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Regioselective Suzuki coupling of benzofuran or benzothiophene boronic acids and dibromo substituted naphthalenes: synthesis of a potent inhibitor of plasminogen activator inhibitor-1

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Abstract—An efficient route to the biologically active naphthyl benzofuran derivative is described. The synthesis highlights a regioselective Suzuki coupling of a benzofuran and a dibromo substituted naphthalene. The scope of regioselective Suzuki coupling has been investigated.

Plasminogen activator inhibitor-1 (PAI-1) is a major regulatory component of the plasminogen–plasmin system. PAI-1 is the principal physiologic inhibitor of both tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). Elevated plasma levels of PAI-1 have been associated with thrombotic events as indicated by animal experiments[1–3] and clinical studies.[4,5] Antibody neutralization of PAI-1 activity resulted in the promotion of endogenous thrombolysis and reperfusion.[6,7] Elevated levels of PAI-1 have also been implicated in diseases of women such as polycystic ovary syndrome[8] and bone loss induced by estrogen deficiency.[9] Accordingly, agents that inhibit PAI-1 would be of utility in treating conditions originating from fibrinolytic disorder such as deep vein thrombosis, coronary heart disease, pulmonary embolism, and polycystic ovary syndrome.

During the course of our investigation to identify novel PAI-1 inhibitors, a series of 2-aryl-3-acyl-benzofuran derivatives typified by compound **1**[10,11] (Fig. 1) were discovered. Compound **1** selectively inhibited active PAI-1 with an IC_{50} of ~5.0 μM, and a dissociation constant (K_d) of 480 nM. Furthermore, **1** exhibited oral efficacy in animal models of thrombosis and advanced to preclinical safety assessment. The initial synthesis of **1** (Scheme 1) was linear. Suzuki coupling of 2-benzofuran boronic acid **8** and naphthalene **2** gave the biaryl derivative **3** in good yield. Acylation of **3** afforded **4** that was demethylated **5** and subsequently brominated to furnish bromonaphthol **6**. Alkylation of **6** yielded nitrile **7**, which was smoothly converted to desired tetrazole **1**.

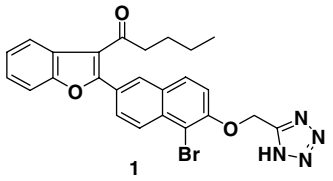

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Figure 1.

We sought to assemble **1** during scale-up synthesis through a convergent route that utilizes the commercially available and low-cost 1,6-dibromo-2-naphthol **10**. Retrosynthetically, the key intermediate **7** could be constructed from three precursors: 2-benzofuran boronic acid **8**, valeryl chloride **9**, and 1,6-dibromo-2-naphthol **10** (Fig. 2). This approach, however, required performing a regioselective Suzuki coupling of 2-benzofuran boronic acid **8** and a dibromo substituted naphthol derivative.

Regioselective palladium catalyzed cross-coupling reactions for nitrogen, oxygen, and sulfur containing heterocycles have been studied.[12] But the regioselective Suzuki coupling of dibromonaphthalene with aryl boronic acids has not been reported. Therefore, we investigated the scope of this reaction. Our convergent approach started

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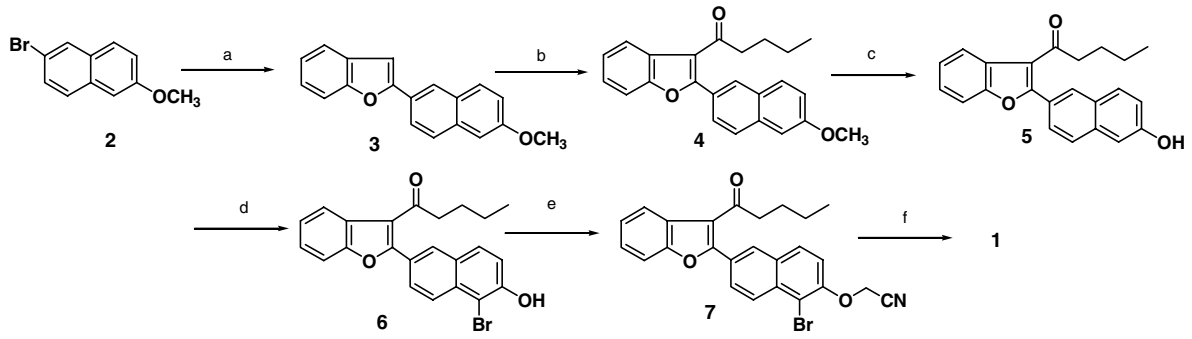


