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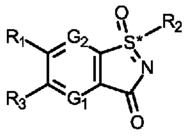
(54) Title: SYNTHESIS OF CYCLIC ACYL SULFOXIMINES



(I)

(57) Abstract: A process for the preparation of compound of formula I is provided: (I) where R_1, R_2, R_3, G_1, and G_2 are as defined in the description.

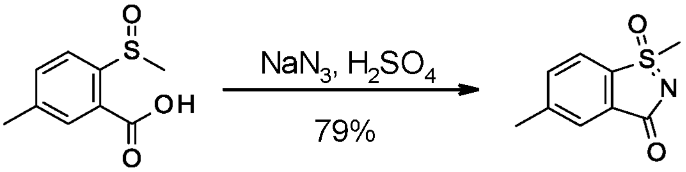
Synthesis of cyclic acyl sulfoximines

The present invention relates to the enantioselective synthesis of cyclic acyl sulfoximines that are useful intermediates for the preparation of agrochemicals.

Pesticidally active heterocyclic sulfoximine derivatives have previously been described in the literature, for example, in WO 2015/071180, WO 2016/039441, WO 2018/206348, WO 2019/219689, WO 2019/229089, WO 2019/234158, WO 2020/084075, WO2020/141136 and WO2022253841.

Synthesis of cyclic benzo fused five membered acyl sulfoximines in a racemic form was first reported 50 years ago (Chemische Berichte, vol. 108, no. 12, 1,(1975-12-01), pages 3855-3863; Angew. Chem. Int. Ed. 1971, 10, 76; J. Am. Chem. Soc. 1971, 93, 7333). In the latter two cases this was accomplished by a classical acyclic sulfoximine synthesis using hydrazoic acid followed by cyclization to an adjacent acid derivative (for example as shown in Scheme 1).

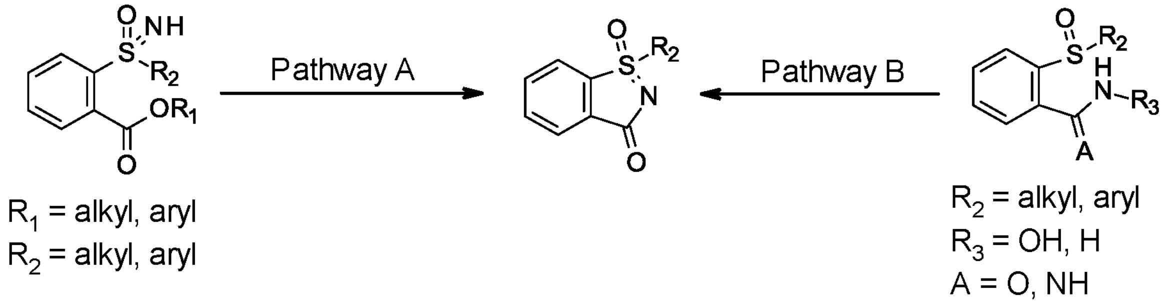
Scheme 1



Starting from an enantioenriched sulfoxide synthesis of enantioenriched cyclic benzo fused acyl sulfoximines has also been reported (Chirality 1995, 7, 541; Tetr. Asym. 1996, 7, 361). More recently cyclic acyl sulfoximines have attracted interest from both agrochemical (WO2018211442) and pharmaceutical (WO2022094218) industries. In both cases the target compounds were made by a classical cyclization of an acyclic sulfoximine on an acid derivative and only in a racemic form.

Such cyclic sulfoximines could in principle be prepared either by cyclization of acyclic sulfoximines as described below (pathway A, Scheme 2) or by an intramolecular nitrogen transfer on an adjacent sulfoxide (pathway B, Scheme 2). Up to this time pathway A has been the dominant method with an oxidative cyclization via pathway B being reported only for very specific compounds and under conditions not applicable for the preparation of enantiopure compounds (Russ. Chem. Bull. Int. Ed. 2004, 53, 916).

Scheme 2

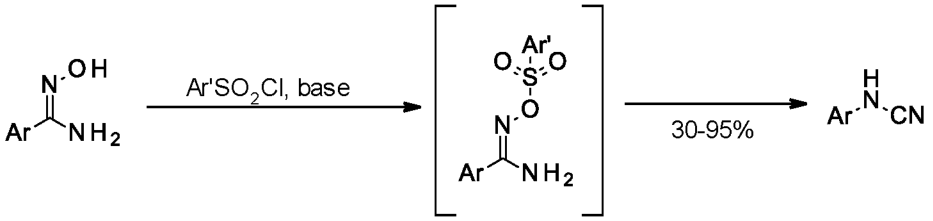


Numerous methods for the synthesis of acyclic N-unsubstituted sulfoximines from sulfoxides needed for pathway A have been described. Hypervalent iodine is commonly used as a reagent, either in combination with a metal catalyst such as rhodium (Org. Lett., 2004, 6, 1305), copper (Tetrahedron Lett. 1998, 39, 4805), iron (Tetrahedron Lett., 1998, 39, 5015) or silver (Org. Lett., 2005,7, 4983) or without a catalyst as described by Bull and Luisi (Angew. Chem. Int. Ed. 2016, 51, 7203). The latter method has been used to synthesize the ATR inhibitor ceralasertib on large scale (Org. Process. Res. Dev. 2021, 25, 43). The method of Liang (Tetrahedron Lett., 2017, 58, 333-337) using NaN_3 and Eaton's reagent avoids hypervalent iodine but leads to racemization of the product when starting from an enantiopure sulfoxide starting material and is therefore inappropriate for the synthesis of chiral sulfoximines. The use of azides is also hazardous on large scale. Other alternative reagents are activated hydroxylamine derivatives such as O-mesityl-hydroxylamine (MSH) (Tetrahedron Lett., 1972, 4137, J. Org. Chem., 1974, 39, 2458), nitrobenzoylhydroxylamine triflate in combination with an iron catalyst (Angew. Chem. Int. Ed. 2018, 57, 32) or dinitrophenylhydroxylamine in combination with a rhodium catalyst (Chem. Commun. 2014, 50, 9687). Despite the large number of methods reported there are usually serious disadvantages such as use of a stoichiometric amount of hypervalent iodine reagents, transition metal catalysts and having to prepare customized and often unsafe amination reagents. This is particularly important for a synthesis on a large scale.

Given the disadvantages of pathway A described above it would be advantageous to develop an alternative method going via pathway B (Scheme 2). This would potentially avoid handling dangerous reagents and expensive metal catalysts.

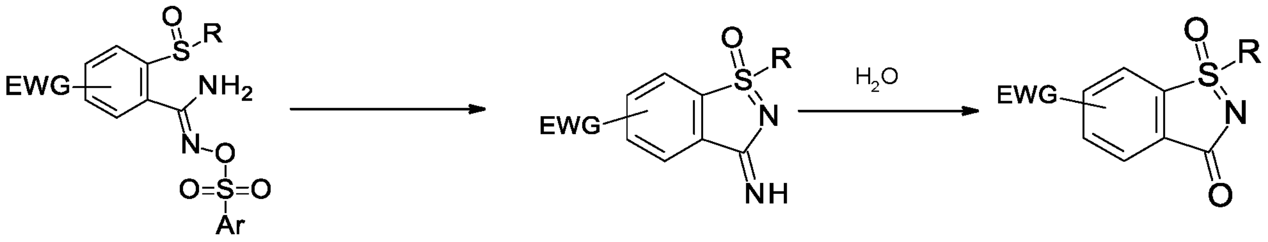
A practical method of a Tiemann rearrangement of amidine oximes derived from aryl nitriles has recently been published (Org. Lett. 2014, 16, 892) as shown in scheme 3.

Scheme 3

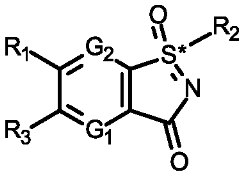


Based on this reactivity we proposed that an adjacent sulfoxide would intercept the activated amidine oxime leading to cyclic imino sulfoximines which could then be hydrolysed to cyclic acyl sulfoximines (Scheme 4). This would be most likely to work if aryl or heteroaryl group in the initial nitrile were electron poor thus inhibiting nitrene type rearrangement. Additionally, the amount of base should be limited to that needed for the activation of amidine oxime.

Scheme 4



The present invention provides a process for the enantioselective preparation of cyclic acyl sulfoximines of formula (I) optionally in an enantiomerically pure, enantiomerically enriched or racemic form



(I)

wherein

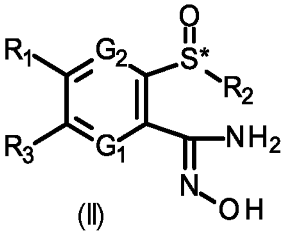
S* is a stereogenic sulfur atom in (R)- or (S)-configuration, in which said S* is in enantiomerically pure, enantiomerically enriched or racemic form;

R_1 and R_3 are independently hydrogen, halogen, haloalkyl, cycloalkyl, cyanocycloalkyl, cyanoalkoxy, cyanoalkyl or optionally substituted aryl;

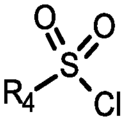
R_2 is alkyl, cycloalkyl, haloalkyl or optionally substituted aryl;

G_1 and G_2 are independently CH or N provided that at least one of G_1 or G_2 is N.

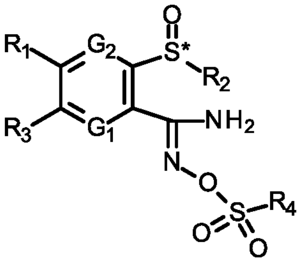
by A) Reaction of the sulfinyl compound of formula (II)


(II)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined for compounds of formula (I);
With a sulfonyl chloride of formula (III)

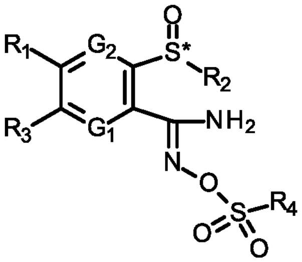

(III)

Wherein R_4 is alkyl or substituted aryl; preferably, R_4 is methyl, p-tosyl, 4-chlorophenyl, 4-cyanophenyl, 4-nitrophenyl or 2,4-dinitrophenyl;
In the presence of an appropriate base and in an appropriate solvent to produce a compound of formula (IV)


(IV)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined for compounds of formula (I) and R_4 is as defined for a compound of formula (III);

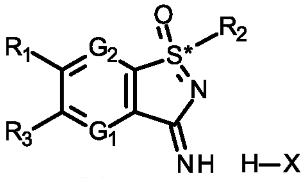
And B) Thermally rearranging the compound of formula (IV)



(IV)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined for compounds of formula (I) and R_4 is as defined for a compound of formula (III);

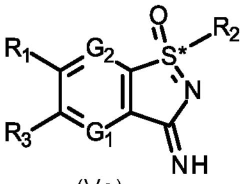
In an appropriate solvent to produce a compound of formula (V)



(V)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined for compounds of formula (I) and X is halogen (preferably, Cl) or SO_2R_4 wherein R_4 is as defined for a compound of formula (III)

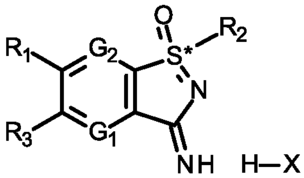
Optionally a compound of formula (Va) could be produced by adding an appropriate base and used in step (C)



(Va)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined for compounds of formula (I)

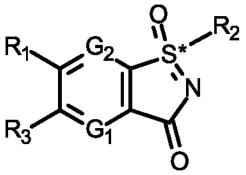
And C) Hydrolyzing the compound of formula (V)



(V)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined for compounds of formula (I) and X is halogen (preferably, Cl) or SO_2R_4 wherein R_4 is as defined for a compound of formula (III);

With water at appropriate temperature and in the presence of an appropriate co-solvent to produce compound of formula (I)

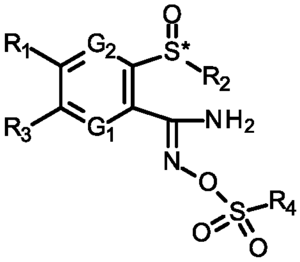


(I)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined previously.

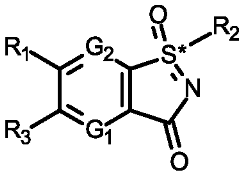
Optionally the compound of formula (Va) could be hydrolyzed instead of a compound of formula (V)

Optionally, the process for the enantioselective preparation of cyclic acyl sulfoximines of formula (I) is carried out in one pot without isolating intermediate compound of formula (IV) (i.e., without the hydrolysis step C)) by direct rearrangement of the compound of formula (IV) obtained from step B)



(IV)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined for compounds of formula (I) and R_4 is as defined for a compound of formula (III);
in the presence of water and an appropriate co-solvent to produce a compound of formula (I)



(I)

Wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined previously.

The enantioselectivity of the inventive process results in the enantiomeric character of the stereogenic sulfur atom S* being fully preserved during the synthesis of compounds of formula (I) when starting from an enantiomerically pure, enantiomerically enriched or racemic compound of formula (II). For example, it has been shown by X-ray analysis of a representative example of a precursor sulfoxide in Example 3 as well a compound of formula (I) in Example 44 that a compound of formula (II) with an (R) stereogenic center at sulfur S* leads to compound of formula (I) with an (R) stereogenic center at sulfur S* with no erosion of enantiomeric purity. Correspondingly, starting with a sulfoxide enriched in (S) enantiomer at sulfur S* leads to a compound of formula (I) enriched in (S) enantiomer.

In one embodiment of the invention step (A) comprises

Reacting a compound of formula (II) with a compound of formula (III) in the presence of an appropriate base in an appropriate solvent (or diluent). The ratio of the compound of formula (III) used, compared to the compound of formula (II), is in the range from 3:1 to 1:1, preferably between 1.5:1 and 1:1, more preferably between 1.2:1 and 1:1.

Example of suitable and preferred bases for step A are trialkylamines such as triethylamine and tributylamine, alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal hydroxide such as potassium hydroxide and sodium hydroxide. Preferably the base is a trialkylamine, more preferably triethylamine. The ratio of a base used, compared to sulfonyl chloride of formula (III), is from 1.5:1 to 1:1, more preferably between 1.2:1 and 1:1.

Examples of suitable and preferred solvents (or diluents) for step A are esters, nitriles, ethers, and aliphatic, aromatic or halogenated hydrocarbons.

Examples include but are not limited to: tetrahydrofuran, 2-methyl tetrahydrofuran, acetonitrile, butyronitrile, dichloromethane, 1,2-dichloroethane, chlorobenzene, ethyl acetate, toluene, xylenes, dioxane, cyclopentylmethyl ether, t-butylmethyl ether, diethyl ether, anisole, fluorobenzene
Preferably the solvent is an ether, nitrile or a halogenated hydrocarbon, for example: tetrahydrofuran, 2-methyl tetrahydrofuran, acetonitrile, dichloromethane and chlorobenzene

Step (B) comprises
A thermal rearrangement of compounds of formula (IV) to compounds of formula (V) in a suitable solvent (or diluent) at an appropriate temperature.

Suitable solvents (or diluents) are polar aprotic solvents, nitriles, esters, ketones, alcohols, aromatic hydrocarbons, carbonates and ethers or mixtures thereof.

Examples of appropriate and preferred solvents include but are not limited to: acetonitrile, butyronitrile, benzonitrile, ethylene glycol, methanol, ethanol, methyl isobutyl ketone, nitrobenzene, trifluorotoluene, polyethelene glycol, chlorobenzene, tetrahydrofuran, 2-methyl-tetrahydrofuran, 1,4-dioxane, anisole, N,N-dimethyl formamide, N-methyl pyrrolidine, sulfolane, 2,5-dimethyl isosorbide, dimethyl acetamide, cyrene, or mixture thereof.

More preferably the solvent (or diluent) is N-methyl pyrrolidine, sulfolane, acetonitrile, ethylene glycol, ethanol, or mixtures thereof.

The rearrangement is advantageously carried out in a temperature range from 0 °C to 150 °C. The preferred temperature is dependent on the electronic nature of R_4 substituent. If R_4 is highly electron withdrawing (for example 2,4-dinitro phenyl) the appropriate reaction temperature is in the range from 0 °C to 40 °C. Whereas, if R_4 is neutral (for example methyl) or moderately electron withdrawing (for example tosyl) the preferred temperature is between 60 °C and 100 °C.

In one embodiment related to the process according to the invention of making compounds of formula (V), steps (A) and (B) could be advantageously carried out in one pot without isolating intermediate compound of formula (IV). This is most preferable when R_4 in sulfonyl chloride of formula (III) is highly electron withdrawing (for example 2,4-dinitrophenyl).

Step (C) comprises

Hydrolysing compounds of formula (V) by heating in an aqueous media using a suitable cosolvent (or diluent) optionally in a presence of an appropriate acid.

Suitable co-solvents (or diluents) are water miscible alcohols, ethers and nitriles.

Examples of appropriate and preferred co-solvents include but are not limited to: methanol, ethanol, tetrahydrofuran, acetonitrile, 1,4-dioxane.

The amount of water used is in the range from a stoichiometric amount to 80%, preferably in the range from 1:3 to 1:1 relative to the co-solvent.

Examples of appropriate acids include but are not limited to: sulfuric, hydrochloric, trifluoracetic, acetic, trifluormethansulfonic, methansulfonic. Most preferably the acid is sulfuric or hydrochloric.

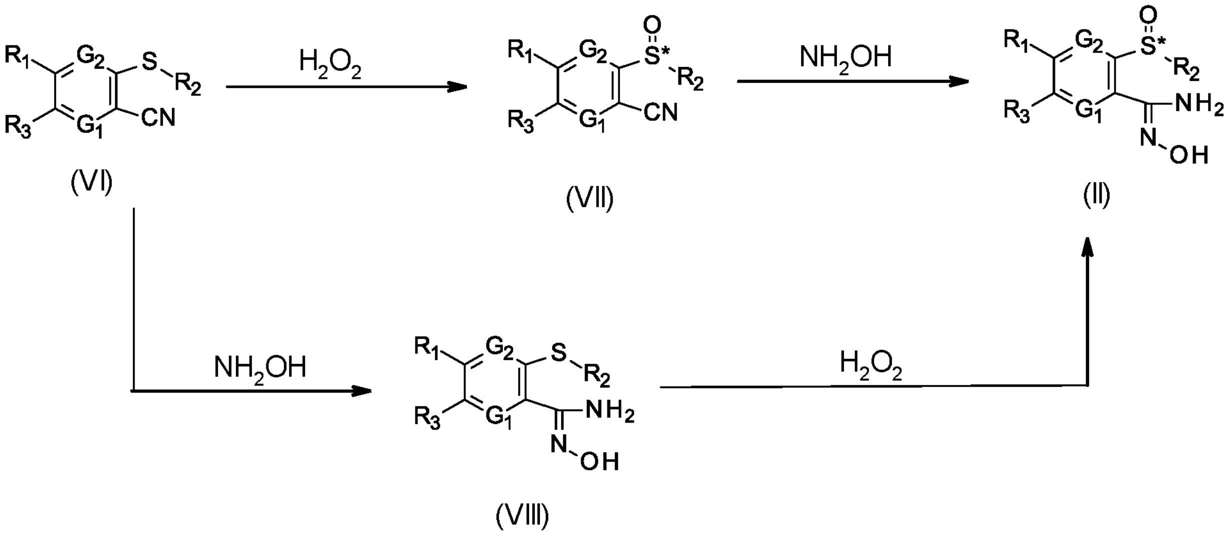
The hydrolysis is advantageously carried out in a temperature range from 0 °C to 100 °C, more preferably between 20 °C and 60 °C.

