NEW SYNTHESIS OF 3-ARYL-2,5-DIHYDROFURANS

Meng-Yang Chang,a Chun-Yu Lin,b and Chun-Li Pai

Abstract – We present a straightforward synthesis of 3-aryl-2,5-dihydrofurans by ring contraction of 4-aryl-3,6-dihydro-2H-pyrans with the repeated treatment of MCPBA and BF₃·OEt₂. The building block 3-aryltetrahydrofuran-3-carboxylic acid with potential biological activities was also prepared.

1. INTRODUCTION

Many natural products and biological active compounds contain five-membered oxygen heterocyclic system. Molecules incorporating either mono-, di-, or poly-substituted furans, dihydrofurans, tetrahydrofurans and other related analogs are well documented in the literature and these often served as key building blocks. A novel and facile preparation of a variety type of substituted furans, dihydrofurans, and tetrahydrofurans remains a current challenge in the organic synthesis. Development of a general and novel procedure for differently substituted five-membered oxygen heterocyclic system provides an expedient entry as shown in Figure 1.

![Figure 1. Some synthetic methods of 3-substituted dihydrofurans](image)

Basically, the synthetic methods of 3-substituted dihydrofurans and its related analogs can be summarized in transition metal-promoted ring-closing cyclization and cycloisomerization or metathesis e.g.
palladium, silver, rhodium, gold, copper, ruthenium, mercury, and zirconium. Here we describe a straightforward strategy to 3-aryl-dihydrofurans by ring contraction of 4-aryl-3,6-dihydro-2H-pyran with m-chloroperoxybenzoic acid (MCPBA) and boron trifluoride etherate (BF$_3$-OEt$_2$).

2. RESULTS AND DISCUSSION

Commercially available tetrahydro-4H-pyran-4-one (1) was chosen as the starting material for the preparation of 3-aryl-2,5-dihydrofurans. Some representative results are shown in Scheme 1 and Scheme 2. 3-Aryltetrahydrofuran-3-carbaldehydes (3a-3e) were prepared by two one-pot transformations. The first one is the easy access to produce 4-aryl-3,6-dihydro-2H-pyran (2a-2e) by the Grignard addition of compound (1) with arylmagnesium bromides (a, Ar=C$_6$H$_5$; b, Ar=3-MeOC$_6$H$_4$; c, Ar=4-MeOC$_6$H$_4$; d, Ar=3,4-CH$_2$O$_2$C$_6$H$_3$; e, Ar=4-C$_6$H$_5$C$_6$H$_4$) in tetrahydrofuran at -78 °C for 2 h and subsequent dehydration of the resulting tertiary alcohols with boron trifluoride etherate for 15 min. The second step is a ring contraction from 4-aryl-3,6-dihydro-2H-pyran (2a-2e) to 3-aryltetrahydrofuran-3-carbaldehydes (3a-3e) by epoxidation with MCPBA at rt for 3 h followed by rearrangement reaction of the resulting epoxides with BF$_3$-OEt$_2$ for 15 min. Thus, 3-aryltetrahydrofuran-3-carbaldehyde (3) could be obtained as a sole product in good yield via these two one-pot reactions, that is, Grignard reaction/dehydration and epoxidation/ring contraction.

Lewis acid-mediated ring contraction of six-membered ring framework was already investigated from the literature reports. There are some different results between 4-aryl-3,4-epoxypiperidine and 1-aryl-1,2-epoxycyclohexane. According to Nagai’s and Lyle’s reports, different N-substituents could affect the distribution of several products in the reaction of 4-aryl-3,4-epoxypiperidine derivatives. For the rearrangement reaction of 1-aryl-1,2-epoxycyclohexane, Schiketanz and Macchia reported totally different results in the reactivity and the structures of products. These interesting differences triggered our attention to examine the rearrangement of 4-aryl-3,4-epoxydihydropyran skeleton. With enough amounts of compounds (3a-3e) in hand, synthesis of 3-aryl-2,5-dihydrofurans (4a-4e) and
3-aryltetrahydrofuran-3-carboxylic acids (5a-5e) was further studied. Conversion of compounds (3a-3e) into 4a-4e was achieved in good yield by the repeated combination of MCPBA and BF$_3$-OEt$_2$ via Baeyer-Villiger oxidation and formic acid elimination. We also tried to prepare 3-methyl-2,5-dihydrofuran by repeated treatment of 4-methyl-3,6-dihydro-2H-pyran with the combination of MCPBA and BF$_3$-OEt$_2$, but complex products were provided. Although the synthetic application is decreased, the present work is complementary to existing methodology. While poring out the related literature of tetrahydrofuran-3-carboxylic acid, we found that it was a useful building block in the synthesis of various potential biological compounds.$^{14}$ Compounds (5a-5e) were afforded in nearly quantitative yield by oxidation of compounds (3a-3e) with sodium chlorite (NaClO$_2$).$^{15}$

