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SYNTHESIS OF DEUTERIUM LABELLED ANALOGS OF FLUAZIFOP AND HALOXYFOP

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SUMMARY

Synthetic routes have been described for the preparation of stable isotope-labelled analogs of two aryloxyphenoxypropionates, each containing approximately four deuterium atoms in the central phenyl ring of the molecule. Fluazifop-2',3',5',6'-$^2H_4$ [2-(4-((5-(trifluoromethyl)-2-pyridinyl)-oxy)phenoxy)propionic acid-2',3',5',6'-$^2H_4$] and haloxyfop-2',3',5',6'-$^2H_4$ [2-(4-((3-chloro-5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propionic acid-2',3',5',6'-$^2H_4$] were synthesized from the common intermediate HPPA-2',3',5',6'-$^2H_4$ [2-(4-hydroxyphenoxy)propionic acid-2',3',5',6'-$^2H_4$]. This intermediate was obtained from HPPA via acid-catalyzed deuterium exchange ($^2H_2SO_4$ in ^2H_2O and CH_3O^2H).

Key words: fluazifop, haloxyfop, deuteration, internal standard, aryloxyphenoxypropionate, 2-(4-hydroxyphenoxy)propionic acid.

INTRODUCTION

Many toxicology and pharmacokinetic/metabolism studies require detection and/or quantitation of a test material in complex matrices such as animal feed, urine, feces, blood or tissues. A selective and sensitive technique often employed in these analyses is gas chromatography/mass spectrometry (GC/MS). The mass spectrometer, however, can be more variable and nonlinear than other, more conventional GC detectors. To overcome these problems internal standards are often employed in quantitative assays using GC/MS. One type of internal standard is a structural analog of the compound of interest. Another type of internal standard for GC/MS analyses is an analog of the test compound which contains one or more stable isotopes (^{13}C, ^{15}N, ^2H, ^{18}O). Claeys, et al., have found that lower experimental variances can be obtained by using stable isotope-labelled internal standards (1). This may be due to the fact that the physical and

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chemical properties for these compounds more closely resemble the test material than do less similar structural analogs.

To aid in a variety of analytical assays dealing with several aryloxyphenoxypropionate herbicides, stable isotope-labelled analogs of two of these compounds were synthesized, each containing approximately four deuterium atoms in the central phenyl ring of the molecule.

RESULTS AND DISCUSSION

Fluazifop-2',3',5',6'-$^2H_4$ ([2-(4-((5-trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propionic acid-2',3',5',6'-$^2H_4$], 2) and haloxyfop-2',3',5',6'-$^2H_4$ ([2-(4-((3-chloro-5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propionic acid-2',3',5',6'-$^2H_4$], 3) were synthesized from the common intermediate HPPA-2',3',5',6'-$^2H_4$ ([2-(4-hydroxyphenoxy)propionic acid-2',3',5',6'-$^2H_4$, 1) (scheme 1).

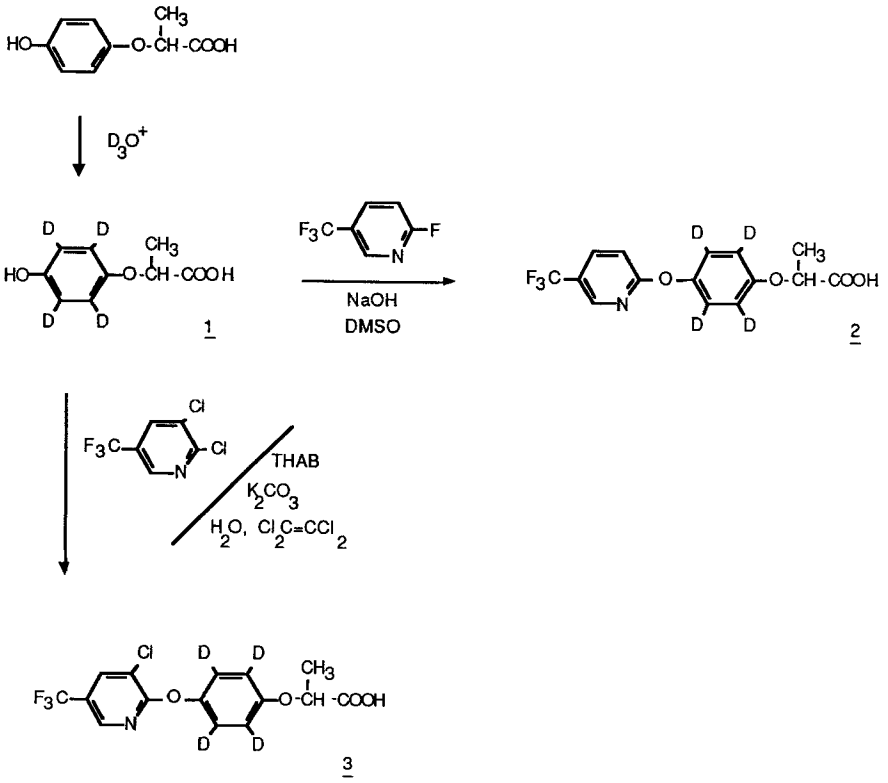
HPPA-2',3',5',6'-$^2H_4$ (1) was obtained from HPPA (2) in a facile manner via acid-catalyzed deuterium exchange. The exchange was carried out in 33% $^2H_2SO_4$ in $^2H_2O/CH_3O^2H$ (v/v) at 95°C for 6 hr. The experimental yield was acceptable (65%). Mass spectral analysis indicated that the crude product contained an average of 3-4 deuterium atoms on the aromatic ring. Subsequent reactions indicated that the exchange was essentially complete after 2 hr. Higher deuterium incorporation was also achieved by decreasing the concentration of HPPA in the reaction mixture. This labelled intermediate was used in the synthesis of both 2 and 3.

