Direct Palladium-Catalyzed Arylations of Aryl Bromides with 2/9-Substituted Pyrimido[5,4-*b*]indolizines

Min Jiang, Ting Li, Linghua Meng, Chunhao Yang,* Yuyuan Xie, and Jian Ding

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, SIBS, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai, 201203 P.R.China

Received October 9, 2008

C-5 arylated 2/9-substituted pyrimido[5,4-*b*]indolizines were synthesized via palladium-catalyzed direct arylation. A variety of substituents on both pyrimido[5,4-b]indolizines and aryl/heteroaryl bromides are tolerated, providing rapid access to substituted pyrimido[5,4-*b*]indolizines in good to excellent yields.

Introduction

Fused heterocyclic ring systems occupy a prominent place in medicinal chemistry because of their significant properties as therapeutics.[1] For example, benzo- or heterofused pyrimidines served as selective inhibitors for multidrug-resistance-associated protein[2] and antiplatelet and antithrombotic agents.[3] Fused pyrimidines are known to exhibit promising antiviral,[4] antibacterial,[5] anti-AIDS,[6] and antinociceptive activities.[7] Furthermore, several marketed drugs such as EGFR tyrosine kinase inhibitors lapatinib, gefitinib, and erlotinib contain a fused-pyrimidine core structure.[8] Therefore, the design and synthesis of novel fused heterocyclic scaffolds attract the attention of both organic and medicinal chemists. Recently we reported the synthesis of novel tricyclic 2-substituted pyrimido[5,4-*b*]indolizines (Figure 1, I).[9] We found that pyrimidine-fused indolizines had not received significant attention.[10−13] As part of our continuing effort in exploring of the chemistry and biology of pyrimido[5,4-*b*]indolizine scaffolds, we were interested in the construction of 5-aryl(heteroaryl)pyrimido[5,4-*b*]indolizines. The core structure of these indolizines is similar to that of the marine alkaloids variolin B (Figure 1, II) and deoxyvariolin B (Figure 1, III), which have potent antitumor activities.[14]

Transition metal-catalyzed transformations at C−H bonds are emerging as economical tools in organic synthesis.[15] In this regard, direct arylation represents an atom economic and efficient alternative to classical coupling processes such as Suzuki coupling reaction. This methodology has been widely used to construct bioactive compounds and materials. Reactions on electron-rich substrates are well documented. Many π-excessive heterocycles such as furans,[16] thiophenes,[17] pyrroles,[18] indoles,[19] oxazoles, thiazoles, imidazoles, and imidazo[1,2-*a*]pyrimidines[20] have been used as reactants with this method. Combined π-deficient/π-excessive ring system has also been reported.[21] Choul-Hong Park et al. have reported a method for the preparation of C-3 aryl- and heteroarylation of indolizines,[22] which inspired us to study the direct palladium-catalyzed arylation of 2/9-substituted pyrimido[5,4-*b*]indolizines with various commercially available aryl bromides. Herein we report an efficient synthesis of C-5 arylated 2/9-substituted pyrimido[5,4-*b*]indolizines (Figure 1, IV) by palladium-catalyzed direct arylation.

Results and Discussion

We selected the coupling of 2-phenylpyrimido[5,4-*b*]indolizine (**1a**) with bromobenzene (**2a**) as a model reaction. We screened three parameters (base, solvent and catalyst) in test reactions (Table 1). The results indicated that these three factors have significant effect on the outcome of this coupling reaction. Organic bases such as triethylamine (TEA) and diisopropylethylamine (DIPEA) did not lead to the desired reaction product (entries 1−2) and KOAc was the most effective inorganic base compared to K_2CO_3 and Cs_2CO_3 (entries 3−5). In studying the effects of solvents, the reaction in HMPA (**Caution***! HMPA is toxic and suspected of being a carcinogen*) gave the best results with a 79% yield of **3aa** (entries 5−12). The catalyst was subsequently optimized, and $Pd(PPh_3)_4$ was found to be the best catalyst. The reaction of 1.0 equiv of 2-phenylpyrimido[5,4-*b*]indolizine, 1.2 equiv of bromobenzene, 2 equiv

