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Synthesis of trialkyl semithioglycolurils from alkylthiourea-glyoxal cyclic adducts and dialkylureas

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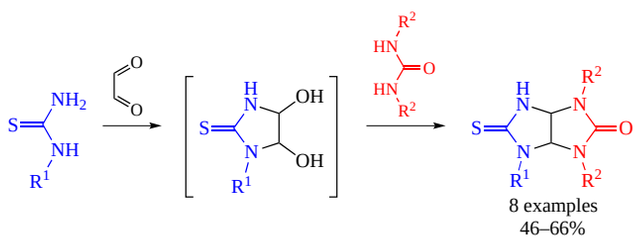
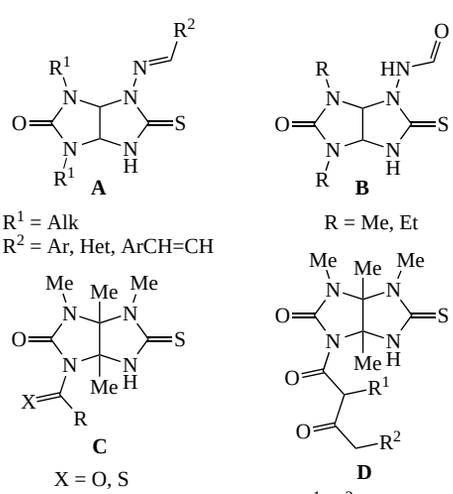
Condensation of 1-alkyl-4,5-dihydroxyimidazolidine-2-thiones (monoalkylthiourea-glyoxal cyclic adducts) with 1,3-dialkylureas affords novel 1,4,6-trialkylsemithioglycolurils having non-substituted NH group linked to C=S function. Such compounds can be accessed in two-stage one-pot reaction sequence from alkylthioureas and glyoxal followed by treatment of the resulting adduct with 1,3-dialkylureas.



Keywords: 1,4,6-trialkylsemithioglycolurils, one-pot synthesis, 4,5-dihydroxyimidazolidin-2-ones, 4,5-dihydroxyimidazolidine-2-thiones, alkylthioureas, dialkylureas.

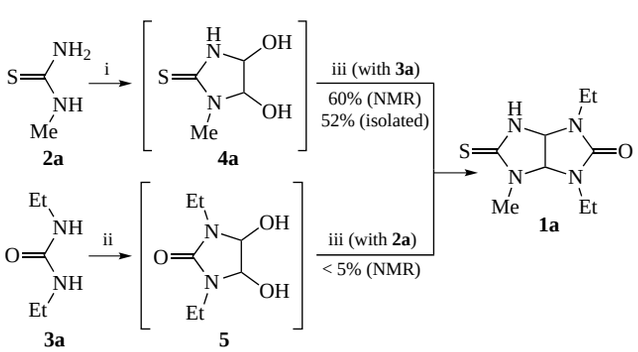
The chemistry of glycolurils (perhydroimidazo[4,5-*d*]imidazole-1(3*H*)-2,5-diones) is developing continuously.[1–5] In the past few decades, methods for the synthesis and properties of semithioglycolurils (5-thioxoperhydroimidazo[4,5-*d*]imidazol-1(3*H*)-4-ones) have been studied.[1,2,6–11] These compounds comprise a thioamide moiety NH–C=S that can be used as the basis for synthesizing new heterocyclic compounds. However, reactions involving semithioglycolurils (in particular, S-methylation, synthesis of iminoglycolurils and the Dimroth-type rearrangements of 1,4,6-trisubstituted semithioglycolurils) have been studied insufficiently.[6,7,10,11]

To expand the range of compounds with the thioamide moiety, we herein developed a method for the synthesis of novel 1,4,6-trialkylsemithioglycolurils **1** by the condensation of 1-alkylated 4,5-dihyroxyimidazolidine-2-thiones (DHITs) with 1,3-dialkylureas. Known trisubstituted semithioglycolurils with the moiety of interest are represented in the literature by types **A**–**D**.[1,2,7] Compounds **A**, **B** were obtained by triazine ring contraction in 5,7-dialkyl-3-hexahydro-1*H*-imidazo[4,5-*e*][1,2,4]-triazine-6(2*H*)-thiones in reactions with aromatic aldehydes or with formic acid.[1,2] Compounds **C** were synthesized by replacement of the oxygen atom by sulfur in 1-acyl-3,3a,4,6a-tetramethylsemithioglycoluril on treatment with the Lawesson reagent.[7] Certain examples of compounds **D** were synthesized by rearrangements of 1,6-diacyl-3,3a,4,6a-tetramethylsemithioglycolurils on treatment with $LiOCMe_2Et$.[7]



These methods are not suitable for synthesizing the target semithioglycolurils **1** (Scheme 1). Therefore, we performed model reactions to synthesize 1,3-diethyl-4-methylsemithioglycoluril **1a** by two methods (see Scheme 1).

