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Graphical Abstract

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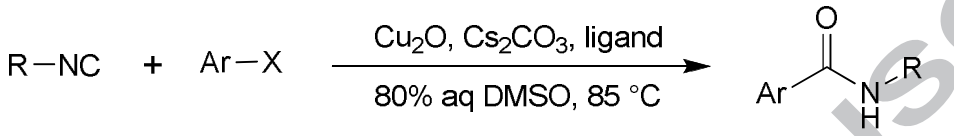

Synthesis of amides *via* copper-catalyzed amidation of aryl halides using isocyanides

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ABSTRACT

An efficient method for intermolecular C-C cross-coupling reactions between isocyanides and aryl halides, catalyzed by copper(I) oxide, is developed. This transformation serves as a direct method for the preparation of benzamides in aqueous DMSO, in moderate to good yields.

Keywords:

Aryl halide

Isocyanide

Amidation

C-C cross-coupling

Copper(I) oxide

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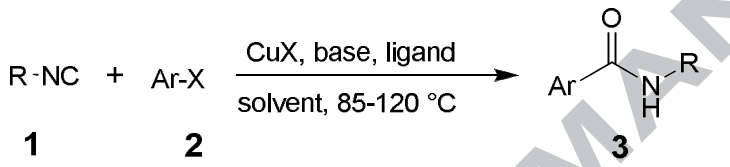
The development of metal-catalyzed cross-coupling reactions has revolutionized the formation of C-C bonds.[1-3] However, the use of toxic carbon monoxide and expensive transition metal catalysts has limited the scope of these types of coupling reactions.[4, 5]

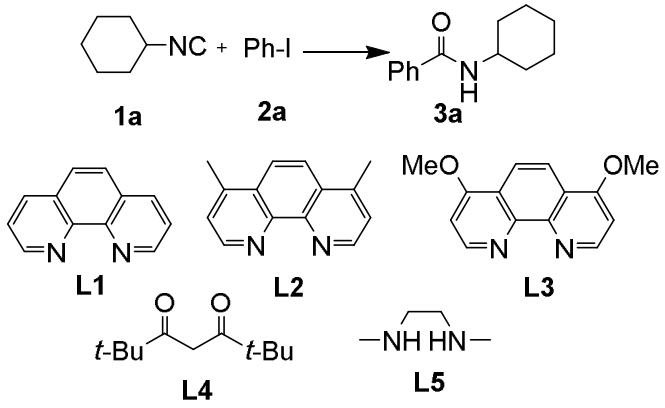
Isocyanides are derivatives of carbon that are similar to carbon monoxide.[6] Recently, Jiang and co-workers reported a method for the synthesis of amides *via* palladium-catalyzed C-C coupling of aryl halides with isocyanides in the presence of CsF in aqueous DMSO.[7] This report, prompted us to describe our results on the direct aminocarbonylation of aryl halides using isocyanides in the presence of Cu_2O, which constitutes a synthesis of benzamides *via* copper-catalyzed C-C cross-coupling of aryl halides with isocyanides (see Scheme 1).[8]



Scheme 1. Reaction between isocyanides and aryl halides.

Cyclohexyl isocyanide (**1**) and iodobenzene (**2a**) were selected for initial development of the reaction conditions. When **1** and **2a** were treated with cesium carbonate and CuI in 80% aqueous DMSO at 85 °C for five hours, *N*-cyclohexylbenzamide (**3a**) was obtained in 14% yield. The presence of a ligand had a beneficial effect on this transformation. Among the various ligands tested for optimization of the reaction conditions, 4,7-dimethoxy-1,10-phenanthroline (L3) gave the best yields (see Table 1).

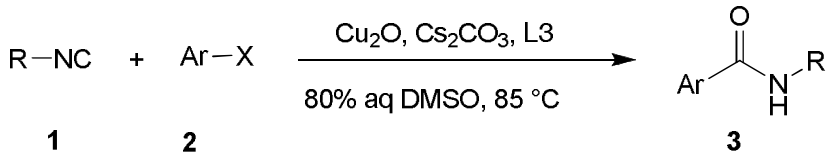
Table 1. Reaction of cyclohexyl isocyanide (**1a**, 1.5 mmol), iodobenzene (**2a**, 1.0 mmol), Cu source (10 mol%), ligand (0.2 mmol), and base (1.5 mmol) at 85 °C for 5 h under argon



