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Synthesis of *endo*- and *exo*-*N*-Protected 5-Arylated 2-Aminothiazoles through Direct Arylation: An Efficient Route to Cell Differentiation Accelerators

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An improved protocol for the direct arylation of *N*-phenyl-*N*-benzyl(thiazol-2-yl)amine by using aryl bromides as aryl donors is reported. The procedure was compared with a previously reported protocol in which aryl iodides were used as arylating agents. The improved direct arylation protocol was applied to structurally isomeric and nonaromatic 3-benzyl-*N*-phenylthiazol-2(3*H*)-imine. The two substrates for direct arylation were obtained from a common starting material, *N*-phenyl(thiazol-2-yl)amine, which was regioselectively benzylated either on the *exo*-cyclic or the *endo*-cyclic nitrogen by using two sets of reaction conditions. For the arylation of the isomeric nonaromatic 3-benzyl-*N*-phenylthiazol-2(3*H*)-imine, exclusive regioselectivity in the 5-position could be achieved.

Introduction

Synthetic organic small molecules have been extremely successful as bioactive compounds. In many of these substances an aromatic heterocyclic ring can be found, which often contains nitrogen. Such heterocyclic substructures introduce rigidity into the molecular scaffold and offer possibilities to interact with functional groups of an active site through their heteroatom(s). Among the many possible heterocycles, thiazole is known to be of significant importance, occurring in a number of biologically relevant molecules such as thiamine (Vitamin B1),[1] ritonavir (an anti-HIV protease inhibitor and one of the active compounds of the blockbuster drug Kaletra),[2a,2b] and the cephalosporin antibiotic cefdinir.[2c,2d] Among the thiazole derivatives, those carrying an amine functionality seem to be of exceptional importance, as can be seen from the examples presented in Figure 1.[3] In particular, arylated thiazolamines seem to be predominant among the bioactive compounds containing thiazole scaffolds.

Two of the examples shown in Figure 1 (**IV** and **V**) have activity as cell differentiation modulators. The use of synthetic small molecules (SySMs) to influence cell differentiation processes would be of significant importance for therapeutic purposes. Intense research in this field is ongoing and an increasing number of such compounds are being disclosed.[3f,3g,4]

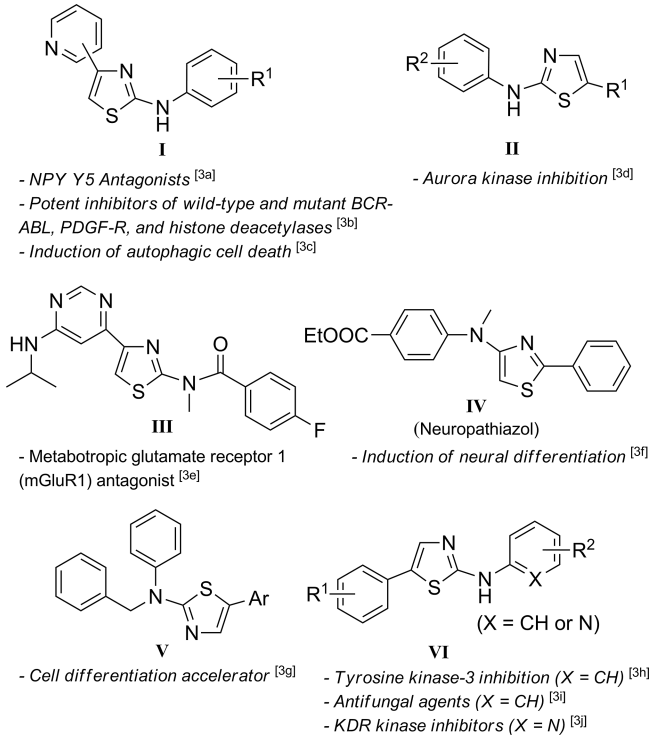

Figure 1. Bioactive (thiazol-2-yl)amine derivatives.

