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ANOMALOUS BEHAVIOUR IN SOME NUCLEOPHILIC RING OPENING OF FURYL-2-OXIRANE

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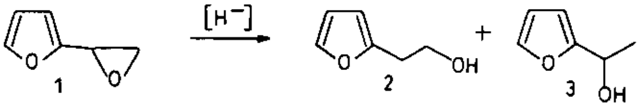
Dedicated to Prof. Rafael Pérez A. Ossorio

Abstract - The behaviour of furyl-2-oxirane in some nucleophilic ring opening reactions was studied.

The reductions of epoxides with metal hydrides have been extensively studied.[1] In the case of $NaBH_4$ reduction the process has long been considered to be very slow[2] and recently reductions of arene oxides with $NaBH_4$ in a single solvent have been performed.[3] The regioselectivity of this reaction indicates that the nucleophile attacks the less hindered carbon of the oxirane ring. An exception is the p-nitrostyrene oxide which affords a nearly 1:1 mixture of regioisomers.[3] Furyloxirane (1)[4] constitutes in our hand an interesting case of anomalous behaviour. Thus, equimolecular amounts of 1 react with $NaBH_4$ in alcoholic solvents at 25°C to give isomeric furyl carbinols (2) and (3) in a ratio strongly dependent on the solvent used. Independently, pure compounds were obtained by reduction of 1 with $NaBH_4$ in t-BuOH[5] (compound 2, Table 1, entry 6) or by reaction of furfural with MeMgI (compound 3).[6] In clear contrast, reaction of 1 with organocopper, organomagnesium and organolithium reagents afforded with high regioselectivity the product (4) arising from nucleophilic attack on the more electrophilic carbon of the epoxide (Table 2). In the same conditions, reactions of styrene oxide are less regioselective.[7]

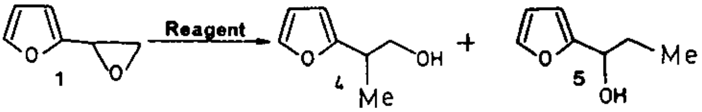
Table 1. Ring opening of furyloxirane (1) with complex metal hydrides



Entry	Reducing agent	Solvent	Reaction time (h)	Ratio 2:3[a]	Overall yield (%)[b]
1	$NaBH_4$	EtOH	2.5	12.8/1	84
2	$NaBH_4$	n-PrOH	5.0	3./1	85
3	$NaBH_4$	i-BuOH	5.0	11.8/1	94
4	$NaBH_4$	i-PrOH	5.0	2.8/1	71
5	$NaBH_4$	s-BuOH	5.0	3.7/1	63
6	$NaBH_4$	t-BuOH	2.0	20/1	86
7	$LiAlH_4$[c]	ether	1.0	1.4/1	80
8	$LiAlH_4$[c]	THF	1.0	1/2	80
9	$LiAlH_4$[c]	dioxane	1.0[d]	1/1.2	80

a: Determined by ^{1}H-nmr (300 MHz). b: In isolated mixture of 2 and 3. c: Reactions with solutions of $LiAlH_4$ gave erratic results. Reproducible yields and isomer ratios were obtained with $LiAlH_4$ suspension. All reactions were conducted at 0°C. d: Reaction was completed in 3 h at room temperature after 1 h at 0°C.

Table 2. Ring opening of 1 with organometallic reagents



Entry	Reagent[e]	Ratio 4/5[f]	Yield (%)[g]
1	Me_2CuLi	h	87
2	$Me(CN)CuLi$	h	90
3	$Me_2(CN)CuLi_2$	9/1	85
4	MeMgI[g]	h	80
5	MeLi	h	65

e: All reactions were performed in ether at 0°C. f: Determined by ^{1}H-nmr (300 MHz). g: Yields in pure, isolated compounds. h: Only isomer (4) was obtained. i: At reflux of ether.

In summary, furyloxirane shows an anomalous behaviour within the field of oxirane chemistry. The origin of this unexpected reactivity and synthetic applications[8] are currently being studied in our laboratories.

EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer, values in cm^{-1}.

