

<sup>14</sup>C-LABELING OF ISOMERIC PERFLUOROALKYL  
CARBOXANILIDE MIXTURES VIA ELECTROFLUORINATION

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Summary

Electrofluorination of benzoyl chloride-ring-UL-<sup>14</sup>C produced an isomer mixture of cyclic C<sub>6</sub>F<sub>11</sub> carbonyl fluorides, principally 1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexane-ring-UL-<sup>14</sup>C carbonyl fluoride, which was derivatized with 2-bromo-4-nitroaniline and triethyl amine. The resultant carboxanilide mixture is designated as EL-499 labeled with <sup>14</sup>C in the perfluoro alkyl ring for use in metabolic studies.

Key Words

electrofluorination, radiolabeled, carbon-14, carboxanilide, perfluoro, EL-499.

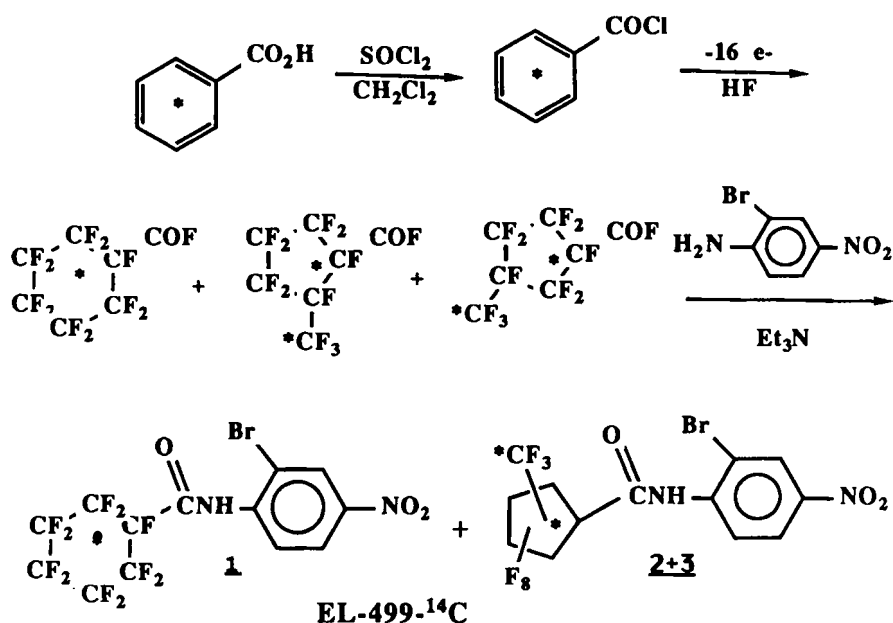
Introduction

Due to its present synthesis via electrofluorination, EL-499 is a mixture of insecticidal isomers typically (91-93%) 2'-bromo-4'-nitro-1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexane carboxanilide 1 and (6-8%) of both the corresponding 2- and 3-trifluoromethyl perfluorocyclopentyl carboxanilides 2 & 3.<sup>1a,b</sup> It represents an interesting new chemical class of soil insecticide, especially for the control of corn rootworm.<sup>2</sup>

Metabolic studies in both soil and corn required the synthesis of both aniline ring labeled and alkyl ring labeled EL-499-<sup>14</sup>C. Aniline ring labeled EL-499-<sup>14</sup>C was prepared by conventional methods.<sup>3</sup> However, perfluorocycloalkyl ring labeled EL-499-<sup>14</sup>C presented an interesting challenge (Scheme I)

due to concerns about radioactive contamination of the electrofluorination cell. It was desired that the cell components be inexpensive and essentially disposable. Furthermore, literature references to  $^{14}\text{C}$ -labeled perfluorinated acids from electrofluorination lacked sufficient detail to adequately precedent the required radiolabeling experiment.<sup>4a-c</sup> Thus, an 80-130 cc Simon Cell was assembled from a Teflon<sup>®</sup> jar, Swagelok<sup>®</sup> fittings, and stainless steel tubing (experimental section). Both reaction conditions and the reactor configuration were optimized for chemical yield using unlabeled benzoyl chloride.

