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Facile synthesis of benzofulvene derivatives from Baylis–Hillman adducts: In-mediated Barbier reaction combined with Pd(0)-catalyzed intramolecular Heck-elimination cascade

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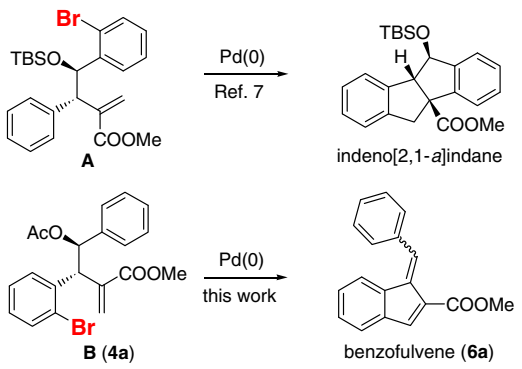
ABSTRACT

A facile synthesis of benzofulvene derivatives was carried out starting from the Baylis–Hillman adducts of 2-bromobenzaldehyde via the sequential bromination, In-mediated Barbier reaction with aldehyde, acetylation, Pd-catalyzed intramolecular Heck reaction, and the elimination of AcOH.

Fulvene and related compounds have been used as building blocks for the preparation of metallocene catalysts,[1a–c] starting materials of polymers,[1d,e] and biologically interesting compounds.[2] Fulvene skeleton could be constructed via the radical cyclization of enediynes,[3a–c] photochemical cyclization of enyne-allenes,[3d,i] Pt-catalyzed diene-yne cyclization,[3e] Cu(I)-catalyzed reaction between vinylidene cyclopropanes and iminophenyliodinane,[3f] Au-catalyzed isomerization of cyclopropenes,[3g] and Nazarov-type cyclization of α-hydroxyallene.[3h] Pd-catalyzed synthesis of fulvene derivatives from [3]cumulene,[4a] butadiyne,[4b] 1,2-dialkynylbenzene,[4c] and a tandem reaction of 1-(2,2-dibromovinyl)-2-alkynylbenzene with arylboronic acid[4d,e] has also been reported.

Recently, Baylis–Hillman adducts have been used extensively for the synthesis of various important compounds.[5–7] Among the numerous chemical transformations of the Baylis–Hillman adducts Pd-catalyzed reactions have received a special attention,[6,7] including inter- and intramolecular Heck type reactions.[6e–g] Recently, we reported a Pd-catalyzed domino reaction of acrylate derivative **A**, prepared from Baylis–Hillman adduct, to form a tetracyclic compound via a 5-*exo*-carbopalladation and aryl C–H activation cascade (Scheme 1).[7] We imagined that a benzofulvene derivative could be synthesized via the tandem intramolecular Heck reaction and the following elimination of AcOH by using **B** (compound **4a**, vide infra).

The starting material **4a** was prepared from the Baylis–Hillman adduct of 2-bromobenzaldehyde via a three-step procedure, that is, a sequential bromination to **1a**,[7,8] In-mediated Barbier reaction with benzaldehyde (**2a**) to form **3a**,[7,9] and the following acetylation (Scheme 2). The reaction of **4a** under the influence of $Pd(OAc)_2$ (10 mol %)/PPh_3 (20 mol %) and Et_3N (2.0 equiv) in refluxing CH_3CN (condition C in Table 1, vide infra) showed the best results, and benzofulvene **6a** was isolated in 95% yield.[10] In the reaction, *E* and *Z* isomers were formed together. Two isomers could be separated easily (**6a**-*E* 85%, **6a**-*Z* 10%) and identified by comparison with the reported spectroscopic data of



Scheme 1.