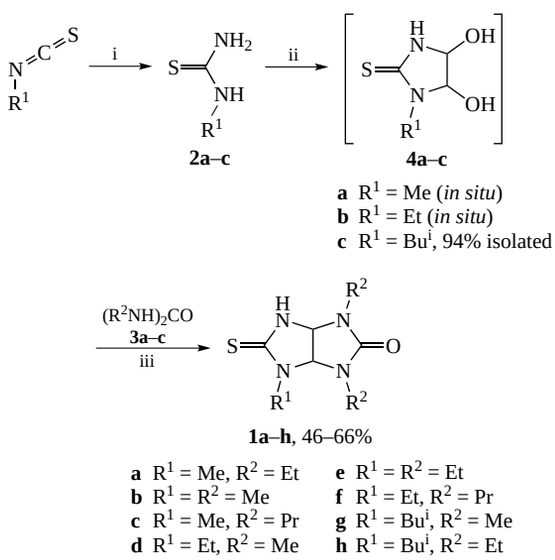
At the first stages, reactions of glyoxal with 1-methylthiourea **2a** (method 1) or 1,3-diethylurea **3a** (method 2) were performed to give 1-methylated DHIT **4a** or 1,3-diethylated 4,5-dihydroxy-1,3-diethylimidazolidin-2-one (DHI) **5**, respectively. The completeness of the reactions was estimated by ^{1}H NMR spectra. In both cases, the reaction mixtures were kept until complete disappearance of signals from NH-groups of thiourea **2a** and urea **3a** and appearance of proton signals of DHIT **4a** at δ 2.95 (s, 3H, Me), 4.62–4.82 (m, 2H, CH), 6.25 (d, 1H, OH, *J* 7.1), 6.54 (d, 1H, OH, *J* 7.1), 8.86 (s, 1H, NH)[8] or DHI **5** at δ 1.08 (t, 6H, Me), 3.15 (m, 2H, NCH_2), 3.30 (m, 2H, NCH_2),



Scheme 1 *Reagents and conditions*: i, glyoxal trimer dihydrate (1/3 equiv.), H_2O, 50 °C, 1 h; ii, glyoxal trimer dihydrate (1/3 equiv.), H_2O, 50 °C, 7 h; iii, **3a** or **2a** (1 equiv.), HCl, 76–80 °C, 15 min.

4.70 (s, 2H, CH).[12,13] The specific feature of our procedure is that a freshly prepared aqueous solution of glyoxal trimer dihydrate is used instead of the commercial 40% aqueous glyoxal solution.[8,12] Compounds **4a** and **5** were formed in quantitative yields and were further used without isolation in the reactions with 1,3-diethylurea or 1-methylthiourea, respectively, similarly to the synthesis of 1-substituted semithioglycolurils from 1-substituted ureas and DHIT.[9] We used the ^{1}H NMR monitoring of dry reaction mixture aliquots (after 5, 10, 15, 20 min). The estimation was based on the disappearance of proton signals for the CH_3CH$_2$ group of urea **3a** at δ 0.97 (t, 6H)[14] and appearance of new proton signals for the CH_3CH$_2$ group semithioglycoluril **1a** at δ 1.06 (t, 3H) and 1.10 (t, 3H). The maximum yield of product **1a** (60%) was observed in the condensation of DHIT **4a** with urea **2a** after 15 min (isolated yield 52%). Longer processing, raising the temperature to the boiling point, and acid catalysis (0.08, 0.04 or 0.12 ml of conc. HCl) did not improve the yield. In the reverse synthesis comprising DHI **5** and 1-methylthiourea **2a** (method 2), the yield of compound **1a** did not exceed 5% under similar conditions.

