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Co-crystals in the series of 4,5-dihydroxy-4,5-diphenylimidazolidine-2-thiones

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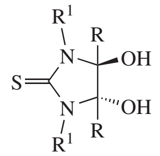
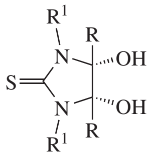
The synthesis of the first co-crystals among 4,5-dihydroxy-4,5-diphenylimidazolidin-2-ones (4,5-dihydroxyimidazolidine-2-thione + 5-hydroxy-4-methoxy-4,5-diphenyl-1,3-diethylimidazolidine-2-thione) and of the *cis* isomer of 1,3-diethyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thione through the regiospecific condensation of 1,3-diethylthiourea with 1,2-dioxo-1,2-diphenylethane was implemented; the structure was ascertained by single crystal X-ray diffraction and X-ray phase analysis.

An insight into the molecule self-assembly and self-organization stands among the most exciting issues of supramolecular chemistry. Therefore, the synthesis of objects capable of generating co-crystals is a step to understanding the origination of these processes. The problem of mixed crystals formation is very timely and wide discussed in the recent chemical literature.[1,2] No data on co-crystals among compounds with thiourea moieties has been reported.

In addition, it is known that hydroxyl groups in 4,5-dihydroxy-imidazolidine-2-thiones (DHITs) may have both *trans* and *cis* orientations relative to the imidazolidine cycle.[3–5] For the first time, a regioselectivity of formation of DHIT *trans* (**1a**) and *cis* (**2a**) isomers was observed for 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidine-2-thione that is a mixture of *trans* and *cis* isomers in the ratio 2:1.[4] We have recently developed methodologies for the DHIT synthesis and, basing on the ^{1}H NMR spectra, identified that the generation of DHIT **1a**–**c** from corresponding thioureas, 1,3-dimethyl- and 1,3-diethyl-thioureas, and glyoxal proceeds regioselectively.[5] Note that DHIT were isolated as a mixture of *trans* (**1b**,**c**) and *cis* (**2b**,**c**) isomers with *trans* isomers **1b**,**c** prevailing, whereas *cis* isomer **2d** predominated over **1d**. Maximal yields of those compounds under the developed conditions were estimated at 45–78% and no regiospecificity was marked. The structure of *trans* isomer **1b** crystallized as a racemate was confirmed by X-ray analysis. *cis*-Isomers were not isolated.



1a–d



2a–d

a R = Ph, R^1 = Me
b R = R^1 = H
c R = H, R^1 = Me
d R = H, R^1 = Et

To prepare the first co-crystals among DHIT series and *cis* isomer of DHIT and to get a new insight into the crystalline state of DHIT, we performed the regiospecific condensation of 1,3-diethylthiourea with 1,2-dioxo-1,2-diphenylethane (benzil), previously non-described, in the alkaline medium for 7 h in a boiling MeOH:H_2O (10:1) mixture (similar to the described procedure[3] for preparing 1,3-dimethyl-4,5-diphenyl-DHIT). The first precipitate from the reaction mass in the form of large colourless crystals with mp 152–154 °C was filtered off. The second product (mp 162–164 °C) precipitated as a fine-crystal residue.[†]

In the ^{1}H NMR spectra of the first product, along with proton signals of the major substance, *viz.*, 1,3-diethyl-4,5-diphenyl-DHIT **3**, signals from protons of the minor product were detected. In the minor substance proton signals from Me, CH_2 and Ph groups were present, which coincided with proton signals from the major substance. In addition, at 3.53 ppm, there was a singlet, which evidenced to a probable presence of the OMe group and a singlet from OH group at 4.27 ppm. The data indicated that the minor product could be 5-hydroxy-4-methoxy-4,5-diphenyl-1,3-diethylimidazolidine-2-thione **4** (Scheme 1).

The ^{1}H and ^{13}C NMR spectra of the second reaction product correspond to pure compound **3**.

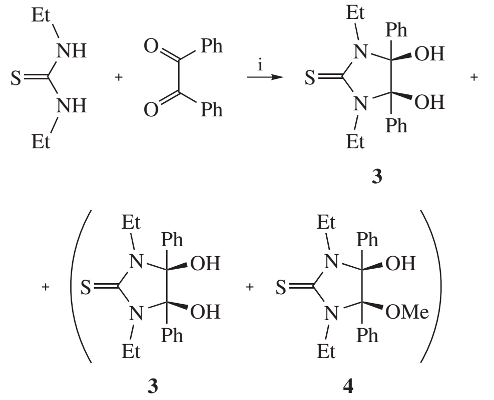
The X-ray diffraction study of the crystals obtained revealed that the product is co-crystals (space group $P\bar{1}$) of the DHIT

[†] Commercially available compounds (benzil and diethylthioureas) from ACROS were used in the syntheses. The solvents were used without preliminary purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (75.5 MHz) instrument. Chemical shifts were measured with reference to the residual protons of $CDCl_3$ as the solvent (δ 7.26 ppm). Mass spectra were recorded on a Kratos MS-30 mass spectrometer (70 eV). Melting points were determined on a Gallenkamp instrument (Sanyo).

