A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2025** (5) 202512344

Palladium-catalyzed tandem reaction toward 2,5-diarylthiazole derivatives

Runsheng Xu*, Jin Xu, and Jiahao Hu

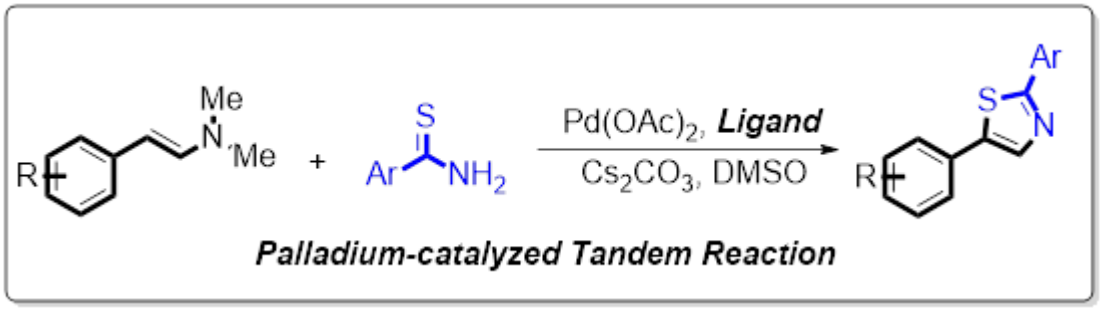
College of Life and Health, Huzhou College, Huzhou, Zhejiang, 211300, China
Email: xurunsheng@zjhzu.edu.cn

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

An efficient palladium-catalyzed tandem reaction for the synthesis of 2,5-diarylthiazole derivatives was developed. Notably, from N,N-dimethyl-2-arylethen-1-amines and benzothioamide parent compounds various 2,5-diarylthiazole derivatives were efficiently synthesized under a moderate condition. Finally, a plausible Pd(II)/Pd(IV) reaction mechanism was devised. This new methodology provides an efficient and economical approach for the synthesis of 2,5-diarylthiazole derivatives.



Keywords: Palladium-catalyzed, tandem reaction, C-S bond, benzothioamides, 2,5-diarylthiazole derivatives

Introduction

Thiazoles are an important class of organic compounds with significant application value in various fields rendering them research hotspots.[1-5] Derivatives containing thiazole rings have diverse structures and exhibit a wide range of biological activities, such as anticancer,[6] antiviral,[7,8] insecticidal,[9] bactericidal,[10] and herbicidal activities.[11]

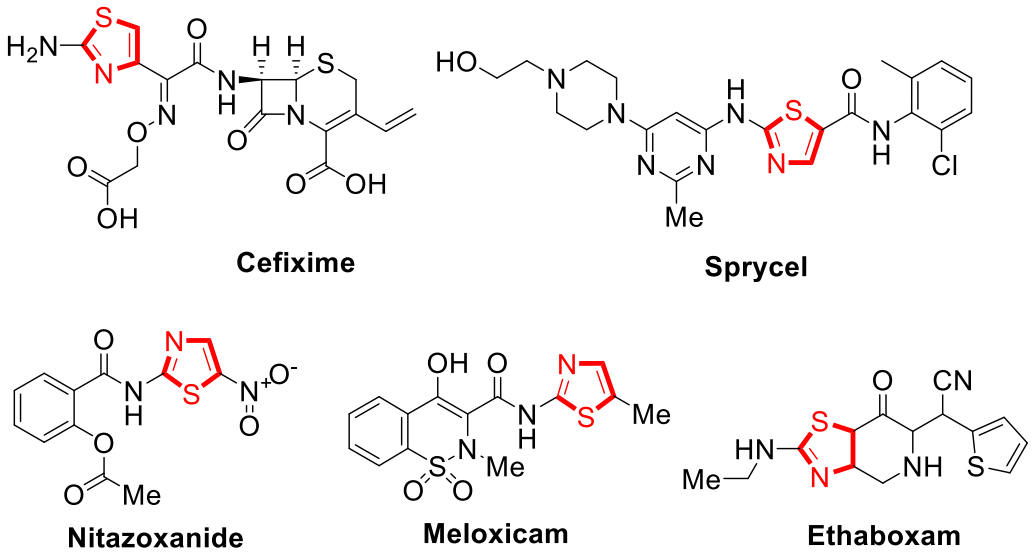


Figure 1. The important clinical drugs of thiazole derivatives.

Researchers have described a large number of thiazole derivatives with excellent bactericidal activity, and have successfully developed multiple commercial products, as shown in Figure 1. These include cefixime,[12] a third-generation cephalosporin antibiotic for oral use, suitable for treating respiratory, urinary, and biliary tract infections caused by sensitive bacteria. Sprycel[13] is used to treat adult patients with Philadelphia chromosome positive (Ph^+) chronic myeloid leukemia in the chronic, accelerated, and rapid phases who are resistant or intolerant to imatinib mesylate. Meloxicam,[14] an enol based nonsteroidal anti-inflammatory drug with anti-inflammatory, analgesic, and antipyretic effects. Nitrozotinide[15] is believed to be related to the enzyme dependent electron transfer reaction that inhibits pyruvate and iron redox protein oxidoreductase, the latter of which is crucial for anaerobic energy metabolism.

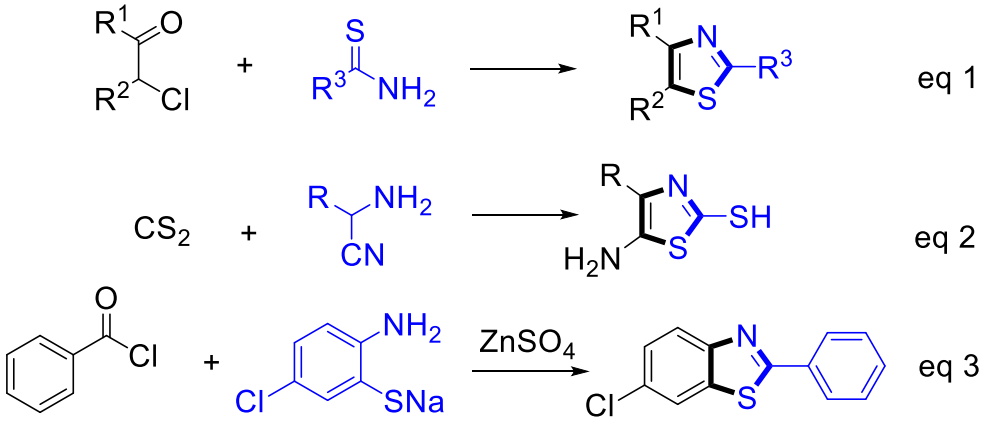


Figure 2. Methods have been proposed for synthesizing thiazole derivatives.