Scheme 1. Reagents and conditions: (a) 2-benzofuran boronic acid **8**, $PdCl_2(dppf)_2$, dioxane/H_2O, K_2CO_3, 81%; (b) valeryl chloride **9**, $SnCl_4$, $CHCl_3$, 59%; (c) BBr_3, CH_2Cl_2, 70%; (d) Br_2, AcOH, 82%; (e) $BrCH_2CN$, Cs_2CO_3, acetone, 95%; (f) NaN_3, DMF, 80%.

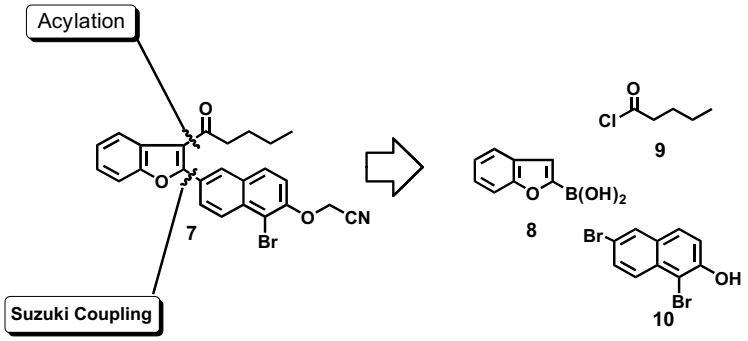
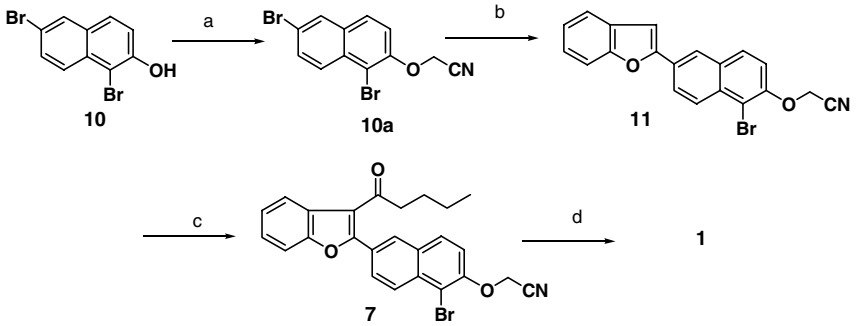


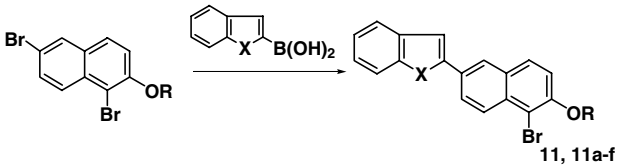
Figure 2.

by alkylating the commercially available 1,6-dibromo-2-naphthol (Scheme 2) to furnish compound **10a** in 98% yield. The key step is a regioselective Suzuki coupling of 2-benzofuran boronic acid **8** and the dibromo substituted naphthalene **10a**. Preferential Suzuki coupling with high regioselectivity at 6-position of the naphthalene is consistent with both electronic and steric factors. It is known that the regioselectivity for Suzuki cross-coupling is largely controlled by the relative rates of oxidative addition for the two carbon–bromide bonds.[13,14] The bromine at 6-position of naphthalene is less hindered than the bromine at 1-position because the latter is ortho to the alkoxy group at 2-position and peri to hydrogen at 8-position. The bromine at 6-position of naphthalene will have less electron-donating effect from the alkoxy group at 2-position;[15] therefore, it is more reactive to Suzuki coupling. As expected, the desired regioisomer **11** was obtained from coupling of **8** and **10a**. We further investigated the optimal conditions with respect to oxygen substituents, catalysts and boronic acids. The results are shown in Table 1. In all cases, the reaction product resulting from the coupling at the 1-position was never observed (Table 1, entries 1–9). Coupling of 2-benzofuran boronic acid **8** with 1,6-dibromo-2-naphthol **10** produced the desired regioisomer; however, the yield was poor (Table 1, entry 9) compared with the corresponding cyanomethoxy and ethoxy derivatives (Table 1, entries 3 and 6). The results indicated that under the basic reaction condition, the 2-naphthol anion formed significantly slows down the oxidative addition step of the coupling. Both attempts to couple 2-benzofuran boronic acid **8** with the methyl carboxyl-

