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Radical cyclization of 4-aryl-1-iodobutene derivatives to form dihydronaphthalene scaffold

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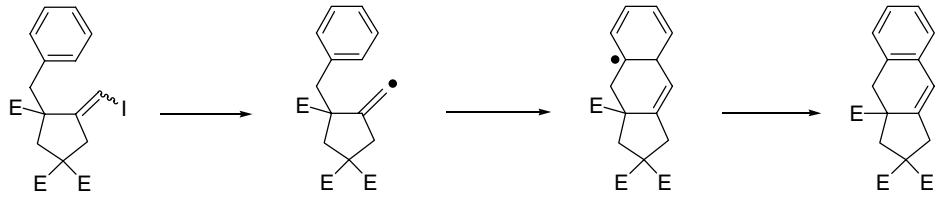
Abstract—Synthesis of dihydronaphthalene derivatives was carried out by allyltributylstannane-mediated vinyl radical cyclization as the key step from 4-aryl-1-iodobutene derivatives, which were derived from Baylis–Hillman adducts via vinyl radical cyclization.

Recently we reported the synthesis of *exo*-methylene tetrahydrofurans,[1] 5-methylene tetrahydropyrancarboxylates,[2] and *exo*-methylene cyclopentanes[3] via the radical cyclization protocol as the key step starting from the modified Baylis–Hillman adducts. Meantime we were interested in the C–C bond formation between the aryl group and the vinyl moiety in order for the synthesis of dihydronaphthalene skeleton.[4] We supposed that the desired dihydronaphthalene **3** could be formed by the consecutive generation of a vinyl radical from **2** and cyclization onto the benzene ring as shown in Scheme 1. There were reported many examples on the intramolecular C–C bond-forming reactions between aryl halides and another arene moiety via radical cyclization process.[5] However, examples of radical cyclizations involving the addition of vinyl radical intermediates to proximal arenes are more limited[5d,6] although vinyl radical cyclizations to various alkene moiety have been extensively studied.[7]

We presumed that treatment of vinyl iodide **2** with *n*-Bu_3SnH and AIBN would generate a vinyl radical intermediate, and that this would rapidly abstract a hydrogen atom from *n*-Bu_3SnH to give vinyl compound **4** (vide infra). However, if we used allyltributylstannane the vinyl radical would not be quenched by stannane as in our previous report,[2] leading to cyclization to give the cyclized compound **3**. The required vinyl iodide **2a** was prepared from the corresponding vinylstannane intermediate with iodine as reported.[7b] Thus, we examined the reaction of **2a** and allyltributylstannane in the presence of AIBN in benzene. To our delight we obtained the expected dihydronaphthalene compound **3a** in 65% in a short time. The compound might be formed via radical cyclization of the corresponding vinyl radical as shown in Scheme 1. In addition, it is interesting to note that the reaction of **2a** in the presence of *n*-Bu_3SnH instead of allyltributylstannane under similar conditions afforded simple reduction compound **4** in 92% as we



Scheme 1.