Addition of 2-fluoro-5-(trifluoromethyl)pyridine to 1, under basic conditions in DMSO, afforded 2 in 61% yield (purity 74%). A crystalline product was obtained after semipreparative HPLC purification (purity 98%). No attempts were made to optimize experimental conditions for this reaction. Product of a higher purity should be attainable with the conditions used for the synthesis of 3.

Haloxyfop-2',3',5',6'-$^2H_4$ (3) was prepared by the addition of 2,3-dichloro-5-(trifluoromethyl)pyridine to 1 in water and tetrachloroethylene with the phase transfer catalyst

tetraheptylammonium bromide. This product was of a higher purity than 2 (>99%); however the yield, based on 1, was lower (32%).

Scheme 1.



Although the yields of the two products (2 and 3) were low, the compounds were of sufficient purity and deuterium incorporation to be highly useful as internal standards in a variety of analytical procedures. NMR and mass spectral analysis of 2 and 3 indicated an average incorporation of 3.7 and 3.3 deuterium atoms into each of these compounds, respectively, with 1% or less remaining unlabelled. The higher incorporation for 2 was due to a more highly labelled lot of 1 used in the preparation of this compound.

The deuterium label for these compounds should be stable to a wide range of pH and chemical conditions, as evidenced by the harsh conditions required to incorporate the label. The deuterium label was stable to EI mass spectral conditions.

In summary, synthetic routes have been described for the preparation of stable isotope-labelled analogs of fluazifop and haloxyfop, each containing approximately four deuterium atoms in the central phenyl ring of the molecule. Both compounds were synthesized from the common intermediate 2-(4-hydroxyphenoxy)propionic acid-2',3',5',6'-$^2H_4$ (1). These compounds should have applications as GC/MS internal standards as well as aiding in identification of parent compound or subsequent metabolites, by the use of the twin ion technique (3). The deuterium-labelled intermediate 1 should also be useful in the synthesis of other aryloxyphenoxypropionates.

EXPERIMENTAL

Melting points were determined on an Exothermal or Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 983 spectrophotometer. NMR spectra were recorded on a Bruker WM360 spectrometer using TMS as an internal standard. Mass spectra were obtained on a Finnigan MAT 4600 GC/MS. HPLC analyses were performed with a Waters model 590 pump, Waters model 660 gradient controller and an Autochrom OPG model 110 one pump gradient accessory to generate a 30 min. linear gradient (100% H_2O to 100% CH_3CN, both with 1% AcOH) using a reverse phase C_{18}-column (10 cm x 8 mm; 10 μm).

2-(4-Hydroxyphenoxy)propionic acid-2',3',5',6'-$^2H_4$ (1). 2-(4-Hydroxyphenoxy)propionic acid (10.5 g, 58 mmol) was added to a solution of 20 ml 50% $^2H_2SO_4$ in ^2H_2O (v/v) and 10 ml CH_3O^2H. The solution was stirred at 95°C for 6 hr. The solution was concentrated, diluted to 100 ml (H_2O) and extracted with ether (4 x 50 ml). The combined ether extracts were washed with H_2O (2 x 50 ml), dried ($MgSO_4$) and evaporated to afford a light brown oil. This oil was dissolved in 10 ml 10% aq. NaOH and 5 ml EtOH and allowed to stand at room temperature for 18 hr. The solution was then concentrated (N_2), adjusted to pH 2 (conc. HCl) and extracted with ether (4 x 30 ml). The combined ether extracts were washed with H_2O (2 x 15 ml), dried ($MgSO_4$) and evaporated to afford 7.0 g (65%) crude 1 as a brown crystalline solid; EI mass spectrum of the methyl ester m/z, 200, 199, 198, 197, 196 (M^+, 55, 41, 13, 2, 1), 141, 140, 139, 138, 137 (58, 47, 15, 3, 1), 114, 113, 112, 111, 110 (93, 100, 47, 12, 4). This material was used without further purification in subsequent reactions.

