PREPARATION OF 3-METHYL-^{3}H-FURAN AND 2-METHYL-^{3}H-FURAN

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SUMMARY

A simple and convenient method for the microsynthesis of tritiated 3-methylfuran and tritiated 2-methylfuran from 3-furfuryl chloride and 2-furfuryl chloride, respectively, has been described. The tritium label was introduced by reductive dehalogenation with tritiated lithium aluminum hydride.

Key Words: 3-Methyl-^{3}H-furan, 2-Methyl-^{3}H-furan, Reductive Dehalogenation

INTRODUCTION

We recently found that, like certain other furan derivatives (1), 3-methylfuran, either after inhalation or after systemic administration, is metabolized in the lung to a potent alkylating agent (2). Acute pulmonary bronchiolar necrosis is a prominent pathologic response to the compound; the chronic effects of 3-methylfuran on the lung are unknown, but should be carefully evaluated, particularly since many alkylating agents are carcinogenic. Further toxicologic evaluation of 3-methylfuran is clearly warranted, since a recent report (3) suggests it may be a predominant atmospheric contaminant in photooxidant smogs.

Since neither radiolabeled 3-methylfuran, nor the unlabeled compound are available commercially, and since they are essential for further biological studies, we have described in the present paper our approach to the synthesis of the compound. We have also described the preparation of radiolabeled 2-methylfuran, which produces lung toxicity similar to that produced by the 3-isomer.

We felt that a tritium-labeled 3-methylfuran would be most useful for biological studies. Tritium in the alkyl moiety appeared to offer optimal metabolic stability. We therefore prepared 3-methyl-^{3}H-furan by reductive dehalogenation of 3-furfuryl chloride with $LiAl^{3}H_{4}$ (figure 1). The 2-methyl-^{3}H-furan was prepared similarly from 2-furfuryl chloride.

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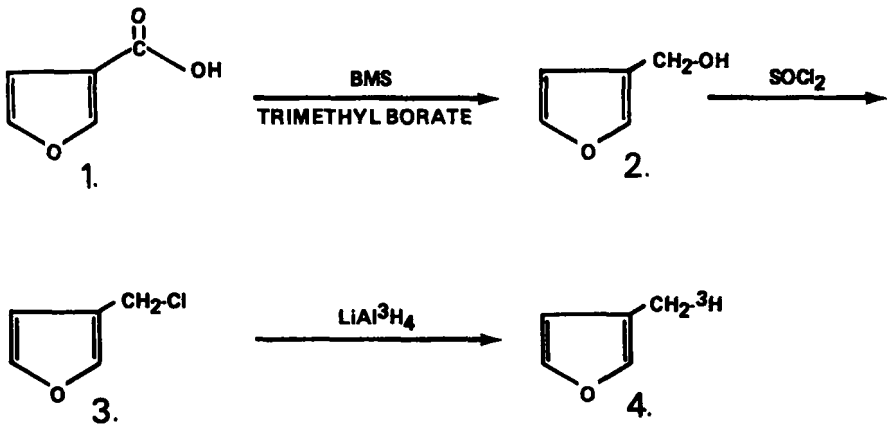

Figure 1. Synthesis of 3-methyl-^{3}H-furan.

MATERIALS AND METHODS

Authentic 2-furfuryl alcohol, 2-methylfuran, 3-furoic acid, thionyl chloride, trimethylborate, borane methylsulfide (BMS), and tetrahydrofuran were purchased from Aldrich Chemical Co., Milwaukee, WI. Powdered lithium aluminum hydride was obtained from Ventron, Gardena, CA., and tritiated lithium aluminum hydride ($LiAl^{3}H_{4}$) was purchased from New England Nuclear, Boston, MA.

Preparative gas chromatography (gc) was carried out on a Varian Aerograph Model 700 (Varian Associates, Palo Alto, CA.) equipped with a thermal conductivity detector and a 25 meter aluminum column (0.7 cm. i.d.) packed with 10% OV-101 on 100/120 mesh Gas-Chrom Q (Applied Science, State College, PA.). Helium was the carrier gas at a flow rate of 120 ml/min. The column oven was maintained at 80°, while the injector and detector were held at 180°.

Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at room temperature on a Varian A-60 spectrometer in $CDCl_3$ with trimethylsilane as internal standard. Mass spectrometric analyses were carried out using a VG Micromass 16F mass spectrometer (VG Industries, Winsford, Cheshire, U.K.) in the electron-ionization mode using a septum-inlet technique, under the following conditions: Accelerating voltage = 4 kV; electron voltage = 70 eV; emission

current = 100 μamps; multiplier output = 2 kV; amplifier range = $3x10^6$; source temperature = 200°C. Infra-red (IR) spectra were recorded on a Perkin-Elmer 21 spectrometer (Perkin-Elmer, Norwalk, CT.) using NaCl plates.

3-Furfuryl Alcohol (2): 3-Furoic acid (1) is the only suitable precursor for 3-furfuryl chloride (3) that is available commercially. The acid (1) (60 g; 0.54 mol) was placed in a 2 liter, 3-necked flask, equipped with a reflux condenser, drying tube, dropping funnel and magnetic stirrer, and flushed with dry N_2. Peroxide-free tetrahydrofuran (400 ml) was added together with trimethyl-borate (183 g; 1.8 mol). Borane-methyl sulfide complex (66 ml) was added over a period of 1 hour to the stirred solution; room temperature was maintained at all times. After allowing the mixture to stir overnight, methanol (200 ml) was added over a period of 1 hour. The mixture was allowed to stir for an additional 45 minutes. The solvent was removed under vacuum, using a rotary evaporator. To the remaining residue was added an additional portion of methanol (200 ml) and the mixture evaporated *in vacuo* again. This process was repeated once more before the residue was dissolved in diethyl ether (150 ml) and dried initially over anhydrous $MgSO_4$ and then allowed to stand over anhydrous K_2CO_3 overnight. The ether was filtered off and evaporated *in vacuo* to give a colorless, viscous liquid which was examined by ^{1}H-NMR (-OH *s* 3.15 δ; $-CH_2$ - *s* 4.5 δ; β-proton *m* 6.4 δ; α-protons *m* 7.4 δ), IR (-OH 3200 cm^{-1}) and mass spectrometry (M^+ = 98). The purity of the crude 3-furfuryl alcohol (51 g; 96% yield; 0.52 mol) was >95% as assessed by NMR and gas chomatography.

3-Furfuryl Chloride (3): The 3-furfuryl chloride was prepared as described previously (4) by the reaction of 2 (29.4 g; 0.3 mol) with thionyl chloride. The product (16.3 g; 47% yield; 0.14 mol) was examined by ^{1}H-NMR ($-CH_2$ - *s* 4.5 δ; β-proton broad *s* 6.5 δ; α-protons *m* 7.5 δ), IR (CH_2-halogen 1429 cm^{-1}) and mass spectrometry (M^+ = 116).

3-Methyl-^{3}H-furan (4): Tritiated lithium aluminum hydride (4.9 mg; specific activity 193 mCi/mmol) was added to a 5 ml reaction vial, previously flushed with dry N_2, and closed tightly with a teflon-sealed cap. The $LiAl^3H_4$ was suspended in 1 ml of diethyl ether and the suspension stirred using a small magnetic bar. A 50 μl syringe was used to carefully introduce 3 (30 mg; 0.26 mmol) into the

reaction mixture and the syringe, with plunger in place, allowed to remain projecting through the teflon seal to act as a vent, if necessary. The suspension was stirred for 48 hours when a further aliquot of 3 (30 mg; 0.26 mmol) was added and stirring continued for an additional 24 hours. At the end of this period, the reaction was halted by the injection of water (100 µl). The slurry was mixed thoroughly on a vortex and transferred to a 13 ml centrifuge tube and spun at 1000 rpm for 15 minutes. The ethereal layer was carefully removed using a glass syringe and dried over anhydrous $MgSO_4$ (≃ 200 mg) for 4 hours, after which time the suspension was vortexed thoroughly and spun at 1000 rpm for 15 minutes. Aliquots of the ether solution were withdrawn using a 1000 µl glass syringe (Pressure-Lok Gas Syringe, Precision Sampling Corp., Baton Rouge, LA.) and injected onto the preparative gc column (column temperature, 80°) (figure 2a). The radioactive 3-methylfuran was trapped in a glass vessel immersed in a Dry Ice/acetone bath. The product was examined by mass spectrometry and found to exhibit exactly the same mass spectrum as pure, nonradioactive 3-methylfuran synthesized as described below. (Yield = 5 mg; 12% yield; 0.06 mmol; specific activity, 13.3 mCi/mmol). The tritiated 3-methylfuran was diluted with pure, nonradioactive 3-methylfuran to a specific activity of 0.5 mCi/mmol and approximately 1 µl of this solution was injected onto the preparative gc column and the effluent was collected every 2 minutes in a glass trap as described above. The condensed material was flushed out of the vessel with 3 ml of ethanol into a scintillation vial to which was added 15 ml Aquasol scintillation cocktail. The samples were counted in a Searle Analytic spectrophotometer for 10 minutes and the data represented graphically. Figure 2 shows typical chromatograms obtained (a) during preparative gc of the crude reaction mixture, and (b) of the final product. As indicated from the analyses shown in the figure and from the other analytical data obtained, the product was homogeneous both chemically and radiochemically.

