ORGANIC LETTERS

2006
Vol. 8, No. 3
395−398

A Highly Regioselective Amination of 6-Aryl-2,4-dichloropyrimidine

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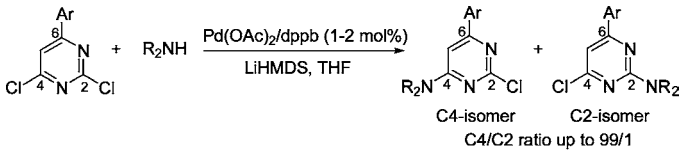
Received October 24, 2005

ABSTRACT



A highly regioselective amination of 6-aryl-2,4-dichloropyrimidine with aliphatic secondary amines and aromatic amines has been developed which strongly favors the formation of the C4-substituted product. The reactions with aliphatic amines are carried out using LiHMDS as the base and are catalyzed by Pd, while the aromatic amines require no catalyst.

Pyrimidines are widespread heterocyclic motifs found in numerous natural products as well as synthetic pharmacophores with antibacterial, antimicrobial, and antimycotic activities.[1] The highly electron-deficient nature of the pyrimidine ring renders the nucleophilic aromatic substitution reaction (S_NAr) a general approach for the synthesis of a large number of pyrimidine derivatives, especially from readily available halopyrimidines.[1] This feature also translates to palladium-catalyzed cross-coupling reactions as even pyrimidine chlorides are highly reactive substrates.[2]

The reactivity of each position of the pyrimidine halides follows the general order C4(6) > C2 ≫ C5. This order has been observed for both palladium-catalyzed reactions and S_NAr displacements.[1,2] In palladium-catalyzed C−C bond formation reactions, Sonogashira reactions showed little difference in reactivity between the C2 and C4 positions of halopyrimidines,[3] while a strong preference for the C4 position has been observed in Suzuki[4] and Stille[5] coupling reactions such that the sequential introduction of different substituents has been achieved.

The nucleophilic substitution reactions of 2,4-dichloropyrimidines are generally only moderately selective toward the formation of the C4-substituted product. For example, the nucleophilic displacement of 2,4-dichloropyrimidines with neutral nitrogen nucleophiles affords only 1:1 to 4:1 ratios of the C4/C2 isomers (eq 1).[6−8] This lack of regioselectivity

(1) (a) Hurst, D. T. In *An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*; Wiley: Chichester, 1980. (b) Brown, D. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, Chapter 2.13. (c) Brown, D. J. In *The Pyrimidines*; Interscience Publishers: New York, 1994.

(2) (a) Undheim, K.; Benneche, T. *Heterocycles* **1990**, *30*, 1155−1193. (b) Undheim, K.; Benneche, T. In *Adv. Heterocycl. Chem.* **1995**, *62*, 305−418. (c) Kalinin, K. N. *Synthesis* **1992**, 413−432. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(3) Edo, K.; Yamanaka, H.; Sakamoto, T. *Heterocycles* **1978**, *9*, 271−274.

(4) (a) Gronowitz, S.; Hornfeldt, A.-B.; Kristjansson, V.; Musil, T. *Chem. Scr.* **1986**, *26*, 305−309. (b) Cocuzza, A. J.; Hobbs, F. W.; Arnold, C. R.; Chidester, D. R.; Yarem, J. A.; Culp, S.; Fitzgerald, L.; Gilligan, P. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1057−1062. (c) Jiang, B.; Yang, C.-G. *Heterocycles* **2000**, *53*, 1489−1498. (d) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829−831. (e) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125−7128.

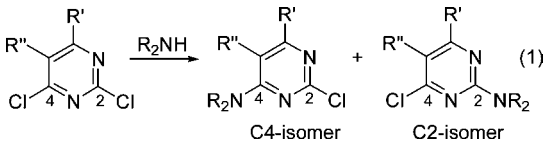
(5) (a) Solberg, J.; Undheim, K. *Acta Chem. Scand., Ser. B* **1989**, *43*, 62−68. (b) Benneche, T. *Acta Chem. Scand.* **1990**, *44*, 927−931.

(6) For early examples, see: (a) Gabriel, S. *Chem. Ber.* **1901**, *34*, 3362−3366. (b) Büttner, E. *Chem. Ber.* **1903**, *36*, 2227−2235. (c) Winkelmann, W. *J. Prakt. Chem.* **1927**, *115*, 292−296. (d) Boon, W. R. *J. Chem. Soc.* **1952**, 1532−1535.

