SYNTHESIS OF *o*- AND *p*-FLUORO-α-METHYLSTYRENES LABELLED WITH CARBON-14 IN THE SIDE CHAIN

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SUMMARY

Ortho- and para-fluoro-α-methylstyrenes specifically ^{14}C-labelled in all three positions of the side chain have been synthesized by a modified Wittig reaction. The appropriate acetophenones were synthesized as intermediates. The yields in all cases were good and any radiochemical impurities could be readily removed by careful fractional distillation.

Keywords: ^{14}C-labelling; fluorinated methylstyrenes.

INTRODUCTION

As part of a continuing study of the kinetics of copolymerisation we require styrenes specifically labelled. Previously[1] we have described the synthesis of [β-^{14}C]styrene and recently the preparation of α-methylstyrenes with specific labelling in all three side chain positions.[2] In the course of this latter study we reviewed the methods available for the synthesis of α-methylstyrenes and concluded that a modified Wittig method[3] was the most efficient. In the present paper we describe the application of this method to two fluorinated analogues of α-methylstyrene, in particular the o- and p-isomers.

It was necessary, firstly, to prepare isomerically pure o- and p-fluoro-acetophenones suitably labelled with ^{14}C. In the case of the p-fluoro isomers this was relatively simple. It has been shown previously that Friedel-Crafts

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acylation of fluorobenzene gives essentially (>95%) para-substituted compounds.[4] Thus, reaction of fluorobenzene with [1-^{14}C]- and [2-^{14}C]acetyl chloride prepared as previously described[2] in the presence of aluminium chloride as catalyst, gave the corresponding p-fluoroacetophenones; these, on careful distillation, gave products which by ^{1}H and ^{19}F n.m.r. spectroscopy were isomerically pure and which were single components on several g.l.c. columns. These ketones, along with unlabelled p-fluoroacetophenone, were converted by reaction with unlabelled and ^{14}C-labelled methyltriphenylphosphonium iodide respectively to the corresponding p-fluoro-α-methylstyrenes.

The synthesis of the o-fluoro-analogues was less simple and required separate methods to prepare the required acetophenones. The introduction of a ^{14}C-label specifically into the α-position of o-fluoroacetophenone was accomplished by use of the reaction described by Friedman,[5] namely reaction of copper(I) cyanide with aryl halides. Thus, reaction of o-bromofluorobenzene with copper(I) [^{14}C]cyanide in DMF gave o-fluorophenyl [^{14}C]cyanide in good yield. Reaction of the latter with methyl magnesium iodide gave o-fluoro-[α-^{14}C]acetophenone in good yield.

o-Fluoro[β-^{14}C]acetophenone was prepared by a sequence beginning with reaction of o-fluorobenzaldehyde with [^{14}C]methyl magnesium iodide to give the corresponding o-fluoro[^{14}C-*methyl*]-α-methylbenzyl alcohol, which was oxidised with chromium(VI) oxide to give the desired acetophenone.

The desired o-fluoro-α-methylstyrenes were then prepared by the Wittig reaction of the appropriate o-fluoroacetophenones and labelled or unlabelled methyltriphenylphosphonium iodides as described for the p-fluoro-isomers. In all cases the yields were good and the isolation procedures simple.

We feel we have now established a general route to ring substituted side chain labelled α-methylstyrenes at low molar specific activity.

EXPERIMENTAL

Radioactive materials were obtained from the Amersham International plc, Amersham. [1-^{14}C]Acetyl chloride, [2-^{14}C]acetyl chloride and [^{14}C-*methyl*]-

methyl triphenylphosphonium iodide were prepared as previously described.[2] Aluminium chloride was freshly sublimed.

p-Fluoro[α-^{14}C]acetophenone - Fluorobenzene (20 g) in carbon disulphide (100 cm^3) and aluminium chloride (40 g) were heated and stirred under reflux. To the suspension [1-^{14}C]acetyl chloride (19.6 g, 0.98 mCi mol^{-1}) was added dropwise. When the addition was complete the mixture was refluxed for a further hour. The carbon disulphide was distilled off and the residue poured onto ice and concentrated hydrochloric acid (100 cm^3). The solution was extracted with ether (2 x 100 cm^3), the ether layers were dried ($MgSO_4$) and the ether was distilled off. The residual oil was distilled in vacuo to yield [α-^{14}C]-4-fluoroacetophenone (21.0 g, 60.9%), b.p. 93°C/200 mmHg.

