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SYNTHESES OF ^{14}C-LABELLED MONOACIDIC METABOLITES OF DITHIOPYR

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SUMMARY

Convenient methods for the selective hydrolysis of the thioester groups of dithiopyr to the corresponding carboxylic acid are described. 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[(methylthio)carbonyl]-6-(trifluoromethyl)-3-pyridine-4-^{14}C-carboxylic acid (2) was obtained by simple potassium hydroxide hydrolysis of ^{14}C-labelled dithiopyr. A more involve strategy was necessary for the preparation of the isomeric carboxylic acid 6-(difluoromethyl)-4-(2-methylpropyl)-5-[(methylthio) carbonyl]-2-(trifluoromethyl)-3-pyridine-4-^{14}C-carboxylic acid (3)

Key Words: Synthesis, dithiopyr, carbon-14, metabolite, herbicide

INTRODUCTION

2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarbothioic acid, S,S-dimethyl ester (1) (common name: dithiopyr) is an experimental herbicidal candidate used for weed control in transplanted rice and in turf. Extensive soil, plant, and animal metabolism studies of this herbicide have all indicated that this compound is metabolized to several acidic metabolites. This paper describes the synthetic procedures utilized to prepare the two isomeric monocarboxylic acid derivatives of dithiopyr in order to complete the metabolism studies required for dithiopyr

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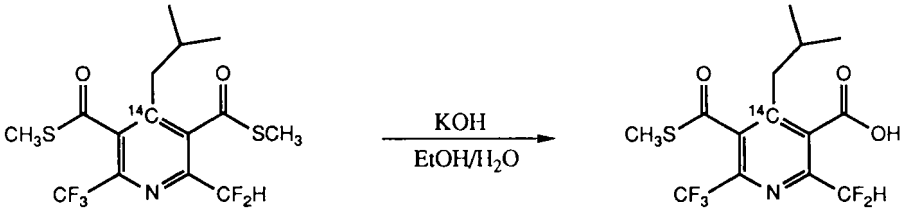
registration and for spectroscopic and chromatographic comparison with isolated metabolites.

RESULTS AND DISCUSSION

Hydrolysis of dithiopyr using potassium hydroxide in refluxing aqueous ethanol gave monoacid 2 in good yield (Scheme I). Remarkably, the thioester group at the 5 position of the ring

SCHEME I

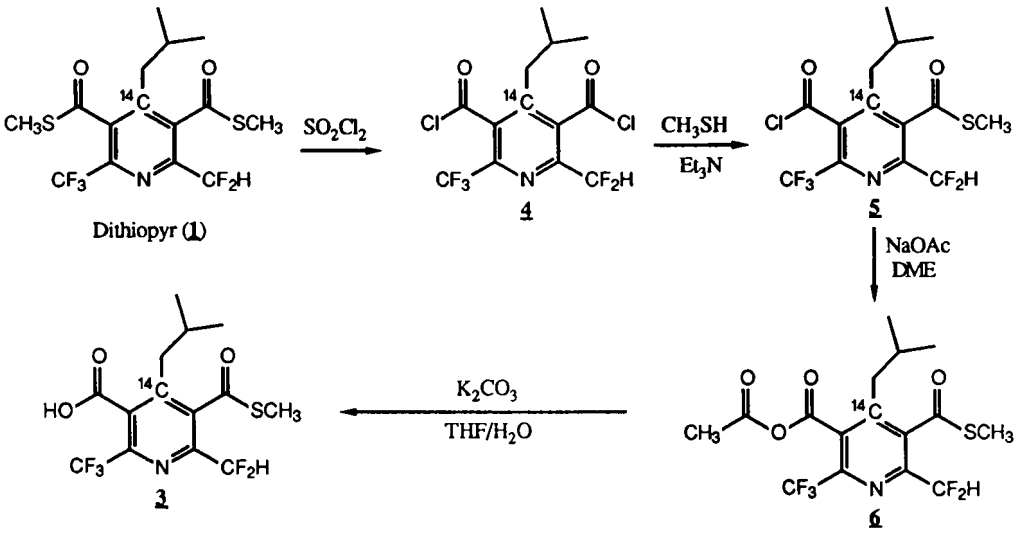


Dithiopyr (1) 2

remains intact, even after prolonged reflux. It is interesting to note the dramatically different reactivities of the two thioester groups under hydrolytic conditions. This substantial reactivity difference could conceivably be explained by hydrogen bonding between the hydrogen of the CHF_2 substituent with the thioester carbonyl group at the 3 position of the pyridine ring, thereby rendering that carbonyl more susceptible to nucleophilic attack. For other examples in which the carbonyl group at the 3 position (rather than 5) of the pyridine ring is more reactive see references 1-4.

A more involved strategy was necessary for the preparation of monoacid 3, as outlined in Scheme II. Dithiopyr was first converted to diacid chloride 4 at room temperature with sulfuryl chloride. This diacid chloride was then treated with one equivalent of methanethiol in the presence of triethylamine to form monoacid chloride 5, which was treated with sodium acetate to form the mixed anhydride 6. Subsequent hydrolysis with potassium carbonate in aqueous THF gave monoacid 3 in 43 % overall yield.

