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Metal-free multicomponent synthesis of novel macrocyclic tetrathiadienes with cyano and amino groups†

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The first synthesis of 5,12-diamino-7,14-bis(aryl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitriles was performed as a multicomponent macroheterocyclization of malononitrile, aryl aldehydes, and 1,2-ethanedithiol in the presence of a catalytic amount of triethylamine in ethanol. The structures of the obtained macroheterocycles were confirmed by spectral methods, X-ray diffraction, and MALDI TOF mass spectrometry.

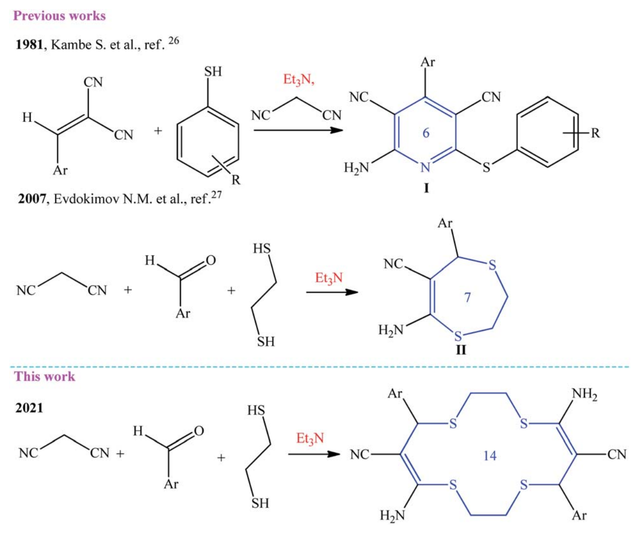
1 Introduction

Organic sulfides form an abundant cluster of biologically active molecules, providing a specific physiological effect. For example, the methionine amino acid serves as a donor of methyl groups in the body; allicin is formed upon mechanical destruction of garlic cells and exhibits bactericidal properties; biotin (vitamin) occurs as a part of enzymes and regulates the protein and fat balance; umifenovir is an antiviral agent, and so on.[1–3] Unlike the traditional Ullmann and Chan Lam coupling reactions, a simple strategy of a non-halide pathway to sulfur compounds is the use of diaryl sulfides as starting substrates.[4–6] Another approach is based on the formation of a C–S bond by transition metal-catalyzed thiomethylation *via* condensation of thioacetals with CH-acids.[7–9]

Meanwhile, the growing demand for new materials, increasing complexity of molecular drug targets, and chemotherapeutic drug and antibiotic resistance account for the increasing relevance of new thiamacrocyclic compounds.[10,11] An example is provided by the synthesis of a macroheterocyclic product containing a disulfide linker, octreotide, used for the treatment of tumors overexpressing growth hormone (somatostatin).[12]

In this connection, a relevant task is to search for conceptually new approaches to the synthesis of sulfur-containing macroheterocycles.[13] One such approach does not require the use of metal ions as template agents.[14] Another original method is multicomponent self-assembly of macroheterocyclic compounds by (2 + 4 + 2)-cyclocondensation of amino alcohols, formaldehyde, and α,ω-dithiols.[15] It is noteworthy that saturated and unsaturated crown ethers of this type possess high complexing capacity towards soft transition and alkali metals and small organic molecules.[16–20] Moreover, unsaturated thiacrown ethers can be used for the creation of hybrid materials in form 1 : 1 host–guest complexes with electron transfer to *endo*-lanthanofullerene [La@C82-A(C2v)].[21]

Conformational features contribute to the unique nature of thia macrocycles. For unsaturated thiacrown ethers oxidative transformations and *Z*/*E* isomerization of double bonds upon heating have been described.[22] It was shown that tetrathiadiene macrocyclic rings (–S–CH=CH–S–)$_2$ preferably exist in a stepped configuration, forming close crystal packing (column



Scheme 1 Evolution of the multicomponent reaction of malononitrile with aldehydes and SH acids in the synthesis of six- to fourteen-membered hetero(macro)cycles.

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Table 1 Dependence of product **4a** yield from MCR condition malononitrile **1** with 1,2-ethanedithiol **2** and 4-fluorobenzaldehyde **3a**[a]

No	Catalyst	Solvent	Product	Yield, %
1	Et_3N	C_2H_5OH	**4a**	67
2	—	C_2H_5OH	**4a**	17
3	Et_3N	H_2O	**4a**	61
4	Et_3N	CH_2Cl_2	**4a**	34
5	Piperidine	C_2H_5OH	**4a**	59
6	DBU[b]	C_2H_5OH	**4a**	63
7	Morpholine	C_2H_5OH	**4a**	29
8	K_2CO_3	C_2H_5OH	**4a**	51
9	L-Lysine·H_2O	C_2H_5OH	**4a**	—
10	H_3BO_3	C_2H_5OH	**4a**	—
11	BF_3·OEt_2	C_2H_5OH	**4a**	—
12	$NiCl_2$·$6H_2O$	C_2H_5OH	**4a**	—

[a] Reaction conditions: malononitrile **1** (2.5 mmol), 4-fluorobenzaldehyde **3a** (2.5 mmol), 1,2-ethanedithiol **2** (2.5 mmol), 5 mol% of the catalyst, 8 mL of solvent, 70 °C, stirring for 5 h. [b] DBU – diazabicycloundecene.

structures) provided by tight (zigzag-like) non-covalent contacts between the sulfur atoms of the neighboring rings, which are similar for hydrogen and π–π stacking bonds.[23] These patterns of intermolecular contacts determine the properties of conducting materials and organic electrodes.[24,25]

The single examples of unsaturated S-containing macroheterocycles and their high practical value stimulated us to design new substituted 1,4,8,11-tetrathiacyclotetradeca-5,12-dienes. The introduction of sulfur atoms with a lone pair of electrons into the macrocycle and the presence of cyano and amino groups can endow macromolecules with complexing and antioxidant properties.

