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The Synthesis of *N*–Substituted *N,S*–Macroheterocycles Derived from Aromatic Carboxylic Acid Hydrazides

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A selective catalytic cyclothiomethylation method for the synthesis of N,S-macroheterocycles having N-amide substituents is elaborated via the reaction between aromatic carboxylic acid hydrazides, formaldehyde, and α,ω-dithiols possessing from 4 to 6 carbon atoms. Transition metal and rare earth metal salts are used as the catalysts.

Keywords: Cyclothiomethylation, *N,S*-macroheterocycles, aromatic carboxylic acid hydrazides, formaldehyde, α,ω-dithiols, catalysis.

Синтез *N*–замещенных *N,S*–макрогетероциклов на основе гидразидов арилкарбоновых кислот

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Разработан селективный способ синтеза S,N-макрогетероциклов с N-амидными заместителями циклотиометилированием гидразидов арилкарбоновых кислот с помощью CH_2O и α,ω-дитиолов (1,4-бутан-, 1,5-пентан-, 1,6-гександитиол). Реакция эффективно проходит в присутствии катализаторов на основе переходных и редкоземельных металлов.

Ключевые слова: Циклотиометилирование, *N,S*-макрогетероциклы, гидразиды арилкарбоновых кислот, формальдегид, α,ω-дитиолы, катализ.

Introduction

Five- and six-membered nitrogen- and sulfur-containing heterocyclic compounds having *N*-amide substituents are of interest due to their diuretic,[1–3] antiviral,[4] antitubercular,[1,5] antitumor,[6,7] and growth-stimulating[8] properties. Additionally, these compounds may hold promise as effective adsorbents and analytical reagents.[9]

The prospects for the use of heterocycles with *N*-amide substituents have stimulated studies of the cyclothiomethylation reaction between carboxylic hydrazides, formaldehyde and hydrogen sulfide. As a result, a new and convenient procedure to obtain *N*-substituted 1,3,5-dithiazinanes[10] has been elaborated. The replacement of gaseous H_2S by ethane-1,2-dithiol or propane-1,3-dithiol in the above reaction allowed derivatization of carboxylic hydrazides to afford *N*-substituted 1,5,3-dithiazepanes and *N*-substituted 1,5,3-dithiazocanes in the presence of Cu complex catalysts.[11]

Experimental

High resolution mass spectra of compounds **1b**, **2b**, **2c** and **4** ("dried droplet method") were recorded on a spectrometer "MALDI-TOF Autoflex III" (Bruker, Germany), with α-cyano-4-hydroxycinnamic acid as a matrix. Compounds **1c**, **2a**, **3a–c** were analyzed by electrospray ionization (ESI) mass spectrometry

on a Shimadzu LCMS-2010 EV instrument of the Center of Collective Use "Chemistry" of the Institute of Organic Chemistry, Ufa Scientific Center of RAS; the temperature of the heating source was 200 °C, the temperature of the vaporizer was 250 °C; nitrogen that was produced by an NM18L ultra-high purity nitrogen generator was used as the nebulizing gas; the liquid flow rate was 0.05 mL·min^{-1}, the nebulizing gas flow rate was 1.5 mL·min^{-1}; the ion source voltage was as follows: (+), 4.5 kV; (–), 3 kV. Infrared spectra (IR) were recorded using FT–IR spectrometer Bruker Vertex 70 v (vaseline oil). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer operating at 400.13 and 100.62 MHz, respectively, in DMSO-d_6 (δ_C, 39.50) and $CDCl_3$ (δ_C, 77.10).

General procedure. A round-bottomed flask equipped with a magnetic stirring bar was charged with formaldehyde (20 mmol) and an α,ω-dithiol (propane-1,3-dithiol, butane-1,4-dithiol, pentane-1,5-dithiol or hexane-1,6-dithiol) (10 mmol). The mixture was stirred at 20 °C for 0.5 h. Then, the $SmCl_3 \cdot 6H_2O$ catalyst (0.5 mmol) and appropriate hydrazide (10 mmol) in EtOH (3 mL) were added. The mixture was stirred for an additional 48 h at 80 °C. The mixture was extracted with $CHCl_3$ (3×20 mL) and the products were isolated by column chromatography on silica gel (SiO_2) with hexane-acetone (1:1) as eluent. The final products **1b,c** and **2,3a–c** were identified by spectral methods.