2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propionic acid-2',3',5',6'-$^2H_4$ (fluazifop-2',3',5',6'-$^2H_4$) (2). Sodium hydroxide (0.37 g, 9.3 mmol), in 0.5 ml H_2O, was added to a solution of 0.81 g (4.4 mmol) 1 (second lot) in 20 ml DMSO. This mixture was heated at 80°C for 15 min. 2-Fluoro-5-(trifluoromethyl)pyridine (0.67 g, 4.1 mmol) was then added dropwise and the resulting solution heated at 105°C for 1.5 hr. The solution was diluted to 100 ml (H_2O), adjusted to pH 2 (1N HCl) and extracted with ether (5 x 30 ml). The combined ether extracts were washed with H_2O (3 x 10 ml), dried ($MgSO_4$) and evaporated to afford a brown oil. This oil was dissolved in 2 ml EtOH and 5 ml 20% aq. KOH and allowed to stand at room temperature for 2 hr. The solution was concentrated, washed with ether (2 x 5 ml), adjusted to pH 1 (conc. HCl) and extracted with ether (4 x 5 ml). The combined ether extracts were evaporated to afford 1.1 g (82%) crude 2 as a brown oil. A portion of this product was purified by semipreparative reverse phase HPLC (purity of crude 2=74%; final purity=98%) to afford 2 as a tan solid, mp 98-103°C; ir (KBr) 3085 (broad), 1725, 1615, 1420, 1330, 1155, 1130, 1080 cm^{-1}; nmr (acetone-$^2H_6$) δ 8.46 (ddq, 1, 6"-H), 8.13 (ddq, 1, 4"-H), 7.15 (ddq, 1, 3"-H), 7.13-6.99 (m, ca. 0.2, 2',3',5',6'-H), 4.87 (q, 1, 2-H), 1.61 (d, 3, 3-H) ($J_{2,3}$ = 6.8 Hz, $J_{3",4"}$ = 8.7 Hz, $J_{3",6"}$ = 0.7 Hz, $J_{4",6"}$ = 2.6 Hz, $J_{3",CF_3}$ = 0.7 Hz, $J_{4",CF_3}$ = 0.6 Hz, $J_{6",CF_3}$ = 0.7 Hz); EI mass spectrum of the methyl ester m/z, 345, 344 (M^+, 100, 34), 286, 285, 284 (86, 27, 3), 258, 257, 256 (60, 36, 7).

2-(4-((3-Chloro-5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propionic acid-2',3',5',6'-$^2H_4$ (haloxyfop-2',3',5',6'-$^2H_4$) (3). 2,3-Dichloro-5-(trifluoromethyl)pyridine (1.9 g, 8.8 mmol) was added to a solution containing 2.2 g (16 mmol) K_2CO_3, 0.3 g (0.9 mmol) tetraheptylammonium bromide and 1.2 g (6.4 mmol) 1 in 12.3 ml tetrachloroethylene and 5 ml H_2O. This mixture was stirred at 100°C for 23 hr. The reaction mixture was diluted with H_2O (100 ml) and the aqueous phase adjusted to pH 1.5 (conc. HCl). After shaking, the aqueous phase was discarded. Following cooling in an ice bath and filtration 0.7 g (32%) of 3 was obtained as off-white crystals, mp 107.5-108.5°C; ir (KBr) 3050 (broad), 1710, 1435, 1410, 1330, 1165, 1135, 1085 cm^{-1}; nmr (C^2HCl_3) δ 8.19 (dq, 1, 6"-H), 7.92 (dd, 1, 4"-H), 7.01-6.86 (m, ca. 0.6, 2',3',5',6'-H), 4.71 (q, 1, 2-H), 1.67 (d, 3, 3-H) ($J_{2,3}$ = 7.0 Hz, $J_{4",6"}$ = 2.2 Hz, $J_{4",CF_3}$ = 0.1 Hz, $J_{6",CF_3}$ = 0.6 Hz); EI mass spectrum of the methyl ester m/z, 379, 378, 377, 376 (M^+, 74, 61, 22, 2), 320, 319, 318, 317 (100, 81, 27, 8), 292, 291, 290, 289 (81, 85, 37, 8).

A portion (1 mg) of the product was derivatized with 50 µl BSTFA at 65°C for 15 min. Capillary GC (TCD) showed the product to be 99.5% pure.

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