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Method for producing Organic Phosphoric Acid Esters

This invention relates to a method of producing organic phosphoric acid ester derivatives having insecticidal, miticidal, fungicidal and other activities and useful as agricultural chemicals. More particularly, the invention relates to an improvement in the method of producing compounds of the general formula:



wherein R_1 is a lower alkoxy group, R_2 is a lower alkoxy group or a lower alkylthio group, R_3 is a substituted or unsubstituted heterocyclic group and X is an oxygen or sulfur atom, which comprises reacting a compound of the general formula:



wherein R_1 , R_2 and X are as defined above and Y is a halogen atom, with a compound of the general formula:



wherein R_3 is as defined above, under basic conditions in

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a solvent, the improvement lying in that the reaction solvent is a mixture of water and a water-immiscible solvent, the mixture forming two layers.

It is widely known that organic phosphoric acid ester derivatives are producible by reacting, in the manner of esterification, an organic phosphoric acid ester halide with a hydroxyl-containing compound such as an alcohol or a phenol (for example, British Patents No. 1306028, No. 1315888, No. 1340297 and No. 2047250, and United States Patents No. 4163052, No. 4315008, No. 3728297 and No. 3723456). This esterification is generally carried out in an organic solvent while the use of water is avoided since the starting organic phosphoric acid ester halide is decomposed very easily in the presence of water. Thus, for instance, United States Patent No. 4315008 discloses a method of reacting a 4-hydroxypyrazole derivative with an O-ethyl S-n-propyl (di)thiophosphoric acid ester halide in an organic solvent inert to the reaction (e.g. acetonitrile) to give the corresponding organic phosphoric acid ester derivative. However, this and other known methods are not yet fully satisfactory because of low yield and low purity of the objective compounds and because of complicated and troublesome procedures resulting from the use of organic solvents in carrying out the reaction.

The present inventors continued their studies in the development of a method of producing the objective compounds (I) in a manner easier and simpler from the industrial standpoint and found that, in the known method for producing the compound (I) which comprises reacting the compound (II) with the compound (III) under basic conditions in a solvent, when the reaction solvent is a mixture of water and a water-immiscible solvent, the mixture forming two layers, unexpectedly, (i) the reaction proceeds in highly improved yield, i.e. almost quantitatively, (ii) the isolation of the objective compound (I) is very easy and simple, and thus (iii) the objective compound (I) is obtained in high

yield and high purity. Continued investigations based on the above finding have led to completion of the present invention.

The reaction of the compounds (II) and (III) in accordance with the present invention proceeds almost quantitatively in a mixture of water and a water-immiscible solvent, the mixture forming two layers, contrary to the so-far prevailing common knowledge in chemistry that water is inadequate as the reaction solvent since organic phosphoric acid ester halides, namely the compounds (II), are very unstable to water. So, the reaction in accordance with the present invention can be used conveniently in a quantitative analysis of the compound (II).

In the above general formulas, R_1 is a lower alkoxy group which includes a straight or branched lower alkoxy group containing 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy; R_2 is (1) a lower alkoxy group which includes a straight or branched lower alkoxy group containing 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy, or (2) a lower alkylthio group which includes a straight or branched lower alkylthio group containing 1 to 4 carbon atoms, such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio or tert-butylthio; R_3 is

a substituted or unsubstituted heterocyclic group which includes a 5- or 6-membered heterocyclic group which is capable of bonding through a carbon atom and contains 1 to 4 nitrogen atoms and which may optionally be substituted by 1 to 3 substituents each selected from (a) a phenyl group which may have 1 to 3

substituents each selected from among a lower alkyl group containing 1 to 4 carbon atoms, a lower alkoxy group containing 1 to 4 carbon atoms, a lower alkylthio group containing 1 to 4 carbon atoms, nitro, halogen and tri-fluoromethyl, (b) a lower alkoxycarbonyl group containing 1 to 4 carbon atoms in the alkoxy moiety, (c) an oxo group, (d) halogen and (e) a lower alkyl group containing 1 to 4 carbon atoms; X is an oxygen or sulfur atom, and Y is a halogen atom such as fluorine, chlorine, bromine or iodine.

Referring to the above R_3 , the halogen includes fluorine, chlorine, bromine and iodine; the lower alkylthio group containing 1 to 4 carbon atoms, the lower alkoxy group containing 1 to 4 carbon atoms, and the lower alkoxy moiety containing 1 to 4 carbon atoms in the lower alkoxycarbonyl group respectively include those specifically mentioned in relation to R_2 ; and the lower alkyl group containing 1 to 4 carbon atoms includes a straight or branched lower alkyl group containing 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl.

