Synthesis of [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines

Lidia S. Konstantinova,[a] Vadim V. Popov,[a] Natalia V. Obruchnikova,[a] Konstantin A. Lyssenko,[b] Ivan V. Ananyev,[b] and Oleg A. Rakitin[a]*

[a]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect, 47, 119991 Moscow, Russia*
[b]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov Str., 28, 119991 Moscow, Russia*
E-mail: orakitin@ioc.ac.ru

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.b07

Abstract

The reaction temperature has a strong impact on the results of chlorination of 5,6-bis(*tert*-butylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine that is readily prepared from 5,6-dichloro[1,2,5]oxadiazolo[3,4-*b*]pyrazine and sodium *tert*-butylsulfide. Mono- and bis(sulfenylchlorides) were selectively obtained in high yield and their structure was confirmed by the reaction with morpholine. Treatment of [1,2,5]oxadiazolo[3,4-*b*]pyrazine-5,6-disulfenyl dichloride with primary aliphatic amines and benzylamine afforded *N*-substituted [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines in moderate yields. Novel pentacyclic [1,2,5]oxadiazolo[3",4":5',6']pyrazino[2',3':5,6][1,2,4]thiadiazino[3,4-*b*][1,3]benzothiazole, whose structure was confirmed by X-ray diffraction, was obtained by the reaction of this disulfenyl dichloride with 2-aminobenzothiazole.

Keywords: Fused 1,3,2-dithiazoles, [1,2,5]oxadiazolo[3,4-*b*]pyrazines, disulfenyl dichlorides, primary amines, bis(*tert*-butylthio) derivatives, chlorination

Introduction

Amongst five-membered sulfur-nitrogen heterocycles 1,3,2-dithiazoles have attracted the largest attention due to their important physical and biological properties.[1] Neutral 1,3,2-dithiazolyl radicals are of interest as compounds which possess significant magnetic properties and conductivity.[2] The optical pure isomers of the 1,3,2-benzodithiazole oxides have been synthesized by oxidation of the corresponding 1,3,2-benzodithiazoles and isolated by chiral liquid chromatography.[3] They can be employed as intermediates for the preparation of

enantiopure amines and alcohols. *N*-Substituted 1,3,2-benzodithiazole *S*-oxides exhibited *in vitro* antifungal activity towards several strains of *Candida*.[4]

Benzofused 1,3,2-dithiazoles or 1.3.2-dithiazolium salts were generally prepared by the reaction of aromatic and heteroaromatic (disulfenyl) dichlorides with aliphatic amines and trimethylsilyl azide, respectively.[1,2] The only known example of heterocyclic fused 1,3,2-dithiazole - 2-(phenylsulfonyl)[1,3,2]dithiazolo[4,5-*b*]quinoxaline have been synthesized by the reaction of corresponding vicinal dithiol with dichlorophenylsulfamide.[5] Here we report an attempt of preparation of substituted [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines **1** and [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazin-5-yl radical **2**. The interest in the synthesis of these compounds was stimulated by two reasons. The first is the intensive investigation of biological activity of [1,2,5]oxadiazolo[3,4-*b*]pyrazine family **3** which reveal significant anticancer activity,[6-9] HIV-1 integrase inhibitory and anti-HIV activity[10,11] and antibacterial properties in relation to methicillin-resistant Staphylococcus aureus (MRSA) and the transglycosylase.[12,13] Also it would be interesting to compare physical properties of [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazin-5-yl radical **2** with those of known stable 1,2,5-thiadiazolo[3,4-*b*]-1,3,2-dithiazolo[3,4-*d*]pyrazin-2-ylium radical **4** (Figure 1).[14]

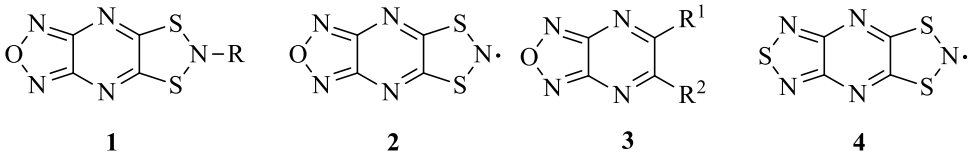
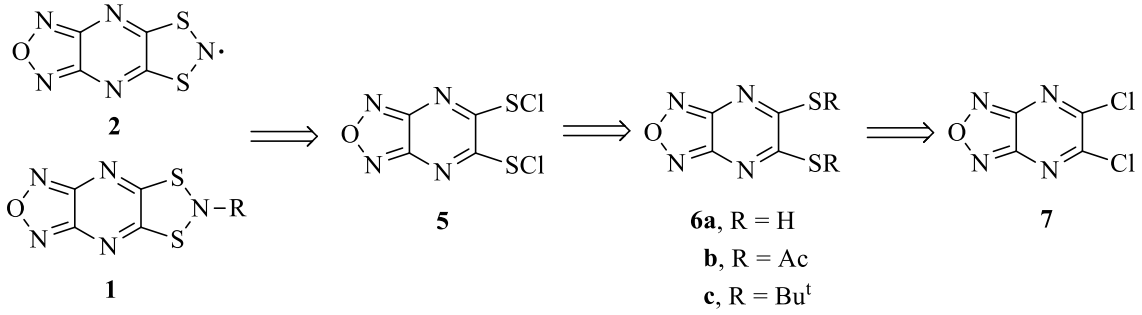


Figure 1. Fused 1,3,2-dithiazoles and [1,2,5]oxadiazolo[3,4-*b*]pyrazines.

