Research Article

Sequential Triple Cross-Coupling towards Synthesis of 2,4,5-Trisarylthiazoles

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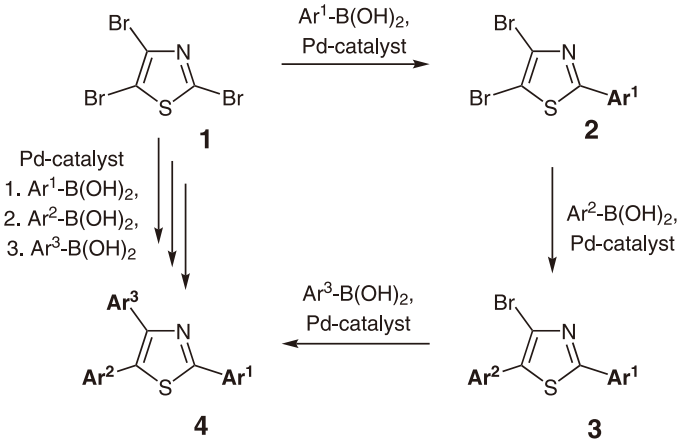
Abstract

Tris-arylated thiazoles were obtained via a simple and efficient protocol starting from tribromo-thiazole in a single operation without intermediate isolation of mono- or bis-arylated intermediates. This protocol showed higher yield as compared to a sequential protocol with isolation of all intermediates. The utility of the method was demonstrated on the synthesis of pharmaceutically relevant thiazolo-neurodazine, an analog of the cell-differentiating compound neurodazine.

Keywords: Suzuki-Miyaura coupling, Boronic acids, Palladium, Thiazole

Triarylated 1,3-azoles play an important role in pharmaceutical chemistry due to their abundance in many biologically active compounds and natural products.[1] Consequently, short and efficient syntheses of such motives enabling rapid and diversity driven compound preparation are highly desirable. Traditionally 1,3-azole derivatives are synthesized via cyclization reactions (condensations) from suitable starting materials.[2],[3] These starting materials usually determine the substitution pattern of the resulting ring system since in most cases the substituents have to be present already in the building blocks prior to cyclization. As a consequence, a slight structural change of the final product may require the synthesis of appropriate starting materials which makes the synthesis of even small compound libraries quite elaborate.

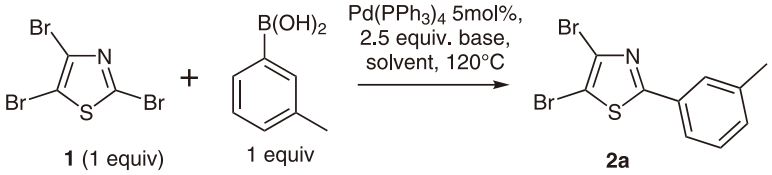
Alternatively, cross-coupling strategies enable direct introduction of aryl substituents on many heterocyclic cores; this opens the possibility to achieve structural variations from a common starting material accelerating library synthesis and, hence, facilitating structure activity relationship studies.[4] In recent years, different protocols for the preparation of triarylated thiazoles were published using either cross-coupling reactions[5],[6],[7] or C-H activation chemistry.[5],[8],[9],[10] However, all these methods were not applicable for further streamlining the synthesis towards a one pot protocol, as they rather required isolation of the mono- and bis-arylated intermediates. Such a one pot protocol would be a facile, time and atom efficient method since purification between synthetic steps can be avoided.[11] Although such a protocol would be highly desirable, it is rarely seen in the literature, so far, since it is difficult to achieve site selectivity under slightly changing reaction conditions. Consequently, addressing and improving such selectivity issues in cascade coupling process is currently receiving substantial interest among the community of synthetic medicinal chemists.[12] Langer *et al*. have successfully demonstrated such one pot syntheses on challenging substrates in context of selectivity issues.[13],[14],[15] With respect to this work we managed to expand this application onto thiazole, benefiting of the speed, the simplicity, the atom-efficiency and the resulting high yields of a one-pot protocol. Herein, we present a site-selective, sequential cross-coupling procedure starting from readily available 2,4,5-tribromothiazole **1** towards 2,4,5-triarylated thiazoles **4** without the purification of intermediate products.



