JOC*Note*

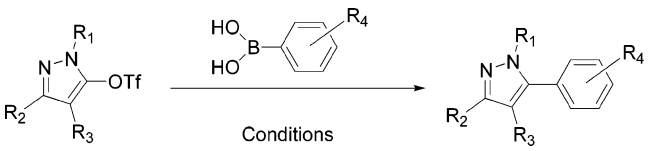
Palladium-Catalyzed Coupling of Pyrazole Triflates with Arylboronic Acids

Curt A. Dvorak,* Dale A. Rudolph, Sandy Ma, and Nicholas I. Carruthers

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 3210 Merryfield Row, San Diego, California 92121

cdvorak@prdus.jnj.com

Received December 17, 2004

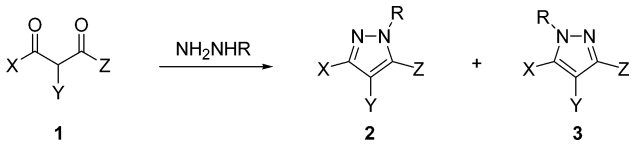


A general protocol for the palladium-mediated Suzuki coupling reaction of pyrazole triflates and aryl boronic acids has been developed. The use of additional dppf ligand was determined to increase product yields allowing for the use of a broad range of reaction substrates.

Recently, we were interested in a general, mild, and efficient method for incorporating an aryl ring onto a pyrazole scaffold. Additionally, it was desirable to add this point of diversity at a late stage in the synthetic sequence. While there are many new and novel methods available for the assembly of the pyrazole nucleus,[1] the most general remains the condensation of a 1,3-dicarbonyl compound or equivalent with a hydrazine derivative.[2] Although this condensation is straightforward, the formation of regioisomers with N-substituted hydrazines can be problematic (Scheme 1). Another major drawback is the necessity to "custom make" the required dicarbonyl components, i.e., **1**, for the condensation reaction.

Thus, we chose to explore transition-metal catalysis as a means of installing the aryl unit onto the fully assembled pyrazole via a carbon−carbon bond-forming reaction. Specifically, we chose to examine the Suzuki reaction,[3] which is unaffected by the presence of water, tolerates a broad range of functional groups, and utilizes

SCHEME 1



1 **2** **3**

air-stable, nontoxic, and commercially available boronic acids as the organometallic coupling partners.

There have been several literature reports of coupling reactions performed on halopyrazoles. Wang et al.[4] performed Suzuki, Stille, and Sonogashira couplings on 1-aryl-5-bromopyrazoles. Zhang[5] and co-workers utilized a Suzuki coupling of a 5-bromopyrazole while exploring the structure−activity relationships of endothelin antagonists. In addition, Organ et al.[6] has prepared a library of COX-2 inhibitors from 4-(5-iodo-3-methylpyrazolyl)phenylsulfonamide and aryl boronic acids by solution phase Suzuki coupling utilizing a solid-supported catalyst. However, we wished to avoid the harsh reaction conditions necessary to form the requisite halopyrazole ($POCl_3$, $POBr_3$, etc.). As for the corresponding pseudohalopyrazoles, Organ noted that the Suzuki reaction failed with the 1-arylpyrazole 5-mesylate and 5-phosphate analogues, thus prompting the suggestion that these heterocyclic precursors might not be suitable substrates for the oxidative addition of the palladium(0).[7] More recently, Collins[8] and co-workers reported the successful application of 3(5)-pyrazolyl nonaflates in palladium-catalyzed cross-coupling reactions. However, they also mentioned that the cross coupling with pyrazole triflates was capricious even under nonaqueous conditions. Not surprisingly, there have been few reports of Suzuki cross-coupling reactions accomplished with pyrazole triflates.[9] Nonetheless, we chose to explore the scope and utility of pyrazole triflates as possible substrates in the palladium catalyzed Suzuki reaction for the synthesis of aryl pyrazoles. In this paper, we wish to communicate the progress of this endeavor.

