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Synthesis of glycolurils and their analogues

Angelina N. Kravchenko,* Vladimir V. Baranov, Galina A. Gazieva

N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences
Leninsky prosp. 47, 119991 Moscow, Russian Federation

Glycolurils — tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones — have found widespread applications in various fields of science and technology. Among them, there are pharmacologically active compounds (antibacterial, nootropic, neurotropic agents, *etc.*), explosives, gelators, *etc*. They are used as building blocks in supramolecular chemistry. Therefore, the development of new methods for the synthesis of glycolurils and their analogues has constantly attracted the attention of researchers. In this review, we analyze various approaches to the synthesis of glycolurils and their analogues. The review covers both classical reactions of ureas and related compounds with α-dicarbonyl compounds or with 4,5-dihydroxyimidazolidin-2-ones (-thiones) and their imino analogues and new original reactions of 4,5-dihydroxyimidazolidin-2-ones (-thiones), imidazolinones and their bicyclic analogues with ureas and KNCS in the presence of acids, condensations of 1,4-disubstituted 1,4-diaza-1,3-dienes with isocyanic and/or isothiocyanic acids or isocyanates, triazine ring contraction in imidazotriazines to give the imidazolidine ring, and transformations of urazoles.
The bibliography includes 129 references.

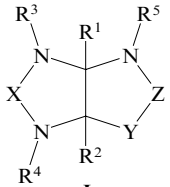
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1. Introduction

Glycolurils — tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones — and their analogues can be described by general formula **I**. These compounds are of great interest due to their applications in various industries and laboratory research. They are used as antibacterial,[1,2] nootropic, neurotropic and anxiolytic agents,[3–6] explosives,[7,8] flame resistant materials,[9] gelators,[10,11] building blocks in organic and supramolecular chemistry (including the synthesis of cucurbit[n] urils, bambusurils, molecular clips, molecular capsules and other).[12–27] Some representatives of thioglycolurils (Y = NH, X = C=O, Z = C=S) exhibit cytotoxic and sedative activities.[28–30] Imino analogues of glycolurils (Y = NR^6, X = O, Z = C=NHet, C=NNO_2) were patented as neutrophil growth factor G-CSF mimetics,[31] show antioxidant activities, which exceed that of trolox,[32] and their nitro derivatives are high-density energetic materials.[33,34] Analogues of glycolurils, *i.e.*, imidazooxazoles, imidazothiazoles, imidazothiadiazole *S*,*S*-dioxides, thiadiazolothiadiazole tetroxides, imidazotriazines, are poorly researched. Only a few examples of syntheses of these compounds are presented in the literature.

Structures I



I

X, Z = C=O, C=S, C=NHet, C=NNO_2, SO_2; Y = O, S, NR^6 (R^6 = H, Alk, Ar), NHNH;
R^1, R^2 = H, Alk, Ar; $R^1 - R^2 = (CH_2)_n$;
R^3, R^4, R^5 = H, Alk, Ar

The chemistry of glycolurils and their analogues is evolving in two main directions: 1) development of methods for synthesizing glycolurils, their derivatives and hetero analogues and 2) studies on their chemical and supramolecular properties. The available recent reviews[12,15] are devoted to the use of glycoluril derivatives in the preparation of various objects of supramolecular chemistry (cucurbiturils, *etc.*). There is a review[35] published back in 1973 on the methods for synthesizing glycolurils and their analogues

A.N.Kravchenko. Doctor of Chemical Sciences, Professor, Leading Researcher at the Laboratory of Nitrogen-containing Compounds at the ZIOC RAS.
Telephone: +7(499)135–8817, e-mail: kani@server.ioc.ac.ru
Current research interests: organic chemistry, heterocyclic pharmacologically active compounds, stereochemistry.
V.V.Baranov. PhD (Chemical Sciences), Researcher at the same Laboratory.
Telephone: +7(499)135–8817, e-mail: ase1313@mail.ru
Current research interests: synthesis of heterocyclic biologically active compounds, stereochemistry.
G.A.Gazieva. PhD (Chemical Sciences), Senior Researcher at the same Laboratory.
Telephone: +7(499)135–8817, e-mail: gaz@ioc.ac.ru
Current research interests: chemistry of heterocyclic compounds, stereochemistry, biologically active compounds.

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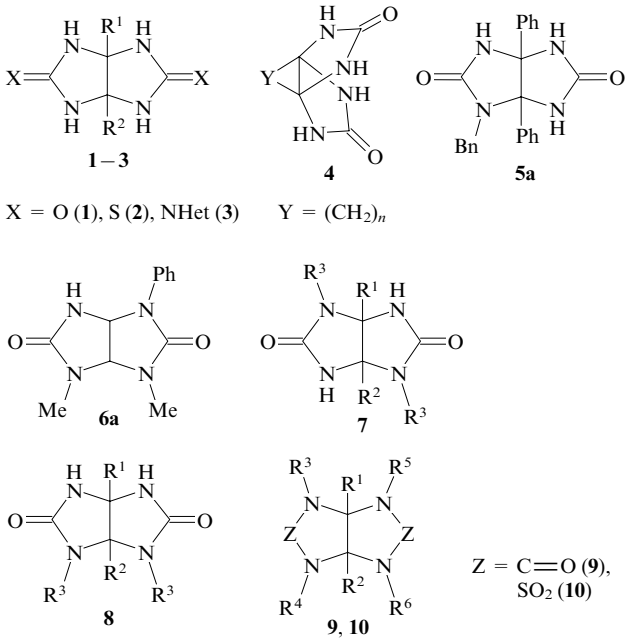
based on α-ureidoalkylation reactions. The contemporary methods for the synthesis of these compounds are much more diverse. There are no reviews on the above-mentioned glycoluril analogues. In this review, we analyze various approaches to the synthesis of glycolurils and their analogues, including reactions of ureas and related compounds [thioureas, sulfamides, guanidines, (thio)semicarbazides] with α-dicarbonyl compounds or with 4,5-dihydroxyimidazolidin-2-ones (-thiones) (DHI, DHIT), 4,5-dihydroxyimidazolidine-2-imines, imidazolinones and their bicyclic analogues; reactions of DHI, DHIT and imidazolinones with KNCS in the presence of acids; condensation of 1,4-disubstituted 1,4-diaza-1,3-dienes with isocyanic and/or isothiocyanic acids or isocyanates; triazine ring contraction in imidazotriazines to give the imidazolidine ring; and transformation of urazoles into imidazooxazolones.

2. Synthesis of glycolurils and their analogues

2.1. Reactions of ureas and related compounds with α-dicarbonyl compounds

This approach has been utilized to obtain glycolurils (**1**) unsubstituted at nitrogen atoms, their thio (**2**) and imino (**3**) analogues; glycolurils with cyclic moieties at C(3a)–C(6a) atoms (**4**); 1-benzyl-3a,6a-diphenylglycoluril (**5a**) and 3,4-dimethyl-1-phenylglycoluril (**6a**); 1,4-di- (**7**), 1,6-di- (**8**) and 1,3,4,6-tetrasubstituted glycolurils (**9**); and 1,3,4,6-tetramethylthiadiazolothiadiazole 2,2,5,5-tetroxide (**10**).

Structures 1–10

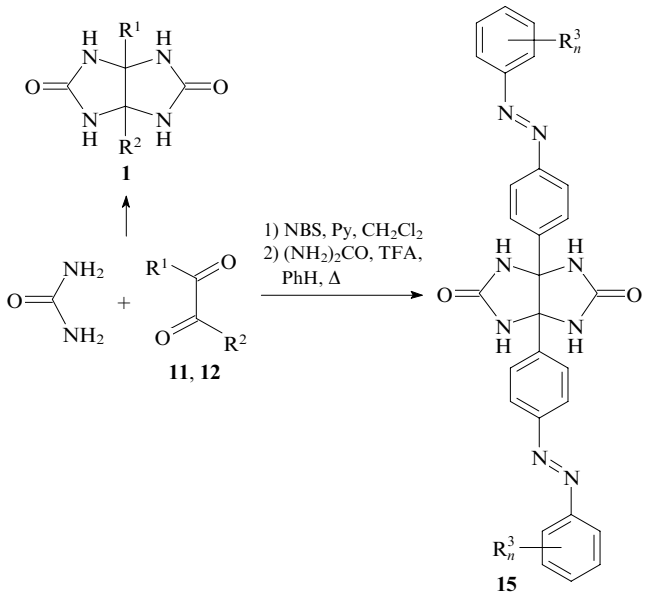


2.1.1. Synthesis of glycolurils unsubstituted at nitrogen atoms

The synthesis of glycolurils **1** and **4** has been comprehensively studied.[7,9–11,35–59] These derivatives can contain either identical or different substituents (including rings) at the bridging carbon atoms C(3a) and C(6a). They were obtained by condensation of urea with a wide range of α-dicarbonyl compounds [1,2-dioxoethanes (glyoxals) **11**, compounds **12**, bis(1,2-diketones) **13** and cyclic diketones **14**] under quite diverse conditions. Water, methanol, ethanol, benzene and toluene were used as solvents. The reaction temperatures ranged from room temperature to the boiling points. The reaction time varied from a few minutes to a few hours. Most of the reactions were catalyzed by classical acids such as H_2SO_4, HCl, HCO_2H, AcOH and trifluoroacetic acid (TFA).[9,11,36,38–43,45–59] Sometimes, alkaline catalysis (in the presence of KOH) was used.[42,47] Nowadays, condensations are carried out in the presence of phosphoric anhydride (P_4O_{10}),[37] $Fe(OTf)_3$ or $Bi(OTf)_3$ (Tf = CF_3SO_2),[44,53] TMSCl (TMS = $SiMe_3$),[38] the HZSM-5 and ZSM-5 nanozeolites,[43] heteropolyacid $H_3PW_{12}O_{40}$ [42] or boron trifluoride etherate ($Et_2O \cdot BF_3$).[57]

Glycolurils **1** with identical substituents at the C(3a) and C(6a) atoms are synthesized by reactions of urea with glyoxal,[7,9,36–43] dimethylglyoxal (diacetyl),[36,37,41–44] diethylglyoxal,[37,41–43] di(n-propyl)glyoxal,[42] diphenylglyoxal (benzil),[38,41,45,47] diethyl tartrate,[46–48] di(*p*-methoxyphenyl)glyoxal[49,50] and di(4-benzyloxyphenyl)-glyoxal[10] (Scheme 1). The yields of glycolurils reach 100% when phosphotungstic acid is used as a catalyst.[42] A technique for synthesizing glycoluril **1** from urea and glyoxal in the presence of sulfuric acid has been patented as an industrial method.[39,40]

Scheme 1



1, **11**: $R^1 = R^2$ = H, Me, Et, Pr^n, CO_2Et, Ph, PMP, 4-$BnOC_6H_4$; R^1 = H: R^2 = Me, Ph, $AcOCH_2CMe_2$; R^1 = Me: R^2 = Et, Pr^n, Ph, $Cl(CH_2)_4$; R^1 = Ph, R^2 = 4-$AlkOC_6H_4$;
12: $R^1 = R^2$ = 4-($R^3_nC_6H_{5-n}$NBocNH)C_6H_4; **12**, **15**: R^3_n = 4-Bu^n, 3,5-Hex_2, 3,5-(3,5-$Bu^t_2C_6H_3)_2$; Hex = n-C_6H_{13}, Py is pyridine, PMP is *p*-methoxyphenyl, Boc = $Bu^tOC(O)$

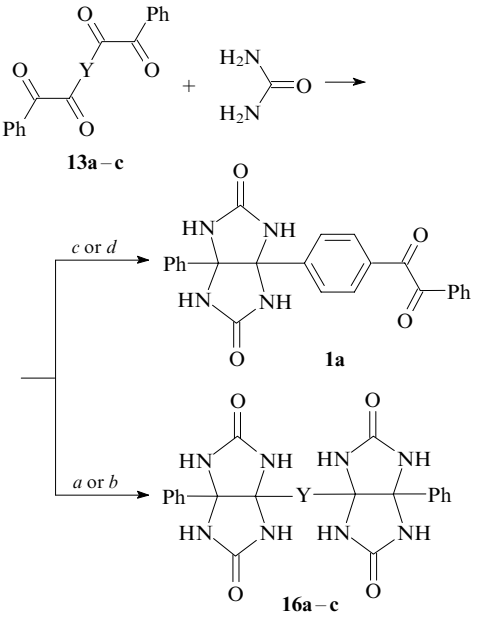
The series of N-unsubstituted glycolurils is complemented by glycolurils **15** with more complex substituents at the C(3a) and C(6a) atoms, which are formed in two steps (see Scheme 1).[11] After oxidation of compounds **12** to the corresponding azobenzenes using *N*-bromosuccinimide (NBS), the glycoluril moiety was formed by refluxing the benzils with urea and TFA in a Dean–Stark apparatus to

give **15** in 32% – 48% yields over the two steps. These compounds are promising gelators.[11]

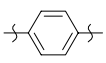
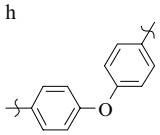
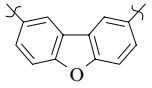
Glycolurils **1** with different substituents at the C(3a) and C(6a) atoms were prepared from urea with unsymmetrically substituted α-dicarbonyl compounds: methyl-,[9, 51 52] phenyl-,[36] (1-acetoxy-2-methylprop-2-yl)glyoxals;[53] 2-ethyl-1-methyl-,[37, 38, 41, 43] 1-methyl-2-propyl-,[37, 41] 1-methyl-2-phenyl-,[37] 1-methyl-2-(4-chlorobutyl)glyoxals[44] and 1-(*p*-alkoxyphenyl)-2-phenylglyoxals[54] (see Scheme 1).

The cyclization of urea with bis-1,2-diketones **13a** – **c** has been studied.[55, 56] It was shown that glycoluril **1** was formed in 85% yield only in the case of bis-1,2-diketone **13a** and with mandatory presence of water in the reaction medium (Scheme 2). If water is continuously distilled off, the reaction gives bis-glycolurils **16a** – **c**.

Scheme 2



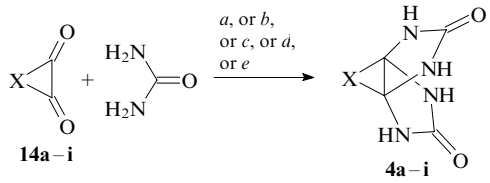
(*a*) HCO_2H ($-H_2O$), 130 – 135 °C, 45 min; (*b*) AcOH ($-H_2O$), 130 – 135 °C, 1.5 h or 120 °C, 5 h; (*c*) HCO_2H, H_2O, 130 °C, 1 h; (*d*) AcOH, H_2O, 120 °C, 10 h

13, **16**: Y =  (**a**),  (**b**),  (**c**)

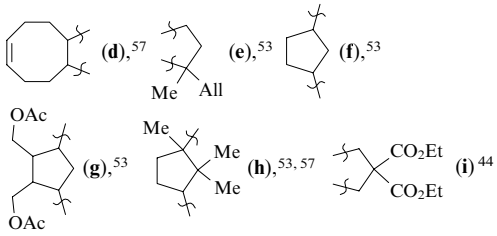
Compound	Conditions	Yield (%)	Ref.	Compound	Conditions	Yield (%)	Ref.
1a	*c*	85	55	**16b**	*a*	79	55
	d	43.6	56				
				16c	*a*	65	55
16a	*a*	92	55				
	b	94	56				

The use of various cyclic diketones **14a** – **i** in reactions with urea gave glycolurils **4a** – **i** (Scheme 3).[37, 41, 44, 53, 57 – 59] Unfortunately, in Ref. 57, the yields of glycolurils were not reported.

