

THE SYNTHESIS OF DEUTERATED METHYL METHACRYLATES

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SUMMARY

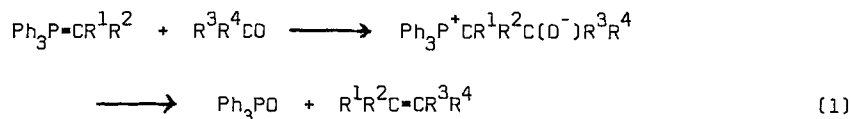
Methyl esters of: 2-methyl[3-<sup>2</sup>H<sub>2</sub>]prop-2-enoic acid (methyl methacrylate-d<sub>2</sub>, CD<sub>2</sub>=C(CH<sub>3</sub>)CO<sub>2</sub>CH<sub>3</sub>) and 2-[Me-<sup>2</sup>H<sub>3</sub>]methylprop-2-enoic acid (methyl methacrylate-d<sub>3</sub>, CH<sub>2</sub>=C(CD<sub>3</sub>)CO<sub>2</sub>CH<sub>3</sub>) were prepared in high yield under mild conditions from carbomethoxymethyltriphenylphosphonium bromide in a new application of the Wittig reaction. The methyl ester of 2-methylprop[<sup>2</sup>H<sub>5</sub>]-2-enoic acid (methyl methacrylate-d<sub>5</sub>, CD<sub>2</sub>=C(CD<sub>3</sub>)CO<sub>2</sub>CH<sub>3</sub>) was prepared from acetone-d<sub>6</sub> via the acetone cyanohydrin method. Densities of all three monomers are reported at 25, 45 and 60°C.

INTRODUCTION

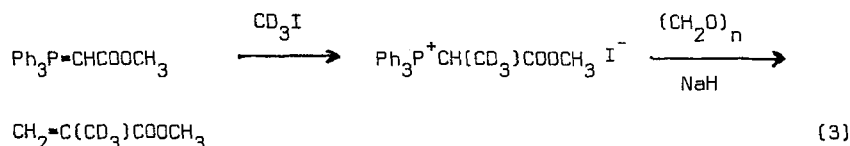
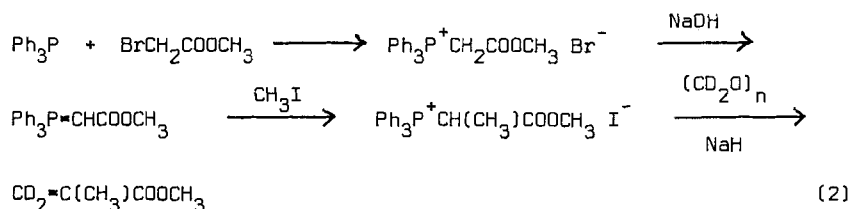
Methyl methacrylate is one of the most important vinyl monomers and many synthetic routes have been devised for laboratory and industrial preparations. Convenient routes for preparation of its deuterium labelled derivatives, however, are not so well developed. Methyl methacrylate-d<sub>2</sub> has previously been prepared via the reaction between formaldehyde-d<sub>2</sub> and the monomethyl ester of methylmalonic acid in the presence of diethylamine.<sup>1</sup> In the present work, trial syntheses

using this method gave rather low yields of only 25-30%. Methyl methacrylate- $d_5$  has also been prepared previously from acetone- $d_6$ .<sup>2</sup> This method was used in the present work and gave yields of 20-25%.

The application of the Wittig reaction<sup>3-6</sup> to the preparation of olefins (reaction 1) has been developed to allow selective labelling



with an isotope of hydrogen in either the vinyl or the alkyl positions.<sup>7</sup> This method was adapted in the present work for synthesis of the deuterated esters methyl methacrylate- $d_2$  and methyl methacrylate- $d_3$  with high yield and deuterium content (reactions 2 and 3).



Crude yields were 80-90% and after careful fractional distillation 65-70%. The deuterium contents were 96-99 atom %. The results obtained indicate the general usefulness of the Wittig reaction as a means of preparing this type of compound. The products obtained are stable under the reaction conditions both chemically and isotopically and are readily separated from the main by-product triphenyl phosphine oxide.

## EXPERIMENTAL

### Analytical Procedures

Gas liquid chromatography (GLC) was carried out on a Pye Argon Chromatograph using a 120 x 0.4 cm column packed with 10% silicone SE 30 on Celite (60-80 mesh) at 75° and a flow rate of 30 ml min<sup>-1</sup>.

Thin layer chromatography (TLC) of the triphenylphosphonium compounds was carried out on Merck pre-cast silica gel F<sub>254</sub> plates which were developed with a mixture of chloroform/methanol (3:1).

