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Synthesis and crystal structures of novel glycoluril carboxylic acids conglomerates

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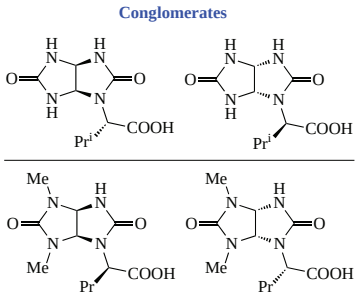
The two novel conglomerates were obtained by crystallization of racemic (2′*S*,3a*S*,6a*R*)/(2′*R*,3a*R*,6a*S*) (glycoluril-1-yl)-3-methylbutanoic acid and (2′*R*,3a*R*,6a*R*)/(2′*S*,3a*S*,6a*S*) (4,6-dimethylglycoluril-1-yl)pentanoic acid synthesized by highly diastereoselective condensation of 4,5-dihydroxyimidazolidin-2-ones with racemic ureido acids. The differences in the molecular geometry of synthesized racemates were studied by X-ray diffraction that showed them to crystallize as conglomerates in non-centrosymmetric space groups *Pna*2$_1$ and *P*2$_1$2$_1$2$_1$, respectively.



Keywords: conglomerats, glycolurils, carboxylic acids, racemates, ureido acids, 4,5-dihydroxyimidazolidin-2-ones, crystallization, crystal structures.

The course of many biological processes is based on molecular recognition, in which various classes of chemical compounds are involved. The processes of crystal formation can serve as models for studying such phenomena in biosystems.[1] In particular, crystallization is used to separate racemic drugs into enantiomers, since enantiomers usually exhibit different pharmacological activities.[2–8] On the other hand, tetrahydroimidazo[4,5-*d*]-imidazole-2,5(1*H*,3*H*)-diones (glycolurils) are capable of forming supramolecular assemblies and supermolecules of varying complexity upon crystallization from different solvents,[9–17] which can lead to spontaneous resolution of racemates into enantiomers (conglomerate formation).[15–17] Some glycoluril carboxylic acids also possess such properties[10,11,13,14,16] (Figure 1). The ability of racemates to spontaneous resolution is very important for obtaining enantiomerically pure glycolurils with various types of biological activity.[8,18–21]

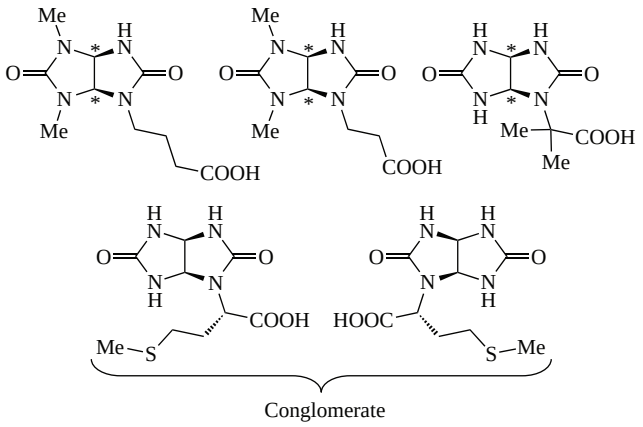
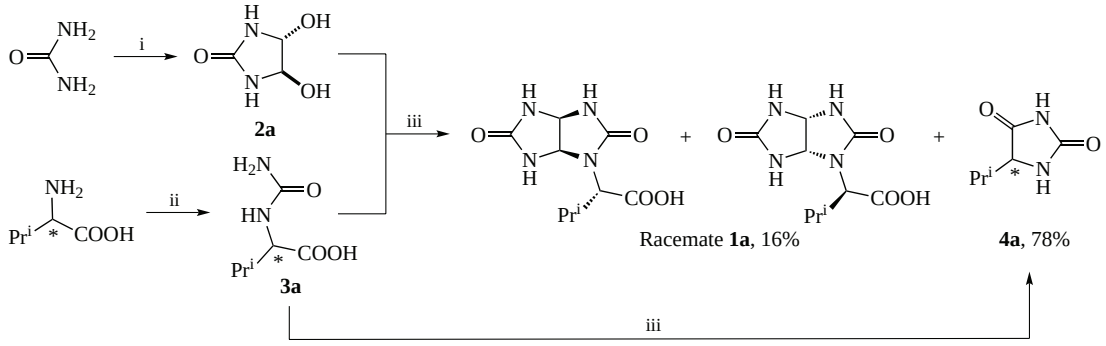