In terms of bioactive thiazoles, neuropathiazole **IV** was reported to induce a differentiation of multipotent adult hippocampal neural progenitor cells towards a neuronal phenotype.[3f] In our group, we have synthesized *N*-benzyl-5-aryl(thiazol-2-yl)amines of general structure **V**. Given that

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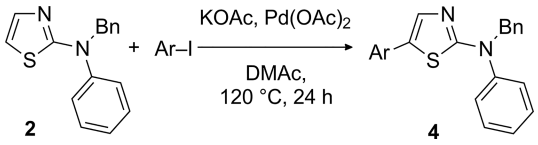
their molecular geometry resembles that of neuropathiazol, we were interested in studying a potentially similar biological activity.[3g] Interestingly, the synthesized compounds indeed had an influence on cell differentiation processes, however in an unexpected way. The compounds showed good activity as differentiation accelerators of C2C12 murine skeletal muscle progenitor cells while at the same time showing no activity as neural differentiation modulators. In this paper, we report an improved synthesis of compounds of general structure **V** and on the synthesis of regioisomers of these compounds bearing a benzyl protecting group on the *endo*-cyclic nitrogen.

Results and Discussion

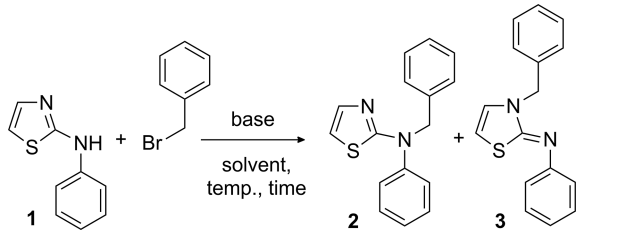
In our previous contribution[3g] we disclosed a new method for the synthesis of 5-aryl-*N*-benzyl-*N*-phenyl-(thiazol-2-yl)amines by regioselective direct C-5 arylation. Under palladium acetate catalysis, a range of substituted 2-aminothiazoles reacted with aryl iodides in the presence of potassium acetate. No ligands were required in this reaction. In agreement with previous reports,[5] the arylation took place selectively at the 5-position of the substrate (Scheme 1).



Scheme 1. Direct arylation of *N*-benzyl-*N*-phenyl(thiazol-2-yl) amine by using aryl iodides as the aryl source.

During the synthesis of the starting material **2** we observed the formation of *endo*-cyclic benzylated compound **3** as a byproduct (Table 1).

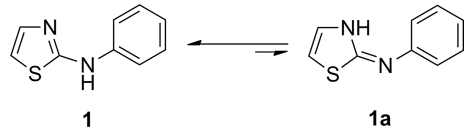
Table 1. Synthesis of *N*-*endo*- and *N*-*exo*-benzylthiazolamine.[a]



Entry	Base	Solvent	*T* [°C]	*t* [h]	Conv. [%][b]	Ratio **2/3**[b]
1	Et_3N	dioxane	120	24	76	1:7
2	Et_3N	dioxane	120	48	78	1:4
3	NaH	DMF	r.t.	5	66	5:1
4[c]	NaH	DMF	r.t.	5	75	5:1
5[c]	NaH	DMF	r.t.	7	76	5:1

[a] Reaction conditions: Substrate **1** (1 equiv.), benzyl bromide (1.3 equiv.), base (1.3 equiv.) as 0.3 M solution in the respective solvent. [b] Conversion and ratio of products was determined by GC analysis with dodecane as internal standard. [c] Base (2.0 equiv.) was used and NaI (0.1 equiv.) was added.

We explained the formation of this compound by considering that **1** is in equilibrium with its *exo*-cyclic imine form **1a** (Scheme 2). Such an equilibrium has been reported previously for *N*-phenyl-(thiazol-2-yl)amine.[6] Both of these compounds can be deprotonated and subsequently benzylated, leading to the two regioisomeric products observed. As judged by their pK_a values, compound **1** (pK_a = 4.33) and **1a** (pK_a = 6.30)[7a] are reasonably acidic, making triethylamine (pK_a = 10.7)[7b,7c] sufficiently basic for their deprotonation. Nevertheless, the type of base used for deprotonation seems to have a pronounced influence on the selectivity of the benzylation reaction.



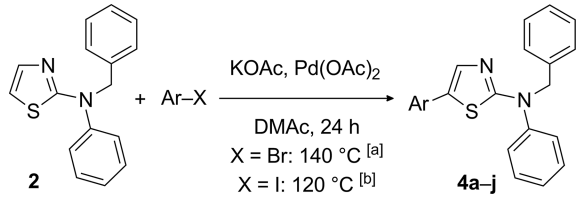
Scheme 2. Amine–imine equilibrium in 2-aminothiazole.

