

PATENT SPECIFICATION

(11) 1301222

1301222

NO DRAWINGS

- (21) Application No. 426/71 (22) Filed 5 Jan. 1971
 (31) Convention Application No. 830 (32) Filed 5 Jan. 1970 in
 (33) United States of America (US)
 (45) Complete Specification published 29 Dec. 1972
 (51) International Classification C07D 91/62
 (52) Index at acceptance
 C2C 172—192—282 215 247 256 25Y 29X 29Y 311 313 31Y
 322 32Y 339 341 342 345 34Y 578 601 620 626
 62X 670 694 695 72X 776 791 KD KV NG

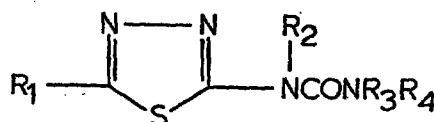


(54) METHOD FOR PREPARING 1,3,4-THIADIAZOL-2-YL UREAS

(71) We AIR PRODUCTS AND CHEMICALS INC. a Corporation organised under the laws of the State of Delaware, United States of America, of 1339 Chestnut Street, Philadelphia, Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

It is known in the art to employ phosgene in methods for preparing urea compounds. For example, phosgene is reacted with a primary or secondary amine to produce intermediate carbamoyl chlorides which intermediates may be, in turn, reacted with other primary or secondary amines to produce urea compounds. However, the 2-alkylamino-1,3,4-thiadiazole intermediates which are needed to obtain the compounds of the invention will not react with phosgene in the normal manner. It has now been discovered that phosgene, under certain conditions, will react with these 2-alkylamino-1,3,4-thiadiazoles to provide an intermediate which when reacted with secondary amines gives the desired urea product.

The present invention is directed to a method for producing 1,3,4-thiadiazol-2-ylurea compounds having the general structure:

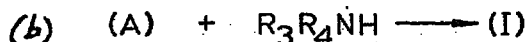
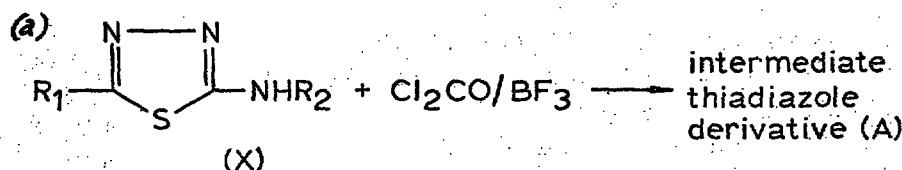


wherein

- R_1 is a lower alkyl radical having from 1 to 4 carbon atoms, a fluoroalkyl radical having from 1 to 4 carbon atoms or a chlorodifluoromethyl radical,
 R_2 is a lower alkyl radical having from 1 to 4 carbon atoms,
 R_3 is a lower alkyl radical having from 1 to 4 carbon atoms, alkoxy or cycloalkyl radical, and
 R_4 is a lower alkyl radical having from 1 to 4 carbon atoms,
 which comprises the steps of reacting phosgene, in the presence of a catalytic amount of boron trifluoride, with a 2-alkylamino-1,3,4-thiadiazole compound to obtain an intermediate thiadiazole derivative and subsequently reacting said derivative with a secondary amine to obtain 1,3,4-thiadiazol-2-ylurea compounds. The 1,3,4-thiadiazol-2-yl urea compounds are disclosed and claimed as new compounds in our specification No. 1,266,172.

The method of the invention may be represented by the following general reaction:

(II)



The definitions of R_1 , R_2 , R_3 and R_4 are as hereinbefore defined.

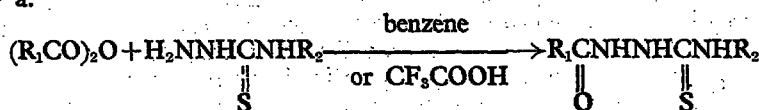
The 2-alkylamino-1,3,4-thiadiazole compounds (X) employed in (II) (a) above may be produced by methods generally known in the art. Examples of such methods are as follows:

(1)

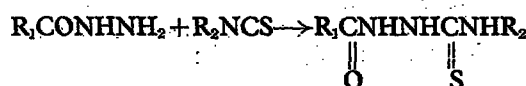


The above reaction uses polyphosphoric acid (PPA) as a dehydrating agent.

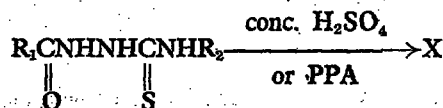
(2) a.



b.



c.



