Synthesis of Four ^{14}C-Isotopomers of Epoxiconazole, a New Triazole Fungicide

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Summary

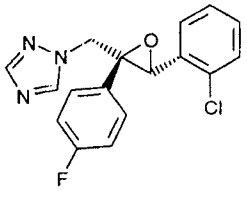
Starting from different ^{14}C-labelled compounds four isotopomers of the title compound epoxiconazole were synthesized. Chemical and radiochemical purities of the products were checked by radio-TLC and radio-HPLC and were found to be > 98 %.

Key words

Epoxiconazole, ^{14}C-radiolabel

Introduction

(Z)-3-(2-Chlorophenyl)-2-(4-fluorophenyl)-2-[1H-1,2,4-triazol-1-yl)methyl]oxirane, (epoxiconazole (OPUS ®)) (**1**) is a new triazole fungicide for the treatment of eyespot and other fungal diseases in cereals. For use in environmental and metabolism studies four ^{14}C-isotopomers **1 a - d** labelled in different rings were required. In this paper we report the synthesis of these four compounds.



1 a : oxirane-2-^{14}C
1 b : triazole-3(5)-^{14}C
1 c : fluorophenyl-U-^{14}C
1 d : chlorophenyl-U-^{14}C

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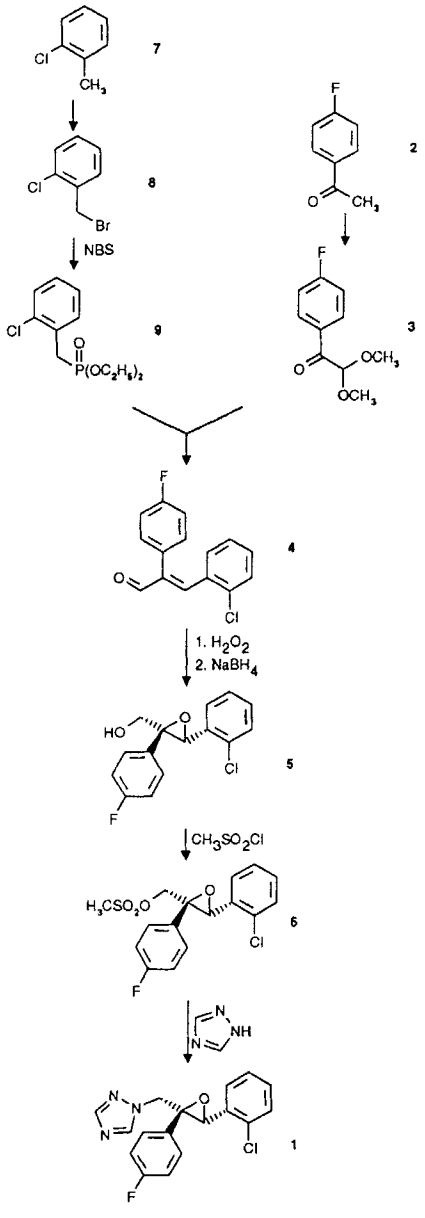
Results and discussion

We developed a synthetic route that allowed us to generate all four isotopomers by starting from different labelled intermediates (Scheme 1).

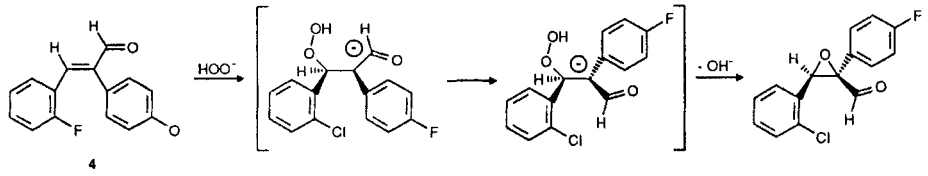


Scheme 1

4-Fluoroacetophenone **2** was oxidized by methylnitrite to give its ω,ω-dimethoxyderivative **3** in 85 % yield. Wittig-Horner reaction with 2-chlorobenzyldiethylphosphonate **9** provided after hydrolysis (E)-2,3-diphenylpropenal **4**. The configuration of **4** was established by X-ray analysis. Phosphonate **9** was synthesized by brominating 2-chloro-toluene **7** by NBS in the presence of AIBN and reacting the resulting 2-chlorobenzylbromide **8** in an Arbusov-reaction with triethylphosphite.

In a one-pot reaction **4** was epoxidized by hydrogen peroxide under alkaline conditions [1] and then reduced by $NaBH_4$ to give epoxyalcohol **5** as a 7 : 1 mixture of stereoisomers. The main isomer had the (Z)-configuration as was shown by X-ray analysis of **1**.

Obviously during oxidation there is a rotation taking place around the single bond between the β- and γ-carbon atoms resulting in a sterically less demanding configuration with the two phenyl rings in trans position:



Mesylation of **5** afforded crude mesylate **6** that was reacted with triazole to yield **1** as a mixture of stereoisomers as described for **5**. From this the (Z)-isomer was isolated by preparative LC.

1 a was prepared in 29 % overall yield starting from 4-fluoro-acetophenon-[carbonyl-^{14}C] (**2 a**), **1 b** in 62 % yield starting from triazole-[3-^{14}C], **1 c** in 41 % yield starting form 4-fluoroacetophenon-[phenyl-U-^{14}C] (**2 c**) and **1 d** in 24 % yield starting from 2-chlorotoluene-[phenyl-U-^{14}C] (**7d**).

