DOI: 10.1002/adsc.201300591

Convenient and Reliable Routes Towards 2-Aminothiazoles: Palladium-Catalyzed *versus* Copper-Catalyzed Aminations of Halothiazoles

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Received: July 3, 2013; Revised: September 9, 2013; Published online: November 11, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300591.

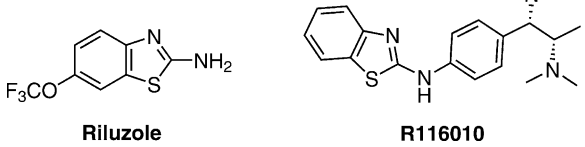
Abstract: Two efficient methods for the amination of 2-halothiazoles are presented here. A first protocol requires a Pd/L system. Several 2-aminothiazoles were synthesized under optimized conditions and isolated in good yields. The first palladium-catalyzed C–N coupling reactions between 2-halothiazoles and primary alkylamines are presented. In a second part, ligand-free copper-catalyzed aminations of 2-halothiazoles by alkylamines and aniline in a green solvent have been developed. The protocol is very effective for primary and secondary amines and perfectly tolerates the presence of another halide moiety on the 2-halothiazole. The reaction occurs under the assistance of microwave irradiation, which drastically decreases the reaction time. The reaction leads to the formation of 2-aminothiazoles, key molecules in pharmaceutical research.

Keywords: 2-aminothiazoles; catalysis; C–N coupling; copper; microwaves; palladium

Introduction

Efficient synthesis of 2-aminothiazoles have attracted a lot of attention since these compounds represent powerful motifs in pharmaceutical research.[1] Riluzole, for instance, has been used since decades in the treatment of amyotrophic lateral sclerosis,[2] a fatal and neurodegenerative disorder. R116010, meanwhile, has been found as an efficient agent to inhibit the all-*trans*-retinoic acid metabolism,[3] playing a role in the differentiation and proliferation of epithelial tissues (Figure 1).

Besides these applications, 2-aminothiazoles are also key intermediates in the synthesis of numerous biological molecules.[4] Classically, the amino moiety is either already present or is introduced subsequently *via* coupling or substitution reactions. Among the most common strategies to form 2-aminothiazoles, nucleophilic substitutions on 2-halothiazoles with amines have been developed.[5] However, this method generally requires long reaction times and harsh reaction conditions which limits the reaction scope to resistant amines. Isothiocyanates are also key precursors, they can lead to 2-aminothiazoles by Cu(I)-[6] or Fe(III)-catalyzed[7] cross-coupling reactions with 2-haloanilines or can generate an intermediate with 2-aminothiophenols which undergoes an oxidative cyclization.[8] Palladium- or copper-catalyzed intramolecular cyclizations of 2-halobenzothioureas have also been reported.[9] In contrast to the numerous Pd-catalyzed C–N coupling reactions reported in the literature[10] only six articles report on Pd-catalyzed arylation of 2-aminothiazoles.[11] Alternatively, the coupling of an amine with a 2-halothiazole has been performed with palladium[12] and copper.[13] Hartwig et al., for example, reported on a $Pd(O_2CCF_3)_2/P(t\text{-}Bu)_3$ system to couple 2-halothiazoles and secondary amines.[12a] Copper was used by Kaushik et al. for the catalytic *N*-arylation of amines.[13a] The reaction was mediated by CuI and performed in a $CHCl_3/H_2O$ solvent system



Riluzole R116010

Figure 1. Structures of Riluzole and R116010.

which necessitates the addition of a phase-transfer catalyst. Moreover, the reaction is limited to alkylamines. To the best of our knowledge no direct palladium-catalyzed couplings of 2-halothiazoles and primary alkylamines have been reported and Kaushik's catalyzed *N*-arylation of alkylamines is the only Cu-mediated coupling reaction with 2-chlorothiazoles. Most of the methods for the synthesis of 2-aminothiazoles require pre-made starting materials, drastic reaction conditions or expensive catalytic systems and generally provide environmentally hazardous waste. Thus, it is of prime interest to develop direct synthetic approaches applicable to thiazoles as an important substrate class in pharmaceutical research[4] and consequently the direct catalytic coupling between a 2-halothiazole and an amine appears as the method of choice. We report here on two different protocols for the preparation of 2-aminothiazoles by either direct palladium- or copper-catalyzed amination of 2-halothiazoles with primary amines.

Results and Discussion

Palladium-Catalyzed Amination of Halothiazoles

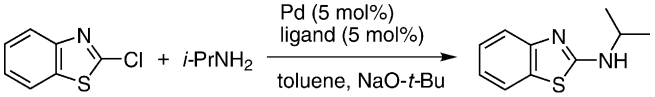
When we started our investigations, various C–N coupling reactions had already been reported based on Pd/Phosphine complexes.[10]

These strategies have shown a high correlation between the phosphine ligand employed and the substrate. In fact, a careful ligand screening has to be performed for optimization in order to get very efficient coupling protocols adapted to each substrate. With this fact in hand, we decided to screen different Pd/ligand systems in order to find the most suitable one for the C–N coupling of primary amines with halothiazoles. As model reaction the 2-chlorobenzothiazole **1a** was submitted to the coupling in toluene with isopropylamine **2a** using NaO-*t*-Bu as base (Table 1).