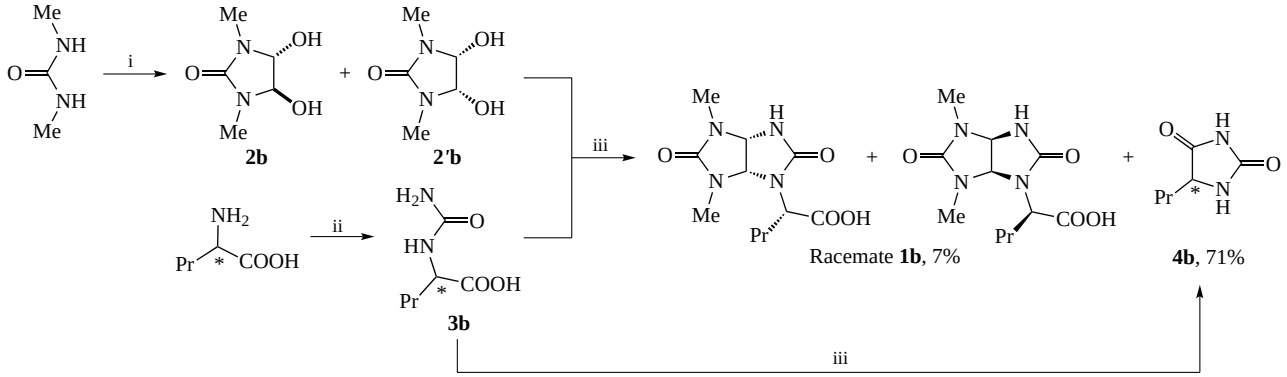
Figure 1 Known examples of conglomerate-forming glycoluril carboxylic acids.

In this work, novel conglomerates were unexpectedly formed during crystallization of racemates, namely, (2′*S*,3a*S*,6a*R*)/(2′*R*,3a*R*,6a*S*)-(2,5-dioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)-3-methylbutanoic acid **1a** and (2′*S*,3a*S*,6a*S*)/(2′*R*,3a*R*,6a*R*)-4,6-dimethyl-2,5-dioxohexahydroimidazo[4,5-*d*]-imidazol-1(2*H*)-yl)pentanoic acid **1b**. New compounds **1a**,**b** were synthesized by highly diastereoselective α-ureidoalkylation of corresponding racemic 2-ureidoalkyl acids with 4,5-dihydroxyimidazolidin-2-ones **2a**,**b** (Schemes 1, 2). In the synthesis of racemate **1a**, racemic 3-methyl-2-ureidobutanoic acid **3a** was used. Racemate **1b** was prepared from *dl*/*meso* mixture **2b**+**2′b** and racemic 2-ureidopentanoic acid **3b** (see Scheme 2). The reactions were accompanied by formation of hydantoins **4a**,**b** as a result of intramolecular cyclization of 2-ureidoalkyl acids **3a**,**b**. Earlier,[22,23] a similar approach to obtain enantiomerically pure (*S*)- and (*R*)-2-(2,5-dioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)-3-methylbutanoic acid and (*S*)-4,6-dimethyl-2-(2,5-dioxohexahydroimidazo[4,5-*d*]-imidazol-1(2*H*)-yl)pentanoic acid was used, however, the relative configuration of chiral centers C(3a) and C(6a) in those glycolurils was not established by X-ray study.

The starting compounds **2a** and **2b**+**2′b** mixture (*dl*/*meso* ratio 15:1) were synthesized from urea or 1,3-dimethylurea, respectively, and 40% aqueous glyoxal according to the literature.[24,25] The ratio of diastereomers was determined from the integral intensity of signals for the protons of CH–CH groups in the ^{1}H NMR spectra (4.53 ppm for **2b** and 4.76 ppm for **2′b**, both s, 1H). The synthesis of new racemic 2-ureidoalkyl acids **3a**,**b** was carried out starting from (*R*,*S*)-Val or (*R*,*S*)-*nor*-Val and KOCN (see Schemes 1 and 2).



Scheme 1 *Reagents and conditions*: i, glyoxal, H_2O, pH 10–11, 50–55 °C, 7.5 h (refs. 24, 25); ii, H_2O, KOCN, reflux, 20 min, then 10 °C, HCl; iii, H_2O : Pr^iOH (1 : 1), HCl, reflux, 2 h.



