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# 2,4- and 2,5-Disubstituted Arylthiazoles: Rapid Synthesis by C–H Coupling and Biological Evaluation

Lilia Lohrey,[a] Takahiro N. Uehara,[b] Satoshi Tani,[b] Junichiro Yamaguchi,*[b] Hans-Ulrich Humpf,*[a] and Kenichiro Itami*[b,c]

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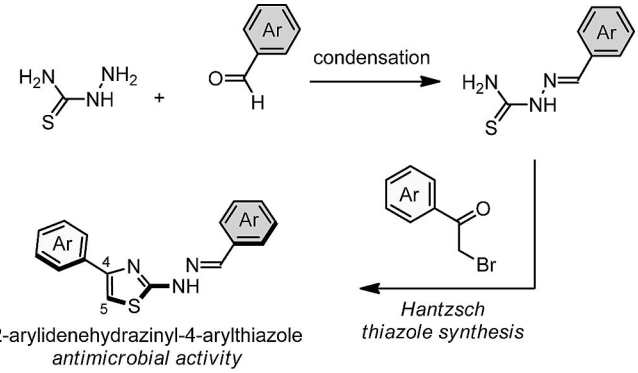
Life-threatening infections caused by bacteria that have developed resistance to common antibiotics, such as methicillin-resistant *Staphylococcus aureus* (MRSA), have become a serious problem in hospitals and other areas all over the world. Thus, the development of an effective class of antibiotics against these bacteria is an urgent subject. Herein, we report a step-economical and diversity-oriented synthesis of a series of 2-arylidenehydrazinyl-4-arylthiazole and 2-arylidenehydrazinyl-5-arylthiazole analogues that utilizes C–H coupling methodologies. A library of 54 new congeners were synthesized and tested for their biological potential. Moreover, new knowledge regarding the structure–activity relationships (SARs) of these heterobiaryl compounds was collected.

## Introduction

The proliferation of resistance against different antibiotics posed by some bacteria strains has become an urgent challenge in the medical community.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA), for instance, has received growing attention owing to its multiresistance. Furthermore, other bacteria strains, including Gram-negative *Pseudomonas aeruginosa* and some *Escherichia coli* species have developed resistance against common antibiotics.[1,2] Infections caused by these bacteria occur widely but are naturally focused in hospital facilities. The design of new antimicrobial agents against multidrug-resistant bacteria is of great importance and provides a steadily growing field of research for the chemical and pharmaceutical community. For the effective development of potential antimicrobial agents, it is mandatory to establish efficient and diversity-oriented syntheses of compound libraries as well as fast biological screening systems.[3] In many natural products and biologically active synthetic compounds, thiazole is an important structural motif and building block and, therefore, it is an attractive scaffold in the pharmaceutical and chemical community.

Recently, Singh and co-workers as well as Lee and co-workers reported a new class of 2-arylidenehydrazinyl-4-arylthiazole analogues that exhibit strong antimicrobial activities against *S. aureus*, *Bacillus subtilis*, and some *Candida* spp.[4]

Other groups also showed the positive biological activity of these 2,4-disubstituted thiazole derivatives.[5] Traditionally, the synthesis of these thiazole derivatives is accomplished by the Hantzsch thiazole synthesis, and the target compounds are mostly obtained in high yield (Scheme 1).[6] However, this strategy necessitates the preparation of a suitable reaction partner for the Hantzsch cyclization for every single target. Moreover, the aryl group at the C-4 position is fixed, for example, C-5-substituted thiazoles such as arylidenehydrazinyl-5-arylthiazole cannot be generated by this method. The effort required to use this




Scheme 1. Structure and conventional synthesis of 2-arylidenehydrazinyl-4-arylthiazole.

[a] Institute of Food Chemistry, Westfälische Wilhelms-Universität Münster,
Corrensstr. 45, 48149 Münster, Germany
E-mail: humpf@uni-muenster.de
http://www.uni-muenster.de/Chemie.lc/en/forschen/humpf/
[b] Institute of Transformative Bio-Molecules (WPI-ITbM) and Department of Chemistry, Graduate School of Science, Nagoya University,
Chikusa, Nagoya 464-8602, Japan
E-mail: junichiro@chem.nagoya-u.ac.jp
itami@chem.nagoya-u.ac.jp
http://synth.chem.nagoya-u.ac.jp/
[c] JST, ERATO, Itami Molecular Nanocarbon Project, Nagoya University,
Nagoya 464-8602, Japan
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conventional synthetic strategy and its limitations in the lack of suitable starting materials render a pathway for the rapid synthesis of compound libraries from a small set of building blocks highly desirable.[3a]

In recent years, the transition-metal-catalyzed direct C–H arylation of heteroarenes has emerged as an attractive and promising alternative to well-established, traditional cross-coupling reactions.[7,8] As the C-5 atom of the thiazole ring is the most electron-rich (nucleophilic) position, we became interested in the literature examples of C-5-selective Pd-catalyzed C–H arylation of thiazoles with aryl halides.[9] In contrast, the regioselective arylation of the least-reactive C-4 position has remained elusive. Recently, our group developed the first example of a Pd-catalyzed C-4-selective oxidative C–H arylation of thiazoles with arylboronic acids. It is crucial to employ $Pd(OAc)_2$/phen (phen = 1,10-phenanthroline) as a catalyst and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as an oxidant, respectively.[8d]

As a part of our program focusing on synthesis-oriented methodology development, we established a step-economical and rapid synthesis of a series of new 2-arylidenehydrazinyl-4-arylthiazole and 2-arylidenehydrazinyl-5-arylthiazole analogues that utilizes C–H coupling methodologies. The scope of this new method is demonstrated, and preliminary results of the biological screening are reported herein.

