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Pd-Mediated synthesis of 7*H*-benzo[3,4]azepino[1,2-*a*]indole-6-carboxylic acid derivatives from indole-containing Baylis–Hillman adducts

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Abstract

We synthesized novel tetracyclic fused indole derivatives via the intramolecular Heck reaction of indole-containing Baylis–Hillman adducts in good to moderate yields.

Keywords: Baylis–Hillman adducts; Benzoazepino[1,2-*a*]indole; Heck reaction; Palladium

Due to the abundance of medium-sized heterocyclic compounds in many natural products, drugs, and preclinical leads, syntheses of these compounds by intramolecular Heck type reaction have received much attention.[1] Palladium-mediated direct aryl–aryl bond-forming protocols have also been studied extensively in this respect.[2] Among the approaches of aryl–aryl bond-forming reactions, the use of indole moiety as one of the aryl group received special interest due to the biological importance of indole moiety-containing heterocyclic compounds.[1c,2a,b,3]

Although palladium-mediated synthesis of medium-sized heterocyclic compounds has been investigated,[1] studies involving the Baylis–Hillman adducts have not been reported much.[4,5] Lamaty and co-workers reported the synthesis of benzazepines starting from the aza-Baylis–Hillman adducts.[4a,b] Vasudevan and co-workers examined the cyclization of sulfonamide derivatives of Baylis–Hillman adducts and prepared seven-membered heterocyclic compounds.[4c] Very recently, we reported the synthesis of pentacyclic benzoazepino[2,1-*a*]isoindole compounds via consecutive carbopalladation using enamides of Baylis–Hillman adducts.[5]

During the continuous studies we reasoned that indole-containing Baylis–Hillman adducts could be used efficiently for the synthesis of poly-fused heterocyclic compounds including benzo[3,4]azepino[1,2-*a*]indoles[6] by applying intramolecular palladium-catalyzed arylation. Poly-fused heterocyclic compounds having indole moiety were known to possess many interesting biological activities[6–8] including hepatitis C virus (HCV) NS5B polymerase inhibitory activity,[6] thus we decided to examine the intramolecular Heck reaction with indole-containing Baylis–Hillman adducts as shown in Scheme 1.

Required starting materials **3a**–**g** were synthesized by the reaction of Baylis–Hillman acetates **1**[4d] and indole derivatives **2** (KOH, DMF, 0 °C)[9] in 45–95% yields. In all cases, *E*-forms of **3a**–**g** were formed as the majors and we separated them easily from the minor *Z*-isomers (5–10%).[4,5] We examined the optimum reaction conditions for the intramolecular palladium-catalyzed arylation with compound **3a**, and the results are summarized in Table 1. Although all the conditions examined afforded desired product **4a** in variable yields (24–65%), the conditions

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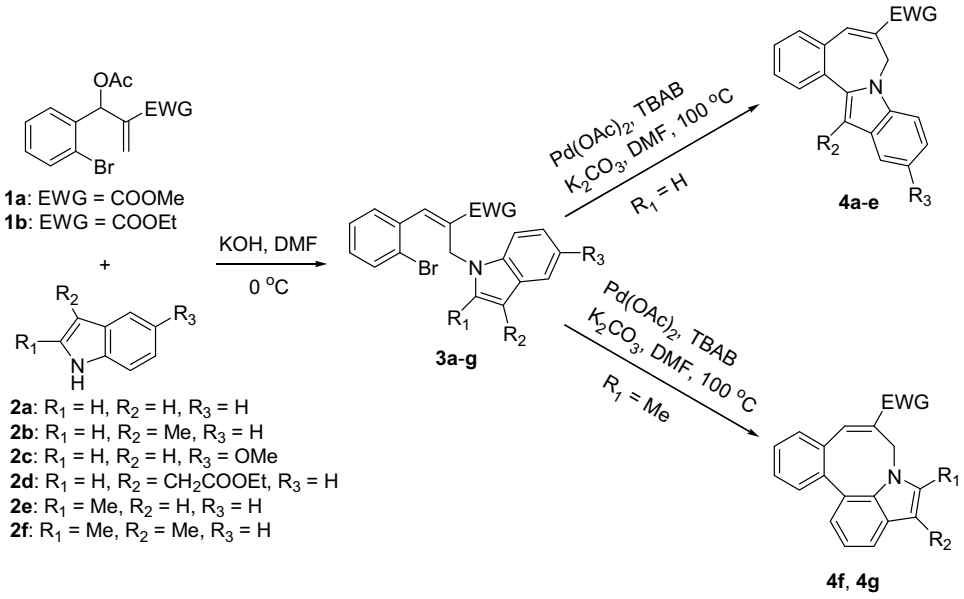


Scheme 1.