Scheme 2 *Reagents and conditions*: i, glyoxal, H_2O, pH 11, 50–55 °C, 5 h; ii, H_2O, KOCN, reflux, 20 min, then 10 °C, HCl; iii, H_2O : Pr^iOH (1 : 1), HCl, reflux, 2 h.

We investigated the crystallization of racemates **1a** and **1b** from H_2O, MeOH, Pr^iOH and a H_2O/Pr^iOH mixture. Single crystals **1a** and **1b** were obtained from a H_2O/Pr^iOH (1 : 1) mixture and from MeOH, respectively. Their X-ray diffraction analysis (Figure 2)† showed them to crystallize as conglomerates in non-centrosymmetric space groups $Pna2_1$ and $P2_12_12_1$ with two and one symmetry-independent molecules, respectively. Owing to the different substituents at the carbon atom C(5), the isopropyl or the propyl group, these compounds feature an important difference in their molecular geometry, which is the rotation of the COOH group relative to the C(2)–C(5) bond. The corresponding torsion angle N(1)C(5)C(6)O(3) being much higher in **1a** [76.0(4) and 77.3(4)° in its two symmetrically-independent molecules] than in **1b** [23.6(3)°] may be attributed to the steric effect of the bulky isopropyl group in the former compound.

Two extra methyl groups at the nitrogen atoms in molecule **1b** results in its supramolecular organization being different from that in **1a**. In both cases, the main structural motif is an infinite chain (Figure 3) formed *via* a hydrogen bond between the hydroxyl group and that of the carboxy groups of the heterocyclic core [O···O 2.596(5) and 2.557(2) Å, OHO 173.8(2) and 171.64(11)° in **1a** and **1b**, respectively]. In case of **1a**, they hold together different symmetry-independent molecules that alternate to produce a 3D-framework through hydrogen bonds of three NH groups [N···O 2.779(6)–3.013(5) Å, NHO 149.1(3)–176.6(3)°] and oxygen atoms of the carboxy groups. In case of **1b**, however, the only NH group is hydrogen-bonded to the oxygen atom of the COOH functionality [N···O 3.089(3) Å, NHO 149.52(12)°], thereby additionally stabilizing the above infinite chains.

In conclusion, new racemates **1a**,**b** of glycoluril alkanoic acid chemotype were found to crystallize as conglomerates (as gauged

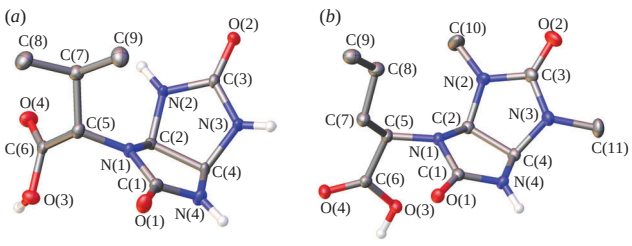


Figure 2 General view of (*a*) molecule **1a** and (*b*) molecule **1b**. Hereinafter, hydrogen atoms except those of OH and NH groups are omitted, and non-hydrogen atoms are shown as thermal ellipsoids at 50% probability level.

† *Crystal data for* **1a**. $C_9H_{14}N_4O_4$, M = 242.24, orthorhombic, space group $Pna2_1$, at 120 K, a = 14.5941(14), b = 7.1221(7) and c = 22.150(2) Å, V = 2302.3(4) Å^3, Z = 8, d_{calc} = 1.398 g cm^{-3}, $F(000)$ = 1024. Intensities of 20691 reflections were measured with a Bruker APEX2 DUO CCD diffractometer [λ(MoKα) = 0.71073 Å, μ(MoKα) = 1.11 cm^{-1}, ω-scans, $2\theta < 54°$], and 5010 independent reflections were used for the structure solution and refinement. Final R factors: R_1 = 0.0616 for 3915 observed reflections with $I > 2\sigma(I)$, wR_2 = 0.1607 and GOF = 0.996 for all the independent reflections.

