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Mendeleev Commun., 2024, **34**, 122–125

Mendeleev Communications

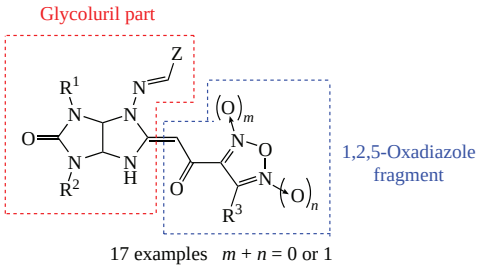
Synthesis of hybrid molecules based on thioglycolurils and 1,2,5-oxadiazoles *via* the Eschenmoser sulfide contraction

Ekaterina E. Vinogradova, Alexander A. Larin and Galina A. Gazieva*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: gaz@ioc.ac.ru

DOI: 10.1016/j.mencom.2024.01.037

A simple synthesis of novel hybrid molecules containing methylidenehexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one and 1,2,5-oxadiazole moieties is based on the Eschenmoser sulfide contraction involving alkylative precoupling of thioglycolurils with 3(4)-bromoacetyl-1,2,5-oxadiazoles. The proposed method does not require using toxic PPh_3 for sulfur extrusion. The synthesized compounds may serve as platforms for constructing both new bioactive and new high-energy compounds.



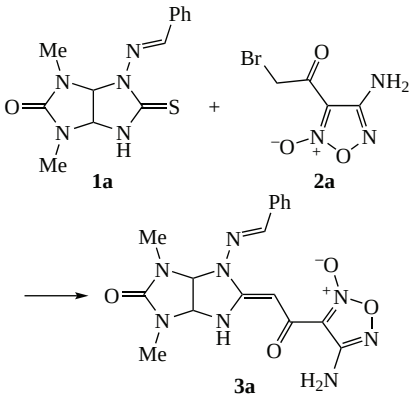
Keywords: glycoluril, thioglycoluril, furazan, furoxan, Eschenmoser sulfide contraction.

Nitrogen- and oxygen-containing heterocyclic compounds have a wide application in medicinal chemistry and advanced materials science.[1] Application potential of heterocyclic derivatives always depends on a set of physicochemical and functional properties which are due to their exact molecular composition. Therefore, a creation of new synthetic methodologies requires fine tunability of the structure of heterocycle derivatives.

Among a broad range of nitrogen heterocycles, glycolurils (tetrahydroimidazo[4,5-*d*]imidazole-2,5-(1*H*,3*H*)-diones) and thioglycolurils (5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones) demonstrate diverse biological activities, including tranquilizing,[2] nootropic,[3] antiproliferative[4] and fungicidal ones.[4(*a*),5] At the same time, nitroglycolurils constitute an important subclass of high-energy, thermally stable explosives.[6] Another type of nitrogen heterocycles possessing both biological activity and high-energy properties is 1,2,5-oxadiazole (furazan) along with its *N*-oxide (furoxan). 1,2,5-Oxadiazoles are promising antibacterial,[7] antiparasitic,[8] and cytotoxic agents[9] and attract much attention as exogenous nitric oxide donors which possess vasodilating and anticoagulant properties.[10] In addition, furazans and furoxans with high nitrogen and oxygen contents may serve as key components of primary and secondary explosives, pyrotechnics and propellants.[11]

Molecular hybridization, a combination of two or more useful fragments in one molecule, is widely used for the development of new biologically active compounds or advanced materials.[8(*a*),12] Taking into account the importance of glycoluril and 1,2,5-oxadiazole scaffolds for the design of new drug candidates and functional materials, molecular hybridization of both these motifs seems to be urgent. Therefore, we intended to develop a simple synthetic approach to access (thio)glycoluril and 1,2,5-oxadiazole hybrid molecules.

For the synthesis of the target hybrids, we chose the reaction of trisubstituted thioglycolurils **1** and 3(4)-bromoacetyl-1,2,5-oxadiazoles **2** (Schemes 1 and 2). It should be noted that we never obtained S-alkylation product. The isolated compounds contained fragments of both starting thioglycoluril and furoxan excluding sulfur atom. We assumed that the formation of amino enones **3** from the cyclic thioamide and α-halo carbonyl compound, which is known as the Eschenmoser sulfide contraction,[13] occurred. The reaction generally requires a base and can be performed with or without a thiophile.

