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(54) Title: PROCESS FOR THE PREPARATION OF SUBSTITUTED CYNOPHENOXY-PYRIMIDINYLOXY-PHENYL ACRYLATE DERIVATIVES

(57) **Abstract:** The present invention provides a process for reacting between a phenol derivative and an aromatic substrate under phenolate forming conditions comprising the following steps: (a) reacting a phenol derivative with a base in a polar organic solvent to obtain a phenolate salt, wherein water is removed from the reaction mixture during the reaction. (b) adding the aromatic substrate to the reaction mixture obtained in step (a), (c) heating the reaction mixture of step (b) to a temperature in the range of 80° to 1300C, preferebly, 90- 1000C for 2 to 7 hours to obtain a phenoxy substituted aromatic substrate, (d) removing the solvent from the mixture of step (c) and further isolating and purifying the phenoxy substituted aromatic substrate. Optionally, the removal of water during step (a) is in conjunction with partial removal of the organic solvent.

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Process for the Preparation of Substituted Cyanophenoxy–Pyrimidinyloxy-phenyl Acrylate Derivatives

Field of the Invention

The present invention relates to the field of chemical synthesis, particularly to improved processes for synthesizing substituted cyanophenoxy–pyrimidinyloxy-phenyl acrylate derivatives.

Background of the Invention

In the field of industrial chemical synthesis, the improvement of the yield and selectivity of chemical processes bears considerable impact on the industry. Particularly, the focus in said improvements is on lowering costs, simplifying unit operations and environmental considerations. These three factors are particularly important in the field of agrochemicals where the volume of chemicals is large and the marginal profit is relatively small.

Of the many agrochemical compounds which are synthesized by multi-stage synthesis, methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate (chemical common name: azoxystrobin), particularly drew the attention of the present inventors. Azoxystrobin, disclosed in U.S. Patent No. 5,395,837, is a plant protection fungicide with protectant, curative, eradicant, translaminar and systemic properties. The preparation of azoxystrobin as described in Example 3 of U.S. 5,395,837 involves an aromatic substitution reaction between 2-cyanophenol and (E)-Methyl 2-[2-(6-chlorpyridimin-4-yloxy)phenyl]-3-methoxypropenoate also known as (E)-Methyl -2-[2-(6-chloropyrimidin-4-yloxy)-phenyl]-3-methoxyacrylate, at temperatures at 95° to 100°C in DMF in the presence of stoichiometric amounts of potassium carbonate and a catalytic amount of copper(I) chloride. The reported yield of azoxystrobin is 65% wherein the product was found to have a melting point of 110°C -111°C, indicating a final product of relatively low purity, which subsequently required further purification. It has been suggested that reactions of 2-cyanophenol or other isomers of cyanophenol or phenols in general under conditions of temperatures of about 90°C and above, in the presence of basic reagents which can promote the formation of phenolate salts, may cause polymerization and the formation of tars. This clearly is a highly undesirable side effect.

Accordingly there is an ongoing and long felt need for a process for aromatic substitution reactions in the presence phenols with improved yield and selectivity.

Thus, it is the objective of the present invention to provide a process for reacting phenols under basic conditions in which the yield and selectivity is improved.

Other objectives of the invention shall become apparent as the description proceeds.

Summary of the Invention

The present invention provides a process for reacting between a phenol derivative and an aromatic substrate under phenolate forming conditions comprising the following steps:

a) reacting a phenol derivative with a base in a polar organic solvent to obtain a phenolate salt, wherein water is removed from the reaction mixture during the reaction.
b) adding the aromatic substrate to the reaction mixture obtained in step (a),
c) heating the reaction mixture of step (b) to a temperature in the range of 80° to 130°C,preferebly, 90-100°C for 2 to 7 hours to obtain a phenoxy substituted aromatic substrate,
d) removing the solvent from the mixture of step (c) and further isolating and purifying the phenoxy substituted aromatic substrate.

Optionally, the removal of water during step (a) is in conjunction with partial removal of the organic solvent.

Detailed Description of the Invention

The following description is illustrative of embodiments of the invention. The following description is not to be construed as limiting, it being understood that the skilled person may carry out many obvious variations to the invention. Throughout the specification the terms “phenols” and “phenol derivative” include phenol and mono and poly-substituted phenols, including 2-cyanophenol and other cyanophenol isomers.

The present invention provides a process for reacting between a phenol derivative and an aromatic substrate under phenolate forming conditions wherein the formation of polymeric by-products and tars are minimized. In minimizing said by-products and tars formation, the present process provides improved yields together with facilitation of product separation and purification. The present process provides yields of 90% and greater, wherein said yield is calculated on the basis of the aromatic substrate. It has been surprisingly found that generating the phenolate salt separately and subsequently reacting said phenolate salt with the aromatic substrate, prevents the formation of undesirable by-products and tars.

The present process comprises the following steps:

a) reacting a phenol derivative with a base in a polar organic solvent to obtain a phenolate salt,, wherein water is removed from the reaction mixture during the reaction.

