Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7363–7365

A mild and general method for the synthesis of 2-substituted-5-hydroxypyrimidines

Jesus R. Medina,* Theresa A. Henry and Jeffrey M. Axten

Microbial, Musculoskeletal and Proliferative Diseases Center of Excellence in Drug Discovery, GlaxoSmithKline, Collegeville, PA 19426, USA

Received 6 March 2006; accepted 4 August 2006
Available online 24 August 2006

Abstract—5-Bromopyrimidines are converted to 5-hydroxypyrimidines using a mild synthetic procedure. The method is general and can be applied to compounds containing functional groups which are not compatible with the other reagents previously available for this conversion.

1. Introduction

Historically, pyrimidine-containing compounds have been of considerable interest in the field of medicinal chemistry. Specifically, drugs containing a pyrimidine with an oxygen in the 5-position have found a wide range of applications in several therapeutic areas. Examples include the antibiotic sulfamethoxydiazine (**1**),[1] the antidiabetic Glycanol (**2**),[2] and the antifungal rimoprogin (**3**)[3] (Fig. 1). Although there are several methods available to prepare 5-hydroxypyrimidines, the overall synthetic route to the substituted pyrimidine core can be long and tedious with a poor overall yield. Common methods for the synthesis of 5-hydroxypyrimidines utilize the condensation/cyclization of a suitably substituted nitrogen-containing intermediate, high temperature alkoxide displacement of a 5-bromopyrimidine,[4] diazotization/hydrolysis of a 5-aminopyrimidine,[5] or the Elbs persulfate oxidation.[6] In the case of the more popular methods it is often necessary to remove an O-protecting group by hydrogenolysis or hydrolysis,[6] which typically requires the use of strongly acidic reagents such as BBr_3,[7] HBr in acetic acid,[8] or $AlCl_3$,[9] limiting the amount of functionality tolerated in the targeted molecules. As part of a medicinal chemistry research program, we sought a mild and practical method for the synthesis of 5-hydroxypyrimidines with potentially wide scope and applicability.

A practical and attractive approach to the synthesis of 5-hydroxypyrimidines applies the reaction of a 5-metallopyrimidine with a trialkylborate followed by oxidation

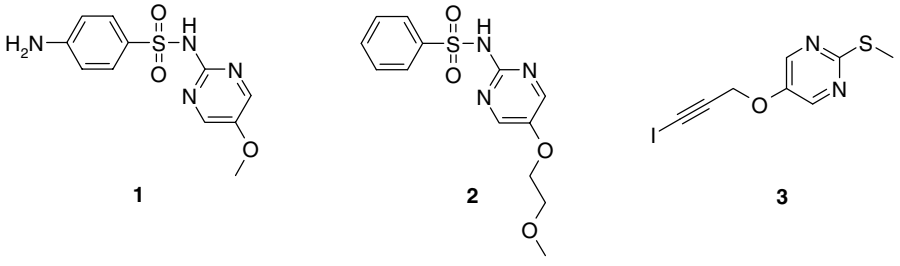


Figure 1.

Keywords: 5-Hydroxypyrimidine; 5-Bromopyrimidine; Bis-(pinacolato)diboron; Sodium perborate.
* Corresponding author. Tel.: +1 610 917 5889; fax: +1 610 917 6020; e-mail: jesus.r.medina@gsk.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.018

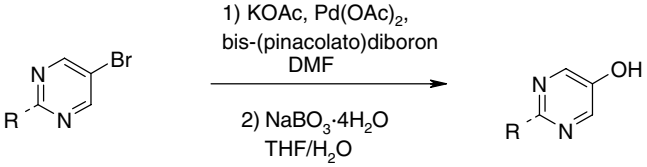
of the resulting boronic ester with 30% aqueous hydrogen peroxide under basic conditions.[10,11] However, this approach is not suitable for the synthesis of compounds with functionality incompatible with organolithium reagents, Grignard reagents, and/or the alkaline nature of the standard oxidation conditions.

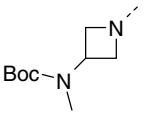
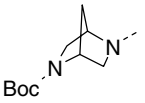
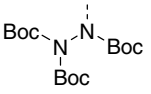
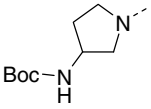
It occurred to us that the Pd catalyzed cross-coupling reaction of bis-(pinacolato)diboron with arylhalides, first reported by Miyaura and co-workers[12] and subsequently modified by Zhang and co-workers,[13] could be a mild and convenient method for the synthesis of 5-pyrimidyl boronic esters. In addition, the use of sodium perborate as the oxidizing agent is a viable alternative to the standard hydrogen peroxide/NaOH oxidation procedure. Since the reagent is mildly basic (pH $\sim$ 9.5), the addition of external base such as sodium hydroxide is not required.[14] Therefore, the synthesis of 2-substituted-5-hydroxypyrimidines with acid or base sensitive functionality can be accomplished from the respective 2-substituted-5-bromopyrimidines under very mild reaction conditions.

