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Synthesis of Dihydroanthracenes *via* Palladium-Catalyzed Tandem Mizoroki–Heck/Reductive Heck Reactions Using Cyclic Diaryliodoniums and Alkenes

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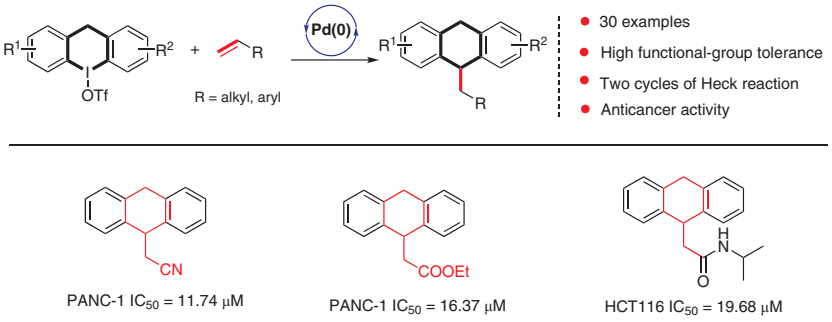

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Abstract An efficient Pd-catalyzed domino Mizoroki–Heck and reductive Heck reaction of terminal alkenes with six-membered cyclic diaryliodoniums is reported for the facile access to a diverse set of novel dihydroanthracenes. The scope of alkenes is general, leading to concise generation of 30 dihydroanthracenes which are not easily accessed by conventional methods. Furthermore, one of the newly synthesized dihydroanthracene displayed excellent antiproliferative activity against PANC-1 cancer cells (IC_{50} = 11.74 μM).

Key words cyclic diaryliodoniums, terminal alkenes, dihydroanthracenes, Heck reaction

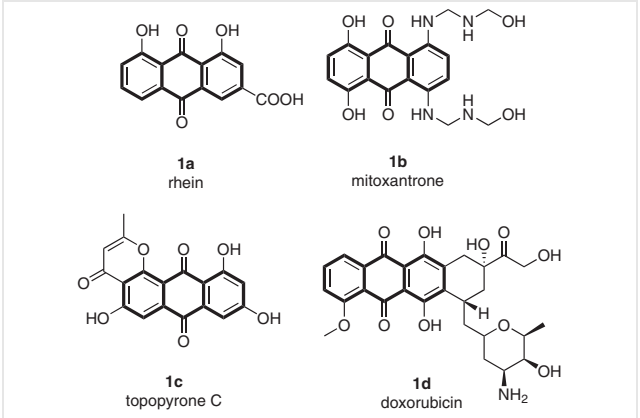

Figure 1 Representative compounds containing anthracene

Anthracene-based derivatives are essential structural motifs in a great number of anticancer drugs,[1] organic functional materials,[2] and natural products.[3] For instance, rhein (**1a**) possesses an anthracene scaffold and exhibits an excellent anti-inflammatory activity[4] (Figure 1). Just like other anthracene-based compounds, there are several anthracene-based drugs such as mitoxantrone (**1b**), topopyrone C (**1c**), and doxorubicin (**1d**) with anticancer activities probably due to their noncovalent binding to DNA duplexes and these drugs are used for treatment of various cancers[5] (Figure 1). In recent years, some studies have found that anthracene-based derivatives can also be used as an effective antidepressant with similar pharmacological properties to tricyclic antidepressants (TCAs).[6]

Thus, the synthesis of various anthracenes had attracted extensive attention by organic chemists and medicinal chemists. A variety of synthetic methods have been developed to construct dihydroanthracene scaffolds over the past few years, including benzylation of arenes,[7] modification of the existing dihydroanthracenes core,[8] and Friedel–Crafts alkylation[9] (Scheme 1a and 1b). However, these present methods still have some challenges that need to be addressed, including harsh conditions, limited substrate scopes, poor accessibility of starting materials, and low yields. In the past decades, cyclic diaryliodonium salts have found numerous applications as electrophilic arylating reagents in both transition-metal-catalyzed and metal-free reactions to construct diverse arenes or heterocycles due to their high reactivity and environmentally benign nature.[10]

