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Synthesis of 3,4-disubstituted 2,5-dihydrofurans starting from the Baylis–Hillman adducts via consecutive radical cyclization, halolactonization, and decarboxylation strategy

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Abstract—A facile synthetic method of 3,4-disubstituted 2,5-dihydrofurans and 2,5-dihydropyrroles starting from the Baylis–Hillman adducts was developed. The 2,5-dihydrofuran skeleton was constructed via the consecutive radical cyclization, hydrolysis, halolactonization, and spontaneous decarboxylation strategy starting from the modified Baylis–Hillman adducts.

Recently, we reported the synthesis of dihydrofuran and dihydropyrrole derivatives by the well-known ring-closing metathesis (RCM) reaction of suitably substituted Baylis–Hillman adducts.[1] Dihydrofurans and dihydropyrroles are found in a variety of natural products and biologically active substances,[2] and have been used as important synthetic intermediates.[3] The most versatile synthesis of these valuable compounds involved the ring-closing metathesis (RCM) reaction of the corresponding enynes or dienes.[1,4] Besides RCM reaction, a variety of synthetic approaches have been published for the synthesis of these valuable compounds.[5]

Recently, Shanmugam and Rajasingh have reported the synthesis of tetrahydrofuran backbone by the radical cyclization of triple bond containing cinnamate derivatives, which were synthesized from the Baylis–Hillman adducts.[6] They used vinyl radical, which was formed in situ via the hydrostannylation of the triple bond with *n*-Bu_3SnH.[6] We were intrigued by the results and envisioned that we could prepare dihydrofuran skeleton by following the sequences shown in Scheme 1.

The starting material **2a** was synthesized from the reaction of Baylis–Hillman adduct **1a** and propargyl alcohol in the presence of H_2SO_4 in methylene chloride in 54% yield.[6,7] Radical cyclization of **2a** was carried out according to the method of Shanmugam and Rajasingh with *n*-Bu_3SnH in the presence of catalytic amounts of AIBN.[6] After destannylation with aq HCl, we obtained tetrahydrofuran derivative **3a** in 62% yield. Compound **3a** was converted into its acid derivative **4a** by treatment with LiOH in aq THF (61%).[8] With this compound **4a** in our hand, we examined the synthesis of desired dihydrofuran derivative **5a**. Fortunately, the reaction of **4a** under the influence of typical iodolactonization conditions (I_2, $NaHCO_3$, and THF) afforded the desired 3,4-disubstituted 2,5-dihydrofuran derivative **5a** directly in moderate yield.[8] During the iodolactonization, cyclization must occur selectively according to 4-*exo*-*trig* mode to give the corresponding β-lactone intermediate (**I**) as expected. The β-lactone intermediate (**I**) converted directly into the final product **5a** by the loss of CO_2 spontaneously at room temperature. Direct synthesis of **5a** from the ester derivative **3a** was found to be inefficient.

Similarly, we obtained 3-bromomethyl-4-benzyl 2,5-dihydrofuran (**5b**) in moderate yield (48%) from **4a** under the bromolactonization conditions (NBS, $NaHCO_3$, and THF).[8] Encouraged by the successful results, we synthesized structurally similar dihydrofurans and dihydropyrroles and the results are summarized in Table 1.

As shown in Table 1, the reaction of **4b** under the bromolactonization conditions afforded **5c** in 56% yield. When we used 3-butyn-2-ol instead of propargyl alcohol from the starting point, we obtained 2-methyl substituted

