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PRODUCTION OF SECONDARY ALKYLIDENE CYANOACETIC ESTERS

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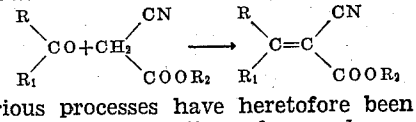
No Drawing. Application June 19, 1937, Serial No. 149,139

14 Claims. (Cl. 260—464)

This invention relates to a new process for the production of secondary alkylidene cyanoacetic esters by the condensation of ketones with cyanoacetic esters, such as cyanoacetic ethyl ester or cyanoacetic methyl ester. It relates more particularly to a process in which the condensation of the ketone with the cyanoacetic ester is carried out in the presence of an acid amide or a soluble salt, particularly a soluble salt of a nitrogen base, such as a primary, secondary, or tertiary amine, or ammonia or a quarternary ammonium base, or other soluble salt. A method of carrying out the process which has important advantages involves the use, in addition to a catalyst, of an organic acid, particularly acetic acid, either alone as a solvent, or with the addition of an inert solvent, such as benzene.

This application is a continuation in part of my prior application Serial No. 105,825 filed October 15, 1936.

When a ketone is condensed with a cyanoacetic ester, a molecule of water is eliminated between the two, the oxygen atom of the ketone combining with the two hydrogen atoms attached to the methylene group of the ester, and the hydrocarbon radical of the ketone attaching itself to the ester radical by a double bond, with the formation of a secondary alkylidene cyanoacetic ester. The reaction which takes place in such condensations is illustrated by the following graphic formula:



Various processes have heretofore been suggested for the formation of secondary alkylidene cyanoacetic esters, but in general these processes have either been difficult to carry out, or have not resulted in sufficiently high yields of the desired products. Among the processes which have been suggested are the condensation of ketones with cyanoacetic esters in the presence of such condensing agents as piperidine, diethylamine, sodium ethoxide and the zinc chloride-aniline complex. It has also been proposed to prepare alkylildene cyanoacetic acids by the reaction of potassium cyanide with the corresponding chlorine derivative, with replacement of the chlorine atom with the nitrile group, or by condensation of cyanoacetic acid with ketones in the presence of various catalysts.

The present invention provides an improved process for the production of the secondary alkylidene cyanoacetic esters, in which a ketone is condensed with a cyanoacetic ester smoothly and with high yields, and with a minimum of side reactions, so that there is a maximum recovery of unreacted starting materials. In its broader aspects, the invention includes the condensation when carried out in the presence of a condensing agent consisting of a soluble salt, advantageously a soluble salt of a nitrogen base, i. e. an ammonium or amine base or an alkali metal salt of an organic acid, or an acid amide, such as acetamide. Preferably, the salts which are used are the acetates of the bases, such as diethylamine acetate, monoethylamine acetate, triethylamine acetate, ammonium acetate, etc. Compounds or condensing agents which have been found to have important advantages for carrying out the condensation are the acetates of primary or secondary amines, or ammonium acetate, which enable the condensation to be accomplished with particularly high yields of the desired product and with a minimum of side reactions, polymerization, etc. Ammonium acetate, on heating, is converted into acetamide. This substance, which may be formed in situ in certain of the reaction mixtures in which ammonium acetate is used as the catalyst, is in itself a good catalyst for these reactions, and may be introduced directly into the reaction mixture to effect the condensation; or, solutions of soluble salts in acetamide may be used with advantage.

An important specific aspect of the invention lies in the use of such a condensing agent in the presence of an organic acid, such as the organic acids of the acetic acid series, for which purpose acetic acid is particularly important. Acetamide, when used in acetic acid solution, is about the most effective catalyst for the reaction which has been found, this mixture or solution yielding particularly high conversions of the reacting materials to the desired secondary alkylidene cyanoacetic ester. In place of acetamide in such an acid solution, other amides and other soluble salts may be used, with improved results as compared with the use of such soluble salts and amides alone. When the reaction is carried out in the presence of an acid such as acetic acid, an additional solvent, such as benzene or other inert solvent may be used, or the acid itself may be used as the solvent.

