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METHOD FOR PREPARING BETA KETO ESTERS OF THIOPHENES

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3 Claims. (Cl. 260—332.2)

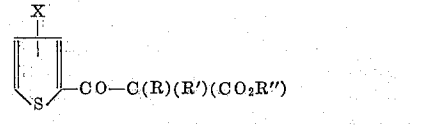
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This invention relates to esters and more particularly, to beta-keto esters of thiophene derivatives.

Among the several objects of the invention may be noted the provision of new chemical compounds which are beta-keto esters of thiophene and thiophene derivatives; the provision of new chemical compounds which are alkylated or aralkylated beta-keto esters of thiophene and thiophene derivatives; and the provision of methods for the economical preparation of the compounds indicated above which are characterized by high yields, inexpensive and readily procurable reaction materials, and the facility with which these methods may be carried out. Other objects will be in part apparent and in part pointed out hereinafter.

The invention accordingly comprises the processes hereinafter described, the scope of the invention being indicated in the following claims.

The present invention relates to beta-keto esters of the following type formula:

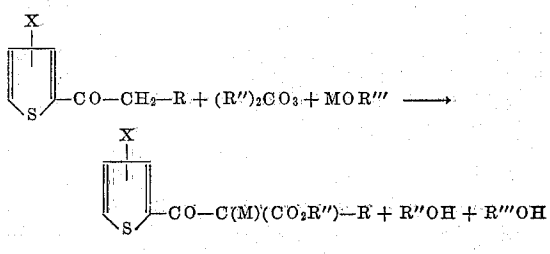


in which R is an alkyl group or hydrogen; R′ is an aralkyl or alkyl group, or hydrogen; R″ is an alkyl group; X is an alkyl group or hydrogen; and metallo-substituted derivatives thereof.

It has been found in accordance with the present invention that beta-keto esters of thiophene or thiophene derivatives may be conveniently prepared by simultaneous carbalkoxylation and metallation of 2-thienyl ketones, followed by acidification or by alkylation or aralkylation either directly or as a separate step.

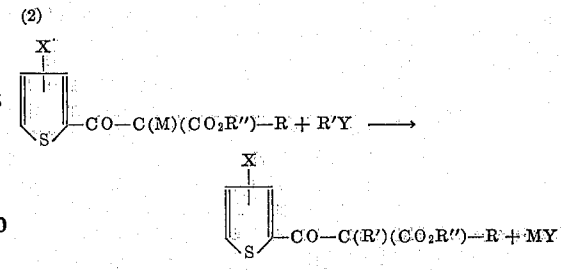
The simultaneous carbalkoxylation and metallation reaction is shown in the first equation while the alkylation or aralkylation reaction is shown in the second equation:

(1)



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(2)



in which R‴ represents an alkyl group. A metal alcoholate of an alkali metal, MOR‴, is used as a condensing agent in the first reaction. Y in the second equation may be either a halogen or a sulfate group.

The condensation as shown in the first equation occurs on the carbon atom of the alkyl group adjacent the carbonyl group. It is preferred that the R‴ radical correspond to the R″ radical so that unmixed beta-keto esters of thiophene or thiophene derivatives will be produced by the reaction as shown in the first equation.

Although this reaction may be carried out using an unsymmetrical dialkyl carbonate, it is preferable that symmetrical dialkyl carbonates be used. If unsymmetrical dialkyl carbonates are used, however, a mixture of carbalkoxylated compounds and product alcohols may be formed. The reaction of the first equation may be carried to substantial completion by heating as it progresses, to distill off the product alcohols, R′OH and R‴OH. In case the original alkali metal alcoholate contains alcohol, such alcohol is likewise removed by this distillation procedure. This procedure, while somewhat optional, is highly advantageous in its improvement in the yield of the carbalkoxylated compound obtained.

In carrying out the reaction of the second equation, it is necessary only to react together the metallo-compound and the alkylating or aralgylating agent in solution in a dialkyl carbonate, an alcohol or any inert reaction medium. A large excess of dialkyl carbonate may be used in the first reaction, the excess serving as the medium for the second reaction. Although it is preferred to use dialkyl carbonate as the sole reaction medium, a portion of this may be replaced by inert solvents if desired.

