A SYNTHETIC SCHEME FOR THE PREPARATION OF OXYGEN LABELLED FURAN COMPOUNDS

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SUMMARY

Four alicyclic furan compounds have been synthesized with incorporation of ^{18}O in the furan oxygen. Basically, a stable ketonic intermediate of the synthetic scheme was exchanged with $H_2{}^{18}O$ in THF with a catalytic amount of HCl.

Key Words: Oxygen-18, Alicyclic Furans, Synthesis

INTRODUCTION

In a previous publication in this journal, we reported on the preparation of ^{13}C and ^{14}C labelled furan compounds for the detection of labelled metabolites (1). Another aspect of this research involved m-chloroperbenzoic acid as an oxidizing mimic of the mixed function oxidase enzyme system. Some of this work has been reported (2). As a result of this latter work it was necessary to prepare several alicyclic furan derivatives in which the furan oxygen was enriched with ^{18}O.

There are two reports in the literature for labelling aryl furans with ^{18}O. The first by Pring (3) involved the hydrolysis of an aryl diazonium fluroborate with $H_2{}^{18}O$. The second method (4) used the procedure of incubating 15-hydroperoxy-5,8,11,13-eicosatetraenoate or PPG_2 in an atmosphere of $^{18}O_2$ with prostaglandin synthetase. In this

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system, dibenzofuran, another aryl furan, was prepared with high incorporation of label. Neither of these systems was applicable to our system since we required labelling of non-aryl furan compounds.

Thus, in order to study the mechanism for the mCPBA oxidation of these systems compounds **6**, **10**,**14** and **15** were synthesized with ^{18}O label.

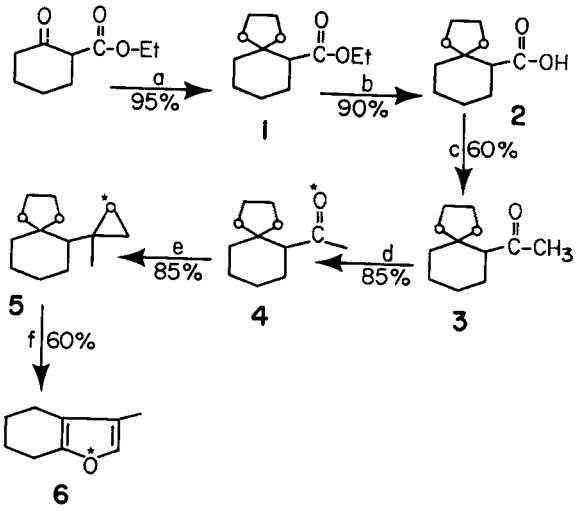
RESULTS

The basis in each labelling experiment was to isolate a ketonic intermediate in the synthetic scheme in which an exchange between the carbonyl oxygen and $H_2{}^{18}O$ could be effected. The conditions for this exchange were ketone, THF, $H_2{}^{18}O$ and a catalytic amount of HCl. Presumably, higher concentrations of ^{18}O label could be incorporated if repeated exchanges were conducted. However, for our studies, we tried for approximately a 1:1 mixture of ^{16}O and ^{18}O substrate.

The methods of detection included mass spectrometry and nuclear magnetic resonance spectroscopy. While the latter technique gave only a rough estimate of how much label had been incorporated (5), it allowed for specific label location. This was done by measuring the ^{13}C NMR spectrum at high resolution. The resonance for the carbon attached to the ^{18}O nucleus is slightly upfield (0.05 ppm) of the resonance for the ^{13}C atom attached to ^{16}O (6).

