Facile Synthesis of N-Aryl Pyrroles via Cu(II)-Mediated Cross Coupling of Electron Deficient Pyrroles and Arylboronic Acids

Shu Yu, James Saenz, and Jayaram K. Srirangam*

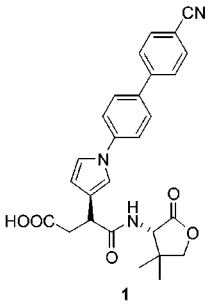
Chemical Research and Development, Pfizer Global Research & Development-La Jolla, 3565 General Atomics Court, San Diego, California 92121

jay.srirangam@pfizer.com

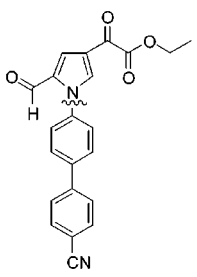
Received September 20, 2001

Abstract: N-Arylation of electron-deficient pyrroles has been achieved by cross-coupling with arylboronic acids at room temperature in the presence of stoichiometric amounts of copper(II) acetate. The generality of this reaction has been established with variously substituted pyrroles as well as boronic acids. A key intermediate in the synthesis of a matrix metalloprotease inhibitor has been acheived using this methodology.

AG3433 (**1**) is a potent inhibitor of matrix metalloproteases (MMPs) currently undergoing preclinical evaluation.[1] During the course of the chemical development of this antiangiogenic drug, an easy entry into an *N*-arylpyrrole (**2**), a key intermediate in the synthesis of AG3433 was required. Of the several routes, the disconnection of the C−N bond between the pyrrole nitrogen atom and the biphenyl moiety, was among the most convergent and very appealing. In the synthetic direction, it required the formation of the C−N bond between the nitrogen atom on an electron deficient pyrrole and a properly functionalized arene.



1



2

C−N cross-coupling of aryl halides with amines has been the subject of studies in recent years.[2,3,4b,6] Although there existed ample precedence of the transition metal promoted cross-coupling of azoles (imidazoles, pyrazoles as well as their benzofused counterparts) and functionalized arenes that included the Cu(II)-mediated coupling of azoles and arylboronic acids,[4a,4b] arylsiloxanes,[5] and arylstannanes[6] developed by Lam et al., arylbismuths,[7] and aryllead,[8] there were only limited reports on the coupling of pyrroles and aryl halides, all at elevated temperature.[2e,3c,d] Buchwald described in a recent account the coupling of 3,5-dimethylphenyl iodide and pyrrole by heating a mixture of the two in dioxane at 110 °C in the presence of CuI.[2e] Hartwig also observed the palladium-mediated coupling of unsubstituted pyrrole and aryl halide, under the optimal conditions that normally worked well on amines.[3c,3d] Lam et al.[4a] reported that the coupling of pyrroles and indoles with arylboronic acids gave very little (<3%) desired product. As such, we postulated that since the azoles employed in the coupling reactions are more electron deficient than pyrrole, electron deficient pyrroles, a priori, ought to exhibit reactivities in the coupling reactions similar to azoles. To test this idea, the protocol employed by Lam et al. to couple azoles and arylboronic acids (vide infra) was chosen based on its mild conditions and ready availability of starting materials as well as its minimal cost.[4a]

To our delight, when a mixture of ethyl 5-formylpyrrole-3-glyoxalate **3**[9] (1.0 equiv), 4-bromophenylboronic acid (2.0 equiv), $Cu(OAc)_2$ (1.5 equiv), and pyridine (2.0 equiv) in methylene chloride (5 mL) was stirred at room-temperature open to air for 2 days, all the pyrrole was consumed and the desired coupling product was isolated in almost quantitative yield. Encouraged by this facile union, a systematic study was conducted to investigate the generality of this coupling reaction, as well as the scope and limitations.

Since electronic effects are expected to play a major role in such coupling reactions, a study of the reaction with variously substituted pyrroles as well as boronic acids was undertaken. As indicated in Tables 1 and 2, for the boronic acid part, electron-releasing groups facilitated the coupling reaction when holding the pyrrole

