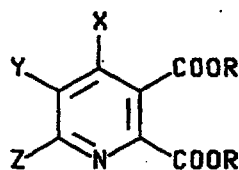


**PROCESS FOR THE PREPARATION OF SUBSTITUTED AND
UNSUBSTITUTED-2,3-PYRIDINEDICARBOXYLATES FROM
CHLOROMALEATE OR CHLOROFUMARATE OR MIXTURES THEREOF**

Pyridine-2,3-dicarboxylates are useful intermediates in the preparation of highly effective herbicidal 2-(2-imidazolin-2-yl)nicotinic acids, esters and salts. It is an object of this invention to
5 provide a method for the preparation of substituted and unsubstituted-2,3-pyridinedicarboxylates utilizing dialkyl chloromaleate or dialkyl chlorofumarate or a mixture thereof, an ammonium salt, optionally in the presence of ammonia and an appropriately substituted
10 α,β -unsaturated aldehyde or ketone.

The invention herein described relates to a novel method for the preparation of substituted and unsubstituted 2,3-pyridinecarboxylates of formula I

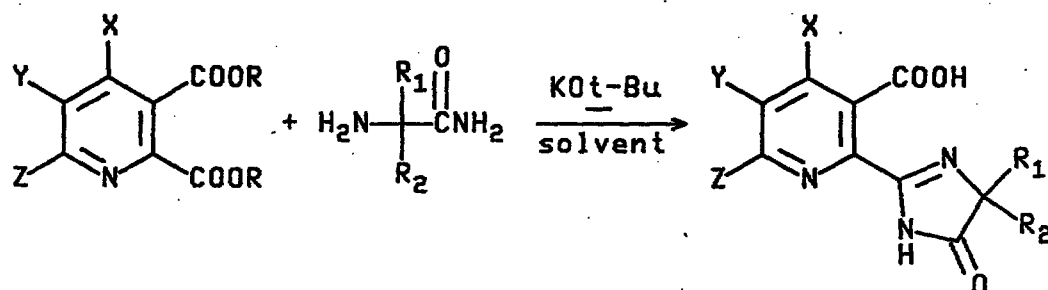


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20 wherein R is C_1-C_6 alkyl; X and Z are independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_5 alkenyl and Y is hydrogen, halogen, C_1-C_6 alkyl optionally substituted with one to three halogens, hydroxy
25 groups, C_1-C_4 alkoxy groups or C_1-C_4 alkylthio groups,

C₁-C₄ alkoxy carbonyl, aminocarbonyl, phenyl, substituted phenyl, phenoxy, substituted phenoxy, phenylthio or substituted phenylthio. Compounds of formula I are useful as intermediates in the preparation of herbicidal 2-(2-imidazolin-2-yl)nicotines. Among the methods of preparation of said herbicidal nicotines is that described in U.S. Patent 4,758,667 and illustrated below.

10

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wherein R₁ is hydrogen or C₁-C₄ alkyl; R₂ is hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl or R₁ and R₂ may be taken together to form a C₃-C₆ cycloalkyl optionally substituted with methyl and X, Y and Z are as described for formula I.

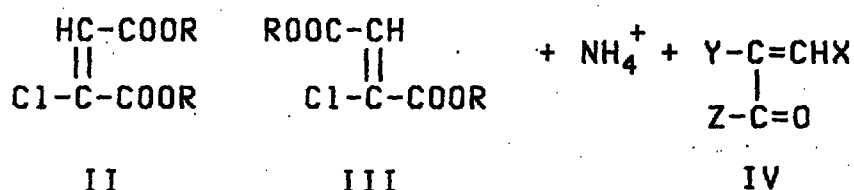
It has now been found that pyridine-2,3-dicarboxylates of formula I can be prepared efficiently and effectively from chloromaleates of formula II or chlorofumarates of formula III or mixtures thereof wherein R is C₁-C₆ alkyl by reacting the chloromaleate or chlorofumarate with at least one molar equivalent of an ammonium salt such as ammonium acetate, optionally in the presence of ammonia, in a suitable solvent such as a C₁-C₄ alkylalcohol to form an enamine intermediate and reacting said intermediate with at least one molar equivalent of an α,β -unsaturated aldehyde or ketone of formula IV wherein X, Y and Z are as described for

formula I in the presence of an acid such as acetic acid. The process is shown in flow diagram I.