The above microsynthesis has also been successfully scaled-up and used for the preparation of much larger quantities of unlabeled 3-methylfuran. This material was also purified by preparative gc and examined by mass spectrometry (M^+ = 82).

2-Methyl-^{3}H-furan: Tritiated 2-methylfuran was synthesized in an identical manner to 3-methyl-^{3}H-furan, but using 2-furfuryl chloride as the precursor

instead of 3. The tritiated material was purified by preparative gc. (Yield = 6 mg; 14% yield; 0.07 mmol; specific activity, 7.3 mCi/mmol).

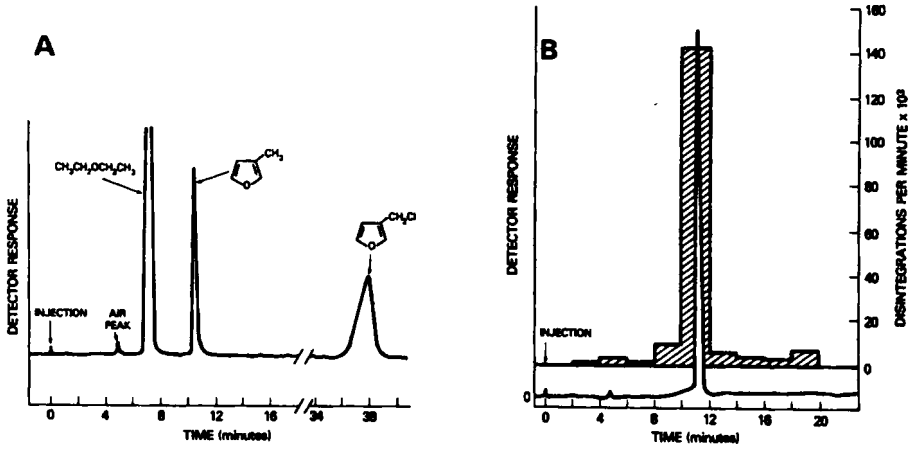

Figure 2. (a) Preparative gas chromatogram of crude reaction mixture of 3 with $LiAl^3H_4$ in ether (see text for gc conditions). (b) Gas chromatogram (lower trace) and radiochromatogram (upper trace) of gc-purified 3-methyl-^{3}H-furan, under same conditions as for (a).

RESULTS AND DISCUSSION

The methods described permit the synthesis of 3-methyl-^{3}H-furan and 2-methyl-^{3}H-furan of high specific activity. The methods are also adaptable to the larger-scale preparation of unlabeled 3-methylfuran, which is not available commercially. Both the chemical and radiochemical yields (12%, and 3%, respectively), in the reductive dehalogenation step, were very low, but this shortcoming was more than offset by the relatively low cost of $LiAl^3H_4$ as the source of the label, and the simplicity of both the syntheses as well as the purification of the compounds. Attempts to dehalogenate the chloride precursors using NaB^3H_4 gave extremely poor yields and recovery of product was much more difficult. The specific activities of the products obtained were considerably lower than would have been predicted, based on the specific activity of the starting material (assayed by the supplier). This leads us to suspect either that the original radioassay of the $LiAl^3H_4$ (the compound was used exactly as received from supplier) was incorrect, or that the material was not chemically homogeneous. Therefore it seems possible that the yields we report herein are excessively low on that basis.

Our preliminary experience with the radiolabeled methylfurans indicate they are somewhat photosensitive and should be stored in the dark at low temperatures. Also, since some degradation invariably occurs on storage, we strongly suggest that the compounds be purified by the gas chromatographic method described herein, immediately prior to use in biological experiments.

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