ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 3, pp. 442–446. © Pleiades Publishing, Ltd., 2017.
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New Phosphorylated Glycoluril Derivatives

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Received October 17, 2016

Abstract—The *N*-acylation of glycoluril with 1-haloacetyl halides was studied. The optimal conditions and reaction regioselectivity, as well as the effect of reagent molar ratios, base nature, temperature, and reaction time on the yield of the target product were established. It was shown that the chemical modification of the synthesized bis(bromoacetyl) derivative of glycoluril by phosphorylation by the classical Arbuzov reaction gave a previously unknown bis(diethylphosphonoacetyl) derivative of glycoluril. The consecutive silylation and hydrolysis of the latter derivative gave the corresponding bis(phosphonoacetyl) derivative which presents interest as a potentially biologically active compound.

Keywords: glycoluril (bisureas), bis(haloacetyl)glycoluril, bis(diethylphosphonoacetyl)- glycoluril, bis(phosphonoacetyl)glycoluril

DOI: 10.1134/S1070363217030124

At present the synthesis and study of the properties of compounds derived from glycoluril, a representative of the class of bicyclic bisureas, remains one of the vigorously developing fields of modern heterocyclic chemistry. Tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (glycoluril, **1**) has several reaction centers and, therefore, presents special interest from the viewpoint of chemical modification [1–3]. In particular, in [4–6] the methods of synthesis of glycoluril **1,** its analogs, as well as derivatives of the latter are summarized and the chemical properties and biological activity of these compounds are described.

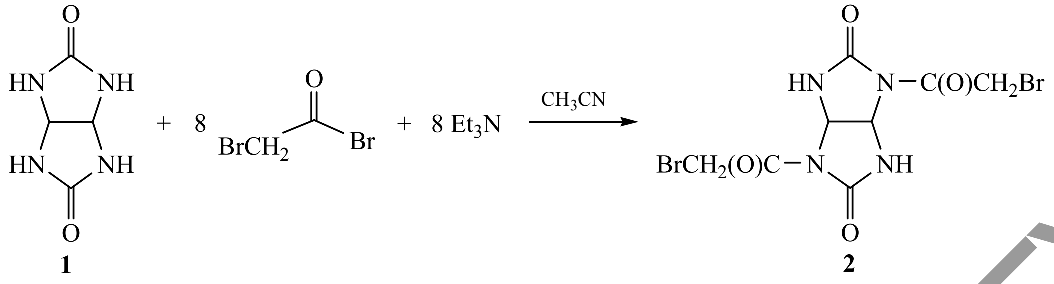
Although the diverse chemical behavior of compound **1** has been well-documented, its *N*-acylation reactions have only been employed in the synthesis of *N,N*-di- and *N,N,N,N*-tetraacetyl derivatives [7, 8], even though the potential of the acylation reaction and the potential applications of the reaction products is much broader and more diversified. Thus, Sibi and He [9] showed that the reaction of 2-pyrrolidin-2-one with 1-bromoacetyl bromide gives rise to 1-(bromoacetyl) pyrrolidin-2-one.

To extend the range of known *N*-acylation reactions of glycoluril **1**, we studied for the first time the reaction of the latter with bromoacetyl bromide. The reaction was performed in acetonitrile in the presence of organic bases in an inert atmosphere to obtain a previously unknown bis(bromoacetyl) glycoluril derivative, namely, 1,4-bis(bromoacetyl)tetrahydroimidazo [4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (**2)** in a reasonable yield (Scheme 1). It should be noted that even using a 8-fold excess of bromoacetyl bromide we could not obtain any appreciable amount of *N,N,N,N*-tetrakis (bromoacetyl)glycoluril derivative under the used reaction conditions.

The structure of compound **2** was assessed by means of NMR spectroscopy. The ^{1}H NMR spectrum contains a multiplet proton signal of two CH_2Br groups (4.42–4.65 ppm), a singlet signal of CH protons (5.61 ppm), and a singlet proton signal of two NH groups (9.27 ppm). The ^{13}C NMR spectrum contains signals at 166.24 ($COCH_2$), 153.87 (CO), 63.18 (CH), and 30.22 ppm (CH_2Br).

