Tetrahedron 66 (2010) 8051–8059

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A guideline for the arylation of positions 4 and 5 of thiazole via Pd-catalyzed cross-coupling reactions

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ARTICLE INFO

Article history:
Received 8 July 2010
Received in revised form 29 July 2010
Accepted 30 July 2010
Available online 11 August 2010

Dedicated to Professor Carmen Najera on the occasion of her 60th birthday

Keywords:
Thiazole
Cross-coupling
Pd-catalysis
Suzuki–Miyaura
Stille
Arylation

ABSTRACT

The arylation of thiazoles in 4- and 5-position was investigated in detail. Suzuki–Miyaura and Stille cross-coupling reactions were tested using thiazoles either as halide or organometal species. The obtained results were critically compared to develop helpful guidelines for selection of the cross-coupling methodology with the best potential for good and reliable results for a given synthetic problem without the need for tedious optimization of reaction parameters.

1. Introduction

Substituted thiazoles are interesting building blocks and frequently encountered structural motifs in a variety of natural products and synthetic bioactive compounds useful as pharmaceuticals or plant protecting agents. Among natural products derived from thiazole, thiamine (vitamin B_1) is a prominent example. More recently discovered compound classes like epothilones,[1] cystothiazoles[2] or thiazolyl peptide antibiotics[3] also contain at least one thiazole ring and show interesting biological activities.

The most frequently encountered method for the synthesis of thiazole derivatives is the classical Hantzsch reaction,[4] where an α-haloketone is condensed with thioamide derivatives. This is definitely a reliable and attractive method for the synthesis of one or only a few products, however, when e.g., a library of differently substituted thiazoles is required this method becomes very elaborate since for each substitution pattern different α-haloketones resp. thioamides have to be prepared. In this regard, transition-metal-catalyzed cross-coupling reactions[5] represent a very attractive alternative since simple building blocks can be decorated in a stepwise manner allowing substitution in every position. Although cross-coupling reactions on thiazole systems have been reported repeatedly in the literature,[2c,6] these papers—with few exceptions[6h]—are usually target-oriented and systematic investigations are still needed and of great interest in order to establish a reactivity platform of the various positions and methods in thiazole cross-coupling chemistry.

So far we contributed to the field by comparing the reactivity of the 4- and 5-positions of 2-phenylthiazoles in Stille cross-coupling reactions[7] as well as by publishing a systematic study of Suzuki–Miyaura cross-coupling reactions on thiazoleboronic acid esters.[8] Within the present contribution we report on a more elaborate and thorough investigation of thiazole cross-coupling chemistry.

Our exploration of the cross-coupling chemistry of thiazole was set up in the following systematic manner: Initially, Suzuki–Miyaura and Stille reactions were carried out with thiazole-5-halides together with phenylboronic acid, 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane or tributylphenylstannane as aryl donors in order to optimize the two coupling protocols and to compare the results without having to consider steric or electronic effects deriving from the aryl donor. Subsequently, 5-organometal thiazoles were cross-coupled with iodo- or bromobenzene to obtain comparative data for the 'inverse' reaction. Then the Suzuki–Miyaura protocol was investigated in more detail with substituted (hetero)arylboronic acids or esters and critically compared to the corresponding experiments under Stille conditions. After investigating the cross-coupling

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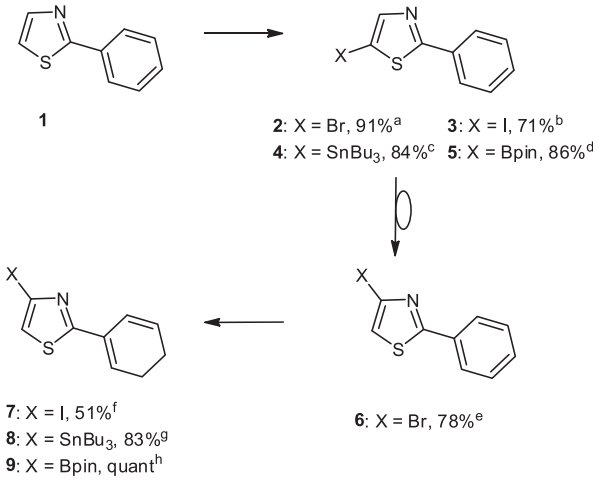
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.07.081

efficiencies in 5-position, the same set of experiments was carried out in 4-position. As conclusion, a set of guidelines is presented to support synthetic chemists when choosing the right coupling method for a defined synthetic problem on the thiazole system with a high chance of success and efficiency, therefore avoiding elaborate optimization of reaction conditions. Additionally, the aim was to use cheap and commercially available catalysts to keep the method also interesting for compound library preparation in industry.

2. Results and discussion

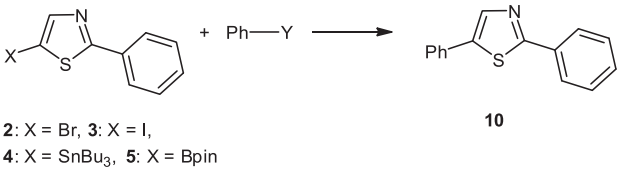
Starting materials, such as 4- and 5-halothiazoles, 4- and 5-thiazolestannanes as well as 4- and 5-thiazoleboronic acid esters were prepared in good to excellent yields according to protocols previously developed in our group (Scheme 1).[7,8] 2-Phenyl-thiazole (**1**) was obtained via a Hantzsch cyclization and subsequently functionalized in 5- or 4-position. The required thiazolestannanes **4** and **8** were prepared via a lithiation strategy, starting from **1** resp. 4-bromo-2-phenylthiazole (**6**), which was obtained from **2** via a halogen dance reaction.[9] In order to perform Suzuki–Miyaura reactions we prepared thiazoleboronic esters **5** and **9** since the corresponding acids turned out to be unstable in our hands. Until recently, only the use of 2-thiazoleboronic acid has been claimed in patents and medicinal chemistry publications lacking detailed experimental procedures.[10] The preparation of 5-thiazoleboronic acid was reported very recently by the group of Rault, however in only 22% yield; due to certain problems its cross-coupling behavior was also not investigated further.[6h] The same starting materials as before (**1** and **6**) were used but the boronic ester functionality in 4-position had to be introduced via a cross-coupling reaction. Regarding the halides, the synthesis of 5-bromo-2-phenylthiazole (**2**) resp. 5-iodo-2-phenylthiazole (**3**) was straightforward starting from **1**. Compound **6** was again used as substrate for the preparation of 4-iodo-2-phenylthiazole (**7**), which was obtained via metal halogen exchange and subsequent quenching with I_2.



Scheme 1. Synthesis of starting materials. Reagents and conditions: (a) Br_2, $CHCl_3$, rt; (b) *n*-BuLi, I_2/THF, −80 °C; (c) *n*-BuLi, Bu_3SnCl/THF, −80 °C; (d) *n*-BuLi, −80 °C to −50 °C; (*i*-PrO)$_3$B, −90 °C to rt; pinacol; AcOH; (e) LDA, H_2O/THF, −80 °C; (f) *t*-BuLi, I_2/THF, −80 °C; (g) *t*-BuLi, Bu_3SnCl/THF, −80 °C; (h) B_2pin_2, KOAc, $Pd_2(dba)_3$, PCy_3, dioxane, MW, 170 °C.

