HETEROCYCLES, Vol. 81, No. 1, 2010, pp. 73 - 77. © The Japan Institute of Heterocyclic Chemistry
Received, 20th October, 2009, Accepted, 12th November, 2009, Published online, 12th November, 2009
DOI: 10.3987/COM-09-11857

AN IMPROVED SYNTHESIS OF ARYLBORONATES TOWARD TWENTY NOVEL 1,3-DISUBSTITUTED 4-AMINO-1*H*-PYRAZOLO[3,4-*d*]PYRIMIDINE ANALOGS

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Abstract – By developing an improved procedure for arylboronates, twenty 1*H*-pyrazolo[3,4-*d*]pyrimidine analogs were efficiently synthesized as a source of a potent kinase inhibitor.

Protein kinases are among the most important classes of enzymes that phosphorylate some 10000 cellular protein hydroxy groups, and account for at least 518 genes (2%) of human genes. Reversible protein phosphorylation, by protein kinases in association with protein phosphatases, is a ubiquitous signaling mechanism in eukaryotes, and changes in the phosphorylation states are associated with metabolism, transcription, cell cycle progression, and cytoskeletal rearrangement. Because it is also related to many diseases including cancer, selective inhibitor for each protein kinase is of significant value not only for biological research, but also for cancer therapy.[1]

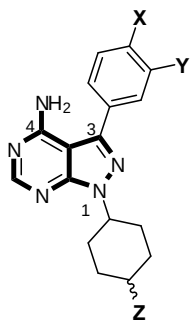
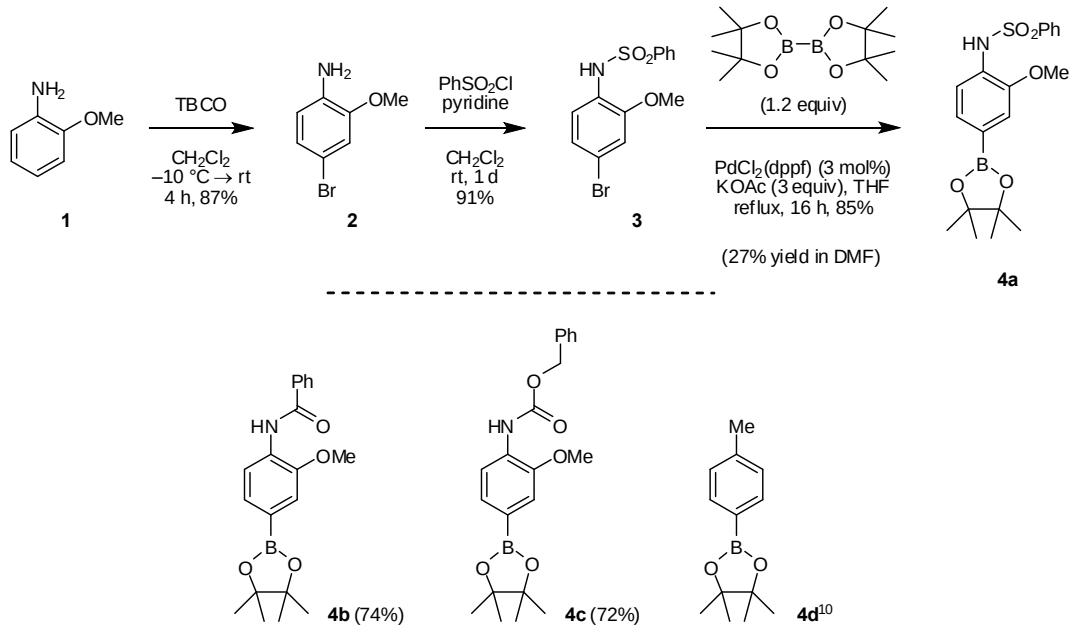


Figure 1. PPs with substituents at C1 and C3. Bold lines denote the PP core. For **X**, **Y**, and **Z**, see Table 1.

Pyrimidine-containing compounds have been studied as a source of a potent inhibitor for a wide range of protein kinases through interaction with the ATP-binding site.[2] In the course of our studies on Src family kinases, we have explored a rapid and diverted access toward 1*H*-pyrazolo[3,4-*d*]pyrimidines (PPs, Figure 1). Here, we report our preliminary results toward twenty PPs bearing substituents at C1 and C3, by developing a modified procedure for arylboronates as a synthetic building block for C3-substituent.[3]

The synthesis outline for PPs is as follows. The PP core skeleton with substituent at C1 (see Figure 1) was expected to be readily prepared by a well established, single-step procedure.[4,5] A sequence of iodination at C3 followed by Suzuki–Miyaura cross-coupling reaction[6] with arylboronate is then applied to introduce aryl substituent at the C3 position.

