650929

SPRUSON & FERGUSON

Australia

Patents Act 1990

Patent Request: Standard Patent

We, the Applicant/Nominated Person specified below, request we be granted a patent for the invention disclosed in the accompanying standard complete specification.

[70,71] **Applicant/Nominated Person:**
American Cyanamid Company, of One Cyanamid Plaza, Wayne, New Jersey, 07470, United States of America

[54] **Invention Title:**
Synthesis of 2-aryl-5-(trifluoromethyl)pyrroles Useful as Pesticidal Agents and as Intermediates for the Preparation of Said Agents

[72] **Inventor:**
Venkataraman Kameswaran

[74] **Address for Service in Australia:**
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Sydney New South Wales Australia [Code **SF**]

Basic Convention Application Details

[31] Application No	**[33]** Country	**[32]** Date of Application
628,751	US	17 December 1990

Basic Applicant: Venkataraman Kameswaran

DATED 4 May, 1994
American Cyanamid Company

Registered Patent Attorney

AUSTRALIAN PATENT OFFICE LS

IRN: 195668

INSTR CODE: 50380

[N:\LIBW]02923:KEH

SPRUSON & FERGUSON 31,564-00

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

I Alphonse R. Noë,
of 470 Haviland Road, Stamford, State of Connecticut, United States of America, being authorized by the Applicant/Nominated Person in respect of an application entitled:

SYNTHESIS OF 2-ARYL-5-(TRIFLUOROMETHYL)PYRROLES USEFUL AS PESTICIDAL AGENTS AND AS INTERMEDIATES FOR THE PREPARATION OF SAID AGENTS

state the following:-

The Applicant/Nominated Person has entitlement from the actual inventor(~~s~~) as follows:-

The Applicant/Nominated Person is the assignee of the actual inventor(~~s~~).

The Applicant/Nominated Person is entitled to rely on the basic application(~~s~~) listed on the Patent Request as follows:

The Applicant/Nominated Person is the assignee of the basic applicant(~~s~~).

The basic application(~~s~~) listed on the Patent Request is/~~are~~ the application(~~s~~) first made in a Convention Country in respect of the invention.

Dated this 16 day of October 1991.

Alphonse R. Noë, Manager
Patent Law Department

IRN: 185135 INSTR CODE: 50380
MOC/7368D

AU9189747

(12) PATENT ABRIDGMENT (11) Document No. AU-B-89747/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 650929

(54) Title
SYNTHESIS OF 2-ARYL-5-(TRIFLUOROMETHYL)PYRROLES USEFUL AS PESTICIDAL AGENTS AND AS INTERMEDIATES FOR THE PREPARATION OF SAID AGENTS

International Patent Classification(s)
(51)[5] C07D 207/34

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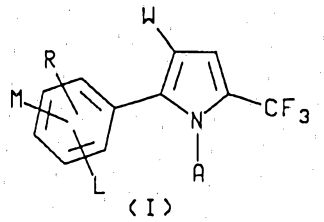
(74) Attorney or Agent
SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001

(56) Prior Art Documents
AU 88301/91 C07D 207/34 A01N 043/36
AU 81510/91 C07D 207/34 C07C 045/65
US 5010098

(57) Claim

1. A process for the preparation of a compound of formula I



(I)

wherein A is hydrogen, phenyl or C_1-C_6 alkyl optionally substituted with phenyl;

W is CN, NO_2, CO_2R_1 or SO_2R_2;

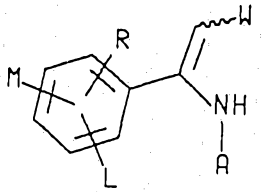
L is hydrogen or halogen;

M and R are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, CN, NO_2, Cl, Br, F, I, CF_3, R_3CF_2Z, R_4CO or NR_5R_6 and when M and R are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which MR represents the structure

$-OCH_2O-$, $-OCF_2O-$ or $-CH=CH-CH=CH-$;

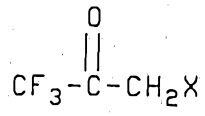
.../2

R_1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl;
R_2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl;
R_3 is hydrogen, F, CHF_2, CHFCl or CF_3;
R_4 is C_1-C_4 alkyl, C_1-C_4 alkoxy or NR_5R_6;
R_5 is hydrogen or C_1-C_4 alkyl;
R_6 is hydrogen, C_1-C_4 alkyl or R_7CO;
R_7 is hydrogen or C_1-C_4 alkyl;
Z is $S(O)_n$ or O and
n is an integer of 0, 1 or 2 characterized by reacting a compound of formula II



(II)

wherein A, W, L, M and R are described above with about one molar equivalent of a compound of formula III



(III)

wherein X is Cl, Br or I in the presence of an acid and a solvent.

