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Synthesis of the Rice Herbicide HW-52 [dichlorophenyl ring-^{14}C(U)]

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SUMMARY

^{14}C-Labeled 2',3'-dichloro-4-(ethoxymethoxy)benzanilide (HW-52) (10) was synthesized in a total of 9 steps from 1,3-dinitrobenzene [^{14}C(U)]. The key intermediate 2,3-dichloroaniline [^{14}C(U)] (7) was prepared from the starting material by a series of aromatic substitutions and functional group manipulations. Conversion to the final product was achieved in high yield by coupling and further functional group manipulations. The overall radiochemical yield was 1.88% and radiochemical purity of the product was greater than 98.8%.

Key Words: Herbicide, radiosynthesis, 2,3-dichloroaniline, 2',3'-dichloro-4-(ethoxymethoxy)benzanilide.

INTRODUCTION

Radiolabeling of HW-52 [2',3'-dichloro-4-(ethoxymethoxy)benzanilide, 1), a new rice herbicide, was required for plant, soil and animal metabolism studies. HW-52 has shown good herbicidal selectivity and gives complete control of Echinochloa spp. in rice paddies.[1]

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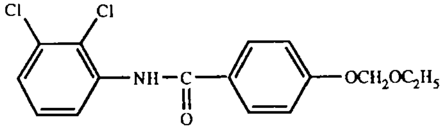

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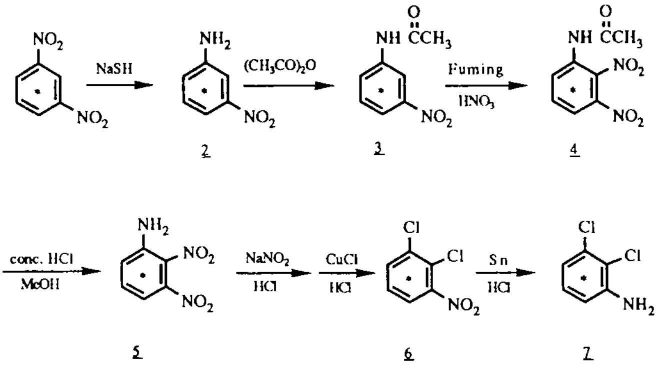
DISCUSSION AND RESULTS

For metabolism studies, HW-52 had previously been labeled with ^{14}C in the benzene ring bearing the ethoxymethyleneoxy group. However, it had not been possible to determine the fate of the dichloroaniline fragment formed enzymatically during metabolism and so it was necessary to label the dichlorophenyl ring.

Readily available 1,3-dinitrobenzene [^{14}C(U)] was used as the starting material for the synthesis. It was first converted to 3-nitroaniline [^{14}C(U)] by reduction with freshly-prepared sodium hydrosulfide (Scheme 1), and the product, partially purified by flash chromatography, was acetylated to 3-nitroacetanilide [ring-^{14}C(U)].

Scheme 1

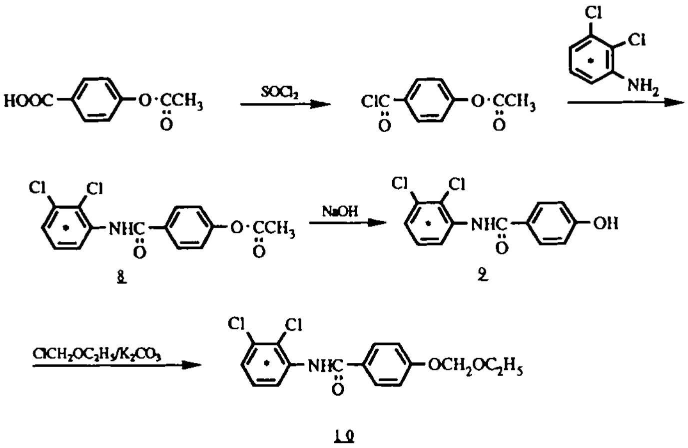


The labeled acetanilide, purified by flash chromatography, was then nitrated at 15°C with fuming nitric acid. The nitration proceeded slowly and with difficulty, and significant isomeric side product was formed[2,3]. Flash chromatography afforded a 26% yield of product. Hydrolysis with concentrated hydrochloric acid in methanol afforded a moderate yield (36%) of 2,3-dinitroaniline [^{14}C(U)] after chromatography. An equal amount of a by-product which was shown by NMR to be 2-chloronitrobenzene [^{14}C(U)] was also isolated. Although previous workers have found that sulfuric acid hydrolysis produces large amounts of isomeric dinitroanilines[4], it appears that deamination has not previously been observed during acid hydrolyses of this material.

