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Regiocontrolled Synthesis of Substituted Thiazoles

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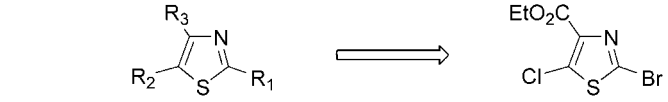
ABSTRACT

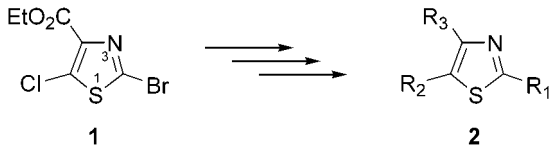


R_1, R_2, R_3 = H, alkyl, alkenyl, alkynyl, aryl **1**

The regiocontrolled synthesis of 2,5-disubstituted and 2,4,5-trisubstituted thiazoles from ethyl 2-bromo-5-chloro-4-thiazolecarboxylate 1 using sequential palladium-catalyzed coupling reactions is described.

Thiazoles occupy a prominent position among heterocycles. In nature, the thiazolium ring is the chemically active center in the coenzyme derived from vitamin B (thiamin). A large number of thiazoles obtained from microbial and marine origins exhibit important biological effects such as antitumor, antifungal, antibiotic, and antiviral activities.[1] Synthetic thiazoles have also been shown to exhibit a wide variety of biological activity,[2] while others have found application as liquid crystals[3] and cosmetic sunscreens.[4]

The classical method for the synthesis of thiazoles is the Hantzsch process, in which an α-haloketone is condensed with a thioamide.[5] This method gives excellent yields for simple thiazoles; however, for some substituted examples low yields have been reported as a result of dehalogenation of the α-haloketone during the reaction.[4,6] Notwithstanding the Hantzsch process and other methods,[7] we required a flexible route that would give high yielding and rapid access to a series of alkyl-, alkenyl-, alkynyl-, and aryl-substituted thiazoles. A method involving a sequence of regioselective palladium-catalyzed coupling reactions based upon a thiazole scaffold was identified as an attractive possibility.[8] The previously unreported ethyl 2-bromo-5-chloro-4-thiazolecarboxylate **1** was identified as a potential precursor. It was anticipated that a palladium-catalyzed coupling reaction[9] would be selective for the more electron-deficient 2-position and that the C-2 substituent could be introduced first. A second cross-coupling reaction could then be utilized for the installation of the second substituent at C-5. The carboxylic functionality could finally be exploited by a range of synthetic maneuvers leading to the installation of a variety of C-4 substituents (Figure 1).



1 **2**

Figure 1.

The synthesis of ethyl 2-bromo-5-chloro-4-thiazolecarboxylate 1 is shown in Scheme 1. The commercially available thiazole **3**[10] was chlorinated at the 5-position by treatment with *N*-chlorosuccinimide in refluxing acetonitrile.[11] The 2-amino substituent was then converted, under

(1) Lewis, J. R. *Nat. Prod. Rep.* **1996**, *13*, 435.
(2) Metzger, J. V. *Thiazole and its Derivatives*; John Wiley & Sons: New York, 1979, and references therein.
(3) Kiryanov, A. A.; Sampson, P.; Seed, A. J. *J. Org. Chem.* **2001**, *66*, 7925.
(4) Bach, T.; Heuser, S. *Tetrahedron Lett.* **2000**, *41*, 1707.
(5) (a) Hantzch, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 942. (b) Wiley, R. H.; England, D. C.; Behr, L. C. In *Organic Reactions*; John Wiley: 1951; Vol. 6, p 367.
(6) Carter, J. S.; Rogier, D. J.; Graneto, M. J.; Seibert, K.; Koboldt, C. M.; Zhang, Y.; Talley, J. J. *Biorg. Med. Chem. Lett.* **1999**, *9*, 1167.
(7) Metzger, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Elmsford, Oxford, 1984; Vol. 6, p 235.

