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# Pd–Cu catalyzed heterocyclization during Sonogashira coupling: synthesis of 3-benzylthiazolo[3,2-*a*]benzimidazole

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**Abstract**—The reaction of 2-mercaptopropargyl benzimidazole with various iodobenzenes catalyzed by Pd–Cu leads to the formation of 3-benzylthiazolo[3,2-*a*]benzimidazoles.

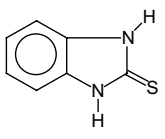

Benzimidazole derivatives are of wide interest because of their diverse biological activities and clinical applications. Their core ring system is present in numerous antiparasitic, fungicide and anti-inflammatory drugs.[1] Various thiazole derivatives are known to exhibit pharmacological activities.[2] Fused thiazoles are of importance not only as medicinal agents but also as organic functional materials such as fluorescent dyes.[3]

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 also described annulation in heterocyclization based Sonogashira coupling.[5] We were intrigued by the prospect of applying this methodology to the synthesis of other systems in particular heterocyclic systems.

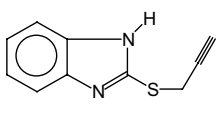
Although, several methods have been reported[6] for the synthesis of thiazolo[3,2-*a*]benzimidazoles, a literature survey showed no reference concerning the use of a Pd–Cu catalyzed preparation of this system.

We have recently reported the synthesis of various heterocyclic systems via a Sonogashira cross-coupling and a subsequent exocyclic cyclization.[7] In this communication we wish to extend our strategy to the synthesis of substituted 3-benzylthiazolo[3,2-*a*]benzimidazoles.

2-Mercaptobenzimidazole **1** was reacted with propargyl bromide in refluxing EtOH in the presence of $NH_4OH$



**1**



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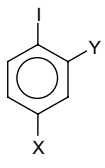

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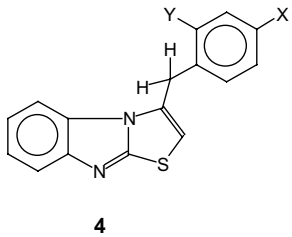

**4**

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**Table 1.** Melting points and yields of 3-benzylthiazolo[3,2-*a*]benzimidazoles **4a–e**

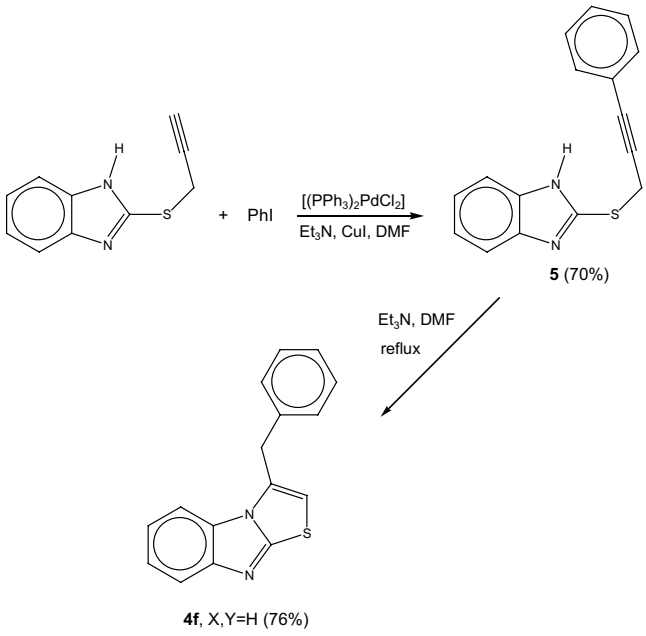
| Product | ArI | | Mp (°C) | [a]Yield (%) |
|---|---|---|---|---|
| | X | Y | | |
| **4a** | $NO_2$ | H | 191–2 | 82 |
| **4b** | $NO_2$ | Cl | 180–1 | 85 |
| **4c** | H | $NO_2$ | 147–8 | 78 |
| **4d** | CN | H | 209–10 | 79 |
| **4e** | Cl | CN | 214–6 | 81 |

[a] Yields refer to isolated products.

to yield 2-propargylmercaptobenzimidazole **2**.[8] When **2** was treated in DMF with aryl halides **3a–e** and triethylamine in the presence of bis(triphenylphosphine)palladium chloride and copper iodide at room temperature, 3-benzylthiazolo-[3,2-*a*]benzimidazoles **4** were obtained in good to high yields (Table 1). The reactions must be carried out under an argon atmosphere and the mixture of DMF and triethylamine must be degassed prior to use. Bis(triphenylphosphine) palladium chloride and triethylamine were found to be the catalyst and base of the choice. However, cuprous iodide was found to be an essential co-catalyst. Reactions carried out with either copper(I) iodide or palladium(II) chloride as catalysts alone led to very poor yields of products.

