JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2006; **49**: 339–343.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1048

Research Article

A facile synthesis of [^{14}C]pyrithiobac-sodium

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Summary

Condensation of thiourea **1** with diethyl malonate **2** in the presence of sodium methoxide furnished 4,6-dihydroxy-2-mercaptopyrimidine **3**. Compound **3** on methylation with diazomethane followed by oxidation with H_5IO_6/CrO_3 in ethyl acetate gave 4,6-dimethoxy-2-methylsulphonylpyrimidine **5**. Compound **5** on condensation with 2-mercapto-6-chlorobenzoic acid in the presence of a phase transfer catalyst, tetrabutylammonium bromide and sodium carbonate gave the title compound – pyrithiobac-sodium **6** with an overall yield of >35% starting from thiourea. Following the above standardized procedure, using [^{14}C]-thiourea in lieu of thiourea, ^{14}C labelled product **6**, was synthesized with an overall radiochemical yield >30% (with respect to [^{14}C]-thiourea) for further evaluations of environmental fate of **6**, in soils and plants. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: [^{14}C]-Thiourea; 4,6-dihydroxy-2-mercaptopyrimidine; 4,6-dimethoxy-2-methylsulphonyl-pyrimidine; [^{14}C]-pyrithiobac-sodium; [^{14}C]sodium 2-chloro-6-(4,6-dimethoxy-2-pyrimidinylthio)benzoate

Introduction

Pyrithiobac-sodium (sodium-2-chloro-6-(4,6-dimethoxy-2-pyrimidinylthio)-benzoate) belongs to the group of acetolactate synthase (ALS) inhibiting herbicides. It inhibits the synthesis of the essential branched chain amino acids (leucine, iso-leucine and valine).[1–3] This herbicide acts against a broad spectrum of weeds associated with the cotton crop. It is used at low rates, as soil or foliar applied, at both pre- and post-emergence stages of the cotton crop. The said herbicide is highly selective for cotton.

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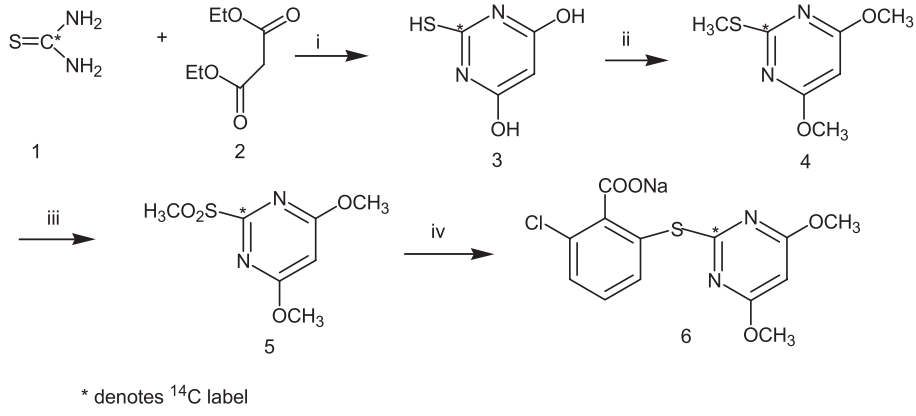
Received 9 December 2005
Revised 22 December 2005
Accepted 22 December 2005

