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Copper-catalyzed N-arylation of oxindoles

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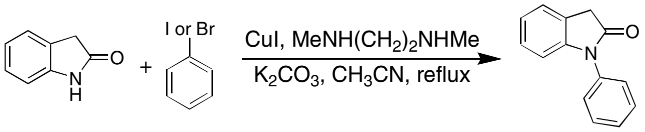
Abstract—The coupling of aryl bromides or iodides with oxindoles using a copper iodide-*N*,*N*′-dimethylethylene diamine system is presented. The reaction proceeds efficiently and tolerates a variety of substitution patterns.

The metal-mediated N-arylation of amines or amides has received considerable interest over the past several years.[1] The Ullmann-type coupling and the related Goldberg reaction is a straightforward method to form the requisite carbon–nitrogen bond via coupling of N–H containing substrate to an aryl halide.[2] Recently Buchwald et al. reported a general method for the coupling of amines or amides, including heterocycles, to aryl halides using a copper-diamine complex.[3] This type of process has been used to prepare a variety of targets that would have otherwise been difficult to prepare.

Although oxindoles are ubiquitous within the pharmaceutical industry only fleeting examples of the Ullmann-type coupling of oxindole derivatives have been reported. Such procedures employed relatively harsh conditions (e.g., NMP, 200 °C, 24 h).[4] It was speculated that Buchwald's conditions for the Ullmann-type coupling reaction could be extended to the preparation of *N*-aryl oxindoles and this would serve as a valuable synthetic tool for the preparation of functionalized oxindole targets. To the best of our knowledge the coupling of oxindoles to aryl halides using a copper-diamine complex has not been reported.

The conditions employed are similar to that described by Buchwald et al. (Scheme 1).[3] The oxindole, aryl bromide, copper (I) iodide, *N*,*N*′-dimethylethylene diamine,[5] and potassium carbonate were heated at reflux in acetonitrile[6] for 4–22 h. This procedure allowed us to generate a number of substituted *N*-aryl oxindoles from readily available starting materials (Table 1). In general the yield of coupled product was good to moderate (37–63%). Electron-withdrawing or donating groups at the 3- or 4-position of the aryl bromide had little effect on the efficiency of the reaction. Likewise the coupling of either 5-Cl or 5-Me oxindole (Table 1, entries 5 and 9) had no impact on the yield of coupled product. In general, substituents adjacent to the reaction centers of either the aryl bromide or oxindole were not well tolerated (Table 1, entry 6). Oxindoles substituted at the 7-position resulted in low yields or the reaction failed altogether.



Scheme 1.

The coupling of oxindoles with aryl iodides (Table 2) under the same conditions led to higher yields (61–92%) than the corresponding aryl bromides. Electron-withdrawing or donating groups at the 3-, 4-, and/or 5-position of the aryl iodide had no impact on the efficiency of the reaction. Substituents at the 5- or 6-position of the oxindole were also well tolerated. In addition, Ullmann-type coupling reaction of oxindoles with aryl iodides required shorter reaction times (4–6 h) than the corresponding aryl bromides (up to 21 h). Prolonged reaction times lead to the formation of isatin and dimerization side products leading to diminished yields. It is

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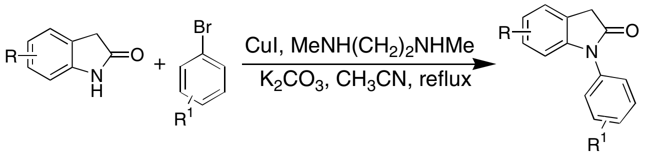
Table 1. N-arylation of oxindoles with aryl bromides[a]



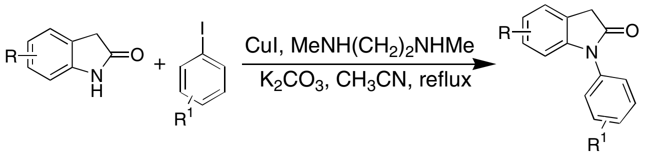
3a-i

Entry	R	R^1	Product	% Yield
1	H	H	**3a**	43
2	H	3-CO_2CH_3	**3b**	40
3	H	4-CF_3	**3c**	50
4	H	3,4-di-Cl	**3d**	49
5	5-Cl	4-Pr	**3e**	47
6	H	2-F,4-CH_3	**3f**	14
7	6-Ph	3,4-di-CH_3	**3g**	37
8	H	$4 + 5 = OCH_2O$	**3h**	63 (57)[b]
9	5-CH_3	3,4-di-CH_3	**3i**	52

