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Synthesis of novel chiral quaternary phosphonium fluorides: reagents for simple asymmetric nucleophilic fluorination reactions

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Abstract

The novel chiral quaternary salt (R_P)-benzylmenthylmethylphenylphosphonium fluoride was synthesised. The compound was used in the asymmetric nucleophilic fluorination of 2-bromopropiophenone to give 2-fluoropropiophenone in a 35% yield with $[\alpha]_D^{20} = +1.94°$.

Keywords: Asymmetric; Nucleophilic; Fluorination; Chiral; Phosphonium; Fluoride

1. Introduction

Chiral organofluorine compounds are interesting and important materials with uses in analytical, biological and medicinal chemistry and also in the chemistry of polymers and materials [1]. In particular, chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic centre have been utilised in studies of enzyme mechanisms, and as intermediates in asymmetric syntheses [2].

There are many reports in the literature concerning the asymmetric synthesis of chiral organofluorine compounds [3], but relatively few involving the asymmetric introduction of fluorine into prochiral starting materials to form chiral products with fluorine attached directly to the stereogenic centre. Only three such asymmetric fluorination systems have been reported [4–6] and these suffer from the problems of utilising reagents that are difficult, expensive and hazardous to prepare, and give reactions with low yield and low enantiomeric excess.

Quaternary ammonium and phosphonium salts have been shown to be effective phase transfer catalysts for nucleophilic fluorination reactions by KF, and the onium fluorides themselves are extremely reactive, with fluorination following a stereospecific S_N2 mechanism [7]. Chiral quaternary ammonium salts have been shown to be effective PTCs, promoting a range of asymmetric base catalysed carbon–carbon bond forming reactions [8]. We, therefore, propose that chiral quaternary ammonium and phosphonium fluorides should have interesting properties as novel reagents for simple asymmetric nucleophilic fluorination reactions. Studies in our laboratory have shown phosphonium compounds to be more effective in these reactions than ammonium compounds.

We now wish to report the synthesis of a pair of novel diastereomeric quaternary phosphonium fluorides with chiral alkyl groups and asymmetric phosphorus centres, and the results of a preliminary study that demonstrates the exciting potential of these compounds as reagents for asymmetric fluorination.

2. Results and discussion

2.1. Synthesis of diastereomeric benzylmenthylmethylphenylphosphonium fluorides

Diastereomeric benzylmenthylmethylphenylphosphonium fluorides **1** and **2** (Fig. 1), with *R* and *S* configuration at phosphorus, respectively, were synthesised in good yield (Scheme 1, synthesis given for R_P diastereomer only) from the diastereomers of menthylmethylphenylphosphine **3** and **4** (Fig. 2). Quaternisation of **3** by reaction with benzyl bromide in refluxing acetonitrile gave quaternary phosphonium bromide **5** in a 65% yield. Conversion of **5** to the corresponding hydroxide **6** was accomplished by passage through the hydroxide form of a strongly basic anion exchange resin. Neutralisation of **6** with aqueous HF yielded fluoride **1** in a 65% yield from **5**. **3** and **4** were synthesised

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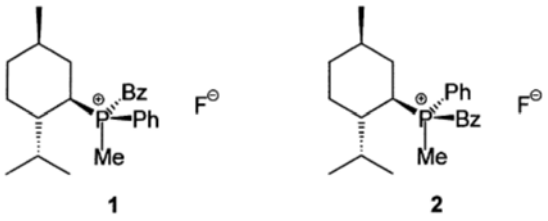


Fig. 1. Diasteremeric benzylmenthylmethylphenylphosphonium fluorides.

