

## Synthesis of Isochroman and Tetrahydroisoquinoline Derivatives from Baylis-Hillman Adducts by Radical Cyclization

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Recently we were interested in radical cyclizations of modified Baylis-Hillman adducts.<sup>1,2</sup> We reported the synthesis of various heterocyclic compounds<sup>1</sup> including 2,3-dihydrobenzofuran derivatives using radical cyclization process.<sup>2</sup> Meantime we reasoned that six-membered heterocyclic compounds such as isochroman<sup>3</sup> and tetrahydroisoquinoline<sup>4</sup> derivatives could be prepared by radical cyclization from suitably modified Baylis-Hillman adducts (*vide infra*, Scheme 1).

Isochroman and tetrahydroisoquinoline derivatives are important backbone in many biologically interesting substances and their synthesis have been studied extensively.<sup>3-5</sup> Especially, appropriately substituted tetrahydroisoquinolines are an important class of natural and synthetic compounds, which exhibit various biological activities including antitumor, antibacterial, antiplasmodial and  $\beta$ -adrenergic receptor antagonism.<sup>4,5</sup>

As an initial trial we examined the synthesis of isochroman derivative **4a** as shown in Scheme 1. The starting material **3a** was synthesized from the reaction of Baylis-Hillman acetate **1a** and 2-bromobenzyl alcohol (**2a**) in good yield (82%). With this compound **3a** in our hand we examined the radical cyclization under the influence of *n*-Bu<sub>3</sub>SnH/AIBN in benzene and we obtained desired 4,4-disubstituted isochroman derivative **4a** in 89% yield (Scheme 1). We did not observe the formation of seven-membered ring compound or reduction product. Most of the radical cyclizations of aryl radical toward tethered unsaturated ester occurred at the  $\beta$ -position of unsaturated moiety.<sup>6</sup> However, we observed the selective formation of six-membered ring compound **4a** presumably due to the special stability of the intermediate benzylic radical as in our previous synthesis of 2,3-dihydrobenzofuran.<sup>2</sup> Encouraged by the results we prepared starting materials **3b-f** (*vide infra*, Table 1 and Scheme 2) and carried out radical cyclizations

under the same conditions, and the results are summarized in Table 1.

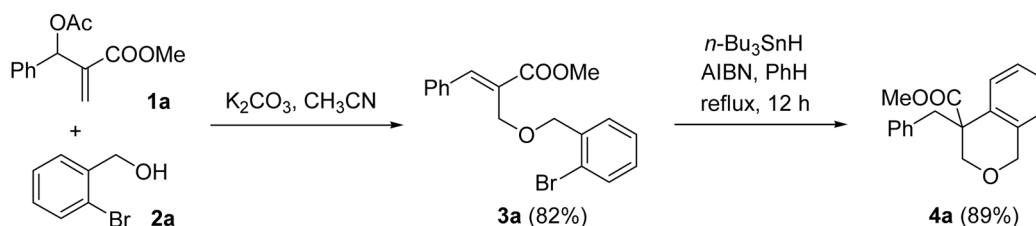
As shown we prepared three isochroman derivatives **4a-c** (entries 1-3) and two tetrahydroisoquinolines **4d** and **4e** (entries 4 and 5) in good yields (85-89%). However, unfortunately, radical cyclization was not completed in the case of nitrile derivative **3f** and we isolated isochroman **4f** and reduction compound **5** together (1:1 mixture based on <sup>1</sup>H NMR) as a mixture. The separation of **4f** and **5** was very difficult by column chromatography due to their same mobility on TLC. At this stage the reason for low yield of cyclized compound **4f** is not clear.

Synthesis of starting materials **3a-e** required somewhat different synthetic approaches depending upon the substrates as shown in Scheme 2. Synthesis of **3a** and **3b** was carried out by the reaction of Baylis-Hillman acetate **1a** and 2-bromobenzyl alcohol (**2a**) in the presence of K<sub>2</sub>CO<sub>3</sub> in acetonitrile (79-82%). The compound **3c** was synthesized from cinnamyl alcohol **1b**<sup>7</sup> and 5-bromo-6-bromomethyl-1,3-benzodioxole (**2b**) in moderate yield (56%) by using potassium *tert*-butoxide in DMF. The compounds **3d** and **3e** were prepared from the reaction of rearranged *aza*-Baylis-Hillman adduct **1c**<sup>7</sup> and **2b** or 2-bromobenzyl bromide (**2c**) in the presence of K<sub>2</sub>CO<sub>3</sub> in DMF in good yields (81-91%). Nitrile derivative **3f** was prepared by the reaction of **2a** and the corresponding Baylis-Hillman acetate in 79% yield by following the same procedure for the synthesis of **3a**.

