Facile Synthesis of Substituted 5-Amino- and 3-Amino-1,2,4-Thiadiazoles from a Common Precursor

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ABSTRACT
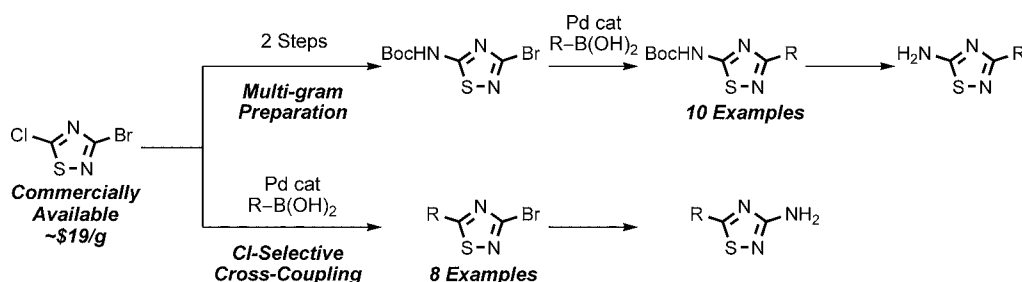
A novel approach to the synthesis of substituted 5-amino- and 3-amino-1,2,4-thiadiazoles beginning from a common precursor has been achieved. Derivatization by palladium-catalyzed Suzuki–Miyaura coupling enables the rapid preparation of analogs around this pharmaceutically relevant core. FMO calculations rationalize the observed chemoselectivity for coupling at chlorine.

As part of a program aimed at the identification of allosteric modulators of the calcium sensing receptor, we became interested in the preparation of 3-aryl-5-amino-1,2,4-thia-diazoles as metabolically stable replacements of a 2-amino-4-aryl-thiazole moiety (eq 1). 2-Amino-thiazoles without blocking substituents at C-5 can undergo oxidation *in vivo* to generate potentially toxic reactive epoxide metabolites.[1]
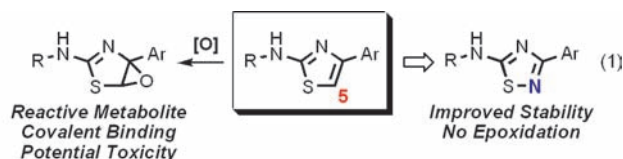
Despite the presence of the 5-amino-3-substituted-1,2,4-thiadiazole and the isomeric 3-amino-5-substituted-1,2,4-

thiadiazole in potential pharmaceuticals[2] and cytotoxic natural products[3] (Figure 1), there is a dearth of methods available for the rapid synthesis of analogs.[4] The most efficient of these methods requires the use of amidine and isothiocyanate intermediates (eq 2).[5,6] For our purposes, access to the unfunctionalized 3-aryl-5-amino-1,2,4-thiadiazoles was required (R = H, eq 2). We envisaged a complementary method that would obviate the need for

(1) Kalgutkar, A. S.; Gardner, I.; Obach, R. S.; Shaffer, C. L.; Callegari, E.; Henne, K. R.; Mutlib, A. E.; Dalvie, D. K.; Lee, J. S.; Nakai, Y.; O'Donnell, J. P.; Boer, J.; Harriman, S. P. *Curr. Drug Metab.* **2005**, *6*, 161–225.

(2) (a) Sutton, J. C.; Pi, Z.; Ruel, R.; L'Heureux, A.; Thibeault, C.; Lam, P. Y. S. U.S. Patent US20060173002A1, 2006. (b) MacNeil, D. J.; McIntyre, J. H.; van der Ploeg, L. H. T.; Ishihara, A. World Intellectual Property Organization Patent WO04009015A2, 2004.

(3) Heitz, S.; Durgeat, M.; Guyot, M. *Tetrahedron Lett.* **1980**, *21*, 1457–1458.

(4) Wilkins, D. J.; Bradley, P. A. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, NY, 1996; Vol. 4, Chapter 10, pp 307–354.

(5) Wu, Y.-J.; Zhang, Y. *Tetrahedron Lett.* **2008**, *49*, 2869–2871.