Keywords: Radical cyclization; Dihydronaphthalene; *n*-Bu_3SnH; Allyltributylstannane; Baylis–Hillman adducts.
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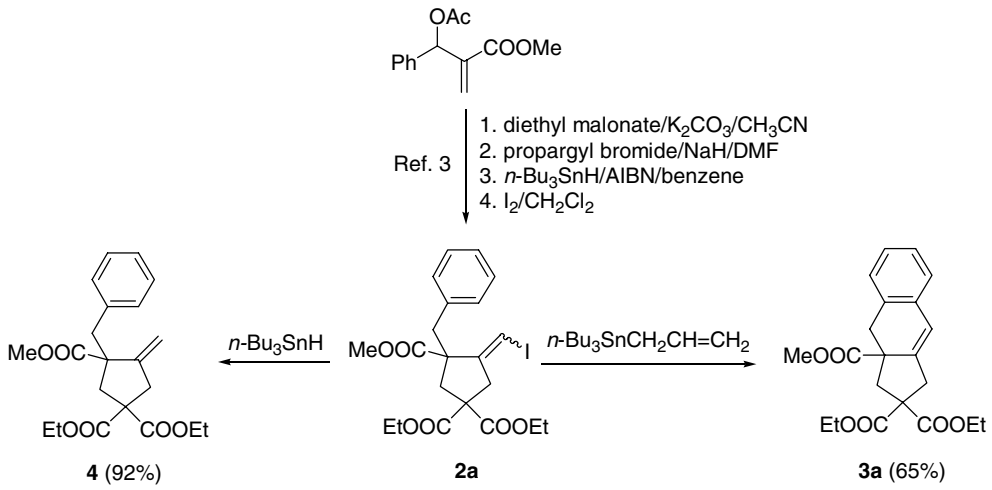
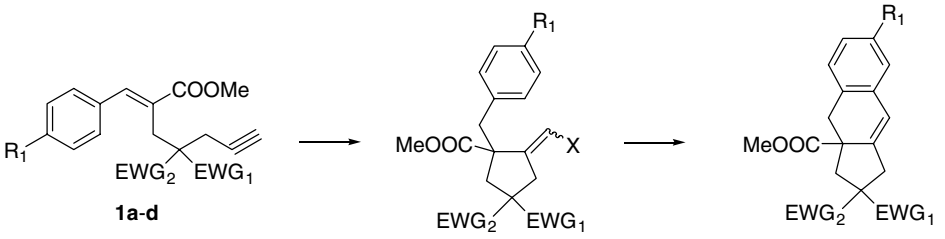


Scheme 2.

expected (Scheme 2). We examined the possibility for the thermal synthesis of **3a** from **2a**.[8] The reaction was conducted either in refluxing benzene or *p*-xylene, but we observed no reaction. When we used quinoline as the solvent, severe decomposition of starting material was observed.

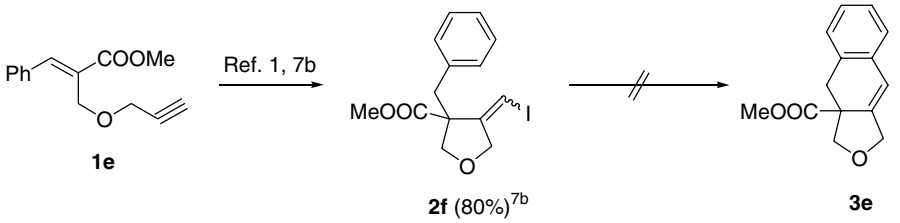
By applying the typical procedure we examined some examples and the results are summarized in Table 1.[9] As shown, the reaction proceeded similarly and we obtained dihydronaphthalene derivatives **3b–d** in good yields irrespective of the substituents both on the cyclopentane ring and aryl moiety. From the reaction of **2c** (entry 3) we could isolate **3c** as the single diastereoisomer, but we did not determine the stereochemistry. As in entry 5, the use of bromovinyl compound gave the same product **3b** in 75%. However, the reaction of **2f**[7b] under the same reaction conditions did not produce the desired compound **3e**. When we used hexabutylditin instead of allyltributylstannane, the result was same (Scheme 3) to show the formation of many intractable compounds.[10]

Table 1. Radical cyclization to dihydronaphthalene derivatives



Entry	Substrate[a]	Vinyl halide[b] (%)	Time (h)	Product[c] (%)
1	**1a**: $R_1 = H$, $EWG_1 = COOEt$, $EWG_2 = COOEt$	**2a**: X = I (82)	12	**3a** (65)
2	**1b**: $R_1 = H$, $EWG_1 = COOMe$, $EWG_2 = COOMe$	**2b**: X = I (92)	8	**3b** (83)
3	**1c**: $R_1 = H$, $EWG_1 = COOMe$, $EWG_2 = CN$	**2c**: X = I (79)	8	**3c** (56)
4	**1d**: $R_1 = CH_3$, $EWG_1 = COOMe$, $EWG_2 = COOMe$	**2d**: X = I (83)	14	**3d** (72)
5	**1b**	**2e**: X = Br (88)[d]	3	**3b** (75)

[a] Starting materials **1a–d** were synthesized as in our previous paper.[3]
[b] Conditions: (i) **1** (1.0 equiv), *n*-Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1 h, (ii) I_2, CH_2Cl_2, rt, 2 h.
[c] Conditions: **2** (1.0 equiv), allyltributylstannane (3.0 equiv), AIBN (0.1 equiv), benzene, reflux, 3–14 h.
[d] Conditions: (i) **1b** (1.0 equiv), *n*-Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1 h, (ii) NBS, CH_2Cl_2, 0 °C, 1 h.



