CRYSTAL GROWTH & DESIGN

Article

pubs.acs.org/crystal

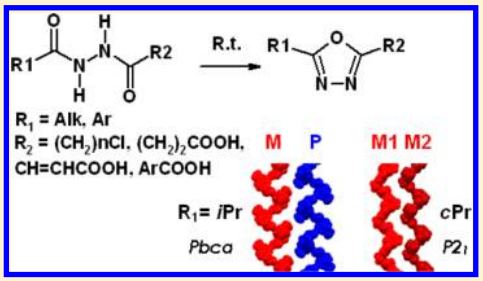
1,3,4-Oxadiazoles for Crystal Engineering. Convenient Synthesis and Self-Assembly: Nonchiral Chains versus Chiral Helices

Oleksii V. Gutov*

Institute of Organic Chemistry, NAS Ukraine, Murmanska st. 5, Kyiv 02094, Ukraine

Supporting Information

ABSTRACT: A series of new 1,3,4-oxadiazoles containing carboxylic and halogen groups and a double bond have been synthesized in good yields and a multigram scale. This was achieved at room temperature from readily available 1,2-diacylhydrazines using a cheap condensation reagent (the solution of P_2O_5 in H_2SO_4). Single-crystal X-ray diffraction analysis has shown that all studied 1,3,4-oxadiazole-containing acids are self-assembled by intermolecular H-bonds into supramolecular zigzag chains or helices, depending on the tecton molecular structure and the type of H-bonding. Factors affecting helix formation have been found, and a Cambridge Structural Database (CSD) survey has been performed to support these findings. Moreover, it has been demonstrated that the tuning of the crystal structure leading to spontaneous symmetry breaking for supramolecular helices based on nonchiral molecules is possible even by as little change in molecular structure as a shift from an isopropyl substituent to a cyclopropyl. Subsequently, the studied 1,3,4-oxadiazole-containing acids and related compounds are found to be easily accessible building blocks for crystal engineering of new chiral materials with tunable supramolecular arrangement.



INTRODUCTION

1,3,4-Oxadiazoles exhibit an exceptionally wide range of biological activities including anticancer, anti-inflammatory, antidiabetic, fungicidal, herbicidal, pesticidal, analgesic, anticonvulsant, anti-HIV, antibacterial, antihypertensive, antiobesity and plant growth regulator activities.[1] Furthermore, azole-containg carboxylic acids possess high potential as polydentate ligands for the synthesis of metal−organic frameworks for storage, separation, catalysis, or other applications. Therefore, efficient synthetic methods are necessary to afford new 1,3,4-oxadiazoles, and evaluate their properties (which can be estimated by crystal structure and self-assembly investigations). Moreover, 1,3,4-oxadiazole-based mimics have been selected as useful peptidomimetics for different purposes, including helical secondary structure emulation.[2] Design of helical structures is of particular interest[3] due to their chiral nature.

Substantial progress has been made recently in crystal structure prediction;[4] however, the design of organic crystals with desired space group symmetry and controlled arrangement of supramolecular motifs still remains a great challenge. The elucidation of the self-assembly principles of organic molecules is of paramount importance to resolve countless biological phenomena, design and create new functional materials, etc. Complete understanding of these processes (especially those leading to spontaneous symmetry breaking[5]) still has not been achieved. Therefore the current study strives to investigate this problem.

Our research is focused on the self-organization of labile polydentate organic ligands.[6] 3-(1,3,4-Oxadiazol-2-yl)propionic and acryl acids were selected as very appropriate candidates for these studies since they possess a H-bond donor and several H-bond acceptors separated by two to three single bonds, allowing a variety of different conformations. The present work describes the illuminating results of the self-assembly studies of 1,3,4-oxadiazole-containing carboxylic acids in the crystal state, which reveal the dependence of helical supramolecular structure on the tectone molecular composition. The current paper also demonstrates the efficient and convenient room temperature synthesis of the series of new 1,3,4-oxadiazoles using as original dehydration reagent a solution of P_2O_5 in sulfuric acid. Different substituents were introduced to the 1,3,4-oxadiazoles to study their effect on crystal packing of labile polydentate organic ligands.