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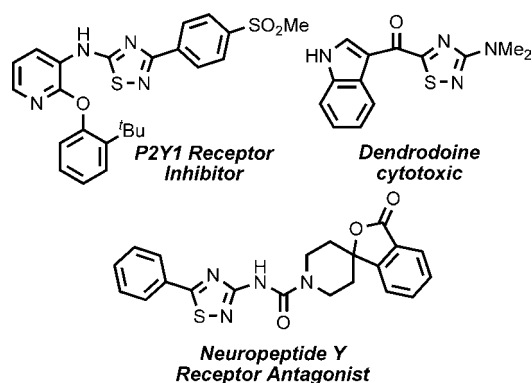§ Dept. of Molecular Structure, So. San Francisco.

Figure 1. Representative amino-1,2,4-thiadiazoles in natural products and potential pharmaceutical agents.

amidines and isothiocyanates by starting with the thiadiazole intact and then functionalizing the nucleus as necessary (eq 3). By taking advantage of the broad functional group tolerance of the Suzuki−Miyaura coupling,[7] it would be possible to efficiently prepare analogs.
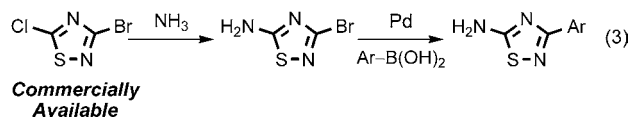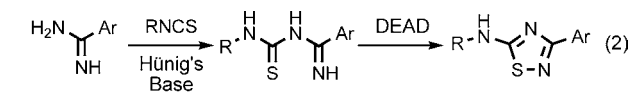
A singular example from the patent literature suggested that such an approach was feasible.[8] The coupling of 5-amino-3-bromo-1,2,4-thiadiazole[9] to phenyl boronic acid using the conditions reported gave only trace amounts of the desired product, however (Table 1, entry 1). Examination of a suite of

catalysts under varying conditions gave uniformly disappointing results (entries 2−5). Of these catalysts, Pd(PtBu3)2 stood out as the best. Interestingly, the use of wet dioxane improved yields slightly (entry 6). We suspected that the unprotected amino group was responsible for the reduced yields[10,11] and investigated a strategy of temporarily protecting the amino group as a t-butyl carbamate.[12] Such protected thiadiazoles improved reactivity (entry 7). A scan of basic additives indicated that reducing the base strength also enhanced the yield slightly (entry 8). Finally, the use of a phosphine analog of PtBu3 improved coupling to synthetically useful levels (entry 9).[13]

With our optimized conditions in hand we explored coupling with a variety of boronic acids and esters[14] (Table 2). Results demonstrate some dependence of reaction yield on the electron richness of the boronic acid component (entries 1−3). Some heteroaryl boronic esters are tolerated (entries 4, 9, and 10) and mild steric crowding at the bononic acid is possible (entry 6). 3- and 4-Pyridylboronic acids, as well as 2,6-dimethylphenylboronic acid, are not viable coupling partners, however. Nonbasic N−H groups do not adversely impact yield (entries 1, 2, and 5). Alkenyl boronates work well (entries 7−8), but aliphatic boronates do not.[15] Deprotection of the t-butyl carbamate products is achieved under standard conditions (eq 4). In the case of the N-t-butyl sulfonamide, it is possible to selectively remove the Boc protecting group (eq 5).

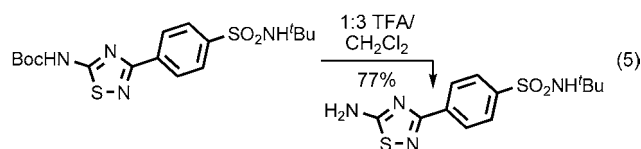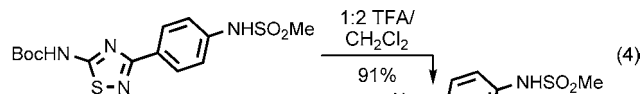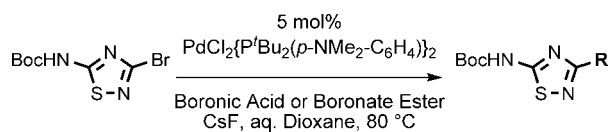**Table 1.** Optimization of Reaction Conditions[a]