650929

S & F Ref: 195668

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

Name and Address of Applicant: American Cyanamid Company
One Cyanamid Plaza
Wayne New Jersey 07470
UNITED STATES OF AMERICA

Actual Inventor(s): Venkataraman Kameswaran

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

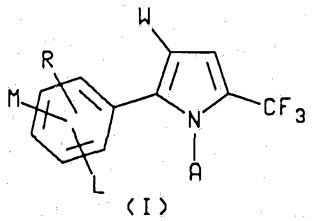
Invention Title: Synthesis of 2-aryl-5-(trifluoromethyl)pyrroles Useful as Pesticidal Agents and as Intermediates for the Preparation of Said Agents

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

SYNTHESIS OF 2-ARYL-5-(TRIFLUOROMETHYL)PYRROLES USEFUL AS PESTICIDAL AGENTS AND AS INTERMEDIATES FOR THE PREPARATION OF SAID AGENTS

Arylpyrrole compounds are highly effective insecticidal, acaricidal and nematocidal agents.

The present invention is directed to a process for the preparation of arylpyrrole compounds of formula I



(I)

wherein A is hydrogen, phenyl or C_1-C_6 alkyl optionally substituted with phenyl;

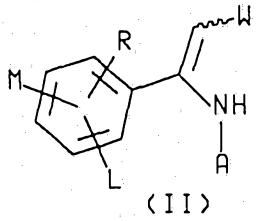
W is CN, NO_2, CO_2R_1 or SO_2R_2;

L is hydrogen or halogen;

M and R are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, CN, NO_2, Cl, Br, F, I, CF_3, R_3CF_2Z, R_4CO or NR_5R_6 and when M and R are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which MR represents the structure

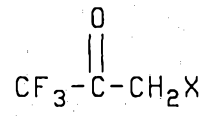
$-OCH_2O-$, $-OCF_2O-$ or $-CH=CH-CH=CH-$;

R_1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl;
R_2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl;
R_3 is hydrogen, F, CHF_2, CHFCl or CF_3;
R_4 is C_1-C_4 alkyl, C_1-C_4 alkoxy or NR_5R_6;
R_5 is hydrogen or C_1-C_4 alkyl;
R_6 is hydrogen, C_1-C_4 alkyl or R_7CO;
R_7 is hydrogen or C_1-C_4 alkyl;
Z is $S(O)_n$ or O and
n is an integer of 0, 1 or 2 which comprises reacting a compound of formula II



(II)

wherein A, W, L, M and R are described above with at least one molar equivalent of a compound of formula III



(III)

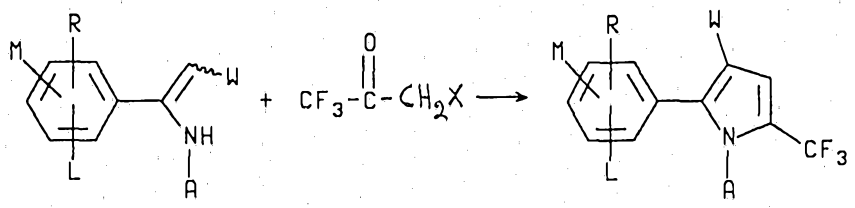
wherein X is Cl, Br or I in the presence of an acid and a solvent.

The arylpyrrole compounds of formula I are highly useful as insecticidal, acaricidal and nematocidal agents and, further, are important intermediates in the manufacture of certain insecticidal arylpyrrole compounds.

Surprisingly, it has been found that pyrrole rings substituted at the α-positions may be effectively prepared in a single step process via the condensation of a suitable enamine with an α-haloketone. Thus, pyrrole compounds of formula I may be prepared by

reacting an enamine of formula II with about one molar equivalent of an α-haloketone of formula III in the presence of an acid and a solvent at preferably an elevated temperature. The reaction is illustrated in flow diagram I.

