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# Pd-mediated synthesis of novel pentacyclic benzoazepino-[2,1-*a*]isoindoles from enamides of Baylis–Hillman adducts

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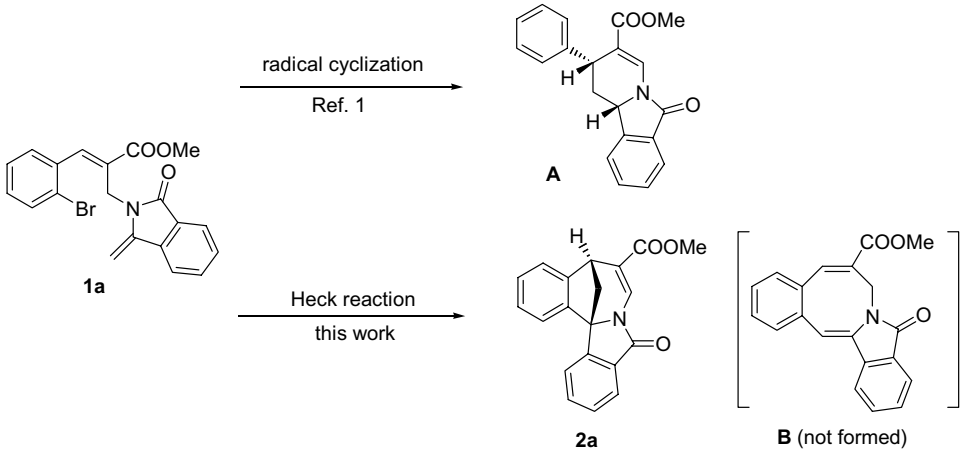
**Abstract**—Novel pentacyclic benzoazepino[2,1-*a*]isoindole derivatives were synthesized by palladium-mediated consecutive cyclization from enamides of Baylis–Hillman adducts.


Very recently, we reported the synthesis of tetrahydropyrido[2,1-*a*]isoindole derivative **A** (Scheme 1) under radical cyclization conditions from enamide derivative **1a**, which was prepared from Baylis–Hillman adducts.[1] During the radical cyclization reaction of **1a**, we did not observe the formation of seven- or eight-membered cyclic compounds. The results could be explained by the faster hydrogen atom abstraction by the aryl radical than the radical cyclization pathways.[1] However, seven- or eight-membered ring compounds could be constructed by using Heck type cyclization of **1a** as shown in Scheme 1.[2–4] We reasoned that if the carbopalladation during the reaction progress would occur to form the eight-membered intermediate we could observe the formation of compound **B**, otherwise we could obtain **2a**, when the first carbopalladation occurs to form the seven-membered intermediate, followed by a second carbopalladation and β-elimination.[2–4]




**Scheme 1.**

*Keywords*: Baylis–Hillman adducts; Benzoazepino[2,1-*a*]isoindole; Carbopalladation; Enamides.
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**Table 1.** Optimization of reaction conditions for the synthesis of **2a** from **1a**

| Entry | Catalyst (equiv) | Base (equiv) | Ligand (equiv) | Additives (equiv) | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (0.2) | $NaHCO_3$ (2.0) | None | TEACl (1.0) | DMF | 80 | 3 | 40 |
| 2 | $Pd(OAc)_2$ (0.2) | $NaHCO_3$ (2.0) | None | TBACl (1.0) | DMF | 80 | 3 | 49 |
| 3 | $Pd(OAc)_2$ (0.2) | $NaHCO_3$ (2.0) | None | TBAB (1.0) | DMF | 80 | 3 | 55 |
| 4 | $Pd(OAc)_2$ (0.2) | $NaHCO_3$ (2.0) | $PPh_3$ (0.2) | TBAB (1.0) | DMF | 80 | 14 | 51[a] |
| 5 | $Pd(OAc)_2$ (0.4) | $Et_3N$ (2.0) | $PPh_3$ (0.4) | TBAB (1.0) | $CH_3CN$ | Reflux | 60 | 29[a,b] |
| 6 | $PdCl_2$ (0.2) | $NaHCO_3$ (2.0) | None | TBAB (1.0) | DMF | 100 | 16 | 33 |

[a] Slow reaction compared to entry 3.
[b] Compound **1a** was recovered in 47%.