Scheme 1. Stepwise versus semi one-pot synthesis of triarylated thiazoles

To develop an operationally simple one-pot protocol, it is necessary to use similar or ideally identical reaction conditions for each individual cross-coupling step. To identify such reaction conditions, we initially investigated each step separately (**Scheme 1**). One premise of our studies was that a commercially available and cheap catalyst should be used in order to make the protocol appealing and easy to use for any synthetic chemist. The most convenient catalyst in this regard is most likely $Pd(PPh_3)_4$ since it is one of the cheapest Pd-catalysts and proved to be effective on thiazole systems already also in our hands.[16] Since the method should be applied especially for library synthesis for structure activity relationship studies, we focused our investigations on the Suzuki-Miyaura cross-coupling protocol based on the large number of commercially available boronic acids and the fact that these building blocks are non-toxic in contrast to the corresponding stannanes.[17]

We started by screening reaction conditions for the arylation at the most reactive position C2 of tribromothiazole **1** using $Pd(PPh_3)_4$ as catalyst, 3-tolylboronic acid as aryl donor at 120 °C (**Scheme 2**). Three different examples of solvents were chosen representing different polarities (toluene, DME, DMF), as well as three different bases: Cs_2CO_3 and K_2CO_3 (both 2 M aqueous solution) were selected since they are frequently employed in cross-coupling chemistry;[4a],[18] additionally, NEt_3 was tested in order to use a homogenous and cost efficient organic base, as well. We found toluene to be superior to the other solvents independent of the base applied. DMF was significantly less efficient and DME did not give reasonable conversion, at all. Regarding the base, K_2CO_3 turned out to be most effective to give 90% conversion in toluene after 4 hours.



Scheme 2. Stepwise versus semi one-pot synthesis of triarylated thiazoles

Subsequently, we attempted to use the same conditions for coupling in C5- and C4-positions. This step was optimized using 4-methoxyphenylboronic acid to facilitate reaction monitoring by spectroscopic and chromatographic methods. Unfortunately, full conversion was never observed (maximum 45%) when toluene was employed as solvent. From previous work in our group it was already established that a solvent mixture of DME:water (3:1) and $NaHCO_3$ as base performs well for coupling either the C5- or the C4-position of thiazole[19] and we decided to use these conditions for further investigations. It seems that more polar conditions favor cross-coupling in positions 5 and 4; this is corroborated by our finding that a significant amount of 2,5-bisarylated by-product is formed when polar solvents were used. Even though this requires for a solvent change, development of an operational facile protocol avoiding intermediate purification is still possible by simply evaporating toluene and adding the new solvent mixture to ensure efficient coupling into position 5.

Finally, these reaction conditions were applied to the synthesis of 2,4,5-triarylated thiazoles. Initially, the 2-aryl-4,5-dibromothiazoles **2** as well as the 4-bromo-2,5-bisarylthiazoles **3** were isolated in order to obtain reference materials for the one-pot protocol and also to determine overall yields of the three step process for

comparison with the one-pot protocol. Within the first example we used phenylboronic acid in the first coupling step to give 4,5-dibromo-2-phenylthiazole **2b** in 50% yield. For the second step 4-methoxyphenylboronic acid was applied to give a similar yield of 51% of **3a**. The final cross-coupling with 3-tolylboronic acid afforded 62% of the triarylated thiazole **4b** which corresponds to 16% overall yield. Compound **4j** was also prepared in 48% yield (step 1: 49%; steps 2&3 99%) using such a stepwise protocol including intermediate isolation.