In one embodiment related to the process according to the invention of making compounds of formula (I), steps (B) and (C) could be advantageously carried out in one pot without isolating intermediate compounds of formula (V). This is accomplished by directly heating compounds of formula (IV) in an aqueous media using an appropriate cosolvent as described above for steps (B) and (C) and optionally in a presence of an appropriate acid.

Examples of appropriate acids include but are not limited to: sulfuric, hydrochloric, trifluoracetic, acetic, trifluormethansulfonic, methansulfonic. Most preferably the acid is sulfuric or hydrochloric.

Compounds of formula (II) could be conveniently prepared from compound of formula (VI) as shown in Scheme 5. In one version (method A) compounds of formula (VI) would be first oxidized, optionally in the presence of a chiral catalyst, to compounds of formula (VII). Hydroxylamine would then be added to the nitrile group in compounds of formula (VII) to yield compounds of formula (II). Alternatively (method B), it is possible to reverse the order of steps and first add hydroxylamine to the nitrile moiety in compounds of formula (VI) to yield compounds of formula (VIII) followed by oxidation to yield compounds of formula (II). If enantioenriched compounds are desired, it is generally advantageous to follow the route with oxidation first (method A). Specific examples for preparation of compounds of formula (II) by either route are provided in the experimental section.

Scheme 5



Compounds of formula (VI) could be prepared by various methods known to a person with an ordinary skill in the art. For example, as described in WO2016113205, WO2014104407 and Tetrahedron 1983, 39, 4153.

Definitions:

The term "alkyl" as used herein, in isolation or as part of a chemical group, represents straight-chain or branched hydrocarbons, preferably with 1 to 6 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, pentyl, 1- methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1 -dimethylpropyl, 2,2- dimethylpropyl, 1 -ethylpropyl, hexyl, 1 -methylpentyl, 2-methylpentyl, 3-methylpentyl, 4- methylpentyl, 1,2-dimethylpropyl, 1,3-dimethylbutyl, 1,4-dimethylbutyl,2,3-dimethylbutyl, 1,1- dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl and 2-ethylbutyl. Alkyl groups with 1 to 4 carbon atoms are preferred, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl or t-butyl.

The term alkoxy as used herein refers to a straight-chain or branched saturated alkyl radical preferably with 1 to 6 carbon atoms (as mentioned above) which is attached via an oxygen atom, i.e., for example, any one of methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, 1-methylpropoxy, 2-methylpropoxy or 1, 1-dimethylethoxy.

The term cyanoalkyl as used herein refers to a straight chain or branched saturated alkyl radicals (as mentioned above) which is substituted by a cyano group, for example cyanomethylene, cyanoethylene, 1,1-dimethylcyanomethyl, cyanoisopropyl, cyanomethyl, cyanoethyl, and 1-dimethylcyanomethyl

The term cyanoalkoxy refers to a straight chain or branched saturated alkyloxy radicals (as mentioned above) which is substituted by a cyano group.

The term "cycloalkyl" as used herein refers to a 3-6 membered cycloalkyl group such as cyclopropane, cyclobutane, cyclopropane, cyclopentane and cyclohexane.

The term “cyanocycloalkyl” as used herein refers to a 3-6 membered cycloalkyl group (as mentioned above) which is substituted by a cyano group.

The term "aryl" represents a mono-, bi- or polycyclical aromatic system with preferably 6 to 14, more preferably 6 to 10 ring-carbon atoms, for example phenyl, naphthyl, anthryl, phenanthrenyl, preferably phenyl. "Aryl" also represents polycyclic systems, for example tetrahydronaphtyl, indenyl, indanyl, fluorenyl, biphenyl. Arylalkyls are examples of substituted aryls, which may be further substituted with the same or different substituents both at the aryl or alkyl part. Benzyl and 1 —phenylethyl are examples of such arylalkyls.

The term "halogen" or "halo" represents fluoro, chloro, bromo or iodo, particularly fluoro, chloro or bromo. The chemical groups which are substituted with halogen, for example haloalkyl, are substituted one or up to the maximum number of substituents with halogen. If "alkyl" is substituted with halogen, the halogen atoms can be the same or different and can be bound at the same carbon atom or different carbon atoms.

Where not otherwise defined the term “optionally substituted” means that the group in question can be substituted with zero up to the maximum number of substituents with groups independently selected from: halogen, methyl, ethyl, propyl, isopropyl, t-butyl, cyclopropyl, cyclobutyl, cyclohexyl, trifluoromethyl, difluoromethyl, chlorodifluoromethyl, trichloromethyl, methoxy, ethoxy, trifluoromethoxy, difluoromethoxy, nitro, cyano, hydroxy, sulfhydryl, acetyl, acetoxy, COOH, COOMe, COOEt, $CONH_2$, CONHMe, $CONMe_2$, amino, methlamino, dimethylamino, phenyl.

The term "enantiomerically enriched" means that one of the enantiomers of the compound is present in excess in comparison to the other enantiomer. This excess will hereafter be referred to as enantiomeric excess or ee. The ee may be determined by chiral GC, HPLC or SFC analysis. The ee is equal to the difference between amounts of enantiomers divided by the sum of the amounts of the enantiomers, which quotient can be expressed as a percentage after multiplication by 100. The ee can also be referred to as the absolute difference between the mole fraction of each enantiomer in the mixture. For example, when there is an isomer with an enantiomeric excess (e.e.) of 40% this means that the mole fraction (or percent) of such excess isomer is 70%. Accordingly, in one embodiment, the term "enantiomerically enriched" also refers to an enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

Certain preferred embodiments according to the invention are provided as set out below.

Embodiment 1 provides a process for the enantioselective preparation of cyclic acyl sulfoximines of formula (I) as defined above optionally in an enantiomerically pure, an enantiomerically enriched or a racemic form as set out in the detailed description above.

Embodiment 2 provides a process for the enantioselective preparation of a compound of formula (I) according to embodiment 1 which process comprises:

(A) reacting a compound of formula (II) with a compound of formula (III) in the presence of an appropriate base in an appropriate solvent (or diluent) to produce a compound of formula (IV);

(B) thermally rearranging a compound of formula (IV) to produce a compound of formula (V) in a suitable solvent (or diluent) at an appropriate temperature and, optionally, producing a compound of formula (Va) by adding an appropriate base; and

(C) hydrolysing the compound of formula (V), or compound of formula (Va), by heating in an aqueous media using a suitable cosolvent (or diluent) optionally in a presence of an appropriate acid, to produce a compound of formula (I) as defined above; wherein steps (B) and (C) are optionally carried out in one pot without isolating intermediate compounds of formula (V) or formula (Va).

Embodiment 3 provides a process for the enantioselective preparation of a compound of formula (I) according to embodiments 1 – 2, wherein the preferred alternatives of steps (A) – (C) including the base and solvent (or diluent) used in step (A), the solvent (or diluent), temperature and base of step (B); and the temperature, cosolvent (or diluent) and optional acid of step (C) that are used in the process of embodiments 1 – 2 and which are, in any combination thereof, as set out in the detailed description above.

Embodiment 4 provides a process according to embodiments 1 – 3, wherein a compound of formula (V) is prepared when steps (A) and (B) are carried out in one pot without isolating the intermediate compound of formula (IV). This is most preferable when R_4 in sulfonyl chloride of formula (III) is highly electron withdrawing (for example 2,4-dinitrophenyl).

With respect to embodiments 1 - 4, preferred values of S*; R_1, R_2, R_3, R_4, G_1 and G_2 are, in any combination thereof, as set out below:

Preferably, S* is a stereogenic sulfur atom in (R)- or (S)-configuration, in which said S* is in enantiomerically pure, enantiomerically enriched or racemic form;
Also preferred is when S* is a stereogenic sulfur atom in (R)- or (S)-configuration, in which said S* is in racemic form;
Also preferred is when S* is a stereogenic sulfur atom in (R)-configuration, in which said S* is in enantiomerically pure or enantiomerically enriched form (as defined above); and
Further preferred is when S* is a stereogenic sulfur atom in (S)-configuration, in which said S* is in enantiomerically pure or enantiomerically enriched form (as defined above).

Preferably, R_1 and R_3 are independently hydrogen, halogen, haloalkyl, cycloalkyl, cyanocycloalkyl, cyanoalkoxy, cyanoalkyl or optionally substituted aryl;
More preferably, R_1 and R_3 are independently hydrogen, halogen, C_1-C_6-haloalkyl, C_1-C_6-cyanoalkyl, C_1-C_6-cyanoalkoxy, C_3-C_6-cycloalkyl, C_3-C_6-cyanocycloalkyl or optionally substituted aryl; and
Most preferably, R_1 and R_3 are independently hydrogen, chloro, bromo, trifluoromethyl, cyclopropyl, cyanocyclopropyl, cyanoisopropoxy, cyanoisopropyl, phenyl or halophenyl.

Preferably, R_2 is alkyl, cycloalkyl, haloalkyl or optionally substituted aryl;
More preferably, R_2 is C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-haloalkyl, phenyl or halophenyl; and
Most preferably, R_2 is ethyl, cyclopropyl, trifluoromethyl, phenyl or fluorophenyl.

Preferably, G_1 and G_2 are independently CH or N provided that at least one of G_1 or G_2 is N.

Also preferred is when G_1 is N and G_2 is CH; or when G_1 is CH and G_2 is N; or when both G_1 and G_2 are N.

Preferably, R_4 is alkyl or substituted aryl;
More preferably, R_4 is methyl, p-tosyl, 4-chlorophenyl, 4-cyanophenyl, 4-nitrophenyl or 2,4-dinitrophenyl.

X is halogen;
Preferably, X is chloro.

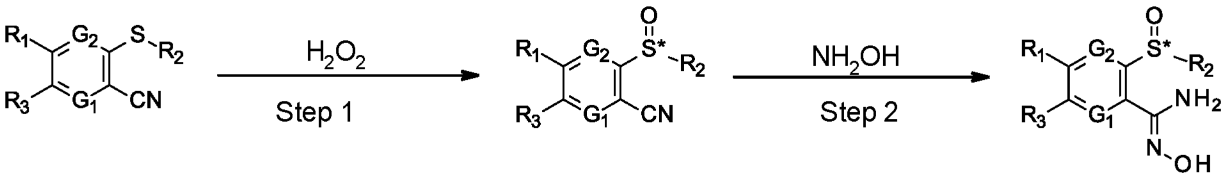
The following examples serve to illustrate the present invention:

Experimental procedures and data

Synthesis of amidine oximes of formula (II):

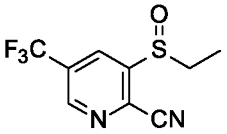
Racemic amidine oximes of formula (II) were prepared by either of the three general methods (A, B and C). All enantioenriched amidine oximes of formula (II) were prepared by method A.

Method A - racemic:



<u>General procedure for oxidation (step 1)</u>: To a solution of starting sulfide in acetic acid was added $Na_2WO_4.2H_2O$ (5-10 mol%) followed by a slow addition of 30% aq H_2O_2 (1.1 eq). The reaction mixture was stirred at ambient temperature till the fully consumption of the starting material. The reaction was quenched by pouring into aq NaOH. The resulting mixture was extracted with EtOAc (2x). The combined organic layer was washed with 10% aq $NaHSO_3$ and brine, then dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the crude product which was purified via silica gel chromatography to yield the desired sulfoxide in a pure form.

Example 1: 3-ethylsulfinyl-5-(trifluoromethyl)pyridine-2-carbonitrile



Isolated in 57% yield as a colorless solid.

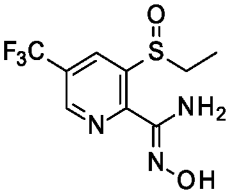
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.27 - 1.40 (m, 3 H), 2.95 - 3.09 (m, 1 H), 3.21 - 3.37 (m, 1 H) 8.65 (d, *J*=1.45 Hz, 1 H), 9.06 (d, *J*=1.09 Hz, 1 H)

^{19}F NMR (377 MHz, $CDCl_3$) δ ppm -62.80 (s, 3 F)

General procedure for hydroxylamine addition (step 2):

To a solution of starting nitrile in ethanol was added 50% aq. NH_2OH (1.55 eq). The reaction mixture was stirred at ambient temperature till the full consumption of starting material. The reaction mixture was evaporated to dryness to yield the crude product which was used in the next step without further purification.

Example 2: 3-ethylsulfinyl-N'-hydroxy-5-(trifluoromethyl)pyridine-2-carboxamidine



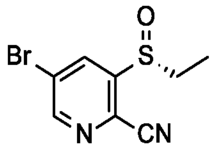
Isolated in 99% yield as a colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (t, *J*=7.45 Hz, 3 H) 2.98 - 3.13 (m, 1 H) 3.33 - 3.49 (m, 1 H) 5.68 (s, 2 H) 8.50 - 8.70 (m, 1 H) 8.73 (d, *J*=1.8 Hz, 1 H) 8.91 (d, *J*=1.1 Hz, 1 H)
^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -62.27 (s, 3 F)

Method A - enantioenriched:

Oxidation with hydrogen peroxide in acetic acid is replaced with an iron catalyzed oxidation with hydrogen peroxide in the presence of a chiral ligand. The second step is analogous to the racemic version. In this case specific oxidation procedures are provided.

Example 3: Preparation of 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-bromo-3-ethylsulfanyl-pyridine-2-carbonitrile (2.157 g, 93% purity, 8.25 mmol) in anisole (8.3 ml) was added (2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol) (0.235 g, 97% purity, 0.602 mmol), 4-methoxybenzoic acid (43 mg, 0.28 mmol) and Fe(acac)$_3$ (0.277 g, 0.0784 mmol). The resulting dark red solution was cooled to 10 °C and 30% aq H_2O_2 (1.35 ml, 13.2 mmol) was added. The resulting biphasic mixture was stirred at 10 °C for 22 h. At this stage (full conversion of starting material) the reaction was quenched by addition of crushed ice (4 g) and 40% aq $NaHSO_3$ (2.6 ml). After warming to ambient temperature, the mixture was diluted with EtOAc (8 ml) and treated with 1M aqueous H_2SO_4 (0.83 ml). After stirring for 30 min phases were separated, organic phase washed with aq $NaHCO_3$ (8 ml) and brine (8 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield a crude product. Quantitative NMR analysis using 1,3,5-trimethoxy benzene as an internal standard indicates a chemical yield of 91% for the desired 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile. The crude product was purified by a reverse phase HPLC (MeCN/water/0.1% formic acid mobile phase) to yield 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile (1.63 g, >99% purity, >99.5% ee, 76% isolated yield) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.45 Hz, 3 H), 2.99 (dq, J=14.0, 7.2 Hz, 1 H), 3.15 - 3.36 (m, 1 H), 8.50 (d, J=2.2 Hz, 1 H), 8.85 (d, J=2.2 Hz, 1 H)

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa
PDA Detector Waters Acquity UPC^2
Column: Daicel SFC CHIRALPAK® IC, 3μm, 0.3cm x 10cm, 40°C
Mobile phase: A: CO_2 B: IPA gradient: 20-60% B in 2 min
ABPR: 1800 psi
Flow rate: 2.0 ml/min

Detection: 240 nm

Sample concentration: 1 mg/mL in ACN

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 1.14	Retention time (min) ~ 1.35
Enantiomeric excess (%) >99.5% (R enantiomer, S enantiomer below HPLC detection limits)	

A single crystal grown from di-isopropyl ether was selected for X-ray data analysis. The crystal sample mounted had dimensions of 0.4 mm x 0.3 mm x 0.3 mm and was a colorless prism. Data collection was performed on a Rigaku Oxford Diffraction Supernova diffractometer at 293 K. The unit cell was determined to be orthorhombic (space group P212121), and the structure contained one molecule in the crystal asymmetric unit (Figure 1, a thin stick representation labelled by chirality). Figure generated in Flare software package (Cresset). The stereochemistry was unambiguously determined to be the R isomer, with a Flack parameter of 0.02 +/- 0.03. Crystallographic data is summarized in Table 1 and selected geometric parameters are listed in Table 2. Crystal data and structure refinement for 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile.

Table 1. Crystal data and structure refinement for 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile

Crystal data	
Chemical formula	$C_8H_7BrN_2OS$
M_r	259.13
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	293
a, *b*, *c* (Å)	6.7404 (2), 9.2441 (3), 15.8051 (5)
V (Å^3)	984.80 (6)
Z	4
Radiation type	Cu *K*α
µ (mm^{-1})	7.37
Crystal size (mm)	0.40 × 0.30 × 0.30
Data collection	
Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan *CrysAlis PRO*, (Agilent, 2011)
T_{min}, T_{max}	0.11, 0.11
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	4140, 2032, 1962
R_{int}	0.037
(sin θ/λ)$_{max}$ (Å^{-1})	0.632
Refinement	

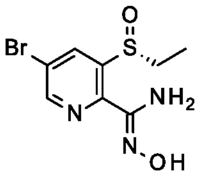
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.041, 0.117, 0.91
No. of reflections	2024
No. of parameters	120
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.72
Absolute structure	Flack (1983), 814 Friedel-pairs
Absolute structure parameter	0.02 (3)

Computer programs: SuperNova, (Oxford Diffraction, 2010), CrysAlis PRO, (Agilent, 2011), SIR92 (Altomare et al., 1994), CRYSTALS (Betteridge et al., 2003), CAMERON (Watkin et al., 1996)

Table 2. Selected geometric parameters (Å, °)

Br1—C2	1.874 (4)	S5—C7	1.806 (4)
C2—C3	1.380 (5)	C7—C8	1.510 (6)
C2—C11	1.394 (6)	C9—N10	1.341 (4)
C3—C4	1.392 (5)	C9—C12	1.436 (5)
C4—S5	1.808 (3)	N10—C11	1.328 (5)
C4—C9	1.388 (5)	C12—N13	1.153 (6)
S5—O6	1.491 (3)		
Br1—C2—C3	121.0 (3)	O6—S5—C7	107.64 (19)
Br1—C2—C11	118.8 (2)	S5—C7—C8	114.3 (3)
C3—C2—C11	120.3 (3)	C4—C9—N10	123.7 (3)
C2—C3—C4	117.2 (3)	C4—C9—C12	121.2 (3)
C3—C4—S5	118.3 (3)	N10—C9—C12	115.1 (3)
C3—C4—C9	118.9 (3)	C9—N10—C11	117.3 (3)
S5—C4—C9	122.6 (3)	C2—C11—N10	122.6 (3)
C4—S5—O6	105.15 (17)	C9—C12—N13	179.2 (4)
C4—S5—C7	98.29 (15)		

Example 4: Preparation of 5-bromo-3-[(R)-ethylsulfinyl'-N'-hydroxy-pyridine-2-carboxamidine

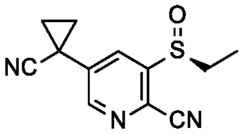


To a solution of 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile (0.774 g, >99% purity, >99.5% ee, 2.99 mmol) in MeTHF (6.0 ml) was added 50% aq NH_2OH (0.37 ml, 5.98 mmol) in two portions over 10 min. After stirring for further 20 min most of the solvent was evaporated under reduced pressure (ca 1.2 ml left). CPME (2.7 ml) was added slowly leading to precipitation. The precipitate was filtered, washed on filter with

CPME/MeTHF (7:3, 1.5 ml) and dried in vacuum to yield the title compound (0.713 g, 95% purity, 78% yield) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J*=7.45 Hz, 3 H), 2.93 (dq, *J*=13.1, 7.4 Hz, 1 H), 3.32 (dq, *J*=13.1, 7.5 Hz, 1 H), 5.58 (br s, 2 H), 7.55 (s, 1 H), 8.59 (d, *J*=2.2 Hz, 1 H), 8.68 (d, *J*=2.2 Hz, 1 H).