Pyrazolones **4a**−**e** were available from commercial sources. Pyrazolones **4f** and **4g** were made according to the procedure of Mendoza et al.[10] by treatment of 2-oxocyclohexanecarboxylic acid ethyl ester with methyl and phenyl hydrazines, respectively. Pyrazole triflates **5a**−**g**

(1) (a) Singh, S. K.; Reddy, M. S.; Shivaramakrishna, S.; Kavitha, D.; Vasudev, R.; Babu, J. M.; Sivalakshmidevi, A.; Rao, Y. K. *Tetrahedron Lett.* **2004**, *45*, 7679. (b) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737. (c) Aggarwal, V. K.; Vincente, J.; Bonnet, R. V. *J. Org. Chem*. **2003**, *68*, 5381. (d) Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D. A.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L. *J. Org. Chem*. **2002**, *67*, 9200. (e) Haddad, N.; Baron, J. *Tetrahedron Lett*. **2002**, *43*, 2171. (f) Molteni, V.; Hamilton, M. M.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. *Synthesis* **2002**, 1669. (g) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V. *J. Org. Chem*. **2001**, *66*, 6787. (h) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett*. **2000**, *2*, 2833. (i) Katritzky, A. R.; Denisenko, A.; Denisenko, S. N. *J. Heterocycl. Chem*. **2000**, *37*, 1309.

(2) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Longman Press: Essex England, 1997.

(3) (a) reviews: Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147. (b) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.

(4) Wang, X.; Tan, J.; Grozinger, K. *Tetrahedron Lett*. **2000**, *41*, 4713.

(5) Zhang, J.; Didierlaurent, S.; Fortin, M.; Lefrancois, D.; Uridat, E.; Vevert, Jean Paul. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2575.

(6) Organ, M. G.; Mayer, S. *J. Comb. Chem*. **2003**, *5*, 118.

(7) For corresponding aryl sulfonate Suzuki couplings, see: (a) Nguyen, H.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 11818. (b) Percec, V.; Bae, J.; Hill, D. H. *J. Org. Chem*. **1995**, *60*, 1060. For vinyl phosphate coupling, see: Lepifre, F.; Buon, C.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett*. **1999**, *40*, 6373.

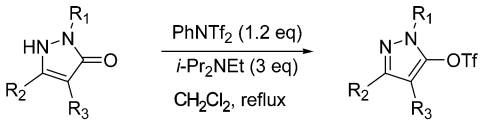
(8) Bourrain, S.; Ridgill, M.; Collins, I. *Synlett* **2004**, 795.

(9) (a) Stille reaction performed on a pyrazole triflate: Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tong, L.; Torcellini, C. *J. Med. Chem*. **2002**, *45*, 2994. (b) Suzuki reaction on N−Boc derivative: PTC WO 03/051797. (c) For *N*-Boc-indazole, see: Patel, M.; Rodgers, J. D.; McHugh, R. J.; Johnson, B. L.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S. and Ko, S. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 3217.

(10) Mendoza, J.; Garcia-Ochoa, S.; Prados, P.; Parra, E. *Tetrahedron* **1986**, *42*, 2377.

10.1021/jo0477897 CCC: $30.25
Published on Web 04/14/2005

TABLE 1. Pyrazole Triflate Synthesis

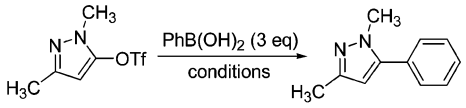


4a-g **5a-g**

no.	R_1	R_2	R_3	triflate	yield[a] (%)
4a	CH_3	CH_3	H	**5a**	62
4b	H	CH_3	H	**5b**	45
4c	CH_3	CF_3	H	**5c**	60
4d	Ph	CH_3	H	**5d**	92
4e	Ph	CF_3	H	**5e**	60
4f	CH_3	-$(CH_2)_4$-		**5f**	88
4g	Ph	-$(CH_2)_4$-		**5g**	97

[a] Isolated yield after chromatography on silica gel.

TABLE 2. Optimization of Suzuki Reaction Conditions



5a **6a**

entry	catalyst[a]/additive	base[h]	solvent	T[b] (°C)	yield[c] (%)
1	$Pd(PPh_3)_4$	K_3PO_4	THF	65	12
2	$Pd(PPh_3)_4$/KBr[d]	K_3PO_4	dioxane	100	74
3	$PdCl_2(PPh_3)_2$	Na_2CO_3	THF	65	1
4	$Pd(OAc)_2/PCy_3$[e]	KF	THF	rt	–
5	$PdCl_2$(dppf)	Na_2CO_3	DMF	80	51
6	$PdCl_2$(dppf)	K_3PO_4	THF	65	43
7	$PdCl_2$(dppf)	K_3PO_4	dioxane	100	68
8	$PdCl_2$(dppf)/PPh_3[a]	K_3PO_4	dioxane	100	79
9	$PdCl_2$(dppf)/dppf[f]	K_3PO_4	dioxane	100	83
10	$Pd_2(dba)_3$/dppf[g]	K_3PO_4	dioxane	100	10

