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Palladium-catalyzed coupling of aryl iodides with 2-alkynylbenzonitriles

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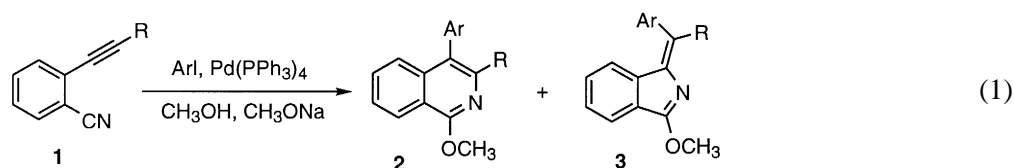
Abstract

The reaction of 2-(2-phenylethynyl)benzonitrile (**1a**) with aryl iodides, in the presence of Pd(PPh₃)₄ and NaOCH₃ in CH₃OH, at refluxing temperature for 24 h, gave 3-diarylmethylideneisoindoles **3a–d** in 18–56% yields. When 2-(1-hexynyl)benzonitrile (**1b**) was employed in this reaction, isoquinolines **2a–c** were obtained in 29–34% yields and isoindoles **3e–g** were obtained in 12–25% yields, respectively. Reaction of 2-ethynylbenzonitrile (**1c**) with 2.5 equiv. of iodobenzene for 48 h gave **3a** in 45% yield along with the monocoupled adduct **3h** in 6% yield. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: palladium; palladium compounds; cyclization; isoindoles; isoquinolines.

The chemistry of palladium has become a powerful tool for organic synthesis in recent years.¹ For example, the intramolecular cyclization of acetylenic molecules containing a heteronucleophile promoted by σ -vinyl and σ -aryl palladium complexes provides an efficient route to various heterocycles. For instance, the palladium-catalyzed cyclization of acetylenic alcohols has been shown to be an efficient route to exocyclic enol ethers.² In the same manner, *o*-ethynylphenols have been converted to 2-substituted-benzo[*b*]furans.³ This strategy has also been applied to molecules containing amino-,⁴ carboxyl-⁵ and carbo-nucleophiles.⁶ Our interest in the direct cyclization of 2-alkynylbenzonitriles to isoquinoline and isoindole derivatives⁷ encouraged us to examine the palladium-catalyzed cyclization of 2-alkynylbenzonitriles. We now report a new strategy for the synthesis of 3,4-disubstituted-isoquinolines **2** and diarylmethylideneisoindoles **3** (R=aryl) via the cross-coupling and cyclization of aryl iodides with 2-alkynylbenzonitriles **1** (Eq. (1)).

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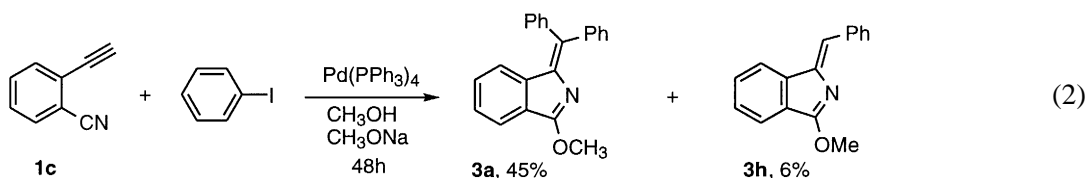
The presented reaction conditions are as follows: to a stirred solution of 2-alkynylbenzonitrile **1** (0.4 mmol) in dry methanol (10 mL) under nitrogen were added sequentially the aryl iodide (0.8 mmol), Pd(PPh₃)₄ (0.02 mmol) and sodium metal (5 atom-mmol). The resulting solution was heated under reflux and stirred at this temperature for 24 h or 48 h. After cooling to room temperature, the solvent was evaporated in vacuo. The residue was diluted with saturated aqueous NaCl solution and extracted with EtOAc (3×15 mL). The extracts were dried over anhydrous MgSO₄. After removal of solvent, the residue was purified by flash column chromatography to give the products. The results are summarized in Table 1.

