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Regioselective, Uncatalyzed Additions of Alcohols and Carboxylic Acids to 2-Furyloxirane. Synthetic Applications.

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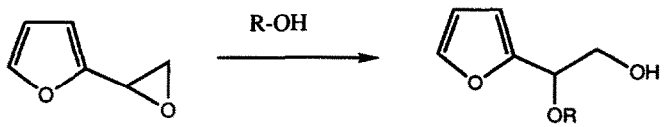
Abstract: *Nucleophilic non-catalyzed additions of alcohols and carboxylic acids to 2-furyloxirane are reported. The intramolecular Diels-Alder reactions of one addition product are also described.*

The reactions of epoxides with alcohols and carboxylic acids constitutes a well known method for the preparation of diolmonoethers and monoesters.[1] The reaction is always a catalytic process and both acidic and basic conditions have been employed. However, to the best of our knowledge, the uncatalyzed, solvolytic additions of these reagents to oxiranes are not precedented in the literature. In our hands, furyloxirane **1**[2] represents an interesting case of unexpected behaviour[3] reacting easily with alcohols and carboxylic acids without catalysis in a regioselective fashion and in high yields (Figure 1). The regioselectivity of the reaction with alcohols was determined using 300 MHz ^{1}H-nmr spectra in DMSO. In these conditions the hydroxylic proton appears, in all cases, as a triplet coupled with the methylene protons.

Figure 1. Addition of alcohols and carboxylic acids to furyloxirane 1



1 **2**

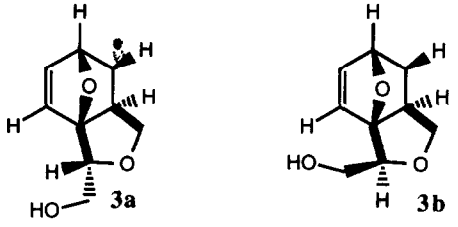
Table 1. Addition of Alcohols and Carboxylic Acids to Furyloxirane 1

R	Reaction time (h)	Compound	Yield(%)[a]
CH_3	18[b]	**2a**	100
CH_3CH_2	18[b]	**2b**	25[c]
CH_2=CH-CH_2	18[b]	**2c**	86
CH≡C-CH_2	1[b]	**2d**	95
CH_3CO	0.4[d,e]	**2e**	95
C_6H_5CO	0.2[d,f]	**2f**	86

a) In pure, isolated yield. b) Under solvolytic conditions at room temperature. c) Quantitative yield in reaction crude. Loss of product was observed during purification. d) In THF as solvent. Stoichiometric amount of **1** and carboxylic acid were employed. e) At 0°C. f) At room temperature (20-22°C).

The synthetic utility of this easy ring opening has been explored.[4] Thus, compound **2c**, on heating in anhydrous benzene at 84°C under argon, affords, after 84 h, a mixture (64% yield) of the adducts **3a** and **3b** arising from the intramolecular Diels-Alder reaction,[5] in ratio **3a**:**3b** = 2.3:1 (300 MHz, ^{1}H-nmr) (Figure 2).

Figure 2. Intramolecular Diels-Alder adducts 3a and 3b



The *exo*[6] nature of the cycloaddition is evident from the coupling constant J_{HaHb} = 4.5 Hz[7] whereas the assignment of the major isomer as **3a** may be rationalized from the deshielding of Hc by effect of the *endo* hydroxymethyl functionality. For the isomer **3a**, δ_{Hc} = 6.54 ppm; for the isomer **3b**, δ_{Hc} = 6.45 ppm.[8] Interesting compound **3a** shows in vitro selective antitumoral activity against P-388 (Limphoyd neoplasm from DBA-2 mouse) cells (IC_{50}= 2.5 μg/ml). Compound **3b** was inactive.

In summary, the described solvolytic uncatalyzed ring opening procedures constitute a versatile method for the synthesis of functionalized furyl derivatives[9] without precedents in the not well known chemistry of hetaryloxides.

