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Technical Notes

Synthesis of Alkyl Glyoxylates

Nikhil R. Trivedi and Samptraj B. Chandalia*

Department of Chemical Technology, University of Mumbai, Matunga, Mumbai-400 019, India

Abstract:

Glyoxylic acid esters are prepared using commercially available 50% w/w aqueous solution of glyoxylic acid. The method involves neutralization of aqueous solution of glyoxylic acid with sodium hydroxide followed by isolation of glyoxylic acid as a calcium salt by double decomposition technique. Suspending this calcium salt of glyoxylic acid in an alcohol and liberating free glyoxylic acid by concentrated sulfuric acid gives an alcoholic solution of glyoxylic acid containing insoluble anhydrous calcium sulfate. Glyoxylic acid being a strong acid readily forms an ester. The effect of various reaction parameters on overall conversion of glyoxylic acid and selectivity with respect to alkyl glyoxylate were studied.

Introduction

Glyoxylic acid esters are useful reagents in organic synthesis and are used as intermediates for synthesis of cephalosporins and retinoic acids,[1] penems, carbapenems, α-hydroxy esters, and β-lactams[2] and in asymmetric synthesis of α-amino acids.[3]

Since glyoxylic acid is commercially available as a 50% aqueous solution and is heat sensitive, most of the methods reported to prepare its esters are indirect methods using substances other than glyoxylic acid. These include electrolytic reduction of ethyl oxalate,[4] ozonolysis of maleate and/or fumarate derivatives,[1] oxidation of ethyl bromoacetates with dimethyl sulfoxide,[5] and oxidative cleavage of tartrate diesters with inorganic oxidants such as red lead,[6] lead tetraacetate,[7] and paraperiodic acid.[8]

Recently James M. Hook has reported an acid-catalyzed exchange of 1 equiv of alcohol between alkyl dialkoxyacetates and glyoxylic acid monohydrate followed by treatment with phosphorus pentoxide to give alkyl glyoxylate in high yield.[9]

We now report a simple and efficient synthesis of alkyl glyoxylate using commercially available 50% w/w aqueous solution of glyoxylic acid. The method involves neutralization of aqueous solution of glyoxylic acid with sodium hydroxide followed by isolation of glyoxylic acid as a calcium salt by double decomposition technique. Suspending this calcium salt of glyoxylic acid in an alcohol and liberating free glyoxylic acid by concentrated sulfuric acid gives an alcoholic solution of glyoxylic acid containing insoluble anhydrous calcium sulfate. Glyoxylic acid being a strong acid readily forms an ester. The effect of various reaction parameters on overall conversion of glyoxylic acid and selectivity with respect to alkyl glyoxylate were studied, and the results are summarized in Tables 1−4.

Table 1. **Effect of mole ratio of sulfuric acid to calcium glyoxylate[a]**

no.	mole ratio of sulfuric acid to calcium glyoxylate	% convn of glyoxylic acid	% select.	
			methyl glyoxylate	methyl dimethoxy acetate
1	1::1	70	95	5
2	1.1:1	85	88	12
3	1.16:1	92	73	27
4	1.5:1	96	60	40

[a] Calcium glyoxylate = 0.105 g mol, methanol = 60 mL, temperature = 30 °C, time = 1 h.

Table 2. **Effect of temperature[a]**

no.	temp, °C	% convn of glyoxylic acid	% select.	
			methyl glyoxylate	methyl dimethoxy acetate
1	30	70	95	5
2	55	75	93	7
3	65	77	91	9

[a] Calcium glyoxylate = 0.105 g mol, methanol = 60 mL, sulfuric acid = 0.105 g mol, time = 1 h.

Experimental Section

The reactions were carried out in a fully baffled mechanically agitated glass reactor of 150 mL capacity. Reaction temperature was maintained constant by keeping the reactor in the constant-temperature bath.

1. Preparation of Calcium Glyoxylate. The aqueous solution of glyoxylic acid (50 g, 50% w/w, 0.338 mol) was

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Table 3. **Effect of period of reaction[a]**

no.	time, h	% convn of glyoxylic acid	% select. methyl glyoxylate	% select. methyl dimethoxy acetate
1	1	77	91	9
2	2	77	88	12
3	3	78	84	16
4	5	78	80	20
5	7	78	76	24

[a] Calcium glyoxylate = 0.105 g mol, methanol = 60 mL, sulfuric acid = 0.105 g mol, temperature = 65 °C.

Table 4. **Esterification using different alcohols[a]**

no.	alcohol	% convn of glyoxylic acid	% select. alkyl glyoxylate	% select. alkyl dialkoxy acetate
1	methanol	70	95	5
2	ethanol	68	97	3
3	*n*-butanol	60	98	2

[a] Calcium glyoxylate = 0.105 g mol, alcohol = 60 mL, sulfuric acid = 0.105 g mol, temperature = 30 °C, time = 1 h.

taken in the reactor, placed in a water bath at 30 °C. Aqueous sodium hydroxide solution (20% w/v) was added slowly with continuous stirring until the pH of the solution was 8−9. Anhydrous calcium chloride (20 g, 0.18 mol) dissolved in 40 mL of water was added slowly to obtain solid calcium glyoxylate. The resulting reaction mixture was stirred for 0.5 h and filtered under suction. Calcium glyoxylate thus obtained was dried in an oven (30 g, 95%) and analyzed for aldehyde content by oximation method[10] (98% pure).

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2. Preparation of Alkyl Glyoxylate. Calcium glyoxylate (20 g, 0.105 mol) was suspended in 60 mL of alcohol in a reactor placed in an ice bath. Concentrated sulfuric acid (10.3 g, 0.105 mol) was added dropwise by an addition funnel in 5 min. The resulting reaction mixture was then heated to desired temperature and stirred for 1 h.

3. Analysis of the Reaction Mixture. Calcium sulfate was allowed to settle, and supernant liquid was withdrawn for analysis. This solution was neutralized with sodium bicarbonate and centrifuged. The supernant liquid was analyzed by gas chromatography (Chemito 8510 gas chromatograph, Toshniwal Instrument, India) using a s. s. column, 0.32 mm × 2 m long packed with 10% SE-30 on Chromosorb-w with nitrogen as the carrier gas. The formation of alkyl dialkoxyacetate was confirmed by comparing GC and TLC results with authentic samples prepared from dichloroacetic acid by the procedure reported by Moffet.[11]

4. Isolation of Alkyl Glyoxylate. The reaction mixture was filtered, and calcium sulfate was washed with 100 mL of alcohol. Filtrate along with washing was subjected to fractional distillation under vacuum. Alcohol was distilled at 50 °C, followed by distillation of alkyl glyoxylate. The isolated yields were comparable to that found by GC analysis of reaction mixture.

The boiling point of the alkyl glyoxylates obtained were as follows: methyl glyoxylate = 44−52 °C/35 mmHg (lit.[1] 45−50 °C/29 mmHg); ethyl glyoxylate = 47−53 °C/35 mmHg (lit.[1] 49 °C/35 mmHg); *n*-butyl glyoxylate = 67−75 °C/20 mmHg (lit.[5] 65−79 °C/20 mmHg).

Unreacted glyoxylic acid was recovered from the undistilled syrupy residue as calcium glyoxylate.

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