Table 1
Palladium-catalyzed cyclization of 2-alkynylbenzonitriles

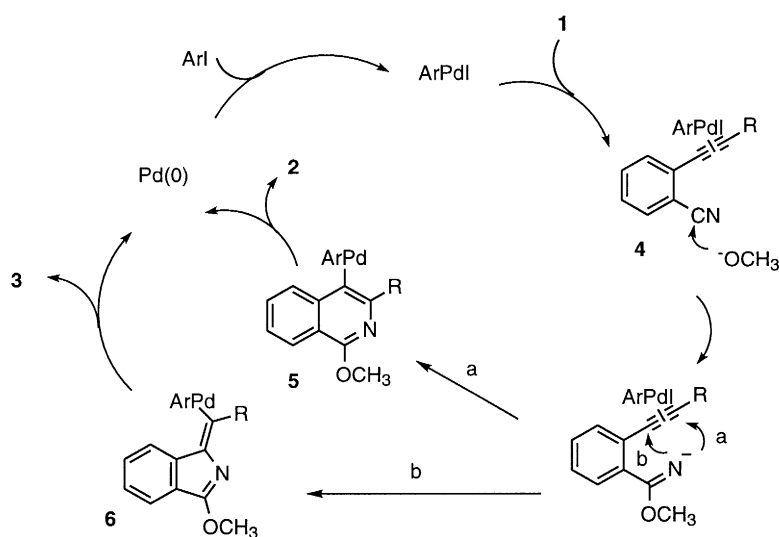
2-Alkynylbenzonitrile	Aryliodide	reaction time	products ^a (yield, %)
1a (R = Ph)	C ₆ H ₅ I	24h	3a (Ar = R = Ph) (46%)
1a	4-CH ₃ C ₆ H ₄ I	24h	3b (Ar = 4-CH ₃ C ₆ H ₄ ; R = Ph) (56%)
1a	4-CH ₃ OC ₆ H ₄ I	24h	3c (Ar = 4-CH ₃ OC ₆ H ₄ ; R = Ph) (40%)
1a	2-CH ₃ OC ₆ H ₄ I	24h	3d (Ar = 2-CH ₃ OC ₆ H ₄ ; R = Ph) (18%)
1b (R = <i>n</i> -Bu)	C ₆ H ₅ I	48h	2a (Ar = Ph; R = <i>n</i> -Bu) (32%)
			3e (Ar = Ph; R = <i>n</i> -Bu) (25%)
1b	4-CH ₃ C ₆ H ₄ I	48h	2b (Ar = 4-CH ₃ C ₆ H ₄ ; R = <i>n</i> -Bu) (34%)
			3f (Ar = 4-CH ₃ C ₆ H ₄ ; R = <i>n</i> -Bu) (19%)
1b	4-CH ₃ OC ₆ H ₄ I	48h	2c (Ar = 4-CH ₃ OC ₆ H ₄ ; R = <i>n</i> -Bu) (29%)
			3g (Ar = 4-CH ₃ OC ₆ H ₄ ; R = <i>n</i> -Bu) (12%)

^aYields refer to isolated yields. All of the compounds gave satisfactory ¹H NMR, ¹³C NMR and MS spectra data.⁸

The reaction of 2-(2-phenylethynyl)benzonitrile (**1a**) with iodobenzene under the described reaction conditions, gave isoindole **3a** in 46% yield after 24 h. The structure of **3a** was unambiguously determined by X-ray crystallographic analysis. Other aryl iodides have also been successfully employed in this cyclization reaction. 4-Methyliodobenzene and 4-methoxyiodobenzene afforded the isoindoles **3b** and **3c** in 56% and 40% yields, respectively. However, 2-methoxyiodobenzene gave **3d** in only 18% yield and unreacted **1a** in 36% yield. This is possibly due to a steric effect reducing the rate of the coupling reaction. Iodobenzenes bearing an electron withdrawing group, such as 4-chloriodobenzene and 4-iodoacetophenone, gave no cross-coupling products, only the cyclization product **3h** in 15–20% yield. On the other hand, the reaction of 2-(1-hexynyl)benzonitrile (**1b**) with iodobenzene under the reaction conditions, gave isoquinoline **2a** and isoindole **3e** in 32% and 25% yields, respectively, after 48 h. Similar results were obtained by employing the other aryl iodides. 4-Methyliodobenzene afforded **2b** and **3f** in 34% and 19% yields and 4-methoxyiodobenzene gave **2c** and **3g** in 29% and 12% yields. From the reaction of 2-ethynylbenzonitrile (**1c**) with iodobenzene (2.5 equiv.) under the standard reaction conditions for 48 h, compound **3a** was isolated in 45% yield along with **3h** in 6% yield (Eq. (2)).



