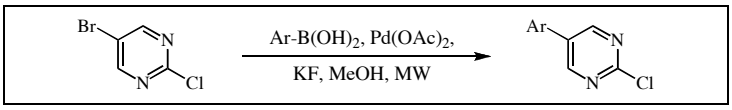
Simple Microwave-assisted Ligand-free Suzuki Cross-coupling: Functionalization of Halo-pyrimidine Moieties

Matteo Colombo,* Marco Giglio [1] and Ilaria Peretto

NiKem Research, via Zambeletti 25, 20021 Baranzate, Milan, Italy

Received July 16, 2007



An advantageous ligand-free protocol for Suzuki couplings is described. The synthetic procedure entails microwave irradiation for the reduction of the reaction times and the use of silica cartridges for the purification. Dihalo-pyrimidine structures, interesting scaffolds in medicinal chemistry, were chosen as test compounds.

J. Heterocyclic Chem., **45**, 1077 (2008).

INTRODUCTION

Suzuki coupling is one of the most widespread and frequently used organic reactions for the formation of new C-C bonds, not only between (hetero)aryls, but also between alkyl and alkenyl groups [2]. The wide success of this coupling is due to some important benefits: the reactants are easily available (often commercially), the organometallic species are non-toxic, air- and water-stable and mild synthetic conditions are required.

Although this reaction was introduced 30 years ago, an incessant series of modifications and improvements have been introduced during these years. Tetrakis-(triphenyl-phosphine)palladium(0) as catalyst, potassium carbonate as base in refluxing benzene are the classical, historical conditions for the coupling of arylboronic acids and bromo- or iodo-arenes. Subsequent studies have been focused on the modifications of palladium(0) source, ligands, bases and solvents, with the main aim of increasing the versatility of this cross-coupling reaction.

In order to develop a reliable synthetic protocol for the Suzuki coupling of simple aryl and heteroaryl structures, we focused our efforts on the choice of reactants and conditions that could be easily applied to different substrates and that could simplify the coupling step, the work-up and purification phase. Specifically, we aimed at the elimination of air-sensitive phosphine ligands (with the advantage of avoiding the use of inert atmosphere and deoxygenated solvents) and at the reduction of reaction times, employing microwave (MW) irradiation.

RESULTS AND DISCUSSION

The use of pyrimidine structures in medicinal chemistry, as scaffold or decoration, is well appreciated since many biologically active compounds contain this heterocyclic ring. Recently, we prepared a collection of pyrimidine derivatives as potential inhibitors of matrix-degrading enzymes. In order to study this heterocyclic ring as synthetic scaffold, halo-pyrimidine structures were chosen as useful, versatile and easily functionalizable building blocks. In particular, compound **1** (5-bromo-2-chloro-pyrimidine, obtained from the corresponding 2-hydroxy-derivative by reaction with $POCl_3$) [3] was selected as test structure. The presence of two different halogen atoms could permit the introduction of two different functional moieties by subsequent reactions. The bromine atom in position 5 will react as an electrophile center in the Suzuki cross-coupling reaction, whereas the chlorine atom in position 2 could be easily replaced by opportune nucleophiles.

Scheme 1

Synthesis of compound **1** and Suzuki couplings.
Reagents and conditions: i. $POCl_3$, 80°C, 88%; ii. $PhB(OH)_2$, Pd-catalyst, base, solvent, heat (see Table 1); iii. $ArB(OH)_2$, $Pd(OAc)_2$, KF, MeOH, MW, 120°C.

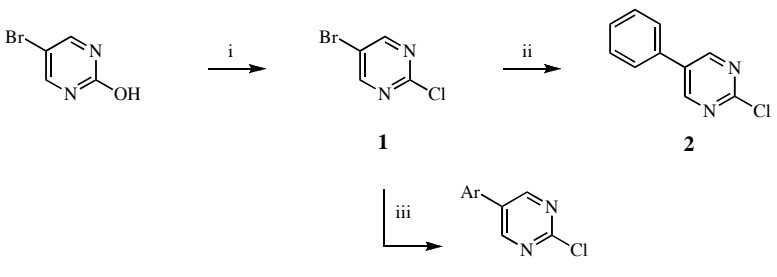


Table 1

Suzuki couplings of **1** and phenylboronic acid. Synthesis of compound **2**

Entry	Catalyst	Base	Conditions	Temp. (°C)	Time	Yield [a]
1	$Pd(OAc)_2$	KF	MeOH, MW	80	20 min	85%
2	$Pd(OAc)_2$	KF	MeOH, MW	100	20 min	86%
3	$Pd(OAc)_2$	KF	MeOH, MW	120	5 min	85%
4	$Pd(OAc)_2$	KF	MeOH, MW	120	20 min	92%
5	$Pd(OAc)_2$	Na_2CO_3	TBAB, H_2O, MW	120	20 min	69%
6	$Pd(PPh_3)_4$	Na_2CO_3	DME	80	16 h	53% [b]
7	$Pd(dppf)Cl_2$	Cs_2CO_3	CH_3CN, MW	120	60 min	72%

[a] Isolated yield after silica cartridge. [b] After chromatographic column.

