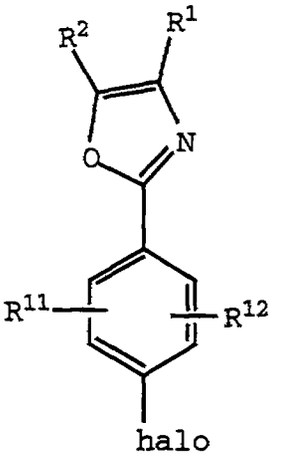
PROCESS FOR PREPARING BIPHENYL ISOXAZOLE SULFONAMIDE INTERMEDIATES

Field of the Invention

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

Brief Description of the Invention

The present methods allow preparation of oxazole phenyl halides of the following formula IIIa(1):



(IIIa(1))

wherein

R^1 and R^2 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) $-Z^4-NR^6R^7$; or

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

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;

R^{11} and R^{12} 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) $-Z^4-N(R^{10})-Z^5-NR^8R^9$;

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;

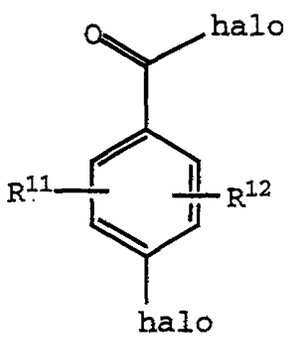
or any two of Z^7, Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

each m is independently 1 or 2; and

each n is independently 0, 1 or 2.

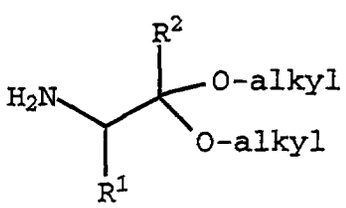
In accordance herewith, a compound of the formula IIIa(1) may be prepared by a method comprising the steps of:

(a) contacting a phenyl acid halide X or salt thereof:



(X)

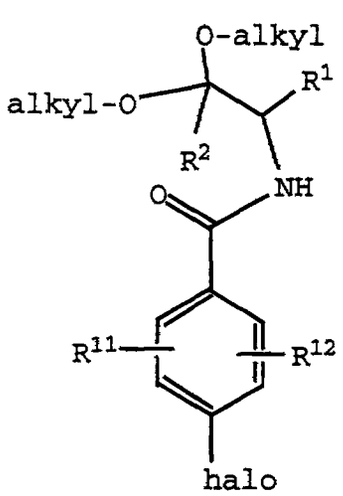
with an amine acetal XI or salt thereof:



(XI)

,

in the presence of a base and a solvent, to form an amide acetal of the formula XII or salt thereof:



(XII)

; and

(b) cyclizing the amide acetal of the formula XII or salt thereof, in the presence of a cyclization agent, to form said oxazole phenyl halide of the formula IIIa(1) or salt thereof.

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 $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH(CH_3)-C\equiv C-$ and $-C\equiv C-CH(C_2H_5)CH_2-$.

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;

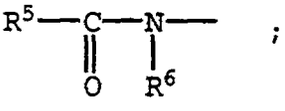
(l) mercapto;

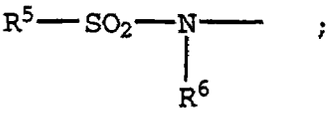
(m) nitro;

(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 IIIa(1)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 IIIa(1) 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 IIIa(1) 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 and salts thereof may exist, therefore, in enantiomeric and diastereomeric forms and in racemic mixtures thereof. All are within the scope of this invention. Additionally, compounds and salts thereof may exist as enantiomers even in the absence of asymmetric carbons. All such enantiomers are within the scope of this invention.

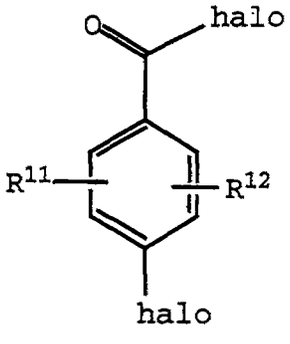
U.S. Patent Application Serial No. 08/493,331, filed July 24, 1995 (Attorney Docket No. HA662c) by Murugesan et al. and continuation-in-part thereof U.S. Patent Application Serial No. 08/603,975, filed February 20, 1996 (Attorney

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 IIIa(1) Compounds

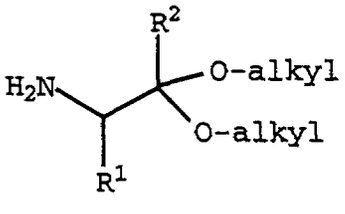
In accordance herewith, a formula IIIa(1) oxazole or salt thereof may be prepared by a method comprising the steps of:

(a) contacting a phenyl acid halide X or salt thereof:



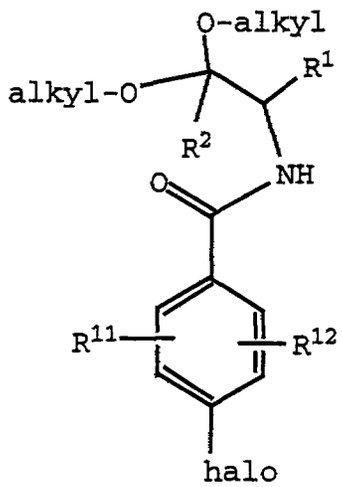
(X)

with an amine acetal XI or salt thereof:



(XI)

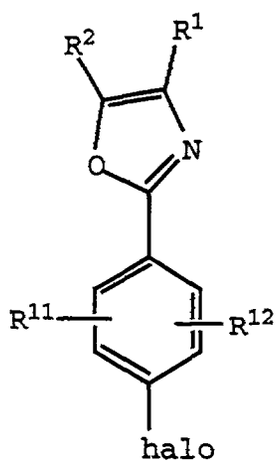
in the presence of a base and a solvent, to form an amide acetal of the formula XII or salt thereof:



(XII)

; and

(b) cyclizing the amide acetal of the formula XII or salt thereof, in the presence of a cyclization agent, to form an oxazole phenyl halide of the formula IIIa(1) or salt thereof:



(IIIa(1))

The starting phenyl acid halide X or salt thereof is commercially available or may readily be prepared by one of ordinary skill in the art. The halo group of the acid halide moiety is preferably chloro; the halo group in the position para to the acid halide moiety is preferably bromo, chloro, or iodo, most preferably iodo. The

starting amine acetal XI or salt thereof is also commercially available or may readily be prepared by one of ordinary skill in the art. The alkyl groups of the acetal moiety are preferably methyl or ethyl, most preferably, methyl.

The base employed in step (a) may be any suitable base, and is preferably an alkali metal carbonate, bicarbonate or hydroxide, most preferably, potassium bicarbonate (in a solvent such as water and/or acetone) or potassium carbonate (in a solvent such as methylene chloride).

Cyclization is conducted by contacting the amide acetal XII or salt thereof with a cyclization agent which may be any compound effecting the cyclization reaction, and is preferably Eaton's reagent (i.e., methanesulfonic acid and phosphoric oxide) or polyphosphoric acid (PPA), most preferably Eaton's reagent. The cyclization is preferably conducted at a temperature of from about 125°C to about 150°C (most preferably from about 130°C to about 135°C), at a pressure of about 1 atm, and under an atmosphere of argon or nitrogen. Amounts of cyclization agent are selected to achieve cyclization and are preferably from about (catalyst/substrate) 8 mL/g to about 15 mL/g when Eaton's reagent is employed. Eaton's reagent is a solution of P_2O_5 in methanesulfonic acid and can also function as a preferred solvent for the cyclization. Exemplary compositions for Eaton's reagent are those containing 7.5 to 15% by weight P_2O_5 in methanesulfonic acid.

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 IIIa(1) and Salts Thereof as Intermediates in the Preparation of Biphenyl Isoxazole Sulfonamides

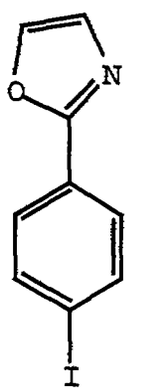
The compounds of the formula IIIa(1) and salts thereof are useful intermediates in the preparation of biphenyl isoxazole sulfonamides, which are antagonists of ET-1, ET-2 and/or ET-3 and are useful in treatment of conditions associated with increased ET levels (e.g., dialysis, trauma and surgery) and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

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

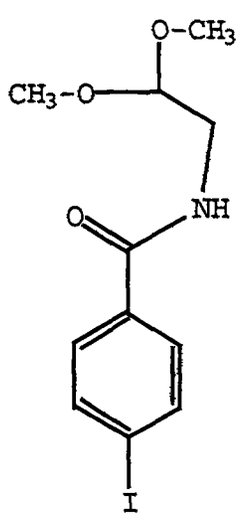
EXAMPLE 1

PREPARATION OF HALOPHENYL COMPOUND IIIa(1)