[a] 8 mol %. [b] 16 h. [c] Isolated yield after chromatography on silica gel. [d] 1.1 equiv. [e] 1 mol % $Pd(OAc)_2$, 1.2 mol % of PCy_3. [f] 4 mol %. [g] dppf/Pd = 1.5. [h] 3 equiv.

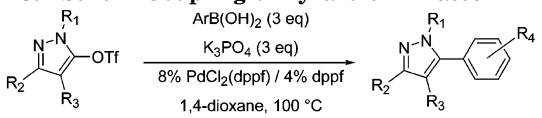
in Table 1 were made with excellent chemoselectivity by treating the corresponding pyrazolones with *N*-phenyltrifluoromethanesulfonimide and a non-nucleophilic tertiary amine base in methylene chloride. Attempts to use the more reactive trifluoromethanesulfonyl anhydride as the triflating agent afforded unwanted mixtures of N- and O-triflation.

Table 2 outlines the reaction conditions that have been examined thus far for the transformation of **5a** to **6a**. In entry 1, the use of $Pd(PPh_3)_4$ as a catalyst with K_3PO_4 resulted in the formation of the desired coupled product **6a** albeit in low yield. The low yield was apparently due to premature decomposition of the catalyst and the precipitation of palladium black. The addition of 1.1 equiv of KBr with $Pd(PPh_3)_4$ and increasing the reaction temperature dramatically improved the coupling yield (entry 2). Suzuki and co-workers also observed improved yields with the addition of KBr while exploring the coupling of vinyl and aryl triflates.[11] Nevertheless, these conditions were not amenable to more complex pyrazole substrates and substituted arylboronic acids.

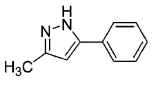
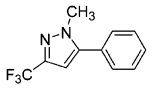
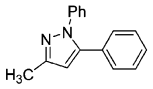
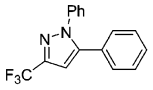
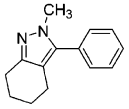
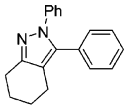
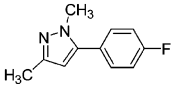
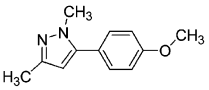
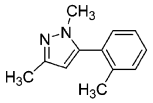
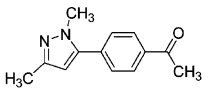
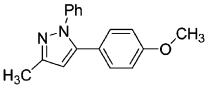
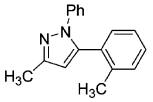
Utilizing $PdCl_2(PPh_3)_2$ as the palladium source with aqueous Na_2CO_3 as the base provided only a trace of the coupling product **6a** (entry 3).[12] Switching to an electron rich bulky phosphine ligand, the conditions developed by Fu[13] and co-workers for the coupling of aryl triflates at

(11) Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem*. **1993**, *58*, 2201.

TABLE 3. Suzuki Coupling of Pyrazole Triflates



5b-g **6b-m**

Entry	Triflate	Product	#	Yield(%)[a]
1	**5b**		**6b**	81
2	**5c**		**6c**	79
3	**5d**		**6d**	81
4	**5e**		**6e**	74
5	**5f**		**6f**	71
6	**5g**		**6g**	74
7	**5a**		**6h**	85(74)[b]
8	**5a**		**6i**	90
9	**5a**		**6j**	79
10	**5a**		**6k**	71
11	**5d**		**6l**	76
12	**5d**		**6m**	92

[a] Isolated yield after chromatography on silica gel. [b] 1.4 equiv of 4-fluoroboronic acid, 1.4 eq of K_3PO_4, 4% $PdCl_2$(dppf), and 2% dppf utilized.

