# Condensation of 1,2,4-Butanetriol with Carbonyl Compounds and Reactions of Hydroxyalkyl-1,3-dioxacyclanes

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**Abstract**—A mixture of isomers of 2-(1,3-dioxolan-4-yl)ethanol and 1,3-dioxan-4-ylmethanol was prepared by reaction of 1,2,4-butanetriol with paraformaldehyde. This mixture was subjected to O-alkylation, O-acylation, condensation with phenyl isocyanate, and substitution of OH groups for Cl. The relative activity of acetone derivatives of glycerol and 1,2,4-butanetriol in reactions with allyl chloride and benzyl chloride was estimated.

Keywords: 1,2,4-butanetriol, O-alkylation, O-acylation, acetone derivatives of glycerol

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Condensation of glycerol with aldehydes is known to give a mixture of isomeric 5- and 6-membered cyclic acetals where 1,3-dioxolanes slightly dominate. With acetone and other ketones, glycerol forms only 5-membered derivatives [1, 2]. These compounds are used as components of motor fuels, additives in the food and perfume industries, and reactants in the synthesis of pharmaceuticals [3].

Data on acetals and ketals of 1,2,4-butanetriol **1** are few and the ratio of 5- to 6-membered isomers is determined by temperature, duration of synthesis, structure of carbonyl compounds, solvent, etc. [4, 5].

In the present work, heterogeneous catalytic condensation of triol 1 with formaldehyde 2 and acetone 3 has been studied and certain transformations of the heterocyclic alcohols obtained have been performed. Condensation of triol 1 with formaldehyde 2 in benzene at 80°C in the presence of cation-exchange resin KU-2 gave rise to a mixture enriched with a 6-membered product (4a : 4b = 1 : 4). The reaction of 1 with acetone 3 carried out under the same conditions resulted in a single product, specifically 2,2-dimethyl-4hydroxyethyl-1,3-dioxolane 5 (Scheme 1). Chromatographic and spectral studies showed the absence of the 6-membered isomer in the reaction mass. In the reaction with ketones, therefore, triol 1 behaves completely similarly to glycerol.

The mixture of formals 4a and 4b (1 : 4) was subjected to a reaction with thionyl chloride (benzene, 4 h) to form the corresponding chlorides 6a and 6b(1 : 4). The presence of 4-chloromethyl-1,3-dioxane 6bin the isomer mixture (6a, 6b) was additionally



#### Scheme 1.

Reagents	Reaction conditions	Reaction products	Yield, %
1+2	Toluene, KU-2, 100°C, 5 h	<b>4a : 4b</b> (1 : 4)	60
$4a, 4b + SO_2Cl$	Pyridine, 10°C, 4 h	<b>6a</b> : <b>6b</b> (1 : 4)	63
<b>4a</b> , <b>4 b</b> + CH <sub>2</sub> =CHCH <sub>2</sub> Cl	50% NaOH, 25°C, 8 h	<b>7a : 7b</b> (1 : 3)	92
$\mathbf{4a}, \mathbf{4b} + \mathrm{ClC}_{2}\mathrm{H}_{4}\mathrm{C}(\mathrm{O})\mathrm{Cl}$	Pyridine, 30°C, 8 h	<b>8a : 8b</b> (1 : 5)	88
4a, 4b + PhN=C=O	Hexane, 30°C, 6 h	<b>9a : 9b</b> (1 : 3)	94

**Table 1.** Conditions for synthesis of triol 1 formals andcompounds 6–9 based thereon

verified by an authentic synthesis of **6b** through condensation of allyl chloride with formaldehyde according to a known method [6] (Scheme 2). Formals **4a** and **4b** in their reactions with allyl chloride, monochloroacetyl chloride, and phenyl isocyanate form the corresponding derivatives **7–9**. The yield of the compounds obtained and the isomer ratio are presented in Table 1.

At the initial stage of O-alkylation of the formals mixture (**4a**, **4b**) by allyl chloride (1–2 8 h, 20–25% conversion) the main product in the reaction mass is a substituted 1,3-dioxane **7b**, whose concentration is 8–10 times greater than that of isomeric 1,3-dioxolane **7a**.

