Copper-catalyzed *N*-Arylation of Aryl Iodides with Benzamides or Nitrogen Heterocycles in the Presence of Ethylenediamine

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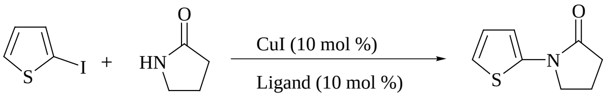
Abstract: The copper-catalyzed *N*-arylation of benzamides or nitrogen heterocycles was carried out with catalytic CuI (10 mol%) in the presence of ethylenediamine (10 mol%) as a ligand and K_3PO_4 or Cs_2CO_3 as a base under mild conditions.

Key words: copper-catalyst, *N*-arylation, benzamides, nitrogen heterocycles

Recently Buchwald, Hartwig and others have developed valuable and new palladium-catalyzed *N*-arylation of aryl halides and amines to form arylamines, which supplanted the classical Ullmann coupling reaction.[1] The reactions can be carried out at a lower temperature under milder conditions than the copper-mediated classical Ullmann condensation.[2] Ma et al.[3] reported the CuI-catalyzed *N*-arylation of a certain type of α-amino acid with aryl halides at 90 °C in DMF. Subsequently, copper-catalyzed amination was achieved by adding 1,10-phenanthroline as a ligand to conduct coupling at lower temperature than the classical Ullmann condensation.[4] Recently Buchwald et al.[5] demonstrated CuI-catalyzed *N*-arylation of aryl halides with nitrogen heterocycles utilizing racemic *trans*-1,2-cyclohexanediamine as a ligand under mild conditions. In connection with our programs to utilize CuI catalyzed carbon-carbon bond formations,[6] we have explored the CuI-catalyzed *N*-arylation of benzamides and heterolytic amines using ethylenediamine (10 mol%) as a simple ligand in the presence of CuI (10 mol%). To find optimum conditions a series of experiments has been performed with 2-iodothiophene (**1a**) and pyrrolidinone (**2a**) as model compounds (Scheme), which are summarized in Table 1. Of the ligands tested ethylenediamine, 1,3-propylenediamine, TMEDA, and 1,2-benzen- diamine, ethylenediamine were the best choice. As a base K_3PO_4 or Cs_2CO_3 was suitable. As a solvent dioxane was better than other solvents even if sometimes CH_3CN was more suitable.



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

Scheme

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1437-2096,E;2002,0,03,0427,0430,ftx,en;Y24201ST.pdf.

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Table 1 *N*-Arylation of 2-Iodothiophene (**1a**) with 2-Pyrrolidinone (**2a**)

Entry	Lignad (10 mol %)	Base	Solvent	Isolated Yield (%)
1	ethylenediamine	K_3PO_4	dioxane	95
2	ethylenediamine	K_3PO_4	CH_3CN	95
3	1,3-propylenediamine	Cs_2CO_3	dioxane	94
4	TMEDA	Cs_2CO_3	dioxane	61
5	1,2-benzenediamine	Cs_2CO_3	dioxane	70
6	ethylenediamine	Cs_2CO_3	dioxane	78
7	ethylenediamine	K_3PO_4	dioxane	47
8	ethylenediamine	K_3PO_4	NMP	40
9	ethylenediamine	K_3PO_4	toluene	20

The *N*-arylation of aryl iodides with benzamides and nitrogen heterocycles was very sensitive to the substrates and reaction conditions and the results were summarized in Table 2. 2-Iodothiophene (**1a**) reacted with pyrrolidinone (**2a**) using CuI (10 mol%) ethylenediamine (10 mol%) as a ligand in dioxane at reflux in the presence of K_3PO_4 for 24 h to afford the *N*-arylation product **3a** in 95% yield (entry 1 in Table 2). However with oxazolidone as a nitrogen heterocycles under the same conditions the *N*-substituted oxazolidinone **3b**[7] was obtained in 59% yield (entry 2).

