Syntheses of 2-benzylsubstituted Imidazo[1,2-*a*]pyrimidines *Via* Coupling–Cyclization Under Pd-Cu Catalysis

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Abstract: The reaction of 1-(prop-2-yn-1yl)pyrimidin-2(1H)-imin with various halobenzenes in the presence of a palladium catalyst leads to the production of 2-benzylsubstituted imidazo[1,2-*a*]pyrimidines.

Keywords: Sonogashira coupling, aryl iodide, imidazo[1,2-*a*]pyrimidines, Pd-catalyzed.

The Sonogashira reaction (i.e., the palladium and copper cocatalyzed coupling of terminal alkynes with aryl and vinyl halides) is one of the most widely used C-C bond formation reactions [1]. 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 [2] and pharmaceuticals [3] to molecular organic materials [4]. Because of the utility of the products, the development of new catalyst systems has received considerable attention. Palladium-catalyzed reactions have been immensely practical for both carboannulation [5] and heteroannulation [6] processes.

Imidazo[1,2-*a*]pyrimidines possess diverse biological activities, and this structural motif is present in analgesics, inflammatory inhibitors [7], and benzodiazepine receptor ligands [8] as well as insecticidal, acaricidal and nematocidal agents [9]. Considering the potent bioactivities of compounds possessing an imidazopyrimidine core, the development of a new strategy to synthesize 2- arylsubstituted imidazo[1,2-*a*]pyrimidines efficiently attracted our attention.

In continuation of our recent studies [10] 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 2-arylsubstituted imidazo[1,2-*a*]pyrimidines.

In this communication, we report that treatment of 2-aminopyrimidine **1** with propargyl bromide in refluxing acetonitrile afforded 1-(prop-2-yn-1yl)pyrimidin-2(1H)-imin **2** in good yield. The ^{1}H-NMR spectrum of **2** shows a CH proton at 3.08 ppm, CH_2 protons at 4.90 ppm and a single resonance for the NH group at 8.80 ppm, this signal was removed on deuteration (Scheme **1**).

For optimization of the reaction conditions, we chose the reaction of compound **2** with p-iodonitrobenzene as the model reaction, and the effects of the base, solvent, and catalyst were examined (Table **1**). First, several bases and solvents were screened for the reaction in the presence of a catalytic amount of the $PdCl_2(PPh_3)_2$. As shown in Table **1**, the reaction is significantly influenced by the base employed. It works very well when a base such as Et_3N, DIEA, K_2CO_3, and Na_2CO_3 is used (entries 1, 2, 5, and 7), with the best result obtained in the case of K_2CO_3 as the inorganic base (entry 5). Among the solvents used, DMF was the best choice (entry 5). Increasing the amount of the palladium catalyst reduced the reaction time but did not increase the yield (entry 23). A low palladium concentration prolonged the reaction time and decreased the yield (entry 24).

Using the optimized reaction conditions (0.03 mmol of $PdCl_2(PPh_3)_2$, 0.06 mmol of CuI, 2.0 mmol of K_2CO_3), compound **2** was treated in DMF with the aryl iodides and aryl bromides **3a-i** at 70 ºC to obtain 2-benzylsubstituted imidazo[1,2-*a*]pyrimidines **4a-i** in moderate to good yields (Scheme **1**, Table **2**). The reactions had to be carried out under an argon atmosphere, and the mixture of DMF had to be degassed prior to use.

Mechanistically, the formation of 2-benzylsubstituted imidazo[1,2-*a*]pyrimidines involves the following steps (as shown in Scheme **1**): **(a)** formation of ArPdX (II) through oxidative addition of Pd(0) (I) to ArX; [11] **(b)** transmetallation of ArPdX with the Cu salt of (III), generating the alkynyl palladium species (IV); **(c)** reductive elimination to yield (V); and **(d)** isomerization to the allenic intermediates [12] (VI) which then cyclize to products **4a-i**.

