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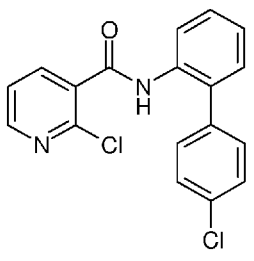
(54) Title: PROCESS FOR PREPARING BOSCALID



(I)

(57) Abstract: A process for preparing the polymorph I of the anhydrate of 2-Chloro-N- (4'-chlorobiphenyl-2-yl) -nicotinamide (boscalid) of the formula (I): is provided, the process comprising the steps of: a) dissolving the polymorph II of the anhydrate of boscalid in a first solvent in an amount and at conditions allowing dissolution of the polymorph II of the anhydrate of boscalid; b) combining the resulting solution with water; c) isolating the solid from the solvent mixture; and d) drying the solid to obtain the polymorph I of the anhydrate of boscalid.

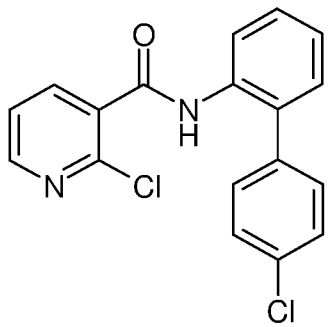
PROCESS FOR PREPARING BOSCALID

Cross Reference of related applications

The present application claims the priority of UK Patent Application No. 1608083.0, filed on May 9, 2016, the contents of which are incorporated herein by reference in its entirety.

The present invention relates to a process for preparing a specific polymorphic form of the anhydrate of 2-Chloro-N-(4'-chlorobiphenyl-2-yl)-nicotinamide (boscalid). In particular, the present invention relates to a process for preparing polymorph I of the anhydrate of boscalid.

2-Chloro-N-(4'-chlorobiphenyl-2-yl)-nicotinamide, having the common name boscalid, is a compound with the structural formula I:



I

Boscalid is a fungicide of the carboxamide group and acts as a succinate dehydrogenase inhibitor (SDHI), a respiratory inhibitor of mitochondria. It was first registered for commercial use in 2003 and is now registered in over 50 countries including Europe and America.

EP 0545099 discloses nicotinamides, anilide derivatives and 2-aminobiphenyl derivatives and their use for controlling Botrytis. The subject compounds are defined by way of a Markush formula.

US 7,241,896 concerns a process for producing 2-halogen-pyridine-carboxylic acid

amides. The preparation of boscalid is disclosed and exemplified. Boscalid is synthesized by the reaction of 2-chloro-3-nicotinyl chloride II with 2-(4-chlorophenyl)aniline in a solvent system. Boscalid was crystallized by cooling an organic solution, after extraction with sodium carbonate solution. Examples of water-immiscible organic solvents indicated in US 7,241,896 include aromatic, aliphatic and cycloaliphatic hydrocarbons, aromatic, aliphatic and cycloaliphatic halogenated hydrocarbons, acyclic ethers, preferably having from 4 to 10 carbon atoms, esters having from 3 to 10 carbon atoms, preferably those of aliphatic or cycloaliphatic alcohols preferably with aliphatic carboxylic acids, for example esters of acetic acid, propionic acid or butyric acid with C_3 C_8 alkanols, such as methyl, ethyl, n-propyl, n-butyl or isobutyl acetate, propionate, butyrate, and the like, ketones, preferably having from 4 to 10 carbon atoms, such as methyl ethyl ketone, and also aliphatic nitriles preferably having from 4 to 10 carbon atoms, such as butyronitrile, as well as mixtures of the aforementioned organic solvents. Xylene appears to be the preferred solvent of US 7,241,896.

US 8,350,046 discloses a process for preparing arylcarboxamides by reacting an acid chloride with an arylamine in a non-aqueous solvent. Toluene appears to be the preferred solvent of US 8,350,046.

US 7,087,239 concerns crystalline hydrates of nicotinic acid anilide and benzoyl anilide derivatives. The synthesis and recovery of the hydrate of boscalid is specifically exemplified in US 7,087,239. The hydrate is obtained by first preparing the anhydrate of boscalid, which is obtained at the end of the synthesis procedure as a solution in hot xylene. Upon cooling, boscalid crystallized from the solution and was dried under vacuum in an oven. The anhydrate is indicated to have the following physical properties:

Molecular weight [g/mol]:	343.2
Melting point [°C] (DSC):	145.2
Density [g/mol]:	1.42
X-ray reflection (2Θ degree):	18; 22.5; 9.5; 6
Cu-Kα	

IR absorption [cm^{-1}]: 1650

Water content [%]: <1

US 7,087,239 discloses that the hydrate can be formed by dissolving the anhydrate in tetrahydrofuran (THF) at 40°C and the resulting solution added to water. The precipitate was removed by filtration and dried, to yield the monohydrate of boscalid. The crystalline modification of the anhydrate of boscalid disclosed in US 7,087,239 is referred to herein as the polymorph I of the anhydrate of boscalid.

