

32355-00

METHOD FOR THE PREPARATION OF 2-PERFLUOROALKYL-3-
OXAZOLIN-5-ONE

Arylpyrrole carbonitrile compounds and
5 derivatives thereof are highly effective insecticidal,
acaricidal and nematocidal agents. In particular 2-
aryl-5-trifluoromethylpyrrole-3-carbonitrile compounds
and their derivatives have been found to have a broad
spectrum of activity at very low rates of application
10 with effectiveness against resistant species. U.S.
Patent 5,030,735 describes methods to prepare said
pyrrole compounds on a manufacturing scale and includes
the 1,3-dipolar cycloaddition of the appropriate 3-
oxazolin-5-one with 2-chloroacrylonitrile. Heretofore
15 the 3-oxazolin-5-one key intermediate has been prepared
through the appropriate phenylglycine compound in a 4
step synthetic route starting from the preceding
aminonitrile.

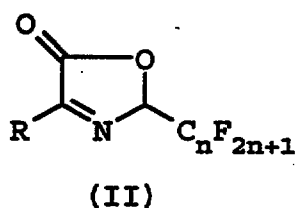
It is an object of this invention to provide
20 a facile and efficient synthesis of 2-perfluoroalkyl-3-
oxazolin-5-one in 2 steps from the aminonitrile
precursor.

In addition is an object of this invention to
provide perfluoroalkanoyl aminonitrile compounds useful
25 in preparing 2-perfluoroalkyl-3-oxazoline-5-one.

It is a further object of this invention to
provide a convenient source of a key intermediate in
the manufacture of insecticidal, acaricidal and nema-
tocidal arylpyrrole compounds.

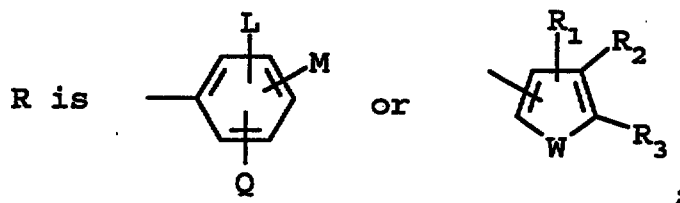
DESCRIPTION OF THE INVENTION

There is provided a method for the preparation of a 2-perfluoroalkyl-3-oxazolin-5-one
 5 compound of formula II



wherein

10 n is an integer of 1, 2, 3, 4, 5, 6, 7 or 8;



L is hydrogen or halogen;

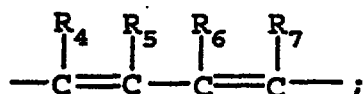
M and Q are each independently hydrogen, halogen,

15 CN, NO₂, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄alkylthio, C₁-C₄alkyl-sulfinyl or when M and Q are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which
 20 MQ represents the structure



with the proviso that at least one of L, M and Q must be other than hydrogen;

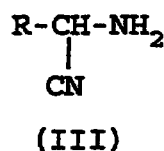
25 R₁, R₂ and R₃ are each independently hydrogen, halogen, NO₂, CHO or R₂ and R₃ may be taken together with the atoms to which they are attached to form a ring in which R₂R₃ is represented by the structure



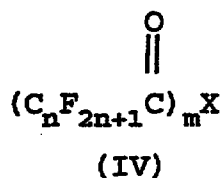
R₄, R₅, R₆ and R₇ are each independently hydrogen, halogen, CN or NO₂; and

5 W is O or S

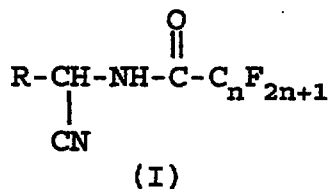
which comprises reacting an aminonitrile of formula III



10 wherein R is as described above with a perfluoro-acylating agent of formula IV

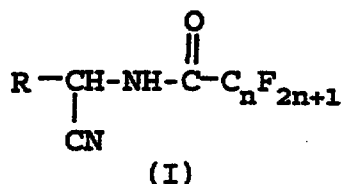


15 wherein m is an integer of 1 or 2, X is OR₁, Cl or O and R₁ is hydrogen or C₁-C₆alkyl with the proviso that when X is O, m must be 2 and when X is Cl or OR₁, then m must be 1 in the presence of a solvent, optionally in the presence of a base, to form a perfluoro-alkanoyl
20 aminonitrile intermediate of formula I



and cyclizing the formula I intermediate in the
25 presence of an acid and at least one molar equivalent of water.

