

A FACILE MICROSYNTHESIS OF ^{14}C -LABELLED PICENE

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SUMMARY

Microscale Wittig olefination of commercially available [7- ^{14}C]-benzaldehyde of high specific radioactivity with aryl bromomethyl phosphonium salt and subsequent oxidative photocyclisation affords pure ^{14}C -labelled picene in efficient yield.

Key Words: [7- ^{14}C]-Benzaldehyde, Wittig-Reaction, Photocyclisation, [5- ^{14}C]-Picene, Polycyclic Aromatic Hydrocarbons

INTRODUCTION

^{14}C -labelled polycyclic aromatic hydrocarbons (PAHs) are required for studying the biological action of these compounds. Some of the PAHs have been shown to exert considerable carcinogenic, mutagenic and/or cytotoxic effects (1-5), whereas others seem to have no or only marginal biological activity. A PAH belonging to the second class is picene - a constituent of lignite tar and a pollutant from combustion processes (6-9). Although picene has been reported to be non-carcinogenic (10,11) it appeared to be a weak papilloma initiator (12). In order to study its metabolism (13) ^{14}C -labelled picene was needed.

RESULTS AND DISCUSSION

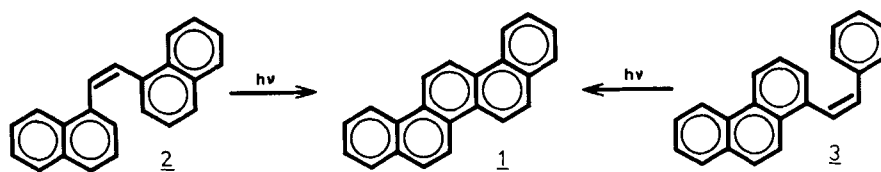
Unlabelled picene 1 has been prepared by photocyclisation (14) of 1,2-di-(1-naphthyl)-ethylene 2 (15). In the course of this reaction the central phenanthrene unit of picene is formed. An alternative photochemical approach to

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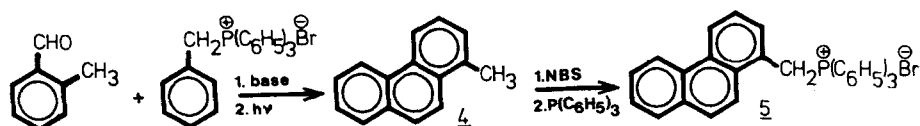
picene would involve the peripheral phenanthrene unit and start from 1-phenyl-2-(1-phenanthryl)-ethylene 3 (Scheme 1). This latter reaction has only been the subject of theoretical considerations by Laarhoven (16). Neither of these photocyclisations have been employed for the synthesis of picene derivatives, although photocyclisation is a well known approach to various other PAHs (17-19). As [7-¹⁴C]-benzaldehyde of very high specific activity (57 Ci/mol) was commercially available, 3 was synthesized via Wittig olefination of benzaldehyde with



Scheme 1

(1-phenanthryl)methyltriphenyl phosphonium bromide 5 followed by irradiation to yield picene.

Phosphonium salt 5 was prepared in 41 % total yield on a 0.1 mol scale by reaction of *o*-tolylaldehyde with benzyl triphenyl phosphonium bromide, oxidative photocyclisation of the resulting 2-methylstilbene to 1-methylphenanthrene 4, bromination of 4 with *N*-bromosuccinimide and reaction of the resulting bromide with triphenyl phosphine (Scheme 2). During the synthesis of various potential

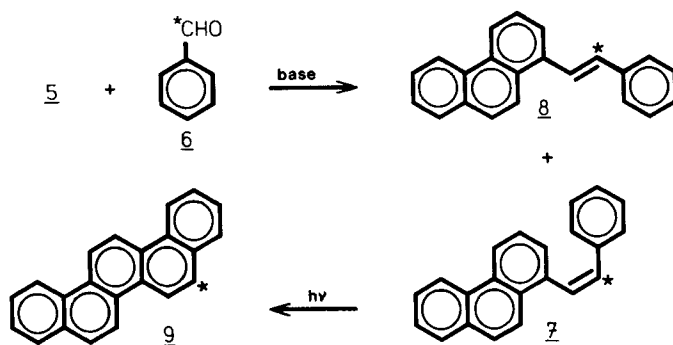


Scheme 2

metabolites of picene, 5 proved to be a valuable synthon (20). Reaction of 5 with unlabelled benzaldehyde in the presence of lithium ethoxide produced 3 in 75 % yield (cis/trans ratio 3 : 2). Pure trans-3 was obtained by treatment with

