Alkylation of Methyl Dihydrofurancarboxylates

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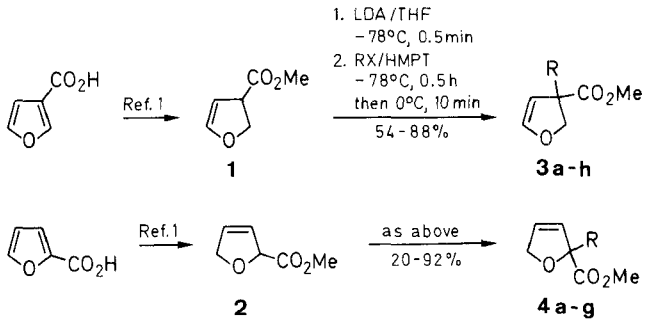
Methyl 3-alkyl-2,3-dihydro-3-furancarboxylates were prepared by the alkylation of methyl 2,3-dihydro-3-furancarboxylate using lithium diisopropylamide as the base, and alkyl halides, acetone or benzaldehyde as the alkylating agent. Likewise alkylation of methyl 2,5-dihydro-2-furancarboxylate gave the corresponding 2-alkylated products.

In a previous paper,[1] we reported the preparation of methyl 2,3-dihydro-3-furancarboxylate **(1)** and methyl 2,5-dihydro-2-furancarboxylate **(2)** via the Birch reduction of 3- and 2-furancarboxylic acids, respectively. The Birch reduction of furancarboxylic acids provides a useful entry towards the total synthesis of natural products, for example, furanomycin,[2] apiose,[3] and dihydrostreptose.[4] Birch and Slobbe have reported that the reduction of 2-furancarboxylic acid with lithium in liquid ammonia by the addition of an alkyl halide, rather than being quenched by a proton source, yields the products of reductive alkylation.[5] However, the reduction of 3-furancarboxylic acid proceeded with β-elimination and ring opening to give a hydroxy lactone[6] in place of the alkylation product.

The introduction of an alkyl group into 3-position of 2,3-dihydro-3-furancarboxylic acid is very useful as they



3, 4	RX	R
a	MeI	Me
b	EtI	Et
c	BuI	Bu
d	allyl	allyl
e	*i*-PI	*i*-Pr
f	$PhCH_2I$	$PhCH_2$
g	CH_3COCH_3	$(CH_3)_2C(OH)$
h	PhCHO	PhCH(OH)