2 Results and discussion

Previously, it was shown that a multicomponent condensation of malononitrile with aldehydes and *S*-mono- or *S*,*S*-binucleophilic reagents in the presence of a basic catalyst gives pyridine skeleton **I** or 6,7-dihydro-1,4-dithiepine structure **II** (Scheme 1).[26,27]

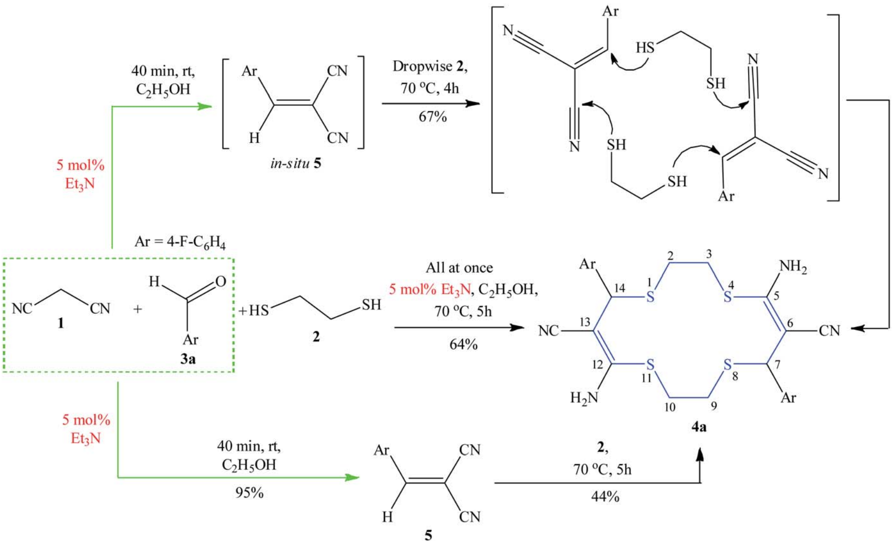
In this study, we demonstrated for the first time a new potential of malononitrile macroheterocyclization with aromatic aldehydes and 1,2-ethanedithiol to give previously unknown macroheterocyclic 5,12-diamino-7,14-bis(aryl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitriles (Scheme 1).

The base-catalyzed condensation of malononitrile with nucleophilic reagents is, most often, highly selective and gives heterocyclic products in high yields.[28] The model reaction involving malononitrile, 1,2-ethanedithiol, and aryl aldehyde containing electron-withdrawing fluorine atom in the *para*-position was utilized to study the effect of the catalyst type on the yield and selectivity of the reaction. This reaction proceeded successfully when the reactant molar ratio was 1 : 1 : 1, triethylamine (5 mol%) was present as the catalyst, and the reaction mixture was heated to 70 °C in ethanol or water. In this case, the target macrocycle was formed in 67% or 61% yield (entries 1 and 3, Table 1).

Ethanol was chosen as the solvent because malononitrile is readily soluble in ethanol, while the resulting macrocycles are poorly soluble (Scheme 2). The reaction was also efficiently implemented with piperidine (59% yield of **4a**) and DBU (63%, entries 5 and 6, Table 1) used as organocatalysts. In the absence of a catalyst, the yield of product **4a** decreased to 17%. Product **4a** was not formed when Lewis acids (H_3BO_3, BF_3·OEt_2, and $NiCl_2$·$6H_2O$) were used as catalysts (5 mol%) (entries 10–12, Table 1).

Fast addition of 1,2-ethanedithiol to the intermediate **5** resulted in complete gumming of the reaction mixture, evidently due to the competing polymerization. A similar outcome was obtained when long-chain α,ω-dithiols (1,3-propane-, 1,4-butanedithiols) were used as *S*-nucleophiles.

The use of 2-furaldehyde, formylferrocene, and acetaldehyde under the developed conditions resulted in the formation of powdered products insoluble in organic solvents such as $CHCl_3$,



Scheme 2 Model synthesis of amino- and cyano-substituted 1,4,8,11-tetrathiacyclotetradeca-5,12-diene **4a**.

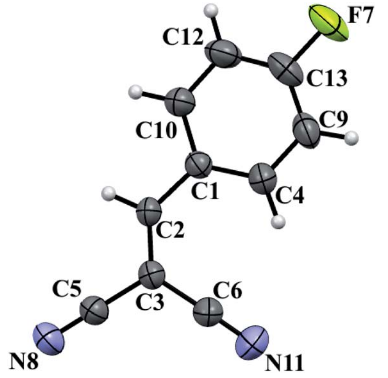


Fig. 1 Molecular structure of the compound **5**.

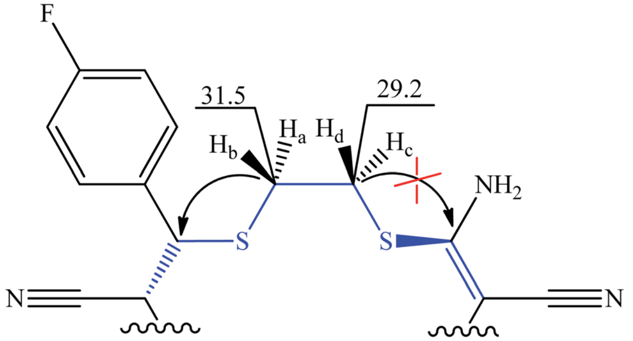


Fig. 3 Fragment of molecule **4a** with indicated long-range interactions according to $^{1}H-^{13}C$ HMBC data (δ_C ppm).

DMSO, or DMF, which precluded the spectroscopic characterization of the reaction mixture.

Another approach that can be successfully implemented is the three-component reaction when reagents have added all at once to the reaction mixture to give thiacrown ether **4a** in 64% yield (Scheme 2). Two-component procedure consisting in preliminary mixing of malononitrile with aldehyde results in the *in situ* intermediate formation of the Knoevenagel product, 2-(4-fluorobenzylydene)malononitrile **5**, within 40 min. Moreover, product **5** was isolated in a pure state in 95% yield and described by X-ray and mass spectral method (Fig. 1). The use of ready compound **5** as the reactant under similar conditions gave macrocycle **4a** in 44% yield (Scheme 2).

The crystals of **5** were obtained by slow evaporation of a DMSO-d_6 solution. The molecules of **5** crystallize in the triclinic system with space group $P\bar{1}$; the crystal lattice parameters are close to those described previously.[29] The C≡N bond length is in line with established parameters,[30] being 1.1384(18) and 1.1380(16) Å for the C6–N11 and C5–N8 bonds, respectively. The molecule has a nearly planar geometry, the root-mean-square deviation of atoms is 0.055 Å.

Thus, as shown in Scheme 2, three reactions follow the same route: first, the Knoevenagel product **5** is formed and then the self-organization of dithiol molecules occurs by location between two molecules of product **5** to realize the (2 + 2)-cycloaddition. Considering the yield of product **4a**, two macroheterocyclization reactions either with simultaneous mixing of all three reactants or *via in situ* synthesis of intermediate 2-(4-fluorobenzylidene)malononitrile **5** are of preparative value.

The ^{1}H NMR spectrum of macroheterocycle **4a** exhibited a triple set of high-field signals at δ_H 2.74–2.84, 3.02–3.05 ppm, and 3.46–3.51 ppm with integrated intensity ratio of 1 : 1 : 2 (Fig. 2).