### SCHEME I. Synthesis of EL-499- $^{14}\text{C}$



### Discussion

In contrast with the electrolysis results of Gambaretto et. al.,<sup>5</sup> who reported a 50% cell yield of carbonyl fluorides (sp. gr. = 1.7) on a 1 kg scale, electrofluorination products from a 2.1 g total quantity of unlabeled benzoyl chloride in 2-3% solution did not cleanly separate from anhydrous HF (sp. gr. = 1.0). Extraction of the cell reaction products with  $\text{CFCl}_3$  was required to maximize carboxanilide yields from only 9.5% to 25% (Table I). The combined cell extracts were added to excess 2-bromo-4-nitroaniline/triethyl

amine, and the carboxanilide product mixture was isolated as a single band from silica gel chromatography. Capillary GC/MS data were obtained on a Hewlett/Packard 5985B system with a 25 meter SE-54 capillary column and temperature programming from 90-260°C at 20°C/min. Compounds 1, 2, 3, and 4, an unspecified C<sub>6</sub>F<sub>13</sub> carboxanilide, were separated as distinct peaks.

TABLE I. Effect of Substrate Concentration and Cell Voltage on Carboxanilide Yield and Product Ratio

Wt. % Conc.	Cell Volt.	Chemical Yield <sup>a</sup>	Product Ratio <sup>c</sup>		
			1	2+3	4
3.0%	5.1-5.2	9.5% <sup>b</sup>	77.1	20.0	2.8
1.6%	4.8-4.9	16.5% <sup>d</sup>	80.4	15.8	2.3
2.5%	4.1-4.5	24% <sup>d</sup>	93.4	5.5	0.5
2.5%	3.9-4.4	24% <sup>d</sup>	92.0	7.2	0.4

<sup>a</sup>From benzoyl chloride

<sup>b</sup>No extraction

<sup>c</sup>Relative GC/MS peak areas uncorrected for detector response

<sup>d</sup>Extraction with CFCl<sub>3</sub>

From Table I, higher substrate concentration, which simultaneously permitted both reasonable current flow (10-14 ma/cm<sup>2</sup>) and lower cell voltage produced a higher chemical yield of 1, 2, and 3. Concurrently, the minimization of the perfluoroalkyl ring opened side product 4 resulted.

Thus, benzoic acid-ring-UL-<sup>14</sup>C (Scheme I) was treated with thionyl chloride to produce a small quantity of benzoyl chloride-ring-UL-<sup>14</sup>C of high specific activity, which was washed into the electrofluorination cell and simultaneously diluted with freshly distilled unlabeled benzoyl chloride to produce EL-499-perfluoroalkyl-ring-UL-<sup>14</sup>C in radiochemical yield of 27%. Subsequent radiochemical assay from sectioned thin-layer chromatography indicated that the isomer composition of the product approximated within 1-2% the isomer composition of unlabeled carboxanilides obtained under optimal conditions above.

Acknowledgement

We wish to acknowledge the determination of specific activity by Mr. Mark Copeland.

## Experimental

### Electrochemical Fluorination Apparatus

The cell design was taken from a classic literature description,<sup>6</sup> except that no cooling coil internal to the cell body was required. An 8 oz Teflon<sup>®</sup> PFA jar with outside threads from Curtin Matheson Scientific served as the cell body. The screw cap was fitted in its center with a 3/8" 316 stainless steel (316 ss) Swagelok<sup>®</sup> bulkhead union for connection with a 316 ss jacketed condenser, and the union was sealed to the Teflon<sup>®</sup> cap with a 015-9548 Viton<sup>®</sup> A O-ring from Crane Packing Co. The condenser was constructed from a 24" X 3/8" 316 ss tube, a 18" X 3/4" 304 ss tube, two 3/4" 316 ss Swagelok<sup>®</sup> union tees, two 316 ss 3/8"-3/4" bored through reducers, and two 316 ss 3/4" port connectors, and it could be maintained from -40 to -50°C by circulating chilled chloroform/methanol (90:10) with a Fisher immersion pump.

Four 1/8" 316 ss Swagelok<sup>®</sup> bulkhead unions were fitted at the corners of a rectangle surrounding the condenser union and were sealed to the cap with 568-011 Viton<sup>®</sup> A O-rings from Ace Glass. One of the smaller unions served as an inlet for both dry nitrogen gas and substrate addition. A second, smaller union was fitted internally by means of a ferrule with a 1/8" copper tube which extended to the bottom of the cell, and externally, it was fitted with a semicircular loop of 1/8" copper tubing which was closed with a 1/8" 316 ss Swagelok<sup>®</sup> union plugged in the end. This arrangement served as both a copper reference electrode during electrolysis and a faucet for removing product extracts while under nitrogen pressure. The two remaining smaller unions in the cap were connected to the electrode pack via 1/8" nickel 200 tubing.