A mechanism of this cyclization reaction is proposed in Scheme 1. The formation of **2** and **3** can proceed through: (a) coordination of the carbon–carbon triple bond of **1** to $\sigma\text{-C}_{\text{sp}^2}$ -palladium complexes to produce the η^2 -palladium complexes **4**, (b) methoxide addition to the cyano group, followed by intramolecular nucleophilic attack of the iminium ion to the activated carbon–carbon triple bond via a 6-*endo* or 5-*exo* transition state, and (c) reductive elimination of Pd^0 species from the resultant σ -arylpalladium complex **5** or σ -vinylpalladium complex **6**. When **1b** ($\text{R}=\text{n-Bu}$) was employed in this reaction, it favored the formation of the isoquinolines **2** via a 6-*endo* transition state overcoming the steric interaction between the two substituents at C3 and C4. However, when this reaction was carried out with **1a** ($\text{R}=\text{Ph}$), the steric interaction between the two aryl groups at C3 and C4 became more significant, and the isoindoles **3** were obtained predominantly instead.



Scheme 1.

In conclusion, the tandem palladium-catalyzed cyclization of 2-alkynylbenzonitriles provides a one-step synthesis of 3,4-disubstituted-isoquinolines and diarylmethylideneisoindoles. These molecules may show interesting biological activities.⁹ Currently, optimization of the regioselectivity of this cyclization reaction and examination of biological activities of these molecules are under investigation.