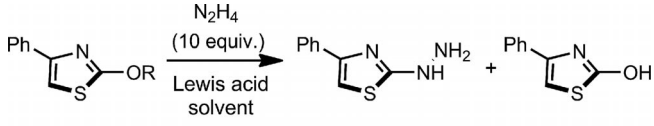
## Results and Discussion

Our synthetic strategy toward 2-arylidenehydrazinyl-4-arylthiazoles **1** as well as 2-arylidenehydrazinyl-5-arylthiazoles **2** is outlined in Scheme 2. With this plan in mind, we developed a route for the synthesis of target compounds **1** and **2** from simple building blocks in a step-economical fashion by utilizing C–H coupling methodologies.

To investigate and to compare the biological activity of the structurally related compounds **1** and **2**, the aryl group introduced at the C-4 and C-5 positions should be identical. We targeted a thiazole core bearing an alkoxy group at the C-2 position. Subsequent to the C–H coupling reaction at the C-4 or C-5 position of alkoxythiazoles **3**, the alkoxy group of the obtained coupling products **5A** and **5B** could be readily displaced by hydrazine in a nucleophilic substitution (**6A** and **6B**), after which a final condensation with a suitable aldehyde would deliver targets **1** and **2** (Scheme 2).

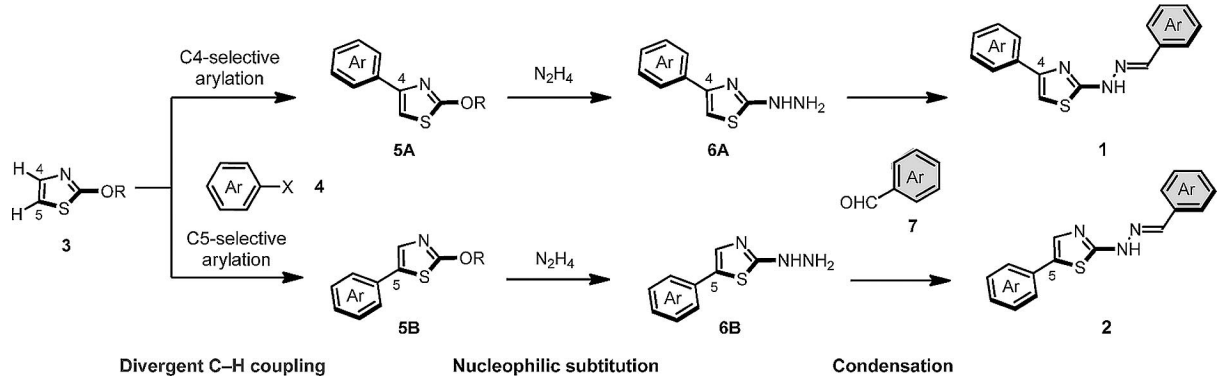
We commenced our study by investigating the nucleophilic substitution of 2-alkoxy-4-arylthiazoles with hydrazine (Table 1). With 2-methoxy-4-phenylthiazole (**5Aa′**) as the starting material, the treatment with anhydrous hydrazine (10 equiv.) as nucleophile (Table 1, Entries 1 and 2) in *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) gave only trace amounts of the desired product **6Aa**, whereas the demethylated product **7** formed in 75 and 85% yield, respectively. To prevent demethylation, some Lewis acids were examined as additives (Table 1, Entries 3–5). However, none of the employed Lewis acids favored the nucleophilic substitution and, thus, did not yield **6Aa**. Next, a better leaving group was investigated, and the methoxy group was changed to a phenoxy group (compound **5Aa**). Surprisingly, the use of DMF resulted in no observable conversion of the starting material (Table 1, Entry 6), whereas DMSO gave the desired **6Aa** in 52% yield without the formation of **7** (Table 1, Entry 7). Finally, the yield can be improved to 85% by increasing the amount of hydrazine to 20 equiv. (Table 1, Entry 8).

Table 1. Nucleophilic substitution of 2-alkoxy-4-phenylthiazole with hydrazine.[a]




| Entry | R | Solvent | Lewis acid | Yield of **6Aa** [%][b] | Yield of **7** [%][b] |
|---|---|---|---|---|---|
| 1 | Me | DMF | – | <1 | 75 |
| 2 | Me | DMSO | – | <1 | 85 |
| 3[c] | Me | DMSO | $BF_3{\cdot}OEt_2$ | <1 | 46 |
| 4[c] | Me | DMSO | $Sc(OTf)_3$ | <1 | 68 |
| 5[d] | Me | DMSO | $Yb(OTf)_3$ | n.d. | 20 |
| 6 | Ph | DMF | – | <1 | n.d. |
| 7 | Ph | DMSO | – | 56 (52) | n.d. |
| 8 | Ph | DMSO | – | 90 (85)[e] | n.d. |

