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Selective, Efficient and Functional Group-Tolerant CuOAc-Mediated *N*-Arylation of 1*H*-Indoles and 9*H*-Carbazole with Aryl Iodides Under Base-Free and Ligandless Conditions

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CuOAc-Mediated *N*-arylation of 1*H*-indole derivatives and 1*H*-carbazole with aryl iodides under base-free and ligandless conditions provides the required *N*-arylazoles with complete *N*-selectivity and in moderate to good yields. The experimental conditions for this new version of the Ullmann reaction allow an unprecedented tolerance of functional groups and facilitate the workup of the reaction mixtures and isolation of the required chemically pure reaction products.

Introduction

1-Arylindoles are central structural elements in many pharmacologically important and bioactive compounds. In fact, these arylazoles are of interest as angiotensin II antagonists,[1] melatonin receptor MT_1 agonists,[2] antiallergic[3] and antipsychotic agents,[4] COX-2 inhibitors[5] and herbicides,[6] and also as synthetic intermediates used to prepare other biologically active compounds.[7] Moreover, numerous *N*-arylindoles bearing 4-fluorophenyl groups are to be found among the most selective ligands with high affinities for the G_2 binding site.[8] On the other hand, 9-arylcarbazoles have attracted attention because of their luminescent properties[9] and as discotic molecules.[10]

Much consideration has thus been directed towards the preparation of such *N*-arylazoles. Methods developed for the synthesis of 1-arylindoles include the Fischer synthesis,[11] Ullmann-type couplings between aryl halides and indoles,[12] nucleophilic aromatic substitution,[13] intramolecular Pd-catalysed annulation of didehydrophenylalanine derivatives,[14] Pd-catalysed *N*-arylation of indoles with aryl halides[8c,15] and Cu-catalysed *N*-arylation of indoles variously with diaryliodonium salts,[16] with aryl iodides or bromides in the presence of a suitable ligand[17] or with zeolite NaY.[18,19] On the other hand, 9-arylcarbazoles have been prepared by Ullmann *N*-arylation of 9*H*-carbazoles with aryl halides,[9,20] Pd/P(*t*Bu)$_3$-catalysed coupling of aryl bromides with carbazole,[15c] or Pd-catalysed double *N*-arylation of primary arylamines with 2,2′-biphenylene ditriflates[21a] or 2,2′-dihalobiphenyls.[21b]

However, several problems limit the synthetic utility of many of these *N*-arylation methods. In particular, the Ullmann-type coupling reactions suffer from limited substrate scope and low to moderate yields, whilst having predominantly been conducted with aryl halides activated by electron-withdrawing groups. The utility of the Pd-catalysed *N*-arylation of 1*H*-indoles, meanwhile, is limited by problems such as C-3 arylation and an intolerance of several functional groups. Moreover, like the Pd-catalysed *N*-arylation of 9*H*-carbazoles, this reaction involves the use of expensive phosphane ligands. Even the Cu-catalysed *N*-arylation of 1*H*-indoles is not entirely satisfactory, since the use of ligands such as L-proline,[17d,17f] 1,10-phenanthroline,[17a] a 1,2-diaminocycloalkane[17b,17e] or a Schiff base[17c,17g] in this method entails increased costs and problems in the isolation of the required chemically pure 1-aryl-1*H*-indoles from the multicomponent crude reaction mixtures. Furthermore, the experimental conditions for the Ullmann-type couplings and the Pd- or Cu-catalysed *N*-arylation reactions, involving the use of base, result in intolerance of base-sensitive groups such as phenolic hydroxy groups.