Example 5: Preparation of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (241.5 mg, 95% purity, 1.00 mmol), $Fe(acac)_3$ (17.5 mg, 0.0500 mmol), 4-methoxybenzoic acid (3.8 mg, 0.0250 mmol) and 2-[(E)-[(1S)-1-(hydroxymethyl)-2,2- dimethyl-propyl]iminomethyl]-4,6-diiodo-phenol (48.8 mg, 97% purity, 0.100 mmol) in PhMe (4.0 ml) was added 30% aq H_2O_2 (0.20 ml, 2.00 mmol) at ambient temperature. After stirring vigorously for 2.5 h the reaction mixture was poured into EtOAc (23 ml) and quenched by addition of 1.0M $Na_2S_2O_3$ (2.4 ml). Phases were separated and the organic phase was washed with 1.0M HCl (2.3 ml) and aq $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN/0.1% formic acid mobile phase) to yield the title compound (234 mg, 97%ee, 95% yield) as a white powder.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.77 (d, *J* = 2.3 Hz, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 3.26 (dq, *J* = 13.6, 7.3 Hz, 1H), 3.04 (dq, *J* = 13.6, 7.3 Hz, 1H), 2.09 –1.79 (m, 4H), 1.12 (t, *J* = 7.4 Hz, 3H)

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IA, 3µm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: IPA gradient: 20-60% B in 1.8 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: DAD 210-500 nm

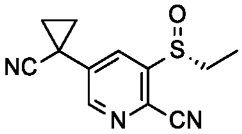
Sample preparation: dissolved in MeOH

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.59	Retention time (min) ~ 1.04
Enantiomeric excess (%): 97% (S enantiomer)	

Example 6a: Preparation of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



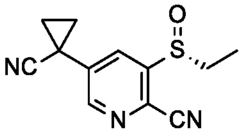
To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (237.0 mg, 97% purity, 1.00 mmol), Fe(acac)$_3$ (3.6 mg, 0.0101 mmol), 4-methoxybenzoic acid (3.8 mg, 0.0251 mmol) and 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2- dimethyl-propyl]iminomethyl]-4,6-dichloro-phenol (32.8 mg, 98% purity, 0.110 mmol) in PhOMe (1.0 ml) was added 30% aq H_2O_2 (0.23 ml, 2.11 mmol) at 0 °C over 1 h using a syringe pump. The resulting reaction mixture was stirred for further 20 h at the same temperature. The reaction mixture was poured into EtOAc (23 ml) and quenched by addition of 1.0M $NaHSO_3$ (2.4 ml). Phases were separated and the organic phase was washed with 1.0M HCl (2.3 ml) and aq $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN/0.1% formic acid mobile phase) to yield the title compound (230 mg, >99.5%ee, 93% yield) as a white powder.

Chiral SFC method: Identical to Example 5

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.59	Retention time (min) ~ 1.04
Enantiomeric excess (%): >99.5% (R enantiomer)	

Example 6b: Preparation of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (10.61 g, 98% purity, 45.5 mmol), Fe(acac)$_3$ (0.153 g, 0.432 mmol), 4-methoxybenzoic acid (0.234 g, 1.54 mmol) and 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol (1.281 g, 97% purity, 3.30 mmol) in PhOMe (46 ml) was added 30% aq H_2O_2 (7.8 ml, 76.3 mmol) at 10 °C over 2 h using a syringe pump. The resulting reaction mixture was stirred vigorously for further 22 h at the same temperature. The reaction was quenched by addition of 40% aq NaHSO3 (10.6 ml) and diluted with PhOMe (53 ml). Phase were separated and the organic phase was washed with 1M H_2SO_4 (21 ml), aq saturated $NaHCO_3$ (21 ml) and brine (21 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN as a mobile phase) to yield the title compound (10.44 g, >99.5% ee, 93% yield) as a white powder.

Chiral SFC method:

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IA, 3μm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: IPA gradient: 5-20% B in 9.8 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 238 nm

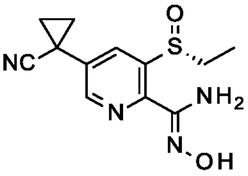
Sample preparation: 1mg/mL canACN

Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 3.07	Retention time (min) ~ 5.73
Enantiomeric excess (%): >99.5% (R enantiomer)	

Example 7: Preparation of 5-(1-cyanocyclopropycan3-[(R)-ethylsu’finyl]-N'-hydroxy-pyridine-2-carboxamidine



A 100 ml reactor with a mechanical stirring was charged with 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (10.60 g, 45.5 mmol, 98% assay), 4-methoxybenzoic acid (0.234 g, 1.54 mmol), Fe(acac)$_3$ (0.153 g, 0.432 mmol), 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol (1.30 g, 3.33 mmol, 97% assay) and anisole (45.5 ml). The resulting deep red solution was cooled to 10 °C and 30% aq H_2O_2 (7.9 ml, 77.0 mmol) was dosed over 1 h via a syringe pump while stirring vigorously (300 rpm). After the end of dosing the reaction mixture was stirred at the same temperature for further 14 h (full conversion by LC/MS). The reaction was quenched by addition of aq 40% $NaHSO_3$ (10.6 ml) in two portions (exothermic). After 15 min the reaction temperature was raised to 20 °C and stirred vigorously (600 rpm) for 30 min (reaction color turns bright yellow). Phases were separated and 1M H_2SO_4 (10.6 ml) was added to the organic phase. The resulting mixture was stirred vigorously for 30 min. Phases were again separated and the organic phase was washed with brine (3 x 10 ml) until washings had a pH > 6. The organic phase was dried over Na_2SO_4. After filtration of the drying agent the obtained solution in PhOMe was telescoped to the next step. qNMR analysis using 1,3,5-trimethoxybenzene as an internal standard indicates 92% chemical yield of the chiral sulfoxide as well as ca 3% of the corresponding sulfone (overoxidation). This solution also contains most of the ligand used for oxidation.

A solution of the chiral sulfoxide prepared above (54.4 g) was charged in a 100 ml reactor with a mechanical stirring. In a separate flask a 4.7M solution of NH_2OH was prepared by treating a solution of $NH_2OH.HCl$ with 50% aq NaOH at 0 °C (exothermic). Thus prepared solution (10.0 ml, 47.2 mmol) was dosed to the sulfoxide solution in PhOMe at ambient temperature over 1.5 h. After stirring for further 2 h (white crystals in an orange liquid) the precipitate was filtered off and washed on filter with PhOMe (23 ml) and water (2 x 23 ml). The resulting white powder was resuspended in water (51 ml) and stirred vigorously for 1.5 h to yield a stable white suspension. The precipitate was filtered, washed on filter with water (20 ml) and dried under high vacuum overnight to yield the title compound (10.42 g, 97% assay, >99.5% ee, 80% isolated yield over two steps) as a white powder.

^{1}H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.59 (d, *J* = 2.3 Hz, 1H), 8.26 (d, *J* = 2.3 Hz, 1H), 6.01 (s, 2H), 3.25 (dq, *J* = 13.0, 7.4 Hz, 1H), 2.77 (dq, *J* = 13.0, 7.4 Hz, 1H), 1.99 – 1.84 (m, 2H), 1.80 – 1.65 (m, 2H), 1.16 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d6) δ 149.0, 146.1, 145.0, 140.1, 132.9, 131.1, 121.4, 48.8, 18.5, 18.5, 11.7, 6.7

Chiral SFC method:

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IA, 3μm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: MeOH gradient: 20-60% B in 1.8 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 227 nm

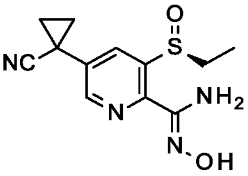
Sample preparation: 1mg/mL in MeOH

Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.85	Retention time (min) ~ 1.15
Enantiomeric excess (%): >99.5% (R enantiomer)	

Example 8: Preparation of 5-(1-cyanocyclopropyl)-3-[(S)-ethy'sulfinyl]-N'-hydroxy-pyridine-2-carboxamidine



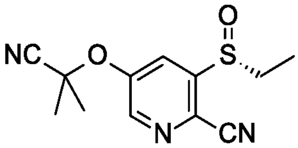
To a suspension of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]pyridine-2-carbonitrile (167.1 mg, 95% purity, 97% ee, 0.648 mmol) in EtOH (1.3 ml) was added 50% aq NH_2OH (0.062 ml, 1.01 mmol). The resulting thick suspension was stirred for 1 h. The solvent was evaporated, and the residue dried under vacuum to yield the title compound (187.4 mg, 92% purity, 97% ee, 96% yield) as a white powder.

Chiral SFC method: Identical to Example 7

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.85	Retention time (min) ~ 1.15
Enantiomeric excess: 97% (S enantiomer)	

Example 9: Preparation of 5-(1-cyano-1-methylcanhoxy)-3-[(*R*)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carbonitrile (2.00 g, 82% purity, 6.64 mmol), iron(III) acetylacetonate (46.9 mg, 0.133 mmol), 2,4-dichloro-6-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]phenol (0.602 g, 1.99 mmol), p-anisic acid (51 mg, 0.332 mmol) in toluene (13 mL) was added 30% aq hydrogen peroxide (1.36 mL, 50.1 mmol) at ambient temperature over 1h. The reaction mixture was stirred for further 5 h and then quenched by adding aq saturated sodium thiosulphate at 0 °C. The organic layer was separated, and aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure to get the crude compound. The crude material was purified by silica gel chromatography using cyclohexane and ethyl acetate as an eluent to yield the title compound (1.55 g, 89% purity, >99.5% ee, 79% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.71 (d, *J*=2.6 Hz, 1H) 8.02 (d, *J*=2.7– Hz, 1H) 3.28 - 3.33 (m, 1H) 2.96-3.02 (m, 1H), 1.84 (s, 6H), 1.09 (t, *J*=7.3 Hz, 3H)

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiralpack-IA (4.6mm x 250mm) 5µm

Mobile phase: A: TBME B: IPA isocratic: 20% B in 13 min

Flow rate: 1.0 ml/min

Detection: 240 nm

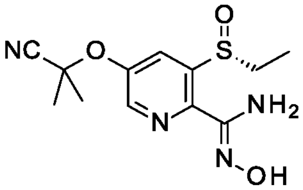
Sample preparation: 1mg/mL in EtOH

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 5.32	Retention time (min) ~ 6.8
Enantiomeric excess (%) >99.5% (R enantiomer, opposite enantiomer below HPLC detection limits)	

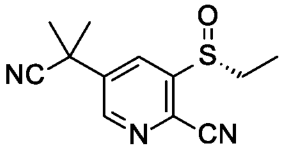
Example 10: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-[(R'-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine



To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfinyl-pyridine-2-carbonitrile (0.500 g, 97% purity, 1.84 mmol) in ethanol (1.3 mL) was added at 0°C 50% aqueous hydroxylamine (1.00 equiv., 1.84 mmol) and the reaction was stirred for further 2 h at ambient temperature. An extra portion of 50% aq hydroxylamine (0.20 equiv., 0.368 mmol) was added and the reaction stirred for a further 1 h. Ethyl acetate was added to the reaction mixture, the organic layer was separated and aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield the title compound (0.54 g, 93% purity, 92% yield)

^{1}H NMR (400 MHz, DMSO-d_6) δ10.35 (s, 1H), 8.53 (d, J=2.7 Hz, 1H), 8.13 (d, J=2.7 Hz, 1H), 6–02 (s, 2H), 3.18 - 3.29 (m, 1H), 2.85 (dd, J=13.1 Hz, 7.4 Hz, 1H), 1.78 (d, J=6.0 Hz, 6 H) 1.11 (t, J=7.4 Hz, 3 H)

Example 11: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyano-1-methyl-ethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (6.00 g, 96.5% purity, 25.0 mmol), iron(III) acetylacetonate (0.177 g, 0.5 mmol), 2,4-dibromo-6-[(E)-[(1R)-1-(hydroxymethyl) -2,2-dimethyl-propyl]iminomethyl]phenol (1.47 g, 3.75 mmol) in toluene (90 mL) was added 30% aq hydrogen peroxide (2.0 equiv., 50.1 mmol) drop wise over 1h at 0 °C. The reaction mixture was stirred for 2 h at 24°C and then quenched by adding saturated $Na_2S_2O_3$ at 0 °C. The organic layer was separated and aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude material was purified by column chromatography using cyclohexane and ethyl acetate as an eluent to yield the title compound (5.48 g, 91% purity, 97% ee, 81% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 9.10 (d, *J*=2.3 Hz, 1H), 8.35 (d, *J*=2.3 Hz, 1H), 3.28 (m , 1H), 3.04 (m, 1H), 1.82 (d, *J*=1.9 Hz, 6H), 1.12 (t, *J*=7.3 Hz, 3H)

Method of Chiral Analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiralpack-IC (4.6mm x 250mm) 5µm

Mobile phase: A: n-hexane B: EtOH isocratic: 30% B in 30 min

Flow rate: 1.0 ml/min

Detection: 225 nm

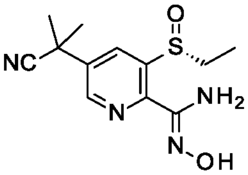
Sample preparation: 1mg/mL in EtOH

Injection: 2 µL

Results:

R enantiomer	S enantiomer
Retention time (min) ~ 18.2	Retention time (min) ~ 21.8
Enantiomeric excess: 97% (R enantiomer)	

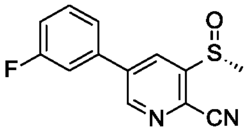
Example 12: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine



To a solution of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile (2.00 g, 91% purity, 7.38 mmol) in ethanol (5.0 ml) was added 50% aqueous hydroxylamine (0.52 ml, 8.49 mmol) at room temperature. After stirring for 1 h at ambient temperature an additional portion of 50% aq hydroxylamine (0.20 ml, 3.4 mmol) was added. Upon full conversion of the starting material the reaction mixture was concentrated under reduced pressure and product collected via filtration. The product was washed on filter with water and dried under high vacuum to yield the title compound (1.78 g, 93% purity, 81% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.87 (d, *J*=2.4 Hz, 1H), 8.39 (d, *J*=2.2 Hz, 1H), 6.06 (s, 2H), 3.21 - 3.31 (m, 1H), 2.78 (m, 1H), 1.79 (s, 6H), 1.15 (t, *J*=7.4 Hz, 3H)

Example 13: Preparation of 5-(3-fluorophenyl)-3-[(R)-methylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(3-fluorophenyl)-3-methylsulfanyl-pyridine-2-carbonitrile (0.800 g, 90% purity, 2.95 mmol), iron(III) acetylacetonate (10.4 mg, 0.0295 mmol), 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-diiodo-phenol (0.213 g, 0.442 mmol), p-anisic acid (11.3 mg, 0.0737 mmol) in toluene (6.0 ml) was added 30% aq H_2O_2 (0.6 mL, 5.9 mmol) drop wise over 15 minutes and the reaction mixture was continued to stir for further 1 hour. The reaction mixture was quenched by saturated sodium thiosulphate and the resulting mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get crude material. Purification by silica gel chromatography using cyclohexane and ethyl acetate as an eluent yielded the title compound (0.73 g, 94% purity, 97% ee, 89% yield)

^{1}H NMR (400 MHz, DMSO-d6) δ 9.29 (d, *J*=2.1 Hz, 1H), 8.64 (d, *J*=2.1 Hz, 1H), 7.89 (m, 1 H), 7.80 (d, *J*=7.8 Hz, 1H), 7.64 (m, 1H), 7.41 (m, 1H), 3.04 (s, 3 H)

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiralpack-IA (4.6mm x 250mm) 5µm

Mobile phase: A: TBME B: IPA isocratic: 30% B in 30 min

Flow rate: 1.0 ml/min

Detection: 225 nm

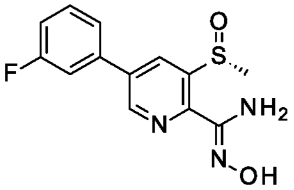
Sample preparation: 1mg/mL in EtOH

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 11.0	Retention time (min) ~ 14.9
Enantiomeric excess: 97% (R enantiomer)	

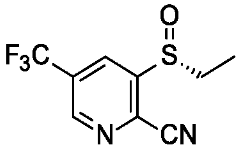
Example 14:’Preparation 5-(3-fluorophenyl) N'-hydroxy-3-[(R)-methylsulfinyl]pyridine-2-carboxamidine



To a solution of 5-(3-fluorophenyl)-3-[(R)-methylsulfinyl]pyridine-2-carbonitrile (0.12 g, 94% purity, 0.434 mmol) into ethanol (0.5 mL) was added 50% aq hydroxylamine (0.030 mL, 0.434 mmol) at room temperature. The reaction mixture was stirred for 2 hours and then diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound (0.11 g, 98% purity, 85% yield) as a brown solid.