The mechanism of the reaction is illustrated in Scheme 1. Most probably a two step process occurs: first a standard Sonogashira coupling and known Pd(II) catalyzed intermolecular cyclization of the nucleophilic nitrogen moiety onto the triple bond followed by base-induced aromatization.

The presence of electron withdrawing groups such as $-NO_2$, –Cl, –CN on the aryl iodide seems to be essential. When PhI was used as the aryl halide, only a small amount of product (**4**, X, Y = H) was isolated by column chromatography. To establish the mechanism, the main product of this reaction was separated by column chromatography and identified as 2-[3-phenylpropargylmercapto]benzimidazole **5** (Scheme 2). This compound was cyclized and aromatized by refluxing in DMF/$Et_3N$




**Scheme 2.**

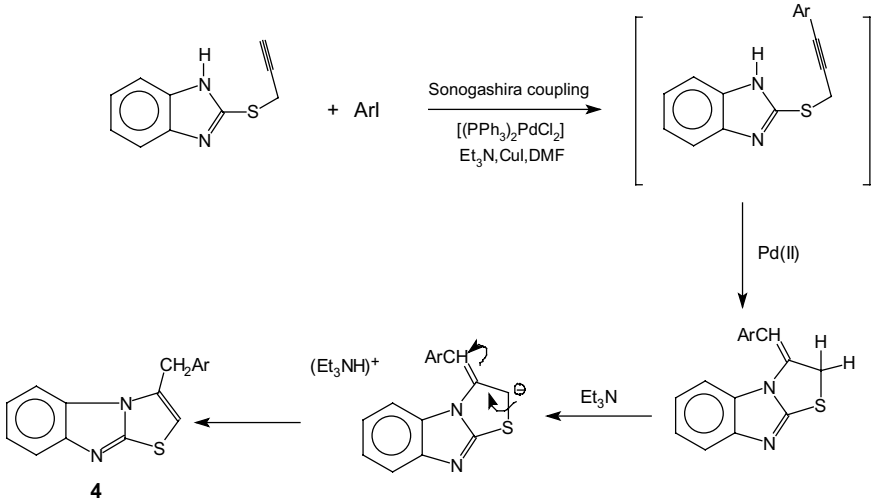
to obtain **4** (X, Y = H). When *p*-iodotoluene **3** (X, Y = Me) was used as the aryl iodide, Sonogashira coupling took place, but cyclization in DMF/$Et_3N$ under reflux conditions, even after a prolonged reaction time, could not be achieved.

In conclusion an efficient and extremely useful methodology for the synthesis of thiazolo[3,2-*a*]benzimidazoles has been reported.

## 1. Experimental

### 1.1. Synthesis of 3-substituted thiazolo[3,2-*a*]benzimidazole. General reaction conditions

A mixture of the aryl iodide (0.75 mmol), $(PPh_3)_2PdCl_2$ (0.025 mmol), CuI (0.055 mmol) and triethylamine




**Scheme 1.**

(2 mmol) was stirred in DMF (25 mL) at room temperature under an argon atmosphere. 2-Propargylmercaptobenzimidazole (1.27 mmol) was then added and the mixture was stirred at room temperature for 24 h. After completion of the reaction, water (5 mL) was added and the mixture was extracted with $CHCl_3$. The chloroform layer was separated and evaporated to dryness and the crude was directly subjected to column chromatography using $CHCl_3$–hexane 80:20 as eluent to afford the pure product (Table 1).

**1.1.1. Selected data for 4a.** Mp 191–2 °C; yield: 82%; $^1$H NMR $\delta$ (100 MHz, $CDCl_3$): 4.51 (s, 2H, $CH_2$), 6.25 (s, 1H, CH of thiazole), 7.12–7.51 (m, 4H, ArH), 7.78 (d, $J = 8.2$ Hz, 2H, ArH), 8.21 (d, $J = 8.2$ Hz, 2H, ArH); IR, $\tilde{\upsilon}$ (KBr disc): 1522, 1349 cm$^{-1}$; MS, $m/z$, 309.