In the first attempt, Suzuki reactions were performed using methanol as solvent and, taking advantage of the high affinity between fluoride ion and boron atoms, potassium fluoride as base [4]. As far as the palladium source is concerned, we chose palladium(II) acetate as pre-catalyst [5], which is promptly reduced to active palladium(0) in the reaction mixture.

The efficiency of the synthetic protocol was evaluated using phenylboronic acid as organometallic species and heating the reaction mixture in a sealed vessel using MW irradiation (Scheme 1). Following the aforementioned conditions, complete conversions and good isolated yields were obtained already at 80°C (Table 1), even though the best isolated yield was reached after 20 min at 120°C (entry 4). The expected cross-coupling product **2** was easily purified by simple silica cartridge. The silica bed retained the inorganic impurities, whereas the homo-coupling by-product was eliminated by elution with an apolar eluent. The product was then quickly recovered with a more polar eluent mixture.

The tested protocol displayed a significant improvement in isolated yields, in reaction times and in work-up procedures when compared to other commonly applied synthetic methodologies of Suzuki coupling (entry 5-7). The reaction performed using the classical Suzuki protocol ($Pd(PPh_3)_4$, Na_2CO_3) deserves an additional comment: the reaction conversion was complete (LC-MS analysis), but the recovery of the product was problematic, because of the presence of triphenylphosphine oxide as by-product (entry 6). After a

Table 2

Suzuki couplings of **1** and commercially available aryl- and heteroaryl boronic acids

Entry	Ar	Product	Yield [a]	^{1}H-NMR [b]	ESI$^+$MS [c]
1	phenyl	**2**	92%	Analytical data reported in [8]	
2	2-CH_3-phenyl	**3**	79%	8.84 (s, 2H); 7.32-7.41 (m, 4H), 2.28 (s, 3H), (DMSO-d6)	205.1
3	3-CH_3-phenyl	**4**	88%	8.82 (s, 2H), 7.29-7.45 (m, 4H), 2.46 (s, 3H)	205.1
4	4-CH_3-phenyl	**5**	91%	8.81 (s, 2H), 7.43-7.49 (m, 2H), 7.31-7.37 (m, 2H), 2.44 (s, 3H)	205.1
5	4-OH-phenyl	**6**	87%	8.75 (s, 2H), 7.39 (m, 2H), 6.99 (m, 2H), 2.91 (bs, 1H)	207.1
6	4-OCH_3-phenyl	**7**	88%	8.79 (s, 2H), 7.50 (m, 2H), 7.05 (m, 2H), 3.88 (s, 3H)	221.1
7	3-F-4-CH_3-phenyl	**8**	66%	8.80 (s, 2H), 7.31-7.38 (m, 1H), 7.20-7.26 (m, 2H), 2.36 (d, J = 1.5 Hz, 3H)	223.0
8	4-$N(CH_3)_2$-phenyl	**9**	<10%	8.78 (s, 2H), 7.46 (m, 2H), 6.82 (m, 2H), 3.04 (s, 6H)	234.1
9	3-NO_2-phenyl	**10**	28%	8.90 (s, 2H), 8.44-8.47 (m, 1H), 8.37 (ddd, J = 7.7 Hz, J = 2.1 Hz, J = 1.2 Hz, 1H), 7.91 (ddd, J = 7.7 Hz, J = 2.1Hz, J = 1.2 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H)	236.0
10	4-Cl-phenyl	**11**	77%	8.81 (s, 2H), 7.48-7.54 (m, 4H)	225.0
11	3-CN-phenyl	**12**	58%	8.84 (s, 2H), 7.88-7.79 (m, 2H), 7.74-7.65 (m, 2H)	216.1
12	4-COOH-phenyl	**13**	85%	12.54 (bs, 1H), 9.02 (s, 2H), 8.05 (m, 2H), 7.87 (m, 2H)	235.1
13	2-F-phenyl	**14**	65%	8.83 (d, J = 1.2 Hz, 2H), 7.42-7.52 (m, 2H), 7.28-7.36 (m, 1H), 7.24-7.26 (m, 1H)	209.1
14	4-F-phenyl	**15**	76%	8.81 (s, 2H), 7.55 (m, 2H), 7.25 (m, 2H)	209.1
15	4-SO_2Et-phenyl	**16**	71%	8.88 (s, 2H), 8.09 (m, 2H), 7.77 (m, 2H), 3.18 (q, J = 7.4 Hz, 2H), 1.34 (t, J = 7.4 Hz, 3H)	283.0
16	4-CHO-phenyl	**17**	77%	10.10 (s, 1H), 9.22 (s, 2H), 8.07 (m, 4H), (DMSO-d6)	219.2
17	6-OCH_3-pyridyl	**18**	81%	8.79 (s, 2H), 8.39 (d, J = 2.6 Hz, 1H), 7.76 (dd, J = 8.6 Hz, J = 2.6 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 4.01 (s, 3H)	222.1
18	3-thienyl	**19**	75%	8.84 (s, 2H), 7.61 (dd, J = 2.9 Hz, J = 1.2 Hz, 1H), 7.53 (dd, J = 5.0 Hz, J = 2.9 Hz, 1H), 7.38 (dd, J = 5.0 Hz, J = 1.2 Hz, 1H)	197.0

