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PROCESS FOR THE REDUCTION OF THIOPHENE-SUBSTITUTED KETOACIDS

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ABSTRACT OF THE DISCLOSURE

An aliphatic ketoacid (C_2-C_{14}) attached to a heterocyclic sulfur substituent is reduced to the corresponding heterocyclic substituted alkanoic acid. An aqueous solution of a water-soluble alkali or alkaline earth metal salt of the ketoacid and hydrogen are contacted with an insoluble sufide of group 6a or 8 metal, and in the presence of H_2S. The product alkanoic acids are subjected to ring closure and to dehydrogenation to 4-hydroxybenzothiophene, which is the procursor for 4-benzothienyl carbamate insecticides.

This invention relates to the reduction of keto groups. It is more particularly concerned with the reduction of keto groups in ketoacids attached to heterocyclic sulfur ring systems.

As is well known to those familiar with the art, several methods are known for reducing a keto group $(=C=O)$ to a methylene group $(-CH_2-)$, such as hydrogen in contact with a metal catalyst and the Clemmenson reduction. When a ketoacid contains a sulfur substituent, such as a thienyl group, however, the sulfur atom poisons the catalyst or is removed by hydrodesulfurization. In an effort to reduce a sulfur-containing ketoacid, e.g., 3-(2-thenoyl)propionic acid to 4-(2-thienyl)butyric acid, the Clemmenson reduction has been used. Results were erratic and yields were low. Better yields were obtained by the Huang-Minlon modification of the Wolff-Kishner reduction, employing very strong caustic solutions at high temperatures with hydrazine. Such a method is sufficient on a small laboratory scale, but it is not feasible for large-scale commercial process. Hydrazine is too expensive and the handling of strong caustic solutions at elevated temperatures is relatively costly.

Campaigne and Diedrich have reported [J. Am. Chem. Soc., 73, 5240 (1951)] the catalytic reduction of 3-(2-thenoyl)propionic acid using a cobalt polysulfide catalyst, hydrogen, and sulfur in acetic acid at 225° C. and 1500 p.s.i.g. hydrogen pressure. At this temperature acetic acid is highly corrosive and handling techniques become difficult. The yield of about 50 percent is too low for commercial operations. It has been found also that an acidic by-product is formed in 25–30 percent yield, that could be separated only with difficulty. Accordingly, this method is not feasible for commercial operation.

It has now been found that ketoacids having heterocyclic sulfur group substituents can be reduced to the corresponding alkanoic acid by a process that is relatively simple and which can be operated at elevated temperatures with little or no corrosion problems to effect commercially feasible yields.

Accordingly, it is a broad object of this invention to provide a process for reducing ketoacids having heterocyclic sulfur group substituents to the corresponding heterocyclic substituted alkanoic acid. Another object is to provide a process for reducing such ketoacids that is commercially feasible. A specific object is to provide a process for reducing such ketoacids in commercially feasible yields, which can be operated at elevated temperatures with little or no corrosion problems. Other objects and advantages of this invention will become apparent to those skilled in the art, from the following detailed description.

In general, this invention provides a method for reducing an aliphatic ketoacid, which is attached to a heterocyclic sulfur ring system, to the corresponding heterocyclic substituted alkanoic acid that comprises contacting an aqueous solution of a water-soluble alkali or alkaline earth metal salt of said ketoacid and hydrogen with a catalyst comprising an aqueous sodium hydroxide insoluble sulfide of a transitional metal, and in the presence of hydrogen sulfide.

The ketoacid reactants that are reduced in accordance with this invention are aliphatic ketoacids containing 2 to 14 carbon atoms and having substituted thereon a heterocyclic sufur ring system. The ketoacid, exclusive of the heterocyclic sulfur ring substituent, can be straight-chain or branched chain, saturated or unsaturated. The heterocyclic sulfur ring substituent (which interferes with the reduction of a keto group by ordinary methods of reduction) can contain other heterocyclic atoms along with heterocyclic sulfur. Typical substituents include thienyl, benzothienyl, thiazolyl, benzothiazolyl, and thiapyranyl. The ketoacid reactant can have, on the chain portion or on the heterocyclic group substituent, other substituents which in general are not readily reduced, such as alkyl, aryl, amino, dialkylamino, methylmercapto, alkoxy, and halogen.

The ketoacid reactant is used in the form of its water-soluble salt in aqueous solution. Either alkali metal or alkaline earth metal water-soluble salts can be employed. The sodium salt is preferred, based on the ready availability of sodium hydroxide. Other salts, however, are utilizable, such as lithium, potassium, and calcium, provided they are water-soluble. The ketoacid must be completely neutralized, i.e., at least stoichiometric amounts of base and acid must be used. When the ketoacid is incompletely neutralized, undesirable by-products are formed. A slight excess of base is not detrimental but a large excess will react with hydrogen sulfide to form metal sulfide which will increase the problem of subsequent product recovery.