Entry	Catalyst	Base	Ligand	Solvent	Yield (%)
1	Cu_2O	Cs_2CO_3	L1	80% aq DMSO	41
2	Cu_2O	Cs_2CO_3	L2	80% aq DMSO	62
3	Cu_2O	Cs_2CO_3	L3	80% aq DMSO	85
4	Cu_2O	Cs_2CO_3	L4	80% aq DMSO	53
5	Cu_2O	Cs_2CO_3	L5	80% aq DMSO	30
6	Cu_2O	K_2CO_3	L3	80% aq DMSO	72
7	Cu_2O	KOH	L3	80% aq DMSO	12
8	Cu_2O	Cs_2CO_3	L3	80% aq DMF	65
9	Cu_2O	Cs_2CO_3	L3	80% aq MNP	57
10	Cu_2O	Cs_2CO_3	L3	80% aq MeCN	42
11	Cu_2O	Cs_2CO_3	L3	H_2O	-
12	AgI	Cs_2CO_3	L3	80% aq DMSO	-
13	CuCl	Cs_2CO_3	L3	80% aq DMSO	45
14	CuI	Cs_2CO_3	L3	80% aq DMSO	63
15	CuBr	Cs_2CO_3	L3	80% aq DMSO	34
16	$Cu(Ac)_2$	Cs_2CO_3	L3	80% aq DMSO	8

With optimized reaction conditions in hand, different substituted aryl halides and isocyanides were subjected to this cross-coupling process to explore the scope of this transformation (Table 2).

Table 2. Copper-catalyzed synthesis of aryl amides **3** from aryl halides **1** and isocyanides **2**



1 **2** **3**

Entry	R	Ar	Product	Yield (%)		
				X = I	X = Br	X = Cl
1	cyclohexyl	Ph	**3a**	85	81	32
2	cyclohexyl	*o*-tol	**3b**	76	72	11
3	cyclohexyl	*m*-tol	**3c**	83	80	30
4	cyclohexyl	4-MeO-C_6H_4	**3d**	80	72	23
5	cyclohexyl	4-O_2N-C_6H_4	**3e**	91	85	48
6	cyclohexyl	2-thienyl	**3f**	78	73	22
7	cyclohexyl	4-NC-C_6H_4	**3g**	88	81	36
8	cyclohexyl	4-Cl-C_6H_4	**3h**	82	80	25
9	*t*-Bu	Ph	**3i**	84	78	34
10	*t*-Bu	4-MeO-C_6H_4	**3j**	80	76	20
11	*t*-Bu	4-O_2N-C_6H_4	**3k**	85	80	45
12	$Me_3CCH_2Me_2C$	4-Ac-C_6H_4	**3l**	79	77	23
13	2,6-Me_2-C_6H_3	Ph	**3m**	76	73	10

Chlorobenzene derivatives needed a higher catalyst loading (30%) and temperature (120 ºC) to furnish products **3**. In most cases the yields were low, except for derivatives bearing an electron-withdrawing group on the aryl ring.

In conclusion, we have described a cheap and efficient method to convert aryl halides into amides *via* a copper-catalyzed reaction of an aryl halide with an isocyanide. The chemistry is optimized through a ligand screen which leads to the use of a dimethoxyphenathroline ligand. Aryl iodides and bromides are particularly good substrates. This chemistry offers a useful alternative to current palladium-catalyzed protocols and can be of general interest to the synthetic community.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi .org/

References and notes

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8. Spectroscopic and analytical data for products **3i-3m** have been reported.[7] Melting points and IR spectroscopic data of these derivatives were in complete agreement with the literature.

Typical procedure for the preparation of benzamides 3a-m:

To a mixture of Cu_2O (0.015 mg, 0.1 mmol) and Cs_2CO_3 (0.555 g, 1.5 mmol) in 80% aqueous DMSO (3 mL), was added the aryl halide (1.0 mmol) at room temperature under argon. After 15 min, the isocyanide (1.5 mmol) was added, and the mixture stirred at 85 °C for 5 h, then cooled to room temperature, diluted with H_2O, and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. The solvent was removed and the residue purified by column chromatography on silica gel (hexane/EtOAc 4:1) to give product **3**.

***N*-Cyclohexylbenzamide (3a).** Colorless solid, mp: 152-154 °C; yield: 0.17 g (85%). IR (KBr) (ν_{max}, cm^{-1}): 3245, 3073, 2928, 1629, 1538, 1332, 1152. ^1H NMR (500.1 MHz, $CDCl_3$): δ_H 1.18-1.27 (2H, m, CH_2), 1.37-1.46 (4H, m, $2CH_2$), 1.77-2.01 (4H, m, $2CH_2$), 3.93-4.01 (1H, m, CH), 6.01 (1H, br s, NH), 7.41 (2H, t, ^3J = 7.3 Hz, 2CH), 7.47 (1H, t, ^3J = 7.0 Hz, CH), 7.75 (2H, d, ^3J = 7.8 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 24.9 ($2CH_2$), 25.6 (CH_2), 33.2 ($2CH_2$), 48.7 (CH), 126.9 (2CH), 128.5 (2CH), 131.2 (CH), 135.2 (C), 166.6 (C=O). EI-MS: *m/z* (%) = 203 (M^+, 1), 174 (16), 120 (83), 105 (67), 98 (65), 77 (100). Anal. Calcd for $C_{13}H_{17}NO$ (203.13): C, 76.81; H, 8.43; N, 6.89%. Found: C, 76.49; H, 8.34; N, 6.95%.