Table 1
Optimization of the reaction conditions for the synthesis of **4a**

Entry	Conditions	Time (h)	**4a**[a] (%)	**3a**[a] (%)
1	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), K_2CO_3 (2.0 equiv), DMF, 100 °C	1	65	0
2	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (2.0 equiv), DMF, 100 °C	1	61	0
3	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), KOAc (2.0 equiv), DMF, 100 °C	1	58	0
4	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN, reflux	1	54	8
5	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), $NaHCO_3$ (2.0 equiv), DMF, 100 °C	8	45	5
6	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N (2.0 equiv), DMF, 100 °C	18	24	32

[a] Isolated yield.

Table 2
Pd-mediated cyclizations of indole moiety-containing Baylis–Hillman adducts

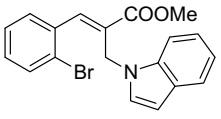
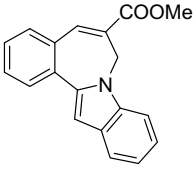
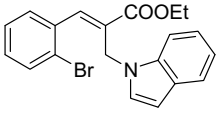
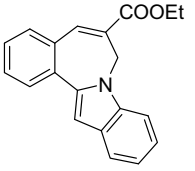
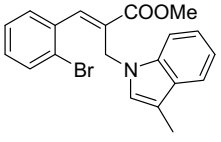
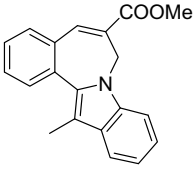
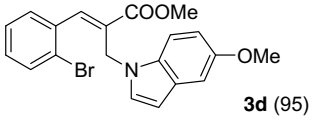
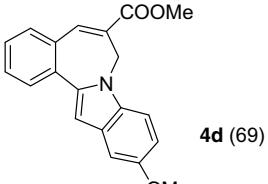
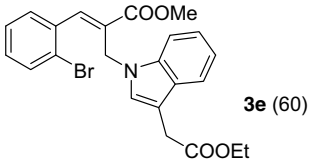
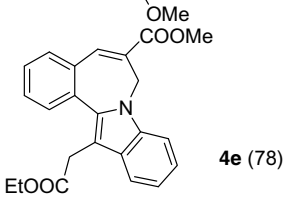
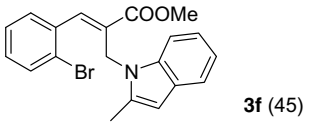
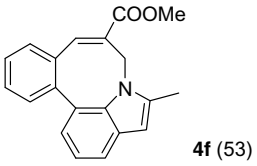
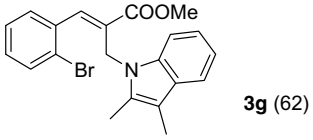
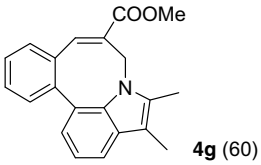
Entry	Substrate[a] (%)	Time (min)	Product[b] (%)
1	 **3a** (73)	60	 **4a** (65)
2	 **3b** (50)	60	 **4b** (82)
3	 **3c** (51)	30	 **4c** (66)

Table 2 (*continued*)

Entry	Substrate[a] (%)	Time (min)	Product[b] (%)
4	 **3d** (95)	120	 **4d** (69)
5	 **3e** (60)	30	 **4e** (78)
6	 **3f** (45)	60	 **4f** (53)
7	 **3g** (62)	300	 **4g** (60)

[a] Conditions: **1** (1.2 equiv), **2** (1.0 equiv), KOH (1.2 equiv), DMF, 0 °C, 30 min to 4 h. The stereochemistry of **3a**–**g** was confirmed as *E* by their chemical shifts of vinyl protons ($\delta = 7.83$–7.98 ppm).