*3-Methoxy-N-{12-[(3-methoxybenzoyl)amino]-1,5,10,14-tetrathia-3,12-diazacyclooctadecan-3-yl}benzamide (**1b**).* Yield 0.18 g (57 %), m.p. 183–185 ºC, R_f 0.21 (hexane:acetone, 1:1). (MALDI TOF) found 647.178 $C_{28}H_{40}N_4NaS_4O_4$ requires 647.183 $[M+Na]^+$. IR ν cm^{-1}: 3225 (N-H); 2854–2924 (C-H); 1646 (C-H); 1587, 1547, 1463 (C=C, N-H); 1377, 1246 (C-N); 1037 (C-O); 688 (C-S). ^{1}H NMR (DMSO–d_6) δ ppm: 1.70 (8H, br s, CH_2); 2.74 (8H, br s, CH_2); 3.80 (6H, s, Me), 4.11 (8H, br s, CH_2); 7.10 (2H, s, Ar); 7.30–7.40 (6H, m, Ar); 9.52 (2H, s, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 29.2 (4C); 29.7 (4C); 55.7 (2C); 56.6 (4C); 113.0 (2C); 117.0 (2C); 120.0 (2C); 129.8 (2C); 135.6 (2C); 159.6 (2C); 165.8 (2C).

*4-Methoxy-N-{12-[(4-methoxybenzoyl)amino]-1,5,10,14-tetrathia-3,12-diazacyclooctadecan-3-yl}benzamide (**1c**).* Yield 0.15 g (48 %), n_D^{20} 1.6045, R_f 0.23 (hexane:acetone, 1:1). *m/z* (ESI) (%) 647 (100) $[M+Na]^+$, 623 (20) $[M–H]^-$. IR ν cm^{-1}: 3220 (N-H); 2853–2924 (C-H); 1645 (C-H); 1587, 1542, 1467 (C=C, N-H); 1376, 1243 (C-N); 1034 (C-O); 685 (C-S). ^{1}H NMR (DMSO-d_6) δ ppm: 1.43 (8H, br s, CH_2); 2.30 (8H, br s, CH_2); 3.59 (6H, s, Me), 3.94 (8H, br s, CH_2); 6.77 (4H, m, Ar); 7.57 (4H, m, Ar); 9.21 (2H, s, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 30.1 (4C); 30.6 (4C); 56.8 (2C); 58.5 (4C); 114.9 (4C); 127.2 (2C); 130.7 (4C); 163.1 (2C); 166.0 (2C).

*2-Methoxy-N-{13-[(2-methoxybenzoyl)amino]-1,5,11,15-tetrathia-3,13-diazacycloicosan-3-yl}benzamide (**2a**).* Yield 0.05 g (15 %), n_D^{20} 1.6204, R_f 0.12 (hexane:acetone, 1:1). *m/z* (ESI) (%) 675 (100) $[M+Na]^+$. IR ν cm^{-1}: 3340 (N-H); 2840–2900 (C-H); 1640 (C-H); 1595, 1540, 1440 (C=C, N-H); 1372, 1265 (C-N); 1001 (C-O); 745 (C-S). ^{1}H NMR ($CDCl_3$) δ ppm: 1.33 (4H, m, CH_2); 1.60 (8H, m, CH_2); 2.73 (8H, m, CH_2); 3.86 (6H, s, Me); 4.31 (8H, m, CH_2); 6.99 (2H, m, Ar); 7.09 (2H, m, Ar); 7.46 (2H, m, Ar); 8.18 (2H, m, Ar); 9.37 (2H, s, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.9 (2C); 29.5 (4C); 32.6 (4C); 56.3 (2C); 58.7 (4C); 111.5 (2C); 120.6 (2C); 121.4 (2C); 132.4 (2C); 133.2 (2C); 157.3 (2C); 163.6 (2C).

