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Synthesis and cross coupling of a highly substituted 2-pyridylboronate: application to the large scale synthesis of a mineralocorticoid antagonist

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Keywords: Suzuki–Miyaura coupling 2-Pyridylboronate Pyrazoline Large-scale synthesis ABSTRACT

The large scale synthesis of a functionalized 2-pyridylboronate **8** and optimization of its Suzuki–Miyaura coupling to chloropyrazoline (R)-**7** to provide a scalable synthesis of mineralocorticoid antagonist (R)-**1** is described.

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The abnormal activation of the mineralocorticoid receptor (MR) by elevated levels of the endogenous agonist aldosterone leads to salt imbalance causing hypertension and other detrimental effects to the cardiovascular system such as glomerular and tubular sclerosis. Selective steroidal MR antagonists, spironolactone and eplerenone, are marketed agents for lowering blood pressure in hypertensive patients. However, these steroidal compounds are contraindicated in diabetic patients. As part of a program to discover nonsteroidal MR antagonists that offer the potential to treat hypertension and diabetic nephropathy, compounds from the pyrazoline chemotype emerged as promising candidates. Compound (R)-1 was identified as a potential follow-on to clinical candidate PF-03882845 (Fig. 1).¹ In order to support preclinical toxicology studies, bulk quantities of (R)-1 were required. Herein, we describe the synthesis of a 2-pyridylboronate and optimization of its coupling to a chloropyrazoline to provide a scalable synthesis of (R)-**1**.

The original route to (*R*)-**1**, depicted in Scheme 1, was suitable for delivering milligram quantities for testing. The sequence began with 6-acetyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid **2** which was obtained from 3,3-dimethoxy-2-butanone using a known multi-gram route.² Conversion of the hydroxy acid **2** into methoxy ester **3** could be effected by treatment with methyl iodide and Ag₂CO₃ in CHCl₃ (58%, 2 g scale) or Cs₂CO₃ in DMF (37%, 3 g

* Corresponding author. E-mail address: david.w.piotrowski@pfizer.com (D.W. Piotrowski). scale). Subsequent Knoevenagel condensation of **3** and cyclopentanecarboxaldehyde in the presence of pyrrolidine provided α , β -unsaturated ketone **5** in 60% yield after chromatography. Condensation of **5** with aryl hydrazine **6** in the presence of sodium ethoxide in ethanol followed by ester hydrolysis provided *rac*-**1** in 78% yield. Compound (*R*)-**1** could be obtained in an enantiopure form by chiral HPLC separation (Scheme 1).³

In examination of this route for suitability for scale up, several drawbacks were uncovered. First, the route is linear and several steps require purification by chromatography. Second, the dimethylation of **2** to provide **3** either required the use of the expensive Ag₂CO₃ reagent to obtain reasonable conversion or required chromatography followed by recrystallization to remove the ethyl ketone by-product **4** formed under the Cs₂CO₃/DMF conditions. Lastly, the late stage chromatographic separation of enantiomers proved to be undesirable because of the low solubility⁴ of *rac*-**1** and disposal of more than half of the final product.

A more convergent route was devised based on the retrosynthetic disconnection depicted in Figure 2. The seemingly obvious bond connection via Suzuki–Miyaura coupling between 2-pyridylboronate (R)-**7** and 3-chloropyrazoline **8** was not without challenges. While scalable chemistry was in place for the required 3-chloropyrazoline **7**,⁵ chloropyrazolines are uncommon coupling partners. Prior to the recent report from Pfizer labs,¹ the only known Suzuki–Miyaura couplings of cyclic imidoyl chlorides⁶ or sulfonates⁷ with aryl boronic acids or aryl trifluoroborates had been performed on milligram scale and most effectively under





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Figure 1. Steroidal and nonsteroidal MR antagonists.

microwave conditions. As such, we expected that coupling reactions with 3-chloropyrazolines would be nontrivial and likely require extensive optimization. Furthermore, the boronate **8** was unknown but was envisaged to be accessible from the commercially available 2,6-dichloropyridine-3-carboxylic acid **9**. While coupling reactions of heterocyclic boron reagents (e.g., 3- or 4-pyridine boronic acid) are common, coupling of 2-pyridine variants are less common and often complicated by homo-coupling or sensitivity to proto-deboronation. Solutions to some of these concerns have been addressed in the context of simply substituted 2-pyridine boron reagents⁸ by the use of solid support⁹ or specialized catalyst systems.¹⁰ Many of the pitfalls associated with the coupling of 2-pyridine reagents are highlighted in a recent review.¹¹

