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N-Arylation of azaindoles in LiCl-mediated catalytic CuI reactions

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Abstract—N-Arylation of 5- and 7-azaindoles was achieved in LiCl-mediated catalytic CuI reactions at 120 °C with moderate to high yields. N-Arylation can be performed with various arylhalides, such as phenyl, pyridine, quinoline, thiophen, and thiazole moieties.

Azaindoles have attracted considerable attention as analogs of the indole nucleus with interesting biological, pharmaceutical, and material properties.[1] Since azaindoles are present in only a few natural products,[2] most azaindole derivatives for study are prepared synthetically.[1] Recently, organometallic complexes of azaindoles have been reported as potential luminescent materials in organic light-emitting devices (OLEDs).[3] One major modification was the replacement of the proton in the azaindole nitrogen atom by an aromatic group to improve the stability and performance of organometallic complexes in OLEDs. Although N-arylated azaindoles are very useful intermediates in material and pharmaceutical sciences, the preparation of arylated azaindoles requires high temperatures and stoichiometric amounts of copper reagents in the classical Ullmann reaction.[4] Recently, copper-catalyzed N-arylation has been applied to many heterocycles with various organic ligands.[5] Only a few examples of N-arylated azaindoles using catalytic CuI and *trans*-1,2-cyclohexanediamine ligand have been reported.[6] However, when we applied the reported N-arylation reaction conditions to various arylhalides to obtain N-arylated azaindoles, the reactions provided variable yields with aryl halide substrates. Therefore, we explored the N-arylation of 5- and 7-azaindoles using copper-catalyzed reactions.

Continuing our research into the diversification of indoles,[7] azaindoles,[8] and quinolines,[9] we applied our palladium-catalyzed reaction conditions[7–9] to the copper-catalyzed reaction. In recently reported catalytic copper reactions, the N-arylation of heterocycles was shown to be quite sensitive to the copper source, bases, ligands, and other additives.[5a] Initially, 7-azaindoles with iodobenzene were chosen as a model study with various additives, copper sources, bases, and solvents. The results are summarized in Table 1.

The reaction with added LiCl gave higher yields of the desired product compared to the reactions using *n*-BuN_4Cl, KCl, CsCl, or no chloride source (entries 1–5). In addition, the reactions using less than 10 mol % CuI needed longer time for completion. From the above results, different cationic species of chloride influenced catalytic activity in this reaction. We also examined the effect of several copper species that are frequently used for Cu coupling reactions (entries 1, 6, and 7). The N-arylation of 7-azaindole using CuI gave higher yields of the desired product than the reactions using other copper sources. The reactions using K_2CO_3 or Cs_2CO_3 as the base gave the desired product in good yields (entries 1 and 8), while the reactions using Na_2CO_3, K_3PO_4, or Li_2CO_3 as the base had poor yields of the desired product (entries 10–12). We also investigated the effect of different solvents at the same reaction temperature (entries 1 and 13–15). Only the reaction using DMF gave good yields of the desired product. The results showed that the optimum conditions for the N-arylation of azaindoles consisted of 1 equiv of LiCl, 3 equiv of K_2CO_3, 10 mol % CuI, and DMF at 120 °C.[10] N-Arylation was examined using various aryl iodides or bromides under the optimum reaction conditions to diversify the N-arylated azaindoles. The results are summarized in Table 2.

The reactions using halo-substituted iodobenzene gave good to excellent yields of *N*-aryl-7-azainoles (entries 1–4). Another reaction using *o*-ethyl ester instead of

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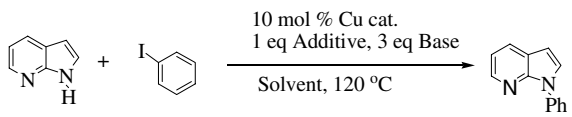
Table 1. Optimization of Cu-catalyzed N-arylation of 7-azaindole