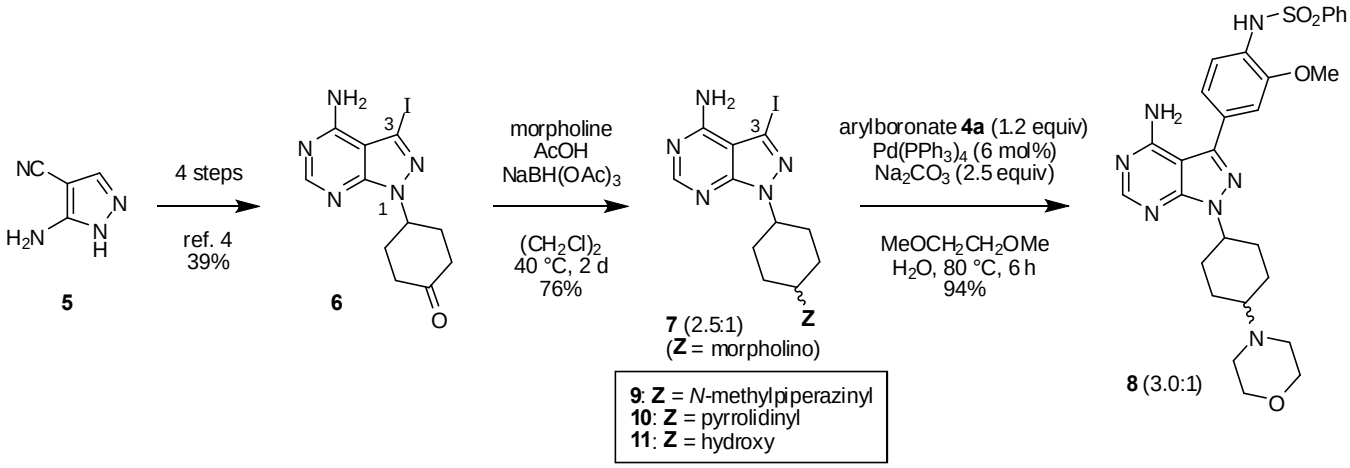
First, preparation of arylboronate **4a** was attempted. According to a reported procedure,[5] *o*-anisidine **1** was brominated with 2,4,4,6-tetrabromo-2,5-cyclohexanedienone (TBCO) to give rise to **2** followed by *N*-sulfonylation ($PhSO_2Cl$, pyridine) to furnish bromide **3** in 79% yield over two steps (Scheme 1). Yield for the subsequent borylation of bromide **3** under standard conditions (bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, DMF, 80 °C, 2 days) was, however, found to be disappointingly low (27%). Careful analysis of the reaction mixture revealed that the major product was a dimer (35%, structure not shown), which indicated that 70% of bromide **3** was consumed by the undesired dimerization process. In fact, it has been reported that, under some conditions with palladium catalyst and inorganic base, homo-coupling of aryl bromide readily takes place to furnish symmetrical biaryl.[7] Miyaura et al. have also reported that stronger bases such as K_2PO_4 promote biaryl formation.[8] Therefore, we then explored mild reaction conditions, and after several attempts with different reaction conditions, it was fortunately found that the undesired side reaction could be largely suppressed simply by changing the solvent to THF. Thus, when



Scheme 1

the reaction was conducted in THF under reflux for 16 h, desired borylation product **4a** was obtained in 85% yield as a sole product. In this case, no dimer was detected. The procedure was also effective for improved preparation of arylboronates **4b** (74%) and **4c** (72%), for which DMF was again inefficient as a solvent in terms of the yields (<30%).[9]

On the other hand, the PP core skeleton was constructed starting from 3-aminopyrazole-4-carbonitrile (**5**) according to a reported procedure[4,5] including pyrimidine formation, iodination, and *N*-alkylation, giving rise to ketone **6** in 39% yield (Scheme 2). Reductive amination of ketone **6** with morpholine (AcOH, $NaBH(OAc)_3$, 40 °C) provided amine **7** in 76% yield as a diastereomeric mixture (*dr* = 2.5:1). Finally, Suzuki–Miyaura cross-coupling reaction of arylboronate **4a** and pyrimidinyl iodide **7** was successfully effected using $Pd(PPh_3)_4$ and Na_2CO_3 at 80 °C to furnish desired PP analog **8** in 94% yield. The diastereomeric ratio was determined from ^{1}H NMR spectrum to be 3.0:1. From **6**, three other pyrimidinyl iodides **9**-**11**, analogous to **7**, were also synthesized.[11]