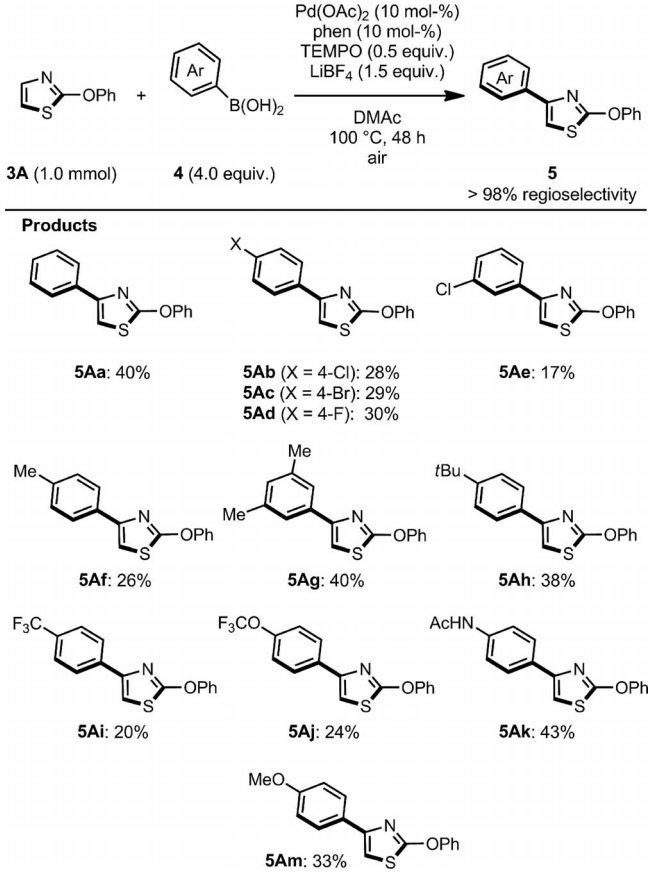
[a] Reaction conditions: **5Aa′** (1.0 equiv.), Lewis acid (1.0 equiv.), 100 °C, 12 h. [b] Yields were determined by LC–UV–MS. The numbers in parentheses for Entries 7 and 8 are the yield of isolated product; n.d.: not detected. [c] The reaction time was 6 h. [d] The reaction time was 21 h. [e] 20 equiv. of hydrazine was used.




Scheme 2. A C–H coupling strategy for the synthesis of target compounds **1** and **2**.

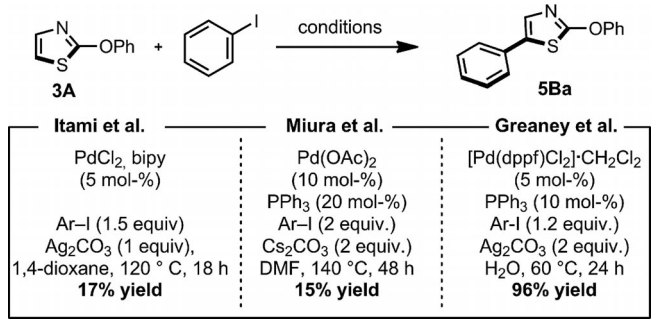
  

Having the optimized conditions for the nucleophilic substitution in hand, we next examined the crucial step of the C-4-selective C–H arylation of 2-phenoxythiazole (**3A**) on the basis of our previous work on the C-4-selective C–H arylation of thiazoles.[8d] After a short optimization of the reaction conditions, the best results were achieved with **3A** (R = Ph, 1.0 equiv.), phenylboronic acid (**4a**, 4.0 equiv.), $LiBF_4$ (1.5 equiv.), and TEMPO (0.5 equiv.) in the presence of 10 mol-% of $Pd(OAc)_2$, and 1,10-phenanthroline (phen) in dimethylacetamide (DMAc) at 100 °C for two days under air, which led to an isolated yield of 40% of arylthiazole **5Aa** with almost complete C-4-selectivity (Scheme 3). Similar yields were obtained with electron-rich arylboronic acids (to yield products **5Ag**, **5Ah**, **5Ak**, and **5Am**), whereas arylboronic acids bearing electron-deficient substituents resulted in decreased yields (of products **5Ab**, **5Ac**, **5Ad**, **5Ai**, **5Aj**), in accordance with our previous studies.[9] *meta*-Substituted arylboronic acids are not tolerated well and afford low yields (of product **5Ae**). Thus, thiazole **3A** can be arylated regioselectively at the C-4 position by using the $Pd(OAc)_2$/phen/TEMPO catalyst system and tolerates a wide range of substituted arylboronic acids to afford the products in good-to-moderate yields.



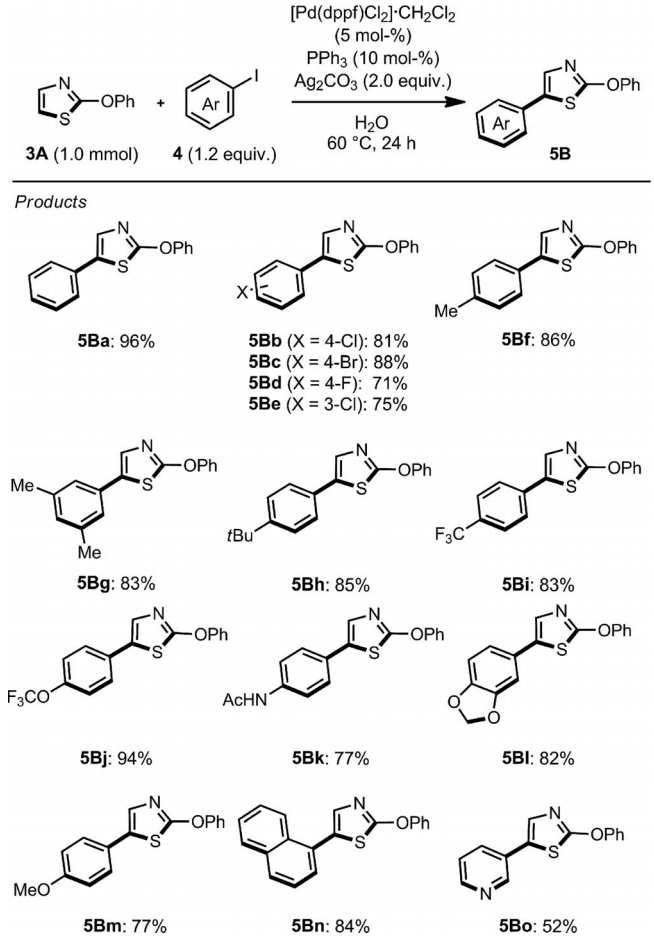

Scheme 3. Scope of the reaction of 2-phenoxythiazole with respect to arylboronic acid coupling partners.

