Notes

Synthesis of 2,3,4-Trisubstituted 2,5-Dihydrofuran Derivatives

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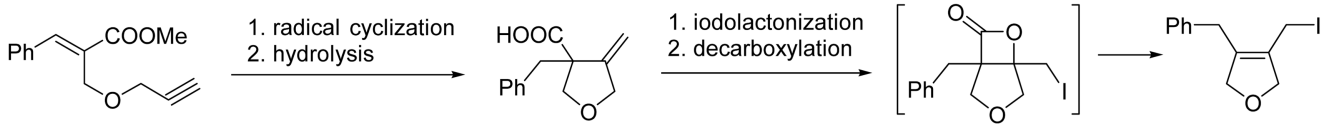
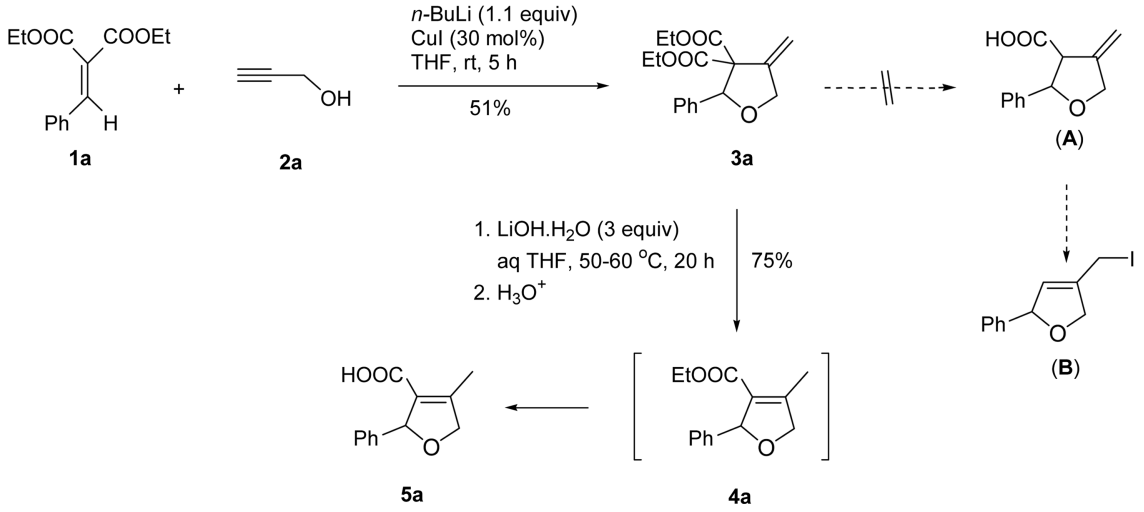
Recently, synthesis of methylenetetrahydrofurans has received much attention due to their versatile usefulness in organic synthesis.[1] The compounds were prepared most frequently either by the Zn(II)/amine-catalyzed coupling reaction of alkylidenemalonates with propargyl alcohol[1a,1j] or Michael addition of propargyl alcohol to alkylidenemalonates followed by a palladium-mediated *exo-dig* cyclization.[1b-e] Methylenetetrahydrofurans can be used for the synthesis of polysubstituted tetrahydrofurans or furans.[2,3] However, chemical transformations of these valuable compounds were not reported much.[2a,2b,3b]

Very recently we reported the synthesis of 2,5-dihydrofuran derivatives by the sequential introduction of propargyl alcohol at the primary position of the Baylis-Hillman adducts, radical cyclization, iodolactonization, and finally decarboxylation strategy (Scheme 1).[4] During the investigations we reasoned that we could prepare 2,4-disubstituted 2,5-dihydrofuran derivative (**B**) by following the similar protocol from the methylenetetrahydrofuran **3a** (Scheme 2).

Starting methylenetetrahydrofuran **3a** was prepared in 51% yield from the reaction of benzylidenemalonate **1a** and propargyl alcohol (**2a**) in the presence of *n*-BuLi (1.1 equiv) and CuI (30 mol%) in THF by following the reported method,[1j] which described the reaction with propargyl amines instead of propargyl alcohol. With the starting material **3a**, we examined the hydrolysis of ester groups. Initially we tried the hydrolysis with LiOH in aq THF at room temperature. From the reaction, we obtained a mixture of starting material **3a** and ethyl 2-phenyl-4-methyl-2,5-dihydrofuran-3-carboxylate (**4a**).[5] After many trials we found that the use of excess LiOH (3 equiv) at elevated temperature (50-60 °C) gave **5a** in good yield (75%) instead