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Flow Diagram I

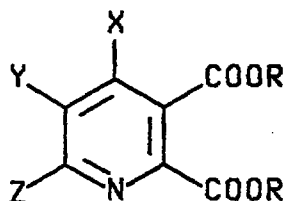
10



15

$\downarrow$ H^+
Solvent

20



25

Ammonium salts which may be used in the process of the invention include ammonium acetate, ammonium propionate, ammonium sulfate, ammonium carbonate, ammonium bicarbonate, ammonium carbamate, ammonium sulfamate and the like.

30

In one embodiment of the invention, a polar solvent may be utilized such as an alcohol, nitrile such as acetonitrile, a carboxylic acid amide such as N,N-dimethylformamide, N-methylpyrrolidone, a sulfoxide such as dimethylsulfoxide, a sulfone and the like.

35

Among the α,β -unsaturated aldehydes or ketones of formula IV which may be used in the process of the invention are acrolein, methacrolein,

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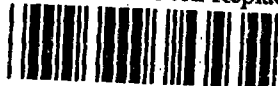
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ethacrolein, crotonaldehyde, methyl vinyl ketone, α -n-butylacrolein, 4-methyl-2-hexanal, α -methoxymethacrolein, α -chloromethacrolein, α -trifluoromethacrolein, cinnamaldehyde, α -ethoxyacrolein, methyl α -formyl-
5 acrylate, α -(2-cyanoethyl)acrolein and the like.

In a further embodiment of the invention, the reaction mixture comprising the above-formed intermediate and the α,β -unsaturated aldehyde or ketone of formula IV may be treated with a dehydrogenation
10 catalyst such as that which is conventional in the art including metals or compounds of platinum, palladium, ruthenium, iridium, nickel, iron, copper, antimony, cobalt, rhodium and the like. The dehydrogenation catalyst is commonly used in the form of the dehydro-
15 genation metal or compound thereof deposited on a suitable support such as alumina, carbon, clay, zeolite, chromia, zirconia and the like.

Thus, pyridine-2,3-dicarboxylates containing substituents in the 4,5 and 6 positions may be conveniently prepared by admixing a formula II dialkyl chloromaleate or a formula III dialkyl chlorofumarate with at least one molar equivalent of an ammonium salt optionally in the presence of anhydrous ammonia in a suitable solvent, optionally heating said mixture until
20 reaction is essentially complete, optionally filtering said reaction mixture and adding to the filtrate or to the unfiltered reaction mixture an acid such as a mineral acid, sulfuric acid, phosphoric acid, an organic acid such as formic acid, acetic acid or propionic acid
25 and the like to obtain a pH of at least about 4 and at least one molar equivalent of an α,β -unsaturated aldehyde or ketone of formula IV optionally in the presence of a dehydrogenation catalyst, optionally heating the resulting reaction mixture until formation
30 of the desired formula I pyridinedicarboxylate is
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complete. The reaction product can be isolated using standard purification techniques such as fractional distillation, recrystallization, extraction, liquid chromatography and the like.

5 The rate of formation of the enamine intermediate and the formula I pyridinedicarboxylate is temperature dependent, thus, reaction time can be effectively diminished by heating the reaction mixtures at temperatures of about 45°C or greater.

10 In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating certain more specific details thereof and the invention is not to be deemed limited thereby. The terms ¹HNMR
15 and IR designate proton nuclear magnetic resonance and infrared respectively. Unless otherwise noted, all parts are parts by weight.

