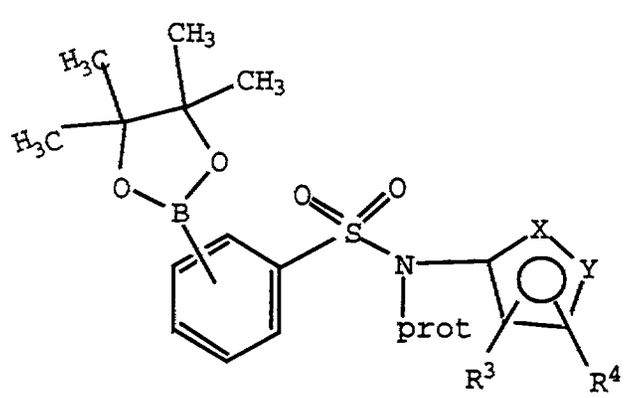
PINACOL ESTER INTERMEDIATES USEFUL FOR THE PREPARATION OF BIPHENYL ISOXAZOLE SULFONAMIDES

Field of the Invention

The present invention relates to novel biphenyl isoxazole sulfonamide intermediates and methods for their preparation. The biphenyl isoxazole sulfonamides prepared from the intermediates of the present invention are endothelin antagonists useful, *inter alia*, for the treatment of hypertension.

Brief Description of the Invention

The present invention provides compounds of the following formula II as well as methods for their preparation:



(II)

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where the phenyl ring of said formula II may be further substituted, and where "prot" denotes a nitrogen-protecting group, and wherein:

one of X and Y is N and the other is O;

R^3 and R^4 are each directly bonded to a ring carbon and are each independently

(a) hydrogen;

(b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1, Z^2 and Z^3;

(c) halo;

(d) hydroxyl;

(e) cyano;

(f) nitro;

(g) $-C(O)H$ or $-C(O)R^5$;

(h) $-CO_2H$ or $-CO_2R^5$;

(i) $-Z^4-NR^6R^7$;

(j) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; or

(k) R^3 and R^4 together may also be alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached;

R^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1, Z^2 and Z^3;

R^6, R^7, R^8, R^9 and R^{10} are each independently

(a) hydrogen; or

(b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1, Z^2 and Z^3; or

R^6 and R^7 together may be alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; or any two of R^8, R^9 and R^{10} together are alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z^1, Z^2 and Z^3 are each independently

(a) hydrogen;

(b) halo;

(c) hydroxy;

(d) alkyl;

(e) alkenyl;

(f) aryl;

(g) aralkyl;

(h) alkoxy;

(i) aryloxy;

(j) aralkoxy;

(k) heterocycle, substituted heterocycle or heterocyclooxy;

(l) $-SH$, $-S(O)_nZ^6$, $-S(O)_m-OH$, $-S(O)_m-OZ^6$, $-O-S(O)_m-Z^6$, $-O-S(O)_mOH$ or $-O-S(O)_m-OZ^6$;

(m) oxo;

(n) nitro;

(o) cyano;

(p) $-C(O)H$ or $-C(O)Z^6$;

(q) $-CO_2H$ or $-CO_2Z^6$;

(r) $-Z^4-NZ^7Z^8$;

(s) $-Z^4-N(Z^{11})-Z^5-H$;

(t) $-Z^4-N(Z^{11})-Z^5-Z^6$; or

(u) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$;

Z^4 and Z^5 are each independently

(a) a single bond;

(b) $-Z^9-S(O)_n-Z^{10}-$;

(c) $-Z^9-C(O)-Z^{10}-$;

(d) $-Z^9-C(S)-Z^{10}-$;

(e) $-Z^9-O-Z^{10}-$;

(f) $-Z^9-S-Z^{10}-$;

(g) $-Z^9-O-C(O)-Z^{10}-$; or

(h) $-Z^9-C(O)-O-Z^{10}-$;

Z^6 is alkyl; alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy; alkenyl; alkynyl; cycloalkyl; cycloalkyl substituted with one to three groups selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring; aryloxy substituted with one or two halogens; cycloalkylalkyl; cycloalkenyl; cycloalkenylalkyl; aryl; aryl substituted with methylenedioxy or one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy and trihaloalkoxy; or heterocycle or substituted heterocycle;

Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached;

Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene;

Z^{11} is

(a) hydrogen; or

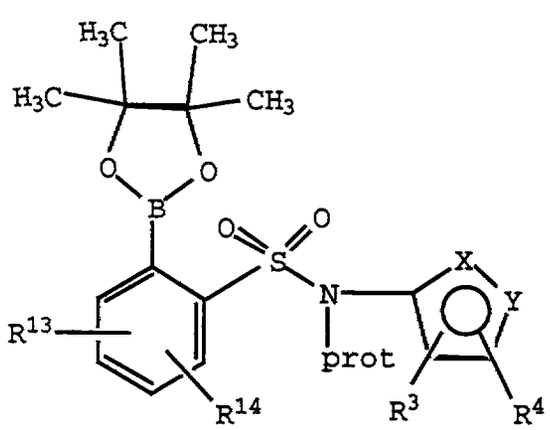
(b) alkyl, alkyl substituted with one, two or three halogens, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl;

or any two of Z^7, Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

each m is independently 1 or 2; and

each n is independently 0, 1 or 2.

Preferred compounds of the following formula II(a) are also provided:



(IIa)

Detailed Description of the Invention

The present invention is described further as follows. Listed below are definitions of terms used in this specification. These definitions apply to the terms as used throughout this specification, individually or as part of another

group, unless otherwise indicated in specific instances.

The term "alkyl" or "alk-" refers to straight or branched chain hydrocarbon groups having 1 to 10 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms.

The term "alkoxy" refers to alkyl-O-.

The term "aryl" or "ar-" refers to phenyl, naphthyl and biphenyl.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10 carbon atoms having at least one double bond. Groups of two to four carbon atoms are preferred.

The term "alkynyl" refers to straight or branched chain groups of 2 to 10 carbon atoms having at least one triple bond. Groups of two to four carbon atoms are preferred.

The term "alkylene" refers to a straight chain bridge of 1 to 5 carbon atoms connected by single bonds (e.g., $-(CH_2)_x-$ wherein x is 1 to 5), which may be substituted with 1 to 3 lower alkyl groups.

The term "alkenylene" refers to a straight chain bridge of 2 to 5 carbon atoms having one or two double bonds that is connected by single bonds and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkenylene groups are $-CH=CH-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-C(CH_3)_2CH=CH-$ and $-CH(C_2H_5)-CH=CH-$.

The term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1 to 3 lower alkyl

groups. Exemplary alkynylene groups are -C≡C-, -CH_2-C≡C-, -$CH(CH_3)$-C≡C- and -C≡C-$CH(C_2H_5)CH_2$-.

The term "alkanoyl" refers to groups of the formula -C(O)alkyl.

The terms "cycloalkyl" and "cycloalkenyl" refer to cyclic hydrocarbon groups of 3 to 8 carbon atoms.

The term "hydroxyalkyl" refers to an alkyl group including one or more hydroxy radicals such as -CH_2CH_2OH, -$CH_2CH_2OHCH_2OH$, -$CH(CH_2OH)_2$ and the like.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl,

isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like.