(7) For recent examples, see: (a) Mossini, F.; Maggiali, C.; Morini, G.; Impicciatore, M.; Morini, G.; Molina, E. *Farmaco, Ed. Sci.* **1984**, *39*, 189−199. (b) Delia, T. J.; Stark, D.; Glenn, S. K. *J. Heterocycl. Chem.* **1995**, *32*, 1177−1180. (c) Schomaker, J. M.; Delia, T. J. *J. Heterocycl. Chem.* **2000**, *37*, 1457−1462. (d) Luthin, D. R.; Hong, Y.; Tompkins, E.; Anderes, K. L.; Paderes, G.; Kraynov, E. A.; Castro, M. A.; Nared-Hood, K. D.; Castillo, R.; Gregory, M.; Vazir, H.; May, J. M.; Anderson, M. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3635−3640. (e) Montebugnoli, D.; Bravo, P.; Brenna, E.; Mioskowski, C.; Panzeri, W.; Viani, F.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2003**, *59*, 7147−7156. (f) Joubran, L.; Jackson, W. R.; Campi, E. M.; Robinson, A. J.; Wells, B. A.; Godfrey, P. D.; Callaway, J. K.; Jarrott, B. *Aust. J. Chem.* **2003**, *56*, 597−606.

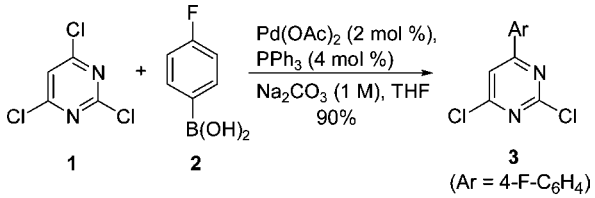
10.1021/ol052578p CCC: $33.50
Published on Web 01/12/2006

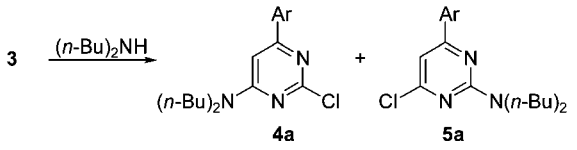
makes these amination reactions of limited use synthetically since the isomers are often difficult to separate. In support of a recent development program, we required an efficient C4 regioselective amination of 6-(4-fluorophenyl)-2,4-dichloropyrimidine **3**. During the course of our investigations, we have discovered a highly regioselective amination protocol of 6-aryl-2,4-dichloropyrimidines which strongly favors the formation of the C4-isomer. In this paper, we report our results of this unprecedented regioselective palladium-catalyzed amination reaction of 2,4-dichloropyrimidines.



Pyrimidine **3** was prepared via the Suzuki coupling reaction of 2,4,6-trichloropyrimidine **1** with 4-fluorophenylboronic acid **2** using a slightly modified literature procedure (Scheme 1).[4e] The reaction of **3** with dibutylamine under the common S_NAr conditions (K_2CO_3, DMAc) gave only a 70:30 ratio of the C4 isomer **4a** to the C2 isomer **5a** (Scheme 1). In an effort to improve the regiochemisty of the reaction, various solvents and bases were examined. Interestingly, very different results were obtained for chromatographed **3** versus crystallized[9] **3** when the reaction was carried out in THF with LiHMDS as the base. The crystallized material gave an impressive 99:1 ratio of **4a**/**5a**, and the reaction was completed in less than 0.5 h to afford **4a** in 95% yield, while the reaction of the chromatographed material was much slower and only afforded a 70:30 ratio of **4a**/**5a**. This dramatic difference was later attributed to the presence of an impurity in the crystallized material, which was isolated by careful chromatography and was determined by X-ray crystallography to be the palladium adduct of 2,4,6-trichloropyrimidine **6** from the Suzuki coupling reaction (Figure 1). Complex **6** was a highly effective catalyst for the amination reaction. When the amination of the pure chromatographed **3** was carried out in the presence of 2 mol % of **6**, the reaction gave the same result as the crystallized material (Scheme 1). A review of the literature revealed that similar palladium-coordinated pyrimidine complexes have been isolated and have shown catalytic activity in Stille coupling reactions.[5b] Although chloro- and bromopyrimidines have occasionally been employed as coupling partners in Pd-catalyzed aminations,[10,11] to the best of our knowledge, no examples of regioselective palladium-catalyzed aminations of 2,4-dichloropyrimidines have been reported.