As the C-5 atom of the thiazole ring is most accessible to electrophiles, many protocols for the C-5-selective Pd-catalyzed C–H arylation with haloarenes have been described;[9] among these, we tested several methods to arylate thiazole **3A** (Scheme 4). Initially, our previous catalytic system $PdCl_2$/2,2′-bipyridyl/$Ag_2CO_3$ afforded **5Ba** in low yields (17%).[9e,10] Similar conditions published by Miura et al. in which $Pd(OAc)_2$/$PPh_3$/$Cs_2CO_3$ is used led to equally unsatisfactory results and yielded **5Ba** in 15% yield.[8a] Eventually, the conditions reported by Greaney and co-workers in which [Pd(dppf)$Cl_2$]·$CH_2Cl_2$/$PPh_3$/$Ag_2CO_3$ [dppf = 1,1′-bis(diphenylphosphino)ferrocene] is employed gave full conversion and 96% isolated yield of **5Ba**.[9b]




Scheme 4. Screening of conditions for the direct C-5-selective C–H arylation of thiazole **3A** with haloarenes.

Under these promising conditions, **3A** was treated with various iodoarenes to give the corresponding C-5-arylated thiazoles **5Ba**–**5Bo** in good-to-excellent yields (Scheme 5).




Scheme 5. Scope of the reaction of 2-phenoxythiazole with respect to iodoarene coupling partners.

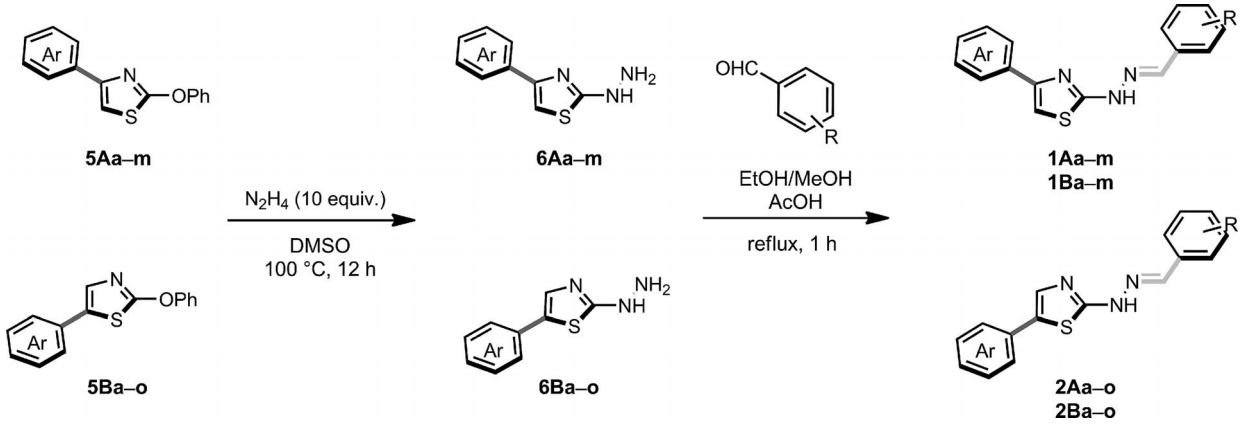
  

Electron-rich (to yield **5Bf**–**5Bh**, **5Bk**, and **5Bm**) as well as electron-poor iodoarenes (to yield **5Bb**–**5Be**, **5Bi**, and **5Bj**) were tolerated. Surprisingly, the sterically hindered 1-naphthyl iodide (to yield **5Bn**) and the strongly coordinating heteroarene 3-iodopyridine (to yield **5Bo**) could be installed successfully on the thiazole ring in good yields.

With the above C-4- and C-5-arylated thiazoles in hand, we performed the nucleophilic substitution with hydrazine, and the corresponding 2-hydrazinyl-4-arylthiazoles **3A** and 2-hydrazinyl-5-arylthiazoles **3B** were obtained. The condensation of **3A** and **3B** with *p*-bromobenzaldehyde and *p*-anisaldehyde afforded the corresponding products **1A**, **1B**, **2A**, and **2B** in high yields after purification by reversed-phase liquid chromatography (Table 2).

