PROCESS FOR MAKING FUSED-RING IMIDAZO-CONTAINING COMPOUNDS

FIELD OF THE INVENTION

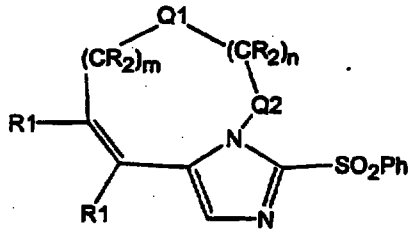
The subject invention relates to processes for making certain substituted fused-ring imidazo compounds.

BACKGROUND

Some fused-ring imidazo compounds have pharmacological activity in processes known to be associated with one or more of cardiovascular activity, inflammatory mechanisms, oncology, and regulation of protein transport from cells. The subject invention processes are useful for making such compounds.

SUMMARY OF THE INVENTION

The subject invention involves processes for making compounds having the structure:



(1)

wherein:

(a) m is an integer from 0 to about 6;

(b) n is an integer from 0 to about 6;

(c) -Q1- is selected from nil, -CR=CR-, -O-, -S-, -NR-, -C(O)-, -NR-C(O)-, -OC(O)-;

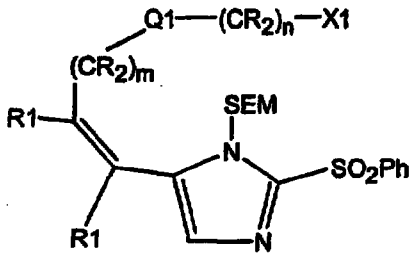
(d) -Q2- is nil or -C(O)-;

(e) each -R is independently selected from hydrogen, alkyl, aryl, and heterocycle;

(f) each -R1 is independently selected from hydrogen, alkyl, aryl, heterocycle, or the two R1's are attached to form a cycloalkenyl, aryl or heterocyclic ring;

the process comprising the following Steps:

(A) treating a compound having the structure:



(2)

wherein m, n, -Q1- and -R1 are the same as for compound (1); and -X1 is selected from -Cl, -Br, -I, -OH and -COOH;

(i) if -X1 is -OH, treating compound (2) with MsOCl or TsOCl and Et_3N in solvent, whereby -X1 is converted to -X2, -X2 being -OMs or -OTs, respectively; or treating compound (2) with a halogenating reactant in solvent, whereby -X1 is converted to -X2, -X2 being -Cl or -Br or -I;

(ii) if -X1 is -COOH, treating compound (2) with phosgene or oxalyl chloride in solvent, whereby -X1 is converted to -X2, -X2 being -C(O)Cl;

whereby some or all of the intermediate thus formed in this Step (A) may further spontaneously react to form compound (1);

(B) if -X1 is -Cl or -Br or -I, or if the conversion to compound (1) in Step (A) is insufficient, treating compound (2) or the reaction product of Step (A), respectively, with nBu_4NF in solvent, whereby conversion to compound (1) occurs.

The subject invention also involves processes having additional Steps before and/or after Steps (A) and/or (B). The subject invention also involves combinatorial libraries of compounds made according to subject processes.

DESCRIPTION OF THE INVENTION

Glossary of Terms

As used herein unless specified otherwise, "alkyl" means a hydrocarbon chain which is branched, linear or cyclic, saturated or unsaturated (but not aromatic), substituted or unsubstituted. The term "alkyl" may be used alone or as part of another word where it may be shortened to "alk" (e.g., in alkoxy, alkylacyl). Preferred linear alkyl have from one to about twenty carbon atoms, more preferably from one to about ten carbon atoms, more preferably still from one to about six carbon atoms, still more preferably from one to about four carbon atoms; most preferred are methyl or ethyl. Preferred cyclic and branched alkyl have from three to about twenty carbon atoms, more preferably from three to about ten carbon atoms, more preferably still from three to about seven carbon atoms, still more preferably from three to about five carbon atoms. Preferred cyclic alkyl have one hydrocarbon ring, but may have two, three, or more, fused or spirocycle hydrocarbon rings. Preferred alkyl are unsaturated with from one to about three double or triple bonds, preferably double bonds; more preferably they are mono-unsaturated with one double bond. Still more preferred alkyl are saturated. Saturated alkyl are referred to herein as "alkanyl". Alkyl unsaturated only with one or more double bonds (no triple bonds) are referred to herein as "alkenyl". Preferred substituents of alkyl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, sulfo, alkylsulfo, arylsulfo, sulfino, alkylsulfino, arylsulfino, phospho, alkylphospho, arylphospho, phosphino, alkylphosphino, arylphosphino, nitro, and cyano. Substituents of cycloalkyl also include cycloalkyl, aryl and heterocycle rings which are fused or spirocycle with the initial cycloalkyl. Also, unsubstituted alkyl are preferred.

As used herein, "heteroatom" means a nitrogen, oxygen, or sulfur atom.

As used herein, "alkylene" means an alkyl which connects two other moieties, "heteroalkylene" means an alkylene having one or more heteroatoms in the connecting chain.

As used herein unless specified otherwise, "aryl" means an aromatic hydrocarbon ring (or fused rings) which is substituted or unsubstituted. The term "aryl" may be used alone or as part of another word (e.g., in aryloxy, arylacyl). Preferred aryl have from six to about fourteen, preferably to about ten, carbon atoms in the aromatic ring(s), and a total of from about six to about twenty, preferably to about twelve, carbon atoms. Preferred aryl is phenyl or naphthyl; most preferred is phenyl (Ph). Preferred substituents of aryl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, sulfo, alkylsulfo, arylsulfo, sulfino, alkylsulfino, arylsulfino, phospho, alkylphospho, arylphospho, phosphino, alkylphosphino, arylphosphino, nitro, and cyano. Substituents of aryl also include cycloalkyl and heterocycle rings which are fused with the aryl ring or rings. Also, unsubstituted aryl are preferred.

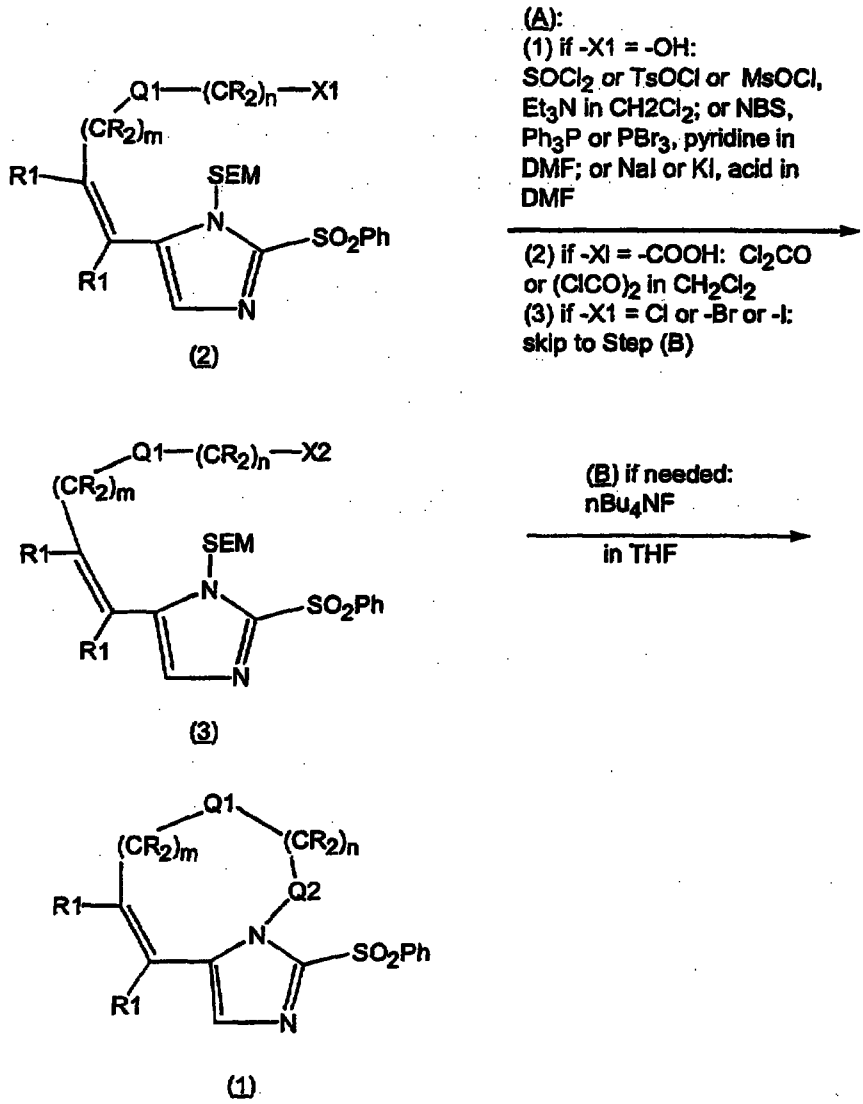
As used herein unless specified otherwise, "heterocycle" or "heterocyclic" means a saturated, unsaturated or aromatic cyclic hydrocarbon ring (or fused rings) with one or more heteroatoms in the hydrocarbon ring(s). Preferred heterocycles have from one to about six heteroatoms in the ring(s), more preferably one or two or three heteroatoms in the ring(s). Preferred heterocycles have from three to about fourteen, preferably to about ten, carbon plus heteroatoms in the ring(s), more preferably from three to about seven, more preferably still five or six, carbon plus heteroatoms in the rings(s); and a total of from three to about twenty carbon plus heteroatoms, more preferably from three to about ten, more preferably still five or six, carbon plus heteroatoms. Preferred heterocycles have one ring, but may have two, three, or more, fused rings. More preferred heterocycle rings include those which are one ring with 5 or 6 carbon plus heteroatoms in the ring with no more than three ring heteroatoms, no more than two of which are O and S. Still more preferred are such 5- or 6-ring atom heterocycles with one or two ring atoms being O or S and the others being C; or with one, two or three ring atoms being N and the

others being C. Such preferred 5- or 6-ring atom heterocycles are preferably saturated, unsaturated with one or two double bonds, or aromatic. Such preferred 5- or 6-ring atom heterocycles are preferably a single ring; or fused with a 3- to 6-ring atom hydrocarbon ring which is saturated, unsaturated with one double bond, or aromatic (phenyl); or fused with another such 5- or 6-ring atom heterocyclic ring. Heterocycles are unsubstituted or substituted. Preferred heterocycle substituents are the same as for alkyl.

