Published in final edited form as:

Tetrahedron Lett. 2011 October 26; 52(43): 5656–5658. doi:10.1016/j.tetlet.2011.08.096.

Suzuki-Miyaura Cross-Coupling of Benzylic Bromides Under Microwave Conditions

Steven W. McDaniel, Charles M. Keyari, Kevin C. Rider, Nicholas R. Natale, and Philippe Diaz*

Core Laboratory for Neuromolecular Production, Dept. of Biomedical and Pharmaceutical Sciences, The University of Montana, Missoula, Montana 59803, United States

Abstract

A procedure for benzylic Suzuki-Miyaura cross-coupling under microwave conditions has been developed. These conditions allowed for heterocyclic compounds to be coupled. Optimum conditions found were Pd(OAc)₂, JohnPhos as the catalyst and ligand, potassium carbonate as base, and DMF as the solvent. Using these conditions, a library of structurally diverse compounds was synthesized.

Keywords

Suzuki-Miyaura; Cross-Coupling; Microwave; Palladium

System x_c^- (Sx_c^-) is a membrane transporter that functions as an obligate exchanger of L-glutamate (L-Glu) and cystine.¹ The high concentration of L-Glu within cells drives the export of L-Glu and the import of cystine in a 1:1 molar ratio.² Sx_c^- transporter has emerged as a very promising target for CNS disorders such as drug addiction,³ viral pathology,⁴ and brain tumor growth because of its role in oxidative protection⁵, blood brain barrier operation, neurotransmitter release, and synaptic organization.⁶ We recently reported a novel series of Sx_c^- inhibitors based on an isoxazole scaffold.⁷ Inhibition of Sx_c^- reduces the tumor cells ability to protect itself from oxidative stress.

To further explore structure-activity relationships of this series we sought to introduce an aromatic cycle at the benzylic C5 position of an isoxazole. One straightforward approach to introduce the aromatic ring at the benzylic C5 position of an isoxazole would be to use a Suzuki-Miyaura cross-coupling reaction. There are very few examples in the literature of Suzuki couplings at the benzylic position and no examples involving heteroaryl benzylic bromide. Benzylic carbonates have been coupled using [Pd]-DPPPEnt with K₂CO₃ and DMF.⁸ McLaughlin coupled benzylic phosphates with Pd(OAc)₂/PPh₃.⁹ Burns et al. coupled heteroarylboronic acids with benzylic carbons.¹⁰ Molander et al. developed protocol using potassium organotrifluoroborates as the nucleophilic boron.¹¹ Chowdhury et al.¹² and

© 2011 Elsevier Ltd. All rights reserved.

philippe.diaz@mso.umt.edu.

Supplementary Data

Experimental procedures for synthesis, characterization data of new compounds, and ¹H and ¹³C NMR spectra for all compounds prepared can be found at doi:

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Ines et al.¹³ also used water in their protocols. Unfortunately, this route fails using previously described protocols because of the water sensitivity of ethyl 1,2-oxazole-3-carboxylate derivatives. Our previous attempts at this coupling have resulted in low yields in our series of compounds. We developed a protocol that is useful for the coupling of water sensitive compounds. Optimizing this coupling is necessary to create a library of Sx_c^- inhibitors. In this present paper, we report a method for the palladium-catalyzed benzylic arylation of isoxazole and benzoate derivatives with arylboronic acids.

The isoxazole was prepared using previously reported synthetic strategy.^{14,15} In our initial attempt at the benzylic coupling, phenyl boronic acid was used, but the compound resulting from Suzuki coupling was only separable from the starting material by HPLC. In order to have a better monitoring of the reaction, 3-methoxybenzeneboronic acids and the isoxazole were used for the optimization of the Suzuki coupling under microwave conditions. Microwave was used instead of classical heating to shorten reaction time. Yields were comparable between conventional and microwave heating. Details on the experimental protocol used are mentioned in Table 1, and 2.

Conversion yields were determined by LCMS analysis. A low yield, approximately 10%, was achieved when coupling 3-methoxybenzeneboronic acid to the isoxazole using $Pd(PPh_3)_4$ as a catalyst, Cs_2CO_3 as a base, and with dioxane as a solvent.