With the aim to optimize *N*-haloacetylation conditions, we studied the effect of reagent ratio, base nature, and reaction temperature and time on the yield of the target product. Table 1 lists the yields of compound **2** at varied reactions conditions. As seen, the

Scheme 1.



yield of *N,N*-bisacetyl bromide **2** depends on the reagent molar ratio. Thus, with equimolar reagent amounts, a lot of unreacted glycoluril remained, and the yield of the main product was no more than 10%. When the proportion of bromoacetyl bromide was doubled, the yield of the main product reached 35%, and the highest yield (78%) was obtained with a 4-fold excess of bromoacetyl bromide.

The reaction temperature, too, had a strong effect on the yield of the target product. Thus, reasonable yields of compound **2** could be obtained only when the reagents were mixed at temperatures below 0°C, whereas at room temperature (25°C) the yield of this compound decreased to 40–59%. By contrast, elevated temperatures during stirring of the reaction mixture, after bromoacetyl bromide has been added, positively affect the yield of the main product and the reaction rate. By performing the reaction at 70–80°C we could decrease the reaction time from 48 to 12 h.

The yield of compound **2** is also dependent on the choice of the base. Thus, when pyridine was used as HBr acceptor, the yield of the target product was 68%, whereas the use of trimethylamine as the base raises the yield to 78%.

Further on we reacted glycoluril **1** with chloroacetyl chloride (Scheme 2). The latter was found to be less reactive toward glycoluril **1**, because the reaction required harsher conditions. The optimal reaction conditions were as follows: pyridine as HCl acceptor and the higher boiling toluene as solvent.

The structure of 1,4-bis(chloroacetyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (**3**) was established by means of NMR spectroscopy. The ^{1}H NMR spectrum contains signals of two CH_2Cl groups (4.33–4.49 ppm), as well as CH (5.34 ppm) and NH groups (8.83 ppm).

Table 2 lists the yields of compound **3** at varied reactions conditions. The optimal chloroacetyl chloride : glycoluril molar ratio, like in the above-described reaction, is 8 : 1. However, even with the 8-fold excess of haloacetyl halide, we could not obtain any appreciable amount of *N,N,N,N*-tetrakis(haloacetyl) glycoluril derivative under the used reaction conditions.

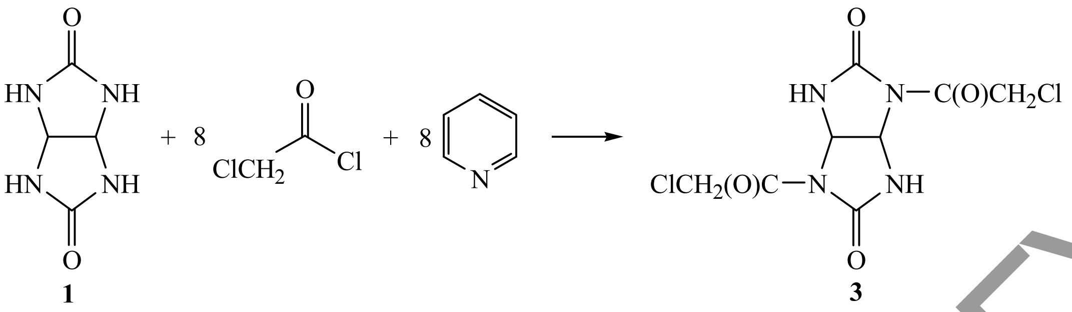
Attempted synthesis of tetrakis(bromoacetyl)glycoluril by the reaction of compound **2** with 4 mol of bromoacetyl bromide, too, failed. In this case, compound **2** was isolated intact. Apparently, the fact that the target *N,N,N,N*-tetrakis(haloacetyl)glycoluril is not formed under the used reaction conditions is due to steric reasons, specifically, to the hindered access of the acylating agent to the four reaction centers.

Thus we have studied the reactions of glycoluril with haloacylating agents. We showed that the synthesized *N,N*-bis(haloacetyl) derivatives of glycoluril

Table 1. Dependence of the yield of 1,4-bis(bromoacetyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione **2** on the reaction conditions

Parameter	Reagents molar ratio					
	1 : 2		1 : 4		1 : 8	
Temperature of reagents mixing, °C	0	25	0	25	0	25
Yield in the presence of pyridine, %	10.33	5.86	35.34	22.30	67.60	40.92
Yield in the presence of triethylamine, %	15.87	8.39	60.67	40.53	78.12	59.52

Scheme 2.



are attractive substrates which contain an active electrophilic center convenient for nucleophilic substitution by different agents.