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

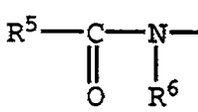
The expression "substituted heterocycle" refers to a heterocycle substituted with 1, 2 or 3 of the following:

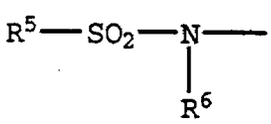
(a) alkyl, especially lower alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo (i.e. = O);
(e) amino, alkylamino or dialkylamino;
(f) alkoxy;
(g) carbocyclo, such as cycloalkyl;
(h) carboxy;
(i) heterocyclooxy;
(j) alkoxycarbonyl, such as unsubstituted lower alkoxycarbonyl;
(k) carbamyl, alkylcarbamyl or dialkylcarbamyl;
(l) mercapto;
(m) nitro;
(n) cyano;
(o) carboalkoxy;
(p) sulfonamido, sulfonamidoalkyl or sulfonamidodialkyl;

(q)  ;

(r)  ;

(s) aryl;
(t) alkylcarbonyloxy;
(u) arylcarbonyloxy;
(v) arylthio;
(w) aryloxy;
(x) alkylthio;
(y) formyl;
(z) arylalkyl; or
(a') aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, halo or trihaloalkyl.

The term "heterocyclooxy" denotes a heterocyclic group bonded through an oxygen bridge.

Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

The compounds of formula II may form salts which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, for example, in isolating or purifying the compounds of this invention.

The compounds of formula II may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, t-butyl amine, benzathine, N-methyl-D-glucamide and hydrabamine, and with amino acids such as arginine, lysine and the like. Such salts may be obtained by reacting these compounds with the desired ion in a medium in which the salt precipitates or in an aqueous medium followed by lyophilization.

When groups such as the R^1 to R^4 or R^{11} to R^{14} substituents comprise a basic moiety, such as amino or substituted amino, the compounds of formula II may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrochloric acid, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, maleic acid, benzenesulfonate, toluenesulfonate and various other sulfonates, nitrates, phosphates, borates, acetates,

tartrates, maleates, citrates, succinates, benzoates, ascorbates, salicylates and the like. Such salts may be formed by reacting these compounds in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by lyophilization.

In addition, when groups such as the R^1 to R^4 or R^{11} to R^{14} substituents comprise a basic moiety such as amino, zwitterions ("inner salts") may be formed.

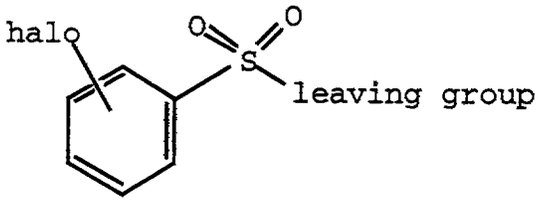
Certain groups such as the R^1 to R^4 and R^{11} to R^{14} substituents of the compounds of the invention may contain asymmetric carbon atoms. The compounds of the invention may exist, therefore, in enantiomeric and diastereomeric forms and in racemic mixtures thereof. All are within the scope of this invention. Additionally, compounds may exist as enantiomers even in the absence of asymmetric carbons. All such enantiomers are within the scope of this invention.

U.S. Patent Application Serial No. 08/493,331, filed July 24, 1995 (Attorney Docket No. HA662c) by Murugesan et al. and continuation-in-part thereof U.S. Patent Application Serial No. 08/603,975, filed February 20, 1996 (Attorney Docket No. HA662d) by Murugesan et al., entitled "Substituted Biphenyl Isoxazole Sulfonamides", describing endothelin antagonists, starting materials and methods, are each incorporated herein by reference in its entirety.

Preparation of Formula II Compounds

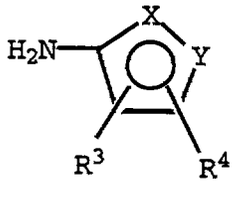
The pinacol esters of the formula II and salts thereof may be formed by novel methods provided herein. In accordance herewith, a pinacol ester of the formula II or salt thereof may be prepared by a method comprising the steps of:

(a) contacting a compound of the formula V or salt thereof:



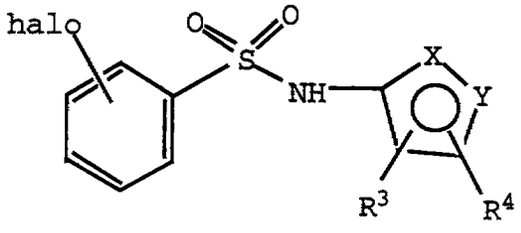
(V)

where the phenyl group of said formula V may be further substituted, such as with one or more groups described for the groups R^{11} to R^{14} herein, and where halo is preferably bromo, chloro or iodo, most preferably bromo, with an amine of the formula VI or salt thereof:



(VI)

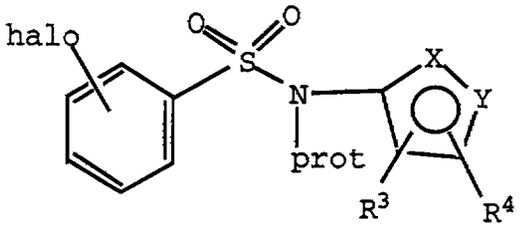
in the presence of an organic base and an organic solvent, to form a compound of the formula VII or salt thereof:



(VII)

where the phenyl group of said formula VII may be further substituted, such as with one or more groups described for the groups R^{11} to R^{14} herein;

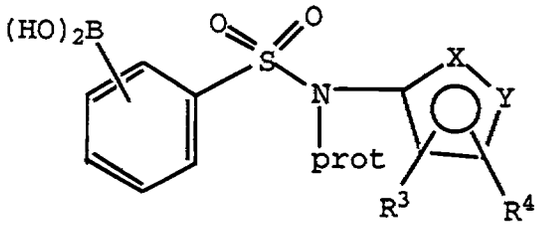
(b) protecting the nitrogen of said compound of the formula VII or salt thereof to form a compound of the formula VIII or salt thereof:



(VIII)

where the phenyl group of said formula VIII may be further substituted, such as with one or more groups described for the groups R^{11} to R^{14} herein;

(c) lithiating said compound of the formula VIII or salt thereof with an alkyl or aryl lithium compound and contacting the lithiated product formed with a trialkylborate, followed by hydrolysis, to form a boronic acid of the formula IX or salt thereof:



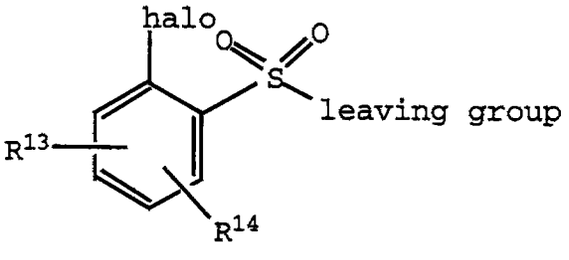
(IX)

where the phenyl group of said formula IX may be further substituted, such as with one or more groups described for the groups R^{11} to R^{14} herein; and

(d) contacting said compound of the formula IX or salt thereof with pinacol (i.e., 2,3-dimethyl-2,3-butanediol), with removal of water, thereby forming said compound of the formula II or salt thereof.

