^{11}C-LABELED OCTANAL AND BENZALDEHYDE*

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SUMMARY

The synthesis of octanal and benzaldehyde, labeled with ^{11}C in the carbonyl position, is reported. Octanal was prepared via an insertion reaction of ^{11}CO into the boron-carbon bond of B-heptyl-9-BBN, followed by oxidative hydrolysis. Benzaldehyde was synthesized by the reaction of phenyl magnesium bromide with $^{11}CO_2$, and subsequent reduction of the labeled benzoic acid to benzylalcohol which was then oxidized to the final product by CrO_2Cl_2. Both aldehydes were purified via GLPC, leading to radiochemical purities of >99.5% in each case. The radiochemical yield for octanal and benzaldehyde was 30 ± 5% and 15 ± 5%, respectively. The overall synthesis time was 50 ± 10 min for each compound

Key Words: ^{11}C-octanal, ^{11}C-benzaldehyde, ^{11}C-organoboranes

INTRODUCTION

There has been an increased interest in aldehydes in a variety of biochemical and physiological studies. They are the key substrate for aldehyde dehydrogenase, an enzyme which itself plays an important role in the metabolic pathway of alcohols and amines in mammals. A large number of investigations on the subcellular localization (1) and function (2) of this enzyme have been reported in the recent literature, but most of them have been *in vitro* studies. In view of the interest of this laboratory in probing *in vivo* enzyme function (3) it was desirable to synthesize aldehydes labeled with the short lived positron emitter ^{11}C ($T_{\frac{1}{2}}$ = 20.04 min).

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Aldehydes are of direct interest in inhalation toxicological studies, since they are important components of air pollution from sources such as auto exhausts (4) and plastics manufacturing (5), etc. The great majority of toxicological studies involve the examination of chronic effects. No attention has been given to a systematic investigation of acute assaults to animal and plant life following exposure to pollutants. The techniques of nuclear medicine particularly in the area of dynamic imaging are an aid in studies of acute effects. Accordingly we began developing equipment for small animal exposure and synthesis of pollutants labeled with carbon-11 and other short lived nuclides. In order to design a system for the measurement of the acute distribution kinetics of such pollutants, benzaldehyde and octanal were chosen as model compounds. Both aldehydes were labeled in the carbonyl position and have been used successfully for enzyme function and inhalation distribution studies (6).

SYNTHETIC PATHWAYS

The most versatile radioactive starting materials for ^{11}C-labeling procedures are ^{11}CO, $^{11}CO_2$, $H^{11}CN$ (7), $H^{11}CHO$ (8), and $^{11}COCl_2$ (9). Due to the short half life of ^{11}C it is necessary to choose an organic compound which will react with one of the radioactive precursors to yield the desired product directly or to yield an intermediate which will require a minimum of subsequent steps.

For the preparation of aliphatic aldehydes insertion reactions of CO into organoboranes seem to be especially suitable (10). The reaction scheme for the preparation of octanal is given in equation 1

$$\text{B-heptyl-9-BBN} + (MeO)_3HLiAl + {}^{11}CO \xrightarrow[30\%\ H_2O_2]{\text{hydrolysis}\ \ pH\ 7} C_7H_{15}{}^{11}CHO \qquad (1)$$

Carbon monoxide inserts into the carbon-boron bond of B-heptyl-9-borobicyclo-[3,3,1]nonane (B-heptyl-9-BBN) and forms an adduct with the trimethoxy-hydrido-

lithium aluminate, which releases the corresponding aldehyde upon oxidative hydrolysis (11). The aldehyde is separated from inorganic products by extraction with ether followed by GLPC purification.

Although benzaldehyde could possibly be synthesized via carbonylation of triphenylboron, the separation of the nearly carrier-free product from relatively large amounts of benzene as a by-product presents considerable separation problems. A fast multi-step synthesis of ^{11}C-labeled benzaldehyde, beginning with the addition of $^{11}CO_2$ to phenyl magnesium bromide, a common reaction in labeling procedures, is given in equation 2

$$C_6H_5MgBr + {}^{11}CO_2 \xrightarrow{HCl} C_6H_5{}^{11}COOH \xrightarrow[HCl]{LiAlH_4} C_6H_5{}^{11}CH_2OH \xrightarrow{CrO_2Cl_2} C_6H_5{}^{11}CHO \quad (2)$$

Benzoic acid is liberated from the Grignard adduct with a small amount of HCl. Reduction with $LiAlH_4$ yields benzylalcohol which is extracted with ether and passed over a column containing CrO_2Cl_2 on an aluminum oxide/silicon oxide support (12). The benzaldehyde in the eluent is purified further by GLPC.