Compound **2** reacted with aryl halides such as *p*-nitrobromobenzene, *p*-nitroiodobenzene, and 1-iodo-2-methyl-4-nitrobenzene, delivering the corresponding products in good to excellent yields (Table **2**). Unsurprisingly, 1-iodo-2-methyl-4-nitrobenzene, (entry 3) was found to be the most reactive amongst the aryl halides studied (entries 1, 3, and 10). As expected, aryl iodides with electron-withdrawing groups reacted better than aryl bromides possessing electron-donating groups to give the desired products in high yields. The presence of electron-withdrawing groups such as $-NO_2$, or –Cl on the aryl halides was essential for successful reaction. When *p*-iodoanisole or iodobenzene were used as the aryl halide, only a small amount of product was isolated by column chromatography.

In conclusion, we have developed a successful palladium-catalyzed reaction for the synthesis of 2-benzyl-

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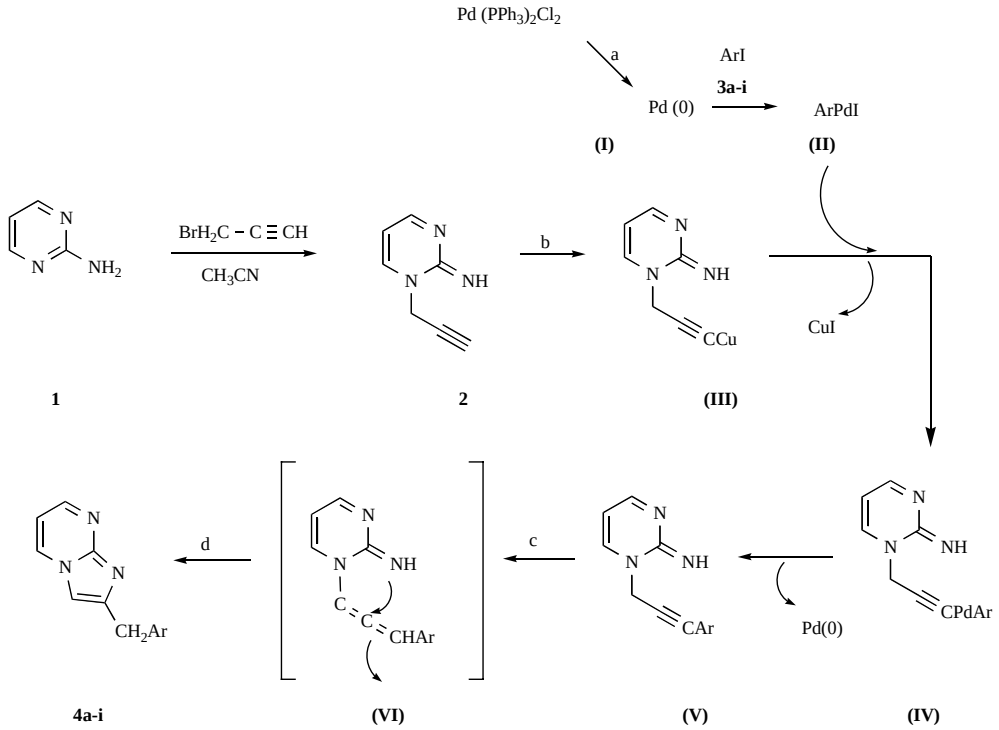


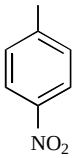
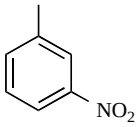
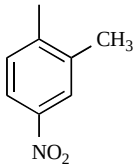
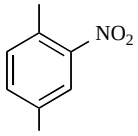
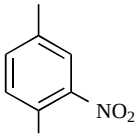
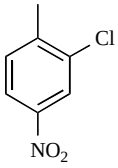
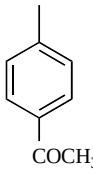
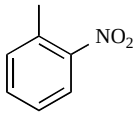
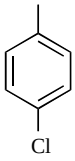
Scheme 1. Proposed mechanism for the formation of 2-arylsubstituted imidazo[1,2-*a*]pyrimidines at 70 ºC. Reagents and conditions: (a) Reduction of Pd(II) to Pd(0) with alkyne and K_2CO_3; (b) CuI, K_2CO_3; (c) isomerization to an allene with CuI, K_2CO_3; (d) nucleophilic attack on the allene (VI) to generate the 2-benzylsubstituted imidazo[1,2-*a*]pyrimidines **4a-i**.