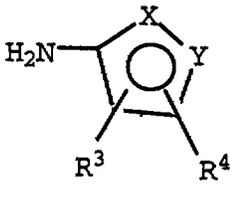
In a preferred embodiment, a pinacol ester of the formula IIa or salt thereof may be prepared by a method comprising the steps of:

(a) contacting a compound of the formula Va or salt thereof:



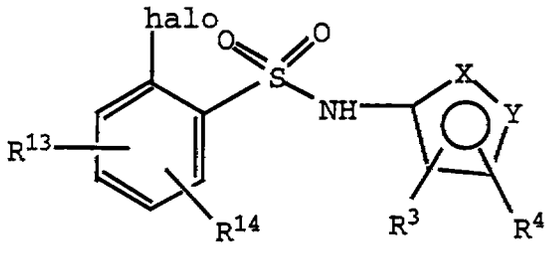
(Va)

with an amine of the formula VIa or salt thereof:



(VIa)

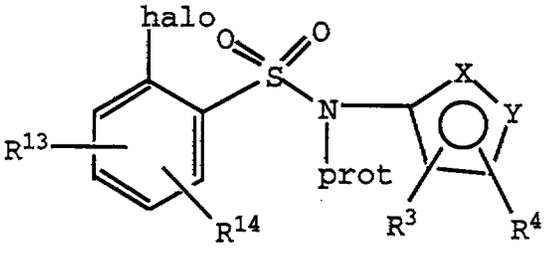
in the presence of an organic base and organic solvent, to form a compound of the formula VIIa or salt thereof:



(VIIa)

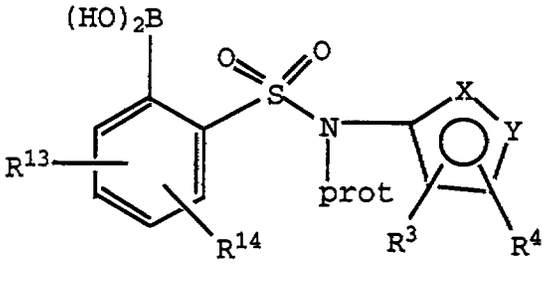
;

(b) protecting the nitrogen of said compound of the formula VIIa or salt thereof to form a compound of the formula VIIIa or salt thereof:



(VIIIa)

(c) lithiating said compound of the formula VIIIa or salt thereof with an alkyl or aryl lithium compound and contacting the lithiated product formed with a trialkylborate, followed by hydrolysis, to form a boronic acid of the formula IXa or salt thereof:



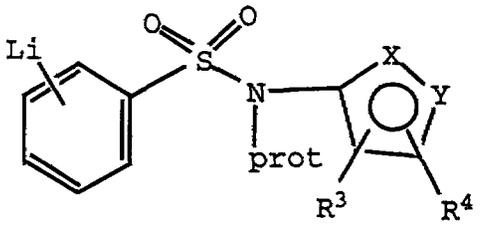
(IXa)

; and

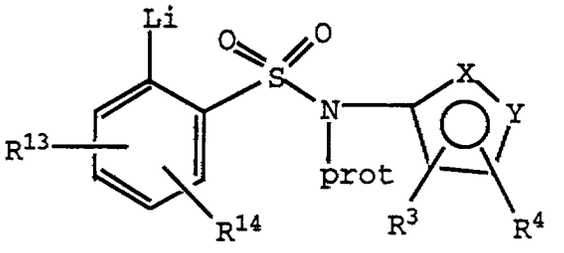
(d) contacting said compound of the formula IXa or salt thereof with pinacol, with removal of water, thereby forming said compound of the formula IIa or salt thereof.

The term "leaving group", as used herein, denotes any suitable leaving group such as a halo group, preferably chloro. Any suitable organic base may be employed in step (a). Preferred organic bases include amines such as pyridine or a trialkylamine. The organic solvent employed in step (a) is preferably a haloalkane, such as dichloromethane or 1,2-dichloroethane, or the organic base, such as neat pyridine, may also function as the solvent.

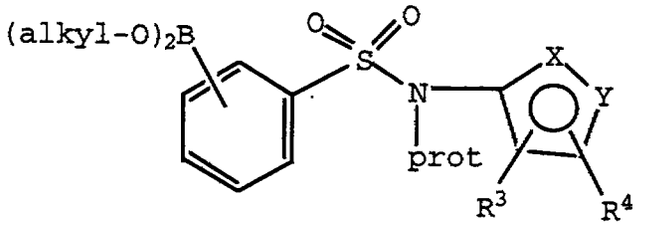
As described above, compounds of the formula VIII and salts thereof may be prepared by contacting a compound of the formula V or salt thereof with an amine compound of the formula VI or salt thereof, and by protecting the nitrogen of the product compound VII or salt thereof. The formula VIII compound or salt thereof obtained is then lithiated with an alkyl or aryl lithium compound, preferably with n-butyl lithium or phenyl lithium, at temperatures which are preferably from about -40°C to about -105°C (especially, from about -70°C to about -100°C), to form the compound:



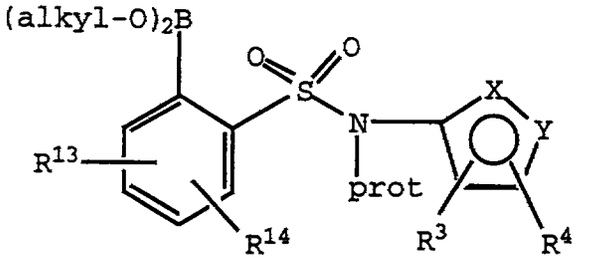
where the phenyl group of said compound may be further substituted, such as with one or more groups described for the groups R^{11} to R^{14} herein, or salt thereof, preferably the compound:



or salt thereof. Treatment of the lithiated compound or salt thereof with a trialkylborate such as triisopropylborate or, preferably, trimethylborate, at temperatures which are preferably from about -40°C to about -105°C (especially, from about -70°C to about -100°C), provides the following boronate ester:



where the phenyl group of said compound may be further substituted, such as with one or more groups described for the groups R^{11} to R^{14} herein, or salt thereof, preferably the boronate ester:



or salt thereof, which may then be hydrolyzed with a suitable acid, preferably an aqueous acid such as aqueous hydrochloric acid, or with a suitable base, to form the boronic acid IX or salt thereof.

The hydrolysis step, forming the boronic acid IX or salt thereof, is advantageous as the boronic acid possesses enhanced stability relative to the boronate ester from which it is obtained. The aforementioned steps may be conducted by methods analogous to those described in, and with starting materials of the formulae V and VI and salts thereof prepared by methods analogous to those described in, European Patent Application Publication No. 569,193 (1993) and in U.S. Patent Application Serial No. 08/493,331 and the aforementioned continuation-in-part thereof.

