SYNTHESIS OF PHENYL[1-^{14}C]ACETYLENE AND 1,4-DIPHENYL[1,4-$^{14}C_2$]BUTADIYNE

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SUMMARY

Phenyl[1-^{14}C]acetylene (0.012mCi/mmole) was synthesized in 12.5% yield from [1-^{14}C]acetic acid through [1-^{14}C]acetophenone, its semicarbazone, and 4-phenyl-[4-^{14}C]1,2,3-selenadiazole obtained by selenium dioxide oxidation. Oxidative coupling gave 1,4-diphenyl[1,4-$^{14}C_2$]butadiyne in 80% yield.

Keywords: Phenyl[1-^{14}C]acetylene, 1,4-diphenyl[1,4-$^{14}C_2$] butadiyne.

RESULTS AND DISCUSSION

1,4-Diphenylbutadiyne (DPB) was recently discovered to possess photoantibiotic activity[1,2], and the investigation of the mechanism of action *in vivo* required the use of a radioactive tracer. Since the synthesis of ^{14}C-labelled DPB had not been reported in the literature, we performed it as shown in Scheme 1. The last step represents the oxidative coupling of a suitably labelled phenylacetylene, and applies the most general procedure for the synthesis of symmetrical 1,3-diacetylenic compounds.[3-5]

The synthesis of phenylacetylene labelled with ^{14}C at either one of the triple bond carbon atoms has not been reported, but the ^{13}C-labelled analogs are known. The isomer labelled at the 1-position was obtained from [carboxyl-^{13}C]benzoic acid, which was itself prepared by reaction of phenyl magnesium bromide with [^{13}C] carbon dioxide generated from barium [^{13}C]carbonate.[6-8] The same Grignard reagent, when reacted with [2-^{13}C] acetonitrile, was converted into phenyl[2-^{13}C]acetylene following the reduction of the labelled acetophenone into an alcohol,

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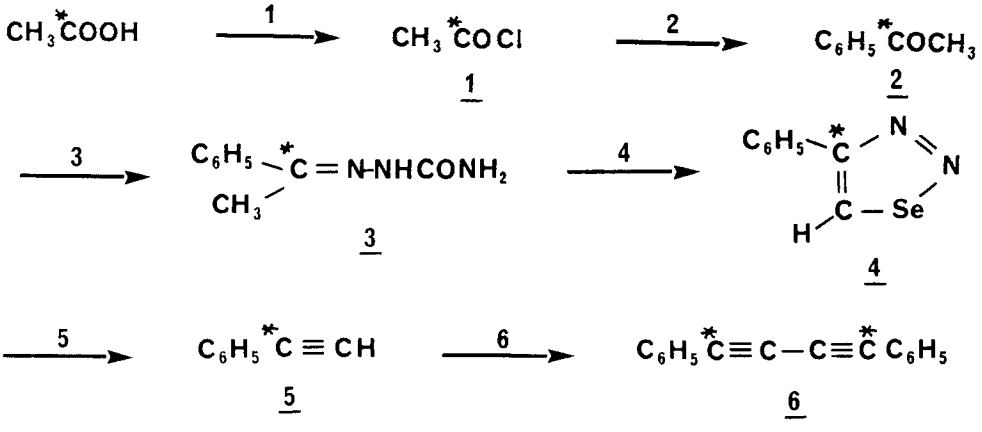
dehydration to styrene, bromination, and double dehydrobromination.[9]

Either of the above procedures could certainly have been followed to make the ^{14}C-labelled phenylacetylenes, but instead we used a different approach based on introducing an acetyl group onto the phenyl ring using [1-^{14}C]acetic acid as precursor, and converting the semicarbazone of the labelled acetophenone into phenyl[1-^{14}C]acetylene in only two steps, utilizing the procedure developed by Lalezari et al.[10]

[1-^{14}C]Acetic acid was treated with phosphorous trichloride and converted into [1-^{14}C]acetyl chloride (1) in 58% yield. Friedel-Crafts acylation of benzene with this product in the presence of aluminum chloride afforded [1-^{14}C]acetophenone (2) in 73.6% yield. Its semicarbazone (3) was oxidized with selenium dioxide in glacial acetic acid to give 4-phenyl-[4-^{14}C]1,2,3-selenadiazole (4) in 65% yield, which upon subsequent pyrolysis at 180 °C in the presence of sand furnished phenyl[1-^{14}C]acetylene (5) in 50% yield. The oxidative coupling of 5 with cuprous ion as described by Fritzsche et al.[5] gave in 80% yield the desired 1,4-diphenyl[1,4-$^{14}C_2$]butadiyne (6, 0.0245mCi/mmole).