FLOW DIAGRAM I

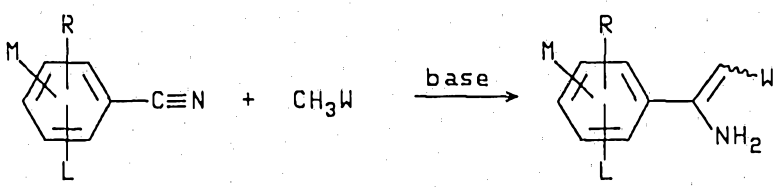


II III I

The solvents suitable for use in the process of the present invention include organic solvents such as hydrocarbons and aromatic hydrocarbons having a boiling range of about 80° to 250°C, such as benzene, toluene, xylene and the like, preferably toluene. Acids suitable for use in the invention include organic acids such as acetic acid, propionic acid and the like, preferably acetic acid. Reaction temperatures of about 80° to 150°C are suitable, with 90°-130°C. being preferred.

The compounds of formula II wherein A is hydrogen may be prepared by reacting the appropriate benzonitrile of formula IV with a compound of formula V in the presence of a base as shown in flow diagram II.

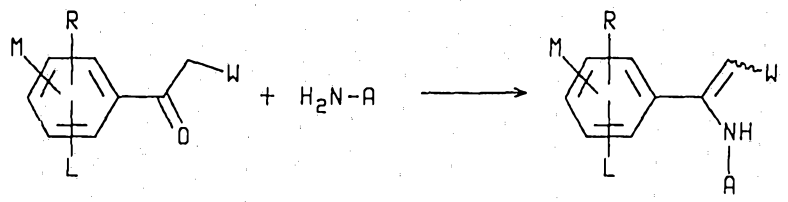
FLOW DIAGRAM II



IV V

The compounds of formula II wherein A is other than hydrogen may be prepared by reacting the appropriate aroyl compound of formula VI with a suitable amine of formula VII as shown in flow diagram III.

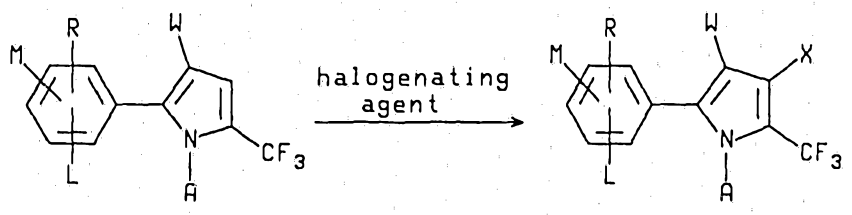
FLOW DIAGRAM III



VI VII II

Arylpyrrole compounds of formula I may be useful as intermediates in the manufacture of insecticidal arylpyrroles. For example, compounds of formula I may be halogenated using a suitable halogenating agent such as a halogen, a hypohalite or the like to afford the corresponding 2-aryl-4-halopyrrole insecticidal agents of formula VIII. The reaction is shown in flow diagram IV.

FLOW DIAGRAM IV



I VIII

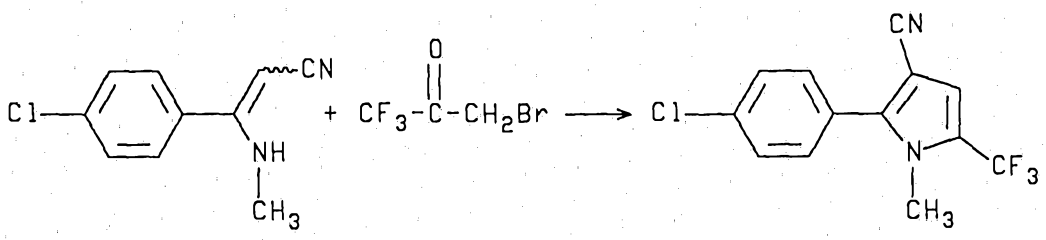
By varying the substituents, A, W, L, M and R and the halogen, X, numerous possible arylpyrroles may be prepared from the intermediate compounds of formula I.

In order to facilitate a further understanding of the present invention, the following examples are set forth primarily for the purpose of

illustrating certain more specific details thereof. The invention is not to be limited, thereby except as defined in the claims. The terms IR and NMR designate infrared and nuclear magnetic resonance, respectively. The term HPLC designates high pressure liquid chromatography.

