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Improved method for synthesis

Technical field

The present invention relates to an improved method for the synthesis of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl-1H-benizimidazole, referred to under its generic name omeprazole throughout the following specification and claims.

Prior art

US-A-4 255 431 discloses a process for the synthesis of omeprazole comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole in a methylene chloride solution with m-chloroperoxybenzoic acid resulting in the formation of omeprazole and m-chlorobenzoic acid. omeprazole is highly sensitive to acids,. and the reaction mixture has to be maintained at a low temperature to prevent excessive decomposition in the reaction mixture.

The product is worked-up by filtering-off of m-chloro-benzoic acid formed during the reaction. The filtrate is diluted with methylene chloride, is extracted with Na_2CO_3 solution, dried and evaporated. The resulting omeprazole product is contaminated with starting materials and by-products.

Summary of the invention

The object of the present invention is to provide an improved method for the synthesis of omeprazole, which eliminates the drawbacks of previously known methods.

This object is achieved according to the present inven-

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tion, which is characterized by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl-thio]-1H-benzimidazole (below denoted Compound I) with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

The m-chloroperoxybenzoic acid is suitably used in an amount of 0.7 - 1.4 molar equivalents of Compound I, and preferably in an amount of 0.9 - 1.2 molar equivalents.

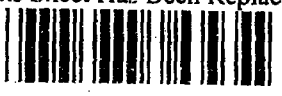
According to one embodiment of the invention, the alkyl formate is methylformate or ethylformate, methylformate being preferred.

The alkyl formate is suitably used in an amount of 1.2 - 2.0 molar equivalents of Compound I, and preferably in an amount of 1.5 - 1.8 molar equivalents.

One important feature of the method according to the invention is that unreacted sulfide is not transferred into the aqueous phase upon the extraction with aqueous NaOH. Another important feature is that m-chlorobenzoic acid does not crystallize upon the addition of methyl-formate to the aqueous phase, thereby eliminating the need of filtering-off of m-chlorobenzoic acid in a previous step.

The pH of the reaction mixture may be maintained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH or with the use of a buffer. Preferred buffers are sodium bicarbonate and potassium bicarbonate.

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A great advantage of the method according to the invention is that the reaction takes place in the organic methylene chloride phase while the m-chlorobenzoic acid formed during the reaction goes into the aqueous phase containing the buffer, in the case a buffer is used. Because of this, omeprazole formed does not stay in contact with the acid and the reaction may be performed at a temperature above 0°C.

According to one embodiment of the invention the pH of the aqueous NaOH phase is kept at above about 12.

According to another embodiment of the invention the crystallization of omeprazole is performed at a pH of above 9.

The invention will be further illustrated below with a non-limiting example.

Example

5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (16.2 g; 0.0492 mol) is reacted with m-chloroperoxybenzoic acid (13.6 g; 0.0537 mol) in CH_2Cl_2 acting as a solvent at a pH of 8.6, which is maintained by the presence of $KHCO_3$ (5.6 g; 0.056 mol) acting as a buffer. The temperature is maintained at about 0°C during the addition.

Diluted NaOH is added to a pH above 12 and the CH_2Cl_2 phase is separated off.

Methylformate (4.7 g) is charged to the water phase and the pH is kept above 9, whereupon omeprazole crystallizes. The crystals are filtered off and are washed with water and methanol at a temperature of about 0°C. The washed crystals are dried under vacuum. Yield: 15.6 g (92 %).

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Claims

1. An improved method for the synthesis of omeprazole, characterized by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl-thio]-1H-benzimidazole (Compound I) with m-chloroperoxy-benzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in the crystal-lization of omeprazole.

2. Method according to claim 1, characteri-zed in that the m-chloroperoxybenzoic acid is used in an amount of 0.7 - 1.4, preferably 0.9 - 1.2, molar equi-valents of Compound I.

3. Method according to claim 1 or 2, characte-rized in that the alkyl formate is methylformate.

4. Method according to claims 1 - 3, characte-rized in that pH of the reaction mixture is main-tained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH.

5. Method according to claims 1 - 4, characte-rized in that pH of the reaction mixture is main-tained within the pH range of 8.0 - 8.6 with the use of a buffer.