room temperature, were found to be ineffective (entry 4). As shown in entry 5, the coupling of pyrazole triflate **5a** with phenylboronic acid was accomplished with $PdCl_2$(dppf) in DMF with aqueous Na_2CO_3 as the base to provide a modest yield of **6a**. However, hydrolysis of the triflate could be observed with aqueous conditions. Good to fair yields of **6a** were obtained using $PdCl_2$(dppf) as the catalyst with K_3PO_4 in solvents such as THF or dioxane (entries 6 and 7). The addition of PPh_3 to the reaction (entry 8) did provide an improvement of the coupling yield, although these conditions have not been fully explored. The addition of a slight excess of dppf ligand with $PdCl_2$(dppf) (dppf/Pd ratio of 1.5) provided a considerable increase in the coupling yield (Table 2, entry 9). The effects of adding extra dppf ligand were most dramatic in reactions that failed to completely consume the pyrazole triflate due to decomposition of the catalyst and precipitation of palladium black. The addition of more dppf ligand[14] (>1.5 dppf/Pd) to $PdCl_2$(dppf) resulted in slower reaction rates requiring extended heating times. More importantly, a dppf/Pd ratio of 1.5 in conjunction with $PdCl_2$(dppf) as the palladium source provided reaction conditions that were found to have broader applicability to a diverse range of substrates. Changing to $Pd_2(dba)_3$ while maintaining a dppf/Pd ratio of 1.5 yielded only 10% of the aryl pyrazole **6a** (Table 2, entry 10).

Table 3 demonstrates the scope of this general coupling protocol toward the synthesis of arylpyrazoles. In entries 1−6 of Table 3, phenylboronic acid was coupled with various pyrazole triflates. The reaction tolerates differing substitution patterns on the pyrazole heterocycle. The pyrazole nitrogen may have a free N-H or be substituted with either aryl or alkyl moieties (entries 1 and 3 and product **6a**). The pyrazole ring may be substituted with an electron-rich alkyl or an electron-withdrawing trifluoromethyl group (entries 3 and 4). In addition, the pyrazole can be fused to a carbocyclic ring system (entries 5 and 6).

Entries 7−12 examine electronic and steric variations on the boronic acid partner. In entries 8 and 11, both the *N*-methyl- and N-phenylpyrazole triflates couple smoothly with 4-methoxyphenylboronic acid in good yields. Entries 7 and 10 demonstrate the coupling with electron-poor aryl boronic acids. The sterically hindered 2-methylphenylboronic acid provides the corresponding aryl pyrazoles with either the *N*-methyl or *N*-aryl functionality in good yields (entries 9 and 12).

In summary, we have developed a general, mild, and efficient route to aryl pyrazoles via the Suzuki cross-coupling of pyrazole triflates. The coupling conditions were found to be tolerant for a broad range of electronic and steric variations in either the boronic acid or pyrazole triflate components. Further investigations into the chemistry of pyrazole triflates are ongoing.

Experimental Section

General Procedure for Pyrazole Triflation. To a 0.1 M solution of the pyrazolone (**4**) in CH_2Cl_2 were added *N*,*N*-diisopropylethylamine (3 equiv) and *N*-phenyltrifluoromethanesulfonimide (1.2 eq). The mixture was then heated to reflux and monitored by TLC (25−50% EtOAc/Hex). Upon disappearance of the starting material (3−16 h), the mixture was cooled to room temperature, diluted with CH_2Cl_2, washed with water and brine, and then dried over $MgSO_4$. Purification was performed on SiO_2 with a Hex/EtOAc gradient (0 to 25%).

General Procedure for the Arylation of Pyrazole Triflates. To a 0.1 M solution of the pyrazole triflate (**5**) in 1,4-dioxane were added anhydrous K_3PO_4 (3 equiv), aryl boronic acid (3 equiv), dppf (4 mol %), and $PdCl_2$dppf (8 mol %). The mixture was then placed under nitrogen and immersed in an oil bath preheated to 100 °C. After 16 h, the mixture was cooled and the solvent removed in vacuo. The residue was taken up in toluene and filtered on Celite. The filter cake was washed with toluene and solvent removed. Purification was performed on SiO_2 with a Hex/EtOAc gradient (0 to 25%).

Acknowledgment. We are grateful for a CORD Fellowship for S.M. awarded by Johnson & Johnson Corporate Office of Science and Technology. We also thank James Edwards, Kate McElhone, and John Keith for their help in the preparation of this manuscript as well as Heather McAllister for the purification of triflate **5a**.

Supporting Information Available: General experimental information as well as characterization data for the compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0477897

(12) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459.
(13) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(14) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447.