With benzamide **2c** as the substrate the coupling product **3c**[5] was afforded in only 41% yield (entry 3). Employing 2-nitrobenzamide (**2d**) as an amide the coupled benzamide (**3d**) was afforded in 52% yield (entry 4). When 3,5-dimethyliodobenzene (**1b**) was treated with indole (**2e**) *N*-aryl-substituted indole **3e**[5] was obtained in 96% yield utilizing Cs_2CO_3 as a base (entry 5). The pyrrole (**2f**) was reacted under the same conditions with **1b** to provide *N*-aryl-substituted pyrrole **3f**[5] in 87% yield (entry 6). For pyrrolidinone (**2a**) with 3,5-dimethyliodobenzene (**1b**) using Cs_2CO_3 as a base the arylated product **3g**[5] was provided in 68% yield (entry 7). Although the coupling reaction of 3,5-dimthyliodobenzene (**1b**) with benzamide gave the coupled product in a very low (20%) yield, it is notable that 2-nitro-substituted benzamide **2d** smoothly coupled with **1b** to provide **3h** in a good (88%) yield (entry 8) presumably because of electronic effect. Accordingly picolinamide (**2g**) was also coupled with **1b** to give **3i** in 50% isolated yield (entry 9). When *p*-methoxyiodobenzene (**1c**) was employed as a substrate for aryl iodides *N*-arylation of pyrrolidine afforded **3j**[8] in 85% yield (entry 10). However oxazolidinone (**2b**) and benzamide (**2c**) were coupled with *p*-methoxyiodobenzene (**1c**) afforded **3k**[9] and **3l**[10] in 45% and 60% isolated yields, respectively (entries 11 and 12). This coupling was applied to 2-nitrobenzamide (**2d**), 4-nitrobenzamide (**2h**), and picolinamide (**2i)**, the *N*-arylated products **3m**, **3n**, and **3o** were afforded in moderate yields (entries 13–15).

Table 2 The Copper-catalyzed *N*-Arylation Iodides with Benzamides and Nitrogen Heterocycles

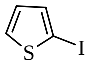
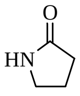
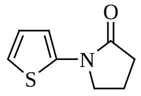
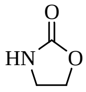
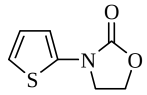
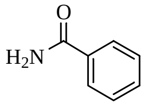
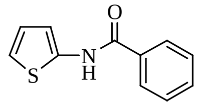
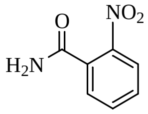
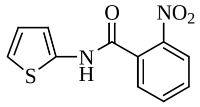
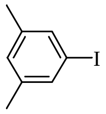
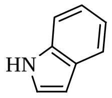
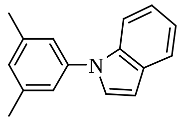
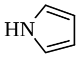
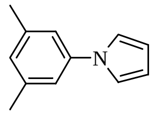
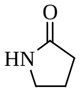
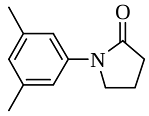
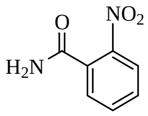
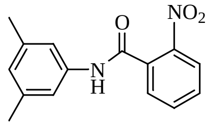
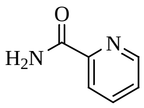
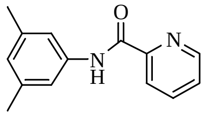
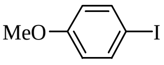
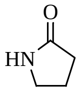
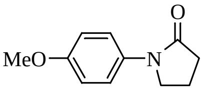
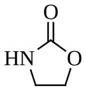
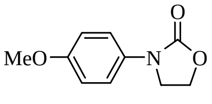
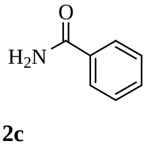
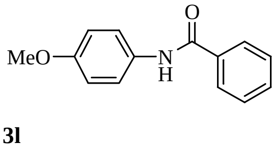
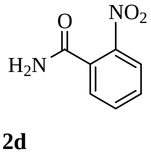
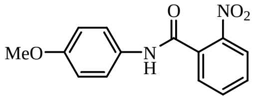
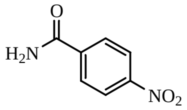
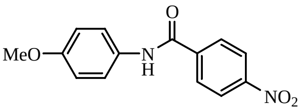
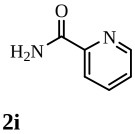
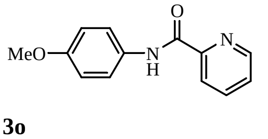
Entry	Ioiodides	Heterocycles or Benzamides	Base	Products	Isolated Yield (%)
1	 **1a**	 **2a**	K_3PO_4	 **3a**	95
2	**1a**	 **2b**	K_3PO_4	 **3b**	59
3	**1a**	 **2c**	K_3PO_4	 **3c**	41
4	**1a**	 **2d**	K_3PO_4	 **3d**	52
5	 **1b**	 **2e**	Cs_2CO_3	 **3e**	96
6	**1b**	 **2f**	K_3PO_4	 **3f**	87
7	**1b**	 **2a**	Cs_2CO_3	 **3g**	68
8	**1b**	 **2d**	K_3PO_4	 **3h**	88
9	**1b**	 **2g**	K_3PO_4	 **3i**	50