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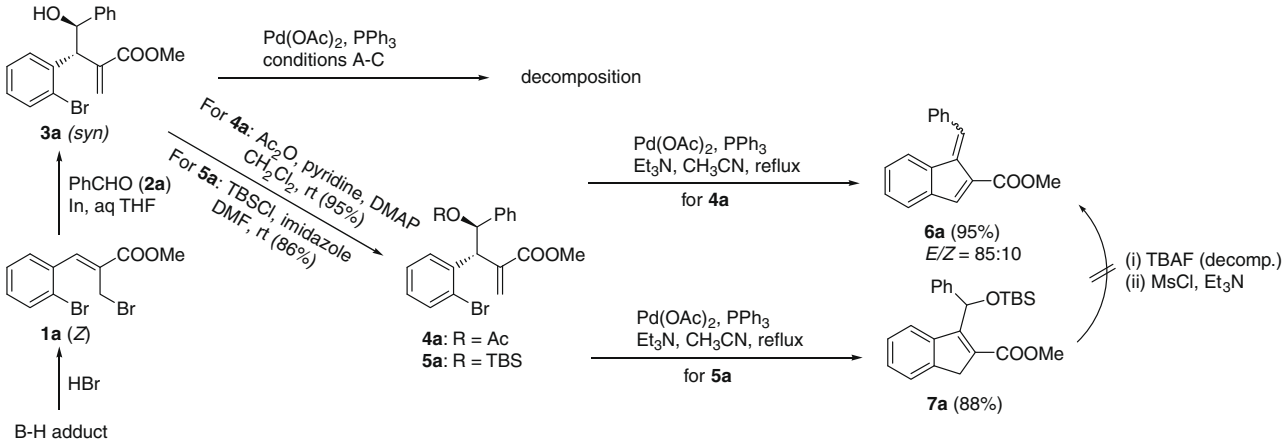
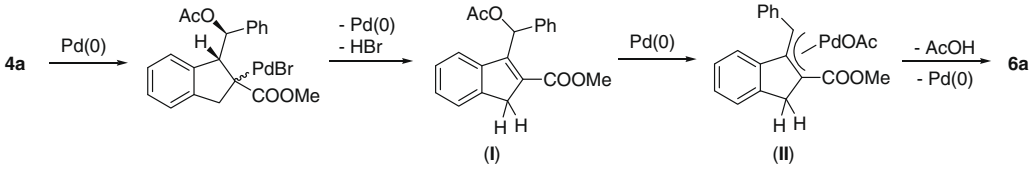


Scheme 2.



Scheme 3.

similar compounds[3e] and via the NOE experiments with **6e**-*E* (vide infra). When the reaction was carried out under condition A (Cs_2CO_3, DMF, 110 °C) or condition B (Et_3N, DMF, 90 °C), the yield of **6a** was somewhat lower (55–61%), as shown in entry 1 in Table 1 (vide infra).

As also shown in Scheme 2, the reaction of alcohol **3a** showed severe decomposition under the conditions A–C. The reaction of TBS derivative **5a** produced indene derivative **7a** (88%), and the synthesis of benzofulvene **6a** from **7a** failed. The formation of many intractable side products was observed during removal of a TBS group with TBAF, unexpectedly. The mechanism for the formation of **6a** could be postulated as shown in Scheme 3 involving a Pd(0)-catalyzed Heck reaction to form (**I**) and the following 1,4-elimination of acetic acid via the π-allylpalladium intermediate (**II**).[11]

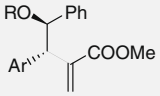
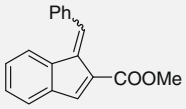
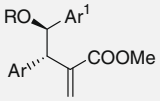
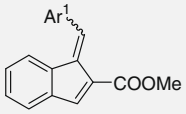
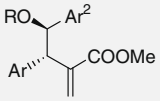
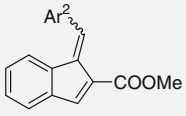
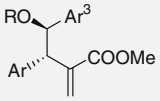
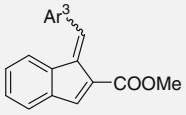
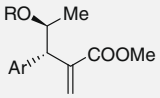
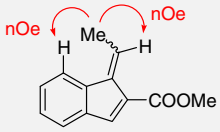
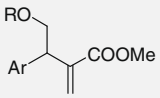
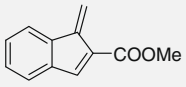
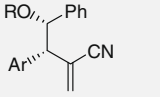
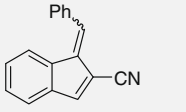
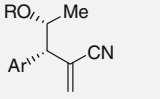
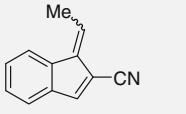
Encouraged by the successful results, we prepared various acetates **4b**–**h** and examined the synthesis of benzofulvene derivatives. Cinnamyl bromides **1a**-*Z* (Scheme 2) and **1b**-*E* (2-bromomethyl-3-phenylacrylonitrile) were prepared stereoselectively from the corresponding Baylis–Hillman adducts, as reported.[7,8] In-mediated Barbier reactions of **1** and various aldehydes, benzaldehyde (**2a**), *p*-tolualdehyde (**2b**), 2-naphthaldehyde (**2c**), *N*-acetyl-indole-3-carboxaldehyde (**2d**), acetaldehyde (**2e**), and formaldehyde (**2f**) were carried out in aqueous THF at room temperature for 1 h.[7,9a] *Syn*-isomers were produced as the major products for the ester derivatives **3a**–**e** while *anti*-isomers for the nitrile derivatives **3g** and **3h**, as reported.[7,9] Separation of the major component by column chromatography afforded *syn*-isomers for **3a**–**e** in high yields (76–92%) and *anti*-isomers for **3g** and **3h** in 65–69%. Acetylation of **3a**–**h** (Ac_2O, pyridine, cat. DMAP, CH_2Cl_2, rt, 1 h) was carried out and the acetates **4a**–**h** were obtained in good yields (87–99%). With these compounds **4b**–**h** in our hands, the next Pd-catalyzed cyclization reactions to benzofulvenes **6b**–**h** were carried out, and the results are summarized in Table 1.

