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Diversification of Pyrazoles by Microwave-assisted Ligand Free Copper Catalyzed *N*-Arylation

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Pyrazole and its derivatives exhibit interesting chemical and biological properties, so the derivatives are widely used in pharmaceuticals, agrochemicals, food additives, dyes, materials, and cosmetic coloring agents.[1] Several synthetic methods for facile preparation of pyrazole derivatives have been reported.[1b,2] The *N*-arylpyrazole moiety is a particularly interesting synthetic target that has exhibited a broad spectrum of biological activities.[3] For example, several *N*-arylated pyrazoles exhibit diverse pharmaceutically relevant characteristics such as anti-inflammatory,[4] antitumor,[5] antiviral,[6] and ORL1 antagonist activity.[7] The *N*-arylpyrazoles are also agrochemically relevant and have been shown to have insecticidal, herbicidal, and fungicidal activity.[8] In addition, several pyrazole derivatives have been used as ligands for the formation of iridium complexes in organic light-emitting diode (OLED) materials.[9] Over the last two decades, many mild and efficient methods have been reported that accomplish heterocycle *N*-arylation using catalytic palladium (Pd) and copper (Cu) reactions.[10] However, despite the mild conditions employed in Pd-catalyzed *N*-arylation of heterocycles, this method is not commonly used due both to the high price of the Pd catalyst and to insufficient ligand specificity for heterocyclic substrates.[11] Recently, significant progress has been made in the development of Cu-catalyzed *N*-arylation of pyrazoles using various organic ligands such as diamine,[12] oxime-phosphine oxide,[13] aminoacid,[14] and organic ionic base.[15] Ligand free Cu-catalyzed *N*-arylation of pyrazole with Cu-pyrazole complexes has also exhibited efficient *N*-arylation of pyrazoles, albeit with long reaction times (18-48 h).[16]

Recently, microwave reactions have attracted considerable attention in organic chemistry for their ability to accelerate slow thermal reactions.[17] Microwave irradiation provides advantages over conventional heating in chemical transformations; these advantages include accelerated reaction rates, significant energy savings, high chemical yields, and cleaner reactions.[18]

Two methods for microwave-assisted Cu-catalyzed *N*-arylation of pyrazole have been studied in which the arylhalides were varied with only one 1*H*-pyrazole under pyrrole-2-carbohydrazides[19] or with L-amino acid[20] ligands. However, the ligand-mediated Cu-catalyzed *N*-arylation of pyrazole has limitations, including non-generalization of the ligands, lack of application to systems for sensitive functional groups, and limited examples of the use of 1*H*-pyrazole. In general, ligand free transition metal catalyzed reactions have some advantages, such as facile product purification, less sensitivity to substrate environment, and mild reaction conditions.

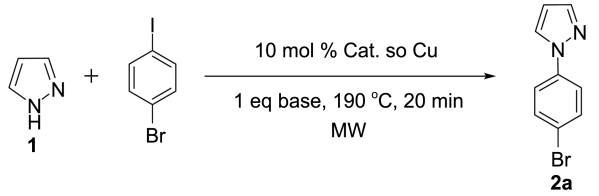
As part of our ongoing investigation of organometallic approaches for diversification of nitrogen-containing heterocycles, such as indoles,[21] azaindoles,[22] quinolines,[23] and carbazole,[24] we examined microwave-assisted *N*-arylation with various pyrazoles under ligand free Cu-mediated *N*-arylation.

Results and Discussion

First, we investigated microwave-assisted ligand free Cu-mediated *N*-arylation of pyrazole with 4-bromo-1-iodobenzene to optimize the *N*-arylation of pyrazole under various reaction conditions and short reaction times. The results are summarized in Table 1.

The reaction using 4-bromo-iodobenzene provided excellent yield of *N*-4-bromophenyl pyrazole with highly selective activity for the *iodo* derivative over bromo derivative. Reactions carried out at 180 °C typically required twice the time to reach completion compared to reactions carried out at 190 °C. Reactions using cesium carbonate (Cs_2CO_3) as a base also produced good yields of the desired product. However, reactions using potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), or rubidium carbonate (Rb_2CO_3) as the base produced only moderate yields of the desired product (Table 1, entries 1-6). Yields in the absence of a chloride source were higher than when LiCl was added (Table 1, entries 1-4). We also investigated the effect of different solvents under the same temperature conditions (Table 1, entries 4, 8, and 9). The reaction using dimethylformamide (DMF) as the solvent produced good yields of the desired product, but the yields were slightly lower in different solvents (entries 7-9). We also examined the effects of several Cu species frequently for Cu-coupling reactions. *N*-Arylation of pyrazole using Cu(I) species such as copper iodide (CuI), copper bromide (CuBr), and copper oxide (Cu_2O) under a Cs_2CO_3 base produced higher yields of the desired product compared to the reactions using Cu(II)

Table 1. Optimization of conditions for microwave-assisted Cu-catalyzed *N*-arylation of pyrazole



