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Regioselective Synthesis of 1-Aklyl-4-(3-pyridyl)-Substituted Imidazole

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Abstract:

A practical and regioselective synthesis of 1-alkyl-4-(3-pyridyl) imidazole via a Suzuki coupling reaction employing 3-pyridyl-boronates has been investigated. The use of *sec*-butyllithium in place of *n*-butyllithium for complete selectivity in removing bromines on tribromoimidazole to provide a key bromoimidazole coupling unit is described. For effective Suzuki coupling reaction, the nature of pyridylboronates and the conditions employed are discussed. The factors affecting the outcome of the Suzuki coupling reaction are presented.

The modified erythromycin macrolides and ketolides are major new classes of semisynthetic compounds which exhibit antibacterial activity against erythromycin-resistant bacteria.[1] Among them, the substances possessing a 4-(3-pyridyl)-substituted imidazole side chain (Figure 1) are of particular interest to various pharmaceutical companies[2] due to their promising biological activities. Generally these compounds are synthesized from a core macrolide unit and a 1-alkyl-4-(3-pyridyl)imidazole side chain.

Early literature examples of the synthesis of 1-alkyl-4-(3-pyridyl) imidazoles were achieved by alkylation[2a] of and Michael addition[2b] to 3-pyridylimidazoles. However both of these approaches suffered from poor yield and regioselectivity. Additionally, the chemistry reported for the synthesis of 4-(3-pyridyl) imidazoles is tedious and expensive.[2b,3] Therefore, it was deemed impractical to rely on existing synthetic methods for any large-scale delivery.

To support our macrolide antibacterial program, we needed to provide a large amount of [4-(3-pyridyl)-1*H*-imidazol-1-yl]acetaldehyde (**1**) for the preparation of macrolide derivatives for further preclinical studies. Work was initiated on discovering and developing a new and more practical synthetic route for 3-{1-[2,2-bis(ethyloxy)ethyl]-1*H*-imidazol-4-yl}pyridine **2**, a precursor to [4-(3-pyridinyl)-1*H*-imidazol-1-yl]acetaldehyde **1** (Scheme 1).

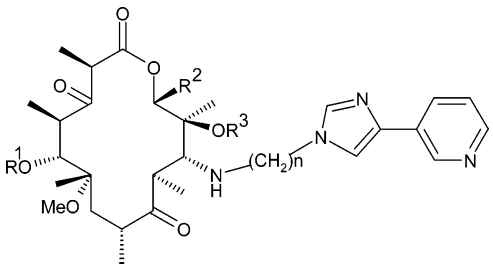
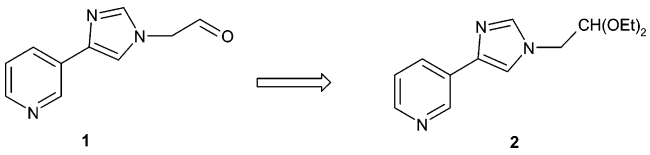
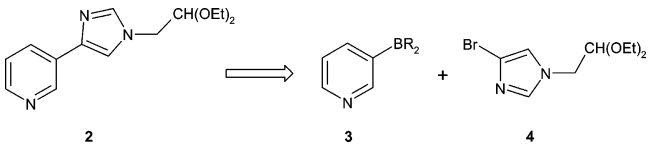


Figure 1.

Scheme 1



Scheme 2



Initial attempts made to improve the regioselectivity of the alkylation of pyridylimidazole with 2-bromo-1,1-bis-(ethyloxy)ethane under various reaction conditions (e.g., solvents, bases, temperature) resulted in poor selectivity and low yields. To circumvent regioselectivity problems, we employed a different strategy, we envisioned that 3-pyridyl-boron **3** and 1-alkyl-4-bromoimidazole **4** could be coupled employing transition-metal-catalyzed Suzuki type reaction conditions (Scheme 2).