The newly synthesized compounds (**1A**, **1B**, **2A**, and **2B**) were tested for their activity (Figure 1) against two Gram-positive bacterial strains, *B. subtilis* and MRSA, and two Gram-negative bacterial strains, *P. aeruginosa* and *E. coli*. Furthermore, the activities against one yeast strain, *Candida glabrata*, and one dermatophytic fungus, *Trichophyton mentagrophytes*, were also tested. The cytotoxicity of these compounds was evaluated on a human colon adenocarcinoma cell line (HT-29) as well as on a mouse fibroblast cell line (NIH-T3). The screening was performed at three different concentration levels of the compounds (10, 50, and 100 μM) in triplicate. The inhibitory activities are displayed in relation to specified control substances for which the highest inhibition is 100%. The antibacterial screening revealed that none of the newly synthesized compounds exhibit activity against Gram-negative bacteria strains, a finding that is in agreement with previous studies.[4] In contrast, moderate-to-good inhibitory activities were observed against Gram-positive bacteria strains. As Gram-negative bacteria have an inner and outer cell membrane, as opposed

Table 2. Synthesis of 2-arylidenehydrazinyl-4-arylthiazole (**1A** and **1B**) and 2-arylidenehydrazinyl-5-arylthiazole (**2A** and **2B**).




| Entry | Compound | Ar | R | Yield [%] | Entry | Compound | Ar | R | Yield [%] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1Aa** | $C_6H_5$ | Br | 71 | 28 | **1Ba** | $C_6H_5$ | OMe | 63 |
| 2 | **1Ab** | 4-$ClC_6H_4$ | Br | 53 | 29 | **1Bb** | 4-$ClC_6H_4$ | OMe | 49 |
| 3 | **1Ac** | 4-$BrC_6H_4$ | Br | 73 | 30 | **1Bc** | 4-$BrC_6H_4$ | OMe | 61 |
| 4 | **1Ad** | 4-$FC_6H_4$ | Br | 47 | 31 | **1Bd** | 4-$FC_6H_4$ | OMe | 49 |
| 5 | **1Ae** | 3-$ClC_6H_4$ | Br | 65 | 32 | **1Be** | 3-$ClC_6H_4$ | OMe | 67 |
| 6 | **1Af** | 4-$MeC_6H_4$ | Br | 66 | 33 | **1Bf** | 4-$MeC_6H_4$ | OMe | 50 |
| 7 | **1Ag** | 3,5-$(Me)_2C_6H_3$ | Br | 69 | 34 | **1bg** | 3,5-$(Me)_2C_6H_3$ | OMe | 69 |
| 8 | **1Ah** | 4-*t*$BuC_6H_4$ | Br | 69 | 35 | **1Bh** | 4-*t*$BuC_6H_4$ | OMe | 55 |
| 9 | **1Ai** | 4-$CF_3C_6H_4$ | Br | 70 | 36 | **1Bi** | 4-$CF_3C_6H_4$ | OMe | 61 |
| 10 | **1Aj** | 4-$OCF_3C_6H_4$ | Br | 59 | 37 | **1Bj** | 4-$OCF_3C_6H_4$ | OMe | 50 |
| 11 | **1Ak** | 4-$NHAcC_6H_4$ | Br | 29 | 38 | **1Bk** | 4-$NHAcC_6H_4$ | OMe | 28 |
| 12 | **1Am** | 4-$OMeC_6H_4$ | Br | 33 | 39 | **1Bm** | 4-$OMeC_6H_4$ | OMe | 36 |
| 13 | **2Aa** | $C_6H_5$ | Br | 61 | 40 | **2Ba** | $C_6H_4$ | OMe | 60 |
| 14 | **2Ab** | 4-$ClC_6H_4$ | Br | 70 | 41 | **2Bb** | 4-$ClC_6H_4$ | OMe | 83 |
| 15 | **2Ac** | 4-$BrC_6H_4$ | Br | 67 | 42 | **2Bc** | 4-$BrC_6H_4$ | OMe | 73 |
| 16 | **2Ad** | 4-$FC_6H_4$ | Br | 72 | 43 | **2Bd** | 4-$FC_6H_4$ | OMe | 65 |
| 17 | **2Ae** | 3-$ClC_6H_4$ | Br | 47 | 44 | **2Be** | 3-$ClC_6H_4$ | OMe | 65 |
| 18 | **2Af** | 4-$MeC_6H_4$ | Br | 48 | 45 | **2Bf** | 4-$MeC_6H_4$ | OMe | 49 |
| 19 | **2Ag** | 3,5-$(Me)_2C_6H_3$ | Br | 49 | 46 | **2Bg** | 3,5-$(Me)_2C_6H_3$ | OMe | 42 |
| 20 | **2Ah** | 4-*t*$BuC_6H_4$ | Br | 65 | 47 | **2Bh** | 4-*t*$BuC_6H_4$ | OMe | 60 |
| 21 | **2Ai** | 4-$CF_3C_6H_4$ | Br | 70 | 48 | **2Bi** | 4-$CF_3C_6H_4$ | OMe | 78 |
| 22 | **2Aj** | 4-$OCF_3C_6H_4$ | Br | 34 | 49 | **2Bj** | 4-$OCF_3C_6H_4$ | OMe | 32 |
| 23 | **2Ak** | 4-$NHAcC_6H_4$ | Br | 31 | 50 | **2Bk** | 4-$NHAcC_6H_4$ | OMe | 30 |
| 24 | **2Al** | benzo[*d*][1,3]dioxole | Br | 62 | 51 | **2Bl** | benzo[*d*][1,3]dioxole | OMe | 50 |
| 25 | **2Am** | 4-$OMeC_6H_4$ | Br | 39 | 52 | **2Bm** | 4-$OMeC_6H_4$ | OMe | 48 |
| 26 | **2An** | 1-naphthalenyl | Br | 56 | 53 | **2Bn** | 1-naphthalnyl | OMe | 59 |
| 27 | **2Ao** | 3-pyridyl | Br | 89 | 54 | **2Bo** | 3-pyridyl | OMe | 60 |

to the single membrane of Gram-positive bacteria, we assume that the additional membrane could be one limiting factor for the activity of this class of compounds. The best activity was observed against *B. subtilis*. Of 54 compounds examined, 14 compounds showed an inhibition of more than 50% for all three concentrations tested. The most po-