Step (a) is conducted wherein the mole ratio between said phenol derivative and base is preferably between 1:1 to 1:1.5, preferably 1:1.125 to 1:1.15. The time required for step (a) to obtain conversion to a phenolate salt is 30 to 120 minutes at a temperature between 60°C to 80°C, while partially removing solvent with water from the reaction mixture by vacuum distillation.

According to a preferred embodiment of the present invention said phenol derivative may be phenol, mono-substituted phenol or poly-substituted phenol, more preferably, cyanophenol derivatives, including 2-cyanophenol and 4-cyanophenol.

Said base may be selected from among hydroxide and carbonate bases, including but not limited to metal hydroxides, alkali metal hydroxides, metal carbonates and alkali metal carbonates preferably, sodium hydroxide or potassium hydroxide.

Non-limiting examples of preferred polar organic solvents are dimethyl formamide (DMF), dimethyl acetamide (DMAA) and dimethyl sulphoxide (DMSO) wherein, preferably the range of the reagent/solvent ratio is 0.1mole/150ml-0.1mole/350ml.

According to a specific embodiment of the invention, the phenolate salt is formed via partial removal of solvent with water under reduced pressure conditions.

b) adding the aromatic substrate to the reaction mixture obtained in step (a).

According to a particular embodiment of the invention said aromatic substrate may be added together with a polar organic solvent selected from the afore-mentioned group of solvents. The aromatic substrate is added in an amount such that the mole ratio between the phenol derivative and aromatic substrate is between 1: 0.8 and 1:1

In yet a further preferred embodiment of the invention, the aromatic substrate is selected from among mono and poly-substituted pyridine, pyrimidine and phenyl groups. Preferably, at least mono-halo substituted and more preferably chloro-pyrimidine derivatives.

c) heating the reaction mixture of step (b) to a temperature in the range of 80° to 130°C, preferably about 100°C for 2 to 7 hours, preferably about 5 hours to obtain a phenoxy substituted aromatic substrate,

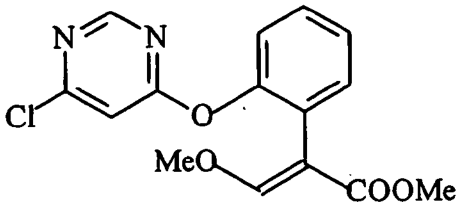
d) removing the solvent from the mixture of step (c) and further isolating and purifying the phenoxy substituted aromatic substrate.

The operations of step (d) can be carried out according to methods known to the skilled artisan. Said methods include; solvent removal by distillation wherein said distillation may be carried out under reduced pressure conditions, separation and purification by washing, extraction and crystallization.

According to a specific preferred embodiment of the present invention, there is provided a process for the preparation of methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate (azoxystrobin) comprising of the following steps:

a) reacting 2-cyanophenol with an alkali metal hydroxide or carbonate, preferably sodium hydroxide in a polar organic solvent preferably selected from among DMF, DMAA and DMSO, more preferably DMAA, at a temperature between 60°C to 80°C , preferably between 60°C to 70°C for about 1 hour, while removing the water which is formed during the reaction via distillation with the solvent under reduced pressure, preferably about 20-30mbar. The mole ratio between 2-cyanophenol and alkali metal hydroxide is between 1:1 and 1:1.5.

b) adding the aromatic substrate which is (E)-Methyl 2-[2-(6-chloropyridimin-4-yloxy)phenyl]-3-methoxypropenoate (Compound of formula (I) to the reaction mixture obtained in step (a). Optionally. Compound (I) is added to the reaction mixture as a solution in DMAA.



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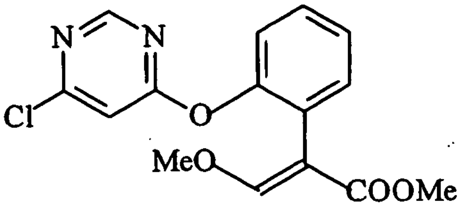
c) heating the reaction mixture of step (b) to a temperature in the range of 80° to 130°C, preferably 90°C to 100°C for 2 to 7 hours, preferably 4 to 6 hours to obtain azoxystrobin,

d) removing the solvent from the mixture of step (c) by distillation under reduced pressure; and further washing and extracting the reaction mixture with a non-polar organic solvent, non-limiting examples being toluene, xylene, at least C_4 acetate esters, preferably, butylacetate and adding water to obtain an organic and aqueous phase, thereafter discarding the aqueous phase and crystallizing the azoxystrobin from the organic phase by cooling the organic solvent, filtering the precipitated solid and rinsing thereafter with an alcohol, preferably methanol to obtain azoxystrobin with purity of 98%-99%.

In yet a further specific embodiment of the present invention azoxystrobin is prepared according to the following process:

a) reacting 2-cyanophenol with sodium hydroxide in DMAA and DMSO, more preferably DMAA, at a temperature between 60°C to 80°C for about 1 hour, while removing the water which is formed during the reaction via distillation with the solvent under reduced pressure of about 20-30mbar, wherein the mole ratio between 2-cyanophenol and sodium hydroxide is between 1:1 and 1:1.5;

b) adding the aromatic substrate which is (E)-Methyl 2-[2-(6-chlorpyridimin-4-yloxy)phenyl]-3-methoxypropenoate (Compound of formula (I) to the reaction mixture obtained in step (a), wherein Compound (I) is added to the reaction mixture as a solution in DMAA.



