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Synthesis of 5-arylthiazoles. Comparative study between Suzuki cross-coupling reaction and direct arylation

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ABSTRACT

A facile synthetic route to the new thiazol-5-ylboronic acid pinacol ester was described herein. Its reactivity toward Suzuki cross-coupling reaction was studied to provide various 5-arylthiazoles. A comparative study between Suzuki cross-coupling reactions and palladium-catalyzed C5–H direct arylation on thiazole ring was achieved.

1. Introduction

The thiazole ring is a widespread heterocycle found in various biologically active natural products like thiamine (vitamin B_1) and penicillins,[1] and also in many naturally based peptides and peptolides isolated from marine organisms such as fungi, algae, etc.[2] Some thiazole derivatives were evaluated for their cyclin-dependent kinase 5/p25 inhibitors as a potential treatment for Alzheimer's disease,[3] and others showed antimicrobial activity.[4] Certain thiazoles are used as pharmaceuticals, agrochemicals,[5] and as potent and selective human adenosine A_3 receptor antagonists.[6] Aryl-substituted thiazoles are important organic functional materials such as fluorescent dyes[7a,b] and liquid crystals.[7b,c] Thiazole orange is used as fluorescent intercalator for determining DNA binding affinity and sequence selectivity of small molecules.[8]

Thiazoles have traditionally been synthesized by Hantzsch synthesis,[9a] which consists of a cyclocondensation between α-haloketones and thioamides.[9a–e] Several other methods have been described.[10] Recently, powerful methods involving palladium mediated coupling processes such as Suzuki coupling,[11,12] Stille reaction,[13] and Negishi coupling[14] have been emerged, allowing the facile introduction of various aryl or alkenyl groups into the thiazole nucleus. Regarding the Suzuki coupling, only one paper described a thiazole carrying the boronic function,[11] the other arylthiazoles were synthesized from the halogenothiazoles.[12] Metal-catalyzed direct heterocycle C–H arylation[15] was also used to synthesize arylthiazole derivatives. The first direct C–H arylation in C-5 position of unsubstituted thiazole was described by Ohta et al. in 1990.[15a] Since this discovery, numerous improvements of palladium-catalyzed direct arylation were achieved by using ligand-free palladium catalyst[15b] and very recently by using low ligand-free catalyst loading;[15d] however there are few examples of direct arylation on C-2 unsubstituted thiazole. Most of examples are described with C-2 position blocked.[15,16]

Therefore, the search for new regioselective methods for the preparation of new thiazole derivatives is always a matter of interest. We wish to describe herein a facile synthetic route to the new boronic ester namely thiazol-5-ylboronic acid pinacol ester **2**, which is hereby described and prepared for the first time. Its ability to be engaged in Suzuki cross-coupling reactions to furnish 5-arylthiazoles was studied. A comparative study with palladium-catalyzed C5–H direct arylation method was then achieved. This work is also a part of a project aiming to compare boronic species in the imidazole,[17] thiazole, and oxazole[18] series.

2. Discussion and results

In the light of the above biological activities of thiazole compounds, and in continuation of our recent work[17] on the synthesis

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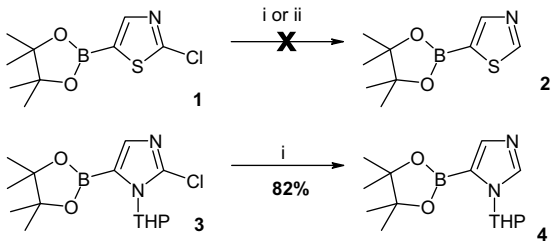


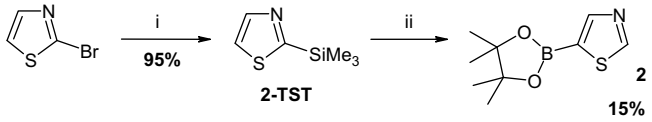
Scheme 1. Investigated reaction and homology with previous works. Reagents and conditions: (i) H_2, Pd/C, MeOH, 0 °C to rt, 2 h and (ii) Zn, AcOH, heating.

of 4(5)-arylimidazoles using the imidazolylboronic ester **4** via Suzuki cross-coupling reaction, it deemed of interest to synthesize the title compounds using the same methodology.

Firstly, we focused our attention on the synthesis of the key thiazolylboronic species **2**. Similar to the synthetic strategy that we have reported for the synthesis of the imidazolylboronic ester **4**[15] (Scheme 1), we prepared the 2-chlorothiazol-5-yl boronic ester **1**, following the method described by Stanetty et al.[11] with the aim to dechlorinate it to gave **2**. Stanetty reported that **1** was sensitive to aqueous conditions and was a poor coupling partner in Suzuki cross-coupling reactions. However, in our hands all attempts to carry out the dechlorination reaction of **1** either via catalytic hydrogenation in the presence of Pd/C as a catalyst or by using Zn/acetic acid reduction failed to proceed.