The retrosynthetic analysis for 1,3,2-dithiazole **1** and **2** led us to the conclusion that the most reliable precursor would be bis(sulfenylchloride) **5** (Scheme 1) which can be prepared from [1,2,5]oxadiazolo[3,4-*b*]pyrazine-5,6-dithiol **6a** or its substituted derivatives **6b** or **6c**. In turn 1,2-dithiols **6** could be obtained from easily available 5,6-dichloro[1,2,5]oxadiazolo[3,4-*b*]pyrazine **7** by nucleophilic substitution of the chlorine atoms.[15]

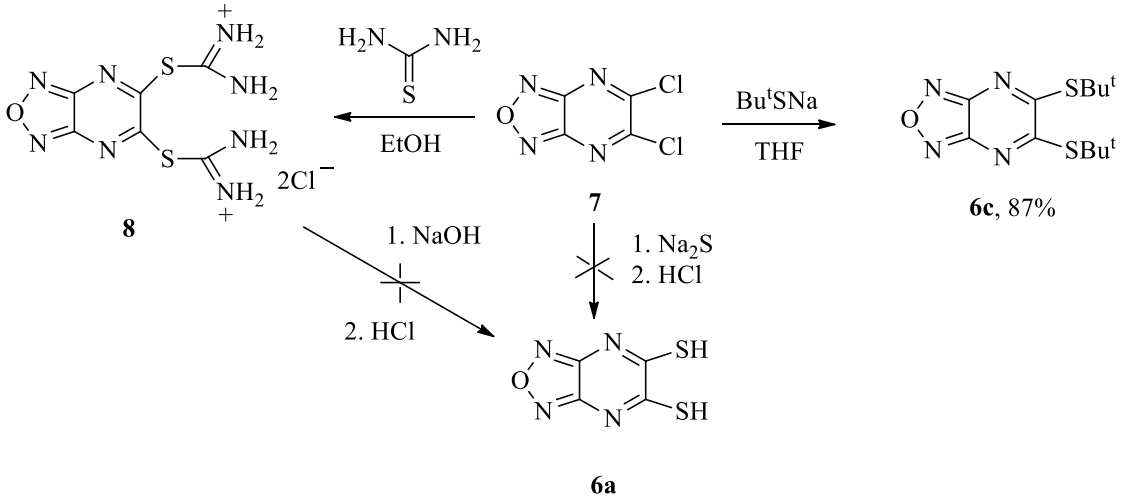


Scheme 1. Retrosynthetic analysis of [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines.

Results and Discussion

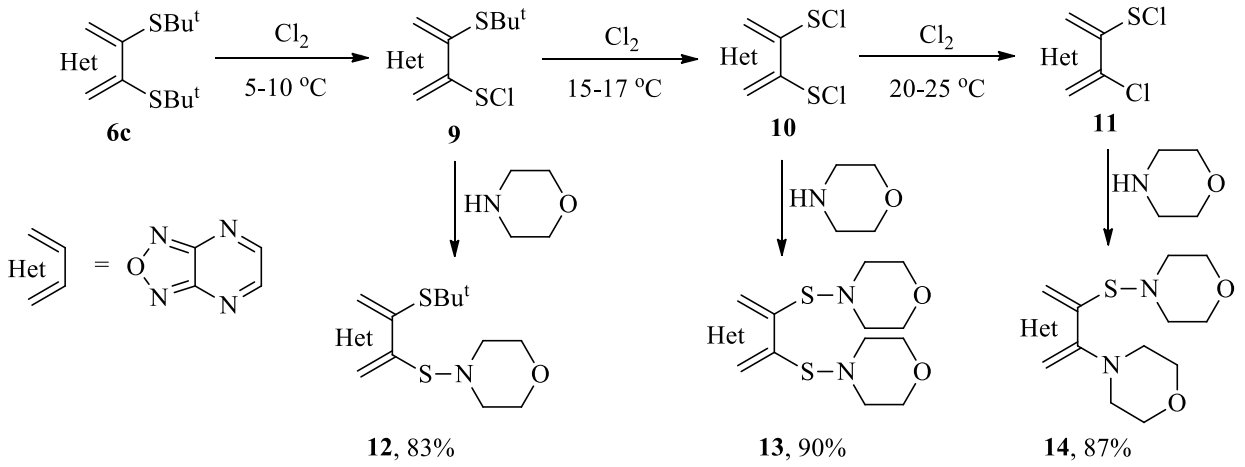
The preparation of dithiol **6a** was described before, but neither detailed procedure, nor its spectral evidence were reported.[15] We have studied the reaction between dichlorooxadiazolopiperazine **7** and sodium sulfide. Unfortunately under all the tested conditions (treatment these reagents in ethanol, water, or their mixtures) only unidentified products were isolated. IR spectra of the products revealed bands of amido groups (about 1560 cm^{-1}) which signify the hydrolysis (at least partly) of chloro substituent to pyrazinone. We attempted to prepare dithiol **6a** by the following route: nucleophilic substitution of the reactive chlorine atoms in **6a** by thiourea obtaining the 2,3-diisothiuronium salt **8** with its subsequent hydrolysis by sodium hydroxide according to the method recently proposed for 2,3-dichloropyrazine[16] and 2,3-dichloroquinoxaline.[17] However, treatment of 5,6-dichloro[1,2,5]oxadiazolo[3,4-*b*]pyrazine **7** with thiourea in ethanol led to formation of a product which decomposed due to alkali conditions.

Another methodology for the synthesis of disulfenyl dichlorides proposed by Rawson[18] includes reaction of *ortho*-dichloroderivatives with "Less' reagent" (Bu^tSNa) resulting in the formation of stable dithiolate derivatives, such as **6c**. Large size of the *tert*-butyl group allows the thiolate to be readily deprotected by chlorination with chlorine at 0 °C to generate the desired disulfenyl dichlorides in high yields. Treatment of a substituted dichlorooxadiazolopiperazine **7** with two equivalents of Bu^tSNa in THF at -10 °C yielded the corresponding bis(*tert*-butylthio) derivative **6c** in 87% yield (Scheme 2).