US 7,501,384 discloses an allegedly novel crystalline modification of the anhydrate of boscalid. The crystalline modification disclosed in US 7,501,384 is referred to herein as the polymorph II of the anhydrate of boscalid. It is suggested in US 7,501,384 that the polymorph II of the anhydrate of boscalid is more suitable for making formulations which require grinding/milling processes.

US 7,501,384 describes that the polymorph II of the anhydrate of boscalid may be prepared by a process comprising:

a) dissolving the polymorph I of the anhydrate of boscalid in a polar organic solvent or an aromatic hydrocarbon; and

b) precipitation of the polymorph II of the anhydrate of boscalid by cooling the solvent.

An alternative process for the preparation of the polymorph II of the anhydrate of boscalid disclosed in US 7,501,384 comprises:

a) heating the polymorph I of the anhydrate of boscalid to above 150°C until melted; and

b) cooling the melt with the addition of seed crystals of the polymorph II of the anhydrate of boscalid.

US 7,501,384 describes the polymorph II of the anhydrate of boscalid as having the

following properties:

Molecular weight [g/mol]:	342
Melting point [°C] (DSC):	147.2
Heat of fusion [J/g] (DSC):	106
Density [g/cm^3]:	1.457
Characteristic IR bands [cm^{-1}]:	868, 917, 1675

The cell parameters from the crystallographic investigations of the polymorph II of the anhydrate of boscalid using a single crystal diffractometer from Siemens are given in US 7,501,384 as follows:

Class:	Monoclinic
Space group:	P21/c
a:	1162.5(6) pm
b:	1134.2(4) pm
c:	1283.2(5) pm
α:	90°
β:	114.52(4)°
γ:	90°
Volume:	1.5390 nm^{-3}
Z:	4
Density (calculated):	1.481 mg/m^{-3}
R^1, wR^2:	0.0489; 0.1264

The parameters indicated above have the following meanings:

a, b, c = edge lengths of the unit cell;

α, β, γ = corresponding angles; and

Z = number of molecules in the unit cell.

FTIR spectrometry may be used to record IR spectra.

Figure 1 is the IR spectrum of the polymorph II of the anhydrate of boscalid; and

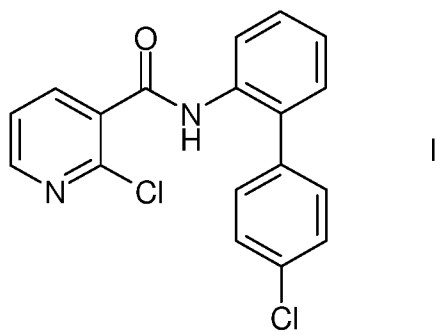
Figure 2 is the IR spectrum of the polymorph I of the anhydrate of boscalid.

Conventionally, the polymorph I of the anhydrate of boscalid is prepared from a solution in xylene. Xylene has a high boiling point and a high toxicity.

Hence, there is a need in the art to provide an improved process for preparing the polymorph I of the anhydrate of boscalid, preferably a process that avoids the shortcomings of the prior art processes, in particular the reliance on a solvent such as xylene.

A novel process for the preparation of the polymorph I of the anhydrate of boscalid has now been found.

Accordingly, the present invention provides a process for preparing the polymorph I of the anhydrate of 2-Chloro-N-(4'-chlorobiphenyl-2-yl)-nicotinamide (boscalid) of the formula I:



I

the process comprising the steps of:

a) dissolving the polymorph II of the anhydrate of boscalid in a first solvent in an amount and at conditions allowing dissolution of the polymorph II of the anhydrate of boscalid;

b) combining the resulting solution with water;

c) isolating the solid from the solvent mixture; and

d) drying the solid to obtain the polymorph I of the anhydrate of boscalid.

