Russian Journal of Applied Chemistry, Vol. 75, No. 9, 2002, pp. 1434–1437. Translated from Zhurnal Prikladnoi Khimii, Vol. 75, No. 9, 2002, pp. 1466–1469.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Optimization of Synthesis of Mono-*O*-methylglycerol Isomers

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Received January 23, 2002

Abstract—Parameters were refined for synthesis of glycerol 1-monomethyl ether by methylation of glycerol with dimethyl sulfate in the presence of alkali; a gas–liquid chromatographic procedure was proposed for identification of structural isomers of mono-*O*-methylglycerol.

Procedures for preparing glycerol 1-monomethyl ether (1-MG) are diverse and are summarized in reviews [1–4]. These procedures give relatively low (compared to other glycerol monoalkyl ethers) yield of the target product, are multistage, and require large (up to tenfold) excess of methanol and sodium metal [5, 6]. Only Fairbaurne [7] reported on preparation of noticeable amounts of the second isomer, glycerol 2-monomethyl ether (2-MG), with the major product being 1-MG.

Glycerol monomethyl ether is a promising cryoprotector in low-temperature preservation of blood cells, bone marrow, and reinoculated cell cultures [8, 9]. In view of the necessity of producing pilot batches of 1-MG for large-scale biological tests and with the aim to reveal the effect of isomerism on the cryoprotective properties, we performed experiments to refine the conditions for preparing 1-MG and 2-MG. Our goal was to find the method and conditions ensuring the highest yield of the target products, with the procedure being as simple as possible. As the route to 1-MG and 2-MG, we chose methylation of glycerol with dimethyl sulfate (DMST) in the presence of alkali. Fairbaurne [7] reported on synthesis of sodium glycerate from excess glycerol and aqueous NaOH; its methylation with DMST, after removing water under reduced pressure, yielded a mixture of 1-MG and 2-MG. Cross and Jacobs [5] reported on another convenient procedure involving preparation of sodium glycerate from equimolar amounts of anhydrous glycerol and powdered NaOH, followed by alkylation with alkyl halides to obtain glycerol 1-monoalkyl ethers. It seemed appropriate to refine the effect of the synthesis parameters (molar ratio of components, concentration of aqueous alkali) on the yield and isomeric composition of the product. To this end, we tested several procedures based on Fairbaurne's method [7] (Table 1).

EXPERIMENTAL

Run no. 1. Synthesis of 1-MG and 2-MG involved the following stages [7]: (1) mixing of glycerol with 47% aqueous NaOH in the molar ratio glycerol : NaOH = 3 : 1; (2) distillation of water under reduced pressure (40 mm Hg) on an oil bath, with the bath temperature gradually increased to 150°C; (3) addition of DMST to the resulting sodium glycerate (GONa) at 120–125°C over a period of 1 h in the molar ratio GONa : DMST = 1 : 0.5; (4) removal of Na_2SO_4 from the reaction mixture; (5) distillation of a mixture of 1-MG and 2-MG from the bottoms at 140°C/2 mm Hg; and (6) separation of 1-MG and 2-MG by repeated vacuum distillation on a column with cutting 1°C fractions in the range 91–140°C/2 mm Hg. The total yield of the isomers was 45%, with the isomer ratio 1-MG : 2-MG = 6 : 1.

Run no. 2 was performed similarly to run no. 1, except that NaOH was taken as 69% solution (instead of 47% solution) to reduce the time for water distillation under reduced pressure. The total yield of the isomers was 41%, with the isomer ratio 1-MG : 2-MG = 8 : 1.

Run no. 3. Sodium glycerate was prepared as described in [5] by heating anhydrous glycerol and powdered NaOH with vigorous stirring, with the molar ratio glycerol : NaOH = 2 : 1. The temperature in the oil bath was raised to 120–145°C. After removal of water, the temperature was decreased to 110–115°C, with the stirring continued, and 0.5 mol of DMST was added dropwise. The resulting Na_2SO_4 was filtered off. After distillation of the bottoms in a vacuum

1070-4272/02/7509-1434$27.00

Table 1. Ratio of reactants and reaction products in methylation of glycerol with DMST in the presence of NaOH

Molar ratio of reactants				Total yield of isomers, %	1-MG : 2-MG ratio
glycerol	NaOH	DMST	H_2O		
3	1	0.5	2.5	45	6 : 1
3	1	0.5	1	41	8 : 1
2	1	0.5	–	33	10 : 1
3	1	0.5	–	63	15 : 1

(up to 140°C/5 mm Hg) and repeated fractionation, 1-MG and 2-MG were obtained in a 10 : 1 ratio; total yield 33%.