Consequently, we tried another strategy to protect C-2 position of the thiazole ring. This could be achieved following the method described by Dondoni et al.,[19] which consists of a C-5 regioselective lithiation of 2-trimethylsilylthiazole (2-TST) in ether since the 5-lithio derivative was found to be unstable in THF at −78 °C.[14c] Thus, starting with 2-TST (purchased or easily prepared[19] from the readily available 2-bromothiazole, Scheme 2), a C-5 lithiation was carried out followed by boronation using triisopropyl borate. Transesterification of the intermediate obtained was achieved by treatment with pinacol followed by adjusting the pH to 5 using acetic acid. The reaction led directly to the corresponding stable pinacol ester **2** where the trimethylsilyl group was cleaved during the last stage work-up. Nevertheless, the yield obtained was very poor: 15% (Scheme 2; Table 1, entry 1).

It seems to us that the trimethylsilyl group was too labile under these reaction conditions. Substitution of this group by a triethylsilyl one did not improve the yield. This encouraged us to look for to other silyl protecting groups more resistant to hydrolysis such as triiso propylsilyl (TIPS) group. Thus starting with either 2-triisopropylsilylthiazole **5** or 5-bromo-2-triisopropylsilylthiazole **6**, previously reported by Stangeland and Sammakia,[13c] a lithiation–boronation



Scheme 2. Synthesis of 5-thiazolylboronic esters **2** and **5**. Reagents and conditions: (i) *n*-BuLi 1.05 equiv, Me_3SiCl 1 equiv, ether, −78 °C and (ii) LDA 1.2 equiv, $B(Oi\text{-}Pr)_3$ 1.2 equiv, pinacol 1 equiv, AcOH pH 5, ether, −78 °C to rt.

Table 1
Lithation–boronation sequence optimization starting from 2-TST or **5**

Entry	SiR_3	Base	Solvent	Yield[a] (%)
1	$SiMe_3$	LDA (1.2 equiv)	Ether	15
2	$SiMe_3$	LDA (1.2 equiv)	THF	0
3	Si-*i*-Pr_3	*n*-BuLi	THF	74[a]
4	Si-*i*-Pr_3	LDA (1.2 equiv)	Ether	0
5	$SiMe_3$	*n*-BuLi	THF	70

[a] Obtained from **5** (83% from **6**).

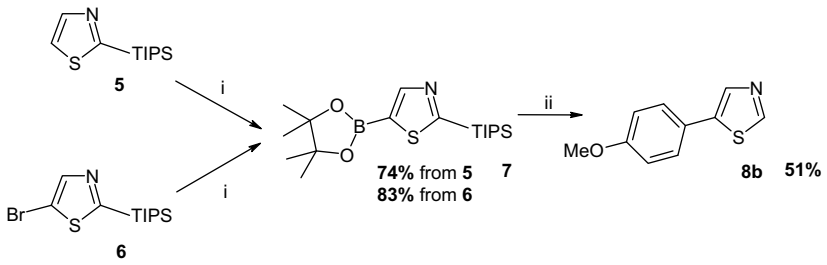
sequence in THF using **5** (direct *ortho*-metalation) or **6** (halogen–metal exchange), followed by transesterification with pinacol gave the corresponding 5-pinacol boronate ester **7** in a good yield (Table 1, entry 3). It is worthy mentioning that the TIPS group of **7** could not be cleaved without affecting the boronic ester function. Thus when **7** was engaged in a Suzuki cross-coupling reaction with 4-iodoanisole under standard aqueous conditions (cf. Scheme 3), the reaction product was identified as 5-(4-methoxyphenyl)thiazole **8b** where the silyl group was cleaved during the purification step on silica gel (Scheme 3). Although the cross-coupling reaction occurred with satisfactory yield (51%), yet this approach was costly due to the expensive triisopropylsilyl chloride.

Since we found that the lithiation–boronation sequence of **5** (or **6**) did not afford the expected boronic ester **7** in ether using LDA (Table 1; entry 4), we have re-investigated several boronation reactions starting from 2-TST. Finally we found that the boronation of 2-trimethylsilylthiazole using *n*-BuLi in THF gave a rather higher yield of **2** (70%) in comparison with that (15%) obtained in ether using LDA (Table 1, entry 5). The neopentylglycol ester **9** was synthesized similarly in 59% yield. It was also possible to obtain, but in a rather modest yield the acid derivative **10** by acidic hydrolysis step instead of the transesterification (Scheme 4). Although the acid **10** was a coupling partner in the Suzuki cross-coupling reaction (with 4-iodoanisole); the difficulties encountered during the purification process of **10** let us to abandon this synthetic methodology.

