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Research Article

Microwave-assisted synthesis of (RS) methyl-2-([2′-^{14}C]4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl [1-^{14}C]ethanoate

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Summary

We report here a facile synthesis of (RS) methyl-2-([2′-^{14}C]4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl [1-^{14}C]ethanoate under microwave irradiation. Copyright © 2006 John Wiley & Sons, Ltd.

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Introduction

(RS) methyl-2-(4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl ethanoate is a herbicide showing excellent herbicidal effects on annual and perennial weed and high-safety crops, especially rice and wheat and is applied to paddy fields, ploughed fields and nonagricultural land.[1] We report here a facile synthesis (RS) methyl-2-([2′-^{14}C]4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl [1-^{14}C] ethanoate for its absorption, translocation and metabolism studies in plants.

In recent times, use of microwave technology in organic synthesis have received wide acceptance as microwave irradiation leads to fast heating of the chemicals at or above their boiling points thus enhancing the reaction rates

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and dramatically reducing the reaction times in comparison with conventional heating. The combination of solvent-free reaction conditions and microwave irradiation leads to large reductions in reaction times and enhancement of yields with several advantages of an eco-friendly approach, termed '*green chemistry*'. Examples of this technology in organic synthesis are numerous.[2,3]

Results and discussion

Condensation of [^{14}C]thiourea **1** with diethyl malonate **2** in the presence of sodium methoxide gave [2-^{14}C]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 cm^{-1} and 1050 cm^{-1} in the IR spectrum. The product also exhibited, PMR signal at δ 5.5–5.7, which on integration accounted for single proton, and thus confirmed the formation of **3**. Methylation of **3** with diazomethane[4,5] furnished [2-^{14}C]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 cm^{-1} 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 δ 3.8, (integrating for six protons) that two methoxyl groups were present. In addition, presence of PMR signal at δ 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[6,7] gave [2-^{14}C]4,6-dimethoxy-2-methylsulphonyl-pyrimidine **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 5μ). 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**.

Toluene **6** was brominated in presence of manganese dioxide[8] to give quantitative yield of benzyl bromide **7**. The formation was confirmed by IR (presence of band at 710 cm^{-1} due to bromine), boiling point and density. It was then reacted with K^{14}CN under microwave irradiation to furnish [1-^{14}C] 2-phenyl ethanoic acid **8**. The formation was confirmed by absence of band at 710 cm^{-1} due to bromine and presence of band at 1710 cm^{-1} due to acid carbonyl group. This on α-bromination followed by hydroxylation furnished [1-^{14}C]2-hydroxy-2-phenyl ethanoic acid (mandelic acid) **10**. The product on methylation with diazomethane followed by condensation with **5** in presence of NaH in toluene under microwave heating (1300 W) for 4 min furnished the title compound **12** (Scheme 1).

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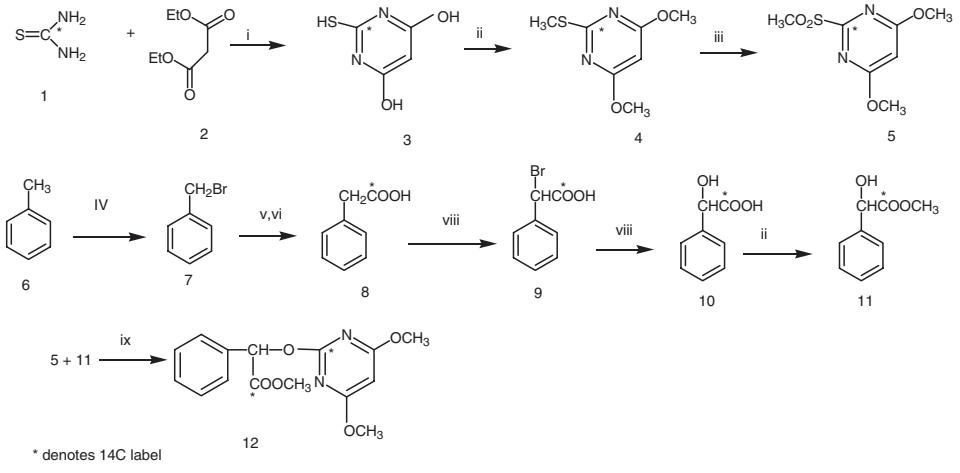

(i) Sodium, methanol (ii) N-methyl-N-nitrosotoluene-p-sulphonamide, NaOH (iii) periodic acid / chromium trioxide
(iv) MnO_2, Br_2, (v) TBAB, K*CN, (vi) HCl ; propionic acid, 1 : 2 v/v, MW, (vii) PCl_3, Br_2 ,
(viii) Aq sodium carbonate, MW, (ix) 60% NaH, toluene, MW

Scheme 1.