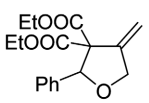
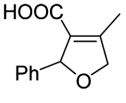
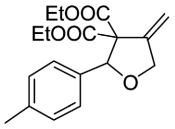
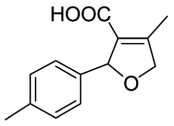
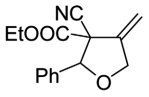
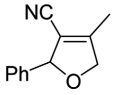
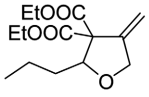
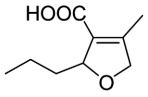
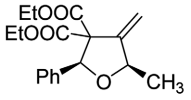
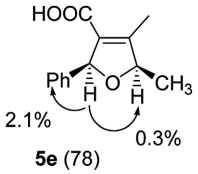
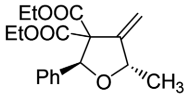
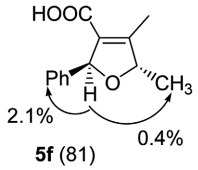


Scheme 1



Scheme 2

Table 1. Synthesis of 2,5-dihydrofuran derivatives[a]

Entry	Substrate (%)[b]	Time (h)	Product (%)
1	 **3a** (51)	20	 **5a** (75)
2	 **3b** (55)	16	 **5b** (75)
3	 **3c** (46)	8	 **5c** (80)
4	 **3d** (48)	10	 **5d** (79)
5	 **3e** (29)	36	 **5e** (78)
6	 **3f** (33)	36	 **5f** (81)

[a]Conditions: Substrate **3a-f** (1 equiv), $LiOH{\cdot}H_2O$ (3 equiv), aq THF, 50-60 °C, given time. [b]Substrates **3a-f** were synthesized from **1** and alkynyl alcohol under *n*-BuLi/CuI conditions (experimental section).

of the desired methylenetetrahydrofuran (**A**) in Scheme 2. Under the same conditions, we prepared analogous derivatives **5b-f** in moderate to good yields. The results are summarized in Table 1.

As shown in Table 1, we prepared **3b-d** (46-55%) and **5b-d** (75-80%) similarly (entries 2-4). For the reaction of diethyl benzylidenemalonate (**1a**) and 3-butyn-2-ol (**2b**) we obtained the two diastereomers **3e** and **3f** in 29 and 33%, respectively. The assignment of the stereochemistry was confirmed unequivocally by comparison with similar compounds in the literature[1b,1c] and NOE results of **5e** and **5f** (shown in Table 1).

Unfortunately, the hydrolysis of **3a** in acidic conditions (HCl, aq THF, heating) gave **5a** also, although the synthesis of 2-aryl-4-methylenetetrahydrofuran-3-carboxylic acid (**A** in Scheme 2) was already reported in the literature by using other route.[6] The reaction mechanism for the formation of **5** from **3** can be thought as sequential hydrolysis, decarboxylation, and isomerization of double bond. In summary, we synthesized 2,3,4-trisubstituted 2,5-dihydrofurans via basic hydrolysis of methylenetetrahydrofurans.

Experimental Section

Synthesis of the starting materials **3a-f** was carried out by the conjugate addition of propargyl alcohol to benzylidenemalonate and the following cyclization protocol according to the reported papers.[1] The compounds **3a**,[1a] **3b**,[1a] and **3c**[1c] were identified by the comparison with the reported data. The spectroscopic data of **3d**, **3e**, and **3f** are as follows.

Compound **3d**: 48%; oil; IR (film) 2962, 1732, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 8.4 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H), 1.41-1.52 (m, 2H), 1.60-1.70 (m, 2H), 4.16-4.43 (m, 6H), 4.57 (dt, J = 12.9 and 2.1 Hz, 1H), 5.19 (t, J = 2.1 Hz, 1H), 5.46 (t, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95 (2C), 14.05, 19.83, 32.97, 61.56, 61.67, 66.15, 70.75, 84.14, 109.06, 145.82, 167.99, 168.28; ESIMS *m/z* 271 (M^++H).