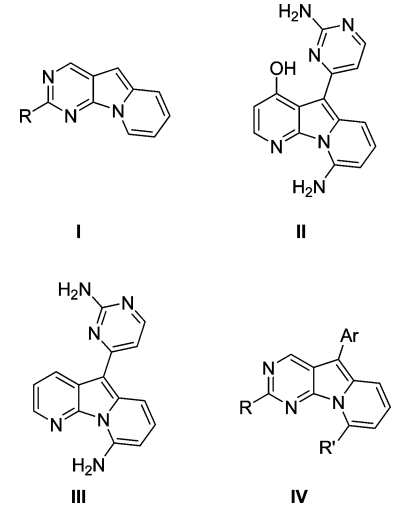
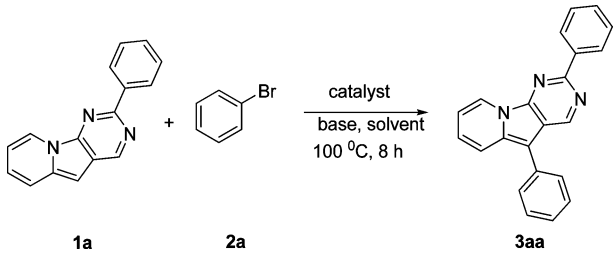


Figure 1. Some heterofused indolizines.

* To whom correspondence should be addressed. E-mail: chyang@mail.shcnc.ac.cn.

10.1021/cc800162k CCC: $40.75
Published on Web 07/31/2009

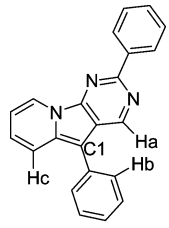
Table 1. Optimization of Palladium-Catalyzed Coupling Reaction of 2-Phenylpyrimido[5,4-*b*]indolizine (**1a**) with Bromobenzene (**2a**)[a]



1a **2a** **3aa**

entry	catalyst	base	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$	TEA	NMP	0
2	$Pd(PPh_3)_4$	DIPEA	NMP	0
3	$Pd(PPh_3)_4$	K_2CO_3	NMP	traces
4	$Pd(PPh_3)_4$	Cs_2CO_3	NMP	49
5	$Pd(PPh_3)_4$	KOAc	NMP	55
6	$Pd(PPh_3)_4$	KOAc	DMSO	17
7	$Pd(PPh_3)_4$	KOAc	DMF	39
8	$Pd(PPh_3)_4$	KOAc	DMA	32
9	$Pd(PPh_3)_4$	KOAc	MeCN	40
10	$Pd(PPh_3)_4$	KOAc	toluene	traces
11	$Pd(PPh_3)_4$	KOAc	THF	traces
12	$Pd(PPh_3)_4$	KOAc	HMPA	79
13	$PdCl_2(PP_3)_2$	KOAc	HMPA	23
14	$Pd(OAc)_2$+PPh_3	KOAc	HMPA	13
15	$PdCl_2$(dppf)	KOAc	HMPA	24

[a] Reactions were carried out with 2-phenylpyrimido[5,4-*b*]indolizine (1 equiv), bromobenzene (1.2 equiv), 5 mol % catalyst and base (2 equiv), and H_2O (1 equiv) in 2 mL solvent at 100 °C for 8 h. [b] Isolated yields.



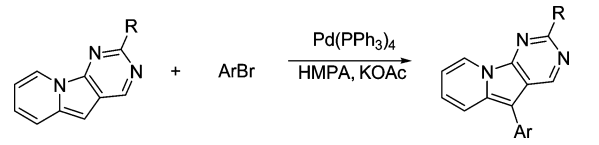
3aa

Figure 2. NOE correlations observed for **3aa**.

of KOAc, 1 equiv of H_2O, and 5 mol % $Pd(PPh_3)_4$ in HMPA at 100 °C with stirring for 8 h gave **3aa** in 79% yield (entry 12). NMR analysis of **3aa** showed a singlet in δ 9.51 for Ha located on the pyrimidine ring, and the correlations between Ha and Hb were shown from the NOESY spectrum (Figure 2, 1D NOE difference spectroscopy). Furthermore, the quaternary carbon signal at 103.8 (C1) correlated with the protons at δ9.51 (Ha) and δ7.72 (Hc) in the HMBC spectrum. **3aa** was also confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and HSQC NMR.

With these optimized reaction conditions in hand, we turned to investigate the scope of the process. Three kinds of 2-substituted pyrimido[5,4-*b*]indolizines were used (Table 2). The reactions appear to be sensitive to electronic effects. Electron-withdrawing groups on the aryl bromide generally resulted in higher yields (Table 2, entries 9, 18, 27) while electron-donating groups led to decreased yields (entries 2, 3, 11, 12, 20, 21). The only exception was 1-bromo-4-nitrobenzene which gave no desired products in all coupling reactions (entries 4, 13, 22). This is different from the reaction of 1-bromo-4-nitrobenzene with indolizines.[22] Heteroaromatic bromides, such as 5-bromopyrimidine and

Table 2. Synthesis of C-5 Arylated 2-Substituted Pyrimido[5,4-*b*]indolizines[a]