EXPERIMENTAL SECTION

NMR spectra were recorded on Bruker Avance and Varian VXR-300 spectrometers. Chemical shifts are reported in ppm units relative to the residual solvent signals. 1,2-Diacylhydrazines were synthesized using literature procedures.[7,8] Single crystals suitable for X-ray diffraction measurements were obtained by the recrystallization of 1,3,4-oxadiazoles from ethanol.

General Cyclization Method. The corresponding 1,2-diacylhydrazine (X mol as indicated) was added under mechanical stirring during 1−2 h at room temperature to a solution of 270X g of P_2O_5 in 270X mL of H_2SO_4. After 12 h of stirring, the resulting mixture was poured into an aqueous solution of sodium hydrogen carbonate. The mixture was extracted with dichloromethane. The solvent was removed in vacuo, and the residue was purified by recrystallization from an appropriate solvent or by vacuum distillation.

Received: April 28, 2013
Revised: July 18, 2013

dx.doi.org/10.1021/cg400649h | Cryst. Growth Des. XXXX, XXX, XXX−XXX

1a. X = 0.029 mol (5 g). Yield 0.9 g (20%, low due to the high water solubility). Mp 80 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.37 (s, ^{1}H), 2.99 (s, 2H), 2.70 (s, 2H), 2.50 (s, 3H). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 172.8, 165.7, 163.5, 29.8, 20.3, 10.4. Anal. Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.18; H, 5.19; N, 17.91.

1b. X = 0.5 mol (101 g). Yield 67 g (73%). Mp 76 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4): δ 12.31 (s, 1H), 3.16 (m, 1H), 3.01 (t, 2H), 2.71 (t, 2H), 1.28 (d, 6H, J = 6.9 Hz). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 172.8, 170.3, 165.6, 29.8, 25.6, 20.4, 19.7. Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.12; H, 6.60; N, 15.24.

1c. X = 0.14 mol (28 g). Yield 17.3 g (68%). Mp 86−88 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.32 (s, 1H), 2.98 (t, 2H), 2.69 (t, 2H), 2.18 (m, 1H), 1.11 (d, 2H), 0.96 (s, 2H). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 172.8, 167.8, 165.0, 29.8, 20.3, 7.7, 5.7. Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.69; H, 5.56; N, 15.42.

1d. X = 0.59 mol (140 g). Yield 90 g (70%). Mp 138−140 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (s, 1H), 7.97 (d, 2H, J = 6.8 Hz), 7.60 (m, 3H), 3.14 (t, 2H), 2.81 (t, 2H). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 173.2, 166.3, 164.2, 131.9, 129.5, 126.6, 123.8, 30.2, 20.9.

3. X = 0.335 mol (66.9 g). Yield 51.2 g (84%). Mp 85−90 °C.^{1}H NMR (400 MHz, CDCl3): δ 10.19 (s, 1H), 6.78 (d, 1H, J = 13 Hz), 6.49 (d, 1H, J = 13 Hz), 3.24 (m, 1H), 1.40 (d, 6H, J = 6.8 Hz). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 170.9, 166.7, 161.3, 131.3, 117.5, 25.8, 19.8. Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.70; H, 5.57; N, 15.41.

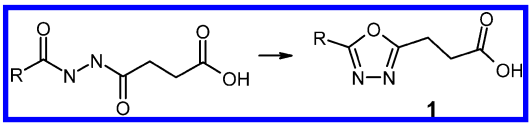
4. X = 0.462 mol (92.4 g). Yield 77.3 g (82%). Mp 160 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.38 (s, 1H), 7.92 (m, 1H), 7.76 (m, 3H), 2.55 (s, 3H). ^{13}C NMR (125.7 MHz, DMSO): δ 168.1, 164.5, 164.2, 133.0, 132.2, 132.1, 130.8, 130.2, 123.9, 10.9. Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.78; H, 4.00; N, 13.76.