We were interested in developing reaction conditions that lead to specific formation of either **2** or **3**. We found the best **2/3** selectivity of 5:1 was obtained by using NaH as base in *N*,*N*-dimethylformamide (DMF) at room temperature for 5 h (Table 1, entries 3–5). While maintaining the selectivity, the conversion of 66% (entry 3) was improved to 76% when NaH (2 equiv.) and a catalytic amount of NaI were applied (entry 4). To invert the regioselectivity, a change in base was most important: When the reaction was conducted at 120 °C in dioxane using triethylamine as base, GC-analysis showed the formation of the products in a **2/3** ratio of 1:7 after 24 h with a conversion of 76% (entry 1). Longer reaction times led to slightly increased conversion but also to a decrease in selectivity (**2/3** ratio 1:4 after 48 h; entry 2). This indicates that isomerization of the products can occur under the applied reaction conditions. The outcome of these experiments can be rationalized by a switch in mechanism depending on the applied base. When NaH is used for deprotonation, benzylation might take place, whereas for deprotonation with triethylamine benzylthiazolium formation could precede deprotonation. This hypothesis is supported by the fact that the *endo*-cyclic nitrogen can be expected to have a lower nucleophilicity when compared with the corresponding anion and therefore requires higher temperatures to react. We were able to isolate both benzylation products **2** and **3** by column chromatography, although this was challenging because of their very similar R_f values in common mobile phases. Both **2** and **3** could be crystallized from their mixture in dichloromethane and both were obtained in pure form.

We have already reported the direct arylation of **2** by using aryl iodides as aryl source.[3g] Before starting to investigate the direct arylation of **3**, we tested whether we could use the corresponding aryl bromides instead because they are more abundantly available reagents. In our original publication,[3g] we noted that bromobenzene gave low conversion under the applied reaction conditions [KOAc (2 equiv.), $Pd(OAc)_2$ (1 mol-%), anhydrous DMAc, 120 °C]. We now revisited this procedure and found that increasing

the temperature to 140 °C was sufficient to obtain good yields of coupled products within 24 h by using only 1.5 equiv. of aryl bromides. The results of the coupling protocol for both aryl halides are compared in Table 2.

Table 2. Direct arylation of **2**.



Entry	R	Product	Yield [%][a]	
			X = Br	X = I
1	phenyl	**4a**	70	85
2	3-chlorophenyl	**4b**	88	n.i.[b]
3	4-ethylbenzoate	**4c**	80	60
4	4-methoxyphenyl	**4d**	62	47[c]
5	*m*-tolyl	**4e**	60	n.i.[b]
6	4-fluorophenyl	**4f**	78	71
7	4-chlorophenyl	**4g**	83	n.i.[b]
8	*p*-tolyl	**4h**	59	77
9	*o*-tolyl	**4i**	60	80
10	4-nitrophenyl	**4j**	44	20
11	2-fluoropyridin-3-yl	**4k**	n.i.[b]	94

[a] Reaction conditions: Procedure A (reaction with ArBr): Substrate **2** (1.0 equiv.), ArBr (1.5 equiv.), KOAc (1.5 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 140 °C for 24 h. Procedure B (reaction with ArI): Substrate **2** (1.0 equiv.), ArI (2.0 equiv.), KOAc (2.0 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 120 °C for 24 h. [b] n.i.: not investigated. [c] Reaction conducted as for Procedure B but with 10 mol-% catalyst loading.

In the case of substrate **2**, there is no clear trend regarding whether bromides or iodides are the preferred aryl source. In several cases, yields were considerably higher when using aryl bromides instead of the corresponding aryl iodides (Table 2, entries 3, 4, 6, and 9), but other iodides proved to be superior (entries 1 and 8).