^1H NMR (400 MHz, DMSO-d6) δ 10.48 (s, 1 H), 9.06 (d, *J*=2.2 Hz, 1 H), 8.61 (d, *J*=2.1 Hz, 1 H), 7.75 (dt, *J*=10.3, 2.2 Hz, 1 H), 7.67 - 7.71 (m, 1 H), 7.58 - 7.65 (m, 1 H), 7.34 (m, 1H), 6.07 (s, 2 H), 2.90 (s, 3 H)

Example 15: Preparation of 3-[(R)-ethylsulfinyl]-5-(trifluoromethyl)pyridine-2-carbonitrile



To a solution of 3-ethylsulfanyl-3-(trifluoromethyl)pyridine-2-carbonitrile (0.237 g, 98% purity, 1.00 mmol) in anisole (1.0 ml) was added (2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol) (28.5 mg, 97% purity, 0.073 mmol), 4-methoxybenzoic acid (5.3 mg, 0.034 mmol) and Fe(acac)$_3$ (3.4 mg, 0.010 mmol). The resulting dark red solution was cooled to 10 °C and 30% aq H_2O_2 (0.136 ml, 1.6 mmol) was added. The resulting biphasic mixture was stirred at 10 °C for 22 h. At this stage (full conversion of starting material) the reaction was quenched by addition of crushed ice (4 g) and 40% aq $NaHSO_3$ (0.30 ml). After warming to ambient temperature, the mixture was diluted with EtOAc (10 ml) and treated with conc. H_2SO_4 (50 µl). After stirring for 30 min phases were separated and the aqueous layer was again extracted with EtOAc (15 ml). The combined organic layer was washed with sat. aq. $NaHCO_3$ (8 ml) and brine (8 ml). The organic layer was dried over anhydrous $MgSO_4$ concentrated under reduced pressure.

The crude material was purified by flash column chromatography (Cyclohexane / EtOAc 100:0 to 60:40) to yield the title compound (127 mg, 98% purity, >99% ee, 50% yield) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 - 1.40 (m, 3 H), 2.95 - 3.09 (m, 1 H), 3.21 - 3.37 (m, 1 H) 8.65 (d, *J*=1.45 Hz, 1 H), 9.06 (d, *J*=1.09 Hz, 1 H)

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.80 (s, 3 F)

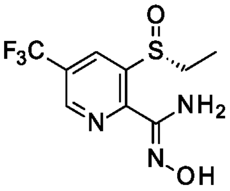
Chiral SFC method

SFC:Waters Acquity UPC^2/QDa
PDA Detector Waters Acquity UPC^2
Column: Daicel SFC CHIRALPAK® IC, 3μm, 0.3cm x 10cm, 40°C
Mobile phase: A: CO_2 B: MeOH isocratic 3% B in 2 min
ABPR: 1800 psi
Flow rate: 2.0 ml/min
Detection: 270 nm
Sample concentration: 1 mg/mL in MeOH
Injection: 1 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.95	Retention time (min) ~ 1.26
Enantiomeric excess: >99 % (R enantiomer; S enantiomer below HPLC detection limits)	

Example 16: 3-[(*R*)-ethylsulfinyl]-*N*'-hydroxy-5-(trifluoromethyl)pyridine-2-carboxamidine

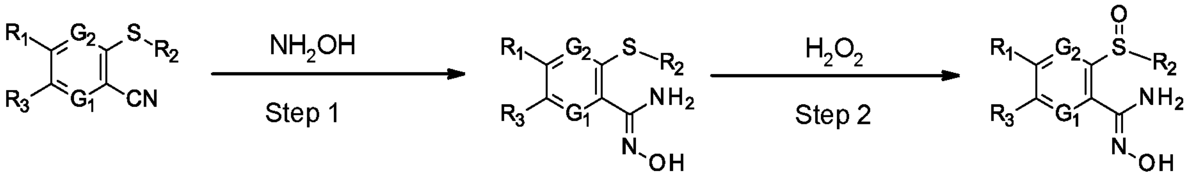


To a solution of 3-[(R)-ethylsulfinyl]-5-(trifluoromethyl)pyridine-2-carbonitrile (800 mg, 3.16 mmol) in EtOH (25 ml) was added 50% aq NH_2OH (300 μl, 4.9 mmol). The resulting colorless solution was stirred at ambient temperature for 14 h. The reaction mixture was then concentrated under reduced pressure to yield the title compound (892 mg, >99% yield) as a colorless solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 1.18 (t, *J*=7.45 Hz, 3 H) 2.98 - 3.13 (m, 1 H) 3.33 - 3.49 (m, 1 H) 5.68 (s, 2 H) 8.50 - 8.70 (m, 1 H) 8.73 (d, *J*=1.8 Hz, 1 H) 8.91 (d, *J*=1.1 Hz, 1 H)

^{19}F NMR (376 MHz, CDCl$_3$) δ -62.27 (s, 3 F)

Method B:

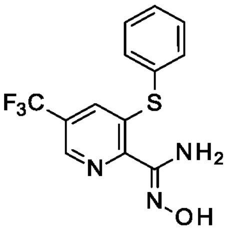


According to method B the steps are reversed with amidine oxime being formed first by addition of hydroxylamine to a functionalized nitrile followed by oxidation of sulfide with hydrogen peroxide.

General procedure Step 1: To a solution of starting nitrile in EtOH (2 ml/mmol) was added a 50% aq NH$_2$OH (1.1 eq). The reaction mixture was stirred at ambient temperature until a full consumption of starting material. The reaction mixture was then evaporated to dryness and the desired product purified either by trituration with diisopropyl ether or via silica gel chromatography.'

Compounds prepared by this method:

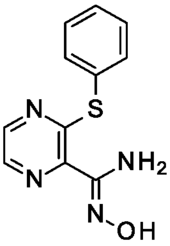
Example 17: N'-hydroxy-3-phenylsulfanyl-5-(trifluoromethyl)pyridine-2-carboxamidine



Isolated in 99% yield as an off white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.57 (s, 1 H), 8.68 (d, *J* = 1.1 Hz, 1 H), 7.57-7.61 (m, 2 H), 7.52-7.56 (m, 3 H), 7.15 (d, *J* = 1.1 Hz, 1 H), 6.01 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 150.0, 148.3, 140.3, 136.7, 135.3, 131.7, 130.6 (q, *J* = 4.0 Hz), 130.5, 130.1, 124.3 (q, *J* = 32.9 Hz), 123.4 (q, *J* = 273.0 Hz)

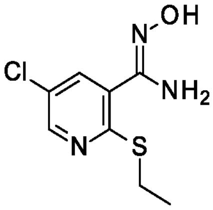
Example 18: N-hydroxy-3-phenylsulfanyl-pyrazine-2-carboxamidine



Isolated as an off-white solid in 78% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (br s, 1 H), 8.33 (br s, 1 H), 8.28 (br s, 1 H), 7.38-7.51 (m, 5 H), 5.96 (br s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.8, 149.2, 142.6, 141.8, 138.2, 135.4, 131.3, 129.1, 128.8

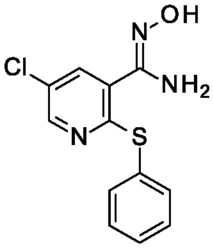
Example 19: 5-chloro-2-ethylsulfanyl-N-hydroxy-pyridine-3-carboxamidine



Isolated as an off-white solid in 76% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1 H), 8.51 (d, J = 2.2 Hz, 1 H), 7.78 (d, J = 2.2 Hz, 1 H), 5.90 (br s, 2 H), 3.03 (q, J = 7.3 Hz, 2 H), 1.22 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4, 148.4, 146.8, 135.4, 129.3, 126.0, 24.4, 14.1

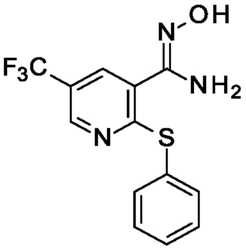
Example 20: 5-chloro-N-hydroxy-2-phenylsulfanyl-pyridine-3-carboxamidine



Isolated as an off-white solid in 91% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1 H), 8.34 (d, *J* = 2.2 Hz, 1 H), 7.90 (d, *J* = 2.2 Hz, 1 H), 7.37-7.47 (m, 5 H), 6.06 (br s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.0, 148.5, 147.2, 135.7, 134.8, 131.8, 129.1, 128.5, 127.2 (overlap of two signals)

Example 21: N-hydroxy-2-phenylsulfanyl-5-(trifluoromethyl)pyridine-3-carboxamidine



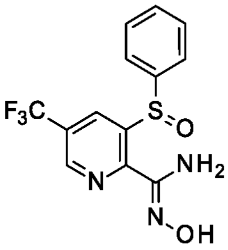
Isolated as an off-white solid in 98% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1 H), 8.64 (d, *J* = 2.2 Hz, 1 H), 8.09 (d, *J* = 2.2 Hz, 1 H), 7.47-7.42 (m, 2 H), 7.39-7.45 (m, 3 H), 6.15 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.8, 148.5, 145.3 (q, *J* = 4.0 Hz), 135.2, 132.8 (q, *J* = 4.0 Hz), 131.0, 129.2, 128.9, 127.5, 121.2 (q, *J* = 32.6 Hz), 123.4 (q, *J* = 272.3 Hz)

General procedure step 2: To a solution of amidine oxime prepared in Step 1 in acetic acid (2 ml/mmol) was added $Na_2WO_4.2H_2O$ (5 mol%) and 30% aq H_2O_2 (1.1 eq). The reaction mixture was then stirred at ambient temperature till a full consumption of starting material. The reaction mixture was quenched by neutralizing with aq saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc (3x). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield the desired sulfoxide. The crude product was either used without further purification or purified via a silica gel chromatography.

Compounds prepared by this method:

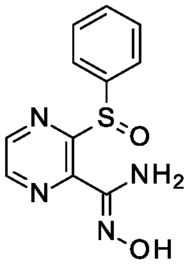
Example 22: 3-(benzenesulfinyl)-N'-hydroxy-5-(trifluoromethyl)pyridine-2-carboxamidine



Isolated in 93% yield as a white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.74 (s, 1 H), 9.10 (d, *J* = 1.1 Hz, 1 H), 8.81 (d, *J* = 1.1 Hz, 1 H), 7.71-7.80 (m, 2 H), 7.39-7.48 (m, 3 H), 6.08 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 149.9, 148.2, 146.5 (q, *J* = 4.0 Hz), 146.3, 142.2, 130.9, 130.2 (q, *J* = 3.8 Hz), 128.9, 126.6, 125.5 (q, *J* = 33.2 Hz), 123.3 (q, *J* = 273.3 Hz)

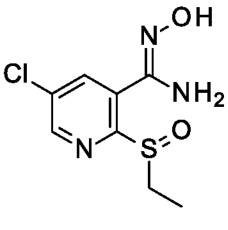
Example 23: 3-(benzenesulfinyl)-N-hydroxy-pyrazine-2-carboxamidine



Isolated in 81% yield as a white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.67 (s, 1 H), 8.84 (br s, 1 H), 8.74 (br s, 1 H), 7.94 (br d, *J* = 4.4 Hz, 2 H), 7.44 (br s, 3 H), 6.11 (br s, 2 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 158.8, 147.9, 145.6, 144.8, 144.3, 143.8, 130.7, 128.7, 126.2

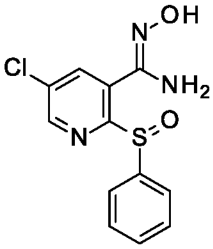
Example 24: 5-chloro-2-ethylsulfinyl-N'-hydroxy-pyridine-3-carboxamidine



Isolated in 86% yield as a white solid

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (br s, 1 H), 8.83 (br s, 1 H), 8.19 (br s, 1 H), 6.21 (br s, 2 H), 3.12 (br s, 1 H), 2.86 (br s, 1 H), 1.20 (br s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.0, 148.4, 147.1, 135.7, 132.1, 129.9, 48.2, 7.3

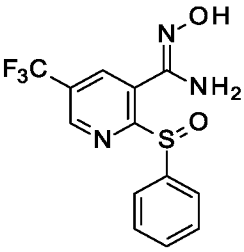
Example 25: 2-(benzenesulfinyl)-5-chloro-N'-hydroxy-pyridine-3-carboxamidine



Isolated in 87% yield as a white solid

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (br s, 1 H), 8.77 (d, J = 2.5 Hz, 1 H), 8.18 (d, J = 2.5 Hz, 1 H), 7.91 (dd, J = 7.8, 1.6 Hz, 2 H), 7.43-7.51 (m, 3 H), 6.29 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.4, 149.0, 147.1, 145.2, 136.1, 132.2, 130.5, 130.1, 128.7, 125.6

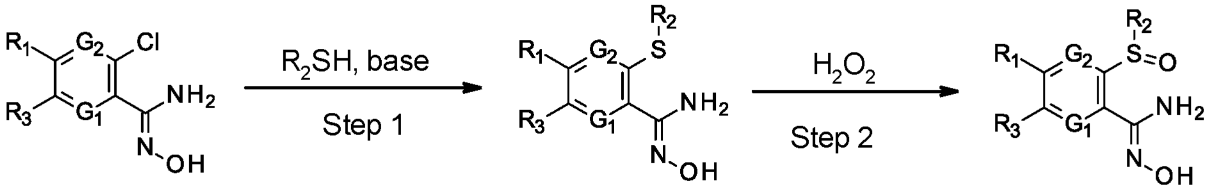
Example 26: 2-(benzenesulfinyl)-N'-hydroxy-5-(trifluoromethyl)pyridine-3-carboxamidine



Isolated in 94% yield as a white solid

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1 H), 9.14 (d, *J* = 1.5 Hz, 1 H), 8.43 (d, *J* = 1.5 Hz, 1 H), 7.91-8.00 (m, 2 H), 7.44-7.51 (m, 3 H), 6.38 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 147.2, 147.0 (q, *J* = 3.3 Hz), 145.0, 134.2 (q, *J* = 3.0 Hz), 130.7, 128.9, 128.7, 125.9, 126.1 (q, *J* = 33.0 Hz), 122.9 (q, *J* = 273.3 Hz)

Method C:



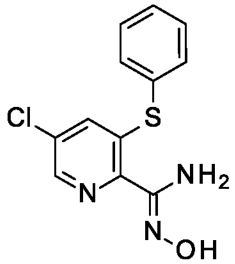
Method C was used specifically for compounds where G_1 = N, G_2 = CH, R_1 =Cl, R_3 = H and R_2 is as defined for a compound of formula (I). In this case starting amidine oxime is commercially available and could also be prepared as described in CN101029023. In the first step nucleophilic aromatic substitution with thiols in the presence of base produces corresponding sulfides which are oxidized using hydrogen peroxide as described for Method B.

General procedure Step 1: To a suspension of NaH (1.1-3.1 eq) in dry 2-methyl tetrahydrofuran (5 ml/mmol) was added the corresponding thiol (1.1-3.1 eq). After stirring for 10 min at ambient temperature heteroaryl hydroxylamine was added. The reaction mixture was stirred at 80 °C until the full conversion of starting material. The reaction was then cooled to ambient temperature and solvent was evaporated under reduced pressure. The residue was taken up in EtOAc and water. Phase were separated and aqueous phase extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over anhydrous

Na_2SO_4. Evaporation of the solvent under reduced pressure yielded a crude product. The crude product was further purified eitherby trituration with diisopropyl ether or by silica gel chromatography.

Compounds prepared by this method:

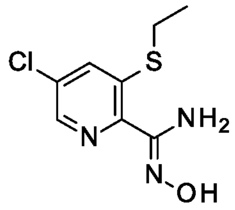
Example 27: 5-chloro-N'-hydroxy-3-phenylsulfanyl-pyridine-2-carboxamidine



Isolated as an off-white solid in 82% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1 H), 8.37 (d, *J* = 2.2 Hz, 1 H), 7.54 - 7.59 (m, 5 H), 6.90 (d, *J* = 2.2 Hz, 1 H), 5.88 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.9, 143.7, 142.4, 137.2, 135.2, 133.0, 131.9, 130.4, 130.4, 130.0

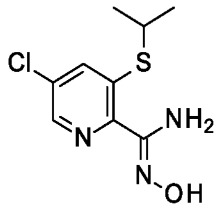
Example 28: 5-chloro-3-ethylsulfanyl-N'-hydroxy-pyridine-2-carboxamidine



Isolated as an off-white solid in 96% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (br s, 1 H), 8.35 (d, *J* = 1.8 Hz, 1 H), 7.77 (d, *J* = 1.8 Hz, 1 H), 5.76 (s, 2 H), 2.93 (q, *J* = 7.4 Hz, 2 H), 1.23 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.0, 144.6, 141.5, 136.5, 132.4, 130.6, 25.7, 12.6

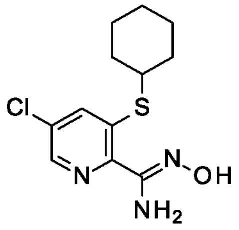
Example 29: 5-chloro-N'-hydroxy-3-isopropylsulfanyl-pyridine-2-carboxamidine



Isolated as an off-white solid in 78% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.12 (s, 1 H), 8.36 (d, *J* = 1.8 Hz, 1 H), 7.86 (d, *J* = 1.8 Hz, 1 H), 5.74 (s, 2 H), 3.65 (spt, *J* = 6.5 Hz, 1 H), 1.25 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 149.9, 145.6, 141.9, 135.6, 133.6, 130.5, 34.5, 22.0

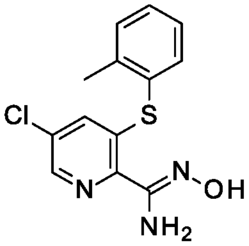
Example 30: 5-chloro-3-cyclohexylsulfanyl-N-hydroxy-pyridine-2-carboxamidine



Isolated as an off-white solid in 61% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.11 (s, 1 H), 8.35 (br s, 1 H), 7.86 (br s, 1 H), 5.73 (br s, 2 H), 3.37-3.52 (m, 1 H), 1.92 (br d, *J* = 10.9 Hz, 2 H), 1.69 (br d, *J* = 8.7 Hz, 2 H), 1.57-1.63 (m, 1 H), 1.37-1.48 (m, 2 H), 1.18-1.30 (m, 3 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 149.9, 145.7, 141.8, 135.1, 133.4, 130.5, 42.5, 32.0, 25.3, 25.2

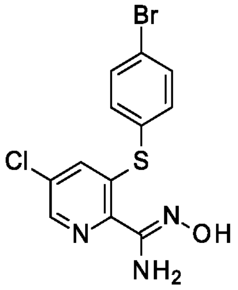
Example 31: 5-chloro-N-hydroxy-3-(o-tolylsulfanyl)pyridine-2-carboxamidine



Isolated as an off-white solid in 52% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.36 (s, 1 H), 8.37 (d, *J* = 2.2 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.48 (d, *J* = 4.0 Hz, 2 H), 7.33-7.38 (m, 1 H), 6.69 (d, *J* = 2.2 Hz, 1 H), 5.89 (s, 2 H), 2.27 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 150.0, 143.7, 142.2, 136.6, 136.4, 132.0, 131.4, 130.7, 130.7, 130.4, 127.9, 20.0 (overlap of two signals)

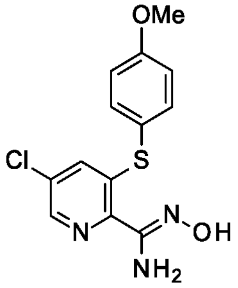
Example 32: 3-(4-bromophenyl)sulfanyl-5-chloro-N-hydroxy-pyridine-2-carboxamidine



