DECAY SYNTHESIS OF CARRIER-FREE 3-METHYL-$\left[^{3}H\right]$-FURAN AND 2-METHYL-$\left[^{3}H\right]$-FURAN.

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SUMMARY

Nuclear decay of $C^{3}H_{4}$ in the presence of gaseous furan represents a simple and convenient synthetic route to carrier-free multitritiated 3-methyl- and 2-methyl-furan. Their application for biological studies appears particularly promising, on account of the favourable characteristics of the followed synthetic approach.

Key Words: Carrier free methyl-$\left[^{3}H\right]$-furans, Decay synthesis, Multitritiated methanes, Tritium.

INTRODUCTION

Recent development of standardized synthetic procedures, allowing isolation of multicurie amounts of $C^{3}H_{4}$ in a state of high radiochemical and isotopic purity, [1] has opened up the way to direct preparation of selectively tritiated molecules in an essentially carrier-free state, namely with a specific activity up to 8.7×10^{4} Ci mol^{-1}. [2] In fact, irrespective of the particular environment, spontaneous β decay of $C^{3}H_{4}$ generates nearly quantitative yields ($>82\%$) of methylium ions $C^{3}H_{3}^{+}$, [3,4] which are so reactive as to attack any nucleophile (S) present at a rate approaching the collision frequency. Fast neutralization of the methylated intermediates with a suitable base B[5] provides a direct route to essentially carrier-free methylated derivatives ($C^{3}H_{3}S$), which generally retain the tritium label in their methyl moiety.[4,6]

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$$C^3H_4 \xrightarrow[\text{decay}]{\beta^-} C^3H_3^+ + {}^3He + \beta^- + \bar{\nu} \quad (>82\%)$$

$$C^3H_3^+ + S \longrightarrow \left[C^3H_3S\right]^+ \xrightarrow{B} C^3H_3S + \ldots$$

Build-up of significant amounts of C^3H_3S may take only a few weeks, if relatively high C^3H_4 activities are used. Thus, two-weeks storage of 0.6 Ci of C^3H_4 in the presence of H_2O (S) afforded 2.8 mCi of methanol labeled exclusively in the methyl group. [2] Should this decay procedure be applied toward particular substrates, such as heteroaromatic compounds, a straightforward source of carrier-free tritiated methyl derivatives of chemical, radiobiological, and genetic interest would be at hand.

Here the first application of the C^3H_4-decay technique for preparation of molecules of biological interest is presented. As recently suggested, [7] synthesis of carrier-free isomeric methylated furans is amply desirable.

In fact, methyl furans are thought to be atmospheric pollutants present in photooxidant smogs, [8] which, like certain other furan derivatives, [9] are suspected to cause chronic diseases and cancer of lung, if inhaled. [10] We therefore believe that the possibility of preparing carrier-free C^3H_3-furans in the gaseous state by a simple and convenient procedure would be of significant interest for biokinetic investigations on the pathogenic activity of these compounds.

The present communication describes the simultaneous preparation of carrier-free multitritiated 3-methyl- and 2-methyl-furan by a synthetic approach based on the spontaneous decay of C^3H_4 in the presence of gaseous furan.

EXPERIMENTAL

Materials. Tritium gas with a stated purity of 99 mol % was purchased from CEN (Mol, Belgium), the major impurities being ^3HH and ^3He. Merck Co. provided pro-analysis copper oxide (99 mol %),

while aluminium carbide (Al_4C_3, minimum purity: 92 mol %) was supplied by Fluka AG. Research-grade furan and 2-methyl-furan were obtained from ICN-Pharmaceuticals Co. and purified by preparative GLC (99.5 mol %) before use. 3-Methyl-furan was synthesized from 3-furoic acid, using the procedure described by Body et al. [7]

