COMMONWEALTH OF AUSTRALIA

Patents Act 1952

Case 09-21(2657)A AS

Form 1 Regulation 9

APPLICATION FOR A STANDARD PATENT OR
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:

"PREPARATION OF N-ACYL-AMINOMETHYLPHOSPHONATES"

which is described in the accompanying complete specification.

This application is a Convention application and is based on an application numbered 275,862 for a patent or similar protection made in United States of America on 25th November 1988.

Our address for service is care of E. F. WELLINGTON & CO., Patent Attorneys, 457 St. Kilda Road, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this 24th day of November, A.D. 1989

For and on behalf of
MONSANTO COMPANY,
By:

. . . . . .

BRUCE S. WELLINGTON
Patent Attorney for Applicant

To: The Commissioner of Patents,
Commonwealth of Australia

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

FORM 8 REGULATION 12(2)

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION ~~UNDER PART XVI~~ FOR A PATENT OR PATENT OF ADDITION.

In support of the Convention Application made ~~under Part XVI of the Patents Act~~ 1952 by MONSANTO COMPANY for a patent for an invention entitled:

PREPARATION OF N-ACYL-AMINOMETHYLPHOSPHONATES

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 application as defined by Section 141 of the Act was made at the Patent Office, Washington, District of Columbia, in the United States of America on the 25th of November 1988, by Sherrol Lee Baysdon and Donald Lee Fields, Jr.

3. Sherrol Lee Baysdon, 2016 Emerald Crest Court, Chesterfield, Missouri 63017, U.S.A., and Donald Lee Fields, Jr., 406 Stephanie Lane, Manchester, Missouri 63011, U.S.A.,

~~is~~ 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).

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

DECLARED at St. Louis, Missouri, aforesaid this 14th day of September, 1989.

William Harry Duffey

WILLIAM HARRY DUFFEY

To Commissioner of Patents
COMMONWEALTH OF AUSTRALIA

(12) PATENT ABRIDGMENT (11) Document No. AU-B-45523/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 616818

(54) Title
PREPARATION OF N-ACYL-AMINOMETHYLPHOSPHONATES

International Patent Classification(s)
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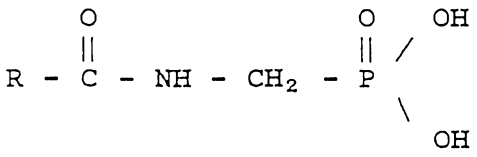
(71) Applicant(s)
MONSANTO COMPANY

(72) Inventor(s)
SHERROL LEE BAYSDON; DONALD LEE FIELDS JR.

(74) Attorney or Agent
E F WELLINGTON & CO , 312 St Kilda Road, MELBOURNE VIC 3004

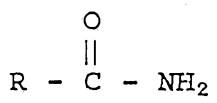
(57) Claim

1. A process for the preparation of N-acylaminomethylphosphonic acids represented by the formula



wherein R is selected from the group consisting of methyl and aryl, which comprises:

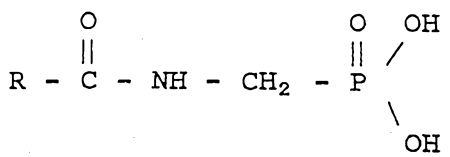
(a) bringing together in an anhydrous organic acid, an amide represented by the formula



wherein R is as defined above and paraformaldehyde; and thereafter,

(b) adding phosphorous trihalide to the reaction mixture.

10. A process for the preparation of an N-acylaminomethylphosphonic acid represented by the formula



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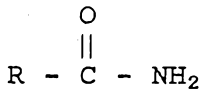
wherein R is selected from the group consisting of methyl and aryl, which comprises:

(a) adding paraformaldehyde and an amide represented by the formula



wherein R is as defined above, to glacial acetic acid;

(b) heating the glacial acetic acid containing the amide and the paraformaldehyde to form a solution;

(c) adding phosphorous trichloride to the solution;

(d) heating the solution with the phosphorous trichloride to about 80°C and about 120°C.

