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(54) Titre : PROCEDE DE PREPARATION DE O,O-DIMETHYL-PHOSPHORAMIDOTHIOATE ET DE N-(METHOXY-METHYLSULFANYLPHOSPHORYL) ACETAMIDE
(54) Title: PROCESS FOR PREPARATION OF O, O-DIMETHYL PHOSPHORAMIDOTHIOATE AND N-(METHOXY-METHYLSULFANYLPHOSPHORYL) ACETAMIDE

(57) **Abrégé/Abstract:**

Preparation of O,O-dimethyl phosphoramidothioate and O,O-dimethyl phosphoroamidothioate. A process of making O,O-dimethyl phosphoroamidothioate is described including reacting sulfur with PCl_3 to form PSCl_3 , reacting the PSCl_3 formed with methanol to form O-methyl phosphorodichloridothioate, and reacting the O-methyl phosphorodichloridothioate formed with methyl lye to form O,O-dimethyl phosphorochloridothioate in solution in CH_2Cl_2 , and reacting the O,O-dimethyl phosphorochloridothioate formed with sodium hydroxide and ammonium hydroxide to form O,O-dimethyl phosphoroamidothioate in solution in CH_2Cl_2 . Reacting the O,O-dimethyl phosphoroamidothioate formed with catalytic dimethyl sulfate to form methamidophos, and reacting the methamidophos formed with acetic anhydride to form N- (methoxymethylsulfanylphosphoryl) acetamide is also described. Throughout the process, the O,O-dimethyl phosphorochloridothioate and the O,O-dimethyl phosphoroamidothioate formed are maintained in solution in CH_2Cl_2 at all times.

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(54) Title: PROCESS FOR PREPARATION OF O, O-DIMETHYL PHOSPHORAMIDOTHIOATE AND N-(METHOXY-METHYLSULFANYLPHOSPHORYL) ACETAMIDE

(57) Abstract: Preparation of O,O-dimethyl phosphoramidothioate and O,O-dimethyl phosphoroamidothioate. A process of making O,O-dimethyl phosphoroamidothioate is described including reacting sulfur with PCl_3 to form PSCl_3 , reacting the PSCl_3 formed with methanol to form O-methyl phosphorodichloridothioate, and reacting the O-methyl phosphorodichloridothioate formed with methyl lye to form O,O-dimethyl phosphorochloridothioate in solution in CH_2Cl_2 , and reacting the O,O-dimethyl phosphorochloridothioate formed with sodium hydroxide and ammonium hydroxide to form O,O-dimethyl phosphoroamidothioate in solution in CH_2Cl_2 . Reacting the O,O-dimethyl phosphoroamidothioate formed with catalytic dimethyl sulfate to form methamidophos, and reacting the methamidophos formed with acetic anhydride to form N-(methoxymethylsulfanylpophoryl) acetamide is also described. Throughout the process, the O,O-dimethyl phosphorochloridothioate and the O,O-dimethyl phosphoroamidothioate formed are maintained in solution in CH_2Cl_2 at all times.

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PROCESS FOR PREPARATION OF O, O-DIMETHYL
PHOSPHORAMIDOTHIOATE AND N-(METHOXY-
METHYLSULFANYLPHOSPHORYL) ACETAMIDE

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims the priority of U.S. Application No. 16/040,136 filed July 19, 2018, the disclosure of which is expressly incorporated by reference herein in its entirety.

TECHNICAL FIELD

[002] The field of art to which this invention generally pertains is insecticidal compositions.

BACKGROUND

[003] Insecticidal compositions, including pesticides, are typically formulated to kill, harm, repel or mitigate one or more species of insect. Insecticides work in different ways. Some insecticides disrupt the nervous system, whereas others may damage their exoskeletons, repel them or control them by some other means. Because of these factors, each insecticide can pose a different level of risk to non-target insects, people, pets and the environment. In addition, the materials used to generate these compositions can present their own handling issues both before, during and after reaction.

[004] Because of the complexity of such insecticidal compositions and the chemicals and reactions associated with their production, there is a constant challenge to generate insecticidal compositions in a safe and effective manner.

