SYNTHESIS OF 1-(2,6-DIFLUOROBENZOYL)-3-(2-FLUORO-4-(2-CHLORO-4-TRIFLUOROMETHYLPHENOXY)[*ring*-U-^{14}C]PHENYL)UREA

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SUMMARY

1-(2,6-Difluorobenzoyl)-3-(2-fluoro-4-(2-chloro-4-trifluoromethylphenoxy)[*ring*-U-^{14}C]phenyl)urea, a potent new acylurea insecticide and acaricide known as flufenoxuron, was labelled with carbon-14 starting from *o*-dinitro[*ring*-U-^{14}C]benzene 1. 2-Fluoronitro[*ring*-U-^{14}C]benzene, 2 obtained by fluorination of 1 with n-tetrabutylammonium fluoride, was converted in two stages to 4-amino-3-fluoro[*ring*-U-^{14}C]phenol 3, coupled with 3-chloro-4-fluorobenzotrifluoride 4 to give 2-fluoro-4-(2-chloro-4-trifluoromethylphenoxy)[*ring*-U-^{14}C]aniline 5, which when reacted with 2,6-difluorobenzoylisocyanate 6 gave the required urea 7. [*aniline ring*-U-^{14}C] flufenoxuron, having a specific activity of 851MBq/mmol (23mCi/mmol), was obtained in 24% overall radiochemical yield and a radiochemical purity of >99%.

Key Words: acaricide, Carbon-14, CASCADE, flufenoxuron, insecticide, synthesis

INTRODUCTION

Although other insecticides of similar type are already on the market, flufenoxuron* is an acylurea chitin inhibitor with very high levels of acaricidal activity, a property unique to this chemical group. It is also an excellent insecticide (1). The product is being developed for use in a wide range of crops. During the development of the compound, radiolabelled flufenoxuron was required for various metabolic and residue studies. For this purpose carbon-14 was incorporated into the aniline ring starting with commercially available *o*-dinitro[*ring*-U-^{14}C]benzene as shown in Scheme 1. The labelled aniline 5 was reacted with non-labelled isocyanate as is usual in the preparation of labelled urea pesticides (4).

* flufenoxuron is marketed under the trade name **CASCADE**

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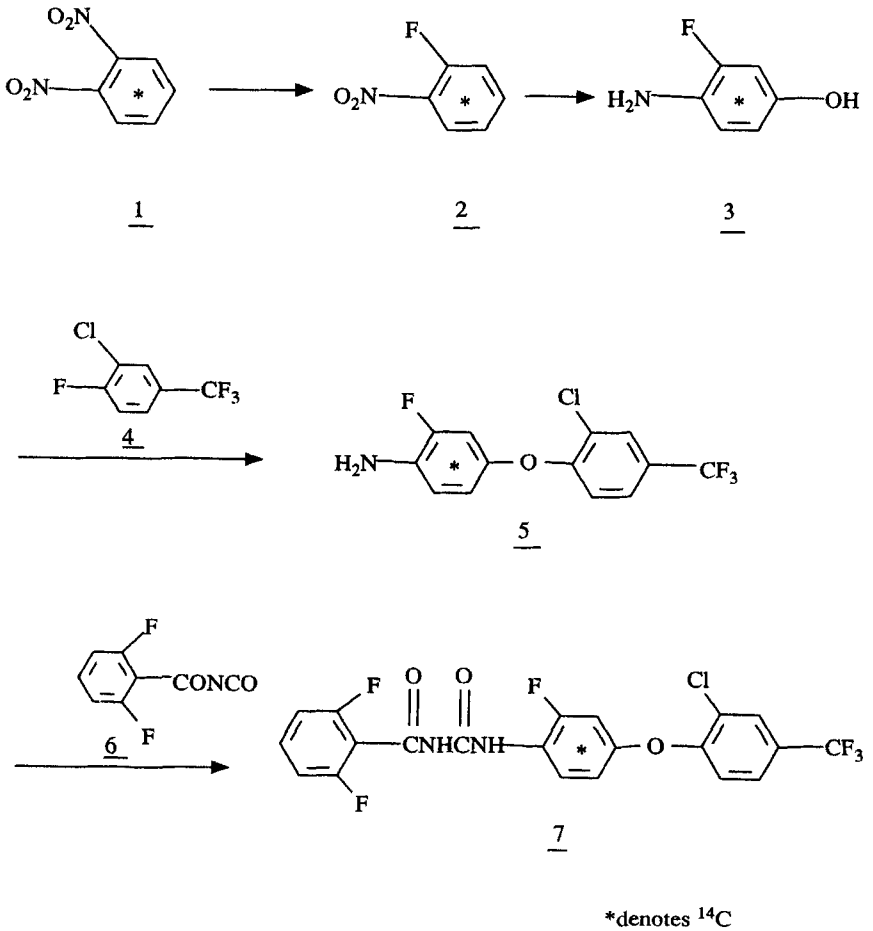
RESULTS

2-Fluoronitro[*ring*-U-^{14}C]benzene 2 was synthesised by the method of Clark (2) in a 96% yield. The reduction of 2 was best carried out under neutral conditions (3) and the rearrangement to 3 under hot acidic conditions. Various by-products were formed, such as 2-fluoroaniline and 2-amino-3-fluorophenol,



Scheme 1

most of which were removed by solvent extraction under carefully controlled pH conditions. It was found, at the specific activity used in this work, that the instability of 4-amino-3-fluorophenol 3 was enhanced by radiolysis, especially under the basic conditions necessary for successful coupling with 4. This resulted in variable yields at this stage. The reaction of 5 with 1 equivalent

of 6 proceeded successfully furnishing the product 7 with a purity of >85%. Purification was achieved by reverse phase HPLC giving a final product in a 24% overall radiochemical yield with a radiochemical purity of >99%.