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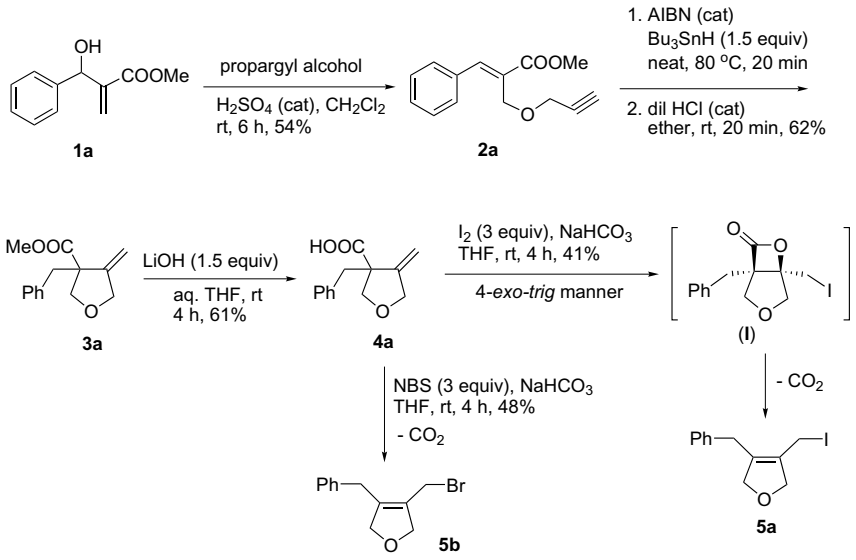
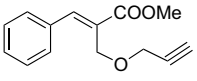
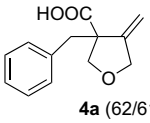
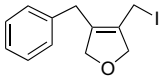
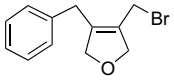
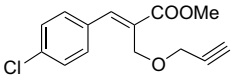
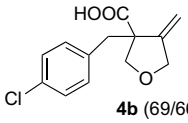
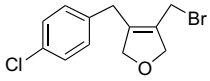
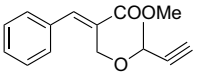
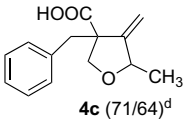
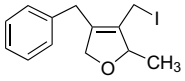
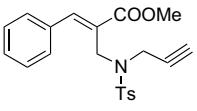
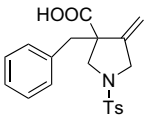
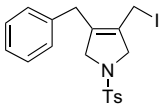
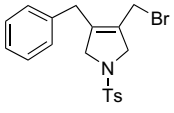


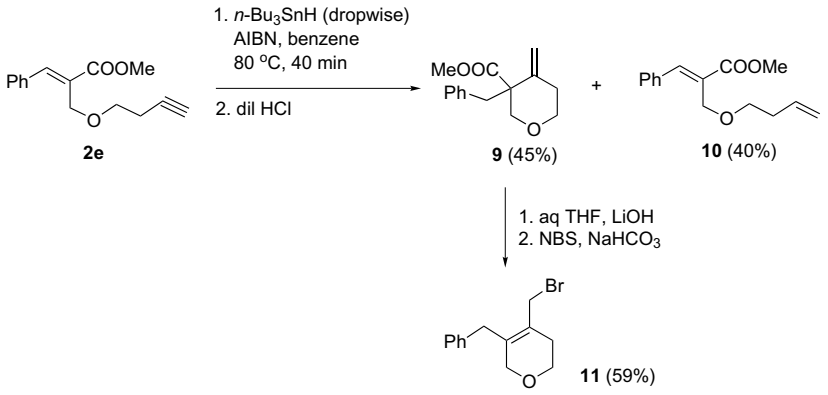
Scheme 1.

Table 1. Synthesis of dihydrofurans and dihydropyrroles

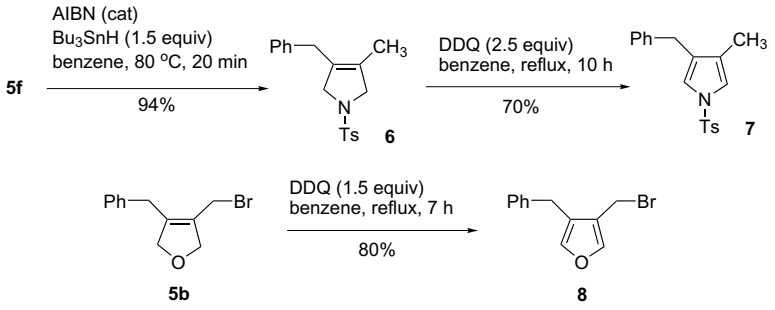
Entry	Substrates[a]	lntermediates[b]	Method[c]	Products (%)
1	 **2a** (54)	 **4a** (62/61)[d]	A	 **5a** (41)
2		**4a**	B	 **5b** (48)
3	 **2b** (64)	 **4b** (69/66)[d]	B	 **5c** (56)
4	 **2c** (71)	 **4c** (71/64)[d]	A	 **5d** (56)
5	 **2d** (75)	 **4d** (87/69)[d]	A	 **5e** (65)
6		**4d**	B	 **5f** (70)