To check the feasibility of the reaction, we examined the reaction conditions with enamide **1a** as the representative example (Table 1). We obtained benzoazepino[2,1-*a*]-isoindole derivative **2a** in variable yields. We could not isolate any other compounds, such as compound **B**, in appreciable amounts. Among the conditions, the use of $Pd(OAc)_2$/*n*-$Bu_4NBr$/$NaHCO_3$/DMF/80 °C (entry 3) gave the best results for the formation of **2a** (55%). The presence of triphenylphosphine reduced the reaction rate (entry 4) and the use of triethylamine was less effective (entry 5). The structure of **2a** was confirmed by its $^1H$, $^{13}C$ NMR, mass data, and eventually by its crystal structure (Fig. 1).[5,6] As shown in Scheme 2, the formation of compound **2a** can be rationalized as follows: oxidative palladation, successive double carbopalladation, and the final β-elimination process.[2–4]

Benzoazepino[2,1-*a*]isoindoles and related compounds have been prepared and studied extensively due to their interesting biological activities and abundance in natural products.[7] However, most of the reported methods for the synthesis of these compounds used *N*-acyliminium ion chemistry.[7] In these contexts, an efficient synthetic approach of benzoazepino[2,1-*a*]isoindole skeleton involving palladium-mediated cyclization protocol could provide an alternative for *N*-acyliminium ion chemistry.

Thus we examined the reactions of enamides **1b–f** under the optimized conditions and the results are summarized in Table 2. The required starting materials **1a–d** and **1f** were prepared from the Baylis–Hillman adducts of 2-bromobenzaldehydes in reasonable yields as reported by following the process in Scheme 3 (**1a** as a typical example).[1] For the preparation of **1e**, we used 3-*n*-propylidenephthalide instead of 2-acetylbenzoic acid at the last stage. With these enamides, **1b–f**, we carried out the reactions under the optimized conditions (entry 3 in Table 1). The reaction of **1b** and **1c** showed similar results (entries 2 and 3) and the reaction can be applied equally well to the benzylidene derivative **1d** and we obtained the corresponding pentacyclic compound **2d** in a similar yield (entry 4). However, as expected, we obtained **2e** in the case of propylidene derivative **1e**. The presence of β-hydrogen in the propylidene moiety

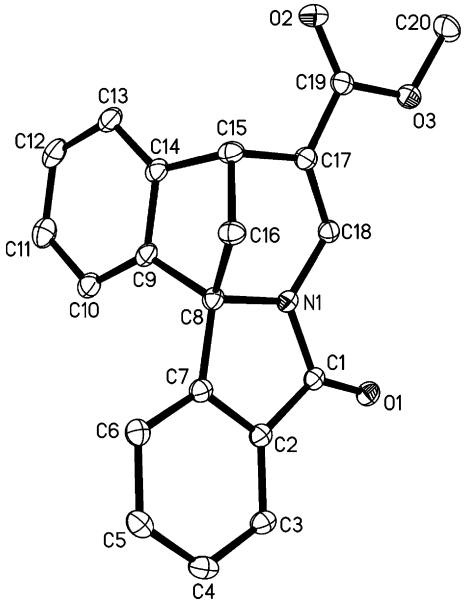
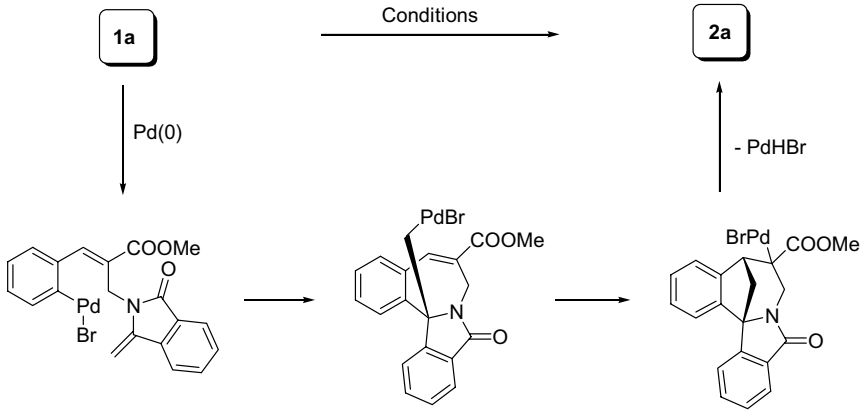
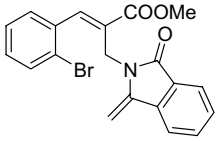
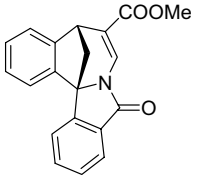
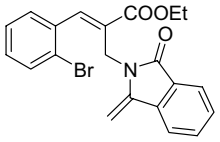
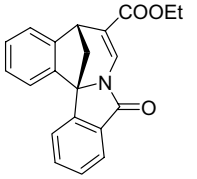
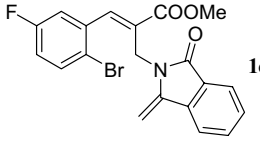
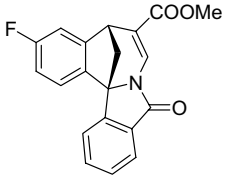
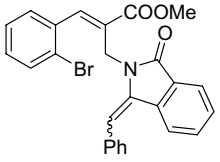
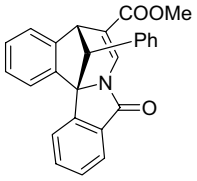
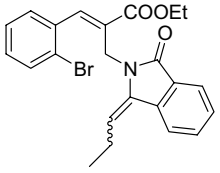
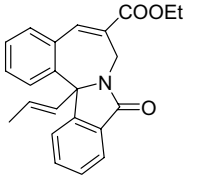
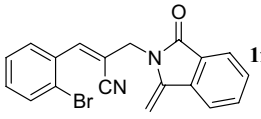
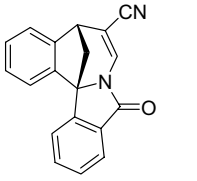