BRIEF SUMMARY

[005] A process of making O,O-dimethyl phosphoroamidothioate is described including reacting sulfur with PCl_3 to form PSCl_3 , reacting the PSCl_3 formed with methanol to form O-methyl phosphorodichloridothioate, reacting the O-methyl phosphorodichloridothioate formed with methyl lye to form O,O-dimethyl phosphorochloridothioate in solution in CH_2Cl_2 , and reacting the O,O-dimethyl phosphorochloridothioate formed with sodium hydroxide and ammonium hydroxide to form O,O-dimethyl phosphoroamidothioate in solution in CH_2Cl_2 , where the O,O-dimethyl phosphorochloridothioate and O, O-dimethyl phosphoramidothioate formed is maintained throughout the process in solution in CH_2Cl_2 at all times.

[006] Additional embodiments include: the process described above where the O,O-dimethyl phosphoroamidothioate formed is reacted with catalytic dimethyl sulfate to form methamidophos, and the methamidophos formed is reacted with acetic anhydride to form N- (methoxy-methylsulfanylphosphoryl) acetamide, and wherein the O,O-dimethyl phosphorochloridothioate formed and the O,O-dimethyl phosphoroamidothioate formed are maintained throughout the process in solution in CH_2Cl_2 at all times; the method described above run as a batch process; and the method described above run as a continuous process.

[007] These, and additional embodiments, will be apparent from the following descriptions.

DETAILED DESCRIPTION

[008] The particulars shown herein are by way of example and for purposes of illustrative discussion of the various embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description making apparent to those skilled in the art how the several forms of the invention may be embodied in practice

[009] The present invention will now be described by reference to more detailed embodiments. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

[0010] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms “a,” “an,” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety.

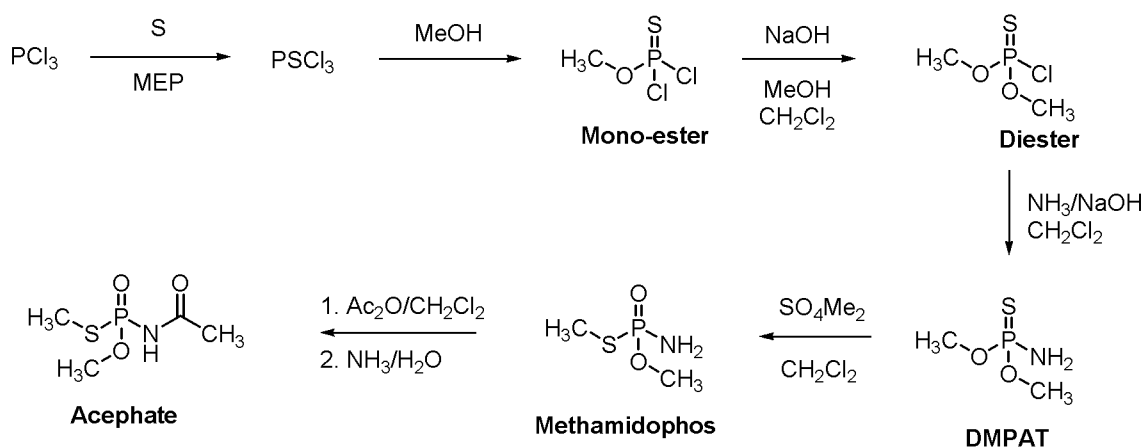
[0011] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0012] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Every numerical range given throughout this specification will include every narrower numerical range that falls within such broader numerical range, as if such narrower numerical ranges were all expressly written herein.

[0013] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

[0014] A process for the manufacture of the insecticide acephate (N-(Methoxy-methylsulfanylmethylphosphoryl) acetamide) and its intermediates is described, resulting in enhanced safety over previously utilized methods. The

process shown below includes the manufacture of DMPAT (O, O-dimethyl phosphoramidothioate) and subsequently acephate without isolation of intermediates downstream of the mono-ester. Explosions have previously been known to occur when handling its intermediates (e.g., the diester shown below) and DMPAT as neat materials.



