ORGANIC LETTERS

2009
Vol. 11, No. 16
3690−3693

Highly Efficient Borylation Suzuki Coupling Process for 4-Bromo-2-ketothiazoles: Straightforward Access to Micrococcinate and Saramycetate Esters

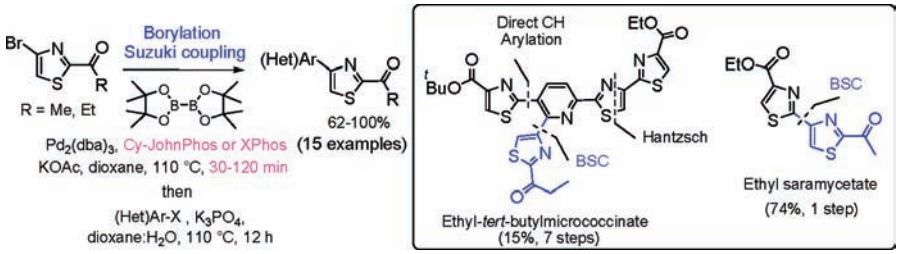
Thibaut Martin, Claire Laguerre, Christophe Hoarau,* and Francis Marsais

UMR 6014 COBRA, CNRS, INSA de Rouen et Université de Rouen, Institut de Chimie Organique Fine (IRCOF) INSA de Rouen, BP08, 76131 Mont Saint Aignan, France

christophe.hoarau@insa-rouen.fr

Received July 3, 2009

ABSTRACT



The first palladium-catalyzed borylation of 4-bromo-2-ketothiazoles followed by a Suzuki cross-coupling reaction with haloheteroaromatics using Buchwald's Cy-JohnPhos and XPhos ligands is reported. The methodology has allowed the fast preparation of highly valuable 4-pyridinyl- and 4-thiazolyl-2-ketothiazoles as common subunits of thiopeptide antibiotics. As direct applications, novel concise syntheses of a sulfomycinamate thio-analogue as well as micrococcinate and saramycetate esters are described.

Thiopeptide antibiotics are a class of highly modified sulfur-containing peptides with at least 77 structures from 29 distinct families.[1] Most of them inhibit protein synthesis through two main modes of action, by binding to the complex of 23S rRNA with ribosomal protein L11 or inhibiting the action of elongation factors Tu. The important *d* series of thiopeptides, exemplified by the first micrococcin P_1 isolated in 1948 from the city of Oxford, are characterized by two main blocks: a peptide chain, derived amino acid including modifications of many cysteine and serine units to thiazole-(line) and oxazole(line) rings and connected to a common complex di- or triazolylpyridine heterocyclic core. As a result of their important biological activity, many groups including Moody, Bagley, Bach, Nicolaou, Hashimoto-Nakata, and Ciufolini have been actively involved in the total synthesis of thiopeptides.[1a,b,2] One of the multiple synthetic challenges is the development of concise synthetic routes toward the complex heterocyclic cores (three main examples are de-

(1) For reviews: (a) Hughes, R. A.; Moody, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2–27. (b) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685–714. (c) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249–263. (d) Li, Y.-M.; Milne, J. C.; Madison, L. L.; Kolter, R.; Walsh, C. T. *Science* **1996**, *274*, 1188–1193. For recent reports on thiopeptide antibiotics, see: (e) Zhang, C.; Occi, J.; Masurekar, P.; Barrett, J. F.; Zink, D. L.; Smith, S.; Onishi, R.; Ha, S.; Salazar, O.; Genilloud, O.; Basilio, A.; Vicente, F.; Gill, C.; Hickey, E. J.; Dorso, K.; Motyl, M.; Singh, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 12102–12110. (f) Morris, R. P.; Leeds, J. A.; Naegeli, H. U.; Oberer, L.; Memmert, K.; Weber, E.; LaMarche, M. J.; Parker, C. N.; Burrer, N.; Esterow, S.; Hein, A. E.; Schmitt, E. K.; Krastel, P. *J. Am. Chem. Soc.* **2009**, *131*, 5946–5955.