Scheme 2. Synthesis of 5,6-bis(*tert*-butylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine **6c**.

Dithiolate **6c** was found inert towards sulfuryl chloride, starting material was isolated from the reaction mixture in practically quantitative yield. Chlorination of dithiolate **6c** with chlorine in dichloromethane led to mixtures of sulfenylchlorides **9-11**. Our attempts to isolate pure sulfenylchlorides from these mixtures were unsuccessful which was not surprising bearing in mind that normally aromatic and heteroaromatic disulfenyl dichlorides are unstable, and used in further reactions *in situ* (see [2] and references therein. In order to investigate this reaction in more detail, we treated the chlorinated mixtures with morpholine to get more stable *S*-morpholino derivatives, which were isolated by chromatography. Three *S*-morpholino derivatives **12-14** which derived from monochlorinated product **9**, disulfenyl dichloride **10** and mono-sulfenylchloride **11**, respectively, were obtained and their structures have been confirmed by elemental analysis, ^{1}H and ^{13}C NMR, IR spectroscopy and mass spectrometry. Our standard procedure was to pass a continuous chlorine stream through a solution of dithiolate **6c** (0.5 mmol) in dichloromethane (10 ml) at the temperature listed in Table 1 followed by evaporation of the reaction mixture at 0 °C and quenching of the residue solution in dichloromethane (10 ml) with morpholine (1 mmol) at 0 °C. The product yields were strongly dependent on the temperature and duration of chlorination of dithiolate **6c**. The reaction conditions and yields of morpholine derivatives **12-14** and the starting material **6c** are given in Table 1.



Scheme 3. Chlorination of 5,6-bis(*tert*-butylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine **6c**.

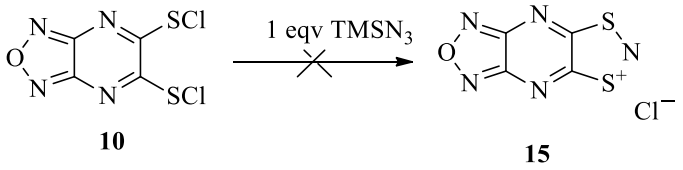
No chlorination occurs at 0-2 °C, and the starting **6c** was isolated from the reaction mixture virtually unchanged (entry 1). The reaction started at 5 °C, chlorination at 5-10 °C gave exclusively mono-chlorinated product **9** (entries 2 and 3), increasing the temperature to 12-15 °C led to reaction of the second *S*-Bu^{t} group, albeit slowly. For the formation of disulfenyl dichloride **10** chlorination at 15-17 °C is optimal: the yield of di(*S*-morpholino) adduct **13** is nearly quantitative (entry 6). Chlorination at higher temperatures (up to 20-25 °C) resulted in the substitution of one sulfenylchloride group by chlorine atom (entries 7 and 8; compound **11**). This reaction is not described in the literature, and it might be envisaged that chlorine attacks the

carbon atom of the pyrazine ring with displacement of sulfur dichloride (SCl_2). The structure of sulfenylchlorides **9-11** was also confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

Table 1. Reaction of dithiolate **6c** with chlorine with subsequent morpholine quenching

No.	Temperature of the reaction, °C	Time, min	Yields, %			
			12	**13**	**14**	**6c**
1	0-2	15	0	0	0	94
2	5-7	15	61	0	0	15
3	8-10	10	83	< 1	0	0
4	12-15	10	28	51	0	0
5	15-17	10	< 1	85	0	0
6	15-17	15	0	90	0	0
7	20-25	150	0	0	87	0
8	20-25	60	0	8	74	0
9	20-25	30	0	30	56	0
10	20-25	15	6	62	19	0

Treatment of disulfenyl dichloride **10** with 1 equivalent of trimethylsilylazide in chloroform or in acetonitrile at room temperature gave a mixture of unidentified compounds. The desired 1,3,2-dithiazolium salt **15** did not form in any of these reactions.



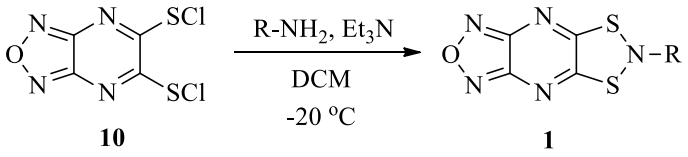
10 **15**

Scheme 4. Attempted synthesis of 1,3,2-dithiazolium salt **15**.

In order to obtain substituted [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines **1** a systematic study of the reactions between disulfenyl dichloride **10** with primary amines has been undertaken. Primary aromatic amines with electron withdrawing chloro or nitrogroups did not react with disulfenyl dichloride **10** in dichloromethane; starting amines were isolated from the reaction mixtures unchanged. Reaction with more basic aniline or 1-naphthylamine in dichloromethane even at low temperature (-10 °C) resulted in the decomposition of disulfenyl dichloride **10**.

Reaction of disulfenyl dichloride **10** with benzylamine in dichloromethane in the presence of 2 equivalents of triethylamine afforded a novel compound, as a yellow solid which according to the mass spectra, elemental analysis and ^1H and ^{13}C NMR data is 1,3,2-dithiazole **1a**. Disulfenyl