To improve the yield of this reaction several modifications were explored. Increasing the time or the temperature did not improve the yield (Table 1, entry 1, 2, 3). We then studied the impact of solvent on the yield. Using DMF slightly increased the yield compared to dioxane and THF (Table 1, entry 5). Changes to the base had no effect on the yield. It has been proposed that silver oxide increases the rate of boron to palladium transfer step of the catalytic cycle.^{16,17} Use of silver oxide (Table 1, entry 8) had no effect on the yield. We decided to use the pre-catalysts $PdCl_2(dppf)$ because of its chelating biphosphine with a large "bite" angle¹⁸ even though β -hydride elimination cannot compete with reductive elimination in our case. The use of $PdCl_2(dppf)$ had no effect on the yield. Several bulky, electron-rich Buchwald phosphine ligands were chosen. These ligands have been shown to accelerate the oxidative addition and reductive elimination processes due to their bulky electron-rich phosphines groups.^{19,20} Use of these phosphine ligands and $Pd(OAc)_2$ as the catalyst resulted in the greatest increase of the yield (Table 2). The conditions that provided the greatest yield of 50% were **L2** as shown in Table 2, entry 12.

Using Table 2, entry 12 protocol we coupled a small series of isoxazoles and benzoates to show the effects of electron donating and electron withdrawing groups, as well as the versatility this protocol (Table 3). The phenylboronic acid had the highest yield with 75% for the benzoate derivative and 69% for the isoxazole derivative. Electron withdrawing groups such as 4-trifluorobenzeneboronic acid had the lowest yields with 35% and 20%. As expected, better yields were obtained with electron donating groups like 4-methoxybenzeneboronic acid. Although the 4-methoxybenzene boronic acid would be expected to have a much higher yield compared to the 3-methoxybenzeneboronic acid, yet the 4-methoxybenzeneboronic acid only had a slightly better yield than the 3-methoxybenzeneboronic acid. This can be attributed to the boronic acids being used as the 4-methoxybenzeneboronic acid was of much lower purity than the 3-methoxybenzeneboronic acid as determined by NMR analysis (data not shown). Comparable moderate to good yields were obtained in the benzyl bromide series.

The current protocol is superior to two other routes to C5 aryl methyl isoxazoles we had previously investigated: (1) the analogous Stille coupling suffers from the limitation of handling the relatively unstable and toxic stannyl methylene isoxazoles²¹ and (2)

nucleophilic addition of lithioalkyl isoxazoles to arene cyclopentadienyl iron cation complexes followed by oxidation²² proceeds in moderate overall yields²³.

To conclude, few examples of Suzuki couplings at a benzylic position and even less with heteroaromatic rings such as isoxazoles have been described in the literature. Our study provides a protocol for achieving benzylic Suzuki coupling with moderate to good yields. Our study also provides a method that is useful for the synthesis of water sensitive compounds using a catalyst system commercially available. Furthermore, our method is quick and versatile with these findings; the synthesis of new class of water sensitive isoxazoles was possible. Our study allowed us to obtain the desired compounds to explore the SARs in this series.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH grant P30-NS055022.

References and notes

1. Lo M, Wang YZ, Gout PW. *J Cell Physiol.* 2008; 215:593–602. [PubMed: 18181196]
2. Savaskan NE, Eyüpoglu IY. *Ann Anat.* 2010; 192:309–313. [PubMed: 20801625]
3. Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK. *J Neurosci.* 2005; 25:6389–6393. [PubMed: 16000629]
4. Kaleeba JAR, Berger EA. *Science.* 2006; 311:1921–1924. [PubMed: 16574866]
5. Bridges CC, Kekuda R, Wang H, Prasad PD, Mehta P, Huang W, Smith SB, Ganapathy V. *Invest Ophth Vis Sci.* 2001; 42:47–54.
6. Shih AY, Erb H, Sun X, Toda S, Kalivas PW, Murphy TH. *J Neurosci.* 2006; 26:10514–10523. [PubMed: 17035536]
7. Patel SA, Rajale T, O'Brien E, Burkhart DJ, Nelson JK, Twamley B, Blumenfeld A, Szabon-Watola MI, Gerdes JM, Bridges RJ, Natale NR. *Bioorg Med Chem.* 2010; 18:202–213. [PubMed: 19932968]
8. Kuwano R, Yokogi M. *Org Lett.* 2005; 7:945–947. [PubMed: 15727481]
9. McLaughlin M. *Org Lett.* 2005; 7:4875–4878. [PubMed: 16235911]
10. Burns MJ, Fairlamb IJS, Kapdi AR, Sehnal P, Taylor RJK. *Org Lett.* 2007; 9:5397–5400. [PubMed: 18047357]
11. Molander GA, Elia MD. *J Org Chem.* 2006; 71:9198–9202. [PubMed: 17109547]
12. Chowdhury S, Georghiou PE. *Tetrahedron Lett.* 1999; 40:7599–7603.
13. Inés B, Moreno I, SanMartin R, Domínguez E. *J Org Chem.* 2008; 73:8448–8451. [PubMed: 18855448]
14. Burkhart DJ, Zhou P, Blumenfeld A, Twamley B, Natale NR. *Tetrahedron.* 2001; 57:8039–8046.
15. Giovannoni MP, Cesari N, Vergelli C, Graziano A, Biancalani C, Biagini P, Ghelardini C, Vivoli E, Dal Piaz V. *J of Med Chem.* 2007; 50:3945–3953. [PubMed: 17629262]
16. Chen J, Cammers-Goodwin A. *Tetrahedron Lett.* 2003; 44:1503–1506.
17. Zou G, Reddy YK, Falck JR. *ChemInform.* 2002; 33
18. Brown JM, Cooley NA. *Organometallics.* 1990; 9:353–359.
19. Wolfe JP, Buchwald SL. *Angew Chem Int Edit.* 1999; 38:2413–2416.
20. Wolfe JP, Tomori H, Sadighi JP, Yin J, Buchwald SL. *J Org Chem.* 2000; 65:1158–1174. [PubMed: 10814067]