Run no. 4. The procedure ensuring the highest content of 1-MG was as follows. A three-necked flask equipped with a stirrer and a thermometer and purged with an inert gas was charged with equimolar amounts of purified anhydrous glycerol and powdered NaOH. The mixture was heated to 145°C with continuous vigorous stirring. At 120°C, release of water formed in the synthesis started, and the mixture warmed up to 145°C with foaming. After short stirring at this temperature, a uniform paste formed. The temperature was decreased to 90°C, and, with the stirring continued, anhydrous glycerol was added over a period of 30 min to dissolve the resulting sodium glycerate; the final molar ratio glycerol : NaOH was 3 : 1. Then, 0.5 mol (relative to NaOH) of DMST was added from a dropping funnel, with the temperature maintained within 90–100°C. In the course of reaction, white fumes liberated, the mixture slightly warmed up, and Na_2SO_4 precipitated. The precipitate was filtered off. 1-MG was isolated by vacuum distillation at 92–93.5°C/5 mm Hg; yield 59%. Along with 1-MG, a small (3–5%) amount of 2-MG was obtained.

Run no. 5. 1-MG was prepared by an independent procedure: reaction of glycerol 1-monochlorohydrin (1-MCHG) with sodium methylate in a tenfold excess of absolute methanol [6]. The synthesis involved the following stages: (1) preparation of sodium methylate; (2) reaction of 1-MCHG with sodium methylate; (3) filtration to remove the NaCl precipitate; (4) distillation of excess methanol under reduced pressure; and (5) isolation of 1-MG. Yield 42%. The necessity of performing this labor-consuming and fire-hazardous procedure was dictated by the need in obtaining a 1-MG sample free of its isomer, 2-MG. The sample was used for identification of structural isomers of glycerol monomethyl ether.

The structures of the products were confirmed by molecular refraction and IR spectroscopy. The spectra are discussed in detail in [10]. The refractive index n_D^{20} was determined with a URL-M1 refractometer. The IR spectra were recorded on a Specord 75-IR spectrophotometer (thin film between KBr plates).

The molecular weight of 1-MG and 2-MG was determined by gel permeation chromatography on a Waters GPC-200-1 Model 200 gel chromatograph under the following conditions: eluent tetrahydrofuran; three styrogel columns 200, 500, and 1000 Å; 25°C; flow rate 1.2 ml min^{-1}. Samples (2 ml) contained about 0.2 wt % of the substance. The product purity was checked by GLC (LKhM-80 chromatograph, 1000 × 3-mm column, stationary phase 20% Carbowax 20M on Chromaton N-Super, flame ionization detector, carrier gas He, flow rate 50 ml min^{-1}, programmed column heating from 60 to 280°C). A 0.1-g sample was dissolved in 0.2 ml of purified anhydrous pyridine, and 0.4 ml of hexamethyldisilazane and 0.1 ml of trimethylchlorosilane were added. The mixture was allowed to stand for 2–3 h and then injected into the chromatograph vaporizer. The main constants of the products are listed in Table 2 together with published data.

The IR spectra contain the following characteristic absorption bands (cm^{-1}): 3385, 3395 (OH); 2928, 1465 (CH_2); 2830 (OCH_3); 1360 (CH_3); 1190 (COC).