The preparation of **8** commenced with esterification of carboxylic acid **9** under classical conditions to provide ester **10** in 75% yield after recrystallization from heptane. Selective conversion of **10** into the 2-methoxy derivative **11** was most effectively conducted by portion-wise addition of solid sodium methoxide to a CH_2Cl_2 solution of **10** (94% yield). Use of other solvents or of a methoxide solution eroded regioselectivity leading to a lower isolated yield of **11** that was contaminated with the undesired 6-methoxy and 2,6-dimethoxy by-products.¹² Boronate **8** was synthesized under standard conditions¹³ using bis(pinacolato)diborane, KOAc and PdCl₂(dppf) in DME to afford a 74% yield after recrystallization from heptanes (Scheme 2). Compound **8** was observed to degrade slowly at room temperature, but could be stored in the refrigerator with no noticeable decomposition over several months. The route described above, with minor modifications, was robust and scalable to provide hundred gram quantities of **8**.⁵

We were pleased to find that coupling between *rac*-**7** and **8** catalyzed by 5% Pd(PPh₃)₄ under standard Suzuki–Miyaura conditions¹⁴ provided ester *rac*-**12** in 56% yield after chromatography (Scheme 3). Analysis of the crude reaction mixture by HPLC revealed ca. 20% of a homocoupled dimer **13** as the major impurity.¹⁵ The racemic ester **12** could be converted into acid (*R*)-**1** on multi-gram scale by subjection to chiral SFC chromatography followed by hydrolysis and crystallization. However, the poor solubility of the ester **12** or acid **1** substrates made chromatography a laborious process. It was clear that the final sequence could be improved by finding conditions that minimized formation of the by-product and by separation of enantiomers at a stage that utilized a more soluble substrate.

Homocoupled side products from Suzuki–Miyaura couplings can often be suppressed by using an alternative phosphine ligand, base or solvent. Parallel optimization of the conditions for the Suzuki–Miyaura coupling was undertaken using Chemspeed SWING platform to first examine a range of ligands and bases in aqueous THF (Tables 1 and 2), followed by assessment of alternative solvent systems. In the first screen, catalysts examined included bis(triphenylphosphine)palladium (II) chloride (6 mol %) and tris(dibenzylideneacetone) dipalladium (0) (3 mol %) with a



Scheme 1. Original synthesis of (*R*)-1. Reaction Conditions: (a) Mel, Ag₂CO₃, CHCl₃, 58%; (b) Mel, Cs₂CO₃, DMF, 37%; (c) cyclopentanecarboxaldehyde, pyrrolidine, MeOH, 60%; (d) **6**, NaOEt, EtOH, 50 °C; (e) aq HCl, 78% (two steps) and (f) chiral SFC chromatography.



Figure 2. Retrosynthesis of (R)-1.



Scheme 2. Preparation of 2-pyridylboronate 8. Conditions: (a) MeOH, SOCI₂, 75%; (b) solid NaOMe, CH₂CI₂, 94% and (c) bis(pinacolato)diborane, PdCI₂(dppf), KOAc, DME, 74%.



Scheme 3. Initial Suzuki–Miyaura coupling of *rac*-7. Conditions: (a) 5% Pd(PPh₃)₄, 2 M Na₂CO₃, DME, 80 °C, 56%; (b) chiral SFC chromatography (column: AD–H, 21 × 250, mobile phase: 65/35 carbon dioxide/methanol, 65 mL/min) and (c) LiOH, aq THF.

Table 1

Different Pd-catalyst/ligands in the presence of K2CO3

Ligand		Normalized HPLC area under the curve					
	rac- 7	8	By-product 13	rac- 12	Other ^a		
Pd ₂ (dba) ₃ /Josiphos	36	1	14	15	34		
Pd ₂ (dba) ₃ /Tri-o-tolylphosphine	27	2	2	3	66		
Pd ₂ (dba) ₃ /S-Phos	14	0	2	40	44		
Pd ₂ (dba) ₃ /Ru-Phos	28	0	3	43	26		
Pd ₂ (dba) ₃ /X-Phos	5	0	2	76	17		
$(Ph_3P)_2PdCl_2$	4	0	8	59	29		