At present, many methods have been proposed for synthesizing thiazole derivatives, as shown in Figure 2. The commercialization of 2,5-diarylthiazole derivatives which was developed as the first synthesis based on Hantzsch method[16] (eq 1), Cook-Heilbron method[17] (eq 2), and Herz method[18] (eq 3). The synthesis of thiazole ring is mainly divided into two categories: synthesis and cyclization of the thiazole ring. The synthesis of the thiazole ring usually involves a substitution reaction between thiazole acid or its derivatives and electrophilic reagents to generate the thiazole ring. The cyclization of the thiazole ring involves chemical reactions involving the thiazole ring using amino, carboxyl, and acyl, functional groups.

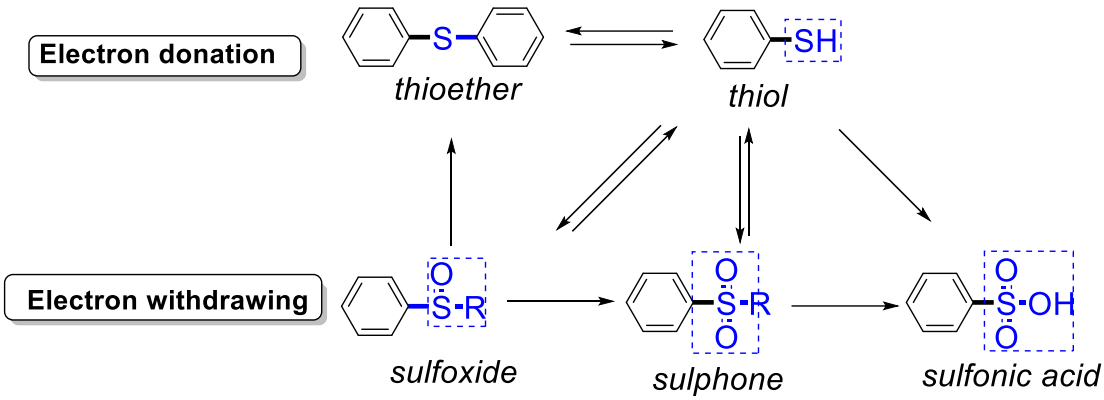
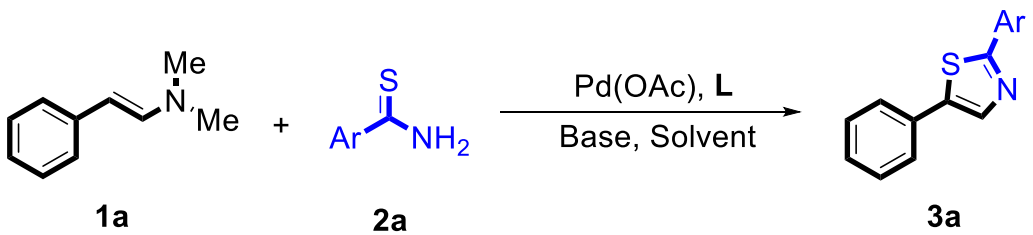


Figure 3. Conversions of sulfur-containing groups.

Due to a larger atomic radius and higher electron density, sulfur has more activation patterns and theoretically allows easier modification, as shown in Figure 3.[19] Developing more efficient strategies of thiolation of C-H bonds is still highly desirable. Considering the need of diversifying synthetic strategies, we focused our interest on the functionization of sulfur-containing C-H bonds.[20-25] Herein, we report a palladium-catalyzed tandem reaction aimed at the synthesis of 2,5-diarylthiazole derivatives. In this reaction, from parent compounds N,N-dimethyl-2-arylethen-1-amines and benzothioamides various 2,5-diarylthiazole derivatives were efficiently synthesized under moderate conditions. Finally, a plausible reaction mechanism is proposed.

Results and Discussion

The reaction conditions were screened based on the model reaction involving N,N-dimethyl-2-phenylethen-1-aminethiophenol **1a** and benzothioamide **2a**. Initially, various structurally similar enaminone ligands **L1**-**L9** were investigated, which were proven to efficiently catalyze the C-S coupling reactions shown in Figure 4. The yields observed increased by changing the substituent to -OH (**L4**-**L6**). Additionally, other enaminone ligands such as **L7**, **L8** and **L9** were produced with lower efficacies. The experimental results indicated that **L4** was the optimal ligand for all reactions.



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

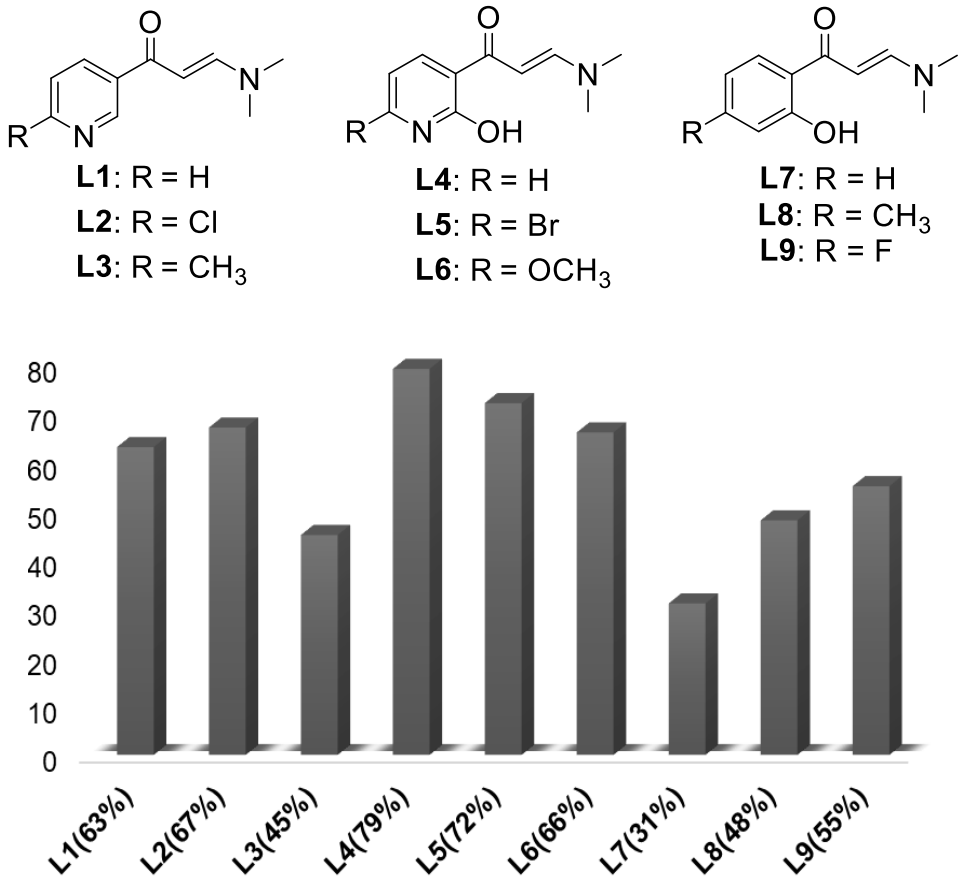


Figure 4. Ligand performances in palladium-catalyzed tandem reaction toward 2,5-diphenylthiazole.

