RAPID CATALYTIC SYNTHESIS OF ^{11}C-LABELLED AROMATICS

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SUMMARY

[11]C-Labelled benzene derivatives were prepared catalytically
by trimerizing acetylene-^{11}C with acetylene and propyne carriers
over 1.5 grams of silica-alumina support activated by potassium
chromate (0.2% by weight). Optimized yields of the ^{11}C-labelled
aromatics were obtained when the reactants were exposed to the
catalyst for 10 minutes at 24°C. A minimum addition of 50 μmole
of alkyne carrier was necessary before the trimerization pro-
ceeded to give appreciable yields of ^{11}C-labelled aromatics. In
the competitive trimerization of acetylene-^{11}C with acetylene and
propyne carriers, three ^{11}C-labelled aromatic products were gen-
erated: benzene, toluene, and xylene. From these studies
acetylene   was   observed to be 1.6 times more reactive than
propyne. In addition, the observed distribution of ^{11}C-labelled
xylenes (3.4% ortho, 10.6% meta, and 86% para) indicates an ap-
parent regiospecificity in the trimerization of ^{11}C-acetylene
with propyne.

INTRODUCTION

Trimerization of acetylene to benzene induced through transition-metal

catalysis is presently a powerful tool in radiocarbon dating laboratories.

Early studies and development of the technique can be found in the works of

Leger et al (1), Tamers (2), Noakes et al. (3,4) and Stipp et al. (5). More

recent works by Tamers (6) and Belluomini (7) describe chemical yield optimi-

zation in the catalytic benzene synthesis using a support of silica-alumina

activated with potassium chromate. It is presumably the reduction of Cr(VI)

to Cr(IV) and Cr(III) which catalyzes the acetylene trimerization (6). Under

the optimal conditions, greater than 99% conversion of acetylene to benzene

was usually obtained; however, this generally required between 1 and 3 hour(s)

of exposure to the catalyst. The major difficulty encountered was insuring

that both the catalyst and acetylene were devoid of water prior to reaction

since this usually resulted in unwanted side reactions.

Our interest in this catalyst was to determine whether a rapid synthetic

route could be developed to introduce a ^{11}C-label into aromatic compounds. As

a positron emitter, ^{11}C ($T_{\frac{1}{2}}$ = 20.4 min) is useful in nuclear medicine in con-

junction with positron emission tomography (8). However, classical synthetic

methods aimed at achieving this goal are usually too time consuming for the

short ^{11}C half-life and are avoided. Our primary effort was therefore aimed

at optimizing the catalytic reaction conditions in conjunction with ^{11}C-label-

ling. This meant that a maximized specific activity of the generated benzene-

^{11}C had to be achieved.

In the synthesis of benzene-^{11}C two studies were performed to ascertain

optimum reaction conditions: (i) the time the reactants were exposed to the

catalyst was varied and (ii) the specific activity of the reacting acetylene-^{11}C

was reduced. Since acetylene-^{11}C was prepared via recoil labelling techniques,

we had a unique advantage of potentially studying the catalytic acetylene

trimerization with concentrations of reactant in the femto mole scale.

Partly as a fundamental interest and as a precedent for further catalytic systems involving alkyne trimerizations, the competitive trimerization of acetylene-^{11}C with acetylene and propyne carriers was also studied. The results from these investigations are described in this work.

EXPERIMENTAL

Materials

A silica-alumina catalyst base (in the form of 2 mm pellets) activated by K_2CrO_4 (0.2% by weight) was used in these trimerization studies. The catalyst is available commercially from Mobil Oil Corporation, New York (type Durahead I) and Kali-Chemie, Hannover, Germany (type KC Perkator Dl). Acetylene, propyne, and cyclopropane (all research grade) were purchased from the Matheson Company. All gases were further purified on a vacuum line using conventional degassing techniques.

Benzene and toluene (analytical grade) were obtained from the Mallinckrodt Chemical Company and used for gas chromatographic calibrations without further purification. The ortho, meta and para xylenes (minimum; 99 mol % pure) were obtained from Phillips Petroleum Company and were also used for gas chromatographic calibrations without further purification.