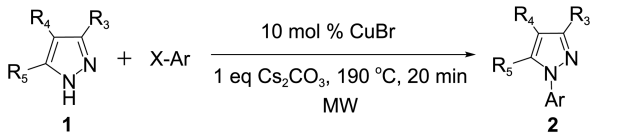
Entry[a,b]	Cu source	Additive	Base	Solvent	Yield (%)
1	CuI	LiCl	K_2CO_3	DMF	56
2	CuI	–	K_2CO_3	DMF	62
3	CuI	LiCl	Cs_2CO_3	DMF	68
4	CuI	–	Cs_2CO_3	DMF	82
5	CuI	–	K_3PO_4	DMF	64
6	CuI	–	Rb_2CO_3	DMF	63
7	CuI	–	Cs_2CO_3	NMP	75
8		–	Cs_2CO_3	DMSO	71
9	CuI	–	Cs_2CO_3	DMAc	60
10	CuBr	–	K_2CO_3	DMF	58
11	CuBr	–	Cs_2CO_3	DMF	86
12	Cu_2O	–	Cs_2CO_3	DMF	83
13	CuO	–	Cs_2CO_3	DMF	47
14	$Cu(OAc)_2$	–	Cs_2CO_3	DMF	75
15	$CuBr_2$	–	Cs_2CO_3	DMF	68

[a]All reactions were conducted on a 1.0-mmol scale under 3 mL of solvent in a Biotage 5-mL vial sealed crimp cap using an initiator instrument (EXP EU, Biotage, 400 W, 2450 MHz). [b]Vapor pressure of the reaction mixture in the vial was monitored as 5-7 bar at 190 °C.

sources (Table 1, entries 4 and 11-15). The vapor pressure of the reaction mixture in the vial was monitored and determined to be 5-7 bar using an online-programmed Biotage microwave reactor at 190 °C.

To diversify pyrazole derivatives, *N*-arylation was examined using various aryl iodides or bromides with variation of substituted pyrazoles under 1 equivalent of Cs_2CO_3, 10 mol % CuBr, and DMF at 190 °C. The results are summarized in Table 2. The reaction using halo-substituted iodobenzene produced high yields of *N*-arylated pyrazoles (Table 2, entries 2-4). Specifically, the reaction using 1-bromo-4-iodobenzene produced *N*-4-bromophenyl with excellent selectivity for the iodo substituent (Table 2, entry 2). Additionally, reactions using bromopyridine produced reasonable yields of *N*-pyridyl bromopyrazole without any side reaction of bromopyrazole (Table 2, entry 5). The optimized reaction conditions were applied for the diversification of substituted pyrazoles with aryliodides (Table 2, entries 6-13). Good yields of *N*-arylated 3-trifuloromethylpyrazoles were obtained with 3-trifloromethylpyrazole and arylhalides (Table 2, entries 7 and 8). However, *N*-arylation of 3,5-dimethylpyrazole provided low yields of *N*-arylated dimethylpyrazole due to the high steric effect in pyrazoles (Table 2, entries 9-11). On the other hand, *N*-arylation of 3-aminopyrazole with aryliodide provided good yields of the desired product with good selectivity for the secondary amine (Table 2, entries 12 and 13). The results showed that yields for *N*-arylation of

Table 2. *N*-Arylation of carbazoles with arylhalides

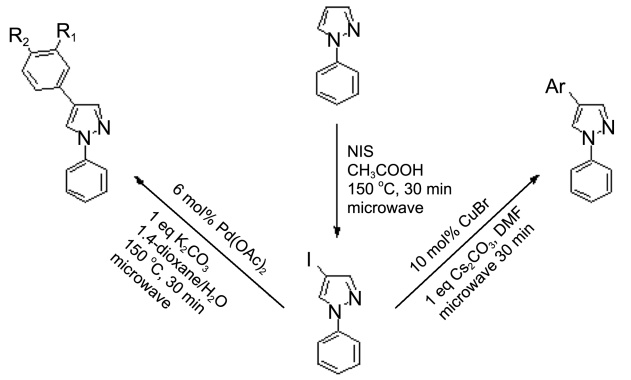


Entry[a,b]	R_3	R_4	R_5	X-Ar	Product	Yield (%)
1	H	BR	H		**2B**	90
2	H	BR	H		**2C**	84
3	H	BR	H		**2D**	78
4	H	BR	H		**2F**	77
5	H	BR	H		**2G**	61
6	H	BR	H		**2H**	78
7	CF_3	H	H		**2I**	75
8	CF_3	H	H		**2J**	73
9	CH_3	H	CH_3		**2K**	35
10	CH_3	H	CH_3		**2L**	32
11	CH_3	H	CH_3		**2M**	29
12	NH_2	H	H		**2N**	82
13	NH_2	H	H		**2O**	71

[a]All reactions were conducted on a 1.0-mmol scale under 3 mL of solvent in a Biotage 5-mL vial sealed crimp cap using an initiator instrument (EXP EU, Biotage, 400 W, 2450 MHz). [b]Vapor pressure of the reaction mixture in the vial was monitored as 5-7 bar at 190 °C.

pyrazoles were highly dependent on the pyrazole substituents.