As shown in Table 1, the yields of benzofulvenes were dependent on the reaction conditions including solvent, base, and reaction temperature (see the footnote in Table 1). Conditions B and/or C were better than condition A in most cases (entries 1, 2, 5, and 7). Arylidene derivatives **6a**–**d** (entries 1–4) were synthesized in good yields (79–95%) while ethylidene derivative **6e** (entry 5) was isolated in moderate yield (57%). As described above, NOE experiments with compound **6e** showed the stereochemistry of the major compound was found to be *E*. Methylene derivative **6f** (entry 6) was isolated in low yield (13%), and **6f** was very unstable. Nitrile derivatives **4g** (entry 7) and **4h** (entry 8) also produced the corresponding benzofulvenes **6g** and **6h** in moderate yields (60–63%); however, the ratio of *E*/*Z* (ca. 3:2) was different from those of esters **6a**–**e** (*E*/*Z* = ca. 9:1).

During the studies we observed the isomerization of prepared benzofulvenes, *E* to *Z* and vice versa. Spectroscopically pure products could be obtained by rapid column chromatographic separation. No severe isomerization and/or decomposition was observed when the compound was kept in the dark at low temperature; however, isomerization occurred somewhat rapidly under the influence of sunlight.[2c,3d,12] As an example, pure **6a**-*E* was converted to a *E*/*Z* mixture (*E*/*Z* = 58:42) when kept in the shelf for 24 h in NMR tube ($CDCl_3$) without prohibiting the exposure to sunlight. After 7 days the ratio was changed to *E*/*Z* = 40:60 and was not changed further. Similarly, **6a**-*Z* was isomerized to a mixture (*E*/*Z* = 38:62) after 1 day, and the ratio was finally changed to *E*/*Z* = 41:59 after 7 days. Based on the ^{1}H NMR monitoring results, the final ratio of *E*/*Z* (after 7 days) was found to be *E*/*Z* = 2:3. Similarly, photoisomerization was also observed for the nitrile derivatives. As an example, pure **6g**-*E* was changed to an *E*/*Z* mixture (*E*/*Z* = 7:3) after 7 days.

In summary, we disclosed a facile synthesis of benzofulvene derivatives from the Baylis–Hillman adducts of 2-bromobenzaldehyde. The synthesis was carried out via the sequential bromination, In-mediated Barbier reaction with aldehyde, acetylation, Pd-catalyzed intramolecular Heck reaction, and the 1,4-elimination of AcOH.

Table 1
Preparation of starting material **4a–h** and Pd-catalyzed synthesis of benzofulvene derivatives **6a–h**

Entry	Substrates	Alcohol[a] (%) Acetate[a] (%)	Conditions[b]	Products (%)
1	**1a** + **2a**	 **3a** (R = H, 92) **4a** (R = OAc, 95)	A B C	 **6a**-*E* (55), **6a**-*Z* (trace) **6a**-*E* (61), **6a**-*Z* (trace) **6a**-*E* (85), **6a**-*Z* (10)
2[c]	**1a** + **2b**	 **3b** (R = H, 90) **4b** (R = OAc, 87)	A B	 **6b**-*E* (52), **6b**-*Z* (trace) **6b**-*E* (74), **6b**-*Z* (7)
3[d]	**1a** + **2c**	 **3c** (R = H, 85) **4c** (R = OAc, 99)	B	 **6c**-*E* (71), **6c**-*Z* (8)
4[e]	**1a** + **2d**	 **3d** (R = H, 87) **4d** (R = OAc, 99)	C	 **6d**-*E* (73), **6d**-*Z* (16)
5	**1a** + **2e**	 **3e** (R = H, 76) **4e** (R = OAc, 99)	A B	 decomposition **6e**-*E* (57), **6e**-*Z* (-)
6	**1a** + **2f**	 **3f** (R = H, 90) **4f** (R = OAc, 95)	B C	 decomposition **6f** (13)
7	**1b** + **2a**	 **3g** (R = H, 69) **4g** (R = OAc, 91)	A B	 decomposition **6g**-*E* (36), **6g**-*Z* (27)
8	**1b** + **2e**	 **3h** (R = H, 65) **4h** (R = OAc, 91)	B	 **6h**-*E*/**6h**-*Z* (60) 3:2 mixture