(2) For recent total synthesis of thiopeptides, see: (a) Lefranc, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4198–4201. (b) Nicolaou, K. C.; Dethe, D. H.; Chen, D. Y.-K. *Chem. Commun.* **2008**, 2632–2634. (c) Nicolaou, K. C.; Dethe, D. H.; Leung, G. Y. C.; Zou, B.; Chen, D. Y.-K. *Chem. Asian J.* **2008**, *3*, 413–429. (d) Müller, H. M.; Delgado, O.; Bach, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4771–4774. (e) Delgado, O.; M̈; uller, H. M.; Bach, T. *Chem.—Eur. J.* **2008**, *14*, 2322–2339. (f) Mori, T.; Higashibayashi, S.; Goto, T.; Kohno, M.; Satouchi, Y.; Shinko, K.; Suzuki, K.; Suzuki, S.; Tohmiya, H.; Hashimoto, K.; Nakata, M. *Chem. Asian J.* **2008**, *3*, 1013–1025. (g) Merritt, E. A.; Bagley, M. C. *Synlett* **2007**, 954–958.

10.1021/ol901525t CCC: $40.75
Published on Web 07/22/2009

picted in Figure 1). An attractive approach would consist of direct interconnections of the heterocyclic subunits, mainly thiazole, pyridine, and sometimes oxazole, using heteroaryl−heteroaryl coupling reactions.

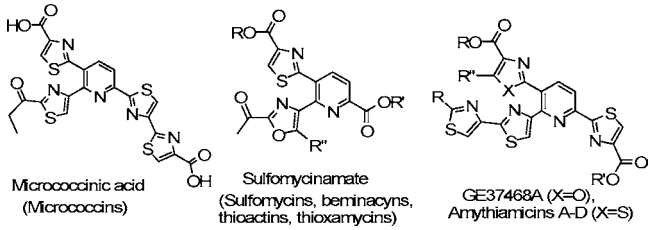
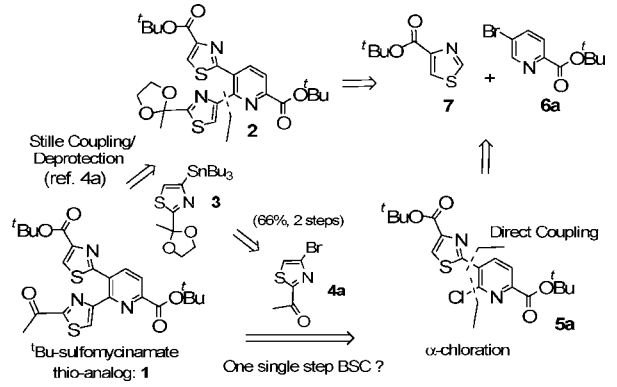


Figure 1. Three main common bi- or triazolylpyridine cores of *d* series thiopeptide antibiotics.