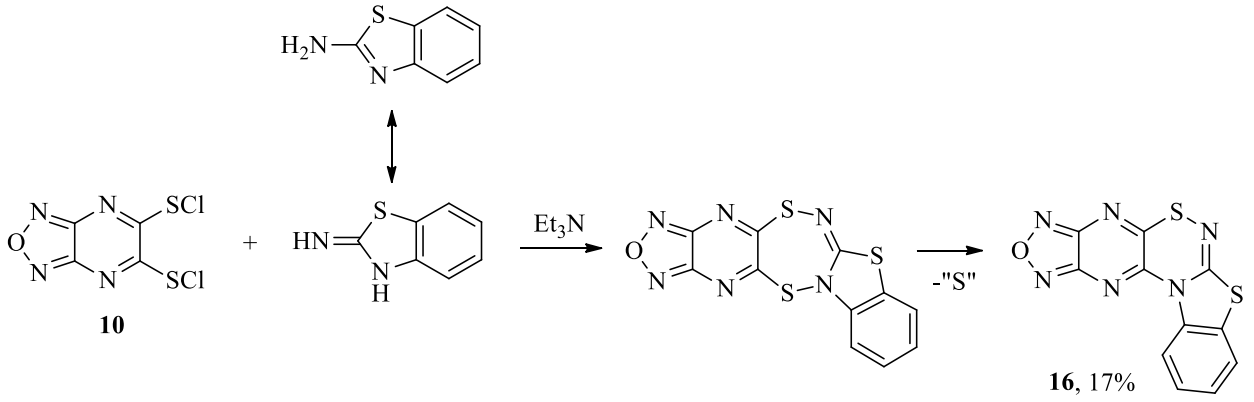
dichloride **10** reacted with other primary aliphatic amines in a similar manner giving the corresponding 1,3,2-dithiazoles **1** in moderate yields (Scheme 5).



1a, R = Bn	38%
b, R = Bu^n	26%
c, R = Pr^i	46%
d, R = Bu^t	55%
e, R = Cyclohexyl	40%
f, R = Allyl	35%

Scheme 5. Synthesis of substituted [1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines **1**.

Treatment of disulfenyl dichloride **10** with heterocyclic 2-aminobenzothiazole in the presence of triethylamine unexpectedly gave an orange solid in a low yield, to which structure **16** ($C_{11}H_4N_6OS_2$) was assigned (Scheme 6). According to the mass spectrometry, ^{13}C and ^1H NMR data, and elemental analysis it is formally a product of amine addition with elimination of sulfur and two HCl molecules. Finally its structure was confirmed by X-ray diffraction analysis (Figure 2).The formation of the previously unknown pentacyclic system **16** can be explained by addition of 2-aminobenzothiazole in its imino-form to disulfenyl dilchloride **10** with subsequent elimination of sulfur atom resulting in virtually planar and stable heterocyclic compound.



Scheme 6. Synthesis of [1,2,5]oxadiazolo[3",4":5',6']pyrazino[2',3':5,6][1,2,4]thiadiazino[3,4-*b*][1,3]benzothiazole **16**.

The pentacyclic structure **16** was confirmed by X-ray diffraction analysis. According to the XRD data, the molecule of **16** is almost flat with the mean deviation of the atoms from its plane not exceeding 0.025Å. The bond length distribution for each of the heterocycles is in the range of the expected values (Figure 2). The flat conformation of the whole molecule can be stabilized by either intra- or intermolecular interactions. Indeed, flattering of the pentacyclic compound is accompanied by the shortening of the C(17)-H(17)….N(6) contact (C…N 2.799(4), H…N 2.22

Å, CHN 111°). On the other hand, the molecules in the crystal of **16** are arranged in columns in the "head to tail" manner; the formation of the shortened C…C contacts (C(7)…C(20), C(16)…C(16), C(11)…C(18)) with the interatomic distances varying in the range of 3.28-3.34Å unambiguously indicate the presence of a significant overlap of the corresponding heterocyclic moieties.