[a] Prepared according to the reported methods. Ref. 6 for **2a**–**c** and Ref. 1 for **2d**.
[b] (1) *n*-Bu_3SnH (1.5 equiv), AIBN (cat), neat, 80 °C, 20 min, (2) 1 N HCI, ether, 20 min, (3) aq THF, LiOH (1.5 equiv), rt, 4 h, and (4) H_3O^+.
[c] Method A: I_2 (3 equiv), $NaHCO_3$ (3 equiv), THF, rt, 4 h. Method B: NBS (3 equiv), $NaHCO_3$ (3 equiv), THF, rt, 4 h.
[d] The first yield refer to the synthesis of **3** and the second one refer to the yield of **4** from **3**.

derivative **5d** (56%), similarly. As a next trial, we examined the synthesis of *N*-tosyl-2,5-dihydropyrrole derivatives. Introduction of tosylamide moiety at the primary position of the Baylis–Hillman adducts and successive propargylation with propargyl bromide gave the starting material **2d**.[7] Radical cyclization of **2d**, and succes-



Scheme 2.



Scheme 3.

sive destannylation, hydrolysis, and finally halolactonization afforded the corresponding dihydropyrrole derivatives **5e** and **f** in 65% and 70% yields, respectively.[8]

In order to check the possibility for the synthesis of 6-membered dihydropyran derivatives, we made the required starting material **2e** by the reaction of **1a** and 3-butyn-1-ol. Unfortunately, however, radical cyclization of **2e** was ineffective. Under the same reaction conditions we obtained the cyclized compound **9** in only 17% yield. Instead we obtained the simple reduction product **10** in 70% yield. The results were the same as those of recent works by Shanmugam and Rajasingh.[6c] They did not obtain the cyclized compound **9** at all. Thus, we modified the reaction conditions in order to increase the cyclization product **9**. To the refluxing solution of **2e** in benzene, we added a solution of *n*-Bu_3SnH and AIBN (benzene) in a dropwise manner and we could obtain the cyclized product **9** in 45% yield together with the reduction product **10** in 40% yield (Scheme 2). By using this compound **9**, we examined the synthesis of **11** according to the same strategy. Fortunately, we could obtain the corresponding dihydropyran **11** in 59% yield from **9**.[8]

Dihydrofurans and dihydropyrroles could be converted into the corresponding furan and pyrrole derivatives as shown in Scheme 3. As an example, consecutive reduction of **5f** into **6** with *n*-Bu_3SnH and the following oxidation of **6** with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) produced the pyrrole derivative **7**.[8] Treatment of **5b** with DDQ generated furan **8** similarly in 80% yield.[8]

In conclusion, we disclosed the successful results for the synthesis of 3,4-disubstituted 2,5-dihydrofurans and 2,5-dihydropyrroles starting from the Baylis–Hillman adducts. We are currently studying the synthesis of bicyclic furo[2,3-*b*]furan derivatives by manipulating the *exo*-methylene double bond of the intermediates.

