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Synthesis of 1-aryl-substituted-4-chloroimidazo[1,2-*a*]quinoxalines catalyzed by $PdCl_2$ in water

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ABSTRACT

The reaction of 2-chloro-3-propargylaminoquinoxaline with various aryl iodides and bromides catalyzed by Pd–Cu in the presence of potassium carbonate as the base in water leads to the one-pot formation of 1-aryl-substituted-4-chloroimidazo[1,2-*a*]quinoxalines in moderate-to-high yields.

The quinoxaline nucleus is present in many pharmaceutical agents exhibiting a broad spectrum of biological activities such as antitumor,[1] antiviral,[2] antiglaucoma,[3] antituberculosis,[4] antiinflammatory,[5] and anticancer.[6] Furthermore, imidazo[1,2-*a*]quinoxaline derivatives have been shown to have antitumor activity[7] and act as adenosine A1 receptor antagonists.[8] Although several procedures have been developed for the synthesis of imidazo[1,2-*a*]quinoxalines,[9] no examples involving the arylation of imidazoquinoxaline via Pd–Cu catalyzed (Sonogashira coupling) reactions have been reported in the literature.

The Sonogashira reaction catalyzed by palladium and copper is a powerful and straightforward method for the construction of arylated internal alkynes.[10] These are important intermediates in organic synthesis, and for the preparation of natural products,[11] biologically active molecules,[12] molecular electronics,[13] and polymers.[14]

The original Sonogashira reaction was generally performed in the presence of palladium and copper(I) iodide as a co-catalyst in organic solvents, which are harmful to the environment. In most catalytic processes, organic solvents are usually employed as the reaction media, often creating safety, health, and environmental issues due to their flammability, toxicity, and volatility. From an economic and environmental standpoint, it is desirable to avoid the use of hazardous and expensive organic solvents. The use of water as a reaction medium demonstrates useful benefits since this solvent is highly polar and therefore immiscible with most organic compounds. Thus water-soluble by-products remain and separation of the organic materials is simple. Several examples of Pd-catalyzed Sonogashira reactions in aqueous medium have been reported.[15]

Continuing our efforts directed toward the straightforward preparation of biologically active target molecules through Sonogashira coupling reactions,[16] we performed the synthesis of new derivatives of imidazo[1,2-*a*]quinoxaline via Pd–Cu catalyzed Sonogashira coupling in water.

Treatment of 2,3-dichloroquinoxaline (**1**) with propargylamine in refluxing 1,4-dioxane gave 2-chloro-3-propargylamino quinoxaline (**2**) in an 88% yield. The ^{1}H NMR spectrum of **2** showed the presence of a CH proton at 2.15 ppm, CH_2 protons at 4.25 ppm, and a single resonance for the NH group at 7.50 ppm that disappeared on deuteration.

When compound **2** was treated with aryl halides **3a–g** and K_2CO_3 in water in the presence of palladium chloride, triphenylphosphine, and copper iodide at 70 °C, 1-aryl-substituted-4-chloroimidazo[1,2-*a*]quinoxalines **4a–g** were obtained in moderate-to-high yields (Scheme 1, Table 1). The reactions were carried out under an argon atmosphere, and the water was degassed prior to use.

The ^{1}H NMR spectrum of product **4a** exhibited an aromatic singlet at 8.02 ppm, which is characteristic of a fused imidazole ring. The other eight aromatic protons appeared at 7.15–8.12 ppm. In the aliphatic region, the singlet proton at 5.10 ppm was due to the benzylic protons.

As shown in Table 1, compound **2** reacted with various aryl iodides such as *p*-nitroiodobenzene, 4-chloro-2-nitroiodobenzene, and 2-chloro-4-nitroiodobenzene delivering the corresponding products in high yields (entries 2–4). Unsurprisingly, 4-chloro-2-nitroiodobenzene (entry 3) was found to be the most reactive