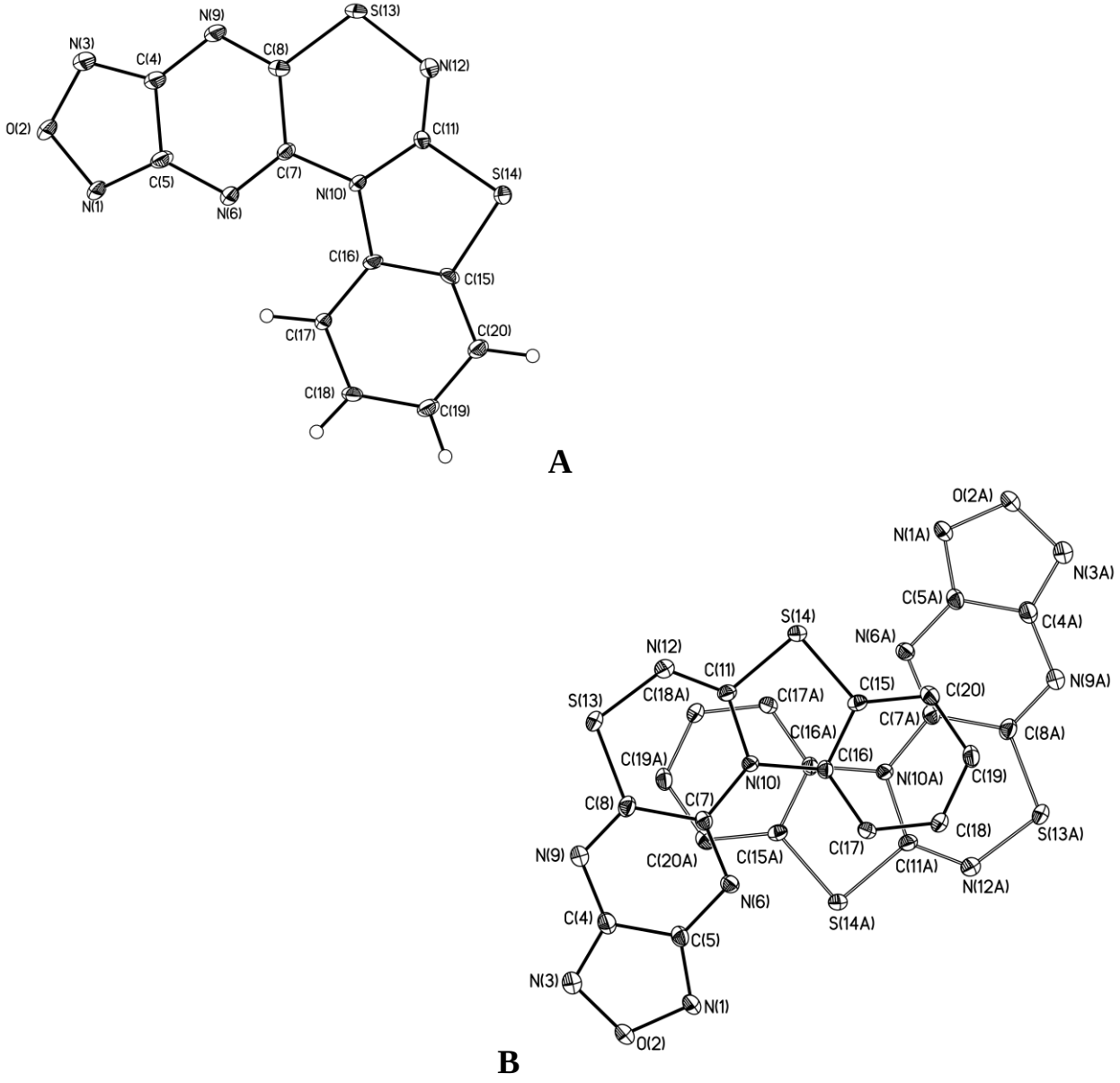


Figure 2. The general view **A** and the fragment illustrating the stacking interactions **B** in the crystal of **16** in representation of atoms by thermal ellipsoids (p=50%). The main bond lengths (Å): N(1)-C(5) 1.307(3), N(1)-O(2) 1.396(2), O(2)-N(3) 1.396(2), N(3)-C(4) 1.312(3), C(4)-N(9) 1.369(3) C(4)-C(5), 1.413(3) C(5)-N(6) 1.371(2), N(6)-C(7) 1.297(2), C(7)-N(10) 1.395(2), C(7)-C(8) 1.485(3), C(8)-N(9) 1.305(3), C(8)-S(13) 1.727(2), N(10)-C(11) 1.410(2), N(10)-

C(16) 1.427(2), C(11)-N(12) 1.276(3), C(11)-S(14) 1.746(2), N(12)-S(13) 1.6595(18), S(14)-C(15) 1.7403(19), C(15)-C(20) 1.386(3).

To estimate the role of the above inter- and intramolecular interactions in the stabilization of the planar conformation of **16**, we have performed the DFT calculation (M06-2X/6-311G**) of an isolated molecule. The optimized geometry was nearly the same as that in the solid state (see SI) . After the geometry optimization, the molecule **16** was found to be slightly non-planar and bent along the N(10)-C(11) bond – the dihedral angle between the two corresponding heterocyclic moieties is equal to 5.5^{o}. Despite this bending, the intramolecular contact is characterized by almost the same geometric parameters as those in a crystal (C…N 2.813, H…N 2.19 Å, CHN 114^{o}). Thus, the main contribution to the pentacycle flattering is the stacking interaction that is characterized by the maximum overlap between the fragments that are linked by the N(10)-C(11) bond.

In order to prepare *S*-oxides of 1,3,2-dithiazoles compounds **1** were treated with m-chloroperoxybenzoic acid in chloroform. No reaction occurred at room temperature but reflux of dithiazoles **1** in chloroform resulted in their slow decomposition and no *S*-oxides were detected in the reaction mixture.

Conclusions

Heterocyclic fused 1,3,2-dithiazoles were prepared from the reaction of [1,2,5]oxadiazolo[3,4-*b*]pyrazine-5,6-disulfenyl dichloride and primary aliphatic amines and benzylamine. Under the same conditions reaction with 2-aminobenzothiazole unexpectedly afforded a new pentacyclic oxadiazolopyrazinothiadiazinobenzothiazole. For the selective synthesis of this disulfenyl dichloride from the corresponding bis(*tert*-butylthio) derivative a careful control of the reaction temperature is required; reaction at lower temperatures led to mono-sulfenyl chloride, while at higher temperatures sulfenyl chloride group is substituted by a chlorine atom.

Experimental Section

General. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Specord M-80 instrument in KBr pellets. ^{1}H NMR were recorded on a Bruker WM 250 spectrometer (250 MHz) and ^{13}C NMR spectra were recorded on a Bruker AM 300 (75.5 MHz). *J* values are given in hertz. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument using electron impact ionization. Elemental analyses were performed on Perkin Elmer 2400 Elemental Analyser. 2-Methyl-2 propanethiol, sodium hydride, morpholine, benzylamine, allylamine, cyclohexylamine, *iso*-propylamine, *tert*-butylamine and 2-aminobenzothiazole were purchased from Acros and used without

purification. 5,6-Dichloro[1,2,5]oxadiazolo[3,4-*b*]pyrazine **7** was prepared as previously reported.[15]

5,6-Bis(*tert*-butylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine (6c). A solution of 5,6-dichloro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine **7** (745 mg, 3.901 mmol) in THF (20 mL) was added at -20 °C to a suspension of sodium *tert*-butylsulfide in THF (30 mL) obtained from 2-methyl-2 propanethiol (704 mg, 7.8 mmol) and sodium hydride (187 mg, 7.8 mmol). After 15 min of stirring at -10 ÷ -5 °C, the reaction mixture was poured into water (350 mL) and extracted with dichloromethane (100 ml). The organic phase was washed with water (3x50 mL) and dried over $MgSO_4$. After filtration solvents were evaporated under reduced pressure, and the residue was separated by column chromatography (Silica gel Merck 60, eluent-CH_2Cl_2). Yellow solid, yield 1.011 g, 87%, mp 194 - 197 ºC (dec). IR (ν_{max}, cm^{-1}): 2920 (C-H), 1616 (C=N). ^1H NMR ($CDCl_3$): δ 1.71 (s, 18H, 6×CH_3). ^{13}C NMR ($CDCl_3$): δ 29.5, 52.7, 149.3, 166.9. MS, *m/z* (%): 298 (M^+, 10), 242 (20), 186 (80), 156 (25), 57 (100), 41 (40). Anal. Calcd for $C_{12}H_{18}N_4OS_2$: C, 48.30; H, 6.08; N, 18.77. Found: C, 48.20; H, 6.11; N, 18.69.