Recently, in the course of our studies on the development of new and efficient methods for highly regioselective direct C-arylation of azoles – including free (NH)-indole, -imidazole and -benzimidazole – with aryl halides[22] we found that $Pd(OAc)_2$- and CuI-mediated reactions between 1*H*-indole (**1a**) and aryl iodides **2** in DMF at 140 °C or in DMA at 160 °C under base-free and ligandless conditions selectively provided 2-aryl-1*H*-indoles **3a** in moderate yields (Scheme 1).[22c–22e]

More recently, in an attempt to improve this result by examining the role of $Pd(OAc)_2$ and the nature of the Cu^I salt in this arylation reaction, we developed a new and inex-

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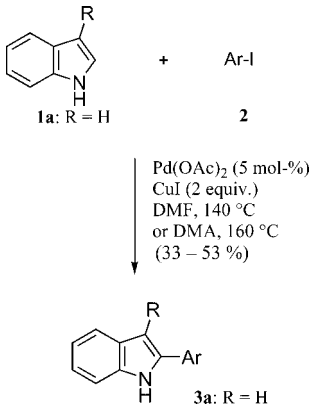
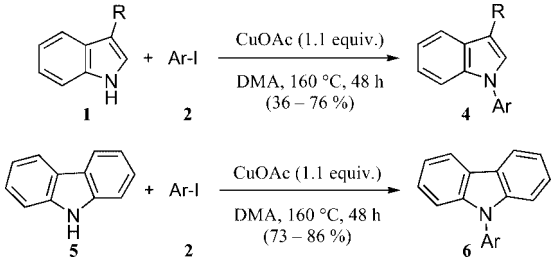


Scheme 1.

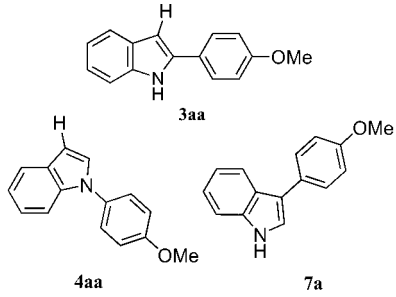
pensive version of the Ullmann reaction that allows the selective, efficient and functional group-tolerant *N*-arylation of 1*H*-indoles **1** and 9*H*-carbazole (**5**) with aryl iodides (Scheme 2).



Scheme 2.

Results and Discussion

This work was initiated by investigation of the role of $Pd(OAc)_2$ and the nature of the Cu^I salt on the Pd- and Cu-mediated arylation of 1*H*-indole (**1a**) with aryl iodides. We found that whereas treatment of **1a** with 2.0 equiv. of 4-iodoanisole (**2a**) in DMF at 140 °C for 48 h in the presence of 5 mol-% $Pd(OAc)_2$ and 2.0 equiv. of CuI produced the 2-aryl derivative **3aa** in 35% isolated yield (Table 1, Entry 1), an analogous reaction performed without use of CuI furnished a crude reaction mixture containing **3aa** and a small amount of 3-(4-methoxyphenyl)-1*H*-indole (**7a**). Chromatographic purification of this mixture allowed us to isolate **3aa** in 22% yield (Table 1, Entry 2). On the other hand, treatment of **1a** with **2a** without use of $Pd(OAc)_2$ but in the presence of 2.0 equiv. of CuI gave **3aa** in only 6% GLC yield (Table 1, Entry 3).



However, when low-grade CuOAc (97%) was used in place of CuI, the reaction between **1a** and **2a** in DMF at 140 °C under base-free and ligandless conditions occurred at position 1 in **1a** rather than at C-2, producing compound **4aa** cleanly and with complete selectivity in 52% isolated yield (Table 1, Entry 4). A very similar result was obtained when the reaction was performed in DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone] (Table 1, Entry 5).

After extensive experimentation, we found that a significant improvement in the yield of **4aa** could be obtained by performing the reaction in dry and deaerated DMA (*N*,*N*-dimethylacetamide) at 160 °C in the presence of 1.1 equiv. of CuOAc with use of a 1.5:1 molar ratio of **1a** and **2a** (Table 1, Entry 6). We also found that CuOAc was an optimal Cu^I source for this *N*-arylation and that the use of $(CuOTf)_2$·toluene or Cu_2O as sources of the oxygen-containing Cu^I derivative gave inferior results (Table 1, Entries 7 and 8).