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c) heating the reaction mixture of step (b) to a temperature in the range of 90°C to 100°C for 4 to 6 hours to obtain azoxystrobin,

d) removing the solvent from the mixture of step (c) by distillation under reduced pressure; and further washing and extracting the reaction mixture with butylacetate and adding water to obtain an organic and aqueous phase, thereafter discarding the aqueous phase and crystallizing the azoxystrobin from the organic phase by cooling the organic solvent, filtering the precipitated solid and rinsing thereafter with methanol to obtain azoxystrobin with purity of 98%-99%.

The process for obtaining azoxystrobin according to the present invention provided azoxystrobin with purity of 98%-99% and a yield of above 90%. This is a significant improvement in comparison to the prior art methods which describe a process with a yield of 64%. Furthermore, no tars were detected in the reaction mixture of the present invention unlike the prior art method which generates tars which affect the purity of the final product. Hence the process of the present invention is more economical, produces less by-products and impurities and further generates considerably less effluents as a result of the improved yield. Accordingly, the work up according to the present process thus the process also provides improvements in terms of environmental and working safety.

Examples

Example I: Preparation of azoxystrobin

Dimethylacetamide (DMAA, 400ml), 2-Cyanophenol (0.2M, 28g) and NaOH (0.225M, 9g) were placed at ambient temperature into the three-necked 1L flask equipped with stirrer, condenser and thermometer. Half the amount of DMAA containing water traces was distilled at vacuum 20mbar/60-65°C and the mixture was kept at vacuum 20mbar/ room temperature for 1h. The same amount of prime DMAA was added and Compound (I) (0.2M, 64g) was fed into the flask.

The reaction mixture was heated to 100 °C and kept at these conditions for 5 hours (monitored by HPLC - conversion of Compound (I) to Azoxystrobin 98-99%).

DMAA was distilled at vacuum 20mbar/65-70°C. At the end of the distillation the temperature can be increased up to 90-100°C.

400g Butylacetate (BuAc) and 200g water were added to the reaction mixture at 50-60°C, the temperature was increased to 80°C and stirred 10-15min. The water phase was separated at 80°C to remove DMAA traces and inorganic salts.

For crystallization the BuAc phase was slowly cooled from 80°C to -5°C. Filtration was done using filter #2. The cake was washed with 60 ml cooled Butylacetate or methanol and further dried in oven at 80°C during 15 hours. Azoxystrobin with purity 98-99% and a yield of 90-92% was obtained.

While embodiments of the invention have been described by way of illustration, it will be apparent that the invention may be carried out with many modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.

Claims

1. A process for reacting between a phenol derivative and an aromatic substrate under phenolate forming conditions comprising the following steps:

   a) reacting a phenol derivative with a base in a polar organic solvent to obtain a phenolate salt, wherein water is removed from the reaction mixture during the reaction,
   b) adding the aromatic substrate to the reaction mixture obtained in step (a),
   c) heating the reaction mixture of step (b) to a temperature in the range of 80° to 130°C,preferebly, 90-100°C for 2 to 7 hours to obtain a phenoxy substituted aromatic substrate,
   d) removing the solvent from the mixture of step (c) and further isolating and purifying the phenoxy substituted aromatic substrate.

2. A process according to claim 1, wherein the removal of water during step (a) is in conjunction with partial removal of the organic solvent..

3. A process according to claim 1, wherein the mole ratio between said phenol derivative and base is 1:1 to 1:1.5, preferably 1:1.125 to 1:1.15..

4. A process according to claims 1 to 3, wherein the time required for step (a) to obtain conversion to a phenolate salt is 30 to 120 minutes at a temperature between 60°C to 80°C, while partially removing solvent with water from the reaction mixture by vacuum distillation.

5. A process according to claims 1 to 4, wherein the phenol derivative may be phenol, mono-substituted phenol or poly-substituted phenol, more preferably, cyanophenol derivatives, including 2-cyanophenol and 4-cyanophenol.

6. A process according to claims 1 to 5, wherein said base is selected from among hydroxide and carbonate bases, including metal hydroxides, alkali metal hydroxides, metal carbonates and alkali metal carbonates, preferably, sodium hydroxide, potassium hydroxide, sodium or potassium carbonate.

7. A process according to claim 1, wherein preferred polar organic solvents are dimethyl formamide (DMF), dimethyl acetamide (DMAA) and dimethyl sulphoxide (DMSO) wherein, preferably the range of the reagent/solvent ratio is 0.1mole/150ml-0.1mole/350ml.

8. A process according to claim 1, wherein said aromatic substrate may be added in step (b) together with a polar organic solvent.

9. A process according to claim 1, wherein the aromatic substrate is added in an amount such that the mole ratio between the phenol derivative and aromatic substrate is between 1: 0.8 and 1:1, preferably 1:1.

