

## Synthesis of Disodium [*benzene*-U-<sup>14</sup>C]-(4-Chlorophenylthio)methylenediphosphonate, [*benzene*-U-<sup>14</sup>C]-Tiludronate

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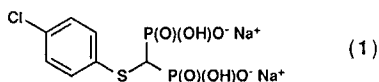
### SUMMARY

Disodium [*benzene*-U-<sup>14</sup>C]-(4-chlorophenylthio)methylenediphosphonate, [*benzene*-<sup>14</sup>C]-Tiludronate, **2**, has been prepared in six steps from [*benzene*-U-<sup>14</sup>C]-acetanilide in an overall radiochemical yield of 41%. A key step in this transformation was the efficient conversion of [U-<sup>14</sup>C]-4-chloroaniline to [*benzene*-U-<sup>14</sup>C]-4-chlorophenylthiocyanate, **5**, in 83% yield by treatment of the corresponding diazonium salt, **9**, with iron(III) thiocyanate. It should be noted that formation of the isomeric [*benzene*-U-<sup>14</sup>C]-4-chlorophenylisothiocyanate, **11**, as a by-product, was observed in only ~1% yield.

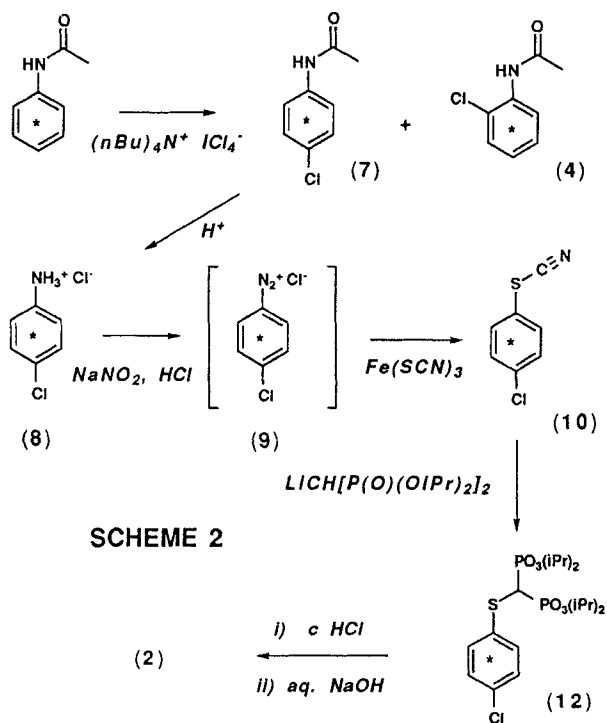
**Key Words:** Disodium [*benzene*-U-<sup>14</sup>C]-(4-chlorophenylthio)methylenediphosphonate, [*benzene*-U-<sup>14</sup>C]-Tiludronate, Disodium (4-chlorophenylthio)methylenediphosphonate, Tiludronate, [*benzene*-U-<sup>14</sup>C]-4'-Chloroacetanilide, [*benzene*-U-<sup>14</sup>C]-4-Chlorophenylthiocyanate.

### INTRODUCTION

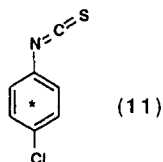
Disodium (4-chlorophenylthio)methylenediphosphonate, Tiludronate, **1**, is a diphosphonate in Development with indications for use in bone disorders such as Paget's disease,<sup>1</sup> and postmenopausal bone loss.<sup>2</sup> The compound has been shown to have beneficial effects on bone mineral density and bone resorption in animal models.<sup>3,4</sup>







