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# Synthesis of 6-substituted imidazo[2,1-*b*]thiazoles via Pd/Cu-mediated Sonogashira coupling in water

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ABSTRACT

The reaction of 2-amino-3-(2-propynyl)thiazolium bromide with various iodobenzenes, catalyzed by Pd/Cu, in the presence of sodium lauryl sulfate as surfactant and cesium carbonate as base, in water, leads to the formation of 6-substituted imidazo[2,1-*b*]thiazoles.



Compounds containing the imidazo[2,1-*b*]thiazole skeleton have been used as anthelmintic agents, anti-hypertensives, anti-inflammatories, immunosuppressive agents, fungicides, herbicides, antitumor agents, and cardiotonic agents.[1] Considering the potent bioactivities of compounds possessing an imidazothiazole core, the development of a new strategy to synthesize 6-substituted imidazo[2,1-*b*]thiazoles efficiently attracted our attention.

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

Alkynes are versatile intermediates in synthesis[3,4] as well as are important functional groups in a wide range of biologically active compounds.[5] The Sonogashira reaction typically employs a palladium catalyst and copper iodide to couple a terminal alkyne with an aryl halide.[6] Several modifications of the original Sonogashira protocol have been reported, prominent among which are phase transfer[7] and copper-free conditions,[8] and the use of a more active catalyst system, including those utilizing N-heterocyclic carbene (NHC) ligands for reaction with less reactive bromo- and chloroarenes.[9] The effect of different solvents has also been studied[10] including aqueous–organic solvent mixtures in the presence of water-soluble phosphine ligands[11] and ionic liquids.[12]

Driven by environmental concerns, much attention has been paid to using water as the solvent for organic and organometallic reactions.[13] The use of aqueous media in palladium-catalyzed reactions has become popular[14] because water-based synthetic processes are inherently safer (water is non-toxic and non-flammable) and inexpensive. Moreover, the products can easily be isolated by extraction, which greatly facilitates the operation. Several examples of Pd-catalyzed Sonogashira reactions in aqueous media have been reported.[15]

In continuation of our recent studies[16] on the synthesis of heterocycles and the Pd-catalyzed reaction of acetylenes leading to heterocyclic compounds of biological significance, we were interested in developing a synthetic route to 6-substituted imidazo[2,1-*b*]thiazoles using water as the solvent.

In this Letter, we report that treatment of 2-aminothiazole **1** with propargyl bromide in refluxing acetonitrile affords 2-amino-3-(2-propynyl)thiazolium bromide **2** in good yield. The $^1$H NMR spectrum of **2** showed a CH proton signal at 3.73 ppm, $CH_2$ protons at 5.03 ppm, and a single resonance for the $NH_2$ group at 9.78 ppm; this signal was removed on deuteration.

When compound **2** was reacted with aryl iodides **3a–f** and cesium carbonate in water in the presence of bis(triphenylphosphine)palladium(II) chloride, copper iodide, and sodium lauryl sulfate at 60 °C, 6-substituted imidazo[2,1-*b*]thiazoles **4a–f** were obtained in moderate to high yields (Scheme 1). The reactions were carried out under an argon atmosphere and water and cesium carbonate were degassed prior to use.

Mechanistically, the formation of 6-substituted imidazo[2,1-*b*]thiazoles involves the following steps (as shown in Scheme 1): (i) formation of ArPdI **B** through oxidative addition of Pd(0) **A** to