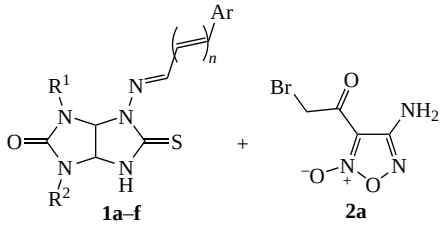


Scheme 1 *Reagents and conditions*: see Table 1.

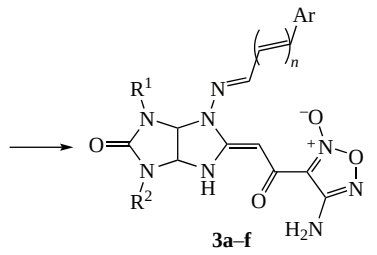
Table 1 Optimization of reaction conditions.[a]

Entry	Solvent	Base (equiv.)	*t*/h	Yield of **3a** (%)
1	MeOH	–	4	–
2	MeOH	K_2CO_3 (1)	4	–[b]
3	DMF	K_2CO_3 (1)	10	20[c]
4	MeCN	NEt_3 (2)	8	traces[b,c]
5	MeCN	K_2CO_3 (1)	6	25[c]
6	MeCN	K_2CO_3 (2)	6	40
7	**MeCN**	**$NaHCO_3$ (3)**	**4**	**65**
8	MeCN	$NaHCO_3$ (3)[d]	7	45[c]

[a] *Reaction conditions*: to a mixture of thioglycoluril **1a** (0.25 mmol) and corresponding base (0–0.75 mmol) in solvent (10 ml), furoxan **2a** (0.5 mol) was added portionwise, and the reaction mixture was stirred under reflux for 4–10 h. [b] The replacement of the thioxo group with the oxo one occurred (*cf.* ref. 14). [c] Incomplete conversion. [d] Three-fold excess of PPh_3 was also used.



1a–f **2a**



3a–f

3a n = 0, R^1 = R^2 = Me, Ar = Ph, 65%
3b n = 0, R^1 = R^2 = Me, Ar = 4-$MeOC_6H_4$, 42%
3c n = 0, R^1 = R^2 = Me, Ar = 4-FC_6H_4, 40%
3d n = 0, R^1 = R^2 = Et, Ar = Ph, 42%
3e n = 0, R^1 = Me, R^2 = Ar = Ph, 55%
3f n = 1, R^1 = R^2 = Me, Ar = 2-$MeOC_6H_4$, 58%

Scheme 2 *Reagents and conditions*: MeCN, 3 equiv. $NaHCO_3$, reflux, 4 h.

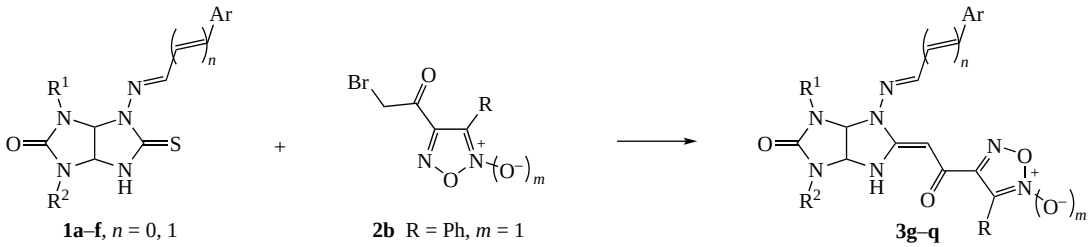
To optimize the reaction conditions, compounds **1a** and **2a** were tested as the model substrates (see Scheme 1, Table 1). With MeOH as a solvent without a base, no product was formed even under reflux (see Table 1, entry 1), while upon addition of 1 equiv. of K_2CO_3 the starting thioglycoluril was quantitatively converted into known glycoluril[14] (the replacement of the thioxo group with the oxo group took place *via* hydrolysis of intermediate *S*-alkyl derivative, entry 2).

Replacing MeOH with DMF made it possible to obtain **3a** in 20% yield, but even prolongation of the reaction time did not lead to complete conversion of the starting compound **1a** (see Table 1, entry 3). Slightly higher yield was achieved using MeCN with 2 equiv. of K_2CO_3 (entry 6), but the replacement of the base with Et_3N resulted only in trace amounts of the product **3a** (entry 4). Replacing the base with a weaker one ($NaHCO_3$) in MeCN caused the improvement in the yield up to 65% (entry 7), which was chosen as the most optimal conditions for obtaining the desired product **3a**. The use of such thiophile as PPh_3 did not increase the yield of the product even with longer reaction time (entry 8). It should be noted that furoxan **2a** slowly decomposed upon treatment with a base, so we used its twofold amount.