COMMONWEALTH OF AUSTRALIA 616818

PATENTS ACT 1952

FORM 10

CASE: 09-21(2657)A AS

Application Number:
Lodged:

Class: Int. Class

Complete specification: Lodged:
Accepted:
Published:

Pricrity:

Related Art:

Name of Applicant: MONSANTO COMPANY

Address of Applicant: 800 North Lindbergh Boulevard,
St. Louis, Missouri 63177, U.S.A.

Actual Inventor: SHERROL LEE BAYSDON; and
DONALD LEE FIELDS, JR.

Address for Service: E.F. WELLINGTON & CO.,
Patent and Trade Mark Attorneys,
457 St. Kilda Road,
Melbourne, 3004, Victoria.

Complete Specification for the invention entitled:

"PREPARATION OF N-ACYL-AMINOMETHYLPHOSPHONATES"

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

Background of the Invention

This invention relates to a process for the preparation of aminomethylphosphonates, and more particularly, to the preparation of an N-acyl-aminomethylphosphonic acid.

N-Substituted-aminomethylphosphonic acids are useful intermediates in the preparation of various products, including sequestering agents and herbicides. Thus, for an example, an N-alkyl-N-phosphonomethyl-glycine, such as N-isopropyl-N-phosphonomethylglycine, can be dealkylated under alkaline conditions to the corresponding N-phosphonomethylglycine using the method disclosed in EPO Patent Application 86 870 047.7.

N-Phosphonomethylglycine, known also by its common name glyphosate, is a highly effective and commercially important phytotoxicant useful in controlling a large variety of weeds. It is applied to the foliage of a very broad spectrum of annual and perennial grasses and broadleaf plants. Industrial uses include control of weeds along roadsides, waterways, transmission lines in storage areas and in other non-agricultural areas. Usually, N-phosphonomethyl-glycine is formulated into herbicidal compositions in the form of its various salts in solution, preferably water. The process of the present invention can be used to prepare N-acylaminomethylphosphonic acid, which is useful in the synthesis of N-phosphonomethyl-glycine.

Numerous methods are known to those skilled in the art for the phosphonomethylation of amides. For example, the disclosure of Miller et al. in U.S. Patent 4,657,705 describes a process for the preparation of an N-substituted aminomethylphosphonic acid, comprising reacting substituted amides with phos-

phorous acid and formaldehyde in an aqueous acidic medium. Under these conditions the amide is readily hydrolyzed to the free amine prior to phosphonomethylation. N-acylaminomethylphosphonic acids are not isolated or formed in this process.

Pulwer and Balthazor in Synthetic Communications, 16(7), 733-739 (1986) report a novel procedure for the preparation of the dimethyl ester of N-benzoylaminomethylphosphonic acid by treating N-hydroxymethylbenzamide with a mixture of phosphorous trichloride and trimethyl phosphite. Hydrolysis of the ester intermediate with acid gave aminomethylphosphonic acid.

U.S. Patent 2,304,156 describes a process for the preparation N-acyl-N-aminomethylphosphonic acid by treatment of a methylol compound with a phosphorus trihalide, and then converting the intermediate ester compound to the phosphonic acid by treatment with water after letting it stand in an enclosed vessel for a long period of time.

Vail, et al., in Journal of Organic Chemistry, 27, pp 2067-2070 (June 1962) report that in general, many N-methylol derivatives of the amide type are unstable products which release formaldehyde on heating, whereas the ethers of these derivatives are more stable.

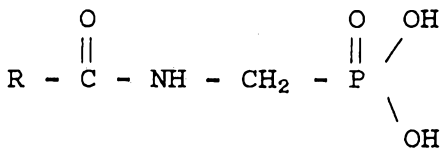
Polish patent application 117780 discloses a method for preparing aminomethylphosphonic acid by reacting phosphorous trichloride with a methylolamide solution in acetic acid and hydrolyzing the reaction mixture. It reports that the reaction is carried out by adding the methylolamide solution to the phosphorous trichloride. It reports that changing the reaction sequence causes an almost complete reaction of methylolamide to give low yields of aminomethylphosphonic acid after hydrolysis.