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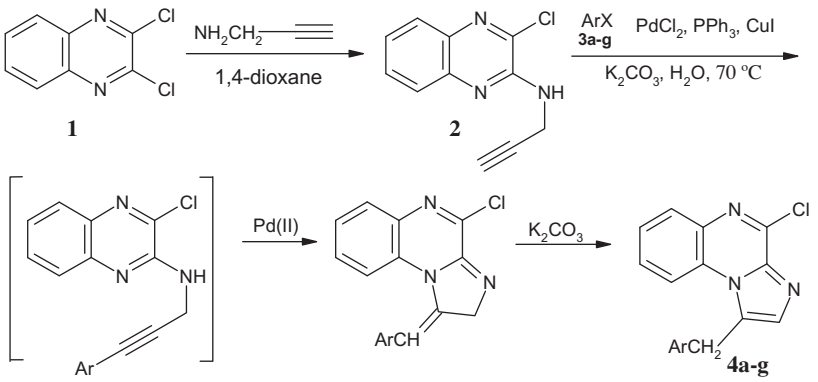
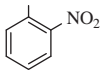
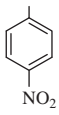
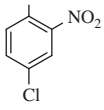
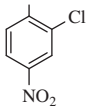
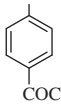
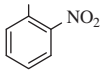
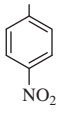
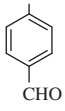
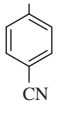


Scheme 1. A plausible mechanism for the formation of 1-aryl-substituted-4-chloroimidazo[1,2-*a*]quinoxalines **4**.

Table 1
Melting points and yields of 1-aryl-substituted-4-chloroimidazo[1,2-*a*]quinoxalines **4a–g**[a]

Entry	X	Ar	Product	Mp (°C)	Yield[b] (%)
1	I		**4a**	220–222	87
2	I		**4b**	211–213	91
3	I		**4c**	250–252	95
4	I		**4d**	240–242	92
5	I		**4e**	216–218	82
6	Br		**4a**	220–222	66
7	Br		**4b**	211–213	68
8	Br		**4f**	230–232	75
9	Br		**4g**	228–230	72

[a] Reaction and conditions: **2** (1.20 mmol), **3a–g** (1.0 mmol), K_2CO_3 (2 mmol), $PdCl_2$ (0.05 mmol), PPh_3 (0.1 mmol), CuI (0.1 mmol), H_2O (5 mL), 70 °C, 12 h.
[b] Isolated yield.

among the aryl halides studied. The reaction of aryl bromides such as *o*-nitrobromobenzene, *p*-nitrobromobenzene, *p*-bromobenzaldehyde, and *p*-bromobenzonitrile with compound **2** gave the corresponding products in moderate yields (entries 6–9). As expected, aryl iodides with electron-withdrawing groups reacted more efficiently than the aryl bromides possessing electron-withdrawing groups to give the desired products in high yields. The presence of electron-withdrawing groups such as $-NO_2$, –CN, –CHO, and –Cl on the aryl halides was essential for a successful reaction. When *p*-iodoanisole or iodobenzene was used as the aryl halide, only a small amount of product was isolated after column chromatography.

It was found that while Pd/C, $PdCl_2(PPh_3)_2$, $PdCl_2/PPh_3$, and $PdCl_2$ all catalyzed the reaction without the aid of any surfactant, $PdCl_2/PPh_3$ proved to be the best catalyst in terms of yields. Although $PdCl_2/PPh_3$ was the catalyst of choice, the addition of copper(I) iodide as a co-catalyst was essential. The reactions carried out with $PdCl_2$ alone led to poor yields of mixtures of products. Among the bases tested, potassium carbonate was found to be the most suitable giving cleaner products and better yields. Unsatisfactory results were obtained with organic bases such as Et_3N, DIEA, pyridine and piperidine.

A plausible two-step mechanism is suggested for the reaction (Scheme 1). First a standard Sonogashira coupling takes place followed by Pd(II)-catalyzed intermolecular cyclization of the nucleophilic nitrogen on the triple bond, and finally base-induced aromatization to afford the product **4**.[17]

In conclusion, we have described a successful synthesis of 1-aryl-substituted-4-chloroimidazo[1,2-*a*]quinoxalines via a $PdCl_2$-mediated Sonogashira coupling reaction in water. Since water-based syntheses are safer and environmentally friendly, the method described may hold promise in organic synthesis.

2-Chloro-3-propargylaminoquinoxaline (2)

A mixture of 1,2-dichloroquinoxaline (1.99 g, 10 mmol) and propargylamine (1.2 mL, 20 mmol) in 1,4-dioxane (10 mL) was heated under reflux for 4 h. The resulting precipitate was filtered and recrystallized from EtOH to afford the title compound in an 88% yield, mp 80–82 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.15 (t, J = 4.0 Hz, 1H), 4.25 (d, J = 4.0 Hz, 2H), 7.50 (s, 1H), 7.70–7.85 (m, 4H), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.23, 70.12, 75.23, 125.14, 129.89, 134.48, 140.56, 160.78; IR, υ (KBr): 3300, 3100, 2230 cm^{-1}; HRMS (ESI): 216.0361.