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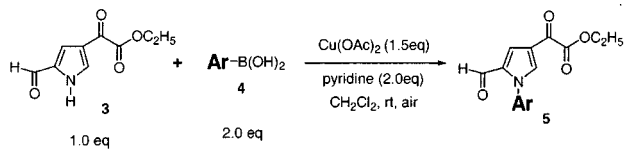
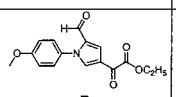
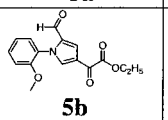
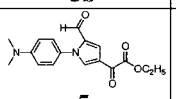
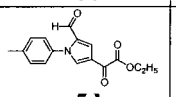
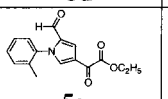
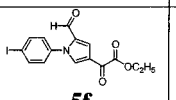
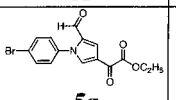
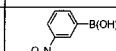
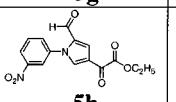
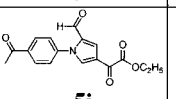
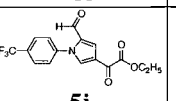
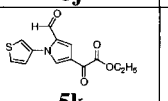
10.1021/jo016131f CCC: $22.00
Published on Web 02/02/2002

Table 1. $Cu(OAc)_2$-Mediated Cross-Coupling of Arylboronic Acid and Ethyl 5-Formylpyrrole-3-glyoxalate 3

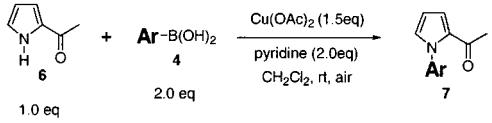


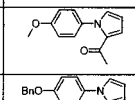
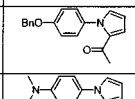
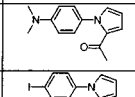
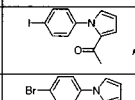
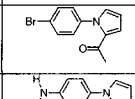
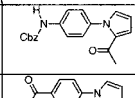
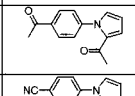
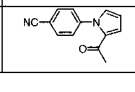
Entry	$ArB(OH)_2$	N-arylpyrrole	Reaction time (day)	Yield (%)
1		 **5a**	2	95
2		 **5b**	2	14%[a]
3		 **5c**	3	87
4		 **5d**	2	97
5		 **5e**	13	56[b]
6		 **5f**	2	95
7		 **5g**	2	Quan.
8		 **5h**	4	97
9		 **5i**	8	91
10		 **5j**	10	90
11		 **5k**	4	44[c]

[a] This was an estimate yield based on proton NMR and HPLC. After chromatography, 125 mg (64%) of the starting material (**3**) was isolated; the desired product **5b** was isolated with an inseparable impurity. Together they constituted 68 mg (22%) of the mass. [b] Balanced with 43% recovered pyrrole starting material (**3**). [c] Balanced with 54% recovered pyrrole starting material (**3**).

moiety constant. While 4-methoxy-, 4-methyl-, 4-iodo-, and 4-bromophenylboronic acids (entries 1, 4, 6, and 7 in Table 1) were completely consumed within 2 days, it took 4-acetyl boronic acid 8 days to complete (see entry 9 in Table 1). A similar trend was observed with 2-acetylpyrrole (Table 2). Boronic acids with electron

Table 2. $Cu(OAc)_2$-Mediated Cross-Coupling of Arylboronic Acids and 2-Acetylpyrrole

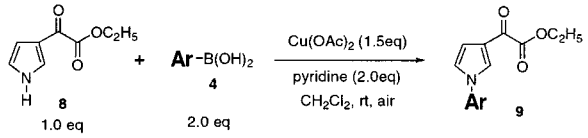


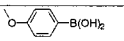
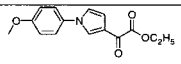
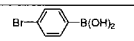
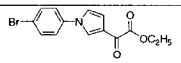
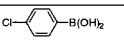
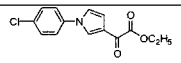
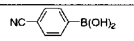
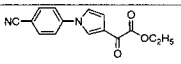
Entry	$ArB(OH)_2$	N-arylpyrrole	Reaction time (day)	Yield (%)
1		 **7a**	3	92
2		 **7b**	4	92
3		 **7c**	4	86
4		 **7d**	4	91
5		 **7e**	3	94
6		 **7f**	2	31
7		 **7g**	7	80
8		 **7h**	13	55

releasing groups (4-methoxy, 4-benzyloxy, and 4-dimethylamino) and weak electron-withdrawing substituents (4-iodo and 4-bromo) reacted smoothly with excellent yields (entries 1−5). In contrast, the boronic acids with strong electron-withdrawing substituents such as 4-acetyl or 4-cyano group, reacted very sluggishly. The coupling between 2-acetylpyrrole and 4-acetylbenzene boronic acid took 7 days, while the coupling of 4-cyanophenylboronic acid was even slower. For reasons not clear, heterocyclic boronic acids did not couple with electron-deficient pyrroles very well. Among 3-pyridylboronic acid, 3-thienylboronic acid, and 2-furanylboronic acid, only 3-thienylboronic acid coupled with 5-formylpyrrole-3-glyoxalate (**3**) in moderate yield (4 days, 44%), the other two did not yield any coupled product even after prolonged reaction time (14 days).

