Synthesis of 1,3,4-Trisubstituted Benzenes from Morita–Baylis–Hillman Adducts of α-Bromocinnamaldehyde via [5+1] Annulation Strategy

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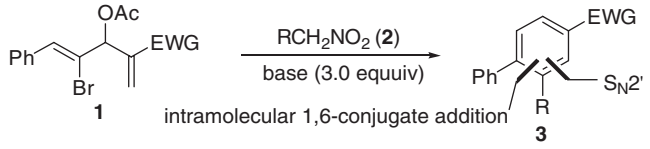
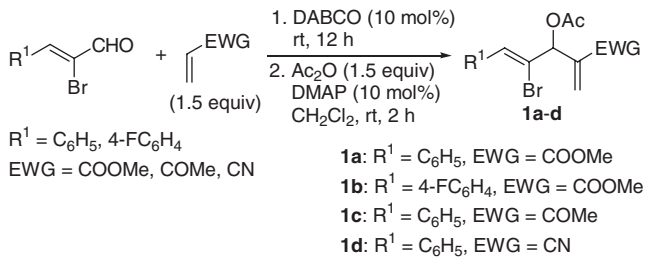
The construction of suitably functionalized benzene ring in a regioselective way is important in organic synthesis. The Morita–Baylis–Hillman (MBH) adducts have been used as useful starting materials for this purpose.[1-6] There have been reported numerous methods including [4+2] cycloaddition,[2] 6π-electrocyclization,[3] [3+3] annulation,[4] and consecutive [3+1+2] annulation protocols.[5] During our recent studies using the MBH adducts of cinnamaldehydes,[7] we reasoned out that the synthesis of 1,3,4-trisubstituted benzenes **3** could be realized by [5+1] annulation protocol[8] from the acetates of MBH adduct of α-bromocinnamaldehyde via a sequential S_N2' reaction of primary nitroalkane, an intramolecular 1,6-conjugate addition,[9] and eliminations of HBr and HNO_2, as shown in Scheme 1.

Thus, starting materials **1a-d** were prepared from α-bromocinnamaldehydes, as shown in Scheme 2. The MBH reaction was carried out in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to produce the corresponding MBH adducts in good to moderate yields (45–83%), and the following acetylation (Ac_2O/DMAP) afforded **1a-d** in good yields (82–88%).[10]



Scheme 1. Synthetic rational of 1,3,4-trisubstituted benzene.



Scheme 2. Preparation of starting materials.

The reaction of MBH acetate **1a** and nitroethane (**2a**) in the presence of Cs_2CO_3 (3.0 equiv) in DMF at room temperature for 4 h afforded the desired product **3a** in moderate yield (45%) along with a small amount (5%) of unexpected phenol **4a**, as shown in Scheme 3. The use of CH_3CN or K_2CO_3 showed a similar result.[11] The reaction mechanism for the formation of **3a** would be a sequential introduction of nitroethane at the primary position of the MBH adduct by S_N2' reaction to afford **I**, and the following intramolecular 1,6-conjugate addition to produce **II**, and the final elimination of HBr and HNO_2 to give **3a**. For the formation of benzene ring, the MBH acetate provided five carbons and nitroethane served one carbon. During the reaction intermediate **II** could be converted to **IV** by S_N2 reaction of the nitronate anion of nitroethane,[12] and the following Hass–Bender oxidation[12] could afford **V**. A subsequent elimination of HNO_2 and keto-enol tautomerization would provide **4a** as a minor product. However, another possibility involving sequential [2,3]-sigmatropic rearrangement of allylic nitro intermediate and the following disproportionation process[13] cannot be ruled out completely at this stage.

Encouraged by the successful results, some representative primary nitroalkanes **2b-i** were examined under the same reaction conditions, and the results are summarized in Table 1. The reactions of **1a** with 1-nitropropane (**2b**), 1-nitrobutane (**2c**), 1-nitropentane (**2d**), 1-nitrohexane (**2e**), ethyl nitroacetate (**2f**), 2-phenylnitroethane (**2g**), 2-(2-thienyl)nitroethane (**2h**), and methyl 4-nitrobutyrate (**2i**) showed similar results. The corresponding benzene derivatives **3b-i** were synthesized in moderate yields (40–68%) along with phenol derivatives **4b-e** (5–9%) as minor products in some cases. For the reactions of **2f-i**, the corresponding phenol derivatives were observed on TLC at the right position; however, they could not be separated in appreciable amount. The reaction of MBH acetate **1b** with **2b** and **2f** also provided **3j** (44%) and **3k** (71%), respectively. The reaction of acetyl derivative **1c** and **2f** provided **3l** (43%) in moderate yield.