EXAMPLE 1

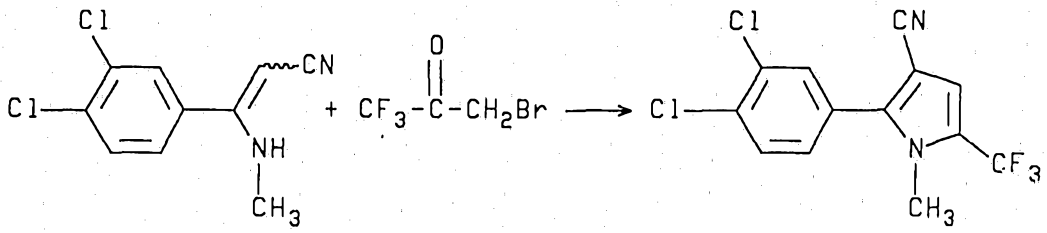
Preparation of 2-(4- chlorophenyl)-1-methyl-5-fluoromethyl)pyrrole-3-carbonitrile



A solution of p-chloro-β-(methylamino)cinnaminitrile (10.0 g, 0.052 mol) in toluene and acetic acid is treated dropwise with 3-bromo-1,1,1-trifluoro-2-propanone (10.0 g, 0.052 mol) at room temperature, heated at reflux temperature for about 1 hour or until the disappearance of starting material by thin layer chromatography, cooled to room temperature and diluted with ethyl acetate. The organic phase is washed sequentially with water and 5N NaOH, dried (Na_2SO_4) and concentrated in vacuo to give a brown oil residue. The residue is flash chromatographed (silica gel, hexanes/-ethyl acetate, 80/20) to give the title product as a pale yellow solid 6.7 g (48% yield) mp 129.5°C to 130.5°C, identified by IR and NMR spectral analyses.

EXAMPLE 2

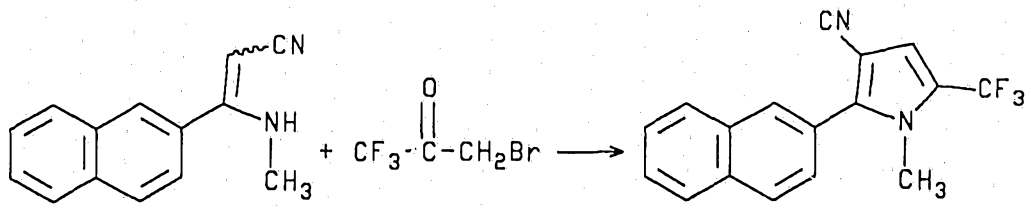
Preparation of 2-(3,4-Dichlorophenyl)-1-methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile



A solution of 3,4-dichloro-β-(methylamino)-cinnaminitrile (7.0 g, 0.031 mol) in toluene and acetic acid is treated dropwise with 3-bromo-1,1,1-trifluoro-2-propanone (6.0 g, 0.031 mol) at room temperature, heated at reflux temperature for 5 hours, cooled and diluted with ethyl acetate. The organic phase is washed sequentially with water and aqueous sodium hydroxide, dried (Na_2SO_4) and concentrated in vacuo to give a brown oil residue. The residue is flash chromatographed (silica gel, hexanes/ethyl acetate, 80/20) to give the title compound as a pale yellow solid, mp 130.2°C, identified by mass spectral, IR and NMR analyses.

EXAMPLE 3

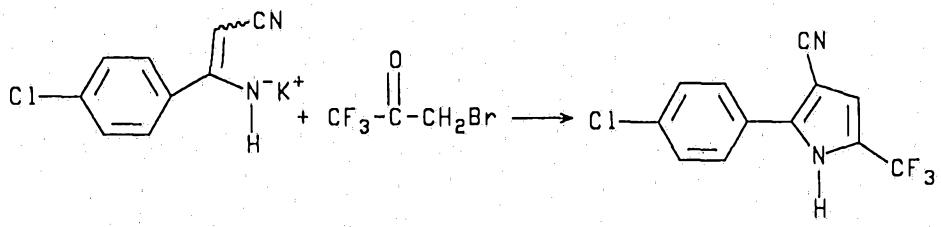
Preparation of 1-Methyl-2-(2-naphthyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile



A solution of β-(methylamino)-2-naphthaleneacrylonitrile (2.5 g, 0.012 mol) in toluene and acetic acid is treated dropwise with 3-bromo-1,1,1-trifluoro-2-propanone (2.3 g, 0.012 mol) at room temperature, heated at reflux temperature for 6 hours, cooled and diluted with ethyl acetate. The organic phase is washed sequentially with water and 5N NaOH, dried (Na_2SO_4) and concentrated in vacuo to give a brown oil residue. The residue is flash chromatographed (silica gel, hexanes/ethyl acetate, 80/20) to give the title compound as a yellow solid, mp 134°C, identified by mass spectral, IR and NMR analyses.

