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COMMONWEALTH OF AUSTRALIA

Case: 39-21(3013)A AS

Patents Act 1952

Form 1

Regulation 9

APPLICATION FOR A STANDARD PATENT OR

A STANDARD PATENT OF ADDITION

We, MONSANTO COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, having its principal place of business at 800 North Lindbergh Boulevard, St. Louis, State of Missouri, United States of America, hereby apply for the grant of a Standard Patent for an invention entitled:

"PROCESS FOR PREPARATION OF FLUOROMETHYL-
SUBSTITUTED PYRIDINE DICARBOXYLATES"

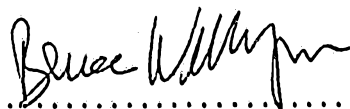
which is described in the accompanying complete specification.

This application is a Convention application and is based on applications numbered 495,185 and 495,174 for a patent or similar protection made in United States of America both being filed on 19th March 1990.

Our address for service is care of E.F. WELLINGTON & CO., Patent and Trade Mark Attorneys, 312 St. Kilda Road, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this 18th day of March, 1991

For and on behalf of
MONSANTO COMPANY,



.....
BRUCE S. WELLINGTON
Patent Attorney for Applicant Company

To: The Commissioner of Patents,
Commonwealth of Australia.

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COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

FORM 8

REGULATION 12(2)

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION
~~XXXXXX~~ FOR A PATENT OR PATENT OF ADDITION.

6 In support of the Convention Application made ~~XXXXXX~~
~~XXXX~~ by MONSANTO COMPANY for a patent for an invention entitled:

PROCESS FOR PREPARATION OF FLUOROMETHYL-SUBSTITUTED
PYRIDINE DICARBOXYLATES

I, William Harry Duffey, General Patent Counsel, Monsanto Company, of 800 North Lindbergh Boulevard, St. Louis, 63167, in the State of Missouri, United States of America, do solemnly and sincerely declare as follows:

1. I am authorized by MONSANTO COMPANY, the applicant for the Patent to make this declaration on its behalf.
2. The basic applications as defined by Section 141 of the Act were made at the Patent Office, Washington, District of Columbia, in the United States of America on the 19th of March 19 90, by WILLIAM HAROLD MILLER and MITCHELL JOEL PULWER.

3. WILLIAM HAROLD MILLER, 1000 Nancy Carol Lane,
Glendale, Missouri 63122 U.S.A.; and
MITCHELL JOEL PULWER, 13115 Old Farm Drive,
St. Louis, Missouri 63146 U.S.A.

6 ~~XX~~ are the actual inventor(s) of the invention, and the facts upon which the MONSANTO COMPANY is entitled to make the application are as follows:
The Company is the assignee of the actual inventor(s).

- 6 4. The basic applications referred to in paragraph 2 of this declaration were the first applications made in a Convention country in respect of the invention, the subject of the application.

DECLARED at St. Louis, Missouri, aforesaid this 20th day of
February, 19 91.

William Harry Duffey
WILLIAM HARRY DUFFEY

To Commissioner of Patents
COMMONWEALTH OF AUSTRALIA



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(12) PATENT ABRIDGMENT (11) Document No. AU-B-73507/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 632911

(54) Title
PROCESS FOR PREPARATION OF FLUOROMETHYL-SUBSTITUTED PYRIDINE DICARBOXYLATES

(51)⁵ International Patent Classification(s)
C07D 213/803 C07D 213/80

(21) Application No. : 73507/91

(22) Application Date : 18.03.91

(30) Priority Data

(31) Number	(32) Date	(33) Country
495174	19.03.90	US UNITED STATES OF AMERICA
495185	19.03.90	US UNITED STATES OF AMERICA

(43) Publication Date : 19.09.91

(44) Publication Date of Accepted Application : 14.01.93

(71) Applicant(s)
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(57) Claim

1. A process for preparing a 4-(lower alkyl)-2-difluoromethyl-6-trifluoromethyl-3,5-pyridinedicarboxylic acid ester from a dihydropyridine starting material having the above substituents at the 3-, 4-, 5-, and 6- positions and having a trifluoromethyl substituent at the 2-position, which comprises contacting the starting material either with at least one half its molar amount of 1,4-diazabicyclo-[2.2.2]-octane (DABCO) or with a catalytic amount of 1,4-diazabicyclo-[2.2.2]-octane and an amount of an additional base sufficient to ensure substantially complete dehydrofluorination.