The catalysts used in the reduction process of this invention are sulfides or mixtures of sulfides of transitional metals that are insoluble in aqueous alkali-metal hydroxide. The preferred catalysts are the sulfides of metals of Groups 6*a* and 8 of the Periodic Arrangement of the Elements Based on Atomic Numbers [J. Chem. Educ., 16, 409 (1939)]. Some transitional metal sulfides are known to be soluble in aqueous caustic (e.g. aqueous solution of sodium hydroxide) when the metal is present in its higher valence state, such as molybdenum trisulfide and tungsten trisulfide. Such soluble sulfides are not per se catalysts for the process of this invention, but they are utilizable when reduced to a lower valence state metal sulfide that is insoluble in aqueous sodium hydroxide solution. The reduced valence state transitional metal sulfide can be prepared by reducing, with hydrogen, a solution of the soluble metal sulfide (e.g. MoS_3) in aqueous sodium hydroxide and collecting, as the catalyst, precipitated metal sulfide in which the metal is in a reduced valence state. In an alternate preparation, a solution of the corresponding oxide (e.g. MoO_3) in aqueous sodium hydroxide can be reacted with hydrogen and hydrogen sulfide to produce a metal sulfide catalyst precipitate. The conditions utilizable to produce the catalytic metal sulfide of reduced valence state are those used in the process of this invention. Accordingly, a soluble metal sulfide, such as MoS_3, can be dissolved in aqueous caustic (NaOH) and added to the reactor along with the solution of the ketoacid salt. In this case, when hydrogen is charged under reaction conditions of the process of this invention, catalytic metal sulfide will be formed in situ. Cobalt polysulfide and a molybdenum sulfide of reduced valence state are particularly preferred. Other catalysts that are utilizable are iron sulfide, nickel sulfide, platinum sulfide, palladium sulfide, vanadium sulfide, titanium sulfide, manganese sulfide, tungsten sulfide, and mixtures of cobalt sulfide and nickel sulfide, cobalt sulfide and manganese sulfide, nickel sulfide and tungsten sulfide, and cobalt sulfide and iron sulfide. The transitional metal sulfide can be used as a slurry of finely divided particles in the aqueous reaction medium.

In accordance with this invention, the reduction of the ketoacid reactant with hydrogen takes place in the presence of hydrogen sulfide. Hydrogen sulfide itself can be used, but it is also contemplated to use sulfur-containing materials that form hydrogen sulfide in situ under the conditions of the reduction reaction. Such substances include elemental sulfur, mercaptans, thioacetamides, alkyl sulfides, disulfides and polysulfides, carbon disulfide, carbonyl sulfide, and metal sulfides, such as ferric sulfide. The term "in the presence of hydrogen sulfide," as used herein and in the claims, includes hydrogen sulfide added per se and also hydrogen sulfide produced in situ from the aforedescribed sulfur-containing materials. Although hydrogen sulfide is preferred, hydrogen selenide, hydrogen telluride and corresponding compounds that can form hydrogen selenide and hydrogen telluride can be used.

Preferably, the reduction is carried out at temperatures of between about 225° C. and about 280° C., for reaction times of between about 15 minutes and about 3 hours varying inversely with temperature; although higher and lower temperatures and longer and shorter times can be used. Longer reaction times would not appear to be detrimental, but are not necessary. Shorter times result in incomplete conversion. At higher temperatures, by-product formation increases. The particularly preferred time and temperature range is from about 240° C. for about 3 hours to about 260° C. for about 40 minutes.

The process of this invention is carried out batchwise or continuously, under pressure in suitable pressure equipment. The hydrogen partial pressure will be between about 1000 p.s.i.g. and about 2300 p.s.i.g. Practical, effective molar ratios of hydrogen were found to be between about 7 and about 22 moles per mole ketoacid reactant.

The product, reduced ketoacid, can be recovered by conventional means for isolating carboxylic acids from solutions of their water-soluble salts. In general, the aqueous solution is acidified with hydrochloric acid or sulfuric acid. The freed carboxylic acid is dissolved in a suitable solvent, such as ether or a low-boiling liquid paraffinic hydrocarbon. The resultant solution is separated, dried, and freed of solvent, as by evaporation or by distillation, to obtain the product acid.

Those skilled in the art will recognize that the process of this invention is applicable to reducing the keto group of ketoacids in general. It is, however, particularly applicable to ketoacids having heterocyclic sulfur group substituents.