Experimental

$K^{14}CN$ and ^{14}C-thiourea were procured from M/s Board of Radiation and Isotope Technology, Mumbai, India.

The PMR spectra were recorded with a Brucker AC-200 (200 MHz) spectrometer using $CDCl_3$ as the solvent. The chemical shift (δ) values were expressed in ppm. The IR spectra were recorded with a Jasco FT/IR 460 spectrophotometer. Analytical HPLC performed (Dionex HPLC system) with C18 5μ, BDS Hypersil (100 × 4.6 mm) column.

LG domestic microwave oven (1300 W) was used for the experiments.

TLC was done on silica gel plates (silica gel 60 F_{254}, Merck), TLC plates were scanned with Bioscan system, AR 2000 TLC Scanner. All yields were reported based on radioactivity.

[2-^{14}C]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 [^{14}C]thiourea (1 mmol, specific activity 185 MBq/mmol) was added to it. 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) followed by radioactivity scanning. R_f for [^{14}C]thiourea was 0.26 and for [2-^{14}C]4,6-dihydroxy-2-mercaptopyrimidine was 0.06. The reaction mixture

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was loaded on to a cation exchanger column (Dowex−50 × 8, 50–100 mesh) in H^+ form. The column was eluted with water to elute [2-^{14}C]4,6-dihydroxy-2-mercaptopyrimidine **3**. Yield: 80%, IR: (KBr film) 3500–3300 cm^{-1}, 2530 cm^{-1}, 1050 cm^{-1} PMR ($CD_3C(O)CD_3$) δ 6.4 ppm (1H, s).

[2-^{14}C]4,6-dimethoxy-2-mercaptomethylpyrimidine **4**

To a cooled solution of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (6 mmol, 1.28 gm) in ether (30 ml), alcoholic sodium hydroxide solution (0.4 gm in 96% ethanol (10 ml) was added drop wise and the solution stirred for 5 min. The resulting ethereal solution of diazomethane was distilled into the flask containing [2-^{14}C]4,6-dihydroxy-2-mercaptopyrimidine (0.5 mmol, specific activity 185 MBq/mmol) in dry methanol (6 ml). The reaction mixture was evaporated to dryness under reduced pressure and loaded on to a silica column. The column was eluted with ethyl acetate to obtain [2-^{14}C]4, 6-dimethoxy-2-mercaptomethylpyrimidine. Yield 85%, TLC (silica, solvent: ethyl acetate) followed by radioactivity scanning. R_f for [2-^{14}C]4,6-dimethoxy-2-mercaptomethylpyrimidine was 0.9 and for [2-^{14}C]4,6-dihydroxy-2-mercaptopyrimidine was 0.06. IR: (KBr film) 2835 cm^{-1}, 1250 cm^{-1}, 717–625 cm^{-1} PMR ($CD_3C(O)CD_3$) δ 3.5 (3H, s), δ 3.0–4.0 (6H, s) δ 6.1 (1H, s).

[2-^{14}C]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 a clear orange solution. H_5IO_6/CrO_3 solution (1.7 ml) was added to the solution of [2-^{14}C]4, 6-dimethoxy-2-methylmercaptopyrimidine (0.23 mmol, specific. activity 185 MBq/mmol) in ethyl acetate and was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated sodium sulphite and was loaded on to a silica column. The column was eluted with acetone to obtain [2-^{14}C]4,6-dimethoxy-2-methylsulphonylpyrimidine. The product was analysed by HPLC, (30% acetonitrile in water, column ODS 5μ, R_t 4.9 min). Yield 75%. TLC (silica, solvent: chloroform) followed by radioactivity scanning. R_f for [2-^{14}C]4,6-dimethoxy-2-mercaptomethylpyrimidine was 0.8 and for [2-^{14}C]4,6-dimethoxy-2-methylsulphonyl-pyrimidine was 0.56, IR: (KBr film) 2835 cm^{-1}, 1350–1300 cm^{-1}, 1250 cm^{-1}, 1160–1110 cm^{-1}, PMR ($CD_3C(O)CD_3$), δ 3.5 (3H, s), δ 3.8–4.0 (6H, s), δ 6.3 (1H, s).

