ORGANIC LETTERS

2003
Vol. 5, No. 25
4779−4782

Siloxane-Based Cross-Coupling of Bromopyridine Derivatives: Studies for the Synthesis of Streptonigrin and Lavendamycin

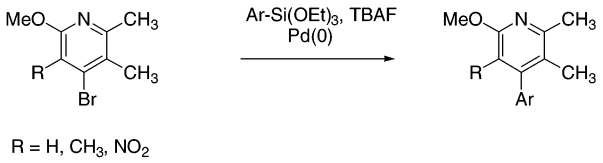
William T. McElroy and Philip DeShong*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742

deshong@umd.edu

Received September 11, 2003

ABSTRACT

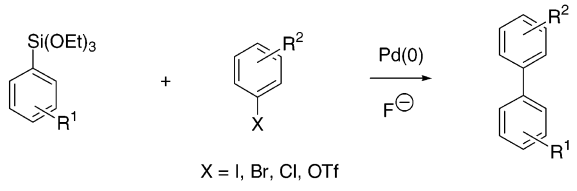


Highly functionalized 4-bromopyridines were prepared and found to undergo fluoride-promoted, Pd-catalyzed cross-coupling with aryltrialkoxysilanes to give sterically demanding biaryls. The 3-nitro-4-bromopyridine derivative coupled in good yield with TBAT (tetrabutylammonium triphenyldifluorosilicate) to provide a biaryl adduct that serves as a model system for the total synthesis of the antitumor antibiotics streptonigrin and lavendamycin.

Palladium-catalyzed coupling reactions continue to be widely employed to form carbon−carbon bonds.[1] In particular, the Stille[2] (organostannane) and Suzuki−Miyaura[3] (organoborane) reactions have been exploited to form unsymmetrical biaryls in the syntheses of numerous natural products.[4] Each of these approaches has its strengths and limitations with regard to the cross-coupling reaction.

Our laboratory has recently demonstrated that hypervalent fluorosilicate derivatives can be employed as substrates in palladium-catalyzed cross-coupling reactions with aryl halides and triflates, respectively (Scheme 1). Either aryl siloxanes or preformed aryl fluorosilicates (i.e., TBAT) can be utilized in the coupling process.[5,6] A goal of our studies has been to determine the scope and limitations of the siloxane method. In this context, we chose to synthesize the antitumor antibiotics streptonigrin[7,8] (**1**) and lavendamycin[9,10]

Scheme 1



(1) (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (b) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995.

(2) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.

(3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

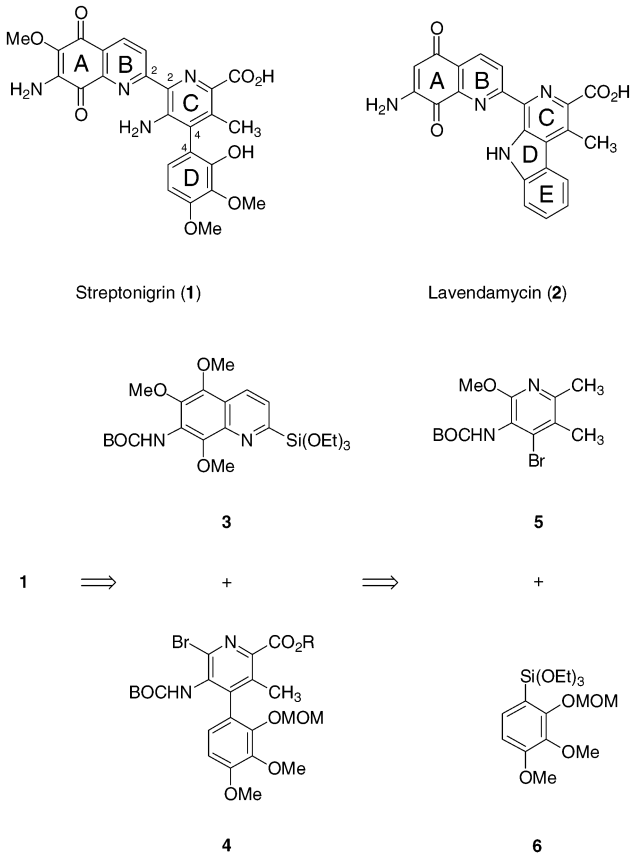
(4) For some recent examples, see: (a) Inoue, M.; Sakazaki, H.; Furuyama, H.; Hirama, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2654−2637. (b) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. *J. Am. Chem. Soc.* **2003**, *125*, 8238−8243.

