ISSN 1070-4280, Russian Journal of Organic Chemistry, 2021, Vol. 57, No. 1, pp. 58–63. © Pleiades Publishing, Ltd., 2021.
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Efficient Synthesis of Tetraacetylglycoluril in the Presence of Phosphorus-Containing Catalysts

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Received October 29, 2020; revised November 11, 2020; accepted November 13, 2020

Abstract—The effect of phosphorus-containing catalysts, namely phosphorous acid, phosphoric acid, diethyl hydrogen phosphite, and 1-hydroxyethane-1,1-diyldiphosphonic acid (HEDP), in the synthesis of tetraacetylglycoluril by acylation of glycoluril with acetic anhydride at 140°C has been studied. The use of 4 equiv of phosphorous or phosphoric acid with respect to glycoluril has been found to be the most appropriate for achieving the maximum yield (95–98%), and specific effect of HEDP leads to N-acetylation–deacetylation of substrates. The positive effect of phosphorus acids on the formation of tetraacetylglycoluril may be related to not only their catalytic action but also the ability to solubilize the substrate.

Keywords: glycoluril, tetraacetylglycoluryl, phosphorous acid, phosphoric acid, 1-hydroxyethane-1,1-diyldiphosphonic acid, catalyst, deacetylation

DOI: 10.1134/S1070428021010085

INTRODUCTION

A particular place in the chemistry of nitrogen-containing heterocycles is occupied by bicyclic ureas [1], among which 2,4,6,8-tetraacetyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione [**2**, tetraacetylglycoluril (TAGU)] attracts much interest due to its acetylating ability [2] and wide application in industry as a peroxide activator for bleaching [3].

Two synthetic approaches are mainly utilized for efficient synthesis of tetraacetylglycoluril (**2**). They are based on preliminary generation of *N*-anions from the substrates in situ and the use of traditional acylating agents in the presence of acid or base catalysts. First reports on the synthesis of **2** by direct acylation of glycoluril (**1**) with acetic anhydride date back to the late 19th–early 20th century [4]. Later on, it was found that the best yields in this reaction were achieved when sodium acetate [5], perchloric acid [6, 7], and sulfuric acid [7] were used as catalysts. However, we have found no published examples of the use of phosphoric acid or its derivatives to catalyze the synthesis of TAGU under similar conditions.

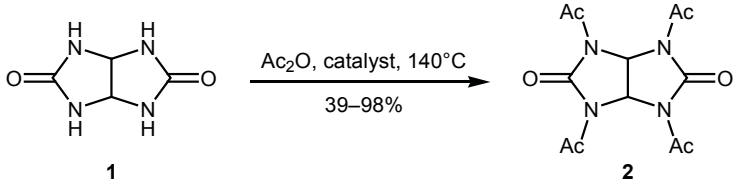
The present study was aimed at studying the catalytic efficiency of phosphorous and phosphoric acids, diethyl hydrogen phosphite, and 1-hydroxyethane-1,1-diyldiphosphonic acid (HEDP) in the synthesis of tetraacetylglycoluril (**2**) by acylation of glycoluril (**1**) with acetic anhydride (Scheme 1).

RESULTS AND DISCUSSION

It was found that the reaction of glycoluril (**1**) with acetic anhydride in the presence of 4 equiv of phosphorous or phosphoric acid afforded 95–98% of TAGU **2** in a fairly short time (20–30 min; Table 1). The progress of reactions was monitored by HPLC, following the disappearance of initial glycoluril (**1**) and quantitating the amount of **2** using an authentic sample (Acros Organics).

When 2 equiv of phosphorous acid with respect to glycoluril (**1**) was used, the reaction time being the same, the yield of **2** significantly decreased (63%). Interestingly, the HPLC data showed the presence in the reaction mixture of triacetylglycoluril (**4**, 30%) and diacetylglycoluril (**3**, 6%) in addition to major

Scheme 1.



1 **2**

product **2** (see Supplementary Materials). Increase of the amount of phosphorous acid to 4 equiv led to the formation of **2** in 95% yield, but compounds **3** (3%) and **4** (2%) were also formed as by-products (see Supplementary Materials).

Compound **2** was obtained in almost quantitative yield (98%) in the presence of 4 equiv of phosphoric acid, whereas only minor amounts of diacetylglycoluril **3** (1.5%) and triacetylglycoluril **4** (0.5%) were detected by HPLC (see Supplementary Materials).