Microanalyses were performed on a Perkin Elmer model 240 analyser. For deuterium compounds the commercial pure acetonitrile-d<sub>3</sub> was used as a reference standard. (found: C, 54.8 ; D, 6.9 ; N, 31.7% ; calc. for CD<sub>3</sub>CN : C, 54.5 ; D, 13.7 ; N, 31.6%). Thus, for microanalysis a deuterium atom can be analysed as a hydrogen atom after due allowance for the mass difference.

Nuclear magnetic resonance (NMR) analyses were performed on a Perkin Elmer model R12 spectrometer. Infrared (IR) analyses were performed on a Perkin Elmer model 325 grating spectrophotometer. Mass spectra (MS) analyses were performed on an AEI model MS 30 double beam spectrometer.

### Materials

All chemicals and solvents were of 'AnalaR' grade or were purified, before use. Deuterated precursors were purchased from Prochem Ltd., London, U.K.

### Formaldehyde-d<sub>2</sub>

The method of Atkinson *et al* was used<sup>8</sup> and gave a yield of 13g (0.41 mol, 74%) of pure paraformaldehyde-d<sub>2</sub>, (CD<sub>2</sub>O)<sub>n</sub>, m.p. 172-174°.

Methyl methacrylate-d<sub>2</sub>(i) Carbomethoxymethyltriphenylphosphonium bromide <sup>4</sup>

To a stirred solution of triphenylphosphine (262g, 1.0 mol) in benzene (1.2l) was added methyl bromoacetate (144g, 0.95 mol) over a period of about 30 minutes. The temperature was maintained at 35-40° during this period and the phosphonium bromide began to crystallise out. The mixture was stirred for a further 16 hours then filtered and the product washed first with benzene then with petroleum ether (bp 40-60°) and dried in a vacuum oven at 50°. The yield was 377g (0.91 mol, 91%), m.p. 162-163° (found: C, 60.9 ; H, 5.0%. calc. for C<sub>21</sub>H<sub>20</sub>BrO<sub>2</sub>P : C, 60.9 ; H, 4.6%). TLC showed one component only. The product had IR absorption at 1715 cm<sup>-1</sup> (ester C=O) and an NMR multiplet in the region δ 7-8 (15H, aryl C-H) as well as a doublet (J ~12 cps) centred at δ 5.6 (2H, P<sup>+</sup>-CH<sub>2</sub>-) and a singlet at δ 3.5 (3H, O-CH<sub>3</sub>).

(ii) Carbomethoxymethylenetriphenylphosphorane <sup>4</sup>

Carbomethoxymethyltriphenylphosphonium bromide (41.4g, 0.1 mol) was dissolved in cold water (1 l) and 2M sodium hydroxide solution added with stirring until the solution was just alkaline to phenolphthalein indicator. The white precipitate was collected and dried and recrystallised from ethyl acetate/petroleum ether (bp 40-60°). The crude yield was about 70%. After two recrystallisations the yield was 13.5g (0.04 mol, 40%) m.p. 161-163°. TLC showed that the product contained traces of triphenylphosphine oxide and starting material (found : C, 75.3 ; H, 5.7%. calc. for C<sub>21</sub>H<sub>19</sub>O<sub>2</sub>P : C, 75.5 ; H, 5.7%). The material had a strong IR absorption at 1620 cm<sup>-1</sup> (characteristic of the system  $\rightarrow P^+C=CO^-OR$ ) and an NMR multiplet at δ 7.2-8.0

(15H, aryl C-H) as well as a singlet at  $\delta$  3.5 (3H, O-CH<sub>3</sub>) and a broad singlet centred at  $\delta$  3.0 (1H,  $\rightarrow$ P<sup>+</sup>CHCO<sup>-</sup>).

(iii) Methyl( $\alpha$ -carbomethoxymethyl)triphenylphosphonium iodide<sup>3</sup>

Carbomethoxymethylenetriphenylphosphorane (50g, 0.15 mol) was dissolved in hot ethyl acetate (400 cm<sup>3</sup>) and treated with methyl iodide (24g, 0.17 mol). The solution was refluxed overnight and then cooled. The precipitated salt was filtered off and dried. It was purified by adding ethyl acetate to a chloroform solution which yielded colourless crystals m.p. 138-140°. The yield was 50g (0.11 mol, 70%). It had IR absorption at 1715 cm<sup>-1</sup> (ester C=O) and an NMR multiplet at  $\delta$  7.4-8.2 (15H, aryl C-H) as well as two quartets - one centred at  $\delta$  1.7 (3H,  $\rightarrow$ P<sup>+</sup>-C-CH<sub>3</sub>) the other centred at  $\delta$  6.35 (1H,  $\rightarrow$ P<sup>+</sup>-CH) and a singlet at  $\delta$  3.5 (3H, O-CH<sub>3</sub>).

