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Diversification of Heteroaryl-Aryl Ether via Ligand-Free, Copper-Catalyzed *O*-Arylation Under Microwave Heating

Sung Min Choi, Jeong Seob Byeon, and Eul Kgun Yum*

Department of Chemistry, Chungnam National University, Yusung, Daejon 34134, Korea.
**E-mail: ekyum@cnu.ac.kr*
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Diverse *O*-arylated pyrrolo[2,3-*d*]pyrimidine and pyrrolo[2,3-*b*]pyridine were obtained using relatively low amounts of Cu catalyst with ligand-free conditions under microwave heating. The *O*-arylation reaction could be applied to less oxidative heteroaryl-chlorides. The microwave-assisted Cu-catalyzed *O*-aryaltion would be useful for preparing potent bioactive compounds for drug discovery while reducing waste, time, and saving energy.

Keywords: Hetroary-aryl ether, Ligand free, Copper catalyst, *O*-arylation, Microwave heating

Introduction

The diaryl ether scaffold is common to a variety of medicinal agents and biologically active compounds.[1,2] In particular, diaryl ethers constitute the core moiety of many important natural products,[3,4] insecticides,[5] herbicides,[6] and therapeutically active materials (Figure 1).[7–10]

Diverse diaryl ethers have been synthesized by the arylation of phenols with aryl halides using the Ullmann reaction and copper reagents.[11–14] However, classical Ullmann reactions are limited by the need for high temperatures, long reaction times, and excess amounts of copper reagent. On the other hand, nucleophilic aromatic substitution (SNAr) showed efficient synthetic method for the formation of heteroaryl C─O bonds with electro deficient heterocycles and alcohol under metal-free conditions.[15] Several transition metal-mediated C─O coupling reactions were also reported with heteroaryl chlorides and phenols under $AlCl_3$, Cu, or Pd.[16–19]

Recently improved Ullmann reactions, using bidentate ligands containing a heteroatom and transition metals, have been shown to significantly promote carbon–heteroatom coupling at moderate temperatures and long reaction times (12–24 h).[14,20] Specially, the most major advances in C─O bond-formation reactions have resulted from the use of heteroatoms containing ligands with Pd-, Cu-, Rh-, or Fe-based catalysts.[21] The reactivity of substituting aryl halides with nucleophiles depends strongly on the species of ligand and catalyst as well as the solvent used and the pH and temperature of the reaction mixture. Although the use of bidentate ligands with a heteroatom and copper catalyst has allowed for milder reaction conditions, the widespread use of these catalytic systems on an industrial scale is limited by the low reactivity of heteroaryl chlorides.[22]

The first microwave-assisted organic syntheses (MAOSes) using domestic microwave ovens were reported by Gedye et al.[23] in 1986. Since then, microwave irradiation has been recognized as an important tool for green chemistry,[24–26] because it reduces waste and enhances energy efficiency. MAOS was shown to be an efficient technology for the production of important drugs, fine chemicals, and materials.[27,28]

Our research to date has focused on green chemical processes incorporating metal-catalyzed MAOS for the diversification of heterocycles.[29–34] This report describes C─O bond formation with biological interesting pyrrolo[2,3-*d*]pyrimidine and 7-azaindole derivatives to diversify hetroaryl-aryl ethers under copper-catalyzed, ligand-free conditions. This synthetic approach affords a variety of heteroaryl-aryl ethers suitable for preparing potent bioactive compounds for drug discovery.

Results and Discussions

The pyrrolo[2,3-*d*]pyrimidine moiety has attracted considerable interest in the synthesis, pharmaceutical, and medicinal fields due to its bioactivities, which include antibacterial, antiinflammatory, and anticancer properties.[35] Especially, the chlorine substituent attached *ortho* or *para* to the nitrogen-deficient aromatic ring is an extremely versatile feature that allows for aromatic substitution with a wide variety of nucleophiles. Here, various copper species and bases were screened to identify the most efficient conditions for heteroaryl-aryl ether formation. The results of these conditions on C─O bond formation between 4-chloro-7-methyl-pyrrolo[2,3-*d*]pyrimidine and phenol are described in Table 1.