The palladium-catalyzed Suzuki cross-coupling of aryl halides with organoboron reagents has become one of the most versatile synthetic methods for C−C bond formation[4] and plays a very important role in the preparation of aryl-substituted heterocycles.[5] The Suzuki coupling reaction generally employs organoboronic acids or borates due to their high reactivity,[6] good stability, and commercial availability. Organoboranes are rarely employed. For our studies, the

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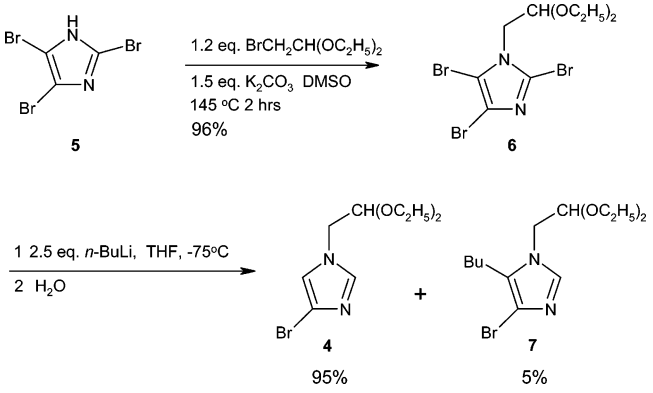
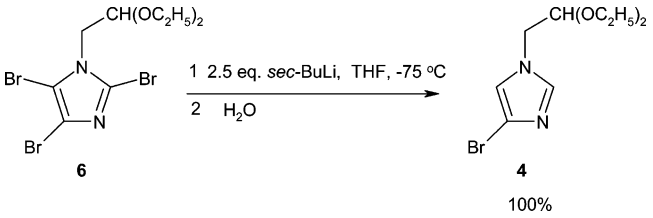
Scheme 3



Scheme 4



organoboron reagents **3** (**3a**, R = OH; **3b**, R = $OC(CH_3)_2C(CH_3)_2O$; **3c**, R = C_2H_5) are commercially available. The coupling partner **4** was easily synthesized from the readily available tribromoimidazole as a starting material (Scheme 3).

Alkylation of commercially available tribromoimidazole **5** with diethoxy bromoacetaldehyde acetal in the presence of potassium carbonate in DMSO at 145 °C afforded **6** in 96% yield. The selective removal of bromine at the 2 and 5 positions of compound **6** to afford **4** could be achieved using *n*-butyllithium according to literature precedent.[7] However, when compound **6** was exposed to *n*-butyllithium, only 95% of desired product **4** was obtained. This was accompanied by 5% butyl-substituted imidazole **7** as shown in Scheme 3. Compound **7** formed presumably from the reaction of the lithiated imidazole ring with byproduct butylbromide generated from lithium−bromine exchange. Interestingly, when *sec*-butyllithium was used in place of *n*-butyllithium, complete regioselectivity was observed and no alkylation product was detected. One explanation for no formation of alkylated compound is the sterics involved in reacting the lithiated imidazole ring with *sec*-BuBr. Thus treating compound **6** with *sec*-butyllithium provided **4** in quantitative yield as shown in Scheme 4.

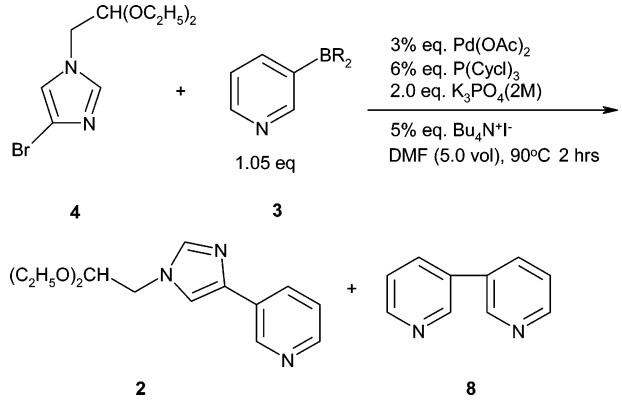
With the bromoimidazole **4** in hand, we investigated the Suzuki coupling reaction conditions for **3** and **4**. A number of organoboron reagents and catalysts were screened, and the results were summarized in Table 1.

