PESTICIDES LABELLED WITH ^{14}C. II. SYNTHESIS OF PROPICONAZOLE LABELLED IN THREE DIFFERENT POSITIONS

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SUMMARY

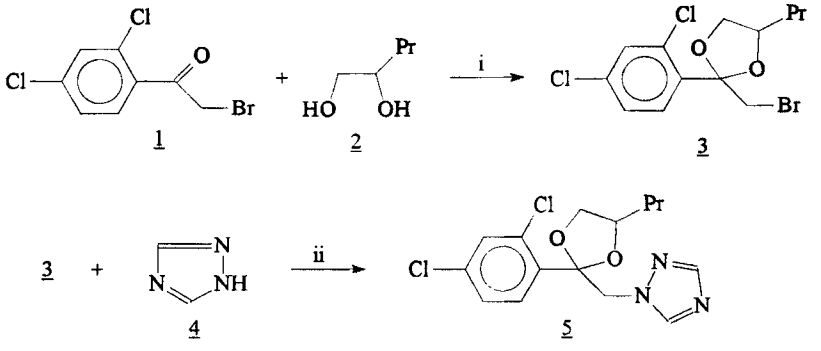
Propiconazole was labelled with ^{14}C in three different positions: in the benzene ring, in the position 5 of the dioxolane ring, and in the triazole ring. The synthesis of three new key intermediates (m-dichloro[U-^{14}C]benzene], 1,2,4-[U-^{14}C]triazole, [1-^{14}C]-pentane-1,2-diol) were also elaborated.

Key Words: Propiconazole; ^{14}C; m-dichlorobenzene; 1,2,4-triazole; pentane-1,2-diol; fungicides

INTRODUCTION

Propiconazole {1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole, 5} is a systemic foliar fungicide with a broad range of activities[1]. Propiconazole labelled with ^{14}C in different positions was needed for scientific and environmental studies. Here we described the syntheses of three isotope isomers: labelled in the benzene ring, in the triazole ring, and in the position 5 of the dioxolane ring. These syntheses patterned after the synthesis of the inactive Propiconazole[2] (Scheme 1.), they only differ using the required key-intermediate (isotope isomers of 1, 2, 4, respectively) in the appropriate step.

Scheme 1.



i = TosOH, toluene, reflux, 6 h; ii = NaH, DMSO, 120°C, 5 h;

All the three radio isomers were prepared in 1-5 mmoles scale, the benzene ring labelled isomer, the dioxolane ring labelled one and the triazole labelled one with 7.4%, 30.6% and 18.4% yield, respectively.

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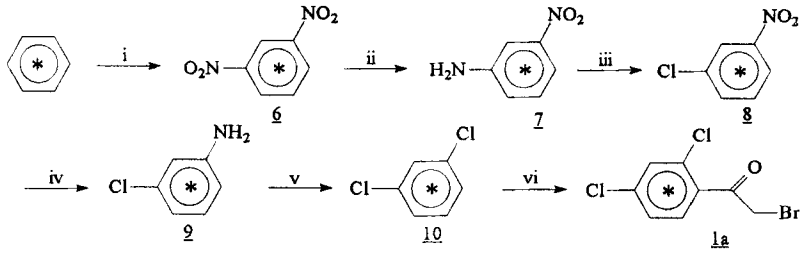
A) Synthesis of the [ring U-^{14}C] 2-bromo-2',4'-dichloro-acetophenone (1a)

This synthesis was a tedious, long one combination of six reaction steps (Scheme 2.): [U-^{14}C]benzene was nitrated with HNO_3/H_2SO_4 to give m-dinitro[U-^{14}C]benzene[3] (6), then it was reduced with Na_2S to give m-[U-^{14}C]nitraniline[4] (7), the amino group was changed to chlorine by diazotation[5]. The obtained m-nitro-chloro[U-^{14}C]benzene (8) was reduced to 3-chloro[U-^{14}C]aniline[6] (9), which was diazotized again to give m-dichloro[U-^{14}C]benzene[7] (10). Finally it was reacted with bromoacetyl bromide under Friedel-Crafts conditions[8] to give 1a. The yield of 1a was 26.3% calculated on [U-^{14}C]benzene.

Scheme 2.