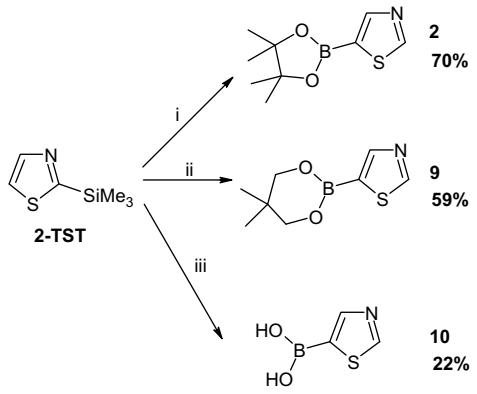
The reactivity of the two boronic esters **2** and **9** toward Suzuki cross-coupling reactions was studied. Thus, the ester **2** was firstly reacted with 4-iodoanisole under standard Suzuki reaction conditions (boronic ester 1.1 equiv; Na_2CO_3 2.5 equiv; $Pd(PPh_3)_4$ 5 mol %; dioxane/water; 80 °C) and the reaction furnished **8b** with a satisfactory yield of 61% (Table 2, entry 1). Using 2 equiv of **2** was found to raise the yield of **8b** to 80% (entry 1a). The use of a stronger base such as Cs_2CO_3 gave a lower yield (36%, entry 2). The use of $PdCl_2$(dppf) instead of $Pd(PPh_3)_4$ in the same conditions that used in entry 1 gave a lower yield (49%, entry 3). When the neopentylglycol ester **9** was used (entry 4) instead of the pinacol ester **2** in the same conditions as in entry 1, the yield decreased notably. Consequently, we have chosen to continue this study with the more reactive ester **2**. Since heteroarylboronic derivatives are known to be prone to deboronation under aqueous conditions,[20] therefore we tried the reaction conditions reported in our previous work (boronic ester 1.1 equiv; CsF 2.5 equiv; CuI 0.1 equiv; $Pd(PPh_3)_4$ 5 mol %; dry DMF; 80 °C), described for sensitive boronic ester[17] where the coupling occurred with 54% yield (Table 1, entry 5). The use of K_3PO_4 instead of CsF/CuI in DMF gave almost the same yield (entry 6). However, the use of $PdCl_2$(dppf) as catalyst in DMF raised the yield to 68% (entry 7).

2.1. Suzuki cross-coupling reactions

Having secured good access to **8b**, then we examined the scope and limitations of our thiazolylboronic ester **2**. Thus, **2** was coupled with a variety of aryl halides using standard aqueous reaction conditions but using 2 equiv of boronic ester in order to rise up the yield (conditions A: boronic ester **2** 2 equiv; aryl halide 1 equiv; Na_2CO_3 2.5 equiv; $Pd(PPh_3)_4$ 5 mol %; dioxane/water 3/1; 80 °C) or using the water free protocol for the aryl halides bearing sensitive groups (conditions B: boronic ester **2** 2 equiv; CsF 2.5 equiv; CuI 0.1 equiv; $Pd(PPh_3)_4$ 5 mol %; dry DMF; 80 °C). The yields were satisfactory and our methodology using the new thiazol-5-ylboronic pinacol ester allows the synthesis of 5-arylthiazoles bearing sensitive groups such as nitriles, esters or aldehydes positioned in any position of the phenyl group (Table 3). The electron-deficient 3-bromobenzaldehyde was found to be less reactive, and afforded **8i** in a poor yield (Table 2, entry 9). Heteroaryl bromides were also suitable reactants in the Suzuki cross-coupling. 3-Bromopyridine



Scheme 3. Synthesis of 2-TIPS-5-thiazolylboronic ester **7** and Suzuki cross-coupling. Reagents and conditions: (i) *n*-BuLi 1.2 equiv, B(O*i*-Pr)$_3$ 1.2 equiv, pinacol 1 equiv, AcOH pH 5, THF, −78 °C to rt and (ii) boronic ester 1.1 equiv, 4-iodoanisole 1 equiv, Na_2CO_3 2.5 equiv, $Pd(PPh_3)_4$ 5 mol %, 80 °C, dioxane/water.



Scheme 4. Synthesis of 5-thiazolylboronic derivatives **2**, **9**, and **10**. Reagents and conditions: (i) *n*-BuLi 1.2 equiv, B(O*i*-Pr)$_3$ 1.2 equiv, pinacol 1 equiv, AcOH pH 5, THF, −78 °C to rt; (ii) *n*-BuLi 1.2 equiv, B(O*i*-Pr)$_3$ 1.2 equiv, neopentylglycol 1 equiv, AcOH pH 5, THF, −78 °C to rt and (iii) *n*-BuLi 1.2 equiv, B(OMe)$_3$ 1.2 equiv, NaOH 4 N, HCl 3 N, THF, −78 °C to rt.

and 5-bromofurfural gave, respectively, **8k** and **8n** in good yields. Moreover, it must be pointed out that it was possible to perform cross-coupling with chlorimine, which was a pharmacological interest molecule precursor[21] (Table 3, entry 13). Furthermore, the 4-amino derivative **8c** (Table 3, entry 3) was obtained with an acceptable yield.

2.2. Direct C5–H arylation

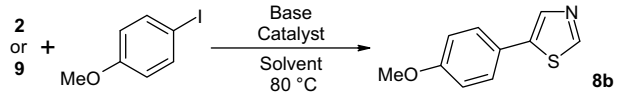
For the C5–H direct arylation of unsubstituted thiazole, we have chosen the conditions described by Bold et al.[15h] using 5 equiv of thiazole, 1 equiv of halide, 3 equiv of KOAc, and 5 mol % of $Pd(PPh_3)_4$ in DMA at 150 °C in a sealed tube (conditions C). The ligand-free conditions described by Parisien et al.[15b] using $Pd(OH)_2$/C as catalyst (conditions D) lead to the same or lower yields (Table 3, entries 8 and 12). During our study an other ligand-free protocol using $Pd(OAc)_2$ was described by Roger et al.[15d] (conditions E). Although this procedure seems to be the most efficient with electron-deficient aryl bromides such as 4-bromobenzonitrile, which conducted to **8d** in 72% yield (Table 3, entry 4), this latter did not permit to obtain better yields than Bold's conditions with other electron-deficient aryl bromides (Table 3, entries 7,11, and 14). Electron-donating aryl halides like 4-iodoanisole were found to be unreactive toward conditions E (Table 3, entry 2). It must be pointed out that direct arylation was not suitable in the case of 4-bromoaniline were no coupling product was isolated (Table 3, entry 3). The direct arylation gave in general lower yield than the Suzuki procedure except in the case of 2-bromobenzonitrile and chlorimine substrates (Table 3, entries 5 and 3).