Bromo- and iodobenzene gave product **4a** in 70 and 85%, respectively (entry 1). Regarding other aryl halides, both electron-deficient and -rich substrates were accepted in the reaction. However, 4-iodoanisole required a higher catalyst loading (10 mol-%), indicating that the reaction is slower with electron-donating substituents. Furthermore, 4-bromo- and 4-iodonitrobenzene gave lower yields of **4j** compared with the other examples, which can be explained by the ability of the nitro group to coordinate metal catalysts.[8] An ester functionality in the *para*-position was also well tolerated, irrespective of the halide leaving group (**4c**, entry 3). Bromobenzenes bearing a chloro- or fluoro- substituent also gave good yields in the reaction (**4b**, **4f**, and **4g**, entries 2, 6, and 7).

Products **4e**, **4h**, and **4i** were obtained in essentially identical yields (59–60%) in the coupling of 2-, 3-, and 4-bromotoluene, which indicates that the reaction is not sensitive to sterically demanding reaction partners (entries 5, 8, and 9). In the case of 2-iodo- and 4-iodotoluene, products **4i** and **4h** were also obtained with the same yield within experimental error; however, the reaction with iodo-precursors was more efficient by about 20% when compared to the bromotoluene series. Three examples were performed with only aryl bromides (entries 2, 5, and 7) and these gave generally good yields. An excellent yield was obtained by using 2-fluoro-3-iodopyridine as coupling partner. In this case, product **4k** was isolated in 94% yield.

We then set out to investigate the direct arylation of regioisomeric imine substrate **3**. 2-Iminothiazoles were previously synthesized by condensation of α-halo ketones and thiourea derivatives through the Hantzsch reaction[9a–9f] or Glaser–Hay oxidative coupling between aryl alkynes and an *N*-hydroxythiourea.[9g] On the other hand, 2-iminothiazoles were observed in the methylation reaction of 2-anilinothiazoles[10a] as well as in copper diacetate-catalyzed phenylation of 2-aminothiazole with triphenylbismuth diacetate.[10b] A selection of medicinally relevant compounds containing the iminothiazole scaffold is shown in Figure 2. These compounds and other members of the compound class have been reported to possess activity as platelet GPIIb/IIIa receptor antagonists,[11a] HIV-1 reverse transcriptase inhibitors,[11b,11c] anti-inflammatory agents, kinase inhibitors,[11d–11g] cytotoxic agents[11h,11i] and a range of other activities.[12] Moreover, pifithrin (Pft-α), a compound containing the 2-iminothiazole skeleton, has recently been identified as a potent inhibitor of p53 in vivo. This might be promising for the treatment of major neurodegenerative disorders (Parkinson's disease, Alzheimer's disease).[13]

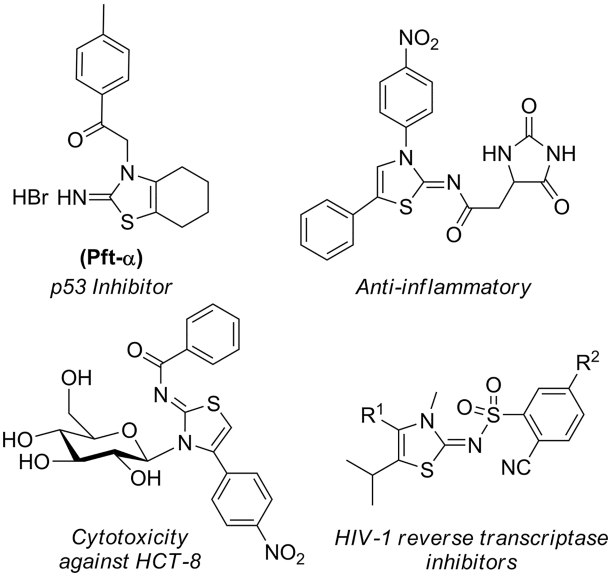


Figure 2. Bioactive 2-iminothiazolines derivatives.

In a preliminary experiment, we found that, under the experimental conditions used for the Pd-catalyzed arylation of 2,2-iminothiazoles, **3** also formed an arylated product with unknown regioselectivity. Due to the loss of aromaticity in **3**, the direct arylation can be considered as a Heck cross-coupling on the only double bond left on the thiazole ring. Both ends of the double bond are substituted with

heteroatoms, which makes prediction of the regiochemistry difficult; both **5a** and **6a** are potential products (Figure 3).

