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

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Recently, synthesis of methylene tetrahydrofurans 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 alkylidene malonates with propargyl alcohol\(^{1a,1j}\) or Michael addition of propargyl alcohol to alkylidene malonates followed by a palladium-mediated exo-dig cyclization.\(^{1b-e}\) Methylene tetrahydrofurans can be used for the synthesis of polysubstituted tetrahydrofurans or furans.\(^2\) 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 methylene tetrahydrofuran 3a (Scheme 2).

Starting methylene tetrahydrofuran 3a was prepared in 51% yield from the reaction of benzylidene malonate 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,\(^3\) 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...
of the desired methylenetetrahydrofurans (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-buten-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\(^{8,10,11}\) 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 another 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 benzylidene-malonate and the following cyclization protocol according to the reported papers.\(^{1}\) The compounds 3a, 3b, 3c, and 3e 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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.95 (t, \(J = 6.9\) 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) \(\delta\) 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; ESI-MS m/z 271 (M\(^+\)H).

**Compound 3e:** 29%; oil; IR (film) 2981, 1728, 1265, 1234 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 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) \(\delta\) 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; ESI-MS m/z 319 (M\(^+\)H).

**Compound 3f:** 33%; oil; IR (film) 2981, 1728, 1261 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 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), 4.21-4.24 (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) \(\delta\) 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 (79%). The spectroscopic data of prepared compounds are as follows.

**Compound 5a:** 75%; oil; IR (film) 3022, 1693, 1265 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 2.18 (d, \(J = 12\) 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) \(\delta\) 12.18, 79.74, 88.60, 126.48, 127.21, 128.18, 128.36, 141.11, 154.14, 168.23; ESI-MS m/z 205 (M\(^+\)H).

**Compound 5b:** 75%; oil; IR (film) 2924, 1689, 1269 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 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) \(\delta\) 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: 79%; oil; IR (film) 2974, 2927, 2222, 1041 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3H), 1.34-1.43 (s, 3H), 4.87-5.84 (m, 1H), 7.27-7.34 (m, 5H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 2.13 (s, 3H), 5.07-5.86 (m, 1H), 7.32-7.43 (m, 5H); 300 MHz).

References and Notes

1. For the synthesis of methylene tetrahydrofurans, see (a) Nakamuni, M.; Liang, C.; Nakamuni, E. Org. Lett. 2004, 6, 175. (b) Bottex, M.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. J. Org. Chem. 2001, 66, 175. (c) Marat, X.; Monteiro, N; Balme, G.


5. We read the peaks of ethyl 2-phenyl-4-methyl-2,5-dihydrofuran-3-carboxylate (3a$+4a$) from the $^1$H NMR spectrum of mixture 3a$+4a$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.11 (t, $J$ = 7.2 Hz, 3H), 2.18 (s, 3H), 3.98-4.12 (m, 2H), 4.70-4.95 (m, 5H), 5.00-5.94 (m, 1H), 7.25-7.48 (m, 5H).