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PATENT SPECIFICATION

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(54) PREPARATION OF METHYL GLYOXAL ACETALS

(71) We, PFIZER INC., a corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, 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:—

This invention relates to the preparation of methyl glyoxal acetals and more particularly to a process for the preparation of methyl glyoxal acetals from dihydroxyacetone wherein dihydroxyacetone, an alkanol and an acid catalyst are reacted to produce the acetals.

The preparation of methyl glyoxal acetals by reacting methyl glyoxal with alcohol in the presence of an acid catalyst is disclosed in United States Patent Specification No. 2,421,559. The required starting material for this synthesis, methyl glyoxal, may be obtained by the oxidation of acetone with selenium dioxide, by the partial oxidation of propylene glycol or by the acid catalyst transformation of dihydroxyacetone. Another known process for preparing methyl glyoxal acetals involves the reaction of acetone with an alcohol and a nitrating agent in the presence of an acid catalyst.

United States Patent Specification No. 2,421,559 discloses that the omission of a water-immiscible organic solvent and the use of the monohydric alcohol as the solvent itself results in the formation of large amounts of undesired alkyl esters of an α -alkoxy propionic acid and methyl glyoxal dialkyl acetal dialkyl ketal.

Surprisingly, it has been found that the production of these side or undesirable products may be avoided by the process of the present invention which preferably employs an excess of alkanol.

In accordance with the present invention there is provided a process for the preparation of a methyl glyoxal acetal having the formula:—

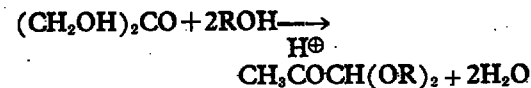


wherein R is an alkyl group containing up to 10 carbon atoms, which comprises reacting at a temperature of 50°—150°C. dihydroxyacetone with at least an equivalent amount of an alkanol containing 1 to 10 carbon atoms in the presence of a catalytic amount of a mineral acid or a cation exchange resin (in its acid form) produced from an acid having a pK value of less than one.

The compounds prepared by the process of the present invention are particularly valuable in the synthesis of growth promotants, for instance, in the synthesis of quinoxalinedi-N-oxide antibacterials.

For the purpose of the present invention, the pK value is defined as the negative logarithm to the base 10 of the equilibrium constant K determined at 25°C.

Mineral acids by themselves may be used as the catalyst, for example, sulphuric acid. The resultant acetal is then obtained by conventional extraction and distillation procedures. Water is a co-product in this reaction, but its continuous removal is not necessary. Impurities present in the dihydroxyacetone starting material do not interfere with the reaction. The reaction is generally illustrated as follows:



wherein R is an alkyl group containing up to 10 carbon atoms, preferably 1 to 4 carbon atoms.

The process of the present invention is operable when an alkanol of up to 10 carbon atoms is employed as a reactant.

The catalyst is preferably used in an amount of 1% to 10% by weight of the dihydroxyacetone.

The cation exchange resins used in the process of the present invention are those based upon the stronger acids as defined above and are generally used in an amount of 1 to 10% by weight of the dihydroxyacetone. Examples of resins which are suitable for the process of the present invention are sulpho-

ated polystyrene, and sulphonated styrene-divinylbenzene copolymer.

The reaction is preferably carried out in the absence of a solvent. However, a non-reactive solvent such as benzene, hexane or chloroform may be used.

The alkanol is used in a least an equivalent amount with respect to the dihydroxyacetone (2 mols to 1 mol), however, it is preferred to use an excess amount within the range of a 2 molar to a 200 molar excess, with a ratio of 10 mols to 1 mol particularly preferred.

A surprising feature of the invention is that the alkanol may be used in excess amounts to serve both as the reactant and the solvent for the reaction.

A wide range of temperature is possible during the reaction which extends from 50° to 150°C., but preferably is from 60° to 120°C.

The reaction may be carried out at either atmospheric, subatmospheric or superatmospheric pressure.

Processing of the resulting reaction mixture may be carried out in routine manner by distillation or by extraction of the reaction mixture with water-immiscible solvent such as methylene chloride after adding water to the reaction mixture.

The acetals prepared by the process of the invention are obtainable in a purity greater than 98% and surprisingly are uncontaminated with any undesirable side products such as 1, 1,2,2-tetraalkoxypropane or alkyl α -dialkoxypionate as occurs with the prior art process mentioned above.

The following Examples illustrate the present invention and the manner in which it may be performed.