Results and discussion

Condensation of thiourea **1** with diethyl malonate **2** in the presence of sodium methoxide gave 4,6-dihydroxy-2-mercaptopyrimidine **3**. The product **3** showed a characteristic –SH band at 2570 cm^{-1} and bands due to hydroxyl group at 3500–3300 and 1050 cm^{-1} in the IR spectrum. Also, product exhibited, PMR signal at $\delta = 5.5-5.7$, which on integration accounted for single proton and thus confirmed the formation of **3**. Methylation of **3** with diazomethane[4] furnished 4,6-dimethoxy-2-methylmercaptopyrimidine **4**. The structure was confirmed by the absence of band at 2570 cm^{-1} due to –SH group and by the absence of bands at 3500–3300 and 1050 cm^{-1} due to hydroxyl group in IR spectrum. The structure was additionally confirmed by the presence of methoxyl group band at 1250 cm^{-1}. Further, it was evident from the presence of PMR signal at $\delta = 3.8$, (integrating for six protons) that two methoxyl groups were present. In addition, presence of PMR signal at $\delta = 3.5$ was observed. On integration the signal accounted for three protons due to $-SCH_3$ group, which in turn confirmed the formation of **4**. Oxidation of **4** with H_5IO_6/CrO_3 in ethyl acetate[5] gave 4,6-dimethoxy-2-methylsulphonylpyrimdine **5**. The formation of **5** was confirmed by HPLC analysis, by comparison with the authentic sample. The results obtained were in good agreement (the product eluted out at 4.980 min, mobile phase was 30% acetonitrile in water, column ODS 5 μ). Presence of bands at 1350–1300 cm^{-1} and at 1160–1110 cm^{-1} (sulphonyl group bands) in IR spectrum confirmed the formation of **5**. The compound **5** on condensation with 2-mercapto-6-chlorobenzoic acid in the presence of tetrabutylammonium bromide in dry acetone medium gave the required product **6**.[6] The product formation was confirmed by HPLC analysis. The results obtained were in good agreement with the authentic sample. The spectral data was compared with that of the authentic sample and was found to be in good agreement [IR: (KBr film) 2835, 1680, 1250, 680 cm^{-1}, PMR: (D_2O), $\delta = 3.75$ (6H, s), $\delta = 5.92$ (1H, s), $\delta = 7.32-7.58$ (3H, m)]. We standardized this method for the synthesis of ^{14}C labelled product **6**, for further evaluations of environmental fate of **6**, in soils and plants (Scheme 1).

Experimental

4,6-Dihydroxy-2-mercaptopyrimidine **3**. Sodium methoxide was generated *in situ* by adding metallic sodium (55 mg) to dry methanol (1 ml) followed by stirring for 10 min. The temperature of the reaction mixture was raised to 60°C and added thiourea (1 mmol, 76.12 mg). The reaction mixture was stirred for 5 min at 60°C. To this reaction mass, diethyl malonate (1.2 mmol, 182 μl) was added and the reaction mixture was stirred continuously for 30 min at 60°C. The product formation was confirmed by TLC (silica, solvent: ethyl acetate). Thiourea $R_f = 0.26$ and 4,6-dihydroxy-2-mercaptopyrimidine $R_f = 0.06$.



Scheme 1. (i) Sodium, methanol; (ii) diazomethane; (iii) periodic acid/chromium trioxide; (iv) 2-mercapto-6-chlorobenzoic acid, sodium carbonate, tetrabutylammonium bromide

The reaction mixture was loaded on cation exchanger column (Dowex – 50 × 8, 50–100 mesh) in H^+ form and was eluted with water to elute 4,6-dihydroxy-2-mercaptopyrimidine **3**. Yield: 80%, IR: (KBr film) 3500–3300, 2530, 1050 cm^{-1} PMR ($CD_3C(O)CD_3$) $\delta = 6.4$ ppm (1H, s).

4,6-dimethoxy-2-mercaptomethylpyrimidine **4**. To a cooled solution of *N*-methyl-*N*-nitrosotoluene-p-sulphonamide (6 mmol, 1.28 gm) in 30 ml ether, alcoholic NaOH solution (0.4 gm in 96% ethanol (10 ml)) was added dropwise and stirred for 5 min. The resulting etheral solution of diazomethane was distilled into the flask containing 4,6-dihydroxy-2-mercaptopyrimidine (0.5 mmol, 72 mg) in dry methanol (6 ml) and the reaction mixture was stirred at 4°C for 30 min. Reaction mixture was evaporated to dryness under reduced pressure and loaded on a silica column. The column was eluted with ethyl acetate to elute 4,6-dimethoxy-2-mercaptomethylpyrimidine. Yield 85%, TLC (silica, solvent: ethyl acetate) 4,6-dimethoxy-2-mercaptomethylpyrimidine $R_f = 0.9$ and 4,6-dihydroxy-2-mercaptopyrimidine $R_f = 0.06$. IR: (KBr film) 2835, 1250, 717–625 cm^{-1} PMR ($CD_3C(O)CD_3$) $\delta = 3.5$ (3H, s), $\delta = 3.0-4.0$ (6H, s) $\delta = 6.1$ (1H, s).