Processes of the Invention

Scheme I

The subject invention processes include those depicted in Scheme I:



In Scheme I and other Schemes herein, m is an integer from 0 to about 6, preferably from 0 to about 2, more preferably 0 or 1; n is an integer from 0 to about 6, preferably from 0 to about 2, more preferably 0 or 1; m + n is from 0 to 12, preferably from 0 to about 4, more preferably from 1 to about 3, more preferably still 2 or 3.

In Scheme I and other Schemes herein, each -R is independently selected from hydrogen, alkyl, aryl, and heterocycle. Non-hydrogen -R are preferably selected from phenyl, heterocycle having 5 or 6 ring atoms including 1 or 2 heteroatoms, and alkyl having from 1 to about 6 carbon atoms; such R are unsubstituted or substituted,

preferably unsubstituted. Preferably no more than 2 of all the -R's is other than hydrogen, more preferably no more than 1; more preferably still all -R's are hydrogen.

In Scheme I and other Schemes herein, each -R1 is independently selected from hydrogen, alkyl, aryl and heterocycle, or both -R1's are attached to form a cycloalkenyl, aryl or heterocyclic ring. Preferably the two -R1's are attached to form a cycloalkenyl, aryl, or heterocyclic ring; more preferably a cycloalkenyl or aryl ring; more preferably still an aryl ring, especially phenyl. When the two -R1's are attached forming a phenyl ring, one or preferably both of the positions on the phenyl ring para to the positions of attachment of the -R1's shown in Scheme I have non-hydrogen substituents attached thereto. Such substituents are preferably attached to the phenyl ring by a heteroatom, the heteroatom preferably being oxygen; such substituents are preferably alkoxy, especially methoxy.

In Scheme I and other Schemes herein, -Q1- is selected from nil, -CR=CR-, -O-, -S-, -NR-, -C(O)-, -NR-C(O)-, and -OC(O)-; preferably from nil, -O-, -S-, -NR-, and -C(O)-. More preferred -Q1- is nil. When -Q1- is nil, m + n is preferably from 1 to about 4, more preferably from 1 to about 3.

In Scheme I and other Schemes herein, -X1 is selected from -Cl, -Br, -I, -OH and -COOH. If -X1 is -OH, then -X2 can be -OMs or OTs, and -Q2- is nil. Alternatively, if -X1 is -OH, -X2 can be -Cl or -Br or -I, and -Q2- is nil. If -X1 is -COOH, then -X2 is -C(O)Cl, and -Q2- is -C(O)-. If -X1 is -Cl or -Br or -I, Step (A) is skipped, and -X2 is the same as -X1 (compound (2) and compound (3) are the same).

In Scheme I and other Schemes herein, -SEM has the structure: -$CH_2OCH_2CH_2$-$Si(CH_3)_3$.

Step (A)

In Step (A) of Scheme I, the reactants are dependent on -X1.

If -X1 is -OH, compound (2) can be treated with either methylsulphonyl chloride (MsOCl) or p-toluenesulfonyl chloride (TsOCl), preferably in the presence of base (e.g. triethylamine (Et_3N)), in solvent, preferably dichlorolmethane. This reaction is preferably carried out under an inert atmosphere, more preferably under an argon atmosphere. The MsOCl or TsOCl is preferably added slowly, preferably over a period

of up to about 2 h, more preferably from about 1/4 h about 1 h. More preferably still over about 1/2 h. During addition of the MsOCl or TsOCl, the temperature of the reaction mixture is preferably from about -20 °C to about 25 °C, more preferably about 0 °C. After addition of MsOCl or TsOCl is complete, the reaction mixture is preferably warmed to a temperature of from about 0 °C to about 40 °C, more preferably to about room temperature; at this temperature, the reaction mixture is stirred preferably for from about 1/2 h to about 6 h, more preferably for about 1 h.

Alternatively, if -X1 is -OH, compound (2) is reacted with a halogenating reactant such that the -OH is converted to -Cl, -Br or -I (-X2), thus forming compound (3). Known halogenating reaction conditions that are compatible with compounds of structure (2), (3), and (1) are suitable. Preferred halogenation reactions are selected from the following:

(a) Compound (2) can be treated with thionyl chloride ($SOCl_2$), preferably in the presence of base (e.g., triethylamine), in solvent, preferably dichloromethane, to produce compound (3) wherein -X2 is Cl. This reaction is preferably carried out under an inert atmosphere, more preferably under an argon atmosphere. The thionyl chloride is preferably added slowly, preferably over a period of up to about 2 h, more preferably from about 1/4 h about 1 h. More preferably still over about 1/2 h. During addition of the thionyl chloride, the temperature of the reaction mixture is preferably from about -20 °C to about 25 °C, more preferably about 0 °C. After addition of thionyl chloride is complete, the reaction mixture is preferably warmed to a temperature of from about 0 °C to about 40 °C, more preferably to about room temperature; at this temperature, the reaction mixture is stirred preferably for from about 1/2 h to about 6 h, more preferably for about 1 h.

(b) Compound (2) can be treated with NBS, preferably in the presence of triphenylphosphine (Ph_3P), in solvent, preferably dimethyl formamide (DMF), or with tribromophosphine (PBr_3), preferably in the presence of base (e.g., pyridine), in solvent, preferably dichloromethane, to produce compound (3) wherein -X2 is -Br. This reaction is preferably carried out under an inert atmosphere, more preferably under a nitrogen atmosphere. The temperature of

the reaction mixture is preferably from about 0 °C to about 40 °C, more preferably about 20 °C. The reaction mixture is stirred preferably for from about 1/2 h to about 12 h, more preferably for about 2 h.

(c) Compound (2) can be treated with sodium iodide (NaI) or potassium iodide (KI), preferably in the presence of strong acid (e.g., phosphoric acid, sulfuric acid), in solvent, preferably DMF, to produce compound (3) wherein -X2 is -I. The temperature of the reaction mixture is preferably from about 0 °C to about 90 °C, more preferably about 20 °C. The reaction mixture is stirred preferably for from about 1 h to about 12 h, more preferably for about 2 h.

If -X1 is -COOH, compound (2) is treated with phosgene (Cl_2CO) or oxalyl dichloride ($(ClCO)_2$) in solvent, preferably dichloromethane. This reaction is preferably carried out under an inert atmosphere, more preferably under an argon atmosphere. The phosgene or oxalyl dichloride is preferably added slowly, preferably over a period of up to about 2 h, more preferably from about 1/4 h about 1 h. More preferably still over about 1/2 h. During addition of the phosgene or oxalyl dichloride, the temperature of the reaction mixture is preferably from about -20 °C to about 25 °C, more preferably about 0 °C. After addition of phosgene or oxalyl dichloride is complete, the reaction mixture is preferably warmed to a temperature of from about 0 °C to about 40 °C, more preferably to about room temperature; at this temperature, the reaction mixture is stirred preferably for from about 1/2 h to about 6 h, more preferably for about 1 h.

In Step (A), -X1 is converted to -X2. If -X1 is -OH, then -X2 is selected from -OMs, -OTs, -Cl, -Br and -I. If -X1 is -COOH, then -X2 is -C(O)Cl.

If -X is -Cl or -Br or -I, Step (A) is not needed, and -X2 is the same as -X1, i.e., compound (2) is also compound (3). In this case, only Step (B) is needed to produce compound (1).

Depending on the reaction conditions in Step (A), the -SEM protective group on the imidazo nitrogen may be split off and the reactive -X2 moiety may spontaneously react at that position to close the ring, thus forming compound (1). If this ring closure is sufficient in Step (A), then Step (B) is not needed; otherwise Step (B) is used to achieve sufficient ring closure.