Scheme I



Reagents: 1. PCl_3, C_6H_6 ; 2. C_6H_6, $AlCl_3$; 3. $NH_2CONHNH_2$, MeOH, pyridine ; 4. SeO_2, AcOH ; 5. 180 °C ; 6. Cu_2Cl_2, O_2, DME, TMEDA.

EXPERIMENTAL

[1-^{14}C]Acetic acid (0.25 mCi,4.0 mCi/mmole) was purchased from New England Nuclear, Boston. The radioactivity measurements were made with a 6801-6806 Nuclear-Chicago liquid scintillation counter. All melting points are uncorrected, and the identity of the reaction products was ascertained by the comparison of the melting points and undepressed mixture melting points with authentic non-radioactive samples.

[1-^{14}C] Acetyl chloride (1). [1-^{14}C]Acetic acid (3.8 mg, 0.063 mmole, 0.25 mCi,4.0 mCi/mmole) was transferred in a vacuum line into a 50 ml three-necked flask which contained 1 ml of dry acetic acid, and which was cooled in liquid nitrogen. The flask was removed after one hour, and was equipped with a condenser and a dropping funnel. Freshly distilled phosphorous trichloride (0.7 ml, 8.0 mmole) was added dropwise over 15 min while the mixture was stirred in a water bath. After further stirring at ambient temperature for 15 min and at 40-50 °C for 30 min, the mixture was cooled, and two layers formed. The upper one was carefully transferred with a pipette into a dry flask, and was treated with one drop of glacial acetic acid to destroy any phosphorous esters present. Distillation of the residue gave 0.800 g (10.2 mmole, 58% yield) of [1-^{14}C]acetyl chloride (1), b.p. 50-52 °C.[11]

[1-^{14}C] Acetophenone (2). To a cold suspension of powdered aluminum chloride (1.5 g, 11.2 mmole) in 5.0 ml of thiophene-free dry benzene was added a solution of 0.800 g (10.2 mmole) of 1 in 2 ml of benzene over a period of 30 min. The mixture was heated on a water bath at 50 °C for 1 hr, then cooled and poured into a mixture of 5 ml of conc. hydrochloric acid and 50 g of crushed ice, and finally extracted with three 25 ml portions of ether. The combined extracts were washed with 5% aqueous sodium hydroxide

and with water, dried over anhydrous magnesium sulfate, and concentrated to give a light yellow syrup which was distilled under reduced pressure to give [1-^{14}C]acetophenone (2, 0.900 g, b.p. 90-92 °C/20 Torr)[12] in 73.6% yield.

[1-^{14}C]Acetophenone semicarbazone (3). To a solution of 2 (0.900 g, 7.5 mmole) in methanol (15.0 ml) was added 0.910 g (8.2 mmole) of semicarbazide hydrochloride in 9.0 ml of water, followed by 0.75 ml of pyridine. The mixture was warmed gently on a water bath until some crystals appeared, and was then cooled and filtered. The solid was recrystallized from methanol and gave 1.270 g (96% yield) of [1-^{14}C]acetophenone semicarbazone (3), m.p.199 °C,[13] with a specific activity of 0.012 mCi/mmole.

4-Phenyl-[4-^{14}C]1,2,3-selenadiazole (4). Powdered selenium dioxide (0.8 g, 7.2 mmole) was added gradually to a solution of 3 (1.25 g,7.1 mmole) in glacial acetic acid (15 ml). The reaction mixture was stirred first at room temperature for 1 hr, and then on a steam bath (2 hr) until the evolution of nitrogen ceased. The mixture was filtered while hot to remove the selenium, and was diluted with 100 ml of water. Light brown flakes appeared, which were filtered and crystallized from dilute acetone to produce 4 (0.96 g, m.p. 76 °C)[10] in 65% yield.

Phenyl[1-^{14}C]acetylene (5). An intimate mixture of 4 (0.96 g, 4.6 mmole) and sea sand (2.0 g) was pyrolyzed at 180 °C in a flask connected to a vacuum line at 0.5 Torr, and 0.235 g (50% yield) of 5 was collected in a vessel kept in liquid nitrogen. The specific activity of 5 was 0.012 mCi/mmole.

Diphenyl[1,4-$^{14}C_2$]butadiyne (6). Cuprous chloride (10 mg, 0.1 mmole) was added to 0.5 ml of dimethoxyethane (DME). After stirring for 10 min, tetramethylethylenediamine (TMEDA, 17.5 mg, 0.16 mmole) was added. The stirring was continued for 15 min, 50 mg of 5 (0.5 mmole) was added, and the mixture was stirred at

30-35 °C for 1 hr while being flushed with air. The black mixture was poured into water, producing a blue solution which was extracted with three 15 ml-portions of ether. The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to give a light yellow solid which was recrystallized from ethanol to yield 40 mg (80% yield) of 6 as colorless needles, m.p. 84-86 °C^{14}, with a specific activity of 0.0245 mCi/mmole.

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