(iv) Methyl methacrylate-d<sub>2</sub>

Purified dimethyl sulphoxide (200 cm<sup>3</sup>) was placed in a 500 cm<sup>3</sup> three necked flask fitted with a condenser and drying tube, thermometer, stirrer and nitrogen inlet. Purified nitrogen gas was passed over the vigorously stirred solvent for 30 minutes before a sodium hydride dispersion (6g, 80% ; 0.2 mol) was added. The mixture was heated at 65° under nitrogen until solution was complete.

To the cooled solution, methyl( $\alpha$ -carbomethoxymethyl)triphenylphosphonium iodide (96g, 0.2 mol) was added in portions over 15-20 minutes. The dark red solution was stirred under nitrogen at room temperature for 1 hr then paraformaldehyde-d<sub>2</sub> (5g, 0.16 mol) was added in one portion. The solution was slowly heated to 90° and maintained at this temperature for 2 hr and then at room temperature for 16 hr.

A trap, cooled in liquid nitrogen, was attached to the apparatus via the condenser and the whole evacuated to  $< 1 \text{ mm}$  ( $< 133 \text{ Nm}^{-2}$ ). The flask was gently warmed with stirring and all volatile products collected in the trap. The volatile material was twice redistilled, trap to trap on a high vacuum line at room temperature. Crude yield 14.4g (0.14 mol, 88%). It was then washed with 2% sodium hydroxide solution, then water and finally dried over anhydrous calcium chloride. Fractional distillation through a short Vigreux yielded a second fraction bp  $49^\circ/110 \text{ mm}$  ( $1.5 \times 10^4 \text{ Nm}^{-2}$ ) (8.7g, 0.085 mol, 54%). In subsequent preparations crude yields of 79, 88 and 91% were obtained and by combining these before purification a final yield of purified monomer of 72% was obtained.

The product had IR absorption at  $1715 \text{ cm}^{-1}$  (ester  $\text{C}=\text{O}$ ,  $1600 \text{ cm}^{-1}$  ( $\text{C}=\text{C}$ ) and  $2230 \text{ cm}^{-1}$  ( $\text{C}-\text{D}$  in  $\text{CD}_2=\text{C}$ ). There were two NMR singlets, one at  $\delta$  3.5 (3H,  $\text{O}-\text{CH}_3$ ) the other at  $\delta$  2.0 (3H,  $\text{C}-\text{CH}_3$ ). Thus, the methyl methacrylate- $\text{d}_2$  contained at least 99 atom % D. In addition a trace of benzene was detected by a tiny peak at  $\delta$  7.25. GLC also showed a trace ( $< 1\%$ ) of benzene. (found: C, 58.8 ; H+D, 8.1%. calc. for  $\text{C}_5\text{H}_6\text{D}_2\text{O}_2$  : C, 58.8 ; H+D, 7.8%).

#### Methyl methacrylate- $\text{d}_3$

##### (i) Methyl- $\text{d}_3$ ( $\alpha$ -carbomethoxymethyl)triphenylphosphonium iodide

Carbomethoxymethylenetriphenylphosphorane (52g, 0.16 mol) was treated with methyl- $\text{d}_3$  iodide (25g, 0.17 mol) as described above. The yield of pure product was 62g (0.13 mol, 80%) (found: C, 55.0 ; H+D, 4.9%. calc. for  $\text{C}_{22}\text{H}_{19}\text{D}_3\text{IO}_2\text{P}$  : C, 55.1 ; H+D, 4.6%). The NMR spectrum had a multiplet at  $\delta$  7.4-8.2 (15H, aryl C-H) as well as a doublet ( $J \sim 12 \text{ cps}$ )

centred at  $\delta$  6.5 (1H,  $P^+-CH$ ) and a singlet at  $\delta$  3.5 (3H, O-CH<sub>3</sub>) and showed that the product contained at least 99 atom % D.