5. X = 0.228 mol (40.5 g). Yield 33.3 g (91%). Colorless liquid, bp 100 °C/2 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.74 (t, 2H), 2.95 (t, 2H), 2.46 (s, 3H), 2.15 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 165.6, 163.6, 43.5, 28.8, 22.4, 10.7. Anal. Calcd for $C_6H_9ClN_2O$: C, 44.87; H, 5.65; N, 17.44. Found: C, 44.83; H, 5.68; N, 17.48.

RESULTS AND DISCUSSION

Synthesis of 1,3,4-Oxadiazoles. The most commonly encountered pathway to the 1,3,4-oxadiazole system is the cyclization of readily available 1,2-diacylhydrazines.[9] However, in our case (general formula **1**), this process is complicated because of the presence of a carboxyl group, which is often affected by the dehydration reagents. We screened different synthetic conditions for the cyclization of 1,2-diacylhydrazines. It has been found that the most widely used reagents for such cyclization, thionyl chloride and phosphorus oxychloride, instead of desired 3-(5-alkyl-1,3,4-oxadiazol-2-yl)propionic acids produce mainly *N*-(2,5-dioxo-pyrrolidin-1-yl)-alkanoylamide **2**, where the carboxyl group is involved in cyclization (Scheme S1, Supporting Information). The protection−deprotection of the carboxyl group also does not seem to be useful due to the possible hydrolysis of the 1,3,4-oxadiazole ring in acidic and basic media. Polyphosphoric and sulfuric acids (which have been successfully applied for the facile formation of 3-(5-phenyl-1,3,4-oxadiazol-2-yl)propionic acids[7]) do not work in the case of dialkyl-1,3,4-oxadiazoles. The usage of oleum as a dehydration reagent also leads to the product **2**. Finally we have found that only the mixture P_2O_5−H_2SO_4 as a dehydration reagent provides the desired, previously unknown 5-alkyl-1,3,4-oxadiazole propionic acids **1** (Scheme 1). To the best of our knowledge this simple but useful reagent was not mentioned previously in the literature.

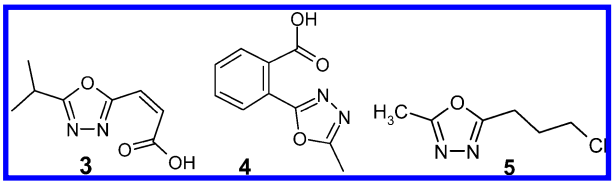
Scheme 1[a]



[a]R = Me (**1a**), *i*-Pr (**1b**), c-Pr (**1c**), or phenyl (**1d**).

Synthetic details are provided in the Experimental Section. Generally, readily available 1,2-diacylhydrazines[7,8] have been converted to the corresponding desired 1,3,4-oxadiazoles by stirring at room temperature in a solution of P_2O_5 in H_2SO_4.

Fortunately this method also successfully affords a variety of other new 1,3,4-oxadiazoles, such as **3**−**5** (bearing carboxyl and haloalkyl groups and a double bond, see structures below), confirming its wide applicability. Most of the 1,3,4-oxadiazoles have been obtained with high yields (up to 91%) on a multigram scale (up to 90 g). Together with the low price of all the required reagents, it makes this new pathway to the 1,3,4-oxadiazole system attractive for industrial applications.



Supramolecular Structures. Molecular and crystal structures of 1,3,4-oxadiazole-containing acids **1a**,**b**,**c**,**d** and **3** have been determined by the X-ray diffraction method (for details, see Supporting Information). It has been found that in all the studied crystals, molecules form endless supramolecular chains or nets defined by intermolecular H-bonds. In the case of compound **1a**, solvent water molecules are incorporated into this supramolecular architecture, preventing the formation of the COO−H···N bonding motif common to all of the remaining compounds in this series. In the following, we focus only on nonsolvated structures.