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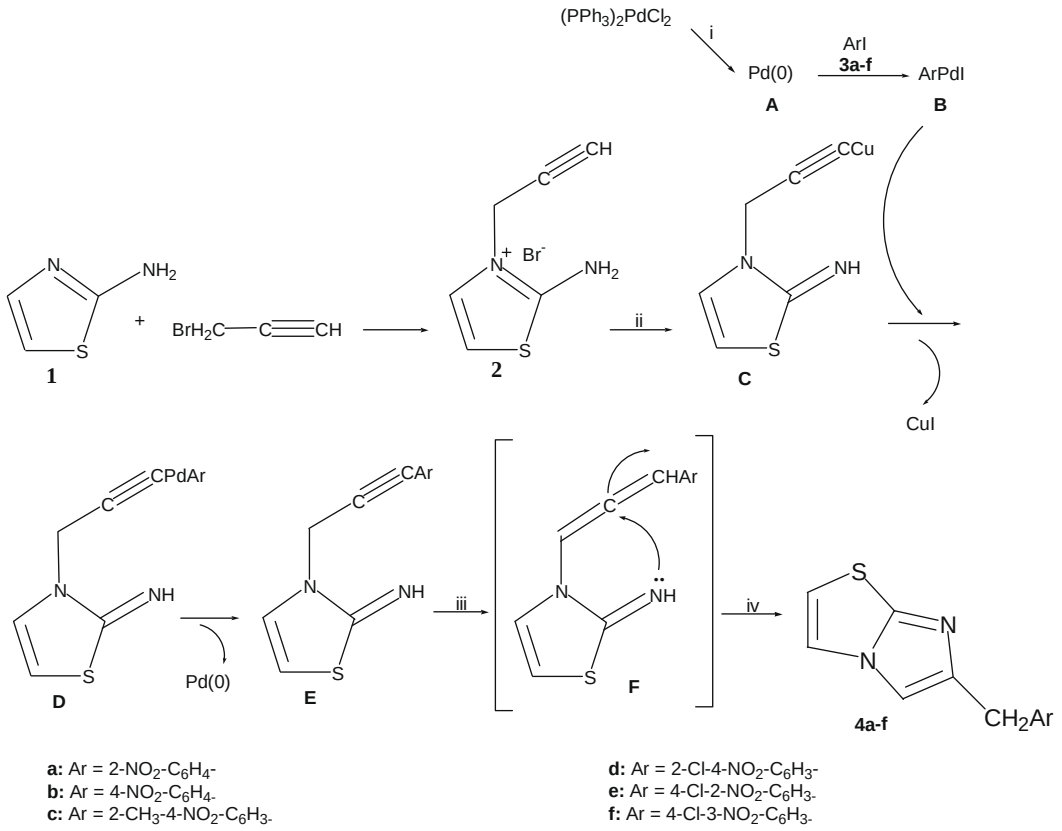



**Scheme 1.** A plausible mechanism for the formation of 6-substituted imidazo[2,1-*b*]thiazoles at 60 °C. Reagents and conditions: (i) reduction of Pd(II) to Pd(0) with alkyne and $Cs_2CO_3$; (ii) CuI, $Cs_2CO_3$; (iii) isomerization to an allene with CuI, $Cs_2CO_3$; (iv) intermolecular nucleophilic attack on the allene F to generate the 6-substituted imidazo[2,1-*b*]thiazoles **4a–f**.

ArI;[17] (ii) transmetallation of ArPdI with the Cu salt of **C**, generating the alkynyl palladium species **D**; (iii) extrusion of Pd(0) to yield the alkyne **E**; and (iv) isomerization to the allenic intermediate[18] **F**, which then cyclizes to the 6-substituted imidazo[2,1-*b*]thiazoles **4a–f**.

For optimization of the reaction conditions, we chose the reaction of **2** with 4-chloro-1-iodo-2-nitrobenzene **3e** as the model reaction, and the effects of the base, surfactant, and catalyst were examined. First, several bases were screened for the reaction in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$. As shown in Table 1, the reaction was influenced significantly by the base employed. The reaction worked very well when inorganic bases such as $K_2CO_3$ and $Cs_2CO_3$ were used (Table 1, entries 2 and 3), with the best result obtained in the case of cesium carbonate (Table 1, entry 3).

