

## SUZUKI COUPLINGS WITH PHTHALIMIDINES - AN EFFICIENT ROUTE TO STAUROSPORINONE ANALOGS

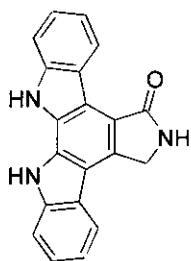
Kenneth C. Rupert, John H. Dodd, and James R. Henry\*

The R.W. Johnson Pharmaceutical Research Institute

Route 202, P.O. Box 300, Raritan, NJ 08869, U.S.A.

**Abstract-** Staurosporinone analogs have been prepared by an efficient process. The key step is a palladium mediated Suzuki coupling between a bromo-phthalimidine and an aromatic boronic acid.

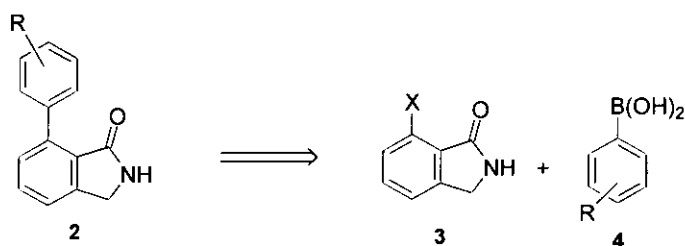
During the course of our work directed towards the identification and synthesis of protein kinase inhibitors, we became interested in staurosporinone (**1**) due to its potent inhibition of protein kinase C.<sup>1</sup>



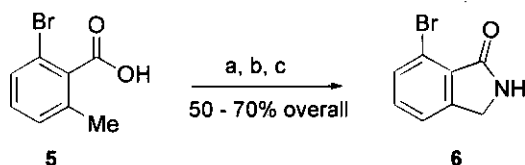
staurosporinone (**1**)

We hoped to prepare novel, potent, and selective kinase inhibitors by simplifying the structure of **1** such that we could readily prepare a variety of substituted analogs. We turned our attention to the preparation of biphenyl analog (**2**). A survey of the literature showed that while there have been several syntheses of **1** reported,<sup>2</sup> no general method existed for the preparation of analogs like lactam (**2**). We chose to pursue a route involving a Suzuki coupling between an aromatic boronic acid (**4**), and a phthalimidine derivative (**3**) (Scheme 1).

Scheme 1

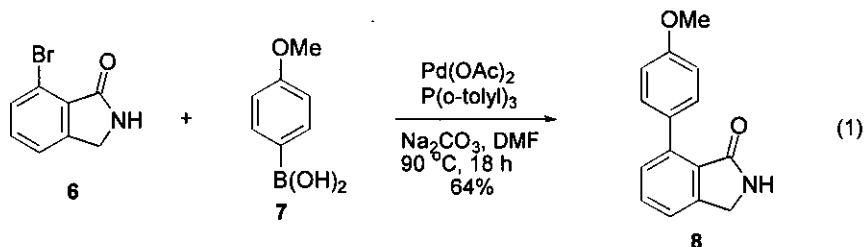


The synthesis of the required lactam (**6**) is simple and high yielding. The bromo acid (**5**)<sup>3</sup> is converted to the methyl ester by sequential treatment with thionyl chloride, followed by methanol. Bromination with NBS in refluxing benzene followed by condensation with ammonium hydroxide gives the desired lactam (**6**) in 50 - 70% overall yield for the 3 step process (Scheme 2).<sup>4</sup> This method is especially attractive since the intermediates do not need to be purified, and unlike the reduction of phthalimide derivatives, the regiochemistry is unambiguous.

Scheme 2<sup>a</sup>

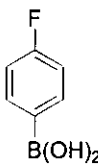
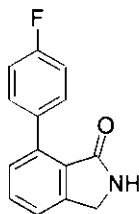
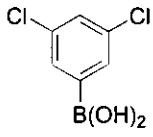
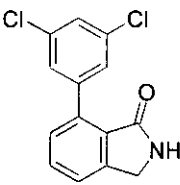
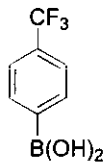
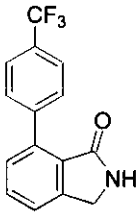
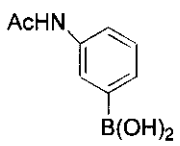
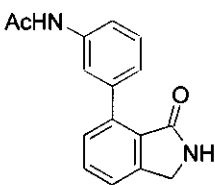
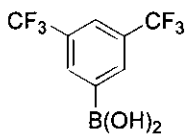
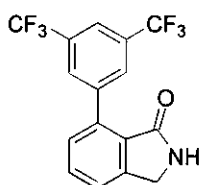
<sup>a</sup>(a) 1. SOCl<sub>2</sub>, 60 °C, 1 h. 2. MeOH, Et<sub>3</sub>N, 0 °C, 1 h (b) NBS, AIBN, PhH, reflux, 18 h. (c) THF, NH<sub>4</sub>OH, rt, 18 h.

The critical coupling reactions were originally run using a typical Suzuki procedure with toluene as solvent, but yields were poor due to low conversion of **6**.<sup>5</sup> Changing the solvent to DMF dramatically improved the yield of the process. In our hands, a catalytic mixture of Pd(OAc)<sub>2</sub> and P(*o*-tolyl)<sub>3</sub> gave higher yields than did Pd(PPh<sub>3</sub>)<sub>4</sub> or Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub>. Thus, bromophthalimidine (**6**) was coupled with boronic acid (**7**) to give the biphenyl phthalimidine (**8**) in good yield as a crystalline solid (eq. 1).