Table 1. Compounds **3a–h** Prepared

Product	Yield[a] (%)	bp (°C)/ Torr	Molecular[b] Formula	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ[e]
3a	86	65–67/20	$C_7H_{10}O_3$ (142.2)	1.40 (s, 3H, CH_3), 3.72 (s, 3H, CO_2CH_3), 4.01 (d, 1H, J = 9.3, H-2), 4.75 (d, 1H, J = 9.3, H-2), 5.03 (d, 1H, J = 2.7, H-4), 6.34 (d, 1H, J = 2.7, H-5)	24.7 (CH_3), 52.4 ($CO_2\underline{C}H_3$), 53.0 (C-3), 78.3 (C-2), 105.7 (C-4), 146.7 (C-5), 175.6 ($\underline{C}O_2CH_3$)
3b	54	85–87/30	$C_8H_{12}O_3$ (156.2)	0.85 (t, 3H, J = 7.6, $CH_2\underline{C}H_3$), 1.75 (m, 2H, $C\underline{H}_2CH_3$), 3.72 (s, 3H, CO_2CH_3), 4.09 (d, 1H, J = 9.3, H-2), 4.71 (d, 1H, J = 9.3, H-2), 5.01 (d, 1H, J = 2.7, H-4), 6.34 (d, 1H, J = 2.7, H-5)	9.0 ($CH_2\underline{C}H_3$), 31.0 ($\underline{C}H_2CH_3$), 52.1 ($CO_2\underline{C}H_3$), 58.0 (C-3), 75.9 (C-2), 103.6 (C-4), 146.7 (C-5), 175.0 ($\underline{C}O_2CH_3$)
3c	72	103[c]/11	$C_{10}H_{16}O_3$ (184.2)	0.89 (t, 3H, CH_3), 1.52 (m, 6H, CH_2), 3.71 (s, 3H, CO_2CH_3), 4.08 (d, 1H, J = 9.3, H-2), 4.71 (d, 1H, J = 9.3, H-2), 5.01 (d, 1H, J = 2.7, H-4), 6.32 (d, 1H, J = 2.7, H-5)	13.8 (CH_3), 22.8 (t, CH_2), 26.9 (t, CH_2), 37.9 (t, CH_2), 52.0 ($CO_2\underline{C}H_3$), 57.4 (C-3), 76.2 (C-2), 104.0 (C-4), 146.5 (C-5), 175.0 ($\underline{C}O_2CH_3$)
3d	85	97–98/25	$C_9H_{12}O_3$ (168.2)	2.48 (dq, 2H, J = 7.0, 14.0, CH_2=CHC$\underline{H}_2$), 3.72 (s, 3H, CO_2CH_3), 4.15 (d, 1H, J = 9.5, H-2), 4.69 (d, 1H, J = 9.5, H-2), 5.01 (d, 1H, J = 2.7, H-4), 5.14 (d, 2H, $C\underline{H}_2$=CH), 5.48–5.85 (m, 1H, J = 9.0, 16.0, CH_2=C$\underline{H}$), 6.35 (d, 1H, J = 2.7, H-5)	42.3 (CH_2=CH–$\underline{C}H_2$), 52.3 ($CO_2\underline{C}H_3$), 57.2 (C-3), 75.5 (C-2), 103.6 (C-4), 118.7 ($\underline{C}H_2$=CH), 132.8 (CH_2=$\underline{C}$H), 147.1 (C-5), 174.4 (CO_2CH_3)
3e	trace	–	–	–	
3f	68	148[c]/10	$C_{13}H_{14}O_3$ (218.3)	3.05 (q, 2H, $C\underline{H}_2$Ph), 3.67 (s, 3H, CO_2CH_3), 4.25 (d, 1H, J = 9.6, H-2), 4.62 (d, 1H, J = 9.6, H-2), 5.03 (d, 1H, J = 2.7, H-4), 6.33 (d, 1H, J = 2.7, H-5), 7.20 (m, 5H, Ph)	44.0 (CH_2), 52.0 ($CO_2\underline{C}H_3$), 58.7 (C-3), 75.6 (C-2), 104.0 (C-4), 126.8, 128.2, 129.5, 136.5, 147.0 (C-5), 174.2 ($\underline{C}O_2CH_3$)
3g	78	130[c]/12	$C_9H_{14}O_4$ (186.2)	1.19 (s, 6H, $C(CH_3)_2$), 3.07 (s, 1H, OH), 3.76 (s, 3H, CO_2CH_3), 4.54 (s, 2H, H-2), 5.05 (d, 1H, J = 2.7, H-4), 6.43 (d, 1H, J = 2.7, H-5)	25.5 (CH_3), 25.6 (CH_3), 52.3 ($CO_2\underline{C}H_3$), 66.0 (C-3), 73.1 (s, C–OH), 73.8 (C-2), 100.6 (C-4), 148.1 (C-5), 175.2 ($\underline{C}O_2CH_3$)
3h	88	solid[d]	$C_{13}H_{14}O_4$ (234.2[c])	2.80 (s, 1H, OH), 3.69 (s, 3H, CO_2CH_3), 4.58 (s, 2H, H-2), 5.00 (d, 1H, J = 2.7, H-4), 5.03 (m, 1H, C$\underline{H}$OH), 6.47 (d, 1H, J = 2.7, H-5); 2.68 (s, 1H, OH), 3.72 (s, 3H, CO_2CH_3), 4.58 (d, 1H, J = 10.0, H-2), 4.65 (d, 1H, J = 10.0, H-2), 5.03 (d, 1H, J = 2.4, H-4), 5.07 (m, 1H, C$\underline{H}$OH), 6.29 (d, 1H, J = 2.4, H-5)	52.3 ($CO_2\underline{C}H_3$), 64.3 (C-3), 72.6 (C-2), 76.2 (d, $\underline{C}$HOH), 100.8 (C-4), 126.6, 128.0, 128.2, 139.2, 149.1 (C-5), 173.4 ($\underline{C}O_2CH_3$); 52.5 ($CO_2\underline{C}H_3$), 64.0 (C-3), 72.9 (C-2), 75.8 (d, $\underline{C}$HOH), 100.2 (C-4), 126.8, 127.9, 128.2, 139.5, 148.8 (C-5), 173.9 ($\underline{C}O_2CH_3$)