[0015] Specifically, the process described herein includes the conversion of PSCl_3 to acephate without isolation of potentially explosive intermediates. Reaction of the mono-ester with MeOH/NaOH (methanol/sodium hydroxide) in a biphasic aqueous/ CH_2Cl_2 system provides the diester as a solution in CH_2Cl_2 , for example, in 85-88% yield and 94-95% purity. The diester is telescoped directly into the reaction with NH_3/NaOH to produce the DMPAT, again as a solution in CH_2Cl_2 , e.g., in 98% yield and 93% purity. This DMPAT solution is then converted into methamidophos by reaction with catalytic dimethyl sulfate and subsequently to acephate by treatment with acetic anhydride, all as solutions in CH_2Cl_2 . Acephate is then isolated via neutralization with aqueous ammonia, crystallization and collection by filtration.

[0016] As described herein, the DMPAT is typically produced by either batch or continuous processing in four steps as demonstrated below.

[0017] The first (PSCl_3) step typically involves conversion of phosphorus trichloride to thiophosphoryl chloride by reacting phosphorus trichloride with sulfur in presence of catalyst under inert atmosphere (e.g., nitrogen - argon). The PSCl_3 product is distilled and separated as colorless, transparent liquid from the reaction mass; while the residue termed as “HEEL” is recycled back for subsequent batches.

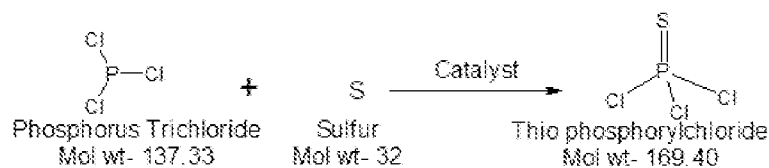
[0018] The second (monoester) step typically involves reacting thiophosphoryl chloride in either a continuous or batch mode with methanol to produce O-methyl phosphorodichloridothioate (monoester). By-product HCl is miscible in excess methanol. The reaction mass is washed with water either in batch or continuous mode and aqueous phase and oil phase (monoester) are separated. The monoester may react further at very slow rate to produce the diester which is entrained in the oil phase. The aqueous wash phase is neutralized with caustic solution. It is further treated to isolate and recycle methanol. Remaining aqueous phase containing mostly water is subjected to a conventional multi-effect evaporator to separate water and sodium chloride (for example, for industrial use).

[0019] The third (DMPTCl: O, O-dimethyl phosphorochloridothioate) step typically involves using the above monoester oil (crude) as such to react again with methanol in presence of base at accelerated rate to give DMPTCl).

[0020] The fourth (DMPAT) step typically involves reacting the diester with aqueous ammonia, liquid ammonia or NaOH/ NH_4OH to produce the DMPAT; ammonium chloride is separated from the reaction, e.g., for

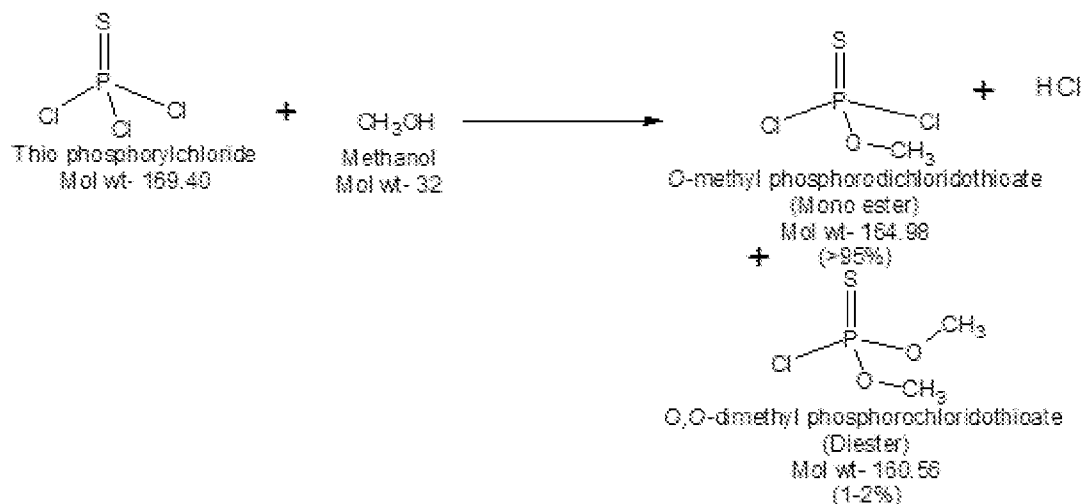
industrial use.