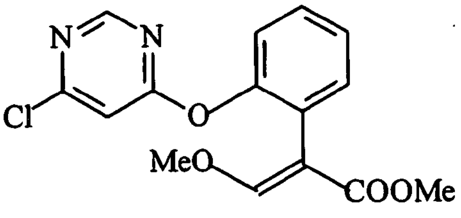
10. A process according to claim 1, wherein the aromatic substrate is selected from among mono and poly-substituted pyridine, pyrimidine and phenyl groups, preferably, at least mono-halo substituted and more preferably chloro-pyrimidine derivatives.

11. A process according to claim 1, wherein heating the reaction mixture of step (b) to a temperature in the range of 80° to 130°C, preferably about 100 °C for 2 to 7 hours, preferably about 5 hours to obtain a phenoxy substituted aromatic substrate,

12. A process according to any of claims 1 to 11 for the preparation of methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate (azoxystrobin) comprising of the following steps:

a) reacting 2-cyanophenol with an alkali metal hydroxide or carbonate, in a polar organic solvent, at a temperature between 60°C to 80°C, preferably between 60°C to 70°C for about 1 hour, while removing the water which is formed during the reaction via distillation with the solvent under reduced pressure,

b) adding the aromatic substrate which is (E)-Methyl 2-[2-(6-chlorpyridimin-4-yloxy)phenyl]-3-methoxypropenoate, Compound of formula (I) to the reaction mixture obtained in step (a), optionally, Compound (I) is added to the reaction mixture as a solution in DMAA;



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c) heating the reaction mixture of step (b) to a temperature in the range of 80° to 130°C, preferably 90°C to 100°C for 2 to 7 hours, preferably 4 to 6 hours to obtain azoxystrobin,

d) removing the solvent from the mixture of step (c) by distillation under reduced pressure; and further washing and extracting the reaction mixture with a non-polar organic solvent, and adding water to obtain an organic and aqueous phase, thereafter discarding the aqueous phase and crystallizing the azoxystrobin from the organic phase by cooling the organic solvent, filtering the precipitated solid and rinsing thereafter with an alcohol, preferably methanol to obtain azoxystrobin with purity of 98%-99%.

13. A process according to claim 12, wherein said base is sodium hydroxide, potassium hydroxide, sodium carbonate or potassium ccarbonate.

14. A process according to claims 12 to 13 wherein said polar organic solvent is selected from a group comprising DMF, DMAA and DMSO, more preferably DMAA.

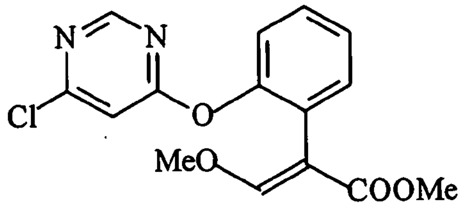
15. A process according to claims 12 to 14 wherein removing the water which is formed during the reaction of step (a) is via distillation with the solvent under reduced pressure, preferably about 20-30mbar., wherein the mole ratio between 2-cyanophenol and base is between 1:1 and 1:1.5.

16. A process according to claims 12 to 15, wherein said non-polar organic solvent of step (d) is selected from a group comprising toluene, xylene, at least C_4 acetate esters, preferably, butylacetate.

17. A process according to claim 12 comprising;

a) reacting 2-cyanophenol with sodium hydroxide in DMAA and DMSO, more preferably DMAA, at a temperature between 60°C to 80°C for about 1 hour, while removing the water which is formed during the reaction via distillation with the solvent under reduced pressure of about 20-30mbar, wherein the mole ratio between 2-cyanophenol and sodium hydroxide is between 1:1 and 1:1.5;

b) adding the aromatic substrate which is (E)-Methyl 2-[2-(6-chlorpyridimin-4-yloxy)phenyl]-3-methoxypropenoate, Compound of formula (I) to the reaction mixture obtained in step (a), wherein Compound (I) is added to the reaction mixture as a solution in DMAA.



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c) heating the reaction mixture of step (b) to a temperature in the range of 90°C to 100°C for 4 to 6 hours to obtain azoxystrobin,

d) removing the solvent from the mixture of step (c) by distillation under reduced pressure; and further washing and extracting the reaction mixture with butylacetate and adding water to obtain an organic and aqueous phase, thereafter discarding the aqueous phase and crystallizing the azoxystrobin from the organic phase by cooling the organic solvent, filtering the precipitated solid and rinsing thereafter with methanol to obtain azoxystrobin with purity of 98%-99%.

18. A process as herein exemplified and described

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2007/001551

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 2004/026305 A (LILLY CO ELI [US]; BLANCO-PILLADO MARIA-JESUS [US]; CHAPPELL MARK DONA) 1 April 2004 (2004-04-01) Schemes 1-11; ex. 1,148,193,198,221,373,376-378,388,437,483, 616,698,701,703; p. 374, int. 4A; p. 377, int. 7A; p. 386, int. 14A; p. 500, int. 4; p. 503-504, int. 7; p. 511, int. 14; p. 516,int. 20; page 530; examples 721,737,768,812	1-18

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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search 7 May 2008	Date of mailing of the international search report 16/05/2008
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Kirsch, Cécile