**Table 1**
Effect of base on the Sonogashira coupling of compound **2** with 4-chloro-1-iodo-2-nitrobenzene **3e** in water[a]

| Entry | Base | Yield[b] (%) |
|---|---|---|
| 1 | KOH | 15 |
| 2 | $K_2CO_3$ | 78 |
| 3 | $Cs_2CO_3$ | 90 |
| 4 | $Et_3N$ | 25 |
| 5 | DIEA | 42 |
| 6 | Pyrrolidine | 28 |
| 7 | Piperidine | 34 |

[a] Reaction conditions: **2** (1 mmol), **3e** (1 mmol), base (3 mmol), $Pd(PPh)_3Cl_2$ (3 mol %), CuI (7 mol %), sodium lauryl sulfate (7 mol %), degassed water (5 mL), 60 °C, 12 h.
[b] Isolated yield.

The influence of the amount of copper(I) iodide, surfactant, and the catalyst was investigated using the reaction of compound **2** with **3e**. The results are shown in Table 2. Increasing the amount of the palladium catalyst shortened the reaction time but did not increase the yield (entry 3). A low palladium concentration prolonged the reaction time and led to a decreased yield (entry 1).

The use of surfactant was also critical for the success of the reaction: without a surfactant/phase-transfer reagent, the yield dropped from 90% to 10% (compare entries 2 and 8). We also found that with an increased amount of surfactant, the reaction yield did not increase (entry 7). A low surfactant concentration decreased the yield (entry 6). No reaction was observed when either Cu(I) alone or Pd(II) alone was used as the catalyst (entries 4 and 5).

Subsequently, the reactions of a variety of aryl iodides **3a–f** and 2-amino-3-(2-propynyl)thiazolium bromide **2** were studied under the optimal conditions. As shown in Table 3, the presence of electron-withdrawing groups such as $NO_2$ and Cl on the aryl iodide was essential for a successful reaction. When iodobenzene or *p*-iodoanisole was used as the aryl iodide, the Sonogashira coupling was not achieved.

In conclusion, we have developed a successful palladium-catalyzed reaction for the synthesis of 6-substituted imidazo[2,1-*b*]thiazoles in the presence of sodium lauryl sulfate as the surfactant and cesium carbonate as the base in water.

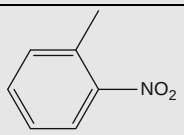
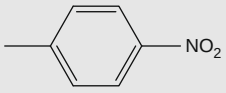
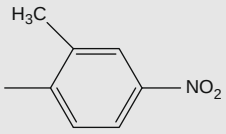
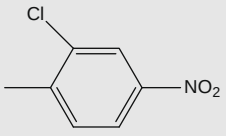
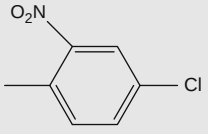
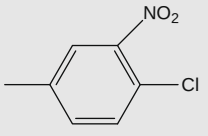
*2-Amino-3-(2-propynyl)thiazolium bromide* **2**: A mixture of 2-aminothiazole **1** (2 g, 20 mmol) and propargyl bromide (2 mL, 24 mmol) in MeCN (10 mL) was heated under reflux for 1 h. The precipitate formed was filtered off and recrystallized from MeCN to afford the title compound. Yield, 95%; mp 159–160 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta_H$ = 3.73 (t, $J$ = 2.4 Hz, 1H, CH), 5.03 (d, $J$ = 2.3 Hz, 2H, $CH_2$), 7.07 (d, $J$ = 4.5 Hz, 1H, CH of thiazole), 7.50 (d, $J$ = 4.5 Hz, 1H,

**Table 2**
Effects of catalyst, co-catalyst, and surfactant on the Sonogashira coupling of compound **2** with 4-chloro-1-iodo-2-nitrobenzene **3e** in water[a]

| Entry | $Pd(PPh_3)_2Cl_2$ (mol %) | CuI (mol %) | Sodium lauryl sulfate (mol %) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 2 | 5 | 7 | 72[c] |
| 2 | 3 | 7 | 7 | 90 |
| 3 | 5 | 10 | 7 | 85[d] |
| 4 | 3 | — | 7 | —[e] |
| 5 | — | 7 | 7 | —[e] |
| 6 | 3 | 7 | 3 | 50 |
| 7 | 3 | 7 | 12 | 60 |
| 8 | 3 | 7 | — | 10 |