CuI-catalyzed *O*-arylation with 4-chloro-7-methylpyrrolo [2,3-*d*]pyrimidine and phenol provided an excellent yield of 4-phenoxy-7-methylpyrrolo[2,3-*d*]pyrimidine compared with those obtained using Cu_2O, CuO, and CuBr catalysts with K_3PO_4 (Table 1, entries 1, 8–10). The efficiency of the coupling reaction also depended strongly on the base. Reactions mixtures containing K_3PO_4 or Cs_2CO_3 resulted in higher yields of the desired product than did those containing K_2CO_3 or Na_2CO_3 (Table 1, entries 1–4).

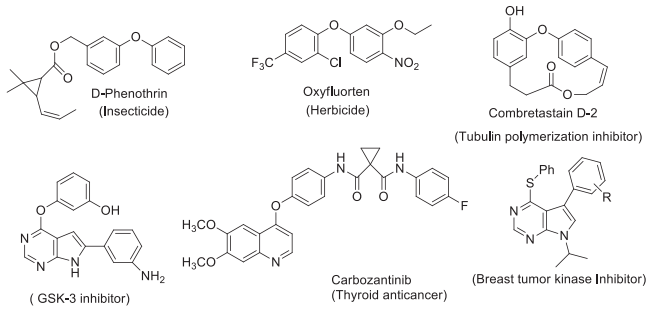


Figure 1. Biologically active compounds containing diaryl ether cores.

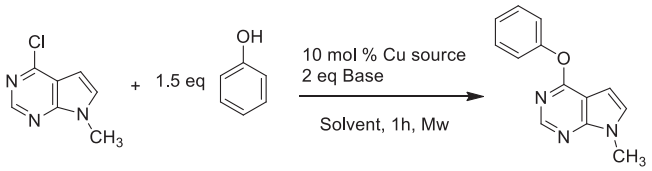
We then investigated the effects of various solvents on reaction efficiency (Table 1, entries 4–7). Excellent yields of the desired product were obtained in DMF, but reactions in DMA, DMSO, and NMP produced only moderate-to-high yields (65–83%). We therefore selected DMF, which exhibits a relatively high dielectric constant and high boiling point, as the best reaction solvent for C─O coupling. Microwave-mediated C─O coupling using bidentate ligands such as L-proline, histidine, and picolinic acid resulted in only moderate yields (39–49%) of the desired product (Table 1, entries 11–13). Thus, based on these results, the best conditions for *O*-arylation of pyrrolo[2,3-*d*]pyrimidine were two equivalents K_3PO_4 with 10 mol % CuI in DMF at 180°C. We then examined the diversification of diaryl ethers with pyrrolopyrimidines and various phenol derivatives. The results are represented in Table 2.

Unprotected 4-chloro pyrrolo[2,3-*d*]pyrimidine and phenol did not yield any coupling product under our optimized conditions due to complex formation between the Cu catalyst and nitrogen atoms. However, *N*-methyl-protected 4-chloro pyrrolo [2,3-*d*]pyrimidine successfully yielded coupled products (**2a**–**2d**). The reaction using 3-hydroxypyridine also proceeded smoothly with good yields of **2e**. However, 4-hydroxypyridine provided only a 15% yield of *N*-coupled product (**2f**) due to the formation of 4-pyridone as carbonyl tautomer. The reaction using the bulkier *N*-isopropyl-4-chloro pyrrolopyrimidine moiety provided excellent yields of the desired product **2g**, but the same reaction using substituted phenols gave only moderate yields of **2h** and **2i**. The reaction of *N*-methyl-2-chloro pyrrolo [2,3-*d*]pyrimidine with phenol proceeded smoothly and gave high yields of **2j**. The reaction of *N*-methyl-2-chloro pyrrolo[2,3-*d*]pyrimidine with methoxy phenols gave moderate yields of **2k**, and the reaction of *N*-methyl-2-chloro pyrrolo[2,3-*d*]pyrimidine with 3-hydroxy pyridine provided good yields of the coupled product **2l**.

Many natural and synthetic 7-azaindole derivatives reportedly exhibit biological properties such as antibacterial, antiinflammatory, and anticancer activities.[36] Here, *O*-arylation was examined using various substituted phenols and 4-bromo- or chloro-7-azaindoles under optimal reaction conditions to produce diverse *O*-arylated 7-azaindole products. The results are shown in Table 3.

Our Cu-catalyzed *O*-arylation system was also extended to functionally substituted phenols and *N*-methyl-4-bromo-

Table 1. Optimization of Cu-catalyzed *O*-arylation 4-chloro-7-methyl–pyrrolo[2,3-*d*]pyrimidine with microwave heating.