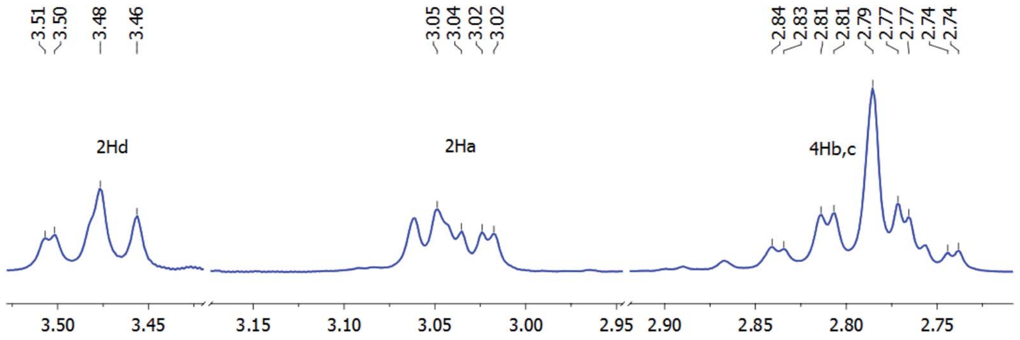
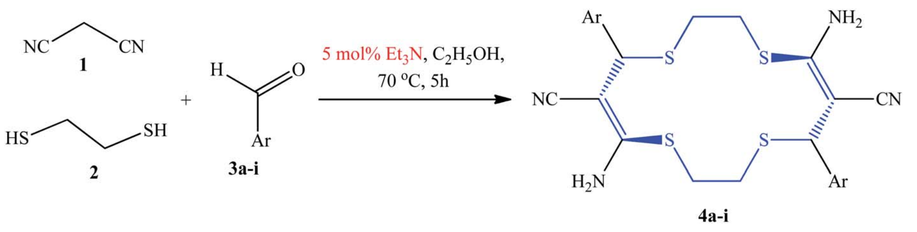


Fig. 2 Splitting of proton signals of the ethylene group $(SCH_2CH_2S)_2$ in the ^{1}H NMR spectrum of macroheterocycle **4a** in DMSO-d_6 (400 MHz) at room temperature (δ_H ppm).



Scheme 3 Catalytic macroheterocyclization of malononitrile with aryl aldehydes and 1,2-ethanedithiol.

Table 2 Yields of compound **4a–i** depending on the substituent (Ar) in the starting aldehydes

Compounds	Substituent Ar	Yield **4**[a], %	Compounds	Substituent Ar	Yield **4**[a], %
4a	4-F-C_6H_4	67	**4f**	3,4-$(CH_3O)_2$–C_6H_3	53
4b	4-Cl-C_6H_4	61	**4g**	4-CH_3-C_6H_4	63
4c	3-F-C_6H_4	58	**4h**	4-$(CH_3)_2N$–C_6H_4	44
4d	4-CF_3-C_6H_4	68	**4i**	1,3-Benzodioxol-5-yl	73
4e	4-(CH_3O)–C_6H_4	59			

[a] The given yields for compounds **4a–i** were obtained by method B.

According to HSQC ^1H–^{13}C NMR experiments, this group of signals was assigned to the ethylene protons (CH_2(2,3,9,10)) between sulfur atoms. Splitting of the geminal proton signals of the $(SCH_2CH_2S)_2$ moieties was due to the magnetic non-equivalence (anisochronous nuclei) of the hydrogen atoms on the NMR time scale and the lack of structural symmetry at the sulfur atoms. It is noteworthy that hydrogen atoms of the CH_2 groups in the SCH_2CH_2S chains are diastereotopic, obviously due to the rigid conformation of the macroheterocycle **4a**.[31]

As a result of the symmetry and conformational rigidity of the macrocycles, the ^{13}C NMR spectra exhibit a moderate number of signals. The ^{13}C NMR spectrum of compound **4a** shows two high-field signals at δ_C 29.2 ppm (C(3)) and 31.5 (C(2)) ppm corresponding to the ethylene moiety between the sulfur atoms. The characteristic signal of the methine carbon atom occurs at δ_C 45.4 ppm. The signal at δ_C 85.6 ppm corresponds to the quaternary carbon atom at the CN-substituted double bond. The enamine carbon atom resonates in a low field at 163.0 ppm. The ^{13}C NMR spectrum of compound **4a** shows splitting of the aromatic carbon signals, due to the presence of fluorine in the *para*-position of the ring, with spin–spin coupling constants corresponding to published data: δ_C 161.8 ($^1J_{CF}$ 242.8 Hz), 152.4, 136.0 ($^4J_{CF}$ 2.4 Hz), 129.5 ($^3J_{CF}$ 8.1 Hz), 120.3, and 115.9 ($^2J_{CF}$ 21.4 Hz) ppm.[32] The MALDI TOF mass spectrum shows intense molecular ion peaks with m/z 555.0307 and 570.9909 corresponding to $[M + Na]^+$ and $[M + K]^+$ ions of the structure ascribed to macroheterocycle **4a**.

The heteronuclear ^1H–^{13}C HMBC 2D NMR spectrum of compound **4a** showed a correlation between the $C(2)H_2$ protons and C(14) methine carbon atom; however, there were no clear-cut cross-peaks with the C(5) quaternary carbon atom at the NH_2 group, probably, due to slow conformational exchange (Fig. 3).

Under the developed conditions, the reaction was carried out for the *para-* and *meta*-substituted aromatic aldehydes **3a–i** with electron-donating (CH_3, OCH_3, $N(CH_3)_2$) and withdrawing (F, Cl, CF_3) substituents (Scheme 3). The yields of the macroheterocycles **4a–i** varied in the 44–73% range. The presence of *para*-substituents in the aromatic ring of aldehydes was favorable for increasing the yield of the target macrocycles (Table 2). With participation of *para-* and *meta*-substituted 1,3-benzodioxol-5-ylmethanal (piperonal) the thiacrown ether **4i** was efficiently synthesized in 73% yield. However, there is information in the literature that in the presence of *ortho-*,*ortho'*-substituents in aromatic aldehydes, this reaction gave substituted 6,7-dihydro-1,4-dithiepines **II.**[27] Obviously, the *meta-* and/or *para*-substituents in the benzene ring in the Knoevenagel product **5** complicate the intramolecular nucleophilic addition of 1,2-dithiol **2** giving 6,7-dihydro-1,4-dithiepines, but promote intermolecular (2 + 2) cycloaddition of **2** to **5**, resulting in the formation of macrocyclic tetrathiadienes with cyano and amino groups.

