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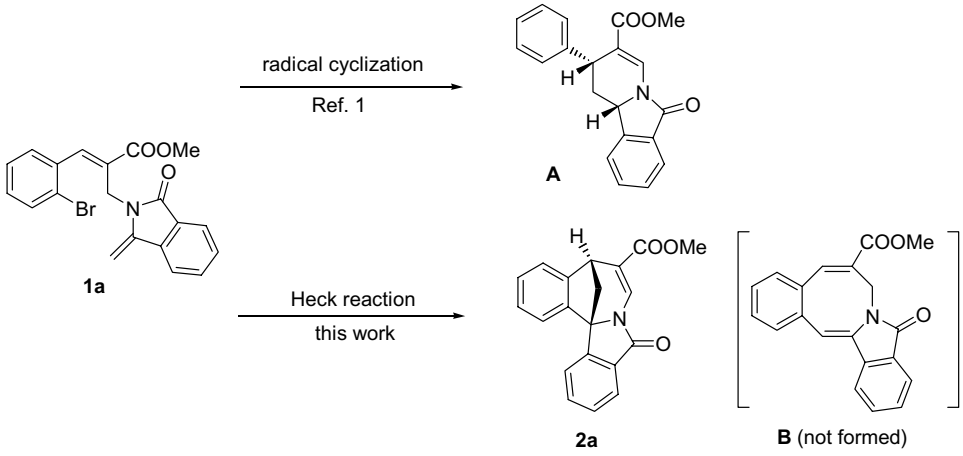
Abstract—Novel pentacyclic benzoazepino[2,1-*a*]isoindole derivatives were synthesized by palladium-mediated consecutive cyclization from enamides of Baylis–Hillman adducts.

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

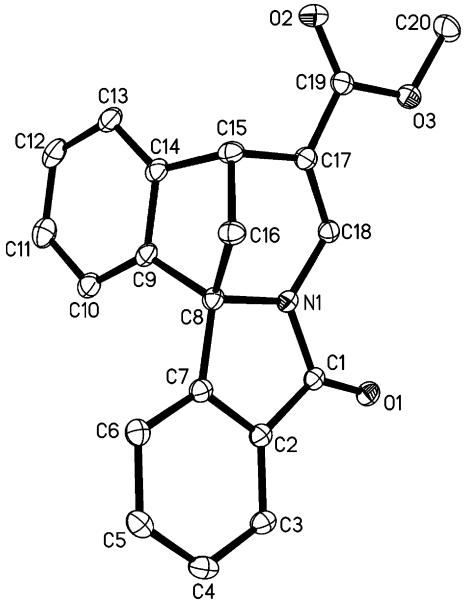
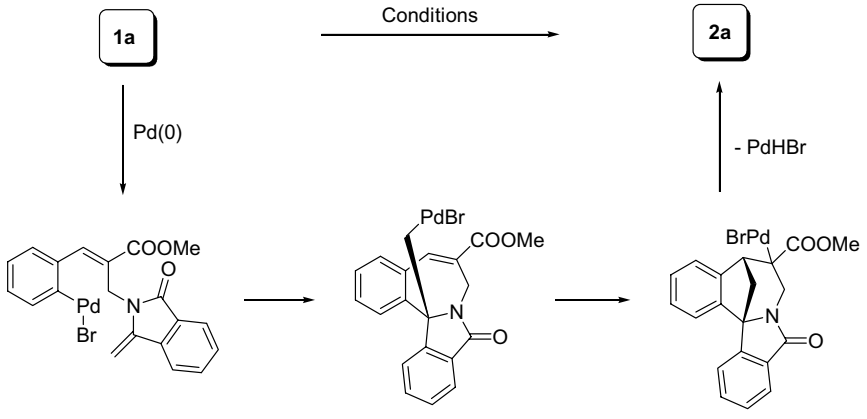


Figure 1. ORTEP drawing of compound **2a**.



Scheme 2.