EXPERIMENTAL SECTION

Ir spectra were recorded on a Perkin-Elmer 257 spectrophometer, ν values in cm^{-1}. ^1H-nmr and ^{13}C-nmr were obtained on a Varian T-300 spectrometer and the chemical shifts δ are reported in ppm (from internal TMS). Silica gel Merk 60 (230-400 mesh) and DC-Alufolien $60F_{254}$ were used for conventional and analytical (t.l.c.) chromatography respectively. Chemical ionization mass spectra (MS) were measured on a Hewlett-Packard GC-MS HP5995 using methane as reactant gas. MMX calculations were obtained on a PC-Model 4-3, Serena Software.

Furyloxirane was distilled prior to use (b.p. 45°C at 0.1 mmHg). Ethanol and methanol were purified after distillation according with conventional procedures.[10] Allylic and propargylic alcohol were distilled prior to use.

***General Procedure for the Preparation of 2-(2-Furyl)-2-alkoxymethanol,* 2a-2d.**

A solution of **1** (110 mg, 1 mmol) in the appropriate alcohol (2.5 ml) was stirred for 18 h at room temperature (1 h in the case of propargylic alcohol). After the reaction was complete, the solvent was distilled to afford an oil which was purified by column chromatography (silica gel, hexane/ ethyl acetate 2:1). The compounds obtained by this method are listed below.

2-(2-Furyl)-2-methoxyethanol, **2a**. Isolated yield 142 mg (100%). Ir (film): 3420. ^1H-nmr ($CDCl_3$): 7.33 (m, 1H, H5'), 6.30-6.27 (m, 2H, H4' and H3'), 4.26 (dd, 1H, J_1 = 4.0 Hz, J_2 = 8.0 Hz, H2), 3.82 (dd, 1H, J_1 = 8.0 Hz, J_2 = 11.6 Hz, H1), 3.66 (dd, 1H, J_1 = 4.0 Hz, J_2 = 11.6 Hz, H1), 3.24 (s, 3H, CH_3). ^1H-nmr (DMSO): 7.59 (dd, 1H, J_1 = 0.9 Hz, J_2 = 1.5 Hz, H5'), 6.40 (dd, 1H, J_1 = 1.5 Hz, J_2 = 3.0 Hz, H4'), 6.37 (d, 1H, J = 3.0 Hz, H3'), 4.82 (t, 1H, J = 5.4 Hz, OH), 4.19 (dd, 1H, J_1 = 5.1 Hz, J_2 = 6.6 Hz, H2), 3.70-3.52 (m, 2H, H1), 3.15 (s, 3H, CH_3). ^{13}C-nmr ($CDCl_3$): 151.40 (C2'), 142.59 (C5'), 110.03 (C4'), 108.71 (C3'), 77.27 (C2), 63.92 (C1), 56.65 (CH_3). MS m/z (relative intensity): 142 (M^+, 23%), 112 (21%), 111 (100%), 95 (30%), 55 (55%), 53 (27%).

2-(2-Furyl)-2-ethoxyethanol, **2b**. Isolated yield 140 mg (25%). Ir (film): 3400. ^1H-nmr ($CDCl_3$): 7.38 (s, 1H, H5'), 6.33 (d, 2H, J = 4.8 Hz, H3' and H4'), 4.43 (dd, 1H, J_1 = 4.2 Hz, J_2 = 8.1 Hz, H2), 3.87 (t, 1H, J = 8.1 Hz, H1), 3.74-3.71 (m, 1H, H1), 3.58-3.39 (m, 2H, CH_2), 2.92 (s, 1H, OH), 1.18 (t, 3H, J = 7.2 Hz, CH_3). ^1H-nmr (DMSO): 7.58-7.57 (m, 1H, H5'), 6.41-6.39 (m, 1H, H4'), 6.36-6.35 (m, 1H, H3'), 4.85 (t, 1H, J = 5.6 Hz, OH), 4.30 (t, 1H, J = 6.0 Hz, H2), 3.65 (dd, 1H, J_1 = 6.8 Hz, J_2 = 11.7 Hz, H1), 3.56 (dd, 1H, J_1 = 6.0 Hz, J_2 = 11.7 Hz, H1), 3.38 (q, 2H, J = 7.0 Hz, CH_2), 1.06 (t, 3H, J = 7.0 Hz, CH_3). ^{13}C-nmr (DMSO): 152.86 (C2'), 142.20 (C5'), 109.94 (C4'), 107.99 (C3'), 75.28 (C2), 63.44 (C1), 62.35 (CH_2), 14.86 (CH_3). MS m/z (relative intensity): 156 (M^+, 35%), 125 (100%), 97 (100%), 69 (37%), 41 (36%).