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C, ±0.18; H, ±0.12.
[c] Bath temperature.
[d] Unseparable mixture of *erythro*/*threo* 1 : 2.
[e] Recorded at 100 MHz on a JEOL FX-100 Spectrometer.

are intermediates in the synthesis of 3,3-dialkyl-4-butanolides. As 2,3-dihydro-3-furancarboxylic acid is unstable, we first esterified with diazomethane, and then attempted alkylation of the 3-position of methyl 2,3-dihydro-3-furancarboxylate (**1**) using lithium diisopropylamide (LDA) as a base (Table 1).

Several of the alkylated compounds were later successfully converted into natural products; i.e., (±)-pantolactone and its homologue. These were synthesized from **3a** and **3b** via the following sequence of reactions: methoxy hydroxylation with 3-chloroperoxybenzoic acid (MCPBA) in methanol, lithium aluminum hydride reduction of the methoxycarbonyl group, tosylate formation of the hydroxymethyl group, lithium aluminum hydride reduction of tosylate and MCPBA/diethyl ether – boron trifluoride oxidation of the cyclic methyl acetal into the γ-lactone, respectively.[7]

In addition to the alkylation of **1**, the related isomer **2** was also alkylated under the same reaction conditions to give methyl 2-alkyl-2,5-dihydro-2-furancarboxylates **4** (Table 2).

All reagents were commercially available (reagent grade) and used without further purification. $PhCH_2I$ was prepared according to the literature.[8] All reactions were carried out in a N_2 atmosphere. THF was dried by distillation from sodium benzophenone ketyl prior to use.

Methyl 3-Alkyl-2,3-dihydro-3-furancarboxylates 3 and Methyl 2-Alkyl-2,5-dihydro-2-furancarboxylates 4; General Procedure:
A magnetically stirred and cooled (−78 °C) solution of LDA, which is prepared from diisopropylamine (4.75 g, 47 mmol) in dry THF (40 mL) and BuLi (1.6 M in hexane, 29 mL, 46 mmol) is used to enolize **1** or **2** (5.3 g, 41.4 mmol) in dry THF (5 mL). After stirring at −78 °C for 0.5 h, the alkyl halide (55.2 mmol) dissolved in hexamethylphosphoric triamide (HMPT) (2.9 mL, 16.6 mmol) is added via syringe. The mixture is stirred at −78 °C for 0.5 h, and