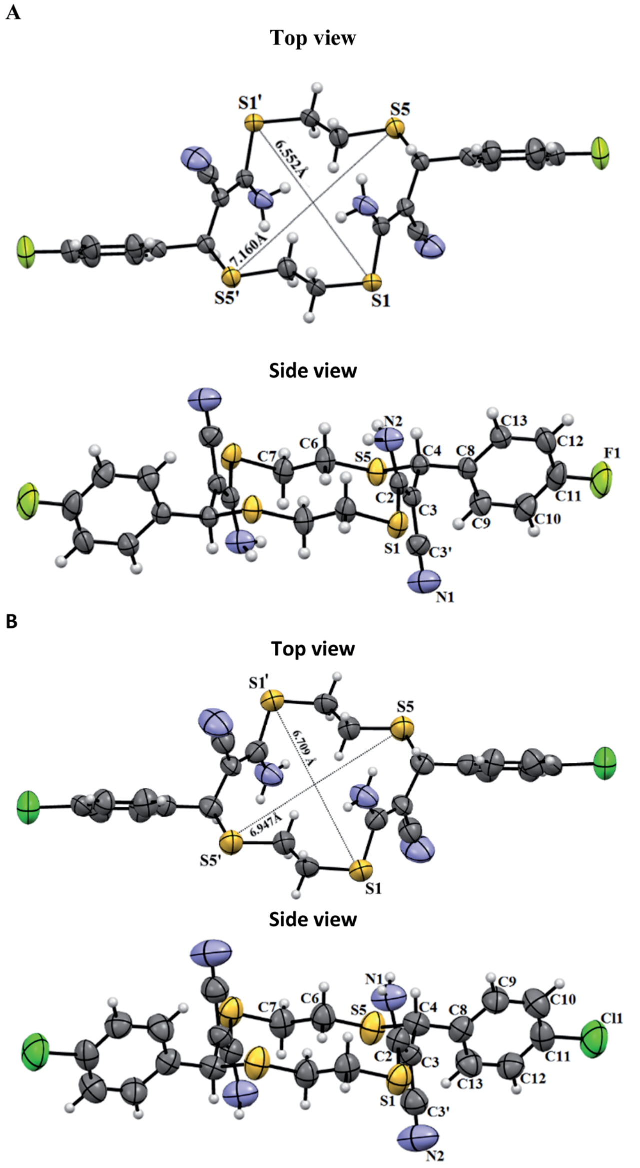
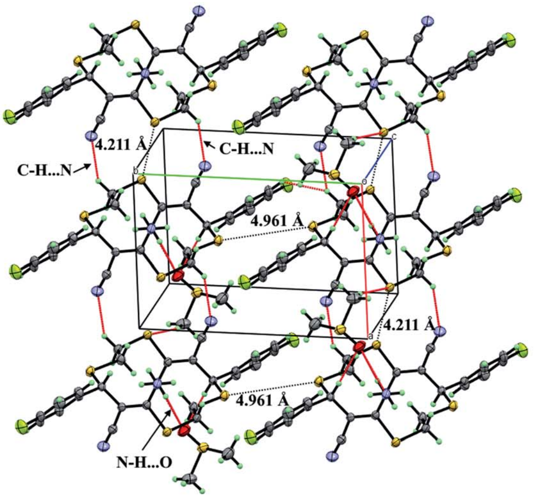
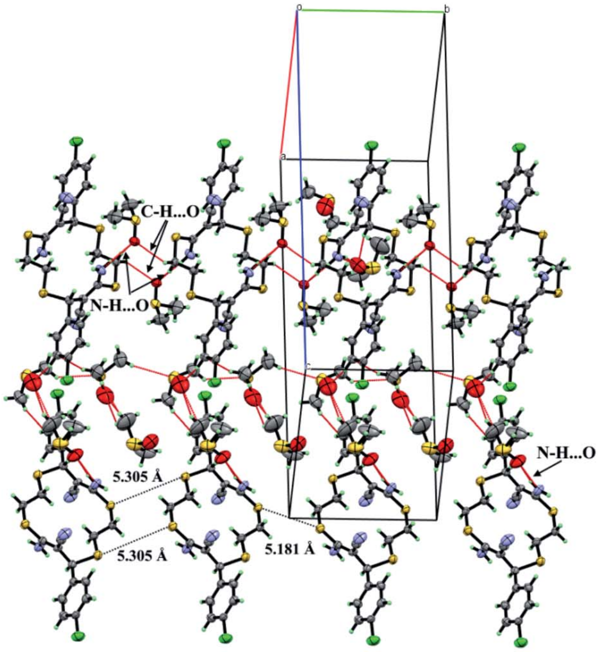


Fig. 4 Molecular structure of unsaturated thiacrown ethers *trans*-**4a** and *trans*-**4b**. Non-hydrogen atoms are shown by thermal ellipsoids (p = 50%).

Unsaturated thiacrown ethers **4a** and **4b** form crystal solvates (Fig. 5) in which the molecules of the major substance are linked by N–H···O hydrogen bonds to DMSO molecules. Note that the solvent molecules are disordered. 14-Membered cyclic products *trans*-**4a** and *trans*-**4b** have *E*-geometry of the olefinic moieties. The $C_{(sp^2)}$–S bond lengths are 1.771(2) and 1.752(6) Å, which agrees with the data for previously studied compounds.[33] There exist *endo*- and *exo*-conformations of macrocyclic thioethers, depending on whether the sulfur lone electron pairs point inside or outside the macrocyclic cavity, respectively. Like other relatively simple thioethers,[33] structures **4a** and **4b** have the *exo*-conformation. The *para*-fluoro- or *para*-chloroaryl moieties are arranged equatorially relative to the macrocycle plane. The obtained *trans*-thiacrown ether molecules have a symmetry center, with the distances between the opposite sulfur atoms, S1–S1′ and S2–S2′, in **4a** and **4b** differing insignificantly (Fig. 4).



4a



4b

Fig. 5 Crystal packing of compounds **4a** and **4b** with indicated intermolecular interactions (red dashed line) and S···S distances (black dashed line).

The molecules of compound **4a** form crystals with a triclinic crystal lattice ($P\bar{1}$), while molecules of **4b** crystallize in the orthorhombic system (space group *Pbca*). In the crystals of **4a**, thiacrown ether molecules form stacks along the *a* axis *via* C–H···N hydrogen bonds, whereas molecules of **4b** are connected into chains along the *b* axis *via* DMSO molecules (Fig. 5). According to published data,[34] molecules in the crystals of unsaturated thiacrown ethers are linked by S···S contacts; the distances between the sulfur atoms are equal to or are shorter than the sum of the van der Waals radii (S···S = 3.7 Å). In the crystals of **4a** and **4b**, the distances between the sulfur atoms of the tetrathiadiene rings are markedly longer than the sum of the van der Waals radii of sulfur atoms (Fig. 5).