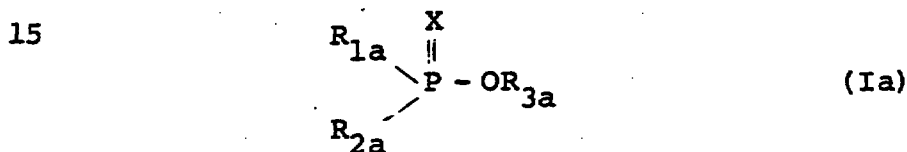
The 5- or 6-membered heterocyclic group containing 1 to 4 nitrogen atoms as represented by the above R_3 includes, among others, (1) saturated or unsaturated 5- or 6-membered heterocyclic groups containing one nitrogen atom, such as pyrrolyl, pyridyl, pyrrolidinyl, pyrrolinyl and piperidyl, (2) saturated or unsaturated 5- or 6-membered heterocyclic groups containing two nitrogen atoms, such as imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl and piperazinyl, and (3) saturated or unsaturated 5- or 6-membered heterocyclic groups containing 3 or 4 nitrogen atoms, such as triazolyl and tetrazolyl.

Among the possible cases mentioned above preferred are those cases where R_1 is a lower alkoxy group, R_2 is a lower alkylthio group, X is an oxygen atom and R_3 is a saturated or unsaturated 5- or 6-membered heterocyclic group

which contains two nitrogen atoms and may optionally be substituted with a phenyl group which may have 1 to 3 substituents each selected from among a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a C₁₋₄ alkylthio group, nitro, halogen and trifluoromethyl.

Among the substituted or unsubstituted heterocyclic groups represented by R₃ particularly preferred are unsaturated 5-membered heterocyclic groups which contain two nitrogen atoms and may optionally be substituted by a phenyl group unsubstituted or substituted by 1 to 3 halogen atoms.

A typical example of the compounds (I) may be a compound of the formula:



wherein R_{1a} is a C₁₋₄ alkoxy group, R_{2a} is a C₁₋₄ alkoxy group or a C₁₋₄ alkylthio group, R_{3a} is

an unsaturated 5- or 6-membered heterocyclic group which contains 1 or 2 nitrogen atoms and may optionally be substituted by 1 to 3 substituents each selected from (i) a phenyl group which may optionally be substituted by a halogen atom, (ii) a C₁₋₄ alkyl group, (iii) an oxo group and (iv) a halogen atom, and X is as defined above. In the formula (Ia), the groups represented by R_{1a}, R_{2a} and R_{3a} respectively include those mentioned in relation to R₁, R₂ and R₃.

More specifically, the compounds represented by the general formula (I) include the following:

35 O,O-Diethyl O-(5-phenyl-3-isoxazolyl) phosphorothioate,

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0,0-Diethyl 0-(3,5,6-trichloro-2-pyridyl) phosphorothioate,
0-Ethyl S-n-propyl 0-[1-(4-chlorophenyl)-4-pyrazolyl]
phosphorothioate,
0,0-Diethyl 0-(2-isopropyl-4-methylpyrimidin-6-yl) phos-
5 phorothioate,

0-(3,5,6-Trichloro-2-pyridyl) 0,0-dimethyl phosphorothioate, and
0,0-Diethyl 0-(2,3-dihydro-3-oxo-2-phenyl-6-pyridazinyl)
phosphorothioate, among others.

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In producing the objective compounds (I) in
accordance with the invention, the compound (II) is preferably used in
an amount of about 0.5 to about 3 moles, more preferably about
1 to about 1.05 moles, per mole of the compound (III).

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The water-immiscible solvent to be used in the
present reaction may be a solvent having a solubility in
water of 0.01-5% (weight/volume) at 25°C, preferably 0.01-
1% (weight/volume) at 25°C. Suitable examples of the
water-immiscible solvent include aromatic hydrocarbons, such
20 as benzene, toluene and xylene, and halogenated hydrocarbons,
such as methylene chloride, chloroform and carbon tetra-
chloride. Among these solvents preferred are aromatic
hydrocarbons such as benzene, toluene and xylene. The
water-immiscible solvent is used in an amount to form two
25 layers with water, the amount preferably being 0.5 to 10 parts by
volume, more preferably about 2 parts by volume relative to
water. The amount of water used in the invention may be

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about 5 to 200 moles, preferably 10 to 30 moles per mole of the compound (III).

The reaction is carried out smoothly under basic conditions wherein a pH value of the reaction mixture under stirring is 7.1 to 14.0, preferably 10 to 11.