2.3. Discussion and conclusion

The Suzuki cross-coupling reaction afforded in all cases the expected compounds in 50–90% yield except for the 3-carboxaldehyde compound (entry 9), which was obtained only with 35% yield. This was probably due to the partial degradation of the 3-bromobenzaldehyde. The electron withdrawing or donating character of the substrate does not affect notably the yield, however, the comparison of entries 1,3, and 4 shows that the results obtained with aryl bromides bearing an electron withdrawing group seem to be better (*p*-benzonitrile 91%) than those obtained with substrates bearing an electron-donating group (*p*-aniline 63%) and the result obtained with bromobenzene is situated at an average value (phenyl 79%).

On the other hand, the influence of the substituent position cannot be clearly established. The good correlation found for the nitrile (*para* 91%, *meta* 55%, *ortho* 50%) was not verified with the carboxaldehyde. It must be also pointed out that the mild conditions

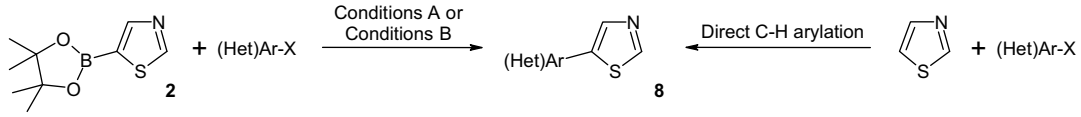
Table 2
Cross-coupling reaction optimization of **2** and **9** with 4-iodoanisole



Entry	Boronic (equiv)	Base	Catalyst (5 mol %)	Solvent	Yield[a] (%)
1	**2** (1.1 equiv)	Na_2CO_3 (2.5 equiv)	$Pd(PPh_3)_4$	Dioxane/H_2O 3/1	61
1a	**2** (2 equiv)	Na_2CO_3 (2.5 equiv)	$Pd(PPh_3)_4$	Dioxane/H_2O 3/1	80
2	**2** (1.1 equiv)	Cs_2CO_3 (2.5 equiv)	$Pd(PPh_3)_4$	Dioxane/H_2O 3/1	36
3	**2** (1.1 equiv)	Na_2CO_3 (2.5 equiv)	$PdCl_2$(dppf)	Dioxane/H_2O 3/1	49
4	**9** (1.1 equiv)	Na_2CO_3 (2.5 equiv)	$Pd(PPh_3)_4$	Dioxane/H_2O 3/1	32
5	**2** (1.1 equiv)	CsF (2.5 equiv) CuI (0.1 equiv)	$Pd(PPh_3)_4$	DMF	5
6	**2** (1.1 equiv)	K_3PO_4 (2.5 equiv)	$Pd(PPh_3)_4$	DMF	54
7	**2** (1.1 equiv)	CsF (2.5 equiv) CuI (0.1 equiv)	$PdCl_2$(dppf)	DMF	68

[a] Isolated yield.

Table 3
Suzuki cross-coupling reactions of ester **2** or direct C5–H arylation oh thiazole with various (het)halides



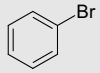
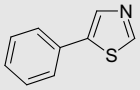
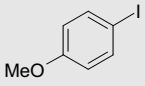
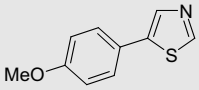
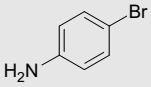
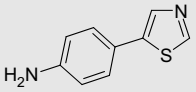
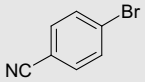
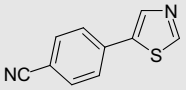
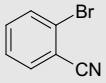
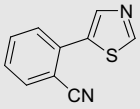
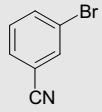
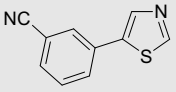
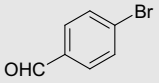
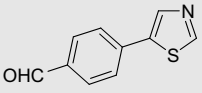
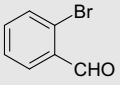
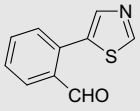
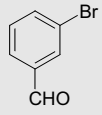
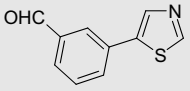
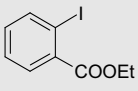
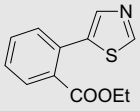
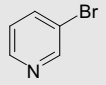
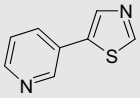
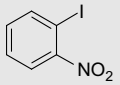
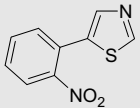
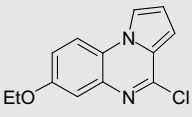
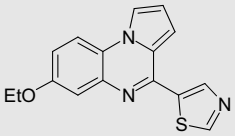
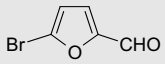
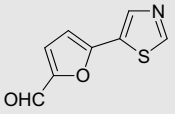
Entry	Halide	Product		Suzuki Conditions	Suzuki yield (%)	Direct arylation conditions	Direct arylation yield (%)
1			**8a**	A	79	C	63
2			**8b**	A	80	C E	36 0
3			**8c**	B	63	C	Traces
4			**8d**	B	91	C E	59 72[a]
5			**8e**	B	50	C	63
6			**8f**	B	55	C	45
7			**8g**	B	54	C E	45[b] 34
8			**8h**	B	67	C D	50 25
9			**8i**	B	35	C	27
10			**8j**	B	65	C	43
11			**8k**	A	67	C E	35 34
12			**8l**	B	57	C D	49 48