3 Conclusions

Thus, here we report the first efficient method for constructing macroheterocyclic structures from available reactants within the framework of the metal-free concept. This method is based on multicomponent macroheterocyclization of malononitrile, *meta*- or *para*-substituted arylaldehydes, and 1,2-ethanedithiol in the presence of triethylamine as a base catalyst. Due to the presence of bifunctional groups in the reactants pseudo-six-component cycloaddition occurs with the participation of SH-groups of dithiol, C═C- and C≡N-bonds of the Knoevenagel adduct. The resulting 14-membered macroheterocycles represent a conceptually novel type of unsaturated systems containing cyano and amino groups. According to X-ray diffraction data 1,4,8,11-tetrathiacyclotetradeca-5,12-dienes have a *E*-geometry of the olefinic moieties and the *exo*-conformation of the macrocyclic thioethers. Owingh to the presence of several functional groups, these tetrathiamacrocycles (thiacrown ethers) would be of interest for chemists specializing in the coordination, supramolecular, and medicinal chemistry.

4 Experimental section

4.1. Materials and instruments

The reaction products were characterized by ^{1}H and ^{13}C NMR spectra that were recorded on spectrometers Bruker Avance 400 NMR (400.13 MHz and 100.62 MHz) and Bruker Ascend III HD 500 (500.17 MHz and 125.78 MHz). Also 2D homo- (COSY) and hetero- (HSQC, HMBC) nuclear spectra were obtained on a Bruker Avance 500 in DMSO-d_6 by Bruker standard procedures, internal reference standard TMS. IR spectra were obtained on a Bruker Vertex-70V FT-IR spectrometer for samples prepared as a Nujol mull. UV spectra were recorded on a Perkin Elmer Lambda 750 UV/VIS-spectrometer for DMSO solutions in the wavelength range of 200–1000 nm using a 1 cm thick cuvette. Matrix-assisted laser desorption/ionization (MALDI) mass spectrum was recorded on a Bruker's device MALDI TOF Autoflex III with sinapinic acid as a matrixes. GC-MS analysis of compound **5** was performed on a Shimadzu GC 2010 chromatograph equipped with a Shimadzu GCMS-QP2010 Ultra mass selective detector and a Supelco 5 ms capillary column (60 m × 0.25 m × 0.25 μm), with helium as carrier gas. Elemental analysis was performed on a Carlo Erba Model 1106 elemental analyzer. Melting points were determined on a Kofler hot-stage microscope (RNMK 80/2617) apparatus. The reaction progress was monitored by TLC method on Sorbfil plates (PTSKh-AF-A), eluent cyclohexane–CH_2Cl_2–EtOAc, 1 : 2 : 10, visualization with iodine vapor.

4.1.1 Preparation of 5,12-diamino-7,14-bis(aryl)-1,4,8,11-tetrasulfanylcyclotetradeca-5,12-diene-6,13-dicarbonitriles 4a–i

Method A. 4-Fluorobenzaldehyde (0.27 mL, 2.5 mmol) and triethylamine (0.02 mL, 0.0125 mmol) are added to a solution of malononitrile (0.17 g, 2.5 mmol) in ethanol (8 mL), and then 1,2-ethanedithiol (0.21 mL, 2.5 mmol) is added dropwise under argon. The reaction mixture is stirred at 70 °C for 4 h, filtered, washed with ethanol (2 × 10 mL), and dried in air to give 5,12-diamino-7,14-bis(4-fluorophenyl)-1,4,8,11-tetrasulfanylcyclotetradeca-5,12-diene-6,13-dicarbonitrile **4a** in 67% yield.

Method B. A mixture of malononitrile (0.17 g, 2.5 mmol), 4-fluorobenzaldehyde (0.27 mL, 2.5 mmol) and triethylamine (0.02 mL, 0.0125 mmol) in 8 mL of ethanol was stirred under argon at room temperature for 40 min. Then 1,2-ethanedithiol (0.21 mL 2.5 mmol) is added dropwise. The reaction mixture is stirred at 70 °C for 4 h, filtered, washed with ethanol (2 × 10 mL), and dried in air to give macroheterocycle **4a** is obtained with a yield of 64%.

Method C. To a suspension of 2-(4-fluorobenzylidene)malononitrile (0.43 g, 2.5 mmol) in 8 mL of ethanol, 1,2-ethanedithiol (0.21 mL, 2.5 mmol) is added dropwise in an argon atmosphere. The reaction mixture is stirred at 70 °C for 4 h, filtered, washed with ethanol (2 × 10 mL) and dried in air to give macroheterocycle **4a** is obtained with a yield of 44%.

4.1.2 5,12-Diamino-7,14-bis(4-fluorophenyl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4a). White powder, yield, 0.45 g (67%). Mp 194–198 °C. Found: C, 54.23; H, 4.25; N, 10.47; S, 24.22. Anal. calc. for $C_{24}H_{22}F_2N_4S_4$: C, 54.11; H, 4.16; N, 10.52; S, 24.08. IR (cm^{-1}): ν = 721, 772, 826, 1092, 1239, 1604, 1632, 2191, 3219, 3324, 3432. UV (nm): λ = 279. ^{1}H-NMR (ppm): δ = 7.42–7.39 (4H, m, Ar), 7.24 (4H, s, NH_2), 7.21–7.18 (4H, m, Ar), 5.47 (2H, s, CH), 3.51–3.46 (2H, m, CH_2), 3.06–3.02 (2H, m, CH_2), 2.84–2.74 (4H, m, CH_2). ^{13}C-NMR (ppm): δ = 161.8 ($^1J_{CF}$ 242.8 Hz), 152.4, 136.1 ($^4J_{CF}$ 2.4 Hz), 129.5 ($^3J_{CF}$ 8.1 Hz), 120.3, 115.9 ($^2J_{CF}$ 21.4 Hz), 85.5, 45.4, 31.5, 29.2. MS (MALDI TOF): 555.0307 [M + Na]$^+$, 570.9909 [M + K]$^+$.