Furthermore, other reaction parameters were optimized, as shown in Table 1. The experimental results demonstrated that the Pd(II) salt had a higher yield than the Pd(0) salt (entries 1-4). By screening different bases for the reaction, Cs_2CO_3 was demonstrated to be more suitable base than others such as Na_2CO_3 and K_2PO_3 (entries 5-7). The results demonstrated that the reaction temperature was as an important parameter; the desired product was formed at a 65% yield at 90°C (entry 8) and at a 77% yield at 100°C (entry 9). Finally, the desired product **3a** was formed at a yield of 83% when the catalyst system **L4** was employed with $Pd(OAc)_2$ at 100°C (entry 10).

Table 1. Optimization of the model reaction.[a]

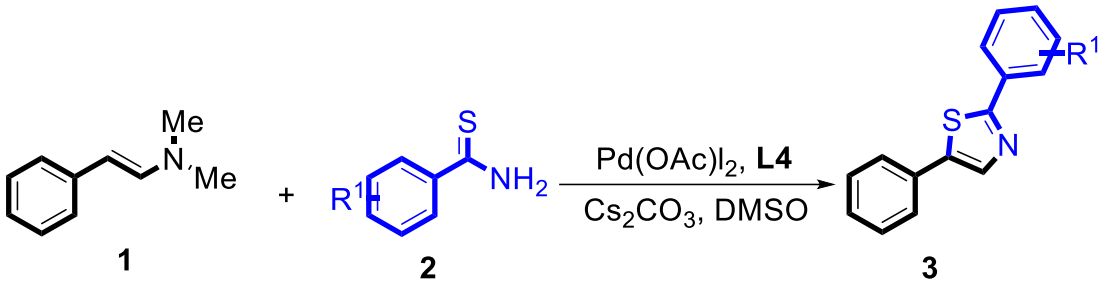
Entry	Copper salt	Base	**1a** : **2a**	**3a** [%][b]
1	$Pd(NH_3)_4Cl_2$	Cs_2CO_3	1:1	42
2	$PdCl_2$	Cs_2CO_3	1:1	79
3	$Pd(PPh_3)_4$	Cs_2CO_3	1:1	nr
4	$Pd(OAc)_2$	Cs_2CO_3	1:1	74
5	$Pd(OAc)_2$	Cs_2CO_3	1:1	81
6	$Pd(OAc)_2$	Na_2CO_3	1:1.2	nr
7	$Pd(OAc)_2$	K_3PO_4	1:1.2	41
8	$Pd(OAc)_2$	Cs_2CO_3	1:1.2	65[c]
9	$Pd(OAc)_2$	Cs_2CO_3	1:1.2	77[d]

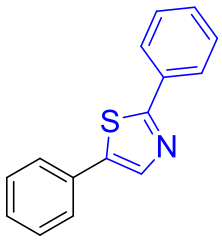
10	$Pd(OAc)_2$	Cs_2CO_3	1:1.2	83

[a] Unless otherwise noted, reaction conditions were **1a** (10 mmol), palladium source (10 mol%), **L4** (10 mol%), Cs_2CO_3 (2 equivalents), DMSO (10 mL), 100°C for 24 h. [b] Isolated yield. [c] reaction at 90 °C. [d] reaction at 110 °C.

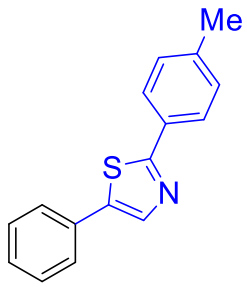
Once the optimized conditions were determined, the reaction scope was investigated. A wide array of N,N-dimethyl-2-arylethen-1-amine **1** and benzothioamide **2** derivatives were produced with good to excellent yields (Table 2). Both the electron-donating and electron-withdrawing *N,N*-dimethyl-2-arylethen-1-amine **1** reacted easily with benzothioamides **2**. *N,N*-dimethyl-2-arylethen-1-amine **1** bearing electron-donating groups showed better activity than those bearing electron-withdrawing groups. Benzothioamides **2** bearing electron-withdrawing groups had better activity than those bearing electron-donating groups.

Table 2. Palladium-catalyzed tandem reactions generating 2,5-diarylthiazole derivatives.[a,b]