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COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

FORM 10

Case: 39-21(3013)A A

Application Number:
Lodged:

Class: Int. Class

Complete specification: Lodged:
Accepted:
Published:

Priority:

Related Art:

Name of Applicant: MONSANTO COMPANY

Address of Applicant: 800 North Lindbergh Boulevard,
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MITCHELL JOEL PULWER.

Address for Service: E.F. WELLINGTON & CO.,
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Complete Specification for the invention entitled:

"PROCESS FOR PREPARATION OF FLUOROMETHYL-
SUBSTITUTED PYRIDINE DICARBOXYLATES"

The following statement is a full description of this invention
including the best method of performing it known to us.

Methods for preparation of 2,6-bis(fluorinated methyl)-pyridine dicarboxylates and pyridine dicarbothioates are disclosed in U.S. Patents 4,692,184 and 4,618,679 and in European Patent 135,491. These compounds are useful as herbicides.

DESCRIPTION OF THE PRIOR ART

As used herein, the following terms have the following meanings:

DABCO - 1,4-diazabicyclo-[2.2.2]-octane

DBU - 1,8-diazabicyclo-[5.4.0]-undec-7-ene

ETFAA - ethyl 4,4,4-trifluoro-3-oxo-butanoate

IVA - isovaleraldehyde, or 3-methyl-butanal

NMR - nuclear magnetic resonance

GLC - gas-liquid chromatography

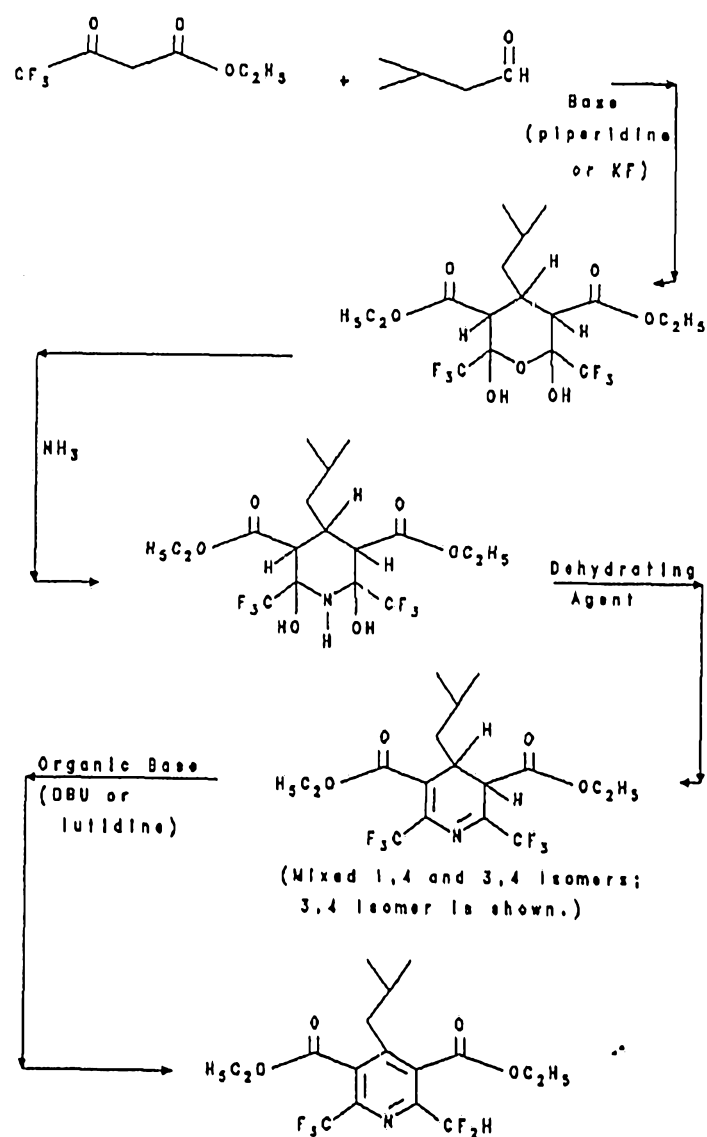
% Assay - weight % desired product compound

% Yield - 100 x mols desired product / mol

initial IVA starting material.