Procedure. Following the method described by Cacace and Schüller,[1b] C^3H_4 was prepared via the following reaction sequence:

$$^3H_2 + CuO \xrightarrow{450^\circ C} Cu + {}^3H_2O$$

$$12\ {}^3H_2O + Al_4C_3 \xrightarrow{200^\circ C} 4Al(O^3H)_3 + 3C^3H_4$$

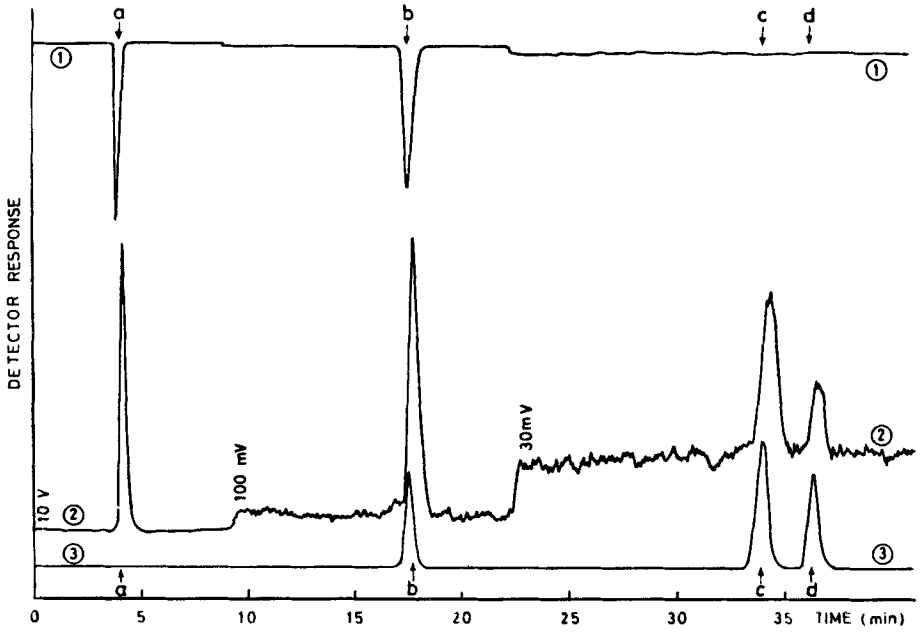
The obtained C^3H_4 (70 ± 10% yield based on the $^3H_2$ gas used) was purified by adsorption on activated silica gel at the liquid nitrogen temperature, [11] a procedure allowing almost quantitative recovery of a C^3H_4 free from the ^3HH, $^3H_2$, and ^3H_2O contaminants. The purity of the recovered methane, in fact, exceeded 95 mol %, as checked by radiogaschromatography on a 2-m 5Å molecular sieves column operated at 55°C.

Approximately 20 mCi of C^3H_4 were diluted with gaseous furan to a molar ratio of ca. 1/1 x 10^4, and stored for 1 month at 100°C and 150 torr, in the presence of 3 mol % O_2, used as an effective thermal radical scavenger; in a few experiments, the dilution was completed by addition of 4 mol % of a strong gaseous base, such as NH_3. After the due lapse of time, weighed aliquots of the crude synthetic mixtures were analyzed by radiogaschromatography. The analyses were carried out on three different columns: i) a 8-m long, 1/8" i.d., 25% dimethylsulfolane on 80/100 mesh Chromosorb W column, operated at 25°C; ii) a 9-m long, 1/8" i.d., 25% Silicone Oil E 301 on 80/100 mesh Chromosorb W column, operated at 70°C; iii) a 50-m, 0.1 mm i.d., stainless steel OV-101 capillary column, operated at 80°C, using helium as the carrier gas. The effluent from the column, diluted with CH_4 (20 mL min^{-1}), was fed into a Berthold flow-ionization chamber kept at 150°C. The radioactive

products were identified by comparison of their retention volumes with those of authentic samples, synthesized and identified by conventional methods.[7]

RESULTS AND DISCUSSION

A typical analysis of the gaseous reaction mixtures is illustrated in the Figure, which shows the predominant formation of three radioactive derivatives of furan: $\left[{}^{3}H\right]$-furan, 2-methyl-$\left[{}^{3}H\right]$-furan, and 3-methyl-$\left[{}^{3}H\right]$-furan. The relative abundance of these products, their absolute yields based on the theoretical yield of the $C^{3}H_{3}^{+}$ ions, and their computed specific activity are reported in the Table.



Radio-gas-chromatographic analysis of a $C^{3}H_{4}$/furan/O_2 mixture. Column: 9 m, 25% Silicone Oil E 301 on 80/100 mesh Chromosorb W, T_C: 70°, He: 10 mL min^{-1}. ① Mass analysis of the radioactive sample; ② Radiochemical analysis of the radioactive sample; ③ Gas chromatographic analysis of the standard compounds. (a) Hydrogen, methane, ethane, etc.; b) furan; c) 2-methyl-furan; d) 3-methylfuran).