In the crystals of nonhydrated compounds **1b**,**c**,**d** and **3**, molecules are self-assembled (by two types of COO−H···N hydrogen bonds with similar geometrical parameters, summarized in the Supporting Information) into two different associations depending on which of the two oxadiazole nitrogen atoms participates (Figure 1).

Molecules of the compounds **1d** and **3** form zigzag chains connected by the α-type hydrogen bonds (Figure 2); however, if the bonding mode is shifted from α to β (compounds **1b** and **1c**), the supramolecular arrangement of the H-bonded associates is changed from zigzag chains to 3D helices with a screw axis along the chains (Figure 3).

This shift in the bonding mode has led us to the assumption that the particular supramolecular architecture assumed by the 1,3,4-oxadiazole-containing carboxylic acids depends upon which H-bonding mode is followed. In order to check the generality of this assumption, a CSD survey has been performed. Since only one crystal structure of an 1,3,4-oxadiazole-containing carboxylic acid has been reported so far (which in fact shows the same binding mode as our helical oxadiazoles and finally adopts helical arrangement as well, Supporting Information, Figure S1f), we have done an

dx.doi.org/10.1021/cg400649h | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

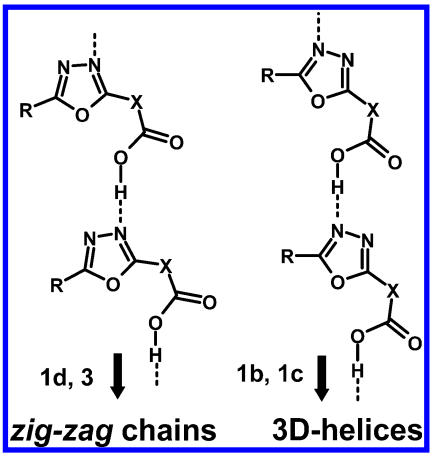


Figure 1. α (left) and β (right) H-bonding modes in oxadiazole-containing acids leading to different supramolecular arrangement. X = $(CH_2)_2$ for **1b**,**c**,**d** and $(CH)_2$ for **3**.

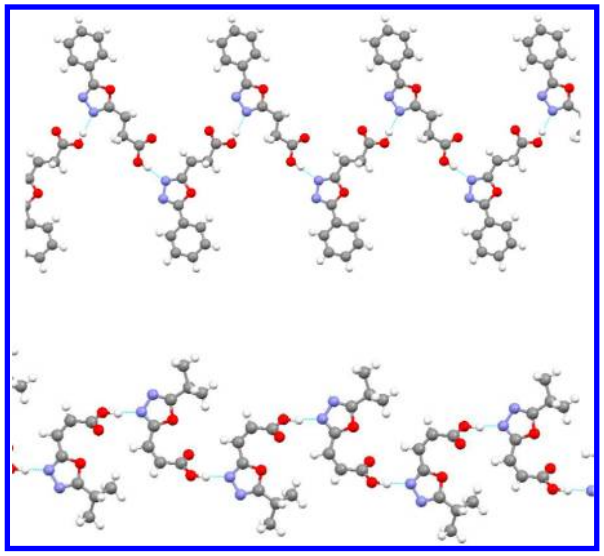


Figure 2. Crystal packing of **1d** (top) and **3** (bottom).