Scheme 3



(*a*) HCl, H_2O, 90 °C or rt;[39, 57 – 59] (*b*) $Et_2O \cdot BF_3$, PhH, Δ;[57] (*c*) P_4O_{10}, rt;[37] (*d*) $Bi(OTf)_3$, PhH or PhMe, rt;[53] (*e*) $Bi(OTf)_3$, PhMe, Δ, 16 h;[44] **4**, **14**: X = $(CH_2)_3$ (**a**),[57] $(CH_2)_4$ (**b**),[37, 41, 57 – 59] $(CH_2)_5$ (**c**),[57]



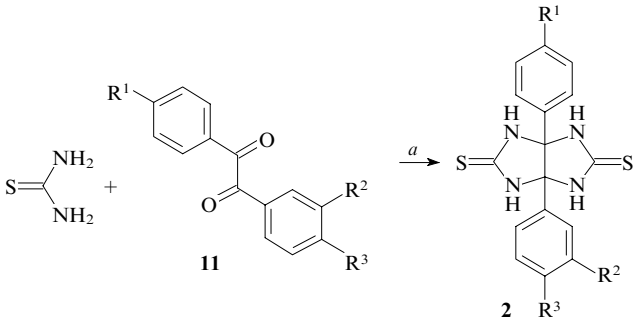
Compound	Yield (%)	Ref.	Compound	Yield (%)	Ref.
4b	52	37	**4f**	5	53
	65	41	**4g**	2	53
	84	58, 59	**4h**	30	53
4e	40	53	**4i**	40	44

2.1.2. Synthesis of thio- and iminoglycolurils unsubstituted at the nitrogen atoms

Dithioglycolurils **2** are represented by a few examples.[60] Iminoglycolurils **3** have been patented.[31]

Dithioglycolurils **2** are obtained by the reaction of thiourea with benzil derivatives **11** (Scheme 4).[60] The low yields (only 12% – 35%) are, apparently, attributable to the insufficient reactivity of thiourea.

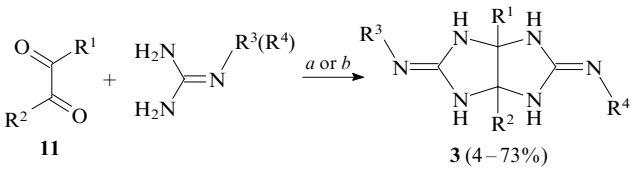
Scheme 4



(*a*) NaOH, PhMe, Bu^nOH, Δ, 2.5 h;
$R^1 = R^2 = R^3 = H$; $R^2 = H$: $R^1 = R^3 = Me$, Cl, OMe;
$R^1 = R^3 = H$, $R^2 = OMe$

Diiminoglycolurils **3** are synthesized by condensation of guanidine derivatives with symmetrically or unsymmetrically substituted 1,2-diaryl(dihetaryl)-1,2-dioxoethanes **11** in alcohols, at temperatures ranging from room temperature to the boiling points, for 1 h to 4 days (Scheme 5).[31]

Scheme 5



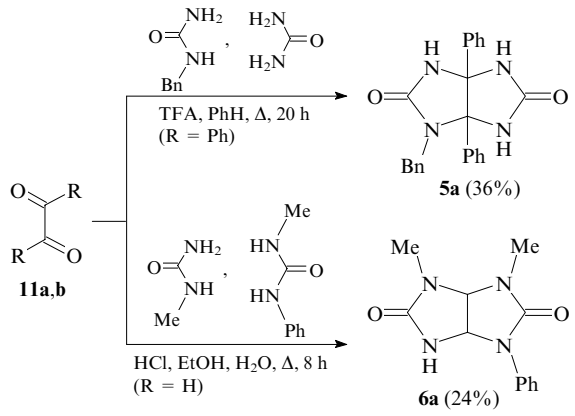
(*a*) MeOH, rt, 2–4 days; (*b*) EtOH, Δ, 1–2 h; R^1, R^2, R^3, R^4 = Ar, Het

2.1.3. Synthesis of 1-mono- and 1,3,4-trisubstituted glycolurils

In a number of studies, reactions with glyoxal and benzil were carried out with two different ureas.[61–63] They resulted in N-monosubstituted and N-trisubstituted glycolurils **5** and **6**. No side products were reported.

1-Benzyl-3a,6a-diphenylglycoluril (**5a**) was synthesized in 36% yield by the reaction of urea and benzylurea with benzil (Scheme 6).[61,62] 3,4-Dimethyl-1-phenylglycoluril (**6a**) was obtained by condensation of glyoxal, 1-methylurea and 1-methyl-3-phenylurea in the presence of hydrochloric acid.[63]

Scheme 6



11: R = H (**a**), Ph (**b**)

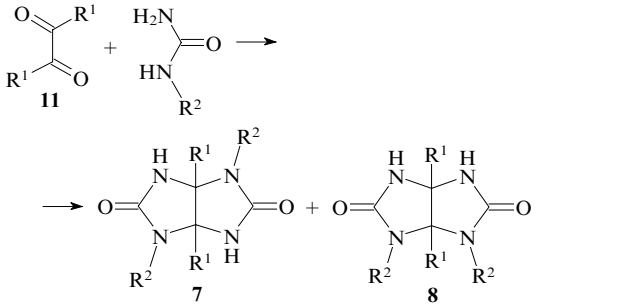
2.1.4. Synthesis of 1,4- and 1,6-disubstituted glycolurils

1,4- (**7**) and 1,6-Disubstituted glycolurils (**8**) are synthesized by regioselective condensation of α-dicarbonyl compounds — glyoxal, diacetyl, diethylglyoxal, dipropylglyoxal, benzil and 1,2-di[4-(benzyloxycarbonylmethoxy)-phenyl]glyoxal — with various substituted ureas,[17,36,42,64–69] including *N*-carbamoylamino acids (ureido acids),[67] or with xylylene- and trimethylenebisureas.[70] The reactions are carried out in water,[36,42,64,68–70] water–propan-2-ol mixture,[64] methanol,[42] ethanol[17] or benzene[65,66] in the presence of acids [HCl,[17,36,64,68–70] TFA,[65,66] $H_3PW_{12}O_{40}$ (0.95 mol.%)].[42] In most cases, the reaction mixtures are refluxed for 1–20 h. In one case,[42] the reactions were carried out at room temperature for 12–48 and 72 h.

Reactions of glyoxal with methyl-,[42,69] ethyl-,[64,68] n-propyl-,[64] n-butyl-,[64] *tert*-butyl-,[36,64] cyclohexyl-,[64] phenyl-[36] and benzylureas,[36] 1-{2-[dimethylamino(acetylamino)]ethyl}ureas,[67] *N*-carbamoylglycine[67] and xylylene-bis- and trimethylenebisureas[70] have been reported. Methylurea was also used in condensations with diacetyl,[42,65] diethylglyoxal[42] and di-n-propylglyoxal.[42] Benzil was employed in reactions with benzylurea,[17] *N*-carbamoylglycine (or β-alanine, or γ-aminobutyric acid)[67] and [(benzyloxycarbonyl)methyl]urea.[66] 1,2-Di[4-(benzyloxycarbonylmethoxy)phenyl]glyoxal was used in a condensation with [(benzyloxycarbonyl)methyl]urea.[66]

As a result, a broad range of 1,4- and 1,6-disubstituted glycolurils **7** and **8** was obtained (Schemes 7–11). A number of studies[36,64,68,69] report the preparation of both 1,4- and

Scheme 7



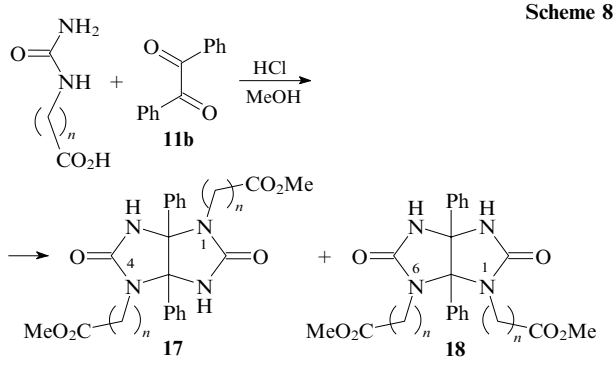
R^1 = H: R^2 = Me, Et, Pr^n, Bu^n, Bu^t, Cy, Ph, Bn, $(CH_2)_2NMe_2 \cdot HCl$, $(CH_2)_2NHAc$, CH_2CO_2H; R^2 = Me: R^1 = Me, Et, Pr^n; R^1 = Ph: R^2 = Bn, CH_2CO_2Bn; R^1 = $C_6H_4OCH_2C(O)OBn$-4: R^2 = Bn, CH_2CO_2Bn; Cy is cyclohexyl

1,6-isomers, with the trend towards the preferential formation of 1,4-isomers **7** being revealed. It was found that 1,4-dimethyl- and 1,4-diethylglycolurils **7** were spontaneously resolved into enantiomers *via* crystallisation from H_2O and sorting of conglomerate crystals.[68,69] 1,4-Dimethylglycoluril co-crystallizes with isomeric 1,6-dimethylglycoluril **8a**.[69] The reactions of glyoxal with *tert*-butyl-,[36] phenyl-,[36] benzyl-[36] and (2-acetylamino)ethylureas[67] and with *N*-carbamoylglycine[67] give only 1,4-isomers **7**. The reactions of methylurea with glyoxal,[42] diacetyl,[42,65] diethylglyoxal[42] or dipropylglyoxal[42] and the condensations of [(benzyloxycarbonyl)methyl]urea with benzil or di[(4-benzyloxycarbonylmethoxy)phenyl]glyoxal[66] predominantly afford the 1,6-isomers. The reactions of benzil with benzylurea[17] and glyoxal with [2-(dimethylamino)ethyl]urea[67] result in the formation of 1,4- (**7**) and 1,6-disubstituted products (**8**) in 1:1 ratio. The conditions of the highly regioselective formation of 1,4-isomers **7** in the reaction of glyoxal with methyl(or ethyl, or n-propyl)ureas were developed.[42] The increase in the steric hindrance in the series of diketones (Me < Et < Pr^n) led to decreasing isolated yields and longer reaction times.

The cyclocondensation of ureido acids with benzil in methanol (see Scheme 8) gave methyl esters of 1,4- (**17**) and 1,6-disubstituted glycolurils (**18**) in various ratios. The fraction of 1,4-di(methoxycarbonylalkyl)glycolurils **17** increases with elongation of the alkyl chain in the ureido acids.[67] The reactions studied involve formation of the bicyclic skeleton and esterification of carboxy groups with methanol.

Some authors propose reaction mechanisms to explain the high regioselectivity of the reactions.[42,64–67]

Scheme 8



n	The **17** : **18** ratio
1	1 : 2
2	3.3 : 1
3	4.4 : 1

Kravchenko *et al.*[64] explained the probabilities of formation of 1,4- (**7**) and 1,6- isomers (**8**) resorting to quantum chemical calculations (using 1,4- and 1,6-dimethylglycolurils as examples). It was concluded that 1,4-isomers **7** are formed preferentially (see Scheme 9). In this case, the condensation with glyoxal first involves the more nucleophilic methylamino group of methylurea, while the attack of the NH_2 group of methylurea is more energetically favourable in the reaction with cation **A**.

Butler and Hussain[65] argue that 1,6-isomer **8** is the major product of the reaction of methylurea with diacetyl. Therefore they suggested another mechanism involving the attack of the intermediate cation by the methylamino group of urea (see Scheme 10).

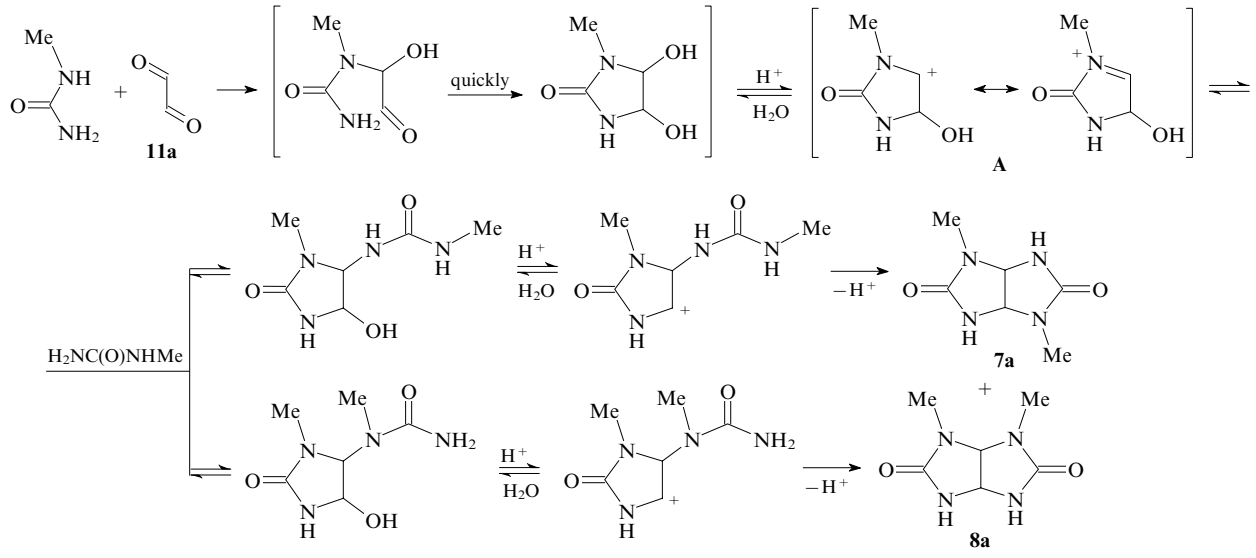
Yet another mechanism of selective formation of 1,6-disubstituted glycolurils was proposed by Pryor and Rebek.[66] They believe that the more nucleophilic centre of 1-[(benzyloxycarbonyl)methyl]urea reacts with the more electrophilic centre of intermediate **B**, resulting in the formation of intermediate **C** followed by cyclization into product **8c** (see Scheme 11).

Stancl *et al.*[70] found that the reaction of bisureas **19**, **20** with glyoxal in water acidified by HCl is regioselective and yields 1,6-protected glycolurils **8** (Scheme 12).