Isolated as an off-white solid in 80% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.32 (s, 1 H), 8.40 (d, *J* = 2.2 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.00 (d, *J* = 2.2 Hz, 1 H), 5.89 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 149.8, 144.0, 142.8, 136.9, 136.3, 133.4’ 133.3, 131.6, 130.5, 123.5

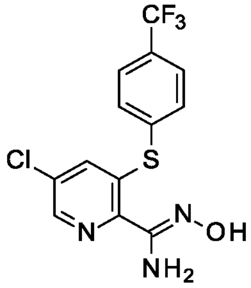
Example 33: 5-chloro-N'-hydroxy-3-(4-methoxyphenyl)sulfanyl-pyridine-2-carboxamidine



Isolated as a white solid in 25% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.30 (s, 1 H), 8.35 (d, *J* = 2.2 Hz, 1 H), 7.50 (d, *J* = 9.1 Hz, 2 H), 7.10 (d, *J* = 9.1 Hz, 2 H), 6.87 (d, *J* = 2.2 Hz, 1 H), 5.86 (s, 2 H), 3.83 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 160.6, 149.9, 143.3, 142.1, 138.3, 137.2, 132.4, 130.4, 121.9, 116.0, 55.4

Example 34: 5-chloro-N'-hydroxy-3-[4-(trifluoromethyl)phenyl]sulfanyl-pyridine-2-carboxamidine



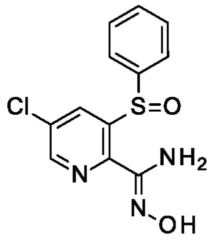
Isolated as an off-white solid in 42% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.32 (s, 1 H), 8.46 (d, *J* = 2.2 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 2.2 Hz, 1 H), 5.91 (br s, 2 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 149.8, 144.9, 143.5, 138.3, 135.0, 134.7, 134.5, 130.5, 129.4 (q, *J* = 31.9 Hz), 126.9 (q, *J* = 3.0 Hz), 123.9 (q, *J* = 272.3 Hz)

General procedure Step 2: Identical to the procedure described for Method B

Compounds prepared by this method:

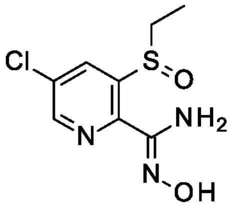
Example 35: 3-(benzenesulfinyl)-5-chloro-N'-hydroxy-pyridine-2-carboxamidine



Isolated as an off-white solid in 81% yield

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.55 (br s, 1 H), 8.62 (d, *J* = 2.5 Hz, 1 H), 8.53 (d, *J* = 2.5 Hz, 1 H), 7.71-7.79 (m, 2 H), 7.30-7.38 (m, 3 H), 5.45 (br s, 2 H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 149.2, 148.3, 145.5, 143.8, 142.9, 133.7, 133.1, 130.9, 129.0, 125.9

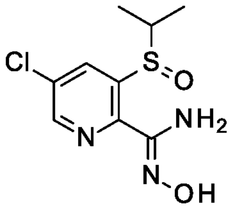
Example 36: 5-chloro-3-ethylsulfinyl-N'-hydroxy-pyridine-2-carboxamidine



Isolated as an off-white solid in 97% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.47 (s, 1 H), 8.76 (d, J = 2.5 Hz, 1 H), 8.23 (d, J = 2.5 Hz, 1 H), 6.04 (s, 2 H), 3.21-3.30 (m, 1 H), 2.76-2.86 (m, 1 H), 1.16 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 148.8, 147.9, 144.7, 141.9, 133.0, 131.6, 48.7, 6.6

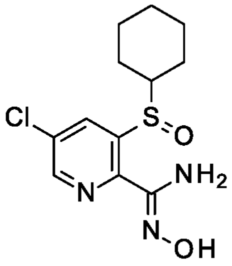
Example 37: 5-chloro-N'-hydroxy-3-isopropylsulfinyl-pyridine-2-carboxamidine



Isolated as a white solid in 99% yield

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.31 (br s, 1 H), 8.55 (d, J = 1.8 Hz, 1 H), 8.35 (d, J = 1.8 Hz, 1 H), 5.57 (br s, 2 H), 3.55 (dt, J = 13.5, 6.9 Hz, 1 H), 1.52 (br d, J = 7.3 Hz, 3 H), 0.89 (br d, J = 6.5 Hz, 3 H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 149.5, 148.0, 143.6, 140.2, 134.1, 133.1, 52.0, 18.5, 12.2

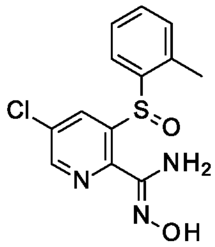
Example 38: 5-chloro-3-cyclohexylsulfinyl-N'-hydroxy-pyridine-2-carboxamidine



Isolated as a white solid in 76% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.48 (br s, 1 H), 8.74 (br s, 1 H), 8.10 (br s, 1 H), 6.03 (br s, 2 H), 3.14-3.25 (m, 1 H), 2.31 (br d, *J* = 10.9 Hz, 1 H), 1.83 (br d, *J* = 12.4 Hz, 1 H), 1.66-1.75 (m, 1 H), 1.48-1.62 (m, 2 H), 1.24-1.45 (m, 2 H), 1.04-1.17 (m, 2 H), 0.98 (br d, *J* = 11.6 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 148.8, 147.7, 144.7, 140.2, 133.3, 131.3, 58.6, 27.8, 25.8, 25.0, 24.6, 20.9

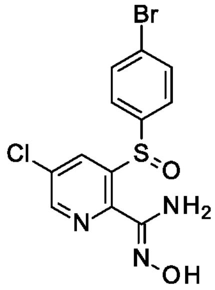
<u>Example 39</u>: 5-chloro-N'-hydroxy-3-(o-tolylsulfinyl)pyridine-2-carboxamidine



Isolated as a white solid in 55% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.09 (br s, 1 H), 8.83 (d, *J* = 2.2 Hz, 1 H), 8.52 (d, *J* = 2.2 Hz, 1 H), 7.30-7.35 (m, 2 H), 7.11-7.16 (m, 1 H), 6.82 (d, *J* = 7.6 Hz, 1 H), 5.91 (s, 2 H), 2.74 (s, 3 H); 13C NMR (101 MHz, DMSO-d6) δ 148.9, 148.2, 145.4, 145.1, 140.5, 137.9, 134.1, 131.8, 130.9, 130.9, 127.0, 125.1, 18.8

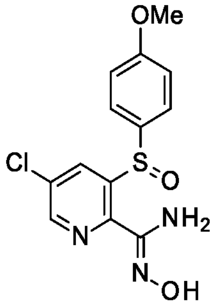
<u>Example 40</u>: 3-(4-bromophenyl)sulfinyl-5-chloro-N'-hydroxy-pyridine-2-carboxamidine



Isolated as a white solid in 83% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.53 (br s, 1 H), 8.76 (br s, 1 H), 8.51 (br s, 1 H), 7.74 (br d, J = 8.4 Hz, 2 H), 7.63 (br d, J = 8.4 Hz, 2 H), 5.99 (br s, 2 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 148.4, 148.1, 145.9, 144.8, 142.5, 132.4, 132.1, 131.8, 128.7, 124.4

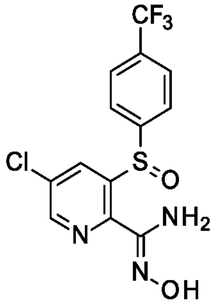
Example 41: 5-chloro-N'-hydroxy-3-(4-methoxyphenyl)sulfinyl-pyridine-2-carboxamidine



Isolated as a white solid in 93% yield

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.23 (br s, 1 H), 8.65 (d, J = 2.2 Hz, 1 H), 8.51 (d, J = 2.2 Hz, 1 H), 7.68 (d, J = 9.1 Hz, 2 H), 6.79 (d, J = 9.1 Hz, 2 H), 5.41 (s, 2 H), 3.73 (s, 3 H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.6, 149.0, 148.1, 143.9, 142.9, 136.1, 133.5, 132.7, 128.0, 114.4, 55.3

Example 42: 5-chloro-N'-hydroxy-3-[4-(trifluoromethyl)phenyl]sulfinyl-pyridine-2-carboxamidine

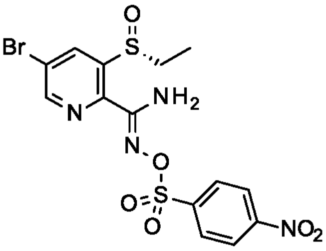


Isolated as a white solid in 75% yield

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.61 (br s, 1 H), 8.79 (d, J = 2.5 Hz, 1 H), 8.53 (d, J = 2.5 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 2 H), 7.79 (d, J = 8.0 Hz, 2 H), 6.02 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 151.2, 148.6, 148.1, 144.9, 142.1, 132.6, 132.2, 130.8 (q, *J* = 32.6 Hz), 127.5, 125.9 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 273.2 Hz)

Preparation of compounds of formula (IV), (V) and (I):

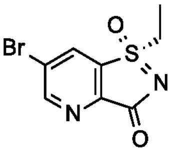
Example 43: Preparation of [(Z)-[amino-[5-bromo-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene] amino] 4-nitrobenzenesulfonate



To a solution of 5-bromo-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (0.611 g, 95% purity, 1.99 mmol) in THF (4.0 ml) was added Et_3N (0.33 ml, 2.39 mmol) followed by NsCl (0.488 g, 2.20 mmol). The reaction mixture was stirred for 3 h at ambient temperature. EtOAc (18 ml) was added and the resulting mixture was washed with water (3.5 ml), 1M aq HCl (2.5 ml), aq $NaHCO_3$ (3.5 ml) and brine (5 ml). Additional EtOAc (58 ml) was added to avoid precipitation. The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield the title compound (1.024 g) in a crude form. This material was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J=7.4 Hz, 3H), 2.85 (dq, *J*=13.35, 7.3 Hz, 1 H), 3.27 (dq, *J*=13.26, 7.4 Hz, 1 H), 5.62 (br s, 1 H), 6.61 (br s, 1 H), 8.21 - 8.29 (m, 2 H), 8.39 - 8.48 (m, 2 H), 8.62 (d, *J*=2.2 Hz, 1 H), 8.69 (d, *J*=2.2 Hz, 1 H).

Example 44: Preparation of (1R)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-one



The crude starting material (1.024 g) prepared in Example 43 was dissolved in a mixture of THF (8.0 ml) and water (2.0 ml). The resulting yellow solution was heated in a closed vial at 80 °C for 7 h. The reaction mixture was cooled to ambient temperature and diluted with brine (20 ml). Phases were separated and the aqueous phase was extracted with EtOAc (2 x 30 ml). The combined organic phase was washed with aq $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue (ca 0.49 g) was crystallized from THF (ca 4.5 ml). The precipitate was filtered, washed on filter with a minimum amount of cold THF and dried in vacuum to yield the title compound (0.329 g, 99% purity, >99.5% ee, 59% yield) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, *J*=7.3 Hz, 3 H), 3.63 - 3.95 (m, 2 H), 8.48 (d, *J*=1.8 Hz, 1 H), 9.16 (d, *J*=1.8 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.64, 49.12, 124.21, 133.71, 134.62, 152.07, 158.54, 168.07.

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa
PDA Detector Waters Acquity UPC^2
Column: Daicel SFC CHIRALPAK® AY, 3µm, 0.3cm x 10cm, 40°C
Mobile phase: A: CO_2 B: EtOH isocratic 30% B in 4.8 min
ABPR: 1800 psi
Flow rate: 2.0 ml/min
Detection: 240 nm
Sample concentration: 1 mg/mL in ACN
Injection: 1 µL
Results:

S enantiomer	R enantiomer
Retention time (min) ~ 1.27	Retention time (min) ~ 2.79
Enantiomeric excess (%) >99.5% (R enantiomer, S enantiomer below HPLC detection limits)	

A single crystal grown from di-isopropyl ether/acetonitrile was selected for X-ray data analysis. The crystal sample mounted had dimensions of 0.8 mm x 0.05 mm x 0.05 mm and was a colorless needle. Data collection was performed on a Rigaku Oxford Diffraction Supernova diffractometer at 293 K. The unit cell was determined to be orthorhombic (space group P212121), and the structure contained one molecule in the crystal asymmetric unit (Figure 2, a thin stick representation labelled by chirality). Figure generated in Flare software package (Cresset). The stereochemistry was unambiguously determined to be the R isomer, with a Flack parameter of -0.04 +/- 0.04. Crystallographic data is summarized in Table 3 and selected geometric parameters are listed in Table 4.

Table 3. Crystal data and structure refinement for (1R)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-one

Crystal data	
Chemical formula	$C_8H_7BrN_2O_2S$
M_r	275.13
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	293
a, *b*, *c* (Å)	7.00005 (17), 8.3741 (2), 17.2042 (4)
V ($Å^3$)	1008.50 (4)
Z	4
Radiation type	Cu *K*α
μ (mm^{-1})	7.32
Crystal size (mm)	0.80 × 0.05 × 0.05
Data collection	
Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan *CrysAlis PRO*, (Agilent, 2011)
T_{min}, T_{max}	0.69, 0.69
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	4239, 2088, 1965
R_{int}	0.030
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.632
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.040, 0.113, 0.99
No. of reflections	2080
No. of parameters	129
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.56, −0.57
Absolute structure	Flack (1983), 840 Friedel-pairs
Absolute structure parameter	−0.04 (4)

Computer programs: SuperNova, (Oxford Diffraction, 2010), CrysAlis PRO, (Agilent, 2011), SIR92 (Altomare et al., 1994), CRYSTALS (Betteridge et al., 2003), CAMERON (Watkin et al., 1996)

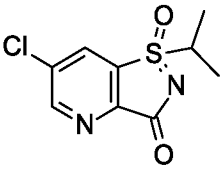
Table 4. Selected geometric parameters (Å, º)

Br1—C2	1.886 (5)	S5—C13	1.769 (4)
C2—C3	1.374 (6)	N7—C8	1.383 (6)
C2—C11	1.390 (7)	C8—C9	1.522 (6)
C3—C4	1.389 (6)	C8—O12	1.193 (6)

C4—S5	1.773 (4)	C9—N10	1.327 (6)
C4—C9	1.368 (6)	N10—C11	1.343 (7)
S5—O6	1.439 (4)	C13—C14	1.500 (7)
S5—N7	1.582 (3)		
Br1—C2—C3	119.7 (4)	N7—S5—C13	106.8 (2)
Br1—C2—C11	118.9 (4)	S5—N7—C8	111.5 (3)
C3—C2—C11	121.4 (4)	N7—C8—C9	111.2 (3)
C2—C3—C4	113.9 (4)	N7—C8—O12	125.0 (5)
C3—C4—S5	132.0 (3)	C9—C8—O12	123.7 (5)
C3—C4—C9	121.8 (4)	C8—C9—C4	112.4 (4)
S5—C4—C9	105.8 (3)	C8—C9—N10	122.9 (4)
C4—S5—O6	112.6 (2)	C4—C9—N10	124.6 (5)
C4—S5—N7	98.5 (2)	C9—N10—C11	114.4 (4)
O6—S5—N7	117.9 (2)	C2—C11—N10	123.9 (4)
C4—S5—C13	109.7 (2)	S5—C13—C14	112.9 (3)
O6—S5—C13	110.6 (2)		

X-ray data presented above allow us to determine by analogy that compounds of formula (I) derived from a sulfoxide enantioenriched in R isomer are also enantioenriched in R isomer and thus the overall process proceeds via retention of stereochemistry. Compounds of formula (I) enantioenriched in S isomer could then be obtained by starting from sulfoxides enantioenriched in S isomer.

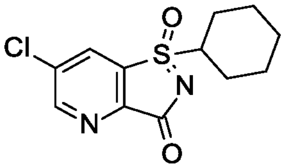
Example 45: 6-chloro-1-isopropyl-1-oxo-isothiazolo[4,5-b]pyridin-3-one



To a solution of 5-chloro-N'-hydroxy-3-isopropylsulfinyl-pyridine-2-carboxamidine (222 mg, 95% purity, 0.806 mmol) in tetrahydrofuran (2.5 ml) was added Et_3N (0.12 ml, 0.886 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.241 g, 0.886 mmol). The reaction was stirred at ambient temperature for 5 h (full conversion of starting material by LC/MS). Water (0.8 ml) was added, and the resulting mixture was stirred for further 48 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (195 mg, 72% purity, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 1.8 Hz, 1 H), 8.26 (d, *J* = 1.8 Hz, 1 H), 3.86 (spt, *J* = 6.9 Hz, 1 H), 1.56 (d, *J* = 6.9 Hz, 3 H), 1.50 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 156.6, 152.3, 135.8, 133.9, 131.5, 56.8, 16.4, 15.8

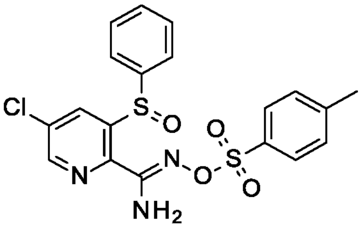
<u>Example 46</u>: 6-chloro-1-cyclohexyl-1-oxo-isothiazolo[4,5-b]pyridin-3-one



To a solution of 5-chloro-3-cyclohexylsulfinyl-N'-hydroxy-pyridine-2-carboxamidine (200 mg, 97% purity, 0.643 mmol) in tetrahydrofuran (1.9 ml) was added Et_3N (0.10 ml, 0.707 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.192 g, 0.707 mmol). The reaction was stirred at ambient temperature for 8 h (full conversion of starting material by LC/MS). Water (0.6 ml) was added, and the resulting mixture was stirred for further 48 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (180 mg, 77% purity, 76% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (br s, 1 H), 9.00-9.12 (m, 1 H), 4.14 (br t, *J* = 11.4 Hz, 1 H), 2.21 (br d, *J* = 11.4 Hz, 1 H), 1.75-1.91 (m, 3 H), 1.58-1.68 (m, 1 H), 1.13-1.53 (m, 5 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 155.9, 151.1, 134.6, 133.7, 133.1, 61.3, 25.0, 24.4, 24.4, 24.2, 24.1

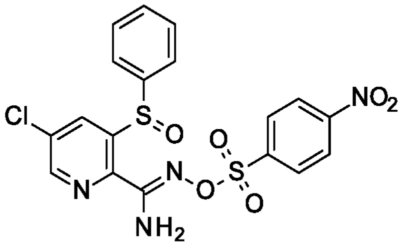
<u>Example 47</u>: [(Z)-[amino-[3-(benzenesulfinyl)-5-chloro-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate



To a solution of 3-(benzenesulfinyl)-5-chloro-N'-hydroxy-pyridine-2-carboxamidine (1.20 g, 88% purity, 3.57 mmol) in dichloromethane (18 ml) was added Et_3N (0.55 ml, 3.93 mmol) and p-toluenesulfonyl chloride (0.764 g, 3.93 mmol). The reaction mixture was stirred at ambient temperature for 2 h and then quenched by addition of aq saturated $NaHCO_3$. Phases were separated, aqueous phase extracted with dichlormethane and the combined organic layers dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure yielded the title compound (1.83 g, 83% purity, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.2 Hz, 1 H), 8.48 (d, *J* = 2.2 Hz, 1 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 7.62-7.67 (m, 2 H), 7.31-7.40 (m, 3 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 5.40-6.65 (m, 2 H), 2.35 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 148.6, 145.4, 145.3, 145.0, 140.9, 135.6, 133.4, 132.1, 130.9, 129.5, 129.0, 128.9, 125.6, 21.5