The product was then converted to 2,3-dichloronitrobenzene [^{14}C(U)] by a carefully controlled Sandmeyer reaction accompanied by replacement of the nitro group in the 2-position by chlorine[3,5]. Pure 2,3-dichloronitrobenzene [^{14}C(U)] was obtained in 72% yield from this reaction after chromatography. Conversion to 2,3-dichloroaniline [^{14}C(U)] was then accomplished in 83% yield by reduction with tin and hydrochloric acid followed by chromatography.

Conversion to HW-52 [^{14}C] was then achieved following the procedure outlined in Scheme 2.

Scheme 2



Cold 4-acetoxybenzoylchloride, prepared from 4-acetoxybenzoic acid, was reacted with 2,3-dichloroaniline [^{14}C(U)] to form the protected benzanilide derivative 8 in 98% yield. Deprotection was accomplished by basic hydrolysis in 88% yield, and the phenol obtained was converted to HW-52 [^{14}C] by reaction with chloromethyl ethyl ether and potassium carbonate in the presence of a catalytic amount of polyethylene glycol 4000. Recrystallization afforded an 85% yield of product with radiochemical purity greater than 98.8% by both HPLC and TLC. The IR, TLC and HPLC properties of this material were shown to be identical with those of an authentic sample of HW-52.

CONCLUSIONS

Successful completion of the synthesis provided the ^{14}C-labeled HW-52 needed for the metabolism studies. The key intermediate, 2,3-dichloroaniline [$^{14}C(U)$], was produced in a radiochemical yield of 2.56%, based on 1,3-dinitrobenzene [$^{14}C(U)$]. Although a six step synthesis was required, the substitution pattern was unequivocal and the intermediate was obtained in high purity. Conversion to the final product was accomplished in three steps with a radiochemical yield of 73% and in high purity.

EXPERIMENTAL

Radioactivity was measured on a United Technologies Packard Minaxi β Tri-Carb 4000 scintillation counter. Thin layer chromatography was performed on Analtech Uniplate Silica GF plates. HPLC was performed on various instruments from Waters Associates Inc. using Du Pont Zorbax columns. Radiochemical detection was accomplished with Canberra brand liquid scintillation flow monitors. NMR spectra were obtained on a Bruker AC-E 300 spectrometer. IR spectra were obtained on a Perkin Elmer 1720 x FT-IR spectrometer.

3-Nitroaniline [$^{14}C(U)$] (2)

Sodium sulfide nonahydrate (22.3 g, 92.8 mmol) was dissolved in 46 ml of water and the flask was cooled in an ice bath. Sodium hydrogen carbonate (7.84 g, 93.3 mmol) was added portionwise with rapid stirring. The cooling bath was removed and the mixture was stirred for a further 15 minutes. Methanol (46 ml) was added and the mixture was stirred for 1.5 hours. The solution was filtered and set aside.

1,3-Dinitrobenzene [$^{14}C(U)$] (8.66 g, 51.5 mmol) was placed in a 300 ml round bottom flask and stirred with 98 ml of methanol until most of it had dissolved. The flask was cooled in an ice bath and the freshly made NaSH solution was added slowly. A reflux condenser and argon balloon were fitted and the mixture was refluxed for 1 hour. The reflux condenser was replaced with a short path distillation head and 90 ml was distilled off. The flask was cooled to room temperature and the aqueous residue was extracted with four portions of CH_2Cl_2. The extracts were combined and dried overnight over anhydrous K_2CO_3 in the refrigerator. The solution was filtered and evaporated to give a deep orange-yellow solid. The product was purified by chromatography on flash silica (18 cm x 6 cm) with hexane:ether, 2:1. The product-containing fractions were combined to afford 4.83 g (68%) of a bright orange-yellow solid.

TLC (Silica GF, hexane:ether, 1:2) showed 85-90% radiochemical purity. The product was used in the next step without further purification.

3-Nitroacetanilide [ring-^{14}C(U)] (3)

3-Nitroaniline [^{14}C(U)] (4.83 g, 35.0 mmol) was mixed with acetic anhydride (3.75 g, 36.8 mmol) in 30 ml of anhydrous toluene, and the mixture was stirred under nitrogen for 2 hours at 85°C. The mixture was evaporated on the rotary evaporator, leaving a bright yellow solid, which was purified by chromatography on flash silica (18 cm x 6 cm) with CH_2Cl_2:CH_3OH, 100:1. Fractions were combined and evaporated to give 5.50 g (87%) of a buff-colored solid. TLC (Silica GF, CH_2Cl_2:CH_3OH, 40:1) showed the material to be approx. 95% radiochemically pure. It was used in the next step without further purification.