[a] Ar in 2-bromophenyl and the stereochemistry of **3a–e** and **4a–e** is *syn* and **3g–h** and **4g–h** is *anti*, as shown.
[b] Condition A: $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Cs_2CO_2 (2.0 equiv), DMF, 110 °C, 60 min; condition B: $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N (2.0 equiv), DMF, 90 °C, 3 h; condition C: $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N (2.0 equiv), CH_3CN, reflux, 60 min.
[c] Ar^1 is *p*-tolyl.
[d] Ar^2 is 2-naphthyl.
[e] Ar^3 is *N*-acetyl-3-indolyl.

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10. *Typical synthetic procedure of* **3a**: To a stirred solution of cinnamyl bromide **1a** (668 mg, 2.0 mmol)[7,8] and benzaldehyde (**2a**, 233 mg, 2.2 mmol) in aqueous THF (1:1, 4 mL) was added indium powder (250 mg, 2.2 mmol) and stirred at room temperature for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 15:1:1) compound **3a** (*syn*) was obtained as colorless oil, 664 mg (92%). Other compounds **3b**–**h** were prepared similarly, and the selected spectroscopic data of **3a** and **3g** are as follows.
Compound **3a** (*syn*): 92%; colorless oil; IR (film) 3479, 2949, 1716, 1437, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (d, J = 3.6 Hz, 1H), 3.57 (s, 3H), 4.86 (d, J = 7.8 Hz, 1H), 5.33 (dd, J = 7.8 and 3.6 Hz, 1H), 5.71 (t, J = 0.9 Hz, 1H), 6.28 (d, J = 0.9 Hz, 1H), 7.07–7.13 (m, 1H), 7.25–7.35 (m, 6H), 7.54 (dd, J = 8.1 and 1.5 Hz, 1H), 7.69 (dd, J = 8.1 and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.86, 52.61, 75.54, 126.86, 126.91, 127.20, 127.88, 128.26 (2C), 128.39, 129.91, 133.22, 138.15, 139.98, 141.73, 166.66. Anal. Calcd for $C_{18}H_{17}BrO_3$: C, 59.85; H, 4.74. Found: C, 60.11; H, 4.98.
Compound **3g** (*anti*): 69%; colorless oil; IR (film) 3448, 3063, 2223, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (br s, 1H), 4.60 (d, J = 9.0 Hz, 1H), 5.26 (d, J = 9.0 Hz, 1H), 6.04 (s, 1H), 6.10 (s, 1H), 7.03 (ddd, J = 9.3, 7.5 and 1.8 Hz, 1H), 7.16–7.31 (m, 6H), 7.42 (dd, J = 8.1 and 1.2 Hz, 1H), 7.60 (dd, J = 7.8 and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.00, 75.18, 117.99, 122.86, 124.79, 126.80, 127.80, 128.28, 128.39, 128.98, 129.14, 133.22, 133.75, 136.81, 140.57. Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.56; H, 4.67; N, 4.13.
Typical synthetic procedure of **4a**: A solution of **3a** (361 mg, 1.0 mmol), acetic anhydride (153 mg, 1.5 mmol), pyridine (158 mg, 2.0 mmol), and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 15:1) compound **4a** was obtained as colorless oil, 383 mg (95%). Other compounds **4b**–**h** were prepared similarly and the selected spectroscopic data of **4a** and **4g** are as follows.
Compound **4a** (*syn*): 95%; colorless oil; IR (film) 2951, 1735, 1724, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.83 (s, 3H), 3.58 (s, 3H), 5.13 (d, J = 9.9 Hz, 1H), 5.63 (s, 1H), 6.28 (s, 1H), 6.41 (d, J = 9.9 Hz, 1H), 7.06–7.12 (m, 1H), 7.24–7.34 (m, 4H), 7.38–7.42 (m, 2H), 7.51 (dd, J = 7.8 and 1.5 Hz, 1H), 7.56 (dd, J = 8.1 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.81, 50.15, 51.93, 76.28, 126.46, 127.26, 127.71, 128.29, 128.35, 128.37, 128.43, 129.30, 133.06, 138.15, 138.25, 138.96, 166.28, 169.78.