*3-Methoxy-N-{13-[(3-methoxybenzoyl)amino]-1,5,11,15-tetrathia-3,13-diazacycloicosan-3-yl}benzamide (**2b**).* Yield 0.12 g (35 %), n_D^{20} 1.6043, R_f 0.20 (hexane:acetone, 1:1). (MALDI TOF) found 675.949 $C_{30}H_{44}N_4NaS_4O_4$ requires 675.192 $[M+Na]^+$. IR ν cm^{-1}: 3286 (N-H); 2854–2929 (C-H); 1660 (C-H); 1586, 1458 (C=C, N-H); 1290, 1238 (C-N); 1040 (C-O); 688 (C-S). ^{1}H NMR ($CDCl_3$) δ ppm: 1.50 (4H, br s, CH_2); 1.51–1.70 (8H, m, CH_2); 2.60–2.80 (8H, m, CH_2); 3.86 (6H, s, Me), 4.20–4.38 (8H, m, CH_2); 7.05 (2H, s, Ar); 7.23–7.40 (6H, m, Ar); 7.68 (2H, s, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.3, 27.4 (2C); 29.3 (4C); 32.3 (4C); 55.5 (2C); 58.2, 58.8, 59.1 (4C); 112.5, 112.7 (2C); 118.0, 118.3 (2C); 119.4 (2C); 129.1, 130.2 (2C); 134.5, 135.3 (2C); 154.6 (2C); 160.5 (2C). ^{1}H NMR (DMSO-d_6) δ ppm: 1.23-1.38 (4H, br s, CH_2); 1.53–1.63 (8H, m, CH_2); 2.56–2.74 (8H, m, CH_2); 3.80 (6H, s, Me), 4.14 (8H, br s, CH_2); 7.05 (2H, s, Ar); 7.23–7.40 (6H, m, Ar); 7.68 (2H, s, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 28.3 (2C); 29.4 (4C); 30.9 (4C); 55.8 (2C); 57.4 (4C); 113.0 (2C); 117.6 (2C), 120.0 (2C); 129.9 (2C); 135.4 (2C); 159.5 (2C).

*4-Methoxy-N-{13-[(2-methoxybenzoyl)amino]-1,5,11,15-tetrathia-3,13-diazacycloicosan-3-yl}benzamide (**2c**).* Yield 0.08 g (25%), m.p. 105–107 ºC, R_f 0.11 (hexane:acetone, 1:1). (MALDI TOF) found 675.949 $C_{30}H_{44}N_4NaS_4O_4$ 675.237 $[M+Na]^+$. IR ν cm^{-1}: 3340 (N-H); 2850–2900 (C-H); 1648 (C-H); 1590, 1440 (C=C, N-H); 1370, 1255 (C-N); 1000 (C-O); 744 (C-S). ^{1}H NMR (DMSO-d_6) δ ppm: 1.25 (4H, m, CH_2); 1.40 (8H, m, CH_2); 2.50 (8H, m, CH_2); 3.60 (6H, s, Me); 3.90 (8H, m, CH_2); 6.99 (2H, d, J = 8.8 Hz, Ar); 7.82 (2H, d, J = 8.8 Hz, Ar); 9.48 (2H, s, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 30.1 (2C); 30.4 (4C); 30.7 (4C); 56.8 (2C); 57.6 (4C); 113.9 (4C); 126.3 (2C); 129.6 (4C); 162.1 (2C); 163.1 (2C).

*2-Methoxy-N-{14-[(2-methoxybenzoyl)amino]-1,5,12,16-tetrathia-3,14-diazacyclodocosan-3-yl}benzamide (**3a**).* Yield 0.04 g (12%), n_D^{20} 1.6232, R_f 0.10 (hexane:acetone, 1:1). *m/z* (ESI) (%) 703 (100) $[M+Na]^+$. IR ν cm^{-1}: 3335 (N-H); 2848–2905 (C-H); 1640 (C-H); 1600, 1445 (C=C, N-H); 1370, 1260 (C-N); 1005 (C-O); 745 (C-S). ^{1}H NMR ($CDCl_3$) δ ppm: 1.35 (8H, m, CH_2); 1.59 (8H, m, CH_2); 2.68 (8H, m, CH_2); 3.99 (6H, s, Me); 4.25 (8H, br s, CH_2); 6.98 (2H, m, Ar); 7.07 (2H, m, Ar); 7.45 (2H, m, Ar); 8.18 (2H, m, Ar); 9.36 (2H, s, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 28.4 (4C); 29.9 (4C); 32.7 (4C); 56.2 (2C); 58.7 (4C); 111.4 (2C); 120.6 (2C); 121.4 (2C); 132.4 (2C); 133.1 (2C); 157.3 (2C); 163.6 (2C).