^a Area of all other peaks combined.

able 2	
Different bases in the presence of $Pd_2(dba)_3/X$ -Phos	

Base	Normalized HPLC area under the curve				
	rac- 7	8	By-product 13	rac- 12	Other ^a
Ba(OH) ₂	20	0	0	0	80
LiOH	8	0	0	0	92
K ₂ CO ₃	6	0	2	76	16
Cs ₂ CO ₃	12	0	2	50	36
CsF	14	2	8	51	25
KF	27	5	10	33	25
Na ₃ PO ₄	13	0	2	64	21
Li ₂ CO ₃	3	0	2	60	35

^a Area of all other peaks combined.

number of different ligands (X-Phos, S-Phos, Ru-Phos, JosiPhos and tri-o-tolylphosphine). Bases assessed included K₂CO₃, LiOH, Ba(OH)₂, Li₂CO₃, Na₃PO₄, CsF, KF, Cs₂CO₃, and HCO₂K. The reactions were monitored by HPLC for starting materials rac-7 and 8, byproduct 13 and conversion to product rac-12 for the different reagent combinations. Overall, we observed that triphenylphosphine almost uniformly produced the most homocoupled by-product and tri-o-tolylphosphine generally led to poor conversion. X-Phos, on the other hand, best balanced high conversion with minimized homocoupled by-product. Cesium or potassium carbonate and trisodium phosphate were among the best bases for overall conversion to product. A secondary screen compared the best bases (Cs₂CO₃, K₂CO₃, and Na₃PO₄) paired with Pd₂(dba)₃/X-Phos in alternative solvents (EtOH or *n*-BuOH, aqueous or anhydrous). Alcoholic solvents offered no particular advantage. Thus, thorough catalyst screening allowed for identification of the best coupling conditions, that is Pd₂(dba)₃/X-Phos with 1 M K₂CO₃ in THF at 65 °C.16

With optimized coupling conditions in hand, the coupling partner (R)-7 was prepared. Indeed, chloropyrazoline rac-7 proved to be a more soluble substrate than **1** thereby allowing for a more practical separation of enantiomers¹⁷ on kilogram scale (over 500 g of (R)-7 was obtained with ee >97%). Suzuki-Miyaura coupling provided (*R*)-12 along with $\sim 2\%$ of the homocoupled by-product 13 (Scheme 4). On scale, by-product 13 was found to be very difficult to remove with either chromatography or crystallization. Therefore, (R)-1 was isolated and purified via MTBE-heptane slurry (product purities by HPLC >96%, ee >99%). The homocoupled by-product was the major HPLC impurity at levels of 1.3-2.5%. Simultaneous hydrolysis of the product and by-product esters was conducted with 1 N aq NaOH in THF at 40 °C. The crude product was taken up in CH₂Cl₂ and filtered through diatomaceous earth in order to remove the insoluble diacid impurity **14**. A stable crystal form of (*R*)-**1** was obtained by heating a crude slurry in ethanol-water at 80 °C. The final product (*R*)-1 was isolated by filtration in 95% yield with >99.9% purity (achiral and chiral HPLC).

As a result of the optimization work described herein, the original chemistry route was transformed into a route capable of preparing hundreds of grams of (R)-**1** in a single campaign. The original linear route that required late-stage separation of enantiomers was replaced with a more convergent route utilizing a key Suzuki–Miyaura coupling between 3-chloropyrazoline (R)-**7** and the highly substituted boronate **8**. The advantages of the latter route include (1) separation of more soluble *rac*-**7** by chiral chromatography at an earlier stage, (2) refinement of Suzuki–Miyaura coupling to minimize by-product formation and (3) removal of purification by chromatography by enabling purity upgrade during crystallization of a stable polymorph of (R)-**1**.



Scheme 4. Scale-up of (R)-1. Conditions: (a) Pd₂(dba)₃, X-Phos, 1 M K₂CO₃, THF, 65 °C, 85%; (b) 1 N NaOH, THF, 40 °C and (c) EtOH/H₂O slurry, 95% (two steps).