1-Aryl-substituted-4-chloroimidazo[1,2-*a*]quinoxalines (4a–g)

A mixture of aryl halide (1.0 mmol), $PdCl_2$ (0.05 mmol), PPh_3 (0.10 mmol), CuI (0.1 mmol) and K_2CO_3 (2.0 mmol) was stirred in H_2O (5 mL) at room temperature under an argon atmosphere. 2-Chloro-3-propargylaminoquinoxaline (**2**) (1.20 mmol) was added, and the mixture stirred at 70 °C for 12 h. After completion of the reaction, the resulting solution was concentrated in vacuo, and the crude residue subjected to column chromatography (silica

gel) using $CHCl_3$–CH_3OH (98:2) as an eluent to afford the pure product (Table 1).

4a: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.10 (s, 2H, CH_2), 7.15–7.21 (m, 2H), 7.42 (s, 1H), 7.45–7.53 (m, 3H), 8.02 (s, 1H), 8.05–8.12 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.20, 115.29, 125.76, 127.04, 128.57, 128.93, 130.36, 131.13, 131.44, 134.11, 135.32, 135.74, 137.38, 143.68, 148.61; IR, υ (KBr): 1540, 1350 cm^{-1}; HRMS (ESI): 338.0542.

4b: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.05 (s, 2H), 7.20–7.32 (m, 4H), 7.42–7.50 (m, 3H), 7.62–7.65 (m, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.75, 115.74, 120.08, 125.82, 127.32, 128.43, 128.92, 130.10, 131.25, 131.85, 134.15, 135.05, 135.60, 137.28, 143.60, 148.52; IR, υ (KBr): 1520, 1340 cm^{-1}; HRMS (ESI): 338.0538.

4c: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.10 (s, 2H), 7.10–7.20 (m, 3H), 7.42–7.52 (m, 3H), 7.95–7.98 (m, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.75, 115.07, 125.90, 127.13, 128.16, 128.49, 129.01, 129.96, 130.47, 132.26, 134.16, 134.81, 135.40, 137.54, 143.83, 148.84; IR, υ (KBr): 1520, 1330 cm^{-1}; HRMS (ESI): 372.0205.

4d: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.03 (s, 2H), 7.40 (d, J = 8.4, 1H), 7.46–7.53 (m, 2H), 7.65–7.73 (m, 3H), 8.40–8.46 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.25, 115.32, 125.70, 126.92, 127.88, 128.23, 129.22, 129.69, 130.32, 132.42, 134.16, 134.72, 135.30, 137.45, 143.90, 148.73; IR, υ (KBr): 1550, 1330 cm^{-1}; HRMS (ESI): 372.0152.

4e: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.65 (s, 3H), 4.89 (s, 2H), 7.11–7.17 (m, 2H), 7.64–7.74 (m, 4H), 8.04–8.10 (m, 2H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.52, 31.28, 115.30, 125.95, 126.80, 127.35, 128.35, 129.42, 129.75, 130.23, 131.55, 132.27, 134.56, 140.74, 143.65, 148.37, 198.34; IR, υ (KBr): 1690 cm^{-1}; HRMS (ESI): 335.0852.

4f: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.27 (s, 2H), 7.35–7.42 (m, 3H), 7.52–7.58 (m, 2H), 7.75–7.78 (m, 1H), 7.80–7.87 (m, 2H), 8.20 (s, 1H), 10.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.69, 115.12, 125.26, 127.35, 128.21, 128.38, 129.13, 129.54, 130.27, 130.79, 132.48, 137.65, 143.25, 148.42, 190.85; IR, υ (KBr): 1710 cm^{-1}; HRMS (ESI): 321.0635.

4g: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.25 (s, 2H), 7.40–7.50 (m, 3H), 7.57–7.63 (m, 2H), 7.76–7.85 (m, 3H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.87, 108.25, 115.25, 115.95, 128.26, 128.83, 129.16, 129.47, 130.68, 131.26, 132.20, 133.35, 133.58, 143.84, 145.28; IR, υ (KBr): 2200 cm^{-1}; HRMS (ESI): 318.0698.

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