6. Method according to claim 5, characteri-zed in that the buffer is sodium bicarbonate or potassium bicarbonate.

7. Method according to claims 1 - 6, characte-rized in that the pH of the aqueous NaOH phase is

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* C L M S *

kept at above about 12.

8. Method according to claims 1 - 7, c h a r a c t e - r i z e d in that the alkyl formate is added in an amount of 1.2 - 2.0, preferably 1.5 - 1.8, molar equivalents of Compound I.

9. Method according to claims 1 - 8, c h a r a c t e - r i z e d in that the crystallization of omeprazole is performed at a pH of above 9.

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A B S T R A C T

The present invention relates to an improved method for the synthesis of omeprazole, comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

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Improved method for synthesis

Technical field

The present invention relates to an improved method for the synthesis of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl-1H-benizimidazole, referred to under its generic name omeprazole throughout the following specification and claims.

Prior art

US-A-4 255 431 discloses a process for the synthesis of omeprazole comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole in a methylene chloride solution with m-chloroperoxybenzoic acid resulting in the formation of omeprazole and m-chlorobenzoic acid. omeprazole is highly sensitive to acids, and the reaction mixture has to be maintained at a low temperature to prevent excessive decomposition in the reaction mixture.

The product is worked-up by filtering-off of m-chloro-benzoic acid formed during the reaction. The filtrate is diluted with methylene chloride, is extracted with Na_2CO_3 solution, dried and evaporated. The resulting omeprazole product is contaminated with starting materials and by-products.

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Summary of the invention

The object of the present invention is to provide an improved method for the synthesis of omeprazole, which eliminates the drawbacks of previously known methods.

This object is achieved according to the present inven-

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tion, which is characterized by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl-thio]-1H-benzimidazole (below denoted Compound I) with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

The m-chloroperoxybenzoic acid is suitably used in an amount of 0.7 - 1.4 molar equivalents of Compound I, and preferably in an amount of 0.9 - 1.2 molar equivalents.

According to one embodiment of the invention, the alkyl formate is methylformate or ethylformate, methylformate being preferred.

The alkyl formate is suitably used in an amount of 1.2 - 2.0 molar equivalents of Compound I, and preferably in an amount of 1.5 - 1.8 molar equivalents.

One important feature of the method according to the invention is that unreacted sulfide is not transferred into the aqueous phase upon the extraction with aqueous NaOH. Another important feature is that m-chlorobenzoic acid does not crystallize upon the addition of methyl-formate to the aqueous phase, thereby eliminating the need of filtering-off of m-chlorobenzoic acid in a previous step.

The pH of the reaction mixture may be maintained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH or with the use of a buffer. Preferred buffers are sodium bicarbonate and potassium bicarbonate.

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REPLACEMENT SHEET
14 NOV 1996

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A great advantage of the method according to the invention is that the reaction takes place in the organic methylene chloride phase while the m-chlorobenzoic acid formed during the reaction goes into the aqueous phase containing the buffer, in the case a buffer is used. Because of this, omeprazole formed does not stay in contact with the acid and the reaction may be performed at a temperature above 0°C.

According to one embodiment of the invention the pH of the aqueous NaOH phase is kept at above about 12.

According to another embodiment of the invention the crystallization of omeprazole is performed at a pH of above 9.

The invention will be further illustrated below with a non-limiting example.

Example

5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (16.2 g; 0.0492 mol) is reacted with m-chloroperoxybenzoic acid (13.6 g; 0.0537 mol) in CH_2Cl_2 acting as a solvent at a pH of 8.6, which is maintained by the presence of $KHCO_3$ (5.6 g; 0.056 mol) acting as a buffer. The temperature is maintained at about 0°C during the addition.

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Diluted NaOH is added to a pH above 12 and the CH_2Cl_2 phase is separated off.

Methylformate (4.7 g) is charged to the water phase and the pH is kept above 9, whereupon omeprazole crystallizes. The crystals are filtered off and are washed with water and methanol at a temperature of about 0°C. The washed crystals are dried under vacuum. Yield: 15.6 g (92 %).

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Claims

1. An improved method for the synthesis of omeprazole, characterized by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (Compound I) with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in the crystallization of omeprazole.

2. Method according to claim 1, characterized in that the m-chloroperoxybenzoic acid is used in an amount of 0.7 - 1.4, preferably 0.9 - 1.2, molar equivalents of Compound I.