In our previous study, we demonstrated that dual arylation of dicarbonyl and C–N Buchwald coupling of nitriles with cyclic diaryliodonium salts could lead to the construction of fluorenes and acridines conveniently.[11] To continue our interest in constructing libraries of complex molecules with cyclic diaryliodonium salts, we envisioned that the careful modulation of two tandem Mizoroki–Heck reactions including one conventional Mizoroki–Heck reaction and one reductive Heck reaction between terminal alkenes and six-membered cyclic diaryliodonium salts could pro-

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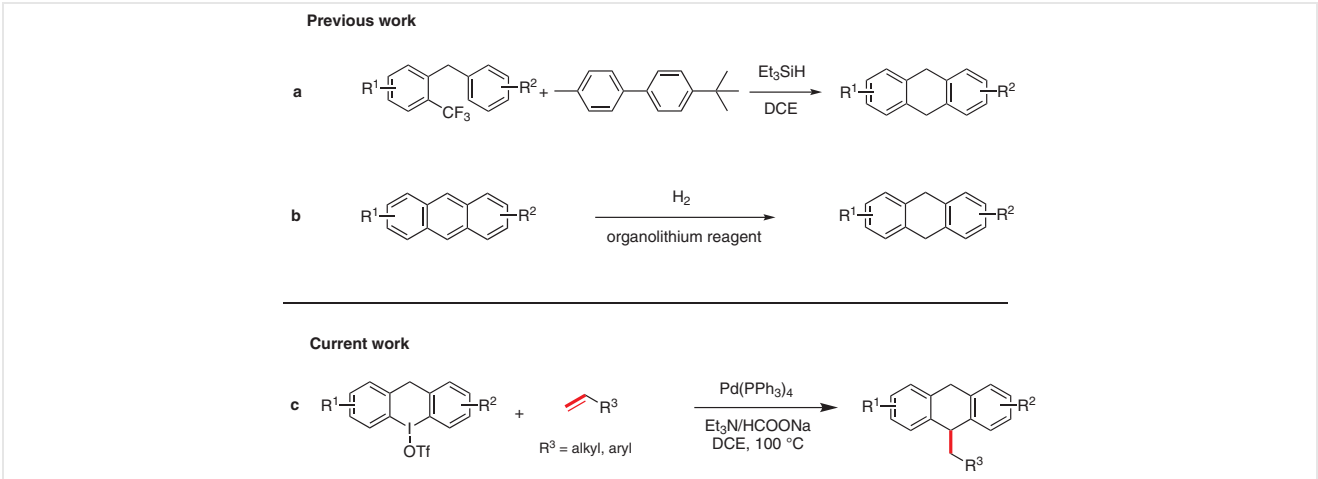


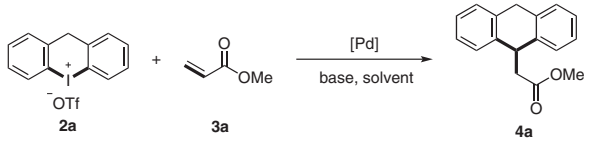
Scheme 1 The strategies to build dihydroanthracenes

vide an alternative route to dihydroanthracenes. Herein, we report an efficient access to modularly generate 9,10-dihydroanthracenes from six-membered cyclic diaryliodonium salts with terminal alkenes, catalyzed by $Pd(PPh_3)_4$ (Scheme 1c).