![Scheme 2. Synthesis of 3-aryl 2,5-dihydrofurans (4a-4e) and tetrahydrofuran-3-carboxylic acids (5a-5e)](image)

### 3. CONCLUSION

In summary, we have developed an easy and straightforward synthesis of 3-aryl-2,5-dihydrofurans (4a-4e) and 3-aryltetrahydrofuran-3-carboxylic acids (5a-5e) via the reaction of 4-aryl-3,6-dihydro-2H-pyrans (2a-2e) with the repeated treatment of MCPBA and BF$_3$-OEt$_2$.

### 4. EXPERIMENTAL

#### 4.1. General.

Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents were obtained from commercial sources and used without further purification. Reaction was routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous MgSO$_4$ before concentration in vacuo. Crude product was purified using column chromatography on SiO$_2$ (MN Kieselgel 60, 70~230 mesh).

#### 4.2. A representative procedure for 4-aryl-3,6-dihydro-2H-pyrans (2a-2e) is as follows: A solution of arylmagnesium bromide (0.5 M in THF, 0.6 mL, 1.2 mmol) was added to a stirred solution of tetrahydro-4H-pyran-4-one (1) (100 mg, 1.0 mmol) in THF (10 mL) at -78 °C. The reaction mixture was stirred at rt for 2 h. The total procedure was monitored by TLC until the reaction was completed. Without
further purification, BF$_3$-OEt$_2$ (1 mL) was added to a stirred solution of the resulting reaction mixture at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated aqueous NaHCO$_3$ solution (1 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. Water (2 mL) and AcOEt (10 mL) was added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with AcOEt (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product.

Purification by column on SiO$_2$ (hexane/AcOEt = 6/1) afforded 4-aryl-3,6-dihydro-2H-pyrans (2a-2e).

For 2a: ^1H NMR (300 MHz, CDCl$_3$) δ 7.45-7.22 (m, 5H), 6.16 (br s, 1H), 4.18 (br s, 2H), 3.96 (t, J = 7.5 Hz, 2H), 2.52 (br s, 2H); HRMS (ESI) m/z calcd for C$_{11}$H$_{13}$O (M$^+$+1) 161.0966, found 161.0968; Anal. Calcd for C$_{11}$H$_{12}$O: C, 82.46; H, 7.55. Found: C, 82.60; H, 7.38. For 2b: ^1H NMR (300 MHz, CDCl$_3$) δ 7.28 (t, J = 8.1 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.95 (br s, 1H), 6.82 (dd, J = 2.4, 8.1 Hz, 1H), 6.18 (br s, 1H), 4.35 (br s, 2H), 3.91 (t, J = 7.5 Hz, 2H), 3.81 (s, 3H), 2.50 (br s, 2H); HRMS (ESI) m/z calcd for C$_{12}$H$_{15}$O$_2$ (M$^+$+1) 191.1072, found 191.1076; Anal. Calcd for C$_{12}$H$_{14}$O$_2$: C, 75.76; H, 7.42. Found: C, 75.94; H, 7.66. For 2c: ^1H NMR (300 MHz, CDCl$_3$) δ 7.37 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.02 (br s, 1H), 4.30 (br s, 2H), 3.93 (t, J = 7.5 Hz, 2H), 3.79 (s, 3H), 2.46 (br s, 2H); HRMS (ESI) m/z calcd for C$_{12}$H$_{15}$O$_2$ (M$^+$+1) 191.1072, found 191.1078; Anal. Calcd for C$_{12}$H$_{14}$O$_2$: C, 75.76; H, 7.42. Found: C, 75.94; H, 7.66. For 2d: ^1H NMR (300 MHz, CDCl$_3$) δ 6.89 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.72 (dd, J = 1.8, 8.1 Hz, 1H), 5.99 (br s, 1H), 5.95 (s, 2H), 4.31 (br s, 2H), 3.91 (br s, 2H), 2.44 (br s, 2H); HRMS (ESI) m/z calcd for C$_{12}$H$_{13}$O$_3$ (M$^+$+1) 205.0865, found 205.0870; Anal. Calcd for C$_{12}$H$_{12}$O$_2$: C, 70.57; H, 5.92. Found: C, 70.21; H, 5.66. For 2e: ^1H NMR (300 MHz, CDCl$_3$) δ 7.62-7.58 (m, 4H), 7.50-7.39 (m, 4H), 7.36-7.32 (m, 1H), 6.10 (br s, 1H), 4.38 (br s, 2H), 3.97 (t, J = 7.2 Hz, 2H), 2.58 (br s, 2H); HRMS (ESI) m/z calcd for C$_{17}$H$_{17}$O (M$^+$+1) 237.1280, found 237.1283; Anal. Calcd for C$_{17}$H$_{16}$O: C, 86.40; H, 6.82. Found: C, 86.11; H, 6.47.