EXAMPLE 4

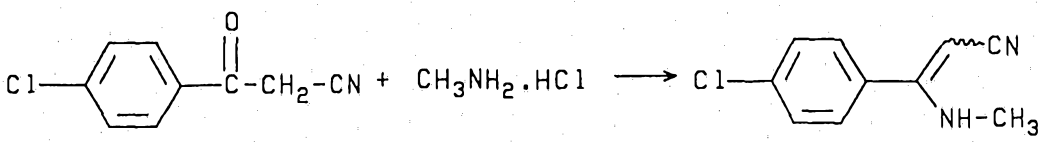
Preparation of 2-(p-Chlorophenyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile



A mixture of β-amino-p-chlorocinnaminitrile potassium salt (2.2 g, 0.01 mol) in acetic acid is treated dropwise with 3-bromo-1,1-trifluoro-2-propanone (1.91 g, 0.01 mol) at room temperature, heated at 100°C for 1 1/2 hours, stirred at room temperature for 16 hours and diluted with water and ethyl acetate. The organic phase is washed sequentially with water and aqueous sodium hydroxide, dried (Na_2SO_4) and concentrated in vacuo to give a semi-solid residue. The residue is crystallized in ethyl acetate/heptane to give the title compound as a brown solid, mp 238°C to 240°C, identified by ^{13}C and ^{1}HNMR analyses.

EXAMPLE 5

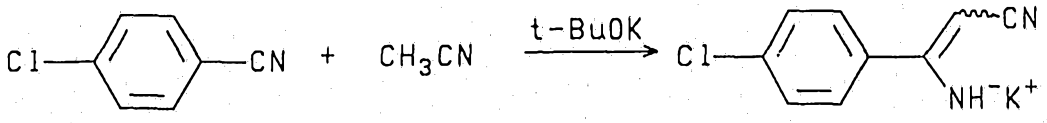
Preparation of p-Chlorophenyl-β-(methylamino)cinnamonitrile



A mixture of p-chlorobenzoylacetonitrile (18.0 g, 0.1 mol), methylamine hydrochloride (10.13 g, 0.15 mol) and sodium acetate (12.3 g, 0.15 mol) in toluene is heated at reflux temperature (with a Dean Stark trap) for 5-6 hours, cooled to room temperature and diluted with water and ethyl acetate. The organic phase is separated and concentrated in vacuo to a residue which is crystallized from toluene/heptane to give the title product as a pale yellow solid, 17.1 g, (89% yield), mp 111.0°C to 113.0°C, identified by ^{13}C and $^{1}HNMR$ spectral analyses.

EXAMPLE 6

Preparation of β-Amino-p-chlorocinnaminitrile, potassium salt

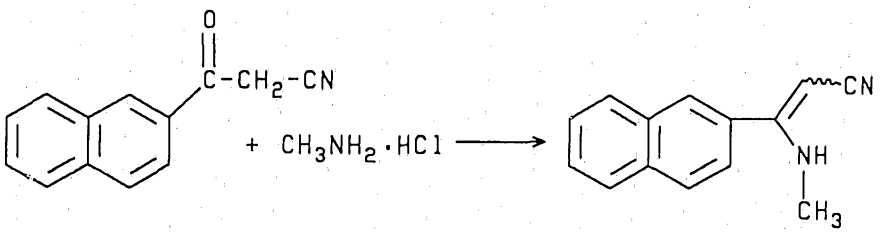


A solution of p-chlorobenzonitrile (13.8 g, 0.1 mol) in dimethoxyethane is treated with acetonitrile (4.93 g, 0.012 mol) at room temperature, treated portionwise with potassium t-butoxide (11.8 g, 0.105 mol), heated at reflux temperature for 1 hour, cooled to room temperature, diluted with ether and filtered. The solid filter cake is air dried and a

10 g sample is recrystallized from ethanol to give the title compound as a white solid, 3.9 g, identified by IR, ^{13}C and $^{1}HNMR$ spectral analyses.

