SUZUKI COUPLINGS WITH PHTHALIMIDINES - AN EFFICIENT ROUTE TO STAUROSPORINONE ANALOGS

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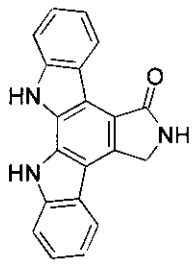
Absract- Staurosporinone analogs have been prepared by an efficient process. The key step is a palladium mediated Suzuki coupling between a bromo-phthalimidine and an aromatic boronic acid.

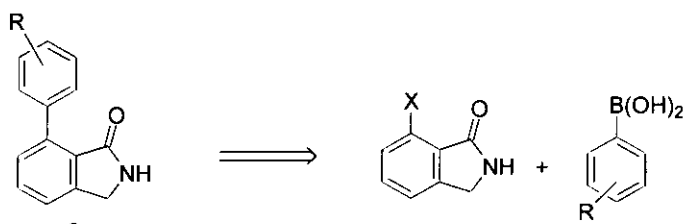
During the course of our work directed towards the identification and synthesis of protein kinase inhibitors, we became interested in staurosporinone (**1**) due to its potent inhibition of protein kinase C.[1]



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,[2] 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).

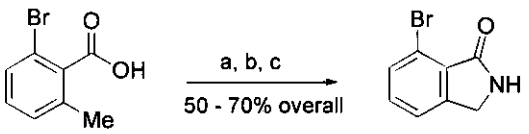
Scheme 1



2 **3** **4**

The synthesis of the required lactam (**6**) is simple and high yielding. The bromo acid (**5**)[3] 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).[4] 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.

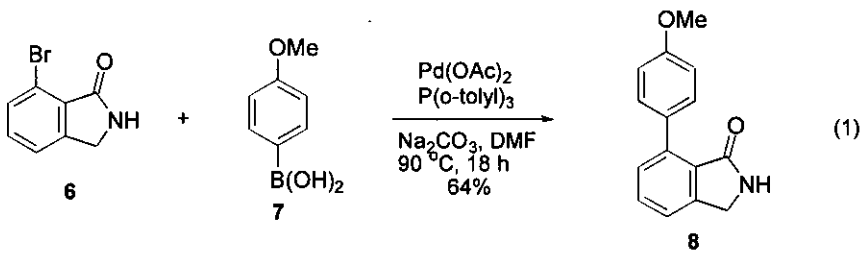
Scheme 2[a]



5 **6**

[a](a) 1. $SOCl_2$, 60 °C, 1 h. 2. MeOH, Et_3N, 0 °C, 1 h (b) NBS, AIBN, PhH, reflux, 18 h. (c) THF, NH_4OH, rt, 18 h.

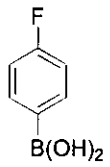
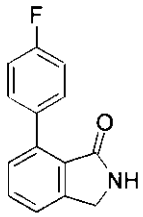
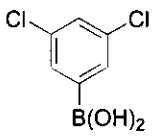
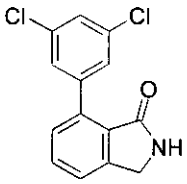
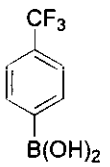
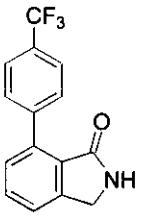
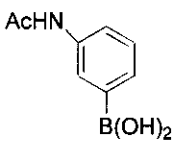
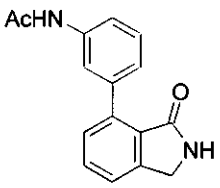
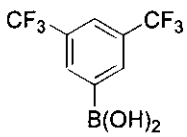
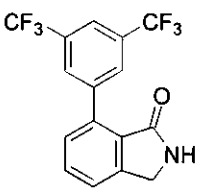
The critical coupling reactions were originally run using a typical Suzuki procedure with toluene as solvent, but yields were poor due to low conversion of **6**.[5] Changing the solvent to DMF dramatically improved the yield of the process. In our hands, a catalytic mixture of $Pd(OAc)_2$ and P(o-tolyl)$_3$ gave higher yields than did $Pd(PPh_3)_4$ or $Pd(CH_3CN)_2Cl_2$. Thus, bromophthalimidine (**6**) was coupled with boronic acid (**7**) to give the biphenyl phthalimidine (**8**) in good yield as a crystalline solid (eq. 1).



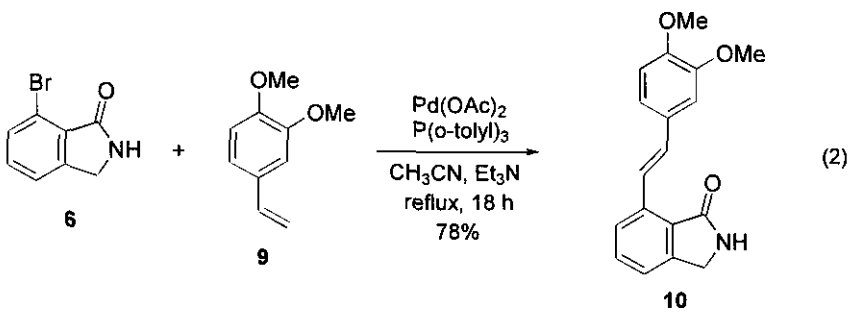
6 **7** **8** (1)

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).



(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), $Pd(OAc)_2$ (0.015 g, 0.067 mmol), P(o-tolyl)$_3$ (0.040 g, 0.13 mmol), boronic acid **7** (0.078 g, 0.52 mmol), and 0.5 mL of a 2M Na_2CO_3 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 $MgSO_4$ 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**). ^{1}H NMR (300 MHz, DMSO-d_6) 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^++1) 240 (100).

Data for products in Table 1:

Entry **1**: ^{1}H NMR (300 MHz, DMSO-d_6) 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^++1) 228(100).

Entry **2**: ^{1}H NMR (300 MHz, DMSO-d_6) 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^++1) 280(70), 278(100).

Entry **3**: ^{1}H NMR (300 MHz, DMSO-d_6) 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) ^{1}H NMR (300 MHz, DMSO-d_6) 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^++1) 267 (100).

Entry **5**: ^{1}H NMR (300 MHz, DMSO-d_6) 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^++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}H NMR (300 MHz, DMSO-d_6) δ 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}C NMR (75 MHz, DMSO-d_6) δ 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