For conducting the reaction under basic conditions, a base is used in an amount about equivalent to an amount based on the compound (II). Suitable examples of the base are inorganic bases, for example, alkali metal hydroxides such as potassium hydroxide and sodium hydroxide, alkaline

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earth metal hydroxides such as calcium hydroxide, alkali metal carbonates such as potassium carbonate and sodium carbonate, alkali metal hydrogen carbonates such as potassium hydrogen carbonate and sodium hydrogen carbonate, alkaline earth metal carbonates such as calcium carbonate and the like. Among them, alkali metal hydroxides such as potassium hydroxide and sodium hydroxide are particularly preferred. The base may be added to the reaction system once or by several portions to keep the reaction mixture under basic conditions.

The reaction proceeds in the two layer solvent system comprising an aqueous layer and a layer of a water-immiscible solvent. Thus, the reaction may be effected, for example, by adding the compound (III) to a mixture of water and a water-immiscible solvent and then adding thereto the compound (II) while maintaining the pH of the reaction mixture under stirring within the basicity region by addition of a base, or by dissolving the compound (III) in a two-layer liquid phase comprising an aqueous solution of a base and a water-immiscible solvent and adding the compound (II) to the resulting solution while maintaining the pH of the reaction mixture under stirring within the basicity region by adding a base as necessary. In the invention, the compound (II) may be added to the reaction system in the form of a solution in a water-immiscible solvent.

The reaction can be effected in practice without particular problems within a temperature range of about 0°C to about 50°C, suitably about 5°C to about 15°C.

The reaction may be complete in about 30 minutes to about 6 hours. The completion of the reaction can be confirmed by high performance liquid chromatography or thin layer chromatography, for instance. After completion of the reaction, the reaction mixture may be adjusted to pH 12 to 13.5 with such a base as mentioned above and the aqueous layer may be separated, whereby the unreacted compound (III) and byproducts may be removed.

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The thus-produced compounds (I) can be isolated and purified by per se known methods of separation and purification, such as concentration, concentration under reduced pressure, distillation under reduced pressure, pH adjustment, solvent replacement, solvent extraction, crystallization, recrystallization and chromatography.

The starting compounds (II) and (III) to be used in practicing the invention are producible by per se known methods, such as the methods described in British Patent No. 2047250 and United States Patents No. 4163052 and No. 4315008, for instance, or their analogous methods.

The present invention will be described hereinafter in further detail by way of an experimental example and working examples.

The symbols used in the examples and the experiment have the following meanings.

ml: milliliter

g: gram

%: percent

ODS(C-18): "LS -410 ODS SIL" manufactured by TOYO SODA MANUFACTURING CO. LTD. in JAPAN

ø: diameter

b.p.: boiling point

d^{20} : density at 20°C (°C: centigrade degree)

m.p.: melting point

cm: centimeter

Example 1

Production of O-[1-(4-chlorophenyl)-4-pyrazolyl]

O-ethyl S-n-propyl phosphorothioate

Water (24.5 ml) is added to 15.02 g (0.075 mole) of

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1-(4-chlorophenyl)-4-hydroxypyrazole, followed by addition of 2.25 g (0.0563 mole) of sodium hydroxide. Stirring promotes dissolution and gives a homogeneous solution. To the solution is added 56.8 ml of toluene and, with
5 vigorous stirring, a toluene solution (30.8 g) containing 15.35 g (0.0757 mole) of O-ethyl S-n-propyl phosphorochloride is added dropwise over 2.5 hours, during which the reaction temperature is maintained at 15°C and the pH of the reaction mixture is kept at 10.5 by addition of
10 10% (weight/volume) aqueous sodium hydroxide. After completion of the dropping, the reaction temperature is raised to 25°C and stirring is continued at this temperature for 2 hours. Thereafter, the mixture is cooled to 5°C, adjusted to pH 13.5 with 28% (weight/volume) aqueous sodium
15 hydroxide and stirred for 30 minutes, followed by phase separation. The toluene layer is washed with 40 ml of water. The toluene solution obtained by phase separation after washing is concentrated under reduced pressure to give the title compound.

20 Yield 27.9 g

Purity 96.4% [determined by HPLC (high performance liquid chromatography; column - ODS (C-18) 4 ϕ x 25 cm, temperature - 40°C, mobile phase - acetonitrile/water)]

Yield on 100% purity basis 26.9 g (99.5%)

25 Comparative experiment

Production of O-[1-(4-chlorophenyl)-4-pyrazolyl]

O-ethyl S-n-propyl phosphorothioate by the method described in British Patent No. 2047250

1-(4-Chlorophenyl)-4-hydroxypyrazole (15.02 g, 0.075
30 mole) is dissolved in 80 ml of acetone. Thereto are added 12.0 g of anhydrous sodium carbonate and 15.35 g (0.0757 mole) of O-ethyl S-n-propyl phosphorochloride. The mixture is heated under reflux for 2.5 hours. Thereafter, the acetone is distilled off, toluene is added to the residue,
35 and the resulting toluene solution is washed with water and dried over anhydrous sodium sulfate. The toluene is

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then distilled off to give O-[1-(4-chlorophenyl)-4-pyrazolyl] O-ethyl S-n-propyl phosphorothioate.

