Novel sulfur-containing amidecrownophanes: synthesis via tandem Claisen rearrangement and an unpredicted mercuration

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Abstract

Two novel sulfur-containing amidecrownophanes, **3a** (N_2S) and **3b** (N_2S_2), were synthesized by diacyl chloride–diamine sulfide coupling reactions followed by the tandem Claisen rearrangement of macrocycles **2a** and **2b** as precursors, respectively. The reactivity of the titled macrocycles with some transition and heavy metal ions was examined. The most salient feature of the reactions is the mercurated dihydrobenzofuran **4** derived from **3b** and $Hg(OAc)_2$. The X-ray crystal structures of **4** as well as **2a** and **2b** were revealed.
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Crownophanes having plural hydroxy groups have been synthesized via tandem Claisen rearrangement (TCR)[1] for the purpose of molecular recognition toward ionic and neutral guest molecules and the construction of the supramolecular systems.[2] Recently, we developed a convenient and efficient route for the synthesis of amidecrownophanes from the 1:1 reaction of diacid dichloride containing isobutenyl ether moiety with diamine derivatives under mild conditions, that is, without high dilution method in high yields.[3]

So far, many kinds of sulfur-containing macrocycles have been reported for the complexation with metal ions and the application to ion sensing agents and metal ion separation.[4] However, there are few examples of sulfur-containing macrocycles having plural hydroxy groups in the same molecule.[5] It is expected that the cooperation between sulfur atom(s) and hydroxy groups might bring a new aspect in the fields of metal ion complexation and molecular recognition.

In this Letter, we report the application of sulfur-containing amidecrownophanes. According to our macrocyclization between diacid dichloride and diamines,[3] macrocyclic polyether compounds having thioethers were prepared firstly. Then, target products were prepared via TCR in the thermal reaction. Preliminary results for the reactions of the sulfur-containing amidecrownophanes with some metal acetates are also discussed.

Sulfur-containing amidecrownophanes **3a** and **3b** were synthesized from diacid dichloride **1**, which was prepared as described previously[6] (Scheme 1). Macrocycles **2**[7] were obtained from the reaction of **1** with 2,2′-thiobis(ethylamine) and 1,2-bis(2-aminoethylthio)ethane[8] in the presence of triethylamine under normal conditions[3] in acceptable yields. In the reaction mixtures, their cyclic oligomers (dimer and trimer) were not detected. The target macrocycles **3a**[9] and **3b**[9] were then obtained by the TCR of macrocycles **2a** and **2b**. Since the TCR in the molten state was not satisfactory, the rearrangement of **2** was carried out in solution of N-methyl-2-pyrrolidinone (NMP), which had been previously reported to be a good solvent for the TCR.[6] The ^1H and ^{13}C NMR spectra together with mass spectra of the target macrocycles were clearly in agreement with the proposed structures.

Structures of **2a** and **2b** were also characterized in solid state by single-crystal X-ray crystallography (Fig. 1).[10] Colorless crystals of **2a** and **2b** suitable for X-ray analysis were