(5) (a) Correia, R.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7159−7165. (b) DeShong, P.; Handy, C. J.; Mowery, M. E. *Pure Appl. Chem.* **2000**, *72*, 1655−1658. (c) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137−2140. (d) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266−3270. (e) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688.

(6) For some recent advances in the Pd-catalyzed coupling reactions of organosilanes, see: (a) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357−1360. (b) Denmark, S. E.; Pan, W. *Org. Lett.* **2003**, *5*, 1119−1122. (c) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61−85. (d) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771−3774. (e) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531−1541.

10.1021/ol0357503 CCC: $25.00
Published on Web 11/11/2003

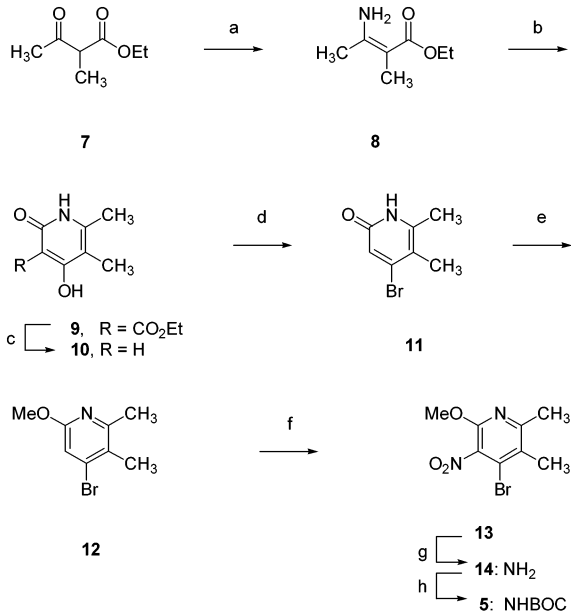
Scheme 2



(**2**) using the siloxane coupling as the key reaction in the approach (see Scheme 2). A particularly challenging feature of this approach to the synthesis of streptonigrin is the sequential coupling of the ring AB and D components to a fully substituted pyridine component (ring C).[11] The coupling at carbon-4 of the pyridine ring (C-4) to carbon-4 (D-4) of the D-ring phenyl group will be challenging since it will result in formation of a highly hindered biaryl derivative. Similarly, the B-2/C-2 coupling of the quinoline ring to the pyridine will require development of new methods for the synthesis of heteroaromatic silicon-based coupling reagents. Previous studies by Godard and Quéguiner have investigated an analogous biaryl coupling strategy employing stannane and boronic acids, and we hoped to overcome some of the limitations that they encountered using siloxane derivatives. In this paper, we describe studies directed to the synthesis of pyridine **5** and related compounds that establish the viability of the C-4/D-4 coupling strategy.

Bromopyridines **5** and **11**−**14** were prepared as summarized in Scheme 3. Ethyl-2-methylacetoacetate (**7**) was converted to its enamine **8** upon reaction with NH_4OH. Condensation under basic conditions with diethylmalonate afforded pyridone **9**.[12] Hydrolysis of the ethyl ester and subsequent decarboxylation gave **10** in high overall yield.

Scheme 3[a]



[a] Conditions: (a) NH_4OH, Bentonite K-10, 93%; (b) $CH_2(CO_2Et)_2$, NaOEt, EtOH, $PhCH_3$, reflux, 69%; (c) NaOH then HCl, 99%; (d) $POBr_3$, DMF, 110 °C; (e) MeI, Ag_2CO_3, PhH, 30% from **10**; (f) HNO_3, H_2SO_4, 97%; (g) Fe, EtOH, H_2O, cat. HCl, 65%; (h) BOC_2O, cat. DMAP, THF, reflux, then K_2CO_3, MeOH, 52%.

(7) (a) Rao, K. V. Cullen, W. P. *Antibiot. Annu.* **1959**−**1960**, 950−953. (b) Rao, K. V.; Biemann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2532−2533.

(8) Three total syntheses of streptonigrin have been reported: (a) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *J. Am. Chem. Soc.* **1982**, *104*, 536−544. (b) Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271−1273. Boger, D. L.; Panek J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745−5754.