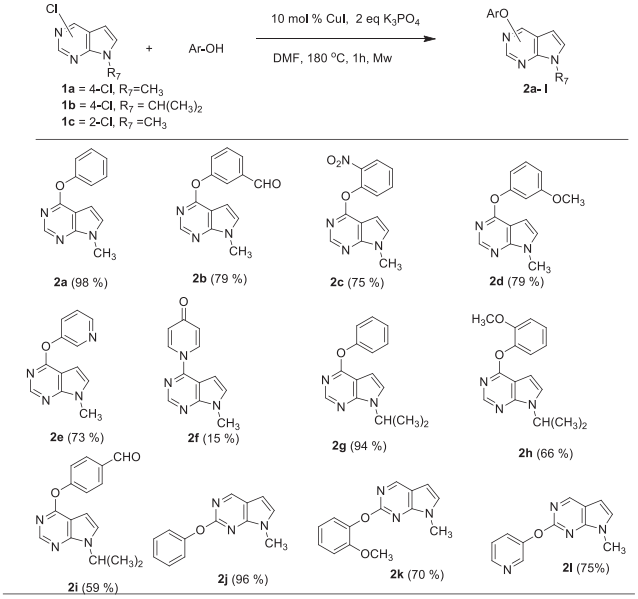


Entry[a,b]	Cu catalyst	Base	Solvent	Isolated yield (%)
1	CuI	K_2CO_3	DMF	87
2	CuI	Na_2CO_3	DMF	84
3	CuI	Cs_2CO_3	DMF	95
4	CuI	K_3PO_4	DMF	98
5	CuI	K_3PO_4	DMA	72
6	CuI	K_3PO_4	DMSO	83
7	CuI	K_3PO_4	NMP	65
8	Cu_2O	K_3PO_4	DMF	80
9	CuBr	K_3PO_4	DMF	75
10	CuO	K_3PO_4	DMF	54
11	CuI (20 mol % L-proline)	K_3PO_4	DMF	49
12	CuI (20 mol % histidine)	K_3PO_4	DMF	39
13	CuI (20 mol % picolinic acid)	K3PO4	DMF	47

[a] All reactions were conducted on a 0.5-mmol scale in 3 mL solvent in a 5-mL Biotage vial sealed with a crimp cap.

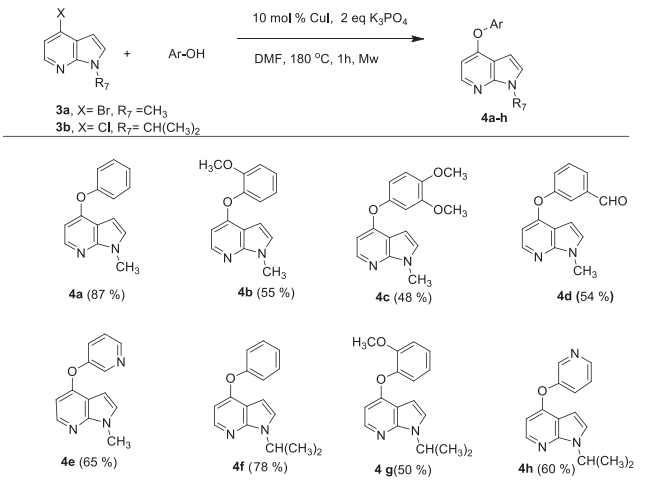
[b] Microwave irradiation was supplied by the Biotage Initiator EXP EU (400 W, 2450 MHz).

Table 2. Diversification of pyrrolo[2,3-*d*]pyrimidine derivatives with *O*-arylation.



7-azaindole. The 2-methoxy or 3-aldehyde substituted phenol provided moderate yields of the desired products **4b** and **4d**. The reaction using 3,4-dimethoxyphenol as a nucleophile yielded 48% of the desired product **4c**. Using 3-hydroxypyridine as a nucleophile resulted in a 65% yield of **4e**. The reaction with *N*-isopropyl- 4-chloro-7-azaindole provided slightly lower yields of **4g** and **4h** compared with the yields obtained with *N*-methyl 4-bromo-7-azaindole. These results indicate that substituted phenols result in slightly lower yields of the desired C─O coupling products than do unsubstituted phenols or 3-hydroxy pyridine.

Table 3. Diversification of 7-azaindole derivatives under ligand-free, Cu-catalyzed C─O arylation.



