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New aspects of reactions of methyl (thio)ureas with benzil

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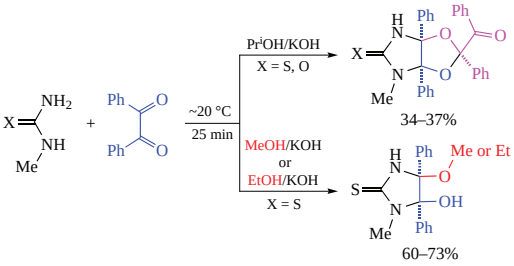
New pathways of reaction between 1-methylthiourea or 1-methylurea and benzil bring about new derivatives of (2*S,3a*R**,6a*S**)-perhydro-3a*H*-[1,3]dioxolo[4,5-*d*]imidazole and racemic (4*S**,5*R**)-4-alkoxy-5-hydroxy-1-methyl-4,5-diphenylimidazolidine-2-thiones. Some of the obtained urea- and thiourea derivatives were characterized by X-ray diffraction, which showed their supramolecular organization governed by the directionality of hydrogen bonds at the acceptor side C=O or C=S groups.**



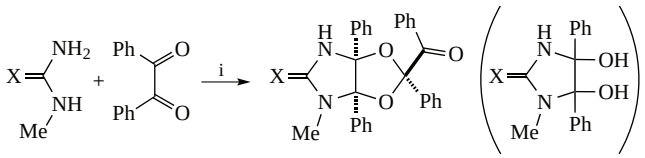
Keywords: [1,3]dioxolo[4,5-*d*]imidazoles, imidazolidines, aminals, benzil, α-diketones, ureas, thioureas.

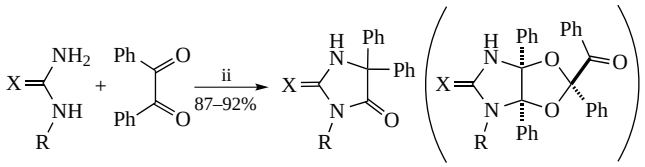
Ureas (thioureas) are widely used in various transformations.[1–12] Condensations of 1-substituted ureas (thioureas) with α-dicarbonyl compounds lead mainly to 1-substituted 2-oxo(thioxo)-4,5-dihydroxyimidazolidines,[1,2] 1,4- and 1,6-disubstituted glycolurils[3–5] as well as 3-substituted imidazolidine-2,4-diones(2-thioxoimidazolidine-4-ones).[6] The reactions between 1-methylthiourea **1a** or 1-methylurea **2a** and 1,2-diphenylethane-1,2-dione (benzil) would bring about a wide range of products[7–11] (for details, see Online Supplementary Materials, Scheme S1).

In this study, we discovered a new direction of reaction between 1-methylthiourea or 1-methylurea and benzil and synthesized new derivatives of perhydro-3a*H*-[1,3]dioxolo[4,5-*d*]imidazole. The reaction between 1-methylthiourea **1a** and benzil carried out at room temperature for 30 min was anticipated to afford typical 4,5-dihydroxy-1-methyl-4,5-diphenylimidazolidine-2-thione **3a** (Scheme 1). In this experiment, we used Pr^{i}OH (instead of MeOH and EtOH[10]) and KOH (instead of NaOH[10]). Surprisingly, instead of **3a**, a previously unknown compound precipitated from the reaction mixture. Its ^{1}H NMR ($CDCl_3$) spectrum contained the signals for the N–Me (s, 2.719 ppm, 3H), N–H (s, 6.614 ppm) and phenyl (m, 6.989–8.157 ppm) groups in the integral ratio 3 : 1 : 20 (see Online Supplementary Materials, Figure S1). The structure of this compound was ultimately determined by X-ray diffraction [Figure 1(*a*)][†] which turned to be racemic (2*S*,3a*R*,6a*S* and 2*R*,3a*S*,6a*R*) (4-methyl-2,3a,6a-triphenyl-5-thioxotetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]imidazol-2-yl)-(phenyl)methanone **4a**. The yield of product **4a** was 34%. In the ^{1}H NMR spectrum of the filtrate, residual signals of compound **4a** and the initial reagents were only observed and nothing of other components was detected. When the filtrate was kept for 12 h at room temperature, hydantoin **5a** was formed (see Scheme 1). The obtained result indicates a high selectivity of the studied reaction.