2.1. Cross-coupling in 5-position

With all required starting materials at hand coupling reactions were investigated under Stille[7] as well as Suzuki–Miyaura[8] conditions. It was decided to keep the substituent in 2-position constant to exclude varying influences of this substituent[6i] in order to get results, which can be compared more easily. Investigating a series of different substituents in 2-positions would have been beyond the scope of this contribution. In all cases $Pd(PPh_3)_4$ was chosen as catalyst since it is commercially available or can be easily prepared freshly in the laboratory.[11] First, 5-halothiazoles **2** and **3** were coupled under Suzuki–Miyaura and Stille conditions, whereas in the Suzuki–Miyaura reaction both boronic acids and esters were investigated (Scheme 2 and Table 1). The reaction mixtures were heated in the respective solvent until complete consumption of the limiting starting material (usually the thiazole component: 20 min–48 h) was observed by TLC or GC/MS analysis. In the Stille series toluene turned out to be a good solvent in test reactions. Usually, CsF was added in order to avoid frequently encountered purification problems.[12] This reagent not only activates the applied stannane, but also simplifies the purification due to generation of insoluble Bu_3SnF.



2: X = Br, **3**: X = I,
4: X = $SnBu_3$, **5**: X = Bpin

Scheme 2. Cross-coupling in 5-position.

Table 1
Cross-coupling in 5-position

Entry	X	Y	Conditions	Yield [%]
1	Br	$B(OH)_2$	**A** (16 h)	92
2	I	$B(OH)_2$	**A** (6 h)	99
3	Br	Bpin	**B** (16 h)	75
4	I	Bpin	**B** (21 h)	80
5	Br	$SnBu_3$	**C** (24 h)	74
6	I	$SnBu_3$	**C** (24 h)	42
7	Bpin	Br	**D** (2 h)	64
8	Bpin	I	**D** (20 min)	57
9	$SnBu_3$	Br	**C** (7 h)	76
10	$SnBu_3$	I	**C** (4 h)	78

For reaction conditions see general procedures **A**–**D** in the Experimental part.

A first series of reaction optimization for the Suzuki–Miyaura protocol was recently disclosed by us (starting from thiazoleboronic esters);[8] when **5** resp. **9** were cross-coupled highest yields were obtained using dioxane as solvent and Cs_2CO_3 as base. These initial results were extended in context of the present study by also investigating cross-coupling of thiazole halides with (hetero)aryl boronic acids. Suitable conditions for the Suzuki–Miyaura reaction were quickly identified. Cross-couplings of halides **2** and **6** with phenylboronic acid served as initial experiments in this series of reactions using 2.5 equiv K_2CO_3 as base (2 M solution in water), 5 mol % of $Pd(PPh_3)_4$ as catalyst and toluene as solvent. Since first test reactions with thiazole bromide **2** and iodide **3** gave the desired product (**10**) in excellent yields (92% resp. 99%) already (Table 1, entries 1 and 2) no further optimization was carried out.

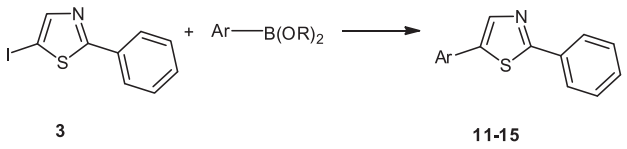
However, successful coupling conditions for phenylboronic acid did not result in any product formation in coupling attempts of **2** and **3** with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane. Different bases [K_2CO_3 (2 M aq solution), K_2CO_3 solid, Cs_2CO_3] as well as different solvents (toluene, dioxane, DME/H_2O, DMF) were tested and the highest yield was obtained when the reaction was performed in DMF at 110 °C using 3.36 equiv of solid K_2CO_3 as base. The obtained yields were good but considerably lower compared to the cross-coupling reactions with phenylboronic acid (entries 3 and 4 vs entries 1 and 2) independent of the nature of the halide; again, the iodide **3** gave a slightly better yield compared to bromide **2** (80% vs 75%). Cross-coupling of bromide **2** with tributylphenylstannane

(entry 5) gave 74% of the desired product, a yield similar to the reaction using phenylboronic acid ester as aryl donor but noticeably lower compared to the use of phenylboronic acid. Interestingly, Stille coupling of iodide **3** only resulted in 42% (entry 6) yield as lowest result in this series. Careful investigation of the reaction mixture revealed that the more reactive iodide favors formation of homo-coupling products and major amounts (20%) of the corresponding 2,2′-diphenyl-[5,5′]-bi-thiazolyl were isolated.

Subsequently, 5-organometal thiazoles were cross-coupled with bromo- and iodobenzene also leading to 2,5-diphenylthiazole **10**. Performing the reactions under Stille conditions (entries 9 and 10) gave comparable yields to reactions in entries 3–5. In this case an iodide coupling partner caused no problem and a good yield of 78% was achieved (entry 10). Lower yields were obtained under Suzuki–Miyaura conditions. This time, bromobenzene gave a higher yield (entry 7, 64%) than iodobenzene (entry 8, 57%). The significantly lower stability of thiazoleboronic acid esters compared to the corresponding stannanes under cross-coupling conditions is certainly a major reason for the lower yields of **10**.

The trend for this first series of experiments can be summarized as follows: By far best results were obtained using halothiazoles in combination with phenylboronic acid as coupling partner. The other methods gave largely comparable results whereas the thiazoleboronic ester gave lower yields. One runaway value is the use of **3** with tributylphenylstannane, which gave the lowest yield of the whole series due to competitive by-product formation.

In the next series of experiments, the applicability of electronically and sterically more challenging coupling partners was investigated (Scheme 3, Table 2). Iodide **3** was initially chosen as starting material since it gave generally better yields in Suzuki–Miyaura transformations. Only yields of 43% (entry 1) resp. 35% (entry 4) of the desired products were obtained under the standard conditions established above when coupling 2-tolyl- and 4-methoxyphenylboronic acids. Since, higher yields were expected, different conditions were tested and using DME/water as solvent and $NaHCO_3$ as base resulted in clearly higher yields (entries 2 and 5), however, still lower as compared to the unsubstituted phenylboronic acids. These findings are in good agreement with previous reports in cross-coupling chemistry.[5–8] Applying the improved conditions when transforming (2-fluoropyridin-4-yl)-boronic acid 55% yield of the desired product (entry 9) was obtained. In this case considerable amounts (17%) of 2,2′-diphenyl-[5,5′]-bi-thiazolyl were isolated, as well.



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Scheme 3. Cross-coupling of **3** with boronic acids and esters.

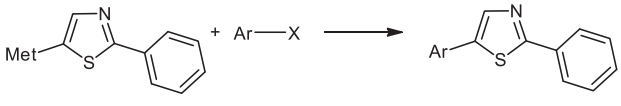
Table 2
Cross-coupling of **3** with boronic acids and esters

Entry	Ar	$B(OR)_2$	Prod.	Conditions	Yield [%]
1	2-Methylphenyl	$B(OH)_2$	**11**	**A** (48 h)	43
2	2-Methylphenyl	$B(OH)_2$	**11**	**E** (16 h)	60
3	2-Methylphenyl	Bpin	**11**	**B** (16 h)	50
4	4-Methoxyphenyl	$B(OH)_2$	**12**	**A** (48 h)	35
5	4-Methoxyphenyl	$B(OH)_2$	**12**	**E** (16 h)	78
6	4-Methoxyphenyl	Bpin	**12**	**B** (16 h)	61
7	2-Thienyl	Bpin	**13**	**B** (16 h)	70
8	3-Pyridinyl	Bpin	**14**	**B** (16 h)	76
9	2-Fluoro-4-pyridinyl	$B(OH)_2$	**15**	**E** (16 h)	55
10	2-Fluoro-4-pyridinyl	Bpin	**15**	**B** (16 h)	63

For reaction conditions see general procedures **A**, **B**, and **E** in the Experimental part.