NOTE: Where a yield is shown herein in discussing the effect of varying a process parameter, all process variables not explicitly shown to be varied are held constant.

As outlined in Scheme I, preparation of diethyl 2-difluoromethyl-4-(2-methylpropyl)-6-trifluoromethyl-3,5-pyridinedicarboxylate is accomplished by a Hantzsch-type base catalyzed intermolecular cyclization of ethyl 4,4,4-trifluoro-3-oxo-butanoate (ethyl trifluoroacetoacetate, or ETFAA) and isovaleraldehyde to form a substituted dihydroxypyran, followed by ammonolysis. Dehydration of the resultant dihydroxypiperidines gives a mixture of 1,4 and 3,4 dihydropyridine isomers. Dehydrofluorination of the dihydropyridines using an organic base such as DBU or



Scheme 1

Prior Art Process

2,6-lutidine affords good yields (80% overall) of the pyridine diethylester. Examples 14 and 16 of U.S. Patent 4,692,184 are reproduced below in relevant part and are illustrative of the prior art.

5 Example 14 OF U.S. Patent 4,692,184

Preparation of dimethyl
2-(difluoromethyl)-6-(trifluoromethyl)-4-isobutyl-3,5-
pyridinedicarboxylate

10

(a) Dehydrofluorination Using DBU.

A mixture of 23.0 g (0.0591 mole) of the dihydropyridine, 12.2 g (0.077 mole) of 96% pure DBU, and 100 ml of THF is held at reflux for 3 days and
15 poured into 250 ml of 3N HCl. The oil precipitate is extracted into ether (2x100 ml). The ether extracts are dried (MgSO₄) and concentrated to give 14.4 g of an oil which, contained the desired product and acidic products. This oil is dissolved in ether and extracted
20 with 100 ml of saturated sodium bicarbonate. The ether layer is dried (MgSO₄) and concentrated to give 8.9 g of an oil which is 71% pure desired product.

The sodium bicarbonate extract is acidified with concentrated HCl to give an oil which is extracted into
25 ether. The ether layer is dried (MgSO₄) and concentrated to give 4.8 g of a residue which contained monocarboxylic acid and dicarboxylic acid (9:1) derived from the desired product. This residue is treated with 3.0 g (0.0217 mole) of potassium carbonate, 20 ml of
30 methyl iodide, and 50 ml of acetone. The mixture is held at reflux for 42 hours and concentrated. The residue is treated with water and extracted with ether (2x100 ml). The ether layer is dried and concentrated. The residue is kugelrohr distilled at 1 torr
35 (0.13 kilopascals) (pot temperature of 130°C.) to give 5.1 g (23.4% from the dihydropyridine) of the desired

product. The 71% pure desired product described previously was chromatographed by HPLC using 3% ethyl acetate/cyclohexane as eluent to give an earlier fraction (0.79 g, retention time 7-8.5 min) which was identified as methyl 6-(difluoromethyl)-4-(isobutyl)-2-(trifluoromethyl)-3-pyridinecarboxylate. The second fraction is an additional 6.4 g (29.4%) of pure pyridine product.

(b) Dehydrofluorination Using Tributylamine.

10 A mixture of 38.9 g of a 80% pure dihydropyridine and 20.5 g of tributylamine is heated to 155°C in 30 minutes. The reaction mixture was cooled to 30°C and diluted with 100 ml of toluene. The toluene solution is washed successively with 6N hydrochloric acid, saturated
15 sodium bicarbonate, and brine, dried and concentrated to give 36.4 g of a 73% pure product which corresponds to a 85% yield. This reaction can also be carried out in excess of tributylamine (10 equivalent) giving essentially similar results.

20 (c) Dehydrofluorination Using Tributylamine in Toluene.

A mixture of 38.9 g of 80% pure dihydropyridine, 20.4 of tributylamine and 30 ml of toluene is heated to 115°C in 40 minutes and held at 115°C for 1 hour and 40 minutes. The reaction mixture is cooled and worked
25 up as in (b) to give 36.3 g of a 76% pure product which corresponds to a 90% yield.