Scheme 1





conditions	ratio(**4a**:**5a**)(yield of **4a**)
K_2CO_3, DMAc, rt, 1 h	70:30 (67%)
LiHMDS, THF, 0 ^{0}C, 5 h	70:30 (60%)
6 (2 mol %), LiHMDS, THF, 0 ^{0}C, 0.5 h	99:1 (95%)

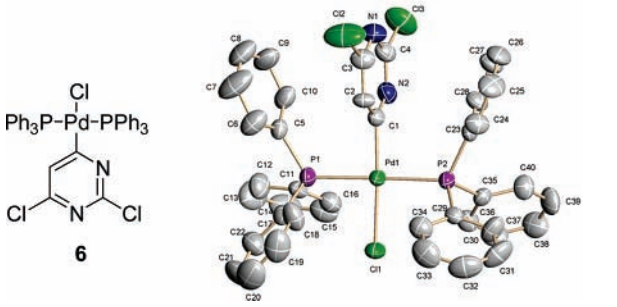


Figure 1. ORTEP view of complex **6**.

Having established that Pd was required for high regioselectivity, the reaction of **3** with dibutylamine was screened with a number of phosphine ligands using $Pd(OAc)_2$ as the palladium source (Table 1). Unexpectedly, several of the most general and highly active monodentate phosphine ligands for the cross-coupling reactions, such as XPhos,[12] Josiphos,[13] and $(t\text{-Bu})_3P$,[14] were poor catalyst systems for the reaction. Not only were the reactions much slower, the regioselectivities were also poor (entries 1−3). On the other hand, the simple and inexpensive monodentate and bidentate

(8) Better regioselectivity has been obtained with *N*-sodium carbamates: (a) Zanda, M.; Talaga, P.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 1757−1761. (b) Montebugnoli, D.; Bravo, P.; Corradi, E.; Dettori, G.; Mioskowski, C.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2002**, *58*, 2147−2154.

(9) Compound **3** could be isolated by crystallization from the crude Suzuki coupling reaction mixture using MTBE−hexanes as the solvents.

(10) For reviews on Pd-catalyzed aminations of aryl halides, see: (a) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; John Wiley & Sons: Weinheim, 2004. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002.

(11) For examples, see: (a) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965−3968. (a) Kamenecka, T. M.; Lanza, T.; de Laszlo, S. E.; Li, B.; McCauley, E. D.; Van Riper, G.; Egger, L. A.; Kidambi, U.; Mumford, R. A.; Tong, S.; MacCoss, M.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2205−2208. (b) Yin, J. J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481−3484.

(12) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655.

(13) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371−1375.

(14) (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

Table 1. Catalyst Screening of the Amination of **3** with Dibutylamine

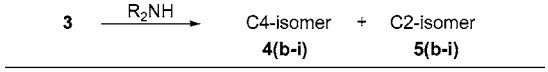
entry	catalyst	time	ratio (**4a**:**5a**)[a]	yield[b] of **4a** (%)
1	$Pd(OAc)_2$/X-phos (5 mol %)[c]	6 h	85:15	74
2	$Pd(OAc)_2$/Josiphos (5 mol %)[c]	10 h	80:20	65
3	$Pd(OAc)_2P(t\text{-}Bu)_3$ (5 mol %)[c]	10 h	78:22	61
4	$Pd(OAc)_2/P(o\text{-}tol)_3$ (5 mol %)[c]	2 h	94:6	88
5	$Pd(OAc)_2/PPh_3$ (5 mol %)[c]	30 min	98:2	92
6	$Pd(OAc)_2$/dppp (5 mol %)	1 h	95:5	83
7	**$Pd(OAc)_2$/dppb (1 mol %)**	**5 min**	**>99:1**	**97**
8	$Pd(OAc)_2$/dpppe (5 mol %)	1 h	97:3	90
9	$PdCl_2(PPh_3)_2$ (5 mol %)	5 min	99:1	96

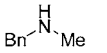
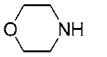
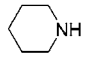
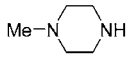
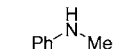
[a] HPLC ratio. [b] HPLC assay yield. [c] 10 mol % of the ligand was used.

phenylphosphine ligands proved to be very effective (entries 4−8). The most active ligand was found to be the bidentate ligand dppb (entry 7). With only 1 mol % catalyst loading, the amination reaction was completed almost instantly at 0 °C to provide >99:1 selectivity for the C4-isomer **4a** in high yield. $PdCl_2(PPh_3)_2$ was another active catalyst for this reaction (entry 9). A screen of bases revealed that only LiHMDS gave rapid reactions as well as high regioselectivity.