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 4 708 734 A (HAYASHI YOSHIHARU [JP] ET AL) 24 November 1987 (1987-11-24) Method A, step (1); col. 12, lines 26-36; example 1; step (a)	1-18
Y	EP 0 053 306 A (CELAMERCK GMBH & CO KG [DE]) 9 June 1982 (1982-06-09) Claim 4; examples 1, 4-6	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2007/001551

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			US	4453972	A	12-06-1984

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权利要求书 3 页 说明书 6 页

[54] 发明名称

取代氰基苯氧基-嘧啶基氧基-苯基丙烯酸酯衍生物的制备方法

[57] 摘要

本发明提供在苯酚盐形成条件下让苯酚衍生物与芳族底物反应的方法，该方法包括以下步骤：(a)让苯酚衍生物与碱在极性有机溶剂中进行反应而获得苯酚盐，其中在反应过程中从反应混合物中除去水，(b)将芳族底物添加到在步骤(a)中获得的反应混合物中，(c)将步骤(b)的反应混合物加热到80℃-130℃、优选90-100℃的温度保持2-7小时，获得苯氧基取代芳族底物，(d)从步骤(c)的混合物中除去溶剂，然后进一步分离和提纯该苯氧基取代芳族底物。任选地，在步骤(a)中水的除去与有机溶剂的部分除去一起进行。

权 利 要 求 书

1. 在苯酚盐形成条件下让苯酚衍生物与芳族底物之间反应的方法，该方法包括以下步骤：

a) 让苯酚衍生物与碱在极性有机溶剂中进行反应而获得苯酚盐，其中在反应过程中从反应混合物中除去水，

b) 将芳族底物添加到在步骤(a)中获得的反应混合物中，

c)将步骤(b)的反应混合物加热到80℃-130℃、优选90-100℃的温度保持2-7小时，获得苯氧基取代芳族底物，

d) 从步骤(c)的混合物中除去溶剂，然后进一步分离和提纯该苯氧基取代芳族底物。

2. 根据权利要求1的方法，其中在步骤(a)中水的除去与有机溶剂的部分除去联合进行。

3. 根据权利要求1的方法，其中苯酚衍生物与碱的摩尔比是在1:1到1:1.5之间，优选1:1.125到1:1.15。

4. 根据权利要求1-3的方法，其中实现向苯酚盐转化的步骤(a)所需的时间是在60℃到80℃之间的温度下30-120分钟，同时通过真空蒸馏从反应混合物中部分地除去溶剂和水。

5. 根据权利要求1-4的方法，其中苯酚衍生物可以是苯酚，单取代苯酚或多取代苯酚，更优选，氰基苯酚衍生物，其中包括2-氰基苯酚和4-氰基苯酚。

6. 根据权利要求1到5的方法，其中该碱选自氢氧化物和碳酸盐碱，其中包括金属氢氧化物，碱金属氢氧化物，金属碳酸盐和碱金属碳酸盐，优选，氢氧化钠，氢氧化钾，碳酸钠或碳酸钾。

7. 根据权利要求1的方法，其中优选的极性有机溶剂是二甲基甲酰胺(DMF)，二甲基乙酰胺(DMAA)和二甲基亚砜(DMSO),其中，试剂/溶剂比率的优选范围是0.1摩尔/150ml-0.1摩尔/350ml。

8. 根据权利要求1的方法，其中该芳族底物可以在步骤(b)中与极性有机溶剂一起添加。

9. 根据权利要求1的方法，其中该芳族底物的添加量使得苯酚衍生物与芳族底物的摩尔比是在1:0.8至1:1之间，优选1:1。

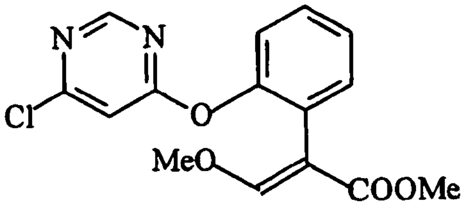
10. 根据权利要求1的方法，其中该芳族底物选自单和多取代吡啶、嘧啶和苯基，优选，至少单卤素取代和更优选氯-嘧啶衍生物。

11.根据权利要求 1 的方法，其中将步骤(b)的反应混合物加热到 80℃-130℃，优选约 100℃的温度保持 2-7 小时，优选约 5 小时，获得苯氧基取代芳族底物。

12. 根据权利要求 1-11 中任何一项的制备(E)-2-{2-[6-(2-氰基苯氧基)嘧啶-4-基氧基]苯基}-3-甲氧基丙烯酸甲基酯(嘧菌酯)的方法，它包括以下步骤：

a) 在极性有机溶剂中，在 60℃到 80℃、优选在 60℃到 70℃之间的温度下，让 2-氰基苯酚与碱金属氢氧化物或碳酸盐反应约 1 小时，同时在减压下通过蒸馏将在反应中形成的水随溶剂除去。

b) 将芳族底物，它是(E)-2-[2-(6-氯嘧啶-4-基氧基)苯基]-3-甲氧基丙烯酸甲基酯 (通式(I)的化合物)，添加到在步骤(a)中获得的反应混合物中，任选地，将化合物(I)作为在 DMAA 中的溶液被添加到反应混合物中；