[a] Reaction conditions: **2** (1 mmol), **3e** (1 mmol), $Cs_2CO_3$ (3 mmol), degassed water (5 mL), 60 °C, 12 h.
[b] Isolated yield.
[c] Reaction time: 14 h.
[d] Reaction time:8 h.
[e] No reaction.

**Table 3**
Melting points and yields of 6-substituted imidazo[2,1-*b*]thiazoles **4a–f**[a]

| Entry | Product | Ar | Yield[b] (%) | Mp (°C) |
|---|---|---|---|---|
| 1 | **4a** |  | 79 | 224–225 |
| 2 | **4b** |  | 78 | 229–230 |
| 3 | **4c** |  | 78 | 254–255 |
| 4 | **4d** |  | 81 | 209–210 |
| 5 | **4e** |  | 90 | 231–232 |
| 6 | **4f** |  | 82 | 243–244 |

[a] Reaction conditions: **2** (1 mmol), **3a–f** (1 mmol), $Cs_2CO_3$ (3 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol %), CuI (7 mol %), sodium lauryl sulfate (7 mol %), degassed water (5 mL), 60 °C, 12 h.
[b] Isolated yield.

CH of thiazole), 9.78 (s, 2H, $NH_2$); IR (KBr): 3300, 3250, 2150 $cm^{-1}$; MS (EI) *m/z*, 220 [$M^+$($^{81}$Br), 22), 218 [$M^+$($^{79}$Br), 22], 139 (100), 112 (18), 99 (20), 80 (22), 58 (26), 45 (27). Anal. Calcd for $C_6H_7BrN_2S$: C, 32.89; H, 3.22; N, 12.79. Found: C, 32.65; H, 3.03; N, 12.55.

*6-Substituted imidazo[2,1-b]thiazoles; typical procedure*: A mixture of aryl iodide (1 mmol), $(PPh_3)_2PdCl_2$ (3 mol %), CuI (7 mol %), sodium lauryl sulfate (7 mol %), and cesium carbonate (3 mmol) was stirred in water (5 mL) at 60 °C for 30 min under an argon atmosphere. 2-Amino-3-(2-propynyl)thiazolium bromide (1 mmol) was then added and the mixture was stirred at 60 °C 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 (Table 3). The spectral ($^1$H NMR, $^{13}$C NMR, IR and mass) data of the 6-substituted imidazo[2,1-*b*]thiazoles are given below.

*6-(2-Nitrobenzyl)imidazo[2,1-b]thiazole* (**4a**, Table 3, entry 1). $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta_H$ 4.25 (s, 2H, $CH_2$), 6.95–7.96 (m, 6H, thiazole, ArH), 8.63 (s, 1H, CH of imidazole); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta_C$ 35.32, 110.46, 122.45, 124.10, 128.93, 129.82, 130.37, 131.25, 131.98, 134.24, 147.67, 154.56; IR (KBr): 1520, 1340 $cm^{-1}$; MS (EI) *m/z*, 259 ($M^+$, 45), 213 (100), 137 (20), 123 (8). Anal. Calcd for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21; S, 12.37. Found: C, 55.32; H, 3.36; N, 16.40; S, 12.21.

*6-(4-Nitrobenzyl)imidazo[2,1-b]thiazole* (**4b**, Table 3, entry 2). $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 4.18 (s, 2H, $CH_2$), 7.25–8.15 (m, 6H, thiazole, ArH), 8.31 (s, 1H, CH of imidazole); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 34.78, 109.67, 122.87, 123.05, 127.93, 128.30, 129.87, 130.64, 131.43, 134.08, 148.20, 154.86; IR (KBr): 1525, 1340 $cm^{-1}$; MS (EI) *m/z*, 259 ($M^+$, 100), 213 (36), 137 (18), 106 (10). Anal. Calcd for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21; S, 12.37. Found: C, 55.37; H, 3.32; N, 16.45; S, 12.18.