The palladium-catalyzed regioselective amination proved to be general for a number of aliphatic secondary amines. As shown in Table 2, while the S_NAr reactions gave only

Table 2. Aminations of **3** with Aliphatic Secondary Amines and Anilines



entry	amine		ratio **4**:**5** (yield of **4**)[a] conditions A[b]	conditions B[c]
1		(**b**)	80:20 (75%)	> 99:1 (98%)
2		(**c**)	66:34 (63%)	> 99:1 (93%)
3		(**d**)	80:20 (75%)	97:3 (92%)
4		(**e**)	82:18 (76%)	98:2 (93%)
5		(**f**)	80:20 (71%)	98:2 (91%)
6		(**g**)	78:22 (74%)	98:2 (94%)
7	$PhNH_2$	(**h**)	70:30 (68%)	91:9 (89%)[d]
8		(**i**)	79:21 (72%)	97:3 (93%)[d]

[a] HPLC ratio and HPLC assay yield. [b] Conditions A: K_2CO_3, DMAc, rt, 1 h (entries 1−6) or BuOH, *i*-Pr_2NEt, 125 °C, 24 h (entries 7 and 8). [c] Conditions B: $Pd(OAc)_2$/dppb (1−2 mol %) or **6** (2 mol %), LiHMDS, THF, 0 °C, 1 h (entry 1) or −20 °C, 1 h (entries 2−6). [d] No catalyst, −60 °C, 0.5 h.

2:1 to 4:1 regioselectivities, the Pd-catalyzed reactions gave >30:1 ratio for all the secondary amines studied. The acyclic secondary amines were the best substrates, giving high regioselectivity with all the effective catalyst systems shown in Table 1 (entries 4−9). For the cyclic secondary amines, however, complex **6** and $Pd(OAc)_2$/dppb were the only catalysts that produced high regioselectivities (Table 2, entries 2−6). The mode of addition was also critical for the more reactive cyclic amines to obtain high regioselectivity. The cyclic secondary amines were premixed with LiHMDS (1 M THF solution) and then added to the THF solution of the pyrimidine and the catalyst to achieve the catalyzed reaction. If the amine was added to the dichloropyrimidine prior to premixing with LiHMDS (with or without the catalyst), the neutral amine reacted quickly with the dichloropyrimidine through the S_NAr pathway to give much lower regioselectivities. Although LiHMDS is not basic enough to fully deprotonate the secondary aliphatic amines,[15] it may complex with the amines to form the active species in the palladium-catalyzed cycle.[16] Unfortunately, the palladium-catalyzed regioselective aminations was not suitable for the aliphatic primary amines due to significant side reactions of bis-arylation of the amines.[17]

Previous studies of the nucleophilic substitution reactions of anilines with 2,4,6-trichloropyrimidine gave rise to higher regioselectivity for the C4-isomer (ca. 10:1) in polar solvents such as ethanol.[7c] The nucleophilic substitution reaction of **3** with aniline, however, gave only 70:30 regioselectivity and the reaction required forcing conditions to go to completion due to the low nucleophilicity of aniline (Table 2, entry 7). When the amination was carried out under the palladium catalyzed conditions, the reaction was completed almost instantaneously[18] even at −60 °C to give a much better ratio of 91:9 (Table 2, entry 7). We subsequently found that the reaction gave the same result in the absence of the catalyst. A plausible explanation was that the aniline was fully deprotonated by LiHMDS to give the anionic anilide,[15] and direct nucleophilic substitution with the anilide was much faster than the palladium-catalyzed reaction. Furthermore, the secondary *N*-methylaniline gave an excellent 97:3 ratio under the same conditions (Table 2, entry 8). Delia and coworker reported that the nucleophilic substitution reaction of 2,4,6-trichloropyrimidine with the anionic phenolate ion gave a good C4/C2 regioselectivity (90:10).[19] This observation was explained by the reaction at C4 giving a more favorable para-quinoid Meisenheimer intermediate than the ortho-quinoid intermediate formed via the C2 substitution pathway.

(15) The pK_a values (in DMSO) for $HN(SiMe)_3$, pyrrolidine, and aniline are 30, 44, and 30.6, respectively.

(16) The anionic lithium amides of the aliphatic amines generated with *n*-BuLi did not give as high regioselectivity.

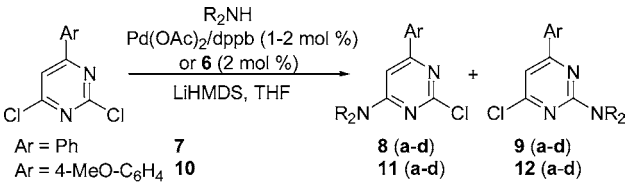
(17) Buchwald reported that Pd/BINAP could minimize bis-arylations for the aminations of primary amines with aryl bromides (Wolf, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157). Unfortunately, this catalyst system provided the same result as our catalyst systems in the aminations of primary amines with **3**.

