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Reductive Heck cyclization versus δ-carbon elimination/decarboxylation: synthesis of dihydroindole and indoles from Baylis–Hillman adducts

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ABSTRACT

Modified Baylis–Hillman adducts having 2-bromoaniline moiety at the primary position underwent Pd-mediated reductive Heck type cyclization to produce dihydroindole derivatives. The same starting materials can also be used for the synthesis of indole derivatives under slightly different conditions via the concomitant δ-carbon elimination and decarboxylation process.

Chemical transformations of Baylis–Hillman adducts have received much attention during the last two decades.[1,2] Various cyclic and acyclic compounds have been prepared from Baylis–Hillman adducts by various chemical transformations.[1,2] Although Pd-mediated chemical transformations of modified Baylis–Hillman adducts started very recently, it provided many interesting heterocyclic compounds.[2,3] Recently, we reported unusual formation of cyclopropane-fused dihydrobenzofuran derivatives from the modified Baylis–Hillman adducts having 2-bromophenol moiety.[3] In the reaction, the palladium intermediate activated C(sp^3)–H bond and produced cyclopropane-fused compound in moderate yield.[3] During the study, we also examined the reaction of **1a** having 2-bromoaniline moiety and found the formation of dihydroindole **2a** (19%) and indole **4a** (21%) instead of cyclopropane derivative **5a** (Scheme 1).[3]

The mechanism for the formation of **2a** can be regarded as the reductive Heck type reaction involving the intermediate (**II**), which might be converted to **2a** by dimethylamine generated from DMF.[4] Compound **4a** could be formed via the base-mediated isomerization of **3a**, which might be generated from (**II**) via the δ-carbon elimination and concomitant decarboxylation process,[5,6] as depicted in Scheme 1.

We reasoned that both compounds **2a** and **4a** can be prepared selectively by choosing the suitable reaction conditions. Thus, we examined the reactions of **1a** under various conditions and found efficient conditions for both products. Some representative trials are summarized in Table 1. As in entry 3, $Pd(OAc)_2/PPh_3/Et_3N$/HCOOH conditions afforded compound **2a** in reasonable yield (64%) in DMF at 80 °C in short time (30 min).[7,8] In the reaction, we did not observe the formation of 3-benzylidene derivative **3a** (vide infra). When the reaction of **1a** was carried out under the influence of $Pd(OAc)_2/PPh_3/Et_3N$ in aqueous CH_3CN (refluxing, 18 h), we isolated **3a** in 72% yield, very fortunately.[8,9]

Encouraged by the results, starting materials **1b–g** were synthesized from the bromide of Baylis–Hillman adduct and 2-bromoanilines as shown in Scheme 2.[2,3] With these compounds **1b–g**, we examined the synthesis of **2b–g** and **3b–g** as summarized in Scheme 3. Reductive Heck type cyclizations of **1b–g** under the optimized conditions (Table 1, entry 3) produced desired dihydroindoles **2b–g** in moderate to good yields (47–80%). The mechanism can be imagined as shown in Scheme 4, involving the intermediates (**I**)–(**III**). Rapid conversion of (**II**) into (**III**) by formate anion and the following elimination of CO_2 and Pd(0) explained the short-reaction time (30 min). Variable amounts of (**I**) produced the reduction compound **7** via the intermediate (**IV**). Actually small amounts of reduction compounds were observed on TLC in all cases, and isolated in appreciable amounts (28–36%) in some case (**7c**,**d**,**g**).

The synthesis of 3-benzylidene dihydroindole **3b–g** was also examined under the optimized conditions (Table 1, entry 6). When the N-substituent of **1** is tosyl (**1b**), acetyl (**1c** and **1d**), and ester group (**1g**), desired compounds **3b–d** and **3g** were obtained in moderate to good yields (56–75%). However, the reaction with *N*-benzyl derivatives (**1e** and **1f**) failed completely. We did not