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7. Starting materials **2b**,**c** and **e** were synthesized similarly.[6] Synthesis of **2d** was carried out via two steps: introduction of tosylamide by the reaction of the corresponding Baylis–Hillman acetate and tosylamide in the presence of K_2CO_3 in DMF, propargylation with propargyl bromide with K_2CO_3 in DMF.[1]
8. Synthesis of **3** was carried out according to the reported method.[6] Hydrolysis of **3** to **4** and halolactonization of **4** was carried out according to the general procedures as shown in the footnotes of Table 1. Selected spectroscopic data of **5a**–**f**, **4a**–**d**, and **7**–**11** are as follows:

Compound **5a**: 41%; viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.44 (s, 2H), 4.00 (s, 2H), 4.32–4.36 (m, 2H), 4.78–4.83 (m, 2H), 7.16–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.92, 31.77, 77.20, 78.55, 126.66, 128.50, 128.73, 129.87, 135.58, 137.28.

Compound **5b**: 48%; viscous oil; IR (neat) 2846, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 2H), 4.11 (s, 2H), 4.47–4.51 (m, 2H), 4.77–4.81 (m, 2H), 7.15–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.29, 31.56, 77.05, 78.20, 126.69, 128.41, 128.73, 128.97, 137.15, 137.34.

Compound **5c**: 56%; viscous oil; IR (neat) 2958, 2850, 1489, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.47 (s, 2H), 4.09 (s, 2H), 4.45–4.49 (m, 2H), 4.77–4.81 (m, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.99, 30.90, 77.20, 78.03, 128.88, 129.52, 129.76, 132.58, 135.78, 136.53.

Compound **5d**: 56%; viscous oil; IR (neat) 2966, 2839, 1670, 1493, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.6 Hz, 3H), 3.39 (d, J = 15.3 Hz, 1H), 3.47 (d, J = 15.3 Hz, 1H), 3.82 (d, J = 9.9 Hz, 1H), 4.09 (d, J = 9.9 Hz, 1H), 4.19–4.37 (m, 2H), 5.02–5.14 (m, 1H), 7.16–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.54, 20.48, 32.07, 76.54, 83.24, 126.62, 128.47, 128.71, 133.57, 135.97, 137.28.

Compound **5e**: 65%; viscous oil; IR (neat) 2920, 2854, 1342, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.31 (s, 2H), 3.79 (s, 2H), 3.89 (s, 2H), 4.30 (s, 2H), 7.00–7.03 (m, 2H), 7.23–7.29 (m, 5H), 7.63 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −4.29, 21.52, 32.77, 56.77, 57.71, 126.77, 127.39, 128.42, 128.74, 129.22, 129.78, 133.83, 134.50, 136.57, 143.50.

Compound **5f**: 70%; viscous oil; IR (neat) 2920, 1597, 1342, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.36 (s, 2H), 3.93 (s, 2H), 3.99 (s, 2H), 4.27 (s, 2H), 6.98–7.02 (m, 2H), 7.21–7.28 (m, 5H), 7.62 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.47, 23.86, 32.54, 56.33, 57.33, 126.76, 127.32, 128.18, 128.30, 128.70, 129.74, 133.74, 136.08, 136.58, 143.48.

Compound **4a**: viscous oil; IR (neat) 3032, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.92 (d, J = 13.8 Hz, 1H), 3.37 (d, J = 13.8 Hz, 1H), 3.90 (d, J = 9.3 Hz, 1H), 4.22 (d, J = 9.3 Hz, 1H), 4.40 (d, J = 2.4 Hz, 1H), 4.42 (d, J = 2.4 Hz, 1H), 5.19 (t, J = 1.8 Hz, 1H), 5.40 (t, J = 2.1 Hz, 1H), 7.18–7.27 (m, 5H), 10.67 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 42.25, 57.90, 71.82, 73.89, 107.58, 127.18, 128.63, 129.93, 137.02, 149.73, 178.51.

Compound **4b**: white solid, mp 72–75 °C; IR (neat) 2993, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.90 (d, J = 13.8 Hz, 1H), 3.31 (d, J = 13.8 Hz, 1H), 3.88 (d, J = 9.6 Hz, 1H), 4.22 (d, J = 9.6 Hz, 1H), 4.40 (d, J = 2.4 Hz, 1H), 4.42 (d, J = 2.4 Hz, 1H), 5.20 (t, J = 2.0 Hz, 1H), 5.37 (t, J = 2.2 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 11.33 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 41.24, 57.56, 71.56, 73.59, 107.55, 128.54, 131.09, 132.94, 135.19, 149.20, 178.10.