*2-Methoxy-N-{14-[(2-methoxybenzoyl)amino]-1,5,12,16-tetrathia-3,14-diazacyclodocosan-3-yl}benzamide (**3b**).* Yield 0.04 g (12%), n_D^{20} 1.6232, R_f 0.10 (hexane:acetone, 1:1). *m/z* (ESI) (%) 703 (100) $[M+Na]^+$. IR ν cm^{-1}: 3335 (N-H); 2848–2905 (C-H); 1640 (C-H); 1600, 1445 (C=C, N-H); 1370, 1260 (C-N); 1005 (C-O); 745 (C-S). ^{1}H NMR ($CDCl_3$) δ ppm: 1.35 (8H, m, CH_2); 1.59 (8H, m, CH_2); 2.68 (8H, m, CH_2); 3.99 (6H, s, Me); 4.25 (8H, br s, CH_2); 6.98 (2H, m, Ar); 7.07 (2H, m, Ar); 7.45 (2H, m, Ar); 8.18 (2H, m, Ar); 9.36 (2H, s, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 28.4 (4C); 29.9 (4C); 32.7 (4C); 56.2 (2C); 58.7 $W_{1/2}$ =12.7 Hz (4C); 111.4 (2C); 120.6 (2C); 121.4 (2C); 132.4 (2C); 133.1 (2C); 157.3 (2C); 163.6 (2C).

*4-Methoxy-N-{14-[(2-methoxybenzoyl)amino]-1,5,12,16-tetrathia-3,14-diazacyclodocosan-3-yl}benzamide (**3c**).* Yield 0.05 g (15%), m.p. 102–104 ºC, R_f 0.10 (hexane:acetone, 1:1). *m/z* (ESI) (%) 703 (100) $[M+Na]^+$, 679 (20) $[M–H]^-$. IR ν cm^{-1}: 3330 (N-H); 2905–2833 (C-H); 1640 (C-H); 1605, 1448 (C=C, N-H); 1370, 1259 (C-N); 1005 (C-O); 740 (C-S). ^{1}H NMR ($CDCl_3$) δ ppm: 1.40 (8H, m, CH_2); 1.62 (8H, m, CH_2); 2.69 (8H, m, CH_2); 3.86 (6H, s, Me); 4.26 (8H, br. s, CH_2); 6.94 (4H, m, J = 8.4 Hz, Ar); 7.69 (2H, s, NH); 7.76 (4H, m, J = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ ppm: 29.2 (4C); 30.0 (4C); 33.7 (4C); 56.5 (2C); 60.1 (4C); 114.9 (4C); 130.0 (4C); 163.6 (2C); 166.4 (2C).

*1,8-Bis-hydroxymethyl-2,7-dithiooctane (**4**).* (MALDI TOF) found 182.306 $C_6H_{14}O_2S_2$ 181.519 $[M–H]^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 1.70 (4H, m, CH_2); 2.65 (4H, m, CH_2); 4.70 (4H, s, CH_2). ^{13}C NMR ($CDCl_3$) δ ppm: 28.5 (2C); 31.5 (2C); 66.8 (2C).

Results and Discussion

We herein report our progress in the catalytic derivatization of carboxylic hydrazides with α,ω-dithiols and formaldehyde using rare-earth or transition metal salts as catalysts.[10–14]

Butane-1,4-dithiol, pentane-1,5-dithiol and hexane-1,6-dithiols were selected as the substrates for this study.

We found that the reaction between hydrazides of isonicotinic, nicotinic and 2-methoxybenzoic acids, formaldehyde and butane-1,4-dithiol at 80 °C, in ethanol over 48 hours in the presence of $CuCl_2 \cdot 2H_2O$ as the catalyst (hydrazide:CH_2O:dithiol:$CuCl_2 \cdot 2H_2O$ = 10:20:10:0.5) afforded

the corresponding *N*-(1,5,3-dithiazonan-3-yl)amides in the yields, which did not exceed 15 %.

Further experiments revealed that the reaction of the hydrazide of 3-methoxybenzoic acid with butane-1,4-dithiol and formaldehyde under the same conditions gave macroheterocycles **1b** in 27 % yield. To select the most efficient catalyst in order to obtain the highest yield, we performed screening of various *d*- and *f*-element catalysts, such as $Sm(NO_3)_3/\gamma\text{-}Al_2O_3$ (56 %), $SmCl_3 \cdot 6H_2O$ (57 %), $Sm(NO_3)_3 \cdot 6H_2O$ (51 %), YbF_3 (48 %), $EuCl_3 \cdot 6H_2O$ (34 %), and $FeCl_3 \cdot 6H_2O$ (26 %) in a mixed solvent ($EtOH/CHCl_3$ = 1:1) for 24 h; $Sm(NO_3)_3/\gamma\text{-}Al_2O_3$ and $SmCl_3 \cdot 6H_2O$ gave the highest yield of **1b.** Without a catalyst the heterocyclization reaction did not occur. Condensation of 4-methoxybenzoic acid hydrazide with butane-1,4-dithiol leds to the corresponding macroheterocycle **1c** in 48 % yield.