Diethyl hydrogen phosphite turned out to be inefficient in the reaction of **1** with acetic anhydride; in this case, only traces of **2** were formed in 2 h (HPLC). This may be due to the presence of a small amount of phosphorous acid in diethyl hydrogen phosphite or its formation as a result of partial hydrolysis of diethyl hydrogen phosphite.

Relatively recently, it has been found [8–12] that 1-hydroxyethane-1,1-diyldiphosphonic acid (HEDP) is a convenient catalyst for the synthesis of dihydropyrimidinones by condensation of carbonyl compounds containing an active methylene group, urea, and aldehydes under both traditional conditions [8–11] and microwave irradiation [12].

Due to stereochemical features [13, 14] and the presence of two phosphonic acid groups, HEDP tends to form complexes, which makes it an attractive subject for studying its catalytic properties. This prompted us to examine the catalytic effect of HEDP in the acetylation of glycoluril (**1**).

We were the first to reveal that the use of an equimolar amount of HEDP (with respect to glycoluril **1**) favored formation of tetraacetylglycoluril (**2**) in 62% yield in the reaction of **1** with acetic anhydride (Scheme 1). In this case, tetraacetylglycoluril (**2**) was not the only product, and diacetylglycoluril **3** and acetylhydantoin **5** were also formed (Scheme 2). Presumably, the formation of compound **5** is the result of concurrent decomposition of the bicyclic skeleton of glycoluril [9, 10], followed by acetylation of hydantoin generated in turn by elimination of urea from one of the reaction intermediates.

Increase of the amount of HEDP to 2 equiv reduced the yield of **2** (39%) with simultaneous increase of the yield of diacetylglycoluril **3**, which may be due to the reverse reaction, deacetylation of **2**, as shown in [15] for nitrogen nucleophiles. When the amount of HEDP was reduced to 0.5 equiv, the yield of **3** was 65% (Table 2).

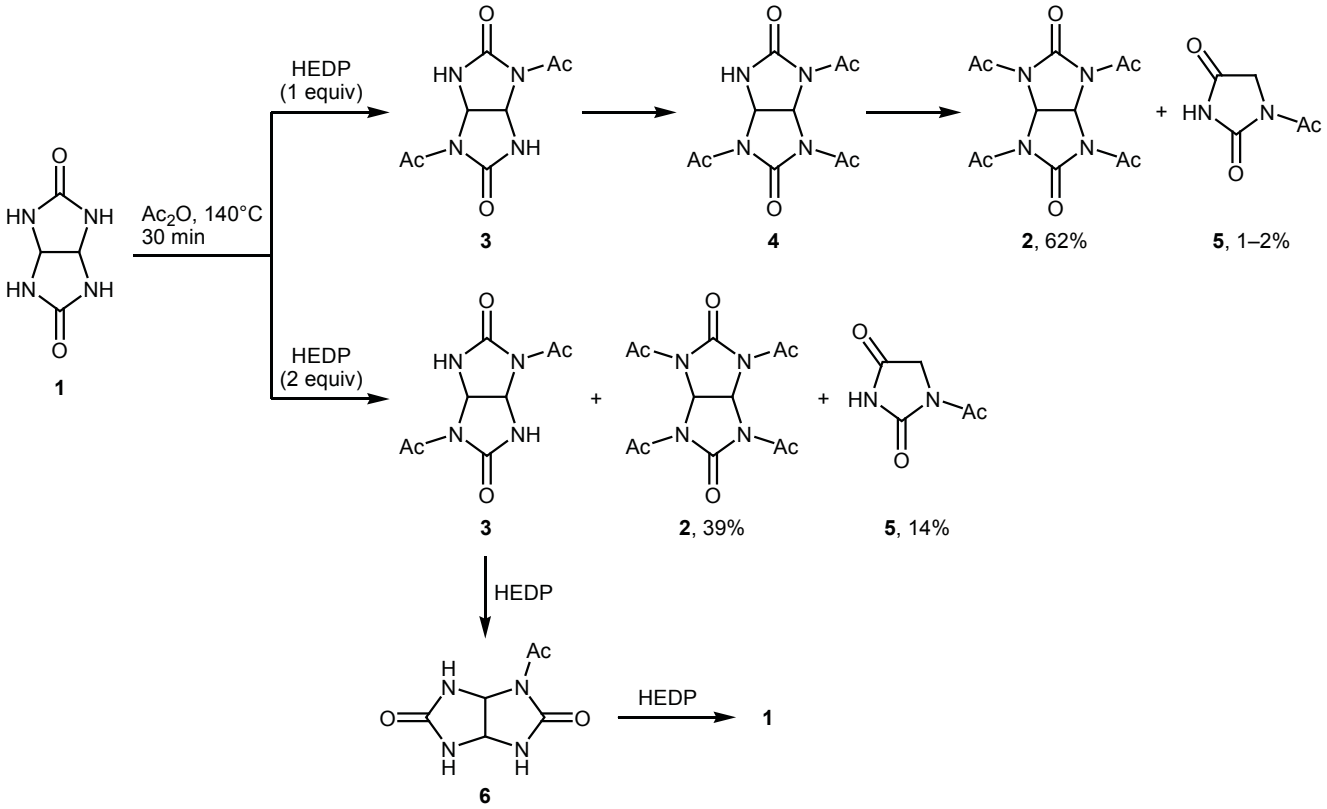
Hase and Kuhling [16] studied in sufficient detail the hydrolysis of tetraacetylglycoluril **2** by the action of various nucleophiles at room temperature, as well as in alkaline medium. Unlike the data of [16], no deacetylation was expected in the reaction in the presence of HEDP, i.e., in acid medium. By carrying out special experiment, we isolated products of stepwise deacetylation of **2**. For example, complete elimination of two acetyl groups from tetraacetylglycoluril **2** with the formation of diacetyl derivative **3** was observed when compound **2** was heated in the presence of HEDP. By heating compound **3** and HEDP at a ratio of 1:1 we obtained monoacetyl derivative **6** as the major product and hydantoin [9] as a minor one; the latter is likely to result from decomposition of glycoluril [9] which is the final deacetylation product.