Benzyl bromide

Toluene (47 mmol, 5 ml), MnO_2 (47 mmol, 4 g), bromine (48 mmol, 2.5 ml) and dichloromethane (0.75 ml) were stirred at room temperature for 10 min. After the reaction was complete, the reaction mixture was filtered over a silica bed

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and washed with hexane. The combined filtrate was distilled off to remove hexane and to give pure benzyl bromide. Yield: Quantitative (3.5 ml). bp 198–199°C, d 1.44.

[1-^{14}C]2-phenyl ethanoic acid **8**

Benzyl bromide (0.18 ml, 1.5 mmol), potassium [^{14}C]-cyanide (0.6 mmol, specific activity 185 MBq/mmol), tetrabutylammonium bromide (5 mg) and water (0.10 ml) were sealed in a glass ampoule. The reaction mixture was heated in a domestic microwave oven (1300 W) for 4 min. The reaction mixture was cooled and the ampoule was cut open. To it was added a mixture of concentrated hydrochloric acid:propionic acid (1:2 v/v, 300 µl) and the glass ampoule was again sealed. It was heated using a domestic microwave oven for 3 min (6×30 s). The ampoule was cut open and the reaction mixture was extracted with ether. The obtained product was purified by column chromatography (silica, 15% ethyl acetate in hexane) furnishing [1-^{14}C] 2-phenyl ethanoic acid in a yield of 99.8%, with respect to K^{14}CN. The radiochemical purity of [1-^{14}C]2-phenyl ethanoic acid was confirmed by TLC (silica gel, 30% ethyl acetate in hexane, v/v) followed by radioactivity scanning (R_f for [1-^{14}C]2-phenyl ethanoic acid was 0.2 and for benzyl bromide was 0.8) IR (KBr film) 1710 cm^{-1}. PMR: (D_2O), δ 3.64–3.71 (2H, s), δ 7.32–7.58 (5H, m) ppm.

[1-^{14}C]2-bromo-2-phenyl ethanoic acid **9**

A mixture of [1-^{14}C]2-phenyl ethanoic acid (0.55 mmol, specific activity 185 MBq/mmol), bromine (0.1 ml, 0.5 mmol) and PCl_3 (0.1 ml) was initially heated at 80°C for 10 min and then at 100°C for 20 min (till the colour of bromine disappeared). The reaction mixture was cooled in an ice bath. Saturated sodium bicarbonate solution was added in drops with stirring until neutral and the solution was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0–5% ethyl acetate/ hexane). Yield: 0.5 mmol (90%). The purity was ascertained by TLC (silica gel, 5% ethyl acetate in hexane v/v) followed by radioactivity scanning (R_f for [1-^{14}C]2-phenyl ethanoic acid was 0.1 and for [1-^{14}C]2-bromo-2-phenyl ethanoic acid was 0.7). IR (KBr, film) 1720 cm^{-1}, 710 cm^{-1}, PMR: (D_2O), δ 4.70 (1H, s), δ 7.32–7.58 (5H, m) ppm.

[1-^{14}C]2-hydroxy-2-phenyl ethanoic acid (mandelic acid) **10**

[1-^{14}C]2-bromo-2-phenyl ethanoic acid (0.5 mmol, specific activity 185 MBq/ mmol) was heated with aqueous saturated sodium carbonate solution (1 ml) under microwave condition for 2 min (4×30 s) to furnish [1-^{14}C]2-hydroxy-2-phenyl ethanoic acid. The reaction mixture was purified by column

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chromatography (silica). The column was first eluted with 5% ethyl acetate in hexane and then with methanol to elute [1-^{14}C]2-hydroxy-2-phenyl ethanoic acid. Yield 99.9%. TLC (silica gel, 20% ethyl acetate: hexane v/v) followed by radioactivity scanning showed the product to be 99% radiochemically pure (R_f for [1-^{14}C]2-bromo-2-phenyl ethanoic acid was 0.9 and for [1-^{14}C]2-hydroxy-2-phenyl ethanoic acid was 0.2). IR (KBr film) 3500–3000 cm^{-1}, 1720 cm^{-1}, 1050 cm^{-1}, PMR: (D_2O), δ 4.50 (1H, s), δ 7.32–7.58 (5H, m) ppm.