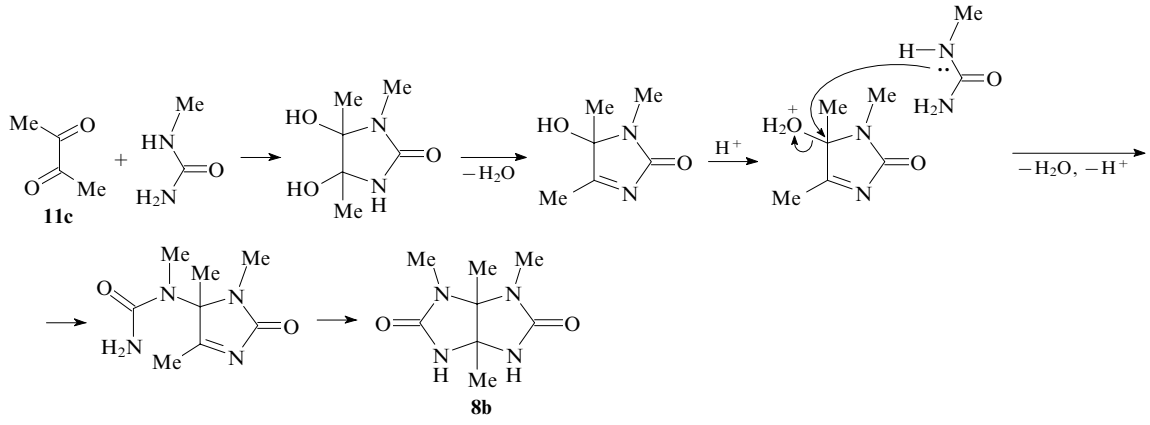
An interesting publication is available,[63] reporting a regioselective synthesis of 1,4-disubstituted glycolurils **7** with different substituents at the nitrogen atoms by a three-component condensation of glyoxal with phenyl- and alkylureas. Glycolurils **7′** with identical substituents are formed as side products (Scheme 13).

The preferential formation of 1,4-isomers is attributed to the formation of linear intermediate **D** (Scheme 14).[63]

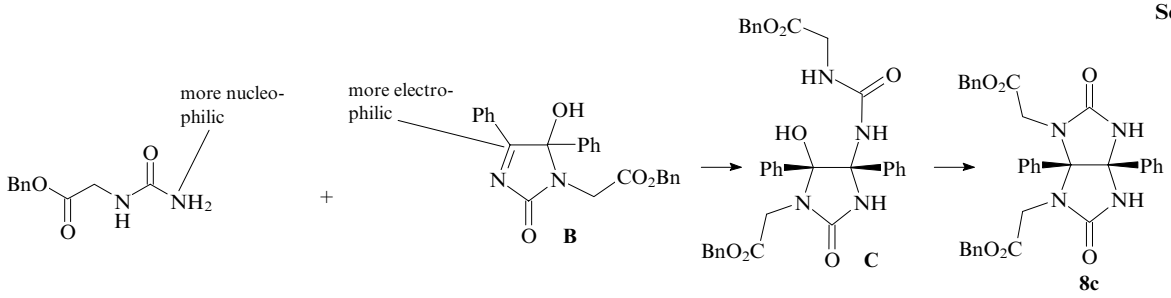
Scheme 9



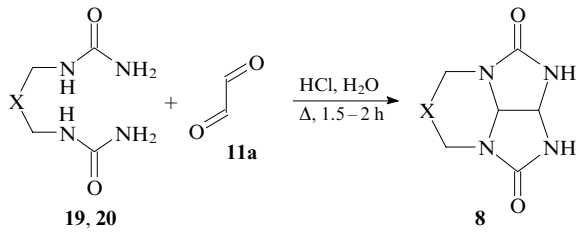
Scheme 10



Scheme 11

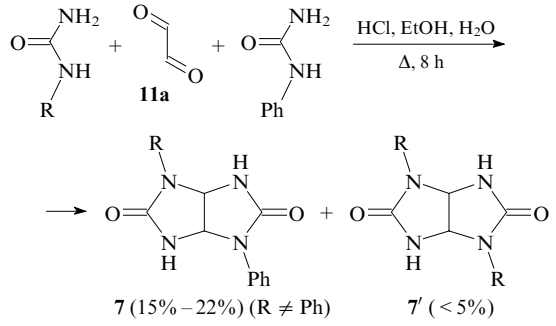


Scheme 12



X = CH_2 (**19**), 1,2-phenylene (**20**) (X = CH_2: 47% yield; 1,2-phenylene: 75%)

Scheme 13

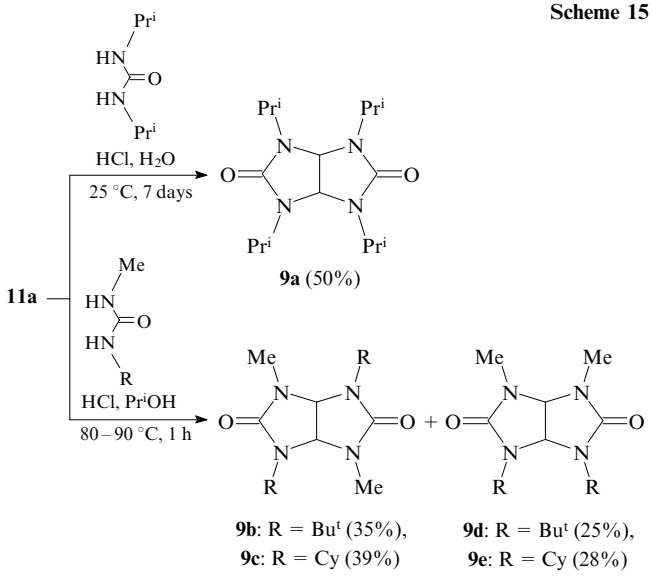


R = Me, Pr^i, Cy, Ph

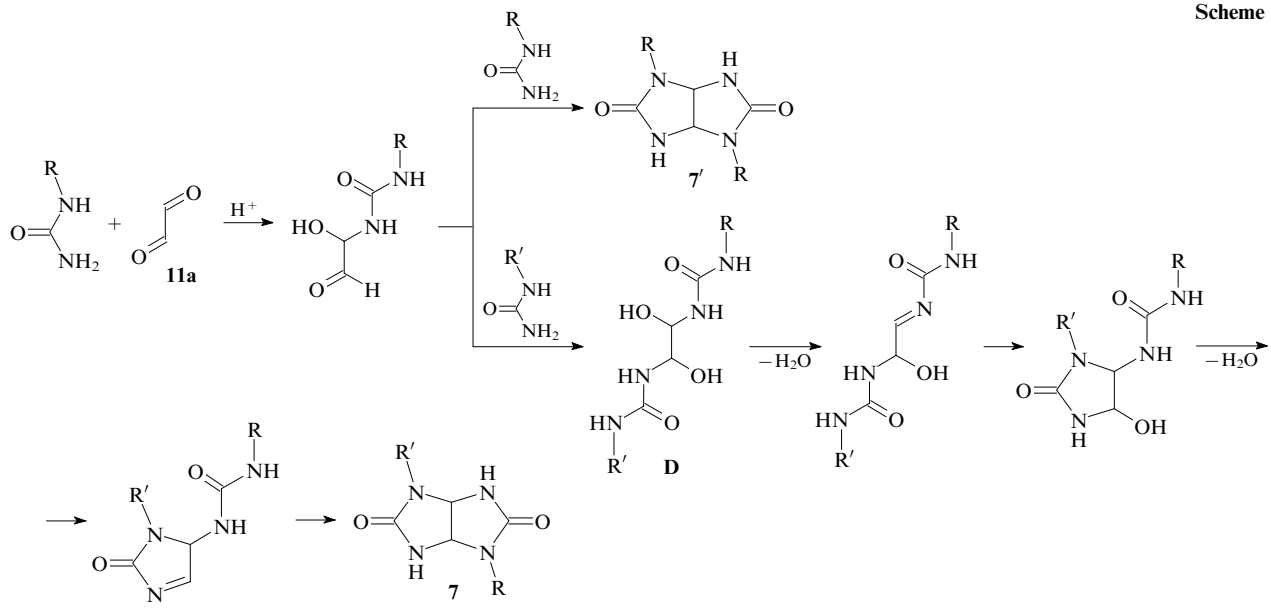
2.1.5. Synthesis of 1,3,4,6-tetraalkyl-substituted glycolurils and 1,3,4,6-tetramethylthiadiazolothiadiazole 2,2,5,5-tetroxide

The condensation of ureas and related compounds with α-dicarbonyl derivatives is scarcely used to prepare 1,3,4,6-tetrasubstituted glycolurils and their hetero analogues.

Scheme 15



Scheme 14

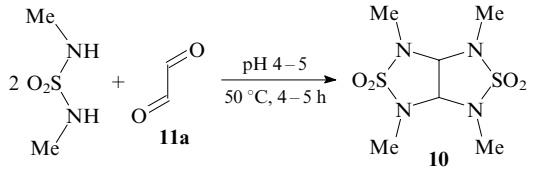


R, R′ = Ph or Alk

1,3,4,6-Tetrasubstituted glycolurils **9a** – **e** are obtained by the reaction of glyoxal with 1,3–di(isopropyl)urea [71] and unsymmetrically substituted 1-*tert*-butyl(cyclohexyl)-3-methylureas [64] (Scheme 15). Glycolurils **9b**,**c** and **9d**,**e** are regioisomers. The authors found that *trans*-isomers **9b**,**c** were formed preferentially.[64]

1,3,4,6-Tetramethylthiadiazolothiadiazole tetraoxide (**10**) was obtained in 22% – 25% yield by the reaction of 1,3-dimethylsulfamide with glyoxal **11a** (Scheme 16).[72]

Scheme 16



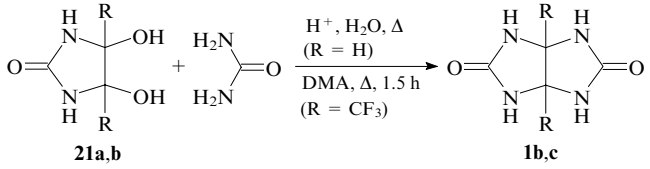
2.2. Reactions of ureas and their analogues with 4,5-dihydroxyimidazolidin-2-ones(-thiones), their imino analogues, imidazolinones and their cyclic analogues

According to the mechanism of α-ureidoalkylation, ureas first react with glyoxal to form 4,5-dihydroxyimidazolidin-2-ones **21**, which are intermediates in the subsequent formation of glycolurils **1**.[35, 42, 64] The diverse substituted DHI **21** and their analogues synthesized to date are widely used in reactions with urea, thiourea and thiosemicarbazide derivatives and other N,N-bis-nucleophiles. This approach is the second method for the synthesis of new types of glycolurils and their hetero analogues **22** – **30**, as well as unsubstituted glycoluril **1b** and new representatives of glycolurils **1**, **5**, **6**, **8** and **9**.

2.2.1. Synthesis of glycolurils with unsubstituted nitrogen atoms and their thio- and imino-analogues based on 4,5-dihydroxyimidazolidin-2-ones and their analogues

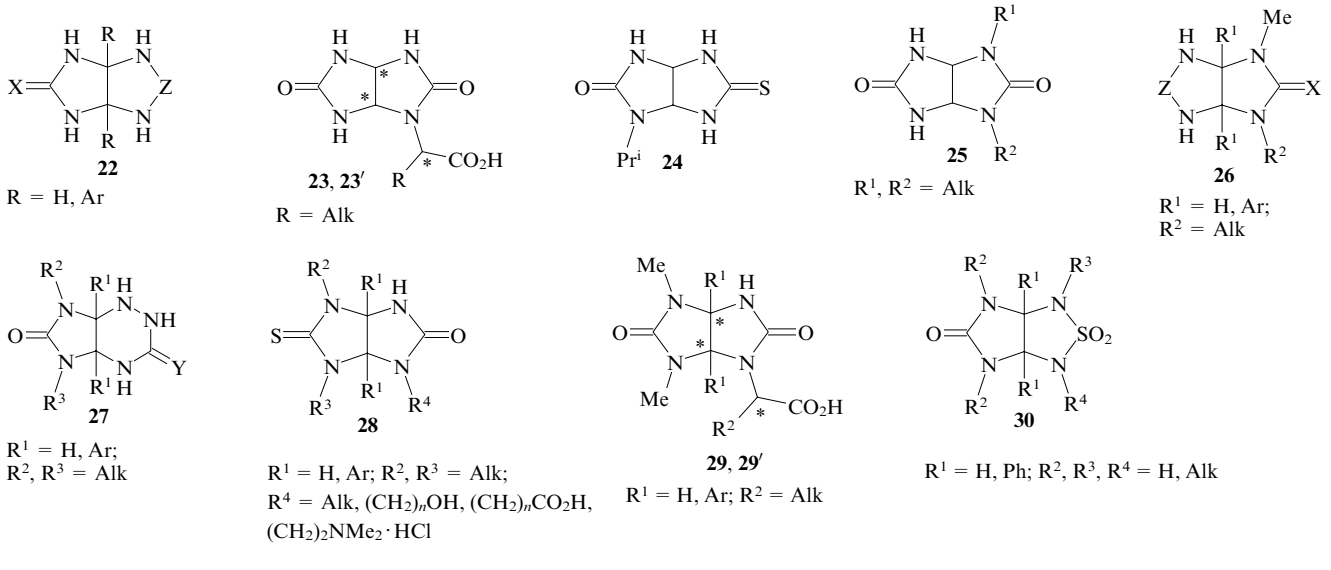
The synthesis of glycolurils **1** on the basis of DHI **21a**,**b** is represented by two examples (Scheme 17).[73, 74] The reactions of DHI **21a** [73] or 4,5-bis(trifluoromethyl)-substituted DHI **21b** [74] with urea gave glycolurils **1b**,**c** in 82% and 88% yield, respectively.

Scheme 17



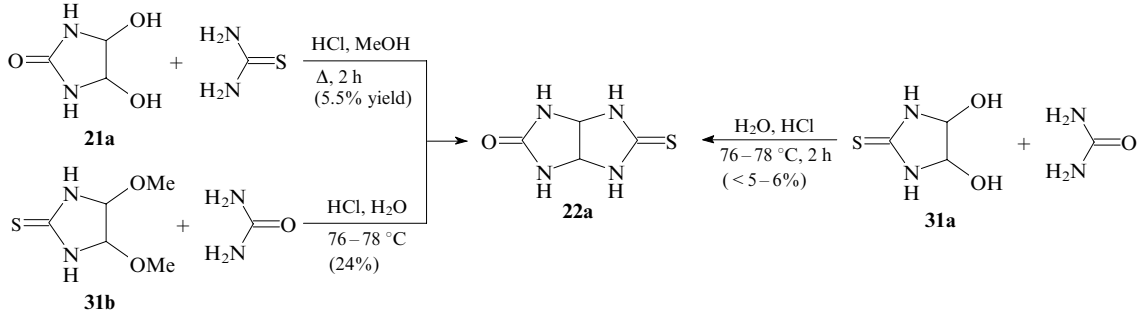
R = H (**21a**, **1b**), CF_3 (**21b**, **1c**); DMA is dimethylacetamide

Structures 22 – 30



Z = C═O, C═S, C═NNO_2; X = O, S; Y = O, S, NH · HCl

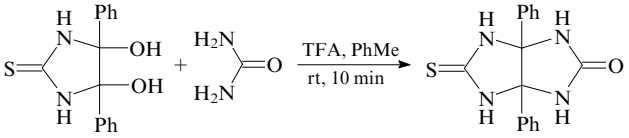
Scheme 18



The synthesis of thioglycolurils **22a**,**b** has been studied.[75,76] Eres'ko *et al.*[75] described two methods for the preparation of thioglycoluril **22a** (Scheme 18). One method was based on the reaction of DHI **21a** with thiourea. The other method included the reaction of 4,5-dihydroxyimidazolidine-2-thione (DHIT) (**31a**) or its dimethyl ether (**31b**) with urea.