[a] Isolated yield after silica cartridge. [b] 300 MHz; $CDCl_3$, otherwise indicated. [c] MH^+ molecular ion.

long and tedious chromatographic purification, the pure product was obtained in lower isolated yield compared to the other protocols.

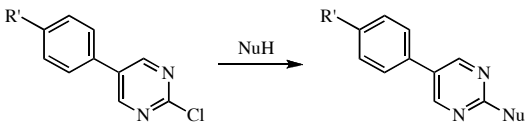
The set up synthetic method was then applied to the Suzuki coupling of **1** and a series of commercially available functionalized aryl and heteroaryl boronic acids, obtaining the intermediate compounds **3-19** (Scheme 1 and Table 2).

The isolated yields of the expected cross-coupling products were good, both with electron releasing and electron withdrawing substituents on the phenyl ring. Interesting results were also obtained with heteroaryl boronic acids (entry 17 and 18).

The couplings with 4-(dimethylamino)phenyl boronic acid and 3-nitrophenyl boronic acid afforded low yields, due to the presence of a series of unknown by-products (entry 8 and 9). In the two latter cases, better results were obtained using the classical Suzuki protocol ($Pd(PPh_3)_4$, Na_2CO_3, DME, 80°C), with isolated yields of 62% and 73%, respectively.

Scheme 2

Replacement of chlorine atom in position 2 by nucleophiles.



2,5 **20-27**

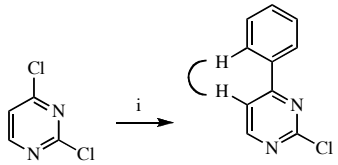
R' = H, Me
Nu = NR_2, OR, SR

All the performed Suzuki coupling reactions were, as expected, completely selective towards the substitution of the bromine atom. In this way, the obtained pyrimidine products were characterized by a 5-(hetero)aryl moiety and a chlorine atom in position 2. These intermediate compounds are expected to be good substrates for the aromatic nucleophilic substitution. With the aim of demonstrating the ease of replacement of the chlorine atom, amines, alcohols and thiols were used as examples of nucleophilic species (Scheme 2). Also in this case, as reported in Table 3, the reaction times of the tested conditions were shortened by the application of MW heating, maintaining high yields.

In order to evaluate a broader applicability of the proposed modified Suzuki protocol, 2,4-dichloro pyrimidine was considered an interesting scaffold, to verify the effect of varying the nature and the position of halogen atom (Scheme 3). The regioselectivity of the applied synthetic protocol followed the reported reactivity order, *i.e.* position 4 > position 6 > position 2 for di- or trichloropyrimidine towards Suzuki coupling [6,7]. The structure of compound **28** was confirmed by the n.O.e. contact between the hydrogen atom in position 5 of pyrimidine ring and the *ortho*-hydrogen atoms of phenyl ring (Scheme 3).

Scheme 3

Suzuki coupling of 2,4-dichloro pyrimidine and phenylboronic acid. The position of phenyl group was confirmed by n.O.e. contact. Reagents and conditions: i. $PhB(OH)_2$, $Pd(OAc)_2$, KF, MeOH, MW, 120°C, 60%.