Table 2 The Copper-catalyzed *N*-Arylation Iodides with Benzamides and Nitrogen Heterocycles (continued)

Entry	Ioiodides	Heterocycles or Benzamides	Base	Products	Isolated Yield (%)
10	 **1c**	 **2a**	K_3PO_4	 **3j**	85
11	**1c**	 **2b**	K_3PO_4	 **3k**	45
12	**1c**	 **2c**	K_3PO_4	 **3l**	60
13	**1c**	 **2d**	K_3PO_4	 **3m**	61
14	**1c**	 **2h**	K_3PO_4	 **3n**	67
15	**1c**	 **2i**	K_3PO_4	 **3o**	59

Typical Procedure:

To a stirred solution of 2-pyrrolidinone (**2a**) (102 mg, 1.20 mmol) and 2-iodothiophene (**1a**) (210 mg, 1.00 mmol) in 1,4-dioxane (2 mL) under argon atmosphere were added CuI (19 mg, 10 mol%), and ethylenediamine (6.7 μL, 10 mol%) followed by K_3PO_4 (652 mg, 2.00 mmol) and stirred at 110 °C for 24 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was separated on SiO_2 column chromatography using EtOAc and hexane (1: 1) as eluents to afford the coupled product **3a**[5] (158 mg, 95%) as white needles.

In summary, the CuI (10 mol%) catalyzed *N*-arylation of some benzamides or nitrogen nucleophiles was carried out in the presence of ethylenediamine (10 mol%) and base under mild conditions.

Acknowledgement

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(7) Selected physical and spectral data are as follows. **3b**: mp 88 °C (hexane–ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 6.90 (1 H, dd, *J* = 5.5 and 1.5 Hz), 6.85 (1 H, dd, *J* = 5.5 and 3.7 Hz), 6.45 (1 H, dd, *J* = 3.7 and 1.5 Hz), 4.50 (2 H, m), 4.00 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 154.62, 140.33, 124.65, 118.13, 110.93, 62.21, 46.03. IR (KBr, cm^{-1}): 1726, 1545, 1483, 1035. HRMS: calcd for $C_7H_7NO_2S$: 169.0197, found: 169.0194.
3d: mp 196 °C (hexane–ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 8.15 (1 H, m), 7.88 (1 H, m), 7.78 (2 H, m), 7.06 (1 H, dd, *J* = 5.5 and 1.5 Hz), 6.91 (1 H, dd, *J* = 5.5 and 3.7 Hz), 6.78 (1 H, dd, *J* = 3.7 and 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 162.83, 147.69, 140.22, 134.88, 132.29, 131.95, 130.30, 125.08, 118.60, 113.18. IR (KBr, cm^{-1}): 3235, 3118, 2888, 1636, 1574, 1527, 1354. HRMS: calcd for $C_{11}H_8N_2O_3S$: 248.0256, found: 248.0254.
3h: mp 162 °C (hexane–ethyl acetate). ^1H NMR (500 MHz,