(9) Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiot.* **1982**, *35*, 259−265. (b) Doyle, T. W.; Balitz, D. M.; Grulich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C.-H.; Moews, A. E. *Tetrahedron Lett.* **1981**, *22*, 4595−4598.

(10) For total syntheses of lavendamycin, see: (a) Behforouz, M.; Haddad, J.; Cai, W.; Arnold, M. B.; Mohammadi, F.; Sousa, A. C.; Horn, M. A. *J. Org. Chem.* **1996**, *61*, 6552−6555. (b) Molina, P.; Murcia, F.; Fresneda, P. M. *Tetrahedron Lett.* **1994**, *35*, 1453−1456. (c) Behforouz, M.; Gu, Z.; Cai, W.; Horn. M. A.; Ahmadian, M. *J. Org. Chem.* **1993**, *58*, 7089−7091. (d) Ciufolini, M. A.; Bishop, M. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1463−1464. (e) Rama Rao, A. V.; Chavan, S. P.; Sivadasan, L. *Tetrahedron* **1986**, *42*, 5065−5071. (f) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790−5795. (g) Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261−264. (h) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *25*, 923−926.

(11) For examples of Pd-catalyzed couplings to form streponigrin analogues, see: (a) Pomel, V.; Rovera, J. C.; Godard, A.; Marsais, F.; Quéquiner, G. *J. Heterocycl. Chem.* **1996**, *33*, 1995−2005. (b) Godard, A.; Rocca, P.; Pomel, V.; Thomas-dit-Dumont, L.; Rovera, J. C.; Thaburet, J. F.; Marsais, F.; Quéquiner, G. *J. Organomet. Chem.* **1996**, *517*, 25−36. (c) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner, G. *Heterocycles* **1995**, *40* 1055−1091. (d) Godard, A.; Fourquez, J. M.; Tamion, R.; Marsais, F.; Quéguiner, G. *Synlett* **1994**, 235−236. (e) Godard, A.; Rocca, P.; Fourquez, J.-M.; Rovera, J.-C.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1993**, *34*, 7919−7922. (f) Godard, A.; Rovera, J.-C.; Marsais, F.; Plé, N.; Quéguiner, G. *Tetrahedron* **1992**, *48*, 4123−4134. (g) Marsais, F.; Rovera, J.-C.; Turck, A.; Godard, A.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2611−2612. (h) Crous, R.; Dwyer, C.; Holzapfel, C. W. *Heterocycles* **1999**, *51*, 721−726. (i) Kimber, M.; Anderberg, P. I.; Harding, M. M. *Tetrahedron* **2000**, *56*, 3575−3581. (j) Fryatt, T.; Goroski, D. T. Nilson, Z. D.; Moody, C. J.; Beall, H. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2195−2198.

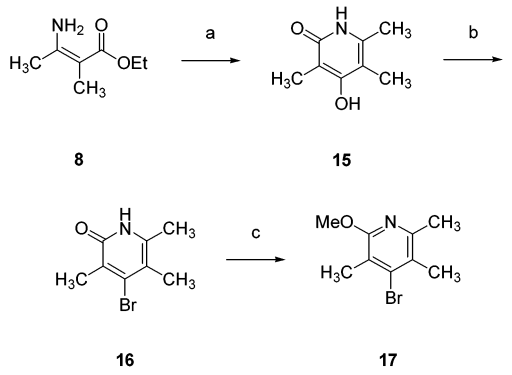
(12) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby. J. F. *J. Org. Chem.* **1981**, *46*, 3040−3048.

Replacement of the hydroxyl group with bromine at C-4 proved to be difficult as a result of competitive bromination at C-2. After surveying a variety of brominating agents and conditions, it was found that bromide **11** could be obtained readily by reaction of hydroxypyridone **10** with 0.70 equiv of $POBr_3$ in DMF.

Attempts to couple bromopyridone **11** with siloxane derivatives using standard coupling protocols failed. It was believed that the high acidity of the N−H proton was interfering with the coupling reaction. Thus, pyridone **11** was O-methylated under standard conditions to afford 2-methoxypyridine **12**.[13] The nitrogen functionality at C-3 required for the synthesis of streptonigrin was introduced by treatment of **12** with HNO_3 to generate nitropyridine **13**. This compound could be subsequently transformed to its amino derivative **14** and BOC-protected amine **5** by standard technology.