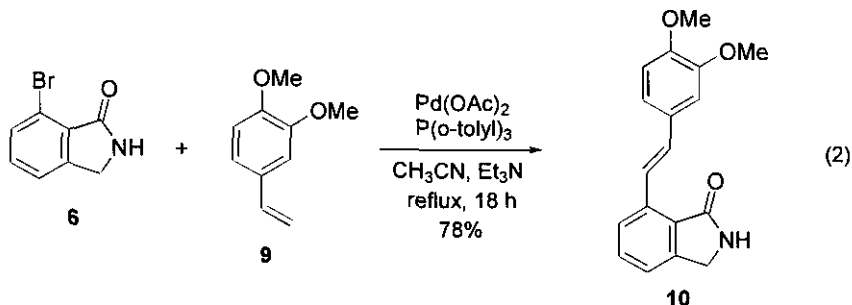


We have tested this procedure on a number of boronic acids listed in Table 1. In general, good yields of coupled products were obtained.

Table 1

entry	boronic acid	product	yield (%)
1			77
2			67
3			65
4			41
5			61

Lactam (6) has also been shown to participate in a Heck type coupling with styrene (9) to give *trans*-stilbene derivative (10), again in good yield (eq. 2).



We have therefore demonstrated that simplified staurosporinone analogs can be rapidly assembled via a simple and high yielding process characterized by a palladium mediated Suzuki or Heck coupling.

**Typical Experimental Procedure.** Lactam (**6**) (0.10 g, 0.47 mmol), Pd(OAc)<sub>2</sub> (0.015 g, 0.067 mmol), P(o-tolyl)<sub>3</sub> (0.040 g, 0.13 mmol), boronic acid **7** (0.078 g, 0.52 mmol), and 0.5 mL of a 2M Na<sub>2</sub>CO<sub>3</sub> solution in water were added to 5 mL of DMF and the mixture was heated at 90 °C for 18 h. The mixture was cooled, diluted with 50 mL of water and extracted with 2 x 40 mL of ethyl acetate. The organics were washed with brine, dried with MgSO<sub>4</sub> and concentrated to give a solid residue. This residue was rinsed with 50 mL of ether to give 70 mg (64%) of pure biphenyl lactam (**8**). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.47 (1H, br s), 7.59 (1H, t, J=8.5 Hz), 7.48 (1H, d, J=8.5 Hz), 7.43 (2H, d, J=7.7 Hz), 7.31 (1H, d, J=8.5 Hz), 6.92 (2H, d, J=7.7 Hz), 4.35 (2H, s), 3.80 (3H, s). CI MS *m/z* (relative intensity) (M<sup>+</sup>+1) 240 (100).

#### Data for products in Table 1:

Entry 1: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.53 (1H, br s), 7.61-7.42 (4H, m), 7.33 (1H, d, J=8.5 Hz), 7.23 (2H, t, J=8.7 Hz), 4.36 (2H, s). CI MS *m/z* (relative intensity) (M<sup>+</sup>+1) 228(100).

Entry 2: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.61 (1H, br s), 7.68-7.55 (3H, m), 7.50 (2H, s), 7.39 (1H, d, 8.6 Hz), 4.40 (2H, s). CI MS *m/z* (relative intensity) (M<sup>+</sup>+1) 280(70), 278(100).

Entry 3: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.62 (1H, br s), 7.70-7.61 (4H, m), 7.39 (1H, d, J=7.0 Hz), 4.39 (2H, s). GC MS *m/z* (relative intensity) 277(100), 249(80).

Entry 4: (60/40 mixture of diastereomers) <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.05 (0.4H, s), 9.95 (0.6H, s), 8.50 (0.6H, s), 7.87 (0.4H, s), 7.62-7.53 (4H, m), 7.37-7.26 (2H, m), 7.11 (1H, d, J=7.7 Hz), 4.37 (2H, s), 2.04 (3H, s). CI MS *m/z* (relative intensity) (M<sup>+</sup>+1) 267 (100).

Entry 5: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.63 (1H, br s), 8.17 (2H, s), 8.11 (1H, s), 7.68-7.60 (2H, m), 7.51 (1H, d, J=7.7 Hz) 4.42 (2H, s). CI MS *m/z* (relative intensity) (M<sup>+</sup>+1) 346 (100).

#### REFERENCES

1. See: P.A. Horton, R.E. Longley, O.J. McConnell, and L.M. Balls, *Experientia*, **1994**, *50*, 843 and

references therein.

2. For more recent examples see: G. Xie, and J.W. Lown, *Tetrahedron Lett.*, **1994**, *35*, 5555; W. Harris, C.H. Hill, E. Keech, and P. Malsher, *Tetrahedron Lett.*, **1993**, *34*, 8361; C.J. Moody, K.F. Rahimtoola, B. Porter, and B.C. Ross, *J. Org. Chem.*, **1992**, *57*, 2105.
3. G.J.Thomas, *J. Agric. Food. Chem.*, **1984**, *32*, 747.
4. Compound **6**:  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.71 (1H, br s), 7.62 (1H, d,  $J=8.4$  Hz), 7.59 (1H, d,  $J=8.4$  Hz), 7.49 (1H, t,  $J=8.4$  Hz), 4.35 (2H, s).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  169.8, 149.2, 134.7, 134.1, 131.5, 125.2, 119.5, 45.5.
5. A. Suzuki, *Pure Appl. Chem.*, **1985**, *57*, 1749.

Received, 4th August, 1997