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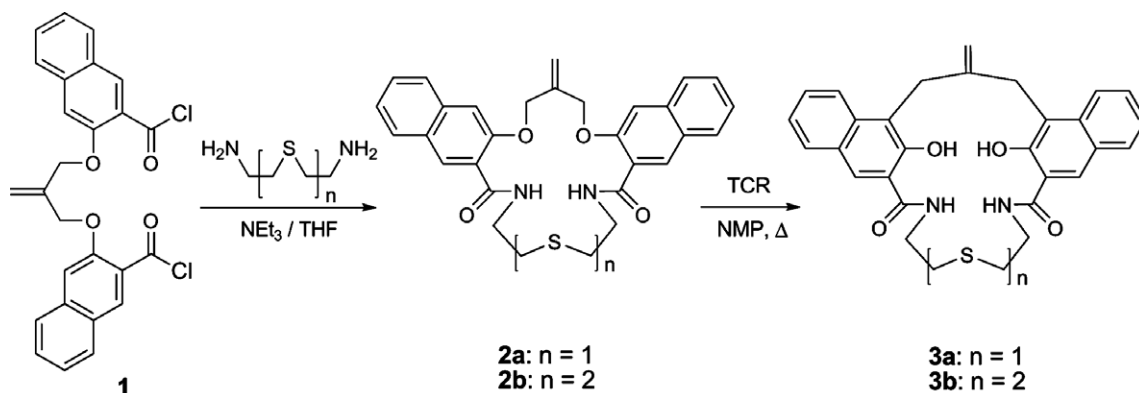
Scheme 1. Synthesis of **3a** and **3b** via macrocyclization and TCR.
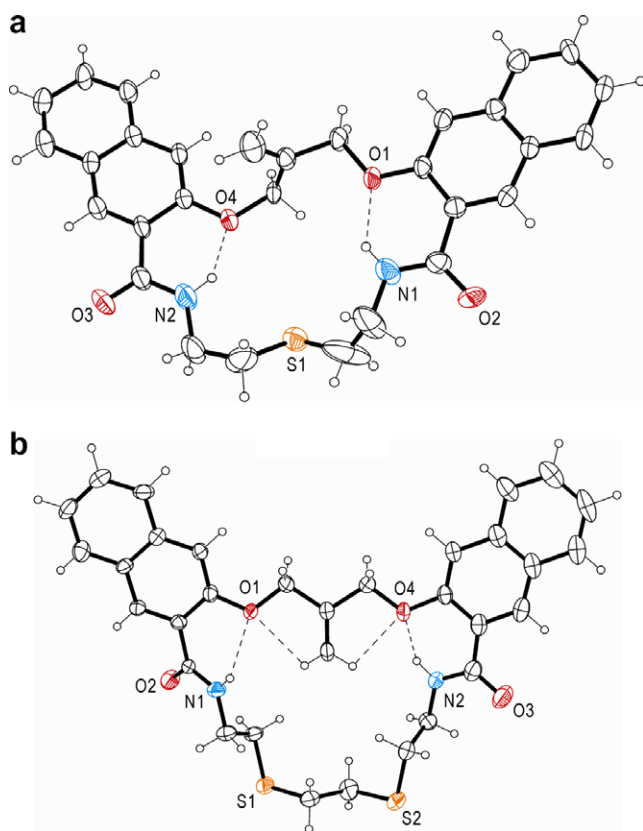
Fig. 1. Molecular structures of (a) **2a** and (b) **2b** with intramolecular hydrogen bonds (dashed lines).

obtained by slow evaporation from ethyl acetate/dichloromethane and chloroform, respectively. In **2a**, the macrocyclic ring is relatively flattened and the nitrogen, sulfur and oxygen donor atoms are oriented endodentate, while the two carbonyl oxygen atoms are arranged exodentate with respect to the ring cavity. Accordingly, the torsion angles between nitrogen and sulfur donors in the ring showgauche–gauche arrangement [N1–C–C–S1 −48.9(2.3)° and S2–C–C–N2 −49.5(1.6)°]. In **2b**, the macrocyclic ring is also flattened and their nitrogen and ethereal oxygen donor atoms are oriented endodentate, while the two sulfur

donors and two carbonyl oxygen atoms are arranged exodentate with respect to the ring cavity. The conformation between nitrogen and sulfur donors shows a trans–trans–trans arrangement [S1–C–C–N1 179.6(4)°, S1–C–C–S2 178.0(3)°, and S2–C–C–N2 180.0(4)°]. The planar conformations of **2a** and **2b** are stabilized by N–H···O type intramolecular hydrogen bonds, which have lengths of ca. 1.9 Å and 2.3 Å, respectively. In **2b**, C–H···O type intramolecular hydrogen bonds (ca. 2.3 Å) between C=C bond of the isobutenylene moiety and oxygen donors also stabilize the conformation. Dihedral angles between two naphthalene rings in **2a** and **2b** are 18.3(1)° and 6.1(2)°, respectively.

The reactivity of amidecrownophanes **3a** and **3b** with some metal salts such as $Hg(OAc)_2$, $Pb(OAc)_2$ and $Ni(OAc)_2$ was examined. Somewhat surprisingly, the reaction between **3b** and mercury(II) did not produce a complex form but rather an organomercurated product. In fact, the reaction of $Hg(OAc)_2$ with **3b** in DMF/ether yields colorless crystalline product **4**. X-ray analysis[10] revealed that **4** is an intramolecular mercurated dihydrobenzofuran product[11] (Fig. 2). We assumed that a reasonable starting point in understanding the observed crystalline product is to consider that the mercury(II) salt may induce such reaction, since no other metal salts have resulted in the same reactions in this work. Worthy to note, this reaction is known to proceed through electrophilic attack of mercury(II) on the double bond to produce a positively charged species, which is trapped by the nucleophilic neighboring group.[12] As illustrated in Scheme 2a, the internal nucleophilic attack usually occurs at the C-2 carbon of the allylic side chain giving rise to the mercurated dihydrobenzofuran ring.[12–14] According to our comparative NMR experiment, this reaction was completed within several minutes at room temperature (see Fig. 4c).