General procedure for chlorination of 5,6-bis(*tert*-butylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine (6c)

A continuous chlorine stream was passed through a solution of dithiolate **6c** (149 mg, 0.5 mmol) in dichloromethane (10 ml) at the temperature and for a time indicated in Table 1. The solvent, excess of chlorine and 2-chloro-2-methylpropane were evaporated under reduced pressure at 0 °C.

6-(*tert*-Butylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine-5-sulfenyl chloride (9). Yellow oil. ^1H NMR ($CDCl_3$): *δ* 1.77 (s, 9H, 3×CH_3). ^{13}C NMR ($CDCl_3$): δ 30.2, 56.9, 150.2, 150.8, 162.3, 164.3. MS, *m/z* (%): 278 (M^+, 6), 276 (M^+, 15), 241 (65), 184 (40), 154 (25), 140 (10), 102 (50), 70 (100), 44 (100), 35 (55).

[1,2,5]Oxadiazolo[3,4-*b*]pyrazine-5,6-disulfenyl dichloride (10). Yellow oil. ^{13}C NMR ($CDCl_3$): δ 151.2, 159.6. MS, *m/z* (%): 258 (M^+, 10), 256 (M^+, 16), 254 (M^+, 95), 219 (85), 184 (35), 154 (20), 140 (15), 102 (50), 70 (85), 44 (100), 35 (65).

6-Chloro[1,2,5]oxadiazolo[3,4-*b*]pyrazine-5-sulfenyl chloride (11). Yellow oil. ^{13}C NMR ($CDCl_3$): *δ* 149.5, 150.8, 151.1, 163.3.

General procedure for reaction of sulfenyl chlorides with morpholine

A sulfenyl chloride obtained by the method described above was dissolved in dichloromethane (10 mL) and added dropwise at -10 °C to a solution of morpholine (1 mmol) in dichloromethane (10 ml). The reaction mixture was stirred for 15 min at -10 °C and 1 h at room temperature, the organic phase was washed with water (10 mL) and dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel Merck 60, light petroleum, and then light petroleum-CH_2Cl_2 mixtures).

5-(*tert*-Butylthio)-6-(morpholin-4-ylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine (12). Yellow solid, mp 95-97 ºC. IR (ν_{max}, cm^{-1}): 2960, 2924, 2857 (C-H), 1530 (C=N). ^1H NMR ($CDCl_3$): δ 1.73 (s, 9H, 3×CH_3), 3.59 (br s, 4H, 2×CH_2), 3.76 (t, *J* = 4.0 Hz, 4H, 2×CH_2). ^{13}C NMR ($CDCl_3$): δ 29.8, 53.6, 53.7, 67.8, 149.5, 150.2, 164.5, 171.7. MS, *m/z* (%): 327 (M^+, 20), 186 (25), 156 (15), 86 (100), 57 (45), 41 (20). Anal. Calcd for $C_{12}H_{17}N_5O_2S_2$: C, 44.02; H, 5.23; N, 21.39. Found: C, 44.15; H, 5.11; N, 21.23.

5,6-Bis(morpholin-4-ylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine (13). Yellow solid, mp 167-169 ºC (dec). IR (ν_{max}, cm^{-1}): 2956, 2904, 2856 (C-H). ^1H NMR ($CDCl_3$): δ 3.60 (br s, 8H, 4×CH_2), 3.76 (t, *J* = 4.4 Hz, 8H, 4×CH_2). ^{13}C NMR ($CDCl_3$): δ 54.0, 67.8, 150.1, 169.4. MS, *m/z* (%): 356 (M^+, 10), 271 (5), 186 (10), 156 (5), 86 (100), 56 (40), 41 (20). Anal. Calcd for $C_{12}H_{16}N_6O_3S_2$: C, 40.44; H, 4.52; N, 23.58. Found: C, 44.30; H, 4.57; N, 23.52.

5-(Morpholin-4-yl)-6-(morpholin-4-ylthio)[1,2,5]oxadiazolo[3,4-*b*]pyrazine (14). Yellow solid, mp 126-128 ºC. IR (ν_{max}, cm^{-1}): 2957, 2918, 2856 (C-H), 1537 (C=N). ^1H NMR ($CDCl_3$): δ 3.64 (t, *J* = 5.1 Hz, 4H, 2×CH_2), 3.75 (br s, 4H, 2×CH_2), 3.85 (t, *J* = 4.4 Hz, 8H, 4×CH_2). ^{13}C NMR ($CDCl_3$): δ 49.9, 53.9, 66.3, 67.8, 149.3, 150.8, 155.1, 169.7. MS, *m/z* (%): 324 (M^+, 10), 239 (50), 209 (15), 86 (100), 56 (40), 41 (25). Anal. Calcd for $C_{12}H_{16}N_6O_3S$: C, 44.43; H, 4.97; N, 25.91. Found: C, 44.28; H, 4.85; N, 25.93.

General procedure for reaction of disulfenyl dichloride (10) with primary amines

A solution of triethylamine (0.10 g, 1 mmol) in dichloromethane (2 mL) and primary amine (0.5 mmol) in dichloromethane (2 mL) were added successively at -40 ÷ -35 °C to a solution of disulfenyl dichloride **10** obtained from dithiolate **6c** (149 mg, 0.5 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 1 h at this temperature and 1 h at room temperature. Solvents were evaporated under reduced pressure and the residue was separated by column chromatography (Silica gel Merck 60, light petroleum, and then light petroleum-CH_2Cl_2 mixtures).

