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(54) Title: METHOD FOR PREPARING BENZENESULFONYL COMPOUNDS

(57) Abstract: The present disclosure provides a method for the preparation of aromatic sulfonyl halides by contacting a substituted phenyl compound with a halosulfonic acid and trifluoroacetic acid. The present disclosure further provides a method for the preparation of 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide which is useful in treating cyclooxygenase-2 related disorders.

METHOD FOR PREPARING BENZENESULFONYL COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a method of preparing aromatic sulfonyl chlorides and isoxazolyl benzenesulfonamides. This method especially relates to a method for the preparation of valdecoxib, parecoxib, parecoxib sodium and 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonyl chloride.

Description of Related Art

Substituted isoxazolyl compounds useful in treating inflammation are described in U.S. Patent 5,633,272. Methods for preparing substituted isoxazol-4-yl benzenesulfonamide compounds are described in U.S. Patent 5,859,257. Methods for preparing prodrugs of COX-2 inhibitors are described in U.S. Patent 5,932,598. Ullmann's Encyclopedia of Industrial chemistry, 5th Edition Vol. A3 page 513 describes the preparation of aromatic sulfonyl chlorides using excess chlorosulfonic acid. Ullmann's Encyclopedia also describes the preparation of aromatic sulfonamides from aromatic sulfonyl chlorides.

In the chlorosulfonation reaction, secondary reactions such as sulfone formation and poly-chlorosulfonation may be minimized with the use of large excesses of chlorosulfonic acid, by diluting with a solvent, or adding sulfone formation inhibiting substances as described in U.S. Patent 5,136,043. Addition of extra chlorinating agents such as thionyl chloride (EP 115,328) complicate the process by incorporating additional operations and complicating waste handling while not

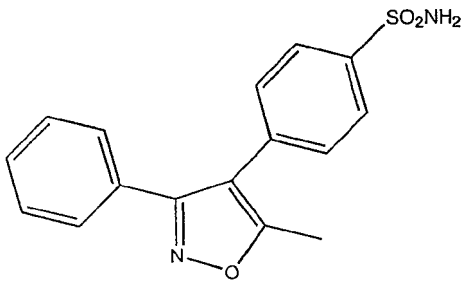
addressing reactivity issues due to insolubility of the reactants. The use of chlorinated solvents such as carbon tetrachloride, chloroform or methylene chloride, while partially addressing some solubility concerns, complicate the operation of the process by creating a two phase reaction mass, generate employee exposure concerns due to the volatility and toxic nature of these solvents and further introduce these chlorinated solvents to the waste streams. Japanese patent application number JP06-145227 describes the reaction of high-density polyethylene (HDPE) with sulfuryl chloride in trifluoroacetic acid in the presence of AIBN (radical generator) to give chlorosulfonated polyethylene which is used in rubber manufacture.

Summary of the Invention

The on-going work in the area of aromatic sulfonamide synthesis and the utility of isoxazolylbenzenesulfonamide compounds in treating inflammation points to the continuing need for economical, practical and environmentally acceptable methods to prepare these compounds.

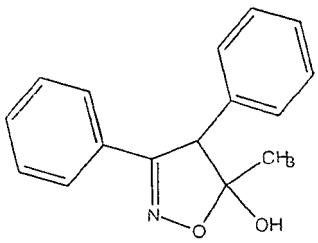
The present invention provides a novel method of preparing aromatic sulfonyl halide compounds generally and the corresponding isoxazolylbenzenesulfonamide compounds, N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compounds and N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compounds. Among the several embodiments of the present invention may be noted the provision of a process for the preparation of aromatic sulfonyl halide compounds; the provision of a process for preparing [isoxazol-4-yl]benzenesulfonamide compounds, N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compounds and N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compounds. In one embodiment the present invention provides a method of preparing an

[isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula 1:



1

wherein the method comprises contacting a precursor compound selected from the group consisting of Formula 2 and Formula 3:



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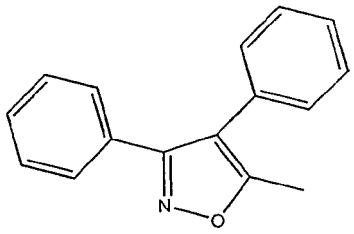
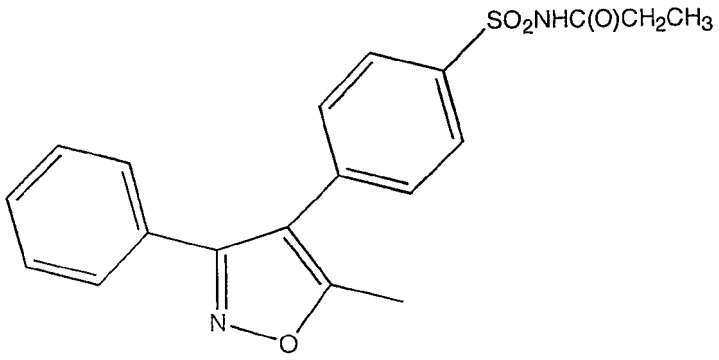


3

with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product; and contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula 1 (valdecoxib).

In another embodiment the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-

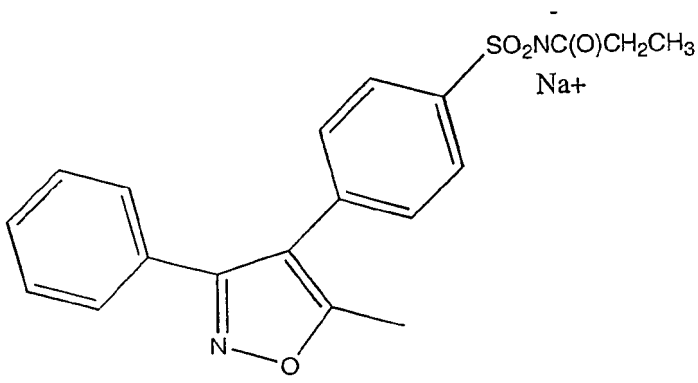
yl)phenyl]sulfonyl]propanamide having the structure of Formula **1a** (parecoxib)



1a

wherein the method comprises contacting a precursor compound selected from the group consisting of Formula **2** and Formula **3** with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product; and contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide; and contacting the sulfonamide with a propionating agent to produce the N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a**.

In another embodiment the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide sodium salt having the structure of Formula **1b** (parecoxib sodium)



1b

wherein the method comprises contacting a precursor compound selected from the group consisting of Formula **2** and Formula **3** with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product; and contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide; and contacting the sulfonamide with a propionating agent to produce the N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide; and contacting the propanamide with a sodium base to produce the N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b.**

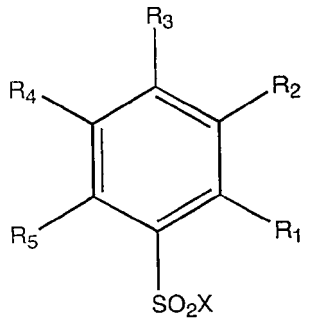
In another embodiment the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]sulfonamide having the structure of Formula **1**, wherein the method comprises forming a diphenylethanone oxime derivative compound by contacting a 1,2-diphenylethanone with a source of hydroxylamine; and contacting said oxime compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative compound; and contacting the diphenylisoxazoline derivative compound with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product; and contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1.**

In another embodiment the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide of Formula **1a**, wherein the method comprises forming a diphenylethanone oxime derivative compound by contacting a 1,2-diphenylethanone with a source of hydroxylamine; and contacting said oxime derivative compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative compound; and contacting the diphenylisoxazoline derivative compound with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product; and contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**; and contacting the sulfonamide compound with a propionating agent

to produce the N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a**.

In another embodiment the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b**, wherein the method comprises forming a diphenylethanone oxime derivative compound by contacting a 1,2-diphenylethanone with a source of hydroxylamine; contacting said oxime derivative compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative; contacting the diphenylisoxazoline derivative with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product; contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide **1**; contacting the sulfonamide with propionating agent to produce the N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a**; and contacting the propanamide compound with a sodium base to produce the N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b**.

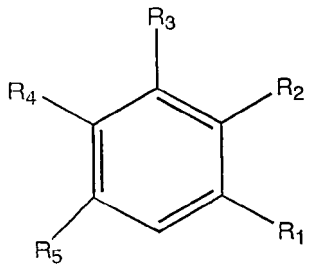
In another embodiment the present invention provides a method of preparing a benzenesulfonyl halide compound having the structure of Formula **4**:



4

wherein X is a halogen atom and R^1, R^2, R^3, R^4 and R^5 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl,

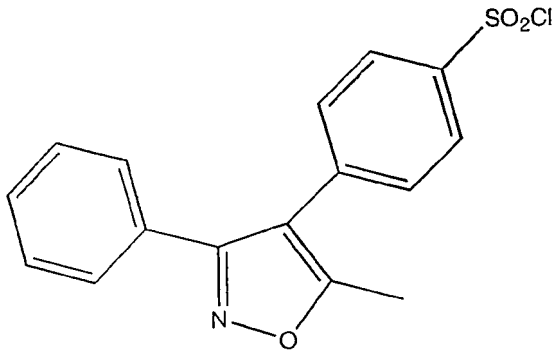
cycloalkyl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl is each optionally substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl, halo, haloalkylaryl, alkoxyaryl, haloalkyl, and alkoxyhaloalkyl; wherein the method comprises contacting a substituted phenyl compound having the structure of Formula 5:



5

with a halosulfonic acid in the presence of trifluoroacetic acid, thereby forming a benzenesulfonyl halide compound.

In another embodiment the present invention provides a method of preparing a 5-phenylisoxazol-4-yl benzenesulfonyl halide wherein the method comprises contacting a 4,5-diphenylisoxazole compound with a halosulfonic acid in the presence of trifluoroacetic acid, thereby forming a 5-phenylisoxazol-4-yl benzenesulfonyl halide compound having the structure of Formula 6:



6

Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modification within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a process by which 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide having the structure of Formula 1 can be prepared.

Figure 2 shows the process by which the compounds having the structure of Formulae 1a and 1b can be prepared from the compound having the structure of Formula 1.

DETAILED DESCRIPTION OF THE PREFERED EMBODIMENTS

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

a. Definitions

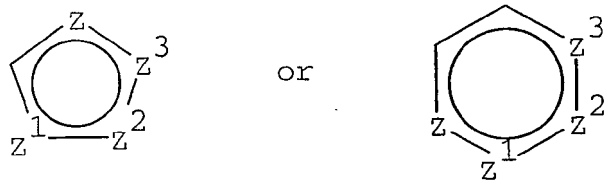
The following definitions are provided in order to aid the reader in understanding the detailed description of the present invention:

"Alkyl," "alkenyl," and "alkynyl" unless otherwise noted are each straight chain or branched chain hydrocarbon groups of from one to about twenty carbons for alkyl or two to about twenty carbons for alkenyl and alkynyl in the present invention and therefore mean, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and ethenyl, propenyl, butenyl, pentenyl, or hexenyl and ethynyl, propynyl, butynyl, pentynyl, or hexynyl respectively and isomers thereof.

"Cycloalkyl" is a mono- or multi-ringed carbocycle wherein each ring contains three to ten carbon atoms, and wherein any ring can contain one or more double or triple bonds. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl.

"Aryl" means a fully unsaturated mono- or multi-ring carbocycle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

"Heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms can be replaced by N, S, P, or O. This includes, for example, the following structures:



wherein Z, Z^1, Z^2 or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2 or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2 or Z^3 only when each is C. The point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.

The term "alkoxy" means a radical comprising an alkyl radical that is bonded to an oxygen atom, such as a methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to ten carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

The term "alkylamino" means a radical comprising an alkyl radical that is bonded to a nitrogen atom, such as a N-methylamino radical. More preferred radicals are "lower alkylamino" radicals having one to ten carbon atoms. Examples of such radicals include N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N,N-dipropylamino, N-butylamino, and N-methyl-N-ethylamino.

The term "alkylthio" means a radical comprising an alkyl radical that is bonded to a sulfur atom, such as a methylthio radical. More preferred alkylthio radicals are "lower alkylthio" radicals having one to ten carbon atoms. Examples of such radicals include methylthio, ethylthio, propylthio and butylthio.

The term "acyl" means a radical comprising an alkyl or aryl radical that is bonded to a carboxy group such as a carboxymethyl radical. More preferred acyl radicals are "carboxy lower alkyl" radicals having one to ten carbon atoms and carboxyphenyl radicals. Examples of such radicals include carboxymethyl, carboxyethyl and carboxypropyl.

The term "halo" means a fluoro, chloro, bromo or iodo group.

The term "haloalkyl" means alkyl substituted with one or more halogens. Examples of such radicals include chloromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, dichloromethyl and trichloromethyl.

When used in combination, for example "haloalkylaryl", "alkoxyaryl" or 'alkoxyhaloalkyl" the individual terms listed above have the meaning indicated above.

As used herein, Me means methyl; Et means ethyl; Pr means propyl; i-Pr or Pr^i each means isopropyl; Bu means butyl; t-Bu or Bu^t each means tert-butyl.

Weak acid is an acid of such strength to produce sufficient protonated hydroxylamine to react with a diphenylethanone compound to produce a diphenylethanone oxime derivative compound.

Strong base is a base that upon contacting an oxime derivative compound produces sufficient di-anion species to further react with an acetylating agent.

Deprotonating base is a base which reacts with a hydroxylamine salt to produce sufficient hydroxylamine to further react with a diphenylethanone compound to produce a diphenylethanone oxime derivative compound.

Propionating agent means an agent that upon contacting a benzenesulfonamide compound having the structure of Formula **1** produces a sulfonyl propanamide compound. A propionating agent can include an active ester such as a propionyl anhydride, a propionyl mixed anhydride, a propionyl thioester, a propionyl carbonates or the like. A propionating agent also includes a propionyl halide preferably propionyl chloride, an active amides such as N-propionyl imidazole, N-alkyl-N-alkoxypropionamides and the like. Many more active propionating agents are described in M. Bodanszky, Principles of Peptide Synthesis 14-61 (second revised edition, Springer Verlag 1993).

An acylating agent is an agent which upon contacting a 1,2-diphenyl ethanone derivative oxime in the presence of a strong base produces an isoxazolyl compound or an isoxazole compound having the structure of Formula 2 and/or 3. Acylating agents can include an acetic anhydride, preferably diacetic anhydride. An acylating agent can also include an acyl halide, preferably acetyl chloride. An acylating agent can also include a C1 to about C6 alkyl acetate selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate and butyl acetate and more preferably ethyl acetate.

A sodium base is a base which upon contacting with the benzenepropanamide compound having the structure of Formula **1a** produces a sulfonyl propanamide sodium salt compound. Sodium bases can include sodium hydroxide, a sodium alkoxide such as sodium ethoxide or sodium methoxide. A sodium base can also be sodium hydride or sodium carbonate.

A protecting group is a chemical moiety which serves to protect a chemical functionality of a molecule while the molecule is undergoing a chemical reaction at a different locus in the molecule. Preferably, after the chemical reaction, the protecting group can be removed to reveal the original chemical functionality. A hydroxyl protecting group for example can protect a hydroxyl group. A protected hydroxymethyl group comprises a hydroxymethyl group in which the hydroxyl group is protected by a protecting group. Useful protecting groups can vary widely in chemistry. Numerous hydroxyl protecting groups are described in Theodora W. Greene and Peter G.M. Wuts Protective Groups in Organic Chemistry 86-97 (Third Edition , John Wiley & Sons, 1999). An example of a protected hydroxymethyl group is a deactivated benzyloxymethyl group and the like.

b. Process Details

In accordance with the present invention, a process is now provided for preparing benzenesulfonyl derivatives, in particular 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonyl chloride having the structure of Formula **6**, 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (valdecoxib) having the structure of Formula **1**, N-[[4-(5-methyl-4-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide (parecoxib) having the structure of Formula **1a** and N-[[4-(5-methyl-4-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide sodium salt (parecoxib sodium) having the structure of Formula **1b**. A schematic of a method for the preparation of valdecoxib using the present invention is provided in Figure **1**. A schematic of a method for the preparation of parecoxib and parecoxib sodium from valdecoxib using the present invention is provided in Figure **2**.

In one embodiment, the present invention provides a method of preparing an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1** comprising contacting a precursor compound selected from the group consisting of Formula **2** and Formula **3** with a halosulfonic acid in the

presence of trifluoroacetic acid to produce a halosulfonated product and contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula 1. The halosulfonic acid useful in the various embodiments of the present invention, for example, can be any convenient halosulfonic acid. Preferably the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid, and more preferably chlorosulfonic acid. The source of ammonia useful in the various embodiments of the present invention, for example, can be selected from the group consisting of ammonium hydroxide and anhydrous ammonia. More preferred the source of ammonia comprises ammonium hydroxide. In another preferred embodiment, the source of ammonia comprises anhydrous ammonia.

In another embodiment, the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a** comprising contacting a precursor compound selected from the group consisting of Formula 2 and Formula 3 with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product and contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula 1 and contacting the [isoxazol-4-yl]benzenesulfonamide compound with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a.** The propionating agent useful in the various embodiments of the present invention, for example, can be selected from the group consisting of an anhydride of propionic acid, a propionyl halide, a propionyl thioester, a propionyl carbonate and an N-propionyl imidazole. Preferably the propionating agent is an anhydride of propionic acid and more preferably propionic anhydride and still more preferably a propionyl halide and still more preferably propionyl chloride.

In another embodiment, the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

sodium salt compound having the structure of Formula **1b** comprising contacting a precursor compound selected from the group consisting of Formula 2 and Formula 3 with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product and contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1** and contacting the [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1** with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a** and further contacting the compound of Formula **1a** with a sodium base to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b**. The sodium base useful in the various embodiments of the present invention, for example, is selected from the group consisting of sodium hydroxide, a sodium alkoxide, sodium hydride and sodium carbonate. Preferably the sodium base is sodium methoxide and more preferably the sodium base is sodium hydroxide.

In another embodiment the present invention provides a method of preparing an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1** comprising contacting a 1,2-diphenylethanone compound with a source of hydroxylamine to form a diphenylethanone oxime derivative compound, and contacting the oxime derivative compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative and contacting the diphenylisoxazoline derivative with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product and contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**. The source of hydroxylamine useful in the various embodiments of the present invention, for example, can be, an aqueous solution comprising hydroxylamine. Preferably the source of hydroxylamine is an aqueous solution comprising hydroxylamine and a weak acid wherein the weak acid is a carboxylic acid and preferably an alkyl carboxylic acid and still more preferably the alkyl carboxylic acid selected from

the group consisting of formic acid, acetic acid and propionic acid and more preferably is acetic acid. Most preferably the source of hydroxylamine is an aqueous solution of hydroxylamine and acetic acid.

The source of hydroxylamine can also comprise a hydroxylamine salt and a deprotonating base. The hydroxylamine salt is selected from the group consisting of hydroxylamine hydrochloride, hydroxylamine sulfate and hydroxylamine acetate. The hydroxylamine salt is preferably hydroxylamine hydrochloride. The deprotonating base is selected from the group consisting of sodium hydroxide, potassium hydroxide and sodium acetate. The deprotonating base is preferably sodium acetate. Another more preferred source of hydroxylamine comprises hydroxylamine hydrochloride and sodium acetate.