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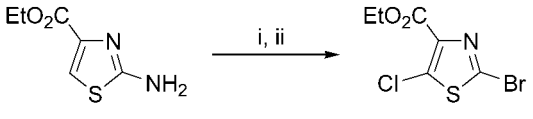
Scheme 1[a]



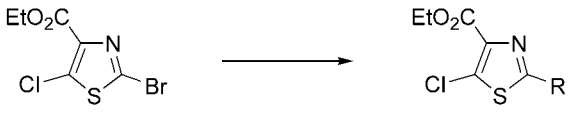
3 **1**

[a] Reaction conditions: (i) NCS, CH_3CN, reflux, (91%); (ii) ^tBuONO, $CuBr_2$, CH_3CN, 80 °C, (82%).

modified Sandmeyer conditions, to the 2-bromothiazole **1** in 82% yield. The synthesis of **1** was performed on a multigram scale and required no chromatography.

The regioselectivity of palladium-catalyzed cross-coupling reactions of **1** with a variety of organometallic reagents was examined. Under standard Suzuki conditions[12] and 1 equiv of phenylboronic acid, exclusive coupling at the more electron-deficient 2-position was observed, affording the major product **4a** in 81% isolated yield (entry 1, Table 1).

Table 1. Palladium-Catalyzed Coupling Reactions of **1**



1 **4a-f**

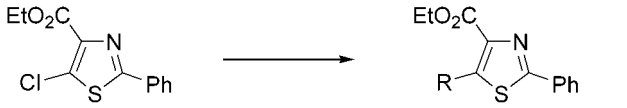
entry	R	conditions[a]	time (h)	product	yield (%)
1	Ph	i	4	**4a**	81
2	2-MeOPh	i	16	**4b**	76
3	4-MeOPh	i	1	**4c**	92
4	4-MeOPh	ii	16	**4c**	88
5	vinyl	iii	12	**4d**	91
6	2-Pyridyl	iv	12	**4e**	74
7	CCPh	v	4	**4f**	19

[a] Reaction conditions: (i) $Pd(Ph_3P)_4$, $RB(OH)_2$, aq. K_2CO_3, PhMe, 80 °C; (ii) $Pd(Ph_3P)_4$, $RB(OH)_2$, aq. K_2CO_3, PhMe, 20 °C; (iii) $Pd(Ph_3P)_2Cl_2$, $CH_2CHSnBu_3$, dioxane, 100 °C; (iv) $Pd(Ph_3P)_4$, 2-pyridylzinc bromide, THF, 65 °C; (v) $Pd(Ph_3P)_2Cl_2$, CuI, phenyl acteylene, Et_3N, 80 °C.

No coupling at the 5-position was observed. Two minor byproducts (<5% yield) were formed during the reaction: debromination of the starting material **1** and dechlorination of the product **4a**.[13] Under the same conditions 2-methoxyphenylboronic acid gave exclusive coupling at the 2-position although the reaction time for this hindered example was considerably longer (entry 2). The less hindered 4-methoxyphenylboronic acid proved significantly more reactive and gave a much shorter reaction time (entry 3). Indeed, this coupling could be accomplished in 16 h at room temperature (entry 4). The Stille coupling reaction was investigated next.[14] Using standard conditions and 1 equiv of vinyltributyltin, exclusive coupling at the 2-position was observed, affording **4d** in 91% isolated yield (entry 5). The Negishi coupling reaction of **1** with 2-pyridylzinc bromide in THF at reflux also gave exclusive coupling at C-2, producing **4e** in 74% yield (entry 6).[15] Sonogashira reaction of **1** with phenylacteylene gave **4f** as the major-coupled product; however, the yield was low and a large amount of resinous material was formed during the reaction (entry 7).[16] Low yields for the Sonogashira and Heck reaction of 2-bromothiazoles have previously been reported, and this was attributed to ring cleavage of the thiazole following palladation at the 2-position.[17] In summary, the Suzuki, Stille, and Negishi reactions were all regioselective for the electron-deficient 2-position, and any byproducts (<5% yield) were due to dehalogenation of the starting material **1** and product **4**.

Under controlled conditions and 1 equiv of the organometallic, there was no coupling at the 5-position during the palladium-catalyzed coupling reaction. The next step, however, was to study the reactivity of the 5-chlorothiazole **4a** in a variety of coupling reactions (Scheme 2).