(d) Dehydrofluorination Using Triethylamine.

A mixture of 11.8 g of 80% pure dihydropyridine and 3.34 g of triethylamine is heated at 100°C for
30 10 minutes, then at 125°C for 10 minutes. The reaction mixture was cooled and worked up as in (b) to give 8.14 g of a 76% pure product which corresponds to a 63% yield.

(e) Dehydrofluorination Using 2,6-Lutidine in the Presence of a Catalytic Amount Of DBU.

35

A mixture of 5.0 g of dihydropyridine and 2.13 g of 2,6-lutidine is heated at 143°C for 30 minutes. Two drops of DBU is added and the reaction mixture is heated for an additional one hour and 30 minutes, cooled and worked up as in (b) to give 4.23 g of the desired product. The reaction can also be carried out in excess of 2,6-lutidine and catalytic amount of DBU without solvent or in the presence of toluene as solvent giving similar results.

EXAMPLE 16 OF U.S. Patent 4,692,184

Preparation of diethyl

2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate

A mixture of 10.0 g (0.0240 mole) of diethyl 2,6-bis(-trifluoromethyl)-1, 4-dihydro-4-isobutyl-3, 5-pyridine-dicarboxylate, 3.65 g (0.0240 mole) of DBU and 150 ml of THF is held at reflux for 18 hours and concentrated. The residue is dissolved in ether and washed with diluted hydrochloric acid, dried (MgSO₄) and concentrated. The residue is kugelrohr distilled at 0.1 torr (0.01 kilopascals) to give 4.80 g (50%) of the desired product.

SUMMARY OF THE INVENTION

The present invention provides a process for preparing a 4-(lower alkyl)-2-difluoromethyl-6-trifluoromethyl-3, 5-pyridinedicarboxylic acid ester from a dihydropyridine starting material having the above substituents at the 3-, 4-, 5-, and 6- positions and having a trifluoromethyl substituent at the 2-position, which comprises contacting the starting material either with at least one half its molar amount of 1,4-diazabicyclo-[2.2.2]-octane (DABCO) or with a catalytic amount of 1,4-diazabicyclo-[2.2.2]-octane and an amount of an additional base sufficient to ensure substantially complete dehydrofluorination.



In preferred embodiments of the present invention, the process is characterized in that:

- 5 (i) the amount of DABCO is about 1.0 times the molar amount of the dihydropyridine starting material; or
- (ii) the catalytic amount of DABCO is about 0.01 to less than 0.5 of the molar amount of the dihydropyridine starting material; or
- 10 (iii) the DABCO is in the form of an aqueous solution; or
- (iv) the process is conducted in an inert aprotic solvent; or
- 15 (v) the aprotic solvent is selected from benzene, toluene, xylenes, cyclohexane, methylcyclohexane, monochlorobenzene, and butyronitrile; or
- (vi) the process is conducted in the substantial absence of molecular oxygen.

20 In particular, the present invention provides a process for preparing 2-difluoromethyl-6-trifluoromethyl-4-(2-methylpropyl)-3, 5-pyridinedicarboxylic acid esters selected from dimethyl and diethyl esters from a dihydropyridine starting material having the above substituents at the 3-, 4-, 5-, and 6- positions and having a trifluoromethyl substituent at the 2-position, which comprises

25 contacting the starting material either with at least one half its molar amount of 1, 4-diazabicyclo-[2.2.2]-octane (DABCO) or with a catalytic amount of 1, 4-diazabicyclo-[2.2.2]-octane with an amount of an additional base



sufficient to ensure substantially complete dehydrofluorination.

DESCRIPTION OF THE INVENTION

As in the Comparative Example above, the process of this invention is illustrated in detail below with reference to the preparation of the specific pyridine dicarboxylate compound prepared in Example 16 of U.S. Patent 4,692,184.

To improve yield of the desired pyridine dicarboxylate product, the following process of the present invention generally employs the same reaction steps as Scheme I. According to the present invention, the final step of the process of Scheme I, dehydrofluorination of the dihydropyridines prepared in the previous step to afford the final pyridine dicarboxylate product, is accomplished by treatment with DABCO in contrast to the prior art dehydrofluorination step which employs DBU or 2, 6-lutidine as the organic base.

