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Synthesis of trisubstituted thiazoles by ligand-free palladium-catalyzed direct 5-arylation of 2,4-disubstituted thiazoles under conventional and microwave-assisted heating

Su Kang Kim, Ji-Hyun Kim, Young Chul Park, Jae Won Kim, Eul Kgun Yum *

Department of Chemistry, Chungnam National University, Yusung, Daejon 305-764, Republic of Korea

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ABSTRACT

Trisubstituted thiazoles were synthesized with excellent yields using ligand-free, palladium-catalyzed, direct 5-arylation of 2,4-disubstituted thiazole and conventional or microwave-assisted heating. The palladium-catalyzed reaction yields were significantly influenced by LiCl additive, solvent, and heating method. The reaction times were reduced dramatically by employing microwave radiation instead of conventional heating. The synthetic methods can be applied to diverse 2,4,5-trisubstituted thiazoles by varying the aryl bromide and disubstituted thiazole reactants.

1. Introduction

Sulfur-containing azaheteroaromatic moieties are an important classes of heterocyclic compounds in pharmaceuticals and organic syntheses due to their unique biological and physical properties.[1] Thiazoles are present in many natural materials[2] and are potent biologically active compounds that exhibit, e.g., antimicrobial, antifungal, antihypertensive, anti-inflammatory, antitumor, and cytotoxic activities.[3–6] Some functionalized thiazoles have found diverse applications in materials science.[7,8] The most frequently used synthetic method of generating thiazoles is the Hantzsch process,[9] in which an α-haloketone is condensed with a thioamide. Synthetic methods have also been reported for trisubstituted thiazoles.[10–14] Although the Hantzsch method is attractive for the preparation of substituted thiazole compounds, diversification of thiazole moieties is limited due to the requirement for elaborate preparation of each α-haloketone and thioamide.

The palladium-catalyzed coupling reaction of a thiazole halide with a stoichiometric amount of an arylmetal, such as the arylboronic acids or arylstannane and arylzinc reagents, represents one of the most effective strategies for synthesizing arylthiazoles.[15] However, palladium-catalyzed cross-coupling reactions require prior preparation of related organometallic derivatives and arylhalides. Since the publication of Ohta's reports[16–18] describing the direct arylation of heterocyclic compounds via palladium-catalyzed C–H activation, palladium-catalyzed, direct arylation has been shown to be a practical method for the preparation of disubstituted thiazoles under mild conditions.[19–24] Palladium-catalyzed, direct arylation of thiazoles generally requires 5–10 mol % of palladium catalyst associated with 5–20 mol % of mono-or bidentate phosphine ligands and a relatively long reaction time.[21] In addition, palladium-catalyzed sequential arylation using thiazoles[25] or thiazole *N*-oxides[26] is promising for the preparation of triarylated thiazoles. Practical, one-pot sequential arylation has been demonstrated with these reaction methods compared with other reported stepwise C–H bond arylation methods.

Recently, the use of microwave radiation to accelerate organic reactions has attracted considerable attention because it often reduces reaction times dramatically from days or hours to minutes.[27] In the course of establishing a chemical compound library of biologically active thiazole derivatives,[28] we needed a convenient synthetic procedure to generate 2,4,5-trisubstituted thiazoles. In this study, we examined and compared conventional and microwave-assisted heating as a means of accelerating ligand-free, palladium-catalyzed direct arylation of several 2,4-disubstituted thiazoles for the preparation of diverse trisubstituted thiazoles.

* Corresponding author. Tel.: +82 428215474; fax: +82 428218896; e-mail address: ekyum@cnu.ac.kr (E.K. Yum).

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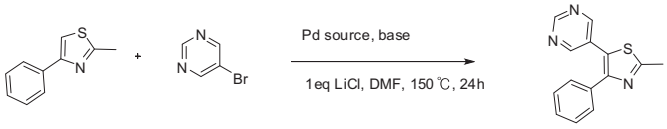
2. Results and discussions

Starting materials (**1**–**5**) were prepared in good to excellent yields using the Hantzsch method with α-bromoketones and methyl and phenylthioamide, as shown in Scheme 1. Most palladium-catalyzed, direct arylation reactions used to generate thiazoles use aryliodide, as opposed to the corresponding bromide or chloride, due to the speed with which the palladium oxidative addition occurs at low temperatures. In the current study, however, 5-bromopyrimidine was used as a model aryl halide with 2-methyl-4-phenylthiazole (**1**) to optimize the reaction conditions with our previously reported LiCl-mediated transition metal-catalyzed heteroannulation and N-arylation.[29] The results using several palladium species and bases are summarized in Table 1. Although direct arylation of monosubstituted thiazoles using low percentages of palladium catalyst has been reported,[21] in the current study, low yields of product and high levels of starting materials resulted from 1 mol % palladium-catalyzed direct arylation of disubstituted thiazoles, even after 24 h. Ligand-free, LiCl-mediated direct arylation of 2-methyl-4-phenyl (**1**) required 5 mol % $Pd(OAc)_2$ with 1 equiv of Cs_2CO_3 base to reach completion within 24 h (Entries 1–5). The same reaction conditions were also applied at 180 °C with variations in reaction time (Entry 2). The results indicated incomplete reaction after 12 h at 180 °C.

Scheme 1.