[*benzene-U-<sup>14</sup>C]-Acetanilide was chlorinated with tetrabutylammonium iodotetrachloride, by analogy with work of Kajigaeshi *et al.*,<sup>13</sup> to afford a mixture of [*benzene-U-<sup>14</sup>C]-2'-chloroacetanilide, 6, and the desired [*benzene-U-<sup>14</sup>C]-4'-chloroacetanilide, 7, which were separated chromatographically to give 7 in 77% radiochemical yield. The [*benzene-U-<sup>14</sup>C]-4'-chloroacetanilide, 7, was hydrolysed to [*U-<sup>14</sup>C]-4-chloroanilinium hydrochloride, 8, in quantitative yield by treatment with concentrated hydrochloric acid at 60°C over 48 hours. The [*U-<sup>14</sup>C]-4-chloroanilinium hydrochloride, 8, was converted to the corresponding diazonium salt, 9, by treatment with sodium nitrite in hydrochloric acid at 0°C for 30 minutes, by which time TLC revealed no 4-chloroaniline remaining. Iron(III) thiocyanate was prepared *in situ* at by treatment of an aqueous solution of iron(III) chloride with potassium thiocyanate. To this solution, at 0°C, was added the crude diazonium salt, 9, and, following addition of ethyl acetate, the mixture was warmed to 80°C until gas evolution ceased. After quenching with aqueous sodium hydrogen carbonate, the desired [*benzene-U-<sup>14</sup>C]-4-chlorophenylthiocyanate, 10, was isolated in 83% radiochemical yield after purification by chromatography. It should be noted that gc/ms analysis of the crude product revealed only ~1% of the isomeric [*benzene-U-<sup>14</sup>C]-4-chlorophenylisothiocyanate, 11.********



Treatment of tetraisopropyl methylenediphosphonate with n-butyllithium followed by addition of the [*benzene-U-<sup>14</sup>C]-4-chlorophenylthiocyanate, **10**, afforded the desired sulphenylated product, **12**, in 73% radiochemical yield after chromatography. This material was hydrolysed with concentrate hydrochloric acid and then treated with aqueous sodium hydroxide to afford the desired disodium [*benzene-U-<sup>14</sup>C]-4-(4-chlorophenylthio)methylenediphosphonate, [*benzene-U-<sup>14</sup>C]-Tiludronate, **2**, in 92% radiochemical yield with both a chemical and radiochemical purity of >98.8%. The overall radiochemical yield of the above synthesis of [*benzene-U-<sup>14</sup>C]-Tiludronate, **2**, from [*benzene-U-<sup>14</sup>C]-acetanilide was 41%.*****

## EXPERIMENTAL

**[*benzene-U-<sup>14</sup>C]-4'-Chloroacetanilide, **7**:*** [*benzene-U-<sup>14</sup>C]-Acetanilide (208 mCi, specific activity 130 mCi/mmol, 1.6 mmol)<sup>14</sup> was dissolved in dichloromethane (30 ml) with cooling to 0°C in an ice/water bath. To this solution was added tetrabutylammonium iodotetrachloride (840 mg, 1.6 mmol) over a period of 10 minutes. The reaction mixture was stirred at this temperature for 8 hours and then stored at -20°C overnight. After this time the mixture was warmed to room temperature and further tetrabutylammonium iodotetrachloride (136 mg, 0.27 mmol) added and the resulting mixture stirred at room temperature for two hours. The reaction was then quenched by addition of aqueous sodium thiosulfate and extracted with further dichloromethane. The solvent removed under reduced pressure and the crude product chromatographed on silica gel eluting with dichloromethane : ethyl acetate (9:1) to afford first [*benzene-U-<sup>14</sup>C]-2'-chloroacetanilide, **6** (37.2 mCi, 18% yield) and then the desired [*benzene-U-<sup>14</sup>C]-4'-chloroacetanilide, **7** (154.4 mCi, 74% radiochemical yield).***

**[U-<sup>14</sup>C]-4-Chloroanilinium hydrochloride, **8**:** [*benzene-U-<sup>14</sup>C]-4'-Chloroacetanilide, **7**, (54.4 mCi, 0.42 mmol) and 4'-chloroacetanilide (236 mg, 1.39 mmol) were suspended in concentrated hydrochloric acid (25 ml) and warmed to 60°C. After 48 hours tlc (silica gel, chloroform : isopropylamine (97:3)) revealed no remaining 4'-chloroacetanilide and the solvent was removed under reduced pressure to afford, as a white solid, the desired [U-<sup>14</sup>C]-4-chloroanilinium hydrochloride, **8** (54.4 mCi, specific activity 30 mCi/mmol, 1.81 mmol) which was used directly in the following reaction.*