**Figure 1.** ORTEP drawing of compound **2a**.

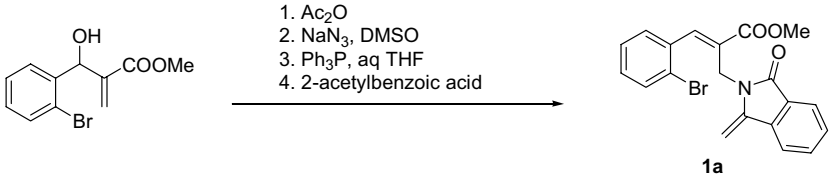



**Scheme 2.**

**Table 2.** Synthesis of benzoazepino[2,1-*a*]isoindole compounds[a]

| Entry | Substrate | Time (h) | Products (%) |
|---|---|---|---|
| 1 |  **1a** | 3 |  **2a** (55) |
| 2 |  **1b** | 10 |  **2b** (52) |
| 3 |  **1c** | 13 |  **2c** (53) |
| 4[b] |  **1d** | 14[d] |  **2d** (46)[e] |
| 5[b] |  **1e** | 10 |  **2e** (57) |
| 6[c] |  **1f** | 4 |  **2f** (5)[f] |

[a] Conditions: Substrate (1.0 equiv), $Pd(OAc)_2$ (0.2 equiv), $NaHCO_3$ (2.0 equiv), *n*-$Bu_4NBr$ (1.0 equiv), DMF, 80 °C.
[b] Single isomer was obtained but not determined the stereochemistry.
[c] Pure *Z*-isomer was used.
[d] $Pd(OAc)_2$ (0.5 equiv) was used.
[e] Single isomer was obtained but stereochemistry is arbitrary.
[f] Impure and **1f** (20%) was recovered.




**Scheme 3.**

permits β-elimination after the first carbopalladation to product **2e** in moderate yield (57%).

Next, we examined the reaction of nitrile derivative **1f**, which has *Z*-configuration around the double bond. We thought that the formation of the corresponding pentacyclic compound would be difficult presumably due to the inaccessibility of the reaction sites. Actually, we observed the formation of many intractable polar compounds, however, trace amounts of product **2f**[8]

were isolated with recovered starting material **1f** (ca 20%).

In summary, we described the synthesis of novel pentacyclic benzoazepino[2,1-*a*]isoindole compounds from enamide derivatives of the Baylis–Hillman adducts under Heck type cyclization conditions via a double carbopalladation. Further synthetic applications of these findings are currently underway.