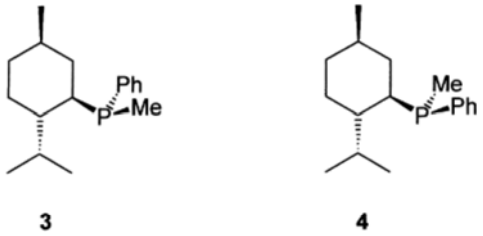
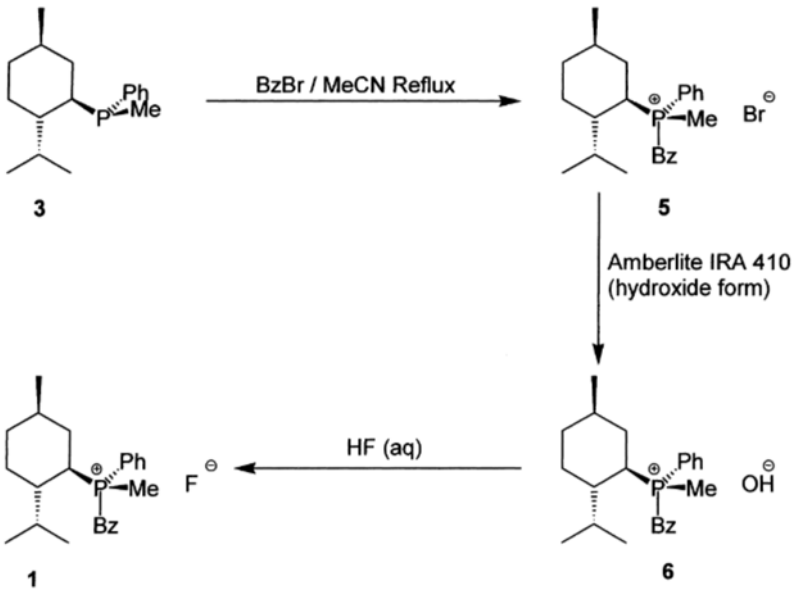
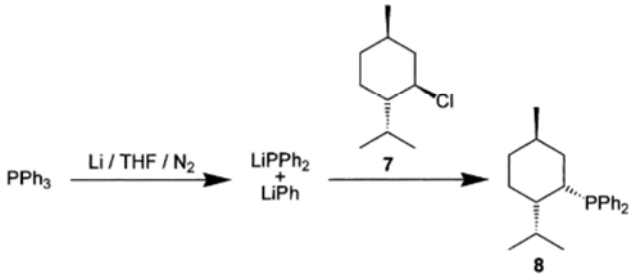


Fig. 2. Diastereomers of menthylmethylphenylphosphine.



Scheme 1. Synthesis of *R*-benzylmenthylmethylphenylphosphonium fluoride **1**.

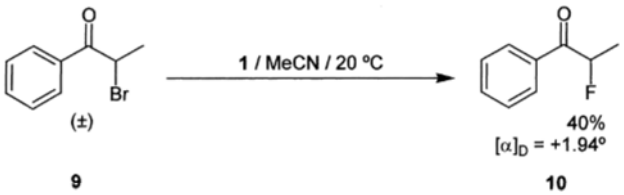
from neomenthyldiphenylphosphine **8** by literature methods [9]. **8** was synthesised from triphenylphosphine according to Scheme 2. Triphenylphosphine was reacted with lithium metal in THF under an atmosphere of nitrogen to form lithium diphenylphosphide, which was reacted in situ with (−)-menthyl chloride **7** to form **8**. Careful recrystallisation from ethanol gave **8** in a 40% yield based on triphenylphosphine. **7** was formed from the reaction of (−)-menthol with zinc chloride in hydrochloric acid [10].



Scheme 2. Synthesis of neomethyldiphenylphosphine.

2.2. Asymmetric fluorination of 2-bromopropiophenone

Chiral quaternary phosphonium fluorides **1** and **2** were expected to exhibit interesting properties with respect to their abilities to act as reagents for asymmetric nucleophilic fluorination. In order to test this, a two fold excess of **1** was reacted with racemic 2-bromopropiophenone **9** in acetonitrile at room temperature (Scheme 3). The reaction was followed by gas chromatography and after 38 h, a 40% conversion to 2-fluoropropiophenone **10** had occurred. The reaction was quenched at this time and the fluorinated product was isolated. The specific rotation of the sample of **10** (pure by g.c.) produced was $[\alpha]_D^{20} = +1.94°$. This shows



Scheme 3. Asymmetric fluorination of 2-bromopropiophenone by **1**.

that the stereospecific S_N2 fluorination of **9** by the chiral phosphonium fluoride **1** was faster for one enantiomer of **9** (presumably the (−)-enantiomer, with inversion of configuration occurring) than for the other. Thus, an excess of the (+)-enantiomer of **10** was formed by kinetic resolution of the racemic starting material.

The preliminary results presented here demonstrate the feasibility of the synthesis of chiral quaternary phosphonium fluorides and the exciting potential of these compounds as novel reagents for asymmetric nucleophilic fluorination reactions.

3. Experimental

3.1. Equipment used

The NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 300 MHz for ^{1}H and at 308C. Gas chromatography was carried out on a Hewlett-Packard 5890 Series II gas chromatograph, using a capillary type DB-1 column.

3.2. General procedures

All solvents used were dried, distilled from calcium hydride and stored under nitrogen over 4 Å molecular sieves.