Table 3 (*continued*)

Entry	Halide	Product		Suzuki Conditions	Suzuki yield (%)	Direct arylation conditions	Direct arylation yield (%)
13			**8m**	A	54	C	60
14			**8n**	B	74	C E	28 18

Conditions A: boronic ester 2 equiv; aryl halide 1 equiv; Na_2CO_3 2.5 equiv; $Pd(PPh_3)_4$ 5 mol %; dioxane/water 3/1; 80 °C.
Conditions B: boronic ester 2 equiv; aryl halide 1 equiv; CsF 2.5 equiv; CuI 0.1 equiv; $Pd(PPh_3)_4$ 5 mol %; dry DMF; 80 °C.
Conditions C (direct arylation): thiazole 5 equiv; aryl halide 1 equiv; KOAc 3 equiv; $Pd(PPh_3)_4$ 5 mol %; DMA; 150 °C in sealed tube.
Conditions D (direct arylation): thiazole 1 equiv; aryl halide 3 equiv; KOAc 3 equiv; $Pd(OH)_2$/C 0.1 equiv; DMA; 145 °C in sealed tube.
Conditions E (direct arylation): thiazole 2 equiv; aryl halide 1 equiv; KOAc 2 equiv; $Pd(OAc)_2$ 0.4 mol %; DMA; 130 °C in sealed tube.
[a] Described as 88%.[15d]
[b] Described as 61%.[15h]

of the Suzuki reaction allow a high yield with 5-bromofurfural, which is known to be a fragile substrate.

Using the direct arylation procedures C and E, the yield rarely exceed 60%. The drastic conditions conjugated with the presence of sensitive groups such as aldehydes lead to poor yields (25–45%). It is noteworthy that the direct arylation procedure is not suitable for substrate bearing a free amino group (entry 3), and finally, we confirm that direct arylation, particularly in E conditions is not suitable for substrates bearing an electron-donating group (entry 2).[15d]

In conclusion, we have performed an efficient synthesis of the 5-thiazolylboronic acid pinacol ester **2**. This latter is stable in the Suzuki cross-coupling reactions and permits in mild conditions the synthesis of 5-arylthiazoles variously substituted. The comparison of the results of the Suzuki cross-coupling reaction with the straightforward direct arylation procedures indicate that the former method must be preferred with sensitive substrate even if it needs the preparation of the thiazol-5-ylboronic acid pinacol ester. Finally, these two procedures remain complementary. We are now studying the usefulness of **2** in Chan-Lam *C*-heteroatom cross-coupling reactions.

3. Experimental

3.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin Elmer Spectrum BX FT-IR System spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemicals shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at a ionizing potential of 30 eV. Thin layer chromatographies (TLC) were performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light (234 nm) or by iodine. Column chromatographies were carried out using silica gel 60 (0.063–0.2 mm) (Merck). Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Fine' (Rouen). 2-TST was prepared according to the literature.[19]

3.2. 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiazole (2)

To a stirred solution under nitrogen of 2-trimethylsilylthiazole (9.0 g, 57.2 mmol) in dry THF (150 mL) cooled to −78 °C was added *n*-BuLi (2.5 M) (27.5 mL, 68.7 mmol, 1.2 equiv) over a period of 20 min. After 15 min of stirring at this temperature was added triisopropyl borate (15.8 mL, 68.7 mmol, 1.2 equiv). The resulting mixture was allowed to react at this temperature for 1.5 h and then left to warm to room temperature over a course of 45 min. After an additional stirring for 30 min at room temperature, a solution of pinacol (6.76 g, 57.2 mmol, 1 equiv) in THF (20 mL) was added and after 10 min, glacial acetic acid was added dropwise until the pH reached 5. The mixture was diluted with ether, filtered, and the filtrate was concentrated to one-third of its volume. This was diluted with cyclohexane and concentrated under vacuum three times to eliminate the excess of AcOH. The resulting residue was then triturated with *n*-hexane. The solid precipitate was filtered to afford **2** as a white powder (8.46 g, 70%). Mp 98 °C. IR (KBr): 3060, 2968, 1537, 1383, 1127, 713, 653. ^{1}H NMR ($CDCl_3$): δ 9.02 (s, 1H), 8.36 (s, 1H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 158.3, 152.6, 84.5, 24.6 (the boron-carrying C-5 did not appear). HRMS (EI) *m*/*z* calcd: 211.0838, found: 211.0837. Anal. Calcd for $C_9H_{14}BSNO_2$: C, 51.21; H, 6.69; N, 6.64. Found: C, 51.59; H, 7.01; N, 6.60.