Trimethylated pyridine **17** was synthesized to provide an *ortho*,*ortho*′-disubstituted substrate that could be employed to assess the steric limitations of the coupling reaction. Comparison of the couplings of pyridine **17** with pyridines **5** and **12**−**14** should provide information regarding both steric and electronic effects in this system. In a fashion analogous to the synthesis of pyridine **12**, trimethyl pyridine **17** was prepared as depicted in Scheme 4. Condensation of

Scheme 4[a]

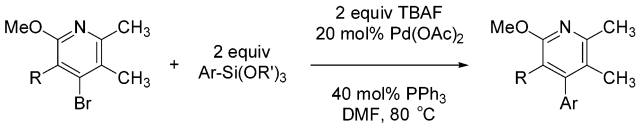


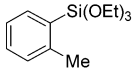
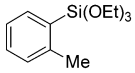
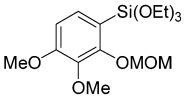
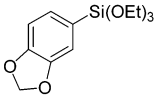
[a] Conditions: (a) $CH_3CH(CO_2Et)_2$, NaOEt, EtOH, $PhCH_3$, reflux, 69%; (b) $POBr_3$, 110 °C, 60%; (c) MeI, Ag_2CO_3, PhH, 45 °C, quant.

amino ester **8** with diethyl methylmalonate gave pyridone **15**, which upon heating with neat $POBr_3$ produced bromopyridone **16**[14] in good yield. Finally, treatment with methyl iodide yielded 2-methoxypyridine **17**.

A major concern of the outlined approach was the steric tolerance of the coupling reaction. This matter was probed using a series of 4-bromopyridine derivatives, and the results are summarized in the Table. 3-*H*-4-Bromopyridine **12** was chosen as the initial substrate as it is the least sterically hindered of the bromopyridines. At a typical (10 mol %) catalyst loading, pyridine **12** coupled with phenyltrimethoxysilane in 62% yield. Increasing the catalyst loading from 10 to 20 mol % led to an increase in yield to 97%. To ascertain if more sterically congested systems could be prepared in a similar manner, bromopyridine **12** was coupled with *o*-tolyl siloxane (entry 2); however, the expected biaryl was obtained in only 10% yield. Increasing the catalyst loadings as high as 50 mol % resulted in no improvement in yield. The low yield in the coupling of the *o*-tolyl siloxane was surprising because previously it had been shown that this siloxane efficiently coupled to a variety of aryl halides.

Table 1. Cross-Couplings of 4-Bromopyridines with Siloxanes



entry	R	ArSi (OR')$_3$	yield (%)
1	H	$Ph(SiOMe)_3$	97
2	H		10[a]
3	Me	$Ph(SiOMe)_3$	89
4	Me		10[a]
5	Me		0
6	Me		61
7	NO_2	$Ph(SiOMe)_3$	36[b]
8	NH_2	$Ph(SiOMe)_3$	0
9	NHBOC	$Ph(SiOMe)_3$	0

[a] No improvement of yield was obtained with higher catalyst loadings. [b] 36% reduced pyridine was also obtained (see Scheme 5).

To determine if biaryls possessing two methyl groups in *ortho* positions to the biaryl bond could be prepared, 3,5-dimethyl-4-bromopyridine **17** was allowed to react with $PhSi(OMe)_3$. Gratifyingly, the coupled product was isolated in 89% yield (entry 3). Therefore, the reaction is tolerant of the *ortho*,*ortho*′ substitution pattern present in the bromopyridine. Given that 20 mol % catalyst was necessary for maximum yields, subsequent reactions were performed at this catalyst loading. As expected on the basis of the results above, bromopyridine **17** gave a low yield of biaryl product on reaction with *o*-tolyl siloxane (entry 4).

Couplings of more highly functionalized siloxane derivatives were investigated employing bromopyridine **17**. The trisubstituted siloxane corresponding to the intact D ring of

(13) Shiao, M.-J.; Tarng, K.-Y. *Heterocycles* **1990**, *31*, 819−824.
(14) Mittelbach, M.; Schmidt, H.-W.; Uray, G.; Junek, H.; Lamm, B.; Ankner, K.; Brändström, A.; Simonsson, R. *Acta Chem. Scand. B* **1988**, *42*, 524−529.