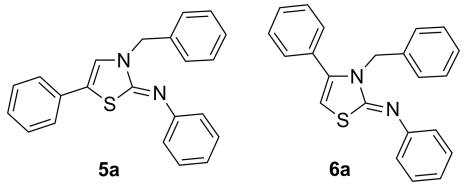
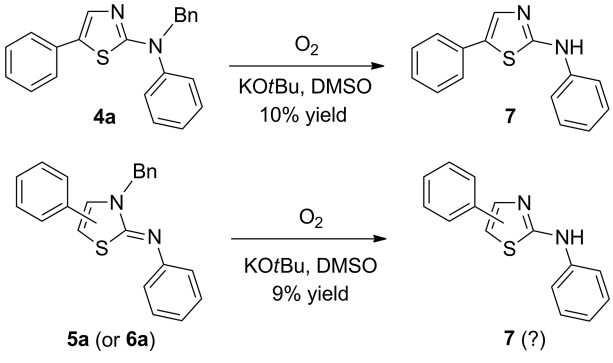


Figure 3. Possible arylation products of *endo*-*N*-benzyl(thiazol-2-yl)amine.

We subjected **3** to the direct arylation conditions and were very pleased to find that arylation of **3** occurred with similar efficiency to that observed with **2**, in spite of its nonaromatic character, giving 55 and 79% yield using bromobenzene and iodobenzene, respectively. However, assignment of regiochemistry was not possible at this point because arylation could occur either in position 5 to give **5a** or in position 4 to give **6a** (Figure 3). Therefore, it was necessary to determine the structure of the obtained product unambiguously. Attempts to elucidate the structure by comparison of NMR spectra with predicted values or by 2D-NMR experiments were inconclusive. We therefore decided to cleave the benzyl group of **4a** (product of aminothiazole arylation with proven regiochemistry) and **5a**/**6a** and to compare the deprotected products. If the arylation of **3** had occurred in position 5, the same product should be obtained after deprotection.[13]

Initially, reductive cleavage was attempted. However, **4a** and **5a**/**6a** were completely unreactive, even under high pressure (up to 100 bar H_2), high temperature (100 °C) or high loadings of the Pd/C catalyst in a continuous flow reactor. The reason is likely catalyst poisoning by the sulfur-containing thiazole moiety.[14] Alternatively, an oxidative method for N-debenzylation was applied: Treatment of compounds **4a** and **5a**/**6a** with potassium *tert*-butoxide and oxygen in dimethyl sulfoxide (DMSO) at room temperature gave the deprotected compounds,[15] albeit in low yield (10% starting from **4a** and 9% starting from **5a**/**6a**; Scheme 3).

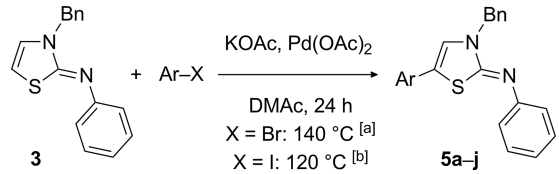


Scheme 3. Deprotection of compounds **4a** and **5a** (**6a**).

The remaining starting materials were decomposed after the reaction. Given that the only purpose of these reactions was to prove the regioselectivity of arylation, we did not optimize the deprotection protocol further. The results of the GC/MS analysis and the data from the ^{1}H NMR and ^{13}C NMR spectra of the two deprotection products were compared and these turned out to be identical. Compound **7** was obtained in both cases, establishing that the direct arylation of **3** occurred in position 5, giving access to compound **5**.

An arylation reaction such as this is, to our knowledge, unprecedented; hence, we investigated its substrate scope. In the case of substrate **3**, aryl iodides gave considerably higher yields compared with those of the corresponding aryl bromides (Table 3), yields were slightly lower compared with those of **2**, especially in the case of aryl bromides as reaction partners.

Table 3. Direct arylation on **3**.