Table 1
Optimization of a conventionally heated, palladium-catalyzed 5-arylation reaction to 2-methyl-4-phenylthiazole



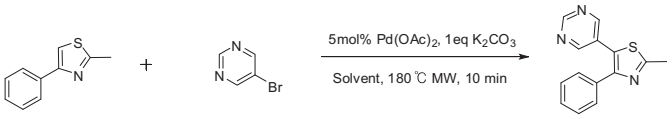
Entry[a]	Pd source	1 equiv LiCl	Base	Isolated yield (%)
1	1 mol % $Pd(OAc)_2$	+	1 equiv Cs_2CO_3	45
2[b]	5 mol % $Pd(OAc)_2$	+	1 equiv Cs_2CO_3	80
3	5 mol % $Pd(OAc)_2$	—	1 equiv Cs_2CO_3	10
4	5 mol % $Pd(OAc)_2$	+	2 equiv Cs_2CO_3	52
5	10 mol % $Pd(OAc)_2$	+	1 equiv Cs_2CO_3	82
6	5 mol % $Pd(PPh_3)_4$	+	1 equiv Cs_2CO_3	46
7	5 mol % $PdCl_2(PPh_3)_2$	+	1 equiv Cs_2CO_3	33
8	5 mol % $Pd(OAc)_2$	+	1 equiv K_2CO_3	76
9	5 mol % $Pd(OAc)_2$	+	1 equiv Li_2CO_3	34
10	5 mol % $Pd(OAc)_2$	+	1 equiv Na_2CO_3	45
11	5 mol % $Pd(OAc)_2$	+	1 equiv NaOAc	36
12	5 mol % $Pd(OAc)_2$	+	1 equiv KOAc	40

[a] All reactions were conducted at the 1.0 mmol scale in 5 mL of DMF at 150 °C for 24 h in a sealed vial.
[b] The reaction conditions were 150 °C (80% after 24 h) and 180 °C (48% after 12 h and 80% after 24 h).

Increasing the percentage of palladium catalyst or the amount of base did not improve yields of the desired products (Entries 4 and 5). Reactions using $Pd(PPh)_4$ or $Pd(PPh)_2Cl_2$ as the palladium catalyst gave moderate-to-low yields of 5-arylated thiazole (Entries 6 and 7). Arylation reactions employing several alkali metal carbonates or acetates were also examined (Entries 3, 8–12). The reaction using K_2CO_3 as the base provided relatively high yields of trisubstituted thiazole, comparable to those obtained with Cs_2CO_3. The above results show that the optimal conditions for conventionally heated direct arylation of disubstituted thiazoles were 5 mol % $Pd(OAc)_2$, 1 equiv LiCl, 1 equiv Cs_2CO_3, and DMF at 150 °C for 24 h.

The microwave-assisted, palladium-catalyzed, direct arylation of 2-methyl-4-phenyl thiazole (**1**) was reexamined using the above conditions optimized for the conventionally heated reaction. Frequently, microwave irradiation of chemical reactions boasts several advantages over conventional heating, including accelerated reaction rates and significant energy savings. Microwave irradiation results in efficient internal heating by direct coupling of microwave energy to the molecules (solvents, reagents, catalyst) present in the reaction mixture. Preliminary, microwave-assisted, palladium-catalyzed direct arylation reactions proceeded rapidly with high yields of the desired product, even in the absence of the LiCl additive. Therefore, we investigated the microwave-assisted, palladium-catalyzed arylation of 2-methyl-4-phenylthiazole. The reaction parameters included variations in the solvent (DMF, NMP, and DMAc), alkali metal carbonate, and acetate base. The results are shown in Table 2.

Table 2
Optimization of microwave-assisted, palladium-catalyzed arylation to 2,4-disubstituted thiazole



Entry[a]	Base	Solvent	Isolated yield (%)
1	K_2CO_3	DMF	81
2	K_2CO_3	NMP	81
3	K_2CO_3	DMA	81
4	Cs_2CO_3	DMF	47
5	Cs_2CO_3	NMP	81
6	Cs_2CO_3	DMA	59
7	Na_2CO_3	DMF	24
8	Na_2CO_3	NMP	29
9	Li_2CO_3	NMP	34
10	KOAc	DMA	22
11	KOAc	NMP	51
12	NaOAc	NMP	31

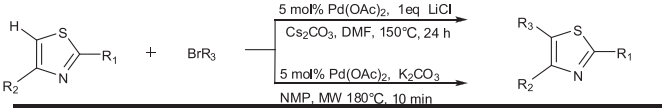
[a] All reactions were conducted at the 1.0 mmol scale in 2 mL of solvent in a Biotage 5-mL vial sealed with a crimp cap. Microwave radiation was supplied with a Biotage Initiator EXP EU (400 W, 2450 MHz).

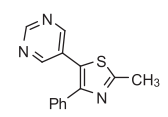
The reactions employing K_2CO_3 as the base provided the same 81% yield of desired product, irrespective of the solvent used (Entries 1–3). Reactions using Cs_2CO_3 as the base provided the highest yields (81%) only when NMP was used as the solvent. Other bases (Li_2CO_3, Na_2CO_3, NaOAc, and KOAc) gave low yields in all of the solvents. Therefore, the optimum reaction conditions for microwave-assisted, palladium-catalyzed arylation of disubstituted thiazoles were 5 mol % $Pd(OAc)_2$, 1 equiv K_2CO_3, and NMP solvent at 180 °C for 10 min. During the reaction, the internal vapor pressure in the reaction vial was 2–4 bar, as indicated by the online monitor of the Biotage microwave reactor.

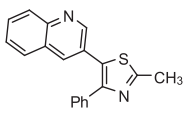
The palladium-catalyzed arylation of various disubstituted thiazoles using conventional heating and microwave-assisted heating to prepare diverse trisubstituted thiazoles was examined. The results are shown in Table 3.