Scheme 3.

In summary, we disclosed an efficient synthesis of novel tricyclic compounds by using the vinyl radical cyclization protocol starting from the corresponding vinyl iodides, which were derived from Baylis–Hillman adducts. Desired vinyl radical cyclization process was successfully carried out by using allyltributylstannane-assisted vinyl radical generation.

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9. Typical procedure for the synthesis of **2a**: To a stirred solution of **1a**[3] (250 mg, 0.67 mmol), *n*-Bu_3SnH (233 mg, 0.8 mmol) in benzene (10 mL) was added AIBN (11 mg, 0.07 mmol) and heated to reflux for 1 h under nitrogen atmosphere. The reaction mixture was diluted with CH_2Cl_2 and a solution of iodine in CH_2Cl_2 was added at 0 °C until the purple color persists and stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with $NaHSO_3$ solution and brine. After the usual purification process using flash column chromatography (hexanes/EtOAc, 7:3), we obtained **2a** as colorless oil, 275 mg (82%). Spectroscopic data of **2a–e** are as follows:
Compound **2a**: colorless oil; 82%; IR (neat) 3084, 1734, 1448, 1298 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, $J = 7.0$ Hz, 3H), 1.26 (t, $J = 7.0$ Hz, 3H), 2.73 (d, $J = 14.5$ Hz, 1H), 2.77 (dd, $J = 17.5$ and 2.5 Hz, 1H), 2.83 (d, $J = 13.0$ Hz, 1H), 3.00 (d, $J = 14.0$ Hz, 1H), 3.20 (dq, $J = 17.5$ and 0.5 Hz, 1H), 3.35 (d, $J = 13.5$ Hz, 1H), 3.65 (s, 3H), 4.09–4.24 (m, 4H), 6.55 (t, $J = 2.5$ Hz, 1H), 7.11–7.13 (m, 2H), 7.22–7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.89, 13.95, 41.31, 44.89, 45.01, 52.47, 57.02, 58.84, 61.72, 61.84, 76.52, 126.94, 128.32, 129.68, 136.55, 152.43, 170.72, 171.16, 172.62.
Compound **2b**: colorless oil; 92%; IR (neat) 2953, 1736, 1435, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72 (d, $J = 14.1$ Hz, 1H), 2.73 (dd, $J = 18.0$ and 2.6 Hz, 1H), 2.81 (d, $J = 13.5$ Hz, 1H), 3.00 (dd, $J = 14.4$ and 1.5 Hz, 1H), 3.25 (d, $J = 17.7$ Hz, 1H), 3.37 (d, $J = 13.8$ Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 6.58 (t, $J = 2.6$ Hz, 1H), 7.09–7.12 (m, 2H), 7.22–7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.64, 44.94, 45.04, 52.56, 52.92, 53.01, 56.88, 58.86, 76.76, 127.00, 128.37, 129.61, 136.45, 152.24, 171.16, 171.55, 172.53; ESIMS m/z 473 (M^++H).
Compound **2c**: colorless oil; 79%; IR (neat) 2954, 2245, 1741, 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, $J = 7.2$ Hz, 3H), 2.53 (d, $J = 14.4$ Hz, 1H), 2.90 (d, $J = 13.5$ Hz, 1H), 2.97 (dd, $J = 17.4$ and 3.0 Hz, 1H), 3.07–3.15 (m, 2H), 3.38 (d, $J = 13.5$ Hz, 1H), 3.75 (s, 3H), 4.28 (q, $J = 7.2$ Hz, 2H), 6.76 (t, $J = 2.7$ Hz, 1H), 7.05–7.09 (m, 2H), 7.25–7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.88, 43.51, 45.00, 45.45, 47.70, 52.81, 58.99, 63.45, 78.58, 118.94, 127.30, 128.53, 129.60, 135.80, 150.01, 168.06, 171.90.
Compound **2d**: colorless oil; 83%; IR (neat) 2953, 1736, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 2.71 (d, $J = 14.4$ Hz, 1H), 2.73 (dd, $J = 18.0$ and 2.6 Hz, 1H), 2.76 (d, $J = 13.5$ Hz, 1H), 3.00 (dd, $J = 14.1$ and 1.4 Hz, 1H), 3.24 (d, $J = 17.7$ Hz, 1H), 3.32 (d, $J = 13.5$ Hz, 1H), 3.64 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 6.56 (t, $J = 2.6$ Hz, 1H), 6.98 (d, $J = 8.1$ Hz, 2H), 7.06 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.93,