3.3. 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilylthiazole (7)

To a stirred solution under nitrogen of 2-triisopropylsilylthiazole[13c] (2.21 g, 9.16 mmol) in dry THF (100 mL) cooled to −78 °C was added *n*-BuLi (2.5 M) (4.4 mL, 11.0 mmol, 1.2 equiv) over a period of 20 min. After 40 min of stirring at this temperature was added triisopropyl borate (2.5 mL, 11.0 mmol, 1.2 equiv). The resulting mixture was allowed to react at this temperature for 1.5 h and then left to warm to room temperature over a course of 1 h. After an additional stirring for 30 min at room temperature, a solution of pinacol (1.08 g, 9.16 mmol, 1 equiv) in THF (10 mL) was added and after 5 min, glacial acetic acid was added until the pH reached 5. After 45 min of stirring at room temperature, the mixture was diluted with ether, filtered, and concentrated. The ethereal solution was washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated to obtain **7** (2.50 g, 74%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.56 (s, 1H), 1.48 (sept, J=7.8 Hz, 3H), 1.36 (s, 12H), 1.13 (d, J=7.8 Hz, 18H). ^{13}C NMR ($CDCl_3$): δ 176.3, 154.2, 145.3, 84.4, 24.7, 18.4, 11.6. HRMS (EI) *m*/*z* calcd: 367.21726,found: 367.21720.

3.4. 5-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)thiazole (9)

This compound was obtained following the same procedure described for **2** using 2-TST (5.85 g) and neopentylglycol (3.87 g).

White solid 4.26 g (59%). Mp 82 °C. ^{1}H NMR ($CDCl_3$): δ 8.83 (s, 1H), 8.12 (s, 1H), 3.61 (s, 4H), 0.90 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 157.6, 151.2, 72.4, 32.1, 21.9 (the boron-carrying C-5 did not appear). HRMS (EI) *m*/*z* calcd: 197.06817, found: 197.06815.

3.5. 5-thiazolylboronic acid (10)

To a stirred solution under nitrogen of 2-trimethylsilylthiazole (2.0 g, 12.7 mmol) in dry THF (80 mL) cooled to −78 °C was added *n*-BuLi (2.5 M) (6.10 mL, 15.3 mmol, 1.2 equiv) over a period of 20 min. After 30 min of stirring at this temperature was added trimethylborate (1.59 mL, 14.0 mmol, 1.1 equiv). The resulting mixture was allowed to react at this temperature for 30 min and then left to warm to room temperature over a course of 45 min. The solution was quenched with HCl 1 N until pH 2. The mixture was extracted three times with EtOAc, dried over $MgSO_4$, and concentrated. The residue was triturated with ether and filtered to give **10** as a white solid (360 mg, 22%). Mp>250 °C. ^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H), 8.44 (br s, 2H), 8.31 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 158.3, 151.1 (the boron-carrying C-5 did not appear). MS (ESI^+) calcd for $C_3H_4BO_2NS$ [$M-H^+$] 129.88.

3.6. Typical procedure A for the cross-coupling reaction

To a mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-thiazole **2** (500 mg, 2.4 mmol, 2 equiv), aryl halide (1.2 mmol, 1 equiv) in a mixture of dioxane and water 3/1 (20 mL) under argon were added Na_2CO_3 (314 mg, 3.0 mmol, 2.5 equiv) and $Pd(PPh_3)_4$ (68 mg, 0.06 mmol, 0.05 equiv). The reaction mixture was heated at 80 °C and the consumption of halocompound was followed by TLC. The reaction mixture was then diluted with EtOAc and filtered through a pad of Celite®. The filtrate was washed three times with brine. The organic layer was dried on $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified using column chromatography on silica gel (cyclohexane/EtOAc 7/3).

3.7. Typical procedure B for the cross-coupling reaction

To a mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-thiazole 2 (500 mg, 2.4 mmol, 2 equiv), aryl halide (1.2 mmol, 1 equiv) in dry DMF (20 mL) under argon were added CsF (450 mg, 3.0 mmol, 2.5 equiv), CuI (23 mg, 0.12 mmol, 0.1 equiv), and $Pd(PPh_3)_4$ (68 mg, 0.06 mmol, 0.05 equiv). The reaction mixture was heated at 80 °C and the consumption of halocompound was followed by TLC. The reaction mixture was then diluted with EtOAc and filtered through a pad of Celite®. The filtrate was washed three times with brine. The organic layer was dried on $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified using column chromatography on silica gel (cyclohexane/EtOAc 7/3).

3.8. Typical procedure C for the C–H direct arylation

Thiazole (500 mg, 5.9 mmol, 5 equiv), aryl halide (1.2 mmol, 1 equiv), KOAc (3.5 mmol, 3 equiv), and $Pd(PPh_3)_4$ (124 mg, 0.06 mmol, 0.05 equiv) in dimethyl acetamide (5 mL) were degassed and then heated in a sealed tube for 24 h at 150 °C. The dark suspension was filtered and concentrated. The resulting mixture was redissolved in water and extracted three times with EtOAc. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (silica gel, cyclohexane/EtOAc) afforded 5-arylthiazole.