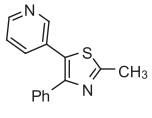
The reactions employing 3- or 5-heteroaromatic bromides, such as pyrimidine, quinolone, and pyridine bromides, provided high

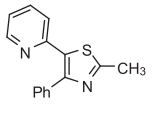
Table 3
Conventional and microwave-assisted heating in the ligand-free palladium-catalyzed direct arylation of disubstituted thiazoles

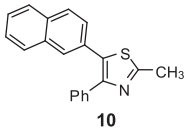


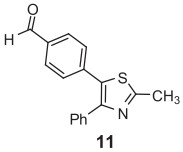

6
Thermal = 80%
MW = 81%

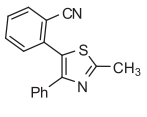

7
Thermal = 94%
MW = 89%

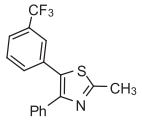

8
Thermal = 81%
MW = 80%

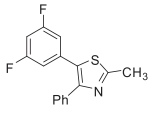

9
Thermal = 7%
MW = 21%

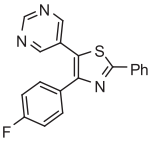

10
Thermal = 55%
MW = 60%

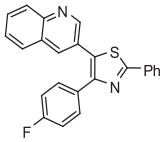

11
Thermal = 64%
MW = 71%

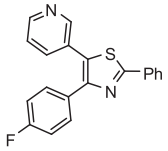

12
Thermal = 77%
MW = 80%

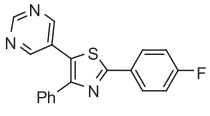

13
Thermal = 86%
MW = 85%

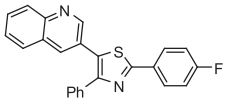

14
Thermal = 30%
MW = 56%

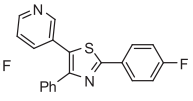

15
Thermal = 70%
MW = 88%

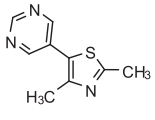

16
Thermal = 63%
MW = 75%

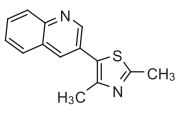

17
Thermal = 64%
MW = 83%

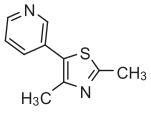

18
Thermal = 78%
MW = 93%

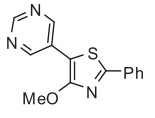

19
Thermal = 63%
MW = 75%

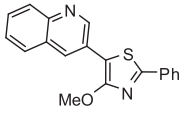

20
Thermal = 60%
MW = 73%

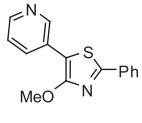

21
Thermal = 49%
MW = 65%


22
Thermal = 82%
MW = 73%


23
Thermal = 60%
MW = 83%


24
Thermal = 67%
MW = 74%


25
Thermal = 65%
MW = 78%


26
Thermal = 65%
MW = 79%

yields of 5-heteroaryl trisubstituted thiazoles (compounds **6**–**8**). However, the reaction with 2-bromopyridine gave a low yield of the desired product using both conventional and microwave-assisted heating (compound **9**). The 2-bromopyridine likely complexed with the palladium metal. Variation of substituted phenylbromides also gave high-to-moderate yields of trisubstituted thiazoles (compounds **10**–**14**). Although the yields of direct arylation to 2-methyl-4-phenylthiazoles varied with the functional group on the phenyl moiety, substituted aryl bromides were generally effective for the direct 5-arylation of disubstituted thiazoles. Optimized reaction conditions were used with various disubstituted thiazoles and 5-bromopyrimidine, 3-bromoquinoline, and 3-bromopyridine. The microwave-assisted, direct arylation of diarylthiazoles gave high yields of triarylthiazoles (compounds **15**–**20**) with short reaction times. The same reaction also proceeded efficiently with 2,4-dimethylthiazole and 5-aryl-4-methoxy-2-phenylthiazole. Diverse trisubstituted thiazoles (compound **21**–**26**) were easily prepared using ligand-free, palladium-catalyzed direct arylation of various disubstituted thiazoles with both conventional and microwave-assisted heating.

3. Conclusions

Conventional and microwave-assisted heating provided similar reactivity with the same substrates, although the yields of microwave-assisted reactions were slightly higher. However, reaction times were reduced dramatically by employing microwave radiation instead of conventional heating. Ligand-free, palladium-catalyzed arylation is an effective method of producing diverse 2,4,5-trisubstituted thiazoles.

4. Experimental

4.1. Instrumentation and analysis

All ^{1}H and ^{13}C NMR spectra were recorded on a Jeol 400 MHz spectrometer, and chemical shifts were referenced to tetramethylsilane (TMS) as an internal standard. The infrared spectra were obtained on Bio-Rad Laboratories/FTS-175C. The GC–MS spectra were obtained using a Shimadzu QP 1000GC-MS. Elemental analyses were carried out by Chungnam National University using an elemental analyzer (EA-1110). Microwave-assisted reactions were performed with an initiator instrument (EXP EU, Biotage, 400 W, 2450 MHz). Reaction temperatures were measured using infrared sensors on the outer surface of the reaction vial. Products were purified by flash chromatography on 230–400 mesh ASTM 60 silica gel. All base and palladium species were purchased from Sigma–Aldrich Chemical Co. Chemicals were used directly as obtained from commercial sources unless otherwise noted.

4.2. Preparation of 2,4-disubstituted thiazoles

*4.2.1. Methyl-4-phenylthiazole (**1**).*[30] Thioamide 0.75 g (10 mmol) and bromoacetophenone 1.99 g (10 mmol) were dissolved 5 mL of DMF in a 20 mL pressure tube. The reaction mixtures were sealed and heated 1 h at 60 °C in oil bath. The resulting mixture was diluted with saturated aqueous ammonium chloride. The product was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The product was purified by silica gel column chromatography using hexane:ethyl acetate. 2-Methyl-4-phenyl-thiazole was obtained in 99% yield as a white solid. Mp: 68–69 °C; IR (KBr) 3054, 1583, 1432, 1186, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.11 (1H, s, Ar–H), 8.65 (2H, s, Ar–H), 7.43 (2H, m, Ar–H), 7.34 (3, m, Ar–H), 2.89 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 155.1, 134.5, 128.6, 127.9, 126.2, 112.2, 19.3; Ms (*m*/*z*, relative intensity): 176.3 (M+1, 100);

Anal. Calcd for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99; S, 18.30; Found: C, 68.71; H, 5.02; N, 8.15; S, 18.12.