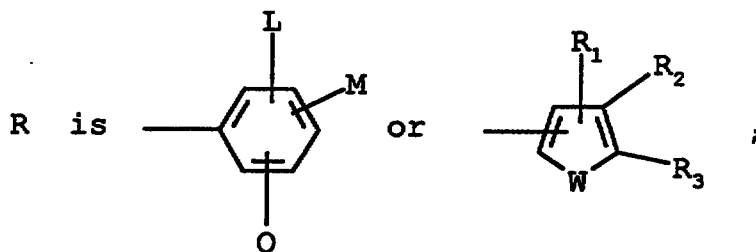
There is also provided a perfluoroalkanoyl aminonitrile intermediate of formula I



5

wherein

n is an integer of 1, 2, 3, 4, 5, 6, 7 or 8;



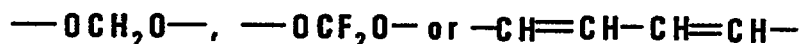
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L is hydrogen or halogen;

M and Q are each independently hydrogen, halogen, CN, NO₂, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄alkylthio, C₁-C₄alkyl-sulfinyl or when M and Q are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which MQ represents the structure

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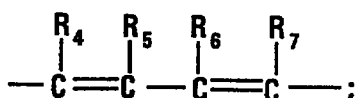
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with the proviso that at least one of L, M and Q must be other than hydrogen;

R₁, R₂ and R₃ are each independently hydrogen, halogen, NO₂, CHO or R₂ and R₃ may be taken together with the atoms to which they are attached to form a ring in which R₂R₃ is represented by the structure

25





R_4 , R_5 , R_6 and R_7 are each independently hydrogen, halogen, CN or NO_2 ; and W is O or S.

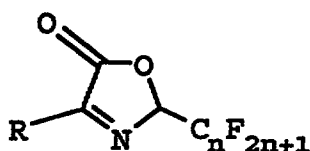
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The 2-perfluoroalkyl-3-oxazolin-5-one compound is a key intermediate in the manufacture of insecticidal, acaricidal and nematocidal pyrrole compounds.

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Arylpyrrole compounds, particularly 2-aryl-5-trifluoromethylpyrrole-3-carbonitrile compounds are a new class of highly effective insecticidal, acaricidal and nematocidal agents. A key intermediate in their preparation is the 2-perfluoroalkyl-3-oxazolin-5-one compound of formula II

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(II)

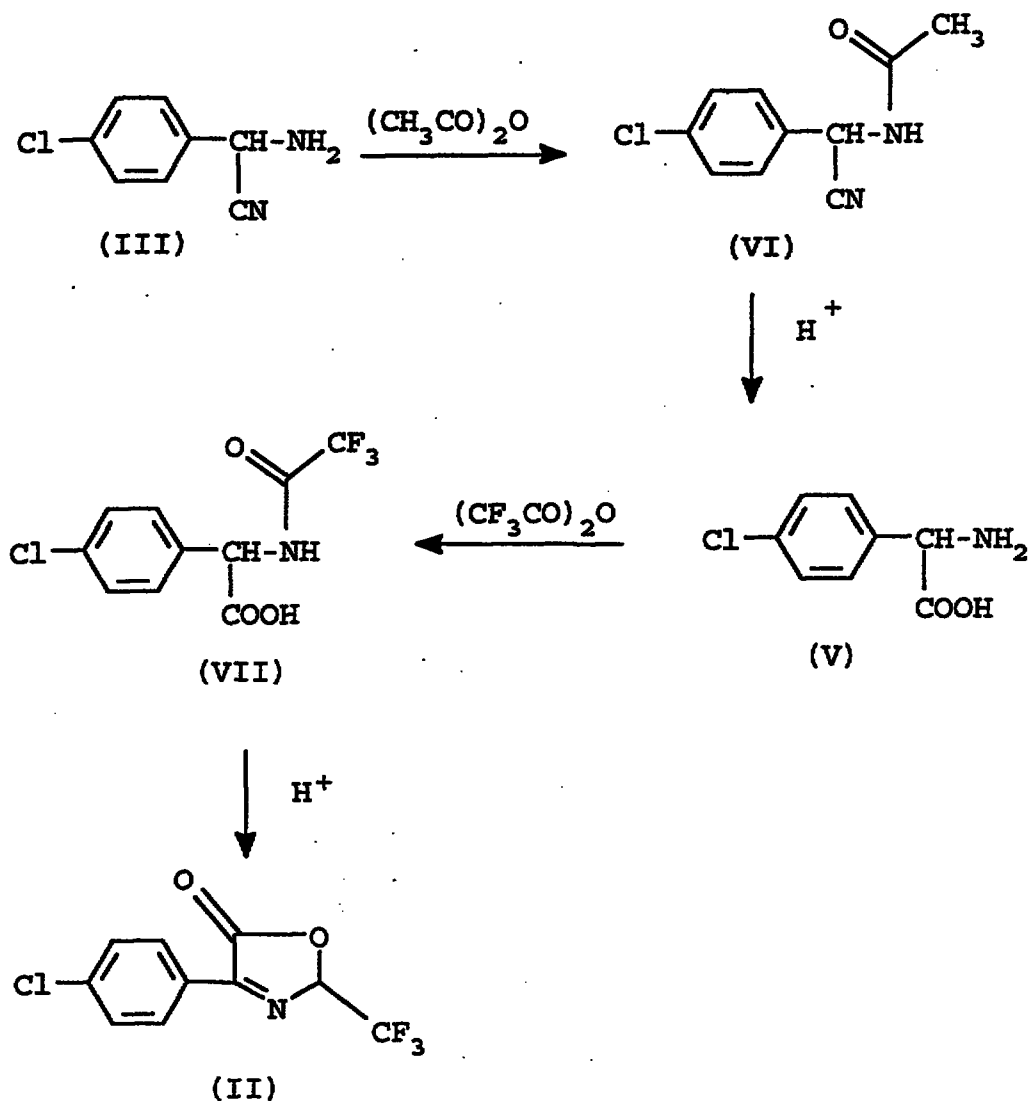
wherein n and R are as described hereinabove. Methods currently known to prepare the formula II oxazolinone involve the preparation of an appropriate arylglycine compound V via the hydrolysis of the aminonitrile III. The aminonitrile is obtained via the Strecker synthesis from the appropriate aldehyde precursor (W. L. Matier et al, J. Med. Chem., 1973, 16, 901). Protection of the amino group in the aminonitrile III by acetylation to VI followed by acidic hydrolysis of both the cyano and the protecting groups is required due to the instability of the aminonitrile III under hydrolysis conditions. The thus-obtained glycine V is then trifluoroacetylated to give VII and cyclized to give the desired oxazolinone II in 4 steps. The reaction