(3)



In each of the equations (1), (2) and (3), R_1 and R_2 are as defined above. Any of the above methods will yield the compound (X). For given substituents R_1 and R_2 , each of the above methods will give a different yield. Selection of the preferred method, consequently, is an empirical decision based on experience with given substituents. Choice of method will be obvious to those skilled in the art, having the above disclosure before them.

Phosgene and boron trifluoride employed in the method are commercially available and any technical grade of each compound should provide desirable results. It has been found that beneficial reaction conditions are obtained in reaction (II) (a) above when the phosgene is employed in the presence of a boron trifluoride-ether complex catalyst. It is to be understood, however, that boron trifluoride without the ether complex will also produce desirable reaction conditions and resulting compounds.

Phosgene is preferably present in the reaction in an amount from 1 mol equivalent to 4 mol equivalents, based on the 2-alkylamino-1,3,4-thiadiazole employed, and

most preferably from 1 mol equivalent to 2 mol equivalents. The boron trifluoride is preferably present in an amount from 0.025% to 10%, by weight, based on the amount of phosgene present and most preferably from 3% to 7% by weight.

Although the exact structure of intermediate (A) is not known, it is significant to note that such intermediates will react with secondary amines, as in (II) (b) above, to give compounds of Structure (I). The prior art methods of using phosgene do not provide an intermediate that will react as in (II) (b) to give compounds of Structure (I).

The secondary amines that may be employed in the method of the invention include dimethylamine, methylpropylamine, dibutylamine, O,N-dimethylhydroxylamine, methylcyclohexylamine, and dipropylamine.

Reaction (II) (a) is normally conducted in the presence of an inert solvent such as benzene, toluene or xylene. Such reaction is generally conducted at temperatures of from 40°C to 70°C and preferably from 50°C to about 60°C.

Reaction (II) (b) is generally conducted at a temperature range of from 0°C to 40°C and preferably from 20°C to 30°C.

The method of the invention is particularly suited for preparing 1,3,4-thiadiazol-2-ylurea compounds having desirable biological activity, i.e. for use as herbicides, insecticides, and fungicides.

The following examples are illustrative of the invention and are not intended to limit the scope thereof.

Example 1

To 122 gms of a solution of phosgene in 2200 mls of anhydrous toluene was added 14 gms of boron trifluoride-ether complex. A dry ice condenser was used to prevent loss of the phosgene. To this solution was added, with stirring and at room temperature, 150 gms of 2-methylamino-5-trifluoromethyl-1,3,4-thiadiazole, the resulting mixture being heated to temperatures of from 50°C to 60°C for a period of 3 hours. The mixture was cooled in an ice bath to 15°C and subsequently dimethylamine was slowly bubbled through the reaction mixture until there was no evidence of an exothermic reaction. Temperature of the reaction during the addition of dimethylamine was maintained below 30°C. An insoluble material of dimethylamine hydrochloride was filtered off and the filtrate washed with 6N hydrochloric acid and water. The filtrate was dried over anhydrous sodium sulfate and subsequently concentrated under vacuum. The resulting product had a yield of 136 gms and was identified to be 1,1,3-Trimethyl-3-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)urea.

Example 2

To a solution of 54.5 gms of phosgene in 1100 mls of anhydrous toluene was added 8 gms of boron trifluoride-ether complex. A dry ice condenser was employed to prevent loss of phosgene. To the solution was added 85.5 gms of 2-methylamino-5-pentafluoroethyl-1,3,4-thiadiazole, the mixture being heated to a temperature of 50°C to 60°C for a period of 3 hours. The resulting mixture was cooled in an ice bath to 15°C and dimethylamine was slowly bubbled through the mixture until there was no evidence of an exothermic reaction. The temperature was maintained below 30°C during addition of the dimethylamine. The insoluble material of dimethylamine hydrochloride was separated by filtration and the filtrate washed with 6N hydrochloric acid and water. The filtrate was subsequently dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting product had a yield of 62 gms and was identified to be 1,1,3-trimethyl-3-(5-pentafluoroethyl-1,3,4-thiadiazol-2-yl)urea.