Such a strategy was initially explored by Kelly some 20 years ago[3a,b] and remained largely unexplored until the recent remarkable Bach synthesis of the GE2270A central core based upon a three-step sequence of cross-coupling reactions starting from 2,3,6-tribromopyridine, as reported in 2005.[3c] In this context, we have recently reported a palladium-catalyzed direct connection of the common oxazole and thiazole-4-carboxylate blocks to a central pyridine unit, thus avoiding the intermediary preparation of thiazolyl- or pyridinylmetals classically used in cross-coupling methodologies.[4] The method was directly applied to a neat synthesis of a *tert*-butyl sulfomycinamate thio-analogue through a three-step direct arylation, chlorination, and Stille cross-coupling sequence (Scheme 1). Following this work, we focused on a novel friendly protocol for the direct introduction of the 2-ketothiazole unit at position-4 to the central pyridine core. Indeed, the Stille cross-coupling methodology, currently employed for this last connection, requires prior preparation of the 4-stannyl intermediate **3** using a two-step keto-protection, transmetalation−stannylation protocol[4c] followed by a coupling step and a final hydrolysis as depicted in Scheme 1. Herein we report the borylation Suzuki coupling (BSC) of 4-bromo-2-ketothiazoles **4a,b** with 2-halopyridines to give direct access to 4-pyridinyl-2-ketothiazoles. These are common features of the heterocyclic cores of thiopeptide antibiotics. The methodology was directly applied to an innovative synthesis of the *tert*-butyl sulfomycinamate thio-analogue **1** and the micrococcinate **13** ester. The scope of this novel BSC protocol for ketothiaozles **4a,b**, using various coupling partners, was also evaluated for the further synthesis of 4-substituted 2-ketothiazole-based natural products and pharmaceutics. As a first example, a synthesis of the ethyl saramycetate subunit of the cyclothiazomycin thiopeptide was proposed.

Scheme 1. Study of Single-Step BSC Protocol for Introduction of 2-Ketothiazol-4-yl Unit in Our Previously Reported *tert*-Butyl Sulfomycinamate Thio-analogue **1** Synthesis



The 4-bromo-2-ketothiazoles **4a,b** were ready prepared in high yield from the commercially available 2,4-dibromothiazole via regioselective lithium−bromide exchange and quenching with *N*-acetyl and propionylmorpholines.[5]

A first set of palladium-catalyzed borylations of 4-bromo-2-acetyl and propionylthiazoles **4a,b** was carried out under the Masuda and Baudoin processes using pinacolborane as a cheaper borylating agent.[6] In both cases, production of borylated thiazoles was not observed. We then turned to bis(pinacol)borane as employed by Miyaura,[7g] and we decided to check the nature of the ligand as the main borylation parameter using $Pd_2(dba)_3$ as recently suggested by Buchwald,[7a] KOAc as base, and dioxane as solvent (Table 1).[7] Except for the bidentate ligand dppf (entry 1), we were pleased to observe that all Buchwald ligands, as well as the carbene ligand IMes, allowed good conversion of the starting material as measured by GC monitoring to give the expected 4-borylated thiazoles **8a,b** in short reaction time (0.5−3 h).

We then immediately evaluated the performance of the same catalyst systems that proved efficient in the prior borylation reaction[8] for a subsequent Suzuki coupling of 2-chloropyridine using the K_3PO_4 base, following the

(3) (a) Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263–4266. (b) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623–4633. (c) First synthesis of a heterocyclic core of a thiopeptide antibiotic (GE2270A) in a complete cross-coupling approach: Heckmann, G.; Bach, T. *Angew. Chem., Int. Ed* **2005**, *44*, 1199–1201.

(4) (a) Martin, T.; Verrier, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2008**, *10*, 2909–2912. (b) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383–7386. (c) Direct palladium-catalyzed stannylation of **4a** using bistrimethystannane is penalized by the side production of 2,2′-acetyl-4,4′-bithiazole (35% GC yield), which could not be isolated from the expected 2-acetylthiazol-4-ylstannane (51% GC yield).

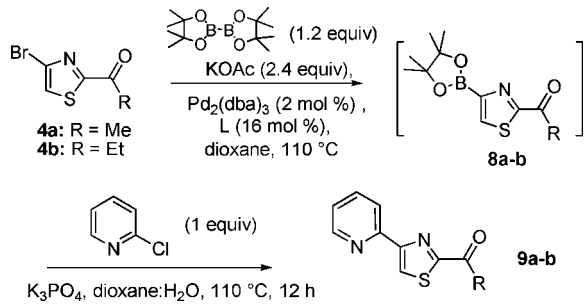
(5) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 3425–3427.