^{1}H-Nmr and ^{13}C-nmr were obtained on a Varian T-300 spectrometer for $CDCl_3$ solutions and the chemical shifts 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 (tlc) chromatography respectively. Furyloxirane was distilled prior to use (bp. 45°C at 0.1 mmHg). Ethanol was purified after distillation according with conventional procedures.[9] Isopropanol, n-butanol, n-propanol, sec-butanol and tert-butanol were distilled prior use. Dioxane was purified by treatment with HCl (14 ml HCl/ 1 l dioxane) and reflux by 3 h under argon. After separation of aqueous layer, dioxane was dried over KOH, filtered, distilled, and stored over sodium. THF was distilled over KOH, stored over sodium and freshly distilled before use. Diethyl ether was dried over $CaCl_2$, then over sodium, and freshly distilled over $LiAlH_4$ before use. Reducing agents ($NaBH_4$, $LiAlH_4$), methyl iodide, copper(I)iodide and copper(I)cyanide were available through commercial sources. Standarized (1.6M) methyllitium in ether was obtained by Aldrich Chemical Co.

Reactions of furyl-2-oxirane with $LiAlH_4$

To a stirred, cold (0°C) solution of furyl-2-oxirane (110 mg, 1 mmol) in 2 ml of the solvent, was slowly added, under an argon atmosphere, a suspension of $LiAlH_4$ (38 mg, 1 mmol) in 5 ml of the solvent. After the addition was complete, the reaction mixture was stirred for 1 h at 0°C (3 h at room temperature in the case of dioxane as solvent), after which it was hydrolized with the minimum amount of water. The organic layer was dried over $MgSO_4$. The drying agent was removed by filtration, and the solvent was distilled to afford a mixture of 2-(2'-furyl)ethanol (2) and 1-(2'-furyl)ethanol (3), which was purified by column chromatography (hexane-ethyl acetate 2:1).

Reactions of furyl-2-oxirane with $NaBH_4$

To a stirred solution of furyl-2-oxirane (440 mg, 4 mmol) in the appropriate solvent (10 ml), $NaBH_4$ (125 mg, 4 mmol) was added in portions under an argon atmosphere. After the addition was complete the reaction mixture was stirred for 18 h at room temperature, after which it was hydrolized with 4 ml of water. The solvent was distilled and 16 ml of water were added to the residue. The resulting solution was extracted with ether (4x4 ml) and the organic extracts were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was distilled to afford a mixture of 2-(2'-furyl)ethanol (2) and 1-(2'-furyl)ethanol (3) which was purified as above.

2-(2'-furyl)ethanol (2). Ir (KBr): 3380 cm^{-1}. ^{1}H-Nmr 2.82 (t, J= 6.4 Hz, 2H, H-2), 2.5-3.2 (br s, OH), 3.78 (t, J= 6.4 Hz, 2H, H-1), 6.06 (d, J'= 3.3 Hz, 1H, H-3'), 6.26 (m, 1H, H-4'), 7.29 (d, J''= 2.1 Hz, 1H, H-5'). ^{13}C-Nmr 152.8 (C-2'), 141.1 (C-5'), 110.4 (C-4'), 106.4 (C-3'), 60.9 (C-1), 31.4 (C-2).

1-(2'-furyl)ethanol (3). Ir (KBr): 3420 cm^{-1}. ^{1}H-Nmr 1.51 (d, J= 6.6 Hz, 3H, CH$_3$), 4.85 (q, J= 6.6 Hz, 1H, H-1), 6.20 (d, J'= 3.3 Hz, 1H, H-3'), 6.30 (dd, J'= 3.3Hz, J''= 2.1 Hz, 1H, H-4'), 7.35 (d, J''= 2.1 Hz, 1H, H-5'). ^{13}C-Nmr 157.6 (C-2'), 141.9 (C-5'), 110.1 (C-4'), 105.1 (C-3'), 63.6 (C-1), 21.2 (C-2).