4-Fluoro-α-methyl[α-^{14}C]styrene - n-Butyllithium (50 cm^3, 1.6 M in n-hexane) was added to a suspension of methyltriphenylphosphonium iodide (32.3 g) in dry ether (100 cm^3) and the mixture stirred at 18°C for 4 hours to give a yellow orange suspension; 4-fluoro[α-^{14}C]acetophenone (11.05 g, 0.98 mCi mol^{-1}) in ether (20 cm^3) was then added. After one hour potassium t-butoxide (22.4 g) in t-butanol (0.2 mol) was added and the mixture stirred overnight at 18°C. The precipitated triphenylphosphine oxide was filtered off and washed with ether (100 cm^3). The combined ether layers were washed with water (100 cm^3) and then dried ($MgSO_4$). Distillation of the ether, followed by distillation of the residue in vacuo, gave 4-fluoro-α-methyl-[α-^{14}C]styrene (5.3 g) (53.4%), b.p. 67°C/20 mmHg.

p-Fluoro[β-^{14}C]acetophenone - In a repeat of the experiment described above for p-fluoro[α-^{14}C]acetophenone, p-fluoro[β-^{14}C]acetophenone (21.2 g) was obtained from [2-^{14}C]acetyl chloride (19.6 g, 1.0 mCi mol^{-1}).

p-Fluoro[^{14}C-*methyl*]-α-methylstyrene - The styrene (5.8 g) was obtained from p-fluoro[β-^{14}C]acetophenone (11.05 g) and methyltriphenylphosphonium iodide (32.3 g) as described above.

p-Fluoro-α-methyl[β-^{14}C]styrene - The styrene (5.7 g) was obtained similarly from [^{14}C]methyltriphenylphosphonium iodide (32.3 g) and p-fluoroacetophenone (11.06 g).

o-Fluorobenzo[^{14}C]nitrile - o-Bromofluorobenzene (16.8 g) and copper(I) [^{14}C]cyanide (10 g, 0.88 mCi mol^{-1}) in dry DMF were heated under reflux for 16 hours. The mixture was cooled, iron(III) chloride (11.0 g) in 1 M hydrochloric acid (45 cm^3) was added and the mixture heated and stirred for 30 minutes.

Steam distillation of the resulting mixture afforded an oily layer in the distillate which was extracted with ether. The dried ($CaCl_2$) ether layer was distilled to leave an oil which was distilled *in vacuo* to yield o-fluorobenzo[^{14}C]nitrile (11.0 g), b.p. 105°C/20 mmHg (cited 95-96°C/15 mmHg for the unlabelled product[6]).

o-Fluoro[α-^{14}C]acetophenone - To methyl magnesium iodide (from methyl iodide, 27 g) in dry ether was added o-fluorobenzo[^{14}C]nitrile (7.5 g) in ether (20 cm^3). The mixture was stirred at 18°C for 2 hours and then refluxed for ½ hour. Work up by hydrolysis and distillation afforded o-fluoro[α-^{14}C]-acetophenone (4.8 g), b.p. 85°C/20 mmHg (cited[7] 80-85°C/16 mmHg).

o-Fluoro-α-methyl[α-^{14}C]styrene - The styrene (1.5 g), b.p. 55°C/20 mmHg, was prepared from o-fluoro[α-^{14}C]acetophenone (3.0 g, 0.88 mCi mol^{-1}) as described above for the p-fluoro isomer.

o-Fluoro-[^{14}C-*methyl*]-α-methylbenzyl alcohol - To [^{14}C]methyl magnesium iodide (from [^{14}C]methyl iodide, 20 g, 2.0 mCi mol^{-1}) in dry ether was added o-fluorobenzaldehyde (17.5 g). Work up by hydrolysis and distillation afforded o-fluoro[^{14}C-*methyl*]-α-methylbenzyl alcohol (15 g), b.p. 95°C/20 mmHg (cited[8] 117°C/45 mmHg for the unlabelled material).

o-Fluoro[β-^{14}C]acetophenone - The benzyl alcohol above (11.0 g) in glacial acetic acid (90 cm^3) was added to chromium(VI) oxide (6.0 g) in water (16 cm^3) and acetic acid (60 cm^3). The mixture was stirred at 18°C for 12 hours, poured into water and extracted with ether; after washing with water, the ether layer was dried ($CaCl_2$) and distilled to give an oil which on distillation *in vacuo* afforded o-fluoro[β-^{14}C]acetophenone (8.7 g).

o-Fluoro[^{14}C-*methyl*]-α-methylstyrene - The styrene (1.55 g) was obtained as above from o-fluoro[β-^{14}C]acetophenone (3.0 g).

o-Fluoro-α-methyl[β-^{14}C]styrene - The styrene (5.7 g) was obtained as above from o-fluoroacetophenone and [^{14}C]methyltriphenylphosphonium iodide (32.3 g).

REFERENCES

(1) Barson, C.A. and Burns, D.K. - J. Labelled Comp. Radiopharm. *15*: 339 (1978).

(2) Ali, H.M., Barson , C.A. and Coe, P.L. - J. Labelled Comp. Radiopharm. *21*: 799 (1984).

(3) Schlosser, M. and Christmann, K.F. - Angew. Chem. Intl. Ed. *3*: 636 (1964).

(4) Buu-Hoi, N.G. PH, Hoan, N.G. and Jacquigon, P. - Rec. Trav. Chim. *68*: 781 (1949).

(5) Friedman, L. and Shechter, H. - J. Org. Chem. *26*: 2522 (1961).

(6) Lohaus, G. - Ger. Patent 1,259,893 (1968).

(7) Borsche, W. and Roemich, M.W. - Ann. *546*: 273 (1941).

(8) Brooks, L.A. - J. Amer. Chem. Soc. *66*: 1295 (1944).