entry	-R	X mol % cat	base	solvent	yield
1[b]	-H	5% Pd(PPh3)4	K2CO3	aq. CH3CN 175 °C, μW	trace[c]
2	-H	20% Pd(PPh3)4	Cs2CO3	Dioxane 80 °C	trace[c]
3	-H	20% Pd(PtBu3)2	Cs2CO3	Dioxane 80 °C	8%[d]
4	-H	4% Pd2(dba)3 8% XPhos	K3PO4	1-Butanol 100 °C	ND[c]
5	-H	20% PdCl2(DPPF)	Cs2CO3	Dioxane 80 °C	trace[c]
6	-H	20% Pd(PtBu3)2	Cs2CO3	aq. Dioxane 80 °C	13%[d]
7	-CO2tBu	5% Pd(PtBu3)2	Cs2CO3	aq. Dioxane 80 °C	27%[e]
8	-CO2tBu	5% Pd(PtBu3)2	CsF	aq. Dioxane 80 °C	33%[e]
9	-CO2tBu	5% PdCl2{PtBu2(p-NMe2-C6H4)}2	CsF	aq. Dioxane 80 °C	68%[e]

[a] Reaction time (8−16 h), aqueous solvent denotes 10% H2O. [b] Reaction time (15 min). [c] As determined by LCMS monitoring using UV detection at 254 nM. [d] Complete conversion, isolated yield, see footnote 11. [e] Incomplete conversion, yield estimated by integration of 1H NMR from purified mixture containing product and unreacted bromide.

Table 2. Suzuki−Miyaura Couplings of *tert*-Butyl 3-Bromo-1,2,4-thiadiazol-5-ylcarbamate[a]

Entry	Boronic Acid/ Boronate Ester	Yield[b]
1	(HO)₂B—⟨aryl⟩—NHSO₂Me	80%
2	(HO)₂B—⟨aryl⟩—SO₂NH^tBu	63%
3	(HO)₂B—⟨aryl⟩—SO₂Me	60%
4	pinacol boronate—⟨aryl⟩—N₃N (triazole)	79%
5	pinacol boronate—⟨aryl⟩—NHAc	74%[c]
6	(HO)₂B—⟨o-tolyl⟩	94%
7	pinacol boronate—⟨tetrahydropyridine⟩NBoc	97%
8	pinacol boronate—vinyl	95%
9	pinacol boronate—⟨pyrazole⟩NMe	85%
10	(HO)₂B—⟨pyridine⟩—Cl	54%

a Reaction conditions: thiadiazole bromide (1.0 equiv), boronic acid or boronate (1.3 equiv), CsF (2.1 equiv), 10% aqueous 1,4-dioxane (3 mL/ mmol thiadiazole), scale (1−6 mmol thiadiazole), reaction time (6 h). *b* Isolated yield based on an average of two runs. *c* Pd cat (8 mol %) was used and reaction heated to 90 °C for 16 h.

As an alternative to coupling the problematic 3-bromo-5-amino-1,2,4-thiadiazole, we explored the possibility of performing a chemoselective coupling on the parent 3-bromo-

5-chloro-1,2,4-thiadiazole. The sequential selective cross-coupling of such polyhalogenated heterocycles has emerged as an efficient strategy for the construction of polysubstituted heterocycles.[16] Our prediction was that reaction should occur at the C-3 bromide exclusively. However, upon using the optimized conditions developed previously, *the product of selective coupling at the C-5 chloride was observed* (Table 3, entry 1).[17] Further investigation of the reaction with a

Table 3. Suzuki−Miyaura Couplings of 3-Bromo-5-chloro-1,2,4-thiadiazole[a]

Entry	Boronic Acid/ Boronate Ester	Yield[b]
1	(HO)₂B—⟨phenyl⟩	71%[c]
2	(HO)₂B—⟨aryl⟩—SMe	72%[c]
3	(HO)₂B—⟨aryl⟩—SO₂Me	61%
4	(HO)₂B—⟨aryl⟩—SO₂NH^tBu	63%
5	(HO)₂B—⟨aryl⟩—NHBoc	67%
6	(HO)₂B—⟨aryl,Me⟩—OMe	49%
7	pinacol boronate—⟨tetrahydropyridine⟩NBoc	55%
8	(HO)₂B—⟨pyridine⟩—OBn	40%

a Reaction conditions: thiadiazole (1.0 equiv), boronic acid or boronate (1.2 equiv), CsF (2.0 equiv), 10% aqueous 1,4-dioxane (5 mL/mmol thiadiazole), scale (2 mmol thiadiazole), reaction time (16 h). *b* Isolated yield based on an average of two runs. *c* Conditions changed: thiadiazole (1.75 equiv), boronic acid (1.0 equiv), see ref 18.