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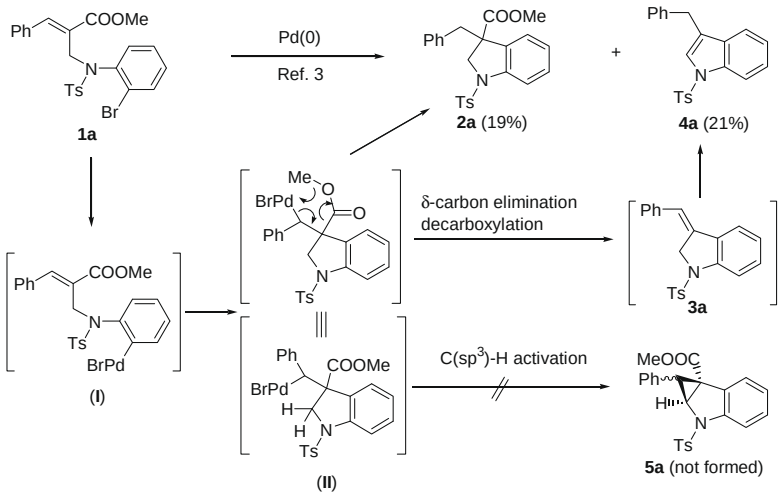
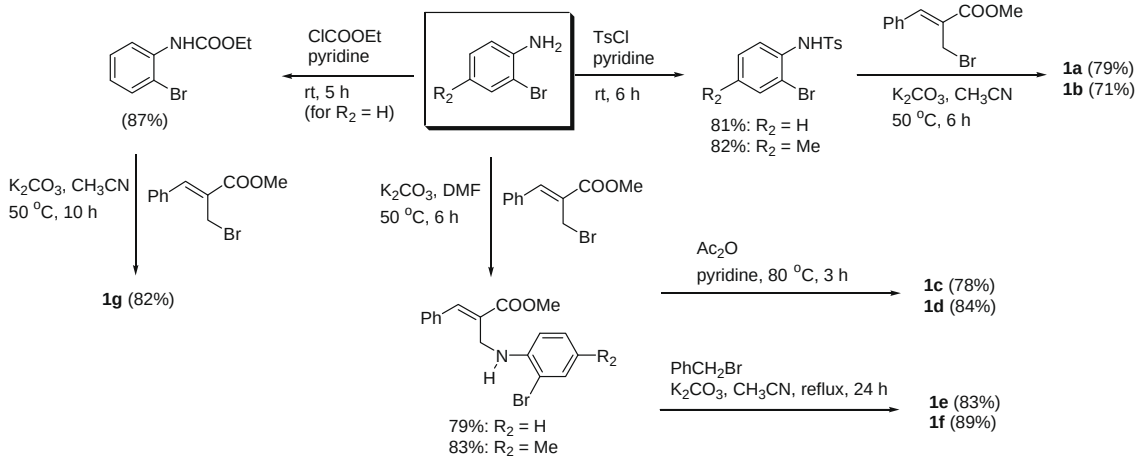


Scheme 1.

Table 1
Optimization of reaction conditions with compound **1a**

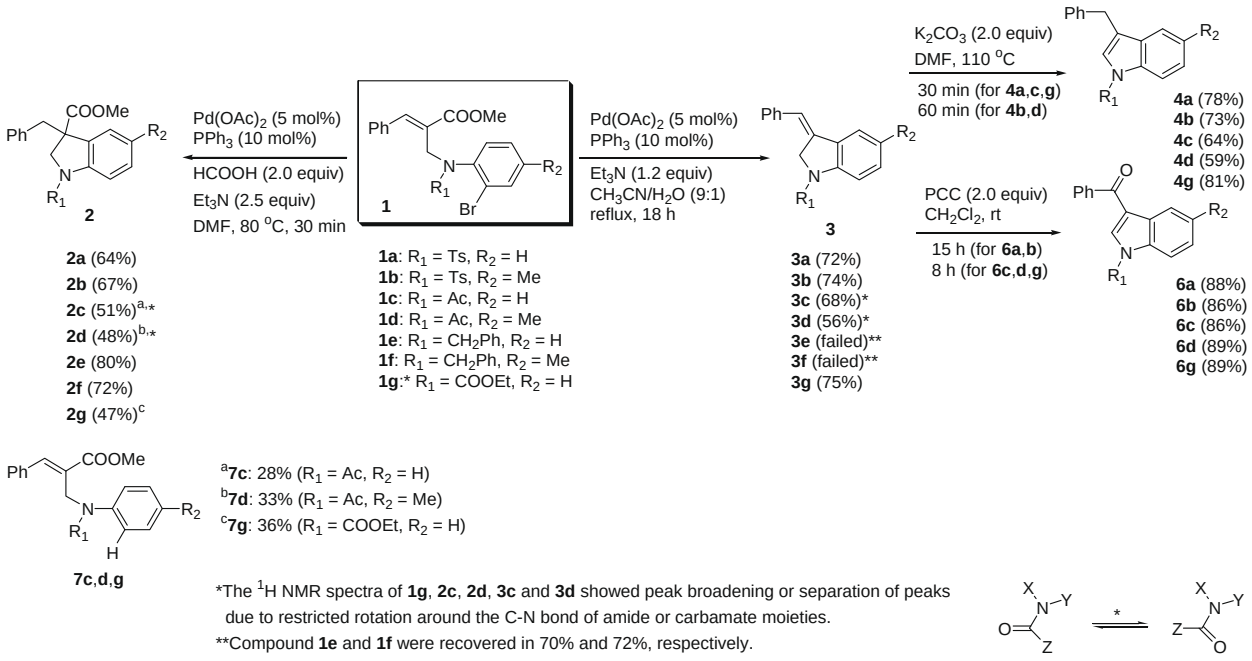
Entry	Conditions	**1a** (%)	**2a** (%)	**3a** (%)	**4a** (%)
1[Ref. 3]	$Pd(OAc)_2$ (10 mol %)/K_2CO_3 (20 equiv) TBAB (10 equiv)/DMF, 110 °C, 90 min	nd	19	nd	21
2	$Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) Et_3N (2.5 equiv)/HCOOH (2.0 equiv)/THF, 80 °C, 48 h	33	34	nd	nd
3	$Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) Et_3N (2.5 equiv)/HCOOH (2.0 equiv)/DMF, 80 °C, 30 min	nd	64	nd	nd
4	$Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) CH_3CN/reflux, 6 h	70	<5	nd	nd
5	$Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) Et_3N (1.2 equiv)/CH_3CN/reflux, 12 h	nd	10	60	nd
6[Ref. 9]	$Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) Et_3N (1.2 equiv)/CH_3CN–H_2O (9:1)/reflux, 18 h	nd	9	72	nd



