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TWO-THREE STEPS SYNTHESES OF [^{14}C-ring]o-XYLENE, [^{14}C-ring]o-TOLUIC ACID ; [^{14}C-ring]-PHTHALIC ACID FROM [^{14}C] BARIUM CARBONATE

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SUMMARY

Cocyclotrimerisation of [$^{14}C_2$] acetylene with 2-butyne gave [3,4,5,6-$^{14}C_4$] ortho-xylene (50 % overall yield based on [^{14}C] $BaCO_3$). 93 % Nitric acid oxidation at 145 °C for 55 hours of the crude [3,4,5,6-$^{14}C_4$] ortho-xylene gave [3,4,5,6-$^{14}C_4$] ortho-toluic acid (25 % overall yield based on [^{14}C] $BaCO_3$). Under the same set of reaction conditions but in a sealed tube the crude [3,4,5,6-$^{14}C_4$] ortho-xylene gave [3,4,5,6-$^{14}C_4$] phthalic acid (50 % overall yield based on [^{14}C] $BaCO_3$) (specific activity 1.6 GBq.mmol^{-1}).

Key words : [^{14}C] acetylene, [^{14}C] xylene, [^{14}C] toluic acid, [^{14}C] phthalic acid

DISCUSSION

The cyclotrimerisation of [^{14}C] acetylene to [U-^{14}C] benzene was achieved by C. BARET and L. PICHAT in 1957 in these laboratories using the Reppe's catalyst : Ph_3 $PNi(CO)_2$ (1). This reaction was carried out under 15 at. of [^{14}C] acetylene in acetonitrile. More recently this trimerisation was realised more conveniently at room temperature and atmospheric pressure (2) in presence of a silica alumina supported activated potassium chromate (2). This high yielding method of preparation of [$^{14}C_6$] benzene has been used in this laboratory for several decades. From [$^{14}C_6$] benzene a large array of diversely substituted [$^{14}C_6$] benzenes were prepared mainly via [U-^{14}C] aniline (3, 4, 5, 6, 7, 8). However, this strategy is often quite time consuming because many steps are required to place in the

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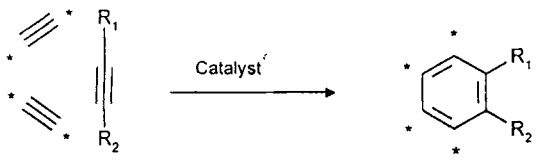
proper order the various requested substitutions on the [$^{14}C_6$] benzene. On certain occasions the "cocyclotrimerisation" of [$^{14}C_2$] acetylene with unlabelled substituted alkynes :



$R_1 = CH_3$; $R_2 = H$ (9) ; $R_1 = CH_2$ - C(NHCHO) $(CO_2Et)_2$ $R_2 = H$ (10)
$R_1 = CH_3$: $R_2 = CH_3$ (11, 14)

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was used to advantage. Our first report of the cotrimerisation of [$^{14}C_2$] acetylene with propyne in presence of Reppe's catalyst in isooctane at 100 °C in a Conference Review (9). The cocyclotrimerisation of [$^{14}C_2$] acetylene with diethyl 2-formamido-2-(3-propynyl) malonate in acetonitrile at 80 °C for 12 hours, followed by hydrolysis and purification by chromatography successively on a Dowex 50 column and Sephadex resulted in a rather unusual synthesis of [2',3',4',5'-$^{14}C_4$] DL-phenylalanine in a 14 % overall yield based on [^{14}C] $BaCO_3$ (10). A preparation of [2,3,4,5-$^{14}C_4$] o-xylene from [$^{14}C_2$] acetylene and 2-butyne in presence of Reppe's catalyst was issued from CEA-SMM in 1972 when this [$^{14}C_4$] xylene was necessary in a custom synthesis of "xibornol" (6-isobornyl-3,4[2,3,4,5-$^{14}C_4$] xylenol) (11). Others (12) cocyclized [^{11}C] acetylene and propyne over a silica alumina supported activated potassium chromate catalyst into [^{11}C] xylenes, a mixture of ortho : 3.4 % ; meta 10.6 % ; para : 86 %. This distribution might be due to the steric hindrance or electron density effects of the methyl group of propyne. [^{3}H-ring] Toluene was also obtained by the same technique (13) [^{3}H-ring] xylene being a side product of the reaction.