Compound **4g** (*anti*): 91%; pale yellow solid; mp 99–101 °C; IR (film) 3063, 3034, 2223, 1743, 1226 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (s, 3H), 4.79 (d, J = 9.9 Hz, 1H), 6.00 (d, J = 0.9 Hz, 1H), 6.04 (s, 1H), 6.30 (d, J = 9.9 Hz, 1H), 7.04 (ddd, J = 7.5, 7.5 and 1.8 Hz, 1H), 7.16–7.31 (m, 6H), 7.44 (dd, J = 8.1 and 1.2 Hz, 1H), 7.52 (dd, J = 8.1 and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.97, 52.86, 75.79, 117.62, 122.40, 124.95, 127.41, 127.85, 128.33, 128.50, 129.26, 129.30, 133.33, 133.67, 135.61, 136.94, 169.59; ESIMS m/z 392 $[M+Na]^+$, 394 $[M+2+Na]^+$.
Typical synthetic procedure of **6a** (condition C): A stirred solution of **4a** (202 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (26 mg, 0.1 mmol), and TEA (101 mg, 1.0 mmol) in CH_3CN (4 mL) was heated to reflux for 1 h under nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature, the reaction was quenched with water (10 mL), and the reaction mixture was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with dilute HCl solution, brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 20:1) to afford compounds **6a**-*E* (111 mg, 85%), and **6a**-*Z* (13 mg, 10%). Other compounds **6b**–**h** were prepared similarly and the selected spectroscopic data of compounds **6a**, **6e**, and **6g** are as follows.
Compound **6a**-*E*: 85%; pale yellow solid; mp 35–36 °C; IR (film) 3056, 2948, 1710, 1349, 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H), 7.06 (t, J = 8.1 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.36–7.47 (m, 5H), 7.52–7.55 (m, 2H), 7.72 (s, 1H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.74, 118.43, 119.07, 122.93, 123.31, 123.67, 123.73, 124.43, 125.17, 131.66, 132.15, 132.31, 133.40, 135.65, 135.78, 160.36; ESIMS m/z 285 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.33; H, 5.64.
Compound **6a**-*Z*: 10%; pale yellow oil; IR (film) 2945, 1716, 1431, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 3H), 7.28–7.45 (m, 8H), 7.60 (d, J = 0.9 Hz, 1H), 7.72–7.75 (m, 1H), 7.82 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.54, 119.84, 123.03, 127.68, 128.20, 128.43, 128.62, 130.42, 131.75, 132.47, 136.70, 137.62, 139.00, 139.16, 141.72, 167.01; ESIMS m/z 285 (M^++Na).
Compound **6e**-*E*: 57%; colorless oil; IR (film) 2949, 1710, 1362, 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.41 (d, J = 7.5 Hz, 3H), 3.84 (s, 3H), 7.26–7.39 (m, 2H), 7.44–7.47 (m, 1H), 7.61–7.68 (m, 2H), 7.82 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.21, 51.35, 123.29, 124.40, 127.31, 127.75, 129.59, 136.79, 137.23, 137.55, 138.66, 140.16, 165.19; ESIMS m/z 223 (M^++Na). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.23; H, 6.25.
Compound **6g**-*E*: 36%; pale yellow oil; IR (film) 3054, 2919, 2215, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (ddd, J = 7.5, 7.5 and 1.2 Hz, 1H), 7.31 (ddd, J = 7.5, 7.5 and 0.9 Hz, 1H), 7.42–7.53 (m, 5H), 7.58–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 113.22, 115.57, 123.24, 123.56, 128.29, 128.68, 128.95, 129.42, 129.47, 133.83, 135.01, 136.73, 137.68, 141.00, 141.74; ESIMS m/z 252 (M^++Na). Anal. Calcd for $C_{17}H_{11}N$: C, 89.06; H, 4.84; N, 6.11. Found: C, 88.94; H, 4.97; N, 6.02.
Compound **6g**-*Z*: 27%; pale yellow oil; IR (film) 3058, 2217, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.51 (m, 6H), 7.58–7.62 (m, 2H), 7.74–7.77 (m, 2H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.01, 116.71, 119.72, 122.93, 128.24, 128.45, 128.59, 129.82, 130.88, 133.70, 133.89, 135.74, 137.49, 138.22, 147.94; ESIMS m/z 252 (M^++Na).
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