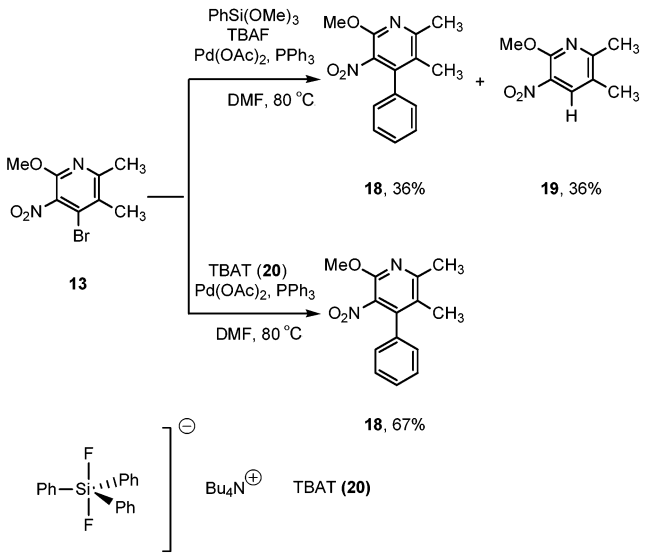
streptonigrin was subjected to the coupling conditions, but no biaryl product was obtained (entry 5). Instead protodesilylated siloxane was recovered quantitatively. These results are consistent with previous observations that siloxanes with heteratoms in the *ortho* position rapidly underwent protodesilylation under the reaction conditions. On the other hand, 3,4-methylenedioxy-substituted siloxane (entry 6) underwent coupling in good yield with **17**, indicating that electron-rich biaryls can be prepared using this technology, provided the siloxane does not possess a heteroatom in the *ortho* position.

Streptonigrin and lavendamycin possess an amino function at C-3 rather than a methyl substituent, and bromopyridine substrates that had a (nascient) amino group in this position were investigated. Nitropyridine **13** (R = NO_2) and bromopyridine **17** (R = Me) have approximately the same steric environment, and it was anticipated that the nitro analogue would give the adduct with efficiency comparable to its methyl counterpart. Coupling of nitropyridine **13** with PhSi(OMe)$_3$ provided the expected biaryl in 36% yield. An additional 36% of debrominated pyridine was isolated also. Since trimethylated bromopyridine **17** had coupled in excellent yield (entry 3), it is apparent that the lower yields obtained with the nitropyridine analogue were the result of electronic rather than steric factors. Reduction of the nitro group to the amino and urethane derivatives, followed by coupling with PhSi(OMe)$_3$ (entries 8 and 9) failed to give biaryl product. The results are comparable to those obtained by Godard and Quéguiner with boronic acid derivatives and indicate that electronic effects play a significant role in the oxidative addition step.[11]

Alternative silicon-based aryl transfer reagents were investigated in an effort to improve the yield of the coupling reactions with nitropyridine **13**. We had previously demonstrated that TBAT (tetrabutylammonium triphenyldifluorosilicate, **20**) was capable of phenyl transfer to a wide range of aryl halides and triflates.[15] We were pleased to find that TBAT underwent cross-coupling in good yield with bromopyridine **17** (Scheme 5). Notably, none of debrominated pyridine **19** was obtained under these conditions.

In conclusion, the scope of Pd-catalyzed siloxane couplings has been extended to include highly functionalized 4-bromopyridines. These studies have demonstrated that sterically demanding substrates can be employed in the coupling reaction but that electronic effects play a pivotal role in the coupling process for both the siloxane and pyridine substrates. Coupling of nitropyridine **13** is of particular interest to the synthesis of streptonigrin (**1**) and lavendamycin (**2**) since this substrate incorporates the requisite nitrogen functionality at C-3 found in ring C of the natural products. Studies directed at the synthesis of streptonigrin and lavendamycin are underway, and the results of these studies will be reported in due course.

Scheme 5



Acknowledgment. We thank the National Cancer Institute (CA-82169) for generous financial support. We also thank Dr. Yiu-Fai Lam (NMR) and Noel Whittaker (MS) for their assistance in obtaining spectral data. This manuscript is dedicated to Professor Duilio Arigoni on the occasion of his 75th birthday.

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

OL0357503

(15) Brescia, M.-R.; DeShong P. *J. Org. Chem.* **1998**, *63*, 3156−3157.