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Palladium- and Copper-Mediated Direct C-2 Arylation of Azoles − Including Free (NH)-Imidazole, -Benzimidazole and -Indole − Under Base-Free and Ligandless Conditions

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The first palladium- and copper-mediated C-2 arylations of thiazole, oxazole, *N*-methylimidazole and *N*-arylimidazoles, as well as of free (NH)-imidazole, -benzimidazole and -indole, with aryl iodides under ligandless and base-free conditions are described. Complete selectivity has been achieved under these unprecedented conditions, which allow the use of substrates containing base-sensitive groups, such the NH groups of imidazole, benzimidazole or indole, without their prior protection. No *N*-arylation products were detected in the arylation of free (NH)-imidazole, -benzimidazole and -indole.

Introduction

The π-electron-sufficient heteroarenes oxazoles, thiazoles, imidazoles and benzimidazoles are important structural units frequently found in natural products,[1] pharmacologically active substances,[2] agrochemicals,[3] compounds used to treat endoparasitic diseases of domestic animals[4] and organic functional materials such as liquid crystals and fluorescent dyes.[5] The complicated structures and biological importance of some of these heterocyclic derivatives have provided a challenge to modern synthetic methodology, and in the last fifteen years the direct functionalization of C–H bonds of five-membered heterocycles through selective transition metal-catalysed *C*-arylation with aryl halides has been developed as a very attractive and practical synthetic methodology.[6–10] In fact, it appears to have a synthetically significant advantage, being able to effect C–C bond formation without the need for preactivation of the heterocycles by halogenation or stoichiometric metallation reactions.

In the course of our investigations into the synthesis of biologically active vicinal diaryl-substituted five-membered heterocyclic derivatives[11] we recently developed a selective and efficient procedure for the preparation of a large variety of 1,2-diaryl-1*H*-imidazoles through direct coupling between 1-aryl-1*H*-imidazoles and aryl halides in the presence of CuI and of CsF and a catalytic amount of $Pd(OAc)_2$ in DMF at 140 °C under ligandless conditions.[9b] This work encouraged us to investigate more deeply the most suitable reaction conditions under which to perform direct Pd- and Cu-mediated C-2 arylation of 1-aryl-1*H*-imidazole and other azoles, together with their mechanisms. Here we report that π-electron-sufficient heteroarenes such as oxazole, thiazole, 1-aryl-1*H*-imidazoles and 1-methyl-1*H*-imidazole, as well as free (NH)-imidazole, -benzimidazole and -indole, can be effectively transformed in highly selective Pd- and Cu-mediated C-2 arylation under base-free and ligandless conditions.[12] These experimental conditions are very different from those employed so far for performing the transition metal-catalysed arylation of π-excessive or π-sufficient heteroarenes, which invariably involve the use of a base.[6–10] Moreover, these unprecedented conditions allow the use of substrates containing base-sensitive groups – such as the NH groups in imidazole, benzimidazole and indole – without their prior protection.

Results and Discussion

We first examined the reaction between 1-phenyl-1*H*-imidazole (**1a**) and 4-iodoanisole (**2a**) in DMF at 140 °C in the presence of 5 mol-% $Pd(OAc)_2$ and 2 equiv. of CuI and found that after 26 h the reaction was complete and had cleanly and selectively given the required imidazole **3a** in 76% isolated yield [Equation (1)].

Interestingly, the crude reaction mixture did not contain the biaryl derivative that would have resulted from homocoupling of **2a** or the triaryl derivative that would have derived from the C-2 and C-5 arylation of **1a**. In contrast, these substances were found in the crude mixture obtained from the reaction between **1a** and **2a** in DMF at 140 °C in

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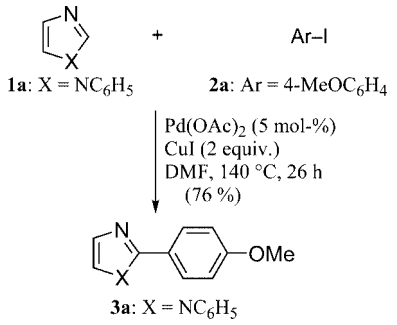
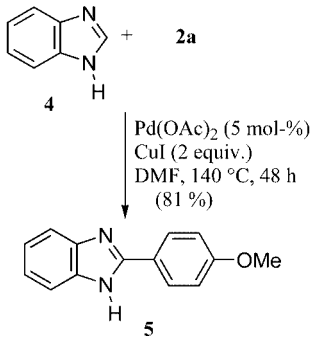
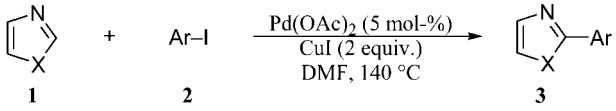


(1)



(2)

Table 1. Highly selective Pd- and Cu-mediated C-2 arylation of some π-sufficient heteroarenes including free (NH)-imidazole.