diverse set of boronic acids and esters confirmed this selectivity.[18] Coupling is possible with electron-rich and -poor boronic acids (entry 2 vs 3). The presence of nonbasic

(6) Other efficient methods: (a) Martin, D.; Graubaum, H.; Kulpe, S. *J. Org. Chem.* **1985**, *50*, 1295–1298. (b) Dürüst, Y.; Yildirim, M.; Aycan, A. *J. Chem. Res.* **2008**, 235–239.
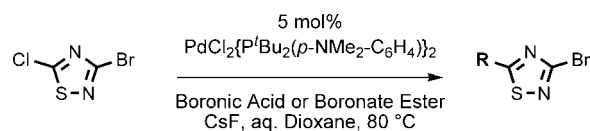
(7) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419–2440.

(8) (a) No yield reported: Krenitsky, P.; Joshi, P.; Wilson, D. M.; Termin, A. P.; Fanning, L. T. D. World Intellectual Property Organization Patent, WO06130493A2, 2006. A patent claiming Suzuki coupling on a related chloride derivative in a single example: (b) Apodaca, R.; Breitenbucher, J. G.; Pattabiraman, K.; Seierstad, M.; Xiao, W. U.S. Patent US20070004741A1, 2007.

(9) Prepared on multigram scale by reacting 3-bromo-5-chloro-1,2,4-thiadiazole with ammonia in EtOH (see Supporting Information).

(10) There are few reports of successful Suzuki−Miyaura reactions in the presence of unprotected heteroaryl amines. For leading approaches see the following and references therein: (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (b) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104–5112. (c) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed* **2006**, *45*, 1282–1284. (d) Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573–3577.

(11) Heating the unprotected 5-amino-3-bromo-1,2,4-thiadiazole in the presence of carbonate base leads to decomposition.

N−H functionality is not deleterious (entries 4−5). Mono-substitution *ortho* to the boronic acid is tolerated (entry 6) and alkenyl boronic esters are viable coupling partners (entry 7). Lastly, weakly basic heterocyclic boronic acids may be used, but the yield is reduced (entry 8). Coupling with unsubstituted 3- or 4-pyridylboronic acids was ineffective.

The 3-bromo-5-substituted-1,2,4-thiadiazoles are versatile intermediates readily affording access to other derivatives.[19] For our purposes, however, preparation of the regioisomeric 3-amino-5-substituted-1,2,4-thiadiazoles[20] would complete the investigation. To this end, treatment of the 3-bromo-5-substitued-1,2,4-thiadiazoles with LHMDS affords the aminated derivatives (eq 6).

R = H, 73%
R = SO$_2$NH^{t}Bu, 76%
R = NHBoc, 74%
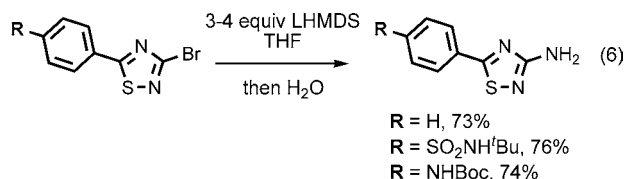
While chemoselectivity in cross-coupling reactions normally follows the pattern of C−I > C−Br > C−Cl, there are rare examples when that trend is broken.[21] Houk and co-workers have invoked the analysis of the frontier molecular orbitals (FMO) to explain chemoselectivity in the cross-coupling of polyhalogenated heterocycles.[22] The key interaction determining selectivity is the magnitude of a stabilizing π^* LUMO − Pd d$_{xy}$ HOMO secondary orbital interaction. Mapping of the LUMO for 3-bromo-5-chloro-1,2,4-thiadiazole identifies a π^* LUMO at the 5-position (Figure 2), thus validating the observed selectivity.[23]
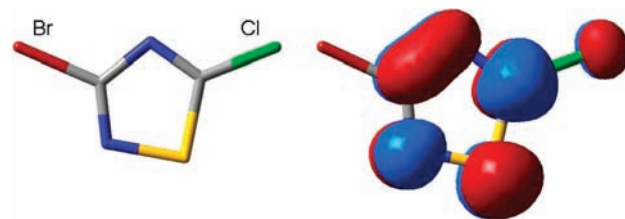
Figure 2. High level ab initio calculations showing the π^* LUMO of 3-bromo-5-chloro-1,2,4-thiadiazole.