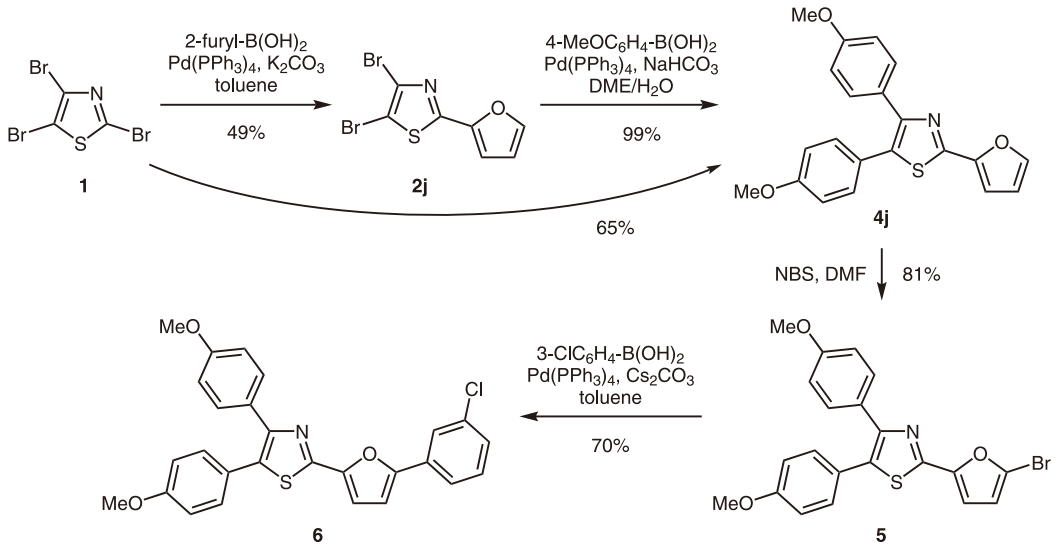
We then streamlined the protocol avoiding intermediate purification. Since a different solvent is used in the first vs. the second and third coupling step the solvent and base had to be changed in between steps 1 and 2. After some optimization, best results were obtained when the reaction solution was filtered through a pad of Celite after the first coupling step and solvent was evaporated (an adapter for directly attaching reaction vials to a rotavap was used). Upon addition of the new solvent mixture (DME:water 3:1), base ($NaHCO_3$), and another 5 mol% catalyst the second and third reaction step were successfully performed by adding the corresponding boronic acids. This represents a good compromise between operational simplicity, reaction rate, and cross-coupling selectivity.

Table 1. Triarylated thiazoles prepared via sequential arylation of tribromothiazole

Entry	Ar^1	Ar^2	Ar^3	Product	Yield [%]
1	Ph	Ph	Ph	**4a**	50
2	Ph	4-$MeOC_6H_4$	3-MeC_6H_4	**4b**	42 (16)
3	Ph	3-MeC_6H_4	4-$MeOC_6H_4$	**4c**	41
4	3-MeC_6H_4	4-$MeOC_6H_4$	Ph	**4d**	46
5	3-MeC_6H_4	Ph	4-$MeOC_6H_4$	**4e**	50
6	4-$MeOC_6H_4$	Ph	3-MeC_6H_4	**4f**	44
7	4-$MeOC_6H_4$	3-MeC_6H_4	Ph	**4g**	41 (31)
8	Ph	4-$MeOC_6H_4$	3-$NO_2C_6H_4$	**4h**	54
9	Ph	3-$NO_2C_6H_4$	4-$MeOC_6H_4$	**4i**	42
10	2-furanyl	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4j**	65 (48)

We applied this semi-one-pot protocol to the synthesis of a series of triarylated thiazoles (**Table 1**). Initially, we simply used phenylboronic acid for all three coupling steps and isolated 2,4,5-triphenylthiazole **4a** in 50% yield which would correspond to a good 79% yield for each individual step (entry 1). The simplified protocol was applied to the synthesis of **4b** and **4j** giving higher yields in much shorter reaction times (entries 2 & 10); we attribute these improvements to significantly lower losses of product upon workup and purification. To demonstrate the utility of the method for library synthesis, we prepared all six possible permutations of triarylated thiazoles **4b**-**4g** using the three boronic acids phenyl-, 3-tolyl-, and 4-methoxyphenylboronic acid. Yield via the simplified protocol are very reproducible yields (average 40-50%) showing that the order in which the different boronic acids are added does not have a significant influence on the efficiency of the coupling (entries 2-7). Even electron withdrawing substituents (e.g. NO_2) were well tolerated and compounds **4h** and **4i** were isolated in 54% and 42% yield.