In this process step, DABCO may be employed in either stoichiometric or catalytic amounts. Because DABCO is a difunctional base, the stoichiometric DABCO method uses at least one half mol of DABCO per mol of starting IVA. Use of about one mol of DABCO is preferred. The catalytic DABCO method, on the other hand, employs substantially less DABCO such as about 0.01 to less than 0.50, and preferably about 0.05 to about 0.20 mol DABCO per theoretical mol of dihydropyridines (i.e., per mol of original IVA) in conjunction with an amount of an additional base which is adequate to effect substantially complete dehydrofluorination. The additional base used in the process in which DABCO is employed as a catalyst is a base selected from the group consisting of



KOH, NaOH, K_2CO_3 , Na_2CO_3 , $Ca(OH)_2$, triethylamine, and tributylamine. Use of a catalytic amount of DABCO thus may result in a substantial economic benefit in the process.

5 Whichever dehydrofluorination method is employed, it is desirable to have some water present in the process to act as a solvent for salts (such as, for example, the hydrofluoride salt of DABCO and/or of the additional base if one is used) which may be formed in the process.

10 Whichever specific dehydrofluorination method is used, it is desirable to conduct this process step in the presence of an inert aprotic solvent. Such solvents include, but are not limited to, benzene, toluene, xylenes, cyclohexane, methylcyclohexane, monochlorobenzene, buty-
15 ronitrile, and like solvents. Moreover, while the temperature used in this process step is not particularly critical, it is preferred to use temperatures in the range of 50°C to 120°C, preferably 60°C to 90°C.

20 Using the stoichiometric DABCO dehydrofluorination method, the toluene solution from Step 2 is sparged vigorously with nitrogen to minimize oxidation byproducts. DABCO in an aqueous solution preferably at or near saturation in a ratio greater than 0.50 mol, and preferably about 1 mol per estimated mol of dihydropyridine is likewise sparged with nitrogen, and the two solutions are combined.

25 Using the catalytic DABCO dehydrofluorination method, the toluene solution from Step 2 is sparged vigorously with nitrogen to minimize formation of oxidation byproducts. An aqueous solution of 40% K_2CO_3 containing 0.6 to 1.0 mol K_2CO_3 per theoretical mol of dihydropyridine (or per
30 mol/original mol IVA) is likewise degassed with nitrogen. The two solutions are combined and a catalytic

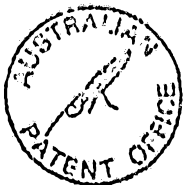


amount (5 to 20 mol % based on mols of original IVA charge) of DABCO is added as a solid.

Example 1

5 To a 3 L flask was added 502 g (1.2 mol) of
diethyl 1, 4-dihydro-2, 6-bis(trifluoromethyl)-4-(2-methyl-
propyl)-3, 5-pyridinedicarboxylate in 600 g of toluene.
This solution was sparged subsurface with N₂ for 30
minutes. Subsequently, 146 g (1.3 mol) of DABCO and 219 g
10 of H₂O were added as an aqueous solution. The reaction
mixture was heated at 75-80°C for 4.75 hours while it was
monitored for completion by GC. At completion of the
reaction, the mixture was cooled to 50°C and the aqueous
phase was removed. The toluene solution was washed with
15 130 g of a 15% brine solution, and the pH of the aqueous
phase was adjusted to 4-5 with a small amount of
concentrated sulfuric acid. The aqueous phase was then
removed to leave a toluene solution of the desired
product. Assay of the reaction mixture indicated the
20 presence of 454 g (95%) of diethyl 2-difluoromethyl-4-
(2-methylpropyl)-6-trifluoromethyl-3, 5-pyridine-
dicarboxylate.

25 The experimental procedure above is
representative of the procedure for the use of DABCO in the
dehydrofluorination reaction. Additional examples
utilizing different amounts of the base, solvents, and
temperatures are included below. All materials were



charged on the basis of the amount of dihydropyridine starting material used.