*4.2.2. 2-(4-Fluorophenyl)-4-phenylthiazole (**2**).* The compound **2** was obtained from 4-fluorobenzothioamide 1.55 g (10 mmol) and bromoacetophenone 2.0 g (10 mmol) in 97% yields as a white solid. Mp: 114–115 °C; IR (KBr) 3052, 1602, 1223, 978, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (2H, d, J=7.6 Hz, Ar–H), 7.99 (2H, d, J=7.6 Hz, Ar–H), 7.44 (3H, t, J=7.6 Hz, Ar–H), 7.35 (1H, t, J=7.6 Hz, Ar–H), 7.14 (2H, t, J=7.6 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 165.1, 162.6, 156.3, 134.3, 130.1, 130.0, 128.7, 128.5, 128.4, 128.2, 126.4, 116.0, 115.8, 112.5. Ms (*m*/*z*, relative intensity): 255 (M^+, 89), 134 (100), 89 (25); Anal. Calcd for $C_{15}H_{10}FNS$: C, 70.57; H, 3.95; F, 7.44 N, 5.49; S, 12.56; Found: C, 70.11; H, 4.05; F, 7.45; N, 5.30; S, 12.40.

*4.2.3. 4-(4-Fluorophenyl)-2-phenylthiazole (**3**).*[31] The compound **3** was obtained from benzothioamide 1.37 g (10 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone 2.17 g (10 mmol) in 69% yields as a white solid. Mp: 104–105 °C; IR (KBr) 3052, 1602, 1480, 1224, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (2H, dd, J=5.6 Hz, J=1.2 Hz, Ar–H), 7.97 (2H, dd, J=5.6 Hz, J=1.2 Hz, Ar–H), 7.45 (3H, m, Ar–H), 7.41 (1H, s, Ar–H), 7.13 (2H, t, J=5.6 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 163.9, 161.5, 155.2, 133.6, 130.8, 130.7, 130.1, 129.0, 128.2, 128.1, 126.5, 115.7, 115.5, 112.2; Ms (*m*/*z*, relative intensity): 255 (M^+, 85), 134 (100), 89 (22); Anal. Calcd for $C_{15}H_{10}FNS$: C, 70.57; H, 3.95; F, 7.44 N, 5.49; S, 12.56; Found: C, 70.11; H, 4.05; F, 7.45; N, 5.30; S, 12.40.

*4.2.4. 2,4-Dimethylthiazole (**4**).* The compound **4** was obtained from thioamide 0.75 g (10 mmol) and bromoacetone 1.37 g (10 mmol) in 75% yields as a colorless oil. IR (KBr) 1486, 1178, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.69 (1H, s, Ar–H), 2.67 (3H, s, CH_3), 2.40 (3H, s, CH_3), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 152.0, 112.6, 19.0, 16.9; Ms (*m*/*z*, relative intensity): 113 (M^+, 100), 71 (89), 45 (59); Anal. Calcd for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38; S, 28.33; Found: C, 53.11; H, 12.22; N, 12.54; S, 28.07.

*4.2.5. 4-Methoxy-2-phenylthiazole (**5**).* The compound **5** was obtained from methyl 2-bromoacetate 0.15 g (1 mmol) and benzothioamide 0.14 g (1 mmol) and in 50% yields as a yellow oil. IR (KBr) 3021, 1528, 1342, 1094, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (2H, m, Ar–H), 7.40 (3H, m, Ar–H), 6.06 (1H, s, Ar–H), 3,93 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 136.4, 130.4, 130.1, 130.0, 129.6, 126.8, 126.7, 90.0, 57.8; Ms (*m*/*z*, relative intensity): 191 (M^+, 100), 88 (48), 45 (40); Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32; O, 8.37; S, 16.77; Found: C, 62.78; H, 4.69; N, 7.22; O, 8.21; S, 28.07.

4.3. General experimental procedure for conventional heating in the ligand-free palladium-catalyzed 5-arylation of 2,4-disubstituted thiazoles

2-Methyl-4-phenylthiazole (0.175 g, 1.0 mmol), 5-bromopyrimidine (0.318 g, 2 mmol), LiCl (1.0 mmol), Cs_2CO_3 (1.0 mmol), 5 mol % $Pd(OAc)_2$, and DMF (5 mL) were added in 10 mL vial with screw cap. The vial was sealed and stirred at 150 °C in oil bath. After heating the reaction mixture at 150 °C for 24 h, the reaction mixture was diluted with saturated aqueous ammonium chloride. The product was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The product was purified by silica gel column chromatography using hexane:ethyl acetate eluent. 2-Methyl-4-phenyl-5-(pyrimidin-5yl)thiazole (**6**) was obtained in 80% yield as a yellow oil. IR (KBr) 3045, 1494, 1149, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.11(1H, s, Ar–H), 8.65 (2H, s, Ar–H), 7.43 (2H, m, Ar–H), 7.34 (3, m, Ar–H), 2.89 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2, 167.7, 166.7, 162.5, 143.9, 139.2, 139.1, 138.9, 137.6, 134.5, 29.6 Ms (*m*/*z*, relative intensity): 253 (M^+, 100), 212 (20), 185 (18); Anal. Calcd for $C_{14}H_{11}N_3S$: C, 66.38; H, 4.38; N, 16.59; S, 12.66; Found: C, 66.47; H, 4.48; N, 16.28; S, 12.77.