In the first step of the process of the present invention, a solution of boscalid is formed by dissolving in a first organic solvent the polymorph II of the anhydrate of boscalid. The first solvent is an organic solvent. Suitable solvents of boscalid for use as the first solvent include ethers, preferably linear or cyclic lower ethers (that is ethers having from 1 to 12 carbon atoms), more preferably linear or cyclic C_2 to C_6 ethers, such as tetrahydrofuran (THF), methylether, methylethylether or ethylethylether; ketones, preferably C_2 to C_6 ketones, such as acetone, propanone, or butanone; esters, preferably linear C_2 to C_6 esters, such as ethyl acetate, methyl acetate or propyl acetate; dimethyl formamide (DMF); alcohols, preferably straight or branched C_1 to C_8 aliphatic alcohol, more preferably at least one straight or branched C_1 to C_4 aliphatic alcohol, such as methanol, ethanol, propanol, n-butanol; acetonitrile; aromatic hydrocarbons, preferably substituted with one or more substituents, which may be the same or different, selected from the group consisting of alkyl, optionally substituted by one or more halogens, which may be the same or different, nitro, halogen, ether, and the like such as benzene, toluene, or chlorobenzene; halogenated alkanes; and mixtures thereof. Preferred halogenated alkanes are mono- or di-substituted alkanes. Chloride moieties are preferred substituents for the alkanes. The halogenated alkanes are preferably lower alkanes (that is alkanes having from 1 to 12 carbon atoms), more preferably C_1 to C_6 halogenated alkanes, such as mono- or di-chloromethane, mono- or 1,1-dichloro- or 1,2-di-chloroethane, mono- or 1,1-di-chloro, or 1,2-dichloro- or 1,3 di-chloropropane.

Ketones are particularly preferred as the first solvent, especially acetone. Esters are

also preferred as the first solvent, especially ethyl acetate; alcohols are also preferred, especially methanol; aromatic hydrocarbons are also preferred, especially toluene; ethers are also preferred as the first solvent, especially tetrahydrofuran.

Other preferred solvents include acetonitrile and dimethyl formamide (DMF).

The polymorph II of the anhydrate of boscalid is dissolved in an amount of the first solvent under conditions allowing complete dissolution of the polymorph I of the anhydrate of boscalid. The dissolution in step a) may be carried out at any suitable temperature. If an elevated temperature is employed in step a), the temperature is below the boiling point of the first solvent. Optionally, for example depending on the type and the amount of the solvent used, dissolution of the polymorph II of the anhydrate of boscalid may be carried out by heating the solvent to elevated temperatures. A minimum temperature of 20°C may be used, preferably at least 30°C, more preferably at least 40°C. Depending upon the solvent system being used, the temperature may be up to 90°C, preferably up to 85°C, more preferably up to 80°C, still more preferably up to 75°C. Suitable temperatures are a temperature of from 20 to 90°C, preferably from 30 to 90°C, more preferably from 30 to 80°C, even more preferably from 40 to 70°C, more preferably still to a temperature of from 40 to 60°C.

The dissolution of the polymorph II of the anhydrate of boscalid in the first solvent may be carried out with agitation, preferably with stirring and/or shaking.

Once the polymorph II of the anhydrate of boscalid has been fully dissolved in the first solvent, the resulting solution is combined with a second solvent in step b) of the process. In the present invention, the second solvent is water.

The combination of water to the solution of boscalid is preferably effected in a slow manner, such as dropwise. The combination may be carried out stepwise or continuously. The water is preferably combined with the boscalid solution with agitation, for example stirring, to avoid a local high concentration of the boscalid solution. The solution of boscalid may be added to the water. More preferably, the water is added to the solution of

boscalid.

Water is employed in step b) in an amount until precipitation of a solid commences and is preferably continued to achieve full precipitation of the solid boscalid from the solution.

Water may be employed in any suitable amount to effect precipitation of boscalid from the solution. Preferably, water is employed in step b) in an amount sufficient to cause substantially complete precipitation of solid boscalid from the solution. For example, water may be used in an amount by weight equal to the amount by weight of the first solvent used in step a).

Water may be combined with the solution prepared in step a) at any suitable temperature below the boiling point of water. A lower temperature of 10°C is suitable, preferably 15°C, more preferably at least 20°C, still more preferably at least 30°C, more preferably still at least 40°C. An upper temperature of 85°C is suitable, preferably 75°C, more preferably 70°C, still more preferably 75°C, more preferably still up to 70°C. A temperature in the range of from 10 to 85°C is suitable, preferably from 15 to 75°C, more preferably from 20 to 65°C. Preferably, step b) is conducted at a temperature in the range of from 30 to 60°C, more preferably from 40 to 55°C, especially from 50 to 55°C.

