ORGANIC LETTERS

2008
Vol. 10, No. 13
2909−2912

# Direct C-2 Arylation of Alkyl 4-Thiazolecarboxylates: New Insights in Synthesis of Heterocyclic Core of Thiopeptide Antibiotics

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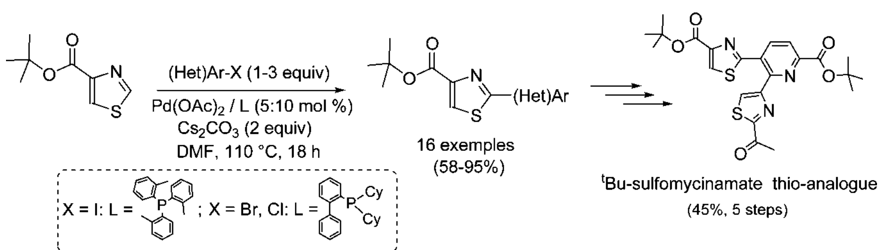
**Received May 5, 2008**

## ABSTRACT




**The Pd(0)-catalyzed regioselective C-2 (hetero)arylation of *tert*-butyl 4-thiazolecarboxylate with a broad (hetero)aryl halide is reported, including the direct coupling of pyridinyl halides. The process has allowed the preparation of valuable 2-pyridynyl-4-thiazolecarboxylates which are components of the complex heterocyclic core of thiopeptides antibiotics. As a first application, a synthesis of a *tert*-butyl sulfomycinamate thio-analogue from *tert*-butyl 4-thiazolecarboxylate is here described through a three-step direct pyridinylation, halogenation, and Stille cross-coupling sequence.**

Aryl-substituted thiazoles are common features of a wide range of biologically active natural products exemplified by the thiopeptide antibiotics family.[1] They are also of considerable interest in medicinal chemistry and as organic materials such as liquid crystal and cosmetic sunscreens.[2] Current arylating methods employed to build up diaromatic systems are based upon a preliminary halogenation or metalation reaction followed by transition-metal-catalyzed cross-coupling reactions with arylmetals or aryl halides. In recent years, direct C−H arylation has emerged as an attractive alternative to the commonly employed cross-coupling reactions since it does not require the rather tricky preliminary preparation of the requisite organometallic or halogenated arenes. Several reviews highlight the broad scope, the high functional group tolerance, the atom economy, and the mild reaction conditions of this strategy.[3] The palladium-catalyzed direct C−H arylation of thiazole is well precedented.[2b,4] In

(1) Reviews: (a) Hughes, R. A.; Moody, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2–27. (b) Bagley, M. C.; Dale, J. W.; Meritt, E. A. E.; 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.

(2) (a) Vinícius, M.; De Souza, N. *J. Sulfur Chem.* **2005**, *26*, 429–449. (b) Mori, A.; Sekigushi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701. (c) Kiryanov, A. A.; Sampson, P.; Seed, A. J. *J. Org. Chem.* **2001**, *66*, 7925–7929. (d) Bach, T.; Heuser, S. *Tetrahedron Lett.* **2000**, *41*, 1707–1710.

(3) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41. (c) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1131–1132. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *354*, 1077–1101. (e) Lablinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514. (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (g) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (h) Fujiwara, Y.; Chengguo, J. *Pure Appl. Chem.* **2001**, *73*, 319–324. (i) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698–1712. (j) Shilov, A.; Shul'pin, G. *Chem. Rev.* **1997**, *97*, 2879–2932.

10.1021/ol801035c CCC: $40.75 
**Published on Web 06/10/2008**

this paper, we report the first developments on direct arylation of 4-thiazolecarboxylic esters scaffolds **1** and **2** which are common features of the heterocyclic core in the important *d* series of thiopeptide antibiotics exemplified by the sulfomycinamate and micrococcinate esters **3**−**5** (Figure 1).