[0021] In greater detail, the first reaction is shown as follows:



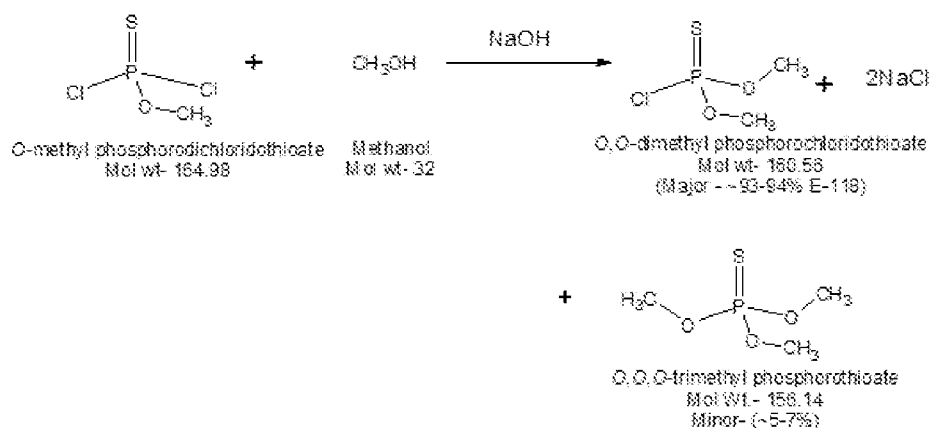
[0022] This reaction typically runs very clean, i.e., goes to complete conversion with no specific impurities present in the distilled PSCl_3 product at this step.

[0023] In the second step, the thiophosphorylchloride is reacted in excess methanol to produce the monoester:



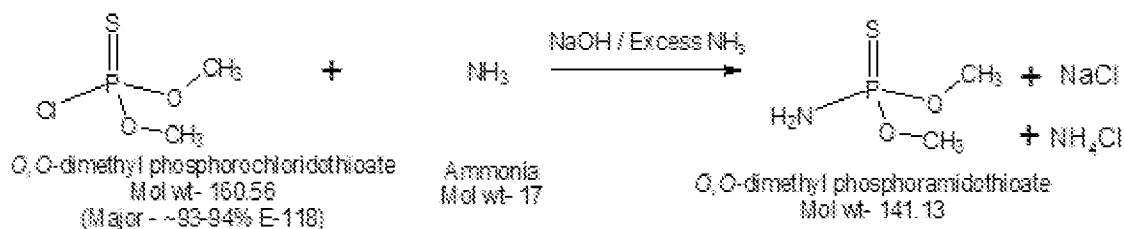
[0024] As shown above, in a side reaction the diester is formed in low concentration, being slow to react in the absence of caustic.

[0025] In the third step, the monoester reacts at significant rate (e.g., 2 to 3 hours) to give the diester (O,O-dimethyl phosphorochloridothioate).



[0026] As a side reaction a small quantity of triester is also formed during this diester formation.

[0027] In the last step shown, the diester is reacted with ammonium hydroxide and sodium hydroxide (e.g., in a continuous mode) to produce the DMPAT (O,O-dimethylphosphoramidothioate). The primary impurity in this step is trimethyl thiophosphate carried over from the previous step. The DMPAT formed may also rearrange to form methamidophos.



[0028] It is important to note that the diester and the DMPAT should be kept in solution at all times. Explosions can occur when these compounds are prepared neat.