The strong base which is contacted with the oxime derivative compound useful in the various embodiments of the present invention, for example, can be preferably selected from the group consisting of a lithium dialkylamide, an aryl lithium, an arylalkyl lithium and an alkyl lithium. The strong base can be a lithium dialkylamide and preferably lithium diisopropylamide. More preferably the strong base is a C_1 to about C_{10} alkyl lithium and more preferably selected from the group consisting of butyl lithium, hexyl lithium, heptyl lithium, octyl lithium and still more preferably butyl lithium or hexyl lithium.

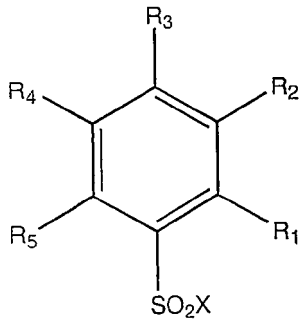
The acetylating agent useful in the various embodiments of the present invention, for example, can be selected from the group consisting of an alkyl acetate, an acetic anhydride, an N-alkyl-N-alkoxyacetamide and an acetyl halide. The acetylating agent can be an acetic anhydride and is preferably acetic anhydride and can be an acetyl halide and preferably acetyl chloride and more preferably a C1 to about C6 alkyl acetate selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate and butyl acetate and more preferably ethyl acetate.

In another embodiment the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a** comprising contacting a 1,2-diphenylethanone compound with a source of hydroxylamine to form a

diphenylethanone oxime derivative compound; contacting the oxime derivative compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative; contacting the diphenylisoxazoline derivative with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product; contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**; and contacting the [isoxazol-4-yl]benzenesulfonamide compound with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a.**

In another embodiment the present invention provides a method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b** comprising forming a diphenylethanone oxime derivative compound by contacting a 1,2-diphenylethanone compound with a source of hydroxylamine and contacting the oxime derivative compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative and contacting the diphenylisoxazoline derivative with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product and contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1** and contacting the [isoxazol-4-yl]benzenesulfonamide compound with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a** and further contacting the compound of Formula **1a** with a sodium base to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b**.

In another embodiment the present invention provides a method of preparing a benzenesulfonyl halide compound having the structure of Formula **4:**



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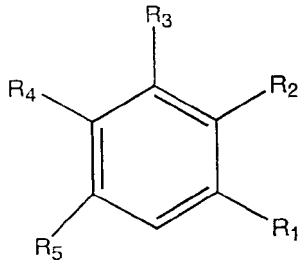
wherein X is a halogen atom and R^1, R^2, R^3, R^4 and R^5 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl is each optionally substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl, halo, haloalkylaryl, alkoxyaryl, haloalkyl, protected hydroxymethyl, arylalkoxymethyl, and alkoxyhaloalkyl; wherein the method comprises contacting a substituted phenyl compound having the structure of Formula 5:



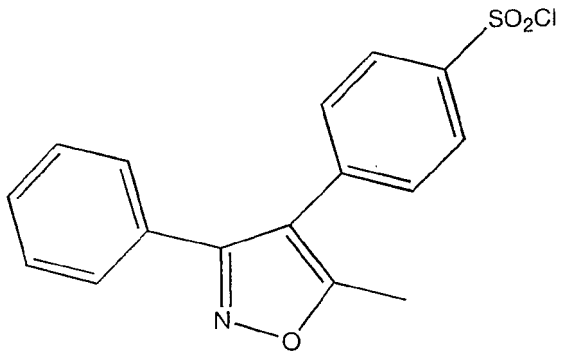
5

with a halosulfonic acid in the presence of trifluoroacetic acid, thereby forming a benzenesulfonyl halide compound.

More preferred embodiment of the present invention a method wherein R^3 is heterocyclyl optionally substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl, halo, haloalkylaryl, alkoxyaryl,

haloalkyl, alkoxycarbonyl, protected hydroxymethyl, arylalkoxymethyl, and alkoxyhaloalkyl; and R^1, R^2, R^4 and R^5 are hydrogen. Still further preferred is the method wherein R3 is selected from the group consisting of isoxazolyl and pyrazolyl wherein R^3 is optionally substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl, halo, haloalkylaryl, alkoxyaryl, haloalkyl, alkoxycarbonyl, protected hydroxymethyl, arylalkoxymethyl, and alkoxyhaloalkyl; and R^1, R^2, R^4 and R^5 are hydrogen.

In another embodiment the present invention provides a method of preparing a 5-phenylisoxazol-4-yl benzenesulfonyl halide wherein the method comprises contacting a 4,5-diphenylisoxazole with a halosulfonic acid in the presence of trifluoroacetic acid, thereby forming a 5-phenylisoxazol-4-yl benzenesulfonyl halide compound having the structure of Formula **6**:



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In another embodiment the present invention provides a method of preparing a 5-phenylisoxazol-4-yl benzenesulfonyl halide wherein the method comprises contacting a compound selected from the group consisting of Formula **2** and Formula **3** with a halosulfonic acid in the presence of trifluoroacetic acid, thereby forming a 5-phenylisoxazol-4-yl benzenesulfonyl halide compound having the structure of Formula **6**.

As provided herein trifluoroacetic acid is a useful solvent for the halosulfonation of aromatic compounds to give the corresponding aryl sulfonyl

halides. The use of trifluoroacetic acid provides solubilization of many solid substrates. The higher boiling point of trifluoroacetic acid versus methylene chloride enables the halosulfonation reaction to be carried out at higher temperatures and which can have the benefit of shorter reaction times. In addition, trifluoroacetic acid can be used to pre-dissolve the solid aromatic substrates making it easier and safer to transfer the substrate from a filtration device to a halosulfonation reactor. The use of trifluoroacetic acid also eliminates chlorinated hydrocarbons from air emissions and aqueous waste streams.

The halosulfonation reaction under which compounds **2**, **3**, and **5** react to form the aromatic sulfonyl chlorides of structures **4** and **6** is carried out in the presence of trifluoroacetic acid.

The ratio of trifluoroacetic acid used and reaction time can vary as shown in the table below.

TFA Equivalents	Temperature °C	Reaction time Hours (h)	Completion time	Valdecoxib[1]
2.0	70	2	<30 min	78
2.0	40	6	3.3 h	80
3.0	60	3	50 min	76
4.0	70	2.5	1 h	87
4.0	40	4	4 h	77

[1] Endpoint mol % values from in process samples quenched with acetonitrile, water, and ammonium hydroxide mixture.

It is preferable to use sufficient trifluoroacetic acid to ensure a fluid reaction mass. For the conversion of **2** and **3** to **6**, the amount of trifluoroacetic

acid can range from about 1.5 to about 4 weight equivalents relative to 2 and 3. In one preferred embodiment, the weight equivalent of trifluoroacetic acid was equal to the weight of 2 and 3.

The halosulfonation reaction can proceed over a range of temperatures and preferably is performed within the range of –20°C to 100°C and more preferably about 30°C to 70°C, still more preferably about 55°C to 65°C. The chlorosulfonation reaction can proceed at atmospheric pressure or under pressure and is preferably carried out below the boiling point of trifluoroacetic acid under atmospheric pressure. The chlorosulfonation can proceed at higher temperatures with enough pressure on the reactor system to prevent losses due to volatilization.

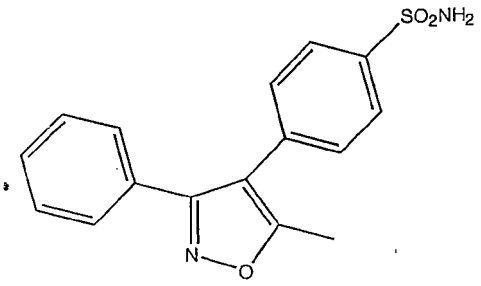
c. Detailed Preparative Methods

The starting materials for use in the methods of preparation of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art. The following examples are intended to be illustrative of the many embodiments of the present invention and are not meant to be limiting in scope.

Generally, the process methods of the present invention can be performed as follows. Larger scale preparation can be performed, for example, by proportionately increasing ingredient quantities.

Example 1.

Preparation of 4-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib, 1)



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Step 1: Preparation of 1,2-Diphenylethanone, oxime 7.

To a solution of deoxybenzoin (2.3 kg, 11.7 mol), acetic acid (669 mL, 11.7 mol), and ethanol 3A (8.05 L, 190 proof) at 70 °C was added 50 weight percent hydroxylamine (800 mL, 13.3 mol) via an addition funnel. The addition funnel was rinsed with water (460 mL) and the reaction mixture held at 70 °C for 1 hour. The reaction was monitored for reaction completion by HPLC. Water was charged to the reactor (2.87 L) and the temperature reduced to 50 °C. An aliquot (250 mL) was removed from the reactor, cooled, and allowed to crystallize. This mixture was reintroduced into the reactor to seed the batch and initiate crystallization. Seeding is not necessary, but, if used, helps increase the bulk density of the oxime product thereby enhancing the handling properties of the resulting oxime. After stirring for 1 hour, water (8.78 L) was added over 2.5 hours and the mixture cooled to 20 °C. The mixture was pressure filtered; and the cake was washed with 2:1 Water/ethanol 3A (10.8 L), and then water (4.5 L). The cake was blown dry with N_2 overnight to afford a white solid (2.34 kg, 95% yield, 96:4 E/Z oxime isomers). High-resolution MS (ES) *m/z* $(M + H)^+$ calculated: 212.1075; found 212.1085.

Step 1 (alternate procedure) Preparation of 1,2-Diphenylethanone, oxime 7.

To a solution of deoxybenzoin (75.0 g, 0.382 mole), sodium acetate (34.5 g, 0.420 mole), and ethanol 3A (267 mL, 190 proof) at 70 °C was added 35 weight percent hydroxylamine hydrochloride (72.0 mL, 0.420 mole) via a syringe pump. The reaction mixture held at 70 °C for 1 hour and was monitored for reaction completion by HPLC. Water was charged to the reactor (75.0 mL) and the temperature reduced to 50 °C. An aliquot (0.5 mL) was removed from the reactor, cooled, and allowed to crystallize. This mixture was reintroduced into the reactor to seed the batch and initiate crystallization. Seeding is not necessary, but, if used, helps increase the bulk density of the oxime product thereby enhancing the handling properties of the resulting oxime. After stirring for 1 hour, water (274 mL) was added over 1 hour and the mixture cooled to 20 °C. The mixture was filtered; and the cake was washed with 2:1 Water/ethanol 3A (188 mL), and then water (100 mL). The cake was dried in a vacuum oven at 50 °C for 16 h to afford a white solid (76.39 g, 95% yield, 97:3 E/Z oxime isomers).

Step 2: Preparation of 4,5-Dihydro-5-methyl-3, 4-diphenyl-5-isoxazolol, 2.

To a 500 mL jacketed reactor equipped with a mechanical stirrer, thermocouple, and positive pressure nitrogen inlet was charged 1,2-diphenylethanone, oxime (31.4 grams). Tetrahydrofuran (THF) (160 mL) was added while stirring to dissolve the solid. The reaction was cooled using a jacket temperature of –15°C. n-Hexyllithium in hexanes (131 mL, 2.3 M) was charged to the reaction vessel while keeping the temperature below 10 °C. After addition was complete, the mixture was stirred for 30 minutes using a jacket temperature of –15°C. Ethyl acetate (120 mL) was added keeping the temperature below 10 °C. The reaction mixture was then transferred via cannula to a mixture of sodium chloride (14.0 g) in water (160 mL) that was cooled to 5 °C. The reaction vessel was rinsed with 40 mL THF and this mixture was transferred to the quench flask. The quench mixture was warmed to 20°C and the layers were separated. The

organic layer was washed with a sodium bicarbonate ($NaHCO_3$) solution (9.6 g $NaHCO_3$/160 mL water). Toluene (120 mL) was added to the organic layer and the mixture was distilled until a pot temperature of 90.2 °C was attained. Heptane (439 mL) was added and the mixture was cooled at 0.5 °C/min to 5 °C during which time crystals formed. The mixture was filtered through polypropylene mesh and the solid cake was washed with 100 mL of 50:50 (volume/volume) heptane:toluene. The solid was dried in a vacuum oven with nitrogen bleed overnight at 50 °C. The product was obtained as a white solid (19.75 g, 52% yield). High-resolution mass spectrometry calculated for $C_{16}H_{16}NO_2$: 254.1193 $(M+H)^+$, found 254.1181.

Step 2 (alternate procedure): Preparation of 4,5-Dihydro-5-methyl-3, 4-diphenyl-5-isoxazolol, 2.

To a 500 mL jacketed reactor equipped with a mechanical stirrer, thermocouple, and positive pressure nitrogen inlet is charged 1,2-diphenyl-ethanone, oxime (31.4 grams). Tetrahydrofuran (THF) (209 mL) is added while stirring to dissolve the solid. The reaction is cooled until a batch temperature of –15°C is obtained. n-Hexyllithium in hexanes (131 mL, 2.3 M) is charged to the reaction vessel while keeping the temperature below 10 °C. After addition is complete, the mixture is cooled down to a batch temperature of –15°C. Ethyl acetate (80 mL) is added as fast as possible. The reaction mixture is adjusted to 0 °C and then transferred to a mixture of sodium chloride (14.0 g) in water (160 mL) that is cooled to <5 °C. This mixture is kept below 15 °C during the quench. The reaction vessel is rinsed with 40 mL ethyl acetate and this mixture is transferred to the quench flask. The quench mixture is warmed to 20°C and the layers are separated. The organic layer is washed with a sodium bicarbonate ($NaHCO_3$) solution (9.6 g $NaHCO_3$/160 mL water). Toluene (120 mL) is added to the organic layer and the mixture is distilled until 67% of the pot contents are removed

(temperature ~90-93 °C). Heptane (439 mL) is added and the mixture is cooled at 0.5 °C/min to 5 °C during which time crystals form. The mixture is filtered and the solid cake is washed with 100 mL of 50:50 (volume/volume) heptane:toluene. The solid is dried in a vacuum oven with nitrogen bleed overnight at 50 °C. The product is obtained as a white solid (typical manufacturing yield: 59%). High-resolution mass spectrometry calculated for $C_{16}H_{16}NO_2$: 254.1193 $(M+H)^+$, found 254.1181.

Step 3: Preparation of 4-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib, 1).

4,5-Dihydro-5-methyl-3, 4-diphenyl-5-isoxazolol (50.0 g, 0.197 mol) was charged to a 500 mL reactor, which had been cooled to 5 °C. Trifluoroacetic acid (38.3 mL, 0.496 mol) was charged with stirring to the reactor and the 35 °C solution was cooled to ~5 °C. Chlorosulfonic acid (232 g, 1.99 mol) was added slowly to control evolution of hydrogen chloride (HCl) and maintain < 25 °C during the addition. The reaction solution was then heated to 60 °C and held at 60 °C for 2.5 hours. After cooling the reaction solution to 0 °C it was added slowly to a stirred 2 to 25 °C mixture of toluene (172 mL) and water (150 mL). The reactor was rinsed with a mixture of toluene (18.4 mL) and water (50 mL), which was then added to the quench mixture. The toluene layer was extracted with water (50 mL) and cooled to 0.2 °C. Concentrated ammonium hydroxide (62 mL, 1.60 mol) was added slowly with cooling to maintain ~ 10 to 15 °C during the addition. The mixture was warmed slowly to 35 °C and held there for ~40 minutes. Isopropanol (240 mL) was added, and the reaction mixture was reheated to 35 °C and held at 35 °C for 90 minutes. The crystalline mixture was slowly cooled to 20 °C and the crude product was filtered, washed with isopropanol (100 mL) and water (100 mL). The wet cake was transferred to a 500 mL crystallizer and dissolved in methanol (350 mL) at ~58 °C. Water (92 mL) was added to the methanol solution and the solution was heated to ~70 °C. This solution was

slowly cooled to 50 °C, held for 60 minutes and then cooled to 5 °C. After one hour at 5 °C the crystalline product was collected by filtration, the cake washed with 75% methanol-water (100 mL) and dried under vacuum at ~70 °C. A differential scanning calorimetry (DSC) melting point of 171 to 174 deg C (determined at 10 degrees C / minute) was found.

Example 2.

Preparation of *N*-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]-propanamide (parecoxib, **1a**).

4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (10.0 g, 0.032 mol) and propionic anhydride (40 mL, 0.31 mol) were charged to the 500 mL reactor. The slurry was stirred and heated to 50 °C. Sulfuric acid (40 μL, 0.8 mmol) was added in one portion. All the solids dissolved and the mixture warmed to 55.5 °C within a 10 minute period after the addition was completed. The reaction mixture was then heated to 80 °C and held for approximately 10 minutes. Heating was discontinued, and the mixture was allowed to cool to 50 °C and held for about 60 minutes; solid started to crystallize from the reaction mixture at about 65 °C. The mixture was slowly cooled to 0 °C and was held at 0 °C for about 60 minutes. The solid was collected by vacuum filtration. The wet cake was washed with two 45-mL portions of methyl *tert*-butyl ether and pulled dry at ambient temperature for about 15 minutes. The solid was further dried in a vacuum oven with a nitrogen bleed at 60 °C for 18 hours to give the solid product (8.72 g 75 % yield). DSC maximum endotherm for the high melting point parecoxib is 168.95. DSC maximum endotherm for the low melting point parecoxib is 147.44.

Example 3.

Preparation of *N*-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]-propanamide, sodium salt (parecoxib sodium, **1b**).

N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propanamide (10.0 g, 0.026 mol) and 160 ml of absolute ethanol were charged to a 500 mL reactor. The slurry was heated to 45 °C and held for 30 minutes and a solution of approximately 5 weight percent sodium hydroxide in ethanol (22.4 g, 0.028 mol) was added to the reaction vessel at 45 °C. After addition was completed, the solution was seeded with *N*-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propanamide, sodium salt, to initiate crystallization. The temperature of the reaction mixture was raised to 50 °C and held for 30 min. The mixture was slowly cooled to 0 °C and held for about 60 min. The solid was collected by vacuum filtration. The wet cake was washed twice with two 20-mL portions of absolute ethanol and was pulled dry under house vacuum with a purge of nitrogen. The solid was further dried in a vacuum oven with the nitrogen bleed at 120 °C overnight to give the solid product (9.11g, 85 % yield). DSC maximum endotherm for the form I parecoxib sodium is 274.28 °C

Example 4.

Preparation of 5-methyl-3,4-diphenyl isoxazole, 3

4,5-dihydro-5-methyl-3,4-diphenyl-5-isoxazolol (15.0 grams, 0.059 mol) was charged to a 250 mL flask. Trifluoroacetic acid (10.5 mL) was added with stirring, and an exotherm to 44 °C was observed. The solution was heated between 44 and 57 °C for 60 minutes, cooled to room temperature, and vacuum distilled to remove trifluoroacetic acid. The residue was dissolved in 100 mL of toluene and vacuum distilled. The process was repeated a second time to provide a semi-crystalline concentrate. The concentrate was dissolved in 250 mL of hot heptane, decanted into a 500 mL flask, cooled to room temperature and held for 18 hours. The crystalline cake was broken up and the crystals were collected by filtration. The cake was dried to provide 10.19 g (73 wt %

yield) of the desired product. DSC melting point: 95.55-96.24 °C at 10 °C/min in an unsealed pan.