Adjusting the temperature of the solution of the polymorph II of the anhydrate of boscalid in the first solvent is required to the extent that the temperature of step b) of the process is above or below the temperature of the solution resulting in step a). Preferably, the temperature in step a) of the process at which dissolution is effected is above the temperature or at least equal to the temperature in step b).

This may be achieved in a number of ways. For example, the temperature of the solution resulting from step a) may be adjusted, as required, during step b) before combination with water. In one convenient processing scheme, the boscalid solution in step a) is formed at the same temperature as water used in step b).

The solution of the polymorph II of the anhydrate of boscalid produced in step a) may be adjusted at any suitable rate, if required. Preferably adjusting the temperature in step b) is carried out at a rate of from about 1 to 20°C/minute, more preferably from 1 to 10°C/minute, still more preferably from about 5 to 10°C/minute. Preferably adjusting is carried out while agitating the solution, for example by stirring.

After the solution has reached the desired temperature in step b), this temperature is preferably maintained at the selected level for a time period sufficient to ensure a uniform temperature throughout the solution.

Alternatively, the solution resulting from step a) may be adjusted by first adjusting the temperature of the water to an appropriate temperature, before it is combined with the solution. For example, the water may be at a temperature lower than the temperature of the solution produced in step a) and thereby cool the solution when added thereto.

Preferably, both the temperature of the boscalid solution resulting from step a) is adjusted, as required to be within the temperature range in step b) discussed above and the temperature of the second solvent is adjusted to be within the aforementioned range. In this way, both the boscalid solution and the second solvent are at a temperature in the aforementioned range when combined in step b) of the process. Preferably, the temperature of the boscalid solution and the temperature of the water are substantially the same when being combined.

Preferably, after complete combination of the boscalid solution resulting from step a) with water, the resulting mixture is maintained within the temperature range in step b) discussed above for any suitable time period, in particular from 10 to 60 minutes, preferably from 15 to 50 minutes, more preferably from 20 to 40 minutes, particularly about 30 minutes. Thereafter, the resulting mixture is cooled, for example to a temperature of from 20 to 25°C. Preferably, the resulting mixture is maintained at this temperature after cooling, for example for 1 to 3 hours, to allow for complete precipitation of the boscalid solid.

The solid precipitated from the solution in step b) of the process may then be

recovered in any suitable manner, such as by one or more of decanting the solvent, filtration, and/or evaporation of the solvent.

The solid of boscalid recovered in step c) is then dried in step d), for example under reduced pressure, preferably under a vacuum. Suitable drying techniques are known in the art. Due to the use of water as the second solvent in step b), the boscalid solid precipitated is hydrated. Drying of the precipitate is therefore carried out to a sufficient extent to produce a substantially anhydrous solid product. Suitable drying temperatures are, for example, from 40 to 80°C, more preferably from 50 to 70°C, still more preferably from 55 to 60°C. Suitable drying periods are, for example, up to 5 hours or longer, such as up to 6 hours or 8 hours, in particular from 8 to 10 hours. The drying time will vary according to the drying conditions and the drying technique employed.

During the process of preparing the polymorph I of the anhydrate of boscalid, the conversion rate from polymorph II to polymorph I can be monitored using appropriate analysis methods and based on the chemical and physical properties of the two polymorphic forms, some of which are listed in Table 1 below.

Table1

Physical properties of anhydrous boscalid polymorph I and polymorph II

Properties	Anhydrous boscalid, polymorph I	Anhydrous boscalid, polymorph II
Molecular weight [g/mol]	342	342
Melting point [°C] (DSC)	144.8	147.2
Heat of fusion [J/g] (DSC)	85	106
Density [g/cm^3]	1.399	1.457
IR characteristic band [cm^{-1}]	924,1310,1650	868,917,1675

Any suitable analysis method may be employed. One suitable analysis technique is IR spectroscopy, which also allows for quantification of the conversion, for example by the shifting of a characteristic band, such as the C=O stretching vibration. For example, the C=O stretching vibration shifts from 1675cm^{-1} to 1650cm^{-1} when polymorph II of anhydrous boscalid is converted to polymorph I. The disappearance from the IR spectrograph of a band at 1675cm^{-1} indicates complete conversion from polymorph II to polymorph I.

Alternatively, single-crystal X-ray diffraction may be used for monitoring the conversion. Table 2 below lists cell parameters of the two polymorphic forms.