*6-(2-Methyl-4-nitrobenzyl)imidazo[2,1-b]thiazole* (**4c**, Table 3, entry 3). $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 2.50 (s, 3H, $CH_3$), 4.10 (s, 2H, $CH_2$), 7.22–8.06 (m, 5H, thiazole, ArH), 8.14 (s, 1H, CH of imidazole); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 21.30, 35.74, 110.21, 122.13, 122.90, 123.65, 126.92, 130.12, 130.65, 131.15, 133.16, 147.43, 155.30; IR (KBr): 1530, 1345 $cm^{-1}$; MS (EI) *m/z*, 273 ($M^+$, 100), 227 (48), 137 (42), 123 (10). Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 57.31; H, 3.90; N, 15.51; S, 11.61.

*6-(2-Chloro-4-nitrobenzyl)imidazo[2,1-b]thiazole* (**4d**, Table 3, entry 4). $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 4.28 (s, 2H, $CH_2$), 7.24–8.28 (m, 5H, thiazole, ArH), 8.32 (s, 1H, CH of imidazole); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 34.88, 109.53, 123.20, 123.78, 128.31, 130.62, 131.15, 131.85, 132.21, 133.90, 151.10, 155.06; IR (KBr): 1525, 1340 $cm^{-1}$; MS (EI) *m/z*, 295 [$M^+$($^{37}$Cl), 10], 293 [$M^+$($^{35}$Cl), 28], 247 (100), 212 (42), 156 (37), 137 (22). Anal. Calcd for $C_{12}H_8ClN_3O_2S$: C, 49.07; H, 2.75; N, 14.31; S, 10.92. Found: C, 49.29; H, 2.87; N, 14.20; S, 11.02.

*6-(4-Chloro-2-nitrobenzyl)imidazo[2,1-b]thiazole* (**4e**, Table 3, entry 5). $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 4.34 (s, 2H, $CH_2$), 7.26–7.93 (m, 5H, thiazole, ArH), 8.08 (s, 1H, CH of imidazole); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 35.52, 110.30, 123.60, 129.21, 130.05, 130.95, 131.46, 132.04, 132.65, 134.32, 148.90, 155.45; IR (KBr): 1520, 1340 $cm^{-1}$; MS (EI) *m/z*, 295 [$M^+$($^{37}$Cl), 7], 293 [$M^+$($^{35}$Cl), 18], 276 (100), 248 (75), 213 (50), 153 (42), 127 (40), 111 (38). Anal. Calcd for $C_{12}H_8ClN_3O_2S$: C, 49.07; H, 2.75; N, 14.31; S, 10.92. Found: C, 48.88; H, 2.62; N, 14.47; S, 10.77.

*6-(4-Chloro-3-nitrobenzyl)imidazo[2,1-b]thiazole* (**4f**, Table 3, entry 6). $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 4.13 (s, 2H, $CH_2$), 7.25–7.95 (m, 5H, thiazole, ArH), 8.02 (s, 1H, CH of imidazole); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 34.95, 109.85, 127.02, 129.12, 129.95, 130.64, 131.14, 134.87, 135.56, 135.98, 148.80, 154.48; IR (KBr): 1530, 1350 $cm^{-1}$; MS (EI) *m/z*, 295 [$M^+$($^{37}$Cl), 13], 293 [$M^+$($^{35}$Cl), 40], 248 (100), 214 (35), 156 (42), 138 (15). Anal. Calcd for $C_{12}H_8ClN_3O_2S$: C, 49.07; H, 2.75; N, 14.31; S, 10.92. Found: C, 49.23; H, 2.90; N, 14.45; S, 10.81.

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