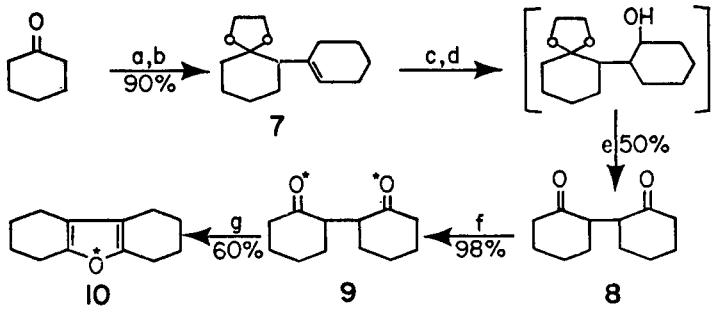
Compounds **6**, **10**, **14** and **15** were synthesized via straightforward methods which are exhibited in the following schemes. Except for the 3rd and 6th steps, the yields in the formation of **6** were quite respectable. The labelling step occurred with 55% incorporation of ^{18}O from 99% $H_2{}^{18}O$. Fortunately, only one poor step followed the labelling step.

Scheme 1



a-$HOCH_2CH_2OH$, pTSOH, $\emptyset H$, Δ, b-5 N NaOH, c-$2CH_3Li$, d-H^+, H_2O^*, THF, e-$CH_2=S(CH_3)_2$, f-H_3O^+, pentane.

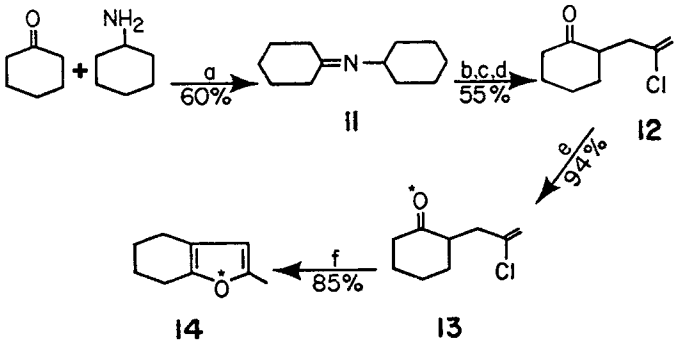
Scheme 2



a-HCl(g), b-$HOCH_2CH_2OH$, pTSOH, $\emptyset CH_3$, Δ, c-$NaBH_4$, BF_3, THF, d-HO^-, H_2O_2, e-Jones oxidation (CrO_3, H_2SO_4, CH_3CCH_3 ‖ O), f-H_2O^*, H^+, THF, g-H_2SO_4.

In this sequence, 54% of label was incorporated with 41% being carried on to the product.

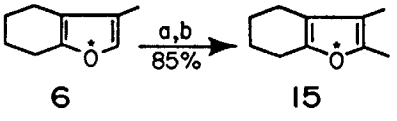
Scheme 3



a-4Å molecular sieves, ether, b-EtMgBr, THF, c-CH_2=CCl-CH_2Cl, d-H_3O^+, e-H_2O*, H^+, THF, f-90% H_2SO_4.

Fortunately, in this sequence, the labelling step for preparing **14** was the penultimate step as the final step reduced the already poor incorporation by half (See experimental section).

Scheme 4



a-nbuLi, b-CH_3I.

This sequence is basically the same as that for the preparation of **6** except that there is an additional step to put the second methyl group in

position. In this latter reaction, 100% of incorporated label was carried forward to the product.

EXPERIMENTAL SECTION

General. NMR spectra were recorded on a Bruker WM 250 MHz spectrometer using tetramethylsilane as an internal standard. In the determination of ^{18}O incorporation by ^{13}C NMR, typically, sweep widths of 500 Hz were used, 4K data points were acquired which were transformed as 8K blocks following 0.3 Hz exponential multiplication. Mass spectra were obtained from a Varian Mat CH-5 spectrometer. IR spectra were recorded on a Beckman IR 5A spectrometer.

Preparation of Ethyl and Methyl 1,4-dioxaspiro[4.5]decane-6-carboxylate 1. A solution of ethyl and methyl 2-oxocyclohexane-carboxylate (22 g, 134 mmol, Aldrich), ethylene glycol (14.4g, 233 mmol) and 0.5 g p-toluenesulfonic acid in 125 ml benzene was refluxed with a Dean-Stark water trap for 12 hours. The reaction mixture was washed with water, twice with 10% $NaHCO_3$, with brine and dried over $MgSO_4$. Removal of solvent gave a yellow oil which was distilled to yield 26 g (93%) of 1 as a clear liquid: bp 131-136° (10 mm Hg) [lit (7) bp 120-124° (8 mm Hg)].