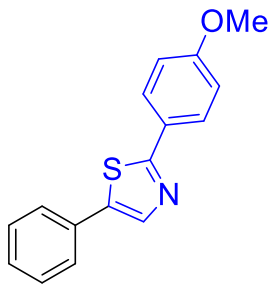




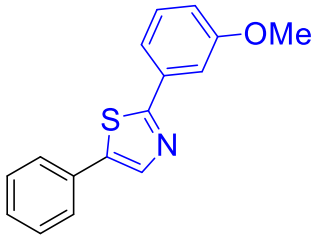
3a, 87%



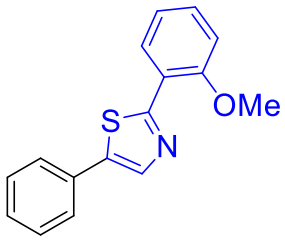
3b, 84%



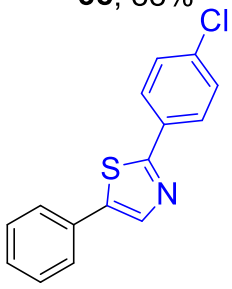
3c, 88%



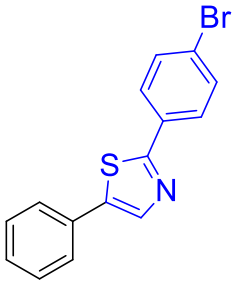
3d, 81%



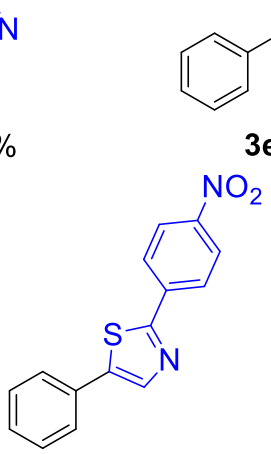
3e,76%



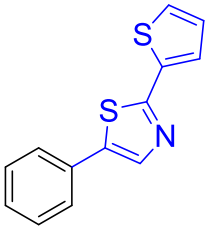
3f, 79%



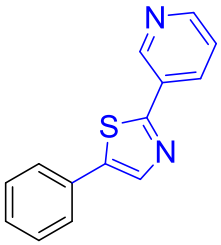
3g, 80%



3h, 83%



3i, 82%

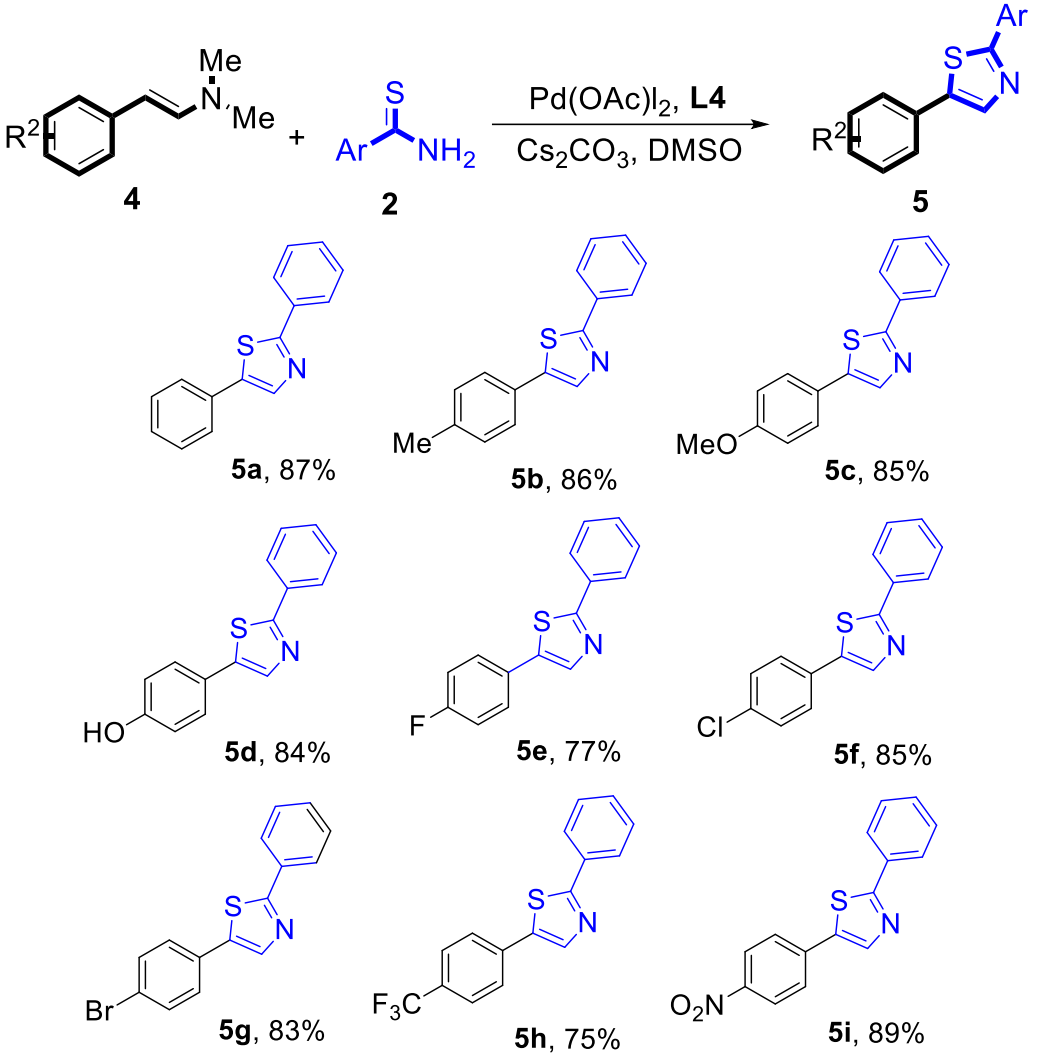


3j, 78%

[a] Reaction conditions: **1** (10 mmol)**, 2** (12 mmol), $Pd(OAc)_2$ (10 mol%), **L4** (10 mol%), Cs_2CO_3 (2 equivalents), DMSO (10 mL), 100°C for 24 h and [b] isolated yields.

Next, we turned our attention to other N,N-dimethyl-2-arylethen-1-amines **4** and benzothioamide **2** (Table 3). Of note, N,N-dimethyl-2-arylethen-1-amines **4** worked well in this reaction. The corresponding products were isolated in 75-89% yield. Nitro and trifluoromethyl substituted reactants also reacted well and retained in corresponding products **5** achieve in good yields (entries **5h** and **5l**).

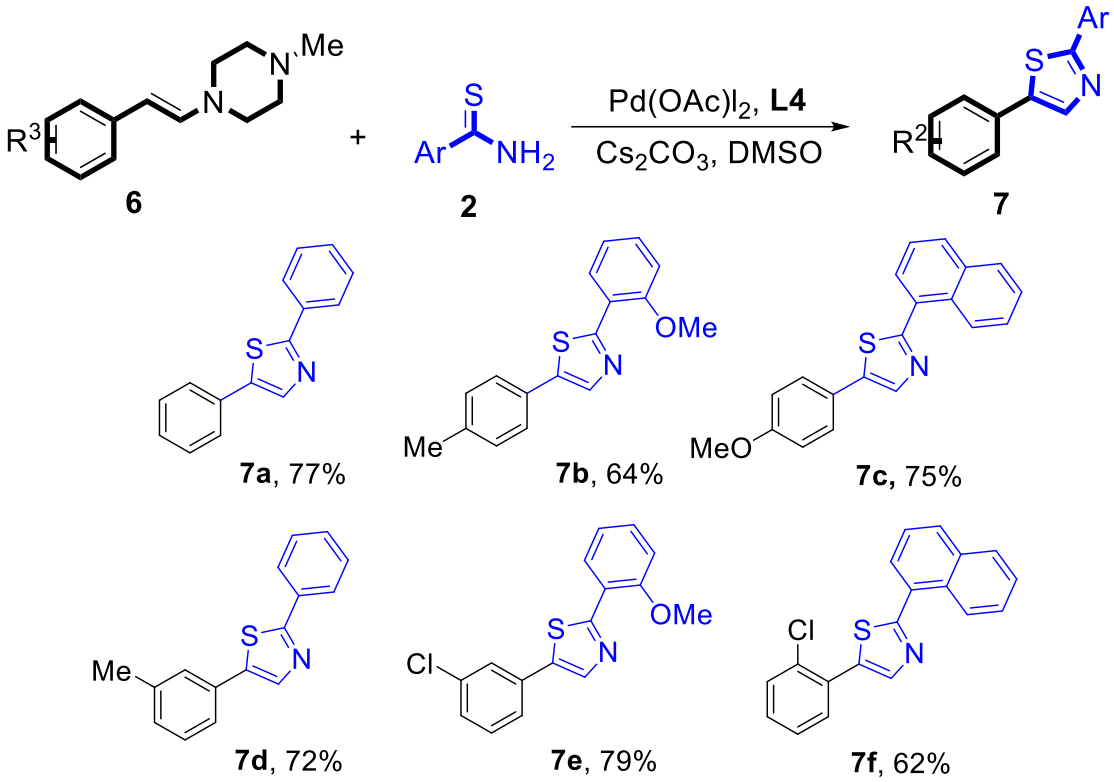
Table 3. Palladium-catalyzed tandem reaction for the synthesis of 2,5-diarylthiazole derivatives.[a,b]



[a] Reaction conditions: **4** (10 mmol)**, 2** (12 mmol), $Pd(OAc)_2$ (10 mol%), **L4** (10 mol%), Cs_2CO_3 (2 equiv), DMSO (10 mL), 100°C for 24 h and [b] Isolated yields.