Table 2

Table cell parameters from the crystallographic investigations using a single crystal

diffractometer

Parameters	Anhydrous boscalid, polymorph I	Anhydrous boscalid, polymorph II
Space group	P21/c	P21/c
a	1479.2(3)pm	1163.2(8)pm
b	1157.67(19)pm	1136.3(5)pm
c	1872.1(3)pm	1287.3(8)pm
α	90°	90°
β	91.993(17) °	114.57(1) °
γ	90°	90°
Melting point	144-145℃	147-148℃

where the symbols have the following meaning:

a, b, c = edge length of unit cell;

α, β, γ = corresponding angles; and

Z = number of molecular in unit cell.

The process of the present invention has the advantage of being easy to carry out and is suitable for use on an industrial scale. The process of the present invention also provides

the advantage that a reduction in the use of toxic solvents can be obtained, thereby diminishing harm to the environment.

The present invention will be further described, for illustration purposes only, by way of the following examples.

Unless otherwise indicated, percentages are percent by weight.

EXAMPLES

Example 1

Anhydrous boscalid polymorph II (200 g, 0.583 mol) was added to a reaction bottle with the addition of acetone (1000 mL). The mixture was heated to a temperature of from 50 to 55°C while stirring until the boscalid had dissolved completely. The resulting solution was maintained at a temperature of from 50 to 55°C.

Water (800 mL) was heated to a temperature of from 50 to 55°C in a reaction bottle and transferred to a dropping funnel.

The water was added dropwise from the dropping funnel to the reaction bottle and combined with the boscalid solution with stirring. Gradually, solid was seen to precipitate from the solution. After the addition of the water had been completed, the resulting mixture was held at a temperature of from 50 to 55°C for 30 minutes, after which the resulting mixture was cooled to a temperature of from 20 to 25°C and maintained at this temperature for from 1 to 2 hours. Thereafter, the mixture was filtered and the filter cake was washed with water. The resulting solid was dried at 55 to 60°C in a vacuum for from 8 to 10 hours. 192g of white powder with yield of 96% was obtained.

Single-crystal X-ray diffraction and IR spectroscopy were used to identify the solid product as the polymorph I of the anhydrate of boscalid.

Example 2

Anhydrous boscalid polymorph II (200 g, 0.583 mol) was added to a reaction bottle with the addition of dimethyl formamide (1000 mL). The mixture was heated to a temperature of from 85 to 90°C while stirring until the boscalid had dissolved completely. The resulting solution was cooled and maintained at a temperature of from 50 to 55°C.

Water (1000 mL) was heated to a temperature of from 50 to 55°C in a reaction bottle and transferred to a dropping funnel.

The water was added dropwise from the dropping funnel to the reaction bottle and combined with the boscalid solution with stirring. Gradually, solid was seen to precipitate from the solution. After the addition of the water had been completed, the resulting mixture was held at a temperature of from 50 to 55°C for 30 minutes, after which the resulting mixture was cooled to a temperature of from 20 to 25°C and maintained at this temperature for 1 to 2 hours. Thereafter, the mixture was filtered and the filter cake was washed with water. The resulting solid was dried at a temperature of from 55 to 60°C in a vacuum for 8 to 10 hours. 168g of white powder with yield of 84% was obtained.

Single-crystal X-ray diffraction and IR spectroscopy were used to identify the solid product as the polymorph I of the anhydrate of boscalid.

Example 3

Anhydrous boscalid polymorph II (200 g, 0.583 mol) was added to a reaction bottle with the addition of tetrahydrofuran (1000 mL). The mixture was heated to a temperature of from 60 to 65°C while stirring until the boscalid had dissolved completely. The resulting solution was cooled and maintained at a temperature of from 50 to 55°C.

Water (800 mL) was heated to a temperature of from 50 to 55°C in a reaction bottle and

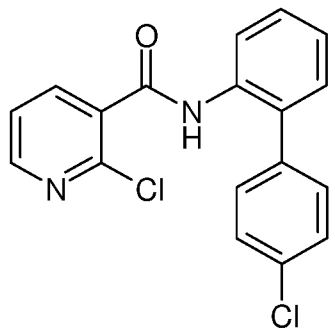
transferred to a dropping funnel.

The water was added dropwise from the dropping funnel to the reaction bottle and combined with the boscalid solution with stirring. Gradually, solid was seen to precipitate from the solution. After the addition of the water had been completed, the resulting mixture was held at a temperature of from 50 to 55°C for 30 minutess, after which the resulting mixture was cooled to a temperature of from 20 to 25°C and maintained for at this temperature for 1 to 2 hours. Thereafter, the mixture was filtered and the filter cake was washed with water. The resulting solid was dried at a temperature of from 55 to 60°C in a vacuum for from 8 to 10 hours. 168g of white powder with yield of 84% was obtained.