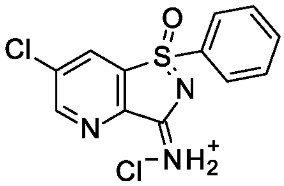
Example 48: [(Z)-[amino-[3-(benzenesulfinyl)-5-chloro-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate



To a solution of 3-(benzenesulfinyl)-5-chloro-N'-hydroxy-pyridine-2-carboxamidine (300 mg, 92% purity, 0.933 mmol) in dichloromethane (5.0 ml) was added Et_3N (0.14 ml, 1.03 mmol) and 4-nitrobenzenesulfonyl chloride (0.235 g, 1.03 mmol). The reaction mixture was stirred at ambient temperature for 40 min and then quenched by addition of aq saturated $NaHCO_3$. Phases were separated, aqueous phase extracted with dichlormethane and the combined organic layers dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure yielded the title compound (433 mg, 82% purity, 79% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (d, *J* = 2.2 Hz, 1 H), 8.35 (d, *J* = 9.1 Hz, 2 H), 8.30 (d, *J* = 2.2 Hz, 1 H), 8.18 (d, *J* = 8.7 Hz, 2 H), 7.32-7.63 (m, 7 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.1, 150.5, 149.8, 145.0, 144.7, 142.7, 140.7, 134.5, 133.0, 131.1, 130.0, 129.2, 125.3, 124.5

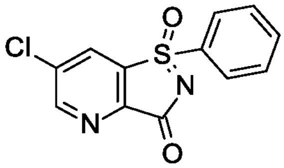
Example 49: (6-chloro-1-oxo-1-phenyl-isothiazolo[4,5-b]pyridin-3-ylidene)ammonium chloride



To a solution of 3-(benzenesulfinyl)-5-chloro-N'-hydroxy-pyridine-2-carboxamidine (1.12 g, 95% purity, 3.60 mmol) in dichloromethane (11 ml) was added Et_3N (0.53 ml, 3.78 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (1.03 g, 3.78 mmol). The reaction was stirred at ambient temperature for 16 h. The resulting precipitate was filtered, washed on filter with dry dichloromethane and dried under high vacuum to yield the title compound (0.925 g, >99% purity, 82% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (br s, 2 H), 9.48 (d, *J* = 1.1 Hz, 1 H), 9.33-9.39 (m, 1 H), 8.28 (br d, *J* = 8.0 Hz, 2 H), 7.99 (t, *J* = 8.0 Hz, 1 H), 7.82 (t, *J* = 8.0 Hz, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 156.0, 147.4, 137.2, 136.5, 135.3, 133.7, 130.6, 130.1, 129.3

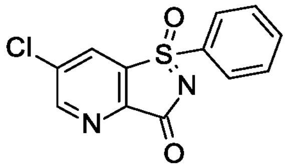
Example 50a: 6-chloro-1-oxo-1-phenyl-isothiazolo[4,5-b]pyridin-3-one



To a solution of 3-(benzenesulfinyl)-5-chloro-N'-hydroxy-pyridine-2-carboxamidine (1.050 g, 95% purity, 3.37 mmol) in tetrahydrofuran (10 ml) was added Et_3N (0.52 ml, 3.71 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (1.01 g, 3.71 mmol). The reaction was stirred first at ambient temperature for 30 min and then at 50 °C for 2 h (full conversion of starting material). Water (3.4 ml) and 4% aq HCl (0.05 ml) were added, and the resulting mixture was stirred for further 2 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (1.11 g, 83% purity, 98% yield). A higher purity (97%) material could be obtained by trituration with as small amount of EtOAc, filtration of the precipitate and drying under high vacuum.

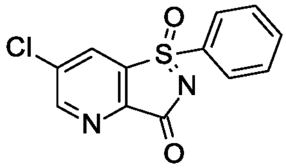
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 1.8 Hz, 1 H), 7.98-8.11 (m, 3 H), 7.82 (br t, *J* = 7.4 Hz, 1 H), 7.65-7.72 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 155.9, 149.6, 138.5, 136.0, 135.7, 132.8, 130.5, 130.3, 129.0

Example 50b: 6-chloro-1-oxo-1-phenyl-isothiazolo[4,5-b]pyridin-3-one



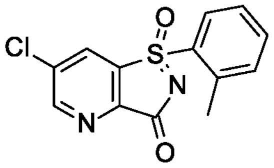
A solution of [(Z)-[amino-[3-(benzenesulfinyl)-5-chloro-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate (1.30 g, 87% purity, 2.51 mmol) in a mixture of THF (25 ml) and water (5 ml) was heated at 80 °C for six days (full conversion of starting material by LC/MS). The reaction mixture was cooled to ambient temperature and quenched by addition of aqueous saturated $NaHCO_3$. The resulting mixture was extracted with dichloromethane (3x). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded the title compound (0.679 g, 88% purity, 85% yield) as an off-white solid.

Example 50c: 6-chloro-1-oxo-1-phenyl-isothiazolo[4,5-b]pyridin-3-one



A solution of [(Z)-[amino-[3-(benzenesulfinyl)-5-chloro-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate (235 mg, 82% purity, 0.40 mmol) in a mixture of THF (1.2 ml) and water (0.4 ml) was heated at 80 °C for 16 h (ca 96% conversion). The reaction mixture was cooled to ambient temperature and quenched by addition of aqueous saturated $NaHCO_3$. The resulting mixture was extracted with dichloromethane (3x). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded the title compound (160 mg, 66% purity, 95% yield) as an off-white solid.

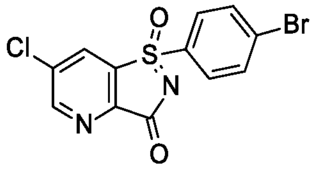
Example 51: 6-chloro-1-(o-tolyl)-1-oxo-isothiazolo[4,5-b]pyridin-3-one



To a solution of 5-chloro-N'-hydroxy-3-(o-tolylsulfinyl)pyridine-2-carboxamidine (140 mg, 95% purity, 0.429 mmol) in tetrahydrofuran (1.3 ml) was added Et_3N (0.066 ml, 0.47 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.128 g, 0.47 mmol). The reaction was stirred at ambient temperature for 8 h (full conversion of starting material by LC/MS). Water (0.4 ml) and one drop of 4% aq HCl was added (pH <2), and the resulting mixture was stirred for further 16 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (136 mg, 81% purity, 88% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (br s, 1 H), 8.96-9.12 (m, 1 H), 8.10 (br d, J = 7.3 Hz, 1 H), 7.78 (br s, 1 H), 7.49-7.69 (m, 2 H), 2.41 (br s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.4, 156.1, 149.8, 138.9, 136.9, 136.0, 135.2, 133.9, 132.3, 130.6, 130.6, 127.8, 19.7

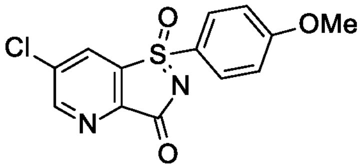
Example 52: 1-(4-bromophenyl)-6-chloro-1-oxo-isothiazolo[4,5-b]pyridin-3-one



To a solution of 3-(4-bromophenyl)sulfinyl-5-chloro-N'-hydroxy-pyridine-2-carboxamidine (250 mg, 95% purity, 0.634 mmol) in tetrahydrofuran (1.9 ml) was added Et_3N (0.10 ml, 0.70 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.189 g, 0.70 mmol). The reaction was stirred at ambient temperature for 8 h (full conversion of starting material by LC/MS). Water (0.6 ml) was added, and the resulting mixture was stirred for further 16 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (230 mg, 77% purity, 78% yield).

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.00 (d, *J* = 1.8 Hz, 1 H), 8.07 (d, *J* = 1.8 Hz, 1 H), 7.87-7.92 (m, 2 H), 7.80-7.85 (m, 2 H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 168.6, 156.1, 149.5, 138.1, 135.8, 133.9, 132.2, 131.8, 130.4, 130.3

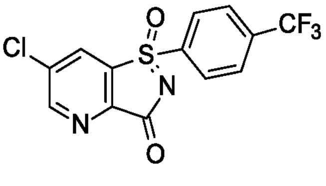
Example 53: 6-chloro-1-(4-methoxyphenyl)-1-oxo-isothiazolo[4,5-b]pyridin-3-one



To a solution of 5-chloro-N'-hydroxy-3-(4-methoxyphenyl)sulfinyl-pyridine-2-carboxamidine (174 mg, 95% purity, 0.507 mmol) in tetrahydrofuran (1.5 ml) was added Et$_3$N (0.078 ml, 0.56 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.151 g, 0.56 mmol). The reaction was stirred at ambient temperature for 8 h (full conversion of starting material by LC/MS). Water (0.5 ml) was added, and the resulting mixture was stirred for further 16 h. The reaction was then quenched by addition of aq NaHCO$_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (142 mg, 82% purity, 74% yield).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.13 (d, *J* = 2.2 Hz, 1 H), 9.05 (d, *J* = 2.2 Hz, 1 H), 8.04-8.09 (m, 2 H), 7.24-7.29 (m, 2 H), 3.89 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 168.7, 165.3, 155.5, 148.9, 138.3, 134.9, 131.7, 131.6, 122.4, 115.8, 56.2

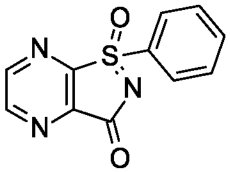
Example 54: 6-chloro-1-oxo-1-[4-(trifluoromethyl)phenyl]isothiazolo[4,5-b]pyridin-3-one



To a solution of 5-chloro-N'-hydroxy-3-[4-(trifluoromethyl)phenyl]sulfinyl-pyridine-2-carboxamidine (180 mg, 95% purity, 0.470 mmol) in tetrahydrofuran (1.4 ml) was added Et$_3$N (0.073 ml, 0.52 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.141 g, 0.52 mmol). The reaction was stirred at ambient temperature for 7 h (full conversion of starting material by LC/MS). Water (0.5 ml) and few drops of 4% aq HCl were added (pH <2), and the resulting mixture was stirred for further 16 h. The reaction was then quenched by addition of aq NaHCO$_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (172 mg, 84% purity, 89% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (d, *J* = 1.5 Hz, 1 H), 9.15 (d, *J* = 1.5 Hz, 1 H), 8.39 (d, *J* = 8.4 Hz, 2 H), 8.13 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 156.0, 149.7, 137.2, 136.8, 135.0, 135.1 (q, *J* = 32.6 Hz), 132.5, 130.4, 127.4 (q, *J* = 4.0 Hz), 123.1 (q, *J* = 273.9 Hz)

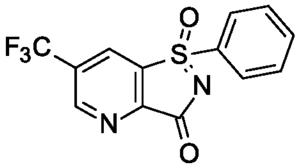
Example 55: 1-oxo-1-phenyl-isothiazolo[4,5-b]pyrazin-3-one



To a solution of 3-(benzenesulfinyl)-N-hydroxy-pyrazine-2-carboxamidine (250 mg, 95% purity, 0.905 mmol) in tetrahydrofuran (2.7 ml) was added Et_3N (0.14 ml, 1.0 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.271 g, 1.0 mmol). The reaction mixture was stirred at 50 °C for 16 h (full conversion of starting material by LC/MS). Water (0.9 ml) and few drops of 4% aq HCl were added (pH <2) and the resulting mixture was stirred at 50 °C for further 7 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by a reverse phase silica gel chromatography to yield the title compound as an off-white solid (167 mg, >99% purity, 75% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (d, *J* = 2.2 Hz, 1 H), 9.00 (d, *J* = 2.2 Hz, 1 H), 8.15 (d, *J* = 7.4 Hz, 2 H), 7.93 (t, *J* = 7.4 Hz, 1 H), 7.78 (t, *J* = 7.4 Hz, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.5, 155.2, 151.0, 148.0, 145.4, 136.4, 130.6, 130.6, 129.6

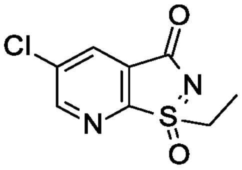
Example 56: 1-oxo-1-phenyl-6-(trifluoromethyl)isothiazolo[4,5-b]pyridin-3-one



To a solution of 3-(benzenesulfinyl)-N'-hydroxy-5-(trifluoromethyl)pyridine-2-carboxamidine (515 mg, 99% purity, 1.55 mmol) in tetrahydrofuran (4.6 ml) was added Et_3N (0.24 ml, 1.70 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.463 g, 1.70 mmol). The reaction was stirred at 60 °C for 8 h (full conversion of starting material by LC/MS). Water (1.5 ml) and few drops of 4% aq HCl were added (pH <2), and the resulting mixture was stirred for further 16 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound as an off-white solid (540 mg, 86% purity, 96% yield).

^1H NMR (400 MHz, DMSO-d_6) δ 9.54 (d, *J* = 1.1 Hz, 1 H), 9.45 (d, *J* = 1.1 Hz, 1 H), 8.16-8.23 (m, 2 H), 7.88-7.93 (m, 1 H), 7.73-7.80 (m, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.4, 154.3, 154.2 (q, *J* = 3.3 Hz), 136.6, 136.1, 132.3, 131.1 (q, *J* = 3.5 Hz), 130.3, 129.3, 127.6 (q, *J* = 33.9 Hz), 122.8 (q, *J* = 273.8 Hz)

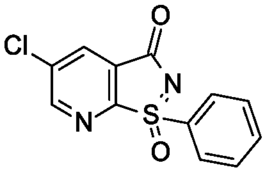
Example 57: 5-chloro-1-ethyl-1-oxo-isothiazolo[5,4-b]pyridin-3-one



To a solution of 5-chloro-2-ethylsulfinyl-N'-hydroxy-pyridine-3-carboxamidine (400 mg, 95% purity, 1.53 mmol) in tetrahydrofuran (4.6 ml) was added Et_3N (0.24 ml, 1.70 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.412 g, 1.69 mmol). The reaction was stirred at 50 °C for 4 h (full conversion of starting material by LC/MS). Water (1.5 ml) and few drops of 4% aq HCl were added (pH <2), and the resulting mixture was stirred for further 48 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by a reverse phase HPLC (5-20% MeCN in water) to yield the title compound (145 mg, >99% purity, 41% yield).

^1H NMR (400 MHz, DMSO-d_6) δ 9.12 (d, *J* = 2.2 Hz, 1 H), 8.59 (d, *J* = 2.2 Hz, 1 H), 3.96-4.12 (m, 2 H), 1.33 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 156.8, 153.0, 137.7, 134.0, 130.9, 46.3, 7.0

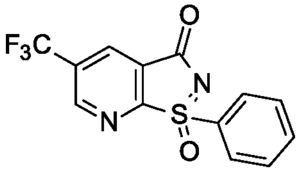
Example 58: 5-chloro-1-oxo-1-phenyl-isothiazolo[5,4-b]pyridin-3-one



To a solution of 2-(benzenesulfinyl)-5-chloro-N'-hydroxy-pyridine-3-carboxamidine (400 mg, 86% purity, 1.53 mmol) in tetrahydrofuran (3.4 ml) was added Et_3N (0.18 ml, 1.25 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.305 g, 1.25 mmol). The reaction was stirred at 50 °C for 6 h (full conversion of starting material by LC/MS). Water (1.1 ml) and few drops of 4% aq HCl were added (pH <2), and the resulting mixture was stirred for further 16 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by a reverse phase silica gel chromatography (10-100% MeCN in water) to yield the title compound (151 mg, 90% purity, 43% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 2.2 Hz, 1 H), 8.32 (d, J = 2.2 Hz, 1 H), 8.10 (d, J = 7.6 Hz, 2 H), 7.80 (t, J = 7.6 Hz, 1 H), 7.67 (t, J = 7.6 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 159.8, 153.1, 138.2, 135.9, 133.9, 131.5, 130.2, 129.5, 129.2

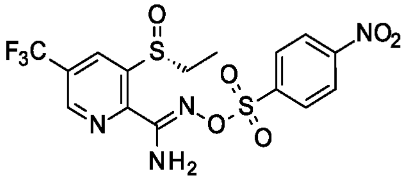
Example 59: 1-oxo-1-phenyl-5-(trifluoromethyl)isothiazolo[5,4-b]pyridin-3-one



To a solution of 2-(benzenesulfinyl)-N'-hydroxy-5-(trifluoromethyl)pyridine-3-carboxamidine (200 mg, 98% purity, 0.595 mmol) in tetrahydrofuran (1.8 ml) was added Et_3N (0.094 ml, 0.67 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (0.182 g, 0.67 mmol). The reaction was stirred at 50 °C for 4 h (full conversion of starting material by LC/MS). Water (0.6 ml) and few drops of 4% aq HCl were added (pH <2), and the resulting mixture was stirred for further 6 h. The reaction was then quenched by addition of aq $NaHCO_3$ and the resulting mixture was extracted with EtOAc (3x). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by a reverse phase silica gel chromatography (10-100% MeCN in water) to yield the title compound (129 mg, 97% purity, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 1.1 Hz, 1 H), 8.61 (d, *J* = 1.1 Hz, 1 H), 8.09-8.14 (m, 2 H), 7.83 (t, *J* = 7.4 Hz, 1 H), 7.66-7.72 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 165.0, 151.3, 136.2, 132.2 (q, *J* = 3.0 Hz), 130.8, 131.4 (q, *J* = 33.9 Hz), 130.3, 129.7, 127.7, 122.2 (q, *J* = 274.3 Hz)

Example 60: Preparation of [(*Z*)-[amino-[3-[(*R*)-ethylsulfinyl]-5-(trifluoromethyl)-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate

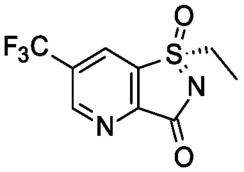


To a solution of 3-[(R)-ethylsulfinyl]-N'-hydroxy-5-(trifluoromethyl)pyridine-2-carboxamidine (880 mg, 3.13 mmol) in THF (10 ml) was added Et_3N (523 µl, 3.75 mmol) followed by nosyl chloride (763 mg, 3.44 mmol). The reaction was stirred at room temperature for 7 h before being diluted with water (20 ml) and EtOAc (15 ml). Phases were separated and aqueous phase extracted with EtOAc (2 x 15 ml). The combined organic phase was washed with 1N aq. HCl (20 ml) and brine (20 ml). Drying over anhydrous $MgSO_4$ and concentration under reduced pressure yielded the title compound (1.32 g, 91% yield) as a colorless foam.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05 (t, *J* = 7.45 Hz, 3 H) 2.64 - 2.84 (m, 1 H) 2.92 - 3.13 (m, 1 H) 7.42 - 8.07 (m, 2 H) 8.27 (d, *J* = 8.7 Hz, 2 H) 8.42 - 8.55 (m, 3 H) 9.18 (d, *J* = 1.1 Hz, 1 H)

^{19}F NMR (376 MHz, DMSO-d_6) δ -61.22 (s, 3 F)

Example 61: Preparation of (1R)-1-ethyl-1-oxo-6-(trifluoromethyl)isothiazolo[4,5-b]pyridine-3-one



A solution of [(*Z*)-[amino-[3-[(*R*)-ethylsulfinyl]-5-(trifluoromethyl)-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate (200 mg, 0.43 mmol) in THF (2.14 ml) and water (0.643 ml) was heated to 65°C for 22 h. After cooling down the reaction mixture was diluted with EtOAc (20 ml). The organic layer was washed with 1N aq. NaOH (10 ml) and brine (15 ml). After drying over anhydrous $MgSO_4$ it was concentrated under reduced pressure. The crude material was purified by silica gel chromatography (EtOAc 20 to 100% in cyclohexane) to yield the title compound (21 mg, >99% ee, 19% yield) as colorless crystals.