28

Unfortunately, the good yields obtained with the bromo-derivative were not confirmed. Even though the starting material was completely converted after 20 min, the isolated yield of the expected mono-phenyl substituted chloro-pyrimidine **28** was only 60%, because of the presence of by-products, mainly 2,4-diphenylpyrimidine and the dihydroxylated analogue.

In conclusion, we have described an improved simple protocol for the Suzuki cross-coupling. This method entails three main advantages: the absence of phosphine ligands (inert conditions are not necessary), the use of MW heating (with reduced reaction times) and the simple

Table 3

Nucleophilic replacements

Entry	R'	NuH	Conditions	Product	Isolated yield
1	H	morpholine	rt, 16 h	**20**	95%
2	H	morpholine	THF, MW, 100°C, 10 min	**20**	93%
3	CH_3	morpholine	rt, 16 h	**21**	87%
4	CH_3	morpholine	THF, MW, 100°C, 10 min	**21**	81%
5	H	isopropylamine	rt, 16 h	**22**	92%
6	CH_3	isopropylamine	THF, MW, 100°C, 6 h	**23**	94%
7	H	aniline	THF, MW, 130°C, 6 h	**24**	78%
8	CH_3	MeOH	Na, MW, 100°C, 10 min	**25**	98%
9	CH_3	iPrOH	Na, MW, 100°C, 10 min	**26**	96%
10	CH_3	Ethanethiol	Na, THF, MW, 100°C, 20 min	**27**	93%

work-up and purification procedures based on silica cartridge.

The synthetic method was applied to the functionalization of dihalo-pyrimidine structures, but good unpublished results were also obtained with bromo- and iododerivatives of aryl derivatives and indole derivatives.

EXPERIMENTAL

All the MW-assisted reactions were performed in sealed tube with an Emrys Optimizer – Biotage MW oven. 1H spectra were recorded in $CDCl_3$ or DMSO-d_6 solution as indicated, using a Bruker Avance II – 300 MHz instrument. The MS-spectra were recorder using a micromass ZQ Waters spectrometer, ionization method: positive ESI. Abbreviations: DME: 1,2-dimethoxy-ethane, TBAB: tetrabutyl ammonium bromide, $Pd(dppf)Cl_2$: 1,1'-bis(diphenylphosphino)ferrocene dichloro palladium(II).

General procedure A: Suzuki coupling. A mixture of **1** (0.3 mmol), arylboronic acid (0.36 mmol), KF (0.6 mmol) and $Pd(OAc)_2$ (5% mol) in MeOH (1.5 mL) was heated in a sealed tube at 120°C for 20 min by MW irradiation. The solvent was evaporated and the crude was purified by silica cartridge (petroleum ether/EtOAc).

General procedure B: Suzuki coupling. To a solution of **1** (0.3 mmol) and $Pd(PPh_3)_4$ (5% mol) in DME (3 mL), arylboronic acid (0.36 mmol) and Na_2CO_3 (2 *M* aqueous solution, 0.6 mmol) were added. The mixture was refluxed for 16h and then the solvent was evaporated. The solvent was evaporated and the crude was purified by flash chromatography (petroleum ether/EtOAc).

Yields, ^{1}H-NMR and ESI$^+$MS data of compounds **2-19**, prepared according to general procedure A or B, are reported in Table 2.

4-(5-Phenyl-pyrimidin-2-yl)-morpholine (20).

Procedure 1. A mixture of **2** (57 mg, 0.3 mmol) and morpholine (0.8 mL, 9 mmol) was stirred at room temperature for 16 h. 1 *N* HCl was added until pH 2-3 and then the mixture was extracted with CH_2Cl_2 (2×30 mL). The collected organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Yield: 95%.

Procedure 2. A mixture of **2** (57 mg, 0.3 mmol) and morpholine (52 µL, 0.6 mmol) in THF (1.5 mL) was heated by MW oven (100°C, 10min). The solvent was evaporated and the crude was purified by silica cartridge (petroleum ether/EtOAc 9:1). Yield: 93%.

M.p. 142-143°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 2H), 7.42-7.52 (m, 4H), 7.36 (m, 1H), 3.85-3.89 (m, 4H), 3.78-3.84 (m, 4H). ESI$^+$MS: calcd for $C_{14}H_{15}N_3O$: 241.12; found: 242.1 (MH^+). Elem. Anal.: calcd: C, 69.7%; H, 6.3%; N, 17.4%. Found: C, 69.8%; H, 6.2%; N, 17.6%.