To test our hypothesis, we initiated the investigation by reacting the readily available methyl acrylate **3a** with six-membered cyclic diaryliodonium salts **2a** using $Pd(OAc)_2$ as a catalyst and Na_2CO_3 as the base in DMF under an argon atmosphere at 120 °C (Table 1). The reaction provided the desired dihydroanthracene **4a** albeit in 6% yield (entry 1). We then undertook some optimization mainly by changing different palladium species (entries 2–4). When $Pd(PPh_3)_4$ was employed, to our delight the desired compound **4a** was obtained with a relatively high yield (16%). Next a base screening was carried out to optimize the yield (entries 5–8), and it was found that the yield could be improved to 39% with trimethylamine as the base source. From these observations, the base has an apparently influence on the reaction. Due to the reductive property of HCOONa to accelerate reductive Heck reaction, not surprisingly, its addition increased the yield significantly (entries 9 and 10). Thus, the Et_3N/HCOONa system was selected for further optimization of reaction conditions (entry 10). The influence of the solvents was then studied (entries 11–14). We found the yield was improved to 69% by using 1,2-dichloroethane (DCE) as the solvent, and we were surprised to observe that no desired product was generated in the presence of MeOH as solvent (entry 13 vs. 14). A further jump in yield could be attained by reducing the temperature to 100 °C (78%, entry 15).

However, the yield was dropped to 51% and 32% by decreasing the temperature to 80 °C and 60 °C, respectively (entries 16, 17). And no reaction occurred at room temperature (entry 18). Thus, the optimal catalytic system for this

Table 1 Optimization of Reaction Conditions[a]



2a 3a 4a

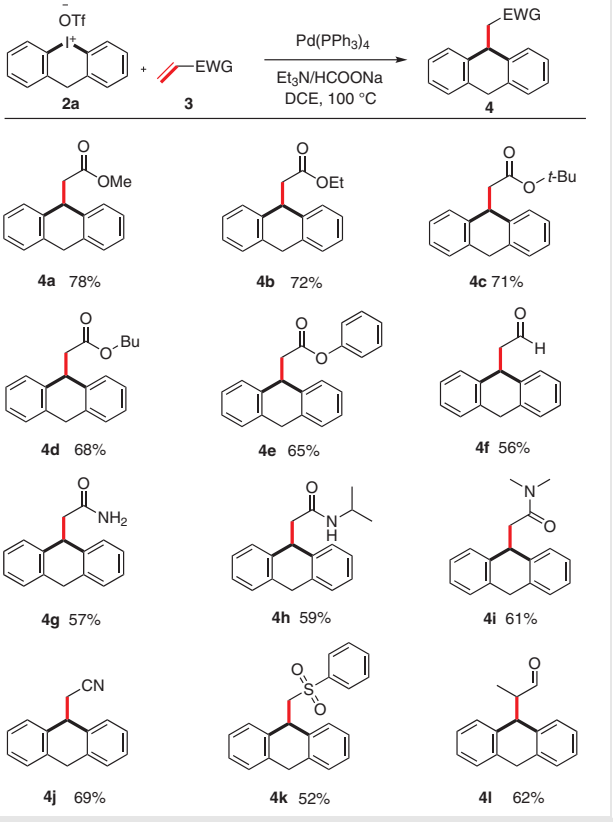
Entry	Catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	Na_2CO_3	DMF	120	6
2	$PdCl_2(dppf)_2$	Na_2CO_3	DMF	120	8
3	$PdCl_2(PPh_3)_2$	Na_2CO_3	DMF	120	11
4	$Pd(PPh_3)_4$	Na_2CO_3	DMF	120	16
5	$Pd(PPh_3)_4$	K_2CO_3	DMF	120	19
6	$Pd(PPh_3)_4$	$NaHCO_3$	DMF	120	6
7	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	120	trace
8	$Pd(PPh_3)_4$	Et_3N	DMF	120	39
9	$Pd(PPh_3)_4$	Et_3N/MeCOONa	DMF	120	35
10	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	DMF	120	48
11	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	DMSO	120	39
12	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	toluene	120	25
13	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	MeOH	120	trace
14	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	DCE	120	69
15	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	DCE	100	78
16	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	DCE	80	51
17	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	DCE	60	32
18	$Pd(PPh_3)_4$	Et_3N/HCOONa[c]	DCE	rt	trace

[a] Unless otherwise stated, **2a** (1.0 equiv), **3a** (2.0 equiv), catalyst (0.1 equiv), base (3.0 equiv), 15 h, Ar (using sealed tube).
[b] HPLC yield.
[c] Et_3N (3.0 equiv), HCOONa (2.0 equiv); note: DCE, 1,2-dichloroethane.