Compound **4c**: viscous oil; IR (neat) 2978, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 6.3 Hz, 3H), 2.91 (d, J = 13.8 Hz, 1H), 3.28 (d, J = 13.8 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 4.08 (d, J = 9.6 Hz, 1H), 4.42–4.50 (m, 1H), 5.08 (d, J = 2.4 Hz, 1H), 5.36 (d, J = 2.1 Hz, 1H), 7.20–7.30 (m, 5H), 9.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.95, 42.77, 58.22, 71.02, 77.85, 107.35, 126.94, 128.33, 130.03, 136.88, 154.45, 178.35.

Compound **4d**: white solid, mp 51–53 °C; IR (neat) 3032, 1705, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.92 (d, J = 13.8 Hz, 1H), 3.28 (d, J = 13.8 Hz, 1H), 3.37 (d, J = 9.9 Hz, 1H), 3.44 (d, J = 9.9 Hz, 1H), 3.70 (d, J = 13.8 Hz, 1H), 4.02 (d, J = 13.8 Hz, 1H), 5.18 (s, 1H), 5.41 (s, 1H), 7.14–7.32 (m, 7H), 7.67 (d, J = 7.8 Hz, 2H), 10.15 (br s, 1H); ^{13}C NMR($CDCl_3$) δ 21.74, 42.67, 52.21, 53.03, 57.42, 110.52, 127.42, 128.15, 128.76, 129.90, 129.99, 132.13, 136.24, 144.15, 145.62, 177.67.

Compound **7**: 70%; viscous oil; ^{1}H NMR ($CDCl_3$) δ 1.85 (d, J = 0.9 Hz, 3H), 2.41 (s, 3H), 3.66 (s, 2H), 6.80 (s, 1H), 6.90 (d, J = 0.9 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 2H), 7.18–7.31 (m, 5H), 7.70 (d, J = 8.4 Hz, 2H).

Compound **8**: 80%; viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 2H), 4.18 (s, 2H), 7.14 (s, 1H), 7.19–7.33 (m, 5H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.82, 29.53, 121.97, 123.87, 126.41, 128.53, 128.59, 139.11, 141.46, 142.11.

Compound **9**: 45%; viscous oil; IR (neat) 1107, 1261, 1732, 2951 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30–2.35 (m, 1H), 2.45–2.52 (m, 1H), 3.04 (d, J = 13.4 Hz, 1H), 3.22 (d, J = 13.4 Hz, 1H), 3.48 (d, J = 11.3 Hz, 1H), 3.66 (s, 3H), 3.67–3.84 (m, 2H), 3.97 (d, J = 11.3 Hz, 1H), 5.01 (s, 1H), 5.04 (s, 1H), 7.09–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 34.27, 38.88, 51.77, 54.64, 69.54, 72.08, 110.21, 126.79, 128.21, 130.08, 136.34, 145.69, 172.78.

Compound **10**: 40%; viscous oil; ^1H NMR ($CDCl_3$) δ 2.36–2.44 (m, 2H), 3.61 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 4.29 (s, 2H), 5.03–5.16 (m, 2H), 5.80–5.94 (m, 1H), 7.36–7.56 (m, 5H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.10, 52.15, 64.79, 70.06, 116.33, 128.48, 128.70, 129.34, 129.91, 134.74, 135.32, 144.67, 168.13.

Compound **11**: 59%; viscous oil; IR (neat) 1099, 1261, 1454, 2924 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (t, J = 5.7 Hz, 2H), 3.44 (s, 2H), 3.82 (t, J = 5.7 Hz, 2H), 3.96 (s, 2H), 4.10 (s, 2H), 7.16–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.26, 32.69, 34.63, 64.60, 68.02, 126.49, 126.88, 128.31, 128.66, 135.06, 138.08.