6-Benzyl[1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine (1a). Yellow solid, mp 111-112 ºC, yield 55 mg, 38%. IR (ν_{max}, cm^{-1}): 3106, 3064, 3034, 2957, 2922, 2853 (C-H), 1561 (C=N). ^1H NMR ($CDCl_3$): δ 4.36 (s, 2H, CH_2), 7.39 (m, 5H, 5×ArH). ^{13}C NMR ($CDCl_3$): δ 72.7, 128.8, 129.7, 131.1, 132.6, 150.1, 171.7. MS, *m/z* (%): 289 (M^+, 10), 258 (5), 211 (5), 102 (20), 91 (100), 57 (50), 43 (20). Anal. Calcd for $C_{11}H_7N_5OS_2$: C, 45.66; H, 2.44; N, 24.20. Found: C, 45.60; H, 2.35; N, 24.05.

6-Butyl[1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine (1b). Yellow solid, mp 95-96 ºC, yield 33 mg, 26%. IR (ν_{max}, cm^{-1}): 2958, 2931, 2865 (C-H). ^1H NMR ($CDCl_3$): δ 0.95 (t, *J* = 7.3 Hz, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.71 (t, *J* 7.3 Hz, 2H, CH_2), 3.29 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 13.8, 19.6, 30.7, 71.1, 150.3, 171.8. MS, *m/z* (%): 255 (M^+, 90), 212 (35), 199 (55), 169 (100), 111 (10), 102 (40), 84 (55), 70 (100), 46 (20). Anal. Calcd for $C_8H_9N_5OS_2$: C, 37.63; H, 3.55; N, 27.43. Found: C, 37.55; H, 3.57; N, 27.32.

6-Isopropyl[1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine (1c). Yellow solid, mp 104-105 ºC, yield 55 mg, 46%. IR (ν_{max}, cm^{-1}): 2979, 2924, 2886, 2853 (C-H). ^1H NMR

($CDCl_3$): δ 1.28 (d, *J* 6.4 Hz, 6H, 2 CH_3), 3.45 (sept, *J* 6.4 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 19.3, 67.6, 150.3, 172.9. MS, *m/z* (%): 241 (M^+, 20), 199 (100), 169 (55), 111 (10), 102 (15), 76 (55), 70 (45), 43 (70). Anal. Calcd for $C_7H_7N_5OS_2$: C, 34.84; H, 2.92; N, 29.02. Found: C, 34.79; H, 2.88; N, 29.10.

6-*tert*-Butyl[1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine (1d). Yellow solid, mp 149-150 ºC, yield 70 mg, 55%. IR (ν_{max}, cm^{-1}): 2975, 2929, 2856 (C-H). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9H, 3×CH_3). ^{13}C NMR ($CDCl_3$): δ 25.9, 68.8, 150.3, 173.5. MS, *m/z* (%): 255 (M^+, 45), 199 (95), 169 (50), 102 (35), 88 (30), 83 (55), 77 (80), 70 (100), 52 (50), 46 (45). Anal. Calcd for $C_8H_9N_5OS_2$: C, 37.63; H, 3.55; N, 27.43. Found: C, 37.55; H, 3.62; N, 27.37.

6-Cyclohexyl[1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine (1e). Yellow solid, mp 159-160 ºC, yield 57 mg, 40%. IR (ν_{max}, cm^{-1}): 2955, 2928, 2851 (C-H), 1563 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.28 (m, 5H, CH_2), 1.66 (m, 1H, CH), 1.85 (m, 2H, CH_2), 2. 07 (m, 2H, CH_2), 3.01 (m, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 25.0, 25.2, 29.9, 74.9, 150.3, 173.0. MS, *m/z* (%): 281 (M^+,100), 260 (25), 199 (100), 169 (50), 149 (15), 125 (55), 82 (80), 70 (40), 56 (70), 45 (20). Anal. Calcd for $C_{10}H_{11}N_5OS_2$: C, 42.69; H, 3.94; N, 24.89. Found: C, 42.60; H, 3.72; N, 24.91.

6-Allyl[1,3,2]dithiazolo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine (1f). Yellow solid, mp 108-110 ºC, yield 42 mg, 35%. IR (ν_{max}, cm^{-1}): 2921, 2851 (C-H), 1562 (C=N). ^{1}H NMR ($CDCl_3$): δ 3.84 (d, *J* 6.6 Hz, 2H, CH_2), 5.43 (m, 2H, CH_2), 5.92 (m, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 71.8, 124.8, 129.9, 150.3, 171.9. MS, *m/z* (%): 239 (M^+, 55), 209 (75), 198 (70), 168 (30), 139 (55), 111 (10), 102 (5), 83 (25), 70 (100), 57 (60), 43 (15). Anal. Calcd for $C_7H_5N_5OS_2$: C, 35.14; H, 2.11; N, 29.27. Found: C, 35.10; H, 2.13; N, 29.20.

[1,2,5]Oxadiazolo[3'',4'':5',6']pyrazino[2',3':5,6][1,2,4]thiadiazino[3,4-*b*][1,3]benzothiazole (16). Orange solid, mp 203-205 ºC (dec), yield 26 mg, 17%. ^{1}H NMR (DMSO-d_6 in the presence of CF_3COOH): *δ* 7.49 (m, 2H, 2×ArH), 7.79 (d, *J* = 8.1 Hz, 1H, CH), 8.86 (d, *J* = 8.1 Hz, 1H, CH). ^{13}C NMR (DMSO-d_6 + CF_3COOH): *δ* 120.2, 122.6, 124.0, 127.0, 127.3, 135.2, 147.9, 150.6, 151.3, 158.1, 158.6. MS, *m/z* (%): 300 (M^+, 50), 270 (90), 238 (15), 218 (30), 200 (30), 160 (40), 134 (25), 101 (100), 90 (90), 82 (30), 70 (65), 55 (40), 45 (45). Anal. Calcd for $C_{11}H_4N_6OS_2$: C, 43.99; H, 1.34; N, 27.98. Found: C, 43.75; H, 1.25; N, 28.04.