Table 1. The Reaction of Compound 2 with p-iodonitrobenzene in the Presence of Several Bases and Solvents[a]

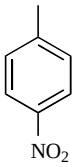
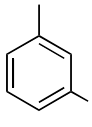
Entry	Solvent	Base	$PdCl_2(PPh_3)_2$ (mol%)	Time (h)	Yield[b] (%)
1	DMF	Et_3N	3.0	10	90
2	DMF	DIEA	3.0	10	90
3	DMF	Pyrrolidine	3.0	12	85
4	DMF	Morpholine	3.0	10	85
5	DMF	K_2CO_3	3.0	12	92
6	DMF	Cs_2CO_3	3.0	8	87
7	DMF	Na_2CO_3	3.0	9	90
8	DMF	KOH	3.0	10	88
9	CH_3CN	Et_3N	3.0	15	80
10	CH_3CN	DIEA	3.0	15	82
11	CH_3CN	Pyrrolidine	3.0	13	75
12	CH_3CN	Morpholine	3.0	17	70
13	NMP	Et_3N	3.0	12	75
14	NMP	DIEA	3.0	10	57
15	NMP	Pyrrolidine	3.0	15	55
16	NMP	Morpholine	3.0	15	70
17	DMAC	Et_3N	3.0	12	85
18	DMAC	DIEA	3.0	12	80
19	DMAC	Pyrrolidine	3.0	15	40
20	DMAC	Morpholine	3.0	10	85
21	Morpholine	Morpholine	3.0	20	35
22	Pyrrolidine	Pyrrolidine	3.0	18	78
23	DMF	K_2CO_3	5.0	8	92
24	DMF	K_2CO_3	1.0	15	70

[a]Reaction conditions: compound **2** (1.2 mmol), *p*-iodonitrobenzene (1.0 mmol), base (2.0 mmol), $PdCl_2(PPh_3)_2$ (3 mol%), CuI (6 mol %), solvent (5 mL) at 70 ºC.
[b]Isolated yield.

Table 2. Yields of 2-benzylsubstituted Imidazo[1,2-*a*]pyrimidines 4a-i[a]

Entry	X	Ar	Product	Yield(%)
1	I		4a	92
2	I		4b	70
3	I		4c	95
4	I		4d	68
5	I		4e	75
6	I		4f	70
7	I		4g	65
8	Br		4h	60
9	Br		4i	56

(Table 2). Contd…..

Entry	X	Ar	Product	Yield(%)
10	Br		4a	70
11	Br		4b	62

[a]Reaction conditions: **2** (1.20 mmol), **3a-i** (1.0 mmol), K_2CO_3 (2 mmol), $PdCl_2(PPh_3)_2$(0.03 mmol), CuI (0.06 mmol), DMF (5 mL), at 70 ºC for 12 h.

substituted imidazo[1,2-*a*]pyrimidines from readily available starting materials. To our knowledge, this is the first reported general procedure for the palladium-copper catalyzed synthesis of 2-2-benzylsubstituted imidazopyrimidines.

Synthesis of 2-imino-1-(2-propynyl)pyrimidine 2

A mixture of 2-aminopyrimidine (1.9 g, 20 mmol) and propargyl bromide (2 mL, 24 mmol) in acetonitrile (10 mL) was heated under reflux for 2 h. The precipitate formed was filtered off and recrystallized from ethanol to afford the title compound. yield, 80%; MP 220-222 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 3.08 (t, *J*=3.0 Hz, 1H, CH), 4.90 (d, *J*=3.0 Hz, 2H, CH_2), 7.15 (dd, *J*=8.0 Hz, *J*=5.5 Hz, 1H, CH), 8.75 (dd, *J*=8.5 Hz, *J*=2.5 Hz, 1H, CH), 8.90 (dd, *J*=5.3 Hz, *J*=2.5 Hz, 1H, CH), 8.80 (s, 1H, NH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 44.21, 74.71, 81.18, 111.24, 149.37, 155.43, 167.07; IR, υ (KBr): 3300, 2100, 1650 cm^{-1}; Anal. Calcd. for $C_7H_8N_3$: C, 63.14; H, 5.30; N, 31.56%. Found: C, 63.43; H, 5.45; N, 31.36%.