Irradiation and Counting Techniques

Acetylene-^{11}C. All irradiations for carbon-11 generation were performed on the Brookhaven National Laboratory 60-inch cyclotron. No carrier added (NCA) acetylene-^{11}C was produced by bombarding a cyclopropane gas target with a 33 MeV proton beam to induce the ^{12}C(p,pn)^{11}C nuclear transformation. Irradiation samples were prepared by sealing 300 torr of cyclopropane within a quartz static irradiation vessel using standard high vacuum techniques. Typical beam intensities were 1 µA with exposure times of 100 seconds. The radiation dose was 3.48×10^{-4} eV molecule^{-1} µA^{-1} s^{-1} as determined by acetylene to benzene dosimetry (9). The total gaseous carbon-11 activity was determined by counting an aliquot using a well-type NaI (Tl) scintillation crystal. The acetylene-^{11}C

was purified through preparative gas chromatography using a 12-ft. Porapak N
column for separation purposes and its radioactive yield was measured in the
usual manner by using gas effluent counting (10). Polymer activity within the
irradiation vessel was also measured by washing the vessel with acetone and
with methyl alcohol, and counting solvent aliquots. The total carbon-11
activity (TA) was then determined by summing the combined gaseous and polymeric
activities. The acetylene-^{11}C yield generated from this cyclopropane system
was measured at 48% TA ($\sim$ 70 μCi). Unfortunately, a trace of carrier acetylene
was detected after irradiation which suggests some radiolytically induced reactions
on cyclopropane.

General Synthetic Procedures

Prior to reaction, 1.5 grams of catalyst were placed in a 15 cc pyrex tube
equipped with a teflon stopcock. The catalyst was heated to 400°C and vacuum
pumped for 1 hour to remove any water adsorbed on the surface. (After reaction,
the catalyst could be reactivated by flowing oxygen over the heated catalyst at
550-600°C for 1 hour.) Reactants were then introduced by means of condensing
the gases onto the catalyst with liquid nitrogen. The reaction tube was sealed
and warmed to room temperature where reaction was allowed to ensue. At the
completion of the pre-determined reaction time, products were desorbed from the
catalyst by first opening the reaction tube to an evacuated U-trap submerged in
liquid nitrogen and then by heating the catalyst to 225°C. Vacuum cross-pumping
through the U-trap was also employed to aid in product transfer. In all studies,
the total desorption time used was 10 minutes.

Benzene-^{11}C. Two studies were performed on catalytic benzene-^{11}C
synthesis from acetylene-^{11}C: (i) the time the reactants were exposed to the
catalyst was varied and (ii) the specific activity of the reacting acetylene-^{11}C
was varied by adding carrier acetylene. In this first study, between 160 and
170 μmole of carrier acetylene was mixed with the acetylene-^{11}C prior to
condensation onto the catalyst. The acetylene was exposed to the catalyst for

5, 10, and 20 minute periods at room temperature and then desorbed by the pro-
cedures previously described. In the second study, the exposure time on the
catalyst was maintained at 10 minutes while between 5 and 170 μmole of carrier
acetylene was mixed with the acetylene-^{11}C for trimerization.

   Benzene-^{11}*C, Toluene-*^{11}*C, Xylene-*^{11}*C.* When a mixture of acetylene and
propyne was added to acetylene-^{11}C prior to catalytic reaction, three carbon-11
labelled aromatic products were generated (benzene, toluene, xylenes) from mixed
acetylene-propyne trimerization. (Trimethylbenzene was also generated from pure
propyne trimerization but was not carbon-11 labelled since acetylene-^{11}C was
the only source of the label.) The exposure to the catalyst was maintained at
10 minutes for all samples reacted in this way. In addition, the total amount
of carrier gas mixed with acetylene-^{11}C was maintained at about 160 μmol;
however, the mol fractions of acetylene and propyne were varied to determine
change in product distribution.

Product Analysis

   All product analyses were carried out using a radio gas chromatograph
equipped with a thermal conductivity response detector and a Wolf flow-through
gas proportional counter (11). A major modification to the standard radio gas
chromatograph was the inclusion of an effluent combustion chamber at the column
outlet (12,13). This combustion chamber, made of 0.2-in.-i.d. quartz tubing
and filled with oxidized copper wool, was operated at 800°C. Here the carbon-11
labelledcompounds were quantitatively oxidized to ^{11}CO$_2$ and H$_2$O. Water was
removed by means of a Mg(ClO$_4$)$_2$ trap located in the exit end of the combustion
chamber, and the ^{11}CO$_2$ radioactivity was measured in the flow-through gas
proportional counter.