^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (t, *J*=7.3 Hz, 4 H) 4.14 (dd, *J*=7.3, 4.00 Hz, 1 H) 9.45 (d, *J*=1.45 Hz, 1 H) 9.55 - 9.59 (m, 1 H)

^{19}F NMR (376 MHz, DMSO-d_6) δ -60.35 (s, 3 F)

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IC, 3μm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: MeOH gradient: 20-60% B in 2 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 270 nm

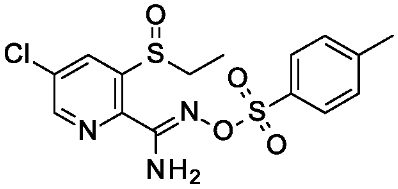
Sample concentration: 1 mg/mL in ACN

Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.81	Retention time (min) ~ 1.23
Enantiomeric excess: >99% (R enantiomer; S enantiomer below HPLC detection limits)	

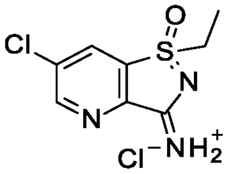
Example 62: [(Z)-[amino-(5-chloro-3-ethylsulfinyl-2-pyridyl)methylene]amino] 4-methylbenzenesulfonate



To a solution of 5-chloro-3-ethylsulfinyl-N'-hydroxy-pyridine-2-carboxamidine (5.00 g, 97% purity, 19.6 mmol) in dichloromethane (130 ml) was added at 0 °C Et_3N (2.9 ml, 20.6 mmol) and p-toluenesulfonyl chloride (4.00 g, 20.6 mmol). The reaction mixture was stirred at ambient temperature for 1.5 h and then quenched by addition of 10% aqueous NH_4Cl (40 ml). Phases were separated and the aqueous phase extracted with dichlormethane (2x). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure yielded the title compound (8.01 g, 93% purity, 95% yield) as a gray powder.

^1H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, *J* = 2.2 Hz, 1 H), 8.22 (d, *J* = 2.2 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.30-7.66 (m, 4 H), 2.92-3.02 (m, 1 H), 2.64-2.74 (m, 1 H), 2.39 (s, 3 H), 1.03 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.2, 148.9, 145.0, 143.3, 142.3, 133.9, 133.5, 132.5, 129.9, 128.1, 48.2, 21.1, 6.0

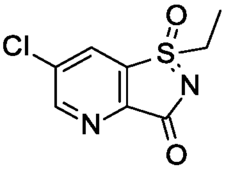
Example 63: (6-chloro-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-ylidene)ammonium chloride



To a solution of 5-chloro-3-ethylsulfinyl-N'-hydroxy-pyridine-2-carboxamidine (1.00 g, 99% purity, 4.00 mmol) in dichloromethane (10 ml) was added Et_3N (0.56 ml, 4.04 mmol) followed by 2,4-dinitrobenzene sulfonyl chloride (1.10 g, 4.04 mmol). The reaction was stirred at ambient temperature for 8 h. The resulting precipitate was filtered, washed on filter with dry dichloromethane and dried under high vacuum to yield the title compound (1.03 g, 98% purity, 95% yield) as a white solid.

^1H NMR (400 MHz, DMSO-d_6) δ 11.19 (br s, 2 H), 9.55 (br s, 1 H), 9.36 (br s, 1 H), 4.32-4.63 (m, 2 H), 1.42 (br s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 156.0, 148.4, 136.0, 134.5, 132.8, 48.0, 6.2

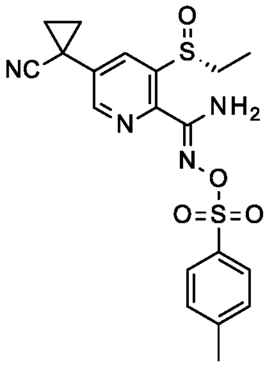
Example 64: 6-chloro-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-one



A solution of [(Z)-[amino-(5-chloro-3-ethylsulfinyl-2-pyridyl)methylene]amino] 4-methylbenzenesulfonate (8.00 g, 96% purity, 19.1 mmol) in a mixture of THF (85 ml) and water (85 ml) was heated at 80 °C for seven days (full conversion of starting material by LC/MS). The reaction mixture was cooled to ambient temperature and quenched by addition of aqueous saturated $NaHCO_3$. The resulting mixture was extracted with dichloromethane (3x). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded a crude residue which was triturated with diisopropyl ether (15 ml). The precipitate was dried under high vacuum to yield the title compound (3.24 g, 94% purity, 69% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.18 (d, *J* = 2.2 Hz, 1 H), 9.10 (d, *J* = 2.2 Hz, 1 H), 4.08 (qd, *J* = 7.3, 1.3 Hz, 2 H), 1.26 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 167.9, 155.7, 151.1, 134.5, 134.4, 132.7, 47.4, 6.8

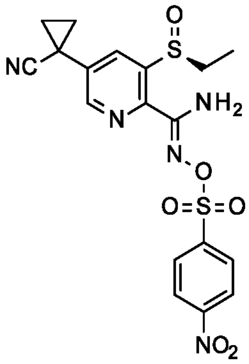
Example 65: Preparation of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate



To a suspension of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (14.817 g, 94% purity, 49.9 mmol) in MeCN (50 ml) was added Et$_3$N (13.8 ml, 98.8 mmol). After stirring for 10 min pTsCl (10.13 g, 53.15 mmol) was added in five portions over 20 min. After stirring for 2 h at ambient temperature the reaction mixture was diluted with EtOAc (200 ml). The resulting solution was washed with 1M HCl (3 x 40 ml), aq saturated NaHCO$_3$ (40 ml) and brine (40 ml). The organic layer was dried over anhydrous Na$_2$SO$_4$ and solvents partially evaporated at 50 °C and 150 mbar to ca 20 ml. The resulting precipitate was filtered, washed on filter with EtOAc (20 ml) and dried under high vacuum to yield the title compound (14.00 g, 97% purity, 90% yield) as a grey crystalline solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.80 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 2.2 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.58 (s, 1H), 5.68 (s, 1H), 3.18 (qd, *J* = 7.4, 13.3 Hz, 1H), 2.76 (qd, *J* = 7.3, 13.3 Hz, 1H), 2.44 (s, 3H), 1.96 - 1.87 (m, 2H), 1.58 (ddd, *J* = 1.6, 4.2, 5.4 Hz, 2H), 1.15 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 153.1, 147.6, 145.4, 142.3, 141.8, 135.6, 132.4, 129.9, 129.7, 128.6, 120.4, 48.2, 21.7, 19.5, 19.5, 12.0, 6.2

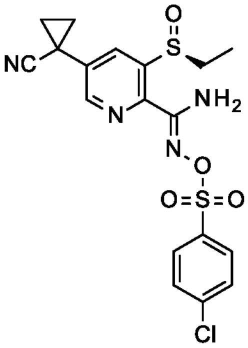
Example 66: Preparation of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate



To a suspension of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (2.942 g, 94% purity, 9.92 mmol) in MeTHF (30 ml) was added Et_3N (2.76 ml, 19.8 mmol) followed by 4-nitrobenzenesulfonyl chloride (2.309 g, 10.42 mmol) in three portions over 10 min. After stirring at ambient temperature for 1.5 h the reaction was quenched by addition of water (11 ml). Phases were separated, organic phase washed with 1M HCl (2 x 11 ml) and sat. $NaHCO_3$ (11 ml). The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (30 °C, 50 mbar). The foamy residue was redissolved in MeTHF (9 ml) and aged for 1 h. During this time precipitate was formed which was filtered, washed on filter with MTBE and dried under high vacuum to yield the title compound (3.961 g, 93% purity, 85% yield) as an off-white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 7.4 Hz, 3 H) 1.55 - 1.62 (m, 2 H) 1.90 - 1.99 (m, 2 H) 2.79 (dq, *J*=13.3, 7.3 Hz, 1 H) 3.18 - 3.33 (m, 1 H) 5.44 - 5.84 (m, 1 H) 6.49 - 6.90 (m, 1 H) 8.09 (d, *J*=2.5 Hz, 1 H) 8.21 - 8.27 (m, 2 H) 8.37 - 8.44 (m, 2 H) 8.83 (d, *J*=2.5 Hz, 1 H)

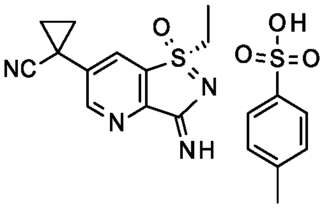
Example 67: Preparation of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-chlorobenzenesulfonate



To a solution of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (111.5 mg, 97% purity, 0.390 mmol) in MeCN (0.4 ml) was added Et_3N (0.121 ml, 0.872 mmol) and 4-chlorobenzenesulfonyl chloride (103.3 mg, 90% purity, 0.442 mmol). After stirring for 1 h the reaction mixture was partitioned between EtOAc (10 ml) and sat. $NaHCO_3$ (10 ml). Phases were separated, the organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield the title compound (202 mg, 87% purity, 99% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.4 Hz, 3 H) 1.56 - 1.63 (m, 2 H) 1.88 - 1.96 (m, 2 H) 2.76 (dq, *J*=13.3, 7.4 Hz, 1 H) 3.15 - 3.29 (m, 1 H) 5.45 - 5.96 (m, 1 H) 6.46 (s, 1 H) 6.49 - 6.82 (m, 1 H) 7.51 - 7.58 (m, 2 H) 7.93 - 8.01 (m, 2 H) 8.08 (d, *J*=2.2 Hz, 1 H) 8.81 (d, *J*=2.5 Hz, 1 H)

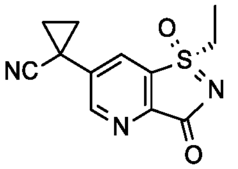
Example 68: Preparation of 1-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]cyclopropanecarbonitrile 4-methylbenzenesulfonic acid salt



A solution of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene] amino] 4-methylbenzenesulfonate (1.99 g, 97% purity, 4.47 mmol) in dry acetonitrile (8.9 ml) was heated in a sealed tube at 80 °C for 18 h. The reaction mixture was evaporated under reduced pressure and the residue purified by a reverse phase silica gel chromatography (0.25-20% MeCN in water) to yield after lyophilization the title compound as a white solid (1.15 g, 85% purity, 51% yield)

^{1}H NMR (400 MHz, CD_3CN) δ 10.19 (br s, 1H), 9.45 (br s, 1H), 9.07 (d, J = 1.8 Hz, 1H), 8.67 (d, J =1.8 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 4.19 - 3.91 (m, 2H), 2.34 (s, 3H), 2.05 - 1.96 (m, 2H), 1.87 - 1.76 (m, 2H), 1.39 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ 168.2, 156.6, 149.5, 145.8, 140.7, 140.2, 133.2, 132.6, 129.5, 126.8, 121.4, 49.9, 21.4, 21.4, 13.6, 7.2

Example 69a: Preparation of 1-[(1R)-1-ethyl-1,3-dioxo-isothiazolo[4,5-b]pyridin-6-yl]cyclopropanecarbonitrile



A solution of 1-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl] cyclopropane carbonitrile 4-methylbenzenesulfonic acid salt (0.134 g, 85% purity, 0.263 mmol) in a mixture of THF (0.9 ml) and water (0.9 ml) was heated in a sealed vial at 80 °C for 20 h. The organic layer was evaporated under reduced pressure and the aqueous layer was lyophilized over 16 h to yield the title compound (0.131 g, 52% purity, 99% yield) as a white fluffy powder. For determination of enantiopurity part of the sample was purified via silica gel chromatography (EtOAc/MeOH 9:1)

^{1}H NMR (400 MHz, 2-DMSO) δ 9.08 (d, *J* = 1.8 Hz, 1H), 8.81 (d, *J* = 1.8 Hz, 1H), 4.09 (dq, *J* = 1.8, 7.3 Hz,2H), 2.08 - 1.94 (m, 2H), 1.91 - 1.86 (m, 1H), 1.85 - 1.80 (m, 1H), 1.20 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, 2-DMSO) δ 168.5, 154.5, 151.8, 136.3, 133.5, 130.2, 121.0, 47.1, 19.7, 19.2, 12.0, 6.8

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® AY, 3µm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: EtOH isocratic: 25% B in 4.8 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 230 nm

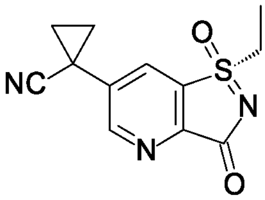
Sample concentration: 1 mg/mL in ACN/MeOH

Injection: 1 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 1.51	Retention time (min) ~ 3.58
Enantiomeric excess: >99% (R enantiomer; S enantiomer below HPLC detection limits)	

Example 69b: Preparation of 1-[(1R)-1-ethyl-1,3-dioxo-isothiazolo[4,5-b]pyridin-6-yl]cyclopropanecarbonitrile

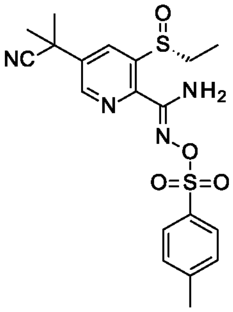


A solution of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene] amino] 4-methylbenzenesulfonate (0.267 g, 97% purity, 0.599 mmol) in a mixture of THF (2.0 ml) and water (2.0 ml) was heated in a sealed tube at 90 °C for 20 h. After cooling to ambient temperature THF was evaporated and the aqueous layer lyophilized over 16 h to yield a crude title compound as a white solid (0.258 g, 55% purity, 90% yield).

Chiral SFC method Identical to example 69a

S enantiomer	R enantiomer
Retention time (min) ~ 1.51	Retention time (min) ~ 3.58
Enantiomeric excess: >99% (R enantiomer; S enantiomer below HPLC detection limits)	

Example 70: Preparation of [(Z)-[amino-[5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate

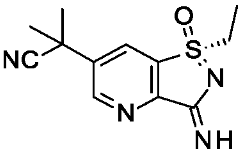


To a solution of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (1.00 g, 83% purity, 2.96 mmol) in 2-methyltetrahydrofuran (10 mL) was added triethylamine (0.83 mL, 5.92

mmol) and p-toluenesulfonyl chloride (0.624 g, 3.11 mmol) at room temperature. The reaction mixture was stirred for 2 hours and quenched by addition of water (10 mL). Layers were separated and organic phase was washed with 2 N HCl and water. Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound (1.63 g, 71.5% purity, 91% yield) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.91 (d, *J*=2.3 Hz, 1H), 8.36 (d, *J*=2.3 Hz, 1H), 7.86 (d, *J*=8.3 Hz, 2H), 7.44 (d, *J*=8.1 Hz, 2H), 6.50 (s, 2H), 2.97 (m, 1H), 2.65 (m, 1H), 2.38 (s, 3H), 1.76 (s, 6H), 1.01 - 1.04 (m, 3H)

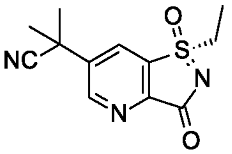
<u>Example 71</u>: Preparation of 2-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]-2-methyl-propanenitrile



A solution of [(Z)-[amino-[5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-2-pyridyl] methylene]amino] 4-methylbenzenesulfonate (1.00 g, 70% purity, 1.60 mmol) in acetonitrile (10 mL) was stirred at 80°C for 18 h and then cooled down to ambient temperature and concentrated under reduced pressure. To the resulting residue was added saturated sodium bicarbonate solution and the resulting mixture was extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure and purified by silica gel column chromatography using tert-butyl methyl ether and methanol as an eluent to yield the title compound (0.25 g, 85% purity, 50% yield) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 9.26 (d, *J*=2.1 Hz, 1H), 8.95 (d, *J*=2.1 Hz, 1H), 3.91 - 4.15 (m, 2H), 3.13 - 3.19 (s, 1H), 1.84 (s, 3H), 1.83 (s, 3H), 1.09 - 1.25 (t, *J* = 7.4 Hz, 3H)

<u>Example 72</u>: Preparation of 2-[(1R)-1-ethyl-1,3-dioxo-isothiazolo[4,5-b]pyridin-6-yl]-2-methyl-propanenitrile



A solution of 2-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]-2-methyl-propanenitrile (0.94 g, 85% purity, 3.05 mmol) in a mixture of 1,4-dioxane (9 mL) and water (3 mL) was stirred at 80°C for 16 hours and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using tert-butyl methyl ether and methanol as an eluent to yield the title compound (0.17 g, 92% purity, 94.5% ee, 23% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 9.33 (d, *J*=2.1 Hz, 1H), 9.05 (d, *J*=2.1 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2 H), 1.86 (s, 3H), 1.84 (s, 3H), 1.23 (t, *J* = 7.4 Hz, 3H).