The condensation of benzil with 1-methylurea **2a** under the found conditions (Pr^{i}OH/KOH, room temperature, 25 min) also proceeds highly selectively with the formation of racemic (2*S*,3a*R*,6a*S* and 2*R*,3a*S*,6a*R*) 2-benzoyl-4-methyl-2,3a,6a-triphenyldihydro-3a*H*-[1,3]dioxolo[4,5-*d*]imidazol-5(4*H*)-one **4b** (see Scheme 1, yield 37%), whose structure was also confirmed by the X-ray method [Figure 1(*b*)].[†]

Interestingly, when using MeOH and EtOH under the same conditions, product **4b** was also obtained. With the prolongation of the reaction, a decrease in the yield of compound **4b** was observed, and when the reaction time was extended to 12 h, the only reaction product was hydantoin **6a**. The reaction of other





Scheme 1 *Reagents and conditions*: i, KOH, Pr^{i}OH, room temperature, 25 min; ii, the same, 12 h.

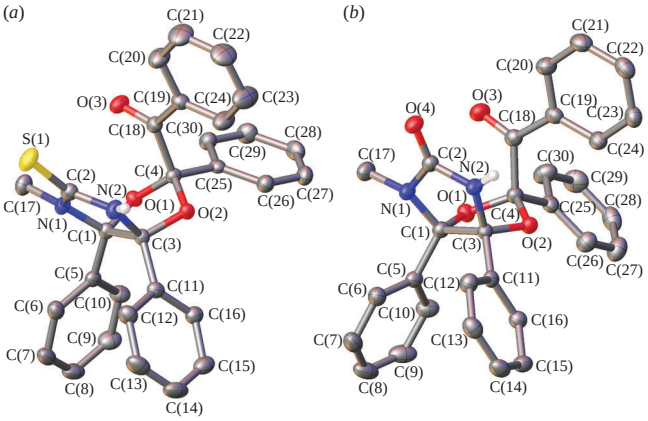


Figure 1 General view of (*a*) molecule **4a** and (*b*) molecule **4b**. Hydrogen atoms except those of NH groups are omitted for clarity. Non-hydrogen atoms are shown as thermal ellipsoids (p = 50%).

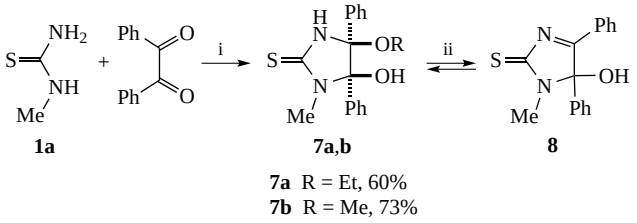
1-substituted thioureas **1b**,**c** and ureas **2b**–**d** with benzil under these conditions gave exclusively known hydantoin-type products **5b**,**c**[16,17] and **6b**–**d**[6,18] (see Scheme 1).

It seemed reasonable to test the reaction of 1-methylthiourea **1a** with benzil in MeOH and EtOH in the presence of KOH (instead of NaOH[7]) (Scheme 2). As documented previously,[7] ethers **7a**,**b** were obtained. This result may be explained by the fact that ethers **7a**,**b** would quickly precipitate from the reaction mixture so other products cannot be formed. Nothing of the corresponding ethers were formed in Pr^{i}OH.

^{1}H NMR spectra ($CDCl_3$) of compounds **7a**,**b** contain only one set of signals for diastereomeric racemic (4*S*,5*R* and 4*R*,5*S*) 4-alkoxy-5-hydroxy-1-methyl-4,5-diphenylimidazolidine-2-thione [for the case of **7b**, see Online Supplementary Materials, Figure S2(*a*)]. The structure of compound **7a** was also proven by X-ray diffraction† (Figure 2; for **7b**, it was not possible to grow crystals). The phenyl groups in **7a** have a *cis* arrangement relative to the plane of the imidazolidine cycle. This fact conforms with the high selectivity of the reactions herein studied.