The following trends were observed when performing the reactions with substituted aryl- and hetarylboronic esters: In the case of 2-tolyl- and 4-methoxyphenylboronic ester (entries 3 and 6) the obtained yields were lower compared to the corresponding acids (entries 2 and 5), whereas the use of (2-fluoropyridin-4-yl)-boronic ester resulted in a higher yield (entry 10 vs entry 9). Coupling with 2-thienyl- and 3-pyridinylboronic ester gave satisfying 70% resp. 76% yield (entries 7 and 8). In this case no experiments with the corresponding free acids were carried out due to stability problems of these heteroaryl donors. Additionally, two more Stille examples using tributyl(2-thienyl)stannane and tributyl(3-thienyl)stannane with 5-bromo-2-phenylthiazole **2** as coupling partners (not shown) were carried out. The corresponding products **13** (2-thienyl, 46%) and **16** (3-thienyl, 29%) were obtained in relatively low yield. Therefore, and due to critical toxicity and lower commercial availability of (hetero)aryl stannanes no further Stille coupling reactions were performed since such transformations would not be competitive to the corresponding Suzuki–Miyaura reactions.

Next, the reactivity of the 5-organometal thiazoles **4** and **5** was investigated in more detail (Scheme 4, Table 3). In order to test and compare the cross-coupling capabilities of **4** and **5** steric and electronic effects were explored by applying substituted coupling partners, such as 2-bromotoluene, 4-bromoanisole, and 4-nitrobromo-benzene.



4: X = $SnBu_3$
5: X = Bpin

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Scheme 4. Suzuki–Miyaura and Stille in 5-position.

In the Suzuki–Miyaura series 2-bromotoluene gave higher yields (entry 1, 76%) than bromobenzene (Table 1, entry 7, 64%), an interesting finding, which might be explained by its less pronounced tendency to undergo homo-coupling reactions to the corresponding biaryl by-product. In contrast to the coupling reactions performed with bromo- and iodobenzene (biphenyl formation) no 2,2′-bitolyl was formed in this case. Using 4-bromoanisole as coupling partner led to a decrease in yield by 20% (entry 3) compared to that with bromobenzene (Table 1, entry 7), whereas 4-nitrobromobenzene resulted in comparable yields (entry 5).

When 2-bromotoluene was used as coupling partner in the Stille series the yield was only slightly lower (entry 2) compared to sterically unhindered iodo- or bromobenzene (Table 1, entries 9 and 10) as well as to the corresponding Suzuki–Miyaura reaction (Table 3, entry 1). Electron poor 4-bromonitrobenzene (entry 6) yielded 69% of the desired product, which is significantly higher compared to the corresponding Suzuki–Miyaura reaction (entry 5). The coupling reaction with electron rich 4-bromoanisole resulted in a significantly lower yield of 38% (entry 4), similar to the Suzuki–Miyaura reaction (entry 3). Apart from the desired compound **12** 16% of 4-bromoanisole as well as 25% of 2,5-diphenylthiazole (as a result of a ligand-exchange reaction)[13] were obtained. Such a by-product was not obtained in any case when halothiazoles were applied as starting materials in cross-coupling reactions indicating that the aforementioned ligand-exchange reaction is not an issue in these cases.

To further broaden the substrate scope of this transformation a series of heteroaryl halides was selected as coupling partners. In the Suzuki–Miyaura series 3-bromopyridine (entry 9) as well as 2-fluoro-4-iodopyridine (entry 11) gave similar yields compared to bromobenzene whereas lower yields were obtained with 2-bromothiophene (entry 7) and 4-chloro-2-methylsulfanylpyrimidine

Table 3
Suzuki–Miyaura and Stille in 5-position

Entry	Met	ArX	Product	Ar	Conditions	Yield [%]
1	Bpin	2-Bromotoluene	**11**	2-Methylphenyl	**D** (60 min)	76
2	$SnBu_3$	2-Bromotoluene	**11**	2-Methylphenyl	**C** (18 h)	68
3	Bpin	4-Bromoanisole	**12**	4-Methoxyphenyl	**D** (60 min)	44
4	$SnBu_3$	4-Bromoanisole	**12**	4-Methoxyphenyl	**C** (48 h)	38
5	Bpin	4-Nitrobromobenzene	**17**	4-Nitrophenyl	**D** (60 min)	58
6	$SnBu_3$	4-Nitrobromobenzene	**17**	4-Nitrophenyl	**C** (18 h)	69
7	Bpin	2-Bromothiophene	**13**	2-Thienyl	**D** (60 min)	44
8	$SnBu_3$	2-Bromothiophene	**13**	2-Thienyl	**C** (24 h)	67
9	Bpin	3-Bromopyridine	**14**	3-Pyridinyl	**D** (6 h)	58
10	$SnBu_3$	3-Bromopyridine	**14**	3-Pyridinyl	**C** (24 h)	75
11	Bpin	2-Fluoro-4-iodopyridine	**15**	2-Fluoro-4-pyridinyl	**D** (60 min)	57
12	$SnBu_3$	2-Fluoro-4-iodopyridine	**15**	2-Fluoro-4-pyridinyl	**C** (21 h)	76
13	Bpin	4-Chloro-2-methylsulfanylpyrimidine	**18**	2-Methylsulfanyl-4-pyrimidinyl	**D** (60 min)	43
14	$SnBu_3$	4-Chloro-2-methylsulfanylpyrimidine	**18**	2-Methylsulfanyl-4-pyrimidinyl	**C** (16 h)	73
15	Bpin	2,4-Dichloropyrimidine	**19**	2-Chloro-4-pyrimidinyl	**D** (7 h)	—
16	$SnBu_3$	2,4-Dichloropyrimidine	**19**	2-Chloro-4-pyrimidinyl	**C** (24 h)	48

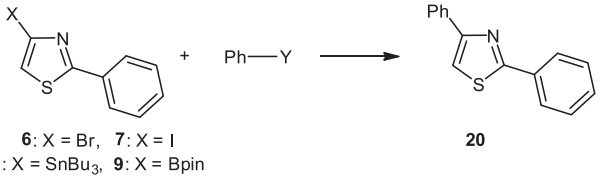
(entry 13). No coupling reaction took place applying 2,4-dichloropyrimidine (entry 15).

In the Stille series we found that **6** undergoes cross-coupling with a wide variety of halides and similar yields compared to iodo- and bromobenzene were obtained except for 2,4-dichloropyrimidine (entry 16). In all cases, the Stille protocol gave significantly higher yields (by 19–48%) compared to the Suzuki–Miyaura protocol.

The trend of this series of experiments shows that 5-thiazolylstannane **6** gives higher yields for most halide coupling partners. Especially, when heteroaryl halides are used this trend is observed in every example. For aryl halides a general trend was not observed. Therefore, if the thiazole has to be applied as organometal coupling partner in 5-position, thiazolestannanes are clearly the more reliable and robust starting materials.