First attempts were performed with $Pd(OAc)_2$ (entries 1 and 2) or $Pd(dba)_2$ (entries 3 and 4) leading in best cases to a 16% yield of **3a**. Further attempts with $Pd(O_2CCF_3)_2$ and different phosphine ligands (entries 5–9) led to low yields of the thiazole **3a**, whereas RuPhos (entry 10) or P(*o*-tolyl)$_3$ (entry 11) afforded the product in comparatively good yields. Finally, microwave irradiation and a $Pd(O_2CCF_3)_2$/P(*o*-tolyl)$_3$ catalyst system gave 64% of the desired product **3a** (entry 12). Without catalyst, no coupling has been observed (entry 13).

The catalyst system $Pd(O_2CCF_3)_2$/P(*o*-tolyl)$_3$ was then applied to the synthesis of several 2-aminothiazoles (Table 2). Amination of **1a** with propylamine **2b** led to **3b** in 62% yield (entry 1). The method tolerates an increase of the alkyl chain by forming **3c** and **3d** (entries 2 and 3) and the presence of a cyclic amine

Table 1. Amination of 2-chlorobenzothiazole *via* Pd/phosphine systems.[a]



1a **2a** **3a**

Entry	Pd	Ligand	Conditions	Yield [%][b]
1	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	22 °C/48 h	–
2	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	60 °C/20 h	10
3	$Pd(dba)_2$	P(*o*-tolyl)$_3$	22 °C/20 h	10
4	$Pd(dba)_2$	P(*o*-tolyl)$_3$	40 °C/2 h[c]	16
5	$Pd(O_2CCF_3)_2$	P*t*Bu$_3$	22 °C/20 h	10
6	$Pd(O_2CCF_3)_2$	dppf	22 °C/20 h	–
7	$Pd(O_2CCF_3)_2$	(*o*-biphen)PCy$_2$	22 °C/20 h	5
8	$Pd(O_2CCF_3)_2$	XPhos	22 °C/20 h	26
9	$Pd(O_2CCF_3)_2$	Diphos	22 °C/20 h	31
10	$Pd(O_2CCF_3)_2$	RuPhos	22 °C/20 h	57
11	$Pd(O_2CCF_3)_2$	P(*o*-tolyl)$_3$	22 °C/20 h	62
12	$Pd(O_2CCF_3)_2$	P(*o*-tolyl)$_3$	40 °C/2 h[c]	64
13	–	–	22 °C/48 h	–

[a] *Reaction conditions:* **1a** (1 mmol), **2a** (4 mmol), Pd (5 mol%), ligand (5 mol%), NaO*t*Bu (1.1 mmol), toluene (1 mL).
[b] Isolated yield.
[c] Reaction realized under microwave irradiation.

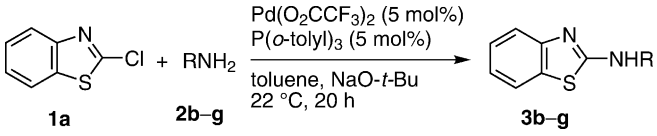
yielding to **3e** (entry 4). Benzothiazole **1a** was also successfully coupled with ethylenediamine **2f** and led only to the monoalkylated thiazole **3f** in almost quantitative yield (entry 5). When applying these conditions to the coupling with aniline (entry 6), aminothiazole **3g** was not obtained when P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$, RuPhos or (*o*-biphen)PCy$_2$ was used as ligands. Poor yields of **3g** were obtained with Xantphos, XPhos or dppf and further attempts with Diphos or BrettPhos led to more than 30% yield of **3g**.

An increase of the temperature led to the formation of 43% of the expected product. When applying microwave irradiation, thiazole **3g** was obtained in a good yield of 62%. BrettPhos revealed to be the best performing ligand for this coupling as already observed by Buchwald et al. in the case of other C–N coupling reactions with arylamines.[14] Despite several attempts, this methodology could not be extended to the coupling of **1a** with other primary arylamines (see the Supporting Information).

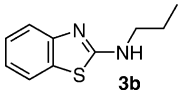
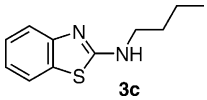
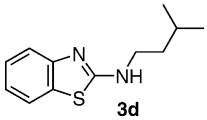
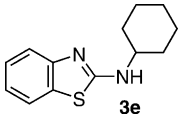
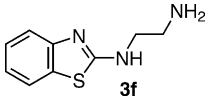
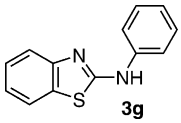
These amination protocols were then applied to the coupling of 2-bromothiazole **4a** and primary alkyl- or arylamines. However, none of the expected aminothiazoles were formed in satisfactory yields. Even under different Pd/phosphine catalytic system, **4a** did not undergo any coupling with primary amines.

