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Pd–Cu catalyzed heterocyclization during Sonogashira coupling: synthesis of 2-benzylimidazo[1,2-*a*]pyridine

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Abstract

The reaction of 2-amino-1-(2-propynyl)pyridinium bromide with various iodobenzenes, catalyzed by Pd–Cu, leads to the formation of 2-benzylimidazo[1,2-*a*]pyridines.

Keywords: Sonogashira coupling; Aryl iodide; Imidazole; Pd-catalyzed; Imidazopyridines

Imidazopyridine derivatives are of wide interest because of their diverse biological activities and clinical applications.[1] Their core ring system is present in numerous antivirial,[2] antiprotozoal[3] and antiherpes[4] drugs.

Although several procedures have been developed for the synthesis of imidazo[1,2-*a*]pyridines,[5] no examples involving arylation of imidazopyridine by Pd–Cu catalyzed (Sonogashira coupling) reactions have been reported in the literature.

The Sonogashira reaction, that is, the palladium and copper co-catalyzed coupling of terminal alkynes with aryl and vinyl halides, is one of the most widely used C–C bond forming reactions.[6,7] It provides an efficient route to aryl alkynes, which are interesting intermediates for the preparation of a variety of target compounds with applications ranging from natural products[8] and pharmaceuticals[9] to molecular organic materials.[10] Due to the utility of the products, the development of new catalyst systems has received considerable attention.

Palladium catalyzed reactions[11] have been immensely practical for both carboannulation[12] and heteroannulation[13] processes. In continuation of our recent studies[14] on the synthesis of fused heterocycles and the Pd-catalyzed reaction of acetylenes leading to heterocyclic compounds of biological significance, we became interested in developing a synthetic route to substituted imidazo[1,2-*a*]pyridines.

In this Letter, we report that the treatment of 2-aminopyridine **1** with propargyl bromide in refluxing ethanol affords 2-amino-1-(2-propynyl)pyridinium bromide **2** in good yield.

The ^{1}H NMR spectrum of **2** showed a CH proton at 3.85 ppm, CH_2 protons at 5.12 ppm and a single resonance for the NH_2 group at 8.72 ppm; this signal was removed on deuteration.

When compound **2** was treated in DMF with the aryl halides **3a–i** and triethylamine in the presence of bis(triphenylphosphine)palladium chloride(II) and copper iodide at room temperature, the 2-substituted imidazo[1,2-*a*]pyridines **4a–i** were obtained in good to high yields (Scheme 1, Table 1).

The reactions had to be carried out under an argon atmosphere, and the mixture of DMF and triethylamine had to be degassed prior to use.

A possible two step mechanism for the reaction is illustrated in Scheme 1. First a standard Sonogashira coupling, then a known Pd(II) catalyzed intermolecular cyclization of a nucleophilic nitrogen moiety with the triple bond, and finally base induced aromatization could give product **4**.[15]

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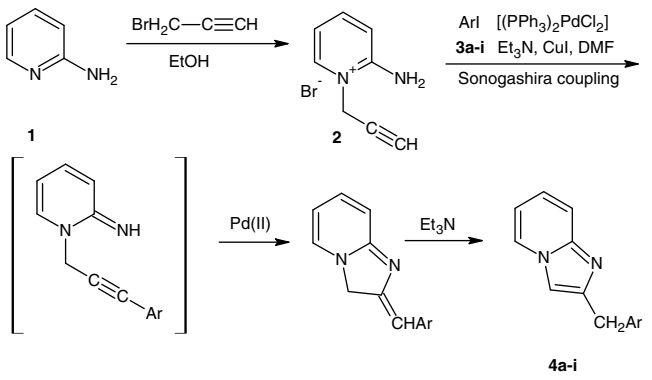


Scheme 1.

However, other mechanisms for this reaction are also plausible, for example, cyclization via initial generation of the exocyclic olefin followed by an intermolecular Heck reaction, which would provide a facile pathway for the migration of the double bond into the endocyclic position,[16] or alternatively a 5-*exo*-dig cyclization may be triggered simply by the formation of an Ar–Pd(II) species followed by reduction, elimination and isomerization. This type of cyclization has been observed for acetylenic lactams.[17]

The presence of electron withdrawing groups such as NO_2, Cl and CN on the aryl iodide seems to be essential. When *p*-iodoanisole was used as the aryl iodide, Sonogashira coupling could not be achieved.