EXAMPLE 7

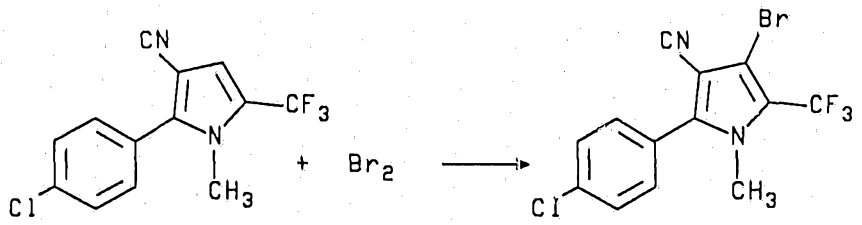
Preparation of β-(Methylamino)-2-naphthaleneacrylonitrile



A solution of β-oxo-2-naphthalenepropionitrile (5.0 g, 0.0256 mol) in toluene is treated with methylamine hydrochloride ()2.6 g, 0.0384 mol), sodium acetate (3.15 g, 0.0386 mol) and a catalytic amount of acetic acid, heated at reflux temperature (fitted with a Dean Stark trap) for 6 hours, cooled, diluted with ethyl acetate and dilute hydrochloric acid. The organic phase is dried over Na_2SO_4 and concentrated <u>in vacuo</u> to give a residue which is triturated under hexanes to give the title compound as a yellow solid, 3.1 g (58% yield) mp 138°C, identified by IR, $^{1}NHMR$ and mass spectral analyses.

EXAMPLE 8

Preparation of 2-p-(Chlorophenyl)-4-bromo-1-methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile

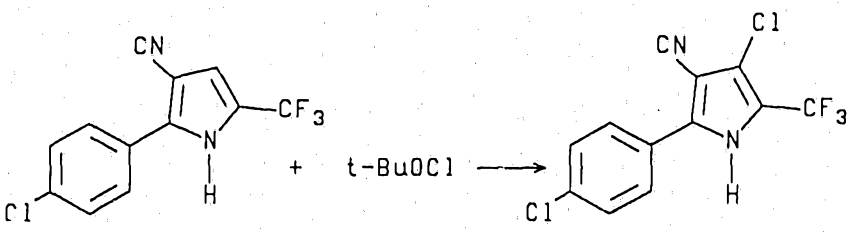


A solution of 2-(p-chlorophenyl)-1-methyl-

5-(trifluoromethyl)pyrrole-3-carbonitrile (5.70 g, 0.02 mol) in chlorobenzene is treated with bromine (3.52 g, 0.022 mol), heated at 80°C for 20 hours, cooled to room temperature, treated with additional bromine (3.52 g, 0.022 mol) and heated at 100°C until reaction is complete by HPLC analysis. The reaction mixture is cooled to room temperature and diluted with ethyl acetate and water. The organic phase is washed with aqueous sodium metabisulfite, dried ($MgSO_4$) and concentrated <u>in vacuo</u> to afford a solid residue. The residue is recrystallized from ethyl acetate/heptane to give the title product as a white solid, 6.50 g (89.4% yield), mp 126°C to 129°C.

EXAMPLE 9

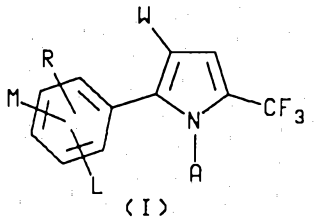
Preparation of 2-p-(Chlorophenyl)-4-chloro-5-(trifluoromethyl)pyrrole-3-carbonitrile



A solution of 2-(p-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (20.0 g, 0.0739 mol) in monochlorobenzene is treated with t-butylhypochlorite (19.6 g, 0.087 mol), heated at 70°C for 2 hours, treated with additional t-butylhypochlorite (2.0 g, 0.009 mol), heated at 80°C to 82°C for 1 hour, cooled to room temperature, diluted with heptane and filtered. The filter cake is air-dried to give the title product as a pale solid, 18.5 g, (82.5% yield), mp 242.5°C to 243.0°C, identified by ^{19}F and $^{1}HNMR$ spectral analyses.