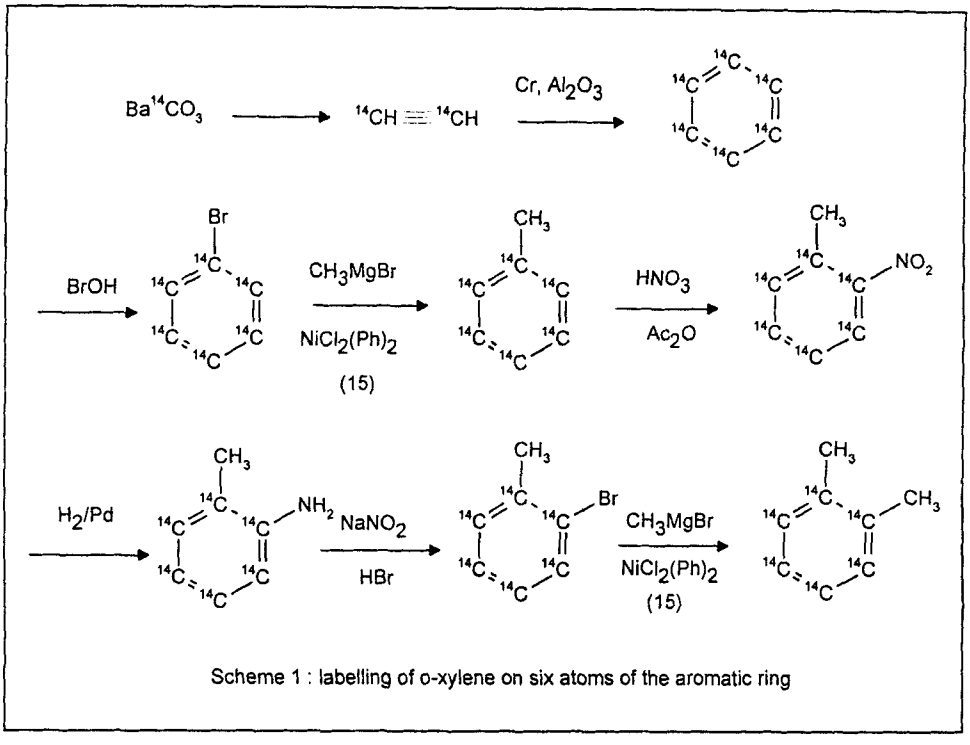
The same catalyst "Perlkatalysator New" (Kalie Chemie AG - Hanover) was used in this laboratory to achieve the cotrimerisation of [$^{14}C_2$] acetylene with 2-butyne into [2,3,4,5-$^{14}C_4$] o-xylene necessary for the production of a new batch of [^{14}C] xibornol (14).

Recently we were interested in [^{14}C-ring] o-xylene, [^{14}C-ring] o-toluic acid and [^{14}C-ring] phthalic acid as starting materials for the elaboration of more complex molecules useful in environmental chemistry.