Single-crystal X-ray diffraction and IR spectroscopy were used to identify the solid product as the polymorph I of the anhydrate of boscalid.

CLAIMS

1. A process for preparing the polymorph I of the anhydrate of 2-Chloro-N-(4'-chlorobiphenyl-2-yl)-nicotinamide (boscalid) of the formula I:



I

the process comprising the steps of:

a) dissolving the polymorph II of the anhydrate of boscalid in a first solvent in an amount and at conditions allowing dissolution of the polymorph II of the anhydrate of boscalid;

b) combining the resulting solution with water;

c) isolating the solid from the solvent mixture; and

d) drying the solid to obtain the polymorph I of the anhydrate of boscalid.

2. The process according to claim 1, wherein the first solvent is selected from a linear or cyclic lower ether, a ketone, an ester, an alcohol, an aromatic hydrocarbon, a halogenated alkane, dimethyl formamide (DMF), acetonitrile and mixtures thereof.

3. The process according to claim 2, wherein the first solvent is selected from a linear or cyclic C_2 to C_6 ether, a C_2 to C_6 ketone, a C_1 to C_6 halogenated alkane, an aromatic hydrocarbon substituted by one or more halogens, a linear C_2 to C_6 esters, a straight or branched C_1 to C_4 aliphatic alcohol, dimethyl formamide (DMF), acetonitrile or a mixture thereof.

4. The process according to claim 3, wherein the first solvent is selected from

tetrahydrofuran, acetone, ethyl acetate, dimethyl formamide (DMF), methanol, acetonitrile, toluene, mono- or di-chloromethane, mono- or 1,1-dichloro- or 1,2-di-chloroethane, or mixtures thereof.

5. The process according to any preceding claim, wherein step a) is conducted at an elevated temperature.

6. The process according to claim 5, wherein step a) is conducted at a temperature of from 20 to 90°C.

7. The process according to claim 6, wherein step a) is conducted at a temperature of from 30 to 90°C.

8. The process according to claim 7, wherein step a) is conducted at a temperature of from 30 to 80°C.

9. The process according to claim 8, wherein step a) is conducted at a temperature of from 40 to 60°C.

10. The process according to any preceding claim, wherein in step b) the water is added to the solution resulting from step a).