41.61, 44.65, 44.92, 52.44, 52.83, 52.91, 56.81, 58.92, 76.63, 129.00, 129.42, 133.27, 136.47, 152.21, 171.11, 171.47, 172.51.

Compound **2e**: colorless oil; 88%; IR (neat) 2953, 1738, 1435, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.68 (d, $J = 14.4$ Hz, 1H), 2.80 (dd, $J = 15.3$ and 2.7 Hz, 1H), 2.84 (d, $J = 13.5$ Hz, 1H), 2.94 (dd, $J = 14.4$ and 1.5 Hz, 1H), 3.29 (dq, $J = 15.6$ and 1.2 Hz, 1H), 3.33 (d, $J = 13.5$ Hz, 1H), 3.65 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 6.47 (t, $J = 2.7$ Hz, 1H), 7.09–7.12 (m, 2H), 7.21–7.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.68, 41.35, 45.03, 52.45, 52.81, 52.90, 57.16, 58.40, 104.47, 126.97, 128.30, 129.56, 136.36, 146.49, 171.08, 171.48, 172.59.

Typical procedure for the synthesis of **3a**: To a stirred solution of **2a** (84 mg, 0.17 mmol), allyltributylstannane (167 mg, 0.5 mmol) in benzene (2 mL) was added AIBN (3 mg, 0.018 mmol) and heated to reflux for 12 h under nitrogen atmosphere. After the usual aqueous extractive workup with CH_2Cl_2 and the following column chromatographic purification process (hexanes/EtOAc, 6:4), we obtained **3a** as colorless oil, 41 mg (65%). Spectroscopic data of **3a–d** are as follows:

Compound **3a**: colorless oil; 65%; IR (neat) 2926, 1734, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, $J = 7.2$ Hz, 6H), 2.54 (d, $J = 14.1$ Hz, 1H), 2.88 (d, $J = 13.8$ Hz, 1H), 2.92 (d, $J = 15.3$ Hz, 1H), 3.15 (d, $J = 16.8$ Hz, 1H), 3.39 (d, $J = 15.3$ Hz, 1H), 3.47 (d, $J = 16.8$ Hz, 1H), 3.52 (s, 3H), 4.16–4.24 (m, 4H), 6.39 (s, 1H), 6.99–7.01 (m, 1H), 7.07–7.12 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.00 (2C), 38.46, 39.74, 44.62, 51.81, 52.24, 59.63, 61.77, 61.87, 121.73, 125.84, 126.83, 126.97, 127.55, 132.97, 133.61, 142.26, 170.97, 171.50, 174.84.

Compound **3b**: colorless oil; 83%; IR (neat) 2954, 1739, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (d, $J = 14.4$ Hz, 1H), 2.83 (d, $J = 14.4$ Hz, 2H), 3.09 (d, $J = 17.1$ Hz, 1H), 3.32 (d, $J = 15.3$ Hz, 1H), 3.42 (d, $J = 17.1$ Hz, 1H), 3.45 (s, 3H), 3.67 (s, 3H), 3.68 (s, 3H), 6.33 (s, 1H), 6.93–6.95 (m, 1H), 7.01–7.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.43, 39.81, 44.73, 51.80, 52.28, 52.98, 53.10, 59.55, 121.87, 125.89, 126.87, 127.04, 127.57, 132.93, 133.56, 142.0, 171.43, 171.97, 174.76; ESIMS m/z 345 (M^++H).

