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Synthesis of 2-benzylimidazo[2,1-*b*][1,3]benzothiazoles through palladium-catalyzed heteroannulation of acetylenic compounds

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ABSTRACT

The reaction of 2-imino-3-(2-propynyl)-1,3-benzothiazole with various iodobenzenes in the presence of a palladium catalyst leads to the production of 2-benzylimidazo[2,1-*b*][1,3]benzothiazoles.

Imidazobenzothiazole derivatives are common substructures of synthetic molecules displaying important medicinal activities.[1] Their core ring system is present in numerous cardiotonic[2] and immunosuppressive[3] drugs. Considering the potent bioactivities of compounds possessing an imidazobenzothiazole core, the development of a new strategy to synthesize efficiently 2-benzylimidazo[2,1-*b*][1,3]benzothiazoles has attracted our attention.

The Pd–Cu-catalyzed cross-coupling reaction of terminal acetylenes with sp^2-C halides provides a useful method for synthesizing conjugated acetylenic compounds, which are an important class of molecules.[4] Several groups have described annulation reactions in heterocyclization-based Sonogashira coupling.[5] We were intrigued by the prospect of applying this methodology to the synthesis of other heterocyclic systems.

Although several methods have been reported for the synthesis of imidazo[2,1-*b*][1,3]benzothiazoles,[6] a literature survey showed no reports on the Pd–Cu-catalyzed preparation of this system.

To introduce a benzyl substituent to imidazo[2,1-*b*][1,3]benzothiazole, our retrosynthetic analysis implicated the use of propargyl bromide, 2-aminobenzothiazole and an aryl iodide as the starting materials, with a palladium-catalyzed cross coupling-cyclization as the key step (Fig. 1).

Treatment of 2-imino-3-(2-propynyl)-1,3-benzothiazole **1**[7] in DMF with aryl iodides **2a–i** and triethylamine in the presence of bis(triphenylphosphine)palladium(II) chloride and cuprous iodide at room temperature gave 2-substituted imidazo[2,1-*b*][1,3]benzothiazoles **3a–i** in moderate to high yields (Scheme 1, Table 1). The reactions were carried out under an argon atmosphere, and DMF and triethylamine were degassed prior to use.

Mechanistically, the formation of 2-benzylimidazo[2,1-*b*][1,3]benzothiazoles involves the following steps (as shown in Scheme 1): (i) formation of ArPdI **[B]** through oxidative addition of Pd(0) **[A]** to ArI;[8] (ii) transmetallation of ArPdI with the Cu salt of **[C]**, generating the alkynyl palladium species **[D]**; (iii) extrusion of Pd(0) to yield the alkynes **[E]**; (iv) isomerization to the allenic intermediates[9] **[F]** which then cyclize to products **3a–i**.

The presence of electron-withdrawing groups such as $-NO_2$, –Cl or –CN on the aryl iodide was essential for successful reaction. When *p*-iodoanisole was used as the aryl iodide, Sonogashira coupling did not occur. It is also noteworthy that in the case of iodobenzene as the aryl iodide, the cyclization occurred without any involvement of the aryl iodide. The product of this reaction was identified as 2-methylimidazo[2,1-*b*][1,3]benzothiazole **4** (Scheme 2).[7]

In conclusion, we have developed an efficient and useful method for the synthesis of 2-substituted imidazo[2,1-*b*][1,3]benzothiazoles. To our knowledge, this is the first reported general procedure for the palladium–copper-catalyzed synthesis of 2-substituted imidazobenzothiazoles.

Synthesis of 2-substituted imidazo[2,1-b][1,3]benzothiazoles 3a–i: A mixture of the aryl iodides **2a–i** (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-Imino-3-(2-propynyl)-1,3-benzothiazole **1** (1.27 mmol,