(ii) Methyl methacrylate-d<sub>3</sub>

The experimental method used was exactly the same as described for methyl methacrylate-d<sub>2</sub> and yields were very similar. However, if yields were based on the methyl-d<sub>3</sub> iodide, overall recovery varied from 45-50% in repeat experiments. As before the product contained a minute trace of benzene impurity (found : C, 58.1 ; H+D, 7.9%. calc. for C<sub>5</sub>H<sub>5</sub>D<sub>3</sub>O<sub>2</sub> : C, 58.3 ; H+D, 7.8%). The product had IR absorption at 1715 cm<sup>-1</sup> (ester C=O) 1630 cm<sup>-1</sup> (C=C) and bands at 2240, 2220, 2120 and 2058 cm<sup>-1</sup> (C-D). The NMR spectrum had two doublets, one centred at  $\delta$  6.0 (1H,  $\begin{smallmatrix} H \\ \diagdown \\ C= \end{smallmatrix}$ ) the other at  $\delta$  5.5 (1H,  $\begin{smallmatrix} & C= \\ / & H \end{smallmatrix}$ ) and a singlet at  $\delta$  3.5 (3H, O-CH<sub>3</sub>). Incomplete deuteration was indicated by a tiny peak at  $\delta$  1.8 (=C-CH<sub>3</sub>) from which it was estimated that the methyl methacrylate-d<sub>3</sub> contained at least 96 atom % D.

Methyl methacrylate-d<sub>5</sub>

(i) Acetone-d<sub>6</sub>

Acetone-d<sub>6</sub> was prepared from acetone by 20 successive exchanges with deuterium oxide in the presence of anhydrous potassium carbonate. The final product (85% yield) had a deuterium content > 99 atom %.

(ii) Acetone-cyanohydrin-d<sub>7</sub>

A stirred solution of sodium cyanide (105g, 2.14 mol) in deuterium oxide (250 cm<sup>3</sup>) and acetone-d<sub>6</sub> (194 cm<sup>3</sup>, 169g, 2.6 mol) in a three necked

flask was cooled in ice to  $\sim 15^{\circ}\text{C}$ . Then sulphuric acid- $\text{d}_2$  (200g, 2 mol) in deuterium oxide ( $300\text{ cm}^3$ ) was slowly added over a period of 2 hours with the temperature maintained between  $10\text{--}20^{\circ}$ . After a further period of 1 hour a layer of acetone cyanohydrin- $\text{d}_7$  was separated off and subsequently combined with the ether washings of the aqueous layer and precipitated sodium bisulphate. The ether solution was dried over anhydrous sodium sulphate, the ether removed and the product distilled under reduced pressure. Acetone cyanohydrin- $\text{d}_7$  was collected at bp  $80^{\circ}/13\text{ mm}$  ( $1.7 \times 10^3\text{ Nm}^{-2}$ ) yield 160g (1.74 mol, 67%).

### (iii) Methyl methacrylate- $\text{d}_5$

Acetone cyanohydrin- $\text{d}_7$  (160g, 1.74 mol) was added to concentrated sulphuric acid- $\text{d}_2$  (255g, 2.55 mol) at  $70^{\circ}$  over a period of 1 hour. The solution was heated slowly to  $140^{\circ}$  over 30 minutes and then left to stand for 10 minutes. Purified methyl alcohol (96g, 3 mol) in deuterium oxide ( $80\text{ cm}^3$ ) containing hydroquinone (0.5g) was then added and the mixture refluxed at  $80^{\circ}$  for 7 hours. Crude methyl methacrylate- $\text{d}_5$  was isolated by steam distillation. It was washed with 2% sodium hydroxide solution and water, dried over anhydrous calcium chloride and distilled through a short Vigreux column. A fraction bp  $49^{\circ}/105\text{ mm}$  ( $1.4 \times 10^4\text{ Nm}^{-2}$ ) was collected, yield 56g (0.53 mol, 20% based on acetone- $\text{d}_6$ ). In trial experiments the yields were usually around 20-25%. The product was shown by GLC to contain one component only (found: C, 57.1, H+D, 7.8%. calc. for  $\text{C}_5\text{H}_3\text{D}_5\text{O}_2$  : C, 57.1, H+D, 7.6%). It showed the expected IR spectrum with strong bands at  $1715\text{ cm}^{-1}$  (C=O),  $1600\text{ cm}^{-1}$  (C=C) and bands at 2240, 2220, 2120 and  $2058\text{ cm}^{-1}$  (C-D). The NMR spectrum contained only one peak at  $\delta\ 3.8$  corresponding to the  $-\text{OCH}_3$  group and deuterium content was  $> 99$  atom %. MS analysis further confirmed the deuterium content and structure.



Density measurements

Densities of the monomers were measured in calibrated dilatometers totally immersed in an oil bath which was thermostatted at the specified temperature  $\pm 0.1^\circ\text{C}$ .

Monomer	Density ( $\text{g cm}^{-3}$ )		
	25 $^\circ\text{C}$	45 $^\circ\text{C}$	60 $^\circ\text{C}$
methyl methacrylate- $\text{d}_2$	0.953	0.931	0.916
" " - $\text{d}_3$	0.972	0.942	0.925
" " - $\text{d}_5$	0.986	0.961	0.944

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