Example 5.

Preparation of 4-(5-methyl-3-phenyl-4- isoxazolyl)benzenesulfonyl chloride, 6.

4,5-dihydro-5-methyl-3,4-diphenyl-5-isoxazolol (13.0 grams, 0.0513 mol) was charged to a 200 mL jacketed flask which was cooled with 0.2 °C jacket fluid. Trifluoroacetic acid (9.1 mL, 0.118 mol) was charged to the solids to provide a solution at 38.6 °C. The solution was cooled to 2.1 °C and chlorosulfonic acid (34.7 mL, 0.522 mol) was added slowly while maintaining the temperature below 14 °C. The solution was heated to 60 °C, held for 2.5 hours, cooled to 20 °C, and transferred to a 125 mL addition funnel. Toluene (52 mL) and water (52 mL) were charged to the 200 mL jacketed reactor, and cooled to 4 °C. The reaction solution was then added slowly to the 200 mL jacketed reactor while maintaining the temperature below 20 °C. The multi-phase mixture was warmed to 20 °C, and transferred to a 250 mL separatory funnel. Toluene (50 mL) and water (10 mL) were added and the mixture was shaken. Settling of the mixture resulted in two cloudy phases. The toluene phase was washed twice with 15 mL of water, transferred to a 250 mL flask with a 20 mL toluene rinse, and vacuum distilled to 17.4 g of an oil. After initiating crystallization with a glass rod and cooling, heptane (20 mL) was added to the crystalline mass which was broken up to form a powder. The off white powder was collected by filtration. Portions of 50 mL of heptane were used to aid the transfer of solids to the filter. The cake was dried in a vacuum oven (35 °C) to provide 13.6 g (79.4 wt %) of the sulfonyl chloride as an 85:15 mixture of the para and meta isomers. HRMS Calculated for (M+1) $C_{16}H_{13}NO_3Cl$: 334.0305; Found (M+1): 334.0309.

Example 6.

Preparation of 4-(5-methyl-3-phenyl-4- isoxazolyl)benzenesulfonyl chloride, 6.

5-methyl-3, 4-diphenyl isoxazole (5.0 g, 0.0213 mol) was charged to a 100 mL jacketed reactor which was cooled with 0.2 °C jacket fluid. Trifluoroacetic acid (3.5 mL, 0.045 mol) was charged to the solids to provide a solution at 3 °C. Chlorosulfonic acid (13.3 mL, 0.201 mol) was added slowly while maintaining the reaction temperature below 20 °C. The solution was heated to 60 °C and held for 2.2 hours. The solution was then cooled to 6 °C and transferred to a 60 mL addition funnel. Toluene (20 mL) and water (20 mL) were charged to the 100 mL jacketed reactor and cooled to 6 °C. The reaction solution was then added slowly to the 100 mL jacketed reactor while maintaining the temperature below 16 °C. The multi-phase mixture was transferred to 125 mL separatory funnel. Toluene (20 mL) and water (5 mL) were added and the mixture was shaken. Settling of the mixture resulted in two cloudy phases. The toluene phase was washed twice with 5 mL of water, transferred to a 125 mL flask with a 17 mL toluene rinse, and vacuum distilled to a semi-crystalline concentrate. The concentrate was dissolved in 100 mL of toluene and vacuum distilled to an oil. After initiating crystallization with a glass rod, heptane (11 mL) was added, and the mass broken up to produce an off white powder. The solids were collected by filtration. Portions of 25 mL of heptane were used to aid the transfer of solids to the filter. The cake was dried to provide 7.07 g (100 wt %) of the sulfonyl chloride as an 85:15 mixture of the para and meta isomers. HRMS Calculated for (M+1) $C_{16}H_{13}NO_3Cl$: 334.0305; Found: (M+1): 334.0299.

Example 7.

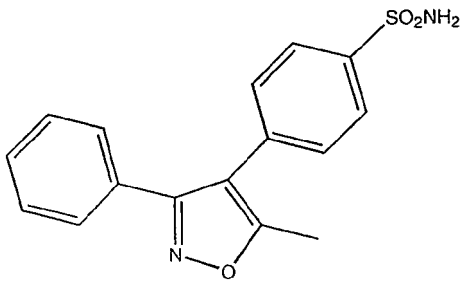
Preparation of 4-(5-Methyl-3-phenyl-4-isoxazole)benzenesulfonic acid.

4-(5-Methyl-3-phenyl-isoxazole)benzenesulfonyl chloride (39.6 grams, 0.11 mol), water (99.5 mL, 5.5 mol) and tetrahydrofuran (558 mL) were charged to a 1-liter flask and heated to reflux overnight. After cooling to ambient temperature, the solvents were removed under pressure. The residual yellow oil was further dried under high vacuum. The resulting solid was covered with toluene (500 mL) and heated to reflux. After about 30 minutes, the solid melted and collected at the bottom of the flask. The mixture was stirred at reflux temperature for 4 hours, cooled to room temperature and stirred overnight. The solids were collected by filtration, briefly air dried and ground to a powder. The powder was suspended in toluene (500 mL), heated to reflux temperature and resolidified during the cool down to room temperature. The solids were collected by filtration and dried giving 23.8 grams of product with a melting point of 174-176°C.

CLAIMS

What is claimed is:

1. A method of preparing an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**:



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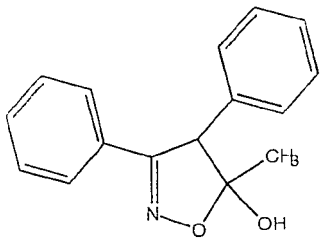
comprising:

contacting a precursor compound selected from the group consisting of Formula **2** and Formula **3**:



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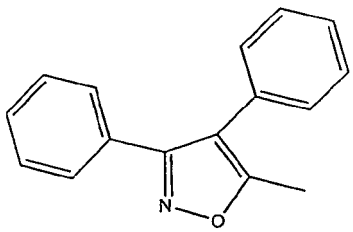

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with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product;

and contacting the halosulfonated product with a source of ammonia to produce the [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**.

2. The method of claim 1 wherein the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid.

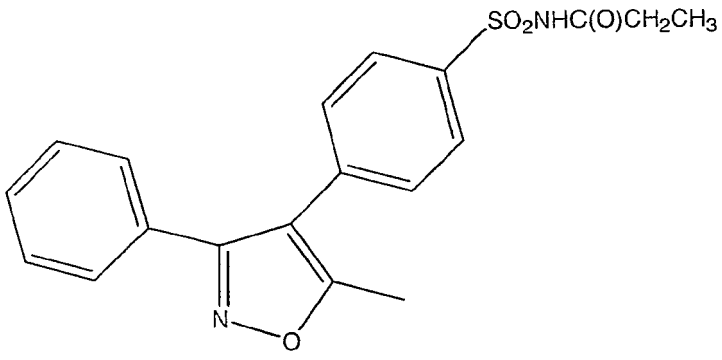
3. The method of claim 1 wherein the halosulfonic acid is chlorosulfonic acid.

4. The method of claim 1 wherein the source of ammonia is selected from the group consisting of ammonium hydroxide and anhydrous ammonia.

5. The method of claim 1 wherein the source of ammonia is ammonium hydroxide.

6. The method of claim 1 wherein the source of ammonia is anhydrous ammonia.

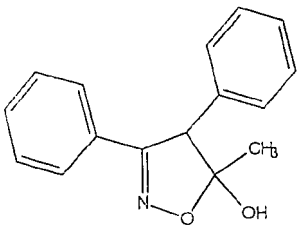
7. A method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a**:



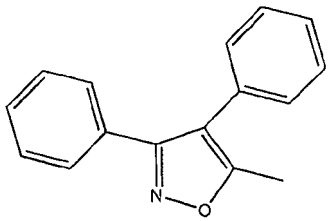
1a

comprising:

contacting a precursor compound selected from the group consisting of Formula **2** and Formula **3**:



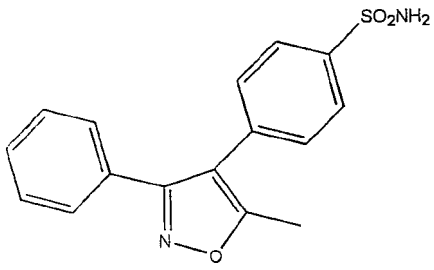
2



3

with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product;

contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula 1 :



1

and contacting the [isoxazol-4-yl]benzenesulfonamide compound with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula 1a.

8. The method of claim 7 wherein the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid.

9. The method of claim 7 wherein the halosulfonic acid is chlorosulfonic acid.

10. The method of claim 7 wherein the source of ammonia is selected from the group consisting of ammonium hydroxide and anhydrous ammonia.

11. The method of claim 7 wherein the source of ammonia is ammonium hydroxide.

12. The method of claim 7 wherein the source of ammonia is anhydrous ammonia.

13. The method of claim 7 wherein the propionating agent selected from the group consisting of an anhydride of propionic acid, a propionyl halide, a propionyl thioester, a propionyl carbonate and a N-propionyl imidazole.

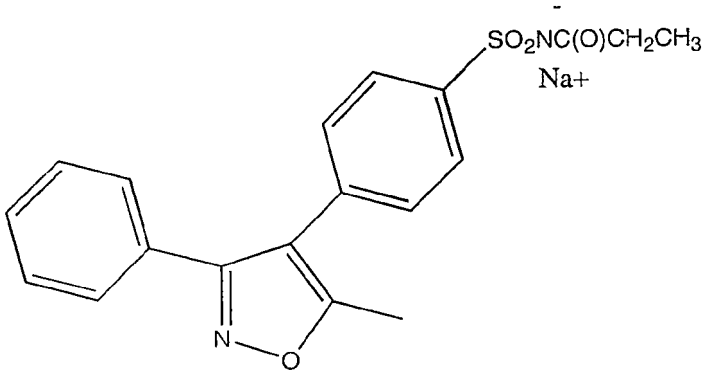
14. The method of claim 13 wherein the propionating agent is a propionyl halide.

15. The method of claim 14 wherein the propionating agent is a propionyl chloride.

16. The method of claim 13 wherein the propionating agent is an anhydride of propionic acid.

17. The method of claim 13 wherein the anhydride of propionic acid is propionic anhydride.

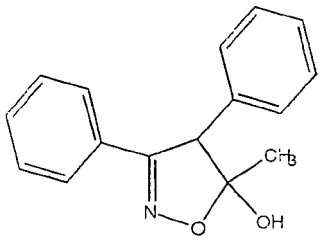
18. A method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b**:



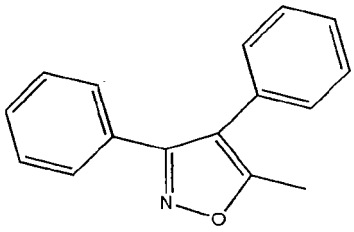
1b

comprising:

contacting a precursor compound selected from the group consisting of Formula **2** and Formula **3**:



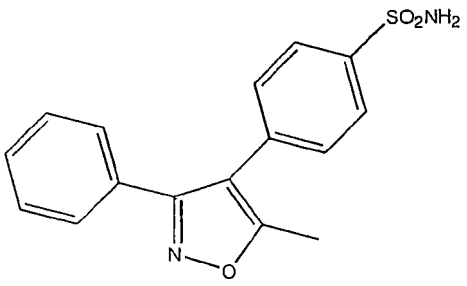
2



3

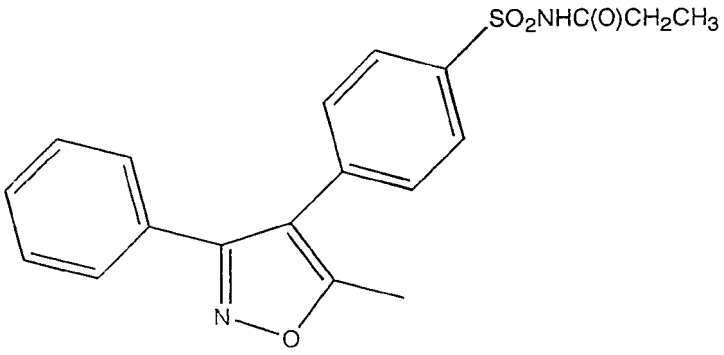
with a halosulfonic acid in the presence of trifluoroacetic acid to produce a halosulfonated product;

contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**:



1

and contacting the [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula 1 with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula 1a:



1a

and further contacting the compound of Formula 1a with a sodium base to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula 1b.

19. The method of claim 18 wherein the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid.

20. The method of claim 18 wherein the halosulfonic acid is chlorosulfonic acid.

21. The method of claim 18 wherein the source of ammonia is selected from the group consisting of ammonium hydroxide and anhydrous ammonia.

22. The method of claim 18 wherein the source of ammonia is ammonium hydroxide.

23. The method of claim 18 wherein the source of ammonia is anhydrous ammonia.

24. The method of claim 18 wherein the propionating agent is selected from the group consisting of an anhydride of propionic acid, a propionyl halide, a propionyl thioester, a propionyl carbonate and a N-propionyl imidazole.

25. The method of claim 24 wherein the propionating agent is a propionyl halide.

26. The method of claim 25 wherein the propionating agent is a propionyl chloride.

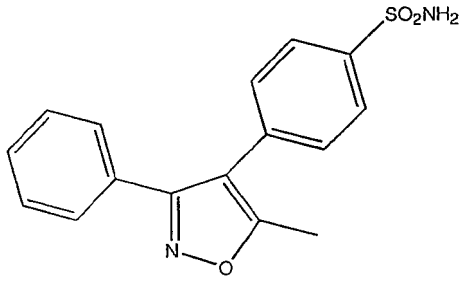
27. The method of claim 24 wherein the propionating agent is an anhydride of propionic acid.

28. The method of claim 24 wherein the anhydride of propionic acid is propionic anhydride.

29. The method of claim 18 wherein the sodium base is selected from the group consisting of sodium hydroxide, a sodium alkoxide, sodium hydride and sodium carbonate.

30. The method of claim 29 wherein the sodium base is sodium hydroxide.

31. A method of preparing an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**:



1

comprising:

forming a diphenylethanone oxime derivative compound by contacting a 1,2-diphenylethanone compound with a source of hydroxylamine;

contacting the oxime derivative compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative;

contacting the diphenylisoxazoline derivative with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product;

and contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**.

32. The method of claim 31 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine.

33. The method of claim 31 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine and a weak acid.

34. The method of claim 33 wherein the weak acid is a carboxylic acid.

35. The method of claim 33 wherein the carboxylic acid is an alkyl carboxylic acid.

36. The method of claim 33 wherein the alkyl carboxylic acid selected from the group consisting of formic acid, acetic acid and propionic acid.

37. The method of claim 33 wherein the alkyl carboxylic acid is acetic acid.

38. The method of claim 31 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine and a conjugate base of a weak acid.

39. The method of claim 38 wherein the conjugate base of a weak acid is sodium acetate.

40. The method of claim 31 wherein the source of hydroxylamine comprises a hydroxylamine salt and a deprotonating base.

41. The method of claim 40 wherein the hydroxylamine salt is selected from a group consisting of hydroxylamine hydrochloride, hydroxylamine sulfate and hydroxylamine acetate.

42. The method of claim 41 wherein the hydroxylamine salt is hydroxylamine hydrochloride.

43. The method of claim 40 wherein the deprotonating base is selected from the group consisting of sodium hydroxide, potassium hydroxide, and sodium acetate.

44. The method of claim 40 wherein the deprotonating base is sodium acetate.

45. The method of claim 40 wherein the source of hydroxylamine comprises hydroxylamine and acetic acid.

46. The method of claim 31 wherein the strong base is selected from the group consisting of a lithium dialkylamide, an aryl lithium, an arylalkyl lithium and an alkyl lithium.

47. The method of claim 31 wherein the strong base is a lithium dialkylamide.

48. The method of claim 47 wherein the strong base is lithium diisopropylamide.

49. The method of 46 wherein the strong base is a C_1 to about C_{10} alkyl lithium.

50. The method of claim 31 wherein the strong base is butyl lithium.

51. The method of claim 31 wherein the strong base is hexyl lithium.

52. The method of claim 31 wherein the strong base is heptyl lithium.

53. The method of claim 31 wherein the strong base is octyl lithium.

54. The method of claim 31 wherein the acetylating agent is selected from the group consisting of an alkyl acetate, an acetic anhydride, an N-alkyl-N-alkoxyacetamide and an acetyl halide.

55. The method of claim 54 wherein the acetylating agent is a C1 to about C6 alkyl acetate.

56. The method of claim 31 wherein the acetylating agent is selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate and butyl acetate.

57. The method of claim 56 wherein the alkyl acetate is ethyl acetate.

58. The method of claim 31 wherein the acetylating agent is an acetyl halide.

59. The method of claim 58 wherein the acetyl halide is acetyl chloride.

60. The method of claim 31 wherein the acetylating agent is acetic anhydride.

61. The method of claim 31 wherein the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid.

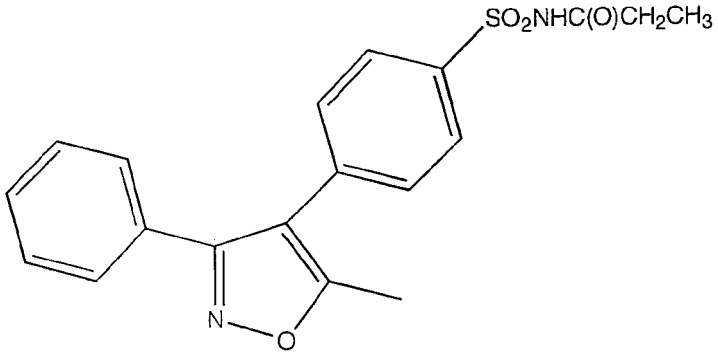
62. The method of claim 31 wherein the halosulfonic acid is chlorosulfonic acid.

63. The method of claim 31 wherein the source of ammonia is selected from the group consisting of ammonium hydroxide and anhydrous ammonia.

64. The method of claim 31 wherein the source of ammonia is ammonium hydroxide.

65. The method of claim 31 wherein the source of ammonia is anhydrous ammonia.

66. A method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a**:



1a

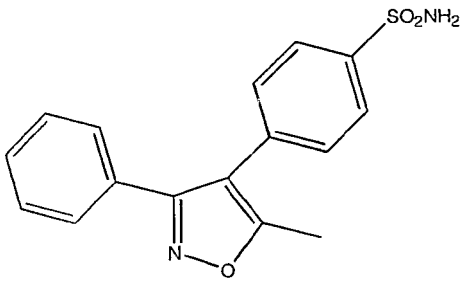
comprising:

forming a diphenylethanone oxime derivative by contacting a 1,2-diphenylethanone compound with a source of hydroxylamine;

contacting the oxime with a strong base and an acetylating agent to form a diphenylisoxazoline derivative;

contacting the diphenylisoxazoline derivative with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product;

contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**:



1

and contacting the [isoxazol-4-yl]benzenesulfonamide compound of Formula **1** with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a**.