In this connection we considered it promising to introduce phosphorus-containing groups to bisacetylated glycoluril using the Arbuzov reaction. As known, phosphonic acid derivatives exhibit a high and diverse biological activity, and, therefore, combining pharmacophoric fragments with different properties in one molecule could lead to new and unexpected results.

Analysis of published data revealed a lack of information of the phosphorylation reactions of both glycoluril **1** and its derivatives. We used triethyl phosphite as the phosphorylating agent. *N,N*-Bis(acetyl bromide) **2** was phosphorylated by heating it with equimolar amount of triethyl phosphite at 90–100°C for 2 h under argon (Scheme 3). The reaction progress was monitored by TLC. As a result, we obtained {(2,5-dioxohexahydroimidazo[4,5-*d*]imidazole-1,4-diyl)bis(2-oxoethane-2,1-diyl)}bis(diethyl phosphonate) (**4**) as an undistillable oil.

The structure of diethyl phosphonate **4** was established by means of IR and NMR spectroscopy. The IR spectrum shows a broad NH band at 3051 cm^{-1}. The band at 1734 cm^{-1} is assignable to C=O stretching modes. The $COCH_2$ group appears at 1683 cm^{-1}. The band at 1258 cm^{-1} corresponds to P=O vibrations.

Table 2. Dependence of the yield of 1,4-bis(chloroacetyl)-tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione **3** on the reaction conditions

Base	Reaction temperature, °C	Yield, %
Pyridine	70	50.46
	100	68.62
Triethylamine	70	53.28
	100	–

The multiplet at 1.23–1.39 ppm in the ^{1}H NMR spectrum is associated with protons of the four CH_3 groups. The $COCH_2$ protons appear as a multiplet at 3.49–3.98 ppm. The methylene protons give a multiplet at 4.04–4.24 ppm and the NH protons give a singlet at 7.03 ppm.

The ^{31}P NMR spectrum displays a single signal of two equivalent ^{31}P nuclei at 20.17 ppm, which provides an unambiguous evidence for the phosphonate structure of compound **4**. Further evidence for the structure of compound **4** comes from the mass spectra, where the molecular ion peak is observed at *m/z* 497.12.

Phosphonic acids are known to exhibit a higher biological activity than their esters. Therefore, we subjected bisphosphonate **4** to acid hydrolysis (Scheme 4). At the first stage compound **4** was treated with tribromosilane to obtain tribromosilyl esters **4a** which then underwent a facile acid hydrolysis. The reaction progress was detected by the complete disappearance of the ethyl proton signals in the ^{1}H NMR spectrum of the reaction mixture. Further on the reaction mixture was treated with 10% HCl to obtain {(2,5-dioxohexahydroimidazo[4,5-*d*]imidazole-1,4-diyl)bis(2-oxoethane-2,1-diyl)}bisphosphonic acid (**5**).