However, the reaction of nitrile derivative **1d** and **2b** afforded **3m** in low yield (13%). As reported in many similar cases,[1,14] the S_N2' reaction of a nucleophile to MBH acetate produced a *Z*-form intermediate as a major as shown in Scheme 4, and the following 1,6-conjugate addition could

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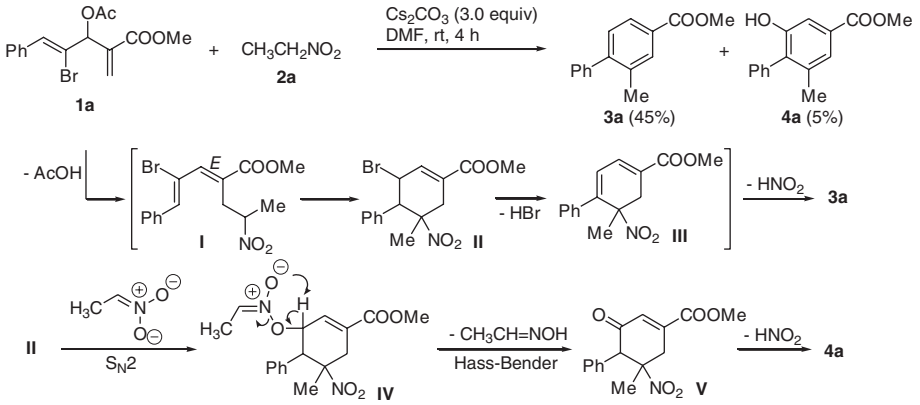
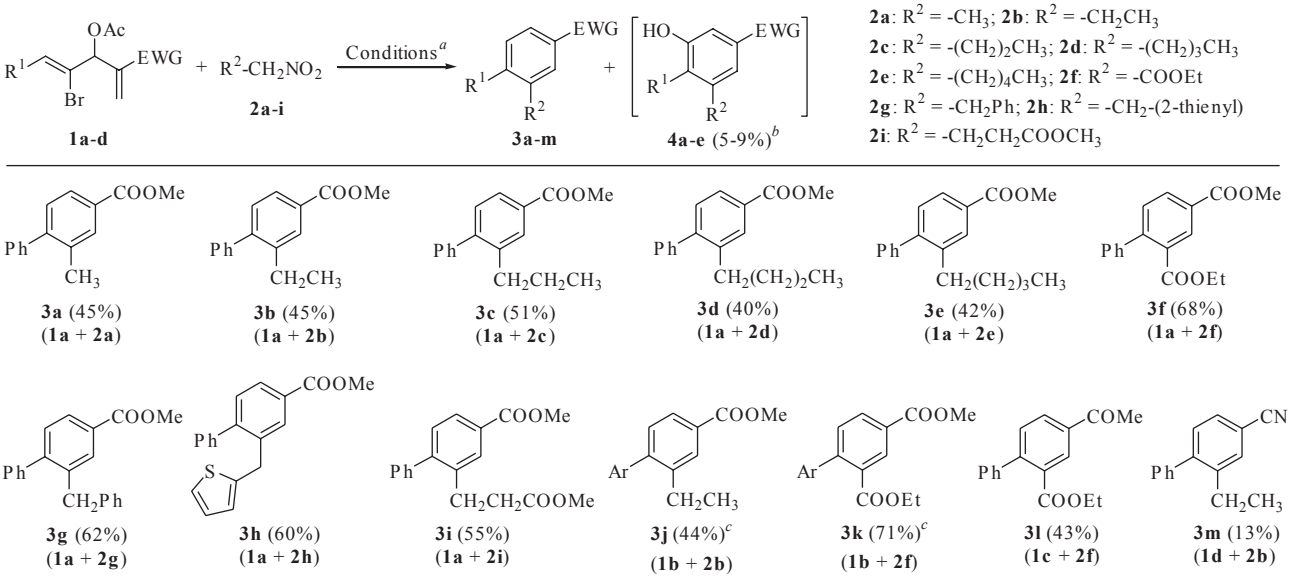


Scheme 3. One-pot synthesis of **3a** and **4a**.

Table 1. Synthesis of poly-substitutes benzenes.



a Conditions: **1** (0.5 mmol), **2** (0.5 mmol), Cs_2CO_3 (3.0 equiv), DMF, rt, 4 h.

b The yield of phenols: **4a** (5%), **4b** (7%), **4c** (9%), **4d** (7%), **4e** (7%).

The formation of corresponding phenols were observed in other entries; however, they were not isolated in appreciable amounts.