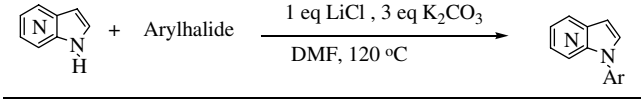


Entry[a]	Additive	Cu source	Base	Solvent	Reaction time (h)	Isolated yield (%)
1[b]	LiCl	CuI	K_2CO_3	DMF	24	70
2	None	CuI	K_2CO_3	DMF	48	10<
3	*n*-Bu_4NCl	CuI	K_2CO_3	DMF	48	55
4	KCl	CuI	K_2CO_3	DMF	48	60
5	CsCl	CuI	K_2CO_3	DMF	48	57
6	LiCl	$Cu(OAc)_2$	K_2CO_3	DMF	36	60
7	LiCl	$CuSO_4$	K_2CO_3	DMF	36	25
8	LiCl	CuI	Cs_2CO_3	DMF	36	60
9	LiCl	CuI	KOAc	DMF	48	45
10	LiCl	CuI	Na_2CO_3	DMF	48	30
11	LiCl	CuI	K_3PO_4	DMF	48	5<
12	LiCl	CuI	Li_2CO_3	DMF	48	10<
13	LiCl	CuI	K_2CO_3	DMAc	36	30
14	LiCl	CuI	K_2CO_3	NMP	36	30
15[c]	LiCl	CuI	K_2CO_3	1,4-Dioxane	36	—

[a] All of the reactions were run on a 1.0-mmol scale with 10 mL of dimethyl formamide (DMF).
[b] The reactions using less than 10% CuI needed longer times for completion.
[c] The reaction did not proceed at refluxing temperature.

iodobenzene also gave excellent yields of the desired product (entry 5). In addition, the reactions using a heteroaryl bromide, such as pyridine, quinoline, thiophen, or thiazole, gave N-heteroarylated 7-azaindoles in good to reasonable yields (entries 6–9). The results showed that reactions using nitrogen-containing heterocycles had the same reactivity with the benzene ring, while the reactions using sulfur-containing heterocycles gave low yields of the desired product after a long reaction time. Finally, the reaction conditions were applied to the diversification of 5-azaindole with halo-substituted iodobenzene and heterocyclic bromides (entries 10–15). The results showed that N-arylation of 5-azaindole with high yields was also possible under our optimized reaction conditions.

Table 2. Diverse N-arylation to 5- and 7-azaindoles



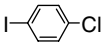
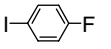
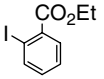
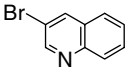
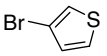
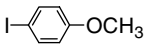
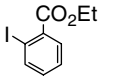
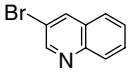
Entry[a]	Azaindole	Aryl halide	Reaction time (h)	Isolated yield (%)
1			24	60
2			24	85
3			24	75
4			24	78
5			36	92
6			36	85
7			48	50
8			48	40
9			48	40

Table 2 (*continued*)

Entry[a]	Azaindole	Aryl halide	Reaction time (h)	Isolated yield (%)
10			24	85
12			24	65
13			24	88
14			36	75
15			36	80

[a] All reactions were run on a 1.0-mmol scale in 10 ml DMF.

In conclusion, simple, efficient N-arylation to 5- and 7-azaindole was achieved in a LiCl-mediated catalytic CuI reaction without any organic ligand. Various N-arylated azaindoles were synthesized at low reaction temperatures with high yields. We will further explore

the possible synthetic applications to biologically active azaheterocycles.

Acknowledgment

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10. *Typical reaction procedures*. 7-Azaindole (1.0 mmol), LiCl (1.0 mmol), K_2CO_3 (3.0 mmol), iodobenzene (1.1 mmol), CuI (0.1 mmol), and DMF (10 mL) were added to a screw-capped pressure tube. The reaction mixture was stirred for 24 h at 120 °C, and then diluted with saturated aqueous ammonium chloride. The product was isolated with ethyl acetate, the organic layer was dried over anhydrous magnesium sulfate, and the reaction mixture was filtered and concentrated. The product was purified by silica gel column chromatography using hexane:ethyl acetate (3:1) solvent. *N*-Phenyl-7-azaindole was obtained in 70% yield as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (dd, 1H, $J = 3.2$, 1.6 Hz, ArH), 7.54 (dd, 1H, $J = 6.4$, 1.2 Hz, ArH), 7.72 (m, 2H, ArH), 7.64 (m, 3H, ArH), 7.30 (m, 1H, ArH), 7.10 (dd, 1H, $J = 5.0$, 2.8 Hz, ArH), 6.59 (d, 1H, $J = 4.0$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.3, 134.4, 138.3, 129.2, 128.9, 127.7, 126.1, 123.8, 121.4, 116.5, 101.5; MS (*m*/*z*) 194 (M^+, 100), 193 (M−1, 82), 167 (14), 139 (10), 97 (25), 77 (18). Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19, N, 214.42. Found: C, 80.40; H, 5.17, N, 7.65.