Entry	Ar	Product	Yield [%]	
			X = Br[a]	X = I[b]
1	phenyl	**5a**	55	79
2	3-chlorophenyl	**5b**	58	n.i.[c]
3	4-ethylbenzoate	**5c**	49	58
4	4-methoxyphenyl	**5d**	21	41
5	*m*-tolyl	**5e**	56	n.i.[c]
7	4-fluorophenyl	**5f**	34	51
6	4-chlorophenyl	**5g**	50	n.i.[c]
8	*p*-tolyl	**5h**	52	68
9	*o*-tolyl	**5i**	50	73
10	4-nitrophenyl	**5j**	41	86
11	2-fluoropyridin-3-yl	**5k**	n.i.[c]	51

[a] Reaction with ArBr: Substrate **3** (1.0 equiv.), ArBr (1.5 equiv.), KOAc (1.5 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 140 °C for 24 h. [b] Reaction with ArI: Substrate **3** (1.0 equiv.), ArI (2.0 equiv.), KOAc (2.0 equiv.) and $Pd(OAc)_2$ (0.01 equiv.) in DMAc (0.33 M) at 120 °C for 24 h. [c] n.i.: not investigated.

For some products, the differences in product yield were particularly pronounced. 1-Bromo-4-fluorobenzene (**5f**; 34 vs. 51%; entry 7) and 4-bromoanisole (**5d**; 21 vs. 41%; entry 4) gave a notably lower yield. The most striking difference was observed for the reaction of 4-iodonitrobenzene, for which a yield of 86% was obtained when compared with 41% for the corresponding bromide reaction (**5j**; entry 10). 2-Bromotoluene as a sterically demanding coupling partner gave 50% yield (entry 9), which is in the same range as for 3-bromo- and 4-bromotoluene (56% **5e** and 52% **5i**; entries 5 and 8). This indicates that steric bulk is not an issue in this coupling reaction.

Electron-deficient coupling partners, such as 4-nitro or 4-carboxyethyl-substituted benzenes were well tolerated (49%, **5c**; 41%, **5j**; entries 3 and 11). Finally, 1-bromo-3-chlorobenzene and 1-bromo-4-chlorobenzene worked as well as most other aryl bromides (entries 2 and 6). As a heteroaromatic example, 2-fluoro-3-iodopyridine (**5k**, 51%; entry 11) was well tolerated.

Conclusions

We have described an improved method for the direct arylation of *N*-phenyl-2-aminothiazole **2**, applying aryl bromides as arylating reagents. Compared with our previously disclosed protocol using aryl iodides, the new method has the advantage of using less expensive and more readily available reagents. In the direct arylation reaction of **2**, comparable yields were obtained when using aryl bromides or iodides. The same protocol was also used for the arylation of iminothiazole **3** in position 5. In this case, higher yields were achieved by using aryl iodides. The regioselectivity of this reaction was unequivocally determined by deprotection of **4a** and **5a**, which resulted in the formation of the same compound **7**. Biological activity evaluation of compounds of general structure **5** is underway. Preliminary results point to an activity as cell differentiation accelerators similar to that of compounds **4**. Details of this biological study will be reported in due course.

Experimental Section

General Methods: Chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted. Palladium catalysts and ligands were stored under argon in a desiccator and weighed in air. Reactions were followed by TLC (0.25 mm silica gel 60-F plates). Visualization was accomplished with UV light. Flash chromatography was carried out on silica gel 320–400 mesh by MPLC. All solvents for MPLC were distilled prior to use. Kugelrohr distillation was carried out with Büchi GKR-51 apparatus. ^{1}H and ^{13}C NMR spectra were recorded from $CDCl_3$ solutions with a Bruker AC 200. Chemical shifts (δ) are reported in parts per million (ppm) with tetramethylsilane (TMS) as internal standard. The abbreviations used to report the data are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). GC–MS spectra were recorded either with a Thermo Finnigan Focus GC/DSQ II using a standard capillary column BGB 5 (30 m × 0.25 mm ID) or with a Thermo Trace 1300/ISQ LT using a standard capillary column BGB 5 (30 m × 0.25 mm ID). HRMS for compounds that were not previously reported were analyzed by LC-IT-TOF-MS in only positive ion detection mode with the recording of MS and MS/MS spectra. Melting points were determined with a Stanford Research Systems MPA100 OptiMelt Automatic Melting Point System. Data is given in 0.5 °C intervals.