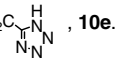


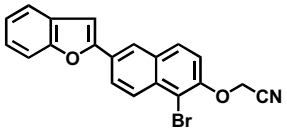
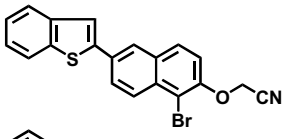
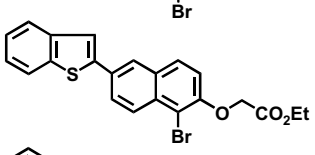
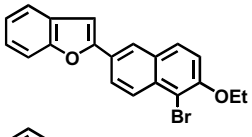
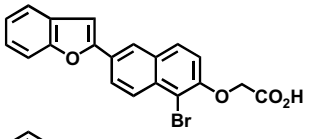
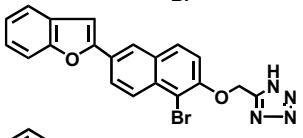
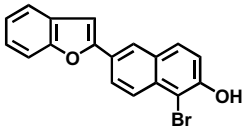
Scheme 2. Reagents and conditions: (a) $BrCH_2CN$, Cs_2CO_3, acetone, 98%; (b) 2-benzofuran boronic acid **8**, $Pd(OAc)_2$, THF/H_2O, K_2CO_3, Bu_4NBr, 90%; (c) valeryl chloride **9**, $SnCl_4$, $CHCl_3$ 60%; (d) NaN_3, DMF, 80%.

Table 1.



X = O, **8**; S, **8a**.

R = H, **10**; CH_2CN, **10a**; CH_2CO_2COEt, **10b**; CH_2CH_3, **10c**; CH_2CO_2H, **10d**;  , **10e**.

Entry	Starting material	Boronic acid	Product		Yield[a]
1	**10a**	**8**		**11**	40%[b]
2	**10a**	**8**		**11**	52%[c]
3	**10a**	**8**		**11**	90%[d]
4	**10a**	**8a**		**11a**	86%[e]
5	**10b**	**8a**		**11b**	42%[e]
6	**10c**	**8**		**11c**	80%[d]
7	**10d**	**8**		**11d**	NR[f]
8	**10e**	**8**		**11e**	NR[f]
9	**10**	**8**		**11f**	21%[d]

[a] Isolated yields based on dibromo naphthalene derivatives.

[b] 10 mol % of $Pd(PPh_3)_4$, 1.0 equiv of **10a**, 1.1 equiv of **8**, 4 equiv of Na_2CO_3 at 80 °C in 8 h in 1,2-dimethoxyethane.

[c] 10 mol % of $Pd(dppf)_2Cl_2$, 1.0 equiv of **10a**, 1.2 equiv of **8**, 4 equiv of Na_2CO_3 at 80 °C in 5 h in 1,2-dimethoxyethane.

[d] 1.5 mol % of $Pd(OAc)_2$, 1.0 equiv of dibromo naphthalene derivative (**10a–e**), 1 equiv of **8** or **8a**, 1 equiv of Bu_4NBr and 2 equiv of K_2CO_3 at room temperature in 15 h in THF/H_2O.

[e] 1.2–2.7 mol % $Pd(OAc)_2$, 1.0 equiv of dibromo naphthalene derivative (**10a** or **10b**), 1 equiv of **8** or **8a**, 1–3 equiv of Bu_4NBr and 2 equiv of K_2CO_3 at 70 °C in 3.5–7 h in THF/H_2O.