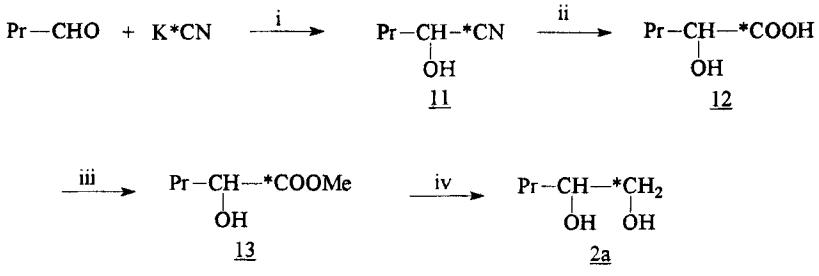


i = HNO_3, H_2SO_4; ii = Na_2S_x; iii = HNO_2, CuCl; iv = Sn, HCl; v = HNO_2, CuCl; vi = $BrCH_2COBr$, $AlCl_3$, CS_2

B) Synthesis of [1-^{14}C]pentane-1,2-diol (2a)

2-Hydroxy-[1-^{14}C]valeronitrile (11) was prepared by the cyanohydrine synthesis from butyraldehyde; it was hydrolized to 2-hydroxy-[1-^{14}C]valeric acid (12), (as described at the synthesis of lactic acid[9]). The acid was treated with diazomethane (13), and reduced with $LiAlH_4$ to give 2a with about 80% yield, calculated on K^{14}CN.

Scheme 3.



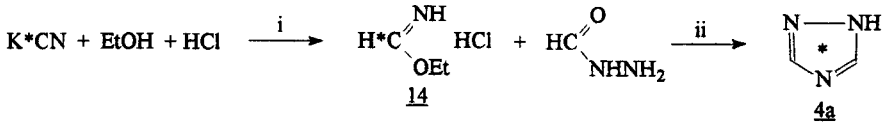
i = H_2SO_4, 0°C; ii = HCl, refl, 10 min; iii = CH_2N_2, ether; iv = $LiAlH_4$, ether

C) Synthesis of [U-^{14}C]-1,2,4-triazole (4)

Although 1,2,4-triazole has been known for a long time and it has voluminous literature[10], the synthetic approaches used earlier, namely heating of formamide and formyl hydrazide[11], or hydrazine hydrate[12] were unpractical, because neither labelled formamide nor formyl hydrazide were not easily attainable. So we modified the reaction using labelled formiminoester hydrochloride[13], as starting material, which reacted with formyl hydrazide and ammonia to give the labelled triazole with 60% yield (calculated on K^{14}CN). Theoretically 14 and formyl

hydrazide also could condense to triazole without ammonia, but this reaction was not succesful. In this case ammonia did not only serve as antacid, but probably reacted with 14 and formamide or formamidine formed, which condensed with formyl hydrazide to triazole. Without dissolving the solids in liquid ammoniak the yield was substantially lower.

Scheme 4.



i = 0°C; ii = NH_3, 160-170°C

EXPERIMENTAL

Melting points are uncorrected and were determined with a PHMK microscope. Chromatography was performed on Silica gel 60 HF_{254} plates (MERCK) and Silica gel 60 (0.063-1.00 mm), respectively. The spots were visualised by UV light and/or chloro-tolidine developper. HPLC was performed by a Gilson HPLC system, on a Nucleosil 5C-18 column.

[U-^{14}C]Benzene and K[^{14}C]N were synthesized in our lab according to known procedures[14,15]. Radioactivity was measured on an LKB 1217 Rackbeta liquid scintillation counter.

Usual work-up means extraction with ether or any other solvent, washing with 5% $NaHCO_3$ and brine succesively, drying over $MgSO_4$ and evaporation.

m-Dinitro[U-^{14}C]benzene(6)

[U-^{14}C]Benzene (189.4 mg; 2.43 mmoles; 182 mCi) was added to a mixture of conc. nitric acid (0.49 ml, d=1.51 g/ml) and conc. sulfuric acid (0.68 ml) at 0°C, and the mixture was stirred overnight at room temperature. Then it was poured to ice, and after the usual work-up 370.8 mg of 6 was obtained as yellow crystals (91%). TLC showed only one spot (benzene - hexanes 7:3; R_f = 0.4 and hexanes - ethylacetate 7:3; R_f = 0.8). A_{sp} = 448 mCi/g; A_t = 166 mCi.

m-[U-^{14}C]Nitraniline (7)

Sodium sulfide (0.6 g, 7.7 mmoles) was dissolved in water (2.5 ml) and sulfur (150 mg, 4.7 mgA) was added, the mixture was stirred and warmed while sulfur dissolved. This solution was dropped (30 min) into the hot mixture of 6 (370 mg, 2.20 mmoles, 166 mCi) and water (3.5 ml). It was refluxed for 30 min, then after cooling and usual work up the row product was puified by chromatography.(hexane - ethyl acetate 6:4). 254 mg (84%) of 7 was obtained as greenish solid. TLC (hexanes - ethyl acetate 7:3; R_f = 0.7)) shows only one active spot.

m-Nitro chloro[U-^{14}C]benzene (8)

7 (254 mg, 1.77 mmoles, 139 mCi) was suspended in aq. HCl (2 ml, 6N), cooled in an ice bath and aq. $NaNO_2$ (128 mg in 0.5 ml of water) was added during 30 min. Then this cold solution was dropped into a solution of Cu_2Cl_2 (prepared from 1.0 g of $CuSO_4$*$5H_2O$ according the known procedures[16]) in conc. HCl (1.6 ml) at 30°C. After 30 min the product was purified by stream-destillation (250 ml) and after usual work up (extraction with benzene) 210 mg of 8 was obtained (76 %). It was pure by TLC (hexanes - benzene 6:4; R_f = 0.55). A_t = 105 mCi (calcd.).