2.2. Cross-coupling in 4-position

Next, the same series of coupling reactions was investigated in 4-position (Scheme 5). When coupling **6** and **7** the same conditions as in the case of 5-halothiazoles **2** and **3** were applied. In the case of phenylboronic acid as coupling partner also good to excellent yields of 83% resp. 94% were obtained (Table 4, entries 1 and 2). Again the iodide starting material gave a higher yield.



Scheme 5. Cross-coupling in 4-position.

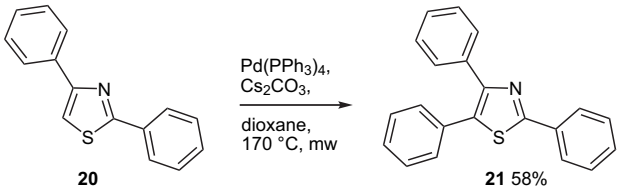
Table 4
Cross-coupling in 4-position

Entry	X	Y	Conditions	Yield [%]
1	Br	$B(OH)_2$	**A** (16 h)	83
2	I	$B(OH)_2$	**A** (16 h)	94
3	Br	Bpin	**B** (21 h)	61
4	I	Bpin	**B** (16 h)	67
5	Br	$SnBu_3$	**C** (16 h)	81
6	I	$SnBu_3$	**C** (16 h)	39
7	Bpin	Br	**D** (2 h)	33
8	Bpin	I	**D** (2 h)	55
9	Bpin	I	**D** (2 h)	70
10	$SnBu_3$	Br	**C** (7 h)	75
11	$SnBu_3$	I	**C** (16 h)	77

For reaction conditions see general procedures **A**–**D** in the Experimental part.

Using phenylboronic acid ester the cross-coupling reactions in 4-position were performed under already optimized conditions resulting in moderate 61% resp. 67% yield of **20** (Table 4, entries 3 and 4). This finding goes in line with the corresponding results in 5-position. Also similar to the 5-position, bromothiazole **6** gave satisfying 81% yield when cross-coupled with tributylphenylstannane (entry 5), whereas iodothiazole **7** provided only 39% of the coupling product (entry 6), which can be explained again by the formation of a homo-coupling product, this time of course 2,2′-diphenyl-[4,4′]-bi-thiazolyl.

When testing the cross-coupling capability of **9** some interesting results were obtained. The same coupling conditions were applied as in the case of **5**. Interestingly, similar yields as in 5-position were obtained when coupling **9** with iodobenzene (entry 8, 55%), whereas only 33% (entry 7) were yielded when using bromobenzene. This observation was quite unexpected since bromobenzene gave better yields than iodobenzene in the case of **5**. Applying bromobenzene as coupling partner 25% of 2,4,5-triphenylthiazole[6g] (**21**) were isolated as well, which suggested an arylation via C–H-activation at the initially formed 2,4-diphenylthiazole (**20**) in 5-position. In a control experiment it could be proven that 2,4-diphenylthiazole (**20**) in fact undergoes C–H-activation under the applied conditions (Scheme 6). A similar transformation was already reported by Otha.[13] Only trace amounts of 2,4,5-triphenylthiazole were formed when using iodobenzene as coupling partner. Since **9** showed limited stability under cross-coupling conditions the coupling reaction with iodobenzene was repeated with an excess of **9** and yielded 70% of the desired coupling product (entry 9).



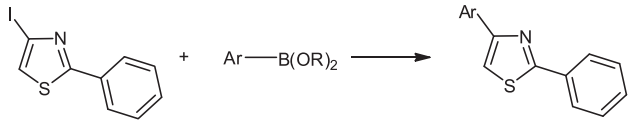
Scheme 6. Control experiment.

Cross-coupling of stannane **8** with bromo- and iodobenzene gave 75% resp. 77% yield, almost identical to the results obtained in 5-position.

The trend for this series of experiments can be summarized as follows: The by far best results were again obtained using halothiazoles in combination with phenylboronic acids as coupling partners followed by the coupling reaction of **6** with tributylphenylstannane. Iodide **7** gave here much lower yield and suffered from by-product formation. 4-Thiazolylstannane **8** gave good results with both halides, whereas boronic ester **9** only with an

excess of iodobenzene. Arylboronic esters did not perform as well as the corresponding boronic acids.

In the next series of experiments, the performance of electronically and sterically more challenging coupling partners was investigated (Scheme 7, Table 5). Coupling of 2-tolyl-, 4-methoxyphenyl- and (2-fluoropyridin-4-yl)-boronic acid gave moderate yields (entries 1, 3, and 7). In all cases these yields were lower compared to the results obtained for the 5-position (Table 5 vs Table 2).



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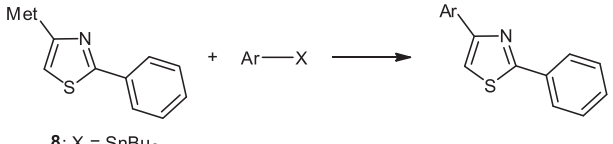
Scheme 7. Cross-coupling of **7** with boronic acids and esters.

Table 5
Cross-coupling of **7** with boronic acids and esters

Entry	Ar	$B(OR)_2$	Product	Conditions	Yield [%]
1	2-Methylphenyl	$B(OH)_2$	**22**	**E** (16 h)	52
2	2-Methylphenyl	Bpin	**22**	**B** (16 h)	80
3	4-Methoxyphenyl	$B(OH)_2$	**23**	**E** (16 h)	62
4	4-Methoxyphenyl	Bpin	**23**	**B** (16 h)	60
5	2-Thienyl	Bpin	**24**	**B** (16 h)	86
6	3-Pyridinyl	Bpin	**25**	**B** (16 h)	70
7	2-Fluoro-4-pyridinyl	$B(OH)_2$	**26**	**E** (16 h)	32
8	2-Fluoro-4-pyridinyl	Bpin	**26**	**B** (16 h)	51

In contrast to the results of the initial series of experiments (Scheme 3, Table 2) substituted aryls where cross-coupled in higher yields when using boronic acid esters as aryl donors (Table 5, entries 2, 4, and 8). In case of heteroaryl coupling partners this can again be attributed to the significantly higher stability of the boronic esters over the boronic acids (entries 7 and 8). The 4-methoxyphenyl group was introduced in basically the same yield with both aryl donors (entries 3 and 4), whereas 2-methylphenyl surprisingly gave a much higher yield using the boronic ester (entries 1 and 2). Regarding a comparison between the results in 4- and 5-position when cross-coupling reactions were performed with boronic esters a general trend was not observed. Applying phenyl- or (2-fluoropyridin-4-yl)-boronic ester as coupling partner better yields were obtained in 5-position, whereas the opposite was true for 2-tolyl- and 2-thienylboronic ester. Especially in the case of 2-tolylboronic ester the yield for coupling into 4-position was much higher than in 5-position. The cross-coupling with 4-methoxyphenyl- and 3-pyridinylboronic ester resulted in similar yields in both positions (Scheme 8).