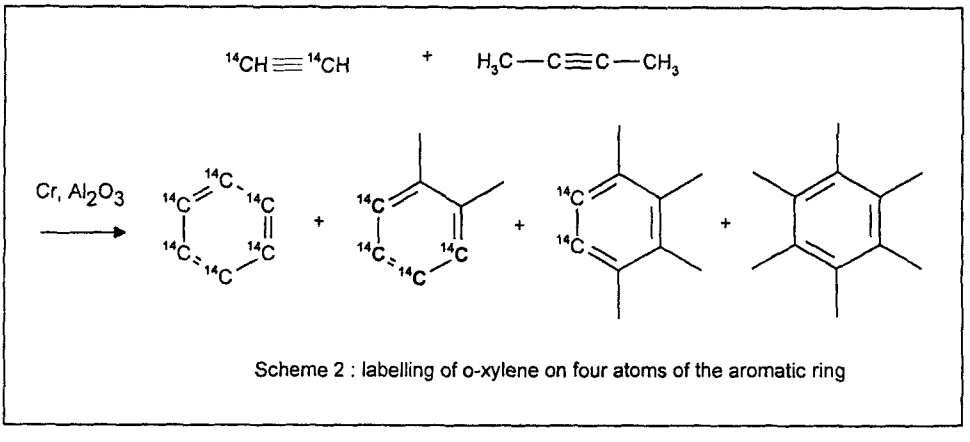
[$^{14}C_6$-ring] o-xylene could have been prepared from [$^{14}C_6$] benzene following scheme 1 via [$^{14}C_6$] bromobenzene (3) [$^{14}C_6$-ring] toluene (5) in a 8 steps synthesis from [^{14}C] $BaCO_3$ with a rather low overall yield (# 5 %).

We preferred to use the approach based on the catalytic cotrimerisation (scheme 2) of [$^{14}C_2$] acetylene with 2-butyne already alluded to (11, 14) which we describe now in detail in the experimental part.

The oxidation of polyalkylated benzene compounds can be achieved with potassium permanganate, ozone, nitric acid or chromic nitrates (18). Oxidation is enhanced by attracting effects on aromatic ring but this is not the case for o-xylene. Preparation of o-toluic acid from o-xylene is commonly obtained by nitric acid (19) or ozonation (20). p-Toluic acid is obtained from p-xylene with a quantitative yield by potassium permanganate oxidation and a phase transfer catalyst (21). Using these mild operating



Scheme 1 : labelling of o-xylene on six atoms of the aromatic ring

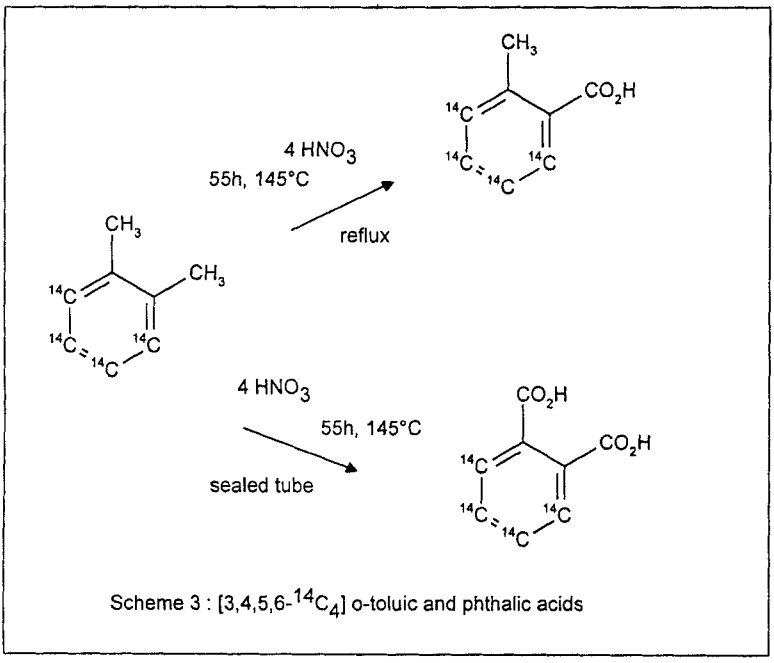


Scheme 2 : labelling of o-xylene on four atoms of the aromatic ring

conditions we did not obtain o-toluic acid from o-xylene. This is due to the steric hindrance of the two adjacent methyl groups of the o-xylene. We decided to use the nitric acid method.