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EXAMPLE 1

Preparation of diethyl 5-ethyl-2,3-pyridinedicarboxylate from diethyl chloromaleate in the presence of ammonia and ammonium acetate

A mixture of diethyl chloromaleate (4.10 g, 0.02 mol) and ammonium acetate (1.54 g, 0.02 mol) in ethanol is treated with anhydrous ammonia (1.0 g, 0.06 mol), stirred at room temperature 16 hours, treated
5 with 10 mL of acetic acid and 2-ethacrolein (5.04 g, 0.06 mol) in two portions over a total of 16 hours at 70°C and concentrated in vacuo to afford an oil residue. The residue is taken up in toluene, filtered and the filtrate is evaporated to dryness in vacuo to
10 afford an oil. The resultant oil is vacuum distilled to afford the title product as a tan oil, bp 151-152°C/2 mm Hg.

EXAMPLE 2

15

Preparation of diethyl 5-ethyl-2,3-pyridinedicarboxylate from diethyl chloromaleate in the presence of ammonium acetate

A mixture of a total of 4.62 g (0.06 mol) of
20 ammonium acetate and diethyl chloromaleate (4.10 g, 0.02 mol) in ethanol is heated at 70°C for a total of 48 hours, filtered and the filter cake is washed with ethanol. The combined filtrates are treated with 10 mL acetic acid and 2-ethacrolein (4.62 g, 0.06 mol) in two
25 portions, heated at 70°C for a total of 6 hours and concentrated in vacuo to give an oil residue. The thus-obtained oil is vacuum distilled to afford the title product as a tan oil, bp 151-152°C/2 mm Hg.

EXAMPLE 3

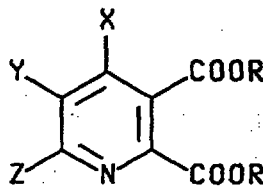
Preparation of diethyl 5-ethyl-2,3-pyridinedicarboxylate from diethyl chlorofumarate

A stirred mixture of ammonium acetate (7.0 g, 0.09 mol), anhydrous ammonia (0.2 g, 0.012 mol) and a 7:1 mixture of diethyl chlorofumarate and diethyl chloromaleate in ethanol is heated at 70°C for 12 hours, cooled to 25°C and filtered. The filter cake is washed with ethanol and the combined filtrates are concentrated in vacuo. The thus-obtained concentrated reaction mixture is treated with acetic acid and 2-ethacrolein (5.0 g, 0.06 mol), heated at 70°C with stirring for 6 hours and concentrated in vacuo to give an oil residue. The resultant residue is taken up in methylene chloride, washed with water and fractionally distilled to obtain the title product as a tan oil, bp 151-152°C/2 mm Hg.

EXAMPLE 4

Preparation of dialkyl substituted-2,3-pyridinedicarboxylate from dialkyl chloromaleate

Using essentially the same procedure described in Example 1 and substituting the appropriate α,β -unsaturated aldehyde, the following compounds are obtained and identified by $^1\text{HNMR}$ and IR spectral analysis.



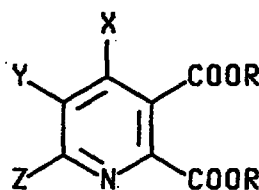
	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>
	H	CH ₃	H	C ₂ H ₅
	H	CH ₂ OCH ₃	H	C ₂ H ₅
	H	CH ₂ Cl	H	C ₂ H ₅
5	H	H	H	C ₂ H ₅

EXAMPLE 5

10 **Preparation of dialkyl substituted-2,3-pyridinedicarboxylate from dialkyl chlorofumarate**

Using essentially the same procedure described in Example 3 and substituting the appropriate α,β -unsaturated aldehyde gives the following compounds

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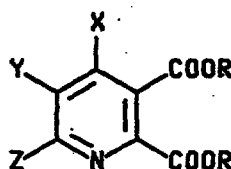
	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>
	H	CH ₃	H	C ₂ H ₅
	H	CH ₂ OCH ₃	H	C ₂ H ₅
	H	CH ₂ Cl	H	C ₂ H ₅
25	H	H	H	C ₂ H ₅

The above compounds are identified by ¹HNMR and IR spectral analysis.