Figure 1. Biological activities of **1Aa**–**1Am**, **1Ba**–**1Bm**, **2Aa**–**2Ao**, and **2Ba**–**2Bo**.

tent compound was **2Bn** with 78% inhibition at 10 μM incubation and 95% inhibition at 100 μM incubation relative to the control substance. Furthermore, good inhibitory activities were detected for **1Aj** (65% inhibition at 10 μM and 81% inhibition at 100 μM), **2Bj** (65% inhibition at 10 μM and 48% inhibition at 100 μM), and **2Ad** (70% inhibition at 10 μM and 32% inhibition at 100 μM). Surprisingly, the two latter compounds showed less activity at higher concentrations, possibly because of solubility issues in the given medium. This phenomenon of reduced or steady inhibition as the concentration increased was also observed for other substances (**2Ab**, **2Bb**, **2Ac**, **2Bc**, **2Ad**, **2Ae**, **2Af**, **2Bi**, **2Aj**, **2Bj**, and **2An**). Concerning the structure–activity relationship (SAR) of the tested compounds against *B. subtilis*, it is noticeable that the aryl group at the C-5 position is mandatory for activity (**2Ab**, **2Bb**, **2Ae**, **2Ad**, **2Ac**, **2Bc**, **2Bi**, **2Aj**, **2Bj**, **2Bh**, **2An**, **2Bn**, and **2Af**), as the structural analogues of these compounds (i.e., those arylated at the C-4 position) showed less or no activity. Interestingly and in contrast to these observations, **1Aj** exhibits similar activity at 10 μM concentration (65%) and even stronger activity at 100 μM concentration (81%) than its structural analogue **2Bj** (68% at 10 μM and 75% at 100 μM). Regarding the substituents at the C-5 phenyl ring, it can be concluded that electron-withdrawing substituents such as halogens (in **2Ab**, **2Bb**, **2Ae**, **2Ad**, **2Ac**, and **2Bc**) or a trifluoromethoxy group (in **1Aj**, **2Aj**, and **2Bj**) showed higher activity compared to compounds without any substituents (**2Aa**, **2Ba**, **1Aa**, and **1Ba**). This might be due to the higher lipophilicity of these compounds, which is an important parameter in medicinal chemistry because it facilitates cellular penetration.[11] Compounds with electron-donating substituents (**2Bh**, **2An**, **2Bn**, and **2Af**) also exhibited good activities against *B. subtilis*. Owing to the comparable activity of **2Ab** (*para*-Cl substitution) and **2Ae** (*meta*-Cl substitution), the activity is likely not dependent on the position of the substituent.

Some of the tested compounds exhibited activity against MRSA. Compound **1Aj** showed the highest inhibition of 78% at 10 μM and 90% at 100 μM; this was similar to the activity of **1Ai**, which displayed high inhibition at 10 μM (76%) but no inhibition at 100 μM, possibly because of solubility issues as already mentioned above. In general, the following can be stated about the SAR of the compounds against MRSA: of all tested compounds, the ones that are arylated at the C-4 position and have a bromine substituent at the R position (**1Ab**, **1Ae**, **1Ad**, **1Aj**, and **1Ai**) showed good activities. In contrast, structural analogues that are arylated at the C-5 position or have a methoxy substituent at the R position showed less activity or no activity. In addition, we observed that the introduction of electron-withdrawing groups (halogen, $CF_3$, or $OCF_3$) led to higher activities.

The antifungal screening results revealed that none of the synthesized compounds showed activity against the yeast *C. glabrata*, whereas we observed moderate activities at lower concentrations (10 μM, 50 μM) and good activities at higher concentrations (100 μM) of some compounds against the dermatophyte *T. mentagrophytes*. Compounds **1Ba** and **1Bf** exhibited the highest inhibition relative to that of the specified control substance. At concentration levels of 10 μM, inhibitions of 31 (**1Ba**) and 29% (**1Bf**) were obtained; at 100 μM concentration, inhibitions of 100 (**1Ba**) and 93% (**1Bf**) were observed. Compound **2Bo** also showed moderate activity (65% inhibition at 100 μM). One can assume that the methoxy group at the R position is mandatory for activity against *T. mentagrophytes* as the structural analogues of the active compounds with a bromine tom at the R position (**1Ab**, **1Af**, and **2Ao**) showed no activity.

The cytotoxicity evaluation was performed with two different cell lines (NIH-3T3 and HT-29) at two different concentration levels (10 and 50 μM). At a concentration of 10 μM, no effect was observed against both cell lines. At 50 μM, it is worth noting that nine compounds showed notable activities (over 50%) against NIH-3T3, and **2Bh** (90%) was the most potent. Among all tested compounds, only **2Bh** exhibited moderate activity against HT-29 cells (53%). The SAR of the cytotoxicity evaluation revealed that compounds arylated at the C-5 position of the thiazole showed higher cytotoxicity than their analogues arylated at the C-4 position.

Finally, the highest biologically active compounds against *B. subtilis*, MRSA, dermatophyte *T. mentagrophytes*, and NIH-3T3 are summarized in Figure 2.