8: X = $SnBu_3$
9: X = Bpin

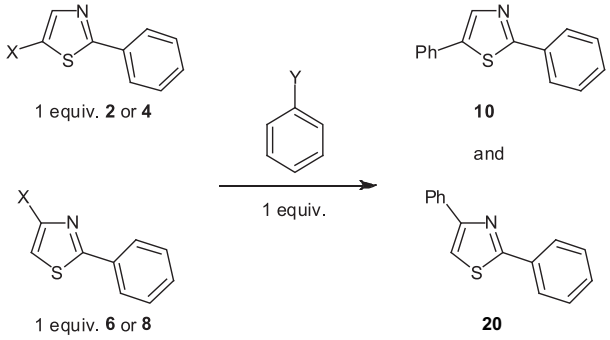
22-28

Scheme 8. Suzuki–Miyaura and Stille in 4-position.

When testing the cross-coupling capability of thiazole-4-boronic ester **9** by applying substituted coupling partners the yields dropped significantly and great purification problems were faced. In the case of 2-bromotoluene two columns were necessary and only 15% of the desired coupling product was obtained (entry 1). The coupling products of 4-bromoanisole and 4-nitrobenzene still contained some by-products after three-resp. twofold column chromatography (entries 3 and 5). Because of the poor results and the elaborate and expensive preparation of starting material **9** no further coupling reactions were carried out in the Suzuki–Miyaura series.

In the case of stannane **8** similar results were observed when performing the coupling reactions in the 4- instead of the 5-position. Good yields were obtained with 4-bromonitrobenzene (entry 6), 2-fluoro-4-iodopyridine (entry 9), and 4-chloro-2-methyl-sulfanylpyrimidine (entry 10) as coupling partners. 3-Bromopyridine (entry 8) gave slightly lower yields when coupled into 4-position, whereas sterically hindered 2-bromotoluene (entry 2) resulted in comparable yields regardless of the coupling position. Only in the cases of 2-bromothiophene (entry 7) and 2,4-dichloropyrimidine (entry 11) considerable lower yields were observed in 4-position. In accordance to the findings before the lowest yields were obtained with 4-bromoanisole (entry 4) and 2,4-dichloropyrimidine (entry 11) as coupling partners. Usually, the formation of 2,2′-diphenyl-[4,4′]-bi-thiazolyl was observed in the range of 2–11%. In some cases (entries 2, 4, 7, and 8) 2,4-diphenylthiazole (**20**) was also formed (2–16%) derived again from a ligand-exchange reaction[14] with the catalyst.

Finally, in order to establish a direct ranking of reaction rates and coupling efficiencies of the two positions a set of competition experiments was set up. In each experiment 1 equiv of 5-substituted 2-phenylthiazole (**2** resp. **4**) and 1 equiv of 4-substituted 2-phenylthiazole (**6** resp. **8**) were coupled with only 1 equiv of the corresponding aryl donor. Standard conditions were applied and the reactions were run over night before the composition of the reaction mixture was determined via GC/MS (Scheme 9).



2: X = Br; **4**: X = $SnBu_3$, **6**: X = Br; **8**: X = $SnBu_3$

Scheme 9. Competition experiments.

When tributylstannanes **4** and **8** were cross-coupled with 1 equiv of bromobenzene the ratio of 2,5-diphenylthiazole (**10**) to 2,4-diphenylthiazole (**20**) was 71:21 (Table 7, entry 1) showing that cross-coupling in position 5 is significantly faster. When bromothiazoles **2** and **6** were cross-coupled with 1 equiv of tributylphenylstannane resp. 1 equiv of phenylboronic acid the ratio of **10** to **20** was 82:18 (Table 7, entry 2) and 86:14 (Table 7, entry 3). These results show that the cross-coupling capabilities of **2** and **6** behave similarly under both Stille and Suzuki conditions, again with higher reaction rates for cross-coupling in position 5.

2.3. Evaluation of the cross-coupling results

Both, Suzuki–Miyaura and Stille reaction proved to be reliable and often high yielding protocols for cross-coupling reactions on thiazoles in certain cases. The Suzuki–Miyaura protocol is certainly favored when thiazole can be used as the halide coupling partner

since much more boronic acids and esters are commercially available and no toxicity issues have to be considered. Furthermore, the Stille reaction with halothiazoles and arylstannanes gave a lower yield and the availability of arylstannanes cannot compete with the availability of the corresponding boronic acids or esters.[15] Additionally, formation of homo-coupling products was favored in the Stille protocol when the more reactive iodothiazoles were used, another disadvantage. Due to stability issues the Suzuki–Miyaura reaction generally results in higher yields when the thiazole component is applied as halide no matter if the other coupling partner is a boronic acid or ester. However, since many different aryl and heteroaryl halides are commercially available and cheap it is usually more practical to perform the reactions when the metal is present on the thiazole system. In this case the application of thiazolestannanes certainly has to be favored since thiazoleboronic esters display pronounced stability problems.

Regarding the generality of the coupling methods, unsubstituted aromatic coupling partners by trend gave better yields than their substituted or hetero-aromatic analogs, which goes in line with previous reports also on other ring systems.[5,16] The only exception encountered was cross-coupling of 4-iodo-2-phenylthiazole (**3**) with phenylboronic acid esters. Generally, the introduction of 4-methoxyphenyl, 2-thienyl- and 2,4-dichloropyrimidinyl resulted in lower yields compared to other coupling partners. The overall best yield was obtained when 5-iodo-2-phenylthiazole (**3**) was coupled with phenylboronic acid. Still, the two preferable protocols show a good functional group tolerance and can be considered as general methods for the preparation of bisarylated thiazoles.

In case of the Stille reaction similar yields were obtained in the 5- as well as in 4-position of the thiazole ring, whereas reactions with boronic acids gave better yields when performed in 5-position. When coupling thiazole halides with boronic esters no general trend could be observed. Performing the reactions in the other direction, i.e., the boronic ester was present on the thiazole, thiazoleboronic esters **5** and **9** gave similar yields only when coupled with iodobenzene, whereas in all other cases better yields could be obtained in 5-position.

2.4. Direct arylation

Additionally, the more recently developed methods for direct arylation in the 5-position of azoles[6h,17] have to be considered as alternative methods in the future and investigations in this regard are also under way in our laboratory. One initial result was already discussed in this contribution (Scheme 6) and further investigations will be reported in due course. A study of the direct arylation of 2-phenylthiazoles on water was published by Turner et al.[17i] Under their conditions, good to excellent yields for the arylation in 5-position were obtained for a series of aryliodides but also some heteroaryliodides. This is definitely a very competitive process since in the two overlapping examples (compounds **12** and **14**) a quantitative yield was obtained when water was used as solvent. Switching to acetonitrile, the yields dropped to 78% (**12**) and 36% (**14**), respectively. Our method using arylboronic acids to get to **12** and **14** gave 78% (**12**) yield and 76% (**14**) indicating that this process is competitive with direct arylation methods under these circumstances. It has to be mentioned that functional group tolerance proved to be good in the direct arylation protocol, for example, even a bromine substituent was tolerated and only the iodide reacted in the direct arylation process.[17i] This indicates that aryliodides are mandatory to get the arylation process to work. Still, direct arylations are limited to the 2- and 5-position on thiazole (if no N-oxidation in 4-position is carried out[17j]), which is still a strong argument for cross-coupling reactions.

2.5. Conclusions

In conclusion, the performed investigations can be used as guidelines for synthetic chemists when choosing their reaction conditions for the arylation of thiazoles. This is certainly of high value since it will help to avoid tedious optimizations when such a synthetic problem is encountered. Additionally, these results might be applicable to some extent also for other azole systems since initial results from our group show a very similar trend on oxazole systems. These results will be reported in due course.

