A General Synthesis for 4-Alkyl-2,3-dihydrofurans

Paul C. Zenk, Robert A. Wiley*

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045, U.S.A.

We report here a general and efficient synthesis for 4-alkyl-2,3-dihydrofurans (**5**), which are of interest because of their toxicity to mammalian metabolic organs[1]. Surprisingly, the only published synthesis for this class of compounds[2] is very lengthy, almost totally non-convergent, and is reported for only the methyl (**5**; R = CH_3) and a few branched chain compounds. We have therefore developed the synthesis shown, which begins with 3-ethoxycarbonyl-2-oxotetrahydrofuran (**1**)[3,4]. In principle, it would be possible to alkylate butyrolactone, but unfortunately this reaction proceeds only

Table. Dihydrofurans and Intermediates

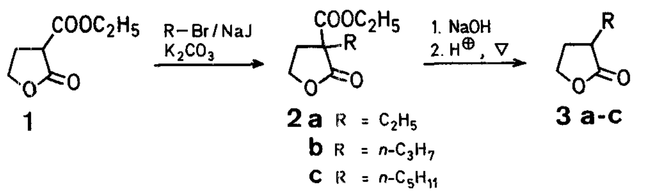
Reaction	Yield [%]	Molecular Formula[a] or Exact Mass (Calc/Found)	^{1}H-N.M.R. ($CDCl_3$)[b] δ [ppm] J [Hz]	Mass Spectrum[c] *m/e* (Intensity)
1a → **2a**	78	$C_9H_{14}O_4$ (186.2)	4.50–4.10 (m, 4H), 3.00–1.60 (m, 4H), 1.26 (t, 3H, J = 8), 0.90 (t, 3H, J = 8)	158 (96), 141 (29), 99 (100), 69 (84)
1b → **2b**	70	$C_{10}H_{16}O_4$ (200.2)	4.33–3.86 (m, 4H), 2.83–1.60 (m, 6H), 1.39 (t, 3H, J = 8), 1.26 (t, 3H, J = 8)	158 (100), 130 (73), 127 (49), 113 (40), 112 (52), 99 (90), 84 (62), 81 (35)
1c → **2c**	83	$C_{12}H_{20}O_4$ (228.3)	4.40–3.93 (m, 4H), 2.86–160 (m, 4H), 1.50–1.18 (m, 9H), 0.98 (t, 3H, J = 8)	169 (17), 158 (100), 130 (66), 112 (41), 99 (49), 55 (34)
2a → **3a**	81	$C_6H_{10}O_2$ (114.1)	4.33–3.96 (m, 2H), 2.63–1.26 (m, 5H), 0.96 (t, 3H, J = 8)	114 (0.2), 86 (100), 55 (76)
2b → **3b**	79	$C_7H_{12}O_2$ (128.2)	4.40–4.06 (m, 2H), 2.76–0.84 (m, 7H), 0.98 (t, 3H, J = 8)	128 (0.2), 99 (11), 86 (100), 55 (28)
2c → **3c**	93	$C_9H_{16}O_2$ (156.2)	4.40–4.06 (m, 2H), 2.76–1.82 (m, 3H), 1.50–1.15 (m, 8H), 0.96 (t, 3H, J = 8)	156 (10), 135 (21), 99 (25), 86 (100), 55 (14)
3a → **4a**	95	$C_6H_{12}O_2$ (116.2)	4.85 and 4.70 (d, J = 3.6 and d, J = 1.8, 1H), 4.00–3.40 (m, 3H), 2.15–1.10 (m, 5H), 0.93 (t, 3H, J = 8)	116 (0.1), 83 (28), 70 (65), 55 (100)
3b → **4b**	74	$C_7H_{14}O_2$ (130.2)	5.30 and 5.15 (d, J = 3.6 and d, J = 1.6, 1H), 4.57 (br s, 1H), 4.10–3.73 (m, 2H), 2.33–1.77 (m, 2H), 1.77–1.18 (m, 5H), 1.10 (t, 3H, J = 8)	112 (10), 84 (33), 69 (38), 57 (22), 56 (100), 55 (74)
3c → **4c**	83	$C_9H_{18}O_2$ (158.2)	5.20 and 5.05 (d, J = 3.6 and d, J = 1.2, 1H), 4.05–3.60 (m, 3H), 2.50–1.05 (m, 12H), 1.02 (t, 3H, J = 8)	157 (6), 141 (100), 83 (20), 81 (14), 69 (32)
4a → **5a**	58	98.0731/98.0724	6.00 (s, 1H), 4.27 (t, 2H, J = 9), 2.52 (t, 2H, J = 10), 2.00 (q, 2H, J = 6), 1.05 (t, 3H, J = 8)	98 (54), 83 (100), 55 (40)
4b → **5b**	14	112.0887/112.0882	6.00 (s, 1H), 4.25 (t, 2H, J = 9), 2.45 (t, 2H, J = 9), 1.96 (t, 2H, J = 8), 1.55–1.10 (m, 2H), 0.90 (t, 3H, J = 8)	112 (25), 83 (100), 55 (51)
4c → **6**	77	$C_{10}H_{20}O_2$ (172.3)	4.70–4.46 (m, 1H), 4.00–3.63 (m, 2H), 3.23 (s, 3H), 2.23–1.66 (m, 3H), 1.66–1.00 (m, 8H), 0.90 (t, 3H, J = 8)	172 (0.7), 141 (52), 83 (100), 69 (44)
6 → **5c**	39	$C_9H_{16}O$ (140.2)	6.00 (s, 1H), 4.21 (t, 2H, J = 9), 3.50 (t, 2H, J = 9), 2.10–1.95 (m, 2H), 1.60–1.10 (m, 6H), 0.90 (t, 3H, J = 8)	140 (10), 95 (8), 83 (100)