EXAMPLE 1

Step 1: Thiolation (Conversion of PCl_3 to PSCl_3)

[0028] In a multipurpose glass lined reactor of suitable size, molten sulfur (120°C) is charged (see Table 1) under nitrogen blanket (For the 1st batch (Recycle-0), Sulfur is charged 40% excess with respect to PCl_3 to ensure proper conversion and reflux temperature). From the metering tank, phosphorus trichloride is added under working condensers and reflux valves open to ensure reflux back of vaporized PCl_3 . The required quantity (see Table 1) of MEP (methyl ethyl pyridine) is added to the above reaction mixture and the reaction mass is started to be heated. (MEP Catalyst is added only for 1st and 2nd batches, while in subsequent batches it gets carried /recycles via the “HEEL”). Agitator and jacket heating (via high pressure steam) of the reactor is started. The temperature of the reaction mass is raised from initial reflux of 80°C to 130°C from 1 to 2 hours. The reaction mass is cooked at 130°C for another 2 to 3 hours maintaining a nitrogen blanket throughout (Under air or the presence of oxygen, may lead to formation of POCl_3 impurity). The reaction mass is checked for PSCl_3 ; PCl_3 content (end of reaction: PCl_3 is less than 0.5%). Once the reaction is completed, the reaction mass is cooled down to 40°C before distillation. Distillation of the PSCl_3 is started under vacuum (700-710 mm (millimeters) Hg absolute; Temperature 40°C to 70°C (reactor temperature) and distilled clear water-like material is collected into a glass distillate receiver. Distillate is collected at about 70% to about 75% based on the reaction mass volume. The residue at the bottoms (HEEL) is cooled down and recycled for a subsequent batch (see Table 1). Subsequent conversions are continued and after about 8 to about 10 recycles, % molar yield in-hand of PSCl_3 with regard to

PCl_3 reaches 98% (After 3 to 4 recycles, distillate exceeds 100%; after about 9 to about 10 recycles in-hand molar yield of PSCl_3 with regard to PCl_3 reaches 98%).

TABLE 1: Representative Process Parameters

Parameter	Charge Ratio (K moles)			Cook Temp, °C	Distillate recovered, %
	Sulfur	PCl_3	MEP (catalyst)		
Recycle-0	1.4	1.0	0.008	120-135	70-75
Recycle-1	1.0	1.0	0.008	120-135	75-80
Recycle-2	1.0	1.0	0	120-135	80
Recycle-3	1.0	1.0	0	120-135	85
Recycle-4	1.0	1.0	0	120-135	90
Recycle-5	1.0	1.0	0	120-135	100
Recycle-6 (See Note-4)	1.0	1.0	0	120-135	110

EXAMPLE 2

Step 2: O-methyl Phosphorodichloridothioate (Methanolysis of PSCl_3)

[0029] In a glass lined reactor of suitable size with external heat exchanger & circulatory pump, pre-cooled Thiophosphoryl chloride (PSCl_3 99.5% pure) is charged 40% of the total batch requirement & maintained at the same temperature in the reactor. The bottom valve of the reactor is switched on and PSCl_3 is looped back to the reactor via an external heat exchanger. Once the circulation is stabilized, pre-cooled methanol (4 molar ratio; 0-5°C) is added

into a circulatory pump inlet line at the rate so as to complete its addition in 3 hours. The remaining quantity of PSCl_3 (60%, 0-5°C) is also added in parallel to methanol, however, it is added via a top liquid addition port into the reactor. Post completion of addition, reaction mass is maintained at 0-10°C under agitation for another 2 to 3 hours. Reaction mass is analyzed for completion of reaction (PSCl_3 less than 0.5%; Mono-ester greater than 95%; Diester 2-3%; Triester less than 1%). Reaction mass is then transferred to a wash reactor & Water is added into it at 0-10°C and agitated for another 1 to 2 hours. The phases are separated to provide the mono-ester which is carried forward without additional processing.