Procedure for the synthesis of co-crystals (**3** + **4**, 7:3) *and DHIT* **3**. A solution of potassium hydroxide (0.28 g, 0.005 mol) in H_2O (1 ml) was added to a solution of 1,3-diethylthiourea (0.76 g, 0.01 mol) and benzil (2.1 g, 0.01 mol) in MeOH (10 ml). The reaction mixture was refluxed for 7 h, cooled to 20 °C and H_2O (7 ml) was added. A precipitate of co-crystals (**3** + **4**) was filtered off to give 0.24 g of crude product. Filtrate was evaporated and residue of DHIT **3** (1.41g) was crystallized from MeOH.

Co-crystals of 1,3-diethyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thione **3** + *5-hydroxy-4-methoxy-4,5-diphenyl-1,3-diethylimidazolidine-2-thione* **4** (7:3): mp 152–154 °C. ^{1}H NMR ($CDCl_3$) δ: 1.33 [t, 6H(**3**) + + 6H(**4**), 2Me(**3**) + 2Me(**4**), ^3J 7.1 Hz], 3.26–3.38 [m, 2H(**3**) + 2H(**4**), CH_2(**3**) + CH_2(**4**)], 3.56 [s, 3H(**4**), OMe(**4**)], 3.85–3.97 [m, 2H(**3**) + + 2H(**4**), CH_2(**3**) + CH_2(**4**)], 4.24 [s, 2H(**3**), 2OH(**3**)], 4.27 [s, 2H(**4**), 2OH(**4**)], 6.89–6.93 [m, 4H(**3**) + 4H(**4**), Ph(**3**) + Ph(**4**)], 7.01–7.14 [m, 6H(**3**) + 6H(**4**), Ph(**3**) + Ph(**4**)].

1,3-Diethyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thione **3**: yield 41%, mp 162–164 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, 6H, 2Me, ^3J 7.1 Hz), 3.26–3.38 (m, 2H, CH_2), 3.85–3.97 (m, 2H, CH_2), 4.24 (s, 2H, 2OH), 6.89–6.93 (m, 4H, Ph), 7.01–7.14 (m, 6H, Ph). ^{13}C NMR ($CDCl_3$) δ: 14.90 (Me), 39.83 (CH_2), 96.45 (C, C–Ph), 127.12 (C, Ph), 127.84 (C, Ph), 128.52 (C, Ph), 136.12 (C, Ph), 183.51 (CS). MS, *m/z* (%): 342 (M$^+$, 5), 324 (12.5), 194 (100), 166 (77), 165 (64), 104 (32).



Scheme 1 *Reagents and conditions*: i, MeOH–H_2O (10:1), KOH, reflux, 7 h.

monohydrate **3** with 5-hydroxy-4-methoxy-4,5-diphenyl-1,3-diethylimidazolidine-2-thione **4** in a 7:3 ratio (Figure 1). The pattern in the ^1H NMR spectrum did not change even after double recrystallization from methanol. This phenomenon, observed for this class of compounds for the first time, was unambiguously proven by X-ray phase analysis of product **3 + 4**.[‡] Its results indicated the identity of the experimental powder pattern to that obtained on a basis of the single crystal X-ray diffraction data.

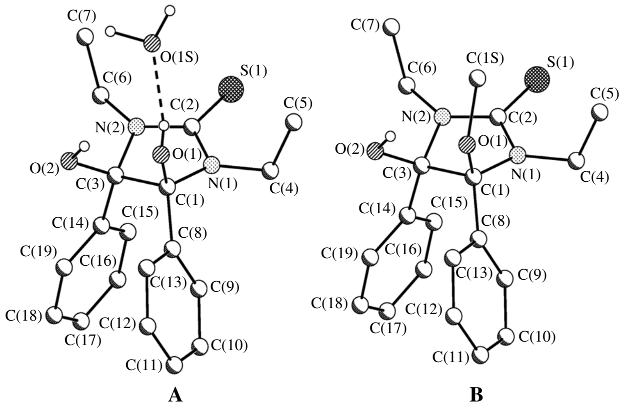


Figure 1 General view of compound **3 + 4**, which is a superposition of DHIT monohydrate **A** and its ether derivative **B** in a 7:3 ratio. Hydrogen atoms except for those of OH groups and water molecules are omitted for clarity.