4.4. General experimental procedure for microwave-assisted ligand-free palladium-catalyzed 5-arylation of 2,4-disubstituted thiazole

2-Methyl-4-phenyl thiazole (0.175 g, 1.0 mmol), K_2CO_3 (1.0 mmol), 5-bromopyridine (0.318 g, 2 mmol), $Pd(OAc)_2$ (0.05 mmol), and NMP (2 mL) were added to a 5-mL vial. The vial was sealed with a crimp cap and placed in a Biotage initiator microwave cavity. After irradiation at 180 °C for 10 min and subsequent cooling, the reaction mixture was diluted with saturated aqueous ammonium chloride. Products were isolated by extraction into ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Products were purified by silica gel column chromatography using a hexane/ethyl acetate eluent. 2-Methyl-4-phenyl-5-(pyrimidin-5yl)thiazole (**6**) was obtained in 81% yield as a yellow oil.

The following compounds (**7**–**26**) were prepared with conventionally and microwave-assisted heating in the ligand-free palladium-catalyzed general experimental procedures.

*4.4.1. 2-Methyl-4-phenyl-5-(quinolin-3-yl)thiazole (**7**).* The product **7** was obtained from 2-methyl-4-phenylthiazole and 3-bromoquinoline. Yield: 94% (Thermal); 89% (MW). Yellow oil. IR (KBr) 3065, 1509, 1209, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.77 (1H, d, J=2.4 Hz, Ar–H), 8.11 (1H, d, J=2.4 Hz, Ar–H), 8.07 (1H, d, J=8.4 Hz, Ar–H), 7.72 (2H, m, Ar–H), 7.54 (1H, t, J=8.4 Hz, Ar–H), 7.50 (2H, m, Ar–H), 7.28 (H, d, J=6.2 Hz, Ar–H), 2.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 150.9, 150.6, 146.9, 145.7, 134.2, 129.8, 129.2, 128.9, 128.6, 128.2, 127.8, 127.6, 127.2, 125.7, 19.3; Ms (*m*/*z*, relative intensity): 302 (M^+, 100), 260 (27), 216 (21); Anal. Calcd for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26; S, 10.60; Found: C, 75.22; H, 4.77; N, 9.52; S, 10.49.

*4.4.2. 2-Methyl-4-phenyl-5-(pyridin-3-yl)thiazole (**8**).* The product **8** was obtained from 2-methyl-4-phenylthiazole (**1**) and 3-bromopyridine. Yield: 85% (Thermal); 80% (MW). Yellow oil. IR (KBr) 3066, 1486, 1152, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (1H, s, Ar–H), 8.50 (1H, d, J=4.8 Hz, Ar–H), 7.56 (1H, d, J=7.6 Hz, Ar–H), 7.44 (2H, m, Ar–H), 7.27 (3H, m, Ar–H), 7.19 (1H, d, J=7.6 Hz, Ar–H), 2.75 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 150.8, 149.8, 148.7, 136.5, 134.2, 128.8, 128.4, 128.1, 128.0, 123.2, 19.2; Ms (*m*/*z*, relative intensity): 251 (M^+, 100), 210 (41), 166 (20); Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10; S, 12.71. Found: C, 71.36; H, 4.43; N, 11.49; S, 12.72.

*4.4.3. 2-Methyl-4-phenyl-5-(pyridin-2-yl)thiazole (**9**).* The product **9** was obtained from 2-methyl-4-phenylthiazole (**1**) and 2-bromopyridine. Yield: 7% (Thermal); 21% (MW). Yellow oil. IR (KBr) 3054, 1583, 1432, 1186, 771, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.57 (1H, d, J=4.8 Hz, Ar–H), 7.54 (2H, m, Ar–H), 7.43 (1H, m, Ar–H), 7.37 (3H, m, Ar–H), 7.16 (1H, d, J=7.6 Hz, Ar–H), 7.10 (1H, dd, J=7.6 Hz, J=4.8 Hz, Ar–H), 2.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 151.7, 151.2, 149.6, 149.2, 136.9, 136.0, 135.4, 133.9, 129.2, 128.6, 128.4, 123.7, 122.1, 122.0, 121.1, 19.3; Ms (*m*/*z*, relative intensity): 251 (M^+, 100), 210 (70), 166 (40); Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10; S, 12.71. Found: C, 71.38; H, 4.47; N, 11.18; S, 12.69.

*4.4.4. 2-Methyl-5-(naphthalen-2-yl)-4-phenylthiazole (**10**).* The product **10** was obtained from 2-methyl-4-phenylthiazole (**1**) and 2-bromonaphthalene. Yield: 55% (Thermal); 60% (MW). Yellow solid; mp: 108–109 °C; IR (KBr) 3054, 1502, 1182, 773, 697 cm^{-1}; ^1H

NMR ($CDCl_3$, 400 MHz) δ 7.89 (2H, m, Ar–H), 7.80 (1H, d, J=7.6 Hz, Ar–H), 7.47 (2H, dd, J=4.6 Hz, J=1.2 Hz, Ar–H), 7.45 (1H, t, J=7.6 Hz Ar–H), 7.40 (3H, m, Ar–H), 7.09 (3H, m, Ar–H), 2.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 151.0, 134.6, 133.7, 132.4, 129.6, 129.5, 129.4, 129.1, 128.3, 128.1, 127.3, 126.6, 126.2, 125.7, 125.4, 19.3; Ms (m/z, relative intensity): 301 (M^+, 100), 259 (11), 215 (39), 129 (18); Anal. Calcd for $C_{20}H_{15}NS$: C, 79.70; H, 5.02; N, 4.65; S, 10.64. Found: C, 79.64; H, 4.98; N, 4.78; S, 10.43.