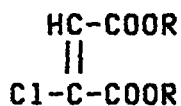
WHAT IS CLAIMED IS:

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

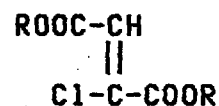


I

wherein R is C₁-C₆ alkyl; X and Z are independently hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy or C₂-C₅ alkenyl and Y is hydrogen, halogen, C₁-C₆ alkyl optionally substituted with one to three halogens, hydroxy groups, C₁-C₄ alkoxy groups or C₁-C₄ alkylthio groups, C₁-C₄ alkoxy carbonyl, aminocarbonyl, phenylthio, substituted phenylthio, phenoxy, substituted phenoxy, phenyl or substituted phenyl which comprises reacting a compound of formula II or formula III or a mixture thereof

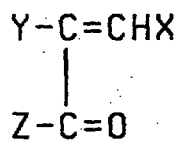


II



III

wherein R is C₁-C₆ alkyl with an ammonium salt in the presence of a solvent, optionally in the presence of ammonia, to form an intermediate, reacting said intermediate with an α,β -unsaturated aldehyde or ketone of formula IV



IV

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wherein X, Y and Z are as described above in the presence of an acid to form the formula I pyridine-dicarboxylate compound.

2. The process according to claim 1 for the preparation of the pyridinedicarboxylate compound of formula I wherein X and Z are hydrogen and Y is hydrogen, halogen or C_1-C_4 alkyl optionally substituted with one to three halogens, C_1-C_4 alkoxy groups or C_1-C_4 alkylthio groups.

3. The process according to claim 1 wherein the solvent is a polar solvent, the acid is acetic acid and the intermediate is formed at a temperature of $45^{\circ}C$ or greater.

4. The process according to claim 1 wherein the formula I pyridinedicarboxylate compound is formed at a temperature of $45^{\circ}C$ or greater.

5. The process according to claim 2 wherein the formula I compound prepared is selected from the group consisting of dialkyl pyridine-2,3-dicarboxylate, dialkyl 5-methyl-2,3-pyridinedicarboxylate, dialkyl 5-ethyl-2,3-pyridinedicarboxylate, dialkyl 5-(methoxymethyl)-2,3-pyridinedicarboxylate and dialkyl 5-(chloromethyl)-2,3-pyridinedicarboxylate.

6. The process according to claim 5 wherein the formula I compound is selected from the group consisting of diethyl pyridine-2,3-dicarboxylate, diethyl 5-methyl-2,3-pyridinedicarboxylate, diethyl 5-ethyl-2,3-pyridinedicarboxylate, diethyl 5-(methoxymethyl)-2,3-pyridinedicarboxylate and diethyl 5-(chloromethyl)-2,3-pyridinedicarboxylate.

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7. A pyridinedicarboxylate compound of formula I prepared by the process according to claim 1.

8. A pyridinedicarboxylate compound of formula I wherein X and Z are hydrogen and Y is hydrogen, halogen or C_1-C_4 alkyl optionally substituted with one to three halogens, C_1-C_4 alkoxy groups or C_1-C_4 alkylthio groups prepared by the process according to claim 1.

9. A pyridinedicarboxylate compound of formula I, diethyl 5-ethyl-2,3-pyridinedicarboxylate prepared by the process according to claim 1.

10. A pyridinedicarboxylate compound of formula I, diethyl 5-(methoxymethyl)-2,3-pyridinedicarboxylate prepared by the process according to claim 1.