No desired coupled product formed when pyridyl boronic acid **3a** was reacted with **4** in the presence of palladium acetate as shown; instead the self-coupled bipyridine **8** product was exclusively observed (entry 1). Substituting borate **3b** in place of acid **3a** afforded a mixture of products

Table 1. **Suzuki coupling reaction between organoboron reagents 3 and bromoimidazole 4**

entry	catalyst	ligand	organoboron reagent	ratio of **2**/**8** (HPLC area%)	time (h)
1	$Pd(OAc)_2$	$P(Cycl)_3$	**3a**	0/100	10
2	$Pd(OAc)_2$	$P(Cycl)_3$	**3b**	40/60	7
3	$Pd(OAc)_2$	$P(Cycl)_3$	**3c**	96/4	2
4	$Pd(OAc)_2$	$P(O\text{-tolyl})_3$	**3c**	83/17	96
5	$Pd(OAc)_2$	$P(t\text{-Bu})_3$	**3c**	96/4	2

Scheme 5



2/**8** with a 40/60 ratio (Scheme 5). Interestingly, a higher yield of cross coupled product was obtained when pyridyl borane **3c** was used under identical conditions (entry 3). It should be noted that **3c** has recently been employed in a large-scale Suzuki reaction.[8]

The outcome of Suzuki coupling reactions depends heavily on the reaction conditions employed. Among the reaction parameters, palladium catalyst and phosphine ligands are found to be the most important factors for the success of this reaction. Tetrakis(triphenylphosphine)palladium, frequently used for such types of reactions, was too labile under the reaction conditions and failed to deliver any of the desired product in all cases. The combination of $Pd(OAc)_2$ and tri-*o*-tolylphosphine only gave low yields (50%) of cross coupled product even after prolonged reaction time. When more electron rich ligands such as tricyclohexylphosphine and tri-*tert*-butylphosphine were employed, a clean conversion to **2** was observed (entry 3, 5) and the product **2** was isolated as HCl salt **9** in a yield of 81% with a purity >99%. The use of electron rich phosphines in Suzuki reactions has been well documented.[9] They may not only stabilize the active $Pd(0)L_2$ species but also promote reductive elimination. The stability of oraganoborons is believed to play an important role in the cross coupling reactions. The observed low yield of coupled product in our reactions with **3a** and **3b** may be partly due to a facile protodeboronation[10] or partial decomposition under the strong basic conditions employed to promote the coupling reaction.

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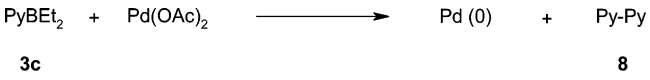
Scheme 6



Oxygen is known in the literature to promote the self-coupling of arylborons.[11] We observed that the impurity level of 3,3-bipyridine **8** generated in the reaction was related to the oxygen level in the reaction mixture. Pre-exclusion of oxygen at the beginning of reaction was critical to maintain low levels of **8**. Introduction of trace amounts of oxygen when taking samples to monitor the reaction consumed active Pd (0), requiring more pyridylborane **3c** to regenerate the active catalyst and consequently producing more 3,3-bipyridine **8** (Scheme 6).

In conclusion an efficient and practical process for the production of 1-alkyl-4-pyridyl-imidazole was developed. Suzuki coupling between pyridylborane and imidazolylbromide under the conditions above-described in this communication would be suitable for large-scale preparation of pyridylimidazole derivatives.

Experimental Section

1-[2,2-Bis(ethyloxy)ethyl]-2,4,5-tribromo-1*H*-imidazole 6: A mixture of tribromoimidazole (6.1 g, 20 mmol, 1.0 equiv), bromoacetaldehyde diethyl acetal (4.73 g, 24 mmol, 1.2 equiv), and potassium carbonate (4.14 g, 30 mmol, 1.5 equiv) in DMSO (6.5 mL) was heated to 145 °C for 2 to 4 h. The reaction mixture was cooled to room temperature before addition of water (40 mL) and *tert*-butyl methyl ether (TBME) (40 mL). The aqueous layer was extracted with TBME (40 mL). The combined organic layers were washed with water (20 mL) and brine (10 mL) and then dried with Na_2SO_4 (anhydrous). After evaporation of solvents, an oil (7.96 g, 96%) was obtained; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (t, $J = 5.5$ Hz, 1H), 4.09 (d, $J = 5.5$ Hz, 2 H), 3.73 (m, 2 H), 3.43 (m, 2 H), 1.15 (t, $J = 7.1$ Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.1, 116.7, 105.8, 100.4, 64.3, 50.6 (2C), 15.2 (2C).