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiralpack-IA (4.6mm x 250mm) 5µm

Mobile phase: A: TBME B: EtOH isocratic: 10% B in 22 min

Flow rate: 1.0 ml/min

Detection: 230 nm

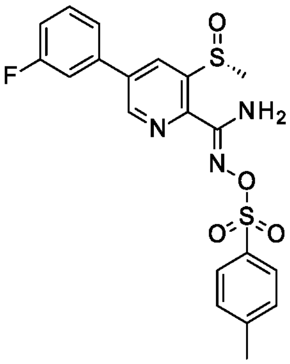
Sample preparation: 1mg/mL in EtOH

Injection: 1 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 11.69	Retention time (min) ~ 14.33
Enantiomeric excess: 94.5% (R enantiomer)	

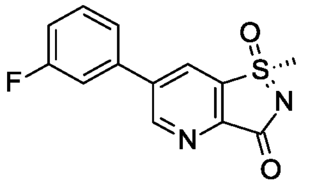
Example 73: Preparation of [(*Z*)-[amino-[5-(3-fluorophenyl)-3-[(*R*)-methylsulfinyl]-2-pyridyl]methylene] amino] 4-methylbenzenesulfonate



To a solution of 5-(3-fluorophenyl)-N'-hydroxy-3-methylsulfinyl-pyridine-2-carboxamidine (0.50 g, 89% purity, 1.51 mmol) in 2-methyltetrahydrofuran (3.0 mL) was added triethylamine (0.42 mL, 3.0 mmol) and p-toluenesulfonyl chloride (0.318 g, 1.58 mmol). The reaction mixture was stirred at ambient temperature for 4 hours and quenched by addition of water (10 mL). Layers were separated and the organic phase was washed with 2 N HCl and water. Combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to yield the title compound (0.685 g, 84% purity, 85% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.10 (d, *J*=2.2 Hz, 1H), 8.56 (d, *J*=2.2 Hz, 1H), 7.89 (d, *J*=8.4 Hz, 2H), 7.76 (d, *J*=9.9 Hz, 1H), 7.65 - 7.71 (m, 1H), 7.62 (dd, *J*=8.0, 6.0 Hz, 1H), 7.50 (d, *J*=8.0 Hz, 2H), 7.35 (br d, *J*=2.4 Hz, 1H), 2.65 (s, 3H), 2.42 (s, 3H)

Example 74: Preparation of (1*R*)-6-(3-fluorophenyl)-1-methyl-1-oxo-isothiazolo[4,5-b]pyridin-3-one



A solution of [5-(3-fluorophenyl)-3-[(R)-methylsulfinyl]pyridine-2-carboximidoyl]amino] 4-methylbenzenesulfonate (0.235 g, 85% purity, 0.447 mmol) in a mixture of 1,4-dioxane (1.3 mL) and water (0.45 mL) was stirred at 80°C for 4 hours. The reaction mixture was then cooled to ambient temperature and quenched by addition of aqueous saturated sodium bicarbonate solution. Dioxane was evaporated under reduced pressure and aqueous layer extracted with ethyl acetate. Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using cyclohexane and ethyl acetate as an eluent to yield the title compound (0.100 g, 99% purity, >99.5% ee, 80% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 9.49 (d, *J*=2.0 Hz, 1H), 9.25 (d, *J*=2.0 Hz, 1H), 7.85 (m, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 7.65-7.67 (m, 1H), 7.38-7.43 (m, 1H), 3.91 (s, 3H).

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC
Column: Chiralpack-IG (4.6mm x 250mm) 5µm
Mobile phase: A: n-hexane B: EtOH/EtOAc (1:1) isocratic: 30% B in 35 min
Flow rate: 1.0 ml/min
Detection: 257 nm

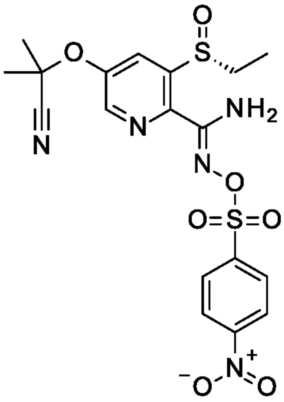
Sample preparation: 1mg/mL in EtOH

Injection: 1 µL

Results:

R enantiomer	S enantiomer
Retention time (min) ~ 18.8	Retention time (min) ~ 24.0
Enantiomeric excess: >99.5% (R enantiomer, opposite enantiomer below detection limits)	

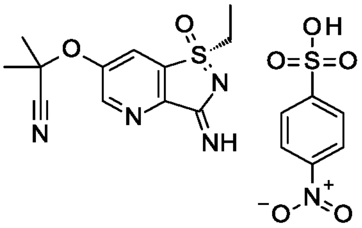
Example 75: Preparation of [(*Z*)-[amino-[5-(1-cyano-1-methyl-ethoxy)-3-[(*R*)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate



To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (0.500 g, 95% purity, 1.60 mmol) in 2-methyltetrahydrofuran (5.0 mL) was added triethylamine (0.45 mL, 3.21 mmol) and 4-nitrobenzenesulfonyl chloride (0.393 g, 1.68 mmol) at room temperature. The reaction mixture was stirred for 2 hours and quenched by addition of water (5 mL) and 2-methyltetrahydrofuran (5 mL). Layers were separated and the organic phase was washed with 2N HCl and water. The combined organic phase was further washed with saturated aqueous $NaHCO_3$ solution (10 mL) and aqueous layer extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the title compound (0.82 g, 81% purity, 81% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.57 (d, *J*=2.6 Hz, 1H), 8.46-8.50 (m, 2H), 8.24-8.28 (m, 2H), 8.07 (d, *J*=2.6 Hz, 1H), 7.83 (br s, 2H), 2.97-3.02 (m, 1H), 2.63 - 2.73 (m, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 0.98 - 1.02 (m, 3H).

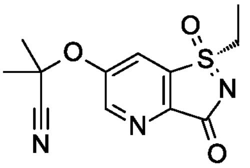
Example 76: Preparation of (1R)-6-(1-cyano-1-methyl-ethoxy)-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-ylidene]ammonium 4-nitrobenzenesulfonate



A solution of [(Z)-[amino-[5-(1-cyano-1-methyl-ethoxy)-3-[(R)-ethylsulfinyl]-2-pyridyl] methylene]amino] 4-nitrobenzenesulfonate (0.500 g, 86.5% purity, 0.900 mmol) in acetonitrile (5 mL) was stirred at 60°C for 2h. After full consumption of starting material the reaction mixture was evaporated under reduced pressure. The crude material was washed with tert-butyl methyl ether and residue dried under high vacuum to afford the title compound (0.470 g, 86% purity, 99% yield) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 10.95 (d, *J*=5.0 Hz, 2H), 9.04-9.05 (m, 2H), 8.18 – 8.22 (m, 2H), 7.82 – 7.86 (m, 2H), 4.46-4.53 (m, 1H), 4.27-4.32 (m, 1H), 1.90 (s, 6H), 1.41 (t, *J*=7.4 Hz, 3H).

Example 77: Preparation of 2-[(1R)-1-ethyl-1,3-dioxo-isothiazolo[4,5-b]pyridin-6-yl]oxy-2-methyl-propanenitrile



A solution of (1R)-6-(1-cyano-1-methyl-ethoxy)-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-ylidene]ammonium 4-nitrobenzenesulfonate (0.25 g, 86% purity, 0.447 mmol) in a mixture of 1,4-dioxane (3.0 mL) and water (1.0 mL) was stirred at 70 °C for 2h and then concentrated under reduced pressure. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the reaction mixture was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel chromatography by using tert-butyl methyl ether and methanol as an eluent to yield the title compound (0.0670 g, 98% purity, 93% ee, 53% yield) as a color less semi solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.91 (d, *J*=2.5 Hz, 1H), 8.78 (d, *J*=2.5 Hz, 1H), 4.05-4.19 (m, 2H), 1.86 (s, 3H), 1.85 (s, 3H), 1.20 (t, *J* = 8.0 Hz, 3H).

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiral pack-IA (4.6mm x 250mm) 5µm

Mobile phase: A: n-hexane B: EtOH isocratic: 30% B in 30 min

Flow rate: 1.0 ml/min

Detection: 235 nm

Sample preparation: 1mg/mL in EtOH

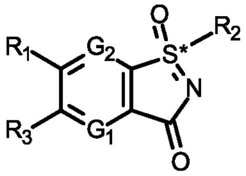
Injection: 1 µL

Results:

R enantiomer	R enantiomer
Retention time (min) ~ 11.4	Retention time (min) ~ 14.0
Enantiomeric excess: >93% (R enantiomer)	

Claims:

1. A process for the enantioselective preparation of cyclic acyl sulfoximines of formula (I)



(I)

wherein

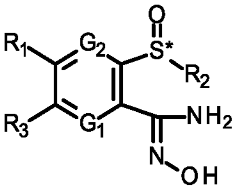
S* is a stereogenic sulfur atom in (R)- or (S)-configuration, in which said S* is in enantiomerically pure, enantiomerically enriched or racemic form;

R_1 and R_3 are independently hydrogen, halogen, haloalkyl, cycloalkyl, cyanocycloalkyl, cyanoalkoxy, cyanoalkyl or optionally substituted aryl;

R_2 is alkyl, cycloalkyl, haloalkyl or optionally substituted aryl; and

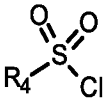
G_1 and G_2 are independently CH or N provided that at least one of G_1 or G_2 is N; which process comprises:

A) reacting a sulfinyl compound of formula (II)



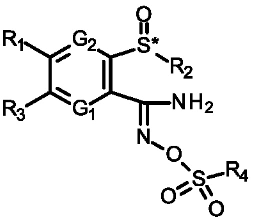
(II)

wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined in formula (I), with a sulfonyl chloride of formula (III)



(III)

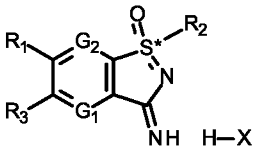
wherein R_4 is alkyl or substituted aryl; in the presence of an appropriate base and in an appropriate solvent to produce a compound of formula (IV)



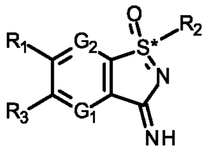
(IV)

wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined in formula (I) and R_4 is as defined in formula (III);

B) thermally rearranging the compound of formula (IV) in an appropriate solvent to produce a compound of formula (V) or (Va)


(V)

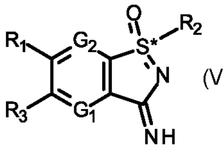
or


(Va)

wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined in formula (I) and X is halogen or SO_2R_4 and R_4 is as defined in formula (III); and

C) hydrolyzing the compound of formula (V) or (Va) with water at appropriate temperature and in the presence of an appropriate co-solvent to produce compound of formula (I).

2. The process according to claim 1, wherein step B) comprises thermally rearranging the compound of formula (IV) in the presence of an appropriate base in an appropriate solvent to produce a compound of formula (Va)


(Va)

wherein R_1, R_2, R_3, G_1, G_2 and S* are as defined in formula (I); and

C) hydrolyzing the compound of formula (Va) with water at appropriate temperature and in the presence of an appropriate co-solvent to produce compound of formula (I).

3. The process according to claim 1, which is carried out by direct rearrangement of the compound of formula (IV) obtained from step B) in the presence of water and an appropriate co-solvent to produce a compound of formula (I).

4. The process according to claim 1, wherein the suitable base for step A is selected from trialkylamines, alkali metal carbonates and alkali metal hydroxides.

5. The process according to claim 1, wherein the suitable solvent (or diluent) for step A is selected from esters, nitriles, ethers, and aliphatic, aromatic and halogenated hydrocarbons.

6. The process according to any one of claims 1 - 2, wherein the suitable solvent (or diluent) for step B is selected from polar aprotic solvents, nitriles, esters, ketones, alcohols, aromatic hydrocarbons, carbonates, ethers and mixtures thereof.

7. The process according to any one of claims 1 – 2 or 6, wherein the rearrangement reaction is carried out in a temperature range from 0 °C to 150 °C.

8. The process according to any one of claims 1 – 3, wherein hydrolyses of the compounds of formula (V) is carried out by heating in an aqueous media using a suitable cosolvent (or diluent) selected from water miscible alcohols, ethers and nitriles and optionally in a presence of an appropriate acid selected from sulfuric, hydrochloric, trifluoracetic, acetic, trifluormethansulfonic, and methansulfonic.

9. The process according to any one of claims 1 – 3 and 8, wherein the hydrolysis is carried out in a temperature range from 0 °C to 100 °C.

10. The process according to any one of claims 1 – 2 and 4 - 5, wherein steps (B) and (C) are carried out in one pot without isolating intermediate compounds of formula (V) by directly heating compounds of formula (IV) in an aqueous media and a cosolvent selected from water miscible alcohols, ethers and nitriles and optionally in a presence of an appropriate acid selected from sulfuric, hydrochloric, trifluoracetic, acetic, trifluormethansulfonic, and methansulfonic.

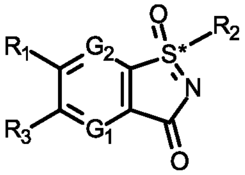
11. The process according to any one of the previous claims, wherein R_1 and R_3 are independently hydrogen, chloro, bromo, trifluoromethyl, cyclopropyl, cyanocyclopropyl, cyanoisopropoxy, cyanoisopropyl, phenyl or halophenyl.

12. The process according to any one of the previous claims, wherein R_2 is C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-haloalkyl, phenyl or halophenyl.

13. The process according to any one of the previous claims, wherein G_1 is N and G_2 is CH; or G_1 is CH and G_2 is N; or both G_1 and G_2 are N.

14. The process according to any one of the previous claims, wherein R_4 is methyl, p-tosyl, 4-chlorophenyl, 4-cyanophenyl, 4-nitrophenyl or 2,4-dinitrophenyl.

15. A compound of formula I



(I) wherein

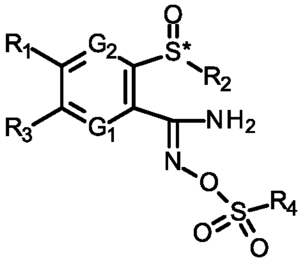
S* is a stereogenic sulfur atom in (R)- or (S)-configuration,

R_1 and R_3 are independently hydrogen, halogen, haloalkyl, cycloalkyl, cyanocycloalkyl, cyanoalkoxy, cyanoalkyl or optionally substituted aryl;

R_2 is alkyl, cycloalkyl, haloalkyl or optionally substituted aryl; and

G_1 and G_2 are independently CH or N provided that at least one of G_1 or G_2 is N.

16. A compound of formula IV



(IV) wherein

S* is a stereogenic sulfur atom in (R)- or (S)-configuration,

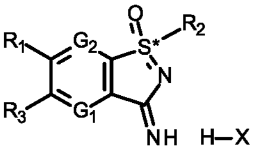
R_1 and R_3 are independently hydrogen, halogen, haloalkyl, cycloalkyl, cyanocycloalkyl, cyanoalkoxy, cyanoalkyl or optionally substituted aryl;

R_2 is alkyl, cycloalkyl, haloalkyl or optionally substituted aryl;

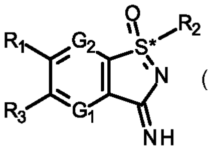
G_1 and G_2 are independently CH or N provided that at least one of G_1 or G_2 is N; and

R_4 is alkyl or substituted aryl.

17. A compound of formula V or Va



(V) ; or



(Va) wherein

S* is a stereogenic sulfur atom in (R)- or (S)-configuration,

R_1 and R_3 are independently hydrogen, halogen, haloalkyl, cycloalkyl, cyanocycloalkyl, cyanoalkoxy, cyanoalkyl or optionally substituted aryl;

R_2 is alkyl, cycloalkyl, haloalkyl or optionally substituted aryl;

G_1 and G_2 are independently CH or N provided that at least one of G_1 or G_2 is N and X is Cl or SO_2R_4; and

R_4 is methyl, p-tosyl, 4-chlorophenyl, 4-cyanophenyl, 4-nitrophenyl or 2,4-dinitrophenyl.

18. A compound according to any one of claims 15 – 17, wherein R_1 and R_3 are independently hydrogen, chloro, bromo, trifluoromethyl, cyclopropyl, cyanocyclopropyl, cyanoisopropoxy, cyanoisopropyl, phenyl or halophenyl.

19. A compound according to any one of claims 15 – 17, wherein R_2 is C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-haloalkyl, phenyl or halophenyl.

20. A compound according to any one of claims 15 – 17, wherein G_1 is N and G_2 is CH; or G_1 is CH and G_2 is N; or both G_1 and G_2 are N.

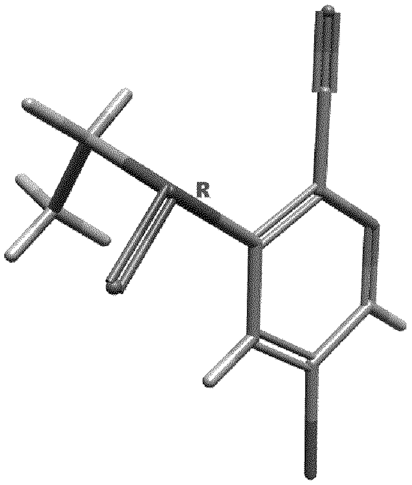


Fig. 1

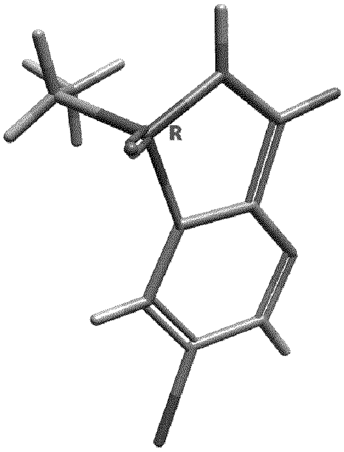


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/065831

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D513/04 C07D241/24 C07D213/81
ADD.

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)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PETER STOSS ET AL: "Cyclische Sulfoximide, VI. 3-Imino-3H-1[lambda]4,2-benzisothiazol-1-oxide", CHEMISCHE BERICHTE, vol. 108, no. 12, 1 December 1975 (1975-12-01), pages 3855-3863, XP055124548, ISSN: 0009-2940, DOI: 10.1002/cber.19751081218	15,17-20
A	reaction schemes on page 3856 -----	1-14,16
A	DE 19 14 016 B1 (GOEDECKE AG) 22 October 1970 (1970-10-22) claims 1,2; examples 1-5 ----- -/--	1-20

☒ 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 3 September 2024	Date of mailing of the international search report 18/09/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Guspanová, Jana

International application No
PCT/EP2024/065831

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ALLENMARK STIG ET AL: "Routes to Endocyclic Sulfoximides Via Electrophilic Amination Reactions", PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS, vol. 153, no. 1, 1 January 1999 (1999-01-01), pages 359-360, XP093097596, ISSN: 1042-6507, DOI: 10.1080/10426509908546470 abstract, reaction scheme on page 359; Scheme 1 -----	1-20
Y	DE 23 40 815 A1 (GOEDECKE AG) 27 February 1975 (1975-02-27)	17-20
A	claims 1,2; examples 1,2 -----	1-16
Y	WO 2020/254697 A1 (AC IMMUNE SA [CH]) 24 December 2020 (2020-12-24)	15,17-20
A	embodiment 30 on page 18; radicals on page 36, especially 2nd, 5th, 6th; claim 4 -----	1-14,16

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/065831

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
DE 1914016	B1	22-10-1970	NONE			
DE 2340815	A1	27-02-1975	AU	477130	B2	14-10-1976
			DE	2340815	A1	27-02-1975
			DK	426474	A	21-04-1975
			FR	2245646	A1	25-04-1975
			GB	1418854	A	24-12-1975
			JP	S5049277	A	01-05-1975
			US	3951997	A	20-04-1976
WO 2020254697	A1	24-12-2020	CN	114008030	A	01-02-2022
			EP	3986879	A1	27-04-2022
			US	2022378801	A1	01-12-2022
			WO	2020254697	A1	24-12-2020