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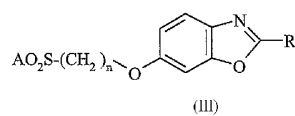
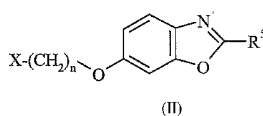
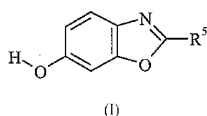
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(54) Title: IMPROVED PROCESS FOR PREPARING (DIHALOPROPENYL)PHENYLALKYL SUBSTITUTED BENZOXAZOLES



(57) Abstract: An improved process is described for preparing (dihalopropenyl)phenylalkyl substituted benzoxazoles. This improved process is focused on steps to produce key intermediates, namely disubstituted benzoxazoles of formulae (I), (II) and (III); wherein R⁵ is alkyl or haloalkyl; n is 1, 2, 3, 4, 5 or 6; X is hydroxyl or halogen; and A is methyl or 4-methylbenzene.



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Improved Process for Preparing (Dihalopropenyl)Phenylalkyl Substituted Benzoxazoles

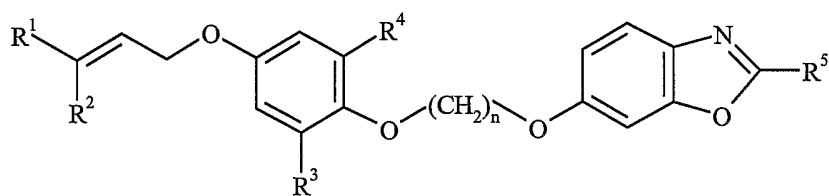
This application claims the benefit of U.S. Provisional Application No. 60/647,731, filed January 27, 2005.

Field of Invention

This invention is in the field of chemical processes; more specifically, an improved process for preparing (dihalopropenyl)phenylalkyl substituted benzoxazoles.

Background:

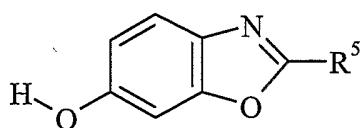
(Dihalopropenyl)phenylalkyl substituted benzoxazoles, such as:



wherein R^1 and R^2 are halogen; R^3 and R^4 are independently selected from halogen, alkyl and haloalkyl; R^5 is alkyl or haloalkyl; and n is 1, 2, 3, 4, 5 or 6; are useful insecticides and have been described in PCT published application WO 2004/099105. There is a need for processes to produce these compounds at higher yields, at optimal cycle times and with lower catalyst loadings.

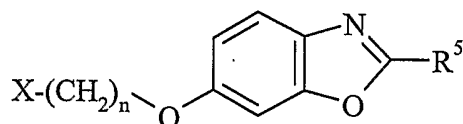
Summary of the Invention

The present invention relates to compounds known as disubstituted benzoxazoles, such as those represented by formula I:

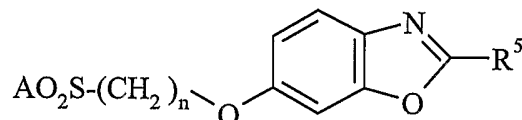


I,

by formula II:

**II**,

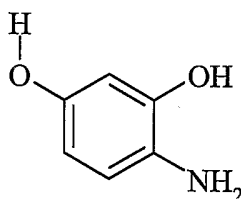
and by formula **III**:

**III**

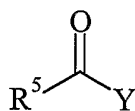
wherein R^5 is alkyl or haloalkyl; n is 1, 2, 3, 4, 5 or 6; X is halogen or hydroxyl and A is methyl or 4-methylbenzene; which are key intermediates in the process for preparing (dihalopropenyl)phenylalkyl substituted benzoxazoles.

The present invention also improves the process for preparing disubstituted benzoxazoles of formula **I**, formula **II** and formula **III**. As a result of the present invention, overall yield, cycle times and catalyst loading are improved for the production of (dihalopropenyl)phenylalkyl substituted benzoxazoles. Specifically, it has now been found that a disubstituted benzoxazole of formula **I**, formula **II** or formula **III** can be prepared in excellent yield and purity by a process comprising:

- a) reacting a compound of formula **(A)**:

Formula **(A)**;

with a compound of formula **(B)**:

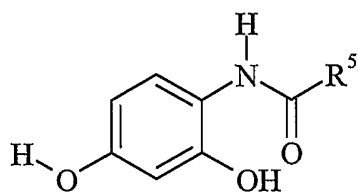
Formula **(B)**

wherein

Y is hydroxyl, halogen or $-\text{OC}(=\text{O})\text{CF}_3$; and

R^5 is alkyl or haloalkyl;

to form intermediate **(C)**:



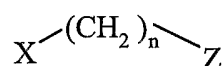
Intermediate **(C)**;

wherein R^5 is as defined above;

and

- b) forming a second ring in intermediate **(C)** at elevated temperature to provide a compound of formula **I**;

optionally, further reacting a compound of formula **I** with a compound of formula **(D)**:



Formula **(D)**

wherein

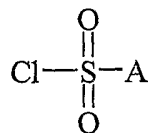
Z is halogen;

X is halogen or hydroxyl; and

n is 1, 2, 3, 4, 5 or 6;

to form a compound of formula **II**;

optionally, further reacting a compound of formula **II**, wherein X is hydroxyl, with a compound of formula **(E)** :



Formula **(E)**

wherein A methyl or 4-methylbenzene;

to form a compound of formula **III**.

Definitions

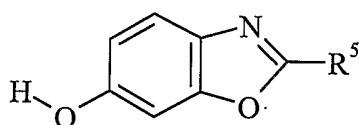
The modifier "about" is used herein to indicate that certain preferred operating ranges, such as ranges for molar ratios for reactants, material amounts, and temperature, are not fixedly determined. The meaning will often be apparent to one of ordinary skill. For example, a recitation of a temperature range of about 120° C to about 135° C in reference to, for example, an organic chemical reaction would be interpreted to include other like temperatures that can be expected to favor a useful reaction rate for the reaction, such as 105° C or 150° C. Where guidance from the experience of those of ordinary skill is lacking, guidance from the context is lacking, and where a more specific rule is not recited below, the "about" range shall be not more than 10% of the absolute value of an end point or 10% of the range recited, whichever is less.

As used in this specification and unless otherwise indicated the substituent terms "alkyl", "alkoxy", and "haloalkyl", used alone or as part of a larger moiety, includes straight or branched chains of at least one or two carbon atoms, as appropriate to the substituent, and preferably up to 12 carbon atoms, more preferably up to ten carbon atoms, most preferably up to seven carbon atoms. "Halogen", "halide" or "halo" refers to fluorine, bromine, iodine, or chlorine. The term "ambient temperature" refers to a temperature in the range of about 20° C to about 30° C. Certain solvents, catalysts, and the like are known by their acronyms. These include the acronyms "DMAC" meaning N,N-dimethylacetamide, "DMF" meaning

N,N-dimethylformamide, "THF" meaning tetrahydrofuran. The term "glymes" refers to a class of solvents comprised of monoglyme, diglyme, triglyme, tetraglyme, and polyglyme. The term "GC" refers to gas chromatography or gas chromatographic methods of analyses.

Detailed Description of the Invention

The present invention relates to a process for preparing a disubstituted benzoxazole of formula **I**:

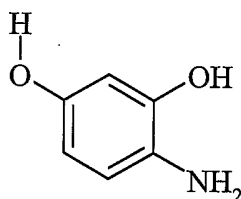


I

wherein R^5 is alkyl or haloalkyl;

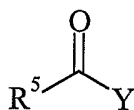
the process comprising:

a) reacting a compound of formula **(A)**:



Formula **(A)**;

with a compound of formula **(B)**:



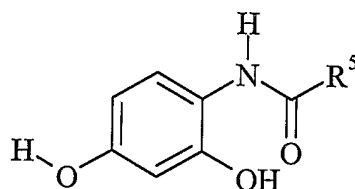
Formula **(B)**

wherein

Y is hydroxyl, halogen or $-OC(=O)CF_3$; and

R^5 is as defined above;

to form intermediate (C):



Intermediate (C);

wherein R^5 is as defined above;

and

- b) forming a second ring in intermediate (C) at elevated temperature to provide a compound of formula I.

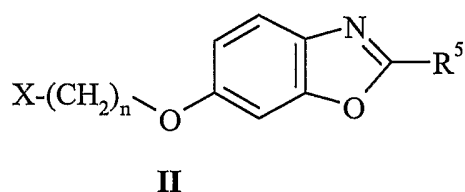
Preferably, Y is hydroxyl, chlorine or $-OC(=O)CF_3$; and R^5 is haloalkyl. More preferably, Y is hydroxyl or $-OC(=O)CF_3$; and R^5 is CF_3 .