An unexpected observation was noticed when registering the ^{1}H NMR spectra of compounds **7a**,**b** in DMSO-d_6. After 1 min heating to 40 °C, signals for the NH protons disappear, and the appearance Ph groups changes while the signals for free alcohol molecules (MeOH or EtOH) would emerge [see Online Supplementary Materials, Figure S2(*b*)]. These data indicate the elimination of alcohol molecules and the formation of new hydroxy imidazolinethione **8** (see Scheme 2).

Based on studies of the interaction of 1-methylthiourea with benzil and the presumed formation of intermediate **A**,[10] a



7a R = Et, 60%
7b R = Me, 73%

Scheme 2 *Reagents and conditions*: i, KOH, ROH, room temperature, 25 min; ii, DMSO-d_6, heating, 1 min.

mechanism for the selective formation of compounds **4a**,**b** and **7a**,**b** can be proposed (Scheme 3). Anion **A** attacks the carbonyl group of benzil to form intermediate **B**, which is selectively cyclized into adduct **C**. Further protonation leads to ketals **4a**,**b**. In a similar way, compounds **7a**,**b** can be formed. Due to the occurrence of a hydrogen bond between the intermediate **A** and the alcohol molecule, intermediate **D** is formed with the further generation of anion **E** whose protonation completes this pathway.

The structure of products **4a**,**b** and **7a** confirmed by X-ray diffraction reveals a molecular geometry typical of this type of compounds and showing minor differences between the urea- and thiourea-based derivatives **4a** and **4b**. Indeed, both the imidazolyl and the dioxolyl fragments in them adopt an envelope conformation with the atom C(2) or C(4) deviating by 0.03–0.06 Å from the mean plane of the other atoms in these heterocycles which locate at an angle of 75.10(6) and 72.73(6)° to each other. The imidazolyl fragment in the absence of the second heterocycle in **7a** features a more twist-like conformation, as judged by the deviation of the neighboring carbon atoms C(1) and C(3) by 0.18 and 0.22 Å, respectively. In all cases, the phenyl substituents locate on the same side of the heterocyclic plane with the torsion angle C(5)–C(1)–C(3)–C(11) varying from

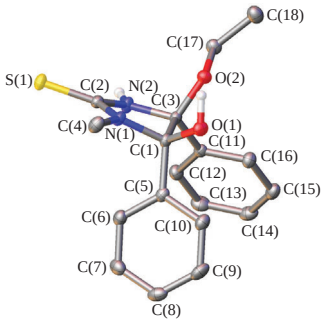


Figure 2 General view of molecule **7a**.

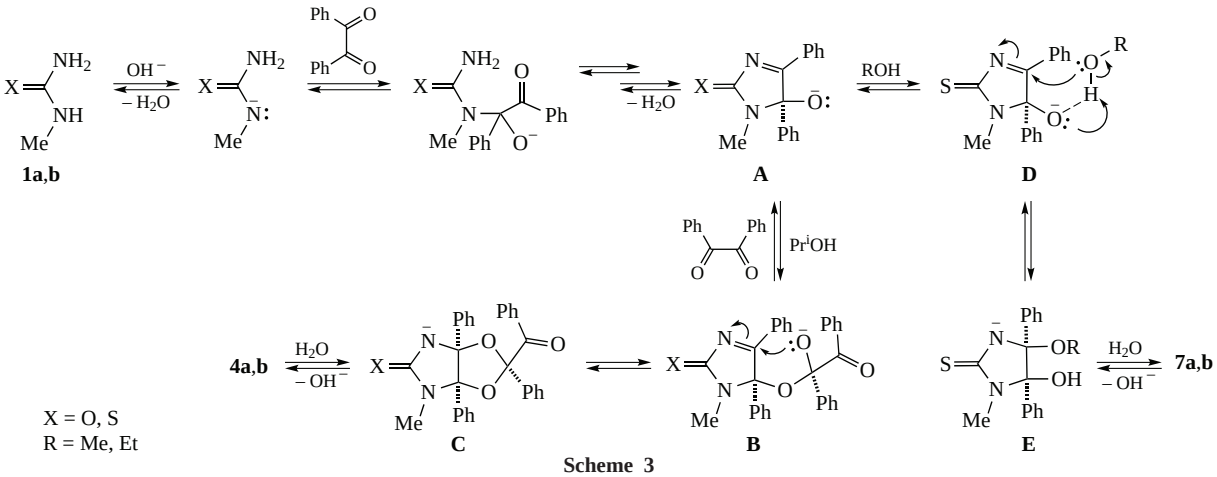
† *Crystal data for* **4a**. $C_{30}H_{24}N_2O_3S$, M = 492.57, monoclinic, space group $P2_1/n$, at 120 K: a = 12.7192(7), b = 14.3339(7) and c = 13.8527(7) Å, β = 101.2240(10)°, V = 2477.3(2) Å^3, Z = 4, d_{calc} = 1.321 g cm^{-3}, $F(000)$ = 1032. Intensities of 17581 reflections were measured with a Bruker APEX2 DUO CCD diffractometer [λ(MoKα) = 0.71073 Å, μ(MoKα) = 1.66 cm^{-1}, ω-scans, $2\theta < 56°$], and 5941 independent reflections (R_{int} = 0.0237) were used for the structure solution and refinement. Final R factors: R_1 = 0.0480 for 4552 observed reflections with $I > 2\sigma(I)$, wR_2 = 0.1375 and GOF = 1.057 for all the independent reflections.