1-[2,2-Bis(ethyloxy)ethyl]-4-bromo-1*H*-imidazole 4: Crude product from the previous step (7.96 g, 18.9 mmol, 1.0 equiv) was dissolved in THF (40 mL). The resulting solution was cooled to −75 °C. *sec*-Butyllithium (1.3 M in cyclohexane, 36.3 mL, 47.3 mmol, 2.5 equiv) was added at a rate to maintain the reaction temperature below −55 °C. After 30 min water (6.0 mL) was added to quench the reaction at −75 °C and then the mixture was warmed to room temperature. TBME (30 mL) and water (4.0 mL) were added. The aqueous layer was extracted with TBME (20 mL). The combined organic layers were washed with brine (10 mL) and then dried with Na_2SO_4 (anhydrous). After evaporation of solvents, an oil (4.95 g, 99%) was obtained; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, $J = 1.5$ Hz, 1 H), 6.95 (d, $J = 1.5$ Hz, 1 H), 4.56 (t, $J = 5.1$ Hz, 1 H), 3.98 (d, $J = 5.1$ Hz, 2 H), 3.70 (m, 2 H), 3.47 (m, 2 H), 1.18 (t, $J = 7.1$ Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 119.1, 114.7, 101.1, 63.7, 50.5 (2C), 15.2 (2C).

3-{1-[2,2-Bis(ethyloxy)ethyl]-1*H*-imidazol-4-yl}pyridine Hydrochloride Salt 9: Tetrabutylammonium iodide (2.45 g, 6.65 mmol, 0.05 equiv), 1,1-diethoxy-2-(4-bromoimidazolyl)ethane **4** (35 g, 133 mmol, 1.0 equiv), DMF (166 mL), and $Pd(OAc)_2$ (0.9 g, 4.0 mmol, 0.03 equiv) were added to a round-bottom flask (500 mL) at room temperature. Then a solution of K_3PO_4 in water (2.0 M, 133 mL, 266 mmol, 2.0 equiv) was added. The mixture was degassed by house vacuum (1.0 min) at ambient temperature and then filled with argon (three times). Tricyclohexylphosphine (2.2 g, 8.0 mmol, 0.06 equiv) and diethyl-(3-pyridyl)borane (20.6 g, 140 mmol, 1.05 equiv) were added into a reaction flask at room temperature. The mixture was degassed as described above once again. The reaction mixture was stirred and heated at 100 °C for 3−5 h. The reaction was deemed complete when less than 0.5% of the starting bromide material remained. The reaction contents were cooled to 70 °C and distilled under house vacuum until 175 mL of residue was left. The residue was cooled to room temperature. Water (17.5 mL) and methylene chloride (350 mL) were added. Two layers were separated, and the aqueous layer was extracted with methylene chloride (350 mL). The combined organic layers were filtered through a pad of Celite (20 g). The solvent was distilled until 70 mL of solution remained, and TBME (210 mL) was added followed by addition of a solution of HCl in ethanol (4.4 N, 62 mL, 273 mmol, 2.05 equiv). The slurry was stirred for another 30 min. The solid product was filtered and washed with TBME (70 mL). The wet cake was then dried under house vacuum at 50 °C for 2 h to give **2** (32 g, 81%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (d, $J = 1.5$ Hz, 1 H), 8.69 (m, 1 H), 8.67 (dd, $J = 5.4$, 1.5 Hz, 1 H), 8.54 (dt, $J = 8.1$, 1.5 Hz, 1 H), 8.23 (d, $J = 1.5$ Hz, 1 H), 7.77 (dd, $J = 7.8$, 5.4 Hz, 1 H), 4.83 (t, $J = 5.1$ Hz, 1 H), 4.26 (d, $J = 5.1$ Hz, 2 H), 3.66 (m, 2 H), 3.51 (m, 2 H), 1.10 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ145.6, 142.9, 138.7, 136.0, 131.9, 127.9, 125.8, 120.5, 100.0, 63.0, 50.6 (2C), 15.5 (2C).

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