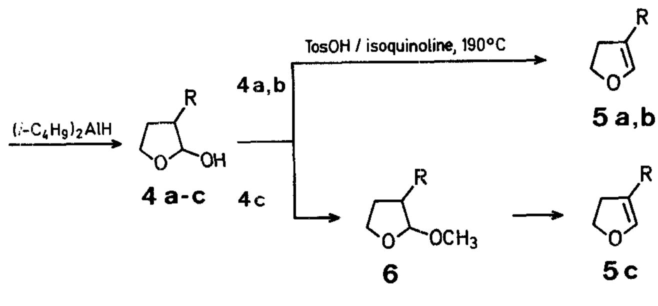
[a] Satisfactory microanalyses were obtained for C and H to within ±0.4%; **5a** and **5b** volatilized during attempted combustion; therefore, these compounds were characterized by exact mass measurements.

[b] I.R. spectra consistent with the assigned structure were obtained for all compounds.

[c] Peaks of intensity less than 25% of the base are ignored, except that molecular ions are shown if observed and at least three peaks per compound are reported.

in the case of very reactive alkylating agents such as short chain iodides and propargyl bromide[5,6]. Alkylation of **1** to give **2a–c** occurs readily under mild conditions using alkyl bromides and potassium iodide.





The next two steps proceed in high yields as expected; the final dehydration goes far better using conditions employed by Wenkert et al. with related compounds[7] rather than the original procedures[2]. This requires that products be distilled from the reaction mixture, and is difficult with longer chain compounds. To circumvent this problem, one can use acetals such as **6** as intermediates. Using these procedures, one can prepare many 4-alkyl-2,3-dihydrofurans from readily available alkyl bromides and butyrolactone.

Ethyl 3-Alkyl-2-oxotetrahydrofuran-3-carboxylates 2a–c:

A solution of **1** (13.9 g, 88 mmol) in acetone (200 ml) is treated with sodium iodide (26.4 g, 176 mmol). After the sodium iodide dissolves, the desired alkyl bromide (176 mmol) and anhydrous potassium carbonate (30.3 g, 220 mmol) are added and the mixture is heated under reflux for 12 h. The mixture is allowed to cool and then diluted with hexane (150 ml), filtered, concentrated in vacuo, and the dilution procedure repeated to give the crude product **2** which is purified by M.P.L.C. (SiO_2, 20% ethyl acetate/hexane).

3-Alkyl-2-oxotetrahydrofurans 3a–c:

A solution of **2** (40 mmol) in ethanol (50 ml) is treated with 10% aqueous sodium hydroxide (25 ml) and stirred at room temperature for 5 h. Most of the water and ethanol are removed in vacuo and the solution is acidified with 10% aqueous sulfuric acid (10 ml). This solution is heated under reflux for 12 h; after cooling the product is extracted with dichloromethane (3 × 15 ml). The organic layer is washed with saturated aqueous sodium hydrogen carbonate (25 ml), saturated aqueous sodium hydroxide (10 ml), dried with sodium sulfate, and the solvent removed in vacuo. Final purification is carried out using M.P.L.C. (SiO_2, 20% ethyl acetate/hexane).

3-Alkyl-2-hydroxytetrahydrofurans 4a–c:

To a dry three-neck flask is added **3** (40 mmol) in tetrahydrofuran (20 ml). The solution is cooled to −20 °C and diisobutylaluminum hydride in hexane (44 mmol) is added with vigorous stirring. After 1 h, the reaction is quenched by adding methanol (30 ml) and allowing the mixture to warm to 5 °C. The mixture solidifies and is washed with methanol (100 ml). The methanol is removed in vacuo and the product purified by M.P.L.C. (SiO_2; 20% ethyl acetate/hexane).

4-Alkyl-2,3-dihydrofurans (5a, 5b):

The lactol **4** (76 mmol) is rapidly added to a stirred solution, at 175 °C, of *p*-toluenesulfonic acid (20 mg) in isoquinoline (3 ml) in an apparatus set up for simultaneous distillation of low boiling products. The flask in which the distillate collects is cooled to −78 °C during the distillation. The desired product co-distilled with water. The top layer is carefully removed from the frozen bottom layer and filtered through a small plug of anhydrous sodium sulfate to afford the dihydrofurans **5**.

2-Methoxy-3-pentyltetrahydrofuran (6):

A solution of **4c** (3.07 g, 19.4 mmol), in methanol (15 ml) is treated with boron trifluoride etherate (0.5 ml) and the mixture allowed to stir for 24 h. The solvent is removed in vacuo and the resulting product chromatographed (SiO_2, 10% ether/hexane) to afford pure **6**; yield: 2.42 g (77%).

4-Pentyl-2,3-dihydrofuran (5c):

Compound **6** (2.42 g, 14.1 mmol) is rapidly added to a heated solution (200 °C) of isoquinoline (3 ml) and *p*-toluenesulfonic acid (20 mg) in an apparatus set up for simultaneous distillation of low boiling products. After 3 h, the pot residue and distillate are combined and chromatographed (SiO_2, hexane) to afford pure **5c**; yield: 769 mg (39%).

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* Address for correspondence.

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