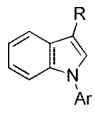
Encouraged by the promising result shown in Entry 6 in Table 1, we then applied the experimental conditions used in this entry to *N*-arylation reactions of 1*H*-indoles **1a**–**d** with aryl iodides **2a**–**f**. Compounds **1** included a particular derivative, indoxyl acetate (**1c**), never before successfully used in a Cu-catalysed *N*-arylation. On the other hand, iodides **2** included an electron-neutral derivative (**2b**) and compounds bearing either electron-withdrawing or electron-donating groups, as well as one derivative – 4-iodophenol (**2f**) – previously unsuccessfully used in an attempted Cu-catalysed *N*-arylation of 1*H*-indole reported in the literature.[17e]

Table 1. Regioselective *C*-2 or *N*-1 arylation of 1*H*-indole (**1a**) with 4-iodoanisole (**2a**).

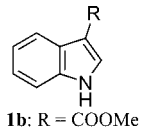
Entry[a]	$Pd(OAc)_2$ [mol-%]	CuX (equiv.)	**1a**/**2a** molar ratio	Solvent	Product	Yield (%)[c]
1	5	CuI (2.0)	0.5	DMF	**3aa**	35
2[b]	5	–	0.5	DMF	**3aa**	22
3	–	CuI (2.0)	0.5	DMF	**3aa**	(6)
4	–	CuOAc (2.0)	0.5	DMF	**4aa**	52
5	–	CuOAc (2.0)	0.5	DMPU	**4aa**	52
6	–	CuOAc (1.1)	1.5	DMA	**4aa**	70
7	–	$(CuOTf)_2$·toluene (1.0)	0.5	DMF	**4aa**	(37)
8	–	Cu_2O (0.55)	1.5	DMA	**4aa**	33

[a] The reactions were run at 140 °C, unless otherwise stated. [b] The crude reaction mixture was contaminated with a small amount of **7a**. [c] Isolated chemical yields. In parenthesis, GLC yield evaluated with naphthalene as an internal standard.

Table 2. *N*-Arylation of 1*H*-indoles **1** with aryl iodides **2**.

Entry[a]	**1**	**2**	1-Aryl-1*H*-indole derivative **4**			
				R	Ar	Isolated yield (%)
1	**1a**	**2b**	**4ab**	H	C_6H_5	76
2	**1a**	**2c**	**4ac**	H	4-$CF_3C_6H_4$	66
3	**1a**	**2d**	**4ad**	H	4-$NO_2C_6H_4$	63
4	**1a**	**2e**	**4ae**	H	3,4,5-$(MeO)_3C_6H_2$	36
5	**1a**	**2f**	**4af**	H	4-HOC_6H_4	49
6	**1b**	**2a**	**4ba**	COOMe	4-$MeOC_6H_4$	60
7	**1c**	**2a**	**4ca**	OCOMe	4-$MeOC_6H_4$	49
8	**1d**	**2a**	**4da**	CHO	4-$MeOC_6H_4$	54
9	**1d**	**2d**	**4dd**	CHO	4-$NO_2C_6H_4$	55

[a] The reactions were run in DMA at 160 °C for 48 h with 1.1 equiv. of 97% CuOAc and a 1.5:1 molar ratio between **1** and **2**.



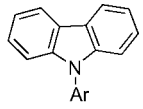
1b: R = COOMe
1c: R = OCOMe
1d: R = CHO

Ar–I

2b: Ar = C_6H_5
2c: Ar = 4-$CF_3C_6H_4$
2d: Ar = 4-$NO_2C_6H_4$
2e: Ar = 3,4,5-$(MeO)_3C_6H_2$
2f: Ar = 4-HOC_6H_4

As shown in Table 2, these couplings between aryl iodides **2** and 1*H*-indoles **1** afforded the required 1-aryl-1*H*-indoles in moderate to good yields. Table 2 also shows that the presence of electron-withdrawing or electron-donating groups at the 4-positions in the aryl iodides had no impact on the efficiencies of the arylation reactions. Moreover, a phenolic hydroxy group at the 4-position of the aryl iodide was well tolerated. In fact, the CuOAc-mediated reaction between **1a** and **2f** under base-free and ligandless conditions gave the required 1-aryl-1*H*-indole **4f** in 49% isolated yield (Table 2, Entry 5).