4.3. A representative procedure for 3-aryltetrahydrofuran-3-carbaldehydes (3a-3e) is as follows: MCPBA (255 mg, 75%, 1.1 mmol) was added to a mixture of 3-aryltetrahydrofuran-3-carbaldehydes (2a-2e) (0.5 mmol) and Na$_2$CO$_3$ (130 mg, 1.2 mmol) in CH$_2$Cl$_2$ (10 mL). The reaction mixture was stirred at rt for 3 h. The total procedure was monitored by TLC until the reaction was completed. Saturated aqueous Na$_2$CO$_3$ solution (5 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, BF$_3$-OEt$_2$ (1 mL) was added to a stirred solution of crude product in CH$_2$Cl$_2$ (10 mL) at rt. The reaction mixture was stirred at rt for 15 min. Saturated aqueous NaHCO$_3$ solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with
AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification by column on SiO₂ (hexane/AcOEt = 6/1~4/1) afforded 3-aryltetrahydrofuran-3-carbaldehydes (3a-3e). For 3a: ¹H NMR (300 MHz, CDCl₃) δ 9.45 (s, 1H), 7.32-7.23 (m, 3H), 7.18-7.10 (m, 2H), 4.59 (d, J = 8.4 Hz, 1H), 3.95-3.86 (m, 2H), 3.81 (d, J = 8.4 Hz, 1H), 2.83-2.75 (m, 1H), 2.21-2.10 (m, 1H); HRMS (ESI) m/z calcd for C₁₁H₁₂O₂ (M⁺+1) 177.0916, found 177.0915; Anal. Calcd for C₁₁H₁₂O₂: C, 74.98; H, 6.86. For 3b: ¹H NMR (300 MHz, CDCl₃) δ 9.56 (s, 1H), 7.30 (t, J = 8.1 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.78 (dd, J = 2.1, 8.1 Hz, 1H), 6.71 (br s, 1H), 4.61 (d, J = 8.4 Hz, 1H), 3.96-3.83 (m, 3H), 3.83 (s, 3H), 2.88-2.80 (m, 1H), 2.28-2.09 (m, 1H); HRMS (ESI) m/z calcd for C₁₂H₁₄O₃ (M⁺+1) 207.1021, found 207.1023; Anal. Calcd for C₁₂H₁₄O₃: C, 69.88; H, 6.84. For 3c: ¹H NMR (300 MHz, CDCl₃) δ 9.48 (s, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.61 (d, J = 8.1 Hz, 1H), 3.96-3.84 (m, 3H), 3.85 (s, 3H), 2.86-2.78 (m, 1H), 2.24-2.06 (m, 1H); HRMS (ESI) m/z calcd for C₁₂H₁₄O₃ (M⁺+1) 207.1021, found 207.1025; Anal. Calcd for C₁₂H₁₄O₃: C, 69.88; H, 6.84. For 3d: ¹H NMR (300 MHz, CDCl₃) δ 9.43 (br s, 1H), 6.78 (d, J = 1.2 Hz, 1H), 6.62-6.45 (m, 2H), 5.98 (s, 2H), 4.59 (d, J = 8.4 Hz, 1H), 3.98-3.83 (m, 2H), 3.80 (d, J = 8.4 Hz, 1H), 2.84-2.74 (m, 1H), 2.23-2.08 (m, 1H); HRMS (ESI) m/z calcd for C₁₂H₁₃O₄ (M⁺+1) 221.0814, found 221.0816; Anal. Calcd for C₁₂H₁₃O₄: C, 65.45; H, 5.49. For 3e: ¹H NMR (300 MHz, CDCl₃) δ 9.58 (s, 1H), 7.61-7.58 (m, 4H), 7.50-7.41 (m, 4H), 7.38-7.34 (m, 1H), 4.63 (d, J = 8.4 Hz, 1H), 4.03-3.96 (m, 2H), 3.92 (d, J = 8.4 Hz, 1H), 2.98-2.83 (m, 1H), 2.38-2.22 (m, 1H); HRMS (ESI) m/z calcd for C₁₇H₁₇O₂ (M⁺+1) 253.1229, found 253.1233; Anal. Calcd for C₁₇H₁₆O₂: C, 80.93; H, 6.39. For 4a: ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.27 (m, 5H), 6.24 (t, J = 2.0 Hz, 1H), 5.02 (dd, J = 2.0, 5.0 Hz) HETEROCYCLES, Vol. 68, No. 9, 2006