[b] Conditions: **3** (1.0 equiv), $Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), K_2CO_3 (2.0 equiv), DMF, 100 °C, 30 min to 5 h.

using $Pd(OAc)_2$/TBAB (tetrabutylammonium bromide)/K_2CO_3 in DMF (entry 1) was the best (65%). Under the optimized conditions we examined the reactions of **3b**–**g** and the results are summarized in Table 2.[10] For the indole derivatives **3a**–**e**, the reactions produced seven-membered benzoazepino[1,2-*a*]indole derivatives **4a**–**e** in good yields (65–82%). However, 2-methyl group in compounds **3f** and **3g** rendered the formation of seven-membered ring impossible, and aryl–aryl bond-formation occurred to form the eight-membered compounds **4f** and **4g** in moderate yields (53–60%).[10] The extreme selectivity between seven- and eight-membered ring-formation could be used for further elaboration of this strategy.

In summary, we synthesized tetracyclic indole derivatives via the palladium-mediated intramolecular Heck reaction from indole-containing Baylis–Hillman adducts.

Acknowledgments

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10. *Typical procedure for the synthesis of* **3a** *and* **4a**: To a stirred solution of indole (**2a**, 117 mg, 1.0 mmol) and KOH (79 mg, 1.2 mmol) in DMF (1.5 mL) was added a solution of Baylis–Hillman acetate **1a** (376 mg, 1.2 mmol) in DMF (0.5 mL) at 0 °C, and maintained at 0 °C for 4 h with stirring. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 10:1), we obtained **3a** (271 mg, 73%) as a white solid. A stirred mixture of **3a** (185 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), TBAB (161 mg, 0.5 mmol), and K_2CO_3 (138 mg, 1.0 mmol) in DMF (2 mL) was heated to 100 °C for 1 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 10:1), we obtained **4a** (95 mg, 65%) as a pale yellow solid. Other compounds **3b–g** and **4b–g** were synthesized similarly and the representative spectroscopic data of compounds **3a**, **4a**, and **4f** are as follows:
Compound **3a**: 73%; white solid, mp 95–97 °C; IR (film) 1717, 1463, 1435, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, 3H), 5.03 (s, 2H), 6.43 (d, $J = 3.3$ Hz, 1H), 6.99–7.30 (m, 7H), 7.56 (d, $J = 6.9$ Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.26, 52.36, 101.54, 109.52, 119.36, 120.72, 121.41, 123.87, 127.47, 127.48, 128.50, 129.51, 130.14, 130.53, 133.10, 134.90, 136.04, 142.48, 166.81; ESIMS *m*/*z* 370.09 (M^++H).
Compound **4a**: 65%; yellow solid, mp 142–144 °C; IR (film) 1705, 1457, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 4.97 (s, 2H), 6.74 (s, 1H), 7.08–7.13 (m, 1H), 7.20–7.28 (m, 1H), 7.35–7.48 (m, 3H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.19, 52.41, 101.23, 109.27, 119.78, 120.71, 122.00, 127.58, 128.16, 129.66, 129.98, 130.22, 131.82 (2C), 133.15, 136.33, 139.21, 142.71, 166.03; ESIMS *m*/*z* 290.19 (M^++H). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.67; H, 5.47; N, 4.76.
Compound **4f**: 53%; white solid, mp 179–181 °C; IR (film) 1714, 1438, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.57 (d, $J = 0.6$ Hz, 3 H), 3.73 (s, 3H), 4.82 (d, $J = 14.1$ Hz, 1H), 5.01 (d, $J = 14.1$ Hz, 1H), 6.21 (d, $J = 0.6$ Hz, 1H), 6.77 (dd, $J = 7.2$ and 0.6 Hz, 1H), 7.05–7.10 (m, 1H), 7.18 (d, $J = 7.2$ Hz, 1H), 7.35–7.52 (m, 4H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.65, 40.91, 52.03, 100.52, 119.47, 119.98, 125.76, 125.78, 126.74, 127.39, 129.47, 130.08, 131.65, 133.48, 134.62, 135.23, 137.72, 140.25, 145.46, 166.62; ESIMS *m*/*z* 304.18 (M^++H). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.05; H, 5.78; N, 4.53.