4,6-dimethoxy-2-methylsulphonylpyrimidine **5**. Periodic acid (2.63 mmol, 600 mg) was dissolved in acetonitrile (6 ml) by stirring at room temperature for 60 min. To this solution, chromium trioxide (0.125 mmol, 12.5 mg) was added and stirred for 5 min, to give clear orange solution. H_5IO_6/CrO_3 solution (1.7 ml) was added to solution of 4,6-dimethoxy-2-methylmercaptopyrimidine (0.23 mmol, 42.8 mg) in ethyl acetate and was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated sodium thiosulphate and was loaded on silica column. The column was eluted

with acetone to obtain 4,6-dimethoxy-2-methylsulphonylpyrimidine. The product was analyzed by HPLC, (30% acetonitrile in water, Column ODS 5 μ, Rt 4.980). Yield 75%. TLC: (silica, solvent: chloroform) 4,6-dimethoxy-2-mercaptomethylpyrimidine $R_f = 0.8$ and 4,6-dimethoxy-2-methylsulphonylpyrimidine $R_f = 0.56$, IR: (KBr film) 2835, 1350–1300, 1250, 1160–1110 cm^{-1}, PMR ($CD_3C(O)CD_3$), $\delta = 3.5$ (3H, s), $\delta = 3.8-4.0$ (6H, s), $\delta = 6.3$ (1H, s).

Pyrithiobac sodium (sodium 2-chloro-6-(4,6-dimethoxy-2-pyrimidinylthio) benzoate) **6**. Acetone (3 ml) was added to a flask containing 2-mercapto-6-chlorobenzoic acid (0.119 mmol, 22.5 mg), 4,6-dimethoxy-2-methylsulphonylpyrimidine (0.117 mmol, 25.5 mg), sodium carbonate (0.2 mmol, 21.2 mg) and tetrabutylammonium bromide. The reaction mixture was stirred at room temperature for 4 h. Acetone was evaporated and the residue was dissolved in water. The compound was purified on silica column. The compound was eluted with 10% methanol in chloroform to separate pyrithiobac sodium **6**: Yield 70%, HPLC (solvent 30% acetonitrile in water, Column ODS 5 μ, Rt 19.92), TLC (silica, solvent: chloroform : methanol 95 : 5 v/v) 4,6-dimethoxy-2-methylsulphonylpyrimidine $R_f = 0.56$ and pyrithiobac-sodium $R_f = 0.2$, IR (KBr film) 2835, 1680, 1250, 680 cm^{-1}, PMR: (D_2O), $\delta = 3.75$ (6H, s), $\delta = 5.92$ (1H, s), $\delta = 7.32-7.58$ (3H, m).

[^{14}C] Pyrithiobac-sodium. Following the above standardized procedure [^{14}C]-pyrithiobac-sodium was synthesized using [^{14}C]-thiourea *in lieu* of thiourea, with an overall radiochemical yield 33% (with respect to [^{14}C]-thiourea) having a specific radioactivity 5 mCi/mmol and radiochemical purity >98% (assayed by HPLC followed by liquid scintillation counting of the fraction eluting at 19.9 min and also by TLC followed radiochromatogram scanning).

Acknowledgements

The authors wish to express their thanks to Mr J. K. Ghosh, Chief Executive, BRIT for his support and encouragement in the work and to all the colleagues from Labelled Compounds, BRIT for their help.

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