The boronic acid IX or salt thereof may then be contacted with pinacol, with the removal of water, to form the corresponding pinacol ester II or salt thereof. Removal of water may be conducted, for example, by the addition of a drying agent such as magnesium sulfate or by azeotropic removal of water by heating with a solvent such as toluene. This reaction is preferably conducted at a temperature of from about 110°C to about 120°C (most preferably from about 112°C to about 115°C), at a pressure of about 1 atm, and under an atmosphere of argon or nitrogen. Molar ratios of pinacol to the boronic acid IX or salt thereof are preferably from about 1:1 to about 1.1:1. Solvents are preferably employed which are selected from organic liquids such as toluene. Amounts of solvent are preferably those wherein the boronic acid IX or salt thereof is from about 4 to about 10% by weight, based on the combined weight of solvent and boronic acid IX or salt thereof.

Preferred Compounds

It is preferred that the compounds employed in or prepared by the present methods contain one or more, preferably all where appropriate, of the following substituents:

X is O and N is Y;

the ring bearing K, L and J is 2-oxazole;

p is zero;

R^1 and R^2 are each independently hydrogen, alkyl, alkoxy, aryl, hydroxyalkyl, $-CO_2R^5$ or $-Z^4-NR^6R^7$, most preferably lower alkyl or hydrogen;

R^3 and R^4 are each independently alkyl, most preferably lower alkyl, especially methyl; and

R^{11}, R^{12}, R^{13} and R^{14} are each independently hydrogen, hydroxy, amino, heterocyclo, alkenyl, alkoxy, carboxamide or substituted lower alkyl, most preferably, R^{12} to R^{14} are hydrogen and R^{11} is hydrogen, hydroxy, amino, heterocyclo, alkenyl, alkoxy, carboxamide or substituted lower alkyl.

Compounds of interest include those, *inter alia*, wherein at least one of (i) to (iv) applies: (i) at least one of R^{11}, R^{12}, R^{13} or R^{14} is heterocycle, substituted heterocycle or heterocyclooxy; (ii) at least one of Z^1, Z^2 or Z^3 is aryl, heterocycle, substituted heterocycle or heterocyclooxy; (iii) Z^6 is alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy, wherein at least one substituent is other than aryl; alkyl substituted with two or three aryl groups; cycloalkyl substituted with one to three groups selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring; aryloxy substituted with one or two halogens; aryl substituted with

methylenedioxy; aryl substituted with one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy and trihaloalkoxy; or heterocycle or substituted heterocycle; or (iv) Z^{11} is alkyl substituted with one, two or three halogens.

Utility of Compounds of Formula II and Salts Thereof as Intermediates in the Preparation of Biphenyl Isoxzole Sulfonamides

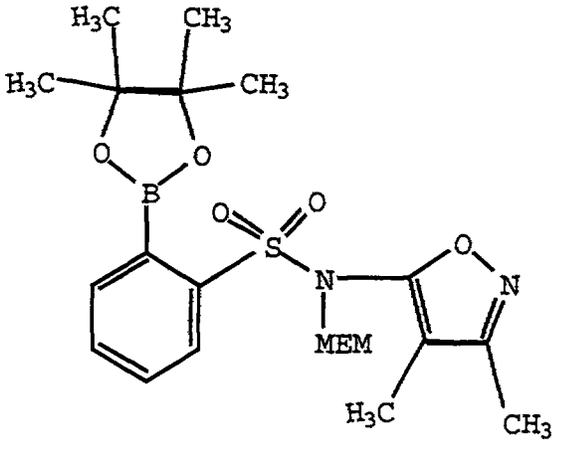
The compounds of the formula II and salts thereof are useful intermediates in the preparation of biphenyl isoxazole sulfonamides, which are antagonists of ET-1, ET-2 and/or ET-3 and are thus useful in treatment of conditions associated with increased ET levels (e.g., dialysis, trauma and surgery) and of all endothelin-dependent disorders.

The present invention will now be further described by the following working example, which illustrates preferred embodiments of the invention.

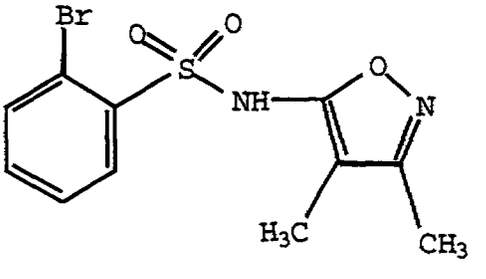
EXAMPLE 1

PREPARATION OF PINACOL ESTER II

N-[(2-Methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfanamide



A. 2-Bromo-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide



A 2 L three necked flask, equipped with an overhead mechanical stirrer, a 250 mL addition funnel and an argon line, was charged with 2-bromobenzenesulfonyl chloride (150 g, 587 mmol, commercially available) and anhydrous pyridine (150 mL). The resulting light yellow solution was cooled to -18°C (internal temperature) by an ice/salt bath. With stirring, a solution of 5-amino-3,4-dimethylisoxazole (69.1 g, 616 mmol,

commercially available) in anydrous pyridine (195 mL) was added dropwise through the addition funnel in 1 hour. The internal reaction temperature did not exceed -6°C during the course of the addition. After the addition, the ice/salt bath was removed and the reaction mixture was then warmed up to room temperature, stirred for 1 hour, and then stirred at 40°C for 21 hours.

The reaction mixture was cooled to room temperature and poured into a mixture of ice water (3 L) and celite (37.5 g). After stirring for 20 minutes, it was filtered and rinsed with water (250 mL x 3). Charcoal (45 g) was added to the filtrate. The mixture was stirred at room temperature for 40 minutes and was filtered through a pad of celite. The celite pad was rinsed with water (500 mL x 3). The filtrate was acidified by dropwise addition of cold HCl (6N, 750 mL) with vigorous stirring over 2 hours. Precipitation of the product occurred and the mixture was stirred for another 1 hour after the addition of HCl.

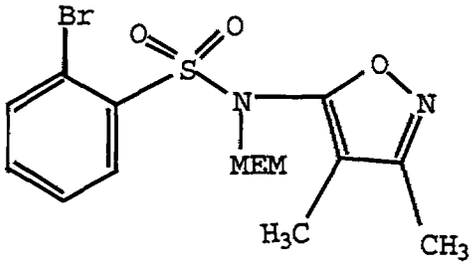
The mixture was filtered, the solid was rinsed with cold water (750 mL x 4), and suction dried for 3 days. The title compound of this step was obtained as a yellowish white solid (171 g) in 88% yield (HPLC area percent = 97.4%).

Thin layer chromatography (TLC): Rf = 0.47 (Silica gel from Whatman; Ethyl acetate (EtOAc):hexanes/1:1; Visualization CAM or UV)

Alternative preparation for title compound of this step:

A 1 L three necked flask was charged with 2-bromobenzenesulfonyl chloride (50 g, 196 mmol) and anhydrous 1,2-dichloroethane (125 mL) under an argon atmosphere. The resulting colorless solution was cooled to 0°C and anhydrous pyridine (40 mL, 396 mmol) was added, followed by the addition of 5-amino-3,4-dimethylisoxazole (24.1 g, 196 mmol) as a solid. After the addition, the ice bath was removed and the reaction mixture was heated to 55°C for 21 hours, yielding a crude reaction mixture containing the title compound of this step.