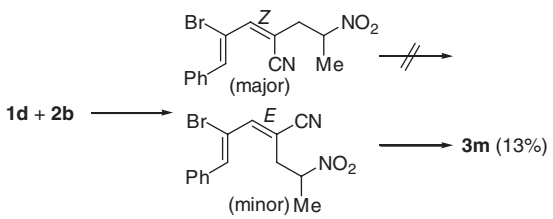
c Ar is 4-fluorophenyl.

not proceed. The minor *E*-isomer might produce **3m** in low yield.

In summary, an efficient synthetic method of 1,3,4-trisubstituted benzenes from Morita–Baylis–Hillman adducts has been developed. The method involved a sequential nucleophilic substitution (S_N2') reaction, an intramolecular 1,6-conjugate addition, and E2 elimination process.

Experimental

The starting materials **1a-d** were prepared according to the reported method,[7,10] and the spectroscopic data are reported in Supporting Information.



Scheme 4. The reaction of nitrile derivative **1d**.

Typical procedure for the synthesis of 3a and 4a. To a stirred solution of **1a** (170 mg, 0.5 mmol) and **2a** (37 mg, 0.5 mmol) in DMF (3.0 mL) was added Cs_2CO_3 (489 mg, 1.5 mmol), and the reaction mixture was stirred at room

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temperature for 4 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 25:1), compound **3a** (51 mg, 45%) was obtained as colorless oil along with **4a** (6 mg, 5%) as a white solid. Other compounds were synthesized similarly, and the selected spectroscopic data of **3a-i**, **4b**, and **4c** are as follows.

Compound 3a: 45%. Colorless oil; IR (film) 1722, 1436, 1296 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 3.94 (s, 3H), 7.28–7.36 (m, 3H), 7.37–7.47 (m, 3H), 7.90 (d, J = 7.8 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.41, 52.07, 126.95, 127.33, 128.19, 128.85, 129.88, 131.46, 135.62, 140.90, 146.53, 167.14, one carbon was overlapped; ESIMS *m/z* 227 $[M+H]^+$. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.81; H, 6.13.

Compound 3b: 45%. Colorless oil; IR (film) 1723, 1436, 1291 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, J = 7.5 Hz, 3H), 2.66 (q, J = 7.5 Hz, 2H), 3.96 (s, 3H), 7.25–7.36 (m, 3H), 7.38–7.48 (m, 3H), 7.91 (d, J = 8.1 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.44, 26.03, 52.08, 126.71, 127.25, 128.13, 128.82, 129.11, 129.83, 130.09, 140.93, 141.88, 146.27, 167.19; ESIMS *m/z* 241 $[M+H]^+$. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.14; H, 6.97.

Compound 3c: 51%. Colorless oil; IR (film) 1723, 1436, 1294 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 7.2 Hz, 3H), 1.46–1.60 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 3.94 (s, 3H), 7.24–7.33 (m, 3H), 7.36–7.50 (m, 3H), 7.90 (d, J = 7.5 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.89, 24.27, 34.91, 52.03, 126.70, 127.21, 128.10, 128.86, 128.96, 130.14, 130.46, 140.39, 141.04, 146.52, 167.19; ESIMS *m/z* 255 $[M+H]^+$. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.10; H, 7.31.

Compound 3d: 40%. Colorless oil; IR (film) 1724, 1436, 1291, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7.2 Hz, 3H), 1.14–1.27 (m, 2H), 1.40–1.52 (m, 2H), 2.60 (t, J = 7.8 Hz, 2H), 3.93 (s, 3H), 7.23–7.30 (m, 3H), 7.32–7.44 (m, 3H), 7.87 (dd, J = 8.1 and 1.5 Hz, 1H), 7.97 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.75, 22.41, 32.53, 33.37, 52.05, 126.65, 127.21, 128.09, 128.87, 128.94, 130.12, 130.46, 140.64, 140.99, 146.46, 167.21; ESIMS *m/z* 269 $[M+H]^+$. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.59; H, 7.82.

Compound 3e: 42%. Colorless oil; IR (film) 1724, 1436, 1291 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 6.9 Hz, 3H), 1.10–1.30 (m, 4H), 1.41–1.54 (m, 2H), 2.61 (t, J = 7.8 Hz, 2H), 3.94 (s, 3H), 7.25–7.32 (m, 3H), 7.34–7.46 (m, 3H), 7.89 (dd, J = 7.8 and 1.8 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.88, 22.26, 30.85, 31.53, 32.82, 52.05, 126.66, 127.22, 128.10, 128.86, 128.98, 130.12, 130.46, 140.70, 141.02, 146.47, 167.21; ESIMS *m/z* 283 $[M+H]^+$. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.68; H, 7.96.