Acknowledgements

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8. Selected data: **3a**: a white solid. Mp 116–117°C; ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, 2H, *J*=7.1, 1.2 Hz), 7.53 (dt, 1H, *J*=7.5, 1.0 Hz), 7.46–7.49 (m, 2H), 7.23–7.39 (m, 7H), 7.06 (td, 1H, *J*=7.0, 1.1 Hz), 6.25 (dt, 1H, *J*=7.9, 1.0 Hz), 4.22 (s, 3H). Anal. calcd for C₂₂H₁₇NO: C, 84.85; H, 5.51; N, 4.50. Found: C, 84.78; H, 5.52; N, 4.45. Compound **3b**: a white solid. Mp 113–114°C; ¹H NMR (200 MHz, CDCl₃) δ 7.64 (d, 2H, *J*=8.1 Hz), 7.13–7.55 (m, 9H), 7.05 (td, 1H, *J*=7.3, 1.0 Hz), 6.23 (d, 1H, *J*=7.0 Hz), 4.22 (s, 3H), 2.37 (s, 3H). Anal. calcd for C₂₃H₁₉NO: C, 84.88; H, 5.89; N, 4.31. Found: C, 84.76; H, 5.95; N, 4.33. Compound **3c**: a white solid. Mp 150–152°C; ¹H NMR (200 MHz, CDCl₃) δ 7.74 (d, 2H, *J*=9.1 Hz), 7.36–7.54 (m, 6H), 7.22 (td, 1H, *J*=7.4, 1.0 Hz), 7.04 (td, 1H, *J*=7.3, 1.0 Hz), 6.88 (d, 2H, *J*=9.1 Hz), 6.17 (d, 1H, *J*=7.9 Hz), 4.23 (s, 3H), 3.83 (s, 3H). Anal. calcd for C₂₃H₁₉NO₂: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.88; H, 5.62; N, 4.06. Compound **3d**: a white solid. Mp 147–149°C; ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, 1H, *J*=7.5 Hz), 7.24–7.46 (m, 8H), 7.10 (td, 1H, *J*=7.3, 1.1 Hz), 6.98 (td, 1H, *J*=7.5, 1.1 Hz), 6.89 (dd, 1H, *J*=8.2, 0.9 Hz), 6.71 (d, 1H, *J*=7.9 Hz), 4.05 (s, 3H), 3.61 (s, 3H). Anal. calcd for C₂₃H₁₉NO₂: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.94; H, 5.63; N, 4.12. Compound **3e**: an oil. ¹H NMR (200 MHz, CDCl₃) δ 7.42–7.51 (m, 4H), 7.30–7.35 (m, 2H), 7.20 (td, 1H, *J*=7.4, 1.2 Hz), 7.03 (td, 1H, *J*=7.6, 1.2 Hz), 6.38 (dd, 1H, *J*=7.8, 1.0 Hz), 4.22 (s, 3H), 3.10 (t, 2H, *J*=7.4 Hz), 1.30–1.50 (m, 4H), 0.93 (t, 3H, *J*=7.0 Hz); EI(MS) *m/z* (rel. intensity) 291 (M⁺, 49), 276 (99), 249 (70), 234 (100). Compound **2a**: an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, 1H, *J*=7.9 Hz), 7.63 (dd, 2H, *J*=7.1, 1.2 Hz), 7.58 (dt, 1H, *J*=7.5, 1.0 Hz), 7.48 (td, 1H, *J*=7.3, 1.2 Hz), 7.36–7.41 (m, 3H), 7.31 (dd, 1H, *J*=7.3, 1.2 Hz), 4.05 (s, 3H), 3.11 (t, 2H, *J*=8.0 Hz), 1.44–1.65 (m, 4H), 0.93 (t, 3H, *J*=7.3 Hz); EI(MS) *m/z* (rel. intensity) 291 (M⁺, 46), 249 (70), 133 (100). Compound **3f**: an oil. ¹H NMR (200 MHz, CDCl₃) δ 7.48 (dd, 1H, *J*=7.3, 1.1 Hz), 7.17–7.29 (m, 5H), 7.05 (td, 1H, *J*=7.3, 1.1 Hz), 6.47 (dd, 1H, *J*=7.7, 1.0 Hz), 4.21 (s, 3H), 3.09 (t, 2H, *J*=7.4 Hz), 2.46 (s, 3H), 1.36–1.49 (m, 4H), 0.93 (t, 3H, *J*=7.0 Hz); EI(MS) *m/z* (rel. intensity) 305 (M⁺, 67), 290 (100), 248 (68). Compound **2b**: an oil. ¹H NMR (200 MHz, CDCl₃) δ 7.91 (d, 1H, *J*=8.0 Hz), 7.58–7.60 (m, 3H), 7.49 (td, 1H, *J*=7.6, 1.1 Hz), 7.38 (td, 1H, *J*=7.5, 1.0 Hz), 7.22 (d, 2H, *J*=7.8 Hz), 4.08 (s, 3H), 1.63–1.65 (m, 2H), 1.48–1.52 (m, 2H), 0.96 (t, 3H, *J*=7.3 Hz); EI(MS) *m/z* (rel. intensity) 305 (M⁺, 76), 290 (100), 248 (66). Compound **3g**: an oil. ¹H NMR (200 MHz, CDCl₃) δ 7.49 (d, 1H, *J*=7.4 Hz), 7.17–7.27 (m, 3H), 7.06 (td, 1H, *J*=7.7, 1.2 Hz), 6.98 (d, 2H, *J*=8.8 Hz), 6.50 (dd, 1H, *J*=7.8, 0.8 Hz), 4.20 (s, 2H), 3.89 (s, 3H), 3.08 (t, 2H, *J*=7.3 Hz), 1.30–1.50 (m, 4H), 0.92 (t, 3H, *J*=7.0 Hz); EI(MS) *m/z* (rel. intensity) 321 (M⁺, 81), 306 (100), 264 (49). Compound **2c**: an oil. ¹H NMR (200 MHz, CDCl₃) δ 7.89 (d, 1H, *J*=7.7 Hz), 7.66 (d, 2H, *J*=9.0 Hz), 7.36–7.56 (m, 3H), 6.93 (d, 2H, *J*=9.0 Hz), 4.08 (s, 3H), 3.86 (s, 3H), 3.11 (t, 2H, *J*=7.5 Hz), 1.35–1.70 (m, 4H), 0.94 (t, 2H, *J*=7.2 Hz). Compound **3h**: an oil. ¹H NMR (400 MHz, CDCl₃) δ 8.22 (m, 2H), 7.77 (dt, 1H, *J*=7.7, 1.0 Hz), 7.57 (dt, 1H, *J*=7.5, 1.0 Hz), 7.26–7.50 (m, 6H), 6.91 (s, 1H), 4.28 (s, 3H); EI(MS) *m/z* (rel. intensity) 235 (M⁺, 54), 220 (100), 165 (22).
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