Thioglycoluril **22b** has been synthesized by condensation of urea with DHIT **31c** (Scheme 19).[76]

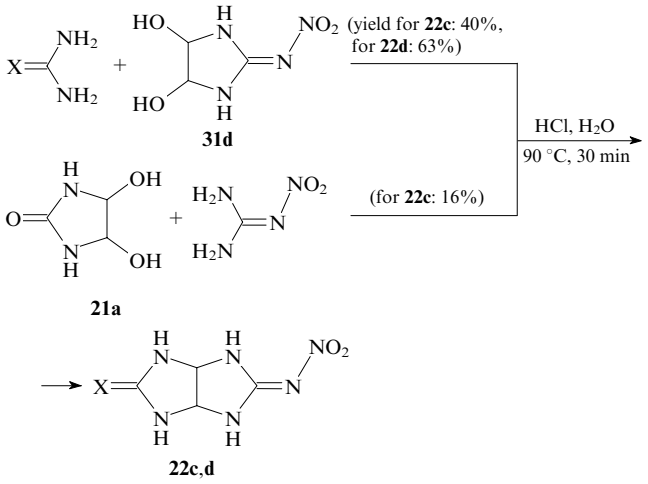
Scheme 19



31c **22b** (90%)

Iminoglycoluril **22c** and iminothio analogue **22d** have been prepared by the reaction of urea and thiourea with nitroimino DHI derivatives **31d**[77] (Scheme 20). Iminoglycoluril **22c** was also obtained by an alternative synthesis from nitroguanidine and DHI **21a**.[77]

Scheme 20



31d **21a** **22c**,**d**

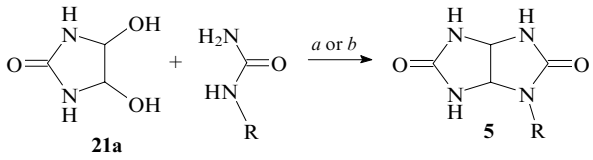
22: X = O (**c**), S (**d**)

2.2.2. Synthesis of 1-monosubstituted glycolurils from N-substituted ureas and 4,5-dihydroxyimidazolidin-2-ones and their derivatives

1-Monosubstituted glycolurils **5** have been prepared by α-ureidoalkylation of various monosubstituted ureas, such as alkyl-, hydroxyalkyl-, (2-acetylamino)ethyl- and [2-(dimethylamino)ethyl]-ureas and *N*-carbamoylamino acids, including enantiomerically pure ones, with DHI **21a** (Scheme 21).[64,73,78–88] The reactions were carried out in H_2O,[64,73,78–88] Pr^iOH [64,72,78–86] or their mixtures in the presence of hydrochloric acid upon refluxing for 1–3 h.

Dependences of the yields of *N*-alkyl(hydroxyalkyl, carboxyalkyl)glycolurils **5** on the reaction time and also on the branching and length of the alkyl chain of monoalkyl(hydroxyalkyl, carboxyalkyl)ureas have been studied.[64,80–82] It has been shown that the yields of the products decrease with increasing length (or with branching) of the alkyl chain of the ureas used.

Scheme 21



21a **5**

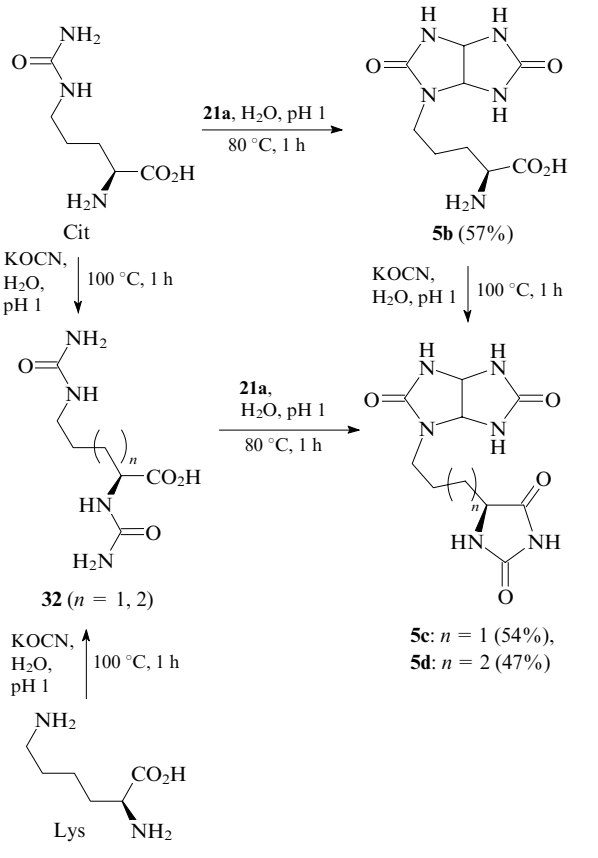
(*a*) H^+, Δ;[73] (*b*) H_2O (Pr^iOH), pH 1, 1 h;[64,80–85]
R = Me,[73] Et,[64] Pr^n (see [64]), Bu^s (see [64]), Bu^t (see [64]), Cy,[64] Ph,[64,73] Bn,[64,73] n-$C_{12}H_{25}$,[64] $(CH_2)_2OH$,[79,82] CMe_2CH_2OH,[79,82] $(CH_2)_3OH$,[82] $CHEtCH_2OH$,[82] $(CH_2)_2C_6H_4OH$-4,[82] CH_2CO_2H,[78–81,83] CMe_2CO_2H,[80] $(CH_2)_2CO_2H$,[78–81,83] $(CH_2)_3CO_2H$,[79–81,83] $(CH_2)_4CO_2H$,[79,81] $CH_2C(O)NHCH_2CO_2H$,[79,80] $(CH_2)_2NMe_2 \cdot HCl$,[84] $(CH_2)_2NHAc$ (see [85])

Among the synthesized glycolurils **5**, three conglomerates (glycolurils with dimethylaminoethyl, hydroxyalkyl or carboxypropyl groups) have been prepared by crystallization from H_2O.[80,82–84]

2.2.3. Reactions of α,ω-diureido acids with 4,5-dihydroxyimidazolidin-2-one

Glycoluril **5b** was prepared from (*S*)- citrulline (Cit) and DHI **21a**[81,86] (Scheme 22) and used in the reaction with KOCN; the reaction unexpectedly led to its transformation to glycoluril **5c** with a hydantoin-5-ylpropyl substituent. The authors assumed that cyclization of the ω-ureide moiety to hydantoin occurs immediately after *N*-carbamoylation

Scheme 22



Cit **5b** (57%)

32 (*n* = 1, 2) **5c**: *n* = 1 (54%), **5d**: *n* = 2 (47%)

Lys

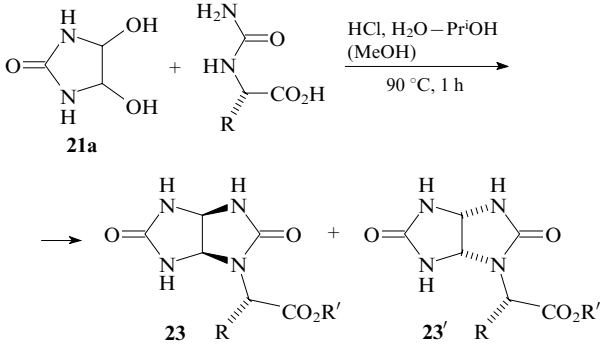
when the reaction medium is acidified to pH ~1. (*S*)-*N*-Hydantoin-5-ylalkylglycolurils **5c**,**d** were also prepared, using the one-pot double cyclization strategy, from α,ω-diureido acids **32** under the action of DHI **21a**. α,ω-Diureido acids **32** were synthesized by the reaction of (*S*)-lysine and (*S*)-citrulline with KOCN.

2.2.4. Diastereoselective synthesis of monosubstituted (3a*S*,6a*R*)- and (3a*R*,6a*S*)-glycolurils based on (*S*)- and (*R*)-*N*-carbamoyl-α-amino acids

At the Laboratory of Nitrogen-Containing Compounds of ZIOC RAS, Professor Kravchenko and co-workers [78, 81, 87, 88] have worked out the first diastereoselective synthesis of 1-monosubstituted (3a*S*,6a*R*)- and (3a*R*,6a*S*)-glycolurils **23** and **23′** using the reaction of DHI **21a** with *N*-carbamoyl-α-amino acids obtained by N-carbamoylation of (*S*)- amino acids (Ala, Nva, Abu, Met, Glu; Nva is norvaline, Abu is α-aminobutyric acid).

The reactions of (*S*)-*N*-carbamoyl-α-amino acids with DHI **21a** afford mixtures of glycolurils with various major (**23**) to minor (**23′**) diastereoisomer ratios ranging from 5 : 2 to 15 : 1 (Scheme 23).[78, 81, 87] Detailed investigation of these processes allowed the researchers to prepare four diastereomerically pure glycolurils with (*S*)-methionine and (*S*)-valine moieties in which configurations of the asymmetric bridging carbon atoms were (3a*S*,6a*R*) for the major stereoisomers and (3a*R*,6a*S*) for the minor ones.

Scheme 23

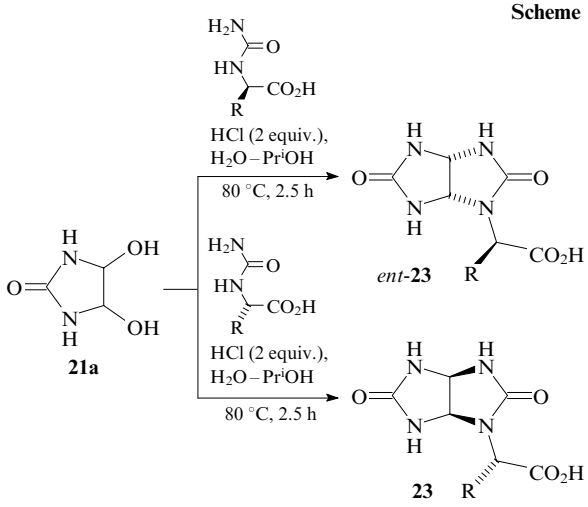


R	R′	Yield (%)		
		23 + **23′**	**23**	**23′**
Me	H	33		
Et	H	33		
Pr^n	H	35		
$(CH_2)_2SMe$	H		37	6
$(CH_2)_2CO_2Me$	Me		34	

Study of the effects of the reaction time and the amount of hydrochloric acid on the yields of glycolurils **23** in the cyclocondensation of DHI **21a** with (*S*)- and some (*R*)-*N*-carbamoyl-α-amino acids has shown that the formation of bicyclic compound is highly diastereoselective if 2 equiv. of the acid are used and the reaction time is 2.5 h; this gives only the major (3a*S*,6a*R*)- (**23**) and (3a*R*,6a*S*)-glycolurils (*ent*-**23**), respectively (Scheme 24).[81, 88]

The configurations of the asymmetric carbon atoms of the resulting enantiomerically pure compounds **23** and *ent*-**23** were established by X-ray diffraction analysis of

Scheme 24



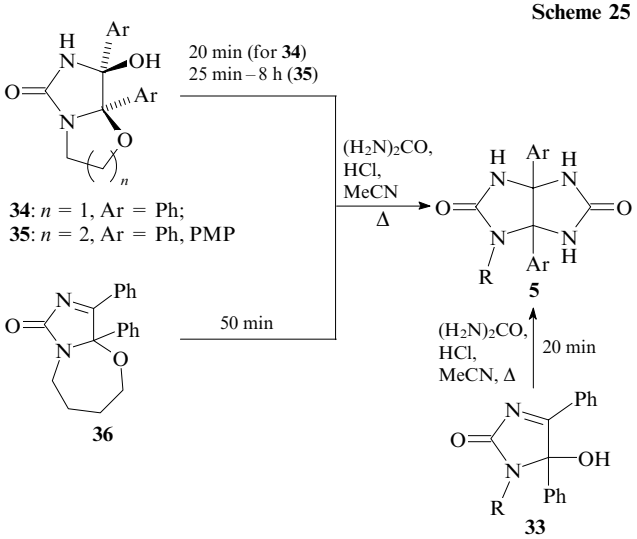
ent-**23**: R = (*R*)-$(CH_2)_2SMe$ (37% yield); (*R*)-Pr^i (30.5%);
23: R = (*S*)-$(CH_2)_2SMe$ (37%), (*S*)-Pr^i (30.5%), (*S*)-Bn (35%), (*S*)-Bu^s (35.5%)

glycolurils with the (*S*)- and (*R*)-methionine [R = $(CH_2)_2SMe$] moieties.[87, 88]

2.2.5. Synthesis of 1-substituted 3a,6a-diarylglycolurils from urea and imidazolinone or its bicyclic analogues

Recently, a new approach has been developed for the synthesis of 1-substituted 3a,6a-diarylglycolurils **5** based on the reaction of imidazolinones **33**, imidazooxazolone **34**, imidazooxazinone **35** or imidazooxazepinone **36** with urea in the presence of hydrochloric acid (Scheme 25).[89]

Scheme 25

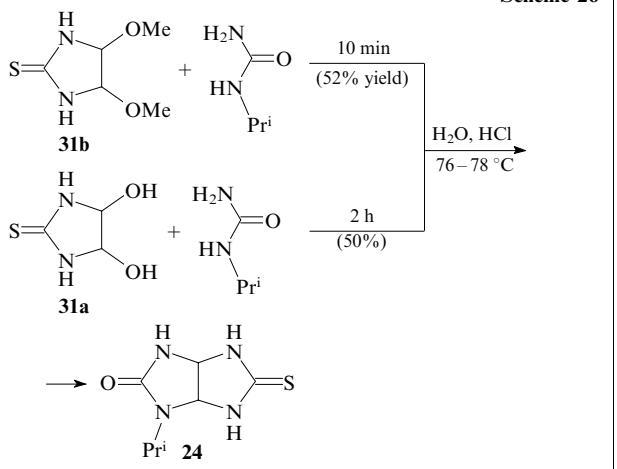


Ar = Ph: R = Me (72% yield), Et (73%), Pr^n (70%), Bu^n (59%), Bn (75%), $(CH_2)_2OAc$ (63%), $(CH_2)_4OAc$ (74%), $(CH_2)_2OH$ (85%), $(CH_2)_3OH$ (66%), $(CH_2)_4OH$ (91%);
Ar = PMP, R = $(CH_2)_3OH$ (82%)

2.2.6. Synthesis of 1-isopropylthioglycoluril

1-Isopropylthioglycoluril (**24**) was prepared by reaction of 1-isopropylurea with either DHIT **31a** or its diether **31b** (Scheme 26).[75]

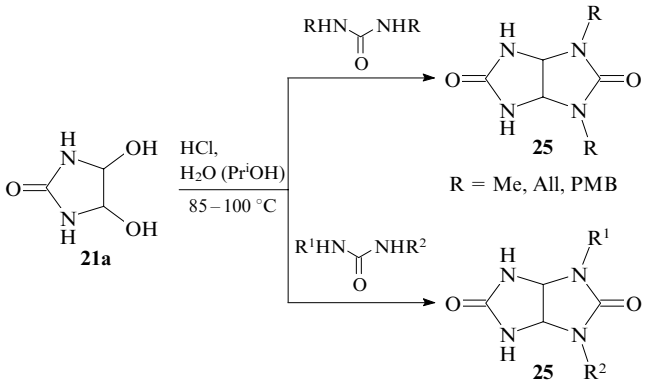
Scheme 26



2.2.7. Synthesis of 1,3-dialkylglycolurils and their thio or imino analogues based on 4,5-dihydroxyimidazolidin-2-one

1,3-Disubstituted glycolurils **25** were prepared by the condensation of DHI **21a** with either symmetrically [1,3-dimethyl-,[65, 73, 90, 91] diallyl-,[92] di(*p*-methoxybenzyl)ureas[93]] or asymmetrically substituted ureas {1-alkyl-3-methyl-,[64] 1-hydroxyalkyl-3-methyl-,[60, 78, 82] 1-[(2-acetylamino)ethyl]-3-methyl(phenyl)ureas[85]] (Scheme 27). The reactions were conducted in water,[60, 64, 73, 78, 82, 85, 90, 91] methanol[92] or propan-2-ol[64] in the presence of hydrochloric acid upon refluxing for 1–12 h.