It has been found that the condensation of the ketones with cyanoacetic esters to give secondary alkylidene cyanoacetic esters and water is reversible, with the result that if the water remains in the reaction mixture, the reaction is an equilibrium reaction and does not go to comple-

tion. Accordingly, an important feature of the present invention involves the removal of the water formed during the reaction in a suitable manner, so as to cause the reaction to go further toward completion than would be possible if the water remained in the reaction mixture. This removal of water may be accomplished in various ways, such as by the addition of a neutral drying agent such as anhydrous calcium sulfate (Drierite), or by the distillation of benzene, or other volatile liquid, from the mixture to effect the vaporization of the water at relatively low temperatures. When an acid such as acetic acid is used along with a soluble salt or amide for effecting the condensation, the acid provides a particularly advantageous method of removing the water which is formed, as such water may be removed from the reaction mixture by distillation with excess acid, and the water may be separated from the acid by passing the vapors over a suitable water absorbing agent, such as anhydrous calcium sulfate, with refluxing of the acid, the refluxed acid thus being continuously dried with removal of water from the reaction mixture. This same refluxing technique may be used, of course, where an inert solvent such as benzene is used, or where a mixture of an inert solvent and organic acid is used.

The rate of reaction between the ketones and the cyanoacetic esters varies widely with different ketones, the reaction being quite rapid with ketones in which one of the radicals attached to the CO group is a methyl group, or such ketones as cyclohexanone and cyclopentanone, and in such cases the removal of water may be advantageously carried out by simple distillation of the water from the reaction mixture by distillation of the acid or inert solvent or acid and inert solvent used; whereas with the higher ketones, such as ketones in which both of the groups attached to the CO group are higher than methyl, including aryl ketones such as acetophenone, propiophenone, butyrophenone or caprophenone, and aliphatic ketones, such as dipropyl ketone or propyl butyl ketone, the reaction is relatively slow, and it is more advantageous to dry the reaction mixture under refluxing conditions such as described above, or by the use of an absorbing agent in the reaction mixture itself.

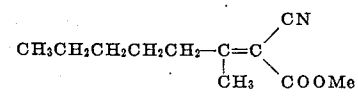
With some of the very volatile ketones, such as acetone and methyl ethyl ketone, the reaction does not proceed quite so efficiently, because of the volatility of the ketone. In such cases, the condensation is advantageously carried out by refluxing an excess of the ketone with the cyanoacetic ester in the presence of an acid solution of the condensing agent; but even under these conditions, the yields are relatively low because the water formed is difficult to remove and because it is difficult to separate the resulting secondary alkylidene esters from unreacted methyl cyanoacetate by fractional distillation.

A wide range of ketones may be condensed with cyanoacetic esters in accordance with the present invention, including open chain ketones, such as acetone, methylethyl ketone, methyl-n-propyl ketone, methyl-n-amyl ketone, di-n-propyl ketone, mesityl oxide, diethyl ketone, methyl isobutyl ketone, methylhexyl ketone, etc., as well as cyclic ketones, such as cyclohexanone, cyclopentanone, etc., and aryl ketones, such as acetophenone, propiophenone, butyrophenone, etc.

The products which are produced by the process of the present invention are valuable as intermediates for a variety of purposes, including the production of secondary alkylidene barbituric and thiobarbituric acids, the preparation of unsaturated mono-basic acids, the production of alkyl alkenyl cyanoacetic esters, and the production of corresponding barbituric and thiobarbituric acids therefrom.

The invention will be further illustrated by the following examples, which are given by way of illustration only, and the invention is not to be considered as limited thereto.

Example 1.—Preparation of 1-methyl hexylidene cyanoacetic acid methyl ester.



A mixture of 99 parts (1 mole) of methyl cyanoacetate, 137 parts (1.2 moles) of methyl n-amyl ketone and 0.04 mole of ethylene diamine diacetate is allowed to stand at room temperature for about 12 hours and is then heated on a steam bath for about 4 hours. After the mixture has been heated on a steam bath for about 4 hours, it is cooled, washed twice with water, and the organic material distilled in a vacuum. The distillate consists of unchanged ketone, methyl cyanoacetate, and the desired product, 1-methyl hexylidene cyanoacetic acid methyl ester, which is recovered by fractionation. The product distills at 121–124°C./3 mm.