3. Experimental

3.1. General

All reactions were conducted under argon using dried glassware and magnetic stirring. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were dried over Al_2O_3 cartridges prior to use. Flash column chromatography was performed on silica gel 60 from Merck (40–63 μm) using a Büchi Sepacore preparative column. The ratio of crude product to silica gel was 1:30 and in case of cross-coupling products cartridges with 45 g of SiO_2 were used. For thin layer chromatography (TLC) aluminum backed silica gel was used. The solvent mixture used for TLC was also used for column chromatography. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. NMR-spectra were recorded from $CDCl_3$ solution on a Bruker AC 200 (200 MHz) and chemical shifts are reported in parts per million using TMS as internal standard. Elemental analyses were carried out in the Microanalytical Laboratory, Institute of Physical Chemistry, Vienna University.

3.2. 5-Iodo-2-phenylthiazole (3)

To a solution of **1** (1 equiv, 3.10 mmol, 500 mg) in dry THF (15 mL) under argon, *n*-BuLi (1.1 equiv, 3.41 mmol, 1.36 mL, 2.5 M in hexane) was added dropwise at −80 °C. Then, the mixture was stirred at that temperature for 20 min and then warmed to −10 °C. Iodine (1.2 equiv, 3.72 mmol, 944 mg) was dissolved in dry THF (5 mL) and slowly added to the reaction mixture. Before warming to rt the solution was stirred at −10 °C for 1 h and then quenched with saturated NaCl-solution. The obtained aq solution was extracted with three portions of Et_2O, the organic phases were combined and washed with saturated aq $NaHCO_3$, saturated aq $Na_2S_2O_3$, and saturated aq NaCl-solution, dried over Na_2SO_4, filtered, and evaporated. The crude material was purified by MPLC (110 g SiO_2, PE/EtOAc, 10:1) to give **3** (630 mg, 71%) as a pale yellow solid; Anal. Calcd for C_9H_6INS: C, 37.65; H, 2.11; N, 4.88. Found: C, 37.67; H, 2.05; N, 4.78; R_f=0.49 (PE/EtOAc, 10:1); mp 99–102 °C (lit.[6g] mp 101 °C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.39–7.48 (m, 3H), 7.81–7.93 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=70.0 (s), 126.4 (d), 129.1 (d), 130.5 (d), 133.0 (s), 151.5 (d), 173.6 (s).

3.3. 4-Iodo-2-phenylthiazole (7)

To a solution of **6** (1 equiv, 0.42 mmol, 100 mg) in dry Et_2O (7 mL) under argon, *t*-BuLi (1.2 equiv, 0.50 mmol, 0.31 mL, 1.63 M in pentane) was added dropwise at −80 °C. The mixture was stirred for 30 min and then warmed to −10 °C. Iodine (1.2 equiv, 0.50 mmol, 127 mg) was dissolved in dry THF (2 mL) and slowly added to the reaction mixture. Before warming to rt the solution was stirred at −10 °C for 1 h and then quenched with saturated NaCl-solution. The obtained aq solution was extracted with three portions of Et_2O, the organic phases were combined and washed with saturated aq $NaHCO_3$, saturated aq $Na_2S_2O_3$ and saturated aq NaCl-solution, dried

over Na_2SO_4, filtered, and evaporated. The crude material was purified by MPLC (45 g SiO_2, PE/ CH_2Cl_2, 3:1) to give **7** (61 mg, 51%) as a colorless solid. Anal. Calcd for C_9H_6INS: C, 37.65; H, 2.11; N, 4.88; Found: C, 37.58; H, 2.01; N, 4.71; R_f=0.58 (PE/CH_2Cl_2, 3:1); mp 83–85 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.36–7.49 (m, 4H), 7.87–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=95.1 (s), 123.2 (d), 126.5 (d), 129.0 (d), 130.6 (d), 132.4 (s), 170.1 (s).

3.4. General cross-coupling procedures

Except for procedure D all reactions were performed in 12 mL of the corresponding solvent and heated under nitrogen. The reactions were performed on a scale where 100% yield corresponded to 100 mg of the desired product.

*3.4.1. General procedure **A**.* Boronic acid (1 equiv) resp. boronic ester (1 equiv), halide (1.1 equiv), K_2CO_3 (2.5 equiv, 2 M aq solution), and $Pd(PPh_3)_4$ (5 mol %) were dissolved in toluene and refluxed.

*3.4.2. General procedure **B**.* Boronic ester (1 equiv), halide (1.1 equiv), dry K_2CO_3 (3.36 equiv), and $Pd(PPh_3)_4$ (5 mol %) were dissolved in dry DMF and heated at 110 °C.

*3.4.3. General procedure **C**.* The corresponding stannane (1 equiv), halide (1.1–2 equiv), CsF (2.2 equiv), and $Pd(PPh_3)_4$ (5 mol %) were dissolved in dry toluene and refluxed.

*3.4.4. General procedure **D**.* Boronic ester (1 resp. 1.5 equiv), halide (1.1 equiv), Cs_2CO_3 (3.4 equiv, dry), and $Pd(PPh_3)_4$ (5 mol %) were dissolved in dry dioxane (3 mL) and heated under microwave conditions (170 °C, 150 W).

*3.4.5. General procedure **E**.* Boronic acid (1 equiv), halide (1.1 equiv), $NaHCO_3$ (3.3 equiv), and $Pd(PPh_3)_4$ (5 mol %) were dissolved in DME/H_2O (3:1) and heated at 120 °C.

*3.4.6. General workup and purification (**A**–**E**).* The reaction was monitored by TLC and/or GC/MS and stopped when reaction control showed complete consumption of the halide. The reaction mixture was cooled to rt, filtered through Celite and evaporated. The desired, pure product was obtained after MPLC where the solvent mixture used for TLC was also used for column chromatography.

3.5. 2,5-Diphenylthiazole (10)

Appearance: colorless solid; yield see Table 1 (entries 1–10); R_f=0.46 (PE/EtOAc, 10:1); mp: 103–104 °C (lit.[18] 103–104 °C); NMR data of the obtained product were in agreement with the literature.[6g]

3.6. 2-Phenyl-5-*o*-tolyl-thiazole (11)

Appearance: colorless oil; yield see Table 2 (entries 1–3) and Table 3 (entries 1 and 2). Anal. Calcd for $C_{16}H_{13}NS$: C, 76.46; H, 5.21; N, 5.57. Found: C, 76.40; H, 5.14; N, 5.54; R_f=0.64 (PE/EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.51 (s, 3H), 7.27–7.39 (m, 3H), 7.45–7.55 (m, 4H), 7.86 (s, 1H), 8.00–8.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=21.2 (q), 126.2 (d), 126.4 (d), 128.6 (d), 129.0 (d), 130.0 (d), 130.6 (d), 131.0 (d), 133.7 (s), 136.4 (s), 137.6 (s), 142.0 (d), 167.8 (s).