In the crystal of **4**, the Hg1–C3 bond distance [2.053(6) Å] is comparable with that reported in the literature.[15] The bond angle of C3–Hg1–O5 is 175.4(2)° due to the Hg1···O4 interaction (dashed line, 3.186 Å) that is shorter than the sum of van der Waals radii for mercury and oxygen. As we understand, **4** is the first characterized example of a macrocyclic organomercuric product
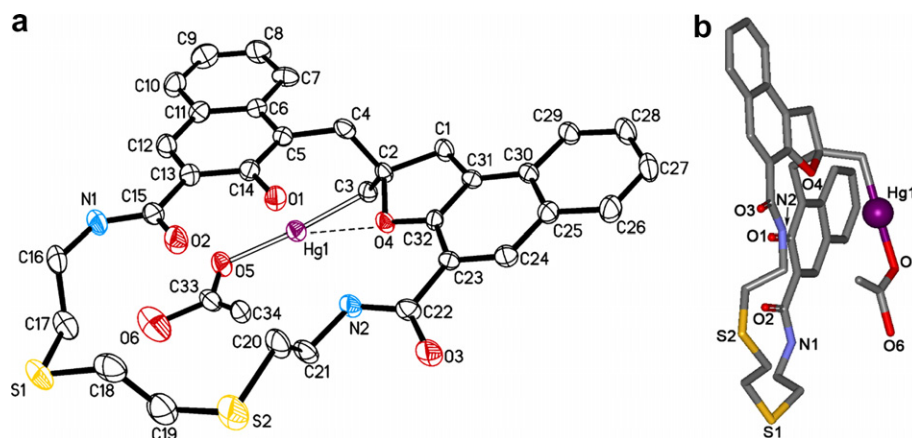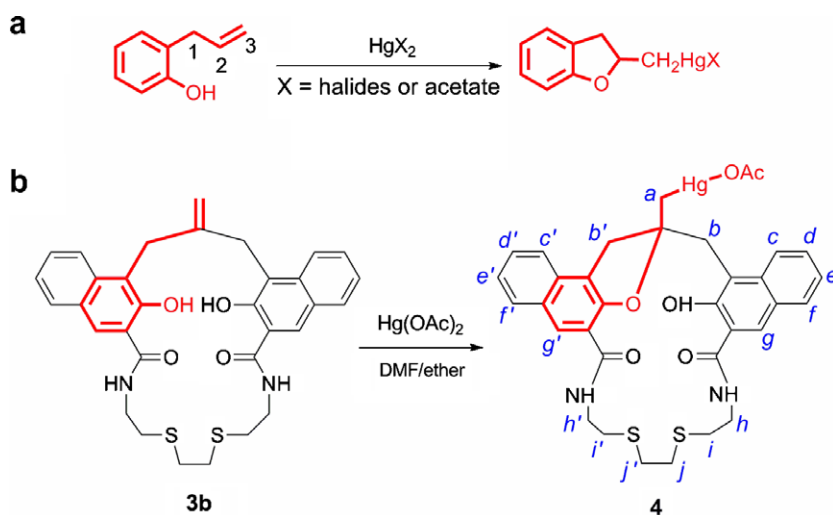
Fig. 2. Molecular structure of **4**: (a) general view (ORTEP drawing) and (b) side view (ball and stick drawing).

Scheme 2. Formation of mercurated dihydrobenzofurans: (a) intramolecular addition reactions from Adams et al.[12] and (b) this work.

produced by the attack of a C=C double bond by a phenolic hydroxyl group. FAB mass spectrum of **4** showed a cluster of peaks at m/z 773, with the correct isotope pattern corresponding to the $[\mathbf{4}\text{-OAc}]^+$ (Fig. S1).