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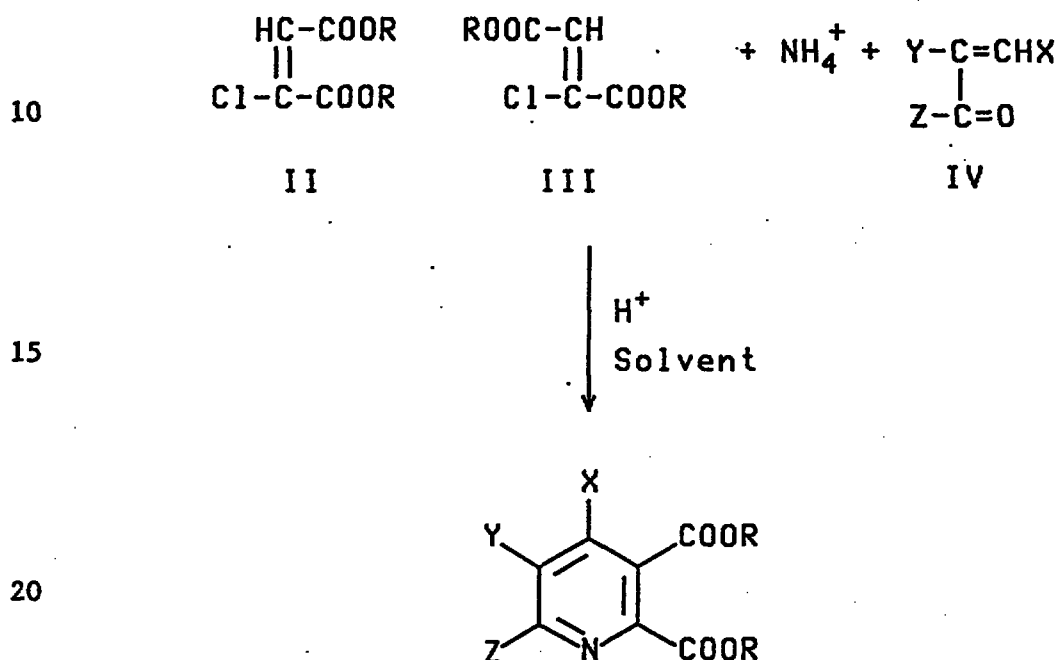


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formula I in the presence of an acid such as acetic acid. The process is shown in flow diagram I.

5 Flow Diagram I



Ammonium salts which may be used in the process of the invention include ammonium acetate, ammonium propionate, ammonium sulfate, ammonium carbonate, ammonium bicarbonate, ammonium carbamate, ammonium sulfamate.

In one embodiment of the invention, a polar solvent may be utilized such as an alcohol, nitrile such as acetonitrile, a carboxylic acid amide such as N,N-dimethylformamide, N-methylpyrrolidone, a sulfoxide such as dimethylsulfoxide, a sulfone.

Among the α,β -unsaturated aldehydes or ketones of formula IV which may be used in the process of the invention are acrolein, methacrolein,

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ethacrolein, crotonaldehyde, methyl vinyl ketone, α -n-butylacrolein, 4-methyl-2-hexanal, α -methoxymethacrolein, α -chloromethacrolein, α -trifluoromethacrolein, cinnamaldehyde, α -ethoxyacrolein, methyl α -formylacrylate, α -(2-cyanoethyl)acrolein.

In a further embodiment of the invention, the reaction mixture comprising the above-formed intermediate and the α,β -unsaturated aldehyde or ketone of formula IV may be treated with a dehydrogenation catalyst such as that which is conventional in the art including metals or compounds of platinum, palladium, ruthenium, iridium, nickel, iron, copper, antimony, cobalt, rhodium. The dehydrogenation catalyst is commonly used in the form of the dehydrogenation metal or compound thereof deposited on a suitable support such as alumina, carbon, clay, zeolite, chromia, zirconia.

Thus, pyridine-2,3-dicarboxylates containing substituents in the 4,5 and 6 positions may be conveniently prepared by admixing a formula II dialkyl chloromaleate or a formula III dialkyl chlorofumarate with at least one molar equivalent of an ammonium salt optionally in the presence of anhydrous ammonia in a suitable solvent, optionally heating said mixture until reaction is essentially complete, optionally filtering said reaction mixture and adding to the filtrate or to the unfiltered reaction mixture an acid such as a mineral acid, sulfuric acid, phosphoric acid, an organic acid such as formic acid, acetic acid or propionic acid and the like to obtain a pH of at least about .4 and at least one molar equivalent of an α,β -unsaturated aldehyde or ketone of formula IV optionally in the presence of a dehydrogenation catalyst, optionally heating the resulting reaction mixture until formation of the desired formula I pyridinedicarboxylate is

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complete. The reaction product can be isolated using standard purification techniques such as fractional distillation, recrystallization, extraction, liquid chromatography.

5 The rate of formation of the enamine intermediate and the formula I pyridinedicarboxylate is temperature dependent, thus, reaction time can be effectively diminished by heating the reaction mixtures at temperatures of about 45°C or greater.