Step (B)

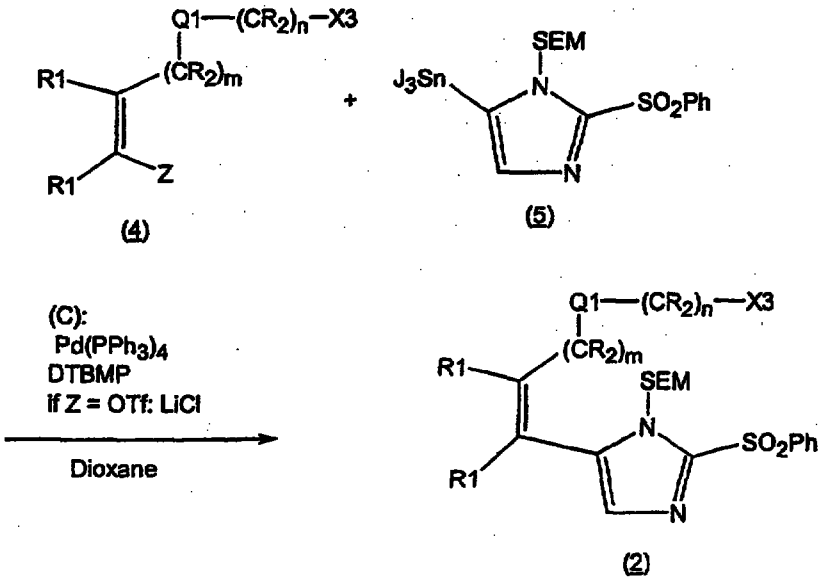
If the solvent for Step (B) is different from that used in Step (A), the Step (A) solvent is removed from the final Step (A) reaction mixture, preferably by evaporation under vacuum at room temperature.

Compound (3) or the reaction product from Step (A) is treated with tetrabutylammonium fluoride (nBu_4NF) in solvent, preferably tetrahydrofurane (THF). This treatment is preferably carried out at a temperature of from about 0 °C to about 60 °C, more preferably at about room temperature, preferably for a period of from about 1/2 h to about 12 h, more preferably for about 4 h.

Compound (1) is preferably isolated and purified from the reaction mixture of Step (A) or/and Step (B) by evaporating off organic solvent, washing the product with water and/or aqueous solutions, separating the organic layer from the aqueous layer, drying off the organic layer by evaporation, and purifying by chromatography.

Scheme II

The subject invention processes disclosed in Scheme I above optionally include additional Step (C) shown in Scheme II:



In Scheme II, m, n, -R, -Q1-, and -R1 are the same as defined for Scheme I above. -X3 is a subset of -X1, and is -OH or -COOH.

In Scheme II and other Schemes herein, -Z is -Br, -I, or -OTf, preferably -Br.

In Scheme II and other Schemes herein, -J is alkanyl having from 1 to about 4 carbon atoms; preferred J is methyl or n-butyl.

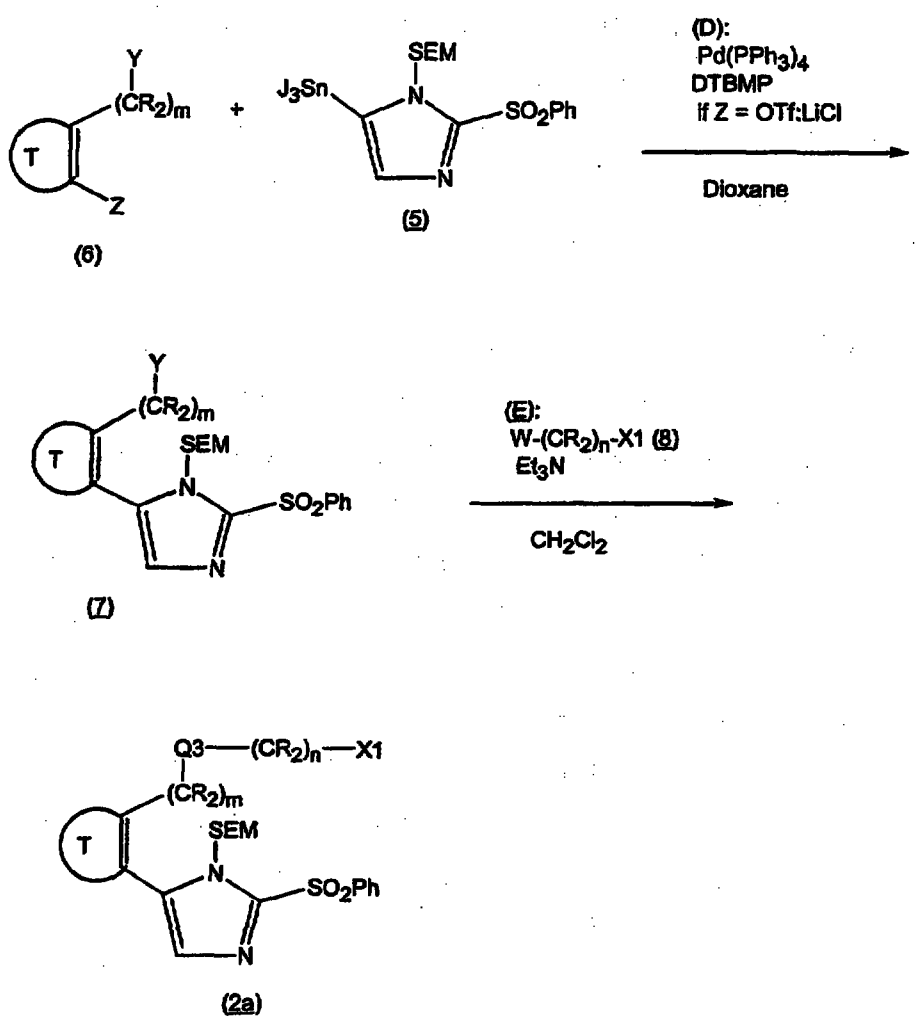
Step (C)

In Step (C), compound (4) and compound (5) are reacted in solvent, preferably dioxane, preferably in the presence of $Pd(PPh_3)_4$ catalyst, to produce compound (2). A small amount of a radical scavenger, preferably 2,6-di-tert-butyl-4-methylphenol (DTBMP) is included in the reaction mixture for Step (C). If -Z is trifluoromethanesulfonate (-OTf), lithium chloride (LiCl) is also preferably included in the reaction mixture. The components of the reaction mixture are preferably combined at about room temperature; then the reaction mixture is heated to about reflux temperature. The reaction mixture is held at about reflux temperature for a period of from about 2 h to about 24 h, preferably for about 5 h. The reaction mixture is preferably retained under an inert atmosphere, preferably under an argon atmosphere during Step (C). The reaction mixture is preferably cooled to about room temperature. The cooled reaction mixture is preferably treated with a mixture of ether and saturated aqueous potassium fluoride solution, preferably about a 1:1 mixture, preferably for from about 1 h to about 24 h, more preferably for about 15 h.

Purified compound (2) is obtained from the reaction mixture, preferably by filtration, ether washing, water and aqueous solution washing, drying, and purifying by chromatography.

Scheme III

For the processes of the subject invention, the Steps shown in Scheme III are an alternative to those of Scheme II, and are an optional addition to the Steps of Scheme I. Scheme III below is used to produce compound (2a) which is a subset of compound (2):



In Scheme III, m, n, -R, -J, and -X1 are the same as for Schemes I and II. Ring T represents all ring moieties that the two -R1's of compound (2) can form when they are attached. -Q3- is a subset of the moieties of -Q1-; -Q3- is selected from -O-, -S-, -NR-, -NR-C(O)-, and -OC(O)-; preferably from -O-, -S-, and -NR-.

In Scheme III, -Y is -NHR, -OH, or -SH; preferably -NHR or -OH; more preferably -OH.

In Scheme III, -W is -I, -Br, or -C(O)V, preferably -Br or -C(O)V, more preferably -Br. -V is -OH, -Cl, or -Br, preferably Cl.

Step (D)

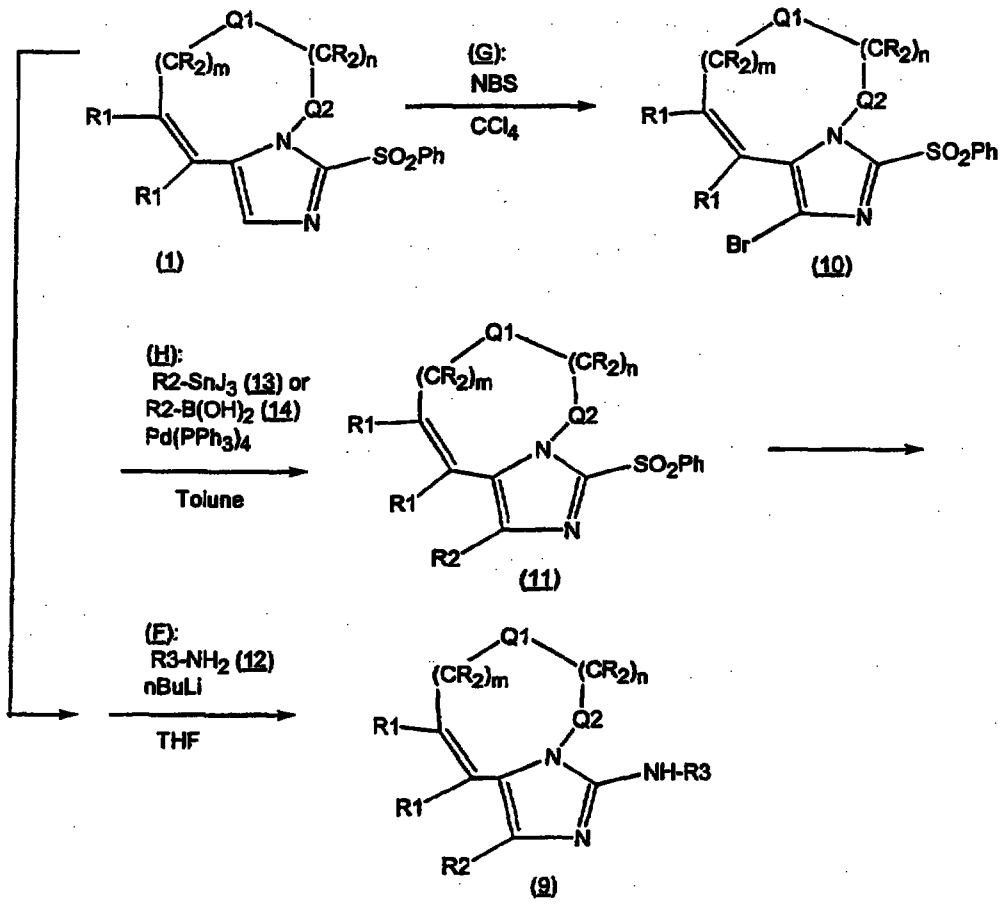
In Step (D) of Scheme III, compound (6) and compound (5) are reacted in solvent, preferably dioxane, preferably in the presence of $Pd(PPh_3)_4$ catalyst to produce compound (7). The preferred conditions for Step (D) of Scheme III are the same as those for Step (C) of Scheme II.