The isomers are difficult to separate and identify, as their have close physicochemical parameters (except n_D^{20}) and similar IR spectra. In the gel chromatogram, both compounds give a narrow symmetrical peak with the same retention volume V_R corresponding to M 106. Their separation by vacuum distillation requires repeated thorough fractionation with collection of close-cut (1–2°C) fractions; the isomer percentage in the fractions gradually changes with increasing temperature. Fairbaurne [7] suggested to identify isomers by refractive indices. However, examination using an LKhM-80 chromatograph and the procedure developed in [12] showed that, even at the same n_D^{20}, samples may contain 1-MG and 2-MG in

Table 2. Physicochemical characteristics of 1-MG and 2-MG at 25°C (molecular weight of 1-MG and 2-MG 106)

Compound*	bp, °C/*p*, mm Hg	n_D^{20}	d_4^{20}	Molecular refraction	
				experimental	calculated
1-MG	92–95/5	1.4444	1.1169	25.23	25.37
		1.4445 [11]	1.1163 [11]	25.28	25.37
2-MG	109–110/4	1.4480	1.1311	25.12	25.37
		1.4456 [7]	1.124 [7]	25.16	25.37

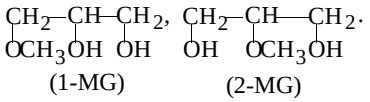
* Structural formulas: 

Table 3. Results of GLC analysis of 1-MG–2-MG fractions from run no. 1

Fraction	bp, °C	n_D^{20}	Content, %		Impurities, %
			1-MG	2-MG	
I	92–93.5	1.4444	99.9	–	0.1
II	93.5–95	1.4444	96.1	3.4	0.5
III	95–97	1.4444	83.6	16.4	–
IV	97–99	1.4446	57.0	43.0	–
V	99–101	1.4450	57.9	45.1	–
VI	101–104	1.4454	22.4	77.6	–
VII	104–106	1.4464	20.8	79.2	–
VIII	106–108	1.4476	19.1	80.9	–
IX	108–109	1.4478	18.4	80.3	1.3
X	109–110	1.4480	–	99.0	1.0

different ratios. The chromatograms contain two major narrow symmetrical peaks. The isomer ratio was evaluated from the peak areas. The scheme of fractionation of structural isomers obtained in run no. 1 is given in Table 3.

Table 3 shows that the first three fractions have the same refractive index, n_D^{20} = 1.4444, but differ in the isomeric composition by up to 15%. The refractive index of fraction IV is very close, n_D^{20} = 1.4446, at the isomer ratio 1-MEG : 2-MEG = 57 : 43. Comparison of these data shows that the refractive index n_D^{20} is unsuitable for identifying 1-MG and 2-MG in synthesis of glycerol methyl ethers by methylation of glycerol with DMST in the presence of aqueous alkali (run nos. 1, 2). Run nos. 1–4 show that variation of the reactant ratio (Table 1) and the use of aqueous alkali as solvent result in formation of products containing different ratios of 1-MG and 2-MG. The highest content of 1-MG was obtained in run no. 4. Heating of glycerol with equimolar amount of powdered NaOH, followed by addition of excess glycerol (to the ratio glycerol : NaOH = 3 : 1) to dissolve the resulting sodium glycerate ensure increased yield of 1-MG (59%). Excess glycerol (run no. 3) complicates fast removal of water from sodium glycerate, which is hygroscopic and moisture-sensitive [5]. It is also known that prolonged heating of glycerol in the presence of alkali favors formation of polyglycerol [13]. Apparently, these facts are responsible for the low yield of 1-MG in run no. 3. The synthesis under conditions of run no. 4 is simpler, because no water is added (cf. run nos. 1, 2) and hence the stage of water removal under reduced pressure after the completion of sodium glycerate formation and before isolation of 1-MG is eliminated. Furthermore, under conditions of run no. 4 the by-product 2-MG is formed in a small amount and does not appreciably complicate isolation of 1-MG.

At the same time, if 2-MG is the target product, the conditions of run no. 1 are preferable. The use of water as solvent in the reaction of glycerol with aqueous alkali favors formation of appreciable amount of

2-MG along with 1-MG. As the water content in the NaOH solution is decreased from 63 (run no. 1) to 31% (run no. 2), the content of 2-MG decreases (Table 1), and with anhydrous glycerol and dry NaOH (run no. 4) it becomes as low as 3%. More dilute NaOH solutions were not tested because of more difficult isolation of the reaction product.

CONCLUSIONS

(1) The procedure for preparing glycerol 1-monomethyl ether by methylation of glycerol with dimethyl sulfate in the presence of NaOH was optimized by varying the reactant ratio; the yield of the target product was increased to 59%, and the isolation procedure was simplified.

(2) The highest yield of glycerol 2-monomethyl ether is attained when methylation of glycerol with dimethyl sulfate is performed using 47% NaOH.

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