Scheme 3 shows a plausible mechanism of deacetylation by the action of HEDP. Intermediate **A** generated by protonation of tetraacetylglycoluril **2** or compound **3** is likely to undergo nucleophilic attack by HEDP dianion **7** (Scheme 4) to give intermediate **B**.

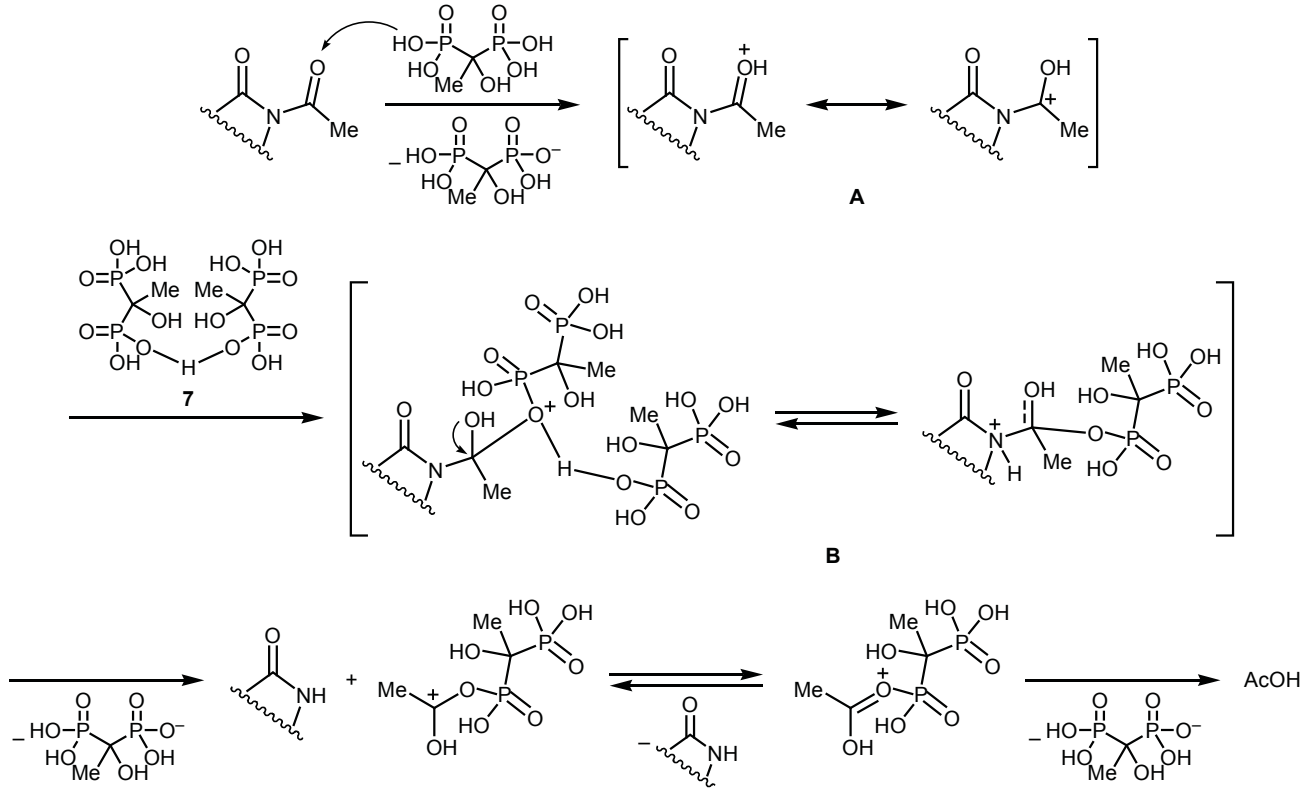
Table 1. Synthesis of tetraacetylglycoluril **2** in the presence of phosphorous acid, phosphoric acid, diethyl hydrogen phosphite, and HEDP