10 In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating certain more specific details thereof and the invention is not to be deemed limited thereby. The terms ¹HNMR
15 and IR designate proton nuclear magnetic resonance and infrared respectively. Unless otherwise noted, all parts are parts by weight.

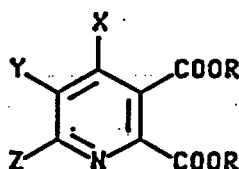
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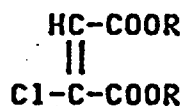
CLAIMS:

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

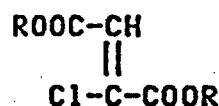


I

wherein R is C₁-C₆ alkyl; X and Z are independently hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy or C₂-C₅ alkenyl and Y is hydrogen, halogen, C₁-C₆ alkyl optionally substituted with one to three halogens, hydroxy groups, C₁-C₄ alkoxy groups or C₁-C₄ alkylthio groups, C₁-C₄ alkoxy carbonyl, aminocarbonyl, phenylthio, substituted phenylthio, phenoxy, substituted phenoxy, phenyl or substituted phenyl which comprises reacting a compound of formula II or formula III or a mixture thereof

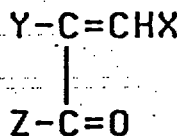


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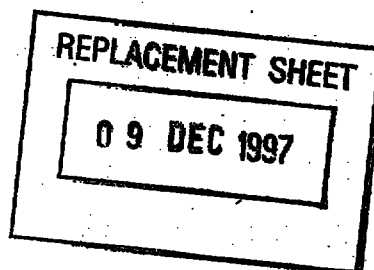


III

wherein R is C₁-C₆ alkyl with an ammonium salt in the presence of a solvent, optionally in the presence of ammonia, to form an intermediate, reacting said intermediate with at least one molar equivalent of an $\alpha\beta$ -unsaturated aldehyde or ketone of formula IV



IV





wherein X, Y and Z are as described above in the presence of an acid which has been added to obtain a pH of at least 4 to form the formula I pyridinedicarboxylate compound.

2. The process according to claim 1 for the preparation of the pyridinedicarboxylate compound of formula I wherein X and Z are hydrogen and Y is hydrogen, halogen or C_1-C_4 alkyl optionally substituted with one to three halogens, C_1-C_4 alkoxy groups or C_1-C_4 alkylthio groups.

3. The process according to claim 1 wherein the solvent is a polar solvent, the acid is acetic acid and the intermediate is formed at a temperature of 45°C or greater.

4. The process according to claim 1 wherein the formula I pyridinedicarboxylate compound is formed at a temperature of 45°C or greater.

5. The process according to claim 2 wherein the formula I compound prepared is selected from the group consisting of dialkyl pyridine-2,3-dicarboxylate, dialkyl 5-methyl-2,3-pyridinedicarboxylate, dialkyl 5-ethyl-2,3-pyridinedicarboxylate, dialkyl 5-(methoxymethyl)-2,3-pyridinedicarboxylate and dialkyl 5-(chloromethyl)-2,3-pyridinedicarboxylate.

6. The process according to claim 5 wherein the formula I compound is selected from the group consisting of diethyl pyridine-2,3-dicarboxylate, diethyl 5-methyl-2,3-pyridinedicarboxylate, diethyl 5-ethyl-2,3-pyridinedicarboxylate, diethyl 5-(methoxymethyl)-2,3-pyridinedicarboxylate and diethyl 5-(chloromethyl)-2,3-pyridinedicarboxylate.

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**PROCESS FOR THE PREPARATION OF SUBSTITUTED AND
UNSUBSTITUTED-2,3-PYRIDINEDICARBOXYLATES FROM
CHLOROMALEATE OR CHLOROFUMARATE OR MIXTURES THEREOF**

ABSTRACT

There is provided a process for the preparation of dialkyl pyridinedicarboxylate compounds and derivatives thereof by reacting a dialkyl chloromaleate or chlorofumarate or a mixture thereof with an ammonium salt optionally in the presence of ammonia and an appropriately substituted α,β -unsaturated aldehyde or ketone.