Scheme 27



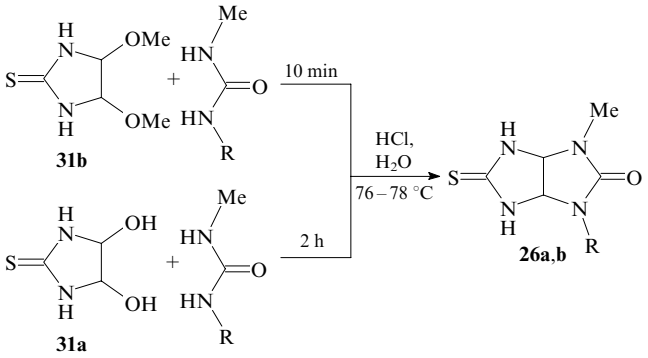
R^1 = Me: R^2 = Et, Pr^n, Bu^n, Bu^s, Bu^t, Cy, $(CH_2)_2OH$, CMe_2CH_2OH, $(CH_2)_2NHAc$; R^1 = Ph, R^2 = $(CH_2)_2NHAc$;
PMB is *p*-methoxybenzyl

1,3-Disubstituted thioglycolurils **26a–c** have been described in two papers.[75, 76] When dimethyl ether **31b** was used in the reaction with 1,3-dimethyl- and 1-n-butyl-3-methylurea, thioglycolurils **26a**,**b** were formed in 71% and 77% yields, respectively (Scheme 28).[75]

When the same ureas were used in the reaction with DHIT **31a**, the yields of thioglycolurils **26a**,**b** decreased to 48% and 45%, respectively.

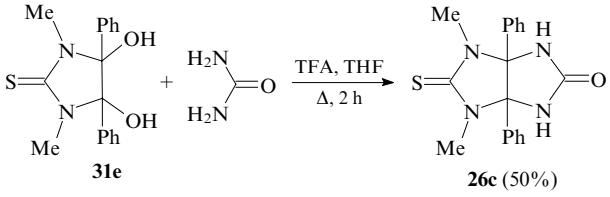
There is an example of synthesis of thioglycoluril **26c** from DHIT **31e** and urea in boiling tetrahydrofuran with addition of trifluoroacetic acid (Scheme 29).[76]

Scheme 28



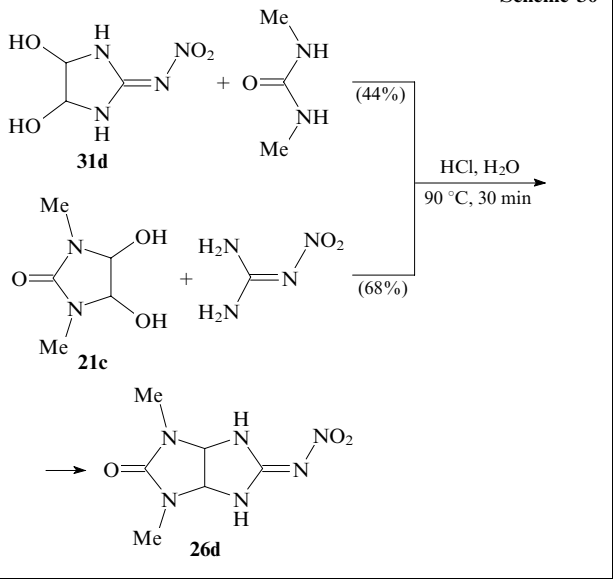
26: R = Me (**a**), Bu^n (**b**)

Scheme 29



4,6-Dimethyl-2-nitroiminoglycoluril (**26d**) was prepared by α-ureidoalkylation of nitroguanidine using 1,3-dimethyl-substituted DHI **21c** or by iminoureidoalkylation of 1,3-dimethylurea with nitroimino derivative of DHI **31d** (Scheme 30).[77]

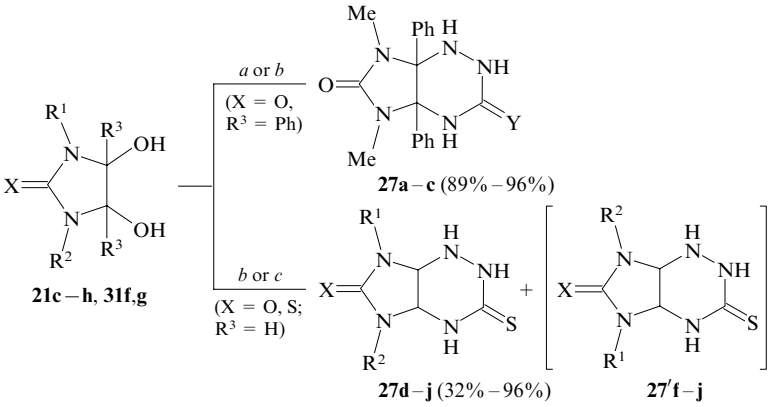
Scheme 30



2.2.8. Reactions of 4,5-dihydroxyimidazolidin-2-ones(thiones) with semi- and thiosemicarbazides and aminoguanidine hydrochloride

Professor Kravchenko and co-workers[94–98] were the first to develop methods for the preparation of new types of glycoluril analogues, *i.e.*, 5,7-dialkyl-substituted imidazotriazines **27a–j**, based on α-ureidoalkylation and α-thioureidoalkylation of (thio)semicarbazide and aminoguanidine as

Scheme 31



(*a*) $H_2NNHC(O)NH_2$, HCl, MeOH, 40 °C (see [94, 96]);
(*b*) $H_2NNHC(S)NH_2$ or $H_2NNHC(NH)NH_2 \cdot HCl$, HCl, MeOH, Δ (see [94, 95]);
(*c*) $H_2NNHC(S)NH_2$, HCl, EtOH, H_2O, Δ (see [97, 98]);
21: X = O, R^3 = H: $R^1 = R^2$ = Me (**c**), Et (**d**); R^1 = Me, $R^2 = Bu^t$ (**f**); R^1 = Me, R^2 = Ph (**g**); R^1 = Et, R^2 = Ph (**h**); X = O, $R^1 = R^2$ = Me, R^3 = Ph (**e**);
31: X = S, R^2 = Ph, R^3 = H: R^1 = Me (**f**), Et (**g**);
27: Y = O (**a**), S (**b**), NH · HCl (**c**);
27, **27′**: X = O: $R^1 = R^2$ = Me (**d**), Et (**e**); $R^1 = Bu^t$, R^2 = Me (**f**); R^1 = Me, R^2 = Ph (**g**); R^1 = Et, R^2 = Ph (**h**); X = S, R^2 = Ph: R^1 = Me (**i**), Et (**j**)

hydrochloride with DHI **21c–h** and DHIT **31f,g** (Scheme 31).

The reaction of DHI **21e** ($R^1 = R^2$ = Me, R^3 = Ph) with the indicated binucleophilic reagents led to imidazotriazines **27a–c** in almost quantitative yields.[94, 95] Compounds **27d,e** were synthesized in high yields (up to 96%) under the same conditions by the reactions of DHI **21c,d** [R^3 = H: $R^1 = R^2$ = Me (**c**), Et (**d**)] devoid of phenyl substituents at the C(4) and C(5) atoms with thiosemicarbazide.[95, 96] Semicarbazide does not react with DHI **21c,d**, while aminoguanidine hydrochloride reacts to give 4,5-bis(aminoguanidino)imidazolidin-2-ones rather than imidazotriazines.[96] Gazieva and co-workers [97, 98] have shown that the asymmetrically substituted DHI **21f–h** and DHIT **31f,g** react with thiosemicarbazide regioselectively to form preferably 7-alkyl(*tert*-butyl)-5-phenyl(methyl)imidazotriazines **27**. The yields of the major regioisomers of the asymmetrically substituted imidazotriazines **27f–j** were 32% – 63% (the minor regioisomers **27′f–j** detected by ^{1}H NMR spectroscopy were not isolated).

2.2.9. Synthesis of 1,6-disubstituted glycolurils based on imidazooxazolone, imidazooxazinone and imidazooxazepinone derivatives

A new regioselective synthetic approach to 1,6-disubstituted 3a,6a-diarylglycolurils **8** is based on condensation of 1-(hydroxyalkyl)ureas [99] and methylurea [100] with tetrahydroimidazooxazolones **34** and tetrahydroimidazooxazinone **35** (Scheme 32). Dihydroimidazooxazepinone **36** reacts only with methylurea.[100]

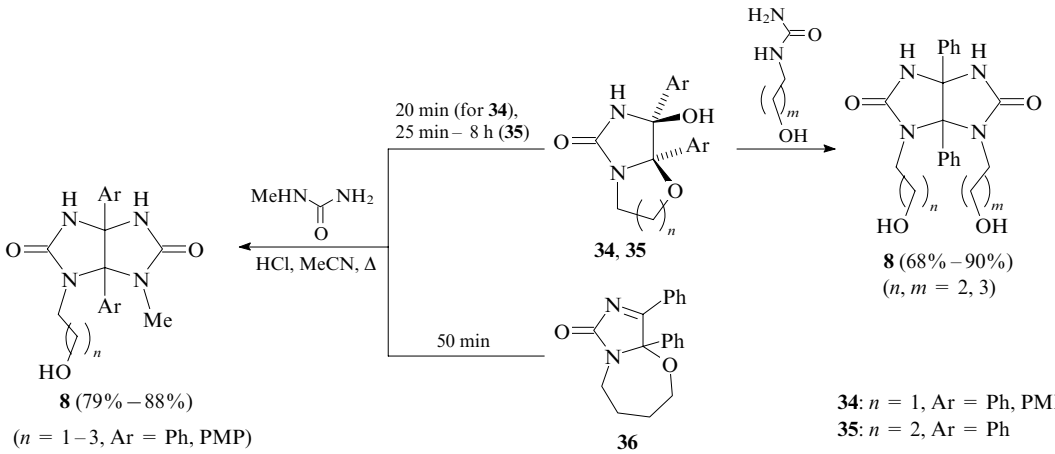
It was shown that the reactions are highly regioselective, resulting in the formation of previously inaccessible 1,6-bis(hydroxyalkyl)-3a,6a-diphenylglycolurils [99] and 3a,6a-diaryl-1-hydroxyalkyl-6-methylglycolurils [100] in high yields. An X-ray diffraction study of the supramolecular organization of 1,6-bis(hydroxyalkyl)-3a,6a-diphenylglycolurils **8** revealed the chirality of the crystals of the achiral glycoluril molecules.[99]

2.2.10. Synthesis of 1,3,4-trisubstituted glycolurils and their thio analogues

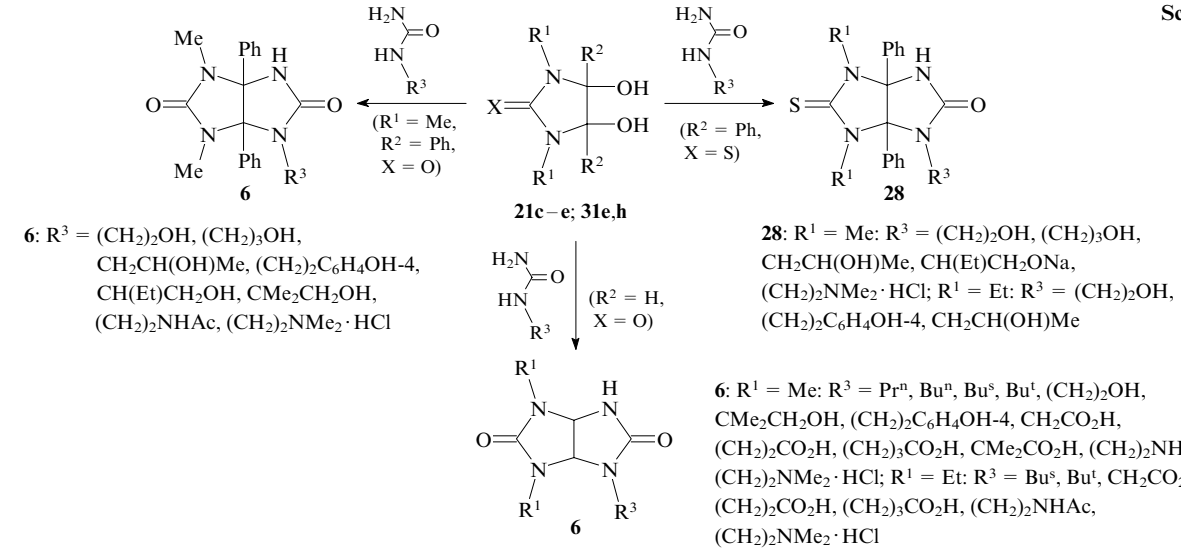
A wide range of 1,3,4-trisubstituted glycolurils **6** have been prepared by condensation of alkyl-,[64, 101, 102] hydroxyalkyl-,[82, 103] carboxyalkyl-,[78, 80, 81, 83, 104] 2-(dimethylamino)ethyl-[84] and 2-(acetylamino)ethylureas [85] with 1,3-dialkyl-substituted DHI **21c,d** [78, 80 – 85, 101, 102] or 1,3-dimethyl-4,5-diphenyl derivative of DHI **21e** [84, 85, 103, 104] (Schemes 33 – 35). The synthesis of 1,3,4-trisubstituted thio analogues **28** was studied systematically in the reactions of DHIT **31e,h** with hydroxyalkylureas [105] (see Scheme 33) and *N*-carbamoylamino acids [106] (see Scheme 35). Thioglycoluril **28** with a dimethylaminoethyl substituent was also synthesized by the reaction of DHIT **31e** with [2-(dimethylamino)ethyl]urea [84] (see Scheme 33).