[f] No reaction was observed under either reaction condition d or e. The starting materials, **8** and **10d** or **10e**, were recovered.

ate acid and methyl tetrazole derivatives failed to give the corresponding coupling products (Table 1, entries 7 and 8). It was possible that under basic condition, either carboxylate group or the tetrazole group may form a strong complex with the catalyst and thereby suppress its activity although there are successful couplings reported using both aromatic[16,17] and aliphatic carboxylic acids.[18] Various Pd catalysts have been evaluated in order to optimize this cross-coupling. When $Pd(OAc)_2$ was used, the cross-coupling product was obtained in good yields (Table 1, entries 3, 4 and 6). Both $Pd(dppf)_2Cl_2$ and $Pd(PPh_3)$ gave moderate yields

(Table 1, entries 1 and 2). Benzothiophene-2-boronic acid also gave good yield in the optimized condition (Table 1, entry 4) although the corresponding ester gave lower yield (Table 1, entry 5); presumably part of the product could be hydrolyzed under basic condition.

Acylation of **11** proceeded smoothly and introduced the side chain of this molecule (from **11** to **7**). Finally, the formation of the tetrazole ring furnished the target molecule **1**.[19]

In conclusion, an efficient synthesis of a potent PAI-1 inhibitor **1** was developed in four steps with 42% overall yield (Scheme 2). The synthesis featured regioslective Suzuki coupling, which gave the desired product. $Pd(OAc)_2$ was found to be the best catalyst in the Suzuki coupling of 1,6-dibromo-2-methylcyano naphthalene with aryl boronic acids to give biaryl derivatives in good yield. This methodology offers a concise and convergent synthesis of compound **1**.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.090.

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15. In the ^{13}C NMR spectrum (DMSO-d_6, 400 MHz), δ of C1 is 108.80 ppm and δ of C6 is 118.45 ppm, which indicated C1 is more electron rich than C6.
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19. Experimental procedure for the preparation of **10a**: To a mixture of 1,6-dibromo-2-naphthol (**10**, 69 g, 0.228 mol) and cesium carbonate (148 g, 0.456 mol) in acetone (2.5 L), bromoacetonitrile (41 g, 0.342 mol) was added in one portion. Then, the mixture was stirred for 4 h at room temperature, then filtered through Celite to remove all inorganic salt. The filtrate was concentrated and purified by flash chromatography using 5–20% *tert*-butyl methyl ether in hexane as an eluant to afford 76 g of **10a** as light yellow solid (yield 98%). ^1H NMR (400 MHz, DMSO-d_6): δ 8.26 (s, 1H), 8.04 (d, 2H, $J = 12$ Hz), 8.03 (d, 2H, $J = 8$ Hz), 7.76 (d, 2H, $J = 8$ Hz), 7.76 (d, 2H, $J = 8$ Hz), 7.63 (d, 2H, $J = 8$ Hz), 5.38 (s, 2H). ^{13}C NMR δ 151.40, 131.30, 131.23, 130.86, 130.10, 128.80, 127.94, 118.45, 116.42, 116.27, 108.80, 55.26. Mass spectrum ESI $[M+H]^+$ *m/z* 342. Elemental Analysis for $C_{12}H_7Br_2NO$: Calculated: C, 42.27; H, 2.07; N, 4.11. Found: C, 42.42; H, 2.04; N, 4.15. Preparation of **11**: To a mixture of **10a** (682 mg, 2 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), tetrabutylammonium bromide (645 mg, 2 mmol), potassium carbonate (552 mg, 4 mmol) in tetrahydrofuran (8 mL) and water (8 mL) was added 2-benzofuran boronic acid (**8**, 323 mg, 2 mmol). Then the mixture was stirred at room temperature for 15 h. Then the mixture was filtered through Celite to remove inorganic residues. The filtrate was concentrated and purified by flash chromatography using 15–75% chloroform in hexane as eluant to afford 681 mg of **11** as yellow oil (yield 90%). ^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 8.20 (d, 1H, $J = 12$ Hz), 8.18 (s, 2H), 7.67 (m, 2H), 7.64 (d, 1H, $J = 12$ Hz), 7.56 (s, 1H), 7.32 (t, 1H, $J = 8$ Hz), 7.25 (t, 1H, $J = 8$ Hz) (m, 2H), 5.41 (s, 2H). ^{13}C NMR δ (ppm) 154.51, 154.39, 151.55, 131.97, 130.28, 130.13, 128.77, 126.51, 126.49, 125.14, 124.92, 123.70, 123.34, 121.31, 116.37, 116.00, 111.09, 108.88, 103.09, 55.26. Mass spectrum ESI $[M+H]^+$ *m/z* 378. Elemental Analysis for $C_{20}H_{12}BrNO_2$: Calculated: C, 63.51; H, 3.20; N, 3.70. Found: C, 63.30; H, 3.11; N, 3.39. Preparation of **7**: To a solution of **11** (15 g, 39.6 mmol) in dichloromethane (77 mL) at −78 °C was added valeryl chloride (4.8 mL, 39.6 mmol) slowly. Then tin(IV) chloride (4.68 mL, 39.6 mmol) was added slowly. The mixture was allowed to warm up to room temperature and then stirred at room temperature for 3.5 h. To the above solution was added saturated KH_2PO_4 (750 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and the solvent removed to afford a yellow oil. The crude product was purified by flash chromatography using toluene as eluant to afford 11 g (60%) of a light yellow solid (**7**). ^1H NMR (400 MHz, DMSO-d_6): δ 8.55 (d, 1H, $J = 0.98$ Hz), 8.25 (d, 2H, $J = 9.3$ Hz), 8.0–8.05 (m, 2H), 7.7–7.75 (m, 2H), 7.4–7.5 (m, 2H), 5.5 (s, 2H), 2.75 (t, 2H, $J = 7.2$ Hz), 1.5–1.6 (m, 2H), 1.1–1.2 (m, 2H), and 0.7 ppm (t, 3H, $J = 7.2$ Hz). ^{13}C NMR δ 197.79, 157.91, 153.44, 152.32, 132.77, 130.53, 129.99, 129.56, 128.31, 126.31, 126.20, 126.11, 125.83, 124.44, 121.93, 118.03, 116.32, 116.06, 111.45, 108.60, 55.23, 41.70, 25.98, 21.60, 13.61. Mass spectrum ESI $[M+H]^+$ *m/z* 462. Elemental Analysis for $C_{25}H_{20}BrNO_3$: Calculated: C, 64.95; H, 4.36; N, 3.03. Found: C, 64.87; H,