These satisfactory results induced us also to investigate the *N*-arylation of 9*H*-carbazole (**5**) with aryl iodides by a method very similar to that employed for the synthesis of 1-aryl-1*H*-indoles **4** and we were pleased to find that **5** was effectively coupled with iodides **2a** and **2d** in DMA at 160 °C for 48 h in the presence of 1.1 equiv. of CuOAc to give 9-aryl-9*H*-carbazoles **6a** and **6b** in 86 and 73% yields, respectively.



6a: Ar = 4-$MeOC_6H_4$
6b: Ar = 4-$NO_2C_6H_4$

With regard to the mechanism of these Cu-mediated *N*-arylation reactions, we speculated that it involves N–Cu^I derivatives resulting from reactions between CuOAc and the azoles **1** and **5** in the presence of DMA or DMF, which are solvents with mildly basic characteristics. The subsequent steps of this mechanism might be similar to those proposed by Cristeau et al.[17c] for a mechanistic pathway for Cu-catalysed *N*-arylations. In particular, they might involve oxidative addition of the aryl iodide to the N–Cu^I derivative, followed by reductive elimination. Uncertainty remains, however, since no mechanistic studies on Cu-catalysed *N*-arylation resulting in full elucidation of the catalytic pathway have been reported in the literature.[17c,17g,23] Moreover, the mechanistic pathway proposed above is not suitable to explain the fact that the CuOAc-mediated *N*-arylations of 1*H*-indoles and 9*H*-carbazole under base-free and ligandless conditions are reactions that require the use of stoichiometric amounts, rather than catalytic quantities, of CuOAc.

Conclusions

In summary, we have developed highly selective and efficient Cu-mediated C–N coupling reactions of 1*H*-indoles and 9*H*-carbazole with aryl iodides. This new and inexpensive version of the classical Ullmann reaction, which does not require the use of base or ligand, offers an unprecedented tolerance of functional groups both in the 1*H*-indoles and in the aryl iodides and works well with both electron-rich and electron-poor aryl iodides. Interestingly, the experimental conditions for this method facilitate the workup of the reaction mixtures and the isolation of the required chemically pure *N*-aryl derivatives. Because of these attributes, we believe that this method will find more general applications in organic synthesis.

Experimental Section

General Procedure for the Cu-Mediated Synthesis of *N*-Arylindoles 4: A 1*H*-indole derivative **1** or 9*H*-carbazole (**5**) (1.5 mmol), CuOAc (0.13 g, 1.1 mmol) and the aryl iodide **2** (1.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum and evacuated and backfilled with argon, and this sequence was repeated twice. Dearated DMA (5 mL) was then added by syringe at room temperature under a stream of argon and the mixture was stirred under argon at 160 °C for 48 h. After this period, the reaction – monitored by GLC and GLC-MS analyses of a sample of the crude reaction mixture after it had been treated with a saturated aqueous NH_4Cl solu-

tion and extracted with AcOEt – was complete. The reaction mixture was then allowed to cool to room temperature, diluted with AcOEt and poured into a saturated aqueous NH_4Cl solution, and the resulting mixture was stirred in the open air for 0.5 h and then extracted with toluene. The organic extract was washed with brine, dried, filtered through Celite® and concentrated under reduced pressure, and the residue was purified either by crystallization or by MPLC on silica gel. This procedure was employed to prepare 1-aryl-1*H*-indoles **4aa**–**4af**, **4ba**–**4da**, **4dd** and 9-aryl-9*H*-carbazoles **6a**–**b**.

1-(4-Methoxyphenyl)-1*H*-indole (4aa): The crude product obtained from the CuOAc-mediated reaction between 1*H*-indole (**1a**) and 4-iodoanisole (**2a**) (Table 1, Entry 6) was purified by MPLC on silica gel with a mixture of hexane and toluene (70:30) as eluent to give **4aa** (156 mg, 70%) as a colourless solid: m.p. 56–58 °C (ref.[24] m.p. 57–58 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.8 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.38 (m, 2 H), 7.26 (d, J = 3.2 Hz, 1 H), 7.19 (t, J = 6.5 Hz, 1 H), 7.14 (t, J = 6.5 Hz, 1 H), 7.01 (m, 2 H), 6.64 (dd, J = 3.0 and 0.6 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.2, 136.3, 132.8, 129.0, 128.3, 126.0 (2 C), 122.1, 121.0, 120.1, 114.7 (2 C), 110.3, 102.9, 55.6 ppm. EI-MS: *m*/*z* (%) = 224 (17) $[M + 1]^+$, 223 (100) $[M]^+$, 209 (11), 208 (71), 190 (7), 180 (19), 178 (10), 152 (17). GLC analysis proved a chemical purity higher than 99% for **4aa**. The spectroscopic data for this compound were in agreement with those previously reported.[25]