To assess the effect of the OH group position remote from the heterocycle on the OH group's activity, the rate of ethers formation during the reaction of ketals of glycerol **5** and triol **1** with allyl chloride and benzyl chloride was investigated by

**Table 2.** Relative reactivity<sup>a</sup> of alcohols **5** and **10** with respect to allyl chloride and benzyl chloride (NaOH,  $30^{\circ}$ C, 2 h)

Reagent X	Molar ratio <b>5</b> : <b>10</b> : X	Reaction products
CH <sub>2</sub> =CHCH <sub>2</sub> Cl	$1:1:2B^{b}$	<b>11</b> : <b>12</b> = 10 : 1
	1.5 : 1.5 : 0.5 <sup>c</sup>	<b>11</b> : <b>12</b> = 10 : 1
BnCl	$1:1:2^{c}$	<b>13</b> : <b>14</b> = 12 : 1

<sup>a</sup> The relative reactivity was calculated by GLC. <sup>b</sup> Conversion of alcohol was no more than 30%. <sup>c</sup> Conversion of chloride was no more than 30%.

means of competitive reaction method (Scheme 3, Table 2). Judging from the yields of ethers 11 and 12, 13 and 14 in the initial stages (conversion up to 30%), the glycerol derivative 5 is an order of magnitude more reactive than ketal 10. Consequently, the farther the OH group is from the cycloacetal moiety, the lower is its activity in O-alkylation reactions.

The structure of the resulting five- and sixmembered heterocycles is confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. The signals of triol formals 4a and 4b and substituted 1,3-dioxoacyclanes 6-9 were assigned based on the analysis of the chemical shifts and the spin-spin coupling constants of the heterocyclic moiety's protons. Specifically, in the <sup>1</sup>H NMR spectrum of the 6a-6b isomer mixture, the singlets at 4.85 and 5.00 ppm correspond to the  $C^2$  methylene group of 4-(2-chloroethyl)-1,3-dioxolane 6a, and the  $C^4$  methine protons of the five-membered cycle appear as a multiplet at 4.20-4.25 ppm. The chloromethyl group resonates as multiplets at 3.62–3.66 ppm. The <sup>1</sup>H NMR spectrum of chloride **6b** is characterized with doublets in the region of 5.01 and 4.73 ppm with the coupling constant of 6.3 Hz, which correspond to the  $C^2$  methylene group of 1.3-dioxane, with  $C^4$  methine



 $R = Cl (6a, 6b), OCH_2CH=CH_2 (7a, 7b), OCOCH_2Cl (8a, 8b), OCONHC_6H_5 (9a, 9b).$ 



protons of the six-membered cycle appearing as a multiplet at 4.00–4.04 ppm. The chloromethyl group is detected as a triplet in the region of 3.60 ppm with the coupling constant of 3.2 Hz.

In the <sup>13</sup>C NMR spectra of the **6a–6b** isomer mixture the C<sup>7</sup> signals observed in the 35 and 42 ppm regions are characteristic of compounds **6a** and **6b**, respectively. Note the difference between the signals of the C<sup>2</sup> atom adjacent to the two heteroatoms for a five- (**6a**) and six-membered (**6b**) molecules: the C<sup>2</sup> signal for 1,3-dioxolane derivative **6a** is downfield (96 ppm) as compared with 1,3-dioxane derivative **6b** (93 ppm).

For the ether mixture of 4-[2-(allyloxy)ethyl]-1,3dioxolane **7a** and 4-[(allyloxy)methyl]-1,3-dioxane **7b**, the <sup>1</sup>H NMR spectral signals are confirmed by the presence of a terminal double bond. The CH group of **7a** and **7b** at a multiple bond resonates at 5.90 ppm as a multiplet, and the protons of the methylene group (CH<sub>2</sub>) are detected as a doublet at 5.11–5.30 ppm with the coupling constant of 1.2 and 2.8 Hz. The presence of a heterocyclic moiety is indicated by singlets of the  $C^2$  atom of 1,3-dioxane moiety (**7b**) at 4.83 and 5.00 ppm and doublets of 1,3-dioxolane moiety (7a) at 4.70 and 5.02 ppm with the coupling constant of 6.3 Hz. It should be noted that the presence of a  $C^7$  ether bond promotes an upfield shift of the proton signal. For instance, while these protons resonate at 3.80 and 3.88 ppm in the mixture of 4a–4b triol formals obtained, their signals appear at 3.70 and 3.75 ppm, respectively, in the 7a–7b ether mixture.

The <sup>13</sup>C NMR spectra of **7a–7b** ether mixture show the presence of terminal double bond signals at 117 and 135 ppm, as well as the appearance of  $C^7$  signals at 72 ppm both for 4-[2-(allyloxy)ethyl]-1,3-dioxolane **7a** and for 4-[(allyloxy)methyl]-1,3-dioxane **7b**.