(6) For palladium-catalyzed borylation of aromatics methods using pinacolborane, see: (a) Broutin, P.-E.; Cerna, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6*, 4419–4422. (b) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268–9271. (c) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459.

(7) For palladium-catalyzed borylation of aromatics methods using bis(pinacol)borane, see: (a) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359–5363. (b) Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729–3732. (c) Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541–543. (d) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813–9816. (e) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450. (f) Giroux, A.; Han, Y.; Prasit, P. *Tetrahedron Lett.* **1997**, *38*, 3841–3844. (g) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.

(8) Both borylated thiazoles **8a,b** proved to be highly unstable under usual isolating procedures.

Table 1. Evaluation of 4-Bromo-2-ketothiazoles **4a,b** in Palladium-Catalyzed BSC Methodology[a]



entry	ligand	time (min)[b] from **4a**	time (min)[b] from **4b**	yield of **9a,b** (%)[c] from **8a**	yield of **9a,b** (%)[c] from **8b**
1	dppf	1000[f]	1000[f]		
2	JohnPhos[d]	40	30	90 (84)[g]	100 (97)[g]
3	SPhos	180	60	68	99 (96)[g]
4	XPhos	120	30	84 (81)[g]	94(90)[g]
5	DavePhos	90	45	30	52
6	IMes[e]	150	180 [h]	n.r.	n.r.

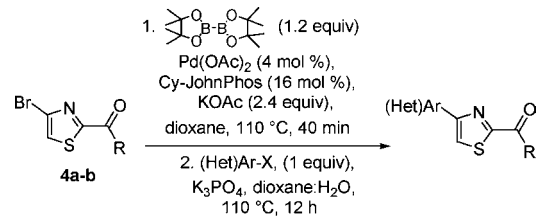
[a] Reaction run on sealed vials under N_2 from 0.25 mmol of ketothiazole. [b] Time to 100% completion of starting material followed by GC analysis. [c] GC yield using *n*-eicosane as an internal standard. [d] Cy-JohnPhos = 2-(dicyclohexylphosphino)-biphenyl. [e] IMes = 1,3-bis-(mesitylimidazolyl)-carbene. [f] <10% of **8a,b**. [g] Isolated yield. [h] 80% of completion of **4b**.

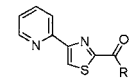
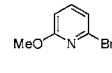
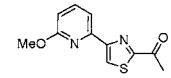
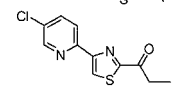
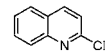
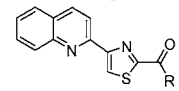
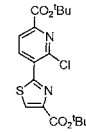
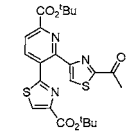
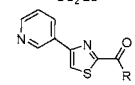
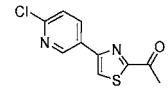
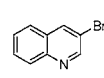
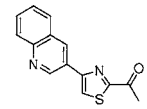
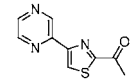
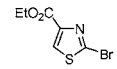
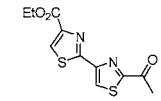
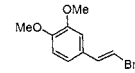
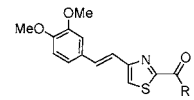
Baudoin[6b] and Buchwald[7a] BSC procedures (Table 1). Under these conditions, the IMes-based catalyst system proved to be completely ineffective for subsequent Suzuki reaction (entry 6), whereas all Buchwald ligand-based catalysts provided 4-pyridin-2-ylthiazoles **9a,b** in fair to quantitative yield (entries 2−5) without any notable α-arylation reaction of the ketones. Nevertheless, the Cy-JohnPhos- and XPhos-based catalysts proved to be slightly more effective than the SPhos- and DavePhos-based catalysts for the Suzuki coupling of both ketothiazoles **4a,b**, providing **9a,b** in a range of 81−97% isolated yields. These good results probably came from a better preservation of the active catalyst in the prior clean and fast palladium-catalyzed borylation reaction.