Yield 22.77 g

Purity 93.9% (determined by HPLC (high performance liquid chromatography) in the same manner as Example 1)

Yield on 100% purity basis 21.38 g (78.1%)

Example 2

The following organic phosphoric acid ester derivatives are producible in the same manner as Example 1:

(1) O,O-Diethyl O-(2-isopropyl-4-methylpyrimidin-6-yl) phosphorothioate

dark brown liquid

b.p. 83-84°C/0.0002 mmHg, d^{20} 1.116

(2) O-(3,5,6-Trichloro-2-pyridyl) O,O-dimethyl phosphorothioate

white crystals

m.p. 45.5-46.5°C

(3) O,O-Diethyl O-(2,3-dihydro-3-oxo-2-phenyl-6-pyridazinyl) phosphorothioate

white crystals

m.p. 54.5-56.0°C



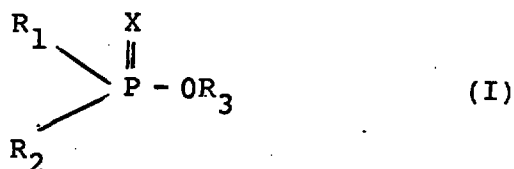
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CLAIMS

1. A method for producing a compound of the formula:

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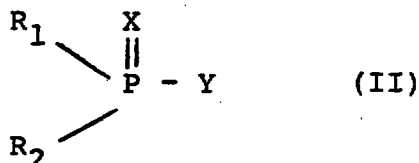


wherein R_1 is a lower alkoxy group, R_2 is a lower alkoxy
10 group or a lower alkylthio group, R_3 is

a substituted or

unsubstituted heterocyclic group and X is an oxygen or
sulfur atom which comprises reacting a compound of the
formula:

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wherein R_1 , R_2 and X are as defined above and Y is a halogen
atom with a compound of the formula:

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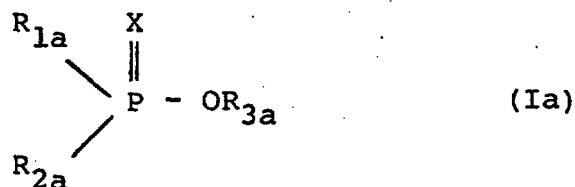
wherein R_3 is as defined above under basic conditions in a
solvent, characterised in that the reaction solvent
is a mixture of water and a water-immiscible solvent, the
25 mixture forming two layers.

2. A method according to claim 1, wherein the compound
(I) is a compound of the formula:



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wherein R_{1a} is a C_{1-4} alkoxy group, R_{2a} is a C_{1-4} alkoxy group or a C_{1-4} alkylthio group, R_{3a} is

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an unsaturated 5- or 6-membered

heterocyclic group which contains 1 or 2 nitrogen atoms and may optionally be substituted by 1 to 3 substituents

each selected from (i) a phenyl group which may optionally be substituted by a halogen atom, (ii) a C_{1-4} alkyl group,

15 (iii) an oxo group and (iv) a halogen atom, and X is an oxygen or sulfur atom.

3. A method according to claim 1, wherein R_1 is a lower alkoxy group, R_2 is a lower alkylthio group, X is an oxygen
20 atom and R_3 is a saturated or unsaturated 5- or 6-membered heterocyclic group which contains two nitrogen atoms and may optionally be substituted with a phenyl group which may have 1 to 3 substituents each selected from among
a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a C_{1-4}
25 alkylthio group, nitro, halogen and trifluoromethyl.



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4. A method according to claim 1 or 3, wherein R_3 is an unsaturated 5-membered heterocyclic group which contains two nitrogen atoms and may optionally be substituted with a phenyl group unsubstituted or substituted by
5 1 to 3 halogen atoms.

5. A method according to claim 1, wherein the compound of formula (I) is 0-Ethyl S-n-propyl 0-[1-(4-chlorophenyl)-4-pyrazolyl] phosphorothioate.

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6. A method according to claim 1, wherein the compound (I) is selected from any one of:

0,0-Diethyl 0-(2-isopropyl-4-methylpyrimidin-6-yl) phosphorothioate,

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0-3,5,6-Trichloro-2-pyridyl, 0,0-dimethyl phosphorothioate and

0,0-Diethyl 0-(2,3-dihydro-3-oxo-2-phenyl-6-pyridazinyl) phosphorothioate

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7. A method according to claim 1 substantially as herein described with reference to either of the specific examples. ...

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