Parameter	Phosphorous acid		Phosphoric acid	Diethyl hydrogen phosphite	HEDP	
Ratio	1:2	1:4	1:4	1:4	1:1	1:2
Time, min	30	30	20	120	30	30
Yield of **2**, %	63	95	98	Traces	62	39

Scheme 2.



Scheme 3.



Decomposition of the latter with elimination of glycoluril **3** or **1**, followed by hydrolysis, led to the formation of acetic acid and initial HEDP.

Thus, in the examined reaction HEDP acts as both acid and nucleophile. Taking into account the data of [17], according to which HEDP tends to undergo deprotonation, we presume that one HEDP molecule dissociates as a Brønsted acid while another HEDP molecule forms stable anion **7** (Scheme 4). This anion acts as a nucleophile contributing to the deacetylation process. On the other hand, it should be noted that HEDP is a fairly soft nucleophile, since monoacetylglyvoluril **5** is known [16] to be difficult to isolate in an appreciable amount.

The results of our study led us to conclude that the observed accelerating effect of phosphorus acids on the synthesis of tetraacetylglycoluril (**2**) is related to not only its catalytic action but also its ability to solubilize glycoluril **1**, i.e., to transfer molecules **1** from the tight crystal packing to solution. This is supported by the X-ray diffraction data [18], which showed that glycoluril **1** is represented by two polymorphs both of which are orthorhombic. In one of these forms (space group *Cmcm*), the crystals have approximately square cross section and are pyramidally blocked; molecules **1** are linked through hydrogen bonds to form two-dimensional networks; in the other form, elongated crystals with irregularly hexagonal cross section belong to the *Pnma* space group, and intermolecular hydrogen bonds form a three-dimensional, i.e., more complicated and less symmetric, structure. Undoubtedly, the polymorphism of glycoluril **1** significantly hinders its dissolution due to developed two- and three-dimensional H-bond networks. Presumably, the observed efficiency of phosphorus acids in the synthesis of TAGU in comparison to other acids is determined by more effective decomposition of the crystal packing of **1** (Scheme 5), which significantly accelerates the formation of target product **2**.

Table 2. Synthesis of tetraacetylglycoluril **2** in the presence of HEDP (reaction time 30 min)

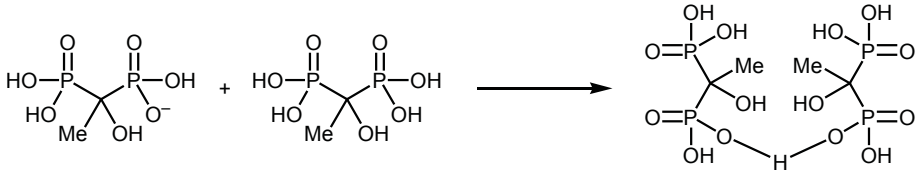
Ratio **1**–HEDP	Yield, %	
	2	**3**
1:0.5	–	65
1:1	62	10
1:2	39	40

The crucial role of free phosphoryl group in the examined phosphorus-containing reagents is emphasized by the fact that diethyl hydrogen phosphite showed no catalytic properties; moreover, it inhibited the acetylation of glycoluril **1**, which should occur even in the absence of a catalyst.