Scheme 2[a]



4a

5a R = Ph, 87%
5b R = vinyl, 72%
5c R = 2-pyridyl, 70%
5d R = Ph—≡, 56%

[a] Reaction conditions: (i) $Pd(Ph_3P)_4$, $PhB(OH)_2$, aq. K_2CO_3, PhMe, 80 °C, 16 h; (ii) $Pd(Ph_3P)_2Cl_2$, $CH_2CHS^nBu_3$, dioxane, 100 °C, 24 h; (iii) $Pd(Ph_3P)_4$, 2-pyridylzinc bromide, THF, 65 °C, 24 h; (iv) $Pd(Ph_3P)_2Cl_2$, CuI, phenyl acteylene, Et_3N, 80 °C, 24 h.

As expected, longer reaction times and an excess of the organometallic proved necessary to drive the reaction to completion. In the Suzuki coupling, **4a** required 2 equiv of phenylboronic acid and a 16 h reaction time for complete conversion at 80 °C, affording **5a** in 87% yield. The Stille and Negishi coupling reactions both required 3 equiv of the organometallic and prolonged reaction times for complete

(8) For recent reviews of this general strategy, see: (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2845. (b) Snieckus, V. *Med. Res. Rev.* **1999**, *19*, 342 and references therein.

(9) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Pergamon: Elmsford, Oxford, 2000; Chapter 7, p 297.

(10) (a) Maybridge Chemical Company, Trevillet, Tintagel, Cornwall, PL34 OHW, U.K. (b) Plouvier, B.; Houssin, R.; Bailly, C.; Henichart, J.-P. *J. Heterocycl. Chem.* **1989**, *26*, 1643.

(11) South, M. S. *J. Heterocycl. Chem.* **1991**, *28*, 1003.

(12) (a) Miyaura, N.; Suzuki, A. *Chem Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(13) Kim, H.; Kwon, I.; Kim, O. *J. Heterocycl. Chem.* **1995**, *32*, 937.

(14) (a) Stille, J. K. *Angew. Chem.* **1986**, *98*, 504. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.

(15) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

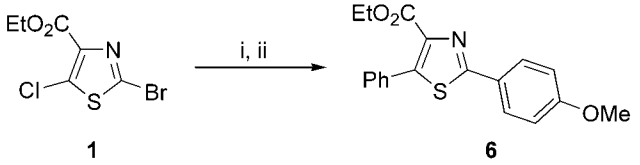
(16) (a) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. (b) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259. (c) Sonogashira, K.; Tohda, Y.; Nagihara, N. *Tetrahedron Lett.* **1975**, 4467. (d) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Nagihara, N. *Synthesis* **1980**, 627.

(17) Sakamoto, T.; Nagata, H.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 823.

consumption of the starting material, affording **5b** and **5c** in 72% and 70% yield, respectively. The Sonogashira reaction, which was problematic with the 2-bromothiazole **1**, gave a cleaner reaction, affording **5d** in 56% yield. In general, the palladium-catalyzed coupling reactions of the 5-chlorothiazole **4a** gave good yields of the expected 5-substituted thiazole, although 2−3 equiv of the organometallic and longer reaction times were required for complete conversion.

Sequential regioselective palladium coupling reactions facilitated the installation of a variety of substituents at first the C-2 and then the C-5 position of the thiazole. To extend the usefulness of this process, a one-pot Suzuki coupling procedure was investigated (Scheme 3). Using standard

Scheme 3[a]



[a] Reaction conditions: (i) $Pd(Ph_3P)_4$ (5 mol %), 1 equiv of 4-MeOPhB$(OH)_2$, aq. K_2CO_3, toluene, 80 °C, 1 h; (ii) $Pd(Ph_3P)_4$ (5 mol %), 2 equiv of PhB$(OH)_2$, 80 °C, 16 h (72%).

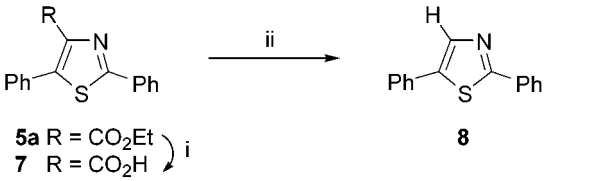
Suzuki conditions the thiazole **1** was treated with 1 equiv of 4-methoxyphenylboronic acid at 80 °C. After 1 h no starting material remained by TLC, and a further 5 mol % of $Pd(Ph_3P)_4$ and 2 equiv of phenylboronic acid were added. The reaction was reheated to 80 °C for a further 16 h and following flash chromatography thiazole **6** was isolated in 72% yield. The structure of **6** was confirmed by treating the 5-chlorothiazole **4c** with phenylboronic acid, which gave a compound with spectral and physical properties identical to those of **6**. It was necessary to add the second 5 mol % of $Pd(Ph_3P)_4$ to the reaction; failure to do so resulted in no coupling at the 5-position and the intermediate **4c** was isolated as the major product.