   Three gas chromatography columns were used for the analysis of benzene,
toluene and the xylenes: (i) a 16-ft. 20% SE-30 on 50-80 mesh Anakrom ABS column
operated at 120°C; (ii) a 12-ft. 5% bentone 34 + 5% diisodecylphthalate on

60-80 mesh Chromosorb P column operated at 90°C; and (iii) a 12-ft. 20% Apiezon L

on 60-80 mesh Chromosorb P column operated at 120°C. The 5% bentone 34 + 5%

diisodecylphthalate column allowed for complete resolution of the ortho, meta and

para xylene isomers. The carbon-11 labelled products were identified by coin-

jection of authentic samples with the labelled products on these columns.

RESULTS AND DISCUSSION

The radiochemical yields, conditions of reaction, and the degree of

acetylene-^{11}C conversion are summarized in Table I for the benzene-^{11}C synthetic

system. The fraction of acetylene-^{11}C conversion was calculated by dividing the

observed benzene-^{11}C activity (dpm) by the initial acetylene-^{11}C activity (dpm)

after decay and sample corrections were made. The radiochemical yield of

benzene-^{11}C could then be calculated by multiplying this conversion fraction by

the acetylene-^{11}C radiochemical yield for a particular sample.

Results from the time dependence study indicated a greater than four-fold

increase in the reaction conversion for an increase in the catalyst exposure time

from 5 to 10 minutes. Since no further enhancement of reaction was observed when

the exposure time was increased from 10 to 20 minutes, a standard of 10 minute

exposures was set for the remainder of the studies.

Results from Table I on the effects of acetylene-^{11}C dilution on the reaction

conversion are also presented graphically in Figure 1. The % acetylene-^{11}C to

benzene-^{11}C conversion was plotted as a function of the amount of acetylene

carrier (μmol) mixed with acetylene-^{11}C prior to reaction. It can be seen that

with the addition of 5 to 50 μmol of acetylene, the reaction conversion increases

drastically from 1 to 50%. However, further addition of carrier did little to

enhance the reaction. Since high specific activity was a goal, the addition of

even greater quantities of acetylene in order to obtain a near quantitative

benzene yield were not carried out. The extreme cut off at 50 μmol carrier

indicates that a minimum number of catalyst sites must be saturated with

Table I. Preparation of Benzene-^{11}C via the Catalytic Trimerization of Acetylene-^{11}C with Carrier Acetylene.

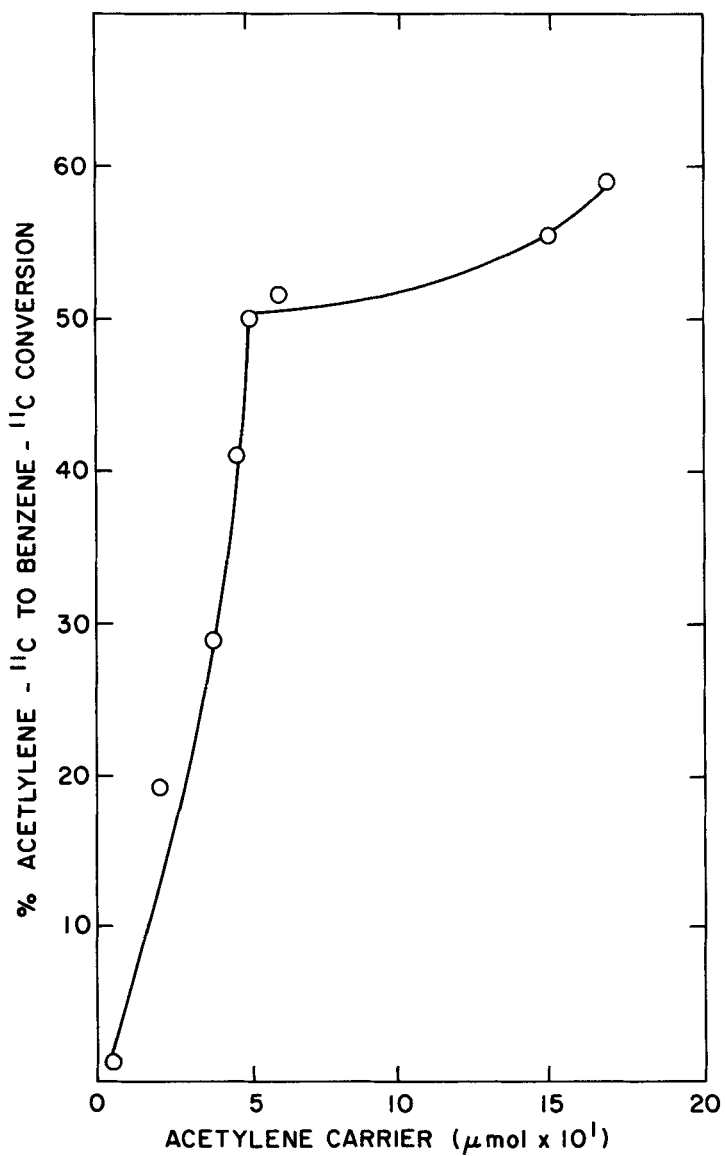| Radiochemical Yield of Acetylene-^{11}C (%)	Amount of Carrier Acetylene (µmol × 10^2)	Catalyst Exposure Time (min)	Radiochemical Yield of Benzene-^{11}C (%)	% Acetylene-^{11}C to Benzene-^{11}C Conversion
46.9	1.79	5	6.4	13.7
49.2	1.89	20	29.0	59.0
47.1	2.20	10	28.0	59.4
45.3	2.04	10	25.0	55.1
47.8	0.62	10	24.8	51.9
49.2	0.61	10	24.6	50.1
49.6	0.45	10	20.3	41.0
47.8	0.38	10	14.1	29.5
45.9	0.26	10	8.9	19.3
47.2	0.03	10	0.7	1.5