Step (E)

In Step (E), compound (7), and compound (8) are reacted, preferably in the presence of a base, in solvent, preferably dichlorolmethane, to produce compound (2a). Preferred bases useful for this step include sodium carbonate and triethylamine; more preferred is triethylamine. This step is preferably carried out at a temperature of from about 0 °C to about 45 °C, more preferably at about room temperature, preferably for a period of from about 2 h to about 14 h, more preferably for about 6 h.

Scheme IV

The subject invention processes include the preparation of compound (9) from compound (1) or compound (11) as depicted Scheme IV:



In Scheme IV, m, n, -R, -Q1-, -Q2-, -J, and -R1 are the same as specified for Schemes I and II above.

In Scheme IV, -R2 may be hydrogen in which case Steps (G) and (H) are not used. -R2 is selected from hydrogen, halo, alkyl, aryl, heterocycle, carboxy and its alkyl esters and amides. Preferred -R2 is selected from hydrogen, halo, C_1-C_4 alkyl, and phenyl. More preferred -R2 is selected from hydrogen and unsubstituted and substituted phenyl; substituents on such phenyl are preferably selected from hydroxy, alkoxy, thio and alkylthio. Most preferred -R2 is hydrogen.

In Scheme IV, -R3 is selected from hydrogen, alkyl, aryl, and heterocycle. Preferred -R3 is selected from alkyl, aryl, and heterocycle. More preferred -R3 is unsubstituted and substituted phenyl and benzyl. Preferred substituents for such phenyl

and benzyl are selected from halo, C_1-C_4 alkyl, aryl, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters, amides, thioesters and thioamides. More preferred -R3 is benzyl, wherein the alpha carbon of the benzyl is unsubstituted or substituted; preferred substituents are selected from alkyl (preferably C_1-C_4), aryl and heterocycle.

Step (F)

In Step (F), compound (1) or compound (11) is combined with compound (12) and n-butyllithium (nBuLi) in solvent, preferably tetrahydrofuran, to produce compound (9). Compound (12) is preferably dissolved in solvent first, and the resulting solution is cooled to a temperature of from about -30 °C to about 5 °C, preferably about 0 °C. The solution is preferably under an inert atmosphere, more preferably under an argon atmosphere. nBuLi is preferably added slowly to the solution over a period of from about 0.2 h to about 1 h, more preferably over a period of about 0.5 h. The resulting mixture being stirred for a period of from about 1/2 h to about 1 h, more preferably about 3/4 h. Compound (1) or compound (11) dissolved in solvent, preferably THF, is then added. The reaction mixture is preferably warmed to room temperature, and then preferably heated to about reflux temperature for a period of from about 2 h to about 24 h, more preferably for about 12 h. When the reaction is complete, the reaction mixture is preferably quenched with methanol.

Compound (9) is preferably purified from the reaction mixture by evaporating the solvent, redesolving in solvent, preferably dichloromethane, washing with water and aqueous solutions, drying, and purifying by chromatography.

Steps (G) and (H)

A non-hydrogen -R2 is optionally obtained on compound (9) by performing optional Steps (G) and (H) of Scheme IV.

In Step (G), compound (1) and N-bromosuccinimide (NBS) are combined in solvent, preferably carbon tetrachloride. A radical initiator, preferably benzoyl peroxide, is preferably added. The reaction mixture is heated to a temperature, preferably from about 0 °C to about 100 °C, more preferably about 90 °C. The reaction mixture is held at

this elevated temperature for a period of from about 5 min to about 120 min, more preferably for about 10 min.

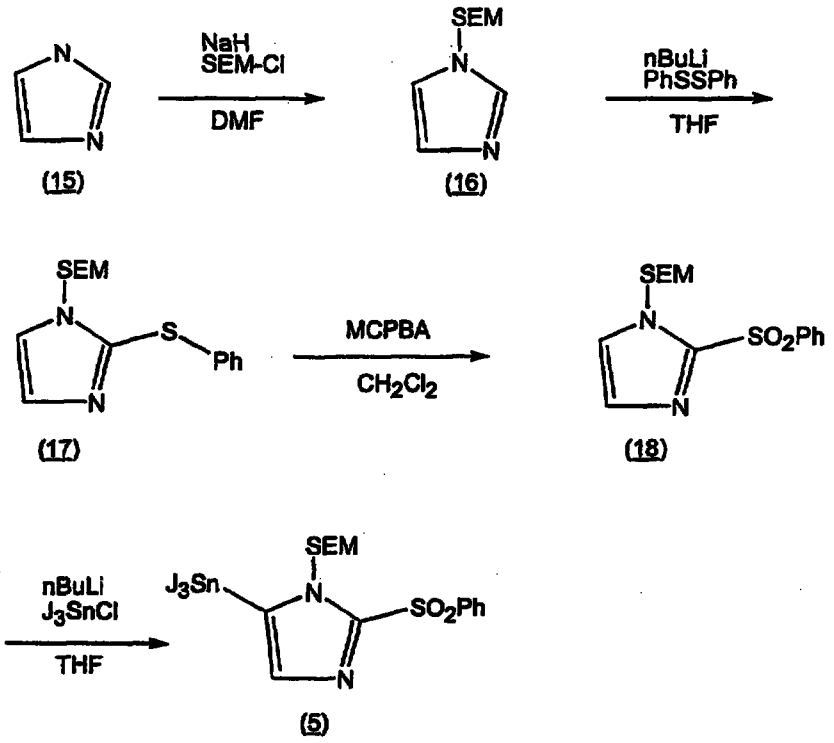
Purified compound (10) is preferably obtained by filtration, evaporation, and purification by chromatography.

In Step (H), compound (10) is combined with compound (13) or compound (14) in the presence of $Pd(PPh_3)_4$ catalyst in solvent, preferably toluene, to produce compound (11). A small amount of radical scavenger, preferably DTBMP, is preferably added to the reaction mixture of Step (H). The reaction mixture is heated, preferably to reflux, under an inert atmosphere, preferably a nitrogen atmosphere, preferably for a period of from about 3 h to about 24 h, more preferably for about 6 h. After the reaction is complete, the reaction mixture is preferably cooled to about room temperature.

Purified compound (11) is obtained from the reaction mixture, preferably by extraction, treating with aqueous KF, filtration, washing with water and aqueous solutions, extracting, drying, and purification by chromatography.

Scheme V

The subject invention processes optionally includes one or more additional steps to produce compound (5), as depicted in Scheme V:



In Scheme V, -J and -SEM are the same as specified in Schemes II and III above.

The steps of Scheme V needed as additions to the subject invention processes depends on which of compounds (15), (16), (17), and (18) is available as a starting raw material.

Compound (15), imidazole, is reacted with SEM-Cl, preferably in the presence of sodium hydride, in solvent, preferably dimethylformamide (DMF), preferably under an inert atmosphere, preferably at a temperature of from about -20 °C to about 60 °C, more preferably at about room temperature, preferably for a period of from about 1/2 h to about 12 h, more preferably for about 2 h, to produce compound (16).

Compound (16) is reacted with phenyldisulfide, preferably in the presence of n-butyllithium, in solvent, preferably THF, preferably at a temperature of from about -80 °C to about 25 °C, more preferably starting at a temperature of about -80 °C and ending at about room temperature, preferably for a period of from about 1/2 h to about 6 h, more preferably for a period of about 1/2 h after addition of the n-butyllithium at

about -80 °C, for about 1 h after addition of the phenyldisulfide at about 0 °C, and for about 1 h at about room temperature, to produce compound (17).

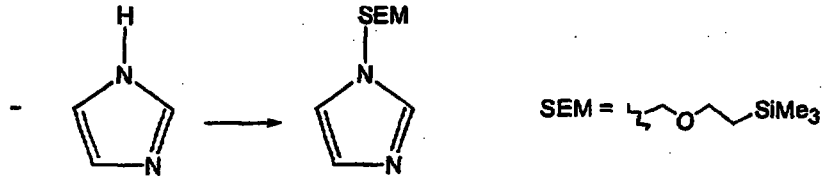
Compound (17) is reacted with an oxidizing agent, preferably MCPBA, in solvent, preferably dichloromethane, preferably under an inert atmosphere, preferably at a temperature of from about 0 °C to about 40 °C, more preferably at about room temperature, preferably for a period of from about 2 h to about 24 h, more preferably for about 15 h, to produce compound (18).