2-(4-Iodophenyl)oxazole



A. N-(2,2-Dimethoxyethyl)-4-iodobenzamide



$KHCO_3$ (80.0 g, 0.80 mol) was added to a solution of aminoacetaldehyde dimethyl acetal (82.9 g, 86.0 mL, 0.79 mol, commercially available) in water (900 mL) and acetone (400 mL) and the resulting solution was cooled in an ice bath to 0°C. A solution of 4-iodobenzoyl chloride (200.0 g, 0.75 mol) in acetone (600 mL) was added

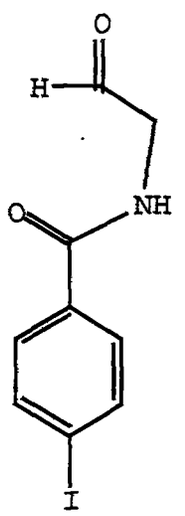
dropwise via an addition funnel, to the aminoacetaldehyde dimethyl acetal solution over the course of 1.5 hr, with mechanical stirring. The addition funnel and the walls of the flask were washed with acetone (50 mL) and the ice bath was removed. The reaction mixture was allowed to stir at room temperature for 3 hr (reaction was completed in 1.5 hr).

The reaction mixture was concentrated by removing 1.0 L of solvent on a rotary evaporator and then extracted with EtOAc (4 X 350 mL). The organic layers were pooled, washed with saturated $NaHCO_3$ (1 X 250 mL) followed by H_2O (1 X 250 mL), dried over anhydrous $MgSO_4$ (50.0 g), filtered and concentrated at reduced pressure to give a white solid (during solvent evaporation, the solid was occasionally scraped off the sides of the flask). The solid was dried under house vacuum for 12 hr (246.5 g, 98%, HPLC area percent = 99.7%).
melting point (mp) = 89-90°C
Elemental Analysis (%) $C_{11}H_{14}NO_3I$
Calc'd: C, 39.42; H, 4.21; N, 4.18
Found: C, 39.42; H, 4.22; N, 4.07

B. <u>2-(4-Iodophenyl)oxazole</u>

Eaton's reagent was prepared by adding P_2O_5 (200 g) in approximately 50 g portions to methanesulfonic acid (2000 mL) at 95°C under argon with vigorous mechanical stirring. The addition of P_2O_5 in portions prevented it from forming a hard mass at the bottom of the flask. A clear, very pale brown solution was obtained. Eaton et al. *J. Org. Chem.*, <u>38</u>, 4071-4073 (1973).

A 3 L 3-neck round-bottom flask containing the Eaton's reagent (2000 mL) was equipped with a condenser and charged with the title compound of step A (200.0 g, 0.60 mol). The reaction mixture was placed in an oil bath and heated with stirring, under a positive pressure of argon. (It was found to be beneficial to warm the reaction mixture to the required temperature rather than set it in a pre-heated bath.) Monitoring the reaction by TLC indicated that the first step of the reaction was hydrolysis of the dimethylacetal group to the corresponding aldehyde (Rf = 0.11):



followed by cyclization. The oil bath temperature was adjusted so as to maintain the internal temperature of the reaction mixture between 130-134°C. (The temperature of the oil bath was maintained between 138-141°C). After 7.5 hr, analysis of an aliquot (worked up by addition to H_2O and extraction with EtOAc) by TLC indicated the complete disappearance of the starting material and the production of a single new spot.

The reaction mixture was cooled to 30°C under argon, divided into three approximately equal portions, and each portion was poured onto a slurry of ice/water (approximately 6.0 L) with vigorous stirring using a mechanical stirrer, with external cooling. This resulted in the formation of a brownish-gray precipitate. The resulting suspension was stirred for 2 hr and the solid was collected by suction filtration through a medium porosity sintered glass funnel, washed with ice cold water (1 L) and the filter cake broken. The solid was air dried for 5 days to give a gray powder (151.7 g, 93%). The crude material (151.7 g) was dissolved in acetonitrile (2 L) (by warming gently with a heat gun; a small amount of black flocculent solid remained undissolved in the flask) and activated charcoal (15.2 g) was added and the mixture stirred at room temperature for 1 hr. The mixture was filtered through a pad of celite (100.0 g). The celite pad was washed with acetonitrile (2 X 100 mL). The filtrate was concentrated under reduced pressure to approximately 1180 mL in a 5 L round bottom flask. The flask was warmed with a heat gun until the solid completely dissolved. To the resulting hot solution, boiling water (295 mL) was added in two portions, the flask was heated to near boiling and gently swirled after each addition. The solution was once again heated to near boiling, the flask was covered and allowed to stand at room temperature for 48 hr (some crystals were observed within 1.5 hr), following which it was stored at 4°C for 4 days. The crystals which formed were collected by suction filtration and washed with an

ice cold solution of acetonitrile:water (4:1, 150 mL), and air dried for 20 hr. The title compound of this Example was obtained as very pale yellow crystals which were further dried under house vacuum (107.2 g, 66%, HPLC area percent = 99.7%). A second crop of the title compound was collected upon recrystallization of the yellow solid obtained upon concentration of the mother liquor (27.4 g, 17%, HPLC area percent = 98.4%).