*4.4.5. 4-(2-Methyl-4-phenylthiazol-5-yl)benzaldehyde (**11**).* The product **11** was obtained from 2-methyl-4-phenylthiazole (**1**) and 4-bromobenzaldehyde. Yield: 64% (Thermal); 71% (MW). Yellow solid; mp: 133–134 °C; IR (KBr) 3059, 1700, 1601, 1176, 829, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.90 (1H, s, Ar–H), 7.80 (2H, d, J=8.4 Hz, Ar–H), 7.47 (4H, m, Ar–H), 7.31 (3H, m, Ar–H), 2.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.5, 165.1, 151.1, 138.6, 135.4, 134.5, 130.9, 130.0, 129.9, 129.1, 128.5, 128.2, 19.3; Ms (m/z, relative intensity): 279 (M^+, 100), 238 (42), 208 (40); Anal. Calcd for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01 O, 5.73; S, 11.48; Found: C, 73.01; H, 4.58; N, 4.97; O, 5.65; S, 11.43.

*4.4.6. 2-(2-Methyl-4-phenylthiazol-5-yl)benzonitrile (**12**).* The product **12** was obtained from 2-methyl-4-phenylthiazole (**1**) and 2-bromobenzonitrile. Yield: 77% (Thermal); 80% (MW). Yellow solid; mp: 123–124 °C; IR (KBr) 3061, 2227, 1497, 1179, 767 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.70 (1H, d, J=1.6 Hz, Ar–H), 7.56 (1H, td, J=7.6 Hz, J=1.6 Hz, Ar–H), 7.44 (2H, m, J=2.0 Hz, Ar–H), 7.39 (2H, m, J=2.0 Hz, Ar–H), 7.25 (3H, m, J=2.0 Hz, Ar–H), 2.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 165.8, 152.5, 136.2, 134.1. 133.6, 132.8, 132.1, 130.6, 129.2, 128.8, 128.7, 128.4, 128.1, 126.9, 117.4, 113.8, 19.3; Ms (m/z, relative intensity): 276 (M^+, 100), 238 (16), 208 (73); Anal. Calcd for $C_{17}H_{12}N_2S$: C, 73.88; H, 4.38; N, 10.14; S, 11.60; Found: C, 73.77; H, 4.51; N, 10.22; S, 11.23.

*4.4.7. 2-Methyl-4-phenyl-5-(3-(trifluoromethyl)phenyl)thiazole (**13**).* The product **13** was obtained from 2-methyl-4-phenylthiazole (**1**) and 3-bromobenzotrifluoride. Yield: 86% (Thermal); 85% (MW). Brown oil; IR (KBr) 3062, 1496, 1317, 1123, 801, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (1H, s, Ar–H), 7.54 (1H, d, J=7.6 Hz, Ar–H), 7.46 (3H, m, Ar–H), 7.40 (1H, t, J=7.6 Hz, Ar–H), 7.29 (3H, m, Ar–H), 2.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 150.6, 134.4, 133.2, 132.8, 131.3, 131.1, 130.9, 130.6, 129.2, 129.0, 128.5, 128.1, 126.3, 124.6, 122.9, 19.3; Ms (m/z, relative intensity): 319 (M^+, 100), 278 (31), 233 (36), 208 (42), 165 (79); Anal. Calcd for $C_{17}H_{12}F_3NS$: C, 63.94; H, 3.79; F, 17.85; N, 4.39; S, 10.04; Found: C, 64.01; H, 3.88; F, 17.59; N, 4.39; S, 10.03.

*4.4.8. 5-(3,5-Difluorophenyl)-2-methyl-4-phenylthiazole (**14**).* The product **14** was obtained from 2-methyl-4-phenylthiazole (**1**) and 1-bromo-3,5-difluorobenzene. Yield: 30% (Thermal); 56% (MW); Yellow solid; mp: 100–101 °C; IR (KBr) 3061, 1619, 1591, 1433, 1120, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.47 (2H, m, Ar–H), 7.32 (3H, m, Ar–H), 6.83 (2H, m, Ar–H), 6.74 (3H, m, Ar–H), 2.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 164.7, 163.8, 162.1, 150.8, 135.4, 134.2, 129.6, 129.0, 128.5, 128.2, 112.5, 112.4, 103.4, 19.3, Ms m/z (relative intensity): 286.9 (M^+, 100), 238.0 (54), 201.0 (55); Anal. Calcd for $C_{16}H_{11}F_2NS$: C, 66.88; H, 3.86; F, 13.22; N, 4.87; S, 11.16; Found: C, 66.78; H, 3.88; F, 13.35; N, 4.39; S, 11.03.

*4.4.9. 4-(4-Fluorophenyl)-2-phenyl-5-(pyrimidin-5-yl)thiazole (**15**).* The product **15** was obtained from 4-(4-fluorophenyl)-2-phenylthiazole (**2**) and 5-bromo-pyrimidine. Yield: 80% (Thermal); 88% (MW). Yellow solid; mp: 153–154 °C; IR (KBr) 3052, 1602, 1497, 1223, 839, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (1H, s, Ar–H), 8.70 (2H, s, Ar–H), 8.00 (2H, s, Ar–H), 7.52 (2H, m, Ar–H), 7.47 (3H, s, Ar–H), 7.05 (2H, m, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 164.0, 157.6, 156.4, 152.1, 132.7, 130.8, 130.7, 130.6, 128.9, 126.9, 126.5, 115.9, 115.7; Ms (m/z, relative intensity): 333 (M^+, 100), 300 (34), 203 (24).