Compound (18) is reacted with trialkyltin chloride, preferably tributyltin chloride, in solvent, preferably THF, preferably in the presence of n-butyllithium, preferably under inert atmosphere, preferably at a temperature of from about -80 °C to about 40 °C, more preferably at about room temperature, preferably for a period of from about 1/2 h to about 6 h, more preferably for a period of about 1/2 h after the addition of n-butyllithium at about -80 °C, for about 1 h after addition of tributyltin chloride at about 0 °C, and for about 4 h at room temperature, to produce compound (5).

Examples

The following examples provide further information regarding the subject invention processes. They are simply exemplary and do not limit the scope of the subject invention.

Step Example 1

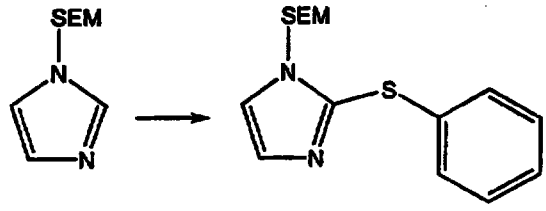


A

A suspended solution of NaH (6.5 g, 0.162 mol, washed with hexane twice) in anhydrous DMF (300 ml) is cooled in an ice/acetone bath (bath temp. -15 °C). Solid imidazole (10 g, 0.145 mol) is added in small portions and the mixture is stirred at room temperature (r.t.) for 0.5 h; the solution becomes clear. SEM-Cl (25 g, 0.150 mol) is added dropwise by a syringe pump at r.t. over 1 h; NaCl precipitates during the addition. The mixture is

stirred at r.t. for about 1 h. Progress of the reaction is monitored by TLC (CH_2Cl_2/MeOH, 9:1). H_2O (10 ml) is added with caution to quench the reaction. The solvent is evaporated in vacuo. The residue is dissolved in Et_2O (200 ml) and washed with H_2O (4 x 50ml), brine (50 ml), dried ($MgSO_4$), filtered, and evaporated in vacuo to give compound A as an orange liquid.

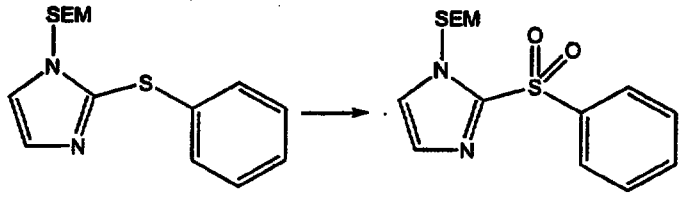
Step Example 2



A B

To a solution of SEM-protected imidazole A (1.48 g, 7.50 mmol) in dry THF (75 ml) under argon at -78 °C, n-BuLi (1.6 M in hexane) (6 ml, 9.60 mmol) is added dropwise and the mixture is stirred at -78 °C for 30 min. Phenyl disulfide (2.1 g, 9.60 mmol) in THF (2 ml) is then added dropwise. The dry ice/acetone bath is replaced with an ice bath after this addition. The mixture is stirred at 0 °C for 1 h, then at r.t. for 1 h. Progress is monitored by TLC (CH_2Cl_2/MeOH, 9:1). H_2O (5 ml) is added to quench the reaction. The solvent is evaporated in vacuo, and the residue is dissolved in Et_2O, washed with 5% $NaHCO_3$ (3 x 20ml), brine (20 ml), dried ($MgSO_4$), evaporated in vacuo, and purified by chromatography (silica gel, hexane/EtOAc 3:1) to give B as a yellow oil.

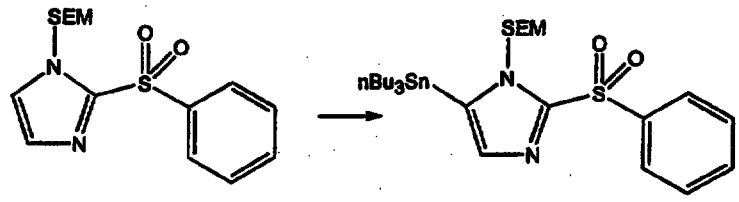
Step Example 3



B C

3-chloroperoxybenzoic acid (MCPBA, 80-85%) (17.03 g, 78.9 mol) is added to a solution of SEM-protected 2-phenylsulfide imidazole **B** (9.71 g, 31.6 mmol) in anhydrous CH_2Cl_2 (160mL), and the reaction is stirred under argon at room temperature for 15 hours. Progress monitored by TLC (hexane/EtOAc, 3:1). Sodium thiosulfate (3.9 g) is added to remove excess MCPBA. The mixture is filtered. The filtrate is washed with 5% Na_2CO_3 (3 x 150 mL), brine (150 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, hexane/EtOAc 3:1) to give **C** as a light yellow oil.

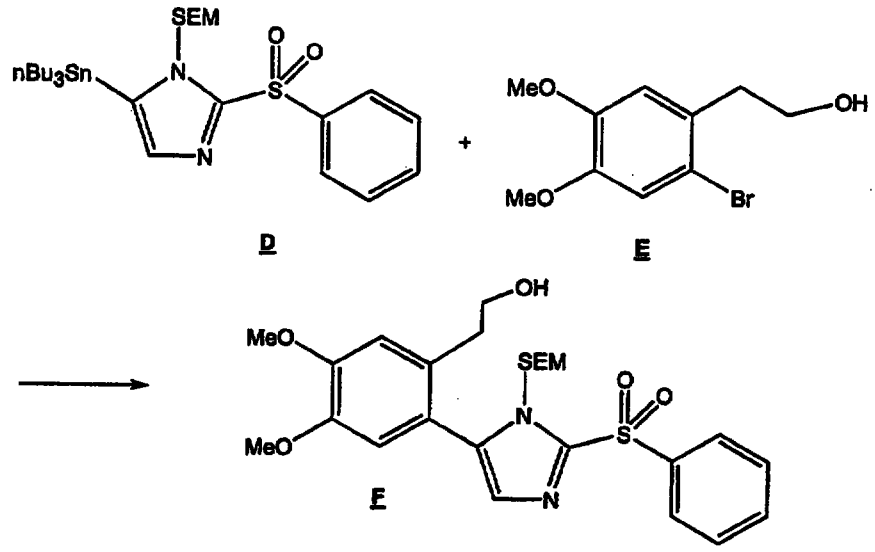
Step Example 4



C **D**

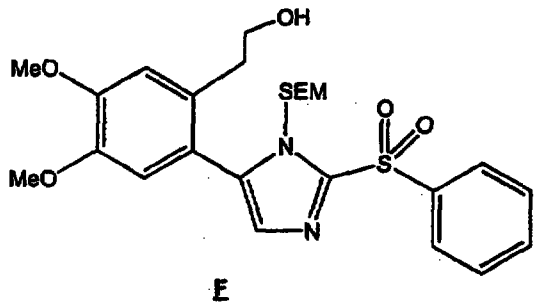
To a solution of SEM-protected 2-phenylsulfone imidazole **C** (8.61 g, 25.4 mmol) in anhydrous THF (250 mL) under argon at -78 °C, n-BuLi (1.6 M in hexane) (19.0 mL, 30.0 mmol) is added dropwise by a syringe pump; the solution is stirred at -78 °C for 30 minutes. Tributyltin chloride (6.9 mL, 25.4 mmol) is added dropwise by a syringe pump. The mixture is stirred at room temperature for one hour. Progress is monitored by TLC (hexane/EtOAc, 9:1). H_2O (30 mL) is added to quench the reaction. The solvent is evaporated in vacuo. The residue is dissolved in ether (550 mL) and washed with saturated NH_4Cl (3 x 150 mL), brine (150 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, gradient: hexane (500 mL), hexane/EtOAc, 50:1; hexane/EtOAc, 12:1) to give **D** as a clear oil.

Step Example 5

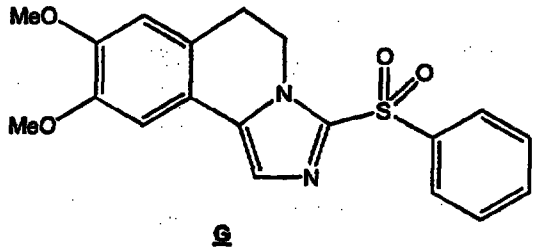


$Pd(PPh_3)_4$ (0.0177g, 0.015 mmol) is added to a solution of stannylimidazole **D** (0.51 g, 0.80 mmol), 4,5-dimethoxy-2-(2-hydroxyethyl)phenyl bromide **E** (0.33 g, 1.1 mmol), and LiCl (0.087 g, 2.1 mmol) in anhydrous dioxane (4.0 mL) at room temperature. A few crystals (~ 2 mg) of a radical scavenger, 2,6-di-tert-butyl-4-methylphenol, is added and the reaction is heated to reflux under argon for 5 hours. The reaction is cooled to room temperature and treated with a 1:1 mixture of ether and saturated aqueous KF solution (10 mL) for 15 hours. Progress is monitored by TLC (hexane/EtOAc, 3:1). The mixture is filtered through a pad of Celite with ether rinses. The filtrate is washed with water (3 x 12 mL), brine (3 x 12 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, hexane/EtOAc, 2:3) to give **F** as an orange oil.