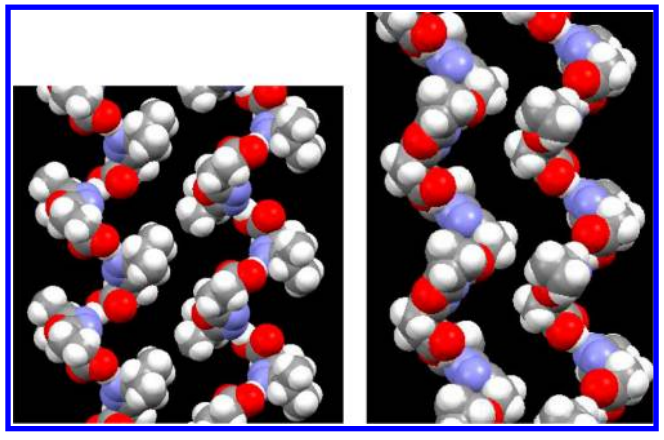
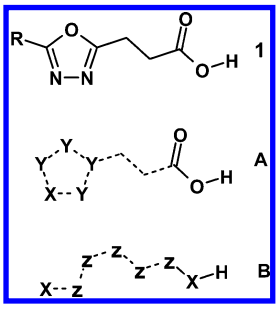


Figure 3. Right- and left-handed symmetrical helices in **1b** (left) and two different but one-handed helices in **1c** (right). Helical pitch is 10.98 Å in **1b** and 11.85 Å in **1c**.

extended CSD-search. For that we used the query "A" (Scheme 2) covering all common five-membered heterocyclic carboxylic acids bearing H-bond donors (N,O) with the same number of atoms in the molecule between the H-bond donor and acceptor.

Scheme 2. Queries Used for the CSD Search[a]



[a]X = N, O; Y = C, N, O; Z = any non-metal.

The search using the query "A" provided us with 275 structures of organic molecules, among which only 25 possess the same bonding mode (β) as our helical oxadiazoles. Most of these 25 structures adopt a helical arrangement of H-bonded chains as well (Supporting Information Table S2, Figure S1), demonstrating a general tendency in β H-bonded tectones to form helical supramolecular structures. Additionally two more helical supramolecular associations have been found in the structures based not on the β bonding mode but on a similar arrangement formed by the same number of atoms in the monomer between the H-bond donor and acceptor as in **1b** and **1c** (Supporting Information, Figure S2). There are several exceptions (where β bonding mode does not lead to a screw axis, Supporting Information, Figure S3), in which additional strong intermolecular interactions (such as ionic and multiple H-bonding, π-stacking) appear to determine the crystal arrangement.

Further generalization of this study is possible only after much wider analysis of the CSD. For example, the query "B" search covers all organic structures containing H-donor and acceptor distant by the same number of atoms as in **1b** and **1c** but without the restriction for five-membered heterocyclic carboxylic acids. Such a search in the current version of CSD provided 72423 structures, and the study of all of them is beyond the scope of the current paper.

We have found also several helical supramolecular associations formed by α H-bonds as a result of the query "A" search. This indicates that helicates are probably common for long labile chains generally, which is supported by many well-known examples in Nature. So there should be an additional reason why the H-bonded associations of compounds **1d** and **3**, as previously mentioned, do not necessarily lead to a helical supramolecular structure. Similarly to the exceptions presented in Table S2 and Figure S3 (Supporting Information), the reason is an additional intermolecular interaction; here that is the π-stacking effect, which plays a substantial role in the crystal packing of the compounds **1d** and **3** due to the extended π-orbital surface with the presence of a phenyl ring or a double bond. In compound **1d**, neighboring H-bonded chains are stabilized by the π-stacking of the phenyl and oxadiazole rings (Supporting Information, Figure S4) with shortest C−C distances of about 3.3 Å. In compound **3**, molecules in the neighboring H-bonded chains are linked by the π-stacking of the double bond with the oxadiazole moiety (Supporting Information, Figure S5, the shortest contact, C−C 3.32 Å).

dx.doi.org/10.1021/cg400649h | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

In contrast, there is no obvious π-stacking in the crystals of compounds **1b** and **1c**, and finally the molecules are organized into supramolecular helices by β-H-bonding.