Preparation of 1,4-dioxaspiro[4.5]decane-6-carboxylic acid 2. A solution of ketal-esters 1 (5.02g, 24 mmol) in 25 ml 5 M NaOH was refluxed for six hours. The solution was cooled, acidified with HCl (pH<2), and extracted with ether. The ethereal extracts were dried with $MgSO_4$. Removal of solvent afforded 4.17 g (93%) of 2 as a white solid: mp 99.5-100.5° (benzene) [lit(8) mp 73° (ethanol-H_2O)], ^1H NMR ($CDCl_3$) 10.7 (1H, br), 4.0 (4H,S), 2.7 (1H, m), 2.0 - 1.3 (8H, m) ppm, ^{13}C NMR ($CDCl_3$)

176.3 (s), 108.9 (s), 64.9 (t), 64.5 (t), 49.6 (d), 34.2 (t), 27.1 (t), 23.3 (t), 23.0 (t) ppm. IR ($CHCl_3$) 3050(br), 1760, 1720, 1205 cm^{-1}, Mass spectrum M^+ 186 m/e.

Preparation of 6-acetyl-1,4-dioxaspiro[4.5]-decane **3**. To a solution of ketal-acid **2** (5.06 g, 27 mmol) in 250 ml of ether at 0° under an inert atmosphere was added dropwise with vigorous stirring a solution of CH_3Li (59 mmol, Aldrich 1.55 M in ether) in 70 ml ether over a period of two hours. The ice bath was removed and stirring continued for 10 hours. The reaction mixture was hydrolyzed in 50 ml aliquots by dropwise addition to 25 ml portions of ice water with stirring. The layers were separated and the aqueous portion extracted several times with ether. The combined ether layers were washed with brine and dried over $MgSO_4$. The aqueous layer was acidified and extracted to reclaim 1.16 g of unreacted acid. Removal of solvent afforded a light yellow oil which was chromatographed on silica gel (eluted with hexane:ethyl acetate) to yield 3.04 g of **3** (79% based on recovered acid) as a clear oil: ^1H NMR ($CDCl_3$) 4.0 - 3.8 (4H, m), 2.81 (1H, dd), 2.23 (3H, S), 2.0 - 1.5 (8H, m) ppm, ^{13}C NMR ($CDCl_3$) 209.2 (s), 109.5 (s), 64.7 (t), 64.3 (t), 57.0 (d), 35.1 (t), 31.5 (q), 26.7 (t), 23.6 (t), 23.5 (t) ppm, IR (neat) 2970, 2870, 1710, 1450, 1360, 1090, 1040 cm^{-1}, Mass spectrum M^+ 184, 99 (100) m/e.

Preparation of 6-acetyl-^{18}O-1,4-dioxasprio[4.5]decane **4**. A solution of **3** (0.56 g, 3 mmol), 60 µl H_2O (99% ^{18}O, Stohler Isotope Chemicals), and 1 µl concentrated HCl in 1.3 ml of tetrahydrofuran (sufficient to solubilize) was allowed to stand for 1 1/4 hours. The reaction mixture was quenched by pouring into 30 ml of CH_2Cl_2, washing with 10% $NaHCO_3$, brine and drying over K_2CO_3. Removal of solvent afforded 0.51 g (92%) **4** as a clear oil: ^{13}C NMR spectrum as above. The

carbonyl resonance at 209.2 ppm could be resolved into two lines with the upfield resonance ($C^{18}O$) shifted by 0.051 ppm. Comparison of relative intensities of these lines showed 54% incorporation of ^{18}O, IR (neat) 1710 ($C^{16}O$), 1685 ($C^{18}O$) cm^{-1}, Mass spectral analysis showed 55% incorporation of ^{18}O.