Table 2. Compounds **4a–g** Prepared

Product	Yield (%) found[a] reported[b]	bp (°C)/ Torr	Molecular[c] Formula	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ
4a	84 (75)	82–83/30	$C_7H_{10}O_3$ (142.2)	1.54 (s, 3H, CH_3), 3.73 (s, 3H, CO_2CH_3), 4.76 (m, 2H, H-5), 5.84 (dt, 1H, J = 2.3, 6.0, H-4), 6.01 (dt, 1H, J = 1.5, 6.0, H-3)	24.2 (CH_3), 52.1 ($CO_2\underline{C}H_3$), 75.7 (C-5), 90.1 (C-2), 128.2 (C-4), 130.0 (C-3), 173.6 ($\underline{C}O_2CH_3$)
4b	83 (75)	93–94/25	$C_8H_{12}O_3$ (156.2)	0.90 (t, 3H, J = 7.5, CH_3), 1.75–2.02 (m, 2H, $C\underline{H}_2CH_3$), 3.74 (s, 3H, CO_2CH_3), 4.75 (dt, 2H, J = 1.7, 2.2, H-5), 5.79 (dt, 1H, J = 2.2, 6.0, H-4), 6.00 (dt, 1H, J = 1.7, 6.0, H-3)	7.8 (CH_3), 30.4 ($\underline{C}H_2CH_3$), 52.1 ($CO_2\underline{C}H_3$), 76.2 (C-5), 93.8 (C-2), 128.6 (C-3), 128.4 (C-4), 173.6 ($\underline{C}O_2CH_3$)
4c	37 (–)	118–120/30	$C_{10}H_{16}O_3$ (184.2)	0.89 (t, 3H, CH_3), 1.30–1.40 (m, 4H), 1.70–2.02 (m, 2H), 3.73 (s, 3H, CO_2CH_3), 4.72–4.76 (m, 2H, H-5), 5.80 (dt, 1H, J = 2.3, 6.0, H-4), 6.01 (dt, 1H, J = 1.5, 6.0, H-3)	13.9 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 37.1 (CH_2), 52.0 ($CO_2=\underline{C}H_3$), 76.0 (C-5), 93.4 (C-2), 128.5 (C-4), 129.0 (C-3), 173.6 ($\underline{C}O_2CH_3$)
4d	72 (68)	110–115/35	$C_9H_{12}O_3$ (168.2)	2.62 (dq, 2H, J = 7.0, 14.0, $CH_2=CHC\underline{H}_2$), 3.71 (s, 3H, CO_2CH_3), 4.73 (br s, 2H, H-5), 5.07 (d, 2H, J = 16.0, $C\underline{H}_2=CH$), 5.50–5.92 (m, 2H, H-4, $CH_2=C\underline{H}$), 5.98 (dt, 1H, J = 2.7, 9.0, H-3)	41.9 ($CH_2=CH\underline{C}H_2$), 52.1 ($CO_2=\underline{C}H_3$), 76.2 (C-5), 92.9 (C-2), 118.6 ($\underline{C}H_2=CH$), 128.4 (C-4), 128.9 (C-3), 132.0 ($CH_2=\underline{C}H$), 172.8 ($\underline{C}O_2CH_3$)
4e	20 (95)	102–104/25	$C_9H_{14}O_3$ (170.2)	0.89 [t, 6H, J = 6.5, $(C\underline{H}_3)_2CH$], 2.30 [quint, 1H, $(CH_3)_2C\underline{H}$], 3.74 (s, 3H, CO_2CH_3), 4.70 (br s, 2H, H-5), 5.70–5.81 (m, 1H, H-4), 5.98 (dd, 1H, J = 1.3, 6.0, H-3)	16.2 (CH_3), 17.2 (CH_3), 34.3 (CH), 52.0 ($CO_2\underline{C}H_3$), 76.5 (C-5), 96.7 (C-2), 128.1 (C-3), 128.7 (C-4), 173.6 ($\underline{C}O_2CH_3$)
4f	67 (75)	140[d]/3	$C_{13}H_{14}O_3$ (218.3)	3.15 (q, 2H, $PhC\underline{H}_2$), 3.69 (s, 3H), 4.42 (d, 1H, J = 13.2, H-5), 4.69 (d, 1H, J = 13.2, H-5), 5.84 (s, 2H, H-3, H-4), 7.21 (s, 5H, Ph)	43.4 ($Ph\underline{C}H_2$), 52.2 ($CO_2\underline{C}H_3$), 76.2 (C-5), 93.7 (C-2), 126.6 (Ph), 127.8 (Ph), 128.2 (C-3), 129.1 (C-4), 130.3 (Ph), 172.9 ($\underline{C}O_2CH_3$)
4g	92 (–)	98–100[d]/3	$C_9H_{14}O_4$ (186.2)	1.19 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 3.28 (s, 1H, OH), 3.77 (s, 3H, CO_2CH_3), 4.78 (q, 2H, J = 14.0, H-5), 5.95 (dt, 1H, J = 2.0, 7.0, H-4), 6.10 (dt, 1H, J = 1.5, 7.0, H-3)	23.8 (CH_3), 25.1 (CH_3), 52.1 ($CO_2\underline{C}H_3$), 74.3 [$(CH_3)_2\underline{C}(OH)$], 76.8 (C-5), 97.8 (C-2), 126.7 (C-3), 129.7 (C-4), 173.2 ($\underline{C}O_2CH_3$)

[a] Yield of isolated pure product.
[b] Isolated as cyclohexylamine salt.[5]
[c] Satisfactory microanalyses obtained: C ±0.45, H ±0.17.
[d] Bath temperature.

then at 0 °C for 10 min, and finally quenched by addition of sat. aq NH_4Cl (80 mL). The product ix extracted with Et_2O (3 × 60 mL), then washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a brown oil which is purified by distillation to afford the product **3** or **4** (Tables 1, 2).

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