30

sequence is shown in flow diagram I, wherein R is p-chlorophenyl and n is 1.

FLOW DIAGRAM I

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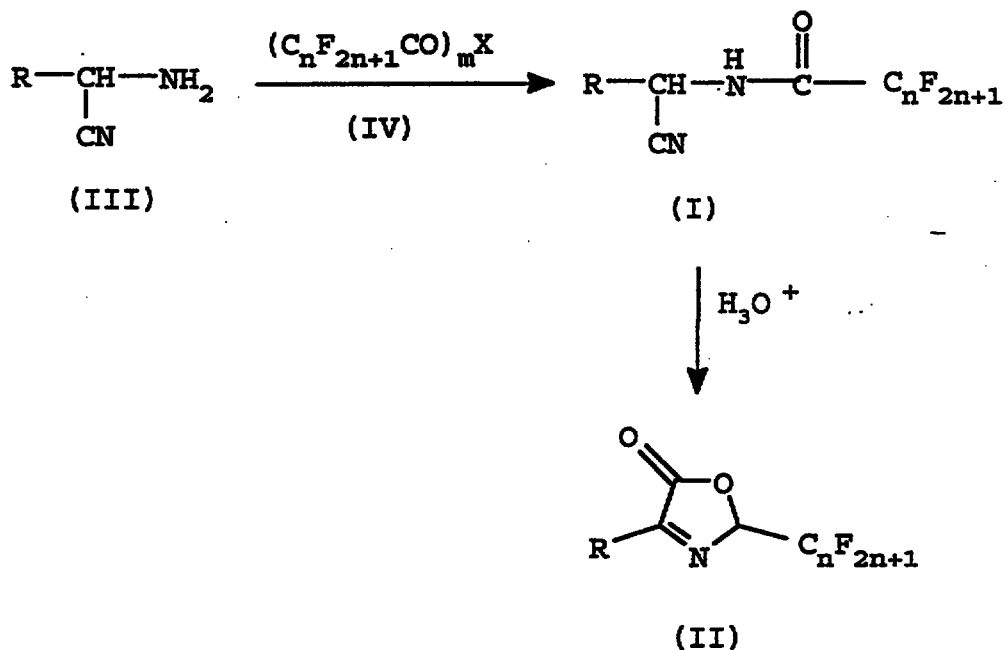
It has now been found that direct perfluoroacylation of the Strecker product III gives the perfluoroalkanoyl aminonitrile intermediate I which may be readily converted to the desired 2-perfluoroalkyl-3-oxazolin-5-one compound II. The reaction is shown in flow diagram II wherein m is 1 or 2, X is Cl, OR_1 or O and R_1 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with the proviso that

10

when X is O, then m must be 2 and when X is Cl or OR₁, then m must be 1.