The <sup>1</sup>H NMR spectra of the ester mixture of 2-(1,3dioxolan-4-yl)ethylchloroacetate **8a** and 1,3-dioxan-4ylmethylchloroacetate **8b** are distinguished by the presence of a singlet of the chloromethylene (CH<sub>2</sub>Cl) group that appears in the region of 4.11 ppm. The proton signals of C<sup>7</sup> adjacent to the ester group resonate between 4.13 and 4.19 ppm as a multiplet for the 1,3-dioxolane derivative and at 4.22 ppm as a doublet of doublets with the coupling constant of 5.1 and 6.6 Hz for the 1,3-dioxane derivative. The common features of the <sup>13</sup>C NMR spectrum for the mixture of **8a** and **8b** are the presence of the chlorine-containing CH<sub>2</sub>Cl group, which has a chemical shift at 41 ppm, and significantly more downfield signals of the ester group at 167 ppm. The protons of the methylene group bonded to two heteroatoms, appear at 95 ppm for 2-(1,3-dioxolan-4-yl)ethylchloroacetate **8a** and 94 ppm for 1,3-dioxane-4-ylmethylchloroacetate **8b**.

The <sup>1</sup>H NMR spectra of a mixture of substituted isocyanates **9a** and **9b** are characterized by the benzene ring's doublets between 7.00 and 7.50 ppm and the NH group's singlet in a downfield position (8.53 ppm) indicating the formation of the corresponding amides **9a** and **9b**.

The C<sup>7</sup> signals in the <sup>13</sup>C NMR spectra of the mixture of 2-(1,3-dioxolan-4-yl)ethylphenylcarbamate **9a** and 1,3-dioxan-4-ylmethylphenylcarbamate **9b** resonate at 65 ppm. The signals appearing at 118–140 ppm are due to the presence of an aromatic moiety linked to the amide group. As such, the chemical shifts of the characteristic protons at the C<sup>2</sup>, C<sup>4</sup>, and C<sup>5</sup> atoms of heterocyclic structures did not change significantly.

The obtained data indicate that ketones, in particular acetone, are effective for selective protection of vicinal hydroxyl groups in polyols, and that the 1,3-dioxolane moiety does not interfere with the glycerol reaction by free  $CH_2OH$  group.

# **EXPERIMENTAL**

The reaction products were analyzed on an HRGS 5300 Mega Series Carlo Erba chromatograph equipped with a flame ionization detector, with helium as carrier gas, flow rate 30 ml/min, 25 m column, temperature 50-280°C, programmable heating at a rate 8 deg/min, detector temperature 250°C, and vaporizer temperature 300°C. Chromato-mass spectra were recorded on a Chromatec-crystal 5000.2 instrument (30 m capillary quartz column, analysis duration 20 min, ion source temperature 260°C, transfer line temperature 300°C, scanning range 30-300 Da, pressure 37-43 mTorr, helium as carrier gas, heating rate 20 deg/min). To obtain the mass spectra of the compounds, the electron impact ionization method was used. NMR spectra were recorded on a Bruker AVANCE-400 (400.13 MHz) spectrometer in CDCl<sub>3</sub>.

Commercially available reagents, like glycerol, allyl chloride, benzyl chloride, acetone, and benzene,

were used. 4-[(Hydroxy)ethyl]-2,2-dimethyl-1,3-dioxolane, 4-[(allyloxy)methyl]-2,2-dimethyl-1,3-dioxolane, 4-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolane, and 4-[(allyloxy)ethyl]-2,2-dimethyl-1,3-dioxolane were prepared according to known procedures [1–4].

**2-(1,3-Dioxolan-4-yl)ethanol (4a) and 1,3-dioxan-4-ylmethanol (4b)** (isomer mixture). A mixture of 5 g (0.04 mol) of 1,2,4-butanetriol, 1 g (0.03 mol) of paraformaldehyde, 30 mL of anhydrous toluene, and 10% by weight of activated cation-exchange resin KU-2 were boiled until the calculated amount of water (0.7 mL) was obtained. Upon completion of the reaction (5 8 h), the solution was cooled and the cation-exchange resin was filtered off. The filtrate was evaporated and the residue was distilled in vacuo (80°C, 10 mmHg). Yield 3 g (60%).

**2-(1,3-Dioxolan-4-yl)ethanol (4a).** Mass spectrum, *m*/*z* (*I*<sub>rel</sub>, %): 117 (1), 87 (22), 73 (25), 57 (20), 44 (100), 30 (30).

