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Research Article

Synthesis of [^{14}C] Sarin

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Summary

Synthetic routes for the synthesis of [^{14}C] sarin and related nerve agents are described. Triethyl phosphite and [^{14}C] methyl iodide are reacted in the Michaelis–Arbusov reaction to produce diethyl methyl phosphonate which is converted to methylphosphonic acid by hydrolysis. After chlorination and subsequent fluorination the final product is formed by reaction with the appropriate alcohol. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: [^{14}C] sarin; synthesis; chemical warfare agents; O-isopropyl methyl phosphono fluoridate

Introduction

To get a better understanding of the mechanisms controlling the interaction of acetyl cholinesterase (AChE) with nerve agents, in particular the aging of the inhibited enzyme that is caused by longer exposures, studies using radio-labelled compounds are invaluable. Other types of labelling have been reported, for instance fluorescent labels,[1] but in this case the activity of the sarin molecule was considered to be affected by this label and was not therefore useful.

In the synthesis of this type of highly toxic radio-labelled compounds the labelled atom usually has to be introduced early in the synthesis,[2, 3] which of course affects the radiochemical yield. This problem is not

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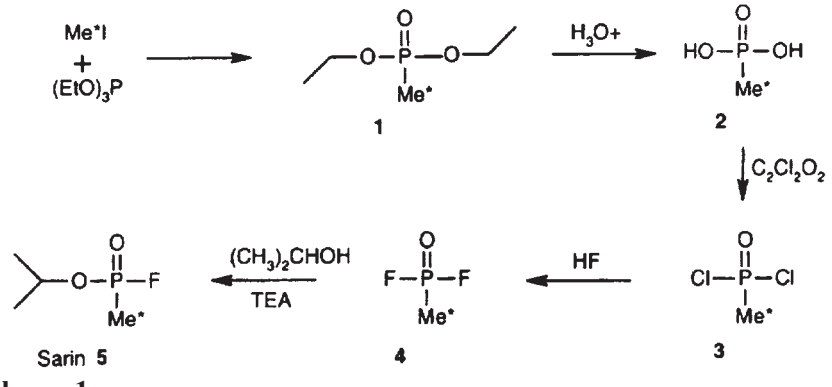
easily avoided since one wants to label the carbon directly bound to phosphorous. The carbons in the ester part could of course be labelled but since they are not as tightly bound to the phosphorous they are of less interest. A synthesis of sarin where the labelled carbon is introduced in the final step has been reported[4] but this method is less suitable for the synthesis of related compounds such as soman, which is of special interest due to the fast aging of AChE caused by soman. Aging of the enzyme is irreversible and is not amenable to treatment. The synthesis presented in this paper is convenient and easily performed using small amounts of labelled agent and is applicable to most related chemical warfare agents.

Note: Due to the high toxicity of the agents considerable caution is required in their handling, not only by inhalation but also by exposure to the skin. Some of the compounds involved in the syntheses are listed in the Chemical Weapons Convention (CWC) and must be declared to the Organization for the Prohibition of Chemical Warfare agents (OPCW).

Results and discussion

Sarin(**5**) was prepared in a five-step sequence (Scheme 1). The whole synthesis was carried out in a single small vial with Teflon linen except for the fluorination step for which the solution had to be transferred to a plastic vial before treatment with hydrogen fluoride. In this way the number of transfers and hence potential loss could be minimized. The diethyl methyl phosphonate (**1**) was hydrolysed without any purification



Scheme 1.

because the by-products could be removed after the hydrolysis step without affecting the reaction. The methyl phosphonic acid dichloride (**3**) was also not purified before fluorination without any deleterious effect.

Diethyl methyl phosphonate (**1**) was synthesized from triethyl phosphite and ^{14}C-labelled methyl iodide in accordance with the Michaelis–Arbusov reaction[5] Triethyl phosphite was used instead of trimethyl phosphite because of the loss of radio-labelled material which occurs with the latter.[6] During the reaction with trimethyl phosphite unlabelled methyl iodide is formed which competes with the labelled material. If instead triethyl phosphite is used, ethyl iodide is formed which is not as reactive as methyl iodide and therefore the desired product is favoured. The product of this reaction is also different from the desired substance, which means that the radio-labelled compound is not diluted. The amount of ethyl diethyl phosphite formed was in the range of 2–6%. It is important that the amount of triethyl phosphite does not exceed the amount of [^{14}C] methyl iodide, otherwise the amount of undesired diethyl ethyl phosphonate will increase. Triisopropyl phosphite was also evaluated as starting material and indeed the reaction was even more selective but we noticed that the steps following hydrolysis became more difficult and the yields were not as good as when triethyl phosphite was used.

Diethyl methyl phosphonate (**1**) could be chlorinated directly but we found that introducing a hydrolysis step made the reactions proceed more smoothly with good yields and better purity. The diethyl methyl phosphonate (**1**) was used without any purification and the hydrolysis was performed in the same vial with aqueous hydrochloric acid at 100°C. The main advantage of this procedure was that after the reaction and evaporation of the solvent the by-products could be removed by placing the product in an open container at 100°C for 24 h.