3. Method according to claim 1 or 2, characterized in that the alkyl formate is methylformate.

4. Method according to claims 1 - 3, characterized in that pH of the reaction mixture is maintained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH.

5. Method according to claims 1 - 4, characterized in that pH of the reaction mixture is maintained within the pH range of 8.0 - 8.6 with the use of a buffer.

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6. Method according to claim 5, characterized in that the buffer is sodium bicarbonate or potassium bicarbonate.

7. Method according to claims 1 - 6, characterized in that the pH of the aqueous NaOH phase is

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kept at above about 12.

8. Method according to claims 1 - 7, c h a r a c t e - r i z e d in that the alkyl formate is added in an amount of 1.2 - 2.0, preferably 1.5 - 1.8, molar equivalents of Compound I.

9. Method according to claims 1 - 8, c h a r a c t e - r i z e d in that the crystallization of omeprazole is performed at a pH of above 9.

REPLACEMENT SHEET

14 NOV 1996

IMPROVED METHOD FOR SYNTHESIS

A B S T R A C T

The present invention relates to an improved method for the synthesis of omeprazole, comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

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Improved method for synthesis

Technical field

The present invention relates to an improved method for the synthesis of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl-1H-benizimidazole, referred to under its generic name omeprazole throughout the following specification and claims.

Prior art

EP-A-197013 discloses a process for the preparation of 5-methoxy-2-[[[4-(4-methylphenoxy)-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole by oxidization of 5-methoxy-2-[[[4-(4-methylphenoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole at -5 °C with m-chloroperbenzoic acid in CH_2Cl_2. NaOH is then added to the reaction mixture, separation of the two phases, addition of CH_2Cl_2, adjustment of the pH to 9.5 by HCl addition and separation of the phases. After drying of the CH_2Cl_2 phase the solvent is evaporated and the product crystallized from CH_3CN. Omeprazole is highly sensitive to acids, and the reaction mixture has to be maintained at a low temperature to prevent excessive decomposition in the reaction mixture.

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US-A-4 255 431 discloses a process for the synthesis of omeprazole comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole in a methylene chloride solution with m-chloroperoxybenzoic acid resulting in the formation of omeprazole and m-chlorobenzoic acid. omeprazole is highly sensitive to acids, and the reaction mixture has to be maintained at a low temperature to prevent excessive decomposition in the reaction mixture.

The product is worked-up by filtering-off of m-chloro-benzoic acid formed during the reaction. The filtrate is diluted with methylene chloride, is extracted with Na_2CO_3 solution, dried and evaporated. The resulting omeprazole product is contaminated with starting materials and by-products.

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REPLACEMENT SHEET
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Summary of the invention

The object of the present invention is to provide an improved method for the synthesis of omeprazole, which eliminates the drawbacks of previously known methods.

This object is achieved according to the present invention, which is characterized by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (below denoted Compound I) with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

The m-chloroperoxybenzoic acid is suitably used in an amount of 0.7 - 1.4 molar equivalents of Compound I, and preferably in an amount of 0.9 - 1.2 molar equivalents.

According to one embodiment of the invention, the alkyl formate is methylformate or ethylformate, methylformate being preferred.

The alkyl formate is suitably used in an amount of 1.2 - 2.0 molar equivalents of Compound I, and preferably in an amount of 1.5 - 1.8 molar equivalents.

One important feature of the method according to the invention is that unreacted sulfide is not transferred into the aqueous phase upon the extraction with aqueous NaOH. Another important feature is that m-chlorobenzoic acid does not crystallize upon the addition of methylformate to the aqueous phase, thereby eliminating the need of filtering-off of m-chlorobenzoic acid in a previous step.

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REPLACEMENT SHEET
02 FEB 1998

The pH of the reaction mixture may be maintained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH or with the use of a buffer. Preferred buffers are sodium bicarbonate and potassium bicarbonate. A great advantage of the method according to the invention is that the reaction takes place in the organic methylene chloride phase while the m-chlorobenzoic acid formed during the reaction goes into the aqueous phase containing the buffer, in the case a buffer is used. Because of this, omeprazole formed does not stay in contact with the acid and the reaction may be performed at a temperature above 0°C.

According to one embodiment of the invention the pH of the aqueous NaOH phase is kept at above about 12.