Method 1 was used to synthesize a series of 1,3,4-trialkylsemithioglycolurils **1a**–**h** in reasonable yields (Scheme 2).† To synthesize compounds **1a**–**f**, at stage ii we performed reactions of glyoxal trimer dihydrate with 1-methyl- and 1-ethylthioureas **2a**,**b** to *in situ* obtain the corresponding DHITs **4a**,**b**, which were used at stage iii in condensations with 1,3-dialkylureas **3a**–**c**. Compounds **1g**,**h** were obtained by the reaction of 1,3-dialkylureas **3a**,**b** with pure 1-isobutyl-containing DHIT **4c**. Compound **4c** could be obtained pure as it precipitated during its preparation due to poor solubility in water.



Scheme 2 *Reagents and conditions*: i, NH_3, MeOH, 50–55 °C, 3 h; ii, glyoxal trimer dihydrate (1/3 equiv.), H_2O, 50 °C, 1 h; iii, $(R^2NH)_2CO$ **3a**–**c**, H_2O, HCl, 76–80 °C, 15 min.

† *Synthesis of compounds* **1a**–**f** *(general procedure)*. A suspension of 1-substituted thiourea **2a**,**b** (3.0 mmol) and glyoxal trimer dihydrate (0.210 g, 1.0 mmol) in water (10 ml) was stirred at 50 °C for 1 h. Then HCl (80 µl, 35% aq.) and the corresponding 1,3-disubstituted urea **3a**–**c** (2.5 mmol) were added, and this was stirred at 76–80 °C for 15 min. The resulting mixture was cooled to room temperature and extracted with $CHCl_3$ (2 × 10 ml). The organic extract was evaporated to dryness, and the residue was triturated with EtOAc. The resulting solid crude product was filtered and recrystallized from water.

Synthesis of semithioglycolurils **1g**,**h** *(general procedure)*. A suspension of DHIT **4c** (0.475 g, 2.5 mmol) and the corresponding 1,3-disubstituted urea **3a**,**b** (2.5 mmol) in water (10 ml) with addition of HCl (80 µl, 35% aq.) was stirred at 76–80 °C for 15 min. In case of compound **1g**, water (5 ml) was added, the mixture was heated to boiling and filtered hot. The filtrate was cooled to room temperature, and the precipitate of compound **1g** that formed was filtered off. In the preparation of **1h**, the product did not precipitate and was extracted with $CHCl_3$ (10 ml). This extract was evaporated to dryness, and the residue was recrystallyzed from EtOAc (4 ml).

The required starting 1,3-dipropylurea **3c** was synthesized from 1-propylurea and PrBr.[15] Commercially unavailable thioureas **2b**,**c**[16,17] were synthesized in quantitative yields by a modified technique reported previously[18] when gaseous ammonia was bubbled through solutions of the corresponding isothiocyanates in MeOH.

To summarize, two reverse methods for the synthesis of semithioglycolurils **1** by condensation of 1-alkylated DHIT **4** with 1,3-dialkylurea **3** (method 1) or 1,3-dialkylated DHI **5** with alkylthiourea **2** (method 2) were tested, the practical one having been method 1. New eight 1,4,6-trialkylsemithioglycolurils were obtained in two-stage one-pot reactions of alkylthioureas with glyoxal followed treatment with 1,3-dialkylureas.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.11.021.

References

1 A. N. Kravchenko, V. V. Baranov and G. A. Gazieva, *Russ. Chem. Rev*., 2018, **87**, 89.

2 N. N. Makhova, L. I. Belen'kii, G. A. Gazieva, I. L. Dalinger, L. S. Konstantinova, V. V. Kuznetsov, A. N. Kravchenko, M. M. Krayushkin, O. A. Rakitin, A. M. Starosotnikov, L. L. Fershtat, S. A. Shevelev, V. Z. Shirinian and V. N. Yarovenko, *Russ. Chem. Rev*., 2020, **89**, 55.