67. The method of claim 66 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine.

68. The method of claim 66 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine and a weak acid.

69. The method of claim 68 wherein the weak acid is a carboxylic acid.

70. The method of claim 68 wherein the carboxylic acid is an alkyl carboxylic acid.

71. The method of claim 68 wherein the alkyl carboxylic acid selected from the group consisting of formic acid, acetic acid and propionic acid.

72. The method of claim 68 wherein the alkyl carboxylic acid is acetic acid.

73. The method of claim 66 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine and a conjugate base of a weak acid.

74. The method of claim 73 wherein the conjugate base of a weak acid is sodium acetate.

75. The method of claim 66 wherein the source of hydroxylamine comprises a hydroxylamine salt and a deprotonating base.

76. The method of claim 75 wherein the hydroxylamine salt is selected from a group consisting of hydroxylamine hydrochloride, hydroxylamine sulfate and hydroxylamine acetate.

77. The method of claim 76 wherein the hydroxylamine salt is hydroxylamine hydrochloride.

78. The method of claim 75 wherein the deprotonating base is selected from the group consisting of sodium hydroxide, potassium hydroxide, and sodium acetate.

79. The method of claim 75 wherein the deprotonating base is sodium acetate.

80. The method of claim 75 wherein the source of hydroxylamine comprises hydroxylamine and acetic acid.

81. The method of claim 66 wherein the strong base is selected from the group consisting of a lithium dialkylamide, an aryl lithium, an arylalkyl lithium and an alkyl lithium.

82. The method of claim 66 wherein the strong base is a lithium dialkylamide.

83. The method of claim 82 wherein the strong base is lithium diisopropylamide.

84. The method of claim 81 wherein the strong base is a C_1 to about C_{10} alkyl lithium.

85. The method of claim 66 wherein the strong base is butyl lithium.

86. The method of claim 66 wherein the strong base is hexyl lithium.

87. The method of claim 66 wherein the strong base is heptyl lithium.

88. The method of claim 66 wherein the strong base is octyl lithium.

89. The method of claim 66 wherein the acetylating agent is selected from the group consisting of an alkyl acetate, an acetic anhydride, an N-alkyl-N-alkoxyacetamide and an acetyl halide.

90. The method of claim 89 wherein the acetylating agent is a C1 to about C6 alkyl acetate.

91. The method of claim 66 wherein the acetylating agent is selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate and butyl acetate.

92. The method of claim 91 wherein the alkyl acetate is ethyl acetate.

93. The method of claim 66 wherein the acetylating agent is an acetyl halide.

94. The method of claim 93 wherein the acetyl halide is acetyl chloride.

95. The method of claim 66 wherein the acetylating agent is acetic anhydride.

96. The method of claim 66 wherein the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid.

97. The method of claim 66 wherein the halosulfonic acid is chlorosulfonic acid.

98. The method of claim 66 wherein the source of ammonia is selected from the group consisting of ammonium hydroxide and anhydrous ammonia.

99. The method of claim 66 wherein the source of ammonia is ammonium hydroxide.

100. The method of claim 66 wherein the source of ammonia is anhydrous ammonia.

101. The method of claim 66 wherein the propionating agent selected from the group consisting of an anhydride of propionic acid, a propionyl halide, a propionyl thioester, a propionyl carbonate and a N-propionyl imidazole.

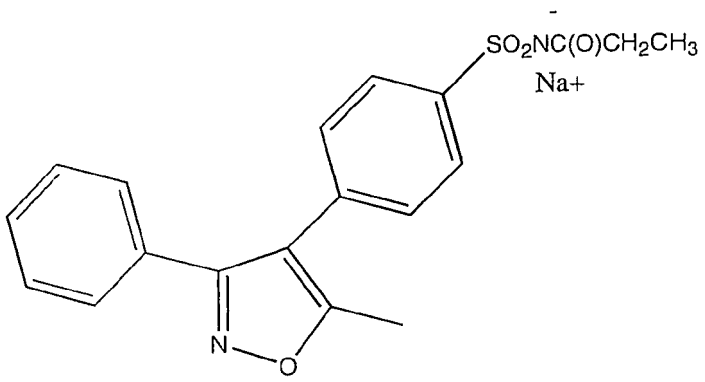
102. The method of claim 101 wherein the propionating agent is a propionyl halide.

103. The method of claim 102 wherein the propionating agent is a propionyl chloride.

104. The method of claim 101 wherein the propionating agent is an anhydride of propionic acid.

105. The method of claim 104 wherein the anhydride of propionic acid is propionic anhydride.

106. A method of preparing an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b**:



1b

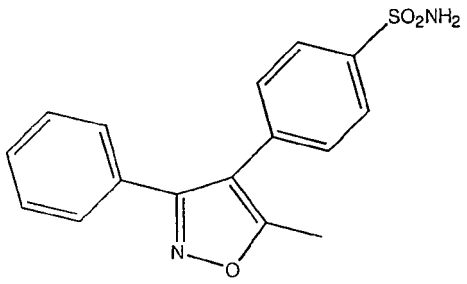
comprising:

forming a diphenylethanone oxime derivative by contacting a 1,2-diphenylethanone compound with a source of hydroxylamine;

contacting the oxime compound with a strong base and an acetylating agent to form a diphenylisoxazoline derivative;

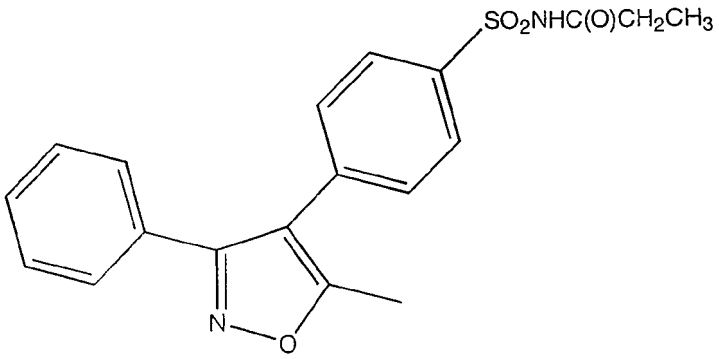
contacting the diphenylisoxazoline derivative with trifluoroacetic acid and a halosulfonic acid to form a halosulfonated product;

contacting the halosulfonated product with a source of ammonia to produce an [isoxazol-4-yl]benzenesulfonamide compound having the structure of Formula **1**:



1

contacting an [isoxazol-4-yl]benzenesulfonamide compound with a propionating agent to produce an N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound having the structure of Formula **1a**:



1a

and contacting the N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide compound

with a sodium base to produce a N-[[4-(3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt compound having the structure of Formula **1b.**

107. The method of claim 106 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine.

108. The method of claim 106 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine and a weak acid.

109. The method of claim 108 wherein the weak acid is a carboxylic acid.

110. The method of claim 108 wherein the carboxylic acid is an alkyl carboxylic acid.

111. The method of claim 108 wherein the alkyl carboxylic acid selected from the group consisting of formic acid, acetic acid and propionic acid.

112. The method of claim 108 wherein the alkyl carboxylic acid is acetic acid.

113. The method of claim 106 wherein the source of hydroxylamine is an aqueous solution comprising hydroxylamine and a conjugate base of a weak acid.

114. The method of claim 113 wherein the conjugate base of a weak acid is sodium acetate.

115. The method of claim 106 wherein the source of hydroxylamine comprises hydroxylamine salt and a deprotonating base.

116. The method of claim 106 wherein the hydroxylamine salt is selected from a group consisting of hydroxylamine hydrochloride, hydroxylamine sulfate and hydroxylamine acetate.

117. The method of claim 116 wherein the hydroxylamine salt is hydroxylamine hydrochloride.

118. The method of claim 115 wherein the deprotonating base is selected from the group consisting of sodium hydroxide, potassium hydroxide, and sodium acetate.

119. The method of claim 115 wherein the deprotonating base is sodium acetate.

120. The method of claim 115 wherein the source of hydroxylamine comprises hydroxylamine and acetic acid.

121. The method of claim 106 wherein the strong base is selected from the group consisting of a lithium dialkylamide, an aryl lithium, an arylalkyl lithium and an alkyl lithium.

122. The method of claim 106 wherein the strong base is a lithium dialkylamide.

123. The method of claim 122 wherein the strong base is lithium diisopropylamide.

124. The method of 121 wherein the strong base is a C_1 to about C_{10} alkyl lithium.

125. The method of claim 106 wherein the strong base is butyl lithium.

126. The method of claim 106 wherein the strong base is hexyl lithium.

127. The method of claim 106 wherein the strong base is heptyl lithium.

128. The method of claim 106 wherein the strong base is octyl lithium.

129. The method of claim 106 wherein the acetylating agent is selected from the group consisting of an alkyl acetate, an acetic anhydride, an N-alkyl-N-alkoxyacetamide and an acetyl halide.

130. The method of claim 240 wherein the acetylating agent is a C1 to about C6 alkyl acetate.

131. The method of claim 106 wherein the acetylating agent is selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate and butyl acetate.

132. The method of claim 131 wherein the alkyl acetate is ethyl acetate.

133. The method of claim 106 wherein the acetylating agent is an acetyl halide.

134. The method of claim 133 wherein the acetyl halide is acetyl chloride.

135. The method of claim 106 wherein the acetylating agent is acetic anhydride.

136. The method of claim 106 wherein the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid.

137. The method of claim 106 wherein the halosulfonic acid is chlorosulfonic acid.

138. The method of claim 106 wherein the source of ammonia is selected from the group consisting of ammonium hydroxide and anhydrous ammonia.

139. The method of claim 106 wherein the source of ammonia is ammonium hydroxide.

140. The method of claim 106 wherein the source of ammonia is anhydrous ammonia.

141. The method of claim 106 wherein the propionating agent selected from the group consisting of an anhydride of propionic acid, a propionyl halide, a propionyl thioester, a propionyl carbonate and a N-propionyl imidazole.

142. The method of claim 141 wherein the propionating agent is a propionyl halide.

143. The method of claim 142 wherein the propionating agent is a propionyl chloride.

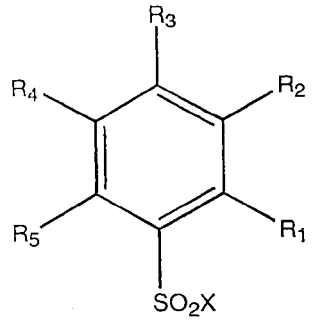
144. The method of claim 141 wherein the propionating agent is an anhydride of propionic acid.

145. The method of claim 144 wherein the anhydride of propionic acid is propionic anhydride.

146. The method of claim 106 wherein the sodium base is selected from the group consisting of sodium hydroxide, a sodium alkoxide, sodium hydride and sodium carbonate.

147. The method of claim 146 wherein the sodium base is sodium hydroxide.

148. A method of preparing a benzenesulfonyl halide compound having the structure of Formula 4



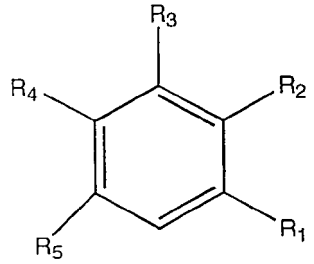
4

wherein:

X is a halogen atom and R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio and acyl;

wherein alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl is each independently optionally substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, alkylaryl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl, halo, haloalkylaryl, alkoxyaryl, haloalkyl, protected hydroxymethyl, arylalkoxymethyl and alkoxyhaloalkyl;

wherein the method comprises contacting a substituted phenyl compound having the structure of Formula **5:**



5

with a halosulfonic acid in the presence of trifluoroacetic acid, thereby forming a benzenesulfonyl halide compound having the structure of Formula **4**.

149. A method of claim 148 wherein the halosulfonic acid is selected from the group consisting of bromosulfonic acid and chlorosulfonic acid.

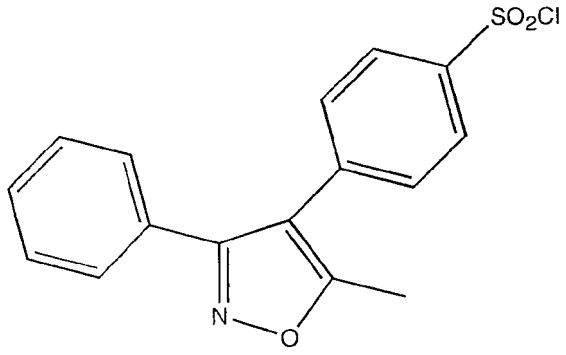
150. A method of claim 148 wherein the halosulfonic acid is chlorosulfonic acid.

151. A method of claim 148 wherein R^3 is heterocyclyl optionally substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, alkylaryl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl, halo, haloalkylaryl, alkoxyaryl, haloalkyl, protected hydroxymethyl, arylalkoxymethyl and alkoxyhaloalkyl; and R^1, R^2, R^4 and R^5 are hydrogen.

152. A method of claim 151 wherein R^3 is selected from the group consisting of isoxazolyl and pyrazolyl, wherein R^3 is optionally substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl,

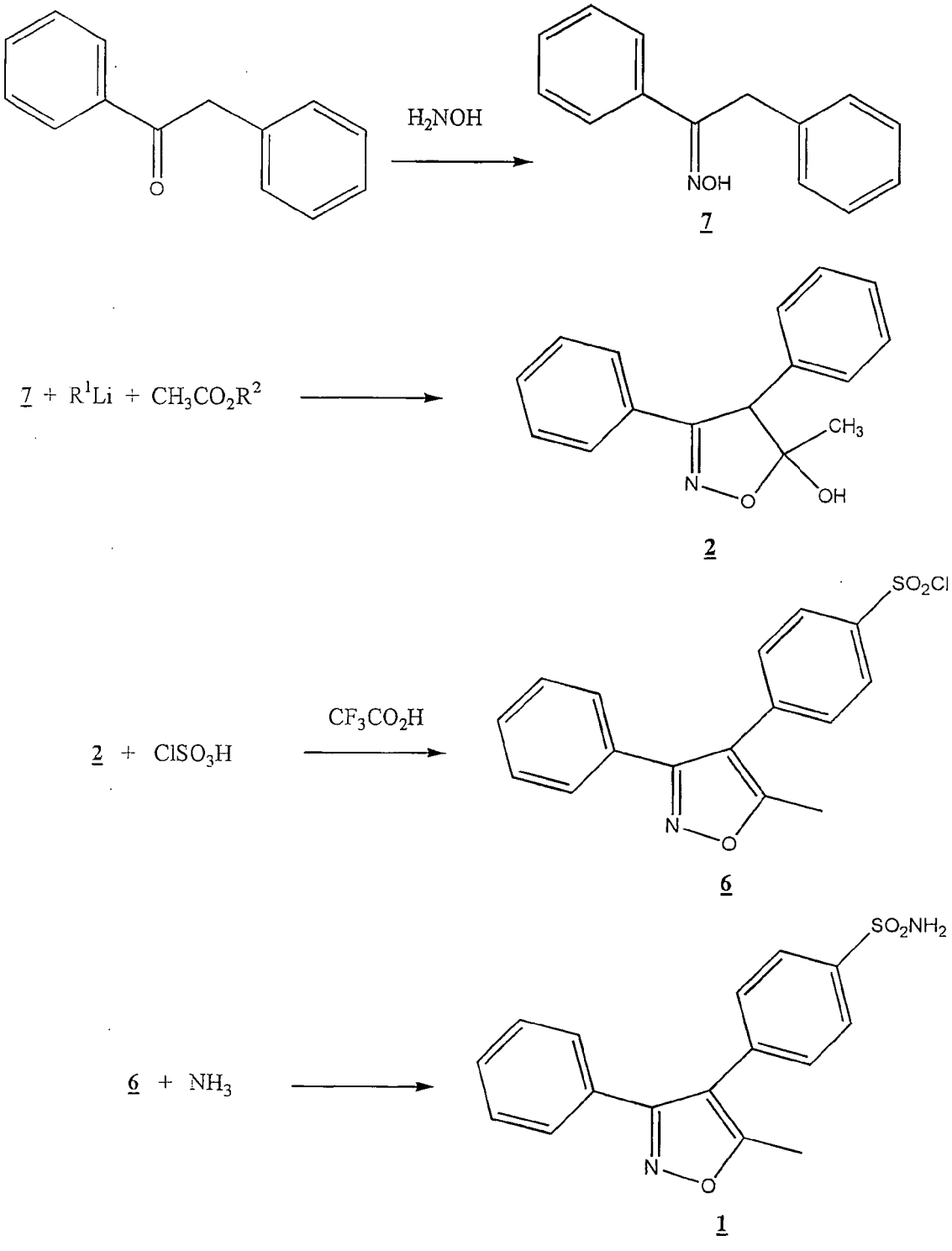
cycloalkyl, alkylaryl, aryl, heterocyclyl, alkoxy, alkylamino, alkylthio, acyl, halo, haloalkylaryl, alkoxyaryl, haloalkyl, protected hydroxymethyl, arylalkoxymethyl and alkoxyhaloalkyl; and R^1, R^2, R^4 and R^5 are hydrogen.