According to another embodiment of the invention the crystallization of omeprazole is performed at a pH of above 9.

The invention will be further illustrated below with a non-limiting example.

Example

5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (16.2 g; 0.0492 mol) is reacted with m-chloroperoxybenzoic acid (13.6 g; 0.0537 mol) in CH_2Cl_2 acting as a solvent at a pH of 8.6, which is maintained by the presence of $KHCO_3$ (5.6 g; 0.056 mol) acting as a buffer. The temperature is maintained at about 0°C during the addition.

Diluted NaOH is added to a pH above 12 and the CH_2Cl_2 phase is separated off.

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Methylformate (4.7 g) is charged to the water phase and the pH is kept above 9, whereupon omeprazole crystallizes. The crystals are filtered off and are washed with water and methanol at a temperature of about 0°C. The washed crystals are dried under vacuum. Yield: 15.6 g (92 %).

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* C L M S *

C l a i m s

1. An improved method for the synthesis of omeprazole, c h a r a c t e r i z e d by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl-thio]-1H-benzimidazole (Compound I) with m-chloroperoxy-benzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in the crystal-lization of omeprazole.

2. Method according to claim 1, c h a r a c t e r i - z e d in that the m-chloroperoxybenzoic acid is used in an amount of 0.7 - 1.4, preferably 0.9 - 1.2, molar equi-valents of Compound I.

3. Method according to claim 1 or 2, c h a r a c t e - r i z e d in that the alkyl formate is methylformate.

4. Method according to claims 1 - 3, c h a r a c t e - r i z e d in that pH of the reaction mixture is main-tained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH.

5. Method according to claims 1 - 4, c h a r a c t e - r i z e d in that pH of the reaction mixture is main-tained within the pH range of 8.0 - 8.6 with the use of a buffer.

6. Method according to claim 5, c h a r a c t e r i - z e d in that the buffer is sodium bicarbonate or potassium bicarbonate.

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7. Method according to claims 1-6, c h a r a c t e r - i z e d in that the pH of the aqueous NaOH phase is kept at above about 12.

8. Method according to claims 1-7, c h a r a c t e r - i z e d in that the alkyl formate is added in an amount of 1.2-2.0, preferably 1.5-1.8, molar equivalents of Compound I.

9. Method according to claims 1-8, c h a r a c t e r - i z e d in that the crystallization of omeprazole is performed at a pH of above 9.

REPLACEMENT SHEET
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IMPROVED METHOD FOR SYNTHESIS

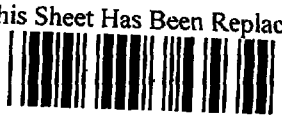
A B S T R A C T

The present invention relates to an improved method for the synthesis of omeprazole, comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

REPLACEMENT SHEET
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IMPROVED METHOD FOR SYNTHESIS

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Description

Technical field

The present invention relates to an improved method for the synthesis of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl-1H-benzimidazole, referred to under its generic name omeprazole throughout the following specification and claims.

Prior art

EP-A-197013 discloses a process for the preparation of 5-methoxy-2-[[[4-(4-methylphenoxy)-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole by oxidization of 5-methoxy-2-[[[4-(4-methylphenoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole at -5 °C with m-chloroperbenzoic acid in CH_2Cl_2. NaOH is then added to the reaction mixture, separation of the two phases, addition of CH_2Cl_2, adjustment of the pH to 9.5 by HCl addition and separation of the phases. After drying of the CH_2Cl_2 phase the solvent is evaporated and the product crystallized from CH_3CN. The product is highly sensitive to acids, and the reaction mixture has to be maintained at a low temperature to prevent decomposition in the reaction mixture.

US-A-4 255 431 discloses a process for the synthesis of omeprazole comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (below denoted Compound I) in a methylene chloride solution with m-chloroperoxybenzoic acid resulting in the formation of omeprazole and m-chlorobenzoic acid. Omeprazole is highly sensitive to acids, and the reaction mixture has to be maintained at a low temperature to prevent decomposition of omeprazole in the reaction mixture.

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The product is worked-up by filtering-off of m-chlorobenzoic acid formed and precipitated during the reaction. The filtrate is diluted with methylene chloride, is extracted with Na_2C0_3 solution, dried and evaporated. The resulting crude omeprazole is contaminated with starting materials and by-products.