Compound **3e**: 29%; oil; IR (film) 2981, 1728, 1265, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.5 Hz, 3H), 1.57 (d, J = 6.0 Hz, 3H), 3.48-3.51 (m, 1H), 3.54-3.56 (m, 1H), 4.38-4.79 (m, 2H), 4.51-4.53 (m, 1H), 5.19 (s, 1H), 5.50 (s, 1H), 5.67 (s, 1H), 7.40-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.32, 13.96, 19.47, 61.23, 61.75, 69.30, 77.09, 83.60, 109.71, 126.73, 127.83, 128.08, 137.15, 150.49, 167.87, 168.30; ESIMS *m/z* 319 (M^++H).

Compound **3f**: 33%; oil; IR (film) 2981, 1728, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.41 (d, J = 6.6 Hz, 3H), 3.44-3.55 (m, 1H), 3.72-3.93 (m, 1H), 4.21-4.41 (m, 2H), 5.03-5.17 (m, 1H), 5.24 (s, 1H), 5.53 (s, 1H), 5.85 (s, 1H), 7.21-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.30, 13.97, 21.38, 61.30, 61.84, 69.01, 77.53, 82.68, 110.09, 126.85, 127.92, 128.13, 137.66, 150.49, 167.57, 168.03.

Typical procedure for the synthesis of 5a. The stirred reaction mixture of **3a** (304 mg, 1 mmol) and LiOH monohydrate (126 mg, 3 mmol) in aq THF (1 : 1, 4 mL) was heated at 50-60 °C for 20 h. After quenching the reaction mixture with dilute HCl solution, usual workup, and column chromatographic purification process (hexanes/EtOAc, 6 : 4) we obtained **5a**, 154 mg (75%). The spectroscopic data of prepared compounds are as follows.

Compound **5a**: 75%; oil; IR (film) 3032, 1693, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.18 (d, J = 1.2 Hz, 3H), 4.70-4.77 (m, 1H), 4.87-4.94 (m, 1H), 5.89-5.93 (m, 1H), 7.24-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.18, 79.74, 88.60, 126.48, 127.21, 128.18, 128.36, 141.11, 154.14, 168.23; ESIMS *m/z* 205 (M^++H).

Compound **5b**: 75%; oil; IR (film) 2924, 1689, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.18 (d, J = 1.5 Hz, 3H), 2.33 (s, 3H), 4.69-4.76 (m, 1H), 4.85-4.93 (m, 1H), 5.87-5.90 (m, 1H), 7.13 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.19, 21.19, 79.59, 88.44, 126.35, 127.13, 129.09, 137.94, 138.18, 153.92, 167.06;

ESIMS *m/z* 219 (M^++H).

Compound **5c**: 80%; oil; IR (film) 2924, 2854, 2222, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (dd, J = 3.0 and 1.2 Hz, 3H), 4.76-4.95 (m, 2H), 5.81-5.86 (m, 1H), 7.32-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.60, 78.79, 87.86, 110.51, 113.40, 126.27, 128.82, 128.86, 138.91, 155.26; ESIMS *m/z* 186 (M^++H).

Compound **5d**: 79%; oil; IR (film) 2927, 1728, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.2 Hz, 3H), 1.34-1.50 (m, 2H), 1.54-1.68 (m, 1H), 1.76-1.90 (m, 1H), 2.11 (s, 3H), 4.58-4.75 (m, 2H), 5.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.24, 14.08, 18.26, 36.76, 79.10, 86.67, 126.31, 153.94, 168.92.

Compound **5e**: 78%; oil; IR (film) 2927, 1689, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (d, J = 6.6 Hz, 3H), 2.13 (s, 3H), 4.87-4.92 (m, 1H), 5.81-5.84 (m, 1H), 7.27-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.35, 20.43, 85.23, 87.14, 126.20, 127.71, 128.15, 128.29, 141.10, 156.97, 167.90; ESIMS *m/z* 219 (M^++H).

Compound **5f**: 81%; oil; IR (film) 2974, 2927, 1689, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (d, J = 6.6 Hz, 3H), 2.15 (s, 3H), 5.07-5.12 (m, 1H), 5.88-5.92 (m, 1H), 7.23-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.28, 19.85, 85.38, 86.76, 126.12, 127.17, 128.08, 128.37, 141.21, 157.34, 168.43.

References and Notes

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5. We read the peaks of ethyl 2-phenyl-4-methyl-2,5-dihydrofuran-3-carboxylate (**4a**) from the ^1H NMR spectrum of mixturic **3a** + **4a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, J = 7.2 Hz, 3H), 2.18 (s, 3H), 3.98-4.12 (m, 2H), 4.70-4.95 (m, 2H), 5.90-5.94 (m, 1H), 7.25-7.48 (m, 5H).
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