EXPERIMENTAL

o-Dinitro[*ring*-U-^{14}C]benzene (1, >97% radiochemically pure) with a specific activity of 4.33GBq/mmol (117mCi/mmol) was purchased from Amersham International plc, U.K. 3-Chloro-4-fluorobenzotrifluoride 4 was supplied by Occidental Chemical Co. Reverse phase preparative high performance liquid chromatography (HPLC) was carried out on the crude product (dissolved in 1,4-dioxane, 230mg/ml) using equipment consisting of Spherisorb S5 ODS2 column (25cm x 20mm), LKB 2151 Variable Wavelength UV-detector (239nm), LKB 1208 Betacord radioactivity detector and a mobile phase of CH_3CN : H_2O : IPA (6:3:1, v/v/v) at 18ml/min.. The required product was isolated by evaporation of the appropriate fractions of eluant. Thin layer chromatography (TLC) was carried out on silica gel plates (MERCK 60 F-254) and radiochromatogram scans performed on a Berthold LB2722 scanner. Liquid scintillation counting was performed using a LKB 1215 Rackbeta II liquid scintillation counter.

2-Fluoronitro[*ring*-U-^{14}C]benzene 2

Carrier *o*-dinitrobenzene (242.3mg ; 1.44mmol) was added to *o*-dinitro[*ring*-U-^{14}C]benzene 1 (1.52GBq @ 4.33GBq/mmol) in diethyl ether and evaporated to dryness to give material of specific activity 851MBq/mmol. Tetrabutylammonium fluoride (10ml of 1M THF solution) was added and the solution stirred at room temperature under nitrogen for 5hr. Water (15ml) was added followed by diethyl ether (10ml). The phases were separated, the aqueous phase extracted with ether (3 x 10ml), and the combined organic extracts washed twice with hydrochloric acid (1M), water and dried (anhydrous M_gSO_4). This solution was evaporated at 30°C to low volume and the product purified by preparative TLC (1 x 20cm x 20cm. Uniplate taper silica plate eluted in ethyl acetate : 40-60° Pet.spirit (1:4)). The appropriate zone was removed and washed with ethyl acetate. Yield 1.46GBq (96%) of 2.

4-Amino-3-fluoro[*ring*-U-^{14}C]phenol 3

The solution of 2-fluoronitro[*ring*-U-^{14}C]benzene 2 (1.46GBq @ 851MBq/mmol)

was evaporated, dissolved in methyl *tert*-butyl ether (MTBE; 2ml) and added to water (0.2ml) containing 5%Rh/C catalyst (30mg). Hydrazine hydrate (0.2ml in 0.02ml portions) was added over 1.5hr. at room temperature, and additional catalyst (30mg) added after 1hr. The upper ether phase and subsequent ether extracts of the aqueous phase, were added to pre-heated (90°C) sulphuric acid (2.5M; 10ml) such that the ether was allowed to blow off in a stream of nitrogen. The resultant red solution was heated @ 85°C for 1hr. then cooled to room temperature. Dichloromethane (4ml) was added and the pH adjusted to 3.8 using ammonia (50%). The organic phase was removed and the aqueous phase washed once with more dichloromethane (4ml). Ethyl acetate (5ml) was added to the aqueous phase and the pH adjusted to 10.0 using ammonia (0.880 S.G.). The phases were separated, and the aqueous extracted with ethyl acetate (x4). Yield 1.29GBq (88%) of 3.

2-Fluoro-4-(2-chloro-4-trifluoromethylphenoxy)[*ring*-U-^{14}C] aniline 5.

Using a Dean and Stark apparatus under nitrogen, the solution of crude 4-amino-3-fluoro[*ring*-U-^{14}C]phenol 3 (1.29GBq) was added, portionwise, to a mixture of sulfolane (2.5ml) and 80-100° pet.spirit pre-heated to 85°C, such that ethyl acetate and any water was removed by azeotropic distillation. Potassium hydroxide (64mg) in water (0.1ml) was added and the water removed by azeotropic distillation using 80-100° pet.spirit. The resultant purple solution was cooled to 65°C and 3-chloro-4-fluorobenzotrifluoride 4 (200mg) added. The mixture is stirred at 65°C for 2.5hr. then cooled to room temperature. Water : carbon tetrachloride (3:1, 20ml) was added, the mixture shaken and the lower phase separated. The upper phase was washed with carbon tetrachloride (x4) and the combined extracts washed with water. Yield, 0.52GBq (40%). TLC eluted in ethyl acetate : dichloromethane (1:9) indicated a radiochemical purity of 90%.

[*aniline ring*-U-^{14}C]flufenoxuron 7.

Using a Dean and Stark apparatus containing toluene under nitrogen, the solution of 2-fluoro-4-(2-chloro-4-trifluoromethylphenoxy)[*ring*-U-^{14}C]aniline 5 (0.52GBq) was added such that the carbon tetrachloride and any water is removed by azeotropic distillation. The resultant dry

toluene solution was cooled to room temperature, 2,6-difluorobenzoylisocyanate 6 (0.05ml-75mg) is added and the solution stirred for 0.75hr., then stored at -20°C overnight. TLC eluted in diethyl ether;hexane (2:1) indicated a 86% conversion to 7. Purification by preparative HPLC gave 0.36GBq (206mg;24% overall yield) of product with a specific activity of 851MBq/mmol. TLC eluted in diethyl ether : 60-80° pet.spirit (2:1) or ethyl acetate : dichloromethane (1:9) indicated a radiochemical purity of >99%. The chemical purity was confirmed by ^{1}H NMR (360MHz; $CDCl_3$) and mass spectroscopy (EI and CI) and found to be >99%.

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