[a] Conditions: 1:1.2 equiv oxindole/aryl bromide, 2.2 equiv K_2CO_3, 5–10 mol % CuI, 10–20 mol % $CH_3NH(CH_2)_2NHCH_3$, CH_3CN, reflux 4–22 h. Yields are unoptimized.

[b] Microwave irradiation, 120 °C, 1 h.

Table 2. N-arylation of oxindoles with aryl iodides[a]



3j–t

Entry	R	R^1	Product	% Yield
1	H	3,5-di-CH_3	**3j**	86
2	H	3,4-di-CH_3	**3k**	92
3	H	3-CO_2CH_3	**3l**	74
4	H	4-OH	**3m**	73
5	5-F	3-CO_2CH_3	**3n**	61
6	6-Cl	3,5-di-CH_3	**3o**	69
7	6-CF_3	3,4-di-CH_3	**3p**	77
8	6-CF_3	3-CO_2CH_3	**3q**	65
9	6-Cl	3-CO_2CH_3	**3r**	82
10	6-CO_2CH_3	3,4-di-CH_3	**3s**	66
11	6-Br	3,4-di-CH_3	**3t**	72

[a] Conditions: 1:1.2 equiv oxindole/aryl iodide, 2.2 equiv K_2CO_3, 5–10 mol % CuI, 10–20 mol % $CH_3NH(CH_2)_2NHCH_3$, CH_3CN, reflux 4–6 h. Yields are unoptimized.

worth noting that the use of microwave irradiation reduced reaction times and thus minimized formation of byproducts. For example, under conventional heating the synthesis of compound **3h** was complete in 21 h, whereas under microwave irradiation (120 °C) the reaction time was reduced to 1 h (57% yield).

In conclusion, we have demonstrated that the Ullmann-type coupling of oxindoles is an efficient and general method for the preparation of substituted *N*-aryl oxindoles. The reaction works well with electron-rich and electron-poor substrates on either reacting partner. Aryl iodides tend to give higher yields and shorter reaction times than the corresponding aryl bromides.

Typical procedure: 1-bromo-3,4-(methylenedioxy) benzene (1.2 ml, 10 mmol) was added to a suspension of oxindole (1.49 g, 11.2 mmol) in acetonitrile (33 ml) under a nitrogen atmosphere. A steady stream of nitrogen was bubbled through the suspension as it was heated to 40 °C over 15 min. Potassium carbonate (3.09 g, 22.4 mmol), copper (I) iodide (220 mg, 1.15 mmol, 10 mol %), and *N*,*N′*-dimethylethylenediamine (0.24 ml, 2.3 mmol, 20 mol %) were added and the reaction mixture was heated to 80 °C for 21 h under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature, 1 M HCl (100 ml) was added, and the solution was extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexanes, gave *N*-aryl oxindole **3h** as a white powder (1.59 g, 63%). Mp 110–111 °C (from hexanes); IR (film, cm^{-1}) 1717, 1613, 1492, and 1241; ^1H NMR ($CDCl_3$) 300 MHz δ 7.29 (d, *J* 7.3, 1H) 7.21 (t, *J* 7.8, 1H), 7.06 (t, *J* 7.3, 1H), 6.96–6.82 (m, 3H), 6.75 (d, *J* 7.9, 1H), 6.03 (s, 2H), and 3.69 (s, 2H); ^{13}C NMR ($CDCl_3$) 174.7, 148.5, 147.4, 145.5, 128.0, 127.8, 124.6, 124.2, 122.8, 120.4, 109.4, 108.8, 108.0, 101.8, and 36.0; MS (ESI) *m*/*z* 254 (MH^+).

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5. Increasing the catalytic loading of the diamine led to no deterioration in yield.
6. CH_3CN is an atypical solvent choice for this type of reaction but was found to be optimal for this system.