2,3-Dinitroacetanilide [ring-^{14}C(U)] (4)

3-Nitroacetanilide [ring-^{14}C(U)] (5.50 g, 30.6 mmol) was placed in a 50 ml round bottom flask with a magnetic stirbar and cooled in an ice bath. Fuming nitric acid (d 1.52 g/ml, 13 ml), precooled in an ice bath, was added dropwise and the mixture, gummy at first, was warmed slowly to 15°C and maintained at 15-20°C for 1.5 hours. It was then poured onto ice and stored overnight. The precipitated solid was filtered, washed with water, and pumped dry to afford 4.77 g of a yellow-brown solid.

However, TLC (Silica GF, $CHCl_3$:CH_3OH, 20:1) showed mostly recovered starting material.

The nitration was repeated on the recovered material, using 11 ml of fuming nitric acid from a different bottle. TLC (as above) showed that nitration was progressing very slowly, and further fuming nitric acid (5 ml) was added twice more - once after approx. 1.5 hours and once after approx. 3.5 hours. After a total reaction time of approx. 5 hours, reaction progress seemed to stop, and so the reaction mixture was added to ice. After the ice melted, the solid was filtered, washed with H_2O, and pumped dry to afford 3.42 g of a yellow solid. Further product was obtained by extraction of the aqueous filtrate with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered, and evaporated to afford approx. 0.9 g of material.

Both batches of crude material were purified by chromatography on flash silica (18 cm x 6 cm) with CH_2Cl_2:CH_3OH, 100:1. Fractions were combined to afford 1.77 g (26%) of a pale yellow-brown solid. TLC (Silica GF, CH_2Cl_2:CH_3OH, 20:1) showed >95% radiochemical purity.

<u>2,3-Dinitroaniline [^{14}C(U)] (5)</u>

2,3-Dinitroacetanilide [ring-^{14}C(U)] (1.77 g, 7.87 mmol) was mixed with 44 ml of methanol in a three neck flask equipped with a magnetic stirbar, rubber septum, and reflux condenser and stirred rapidly at 60°C. Some of the material remained undissolved. Concentrated hydrochloric acid (5.3 ml) was added slowly, giving an orange-red solution. The mixture was refluxed gently for one hour and cooled to room temperature. The mixture was concentrated to approx. 5 ml on the rotary evaporator and extracted with three portions of ethyl acetate. The combined ethyl acetate extracts were washed with 2 small portions of 4% aqueous sodium hydroxide solution. (The second portion turned the organic layer deep red). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a dark brown solid. The product was purified by chromatography on flash silica (18 cm x 6 cm) with CH_2Cl_2:CH_3OH, 100:1. Pure fractions were combined and evaporated to give 0.519 g (36%)

of a deep yellow solid. TLC (Silica GF, CH_2Cl_2:CH_3OH, 20:1) showed approximately 98% radiochemically pure material.

Column fractions containing a front-running impurity were combined separately to afford 0.457 g of a red oil. ^1H and ^{13}C NMR in $CDCl_3$ showed it to be 2-chloronitrobenzene [^{14}C(U)].

2,3-Dichloronitrobenzene [^{14}C(U)] (6)

2,3-Dinitroaniline [^{14}C(U)] (0.500 g, 2.73 mmol) was stirred with a mixture of 17.7 ml of acetic acid and 3.7 ml of concentrated hydrochloric acid in a round bottom flask. The mixture was cooled in an ice bath and treated, dropwise, with sodium nitrite (0.207 g, 3.00 mmol) in 0.75 ml of water. The bath was warmed to 10-15°C and the mixture was stirred at that temperature for 1 hour. The entire mixture was then added dropwise to a stirred mixture of cuprous chloride (2.00 g, 20.2 mmol) and concentrated hydrochloric acid (20 ml) at 53°C. The mixture was heated to 70°C and stirred at that temperature for 1 hour. It was then cooled to room temperature, diluted with water, and extracted with ethyl acetate. The ethyl acetate extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to afford 0.802 g of a brown solid. The product was purified by chromatography on flash silica (18 cm x 6 cm) with hexane:ether, 2:1. Fractions were combined to afford 0.379 g (72%) of a pale yellow solid. TLC (Silica GF, hexane:ether, 2:1) showed approximately 99% radiochemical purity.