2-(2-Furyl)-2-(2-propenyloxy)ethanol, **2c**. Isolated yield 145 mg (86%). Ir (film): 3400. ^1H-nmr ($CDCl_3$): 7.37 (s, 1H, H5'), 6.31 (s, 2H, H3' and H4'), 5.92-5.78 (m, 1H, =CH), 5.23 (d, 1H, J = 17.1 Hz, $=CH_{2t}$), 5.14 (d, 1H, J = 10.2 Hz, $=CH_{2c}$), 4.48 (dd, 1H, J_1 = 4.2 Hz, J_2 = 7.5 Hz, H2), 4.04-3.72 (m, 4H, H1 and CH_2), 3.27 (s, 1H, OH). ^1H-nmr (DMSO): 7.61 (s, 1H, H5'), 6.43-6.38 (m, 2H, H3' and H4'), 5.92-5.75 (m, 1H, =CH), 5.24 (d, 1H, J = 24.0 Hz, $=CH_{2t}$), 5.12 (d, 1H, J = 15.6 Hz, $=CH_{2c}$), 4.90 (t, 1H, J = 9.1 Hz, OH), 4.39 (t, 1H, J = 6.4 Hz, H2), 3.93 (d, 2H, J = 6.4 Hz, H1), 3.80-3.57 (m, 2H, CH_2). ^{13}C-nmr (DMSO): 152.84 (C2'), 142.61 (C5'), 135.14 (=CH), 116.34 ($=CH_2$), 110.22 (C4'), 108.55 (C3'),

75.21 (C2), 69.08 (CH_2), 62.78 (C1). MS m/z (relative intensity): 168 (M^+, 11%), 137 (100%), 95 (87%), 81 (59%), 41 (100%).

2-(2-Furyl)-2-(2-propynyloxy)ethanol, **2d**. Isolated yield 158 mg (95%). Ir (film): 3440. ^{1}H-nmr ($CDCl_3$): 7.32 (d, 1H, J = 1.7 Hz, H5'), 6.31-6.28 (m, 1H, H4'), 6.27-6.26 (m, 1H, H3'), 4.61 (dd, 1H, J_1 = 4.2 Hz, J_2 = 7.9 Hz, H2), 4.12 (dd, 1H, J_1 = 2.4 Hz, J_2 = 15.8 Hz, CH_2), 3.93 (dd, 1H, J_1 = 2.4 Hz, J_2 = 15.8 Hz, CH_2), 3.89-3.67 (m, 2H, H1), 2.54 (s, 1H, OH), 2.38 (t, 1H, J = 2.4 Hz, ≡CH). ^{1}H-nmr (DMSO): 7.63 (dd, 1H, J = 1.8 Hz, J = 3.3 Hz, H5'), 6.42 (d, 2H, J = 1.8 Hz, H3' and H4'), 4.95 (t, 1H, J = 9.1 Hz, OH), 4.53 (t, 1H, J = 9.1 Hz, H2), 4.14 (ddd, 1H, J_1 = 1.2 Hz, J_2 = 3.7 Hz, J_3 = 23.9 Hz, CH_2), 3.96 (ddd, 1H, J_1 = 1.2 Hz, J_2 = 3.7 Hz, J_3 = 23.9 Hz, CH_2), 3.78-3.60 (m, 2H, H1), 3.40-3.38 (m, 1H,≡CH). ^{13}C-nmr (DMSO): 151.95 (C2'), 143.06 (C5'), 110.46 (C4'), 109.44 (C3'), 80.25 (≡CH), 77.21 (C2), 74.52 (≡C), 62.56 (C1), 55.60 (CH_2). MS m/z (relative intensity): 167 ($M+1^+$, 1%), 166 (M^+, 3%), 135 (100%), 95 (51%), 77 (62%).