3.7. 5-(4-Methoxyphenyl)-2-phenylthiazole (12)

Appearance: colorless solid; yield see Table 2 (entries 4–6) and Table 3 (entries 3 and 4); R_f=0.35 (PE/EtOAc, 10:1); mp: 98–100 °C (lit.[19] 102–103 °C); NMR data of the obtained product were in agreement with the literature.[19]

3.8. 2-Phenyl-5-(2-thienyl)-thiazole (13)

Appearance: pale yellow solid; yield see Table 2 (entry 7) and Table 3 (entries 7 and 8). Anal. Calcd for $C_{13}H_9NS_2$: C, 64.16; H, 3.73; N, 5.76. Found: C, 63.97; H, 3.79; N, 5.63; R_f=0.12 (PE/EtOAc, 50:1); mp: 76–78 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.01–7.10 (m, 1H), 7.21 (dd, J^1=4.1 Hz, J^2=1.0 Hz, 1H), 7.29 (dd, J^1=6.1 Hz, J^2=1.0 Hz, 1H), 7.39–7.49 (m, 3H), 7.90 (s, 1H), 7.92–8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=125.5 (d), 125.6 (d), 126.4 (d), 128.0 (d), 129.0 (d), 130.1 (d), 132.5 (s), 133.3 (s), 133.5 (s), 139.4 (d), 166.6 (s).

3.9. 3-(2-Phenylthiazol-5-yl)-pyridine (14)

Appearance: colorless solid; yield see Table 2 (entry 8) and Table 3 (entries 9 and 10); R_f=0.25 (PE/EtOAc 1:1); mp: 90–92 °C (lit.[20] 90–91 °C); NMR data of the obtained product were in agreement with the literature.[20]

3.10. 2-Fluoro-4-(2-phenylthiazol-5-yl)-pyridine (15)

Appearance: beige solid; yield see Table 2 (entries 9 and 10) and Table 3 (entries 11 and 12). Anal. Calcd for $C_{14}H_9FN_2S$: C, 65.61; H, 3.54; N, 10.93. Found: C, 65.37; H, 3.47; N, 10.86; R_f=0.40 (PE/EtOAc, 1:1); mp: 126–128 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.07 (s, 1H), 7.30–7.39 (m, 1H), 7.41–7.51 (m, 3H), 7.90–8.02 (m, 2H), 8.15–8.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=106.0 (d, J_{CF}=39.2 Hz), 118.4 (d, J_{CF}=3.9 Hz), 126.6 (d), 129.1 (d), 130.9 (d), 132.9 (s), 134.9 (d, J_{CF}=3.9 Hz), 142.1 (d), 144.0 (d, J_{CF}=8.6 Hz), 148.5 (d, J_{CF}=15.9 Hz), 164.4 (d, J_{CF}=243.0 Hz), 169.8 (s).

3.11. 2-Phenyl-5-(3-thienyl)-thiazole (16)

Prepared according to general procedure C; Appearance: Colorless solid; yield: 29%. Anal. Calcd for $C_{13}H_9NS_2 \cdot 0.20H_2O$ C, 63.23; H, 3.84; N, 5.67. Found: C, 63.35; H, 3.68; N, 5.73; R_f=0.43 (CH_2Cl_2); mp: 100–103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.33 (dd, J^1=4.9 Hz, J^2=1.4 Hz, 1H), 7.37–7.49 (m, 5H), 7.90–8.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=121.5 (d), 126.1 (d), 126.3 (d), 126.9 (d), 129.0 (d), 130.0 (d), 132.0 (s), 133.6 (s), 134.0 (s), 139.2 (d), 166.3 (s).

3.12. 5-(4-Nitrophenyl)-2-phenylthiazole (17)

Appearance: yellow solid; yield see Table 3 (entries 5 and 6); R_f=0.32 (PE/EtOAc, 10:1); mp: 191–194 °C (Lit.[21] 173 °C); NMR data of the obtained product were in agreement with the literature.[21]

3.13. 2-Methylsulfanyl-4-(2-phenylthiazol-5-yl)-pyrimidine (18)

Appearance: colorless solid; yield see Table 3 (entries 13 and 14). Anal. Calcd for $C_{14}H_{11}N_3S_2$: C, 58.92; H, 3.89; N, 14.72. Found: C, 58.77; H, 3.92; N, 14.45; R_f=0.06 (PE/EtOAc, 10:1); mp: 143–144 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.60 (s, 3H,), 7.21 (d, J=5.1 Hz, 1H), 7.37–7.52 (m, 3H), 7.92–8.07 (m, 2H), 8.38 (s, 1H), 8.47 (d, J=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=14.2 (q), 110.8 (d), 126.7 (d), 129.1 (d), 130.8 (d), 133.2 (s), 137.5 (s), 143.7 (d), 157.2 (s), 157.4 (d), 171.6 (s), 173.2 (s).

3.14. 2-Chloro-4-(2-phenylthiazol-5-yl)-pyrimidine (19)

Appearance; pale yellow solid; yield see Table 3 (entries 15 and 16). Anal. Calcd for $C_{13}H_8ClN_3S$: C, 57.04; H, 2.95; N, 15.35. Found: C, 56.84; H, 2.81; N, 14.96; R_f=0.33 (PE/EtOAc, 3:1); mp: 180–183 °C;

^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.42–7.56 (m, 4H), 7.93–8.09 (m, 2H), 8.47 (s, 1H), 8.58 (d, J=5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=114.2 (d), 126.8 (d), 129.2 (d), 131.2 (d), 132.9 (s), 135.8 (s), 144.9 (d), 159.6 (d), 160.2 (s), 161.7 (s), 172.6 (s).

3.15. 2,4-Diphenylthiazole (20)

Appearance: colorless solid; yield see Table 4 (entries 1–11); R_f=0.56 (PE/EtOAc, 15:1); mp: 75–78 °C (lit.[18] 93–94 °C); ^{1}H data of the obtained product were in agreement with the literature.[18] ^{13}C NMR ($CDCl_3$, 50 MHz): δ=112.7 (d), 126.5 (d), 126.6 (d), 128.2 (d), 128.8 (d), 128.9 (d), 130.0 (d), 133.8 (s), 134.5 (s), 156.3 (s), 167.9 (s).

3.16. 2,4,5-Triphenylthiazole (21)

Compound **20** (76 mg, 0.32 mmol, 1 equiv) and bromobenzene (55 mg, 0.35 mmol, 1.1 equiv), Cs_2CO_3 (354 mg, 1.085 mmol, 3.4 equiv), and $Pd(PPh_3)_4$ were heated in dioxane (2 mL) as solvent to 170 °C under microwave irradiation for 2 h. Workup and purification according to the general workup procedure (3.4.6.) gave **21** in 58% yield as colorless oil. *Rf* 0.45 (PE/THF 25:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.27–7.51 (m, 11H), 7.58–7.71 (m, 2H), 7.97–8.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=126.4 (d), 127.8 (d), 128.1 (d), 128.3 (d), 128.7 (d), 128.9 (d), 129.1 (d), 129.6 (d), 130.0 (d), 132.1 (s), 133.1 (s), 133.6 (s), 134.9 (s), 150.8 (s), 165.5 (s).

3.17. 2-Phenyl-4-(*o*-tolyl)thiazole (22)

Appearance: yellow oil; yield see Table 5 (entries 1 and 2) and Table 6 (entries 1 and 2). Anal. Calcd for $C_{16}H_{13}NS$ C, 74, 46; H, 5.21; N, 5.57. Found: C, 76.52; H, 5.34; N, 5.64; R_f=0.47 (PE/CH_2Cl_2, 1:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.43 (s, 3H), 7.11–7.24 (m, 4H), 7.29–7.40 (m, 3H), 7.51–7.62 (m, 1H), 7.88–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=21.2 (q), 115.8 (d), 125.9 (d), 126.6 (d), 128.3 (d), 128.9 (d), 129.9 (d), 130.0 (d), 131.0 (d), 133.8 (s), 134.7 (s), 136.4 (s), 156.7 (s), 166.9 (s).

were in agreement with the literature.[19] ^{13}C NMR ($CDCl_3$, 50 MHz): δ=55.3 (q), 110.9 (d), 114.1 (d), 126.6 (d), 127.5 (s), 127.7 (d), 128.9 (d), 129.9 (d), 133.8 (s), 156.1 (s), 159.6 (s), 167.7 (s).