Syntheses of 2-arylsubstituted imidazo [1,2-a]pyrimidines 4a-i

A mixture of the aryl halide (1.0 mmol), $(PPh_3)_2PdCl_2$ (0.03 mmol), CuI (0.06 mmol) and K_2CO_3 (2 mmol) was stirred in DMF (5 mL) at room temperature under an argon atmosphere. 2-Imino-1-(2-propynyl)pyrimidine (1.20 mmol) was then added and the mixture was stirred at 70 ºC 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 (98:2) as eluent to afford the pure product (Table **2**).

2-(4-Nitrobenzyl)imidazo[1,2-a]pyrimidine 4a

MP 154-155 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 4.35 (s, 2H, CH_2), 6.90-7.00 (m, 1H, CH), 7.50 (s, 1H, CH), 7.60-7.75 (m, 2H, CH), 8.20-8.38 (m, 2H, CH), 8.50 (dd, *J*=5.2 Hz, *J*=2.5 Hz, 1H, CH), 8.65 (dd, *J*=8.3 Hz, *J*=2.5 Hz, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.25, 108.55, 109.42, 122.90, 124.86, 127.82, 133.20, 134.63, 139.33, 146.65, 147.24, 148.16, 150.04; IR, υ (KBr): 1525, 1350 cm^{-1}; Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.26; H, 3.84; N, 21.88.

2-(3-Nitrobenzyl)imidazo[1,2-a]pyrimidine 4b

MP 118-119 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 4.22 (s, 2H, CH_2), 6.97 -7.10 (m, 1H, CH), 7.55 (s, 1H, CH), 7.70-,7.87 (m, 2H, CH), 8.01-8.20 (m, 2H, CH); 8.40-8.55 (m, 1H, CH), 8.80-8.90 (m, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.50, 108.05, 109.38, 121.94, 128,08, 128.55, 132.54, 133.78, 138.91, 146.10, 146.68, 147.89, 150.32; IR, υ (KBr): 1500, 1335 cm^{-1}; Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.65; H, 4.05; N, 22.26.

2-(2-Methyl-4-nitrobenzyl)imidazo[1,2-a]pyrimidine 4c

MP 246-247 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 2.30 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.92-7.10 (m, 1H, CH); 7.45 (d, *J*=10.5, 1H, CH), 7.62 (s, 1H, CH), 8.02 (dd, *J*=10.4 Hz, *J*=3.0 Hz, 1H, CH), 8.08 (d, *J*=3.0 Hz, 1H, CH), 8.40-8.50 (m, 1H, CH), 8.77 (dd, *J*=8.5 Hz, *J*=2.5 Hz, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 19.61, 33.02, 108.91, 109.44, 121.37, 124.86, 131.27, 135.27, 139.03, 145.92, 146.49, 146.75, 148.11, 150.24; IR, υ (KBr): 1520, 1340 cm^{-1}; Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.89; H, 4.64; N, 20.68.

2-(4-Chloro-2-nitrobenzyl)imidazo[1,2-a]pyrimidine 4d

MP 235-236 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 4.30 (s, 2H, CH_2), 7.02-7.20 (m, 2H, CH), 7.50-8.10 (m, 2H, CH), 8.20 (s, 1H, CH), 8.50-8.60 (m, 1H, CH), 8.75-8.90 (m, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.40, 108.26, 108.88, 123.24, 128.20, 131.31, 132.72, 134.43, 139.14, 146.67, 147.54, 149.20, 150.32; IR, υ (KBr): 1510, 1350 cm^{-1} Anal. Calcd. for $C_{13}H_9ClN_4O_2$: C, 54.09; H, 3.14; N, 19.41. Found: C, 54.32; H, 3.23; N, 19.58.