3 (*a*) V. A. Karnoukhova, V. V. Baranov, A. V. Vologzhanina, A. N. Kravchenko and I. V. Fedyanin, *CrystEngComm*, 2021, **23**, 4312; (*b*) V. V. Baranov, T. N. Vol'khina, N. G. Kolotyrkina and A. N. Kravchenko, *Mendeleev Commun*., 2022, **32**, 537; (*c*) M. Kölbel and M. Menger, *Chem. Commun*., 2001, 275; (*d*) J. Kang, H. K. Ju and J. H. Jo, *Supramol. Chem*., 2004, **16**, 175; (*e*) J. Kang, J.-H. Jo and S. In, *Tetrahedron Lett*., 2004, **45**, 5225; (*f*) S. In and J. Kang, *Tetrahedron Lett.*, 2005, **46**, 7165; (*g*) F. Moretti, G. Poisson and A. Marsura, *Heteroat. Chem*., 2016, **27**, 173; (*h*) A. A. Prokopov, A. S. Berlyand and O. N. Kazantseva, *Pharm. Chem. J*., 2003, **37**, 132 [*Khim.-Farm. Zh*., 2003, **37** (3), 25]; (*i*) D. Ajami and J. Rebek, Jr., *J. Org. Chem*., 2009, **74**, 6584; (*j*) D. Ajami and J. Rebek, Jr., *Supramol. Chem*., 2009, **21**, 103; (*k*) D. Ajami, L. Liu and J. Rebek, Jr., *Chem. Soc. Rev*., 2015, **44**, 490; (*l*) T. Lizal and V. Sindelar, *Isr. J. Chem*., 2018, **58**, 326; (*m*) R. P. Sijbesma and R. J. M. Nolte, *Top. Curr. Chem*., 1995, **175**, 25; (*n*) Y. Cotelle, M. Hardouin-Lerouge, S. Legoupy, O. Alévêque, E. Levillain and P. Hudhomme, *Beilstein J. Org. Chem*., 2015, **11**, 1023; (*o*) M. Hardouin–Lerouge, P. Hudhomme and M. Sallé, *Chem. Soc. Rev*., 2011, **40**, 30; (*p*) K. I. Assaf and W. M. Nau, *Chem. Soc. Rev*., 2015, **44**, 394.

4 (*a*) S. K. M. Pothinathan, M. Muthukannan, N. Selvapalam and S. C. Gnanaraj, *Int. Rev. Appl. Sci. Eng*., 2021, **12**, 278; (*b*) A. N. Jadhav, S. B. Singh, M. V. Mane and A. S. Kumbhar, *Inorg. Chim. Acta*., 2022, **538**, 120934; (*c*) M. Shin, M. H. Kim, T. H. Ha, J. Jeon, K.-H. Chung, J. S. Kim and Y. G. Kim, *Tetrahedron*, 2014, **70**, 1617; (*d*) B. Lee, M. Shin, Y. Seo, M. H. Kim, H. R. Lee, J. S. Kim, K. Chung, D. Yoo and Y. G. Kim, *Tetrahedron*, 2018, **74**, 130; (*e*) B. Lee, N. Kim, S. Jang, J. H. Park, M. Song, K. Kwon, S. Kim and Y. G. Kim, *J. Ind. Eng. Chem*., 2022, **113**, 360; (*f*) T. Shimizu, *Soil Sci. Plant Nutr*., 1987, **33**, 291.

5 (*a*) E. Berdimurodov, A. Kholikov, K. Akbarov, L. Guo, S. Kaya, D. K. Verma, M. Rbaa and O. Dagdag, *J. Electroanal. Chem*., 2022, **907**, 116055; (*b*) P. Patel, S. Nandi, T. Menapara, A. V. Biradar, R. K. Nagarale, N. H. Khan and R. I. Kureshy, *Appl. Catal., A*, 2018, **565**, 127; (*c*) V. S. Mane, A. S. Kumbhar and R. P. Thummel, *Dalton Trans*., 2017, **46**, 12901; (*d*) M. Zarei, H. Sepehrmansourie, M. A. Zolfigol, R. Karamian and S. H. M. Farida, *New J. Chem*., 2018, **42**, 14308; (*e*) J. P. Bruekers, J. A. A. W. Elemans and R. J. M. Nolte, in *Supramolecular Catalysis: New Directions and Developments*, eds. P. W. N. M. van Leeuwen and

M. Raynal, Wiley-VCH, 2022, ch. 21, pp. 303–320; (*f*) L. Isaacs and D. Witt, *Angew. Chem., Int. Ed*., 2002, **41**, 1905; (*g*) W. Sliwa, G. Matusiak and J. Peszke, *Heterocycles*, 2004, **63**, 419; (*h*) Ya. A. Barsegyan, V. V. Baranov and A. N. Kravchenko, *Chem. Heterocycl. Compd*., 2017, **53**, 116.