Direct oxidation of the crude mixture of aromatics obtained by cocyclisation of [$^{14}C_2$] acetylene and 2-butyne leaves the [U-^{14}C] benzene unchanged. The oxidation products were easily separated by alcaline extraction followed by chromatographic purification. The main advantage of this method is that it is one only three steps route to [3,4,5,6-$^{14}C_4$] o-toluic acid from [^{14}C] barium carbonate. The yield was 50 % from [3,4,5,6-$^{14}C_4$] o-xylene as reported in (8) for the unlabelled product.

When the oxidation was conducted in a sealed tube, [3,4,5,6-$^{14}C_4$] phthalic acid was obtained with a quantitative yield from [3,4,5,6-$^{14}C_4$] o-xylene. This is a new and fast preparation of [^{14}C] phthalic acid in three steps from [^{14}C] barium carbonate with a 50 % overall yield (scheme 3).



Scheme 3 : [3,4,5,6-$^{14}C_4$] o-toluic and phthalic acids

EXPERIMENTAL

Materials

Barium carbonate, specific activity : 2.035 GBq.mmol^{-1}, was obtained from Nordion International Inc.

The catalyst (KC Perkator D1) has the following formula : SiO_2 (approx. 90 %), Al_2O_3 (approx. 10 %), activated by Cr_2O_3 (approx. 0.1 %). The catalyst, in the form of 2 mm pellets, is commercially available from the Solvay Catayst Company.

All reagents and authentic samples were purchased from Fluka (analytical grade).

The yields were determined by weighings in the unlabelled studies or by scintillation counting in the studies with labelled products.

Products analyses

G.P.C. analyses for benzene, xylene and side-products were carried on a Varian 3300 with FID detector and proportionnal gas counter for radioactive detection after the products were reduced in [^{14}C] methane on platinum at 750 °C (Raga from Raytest). The column was a 30 m DB-1 Megabore (J.W. Scientific) operating with temperature gradient from 45 °C to 100 °C. [^{14}C] labelled products were identified by coinjection with authentic samples.

H.P.L.C. analyses for o-toluic acid and phthalic acids were carried on Zorbax C-18 column eluted with 1-heptanesulfonic acid, sodium salt (5 mM) : 90 % and acetonitrile : 10 %. The detections were ensured

by U.V. detector at 260 nm and radioactive scintillation detector. [^{14}C] o-Toluic acid and side-products can be purified by preparative H.P.L.C. on Zorbax SAX NH_4^+ 25 x 1.25 cm ; elution with water : 90, acetonitrile : 10, acetic acid : 0.5.

$^{14}C_2$ acetylene

$^{14}C_2$ acetylene was obtained by a modification of Cox's method (4, 16, 17) in which barium metal is replaced by calcium with a quantitative yield from barium carbonate. 6.78 g of unlabelled $BaCO_3$ (34 mmol) were mixed with 1.6 g of $Ba^{14}CO_3$ (8 mmol - 2.035 GBq.mmol^{-1} - total activity 16.28 GBq) and 21.3 g of calcium (particle size : 0.6 mm - 1.2 mm). [$^{14}C_2$] Acetylene was gauged in a standard vacuum apparatus. 470 mL of gaseous [$^{14}C_2$] acetylene (21 mmol - specific activity : 790 MBq.mmol^{-1} - total activity : 16.59 GBq) were obtained. Gaseous [$^{14}C_2$] acetylene was dried over phosphorus pentoxide.