EXAMPLE 3

Step 3: O,O-dimethyl Phosphorochloridothioate (Diester E-118 formation)

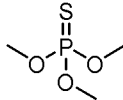
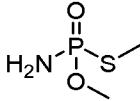
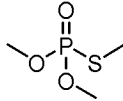
[0030] O-Methyl Phosphorodichloridothioate is charged to a reactor and diluted with CH_2Cl_2 (3 liters per kilogram (L/kg)). The batch is stirred and the temperature is adjusted to -5 to 5 °C. “Methyl lye” (1.1 equivalent) is added to the batch over 2-3 hours maintaining the temperature at -5 to 5°C. “Methyl lye” is prepared by reaction of pre-chilled (0-5°C) methanol (1.1 equivalent) with aqueous sodium hydroxide (1.1 equivalent) under an inert atmosphere. Commercial “methyl lye” may also be used. Stirring is continued at -5 to 5°C for 1 hour then analyzed for reaction completion by gas chromatography (GC). The reaction is deemed complete when the relative mono-ester concentration is less than 0.5%. Stirring is stopped and the phases are separated. O,O-dimethyl Phosphorochloridothioate (E-118, Diester) is isolated as a solution in CH_2Cl_2 in 85% to 88% yield and 94% to 95% purity (GC analysis). E-118 must be maintained in solution at all times.

EXAMPLE 4

Step 4: DMPAT (ammonolysis)

[0031] To a continuously stirring reactor system (CSTR) maintained at 40°C is simultaneously added a DCM (dichloromethane) O,O-Dimethyl phosphorochloridothioate (E-118), 25% sodium hydroxide maintained at 0.93 molar equivalents with respect to E-118, 18% ammonium hydroxide maintained at 1.41 molar equivalents with respect to E-118. The residence time of the reaction is 3 hours at 40°C. The reaction mixture is continuously removed to maintain the desired volume. The phases are separated and the aqueous phase is extracted with CH₂Cl₂ to recover O,O-dimethyl phosphoroamidothioate (DMPAT). The organic extracts are combined to give DMPAT as a solution in CH₂Cl₂ which may be used without further purification. DMPAT is isolated in 98% yield and about 93% purity containing about 7% trimethylthiophosphate. This product must be maintained in solution at all times.

TABLE 2: Representative Impurity Profile

Anticipated Impurities	Structure	Source
Trimethyl thiophosphate (triester)		Over reaction in Step 3
Methamidophos		Rearrangement of DMPAT
O,O,S-Trimethyl phosphorothioate		Rearrangement of triester

[0032] As used herein, the term "about" refers to a measurable value such as a parameter, an amount, a temporal duration, and the like and is meant to include variations of +/-15% or less, preferably variations of +/-10% or less, more preferably variations of +/-5% or less, even more preferably variations of +/-1% or

less, and still more preferably variations of $\pm 1-0.1\%$ or less of and from the particularly recited value, in so far as such variations are appropriate to perform in the invention described herein. Furthermore, it is also to be understood that the value to which the modifier "about" refers is itself specifically disclosed herein.

[0033] These examples are merely illustrations and are not to be understood as limiting the scope and underlying principles of the invention in any way. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the following examples and foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

[0034] As described herein, these problems and others in this area are addressed by the invention described herein. Thus, the scope of the invention shall include all modifications and variations that may fall within the scope of the attached claims. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A process of making O,O-dimethyl phosphoroamidothioate comprising,
 - a. reacting sulfur with PCl_3 to form PSCl_3 ,
 - b. reacting the PSCl_3 formed with methanol to form O-methyl phosphorodichloridothioate,
 - c. reacting the O-methyl phosphorodichloridothioate formed with methyl lye to form O,O-dimethyl phosphorochloridothioate in solution in CH_2Cl_2 , and
 - d. reacting the O,O-dimethyl phosphorochloridothioate formed with sodium hydroxide and ammonium hydroxide to form O,O-dimethyl phosphoroamidothioate in solution in CH_2Cl_2 ,wherein the O,O-dimethyl phosphorochloridothioate and O, O-dimethyl phosphoramidothioate formed is maintained throughout the process in solution in CH_2Cl_2 at all times.
2. The process of claim 1 wherein the O,O-dimethyl phosphoroamidothioate formed is reacted with catalytic dimethyl sulfate to form methamidophos, and the methamidophos formed is reacted with acetic anhydride to form N-(methoxy-methylsulfanylphosphoryl) acetamide, and wherein the O,O-dimethyl phosphorochloridothioate formed and the O,O-dimethyl phosphoroamidothioate formed are maintained throughout the process in solution in CH_2Cl_2 at all times.
3. The method according to claim 2 run as a batch process.
4. The method according to claim 2 run as a continuous process.