4.4. A representative procedure for 3-aryl-2,5-dihydrofurans (4a-4e) is as follows: MCPBA (255 mg, 75%, 1.1 mmol) was added to a mixture of 3-aryltetrahydrofuran-3-carbaldehydes (3a-3e) (0.5 mmol) and Na₂CO₃ (130 mg, 1.2 mmol) in CH₂Cl₂ (10 mL). The reaction mixture was stirred at rt for 3 h. The total procedure was monitored by TLC until the reaction was completed. Saturated aqueous Na₂CO₃ solution (5 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, BF₃-ΟEt₂ (1 mL) was added to a stirred solution of crude product in CH₂Cl₂ (10 mL) at rt. The reaction mixture was stirred at rt for 15 min. Saturated aqueous NaHCO₃ solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification by column on SiO₂ (hexane/AcOEt = 10/1~8/1) afforded 3-aryl-2,5-dihydrofurans (4a-4e). For 4a: ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.27 (m, 5H), 6.24 (t, J = 2.0 Hz, 1H), 5.02 (dd, J = 2.0, 5.0 Hz)
Hz, 2H), 4.86 (dd, J = 2.0, 5.0 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ 138.44, 132.46, 128.60 (2x), 127.99, 125.74 (2x), 120.43, 76.75, 75.35; HRMS (ESI) m/z calcd for C10H11O (M+1) 147.0810, found 147.0813; Anal. Calcd for C10H10O: C, 82.16; H, 6.89. For 4b: 1H NMR (500 MHz, CDCl3) δ 7.27 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.88 (br s, 1H), 6.85 (dd, J = 2.5, 8.0 Hz, 1H), 6.23 (t, J = 2.0 Hz, 1H), 5.00 (dd, J = 2.0, 5.0 Hz, 2H), 4.85 (dd, J = 2.0, 5.0 Hz, 2H), 3.83 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 159.70, 138.37, 133.81, 129.60, 120.90, 118.32, 113.23, 111.58, 76.71, 75.38, 55.24; HRMS (ESI) m/z calcd for C11H13O2 (M++1) 177.0916, found 177.0916; Anal. Calcd for C11H12O2: C, 74.98; H, 6.86. For 4c: 1H NMR (500 MHz, CDCl3) δ 7.28 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.09 (t, J = 1.5 Hz, 1H), 4.98 (dd, J = 2.0, 5.0 Hz, 2H), 4.85 (dd, J = 2.0, 5.0 Hz, 2H), 3.80 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 159.35, 137.84, 129.98 (2x), 125.27, 118.23, 113.99 (2x), 76.79, 75.43, 55.28; HRMS (ESI) m/z calcd for C11H13O2 (M++1) 177.0916, found 177.0917; Anal. Calcd for C11H12O2: C, 74.73; H, 6.62. For 4d: 1H NMR (500 MHz, CDCl3) δ 6.90 (d, J = 1.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.74 (dd, J = 1.5, 8.0 Hz, 1H), 6.07 (t, J = 2.0 Hz, 1H), 5.97 (s, 2H), 4.95 (dd, J = 2.0, 5.0 Hz, 2H), 4.84 (dd, J = 2.0, 5.0 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ 147.94, 147.41, 137.96, 126.77, 119.49, 118.98, 108.27, 106.04, 101.13, 76.71, 75.44; HRMS (ESI) m/z calcd for C11H11O3 (M++1) 191.0708, found 191.0709; Anal. Calcd for C11H10O3: C, 69.46; H, 5.30. Found: C, 69.68; H, 4.98. For 4e: 1H NMR (500 MHz, CDCl3) δ 7.62-7.59 (m, 4H), 7.48-7.41 (m, 4H), 7.38-7.35 (m, 1H), 6.28 (t, J = 2.0 Hz, 1H), 5.06 (dd, J = 2.0, 5.0 Hz, 2H), 4.89 (dd, J = 2.0, 5.0 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ 140.73, 140.46, 138.07, 131.41, 128.82 (2x), 127.46, 127.26 (2x), 126.93 (2x), 120.55, 76.81, 75.36; HRMS (ESI) m/z calcd for C16H15O (M++1) 223.1123, found 223.1124; Anal. Calcd for C16H14O: C, 86.45; H, 6.35. Found: C, 86.68; H, 6.20.