We also carried out several experiments to examine the solution behavior of **3b** with metal ions. More detailed information on the solution structure could be convincingly obtained from the ESI-mass. Figure 3 shows the ESI-MS spectrum of **3b** with a mixture of 3.0 equiv of Hg(OAc)$_2$. The peaks at m/z 773, 833, 973, and 1032 evidently indicate the formation of species $[\mathbf{4}\text{-OAc}]^+$, $[\mathbf{4}\text{+H}]^+$, $[\mathbf{4}\text{-OAc+Hg-2H}]^+$, and $[\mathbf{4}\text{+Hg-H}]^+$. And these are assigned to mercurated **4** and potential coordination species, suggesting that mercury(II) may be bound to **4** when the excess of Hg(OAc)$_2$ exists. This peak is also verified by comparison of the isotopic patterns between the observed peak and the theoretical simulation.

^{1}H NMR spectra of **3b** show two different situations after the addition of metal acetates (Fig. 4). Added nickel(II) acetate induces the resonance signals shifted relative to the free ligand with peak broadening (Fig. 4b).
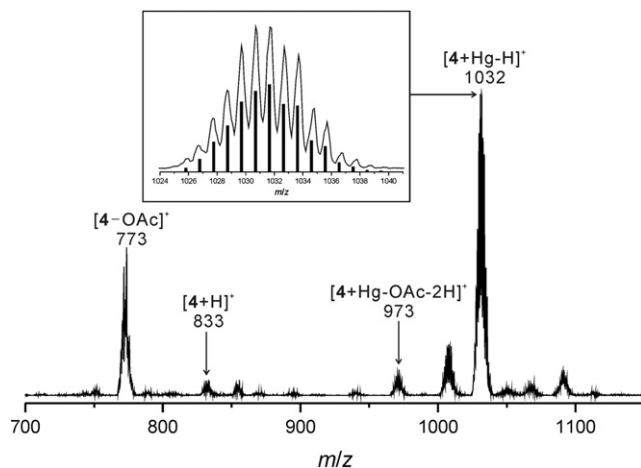

Fig. 3. ESI-MS spectrum of **3b** with Hg(OAc)$_2$ (3.0 equiv) in CH$_3$CN/ DMSO.

A similar effect is also observed for lead(II) acetate (Fig. S2). This indicates the binding of nickel(II) or lead(II) to **4b** with a fast exchange rate between free and complexed
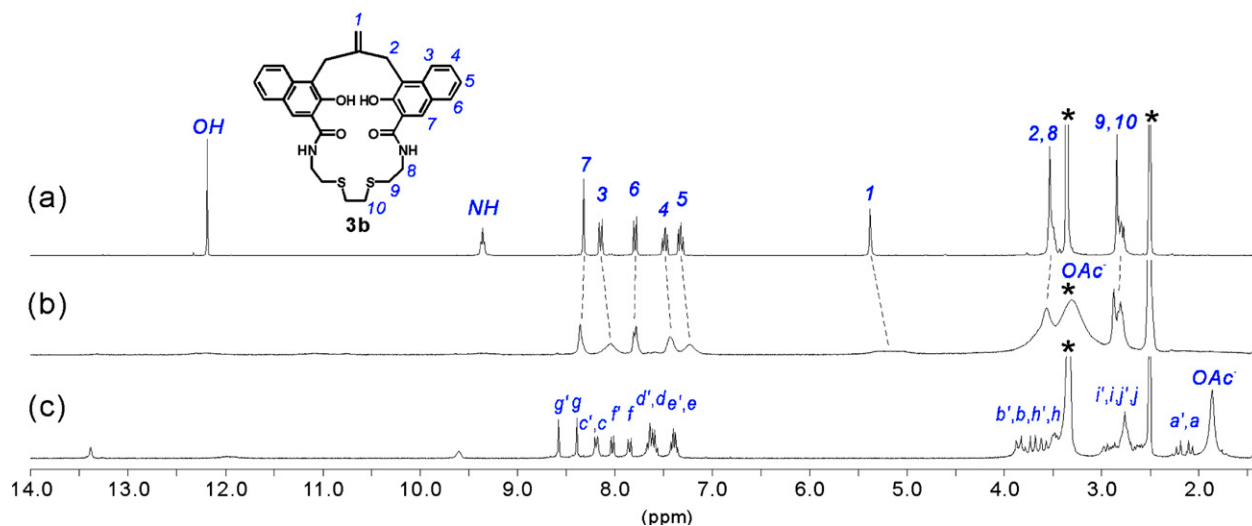
Fig. 4. ^{1}H NMR spectra for (a) **3b**, (b) **3b** + Ni(OAc)$_2$·4H$_2$O (1.0 equiv) and (c) **3b** + Hg(OAc)$_2$ (1.0 equiv; for the peak assignment, see the labels for **4** in Scheme 2) in DMSO-d_6. The asterisk denotes NMR solvent or water peaks.

ligand. Unlike nickel(II) or lead(II), the addition of mercury(II) to **3b** shows the characteristic resonance signal pattern for the formation of the mercurated product **4** (Fig. 4c). As mentioned above, this reaction proceeds within a few minutes in the NMR tube at room temperature. Although no crystal structure was obtained, the mercuration of **3a** with Hg(OAc)$_2$ was also confirmed by ^{1}H NMR and FAB- mass studies (Figs. S3 and S4).