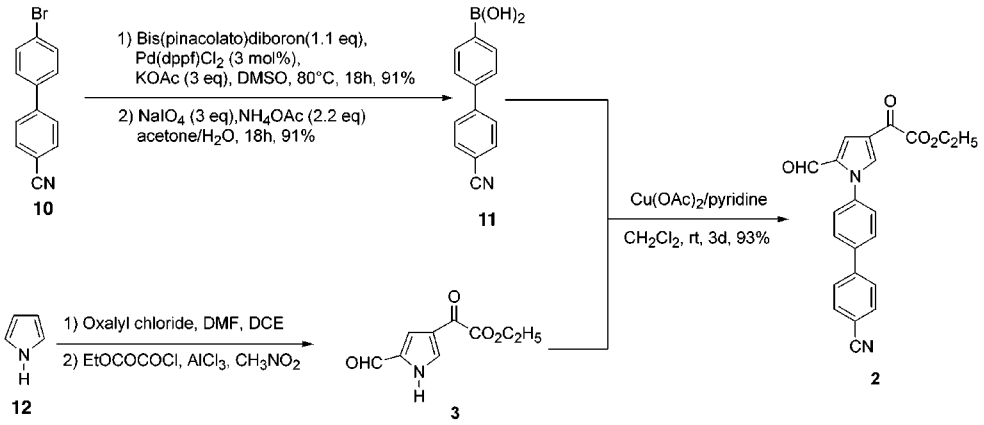
When holding the arylboronic acid part constant, as 4-methoxy or 4-bromo, and varying the pyrrole portion, it could be concluded that the 2-substitution had a much more profound effect on the reactivity of pyrroles than the 3-substitution, as indicated in Tables 2 and 3. While the reactions of 4-methoxy- and 4-bromophenylboronic acids with 2-acetylpyrrole was complete in a couple of days (entries 1 and 5 in Table 2), their reactions with ethyl pyrrole-3-glyoxalate were incomplete even after prolonged reaction time (entries 1 and 2 in Table 3). Considering that the difference in electron-withdrawing abilities between the acetyl group and ethoxyglyoxalyl group is minimal, the aforementioned stronger 2-substitution effect might in part be attributed to the chelation of carbonyl oxygen to the pyrrole nitrogen−Cu complex. When the 2- and 3- positions were both occupied by electron-withdrawing groups, the reaction occurred with the most ease (Table 1). Here even the 4-acetyl- and 4-(trifluoromethyl)phenylboronic acids reacted smoothly. No coupling was observed with pyrrole itself, even with 4-methoxyphenylboronic acid.

Table 3. $Cu(OAc)_2$-Mediated Cross-Coupling of Arylboronic Acid and Ethyl Pyrrole-3-glyoxalate



Entry	$ArB(OH)_2$	N-arylpyrrole	Reaction time(day)	Yield (%)
1		 **9a**	11	25
2		 **9b**	1	trace
3		 **9c**	3	trace
4		 **9d**	2	trace

Scheme 1. Synthesis of Intermediate 2



A large variety of functional groups survived in these coupling processes, including nitro, ether, ester, ketone, aldehyde, amide, bromo, and iodo groups. The results demonstrate this coupling process as a highly specific transformation with no significant complications caused by other reaction pathways, such as, Ullmann coupling reactions. Survival of the aryliodide functionality, considering that copper at all oxidation states was available in the reaction vessel, is remarkable. In addition, since many of the functional groups in Tables 1 and 2, such as iodo, bromo, benzyloxy, amide, aldehyde, ketone, etc., are eligible for further elaboration, this coupling reaction should be of general use in *N*-arylpyrrole synthesis.

It appeared that the coupling reactions were also sensitive to steric hindrance. The phenyl boronic acids with ortho substitutions reacted sluggishly, in sharp contrast to the corresponding boronic acids with para substitutions. For example, the coupling of ethyl 5-formylpyrrole-3-glyoxalate and *p*-methoxyphenylboronic acid took 2 days and afforded the corresponding N-(*p*-methoxyphenyl)pyrrole in 95% yield (entry 1 in Table 1). Under identical reaction conditions, *o*-methoxyphenylboronic acid gave only a meager 14% yield (entry 2 in Table 1). A similar trend was observed with *p*-tolylboronic acid and *o*-tolylboronic acid (entries 4 and 5 in Table 1). Extending the reaction time did not seem to help (entry 5 in Table 1).