In summary, the serendipitous discovery of preferential cross-coupling at the chloride of 3-bromo-5-chloro-1,2,4-thiadiazole has enabled the delineation of a convenient protocol for the expeditious synthesis of both 3-substituted-5-amino- and 3-amino-5-substituted-1,2,4-thiadiazoles from this common starting material. These intermediates should find utility as synthons for the preparation of medicinally relevant agents. In addition, the current methodology complements existing technologies for the construction of 3-substituted-5-amino-1,2,4-thiadiazoles. Finally, results from these investigations reinforce the use of FMO analysis in predicting chemo/regioselectivity for the cross-coupling of polyhalogenated heterocycles.

Supporting Information Available: Experimental procedures, characterization data, and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Caron, S.; Masset, S. S.; Bogle, D. E.; Castaldi, M. J.; Braish, T. F. *Org. Process Res. Dev.* **2001**, *5*, 254–256.

(13) Shortly before submission of this manuscript, we discovered that PdCl$_2$(D-tBPF) (ref 10d) delivers slightly improved results relative to PdCl$_2${P^{t}Bu$_2$(*p*-NMe$_2$-C$_6$H$_4$)}$_2$ (ref 10b). For the reaction in Table 2, complete conversion and 83% isolated yield are observed with 5 mol% of PdCl$_2$(D-tBPF). Both catalysts were ineffective when coupling was attempted in the presence of the unprotected amino group.

(14) The use of boronic acids or esters reflects availability and not an attempt to optimize yield.

(15) MeBF$_3$K gives no product. The incompatibility of PdCl$_2${P^{t}Bu$_2$(*p*-NMe$_2$-C$_6$H$_4$)}$_2$ with aliphatic boronates has been observed previously, see ref 10b.

(16) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245–2267.

(17) Such reactivity has been observed before for 3-bromo-5-chloro-1,2,4-thiadiazole. Single example of Stille coupling of a vinyl stannane, see: (a) Dart, M. J.; Searle, X. B.; Tietje, K.; Toupence, R. B. U.S. Patent US20040044029A1, 2004. Single example of Suzuki−Miyaura coupling, see: (b) Sawyer, J. S.; Beight, D. W.; Smith, E. C. R.; McMillen, W. T. U.S. Patent US6797723, 2004.

(18) Yield is reduced by formation of small amounts of the bis-coupled product. For non-polar products, the use of 1.75 equiv of thiadiazole minimizes formation of the bis-coupled product that can complicate purification of the mono-coupled product.

(19) Buchwald−Hartwig amination: Blurton, P.; Fletcher, S.; Teall, M.; Harrison, T.; Munoz, B.; Rivkin, A.; Hamblett, C.; Siliphaivanh, P.; Otte, K. World Intellectual Property Organization Patent, WO08099210A2, 2008.

(20) For a related approach to the synthesis of 3-amino-5-substituted-1,2,4-thiadiazoles see: Reiter, L. A.; Subramanyam, C.; Mangual, E. J.; Jones, C. S.; Smeets, M. I.; Brissette, W. H.; McCurdy, S. P.; Lira, P. D.; Linde, R. G.; Li, Q.; Zhang, F.; Antipas, A. S.; Blumberg, L. C.; Doty, J. L.; Driscoll, J. P.; Munchhof, M. J.; Ripp, S. L.; Shavnya, A.; Shepard, R. M.; Sperger, D.; Thomasco, L. M.; Trevena, K. A.; Wolf-Gouveia, L. A.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5447–5454.

(21) Mangalagiu, I.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1996**, *50*, 914–917.

(22) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12664–12665. (b) Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6632–6639.

(23) The calculated bond dissociation energies for the C−Cl and C−Br bonds are 88.2 and 80.4 kcal/mol, respectively. The bond dissociation energies of the carbon-halogen bonds were calculated using B3LYP/6-31G(d). These results strongly suggest control of chemoselectivity by FMO interactions between the heterocycle and palladium catalyst.