$CDCl_3$, δ ppm) 8.13 (1 H, d, *J* = 8.8 Hz), 7.74 (1 H, m), 7.64 (2 H, m), 7.38 (1 H, s), 7.23 (1 H, s), 6.84 (1 H, s), 2.33 (6 H, s). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm) 164.85, 147.36, 139.67, 138.68, 134.92, 133.69, 131.74, 130.12, 126.32, 125.09, 118.29, 21.96. IR (KBr, cm^{-1}): 3256, 1657, 1523, 1350, 836. HRMS: calcd for $C_{15}H_{14}N_2O_3$: 270.1004, found: 270.1007.

3i: mp 80 °C (pentane–ether). ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 9.95 (1 H, s), 8.61 (1 H, m), 8.23 (1 H, m), 7.91 (1 H, m), 7.48 (1 H, m), 7.44 (2 H, s) 6.80 (1 H, s) 2.34 (6 H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 162.31, 150.40, 148,36, 139.21, 138.08, 138.00, 126.77, 126.52, 122.78, 117.87, 21.85. IR (KBr, cm^{-1}): 3341, 2913, 1683, 1540, 1458. HRMS: calcd for $C_{14}H_{14}N_2O$: 226.1106, found: 226.1117.

3m: mp 154 °C (methylene chloride). ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 10.53 (1 H, s), 8.13 (2 H, d, *J* = 8.1 Hz), 7.86 (2 H, m), 7.75 (2 H, m), 7.57 (2 H, d, *J* = 8.8 Hz), 6.94 (2 H, d, *J* = 8.8 Hz) 3.74 (3 H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 164.49, 156.61, 147.48, 134.84, 133.65, 132.83, 131.72, 130.14, 125.09, 122.11, 114.82, 56.08. IR (KBr, cm^{-1}): 3263, 1650, 1532, 1350, 1251. HRMS: calcd for $C_{14}H_{12}N_2O_4$: 272.0797, found: 272.0793.

3n: mp 192 °C (hexane–ethyl acetate). ^1H NMR (500 MHz, DMSO-d_6, δ ppm) 10.46 (1 H, s), 8.37 (2 H, d, *J* = 9.2 Hz), 8.17 (2 H, d, *J* = 9.2 Hz), 7.68 (2 H, d, *J* = 9.2 Hz), 6.95 (2 H, d, *J* = 9.2 Hz), 3.75 (3 H, s). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm) 164.23, 156.75, 149.91, 141.57, 132.61, 129.95, 124.38, 122.94, 114.69, 56.05. IR (KBr, cm^{-1}): 3295, 2951, 1648, 1527, 1342. HRMS: calcd for $C_{14}H_{12}N_2O_4$: 272.0797, found: 272.0793.

3o: mp 90 °C (hexane–ethyl acetate). ^1H NMR (500 MHz, DMSO-d_6, δ ppm) 10.54 (1 H, s), 8.73 (1 H, m), 8.14 (1 H, m), 8.01 (1 H, m), 7.81 (2 H, d, *J* = 8.8 Hz), 7.66 (1 H, m) 6.93 (2 H, d, *J* = 8.8 Hz), 3.75 (1 H, m). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm) 163.09, 156.65, 150.64, 149.32, 138.98, 132.05, 127.68, 123.06, 122.76, 114.72, 56.05. IR (KBr, cm^{-1}): 3263, 1650, 1532, 1350, 1251. HRMS: calcd for $C_{13}H_{12}N_2O_2$: 228.0899, found: 228.0897.

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