4-(5-*p*-Tolyl-pyrimidin-2-yl)-morpholine (21). Prepared according to procedures 1 and 2 described for the compound **20** in 87% and 81% yield, respectively. M.p. 157-158°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 2H), 7.39 (m, 2H), 7.27 (m, 2H), 3.79-3.89 (m, 8H), 2.41 (s, 3H). ESI$^+$MS: calcd for $C_{15}H17N_3O$: 255.14; found: 256.1 (MH^+). Elem. Anal.: calcd: C, 70.6%; H, 6.7%; N, 16.5%. Found: C, 70.5%; H, 6.7%; N, 16.4%.

Isopropyl-(5-phenyl-pyrimidin-2-yl)-amine (22). Prepared according to procedure 1 described for the compound **20** in 92% yield. M.p. 115-116°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 2H), 7.41-7.51 (m, 4H), 7.35 (m, 1H), 5.03 (bs, 1H), 4.13-4.26 (m, 1H), 1.29 (d, J = 6.5 Hz, 6H). ESI$^+$MS: calcd for $C_{13}H_{15}N_3$: 213.13; found: 214.1 (MH^+). Elem. Anal.: calcd: C, 73.2%; H, 7.1%; N, 19.7%. Found: C, 73.4%; H, 7.2%; N, 19.8%.

Isopropyl-(5-*p*-tolyl-pyrimidin-2-yl)-amine (23). Prepared according to procedure 2 (reaction time: 6h) described for the compound **20** in 94% yield. M.p. 124-125°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (s, 2H), 7.38 (m, 2H), 7.25 (m, 2H), 5.02 (bs, 1H), 4.20 (m, 1H), 2.41 (s, 3H), 1.29 (d, J = 6.5 Hz, 6H). ESI$^+$MS: calcd for $C_{14}H_{17}N_3$: 227.14; found: 228.1 (MH^+). Elem. Anal.: calcd: C, 74.0%; H, 7.5%; N, 18.5%. Found: C, 73.9%; H, 7.3%; N, 18.4%.

Phenyl-(5-phenyl-pyrimidin-2-yl)-amine (24). Prepared according to procedure 2 (reaction time: 6h, temperature: 130°C) described for the compound **20** in 78% yield. M.p. 168-169°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.74 (s, 1H), 8.83 (s, 2H), 7.77-7.83 (m, 2H), 7.68-7.75 (m, 2H), 7.44-7.52 (m, 2H), 7.37 (m, 1H), 7.25-7.34 (m, 2H), 6.93-7.02 (m, 1H). ESI$^+$MS: calcd for $C_{16}H_{13}N_3$: 247.11; found: 248.2 (MH^+). Elem. Anal.: calcd: C, 77.7%; H, 5.3%; N, 17.0%. Found: C, 77.9%; H, 5.4%; N, 17.2%.

2-Methoxy-5-*p*-tolyl-pyrimidine (25). To a solution of sodium methylate (prepared dissolving 9 mg (0.39 mmol) of sodium in 1.5 mL of MeOH at room temperature), 2-chloro-5-tolyl-pyrimidine (61 mg, 0.3 mmol) was added and the mixture was heated by MW oven (100°C, 10min). The solvent was evaporated, the residue suspended in water (5 mL) and extracted with EtOAc (2×5 mL). The organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Yield: 98%. M.p. 80-81°C (lit. [9], 82-83°C) ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.90 (s, 2H), 7.61 (m, 2H), 7.31 (m, 2H), 3.96 (s, 3H), 2.36 (s, 3H). ESI$^+$MS: calcd for $C_{12}H_{12}N_2O$: 200.09; found: 201.1 (MH^+). Elem. Anal.: calcd: C, 72.0%; H, 6.0%; N, 14.0%. Found: C, 71.9%; H, 6.2%; N, 14.2%.

2-Isopropoxy-5-*p*-tolyl-pyrimidine (26). Prepared according to the procedure described for the compound **25** in 96% yield. M.p. 79-80°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (s, 2H), 7.42 (m, 2H), 7.29 (m, 2H), 5.34 (m, 1H), 2.42 (s, 3H), 1.44 (d, J = 6.2 Hz, 6H). ESI$^+$MS: calcd for $C_{14}H_{16}N_2O$: 228.13; found: 229.2 (MH^+). Elem. Anal.: calcd: C, 73.7%; H, 7.1%; N, 12.3%. Found: C, 73.9%; H, 7.2%; N, 12.2%.