1-Phenyl-1*H*-indole (4ab): The crude product obtained from the CuOAc-mediated reaction between 1*H*-indole (**1a**) and phenyl iodide (**2b**) (Table 2, Entry 1) was purified by MPLC on silica gel with a mixture of hexane and toluene (95:5) as eluent to give **4ab** (147 mg, 76%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (m, 1 H), 7.57 (m, 1 H), 7.51 (m, 3 H), 7.38 (m, 2 H), 7.35 (m, 2 H), 7.20 (m, 3 H), 7.01 (m, 2 H), 6.68 (dd, J = 3.2 and 0.8 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.8, 135.9, 129.6 (2 C), 129.3, 127.9, 126.4, 124.4, 122.3, 121.1, 120.3, 110.5, 106.3 ppm. EI-MS: *m*/*z* (%) = 194 (15) $[M + 1]^+$, 193 (100) $[M]^+$, 192 (16) $[M - 1]^+$, 191 (8), 165 (20), 96 (5), 90 (6), 89 (8). GLC analysis showed that **4ab** had chemical purity higher than 98%. The spectroscopic data for this compound were in agreement with those previously reported.[17c]

4-(1*H*-Indol-1-yl)phenol (4af): The crude product obtained from the CuOAc-mediated reaction between 1*H*-indole (**1a**) and 4-iodophenol (**2f**) (Table 2, Entry 5) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **4af** (102 mg, 49%) as an orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68 (dd, J = 7.0 and 3.2 Hz, 1 H), 7.44 (m, 1 H), 7.32 (m, 2 H), 7.25 (d, J = 3.1 Hz, 1 H), 7.18 (m, 2 H), 6.91 (m, 2 H), 6.64 (d, J = 3.1 Hz, 1 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 154.2, 136.3, 132.9, 128.9, 128.3, 126.2 (2 C), 122.2, 121.0, 120.1, 116.2 (2 C), 110.4, 102.9 ppm. EI-MS: *m*/*z* (%) = 210 (16) $[M + 1]^+$, 209 (100) $[M]^+$, 208 (15) $[M - 1]^+$, 181 (14), 180 (13), 152 (8), 89 (6). $C_{14}H_{11}NO$ (209.25): calcd. C 80.36, H 5.30; found: C 80.29, H 5.19%. GLC analysis proved a chemical purity higher than 99% for **4af**.

9-(4-Methoxyphenyl)-9*H*-carbazole (6a): The crude product obtained from the CuOAc-mediated reaction between 9*H*-carbazole (**9**) and 4-iodoanisole (**2a**) was purified by MPLC on silica gel with a mixture of toluene and petroleum ether (30:70) as eluent to give **6a** (235 mg, 80%) as a colourless solid: m.p. 150–152 °C (ref.[21] m.p. 147–149 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.14 (dd, J = 7.7 and 0.7 Hz, 2 H), 7.46 (m, 2 H), 7.41 (m, 2 H), 7.30 (m, 4 H), 7.10 (m, 2 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 158.9, 141.4 (2 C), 130.3, 128.6 (2 C), 125.8 (2 C), 123.1 (2 C), 120.2 (2 C), 119.6 (2 C), 115.1 (2 C), 109.7 (2 C), 55.6 ppm. EI-MS: *m*/*z* (%) = 274 (20) $[M + 1]^+$, 273 (100) $[M]^+$, 259 (10), 258 (50), 230 (13), 228 (22), 202 (7). GLC analysis proved a chemical purity higher than 99% for **6a**.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and characterization for compounds **4ac**–**ae**, **4ba**–**da**, **4dd** and **6b**.

Acknowledgments

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