2,3-Dichloroaniline [^{14}C(U)] (7)

Hot and cold 2,3-dichloronitrobenzene [^{14}C(U)] (combined weight 0.435 g, 2.27 mmol) were mixed with 3.2 ml of ethanol and 11.9 ml of 10% hydrochloric acid, and treated with tin powder (1.35 g, 11.3 mmol). The mixture was heated gently, with stirring, to 115°C over a period of 20 minutes. It was then cooled, concentrated on the rotary evaporator and extracted with 2 portions of ether. Since considerable radioactivity remained in the aqueous phase, the mixture was made basic with concentrated ammonium hydroxide solution and extracted with 6 more portions of ether. All ether extracts were combined and dried over anhydrous K_2CO_3. The solution was filtered and evaporated to afford 0.363 g of a deep brown oil. The product was purified by chromatography on flash silica (18 cm x 2.5 cm) with hexane:ether, 5:1. Pure fractions were combined to afford 0.305 g (83%) of a clear liquid. TLC (Silica, hexane:ether, 3:2) showed approx. 99% radiochemical purity.

The product was diluted with cold standard (0.210 g) and vacuum distilled to afford 0.45 g of a wet solid.

TLC (Silica GF, hexane:ethyl acetate, 4:1):99% radiochemical purity.

HPLC (Zorbax ODS, acetonitrile:water, 1:1):99% radiochemical purity.

<u>2',3'-Dichloro-4-acetoxybenzanilide [dichloroaniline-ring-^{14}C(U)]</u> (<u>8</u>)

A mixture of 4-acetoxybenzoic acid (0.540 g, 3 mmol), dioxane (10 ml), thionyl chloride (0.72 ml, 1.17 g, 9.87 mmol) and N,N-dimethylformamide (a catalytic amount) was refluxed for 2 hrs. Evaporation of the reaction mixture gave the corresponding acid chloride as an oil in theoretical yield. 2,3-dichloroaniline [^{14}C(U)] (0.422 g, 2.61 mmol) was dissolved in acetone (10 ml). To the solution were added $NaHCO_3$ (0.504 g, 6 mmol) and then dropwise the acid chloride in acetone with stirring and the mixture was stirred at room temp. for 3 hrs. The reaction mixture was poured into 0.1M HCl and the precipitate formed was filtered and dried in vacuo to afford compound <u>8</u> (0.829 g) (98% yield).

<u>2',3'-Dichloro-4-hydroxybenzanilide [dichloroaniline-ring-^{14}C(U)]</u> (<u>9</u>)

Compound <u>8</u> (0.829 g, 2.56 mmol) was dissolved in dioxane (28 ml). To the solution was added 2M KOH aqueous (2.56 ml, 5.12 mmol) and the mixture was stirred at room temp. for one hour. The reaction mixture was poured onto crushed ice and adjusted to pH 1-2 with hydrochloric acid. The resulting crystals were filtered and dried in vacuo to give compound <u>9</u> (0.634 g) (88% yield).

<u>2',3'-Dichloro-4-ethoxymethoxybenzanilide [dichlorophenyl-ring-^{14}C(U)], ^{14}C-HW-52</u> (<u>10</u>)

Compound <u>9</u> (0.634 g, 2.25 mmol) was dissolved in acetone (16 ml). To the solution were added polyethylene glycol 4000 (a catalytic amount), K_2CO_3 (0.942 g, 6.82 mmol) and dropwise chloromethyl ethyl ether(0.672

g, 7.11 mmol) over 5 min. with stirring, and the resulting solution was stirred for 2 hrs. at room temp. The reaction mixture was extracted with CH_2Cl_2, and the extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was dissolved in hot methanol and allowed to stand at room temp. The crystals which formed were filtered and dried in vacuo to give compound 10 (0.654 g) (85% yield). The overall radiochemical yield was 1.88% based on ^{14}C-1,3-dinitrobenzene. The IR, TLC and HPLC properties of this material were shown to be identical to those of an authentic sample of HW-52. The specific activity of ^{14}C-HW-52 was 970 MBq/mmol by the gravimetric method and the radiochemical purity was greater than 98.8% by both TLC and HPLC.

TLC (Silica GF, hexane:ethyl acetate, 4:1):99.2% radiochemical purity.

HPLC (Inertsil ODS-2, acetonitrile:0.05M ammonium acetate, 4:6):98.8% radiochemical purity.

References

1. Imamura M. - Chemical Regulation of Plants 18:151 (1983).
2. Welsh L.H. - J. Amer. Chem. Soc. 63:3276 (1941).
3. Kremer C.B. and Bendich A. - J. Amer. Chem. Soc. 61:2658 (1939).
4. Pausacker K.H. and Scroggie J.G. - J. Chem. Soc. 1897 (1955).
5. Sihlbom L. - Acta Chem. Scand. 7:1197 (1953).