Crystal data for **1b**. $C_{11}H_{18}N_4O_4$, M = 270.29, orthorhombic, space group $P2_12_12_1$, at 120 K, a = 9.7011(6), b = 11.1901(7) and c = 12.0069(8) Å, V = 1303.42(14) Å^3, Z = 4, d_{calc} = 1.377 g cm^{-3}, $F(000)$ = 576. Intensities of 13038 reflections were measured with a Bruker APEX2 DUO CCD diffractometer [λ(MoKα) = 0.71073 Å, μ(MoKα) = 1.06 cm^{-1}, ω-scans, $2\theta < 56°$], and 3133 independent reflections were used for the structure solution and refinement. Final R factors: R_1 = 0.0409 for 2826 observed reflections with $I > 2\sigma(I)$, wR_2 = 0.1159 and GOF = 1.072 for all the independent reflections.

Using Olex2,[26] the structures were solved with the ShelXT[27] structure solution program using Intrinsic Phasing and refined with the XL24[28] refinement package using Least-Squares minimisation. Hydrogen atoms of the OH and NH groups were found in difference Fourier synthesis while positions of other hydrogen atoms were calculated, and they all were refined in the isotropic approximation within the riding model.

CCDC 2089267 (**1a**) and 2089265 (**1b**) contain the supplementary crystallographic information for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

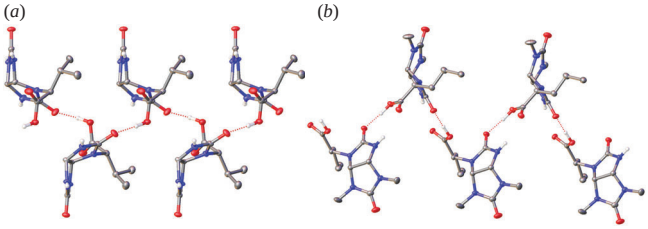


Figure 3 Fragments of the crystal packing of (*a*) molecules **1a** and (*b*) molecules **1b** illustrating the formation of hydrogen-bonded chains along the crystallographic axes *b* and *a*, respectively.

by space groups $Pna2_1$ and $P2_12_12_1$). The key difference between these two compounds, which is the different rotation of the COOH group relative to the C(2)–C(5) bond, may be attributed to the steric effect of the bulky isopropyl group in **1a**.

X-ray diffraction data were collected using the equipment of Center for molecular composition studies of INEOS RAS with the financial support from Ministry of Science and Higher Education of the Russian Federation.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.034.