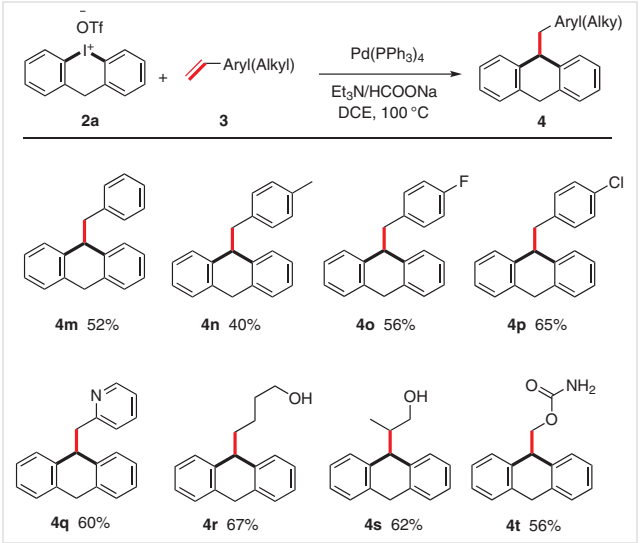
transformation was 0.1 equiv $Pd(PPh_3)_4$ and 3 equiv of Et_3N with 2.0 equiv of HCOONa in DCE at 100 °C for 15 h (using sealed tube).

With the optimal reaction conditions in hand, we next examined the scope of this novel tandem process using a range of commercially available terminal alkenes **3** with different electron-withdrawing groups (Scheme 2). Yields were generally good for terminal alkenes while alkyls in acrylate esters were varied, in a range of 65–78% (**4a–e**). In our method, other important materials acrolein and acrylamides were tolerated to give the corresponding products in good yields (**4f–i**). Furthermore, acrylonitrile successfully provided dihydroanthracenes **4j** which could undergo further transformations to build complex molecular scaffolds. Importantly, we were also pleased to find that the sulfone functional group was suitable in the formation of dihydroanthracenes **4k**, albeit with lower yields. 2-Methylacrylaldehyde also worked smoothly and delivered the corresponding product **4l**. Our results demonstrated a broad substrate generality of alkenes, and a variety of unique dihydroanthracenes could be quickly afforded.

To fully establish the scopes of this one-pot C–C coupling procedure, other types of alkenes were further investigated (Scheme 3). To our delight, generally the styrene derivatives with either simple alkyl (**4m**) or halogen (**4o**,**p**) substituents all gave excellent yield. Importantly, the substitution of halogens (F, Cl) in dihydroanthracenes would provide opportunities to further functionalize the incorporated arene if needed. In addition, due to the special properties of fluorine in drug metabolism, the incorporation of fluorine in arene (**4o**) might show higher metabolic stabilities and better pharmacokinetic properties. Synthetically, both fluorinated and chlorinated species (**4o**,**p**) could undergo further modifications to broaden the structural complexity. Gratifyingly, even pyridine-substituted alkene also reacted as well under the optimum conditions (**4q**). The motifs of this heterocycle compound are frequently found in polycyclic heteroarenes and natural products. More strikingly, we were also pleased to find that alkyl alkenes such as 4-penten-1-ol, methallyl alcohol, and vinyl carbamate were equally effective as the alkenes with electron-withdrawing substituents (**4r–t**). The tethered hydroxyl functional group was compatible and provided opportunities for further transformation.