Oleksyszyn, et al. reported in Synthesis (June 1978), pages 479 and 480, a method for the preparation of aminoalkanephosphonic acids in which the aminoalkanephosphonic acid is directly produced from phosphorus trichloride or di-chlorophosphines, carbonyl compounds (aldehydes or ketones) and alkyl carbamates. The reference discloses that the replacement of the carbonyl compounds with the corresponding acetals, as well as replacement of carbamates with simpler amides (e.g. acetamide or benzamide,) resulted in decreased yields.

Despite the prediction of low yields in the prior art and considering the problems associated with handling the unstable methylol derivative, Applicants have now found that N-acylaminomethylphosphonic acids can be produced in high yields and purity from acetamides and benzamides without pre-forming the methylol derivative by the process of the present invention.

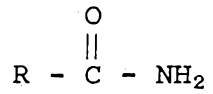
Summary of the Invention

Despite the teachings in the prior art, there is now provided a process for the preparation of N-acyl-aminomethylphosphonic acids represented by the formula



wherein R is selected from the group consisting of methyl and aryl, which comprises:

(a) bringing together under substantially anhydrous reaction conditions an amide represented by the formula

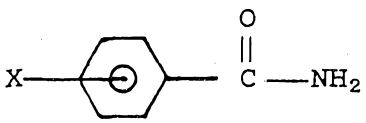


wherein R is as defined above, and paraformaldehyde; and thereafter,

(b) adding phosphorous trihalide to the reaction mixture.

Detailed Description of the Invention

The terms methyl and aryl have the usual meanings known to those skilled in the art. The aryl group can be substituted or unsubstituted, and suitable arylamides can be represented by the formula



where X is selected from hydrogen, alkyl having one to six carbon atoms, halo, alkoxy having one to six carbon atoms, nitro, or any other group that doesn't interfere with the reaction. Satisfactory results are obtained using the less expensive phenyl group.

The acetamide and benzamide, useful as starting materials in the process of the present invention, can be prepared by techniques known to those skilled in the art. For example, acetyl chloride or benzoyl chloride can be reacted with ammonia to form the corresponding amide. On the other hand, acetic acid or benzoic acid can be condensed with ammonia or a suitable salt to form the corresponding amide.

By the process of the present invention, the acetamide or the benzamide is brought together with paraformaldehyde under substantially anhydrous conditions. This can be achieved by bringing the starting materials together in anhydrous organic acids, such as formic acid and glacial acetic acid. Glacial acetic acid is preferred.

After the acetamide or the benzamide is brought together with the paraformaldehyde in substantially equimolar quantities in the anhydrous organic acid solvent, it is usually necessary to heat the mixture for a short period of time to form a solution. Generally, heating the mixture to between 50°C and 100°C for about 30 minutes is sufficient. The time and temperature necessary to form a solution can be readily determined by those skilled in the art.

After the solution of paraformaldehyde and amide has been cooled to below about 30°C, there is then added a slight molar excess of phosphorous trihalide to the reaction mixture. Typical phosphorous trihalides are phosphorous trichloride, phosphorous tribromide and phosphorous triiodide, or mixtures of such halides. Phosphorous trichloride is preferred because of its ready availability.

After the addition of the phosphorous trihalide, the solution is heated to between about 80°C and about 150°C for 2 to 4 hours to complete the phosphonomethylation. Temperatures between about 80°C and 120°C are preferred. If the temperature exceeds the reflux temperature of the solvent, pressure may be required, as will occur to those skilled in the art.