11. The process according to any preceding claim, wherein step b) is conducted at a temperature of from 20 to 65°C.

12. The process according to claim 11, wherein step b) is conducted at a temperature of from 30 to 60°C.

13. The process according to claim 12, wherein step b) is conducted at a temperature of from 40 to 55°C.

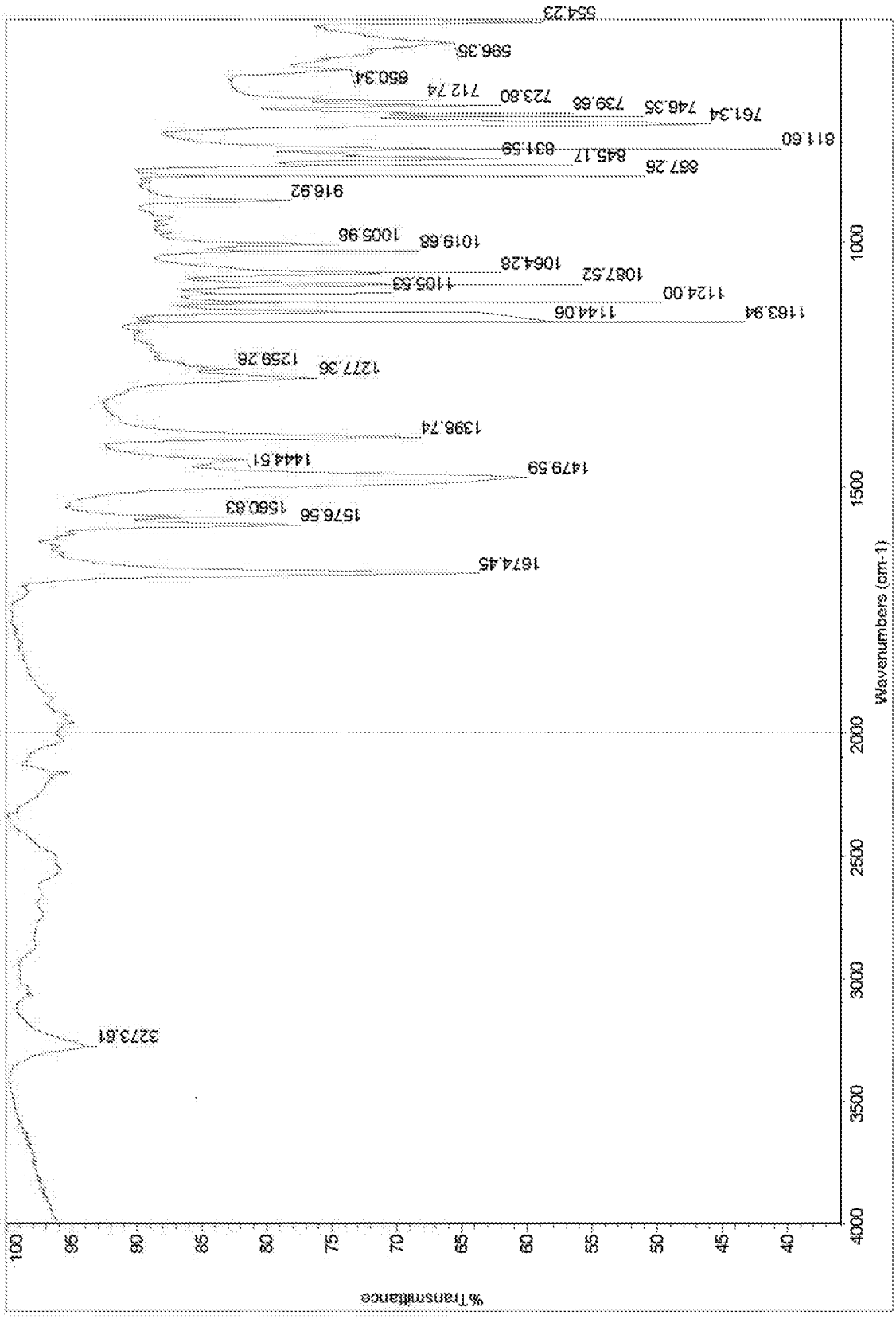
14. The process according to claim 13, wherein step b) is conducted at a temperature of from 50 to 55°C.

15. The process according to any preceding claim, wherein the temperature of both the

solution produced in step a) and the water is adjusted to the temperature required in step b), before being combined.

16. The process according to any preceding claim, wherein drying is conducted under vacuum at an elevated temperature.

17. A process for preparing the polymorph I of the anhydrate of 2-Chloro-N-(4'-chlorobiphenyl-2-yl)-nicotinamide (boscalid) substantially as hereinbefore described having reference to the accompanying figures.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916.92
1005.96
1019.68
1064.28
1087.52
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1163.94
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%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

