A simple synthesis of the regiospecifically deuterium-labeled herbicide MCPA-isopropyl

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In order to investigate the metabolism of the herbicide MCPA-isopropyl [isopropyl 2-(4-chloro-2-methylphenoxy)acetate] in the environment, two isotopologues of this regiospecifically deuterium-labeled in selected positions compound were synthesized. The synthesized compounds were labeled at the methylene group, isopropyl 2-(4-chloro-2-methylphenoxy)[2,2-2H2]acetate, and at the isopropyl group, [3H1]isopropyl 2-(4-chloro-2-methylphenoxy)acetate. © Pesticide Science Society of Japan

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Introduction

Alkyl esters of MCPA undergo transformations in soil (Fig. 1).1-3) The break of the ester bond, catalyzed by carboxylic ester hydroxylase produced by microorganisms in the soil, leads to the release of free MCPA (in acid form) and the appropriate alcohol. Formed as an intermediate, MCPA under the influence of microbial enzymes is transformed into 4-chloro-2-methylphenol and glycolic acid. At low concentration of MCPA labeled with 14C at the benzene ring, the ring cleavage is observed and 14C carbon dioxide release is detected.2)

The methyl group in 4-chloro-2-methylphenol oxidizes easily to the appropriate hydroxymethyl moiety and then to the aldehyde group (CHO), affording 5-chlorosalicylaldehyde. Another important oxidation product of both MCPA and 4-chloro-2-methylphenol is 5-chloro-3-methylpyrocatechol.1,3)

In previous papers, we described both the identification and synthesis of some significant impurities,4 as well as the synthesis of the regiospecifically deuterium-labeled insecticide bromfenvinphos.5) A continuous interest in deuterated pesticides, led to our investigation of phenoxyacetic herbicides. MCPA-isopropyl (1) is a common name for the isopropyl ester of the widely known herbicide and plant growth regulator 4-chloro-2-methylphenoxyacetic acid (MCPA).6,7) MCPA-isopropyl has also been used as a herbicide (e.g., NSC 4097708) as well as some other MCPA esters.9)

There is no data about synthesis of MCPA-isopropyl labeled with deuterium at the methylene group 2, and about the synthesis of its isotopologue 3 when deuterium labeled at the isopropyl group. To the best of our knowledge, the compounds 2 and 3 have never been described. In this paper, the successful synthesis and full characterization of both 2 and 3 are presented.

Herein two 3H isotopologues of 1 labeled at specific carbon atoms were synthesized: at the methylene moiety was isopropyl 2-(4-chloro-2-methylphenoxy)[2,2-2H2]acetate (2), and at the isopropyl group was [3H1]isopropyl 2-(4-chloro-2-methylphenoxy)acetate (3). Further environmental studies will be undertaken as the project progresses. The deuterium-labeled compounds will be used for residue determination in biological matrices and degradation mechanisms (hydrolysis and photolysis). Further results will be published.

Material and Methods

1. General

Reagent-grade chemicals were used without further purification or, if needed, dried and/or distilled using commonly known methods.

1H and 13C NMR spectra were recorded on a UNITY plus-200 "Varian 200" spectrometer, and 2H NMR spectra were recorded on an INOVA-500 "Varian 500" spectrometer (δ, ppm), GC analysis was carried out using a Varian 3300 gas chromatograph (FID, DB-1 column). High-resolution EI mass spectra (EI HRMS) were recorded using a GCT Premier Waters TOF instrument at 70 eV. An AMD 604 sector instrument was used to perform low-resolution EI-MS (70 eV) of nonvolatile or thermally unstable compounds [m/z (int.% assignment)]. FT-IR (ν, cm⁻¹, film) spectra were recorded using a Jasco 420 infrared spectrophotometer.

2. Syntheses of the compounds

2.1. [3H1]Bromoacetyl bromide (4)10) (with some substantial modifications)

Bromine (4.679 g, 1.5 mL, 30 mmol) was added dropwise to 0.208 g (6.7 mmol) of red phosphorus and 1.030 g (0.92 mL, 16 mmol) of [3H1]acetic acid and stirred rapidly for about 5 min while being cooled in an ice bath at 0°C. The solution was allowed to warm to rt during 30 min, and the reaction mixture was heated to 73°C and continuously stirred overnight (15 h). The reaction mixture was then distilled through a short Vigreux column, collecting fraction boiling at 148–151°C. Yield of the compound 4 was 2.348 g (72%) of a pale yellow liquid. 1H NMR: no signals; 13C NMR: δC 160.9 (C=O), 37.6 (CD2, quintet, JCD = 24 Hz). EI GC-MS (DI): 123 (100, [M-Br]+), 95 (32, +CD3Br). FT-IR: ν 1812 (C=O), 2196, 2260, (C-D).
2.2. Isopropyl [2H2]bromoacetate (5) (according to ref. 10 and with some modifications)