The following examples demonstrate the application of the process of this invention to the reduction of 3-(2-thenoyl)-propionic acid [4-(2-thienyl)-4-ketobutyric acid] to 4-(2-thienyl)-butyric acid. This is a step in a method for the synthesis of a class of benzothienyl carbamates that have insecticidal activity. These carbamates are described in copending application Ser. No. 334,581, filed Dec. 30, 1963, and now abandoned, which is a continuation-in-part of copending application Ser. No. 220,-073, filed Aug. 28, 1962, and now abandoned. The other synthesis steps involve cyclicizing the 4-(2-thienyl)butyric acid to 4-keto-4,5,6,7-tetrahydrobenzothiophene and dehydrogenating to 4-hydroxybenzothiophene. Typical methods are shown in J. Am. Chem. Soc., 57, 1611 (1935). The conversion of 4-hydroxybenzothiophene to the carbamate is conventional.

EXAMPLE 1

A solution of 25 parts 3-(2-thenoyl)propionic acid in 5.8 parts sodium hydroxide and 200 parts water is charged in an autoclave with 8 parts sulfur, 10 parts moist cobalt polysulfide catalyst and 1000 p.s.i.g. hydrogen. The autoclave is heated to 260° C. while stirring and held at the temperature for 40 minutes. The autoclave is cooled and the filtered solution is treated with 100 parts diethyl ether to remove 0.4 part neutral materials. Acidification of the remaining aqueous solution followed by extraction with ether and removal of ether gives 21.7 parts (91% yield) of 4-(2-thienyl)butyric acid of high purity (98%).

EXAMPLE 2

A solution of 25 parts 3-(2-thenoyl)propionic acid in 5.8 parts sodium hydroxide and 200 parts water is charged into the autoclave with 10 parts moist cobalt polysulfide catalyst. Hydrogen sulfide gas, equivalent to 8 parts sulfur, and 1000 p.s.i.g. hydrogen are charged. The autoclave is heated to 260° during stirring and is held at this temperature for 60 minutes. After cooling and venting, the mixture is worked-up as described in Example 1 to give 21.7 parts (91% yield, 100% conversion) of 4-(2-thienyl) butyric acid.

EXAMPLE 3

Molybdenum trisulfide, 3 parts, was dissolved in 120 parts of 2 wt. percent sodium hydroxide solution at 80° C. The filtered solution was combined with a solution of 25 parts 3-(2-thenoyl)propionic acid in 5.9 parts sodium hydroxide and 200 parts water and charged to the autoclave. Hydrogen sulfide, 100 p.s.i.g., and 1000 p.s.i.g. hydrogen were charged and the autoclave heated to 260° C. The mixture was stirred and held at this temperature for one hour. The autoclave was cooled and vented. Workup by Example 1 gave 21.2 parts (92%) of 4-(2-thienyl)butyric acid. A precipitate of reduced molybdenum sulfide separated by filtration from the reaction mixture was found to be an active catalyst in subsequent runs.

EXAMPLE 4

An example of the preparation of a catalyst suitable for the present invention is as follows: 30 parts molybdic oxide is dissolved in 16.8 parts sodium hydroxide and 300 parts water and charged to the autoclave and hydrogen sulfide equivalent to 8 moles hydrogen sulfide to 1 mole molybdic oxide is charged. After stirring one hour, 1000 p.s.i.g. hydrogen is charged and the autoclave is heated to 225° C. and held at this temperature for an additional hour. After cooling, the fine black powder is filtered and bottled for use as a reduction catalyst.

In another preparation, molybdenum trisulfide is dissolved in aqueous sodium hydroxide solution and reduced with 1000 p.s.i.g. hydrogen at 225° C. for one hour. After cooling a fine black powder is filtered and bottled for use as a reduction catalyst.

Although the present invention has been described with preferred embodiments, it is to be understood that modifications and variations may be resorted to, without departing from the spirit and scope of this invention, as those skilled in the art will readily understand. Such variations and modifications are considered to be within the purview and scope of the appended claims.

What is claimed is:

1. A method for reducing a ketoacid, 3-(2-thenoyl) propionic acid to 4-(2-thienyl) butyric acid, that comprises contacting an aqueous solution of a water-soluble salt, selected from the group consisting of alkali metals and alkaline earth metals, of said ketoacid and hydrogen at a pressure of about 1000 p.s.i.g. to about 2300 p.s.i.g. with a catalyst consisting essentially of an aqueous sodium

hydroxide-insoluble sulfide of a transitional metal of Groups 6*a* and 8 of the Periodic Arrangement of the Elements Based on Atomic Numbers, at a temperature of about 225° C. to about 280° C. and in the presence of hydrogen sulfide.

2. The method defined in claim **1** wherein said catalyst is cobalt polysulfide.

3. The method defined in claim **1** wherein said catalyst is a molybdenum sulfide, in which the molybdenum is in a reduced valence state.

References Cited

Campaigne et al.: Chem. Abs. 47:560—1 (1953).

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