Glycolurils **6** with various combinations of methyl and ethyl substituents at the nitrogen atoms were prepared by two methods:[64, 102] α-ureidoalkylation of methyl(ethyl)urea with DHI **21c,d** (path *a*) or one-pot α-ureidoalkylation of 1,3-dimethyl(diethyl)ureas with 1-methyl(ethyl)-DHI **21i,j**,

Scheme 32



Scheme 33



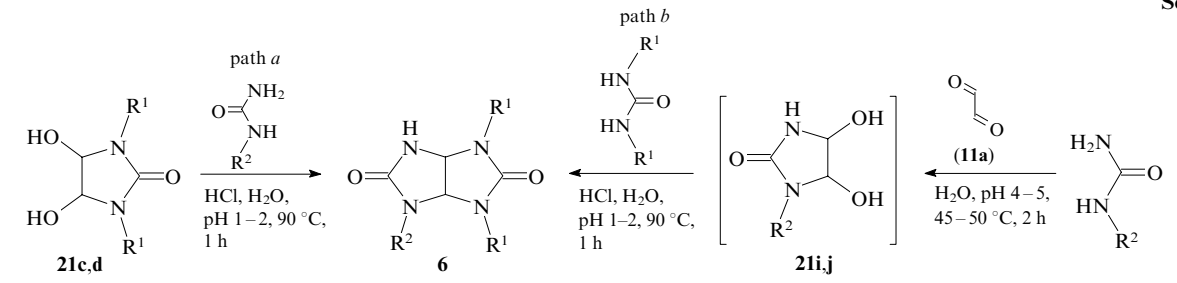
6: R^3 = $(CH_2)_2OH$, $(CH_2)_3OH$, $CH_2CH(OH)Me$, $(CH_2)_2C_6H_4OH$-4, $CH(Et)CH_2OH$, CMe_2CH_2OH, $(CH_2)_2NHAc$, $(CH_2)_2NMe_2 \cdot HCl$

21c–e; **31e**,**h**

28: R^1 = Me: R^3 = $(CH_2)_2OH$, $(CH_2)_3OH$, $CH_2CH(OH)Me$, $CH(Et)CH_2ONa$, $(CH_2)_2NMe_2 \cdot HCl$; R^1 = Et: R^3 = $(CH_2)_2OH$, $(CH_2)_2C_6H_4OH$-4, $CH_2CH(OH)Me$

6: R^1 = Me: R^3 = Pr^n, Bu^n, Bu^s, Bu^t, $(CH_2)_2OH$, CMe_2CH_2OH, $(CH_2)_2C_6H_4OH$-4, CH_2CO_2H, $(CH_2)_2CO_2H$, $(CH_2)_3CO_2H$, CMe_2CO_2H, $(CH_2)_2NHAc$, $(CH_2)_2NMe_2 \cdot HCl$; R^1 = Et: R^3 = Bu^s, Bu^t, CH_2CO_2H, $(CH_2)_2CO_2H$, $(CH_2)_3CO_2H$, $(CH_2)_2NHAc$, $(CH_2)_2NMe_2 \cdot HCl$

Scheme 34



21c,**d**

R^1 = Me (**c**), Et (**d**)

21i,**j**

R^2 = Me (**i**), Et (**j**)

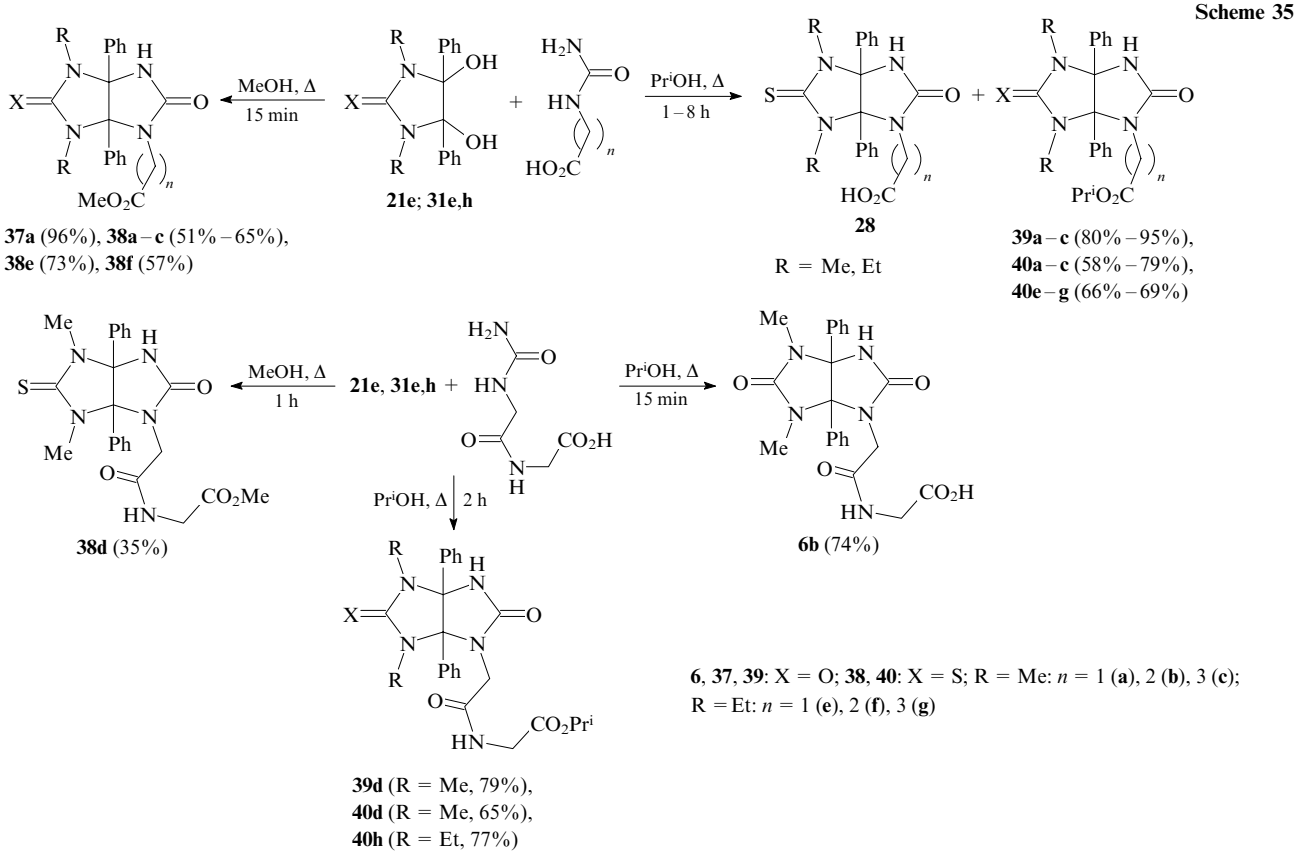
R^1	R^2	Yield of **6** (%)	
		path *a*	path *b*
Me	Me	35	49
Me	Et	52	46
Et	Me	61	42
Et	Et	39	39

formed *in situ* upon the reaction of methyl(ethyl)ureas with glyoxal **11a** (path *b*, see Scheme 34). It was found that the one-pot procedure is the method of choice for the preparation of 1,3,4-trimethylglycoluril from DHI **21i** and 1,3-dimethylurea, whereas 4-ethyl-1,3-dimethyl- and 1,3-diethyl-4-methylglycolurils **6** are better prepared by the former method, that is, the reaction of DHI **21c** with ethylurea and DHI **21d** with methylurea, which results in higher yields. In order to synthesize 1,3,4-triethylglycoluril, both methods can be used.

It is interesting that α-ureidoalkylation of *N*-carbamoylamino acids and *N*-carbamoylglycylglycine with 1,3-dimethyl-4,5-diphenyl-substituted DHI (**21e**) and DHIT **31e**,**h** in methanol or propan-2-ol (DHI **21e** and DHIT **31e**,**h** are insoluble in water) is accompanied by esterification of the carboxy groups of the formed glycolurils **6** and thioglycolurils **28** to give methyl esters (**37a**, **38a–f**) or isopropyl esters of *N*-(carboxyalkyl)glycolurils(thioglycolurils) **39a–d**, **40a–h** (see Scheme 35).[104, 106] The reaction can be terminated after the formation of glycoluril **6** and thioglycolurils **28** only when *N*-carbamoylglycylglycine or *N*-carbamoylglycine is used. Glycolurils **6** containing free carboxy group are synthesized by alkaline hydrolysis of their isopropyl esters **39**.[104]

2.2.11. Diastereoselctive synthesis of 1,3,4-trisubstituted glycolurils 4,5-Dihydroxyimidazolidin-2-ones **21c,e** react with *N*-(*S*)-carbamoylamino acids, prepared by *N*-carbamoylation of corresponding amino acids (Ala, Aba, Nva, Val, Phe) with potassium cyanate, to give diastereomeric mixtures of glycolurils **29a–d,f,g** and **29′a–d**,**f**,**g** (Scheme 36).[107] In the case of DHI **21e**, the formation of bicyclic compounds is accompanied by esterification. When the amount of hydrochloric acid increases (from 0.5 to 1 equiv.), the two reactions afford only major diastereoisomers **29c** and **29e**. The configurations of the asymmetric carbon atoms (3a*R*,6a*R*) of **29c** and **29e** were established by X-ray diffraction analysis. Compound **21e** reacts with a large number of *N*-carbamoylamino acids, with the yields of diastereomeric glycolurils **29d** + **29′d** (88%) and **29e** (91%) being higher than those of analogous glycolurils **29a** + **29′a** (25%) and **29b** + **29′b** (37%). Hence, it was concluded that the carbocation formed from 4,5-diphenyl-substituted DHI **21e** is more stable than the carbocation formed from DHI **21c**. Steric factors are also important.

Scheme 35



37a (96%), **38a** – **c** (51% – 65%), **38e** (73%), **38f** (57%)

21e; **31e**,**h**

28

R = Me, Et

39a – **c** (80% – 95%), **40a** – **c** (58% – 79%), **40e** – **g** (66% – 69%)

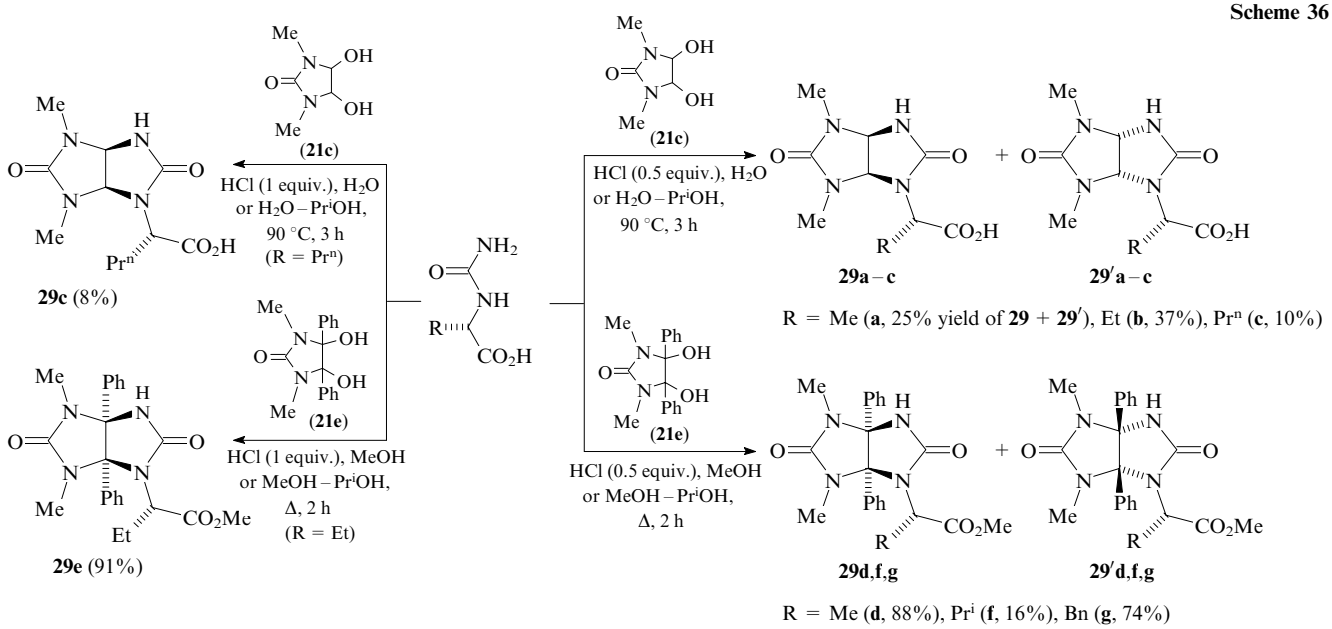
38d (35%)

6b (74%)

39d (R = Me, 79%), **40d** (R = Me, 65%), **40h** (R = Et, 77%)

6, **37**, **39**: X = O; **38**, **40**: X = S; R = Me: *n* = 1 (**a**), 2 (**b**), 3 (**c**); R = Et: *n* = 1 (**e**), 2 (**f**), 3 (**g**)

Scheme 36



29c (8%)

29e (91%)

29a – **c**

29′a – **c**

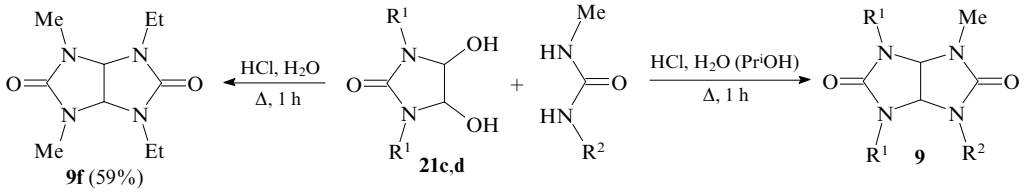
R = Me (**a**, 25% yield of **29** + **29′**), Et (**b**, 37%), Pr^n (**c**, 10%)

29d,**f**,**g**

29′d,**f**,**g**

R = Me (**d**, 88%), Pr^i (**f**, 16%), Bn (**g**, 74%)

Scheme 37



9f (59%)

21c,**d**

9

9: R^1 = Me: R^2 = Pr^n (59% yield), Bu^t (65%), Cy (72%), (CH$_2$CH=CMeCH$_2$)$_3$CH$_2$CH=CMe$_2$ (61%); R^1 = Et: R^2 = Bu^t (61%), Cy (66%)

2.2.12. Synthesis of 1,3,4,6-tetrasubstituted glycolurils

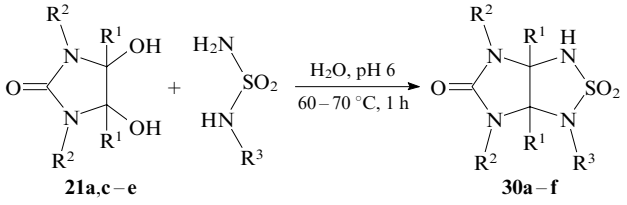
1,3,4,6-Tetrasubstituted glycolurils **9** have been prepared by the reaction of DHI **21c** with 1-methyl-3-propyl(*tert*-butyl,cyclohexyl)ureas or [(2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl]urea and the reaction of DHI **21d** with 1-methyl-3-*tert*-butyl(cyclohexyl)ureas.[64] Using the reaction of DHI **21c** with 1,3-diethylurea, the possibility of the synthesis of 1,3-dimethyl-4,6-diethylglycoluril was demonstrated (Scheme 37).[108]