B. <u>2-Bromo-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]benzene-sulfonamide</u>



A 1 L three necked flask, equipped with a mechanical stirrer, was charged with potassium carbonate (130.5 g, 944 mmol) and anhydrous dimethylformamide (DMF, 286 mL) under an argon atmosphere. The heterogeneous mixture was stirred for 15 minutes at room temperature. The title

compound of step A (125 g, 378 mmol) was added as a solid. The mixture was stirred again for 15 minutes at room temperature. Methoxyethoxymethylchloride (MEMCl, 47.5 mL, 415.8 mmol) was added dropwise through an addition funnel in 40 minutes. After the addition, the reaction mixture was stirred for 40 minutes. The reaction was monitored by HPLC.

The reaction mixture was diluted with the addition of ethyl acetate (400 mL), stirred for 5 minutes and filtered. The solid was washed with ethyl acetate (200 mL x 2) and hexanes (250 mL x 2). The filtrate was treated with charcoal (25 g), stirred at room temperature for 1 hour and filtered through a celite pad. The celite pad was rinsed with ethyl acetate (50 mL x 3). The ethyl acetate layers were combined and washed with Na_2CO_3 (1M, 500 mL). Precipitation occurred in the aqueous layer. It was suppressed by addition of water (750 mL). The aqueous layer was separated and discarded. The organic layer was washed with water (750 mL), brine (500 mL x 2), dried over Na_2SO_4, filtered and concentrated to a yellowish semi-solid (157.3 g, 99% mass balance).

The residue was dissolved in ethanol (125 mL) and set aside in a freezer (0°C) for 20 hours. Crystallization occurred. The solid was filtered and suction dried. The title compound of this step was obtained as a yellowish white solid (75.65% yield, HPLC area percent = 98.2%).
TLC: Rf = 0.55 (Silica gel from Whatman; EtOAc:hexanes/1:1; visualization: CAM or UV)

Alternative preparation for the title compound of this step:

The reaction mixture obtained by the alternative method for the preparation of the title compound of Step A was cooled to room temperature and concentrated at reduced pressure on a rotary evaporator to a dark thick oil (102 g) at 40°C. The dark oil (98 g, 188 mmol) was dissolved in anhydrous dichloromethane (240 mL). Diisopropylethylamine (97 mL, 4 equivalents) was added followed by dropwise addition of methoxyethoxymethyl chloride (25.7 mL, 225.6 mmol). The reaction mixture was stirred at room temperature for 4 hours.

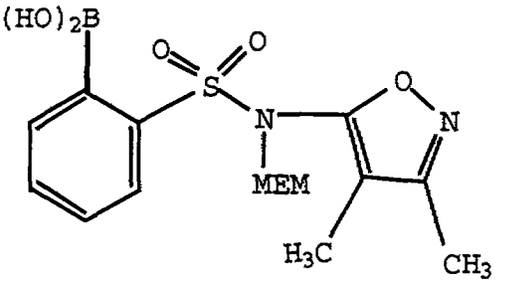
The reaction mixture was concentrated at reduced pressure on a rotary evaporator to a thick oil, dissolved in EtOAc (400 mL) and charcoal (10 g) was added. The charcoal mixture was stirred at room temperature for 30 minutes and was filtered through a celite pad. The celite pad was rinsed with EtOAc (100 mL x 3) and hexanes (200 mL x 2). The filtrate was transferred to a separatory funnel and washed with water (100 mL x 2), HCl (0.5N, 100 mL x 2), water (100 mL x 2) and brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated to a thick oil (64.9 g, 83% mass balance).

The thick oil was dissolved in ethanol (EtOH, 65 mL), cooled to 0°C with an ice bath, seeded with the title product of this step and stirred at 0°C for 6 hours. Crystallization occured. The solid was filtered and suction dried. The title compound of this step was obtained as a yellowish

solid (62% overall yield, HPLC area percent = 98.2%).

TLC: Rf = 0.55 (silica gel from Whatman; EtOAc:hexanes/1:1; visualization: CAM or UV)

C. 2-Borono-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]benzene-sulfonamide



A dry 3-necked 1-liter round-bottomed flask equipped with an overhead mechanical stirrer, gas adapter, thermocouple, and septum was charged with the title compound of Step B (40.0 g; 95.4 mmol), and then thoroughly degassed and placed under an argon atmosphere. Tetrahydrofuran (THF, 185 mL) was added via syringe and the mixture was cooled to about -100°C (internal temperature). n-Butyl lithium (n-BuLi, 42.5 mL, 101 mmol, 2.38 M in hexanes) was dropwise added over a period of 16 minutes, while maintaining the internal temperature between -97°C and -101°C. The pale yellow-orange solution was stirred at about -98°C to -101°C for an additional 16 minutes.

Trimethylborate (16.0 mL, 140.9 mmol) in THF (24 mL) was dropwise added over 14.5 minutes, while maintaining the internal temperature between -96°C and -99°C. The mixture was stirred for

about 44 minutes at about -93°C to -101°C, and an additional 39 minutes at about -93°C to -72°C. HCl (3.0 N, 120 mL, 360 mmol) was added to the reaction (the solution exothermed to about -7°C) and was stirred for 20 minutes (-7°C to +6°C). The two layers were separated in a separatory funnel, and the aqueous phase was washed with toluene (3 x 120 mL) and t-butyl methyl ether (MTBE, 3 x 100 mL). The combined organic layer was washed with brine (4 x 100 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to a volume of about 100 mL containing the title compound of this step (HPLC area percent = 97.7%).

Alternative preparation of the title compound of this step:

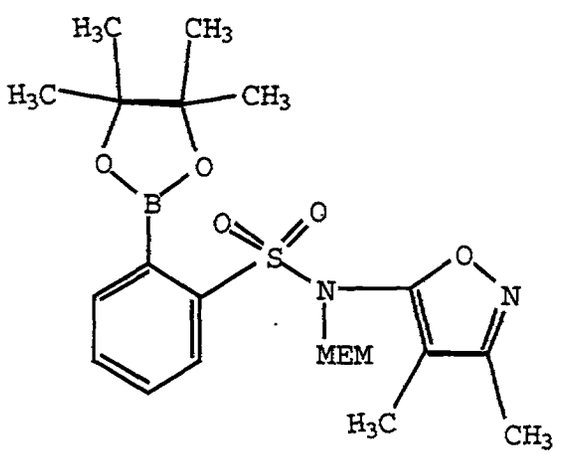
A 500 mL 3-neck flask equipped with a stir bar was charged with the title compound of Step B (20.0 g, 47.7 mmol) and purged with argon for 0.5 hr. Anhydrous THF (200 mL) was added via syringe and the flask was cooled to -78°C in an acetone/dry ice bath. Phenyl lithium (PhLi, 37.1 mL, 48.2 mmol, 1.3 M in cyclohexane-ether, titrated according to *J. Organomet. Chem.*, 186, 155 (1980), and determined to be 1.3 M) was added via an addition funnel over the course of 25 minutes. The rate of addition of PhLi was such that the internal temperature of the reaction mixture was maintained below -75°C. The resulting solution was stirred at -78°C for 15 minutes following which a solution of trimethylborate (10.8 mL, 95.4 mmol) in THF (5 mL) was cannulated dropwise into the reaction mixture over 15 minutes. The trimethylborate/THF solution was