SCHEME II



EXPERIMENTAL

All melting points are uncorrected. To monitor the progress of selected reactions and to assay the purity of the products, a Varian model 3700 gas chromatograph equipped with a flame ionization detector and a J&W scientific DB-5 capillary column, a Waters HPLC system equipped with a Waters model U6K injector, Waters model 481 UV detector, Waters model 680 controller, Waters model 510 solvent pumps, and a Waters radial compression module with NOVA-PAK C_{18}, cartridge (5μ, 10 cm x 8 mm), and a Varian VXR-300 NMR spectrometer were utilized. Liquid scintillation counting (LSC) was performed on Tracor Analytic Mark III Model 6881 counters which were interfaced with a Monsanto-developed data acquisition and processing software system. The radiochemical purity of the ^{14}C-labelled sample was determined by HPLC analysis with monitoring of collected fractions by LSC. Mass spectra of the isotopically labelled samples were obtained on a Finnigan 4535 quadrupole mass spectrometer. The samples were introduced into the mass spectrometer using a Waters liquid chromatography system equipped with a Beckman Ultrasphere C_{18} ODS column (4.6 x 250 mm) and using a 1% formic acid/acetonitrile mobile phase. Analyses were performed in the positive ion mode. All synthetic and analytical operations were initially performed with unlabeled compounds, and the structure of unlabeled intermediates and products were confirmed spectroscopically. The synthesis of ^{14}C-labelled dithiopyr has been reported previously[5]. All other solvents and reagents were reagent grade and obtained from readily available commercial sources.

1. 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[(methylthio)carbonyl]-6-(trifluoromethyl)-3-pyridine-4-^{14}C-carboxylic acid (2).

A solution of dithiopyr-4-^{14}C (26.5 mg, 0.066 mmol, 29.2 mCi/mmol) and potassium hydroxide (4.8 mg, 0.086 mmol, 85%) in 50% aqueous ethanol (7 mL) was heated to gentle reflux for 6.5 hr. The reaction mixture was then cooled, 10 mL of water was added, and the solution was washed with ether (10 mL). The aqueous layer was separated, concentrated HCl was added, and the solution was extracted with ether (4 x 15 mL). The combined ether solutions were dried over magnesium sulfate, filtered and concentrated to give the crude product. Purification by preparative HPLC, using a Waters μ-BONDA-PAK C_{18} column, afforded 14.1 mg (58%) of carbon-14-labeled monoacid 2 as a white crystalline solid. The chemical purity of this sample was determined by HPLC to be 99%. The radiochemical purity was established as 99% by HPLC/LSC analysis, and the specific activity was determined to be 29.1 mCi/mmol. Analysis of this material by LC/MS gave the expected parent peaks and isotopic cluster.

2. 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine-4-^{14}C-dicarbonyl chloride (4).

A solution of dithiopyr-4-^{14}C (38 mg, 0.095 mmol) in sulfuryl chloride (2 mL) was stirred at room temperature under nitrogen for 12 hr, at which time the reaction was complete by GLC analysis. The solution was then concentrated by rotary evaporation to give a yellow-brown oil, which was dissolved in hexane (10 mL) and filtered through a plug of silica gel in a sintered glass funnel with hexane (100 mL). Concentration of this solution gave a colorless oil (30.4 mg, 85%) which was used in the next reaction without further purification.

3. 5-(Chlorocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-4-^{14}C-carbothioic acid, S methyl ester (5).

A solution of diacid chloride 4 (30.4 mg, 0.08 mmol), methanethiol (7.2 mg, 0.15 mmol), triethylamine (11 mg, 64.4 mmol), and toluene (5 mL) was stirred at room temperature for 1/2 hr. The solution was then washed with saturated sodium chloride (10 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration gave a crystalline product (28.9 mg, 92%), which was used in the next step without further purification.

4. 5-(Acetylcarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-4-^{14}C-carbothioic acid, S methyl ester (6).

A solution of the above acid chloride (28.9 mg, 0.074 mmol), sodium acetate (28 mg, 0.34

mmol) in 1,2-dimethoxyethane (2 mL) was stirred at 70°C for one hour. The reaction mixture was allowed to cool to room temperature, and the solvent was removed by rotary evaporation to leave an oily residue (27.6 mg, 90%), which was used in the next step without further purification.

5. 6-(Difluoromethyl)-4-(2-methylpropyl)-5-[(methylthio)carbonyl]-2-(trifluoromethyl)-3-pyridine-4-^{14}C-carboxylic acid (3).

The crude anhydride from the previous step (27.6 mg, mmol) and potassium carbonate (21 mg, 0.15 mmol) in 50% aqueous THF (5 mL) was stirred at room temperature for 12 hr. The reaction mixture was partitioned between water (10 mL) and ether (10 mL). The aqueous layer was separated, concentrated HCl was added, and the solution was extracted with ether (4 x 10 mL). The combined ether solutions were dried over magnesium sulfate, filtered and concentrated to give the crude product. Purification by preparative HPLC, using a Waters μ-BONDAPAK C_{18} column (10 μ, 8mm X 30 cm), mobile phase; acetonitrile : 0.1% aqueous trifluoroacetic acid 20:80, flow rate 3 mL/min, afforded 15.1 mg (43% overall yield) of carbon-14-labeled monoacid **3** as a white crystalline solid. The chemical purity of this sample was determined by HPLC to be 100% . The radiochemical purity was established as 99% by HPLC/LSC analysis, and the specific activity was determined to be 29.2 mCi/mmol. Analysis of this material by LC/MS gave the expected parent peaks and isotopic cluster.

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