2.2.13. Synthesis of sulfo analogues of glycolurils based on 4,5-dihydroxyimidazolidin-2-ones

Unsubstituted and di-, tri- and tetrasubstituted sulfo analogues of glycolurils **30** were synthesized using DHI.[109–112]

Unsubstituted sulfo analogue **30a** was obtained by condensation of DHI **21a** with sulfamide (Scheme 38).[109] Reactions of sulfamide with DHI **21c–e** to form disubstituted sulfo analogues of glycolurils **30b–d** are known (see Scheme 38).[109–111] 1,4,6-Trisubstituted sulfo analogues of glycolurils are represented by two compounds **30e**,**f** prepared by the reaction of DHI **21c**,**d** with 1-propylsulfamide (see Scheme 38).[109]

Scheme 38

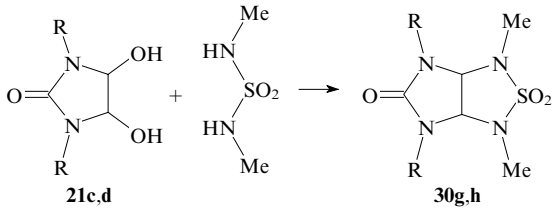


21a,**c–e** **30a–f**

30: $R^1 = R^2 = R^3 = H$ (**a**, 55% yield); $R^1 = R^3 = H$: $R^2 = Me$ (**b**, 49%), Et (**c**, 62%); $R^1 = Ph$, $R^2 = Me$, $R^3 = H$ (**d**, 27%); $R^1 = H$, $R^3 = Pr^n$: $R^2 = Me$ (**e**, 35%), Et (**f**, 13%)

The first representatives of 1,3,4,6-tetraalkyl-5(3*H*)-oxotetrahydro-1*H*-imidazo[4,5-*c*][1,2,5]thiadiazole 2,2-dioxides **30g**,**h** were synthesized in 52% and 8% yields, respectively, by the reaction of DHI **21c**,**d** with 1,3-dimethylsulfamide in water at pH 1, and at 80–90 °C (Scheme 39).[109–111] The yield of compound **30h** increased up to 12%, when the reaction was carried out in acetone in the presence of HCl at high pressure.[112]

Scheme 39



21c,**d** **30g**,**h**

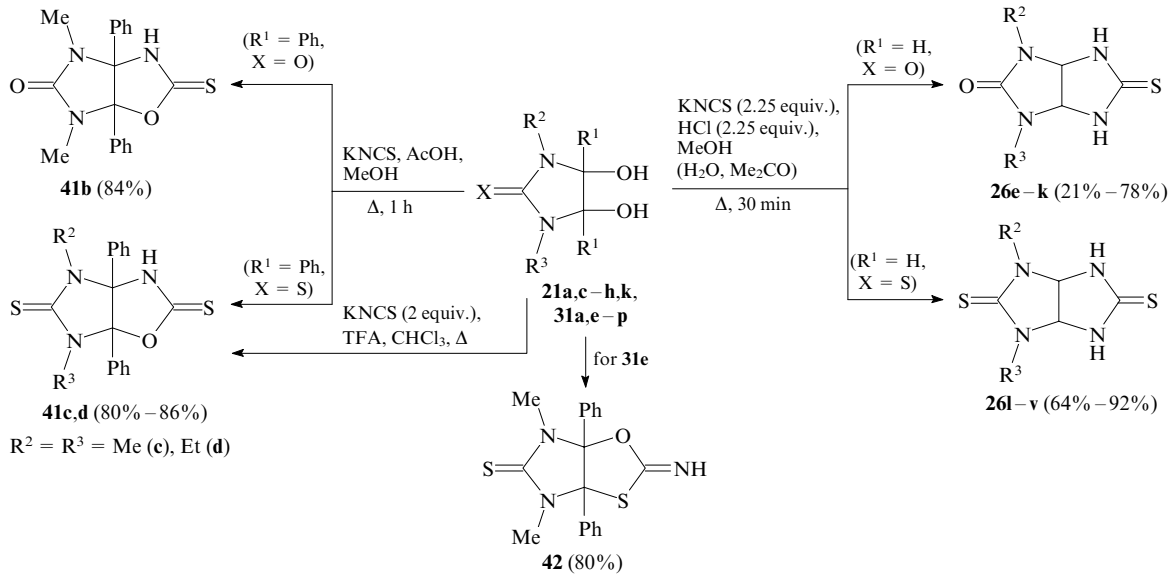
30: R = Me (**g**), Et (**h**)

2.3. Reactions of 4,5-dihydroxyimidazolidin-2-ones(thiones) and imidazolinones with KNCS in the presence of acids

Recently, a new effective synthetic route has been developed to access mono- and dithioglycolurils **26e–v** based on the reaction of DHI **21a**,**c–h**,**k** or DHIT **31a**,**e–p** with potassium thiocyanate and hydrochloric acid [taken in DHI(DHIT) : KNCS : HCl molar ratio of 1 : 2.25 : 2.25] in methanol (for **21a**,**c**,**d**,**g**,**h**), water (for **21f**,**k**) or acetone (for **31a**,**f**,**g**,**k–p**) (Scheme 40, right part).[113]

Some examples of the synthesis of glycoluril hetero analogues were reported in literature.[76,114–117] Compound **41a** was unexpectedly obtained as a side product in a very low yield from the Marckwald synthesis of 1-benzyl-5-hydroxymethyl-2-sulfanylimidazole by the reaction of 1,3-dihydroxyacetone with benzylamine hydrochloride and potassium thiocyanate (Scheme 41).[114] Refluxing of two equivalents of KNCS with 1,3-dimethyl-substituted DHIT **31e** (Scheme 40, bottom part) in acidified THF afforded compound **42**.[76] However, in another study,[115] the reaction

Scheme 40



41b (84%)

41c,**d** (80%–86%)
$R^2 = R^3 = Me$ (**c**), Et (**d**)

21a,**c–h**,**k**, **31a**,**e–p**

42 (80%)

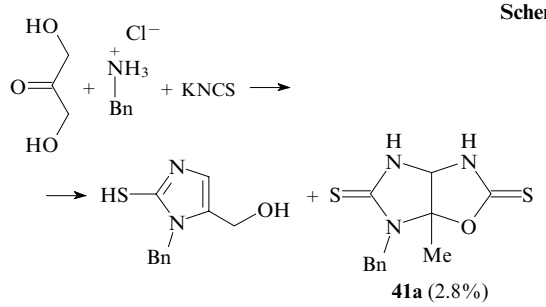
26e–k (21%–78%)

26l–v (64%–92%)

X = O, $R^1 = H$: $R^2 = R^3 = H$ (**21a**, **26e**), Me (**21c**, **26f**), Et (**21d**, **26g**); $R^2 = Ph$: $R^3 = Me$ (**21g**, **26h**), Et (**21h**, **26i**); $R^2 = Me$, $R^3 = Bu^t$ (**21f**, **26j**), $R^2 = H$, $R^3 = Cy$ (**21k**, **26k**); X = O, $R^1 = Ph$, $R^2 = R^3 = Me$ (**21e**); X = S, $R^1 = H$: $R^2 = R^3 = H$ (**31a**, **26l**), Me (**31i**, **26m**), Et (**31j**, **26n**), Ph (**31k**, **26o**); $R^2 = Ph$: $R^3 = H$ (**31l**, **26p**), Me (**31f**, **26q**), Et (**31g**, **26r**), $(CH_2)_2OH$ (**31m**, **26s**), $(CH_2)_3OH$ (**31n**, **26t**); $R^2 = Me$: $R^3 = H$ (**31o**, **26u**), Et (**31p**, **26v**); X = S, $R^1 = Ph$: $R^2 = R^3 = Me$ (**31e**), Et (**31h**)

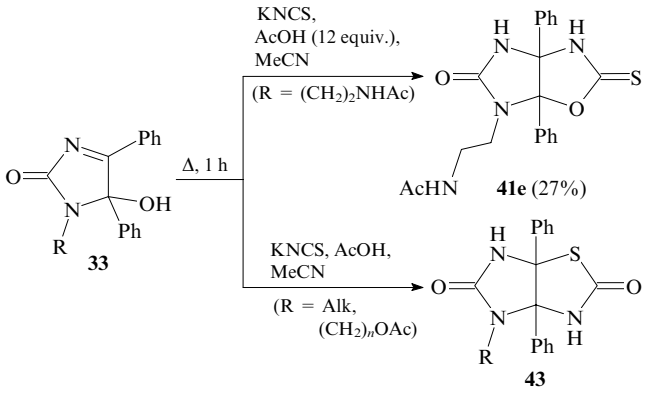
of DHI **21e** or DHIT **31e**,**h** with KNCS and acids was shown to afford imidazooxaloles **41b** – **d** under various conditions (Scheme 40, left part).

Scheme 41



A general and highly selective method for the synthesis of imidazothiazolones **43** has been developed through a new reaction of imidazolinones **33** with potassium thiocyanate and acetic acid in acetonitrile.[116] However, the reaction of 1-[(2-acetylamino)ethyl]imidazolinone **33** [R = $(CH_2)_2NHAc$] led to an unusual outcome, namely, imidazooxazolethione **41e** was formed instead of the expected imidazothiazolone **43** (Scheme 42).[117]

Scheme 42



43: R = Me (92% yield), Et (74%), Pr^n (88%), Bu^n (80%), Bn (85%), $(CH_2)_2OAc$ (53%), $(CH_2)_3OAc$ (57%), $(CH_2)_4OAc$ (79%)

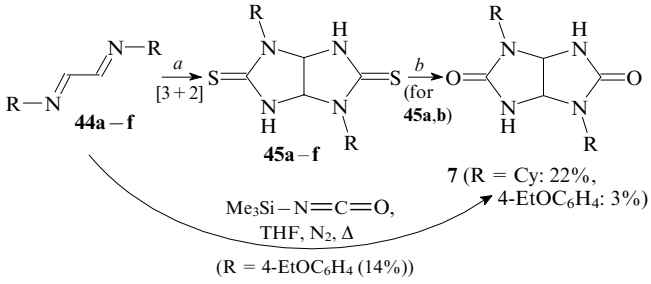
2.4. Condensation of 1,4-disubstituted 1,4-diaza-1,3-dienes with isocyanic and/or isothiocyanic acid or isocyanates

The condensations of 1,4-disubstituted 1,4-diaza-1,3-dienes **44** with isocyanic and/or isothiocyanic acid or isocyanates give di- and monothioglycolurils of new types **45**, **46**. Furthermore, these reactions provide yet another method to synthesize glycolurils **7**, **9**.

2.4.1. Synthesis of 1,4-disubstituted glycolurils and thioglycolurils

The synthesis of 1,4-disubstituted glycolurils **7** is closely related to the synthesis of 1,4-disubstituted thioglycolurils **45a** – **f** upon [3 + 2]-cycloaddition of 1,4-diaza-1,3-dienes **44a** – **f** to trimethylsilyl isothiocyanate.[118] Further oxidation of thioglycolurils **45a**,**b** with hydrogen peroxide gives 3,6-di(4-ethoxyphenyl)- and 3,6-di(cyclohexyl)glycolurils **7**. Glycoluril **7** (R = 4-$EtOC_6H_4$) was also synthesized in one step by [3 + 2]-cycloaddition of 1,4-diaza-1,3-diene **44b** to trimethylsilyl isothiocyanate. In this case, the yield of compound **7** increased from 3% to 14%. (Scheme 43).

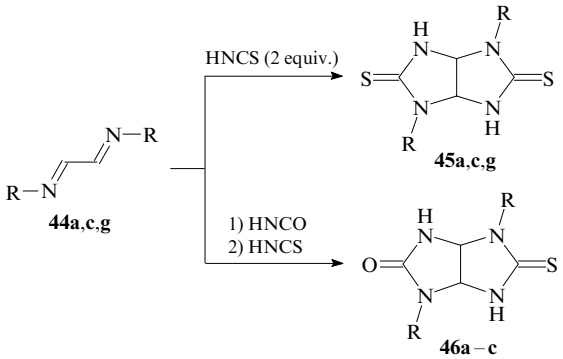
Scheme 43



(*a*) $Me_3Si-N=C=S$, THF, rt, 3 h;
(*b*) H_2O_2, Me_2CO, Δ, 3 – 5 h
R = Cy (**a**), 4-$EtOC_6H_4$ (**b**), PMP (**c**), *p*-Tol (**d**), Pr^i (**e**), Bu^n (**f**);
p-Tol = 4-MeC_6H_4

Similar dithioglycolurils **45a**,**c**,**g** and 1,4-disubstituted monothioglycolurils **46a** – **c** were obtained by reactions of 1,4-diazabuta-1,3-dienes **44a**,**c**,**g**, respectively, with 2 equiv. of isothiocyanic acid or with 1 equiv. of isocyanic acid and 1 equiv. of isothiocyanic acid added sequentially (Scheme 44).[119]

Scheme 44



R = Cy (**44a**, **45a**, **46a**), PMP (**44c**, **45c**, **46b**), Bu^t (**44g**, **45g**, **46c**)

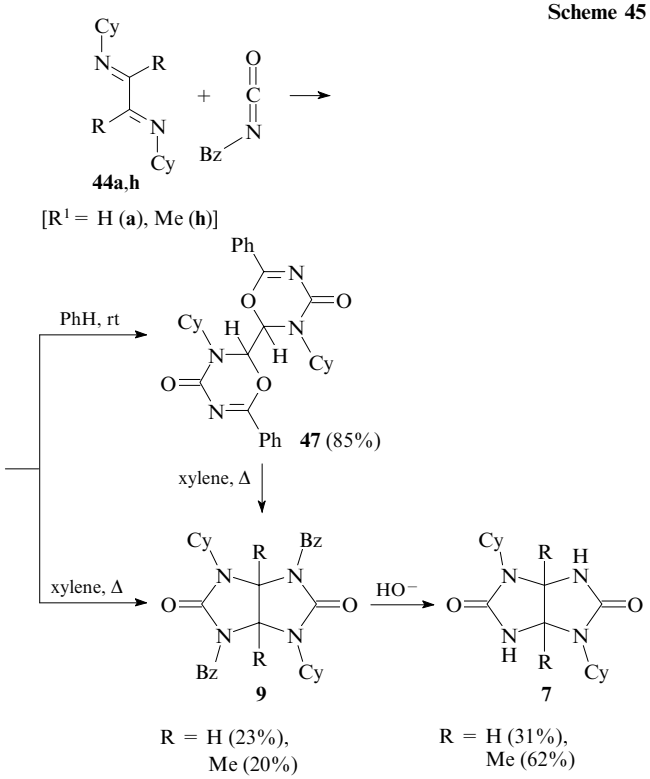
2.4.2. Synthesis of 1,3,4,6-tetrasubstituted glycolurils

Sakamoto *et al.*[120] synthesized tetrasubstituted glycolurils **9** using 1,2-diimines **44a**,**h** and benzoyl isocyanate (Scheme 45). Depending on the reaction conditions and the solvent, glycolurils **9** are formed either in one step or *via* intermediate **47**. 1,4-Disubstituted glycolurils **7** were obtained from tetrasubstituted glycolurils **9**.