3-Chloro-[U-^{14}C]aniline (9)

478 mg (3 mmoles, 105 mCi) of 8 (210 mg of 8 was diluted with 268 mg of inactive material) was suspended in conc. HCl (4 ml) and 796 mg (6.7 mgA) of Sn (spanes) was added. The mixture was stirred for 16 hours, while Sn dissolved. Then aq. NaOH (2.2 g in 10 ml of

water) was added and the product was purified by steam distillation. The distillate was acidified with 2N HCl and evaporated. 452 mg of 9 (as HCl salt) was obtained as white crystals. Yield: 91%. A_{sp}: 209.7 mCi/mg; A_m : 34.3 mCi/mmol; A_t: 94,8 mCi. The material shows only one spot on TLC (benzene - hexanes 9:1, R_f = 0.3).

m-Dichloro-[U-^{14}C]benzene (10)

9 (452 mg, 2.75 mmoles,94.8 mCi,) was dissolved in 6N HCl (2 ml) and diazotized with 199 mg of $NaNO_2$ (in 0.5 ml of water) as described at 8. 247 mg of 10 was obtained. Yield: 61%. A_t = 57 mCi (calculated). It was used for the next step without purification.

2-Bromo-2',4'-dichloro-[ring U-^{14}C]acetophenone (1a)

Into a mixture of 10 (247 mg,1.68 mmoles, 57 mCi), bromoacetyl bromide (170 µl, 392 mg, 1.94 mmoles) and carbon disulfide (3 ml) powdered anhydrous $AlCl_3$ (700 mg, 5.2 mmoles) was added slowly (1-2 minutes) at 0°C. The mixture was stirred for 30 min at 0°C then overnight at room tempereature. A dark brown solution was obtained, which was poured to ice, and after usual work-up 378 mg of 1a was obtained as a yellowish oil. Yield: 84%. A_t = 47.9 mCi (calculated).

2-(2,4-Dichloro[U-^{14}C]phenyl)-2-bromomethyl-4-propyl-1,3-dioxolane (3a)

312 mg (39.6 mCi) of 1a was diluted with inactive 1 (178 mg; total weight 490 mg, 1.83 mmoles) and dissolved in toluene (30 ml), then p-toluene sulfonic acid and 2 (217 mg, 2.08 mmoles) were added. The mixture was refluxed in a Dean-Stark apparatus for 6 hours. Then the solution was washed with 5% Na_2CO_3 solution (15 ml) and brine (15 ml), dried over Na_2SO_4 and toluene was evaporated. The residue was purified by chromatography (hexane - benzene 4:1) to give 3a (378 mg, 58%, 23.0 mCi). The material shows two separate peaks (according to the cis-trans isomers of the dioxolane ring) on TLC (hexane - benzene = 1:1; R_f = 0.6-0.7). Although the isomers could be separated by chromatography, but the mixture of the isomers was satisfactory for the planned investigations, so we collected both together.

1-[2-(2,4-Dichlorophenyl)-4-propyl-1,3-[5-^{14}C]dioxolan-2-ylmethyl]-1H-1,2,4-triazole ([dioxolane 5-^{14}C]Propiconazole; 5a)

1,2,4-Triazole (4; 196 mg, 2.8 mmoles) was dissolved in DMSO (2 ml) and NaH (50% susp. in oil: 115 mg, 2.4 mmoles) was added, and the mixture was stirred at 100°C while a clear solution was formed (about 10 min). Then 3a was added in DMSO (2 ml) and the mixture was stirred for 6 hours at 120°C. After cooling DMSO was evaporated in vac. (1 Hgmm, 100°C bath), the residue was extracted with water. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography (benzene - ethyl acetate = 8:2) and 174 mg of 5a was obtained with 48% yield. TLC (benzene -ethyl acetate = 6:4; R_f = 0.6) also showed a double spot like 3a. A_{sp} = 63.9 mCi/g; A_m = 21.9 mCi/mmole; A_t = 11.1 mCi. HPLC showed the two peaks of the isomers at R_t = 7.2 and 7.9 min., respectively (acetonitrile -water = 7:3, flow 1 ml/min, detector: UV, 254 nm.).