Figure 1

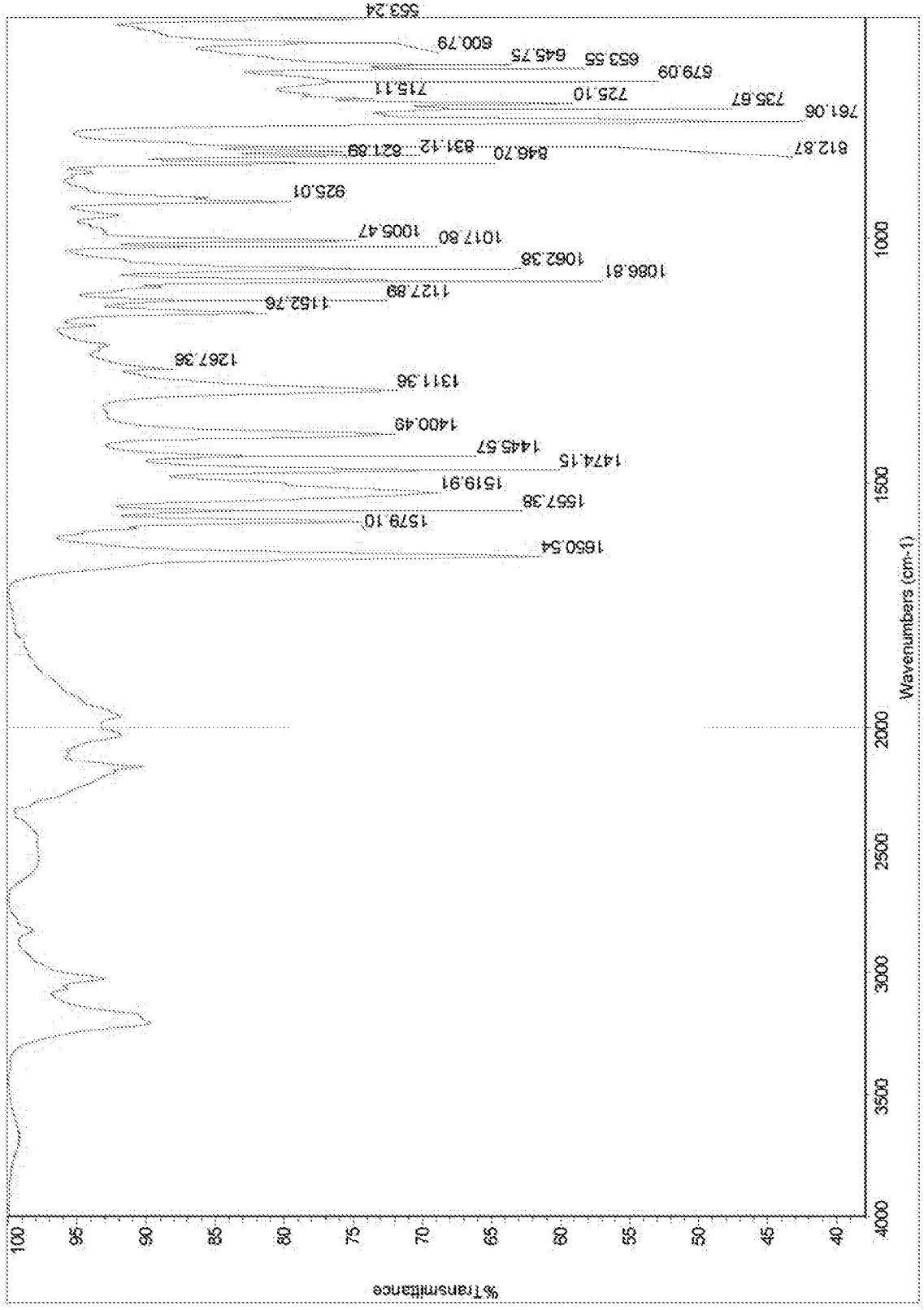
553.24
600.79
645.75
653.55
679.09
715.11
725.10
735.87
761.06
812.87
821.89
831.12
846.70
925.01
1005.47
1017.60
1062.38
1086.81
1127.89
1152.76
1267.36
1311.36
1400.49
1445.57
1474.15
1519.91
1557.38
1579.10
1650.54
%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/070635

A. CLASSIFICATION OF SUBJECT MATTER

C07D 213/82(2006.01)i

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 practicable, search terms used)

VEN, CNABS, CNKI, CAplus, Registry: bascalid, crystal?, polymorph?, CAS RN 188425-85-6

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 1558901 A (BASF AKTIENGESELLSCHAFT) 29 December 2004 (2004-12-29) See the whole documnet, especially description, example 1	1-17
A	CN 1751026 A (BASF AKTIENGESELLSCHAFT) 22 March 2006 (2006-03-22) See the whole document, especially claims 1-7 and description, example 1	1-17
A	CN 103980192 A (TAIZHOU BAILLY CHEMICAL CO., LTD.) 13 August 2014 (2014-08-13) See the whole document, especially description, examples 1-7	1-17

☐ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 April 2017	**13 April 2017**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**SHA,Lei**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62084377**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2017/070635

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				UA	80538	C2	10 October 2007
				ES	2238610	T3	01 September 2005
				TW	I281469	B	21 May 2007
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				CA	2460654	C	03 August 2010
				JP	4401773	B2	20 January 2010
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				DE	50202440	D1	14 April 2005
				IL	160640	A	24 December 2009
				KR	20090127446	A	11 December 2009
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				HU	0402129	A3	28 September 2012
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				ZA	200507344	A	28 February 2007
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2017/070635

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		AT	339405	T	15 October 2006
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		JP	4642743	B2	02 March 2011
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		AR	043175	A1	20 July 2005
		AR	094395	A2	29 July 2015
		MX	PA05007962	A	20 September 2005
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		ES	2273211	T3	01 May 2007
		OA	13150	A	13 December 2006
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		NO	329988	B1	31 January 2011
		NZ	542308	A	31 July 2008
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		PL	219123	B1	31 March 2015
		EA	008004	B1	27 February 2007
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