Biaryl Product Formation from Cross-coupling in Palladium-catalyzed Borylation of a Boc Protected Aminobromoquinoline Compound

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Abstract: The palladium catalyzed borylation of a Boc protected aminobromoquinoline compound with bis(pinacolato)diboron yielded a biaryl compound, resulting from cross coupling, as the major product, instead of the intended boronate, even though no strong base was used. Such results indicate that under certain conditions and with certain substrates, cross coupling can be a major problem during borylation, leading to unintended consequences.

Keywords: Palladium-catalyzed reaction, Borylation, Cross-coupling.

Introduction

Boronic acids compounds have generated much attention in both chemistry and biology in the last decade because of their importance in organic chemistry [1-7], medicinal chemistry [8], and sensor development [9-11]. Boronic acids have been widely used for saccharide sensor design because of their unique high affinity and reversible complexation with diols, which are commonly found on saccharides [12, 13]. Our lab has been engaged in the search for fluorescent sensors for saccharides for various applications [8, 9, 14-22]. Along this line, we are especially interested in the design and synthesis of fluorescent boronic acids that respond to the binding of saccharides by large changes in fluorescent intensities and/or wavelengths, and are water-soluble [18, 22, 23]. The ultimate goal is to use such reporter compounds for the construction of fluorescent sensors for cell surface saccharides for
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biological applications [8, 17, 19, 20]. One specific example is 8-quinoline boronic acid (8-QBA, 1), which shows a 40-fold fluorescence intensity change upon binding to a saccharide [18]. However, to incorporate this reporter compound into a diboronic acid sensor, we need to have a way to functionalize it so that various coupling reactions can be used to tether 8-QBA to other groups for improved specificity and affinity. Therefore, we were interested in the synthesis of 2, which has a protected amino group that can be used for further functionalization. Herein, we report the formation of a somewhat unexpected high level of cross-coupling product during the synthesis of 2 using a palladium catalyst, which can cause problems in the synthesis of arylboronic acids.

Results and Discussion

Generally, there are two types of reactions used for the synthesis of arylboronic acids or arylboronates. One is the transmetalation between an arylmetal and a boron halide or alkoxide [24]; the other is the recently developed PdCl₂(dppf)-catalyzed borylation of aryl halides [25, 26], triflates [27] or diazonium salts [28] with a tetra(alkoxy)diboron [25, 27] or dialkoxyborane reagent [26]. The first method was used to prepare 8-QBA in 1959 [29], but is not compatible with certain sensitive functional groups such as nitro, amide, amine, and hydroxy. The latter coupling reaction can tolerate various functional groups and has been widely applied to the synthesis of arylboronic esters in one step [30]. Therefore, the palladium-catalyzed cross-coupling reaction was chosen for the preparation of monoboronic acid 2 (Scheme 1).

Scheme 1
The synthesis of compound 2 started from 3, that was prepared by reducing 4-bromo-3-nitrotoluene with stannous chloride [31]. A Skraup reaction was carried out using a modified procedure to give quinoline compound 4 [32]. Bromination of the methyl group using NBS in refluxing benzene under irradiation with a tungsten light gave 5 in 70% yield. The amination of 5 with methylamine in THF gave 6. This was followed by the protection of the amino group by the reaction with di-tert-butyldicarbonate [(Boc)₂O] in MeOH in the presence of triethylamine (TEA) to give 7.

The intended borylation to give 9 was carried out by following literature procedures using PdCl₂(dppf) as the catalyst in the presence of KOAc [25]. Unexpectedly, the major product (65%) obtained from this palladium-catalyzed reaction was the biaryl product 8, not the intended boronic acid ester 9. The structure of compound 8 was characterized by ¹H-NMR and mass spectrometry. Biaryl byproducts in palladium-mediated borylations usually result from the further Suzuki coupling reaction of the arylboronate product with the starting material, bromoarene, in the presence of a base such as K₃PO₄ and K₂CO₃. Generally speaking, potassium acetate is not a strong enough base to promote the Suzuki cross-coupling reaction to a significant extent in palladium-catalyzed borylation [25]. Our results indicate that under certain conditions and with certain substrates, such cross coupling reactions can be the major reaction, leading to unintended consequences. In addition, it has been reported that the 8-quinoline boronate can be synthesized by using palladium-catalyzed borylation with arene triflates [26, 27]. This suggests that the corresponding 8-quinoline triflate analog of 7 could be used as new substrate to perform palladium catalyzed borylation in the future in order to avoid this dimerization.

Conclusions

Suzuki cross coupling can be the major side reaction in PdCl₂(dppf) -mediated borylation of haloarenes. This is true even if only a weak base such as KOAc is used. Further studies are needed to better understand the scope that different factors affect this reaction, and how the borylation yield can be improved.

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Experimental

General
Commercially available reagents were used without additional purification unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed with plastic-backed TLC silica gel 60 F hard layer plates. Flash chromatography was performed with silica gel (flash, 32–63 µm). Mass spectrometry (MS) analyses were performed by the Mass Spectrometry Facility at Georgia State University on a Finnigan electrospray/ion trap mass spectrometer. 1H-NMR spectra were recorded at 300 MHz on a Varian Gemini instrument.