We next conducted an investigation of the synthesis of *N*,*S*-macroheterocycles with a larger number of carbon atoms in the ring by using pentane-1,5-dithiol and hexane-1,6-dithiol in the cyclothiomethylation reaction.

Thus, the reactions between the hydrazides of 2-, 3- or 4-methoxybenzoic acids and formaldehyde mediated by the $SmCl_3 \cdot 6H_2O$ or $Sm(NO_3)_3/\gamma\text{-}Al_2O_3$ catalysts in the presence of the above dithiols were found to afford selectively the corresponding macroheterocycles **2a–c** and **3a–c** in 12–35 % yields (Scheme 1).

The cyclothiomethylation reaction takes place exclusively at the primary amino group of the aromatic carboxylic acid hydrazide.

The structures of compounds **1b,c** and **2,3a–c** were proved by analysis of their mass and NMR spectral data.

Thus, the intense molecular ion peaks $[M+K]^+$ at *m/z* 663.156 and $[M+Na]^+$ at *m/z* 647.178 (calc 624.906 for $C_{28}H_{40}N_4O_4S_4$) in the MALDI TOF mass-spectrum provide evidence for the formation of compound **1b**, whereas the molecular ion peaks $[M+Na]^+$ at *m/z* 675.192 and 675.237 (calc 652.959 for $C_{30}H_{44}N_4O_4S_4$) confirm the structures assigned to **2b** and **2c**, respectively.

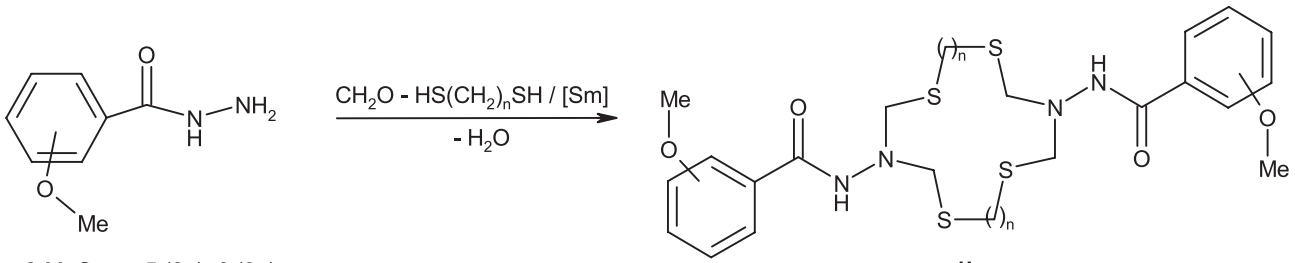
The molecular ion peaks in positive and negative ion electrospray ionization mass spectra recorded on a quadruple liquid chromatography-mass spectrometer (LCMS-2010 EV) were consistent with the structural features of the desired products **1b,c** and **2,3a–c**. Thus, the LCMS mass spectra contain molecular ion peaks at *m/z* $[M+Na]^+$ 675 for *ortho*-isomer **2a,** *meta*-isomer **2b** and *para*-isomer **2c** (ca. 652 for $C_{30}H_{44}N_4O_4S_4$), at *m/z* $[M+Na]^+$ 703 for *ortho*-isomer **3a,** *meta*-isomer **3b** and *para*-isomer **3c** (*ca*. 681 for $C_{32}H_{48}N_4O_4S_4$). They also exhibit molecular ion peaks at *m/z* $[M+2H_2O–H]^-$ 687, 715 and at *m/z* $[M–H]^-$ 651, 679, which provided evidence for the formation of **2,3b** and **2,3c**, respectively.

Our results demonstrate good agreement between mass spectrometric and NMR data. Detailed analysis of one-dimensional (^1H, ^{13}C NMR) and two-dimensional (COSY, HSQC, HMBC) spectra showed that for each compound, a specific set of signals was observed with the expected chemical shifts. Also, the ratio of their integral intensities in the ^1H NMR spectra were consistent with the proposed structures as well.