In summary, we disclosed the synthesis of some isochroman and tetrahydroisoquinoline derivatives by the radical cyclization process starting from the Baylis-Hillman adducts.

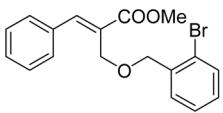
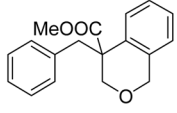
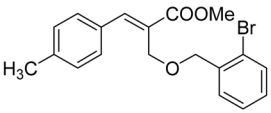
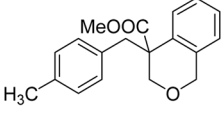
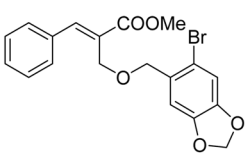
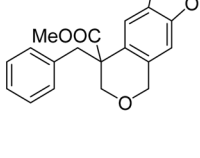
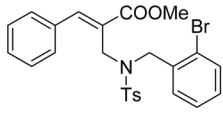
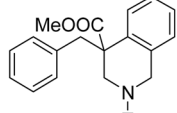
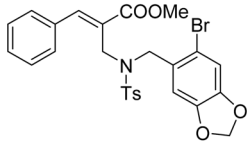
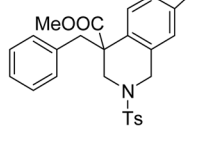
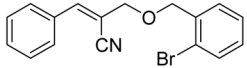
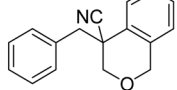
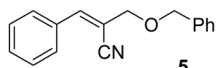
### Experimental Section

**Typical procedure for the synthesis of 3a.** To a stirred solution of Baylis-Hillman acetate (**1a**, 200 mg, 0.85 mmol)