Scheme 2

With four arylboronates **4a**–**4d** (Scheme 1) and five pyrimidinyl iodides **6**, **7**, and **9**–**11** (Scheme 2), mostly unprecedented twenty PP analogs were readily prepared in a parallel fashion combinatorially as shown in Table 1 (46–98% yield over one or two steps from ketone **6**). All PP analogs were obtained as an inseparable diastereomeric mixture with a ratio of 2.4:1 – 10:1, which was characterized by LC-ESI-MS and ^{1}H/^{13}C NMR spectra. The successful synthesis of PP analogs in the present study was apparently owing to the synthetic improvement of arylboronates which eliminates formation of undesired dimer. Efforts are currently underway to synthesize up to hundreds of PP analogs, as well as to screen the members for kinase inhibitors with high specificity.[12] The results will be reported in due course.

Table 1. Synthesis of twenty PPs **8**, **12**–**30** by one- or two-step transformation from **6**. For representative structure, see Figure 1.

PPs	X	Y	Z	Yield from 6 / %	*dr* [a]
8[b]	-NHSO$_2$Ph	-OMe	morphorino	71[d]	3.0 : 1
12	-NHBz	-OMe	morphorino	75[d]	2.8 : 1
13	-NHCbz	-OMe	morphorino	51[d]	3.0 : 1
14	-Me	-H	morphorino	60[d]	2.4 : 1
15	-NHSO$_2$Ph	-OMe	pyrrolidinyl	59[d]	10 : 1
16	-NHBz	-OMe	pyrrolidinyl	46[d]	–[f]
17	-NHCbz	-OMe	pyrrolidinyl	55[d]	–[f]
18	-Me	-H	pyrrolidinyl	58[d]	3.0 : 1
19[c]	-NHSO$_2$Ph	-OMe	*N*-methylpiperazinyl	49[d]	5.1 : 1
20[c]	-NHBz	-OMe	*N*-methylpiperazinyl	51[d]	5.2 : 1
21[c]	-NHCbz	-OMe	*N*-methylpiperazinyl	84[d]	3.0 : 1
22	-Me	-H	*N*-methylpiperazinyl	58[d]	10 : 1
23	-NHSO$_2$Ph	-OMe	=O	67[e]	NA[g]
24	-NHBz	-OMe	=O	96[e]	NA[g]
25	-NHCbz	-OMe	=O	98[e]	NA[g]
26	-Me	-H	=O	84[e]	NA[g]
27	-NHSO$_2$Ph	-OMe	-OH	78[d]	4.5 : 1
28	-NHBz	-OMe	-OH	93[d]	4.6 : 1
29	-NHCbz	-OMe	-OH	67[d]	4.0 : 1
30	-Me	-H	-OH	62[d]	5.5 : 1

[a]*dr*: diastereomeric ratio. In all cases, the diastereomers were not separated for characterization. [b]See Scheme 2. [c]Known compound.[4] [d]Two-steps yield from **6**. [e]Yields for one-step, Suzuki–Miyaura reaction on **6**. [f]Could not be determined from MS and NMR analyses. [g]NA: Not applicable.

ACKNOWLEDGEMENTS

The author is grateful to Professors K. Mizuno, K. Ohashi, and M. Sasaki (Tohoku University) for valuable discussions. The author also thanks Ms. M. Adachi and Mr. R. Hashimoto (Tohoku University) for preliminary experiments on this study.

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9. In reference 5, the yield for borylation toward the synthesis of **4c** was reported to be 47% yield.
10. Arylboronate **4d** was purchased from Wako Pure Chemical Industries, Ltd.
11. Pyrimidyl iodides **9** and **10** were prepared by reductive amination of ketone **6** following the procedure shown in Scheme 2 in 75% and 69% yield, respectively. Compound **11** was synthesized by reduction of ketone **6** by $NaBH_4$ (94% yield).
12. Our preliminary biological evaluation has already identified **29** as a selective inhibitor for some Src family tyrosine kinases.