The electrode pack consisted of four 1-7/8" X 1-7/8" nickel 200 plates and five 1-7/8" X 1-7/8" carbon steel plates. Two 316 ss threaded bolts connected the aggregate anode plates and aggregate cathode plates, respectively. Furthermore, a 3/16" wide 316 ss washer separated each anode and cathode plate on their respective threaded bolts such that after assembly the distance between the anodes and cathodes was 1/16". Higher substrate concentration was achieved by the insertion of custom machined Teflon<sup>®</sup> spacers in the dead

volume of the cell to bring the HF volume down from 130 cc to 80 cc for total immersion of the electrode plates.

A Fluke 8020b solid state multimeter was used to measure the cell voltage from the working anode to the copper reference electrode, which was cleaned with dilute nitric acid prior to each experiment. The D. C. power supply was a Hewlett Packard 6284A.

#### Benzoyl Chloride-Ring-UL-<sup>14</sup>C

Benzoic acid-ring-UL-<sup>14</sup>C obtained from Pathfinder Laboratories (0.29 g, 2.38 mmoles, specific activity 21.03 mCi/mM, total activity 50 mCi) was dissolved in benzene (10 cc), thionyl chloride (0.27 g, 0.23 moles) was added, and the reaction was heated to 60-65°C for 3 hours. The reaction mixture was evaporated to give benzoyl chloride-ring-UL-<sup>14</sup>C in quantitative yield.

#### EL-499-Perfluorinated Ring-UL-<sup>14</sup>C

In the Teflon<sup>®</sup> jar, approximately 80 cc of commercial anhydrous HF (caution) was added from a lecture bottle at 0°C, and the jar was turned into the cap/condenser/electrode pack assembly. The HF underwent a pre-electrolysis to remove the last traces of water under a nitrogen stream leading to a caustic trap at a maximum current density of about 20 ma/cm<sup>2</sup> and at or below a cell voltage of 5.2 volts relative to the copper reference electrode. Pre-electrolysis was considered over when the current level dropped from approximately 2.2 amp to a lower steady state of approximately 0.4 amp @ 5.2 volt. Benzoyl chloride-ring-UL-<sup>14</sup>C above was added and freshly distilled benzoyl chloride as diluent was added through the nitrogen inlet for a total of 2.1 g (15 mmoles) of benzoyl chloride. About 6.1 amp hrs (93% theoretical) corrected for baseline, was passed. The jar was cooled in an ice bath for 1.5-2.0 min, and four 20 cc portions of CFC1<sub>3</sub> was added through the top of the condenser. The Swagelok<sup>®</sup> plug on the end of the copper faucet was removed, and the condenser was plugged with a rubber dam to force the extracts out of the faucet into a polypropylene separatory funnel. The extracts were added to 1.6 g (7.4 mmoles) of 2-bromo-4-nitroaniline and 1.5 g (15 mmoles) of triethylamine in 40 cc methylene chloride at -10°C. The reaction was stirred for one hour at room temperature. The organic layer was washed with dilute

HCl, dried over sodium sulfate, and chromatographed on silica gel (250 g) with cyclohexane/toluene (2:1) to give an oily product, which was dissolved in methanol (5 cc) and added dropwise to cold water yielding 2.0 g of granular product (specific activity of 3.56 mCi/mM, total activity 13.54 mCi).

Radiochemical analysis was performed by thin-layer chromatography using Merck Kieselgel 60 silica gel plates and a developing solvent containing hexane acetone (95:5). Radioactive products were located on the silica gel plate by autoradiographic procedures. The remainder of the silica gel in the sample zone was sectioned in 1.0-1.5 cm segments. Quantitation of sample radioactivity was performed by scraping zones from the thin-layer plate into counting vials, eluting the adsorbent with approximately 1.5 ml methanol, and direct counting in a toluene-based scintillator. Counting efficiency was determined by internal standardization with  $^{14}\text{C}$  toluene. These determinations demonstrated that products 1 and isomers 2 and 3, which were not resolved by thin-layer chromatography, represented 90.8% and 6.6% of the total sample radioactivity. Compound 4 represented 2.2% of the radioactivity. The overall radiochemical yield of the reaction was 27%.

#### References

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