Thus, in the HSQC experiment, the ^1H and ^{13}C NMR spectra of **1b** recorded in DMSO-d_6, together with resonances ascribed to the *N*-amide substituent, three typical (for this 18-membered ring) broad singlet resonances were observed at δ_H 4.58, 2.63, and 1.69 ppm, which correlated with δ_C 56.62, 29.22 and 29.77 ppm, respectively, with an integral intensity ratios of 1:1:1 in the ^1H NMR spectra. Due to the symmetry of molecule **2a,** the carbon atoms and the hydrogen atoms in the N-CH_2-S and S-$(CH_2)_4$-S moieties were magnetically equivalent. Long-range interactions between the protons and carbons in the N-CH_2-S-$(CH_2)_4$-S fragment in the two-dimensional HMBC spectra provided evidence for the structure of macroheterocycle **1b.** Macroheterocycles **2,3a** as well as **2,3b** and **1–3c** were identified in a similar manner.

Only one set of signals in the NMR spectra for both *N*-substituents provides information on their magnetic equivalence, and the predominance of one of the two possible *Z* or *E* invertomers in the amide moiety of the substituent. Apparently, there is the lowest *Z* conformation according to the literature data[15] and our preliminary DFT analysis (PBE/3z, Priroda 6.0).[16]

It should be noted, that a slow conformational inversion of the macrocycle on the NMR time-scale in nonpolar solvent was observed in $CDCl_3$. The ^{13}C NMR spectra, obtained at ambient temperature, for macrocycles **2b** and **3b** (the smallest macrocycle **1b** was not soluble in chloroform) demonstrated the multiple splitting of the ring-carbon signals, especially those defining the N-CH_2-S-moiety. Apparently, this behavior is due to the relatively small size of macrocycles bearing bulky and conformationally rigid substituents at the nitrogen atom.



2-MeO: n = 5 (**2a**), 6 (**3a**);
3-MeO: n = 4 (**1b**), 5 (**2b**), 6 (**3b**);
4-MeO: n = 4 (**1c**), 5 (**2c**), 6 (**3c**).

[Sm] = $SmCl_3 \cdot 6H_2O$, $Sm(NO_3)_3/\gamma\text{-}Al_2O_3$

1b,c
2a-c
3a-c

Scheme 1.

While investigating the dithiazepinane system of compound **1b**, the averaged NMR spectral parameters due to the rapid inversion of heterocycle were observed. There are stereoelectronic interactions between the unshared electrons on the nitrogen and sulfur atoms (for instance, in the dithiazinane[17,18] and dithiazepinane[19] systems), that reduce the energy of the chair conformation and the chair-chair conformation, respectively. However, the macrocycle has a higher conformational mobility, so the number of possible conformations increases. For example, we have optimized the structure of the conformer corresponding to one of the local minima on the potential energy surface of the molecule (Figure 1).

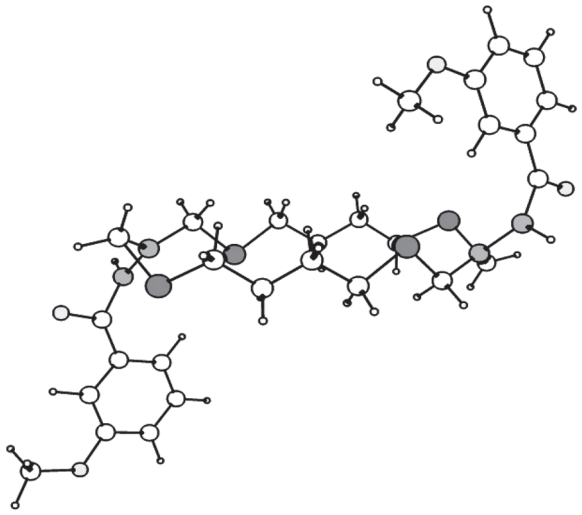


Figure 1. View of one of the stable conformations of compound **1b**.

The proposed catalytic cycle of the cyclothiomethylation reaction of carboxylic acid hydrazides[20–23] includes the activation of α,ω-diol **4** by lanthanide catalyst to form intermediate carbocations **5**. Sequential nucleophilic addition between carboxylic acid hydrazides and carbocations leads to the selective formation of macroheterocycles (Scheme 2).