*4.4.10. 4-(4-Fluorophenyl)-2-phenyl-5-(quinolin-3-yl)thiazole (**16**).* The product **16** was obtained from 4-(4-fluorophenyl)-2-phenylthiazole (**2**) and 3-bromo-quinolone. Yield: 93% (Thermal); 76% (MW). Yellow solid; mp: 112–114 °C; IR (KBr) 3054, 1603, 1442, 1186, 801, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (1H, d, J=2.0 Hz, Ar–H), 8.17 (1H, d, J=2.0 Hz, Ar–H), 8.10 (1H, d, J=8.4 Hz, Ar–H), 8.03 (2H, m, Ar–H), 7.75 (2H, m, Ar–H), 7.57 (3H, m, Ar–H), 7.45 (3H, m, Ar–H), 7.00 (2H, t, J=8.4 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 151.1, 150.5, 147.2, 135.8, 133.2, 130.9, 130.8, 130.5, 130.4, 130.1, 129.3, 128.9, 127.8, 127.5, 127.4, 126.5, 125.4, 115.7, 115.5; Ms (m/z, relative intensity): 382 (M^+, 100), 279 (33), 234 (17).

*4.4.11. 4-(4-Fluorophenyl)-2-phenyl-5-(pyridin-3-yl)thiazole (**17**).* The product **17** was obtained from 4-(4-fluorophenyl)-2-phenylthiazole (**2**) and 3-bromo-pyridine. Yield: 64% (Thermal); 83% (MW). White solid; mp: 122–125 °C; IR (KBr) 3061, 1603, 1492, 1236, 839, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (1H, s, Ar–H), 8.56 (1H, d, J=4.4 Hz, Ar–H), 8.00 (2H, d, J=6.6 Hz, Ar–H), 7.64 (1H, d, J=8.8 Hz, Ar–H), 7.50 (2H, d, J=8.0 Hz, Ar–H), 7.46 (3H, m, Ar–2H, Ar–H), 7.26 (1H, dd, J=8.0 Hz, J=4.4 Hz, Ar–H), 7.01(2H, t, J=8.8 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 162.7, 152.2, 149.9, 149.1, 134.2, 129.0, 128.7, 128.4, 128.5, 128.4, 128.3, 116.1, 115.9; Ms (m/z, relative intensity): 332 (M^+, 100), 229 (32), 184 (14).

*4.4.12. 2-(4-Fluorophenyl)-4-phenyl-5-(pyrimidin-5-yl)thiazole (**18**).* The product **18** was obtained from 4-(4-fluorophenyl)-2-phenylthiazole (**3**) and 5-bromo-pyrimidine. Yield: 78% (Thermal): 93% (MW). White solid; mp: 181–183 °C; IR (KBr) 3058, 1594, 1404, 1226, 842, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.14 (1H, s, Ar–H), 8.72 (2H, s, Ar–H), 8.01 (2H, dd, J=8.4, J=5.2 Hz, Ar–H), 7.53 (2H, m, Ar–H), 7.37 (3H, m, Ar–H), 7.16 (2H, t, J=8.4 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 162.9, 157.6, 156.5, 153.4, 133.6, 128.9, 128.8, 128.7, 128.6, 128.5, 127.1, 116.3, 116.1; Ms (m/z, relative intensity): 333 (M^+, 100), 212 (33), 185 (27).

*4.4.13. 2-(4-Fluorophenyl)-4-phenyl-5-(quinolin-3-yl)thiazole (**19**).* The product **19** was obtained from 4-(4-fluorophenyl)-2-phenylthiazole (**3**) and 3-bromo-quinoline. Yield: 63% (Thermal); 75% (MW). White solid; mp: 121–123 °C; IR (KBr) 3060, 1599, 1487, 1232, 839, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.83 (1H, d, J=2.4 Hz, Ar–H), 8.20 (1H, d, J=8.2 Hz, Ar–H), 8.10 (1H, d, J=8.4 Hz, Ar–H), 8.05 (2H, m, J=5.2 Hz, Ar–H), 7.70 (2H, m, Ar–H), 7.59 (3H, m, Ar–H), 7.33 (3H, m, Ar–H), 7.18 (2H, t, J=8.4 Hz, Ar–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 165.3, 152.3, 150.6, 147.2, 135.8, 134.3, 130.0, 129.7, 129.4, 129.0, 128.7, 128.5, 128.4, 127.9, 127.6, 127.3, 125.5, 116.2, 116.0; Ms (m/z, relative intensity): 382 (M^+, 100), 261 (35), 216 (25).

*4.4.14. 2-(4-Fluorophenyl)-4-phenyl-5-(pyridin-3-yl)thiazole (**20**).* The product **20** was obtained from 4-(4-fluorophenyl)-2-phenylthiazole (**3**) and 3-bromopyridine. Yield: 60% (Thermal); 73% (MW). Yellow solid; mp: 104–106 °C; IR (KBr) 3060, 1583, 1477, 1221, 805, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (1H, s, Ar–H), 8.56 (1H, d, J=5.4 Hz, Ar–H), 8.01(2H, dd, J=8.4 Hz, J=5.4 Hz, Ar–H), 7.65 (1H, d, J=8.4 Hz, Ar–H), 7.55 (2H, d, J=3.6 Hz, Ar–H), 7.33 (3H, m, Ar–H), 7.26 (1H, m, Ar–H), 7.15 (2H, t, J=8.4 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 163.9, 161.4, 149.9, 149.2, 136.6, 133.2, 130.9, 130.8, 130.4, 129.0, 126.5, 123.4, 115.7, 115.4; Ms (m/z, relative intensity): 332 (M^+, 100), 229 (32), 184 (14).