Example 3

A. Intermediate (A) compounds were prepared in accordance with reaction (II) (a) above. Into a 1000 ml round bottom flask equipped with an addition tube, an addition funnel and dry ice condenser was added a mixture containing 500 ml of dry toluene, 38.4 gms of phosgene and 2 gms of boron trifluoride ether complex. To this mixture was added, dropwise and with stirring, 36.6 gms of 2-methylamino-5-trifluoromethyl-1,3,4-thiadiazole dissolved in 300 ml of dry toluene, such addition being made at room temperature. After complete addition of the thiadiazole mixture, the reaction temperature was raised to 50°-60°C and an additional 38.4 gms. of phosgene were added. Nitrogen gas was bubbled through the reaction mixture until acid fumes could no longer be detected in the effluent gases. The resulting reaction mixture was subsequently washed with water and dried over sodium sulfate. Concentration of said mixture, under vacuum, yielded 38.8 grams of product (A). The product on crystallization from petroleum ether was found to have a melting point of 100°-102°C.

B. To 2 gms of the intermediate product of Example 3A above, was admixed 30 mls of an aqueous tetrahydrofuran (THF) solution (10 ml THF, 20 ml water) and to this mixture was added 0.5 gms of an aqueous solution of O,N-dimethylhydroxylamine hydrochloride which was neutralized with 0.6 grams of sodium carbonate. The reaction mixture was stirred for about 1 hour at room temperature and subsequently extracted with toluene. The toluene solution was washed with 6N hydrochloric acid, then with water and concentrated under vacuum to produce an oil product which was identified to be 1,3-dimethyl-1-methoxy-3-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-urea.

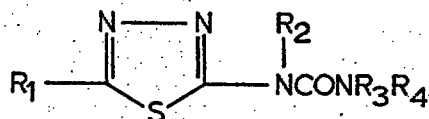
Example 4

To a solution containing 243.3 gms of phosgene and 32.8 gms of boron trifluoride etherate in 1500 gms of toluene contained in a 5-liter, 3-necked flask, equipped with a stirrer and dry ice condenser was added, at room temperature, 328 gms 2-methylamino-5-chlorodifluoromethyl-1,3,4-thiadiazole. After complete addition of the thiadiazole, the reaction temperature was raised to, and maintained at 55°C for three hours. The reaction mixture was then cooled to less than 30°C and gaseous dimethylamine as bubbled through the reaction mixture while the temperature was maintained below 30°C, until no further exotherm was observed. The reaction mixture was washed with 6N hydrochloric acid and water. Removal of the toluene under vacuum yielded 330.6 gms of a product identified to be 1,1,3-trimethyl-3-(5-chlorodifluoromethyl-1,3,4-thiadiazol-2-yl)urea and having a melting point of 50°—52°C.

In place of the particular 2-alkylamino-1,3,4-thiadiazole and secondary amine compounds employed in the Examples, other compounds, as hereinbefore described, may be substituted to obtain substantially the same results.

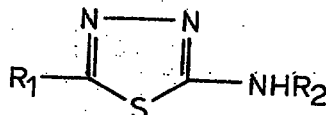
WHAT WE CLAIM IS:—

1. A method for producing 1,3,4-thiadiazol-2-yl urea compounds of the formula:



wherein

- R₁ is lower alkyl having from 1 to 4 carbon atoms, fluoroalkyl having from 1 to 4 carbon atoms, or chlorodifluoromethyl;
 - R₂ is lower alkyl having from 1 to 4 carbon atoms;
 - R₃ is lower alkyl having from 1 to 4 carbon atoms, alkoxy or cycloalkyl, and
 - R₄ is lower alkyl having from 1 to 4 carbon atoms,
- which comprises reacting a 2-alkylamino-1,3,4-thiadiazole compound of the formula:



wherein R₁ and R₂ are as defined above, with phosgene, in the presence of a catalytic amount of boron trifluoride, and reacting the resulting reaction product with a secondary amine of the formula R₃R₄NH, wherein R₃ and R₄ are as defined above.

2. The method of Claim 1, wherein the amount of the phosgene is from 1 mol equivalent to 4 mol equivalents based on the 2-alkylamino-1,3,4-thiadiazole.

3. The method of Claims 1 or 2, wherein the boron trifluoride is present in an amount from 0.025% to 10%, by weight, based on the total weight of the phosgene.

4. The method of Claims 1, 2 or 3, wherein the reaction between the 2-alkylamino-1,3,4-thiadiazole and phosgene is conducted at a temperature in the range of from 40°C to 70°C.

5. The method of any one of Claims 1 to 4, wherein the reaction between said resulting reaction product and said secondary amine is conducted at a temperature in the range of from 0°C to 40°C.