cooled in an ice-water bath prior to addition. The rate of addition was maintained such that the internal temperature of the reaction mixture did not go above -73°C. The reaction mixture was stirred at -78°C for 0.5 hr, and then quenched by the dropwise addition of a solution of acetic acid (15 mL) in THF (10 mL). The acidified solution was stirred at -78°C for 10 minutes following which the solution was warmed to 0°C. To this was added dropwise, 1N HCl (25 mL). (1N HCl was prepared by diluting 42 ml of 12N HCl into 500 mL of water. The excess acid was added in order to ensure complete quenching. The HCl solution was pre-cooled in an ice/water bath prior to addition.) The reaction mixture was then allowed to warm to room temperature and extracted with t-butyl methyl ether (TBME, 4 X 250 mL). The organic layers were combined and extracted with 0.5N aqueous NaOH (4 X 25 mL). The aqueous layers were combined and back extracted with TBME (1 X 100 mL). The aqueous extract was cooled to 0°C and the pH adjusted to 2.0 (pH meter) by the dropwise addition of 6N HCl with rapid stirring. The acidified solution was extracted with TBME (4 X 250 mL), the organic layers pooled and dried over anhydrous $MgSO_4$. The suspension was filtered and the solution concentrated to give the boronic acid title compound of this step as a pale brown oil (17.1 g, 93%, HPLC area percent = 88%).

HPLC Conditions: Column - YMC ODS-A, 6 x 250 mm; Monitored at 233 nm; Flow rate - 1.5 mL/min; Solvent A (%): H_2O/MeOH/H_3PO_4 90:10:0.2; Solvent B (%): H_2O/MeOH/H_3PO_4 10:90:0.2; Gradient: 40% B to 100% B, linear gradient over 10 minutes, 100% B

for 5 minutes, 40% B for 4 minutes; Retention time for the title compound of this step = 8.3 minutes.

D. N-[(2-Methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfanamide



The mixture from step C was diluted with toluene (170 mL) to bring the total volume to about 270 mL, and the flask was equipped with a Dean-Stark trap and magnetic stir bar. Pinacol (11.6 g, 98.2 mmol) was added and the resulting mixture was heated to reflux for about 1.25 hr. Water was drained from the Dean-Stark trap and the solution was then used "as is" in Example 3. (98% conversion, HPLC area percent = 93.6%)
Reverse phase HPLC Column: YMC-Pack ODS-A; 150 x 6 mm; S-5 mm, 120A and monitored @233 nm; Solvent: A = 90% water, 10% methanol and 0.2% H_3PO_4; B = 10% water, 90% methanol and 0.1% $H3PO_4$;
Flow rate: 100 mL per minute; Gradient; 40% B to 100% B in 10 minutes. Hold time: 5 minutes at

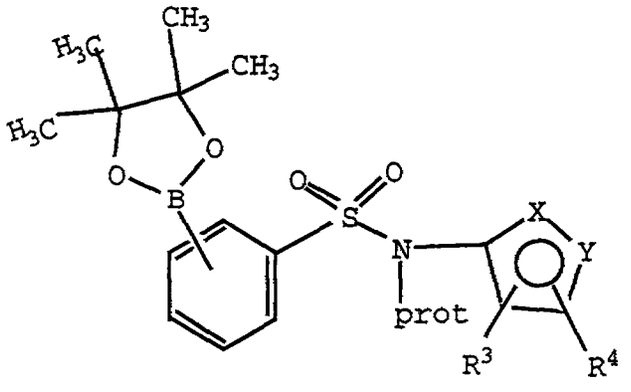
100% B. Step down to 40% B and hold for 5 minutes. Retention Time for title product of this Example - 11.5 minutes.

Alternative preparation of the title compound of this Example:

The boronic acid obtained in the alternative method for preparation of the title compound of Step C (17.1 g, 44.5 mmol) was dissolved in a solution of anhydrous toluene (425 mL) and pinacol (5.51 g, 46.7 mmol). The flask was placed in an oil bath and heated to 120°C for 2 hr (note: reaction was complete in first 40 minutes) and water continuously removed by the use of a Dean-Stark trap (flask and trap covered in foil; mixture boiled rapidly in approximately 0.5 hr) and condensor. Analysis of an aliquot (worked up by repeated azeotroping with $CDCl_3$) by HPLC indicated complete conversion of the boronic acid starting material to the title compound of this Example. The reaction mixture was cooled to room temperature and concentrated to afford the title compound of this Example as a toluene solution, HPLC area percent = 86%. A 100% yield was assumed for conversion of the boronic acid to pinacol ester. A portion of the crude solution of the title compound of this Example was used in Example 3. Retention time of title compound of this Example = 12.4 minutes (using HPLC conditions described for boronic acid starting material).

What is claimed is:

1. A compound of the formula II or salt thereof:



(II)

where the phenyl ring of said formula II may be further substituted, and where "prot" denotes a nitrogen-protecting group, and wherein:

one of X and Y is N and the other is O;

R^3 and R^4 are each directly bonded to a ring carbon and are each independently

(a) hydrogen;

(b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1, Z^2 and Z^3;

(c) halo;

(d) hydroxyl;

(e) cyano;

(f) nitro;

(g) $-C(O)H$ or $-C(O)R^5$;

(h) $-CO_2H$ or $-CO_2R^5$;

(i) $-Z^4-NR^6R^7$;

(j) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; or

(k) R^3 and R^4 together may also be alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached;

R^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1, Z^2 and Z^3;

R^6, R^7, R^8, R^9 and R^{10} are each independently

(a) hydrogen; or

(b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1, Z^2 and Z^3; or

R^6 and R^7 together may be alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; or any two of R^8, R^9 and R^{10} together are alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z^1, Z^2 and Z^3 are each independently

(a) hydrogen;

(b) halo;

(c) hydroxy;

(d) alkyl;

(e) alkenyl;

(f) aryl;
(g) aralkyl;
(h) alkoxy;
(i) aryloxy;
(j) aralkoxy;
(k) heterocycle, substituted heterocycle or heterocyclooxy;
(l) -SH, $-S(O)_nZ^6$, $-S(O)_m-OH$, $-S(O)_m-OZ^6$, $-O-S(O)_m-Z^6$, $-O-S(O)_mOH$ or $-O-S(O)_m-OZ^6$;
(m) oxo;
(n) nitro;
(o) cyano;
(p) -C(O)H or $-C(O)Z^6$;
(q) $-CO_2H$ or $-CO_2Z^6$;
(r) $-Z^4-NZ^7Z^8$;
(s) $-Z^4-N(Z^{11})-Z^5-H$;
(t) $-Z^4-N(Z^{11})-Z^5-Z^6$; or
(u) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$;

Z^4 and Z^5 are each independently
(a) a single bond;
(b) $-Z^9-S(O)_n-Z^{10}-$;
(c) $-Z^9-C(O)-Z^{10}-$;
(d) $-Z^9-C(S)-Z^{10}-$;
(e) $-Z^9-O-Z^{10}-$;
(f) $-Z^9-S-Z^{10}-$;
(g) $-Z^9-O-C(O)-Z^{10}-$; or
(h) $-Z^9-C(O)-O-Z^{10}-$;