~~I CLAIM:~~ The claims defining the invention are as follows:

1. A process for the preparation of a compound of formula I



(I)

wherein A is hydrogen, phenyl or C_1-C_6 alkyl optionally substituted with phenyl;

W is CN, NO_2, CO_2R_1 or SO_2R_2;

L is hydrogen or halogen;

M and R are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, CN, NO_2, Cl, Br, F, I, CF_3, R_3CF_2Z, R_4CO or NR_5R_6 and when M and R are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which MR represents the structure

$-OCH_2O-$, $-OCF_2O-$ or $-CH=CH-CH=CH-$;

R_1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl;

R_2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl;

R_3 is hydrogen, F, CHF_2, CHFCl or CF_3;

R_4 is C_1-C_4 alkyl, C_1-C_4 alkoxy or NR_5R_6;

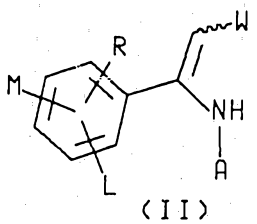
R_5 is hydrogen or C_1-C_4 alkyl;

R_6 is hydrogen, C_1-C_4 alkyl or R_7CO;

R_7 is hydrogen or C_1-C_4 alkyl;

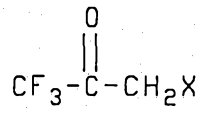
Z is $S(O)_n$ or O and

n is an integer of 0, 1 or 2 characterized by reacting a compound of formula II



(II)

wherein A, W, L, M and R are described above with about one molar equivalent of a compound of formula III



(III)

wherein X is Cl, Br or I in the presence of an acid and a solvent.

2. The process according to claim 1 wherein the reaction takes place at an elevated temperature.

3. The process according to claim 2 wherein the elevated temperature is about 90°C to 130°C.

4. The process according to claim 1 wherein the acid is acetic acid.

5. The process according to claim 1 wherein W is CN.

6. The process according to claim 1 wherein W is NO_2.

7. The process according to claim 5 wherein A is hydrogen or methyl, L and R are hydrogen and M is halogen.

8. The process according to claim 5 wherein A is hydrogen or methyl, L is hydrogen and M and R are halogen.

9. A process for the preparation of 2-aryl-5-(trifluoromethyl)pyrroles substantially as hereinbefore described with reference to any one of ~~the~~ Examples 1 to 7.

10. The product of the process of any one of claims 1 to 9.

DATED this TWENTY-SIXTH day of NOVEMBER 1991

American Cyanamid Company

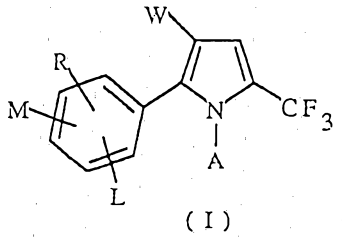
Patent Attorneys for the Applicant

SPRUSON & FERGUSON

SYNTHESIS OF 2-ARYL-5-(TRIFLUOROMETHYL)PYRROLES USEFUL AS PESTICIDAL AGENTS AND AS INTERMEDIATES FOR THE PREPARATION OF SAID AGENTS

Abstract

There is provided a synthesis of 2-aryl-5-(trifluoromethyl)pyrrole compounds of the formula:

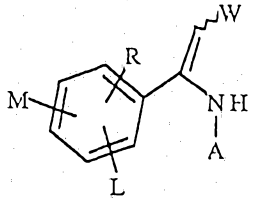


(I)

wherein A is hydrogen, phenyl or C_1-C_6 alkyl optionally substituted with phenyl; W is CN, NO_2, CO_2R_1 or SO_2R_2; L is hydrogen or halogen; M and R are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, CN, NO_2, Cl, Br, F, I, CF_3, R_3CF_2Z, R_4CO or NR_5R_6 and when M and R are on adjacent positions they may be taken together with the carbon atoms to which they are attached to form a ring in which MR represents the structure

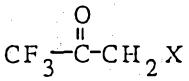
$-OCH_2O-$, $-OCF_2O-$ or $-CH=CH-CH=CH-$;

R_1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl; R_2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl; R_3 is hydrogen, F, CHF_2, CHFCl or CF_3; R_4 is C_1-C_4 alkyl, C_1-C_4 alkoxy or NR_5R_6; R_5 is hydrogen or C_1-C_4 alkyl; R_6 is hydrogen, C_1-C_4 alkyl or R_7CO; R_7 is hydrogen or C_1-C_4 alkyl; Z is $S(O)_n$ or O and n is an integer of 0, 1 or 2 characterized by reacting a compound of formula II



(II)

wherein A, W, L, M and R are described above with about one molar equivalent of a compound of formula III



(III)

wherein X is Cl, Br or I in the presence of an acid and a solvent, via the condensation of a suitable enamine with an α-haloketone.