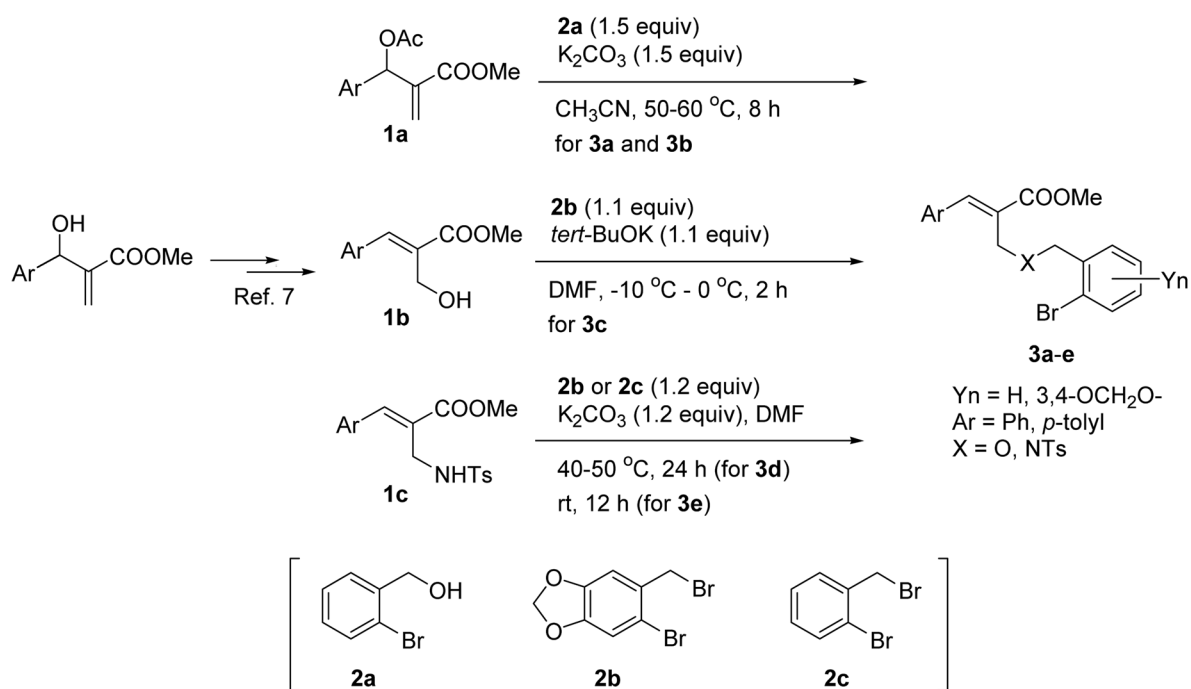


Scheme 1

**Table 1.** Synthesis of isochroman and tetrahydroisoquinoline derivatives

Entry	Substrate <sup>a</sup>	Time (h) <sup>b</sup>	Product (%)
1	 <b>3a</b> (82)	12	 <b>4a</b> (89)
2	 <b>3b</b> (79)	48	 <b>4b</b> (85)
3	 <b>3c</b> (56)	14	 <b>4c</b> (88)
4	 <b>3d</b> (91)	10	 <b>4d</b> (86)
5	 <b>3e</b> (81)	3	 <b>4e</b> (89)
6	 <b>3f</b> (79)	12	 <b>4f</b>  <b>5</b> <b>4f : 5 = 1 : 1 (97)<sup>c</sup></b>

<sup>a</sup>Synthesis of starting materials is summarized in Scheme 2. <sup>b</sup>Conditions: *n*-Bu<sub>3</sub>SnH (1.5 equiv), AIBN (cat), benzene, reflux, given time. <sup>c</sup>Based on <sup>1</sup>H NMR spectrum.

**Scheme 2**

and **2a** (239 mg, 1.28 mmol) in CH<sub>3</sub>CN (3 mL) was added K<sub>2</sub>CO<sub>3</sub> (177 mg, 1.28 mmol), and the reaction mixture was stirred for 8 h at 50–60 °C. After the normal aqueous workup and column chromatographic purification process (hexanes/EtOAc = 15:1) we obtained **3a** as colorless oil, 251 mg (82%). Synthesis of compounds **3b**, **3d**, **3e** and **3f** was carried out similarly and the spectroscopic data are as follows.

Compound **3a**: colorless oil; 82%; IR (film) 3518, 2953, 1732, 1232 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.84 (s, 3H), 4.41 (s, 2H), 4.70 (s, 2H), 7.12–7.18 (m, 1H), 7.28–7.33 (m, 1H), 7.36–7.39 (m, 3H), 7.51–7.57 (m, 4H), 7.96 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  52.17, 64.86, 72.21, 123.07, 127.37, 128.42, 128.52, 129.07, 129.37, 129.78, 129.85, 132.53, 134.62, 137.37, 144.97, 168.02; ESIMS *m/z* 361 (M<sup>+</sup>+1). Anal Calcd for C<sub>18</sub>H<sub>17</sub>BrO<sub>3</sub>: C, 59.85; H, 4.74. Found: C, 60.13; H, 4.55.

Compound **3b**: colorless oil; 79%; IR (film) 3521, 2952, 1747, 1230 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  2.37 (s, 3H), 3.83 (s, 3H), 4.42 (s, 2H), 4.71 (s, 2H), 7.12–7.16 (m, 1H), 7.17–7.20 (m, 2H), 7.28–7.33 (m, 1H), 7.45–7.48 (m, 2H), 7.52–7.57 (m, 2H), 7.94 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  21.40, 52.14, 64.99, 72.17, 123.08, 127.39, 127.48, 129.05, 129.31, 129.79, 130.02, 131.84, 132.54, 137.46, 139.78, 145.17, 168.21; ESIMS *m/z* 375 (M<sup>+</sup>+1).

Compound **3d**: colorless oil; 91%; IR (film) 2958, 1705, 1344, 1244 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  2.43 (s, 3H), 3.56 (s, 3H), 4.37 (s, 2H), 4.38 (s, 2H), 6.99–7.04 (m, 1H), 7.12–7.16 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.34–7.49 (m, 7H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.67 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  21.47, 45.08, 51.97, 52.13, 122.15, 126.39, 127.19, 127.41, 128.48, 128.50, 129.19, 129.27, 129.64, 129.72, 132.21, 133.90, 135.71, 136.07, 143.45, 144.41, 167.41; ESIMS *m/z* 514 (M<sup>+</sup>+1). Anal Calcd for C<sub>25</sub>H<sub>24</sub>BrNO<sub>4</sub>S: C, 58.37; H, 4.70; N, 2.72. Found: C, 58.12; H, 4.95; N, 2.58.