We next examined *N*-arylation of azaheterocycles using 4-bromo-*N*-phenyl pyrazole. Low yields of *N*-arylation products were obtained due to decomposition of starting materials under Cu-catalyzed reaction conditions. However, *N*-arylated 4-iodopyrazole could be converted into aromatic or *N*-heterocyclic-substituted pyrazoles by microwave-assisted coupling using catalytic Cu or Pd reactions (Scheme 1). *N*-Phenyl-4-iodopyrazole was obtained in quantitative yields from *N*-phenylpyrazoles with *N*-iodosuccinimide (NIS) in acetic acid solvent. The *N*-phenyl-4-iodopyrazole converted various *N*-phenyl-4-arylpyrazoles by Pd-catalyzed Suzuki coupling with substituted phenylboric acids. High yields of the coupling products were obtained in the



Entry	R_1	R_2	Yield (%)
1	H	H	95
2	H	CF_3	90
3	H	CH_3	85
4	H	OCH_3	80
5	Cl	F	89
6	F	OCH_3	79

Entry	Ar	Temp. (°C)	Yield (%)
1		200	61
2		220	65
3		220	68
4		220	87

Scheme 1. Diversification of *N*-phenyl-iodo-pyrazole under Cu- and Pd-catalyzed reactions.

presence of electron withdrawing substituents on the phenylboric acids. *N*-Phenyl-4-azaheterocyclic pyrazoles were also prepared with moderate yields by Cu-catalyzed *N*-arylation with azaheterocycles. The *N*-arylation to carbazole with one nitrogen atom provided higher yields of *N*-heterocyclic pyrazole products than the corresponding reaction using heterocycles with two nitrogen atoms.

Conclusions

Simple and efficient *N*-arylation of pyrazoles was achieved using microwave-assisted catalytic Cu reactions without organic ligands and with short reaction times. The *N*-arylation of pyrazole could be extended to various substituted pyrazoles and arylhalides. Yields of *N*-arylated pyrazoles were highly dependent on the steric and electronic effects of the pyrazole substituents. Further functionalization of *N*-arylated iodopyrazoles in Cu- and Pd-catalyzed coupling reactions exhibited promising results for the diversification of pyrazoles.

Experimental

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 GC-MS spectra were obtained using a Shimadzu QP 1000 GC-MS. Microwave-assisted reactions were performed with an initiator instrument (EXP EU, Biotage, 400 W, 2450 MHz). Each reaction was carried out in a 5-mm-thickness Biotage 5-mL vial sealed with a crimp cap. 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 Cu species were purchased from Sigma-Aldrich Chemical Co. Chemicals were used directly as obtained from commercial sources unless otherwise noted.

General Experimental Procedure for Microwave-assisted *N*-Arylation of Pyrazoles. Pyrazole (1.0 mmol), Cs_2CO_3 (1.0 mmol), 4-bromoiodobenzene (1.5 mmol), CuBr(0.1 mmol), and DMF (3 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 190 °C for the appropriate time and subsequent cooling, the reaction mixture was diluted with saturated aqueous ammonium chloride. Products were isolated by extraction with 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 solvent. 1-(4-Bromophenyl)-1*H*-pyrazole[25] was obtained (86% yield) as a white solid. mp 61-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J = 2.5 Hz, J = 0.5 Hz), 7.72 (dd, 1H, J = 1.7 Hz, J = 0.5 Hz), 7.52-7.62 (m, 4H), 6.46 (dd, 1H, J = 2.5 Hz, J = 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.2, 132.4, 126.6, 120.6, 119.6, 108.0; Ms (*m/z*, relative intensity): 224 (M+2, 98), 222(M^+, 100).

General Experimental Procedure for Microwave-assisted Functionalization *N*-Arylated Pyrazoles by Palladium Catalyzed Coupling Reactions. $Pd(OAc)_2$ (0.05 mmol), 4-iodo-*N*-phenylpyrazole (1 mmol) and phenylboronic acid (1.5 mmol) were dissolved in 3 mL of 1,4-dioxane to a 5-mL vial. The vial was sealed with a crimp cap and placed in a Biotage initiator microwave cavity. After irradiation at 150 °C for the appropriate time and subsequent cooling, the reaction mixture was diluted with saturated aqueous ammonium chloride. Products were isolated by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. 1,4-Diphenyl-1*H*-pyrazole[26] was obtained as a white solid in a 95% isolated yield by silica gel column chromatography using a hexane: ethyl acetate solvent. mp 91-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.88 (s, 1H), 7.60 (d, 2H, J = 7.96 Hz), 7.43 (d, 2H, J = 7.47 Hz), 7.25-7.35 (m, 4H), 7.13-7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 138.8, 132.1, 129.5, 129.0, 126.9, 126.6, 125.7, 124.9, 123.3, 119.1; Ms (*m/z*, relative intensity): 221 (M+1, 94), 220 (M^+, 100), 219 (M-1, 71).

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