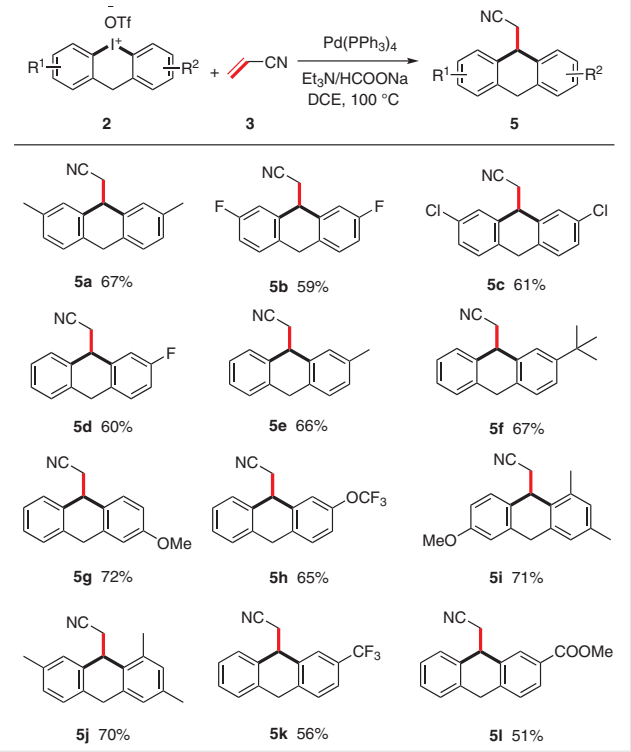
Scheme 2 The scope of α,β-unsaturated alkenes. *Reagents and conditions*: **2a** (1.0 equiv), alkene **3** (2.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), Et_3N (3.0 equiv), HCOONa (2.0 equiv), DCE (3.0 mL), 100 °C, 15 h, Ar (using sealed tube).



Scheme 3 The scope of terminal arylalkenes and alkylalkenes. *Reagents and conditions*: **2a** (1.0 equiv), **3** (2.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), Et_3N (3.0 equiv), HCOONa (2.0 equiv), DCE (3.0 mL), 100 °C, 15 h, Ar (using sealed tube).

The scope of six-membered cyclic diaryliodonium salts was finally investigated for this transformation (Scheme 4). Acrylonitrile was used as alkenes source since the attached nitriles could be further transformed. Under the standard reaction conditions, the iodoniums with either electron-donating or electron-withdrawing groups attached were all transformed to the desired dihydroanthracenes at modest to good yields. Initially we tested the reactions of symmetrical cyclic diaryliodonium salts with acrylonitrile, which afforded the corresponding dihydroanthracenes in moderate to good yields (**5a–c**). Next, a series of unsymmetrical

cyclic diaryliodonium salts were examined (**5d–l**). It was found that both electron-donating groups and electron-withdrawing substituents on cyclic diaryliodonium salts reacted smoothly, although the yield was decreased when the electronically poor substituted unsymmetrical cyclic diaryliodonium salts were employed (**5d–h**).



Scheme 4 The scope of cyclic iodoniums. *Reagents and conditions*: **2** (1.0 equiv), alkene **3** (2.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), Et_3N (3.0 equiv), HCOONa (2.0 equiv), DCE (3.0 mL), 100 °C, 15 h, Ar (using sealed tube).

Based on our observation and previous literature, a possible reaction mechanism was proposed in Scheme S1 (see the Supporting Information). As mentioned above, many dihydroanthracene-containing motifs possess anticancer properties due to their noncovalent binding to DNA duplexes. Therefore, the biological applications of the products were also investigated using a well-established MTT assay (Table 2). To our delight, several new synthesized compounds displayed potent antiproliferative activities against the human cancer cell lines. Among them, **4j** displayed the highest cytotoxicity against PANC-1 cell (IC_{50} = 11.74 μM). Further structural optimization and structure–activity relationship study of these new scaffolds are currently in progress.

In summary, we have successfully achieved a general and efficient one-pot procedure with six-membered cyclic iodoniums and various commercially available terminal alkenes for the construction of structurally diverse dihydroanthracenes derivatives.[12] Two C–C bonds were formed and involved one conventional Mizoroki–Heck reaction and one reductive Heck reaction between cyclic iodoniums and terminal alkenes. Except traditional acrylates and alkenes with γ-electron-withdrawing functional groups, both aryl alkenes and alkyl alkenes are suitable. The present method is straightforward for the diversified synthesis of dihydroanthracenes, providing a complementary strategy to the reported synthetic routes. More importantly, the screening of our new synthetic dihydroanthracenes successfully leads to the discovery of several novel compounds with potent antiproliferative activities.