Step Example 6



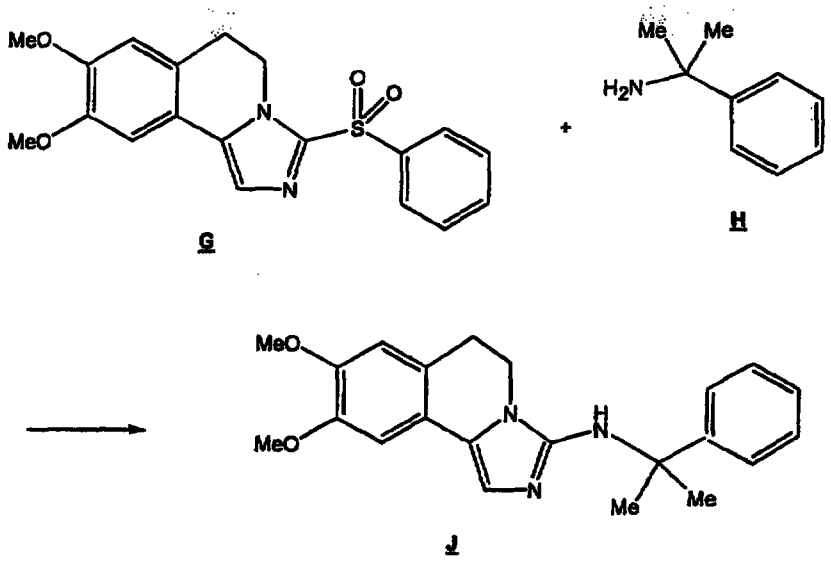
F



G

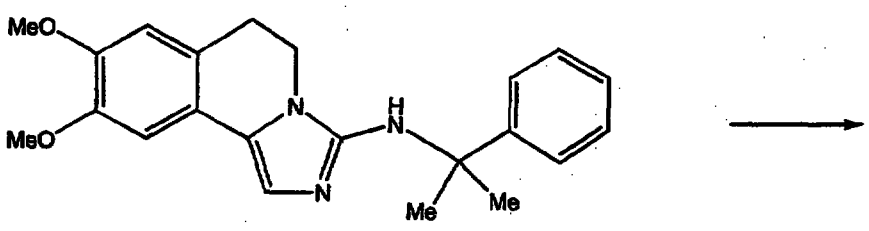
To a solution of F (2.2 g, 4.24 mmol) and Et_3N (886 mL) in dichloromethane (200 mL) under argon atmosphere at 0 °C, methylsulfonyl chloride (MsCl, 492 mL) is added over a period of 0.5 h. The reaction is then warmed to room temperature and stirred for 1 h. TLC (EtOAc:Hexane, 1:1) is used to monitor the reaction; it indicates that MsO-ester formation and the SEM-cleavage followed by ring closure occur in one pot. The mixture is diluted with CH_2Cl_2 (25 mL), and washed with cold HCl aqueous (0.5N), $NaHCO_3$ aqueous, H_2O, brine and dried over $MgSO_4$. Filtration and evaporation of solvent gives a yellow solid. Purification using preparative HPLC (EtOAc:hexane, a gradient from 1:1 to 1:0) provides product G (1.3 g).

Step Example 7

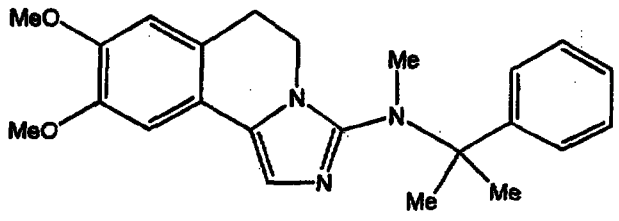


In a 25 mL single neck round bottom flask, equipped with a magnetic stir bar, argon inlet, and rubber septum, 1-methyl-1-phenyl-ethylamine (H) (164 mg, 1.2 mmol) in anhydrous THF under argon atmosphere is cooled to 0 °C. nBuLi in hexane (0.5 mL, 2.4 M) is added to the solution slowly. The reaction turns light yellow. After stirring for 45 minutes, compound G (150 mg, 0.405 mmol) in THF (1 mL) is added. The solution is warmed to room temperature, and is further heated to reflux for 12 h. TLC (CH_2Cl_2:CH_3OH, 99:1) indicates completion of the reaction. The solution is quenched with MeOH and evaporated to give a residue which is redissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%), H_2O, brine, and dried over Na_2SO_4. The crude product, after filtration and evaporation in high vacuum in order to remove any excess amine H, is purified by chromatography (CH_2Cl_2:CH_3OH, 99:1) to provide subject invention compound J.

Step Example 8



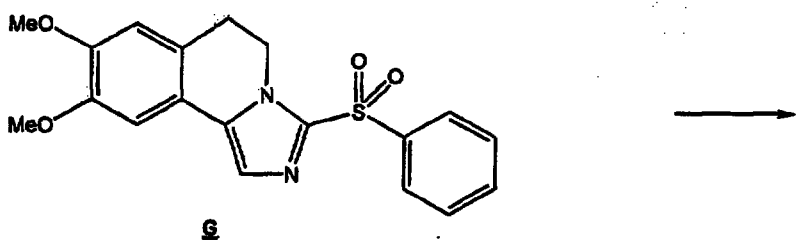
J



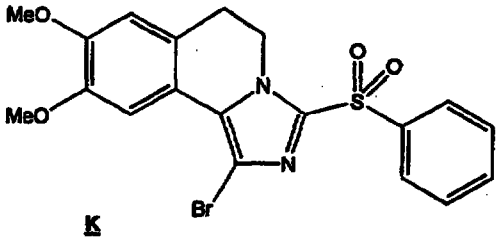
P

In a 25 mL single neck round bottom flask, compound J (181 mg, 0.5 mmol) in anhydrous THF (10 mL) under argon atmosphere is cooled to 0 °C, then NaH (18 mg) pre-washed with hexane is added as a suspension in hexane to the solution. After stirring for 15 minutes, methyl iodide (71 mg, 0.5 mmol) in THF (0.5 mL) is added. The solution is warmed to room temperature, and further heated to reflux for 2 h to complete the reaction. The solution is quenched with MeOH and evaporated to give a residue which is redissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%), H_2O, brine and dried over Na_2SO_4. The crude product is purified by chromatography (CH_2Cl_2:CH_3OH from 99:1 to 95:5) to provide subject invention compound P.

Step Example 9



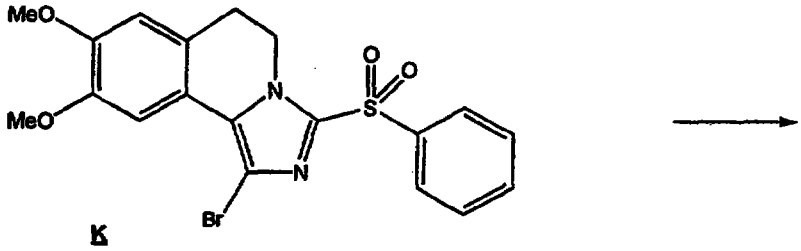
G



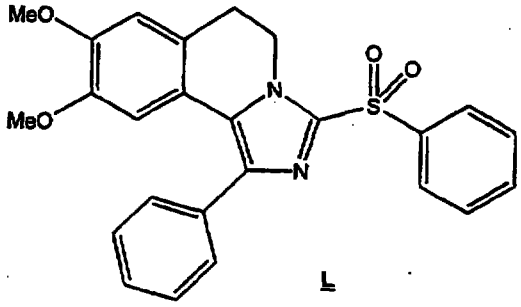
K

N-bromosuccinimide (NBS) solid (98 mg, 0.26 mmol) is added to a solution of compound G (0.5 mmol) in 15 mL of CCl_4. Radical initiator benzoyl peroxide (2 mol%) is subsequently added. The flask is placed into a 90 °C oil bath. After 10 min stirring, the reaction is complete. Filtration of the mixture through a celite pad, and evaporation of the filtrate gives a residue. Purification by chromatography (EtOAc:hexane, 1:3 to 1:1) affords compound K.