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B. To 2 gms of the intermediate product of Example 3A above, was admixed 30 mls of an aqueous tetrahydrofuran (THF) solution (10 ml THF, 20 ml water) and to this mixture was added 0.5 gms of an aqueous solution of O,N-dimethylhydroxylamine hydrochloride which was neutralized with 0.6 grams of sodium carbonate. The reaction mixture was stirred for about 1 hour at room temperature and subsequently extracted with toluene. The toluene solution was washed with 6N hydrochloric acid, then with water and concentrated under vacuum to produce an oil product which was identified to be 1,3-dimethyl-1-methoxy-3-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-urea.

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Example 4

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To a solution containing 243.3 gms of phosgene and 32.8 gms of boron trifluoride etherate in 1500 gms of toluene contained in a 5-liter, 3-necked flask, equipped with a stirrer and dry ice condenser was added, at room temperature, 328 gms 2-methylamino-5-chlorodifluoromethyl-1,3,4-thiadiazole. After complete addition of the thiadiazole, the reaction temperature was raised to, and maintained at 55°C for three hours. The reaction mixture was then cooled to less than 30°C and gaseous dimethylamine as bubbled through the reaction mixture while the temperature was maintained below 30°C, until no further exotherm was observed. The reaction mixture was washed with 6N hydrochloric acid and water. Removal of the toluene under vacuum yielded 330.6 gms of a product identified to be 1,1,3-trimethyl-3-(5-chlorodifluoromethyl-1,3,4-thiadiazol-2-yl)urea and having a melting point of 50°—52°C.

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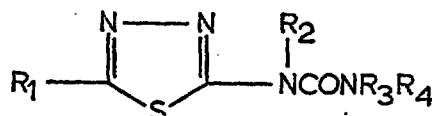
In place of the particular 2-alkylamino-1,3,4-thiadiazole and secondary amine compounds employed in the Examples, other compounds, as hereinbefore described, may be substituted to obtain substantially the same results.

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WHAT WE CLAIM IS:—

1. A method for producing 1,3,4-thiadiazol-2-yl urea compounds of the formula:



wherein

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R₁ is lower alkyl having from 1 to 4 carbon atoms, fluoroalkyl having from 1 to 4 carbon atoms, or chlorodifluoromethyl;

R₂ is lower alkyl having from 1 to 4 carbon atoms;

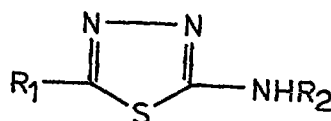
R₃ is lower alkyl having from 1 to 4 carbon atoms, alkoxy or cycloalkyl, and

R₄ is lower alkyl having from 1 to 4 carbon atoms,

which comprises reacting a 2-alkylamino-1,3,4-thiadiazole compound of the formula:

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wherein R₁ and R₂ are as defined above, with phosgene, in the presence of a catalytic amount of boron trifluoride, and reacting the resulting reaction product with a secondary amine of the formula R₃R₄NH, wherein R₃ and R₄ are as defined above.

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2. The method of Claim 1, wherein the amount of the phosgene is from 1 mol equivalent to 4 mol equivalents based on the 2-alkylamino-1,3,4-thiadiazole.

3. The method of Claims 1 or 2, wherein the boron trifluoride is present in an amount from 0.025% to 10%, by weight, based on the total weight of the phosgene.

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4. The method of Claims 1, 2 or 3, wherein the reaction between the 2-alkylamino-1,3,4-thiadiazole and phosgene is conducted at a temperature in the range of from 40°C to 70°C.

5. The method of any one of Claims 1 to 4, wherein the reaction between said resulting reaction product and said secondary amine is conducted at a temperature in the range of from 0°C to 40°C.



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6. The method of any one of the preceding claims, wherein the secondary amine is dimethylamine.

7. The method of any one of the preceding claims, wherein the secondary amine is O,N-dimethylhydroxylamine hydrochloride.

8. The method of any one of claims 1 to 5, wherein R_1 is trifluoromethyl and R_2, R_3 and R_4 are each methyl.

9. The method of any one of claims 1 to 5, wherein R_1 is pentafluoroethyl and R_2, R_3 and R_4 are each methyl.

10. The method of any one of claims 1 to 5, wherein R_1 is trifluoromethyl, R_2 is methyl, R_3 is methoxy and R_4 is methyl.

11. The method of any one of claims 1 to 5, wherein R_1 is chlorodifluoromethyl and R_2, R_3 and R_4 are each methyl.

12. A method for producing 1,3,4-thiadiazol-2-yl urea compounds substantially as hereinbefore described.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
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