Conclusions

In conclusion, we have developed a selective one-pot synthesis of *N*,*S*-macroheterocycles possessing amide substituents, via the cyclothiomethylation of 2-, 3- and 4-methoxybenzoic acid hydrazides with α,ω-dithiols (butane-1,4-dithiol, pentane-1,5-dithiol, hexane-1,6-dithiol) and formaldehyde mediated by $SmCl_3 \cdot 6H_2O$ and $Sm(NO_3)_3$/ γ-Al_2O_3 as the catalysts.

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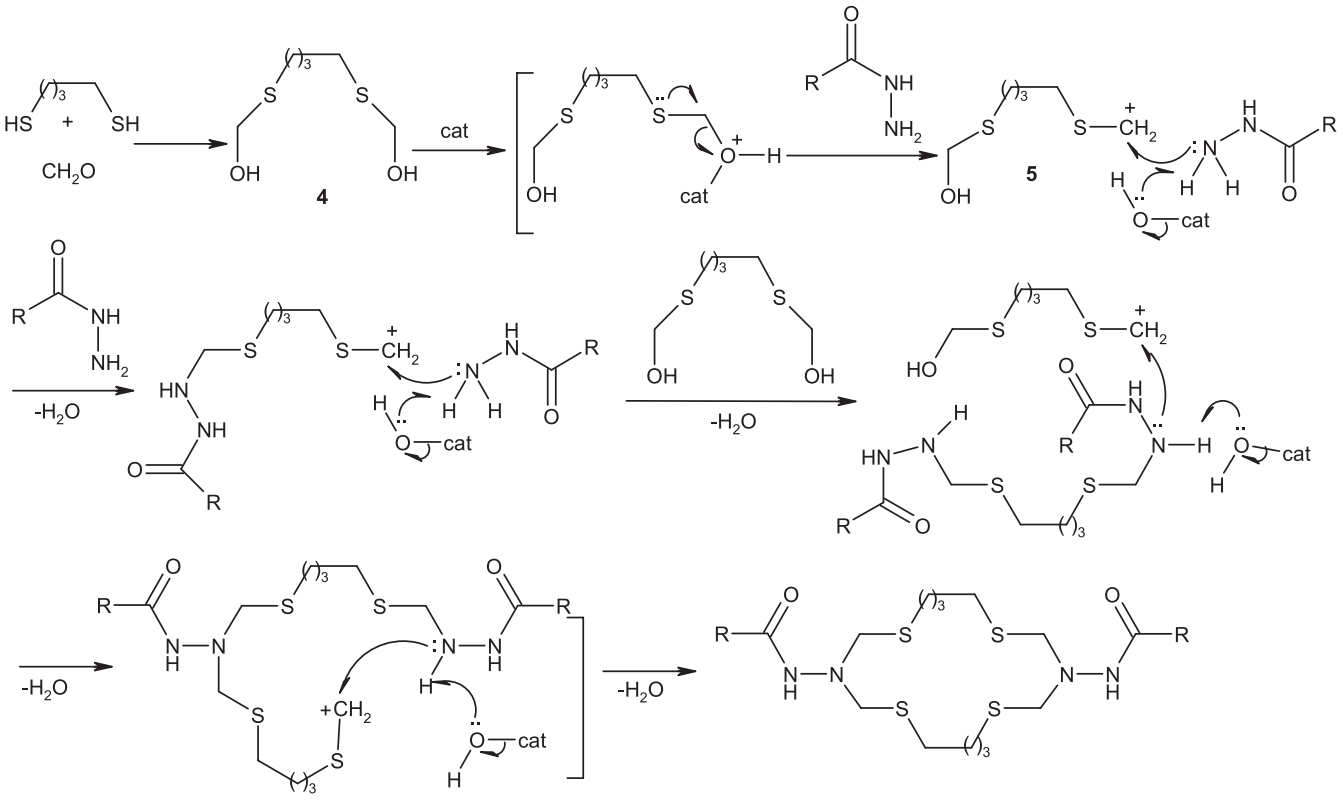
References

1. Mashkovskii M.D. *Medicinal Products,* Moscow: Novaya Volna, **2008**. 1206 p. (in Russ.) [Машковский М.Д. *Лекарственные средства*, М.: «Новая волна», **2008**. 1206 с.].
2. Pawar R.B., Mulwad V.V. *Chem. Heterocycl. Compd.* **2004**, *40*, 219-226.
3. Toldi L.G. *Chem. Heterocycl. Compd.* **1978**, *14*, 705-714.
4. Flekhter O.B., Boreko E.I., Nigmatullina L.P., Pavlova N.I., Nikolaeva S.N., Savinova O.V., Eremin V.F., Baltina L.A., Galin F.Z., Tolstikov G.A. *Russ. J. Bioorg. Chem.* **2003**, *29*, 296-301.