According to the analysis of co-crystals molecular geometry, the conformation of the imidazolidine ring is twist with the C(4) and C(5) atoms deviated from the plane of the others by 0.18(1) and 0.31(1) Å. Both the nitrogen atoms are slightly piramidalized; the sum of the bond angles is 357.1(2) and 358.0(1)° for N(1) and N(2), respectively. Such a distortion of the heterocycle leads to the variation of C–C and C–O bond lengths for the substituents at C(4) and C(5) atoms, *i.e.*, the hydroxyl or methoxy groups in a cisoid configuration with the dihedral angle O(1)–C(4)–C(5)–O(2) of 27.3(2)°. Thus, the C(4)–O(1) [1.421(2) Å] and C(5)–C(14) [1.520(2) Å] bonds are slightly longer than the C(5)–O(2) [1.399(2) Å] and C(4)–C(8) [1.511(2) Å] ones. This is, apparently, due to the anomeric interactions between lone pairs (Lp) of nitrogen atoms and σ^* orbitals of C–O and C–C bonds [the Lp–N(1)–C(4)–O(1) and Lp–N(2)–C(5)–C(14) angles are close to the linear and are equal to 169.4(2) and 166.9(2)°]. The latter can be responsible for the stabilization of cisoid mutual disposition of OH and/or OMe groups.

Note that the diol **3** component of co-crystals **3 + 4** displays the intermolecular H-bonds O(2)–H(2O)···O(1) of the intermediate strength [O···O 2.622(1) Å, O–H···O 127(1)°]. The second OH group of the diol binds only to the water molecule [O···O 2.608(1) Å, O–H···O 159(1)°]. The latter links the diol moiety with its two neighbours *via* O–H···O [O···O 2.936(1) Å, O–H···O 147(1)°] and O–H···S [O···S 3.204(1) Å, O–H···S 171(1)°] interactions of the similar strength, thus resulting in the formation of double chain. These associates are assembled into 3D framework by means of weaker C–H···O, H···π and H···H contacts. In the case of the ether molecule, all the above interactions, except for those involving the water molecule, are also present. As a result, instead of the double chain there are dimers formed though the unusual O···O [2.964(1) Å] contacts between the neighbouring O(2)H groups accompanied by the occurrence of very weak C–H···S ones.

According to published data[5–7] on the structural features of DHIT and 4,5-dihydroxyimidazolidin-2-one (DHI) containing no phenyl substituents at C(4) and C(5) atoms, for instance, **1b**, the isomers with the transoid disposition of OH groups prevail. As a result, we do not expect the components of co-crystals **3 + 4** to be the *cis* isomers. The found single *cis* orientation of hydroxyl groups in the co-crystals **3 + 4** had appeared surprising, which is why we prepared crystals of the second condensation product, pure DHIT **3**, *via* the crystallization from methanol. According to the X-ray diffraction analysis, the latter gives the solvent-free crystals of pure DHIT **3**. As a result, the supramolecular organization in the crystal of pure **3** differs

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[‡] *Crystallographic data*: crystals of **3 + 4** ($C_{19.3}H_{24.9}N_2O_{2.7}S$, $M = 360.17$) are triclinic, space group $P\bar{1}$, at 120 K: $a = 8.1594(7)$, $b = 9.2364(7)$ and $c = 13.0904(11)$ Å, $\alpha = 104.354(5)°$, $\beta = 103.535(5)°$ and $\gamma = 97.904(5)°$, $V = 908.95(13)$ Å^3, $Z = 2$ ($Z' = 1$), $d_{calc} = 1.316$ g cm^{-3}, μ(MoKα) = = 1.97 cm^{-1}, $F(000) = 385$. Intensities of 9456 reflections were measured on a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$] and 4369 independent reflections ($R_{int} = 0.0258$) were used in further refinement.

Crystals of **3** ($C_{19}H_{22}N_2O_2S$, $M = 342.45$) are triclinic, space group $P\bar{1}$, at 120 K: $a = 8.2532(8)$, $b = 9.8748(10)$ and $c = 12.0858(12)$ Å, $\alpha = 99.724(3)°$, $\beta = 106.271(3)°$ and $\gamma = 106.861(3)°$, $V = 870.68(15)$ Å^3, $Z = 2$ ($Z' = 1$), $d_{calc} = 1.306$ g cm^{-3}, μ(MoKα) = 1.99 cm^{-1}, $F(000) = 364$. Intensities of 10610 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 58°$] and 4615 independent reflections ($R_{int} = 0.0190$) were used in further refinement.