3.3. Neomenthyldiphenylphosphine (8)

20 g (76 mmol) of triphenylphosphine, 1.1 g (160 mmol) of lithium metal were added to 200 cm^3 of dry THF. This was stirred at room temperature under N_2 until all the lithium had dissolved (24 h). (−)-Menthyl chloride (26 g, 150 mmol) in 80 cm^3 dry THF was added dropwise to the deep red solution of lithium diphenylphosphide, and the mixture was refluxed under N_2 for 54 h. The resulting pale orange solution was treated with 30 cm^3 of water and the organic layer was separated, washed with more water, and concentrated under reduced pressure. Vacuum distillation of the crude product was continued until no more distillate was collected. The residue was allowed to cool and crystallise overnight. Careful recrystallisation from ethanol gave **8** in 40% yield from triphenylphosphine. ^{31}P NMR analysis showed the crystals to contain ca. 90% **8** and 10% neomenthyldiphenylphosphine oxide, presumably due to aerial oxidation of **8** during work-up. It is possible to increase the purity of **8** to ca. 95% by careful recrystallisation but this is not necessary as the oxide does not interfere with the subsequent quaternisation of **8**.

3.4. (R_P)-benzylmenthylmethylphenylphosphonium bromide (5)

2.7 g (10.3 mmol) of **3**, 2.65 g (15.4 mmol) benzyl bromide were added to 30 cm^3 of dry acetonitrile and the mixture was refluxed with stirring for 72 h. The reaction mixture was extracted into ether, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by passage through a silica column. The column was eluted first with pentane to remove unreacted benzyl bromide. Elution with ethanol then gave the product **5**. Concentration of the ethanol solution under reduced pressure yielded 2.9 g of **5** (65% from **3**).

3.5. (R_P)-benzylmenthylmethylphenylphosphonium fluoride (1)

20 g of Amberlite IRA 410 were packed in a column and washed with 1.0 M NaOH (aq) until the column washings showed no presence of chloride ion when tested with silver nitrate and nitric acid. The column was then washed with deionised water until the washings were pH 7. 2 g of **5** were dissolved in the minimum quantity of deionised water. This solution was passed through the column and eluted with more deionised water. Again washing was continued until the washings were neutral, indicating that all the quaternary phosphonium hydroxide **6** had been removed from the column. The volume of the resulting aqueous solution was reduced to approximately 100 cm^3 using a rotary evaporator connected to a rotary oil pump at room temperature. The volume of the solution was then made accurately to 100 cm^3 in a volumetric flask.

A 5 cm^3 aliquot of the aqueous solution of **6** was removed and titrated with standardised 0.1 M hydrochloric acid. 2.15 cm^3 of HCl were required for neutralisation. The remaining 95 cm^3 of the aqueous solution of **6** was then neutralised with 4.0 cm^3 of standardised 1.07 M aqueous HF. Gentle evaporation of the water from the resulting solution using a rotary evaporator connected to a rotary oil pump at room temperature, yielded **1** (0.95 g, 55% from **5**).

^{13}C NMR ($CDCl_3$): d 14.60, 20.70, 21.78, 24.21, 28.92, 28.96, 29.12, 29.71, 32.12, 34.33, 35.30, 44.08, 119.32, 120.34, 127.45, 128.25, 128.29, 129.20, 129.36, 130.0, 130.07, 131.06, 131.18, 133.40.

^{31}P NMR ($CDCl_3$): d 31.12

^{19}F NMR ($CDCl_3$): d −126.56

Anal. Calc. For $C_{24}H_{34}FP$: C, 77.38; H, 9.20; F, 5.10; P, 8.32.

Anal. Found: C, 75.67; H, 9.28; F, 4.98; P, 8.17.

The discrepancy between the calculated and measured experimental analysis is attributed to the presence of trace quantities of water (and possibly bifluoride ion) in the hygroscopic phosphonium fluoride salt.

3.6. Fluorination of 2-bromopropiophenone

0.40 g (1.1 mmol) of **1** was placed in a dry Schlenk tube. This was maintained under vacuum for 24 h at 308C. 0.152 g (0.54 mmol) of 2-bromopropiophenone was dissolved in 15 cm^3 of dry acetonitrile and this solution was transferred

to the Schlenk tube under N_2 using a canula. After 38 h gas chromatography analysis showed 40% conversion to 2-fluoropropiophenone had occurred. About 30 cm^3 of water was added to the reaction mixture, stopping the reaction. This was then stirred for 4 h to hydrolyse the remaining unreacted 2-bromopropiophenone. The product was then extracted into ether, washed with water, and the ether solution was dried and evaporated under reduced pressure to yield 2-fluoropropiophenone (0.038 g, 35% from 2-bromopropiophenone) with $[\alpha]_D^{20} = +1.94°$(c 0.07, $CHCl_3$).

^1H NMR ($CDCl_3$): d 1.63 (3H, doublet of doublets, $J_{HH} = 6.8$ Hz, $J_{HF} = 24.0$ Hz), d 5.7 (1H, doublet of quartets, $J_{HH} = 6.8$ Hz, $J_{HF} = 48.6$ Hz), d 7.23–9.20 (5H, multiplet).

^{19}F NMR ($CDCl_3$): d -181 (sextet, 24 Hz).

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