When the intended use of the alkali metal metallo-substituted compound is the preparation therefrom of an alkyl or aralkyl substituted compound, the alkali metal metallo-substituted compound need not be recovered from the reaction mixture of the first reaction but this reaction

product may be alkylated or aralkylated (as shown in Equation 2) to form the alkylated or aralkylated beta-keto ester, which may then be recovered from the reaction mixture. On the other hand, if carbalkoxylation alone is desired, the metallo group may be replaced by any suitable method, for example, by acidification.

The thenoyl esters of the present invention are useful intermediates for the preparation of pyrazolones, oximes, isoxazolones, and the like, The pyrazolones are of value for the preparation of dyestuffs, such as those used in color photography, for example.

The following examples illustrate certain specfic embodiments of the present invention, but are intended to be illustrative only:

EXAMPLE 1

Ethyl 2-thenoylacetate

Sodium metal (13 g.) was dissolved in anhydrous ethyl alcohol (200 ml.) and was distilled to dryness, the final temperature being about 160° C. at 25 mm. pressure. After cooling, diethyl carbonate (300 ml.) was added, and then 2-acetothienone (63 g.) was added slowly with stirring. The reaction mixture became red in color and the temperature rose gradually. After stirring for 30 minutes at 45–55° C., alcohol was fractionated out of the reaction mixture through a column at 150 mm. pressure. When nearly all the alcohol had been removed from the reaction mixture, a dark red solid separated forming a thick slurry. After cooling, the reaction mixture was acidified with glacial acetic acid (40 ml.) and stirred with ice and water. The diethyl carbonate layer was separated, washed and dried. Distillation from a Claisen flask yielded 73.5 g. of ethyl thenoylacetate, or 74% of the theoretical yield. It was a yellowish liquid boiling at 128–134° C. at 2 mm. pressure and having a melting point of 2–7.5° C.

Ethyl thenoylacetate (2 ml.) was mixed with 85% hydrazine hydrate (1 ml.) and one drop of hydrochloric acid and the solution was heated. The resulting 3-(2-thienyl)-5-pyrazolone was purified by recrystallization from alcohol diluted with water and by sublimation in a high vacuum at 140° C. It was a colorless solid melting at 205–207° C.

Ethyl thenoylacetate (2 ml.) was mixed with phenyl hydrazine (1.5 ml.), one drop of hydrochloric acid and alcohol (5 ml.) and heated. When petroleum ether was added, 1-phenyl-3-(2-thienyl)-5-pyrazolone was obtained as a white solid melting after purification at 143–143.5° C.

Ethyl thenoylacetate (2 ml.), hydroxylamine hydrochloride (1 g.), alcohol, water and sodium acetate were mixed. Colorless crystals separated and after recrystallization from dilute ethyl alcohol 3-(2-thienyl) isoxazolone melting at 133.5–137° C. was obtained.

EXAMPLE 2

Methyl 2-thenoylacetate

A mixture of sodium methylate (114 g.) and dimethyl carbonate (720 ml.) was placed in a two liter, three necked flask equipped with stirrer, thermometer, dropping funnel, and a column. Acetothienone (252 g.) was added dropwise while stirring the sodium methylate-dimethyl carbonate mixture. After 15 minutes, when about 20% of the ketone had been added, the pot temperature rose to 55° C. and the reaction mixture became too thick to stir. More dimethyl carbonate (500 ml.) was then added to the reddish mixture. The reaction temperature was maintained at 47° C. while stirring two hours.

During the next 15 hours, methyl alcohol-dimethyl carbonate azeotrope (127 ml.) was distilled off at atmospheric pressure. The head temperature was 63° C. and the pot temperature was found to be 80° C. Then the mixture was cooled, acidified with acetic acid (180 ml.), separated, washed and dried in the usual manner. After recovering 685 ml. of dimethyl carbonate by distillating it off through a column, the keto ester was transferred to a Claisen flask and distilled at 133–134° C. at 3 mm. pressure. The yield was 297.3 g. of methyl 2-thenoylacetate which is a light yellow oily liquid. This was 81% of the theoretical yield.

EXAMPLE 3

Methyl 2-thenoylacetate

The process as described in Example 2 was carried out with the same apparatus and procedure except that lithium methylate (2 moles) was substituted for the sodium methylate. After separating, washing and drying, the organic layer was distilled yielding methyl 2-thenoylacetate. This product was a light yellow liquid boiling at 133° C. at 2.5 mm. pressure.