Step Example 10



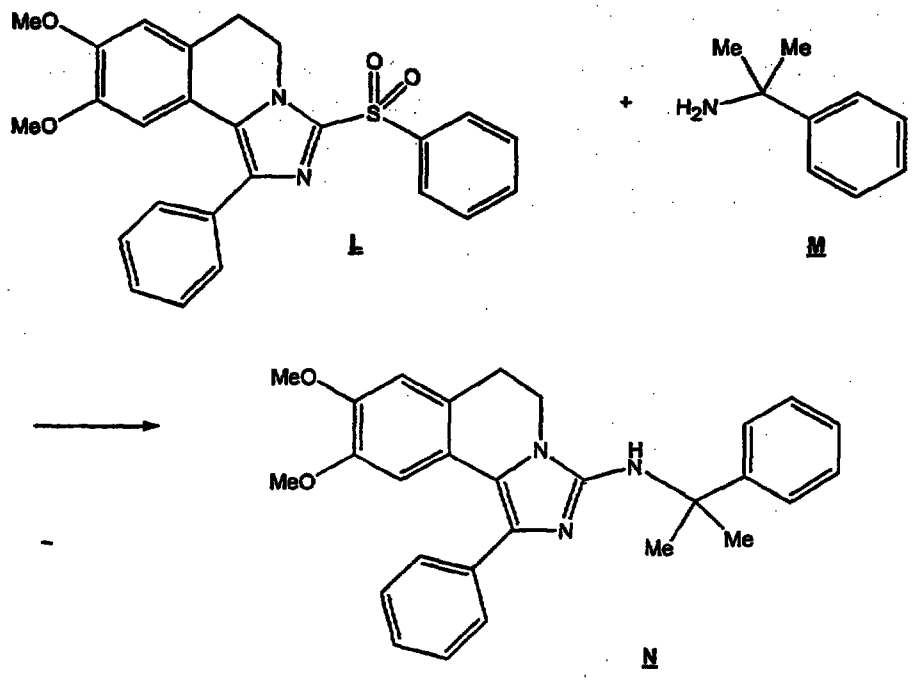
K



L

To a solution of K (0.22mmol) and $Pd(PPh_3)_4$ (13mg, 0.056mmol) in 7 mL of anhydrous toluene are added phenyltributyltin (0.26mmol) and a few crystals (~ 2 mg) of 2,6-di-tert-butyl-4-methylphenol. The reaction mixture is allowed to reflux at 110 °C under nitrogen for 6 hours to complete the reaction. The reaction mixture is allowed to cool, and is then diluted with 1-2 mL of ethyl acetate (EtOAc). The resultant mixture is washed with water, then brine, extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The filtrate is treated with 3 mL of 30% aqueous KF at room temperature for 2h. The solid is filtered off. The filtrate is diluted with CH_2Cl_2 and washed with water, 30% aqueous NH_4OH (3X), brine, extracted with EtOAc, dried (Na_2SO_4), and concentrated *in vacuo* to yield crude product. Chromatography purification (silica gel, EtOAc:hexane, 1:1 to 1:0) yields compound L.

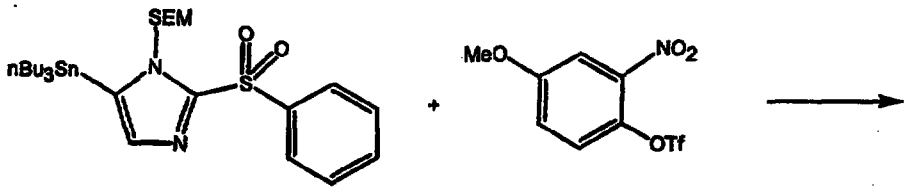
Step Example 11



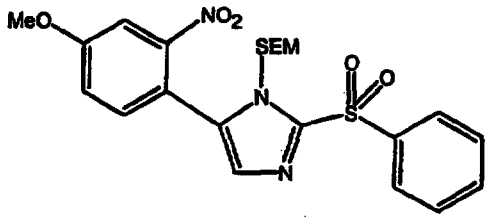
In a 25 mL single neck round bottom flask, equipped with a magnetic stir bar, argon inlet, and rubber septum, (1-methyl-1-phenyl-ethylamine) (M) (1.2 mmol) in anhydrous THF under argon atmosphere is cooled to 0 °C. nBuLi in hexane (0.5 mL, 2.4 M) is added slowly to the solution. The reaction turns light yellow. After stirring for 45 minutes, compound L (180 mg, 0.405 mmol) in THF (1 mL) is added. The solution is

warmed to room temperature, and is further heated to reflux for 12 h to complete the reaction. The solution is quenched with MeOH and evaporated to give a residue which is redissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%), H_2O, brine and dried over Na_2SO_4. The crude product, after filtration and evaporation in high vacuum in order to remove excess amine M, is purified by chromatography to provide subject invention compound N.

Step Example 12



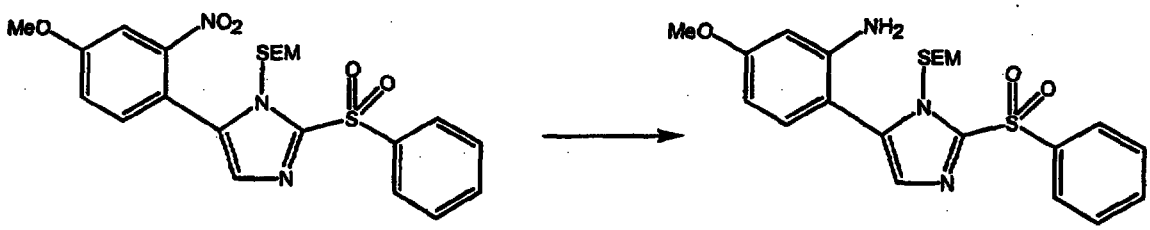
D Q



P

$Pd(PPh_3)_4$ (0.0177g, 0.015 mmol) is added to a solution of stannylimidazole D (0.51 g, 0.80 mmol), 2-nitro-4-methoxyphenol triflate Q (0.33 g, 1.1 mmol), and LiCl (0.087 g, 2.1 mmol) in anhydrous dioxane (4.0 mL) at room temperature. A spatula tipful of radical scavenger, 2,6-di-tert-butyl-4-methylphenol, is added and the reaction is heated to reflux under argon for 5 hours. The reaction then is cooled to room temperature and treated with a 1:1 mixture of ether and saturated aqueous KF solution (10 mL) for 15 hours (monitored by TLC, hexane/EtOAc 3:1). The mixture is filtered through a pad of Celite with ether rinses, and the filtrate is washed with water (3 x 12 mL), brine (3 x 12 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, hexane/EtOAc 3:1) to give compound P as an orange oil.

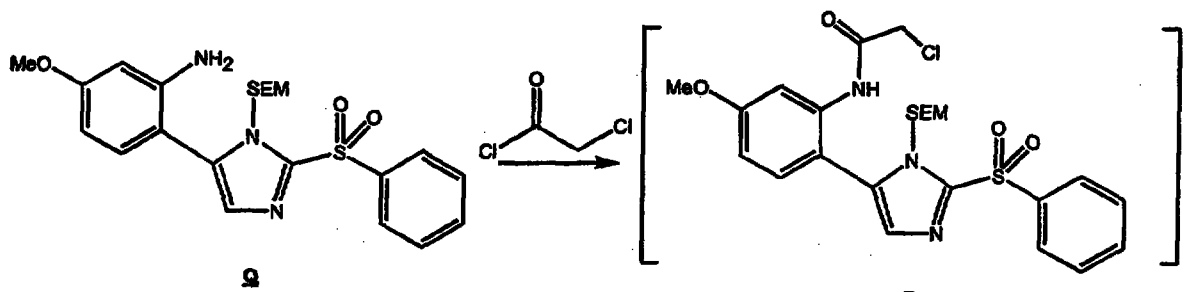
Step Example 13

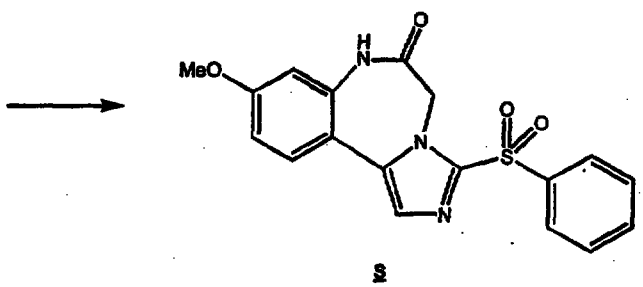


P Q

Pd (0.20 g, 0.19 mmol, 10% on activated carbon) is added to a solution of compound P (0.91 g, 1.85 mmol) in ethyl acetate (37 mL). After the reaction mixture is hydrogenated under H_2 at 40 psi for 2 hours, methanol (10 mL) is added to the mixture and hydrogenation continues for 3 additional hours. The mixture is filtered through silica, and the filtrate is evaporated in vacuo to give compound Q as an orange oil.

Step Example 14

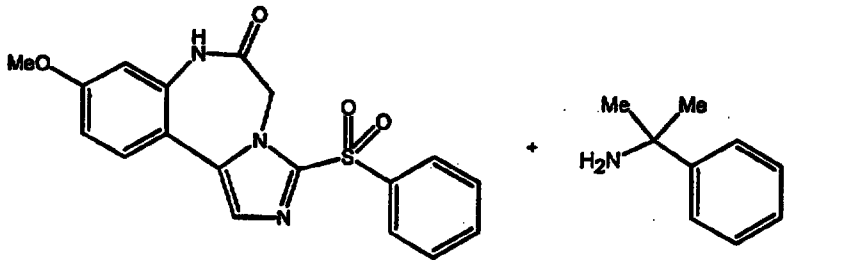




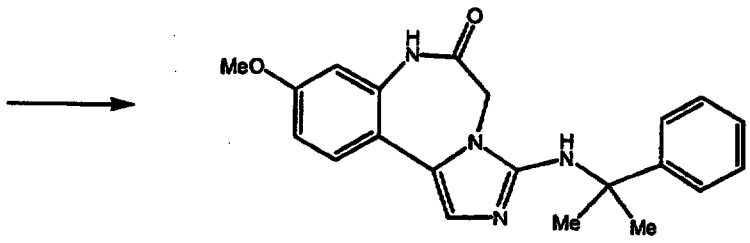
S

A solution of 4-dimethylaminopyridine (0.18 g, 1.5 mmol) in anhydrous CH_2Cl_2 (3 mL) is added to a solution of the compound Q (0.69 g, 1.5 mmol) in anhydrous CH_2Cl_2 (15.7 mL) and the solution is stirred under argon at room temperature. After 10 minutes, chloroacetyl chloride ($ClC(O)CH_2Cl$) (0.12 mL, 1.5 mmol) is added dropwise. The solution is stirred at room temperature for 20 hours (monitored by TLC, hexane/EtOAc 3:1). The solution is diluted with CH_2Cl_2, washed with H_2O (2 x 20 mL) and brine (25 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, gradient: hexane/EtOAc 10:1, 5:1, 1:1) to provide compound S as a white solid (53.3 mg).