Of note, 1-methyl-4-styrylpiperazines **6** and benzothioamides **2** also reacted smoothly using this method (Table 4). The corresponding products were isolated with yields of 62-79%. Naphthyl-substituted reactants **7c** and **7f** generated corresponding products with medium yields.

Table 4. Palladium-catalyzed tandem reaction generating 2,5-diarylthiazole derivatives.[a,b]



[a] Reaction conditions: **6** (10 mmol)**, 2** (12 mmol), $Pd(OAc)_2$ (10 mol%), **L4** (10 mol%), Cs_2CO_3 (2 equiv), DMSO (10 mL), 100°C for 24 h and [b] isolated yields.

Based on the above results, a reaction mechanism was proposed (Figure 5). After the coordination of $Pd(OAc)_2$ with **L4**, a corresponding intermediate **8** was generated.[10] Next, the intermediate **9** was formed from intermediate **8** with *N,N*-dimethyl-2-arylethen-1-amine **1** by an oxidative addition step. Next, intermediate **9** reacted with benzothioamide **2** to produce intermediate **10** via a transamina step. Finally, intermediate **10** furnished the desired products **3** and concomitantly generated intermediate **8** which re-entered the catalytic cycle by heterocyclization and a reductive elimination step.

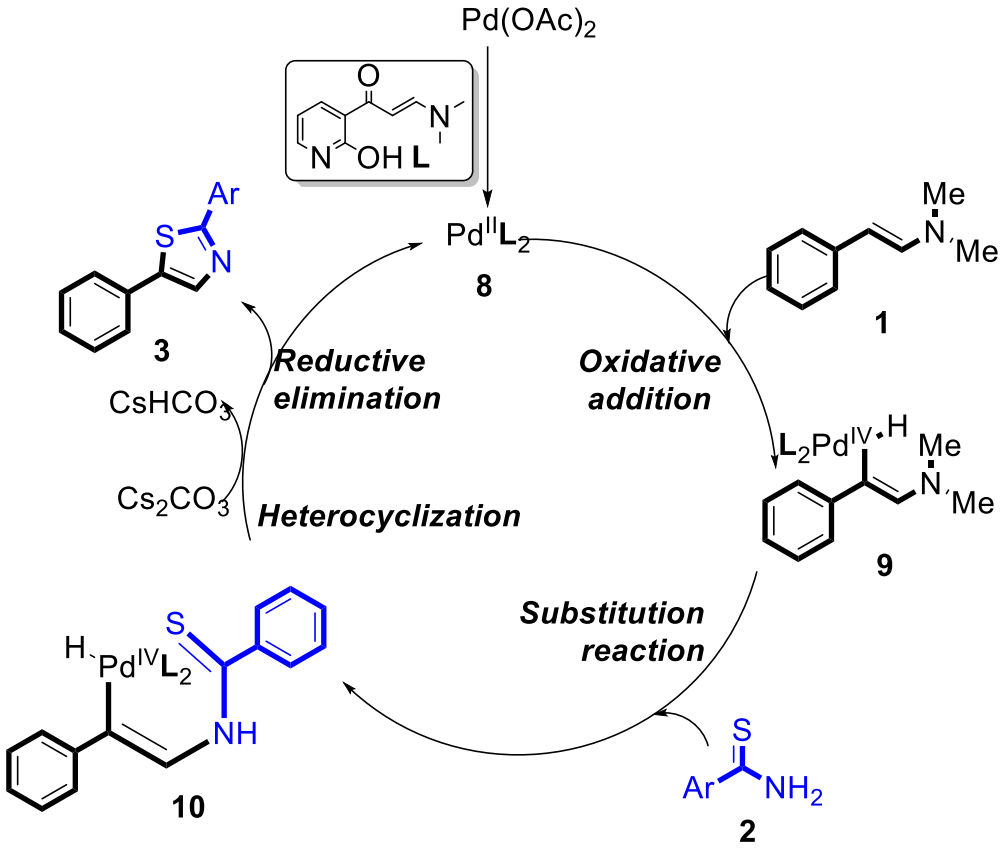


Figure 5. The proposed reaction mechanism.

Conclusions

An efficient palladium-catalyzed tandem reaction producing 2,5-diarylthiazole derivatives was developed. Notably, form reaction of N,N-dimethyl-2-arylethen-1-amines and benzothioamides various 2,5-diarylthiazole derivatives were efficiently synthesized. The process also uses moderate condition. Finally, a plausible Pd(II)/Pd(IV) reaction mechanism was proposed. This new methodology provides an efficient and economical approach toward 2,5-diarylthiazole derivatives.

Experimental Section

General. All reagents used in the experiments were obtained from commercial sources and used without further purification. Solvents for chromatography were technical grade and distilled prior to use. Solvent mixtures were prepared as volume/volume solutions. Chemical yields refer to pure isolated substances. Catalysts were purchased as analytical reagent grade. Thin layer chromatography employed glass 0.25 mm silica gel plates with F-254 indicator, visualized by irradiation with UV light. The NMR spectra were recorded by Bruker AVANCE III-400 spectrometry at 400 MHz and 100 MHz for ^{1}H and ^{13}C NMR in $CDCl_3$, respectively. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively, and chloroform is solvent with TMS as the internal standard. The NMR spectra were reported in delta (δ) units, parts per million (ppm) downfield from the internal standard and coupling constants were reported in Hertz (Hz). Multiplicities were indicated as s (singlet), d

(doublet), t (triplet), q (quartet), and m (multiplet). The mass spectra were performed on a Bruker Esquire 3000plus mass spectrometer equipped with ESI interface and ion trap analyzer. The ESI HR-MS were tested on Bruker 7-tesla FT-ICR MS equipped with an electrospray source.

General procedures for preparation of products 3 and 5. A mixture of N,N-dimethyl-2-arylethen-1-amines **1** or **4** (10 mmol), and benzothioamides **2** (12 mmol), $Pd(OAc)_2$ (10 mol%) and Cs_2CO_3 (2 equiv, 20 mmol), in DMSO (15 mL) was stirred under an N_2 atmosphere. After the reaction mixture was stirred at 100°C for 24 h, it was allowed to cool to ambient temperature. Next, the mixture was quenched with saturated salt water (20 mL), and the solution was extracted with ethyl acetate (3×20 mL). The organic layers were combined and dried by sodium sulfate and concentrated in a vacuum. The pure product 2,5-diarylthiazole derivatives **3** or **5** (76-89% yield) was obtained by flash column chromatography on silica gel.