Methyl [1-^{14}C]2-hydroxy-2-phenyl ethanoate (methyl mandelate) **11**

To a cooled solution of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (0.5 mmol, 106 mg) in 15 ml ether, alcoholic sodium hydroxide solution (0.1 g in 96% ethanol, 5 ml) was added dropwise and stirred for 5 min. The resulting ethereal solution of diazomethane was distilled into the flask containing [1-^{14}C]2-hydroxy-2-phenyl ethanoic acid (0.25 mmol, specific activity 185 MBq/mmol) in ether (3 ml). The reaction mixture was evaporated to dryness under reduced pressure and loaded onto a silica column. The column was eluted with 20% ethyl acetate in *n*-hexane to elute methyl-[1-^{14}C]2-hydroxy-2-phenyl ethanoate. Yield: 98%, TLC (silica, solvent: 20% ethyl acetate in hexane) followed by radioactivity scanning revealed the product to be 99% radiochemically pure (R_f for [1-^{14}C]2-hydroxy-2-phenyl ethanoic acid was 0.2. and methyl-[1-^{14}C]2-hydroxy-2-phenyl ethanoate was 0.8). IR (KBr film), 3500 cm^{-1}, 1750 cm^{-1}, 1050 cm^{-1}, PMR: (D_2O), δ 3.60 (3H, s), δ 4.50 (1H, s), δ 7.32–7.58 (5H, m) ppm.

(RS) methyl-2([2′-^{14}C]4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl-[1-^{14}C]ethanoate

Methyl-[1-^{14}C]2-hydroxy-2-phenyl ethanoate **11** (0.15 mmol, specific activity 185 MBq/mmol)) was stirred with 20 mg of 60% NaH in toluene for 15 min in a glass ampoule. To it was added [2-^{14}C]4,6-dimethoxy-2-mercaptomethylpyrimidine **5** (0.15 mmol, specific activity 185 MBq/mmol), sealed and heated in a domestic microwave oven (1300 W) for 4 min (8 × 30 s). The ampoule was cut open and the reaction mixture was taken up in methanol. The product was purified by column chromatography (silica). The column was washed with 5% methanol in chloroform. (RS) methyl-2-([2′-^{14}C]4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl [1-^{14}C]ethanoate was eluted with methanol. Yield: 98.55%. The product was analysed and confirmed by TLC (silica, solvent: 5% methanol in chloroform) followed by radioactivity scanning. R_f for (RS) methyl-2-([2′-^{14}C]4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl [1-^{14}C]ethanoate is 0.2, R_f for methyl-[1-^{14}C]2-hydroxy-2-phenyl ethanoate 0.92 and [2-^{14}C]4,6-dimethoxy-2-mercaptomethyl-pyrimidine 0.92 IR (KBr film) 2835 cm^{-1},

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1680 cm^{-1}, 1250 cm^{-1}, 680 cm^{-1}, PMR: (D_2O), δ 3.6 (3H, s), δ 3.73 (6H, s), δ 4.5 (1H), δ 5.92 (1H, s), δ 7.32–7.58 (5H, m).

Column: C-18, ODS 5μ, 100 × 4.6 mm

Mobile Phase: 30% Acetonitrile in water (v/v)

Detector UV: 263 nm

Flow rate: 1.00 ml

Retention time for (RS) methyl-2-([2′-^{14}C]-4,6-dimethoxypyrimidin-2′-yloxy)-2-phenyl [1-^{14}C]ethanoate was 3.5 min and [2-^{14}C]4,6-dimethoxy-2-mercapto-methyl-pyrimidine was 7.9 min. Under these conditions it was observed that methyl-[1-^{14}C]-2-hydroxy-2-phenyl ethanoate did not elute from the column.

The fraction corresponding to the product was collected and assayed by liquid scintillation counter for its radioactive content. (A purified product having radioactivity concentration of 16 000 dpm was injected and the fraction at R_t 3.50 contained 15 928 dpm.) Radiochemical purity 99.55%.

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