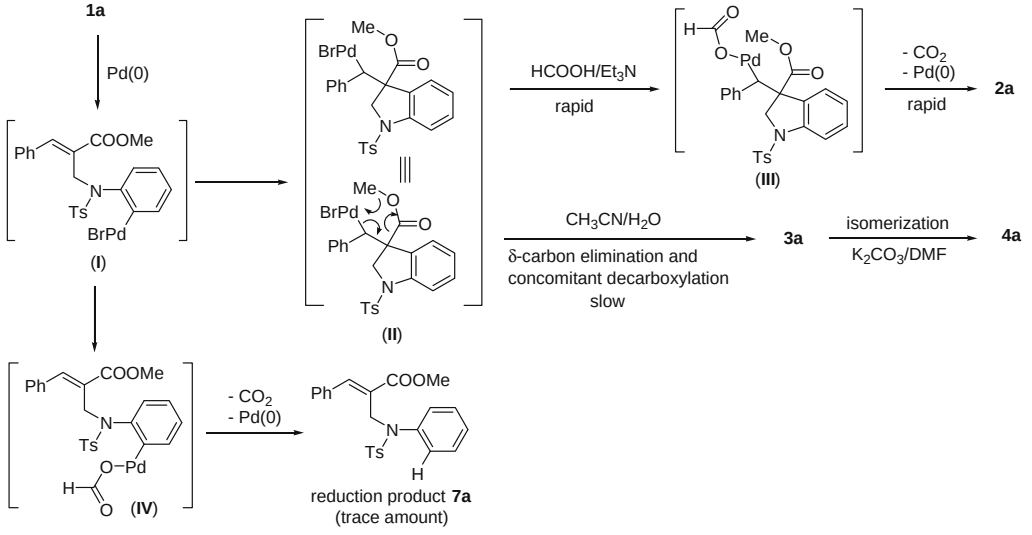
Scheme 2.

detect even the reduction compounds, and starting materials **1e** and **1f** were recovered (70–72%). At this stage, the reason for the failure of benzyl derivatives is not clear. The mechanism for the formation of 3-benzylidene compounds **3** could be explained as shown in Scheme 4, involving the concomitant δ-carbon elimination and decarboxylation process of Pd-intermediate (**II**).[6]

In order to demonstrate the usefulness of the benzylidene compounds, we converted them into their benzyl- and benzoyl-derivatives by base-mediated isomerization and PCC oxidation,[10] respectively (vide supra, Scheme 3). Double bond isomerization was carried out with K_2CO_3 in DMF at 110 °C in moderate yields (59–81%). PCC oxidation was carried out in



Scheme 3.



Scheme 4.