21. (a) Balasubramaniam, TN. PhD Dissertation. University of Idaho; 1993. (b) Natale NR, Mirzaei YR. *Org Prep Proced Intl.* 1993; 25:515–556.
22. Cambie RC, Janssen SJ, Rutledge PS, Woodgate PD. *J Organometallic Chem.* 1989; 359:C14–C16.
23. (a) Stenzel, JR. PhD Dissertation. University of Idaho; 1995. Stenzel, JR.; Natale, NR. 210th ACS National Meeting; Chicago. 1995. p. Abstract ORGN 398

Figure 1.
Buchwald phosphine ligands

Table 1Condition screen for benzylic Suzuki-Miyaura Cross-Coupling Reactions under microwave conditions. ^a

Entry	Base	Solvent	Yield %
1	Cs ₂ CO ₃	Dioxane	10
2 ^b	Cs ₂ CO ₃	Dioxane	10
3 ^c	Cs ₂ CO ₃	Dioxane	10
4	Cs ₂ CO ₃	THF	10
5	Cs ₂ CO ₃	DMF	15
6	NaHCO ₃	DMF	15
7	K ₂ CO ₃	DMF	15
8 ^d	K ₂ CO ₃	DMF	15

^a Reaction conditions: boronic acid (1.5 mmol), isoxazole bromide (1.0 mmol), base (3.0 mmol), Pd (PPh₃)₄ (5 mol %), solvent (2 mL), 20 minutes.

^b duration was 60 minutes.

^c temperature 160°C.

^d Ag₂O (2.5 mmol) was added.

Table 2Condition screen for benzylic Suzuki-Miyaura Cross-Coupling Reactions under microwave conditions. ^a

Entry	Catalyst System	Base	Temp (°C)	Yield %
9 ^a	PdCl ₂ (dppf)	K ₂ CO ₃	140	15
10	PdCl ₂ (dppf)	K ₂ CO ₃	140	15
11	Pd(OAc) ₂ , L1	K ₂ CO ₃	140	25
12	Pd(OAc) ₂ , L2	K ₂ CO ₃	140	50.4 ^d
13	Pd(OAc) ₂ , L2	K ₂ CO ₃	150	40
14	Pd(OAc) ₂ , L2	K ₂ CO ₃	130	44 ^d
15	Pd(OAc) ₂ , L2	K ₂ CO ₃	80	10
16 ^c	Pd(OAc) ₂ , L2	K ₂ CO ₃	80	15
17	Pd(OAc) ₂ , L3	K ₂ CO ₃	140	25
18	Pd(OAc) ₂ , L2	Et ₃ N	140	25
19	Pd(OAc) ₂ , L3	Et ₃ N	140	25

^a Reaction conditions: boronic acid (1.5 mmol), bromide (1.0 mmol), base (3.0 mmol), catalyst (5 mol %), ligand (10 mol %), DMF (2 mL), 20 minutes.

^b Ag₂O (2.5 mmol) was added.

^c duration was 60 minutes.

^d Isolated yield.

Table 3Cross-Coupling of Benzylic Bromides with Arylboronic Acids. ^a

^aReaction conditions: boronic acid (1.5 mmol), bromide (1.0 mmol), K_2CO_3 (3.0 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %), **L2** (10 mol %), DMF (2 mL), 140°C, 20 minutes. Isolated yields are shown.