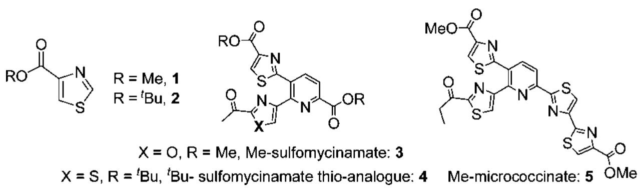
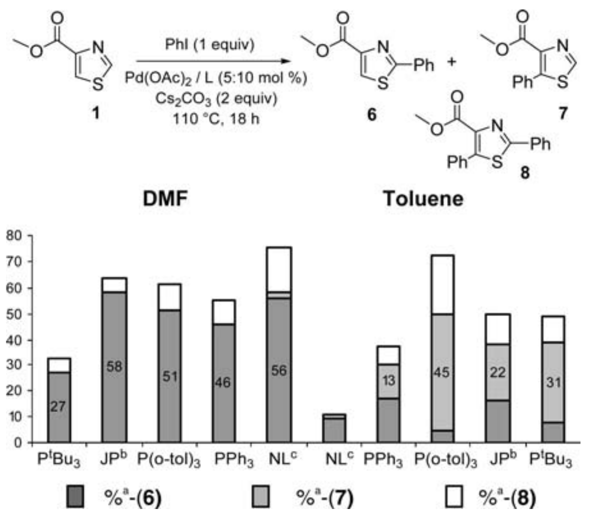



**Figure 1.** 4-Thiazolylcarboxylic esters are units of the heterocyclic core in the *d* series of thiopeptide antibiotics exemplified by sulfomycinamte and micrococcinate.

Current synthetic strategies for the connection at an early stage of the 4-thiazole carboxylate motif to the central pyridine molecule employ mainly the Negishi cross-coupling process.[1a,5] We reasoned that with direct arylation coupling of 4-thiazole carboxylate at 2-position methodology, the current synthesis of the pyridine central core of trisubstituted pyridine thiopeptide antibiotics (series *d*) could be simplified avoiding the preparation of thiazolyl or pyridinyl metals by designing novel synthetic routes. Herein we developed a highly effective protocol for palladium-catalyzed C-2 arylation of *tert*-butyl 4-thiazole carboxylate **2** with a wide range of iodo-, bromo-, and chloroaromatics including halogenopyridines. In the first application, we developed a first route toward the *tert*-butyl sulfomycinamate thio-analogue **4** from **2** through a three-step direct pyridinylation, halogenation, and Stille cross-coupling sequence.

The methyl 4-thiazolecarboxylate **1** was obtained in high yield in multigram quantities by treatment of commercially available 4-thiazolecarboxylic acid with thionyl chloride in methanol. We previously reported that the combination of palladium diacetate and cesium carbonate is effective for phenylation of the structurally related model ethyl 4-oxazolecarboxylate.[6] Accordingly, as a first set of arylation experiments, the methyl 4-thiazolecarboxylate **1** was reacted with 1 equiv of phenyl iodide, 5 mol % of $Pd(OAc)_2$, and 2 equiv of $Cs_2CO_3$ at 110 °C in a sealed tube, and the two parameters, ligand and solvent, were screened. It was immediately clear that the polarity of the solvent was the most significant factor for controlling the regioselectivity of the direct arylation. This trend is summarized graphically in Scheme 1. The apolar toluene solvent delivered a mixture

**Scheme 1.** Study of Direct Phenylation of **1**




[a] ¹H NMR yield based on the amount of **1** used. [b] JP = Buchwald's JohnPhos ligand. [c] NL = no ligand.

of mono- and diphenylated products in which the 5-phenylated compound was slightly predominant. Therefore, the highly polar DMF was tried; it favored the C-2 phenylation of **1**. Moreover it appeared that the nature of the ligand slightly influenced the regiochemical outcome of the phenylation of **1** since reactions with or without phosphine ligand provided the 2-phenylated compound in rather uniform albeit moderate yields (27−58%). It should be noted interestingly that only a trace amount of biphenyl arising from Pd(0)-catalyzed homocoupling side reaction was detected.