FLOW DIAGRAM II

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Surprisingly, the perfluoroalkanoyl aminonitrile of formula I may be cyclized in a single step in good yield under aqueous acid conditions to the 2-perfluoroalkyl-3-oxazolin-5-one compound of formula II.

Advantageously, the desired oxazolinone II may be obtained in just 2 steps from the Strecker product aminonitrile III.

Preferred compounds of formula I are those wherein n is 1, 2 or 3, more preferred are those wherein n is 1. Also preferred are those compounds of formula I wherein R is phenyl optionally substituted with one to three halogen, NO₂, C₁-C₄haloalkyl or C₁-C₄haloalkoxy groups.

In accordance with the method of invention, an aminonitrile of formula III is admixed with approximately an equimolar amount of a perfluoro-

acylating agent of formula IV in the presence of a solvent, optionally in the presence of a base, to form the perfluoroalkanoyl aminonitrile of formula I. The formula I compound is then cyclized in the presence of
5 an aqueous acid to form the formula II compound, 2-perfluoralkyl-3-oxazolin-5 one.

Solvents suitable for use in the method of invention are aromatic hydrocarbons, or halogenated aromatic hydrocarbons, preferably aromatic hydrocarbons
10 such as toluene, benzene, xylene and the like, more preferably, toluene.

Acids suitable for use in the method of invention include sulfuric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid,
15 naphthlenesulfonic acid, fluoroboric acid, boron trifluoride complexes and the like. Boron trifluoride complexes may include BF₃ etherate, BF₃ methanol complex, BF₃ ethanol complex, BF₃ dihydrate and the like. Water may be introduced as a hydrate, i. e. p-
20 toluensulfonic acid monohydrate or as a solute such as 30% - 60% aqueous sulfuric acid.

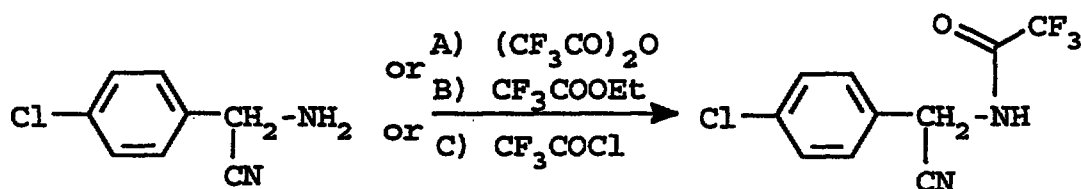
In actual practice, if a perfluoroacyl chloride, such as trifluoroacetyl chloride, is used as the formula IV reagent, then an equimolar amount of a
25 base may be added as an HCl scavenger. Among the bases which may be used are alkali metal carbonates or bicarbonates or mixtures thereof or tertiary amines. Alkalai metal carbonates such as sodium carbonate or potassium carbonate are contemplated as are
30 bicarbonates such as sodium or potassium bicarbonate.

Tertiary amines suitable for use in the method of invention include any trisubstituted amine know in the art such a trialkylamine, dialkylarylamine, triarylamine, and the like preferably trialkylamine,
35 more prefereably triethylamine.

In order to provide a more clear understanding of the invention, the following examples are set forth below. These examples are merely illustrative and are not to be understood to limit the scope or underlying principles of the invention in any way.

The terms ^1H , ^{13}C and ^{19}F NMR designate proton, carbon 13 and fluorine 19 nuclear magnetic resonance, respectively.

10

EXAMPLE 1Preparation of N-[(p-Chlorophenyl) cyanomethyl]-2,2,2-trifluoroacetamide

15

Method A: A stirred slurry of α -cyano-p-chlorobenzylamine (250g, 1.5mol) in toluene is treated with trifluoroacetic anhydride (315g, 1.5mol) at 35°C over a 90 minute period. The mixture is treated with heptane, the resultant precipitate is filtered and the filter-cake is washed with toluene/heptane to give the title product, 323.7g, 82% yield, mp $127-128^\circ\text{C}$, identified by ^1H , ^{13}C and ^{19}F NMR analyses.