Table 2 *In Vitro* Antiproliferative Activity of the Dihydroanthracenes

Compound	IC_{50} (μM ± SEM)			
	PANC-1	Capan-2	HCT116	HL-60
4a	19.48 ± 2.10	25.29 ± 3.62	49.31 ± 1.90	>100
4b	16.37 ± 2.36	34.57 ± 3.58	36.77 ± 4.25	>100
4h	>100	21.30 ± 4.69	19.68 ± 2.51	33.28 ± 4.83
4j	11.74 ± 3.29	26.18 ± 4.58	>100	77.58 ± 6.55
4q	23.24 ± 5.30	>100	36.50 ± 5.69	51.22 ± 7.61
4s	18.35 ± 5.27	46.55 ± 6.74	>100	26.21 ± 7.32
5h	16.33 ± 3.21	31.40 ± 4.28	>100	51.29 ± 6.56
5-Fu	9.08 ± 2.76	32.40 ± 3.70	10.59 ± 9.53	22.25 ± 1.31

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1343-5455.

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(12) **Procedure to Synthesize Dihydroanthracene 4a**

To a seal tube was added cyclic diaryliodonium salt **2a** (0.1 g, 0.226 mmol, 1.0 equiv), methyl acrylate **3a** (0.039 g, 0.45 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (0.026 g, 0.022 mmol, 0.1 equiv), Et_3N (0.069 g, 0.67 mmol, 3.0 equiv), HCOONa (0.031 g, 0.45 mmol, 2.0 equiv), and DCE (3.0 mL). Then the tube was sealed, degassed, and recharged with argon. The reaction proceeded at 100 °C for 15 h under argon atmosphere. The remained mixture was extracted with DCM (20 mL), the combined organic layers were washed with H_2O (3 × 2 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography on a silica gel (PE/EtOAc = 50:1 to 20:1) to provide compound **4a** (0.036 g, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.6 Hz, 2 H), 7.51 (d, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.2 Hz, 2 H), 7.33–7.29 (m, 2 H), 4.46 (t, *J* = 7.2 Hz, 1 H), 4.07 (s, 2 H), 3.81 (s, 3 H), 2.80 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.14, 146.39, 140.91, 127.63, 127.33, 124.47, 120.10, 51.99, 43.72, 41.79, 38.63. HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O_2$ $[M + H]^+$: 253.1150; found: 253.1146.

Procedure to Synthesize Dihydroanthracene 5a

To a seal tube was added cyclic diaryliodonium salt **2** (0.1 g, 0.213 mmol, 1.0 equiv), acrylonitrile **3** (0.022 g, 0.426 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (0.024 g, 0.021 mmol, 0.1 equiv), Et_3N (0.065 g, 0.639 mmol, 3.0 equiv), HCOONa (0.029 g, 0.426 mmol, 2.0 equiv), and DCE (3.0 mL). Then the tube was sealed, degassed, and recharged with argon. The reaction proceeded at 100 °C for 15 h under argon atmosphere. The remained mixture was extracted with DCM (20 mL), the combined organic layers were washed with H_2O (3 × 2 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography on a silica gel (PE/EtOAc = 50:1 to 20:1) to provide compound **5a** (0.033 g, 67%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.6 Hz, 2 H), 7.45 (d, *J* = 0.4 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 4.10 (t, *J* = 7.2 Hz, 1 H), 4.01 (s, 2 H), 2.79 (d, *J* = 7.2 Hz, 2 H), 2.44 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.22, 138.37, 137.19, 129.22, 125.09, 119.82, 118.73, 42.79, 41.75, 22.24, 21.78. HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N$ $[M + H]^+$: 248.1361; found: 248.1375.