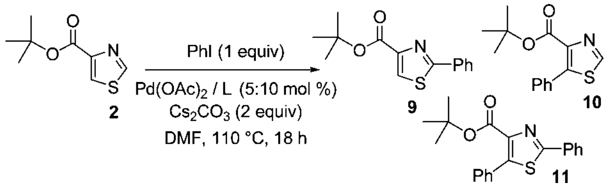
DMF was then chosen to secure the regioselective C-2 phenylation of **1**, and we further directed our efforts to reduce the contamination with the diphenylated compound formed in 5−20% yield. To this end, we reasoned that the addition of internal steric effects (bulky ester) might reduce the undesired subsequent C-5 phenylating process. Thus, the *tert*-butyl 4-thiazole carboxylate **2** was prepared by treatment of 4-carboxythiazole with *tert*-butyl alcohol under CDI activation. Direct phenylation of **2** with phenyl iodide was achieved following a thorough screening of ligands that included bulky $P(o\text{-tol})_3$, P(biphenyl-2-yl)$Cy_2$ (Buchwald's JohnPhos ligand), $P(^tBu)_3$, and 1,3-bis-(mesitylimidazolyl)carbene (IMes) ligands (Table 1). Gratifyingly, the $P(o\text{-tol})_3$ and P(biphenyl-2-yl)$Cy_2$

(4) For examples of direct arylation of thiazole, see: (a) Campeau, L. C.; Bertrand-Laperle, M.; Leclerc, S. P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276–3277. (b) Nandurkar, N. S.; Bhanushali, M. Y.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 1045–1048. (c) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1–6. (d) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405. (e) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970–1980. (f) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, *71*, 1379–1382. (g) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578–7584. (h) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011–2014. (i) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685–5689. (j) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111–3113. (k) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473. (l) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257–272.

(5) Heckmann and Bach reported a first synthesis of an 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.

(6) Hoarau, C.; Du Fou de Kerdaniel, A.; Bracq, N.; Grandclaudon, P.; Couture, A.; Marsais, F. *Tetrahedron Lett.* **2005**, *46*, 8573–8577.

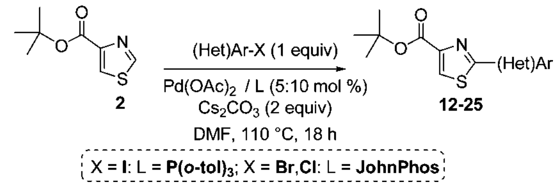
**Table 1.** Study of the Direct Phenylation of **2**

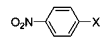
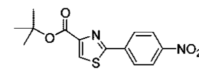
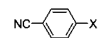
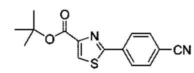
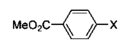
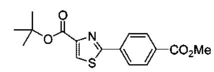
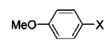
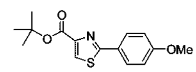
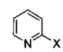
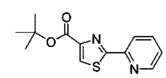
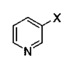
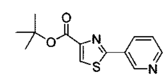
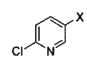
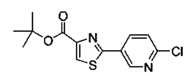
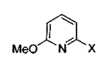
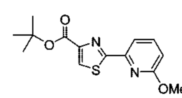
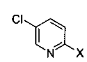
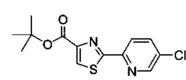
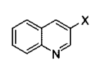
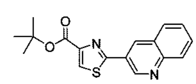
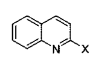
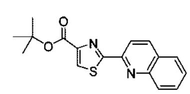
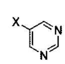
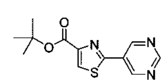
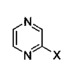
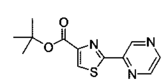
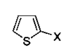
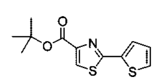



| entry | ligand | **9**[a] (%) | **10**[a] (%) | **11**[a] (%) |
|---|---|---|---|---|
| 1 | none | | | 0 |
| 2 | $PPh_3$ | 47 | 2 | 8 |
| 3 | P(*o*-tol)$_3$ | 82 (81)[d] | 0 | 0 |
| 4 | JohnPhos[b] | 68 (65)[d] | 2 | 5 |
| 5 | $P^tBu_3$ | 38 | 6 | 23 |
| 6 | IMes[c] | 50 | 5 | 10 |

[a] $^1$H NMR yield based on the amount of **2** used. [b] Buchwald's JohnPhos ligand: 2-(dicyclohexylphosphino)-biphenyl. [c] IMes: 1,3-bis-(mesitylimidazolyl)-carbene. [d] Isolated yield.