In order to study if this intriguing difference of reactivity between **1a** and **4a** is due to the substitution

Table 2. Amination of **1a** catalyzed by $Pd(O_2CCF_3)_2$/P(*o*-tolyl)$_3$.[a]



1a **2b–g** **3b–g**

Entry	R	Product	Yield [%][b]
1	*n*-Pr	 **3b**	62
2	*n*-Bu	 **3c**	60
3	isopentyl	 **3d**	63
4	cyclohexyl	 **3e**	52
5	-$(CH_2)_2NH_2$	 **3f**	97
6	Ph	 **3g**	–[c] 3[d] 8[e] 9[f] 31[g] 35[h] 43[i] 62[j]

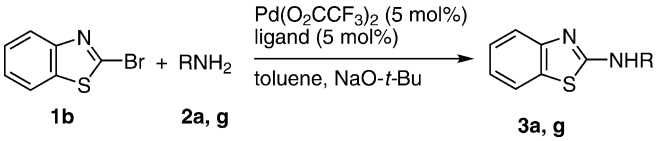
[a] *Reaction conditions:* **1a** (1 mmol), **2b–g** (4 mmol), Pd (5 mol%), ligand (5 mol%), NaO-*t*-Bu (1.1 mmol), toluene (1 mL), room temperature, 20 h.
[b] Isolated yield.
[c] P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$, RuPhos or (*o*-biphen)PCy$_2$ used as ligands.
[d] Xantphos as ligand.
[e] XPhos as ligand.
[f] dppf as ligand.
[g] Diphos as ligand.
[h] BrettPhos as ligand.
[i] BrettPhos as ligand, 100 °C, 20 h.
[j] BrettPhos as ligand, microwave irradiation: 40 °C, 3 h.

pattern or to the nature of the halide, **1a** was replaced by its bromo analogue **1b** and **4a** was replaced by its chloro analogue **4b**. The thiazole **1b** was coupled with **2a** and **2g** using the best previously determined conditions (Table 3). The same method was applied to the coupling with **4b**. Only the base was changed, K_3PO_4 avoided the decomposition of **4b** as observed in presence of NaO-*t*-Bu (Table 4).

These comparative studies underline the higher reactivity of chlorothiazoles with respect to bromothiazoles which led to significantly better yields. A nucleophilic substitution pathway, which would be consistent with the reactivity profile, can be excluded, as no reaction occurs in the absence of palladium (entry 13, Table 1). In addition, Hartwig et al.[12a] and Buchwald et al.[12b] have not used 2-bromobenzothiazole but 2-chlorobenzothiazole in Pd-catalyzed C–N couplings with secondary amines. Some C–C coupling reactions have also been reported to be more efficient with 2-chlorothiazoles compared to 2-bromothiazoles.[15]

The first part of this report describes the syntheses of new 2-aminothiazoles based on the Pd-catalyzed coupling of primary alkylamines or aniline and 2-halothiazoles. The choice of the ligand appears to be a key parameter for the reaction as well as the nature of the thiazole, 2-chlorothiazoles being more reactive than their bromo analogues. We could perform various coupling reactions of 2-chlorothiazoles and pri-

Table 3. Effect of the halobenzothiazole on the C–N coupling with primary amines.[a]

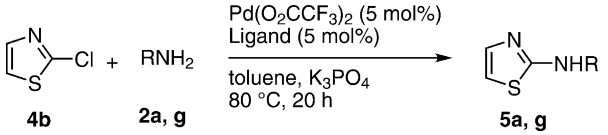


1b **2a, g** **3a, g**

Entry	Ligand	RNH_2	Conditions	Yield [%][b]	Yield [%][b] with **1a**
1	P(*o*-tolyl)$_3$	*i*-$PrNH_2$	40 °C/2 h[c]	32	64
2	BrettPhos	$PhNH_2$	40 °C/2 h[c]	–	62

[a] *Reaction conditions:* **1b** (1 mmol), RNH_2 (4 mmol), Pd (5 mol%), ligand (5 mol%), NaO-*t*-Bu (1.1 mmol), toluene (1 mL).
[b] Isolated yield.
[c] Reaction realized under microwave irradiation.

Table 4. Effect of the halothiazole on the C–N coupling with primary amines.[a]



4b **2a, g** **5a, g**

Entry	Ligand	RNH_2	Yield [%][b]	Yield [%][b] with **4a**
1	P(*o*-tolyl)$_3$	*i*-$PrNH_2$	77	8
2	BrettPhos	$PhNH_2$	–	–

[a] *Reaction conditions:* **4b** (1 mmol), RNH_2 (4 mmol), Pd (5 mol%), ligand (5 mol%), K_3PO_4 (1.1 mmol), toluene (1 mL), 80 °C, 20 h.
[b] Isolated yield.

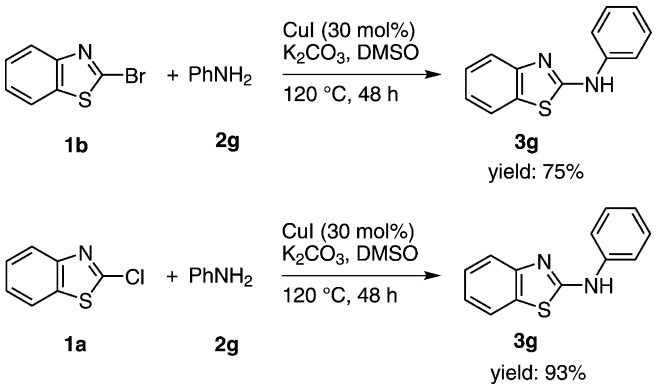
mary alkylamines, however, in the case of arylamines only aniline was reactive enough. The lack of reactivity of primary arylamines towards the coupling and the important relation between the ligand and the substrate prompted us to focus on more general methods to achieve this C–N coupling. Recently, various examples of Cu-catalyzed reactions have emerged in the literature. Copper is for these kind of reactions quite attractive due to its lower cost and lower toxicity compared to palladium.[16] Ullmann-type couplings are well known and documented especially with aryl halides.[17] We therefore focused our attention to Cu-catalyzed C–N bond formations in order to enhance the scope of the coupling between halothiazoles and primary amines.