CH_2Cl_2 at room temperature in high yields (86–89%) as reported by us recently.[10]

In summary, we disclosed an efficient Pd-mediated synthetic approach for both dihydroindole and indole derivatives from the same starting materials by simply adopting different reaction conditions. However, it is difficult to explain the difference between the two reaction pathways in detail at this stage. Detailed mechanistic study and synthetic application of these findings are underway.

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6. Kim, H. S.; Gowrisankar, S.; Kim, E. S.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 6569–6572; Direct elimination of CH_3Br from (**II**) to form the five-membered palladacycle and the following simultaneous elimination of CO_2 and Pd(0) to form **3a** would be also possible. For this type of reductive cleavage process involving decarboxylation, see: Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 2352–2354.
7. Dihydroindole **2a** was synthesized by using the radical cyclization (AIBN, *n*-Bu_3SnH, benzene, reflux, 2 h) in 71% yield also. However, due to the toxicity of tin metal and the fact that more than equivalent amounts of tin compound have to be used, reductive Heck reaction can be regarded as a superior way than the radical process.
8. Typical experimental procedure for the synthesis of **2a**: A stirred mixture of **1a** (250 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 5 mol %), PPh_3 (13 mg, 10 mol %), HCOOH (46 mg, 1.0 mmol), and Et_3N (126 mg, 1.25 mmol) in DMF (2.0 mL) was heated to 80 °C for 30 min. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 15:1), compound **2a** was isolated as colorless oil, 135 mg (64%).[3] Other compounds were synthesized similarly, and the representative spectroscopic data of **2b**, **2e,** and **2g** are as follows.
Compound **2b**: 67%; white solid, mp 39–41 °C; IR (film) 1734, 1489, 1358, 1167, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 2.35 (s, 3H), 2.81 (d, J = 13.5 Hz, 1H), 3.30 (d, J = 13.5 Hz, 1H), 3.59 (s, 3H), 3.96 (d, J = 11.1 Hz, 1H), 4.21 (d, J = 11.1 Hz, 1H), 6.92–6.95 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 7.15–7.24 (m, 6H), 7.52 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.92, 21.44, 44.32, 52.43, 55.60 (2C), 114.08, 125.74, 127.08, 127.36, 128.39, 129.54, 129.56, 129.95, 132.35, 133.20, 133.80, 135.76, 138.85, 140.01, 172.27; ESIMS m/z 436 (M^++1). Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 68.67; H, 5.98; N, 3.13.
Compound **2e**: 80%; yellow oil; IR (film) 1732, 1603, 1495, 1454, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.04 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 9.6 Hz, 1H), 3.37 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 9.6 Hz, 1H), 3.70 (s, 3H), 4.10 (d, J = 15.3 Hz, 1H), 4.33 d, J = 15.3 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 6.72 (t, J = 7.5 Hz, 1H), 6.92–6.98 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 7.15–7.33 (m, 8H), 7.36 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.80, 52.14, 52.56, 56.16, 58.98, 107.27, 117.67, 124.75, 126.68, 127.08, 127.56, 128.12, 128.44, 128.97, 129.67, 130.27, 136.86, 137.91, 151.16, 173.43; ESIMS m/z 358 (M^++1).
Compound **2g**: 47%; colorless oil; IR (film) 1734, 1713, 1487, 1409, 1334 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (br t, J = 7.2 Hz , 3H), 3.06 (d, J = 13.8 Hz, 1H), 3.46 (d, J = 13.8 Hz, 1H), 3.74 (s, 3H), 4.02 (br d, J = 12.0 Hz, 1H), 4.23 (br q, J = 7.2 Hz, 2H), 4.43 (d, J = 12.0 Hz, 1H), 6.98–7.05 (m, 3H), 7.20–7.29 (m, 4H), 7.45 (d, J = 7.8 Hz, 1H), 7.82 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.58, 44.50, 52.56, 53.99, 55.24, 61.46, 114.96, 122.61, 124.75, 127.00, 128.30, 129.18, 129.56, 131.74, 135.92, 141.98, 152.80, 172.95; ESIMS m/z 340 (M^++1).
