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Palladium-Catalyzed Cross-Coupling in the Synthesis of Pyridinyl Boxazomycin C Analogues

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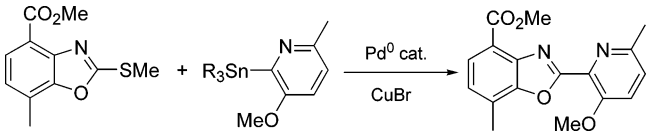
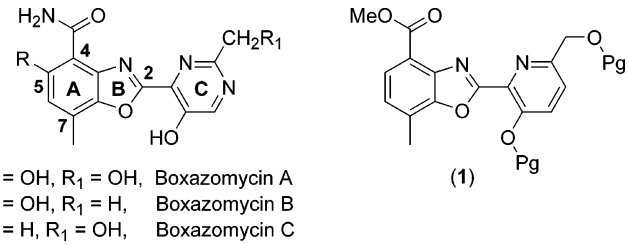


Palladium-catalyzed cross-coupling of 2-thiomethylbenzoxazoles with tri-alkylstannyl pyridines efficiently produces pyridinyl boxazomycin C analogues.

The boxazomycins are a class of gram-positive antibacterial agents[1] that contain a biaryl bond between the benzoxazole (AB) and pyrimidine (C) rings (Figure 1). We were interested in derivatives of boxazomycin C where the pyrimidine ring was replaced with a 2-substituted pyridine ring, such as that generalized by structure **1** (Figure 1). Our aim was to develop a synthetic route, involving mild reaction conditions, that was amenable to analogue preparation. Accordingly, we desired an ester at C-4 in the A-ring and flexibility in the protection of the hydroxyl groups attached to the pyridine ring.

Historically, the synthesis of these types of compounds has employed a two-step sequence involving reaction of appropriately substituted aminophenols with aryl carboxylic acids or their synthetic equivalents (Figure 2, path **A**) to form an amide bond, and then acid-catalyzed cyclocondensation to form the benzoxazole ring.[2] Reagents such as polyphosphoric acid (PPA) and pyridinium *p*-toluenesulfonate (PPTS) have been used to effect the ring closure.[2] However, using such strongly acidic reagents requires substituents to withstand the reaction conditions unaffected, and such substituents are themselves difficult to deprotect. This restricts the choice of protecting groups and leads to synthetic inflexibility. We sought an alternative coupling between the AB and C ring juncture (Figure 2, path **B**) that would avoid the use



R = OH, R_1 = OH, Boxazomycin A
R = OH, R_1 = H, Boxazomycin B
R = H, R_1 = OH, Boxazomycin C

(**1**)

FIGURE 1. Boxazomycins.

of such reagents and offer the promise of introducing sensitive functional groups without the need for additional protection/deprotection sequences or the use of harsh deprotection conditions. Consistent with this aim is the use of palladium chemistry, which is tolerant of many functional groups.

The Stille cross-coupling reaction continues to enjoy success in heterocyclic chemistry.[3] Recently, 2-chlorooxazoles have been shown to be good substrates for a variety of palladium-catalyzed coupling processes including the Stille reaction.[4] Trialkyl organostannanes can be produced by lithiation procedures when quenched with trialkyltin halides. Because we desired an ester at C-4 in the A-ring of the analogues, we determined that the preparation of a trialkylstannyl benzoxazole would be inconsistent with this type of chemistry. On the basis of these considerations, we decided upon a retrosynthesis (Figure 2, path **B**) where the benzoxazole provides the component for oxidative addition, "the electrophile" (X = OTf, halogen), and the pyridine ring is functionalized into an organostannane (Y = R_3Sn) for use in the Stille reaction.

As part of a model system we chose to work with 2-bromo-3-methoxy-6-methyl-pyridine **2**, an easily prepared substrate,[5] although in the future we anticipate using alternative protecting groups that can be removed more easily than the methyl ether.[6] Following lithiation/quench procedures, **2** could be converted into trimethyl- (**3**) and tributylstannyl (**4**) derivatives in good yields (Scheme 1). Compound **3** is sensitive to protodestannylation during both an aqueous workup and upon storage. To circumvent this problem, **3** was used in coupling reactions without isolation. Compound **4** is less sensitive and could be purified by chromatography on alumina and stored without decomposition.