Summary of the invention

The object of the present invention is to provide an improved method for the synthesis of omeprazole, which increases the yield and purity of the crude omeprazole.

This object is achieved according to the present invention, which is characterized by the steps of reacting Compound I with m-chloroperoxybenzoic acid in an inert solvent, preferably methylene chloride, at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous base, preferably NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

The m-chloroperoxybenzoic acid is suitably used in an amount of 0.7 - 1.4 molar equivalents of Compound I, and preferably in an amount of 0.9 - 1.2 molar equivalents.

According to one embodiment of the invention, the alkyl formate is methylformate or ethylformate, methylformate being preferred.

The alkyl formate is suitably used in an amount of 1.2-2.0 molar equivalents of Compound I, and preferably in an amount of 1.5 - 1.8 molar equivalents.

One important feature of the method according to the invention is that Compound I is not transferred into the aqueous phase upon the extraction with aqueous NaOH. Another important feature is that m-chlorobenzoic acid does not crystallize upon the addition of methylformate to the aqueous phase, thereby eliminating the need of filtering-off of m-chlorobenzoic acid in a previous step, prior to isolating the crude omeprazole.

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The pH of the reaction mixture may be maintained within the pH range of 8.0 - 8.6 with the aid of pH static titration with base, preferably NaOH, or with the use of an aqueous buffer solution. Preferred aqueous buffer solutions are sodium bicarbonate and potassium bicarbonate.

A great advantage of the method according to the invention is that the reaction takes place in the organic methylene chloride phase while the m-chlorobenzoic acid formed during the reaction goes into the aqueous phase containing the buffer, in the case a buffer is used. Because of this, the omeprazole formed does not stay in contact with the acid and the reaction may be performed at a temperature above 0°C.

According to one embodiment of the invention the pH of the aqueous NaOH phase is kept at above about 12.

According to another embodiment of the invention the crystallization of crude omeprazole is performed at a pH of above 9.

The invention will be further illustrated below with a non-limiting example.

Example

5-methoxy-2-[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (Compound I) (16.2 g; 0.0492 mol) is reacted with m-chloroperoxybenzoic acid (13.6 g; 0.0537 mol) in CH_2Cl_2 acting as a solvent at a pH of 8.6, which is maintained by the presence of aqueous $KHCO_3$-solution (5.6 g; 0.056 mol) acting as a buffer. The temperature is maintained at about 0°C during the addition.

Diluted NaOH is added to a pH above 12 and the CH_2Cl_2 phase is separated off Methylformate (4. 7 g) is charged to the water phase whereby the pH is kept above 9, whereupon crude omeprazole crystallizes. The

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crystals are filtered off and are washed with water and methanol at a temperature of about 0°C. The washed crystals are dried under vacuum. Yield: 15.6 g (92 %)

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Claims

1. An improved method for the synthesis of omeprazole, comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl-thio]-1H-benzimidazole (Compound I) with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase, **characterized** by adding an alkyl formate to the aqueous phase, resulting in the crysallization of omeprazole.

2. Method according to claim 1, **characterized** in that the m-chloroperoxybenzoic acid is used in an amount of 0.7-1.4, preferably 0.9-1.2, molar equivalents of Compound I.

3. Method according to claim 1 or 2, **characterized** in that the alkyl formate is methylformate.

4. Method according to claims 1-3, **characterized** in that pH of the reaction mixture is maintained within the pH range of 8.0-8.6 with the aid of pH static titration with NaOH.

5. Method according to claims 1-4, **characterized** in that pH of the reaction mixture is maintained within the pH range of 8.0-8.6 with the use of a buffer.

6. Method according to claim 5, **characterized** in that the buffer is sodium bicarbonate or potassium bicarbonate.

7. Method according to claims 1-6, **characterized** in that the pH of the aqueous NaOH phase is kept at above about 12.

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8. Method according to claims 1-7, **characterized** in that the alkyl formate is added in an amount of 1.2-2.0, preferably 1.5-1.8, molar equivalents of Compound I.

9. Method according to claims 1-8, **characterized** in that the crystallization of omeprazole is performed at a pH of above 9.

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IMPROVED METHOD FOR SYNTHESIS

A B S T R A C T

The present invention relates to an improved method for the synthesis of omeprazole, comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

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