(I)

c) 将步骤(b)的反应混合物加热到 80℃-130℃、优选 90-100℃的温度保持 2-7 小时、优选 4-6 小时，获得嘧菌酯，

d) 通过在减压下蒸馏从步骤(c)的混合物中除去溶剂；然后用非极性有机溶剂进一步洗涤和萃取反应混合物，然后添加水以获得有机相和水相，之后废弃水相和通过冷却有机溶剂从有机相中结晶嘧菌酯，过滤所沉淀的固体物和然后用醇(优选甲醇)清洗，获得具有 98%-99%的纯度的嘧菌酯。

13. 根据权利要求 12 的方法，其中该碱是氢氧化钠，氢氧化钾，碳酸钠或碳酸钾。

14. 根据权利要求 12 或 13 的方法，其中该极性有机溶剂选自 DMF、DMAA 和 DMSO，更优选 DMAA。

15. 根据权利要求 12-14 任一项的方法，其中在减压下，优选约 20-30 毫巴，通过蒸馏将在步骤(a)的反应中形成的水与溶剂除去，其

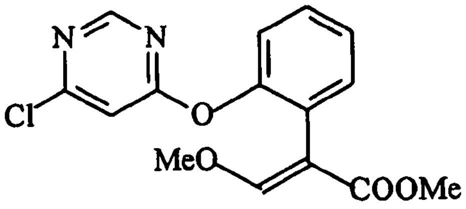
中2-氰基苯酚和碱的摩尔比是在1:1至1:1.5之间。

16. 根据权利要求12到15的方法，其中步骤(d)的非极性有机溶剂选自甲苯，二甲苯，至少C4乙酸酯，优选乙酸丁酯。

17. 根据权利要求12的方法，它包括：

a) 让2-氰基苯酚与氢氧化钠在DMAA和DMSO(更优选DMAA)中在60℃到80℃之间的温度下反应约1小时，同时在约20-30毫巴的减压下通过蒸馏将在反应中形成的水与溶剂除去，其中2-氰基苯酚和氢氧化钠之间的摩尔比是1∶1至1∶1.5；

b) 将芳族底物，它是(E)-2-[2-(6-氯嘧啶-4-基氧基)苯基]-3-甲氧基丙烯酸甲基酯 (通式(I)的化合物)，添加到在步骤(a)中获得的反应混合物中，其中将化合物(I)作为在DMAA中的溶液被添加到反应混合物中；



(I)

c) 将步骤(b)的反应混合物加热到在90℃到100℃范围内的温度保持4-6小时，获得嘧菌酯，

d) 通过在减压下蒸馏从步骤(c)的混合物中除去溶剂；然后用乙酸丁酯进一步洗涤和萃取反应混合物，然后添加水以获得有机相和水相，之后废弃水相和通过冷却有机溶剂从有机相中结晶嘧菌酯，过滤所沉淀的固体物和然后用甲醇清洗，获得具有98%-99%的纯度的嘧菌酯。

18. 在这里举例说明和描述的方法。

取代氰基苯氧基-嘧啶基氧基-苯基丙烯酸酯衍生物的制备方法

本发明的领域

本发明涉及化学合成领域，特别地涉及合成取代氰基苯氧基-嘧啶基氧基-苯基丙烯酸酯衍生物的改进方法。

本发明的背景

在工业化学合成领域中，化学过程的收率和选择性的改进对于工业有相当大的影响。特别地，改进的焦点在于降低成本，简化装置的操作过程和环境考虑。这三个因素在农用化学品领域中是特别重要的，其中化学品的量很大但边际利润相对小。

在由多阶段合成合成的许多农用化学品化合物当中，(E)-2-{2-[6-(2-氰基苯氧基)嘧啶-4-基氧基]苯基}-3-甲氧基丙烯酸甲基酯(化学通用名称：嘧菌酯（azoxystrobin）)，特别地引起本本发明人的注意。公开在美国专利 No. 5,395,837 中的嘧菌酯是具有保护剂、治疗药、铲除剂、片层转移(translaminar)和系统性功能的植物保护杀真菌剂。在 US 5,395,837 中所述的嘧菌酯的制备包括在 DMF 中在 95℃-100℃之间的温度下，在化学计量用量的碳酸钾和催化量的氯化亚铜(I)存在下，在 2-氰基苯酚与(E)-2-[2-(6-氯嘧啶-4-基氧基)苯基]-3-甲氧基丙烯酸甲基酯[也已知为(E)-2-[2-(6-氯嘧啶-4-基氧基)-苯基]-3-甲氧基丙烯酸甲基酯]之间的芳香族取代反应。报导的嘧菌酯收率是 65%，其中该产品发现具有 110℃-111℃的熔点，表明最终产品具有较低纯度，它随后需要进一步提纯。已经提示，2-氰基苯酚或氰基苯酚或苯酚的其它异构体一般在约 90℃和 90℃以上的温度条件下，在碱性试剂(它能够促进苯酚盐的形成)存在的反应可以引起聚合反应和焦油形成。这显然是非常不希望有的副作用。