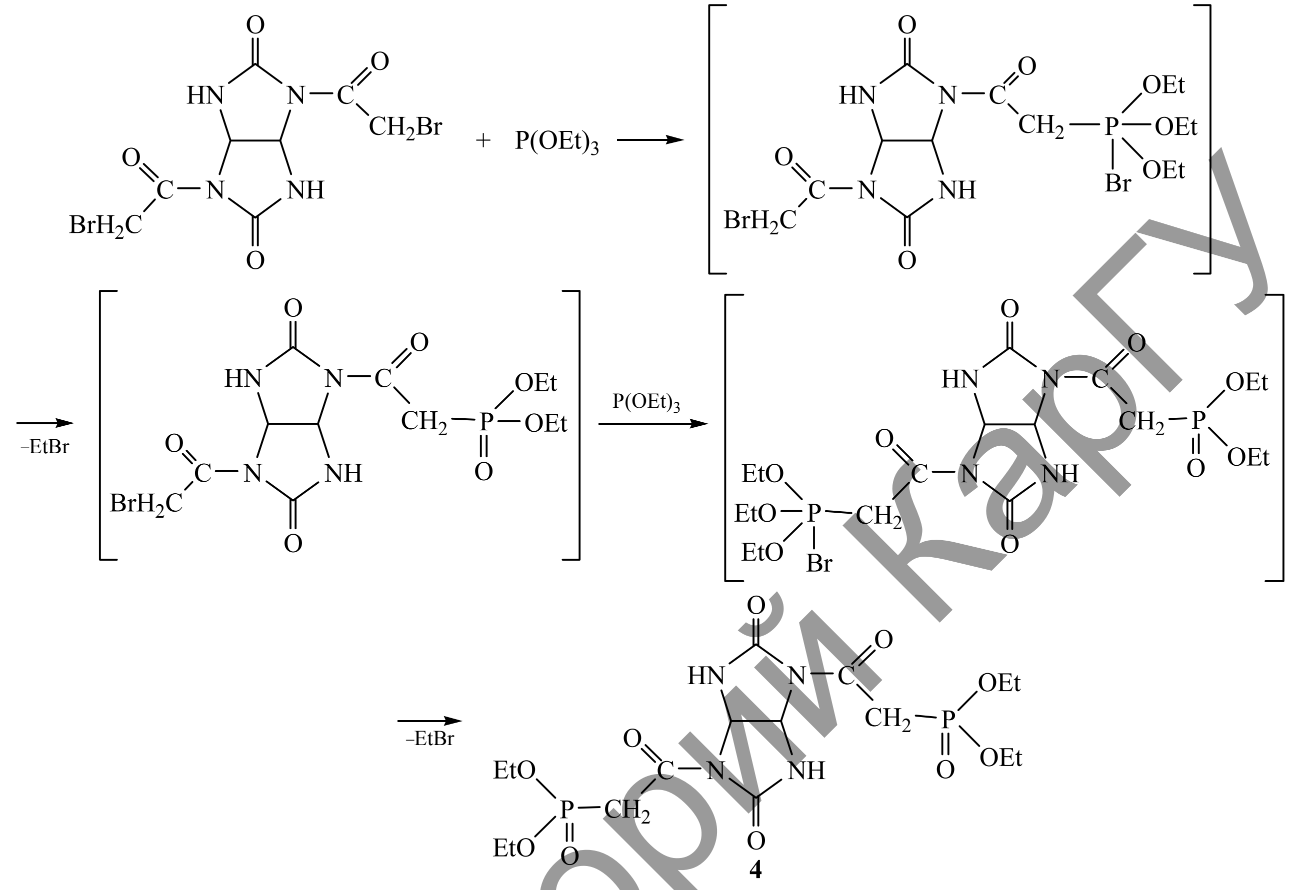
The ^{1}H NMR spectrum of acid **5** contains CH_2 proton signals as multiplets at 3.44–3.58 ppm, as well as a CH proton signal as a singlet at 5.74 ppm. The ^{31}P NMR spectrum shows a signal at 16.04 ppm.

Thus, we are the first to synthesize new phosphorylated glycoluril derivatives which are interesting objects for testing for potential biological activity.

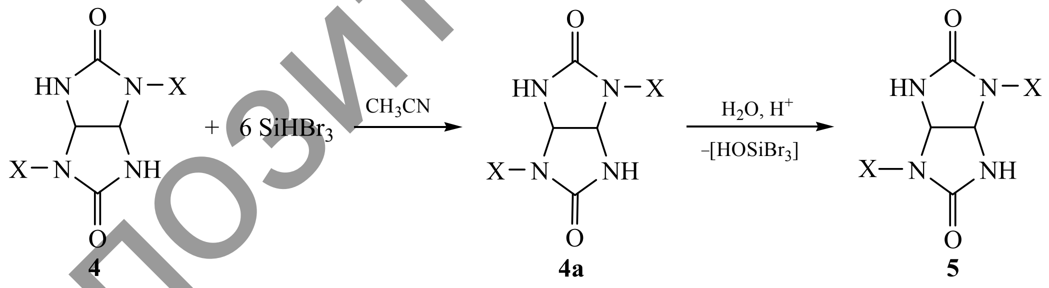
EXPERIMENTAL

The NMR spectra were recorded on a Jeol ECX-400 [162 (^{31}P), 400 (^{1}H), and 100 MHz (^{13}C)] at room

Scheme 3.



Scheme 4.



X = $C(O)CH_2P(O)(OEt)_2$ (**4**), $C(O)CH_2P(O)(OSiBr_3)_2$ (**4a**), $C(O)CH_2P(O)(OH)_2$ (**5**).

temperature. The IR spectra were obtained on a FSM-1201 FTIR spectrometer in the range 450–4000 cm^{-1} in KBr pellets. The mass spectra (ESI-TOF) were taken on a Bruker MicroTOF instrument. The melting points were measured on a Mettler Toledo MP50 melting point system. The reaction progress was followed and purity of the compounds was checked by TLC on standard Silufol UV-254 plates in a 6 : 1 benzene–ethanol system.