The synthetic utility of the carboxylic functionality at C-4 could now be exploited by a variety of transformations. For example, hydrolysis of the ester **5a** with sodium hydroxide in ethanol gave the acid **7** in 92% yield. Heating of the acid **6** in aqueous DMF at 150 °C for 18 h resulted in clean decarboxylation and gave the 2,5-diphenyl thiazole **8** in 74% yield (Scheme 4), thereby providing a route to 2,5-disubstituted thiazoles.

Alternatively, a Hunsdiecker reaction[18] was used to introduce a halogen at the C-4 position that proved suitable for further functionalization via palladium-catalyzed processes. The acid **7** was converted to the corresponding silver salt by treatment with silver nitrate and potassium hydroxide in water. Heating the silver salt in the presence of 1 equiv of bromine gave the 4-bromothiazole **9** in 71% yield.[18] Under standard Suzuki conditions and with 1 equiv of phenyl-

(18) For a review, see: Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219.

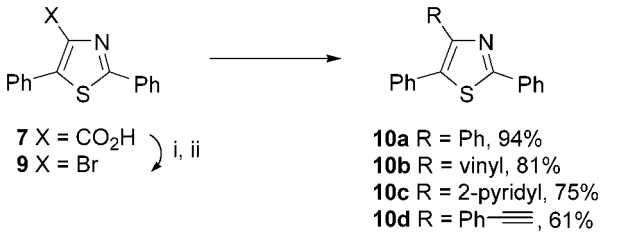
Scheme 4[a]



[a] Reaction conditions: (i) NaOH, EtOH, rt, (92%); (ii) DMF−H_2O (1:1), 150 °C, (74%).

boronic acid, the 4-bromothiazole proved to be reactive, affording after 2 h **10a** in 94% yield. Standard Stille conditions and 2 equiv of vinyltributyltin gave **10b** in 81% yield. Negishi coupling with 2-pyridylzinc bromide gave **10c** in 75% yield, and Sonogashira reaction with phenylacteylene gave **10d** in 61% yield (Scheme 5).

Scheme 5[a]



[a] Reaction conditions: (i) KOH, $AgNO_3$, H_2O; (ii) Br_2, CCl_4, 75 °C, (71%); (iii) $Pd(Ph_3P)_4$, PhB$(OH)_2$, aq. K_2CO_3, PhMe, 80 °C, 2 h; (iv) $Pd(Ph_3P)_2Cl_2$, $CH_2CHSnBu_3$, dioxane, 100 °C, 8 h; (v) $Pd(Ph_3P)_4$, 2-pyridylzinc bromide 0.5 M, THF, 65 °C, 8 h; (vi) $Pd(Ph_3P)_2Cl_2$, CuI, phenyl acteylene, Et_3N, 80 °C, 4 h.

The readily available ethyl 2-bromo-5-chloro-4-thiazolecarboxylate **1** proved to be a versatile template for the synthesis of 2,5-disubstituted and 2,4,5-trisubstituted thiazoles. Regioselective Suzuki, Stille, and Negishi coupling reactions were used to install substituents at the C-2 thiazole position. A second palladium-catalyzed coupling reaction was then used to install substituents at the C-5 position. It was also possible to combine two successive Suzuki coupling reactions into a one-pot procedure. The carboxylic functionality at C-4 was decarboxylated and gave a 2,5-disubstituted thiazole or was converted to the corresponding bromide. The bromide was then exploited in a third palladium-catalyzed coupling reaction to introduce substituents at C-4. The wide range of compatible organometallic reagents offers considerable flexibility for the synthesis of substituted thiazoles.

Acknowledgment. The authors gratefully thank Dr. Dario Doller and Professor Rich Carter for helpful discussions.

Supporting Information Available: Spectroscopic data for compounds **1**, **4a**−**f**, **5a**−**d**, **6**−**9** and **10a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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