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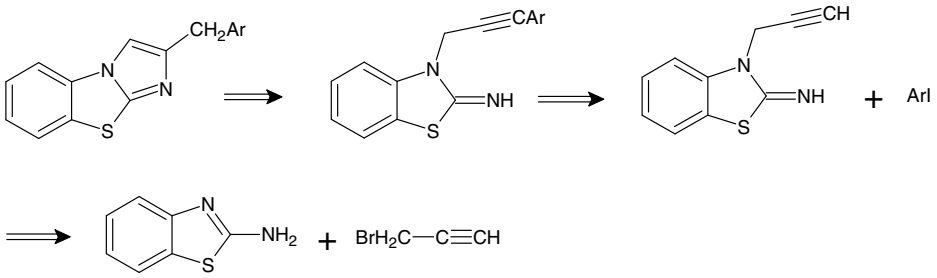
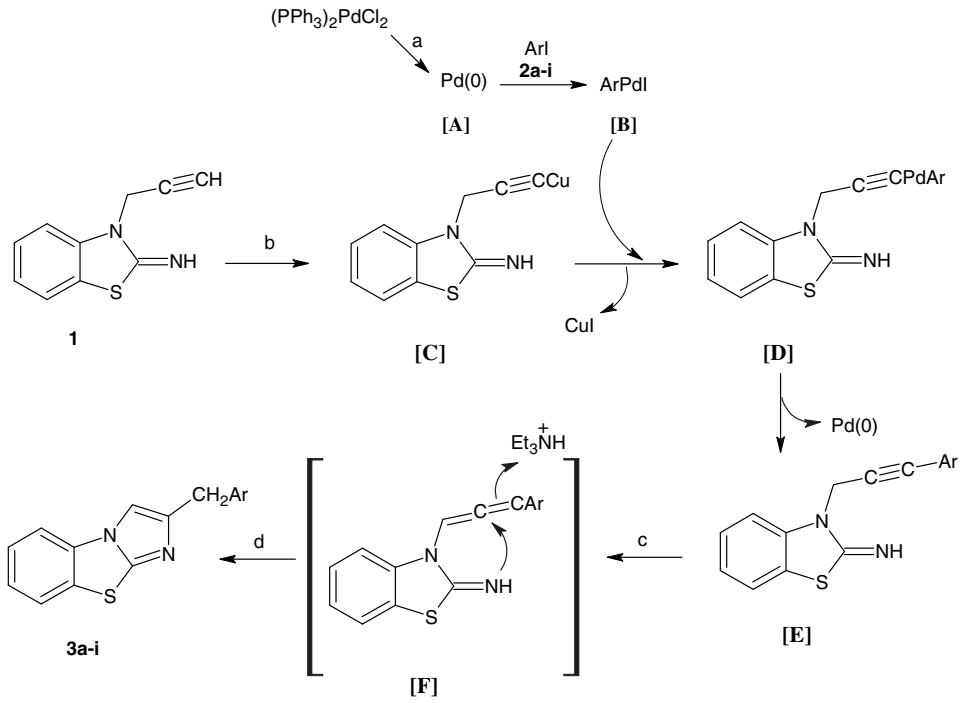


Figure 1. Reterosynthetic analysis of imidazo[2,1-*b*][1,3]benzothiazole.



Scheme 1. A plausible mechanism for the formation of 2-benzylimidazo[2,1-*b*][1,3] benzothiazoles at room temprature. Reagents and conditions: (a) Reduction of Pd(II) to Pd(0) with alkyne and Et_3N; (b) CuI, Et_3N; (c) isomerization to an allene with CuI, Et_3N; (d) nucleophilic attack on the allene (F) to generate the 2-benzylimidazo[2,1-*b*][1,3] benzothiazoles **3a–i**.

0.34 mg) was then added and the mixture was stirred at room temperature for 20 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 the eluent to afford the pure product (Table 1).

Compound **3a:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.37 (s, 2H, CH_2), 7.37–8.00 (m, 8H, ArH), 8.2 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.08, 114.42, 122.12, 122.70, 123.11, 125.43, 127.61, 128.93, 129.27, 130.67, 131.13, 132.02, 134.30, 139.34, 148.20, 153.25; IR, ν (KBr disc): 1490, 1340 cm^{-1}; MS (EI) *m/z,* 309 (M^+, 45), 308(63), 263(100), 186(53), 131(34), 108(47). Anal. Calcd for $C_{16}H_{11}N_3O_2S$: C, 62.12; H, 3.58; N, 13.58; S, 10.37. Found: C, 62.54; H, 3.72; N, 13.82; S, 10.16.