2-Substituted-5-bromopyrimidines were prepared from commercially available 2-chloro-5-bromopyrimidine by chloride displacement with the corresponding amines or thiols. Following the method of Zhang and co-workers, the 5-bromopyrimidines were subjected to a Miyaura-type aryl boronate synthesis. After isolation of the boronic esters, reaction of the crude product with sodium perborate using the method of Kabalka et al.[14] afforded the desired 5-hydroxypyrimidines in good to excellent yields (Table 1). Arylbromides having electron-donating groups, such as amines, usually couple poorly with the diboron reagent under the reaction conditions.[13] In contrast, because pyrimidine ring systems are electron poor relative to their benzene analogs, the coupling works efficiently even in the presence of dialkylamines in the 2-position of the pyrimidine ring. Occasionally, the pyrimidylboronate products were accompanied by a significant amount of the symmetric biaryls in the reaction mixture (Table 1, entries 3 and 4), demonstrating the propensity of these pyrimidylboronic esters to undergo Suzuki coupling under these mild reaction conditions. Increasing the amount of bis-(pinacolato)diboron to 3 equiv relative to the starting bromide minimizes the biaryl formation. The presence of relatively acidic protons was not tolerated in our systems, as observed in example 5 (Table 1) in which a significant amount of reduction by-product (42%) was obtained.

In conclusion, we have shown that the synthesis of 5-hydroxypyrimidines can be accomplished through the combination of the Pd catalyzed cross-coupling reaction of bis-(pinacolato)diboron with 5-bromopyrimidines followed by sodium perborate oxidation. It is a mild and practical method that avoids the use of strong acids or bases while providing the desired products in good yields. We believe, this methodology could be applied to other heterocyclic systems, especially those possessing functionalities which are incompatible with metal/halogen exchange processes.[15]

Table 1.



Entry	Structure (R=)	Yield[a] (%)
1		70
2		48
3[b,e]		96
4[e]		62
5		33[c]
6		48
7		61[d]

[a] Un-optimized; isolated yields.
[b] This compound was not made by chloride displacement; instead it was made by di-protecting the commercially available 2-amino-5-bromopyrimidine.
[c] The starting material was recovered in 13% yield and the corresponding product where the starting bromide had been reduced to H was obtained in 42% yield.
[d] The starting material was recovered in 31% yield.
[e] 3 equiv of bis-(pinacolato)diboron reagent were required.

2. Representative procedure (Table 1, entry 1)

(1,1-Dimethylethyl) [1-(5-bromo-2-pyrimidinyl)-3-azetidinyl]methylcarbamate (94 mg, 0.27 mmol), bis-(pinacolato)diboron (77 mg, 0.30 mmol), potassium acetate (81 mg, 0.82 mmol), and palladium acetate (2 mg, 0.003 mmol) were combined in a single necked round bottomed flask sealed with a rubber septum. The flask was flushed with nitrogen gas for 15 min. DMF (1 mL) was added and the reaction mixture was heated to 85 °C overnight. The dark suspension was diluted with water and extracted (3×) with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, concentrated, and further dried in vacuo. The dark oil was dissolved in THF (2 mL) and water (2 mL). Sodium perborate tetrahydrate (105 mg, 0.69 mmol) was added and the reaction mixture was stirred overnight. Saturated aqueous ammonium chloride solution was added and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with

water and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel column chromatography using a gradient of 30–50% ethyl acetate in chloroform afforded the desired product as a solid (54 mg, 70% yield). ^1H (400 MHz, $CDCl_3$): δ 8.13 (s, 2H), 4.7–5.2 (br s, 1H), 4.32 (m, 2H), 4.14 (dd, $J = 9.5$, 5.7 Hz, 2H), 2.96 (s, 3H), 1.47 (s, 9H). MS (ES) *m/e* 281 $(M+H)^+$.

References and notes

1. Brown, D. J. In *Comprehensive Heterocyclic Chemistry*; Katritzsky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 150.
2. Priewe, H.; Gutsche, K. U.S. Patent 19650729, 1966.
3. Budeschinsky, Z.; Janata, V.; Schvab, A.; Bruna, L.; Tschapek, A.; Schimek, A. DE Patent 2259784 19730628, 1973.
4. Korobeinicheva, I. K.; Sedova, V. F.; Gashev, S. B.; Smirnov, L. D.; Yagodina, O. V.; Mamaev, V. P. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1989**, *8*, 913.
5. Brown, D. J. *The Pyrimidines*; Wiley Interscience: New York, 1962.
6. Hurst, D. T. *Aust. J. Chem.* **1983**, *36*, 1285.
7. Barraclough, P.; Black, J. W.; Cambridge, D.; Capon, E.; Cox, M. R., et al. *Eur. J. Med. Chem. Chim. Ther.* **1992**, *27*, 207.
8. Albrecht, R.; Schroeder, E. *Eur. J. Med. Chem. Chim. Ther.* **1975**, *10*, 595.
9. Budesinsky, Z.; Bruna, L. CS Patent 184103, 1980.
10. Goodby, J. W.; Hird, M.; Lewis, R. A.; Toyne, K. J. *J. Chem. Soc., Chem. Commun.* **1996**, *24*, 2719.
11. Matondo, H.; Ouhaja, N.; Souirti, S.; Baboulene, M. *Main Group Met. Chem.* **2002**, *25*, 163.
12. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
13. Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729.
14. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.
15. For example, we have used this methodology on the nitropyridine shown below.