Using fluorescence spectroscopy as a preliminary tool, we then examined the metal ion binding of **3b** by comparing the fluorescence intensities. The fluorescence spectrum of **3b** exhibits a characteristic emission of naphthalene with $\lambda_{max} = 473$ nm. We found that the fluorescence of **3b** was strongly enhanced by Pb(II) and Ni(II); however, the fluorescence was quenched after the addition of Co(II) and

Cu(II). These results suggest that, at least, Pb(II) and Ni(II) can bind to **3b** efficiently. The bonding affinities of Pb(II) and Ni(II) to **3b** are also supported by ESI-MS and comparative NMR experiments. For example, the chemical shifts of H$_2$ and H$_{8,9,10}$ of **3b** are downfield shifted, and m/z 629 and 779 corresponding to [**3b**+Ni−H]$^+$ and [**3b**+Pb−H]$^+$, respectively, were observed. Unlike other metal ions, Hg(II) induced the wavelength shift, suggesting that the mercuration described above occurs (Fig. 5).

In summary, we have developed the synthesis of sulfur-containing amidecrownophanes **3a** and **3b** via TCR. From the reaction of **3b** with Hg(OAc)$_2$, organomercurated **4** was obtained as a first example of this type of macrocyclic. Further development and potential application of **3a** and **3b** are ongoing.
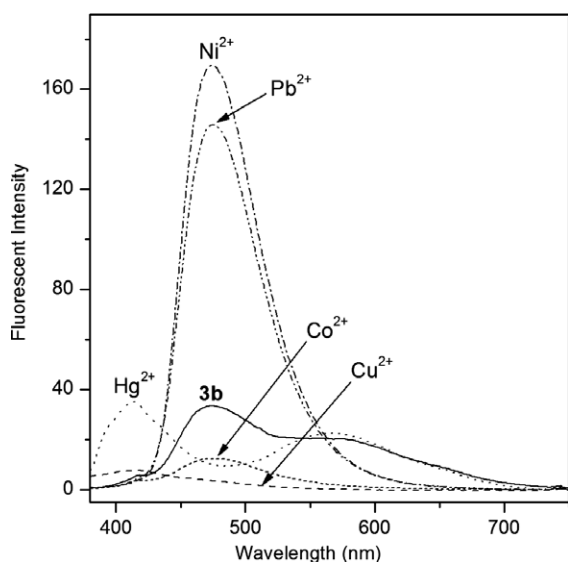
Acknowledgment

Supplementary data

FAB mass for [**4**−AcO$^−$]$^+$ and [**3**+Hg−H]$^+$, and ^{1}H NMR spectra of **3b** and **3b**+Pb(OAc)$_2$, **3a** and **3a**+Hg(OAc)$_2$ are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.013.

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Fig. 5. Fluorescence spectra of **3b** (1.26×10^{-4} M) in DMSO upon the addition of metal acetates (5.0 equiv). $\lambda_{ex} = 370$ nm.