The reaction of step a) can be conducted in the presence of a solvent; in the presence of a catalyst. The solvent can be tetrahydrofuran, toluene, xylene, 1,2-dichloroethane, triethylamine, *p*-dioxane, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, glymes, dimethylsulfoxide or mixtures thereof. Preferably, the solvent can be 1,2-dichloroethane. The catalyst can be polyethylene glycol, dimethylaminopyridine, triethylamine, pyridine, phase transfer catalysts such as *t*-butyl ammonium chloride or *t*-butyl ammonium bromide or mixtures thereof. The catalyst can be present in a concentration of from about 1% by weight to about 20% by weight.

The elevated temperature of step b) can be in the range of 70°C to 150°C. Step b) can be conducted in the presence of a solvent; in the presence of a catalyst. The catalyst can be *p*-toluenesulfonic acid, phosphorous pentoxide or mixtures

thereof. The catalyst can be present in a concentration of from about 1% by weight to about 5% by weight. The solvent can be tetrahydrofuran, toluene, xylene, 1,2-dichloroethane, triethylamine, *p*-dioxane, N,N-dimethylacetamide, N,N-dimethylformamide, glymes, dimethylsulfoxide or mixtures thereof. Preferably, the solvent can be 1,2-dichloroethane.

Another embodiment of the present invention relates to a process for preparing a disubstituted benzoxazole of formula **II**:



wherein

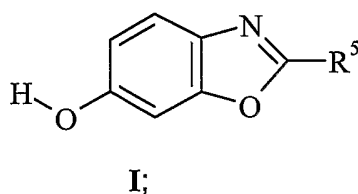
R^5 is alkyl or haloalkyl;

n is 1, 2, 3, 4, 5 or 6; and

X is halogen or hydroxyl;

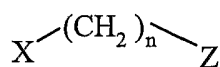
said process comprising:

reacting a compound of formula **I**:



wherein R^5 is as defined above;

with a compound of formula **(D)**:



Formula **(D)**

wherein

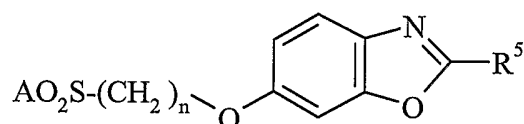
Z is halogen; and

n and X are as defined above;

to form a compound of formula **II**.

The reaction to form a compound of formula **II** can be conducted in the presence of a solvent; at elevated temperature; in the presence of a catalyst; in the presence of a carbonate. The solvent can be tetrahydrofuran, toluene, xylene, 1,2-dichloroethane, triethylamine, *p*-dioxane, N,N-dimethylacetamide, N,N-dimethylformamide, glymes, dimethylsulfoxide or mixtures thereof, preferably the solvent can be 1,2-dichloroethane; the elevated temperature can be in the range of 50°C to 100°C; the catalyst can be polyethylene glycol, triethylamine, pyridine, phase transfer catalysts such as t-butyl ammonium chloride or t-butyl ammonium bromide or mixtures thereof; the carbonate can be sodium carbonate or potassium carbonate. The catalyst can be present in a concentration of from about 1% by weight to about 6% by weight.

Another embodiment of the present invention relates to a process for preparing a disubstituted benzoxazole of formula **III**:



III

wherein

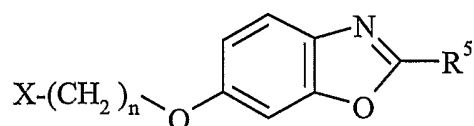
R⁵ is alkyl or haloalkyl;

n is 1, 2, 3, 4, 5 or 6; and

A is methyl or 4-methylbenzene;

said process comprising:

reacting a compound of formula **II**:

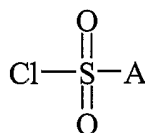
**II**

wherein

R^5 and n are as defined above; and

X is hydroxyl;

with a compound of formula **(E)** :

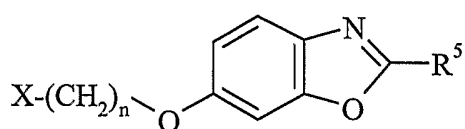
Formula **(E)**

wherein A is as defined above;

to form a compound of formula **III**.