EXAMPLE 4

Ethyl 2-thenoylpropionate

The apparatus and procedure of Example 1 were used and three-tenths molar quantities of the reactants were used as follows: sodium metal (8 g.), ethyl alcohol (120 ml.), diphenylamine (0.5 ml.) as an antioxidant, diethyl carbonate (200 ml.), and 2-propiothienone (42 g.). After the reaction mixture was cooled, acidified, separated, washed and dried in the usual manner, distillation yielded ethyl 2-thenoylpropionate (29.1 g.). It was a yellow oil boiling at 133–134° C. at 4 mm. pressure.

A mixture of ethyl 2-thenoylpropionate (1 ml.), 85% hydrazine hydrate (2 ml.), one drop of hydrochloric acid and alcohol was heated at 80° C., acidified with acetic acid and neutralized with ammonium hydroxide. It yielded 3-(2-thienyl)-4-methyl-5-pyrazolone which was recrystallized from alcohol diluted with water. The colorless solid product melted to a reddish-brown liquid at 205–206.5° C.

A mixture of ethyl 2-thenoylpropionate (1 ml.), hydroxylamine hydrochloride (2 g.) dissolved in water, sodium acetate and alcohol to keep all components in solution was heated at 80° C. The oxime of ethyl thenoylpropionate separated as a solid which when recrystallized from diluted alcohol melted at 121–122.5° C.

EXAMPLE 5

Ethyl 2-thenoylpropionate

Sodium ethylate was prepared by dissolving sodium metal (5 g.) in specially dried ethyl alcohol (80 ml). and distilling to dryness under reduced pressure. After cooling, diethyl carbonate (120 ml.) together with ethyl 2-thenoylacetate (40 g.) were added and the sodio derivative of ethyl 2-thenoylacetate formed. Methyl iodide (35 g.) was then added to the solution which was at a temperature of approximately 50° C. and a rapid exothermic reaction resulted together with the precipitation of sodium iodide. After warming for a time, acetic acid and water were added and the organic layer was separated, washed and

dried. Distillation from a Claisen flask after removing the solvent gave colorless vapors of ethyl thenoylpropionate which darkened on condensation to a reddish liquid boiling at 128–130° C. at 3 mm. pressure. The combined fractions weighed 39 g. which was 91% of the theoretical yield.

EXAMPLE 6

Ethyl alpha, alpha-dimethyl-2-thenoylacetate

The ester described in Example 5 was methylated further by the following reaction. Sodium ethylate was prepared in the usual manner by dissolving sodium metal (2.5 g.) in anhydrous ethyl alcohol (40 ml.) and distilling to a dry powder at reduced pressure. A solution of ethyl alpha-2-thenoylpropionate (21.2 g.) in dry diethyl carbonate (80 ml.) was added to the sodium ethylate, dissolving it to form a yellow solution. Methyl iodide (20 g.) was added and warmed and sodium iodide separated promptly. The mixture was then washed with water and dried, and the diethylcarbonate was distilled off at 200 mm. pressure, giving ethyl alpha, alpha-dimethyl-2-thenoylacetate, a liquid which boiled at 125° C. at 4 mm. pressure. The yield was 18.5 g. which was 82% of the theoretical.

A pyrazolone was prepared from hydrazine and the ester. 3 - (2-thienyl) -4,4-dimethyl-5-pyrazolone crystallized out upon standing, and upon recrystallization from dilute methanol melted at 118–119° C.

EXAMPLE 7

Ethyl 2-thenoylbutyrate

The apparatus and procedure used to prepare this compound are the same as those described in Example 1. One-quarter molar quantities were used as follows: sodium metal (6.4 g.), anhydrous ethyl alcohol (100 ml.), diethyl carbonate (150 ml.), redistilled, and 2-butyrothienone (38.5 g.). The product of this reaction was a liquid boiling at 143–147° C. at 3 mm. pressure. The yield was 22.9 g. which was 42.5% of the theoretical.

A mixture of ethyl 2-thenoylbutyrate (1 ml.), hydrazine hydrate (1 ml.), one drop of hydrochloric acid and ethyl alcohol (5 ml.) was heated for one and one-half hours. After adding methanol (3 ml.) and water (3 ml.), and neutralizing with hydrochloric acid, dense white crystals of 3-(2-thienyl)-4-propyl-5-pyrazolone formed. When recrystallized from dilute methanol the melting point was 162° C.