Example 2.—A mixture of 99 parts (1 mole) of methyl cyanoacetate, 153 parts (1.2 moles) of methyl n-hexyl ketone and 20 parts of acetamid are heated at about 150° C. for about 10 hours. After cooling and washing with water, 1-methyl heptylidene cyanoacetic methyl ester is obtained by fractionation. It boils at 125–126° C./2 mm.

Example 3.—A mixture of 99 parts (1 mole) of methyl cyanoacetate, 153 parts (1.2 moles) of methyl n-hexyl ketone and 0.04 mole of diethanolamine acetate is prepared. Calcium sulfate (Drierite) is added to the mixture, to absorb water as formed, and the reaction is carried out as in Example 1, with the production of 1-methyl heptylidene cyanoacetic acid methyl ester.

Example 4.—A mixture of 121 parts (1.2 moles) of methyl isobutyl ketone, 99 parts (1 mole) of methyl cyanocetate, and 0.04 mole of piperidene oleate is prepared, and heated on a steam bath. Water is removed from the reaction mixture as formed by distilling benzene therefrom, and 1-methyl isopentylidene cyanocetic acid methyl ester, boiling at 138–140° C./23 mm. is obtained.

Example 5.—A mixture of 98 parts (1 mole) of mesityl oxide, 99 parts (1 mole) of methyl cyanoacetate and 5 parts of ammonium acetate is prepared and refluxed for about 7 hours. The mixture is cooled, washed with water, and fractionated to yield 1,3-dimethyl crotylidene cyanoacetic acid methyl ester, which boils at 114–116° C./2 mm.

Example 6.—46 parts of acetophenone, 28 parts of ethyl cyanoacetate and 3 parts of piperidine are added to a mixture of 30 parts of 98.8% acetic acid and 80 parts of dry benzene in a reaction vessel. The vessel is attached to a Soxhlet extractor containing about 70 parts of anhydrous calcium sulfate, which in turn is attached to a reflux condenser. The mixture is refluxed for 100 hours, during which time the benzene and acetic acid mixture is continuously dried in the Soxhlet extractor and returned to the reaction vessel. At the end of this time the benzene and acetic acid are distilled off and the residue is

washed with water and distilled in vacuum, yielding 1-phenyl ethylidene cyanoacetic acid ethyl ester, boiling point 175–180° C./11 mm.

Example 7.—25 parts of methyl cyanoacetate, 35 parts of cyclohexanone and 5 parts of acetamide are placed in a reaction vessel with 60 parts of 99.8% acetic acid and the mixture is slowly distilled for 2 hours, the heating being regulated so that the temperature of the vapors remains between 105 and 115° C. The residue is cooled, washed with water and distilled in vacuum, yielding cyclohexylidene cyanoacetic acid methyl ester, boiling at 146–147° C./9 mm. Cyclopentanone, when similarly treated in about the same molar ratio, yields cyclopentylidene cyanoacetic methyl ester, boiling at 140–141° C./9 mm.

In the following table are shown the high yields which may be obtained according to the present process using a suitable catalyst in the presence of acetic acid with removal of water by distillation of the acid during the process. Each of the condensations was carried out using 0.25 mole of methyl cyanocetate, 0.35 mole of methyl amyl ketone, the catalyst, and 60 cc. of 99.8% acetic acid, the mixture being slowly distilled for 4 hours, with the heating regulated so that the temperature of the vapors remained between 105 and 115° C.

Catalyst (moles)	Yield of methyl 1-methyl-hexylidene cyanoacetate, percent	Recovery of ketone and ester, percent
Acetamide (0.085)	91	5
Acetamide (0.042)	76	17
Acetamide (0.085)[a]	53	30
Ammonium acetate (0.04)	87	6
Ethylene diamine diacetate (0.03)	84	7
Piperidine acetate (0.02)	89	7
None	8	73

[a] In this test, the solution was heated under reflux, without removal of water.