A mixture of 1.868 g (11.4 mmol) sodium phosphate, a catalytic amount (0.1 g) of 4-dimethylaminopyridine, 15 mL of dichloromethane, and 0.934 g (1.19 mL, 15.6 mmol) of [O-2H]2-propanol was cooled in an ice-salt bath. [2H2]bromoacetyl bromide (4) (2.11 g, 10.4 mmol) was added dropwise over 15 min while keeping the temperature below 0°C. Stirring continued for an additional 24 hr while the mixture warmed to rt. The reaction mixture was then filtered. The organic solution was washed with deuterium oxide (2 × 5 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed. The residue was distilled under reduced pressure, affording 1.147 g of the compound (5), a colorless liquid, bp 40°C at 9 Torr, yield 39%. 1H NMR: δH 5.07 (CH, septet, J = 6.4 Hz), 1.28 (2 × CH3, d, J = 6.4 Hz); 13C NMR: δC 166.9 (C = O), 70.2 (CH), 26.2 (CD2, quintet, JC,D = 23 Hz), 21.7 (2 × CH3); EI GC-MS: M+ 167 (17, [M-CH3]+); 141 (46, BrCD2(C=OH)+OH), 123 (100, BrCD2C=O)+; GC: purity 99.6%; FT-IR: ν2983 (C–H), 2180 (C–D), 1733 (C=O).  

2.3. Isopropyl 2-(4-chloro-2-methylphenoxy)[2,2-2H2]acetate (2)

Under a continuous argon flow, 10 mL of dry tetrahydrofuran (THF) was added in drops to 60% sodium hydride (0.192 g, 4.8 mmol). The flask was then cooled in an ice bath for 10 min while a solution of 4-chloro-2-methylphenol (0.772 g, 4.8 mmol) in THF (3 mL) was added dropwise and stirred over 10 min. After the mixture reached 0°C, a solution of isopropyl [2H2]bromoacetate (5) (0.871 g, 4.8 mmol) in THF (3 mL) was added in drops over a period of about 10 min. During the next 10 min, the mixture was stirred and brought to rt. Stirring continued at rt for 24 hr. The reaction mass was filtered through a pad of Celite, the flask was rinsed with hexane (2 × 10 mL) and the rinses were poured over the collected precipitate. The filtrate was concentrated, and the resulting semisolid was dissolved in dry dichloromethane (4 mL) and distilled in a vacuum, affording 0.66 g of the title compound (2). Under a continuous argon flow, a cold (0°C) solution of [2H2]2-propanol (34 μL, 0.44 mmol, 1.1 eq.) in 4 mL of dry dichloromethane was added dropwise while stirring, followed by addition of triethylamine (70 μL, 0.48 mmol, 1.2 eq.). Fig. 1. Some transformations of MCPA and its esters in soil.
continued at 0°C for 20 min and at rt for 24 hr. The reaction mixture was concentrated under vacuum and purified by flash chromatography on silica. The yield was 0.876 mg (82%) of [2H7]isopropyl 2-(4-chloro-2-methylphenoxy)acetate (3), a colorless liquid. 1H NMR δH 4.58 (CH2, s), 2.26 (CH3, s), 6.59-7.14 (3H arom., m); 2H NMR: δD 1.17 (2×CD3, s), 5.03 (CD, s); 13C NMR: δC 168.5 (C=O), 155.0, 130.9, 129.5, 126.4, 126.3, 112.5, 66.2, 16.3; EI GC-MS: M+ 249 (100), 201 (92, [M–CD2CD3]+), 155 (94, [M–CD2CD3–.COOD]+), 125 (56, Cl-tropylium+), 50 (73, C3D7)+; EI HRMS: M+ C12H8D7ClO3 required 249.1149, found 249.1140; GC: purity 94%; FT-IR: ν 2926 (C–H), 2234 (C–D ), 1754, 1730 (C=O).

Results and Discussion

Isopropyl 2-(4-chloro-2-methylphenoxyl)[2,2-2H2]acetate (2), an isotopologue of MCPA-isopropyl 1 regiospecifically labeled with deuterium at the methylene moiety, was synthesized in a three-step sequence of reactions (Fig. 2).


[2H5]Isopropyl 2-(4-chloro-2-methylphenoxy)acetate (3) was obtained in the two-step synthesis, carried out first through transformation of MCPA with thionyl chloride into corresponding acyl chloride 6, followed by direct esterification of the crude MCPA chloride 6 with [2H8]2-propanol and triethylamine, affording 3 in an 82% yield (Fig. 3). The compounds 2, 3, 4 and 5 were fully spectroscopically characterized.

Conclusion

Two novel deuterated isotopologues of the herbicide MCPA-isopropyl were synthesized and fully characterized. Both compounds will be verified according to the lab Quality System and used as analytical Certified Reference Materials (CRM) in environmental studies.

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References