因此长久以来需要具有改进的收率和选择性的在酚类存在下芳香族取代反应的方法。

因此，本发明的目的是提供让酚类在碱性条件下反应的方法，其中收率和选择性得到改进。

本发明的其它目的在展开叙述之后变得清楚。

本发明的概述

本发明提供在苯酚盐(phenolate)形成条件下让苯酚(phenol)衍生物与芳族底物(substrate)反应的方法，该方法包括以下步骤：

a) 让苯酚衍生物与碱在极性有机溶剂中进行反应而获得苯酚盐，其中在反应过程中从反应混合物中除去水。

b) 将芳族底物添加到在步骤(a)中获得的反应混合物中，

c) 将步骤(b)的反应混合物加热到 80℃-130℃、优选 90-100℃的温度保持 2-7 小时，获得苯氧基取代芳族底物，

d) 从步骤(c)的混合物中除去溶剂，然后进一步分离和提纯该苯氧基取代芳族底物。

任选地，在步骤(a)中水的除去与有机溶剂的部分除去联合（in conjunction with）进行。

本发明的详细说明

下列的叙述是本发明的实施方案的举例说明。下面的叙述不认为是限制性的，应该理解的是，本领域中的技术人员可以实施本发明的许多明显的变化形式。在整个说明书中术语“酚类(phenols)”和“酚衍生物（phenol derivative)”包括酚和单和多取代的酚类，其中包括2-氰基酚和其它氰基酚异构体。

本发明提供了在苯酚盐形成条件下让苯酚衍生物与芳族底物反应的方法，其中聚合物副产物和焦油的形成减到最少。在将副产物和焦油形成减到最少时，本发明方法提供了改进的收率，同时有产物分离和提纯的改善。本发明方法获得了 90%和更高的收率，其中该收率是以芳族底物为基础计算的。已经令人吃惊地发现，单独地产生苯酚盐和随后让苯酚盐与芳族底物反应，可防止不希望有的副产物和焦油的形成。

本发明的方法包括下面步骤：

a) 让苯酚衍生物与碱在极性有机溶剂中进行反应而获得苯酚盐，其中在反应过程中从反应混合物中除去水。

进行步骤(a)，其中苯酚衍生物与碱的摩尔比优选是在 1:1 到 1:1.5 之间，优选 1:1.125 到 1:1.15。实现向苯酚盐转化的步骤(a)所需的时

间是在60℃到80℃之间的温度下30-120分钟，同时通过真空蒸馏从反应混合物中部分地除去溶剂和水。

根据本发明的优选实施方案，苯酚衍生物可以是苯酚(phenol)，单取代苯酚或多取代苯酚，更优选，氰基苯酚衍生物(cyanophenol derivatives)，其中包括2-氰基苯酚(2-cyanophenol)和4-氰基苯酚(4-cyanophenol)。

该碱可以选自氢氧化物和碳酸盐碱，其中包括但不限于金属氢氧化物、碱金属氢氧化物、金属碳酸盐和碱金属碳酸盐，优选，氢氧化钠或氢氧化钾。

优选的极性有机溶剂的非限制性例子是二甲基甲酰胺(DMF)，二甲基乙酰胺(DMAA)和二甲基亚砜(DMSO)，其中，试剂/溶剂比率的范围优选是0.1摩尔/150ml-0.1摩尔/350ml。

根据本发明的特定实施方案，通过在减压条件下溶剂与水的部分除去，形成苯酚盐。

b) 将芳族底物添加到在步骤(a)中获得的反应混合物中。

根据本发明的特殊实施方案，该芳族底物与选自前述组的溶剂中的极性有机溶剂一起添加。芳族底物的添加量使得苯酚衍生物与芳族底物的摩尔比是1：0.8至1：1。

在本发明的仍然进一步优选的实施方案中，该芳族底物选自单和多取代的吡啶，嘧啶和苯基。优选，至少单卤素取代的和更优选氯嘧啶衍生物。

c) 将步骤(b)的反应混合物加热到80℃-130℃、优选约100℃的温度保持2-7小时、优选约5小时，获得苯氧基取代芳族底物，

d) 从步骤(c)的混合物中除去溶剂，然后进一步分离和提纯该苯氧基取代芳族底物。

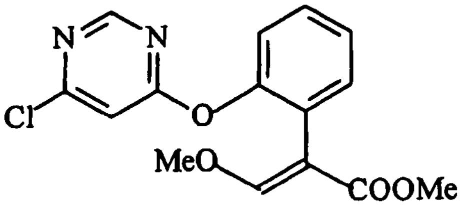
步骤(d)的操作能够根据本领域中的技术人员已知的方法来进行。该方法包括；通过蒸馏的溶剂除去，其中该蒸馏可以在减压条件下进行，通过洗涤、萃取和结晶的分离和提纯。