4.1.3 5,12-Diamino-7,14-bis(4-chlorophenyl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4b). White powder, yield, 0.43 g (61%). Mp 192–194 °C. Found: C, 51.07; H, 3.85; N, 9.87; S, 22.74. Anal. calc. for $C_{24}H_{22}Cl_2N_4S_4$: C, 50.96; H, 3.92; N, 9.91; S, 22.68. IR (cm^{-1}): ν = 723, 817, 1014, 1114, 1207, 1308, 1556, 1630, 2193, 3220, 3329, 3435. UV (nm): λ = 289. ^{1}H-NMR (ppm): δ = 7.43 (4H, d, J 8 Hz, Ar), 7.38 (4H, d, J 8 Hz, Ar), 7.27 (4H, s, NH_2), 5.48 (2H, s, CH), 3.51–3.46 (2H, m, CH_2), 3.07–3.03 (2H, m, CH_2), 2.85–2.74 (4H, m, CH_2). ^{13}C-NMR (ppm): δ = 152.7, 138.7, 132.6, 129.4, 129.2, 129.1, 120.2, 85.2 (C-6,13), 45.5 (C-7,14), 31.5, 29.2. MS (MALDI TOF): 587.1102 [M + Na]$^+$, 603.0500 [M + K]$^+$

4.1.4 5,12-Diamino-7,14-bis(3-fluorophenyl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4c). White powder, yield, 0.39 g (58%). Mp 192–194 °C. Found: C, 54.18; H, 4.23; N, 10.63; S, 24.14. Anal. calc. for $C_{24}H_{22}F_2N_4S_4$: C, 54.11; H, 4.16; N, 10.52; S, 24.08. IR (cm^{-1}): ν = 739, 763, 954, 1154, 1256, 1555, 1634, 2188, 3221, 3322, 3428. UV (nm): λ = 283. ^{1}H-NMR (ppm): δ = 7.45–7.39 (3H, m, Ar), 7.29 (4H, s, NH_2), 7.22–7.14 (5H, m, Ar), 5.49 (2H, s, CH), 3.52–3.46 (2H, m, CH_2), 3.07–3.02 (2H, m, CH_2), 2.87–2.74 (4H, m, CH_2). ^{13}C-NMR (ppm): δ = 162.4 ($^1J_{CF}$ 242 Hz), 152.8, 142.4 ($^4J_{CF}$ 6.8 Hz), 131.2 ($^2J_{CF}$ 8.1 Hz), 123.8 ($^3J_{CF}$ 3 Hz), 120.2, 115.0 ($^2J_{CF}$ 21 Hz), 114.2 ($^2J_{CF}$ 22.2 Hz), 84.9, 45.6, 31.5, 29.2. MS (MALDI TOF) 555.1459 [M + Na]$^+$, 571.0966 [M + K]$^+$.

4.1.5 5,12-Diamino-7,14-bis[4-(trifluoromethyl)phenyl]-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4d). White powder, yield, 0.54 g (68%). Mp 208–210 °C. Found: C, 49.42; H, 3.61; N, 8.79; S, 20.38. Anal. calc. for $C_{26}H_{22}F_6N_4S_4$: C, 49.35; H, 3.50; N, 8.85; S, 20.27. IR (cm^{-1}): ν = 692, 818, 1071, 1123, 1159, 1557, 1625, 2196, 3218, 3329, 3469. UV (nm): λ = 284. ^{1}H-NMR (ppm): δ = 7.76 (6H, d, J 8.4 Hz, Ar), 7.58 (2H, d, J 8 Hz, Ar), 7.35 (4H, s, NH_2), 5.60 (2H, s, CH), 3.55–3.48 (2H, m, CH_2), 3.12–3.06 (2H, m, CH_2), 2.90–2.77 (4H, m, CH_2). ^{13}C-NMR (ppm): δ = 153.1, 144.3, 128.5 ($^2J_{CF}$ 32 Hz), 128.4 ($^4J_{CF}$ 1 Hz), 126.1 ($^3J_{CF}$ 3.7 Hz), 124.6 ($^1J_{CF}$ 271 Hz), 120.1, 84.7, 45.8, 31.4, 29.2. MS (MALDI TOF) 655.0454 [M + Na]$^+$, 670.9974 [M + K]$^+$.

4.1.6 5,12-Diamino-7,14-bis(4-methoxyphenyl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4e). White powder, yield, 0.41 g (59%). Mp 164–166 °C. Found: C, 56.02; H, 5.14; N, 10.11; S, 22.09. Anal. calc. for $C_{26}H_{28}N_4O_2S_4$: C, 56.09; H, 5.07; N, 10.06; S, 20.04. IR (cm^{-1}): ν = 820, 1032, 1179, 1259, 1511, 1554, 1631, 2192, 3218, 3322, 3425. UV (nm): λ = 286. ^{1}H-NMR (ppm): δ = 7.30 (4H, d, J 8.4 Hz, Ar), 7.16 (4H, s, NH_2), 6.91 (4H, d, J 8 Hz, Ar), 5.41 (2H, s, CH), 3.50–3.45 (2H, m, CH_2), 3.33 (6H, s, CH_3), 3.05–3.00 (2H, m, CH_2), 2.82–2.72 (4H, m, CH_2). ^{13}C-NMR (ppm): δ = 159.0, 151.9, 131.8, 128.7, 120.4, 114.3, 86.3 (C-6,13), 55.6 (C-34,36), 45.6 (C-7,14), 31.5, 29.2. MS (MALDI TOF) 579.0371. [M + Na]$^+$, 595.0151 [M + K]$^+$.

4.1.7 5,12-Diamino-7,14-bis(3,4-dimethoxyphenyl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4f). White powder, yield, 0.41 g (53%). Mp 122–124 °C. Found: C, 54.61; H, 5.17; N, 9.12; S, 20.86. Anal. calc. for $C_{28}H_{32}N_4O_4S_4$: C, 54.52; H, 5.23; N, 9.08; S, 20.79. IR (cm^{-1}): ν = 740, 774, 1024, 1141, 1263, 1559, 1640, 2194, 3218, 3317, 3384. UV (nm): λ = 285. ^{1}H-NMR (ppm): δ = 7.16 (4H, s, NH_2), 7.00–6.91 (6H, m, Ar), 5.38 (2H, s, CH), 3.49–3.45 (2H, m, CH_2), 3.36 (12H, s, CH_3), 3.04–3.00 (2H, m, CH_2), 2.81–2.73 (2H, m, CH_2). ^{13}C-NMR (ppm): δ = 151.9, 148.9, 148.7, 132.1, 120.6 (C-16,25), 119.8, 112.2, 111.4, 86.1 (6,13), 56.0 (C-38,34), 55.9 (C-40,36), 45.9, 31.5, 29.2. MS (MALDI TOF) 639.1999 [M + Na]$^+$, 655.1392 [M + K]$^+$.