2-Ethylsulfanyl-5-*p*-tolyl-pyrimidine (27). To a solution of sodium ethanethiolate (prepared dissolving 9 mg (0.39 mmol) of sodium and 111 µL (1.5 mmol) of ethanethiol in 1.5 mL of dry THF at room temperature), 2-chloro-5-*p*-tolyl-pyrimidine (61 mg, 0.3 mmol) was added and the mixture was heated by MW oven (100°C, 20min). The solvent was evaporated, the residue suspended in water (5 mL) and extracted with EtOAc (2×5 mL). The organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (s, 2H), 7.44 (m, 2H), 7.31 (m, 2H), 3.22 (q, J = 7.3 Hz, 2H), 2.42 (s, 3H), 1.45 (t, J = 7.3 Hz, 3H). ESI$^+$MS: calcd for $C_{13}H_{14}N_2S$: 230.09; found: 231.1 (MH^+). Elem. Anal.: calcd: C, 67.8%; H, 6.1%; N, 12.2%. Found: C, 68.0%; H, 6.2%; N, 12.3%.

2-Chloro-4-phenyl-pyrimidine (28). A mixture of 2,4-dichloro-pyrimidine (68 mg, 0.45 mmol), phenylboronic acid (66 mg, 0.54 mmol), KF (52 mg, 0.9 mmol) and $Pd(OAc)_2$ (5% mol) in MeOH (2.2 mL) was heated in a sealed tube at 120°C for 20 min by MW irradiation. The solvent was evaporated and the crude was purified by short chromatographic column

(petroleum ether/EtOAc 8:2) Yield: 60%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.82 (d, J = 5.3 Hz, 1H), 8.17-8.22 (m, 2H), 8.15 (d, J = 5.3 Hz, 1H), 7.48-7.69 (m, 3H). ESI$^+$MS: calcd for $C_{10}H_7ClN_2$: 190.03; found: 191.0 (MH^+).

Acknowledgement. We thank the Analytical Department of NiKem Research for the careful and precious support to our synthetic activities.

REFERENCES AND NOTES

[1] Present address: Dipartimento Farmaco-Chimico, Università di Messina, via Annunziata, 98168 Messina, Italy

[2] (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457-2483; (b) Suzuki, A. *Chem. Commun*. **2005**, 4759-4763.

[3] 5-Bromo-2-hydroxy-pyrimidine can be prepared as reported by Vlad, G.; Horvath, I. T. *J. Org. Chem.* **2002**, *67*, 6550-6552, or purchased from common providers.

[4] Some recent papers involving potassium fluoride as base in Suzuki couplings: (a) Kabalka, G. W.; Namboodiri, V.; Wang, L. *Chem. Commun*. **2001**, 775; (b) Basu, B.; Das, P.; Bhuiyan, Md. M. H.; Jha, S. *Tetrahedron Lett*. **2003**, *44*, 3817-3820; (c) Kabalka, G. W.; Wang, L.; Pagni, R. M.; Hair, C. M.; Namboodiri, V. *Synthesis* **2003**, 217-222; (d) Song, C.; Ma, Y.; Chai, Q.; Ma, C.; Jiang, W.; Andrus, M. B. *Tetrahedron* **2005**, *61*, 7438-7446.

[5] Some recent papers involving palladium(II) acetate as catalyst in Suzuki couplings: (a) Leadbeater, N. E.; Marco, M. *Org. Lett*. **2002**, *4*, 2973-2976; (b) Deng, Y.; Gong, L.; Mi, A.; Liu, H.; Jiang, Y. *Synthesis* **2003**, 337-339; (c) Klingensmith, L. M.; Leadbeater, N. E. *Tetrahedron Lett*. **2003**, *44*, 765-768; (d) Liu, W.-J.; Xie, Y.-X.; Liang, Y.; Li, J.-H. *Synthesis* **2006**, 860-864.

[6] Schomaker, J. M.; Delia, T. J. *J. Org. Chem*. **2001**, *66*, 7125-7128.

[7] Delia, T. J.; Schomaker, J. M.; Kalinda, A. S. *J Heterocycl. Chem*. **2006**, *43*, 127-131.

[8] Coppola, G. M.; Hardtmann, G. E.; Huegi, B. S. *J Heterocycl. Chem*. **1980**, *17*, 1479-1482.

[9] Brown, D. J.; Lee, T. -C. *J. Chem. Soc. (C)* **1970**, 214-219.