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# PREPARATION OF 2-ARYL- AND 2-ALKENYL-SUBSTITUTED CARBAPENEMS UNDER MILD SUZUKI CROSS-COUPLING CONDITIONS

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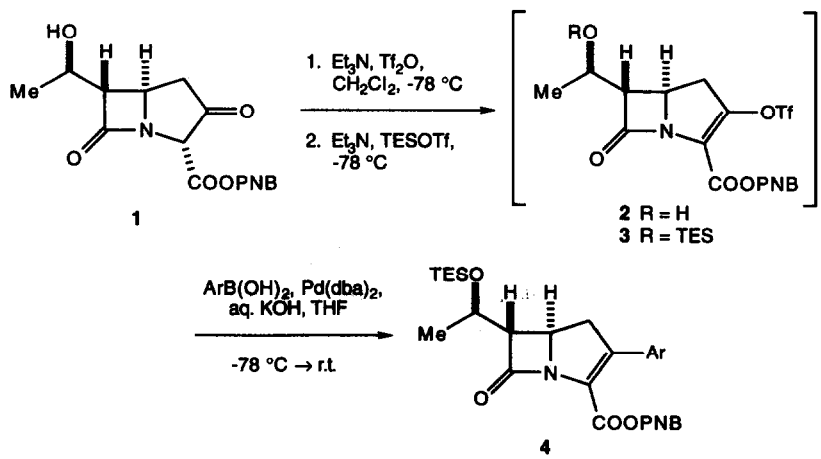
**Abstract:** An extraordinarily mild procedure for the synthesis of 2-aryl- and 2-alkenyl-substituted carbapenems *via* palladium-catalyzed coupling of a vinyl triflate with aryl or vinyl boronic acids is described. A major advantage of this procedure is the use of nontoxic boronic acid intermediates in place of highly toxic organostannane compounds which are used in the corresponding Stille cross-coupling reactions.

Since the discovery of thienamycin,[1] an extensive amount of effort has been devoted to the development of new carbapenem antibiotics.[2] Recently, the Medicinal Chemistry Group at Merck demonstrated the introduction of aryl moieties directly at the 2 position *via* carbon-carbon bond formation.[3] While this is a versatile strategy, these cross-coupling reactions had utilized highly toxic aryl and alkenyl stannane compounds.[3b,4,5] These reagents also produce toxic by-products which are difficult to remove, especially on a large scale. Therefore, we explored the Suzuki cross-coupling reaction[6] between the requisite arylboronic acids and the enol triflate derivative of **1**, which would give non-toxic and easily removed potassium borate as the by-product. β-Keto ester **1** is a

**Scheme 1**



key intermediate for thienamycin synthesis[7] and was chosen as a suitable starting material for preparation of 2-arylcarbapenems *via* palladium-mediated cross-coupling reactions.

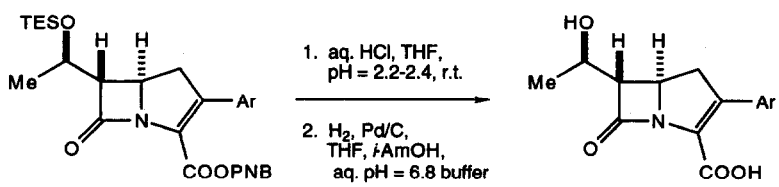
In an initial experiment, the coupling between **3** and phenylboronic acid[8a] gave only 4 % of the coupling product under conventional Suzuki conditions [$(Ph_3P)_4Pd$, $K_2HPO_4$, DMF, THF, 80 °C]. A systematic study of various solvents, bases, and catalysts revealed that the combination of $Pd(dba)_2$ (6 mol %)[8b] and 3 equivalents of 5.4 *M* aq KOH in THF/$CH_2Cl_2$ gave reproducibly high yields of the coupling product under very mild conditions.[9] The details of this study will be disclosed at a later date.

The optimized coupling conditions are illustrated in Scheme 1. Treatment of the bicyclic β-keto ester **1** with triethylamine and $Tf_2O$ in methylene chloride at -78 °C provided the extremely unstable enol triflate **2**.[10] The 8-hydroxyl group of **2** was protected *in situ* by addition of triethylamine and TESOTf at -78 °C to give the relatively stable silylated enol triflate **3**.[11] Although protection as the TBS ether was also possible, the triethylsilyl protecting group was chosen in order to balance the stability of **3** with the ease of deprotection after the coupling reaction. Subsequent addition of the boronic acid as a solution in THF, the catalyst, and base was followed by warming to ambient temperature to give the desired carbapenems **4** in high yields.

Couplings between *in situ* generated **3** and aromatic boronic acids are summarized in the Table.[12] Even though the reaction conditions were not optimized for each individual boronic acid, the yields were uniformly excellent with substituted phenylboronic acids having variety of functional groups, heteroaromatic boronic acids, and even an alkenylboronic acid. The one exception was 2,4-dichlorophenylboronic acid (entry 2). It was observed that introduction of *ortho* substituents on the aromatic ring (entries 2-4) reduced the reaction rate, but there was almost no difference in rate caused by introduction of electron donating groups (entry 5) or electron withdrawing groups (entry 6-8).