**1,3-Dioxan-4-ylmethanol (4b).** Mass spectrum, m/z ( $I_{rel}$ , %): 117 (1), 87 (100), 57 (30), 45 (27), 31 (48).

4-(2-Chloroethyl)-1,3-dioxolane (6a) and 4-chloromethyl-1,3-dioxane (6b). 1.4 g (0.012 mol) of thionyl chloride was added to a mixture of 1 g (0.008 mol) of 2-(1,3-dioxolan-4-yl)ethanol and 1,3-dioxan-4-ylmethanol and 0.7 g (0.008 mol) of pyridine, while cooling to 0°C. The reaction mixture was stirred at 10– 12°C until sulfur dioxide ceased to evolve (5 h), followed by addition of chloroform (30 mL) and water washing of the reaction mass, avoiding boiling up (violent decomposition of thionyl chloride). The residue was distilled. Yield 0.42 g (43%), colorless liquid with a pungent odor.

**4-(2-Chloroethyl)-1,3-dioxolane (6a).** Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 135 (36), 137 (12), 106 (20), 108 (7), 89 (10), 91 (3), 73 (100), 53 (10).

**4-Chloromethyl-1,3-dioxane (6b).** Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 135 (7), 137 (2), 106 (3), 108 (1), 89 (15), 91 (4), 87 (100), 57 (20).

**4-[2-(Allyloxy)ethyl]-1,3-dioxolane (7a) and 4-[(allyloxy)methyl]-1,3-dioxane (7b).** A mixture of 0.5 g (0.004 mol) of 2-(1,3-dioxolan-4-yl)ethanol and 1,3-dioxan-4-ylmethanol, 30 mL of benzene, and 30 g of 50% sodium hydroxide solution and 10 wt % of catamine AB was stirred at 60–65°C for 2 8 h. The mixture was cooled to room temperature and 1.6 g (0.02 mol) of allyl chloride was added. The reaction was carried out until the initial alcohols were completely converted (8 h) while heating to 30°C. After cooling, 30 mL of dichloromethane was added and the mixture was water washed until neutral, then dried and evaporated. The desired product was obtained by vacuum distillation. Yield 0.4 g (60%), colorless liquid.

**4-[2-(Allyloxy)ethyl]-1,3-dioxolane** (7a). Mass spectrum, m/z ( $I_{rel}$ , %): 157 (1), 100 (11), 87 (16), 73 (45), 71 (100), 57 (50).

**4-[(Allyloxy)methyl]-1,3-dioxane (7b).** Mass spectrum, m/z ( $I_{rel}$ , %): 101 (13), 87 (100), 71 (55), 57 (54).

2-(1,3-Dioxolan-4-yl)ethylchloroacetate (8a) and 1,3-dioxan-4-yl-methylchloroacetate (8b). A mixture of 1 g (0.008 mol) of 2-(1,3-dioxolan-4-yl)ethanol and 1,3-dioxan-4-ylmethanol, 0.6 g (0.008 mol) of anhydrous pyridine, and 0.8 g (0.008 mol) of monochloroacetyl chloride was heated to  $30^{\circ}$ C for 8 h. The recovered oil crystallized within 24 8 h under cooling and trituration. The reaction mixture was poured into a mixture of 15 g of ice and 30 mL of 1N HCl and stirred until a suspension was formed. The crude product was filtered off, washed with ice water, dried, and evaporated, the residue was distilled in vacuo. Yield 0.5 g (30%), colorless liquid with a pungent odor.

**2-(1,3-Dioxolan-4-yl)ethylchloroacetate (8a).** Mass spectrum, m/z ( $I_{rel}$ , %): 193 (5), 195 (2), 77 (42), 79 (15), 73 (80), 70 (100), 57 (12).

**1,3-Dioxan-4-yl-methylchloroacetate (8b).** Mass spectrum, m/z ( $I_{rel}$ , %): 100 (15), 87 (100), 77 (20), 79 (6), 57 (21).

2-(1,3-Dioxolan-4-yl)ethylphenylcarbamate (9a) and 1,3-dioxan-4-ylmethylphenylcarbamate (9b). A mixture of 0.5 g (0.004 mol) of 2-(1,3-dioxolan-4-yl)ethanol and 1,3-dioxan-4-ylmethanol in 10 mL of hexane and 1.9 g (0.016 mol) of phenylisocyanate in 5 mL of hexane was stirred at 35°C. Upon completion of the reaction (TLC control), the mixture was cooled to room temperature and the crystals were filtered off, water washed, air dried, and recrystallized from hexane. Yield 0.4 g (40%), white powder.

**2-(1,3-Dioxolan-4-yl)ethylphenylcarbamate (9a).** Mass spectrum, m/z ( $I_{rel}$ , %): 237 (10), 137 (25), 119 (100), 106 (24), 91 (40), 44 (46).

**1,3-Dioxan-4-ylmethylphenylcarbamate (9b).** Mass spectrum, m/z ( $I_{rel}$ , %): 237 (20), 137 (65), 119 (100), 91 (50), 87 (40), 43 (40).

## CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

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