Preparation of 6-(2-methyloxirane-^{18}O)-1,4-dioxaspiro[4,5]decane 5. Following the procedure of Corey (9), NaH (0.26 g, 5.4 mmol, 50% dispersion in mineral oil, Baker) was placed in a 2 necked flask and washed 3 times with petroleum ether. The final traces of petroleum ether were removed under aspirator vacuum, the flask flushed with nitrogen and then maintained under a nitrogen atmosphere. Dimethylsulfoxide(3.3 ml) was added and the flask was heated at 70-75° until the evolution of H_2 ceased (approximately 30 min). The flask was cooled to room temperature and tetrahydrofuran (3.3 ml) added. The reaction mixture was then cooled to -10° and a solution of trimethylsulfonium iodide (1.11 g, 5.4 mmol) in 5 ml DMSO was added with stirring over a period of 2.5 min. After an additional minute at -10°, a solution of **4** (0.50 g 2.7 mmol) in 0.4 ml THF was added. The reaction mixture was stirred at -10° for 10 minutes and room temperature for 1 hour. The reaction mixture was then poured into water and extracted several times with ether. The combined extracts were washed with brine and dried over K_2CO_3. Removal of solvent afforded 0.49 g **5** (92%) as a light yellow oil which was found to be a mixture of diastereomers: IR and ^1H NMR are as reported in the literature (1), ^{13}C NMR: The major diastereomer showed resonances at 56.4 (s) and 55.8 (t) ppm. The resonance at 56.4 ppm could be resolved into two lines with the upfield ($C^{18}O$) line shifted by 0.042 ppm (48% ^{18}O). The resonance at 55.8 ppm could also be resolved with the $C^{18}O$ line shifted by 0.03 ppm

(48% ^{18}O). The minor diastereomer showed resonances at 56.7 (s) and 52.1 (t) ppm which exhibited similar chemical shifts for the labelled material and similar values for isotope incorporation.

Preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 6.

To a solution of 5 (0.49 g, 2.5 mmol) in 40 ml pentane was added 20 ml 1 N aqueous HCl. The resulting biphasic mixture was stirred for 2 1/4 hours. The layers were separated and the aqueous portion extracted four times with pentane. The combined pentane layers were washed with 10% $NaHCO_3$, brine and dried over K_2CO_3. Removal of solvent and chromatography afforded 0.29 g 6 (86%) as a clear oil: IR and ^1H NMR as reported in the literature (10), ^{13}C NMR ($CDCl_3$) 150.9 (s), 136.7 (d), 119.8 (s), 117.9 (s), 23.3 (t), 23.1 (t), 23.1 (t), 20.5(t), 8.0 (q) ppm. The resonance at 150.9 could be resolved into two resonances with the upfield peak shifted by 0.039 ppm (46% ^{18}O). The resonance at 136.7 could be resolved similarly with the upfield line shifted by 0.036 ppm (47% ^{18}O), Mass spectral analysis showed 48% ^{18}O incorporation.

Preparation of 2-cyclohexenyl-1,4-dioxaspiro[4,5]decane 7. Cyclohexanone was coupled by the procedure of Wenkert (11). ^{13}C NMR ($CDCl_3$) 137.9 (s), 124.4 (d), 111.2 (s), 65.1 (t), 65.0 (t), 53.1 (d), 37.1 (t), 29.6 (t), 29.2 (t), 25.9 (t), 25.8 (t), 24.3 (t), 23.8 (t), 22.8 (t) ppm.

Preparation of 2-(2-oxocyclohexyl)-cyclohexanone 8. Following the procedure of Brown (13), to a stirred suspension of $NaBH_4$ (1.7 g, 45 mmol, pulverized before use) in 50 ml tetrahydrofuran containing 7 (22.2 g, 100 mmol) was added a solution of boron triflouride etherate (8.7 g, 61 mmol) in 10 ml tetrahydrofuran over a period of one hour at 25°. The reaction mixture was stirred an additional hour and then 16 ml of 3 M NaOH was added. The product was then oxidized by addition of 16 ml of 30%