Entry[a]	Reagents		Reaction time	Product	Isolated yield
	1	**2**	(h)	**3**	(%)
1	**1b** (X = 4-$MeOC_6H_4N$)	**2a**	48	**3b**	66
2	**1c** (X = 4-$MeO_2SC_6H_4N$)	**2a**	25	**3c**	84
3	**1d** (X = NMe)	**2a**	48	**3d**	99
4	**1e** (X = NH)	**2a**	48	**3e**	53
5	**1e**	**2b** (Ar = C_6H_5)	48	**3f**	89
6	**1e**	**2c** (Ar = 4-$CF_3C_6H_4$)	48	**3g**	84
7	**1e**	**2d** (Ar = 2-MeC_6H_4)	48	**3h**	47
8	**1f** (X = S)	**2a**	48	**3i**	84
9	**1 g** (X = O)	**2a**	48	**3j**	23

[a] Conditions: 2 equiv. of ArI were used.

the presence of 2 equiv. of CuI, 2 equiv. of CsF and 5 mol-% $Pd(OAc)_2$.[9b] It should also be noted that when we attempted to reduce the amount of CuI from 2 equiv. to 0.5 equiv. we found that the reaction time was much longer (126 h) and that compound **3a** was obtained in a lower yield (49%).

The good result obtained in the preparation of **3a** from **1a** and **2a** under the experimental conditions reported in Equation (1) prompted us to extend this new procedure to the selective preparation of other C-2 aryl-substituted azoles, including free (NH)-imidazoles and -benzimidazole.

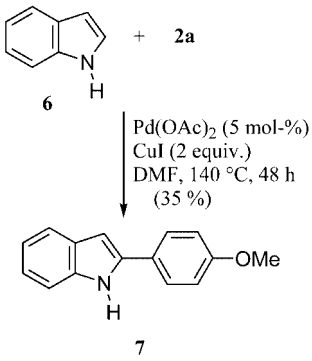
Table 1 and Equation (2) summarize the results obtained in these highly chemo- and regioselective reactions, which generally gave the required 2-arylheteroarenes in high yields. Notably, the reactions were very clean; in fact, the crude reaction mixtures contained no regioisomers of these heterocycle derivatives[13] and, in the cases of free (NH)-imidazole and -benzimidazole, were also free of *N*-aryl derivatives. Moreover, they were also uncontaminated with the biaryls that would have derived from Pd-catalysed Ullmann-type reductive couplings of aryl iodides **2**, which, on the contrary, were present in the reaction mixtures obtained from the Pd- and Cu-mediated reactions between 1-aryl-1*H*-imidazoles **1a**–**c** and aryl halides in the presence of CsF under ligandless conditions.[9b]

On the other hand, the use of ligandless conditions prevented the formation of byproducts that might have resulted from scrambling of the aryl moieties of iodides **2** with the organic groups of the ligands, which had been found in the crude reaction mixtures obtained from the Pd-catalysed arylation of 1-aryl-1*H*-imidazoles in the presence of triarylphosphanes.[9a]

Our method thus also allowed the selective targeting of C–H bonds in the presence of free N–H functionalities [Eq. (2) and Entries 4–7, Table 1] and furnished 2-aryl-1*H*-imidazoles and 2-(4-methoxyphenyl)benzimidazole (**5**) in good to excellent yields without the need for the use of a base such as MgO, which, according to Sezen and Sames,[8d] appeared to be necessary in order to perform the selective C-2 arylation of free (NH)-imidazole and -benzimidazole. Interestingly, compound **3f** was obtained in a yield higher than that reported by Sezen and Sames for the arylation of **1e** in the presence of MgO.[8d] On the other hand, we were unable to reproduce the results of these authors and we did not obtain any trace of **3f** under the exact reaction conditions reported for its preparation [i.e., by treatment of **1e** with 1.2 equiv. of iodobenzene (**2b**) in dioxane at 150 °C for 14 h in the presence of 5 mol-% $Pd(OAc)_2$, 20 mol-% PPh_3, 1.2 equiv. of MgO and 2 equiv. of CuI].[8d,14]

Our results, besides being important from a synthetic point of view, have an important implication in the context of the mechanism of the Pd- and Cu-mediated arylation of π-sufficient heteroarenes. In fact, although this mechanism

still has to be clarified, the results reported in Table 1 indicate that it might require the presence and participation of a basic pyridine-like nitrogen atom in these heterocycles and/or of a solvent such as DMF with mildly basic characteristics,[15] since the Pd- and Cu-mediated C-2 arylation of compounds **1** did not occur when toluene was used in place of DMF. On the other hand, the presence of a basic pyridine-like nitrogen atom in the heterocyclic substrates was unnecessary. In fact, in a preliminary experiment we found that indole (**6**) is able to react with iodide **2a** in DMF at 140 °C over 48 h in the presence of 5 mol-% $Pd(OAc)_2$ and 2 equiv. of CuI to furnish 2-(4-methoxyphenyl)-1*H*-indole in 35% isolated yield [Equation (3)].[16]



(3)

In our opinion, the mechanism of the C-2 arylation of azoles **1**, **4** and **6**, as we recently reported,[9b] might involve the formation of an organocopper(I) derivative followed by a transmetallation reaction with a heteroarylpalladium(II) halide species and a reductive elimination. On the other hand, coordination of heterocycles **1** to CuI to form π complexes might significantly lower the pK_a of their C–H bonds at position 2 and facilitate their conversion into C–Cu bonds.[17] However, we cannot at present exclude a reaction mechanism involving the presence of organopalladium(II) and organopalladium(IV) species and organocopper(I) derivatives.[18]

Conclusion

A reliable new method for the direct and regioselective C-2 arylation of azoles has been developed. The unprecedented reaction conditions for this procedure, which do not involve the use of a base, can also be employed for the arylation of substrates containing base-sensitive groups, such as the NH groups in imidazole, benzimidazole and indole, without their prior protection.

