THE SYNTHESIS OF α-METHYLSTYRENES WITH ^{14}C-LABELLING IN THE SIDE CHAIN

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SUMMARY

α-Methylstyrenes with all three side chain carbons specifically ^{14}C-labelled have been synthesised by Wittig reactions between the appropriately labelled acetophenones or methylene triphenylphosphoranes. The yields in all cases were good and any radiochemical impurities could be readily removed by distillation.

Keywords: ^{14}C-labelled α-methylstyrenes

INTRODUCTION

Although there are a number of methods available for the synthesis of α-methylstyrenes,[1] if they are applied to the preparation of labelled compounds, inseparable mixtures of radio labelled isomers are formed.

As part of a study of the kinetics of copolymerisation we require styrenes specifically labelled. In a previous paper[2] we have described the synthesis of [β-^{14}C]styrene. We now report the preparation of α-methyl-[α-^{14}C]styrene, [^{14}C]methyl-α-methylstyrene and α-methyl-[β-^{14}C]styrene. The method we have used is the variation of the well known Wittig reaction[3] reported by Schlosser and Christmann[4] in which the addition of potassium t-butoxide is found to accelerate the rate of reaction and improve the rather poor yields often observed in reactions of methylene phosphoranes.

For our synthesis we required three labelled intermediates, [α-^{14}C]-acetophenone, [β-^{14}C]acetophenone and [^{14}C]methyltriphenylphosphonium iodide.

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The acetophenones have been reported previously[5] using a number of variations of the Friedel-Crafts reaction. We chose to use the reaction of labelled acetyl chlorides with benzene in the presence of aluminium chloride. The labelled acid chlorides were readily prepared by the treatment of the corresponding acids with benzoyl chloride in excess. We have generally found this method successful and simple to use, since no gases are evolved (e.g. HCl or SO_2 as with thionyl chloride) and the product is readily distilled out of the mixture pure. The Friedel-Crafts reactions proceeded smoothly giving fairly good yields of the desired ketones. The methyltriphenylphosphonium iodides, labelled and unlabelled, were readily obtained by standard procedures. The modified Wittig reactions proceeded readily, the yields were good and the isolation of the pure α-methylstyrenes was straightforward.

EXPERIMENTAL

^{14}C-labelled compounds were obtained from Amersham International, Amersham. Radioactivity measurements were performed by liquid scintillation counting using an Intertechnique SL40 Liquid Scintillation Spectrometer.

[1-^{14}C]Acetic acid and [2-^{14}C]acetic acid were obtained from 1 mCi sodium [1-^{14}C]acetate and sodium [2-^{14}C]acetate respectively by treatment with AR grade glacial acetic acid and a few drops of water to give a solution of [1-^{14}C]acetic acid of specific activity 0.98 mCi mol^{-1} and [2-^{14}C]acetic acid of specific activity 1.0 mCi mol^{-1}.

[1-^{14}C]acetyl chloride:- [1-^{14}C]Acetic acid (15 g, 0.98 mCi mol^{-1}) and benzoyl chloride (52.5 g) were heated together in a flask fitted with a fractionating column (25 x 0.9 cm packed with glass helices). The distillate, b.p. 49-50 °C, was redistilled to give [1-^{14}C]acetyl chloride (17 g, 86.6%).

[α-^{14}C]acetophenone:- [1-^{14}C]Acetyl chloride was added to a cooled suspension of freshly sublimed powdered aluminium chloride (30 g) in dry

benzene (60 cm^3). When the addition was complete the mixture was heated at 50 °C until no more hydrogen chloride was evolved. The mixture was cooled and poured into water (25 cm^3) and the precipitated solids dissolved by the addition of concentrated hydrochloric acid. The benzene layer was separated, washed with 10% sodium hydroxide solution, dried ($CaCl_2$) and the benzene distilled to give [α-^{14}C]acetophenone (14.8 g, 57%, b.p. 94 °C/20 mmHg). ^{1}H n.m.r. gave bands at δ2.6 (3H $CH_3\overset{O}{\overset{\|}{C}}$) and a complex band at δ7.6-8.2 (5H C_6H_5).

α-Methyl-[α-^{14}C]styrene:- n-Butyl lithium (1.6 M, 50 cm^3 in Hexane) was added to methyltriphenylphosphonium iodide (32.3 g, 0.08 mol) in dry ether (100 cm^3). The mixture was stirred in a nitrogen atmosphere for 4 h when an orange suspension was obtained. [α-^{14}C]Acetophenone [10.5 g, 0.98 mCi mol^{-1}] in dry ether (20 cm^3) was added dropwise. After 1 h potassium t-butoxide (22.4 g) in t-butanol (0.2 mol) was added and the mixture was stirred for 12 h at 18 °C. The precipitate which formed was filtered off, washed with ether (100 cm^3) and the combined ether layers washed with water (100 cm^3) and dried ($CaCl_2$). Distillation of the ether followed by distillation of the residue in vacuo gave α-methyl-[α-^{14}C]styrene (5.66 g, 54.2%, b.p. 64 °C/20 mmHg).

[^{14}C]Methyl-α-methylstyrene:- Using the same sequence as above [2-^{14}C]acetic acid (15 g) afforded [2-^{14}C]acetyl chloride (16.8 g, 85.6%) which in turn gave [β-^{14}C]acetophenone (14.6 g, 56.2%) and then [^{14}C]methyl-α-methylstyrene (7.5 g, 52.3%) with a correct ^{1}H n.m.r. spectrum.

[^{14}C]Methyltriphenylphosphonium iodide:- [^{14}C]Methyl iodide [20.58 g specific activity 2.0 mCi mol^{-1}] was added to triphenylphosphine (27.5 g) in dry benzene (45 cm^3). The mixture was allowed to stand for two days at 18 °C and the solid which formed was filtered off, washed with hot, dry benzene (250 cm^3) and dried at 110 °C in vacuo to give [^{14}C]methyltriphenylphosphonium iodide (41.8 g, 71.8%), m.p. 183 °C.

α-Methyl-[β-^{14}C]styrene:- Reaction as above of [^{14}C]methyltriphenylphosphonium iodide (32.3 g) with acetophenone (10.5 g) afforded α-methyl-[β-^{14}C]styrene (5.35 g, 56.7%). ^{1}H n.m.r. spectroscopy confirmed the structure of the styrene.

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