4.5. A representative procedure for 3-aryltetrahydrofuran-3-carboxylic acids (5a-5e) is as follows:

A solution of 3-aryl-2,5-dihydrofurans (4a-4e) (0.3 mmol) and 2-methyl-2-butene (chlorine scavenger) (0.5 mL) in t-BuOH (10 mL) was treated with a solution of NaClO2 (80%, 110 mg, 1.0 mmol) and KH2PO4 (95 mg, 0.7 mmol) in water (5 mL) at rt. The mixture was stirred for an additional 30 min and the solvent was removed under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification by column on SiO2 (hexane/AcOEt = 1/1) afforded 3-aryltetrahydrofuran-3-carboxylic acids (5a-5e). For 5a: 1H NMR (300 MHz, CDCl3) δ 7.37-7.25 (m, 5H), 4.74 (d, J = 8.1 Hz, 1H), 4.02-3.97 (m, 2H), 3.89 (d, J = 8.1 Hz, 1H), 3.03-2.95 (m, 1H), 2.21-2.03 (m, 1H); HRMS (ESI) m/z calcd for C11H13O2 (M++1) 193.0865, found 193.0868; Anal. Calcd for C11H12O3: C, 68.74; H, 6.29. Found: C, 68.92; H, 6.51. For 5b: 1H NMR (300 MHz, CDCl3) δ 6.92-6.90 (m, 4H), 4.70 (d, J = 8.1 Hz, 1H), 4.06-3.97 (m, 2H), 3.88 (d, J = 8.1 Hz, 1H), 3.83 (s, 3H), 3.03-2.94 (m, 1H), 2.31-2.06 (m, 1H); HRMS (ESI) m/z calcd...
for C\textsubscript{12}H\textsubscript{15}O\textsubscript{4} (M\textsuperscript{+1}) 223.0970, found 233.0977; Anal. Calcd for C\textsubscript{12}H\textsubscript{14}O\textsubscript{4}: C, 64.85; H, 6.35. Found: C, 65.02; H, 6.53. For 5c: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 7.27 (d, \( J = 8.7 \) Hz, 2H), 6.87 (d, \( J = 8.4 \) Hz, 1H), 4.02-3.99 (m, 2H), 3.86 (d, \( J = 8.4 \) Hz, 1H), 3.80 (s, 3H), 3.02-2.94 (m, 1H), 2.29-2.19 (m, 1H), 1.92 (br s, 1H); HRMS (ESI) \( m/z \) calcd for C\textsubscript{12}H\textsubscript{15}O\textsubscript{4} (M\textsuperscript{+1}) 223.0970, found 233.0971. For 5d (rotamer): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 6.82-6.63 (m, 3H), 5.88 (br s, 2H), 4.60 (br s, 1H), 3.88-3.74 (m, 3H), 2.89-2.80 (m, 1H), 2.30-2.20 (m, 1H); HRMS (ESI) \( m/z \) calcd for C\textsubscript{12}H\textsubscript{13}O\textsubscript{5} (M\textsuperscript{+1}) 237.0763, found 237.0765. For 5e: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 7.66-7.60 (m, 4H), 7.52-7.30 (m, 5H), 4.79 (d, \( J = 8.1 \) Hz, 1H), 4.08-3.94 (m, 2H), 3.90 (d, \( J = 8.1 \) Hz, 1H), 3.11-2.95 (m, 1H), 2.19-2.11 (m, 1H); HRMS (ESI) \( m/z \) calcd for C\textsubscript{17}H\textsubscript{17}O\textsubscript{3} (M\textsuperscript{+1}) 269.1178, found 269.1180; Anal. Calcd for C\textsubscript{17}H\textsubscript{16}O\textsubscript{3}: C, 76.10; H, 6.01. Found: C, 76.31; H, 6.28.

ACKNOWLEDGEMENTS
The authors would like to thank the National Science Council of the Republic of China for financial support.

REFERENCES AND NOTES