8-Bromo-5-methylquinoline (4)

A solution of 2-bromo-5-methylaniline (3, 6.8 g, 36.5 mmol), glycerol (6.7 g, 72.5 mmol), nitrobenzene (4.5 g, 36 mmol) in 75% H2SO4 (20 mL) was heated at 150 °C for 3 h. The solution was neutralized with NaOH after cooling to room temperature, and then extracted with EtOAc (3 × 120 mL). The combined organic layers was washed with saturated brine, and then dried with MgSO4. After removing solvents under reduced pressure, the crude product was purified by flash column chromatography (hexane/EtOAc, 20:1) to give 4 (5.38 g, 67%): 1H-NMR (CD3OD) δ 8.93 (m, 1H, Ar-H), 8.56 (m, 1H, Ar-H), 7.98 (m, 1H, Ar-H), 7.63 (m, 1H, Ar-H), 7.34 (m, 1H, Ar-H), 2.69 (s, 3H, Ar-CH3); ESI-MS m/z 222/224 (C10H9BrN, M+1).

8-Bromo-5-bromomethylquinoline (5).

A mixture of 8-bromo-5-methylquinoline (4, 5 g, 22.7 mmol) and N-bromosuccinimide (4.9 g, 27.5 mmol) in benzene (55 mL) was refluxed under irradiation with a tungsten light for 12 h. The solution was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 20:1) to give 5 (4.8 g, 70%): 1H-NMR (CD3OD) δ 8.98 (m, 1H, Ar-H), 8.73 (m, 1H, Ar-H), 8.06 (m, 1H, Ar-H) 7.70 (m, 1H, Ar-H), 6.70 (m, 1H, Ar-H), 5.01 (s, 2H, Ar-CH2-Br); ESI-MS m/z 300/302/304 (C10H8Br2N, M+1).

(8-Bromoquinolin-5-yl-methyl)methylamine (6).

To a solution of 8-bromo-5-bromomethylquinoline (5, 0.39 g, 1.3 mmol) in THF (15 mL) was added 40% methylamine aqueous solution (7 mL). The resulting mixture was stirred at RT for 12 h under nitrogen, and then the organic solvent was removed under reduced pressure. The residue was extracted with DCM (3 × 10 mL) and then washed with saturated brine (30 mL). After drying with MgSO4, evaporation of solvent provided compound 6 (0.31 g, 95%): 1H-NMR (CDCl3) δ 9.05 (m, 1H, Ar-H), 8.56 (m, 1H, Ar-H), 7.99 (m, 1H, Ar-H), 7.49 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 4.16 (s, 2H, Ar-CH2-N), 2.53 (s, 3H, N-CH3); ESI-MS m/z 251/253 (C11H12BrN2, M+1).

Tert-butyl N-(8-bromoquinolin-5-yl-methyl)-N-methylcarbamate (7).

A mixture of (Boc)2O (1.0 g, 4.61 mmol) in MeOH (5 mL) was added slowly to a solution containing (8-bromo-quinolin-5-yl-methyl)methylamine (6, 0.96 g, 3.84 mmol) and triethylamine (1
mL) in MeOH (20 mL). The resulting solution was further stirred for 12 h, then the methanol was evaporated and the residue was extracted with EtOAc (3 × 10mL). The combined organic extracts were washed with saturated brine (30 mL), dried over MgSO₄, and concentrated and dried *in vacuo* to give compound 7 (1.27 g, 95%): ¹H-NMR (CD₃OD) δ 8.86(m, 1H, Ar-H), 8.57 (m, 1H, Ar-H), 7.99 (m, 1H, Ar-H), 7.52 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 4.82 (s, 2H, Ar-CH₂-N), 2.71(s, 3H, N-CH₃), 1.39(s, 9H, -C(CH₃)₃); ESI-MS m/z 351/353 (C₁₆H₂₀BrN₂O₂, M+1).

5,5'-Bis[[(tert-butoxycarbonyl)methylamino]methyl]-8,8'-biquinoline (8).

A mixture of PdCl₂(dppf) (20 mg, 0.025 mmol), potassium acetate (0.25 g, 2.55 mmol), bis(pinacolato)diboron (0.23 g, 0.94 mmol) and tert-butyl (8-bromoquinolin-5-yl-methyl)-methyl-carbamate (7, 0.30 g, 0.86 mmol) was added to a flask in a glove box under anhydrous condition. After addition of anhydrous DMSO (10 mL) the mixture was stirred at 80 °C for 16 h. The reaction solution was cooled to room temperature and poured into ice-water. The mixture was extracted with ethyl acetate and the combined organic layers was washed with saturated brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/ethyl acetate, 1:1) to give 8 (0.15 g, 65%): ¹H-NMR (DMSO-d₆) δ 8.68 (m, 4H, Ar-H), 7.70 (m, 2H, Ar-H), 7.52 (m, 4H, Ar-H), 5.00 (s, 2H, Ar-CH₂-N), 2.88 (s, 6H, N-CH₃), 1.49 (s, 18H, -C(CH₃)₃); ESI-MS m/z 543 (C₃₂H₃₉N₄O₄, M+1).

References


*Samples Availability:* Available from the authors.