Crystal data for **4b**. $C_{30}H_{24}N_2O_4$, M = 476.51, monoclinic, space group $P2_1/n$, at 120 K: a = 14.3663(12), b = 8.1635(7) and c = 20.7824(18) Å, β = 101.328(2)°, V = 2389.9(4) Å^3, Z = 4, d_{calc} = 1.324 g cm^{-3}, $F(000)$ = 1000. Intensities of 26933 reflections were measured with a Bruker APEX2 DUO CCD diffractometer [λ(MoKα) = 0.71073 Å, μ(MoKα) = 0.89 cm^{-1}, ω-scans, $2\theta < 60°$], and 6893 independent reflections (R_{int} = 0.0467) were used for the structure solution and refinement. Final R factors: R_1 = 0.0546 for 4688 observed reflections with $I > 2\sigma(I)$, wR_2 = 0.1530 and GOF = 1.047 for all the independent reflections.

Crystal data for **7a**. $C_{18}H_{20}N_2O_2S$, M = 328.42, triclinic, space group $P\bar{1}$, at 120 K: a = 7.974(6), b = 8.464(6) and c = 14.175(10) Å, α = 76.761(15)°, β = 89.571(17)°, γ = 62.30(3)°, V = 819.1(10) Å^3, Z = 2, d_{calc} = 1.332 g cm^{-3}, $F(000)$ = 348. Intensities of 8833 reflections were measured with a Bruker APEX2 DUO CCD diffractometer [λ(MoKα) = 0.71073 Å, μ(MoKα) = 2.09 cm^{-1}, ω-scans, $2\theta < 56°$], and 3939 independent reflections (R_{int} = 0.0277) were used for the structure solution and refinement. Final R factors: R_1 = 0.0386 for 3239 observed reflections with $I > 2\sigma(I)$, wR_2 = 0.0961 and GOF = 1.024 for all the independent reflections.

Using Olex2,[13] the structures were solved with the ShelXT[14] structure solution program using Intrinsic Phasing and refined with the XL[15] refinement package using Least-Squares minimisation. Hydrogen atoms of NH and OH groups were located from difference Fourier synthesis, while positions of other hydrogen atoms were calculated, and they all were refined in isotropic approximation within the riding model.

CCDC 2080192, 2080193 and 2080191 contain the supplementary crystallographic information for **4b**, **4a** and **7a**, respectively. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk.



Scheme 3

4.04(19) to 24.96(14)°; the largest value having been observed for **7a** with only the imidazolyl fragment.