References

1 J.-M. Lehn, *Supramolecular Chemistry: Concept and Perspectives*, Wiley-VCH, Weinheim, 1995.
2 B. Satyanarayana, P. M. Krishna and D. Ramachndran, *Int. J. Chem. Tech. Res.*, 2011, **3**, 234.
3 G. W. Muller, W. E. Konnecke, A. M. Smith and V. D. Khetani, *Org. Process. Res. Dev.*, 1999, **3**, 139.
4 M. E. Franks, G. R. Macpherson and W. D. Figg, *Lancet*, 2004, **363**, 1802.
5 (*a*) Y. Li, J. K. Coller, M. R. Hutchinson, K, Klein, U. M. Zanger, N. J. Stanley, A. D. Abell and A. A. Somogyi, *Drug Metab. Dispos.*, 2013, **41**, 1264; (*b*) K. Fukumoto, H. Toki, M. Iijima, T. Hashihayata, J.-I. Yamaguchi, K. Hashimoto and S. Chaki, *J. Pharmacol. Exp. Ther.*, 2017, **361**, 9; (*c*) H. Ihmsen, G. Geisslinger and J. Schüttler, *Clin. Pharm. Ther.*, 2001, **70**, 431; (*d*) J.-C. Zhang, S.-X. Li and K. Hashimoto, *Pharmacol., Biochem. Behav.*, 2014, **116**, 137; (*e*) K. Hashimoto, *Biochem. Pharmacol.*, 2020, **177**, 113935; (*f*) L. Chang, K. Zhang, Y. Pu, Y. Qu, S.-M. Wang, Z. Xiong, Q. Ren, C. Dong, Y. Fujita and K. Hashimoto, *Pharmacol., Biochem. Behav.*, 2019, **181**, 53; (*g*) C. Yang, Y. Shirayama, J.-C. Zhang, Q. Ren, W. Yao, M. Ma, C. Dong and K. Hashimoto, *Transl. Psychiatry*, 2015, **5**, e632.
6 R. Yokoyama, S. Matsumoto, S. Nomura, T. Higaki, T. Yokoyama and S. Kiyooka, *Tetrahedron*, 1995, **65**, 5181.
7 R. Ishak and O. Abbas, *Am. J. Clin. Dermatol.*, 2013, **14**, 223.
8 L. V. Anikina, Yu. B. Vikharev, V. V. Baranov, O. R. Malyshev and A. N. Kravchenko, *Mendeleev Commun.*, 2018, **28**, 317.
9 (*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, M. M. Antonova, Yu. V. Nelyubina, N. G. Kolotyrkina, I. E. Zanin, A. N. Kravchenko and N. N. Makhova, *Mendeleev Commun.*, 2014, **24**, 173; (*c*) V. V. Baranov, A. A. Baganova, I. E. Chikunov, V. A. Karnoukhova and A. N. Kravchenko, *Tetrahedron Lett.*, 2019, **60**, 1174; (*d*) A. N. Kravchenko, V. V. Baranov, G. A. Gazieva, I. E. Chikunov and Yu. V. Nelyubina, *Russ. Chem. Bull.*, 2014, **63**, 416; (*e*) V. V. Baranov, Yu. V. Nelyubina, A. N. Kravchenko, N. G. Kolotyrkina and K. A. Biriukova, *Tetrahedron Lett.*, 2015, **56**, 6085; (*f*) V. V. Baranov, M. M. Antonova, Yu. V. Nelyubina, N. G. Kolotyrkina and A. N. Kravchenko, *Synlett*, 2017, **28**, 669; (*g*) A. Wu, J. C. Fettinger and L. Isaacs, *Tetrahedron*, 2002, **58**, 9769.
10 (*a*) D. W. Johnson, L. C. Palmer, F. Hof, P. M. Iovine and J. Rebek, *Chem. Commun.*, 2002, 2228; (*b*) N.-F. She, X.-G. Meng, M. Gao, A.-X. Wu and L Isaacs, *Chem. Commun.*, 2008, 3133; (*c*) R. Wyler, J. de Mendoza and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 1993, **32**, 1699; (*d*) N. Branda, R. Wyler and J. Rebek, Jr., *Science*, 1994, **263**, 1267; (*e*) N. Branda, R. M. Grotzfeld, C. Valdés and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1995, **117**, 85; (*f*) R. M. Grotzfeld, N. Branda and J. Rebek, Jr., *Science*, 1996, **271**, 487; (*g*) R. Meissner, X. Garcias, S. Mecozzi and J. Rebek, *J. Am. Chem. Soc.*, 1997, **119**, 77; (*h*) Y. Tokunaga and J. Rebek, *J. Am. Chem. Soc.*, 1998, **120**, 66; (*i*) J. M. Rivera, T. Martin and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 819; (*j*) J. Kang, G. Hilmersson, J. Santamaría and J. Rebek, *J. Am. Chem. Soc.*, 1998, **120**, 3650; (*k*) J. Rebek, Jr., *Acc. Chem. Res.*, 1999, **32**, 278; (*l*) A. E. Rowan, J. A. A. W. Elemans and R. J. M. Nolte, *Acc. Chem. Res.*, 1999, **32**, 995; (*m*) T. Rivera and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2000, **122**, 7811; (*n*) J. M. Rivera, T. Martin and J. Rebek, *J. Am. Chem. Soc.*, 2001, **123**, 5213; (*o*) J. A. A. W. Elemans, A. E. Rowan and R. J. M. Nolte, *Ind. Eng. Chem. Res.