H_2O_2 over a period of one hour. The reaction mixture was poured into water and extracted several times with ether. The combined extracts were washed with water, brine and dried over K_2CO_3. Removal of solvent afforded 25 g of a yellow oil: IR 3400 cm^{-1}. The crude alcohol was dissolved in 150 ml of acetone and cooled to 0°. A solution of Jones reagent (14) (350 mmol, prepared by dissolving 35 g CrO_3 in 250 ml of water and adding 30 ml concentrated H_2SO_4) was added dropwise over a period of 3 hours keeping the temperature below 5°. After the addition was complete, the reaction was stirred for 2 hours at room temperature. A small amount of sodium bisulfite was added to discharge the brown color of chromic acid from the upper layer. The layers were separated and the lower layer extracted 3 times with petroleum ether (35-60°). These extracts were combined with the original upper layer and washed two times with $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was removed to yield a yellow oil. Chromatography on silica gel [eluted with hexane-ethyl acetate (9:1)] afforded 9.89 g **8** (51%) as a clear oil. This material was found to be a mixture of diastereomers with ^1H NMR, ^{13}C NMR, IR and mass spectral properties as reported in the literature (15). Initially this mixture was composed of 90% of the material reported as an oil: ^{13}C NMR($CDCl_3$)210.8(s), 50.3 (d), 41.9 (t), 29.1 (t), 26.5 (t), 25.0 (t) ppm, TLC on silica gel, R_f = 0.22 [hexane-ether (1:1)]. Upon standing at 0°, the material slowly isomerized to the solid: ^{13}C NMR ($CDCl_3$) 211.8 (s), 49.0 (d), 42.4 (t), 30.2 (t), 28.1 (t), 25.5 (t) ppm, TLC on silica gel, R_f = 0.27 [hexane-ether (1:1)].

Preparation of 2-(2-oxo-^{18}O-cyclohexyl)-cyclohexanone-^{18}O **9**. A solution of **8** (0.57 g, 2.9 mmol), 117 µl of H_2O (99% ^{18}O, Stohler Isotope Chemicals) and two µl concentrated HCl in 2 ml tetrahydrofuran was

allowed to stand for 22 hours. The solution was then poured into 10 ml of water and extracted several times with hexane. The combined hexane layers were washed with 10% $NaHCO_3$, brine and dried over K_2CO_3. Removal of solvent afforded 0.56 g **9** (98%) as a clear oil: ^{13}C NMR spectrum as reported above. The resonances at 210.8 and 211.8 ppm could both be resolved into two lines with the upfield resonance shifted 0.053 ppm (52% ^{18}O), Mass spectral analysis showed 54% incorporation of ^{18}O, IR 1705 ($C^{16}O$), 1670 ($C^{18}O$) cm^{-1}.

Preparation of perhydrobiphenyleneoxide-^{18}O **10**. Compound **9** (0.4 g, 2.0 mmol) was placed in a 1 ml flask. Two drops concentrated H_2SO_4 were added and the flask heated to 130° under aspirator vacuum for 10 minutes. The product was collected at 0° as it distilled. The reaction mixture was washed with hexane and combined with the distilled product which was washed with 10% $NaHCO_3$, brine and dried over K_2CO_3. Removal of solvent afforded 0.31 g **10** (85%) as a light yellow oil: ^1H NMR and IR spectra are as reported in the literature (12), ^{13}C NMR 148.4 (s), 116.9 (s), 23.4 (t), 23.3 (t), 23.2 (t), 20.7 (t). The resonance at 148.4 ppm could be resolved into 2 peaks with the upfield peak shifted 0.039 ppm (39% ^{18}O incorporation), Mass spectral analysis showed 41% incorporation of ^{18}O.

Preparation of N-cyclohexylidenecyclohexylamine **11**. This compound was prepared by the procedure of Jacobsen (16). ^{13}C NMR ($CDCl_3$) 170.7 (s), 58.0 (d), 40.4 (t), 34.3 (t), 34.3(t), 29.1 (t), 28.1 (t), 27.8 (t), 26.4 (t), 26.0 (t), 25.2 (t), 25.2 (t) ppm.