153. A method of claim 152 wherein the benzenesulfonyl halide compound is 4-[5-methyl-3-phenylsioxazol-4-yl]benzenesulfonyl chloride compound having the structure of Formula **6**:



6

FIGURE 1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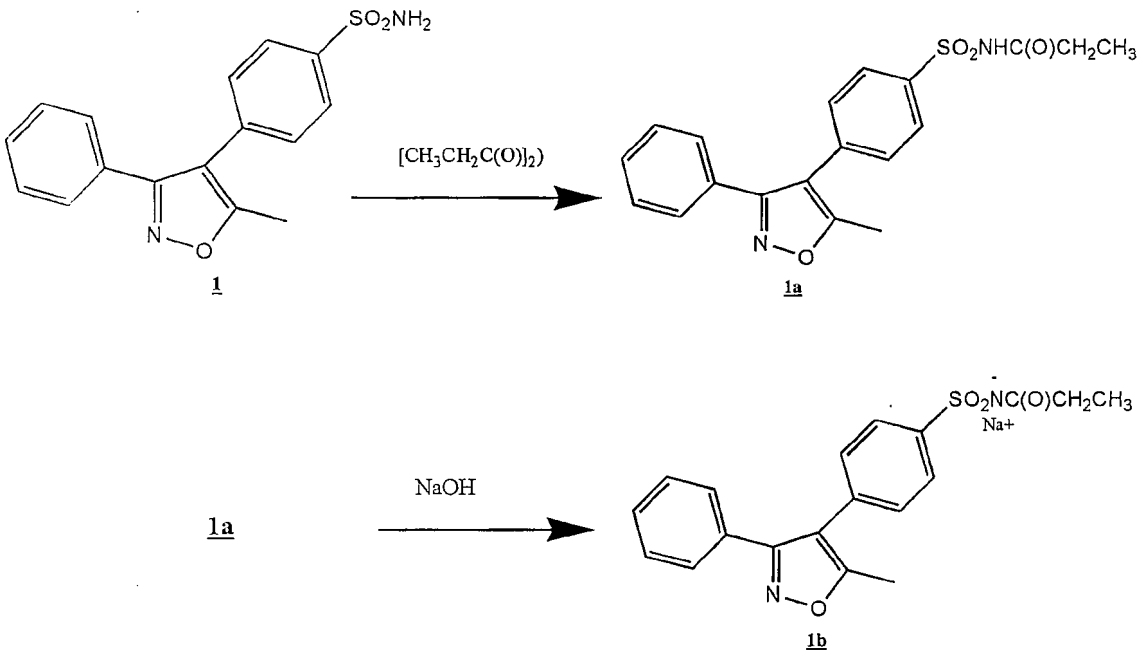
7 + R1Li + CH3CO2R2
CH3
OH
N
O
2
2 + ClSO3H
CF3CO2H
SO2Cl
6
6 + NH3
SO2NH2
1

FIGURE 2


SO2NH2
[CH3CH2C(O)]2)
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O
1
1a
1a
NaOH
SO2NC(O)CH2CH3
Na+
1b

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/31445

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D261/08 C07C303/08

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)
IPC 7 C07D C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 859 257 A (TALLEY JOHN J) 12 January 1999 (1999-01-12) cited in the application column 23, line 33 -column 25, line 67; claim 1; example 1 ---	1-153
Y	US 5 932 598 A (GRANETO MATTHEW J ET AL) 3 August 1999 (1999-08-03) cited in the application column 35, line 42 -column 38, line 52; examples 17,18 ---	1-153
Y	WO 98 51677 A (LIEBERMAN DAVID R ;MILLER ROSS A (US); HUMPHREY GUY R (US); MERCK) 19 November 1998 (1998-11-19) claims 1,7,8; examples 1,2 --- -/--	1-153

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

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

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Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2002	05/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 18954 A (MERCK & CO INC ;BLIZZARD TIMOTHY A (US); RATCLIFFE RONALD W (US)) 22 April 1999 (1999-04-22) page 38 page 39, line 30 -page 40, line 10 ---	1-153
Y	US 4 950 793 A (SOUMA YOSHIE) 21 August 1990 (1990-08-21) column 4, line 14 - line 20; examples 2,7 -----	1-153

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[19] 中华人民共和国国家知识产权局

[51] Int. Cl[7]
C07D261/08
C07C303/08

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[21] 申请号 02821583.4

[43] 公开日 2005 年 2 月 9 日

[11] 公开号 CN 1578774A

[22] 申请日 2002.10.2 [21] 申请号 02821583.4
[30] 优先权
[32] 2001.10.2 [33] US [31] 60/326,677
[86] 国际申请 PCT/US2002/031445 2002.10.2
[87] 国际公布 WO2003/029230 英 2003.4.10
[85] 进入国家阶段日期 2004.4.29
[71] 申请人 法玛西雅公司
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D·J·伽拉赫尔 L·M·肖尼
K·麦克劳格林

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代理人 唐伟杰

IHC040223

权利要求书 14 页 说明书 20 页 附图 2 页

[54] 发明名称 制备苯磺酰基化合物的方法

[57] 摘要

本文提供芳族磺酰卤的制备方法，该方法使取代的苯基化合物与卤磺酸和三氟乙酸接触。本文进一步提供 4 - [5 - 甲基 - 3 - 苯基异噁唑 - 4 - 基] 苯磺酰胺的制备方法，它可用于治疗环加氧酶 - 2 相关性疾病。

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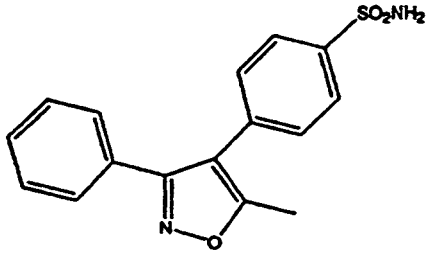
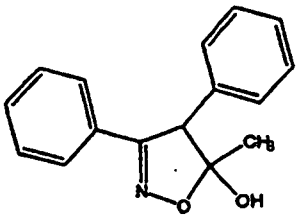
1、制备具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物的方法：



1

包含：

在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物：



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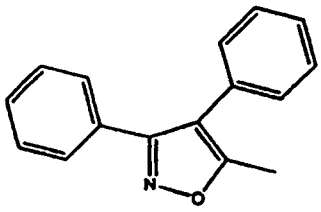


3

与卤磺酸接触，生成卤代磺化产物；

并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物。

2、权利要求 1 的方法，其中该卤磺酸选自溴磺酸和氯磺酸。

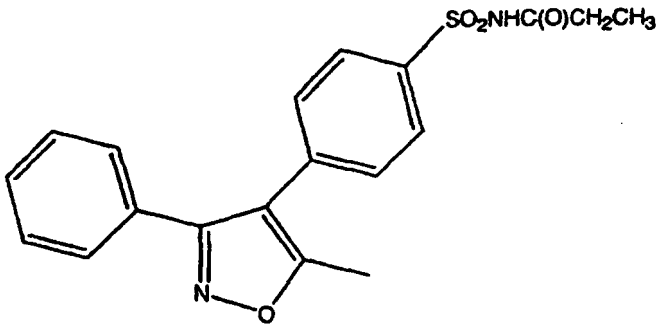
3、权利要求 1 的方法，其中该卤磺酸是氯磺酸。

4、权利要求 1 的方法，其中该氨源选自氢氧化铵和无水氨。

5、权利要求 1 的方法，其中该氨源是氢氧化铵。

6、权利要求 1 的方法，其中该氨源是无水氨。

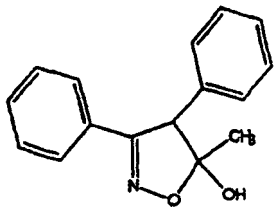
7、制备具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物的方法：



1a

包含:

在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物:



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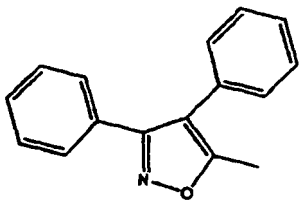
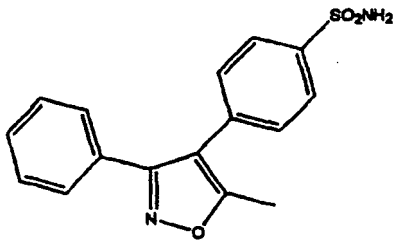


3

与卤磺酸接触，生成卤代磺化产物;

使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物:



1

并使[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物。

8、权利要求 7 的方法，其中该卤磺酸选自溴磺酸和氯磺酸。

9、权利要求 7 的方法，其中该卤磺酸是氯磺酸。

10、权利要求 7 的方法，其中该氨源选自氢氧化铵和无水氨。

11、权利要求 7 的方法，其中该氨源是氢氧化铵。

12、权利要求 7 的方法，其中该氨源是无水氨。

13、权利要求 7 的方法，其中该丙酰化剂选自丙酸的酸酐、丙酰卤、丙酰基硫代酯、丙酰基碳酸酯和 N-丙酰基咪唑。

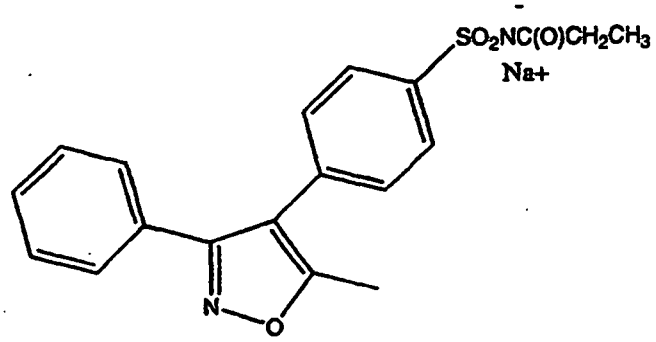
14、权利要求 13 的方法，其中该丙酰化剂是丙酰卤。

15、权利要求 14 的方法，其中该丙酰化剂是丙酰氯。

16、权利要求 13 的方法，其中该丙酰化剂是丙酸的酸酐。

17、权利要求 13 的方法，其中该丙酸的酸酐是丙酸酐。

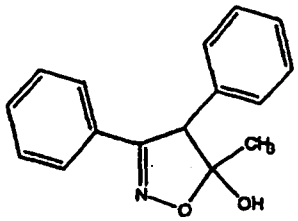
18、制备具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物的方法：



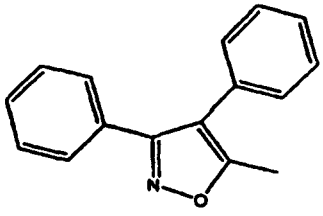
1b

包含：

在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物：



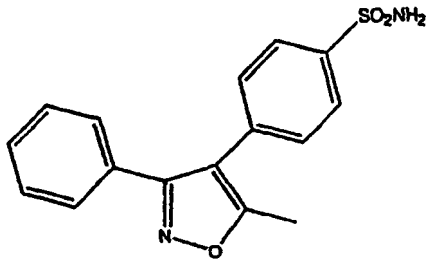
2



3

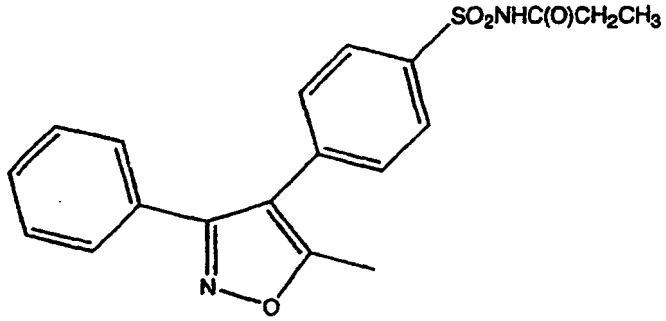
与卤磺酸接触，生成卤代磺化产物；

使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物：



1

并使具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物：



1a

并进一步使式 1a 化合物与钠碱接触，生成具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物。

19、权利要求 18 的方法，其中该卤磺酸选自溴磺酸和氯磺酸。

20、权利要求 18 的方法，其中该卤磺酸是氯磺酸。

21、权利要求 18 的方法，其中该氨源选自氢氧化铵和无水氨。

22、权利要求 18 的方法，其中该氨源是氢氧化铵。

23、权利要求 18 的方法，其中该氨源是无水氨。

24、权利要求 18 的方法，其中该丙酰化剂选自丙酸的酸酐、丙酰卤、丙酰基硫代酯、丙酰基碳酸酯和 N-丙酰基咪唑。

25、权利要求 24 的方法，其中该丙酰化剂是丙酰卤。

26、权利要求 25 的方法，其中该丙酰化剂是丙酰氯。

27、权利要求 24 的方法，其中该丙酰化剂是丙酸的酸酐。

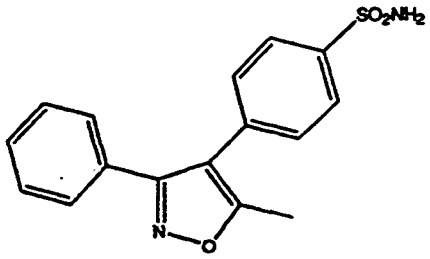
28、权利要求 24 的方法，其中该丙酸的酸酐是丙酸酐。

29、权利要求 18 的方法，其中该钠碱选自氢氧化钠、醇钠、氢化

钠和碳酸钠。

30、权利要求 29 的方法，其中该钠碱是氢氧化钠。

31、制备具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物的方法：



1

包含：

使 1,2-二苯基乙酮化合物与羟胺源接触，生成二苯基乙酮肟衍生物；

使肟衍生化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生物；

使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物；

使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物。

32、权利要求 31 的方法，其中该羟胺源是包含羟胺的水溶液。

33、权利要求 31 的方法，其中该羟胺源是包含羟胺和弱酸的水溶液。

34、权利要求 33 的方法，其中该弱酸是羧酸。

35、权利要求 33 的方法，其中该羧酸是烷基羧酸。

36、权利要求 33 的方法，其中该烷基羧酸选自甲酸、乙酸和丙酸。

37、权利要求 33 的方法，其中该烷基羧酸是乙酸。

38、权利要求 31 的方法，其中该羟胺源是包含羟胺和弱酸共轭碱的水溶液。

39、权利要求 38 的方法，其中该弱酸共轭碱是乙酸钠。

40、权利要求 31 的方法，其中该羟胺源包含羟胺盐和去质子化碱。

41、权利要求 40 的方法，其中该羟胺盐选自盐酸羟胺、硫酸羟胺和乙酸羟胺。

42、权利要求 41 的方法，其中该羟胺盐是盐酸羟胺。

43、权利要求 40 的方法，其中该去质子化碱选自氢氧化钠、氢氧化钾和乙酸钠。

44、权利要求 40 的方法，其中该去质子化碱是乙酸钠。

45、权利要求 40 的方法，其中该羟胺源包含羟胺和乙酸。

46、权利要求 31 的方法，其中该强碱选自二烷基氨基化锂、芳基锂、芳基烷基锂和烷基锂。

47、权利要求 31 的方法，其中该强碱是二烷基氨基化锂。

48、权利要求 47 的方法，其中该强碱是二异丙氨基化锂。

49、权利要求 46 的方法，其中该强碱是 C_1 至约 C_{10} 烷基锂。

50、权利要求 31 的方法，其中该强碱是丁基锂。

51、权利要求 31 的方法，其中该强碱是己基锂。

52、权利要求 31 的方法，其中该强碱是庚基锂。

53、权利要求 31 的方法，其中该强碱是辛基锂。

54、权利要求 31 的方法，其中该乙酰化剂选自烷基乙酸酯、乙酸酐、N-烷基-N-烷氧基乙酰胺和乙酰卤。

55、权利要求 54 的方法，其中该乙酰化剂是 C_1 至约 C_6 烷基乙酸酯。

56、权利要求 31 的方法，其中该乙酰化剂选自乙酸甲酯、乙酸乙酯、乙酸丙酯和乙酸丁酯。

57、权利要求 56 的方法，其中该烷基乙酸酯是乙酸乙酯。

58、权利要求 31 的方法，其中该乙酰化剂是乙酰卤。

59、权利要求 58 的方法，其中该乙酰卤是乙酰氯。

60、权利要求 31 的方法，其中该乙酰化剂是乙酸酐。

61、权利要求 31 的方法，其中该卤磺酸选自溴磺酸和氯磺酸。

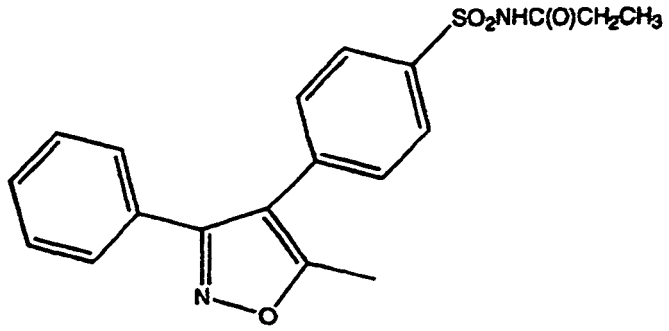
62、权利要求 31 的方法，其中该卤磺酸是氯磺酸。

63、权利要求 31 的方法，其中该氨源选自氢氧化铵和无水氨。

64、权利要求 31 的方法，其中该氨源是氢氧化铵。

65、权利要求 31 的方法，其中该氨源是无水氨。

66、制备具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物的方法：



1a

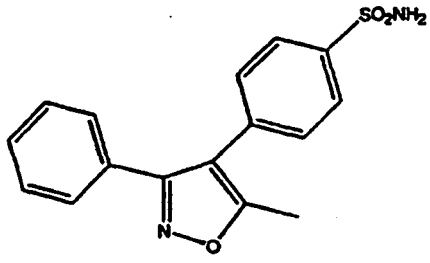
包含：

使 1,2-二苯基乙酮化合物与羟胺源接触，生成二苯基乙酮肟衍生物；

使肟与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生物；

使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物；

使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物：



1

并使式 1[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物。

67、权利要求 66 的方法，其中该羟胺源是包含羟胺的水溶液。

68、权利要求 66 的方法，其中该羟胺源是包含羟胺和弱酸的水溶

液。

69、权利要求 68 的方法，其中该弱酸是羧酸。

70、权利要求 68 的方法，其中该羧酸是烷基羧酸。

71、权利要求 68 的方法，其中该烷基羧酸选自甲酸、乙酸和丙酸。

72、权利要求 68 的方法，其中该烷基羧酸是乙酸。

73、权利要求 66 的方法，其中该羟胺源是包含羟胺和弱酸共轭碱的水溶液。

74、权利要求 73 的方法，其中该羧酸共轭碱是乙酸钠。

75、权利要求 66 的方法，其中该羟胺源包含羟胺盐和去质子化碱。

76、权利要求 75 的方法，其中该羟胺盐选自盐酸羟胺、硫酸羟胺和乙酸羟胺。

77、权利要求 76 的方法，其中该羟胺盐是盐酸羟胺。

78、权利要求 75 的方法，其中该去质子化碱选自氢氧化钠、氢氧化钾和乙酸钠。

79、权利要求 75 的方法，其中该去质子化碱是乙酸钠。

80、权利要求 75 的方法，其中该羟胺源包含羟胺和乙酸。

81、权利要求 66 的方法，其中该强碱选自二烷基氨基化锂、芳基锂、芳基烷基锂和烷基锂。

82、权利要求 66 的方法，其中该强碱是二烷基氨基化锂。

83、权利要求 82 的方法，其中该强碱是二异丙氨基化锂。

84、权利要求 81 的方法，其中该强碱是 C_1 至约 C_{10} 烷基锂。

85、权利要求 66 的方法，其中该强碱是丁基锂。

86、权利要求 66 的方法，其中该强碱是己基锂。

87、权利要求 66 的方法，其中该强碱是庚基锂。

88、权利要求 66 的方法，其中该强碱是辛基锂。

89、权利要求 66 的方法，其中该乙酰化剂选自烷基乙酸酯、乙酸酐、N-烷基-N-烷氧基乙酰胺和乙酰卤。

90、权利要求 89 的方法，其中该乙酰化剂是 C_1 至约 C_6 烷基乙酸酯。

91、权利要求 66 的方法，其中该乙酰化剂选自乙酸甲酯、乙酸乙酯、乙酸丙酯和乙酸丁酯。

92、权利要求 91 的方法，其中该烷基乙酸酯是乙酸乙酯。

93、权利要求 66 的方法，其中该乙酰化剂是乙酰卤。

94、权利要求 93 的方法，其中该乙酰卤是乙酰氯。

95、权利要求 66 的方法，其中该乙酰化剂是乙酸酐。

96、权利要求 66 的方法，其中该卤磺酸选自溴磺酸和氯磺酸。

97、权利要求 66 的方法，其中该卤磺酸是氯磺酸。

98、权利要求 66 的方法，其中该氨源选自氢氧化铵和无水氨。

99、权利要求 66 的方法，其中该氨源是氢氧化铵。

100、权利要求 66 的方法，其中该氨源是无水氨。

101、权利要求 66 的方法，其中该丙酰化剂选自丙酸的酸酐、丙酰卤、丙酰基硫代酯、丙酰基碳酸酯和 N-丙酰基咪唑。

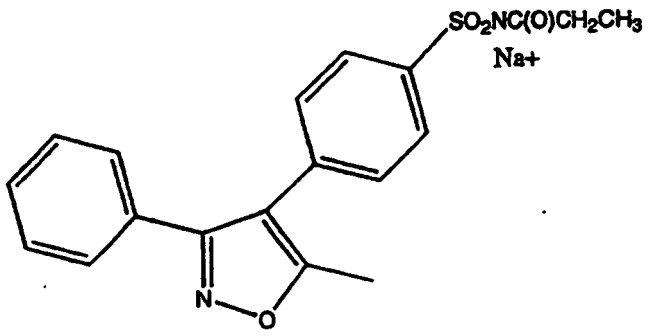
102、权利要求 101 的方法，其中该丙酰化剂是丙酰卤。

103、权利要求 102 的方法，其中该丙酰化剂是丙酰氯。

104、权利要求 101 的方法，其中该丙酰化剂是丙酸的酸酐。

105、权利要求 104 的方法，其中该丙酸的酸酐是丙酸酐。

106、制备具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物的方法：



1b

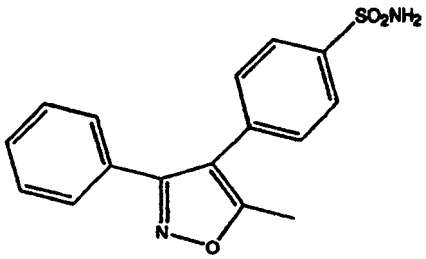
包含：

使 1,2-二苯基乙酮化合物与羟胺源接触，生成二苯基乙酮肟衍生物；

使该肟化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生物；

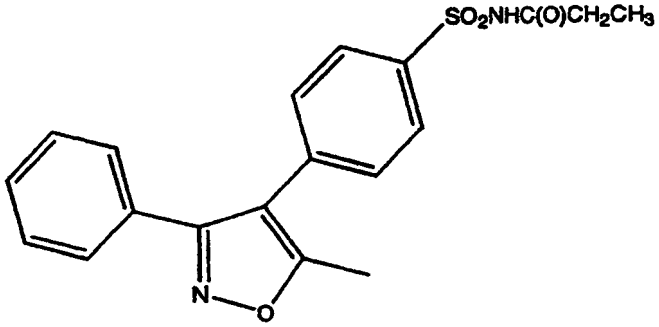
使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物；