Compound **3e**: colorless oil; 81%; IR (film) 2925, 1714, 1479, 1238 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  2.44 (s, 3H), 3.62 (s, 3H), 4.25 (s, 2H), 4.36 (s, 2H), 5.89 (s, 2H), 6.83 (s, 1H), 6.96 (s, 1H), 7.28–7.35 (m, 7H), 7.65–7.68 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  21.48, 44.78, 51.81, 52.01, 101.58, 109.35, 112.11, 112.50, 126.34, 127.41, 128.46, 129.11, 129.31, 129.64, 129.69, 133.90, 135.76, 143.46, 144.33, 147.36, 167.40 and one carbon is overlapped; ESIMS *m/z* 558 (M<sup>+</sup>+1).

Compound **3f**: colorless oil; 79%; IR (film) 3492, 3062, 2864, 2214, 1228 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.33 (s, 2H), 4.69 (s, 2H), 7.13–7.21 (m, 2H), 7.28–7.36 (m, 1H), 7.39–7.44 (m, 3H), 7.51–7.58 (m, 2H), 7.75–7.79 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  71.68, 71.84, 107.89, 117.62, 122.84, 127.57, 128.87, 129.02, 129.32, 129.36, 130.67, 132.62, 132.92, 136.58, 145.12; ESIMS *m/z* 328 (M<sup>+</sup>+1).

**Typical procedure for the synthesis of 3c.** To a stirred mixture of **1b** (40 mg, 0.21 mmol) and **2b** (67 mg, 0.23 mmol) in DMF (0.5 mL) was added *t*-BuOK (26 mg, 0.23 mmol) at –10 °C, and the reaction mixture was stirred at around 0 °C for 2 h. After the usual aqueous workup and

column chromatographic purification process (hexanes/EtOAc = 15:1) we obtained **3c** as colorless oil, 48 mg (56%). Spectroscopic data of compound **3c** are as follows.

Compound **3c**: colorless oil; 56%; IR (film) 2949, 2895, 1714, 1236 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.85 (s, 3H), 4.37 (s, 2H), 4.60 (s, 2H), 5.96 (s, 2H), 7.00 (s, 1H), 7.02 (s, 1H), 7.37–7.39 (m, 3H), 7.51–7.55 (m, 2H), 7.95 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  52.17, 64.67, 72.08, 101.67, 109.78, 112.56, 113.59, 128.38, 128.51, 129.38, 129.84, 130.58, 134.61, 144.96, 147.38, 147.79, 167.98; ESIMS *m/z* 405 (M<sup>+</sup>+1).

**Typical procedure for the synthesis of 4a.** A stirred mixture of **3a** (80 mg, 0.22 mmol), *n*-Bu<sub>3</sub>SnH (97 mg, 0.33 mmol), AIBN (cat) in benzene (5 mL) was heated to reflux for 12 h. After removal of solvent and column chromatographic purification process (hexanes/EtOAc, 15:1) we obtained **4a** as colorless oil, 55 mg (89%).

Compound **4a**: colorless oil; 89%; IR (film) 2950, 1734, 1256 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.16 (d, *J* = 13.5 Hz, 1H), 3.50 (d, *J* = 13.5 Hz, 1H), 3.67 (s, 3H), 3.90 (d, *J* = 11.7 Hz, 1H), 4.13 (d, *J* = 11.7 Hz, 1H), 4.81 (d, *J* = 0.6 Hz, 2H), 6.99–7.03 (m, 1H), 7.13–7.16 (m, 2H), 7.17–7.26 (m, 5H), 7.52–7.56 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  43.48, 50.08, 52.10, 68.71, 69.11, 124.39, 126.63, 126.68, 127.08, 127.78, 128.10, 130.43, 133.92, 135.16, 138.81, 173.46; ESIMS *m/z* 283 (M<sup>+</sup>+1). Anal Calcd for C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>: C, 76.57; H, 6.43. Found: C, 76.43; H, 6.61.

