

PREPARATION OF CARBON 14-LABELLED "SPY DUST"

5-(4-NITROPHENYL)-2,4-[5-<sup>14</sup>C]PENTADIENAL, (NPPD)

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SUMMARY

Preparation of carbon 14-labelled "Spy Dust", 5-(4-nitrophenyl)-2,4-[5-<sup>14</sup>C]pentadienal is described. The facile synthesis of 4-nitro[formyl-<sup>14</sup>C]benzaldehyde from 1-iodo-4-nitrobenzene by reaction with K<sup>14</sup>CN/CuCN, followed by reduction with diisobutylaluminum hydride provided this key intermediate in 50% yield. Subsequent treatment with the resonance-stabilized ylide, formylmethylenetriphenylphosphorane, afforded the title compound.

Key Words: Spy Dust, 5-(4-nitrophenyl)-2,4-[5-<sup>14</sup>C]pentadienal, NPPD, 4-nitro[formyl-<sup>14</sup>C]benzaldehyde.

INTRODUCTION

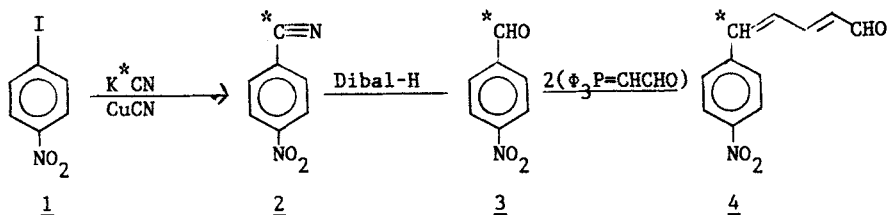
There has been considerable interest in the toxic and biological properties of "Spy Dust" in recent months (1-5). The reported use of 5-(4-nitrophenyl)-2,4-pentadienal (NPPD) by the Soviet Union to track the activities of United States citizens stimulated the State Department to investigate the possible health hazards of this chemical. We have developed a three-step synthesis for the preparation of the carbon 14-labelled analog of this compound which yields highly pure material of moderate specific activity (10.1 mCi/mmmole).

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## RESULTS AND DISCUSSION

The sequence used to prepare the title compound is shown below.



Commercially available 1-iodo-4-nitrobenzene (1) was converted to 4-nitro[cyano-<sup>14</sup>C]benzonitrile (2) via the Rosenmund-von Braun reaction (6). The conversion of this material directly to 4-nitro[formyl-<sup>14</sup>C]benzaldehyde (3) via reduction with diisobutylaluminum hydride in 59% yield was a substantial improvement over other more commonly used multi-step procedures which involve the hydrolysis of the nitrile to the acid and subsequent reduction to the aldehyde. Condensation of 3 with two equivalents of formylmethylenetriphenylphosphorane afforded the desired compound. Isolation of the intermediate, 4-nitrocinnamaldehyde, did not improve in yield. Two sequential additions of phosphorane resulted in the one-step conversion of 3 to the title compound in approximately 54% yield. The final isolation and purification was accomplished by preparative HPLC.

## EXPERIMENTAL

4-Nitro[cyano-<sup>14</sup>C]benzonitrile (2)

A mixture of 1-iodo-4-nitrobenzene (1) (2.86 g, 11.5 mmol), CuCN (0.65g, 7.5 mmol), K<sup>14</sup>CN (0.230 g, 3.5 mmol, 187 mCi) and pyridine (1.5 mL)\* was heated in a Wood's Metal bath at 210°C for two hours under Argon (6). The reaction mixture was allowed to cool and ammonium hydroxide (25 mL) was added with stirring. Water (50 mL) was added and the mixture was extracted with benzene:ether (1:1, 5 x 50 mL). The organic layers were combined, washed

\*In a subsequent preparation, the yield was improved to 80% by increasing the amount of pyridine to 3.5 mL.

with water until neutral to pH paper, washed with saturated sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was chromatographed on a 3.5 x 23 cm column of silica gel prepared and eluted with benzene, to yield 1.3 g (85 mCi, 45%).

#### 4-Nitro[formyl-<sup>14</sup>C]benzaldehyde (3)

Compound 3 was prepared by slowly adding diisobutylaluminum hydride (Dibal-H, 3.0 mL, 16.9 mmol) in 7 mL of benzene, to a solution of 2 (85 mCi, 1.25 g, 8.4 mmol) (7). The rate of addition was controlled to maintain a reaction temperature of 24°C. The reaction mixture was allowed to stir for one hour and methanol (2 mL) was added to quench the reaction. The reaction mixture was poured into dilute H<sub>2</sub>SO<sub>4</sub> and extracted with methylene chloride (4 x 50 mL). The organic layers were combined, washed with water until neutral, washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The crude product was absorbed onto 5 grams of silica gel from methylene chloride and applied as a dry powder onto a column of silica gel (23 x 2 cm) prepared in benzene and the product was eluted with benzene. The product-containing fractions were collected and concentrated to afford 50 mCi (59% radiochemical yield) of 3.

#### 5-(4-nitrophenyl)-2,4-[5-<sup>14</sup>C]pentadienal (4)

Freshly prepared formylmethylenetriphenylphosphorane (8), (2 g, 6.5 mmol) was added to a solution of 3 (50 mCi, 4.9 mmol) and the mixture was heated at reflux for 24 hours under argon (9). An additional 2 grams of phosphorane were added and reflux was continued for an additional 24 hours. The solvent was gently removed under a stream of argon, the compound absorbed onto silica gel from methylene chloride and then applied as a dry powder to a silica gel column (2 x 10 cm) prepared in benzene. The compound was eluted with benzene and 30 mCi of 90% pure product was isolated. Final purification was achieved by reverse phase preparative HPLC (Waters 500A, Magnum 40 stainless steel column, Partisil prep 40-C18 ODS-3, water/acetonitrile (1:1), at 200 mL/min), to yield 14.7 mCi (29% radiochemical yield) of 5-(4-nitrophenyl)-2,4-[5-<sup>14</sup>C]pentadienal,

analyzed by HPLC to be chemically and radiochemically >99% pure, with a specific activity of 10.1 mCi/mmol. HPLC conditions for final analysis for chemical purity were developed on a Whatman Partisil 5, ODS-3 column with a mobile phase consisting of water/acetonitrile (55:45) at a flow rate of 1 mL/min. The retention time of the product was 12.2 minutes. Radiochemical purity was determined with the Radiomatic HP-Flo One with a total flow rate of 2.7 mL/min. An authentic standard was supplied by NIEHS.

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