It is also noteworthy that in the case of iodobenzene as the aryl iodide, the cyclization occurred without the involvement of the aryl iodide. The product of this reaction was identified as 2-methylimidazo[1,2-*a*]pyridine **5** (Scheme 2).

In conclusion, we have developed a successful palladium catalyzed reaction for the synthesis of 2-arylsubstituted imidazo[1,2-*a*]pyridines from the readily available starting materials.

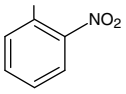
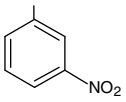
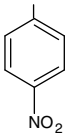
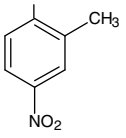
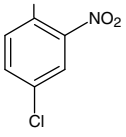
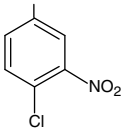
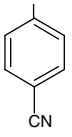
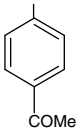
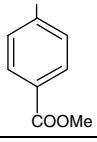
1. Synthesis of 2-amino-1-(2-propynyl)pyridinium bromide 2

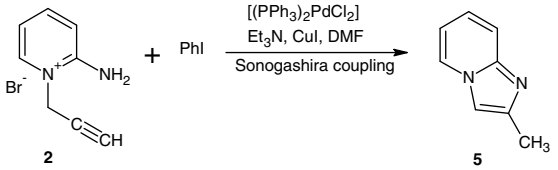
A mixture of 2-aminopyridine (1.9 g, 20 mmol) and propargyl bromide (2 mL, 24 mmol) in ethanol (10 mL) was heated under reflux for 1 h. The precipitate formed was filtered off and recrystallized from ethanol to afford the title compound. Yield, 80%; mp 168–169 °C; ^{1}H NMR δ (500 MHz, DMSO-d_6): 3.85 (s, 1H, CH), 5.12 (s, 2H, CH_2), 6.85–8.23 (m, 4H, PyH), 8.72 (s, 2H, NH_2); ^{13}C NMR δ (125 MHz, DMSO-d_6): 43.86, 76.04, 80.46, 114.00, 115.84, 139.83, 143.57, 154.52; IR, ν (KBr disc): 3300, 3200, 2100 cm^{-1}, MS: m/z, 212. Anal. Calcd for $C_8H_9BrN_2$: C, 45.09; H, 4.26; N, 13.15. Found: C, 45.50; H, 4.08; N, 13.51.

2. Syntheses of 2-substituted imidazo [2,1-*a*]pyridines 4a–i

A mixture of the aryl iodide (0.75 mmol), $(PPh_3)_2PdCl_2$ (0.05 mmol), CuI (0.1 mmol) and triethylamine (3 mmol) was stirred in DMF (5 mL) at room temperature under an argon atmosphere. 2-Amino-1-(2-propynyl)pyridinium bromide (1.27 mmol) was then added and the mixture was stirred at room temperature for 16 h. After completion of the reaction, the resulting solution was concentrated in

Table 1
Melting points and yields of 2-benzylimidazo[1,2-*a*]pyridines **4a–i**

Product	Ar	Mp (°C)	Yield (%)
4a		250–251	78
4b		294–295	76
4c		256–257	85
4d		263–264	92
4e		231–232	69
4f		246–247	66
4g		210–211	80
4h		236–237	75
4i		260–261	82



Scheme 2.

vacuo and the crude product was subjected to silica gel column chromatography using $CHCl_3$–CH_3OH (95:5) as eluent to afford the pure product (Table 1).

Compound **4a:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.46 (s, 2H, CH_2), 6.98–8.00 (m, 8H, PyH, ArH), 8.66 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.25, 114.60, 116.24, 122.85, 123.15, 129.10, 130.22, 130.95, 132.15, 134.27, 136.23, 139.12, 146.25, 148.33; IR, ν (KBr disc): 1510, 1340 cm^{-1}, MS: m/z, 253. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.12; H, 4.11; N, 16.65.

Compound **4b:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.29 (s, 2H, CH_2), 6.97–8.32 (m, 8H, PyH, ArH), 8.58 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 33.92, 114.35, 116.55, 122.30, 127.95, 128.26, 130.15, 130.90, 133.17, 133.86, 135.86, 138.60, 146.20, 147.31; IR, ν (KBr disc): 1500, 1335 cm^{-1}, MS: m/z, 253. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.51; H, 4.42; N, 16.37.