Copper-Catalyzed Amination of 2-Halothiazoles

Cheap copper salts, like CuI, revealed to be suitable catalysts for C-N cross couplings.[18] Most frequently, ligands have to be added in order to promote the reaction. However, some ligand-free C–N couplings have been reported presenting the advantage to be more atom economical processes than Pd-catalyzed reactions.[19] First we applied the conditions reported by Zeng et al. for the coupling of *ortho*-aminobenzenethiols and aryl *ortho*-dihalides.[20] 2-Bromobenzothiazole **1b** and aniline **2g** were submitted to the coupling reaction in presence of 30 mol% of CuI (Scheme 1).

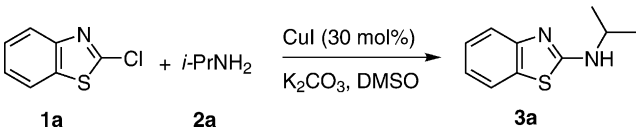
This protocol represents several advantages over the Pd-catalyzed reactions: (i) use of a cheap CuI salt, (ii) use of a green solvent (DMSO) and (iii) catalytic amounts of copper (30 mol%). In this first attempt, the aminothiazole **3g** was obtained in 75% yield. As bromothiazoles had been less reactive in the Pd-catalyzed version of this coupling, we decided to run the reaction using chlorothiazole **1a** (Scheme 1).

The expected product was formed in a very good 93% yield. In this Cu-catalyzed version, 2-chlorobenzothiazole **1a** also seemed to be a better substrate than its bromo analogue **1b**. The following studies have therefore been performed using 2-chlorothiazoles as coupling partners for amines. Despite several attempts to improve the reaction conditions, it appeared that this protocol (48 h at 120 °C) was the most convenient one.



Scheme 1. C–N coupling reaction of **1b** or **1a** and $PhNH_2$ catalyzed by CuI.

Table 5. Screening of conditions for the coupling of 2-chlorobenzothiazole **1a** and **2a** catalyzed by CuI.[a]

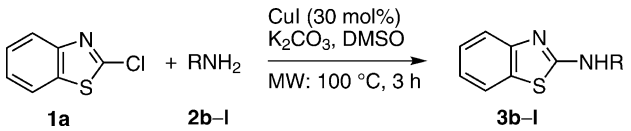


Entry	Conditions	Yield [%][b]
1	120 °C, 48 h	13
2[c]	120 °C, 48 h	6
3	40 °C, 3 h[d]	83
4	100 °C, 3 h[d]	94
5[c]	100 °C, 3 h[d]	–

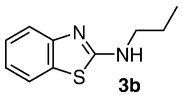
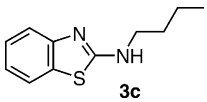
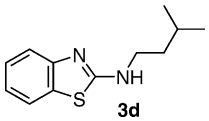
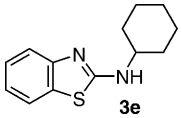
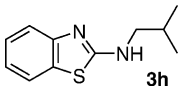
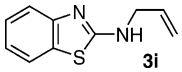
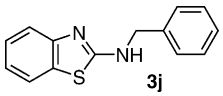
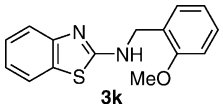
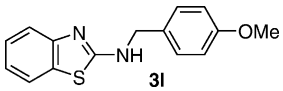
[a] *Reaction conditions:* **1a** (1 mmol), **2a** (2 mmol), CuI (30 mol%), K_2CO_3 (5 mmol), DMSO (3 mL).
[b] Isolated yield.
[c] Reaction realized without CuI.
[d] Reaction realized under microwave irradiation.

Next, these conditions were applied to the coupling of **1a** and **2a** as an alkylamine (Table 5). Low yields after prolonged heating were observed (entry 1). The yields have been significantly increased under microwave irradiation to 83% (entry 3). Finally, an increase of the temperature under microwave assistance formed the desired thiazole **3a** in 94% yield (entry 4). Without any copper no coupling has been observed (entries 2 and 5). Encouraged by this result, we extended the scope of the coupling to several primary alkylamines (Table 6). Prior attempts were realized with the amines also used in the palladium-catalyzed version (entries 1–4). Only propylamine (entry 1) led to **3b** in comparative yields to the Pd-catalyzed system. Otherwise, copper revealed to be superior, forming the aminothiazoles **3c**, **3d** and **3e** in almost quantitative yields (respectively entries 2, 3 and 4). Applying the protocol to other substrates like isobutylamine (entry 5), allylamine (entry 6) and benzylamine (entry 7) demonstrated the efficiency of copper to form **3h**, **3i** and **3j**. The presence of an electron-donating group like OMe at the *ortho* position of benzylamine decreased the yield for **3k** (entry 8), while one at the *para* position tremendously increased it for **3l** (entry 9). Although copper revealed to be the metal of choice in terms of reactivity in the coupling with primary alkylamines or aniline and in comparison with palladium, we are currently unable to extend the scope to other primary arylamines (see the Supporting Information). Chakraborti et al. have reported