(18) Two equivalents of LiHMDS was required.

(19) Delia, T. J.; Nagarajan, A. *J. Heterocycl. Chem.* **1998**, *35*, 269−273.

To investigate the electronic effect of the C6 substituent on the amination reaction, the 6-phenyl- and 6-(4-methoxyphenyl)-substituted 2,4-dichloropyrimidines **7** and **10** were synthesized using the analogous Suzuki reactions as shown in Scheme 1. The electron−neutral C6-phenyl-substituted pyrimidine **7** gave the same high reactivity and high regioselectivity as **3** in the Pd-catalyzed amination reactions with aliphatic amines (Table 3, entries 1−3). The electron-donating C6-(4-methoxyphenyl)-substituted pyrimidine **10** showed slightly lower reactivity and diminished, but still high, regioselectivity (Table 3, entries 1−3). Complex **6** and $Pd(OAc)_2$/dppb were still the most effective catalysts for both substrates. Similar to **3**, the catalyst was not required for the reactions with *N*-methylaniline (Table 3, entry 4).

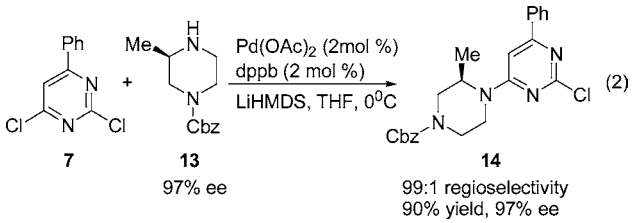
Table 3. Aminations of 6-Phenyl- and 6-(4-Methoxyphenyl)-2,4-dichloropyrimidines



entry	amine		Ar = Ph ratio **8**:**9** (yield[d] of **8**)	Ar = 4-MeO-Ph ratio **11**:**12** (yield[d] of **11**)
1[a]	$(n\text{-Bu})_2$NH	(**a**)	> 99:1 (95%)	98:2 (93%)
2[b]		(**b**)	99:1 (92%)	97:3 (95%)
3[b]		(**c**)	97.5:2.5 (96%)	95.5:4.5 (88%)
4[c]		(**d**)	96.5:3.5 (95%)	95:5 (91%)

[a] 0 °C, 1 h. [b] −20 °C, 1 h. [c] No catalyst, −60 °C, 0.5 h. [d] HPLC assay yield.

In the previously reported Pd-catalyzed amination reactions of amines with a α-chiral center, epimerization occurred through a sequence of the β-hydride elimination of the Pd-amine complex and insertion of the resultant Pd-imine complex.[20] To study whether epimerization was possible in our palladium-catalyzed amination, the chiral 2-methyl piperazine **13** was subjected to the amination reaction with **7** using $Pd(OAc)_2$/dppb (2 mol %) as the catalyst. As shown in eq 2, the reaction gave the C4-substituted product **14** with a 99:1 regioselectivity and essentially no loss of enantiomeric purity. Presumably, the generation of the Pd-amide intermediate and the following reductive elimination in the general catalytic cycle[10] was much faster than β-hydride elimination.



In summary, we have developed a highly regioselective Pd-catalyzed amination of 6-aryl-2,4-dichloropyrimidine which strongly favors the formation of the C4-isomer. One of the most effective Pd catalysts for the reaction is the complex arising from oxidative addition of Pd with 2,4,6-trichloropyrimidine. The scope of the coupling reaction is currently limited to aliphatic secondary amines and anilines. Both electron-withdrawing and electron-donating C6-aryl groups give high regioselectivity with low catalyst loading. We have also discovered that the reactions of aromatic amines require no catalyst and also give high regioselectivity.

Acknowledgment. We thank Dr. Arlene McKeown for X-ray crystallographic analyses, Mirlinda Biba for chiral HPLC analyses, and Bob Reamer for NMR analyses.

Note Added after ASAP Publication. Due to a production error, the Cl at the 4 position of the starting material in the abstract graphic was cut off in the version published ASAP January 12, 2006; the corrected version was published ASAP January 13, 2006.

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

OL052578P

(20) (a) Zhao, S.-H.; Miller, A. K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 4463−4466. (b) Tanatani, A.; Mio, M. J.; Moore, J. S. *J. Am. Chem.* Soc. **2001**, *123*, 1792−1793.