Experimental

Instrumentation and Analysis. All ^{1}H and ^{13}C NMR spectra were recorded on Bruker Fourier 300 MHz spectrometer, and chemical shifts were referenced to tetramethylsilane (TMS) as an internal standard. The LC–MS spectra were obtained using Waters ACQVI (UPLC) SQD 2 with ion trap and ESI. 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 copper species were purchased from Sigma-Aldrich Chemical Co (St.Louis, MO, USA). Chemicals were used directly as obtained from commercial sources unless otherwise noted.

Preparation of Starting and Product Materials

General Procedure for N-Alkyl of Heteroaryl Halide

*4-Chloro-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidine (**1a**)*

4-Chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (2 mmol) was dissolved in 20 mL of anhydrous DMF and added 60% NaH (4 mmol) into 50 mL round bottom flask. Iodomethane (4 mmol) was added and stirred for 4 h at room temperature. The reaction product was extracted with ethyl acetate with aqueous saturated ammonium chloride. The combined organic extracts were washed with brine, then dried over magnesium sulfate, filtered, and evaporated. The filtrate was purified by silica gel column chromatography using hexane:ethyl acetate = 1:1. 4-chloro-7-methyl-7*H*-pyrrolo [2,3-*d*]pyrimidine (**1a**) was obtained in 97% yield as a white solid. mp: 127–129°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.22 (d, J = 3.5 Hz, 1H), 6.61 (d, J = 3.5 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.98, 150.32, 125.69, 117.70, 108.41, 99.48, 46.72, 22.70. MS(*m/z*): 167.59 (M + 1).

4-Chloro-7-isopropyl-7H-pyrrolo[2,3-*d*]pyrimidine (1b) compound **1b** was obtained 95% yields from 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine and 2-iodopropane under 5 h reaction at 60°C. mp: 58–61°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.35 (d, J = 3.7 Hz, 1H), 6.62 (d, J = 3.7 Hz, 1H), 5.13 (hept, 1H), 1.54 (s, 3H), 1.51 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.98, 150.32, 125.69, 117.70, 108.41, 99.48, 46.72, 22.70. MS(*m/z*): 195.65 (M + 1).

*4-Bromo-1-methyl-1H-pyrrolo[2,3-*b*]pyridine (**3a**)*

Compound **3a** was obtained 96% yields as a brown oil from 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine and iodomethane under 1 h reaction at room temperature.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 5.1 Hz, 1H), 7.25 (d, J = 5.2 Hz, 1H), 7.23 (d, J = 3.5 Hz, 1H), 6.49 (d, J = 3.5 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)

δ 147.64, 142.92, 129.56, 125.12, 122.05, 118.76, 99.56, 31.67. MS(*m/z*): 211.06 (M + 1).

Compounds (**1c** and **3b)** were prepared with *N*-alkylation procedure from 2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine or 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine.

***General Procedure for O*-Arylation to Heteroaryl Halides Under Microwave Heating.** 4-Chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.5 mmol), phenol (0.75 mmol), CuI (10 mol%), and K_3PO_4 (1 mmol) and DMF (3 mL) were charged 5 mL vial.[32,33] The reaction mixtures were sealed with vial crimp cap and placed in a Biotage initiator microwave cavity. The microwave heating was conducted under 180°C for 1 h. The resulting mixtures were subsequently cooled, diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The ethyl acetate layer was dried with $MgSO_4$, filtered, and concentrated. *N*-Methyl-4-phenoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (**2a**) was purified by silicagel column chromatography using a hexane:ethyl acetate = 1:1. mp: 82–86°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.50–7.42 (m, 2H), 7.33–7.22 (m, *J* = 1.2 Hz, 3H), 7.08 (d, *J* = 3.5 Hz, 1H), 6.39 (d, *J* = 3.5 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.37, 152.99, 152.92, 150.84, 129.67, 127.73, 125.55, 121.82, 105.67, 98.54, 31.55. MS(*m/z*): 225.25 (M + 1).

***The Heteroaryl-Aryl Eher Products (2b–2l) Were Prepared With General Procedure for O*-Arylation to Heteroaryl Halide**

*3-((7-Methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)oxy) benzaldehyde (**2b**)*

Compound **2b** was obtained 79% yields as a yellow solid. mp: 137–139°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.45 (s, 1H), 7.81–7.76 (m, 2H), 7.65–7.59 (m, 1H), 7.53 (ddd, *J* = 8.1, 2.2, 1.5 Hz, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 6.57 (d, *J* = 3.5 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.34, 161.75, 153.57, 153.07, 150.63, 137.93, 130.29, 128.15, 128.03, 126.85, 122.45, 105.75, 98.26, 31.55. MS(*m/z*): 253.26 (M + 1).