A detailed mechanistic study is beyond the scope of this investigation. A plausible mechanism can be that the deprotonated pyrrole coordinates with Cu(II) first, followed by transmetalation. In the presence of air, this species could be oxidized to Cu(III) which readily go through reductive elimination to afford the *N*-arylpyrrole. It appears that the proposed mechanism agreed with the structure reactivity studies.

Returning to where this study began, this technology was successfully applied to the synthesis of compound **2**, which is a pivotal intermediate in the synthesis of the MMP inhibitor AG3433 (vide supra). As indicated in Scheme 1, boronic acid **11** was prepared in excellent yield from the corresponding bromide **10**, which is commercially available. The coupling of this boronic acid and pyrrole **3** was uneventful. The electron-deficient pyrrole **3** was completely consumed in 3 days and afforded compound **2** in 93% yield.

In summary, *N*-arylpyrroles can be prepared from arylboronic acids and electron-deficient pyrroles via a $Cu(OAc)_2$-mediated coupling reaction at room temperature in air. These reaction conditions are compatible with a variety of functional groups. This coupling reaction

works the best on electron-rich boronic acids and is sensitive to steric hindrance. Although intrinsically cheap, this methodology does require stoichiometric amounts of $Cu(OAc)_2$ to mediate the coupling reaction.

Experimental Section

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker 300 and 75.5 MHz instruments, respectively, using $CDCl_3$ as the solvent. Electron spray low-resolution spectra were determined at an ionizing voltage of 70 eV. Methylene chloride was used as received. Column chromatography was carried out on Universal silica gel (32−63 μm) using the indicated solvents as eluents. HRMS data were determined on Micromass Q-Tof-2 mass spectrometer. Ethyl pyrrole-3-glyoxalate and ethyl 5-formylpyrrole-3-glyoxalate were prepared according to literature procedure.[9]

General Procedure for the $Cu(OAc)_2$-Mediated Coupling of Pyrroles and Arylboronic Acids. To a 25 mL one-neck round-bottom flask fitted with a magnetic stirring bar was added 1.00 mmol of the pyrrole, 1.50 mmol of $Cu(OAc)_2$, 2.00 mmol of the boronic acid, and 2.00 mmol of pyridine in that order, followed by 5.0 mL of methylene chloride. The flask was fitted with a male gas inlet (CHEMGLASS CG-1014-14;[10] used to reduce the evaporation of the solvent), and the dark blue mixture was allow to stir at room-temperature open to air. Note: the reactions will not proceed to completion in the absence of air. The reaction was followed with TLC until all the pyrrole was consumed. The mixture was then poured into 25 mL of water and extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with water, brine, and dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was preadsorbed onto silica gel and subjected to gradient flash chromatography using hexanes and ethyl acetate (6:1 to 1:1) to afford the desired *N*-arylpyrroles. Thus, the reaction of ethyl 5-formylpyrrole-3-glyoxalate (**3**, 195 mg, 1 mM) and *p*-methoxyphenylboronic acid (304 mg, 2mM) in methylene chloride afforded, after purification, **ethyl *N*-(*p*-methoxyphenyl)-5-formylpyrrole-3-glyoxalate** (**5a**, 285 mg, 95%); mp 96−97 °C; ^1H NMR δ 1.42 (t, J = 7.2 Hz, 3H), 3.87 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 6.99 (dd, J = 6.6 and 2.1 Hz, 2H), 7.30 (dd, J = 6.9 and 2.4 Hz, 2H), 7.70 (d, J = 1.5 Hz, 1H), 7.99 (d, J = 1.2 Hz, 1H), 9.62 (s, 1H); ^{13}C NMR δ 13.9, 55.4, 62.4, 114.3, 121.8, 122.7, 126.9, 130.4, 133.4, 136.7, 159.9, 161.8, 177.7, 179.3; FTIR (NaCl) 1256, 1375, 1464, 1514, 1676, 1719 cm^{-1}; MS (ES) *m*/*z* 302.1 (M + 1), 228.0. Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.95; H, 5.07; N, 4.62.