The reaction to form a compound of formula **III** can be conducted in the presence of a solvent; in the presence of a catalyst. The solvent can be tetrahydrofuran, toluene, xylene, 1,2-dichloroethane, triethylamine, *p*-dioxane, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, glymes, dimethylsulfoxide or mixtures thereof, preferably the solvent can be 1,2-dichloroethane; the catalyst can be dimethylaminopyridine, triethylamine, methylamine, phenylamine, pyridine, phase transfer catalysts such as *t*-butyl ammonium chloride or *t*-butyl ammonium bromide or mixtures thereof. The catalyst can be present in a concentration of from about 1% by weight to about 5% by weight.

Another embodiment of the present invention is a compound of formula **II**:



II

wherein

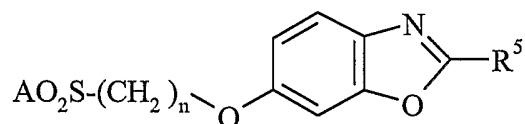
R⁵ is alkyl or haloalkyl;

n is 1, 2, 3, 4, 5 or 6; and

X is halogen or hydroxyl.

Yet another embodiment of the present invention is a compound of formula

III:



III

wherein

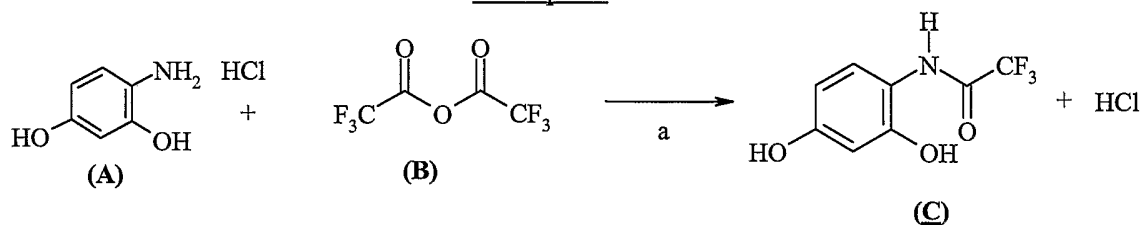
R⁵ is alkyl or haloalkyl;

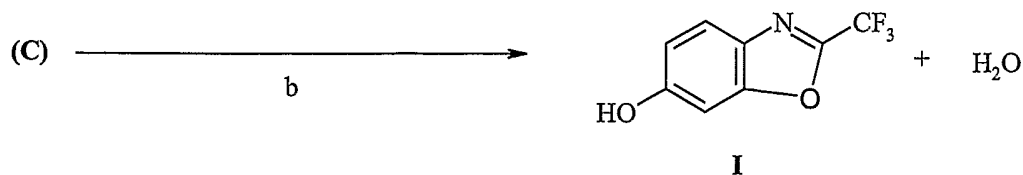
n is 1, 2, 3, 4, 5 or 6; and

A is methyl or 4-methylbenzene.

The following examples illustrate processes for preparing disubstituted benzoxazoles of formulae **I**, **II** and **III**.

Example 1



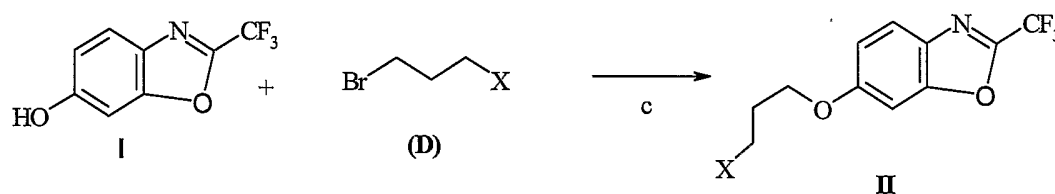


a) Solvent/Catalyst/Ambient Temperature/2-4 hours b) Solvent/Catalyst /90°C-150°C/22-26 hours

In the first step (a) of Example 1, amino-resorcinol hydrochloride (A) was cross-coupled with trifluoroacetic anhydride (B) in the presence of a solvent and a catalyst at ambient temperature to form N-(2,4-Dihydroxy-phenyl)-2,2,2-trifluoroacetamide (C), a dark colored solid.

In the second step (b) of Example 1, N-(2,4-Dihydroxy-phenyl)-2,2,2-trifluoroacetamide (C) underwent a ring closure reaction in the presence of a solvent and a catalyst at a temperature in the range of from about 90 °C to about 150 °C to form 2-(trifluoromethyl)benzoxazol-6-ol (I), a dark solid. NMR data was consistent with the expected product (I).