使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物：



1

使[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物：



1a

并使 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物与钠碱接触，生成具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物。

107、权利要求 106 的方法，其中该羟胺源是包含羟胺的水溶液。

108、权利要求 106 的方法，其中该羟胺源是包含羟胺和弱酸的水溶液。

109、权利要求 108 的方法，其中该弱酸是羧酸。

110、权利要求 108 的方法，其中该羧酸是烷基羧酸。

111、权利要求 108 的方法，其中该烷基羧酸选自甲酸、乙酸和丙

酸。

112、权利要求 108 的方法，其中该烷基羧酸是乙酸。

113、权利要求 106 的方法，其中该羟胺源是包含羟胺和弱酸共轭碱的水溶液。

114、权利要求 113 的方法，其中该羧酸共轭碱是乙酸钠。

115、权利要求 106 的方法，其中该羟胺源包含羟胺盐和去质子化碱。

116、权利要求 106 的方法，其中该羟胺盐选自盐酸羟胺、硫酸羟胺和乙酸羟胺。

117、权利要求 116 的方法，其中该羟胺盐是盐酸羟胺。

118、权利要求 115 的方法，其中该去质子化碱选自氢氧化钠、氢氧化钾和乙酸钠。

119、权利要求 115 的方法，其中该去质子化碱是乙酸钠。

120、权利要求 115 的方法，其中该羟胺源包含羟胺和乙酸。

121、权利要求 106 的方法，其中该强碱选自二烷基氨基化锂、芳基锂、芳基烷基锂和烷基锂。

122、权利要求 106 的方法，其中该强碱是二烷基氨基化锂。

123、权利要求 122 的方法，其中该强碱是二异丙氨基化锂。

124、权利要求 121 的方法，其中该强碱是 C_1 至约 C_{10} 烷基锂。

125、权利要求 106 的方法，其中该强碱是丁基锂。

126、权利要求 106 的方法，其中该强碱是己基锂。

127、权利要求 106 的方法，其中该强碱是庚基锂。

128、权利要求 106 的方法，其中该强碱是辛基锂。

129、权利要求 106 的方法，其中该乙酰化剂选自烷基乙酸酯、乙酸酐、N-烷基-N-烷氧基乙酰胺和乙酰卤。

130、权利要求 240 的方法，其中该乙酰化剂是 C_1 至约 C_6 烷基乙酸酯。

131、权利要求 106 的方法，其中该乙酰化剂选自乙酸甲酯、乙酸乙酯、乙酸丙酯和乙酸丁酯。

132、权利要求 131 的方法，其中该烷基乙酸酯是乙酸乙酯。

133、权利要求 106 的方法，其中该乙酰化剂是乙酰卤。

134、权利要求 133 的方法，其中该乙酰卤是乙酰氯。

135、权利要求 106 的方法，其中该乙酰化剂是乙酸酐。

136、权利要求 106 的方法，其中该卤磺酸选自溴磺酸和氯磺酸。

137、权利要求 106 的方法，其中该卤磺酸是氯磺酸。

138、权利要求 106 的方法，其中该氨源选自氢氧化铵和无水氨。

139、权利要求 106 的方法，其中该氨源是氢氧化铵。

140、权利要求 106 的方法，其中该氨源是无水氨。

141、权利要求 106 的方法，其中该丙酰化剂选自丙酸的酸酐、丙酰卤、丙酰基硫代酯、丙酰基碳酸酯和 N-丙酰基咪唑。

142、权利要求 141 的方法，其中该丙酰化剂是丙酰卤。

143、权利要求 142 的方法，其中该丙酰化剂是丙酰氯。

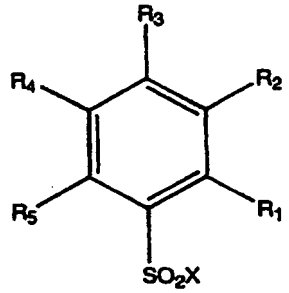
144、权利要求 141 的方法，其中该丙酰化剂是丙酸的酸酐。

145、权利要求 144 的方法，其中该丙酸的酸酐是丙酸酐。

146、权利要求 106 的方法，其中该钠碱选自氢氧化钠、醇钠、氢化钠和碳酸钠。

147、权利要求 146 的方法，其中该钠碱是氢氧化钠。

148、制备具有式 4 结构的苯磺酰卤化合物的方法：



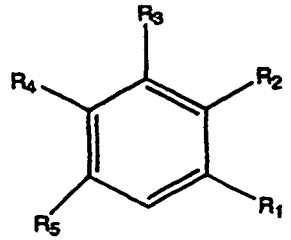
4

其中：

X 是卤原子，R^1、R^2、R^3、R^4和 R^5独立地选自氢、烷基、链烯基、炔基、环烷基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基；

其中烷基、链烯基、环烷基、芳基、杂环基各自可选被一个或多个基团取代，取代基选自烷基、链烯基、炔基、环烷基、烷芳基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基、卤素、卤代烷基芳基、卤代烷基和烷氧基卤代烷基；

其中该方法包含在三氟乙酸的存在下，使具有式 5 结构的取代的苯基化合物：



5

与卤磺酸接触，由此生成具有式 4 结构的苯磺酰卤化合物。

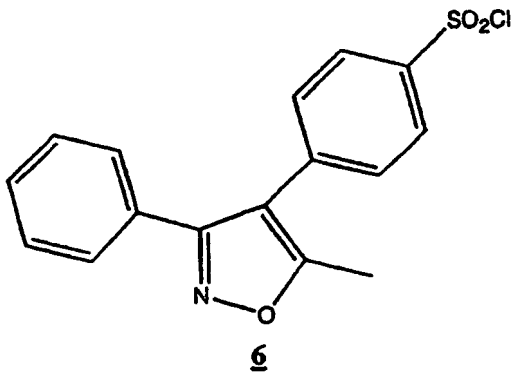
149、权利要求 148 的方法，其中该卤磺酸选自溴磺酸和氯磺酸。

150、权利要求 148 的方法，其中该卤磺酸是氯磺酸。

151、权利要求 148 的方法，其中 R^3 是杂环基，可选地被一个或多个基团取代，取代基选自烷基、链烯基、炔基、环烷基、杂芳基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基、卤素、卤代烷基芳基、烷氧基芳基、卤代烷基、被保护的羟甲基、芳基烷氧基甲基和烷氧基卤代烷基；并且 R^1、R^2、R^4 和 R^5 是氢。

152、权利要求 151 的方法，其中 R^3 选自异噁唑基和吡唑基，其中 R^3 可选被一个或多个基团取代，取代基选自烷基、链烯基、炔基、环烷基、烷芳基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基、卤素、卤代烷基芳基、烷氧基芳基、卤代烷基、被保护的羟甲基、芳基烷氧基甲基和烷氧基卤代烷基；R^1、R^2、R^4 和 R^5 是氢。

153、权利要求 152 的方法，其中该苯磺酰卤化合物是具有式 6 结构的 4-[5-甲基-3-苯基异噁唑-4-基]苯磺酰氯化合物：



6

制备苯磺酰基化合物的方法

发明背景

发明领域

本发明涉及制备芳族磺酰氯和异噁唑基苯磺酰胺的方法。该方法尤其涉及伐地考昔(valdecoxib)、帕来考昔(parecoxib)、帕来考昔钠和和 4-[5-甲基-3-苯基异噁唑-4-基]苯磺酰氯的制备方法。

有关技术的说明

用于治疗炎症的取代的异噁唑化合物描述在美国专利 5,633,272 中。制备取代的异噁唑-4-基苯磺酰胺化合物的方法描述在美国专利 5,859,257 中。制备 COX-2 抑制剂前体药物的方法描述在美国专利 5,932,598 中。Ullmann's Encyclopedia of Industrial chemistry, 5th Edition Vol. A3 page 513 描述了使用过量氯磺酸制备芳族磺酰氯。Ullmann's Encyclopedia 还描述了从芳族磺酰氯制备芳族磺酰胺。

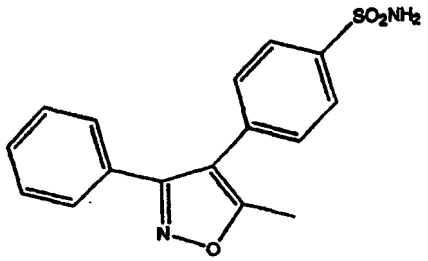
在氯磺化反应中，通过用溶剂稀释或者加入砜生成抑制性物质，利用大为过量的氯磺酸可以最小化次级反应，例如砜的生成和多氯磺化，如美国专利 5,136,043 所述。额外氯化剂、例如亚硫酰氯的加入(EP 115,328)使该方法复杂化，因为掺入了附加的操作，使废物处理复杂化，同时因反应剂的不溶性而没有解决反应性问题。氯化溶剂、例如四氯化碳、氯仿或二氯甲烷的使用尽管在部分程度上解决了一些溶解性问题，不过因生成两相反应物而使方法操作复杂化，因这些溶剂的挥发性与毒性而产生雇员受污染的问题，而且将这些氯化溶剂引入废液。日本专利申请号 JP06-145227 描述了在 AIBN（基团生成剂）的存在下，高密度聚乙烯(HDPE)与磺酰氯在三氯乙酸中反应得到氯磺化的聚乙烯，后者用于橡胶的制造。

发明概述

芳族磺酰胺的合成和异噁唑基苯磺酰胺化合物在治疗炎症中的应

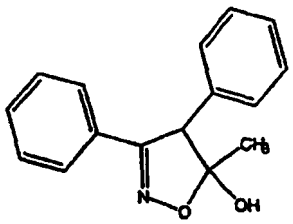
用领域内的工作正在致力于满足对这些化合物的经济、实用和环境上可接受的制备方法的不断需要。

本发明提供新的一般制备芳族磺酰卤化合物和对应的异噁唑基苯磺酰胺化合物，N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物和 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物的方法。在本发明的若干实施方案中可以提到芳族磺酰卤化合物的制备方法；制备[异噁唑-4-基]苯磺酰胺化合物，N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物和 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物的方法。在本发明的一种实施方案中，本发明提供制备具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物的方法：

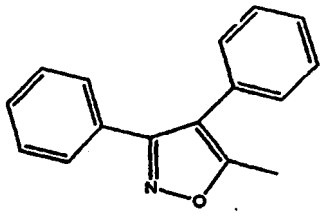


1

其中该方法包含在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物：



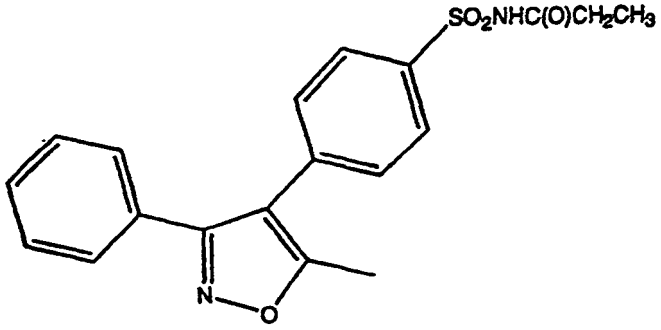
2



3

与卤磺酸接触，生成卤代磺化产物；并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物（伐地考昔）。

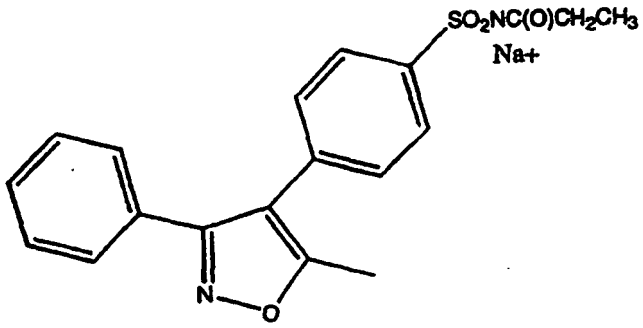
在本发明的另一种实施方案中，本发明提供制备具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺（帕来考昔）的方法：



1a

其中该方法包含在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物与卤磺酸接触，生成卤代磺化产物；并使卤代磺化产物与氨源接触，生成[异噁唑-4-基]苯磺酰胺；并使磺酰胺与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物。

在本发明的另一种实施方案中，本发明提供制备具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐（帕来考昔钠）的方法：



1b

其中该方法包含在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物与卤磺酸接触，生成卤代磺化产物；并使卤代磺化产物与氨源接触，生成[异噁唑-4-基]苯磺酰胺；并使磺酰胺与丙酰化剂接触，生成 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺；并使丙酰胺与钠碱接触，生成具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物。

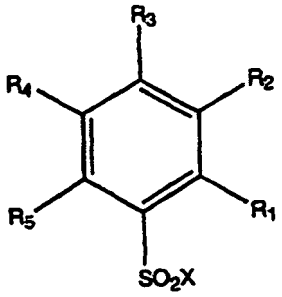
在本发明的另一种实施方案中，本发明提供制备具有式 1 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]磺酰胺的方法，其中该方法包

含使 1,2-二苯基乙酮与羟胺源接触，生成二苯基乙酮肟衍生物；并使所述肟化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生化合物；并使二苯基异噁唑啉衍生化合物与三氟乙酸和卤磺酸接触，生成卤代磺化产物；并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物。

在另一种实施方案中，本发明提供制备具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺的方法，其中该方法包含使 1,2-二苯基乙酮与羟胺源接触，生成二苯基乙酮肟衍生化合物；使所述肟化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生化合物；使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物；使卤代磺化产化合物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物；并使磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物。

在另一种实施方案中，本发明提供制备具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物的方法，其中该方法包含使 1,2-二苯基乙酮与羟胺源接触，生成二苯基乙酮肟衍生化合物；使所述肟衍生化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生物；使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物；使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺；使磺酰胺与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物；并使丙酰胺化合物与钠碱接触，生成具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物。

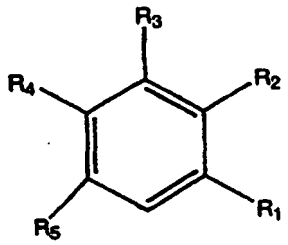
在另一种实施方案中，本发明提供制备具有式 4 结构的苯磺酰卤化合物的方法：



4

其中 X 是卤原子，R^1、R^2、R^3、R^4和 R^5独立地选自氢、烷基、链烯基、炔基、环烷基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基；其中烷基、链烯基、炔基、环烷基、芳基、杂环基各自可选被一个或多个基团取代，取代基选自烷基、链烯基、炔基、环烷基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基、卤素、卤代烷基芳基、烷氧基芳基、卤代烷基和烷氧基卤代烷基；

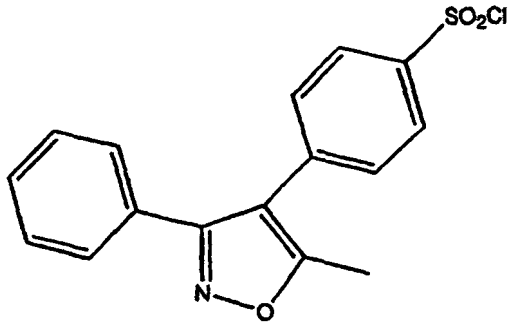
其中该方法包含在三氟乙酸的存在下，使具有式 5 结构的取代的苯基化合物：



5

与卤磺酸接触，由此生成苯磺酰卤化合物。

在另一种实施方案中，本发明提供制备 5-苯基异噁唑-4-基苯磺酰卤的方法，其中该方法包含在三氟乙酸的存在下，使 4,5-二苯基异噁唑化合物与卤磺酸接触，由此生成具有式 6 结构的 5-苯基异噁唑-4-基苯磺酰卤化合物：



6

本发明适用性的进一方面将因下列详细描述而显而易见。不过，应当理解的是下列详细描述和实施例尽管指出了优选的发明实施方案，不过仅供例示，从这种详细描述在发明精神与范围内进行各种改变和修饰都将对本领域技术人员描述显而易见。

附图简述

图 1 显示可以制备具有式 1 结构的 4-[5-甲基-3-苯基异噁唑-4-基]苯磺酰胺的方法。

图 2 显示可以从具有式 1 结构的化合物制备具有式 1a 和 1b 结构的化合物的方法。

优选实施方案的详细描述

下列详细描述供帮助本领域技术人员实施本发明。既便如此，这种详细描述不应被解释为不适当地限制本发明，因为本领域普通技术人员可以在本文所讨论的实施方案中进行修饰和变化，而不背离本发明发现的精神或范围。