*4-(4-Nitrophenoxy)-7-methyl-7H-pyrrolo[2,3-*d*] pyrimidine (**2c**)*

Compound **2c** was obtained 75% yields as a yellow solid. mp: 118–120°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.15–8.11 (m, 1H), 7.75–7.68 (m, 1H), 7.47–7.40 (m, 2H), 7.14 (d, *J* = 3.5 Hz, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.15, 153.12, 150.30, 146.01, 142.58, 134.67, 128.34, 126.17, 125.83, 125.61, 105.48, 98.28, 31.58. MS(*m/z*): 270.25 (M + 1).

*4-(3-Methoxyphenoxy)-7-methyl-7H-pyrrolo[2,3-*d*] pyrimidine (**2d**)*

Compound **2d** was obtained 79% yields as a brown solid. mp: 97–102°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.34 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 3.5 Hz, 1H), 6.88–6.78 (m, 3H), 6.36 (d, *J* = 3.5 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.13, 160.77, 153.87, 152.47, 150.22, 130.09, 128.09, 113.92, 111.63, 107.70, 105.63, 98.93, 55.45, 31.80. MS(*m/z*): 255.28 (M + 1).

*7-Methy-4-(pyridin-3-yloxy)-7H-pyrrolo[2,3-*d*] pyrimidine (**2e**)*

Compound **2e** was obtained 73% yields as a brown solid. mp: 70–72°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.51 (t, *J* = 9.0 Hz, 1H),8.43 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.41(m, 1H), 7.15 (d, *J* = 3.3 Hz, 1H), 6.59 (d, *J* = 3.3 Hz, 1H), 3.90 (s, 3H),). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.54, 153.04, 150.45, 149.59, 146.23, 143.76, 129.60, 128.26, 124.06, 105.64, 98.23, 31.58. MS(*m/z*): 227.26 (M + 1).

*1-(7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)-pyridin-4 (1H)-one (**2f**)*

Compound **2f** was obtained 15% yields as a purple solid. mp: 160–162°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.47–8.33(m, 2H), 7.37(d, *J* = 3.6 Hz, 1H), 6.70 (d, *J* = 3.6 Hz, 1H), 6.61–6.51(m, 2H 3.97 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.11, 153.55, 150.66, 150.55, 136.65, 131.03, 119.08, 107.35, 31.79. MS(*m/z*): 227.23 (M + 1).

*7-Isopropyl-4-phenoxy-7H-pyrrolo[2,3-*d*]pyrimidine (**2g**)*

Compound **2g** was obtained 94% yields as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.6 Hz, 1H), 7.43 (dt, *J* = 5.6, 3.6 Hz, 2H), 7.28–7.21 (m, 3H), 7.19 (d, *J* = 3.5 Hz, 1H), 6.43 (d, *J* = 3.6 Hz, 1H), 5.12 (m, 1H), 1.54 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.37, 153.05, 152.12, 150.55, 129.66, 125.51, 123.12, 121.84, 115.51, 105.87, 98.63, 46.35, 22.83. MS(*m/z*): 253.31 (M + 1).

*7-Isopropyl-4-(2-methoxyphenoxy)-7H-pyrrolo[2,3-*d*] pyrimidine (**2h**)*

Compound **2h** was obtained 66% yields as white solid. mp: 87–90°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.24 (dd, *J* = 9.0, 3.6 Hz, 2H), 7.18 (d, *J* = 3.6 Hz, 1H), 7.07–6.98 (m, 2H), 6.52 (d, *J* = 3.6 Hz, 1H), 5.11 (m, 1H), 3.74 (s, 3H), 1.54 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.35, 152.10, 151.88, 150.61, 141.80, 126.67, 123.29, 122.82, 121.04, 112.92, 105.40, 98.55, 55.93, 46.26, 22.84. MS(*m/z*): 283.33 (M + 1).