2,5-diphenylthiazole (3a). Pale yellow solid, 2.38 g, isolated yield: 87%, m.p. 116-118°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (q, 2H, *J* = 4.0 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.4 (m, 6H), 7.3 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 151, 130, 129, 129, 128, 28, 127, 126, 124, 123; HRMS(ESI): m/z calcd for $C_{15}H_{11}NNaS$ $(M+Na)^+$: 260.0510, found: 260.0508.

5-phenyl-2-(p-tolyl)thiazole (3b). Pale yellow solid, 2.22 g, isolated yield: 84%, m.p. 117-119°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.0 (d, 2H, *J* = 8.0 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.4 (t, 3H, *J* = 7.0 Hz), 7.3 (d, 1H, *J* = 7.6 Hz), 7.3 (d, 2H, *J* = 8.0 Hz), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 151, 140, 129, 128, 128, 128, 126, 124, 124, 123, 21; HRMS(ESI): m/z calcd for $C_{16}H_{13}NNaS$ $(M+Na)^+$: 274.0666, found: 274.0664.

2-(4-methoxyphenyl)-5-phenylthiazole (3c). Pale yellow solid, 2.35 g, isolated yield: 88%, m.p. 108-109°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.7 (t, 3H, *J* = 6.6 Hz), 7.6 (s, 1H), 7.4 (m, 5H), 7.00 (q, 1H, *J* = 4.2 Hz), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 159, 151, 129, 128, 128, 128, 128, 124, 123, 118, 116, 111, 55; HRMS(ESI): m/z calcd for $C_{16}H_{13}NNaOS$ $(M+Na)^+$: 290.0616, found: 290.0614.

2-(3-methoxyphenyl)-5-phenylthiazole (3d). Pale yellow solid, 2.17 g, isolated yield: 81%, m.p. 121-124°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.7 (t, 2H, *J* = 6.6 Hz), 7.6 (s, 1H), 7.4 (m, 5H), 7.00 (q, 1H, *J* = 8.4 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 161, 160, 151, 130, 128, 128, 128, 128, 124, 123, 118, 116, 111, 55; HRMS(ESI): m/z calcd for $C_{16}H_{13}NNaOS$ $(M+Na)^+$: 290.0616, found: 290.0614.

2-(2-methoxyphenyl)-5-phenylthiazole (3e). Pale yellow solid, 2.03 g, isolated yield: 76%, m.p. 127-129°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.7 (t, 2H, *J* = 6.6 Hz), 7.6 (s, 1H), 7.3 (m, 5H), 7.0 (q, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 159, 151, 130, 129, 128, 128, 128, 124, 123, 118, 116, 111, 55; HRMS(ESI): m/z calcd for $C_{16}H_{13}NNaOS$ $(M+Na)^+$: 290.0616, found: 290.0614.

2-(4-chlorophenyl)-5-phenylthiazole (3f). Pale yellow solid, 2.15 g, isolated yield: 79%, m.p. 123-125°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.0 (d, 2H, *J* = 8.8 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.4 (m, 5H), 7.3 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160, 151, 136, 129, 128, 128, 127, 127, 125, 124, 123; HRMS(ESI): m/z calcd for $C_{15}H_{10}ClNNaS$ $(M+Na)^+$: 294.0120, found: 294.0118.

2-(4-bromophenyl)-5-phenylthiazole (3g). Pale yellow solid, 2.53g, isolated yield: 80%, m.p. 120-122°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.9 (d, 2H, *J* = 8.8 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.6 (d, 2H, *J* = 8.8 Hz), 7.4 (m, 3H), 7.3 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171, 160, 151, 132, 128, 128, 127, 127, 126, 124, 124, 123; HRMS(ESI): m/z calcd for $C_{15}H_{10Br}NNaS$ $(M+Na)^+$: 337.9615, found: 337.9613.

2-(4-nitrophenyl)-5-phenylthiazole (3h). Pale yellow solid, 2.34 g, isolated yield: 83%, m.p. 208-210°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34\ (d, 2H, *J* = 9.2 Hz), 8.1 (m, 2H), 7.8 (d, 2H, *J* = 8.8 Hz), 7.6 (s, 1H), 7.5 (t, 3H, *J* = 3.2 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162, 149, 147, 133, 131, 129, 126, 126, 126, 124, 124; HRMS(ESI): m/z calcd for $C_{14}H_5D_5N_2NaOS$ $(M+Na)^+$: 305.0361, found: 305.0359.

5-phenyl-2-(thiophen-2-yl)thiazole (3i). Pale yellow solid, 2.00 g, isolated yield: 82%, m.p. 112-114°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.7 (d, 1H, *J* = 3.6 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.4 (m, 3H), 7.3 (s, 1H), 7.3 (t, 1H, *J* = 7.4 Hz), 7.1 (q, 1H, *J* = 4.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157, 150, 130, 128, 128, 128, 127, 127, 127, 124, 123; HRMS(ESI): m/z calcd for $C_{13}H_9NNaS_2$ $(M+Na)^+$: 266.0074, found: 266.0072.

5-phenyl-2-(pyridin-3-yl)thiazole (3j). Pale yellow solid, 1.86 g, isolated yield: 78%, m.p. 137-139°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.3 (d, 1H, *J* = 1.2 Hz), 8.6 (d, 1H, *J* = 3.2 Hz), 8.3 (d, 1H, *J* = 8.0 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158, 152, 150, 147, 133, 129, 128, 127, 124, 123, 123; HRMS(ESI): m/z calcd for $C_{14}H_{10}N_2NaS$ $(M+Na)^+$: 261.0462, found: 261.0460.

2,5-diphenylthiazole (5a). Pale yellow solid, 2.38 g, isolated yield: 87%, m.p. 116-118°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (q, 2H, *J* = 4.0 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.4 (m, 6H), 7.3 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 151, 130, 128, 128, 128, 28, 127, 126, 124, 123; HRMS(ESI): m/z calcd for $C_{15}H_{11}NNaS$ $(M+Na)^+$: 260.0510, found: 260.0508.

2-phenyl-5-(p-tolyl)thiazole (5b). Pale yellow solid, 2.19 g, isolated yield: 87%, m.p. 129-131°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (d, 2H, *J* = 8.0 Hz), 7.6 (d, 2H, *J* = 8.0 Hz), 7.4 (m, 3H), 7.3 (s, 1H), 7.2 (d, 2H, *J* = 7.6 Hz), 2,39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160, 151, 138, 130, 129, 128, 127, 126, 125, 124, 122, 21; HRMS(ESI): m/z calcd for $C_{16}H_{13}NNaS$ $(M+Na)^+$: 274.0666, found: 274.0664.