4.1.8 5,12-Diamino-7,14-bis(4-methylphenyl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4g). White powder, yield, 0.41 g (63%). Mp 192–194 °C. Found: C, 59.63; H, 5.31; N, 10.74; S, 24.39. Anal. calc. for $C_{26}H_{28}N_4S_4$: C, 59.51; H, 5.38; N, 10.68; S, 24.43. IR (cm^{-1}): ν = 723, 816, 1019, 1113, 1263, 1609, 2183, 3198, 3311, 3435. UV (nm): λ = 290. ^{1}H-

NMR (ppm): $\delta = 7.26$ (4H, d, J 8 Hz, Ar), 7.18 (4H, s, NH_2), 7.15 (4H, d, J 8 Hz, Ar), 5.42 (2H, s, CH), 3.50–3.45 (2H, m, CH_2), 3.05–3.01 (2H, m, CH_2), 2.81–2.73 (4H, m, CH_2), 2.28 (6H, s, CH_3). ^{13}C-NMR (ppm): $\delta = 152.0$, 137.2, 136.8, 129.5, 127.4, 120.3 (C-16,25), 86.1 (C-6,13), 45.9, 31.4, 29.2, 21.1 (C-33,34). MS (MALDI TOF) 547.0865, $[M + Na]^+$, 563.0848 $[M + K]^+$.

4.1.9 5,12-Diamino-7,14-bis[4-(dimethylamino)phenyl]-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4h). Light brown powder, yield, 0.32 g (44%). Mp 152–154 °C. Found: C, 57.74; H, 5.81; N, 14.51; S, 22.06. Anal. calc. for $C_{28}H_{34}N_6S_4$: C, 57.70; H, 5.88; N, 14.42; S, 22.01. IR (cm^{-1}): $\nu =$ 802, 952, 1020, 1232, 1529, 1554, 1632, 2190, 3214, 3311, 3416. UV (nm): $\lambda = 279$. ^1H-NMR (ppm): $\delta = 7.19$ (4H, d, J 8.4 Hz, Ar), 7.08 (4H, s, NH_2), 6.67 (4H, d, J 8 Hz, Ar), 5.33 (2H, s, CH), 3.48–3.43 (2H, m, CH_2), 3.03–2.98 (2H, m, CH_2), 2.87 (12H, s, CH_3), 2.79–2.70 (4H, m, CH_2). ^{13}C-NMR (ppm): $\delta = 151.4$, 150.2, 128.2, 127.1, 120.6, 112.6, 86.8 (C-6,13), 45.8 (C-7,14), 40.6, 31.5, 29.2. MS (MALDI TOF) 581.1190. $[M + H]^+$, 603.1167 $[M + Na]^+$.

4.1.10 5,12-Diamino-7,14-bis(1,3-benzodioxol-5-yl)-1,4,8,11-tetrathiacyclotetradeca-5,12-diene-6,13-dicarbonitrile (4i). White powder, yield, 0.52 g (73%). Mp 186–188 °C. Found: C, 53.49; H, 4.21; N, 9.52; S, 22.04. Anal. calc. for $C_{26}H_{24}N_4O_4S_4$: C, 53.40; H, 4.14; N, 9.58; S, 21.93. IR (cm^{-1}): $\nu = 785$, 928, 1039, 1252, 1326, 1554, 1633, 2195, 3219, 3316, 3416. UV (nm): $\lambda =$ 284. ^1H-NMR (ppm): $\delta = 7.17$ (4H, s, NH_2), 6.86–6.94 (6H, m, Ar), 6.01 (4H, s, OCH_2O), 5.37 (2H, s, CH), 3.49–3.43 (2H, m, CH_2), 3.03–2.98 (2H, m, CH_2), 2.79–2.71 (4H, m, CH_2). ^{13}C-NMR (ppm): $\delta = 152.1$, 147.7, 147.1, 133.6, 120.9, 120.4, 108.7, 107.8, 101.6, 86.1 (C-6,13), 45.8 (C-7,14), 31.6, 29.3. MS (MALDI TOF) 607.1328. $[M + Na]^+$, 623.0609 $[M + K]^+$.

4.1.11 2-(4-Fluorobenzylidene)malononitrile (5). White powder, yield, 0.41 g (95%). Mp 126–128 °C (125–126 °C literature data[35]). MS (GC-MS): 172 (M^+, 100%), 145 (M − CHN, 85%), 121 ($M - FC_6H_5CH{=}C$, 55%), 95 ($M - FC_6H_5$, 15%).

4.2. X-ray diffraction experiments

The X-ray diffraction measurements for compounds **4a**, **4b** and **5** were performed on an Agilent XCalibur (Eos, Gemini) automated four-circle diffractometer (graphite monochromator, MoKα radiation, $\lambda = 0.71073$ Å, ω-scan mode, $2\theta_{max} = 62°$). Data collection, cell refinement, data reduction were carried out using the CrysAlisPro.[36] The structures **4a** and **5** were solved by direct methods with the SHELXS program[37] and structure **4b** was solved by with the SHELXT program.[38] Positional parameters of non-hydrogen atoms were refined by the full-matrix least-squares method in the anisotropic approximation using the SHELXL 2018/3 program.[39] All hydrogen atoms in compounds **4a** and **4b** were generated using the proper HFIX command and refined isotropically using the riding model. The hydrogen atoms in compound **5** were located in the Difference Fourier map and refined isotropically. Crystal data and structure refinement parameters are shown in Table S1 (see ESI).† The crystallographic data, coordinates of atoms, and geometric parameters for compounds **4a**, **4b** and **5** were deposited at the Cambridge Crystallographic Data Centre (entry no. CCDC 2064004 **4a**, CCDC 2064005 **4b**, and CCDC 2064003 **5**).

Conflicts of interest

There are no conflicts of interest to declare.