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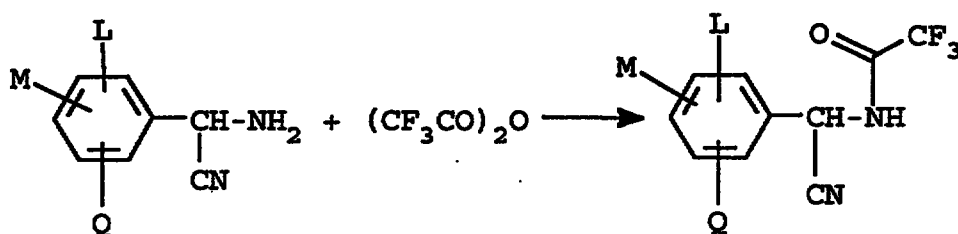
Method B: A solution of α -cyano-p-chlorobenzylamine (83.3g, 0.5mol) in methanol is treated with ethyl trifluoroacetate (85.2g, 0.6mol), stirred at room temperature for about 16 hours and concentrated in vacuo to give a residue. The residue is crystallized from toluene/heptane to give the title product as a pale yellow solid, 88.3g, 67.2% yield, mp $127^\circ-128^\circ\text{C}$.

30

Method C: A mixture of α -cyano-p-chlorobenzylamine (83.3g, 0.5mol) and triethylamine (50.6g, 0.5mol) in toluene is treated dropwise with trifluoroacetyl chloride (66.2g, 0.5mol), stirred at ambient temperature for about 1 hour and filtered. The filtrate is washed once with water and concentrated in vacuo to give a residue. The residue is crystallized in toluene/hexane to give the title product, 114.2g, 87% yield, mp 127°-128°C.

EXAMPLE 2

Preparation of N-(Arylcyanomethyl)-2,2,2-trifluoroacetamide

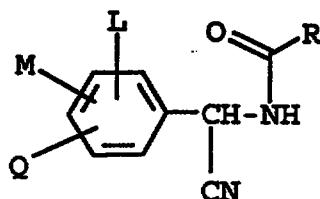


Using essentially the same procedure described as Method A in Example 1 and substituting the appropriate α -cyanobenzylamine as starting material, the following N-(arylcyanomethyl) 2,2,2-trifluoroacetamide products are obtained. The products are identified by ^1H , ^{13}C and ^{19}F NMR analyses.

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Table I

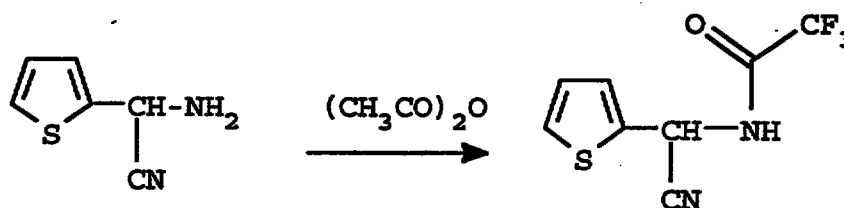


5	<u>L</u>	<u>M</u>	<u>Q</u>	<u>mp °C</u>	<u>% Yield</u>
	H	4-Br	H	128.0-128.5	76
	H	4-CF ₃	H	115.0-116.0	63
10	3-Cl	4-Cl	H	113.0-115.0	35 ^a

^aBased on aldehyde used in Strecker synthesis. (Crude Strecker product used as starting material)

EXAMPLE 3

Preparation of N-(α-Cyanothienyl)-2,2,2-trifluoro-
acetamide

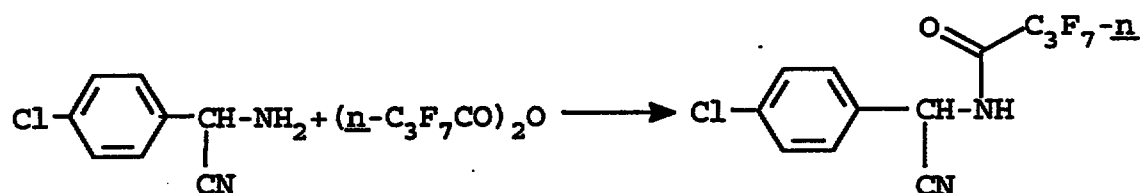


Using essentially the same procedure described as
25 Method A in Example 1 and substituting the crude
Strecker product, α-cyano-2-thiophenemethylamine, as
starting material the title product is obtained in 23%
yield^a, m.p. 73.0-74.5°C, identified by ¹H, ¹³C and
30 ¹⁹FNMR analyses.

^aBased upon starting aldehyde used in Strecker
synthesis.