2-(4-Chloro-3-nitrobenzyl)imidazo[1,2-a]pyrimidine 4e

MP 250-251 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 4.20 (s, 2H, CH_2), 6.95-7.20 (m, 2H, CH), 7.60-7.88 (m, 2H, CH); 8.10 (s, 1H, CH), 8.40-8.51 (m, 1H, CH), 8.85-9.02 (m, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.06, 108.60, 109.08, 126.80, 127.95, 129.45, 134.90, 135.33, 139.47, 146.88, 147.67, 148.56, 149.94; IR, υ (KBr): 1525, 1320 cm^{-1}; Anal. Calcd for $C_{13}H_9ClN_4O_2$: C, 54.09; H, 3.14; N, 19.41. Found: C, 54.38; H, 3.20; N, 19.25.

2-(2-Chloro-4-nitrobenzyl)imidazo[1,2-a]pyrimidine 4f

MP 270-271 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 4.45 (s, 2H, CH_2), 6.90-7.01 (m, 1H, CH), 7.50-8.00 (m, 3H, CH), 8.30 (s, 1H, CH), 8.55-8.70 (m, 1H, CH), 8.94-9.15 (m, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.41, 108.75, 109.55, 122.90, 123.43, 128.87, 132.06, 134.20, 139.30, 146.52, 147.62, 149.54, 150.28; IR, υ (KBr): 1510, 1340 cm^{-1}; Anal. Calcd. for $C_{13}H_9ClN_4O_2$: C, 54.09; H, 3.14; N, 19.41. Found: C, 53.84; H, 3.02; N, 19.62.

2-(4-Acetobenzyl)imidazo[1,2-a]pyrimidine 4g

MP 136-137 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 2.55 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 7.01-7.20 (m, 1H, CH), 7.47 (d, *J*=8.0 Hz, 2H, CH), 7.65 (s, 1H, CH), 7.90 (d, *J*=8.1 Hz, 2H, CH), 8.47 (dd, *J*=4.0 Hz, *J*=1.9 Hz, 1H, CH), 8.90 (dd, *J*=6.6 Hz, *J*=1.8 Hz, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 27.50, 34.15, 108.27, 108.95, 127.12, 128.50, 128.87, 132.73, 138.17, 139.66, 146.42, 147.17, 148.25, 150.22, 197.83; IR, υ (KBr): 1695 cm^{-1}; Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.45; H, 5.05; N, 16.55.

2-(2-Nitrobenzyl)imidazo[1,2-a]pyrimidine 4h

MP 128-129 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 4.20 (s, 2H, CH_2), 7.02 -7.10 (m, 1H, CH), 7.15-7.27 (m, 1H, CH), 7.45-7.60 (m, 2H, CH), 7.88-8.06 (m, 2H, CH), 8.50-8.68 (m, 2H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.20, 108.34, 109.76, 123.10, 124.34, 128.05, 133.43, 134.35, 139.40, 146.24, 147.54, 147.90, 149.85; IR, υ (KBr): 1520, 1345 cm^{-1}; Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.54; H, 4.10; N, 21.90.

2-(4-Chlorobenzyl)imidazo[1,2-a]pyrimidine 4i

mp 146-147 °C; ^{1}H NMR (500 MHz, DMSO-d_6 δ ppm): 4.25 (s, 2H, CH_2), 6.950-7.04 (m, 1H, CH), 7.57 (s, 1H, CH), 7.72-7.90 (m, 2H, CH), 8.22-8.43 (m, 2H, CH), 8.65 (d, *J*=8.2 Hz, 1H, CH), 8.75 (d, *J*=8.0 Hz, 1H, CH); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.46, 108.72, 109.24, 119.56, 131.42, 131.94, 134.80, 139.35, 147.63, 147.92, 149.86; IR, υ (KBr): 1090 cm^{-1}; Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.32; H, 4.25; N, 17.02.

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