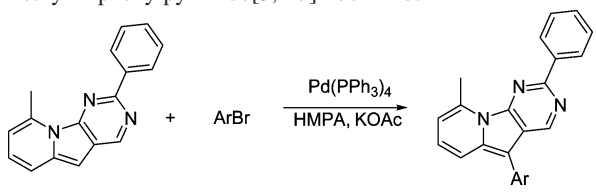
entry	product	R	ArBr	yield[b] (%)
1	**3aa**	Ph	bromobenzene	79
2	**3ab**	Ph	1-bromo-4-methylbenzene	59
3	**3ac**	Ph	1-bromo-4-methoxybenzene	35
4	**3ad**	Ph	1-bromo-4-nitrobenzene	0
5	**3ae**	Ph	2-bromopyridine	0
6	**3af**	Ph	5-bromopyrimidine	99
7	**3ag**	Ph	5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine	0
8	**3ah**	Ph	3-bromoquinoline	94
9	**3ai**	Ph	1-bromo-3-nitrobenzene	99
10	**3ba**	CH_3	bromobenzene	96
11	**3bb**	CH_3	1-bromo-4-methylbenzene	90
12	**3bc**	CH_3	1-bromo-4-methoxybenzene	73
13	**3bd**	CH_3	1-bromo-4-nitrobenzene	0
14	**3be**	CH_3	2-bromopyridine	0
15	**3bf**	CH_3	5-bromopyrimidine	91
16	**3bg**	CH_3	5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine	0
17	**3bh**	CH_3	3-bromoquinoline	77
18	**3bi**	CH_3	1-bromo-3-nitrobenzene	99
19	**3ca**	morpholine	bromobenzene	85
20	**3cb**	morpholine	1-bromo-4-methylbenzene	83
21	**3cc**	morpholine	1-bromo-4-methoxybenzene	45
22	**3cd**	morpholine	1-bromo-4-nitrobenzene	0
23	**3ce**	morpholine	2-bromopyridine	0
24	**3cf**	morpholine	5-bromopyrimidine	98
25	**3cg**	morpholine	5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine	0
26	**3ch**	morpholine	3-bromoquinoline	92
27	**3ci**	morpholine	1-bromo-3-nitrobenzene	98

[a] Reactions were carried out with 2-substituted pyrimido[5,4-*b*]indolizines (1 equiv), ArBr (1.2 equiv), 5 mol % Pd (PPh_3)$_4$, and KOAc (2 equiv), and H_2O (1 equiv) in 2 mL of HMPA at 100 °C for 8 h. [b] Isolated yields.

3-bromoquinoline, led to the desired products in excellent yields (entries 6, 8, 15, 17, 24, 26), while electron-donating heteroaromatic bromides were unreactive (entries 7, 16, 25). Interestingly 2-bromopyridine also gave no desired products with all different substrates (entries 5, 14, 23). TLC detection suggested that the starting material 2-bromopyridine was completely consumed just as 1-bromo-4-nitrobenzene and pyrimido[5,4-*b*]indolizines still existed. We speculate that the oxidative addition palladium intermediates are probably not stable enough to continue the next step of coupling reactions. To expand the reaction scope, a methyl group was introduced to the 9-position on the pyridine ring of the scaffold according to the reported procedure[9] because it could be easily converted into other functional groups such as bromomethyl group, aldehyde group, and carboxyl group. The reactions gave very similar results: bromides with electron-withdrawing group provided higher yields except for 2-bromopyridine (Table 3). All the desired products were new compounds, and were isolated by flash chromatography and fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. All products are stable at room temperature.

The compounds were screened for the inhibition of Akt phosphorylation on Ser-473. The results showed that all of them could not down-regulate Akt Ser-473 phosphorylation in Rh30 cells. The cytotoxicity of compounds was also

Table 3. Synthesis of C-5 Arylated 9-Methyl-2-phenylpyrimido[5,4-*b*]indolizines[a]



entry	product	ArBr	yield[b] (%)
1	**3da**	bromobenzene	82
2	**3db**	1-bromo-4-methylbenzene	65
3	**3dc**	2-bromopyridine	0
4	**3dd**	3-bromoquinoline	88
5	**3de**	5-bromopyrimidine	98

[a] Reactions were carried out with 9-methyl-2-phenylpyrimido[5,4-*b*]-indolizine (1 equiv), ArBr (1.2 equiv), 5 mol % Pd $(PPh_3)_4$ and KOAc (2 equiv), and H_2O (1 equiv) in 2 mL of HMPA at 100 °C for 8 h. [b] Isolated yields.

evaluated by sulforhodamine B (SRB) assay, and compound **3bh** exhibited growth inhibition of 70% for Rh30 cells at 20 μM.

