Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3977–3979

Synthesis of unsymmetrical 4,6-diarylpyrimidines

Bishan Zhou,* Brett Taylor and Kathryn Kornau

Basic Research, Medicinal Chemistry Department, Merck Research Laboratories, Rahway, NJ 07065, USA

Received 29 March 2005; revised 8 April 2005; accepted 11 April 2005

Abstract—Unsymmetrical 4,6-diarylpyrimidines were synthesized using Suzuki coupling reaction via selective arylation of 4,6-dichloropyrimidine.

The pyrimidyl heterocycle is a widely presented subunit in numerous pharmaceuticals, agrochemicals, supramolecules, natural products, and ultimately pyrimidine and purine bases such as the ribo- and deoxyribonucleosides.[1] The syntheses of these pyrimidine entities have attracted extensive attention. The most commonly used methods for the preparation of pyrimidine derivatives are those in which the pyrimidine ring is constructed by condensation of two or more well-defined building blocks. Early work in this field was conducted by Pinner[2] and Dodson and Seyler.[3] Accordingly, 4,6-disubstituted pyrimidine could be synthesized by condensing 1,3-dicarbonyl compounds or their synthetic equivalents with amidines or amidine salts. More recently, a modified one-pot method was described by Muller and Braun,[4] who utilized a three component coupling-isomerization sequence, catalyzed by a palladium complex to produce 2,4,6-tri(hetero)aryl-substituted pyrimidines.

Compared to these conventional methods, which require the preparation of the product-specific intermediates, the direct arylation of halopyrimidine is an alternative approach. Pyrimidines are deactivated, π-electron-deficient heterocycles. However, pyrimidine halides (except fluorides) are very reactive in metal catalyzed cross-couplings such as Suzuki reaction. Such an approach utilizing easily accessible 4,6-dihalopyrimidine has been described by Goodman et al.[5] However, due to the symmetrical nature of the starting material, Goodman's group was not able to obtain desymmetrically substituted diarylpyrimidines via direct Suzuki coupling reaction. Recently, Schomaker and Delia[6] tried to achieve selective arylation of 4,6-dichloropyrimidine by converting it into a mono-iodo derivative under the condition of 57% hydroiodo acid and sodium iodide at 40 °C before the Suzuki reaction. Nevertheless, this method always gave a mixture of products.

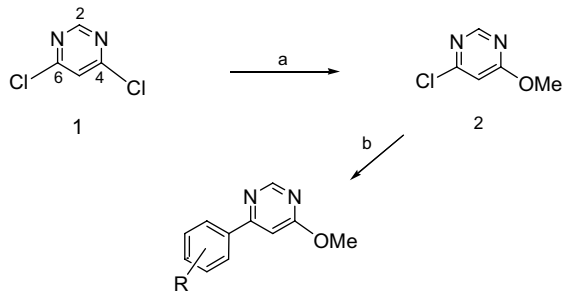
Aware of the difficulty of selective arylation of 4,6-dichloropyrimidine, we decided to distinguish the chloride atoms by masking one of them in such a way so that later on its reactivity can be restored easily. At this stage, two different aryl rings can be installed successively by Suzuki reaction. In this letter, we wish to report a new method of achieving such a synthesis of 4,6-diarylpyrimidines.

Accordingly, the nucleophilic displacement of one chlorine is the key of this methodology. We have examined a few commonly used nucleophiles including alkoxides, sulfoxides, and primary amines. Finally, the methoxyl group was found to be the best choice due to its moderate nucleophilicity and easy convertibility to chloride functionality on a pyrimidine molecule, see Scheme 1.

Thus 4,6-dichloropyrimidine was treated with 1 equiv of sodium methoxide as a 25% w/w solution in methanol at room temperature. The sodium chloride precipitate was formed immediately, and the resulting 4-chloro-6-methoxypyrimidine **2** was isolated by filtration of the reaction mixture through a Celite® pad in excellent yield.[7] Although **2** has been reported as an intermediate in the synthesis of sulfanilamidopyrimidines, a class of anti-bacterial agents,[8] the use of this compound in the regioselective C-arylation of symmetric pyrimidines has not been reported.