Note that compounds **4a**,**b** with very similar molecular geometries feature very different supramolecular organization (Figure 3), which may be attributed to the different nature of the chalcogen atoms, a smaller oxygen atom with a better H-bond donor ability in **4b** and a larger sulfur atom with an inferior H-bond donor ability in **4a**.[19] The hydrogen bonds they produce with the NH group of the imidazolyl fragment [N···O 2.8034(17) Å, NHO 169(2)º and N···S 3.3167(13) Å, NHS 172.25(7)°] result in infinite chains composed of the molecules of the same chirality in **4b** (although the overall crystal packing is centrosymmetric, space group $P2_1/n$) and in centrosymmetric dimers in **4a**. The latter can be explained by the preference of the C=S group to form hydrogen bonds with an average C=S···H(N) angle close to 111° rather than to 120°, the angle between two lone pairs of the chalcogen atom, typical of the C=O group.[23] In **4b** and **4a**, the appropriate values are 143.8(8) and 102.97(5)°; the former being higher than expected may be due to the formation of the second, weak H-bond with the methyl group [C···O 3.471(2) Å, CHO 142.1(19)º, C=O···H(C) 108.2(5)°] that additionally stabilizes the above H-bonded chains. In compound **4a**, one of the phenyl substituents acts as the second H-bond donor to the C=S group [C···S 3.6420(18) Å, CHS 124.05(10)°, C=S···H(C) 153.70(5)º], thus helping to hold together the H-bonded centrosymmetric dimers.

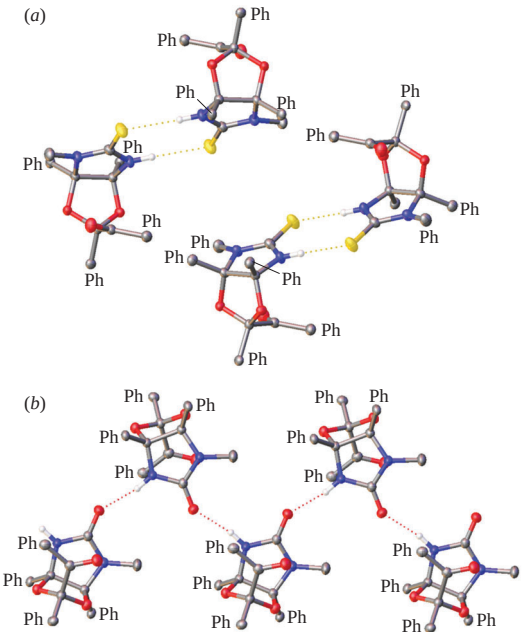


Figure 3 Fragments of the crystal packing in (*a*) compound **4a** and (*b*) compound **4b** illustrating the formation of infinite chains and centrosymmetric dimers, respectively.

The same reasoning, apparently, applies to the supramolecular organization of the other thiourea derivative **7a**. As it has two efficient H-bond donors, the above NH group and an additional OH group, the resulting supramolecular motif is a combination of the centrosymmetric dimers formed by the C=S group with the respective H-bond donor [N···S 3.383(3) Å and O···S 3.346(2) Å, NHS 174.66(7)° and OHS 146.12(9)°]. This would assemble them into the infinite chains (see Online Supplementary Materials, Figure S4). The corresponding C=S···H(N,O) angles of 111.06(8) and 105.71(8)° are close to the above value for **4a**; these values are significantly lower than those in **4b**. This is in a good agreement with the different directionality of hydrogen bonds at the sulfur and oxygen atoms, previously found and explained for related thiourea and urea derivatives.[20]

To conclude, the discovered aspect of the reactions of 1-methylthiourea and 1-methylurea with benzil allowed us to synthesize new derivatives of perhydrodioxoloimidazoles **4a**,**b** and ethers **7a**,**b** with high chemoselectivity, thus confirming the uniqueness of the reactivity of 1-methylthiourea and 1-methylurea in reactions with benzil. A comparison of X-ray diffraction data for some of the obtained urea- and thiourea derivatives showed their supramolecular organization to be governed by the directionality of hydrogen bonds at the acceptor side, the C=O and the C=S group.

X-ray diffraction data were collected using the equipment of Center for molecular composition studies of INEOS RAS with the financial support from the 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.2021.09.027.

References

1 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.

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

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

4 (*a*) V. V. Baranov, M. M. Antonova, E. K. Melnikova and A. N. Kravchenko, *Russ. Chem. Bull., Int. Ed.*, 2020, **69**, 401 (*Izv. Akad. Nauk, Ser. Khim.*, 2020, 401); (*b*) V. A. Karnoukhova, V. V. Baranov, A. V. Vologzhanina, A. N. Kravchenko and I. V. Fedyanin, *CrystEngComm*, 2021, **23**, 4312.