Typical experimental procedure for the synthesis of **3a**: A stirred mixture of **1a** (250 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 5 mol %), PPh_3 (13 mg, 10 mol %), and Et_3N (61 mg, 0.6 mmol) in aqueous CH_3CN (2.0 mL, CH_3CN/H_2O, 9:1) was heated to reflux for 18 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether/CH_2Cl_2, 20:1:2), compound **3a** was isolated as a white solid, 130 mg (72%). Other compounds were synthesized similarly, and the representative spectroscopic data of **3a**, **3b**, and **3g** are as follows.
Compound **3a**: 72%; white solid, mp 156–158 °C; IR (film) 1465, 1357, 1167, 1117, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 4.87 (d, J = 3.0 Hz, 2H), 6.79 (t, J = 3.0 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.20–7.30 (m, 6H), 7.39–7.49 (m, 3H), 7.71–7.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.50, 54.54, 114.70, 118.46, 120.27, 123.75, 127.10, 127.18, 128.27, 128.81, 129.79, 129.83, 131.04, 132.45, 134.04, 136.25, 143.26, 144.33; ESIMS m/z 362 (M^++1). Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 72.87; H, 5.41; N, 3.63.
Compound **3b**: 74%; white solid, mp 150–152 °C; IR (film) 1483, 1356, 1166, 1130, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 2.34 (s, 3H), 4.84 (d, J = 3.0 Hz, 2H), 6.76 (t, J = 3.0 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.19–7.28 (m, 6H), 7.38–7.43 (m, 2H), 7.64–7.72 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.99, 21.50, 54.73, 114.63, 118.10, 120.61, 127.08, 127.14, 128.25, 128.80, 129.79, 130.69, 131.12, 132.62, 133.49, 133.89, 136.34, 141.16, 144.20; ESIMS m/z 376 (M^++1).
Compound **3g**: 75%; white solid, mp 111–113 °C; IR (film) 1714, 1479, 1407, 1384, 1276 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (br t, J = 6.6 Hz, 3H), 4.33 (br s, 2H), 4.82 (br s, 2H), 6.84 (t, J = 3.0 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.22–7.42 (m, 6H), 7.52 (d, J = 7.5 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.43, 52.45, 61.28, 114.86, 117.38, 119.42, 122.46, 126.54, 127.92, 128.40, 129.27, 130.11, 132.96, 136.32, 143.53, 151.86; ESIMS m/z 280 (M^++1).Syntheses of compounds **4** and **6** were carried out as shown in Scheme 3, and the representative spectroscopic data of **4b**, **4g**, **6a**, and **6b** are as follows.
Compound **4b**: 73%; colorless oil; IR (film) 1455, 1370, 1171, 1121, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 2.35 (s, 3H), 3.96 (s, 2H), 7.08–7.31 (m, 10H), 7.69 (t, J = 8.1 Hz, 2H), 7.84 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.32, 21.52, 31.27, 113.50, 119.56, 122.32, 124.14, 126.10, 126.35, 126.70, 128.50, 128.58, 129.71, 131.11, 132.77, 133.77, 135.25, 139.05, 144.58; ESIMS m/z 376 (M^++1).
Compound **4g**: 81%; colorless oil; IR (film) 1733, 1456, 1399, 1380, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 t, J = 7.2 Hz, 3H), 4.03 (d, J = 0.9 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 7.16–7.34 (m, 8H), 7.42 (d, J = 7.8 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.41, 31.38, 62.99, 115.22, 119.34, 120.83, 122.66, 123.16, 124.53, 126.24, 128.46, 128.66, 130.47, 135.74, 139.49, 151.02; ESIMS m/z 280 (M^++1).
Compound **6a**: 88%; yellow oil; IR (film) 1644, 1534, 1447, 1379, 1208, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 7.24–7.28 (m, 2H), 7.35–7.44 (m, 2H), 7.51–7.57 (m, 2H), 7.60–7.66 (m, 1H), 7.78–7.82 (m, 2H), 7.85–7.89 (m, 2H), 7.97–8.00 (m, 1H), 8.03 (s, 1H), 8.29–8.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.59, 113.14, 120.35, 122.94, 124.82, 125.91, 127.10, 128.48, 128.63, 128.99, 130.19, 132.35, 133.54, 134.44, 134.94, 139.14, 145.91, 190.82; ESIMS m/z 376 (M^++1). Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73. Found: C, 70.44; H, 4.76; N, 3.62.
Compound **6b**: 86%; yellow oil; IR (film) 1645, 1533, 1377, 1215, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 2.45 (s, 3H), 7.20–7.26 (m, 3H), 7.50–7.56 (m, 2H), 7.59–7.65 (m, 1H), 7.76–7.80 (m, 2H), 7.84–7.88 (m, 3H), 7.97 (s, 1H), 8.11–8.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.37, 21.55, 112.76, 120.15, 122.67, 127.03, 127.31, 128.59, 128.67, 128.97, 130.13, 132.27, 133.19, 133.68, 134.47, 134.73, 139.20, 145.78, 190.23; ESIMS m/z 390 (M^++1).
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