With the optimized conditions in hand, we then investigated the substrate scope for the reaction. First, reactivity of various thioglycolurils **1b–f** was studied in the coupling with furoxan **2a** under the optimal conditions for the preparation of compounds **3** (see Scheme 2). It was found that along with model substrate **1a**, different 1,3,4-trisubstituted thioglycolurils **1b–f** reacted with furoxan **2a** to give the desired hybrid molecules **3a–f** in the yields of 40–65%. Next, furoxan **2b** and furazan **4a** were subjected to coupling with thioglycolurils **1a–f** under the same conditions (Scheme 3). Both furoxan **2b** and furazan **4a** were suitable substrates to react with thioglycolurils **1b–f** affording the corresponding derivatives **3** bearing 1,2,5-oxadiazole or its *N*-oxide moiety in 37–70% yields.

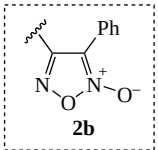
The structures of new hybrid molecules **3a–q** were established by IR, ^{1}H and ^{13}C NMR spectroscopy, and high-resolution mass spectrometry. In the ^{13}C NMR spectra of compounds **3**, the signal for the C=S group disappeared in comparison with the spectra of starting thioglycolurils **1** (178.8–179.4 ppm). The structures of **3e** and **3n** were unambiguously confirmed using single-crystal X-ray diffraction analysis (Figures 1, 2).† The configurations of N=CH and C=CH double bonds were *E* in both cases. For the latter, the observed intramolecular H-bonds between the cyclic NH and exocyclic C=O groups probably stabilized the configuration.

A plausible reaction mechanism is depicted in Scheme 4. The reaction begins with alkylation of thioglycoluril **1** with enolizable α-bromocarbonyl compound **2**, followed by 4π-electrocyclic closure of the intermediate **A** to the episulfide **B**. Extrusion of sulfur from the intermediate **B** gives rise to

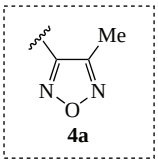


1a–f, n = 0, 1 **2b** R = Ph, m = 1 **4a** R = Me, m = 0 **3g–q**

1a n = 0, R^1 = R^2 = Me, Ar = Ph
1b n = 0, R^1 = R^2 = Me, Ar = 4-$MeOC_6H_4$
1c n = 0, R^1 = R^2 = Me, Ar = 4-FC_6H_4
1d n = 0, R^1 = R^2 = Et, Ar = Ph
1e n = 0, R^1 = Me, R^2 = Ar = Ph
1f n = 1, R^1 = R^2 = Me, Ar = 2-$MeOC_6H_4$



2b



4a

n = 0

3g R^1 = R^2 = Me, Ar = Ph, 70%
3h R^1 = R^2 = Me, Ar = 4-$MeOC_6H_4$, 53%
3i R^1 = R^2 = Me, Ar = 4-FC_6H_4, 50%
3k R^1 = R^2 = Et, Ar = Ph, 50%

n = 1

3j R^1 = R^2 = Me, Ar = 2-$MeOC_6H_4$, 44%

n = 0

3l R^1 = R^2 = Me, Ar = Ph, 58%
3m R^1 = R^2 = Me, Ar = 4-$MeOC_6H_4$, 56%
3n R^1 = R^2 = Me, Ar = 4-FC_6H_4, 50%
3o R^1 = R^2 = Et, Ar = Ph, 43%
3p R^1 = Me, R^2 = Ar = Ph, 37%

n = 1

3q R^1 = R^2 = Me, Ar = 2-$MeOC_6H_4$, 52%

Scheme 3 *Reagents and conditions*: MeCN, 3 equiv. $NaHCO_3$, reflux, 4 h.

† *Crystal data for* **3e**. $C_{22}H_{20}N_8O_4$, M = 460.45, triclinic, space group $P\bar{1}$, 100 K, a = 8.55373(15), b = 12.2726(2) and c = 13.4674(3) Å, V = 1236.66(5) Å^3, Z = 2, d_{calc} = 1.446 g cm^{-3}, μ = 1.625 mm^{-1}, R_1 = 0.0349 [from 4947 unique reflections with $I > 2\sigma(I)$] and wR_2 = 0.0945 (from all 5246 unique reflections).