FIGURE 1. Catalytic Trimerization of
Acetylene-^{11}C with Carrier
Acetylene Gas.

acetylene before the trimerization reaction can proceed to provide an appreciable yield. (No attempts were made to see if this cut off valve was linearly dependent on the total amount of catalyst used.)

For those samples with a 50% or greater conversion, the average recovery of unreacted acetylene-^{11}C was measured at 8.5%. The fate of the remaining acetylene-^{11}C was presumably due to some catalytic polymerization process, since no other detectable carbon-11 labelled compounds were desorbed from the catalyst.

The radiochemical yields, reaction conditions, and the degree of acetylene-^{11}C conversion are summarized in Table II for the mixed benzene-^{11}C, toluene-^{11}C and xylene-^{11}C synthetic system. Catalyst exposure times of 10 minutes were set for all samples. Generally, between 170 and 200 μmol total of acetylene + propyne carrier were employed where the mol fraction ratio of these compounds was varied per sample. The average conversion was calculated to be 50.2%. This corresponded to the cut off value observed for the pure acetylene system in Figure 1.

The radiochemical yields, presented in Table II, for the three carbon-11 labelled trimerization products were plotted in Figure 2 as a function of the acetylene/propyne carrier mol fraction. As the acetylene mol fraction was increased from 0.01 to 1.0, the benzene-^{11}C yield increased linearly from 1.5 to 25% (the 25% yield was an average of four pure acetylene samples). This is to be expected since benzene-^{11}C formation does not depend on the competitive reactivities of acetylene and propyne carriers in the trimerization, but on the extent of acetylene dilution by propyne. On the other hand, the distributions of toluene-^{11}C and the xylenes-^{11}C would be dependent on the relative reactivities of these two carriers. As can be seen in the figure, the toluene-^{11}C yield passed through a maximum of about 15% at an acetylene/propyne molar composition of .30/.70, while the xylene-^{11}C yield decreased exponentially to zero at a composition ratio of .76/.24. One could of course correct the distribution of yields for the statistical chances of acetylene-^{11}C being involved in the trimerization. (This correction would require dividing the yields of benzene-^{11}C,

Table II. Preparation of Benzene-^{11}C, Toluene-^{11}C and Xylene-^{11}C from the Catalytic Trimerization of Acetylene-^{11}C with Carrier Acetylene + Propyne