*, 2000, **39**, 3419; (*p*) T. Szabo, B. M. O'Leary and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 1998, **37**, 3410; (*q*) B. M. O'Leary, T. Szabo, N. Svenstrup, C. A. Schalley, A. Lützen, M. Schäfer and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2001, **123**, 11519; (*r*) A. Lützen, S. D. Starnes, D. M. Rudkevich and J. Rebek, Jr., *Tetrahedron Lett.*, 2000, **41**, 3777; (*s*) F. Hof, C. Nuckolls, S. L. Craig, T. Martin and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2000, **122**, 10991; (*t*) F. Hof, C. Nuckolls and J. Rebek, *J. Am. Chem. Soc.*, 2000, **122**, 4251; (*u*) C. Nuckolls, F. Hof, T. Martin and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 10281; (*v*) D. M. Rudkevich and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 1997, **36**, 846; (*w*) Y. Chen, N.-F. She and A.-X. Wu, *J. Chem. Crystallogr.*, 2011, **41**, 791; (*x*) Y. Tokunaga, D. M. Rudkevich, J. Santamaría, G. Hilmersson and J. Rebek, Jr., *Chem. – Eur. J.*, 1998, **4**, 1449; (*y*) N.-F. She, M. Gao, X.-G. Meng, G.-F. Yang, J. A. A. W. Elmans, A.-X. Wu and L. Isaacs, *J. Am. Chem. Soc.*, 2009, **131**, 11695.
11 V. V. Baranov, Ya. A. Barsegyan, Yu. A. Strelenko, V. A. Karnoukhova and A. N. Kravchenko, *Mendeleev Commun.*, 2020, **30**, 479.
12 (*a*) D. W. Johnson, F. Hof, L. C. Palmer, T. Martín, U. Obst and J. Rebek, Jr., *Chem. Commun.*, 2003, 1638; (*b*) K. Moon, W.-Z. Chen, T. Ren and A. E. Kaifer, *CrystEngComm*, 2003, **5**, 451.
13 M. Kölbel and F. M. Menger, *Chem. Commun.*, 2001, 275.
14 A. N. Kravchenko, K. Yu. Chegaev, I. E. Chikunov, P. A. Belyakov, E. Yu. Maksareva, K. A. Lyssenko, O. V. Lebedev and N. N. Makhova, *Mendeleev Commun.*, 2003, **13**, 269.
15 (*a*) R. G. Kostyanovsky, K. A. Lyssenko, G. K. Kadorkina, O. V. Lebedev, A. N. Kravchenko, I. I. Chervin and V. R. Kostyanovsky, *Mendeleev Commun.*, 1998, **8**, 231; (*b*) K. A. Lyssenko, D. G. Golovanov, A. N. Kravchenko, I. E. Chikunov, O. V. Lebedev and N. N. Makhova, *Mendeleev Commun.*, 2004, **14**, 105; (*c*) A. N. Kravchenko, K. A. Lyssenko, I. E. Chikunov, P. A. Belyakov, M. M. Il'in, V. V. Baranov, Yu. V. Nelyubina, V. A. Davankov, T. S. Pivina, N. N. Makhova and M. Yu. Antipin, *Russ. Chem. Bull.*, 2009, **58**, 395 (*Izv. Akad. Nauk, Ser. Khim.*, 2009, 390).
16 (*a*) G. A. Gazieva, P. V. Lozhkin, V. V. Baranov, Yu. V. Nelyubina, A. N. Kravchenko and N. N. Makhova, *Russ. Chem. Bull.*, 2009, **58**, 2488 (*Izv. Akad. Nauk, Ser. Khim.*, 2009, 2408); (*b*) V. V. Baranov, A. A. Galochkin, Yu. V. Nelyubina, A. N. Kravchenko and N. N. Makhova, *Synthesis*, 2020, **52**, 2563.
17 M. V. Zlokazov and K. K. Pivnitsky, *Mendeleev Commun.*, 2020, **30**, 1.
18 A. N. Kravchenko, V. V. Baranov and G. A. Gazieva, *Russ. Chem. Rev.*, 2018, **87**, 89.
19 L. V. Anikina, G. A. Gazieva and A. N. Kravchenko, *Russ. Chem. Bull.*, 2020, **69**, 563.
20 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.
21 (*a*) R. Kamburg, *US Patent 2008/0227838 A1*, 2008; (*b*) A. N. Kravchenko, V. V. Baranov, L. V. Anikina, Yu. B. Vikharev, I. S. Bushmarinov and Yu. V. Nelyubina, *Russ. J. Bioorg. Chem.*, 2012, **38**, 550 (*Bioorg. Khim.*, 2012, **38**, 621).
22 I. E. Chikunov, A. N. Kravchenko, P. A. Belyakov, K. A. Lyssenko, V. V. Baranov, O. V. Lebedev and N. N. Makhova, *Mendeleev Commun.*, 2004, **14**, 253.
23 V. V. Baranov, A. N. Kravchenko, P. A. Belyakov and N. N. Makhova, *Mendeleev Commun.*, 2008, **18**, 96.
24 S. L. Vail, R. H. Barker and P. G. Mennitt, *J. Org. Chem.*, 1965, **30**, 2179.
25 E. Grillon, R. Gallo, M. Pierrot, J. Boileau and E. Wimmer, *Tetrahedron Lett.*, 1988, **29**, 1015.
26 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.
27 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **A71**, 3.
28 G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.

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