Crystal data for **3n**. $C_{18}H_{18}N_7O_3F$, M = 399.39, monoclinic, space group $P2_1/n$, 100 K, a = 11.92076(12), b = 7.39992(6) and c = 21.5858(2) Å, V = 1900.85(3)Å^3, Z = 4, d_{calc} = 1.396 g cm^{-3}, μ = 0.895 mm^{-1}, R_1 = 0.0364 [from 3789 unique reflections with $I > 2\sigma(I)$] and wR_2 = 0.0961 (from all 4113 unique reflections).

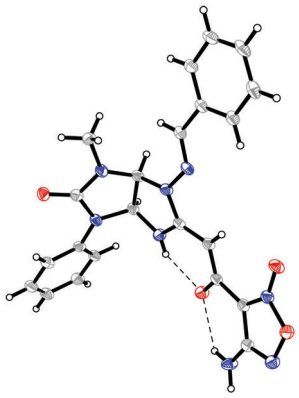


Figure 1 General view of **3e** in representation of non-hydrogen atoms *via* thermal ellipsoids at 50% probability level.

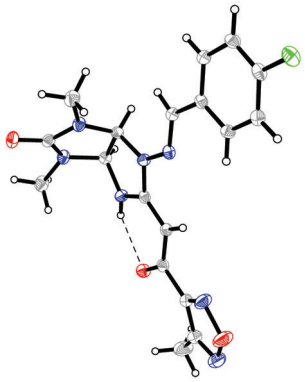
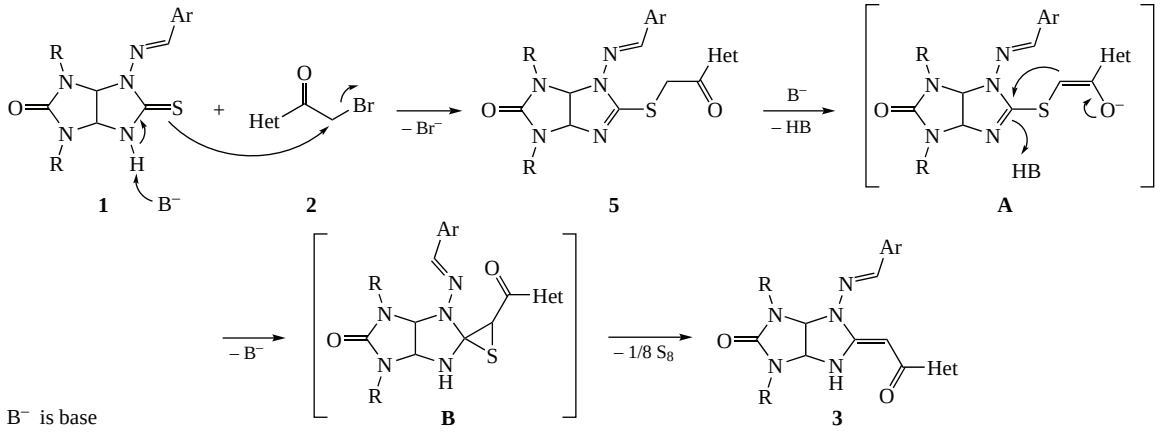


Figure 2 General view of **3n** in representation of non-hydrogen atoms *via* thermal ellipsoids at 50% probability level.



Scheme 4 Plausible reaction mechanism.

product **3**. ^{1}H NMR monitoring of the reaction between compounds **1b** and **2b** showed that conversion of starting compounds was almost complete after 0.5 h, while the alkylation product **5** was formed initially (see Online Supplementary Materials).

In summary, we have developed a simple method for the synthesis of novel hybrid molecules containing glycoluril and 1,2,5-oxadiazole moieties based on the Eschenmoser reaction carried out under mild conditions. The proposed method does not require using toxic PPh_3. The methodology proved to be efficient for the preparation of a series of target compounds with different substituents representing a new class of potentially bioactive heterocyclic substances and can serve for designing new high-energy compounds.

This work was supported by the Russian Science Foundation (grant no. 19-73-20074). Crystal structure determination was performed in the Department of Structural Studies of the N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.037.

X-ray diffraction data were collected at 100 K on a four-circle Rigaku Synergy S diffractometer equipped with a HyPix6000HE area-detector (kappa geometry, shutterless ω-scan technique), using monochromatized Cu Kα-radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program. The structures were solved by direct methods using SHELXT and refined on F^2 using SHELXL-2018 in the OLEX2 program.

CCDC 2298361 and 2298362 contain the supplementary crystallographic data for this paper. The data can obtained free of charge from The Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk.

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Received: 26th October 2023; Com. 23/7286