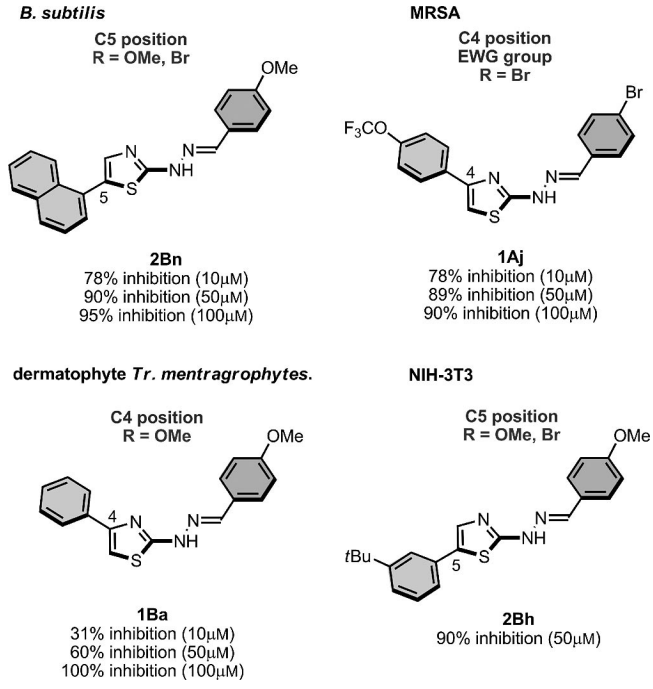



Figure 2. Summary of the biological testing.

## Conclusions

We have established a new step-economical and diversity-oriented synthesis of 2-arylidenehydrazinyl-4-arylthiazoles **1** and 2-arylidenehydrazinyl-5-arylthiazoles **2** that utilizes C-4-selective and C-5-selective C–H coupling methodologies. The coupling of different arylboronic acids and aryl

iodides with 2-phenoxythiazole (**1**) and subsequent nucleophilic substitution with hydrazine and condensation with *p*-bromobenzaldehyde or *p*-anisaldehyde led to the target compounds. The present work highlights the power of C–H-functionalization to medicinal chemistry and drug development; it allows an efficient and facile coupling of simple and readily available components and, thereby, facilitates the setup of highly diverse substance libraries. By application of this strategy, we were able to rapidly create a library of 54 new 2-arylidenehydrazinyl-4-arylthiazole (**1Aa**–**m** and **1Ba**–**m**) and 2-arylidenehydrazinyl-5-arylthiazole (**2Aa**–**o** and **2Ba**–**o**) analogues, which were tested extensively for their biological activity. In particular, the thiazole derivative **1Aj**, arylated at the C-4 position with a 4-trifluoromethoxyphenyl substituent and a bromine atom at the R position, exhibited high antibacterial activity against Gram-positive bacteria strains. The thiazole derivative **1Ba** was the most potent compound in the antifungal screening. The evaluation of the cytotoxicity revealed the high activity exhibited by thiazole derivative **2Bh**. Moreover, important information about the structure-activity relationship of these classes of thiazoles has been gained by this biological evaluation. As a result of this new synthetic pathway and the gathered SAR knowledge, this work will be beneficial for the future design and synthesis of new analogues to promote the discovery of new antimicrobial agents.

## Experimental Section

**General Procedure for C-4-Selective C–H Arylation of 3A with Arylboronic Acids:** To a sealed tube, $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 10 mol-%), 1,10-phenanthroline (18.0 mg, 0.1 mmol, 10 mol-%), $LiBF_4$ (140.6 mg, 1.5 mmol, 1.5 equiv.), the corresponding arylboronic acid **4** (4 mmol, 4.0 equiv.), 2-phenoxythiazole (**3A**; 177 mg, 1 mmol, 1.0 equiv.), TEMPO (78 mg, 0.5 mmol, 0.5 equiv.), and DMAc (2 mL) were added, and the mixture was heated at 100 °C for 48 h in an eight-well reaction block. After cooling, the mixture was filtered through a short silica gel pad with EtOAc (50 mL). Concentration of the filtrate under reduced pressure and purification by silica gel flash column chromatography afforded the desired 2-phenoxy-4-arylthiazole **5A**.

**General Procedure for C-5-Selective C–H Arylation of 3A with Aryl Iodides:** To a sealed tube, $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (20.4 mg, 25 μmol, 5 mol-%), $PPh_3$ (13 mg, 50 μmol, 10 mol-%), $Ag_2CO_3$ (275.8 mg, 1.0 mmol, 2.0 equiv.), the corresponding aryl iodide **4** (0.6 mmol, 1.2 equiv.), **3A** (88.5 mg, 0.5 mmol, 1.0 equiv.), and $H_2O$ (3 mL) were added, and the mixture was stirred at 60 °C for 24 h in an eight-well reaction block. After cooling to room temperature, the mixture was filtered through a short Celite pad, washed with $CH_2Cl_2$ (15 mL) and acetone (15 mL), and concentrated under reduced pressure. $CH_2Cl_2$ (10 mL) and brine (10 mL) were added to the solid residue, and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The organic layers were combined and dried with $Na_2SO_4$, and the volatiles were removed under reduced pressure. Purification by flash column chromatography afforded the desired 2-phenoxy-5-arylthiazoles **5B**.