The N-acyl group can be readily cleaved from the N-acylaminomethylphosphonic acid, if desired, by hydrolysis using a strong mineral acid, such as sulfuric acid or hydrochloric acid. Hydrochloric acid is preferred for acid hydrolysis. On the other hand, the acyl group can be cleaved by a strong base such as an alkali metal hydroxide or carbonate. Sodium hydroxide is preferred for basic hydrolysis. After basic hydrolysis, the product is acidified using a strong mineral acid, such as hydrochloric acid or

sulfuric acid, and upon isolation, a high yield of aminomethlyphosphonic acid is obtained.

The invention is further illustrated by, but not limited to, the following examples.

Example 1

To a 100 ml flask was charged acetamide (2.95 g, 0.05 mol), paraformaldehyde (1.65 g, 0.55 mol) and glacial acetic acid (35 ml). The mixture was heated to about 100°C to form a solution. The solution was cooled to room temperature and phosphorous trichloride (7.9 g, 0.058 mol) was added dropwise over a 5 minute period. Then the solution was heated to 110°C and maintained at this temperature for about 1 hour. The mixture was then cooled to room temperature and water (100 ml) was added. The mixture was then evaporated to an oil under vacuum at 60°C. Analysis by ^{31}P NMR showed the presence of N-acetylaminomethylphosphonic acid.

The above product was converted to aminomethylphosphonic acid by adding a 50% aqueous solution of sodium hydroxide (22 g, 0.275 mole) and stirring at room temperature for 72 hours. The solution was acidified with concentrated HCl and evaporated to a white solid. The residue was taken up in concentrated HCl (50 ml) and the precipitated sodium chloride was filtered off. The filtrate was evaporated to a white solid and purified by ion exchange chromatography (Dowex 50 x 8-400) using water as the eluent to yield aminomethylphosphonic acid (4.71 g, 84.9% yield).

Example 2

The phosphonylmethylation procedure of Example 1 was repeated to prepare N-acetylaminomethylphosphonic acid. After adding water, and evaporating the reaction mixture to an oil, water (25

ml) was added, and the solution was evaporated again to remove residual formaldehyde and formic acid. To the resulting oil was added concentrated hydrochloric acid (60 ml) and the mixture was heated at reflux for about 16 hours. After cooling, the solution was evaporated to an oil and purified by ion exchange chromatography to yield aminomethylphosphonic acid (3.8 g, 68.6% yield).

Example 3

A 250 ml flask was charged with benzamide (12.2 g, 0.10 mol) paraformaldehyde (3.2 g, 0.11 mol) and glacial acetic acid (60 ml). The mixture was heated to about 90°C over a 1 hour period to form a solution. Then, the solution was cooled to room temperature, and phosphorous trichloride (16.4 g, 0.12 mol) was added in one portion, and the solution was heated to 110 °C and held at that temperature for 2 hours. The solution was allowed to cool to room temperature, and water (50 ml) was added to the mixture, which was then evaporated to an oily solid. Analysis by ^{31}P NMR showed the presence of N-benzoyl-aminomethylphosphonic acid.

The above product was converted to amino-methylphosphonic acid by adding concentrated hydro-chloric acid (100 ml) and heating at reflux for about 16 hours. After purification by ion exchange chroma-tography, aminomethylphosphonic acid (9.2 g, 82.9% yield) was obtained.

Example 4

This example illustrates the poor yields obtained using carbamates. To a 50 ml flask was added methyl carbamate (1.98 g, 0.025 mol) paraformaldehyde (0.79 g, 0.026 mol) and glacial acetic acid (20 ml). The mixture was heated to 85°C to form a solution and then cooled to about 15°C in an ice bath. Then, phosphorous trichloride (4.11 g, 0.03 mol) was added

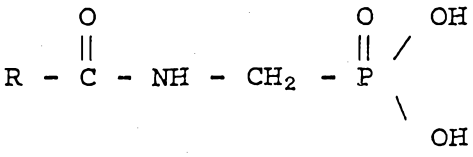
in one portion, and the solution was heated to 107°C over a 1 hour period. After heating at this temperature for about one hour, the solution was evaporated to an oil under vacuum at 60°C. Then, concentrated HCl (50 ml) was added to the solution, and it was heated at reflux for about 14 hours. The mixture was evaporated to a heavy oil again under vacuum at 60°C. Ion exchange purification gave aminomethylphosphonic acid (1.0 g, 36% yield).