*4-((7-isopropyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)oxy) benzaldehyde (**2i**)*

Compound **2i** was obtained 59% yields as green solid. mp: 106–109°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.46 (s, 1H), 7.99 (d, *J* = 1.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 3.6 Hz, 1H), 6.58 (d, *J* = 3.6 Hz, 1H), 5.14 (m, 1H), 1.57 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.97, 161.32, 158.07, 152.37,

150.23, 133.47, 131.48, 123.84, 122.21, 106.18, 98.34, 46.52, 22.81. MS(*m/z*): 281.32 (M + 1).

*7-Methyl-2-phenoxy-7H-pyrrolo[2,3-*d*]pyrimidine (**2j**)*
Compound **2j** was obtained 96% yields as solid mp: 70–72°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.29–7.05 (m, 5H), 6.90 (d, J = 3.6 Hz, 1H), 6.35 (d, J = 3.6 Hz), 3.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 153.9, 152.9, 150.7, 129.3, 124.7, 121.4, 119.6, 115.58, 99.8, 30.80. MS(*m/z*): 226.25 (M + 1).

*2-(2-Methoxyphenoxy)-7-methyl-7H-pyrrolo[2,3-d] pyrimidine (**2k**)*
Compound **2k** was obtained 70% yields as solid. mp: 110–112°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63(s, 1H),, 7.23 (m, 2H), 7.05–7.00 (m, 3H), 6.45 (d, J = 3.6 Hz, 1H), 3.76 (s, 3H), 3.73(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.34, 153.17, 151.88, 150.68, 128.99, 125.95, 122.99, 120.96, 115.33, 112.80, 99.67, 55.90, 30.83. MS(*m/z*): 256.27 (M + 1).

*7-Methyl-2-(pyridine-3-yloxy)-7H-pyrrolo[2,3-*d*] pyrimidine (**2l**)*
Compound **2l** s obtained 75 yields as red soild. mp: 110–112°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70(s, 1H), 8.62(d, J = 2.1 Hz, 1H), 8.48(d, J = 4.5 Hz, 1H), 7.63 (dd, J = 8.1, 1.2 Hz), 7.37 (m, 1H),707 (d, J = 3.6 Hz, 1H), 6.52 (d, J = 3.6 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.34, 152.59, 150.65, 150.32, 145.52, 143.66, 129.50, 123.79, 115.83, 99.86, 30.76. MS(*m/z*): 226.23 (M + 1).

***The O*-arylated-*1H-pyrrolo[2,3-b]pyridines* (4a–4h) Were Prepared by above Described General Procedure for *O*-Arylation to Heteroaryl Halide Under Microwave Heating**

*1-Methyl-4-phenoxy-1H-pyrrolo[2,3-*b*]pyridine (**4a**)*
Compound **4a** was obtained 87% yield from 4-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine and phenol as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 5.5 Hz, 1H), 7.44–7.37 (m, 2H), 7.25–7.12 (m, 3H), 7.06 (d, J = 3.5 Hz, 1H), 6.48 (d, J = 5.5 Hz, 1H), 6.31 (d, J = 3.5 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.07, 155.28, 150.48, 144.42, 129.87, 127.54, 124.74, 120.49, 111.38, 102.88, 97.04, 31.59. MS(*m/z*): 224.26 (M + 1).

*4-(2-Methoxyphenoxy)-1-methyl-1H-pyrrolo[2,3-*b*] pyridine (**4b**)*
Compound **4b** was obtained 55% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 5.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 5.5 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.36 (d, J = 5.5 Hz, 1H), 6.34 (d, J = 4.0 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.59, 151.91, 150.37, 144.34, 143.39, 127.25, 126.24, 122.68, 121.18, 113.03, 110.65, 101.50, 96.95, 55.98, 31.57. MS(*m/z*): 254.29 (M + 1).

*4-(3,4-Dimethoxyphenoxy)-1-methyl-1H-pyrrolo[2,3-*b*] pyridine (**4c**)*
Compound **4c** was obtained 48% yield as brown solid. mp: 121–123°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 5.5 Hz, 1H), 6.91 (d, J = 3.5 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.57 (dd, J = 4.2 Hz, J = 1.2 Hz, 1H), 6.29 (d, J = 5.5 Hz, 1H), 6.19 (d, J = 3.5 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.80, 150.42, 149.88, 148.65, 146.37, 144.44, 127.39, 112.17, 111.55, 110.92, 105.27, 102.03, 96.99, 56.25, 56.02, 31.56. MS(*m/z*): 284.32 (M + 1).