RESULTS

The yields of the reactions are based on the end of bombardment (EOB) yield of ^{11}C-activity. The time required for synthesis from EOB to end of GLPC purification are given in Table I.

Table I. Yields and Purity of ^{11}C-labeled Octanal and Benzaldehyde

Compound	Yield (EOB) (%)	Time (min)	Spec. Act.*	Purity
Octanal	30 ± 5	45 ± 5	1 mCi/0.1 μM	>99.5
Benzaldehyde	15 ± 5	55 ± 5	1 mCi/0.1 μM	>99.5

*The values indicate the actual amount of activity produced. Activities greater than 1 mCi were not required for our experiments. The syntheses would not involve any change in methodology in order to utilize 100 mCi to 1 Ci. The specific activities would probably be higher.

The specific activity of both compounds was determined by ratio GLPC-analysis. The radiochemical purity was established by reinjection of the compounds into the GLPC with addition of carrier octanal or benzaldehyde. The recovery of the radioactivity coincident with the mass peak was >99.5%. Peak shape analysis of the mass- and radioactivity peaks showed excellent agreement. Further proof of identity was not deemed necessary in these instances because of the methods of synthesis and the simplicity of the compounds.

EXPERIMENTAL

Labeled precursors. ^{11}CO and $^{11}CO_2$ were produced at the Brookhaven National Laboratory 60" synchrocyclotron as previously described (7).

1-^{11}C-octanal. B-heptyl-9-BBN was prepared by adding 1 g of dry heptene (10.2 mmole) in 5 ml THF to 20 ml of 0.5 M solution of 9-BBN in THF (Aldrich) at room temperature (13). The solution was stored under N_2 for repeated use. A mixture of 1.0 mmole $(CH_3O)_3HLiAl$ in 1.75 ml THF, prepared by addition of 0.75 mg 4 M CH_3OH in THF to 1 ml 1.0 M $LiAlH_4$ in THF (Ventron) (14) and 1.0 mmole of B-heptyl-9-BBN in THF, was transferred into a simple bubble trap reaction vessel and kept at 0°C. ^{11}CO was then passed through the reaction solution utilizing helium as carrier gas. After completion of the ^{11}CO transfer the reaction mixture was hydrolyzed with 1 ml of pH 7 phosphate buffer followed by the addition of 0.12 ml of 30% H_2O_2. The resulting mixture was extracted with pentane, the organic layer dried over $MgSO_4$, filtered, concentrated and finally injected into the GLPC. An 8 ft stainless steel column, packed with 10% Carbowax on Chromosorb WAW, DMCS, was used for the separation at 135°C and a flow rate of 30 ml He per min.

Carbonyl-^{11}C-Benzaldehyde. $^{11}CO_2$ was transferred to a reaction vessel containing 0.25 ml of C_6H_5MgBr (1 M in ether) and stirred for 5 min. The reaction mixture was hydrolyzed with 50 µℓ of 6 M HCl. The acid was reduced by addition of 0.5 ml 1.0 M $LiAlH_4$ in ether (Ventron) and stirred for 2 min

at room temperature. The reaction mixture was then hydrolyzed with 2 ml of 2 M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated almost to dryness on a rotary evaporator. The evaporator flask was rinsed with dry CH_2Cl_2 (2 ml) to give a solution of ^{11}C-labeled benzyl alcohol in 60% radiochemical yield. This solution was passed through a 1 x 3 cm glass column filled with CrO_2Cl_2 absorbed on silica gel/aluminum oxide (12). The eluent containing ^{11}C-labeled benzaldehyde was concentrated and injected into a GLPC fitted with the same column as used for octanal. The column was operated at a temperature of 150°C.

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