With the aim to include this BSC protocol of **4a,b** as a novel synthetic tool for the construction of heterocyclic cores of thiopeptides, various 2-halopyridines were next evaluated as coupling partners.

The results depicted in Table 2 (entries 1−4) clearly showed that the BSC protocol applied to **4a,b** allowed fair to good yield couplings with various 2-halopyridines bearing electron-attractive or electron-donating group. We then reinvestigated the last connection of the 2-acetylthiazol-4-yl unit to 6-chlorothiazolylpicolinate **5a** in order to simplify our previous synthesis of *tert*-butyl sulfomycinamate thio-analogue **1**[4] as depicted in Scheme 1. Pleasingly, the direct coupling of **4a** with **5a** could be achieved using the novel BSC protocol, affording **1** in an excellent 87% yield (Table 2, entry 7). Finally, the *tert*- butylsulfomycinamate thio-analogue **1** is prepared from *tert*-butyl-5-bromopicolinate **6a** in an excellent 47% overall yield. We then immediately

Table 2. Scope of BSC of **4a,b** Procedure Using Various Bromo and Chlorohetaromatics[a]

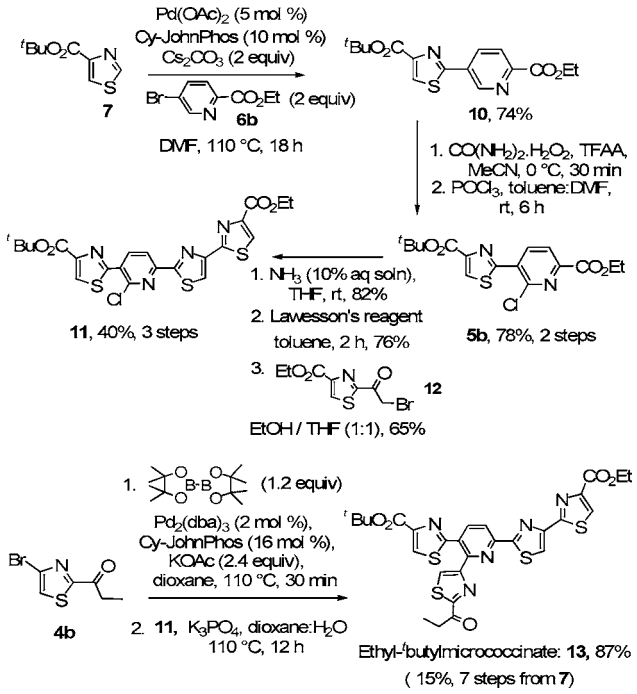


entry	(Het)Ar-X	R	products	Yields[b]
1		**4a**	 **9a**	78% (42%)[c]
2		**4b**	**9b**	62%
3		**4a**	 **14**	75%
4		**4b**	 **15**	95%
5		**4a**	 **16a**	n.r. (98%)[d]
6		**4b**	**16b**	79%
7		**4a**	 **1**	87%
8		**4a**	 **17a**	33% (100%)[d]
9		**4b**	**17b**	n.r. (66%)[d]
10		**4a**	 **18**	70%
11		**4a**	 **19**	80%
12		**4a**	 **20**	64%
13		**4a**	 **21**	74%[e]
14		**4a**	 **22a**	n.r.- (65%)[d]
15		**4b**	**22b**	68%

[a] Reaction run on usual glassware fitted with a condenser under N_2 from 1 mmol of ketothiazole. [b] Yield of isolated product. [c] Coupling with 2-iodopyridine. [d] XPhos as ligand. [e] Isolated yield of saramycetic acid after hydrolysis (see Supporting Information).