Z^6 is alkyl; alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy; alkenyl; alkynyl; cycloalkyl; cycloalkyl substituted with one to three groups selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring;

aryloxy substituted with one or two halogens; cycloalkylalkyl; cycloalkenyl; cycloalkenylalkyl; aryl; aryl substituted with methylenedioxy or one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy and trihaloalkoxy; or heterocycle or substituted heterocycle;

Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached;

Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene;

Z^{11} is

(a) hydrogen; or

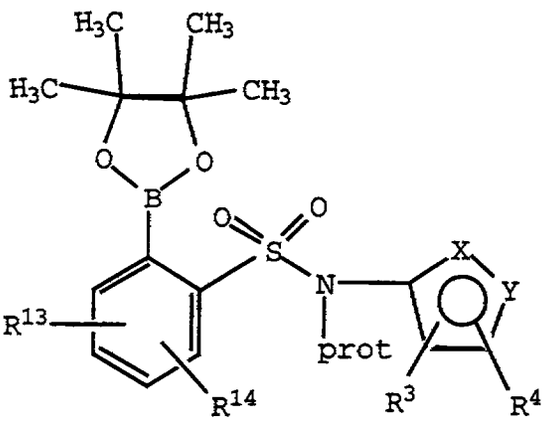
(b) alkyl, alkyl substituted with one, two or three halogens, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl;

or any two of Z^7, Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

each m is independently 1 or 2; and

each n is independently 0, 1 or 2.

2. A compound of claim 1 of the formula IIa or salt thereof:



(IIa)

wherein

R^{13} and R^{14} are each independently

(a) hydrogen;

(b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1, Z^2 and Z^3,

(c) heterocycle, substituted heterocycle or heterocyclooxy;

(d) halo;

(e) hydroxyl;

(f) cyano;

(g) nitro;

(h) $-C(O)H$ or $-C(O)R^5$;

(i) $-CO_2H$ or $-CO_2R^5$;

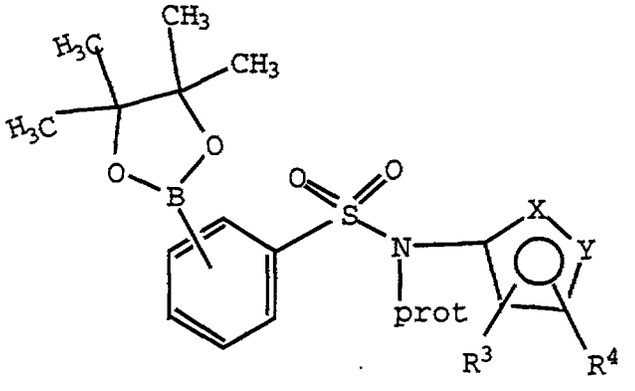
(j) $-SH$, $-S(O)_nR^5$, $-S(O)_m-OH$, $-S(O)_m-OR^5$, $-O-S(O)m-OR^5$, $-O-S(O)_mOH$ or $-O-S(O)_m-OR^5$;

(k) $-Z^4-NR^6R^7$; or

(l) $-Z^4-N(R^{10})-Z^5-NR^8R^9$.

3. The compound of claim 2, which is N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfanamide.

4. A method for the preparation of a pinacol ester of the formula II or salt thereof:



(II)

where the phenyl ring of said formula II may be further substituted, where "prot" denotes a nitrogen-protecting group, and wherein:

one of X and Y is N and the other is O;

R^3 and R^4 are each directly bonded to a ring carbon and are each independently

(a) hydrogen;

(b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1, Z^2 and Z^3;

(c) halo;

(d) hydroxyl;

(e) cyano;

(f) nitro;

(g) -C(O)H or $-C(O)R^5$;

(h) $-CO_2H$ or $-CO_2R^5$;

(i) $-Z^4-NR^6R^7$;

(j) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; or

(k) R^3 and R^4 together may also be alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached;

R^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1, Z^2 and Z^3;

R^6, R^7, R^8, R^9 and R^{10} are each independently

(a) hydrogen; or

(b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1, Z^2 and Z^3; or

R^6 and R^7 together may be alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; or any two of R^8, R^9 and R^{10} together are alkylene or alkenylene, either of which may be substituted with Z^1, Z^2 and Z^3, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z^1, Z^2 and Z^3 are each independently

(a) hydrogen;

(b) halo;

(c) hydroxy;

(d) alkyl;
(e) alkenyl;
(f) aryl;
(g) aralkyl;
(h) alkoxy;
(i) aryloxy;
(j) aralkoxy;
(k) heterocycle, substituted heterocycle or heterocyclooxy;
(l) $-SH$, $-S(O)_nZ^6$, $-S(O)_m-OH$, $-S(O)_m-OZ^6$, $-O-S(O)_m-Z^6$, $-O-S(O)_mOH$ or $-O-S(O)_m-OZ^6$;
(m) oxo;
(n) nitro;
(o) cyano;
(p) $-C(O)H$ or $-C(O)Z^6$;
(q) $-CO_2H$ or $-CO_2Z^6$;
(r) $-Z^4-NZ^7Z^8$;
(s) $-Z^4-N(Z^{11})-Z^5-H$;
(t) $-Z^4-N(Z^{11})-Z^5-Z^6$; or
(u) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$;

Z^4 and Z^5 are each independently
(a) a single bond;
(b) $-Z^9-S(O)_n-Z^{10}-$;
(c) $-Z^9-C(O)-Z^{10}-$;
(d) $-Z^9-C(S)-Z^{10}-$;
(e) $-Z^9-O-Z^{10}-$;
(f) $-Z^9-S-Z^{10}-$;
(g) $-Z^9-O-C(O)-Z^{10}-$; or
(h) $-Z^9-C(O)-O-Z^{10}-$;

Z^6 is alkyl; alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy; alkenyl; alkynyl; cycloalkyl; cycloalkyl substituted with one to three groups

selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring; aryloxy substituted with one or two halogens; cycloalkylalkyl; cycloalkenyl; cycloalkenylalkyl; aryl; aryl substituted with methylenedioxy or one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy and trihaloalkoxy; or heterocycle or substituted heterocycle;

Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached;

Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene;

Z^{11} is

(a) hydrogen; or

(b) alkyl, alkyl substituted with one, two or three halogens, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl;

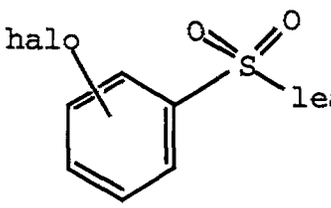
or any two of Z^7, Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

each m is independently 1 or 2; and

each n is independently 0, 1 or 2;

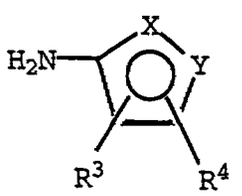
comprising the steps of:

(a) contacting a compound of the formula V or salt thereof:



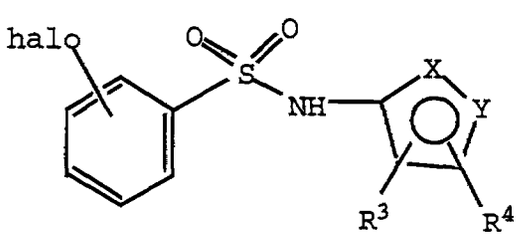
(V)

where the phenyl group of said formula V may be further substituted, with an amine of the formula VI or salt thereof:



(VI)

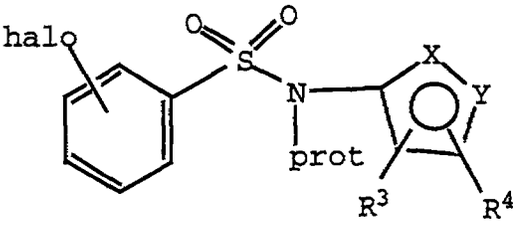
in the presence of an organic base and an organic solvent, to form a compound of the formula VII or salt thereof:



(VII)

where the phenyl group of said formula VII may be further substituted;

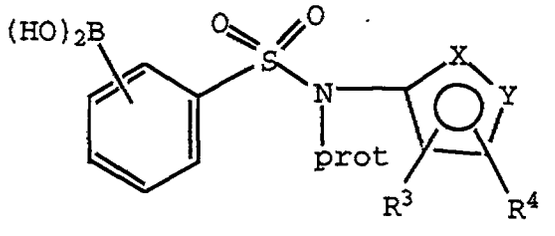
(b) protecting the nitrogen of said compound of the formula VII or salt thereof to form a compound of the formula VIII or salt thereof:



(VIII)

where the phenyl group of said formula VIII may be further substituted;

(c) lithiating said compound of the formula VIII or salt thereof with an alkyl or aryl lithium compound and contacting the lithiated product formed with a trialkylborate, followed by hydrolysis, to form a boronic acid of the formula IX or salt thereof:



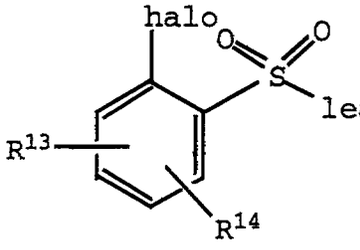
(IX)

where the phenyl group of said formula IX may be further substituted; and

(d) contacting said compound of the formula IX or salt thereof with pinacol, with removal of water, thereby forming said compound of the formula II or salt thereof.

5. A method of claim 4 for the preparation of a pinacol ester of the formula IIa or salt thereof, comprising the steps of:

(a) contacting a compound of the formula Va or salt thereof:



(Va)

where

R^{13} and R^{14} are each independently

(a) hydrogen;

(b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1, Z^2 and Z^3,

(c) heterocycle, substituted heterocycle or heterocyclooxy;

(d) halo;

(e) hydroxyl;

(f) cyano;

(g) nitro;

(h) $-C(O)H$ or $-C(O)R^5$;

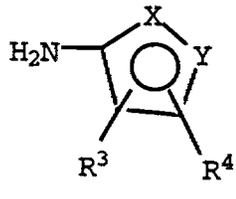
(i) $-CO_2H$ or $-CO_2R^5$;

(j) $-SH$, $-S(O)_nR^5$, $-S(O)_m-OH$, $-S(O)_m-OR^5$, $-O-S(O)m-OR^5$, $-O-S(O)_mOH$ or $-O-S(O)_m-OR^5$;

(k) $-Z^4-NR^6R^7$; or

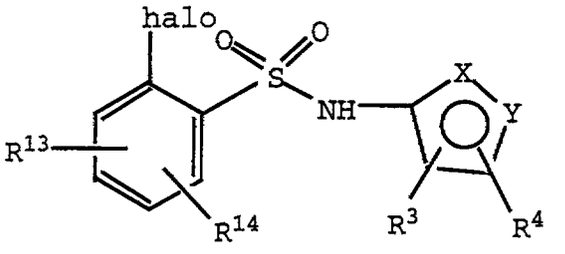
(l) $-Z^4-N(R^{10})-Z^5-NR^8R^9$;

with an amine of the formula VIa or salt thereof:



(VIa)

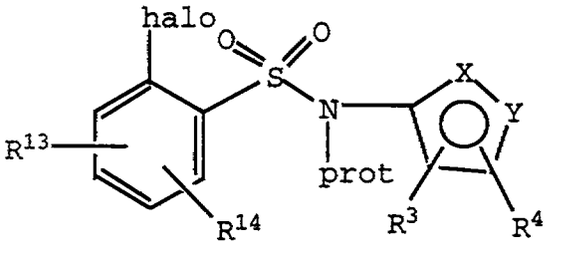
in the presence of an organic base and organic solvent, to form a compound of the formula VIIa or salt thereof:



(VIIa)

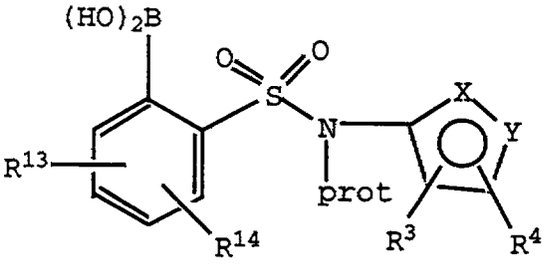
;

(b) protecting the nitrogen of said compound of the formula VIIa or salt thereof to form a compound of the formula VIIIa or salt thereof:



(VIIIa)

(c) lithiating said compound of the formula VIIIa or salt thereof with an alkyl or aryl lithium compound and contacting the lithiated product formed with a trialkylborate, followed by hydrolysis, to form a boronic acid of the formula IXa or salt thereof:



(IXa)

; and

(d) contacting said compound of the formula IXa or salt thereof with pinacol, with removal of water, thereby forming said compound of the formula IIa or salt thereof.

6. The method of claim 5, wherein "prot" is methoxyethoxymethyl or 2-ethoxyethyl.

7. The method of claim 5, wherein the halo group of the compound of the formula Va or salt thereof is bromo, chloro or iodo.

8. The method of claim 5, wherein said leaving group is halo.

9. The method of claim 8, wherein said leaving group is chloro.

10. The method of claim 5, wherein the organic base in step (a) is an amine.

11. The method of claim 10, wherein said organic base is pyridine or a trialkylamine.

12. The method of claim 5, wherein said organic solvent is a haloalkane, or is said organic base which also functions as the organic solvent.

13. The method of claim 5, wherein the alkyl or aryl lithium compound is n-butyl lithium or phenyl lithium.

14. The method of claim 5, wherein said lithiation and/or contact with said trialkylborate is conducted at temperatures from about -40°C to about -105°C.

15. The method of claim 5, wherein said trialkylborate is triisopropylborate or trimethylborate.

16. The method of claim 5, wherein said removal of water is conducted by the addition of a drying agent, or by azeotropic removal of water by heating with a solvent.

17. The method of claim 5, wherein said compound of the formula IIa or salt thereof is N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfanamide, said compound of the formula Va or salt thereof is 2-bromobenzenesulfonyl chloride, and said amine of the formula VIa or salt thereof is 5-amino-3,4-dimethylisoxazole.

18. The method of claim 5, wherein said pinacol ester of the formula IIa or salt thereof is employed in the preparation of a compound of the formula Ia or salt thereof as described in claim 2.