Step Example 15



S H



I

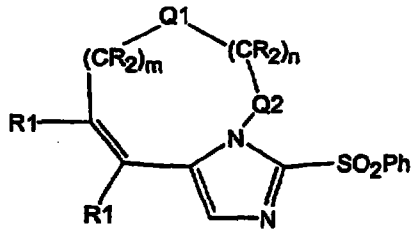
1-Methyl-1-phenyl-ethylamine (68 mg, 0.5 mmol) in anhydrous THF under argon atmosphere is cooled to 0 °C. nBuLi in hexane (0.2 mL, 2.4 M) is added to this solution slowly. The reaction mixture turns light yellow. After stirring for 45 minutes, compound S (39 mg, 0.1 mmol) in THF (1 mL) is added. The solution is warmed to room temperature, and is further heated to reflux for 12 h. The solution is quenched with

MeOH and evaporated to give a residue which is redissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%), H_2O, brine, and dried over Na_2SO_4. The crude product, after filtration and evaporation in high vacuum in order to remove any excess amine H, is purified by chromatography (CH_2Cl_2:CH_3OH, 99:1) to provide compound T.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the arts that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

What is claimed is:

1. A process for making a compound having the structure:



(1)

wherein:

(a) m is an integer from 0 to about 6;

(b) n is an integer from 0 to about 6;

(c) -Q1- is selected from the group consisting of nil, -CR=CR-, -O-, -S-, -NR-, -C(O)-, -NR-C(O)-, and -OC(O)-;

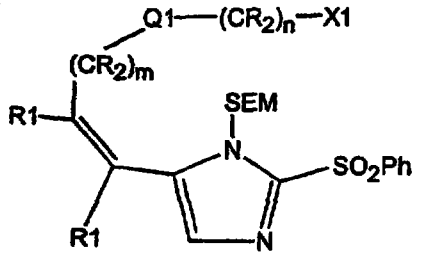
(d) -Q2- is nil or -C(O)-;

(e) each -R is independently selected from the group consisting of hydrogen, alkyl, aryl, and heterocycle;

(f) each -R1 is independently selected from the group consisting of hydrogen, alkyl, aryl, heterocycle, or the two R1's are attached to form cycloalkenyl, aryl or heterocyclic ring;

the process comprising the following Steps:

(A) taking a compound having the structure:



(2)

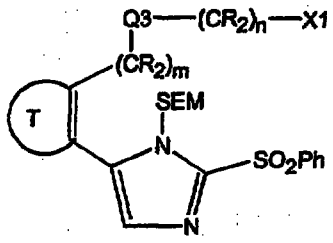
wherein m, n, -Q1- and -R1 are the same as for compound (1); and -X1 is selected from the group consisting of -Cl, -Br, -I, -OH and -COOH; and

(i) if -X1 is -OH, treating compound (2) with MsOCl or TsOCl and Et_3N in solvent, whereby -X1 is converted to -X2, -X2 being -OMs or -OTs, respectively; or treating compound (2) with a halogenating reactant in solvent, whereby -X1 is converted to -X2, -X2 being -Cl or -Br or -I;

(ii) if -X1 is -COOH, treating compound (2) with phosgene or oxalyl chloride in solvent, whereby -X1 is converted to -X2, -X2 being -C(O)Cl;

whereby some or all of the intermediate thus formed in this Step (A) may further spontaneously react to form compound (1); and

(B) if -X1 is -Cl or -Br or -I, or if conversion to compound (1) in Step (A) is insufficient, treating compound (2) or the reaction product of Step (A), respectively, with nBu_4NF in solvent, whereby conversion to compound (1) occurs; preferably wherein m and n are independently integers from 0 to about 2, and no more than two -R's are other than hydrogen; and preferably wherein the two -R1's are attached to form a ring; and wherein preferably compound (2) has the structure:



(2a)



wherein m, n, -R, and -X1 are the same as for compound (2); -Q3- is selected from the group consisting of -O-, -S-, -NR-, -NR-C(O)-, -OC(O)-, and -SC(O)-; and ring T is a cycloalkenyl or aryl or heterocyclic ring.

2. The process of Claim 1 wherein -X1 is -COOH, -Cl or -Br or -I.

3. The process of Claim 1 wherein -X1 is -OH; and in Step (A), compound (2) is treated with $SOCl_2$ and Et_3N or with NBS and Ph_3P or with PBr_3 and pyridine or with NaI or KI and a strong acid or with MsOCl or TsOCl and Et_3N.

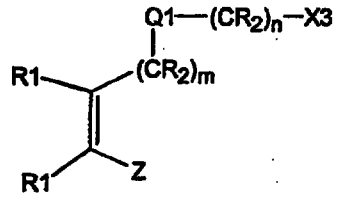
4. The process of Claim 1 wherein -Q1- is selected from the group consisting of nil, -O-, -S-, -NR-, and -C(O)-; -Q2- is nil; and m + n is from 1 to 3.

5. The process of Claim 1 wherein the two -R1's are attached to form an unsubstituted or substituted phenyl ring.

6. The process of Claim 5 wherein -Q2- is nil; and -Q1- is nil and m + n is from 1 to 4, or -Q1- is -CR=CR- and m + n is from 0 to 2.

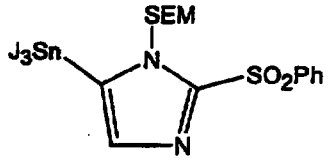
7. The process of Claim 1or 5 wherein compound (2) is prepared by a process comprising the following Step:

(C) reacting a compound having the structure:



(4)

with a compound having the structure:

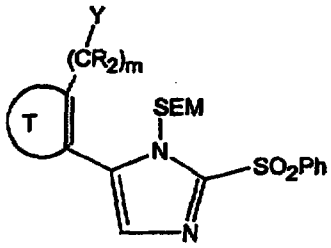


(5)

wherein m, n, -R, -Q1-, and -R1 are the same as for compound (2); -X3 is -OH or -COOH; -Z is -Br or -I or -OTf; and -J is alkanyl having from 1 to about 4 carbon atoms.

8. The process of Claim 1 wherein compound (2a) is prepared by a process comprising the following Step:

(E) reacting a compound having the structure:



(7)

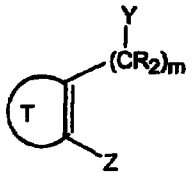
with a compound having the structure:

$$W\text{-}(CR_2)_n\text{-}X1 \quad (8)$$

wherein m, n, -R, -X1, and T are the same as for compound (2a); -Y is -NHR or -OH or -SH; -W is -I or -Br or -C(O)V; and -V is -OH or -Cl or -Br.

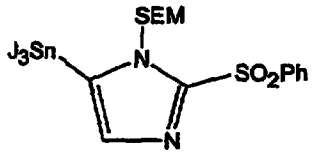
9. The process of Claim 8 wherein compound (7) is prepared by a process comprising the following Step:

(D) reacting a compound having the structure:



(6)

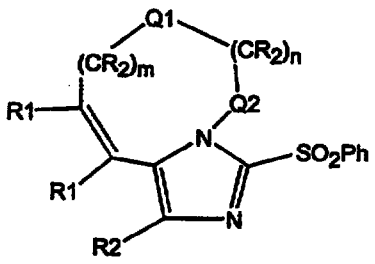
with a compound having the structure:



(5)

wherein m, -R, -Y, and T are the same as for compound (7); Z is -Br or -I or -OTf; and -J is alkanyl having from 1 to about 4 carbon atoms; preferably wherein -Q3- is -O- or -S- or -NR-; -W is -Br or -I; Q2- is nil; and m + n is from 1 to 3.

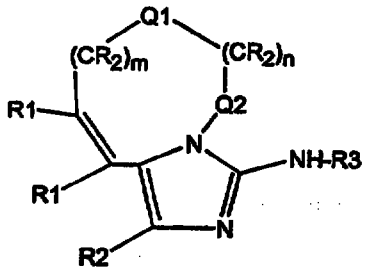
10. The process of Claim 1, 7, or 9 wherein compound (1) already is or is optionally converted to a compound having the structure:



(11)

wherein m, n, -R, -Q1-, -Q2-, and -R1 are the same as for compound (1); and -R2 is selected from the group consisting of hydrogen, halo, alkyl, aryl, heterocycle, carboxy and its alkyl esters and amides;

and wherein a compound having the structure:



(9)

is prepared by a process having the following Step:

(F) reacting compound (11) with a compound having the structure:

$R3\text{-}NH_2$ (12)

wherein -R3 is selected from the group consisting of hydrogen, alkyl, aryl, and heterocycle.