3.9. Typical procedure D for the C–H direct arylation

Thiazole (200 mg, 2.4 mmol, 1 equiv), aryl halide (7.1 mmol, 3 equiv), KOAc (7.1 mmol, 3 equiv), and $Pd(OH)_2$ (34 mg, 0.24 mmol, 0.1 equiv) in dimethyl acetamide (5 mL) were degassed and then heated in a sealed tube for 24 h at 145 °C. The dark suspension was filtered and concentrated. The resulting mixture was redissolved in water and extracted three times with EtOAc. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (silica gel, cyclohexane/EtOAc) afforded 5-arylthiazole.

3.10. Typical procedure E for the C–H direct arylation

Thiazole (500 mg, 5.9 mmol, 2 equiv), aryl halide (2.9 mmol, 1 equiv), KOAc (5.9 mmol, 2 equiv), and $Pd(OAc)_2$ (2.6 mg, 0.01 mmol, 0.004 equiv) in dimethyl acetamide (5 mL) were degassed and then heated in a sealed tube for 24 h at 130 °C. The dark suspension was filtered and concentrated. The resulting mixture was redissolved in water and extracted three times with EtOAc. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (silica gel, cyclohexane/EtOAc) afforded 5-arylthiazole.

*3.10.1. 5-Phenylthiazole (**8a**)*[13b,15b]

White solid using bromobenzene as a halocompound. Mp 45 °C. ^{1}H NMR ($CDCl_3$): δ 8.70 (s, 1H), 8.05 (s, 1H), 7.65–7.20 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 152.0, 138.9, 139.3, 131.0, 129.1, 126.9, 128.6.

*3.10.2. 5-(4-Methoxyphenyl)thiazole (**8b**)*[10l,15b,i]

White solid using 4-iodoanisole as halocompound. Mp 92 °C. ^{1}H NMR ($CDCl_3$): δ 8.70 (s, 1H), 7.98 (s, 1H), 7.50 (d, *J*=8.8 Hz, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.8, 151.2, 139.2, 138.1, 128.3, 123.6, 114.5, 55.4. HRMS (EI) *m*/*z* calcd: 191.04048, found: 191.04038.

*3.10.3. 4-(Thiazol-5-yl)aniline (**8c**)*[14c]

Yellow solid using 4-iodoaniline as halocompound. Mp 149 °C. ^{1}H NMR ($CDCl_3$): δ 8.65 (s, 1H), 7.93 (s, 1H), 7.38 (d, *J*=6.8 Hz, 2H), 6.71 (d, *J*=8.7 Hz, 2H), 3.83 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ 150.5, 146.8, 139.8, 137.3, 128.2, 121.3, 115.3. HRMS (EI) *m*/*z* calcd: 176.04081, found: 176.04095.

*3.10.4. 4-(Thiazol-5-yl)benzonitrile (**8d**)*

White solid using 4-bromobenzonitrile as halocompound. Mp 102 °C. IR (KBr): 2221, 1603, 1417, 1119, 829, 538. ^{1}H NMR ($CDCl_3$): δ 8.86 (s, 1H), 8.19 (s, 1H), 7.71 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 153.7, 140.7, 135.6, 132.9, 127.3, 118.4, 111.8 (a quaternary carbon's signal did not appear). HRMS (EI) *m*/*z* calcd: 186.02516, found: 186.02513. Anal. Calcd for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.04. Found: C, 64.22; H, 3.09; N, 14.81.

*3.10.5. 2-(Thiazol-5-yl)benzonitrile (**8e**)*

White solid using 2-bromobenzonitrile as halocompound. Mp 92 °C. ^{1}H NMR ($CDCl_3$): δ 8.92 (s, 1H), 8.30 (s, 1H), 7.79 (d, *J*=7.8 Hz, 1H), 7.68–7.61 (m, 2H), 7.49 (t, *J*=7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 154.1, 142.7, 134.4, 134.2, 133.1, 130.3, 130.0, 128.6, 118.0, 110.9. HRMS (EI) *m*/*z* calcd: 186.02516, found: 186.02509. Anal. Calcd for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.04. Found: C, 64.30; H, 3.02; N, 14.91.

*3.10.6. 3-(Thiazol-5-yl)benzonitrile (**8f**)*

White solid using 3-iodobenzonitrile as halocompound. Mp 91 °C. ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.10 (s, 1H), 7.81 (s, 1H), 7.76 (d, *J*=7.8 Hz, 1H), 7.59 (d, *J*=6.8 Hz, 1H), 7.50 (t, *J*=7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 153.2, 140.0, 136.7, 132.2, 131.4, 130.8, 130.0, 129.8, 117.9, 113.2. HRMS (EI) *m*/*z* calcd: 186.02516, found: 186.02514. Anal. Calcd for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.04. Found: C, 64.28; H, 2.99; N, 14.78.

