy-L-proline according to the conventional synthesis[2]. The less polar isomer **10** having *S*-configuration was converted into the final product **2b**.
10. Preliminary *in vitro* antimicrobial assay against Gram-positive and Gram-negative bacteria revealed that these carbapenems showed comparable (**3b**) or reduced activity (**1b**, **2b**, **4b**) compared with that of their sulfur analogs **1a-4a**, respectively.
11. Full details of olefin syntheses **7-9** and deprotection to final carbapenems **1b-4b** will be reported in due course.

(*Received in Japan* 11 *January* 1996; *revised* 22 *February* 1996; *accepted* 23 *February* 1996)