***General Procedure for the Preparation of 1-(2-Furyl)-2-hydroxyethyl Esters,* 2e-2f.**

To a stirred solution of **1** (110 mg, 1 mmol) in THF (2 ml) was added a solution of the carboxylic acid (1 mmol) in THF (0.5 ml). After the reaction was complete, it was hydrolized with a 5 % solution of NaOH. The crude product was extracted with ether (3 x 10 ml). The organic extracts were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was distilled to give an oil which was purified by column chromatography (silica gel, hexane/ ethyl acetate 2:1). The compounds obtained by this method are listed below.

1-(2-Furyl)-2-hydroxyethyl acetate, **2e**. Isolated yield 162 mg (95 %). Ir (film): 3450, 1750. ^{1}H-nmr ($CDCl_3$): 7.38 (s, 1H, H5'), 6.39 (d, 1H, J = 3.3 Hz, H4'), 6.34 (s, 1H, H3'), 5.92 (dd, 1H, J_1 = 5.0 Hz, J_2 = 7.2 Hz, H1), 3.97 (dd, 1H, J_1 = 7.2 Hz, J_2 = 12.0 Hz, H2), 3.90 (dd, 1H, J_1 = 5.0 Hz, J_2 = 12.0 Hz, H2), 2.08 (s, 3H, CH_3). ^{13}C-nmr ($CDCl_3$): 170.74 (C=O), 149.85 (C2'), 142.64 (C5'), 110.22 (C4'), 109.26 (C3'), 69.34 (C1), 62.32 (C2), 20.78 (CH_3). MS m/z (relative intensity): 170 (M^+, 1%), 152 (16%), 139 (16%), 110 (54%), 97 (100%), 43 (100%).

1-(2-Furyl)-2-hydroxyethyl benzoate, **2f**. Isolated yield 200 mg (86%). Ir (film): 3450, 1730. ^{1}H-nmr ($CDCl_3$): 8.05 (d, 2H, J = 7.8 Hz, H_{orto}), 7.53 (t, 1H, J =7.5 Hz, H_{para}), 7.42 (t, 3H, J_2 = 7.5 Hz, H_{meta} and H5'), 6.47 (d, 1H, J = 3.3 Hz, H4'), 6.35 (s, 1H, H3'), 6.17 (dd, 1H, J_1 = 4.8 Hz, J_2 = 7.2 Hz, H1), 4.16 (dd, 1H, J_1 = 7.2 Hz, J_2 = 12.0 Hz, H2), 4.06 (dd, 1H, J_1 = 4.8 Hz, J_2 = 12.0 Hz, H2), 2.54 (s, 1H, OH). ^{1}H-nmr (DMSO): 8.03 (d, 2H, J = 11.4 Hz, H_{orto}), 7.69-7.63 (m, 2H, H_{para} and H5'), 7.53 (t, 2H, J = 11.4 Hz, H_{meta}), 6.58 (d, 1H, J = 4.8 Hz, H4'), 6.49-6.45 (m, 1H, H3'), 6.11 (dd, 1H, J_1 = 8.1 Hz, J_2 = 10.5 Hz, H1), 5.31 (t, 1H, J = 8.9 Hz, OH), 4.06-3.85 (m, 2H, H2). ^{13}C-nmr ($CDCl_3$): 165.97 (C=O), 149.95 (C2'), 142.83 (C5'), 133.18 (C_{para}), 129.72 (C_{ipso}), 129.58 (C_{orto}), 128.29 (C_{meta}), 110.36 (C4'), 109.58 (C3'), 70.05 (C1), 62.92 (C2). MS m/z (relative intensity): 110 (87%), 105 (100%), 97 (66%), 77 (47%), 51 (20%).