EXPERIMENTAL

The reactions were carried out in a Syrris Atlas Orbit parallel synthesis module (UK). The NMR spectra of **2**–**6** (see Supplementary Materials) were recorded on a Bruker Avance III HD spectrometer (Germany) at 400 and 100 MHz for ^{1}H and ^{13}C, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The IR spectra (400–4000 cm^{-1}) were recorded in KBr on a Bruker Alpha FTIR spectrometer.

Scheme 4.



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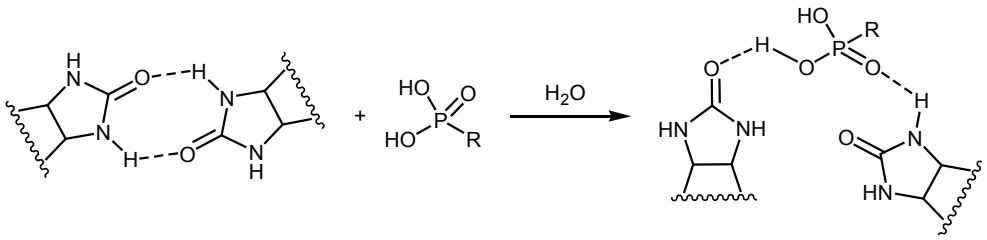
Scheme 5.



R = H, OH, $(HO)_2P(O)C(Me)(OH)$.

The melting points were measured with a Buchi melting point apparatus. The progress of reactions was monitored by TLC on Silufol UV–254 plates using chloroform–methanol–ethyl acetate (70:20:20) as eluent, as well as by HPLC [Phenomenex Luna C18(2) column, 100×4.6 mm, particle size 5 μm (USA), with a pre-column; column temperature 40°C; flow rate 2 mL/min; run duration 1.5×t_r where t_r is the retention time of tetraacetylglycoluril **2** (7 min); eluent water–acetonitrile mixtures, linear gradient from 5% of MeCN (0 min) to 50% of MeCN (6 min) and 75% of MeCN (7 min); injection volume 2 μL]. A reference sample of tetraacetylglycoluril **2** (98.0%) was purchased from Acros Organics.

2,4,6,8-Tetraacetyl-2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,7-dione (2, TAGU). *a*. A reactor equipped with a reflux condenser and magnetic stirrer was charged with 0.284 g (2 mmol) of glycoluril **1**, 0.656 g (8 mmol) of phosphorous acid, and 15 mL of acetic anhydride, and the mixture was refluxed for 30 min. After completion of the reaction, excess acetic anhydride was distilled off (it can be reused), the residue was washed with 50 mL of hot water and recrystallized from 50 mL of methylene chloride (the undissolved material was discarded). Yield of **2** 0.59 g (95%).

b. A reactor equipped with a reflux condenser and magnetic stirrer was charged with 0.284 g (2 mmol) of glycoluril **1**, 0.5 mL (8 mmol) of 85% phosphoric acid, and 15 mL of acetic anhydride, and the mixture was refluxed for 30 min. After completion of the reaction, excess acetic anhydride was distilled off (it can be reused), the residue was washed with 50 mL of hot water and recrystallized from 50 mL of methylene chloride (the undissolved material was discarded). Yield of **2** 0.61 g (98%).

c. A reactor equipped with a reflux condenser and magnetic stirrer was charged with 0.284 g (2 mmol) of glycoluril **1**, 0.41 g (2 mmol) of HEDP, and 15 mL of acetic anhydride, and the mixture was refluxed for 30 min. After completion of the reaction, excess acetic anhydride was distilled off, and the residue was washed with 50 mL of hot water and recrystallized from 50 mL of methylene chloride (the undissolved material was discarded). Yield of **2** 0.39 g (62%).

Samples of **2** obtained according to procedures *a*–*c* were identical to an authentic sample (Acros Organics), mp 244°C (from CH_2Cl_2). IR spectrum, ν, cm^{-1}: 1780 s ($COCH_3$), 1695 s (C=O). ^1H NMR spectrum, δ, ppm: 2.34 s (12H, CH_3), 6.33 s (2H, CH). ^{13}C NMR spectrum, δ_C, ppm: 25.2 (CH_3), 62.7 (CH), 151.6 (C=O), 169.5 (**C**OCH_3). *M* 310.26.