In the following table are shown the results obtained when the process is carried out in the presence of the same catalysts, but without the acetic acid and without the removal of water formed. Each of these condensations was carried out using a mixture of 0.25 mole of methyl cyanoacetate, 0.25 mole of methyl hexyl ketone, and the catalyst, the mixture being allowed to stand for twelve hours at room temperature, after which it was heated for five hours on an oil bath at 125° C. and allowed to stand overnight at room temperature, with recovery of unreacted materials and methyl 1-methyl-heptylidene cyanoacetate by washing and vacuum distillation.

Catalyst (moles)	Yield of methyl 1-methyl-heptylidene cyanoacetate	Recovery of ketone and ester
Piperidine acetate (0.01)	52	28
Ammonium acetate (0.025)	52	26
Ethylene diamine diacetate (0.01)	52	32
Acetamide (0.085)[a]	33	55

[a] In this test, the mixture was heated nine hours at 140° C.

Other ketones show substantially the same results, although the rates of reaction vary with different ketones, the reaction going to completion with some ketones, such as cyclohexanone, in considerably less than 4 hours, while some other ketones takes a much longer time. Thus the yield of methyl 1-propyl butylidene cyano-acetate, using acetamide in acetic acid as the catalyst, is only 20% after 5 hours, but is 73% after 22 hours.

While the invention has been illustrated by specific examples involving the use of acetamide and certain selected salts, other acid amides, and other soluble salts, particularly the salts of nitrogen bases, with or without acetic or other acids, may be used with advantage; and if an inert solvent be used, other inert solvents than benzene may be used, as well as other acids than acetic acid, although acetic acid is particularly advantageous because it is effective in aiding the condensation and also is extremely useful in aiding in the removal of water.

In general, the effectiveness of a salt as a condensing agent in the present process depends directly upon its solubility in the reaction mixture. Catalysts which are typical of those used in accordance with the invention and which may be used with advantage are the following:

Ethylene diamine diacetate
Ammonium acetate
Piperidine acetate
Triethylamine acetate
Diethanolamine acetate
Aniline acetate
Piperidine butyrate
Piperidine oleate
Diethylamine acetate
Glycine
Acetamide
Sodium acetate
Potassium acetate

These condensing agents act catalytically, and their mode of action should not be confused with that of such condensing agents as zinc chloride and related compounds.

It will thus be seen that by the present invention I provide a new process for the production of secondary alkylidene cyanoacetic esters in which the reaction involved proceeds smoothly and enables the production of high yields of the desired product. The terms "alkyl" and "alkylidene" as used in this application and the appended claims, are to be construed in their broader sense, as including both saturated and unsaturated compounds, with straight and branched chains, as well as aralkyl and arylkylidene compounds.

I claim:

1. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of a compound of the class consisting of soluble salts and acid amides.

2. The process of producing secondary alkylidene cyanoacetic esters which compreses reacting a ketone with a cyanoacetic ester in the presence of a soluble salt of a nitrogen base.

3. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of acetamide.

4. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of a soluble salt of an amine.

5. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of ammonium acetate.

6. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of an organic acid and a compound of the class consisting of soluble salts and acid amides.

7. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of acetic acid and a compound of the class consisting of soluble salts and acid amides.

8. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of acetamide and acetic acid.

9. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of a compound of the class consisting of soluble salts and acid amides while removing water formed in the reaction.

10. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of a compound of the class consisting of soluble salts and acid amides while removing water formed in the reaction by distillation.

11. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of acetamide and acetic acid while removing water formed in the reaction.

12. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of acetamide and acetic acid while removing water formed in the reaction by distillation of the acetic acid.

13. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of a compound of the class consisting of soluble salts and acid amides while removing water formed in the reaction by the use of an inert water-absorbing agent.

14. The process of producing secondary alkylidene cyanoacetic esters which comprises reacting a ketone with a cyanoacetic ester in the presence of acetic acid and a compound of the class consisting of soluble salts and acid amides while removing water formed in the reaction by distillation of the acetic acid.

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