Methyl phosphonic acid (**2**) was chlorinated with oxalyl chloride, which is a mild chlorinating agent compared to the harsh methods usually employed.[4,6] Oxalyl chloride is also advantageous because by-products and impurities are low boiling and could be easily removed.[7]

We used hydrogen fluoride as fluorinating agent because of its clean and fast reaction. The disadvantage of the toxicity of hydrogen fluoride was compensated by the practical advantages and the fact that even more toxic substances are produced in the next step which meant that safety measures had to be taken anyway. Alternative methods were considered and among them a method which used benzoyl fluoride and

imidazole[8] was studied, but the simplicity of using hydrogen fluoride made it our first choice as fluorinating agent.

For the final step triethylamine and isopropyl alcohol were used following standard procedures. Methyl red was used to monitor the amount of amine needed because of the problem of analysing the exact amount of hydrogen fluoride remaining from the proceeding step. With an overall yield of 61% over five steps from [^{14}C] methyl iodide and the convenience of the synthesis sequence this method was shown to offer many advantages over other published methods.

If, in the final step, pinacolyl alcohol is used instead of isopropyl alcohol and the temperature is raised to 70°C the final product is soman. The reaction sequence to soman also proceeded with good yields. Typically the total yield (about 55% from [^{14}C] methyl iodide) was slightly lower mainly due to steric factors in the final step.

Experimental

[^{14}C] Methyl iodide, specific activity 53.8 mCi/mmol, was purchased from NEN Life Science Products, Inc. and used without further purification. Triethyl phosphite and triisopropyl phosphite were purchased from Aldrich, and were distilled before use. Hydrogen fluoride was obtained from AGA and used without further purification. All products were analysed and characterized by ^{31}P- and ^{1}H-NMR. NMR spectra were obtained on a Brucker AC-250 spectrometer.

[^{14}C] Diethyl methyl phosphonate (1)

The break seal tube, containing 50 mCi (0.93 mmol)[^{14}C] MeI, was cooled in liquid nitrogen before it was opened and 160 µl(0.92 mmol) pre-cooled triethyl phosphite was added. The mixture was transferred to a 3 ml Teflon lined vial and placed in a thermostat at 100°C for 2 h. After the reaction was complete the vial was placed under vaccum to remove the ethyl iodide formed. Crude product, 131 mg, 93% (from [^{14}C]MeI) was obtained and analyzed.

^{1}H-NMR($CDCl_3$) δ 1.33(t), 1.47(d), 4.09(m);
^{31}P-NMR($CDCl_3$) δ 30.90(s).

[^{14}C] Methyl phosphonic acid (2)

To the vial containing the diethyl methyl phosphonate was added 3 ml of aqueous hydrochloric acid, 1 mM, and the mixture heated to 150°C for 24 h. The solvent was removed under argon and the product placed in a thermostat at 100°C for 12 h to remove all water and impurities. 80.5 mg, 97%, of product was recovered and analyzed.

^{1}H-NMR(D_2O) δ 1.48(d);
^{31}P-NMR(D_2O) δ 33.66(s).

[^{14}C] Methyl phosphonic acid dichloride (3)

When the vial containing the methyl phosphonic acid was removed from the thermostat the vial was cooled to room temperature while the residue solidified. To the vial 2 ml of $CDCl_3$ was added followed by catalytic amounts of triethylamine. Oxalyl chloride, 100 µl, was added in one portion and the reaction mixture heated to 70°C for 6 h by which time the solid material had reacted. The product was analyzed and used without further purification. The yield was 90%, 100.2 mg.

^{1}H-NMR($CDCl_3$) δ 2.51(d);
^{31}P-NMR($CDCl_3$) δ 43.91(s).

[^{14}C] Methyl phosphonic acid difluoride (4)

The solution containing the methyl phosphonic acid dichloride was transferred to a plastic test-tube and flushed for 10 s with hydrogen fluoride. A plastic tube was used to prevent etching of glass by hydrogen fluoride. The test-tube was equipped with a stopper and the contents allowed to react for 30 min at room temperature. The reaction mixture was then placed under vaccum for three minutes to remove excess hydrogen fluoride. Due to the reactivity of methyl phosphonic difluoride no analysis was made at this stage but from previous experiments made with unlabelled material the typical yields were in the range of 90–95%.

^{1}H-NMR($CDCl_3$) δ 1.87(t), 1.95(t);
^{31}P-NMR($CDCl_3$) δ 24.78(t).

O-isopropyl [^{14}C] Methyl phosphono fluoridate, Sarin (5)

The [^{14}C] methyl phosphonic acid difluoride solution was used immediately and without further purification. To this solution was added a small amount of methyl red to monitor the pH. Triethylamine was added until the colour changed and then one further equivalent was added to eliminate hydrogen fluoride formed during the reaction. Isopropyl alcohol, 40 µl, was added and the reaction was stirred at room temperature for 18 h, washed with acidified brine (0,1mM HCl) and dried with $MgSO_4$. The yield was 79.4 mg (0.57 mmol), 75% calculated from methyl phosphonic acid dichloride. Experiments with unlabelled material show yields for the last step to be 80–90%. The overall yield from [^{14}C] methyl iodide was 61%.

^{1}H-NMR($CDCl_3$) δ 1.38(d), 1.60(d), 1.67(d), 4.92(m);
^{31}P-NMR($CDCl_3$) δ 28.97(d).

Conclusion

An improved method for the synthesis of [^{14}C]-labelled sarin and related nerve agents has been developed.

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