Compound **3c**: colorless oil; 56%; IR (neat) 2954, 2254, 1747, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, $J = 7.2$ Hz, 3H), 2.48 (d, $J = 14.4$ Hz, 1H), 3.00 (d, $J = 14.4$ Hz, 1H), 3.04 (d, $J = 15.0$ Hz, 1H), 3.12 (d, $J = 15.3$ Hz, 1H), 3.42 (d, $J = 15.0$ Hz, 2H), 3.55 (s, 3H), 4.31 (q, $J = 7.2$ Hz, 2H), 6.53 (d, $J = 1.8$ Hz, 1H), 7.04–7.06 (m, 1H), 7.12–7.19 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 38.61, 42.88, 46.44, 47.46, 51.17, 52.56, 63.36, 120.22, 123.76, 126.30, 127.15, 127.64, 127.68, 132.73, 132.82, 139.62, 167.67, 174.04.

Compound **3d**: colorless oil; 72%; IR (neat) 2954, 1736, 1433, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.53 (d, $J = 14.4$ Hz, 1H), 2.84 (d, $J = 16.2$ Hz, 1H), 2.89 (d, $J = 14.1$ Hz, 1H), 3.16 (d, $J = 17.1$ Hz, 1H), 3.36 (d, $J = 15.3$ Hz, 1H), 3.48 (d, $J = 17.4$ Hz, 1H), 3.52 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 6.36 (s, 1H), 6.83 (s, 1H), 6.88 (d, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.01, 38.09, 39.79, 44.73, 51.99, 52.23, 52.94, 53.06, 59.53, 121.92, 126.73, 127.37, 127.60, 129.87, 133.45, 136.31, 141.92, 171.44, 171.95, 174.82.

Synthesis of compound **4**: To a stirred solution of **2a** (50 mg, 0.1 mmol), *n*-Bu_3SnH (35 mg, 0.12 mmol) in benzene (2 mL) was added AIBN (2 mg, 0.01 mmol) and heated to reflux for 1 h. After the usual aqueous extractive workup with EtOAc and the following column chromatographic purification process (hexanes/EtOAc, 7:3), we obtained **4** as colorless oil, 34 mg (92%).

Compound **4**: colorless oil; 92%; IR (neat) 2956, 1732, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 2.64 (d, $J = 14.4$ Hz, 1H), 2.76 (d, $J = 16.2$ Hz, 1H), 2.78 (d, $J = 13.5$ Hz, 1H), 2.86 (d, $J = 14.7$ Hz, 1H), 3.18 (d, $J = 16.2$ Hz, 1H), 3.44 (d, $J = 13.8$ Hz, 1H), 3.65 (s, 3H), 4.06–4.24 (m, 4H), 5.20 (t, $J = 2.1$ Hz, 1H), 5.30 (t, $J = 2.1$ Hz, 1H), 7.17–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.96, 13.99, 39.95, 41.03, 44.34, 52.29, 57.09, 57.93, 61.53, 61.66, 110.25, 126.67, 128.24, 129.84, 137.62, 150.76, 171.09, 171.69, 174.04.

10. From the reaction of **2f** (hexabutylditin, AIBN, toluene, reflux, 10 h) we could obtain **3e** in trace amount (5–6%). However, the product was contaminated with appreciable amounts of tin derivatives. ^1H NMR spectrum of crude **3e** is as follows: oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.85 (d, $J = 15.3$ Hz, 1H), 3.41 (d, $J = 15.3$ Hz, 1H), 3.60 (s, 3H), 3.76 (d, $J = 8.7$ Hz, 1H), 4.45 (d, $J = 8.7$ Hz, 1H), 4.54 (dd, $J = 13.8$ and 1.8 Hz, 1H), 4.76 (dd, $J = 13.8$ and 1.8 Hz, 1H), 6.45 (t, $J = 1.8$ Hz, 1H), 7.06–7.17 (m, 4H).