Although the invention has been described in terms of specified embodiments which are set forth in considerable detail, it should be understood that this is by way of illustration only, and that alternative embodiments and operating techniques will become apparent to those skilled in the art in view of the disclosure. Accordingly, modifications can be made without departing from the spirit of the described invention as defined in the following claims.

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

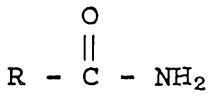
The claims defining the invention are as follows:

1. A process for the preparation of N-acylaminomethylphosphonic acids represented by the formula



wherein R is selected from the group consisting of methyl and aryl, which comprises:

(a) bringing together in an anhydrous organic acid, an amide represented by the formula



wherein R is as defined above and paraformaldehyde; and thereafter,

(b) adding phosphorous trihalide to the reaction mixture.

2. A process of Claim 1 wherein the amide, the paraformaldehyde and the phosphorous trihalide are heated to a temperature between about 80°C and 150°C.

3. A process of Claim 2 wherein the amide, the paraformaldehyde and the phosphorous trihalide are heated to a temperature between about 80°C and 120°C.

4. A process of any one of Claims 1 to 3 wherein the anhydrous organic acid is glacial acetic acid or formic acid.

5. A process of any one of Claims 1 to 4 comprising the further step of hydrolyzing the N-acyl-aminomethylphosphonic acid to form aminomethyl-phosphonic acid.

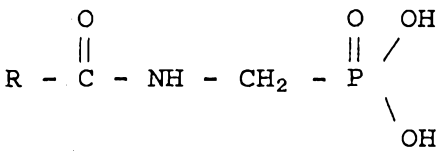
6. A process of Claim 5 wherein an aqueous alkali metal hydroxide is used for the hydrolysis.

7. A process of Claim 6 wherein the alkali metal hydroxide is sodium hydroxide.

8. A process of Claim 5 wherein an aqueous strong mineral acid is used for the hydrolysis.

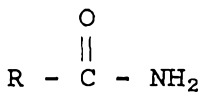
9. A process of Claim 8 wherein the mineral acid is hydrochloric acid or sulfuric acid.

10. A process for the preparation of an N-acylaminomethylphosphonic acid represented by the formula



wherein R is selected from the group consisting of methyl and aryl, which comprises:

(a) adding paraformaldehyde and an amide represented by the formula



wherein R is as defined above, to glacial acetic acid;

(b) heating the glacial acetic acid containing the amide and the paraformaldehyde to form a solution;

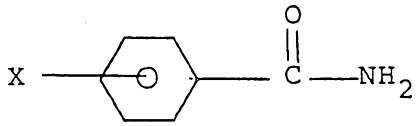
(c) adding phosphorous trichloride to the solution;

(d) heating the solution with the phosphorous trichloride to about 80°C and about 120°C.

11. A process of Claim 10 comprising the further step of hydrolyzing the N-acylaminomethylphosphonic acid with an aqueous alkali metal hydroxide to form aminomethylphosphonic acid.

12. A process of Claim 10 comprising the further step of hydrolyzing the N-acylaminomethylphosphonic acid with an aqueous strong mineral acid.

13. A process of any one of claims 1 to 12 wherein the aryl group R is derived from an arylamide represented by the formula



wherein X is selected from hydrogen, alkyl having one to six carbon atoms, halo, alkoxy having one to six carbon atoms, nitro, or any other non-interferring group.

14. N-acylaminomethylphosphonic acids obtained by the process of any one of claims 1 to 4, 10 and 13.

15. Aminomethylphosphonic acid obtained by the process of any one of claims 5 to 9, 11 and 12.

DATED this 24th day of November, A.D. 1989

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

(B. S. Wellington)