根据本发明的特定的优选实施方案，提供(E)-2-{2-[6-(2-氰基苯氧基)嘧啶-4-基氧基]苯基}-3-甲氧基丙烯酸甲基酯(嘧菌酯)的制备方法，它包括以下步骤：

a) 在优选地选自DMF、DMAA和DMSO(更优选DMAA)的极性

有机溶剂中，在 60℃到 80℃、优选在 60℃到 70℃之间的温度下，让 2-氰基苯酚与碱金属氢氧化物或碳酸盐，优选氢氧化钠，反应约 1 小时，同时在减压下，优选约 20-30 毫巴，通过蒸馏将在反应中形成的水随溶剂除去。2-氰基苯酚和碱金属氢氧化物的摩尔比是在 1:1 至 1:1.5 之间。

b) 将芳族底物，它是(E)-2-[2-(6-氯嘧啶-4-基氧基)苯基]-3-甲氧基丙烯酸（propenoate）甲基酯(通式(I)的化合物)，添加到在步骤(a)中获得的反应混合物中。任选，化合物(I)作为在 DMAA 中的溶液被添加到反应混合物中。



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c) 将步骤(b)的反应混合物加热到 80℃-130℃、优选 90-100℃的温度保持 2-7 小时、优选 4-6 小时，获得嘧菌酯，

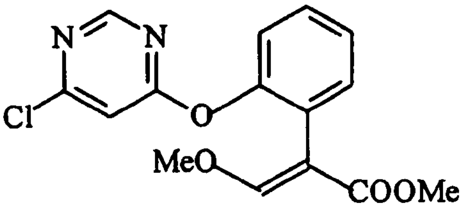
d) 通过在减压下蒸馏从步骤(c)的混合物中除去溶剂；然后用非极性有机溶剂进一步洗涤和萃取反应混合物，溶剂的非限制性例子是甲苯，二甲苯，至少 C4 乙酸酯(优选，乙酸丁酯)，然后添加水以获得有机相和水相，之后废弃水相和通过冷却有机溶剂从有机相中结晶嘧菌酯，过滤所沉淀的固体物和然后用醇(优选甲醇)清洗，获得具有 98%-99%的纯度的嘧菌酯。

在本发明的仍然再一个特定的实施方案中，根据以下方法制备嘧菌酯：

a) 让 2-氰基苯酚与氢氧化钠在 DMAA 和 DMSO(更优选 DMAA)中在 60℃到 80℃之间的温度下反应约 1 小时，同时在约 20-30 毫巴的减压下通过蒸馏将在反应中形成的水与溶剂一起除去，其中 2-氰基苯酚和氢氧化钠之间的摩尔比是 1 : 1 至 1 : 1.5；

b) 将芳族底物，它是(E)-2-[2-(6-氯嘧啶-4-基氧基)苯基]-3-甲氧基丙烯酸甲基酯 (通式(I)的化合物)，添加到在步骤(a)中获得的反应混合

物中，其中化合物(I)作为在DMAA中的溶液被添加到反应混合物中。



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c) 将步骤(b)的反应混合物加热到在90℃到100℃范围内的温度保持4-6小时，获得嘧菌酯，

d) 通过在减压下蒸馏从步骤(c)的混合物中除去溶剂；然后用乙酸丁酯进一步洗涤和萃取反应混合物，然后添加水以获得有机相和水相，之后废弃水相和通过冷却有机溶剂从有机相中结晶嘧菌酯，过滤所沉淀的固体物和然后用甲醇清洗，获得具有98%-99%的纯度的嘧菌酯。

根据本发明的获得嘧菌酯的方法能够以98%-99%的纯度和高于90%的收率得到嘧菌酯。与描述具有64%的收率的过程的现有技术方法相比，这有重要的改进。此外，与现有技术方法不同，在本发明的反应混合物中没有检测到焦油，现有技术方法产生焦油，影响最终产物的纯度。因此本发明的方法是更经济的，生产更低副产物和杂质，此外由于改进的收率，产生显著更低的废液。因此，根据本发明方法的后处理因此也在环境和工作安全上获得改进。

实施例

实施例I：嘧菌酯的制备

将二甲基乙酰胺(DMAA，400ml)，2-氰基苯酚(0.2M，28g)和NaOH(0.225M，9g)在环境温度下加入到装有搅拌器、冷凝器和温度计的三颈1L烧瓶中。含有痕量水的DMAA的量的一半在真空20毫巴/60-65℃下蒸馏掉，混合物在真空20毫巴/室温下保持1小时。添加相同量的打底物（prime）DMAA，将化合物(I) (0.2M，64g)加入到烧瓶中。

反应混合物被加热至100℃并在这些条件下保持5小时(由HPLC监测-化合物(I)转化成嘧菌酯的转化率为98-99%)。

在真空20毫巴/65-70℃蒸馏除去DMAA。在蒸馏结束时，温度能

够提高至 90-100℃。

在 50-60℃下将 400g 乙酸丁酯(BuAc)和 200 g 水添加到反应混合物中，温度提高至 80℃和搅拌 10-15 分钟。在 80℃下分离水相，除去痕量 DMAA 和除去无机盐。

为了结晶，将 BuAc 相慢慢地从 80℃冷却到-5℃。使用过滤器#2 进行过滤。滤饼用 60 ml 冷却了的乙酸丁酯或甲醇洗涤，然后在 15 小时的过程中在烘箱中于 80℃进一步干燥。以 98-99%的纯度和 90-92%的收率获得嘧菌酯。

尽管本发明的实施方案已经利用实施例进行了描述，但是明显的是，在不脱离本发明的精神或不超过本发明的范围的前提下本发明可以有许多改进、变化和修改。