Direct Arylation Using Aryl Bromides. General Procedure A: A 7 mL vial equipped with a screw cap, septum, and a magnetic stir bar was charged with substrate *N*-benzyl-*N*-phenyl(thiazol-2-yl)amine (**2**) or *N*-[3-benzylthiazol-2(3*H*)-ylidene]aniline (**3**) (0.5 mmol, 1.0 equiv.), aryl bromide (0.75 mmol, 1.5 equiv.), KOAc (74 mg, 0.76 mmol, 1.5 equiv.), and $Pd(OAc)_2$ (1 mg, 0.005 mmol, 0.01 equiv.). The vial was closed with a septum, evacuated, and flushed with argon three times. Anhydrous DMAc (3 mL) was added by using a syringe and the mixture was heated to 140 °C for 24 h. The reaction mixture was cooled to room temperature and then diluted with ethyl acetate (5 mL) and filtered through a pad of Celite. The organic phase was washed with saturated ammonium chloride three times and with brine, then dried with sodium sulfate. The solvent was removed under reduced pressure. Purification was conducted by MPLC on silica gel with light petroleum (LP)/EtOAc mixtures containing 1 vol.-%. triethylamine (TEA). In several cases, where some starting material was found as an impurity in the product, Kugelrohr distillation was applied for purification.

Direct Arylation Using Aryl Iodides. General Procedure B: This procedure was similar to procedure A, but it involved the use of an aryl iodide (1.0 mmol, 2.0 equiv.), KOAc (98 mg, 1.0 mmol, 2.0 equiv.) instead of an aryl bromide (0.75 mmol, 1.5 equiv.), KOAc (74 mg, 0.76 mmol, 1.5 equiv.). Reaction heated to only 120 °C for 24 h. The work-up and the procedures for the isolation of the products were as described for Procedure A.

Representative Examples

***N*-Benzyl-*N*-phenylthiazol-2-amine (2):** In a 7 mL vial equipped with a screw cap with septum and a magnetic stir bar, *N*-phenylthiazol-2-amine (1 g, 5.68 mmol), NaH 55% (0.48 g, 11 mmol) and NaI (85 mmg, 0.57 mmol) were dissolved in DMF (5 mL), then benzyl bromide (0.88 mL, 7.39 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with excess H_2O, and the mixture was extracted with EtOAc (15 mL). The organic phase was washed with saturated NH_4Cl solution two times and with saturated Na_2CO_3, then dried with Na_2SO_4. All solvent was evaporated under reduced pressure to give a product mixture (1.133 g) containing *N*-benzyl-*N*-phenylthiazol-2-amine (**2**) and *N*-[3-benzylthiazol-2(3*H*)-ylidene]aniline (**3**) in a ratio of 5:1. The product mixture was dissolved in the minimum amount of warm CH_2Cl_2 (2–3 mL), then cooled to –5 °C and left to crystallize overnight. The crystals were collected by filtration and washed three times with cold LP (–5 °C), then dried under reduced pressure to give *N*-benzyl-*N*-phenylthiazol-2-amine (861 mg, 57% isolated yield) as yellow-brown needle crystals; m.p. 79–80 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.19 (s, 2 H, CH_2), 6.47 (d, J = 3.6 Hz, 1 H), 7.21–7.33 (m, 11 H) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 56.5 (CH_2), 107.7, 126.1 × 2, 126.8, 127.2, 127.7 × 2, 128.5 × 2, 129.8 × 2, 137.6, 139.3, 145.3, 170.9 ppm. MS: *m*/*z* (%) = 266 (56) [M^+], 174 (100), 167 (30), 131(11), 91(16). HRMS: *m*/*z* calcd. for $[M + H]^+$ 267.0850; found: 267.0955, (difference: 1.87 ppm).