Experimental

*1. ω,ω-Dimethoxy-4-fluoroacetophenon-[phenyl-U-^{14}C] (**3 c**)*

1.43 g (10.3 mmol) 4-Fluoroacetophenone (Du Pont de Nemour, spec. activity 1.66 GBq/mmol) was dissolved in 8 ml toluene / 2.45 ml 4.7 N methanolic HCl. After heating at 50° C ~ 20 mmol methylnitrite [2] were fed to the solution during 40 min. In order to remove excess methylnitrite nitrogen was bubbled through the solution for 30 min., 7.5 ml water was added, the mixture made alkaline (pH 9) with 2 N NaOH and shaken twice with a further 10 ml of water. The organic phase was separated, dried over Na_2SO_4 and evaporated to dryness.

Yield: 1.81 g (88 %); radiochemical purity 92 % (HPLC).

*2. (E)-3-(2-Chlorophenyl)-2-(4-fluorophenyl)propenal-[fluorophenyl-U-^{14}C] (**4 c**)*

A suspension of 0.57 g (10.5 mmol) sodium methylate in 10 ml DMF was added at room temperature to a mixture of 1.81 g (9.1 mmol) **3 c** and 2.44 g (9.4 mmol) 2-chlorobenzyldiethylphosphonate (**9**). The resulting brown solution was stirred for 3 hours at room temperature and acidified by the addition of 1.5 ml concentrated HCl. Stirring was continued for 1 hour, the precipitate filtered off, washed four times with 3 ml water and dried in vacuo.

Yield: 2.11 g (89 %); radiochemical purity 94 % (HPLC).

*3. (Z)-3-(2-Chlorphenyl)-2-(4-fluorophenyl)-2-hydroxymethyloxirane-[fluorophenyl-U-^{14}C] (**5 c**)*

To a suspension of 2.11 g (8.1 mmol) **4 c** in 17.5 ml methanol and 0.4 ml 2 N NaOH, 0.83 ml of H_2O_2 (30 %, 8.1 mmol) was added dropwise within 20 min. at 5° C. After stirring for 2 hours at room temperature a solution of 79 mg (2.1 mmol) $NaBH_4$ in 0.8 ml 1 N NaOH was added and stirring was continued for 1 hour. The mixture was cooled to 5° C and the reaction quenched by addition of 40 ml water. The precipitate was filtered off, washed with water and dried in vacuo.

Yield: 2.01 g (89 %); radiochemical purity 84 % ((Z)-isomer).

*4. (Z)-3-(2-Chlorophenyl)-2-(4-fluorophenyl)-2-[(1H-1,2,4-triazol-1-yl)methyl]-oxirane-[fluorophenyl-U-^{14}C] (**1 c**)*

0.85 g (7.5 mmol) Methansulfonylchloride was added dropwise within 40 min. at 40° C to a solution of 2.01 g (7.22 mmol) crude **5 c** in 20 ml toluene and 1.0 ml triethylamine. After stirring for 2 hours at 40° C, the mixture was extracted three times with 10 ml water. The organic phase was dried over Na_2SO_4 and evaporated to dryness.

The residue was redissolved in 10ml DMF and treated dropwise at 60° C with a solution of 0.53 g (7.7 mmol) 1,2,4-triazole and 0.64 g (8.0 mmol) 50 % NaOH in 3 ml DMF. The solution was stirred at 60° C for 3 hours and cooled to 5° C. 50 ml water were added, the precipitate was filtered off, washed with water and dried. The crude **1 c** thus obtained was purified by preparative LC on Lobar, Lichroprep RP 18, size B; mobile phase: aceto nitrile / water / THF (45 / 45 / 10).

Yield: 1.47 g (43 % starting from **2 c**); spec. activity 1.50 GBq/mmol, chemical and radiochemical purity > 99 % (HPLC).

*5. 2-Chlorobenzylbromide-[phenyl-U-^{14}C] (**8 d**)*

A solution of 2.10 g (16.6 mmol) 2-chlorotoluene-[phenyl-U-^{14}C] (Zeneca Fine Chemicals, spec. activity 15.2 GBq/mmol), 2.95 g (16.6 mmol) N-bromosuccinimide and 35 mg α,α'-azodiisobutyronitrile was refluxed for 3 hours. The succinimide was filtered off and the filtrate concentrated. The crude **8 c** (2.45 g, 71 %) was used without further purification.

*6. 2-Chlorobenzyldiethylphosphonate-[phenyl-U-^{14}C] (**9 d**)*

Crude **8 c** (2.45 g) was mixed with 2.22 g (13.3 mmol) triethylphosphite and heated at 150° C for 75 min. The solution was concentrated at 80° C / 50 mbar and the oily residue purified by prep. LC (Lobar B, RP 18, mobile phase: acetonitrile / water / THF (44 / 48 / 8)).

Yield: 2.86 g (66 %); radiochemical purity: > 98.5 % (HPLC).

*7. (Z)-3-(2-Chlorophenyl)-2-(4-fluorophenyl)-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane-[chlorophenyl-U-^{14}C] (**1 d**)*

Using **9 d**, **1 d** was prepared as described above for **1 c**.

Yield: 24 % (starting from **7 d**); radiochemical and chemical purity > 98 % (HPLC).

8. *(Z)-3-(2-Chlorophenyl)-2-(4-fluorophenyl)-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane-[oxirane-1-^{14}C] (**1 a**)*

Starting from 4-fluoroacetophenone-[carbonyl-^{14}C] (Du Pont de Nemour) (**2 a**) **1 a** was prepared as described above for **1 c**.

Yield: 29 %; radiochemical and chemical purity > 98 %.

9. *(Z)-3-(2-Chlorophenyl)-2-(4-fluorophenyl)-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane-[triazole-3(5)-^{14}C] (**1 b**)*

Using 1,2,4-triazole-[3(5)-^{14}C] (Amersham) **1 b** was prepared as described above for **1 c**.

Yield: 62 %; radiochemical and chemical purity > 98 %.

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References

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