Palladium Catalyzed Bispyrimidine Thioether Synthesis

Molly S. Harr, Alice L. Presley, Atli Thorarensen*

Medicinal Chemistry I, Pharmacia and Upjohn, 301 Henrietta Street, Kalamazoo, MI 49001, USA
Fax (616)-833-2232; E-mail: atli.thorarensen@am.pnu.com
Received 18 July 1999

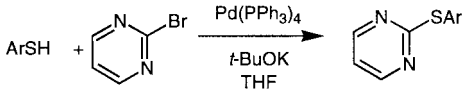
Abstract: The synthesis of sulfur-bridged bispyrimidines via coupling of a halopyrimidine and pyrimidine thiolate anion has been explored utilizing a palladium catalyzed cross coupling reaction. Several reaction parameters including stoichiometry and choice of solvent have been optimized. These reaction conditions have allowed for the preparation of a wide range of functionalized bispyrimidines.

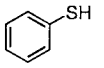
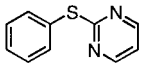
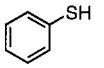
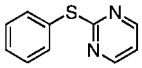
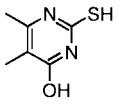
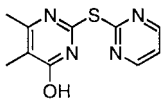
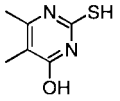
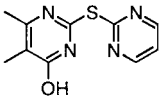
Key words: catalysis, palladium, pyrimidines, thioethers

Palladium catalyzed carbon-sulfur bond formation is of synthetic interest, but relatively unexplored in the literature.[1] The reactivity of thiols is in most instances sufficient to achieve the direct replacement of a halide or a triflate without catalysis, resulting in formation of an arylsulfur bond. Recently we had the need to prepare several unsymmetrical bispyrimidine thioethers to evaluate the effect on antibacterial activity when a nitrogen linker was replaced with a sulfur linkage.[2] The synthesis of bispyrimidine thioethers has been accomplished previously through direct nucleophilic attack of a thiolate anion on a pyrimidine halide, though in low yield.[3,4,5] In our case, the direct displacement reaction failed to afford any of the desired product. Alternatively the synthesis of unsymmetrical bispyrimidine thioethers could involve the intermediate of a substituted thioamidate, followed by cyclization with a ketoester. The lability of thioamidates towards hydrolysis encouraged us to pursue an alternative strategy.[6,7] Reports describing palladium catalyzed bisaryl thioether synthesis from less activated thiols utilizing $Pd(PPh_3)_4$[8,9] or prepared palladium aryl halide complexes, attracted our attention.[10,11] However, the analogous bispyrimidine thioether synthesis has not been investigated and poses a synthetic challenge due to the unreactivity of the reaction partners and the potential multiple coordination of either the substrate or the product to the catalytic metal resulting in inhibition of catalysis. This report details our successful synthesis of unsymmetrical bispyrimidine thioethers utilizing a variation of the Migita palladium catalyzed thioether preparation. In addition, we report our subsequent efforts to explore the scope and utility of this reaction.

In an attempt to understand the need for palladium catalysis as well as the required degree of reactivity of each reaction partner in the coupling reaction, 2-bromopyrimidine was reacted with thiophenol in the presence of potassium *t*-butoxide (Table 1). After workup, a 44% yield of the desired thioether was isolated. Next, the bromopyrimidine was reacted with thiophenol and base along with 0.1 equivalents of palladium ($Pd(PPh_3)_4$), producing a comparable 48% yield of the desired thioether. In a related sequence, 4-hydroxy-5,6-dimethylpyrimidine-2-thiol was reacted with 2-bromopyrimidine and base in the presence and absence of palladium catalysis. In this case, only the palladium catalyzed reaction afforded any of the desired bispyrimidine thioether. In addition when *t*-BuOK was replaced with K_2CO_3 and the reaction was performed in the presence of palladium the desired product could not be detected. Therefore, it appears that with very unreactive thiol nucleophiles, such as the 2-thiopyrimidine, strong base and palladium catalysis is essential. In contrast, there are limited benefits to the addition of palladium in the case of a thiol with sufficient nucleophilicity, such as thiophenol.

Table 1 The effects of nucleophilic strength and the influence of palladium on yield.[12]

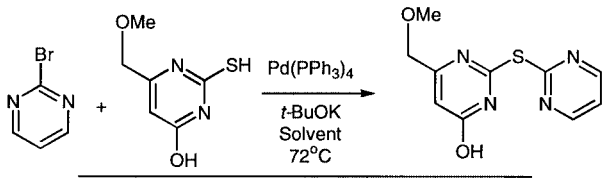


Nucleophile	Palladium %mol	Product	Yield (%)
	10		48
	0		44
	10		88
	0		0

Since the reaction conditions can have a dramatic effect on reaction efficiency, we decided to explore the effect of different solvent systems in an attempt to improve the solubility of both coupling partners. The more readily available 6-hydroxy-4-methoxymethyl-pyrimidine-2-thiol was utilized as the model nucleophile in the coupling reaction (Table 2). Although polar solvents such as DMSO and ethanol afforded homogeneous mixtures and were the sol-

vent systems of choice in Migita's initial report, we generally found that the reaction proceeded more cleanly and afforded a better yield in THF.[13] The use of DMF as a co-solvent had a detrimental effect upon the yield of the reaction. Although the reaction in THF was heterogeneous and resulted in variable yields, dilution of the reaction to 0.05 M in THF and the use of efficient stirring proved beneficial.

Table 2 Solvent effect on the reaction.