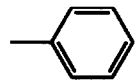
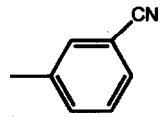
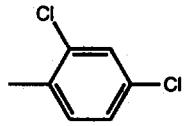
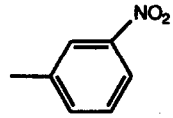
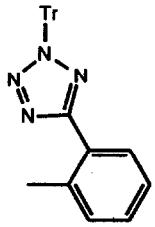
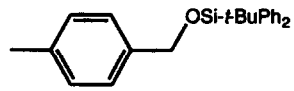
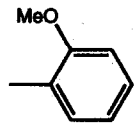
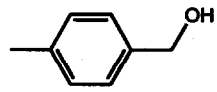
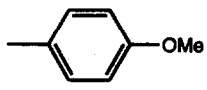
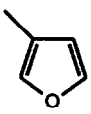
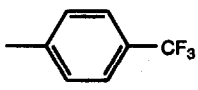
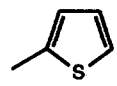
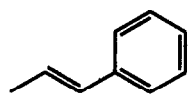
Deprotection of the carbapenem products (**4**) is shown in Scheme 2. The triethylsilyl moiety on the 8-hydroxyl group was removed in excellent yield in aqueous THF by controlling the apparent pH between 2.2 and 2.4 with 2 *N* aqueous HCl at room temperature for 1 to 2 hours. Finally, the PNB moiety was removed by hydrogenolysis to produce the unprotected carbapenems in good yield.

**Scheme 2**




In summary, a new route to 2-aryl or 2-alkenyl carbapenems has been developed. Through the Suzuki cross-coupling method, toxic organostannane compounds have been eliminated. This process would be suitable for large-scale preparation of these antibiotics.

**Table:** Palladium-catalyzed Coupling of Enol Triflate **3** and Boronic Acids.

| Entry | Ar | Ref.[a] | Yield[b] | Entry | Ar | Ref.[a] | Yield[b] |
|---|---|---|---|---|---|---|---|
| 1 |  | 8a | 92% (73%) | 7 |  | 16 | 95% |
| 2 |  | 8b | 36% | 8 |  | 17 | 46%[d] |
| 3 |  | 13 | 60%[c] | 9 |  | 16 | 82% |
| 4 |  | 14, 15 | 73% (82%) | 10 |  | 18 | 70% (67%) |
| 5 |  | 15 | 83% (64%) | 11 |  | 14, 19 | 53% |
| 6 |  | 15 | 72% | 12 |  | 20 | 51%[d] (41%) |
| | | | | 13 |  | 21 | 76% |

[a] References for preparation of the boronic acids.

[b] The yields in parentheses refer to the corresponding Stille couplings using organostannane reagents (Ref. 3b).

[c] In this example, **3** was prepared in THF, $Pd(PPh_3)_4$ was used as catalyst, and the boronic acid was added as a solution in diethoxymethane. The coupling reaction was run at 60 °C for 2.5 h.

[d] The yields of pure product were lower in these cases due to difficult separation from excess **3**.

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8. (a) Purchased from Aldrich. (b) Purchased from Johnson-Matthey.
9. A representative procedure is as follows: To a stirred, precooled (-78 °C) suspension of β-keto ester **1** (802 mg, 2.3 mmol) in $CH_2Cl_2$ (9.2 mL) was added triethylamine (321 μL, 2.3 mmol) under nitrogen (internal T ≤ -70 °C). After 15 minutes, $Tf_2O$ (389 μL, 2.3 mmol) was added to the resulting orange-yellow solution (internal T ≤ -70 °C). After 15 min, triethylamine (385 μL, 2.76 mmol) was added (internal T ≤ -70 °C). After 15 minutes, TESOTf (562 μL, 2.5 mmol) was added to the mixture (internal T ≤ -70 °C). After 30 min at -78 °C, $Pd(dba)_2$ (30 mg, 0.12 mmol), a solution of 2.0 mmol of boronic acid in 15 mL of tetrahydrofuran, and 5.4 *M* aq KOH (1.3 mL, 7 mmol) were added sequentially at -78 to -60 °C. The dry-ice/acetone bath was removed and the mixture was allowed to warm to ambient temperature (on a multigram scale, a mild exotherm was observed (→33 °C)). Upon reaction completion (usually 1 to 4 hours at ambient temperature), the mixture was concentrated *in vacuo* to remove most of the tetrahydrofuran. The residue was extracted with $CH_2Cl_2$. The extract was washed with water and brine, dried over magnesium sulfate, and purified by silica gel column chromatography.
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11. This compound could be purified on silica gel column chromatography. $^1H$ NMR ($CDCl_3$) δ 8.22 (2 H, *m*, PNB), 7.62 (2 H, *m*, PNB), 5.46 (1 H, *d*, *J* = 13.6 Hz, PNB), 5.33 (1 H, *d*, *J* = 13.6 Hz, PNB), 4.20 - 4.37 (2 H, *m*, H-5 and H-8), 3.33 (1 H, *dd*, *J* = 3.2, 5.3 Hz, H-6), 3.08 - 3.27 (2 H, *m*, H-1), 1.26 (3 H, *d*, *J* = 6.2 Hz, H-9), 0.95 (9 H, *t*, *J* = 7.8 Hz, TES), 0.60 (6 H, *m*, TES); $^{13}C$ NMR($CDCl_3$) δ 176.5, 157.8, 148.1, 147.8, 141.8, 128.5, 124.7, 123.7, 118.2 (*q*, $J_{C\text{-}F}$ = 320.3 Hz), 68.8, 65.9, 65.2, 50.4, 35.8, 22.4, 6.7, 4.8; HPLC, column: Zorbax CN (4.6 mm x 25 cm), mobile phase: $CH_3CN$ : 0.01 M $K_2HPO_4$ = (0 min.) 35 : 65; (10 min.) 35 : 65; (30 min.) 65 : 35; (40 min.) 65 : 35, flow rate; 1.5 mL/min., UV detection: 258 nm., retention time: 32 min.
12. The structure assigned to each new compound is in accord with its infrared, $^1H$ and $^{13}C$ NMR, and high resolution mass spectra.
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16. These boronic acids were prepared from the corresponding bromo compounds according to the method in reference 15.
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