*4.4.15. 2,4-Dimethyl-5-(pyrimidin-5-yl)thiazole (**21**).* The product **21** was obtained from 2,4-dimethylthiazole (**4**) and 5-bromopyrimidine. Yield: 49% (Thermal); 65% (MW). White solid; mp: 116–117 °C; IR (KBr) 3066, 1483, 1178, 904, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz)

δ 9.10 (1H, s, Ar–H), 8.74 (2H, s, Ar–H), 2.66 (3H, s, CH_3), 2.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 157.3, 156.1, 149.8, 127.3, 123.6, 19.3, 16.0. Ms (*m*/*z*, relative intensity): 191 (M^+, 100), 150 (55), 122 (39). Anal. Calcd for $C_9H_9N_3S$: C, 56.52; H, 4.74; N, 21.97; S, 16.77. Found: C, 56.33; H, 4.88; N, 21.49; S,17.30.

*4.4.16. Dimethyl-5-(quinol-3-yl)thiazole (**22**).* The product **22** was obtained from 2,4-dimethylthiazole (**4**) and 3-bromopyridine. Yield: 82% (Thermal); 73% (MW). Brown oil. IR (KBr) 3055, 1483, 1370, 1186, 785, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.97 (1H, d, *J*=2.4 Hz, Ar–H), 8.13 (2H, m, Ar–H), 7.83 (1H, d, *J*=7.6 Hz, Ar–H), 7.73 (1H, t, *J*=7.2 Hz, Ar–H), 7.58 (1H, t, *J*=7.6 Hz, Ar–H), 2.73 (3H, s, CH_3), 2.53 (3H s, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 150.5, 148.6, 146.9, 135.1, 129.7, 127.6, 127.4, 127.2, 125.6, 19.0, 15.9. Ms (*m*/*z*, relative intensity): 240 (M^+, 100), 198 (68), 154 (16). Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 69.58; H, 5.11; N, 11.59; S, 13.72.

*4.4.17. 2,4-Dimethyl-5-(pyridyl-3-yl)thiazole (**23**).* The product **23** was obtained from 2,4-dimethylthiazole (**4**) and 3-bromopyridine. Yield: 60% (Thermal); 83% (MW). Yellow oil. IR (KBr) 3055, 1587, 1420, 1104, 802, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.64 (1H, s, Ar–H), 8.53 (1H, d, *J*=4.0 Hz, Ar–H), 7.67 (1H, d, *J*=7.6 Hz, ArH), 7.31 (1H, d, *J*=7.6 Hz, Ar–H), 2.67 (3H, s, CH_3), 2.53 (3H s, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 149.7, 148.6, 148.5, 136.3, 128.7, 127.5, 123.5, 19.2, 16.0. Ms (*m*/*z*, relative intensity): 190 (M^+, 100), 148 (76), 104 (15). Anal. Calcd for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; S, 16.85. Found: C, 63.62; H, 5.49; N, 14.49; S, 16.40.

*4.4.18. 4-Methoxy-2-phenyl-5-(pyrimidin-5-yl)thiazole (**24**).* The product **24** was obtained from 4-methoxy-2-phenylthiazole (**5**) and 5-bromopyrimidine. Yield: 67% (Thermal); 74% (MW). Yellow solid; mp: 169–170 °C; IR (KBr) 3003, 1533, 1427, 1342, 1082, 684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.05 (2H, s, Ar–H), 9.02 (1H, s, Ar–H), 7.94 (2H, m, Ar–H), 7.45 (3H, m, Ar–H), 4.22 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 161.9, 156.0, 153.9, 133.4, 131.0, 129.4, 127.3, 126.2, 58.3. Ms (*m*/*z*, relative intensity): 269 (M^+, 100), 123 (52), 69 (56).

*4.4.19. 4-Methoxy-2-phenyl-5-(quinolin-3-yl)thiazole (**25**).* The product **25** was obtained from 4-methoxy-2-phenylthiazole (**5**) and 3-bromoquinoline. Yield: 65% (Thermal); 78% (MW). White solid; mp: 127–128 °C. IR (KBr) 3021, 1528, 1342, 1094, 750, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.25 (1H, d, *J*=2.4 Hz, Ar–H), 8.45 (1H, d, *J*=2.4 Hz, Ar–H), 8.07 (1H, d, *J*=8.0 Hz, Ar–H), 7.96 (2H, m, Ar–H), 7.82 (1H, dd, *J*=7.8, *J*=1.2 Hz, Ar–H), 7.65 (1H, m, Ar–H), 7.54 (1H, m, Ar–H), 7.44 (3H, m, Ar–H), 4.25 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.8, 161.1, 149.5, 146.6, 133.6, 131.8, 130.5, 129.5, 129.2, 128.2, 128.1, 127.3, 125.9, 125.7, 107.7, 58.0. Ms (*m*/*z*, relative intensity): 268 (M^+, 92), 172 (100), 128 (47).

*4.4.20. 4-Methoxy-2-phenyl-5-(pyridin-3-yl)thiazole (**26**).* The product **26** was obtained from 4-methoxy-2-phenylthiazole (**5**) and 3-bromopyridine. Yield: 61% (Thermal); 79% (MW). Brown solid; mp: 68–70 °C; IR (KBr) 3025, 1533, 1353, 1079, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.93 (1H, d, *J*=2.4 Hz, Ar–H), 8.44 (1H, dd, *J*=4.6 Hz, *J*=1.2 Hz, Ar–H), 8.07 (1H, m, Ar–H), 7.95 (2H, m, Ar–H), 7.44 (3H, m, Ar–H), 7.29 (1H, m, Ar–H), 4.21 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 160.9, 147.8, 147.4, 133.7, 133.6, 130.5, 129.3, 128.5, 126.0, 123.7, 107.3, 58.0. Ms (*m*/*z*, relative intensity): 268 (M^+, 92), 122 (100), 78 (8).

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