Reaction of furyl-2-oxirane with Me$_2$CuLi

To a stirred, cold (0°C), freshly prepared[10] ethereal solution of organocuprate *reagent was added, under an argon atmosphere, a solution of furyl-2-oxirane (110 mg,* 1 mmol) in 5 ml of ether. After the addition was complete, the reaction mixture was stirred at 0°C for 30 min, after which it was hydrolized with a saturated aqueous solution of NH$_4$Cl . The mixture was stirred at room temperature for 1 h. After filtration, the residue was washed with ethyl acetate (2x10 ml). The organic extracts were washed with a saturated aqueous solution of NH$_4$Cl and dried over MgSO$_4$. The drying agent was removed by filtration and the solvent was distilled to yield 2-(2'-furyl)propanol (4) which was purified by column chromatography (hexane-ethyl acetate 2:1). Isolated yield 110 mg (90%).

Reaction of furyl-2-oxirane with Me(CN)CuLi

To a stirred, cold (0°C) freshly prepared ethereal solution of organocuprate reagent[11] was slowly added, under an argon atmosphere, 330 mg (3 mmol) of furyloxirane. The reaction mixture was hydrolized with 12 ml of water. After filtration, the reaction mixture was extracted with AcOEt (2x30 ml) and the organic extracts were dried over MgSO$_4$. The drying agent was removed by filtration and the solvent was distilled to yield 2-(2'-furyl)propanol (4) which was purified by column chromatography as above. Isolated yield 122 mg (97%).

Reaction of furyl-2-oxirane with Me$_2$(CN)CuLi$_2$

The same procedure as above was followed. Removal of the drying agent and concentration afforded the crude product as a mixture of 1-(2'-furyl)propanol (5) and 2-(2'-furyl)propanol (4) in ratio of 1:9.

Reaction of furyl-2-oxirane with MeMgI

To a stirred freshly prepared ethereal solution of MeMgI, was slowly added 440 mg (4 mmol) of furyloxirane in 2.7 ml of ether. The solution was warmed under reflux for 30 min. The reaction mixture was hydrolized with water. The crude product was extracted with ether (4x10 ml) and the organic extracts were dried over MgSO$_4$. The drying agent was removed by filtration and the solvent was distilled to yield 2-(2'-

furyl)propanol (4) which was purified by column chromatography (hexane- ethyl acetate 2:1). Isolated yield 100 mg (80%).

Reaction of furyl-2-oxirane with MeLi

To a stirred, cold (0^{o}C) solution of furyloxirane (330 mg, 3 mmol) in 0.5 ml of ether under an argon atmosphere were added 1.5 ml of a standarized solution of MeLi (1.6M in ether) diluted with 4.5 ml of ether. Then, reaction mixture was warmed to room temperature and stirred for 1 h, after which it was hydrolized with a 5% solution of NaOH. The crude product was extracted with ether (2x20 ml). The organic extracts were washed with a saturated solution of NH_4Cl and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was distilled to give 2-(2'-furyl)propanol (4) which was purified by column chromatography as above. Isolated yield 80 mg (65%).

2-(2'-furyl)propanol (4). Ir (KBr): 3360 cm^{-1}. ^{1}H-Nmr 1.24 (d, J= 6.9 Hz, 3H, CH_3), 2.46 (br s, 1H, OH), 2.99 (m, 1H, H-2), 3.67 (m, 2H, H-1), 6.05 (d, J'= 2.7 Hz, 1H, H-2'), 6.27 (d,J'= 2.7 Hz, 1H, H-4), 7.30 (s, 1H, H-5'). ^{13}C-Nmr 157.4 (C-2'), 141.4 (C-5'), 109.9 (C-4'), 104.8 (C-3'), 66.1 (C-1), 35.9 (C-2), 15.0 (C-3).
1-(2'-furyl)propanol (5). Ir (KBr): 3370, 3120 cm^{-1}. ^{1}H-Nmr 0.98 (t, J= 6.8 Hz, 3H, CH_3), 1.87 (m, 2H, H-2), 2.48 (br s, 1H, OH), 4.56 (t, J'= 6.7 Hz, 1H, H-1), 6.20 (d, J''= 2.7 Hz, 1H, H-3'), 6.30 (m, 1H, H-4'), 7.34 (m, 1H, H-5'). ^{13}C-Nmr 156.6 (C-2'), 141.8 (C-5'), 110.0 (C-4'), 105.8 (C-3'), 69.1 (C-1), 28.5 (C-2), 9.88 (C-3).

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