**[*benzene-U-<sup>14</sup>C]-4-Chlorophenylthiocyanate, **10**:*** [U-<sup>14</sup>C]-4-Chloroanilinium hydrochloride (54.4 mCi, 1.81 mmol) was dissolved in dilute hydrochloric acid (2 ml, 1M) and cooled to 0°C in an ice/water bath. Sodium nitrite (149 mg, 2.16 mmol) was added and the reaction mixture stirred for 30 minutes until tlc (silica gel, chloroform : isopropylamine (97:3)) revealed no remaining 4-chloroaniline, thus affording a solution of the diazonium salt, **9**. Iron(III) chloride hexahydrate (973 mg, 3.6 mmol) was dissolved in water (10 ml) and potassium cyanate (1.05 g, 10.8 mmol) was added. This resulting solution of iron(III) thiocyanate was cooled to 0°C in an ice/water bath. The above formed solution of the diazonium salt, **9**, was added to the solution of iron(III) thiocyanate and the mixture stirred at room temperature for one hour. Ethyl acetate (20 ml) was then added and the resulting mixture warmed to 80°C until no further evolution of gas was observed. The reaction mixture was

then cooled in a water bath before being quenched by addition of saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic phase was washed sequentially with water and saturated aqueous sodium chloride. The solvent was then removed under reduced pressure and the crude product chromatographed on silica gel eluting with hexane : diethyl ether (97:3) to afford the desired [*benzene-U-<sup>14</sup>C]-4-chlorophenylthiocyanate, **10** (45.4 mCi, 83% radiochemical yield).*

**Tetraisopropyl [*benzene-U-<sup>14</sup>C]-4-chlorophenylthio)methylenediphosphonate, **12**:***

Under an atmosphere of nitrogen gas, tetraisopropyl methylenediphosphonate (1.068 g, 3.1 mmole) in tetrahydrofuran (5 ml) was cooled to -78°C and *n*-butyllithium (2 ml, 1.55 M, 3.1 mmole) was added. The reaction mixture was stirred for 10 minutes at this temperature. A solution of [*benzene-U-<sup>14</sup>C]-4-chlorophenylthiocyanate, **10** (45.4 mCi, 1.51 mmole) in tetrahydrofuran (5 ml) was added to this first formed solution and the temperature was allowed to rise to room temperature. After 24 hours the reaction was quenched by addition of saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic solvent was removed under reduced pressure and the crude product chromatographed first on silica gel eluting with toluene : methanol (19:1) and subsequently on silica gel eluting with toluene : isopropanol (19:1) to afford the desired tetraisopropyl [*benzene-U-<sup>14</sup>C]-4-chlorophenylthio)methylenediphosphonate, **12** (33.1 mCi, 73% radiochemical yield)**

**Disodium [*benzene-U-<sup>14</sup>C]-4-chlorophenylthio)methylenediphosphonate, [*benzene-U-<sup>14</sup>C]-Tiludronate, **2**:****

Tetraisopropyl [*benzene-U-<sup>14</sup>C]-4-chlorophenylthio)methylenediphosphonate, **12** (33.1 mCi, 1.1 mmole) was suspended in conc. hydrochloric acid (50 ml) and warmed to 90°C. After two hours, tlc (silica gel, toluene : isopropanol (19:1)) revealed reaction to be complete. The solvent was removed under reduced pressure and the residue dried under high vacuum to constant weight. This residue was then dissolved in water (3.9 ml) and the pH adjusted to 5.1 by addition of aqueous sodium hydroxide (350 µl, 6.6 M). Addition of acetone (20 ml) to this solution produced a precipitate which was removed by filtration, washed with further acetone and then dried under high vacuum to afford the desired disodium [*benzene-U-<sup>14</sup>C]-4-chlorophenylthio)methylenediphosphonate, [*benzene-U-<sup>14</sup>C]-Tiludronate, **2** (30.5 mCi, 391 mg, Specific Activity 78 µCi/mg, 92% yield), with a radiochemical purity of 98.9% by HPLC and a chemical purity of 98.8% (after correction for a water content of 6% confirmed by Karl Fischer analysis).***

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