2,6-Diacetyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (3). Compound **3** was isolated in the synthesis of **2** (methods *a*–*c*) as a solid insoluble in water and methylene chloride. Yield 3% (*a*), 1.5% (*b*), 10% (*c*), mp >300°C. IR spectrum, ν, cm^{-1}: 3343 br (NH), 1784 s ($COCH_3$), 1693 s (C=O). ^1H NMR spectrum, δ, ppm: 2.37 s (6H, CH_3), 5.66 s (2H, CH), 8.89 s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 25.2 (CH_3), 62.4 (CH), 154.4 (C=O), 169.5 (**C**OCH_3). *M* 226.19.

1-Acetylimidazolidine-2,4-dione (5). In the synthesis of **2** (method *c*), compound **5** was detected as an impurity to tetraacetylglycoluril **2** (1–2% according to the NMR data). mp 144°C. IR spectrum, ν, cm^{-1}: 3240 br (NH), 1825 s (C=O), 1750 s (C=O), 1675 s (C=O). ^1H NMR spectrum, δ, ppm: 11.49 s (1H, NH), 4.15 s (2H, CH_2), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 24.5 (CH_3), 49.3 (CH_2), 154.8 (C=O), 168.0 (**C**OCH_3), 170.2 (C=O). *M* 142.11.

2-Acetyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (6) was obtained by refluxing 0.5 g of diacetylglycoluril **3** and HEDP at a ratio of 1:1. Yield 0.3 g (75%), mp 280°C. IR spectrum, ν, cm^{-1}: 3344, 3320 br (NH), 1784 s ($COCH_3$), 1695 s (C=O). ^1H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 5.23 d (1H, CH, J = 8.0 Hz), 5.69 d (1H, CH, J = 8.0 Hz), 7.57 s (1H, NH), 7.49 s (1H, NH), 8.55 s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 23.7 (CH_3), 66.3 (CH), 61.0 (CH), 161.1 (C=O), 154.7 (C=O), 170.2 (**C**OCH_3). *M* 184.15.

Imidazolidine-2,4-dione (hydantoin). Hydantoin [8] was present as a minor impurity to acetylglycoluril **6** (1–2% according to the NMR data) obtained by heating diacetylglycoluril **3** with HEDP at a ratio of 1:1. mp 221°C. IR spectrum, ν, cm^{-1}: 3200, 3121 br (NH), 1770, 1714 s (C=O). ^1H NMR spectrum, δ, ppm: 3.83 s (2H, CH_2), 7.70 s (1H, NH), 10.66 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 47.7 (CH_2), 158.9 (C=O), 174.5 (C=O). *M* 100.08.

CONCLUSIONS

Study of the effect of phosphorus-containing catalysts, phosphorous acid, phosphoric acid, diethyl hydrogen phosphite, and 1-hydroxyethane-1,1-diyldiphosphonic acid (HEDP) on the acetylation of glycoluril **1** with acetic anhydride has shown that the maximum yield of target tetraacetylglycoluril **2** (95–98%) is achieved using 4 equiv of phosphorous or phosphoric acid with respect to glycoluril **1**.

Unlike HEDP, neither phosphorous nor phosphoric acid promotes deacetylation of tetraacetylglycoluril **2**

in the course of its synthesis by acetylation of glycoluril **1**, and no hydantoin is formed. Possible ways of deacetylation of **2** in the presence of HEDP have been proposed, which illustrate its dual reactivity as acid catalyst and nucleophile.

The positive effect of phosphorus acids on the synthesis of tetraacetylglycoluril **2** is related to not only their catalytic activity but also the ability to transfer molecules of glycoluril **1** from the tight crystal packing to solution.

The isolation of **2** from the reaction mixtures involves no difficulties: after removal of excess acetic anhydride by distillation, the solid residue is simply washed with water and acetonitrile.

A fairly simple and practical procedure has been developed for the synthesis of tetraacetylglycoluril **2** by aceylation of glycoluril **1** with acetic anhydride in the presence of phosphorous or phosphoric acid, and the effect of HEDP on the acetylation/deacetylation processes has been demonstrated.

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1134/S1070428021010085.

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