We first examined whether a triflate compound would be a suitable partner in a Stille cross-coupling reaction. Adapting methods used for the preparation of the parent heterocyclic system, **6** was easily produced by reaction of **5**[7] with 1,1′-carbonyldiimidazole (CDI) in refluxing THF solution[8] and was then reacted with Tf_2O in dichloromethane at low temperature (Scheme 2).[9] We found

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(1) Kusumi, T.; Ooi, T.; Walchi, M. R.; Kakisawa, H. *J. Am. Chem. Soc.* **1988**, *110*, 2954−2958.
(2) Suto, M. J.; Turner, W. R. *Tetrahedron Lett.* **1995**, *36*, 7213−7216.
(3) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Pergamon: Amsterdam, 2000.
(4) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905−2907.
(5) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623−4633.
(6) For example, Suto and Turner used LiI in refluxing pyridine to deprotect the aryl methyl ether; see ref 2.
(7) Angyal, S. J.; Bullock, E.; Hanger, W. G.; Howell, W. C.; Johnson, A. W. *J. Chem. Soc.* **1957**, 1592−1602.
(8) Nachman, R. J. *J. Heterocycl. Chem.* **1982**, *19*, 1545−1547.

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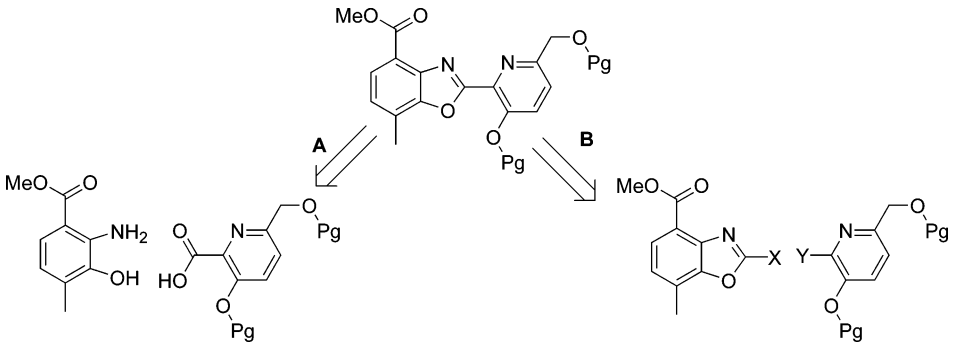
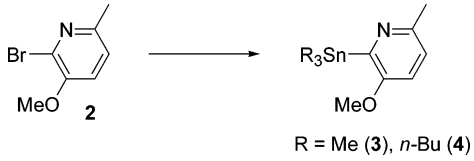


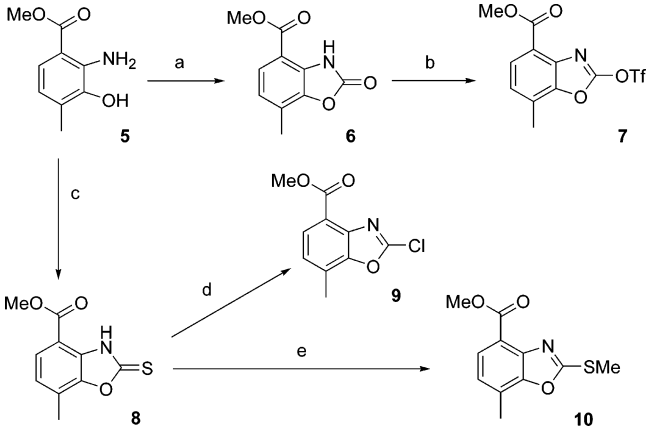
FIGURE 2. Retrosynthetic disconnections.

SCHEME 1[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) R_3SnCl, −78 °C → room temperature (rt). R = Me, 80%; R = *n*-Bu 98%.

SCHEME 2. Preparation of Coupling Partners[a]



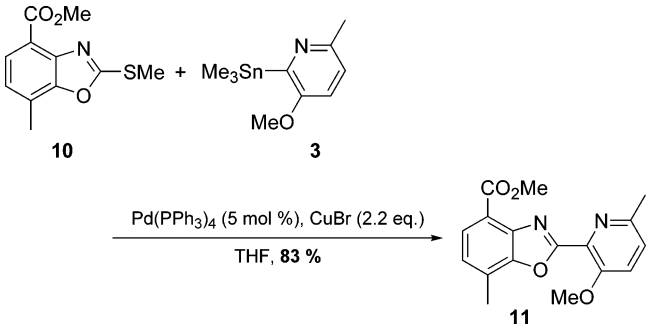
[a] Reagents and conditions: (a) CDI, THF, reflux, 69%; (b) Tf_2O, NEt_3, DCM, −78 °C → rt; (c) CS_2, KOH, EtOH/H_2O, reflux, 66%; (d) PCl_5, chlorobenzene, reflux; (e) MeI, K_2CO_3, acetone, rt, 88%.

that **7** was produced in the reaction with Tf_2O but was prone to reversion to **6** during purification, and thus we were unable to isolate it.