Example 1

Methyl Glyoxal Dimethylacetal

A mixture of 90g. of dihydroxyacetone,

270ml. of methanol and 9g. of a sulphonated polystyrene cationic resin in the acid form is heated at 65° to 70° for 16 hrs. The resin catalyst is removed by filtration and the filtrate is diluted with water followed by extraction with methylene chloride. The distillation of methylene chloride extract gave the dimethylacetal in 82% yield of 98% purity.

Example 2:

The reaction of Example 1 was run at 100°C. in a pressure vessel for 4 hrs. At this point GLPC analysis of the reaction mixture using toluene as an internal standard indicated 96% yield. An 80% isolated yield was achieved upon extraction and distillation as carried out as in Example 1.

Example 3:

Methyl Glyoxal Di-*n*-Propylacetal (1,1-Di-*n*-propoxy-2-propanone):

A mixture of 36g of dihydroxyacetone, 200ml of *n*-propanol, and 4g. of sulphonated polystyrene cationic resin was heated at 80°C. to 90°C. for 5 hrs. The resin catalyst was removed by filtration and the reaction mixture extracted and distilled as described in Example 1 to give the isolated propylacetal product.

Example 4:

Methyl Glyoxal Di-*n*-Butyl Acetal (1,1-Di-*n*-butoxy-2-propane):

A mixture of 30g. of dihydroxyacetone, 100ml of 1-butanol and 2g. of a sulphonated polystyrene cationic resin was heated at 90°C. to 110°C. for 4 hrs. The resin catalyst was removed by filtration and the filtrate extracted and distilled as described in Example 1 to give the butyl acetal product.

The yields and characterization data of representative examples prepared by this procedure are given in Table I.

TABLE I

Synthesis of 1, 1-Dialkoxy-2-propanones ($H_3C-CO-CH(OR)_2$)

No.	R Substituent	% Yield		b.p.	NMR ($CDCl_3$, TMS) δ
		GLPC Assay	Isolated		
1	CH_3-	96	82	82° (70 mm)	2.2 (S, 3H), 2.4 (S, 6H), and 4.43 (S, 1H).
2	C_2H_5-	99	92	82° (50 mm)	1.23 (T, 6H), 2.2 (S, 3H), 3.7 (M, 4H), 4.53 (S, 1H).
3	$CH_2CH_2CH_2-$	98.5	90	82° (14 mm)	0.91 (T, 6H), 1.57 (M, 4H), 2.15 (S, 3H), 3.55 (M, 4H), and 4.5 (S, 1H).
4	$\begin{array}{c} CH_3 \\ \diagdown \\ CH \\ \diagup \\ CH_3 \end{array} -$	98	85	59° (14 mm)	1.1 (pair of doublets, 12H), 2.11 (S, 3H), 3.86 (M, 2H), and 4.55 (S, 14H).
5	$CH_3CH_2CH_2CH_2-$	95	90	92° (29 mm)	0.93 (M,) and 1.5 (M, total 14H), 2.15 (S, 3H), 3.61 (M, 4H), and 4.5 (S, 1H).

WHAT WE CLAIM IS:—

1. A process for the preparation of a methyl glyoxal acetal having the general formula:—



wherein R is an alkyl group containing up to 10 carbon atoms, which comprises reacting at a temperature of 50° to 150°C. dihydroxyacetone with at least an equivalent amount of an alkanol containing 1 to 10 carbon atoms in the presence of a catalytic amount of a mineral acid or a cation exchange resin (in its acid form) produced from an acid having a pK value of less than one.

10 2. A process according to claim 1 wherein the alkanol used contains from 1 to 4 carbon atoms.

15 3. A process according to either one of claims 1 or 2, wherein the cation exchange resin is a sulphonated polystyrene or a sulphonated styrene-divinylbenzene copolymer.

4. A process according to any one of claims 1 to 3, wherein the temperature is maintained at 60° to 120°C. during the reaction.

5. A process according to any one of claims 1 to 4, wherein the catalyst is used in an amount of 1 to 10% by weight of the dihydroxyacetone. 25

6. A process according to any one of the preceding claims, wherein the alkanol is used in an excess amount over the equivalent amount within a range of a 2 molar to a 200 molar excess. 30

7. A process according to claim 6, wherein the alkanol is used in an amount of 10 mols per 1 mol of dihydroxyacetone. 35

8. A process for the preparation of methyl glyoxal acetals according to claim 1 and substantially as hereinbefore described with reference to the Examples. 40

9. Methyl glyoxal acetals of formula (I) herein whenever prepared by a process according to any one of the preceding claims.



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TABLE I

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8. A process for the preparation of methyl glyoxal acetals according to claim 1 and substantially as hereinbefore described with reference to the Examples.

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