Methyl 2- hydroxy-[1-^{14}C]valerate (13)

K^{14}CN (331 mg, 4,0 mmoles, 92.3 mCi) was dissolved in water (1.5 ml) and freshly distilled butyraldehyde (ca. 7 mmoles) was added. The mixture was cooled under 5°C and slowly (during 10 min) cold 2N sulfuric acid (3.5 ml) was dropped. It was stirred for 10 min at 0°C, then conc. HCl (8 ml) was added and the mixture was refluxed for 5 min. After cooling solid K_2CO_3 was added in small portions while crystallization begins. It was diluted with brine to dissolve the crystals and 12 was extracted with ether (4 x 15ml), the combined organic phases were washed with brine and treated with diazomethane while the yellow colour remained. Then it was dried over Na_2SO_4 and the solvent was evaporated. The residue, a light yellowish oil (740 mg, 74.24 mCi, 80%) was almost pure 13 (according to GLC, 140°C), and it was reduced to 2a without purification.

[1-^{14}C]Pentane-1,2-diol (2a)

13 (740 mg, ca. 3 mmoles, 74.24 mCi) was dissolved in ether (10 ml) and this solution was dropped into a suspension of $LiAlH_4$ (0.5 g, 13 mmoles) in ether (10 ml). Then the mixture was refluxed for 2 hours, cooled with an ice-bath and acetone (1 ml), 2N sulfuric acid (2 ml) and 10N sulfuric acid were dropped successively. The reaction mixture was placed into a continous extractor and extracted with ether for 3 hours. The ether solution was dried over Na_2SO_4 and evaporated. The residue (428 mg) was a yellowish oil. Its purity was about 90% according to GLC. It was used for the next step without purification.

2-(2,4-Dichlorophenyl)-2-bromomethyl-4-propyl-1,3-[5-^{14}C]dioxolane (3b)

1.33g (4.9 mmoles) of 1 was reacted with 428 mg (cca. 3 mmoles) of 2a and 400 mg of p-toluene sulfuric acid in toluene (30 ml) as described at 3a. After chromatographic purification (hexane-benzene 7:3) 615 mg (39.7 mCi) of 3b was obtained as a yellowish oil. Yield: 53% calculated on 13. TLC (hexane - benzene 1:1, R_f = 0.6-0.7) shows a double spot according to the cis-trans izomers.

1-[2-(2,4-Dichlorophenyl)-4-propyl-1,3-[5-^{14}C]dioxolan-2-ylmethyl]-1H-1,2,4-triazole ([dioxolane 5-^{14}C]Propiconazole; 5b)

1,2,4-triazole (391 mg, 5.6 mmoles) and NaH (in 50% susp. in oil; 223 mg ,cca. 4.6 mmoles) were reacted with 3b (615 mg, 1.72 mmoles) in DMSO (2 ml) as described in 5a. After purification 379 mg of 5b was obtained with 64 % yield. A_{sp} = 74.46 mCi/g; A_m = 25.69 mCi/mmoles; A_t = 28.29 mCi. TLC (benzene-ethyl acetate 6:4, R_f = 0.6) shows a double spot according to the isomers. HPLC was same as 5a, except the rate of isomers.

Ethyl [^{14}C]formimidate hydrochloride (14)

It was prepared from 260 mg (4.0 mmoles, 102.8 mCi) of K[^{14}C]N, 238 mg (4 mmoles) of NaCl and 232 µl (187 mg, 4.0 mmoles) of ethanol as described earlier[13], with 91% yield. The iminoester (405 mg, 93.5 mCi) was used for the next step without purification.

1,2,4-[U-^{14}C]triazole (4c)

Formyl hydrazide (243 mg, 4.05 mmoles) was added to 14 and in an ammoniak stream it was cooled to -78°C, while 2-3 ml of liquid ammoniak condensed to the bottle. Then the ammoniak was let to warm up to the boiling point and stirred while the solids dissolved. Then the ammoniak was evaporated and the residue was heated at 150-160°C in ammoniak steam. After cooling it was treated with acetonitrile (5 ml), the insoluble residue was filtered off, the filtrate was evaporated and the residue was purified by chromatography (acetonitrile - methanol = 95:5). After evaporation of the pure fractions 146 mg of 4c was obtained (62,3 mCi, 60.6%). M.p.: 115-118°C (Lit.: 120-1°C)

1-[2-(2,4-Dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-[U-^{14}C]triazole ([dioxolane 5-^{14}C]Propiconazole; 5c)

It was prepared from 146 mg (2.1 mmoles, 62.3 mCi) of 4c, 130 mg (2.7 mmoles) NaH (50% oil suspension) and 820 mg (2.3 mmoles) of 3 in 4 ml of DMSO as described at 5a. 213 mg of 5c was obtained. A_{sp}=88.7 mCi A_m=30.6 mCi, A_t=18.9 mCi. Radiochemical yield 18% (calculated on K^{14}CN). HPLC was same as 5a, except the rate of isomers.

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