	<u>Example</u>	<u>Mols DABCO</u>	<u>Solvent</u>	<u>Temp</u> <u>(°C)</u>	<u>Time</u> <u>(h)</u>	<u>Yield</u> <u>(%)</u>
5	2	1.1	toluene	90	2	100
	3	1.1	toluene	70	6	95
	4	1.1	toluene	50	7	93
	5	1.5	methylcyclohexane	70	3	83
10	6	1.5	CCl ₄	70	3	73
	7	1.25	toluene/water	70	2	86
	8	1.0	toluene/water	90	3	86
	9	0.6	toluene/water	80	3	85

While the process of this invention has been specifically illustrated in terms of a specific pyridine dicarboxylate product, it is equally applicable to the preparation of other pyridine compounds. Selection of the aldehyde starting material will, of course, determine the substituent at the 4-position of the final pyridine product. Likewise it is evident that lower alkyl trifluoroacetoacetate esters other than the ethyl ester may equally well be employed. Accordingly, the scope of this invention is to be limited only in accordance with the annexed claims.

The matter contained in each of the following claims is to be read as part of the general description of the present invention.

The claims defining the invention are as follows:

1. A process for preparing a 4-(lower alkyl)-2-difluoromethyl-6-trifluoromethyl-3,5-pyridinedicarboxylic acid ester from a dihydropyridine starting material having the above substituents at the 3-, 4-, 5-, and 6- positions and having a trifluoromethyl substituent at the 2-position, which comprises contacting the starting material either with at least one half its molar amount of 1,4-diazabicyclo-[2.2.2]-octane (DABCO) or with a catalytic amount of 1,4-diazabicyclo-[2.2.2]-octane and an amount of an additional base sufficient to ensure substantially complete dehydrofluorination.

2. A process according to Claim 1 wherein the amount of DABCO is about 1.0 times the molar amount of the dihydropyridine starting material.

3. A process according to Claim 1 wherein the catalytic amount of DABCO is about 0.01 to less than 0.5 of the molar amount of the dihydropyridine starting material.

4. A process according to any one of claims 1 to 3 wherein the DABCO is in the form of an aqueous solution.

5. A process according to Claim 4 wherein the process is conducted in an inert aprotic solvent.

6. A process according to Claim 5 wherein the aprotic solvent is selected from benzene, toluene, xylenes, cyclohexane, methylcyclohexane, monochlorobenzene, and butyronitrile.

7. A process according to any one of Claims 1 to 6 wherein the process is conducted in the substantial absence of molecular oxygen.

8. A process for preparing 2-difluoromethyl-6-trifluoromethyl-4-(2-methylpropyl)-3,5-pyridinedicarboxylic acid esters selected from dimethyl and diethyl esters from a dihydropyridine starting material having the above substituents at the 3-, 4-,



5-, and 6- positions and having a trifluoromethyl substituent at the 2-position, which comprises contacting the starting material either with at least one half its molar amount of 1,4-diazabicyclo-[2.2.2]-octane (DABCO) or with a catalytic amount of 1,4-diazabicyclo-[2.2.2]-octane with an amount of an additional base sufficient to ensure substantially complete dehydrofluorination.

9. A process according to Claim 8 wherein the amount of DABCO is about 1.0 times the molar amount of the dihydropyridine starting material.

10. A process according to Claim 8 or 9 wherein the DABCO is in the form of an aqueous solution.

11. A process according to any one of Claims 8 to 10 wherein the process is conducted in an inert aprotic solvent.

12. A process according to Claim 11 wherein the aprotic solvent is selected from benzene, toluene, xylenes, methylcyclohexane, monochlorobenzene, and butyronitrile.

13. A process according to any one of Claims 8 to 12 wherein the process is conducted in the substantial absence of molecular oxygen.

14. A process according to Claim 1, substantially as hereinbefore described.

15. A process according to Claim 8, substantially as hereinbefore described.

16. A 4-(lower alkyl)-2-difluoromethyl-6-trifluoromethyl-3,5-pyridinedicarboxylic acid ester when prepared by the process of any one of claims 1 to 7 and 14.

17. 2-Difluoromethyl-6-trifluoromethyl-4-(2-methylpropyl)-3,5-pyridinedicarboxylic acid esters



selected from dimethyl and diethyl esters when prepared
by the process of any one of claims 8 to 13 and 15.

DATED this 18th day of March, 1991

MONSANTO COMPANY,
By its Patent Attorneys,
E. F. WELLINGTON & CO.,
By:

[Handwritten signature]

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BRUCE S. WELLINGTON

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