The results of this study also include the observation that the Pd- and Cu-mediated arylation, under base-free conditions, of azoles that do not contain a basic pyridine-like nitrogen atom requires the use of a solvent with mildly basic characteristics. Applications of this method to the synthesis of pharmacologically significant compounds are in development.

Experimental Section

General Procedure for the Pd- and Cu-Mediated Synthesis of 2-Aryl-1*H*-imidazoles 3 and the 2-Arylbenzimidazole 5 from Aryl Iodides 2 and Compounds 1 and 4, respectively: Compound **1** or **4** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CuI (0.38 g, 2.0 mmol), and (if a solid) the aryl iodide **2** (2.0 mmol) were placed in the reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated twice. Deaerated DMF (5 mL) and (if a liquid) the aryl iodide **2** (2.0 mmol) were then added successively by syringe under a stream of argon at room temperature. The resulting mixture was stirred at 140 °C under argon for the period of time reported in Table 1 and Equations 1–2. The degree of completion of the reaction was established by GLC and GLC-MS analysis of a sample of the crude reaction mixture after treatment with a saturated aqueous NH_4Cl solution and extraction with AcOEt. After being cooled to room temperature, the reaction mixture was 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 AcOEt. The organic extract was washed with water, dried and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel. The chromatographic fractions containing the required compound were collected and concentrated. This procedure was employed to prepare 2-aryl-1*H*-imidazoles **3a**–**j** [Eq. (1) and Table 1, Entries 1–9] and 2-(4-methoxyphenyl)benzimidazole (**5**) [Eq. (2)].

It should be noted that the structural identities of compounds **3a**–**c** [Eq. (1) and Entries 1–2 of Table 1], which each had chemical purity higher than 99%, were confirmed by comparison of their GLC and GLC-MS data with those of authentic samples of these compounds obtained by Pd- and Cu-mediated C-2 arylation of the corresponding 1-aryl-1*H*-imidazoles **1a**–**c** with aryl iodide **2a**.[9b]

2-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole (3d): The crude reaction product obtained from the Pd- and Cu-mediated reaction between **1d** and **2a** (Table 1, Entry 3) was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **3d** (186 mg, 99%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (m, 2 H), 7.08 (d, J = 1.0 Hz, 1 H), 6.97 (m, 2 H), 6.92 (d, J = 1.0 Hz, 1 H), 3.83 (s, 3 H), 3.69 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.9, 147.8, 130.0 (2 C), 128.1, 123.2, 122.0, 113.9 (2 C), 55.3, 34.4. GLC analysis showed that **3d** had chemical purity higher than 98%. The spectroscopic data of this compound were in agreement with those previously reported.[19]

2-(4-Methoxyphenyl)-1*H*-indole (7): Indole (**6**, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), CuI (0.38 g, 2.0 mmol) and 4-iodoanisole (**2a**, 2.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated twice. Deaerated DMF (5 mL) was then added by syringe at room temperature under a stream of argon and the mixture was stirred under argon at 140 °C. The reaction was monitored by GLC and GLC-MS analyses of a sample of the crude reaction mixture after treatment with a saturated aqueous NH_4Cl solution and extraction with AcOEt. After 48 h at 140 °C the degree of conversion of the reaction was 72%. The reaction mixture was then cooled 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 AcOEt. The organic extract was washed with water, dried and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel with a mixture of toluene and hexane (60:40) as eluent to give **7** (78 mg, 35%) as a pale yellow solid: m.p. 224–227 °C. ^{1}H NMR

(300 MHz, [D_6]DMSO): δ = 11.43 (s, 1 H), 7.80 (m, 2 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.38 (d, J = 7.9 Hz, 1 H), 7.03 (m, 4 H), 6.76 (d, J = 1.7 Hz, 1 H), 3.80 ppm (s, 3 H). ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 158.7, 137.7, 136.8, 128.8, 126.3 (2C), 124.8, 121.0, 119.6, 119.1, 114.3 (2 C), 111.0, 97.2, 55.1 ppm. GLC analysis showed that **7** had chemical purity higher than 98%. The spectroscopic data of this compound were in agreement with those previously reported.[20]

The characterization of compounds **3e**, **3g**–**j**, and **5** prepared in this study can be found in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Experimental procedures for and characterization of compounds **3e**, **3g**, **3h**, **3i**, **3j** and **5**. This material is available free of charge via the Internet at "http://www.eurjoc.org" or from the author.

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