3.19. 2-Phenyl-4-(2-thienyl)-thiazole (24)

Appearance: beige solid; yield see Table 5 (entry 5) and Table 6 (entry 7); R_f=0.61 (PE/THF, 15:1); mp: 69–71 °C (lit.[21] 77 °C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.10 (dd, J^1=5.1 Hz, J^2=3.7 Hz, 1H), 7.29–7.35 (m, 2H), 7.41–7.51 (m, 3H), 7.53 (dd, J^1=3.7 Hz, J^2=1.2 Hz, 1H), 7.97–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=111.4 (d), 124.3 (d), 125.5 (d), 126.7 (d), 127.7 (d), 128.9 (d), 130.2 (d), 133.4 (s), 138.4 (s), 150.8 (s), 168.0 (s).

3.20. 3-(2-Phenylthiazol-4-yl)-pyridine (25)

Appearance: beige solid; yield see Table 5 (entry 6) and Table 6 (entry 8). Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.75. Found: C, 70.46; H, 4.02; N, 11.61; R_f=0.16 (PE/EtOAc, 3:1); mp: 81–83 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.33 (dd, J^1=7.8 Hz, J^2=4.7 Hz, 1H), 7.38–7.47 (m, 3H), 7.51 (s, 1H), 7.96–8.04 (m, 2H), 8.20–8.30 (m, 1H), 8.56 (dd, J^1=4.7 Hz, J^2=1.4 Hz, 1H), 9.13–9.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=113.8 (d), 123.6 (d), 126.6 (d), 129.0 (d), 130.3 (d), 133.3 (s), 133.7 (d), 147.7 (d), 149.1 (d), 153.1 (s), 168.5 (s).

3.21. 2-Fluoro-4-(2-phenylthiazol-4-yl)-pyridine (26)

Appearance: colorless solid; yield see Table 5 (entries 7 and 8) and Table 6 (entry 9). Anal. Calcd for $C_{14}H_9FN_2S$ C, 65.61; H, 3.54; N, 10.93. Found: C, 65.32; H, 3.45; N, 11.05; R_f=0.23 (PE/EtOAc, 10:1) mp: 153–155 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.47 (t, J=3.0 Hz, 3H), 7.54 (s, 1H), 7.64–7.75 (m, 2H), 7.95–8.10 (m, 2H), 8.25 (d, J=5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=106.4 (d, J_{CF}=39.2 Hz), 117.1 (d), 118.4 (d, J_{CF}=3.9 Hz), 126.7 (d), 129.1 (d), 130.6 (d), 133.0 (s), 146.7 (d, J_{CF}=8.5 Hz), 148.1 (d, J_{CF}=15.5 Hz), 152.4 (d, J_{CF}=3.9 Hz), 164.7 (d, J_{CF}=237.7 Hz), 168.9 (s).

Table 6
Suzuki–Miyaura and Stille coupling reactions in 4-position

Entry	Me	ArX	Product	Ar	Conditions	Yield [%]
1	Bpin	2-Bromotoluene	**22**	2-Methylphenyl	**D** (2 h)	15
2	$SnBu_3$	2-Bromotoluene	**22**	2-Methylphenyl	**C** (23 h)	66
3	Bpin	4-Bromoanisole	**23**	4-Methoxyphenyl	**D** (2 h)	23
4	$SnBu_3$	4-Bromoanisole	**23**	4-Methoxyphenyl	**C** (48 h)	41
5	Bpin	4-Bromonitrobenzene	**27**	4-Nitrophenyl	**D** (2 h)	33
6	$SnBu_3$	4-Bromonitrobenzene	**27**	4-Nitrophenyl	**C** (18 h)	78
7	$SnBu_3$	2-Bromothiophene	**24**	2-Thienyl	**C** (24 h)	51
8	$SnBu_3$	3-Bromopyridine	**25**	3-Pyridinyl	**C** (24 h)	67
9	$SnBu_3$	2-Fluoro-4-iodopyridine	**26**	2-Fluoro-4-pyridinyl	**C** (24 h)	78
10	$SnBu_3$	4-Chloro-2-methylsulfanylpyrimidine	**27**	2-Methylsulfanyl-4-pyrimidinyl	**C** (16 h)	61
11	$SnBu_3$	2,4-Dichloropyrimidine	**28**	2-Chloro-4-pyrimidinyl	**C** (24 h)	30

Table 7
Competition experiments

Entry	Starting Materials	X	Y	Conditions	Products	Ratio
1	4 and 8	$SnBu_3$	Br	C (16 h)	**10** and **20**	71:29
2	2 and 6	Br	$SnBu_3$	C (16 h)	**10** and **20**	82:18
3	2 and 6	Br	$B(OH)_2$	A (16 h)	**10** and **20**	86:14

3.18. 4-(4-Methoxyphenyl)-2-phenylthiazole (23)

Appearance: colorless solid; yield see Table 5 (entries 3 and 4) and Table 6 (entries 3 and 4); R_f=0.49 (PE/EtOAc, 30:1); mp: 130–132 °C (lit.[19] 134.5–135 °C); ^{1}H data of the obtained product

3.22. 2-Methylsulfanyl-4-(2-phenylthiazol-4-yl)-pyrimidine (27)

Appearance: yellow solid; yield see Table 6 (entries 5 and 6). Anal. Calcd for $C_{14}H_{11}N_3S_2$: C, 58.92; H, 3.89; N, 14.72. Found: C, 58.56; H, 3.90; N, 14.55; R_f=0.31 (PE/EtOAc, 10:1); mp: 127–128 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.63 (s, 3H), 7.40–7.52 (m, 3H), 7.82 (d, J=5.1 Hz, 1H), 7.94–8.08 (m, 2H), 8.29 (s, 1H), 8.61 (d, J=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=14.2 (q), 112.8 (d), 120.9 (d), 126.6 (d), 129.0 (d), 130.5 (d), 133.2 (s), 153.9 (s), 158.3 (d), 158.9 (s), 168.7 (s), 172.3 (s).

3.23. 2-Chloro-4-(2-phenylthiazol-4-yl)-pyrimidine (28)

Appearance: colorless solid; yield see Table 6 (entry 11). Anal. Calcd for $C_{13}H_8ClN_3S$: C, 57.04, H, 2.95, N, 15.35. Found: C, 57.12, H, 3.01, N, 14.93; R_f=0.68 (PE/EtOAc, 5:1); mp: 188–190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.43–7.53 (m, 3H), 8.00–8.07 (m, 2H), 8.12 (d, J=5.1 Hz, 1H), 8.39 (s, 1H), 8.69 (d, J=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=114.4 (d), 120.8 (d), 125.1 (d), 127.5 (d), 129.1 (d), 131.3 (s), 150.9 (s), 158.9 (s), 159.8 (s), 160.1 (s), 167.5 (s).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.07.081.

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