EXAMPLE 8

Ethyl 2-thenoylcaprylate

Sodium metal (2.5 g.) was disolved in specially dried ethanol (50 ml.) and ethyl thenoylacetate (20 g.) was added. Then more of the alcohol (50 ml.) was added together with n-hexyl bromide (22 g.). The reaction mixture was stirred, warmed and brought to a temperature of 70° C. After refluxing 6 hours and keeping overnight the reaction mixture was neutral. It was diluted with water, and the oil was separated. The aqueous layer was then extracted with ether. The combined ether solutions were washed with sodium sulfate solution, dried and then distilled in a Claisen flask. The ethyl 2-thenoylcaprylate product boiled at 174° C. at 3 mm. pressure and

the yield was 20.2 g. which was 72% of the theoretical.

EXAMPLE 9

Ethyl 2-thenoylcaprylate

Hexylation of ethyl thenoylacetate without separating it from its reaction mixture is accomplished as follows: A one-mole run of ethyl thenoylacetate was prepared as previously described in Example 1. After 90 ml. of alcohol had been removed through the column at 150 mm. and the dark purple reaction mixture had become extermely thick, the pot was cooled and n-hexyl bromide (220 g.) was added. The reaction mixture, still thick, lightened in color when heated on a water bath at 70° C. for one-half hour. If was allowed to stand overnight, then while being slowly warmed, the mixture thinned and was refluxed for five hours. During this time an additional 37 ml. of alcohol were removed. The pot was cooled and the contents acidified with acetic acid (5 ml.), washed and dried. Distillation from the Claisen flask gave recovered diethyl carbonate (470 ml.), and then yielded 137.8 g. of ethyl 2-thenoylcaprylate, a light yellow oil boiling at 183° C. at 4 mm. pressure. This was 49% of the theoretical yield.

EXAMPLE 10

Isobutyl 2-thenoylacetate

Potassium metal (12.5 g.) was dissolved in dry isobutyl alcohol (100 ml.) and the solution was distilled to dryness under reduced pressure. When cooled, di-isobutyl carbonate (200 ml.) and 2-acetothienone (38 g.) were added. The reaction mixture became purple and thick. Isobutanol was removed at reduced pressure, the bath temperature being 140° C., the head temperature being 40° C. at 20 mm. pressure. The pot was cooled and the contents acidified with acetic acid (25 ml.). The organic layer was separated, washed and dried. Distillation from a Claisen flask at reduced pressure removed the di-isobutyl carbonate, and a yield of 27.3 g. of isobutyl 2-thenoylacetate, a yellow liquid boiling at 129° C. at 1 mm. pressure was obtained. This was 40% of the theoretical.

EXAMPLE 11

Ethyl alpha-benzyl-2-thenoylacetate

Sodium metal (2.5 g.) was dissolved in specially dried alcohol (100 ml.), and ethyl thenoylacetate (20 g.) together with benzyl chloride (15 g.) were added. Separation of sodium chloride began in a few minutes. The mixture was refluxed for 1 hour. A small amount of acetic acid was then added and the reaction mixture was diluted with water, extracted with ether and dried. Distillation from a Claisen flask yielded ethyl alpha-benzyl-2-thenoylacetate, a liquid boiling at 181° C. at 1 mm. pressure. The yield was 22.6 g. which was 78% of the theoretical.

EXAMPLE 12

Ethyl alpha-cetyl-2-thenoylacetate

Sodium metal (2.4 g.) was dissolved in specially dried alcohol (75 ml.) and the reaction mixture was distilled to dryness at reduced pressure. The product was suspended in diethyl carbonate (125 ml.) and ethyl thenoylacetate (19.8 g.) and cetyl bromide (31 g.) were then added. Alcohol and diethyl carbonate were distilled off

until the temperature reached 120° C. Sodium bromide separated while the mixture was refluxed for three and one-quarter hours. At this point a 1 ml. sample of the reaction mixture required 2.2 ml. N/10 H_2SO_4 for neutralization. Refluxing was continued for another one and three-quarter hours, and then the mixture was permitted to stand overnight. Water, ether and acetic acid (5 ml.) were then added. The ether layer was washed, dried and distilled to a 42 g. residue at 100° C. and 5 mm. pressure. This is the exact theoretical weight for ethyl alpha-cetyl-2-thenoylacetate. A portion of this product in a simple Hickman still was evacuated overnight to remove volatile impurities and then molecularly distilled by heating. Samples of the distilled product which were kept in a refrigerator, as well as samples which were diluted with petroleum ether, crystallized. After crystallizing four times from petroleum ether at −30° C., the purified ethyl alpha-cetyl-2-thenoylacetate was a yellowish-white waxy solid melting at 48° C.