EXAMPLE 4

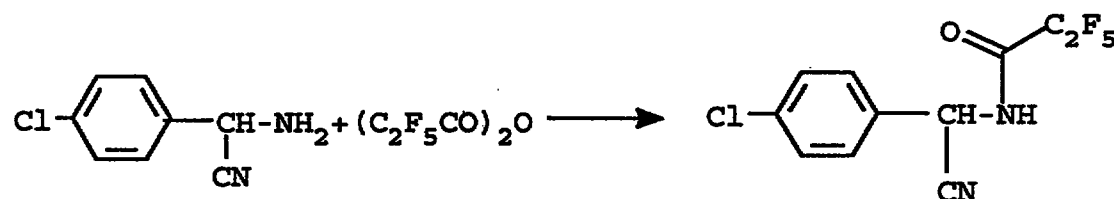
Preparation of N-[(p-Chlorophenyl)cyanomethyl]-
2,2,3,3,4,4,4-heptafluorobutyramide



Using essentially the same procedure described as Method A in Example 1 and substituting heptafluorobutyric anhydride as the perfluoro-acylating agent, the title product is obtained as white crystals in 95% yield, mp 93.0°-95.0°C, identified by ¹H, ¹³C and ¹⁹F NMR analyses.

EXAMPLE 5

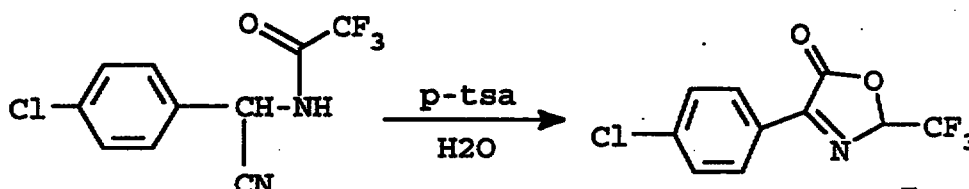
Preparation of N-[(p-Chlorophenyl)cyanomethyl]-
2,2,3,3,3-pentafluoropropionamide



Using essentially the same procedure described as Method A in Example 1 and substituting pentafluoropropionic anhydride as the perfluoro-acylating agent, the title product is obtained as white crystals, 95% yield, mp 118.0°-118.5°C, identified by ¹H, ¹³C and ¹⁹F NMR analyses.

EXAMPLE 6

Preparation of 4-(p-Chlorophenyl)-2-(trifluoromethyl)-3-oxazolin-5-one



Method A: A solution of N-[p-chlorophenyl]-
 10 cyanomethyl]-2,2,2-trifluoroacetamide (0.1mol) in
 toluene at 80°C is treated portion-wise with p-toluene
 sulfonic acid monohydrate (p-tsa·H₂O) (0.11mol) over an
 0.75-1.0 hour period, stirred at 90°-95°C for 2-3
 hours, cooled and filtered. The filtrate is washed
 15 twice with water and concentrated in vacuo to give an
 oil residue. The oil is dissolved in heptane, filtered
 and the filtrate is vacuum distilled to give the title
 product as an oil, 55.6% yield, bp 78°C/0.01mmHg,
 identified by ¹H, ¹³C and ¹⁹F NMR analyses.

20

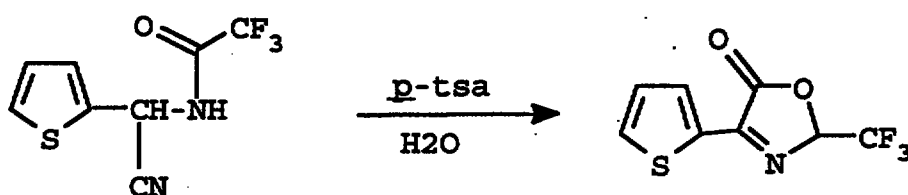
Method B: A solution of N-[p-(chlorophenyl)cyano-
 methyl]-2,2,2-trifluoroacetamide (26.3g, 0.1mol) in
 toluene and methanesulfonic acid (10.7g, 0.11mol) at
 80°C is treated with water (2 mL, 0.11mol) over a 20
 25 minute period, stirred at 90°C for 8 hours and cooled.
 The reaction mixture is washed twice with water. The
 organic layer is concentrated in vacuo to give an oil
 which is vacuum distilled to give the title product as
 an oil 13.7g, bp 80°C/0.01mm Hg.