*3-((1-Methyl-1H-pyrrolo[2,3-*b*]pyridin-4-yl)oxy) benzaldehyde (**4d**)*
Compound **4d** was obtained 54% yield as yellow solid. mp: 75–77°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.24 (d, J = 5.4 Hz, 1H), 7.73 (dt, J = 7.5, 1.2 Hz, 1H), 7.64–7.61 (m, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.42 (ddd, J = 8.1, 2.5, 1.1 Hz, 1H), 7.08 (d, J = 3.5 Hz, 1H), 6.55 (d, J = 5.4 Hz, 1H), 6.26 (d, J = 3.5 Hz, 1H), 3.90 (d, J = 4.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.36, 156.95, 156.34, 150.52, 144.39, 138.16, 130.60, 128.12, 126.03, 125.96, 120.12, 111.68, 103.65, 96.91, 31.67. MS(*m/z*): 252.27 (M + 1).

*1-Methyl-4(pyridine-3-yloxy)-1H-pyrrolo[2,3-*b*] pyridine (**4e**)*
Compound **4e** was obtained 65% yield from 4-bromo-1-methyl-1H-pyrrolo[2,3-*b*]pyridine and 3-hydorxypyridine as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.48 (d, J = 5.4 Hz, 1H),8.23 (d, J = 5.4 Hz, 1H), 7.45–7.34 (m, 2H), 7.10 (d, J = 3.5 Hz, 1H), 6.52 (d, J = 5.4 Hz, 1H), 6.30 (d, J = 3.6 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.97, 152.11, 150.58, 145.70, 144.43, 142.20, 127.21, 128.12, 124.20, 111.40, 103.16, 96.86, 31.63. MS(m/z): 226.25 (M + 1).

*1-Isopropyl-4-phenoxy-1H-pyrrolo[2,3-*b*]pyridine (**4f**)*
Compound **4f** was obtained 78% yield from 4-chloro-1-isopropyl -1*H*-pyrrolo[2,3-*b*]pyridine and phenol as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 5.4 Hz, 1H), 7.40–7.13 (m, 5H), 6.48 (d, J = 3.6 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 5.19 (m, 1H), 0.150 (d.J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.04, 155.27, 149.62, 144.01, 129.86, 124.73, 122.67, 120.56, 115.47, 111.54, 102,85, 97.21, 45.67, 22.93 MS(*m/z*): 253.32 (M + 1).

*1-Isopropyl-4-(2-methoxyphenoxy-1H-pyrrolo[2,3-*b*] pyridine (**4g**)*
Compound **4g** was obtained 78% yield from 4-chloro-1-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridine and 2-methoxyphenol as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 5.4 Hz, 1H), 7.20–7.04 (m, 4H), 6.32(d, 3.6 Hz, 1H), 6.25 (d, J = 3.6 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 5.15 (m, 1H),, 3.72 (s, 3H), 0.144 (d, J= 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.58, 151.98, 143.88, 143.35,

126.25, 122.76, 122.37, 115.20, 113.06, 110.73, 101, 43, 97.17, 56.00, 45.59, 22.94. MS(*m/z*): 283.35 (M + 1).

*1-Isopropyl-4- (pyridine-3-yloxy)-1H-pyrrolo[2,3-*b*] pyridine (**4h**)*

Compound **4h** was obtained 60% yield from 4-chloro-1-isopropyl -1*H*-pyrrolo[2,3-*b*]pyridine and 3-hydroxypyridine as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 2.6 Hz, 1H), 8.41(d, 1H, J = 5.4 Hz, 8.13 (d, J = 5.4 Hz, 1H), 7.39–7.17 (m, 3H), 6.43 (d, 3.6 Hz, 1H), 6.25 (d, J = 3.6 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 5.15 (m, 1H), 0.146 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.88, 152.15, 145.65, 144.05, 142.61, 127.26, 124.21, 123.31, 111.55, 103.18. 97.00, 45.78, 22.90. MS(*m/z*): 254.30 (M + 1).

Conclusions

We examined ligand-free, copper-catalyzed *O*-arylation with heteroaryl chlorides and bromides under microwave heating. Diverse *O*-arylated-7*H*-pyrrolo[2,3-*d*]pyrimidines and 7-azaindole derivatives were obtained using relatively low amounts of Cu catalyst and a variety of heteroaromatic halides and phenols under ligand-free conditions. The synthetic methods described herein would be useful for the rapid preparation of biologically active compounds while reducing waste, time, and saving energy.

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