*3.10.7. 4-(Thiazol-5-yl)benzaldehyde (**8g**)[15h]*

Yellow solid using 4-bromobenzaldehyde as halocompound. Mp 79 °C. ^{1}H NMR ($CDCl_3$): δ 10.04 (s, 1H), 8.86 (s, 1H), 8.23 (s, 1H), 7.94 (d, J=7.8 Hz, 2H), 7.76 (d, J=7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 191.2, 153.5, 140.5, 137.9, 136.8, 135.8, 130.5, 127.2. HRMS (EI) m/z calcd: 189.02484, found: 189.02479.

*3.10.8. 2-(Thiazol-5-yl)benzaldehyde (**8h**)*

Yellow solid using 2-bromobenzaldehyde as halocompound. Mp 85 °C. ^{1}H NMR ($CDCl_3$): δ 10.15 (s, 1H), 8.95 (s, 1H), 8.02 (d, J=7.8 Hz, 1H), 7.87 (s, 1H), 7.67 (t, J=7.8 Hz, 1H), 7.59–7.51 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 190.9, 154.3, 143.7, 134.4, 133.8, 133.7, 133.5, 131.9, 129.2, 128.3. HRMS (EI) m/z calcd: 189.02484, found: 189.02481. Anal. Calcd for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.24; H, 3.49; N, 7.17.

*3.10.9. 3-(Thiazol-5-yl)benzaldehyde (**8i**)*

Pale yellow solid using 3-bromobenzaldehyde as halocompound. Mp 61 °C. ^{1}H NMR ($CDCl_3$): δ 10.07 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 8.07 (s, 1H), 7.87–7.83 (m, 2H), 7.60 (t, J=6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 191.5, 152.7, 139.7, 137.7, 136.9, 132.4, 132.0, 129.8, 129.6, 127.3. HRMS (EI) m/z calcd: 189.02484, found: 189.02478. Anal. Calcd for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.27; H, 3.55; N, 7.28.

*3.10.10. Ethyl 2-(thiazolyl-5-yl)benzoate (**8j**)*

Yellow oil using ethyl 2-iodobenzoate as halocompound. ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H), 7.87 (d, J=7.8 Hz, 1H), 7.77 (s, 1H), 7.55–7.43 (m, 3H), 4,20 (q, J=6.8 Hz, 2H), 1.16 (t, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 167.5, 152.9, 141.5, 136.7, 132.1, 131.8, 131.2, 130.5, 130.0, 128.7, 61.3, 13.8. HRMS (EI) m/z calcd: 233.05105, found: 233.05101. Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.57; H, 4.55; N, 6.21.

*3.10.11. 3-(Thiazol-5-yl)pyridine (**8k**)[13d]*

Yellow oil using 3-bromopyridine as halocompound. ^{1}H NMR ($CDCl_3$): δ 8.87–8.83 (m, 2H), 8.60 (d, J=4.9 Hz, 1H), 8.15 (s, 1H), 7.90 (dd, J=2.0 and 8.8 Hz, 1H), 7.39 (dd, J=4.9 and 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 153.1, 149.4, 147.7, 140.0, 135.5, 134.0, 127.3, 123.8. HRMS (EI) m/z calcd: 162.02516, found: 162.02473.

*3.10.12. 5-(2-Nitrophenyl)thiazole (**8l**)*

Orange solid using 2-iodonitrobenzene as halocompound. Mp 70 °C; ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 7.91 (d, J=6.8 Hz, 1H), 7.88 (s, 1H), 7.65 (t, J=8.8 Hz, 1H), 7.59–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 154.3, 149.2, 142.4, 142.3, 132.9, 132.4, 129.7, 125.1, 124.3. HRMS (EI) m/z calcd: 206.01500, found: 206.01485. Anal. Calcd for $C_9H_6N_2O_2S$: C, 52.42; H, 2.93; N, 13.58. Found: C, 52.19; H, 2.68; N, 13.70.

*3.10.13. 5-(Thiazol-5-yl)furan-2-carbaldehyde (**8m**)[13b]*

Yellow solid using 5-bromofurfural as halocompound. Mp<50 °C. ^{1}H NMR ($CDCl_3$): δ 9.67 (s, 1H), 8.86 (s, 1H), 8.30 (s, 1H), 7.33 (s, 1H), 6.79 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 176.4, 153.7, 152.0, 151.4, 141.6, 127.1, 123.1, 109.5. HRMS (EI) m/z calcd: 179.00410, found: 179.00433.

*3.10.14. 7-Ethoxy-4(thiazol-5-yl)pyrrolo[1,2-a]quinoxaline (**8n**)*

Yellow solid. Following typical procedure using 4-chloro-7-ethoxypyrrolo[1,2-*a*]quinoxaline[21] as halocompound. Mp 175 °C. ^{1}H NMR ($CDCl_3$): δ 8.97 (s, 1H), 8.70 (s, 1H), 7.95 (s, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.42 (d, J=2.9 Hz, 1H), 7.22–7.14 (m, 2H), 6.93 (m, 1H), 4.16 (q, J=6.8 Hz, 2H), 1.49 (t, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.7, 155.1, 145.3, 143.0, 138.3, 136.6, 123.6, 121.2, 118.0, 114.6, 114.5, 114.1, 111.5, 107.1, 64.0, 14.8. HRMS (EI) m/z calcd: 295.07791, found: 295.07845. Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.87; H, 4.42; N, 13.99.

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