The structures were solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms of OH group in **4** and those of OH groups and water molecules in **3 + 4** were located from the Fourier density synthesis and refined in isotropic approximation. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation in riding model with the U_{iso}(H) parameters equal to $1.2U_{eq}(C_i)$, for methyl groups equal to $1.5U_{eq}(C_{ii})$, where $U(C_i)$ and $U(C_{ii})$ are respectively the equivalent thermal parameters of the carbon atoms to which corresponding H atoms are bonded. For **3 + 4** the refinement converged to $wR_2 = 0.1278$ and GOF = 1.002 for all independent reflections [$R_1 = 0.0515$ was calculated against F for 3302 observed reflections with $I > 2\sigma(I)$]. For **3** the refinement converged to $wR_2 = 0.0873$ and GOF = 1.001 for all independent reflections [$R_1 = 0.0345$ was calculated against F for 4055 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[8]

Quantum chemical calculations of the *cis* and *trans* isomers of **3** were performed with the Gaussian 03 program.[9] The standard threshold limits of 4.5×10^{-4} and 1.8×10^{-3} a.u. were applied for the maximum force and displacement, respectively. After optimization the analysis of vibration frequencies was carried out.

XRD powder patterns for **3 + 4** were measured with a Bruker D8 Advance diffractometer ($T = 298$ K, λ(CuKα) = 1.5418 Å, $\theta/2\theta$-scans with a 0.02° step; angle range of 2–60°).

CCDC 735643 and 735644 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

dramatically. The O(1)–H(1O)···S(1) bonds [O···S 3.190(2) Å, O–H···O 146(1)°] assemble the molecular moieties into the centrosymmetric dimers. The second OH group in the crystal of **3** exhibits the unusual O···O [O···O 2.656(1) Å] contacts close to those for the component **4**, which leads to the 'double chain' type of binding. A number of weaker C–H···S and H···π contacts complete the formation of the 3D framework of **3**.

However, the overall geometrical parameters of DHIT molecule, including the mutual disposition of OH groups, remain practically the same. The sum of the CNC bond angles is 352.2(1) and 359.2(1)° for N(1) and N(2) atoms. The corresponding torsion angle Lp–N(1)–C(4)–O(1) is equal to 168.1(2)°, while the second nitrogen atom is planar. The dihedral angle O(1)–C(4)–C(5)–O(2) is 26.9(1)°.

To find out the reason of *cis* isomer stabilization in the case of the above DHIT derivative with phenyl substituents at carbon atoms of heterocycle we performed the quantum chemical calculation (B3LYP/6-311+G**) of the molecule **3** in both its *cis* and *trans* forms. The geometry of the former is close to the experimental one; the sum of bond angles at nitrogen N(1) and N(2) sites was 354.0 and 358.2° with the value of Lp–N(1)–C(4)–O(3) angle equal to 170.5°. Although the corresponding geometrical parameters in the case of the *trans* isomer vary only in a minor way [the sum of the CN(1)C and CN(2)C angles is 352 and 355.6°; the anomeric interactions involve just the C–O bonds with the pseudo-torsion angles Lp–N(1)–C(4)–O(3) and Lp–N(2)–C(5)–O(2) being 163.1 and 166.7°], it is less energetically stable than its *cis* analogue by 2.41 kcal mol^{-1}.

Thus, the study on the interaction of 1,3-diethylthiourea with benzil resulted in identifying regiospecificity of the DHIT generation with *cis*-positioning of hydroxyl groups and preparing the first co-crystals within this class of compounds. The data were ascertained by single crystal X-ray diffraction and X-ray phase analyses. The results obtained are of high promise in terms of attaining a deeper insight into the DHIT synthesis and structure, including their crystalline state, and contribute to understanding of molecule self-assembly and self-arrangement processes such as co-crystallization.

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References

1 G. P. Stahly, *Cryst. Growth Des.*, 2007, **7**, 1007.

2 N. Blagden, D. J. Berry, A. Parkin, H. Javed, A. Ibrahim, P. T. Gavan, L. I. De Matos and C. C. Seaton, *New J. Chem.*, 2008, **32**, 1659.

3 C. J. Broan, A. R. Butler, D. Reed and I. H. Sadler, *J. Chem. Soc., Perkin Trans. 2*, 1989, 731.

4 C. J. Broan and A. R. Butler, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1501.

5 Yu. V. Nelyubina, G. A. Gazieva, V. V. Baranov, P. A. Belyakov, A. O. Chizhov, K. A. Lyssenko and A. N. Kravchenko, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 1315 (in Russian).

6 A. N. Kravchenko, G. K. Kadorkina, A. S. Sigachev, E. Yu. Maksareva, K. A. Lyssenko, P. A. Belyakov, O. V. Lebedev, O. N. Kharybin, N. N. Makhova and R. G. Kostyanovsky, *Mendeleev Commun.*, 2003, 114.

7 S. L. Vail, R. H. Barker and P. G. Mennitt, *J. Org. Chem.*, 1965, **30**, 2179.

8 G. M. Sheldrick, *SHELXTL v. 5.10, Structure Determination Software Suite*, Bruker AXS, Madison, Wisconsin, USA.

9 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. A. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, *Gaussian 98, Revision A.9.*, Gaussian, Inc., Pittsburgh PA, 1998.

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