Extremely interesting is the fact that the small difference between isopropyl and cyclopropyl groups of **1b** and **1c** leads to a substantial difference in supramolecular structure. The space group is changed with the spontaneous chiral resolution of enantiomeric forms of **1c** helices (Figure 3). The crystal of isopropyl-substituted **1b** belongs to the nonchiral space group *Pbca* and consists of antiparallel enantiomeric helices. (Racemic mixtures commonly crystallize in nonchiral space groups.) In contrast, the crystal of cyclopropyl-substituted compound **1c** is chiral (space group $P2_1$); it consists of parallel homochiral supramolecular helices. In this case, asymmetry is apparently compensated by the existence of the molecule in two conformations differentiated by the cyclopropyl group orientation (Figure 4). This packing motif probably cannot be achieved by molecules like **1b** bearing the bulkier isopropyl group.

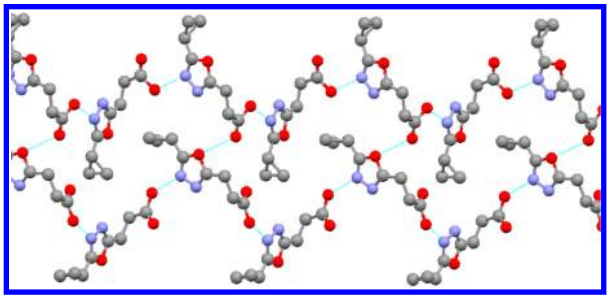


Figure 4. Two different one-handed helices in the **1c** crystal. The cyclopropyl group is oriented toward the oxadiazole oxygen atom (upper strand) or the nitrogen atom (lower strand). Hydrogen atoms have been omitted for clarity.

The difference in crystal packing of two very similar compounds (**1b** and **1c**) demonstrates that the chiral resolution leading to enantiomerically pure crystals of achiral compounds can be selected by Nature as just one of the possible tools for the energy minimization. These tools are the subject of our further studies, involving a wide range of related substrates, with the aim to discover the principles underlying homochiral self-assembly of nonchiral molecules and finally rational design of new chiral materials.

CONCLUSIONS

The current paper demonstrates the efficient and convenient multigram room temperature synthesis of a wide range of new 1,3,4-oxadiazoles using as original dehydration reagent a solution of P_2O_5 in sulfuric acid. Together with the low price of all the required reagents, it makes this new pathway to the 1,3,4-oxadiazole system attractive for industrial applications. X-ray diffraction structure determinations have shown that all the crystalline 1,3,4-oxadiazole-containing acids examined are self-assembled into supramolecular chains or nets defined by the intermolecular H-bonds of two types (α and β). Such chains in most cases form helices; however, the presence of conjugated systems capable of π-stacking promotes the formation of 2D zigzag chains, preventing the formation of bulky helices. Even though helical associates are common for long labile molecules, helix formation could be specifically promoted by the β-type H-bonding motif. This is further supported by the CSD survey that covers all common five-membered heterocyclic acids with the same number of atoms in the molecule between the H-bond donor and acceptor as in **1b** and **1c**. Moreover, it has been shown that the tuning of crystal structure, which leads to spontaneous symmetry breaking for supramolecular helices based on nonchiral molecules, is possible even by as little change in molecular structure as a shift from an isopropyl substituent to a cyclopropyl. Subsequently, studied 1,3,4-oxadiazole-containing acids and related compounds are found to be easily accessible building blocks for crystal engineering of new chiral materials with tunable supramolecular arrangement that depends on a type of substituents.

ASSOCIATED CONTENT

Supporting Information

Compound **2** synthesis scheme, geometry parameters of hydrogen bonds in the compounds **1b,c,d** and **3**, the results of the CSD survey, crystal packing of **1d** and **3**, crystallographic parametrs and thermal ellipsoid plots for the studied 1,3,4-oxadiazoles, and copies of the ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: AVGutov@gmail.com.