Compound **4c:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.31 (s, 2H, CH_2), 6.96–8.31 (m, 8H, PyH, ArH), 8.65 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.21, 114.60, 116.76, 123.25, 128.30, 131.10, 131.87, 132.90, 135.82, 138.86, 145.27, 147.32; IR, ν (KBr disc): 1510, 1340 cm^{-1}, MS: m/z, 253. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.22; H, 4.26; N, 16.41.

Compound **4d:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 2.35 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.00–8.02 (m, 7H, PyH, ArH), 8.58 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 20.03, 33.95, 114.86, 116.46, 121.75, 121.97, 125.30, 128.06, 130.83, 131.38, 133.05, 136.21, 139.13, 146.35, 147.86; IR, ν (KBr disc): 1520, 1340 cm^{-1}, MS: m/z, 267. Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 66.88; H, 4.74; N, 15.89.

Compound **4e:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.41 (s, 2H, CH_2), 6.94–8.32 (m, 7H, PyH, ArH), 8.56 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 33.81, 114.16, 116.32, 123.30, 128.36, 130.04, 130.64, 131.24, 132.43, 134.27, 137.46, 138.87, 144.30, 148.68; IR, ν (KBr disc): 1510, 1350 cm^{-1}, MS: m/z, 287. Anal. Calcd for $C_{14}H_{10}ClN_3O_2$: C, 58.45; H, 3.50; N, 14.61. Found: C, 58.30; H, 3.41; N, 14.50.

Compound **4f:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.25 (s, 2H, CH_2), 6.95–8.03 (m, 7H, PyH, ArH), 8.59 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 33.75, 114.37, 116.86, 123.80, 126.58, 127.72, 128.23, 130.85, 131.47, 132.36, 135.30, 137.65, 141.11, 148.15, IR, ν (KBr disc): 1510, 1345 cm^{-1}, MS: m/z, 287. Anal. Calcd for $C_{14}H_{10}ClN_3O_2$: C, 58.45; H, 3.50; N, 14.61. Found: C, 58.26; H, 3.41; N, 14.27.

Compound **4g:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.31 (s, 2H, CH_2), 6.99–8.32 (m, 8H, PyH, ArH), 8.59 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.26, 113.15, 114.86, 116.34, 120.06, 129.10, 130.55, 131.08, 131.67, 137.35, 140.22, 141.37, 148.24; IR, ν (KBr disc): 2200 cm^{-1}, MS: m/z, 233. Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.52; H, 4.63; N, 18.08.

Compound **4h:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 2.51 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.96–7.87 (m, 8H, PyH, ArH), 8.60 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 27.49, 34.20, 114.33, 116.12, 127.51, 129.26, 130.09, 130.77, 133.27, 135.98, 137.35, 138.49, 145.30, 198.26; IR, ν (KBr disc): 1690 cm^{-1}, MS: m/z, 250. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.60; H, 5.46; N, 11.25.

Compound **4i:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 3.81 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 7.01–8.32 (m, 8H, PyH, ArH), 8.64 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 33.89, 51.76, 114.54, 116.28, 128.36, 129.15, 130.05, 130.68, 132.84, 136.98, 138.08, 139.31, 148.93, 167.35; IR, ν (KBr disc): 1710 cm^{-1}, MS: m/z, 266. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.74; H, 5.45; N, 10.30.

3. Synthesis of 2-methylimidazo[1,2-*a*]pyridine 5

A mixture of iodobenzene (0.75 mmol), $(PPh_3)_2PdCl_2$ (0.05 mmol), CuI (0.1 mmol) and triethylamine (3 mmol) was stirred in DMF (5 mL) at room temperature under an argon atmosphere. 2-Amino-1-(2-propynyl)pyridinium bromide (1.27 mmol) was then added and the mixture was stirred at room temperature for 12 h. After completion of the reaction, the resulting solution was concentrated in vacuo and the crude product was subjected to silica gel column chromatography using $CHCl_3$–CH_3OH (95:5) as eluent to afford the pure product. Yield, 66%, mp 280–281 °C; ^{1}H NMR δ (500 MHz, DMSO-d_6): 1.21 (s, 3H, CH_3), 7.03–7.59 (m, 4H, PyH), 8.29 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.08, 114.54, 116.22, 130.12, 130.78, 137.06, 140.02, 147.95; IR, ν (KBr disc): 1610 cm^{-1}, MS: m/z, 132. Anal. Calcd for $C_8H_8N_2$: C, 72.72; H, 6.06; N, 21.21. Found: C, 72.68; H, 6.02; N, 21.23.

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