EXAMPLE 13

Methyl 5-methyl-2-thenoylacetate

The procedure of Example 1 was followed using one-third molar quantities of sodium methylate, dimethyl carbonate and 5-methyl-2-acetothienone. After adding about one third of the ketone to the stirred dimethyl carbonate-sodium methylate mixture, the pot temperature rose only slightly. Heat was applied to bring the pot to 55° C., and then the heating was stopped, and the remainder of the ketone was added dropwise. The pot temperature continued to rise to 60° C. and then started to drop, and heat was applied to maintain the temperature at 55° C. After adding all the ketone in twenty-five minutes, the mixture was stirred for one and one-quarter hours at 55° C. Then during the next one and one-quarter hours, methyl alcohol dimethyl carbonate mixture (58 ml.) was distilled off at 63.5–88° C. The reaction mixture became pink at the beginning, and then gradually darkened to a brick red, but did not thicken. It was cooled, acidified, separated, and washed and dried over sodium sulfate. Distillation from a Claisen flask yielded 46.6 g. of methyl 5-methyl-2-thenoylacetate, a light yellow oily liquid boiling at 143° C. at 2.5 mm. pressure. This was 71% of the theoretical yield.

A mixture of methyl 5-methyl-2-thenoylacetate (2 ml.), phenyl hydrazine (1.5 ml.), ethyl alcohol (5 ml.) and one drop of hydrochloric acid was heated on the steam bath for one hour. When it was cooled and petroleum ether was added a solid which was 1-phenyl 3-(5-methyl-2-thienyl)-5-pyrazolone, separated. After recrystallization from a mixture of ethyl alcohol and methanol it melted at 136–137.5° C.

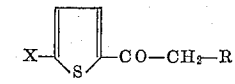
It will be understood that the thiophene ring may contain inert constituents other than the alkyl groups represented by X in the above formulas.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As many changes could be made in the above processes and products without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

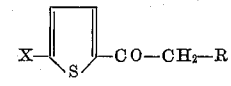
I claim:

1. The process comprising mixing a 2-thienyl ketone of the following type formula:



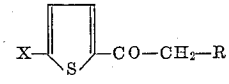
in which R is selected from the group consisting of alkyl radicals and hydrogen, and X is selected from the group consisting of lower alkyl radicals and hydrogen, with an anhydrous alkali metal alcoholate and a lower symmetrical dialkyl carbonate, whereby one of the hydrogens of the CH_2 group is replaced by a carbalkoxy group and the other hydrogen is replaced by an alkali metal, and linking by an alkyl linkage a radical selected from the group consisting of an alkyl radical and a benzyl radical by mixing said reaction mixture with a compound of said radical attached to a substance selected from the group consisting of halogen and sulfate.

2. The process comprising mixing a 2-thienyl ketone of the following type formula:



in which R is selected from the group consisting of alkyl radicals and hydrogen, and X is selected from the group consisting of lower alkyl radicals and hydrogen, with an anhydrous alcohol-free alkali metal alcoholate and a lower symmetrical dialkyl carbonate in quantities sufficient to function as reagent and reaction medium, whereby one of the hydrogens of the CH_2 group is replaced by a carbalkoxy group and the other hydrogen is replaced by an alkali metal, and removing alcohol, and linking by an alkyl linkage a radical selected from the group consisting of an alkyl radical and a benzyl radical by mixing said reaction mixture with a compound of said radical attached to a substance selected from the group consisting of halogen and sulfate.

3. The process comprising mixing a 2-thienyl ketone of the following type formula:



in which R is selected from the group consisting of alkyl radicals and hydrogen, and X is selected from the group consisting of lower alkyl radicals and hydrogen, with an anhydrous alcohol-free alkali metal alcoholate and a large excess of a lower symmetrical dialkyl carbonate the quantities thereof being sufficient to function as reagent and reaction medium, and continuously removing alcohol from the reaction mixture, whereby one of the hydrogens of the CH_2 group is replaced by a carbalkoxy group and the other hydrogen is replaced by an alkali metal, and removing alcohol, and linking by an alkyl linkage a radical selected from the group consisting of an alkyl radical and a benzyl radical by mixing said reaction mixture with a compound of said radical attached to a substance selected from the group consisting of halogen and sulfate.

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