m.p. = 107-109°C

Elemental Analysis C_9H_6NOI

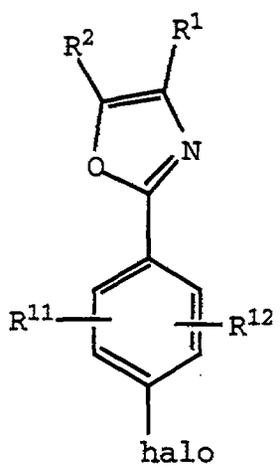
Calcd: C, 39.88; H, 2.23; N, 5.17

Found: C, 40.00; H, 2.09; N, 5.14

* C L M S *

What is claimed is:

1. A method for the preparation of an oxazole phenyl halide of the formula IIIa(1) or salt thereof:



(IIIa(1))

wherein

R^1 and R^2 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) $-Z^4-NR^6R^7$; or

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

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;

R^{11} and R^{12} 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) $-Z^4-N(R^{10})-Z^5-NR^8R^9$;

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;

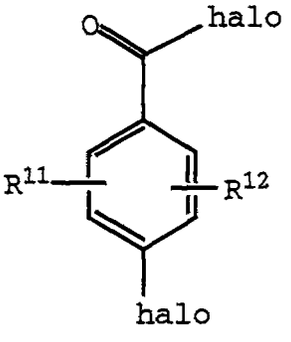
or any two of Z^7, Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

each m is independently 1 or 2; and

each n is independently 0, 1 or 2;

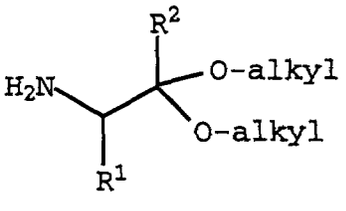
comprising the steps of:

(a) contacting a phenyl acid halide X or salt thereof:



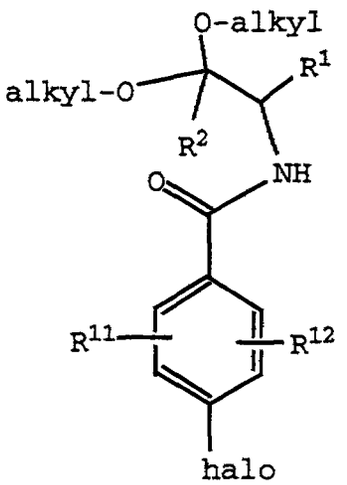
(X)

with an amine acetal XI or salt thereof:



(XI)

in the presence of a base and a solvent, to form an amide acetal of the formula XII or salt thereof:



(XII)

; and

(b) cyclizing the amide acetal of the formula XII or salt thereof, in the presence of a cyclization agent, to form said oxazole phenyl halide of the formula IIIa(1) or salt thereof.

2. The method of claim 1, wherein, in said formula X, the halo group of the acid halide moiety is chloro, and the halo group in the position para to the acid halide moiety is chloro, bromo, or iodo.

3. The method of claim 1, wherein said oxazole of the formula IIIa(1) or salt thereof is employed in the preparation of a compound of the formula Ia or salt thereof as described in claim 2.

4. The method of claim 1, wherein the alkyl groups of the acetal moiety are methyl or ethyl.

5. The method of claim 1, wherein the base employed in step (a) is an alkali metal bicarbonate, carbonate or hydroxide.

* C L M S *

6. The method of claim 1, wherein the cyclization agent is Eaton's reagent, P_2O_5 in methanesulfonic acid, or polyphosphoric acid.

7. The method of claim 1, wherein said oxazole phenyl halide of the formula IIIa(1) or salt thereof is 2-(4-iodophenyl)oxazole, said phenyl acid halide of the formula X or salt thereof is 4-iodobenzoyl chloride, and said amine acetal of the formula X or salt thereof is aminoacetaldehyde dimethyl acetal.