Keywords: Unsymmetrical; 4,6-Diarylpyrimidines.
* Corresponding author. Tel.: +1 732 594 4454; fax: +1 732 594 5350; e-mail: bishan_zhou@merck.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.04.043

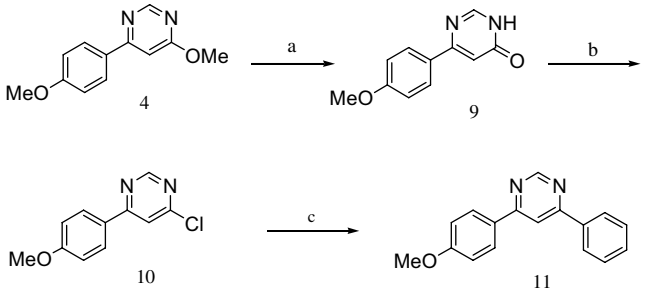


3 R=H, 90%	8 R=*o, m*-diF, 85%
4 R=*p*-OMe, 80%	9 R=*m*-NO_2, 86%
5 R=*m*-COOMe, 64%	10 R=5-pyrimidine, 77%
6 R=*m*-F, 84%	11 R=2-thiophen, 79%
7 R=*p*-F, 91%	12 R=2-furan, 81%

Scheme 1. Reagents and conditions: (a) 1 equiv NaOMe (25%w/w in MeOH), MeOH, rt, 10 min, 95%; (b) 1.4 equiv aryl-$B(OH)_2$, 0.1 equiv $Pd(PPh_3)_4$, 2 equiv Na_2CO_3, toluene, 90 °C, 12 h.

Once the desymmetrization of 4,6-dichloropyrimidine was accomplished, the remaining chlorine atom was utilized to introduce the desired aromatic groups. The arylation of chloropyrimidines via Suzuki cross-coupling reaction have been explored and documented.[9] Among many widely used methods, $Pd(PPh_3)_4$ mediated condition is known to be the most efficient and highest yielding. Therefore, the coupling reactions were carried out in toluene at 90 °C in the presence of 0.1 equiv of $Pd(PPh_3)_4$ and excess of 2 N Na_2CO_3 for 12 hours. As shown in Scheme 1, all the examples including both electron rich and deficient phenyl analogs, as well as the heterocyclic analogs gave very good yields.[10]

At this stage, the masked methoxyl group was converted back to chloride by the treatment of HBr–AcOH and $POCl_3$[11] (see Scheme 2). It is worth noting that the conditions used to restore the chloride are mild enough to leave the methoxy group on the phenyl ring untouched. In addition, this high yielding two-step sequence requires no further purification since the aqueous work up (saturated sodium bicarbonate, then brine) is sufficient to provide fairly pure products (determined by TLC, LCMS, and ^1H NMR).



Scheme 2. Reagents and conditions: (a) HBr–AcOH (1:3), 80 °C, 1 h, then satd $NaHCO_3$; (b) $POCl_3$, 30 m, 100 °C, then satd $NaHCO_3$, 90% over two steps; (c) 1.4 equiv $PhB(OH)_2$, 0.1 equiv $Pd(PPh_3)_4$, 2 equiv Na_2CO_3, toluene, 90 °C, 12 h, 80%.

For demonstration purposes, phenyl boronic acid was employed to complete the second Suzuki coupling under the same condition described earlier. The desired selectively substituted 4,6-diarylpyrimidine **11** was thus obtained.

In summary, we have illustrated a general, versatile, and high yielding method for synthesis of unsymmetrical 4,6-diarylpyrimidines. Starting with 4,6-dichloropyrimidine, we have selectively masked the reactivity of one of the chloro group by displacing it with a methoxyl group. After introduction of the first aryl substituent by Suzuki reaction, the reactivity of the pyrimidine ring is restored by replacing the methoxyl group with a chloro group. The second Suzuki reaction completes the synthesis of the diarylpyrimidine in good to excellent overall yields.

Acknowledgements

We wish to thank Medicinal Chemistry Department at Merck for the generous support, and Dr. Prasun K. Chakravarty and Dr. Patrick Shao for their invaluable discussion and advice.