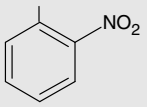
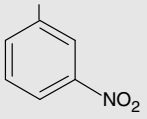
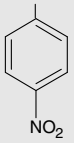
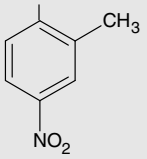
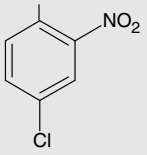
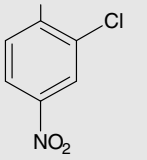
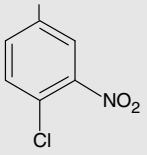
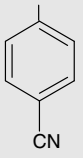
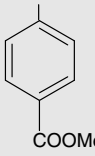
Compound **3b:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.18 (s, 2H, CH_2), 7.39–7.81 (m, 4H, ArH), 7.97–8.09 (m, 4H, ArH), 8.20 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.20, 114.62, 122.40, 123.01, 126.10, 127.61, 128.05, 128.37, 129.21, 130.22, 130.76, 133.87, 138.20, 140.09, 146.80, 154.01; IR, ν (KBr disc): 1510, 1340 cm^{-1}; MS (EI) *m/z,* 309 (M^+, 100), 261(63), 187(42), 130(24), 109(39). Anal. Calcd for $C_{16}H_{11}N_3O_2S$: C, 62.12; H3x, 3.58; N, 13.58; S, 10.37. Found: C, 61.73; H, 3.30; N, 13.25; S, 10.11.

Compound **3c:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.38 (s, 2H, CH_2), 7.38–8.18 (m, 8H, ArH), 8.20 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.26, 114.75, 122.70, 123.02, 125.37, 127.26, 127.95, 128.87, 130.80, 131.13, 133.15, 140.04, 147.75, 153.82; IR, ν (KBr disc): 1500, 1345 cm^{-1}; MS (EI) *m/z,* 309 (M^+, 100), 262(96), 187(55), 131(40), 108(42). Anal. Calcd for $C_{16}H_{11}N_3O_2S$: C, 62.12; H, 3.58; N, 13.58; S, 10.37. Found: C, 62.43; H, 3.70; N, 13.76; S, 10.56.

Compound **3d:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 2.06 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 7.19–7.90 (m, 7H, ArH), 8.00 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 20.12, 33.91, 114.15, 122.21, 122.55, 122.96, 123.90, 126.02, 127.41, 127.86, 128.97, 130.37, 130.95, 133.32, 139.25, 148.03, 153.56; IR, ν (KBr disc): 1520, 1340 cm^{-1}; MS (EI) *m/z* 323 (M^+, 100), 276(49), 187(24), 150(21), 131(37), 39(28). Anal. Calcd for $C_{17}H_{13}N_3O_2S$: C, 63.14; H, 4.05; N, 12.99; S, 9.92. Found: C, 62.78; H, 3.86; N, 12.63; S, 9.73.

Compound **3e:** ^{1}H NMR δ (500 MHz, DMSO-d_6): 4.33 (s, 2H, CH_2), 7.52–7.99 (m, 7H, ArH), 8.11 (s, 1H, CH of imidazole); ^{13}C NMR δ (125MHz, DMSO-d_6): 33.77, 114.71, 123.15, 123.55, 125.87, 127.23, 128.20, 129.10, 130.17, 130.65, 131.35, 132.71,

Table 1
Melting points and yields of 2-benzylimidazo[2,1-*b*][1,3]benzothiazoles **3a–i**

Product	Ar	Mp (°C)	Yield (%)
3a		281–282	74
3b		279–280	72
3c		289–290	87
3d		280–281	70
3e		292–293	85
3f		295–296	67
3g		286–287	55
3h		273–274	77
3i		290–291	75

134.32, 139.77, 149.60, 153.20; IR, ν (KBr disc): 1490 cm^{-1}; MS (EI) *m/z*, 345 ($M^{+37}Cl$, 14), 343 ($M^{+35}Cl$, 46), 326(100), 298(68), 263(93), 203(34), 161(47), 131(51), 108(39). Anal. Calcd for $C_{16}H_{10}ClN_3O_2S$: C, 55.90; H, 2.93; N, 12.22; S, 9.33. Found: C, 55.59; H, 2.66; N, 12.07; S, 9.10.