Solvent	Nucleophile (equiv)	Halide (equiv)	Yield (%)
THF	1.0	1.0	66
5/1 THF, DMF	1.0	1.0	49
2/1 THF, DMF	1.0	1.0	37
DMSO	1.0	1.4	26
EtOH	1.0	1.4	43

In several instances it was observed that the bromide appeared to be consumed while some of the starting thiol was still available. In an attempt to improve the coupling yield, bromide stoichiometry was explored. In both cases tested, higher yields were observed when an excess of 2-bromopyrimidine was utilized in the reaction (Table 3).

The reaction was found to tolerate several different thiol nucleophiles, and in general the desired product was isolated in moderate to good yields (Table 4).[14] In general, unprotected 4-hydroxy thiols were excellent substrates, affording the desired product without the necessity of hydroxyl protection. As the insolubility of the nucleophile became a problem, the reaction afforded only moderate yields. The reaction was not limited to only 2-bromopyrimidine, as other halides such as 2-bromo-4-methyl quinazoline work equally well.

In summary, the unsymmetrical thioether bispyrimidine coupling reaction is performed optimally in THF as the solvent and palladium catalysis is essential. The yield in the reaction can be improved by utilizing excess halide, and a number of complex unprotected nucleophiles are well tolerated under the reaction conditions.

Acknowledgement

We thank Dr. Joel Morris for critical evaluation of this manuscript.

Table 3 Effect of halide stoichiometry.

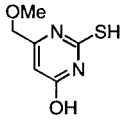
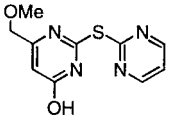
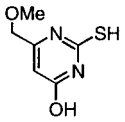
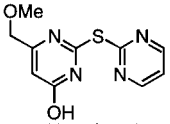
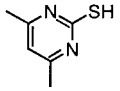
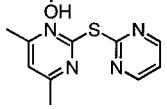
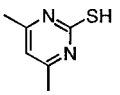
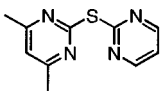
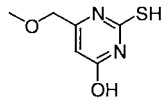
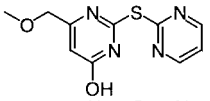
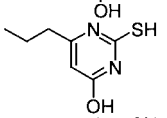
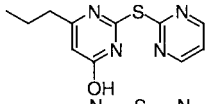
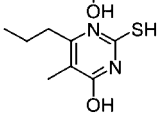
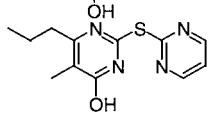
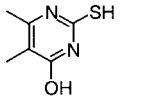
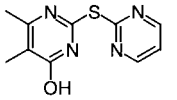
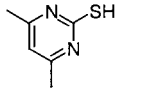
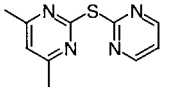
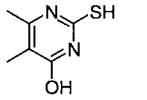
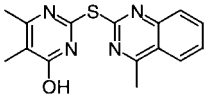
Thiol	Thiol (equiv)	Halide (equiv)	Product	Yield (%)
	1.0	1.0		65
	1.0	1.4		72
	1.0	1.0		38
	1.0	1.4		58

Table 4 Different thiol nucleophiles employed.[12]

Thiol	Halide equiv.[i, ii]	Product	Yield (%)
	A/1.4		72
	A/1.1		69
	A/1.0		72
	A/1.0		88
	A/1.4		58
	B/1.0		60

i) A = 2-Bromopyrimidine; B = 2-Bromo-4-methylquinazoline.
ii) optimized stoichiometry

References and Notes

(1) Review on transition metal catalyzed sulfur-carbon formation. Baranano, D.; Mann, G.; Hartwig, J. F. *Current Org. Chem.* **1997**, *1*, 287.
(2) Brown, J. P. *British Patent* 1 024 908, 1966.
(3) Jamoulle, J.C.; Lapiere, Ch.L.; Bassleer, R.; Heinen, E.; Selak, Z.; De Paermentier, F.; Lhoest-Gauthier, M.P.; Lepoint, A.; Renard, A. *Fr. Ann. Pharm. Fr.* **1980**, *38*, 267.
(4) Benneche, T.; Gacek, M.J.; Undheim, J. *U.S. Patent* 4 423 047, 1983.

(5) Delarge, J.; Thunus, L.; Beckers, C.; Ghys, A.; Denef, J.; Jamoulle, J.-C. *Eur. J. Med. Chem.* **1984**, *19*, 559.
(6) Albert, A.; Barlin, G. B. *J. Chem. Soc.* **1962**, 3129.
(7) Presley, A. L.; Thorarensen, A. unpublished results.
(8) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13.
(9) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385.
(10) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937.
(11) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A.L.; Guzei, I.A. *J. Am. Chem. Soc.* **1998**, *120*, 9205.
(12) The reactions were performed on 1 mmolar scale and all compounds have been characterized by ^{1}H NMR, ^{13}C NMR, IR MS along with satisfactory elemental analysis.
(13) A recent report has disclosed the use of THF as cosolvent for the Pd catalyzed reaction. Rane, A. M.; Miranda, E. I.; Soderquist J. A. *Tetrahedron Lett.* **1994**, *35*, 3225.
(14) General Procedure: Note: extremely air sensitive reaction. In a one-neck round bottom flask place 2-thiopyrimidine (1.0 equiv), 2-bromopyrimidine (1.4 equiv), potassium *tert*-butoxide (1.0 equiv), and $Pd(PPh_3)_4$ (0.10 equiv, Strem). After vacuum purging and refilling with argon (3X) add THF (distilled, Na, benzophenone) to a concentration of 0.05 M. Stir at reflux with a large stir-bar for 12 h or until complete by TLC. Workup: Absorb the crude reaction mixture directly onto silica gel and purify by silica gel chromatography, eluting with either EtOAc-heptane or CH_2Cl_2-methanol.

Article Identifier:
1437-2096,E;1999,0,10,1579,1581,ftx,en;S02499ST.pdf