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EXAMPLE 7

Preparation of 4-(2-Thienyl-2-(trifluoromethyl)-3-oxazolin-5-one

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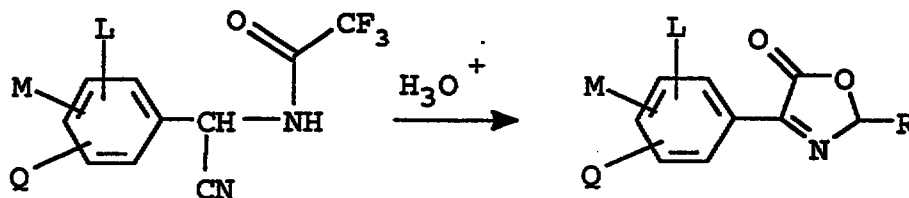
Using essentially the same procedure described as Method A in Example 6 and substituting N-(α-cyanothienyl)-2,2,2-trifluoroacetamide as starting material, the title product is obtained as a pale brown solid, 50% yield, mp 62.0°-65.0°C, identified by IR and ¹H, ¹³C and ¹⁹F NMR analyses.

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EXAMPLE 8

Preparation of 2-perfluoroalkyl-3-oxazolin-5-one

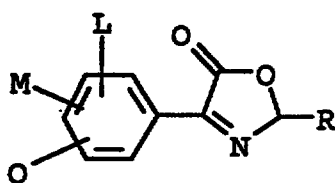
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Using essentially the same procedure described as Method A in Example 6 and substituting the appropriate perfluoroalkylcyanoyl aminonitrile as starting material, the compounds shown in Table II are obtained.

25

Table II



5

	<u>L</u>	<u>M</u>	<u>Q</u>	<u>R</u>	<u>mp °C</u>	<u>% Yield</u>
	H	4-Br	H	CF ₃	48.0-51.0	64
	H	4-CF ₃	H	CF ₃	39.0-40.5	55
10	3-Cl	4-Cl	H	CF ₃	103°/0.1mm ^a	54
	H	4-Cl	H	C ₂ F ₅	39.0-42.0	72
	H	4-Cl	H	n-C ₃ H ₇	93.0-95.0	56

^a bp °C

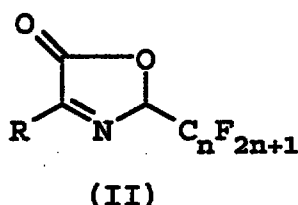
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I CLAIM:

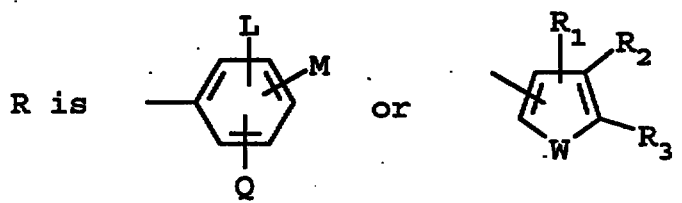
- 5 1. A process for the preparation of a compound of formula II



10

wherein

n is an integer of 1, 2, 3, 4, 5, 6, 7 or 8;

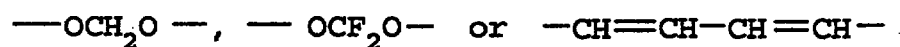


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L is hydrogen or halogen;

M and Q are each independently hydrogen, halogen, CN, NO₂, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄alkylthio, C₁-C₄alkyl-sulfinyl or when M and Q are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which MQ represents the structure

25



with the proviso that at least one of L, M and Q must be other than hydrogen;



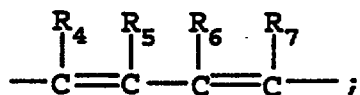
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R_1 , R_2 and R_3 are each independently hydrogen, halogen, NO_2 , CHO or R_2 and R_3 may be taken together with the atoms to which they are attached to form a ring in which R_2R_3 is represented by the structure

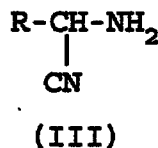
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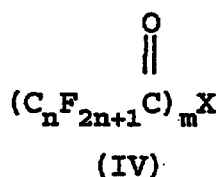
R_4 , R_5 , R_6 and R_7 are each independently hydrogen, halogen, CN or NO_2 ; and

10 W is O or S

which comprises reacting an aminonitrile of formula III



15 wherein R is as described above with a perfluoro-acylating agent of formula IV



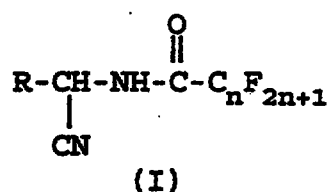
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wherein m is an integer of 1 or 2, X is OR_1 , Cl or O and R_1 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with the proviso that when X is O, m must be 2 and when X is Cl or OR_1 , then m must be 1 in the presence of a solvent, optionally in
25 the presence of a base, to form a perfluoroalkanoyl aminonitrile intermediate of formula I



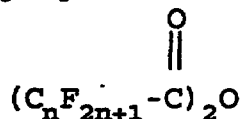


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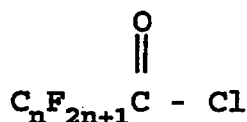
and cyclizing the formula I intermediate in the presence of an acid and at least one molar equivalent
 5 of water.