## Acknowledgements

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5. *Crystal data of compound* **2a**: Solvent of crystal growth (hexanes/$CH_2Cl_2$, 10:90); empirical formula $C_{20}H_{15}NO_3$, Fw = 317.33, crystal dimensions $0.60 \times 0.60 \times 0.20$ mm$^3$, monoclinic, space group $P2(1)/c$, $a = 13.4999(5)$ Å, $b = 13.3510(5)$ Å, $c = 8.4082(3)$ Å, $\alpha = 90°$, $\beta = 91.0160(10)°$, $\gamma = 90°$, $V = 1515.23(10)$ Å$^3$, $Z = 4$, $D_{calcd.} = 1.391$ mg/m$^3$. $F_{000} = 664$, Mo K$\alpha$ ($\lambda = 0.71073$ Å), $R_1 = 0.0459$, $wR_2 = 0.1154$ ($I > 2\sigma(I)$). We omitted hydrogen atoms for clarity (Fig. 1). The X-ray data have been deposited in CCDC with number 655696.
6. *Typical procedure for the synthesis of* **2a**: A mixture of **1a** (52 mg, 0.13 mmol), palladium acetate (6 mg, 0.03 mmol, 20 mol %), tetrabutylammonium bromide (42 mg, 0.13 mmol), and anhydrous $NaHCO_3$ (22 mg, 0.26 mmol) in DMF (1.0 mL) was stirred at around 80 °C for 3 h under $N_2$ atmosphere. After the usual aqueous workup and column chromatographic purification process on silica gel (hexanes/EtOAc, 9:1), we obtained **2a** (23 mg, 55%) as a white solid. The spectroscopic data of selected compounds **2a** and **b** are as follows:
*Compound* **2a**: 55%; white solid, mp 118–120 °C; IR (film) 2949, 3068, 1720, 1699, 1379, 1242 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.93 (d, $J = 10.5$ Hz, 1H), 2.96 (dd, $J = 10.5$ and 4.2 Hz, 1H), 3.79 (s, 3H), 4.46 (d, $J = 4.2$ Hz, 1H), 6.58 (d, $J = 7.5$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.28 (t, $J = 7.8$ Hz, 1H), 7.38 (d, $J = 7.2$ Hz, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.66 (t, $J = 7.5$ Hz, 1H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.88 (s, 1H), 8.06 (d, $J = 7.5$ Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 39.86, 44.25, 51.65, 71.40, 114.38, 121.85, 121.89, 123.17, 125.04, 127.31, 127.93, 129.63 (2C), 132.16, 133.37, 141.29, 145.40, 146.70, 163.44, 166.27; ESIMS *m/z* 318 ($M^+$+1). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.82; H, 4.89; N, 4.23.
*Compound* **2b**: 52%; white solid, mp 123–125 °C; IR (film) 2979, 1720, 1606, 1242 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.32 (t, $J = 7.2$ Hz, 3H), 1.93 (d, $J = 10.5$ Hz, 1H), 2.95 (dd, $J = 10.5$ and 4.2 Hz, 1H), 4.21–4.29 (m, 2H), 4.47 (d, $J = 4.2$ Hz, 1H), 6.58 (d, $J = 7.5$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.28 (t, $J = 7.5$ Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.67 (t, $J = 7.5$ Hz, 1H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.87 (s, 1H), 8.06 (d, $J = 7.5$ Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.39, 39.83, 44.25, 60.49, 71.42, 114.72, 121.83, 121.88, 123.15, 125.02, 127.26, 127.65, 129.58, 129.60, 132.17, 133.32, 141.30, 145.41, 146.76, 163.43, 166.80; ESIMS *m/z* 332 ($M^+$+1). Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.22; H, 5.41; N, 4.21.
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8. Compound **2f** was isolated in impure state in about 5% yield, however, characteristic peaks of compound **2f** in $^1$H NMR confirmed the presence of this compound: the three ABX protons at up-field region appeared, 2.03 (d, $J = 10.5$ Hz, 1H), 2.98 (dd, $J = 10.5$ and 4.2 Hz, 1H), 4.01 (d, $J = 4.2$ Hz, 1H).