6 (*a*) A. O. Kuptsova, E. E. Vinogradova, A. N. Kravchenko and G. A. Gazieva, *Russ. Chem. Bull.*, 2022, **71**, 885; (*b*) V. V. Baranov, Ya. A. Barsegyan, Yu. A. Strelenko, V. A. Karnoukhova and A. N. Kravchenko, *Mendeleev Commun*., 2020, **30**, 479; (*c*) V. V. Baranov, Ya. A. Barsegyan, N. G. Kolotyrkina and A. N. Kravchenko, *Mendeleev Commun*., 2019, **29**, 323; (*d*) M. Singh, E. Solel, E. Keinan and O. Reany, *Chem. – Eur. J.*, 2015, **21**, 536; (*e*) C. Lang, A. Mohite, X. Deng, F. Yang, Z. Dong, J. Xu, J. Liu, E. Keinan and O. Reany, *Chem. Commun*., 2017, **53**, 7557; (*f*) O. Reany, A. Mohite and E. Keinan, *Isr. J. Chem*., 2018, **58**, 449; (*g*) P. Mondal, E. Solel, S. Mitra, E. Keinan and O. Reany, *Org. Lett*., 2019, **22**, 204; (*h*) J. Verner and M. Potáček, *Cent. Eur. J. Chem*., 2004, **2**, 220; (*i*) J. Verner, J. Taraba and M. Potáček, *Tetrahedron Lett*., 2002, **43**, 4833.

7 C. N. Cow and P. H. M. Harrison, *J. Org. Chem*., 1997, **62**, 8834.

8 V. V. Baranov, Yu. V. Nelyubina, A. N. Kravchenko, N. G. Kolotyrkina and K. A. Biriukova, *Tetrahedron Lett*., 2015, **56**, 6085.

9 V. V. Baranov, A. A. Galochkin, Yu. V. Nelyubina, A. N. Kravchenko and N. N. Makhova, *Synthesis*, 2020, **52**, 2563.

10 E. E. Vinogradova, G. A. Gazieva, A. N. Izmest'ev, V. A. Karnoukhova and A. N. Kravchenko, *RSC Adv*., 2021, **11**, 28395.

11 V. V. Baranov, E. L. Yatsenko, E. K. Melnikova, Yu. V. Nelyubina and A. N. Kravchenko, *Chem. Heterocycl. Compd*., 2019, **55**, 160.

12 A. N. Kravchenko, V. V. Baranov, Yu. V. Nelyubina, G. A. Gazieva and I. V. Svitan'ko, *Russ. Chem. Bull*., 2012, **61**, 64 (*Izv. Akad. Nauk, Ser. Khim*., 2012, 63).

13 G. A. Gazieva, A. N. Kravchenko, O. V. Lebedev, Yu. A. Strelenko and K. Yu. Chegaev, *Russ. Chem. Bull.*, 1998, **47**, 1561 (*Izv. Akad. Nauk, Ser. Khim*., 1998, 1604).

14 C. Jia, Q. Q. Wang, R. A. Begum, V. W. Day and K. Bowman-James, *Org. Biomol. Chem*., 2015, **13**, 6953.

15 A. N. Izmest'ev, L. V. Anikina, I. E. Zanin, N. G. Kolotyrkina, E. S. Izmalkova, A. N. Kravchenko and G. A. Gazieva, *New J. Chem*. 2022, **46**, 11632.

16 J. R. Prevost, A. Kozlova, B. E. Saadi, E. Yildiz, S. Modaffari, D. M. Lambert, L. Pochet, J. Wounters, E. Dolušić and R. Frédérick, *Tetrahedron Lett.*, 2018, **59**, 4315.

17 V. V. Baranov, T. N. Vol'khina, Yu. V. Nelyubina and A. N. Kravchenko, *Mendeleev Commun*., 2021, **31**, 673.

18 S. Guihéneuf, L. Paquin, F. Carreaux, E. Durieu, L. Meijer and J. P. Bazureau, *Org. Biomol. Chem*., 2012, **10**, 978.

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