Compound **3f:** ^1H NMR δ (500 MHz, DMSO-d_6): 4.34 (s, 2H, CH_2), 7.38–8.1 (m, 7H, ArH), 8.17 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.10, 114.21, 122.67, 123.09, 123.67, 126.20, 127.62, 128.80, 129.18, 130.70, 131.12, 132.15, 134.48, 139.23, 150.02, 154.10; IR, ν (KBr disc): 1510, 1340 cm^{-1}; MS(EI) *m/z*, 345 ($M^{+37}Cl$, 20), 343 ($M^{+35}Cl$, 56), 308(53), 297(100), 261(43), 186(47), 170(23), 133(41), 107(27). Anal. Calcd for $C_{16}H_{10}ClN_3O_2S$: C, 55.90; H, 2.93; N, 12.22; S, 9.33. Found: C, 55.73; H, 2.77; N, 12.36; S, 9.15.

Compound **3g:** ^1H NMR δ (500 MHz, DMSO-d_6): 4.35 (s, 2H, CH_2), 7.38–8.07 (m, 7H, ArH), 8.32 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 33.87, 114.85, 122.78, 123.67, 125.76, 126.88, 127.61, 129.17, 129.57, 130.75, 131.20, 135.02, 135.47, 139.34, 148.45, 153.27; IR, ν (KBr disc): 1510, 1335 cm^{-1}; MS (EI) *m/z*, 345 ($M^{+37}Cl$, 12), 343 ($M^{+35}Cl$, 31), 298(100), 262(68), 201(27), 132(43), 109(35). Anal. Calcd for $C_{16}H_{10}ClN_3O_2S$: C, 55.90; H, 2.93; N, 12.22; S, 9.33. Found: C, 55.67; H, 2.69; N, 11.97; S, 9.41.

Compound **3h:** ^1H NMR δ (500 MHz, DMSO-d_6): 4.11 (s, 2H, CH_2), 7.12–7.69 (m, 5H, ArH), 7.85 (d, J = 5Hz, 1H, ArH), 7.96–8.02 (m, 2H, ArH), 8.10 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.15, 113.30, 114.56, 120.02, 122.65, 125.83, 127.32, 128.85, 129.31, 130.36, 130.74, 131.16, 139.37, 141.43, 154.17; IR, ν (KBr disc): 2200 cm^{-1}; MS (EI) *m/z* 289 (M^+, 22), 286(32), 261(45), 187(100), 130(28), 116(23). Anal. Calcd for $C_{17}H_{11}N_3S$: C, 70.56; H, 3.83; N, 14.52; S, 11.08. Found: C, 70.82; H,3.92; N, 14.70; S, 11.26.

Compound **3i:** ^1H NMR δ (500 MHz, DMSO-d_6): 3.86 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 7.39–8.00 (m, 8H, ArH), 8.20 (s, 1H, CH of imidazole); ^{13}C NMR δ (125 MHz, DMSO-d_6): 34.15, 51.23, 114.76, 122.37, 125.64, 127.43, 128.32, 129.07, 129.49, 130.15, 130.68, 132.78, 138.25, 140.10, 154.08, 167.23; IR, ν (KBr disc): 1710 cm^{-1}; MS (EI) *m/z* 322 (M^+,100), 306(87), 262(43), 186(44), 170(24), 147(23), 131(33). Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69; S, 9.95. Found: C, 66.85; H, 4.22; N, 8.90; S, 9.72.

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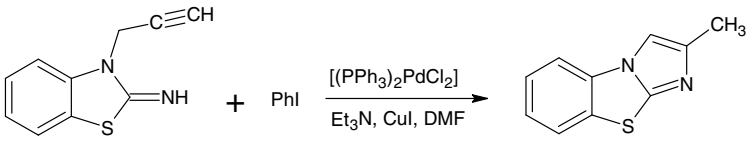

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Scheme 2. Synthesis of 2-methylimidazo[2,1-*b*][1,3]benzothiazole.

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