**Table 2.** Direct regioselective C-2 arylation of **2**




| entry | (Het)Ar-X | X | products | | yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  | I |  | **12** | 67 |
| 2 |  | I |  | **13** | 68 |
| 3 |  | I |  | **14** | 72 |
| 4 |  | I |  | **15** | 65 |
| 5 |  | I |  | **16** | 73 |
| 6 | | Br | | | 65 |
| 7 | | Cl | | | 95 |
| 8 |  | I |  | **17** | 43 (53)[b] |
| 9 | | Br | | | 42[e] (47)[b,f] |
| 10 | | Cl | | | 36 (70)[d] |
| 11 |  | I |  | **18** | 58[b] |
| 12 |  | Br |  | **19** | 71 |
| 13 |  | Cl |  | **20** | 37 (85)[d] |
| 14 |  | Br |  | **21** | 76 |
| 15 |  | Cl |  | **22** | 50 (66)[c] |
| 16 |  | Br |  | **23** | 55 (77)[b] |
| 17 |  | Cl |  | **24** | 72 |
| 18 |  | I |  | **25** | 84 |

[a] Isolated yield. [b] Halogenoaromatic (2 equiv). [c] Halogenoaromatic (3 equiv). [d] Halogenoaromatic (3 equiv), $Pd(OAc)_2$/L (10:20 mol %). [e] The 2,5-pyridiny-3-yl thiazolecarboxylate was isolated in 15% yield. [f] The 2,5-pyridin-3-yl thiazolecarboxylate was isolated in 45% yield.

ligands proved highly effective in selective direct C-2 phenylation of **2**, providing the 2-phenylated thiazolecarboxylate **9** in 82% and 68% yields respectively (entries 3,4). Remarkably, the reaction became fully regioselective using P(*o*-tol)$_3$ as ligand.

With an optimized palladium-catalyzed C-2 phenylating process of **2** in place using P(*o*-tol)$_3$ and P(biphenyl-2-yl)$Cy_2$, we first examined the C-2 arylation of **2** with a wide range of iodoaromatics. All aryl iodides bearing either electron-withdrawing or electron-donating groups underwent C-2 arylation with **2** using P(*o*-tol)$_3$ as ligand affording the 2-arylated thiazoles **12**−**15** in fair 65−71% yields (Table 2, entries 1−4). Thus, the previous conditions were verified for the C-2 heteroarylation of **2** with various commercially available iodo-, bromo-, and chloroheteroaromatics, especially pyridine substrates. Initial screens were executed with three 2-halogenopyridine models. Surprisingly, although P(*o*-tol)$_3$ proved effective for the direct coupling of **2** with 2-iodopyridine, leading to the corresponding 2-pyridin-2-ylthiazolecarboxylate **16** in 73% yield (Table 2, entry 5), the direct coupling of **2** proceeded smoothly with 2-bromopyridine (42%) and failed with 2-chloropyridine using the same ligand. Buchwald's JohnPhos ligand proved to be more appropriate than P(*o*-tol)$_3$ for the direct coupling of **2** with bromo- and chloroheteroaromatics. Indeed, the first set of direct couplings of **2** with 2-bromo- and 2-chloropyridines using P(biphenyl-2-yl)$Cy_2$ provided the expected 2-pyridin-2-ylthiazolecarboxylate **16** in a fair (65%) and excellent (95%) yield (Table 2, entries 6 and 7) and notably without side formation of any other coupling product.

Further direct C-2 heteroarylations of **2** including numbers of pyridine halides were then investigated using P(biphenyl-2-yl)$Cy_2$ (Table 2, entries 8−18). Two major classes of heteroaryl halides have to be distinguished. Several bromo- and chloroheteroaromatics such as 2-bromo-6-methoxypyridine, 3-bromoquinoline, 2-chloropyrazine, and 2-iodothiophene underwent direct arylation with **2** providing the expected 2-heteroaryl thiazolecarboxylates in good yields (71−84%) (entries 12, 14, 17, and 18). With other heteroaromatics, direct coupling with **2** proceeded smoothly due to the formation of the biheteroarene arising from the competitive homocoupling reaction of the heteroaryl halide. Nevertheless, except for 3-bromopyridine (entry 9), only traces of 5-heteroarylated and 2,5-diheteroarylated compounds were detected, indicating that the second C-5 arylation was slower than the first C-2 arylation under these conditions. Thus, as expected, complete conversion of **2** and a significant yield increase of 2-heteroaryl thiazolecarboxylates **17**, **18**, **20**, **22**, and **23** could thereby be obtained by using an excess of heteroaryl halides (2- or 3-fold excess) while adjusting amounts of catalyst and ligand (entries 8, 10, 11, 13, 15, and 16).