Finally, we wanted to use this methodology also in the synthesis of a compound with potentially interesting biological activity: Neurodazine was recently discovered as agent to partially transform a skeletal muscle progenitor cell line (C2C12, mouse) into neurons.[20] The compound contains a triarylated imidazole ring as central motif. Since only a partial transformation towards neuronal cells was reported, this lead compound offers room for further improvement of biological activity. In an effort to approach this issue, we became interested in studying different heterocyclic scaffold starting with the synthesis of the thiazole analog of Neurodazine as a demonstration example of the above outlined cascade coupling methodology (**Scheme 3**). The triarylated precursor necessary for "*thiazolo-Neurodazine*" was prepared via the stepwise protocol in 48% overall yield. When employing the simplified semi-one-pot protocol an overall yield of 65% was obtained for **4j**, which corresponds to an excellent 86% yield per individual coupling step. To complete the synthesis of *thiazolo-Neurodazine* **4j** had to be brominated in position 5 of the furyl ring using NBS (81% yield). Finally, **5** was cross-coupled with 3-chlorophenylboronic acid to give the target compound **6** (70% yield).



Scheme 3. Synthesis of thiazolo-Neurodazine

In conclusion an operationally simple protocol for the synthesis of triarylated thiazoles was developed. The target compounds were obtained in higher yields in the semi-one-pot protocol compared to a stepwise procedure. The utility for library synthesis was demonstrated by synthesizing all possible permutations of a combination of three different boronic acids. Additionally, thiazolo-Neurodazine was prepared as an interesting target molecule via the developed methodology. Additional investigations regarding the substrate profile and further improving the selectivity for each coupling step are under way in our laboratory.

Exemplary experimental procedures

General procedure for triarylations in one-pot exemplified for 2-(4-methoxyphenyl)-5-phenyl-4-(3-methylphenyl)thiazole (4e)

An 8 mL vial was charged with 2,4,5-tribromothiazole **1** (1 equiv., 177 mg, 0.55 mmol), 4-methoxyphenylboronic acid (1 equiv., 84 mg, 0.55 mmol), K_2CO_3 (2.5 equiv., 1.38 mmol, 0.69 mL 2 M solution), $Pd(PPh_3)_4$ (0.05 equiv., 32 mg, 0.0275 mmol) and toluene (6 mL). The solution was heated at 120 °C over a period of 20 h until reaction control via GC-MS showed complete consumption of the starting material. The reaction mixture was then allowed to cool to rt, before it was filtrated through celite. The solution was concentrated and re-dissolved in 6 mL of a DME/water mixture (3:1). Phenylboronic acid (1 equiv., 67 mg, 0.55 mmol), $NaHCO_3$ (3.3 equiv., 153 mg, 1.82 mmol) and $Pd(PPh_3)_4$ (5 mol%, 32 mg) were added. The mixture was heated to 120 °C for another 20 h. Then 3-methylphenylboronic acid (1.5 equiv., 112 mg, 0.83 mmol) was added at around 80 °C and the reaction mixture was again heated to 120 °C for 20 h. After cooling to room-temperature the solution was filtrated through celite product **4e** was purified via column chromatography to afford 87 mg (44%) of a yellow oil. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 2.25 (s, 3H), 3.82 (s, 3H), 7.03-7.36 (m, 11H), 7.91 (d, J = 8.61 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 21.0, 55.3, 114.5, 125.6, 125.7, 127.6, 128.0, 128.3, 128.5, 128.8, 129.2, 129.3, 131.4, 131.5, 134.4, 137.4, 149.9, 161.0, 164.4.

One-pot protocol towards 2-(Furan-2-yl)-4,5-bis-(4-methoxyphenyl)thiazole (4j)

Compound **4j** was obtained according to the general procedure above using 2-furylboronic acid (1 equiv., 260 mg, 2.32 mmol) in the first step and 4-methoxyphenylboronic acid (2.25 equiv., 795 mg, 5.23 mmol) in the second step to afford 549 mg **4j** as light brown solid in 65 % yield. mp: 121-124 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.81 (s, 3H), 3.82 (s, 3H), 6.54 (dd, J^1 = 3.52 Hz, J^2 = 1.96 Hz, 1H), 6.78-6.92 (m, 4H), 6.99-7.06 (m, 1H), 7.23-7.36 (m, 2H), 7.43-7.59 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.2, 55.3, 108.6, 112.2, 113.7, 114.2, 124.1, 127.5, 130.3, 130.8, 131.1, 143.4, 149.1, 150.0, 154.9, 159.2, 159.5.