5-(4-methoxyphenyl)-2-phenylthiazole (5c). Colorless solid, 2.27 g, isolated yield: 85%, m.p. 128-129°C. ^{1}H ($CDCl_3$, 400 MHz): δ 8.1 (d, 2H, *J* = 6.4 Hz), 7.6 (d, 2H, *J* = 8.8 Hz), 7.4 (m, 3H), 7.3 (s, 1H), 6.9 (d, 2H, *J* = 8.8 Hz), 3.8 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160, 159, 151, 130, 128, 127, 126, 125, 122, 121, 114, 55; HRMS(ESI): m/z calcd for $C_{16}H_{13}NNaOS$ $(M+Na)^+$: 290.3358, found: 290.3356.

4-(2-phenylthiazol-5-yl)phenol (5d). Pale yellow solid, 2.13 g, isolated yield: 84%, m.p.89-91°C. ^{1}H MR (DMSO-*d*, 400 MHz): δ 9.8 (s, 1H), 8.0 (t, 2H, *J* = 6.4 Hz), 7.6 (d, 2H, *J* = 8.8 Hz), 7.5 (s, 1H), 7.4 (m, 3H), 6.8 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (DMSO-*d*, 100 MHz): δ 159, 158, 151, 130, 129, 127, 126, 126, 122, 119, 116; HRMS(ESI): m/z calcd for $C_{14}H_5D_5N_2NaOS$ $(M+Na)^+$: 276.0459, found: 276.0457.

5-(4-fluorophenyl)-2-phenylthiazole (5e). Pale yellow solid, 1.97g, isolated yield: 77%, m.p. 98-100°C. ^{1}H MR ($CDCl_3$, 400 MHz): δ 8.0 (q, 2H, *J* = 7.2 Hz), 7.6 (m, 2H), 7.4 (m, 3H), 7.3 (s, 1H), 7.1 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 150, 130, 129, 128, 129, 127, 126, 126, 123, 116; HRMS(ESI): m/z calcd for $C_{15}H_{10}FNNaS$ $(M+Na)^+$: 278.0416, found: 278.0414.

5-(4-chlorophenyl)-2-phenylthiazole (5f). Colorless solid, 2.31 g, isolated yield: 85%, m.p. 110-112°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.0 (q, 2H, *J* = 3.8 Hz), 7.6 (d, 2H, *J* = 8.4 Hz), 7.4 (m, 3H), 7.4 (d, 2H, *J* = 3.6 Hz), 7.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 150, 134, 130, 129, 128, 127, 126, 126, 125, 123; HRMS(ESI): m/z calcd for $C_{15}H_{10}ClNNaS$ $(M+Na)^+$: 294.0120, found: 294.0118.

5-(4-bromophenyl)-2-phenylthiazole (5g). Pale yellow solid, 2.62 g, isolated yield: 83%, m.p. 111-113°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.0 (q, 2H, *J* = 4.0 Hz), 7.5 (s, 4H), 7.4 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 150, 132, 130, 128, 127, 127, 126, 125, 124, 123; HRMS(ESI): m/z calcd for $C_{15}H_{10}BrNNaS$ $(M+Na)^+$: 337.9615, found: 337.9613.

2-phenyl-5-(4-(trifluoromethyl)phenyl)thiazole (5h). Colorless solid, 2.29 g, isolated yield: 75%, m.p. 203-205°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (q, 2H, *J* = 3.8 Hz), 7.8 (d, 2H, *J* = 8.0 Hz), 7.6 (d, 2H, *J* = 8.0 Hz), 7.5 (s, 1H), 7.4 (q, 3H, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162, 149, 131, 131, 130, 129, 128, 127, 126, 126, 125, 124; HRMS(ESI): m/z calcd for $C_{16}H_{10}F_3NNaS$ $(M+Na)^+$: 328.0384, found: 328.0382.

5-(4-nitrophenyl)-2-phenylthiazole (5i). Pale yellow solid, 2.51 g, isolated yield: 89%, m.p. 132-135°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.3 (d, 2H, *J* = 9.2 Hz), 8.1 (m, 2H), 7.8 (d, 2H, *J* = 8.8 Hz), 7.6 (s, 1H), 7.5 (d, 3H, *J* = 3.2 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162, 149, 147, 133, 131, 129, 126, 126, 126, 124, 124; HRMS(ESI): m/z calcd for $C_{15}H_{10}N_2NaO_2S$ $(M+Na)^+$: 305.3068, found: 305.3066.

2,5-diphenylthiazole (7a). Pale yellow solid, 2.11 g, isolated yield: 87%, m.p. 118-120°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (q, 2H, *J* = 4.0 Hz), 7.7 (d, 2H, *J* = 7.6 Hz), 7.4 (m, 6H), 7.3 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 151, 130, 128, 128, 128, 28, 127, 126, 124, 123; HRMS(ESI): m/z calcd for $C_{15}H_{11}NNaS$ $(M+Na)^+$: 260.0510, found: 260.0508.

2-(2-methoxyphenyl)-5-(p-tolyl)thiazole (7b). Pale yellow solid, 1.80 g, isolated yield: 74%, m.p. 117-119°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.7 (t, 2H, *J* = 6.6 Hz), 7.6 (s, 1H), 7.3 (m, 5H), 7.0 (q, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 159, 151, 130, 129, 128, 128, 128, 124, 123, 118, 116, 111, 55; HRMS(ESI): m/z calcd for $C_{17}H_{15}NNaOS$ $(M+Na)^+$: 304.0772, found: 304.0770.

5-(4-methoxyphenyl)-2-(naphthalen-1-yl)thiazole (7c). Pale yellow solid, 2.38 g, isolated yield: 85%, m.p. 109-112°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.6 (s, 1H),8.1 (d, 1H, *J* = 8.4 Hz), 7.7 (m, 5H), 7.47 (m, 5H), 7.3 (t, 1H, *J* = 7.2 5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 151, 134, 133, 128, 128, 128, 128, 128, 127, 127, 126, 126, 124, 124, 123, 123; HRMS(ESI): m/z calcd for $C_{20}H1_5NNaOS$ $(M+Na)^+$: 340.0772, found: 340.0770.

2-phenyl-5-(m-tolyl)thiazole (7d). Pale yellow solid, 1.81 g, isolated yield: 82%, m.p. 119-121°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (d, 2H, *J* = 8.0 Hz), 7.6 (d, 2H, *J* = 8.0 Hz), 7.4 (m, 3H), 7.4 (s, 1H), 7.2 (d, 2H, *J* = 7.6 Hz), 2,3 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160, 151, 138, 130, 129, 128, 127, 126, 125, 124, 122, 21; HRMS(ESI): m/z calcd for $C_{16}H_{13}NNaS$ $(M+Na)^+$: 274.0666, found: 274.0664.

5-(3-chlorophenyl)-2-(2-methoxyphenyl)thiazole (7e). Pale yellow solid, 2.39 g, isolated yield: 89%, 112-114°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (m, 2H), 7.6 (s, 1H), 7.5 (d, 1H, *J* = 8.0 Hz), 7.4 (m, 4H), 7.3 (t, 1H, *J* = 8.0 Hz), 7.2 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 149, 135, 130, 130, 129, 128, 128, 127, 126, 124, 124, 122; HRMS(ESI): m/z calcd for $C_{16}H_{12}ClNNaOS$ $(M+Na)^+$: 324.0226, found: 324.0224.