[3,4,5,6-$^{14}C_4$] o-xylene

The catalyst (42 g) was placed in a reacting tube under vacuum. It was heated at 300 °C overnight under dynamic vacuum. The temperature was allowed to cool to 50 °C. Gaseous [$^{14}C_2$] acetylene (470 mL - 21 mmol - 16.59 GBq) was mixed with 1.6 mL of 2-butyne (21 mmol - 470 mL in gaseous form expanded in the gauge) in the standard vacuum apparatus. The capacity of the gauge (2650 mL was calculated to allow a good expansion of the gaseous mixture to have the best homogeneity). The gaseous mixture was statically vacuum transferred onto the catalyst at 50 °C. The adsorption was followed with the vacuum manometer. After two hours, the adsorption was complete. The transfer was ended with the aid of liquid nitrogen into a side flask connected to the reacting tube. The reacting tube was isolated from the rest of the apparatus and allowed to react one more hour at 50 °C. [3,4,5,6-$^{14}C_4$] o-xylene and by products were transferred under vacuum and trapped into a by-pass cooled at - 80 °C and -196 °C. G.P.C. analysis showed [U-^{14}C] benzene (R_t : 3.45 mn) : 11 %, [3,4,5,6-$^{14}C_4$] o-xylene (R_t : 6.13 mn) : 82.7 % and [5,6-$^{14}C_2$] tetramethyl benzene (R_t : 17.60 mn) : 5.3 %. The radioactive yield was 50 % from barium carbonate.

[3,4,5,6-$^{14}C_4$] o-toluic acid

The crude [3,4,5,6-$^{14}C_4$] o-xylene (5 mmol - 8.14 GBq) was vacuum transferred into a cone-shaped flask containing 1.2 mL (26.4 mmol) of 93 % nitric acid and 2.4 mL of water sealed to a reflux condenser. The reflux was maintained with an oil bath at 145 °C for 55 hours. At the end of the reaction, a yellow solid was present at the surface of the solution. The reaction mixture was taken up with diethyl ether and water. For safety reasons, the radioactive solutions were transferred with a teflon tube gently sucked out with vacuum pump. The extraction of the ethereal solution with 1N sodium hydroxyde was carried out in a fume hood to avoid contamination of the air with the residual [^{14}C] xylene present in the ethereal extract. Unreacted aromatics, (4 GBq) including 84 % [3,4,5,6$^{14}C_4$] o-xylene, were present in the residual ethereal phase. The aqueous phase was acidified and extracted with diethyl ether. 4 GBq of [3,4,5,6-$^{14}C_4$] o-toluic acid were obtained (50 % yield from [3,4,5,6-$^{14}C_4$] o-xylene). The purity of the acid, determined by H.P.L.C. was 95 % (R_t : 6.7 mn). ^{1}H(Dioxane D_8) N.M.R. spectra was identical to an authentic sample : ppm : 7.9 (d 1H Ar) ppm : 7.45 (m 1H Ar) ppm : 7.25 (m 2H Ar) ppm : 2.6 (s 3H Me). The specific activity was 1.6 GBq.mmol^{-1} (mass spectrometry : DCI/CH_4).

[3,4,5,6-$^{14}C_4$] phthalic acid

The crude [3,4,5,6-$^{14}C_4$] o-xylene (5 mmol - 8.14 GBq) was vacuum transferred in a thick Pyrex tube containing 1.2 mL (26.4 mmol) of 93 % nitric acid and 2.4 mL of water. The tube was sealed under vacuum and placed inside a steel autoclave containing water to exercise a counter pressure against the Pyrex tube. The autoclave was maintained in an oil bath at 145 °C for 55 hours. The sealed tube contained a white solid. It was cooled and opened in a fume hood. The reaction mixture was taken up with diethyl ether and water. For safety reasons, the radioactive solutions were transferred with a Teflon tube gently sucked out with a vacuum pump. The [^{14}C] phthalic acid was extracted with 1N sodium hydroxyde. The residual ethereal solution contained unreacted aromatics ([U^{14}C] benzene present in the crude mixture of [^{14}C] o-xylene). The aqueous phase was acidified and extracted with diethyl ether to give [3,4,5,6-$^{14}C_4$] phthalic acid (8 GBq) (98 % yield from [3,4,5,6-$^{14}C_4$] o-xylene. The radiochemical purity was 99 % checked by H.P.L.C. (R_t : 12.7 mn). ^1H (CD_3CN) N.M.R. spectra was identical to an authentic sample of phthalic acid : ppm : 7.8 (m, 2H Ar) ppm : 7.6 (m, 2H Ar) ; specific activity 1.6 GBq.mmol^{-1} (mass spectrometry : DCI/CH_4).

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