***N*-[3-Benzylthiazol-2(3*H*)-ylidene]aniline (3):** In a 50 mL round-bottom flask with magnetic stirrer bar and condenser, *N*-phenylthiazol-2-amine (1 g, 5.68 mmol), benzyl bromide (0.90 mL, 7.58 mmol) and triethylamine (0.80 mL, 5.68 mmol) were dissolved in 1,4-dioxane (15 mL). The mixture was heated to 120 °C for 24 h, then the reaction was quenched with excess H_2O and extracted with EtOAc (15 mL). The organic phase was washed three times with brine, then dried with Na_2SO_4. All solvent was evaporated under reduced pressure to obtain the product mixture (1.178 g) containing **2** and **3** in a ratio of 1:7. The product mixture was dissolved in the minimum amount of warm CH_2Cl_2 (2–3 mL), then cooled to –5 °C and left to crystallize overnight. The crystals were filtered and washed three times with cold LP (–5 °C) then dried under reduce pressure to obtain *N*-benzyl-*N*-phenylthiazol-2-amine (831 mg, 55% isolated yield) as light-brown needle crystals; m.p. 94–95 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.06 (s, 2 H, CH_2), 6.50 (d, J = 4.9 Hz, 1 H), 6.85 (d, J = 4.9 Hz, 1 H), 7.04–7.10 (m, 3 H), 7.26–7.36 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 49.7 (CH_2), 97.6, 121.4 × 2, 122.9, 126.6, 127.8, 128.1 × 2, 128.8 × 2, 129.4 × 2, 136.7, 151.6, 158.6 ppm. MS: *m*/*z* (%) = 266 (42) [M^+], 167 (100), 131 (10), 91 (18), 15 (8). HRMS: *m*/*z* calcd. for $[M + H]^+$ 267.0950; found: 267.0954 (difference: 1.50 ppm).

***N*-Benzyl-*N*,5-diphenylthiazol-2-amine (4a):** This compound was synthesized according to General Procedure A starting from *N*-benzyl-*N*-phenylthiazol-2-amine (**2**) (266 mg, 1.0 mmol), bromobenzene (105 μL, 157 mg, 1.5 mmol), KOAc (147 mg, 1.5 mmol), and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol). Purification was carried out in

two steps: First MPLC was carried out (silica gel; LP/EtOAc with 1 vol.-%. TEA as eluent), which yielded the product mixture (262 mg) containing the desired product **4a** and starting material. The product mixture was purified by Kugelrohr distillation at 100 °C in vacuo to obtain *N*-benzyl-*N*,5-diphenylthiazol-2-amine (239 mg, 70%) as a light-brown solid; m.p. 65–66 °C; R_f = 0.45 (LP/EtOAc, 5:2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.20 (s, 2 H, CH_2), 7.26–7.39 (m, 15 H), 7.46 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 49.7 (CH_2), 97.6, 121.4×2, 122.9, 126.6, 127.8, 128.1×2, 128.8×2, 129.4×2, 136.7, 151.6, 158.6 ppm. MS: *m*/*z* (%) = 343 (9), 342 (38) [M$^+$], 252 (17), 251 (85), 250 (61), 219 (16), 167 (77), 134 (20), 91 (100). HRMS: *m*/*z* calcd. for [M + H]$^+$ 343.1263; found: 343.1281 (difference 5.25 ppm).

***N*-[3-Benzyl-5-(2-fluoropyridin-3-yl)thiazol-2(3*H*)-ylidene]aniline (5j):** Synthesized according to General Procedure B on a 0.26 mmol scale, yield 48 mg (51%); light-brown solid; m.p. 139–140 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.06 (s, 2 H, CH_2), 6.98–7.07 (m, 4 H, ArH), 7.16 (d, $J_{H,F}$ = 1.2 Hz, 1 H, H-4), 7.18–7.42 (m, 8 H, ArH), 7.86–7.90 (m, 1 H, Pyr-H6) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.0 (CH_2), 106.9 (d, $^3J_{C,F}$ = 8.6 Hz), 115.6 (d, $^2J_{C,F}$ = 28 Hz), 121.3 (2 C), 121.8 (d, $^4J_{C,F}$ = 4.1 Hz), 123.6, 127.8 (d, $^3J_{C,F}$ = 16.1 Hz), 128.1 (3 C), 128.9 (2 C), 129.6 (2 C), 136.2 (d, $^4J_{C,F}$ = 3.8 Hz), 136.3, 143.6 (d, $^3J_{C,F}$ = 15.2 Hz), 151.1, 155.7, 158.7 (s, $^1J_{C,F}$ = 240.6 Hz) ppm. MS: *m*/*z* (%) = 361 (26) [M$^+$], 269 (30), 167 (100), 110 (8), 91 (75). HRMS: *m*/*z* calcd. for [M + H]$^+$ 362.1114; found: 388.1118 (difference: 1.03 ppm).

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