Scheme 2.

5. Glushkov R.G., Modnikova G.A., L'vov A.I., Krylova L.Yu., Pushkina T.V., Gus'kova T.A., Solov'eva N.P. *Pharm. Chem. J.* **2004**, *38*, 420-424.
6. Iradyan M.A., Iradyan N.S., Stepanyan G.M., Arsenyan F.G., Paronikyan G.M., Darbinyan G.A., Kazaryan E.V., Garibdzhanyan B.T. *Pharm. Chem. J.* **2003**, *37*, 67-70.
7. Jadhav P.K., Woerner F.J. *Tetrahedron Lett.* **1995**, *36*, 6383-6386.
8. Avetissyan A.A., Tokmajyan G.G., Karapetyan L.V., Soghomonyan S.A. *Chem. J. Armenia* **2002**, *55*, 78-83.
9. Zasedatelev A.S., Zhuze A.L., Zimmer K., Grokhovsky S.L., Tumanyan V.G., Gursky G.V., Gottikh B.P. *Dokl. Akad. Nauk SSSR* **1976**, *231*, 1006-1009 (in Russ.).
10. Akhmetova V.R., Khairullina R.R., Tyumkina T.V., Nelyubina Yu.V., Smolyakov A.F., Bushmarinov I.S., Starikova Z.A., Abdullin M.F., Kunakova R.V. *Russ. Chem. Bull. Int. Ed.* **2010**, *59*, 425-433.
11. Khairullina R.R., Akmanov B.F., Kunakova R.V., Ibragimov A.G., Dzhemilev U.M. *Russ. Chem. Bull. Int. Ed.* **2013**, *62,* 98-103.
12. Rakhimova E.B., Vasil'yeva I.V., Khalilov L.M., Ibragimov A.G., Dzhemilev U.M. *Chem. Heterocycl. Compd.* **2012**, *48*, 1050-1057.
13. Murzakova N.N., Rakhimova E.B., Vasilieva I.V., Prokofyev K.I., Ibragimov A.G., Dzhemilev U.M. *Tetrahedron Lett.* **2011**, *52*, 4090-4092.
14. Rakhimova E.B., Efremova E.A., Bushmarinov I.S., Goloveshkin A.S., Khalilov L.M., Ibragimov A.G., Dzhemilev U.M. *Tetrahedron Lett.* **2012**, *53*, 4225-4227.
15. Potapov V.M. *Stereochemistry,* Moscow: Khimiya, **1976**. 696 p. (in Russ.) [Потапов В.М. *Стереохимия*, М.: Химия, **1976**. 696 с.].
16. Laikov D.N. *Chem. Phys. Lett*. **1997**, *281*, 151-156.
17. Akhmetova V.R., Khabibullina G.R., Rakhimova E.B., Vagapov R.A., Khairullina R.R., Niatshina Z.T., Murzakova N.N. *Mol. Divers*. **2010**, *14*, 463-471.
18. Kuznetsov V.V., Khabibullina G.R., Akhmetova V.R. *Russ. J. Gen. Chem.* 2012, 82*,* 517-518.
19. Akhmetova V.R., MurzakovaN.N., Tyumkina T.V., Khabibullina G.R., Bushmarinov I.S., Korzhova L.F., Galimzyanova N.F. *Russ. Chem. Bull. Int. Ed.* **2012**, *61*, 2140-2148.
20. Kharchenko V.G., Gubina T.I., Markushina I.A. *Zh. Org. Khim.* **1982**, *18*, 394-399 (in Russ.).
21. Voronin S.P., Gubina T.I., Trushin S.A., Markushina I.A., Kharchenko V.G. *Chem. Heterocycl. Compd.* **1989**, *25*, 1216-1220.
22. Mokrov G.V., Likhosherstov A.M., Lezina V.P., Gudasheva T.A., Bushmarinov I.S., Antipin M.Yu. *Russ. Chem. Bull. Int. Ed.* **2010**, *59*, 1254-1266.
23. Krohn K., Cludius-Brandt S. *Synthesis* **2010**, 1344-1348.

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