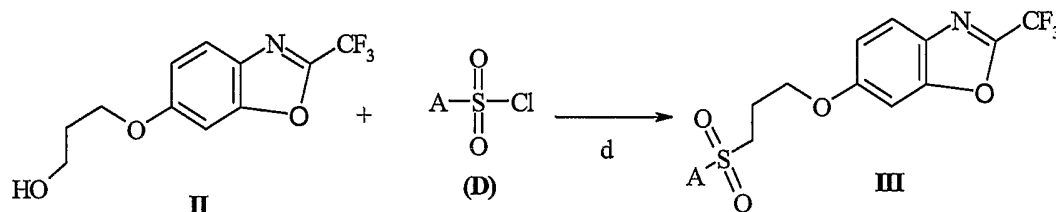
Example 2



where X is halogen or hydroxy

c) Carbonate/Solvent/Catalyst/50-100 °C/7-9 hours

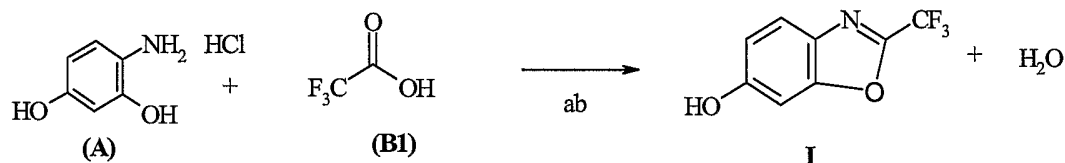
In step (c) of Example 2, (trifluoromethyl)benzoxazol-6-ol (I) was cross-coupled with a 1-bromo-3-halo-3-propane (D), for example 1-bromo-3-chloropropane, in the presence of a carbonate, for example potassium carbonate, a solvent and a catalyst at a temperature from about 50 °C to about 100°C to afford a 3-halo-1-[2-(trifluoromethyl)benzoxazol-6-yloxy]propane (II), for example 3-chloro-1-[2-(trifluoromethyl)benzoxazol-6-yloxy]propane, an amber oil. NMR data was consistent with the expected product (II).

Example 3

where A is methyl or 4-methylbenzene

d) Solvent/Catalyst/Ambient Temperature/4-6 hours

In step (d) of Example 3, 3-hydroxy-1-[2-(trifluoromethyl)benzoxazol-6-yloxy]propane can be reacted with a substituted chlorosulfone, for example chloromethylsulfone, in the presence of a solvent and a catalyst at ambient temperature to form a 1-(substitutedsulfonyl)-3-[2-(trifluoromethyl)benzoxazol-6-yloxy]propane (**III**), for example 1-(methylsulfonyl)-3-[2-(trifluoromethyl)benzoxazol-6-yloxy]propane.

Example 4

ab) Solvent/Molecular Sieve /70°C-140°C/42-46 hours

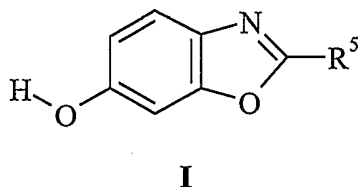
In step (ab) of Example 4, amino-resorcinol hydrochloride (**A**) was cross-coupled with 2,2,2-trifluoroacetic acid (**B1**) and then condensed in the presence of a solvent and molecular sieves at a temperature in the range of from about 70 °C to about 140 °C to form 2-(trifluoromethyl)benzoxazol-6-ol (**I**), a dark solid. NMR data was consistent with the expected product (**I**).

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly this

invention includes all modifications encompassed within the spirit and scope as defined by the following claims.

What is claimed is:

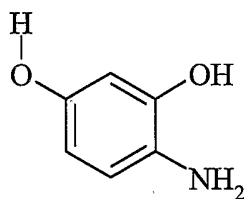
1. A process for preparing a disubstituted benzoxazole of formula I:



wherein R^5 is alkyl or haloalkyl;

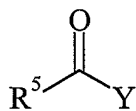
said process comprising:

- a) reacting a compound of formula (A):



Formula (A);

with a compound of formula (B):



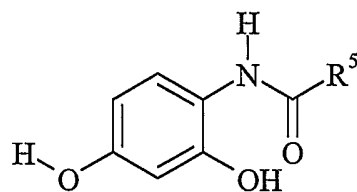
Formula (B)

wherein

Y is hydroxyl, halogen or $-OC(=O)CF_3$; and

R^5 is as defined above;