4′-Cyano-4-biphenylboronic Acid (17). 4′-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-biphenyl-4-carbonitrile. To a 250 mL round-bottom flask charged with 2.79 g (11.0 mmol) of bis(pinacolato)diboron, 2.94 g (30.0 mmol) of KOAc, and 245 mg (0.30 mmol) of $Pd(dppf)Cl_2$ was added a solution of 2.58 g (10.0 mmol) of 4-bromo-4′-cyanobiphenyl in 60 mL of DMSO. The mixture was thoroughly degassed by alternately connecting the flask to vacuum and nitrogen. This red solution was then heated at 80 °C for 18 h at which time it was observed that all the bromide was consumed (HPLC). The solvent was removed by Kugelrohr distillation. The residue was preadsorbed onto silica gel and was subjected to flash chromatography using hexanes/EtOAc (6:1 → 2:1) to afford 2.78 g (91%) of the desired product as a white solid: mp 190.5−191.5 °C; ^1H NMR δ 1.41 (s, 12H), 7.63 (d, J = 8.1 Hz, 2H), 7.65−7.80 (m, 4H), 7.96 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 25.3, 83.9, 111.1, 118.8, 126.4, 127.7, 132.5, 135.4, 141.6, 145.4; FTIR (NaCl) 1331, 1366, 1462, 1605, 2226 cm^{-1}; MS (ES) *m*/*z* 306.1 (M + 1). Anal. Calcd for $C_{19}H_{20}NO_2B$: C, 74.78; H, 6.61; N, 4.59. Found: C, 74.72; H, 6.64; N, 4.59.

To a solution of 2.38 g (7.80 mmol) of the above boronate in 80 mL of acetone were added at room temperature 5.06 g (23.6 mmol) of $NaIO_4$, 1.34 g (17.4 mmol) of NH_4OAc, and 80 mL of water. The thick suspension was allowed to stir at room temperature for 18 h at which time all the boronate was consumed (TLC). Acetone was removed in vacuo, and the aqueous solution was basified with 80 mL of 2 M NaOH. The aqueous solution was washed once with CH_2Cl_2 (discarded). This aqueous solution was acidified with concentrated HCl to pH = 3 and chilled in ice bath for 2 h. The precipitate was filtered, washed with water, and air-dried. The off white solid was purified by flash chromatography using hexanes/THF (1:1) to give 1.58 g (91%) of the desired boronic acid as a white solid: mp 230−233 °C; ^1H NMR (300 MHz, THF-d_8) δ 7.65 (d, J = 8.4 Hz, 2H), 7.65−7.80 (dd, J = 8.4 and 8.4 Hz, 4H), 7.90 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75.5 MHz, THF-d_8) δ 107.6, 114.5, 121.3, 122.2, 123.8, 128.7, 131.0, 136.7, 141.6; FTIR (NaCl) 1333, 1377, 1462, 1603, 2224 cm^{-1}. Anal. Calcd for $C_{13}H_{10}NO_2B$: C, 70.01; H, 4.52; N, 6.28. Found: C, 70.08; H, 4.76; N, 6.06.

Ethyl *N*-(4′-Cyanobiphenyl-4-yl)-5-formylpyrrole-3-glyoxalate (2). This compound was prepared according to the general procedure. The pyrrole starting material was completely consumed after 3 days. After workup and purification a total of 347 mg (93%) of the arylpyrrole was isolated as a yellowish solid: mp 159−161 °C; ^1H NMR δ 1.47 (t, J = 7.2 Hz, 3H), 4.47 (q, J = 7.2 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.70−7.85 (m, 7H), 8.13 (dd, J = 1.5 and 0.9 Hz, 1H), 9.73 (d, J = 0.6 Hz, 1H); ^{13}C NMR δ 14.0, 62.6, 111.7, 116.0, 118.6, 122.4, 124.6, 126.4, 127.8, 132.7, 133.2, 136.9, 138.1, 140.1, 144.0, 161.7, 177.6, 179.2; FTIR (NaCl) 1377, 1462, 1537, 1682, 1721, 2228 cm^{-1}; MS (ES) *m*/*z* 373.1 (M + 1), 299.0; Anal. Calcd for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52. Found: C, 71.26; H, 4.37; N, 7.33.

Acknowledgment. The authors wish to thank Drs. Kim Albizati, Victor Snieckus, and Mike Deason for their valuable suggestions and help with the manuscript and Dr. Matt Renner for the HRMS data.

Supporting Information Available: Preparation and full characterization of compounds in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016131F

(10) CHEMGLASS Catalog 2000, p 5.