Present Address

[†]Center for Nanofabrication and Molecular Self-Assembly, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208-3113, USA.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The author is grateful to Prof. A. N. Chernega, Dr. E. B. Rusanov, and Yu. G. Vlasenko for support and fruitful discussions and to Dr. V. V. Pirozhenko for assistance with the NMR spectra. The work has been done in the Institute of Organic Chemistry, National Academy of Sciences of Ukraine, under its support.

REFERENCES

(1) Boström, J.; Hogner, A.; Llinàs, A.; Wellner, E.; Plowright, A. T. *J. Med. Chem.* **2012**, *55*, 1817−1830. Somani, R. R.; Shirodkar, P. Y. *Pharma Chem.* **2009**, *1*, 130−140.

(2) Ko, E.; Liu, J.; Perez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. *J. Am. Chem. Soc.* **2011**, *133*, 462−477.

(3) Saito, N.; Terakawa, R.; Shigeno, M.; Amemiya, R.; Yamaguchi, M. *J. Org. Chem.* **2011**, *76*, 4841−4858. Stringer, J. R.; Crapster, J. A.; Guzei, I. A.; Blackwell, H. E. *J. Am. Chem. Soc.* **2011**, *133*, 15559−15567. Yamada, H.; Wu, Z.-Q.; Furusho, Y.; Yashima, E. *J. Am. Chem. Soc.* **2012**, *134*, 9506−9520. Sasaki, T.; Hisaki, I.; Tsuzuki, S.; Tohnaia, N.; Miyata, M. *CrystEngComm* **2012**, *14*, 5749−5752. Hatakeyama, T.; Hashimoto, S.; Oba, T.; Nakamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 19600−19603.

(4) Bardwell, D. A.; et al. *Acta Crystallogr., Sect. B: Struct. Sci.* **2011**, *B67*, 535−551. Jones, J. T. A.; Hasell, T.; Wu, X.; Bacsa, J.; Jelfs, K. E.; Schmidtmann, M.; Chong, S. Y.; Adams, D. J.; Trewin, A.; Schiffman, F.; Cora, F.; Slater, B.; Steiner, A.; Day, G. M.; Cooper, A. I. *Nature* **2011**, *474*, 367−371. Wen, S.; Nanda, K.; Huang, Y.; Beran, G. J. O. *Phys. Chem. Chem. Phys.* **2012**, *14*, 7578−7590. Zhu, Q.; Oganov, A. R.; Glass, C. W.; Stokes, H. T. *Acta Crystallogr., Sect. B: Struct. Sci.* **2012**, *B68*, 215−226.

(5) Matsuura, T.; Koshima, H. *J. Photochem. Photobiol., C* **2005**, *6*, 7−24. Pérez-García, L.; Amabilino, D. B. *Chem. Soc. Rev.* **2007**, *36*, 941−967.
(6) Gutov, O. V.; Rusanov, E. B.; Kudryavtsev, A. A.; Garasevych, S. G.; Slobodyanyuk, O. V.; Yashchuk, V. M.; Chernega, A. N. *CrystEngComm* **2011**, *13*, 1373−1377. Gutov, O. V.; Rusanov, E. B.; Egorov, O. A.; Chernega, A. N. *Zh. Org. Farm. Khim.* **2008**, *6*, 46−48. Gutov, A. V.; Rusanov, E. B.; Ryabitskii, A. B.; Tsimbal, I. F.; Chernega, A. N. *Russ. J. Gen. Chem.* **2009**, *79*, 1910−1918.
(7) Short, F. W.; Long, L. M. *J. Heterocycl. Chem.* **1969**, *6*, 707−712.
(8) Kolotova, N. V.; Koz'minykh, E. N.; Kolla, V. E.; Syropyatov, B.Ya.; Voronina, E. V.; Koz'minykh, V. O. *Khim.-Farm. Zh.* **1999**, *33* (5), 22−28.
(9) Pouliot, M.; Angers, L.; Hamel, J.; Paquin, J. *Org. Biomol. Chem.* **2012**, *10*, 988 and references therein..