Table 6. Scope of the C–N coupling mediated by copper and comparison with the palladium protocol.[a]



1a **2b–l** **3b–l**

Entry	RNH_2	Product	Yield [%][b,c]
1	*n*-Pr	 **3b**	57 (62)
2	*n*-Bu	 **3c**	97 (60)
3	isopentyl	 **3d**	99 (63)
4	cyclohexyl	 **3e**	98 (52)
5	*i*-Bu	 **3h**	92
6	allyl	 **3i**	42
7	Bn	 **3j**	42
8	2-(OMe)Bn	 **3k**	29
9	4-(OMe)Bn	 **3l**	92

[a] *Reaction conditions:* **1a** (1 mmol), RNH_2 (2 mmol), CuI (30 mol%), K_2CO_3 (5 mmol), DMSO (3 mL), MW, 100 °C, 3 h.
[b] Isolated yield.
[c] In brackets, isolated yield obtained with the palladium coupling (Table 4).

solvent- and catalyst-free microwave-assisted nucleophilic substitutions between 2-chlorobenzothiazoles and substituted anilines.[5d] The reactions needed 600 W in a domestic microwave to be achieved in a few minutes. Attempts to reproduce the reaction with 2-chlorobenzothiazole and aniline could not have been performed due to the limit of 400 W and 250 °C of the microwave system.

Nevertheless, in a further approach, we decided to keep on extending this scope to the synthesis of various 2-aminothiazoles. Due to their importance in pharmaceutical research, we studied the coupling reactions between 2-chlorothiazoles and various primary and secondary amines. In addition, we compared thermal conditions (Method A) and microwave irradiation (Method B) (Table 7). In general, Method B revealed to be more efficient in these coupling reactions. However two exceptions were observed. The first one concerned the reaction of **1a** and methylamine (entry1), where the yield of **9a** was nearly quantitative after a prolonged heating. A second one was observed for the coupling of **1a** and **8e**, where only Method A afforded in low yield the product **9e** (entry 5). A further reaction with 2-chlorobenzothiazole and **8b** provided **9b** in good yield (entry 2). Ethanolamine **8c** afforded **9c** only under microwave irradiation (entry 3). A sterically more hindered amine (entry 4), a cyclic one (entry 6) and pyrazole (entry 7) led to the coupling products **9d**, **9f** and **9g** in good yields. 2-Chloro-6-fluorobenzothiazole **6** was also subjected to the coupling with methyl-, ethyl- and phenethylamine (entries 8, 9 and 10) giving efficiently **10a**, **10b** and **10c**. The coupling between piperidine (entry 11) and pyrazole (entry 12) with **6** also afforded **10d** and **10e** in very good yields. The absence of any coupling reaction at the 6 position of the thiazole **6** indicates that the protocol tolerates the presence of an extra fluoride atom on the thiazole. With 2-chloro-4-(4-chlorophenyl)thiazole **7** as substrate and methyl-, ethylamine and pyrazole (entries 13–15) low yields were obtained for **11a**, **11b** and **11c**. No C–N coupling on the phenyl ring has been observed.

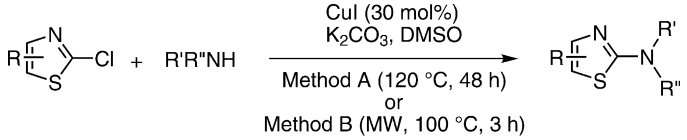
In summary, we have developed optimal microwave-assisted conditions for the coupling of different 2-chlorothiazoles with primary and secondary amines, affording 2-aminothiazoles as potential candidates for pharmaceutical research.

Conclusions

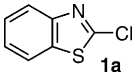
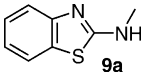
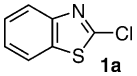
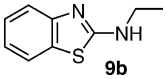
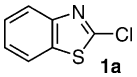
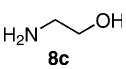
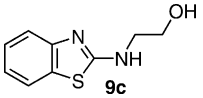
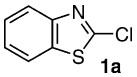
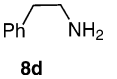
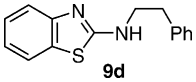
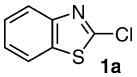
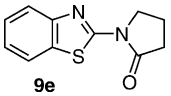
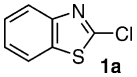
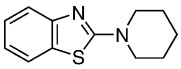
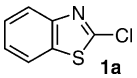
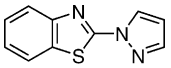
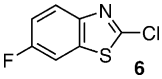
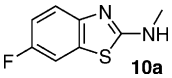
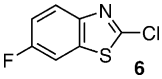
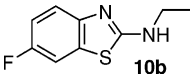
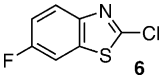
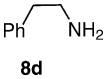
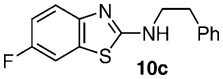
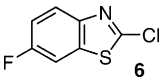
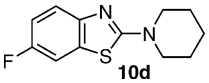
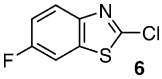
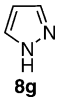
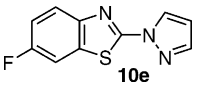
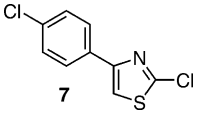
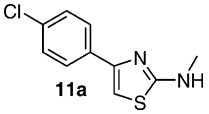
The syntheses of novel 2-aminothiazoles *via* two transition metal-catalyzed C–N coupling protocols between halothiazoles and amines have been developed. A complete screening in palladium and phosphine ligands allowed us to determine optimum conditions for the coupling of 2-chlorobenzothiazole with primary alkylamines. We also demonstrated that 2-chlorothiazoles are much more efficient coupling partners for aminations than their bromo analogues. However, we were not able to extend this coupling to other arylamines except aniline.