Our next target was a 2-chloro-benzoxazole and again we used conditions described for preparation of the parent compound.[10] Starting from **5**, compound **9** could be produced after reaction with potassium xanthate in ethanol/water and then reaction with PCl_5. We found this material sensitive to moisture with decomposition to **6** upon standing at room temperature, precluding its utility. The sensitivity to water at C-2 of the benzoxazole ring with an ester present at the 4-position has been noted before.[11]

Our attention then turned to the use of heteroaromatic thioether compounds as cross-coupling partners. Recently, the groups of Lebeskind[12] and Guillaumet[13] reported palladium-catalyzed, copper-promoted cross-coupling of such compounds with organostannanes. Starting from **8**, the preparation of **10** was easily accomplished with MeI/K_2CO_3 in acetone solution. This compound is stable to storage at room temperature, and its synthesis is fully consistent with our aim of using mild chemistry conditions.

SCHEME 3



For the coupling reaction, we used a protocol where the trimethylstannyl pyridine is generated in situ, then the palladium catalyst, copper promoter, and coupling partner are simply added, and the mixture is refluxed. This gave the convenience of conducting all operations in one pot. A copper(I) source is required in the coupling reaction,[12,13] and we first examined the use of CuBr. Given that this worked well, no other source was investigated.[14] Our preference for the trimethylstannyl derivative was based upon the byproduct Me_3SnCl being water soluble and able to be removed during an aqueous workup. In this case, the desired product is ideally set up to chelate the copper salt, and must be decomplexed by treatment with EDTA for isolation. Even so, the yield of coupled product after separation and purification is very good (83%, Scheme 3).

The advantages of using thiomethyl compound **10** are its stability as compared to the corresponding triflate and chloro compounds, the more traditional coupling partners in palladium-catalyzed reactions, and the mild reaction conditions used to prepare it.

(9) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485−2488.
(10) Chen, W.-B.; Jin, G.-Y. *Heteroat. Chem.* **2001**, *12*, 151−155.
(11) Goldstein, S. W.; Dambek, P. J. *J. Heterocycl. Chem.* **1990**, *27*, 335−336.
(12) Egi, M.; Lebeskind, L. S. *Org. Lett.* **2003**, *5*, 801−802.
(13) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803−805.
(14) Egi and Lebeskind advocate the use of copper(I) 3-methylsalicylate (CuMeSal); see ref 12.

In conclusion, palladium-catalyzed cross-coupling chemistry has been successfully applied in the model synthesis of a precursor to pyridinyl boxazomycin C analogues. This is also an example where thioether compounds provide an attractive alternative when other coupling partners cannot be used.

Experimental Section

3-Methoxy-6-methyl-2-(tributylstannyl)pyridine (4). A 2.5 M solution of *n*-BuLi in hexanes (1.76 mL, 4.40 mmol) was added dropwise over 5 min to **2**[5] (877.9 mg, 4.35 mmol) dissolved in THF (11 mL) at −78 °C. After a further 5 min *n*-Bu_3SnCl (1.20 mL, 4.42 mmol) was added, the cooling bath was removed, and the solution was allowed to attain room temperature. Saturated aqueous NH_4Cl (2 mL) was added, and the mixture was stirred vigorously. Ether (30 mL) was added, and the organic solution was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on alumina (hexanes/EtOAc, 100:1) to give **4** as a colorless oil, 1.70 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 9H), 1.10 (m, 6H), 1.33 (m, 6H), 1.55 (m, 6H), 2.49 (s, 3H), 3.74 (s, 3H), 6.86 (d, J = 8.5 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 13.2, 23.1, 26.8, 28.6, 54.7, 113.9, 120.8, 150.6, 158.2, 162.7. Anal. Calcd for $C_{19}H_{35}NOSn$: C, 55.37; H, 8.56; N, 3.40. Found: C, 55.48; H, 8.65; N, 3.12.