Preparation of 2-(2-chloroprop-2-enyl)-cyclohexanone **12**. Compound **12** was prepared by the procedure of Stork (17). ^{13}C NMR ($CDCl_3$), 210.8(s), 140.5(s), 113.8(t), 47.4(d), 41.8(t), 38.7(t), 32.7(t), 27.6(t), 24.8(t) ppm.

Preparation of 2-(2-chloroprop-2-enyl)-cyclohexanone-^{18}O **13.** A solution of **12** (0.69 g, 4.0 mmol), 75 µl H_2O (99% ^{18}O, Stohler Isotope Chemicals) and 2 µl concentrated HCL in 3 ml tetrahydrofuran was allowed to stand at room temperature for 12 hours. It was then poured into 10 ml of water and extracted several times with hexane. The combined extracts were washed with 10% $NaHCO_3$, brine and dried over K_2CO_3. Removal of solvent afforded 0.65 g **13** (94%) as a clear oil: ^1H NMR as above, ^{13}C NMR showed the resonance at 210.8 ppm resolvable into two peaks with the upfield peak shifted by 0.053 ppm (38% incorporation of ^{18}O), IR 1705 ($C^{16}O$), 1675 ($C^{18}O$) cm^{-1}, Mass spectral analysis showed 37% isotope incorporation.

Preparation of 2-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O **14.** Following the procedure of Neinhouse (18), 1.2 ml of cold 90% H_2SO_4 (prepared using 97% ^{18}O water, MSD Isotopes) was added dropwise to **13** (0.64 g, 3.7 mmol) at 0° with vigorous stirring under a nitrogen atmosphere. The mixture was stirred an additional hour and then poured into 10 ml ice water. This was extracted several times with hexane. The combined extracts were washed with 10% $NaHCO_3$ and brine and then dried over K_2CO_3. Removal of solvent followed by chromatography on silica gel (pentane) afforded 0.37 g **14** (74%) as a clear oil: ^1H NMR and IR as reported in the literature (18), ^{13}C NMR ($CDCl_3$) 149.8(s), 149.0(s), 117.6(s), 106.5(d), 23.4(t), 23.4(t), 23.2(t), 22.3(t), 13.5(q) ppm. The resonances at 149.8 and 149.0 ppm could both be resolved into two lines with the upfield line shifted by 0.04 ppm (12% ^{18}O), Mass spectral analysis showed 14% incorporation of ^{18}O.

Preparation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran-^{18}O **15.** Following the procedure of Cohen (19), to a solution of **6** (0.5 g, 3.7

mmol, 44% ^{18}O) in 15 ml tetrahydrofuran at -22° was added n-butyllithium (3.3 ml of a 1.6 M solution in hexane, 5.3 mmol, Aldrich). The resulting solution was stirred for 2 hours at -22° and then iodomethane (1.1g, 8.0 mmol) was added. After an additional hour at -22°, the flask was warmed to room temperature and stirred for 3 hours. The reaction mixture was quenched with water and extracted several times with pentane-ether (1:1). The combined organic layer was washed with 5% sodium bisulfite, water and brine and then dried over K_2CO_3. Removal of solvent followed by chromatography on silica gel (pentane) yielded 0.42 g of **15** (75%) as a clear oil: ^{1}H NMR ($CDCl_3$) 2.6-2.5 (2H, m), 2.35-2.25 (2H, m), 2.2 (3H,s), 1.8 (3H,s), 1.85-1.65 (4H, m) ppm, ^{13}C NMR ($CDCl_3$) 147.8 (s), 144.8(s), 118.3(s), 113.7(s), 23.3(t), 23.3(t), 23.2(t), 20.8(t), 11.3(q), 8.0(q) ppm. The resonances at 147.8 and 144.8 could both be resolved into two lines with the upfield lines shifted by 0.04 ppm (43% ^{18}O), Mass spectral analysis showed 45% isotope incorporation. IR 1600, 1450, 1270, 1250, 1230, 1150 cm^{-1}.

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