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References

1 S. Shekh, K. K. Amarnath Reddy and K. H. Gowd, *J. Sulfur Chem.*, 2021, **42**, 109, DOI: 10.1080/17415993.2020.1817457.
2 C. Jacob, *Nat. Prod. Rep.*, 2006, **23**, 851, DOI: 10.1039/B609523M.
3 Z. V. F. Wright, N. C. Wu, R. U. Kadam, I. A. Wilson and D. W. Wolan, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 3744, DOI: 10.1016/j.bmcl.2017.06.074.
4 R. Zhang, H. Ding, X. Pu, Z. Qian and Y. Xiao, *Catalysts*, 2020, **10**, 1339, DOI: 10.3390/catal10111339.
5 P. Mampuys, C. R. McElroy, J. H. Clark, R. V. A. Orru and B. U. W. Maes, *Adv. Synth. Catal.*, 2020, **362**, 3, DOI: 10.1002/adsc.201900864.
6 Y. Qin, Y. Han, Y. Tang, J. Wei and M. Yang, *Chem. Sci.*, 2020, **11**, 1276, DOI: 10.1039/c9sc04169a.
7 V. R. Akhmetova, N. S. Akhmadiev, Z. A. Starikova, A. R. Tulyabaev, E. S. Mescheryakova and A. G. Ibragimov, *Tetrahedron*, 2015, **71**, 7722, DOI: 10.1016/j.tet.2015.07.055.
8 N. S. Akhmadiev, E. S. Mescheryakova, V. R. Khairullina, V. R. Akhmetova, L. M. Khalilov and A. G. Ibragimov, *J. Mol. Struct.*, 2021, **1228**, 129734, DOI: 10.1016/j.molstruc.2020.129734.
9 V. R. Akhmetova, N. S. Akhmadiev, R. A. Zainullin, V. R. Khayrullina, E. S. Mescheryakova and N. A. Glushkova, *Can. J. Chem.*, 2020, **98**, 725, DOI: 10.1139/cjc-2019-0186.
10 A. K. Yudin, *Chem. Sci.*, 2015, **6**, 30, DOI: 10.1039/C4SC03089C.
11 X. Yu and D. Sun, *Molecules*, 2013, **18**, 6230, DOI: 10.3390/molecules18066230.
12 A. Iarov, I. Avrutov, N. Lazarowych and S. Houldsworth, *WO Pat.*, 2005087794A1, 2005.
13 A. V. Chuchuryukin, P. A. Chase, H. P. Dijkstra, B. M. J. M. Suijkerbuijk, A. M. Mills, A. L. Spek, G. P. M. van Klink and G. van Koten, *Adv. Synth. Catal.*, 2005, **347**, 447, DOI: 10.1002/adsc.200404282.
14 N. E. Borisova, M. D. Reshetova and Yu. A. Ustynyuk, *Russ. Chem. Rev.*, 2007, **76**, 785, DOI: 10.1070/RC2007v076n09ABEH003705.
15 G. R. Khabibullina, V. R. Akhmetova, M. F. Abdullin, T. V. Tyumkina, L. M. Khalilov, A. G. Ibragimov and

U. M. Dzhemilev, *Tetrahedron*, 2014, **70**, 3502, DOI: 10.1016/j.tet.2014.03.053.

16 Y. Suzaki, H. Nagai and K. Osakada, *Chem. Lett.*, 2014, **43**, 714, DOI: 10.1246/cl.131213.

17 Y.-F. Han, H. Lia and G.-X. Jin, *Chem. Commun.*, 2010, **46**, 6879, DOI: 10.1039/C0CC00770F.

18 T. Tsuchiya, T. Shimizu, K. Hirabayashi and N. Kamigata, *J. Org. Chem.*, 2002, **67**, 6632, DOI: 10.1021/jo020269w.

19 M. Ashram, G. M. Al-Mazaideh, W. Al-Zereini, A. Al-Mustafa and S. Mizyed, *J. Sulfur Chem.*, 2019, **40**, 277, DOI: 10.1080/17415993.2019.1579816.

20 A. Holzberger and E. Kleinpeter, *Magn. Reson. Chem.*, 2004, **42**, 589, DOI: 10.1002/mrc.1378.

21 T. Takahiro, K. Hiroki, S. Kumiko, W. Takatsugu, A. Takeshi, S. Toshio, K. Nobumasa, M. Naomi and N. Shigeru, *Chem. Commun.*, 2006, 3585, DOI: 10.1039/b606183d.

22 T. Shimizu, S. Komatsuzaki and K. Hirabayashi, *Heteroat. Chem.*, 2011, **22**, 287, DOI: 10.1002/hc.

23 R. Gleiter, G. Haberhauer, D. B. Werz, F. Rominger and C. Bleiholder, *Chem. Rev.*, 2018, **118**, 2010, DOI: 10.1021/acs.chemrev.7b00449.

24 J. Heiska, M. Nisula and M. Karppinen, *J. Mater. Chem. A*, 2019, **7**, 18735, DOI: 10.1039/C9TA04328D.

25 A. I. Konovalova, I. S. Antipina, V. A. Burilov, *et al.*, *Russ. J. Org. Chem.*, 2018, **54**, 157, DOI: 10.1134/S107042801802001X.

26 S. Kambe, K. Saito, A. Sakurai and H. Midorikawa, *Synthesis*, 1981, 531, DOI: 10.1055/s-1981-29513.

27 N. M. Evdokimov, A. S. Kireev, A. A. Yakovenko, M. Yu. Antipin, I. V. Magedov and A. Kornienko, *J. Org. Chem.*, 2007, **72**, 3443, DOI: 10.1021/jo070114u.

28 V. V. Dotsenko, S. G. Krivokolysko and A. M. Semenova, *Chem. Heterocycl. Compd.*, 2018, **54**, 989, DOI: 10.1007/s10593-018-2383-y.

29 M. Yu. Antipin, V. N. Nesterov, S. Jiang, O. Y. Borbulevych, D. M. Sammeth, E. V. Sevostianova and T. V. Timofeeva, *J. Mol. Struct.*, 2003, **650**, 1, DOI: 10.1016/S0022-2860(02)00468-4.

30 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1, DOI: 10.1039/P298700000S1.

31 A. de Leon, J. Pons, J. García-Antón, X. Solans, M. Font-Bardia and J. Ros, *Polyhedron*, 2007, **26**, 2498, DOI: 10.1016/j.poly.2006.12.034.

32 N. S. Akhmadiev, E. S. Mescheryakova, V. R. Khairullina, V. R. Akhmetova and A. G. Ibragimov, *Chem. Heterocycl. Compd.*, 2020, **56**, 473, DOI: 10.1007/s10593-020-02683-8.

33 S. J. Lange, J. W. Sibert, C. L. Stern, A. G. M. Barrett and B. M. Hoffman, *Tetrahedron*, 1995, **51**, 8175, DOI: 10.1016/0040-4020(95)00439-F.

34 T. H. Staeb, R. Gleiter and F. Rominger, *Eur. J. Org. Chem.*, 2002, 2815–2822, DOI: 10.1002/1099-0690(200208)2002:16<2815::AID-EJOC2815>3.0.CO;2-9.

35 M. Trilla, R. Pleixats, M. W. Chi Man and C. Bied, *Green Chem.*, 2009, **11**, 1815, DOI: 10.1039/b916767f.

36 Agilent A. T. Ltd, *CrysAlis PRO/2012*, Yarnton, Oxfordshire, England.

37 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2008, **64**, 112, DOI: 10.1107/S0108767307043930.

38 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2015, **71**, 3, DOI: 10.1107/S2053273314026370.

39 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2015, **71**, 3, DOI: 10.1107/S2053229614024218.