4.22; N, 2.91. Preparation of **1**: To a solution of **7** (5.16 g, 11.1 mmol) in *N*,*N*-dimethylformamide (55 mL), sodium azide (3.6 g, 55.5 mmol) and ammonium chloride (2.96 g, 55.5 mmol) were added. The mixture was heated to 90 °C for 4.5 h. The mixture was allowed to cool to room temperature. Then to the above solution were added saturated KH_2PO_4 (800 mL) and ethyl acetate (500 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and the solvent removed to afford a brown oil. The crude product was purified by reverse phase chromatography using 0.1% trifluoroacetic acid in 80% acetonitrile/20% water as eluant to afford 4.5 g (80%) of **1** as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 16.8–17.2 (br, s, 1H), 8.5 (d, 1H, $J = 1.7$ Hz), 8.25 (t, 2H, $J = 9.1$ Hz), 8.0–8.05 (m, 2H), 7.75–7.8 (m, 2H), 7.4–7.5 (m, 2H), 5.8 (s, 2H), 2.75 (t, 2H, $J = 7.3$ Hz), 1.5–1.6 (m, 2H), 1.1–1.2 (m, 2H), and 0.7 ppm (t, 3H, $J = 7.3$ Hz). ^{13}C NMR δ 198.47, 158.73, 154.13 (br, C5 in tetrazole), 154.13, 154.11, 133.51, 131.02, 130.62, 129.88, 128.75, 127.02, 126.64, 126.46, 126.45, 125.09, 122.58, 118.61, 117.27, 112.09, 108.91, 61.48, 42.36, 26.68, 22.27, 14.28. Mass spectrum ESI $[M+H]^+$ *m*/*z* 505. Elemental Analysis for $C_{25}H_{21}BrN_4O_3$: Calculated: C, 59.42; H, 4.19; N, 11.09. Found: C, 59.42; H, 4.04; N, 10.88.