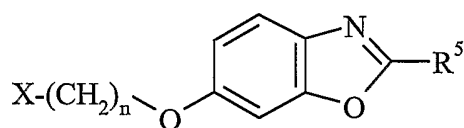
to form intermediate (C):

Intermediate **(C)**;

wherein R^5 is as defined above;

and

- b) forming a second ring in intermediate **(C)** at elevated temperature to provide a compound of formula **I**.
2. The process of claim 1 wherein Y is hydroxyl, chlorine or $-OC(=O)CF_3$ and R^5 is haloalkyl.
 3. The process of claim 1 wherein the reacting of step a) is conducted in the presence of a solvent.
 4. The process of claim 1 wherein the reacting of step a) is conducted in the presence of a catalyst.
 5. The process of claim 1 wherein step b) is conducted in the presence of a catalyst.
 6. The process of claim 1 wherein step b) is conducted in the presence of a solvent.
 7. A process for preparing a disubstituted benzoxazole of formula **II**:

**II**

wherein

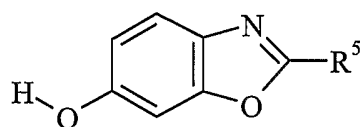
R^5 is alkyl or haloalkyl;

n is 1, 2, 3, 4, 5 or 6; and

X is halogen or hydroxyl;

said process comprising:

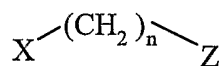
reacting a compound of formula **I**:



I;

wherein R^5 is as defined above;

with a compound of formula **(D)**:



Formula **(D)**

wherein

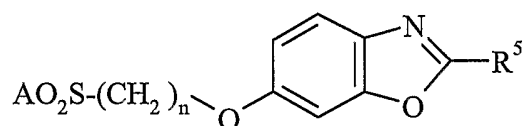
Z is halogen; and

n and X are as defined above;

to form a compound of formula **II**.

8. The process of claim 7 wherein n is 3.
9. The process of claim 7 wherein the reacting is conducted in the presence of a solvent.

10. The process of claim 7 wherein the reacting is conducted at elevated temperature.
11. The process of claim 7 wherein the reacting is conducted in the presence of a carbonate.
12. The process of claim 7 wherein the reacting is conducted in the presence of a catalyst.
13. A process for preparing a disubstituted benzoxazole of formula **III**:

**III**

wherein

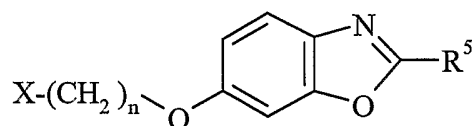
R^5 is alkyl or haloalkyl;

n is 1, 2, 3, 4, 5 or 6; and

A is methyl or 4-methylbenzene;

said process comprising:

reacting a compound of formula **II**:

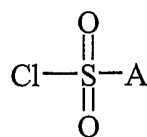
**II**

wherein

R^5 and n are as defined above; and

X is hydroxyl;

with a compound of formula **(E)** :

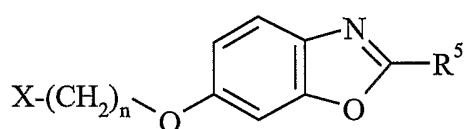


Formula **(E)**

wherein A is as defined above;

to form a compound of formula **III**.

14. The process of claim 13 wherein n is 3.
15. The process of claim 13 wherein the reacting is conducted in the presence of a solvent.
16. The process of claim 13 wherein the reacting is conducted in the presence of a catalyst.
17. A compound of formula **II**:

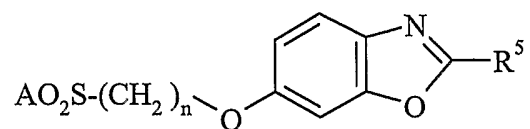


II

wherein

R^5 is alkyl or haloalkyl;
 n is 1, 2, 3, 4, 5 or 6; and
 X is halogen or hydroxyl.

18. A compound of formula **III**:

**III**

wherein

R^5 is alkyl or haloalkyl;

n is 1, 2, 3, 4, 5 or 6; and

A is methyl or 4-methylbenzene.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/02235

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07D 277/82(2006.01)

USPC: 548/216

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/216

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN CAS ON LINE; EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,376,428 B1 (SAKAMATO et al) 23 April 2002 (23.04.2002) entire document	1-18

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
13 May 2006 (13.05.2006)

Date of mailing of the international search report

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