iodine and was characterized by its melting point, ^1H -nmr and uv spectra. Photocyclisation of 3 was achieved by irradiation of a 0.003 molar solution in benzene with a high pressure mercury lamp (150 W) in the presence of iodine. After chromatographic filtration of the crude product through alumina and recrystallisation from hot xylene, pure 1 was isolated in 60 % yield. Melting point (364 °C) and uv spectrum (λ_{max} 283, $\log \epsilon$ 5.03) of this product were in good agreement with published data (21).

The microscale synthesis of [5- ^{14}C]-picene 9 (Scheme 3) started from 35 μmol [7- ^{14}C]-benzaldehyde 6 (2 mCi). After reaction with 5, the crude olefins 7 and 8 were subjected to photocyclisation without prior purification. After completion of the photoreaction the crude product was adsorbed onto alumina which was first extensively eluted with pentane and then with benzene. GLC and HPLC analyses of



Scheme 3

the benzene fraction showed [5- ^{14}C]-picene to be the only product present. From the uv absorption of the solution the overall yield of the two step microsyntheses was calculated to be 54 % (based on [7- ^{14}C]-benzaldehyde). The specific radioactivity of the product was determined by liquid scintillation counting to be 57 Ci/mol.

EXPERIMENTAL

[7- ^{14}C]-benzaldehyde was purchased from Amersham Radiochemical Centre and had chemical and radiochemical purities of 98 % each, with a specific activity of 57 Ci/mol. All other chemicals were products of Merck (Darmstadt, FRG). The

^1H -nmr spectra were run on a Varian EM-360 at 60 MHz with deuterio-chloroform as solvent using tetramethylsilane as an internal standard. Chemical shifts are reported in δ (ppm). UV spectra were recorded on a Beckman Model 25 photometer. GLC analyses were run on a Packard 427 instrument equipped with a FID and a 6 ft. OV-17 column (3 % on chromosorb W-AW-DMCS, 80-100 mesh). Nitrogen at a flow rate of 30 ml/min was used as the carrier gas. Each analysis was run with a programmed temperature gradient (250-330 °C at 8 °C/min). For purity determinations, a Spectra Physics SP 8700 HPLC system with a DuPont Zorbax column (4.6 mm x 25 cm) and a DuPont UV-detector at 280 nm was used, applying a gradient of 50 % to 100 % methanol in water over 50 min with 1 min delay time and a flow rate of 1.0 ml/min. Samples were counted on a Packard TRI-CARB 300C scintillation counter using Unisolve I (Zinsser, Frankfurt, FRG) as the counting medium.

(1-phenanthryl)methyl triphenyl phosphonium bromide 5:

9.6 g (50 mmol) 1-Methylphenanthrene were heated at reflux with 7.2 g (51 mmol) N-bromosuccinimide in dry carbon tetrachloride (170 ml) using 20 mg AIBN as radical source. Thirty min were required to complete the reaction. The usual work up, followed by recrystallisation from methanol/pentane (2 : 1, v/v) provided pure 1-bromomethyl-phenanthrene as pale yellow crystals (11.4 g, 84 %), m.p. 95 °C (lit. (22) mp. 95-96 °C); ^1H -nmr (CCl_4): δ 4.90 (s, 2H), 7.43-8.16 (m, 7H), 8.43-8.80 (m, 2H).