Representative experimental procedures

Preparation of methyl 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2dioxaborolan-2-yl)nicotinate 8

A mixture of methyl 6-chloro-2-methoxynicotinate 11 (94.0 g, 0.47 mol), bis(pinacolato) diboron (130.0 g, 0.51 mol), potassium acetate (137.0 g, 1.4 mol), and 1,2-dimethoxyethane (705 mL) was sparged for 30 min with rapid nitrogen bubbling. [1,1'bis(diphenylphosphino)ferrocene] palladium (II) chloride (19.0 g, 23.3 mmol) was added and the mixture was heated under reflux. After 12 h, the mixture was diluted with ethyl acetate (150 mL) and concentrated to dryness. The residue was taken up in ethyl acetate (750 mL), aqueous saturated sodium bicarbonate (300 mL), and water (200 mL). The organic layer was washed with water (500 mL) and concentrated to dryness. The residue was taken up in 500 mL hot heptane (78 °C), hot filtered through Celite and cooled with stirring. The resulting slurry was filtered and dried to yield boronate 8 (95 g, 70%) as a tan solid. Another campaign under similar conditions afforded 242.0 g (73.6%) of boronate 8 as an off-white solid. GC purity 98%. ¹H NMR (400 MHz, DMSO d_6) δ 8.02 (1H, d, I = 7.2 Hz), 7.42 (1H, d, I = 7.3 Hz), 3.90 (3H, s), 3.78 (3H, s), 1.28 (12H, s).

Suzuki–Miyaura coupling of (*R*)-7 and 8 to provide ester (*R*)-12

(R)-3-Chloropyrazoline 7 (116.6 g, 405.0 mmol) and 2-pyridylboronate 8 (132.1 g, 450.6 mmol) were combined in THF (1.0 L) and 1 M aq K_2CO_3 (1.0 L) and the mixture was sparged with nitrogen for 1 h. Tris(dibenzylideneacetone)dipalladium-chloroform adduct (3.53 g, 3.4 mmol) and X-Phos (6.5 g, 13.3 mmol) were added and the mixture was heated at 60 °C for 4 h. The reaction was cooled to room temperature, charged with ethyl acetate (500 mL) and filtered through Celite. The Celite was washed with 2×250 mL ethyl acetate. The combined organic layers were washed sequentially with water (250 mL) and brine (250 mL), and then concentrated. The residue was taken up in methyl *t*-butyl ether (850 mL) and heptane (850 mL). After stirring at room temperature for 3 h, the resulting slurry was filtered. The collected solids were rinsed with 50% methyl t-butyl ether in heptane (500 mL) and dried under vacuum at 35 °C to give ester (R)-12 (143.9 g, 85%) as a yellow solid with HPLC purity 98.1% (1.4% of by-product 13) that was carried forward crude.

Hydrolysis of (R)-12 to provide (R)-1

To 1 N sodium hydroxide (1.4 L) was added a solution of ester (R)-12 (398.3 g, 951.6 mmol) dissolved in THF (4.0 L). After heating

at 40 °C for 5.5 h, the mixture was cooled and the pH was adjusted to pH 3 with 1 N aq HCl (1.2 L). Ethyl acetate (3.0 L) was added and the mixture was phase separated. The organic layer was washed with half-saturated brine (1.0 L), filtered through Celite, and concentrated. The thick paste was taken up in CH₂Cl₂ (2.0 L), dried over MgSO₄, filtered through Celite, concentrated, and dried under vacuum. The amorphous solid was crystallized from 1:1 ethanol/ water (4.2 L, heated for 2 h at 80 °C), cooled, filtered, and dried under vacuum to yield (*R*)-1 (364 g, 95%) as a crystalline solid. mp 179–181 °C. HPLC (purity) 99.5%. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.94 (1H, b s), 8.11 (1H, d, J = 8.2 Hz), 7.66 (1H, d, J = 8.2 Hz), 7.56 (1H, d, J = 8.2 Hz), 7.22 (1H, d, J = 1.9 Hz), 7.10 (1H, dd, J = 8.6, 2.2 Hz), 4.87 (1H, dt, J = 11.7, 4.0 Hz), 3.94 (3H, s), 3.45 (1H, dd, J = 18.7, 11.9 Hz), 3.19 (1H, dd, J = 18.7, 4.3 Hz), 2.41 (3H, s), 1.79-1-69 (1H, m), 1.63-1.17 (7H, m), 1.08-0.95 (1H, m). MS (AP) m/z 405.2 (M+H)⁺. Anal. Calcd for C₂₃H₂₄N₄O₃: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.31; H, 6.05; N, 13.81.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.052.

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