Synthesis of 2-(5-bromofuran-2-yl)-4,5-bis-(4-methoxyphenyl)-thiazole (5)

Substrate **4j** (549 mg, 1.51mmol) was dissolved in 20 mL dry DMF and NBS (1.1 equiv., 296 mg, 1.66 mmol) was added in portions at -3 °C. After complete addition the reaction mixture was stirred at -3 °C for 10 minutes before it was warmed to rt. After complete consumption of **4j** (monitored via TLC) the solvent was evaporated and the crude material purified by column chromatography (LP/EtOAc=10:1) to afford 542 mg (81%) of **5** as yellow solid. mp: 150-153 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 3.80 (s, 3H), 3.82 (s, 3H), 6.46 (d, J = 3.52 Hz, 1H), 6.78-6.91 (m, 4H), 6.98 (d, J = 3.5 Hz), 7.28 (d, J = 8.80 Hz, 2H), 7.48 (d, J = 8.80 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ = 55.2, 55.3, 110.8, 113.7, 114.1, 114.2, 123.3, 123.9, 127.2, 130.3, 130.8, 131.5, 150.0, 150.9, 153.6, 159.3, 159.6.

Synthesis of 2-[5-(3-chlorophenyl)furan-2-yl]-4,5-bis-(4-methoxyphenyl)thiazole (6)

3-Chlorophenylboronic acid (1.1 equiv., 66 mg, 0.46 mmol), bromide **5** (1 equiv., 187 mg, 0.42 mmol), dry Cs_2CO_3 (2 equiv., 273 mg, 0.84 mmol) and $Pd(PPh_3)_4$ (5 mol%, 24 mg) were dissolved in 6 mL dry toluene and heated at 120 °C for 24 h. The reaction mixture was cooled to room temperature, filtered through celite and the solvent was evaporated. The crude material was subjected to column chromatography (LP/EtOAc= 4:1) to afford 140 mg (70%) of **6** as orange solid. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ = 3.73 (s, 3H), 3.75 (s, 3H), 6.69-6.86 (m, 5H), 7.06 (d, J = 3.52 Hz, 1H),7.14-7.28 (m, 4H),7.38-7.50 (m, 2H), 7.50-7.59 (m, 1H), 7.66 (bs, 1H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ = 55.3, 55.3, 107.7, 110.0, 112.7, 113.2, 121.2, 123.0, 123.0, 126.2, 126.9, 129.1, 129.4, 129.8, 130.4, 130.6, 133.8, 147.8, 149.1, 152.2, 153.4, 158.3, 158.5.

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Assoc. Prof. Michael Schnürch, Experienced researcher Michael Schnürch has carried out his diploma and PhD thesis in the group of Prof. Peter Stanetty and received his PhD in 2005 from TU Wien. During his PhD-studies, he was on a 4-month sabbatical in Canada where he worked in the group of Prof. Victor Snieckus at Queens University (Kingston, Ontario). He was then Post-Doc with Prof. Dalibor Sames at the Columbia University in New York City (as Erwin Schrödinger fellow) and conducted research in the field of decarbonylative coupling reactions and sp^3 C-H activation. After his return, he became Assistant Professor at TU Wien and completed his habilitation in 2013. He was promoted to privatdozent and in 2016 to Associate Professor for Organometallic Chemistry, a position he still holds. Additionally, he was the Chair of the very successful COST Action CHAOS (C-H Activation in Organic Synthesis) and was chairing (together with Prof. Nuno Maulide) the European Symposium on Organic Chemistry (ESOC 2019) in Vienna.
His research interests are located in the field of synthesis of heterocyclic compounds for the manipulation of cell differentiation and $GABA_A$ receptors, C-H activation of sp^3 centers, the substitution of gaseous reagents for solid alternatives, organic compounds as phase changes materials for energy storage, green chemistry, photochemistry, and flow chemistry. He has (co)supervised >20 PhD and master students, of which several won best-thesis of the year awards.

Related Products

3-Methylphenylboronic Acid	1g	5g	25g	M1314
Tetrakis(triphenylphosphine)palladium(0)	1g	5g	25g	T1350
2-Furylboronic Acid		1g	5g	F0394
Potassium Carbonate			300g	P1748
4-Methoxyphenylboronic Acid		5g	25g	M1252
Sodium Hydrogen Carbonate			300g	S0561
N-Bromosuccinimide	25g	100g	500g	B0656
3-Chlorophenylboronic Acid		5g	25g	C1613
Cesium Carbonate		25g	100g	C2160