本文引用的每份参考文献的内容、包括在这些原始参考文献内引用的参考文献的内容都完整结合在此作为参考。

a. 定义

为了帮助读者理解本发明的详细说明，提供下列定义。

“烷基”、“链烯基”和“炔基”除非另有注释，在本发明中各自是直链或支链烃基，就烷基而言具有一至约二十个碳，或者就链烯基和炔基而言具有二至约二十个碳，并因此例如分别表示甲基、乙基、丙基、丁基、戊基或己基，和乙烯基、丙烯基、丁烯基、戊烯基或己

烯基，和乙炔基、丙炔基、丁炔基、戊炔基或己炔基和它们的异构体。

“环烷基”是单环或多环的碳环，其中每个环含有三至十个碳原子，其中任意环可以含有一个或两上双键或叁键。实例包括环丙基、环丁基、环戊基、环己基、环烯基和环庚基。

“芳基”表示完全不饱和的单环或多环碳环，包括但不限于取代或未取代的苯基、萘基或蒽基。

“杂环基”表示饱和或不饱和的单环或多环碳环，其中一个或多个碳 原子可以被 N、S、P 或 O 代替。这例如包括下列结构：

其中 Z、Z^1、Z^2或 Z^3是 C、S、P、O 或 N，其条件是 Z、Z^1、Z^2或 Z^3之一不是碳，但是当通过双键附着于另一 Z 原子或者附着于另一 O 或 S 原子时不是 O 或 S。此外，仅当各自是 C 时，可选的取代基被理解为附着于 Z、Z^1、Z^2或 Z^3。有关分子的附着点可以是杂原子或者环内别处。

术语“烷氧基”表示包含与氧原子键合的烷基基团的基团，例如甲氧基基团。更优选的烷氧基基团是具有一至十个碳原子的“低级烷氧基”基团。这类基团的实例包括甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基和叔丁氧基。

术语“烷基氨基”表示包含与氮原子键合的烷基基团的基团，例如 N-甲基氨基基团。更优选的基团是具有一至十个碳原子的“低级烷基氨基”基团。这类基团的实例包括 N-甲基氨基、N,N-二甲基氨基、N-乙基氨基、N,N-二乙基氨基、N,N-二丙基氨基、N-丁基氨基和 N-甲基-N-乙基氨基。

术语“烷硫基”表示包含与硫原子键合的烷基基团的基团，例如甲硫基基团。更优选的烷硫基基团是具有一至十个碳原子的“低级烷硫基”基团。这类基团的实例包括甲硫基、乙硫基、丙硫基和丁硫基。

术语“酰基”表示包含与羧基键合的烷基或芳基基团的基团，例

如羧甲基基团。更优选的酰基基团是具有一至十个碳原子的“羧基低级烷基”基团和羧基苯基基团。这类基团的实例包括羧甲基、羧乙基和羧丙基。

术语“卤素”表示氟、氯、溴或碘基团。

术语“卤代烷基”表示被一个或多个卤素取代的烷基。这类基团的实例包括氯甲基、二氟甲基、三氟甲基、五氟乙基、二氯甲基和三氯甲基。

当联合使用时，例如“卤代烷基芳基”、“烷氧基芳基”或“烷氧基卤代烷基”，上列各术语具有如上所示含义。

本文所用的 Me 表示甲基，Et 表示乙基，Pr 表示丙基，i-Pr 或 Pr^i 各自表示异丙基，Bu 表示丁基，t-Bu 或 Bu^t 各自表示叔丁基。

弱酸是这样一种强度的酸，以生成足够的质子化羟胺，与二苯基乙酮化合物反应生成二苯基乙酮肟衍生物。

强碱是这样一种碱，一旦接触肟衍生化合物即生成足够的二阴离子物质，以进一步与乙酰化剂反应。

去质子化碱是这样一种碱，它与羟胺盐反应生成足够的羟胺，以进一步与二苯基乙酮化合物反应生成二苯基乙酮肟衍生物。

丙酰化剂表示这样一种试剂，一旦接触具有式 1 结构的苯磺酰胺化合物即生成磺酰基丙酰胺化合物。丙酰化剂可以包括活性酯，例如丙酰基酸酐、丙酰基混合酸酐、丙酰基硫代酯、丙酰基碳酸酯等。丙酰化剂还包括丙酰卤，优选丙酰氯；活性酰胺，例如 N-丙酰基咪唑、N-烷基-N-烷氧基丙酰胺等。更多的活性丙酰化剂描述在 M. Bodanszky, Principles of Peptide Synthesis 14-61 (second revised edition, Springer Verlag 1993)中。

酰化剂是这样一种试剂，一旦在强碱的存在下接触 1,2-二苯基乙酮衍生物肟即生成具有式 2 和/或 3 结构的异噁唑基化合物或异噁唑化合物。酰化剂可以包括乙酸酐，优选二乙酸酐。酰化剂还可以包括酰卤，优选乙酰氯。酰化剂还可以包括 C1 至约 C6 烷基乙酸酯，选自乙酸甲酯、乙酸乙酯、乙酸丙酯和乙酸丁酯，更优选乙酸乙酯。

钠碱是这样一种碱，一旦与具有式 1a 结构的苯丙酰胺化合物接触即生成磺酰基丙酰胺钠盐化合物。钠碱可以包括氢氧化钠，醇钠，例如乙醇钠或甲醇钠。钠碱还可以是氢化钠或碳酸钠。

保护基团是这样一种化学部分，它能够保护分子的化学官能度，同时该分子在分子的不同位置经历化学反应。优选地，在化学反应之后可以除去保护基团，以暴露原来的化学官能度。例如，羟基保护基团可以保护羟基。被保护的羟甲基包含这样一种羟甲基，其中该羟基被保护基团所保护。有用的保护基团可以在化学性质上有很多变化。大量羟基保护基团描述在 **Theodora W. Greene and Peter G. M. Wuts Protective Groups in Organic Chemistry 86-97 (Third Edition, John Wiley & Sons, 1999)**中。被保护的羟甲基的实例有失活的苄氧基甲基等。

b. 方法细节

按照本发明，现在提供制备苯磺酰基衍生物的方法，特别是具有式 6 结构的 4-[5-甲基-3-苯基异噁唑-4-基]苯磺酰氯、具有式 1 结构的 4-[5-甲基-3-苯基异噁唑-4-基]苯磺酰胺（伐地考昔）、具有式 1a 结构的 N-[[4-(5-甲基-4-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺（帕来考昔）和具有式 1b 结构的 N-[[4-(5-甲基-4-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐（帕来考昔钠）。图 1 提供利用本发明制备伐地考昔的方法图示。图 2 提供利用本发明从伐地考昔制备帕来考昔和帕来考昔钠的方法图示。

在一种实施方案中，本发明提供制备具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物的方法，包含在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物与卤磺酸接触，生成卤代磺化产物，并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物。用于本发明多种实施方案的卤磺酸例如可以是任意适宜的卤磺酸。优选地，卤磺酸选自溴磺酸和氯磺酸，更优选氯磺酸。用于本发明多种实施方案的氨源例如可以选自氢氧化铵和无水氨。更优选的氨源包含氢氧化铵。在另一种优选的实施方案中，氨源包含无水氨。

在另一种实施方案中，本发明提供制备具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物的方法，包含在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物与卤磺酸接触，生成卤代磺化产物，并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物，使[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物。用于本发明多种实施方案的丙酰化剂例如可以选自丙酸的酸酐、丙酰卤、丙酰基硫代酯、丙酰基碳酸酯和 N-丙酰基咪唑。优选地，丙酰化剂是丙酸的酸酐，更优选丙酸酐，进而更优选丙酰卤，进而更优选丙酰氯。

在另一种实施方案中，本发明提供制备具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物的方法，包含在三氟乙酸的存在下，使选自式 2 和式 3 的前体化合物与卤磺酸接触，生成卤代磺化产物，并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物，使[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物，进一步使式 1a 化合物与钠碱接触，生成具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物。用于本发明多种实施方案的钠碱例如选自氢氧化钠、醇钠、氢化钠和碳酸钠。优选地，钠碱是甲醇钠，更优选地，钠碱是氢氧化钠。

在另一种实施方案中，本发明提供制备具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物的方法，包含使 1,2-二苯基乙酮与羟胺源接触，生成二苯基乙酮肟衍生化合物，使肟衍生化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生物，使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物，并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物。用于本发明多种实施方案的羟胺源例如可以是包含羟胺的水溶液。优选地，羟胺源是包含羟胺和弱酸的水溶液，其中该弱酸是羧酸，并优选烷基羧酸，进而更优选地，该烷基羧酸选自甲酸、乙酸和丙酸，更优选地是乙酸。最

优选地，羟胺源是羟胺与乙酸的水溶液。

羟胺源还可以包含羟胺盐和去质子化碱。羟胺盐选自盐酸羟胺、硫酸羟胺和乙酸羟胺。羟胺盐优选地是盐酸羟胺。去质子化碱选自氢氧化钠、氢氧化钾和乙酸钠。去质子化碱优选地是乙酸钠。另一种更优选的羟胺源包含盐酸羟胺和乙酸钠。

可用于本发明多种实施方案中与肟衍生物接触的强碱例如可以优选地选自二烷基氨基化锂、芳基锂、芳基烷基锂和烷基锂。强碱可以是二烷基氨基化锂，并优选二异丙氨基化锂。更优选地，强碱是 C_1 至约 C_{10} 烷基锂，更优选地选自丁基锂、己基锂、庚基锂、辛基锂，进而更优选丁基锂或己基锂。

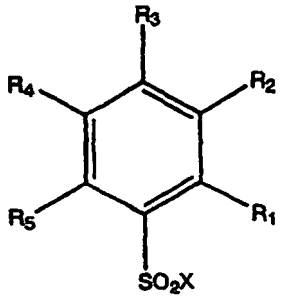
用于本发明多种实施方案中乙酰化剂例如可以选自烷基乙酸酯、乙酸酐、N-烷基-N-烷氧基乙酰胺和乙酰卤。乙酰化剂可以是一种乙酸酐，并优选是乙酸酐，也可以是乙酰卤，并优选乙酰氯，更优选 C_1 至约 C_6 烷基乙酸酯，选自乙酸甲酯、乙酸乙酯、乙酸丙酯和乙酸丁酯，更优选乙酸乙酯。

在另一种实施方案中，本发明提供制备具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺的方法，包含使 1,2-二苯基乙酮化合物与羟胺源接触，生成二苯基乙酮肟衍生化合物，使肟衍生化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生物，使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物，使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁唑-4-基]苯磺酰胺化合物，使[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物。

在另一种实施方案中，本发明提供制备具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物的方法，包含使 1,2-二苯基乙酮化合物与羟胺源接触，生成二苯基乙酮肟衍生化合物，使肟衍生化合物与强碱和乙酰化剂接触，生成二苯基异噁唑啉衍生化合物，并使二苯基异噁唑啉衍生物与三氟乙酸和卤磺酸接触，生成卤代磺化产物，并使卤代磺化产物与氨源接触，生成具有式 1 结构的[异噁

唑-4-基]苯磺酰胺化合物，使[异噁唑-4-基]苯磺酰胺化合物与丙酰化剂接触，生成具有式 1a 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺化合物，并进一步使式 1a 化合物与钠碱接触，生成具有式 1b 结构的 N-[[4-(3-苯基异噁唑-4-基)苯基]磺酰基]丙酰胺钠盐化合物。

在另一种实施方案中，本发明提供制备具有式 4 结构的苯磺酰卤化合物的方法：



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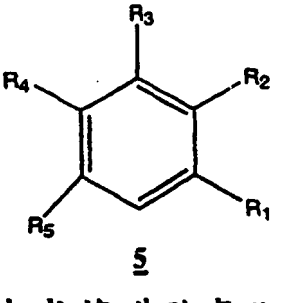
其中 X 是卤原子，R^1、R^2、R^3、R^4和 R^5独立地选自氢、烷基、链烯基、炔基、环烷基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基；其中烷基、链烯基、炔基、环烷基、芳基、杂环基各自可选地被一个或多个基团取代，取代基选自烷基、链烯基、炔基、环烷基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基、卤素、卤代烷基芳基、烷氧基芳基、卤代烷基、保护的羟甲基、芳烷氧基甲基和烷氧基卤代烷基；

其中该方法包含在三氟乙酸的存在下，使具有式 5 结构的取代的苯基化合物：



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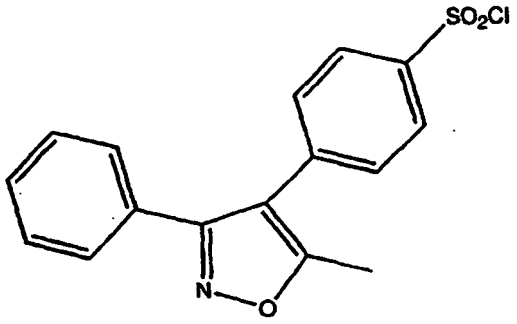
与卤磺酸接触，由此生成苯磺酰卤化合物。

本发明更优选的实施方案提供这样一种方法，其中 R^3是杂环基，可选地被一个或多个基团取代，取代基选自烷基、链烯基、炔基、环烷基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基、卤素、卤

代烷基芳基、烷氧基芳基、卤代烷基、烷氧基羰基、被保护的羟甲基、芳基烷氧基甲基和烷氧基卤代烷基；R^1、R^2、R^4和R^5是氢。进一步优选这样的方法，其中R^3选自异噁唑基和吡唑基，其中R^3可选地被一个或多个基团取代，取代基选自烷基、链烯基、炔基、环烷基、芳基、杂环基、烷氧基、烷基氨基、烷硫基、酰基、卤素、卤代烷基芳基、烷氧基芳基、卤代烷基、烷氧基羰基、被保护的羟甲基、芳基烷氧基甲基和烷氧基卤代烷基；R^1、R^2、R^4和R^5是氢。

在另一种实施方案中，本发明提供制备5-苯基异噁唑-4-基苯磺酰卤的方法，其中该方法包含在三氟乙酸的存在下，使4,5-二苯基异噁唑与卤磺酸接触，由此生成具有式6结构的5-苯基异噁唑-4-基苯磺酰卤化合物：



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在另一种实施方案中，本发明提供制备5-苯基异噁唑-4-基苯磺酰卤的方法，其中该方法包含在三氟乙酸的存在下，使选自式2和式3的化合物与卤磺酸接触，由此生成具有式6结构的5-苯基异噁唑-4-基苯磺酰卤化合物。

正如本文所提供的，三氟乙酸是用于芳族化合物的卤代磺化作用的溶剂，得到对应的芳基磺酰卤。三氟乙酸的使用提供很多固体底物的增溶作用。三氟乙酸的沸点高于二氯甲烷，使卤代磺化反应能够在更高的温度下进行，这可以具有反应时间更短的益处。另外，三氟乙酸可以用于预先溶解固体芳族底物，使从过滤装置转移底物至卤代磺化反应器更加容易和安全。三氟乙酸的使用还消除了氯代烃向空气中的释放和废液的排放。

化合物2、3和5反应生成结构4和6的芳族磺酰氯的卤代磺化反

应是在三氟乙酸的存在下进行的。

所用三氟乙酸的比例和反应时间可以各不相同，如下表所示。

TFA 当量	温度°C	反应时间 小时(h)	完成时间	伐地考昔[1]
2.0	70	2	<30min	78
2.0	40	6	3.3h	80
3.0	60	3	50min	76
4.0	70	2.5	1h	87
4.0	40	4	4h	77

[1]来自用乙腈、水和氢氧化铵混合物淬灭的处理样本的终点 mol% 值

优选地使用足量的三氟乙酸，以确保流体反应量。就 2 和 3 向 6 的转化而言，三氟乙酸的量可以从约 1.5 至约 4 重量当量，相对于 2 和 3 而言。在一种优选的实施方案中，三氟乙酸的重量当量等于 2 和 3 的重量。

卤代磺化反应可以在一定温度范围内进行，优选地在-20°C 至 100°C 的范围内进行，更优选约 30°C 至 70°C，进而更优选约 55°C 至 65°C。氯磺化反应可以在大气压或一定压力下进行，优选地在大气压下、在三氟乙酸的沸点以下进行。氯磺化作用可以在更高的温度下、在足够的压力下进行，这依赖于反应器系统，以防止由挥发引起的损失。

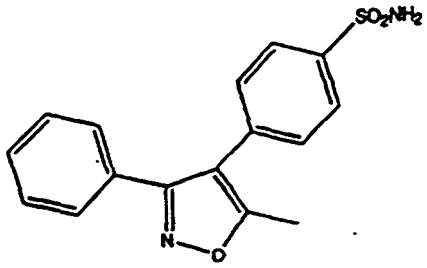
c. 详细的制备方法

用在本发明制备方法中的原料是已知的或者可以借助本领域技术人员已知的常规方法或类似于本领域所述方法的方式加以制备。下列实施例打算阐述本发明的很多实施方案，并不意味着限制其范围。

一般而言，本发明的方法可以如下进行。例如借助成比例地增加成分用量，可以进行更大规模的制备。

实施例 1

4-(5-甲基-3-苯基-4-异噁唑基)苯磺酰胺（伐地考昔，1）的制备



1

步骤 1：1,2-二苯基乙酮肟 7 的制备

在 70°C 下，向脱氧苯偶姻(2.3kg, 11.7mol)、乙酸(669ml, 11.7mol)与乙醇 3A (8.05L, 190 标准强度(proof))的溶液经由加液漏斗加入 50 重量百分比的羟胺(800mL, 13.3mol)。加液漏斗用水(460mL)冲洗，反应混合物在 70°C 下保持 1 小时。用 HPLC 监测反应完全与否。向反应器加入水(2.87L)，温度降低至 50°C。从反应器中取出等分试样(250mL)，冷却，使结晶。将该混合物重新引入到反应器内，以接种引发结晶。接种不是必要的，但是如果使用的话，有助于增加肟产物的容积密度，由此提高所得肟的操作性质。搅拌 1 小时后，历经 2.5 小时加入水(8.78L)，将混合物冷却至 20°C。将混合物加压过滤；滤饼用 2:1 水/乙醇 3A (10.8L)和水(4.5L)洗涤。将滤饼用 N_2 吹干过夜，得到白色固体(2.34kg, 95%收率, 96:4 E/Z 肟异构体)。高分辨率 MS (ES) m/z $(M+H)^+$计算值：212.1075；实测值：212.1085。

步骤 1（替代工艺）：1,2-二苯基乙酮肟 7 的制备

在 70°C 下，向脱氧苯偶姻(75.0g, 0.382mol)、乙酸钠(34.5g, 0.420mol)与乙醇 3A (267mL, 190 标准强度)的溶液经由注射泵加入 35 重量百分比的盐酸羟胺(72.0mL, 0.420mol)。反应混合物在 70°C 下保持 1 小时，用 HPLC 监测反应完全与否。向反应器加入水(75.0mL)，温度降低至 50°C。从反应器中取出等分试样(0.5mL)，冷却，使结晶。将该混合物重新引入到反应器内，以接种引发结晶。接种不是必要的，但是如果使用的话，有助于增加肟产物的容积密度，由此提高所得肟的操作性质。搅拌 1 小时后，历经 1 小时加入水(274mL)，将混合物