focused on an extension of this strategy to the synthesis of micrococcinate **13** mainly by modulating the *tert*-butyl ester group to a 4-(4′-ethoxycarbonylthiazol-2′-yl)thiazol-2-yl subunit (Scheme 2). With this purpose in mind, the ethyl-*tert*-butyl pyridinylthiazolecarboxylate **5b** was first produced through a palladium-catalyzed direct coupling of 4-thiazole-carboxylate **7** with picolinate **6b** followed by α-chlorination of the pyridine. The latter was then submitted to a modified Shin procedure.[9] Thus, treatment of **5b** with aqueous

Scheme 2. Innovative Synthesis of ethyl-*tert*-Butylmicrococcinate **13**



ammonia followed by subsequent thioamidation with the Lawesson's reagent and a final Hantzsch condensation under mild conditions (EtOH/THF 1:1 mixture) provided **11** in 40% overall yield. Pleasingly, the final connection of 2-acetylthiazole unit to the highly substituted 2-chloropyridine **11** was achieved using the BSC protocol of **4b** to give the ethyl-*tert*-butylmicrococcinate ester **13** in 87% yield.

As the last part of this work and to design novel synthetic routes toward 4-substituted 2-ketothiazole-based natural products and pharmaceutics, various other coupling partners were also evaluated in the BSC process of **4a,b** (Table 2, entries 5, 6, 8−15). Remarkably, several haloheteroaromatics could be directly introduced to **4a,b** to produce the 4-heteroaryl-2-ketothiazoles **16**−**20** in high yields using the BSC procedure with Cy-JohnPhos and Xphos as ligands. Thus, interestingly, while the Cy-JohnPhos ligand appeared poorly or completely inefficient in the BSC reaction, the XPhos ligand allowed attainment of fair to good yields of coupling products (Table 2, entries 5, 8−9, 15). As an application, the commercially available ethyl 2-bromothiazole-4-carboxylate was used as a coupling partner to prepare the ethyl saramycetate subunit of cyclothiazomycin thiopeptide **21** recently identified by Bagley.[10,11]

Moreover, two first direct vinylations of **4a,b** with bromoalkene derivatives (Table 1, entries 14 and 15) were also achieved in good yield using the BSC procedure. This methodology could be directly used for novel synthetic approaches to 4-vinylated-2-ketothiazole-based natural products, as exemplified by melithiazole C.[12]

In summary, we have developed here a highly efficient borylation Suzuki coupling process of 4-bromo-2-ketothiazoles with various haloheteroaromatics and bromoalkenes. This methodology is suitable to simplify current syntheses or to design concise routes to 4-substituted 2-ketothiazole-based natural products and pharmaceutics. As examples, in the current context of active research in the design of concise routes toward complex heterocyclic units of *d* thiopeptide antibiotics, innovative syntheses of sulfomycinamate thioanalogue **1**, micrococcinate **13**, and saramycetate **21** esters are described here.

Acknowledgment. This work has been supported by the CNRS, the interregional CRUNCH network, INSA and University of Rouen (I.U.T.).

Supporting Information Available: Experimental procedures and spectroscopic characterization (IR, analytical analysis, ^{1}H, ^{13}C data) of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901525T

(9) Yasuchika, S. S.; Yonezawa, Y.; Shin, C. *Chem. Lett.* **2004**, *33*, 814–815.

(10) Bagley and co-workers recently reported the first and unique synthesis of ethyl saramycetate in 8 steps and 11% overyield from diethoxyacetonitrile: Glover, C.; Merritt, E. A.; Bagley, M. C. *Tetrahedron Lett.* **2007**, *48*, 7027–7030.

(11) For a general access to 2′-substituted 4-bromo-2,4′-bithiazoles using regioselective Negishi and Stille cross-coupling reactions, see: Bach, T.; Heuser, S. *J. Org. Chem.* **2002**, *67*, 5789–5795.

(12) (a) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 3425–3427. (b) Böhlendorf, B.; Hermann, M.; Hecht, H. J.; Sasse, F.; Forche, E.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, *10*, 2601–2608.