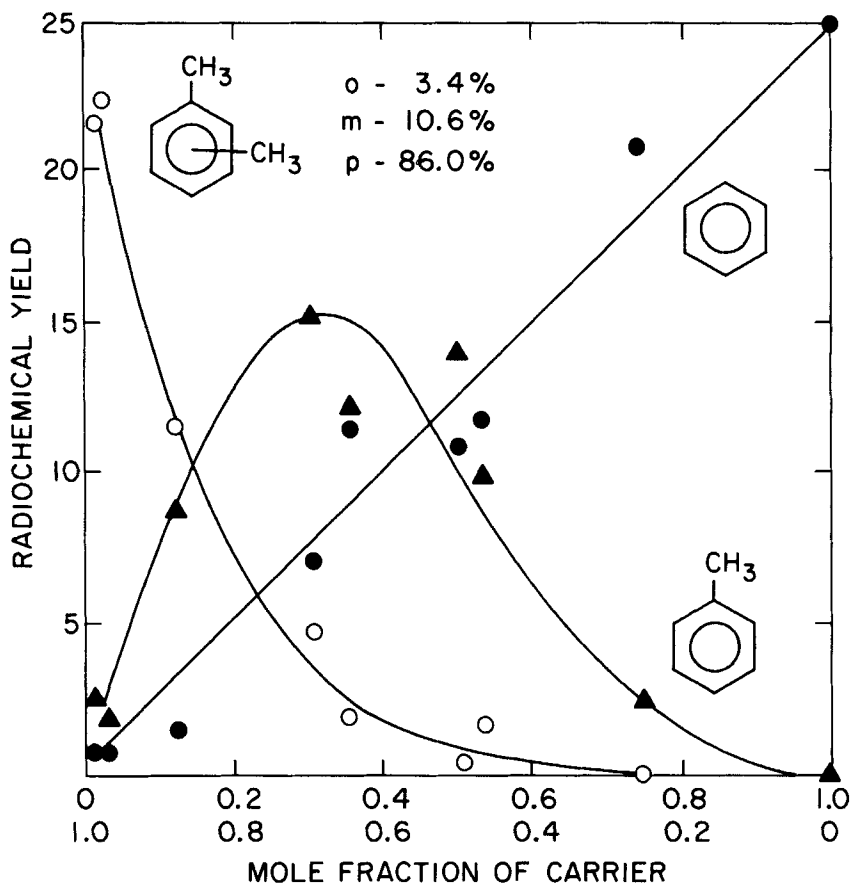| Radiochemical Yield of Acetylene-^{11}C (%)	Amount of Carrier (μmol × 10²)		Catalyst Exposure Times (min)	Radiochemical Yields (%)			Acetylene-^{11}C Conversion (%)			
	C_2H_2	C_3H_4		Benzene-^{11}C	Toluene-^{11}C	Xylene-^{11}C	Benzene-^{11}C	Toluene-^{11}C	Xylene-^{11}C	Total
50.2	1.49	0.50	10	21.9	2.5	0	43.6	5.0	0	48.6
47.8	1.10	0.98	10	11.7	9.8	1.6	24.5	20.5	3.4	48.4
50.1	1.69	1.69	10	10.7	14.1	0.25	21.4	28.2	0.5	50.0
48.7	1.20	2.42	10	11.3	10.8	1.6	23.2	22.2	3.3	51.3
49.9	0.63	1.42	10	7.2	15.9	4.8	14.5	31.8	9.6	55.9
47.2	0.25	1.77	10	1.3	8.5	11.3	2.7	18.1	24.0	44.8
50.6	0.02	1.70	10	0.7	2.8	23.3	1.4	5.5	46.0	52.9
45.2	0.02	1.76	10	0.1	2.3	20.0	0.3	4.9	44.3	49.5

FIGURE 2.   Catalytic Trimerization of Acetylene-^{11}C
with Carrier Acetylene + Propyne Gases.

toluene-^{11}C and xylene-^{11}C by 3, 2 and 1, respectively.) The effect of this

correction was to shift the toluene-^{11}C maximum from a molar composition of

.30/.70 (acetylene/propyne) to .38/.62. This suggests that acetylene is approx-

imately 1.6 times more reactive than propyne towards catalytic trimerization.

Preliminary studies to distinguish between the individual xylene-^{11}C isomers

have shown a relative distribution for ortho, meta and para xylenes-^{11}C of

3.4%, 10.6%, and 86.0%, respectively. Statistically, one would expect a distribution of 25%, 50%, and 25% for the respective isomers. It is not known whether the apparent regiospecificity of this trimerization is attributable to steric hindrance or electron density effects from the methyl group on propyne. Further studies are presently being performed to shed some light on this question.

This catalytic approach to ring labelling of aromatics may be of value in radiopharmaceutical synthesis where uniformly and/or randomly ring labelled aromatic precursors are required. The rapid synthesis of labelled aromatics in high yield and high specific activity make this approach favorable. It should be further noted that even greater advantages from this method may be gained when considering ring labelling with carbon-14 where the pressures of time are not determining. Because of the high yield and simplicity of experimental procedure it has distinct advantages over some of the published procedures for benzene-^{14}C (14, 15, 16), toluene-^{14}C (17, 18) and other ^{14}C-labelled aromatic syntheses (19).

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