Methyl 7-Methyl-2-oxo-2,3-dihydrobenzoxazole-4-carboxylate (6). A mixture of **5**[7] (2.5 g, 15 mmol) and CDI (4.1 g, 25 mmol) in THF (50 mL) was refluxed with stirring for 2 h. The reaction mixture was filtered over Celite while hot, the filter pad was washed with THF (2 × 25 mL), and the solvent was removed. The residue was partitioned between $CHCl_3$ (150 mL) and 2 N HCl (75 mL), and the organic layer was further washed with 2 N HCl (75 mL), water (75 mL), and brine (25 mL), dried over Na_2SO_4, and concentrated. The residue was crystallized from EtOAc to give 2.0 g (69%) of **6** as colorless needles: mp 220−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.97 (s, 3H), 6.96 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H); 9.2 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 52.4, 110.3, 123.6, 124.3, 125.7, 130.9, 142.6, 154.2, 165.6. Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.90; H, 4.30; N, 6.67.

Methyl 7-Methyl-2-thioxo-2,3-dihydro-benzoxazole-4-carboxylate (8). CS_2 (2.0 g, 26 mmol) was added dropwise with stirring to KOH (2.6 g, 46 mmol) dissolved in an ethanol/water mixture (2.5:1, 35 mL) to give a clear yellow solution. The hydrochloride salt of **5**[7] (5.0 g, 23 mmol) was added as a solid, and the mixture was brought to reflux with stirring for 2 h. The contents were poured into hot water (100 mL), and AcOH (2 mL) was added to precipitate the product. The yellow solid was collected by filtration and recrystallized from ethanol/water to give 3.4 g (66%) of **8** as colorless needles: mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.98 (s, 3H), 7.08 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H); 10.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 52.6, 110.4, 125.1, 125.6, 126.2, 131.4, 147.8, 165.1, 180.8. Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.67; H, 4.10; N, 6.20.

Methyl 7-Methyl-2-(methylthio)benzoxazole-4-carboxylate (10). A mixture of **6** (2.1 g, 9.5 mmol), anhydrous K_2CO_3 (5 g), and iodomethane (1.0 mL, 16 mmol) in acetone (200 mL) was stirred rapidly at room temperature for 3 h. The reaction mixture was filtered over Celite, the filter pad was washed with acetone (50 mL), and the solvent was removed. The residue was partitioned between EtOAc (75 mL) and H_2O (20 mL), and the organic phase was further washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (25% EtOAc in hexanes, R_f 0.50) and recrystallized from acetone/water to give 2.05 g (88%) of **10** as colorless needles: mp 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 2.83 (s, 3H), 3.99 (s, 3H), 7.08 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 15.4, 52.2, 118.0, 124.4, 125.5, 126.7, 141.2, 151.7, 165.7, 167.7. Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.67; H, 4.61; N, 5.77.

Methyl 2-(3-Methoxy-6-methylpyridin-2-yl)-7-methylbenzoxazole-4-carboxylate (11). A 2.5 M solution of *n*-BuLi in hexanes (0.75 mL, 1.88 mmol) was added dropwise over 5 min to **2**[5] (370.4 mg, 1.83 mmol) dissolved in THF (5 mL) at −78 °C. After a further 5 min, Me_3SnCl (480.4 mg, 2.41 mmol) dissolved in THF (2 mL) was added, the cooling bath was removed, and the solution was allowed to attain room temperature. CuBr (386.0 mg, 2.69 mmol) was added as a solid before **10** (283.6 mg, 1.20 mmol) and $Pd(PPh_3)_4$ (80.7 mg, 5 mol %) dissolved in THF (5 mL) were added via syringe. The mixture was then heated to reflux for 1.5 h. After cooling to room temperature, Na_4EDTA (1.2 g) and LiCl (1.1 g) in H_2O (5 mL) were added, and the mixture was refluxed in the air for 5.5 h. The mixture was filtered through Celite, and the filter pad was washed with THF (2 × 10 mL). The organic layer was washed with new EDTA solution (1.2 g in 10 mL of H_2O, pH = 8) and brine (2 × 10 mL), before being dried over Na_2SO_4 and concentrated to dryness. Following silica gel column chromatography (EtOAc, R_f 0.20) and recrystallization (EtOAc), 309.0 mg (83%) of **11** was obtained as colorless blocks: mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 2.68 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 7.24 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 23.4, 52.3, 56.3, 120.0, 120.8, 126.1, 126.6, 126.9, 127.4, 133.9, 140.67, 150.2, 150.6, 154.4, 161.5. 166.1. Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.51; H, 5.17; N, 8.91.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **4**, **6**, **8**, **10**, and **11**. LC−MS spectra for compounds **4**, **6**, **8**, **10**, **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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