冷却至 20°C。将混合物过滤；滤饼用 2:1 水/乙醇 3A (188mL)和水(100mL)洗涤。将滤饼在 50°C 真空烘箱内干燥 16 小时，得到白色固体(76.39g, 95%收率, 97:3 E/Z 肟异构体)。

步骤 2: 4,5-二氢-5-甲基-3,4-二苯基-5-异噁唑醇，2 的制备

向装有磁搅拌器、热电偶和正压氮入口的 500mL 夹套式反应器加入 1,2-二苯基乙酮肟(31.4g)。加入四氢呋喃(THF) (160mL)，同时搅拌以溶解固体。利用-15°C 的夹套温度冷却反应。向反应容器加入正己基锂的己烷溶液(131mL, 2.3M)，同时保持温度低于 10°C。加入完全后，将混合物搅拌 30 分钟，使用夹套温度为-15°C。加入乙酸乙酯(120mL)，保持温度低于 10°C。然后将反应混合物经由导管转移至冷却至 5°C 的氯化钠(14.0g)和水(160mL)的混合物中。反应容器用 40mL THF 冲洗，将该混合物转移至淬灭烧瓶。将淬灭混合物温热至 20°C，分离各层。有机层用碳酸氢钠($NaHCO_3$)溶液(9.6g $NaHCO_3$/160mL 水)洗涤。向有机层加入甲苯(120mL)，蒸馏混合物，直至罐温达到 90.2°C。加入庚烷(439mL)，将混合物按 0.5°C/min 冷却至 5°C，在此期间有晶体生成。将混合物通过聚丙烯筛过滤，固体滤饼用 100mL 50:50（体积/体积）庚烷:甲苯洗涤。将固体在带有氮流的 50°C 真空烘箱内干燥过夜。得到产物，为白色固体(19.75g, 52%收率)。$C_{16}H_{16}NO_2$ 的高分辨率质谱计算值: 254.1193$(M+H)^+$; 实测值: 254.1181。

步骤 2（替代工艺）: 4,5-二氢-5-甲基-3,4-二苯基-5-异噁唑醇，2 的制备

向装有磁搅拌器、热电偶和正压氮入口的 500mL 夹套式反应器加入 1,2-二苯基乙酮肟(31.4g)。加入四氢呋喃(THF) (209mL)，同时搅拌以溶解固体。冷却反应，直至得到-15°C 的批温度。向反应容器加入正己基锂的己烷溶液(131mL, 2.3M)，同时保持温度低于 10°C。加入完全后，将混合物冷却至-15°C 的批温度。尽可能迅速地加入乙酸乙酯(80mL)。调节反应混合物至 0°C，然后转移至冷却至<5°C 的氯化钠(14.0g)和水(160mL)的混合物中。在淬灭方法中混合物保持低于 15℃。反应容器用 40mL 乙酸乙酯冲洗，并将该混合物转移至淬灭烧瓶。将

淬灭混合物温热至 20°C，分离各层。有机层用碳酸氢钠($NaHCO_3$)溶液(9.6g $NaHCO_3$/160mL 水)洗涤。向有机层加入甲苯(120mL)，蒸馏混合物，直至除去 67%罐内容物（温度~90-93°C）。加入庚烷(439mL)，将混合物按 0.5°C/min 冷却至 5°C，在此期间有晶体生成。将混合物过滤，固体滤饼用 100mL 50:50（体积/体积）庚烷:甲苯洗涤。将固体在带有氮流的 50°C 真空烘箱内干燥过夜。得到产物，为白色固体(典型制造收率 59%)。$C_{16}H_{16}NO_2$ 的高分辨率质谱计算值：254.1193$(M+H)^+$；实测值：254.1181。

步骤 3：4-(5-甲基-3-苯基-4-异噁唑基)苯磺酰胺（伐地考昔，1）的制备

向已经冷却至 5°C 的 500mL 反应器加入 4,5-二氢-5-甲基-3,4-二苯基-5-异噁唑醇(50.0g，0.197mol)。向反应器加入三氟乙酸(38.3mL，0.496mol)，同时搅拌，将 35°C 溶液冷却至~5°C。缓慢加入氯磺酸(232g，1.99mol)；在加入期间控制氯化氢(HCl)的放出，并且维持<25°C。然后将反应溶液加热至 60°C，在 60°C 下保持 2.5 小时。将反应溶液冷却至 0°C 后，缓慢加入到搅拌着的 2 至 25°C 的甲苯(172mL)与水(150mL)混合物中。反应器用甲苯(18.4mL)与水(50mL)的混合物冲洗，然后加入到淬灭混合物中。将甲苯层用水(50mL)萃取，并冷却至 0.2°C。缓慢加入浓氢氧化铵(62mL，1.60mol)，同时冷却，以在加入期间维持~10 至 15°C。将混合物缓慢温热至 35°C，在该温度下保持~40 分钟。加入异丙醇(240mL)，将反应混合物重新加热至 35°C，在 35°C 下保持 90 分钟。将结晶性混合物缓慢冷却至 20°C，过滤粗产物，用异丙醇(100mL)和水(100mL)洗涤。将湿滤饼转移至 500mL 结晶器内，在~58°C 下溶于甲醇(350mL)。向甲醇溶液加入水(92mL)，将溶液加热至~70°C。将该溶液缓慢冷却至 50°C，保持 60 分钟，然后冷却至 5°C。在 5°C 下 1 小时后，过滤收集结晶产物，将滤饼用 75%甲醇-水(100mL)洗涤，在~70°C 真空下干燥。利用示差扫描量热法(DSC)测定熔点为 171 至 174°C（按 10°C/分钟测定）。

实施例 2

N-[[4-(5-甲基-3-苯基-4-异噁唑基)苯基]磺酰基]丙酰胺（帕来考昔，1a）的制备

向 500mL 反应器加入 4-(5-甲基-3-苯基-4-异噁唑基)苯磺酰胺(10.0g, 0.032mol)和丙酸酐(40mL, 0.31mol)。搅拌该浆液，加热至 50°C。一次性加入硫酸(40μL, 0.8mmol)。加入完成后所有固体溶解，在 10 分钟内将混合物温热至 55.5°C。然后将反应混合物加热至 80°C，保持大约 10 分钟。中断加热，使混合物冷却至 50°C，保持约 60 分钟；在约 65°C 下固体开始从反应混合物中结晶出来。将混合物缓慢冷却至 0°C，在 0°C 下保持约 60 分钟。真空过滤收集固体。将湿滤饼用两份 45mL 甲基叔丁基醚洗涤，在环境温度下吸干约 15 分钟。将固体在带有氮流的 60°C 真空烘箱内进一步干燥 18 小时，得到固体产物(8.72g, 75%收率)。高熔点帕来考昔的 DSC 最大吸热量为 168.95。低熔点帕来考昔的 DSC 最大吸热量为 147.44。

实施例 3

N-[[4-(5-甲基-3-苯基-4-异噁唑基)苯基]磺酰基]丙酰胺钠盐（帕来考昔钠，1b）的制备

向 500mL 反应器加入 N-[[4-(5-甲基-3-苯基-4-异噁唑基)苯基]磺酰基]丙酰胺(10.0g, 0.026mol)和 160mL 无水乙醇。将该浆液加热至 45°C，保持 30 分钟，在 45°C 下向反应容器加入大约 5 重量百分比的氢氧化钠的乙醇溶液(22.4g, 0.028mol)。加入完成后，向溶液接种 N-[[4-(5-甲基-3-苯基-4-异噁唑基)苯基]磺酰基]丙酰胺钠盐，引发结晶。将反应混合物的温度升至 50°C，保持 30 分钟。将混合物缓慢冷却至 0°C，保持约 60 分钟。真空过滤收集固体。将湿滤饼用两份 20mL 无水乙醇洗涤两次，在真空下吸干，用氮净化。将固体在带有氮流的 120°C 真空烘箱内进一步干燥过夜，得到固体产物(9.11g, 85%收率)。I 型帕来考昔钠的 DSC 最大吸热量为 274.28°C。

实施例 4

5-甲基-3,4-二苯基异噁唑 3 的制备

向 250mL 烧瓶加入 4,5-二氢-5-甲基-3,4-二苯基-5-异噁唑醇(15.0g,

0.059mol)。加入三氟乙酸(10.5mL)，同时搅拌，观察到放热至 44°C。将溶液在 44 与 57°C 之间加热 60 分钟，冷却至室温，真空蒸馏以除去三氟乙酸。将残余物溶于 100mL 甲苯，并真空蒸馏。该方法重复第二次，得到半结晶性浓缩物。将浓缩物溶于 250mL 热庚烷，倾析至 500mL 烧瓶内，冷却至室温，并保持 18 小时。打碎结晶滤饼，过滤收集晶体。将滤饼干燥，得到 10.19g (73wt%收率)所需产物。在未密封的锅内按 10°C/min 测定 DSC 熔点为 95.55－96.24°C。

实施例 5

4-(5-甲基-3-苯基-4-异噁唑基)苯磺酰氯 6 的制备

向 200mL 夹套式烧瓶加入 4,5-二氢-5-甲基-3,4-二苯基-5-异噁唑醇(13.0g, 0.0513mol)，用 0.2°C 夹套流体冷却烧瓶。向固体加入三氟乙酸(9.1mL, 0.118mol)，得到 38.6°C 的溶液。将该溶液冷却至 2.1°C，缓慢加入氯磺酸(34.7mL, 0.522mol)，同时维持温度低于 14°C。将溶液加热至 60°C，保持 2.5 小时，冷却至 20°C，转移至 125mL 加液漏斗。向 200mL 夹套式反应器加入甲苯(52mL)和水(52mL)，冷却至 4°C。然后将反应溶液缓慢加入到 200mL 夹套式反应器内，同时维持温度低于 20°C。将多相混合物温热至 20°C，转移至 250mL 分液漏斗。加入甲苯(50mL)和水(10mL)，摇动混合物。混合物沉降，导致两个浑浊的相。将甲苯相用 15mL 水洗涤两次，转移至 250mL 烧瓶，用 20mL 甲苯冲洗，真空蒸馏得到 17.4g 油。用玻璃棒引发结晶和冷却后，向结晶物加入庚烷(20mL)，前者打碎成粉末。过滤收集乳白色粉末。使用每份 50mL 的庚烷帮助转移固体至滤器。在真空烘箱(35°C)内干燥滤饼，得到 13.6g (79.4wt%)磺酰氯，为对位与间位异构体的 85:15 混合物。$C_{16}H_{13}NO_3Cl$ 的 HRMS 计算值(M + 1): 334.0305; 实测值(M + 1): 334.0309。

实施例 6

4-(5-甲基-3-苯基-4-异噁唑基)苯磺酰氯 6 的制备

向 100mL 夹套式烧瓶加入 5-甲基-3,4-二苯基异噁唑(5.0g, 0.0213mol)，用 0.2°C 夹套流体冷却。在 3°C 下向固体加入三氟乙酸

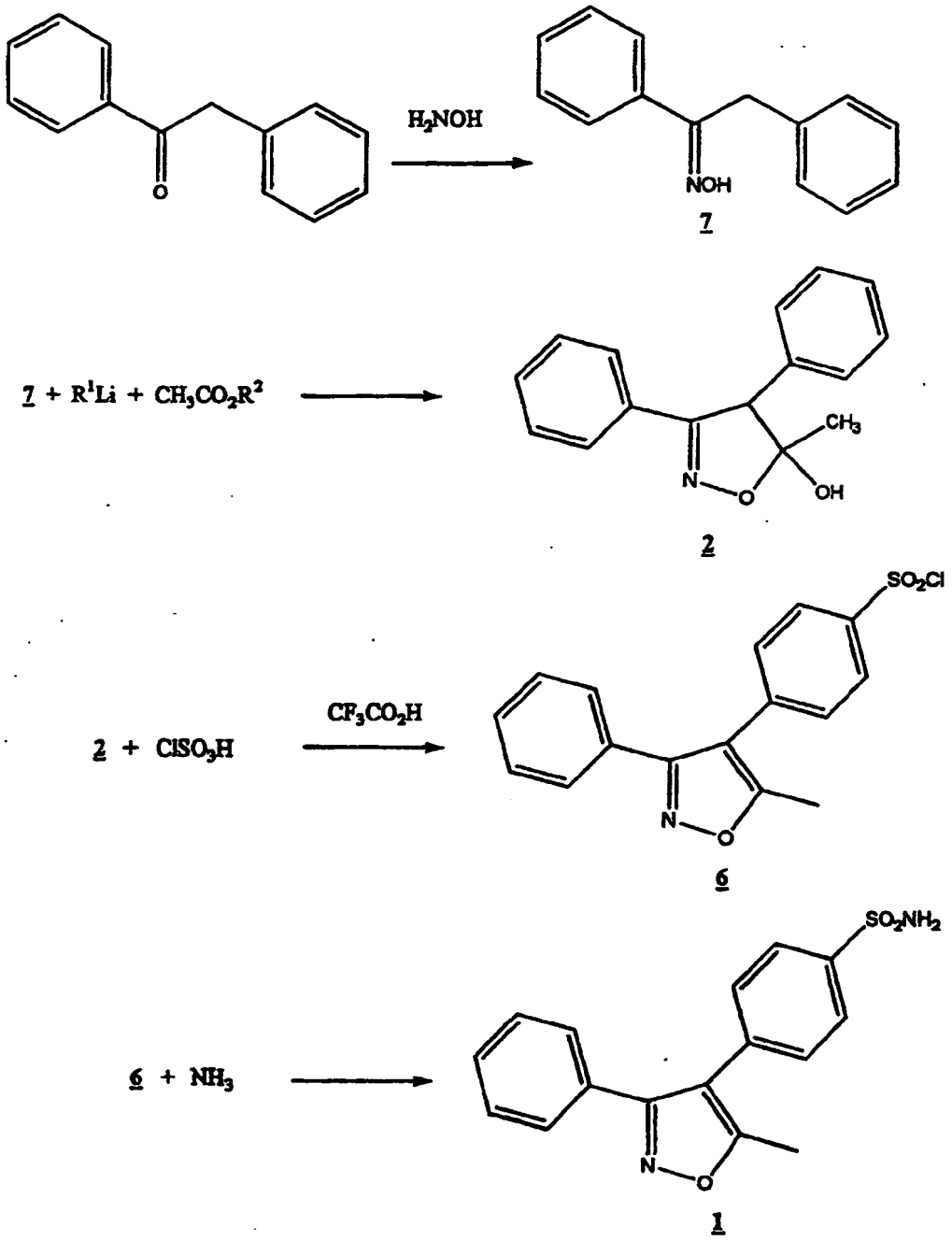
(3.5mL, 0.045mol)，得到溶液。缓慢加入氯磺酸(13.3mL, 0.201mol)，同时维持反应温度低于 20°C。将溶液加热至 60°C，保持 2.2 小时。然后将溶液冷却至 6°C，转移至 60mL 加液漏斗。向 100mL 夹套式反应器加入甲苯(20mL)和水(20mL)，冷却至 6°C。然后将反应溶液缓慢加入到 100mL 夹套式反应器内，同时维持温度低于 16°C。将多相混合物转移至 125mL 分液漏斗。加入甲苯(20mL)和水(5mL)，摇动混合物。混合物沉降，导致两个浑浊的相。将甲苯相用 5mL 水洗涤两次，转移至 125mL 烧瓶，用 17mL 甲苯冲洗，真空蒸馏得到半结晶性浓缩物。将浓缩物溶于 100mL 甲苯，真空蒸馏得到油。用玻璃棒引发结晶后，加入庚烷(11mL)，并打碎结晶成乳白色粉末。过滤收集固体。使用每份 25mL 的庚烷帮助转移固体至滤器。干燥滤饼，得到 7.07g (100wt%)磺酰氯，为对位与间位异构体的 85:15 混合物。$C_{16}H_{13}NO_3Cl$ 的 HRMS 计算值(M + 1)：334.0305；实测值(M + 1)：334.0299。

实施例 5

4-(5-甲基-3-苯基-4-异噁唑)苯磺酸的制备

向 1 升烧瓶加入 4-(5-甲基-3-苯基异噁唑)苯磺酰氯(39.6g, 0.11mol)、水(99.5mL, 5.5mol)和四氢呋喃(558mL)，加热回流过夜。冷却至环境温度后，在压力下除去溶剂。将残余的黄色油进一步在高真空下干燥。用甲苯(500mL)覆盖所得固体，加热回流。约 30 分钟后，固体熔化和汇集在烧瓶的底部。将混合物在回流温度下搅拌 4 小时，冷却至室温，搅拌过夜。过滤收集固体，简单风干，研磨成粉末。将粉末悬浮在甲苯(500mL)中，加热至回流温度，并在冷却至室温期间重新固化。过滤收集固体，干燥，得到 23.8g 产物，熔点为 174－176°C。

图1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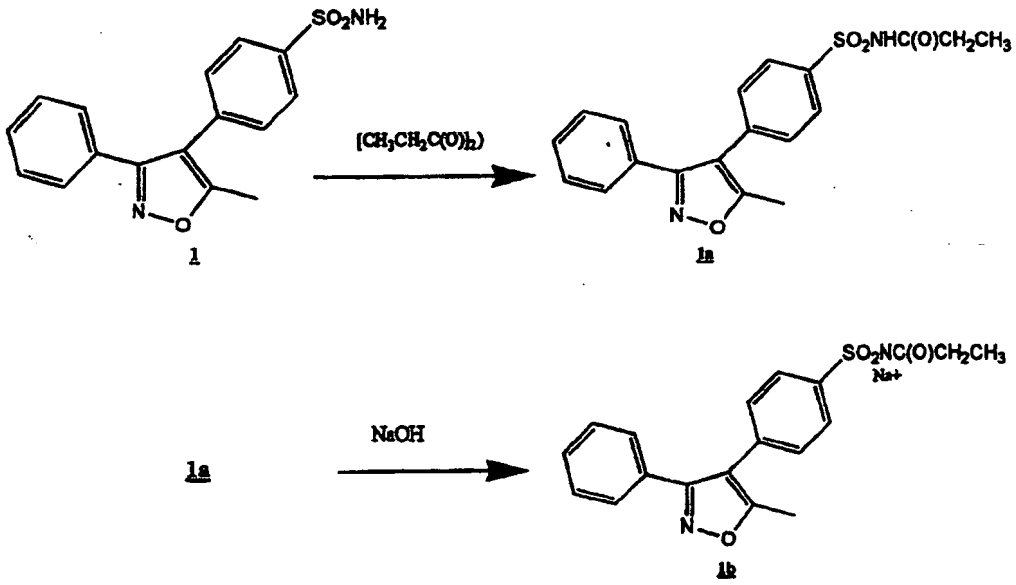
7
7 + R1Li + CH3CO2R2
CH3
OH
N
O
2
2 + ClSO3H
CF3CO2H
SO2Cl
6
6 + NH3
SO2NH2
1

图2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SO2NHC(O)CH2CH3
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1a
SO2NC(O)CH2CH3
Na+
NaOH
1a
1b