Crystals of **16** ($C_{11}H_4N_6OS_2$, M= 300.32) are monoclinic, space group $P2_1/c$, at 100 K: *a* = 11.1014(16), *b* = 15.127(2), *c* = 6.637(1) Å, *β* = 93.546(3)°, V = 1112.4(3) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.793 g cm^{-3}, *μ*(Mo Kα) = 4.83 cm^{-1}, F(000) = 608. The intensities of 8611 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [*λ*(Mo Kα) = 0.71072 Å, ω-scans, 2*θ* < 58°], and 2945 independent reflections [R_{int} = 0.0364] were used in further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms were located from the Fourier synthesis of electron density and refined in the isotropic approximation. For **16,** the refinement converged to *wR*2 = 0.0955 and GOF = 1.033 for all independent reflections (*R*1 = 0.0399 was calculated against *F* for 2357 observed reflections with $I > 2\sigma(I)$). All calculations were performed with the SHELXTL software package.[19] CCDC 829170 contains the supplementary crystallographic data for **16**. These data can be obtained free

of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB21EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.ac.uk).
The DFT calculations of the isolated molecule of **16** was performed with the Gaussian09 program package[20] using the M06-2X functional. Full optimization of the geometry was carried starting from the X-ray structural data with the 6-311G** basis set for all atoms. The extremely tight threshold limits of $2 \cdot 10^{-6}$ and $6 \cdot 10^{-6}$ a.u. were applied for the maximum force and displacement, respectively.

Acknowledgements

We gratefully acknowledge financial support from the Russian Foundation for Basic Research (grant no. 08-03-00003). We also thank Professor F. S. Sirovski for helpful discussions.

References

1. (a) Khmelnitsky, L. I.; Rakitin O. A. in *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996, Vol. 2, Chapter 4.11, pp 433-452. (b) Rakitin O. A. in *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 6, Ch. 6.01, pp 1-36.
2. Hicks, R. G. In *Stable Radicals. Fundamentals and applied aspects of odd-electron compounds*. Hicks, R. G. Ed.; Wiley: Chichester, 2010; pp 317-380.
3. Allenmark, S.; Oxelbark, J. *Enantiomer* **1996**, *1*, 13.
4. Klein, L. L.; Yeung, C. M.; Weissing, D. E.; Lartey, P. A.; Tanaka, S. K.; Plattner, J. J.; Mulford, D. J. *J. Med. Chem*. **1994**, *37*, 572.
5. Wolmershäuser, G.; Kraft, G. *Chem. Ber*. **1989**, *122*, 385.
6. Neamati, N.; Deng, J. U. S. Patent, 0160313, 2010.
7. Baures, P. W.; James, D. R.; Gless, R. D.; Tran, T.; Verheij, H. J.; Schultz, J. C. C. WO Patent 044402, 2006.
8. Jeanette, H. C. WO Patent, 005403, 2007.
9. Dayam, R.; Aiello, F.; Deng, J.; Wu, Y.; Garofalo, A.; Chen, X.; Neamati, N. *J. Med. Chem*. **2006**, *49*, 4526.
10. Neamati, N.; Dayam, R. S. U. S. Patent, 0088420, 2009.
11. Deng, J.; Sanchez, T.; Al-Mawsawi, L. Q.; Dayam, R.; Yunes, R. A.; Garofalo, A.; Bolger, M. B.; Neamati, N. *Bioorg. Med. Chem*. **2007**, *15*, 4985.
12. Cheng, T.-J. R.; Wu, Y.-T.; Yang, S.-T.; Lo, K.-H.; Chen, S.-K.; Chen, Y.-H.; Huang, W.-I.; Yuan, C.-H.; Guo, C.-W.; Huang, L.-Y.; Chen, K.-T.; Shih, H.-W.; Cheng, Y.-S. E.; Cheng, W.-C.; Wong, C.-H. *Bioorg. Med. Chem*. **2010**, *18*, 8512.

13. Beebe, X.; Nilius, A. M.; Merta, P. J.; Soni, N. B.; Bui, M. H.; Wagner, R.; Beutel, B. A. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3133.
14. Barclay, T. M.; Cordes, A. W.; George, N. A.; Haddon, R. C.; Itkis, M. E.; Mashuta, M. S.; Oakley, R. T.; Patenaude, G. W.; Reed, R. W.; Richardson, J. F.; Zhang, H. *J. Am. Chem. Soc.* **1998**, *120*, 352.
15. Starchenkov, I. B.; Andrianov, V. G. *Chem. Heterocycl. Comp*. **1997**, *33*, 1219.
16. Brusso, J. L.; Clements, O. P.; Haddon, R. C.; Itkis, M. E.; Leitch, A. A.; Oakley, R. T.; Reed, R. W.; Richardson, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 8256.
17. Voloshin, Ya. Z.; Belov, A. S.; Lebedev, A. Yu.; Varzatskii, O. A.; Antipin, M. Yu.; Starikova, Z. A.; Kron, T. E. *Russ. Chem. Bull*. **2004**, *53*, 1218.
18. Alberola, A.; Collis, R. J.; Less, R. J.; Rawson, J. M. *J. Organomet. Chem.* **2007**, *692*, 2743.
19. Sheldrick, X. G. M. *Acta*. *Cryst.* **2008**, *A64*, 112.
20. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, *Revision *A.1**, Gaussian Inc., Wallingford (CT), 2009.