References and notes

1. (a) Guan, A. W. *Proc. Natl. Acad. Sci.* **1992**, *89*, 11456; (b) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry: Tetrahedron Organic Chemistry series*; Pergmon: Amsterdam, 2000; Vol. 20.
2. Pinner, E. L. *Ber.* **1893**, *26*, 2122.
3. Dodson, R. M.; Seyler, J. K. *J. Org. Chem.* **1952**, *16*, 461.
4. Muller, T. J. J.; Braun, R. *Org. Lett.* **2000**, *2*, 1967.
5. Goodman, A. J.; Stanforth, P. S.; Tarbit, B. *Tetrahedron* **1999**, *55*, 15067.
6. Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125.
7. General procedure: To a stirred solution of 4,6-dichloropyrimidine (2 g, 13.4 mmol) in anhydrous methanol (20 mL) at room temperature was added a solution of NaOMe (3.1 mL, 25 w/w, 13.4 mmol). The sodium chloride precipitate was formed immediately. The resulting white suspension was refluxed for 30 min. After cooling down to room temperature, the reaction mixture was concentrated and diluted with ether and filtered through a Celite® pad. The filtrate was concentrated to give a white solid (1.8 g, 93%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.54 (s, 1H), 6.73 (s, 1H), 3.96 (s, 3H); LC–MS *m/z* [M^++1] 144.9.
8. Shepherd, R. G.; Taft, W. E.; Krazinski, H. M. *J. Org. Chem.* **1961**, *26*, 2764.
9. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Cooke, G.; Cremiers, H. A.; Rotello, V. M.; Tarbit, B.; Vanderstraeten, P. E. *Tetrahedron* **2001**, *57*, 2787; (c) Qing, F.-L.; Wang, R.; Li, B.; Zheng, X.; Meng, W.-D. *J. Fluro. Chem.* **2003**, *120*, 21.
10. General procedure: To a stirred solution of 4-chloro-6-methoxypyrimidine (0.94 g, 6.5 mmol) in *n*-PrOH (20 mL) at room temperature was added phenylboronic acid (1.1 g, 9.1 mmol), $Pd(PPh_3)_4$ (0.75 g, 0.65 mmol), and aqueous Na_2CO_3 (9.75 mL, 2 N, 19.5 mmol). The resulting dark suspension was stirred at 90 °C for 14 h. After cooling down to room temperature, the reaction mixture was concentrated and diluted with ethyl acetate and filtered through a Celite® pad. The filtrate was washed with

saturated $NaHCO_3$ aqueous and brine. The organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the product was purified via silica gel chromatography as a white solid (1.2 g, 90%) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.83 (s, 1H), 8.00 (dd, $J = 7$, 3.5 Hz, 2H), 7.47 (t, J = 4 Hz, 3H), 7.09 (s, 1H), 4.02 (s, 3H); LC–MS m/z [M^++1] 186.9.

11. General procedure: To a stirred solution of 4-methoxy-6-(*p*-methoxyphenyl)pyrimidine (150 mg, 0.69 mmol) in acetic acid (1.5 mL) was added HBr (0.5 mL). The resulting solution was stirred at 85 °C for 1 h. After cooling down to room temperature, the solvent was removed under reduced pressure. The residue was taken by ethyl acetate and washed with saturated $NaHCO_3$ aqueous and brine. After filtration and concentration, the product was dried under reduced pressure (132 mg, 94%). Dry pyrimidone was then dissolved in $POCl_3$, and the reaction mixture was stirred at 100 °C for 30 min. After cooling down to room temperature, the solvent was removed under reduced pressure. The residue was taken by ethyl acetate and washed with saturated $NaHCO_3$ aqueous and brine. After filtration and concentration, the product was dried under reduced pressure to give a white solid (136 mg, 95%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.94 (s, 1H), 8.04 (dd, $J = 6.5$, 1.5 Hz, 2H), 7.65 (s, 1H), 7.00 (dd, $J = 7.0$, 2.0 Hz, 2H), 3.87 (s, 3H); LC–MS m/z [M^++1] 220.9.