Compound 3f: 68%. Colorless oil; IR (film) 1727, 1437, 1306, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, J = 7.2 Hz, 3H), 3.96 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 7.30–7.34 (m, 2H), 7.37–7.48 (m, 4H), 8.17 (dd, J = 8.1 and 1.8 Hz, 1H), 8.48 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.63, 52.31, 61.20, 127.75, 128.11, 128.15, 129.03, 130.82, 130.95, 131.61, 131.85, 140.38, 146.63, 166.12, 167.92; ESIMS *m/z* 285 $[M+H]^+$. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.98; H, 5.43.

Compound 3g: 62%. Colorless oil; IR (film) 1723, 1435, 1291, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3H), 3.94 (s, 2H), 6.89 (d, J = 7.2 Hz, 2H), 7.05–7.21 (m, 5H), 7.25–7.35 (m, 4H), 7.88 (dd, J = 6.6 and 1.8 Hz, 1H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.88, 52.09, 125.93, 127.37, 127.42, 128.15, 128.30, 128.66, 128.93, 129.21, 130.34, 131.61, 138.55, 140.63, 140.79, 146.91, 167.02; ESIMS *m/z* 303 $[M+H]^+$. Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.64; H, 6.15.

Compound 3h: 60%. Colorless oil; IR (film) 1723, 1436, 1290, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 3H), 4.14 (s, 2H), 6.58–6.61 (m, 1H), 6.87 (dd, J = 5.1 and 3.3 Hz, 1H), 7.11 (dd, J = 5.1 and 1.2 Hz, 1H), 7.26–7.31 (m, 2H), 7.32–7.44 (m, 4H), 7.97 (dd, J = 8.1 and 1.8 Hz, 1H), 8.05 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.32, 52.13, 123.88, 125.17, 126.69, 127.56, 127.72, 128.22, 128.90, 129.33, 130.40, 131.29, 137.96, 140.27, 143.83, 146.49, 166.91; ESIMS *m/z* 309 $[M+H]^+$. Anal. Calcd for $C_{19}H_{16}O_2S$: C, 74.00; H, 5.23. Found: C, 74.07; H, 5.36.

Compound 3i: 55%. Colorless oil; IR (film) 1723, 1436, 1294, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (t, J = 7.5 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H), 3.60 (s, 3H), 3.93 (s, 3H), 7.26–7.32 (m, 3H), 7.34–7.47 (m, 3H), 7.92 (dd, J = 8.1 and 1.8 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.12, 34.84, 51.57, 52.11, 127.41, 127.53, 128.35, 128.69, 129.25, 130.20, 130.40, 138.14, 140.42, 146.61, 166.91, 172.91; ESIMS *m/z* 299 $[M+H]^+$. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.35; H, 6.30.

Compound 4b: 7%. White solid, m.p. 94–96 °C; IR (KBr) 3429, 1721, 1310, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (t, J = 7.5 Hz, 3H), 2.43 (q, J = 7.5 Hz, 2H), 3.94 (s, 3H), 4.83 (br s, 1H), 7.28 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 1.5 Hz, 1H), 7.44–7.62 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.24, 26.50, 52.15, 113.68, 121.59, 128.62, 129.49, 129.93, 130.56, 132.26, 134.19, 143.69, 152.84, 166.99; ESIMS *m/z* 257 $[M+H]^+$. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.11; H, 6.50.

Compound 4c: 9%. White solid, m.p. 102–103 °C; IR (KBr) 3428, 1722, 1321, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, J = 7.2 Hz, 3H), 1.37–1.54 (m, 2H), 2.37 (t, J = 7.5 Hz, 2H), 3.92 (s, 3H), 4.83 (br s, 1H), 7.26 (s, 1H), 7.28 (s, 1H), 7.39–7.62 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.89, 24.05, 35.29, 52.15, 113.62, 122.26, 128.58, 129.43, 129.97, 130.33, 132.52, 134.22, 142.16, 152.87, 167.00; ESIMS *m/z* 271 $[M+H]^+$. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.29; H, 6.94.

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Supporting Information. Additional supporting information is available in the online version of this article.

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10. For synthetic details of starting materials, see supporting information. The synthesis of MBH acetate of (*Z*)-2-bromohex-2-enal was examined; however, the MBH reaction with methyl acrylate failed.
11. Many conditions were examined in order to increase the yield of **3a**; however, the yield was not increased due to the formations of many side products including a rearranged primary acetate of **1a** and a trace amount of unreactive *Z*-form S_N2' intermediate.
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