5-(2-chlorophenyl)-2-(naphthalen-1-yl)thiazole (7f). Colorless solid, 2.00 g, isolated yield: 72%, 111-112°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (q, 2H, *J* = 3.8 Hz), 7.7 (s, 1H), 7.5 (d, 1H, *J* = 8.0 Hz), 7.4 (m, 4H), 7.3 (t, 1H, *J* = 8.0 Hz), 7.3 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161, 149, 135, 130, 130, 129, 128, 128, 127, 126, 124, 124, 122; HRMS(ESI): m/z calcd for $C_{19}H_{12}ClNNaS$ $(M+Na)^+$: 344.0277, found: 344.0275.

Acknowledgements

Financial support was provided by the Scientific Research Fund of Zhejiang Provincial Education Department (No. Y202454916) and the Huzhou Science and Technology Plan Project (No. 2024YZ11). The authors Runsheng Xu and Jin Xu should be considered as co-first authors.

Supplementary Material

Spectroscopic data of synthesized compounds are available in the Supplementary material file associated with this manuscript.

References

1. Ungureanu, D.; Tiperciuc, B.; Nastas, C.; Ionu, I.; Marc, G.; Oniga, I; Oniga, O. *Pharmaceutics* **2024**, *16*, 89.

https://doi.org/10.3390/pharmaceutics16010089

2. Prasad, K. D. V.; Kallauraya, B.; Bhat, R. S.; Bhat, S. I.; Kamat, V.; Akki, M.; Kumar, A.; Jyothi, K.; Bharat, B. R. *Heliyon* **2024**, *10*, 1-10.

3. El-Sabbagh, O. I.; Baraka, M. M.; Ibrahim, S. M.; Pannecouque, C.; Andrei, G.; Snoeck, R.; Balzarini, J.; Rashad, A. A. *Eur. J. Med. Chem.* **2009**, *44*, 3746-3753.

https://doi.org/10.1016/j.ejmech.2009.03.038

4. Nepali, K.; Sharma, S.; Sharma, M.; Bedi, P.; Dhar, K. *Eur. J. Med. Chem.* **2014**, *77*, 422-487.

https://doi.org/10.1016/j.ejmech.2014.03.018

5. Luo, M.; Li, L.; Chen, S.; Luo, M. X.; Li, L.; Chen, S. X.; Yan, Q. J.; Lv, J.; Zeng, J.; Wang, H. F.; Gu, S. X.; Chen, F. *J. Org. Chem.* **2024**, *89*, 5038-5048.

https://doi.org/10.1021/acs.joc.4c00269

6. Sayed, A. R.; Gomha, S. M.; Taher, E. A.; Muhammad, Z. A.; Ahmed, M. M. *Drug Des. Dev. Ther.* **2020**, *14*, 1363-1375.

https://doi.org/10.2147/DDDT.S221263

7. Kleinman, E. F.; Hiroko, M.; Parikh, V. D. Thiazoles as Antiviral EP, EP0714393B1. 1998.

8. Khan, Y.; Khan, S.; Hussain, R.; Maalik, A.; Rehman, W.; Attwa, M. W.; Masood, R.; Darwish, H. W.; Ghabbour, H. A. *Pharmaceuticals* **2023**, *16*, 1612-1650.

https://doi.org/10.3390/ph16121650

9. Jorge, H. M.; Daniel, A. Z.; José Eduardo, C. C.; Christian, D.; Alcívar-León, C. D. *Molecules* **2022**, *27*, 6708.

https://doi.org/10.3390/molecules27196708

10. Mittersteiner, M.; Faria, F. F.; Bonacorso, H. G.; Martins, M. A.; Zanatta, N. *Ultrason. Sonochem.* **2021**, *79*, 105683.

https://doi.org/10.1016/j.ultsonch.2021.105683

11. Arshad, M. F.; Alam, A.; Alshammari, A. A.; Alhazza, M. B.; Alzimam, I. M.; Alam, M. A.; Mustafa, G.; Ansari, M. S.; Alotaibi, A. M.; Alotaibi, A. A.; Kumar, S.; Asdaq, S. M. B.; Imran, M.; Deb, P.K.; Venugopala, K. N.; Jomah, S. *Molecules* **2022,** *27*, 3994.

https://doi.org/10.3390/molecules27133994

12. Brogden, R. N.; Campoli-Richards, D. M. *Drugs* **1989**, *38*, 524-550.

https://doi.org/10.2165/00003495-198938040-00004

13. Shah, N. P.; Skaggs, B. J.; Branford, S. *J. Clin. Invest***. 2007**, *117*, 2562-2569.

https://doi.org/10.1172/JCI30890

14. Noble, S.; Balfour, J. A. *Drugs* **1996**, *51*, 424-430.

https://doi.org/10.2165/00003495-199651030-00007

15. Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Kumar, A.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158.

16. Hantzsch, A.; Weber J. H. *Ber. Dtsch. Chem. Ges.***1887**, *20*, 3118-3132.

https://doi.org/10.2165/00003495-199651030-00007
17. Cook, J. W.; Hewett, C. L. *J. Chem. Soc.* **1933**,1098.
https://doi.org/10.1039/jr9330001098
18. Warburton, W. K. *Chem. Rev.*, **1957**, *57*, 1011-1020.
https://doi.org/10.1021/cr50017a004
19. Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*,600-604.
https://doi.org/10.1038/nature14127
20. Yan, K.; Liu, M.; Wen, J. W.; Wang, S.; Li, J.; Wang, H. *Org. Lett.* **2020**, *22*, 7825-7830.
https://doi.org/10.1021/acs.orglett.0c02703
21. Xu, R. S.; Zhu, Y.; Xiong, F. X.; Tong, S. L. *Catalysts* **2019**, *9*, 105.
https://doi.org/10.3390/catal9010105
22. Zhou, X.; Hao, J.; Kong, Y.; Xu, R. S. *Chem. Comm.* **2021**, *57*, 5426-5429.
https://doi.org/10.1039/D1CC01564H
23. Guan, S. L.; Chen, Y.; Wu, H. J.; Xu, R. S. *RSC Adv.* **2018**, *8*, 26828-26836.
https://doi.org/10.1039/C8RA05311A
24. Cai, R. R.; Zhou, Z. D.; Chai, Q. Q.; Zhu, Y. E.; Xu, R. S. *RSC Adv*. **2020**, *8*, 26828-26836.
https://doi.org/10.1039/C8RA05311A
25. Zhou, X. Y.; Xue, Y. Q.; Cheng, Y. Y.; Xu, R. S. *Arkivoc* **2021**, *4*, 119-129.
https://doi.org/10.24820/ark.5550190.p011.478