Compound **4b**: colorless oil; 85%; IR (film) 2952, 1731, 1255 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  2.30 (s, 3H), 3.11 (d, *J* = 13.5 Hz, 1H), 3.46 (d, *J* = 13.5 Hz, 1H), 3.66 (s, 3H), 3.90 (d, *J* = 11.7 Hz, 1H), 4.14 (d, *J* = 11.7 Hz, 1H), 4.80 (d, *J* = 0.9 Hz, 2H), 6.99–7.00 (m, 1H), 7.05 (s, 4H), 7.19–7.25 (m, 2H), 7.56–7.59 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  20.98, 43.07, 49.98, 52.04, 68.69, 69.06, 124.33, 126.60, 127.01, 127.76, 128.80, 130.24, 133.59, 133.92, 135.20, 136.17, 173.47; ESIMS *m/z* 297 (M<sup>+</sup>+1).

Compound **4c**: colorless oil; 88%; IR (film) 2951, 1728, 1484, 1240 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.10 (d, *J* = 13.5 Hz, 1H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.68 (s, 3H), 3.84 (d, *J* = 11.7 Hz, 1H), 4.08 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 15.0 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 5.92 (d, *J* = 1.2 Hz, 1H), 5.95 (d, *J* = 1.2 Hz, 1H), 6.45 (s, 1H), 7.06 (s, 1H), 7.13–7.16 (m, 2H), 7.19–7.28 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  43.64, 49.95, 52.17, 68.84, 69.19, 101.00, 104.17, 107.98, 126.76, 127.66, 128.17, 128.20, 130.36, 136.72, 146.41, 146.75, 173.58; ESIMS *m/z* 327 (M<sup>+</sup>+1).

Compound **4d**: colorless oil; 86%; IR (film) 2954, 1733, 1159 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  2.42 (s, 3H), 3.30 (d, *J* = 13.5 Hz, 1H), 3.31 (d, *J* = 13.5 Hz, 1H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.62 (d, *J* = 13.5 Hz, 1H), 3.65 (s, 3H), 3.93 (d, *J* = 14.7 Hz, 1H), 4.39 (d, *J* = 14.7 Hz, 1H), 7.02–7.05 (m, 1H), 7.14–7.28 (m, 7H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.47–7.50 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  21.51, 44.25, 48.62, 49.14, 52.05, 52.25, 126.47, 126.79, 126.86, 127.37, 128.03 (2C), 128.61, 129.73, 130.89, 131.26, 132.14, 134.38, 136.21, 143.94, 173.01; ESIMS *m/z* 436 (M<sup>+</sup>+1). Anal Calcd for C<sub>25</sub>H<sub>25</sub>NO<sub>4</sub>S: C,

68.94; H, 5.79; N, 3.22. Found: C, 68.75; H, 5.88; N, 3.15.

Compound **4e**: colorless oil; 89%; IR (film) 2924, 1730, 1487, 1242  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.43 (s, 3H), 3.24 (d,  $J = 13.8$  Hz, 1H), 3.25 (d,  $J = 12.0$  Hz, 1H), 3.39 (d,  $J = 13.8$  Hz, 1H), 3.54 (d,  $J = 12.0$  Hz, 1H), 3.64 (s, 3H), 3.83 (d,  $J = 14.4$  Hz, 1H), 4.24 (d,  $J = 14.4$  Hz, 1H), 5.89 (d,  $J = 1.2$  Hz, 1H), 5.93 (d,  $J = 1.2$  Hz, 1H), 6.46 (s, 1H), 7.01 (s, 1H), 7.22-7.24 (m, 5H), 7.34 (d,  $J = 8.4$  Hz, 2H), 7.69 (d,  $J = 8.4$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  21.50, 44.38, 48.69, 49.02, 51.91, 52.26, 101.19, 105.86, 108.41, 124.89, 126.93, 127.69, 128.02, 128.09, 129.73, 130.81, 132.14, 136.12, 143.95, 146.62, 146.96, 173.05; ESIMS  $m/z$  480 ( $\text{M}^+ + 1$ ).

Compound **4f** and compound **5** were not separated, however, we could assign their  $^1\text{H}$  NMR data as follows: Compound **4f**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.18 (d,  $J = 12.0$  Hz, 1H), 3.23 (d,  $J = 12.0$  Hz, 1H), 3.85 (d,  $J = 11.4$  Hz, 1H), 4.11 (d,  $J = 11.4$  Hz, 1H), 4.88 (d,  $J = 15.0$  Hz, 1H), 4.90 (d,  $J = 15.0$  Hz, 1H), 7.25-7.79 (m, 9H); Compound **5**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  4.26 (s, 2H), 4.63 (s, 2H), 7.17 (s, 1H), 7.74-7.79 (m, 10H).

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