As an application of the previous methodology in the course of a research program to design neat synthetic routes toward heterocyclic core of thiopeptide antibiotics, the *tert*-butyl sulfomycinamate thio-analogue **4**[7] was synthesized from **2** in five synthetic steps and 45% overall yield. The synthesis is depicted in Scheme 2. Direct C−H coupling of **2** with *tert*-butyl 5-bromopicolinate **26** at its 2-position led to the pyridinylthiazolecarboxylate **27** in good 70% yield. The regiocontrolled chlorination of **27** was then accomplished through a selective *N*-pyridine oxidation with UHP[8] followed by treatment of the *N*-oxide intermediate with $POCl_3$ under Fagnou's conditions[9] providing **28** in excellent 78% yield. Stille cross-coupling between chloropyridinylthiazolecarboxylate **28** and the 4-thiazolylstannane **29**[10] afforded the *tert*-butyl sulfomycinamate thio-analogue **4** in 82% yield after Pd(II)-catalyzed acetal deprotection.[11]

In summary, our study of the regioselective direct phenylation of 4-thiazolecarboxylate esters **1** and **2** has demonstrated that the process is viable. Our methodology provides efficient conditions for highly selective direct C-2 arylation of *tert*-butyl-4-thiazolecarboxylate **2** with a wide range of iodo-, bromo-, and chloro(hetero)arenes including halogenopyridines, providing rapid access to valuable 2-pyridynyl-4-thiazolylcarboxylates, which are unit of the complex heterocyclic thiopeptides antibiotics. Thanks to this route, the *tert*-butyl sulfomycinamate thio-analogue **4** could be prepared from **2** in three-step via direct C-2 pyridinylation, C-2 chlorination of the pyridine, and Stille cross-coupling in 45% overall yield.

(7) For previous reports on syntheses of dimethyl sulfomycinamate, see: (a) Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.* **2005**, *70*, 1389–1399. (b) Xiong, X.; Bagley, M. C.; Chapaneri, K. *Tetrahedron Lett.* **2004**, *45*, 6121–6124. (c) Bagley, M. C.; Dale, J. W.; Xiong, X.; Bower, J. *Org. Lett.* **2003**, *5*, 4421–4424. (d) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623–4633.

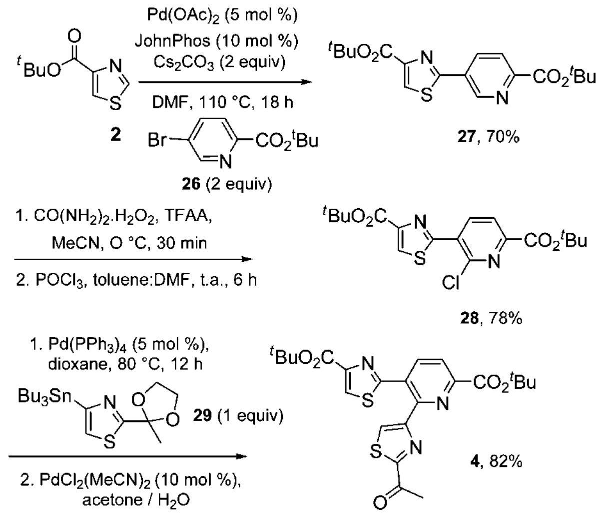
(8) Caron, S.; Do, N. M.; Sieser, J. *Tetrahedron Lett.* **2000**, *41*, 2299–2302.

(9) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781–7786.

(10) Compound **28** was prepared through a three-step C-2 acylation, acetal protection, and C-4 stanylation sequence from commercially available 2,4-dibromothiazole (see the Supporting Information).

(11) Ung, A.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **1996**, *52*, 14069–14078.

**Scheme 2.** Synthesis of *tert*-Butyl Sulfomycinamate Thio-Analogue **4**




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

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

OL801035C