1,4-Bis(bromoacetyl)tetrahydroimidazo[4,5-*d*]-imidazole-2,5(1*H*,3*H*)-dione (2). Bromoacetyl bromide (56.84 g, 0.28 mol) was added at 0°C to a mixture of 5.0 g (0.035 mol) of glycoluril **1** and 28.3 g (0.28 mol) of triethylamine in acetonitrile. The mixture was heated at 70–80°C for 12 h and then poured into acidified water (pH 3). The precipitate was filtered off, washed with water and diethyl ether, and dried. Yield 10.5 g (78%), mp 260°C. ^{1}H NMR spectrum (DMSO-

d_6), δ, ppm: 4.42–4.65 m (4H, CH_2Br), 5.61 s (2H, CHCH), 9.27 s (2H, NH). ^{13}C NMR spectrum (DMSO-d_6), $δ_C$, ppm: 166.24 ($COCH_2$), 153.87 (CO), 63.18 (CH), 30.22 (CH_2Br). Found, %: C 25.23; H 2.22; Br 41.54; N 14.68. $C_8H_8Br_2N_4O_4$. Calculated, %: C 25.02; H 2.10; Br 41.62; N 14.59.

1,4-Bis(chloroacetyl)tetrahydroimidazo[4,5-*d*]-imidazole-2,5(1*H*,3*H*)-dione (3). Chloroacetyl chloride (31.64 g, 0.28 mol) was added at 0°C to a mixture of 5.0 g (0.035 mol) of glycoluril **1** and 22.0 g (0.28 mol) of pyridine in toluene. The mixture was heated at 90–105°C for 16 h and then treated with saturated $NaHCO_3$ solution. The precipitate that formed was filtered off and washed with methanol. Yield 7.12 g (69%), mp 250°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 4.33–4.49 m (4H, CH_2Cl), 5.34 s (2H, CHCH), 8.83 s (2H, NH). ^{13}C NMR spectrum (DMSO-d_6), $δ_C$, ppm: 166.24 ($COCH_2$), 153.87 (CO), 63.18 (CH), 30.22 (CH_2Cl).

{(2,5-Dioxohexahydroimidazo[4,5-*d*]imidazole-1,4-diyl)bis(2-oxoethane-2,1-diyl)}bis(diethyl phosphonate) (4). Triethyl phosphite (3.45 g, 0.0208 mol) was added with stirring under argon to 4.0 g (0.0104 mol) of compound **2**. The mixture was heated at 90–100°C for 2 h. The oil that formed was washed with dichloromethane, and the solvent was removed by distillation. Yield 4.6 g (89%). IR spectrum, ν, cm^{-1}: 3051 (NH), 1734 (C=O), 1683 ($COCH_2$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.23–1.39 m (12H, CH_3), 3.49–3.98 m (4H, $COCH_2$), 4.04–4.24 m (8H, CH_2), 5.93 m (2H, CHCH), 7.03 s (2H, NH). ^{31}P NMR spectrum ($CDCl_3$): $δ_P$ 20.17 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 497.12 $[M]^+$. Found, %: C 38.68; H 5.42; N 11.13; P 12.28. $C_{16}H_{28}N_4O_9P_2$. Calculated, %: C 38.56; H 5.66; N 11.24; P 12.43.

{(2,5-Dioxohexahydroimidazo[4,5-d]imidazole-1,4-diyl)bis(2-oxoethane-2,1-diyl)}bisphosphonic acid (5). Tribromosilane, 9.2 g (0.06 mol), was added with stirring under argon to a solution of 5.0 g (0.01 mol) of compound **4** in acetonitrile. The mixture was stirred for 3 h at 70°C. An amorphous precipitate of the silylbromo derivative formed and was filtered off, after which water was removed by distillation. The resulting bisphosphonic acid **5** was washed with diethyl ether and dried. Yield 3.5 g (93%), mp 217–218°C. ^1H NMR spectrum (D_2O), δ, ppm: 3.44–3.58 m (4H, CH_2); 5.74 s (2H, CHCH). ^{31}P NMR spectrum (D_2O): $δ_P$ 16.04 ppm. Found, %: C 24.71; H 3.31; N 14.42; P 16.19. $C_8H_{12}N_4O_9P_2$. Calculated, %: C 24.88; H 3.13; N 14.51; P 16.04.

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