10.8 g (40 mmol) 1-Bromomethyl-phenanthrene were reacted with 10.7 g (41 mmol) triphenylphosphine in toluene for 6 h under gentle reflux. After the reaction mixture was cooled, the phosphonium salt 5 was collected by suction filtration, washed with cold toluene and dried under vacuum at 0.1 torr (20.2 g, 95 %), m.p. 276-277 °C; ^1H -nmr: δ 5.78 (d, 2H), 6.93-7.90 (m, 7H), 8.10-8.56 (m, 2H).

cis/trans-1-phenyl-2-(1-phenanthryl)ethylene 3:

To a stirred solution of 7.5 g (14 mmol) of 5 and 1.5 g (14 mmol) benzaldehyde in 200 ml freshly distilled DMF, at 60 °C, was added dropwise over a 45 min period, a solution of lithium ethoxide prepared from lithium (0.12 g, 17 mmol) in absolute ethanol (60 ml). After 2 h the mixture was cooled and poured into H_2O , extracted with ether, washed with H_2O , dried (Na_2SO_4), and concentrated to give a residue of the olefins (cis/trans-ratio 3 : 2; determined by GLC) which was

further purified by several recrystallisations from methanol affording a mixture of cis/trans-3 (2.95 g, 74 %).

The pure trans-isomer 3 was obtained by treatment of an analytical sample of the cis/trans-mixture in hot benzene containing a small amount of iodine. The isomerisation was followed by GLC until the reaction was essentially complete. The iodine was removed by passing the benzene solution through a short column of alumina. Recrystallisation from methanol gave shiny, colourless crystals, m.p. $196\text{ }^\circ\text{C}$ $^1\text{H-nmr}$: δ 7.20-8.20 (m, 12H, aromatic; 2H, olefinic), 8.50-8.75 (m, 2H, aromatic); uv (EtOH): λ_{max} (nm) 227, 263, 318.

Picene 1:

1 g (3.5 mmol) of cis/trans-3 was irradiated with a water-cooled high pressure mercury lamp (Hanau, 150 W) in 960 ml of a 10^{-4} M solution of iodine in benzene until GLC monitoring indicated that more than 97 % of the starting material had reacted. The reaction mixture was concentrated and purified by chromatography on alumina. Elution with benzene followed by recrystallisation from xylene gave pure 1 (0.6 g, 60 %); m.p. $364\text{ }^\circ\text{C}$ (lit. (20) m.p. $364\text{ }^\circ\text{C}$); uv (EtOH), λ_{max} (nm): 227, 255, 273, 283 ($\log \epsilon$ 5.03), 300, 325.

Microsynthesis of [5- ^{14}C]-picene 9:

To a stirred solution of 3.7 mg (3.5×10^{-5} mol) [$7\text{-}^{14}\text{C}$]-benzaldehyde (2 mCi) and 21.5 mg (4×10^{-5} mol) 3 in 2.5 ml freshly distilled DMF, at $60\text{ }^\circ\text{C}$, was added dropwise over a 45 min period, a solution of lithium ethoxide (5×10^{-5} mol) in 0.75 ml absolute ethanol. After 30 min the mixture was cooled and diluted with 10 ml H_2O , extracted with ether and dried over Na_2SO_4 . Removal of the solvent furnished a crude mixture of 7 and 8 as a yellow oil, which was dissolved in 160 ml benzene containing 10^{-5} mol iodine. Irradiation of this solution with a water-cooled high pressure mercury lamp (Hanau, 150 W) for 1 h produced [$5\text{-}^{14}\text{C}$]-picene 9, which was purified after evaporation of the solvent by chromatography on alumina with benzene as eluent. The fraction containing [$5\text{-}^{14}\text{C}$]-picene was analyzed by GLC and HPLC, both of which showed one single peak with a retention time identical with that of authentic picene. From the uv absorption of the solution the overall yield of the two step microsynthesis was calculated to be 54 %. The specific radioactivity of the product was determined by liquid

scintillation counting to be the same as that of the starting material [7-¹⁴C]-benzaldehyde, i.e. 57 Ci/mol.

CONCLUSION

Starting from commercially available [7-¹⁴C]-benzaldehyde various other ¹⁴C-labelled PAHs (e.g. phenanthrene, chrysene, benzo[c]phenanthrene) can be prepared by the simple two step synthesis described. The advantages of this method are: (a) the production of the desired ¹⁴C-labelled PAH free of any isomeric impurities, (b) the adaptability of the reaction sequence to microscale preparation and (c) the high chemical and radiochemical yield. The full scope and limitations of the method described above for the synthesis of picene derivatives is currently under investigation.

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