To achieve this aim, we focused therefore on the catalytic coupling mediated by copper. A survey of the conditions allowed us to synthesize numerous 2-aminothiazoles under microwave irradiation. A comparison of the yields obtained with the copper-catalyzed protocol and the palladium-catalyzed one demonstrated the efficiency of the cheaper CuI salt. In addition, the ligand-free catalytic copper reactions are

Table 7. Scope of the C–N couplings catalyzed by copper.[a]



1a, 6, 7 **8a–g** **9, 10, 11**

Entry	Thiazole	R′R″NH	Product	Yield [%][b] Method A[c]	Yield [%][b] Method B[d]
1	 **1a**	 **8a**	 **9a**	96	55
2	 **1a**	 **8b**	 **9b**	84	84
3	 **1a**	 **8c**	 **9c**	–	38
4	 **1a**	 **8d**	 **9d**	75	92
5	 **1a**	 **8e**	 **9e**	23	-
6	 **1a**	 **8f**	 **9f**	93	92
7	 **1a**	 **8g**	 **9g**	74	74
8	 **6**	 **8a**	 **10a**	96	98
9	 **6**	 **8b**	 **10b**	81	96
10	 **6**	 **8d**	 **10c**	53	70
11	 **6**	 **8f**	 **10d**	93	93
12	 **6**	 **8g**	 **10e**	73	82
13	 **7**	 **8a**	 **11a**	< 5	94
14	**7**	**8b**	**11b**	33	47
15	**7**	**8g**	**11c**	13	38

[a] *Reaction conditions:* 2-chlorothiazole (1 mmol), R′R″NH (2 mmol), CuI (30 mol%), K_2CO_3 (5 mmol), DMSO (3 mL).
[b] Isolated yield.
[c] Method A: 120 °C, 48 h.[d] Method B: MW, 100 °C, 3 h.

faster and are performed in a green solvent (DMSO), placing the copper-catalyzed C–N bond formation as a method of choice to achieve the coupling between 2-chlorothiazoles and amines. We also demonstrated that the copper-mediated reaction tolerates the presence of primary as well as secondary amines and can be applied to 2-chlorothiazoles substituted by extra halide atoms. Unfortunately, we were not able to extend the coupling to the synthesis of aminoarylthiazoles, work which is currently in progress.

Experimental Section

Materials and Analysis

^{1}H and ^{13}C NMR spectra were acquired with a Bruker AM-300 spectrometer at 300 and 75 MHz, respectively. ^{19}F spectra were acquired with a Bruker AM-400 spectrometer at 376 MHz. Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. Column chromatography was performed on silica gel. Microwave-assisted reactions were performed in an Initiator 2.5 microwave system (Biotage, Inc.) at the specified temperature using the standard mode of operation. MS experiments were performed *via* a TOF spectrometer equipped with an orthogonal electrospray (ESI) interface. The reagents were purchased from commercial chemical reagent companies, and used without further purification unless otherwise stated.

General Procedure for the Palladium-Catalyzed Coupling Reactions between 2-Halobenzothiazoles and Alkylamines

To a solution of $Pd(O_2CCF_3)_2$ (0.05 mmol), P(*o*-tolyl)$_3$ (0.05 mmol) and NaO-*t*-Bu (1.1 mmol) in toluene (1 mL) at room temperature were added the 2-halobenzothiazole (1 mmol) and the amine (4 mmol). The solution was stirred at room temperature during 20 h. The reaction mixture was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with cyclohexane/AcOEt = 4/1) to provide the desired aminothiazole.

***N*-Isopropylbenzo[*d*]thiazol-2-amine (3a):** Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (d, $J = 6.3$ Hz, 6H), 3.85–4.00 (m, 1H), 5.33 (br. s, 1H), 7.07 (t, $J = 7.2$ Hz, 1H), 7.28 (t, $J = 7.2$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.57 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.05$, 47.62, 118.82, 120.73, 121.38, 125.88, 130.44, 152.56, 166.53; HR-MS (ESI): $m/z = 193.078$, calcd. for $C_{10}H_{12}N_2S$ $[M+H]^+$: 193.079.