**1.1.2. Selected data for 4b.** Mp 180–1 °C; yield: 85%; $^1$H NMR $\delta$ (100 MHz, DMSO-$d_6$): 4.76 (s, 2H, $CH_2$), 6.67 (s, 1H, CH of thiazole), 7.16–7.74 (m, 5H, ArH), 8.15 (dd, $J = 9.3$ Hz, 1H, ArH), 8.4 (d, $J = 2.2$ Hz, 1H, ArH); IR, $\tilde{\upsilon}$ (KBr disc): 1524, 1346 cm$^{-1}$; MS, $m/z$, $M^+$ 343, $M^{+2}$ 345 (= $^{37}$Cl).

**1.1.3. Selected data for 4c.** Mp 147–8 °C; yield: 78%; $^1$H NMR $\delta$ (100 MHz, $CDCl_3$): 4.78 (s, 2H, $CH_2$), 6.16 (s, 1H, CH of thiazole), 7.12–7.56 (m, 6H, ArH), 7.77 (d, $J = 7.8$ Hz, 1H, ArH), 8.2 (d, $J = 7.4$ Hz, 1H, ArH); IR, $\tilde{\upsilon}$ (KBr disc): 1527, 1340 cm$^{-1}$; MS, $m/z$, 309.

**1.1.4. Selected data for 4d.** Mp 209–10 °C; yield: 79%; $^1$H NMR $\delta$ (100 MHz, DMSO-$d_6$): 4.67 (s, 2H, $CH_2$), 6.78 (s, 1H, CH of thiazole), 7.15–7.89 (m, 8H, ArH); IR, $\tilde{\upsilon}$ (KBr disc): 2232 cm$^{-1}$; MS, $m/z$, $M^+$ 289.

**1.1.5. Selected data for 4e.** Mp 214–6 °C; yield: 81%; $^1$H NMR $\delta$ (100 MHz, DMSO-$d_6$): 4.76 (s, 2H, $CH_2$), 6.58 (s, 1H, CH of thiazole), 7.20–7.84 (m, 6H, ArH), 8.17 (d, $J = 2$ Hz, 2H, ArH); IR, $\tilde{\upsilon}$ (KBr disc): 2210 cm$^{-1}$ ; MS, $m/z$, $M^+$ 323, $M^{2+}$ 325 (= $^{37}$Cl).

### 1.2. Synthesis of 2-[3-phenylpropargyl]mercaptobenzimidazole 5

A mixture of iodobenzene (0.75 mmol), $(PPh_3)_2PdCl_2$ (0.025 mmol), CuI (0.055 mmol) and triethylamine (2 mmol) was stirred in DMF (25 mL) at room temperature under an argon atmosphere. 2-Propargylmercaptobenzimidazole (1.27 mmol) was then added and the mixture was stirred at room temperature for 24 h. After completion of the reaction, water (5 mL) was added and the mixture was extracted with $CHCl_3$. The chloroform layer was separated and evaporated to dryness and the crude was directly subjected to column chromatography using $CHCl_3$–hexane 80:20 as eluent to afford the pure product. Yield 70%; mp 144–5 °C; $^1$H NMR $\delta$ (100 MHz, $CDCl_3$): 4.26 (s, 2H, $CH_2$), 7.17–7.48 (m, 9H, ArH); IR, $\tilde{\upsilon}$ (KBr disc): 3059, 2500, 1416, 1278 cm$^{-1}$.

### 1.3. Synthesis of 3-benzthiazolo[3,2-*a*]benzimidazole 4f

Compound **5** was dissolved in triethylamine (2 mmol) and DMF (3 mL). The reaction mixture was refluxed for 3 h. After completion of the reaction, water (5 mL) was added and the mixture extracted with $CHCl_3$. The chloroform layer was separated and evaporated to dryness. The crude was directly subjected to column chromatography using $CHCl_3$ as eluent to afford the title compound. Yield 76%; mp 82–3 °C; $^1$H NMR $\delta$ (100 MHz, $CDCl_3$): 4.37 (s, 2H, $CH_2$), 6.14 (s, 1H, CH of thiazole), 7.12–7.80 (m, 9H, ArH); IR, $\tilde{\upsilon}$ (KBr disc): 3063 cm$^{-1}$; MS, $m/z$, $M^+$ 264.

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