**General Procedure for Synthesis of 2-(Arylidenehydrazinyl)-arylthiazoles:** To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 2-phenoxy-arylthiazole **5Aa**–**5Am** or **5Ba**–**5Bo** (1.0 equiv.) and DMSO (0.5 mL). To this solution, anhydrous hydrazine (20 equiv.) was added, and the reaction mixture was stirred at 100 °C for 12 h in an eight-well reaction block. Purification by preparative MPLC afforded the desired thiazoles **6Aa**–**6Am** or **6Ba**–**6Bo**. To a stirred solution of **6Aa**–**6Am** or **6Ba**–**6Bo** in EtOH/MeOH (v/v 1:1, 4 mL), the corresponding aldehyde (1.2 equiv.) and a catalytic amount of AcOH were added, and the reaction mixture was stirred at 80 °C for 1 h in an eight-well reaction block. Purification by preparative MPLC afforded the corresponding 2-(arylidenehydrazinyl)-arylthiazoles **1Aa**–**1Am**, **1Ba**–**1Bm**, **2Aa**–**2Ao**, **and 2Ba**–**2Bo**.

**Supporting Information** (see footnote on the first page of this article): Experimental details and copies of the $^1H$ and $^{13}C$ NMR spectra of all new compounds.

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[1] G. Taubes, *Science* **2008**, *321*, 356.
[2] V. Aloush, S. Navon-Venezia, Y. Seigman-Igra, S. Cabili, Y. Carmeli, *Antimicrob. Agents Chemother.* **2006**, *50*, 43.
[3] a) S. L. Schreiber, *Science* **2000**, *287*, 1964; b) S. Shang, D. S. Tan, *Curr. Opin. Chem. Biol.* **2005**, *9*, 248.
[4] a) M. S. Alam, L. Liu, Y.-E. Lee, D.-U. Lee, *Chem. Pharm. Bull.* **2011**, *59*, 568; b) S. K. Bharti, G. Nath, R. Tilak, S. K. Singh, *Eur. J. Med. Chem.* **2010**, *45*, 651.
[5] P. Karegoudar, M. S. Karthikeyan, D. J. Prasad, M. Mahalinga, B. S. Holla, N. S. Kumari, *Eur. J. Med. Chem.* **2008**, *43*, 261.
[6] A. Hantzsch, J. H. Weber, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118.
[7] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; *Angew. Chem.* **2009**, *121*, 9976; d) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; e) T. Satoh, M. Miura, *Synthesis* **2010**, 3395; f) J. Bouffard, K. Itami, *Top. Curr. Chem.* **2010**, *292*, 231; g) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; h) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369.
[8] For selected examples of our discovered C–H couplings, see: a) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748; b) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622; c) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2010**, *49*, 8946; *Angew. Chem.* **2010**, *122*, 9130; d) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer, K. Itami, *Angew.*

  

*Chem. Int. Ed.* **2011**, *50*, 2387; *Angew. Chem.* **2011**, *123*, 2435; e) K. Mochida, K. Kawasumi, Y. Segawa, K. Itami, *J. Am. Chem. Soc.* **2011**, *133*, 10716; f) D. Mandal, A. D. Yamaguchi, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2011**, *133*, 19660; g) K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 169; h) K. Yamaguchi, J. Yamaguchi, A. Studer, K. Itami, *Chem. Sci.* **2012**, *3*, 2165; i) K. Amaike, K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 13573; j) C. Meyer, D. Schepmann, S. Yanagisawa, J. Yamaguchi, V. Dal Col, E. Laurini, K. Itami, S. Pricl, B. Wünsch, *J. Med. Chem.* **2012**, *55*, 8047; k) K. Yamaguchi, H. Kondo, J. Yamaguchi, K. Itami, *Chem. Sci.* **2013**, *4*, 3753.

[9] For selected examples of C-5-(selective) arylation of thiazoles, see: a) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467; b) G. L. Turner, J. A. Morris, M. F. Greaney, *Angew. Chem. Int. Ed.* **2007**, *46*, 7996; *Angew. Chem.* **2007**, *119*, 8142; c) A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto, T. Ikeda, *J. Am. Chem. Soc.* **2003**, *125*, 1700; d) M. Parisien, D. Valette, K. Fagnou, *J. Org. Chem.* **2005**, *70*, 7578; e) S. Yanagisawa, K. Itami, *Tetrahedron* **2011**, *67*, 4425; f) F. Shibahara, E. Yamaguchi, T. Murai, *J. Org. Chem.* **2011**, *76*, 2680.

[10] C. Meyer, B. Neue, D. Schepmann, S. Yanagisawa, J. Yamaguchi, E.-U. Würthwein, K. Itami, B. Wünsch, *Org. Biomol. Chem.* **2011**, *9*, 8016.

[11] F. R. Leroux, B. Manteau, J.-P. Vors, S. Pazenok, *Beilstein J. Org. Chem.* **2008**, *4*, 13.

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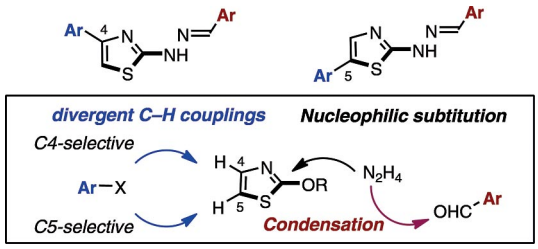


We have established a step-economical and diversity-oriented synthesis of 2-arylidenehydrazinyl-4-arylthiazoles and 2-arylidenehydrazinyl-5-arylthiazoles that utilizes C-4- and C-5-selective C–H coupling methodologies. A rapidly created library of 54 new 2-arylidenehydrazinyl-4-arylthiazole and 2-arylidenehydrazinyl-5-arylthiazole analogues were tested extensively for their biological activity.



**Keywords:** C–H arylation / Thiazoles / Antibiotics / Cross-coupling / Structure–activity relationships

  