***N*-Propylbenzo[*d*]thiazol-2-amine (3b):** Colorless solid. Characterization data were identical with the reported data.[9e]

***N*-Butylbenzo[*d*]thiazol-2-amine (3c):** Colorless solid. Characterization data were identical with the reported data.[21]

***N*-Isopentylbenzo[*d*]thiazol-2-amine (3d):** Orange solid. Characterization data were identical with the reported data.[22]

***N*-*cyclo*-Hexylbenzo[*d*]thiazol-2-amine (3e):** Colorless solid. Characterization data were identical with the reported data.[9e]

***N*^{1}-(Benzo[*d*]thiazol-2-yl)ethane-1,2-diamine (3f):** Colorless solid. Characterization data were identical with the reported data.[23]

General Procedure for the Palladium-Catalyzed Coupling Reactions between 2-Halobenzothiazoles (1a, 1b) and Aniline 2g

To a solution of $Pd(O_2CCF_3)_2$ (0.05 mmol), BrettPhos (0.05 mmol) and NaO-*t*-Bu (1.1 mmol) in toluene (1 mL) at room temperature were added the 2-halobenzothiazole (1 mmol) and the aniline (4 mmol). The solution was stirred under microwave irradiation at 40 °C during 3 h. The reaction mixture was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with cyclohexane/AcOEt = 4/1) to provide the desired aminothiazole.

***N*-Phenylbenzo[*d*]thiazol-2-amine (3g):** Colorless solid. Characterization data were identical with the reported data.[9e]

General Procedure for the Palladium-Catalyzed Coupling Reactions between 2-Halothiazoles (4a, 4b) and *i*-PrNH$_2$ 2a

To a solution of $Pd(O_2CCF_3)_2$ (0.05 mmol), P(*o*-tolyl)$_3$ (0.05 mmol) and K_3PO_4 (1.1 mmol) in toluene (1 mL) at room temperature were added the 2-halothiazole (1 mmol) and *i*-PrNH$_2$ (4 mmol). The solution was stirred at 80 °C during 20 h. The reaction mixture was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with Cyclohexane/AcOEt = 4/1) to provide the desired aminothiazole.

***N*-Isopropylthiazol-2-amine (5a):** Pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (d, $J = 6.6$ Hz, 6H), 3.66–3.77 (m, 1H), 5.03 (br. s, 1H), 6.48 (d, $J = 3.6$ Hz, 1H), 7.10 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 22.88, 47.90, 106.24, 139.08, 169.42; HR-MS (ESI): $m/z =$ 143.064, calcd. for $C_6H_{10}N_2S$ $[M+H]^+$: 143.064.

General Procedure for the Copper-Catalyzed Coupling Reactions between 2-Halobenzothiazoles and Amines

Method A: To a solution of CuI (0.3 mmol) and K_2CO_3 (5 mmol) in DMSO (5 mL) at room temperature were added the 2-chlorothiazole (1 mmol) and the amine (2 mmol). The solution was stirred at 120 °C during 48 h. The reaction mixture was then diluted in 20 mL of AcOEt and washed twice with portions of 20 mL of H_2O. The aqueous layers were then extracted three times with portions of 20 mL of AcOEt. The organic layers were dried on Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with cyclohexane/AcOEt = 4/1) to provide the desired aminothiazole.

Method B: To a solution of CuI (0.3 mmol) and K_2CO_3 (5 mmol) in DMSO (5 mL) at room temperature were added the 2-chlorothiazole (1 mmol) and the amine

(2 mmol). The solution was stirred under microwave irradiation at 100 °C for 3 h. The reaction mixture was then diluted in 20 mL of AcOEt and washed twice with portions of 20 mL of H_2O. The aqueous layers were then extracted three times with portions of 20 mL of AcOEt. The organic layers were dried on Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with cyclohexane/AcOEt = 4/1) to provide the desired aminothiazole.

***N*-Isobutylbenzo[*d*]thiazol-2-amine (3h):** Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.01$ (d, $J = 6.6$ Hz, 6H), 1.91–2.02 (m, 1H), 3.23 (d, $J = 6.9$ Hz, 2H), 5.50 (br. s, 1H), 7.07 (t, $J = 7.8$ Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.58 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.12$, 28.61, 53.28, 118.80, 120.75, 121.39, 125.94, 130.39, 152.55, 167.85; HR-MS (ESI): $m/z = 207.096$, calcd. for $C_{11}H_{14}N_2S$ $[M+H]^+$: 207.095.

6-Fluoro-*N*-methylbenzo[*d*]thiazol-2-amine (10a): Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.11$ (s, 3H), 5.88 (br. s, 1H), 7.03 (td, $J = 9$ Hz, $J = 2.4$ Hz, 1H), 7.31 (dd, $J = 8.1$ Hz, $J = 2.7$ Hz, 1H), 7.46 (dd, $J = 8.7$ Hz, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.65$, 107.59 (d, $^2J_{F,C} = 26.2$ Hz, CH arom), 113.56 (d, $^2J_{F,C} = 23.2$ Hz, CH arom), 119.12 (d, $^3J_{F,C} = 9$ Hz, CH arom), 131.14 (d, $^3J_{F,C} = 10.5$ Hz, C arom), 148.99, 158.16 (d, $J_{F,C} = 237.7$ Hz, C arom), 167.97; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -121.56$; HR-MS (ESI): $m/z = 183.037$, calcd. for $C_8H_7N_2S$ $[M+H]^+$: 183.039.