TABLE

RADIOCHEMICAL YIELDS OF THE TRITIATED PRODUCTS RECOVERED IN THE C^3H_4/FURAN/O_2 SYSTEMS

PRODUCTS	RELATIVE YIELDS (%)	% OF THEORETICAL YIELDS	YIELD RELATIVE TO TOTAL $^3H_2$ EMPLOYED (%)	ACTIVITY (μCi)	SPECIFIC ACTIVITY (Ci mol^{-1})
FURAN-^{3}H	64(69)	24(22)	4.2(3.7)	18(16)	$8(7)\times10^{-5}$
2-METHYL-FURAN-^{3}H	24(22)	9(7)	1.6(1.2)	7(5)	Carrier-free $3 \div 8 \times 10^4$
3-METHYL-FURAN-^{3}H	12(9)	4(3)	0.7(0.5)	3(2)	Carrier-free $3 \div 8 \times 10^4$
TOTAL	100(100)	37(32)	6.5(5.4)	28(23)	

a) Values in parentheses pertain to activities measured in the system containing 4 mol % NH_3 .

It is apparent from the Table that the total activity recovered in the heteroaromatic products accounts for ca. 37% of the theoretical yield, a percent that decreases to ca. 32% when the reaction occurs in the presence of 4 mol % of NH_3. The overall yields of the methyl furans (10-13%) are limited by the occurrence of parasitic reaction channels such as extensive fragmentation of the methylated ionic intermediates, hydride-ion transfer from furan to the methylium ion, etc., which are triggered by the exceedingly high exothermicity (from 90 to 120 kcal mol^{-1}) of the $C^3H_3^+$ attack on the heteroaromatic substrate. Extensive ^3H scrambling between the side chain and the ring of the methylated ionic intermediates $\left[C^3H_3\text{-}S\right]^+$, followed by loss of the methyl group to a suitable acceptor, [5] accounts for the high yields of tritiated substrate, a recurring feature of the $C^3H_3^+$ attack on aromatic compounds both in the liquid and gaseous phase. [12] The small, but appreciable effect of NH_3, is explained by the indiscriminate reactivity of the very powerful electrophile $C^3H_3^+$ toward the two competing nucleophilic species, furan and NH_3, present in these systems.

The results obtained indicate that fairly good activities of carrier-free 3-methyl- and 2-methyl- $\left[^3H\right]$ - furan can be easily produced by the C^3H_4-decay technique, with reasonable overall radiochemical yields. No attempt to scaling-up the decay synthesis of methylated furans has been undertaken. It appears quite feasible to increase the activity of the starting C^3H_4 by orders of magnitude over the modest (20 mCi) level used in the present study.

Apart from furan- $\left[^3H\right]$, the parent C^3H_4 and other low-boiling fragmentation radioactive products (^3HH, CH^3H_3, ethane, etc.), the isomeric methylfurans obtained by the proposed procedure are not accompanied by other radioactive products which interfere with their purification. Further advantages of this unique approach to carrier-free methyl furans are the followings. Once suitable amounts of C^3H_4 are available, set-up of a number of individual methylfurans synthetic runs is possible, whose use for biological investigations can be deferred ad libitum. In fact, the decay syn

thesis offers the truly remarkable advantage of a continuous build-up of the radioactive decay products, which, being formed in a carrier-free state, are less prone to thermal or photolytic decomposition, since buffered by a huge excess of the parent substrate. The features of the decay method, therefore, avoid the necessity of repeated syntheses for delayed biological experiments or, alternatively, the need of storage of the radioactive products, from a single conventional synthetic run, in the dark and at low temperature, in order to reduce their inevitable degradation.[7] Furthermore, besides being relatively simple, the proposed procedure is characterized by limited costs, since the radiochemical precursor of the tritiated products is $^3H_2$ gas, nowadays a very cheap radioactive material.

In conclusions, the C^3H_4-decay synthesis, if accompanied by an appropriate mechanistic cognition, opens intriguing perspectives for new convenient synthetic routes to a number of carrier-free tritiated compounds of biological interest, whose preparation by conventional techniques has been regarded as an almost unattainable goal to date.

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