2. The process according to claim 1 wherein the perfluoroacylating agent of formula IV is



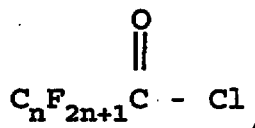
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or



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3. The process according to claim 2 wherein the perfluoroacylating agent is

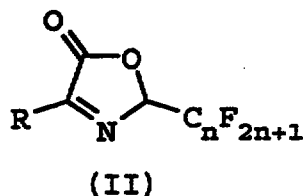


20 a base is present and the base is sodium or potassium carbonate or a tertiaryamine.

4. The process according to claim 1 wherein the solvent is an aromatic hydrocarbon or a halogenated
 25 aromatic hydrocarbon and the acid is sulfuric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, fluoroboric acid or a boron trifluoride complex.

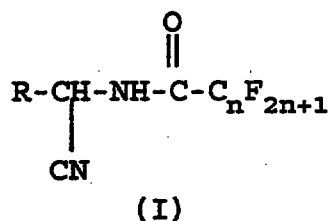


5. A process for the preparation of a compound of formula II



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wherein n and R are as defined in claim 1 which comprises cyclizing a compound of formula I



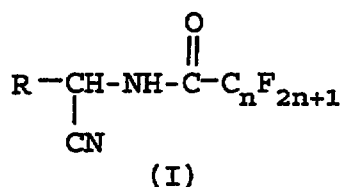
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in the presence of an acid and at least one molar equivalent of water.

6. The process according to claim 5 wherein the acid is sulfuric acid methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, fluoro-boric acid or a boron trifluoride complex.

20

7. A compound having formula I



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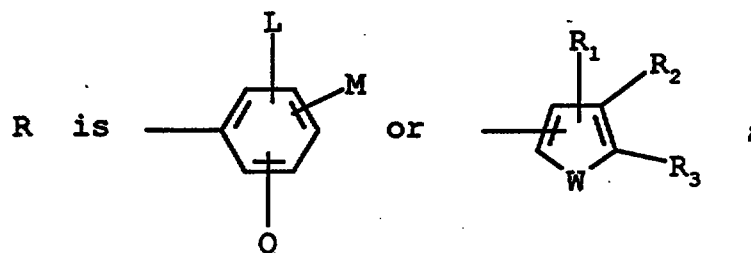
wherein

n is an integer of 1, 2, 3, 4, 5, 6, 7 or 8;



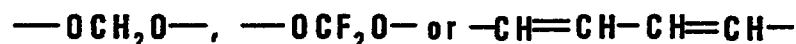


-20-



L is hydrogen or halogen;

- 5 M and Q are each independently hydrogen, halogen, CN, NO₂, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄haloalkoxy, C₁-C₄alkylthio, or when M and Q are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which MQ represents the structure



with the proviso that at least one of L, M and Q must be other than hydrogen;

- 15 R₁, R₂ and R₃ are each independently hydrogen, halogen, NO₂, CHO or R₂ and R₃ may be taken together with the atoms to which they are attached to form a ring in which R₂R₃ is represented by the structure



R₄, R₅, R₆ and R₇ are each independently hydrogen, halogen, CN or NO₂; and

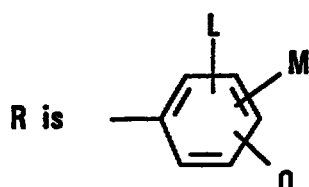
W is O or S.

- 25 8. The compound according to claim 7 wherein n is an integer of 1 or 2.





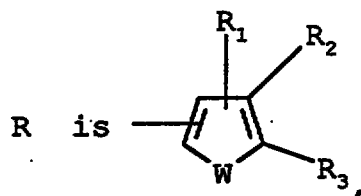
9. The compound according to claim 8 wherein



5 and L is hydrogen and M and Q are each independently hydrogen, halogen or C₁-C₄haloalkyl.

10. The compound according to claim 8 wherein

10



15 R₁ is in the 3 position and is hydrogen, R₂ and R₃ are each independently hydrogen or halogen and W is S.