6-Fluoro-*N*-phenethylbenzo[*d*]thiazol-2-amine (10c): Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.02$ (t, $J = 6.9$ Hz, 2H), 3.71 (t, $J = 6.9$ Hz, 2H), 5.30 (br. s, 1H), 7.03 (td, $J = 9.0$ Hz, $J = 2.7$ Hz, 1H), 7.24–7.37 (m, 6H), 7.46 (dd, $J = 8.7$ Hz, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 35.53$, 46.40, 107.55 (d, $^2J_{F,C} = 27$ Hz, CH arom), 113.56 (d, $^2J_{F,C} = 23.2$ Hz, CH arom), 119.36 (d, $^3J_{F,C} = 9$ Hz, CH arom), 126.80, 128.81, 131.19 (d, $^3J_{F,C} = 10.5$ Hz, C arom), 138.22, 148.93, 158.27 (d, $J_{F,C} = 238.5$ Hz, C arom), 166.52; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -121.30$; HR-MS (ESI): $m/z = 273.088$, calcd. for $C_{15}H_{13}FN_2S$ $[M+H]^+$: 273.086.

6-Fluoro-2-(1*H*-pyrazol-1-yl)benzo[*d*]thiazole (10e): Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.55$ (m, 1H), 7.22 (td, $J = 9$ Hz, $J = 2.7$ Hz, 1H), 7.54 (dd, $J = 8.1$ Hz, $J = 2.7$ Hz, 1H), 7.79 (m, 1H), 7.84 (dd, $J = 9$ Hz, $J = 4.8$ Hz, 1H), 8.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 108.13$ (d, $^2J_{F,C} = 27$ Hz, CH arom), 109.42, 114.97 (d, $^2J_{F,C} = 24.7$ Hz, CH arom), 123.28 (d, $^3J_{F,C} = 9$ Hz, CH arom), 127.83, 134.10 (d, $^3J_{F,C} = 11.2$ Hz, C arom), 143.41, 147.46, 159.90, 160.14 (d, $J_{F,C} = 243.7$ Hz, C arom); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -116.02$; HR-MS (ESI): $m/z = 242.019$, calcd. for $C_{10}H_6FN_3S$ $[M+Na]^+$: 242.016.

4-(4-Chlorophenyl)-*N*-ethylthiazol-2-amine (11b): Pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.2$ Hz, 3H), 3.28–3.37 (m, 2H), 5.54 (br. s, 1H), 6.69 (s, 1H), 7.35 (d, $J = 8.7$ Hz, 2H), 7.74 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.67$, 40.79, 101.01, 127.29 (2C), 128.64 (2C), 133.23, 133.51, 150.41, 169.75; HR-MS (ESI): $m/z = 239.039$, calcd. for $C_{11}H_{11}ClN_2S$ $[M+H]^+$: 239.040.

4-(4-Chlorophenyl)-2-(1*H*-pyrazol-1-yl)thiazole (11c): Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.52$ (m, 1H), 7.25 (s, 1H), 7.43 (d, $J = 8.7$ Hz, 2H), 7.76 (d, $J = 1.8$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 2H), 8.44 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 108.67$, 109.49, 127.38 (2C), 127.47, 128.94 (2C), 132.50, 134.15, 142.79, 151.47, 161.15; HR-MS (ESI): $m/z = 283.999$, calcd. for $C_{12}H_8ClN_3S$ $[M+Na]^+$: 284.002.

***N*-Allylbenzo[*d*]thiazol-2-amine (3i):** Pale yellow solid. Characterization data were identical with the reported data.[24]

***N*-Benzylbenzo[*d*]thiazol-2-amine (3j):** Colorless solid. Characterization data were identical with the reported data.[8d]

***N*-(2-Methoxybenzyl)benzo[*d*]thiazol-2-amine (3k):** Colorless solid. Characterization data were identical with the reported data.[8d]

***N*-(4-Methoxybenzyl)benzo[*d*]thiazol-2-amine (3l):** Colorless solid. Characterization data were identical with the reported data.[8d]

***N*-Methylbenzo[*d*]thiazol-2-amine (9a):** Colorless solid. Characterization data were identical with the reported data.[1a]

***N*-Ethylbenzo[*d*]thiazol-2-amine (9b):** Colorless solid. Characterization data were identical with the reported data.[9e]

2-(Benzo[*d*]thiazol-2-ylamino)ethanol (9c): Colorless solid. Characterization data were identical with the reported data.[1a]

***N*-Phenethylbenzo[*d*]thiazol-2-amine (9d):** Colorless solid. Characterization data were identical with the reported data.[22]

1-(Benzo[*d*]thiazol-2-yl)pyrrolidin-2-one (9e): Orange solid. Characterization data were identical with the reported data.[25]

2-(Piperidin-1-yl)benzo[*d*]thiazole (9f): Colorless solid. Characterization data were identical with the reported data.[8d]

2-(1*H*-Pyrazol-1-yl)benzo[*d*]thiazole (9g): Colorless solid. Characterization data were identical with the reported data.[26]

***N*-Ethyl-6-fluorobenzo[*d*]thiazol-2-amine (10b):** Colorless solid. Characterization data were identical with the reported data.[7b]

6-Fluoro-2-(piperidin-1-yl)benzo[*d*]thiazole (10d): Colorless solid. Characterization data were identical with the reported data.[27]

4-(4-Chlorophenyl)-*N*-methylthiazol-2-amine (11a): Pale yellow solid. Characterization data were identical with the reported data.[28]

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique (CNRS) and the University of Strasbourg. Merck KGaA is gratefully acknowledged for a postdoctoral grant to S.T.

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