***2-Endo-hydroxymethyl-exo-3,10-dioxabicyclo[5.2.1.0^{1,5}]dec-8-ene,* 3a *and 2-exo-hydroxymethyl-exo-3,10-dioxabicyclo[5.2.1.0^{1,5}]dec-8-ene,* 3b.**

A solution of **2c** (504 mg, 3 mmol) in anhydrous benzene (9 ml) under an argon atmosphere, was heated at 84°C for 84 h. The solvent was distilled to afford an oil which was chromatografied (silica gel,

hexane/ ethyl acetate 2:1) to give 225 mg (45%) of colorless **3a** which crystallized on standing, 98 mg (19%) of pale yellow oil **3b** and 181 mg (36%) of **2c**.

Data of **3a:** m.p. 55-57°C. Ir (KBr): 3410, 2930, 2865. ^{1}H-nmr ($CDCl_3$): 6.54 (d, 1H, J = 5.7 Hz, H9), 6.40 (dd, 1H, J_1 = 5.7 Hz, J_2 = 1.8 Hz, H8), 5.09 (dd, 1H, J_1 = 4.5 Hz, J_2 = 1.8 Hz, H7), 4.25 (t, 1H, J = 8.1 Hz, $H4_{endo}$), 4.16 (t, 1H, J = 3.6 Hz, H2), 3.91 (dd, 1H, J_1 = 12.4 Hz, J_2 = 3.6 Hz, CH_2OH), 3.80 (dd, 1H, J_1 = 12.0 Hz, J_2 = 3.6 Hz, CH_2OH) 3.45 (dd, 1H, J_1 = 10.5 Hz, J_2 = 8.1 Hz, $H4_{exo}$), 2.95 (s, 1H, OH), 2.18-2.08 (m, 1H, H5), 1.73 (ddd, 1H, J_1 = 11.7 Hz, J_2 = 4.7 Hz, J_3 = 3.0 Hz, $H6_{exo}$), 1.37 (dd, 1H, J_1 = 11.7 Hz, J_2 = 7.8 Hz, $H6_{endo}$). ^{13}C-nmr ($CDCl_3$): 136.42 (d), 133.50 (d), 98.76 (s), 79.73 (d), 78.24 (d), 73.03 (t), 62.46 (t), 44.81 (d), 29.13 (t).

Data of **3b:** Ir (film): 3410, 2940, 2865. ^{1}H-nmr ($CDCl_3$): 6.45 (d, 1H, J= 5.7 Hz, H9), 6.40 (dd, 1H, J_1 = 5.7 Hz, J_2 = 1.8 Hz, H8), 5.14 (dd, 1H, J_1 = 4.5 Hz, J_2 = 1.8 Hz, H7), 4.43 (t, 1H, J= 5.7 Hz, H2), 4.20 (t, 1H, J= 8.1 Hz, $H4_{endo}$), 3.83 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.7 Hz, CH_2OH), 3.77 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.7 Hz, CH_2OH), 3.51 (dd, 1H, J_1 = 10.5 Hz, J_2 = 8.1 Hz, $H4_{exo}$), 2.46 (s, 1H, OH), 2.28-2.19 (m, 1H, H5), 1.74 (ddd, 1H, J_1 = 11.7 Hz, J_2 = 4.5 Hz, J_3 = 3.0 Hz, $H6_{exo}$), 1.39 (dd, 1H, J_1 = 11.7 Hz, J_2 = 8.1 Hz, $H6_{endo}$). ^{13}C-nmr ($CDCl_3$,): 136.87 (d), 134.13 (d), 97.91 (s), 80.84 (d), 76.80 (d), 73.02 (t), 61.75 (t), 45.32 (d), 29.25 (t).

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7. In our cases, MMX calculations (PCModel 4,3. Serena Software) indicates a dihedral angle $H_aC\text{-}CH_b$= 41.6° (J_{HaHb}= 6.6 Hz) for the *exo* isomers, whereas, for the *endo* isomer the calculated values were $HaC\text{-}CH_b$= 29.7° (J_{HaHb}= 8.2 Hz).
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