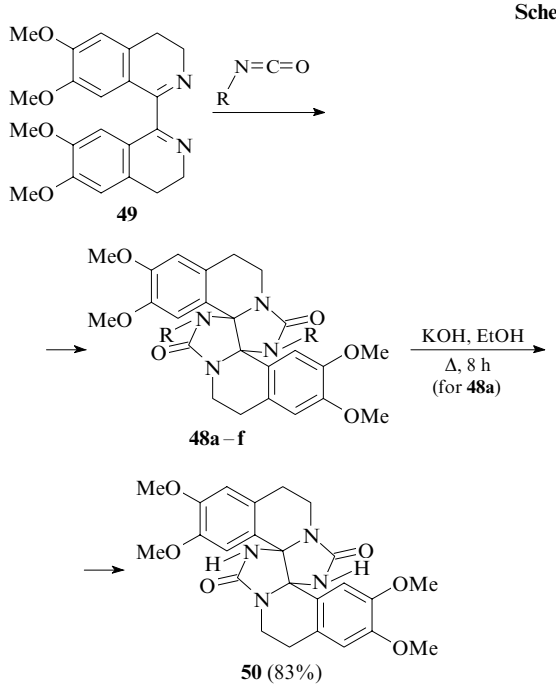
Annulated tetrasubstituted glycolurils **48a** – **f** were prepared by the reaction of 6,6′,7,7′-tetramethoxy-3,3′,4,4′-tetrahydro-1,1′-biisoqiunoline (**49**) with aryl isocyanates (Scheme 46).[120] Using compound **48a** as an example, it was shown that it can be converted to *trans*-annulated disubstituted glycoluril **50** by refluxing in an ethanol solution of alkali.

A single example of the synthesis of glycoluril **9g** from dihydrazone **51** and tosyl isocyanate has been reported; however, this reaction also gives compound **52** (Scheme 47).[121]

Scheme 45



Scheme 46

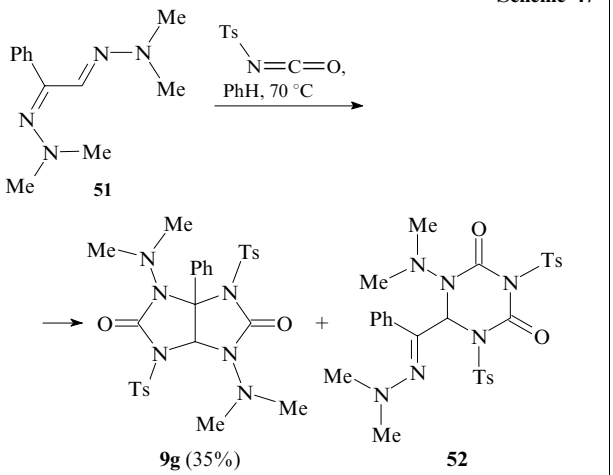


48: R = Bz (**a**, 34% yield), Ph (**b**, 35%), 4-ClC_6H_4 (**c**, 54%), 3-ClC_6H_4 (**d**, 41%), 4-BrC_6H_4 (**e**, 43%), *p*-Tol (**f**, 21%)

2.5. Triazine-to-imidazolidine ring contraction reaction of imidazotriazines

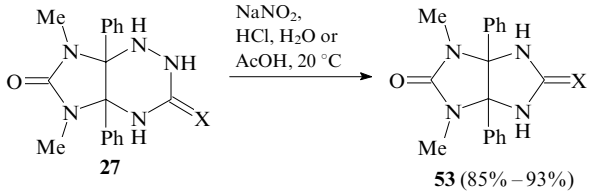
Triazine ring-contraction reactions of 5,7-disubstituted 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones(thiones) are used to prepare 1,3-di- and 1,3,4-trisubstituted mono- and dithio analogues of glycolurils and can be extended to glycolurils and their imino analogues. The method was developed by our research group.[28–30, 97, 98, 122–126]

Scheme 47



The contraction of a triazine ring to the imidazolidine one occurs upon treatment of imidazotriazines **27** with nitrous acid obtained *in situ* from sodium nitrite in acidic medium. 3a,6a-Diphenyl-substituted compounds **53** were formed in almost quantitative yields (Scheme 48).[122]

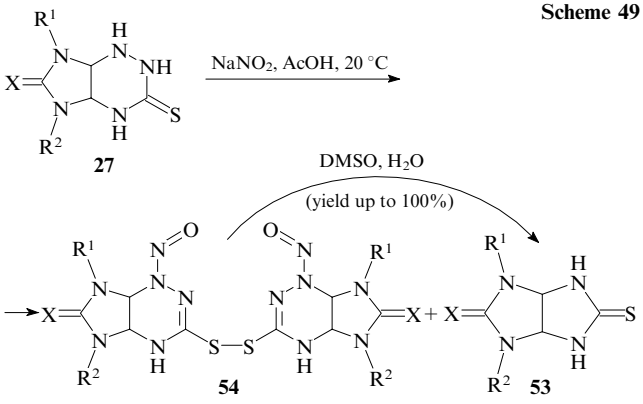
Scheme 48



The nitrosation of C(3a)- and C(6a)-unsubstituted compounds **27** affords, along with the thioglycolurils **53**, also disulfides **54**, which are gradually converted almost quantitatively to the corresponding compounds **53** in the presence of water (Scheme 49). The authors suggest plausible reaction mechanisms.[97, 122]

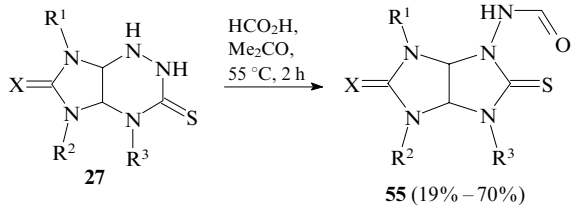
A simple synthetic route to *N*-{5-oxo-2-thioxo(2,5-dithioxo)hexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl}formamides

Scheme 49



55 was developed *via* a tandem N-formylation and ring-contraction reaction of imidazotriazines **27** with formic acid (Scheme 50).[98] Imidazotriazines **27** unsubstituted in the triazine ring are converted to formamides **55** in 54% – 70% yields. Introducing a methyl substituent into the triazine ring (R^3 = Me) leads to a significant decrease in the yield of the reaction product (19%).

Scheme 50

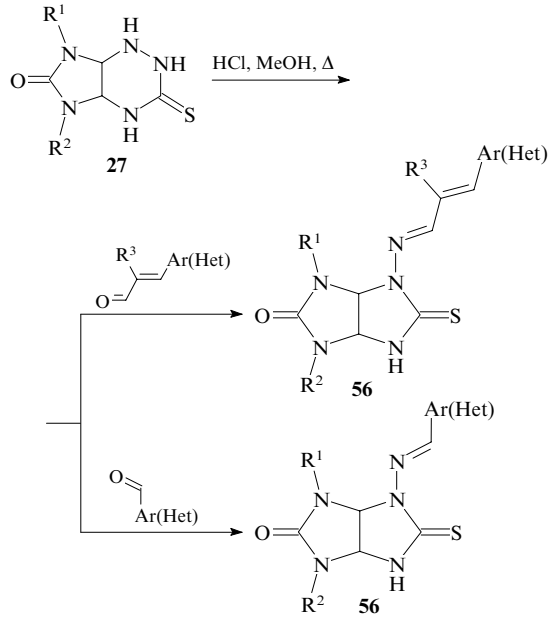


27 **55** (19% – 70%)

X = O, S; R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Me

A large group of 1,3-dialkyl-4-{[(het)arylmethyliden]-amino}thioglycolurils **56** was synthesized in 32% – 65% yields by the reaction of imidazotriazines **27** with (hetero)-aromatic aldehydes or phenylacrylaldehyde derivatives in methanol in the presence of hydrochloric acid (Scheme 51). Introducing a methyl group in position 2 of phenylacrylal-dehyde (R^3 = Me) results in decreasing yield of the reaction products **56** (32% – 36%).[28 – 30, 123 – 126]

Scheme 51



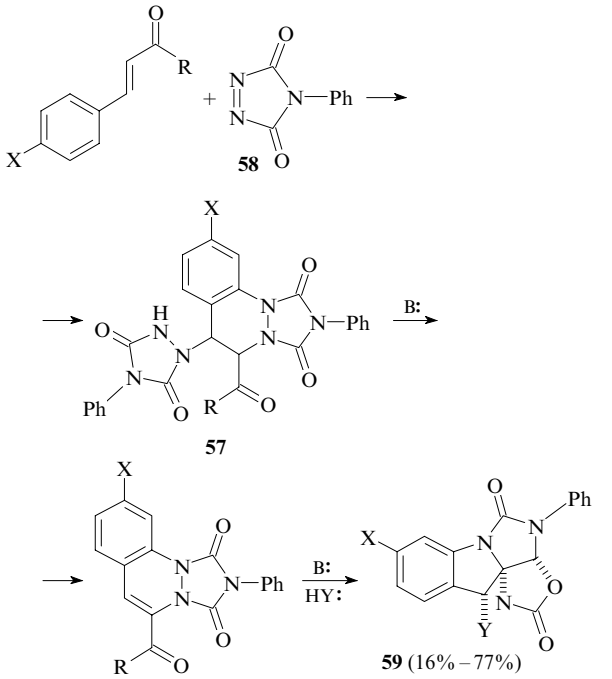
27 **56** **56**

R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Me; Ar = Ph, 2-HOC_6H_4, 2-$O_2NC_6H_4$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-HO-3-$MeOC_6H_3$, 2-HO-5-BrC_6H_3, 2-HO-5-ClC_6H_3, 2-HO-3,5-$I_2C_6H_2$, 4-HO-3,5-$(MeO)_2C_6H_2$, 2-$(MeOC(O)CH_2O)C_6H_4$, 4-$(MeOC(O)CH_2O)C_6H_4$; Het = 2-Fu, 2-Th, 5-methylfuran-2-yl, 3-methylthiophen-2-yl, 9-methyl-9*H*-carbazol-3-yl, 9-ethyl-9*H*-carb-azol-3-yl; Fu is furtyl, Th is thienyl

2.6. Synthesis of imidazooxazoles

Alcoholysis and aminolysis of urazoles **57** prepared by the reactions of benzylidene ketones with 4-phenyl-4,5-dihydro-3*H*-1,2,4-triazole-3,5-dione (**58**) afforded tricyclic oxazolidinone derivatives **59** in moderate yields (16% – 77%) (Scheme 52). The reaction proceeded *via* opening of the urazole ring through initial Michael addition of nucleophiles (solvent HY:) to the enone fragment, followed by skeletal rearrangement.[127]

Scheme 52

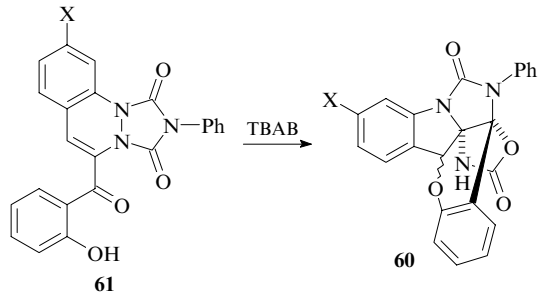


58 **57** **59** (16% – 77%)

R = Me, Ph, 2-Fu, 2-Th, 2-Py, Bu^t; X = H, OMe; Y = OMe, OEt, OPr^i, OBu^t, $NHBu^n$; B: is base

Novel propellane hetero analogues **60** comprising an imidazooxazole moiety were prepared from N-phenyl-substituted 3-acyl-1,2-dihydrocinnoline-1,2-dicarboxamides **61** with phase transfer catalysis (Scheme 53).[128]

Scheme 53

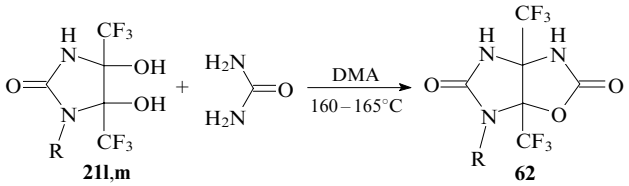


61 **60**

X = H (53% yield), OMe (30%); TBAB = $[Bu^n_4N]Br$

N-Alkyl(aryl)bis(trifluoromethyl)imidazooxazoles **62** were obtained by Saloutina *et al.*[129] as unexpected products of the reaction of 1-alkyl-(aryl)-4,5-dihydroxy-4,5-bis(trifluoromethyl)imidazolidin-2-ones **21l**,**m** with urea in dimethylacetamide. The reaction was accompanied by the rearrangement of imidazolidin-2-ones into *N*-alkyl(aryl)-5,5-bis(trifluoromethyl)hydantoins with CF_3 group migration from position 5 to position 4 of the starting heterocycle. The structures of 3-(4-ethoxyphenyl)-5,5-bis(trifluoromethyl)-imidazolidine-2,4-dione and 6-(4-ethoxyphenyl)-

Scheme 54



[R = 4-EtOC$_6$H$_4$ (**l**), Me (**m**)]

(R = 4-EtOC$_6$H$_4$: 38%), Me: 42%)

3a,6a-bis(trifluoromethyl)tetrahydroimidazo[4,5-*d*]oxazole-2,5-dione) were proved by X-ray diffraction studies.

3. Conclusion

This review covers all currently available methods for the synthesis of glycolurils and their hetero analogues. The reactions of ureas and their analogues with α-dicarbonyl compounds mainly serve for a preparatiion of a single type of glycolurils and their hetero analogues devoid of substituents at the nitrogen atoms. The approach involving the condensations of ureas and their analogues with DHI, DHIT, their imino analogues, imidazolinones and their bicyclic analogues covers most fully all known types of glycolurils, thioglycolurils, imino and sulfo analogues of glycolurils, as well as other types of their hetero analogues, namely imidazotriazines. These compounds contain diverse substituents both at the nitrogen atoms and at the C(3a) and C(6a) carbon atoms. Using this approach, enantiomerically pure glycolurils were synthesized for the first time. Recently, new original general methods for the synthesis of previously inaccessible thioglycolurils have been developed using the reaction of DHI, DHIT and imidazolinones with KNCS in the presence of acids and triazine-to-imidazolidine ring contraction reactions of imidazotriazines. Condensations of 1,4-disubstituted 1,4-diaza-1,3-dienes with isocyanic and/or isothiocyanic acids or isocyanates have been studied to a much lesser extent, apparently, due to low availability of 1,4-diaza-1,3-dienes. Imidazothiazole and imidazooxazole derivatives were synthesized by an unusual transformation of DHI, DHIT and imidazolinones in the reactions with KNCS as well as through a transformation of urazoles.

The information presented in this review demonstrates that methods for the synthesis of glycolurils and their analogues are constantly developing. These heterocycles are of interest not only as biologically active compounds, but also as precursors for the preparation of a large series of practically useful products. Taken into account the data presented in the review, we expect that glycolurils and their analogues will be actively used in supramolecular chemistry.

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