5 L. V. Anikina, G. A. Gazieva and A. N. Kravchenko, *Russ. Chem. Bull., Int. Ed*., 2020, **69**, 563 (*Izv. Akad. Nauk, Ser. Khim.*, 2020, 563).
6 G. G. Muccioli, N. Fazio, G. K. E. Scriba, W. Poppitz, F. Cannata, J. H. Poupaert, J. Wouters and D. M. Lambert, *J. Med. Chem*., 2006, **49**, 417.
7 R. G. Neville, *J. Org. Chem.*, 1958, **23**, 1588.
8 C. K. Lee, S. H. Kim and Y. B. Kim, *J. Heterocycl. Chem*., 1996, **33**, 1019.
9 A. R. Butler and E. Leitch, *J. Chem. Soc., Perkin Trans. 2*, 1980, 103.
10 C. J. Broan and A. R. Butler, *J. Chem. Soc., Perkin Trans. 2*, 1989, 731.
11 C. J. Broan and A. R. Butler, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1501.
12 (*a*) A. A. Alexeev, E. V. Nurieva, T. P. Trofimova, E. A. Chesnakova, Yu. K. Grishin, K. A. Lyssenko, M. V. Filimonov and O. N. Zefirova, *Mendeleev Commun*., 2019, **29**, 14; (*b*) A. V. Kalistratova, L. V. Kovalenko, M. S. Oshchepkov, A. M. Gamisoniya, T. S. Gerasimova, Yu. A. Demidov and M. G. Akimov, *Mendeleev Commun*., 2020, **30**, 153; (*c*) V. V. Baranov, A. B. Ivanova, N. G. Kolotyrkina and A. N. Kravchenko, *Mendeleev Commun.*, 2019, **29**, 94; (*d*) V. V. Baranov, M. M. Antonova, N. G. Kolotyrkina, I. E. Zanin and A. N. Kravchenko, *Synlett*, 2019, **30**, 299.
13 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr*., 2009, **42**, 339.
14 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **A71**, 3.
15 G. M. Sheldrick, *Acta Crystallogr*., 2008, **A64**, 112.
16 G. G. Muccioli, J. H. Poupaert, J. Wouters, B. Norberg, W. Poppitz, G. K. E. Scriba and D. M. Lambert, *Tetrahedron*, 2003, **59**, 1301.
17 G. G. Muccioli, D. Martin, G. K. E. Scriba, W. Poppitz, J. H. Poupaert, J. Wouters and D. M. Lambert, *J. Med. Chem*., 2005, **48**, 2509.
18 N. Trišović, N. Valentić and G. Uščumlić, *Chem. Cent. J.*, 2011, **5**, 62, doi: 10.1186/1752-153X-5-62.
19 Yu. V. Nelyubina, G. A. Gazieva, V. V. Baranov, P. A. Belyakov, A. O. Chizhov, K. A. Lyssenko and A. N. Kravchenko, *Russ. Chem. Bull., Int. Ed*., 2009, **58**, 1353 (*Izv. Akad. Nauk, Ser. Khim.*, 2009, 1315).
20 F. H. Allen, C. M. Bird, R. S. Rowland and P. R. Raithby, *Acta Crystallogr*., 1997, **B53**, 680.
21 S. Guihèneuf, L. Paquin, F. Carreaux, E. Durieu, L. Meijer and J. P. Bazureau, *Org. Biomol. Chem*., 2012, **10**, 978.
22 T. L. Boehm, L. C. Christie, B. Devadas, H. M. Madsen, L. Marrufo and S. Selness, *Patent WO 2006/040666*, 2006.
23 A. N. Kravchenko, I. E. Chikunov, G. A. Gazieva and N. N. Makhova, *Mendeleev Commun*., 2016, **26**, 136.
24 B. Raux, Yu. Voitovich, C. Derviaux, A. Lugari, E. Rebuffet, S. Milhas, S. Priet, T. Roux, E. Trinquet, J.-C. Guillemot, S. Knapp, J.-M. Brunel, A. Yu. Fedorov, Y. Collette, P. Roche, S. Betzi, S. Combes and X. Morelli, *J. Med. Chem*., 2016, **59**, 1634.

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