Conclusion

In summary, we have developed a useful method for the construction of 5-aryl(heteroaryl)- pyrimido[5,4-*b*]indolizines via palladium-catalyzed direct arylation. A variety of substituents on pyrimido[5,4-*b*]indolizines are tolerated, and aryl/heteroaryl bromides with electron-withdrawing groups provided direct arylated pyrimido[5,4-*b*]indolizines in good to excellent yields except for 1-bromo-4-nitrobenzene and 2-bromopyridine. Although electron-donating groups on aryl/heteroaryl bromides were unfavorable, some of them also gave good yields. Through biological activity screening, we obtained one novel compound **3bh**, which exhibited moderate inhibition against Rh30 cells. This result could be a useful clue in the design and synthesis of novel antitumor drugs.

Acknowledgment. This work was financially supported by the Innovation Program of the Chinese Academy of Sciences (Grant KSCX2-YW-R-25) and the National Natural Science Foundation of China (20772138, 90713034, and 30721005). The authors thank Prof. Binghe Wang of Georgia State University for his helpful discussion and proof-reading the manuscript.

Supporting Information Available. Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
(2) Wang, S.; Folkes, A.; Chuckowree, I.; Cockcroft, X.; Sohal, S.; Miller, W.; Milton, J.; Wren, S. P.; Vicker, N.; Depledge, P.; Scott, J.; Smith, L.; Jones, H.; Mistry, P.; Faint, R.; Thompson, D.; Cocks, S. *J. Med. Chem.* **2004**, *47*, 1329–1338.
(3) Bruno, O.; Brullo, C.; Schenone, S.; Bondavalli, F.; Ranise, A.; Tognolini, M.; Impicciatore, M.; Ballabeni, V.; Barocelli, E. *Bioorg. Med. Chem.* **2006**, *14*, 121–130.
(4) Hossain, N.; Rozenski, J.; De Clercq, E.; Herdewijn, P. *J. Org. Chem.* **1997**, *62*, 2442–2447.
(5) Sabnis, R. W.; Rangnekar, D. W. *Indian J. Technol.* **1990**, *28*, 54.
(6) Joseph, S.; Burke, J. *J. Biol. Chem.* **1993**, *268*, 24515–24518.
(7) Bookser, B. C.; Ugarkar, B. G.; Matelich, M. C.; Lemus, R. H.; Allan, M.; Tsuchiya, M.; Nakane, M.; Nagahisa, A.; Wiesner, J. B.; Erion, M. D. *J. Med. Chem.* **2005**, *48*, 7808–7820.
(8) Abouzid, K.; Shouman, S. *Bioorg. Med. Chem.* **2008**, *16*, 7543–7551.
(9) Jiang, M.; He, Q.; Yang, C. H.; Xie, Y. Y. *Heterocycles* **2008**, *75*, 2659–2666.
(10) Khoroshilov, G. E.; Demchak, I. V.; Emelyanova, M. V. *Chem. Heterocycl. Compd.* **2007**, *43*, 116–117.
(11) Volovenko, Yu. M.; Babichev, F. S.; Fursii, T. A.; Litvinenko, S. U. *Khim. Geterotsikl. Soedin.* **1991**, *6*, 852.
(12) Yoon, T. Preparation of pyrido[2,3-*b*]indolizine derivatives and their aza analogues as CRF1 specific ligands. Int. Patent WO 9964422, 1999.
(13) Horvath, R. F.; Tran, J.; De, Lombaert S.; Hodgetts, K. J.; Carpino, P. A.; Griffith, D. A. Preparation of certain alkylene diamine-substituted heterocycles as NPY1 receptor inhibitors. Int. Patent WO 2001023389, 2001.
(14) Echalier, A.; Bettayeb, K.; Ferandin, Y.; Lozach, O.; Clement, M.; Valette, A.; Liger, F.; Marquet, B.; Morris, J. C.; Endicott, J. A.; Joseph, B.; Meijer, L. *J. Med. Chem.* **2008**, *51*, 737–751.
(15) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (c) Campeau, L. C.; Fagnou, K. *J. Chem. Soc., Chem. Commun.* **2006**, 1253–1264. (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.
(16) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677–1680.
(17) (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286–5287. (b) Lavenot, L.; Gozzi, C.; Ilg, K.; Orlova, I.; Penalva, V.; Lemaire, M. J. *J. Organomet. Chem.* **1998**, *567*, 49–55. (c) Gozzi, C.; Lavenot, L.; Ilg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 8867–8870.
(18) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981–3983.
(19) (a) Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477–1480. (b) Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981**, 254–255. (c) Akita, Y.; Inoue, A.; Yamamoto, K.; Ohta, A.; Kurihara, T.; Shimizu, M. *Heterocycles* **1985**, *23*, 2327–2333. (d) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174. (e) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973.
(20) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem.* **2005**, *70*, 3997–4005.
(21) Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923–2926.
(22) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159–1162.

CC800162K