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7. General procedure for the synthesis of **2**: A solution of diamine derivatives (1.0 mmol) containing Et$_3$N (200 mg, 2.0 mmol) in 20 mL tetrahydrofuran (THF) was prepared in a flask and cooled by ice-water bath, then isobutenyl binaphthyl di(acid chloride) **1** (0.465 g, 1.0 mmol), also in 20 mL THF, was added dropwise to the solution over a period of about 20 min and stirring was continued overnight at room temperature. THF was evaporated off under reduced pressure and extracted with CHCl$_3$. Purification was performed by column chromatography with mixed AcOEt and CHCl$_3$ as the eluent. Compound **2a**: white solid; yield 30%; mp 235–239 °C; ^{1}H NMR (300 MHz, CDCl$_3$), δ 2.90 (m, 4H, SCH$_2$), 3.73 (m, 4H, NCH$_2$), 4.98 (s, 4H, OCH$_2$), 5.72 (s, 2H, =CH$_2$), 8.68 (br, 2H, NH), 7.4–8.8 (m, 12H, Ar) ppm; ^{13}C NMR (75 MHz, CDCl$_3$), δ 34.07, 39.59, 69.69, 108.17, 120.05, 122.08, 124.95, 126.22, 128.47, 128.49, 129.23, 134.25, 135.51, 139.02, 153.76, 164.83 ppm; EI-HRMS *m/z* calcd for C$_{30}$H$_{28}$N$_2$O$_4$S (M$^+$), 512.1770; Found 512.1771. Compound **2b**: white solid; yield 41%; mp 140–145 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.84 (m, 8H, CH$_2$SCH$_2$), 3.72 (m, 4H, NCH$_2$), 5.05 (s, 4H, OCH$_2$), 5.63 (s, 2H, =CH$_2$), 8.40 (br, 2H, NH), 7.2–8.7 (m, 12H, Ar) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 32.94, 32.98, 39.12, 69.81, 108.05, 117.93, 122.72, 124.93, 126.32, 128.43, 128.47, 129.15, 133.86, 135.49, 138.23, 153.45, 165.19 ppm.

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9. General procedure for the synthesis of **3**: Corresponding macrocyclic compound **2** was dissolved in NMP (2.0 mL). The solution was heated at 170 °C for 17 min (**3a**) and for 50 min (**3b**) under argon atmosphere. The mixture was concentrated under reduced pressure to afford a brown solid. Purification was performed by recrystallization from CHCl$_3$. Compound **3a**: white solid; yield 33%; mp 219–225 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.95 (m, 4H, SCH$_2$), 3.54 (m, 4H, NCH$_2$), 3.64 (s, 4H, ArCH$_2$), 5.49 (s, 2H, =CH$_2$), 7.2–8.2 (m, 10H, Ar), 9.19 (br, 2H, NH), 12.04 (s, 2H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.34, 31.94, 114.58, 116.04, 117.34, 123.01, 123.14, 126.40, 127.59, 127.90, 129.67, 136.71, 150.50, 155.14, 170.15 ppm; EI-HRMS *m/z* calcd for C$_{30}$H$_{28}$N$_2$O$_4$S (M$^+$), 512.1770; Found 512.1769. Compound **3b**: white solid, yield 40% mp 213–220 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.82 (m, 8H, CH$_2$SCH$_2$), 3.52 (m, 8H, ArCH$_2$, NCH$_2$), 5.38 (s, 2H, =CH$_2$), 7.3–8.3 (m, 10H, Ar), 9.35 (br, 2H, NH), 12.19 (s, 2H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.37, 30.79, 32.02, 115.59, 116.56, 117.96, 123.26, 123.55, 126.53, 127.46, 128.09, 129.85, 136.39, 149.84, 155.23, 170.27 ppm; EI-HRMS *m/z* calcd for C$_{32}$H$_{32}$N$_2$O$_4$S$_2$ (M$^+$), 572.1803; Found 572.1802.

10. Crystal data for **2a**: monoclinic, space group $P2_1/n$, $a = 12.120(9)$ Å, $b = 11.0494(7)$ Å, $c = 12.120(9)$ Å, $\beta = 96.64°$, $V = 2566(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.327$ mg/m^3, $R_1 = 0.1033$, $wR_2 = 0.2338$ [$I > 2\sigma(I)$]. Crystal data for **2b**: triclinic, space group $P\bar{1}$, $a = 10.1410(13)$ Å, $b = 12.4857(16)$ Å, $c = 14.5963(18)$ Å, $\alpha = 102.426(3)°$, $\beta = 109.773(2)°$, $\gamma = 102.465(2)°$, $V = 1612.5(4)$ Å^3, $Z = 2$, $D_{calcd} = 1.425$ mg/m^3, $R_1 = 0.0714$, $wR_2 = 0.1700$ [$I > 2\sigma(I)$]. Crystal data for **4**: triclinic, space group $P\bar{1}$, $a = 12.7930(11)$ Å, $b = 13.0291(11)$ Å, $c = 13.4657(11)$ Å, $\alpha = 74.606(2)°$, $\beta = 64.695(2)°$, $\gamma = 84.074(2)°$, $V = 1956.2(3)$ Å^3, $Z = 2$, $D_{calcd} = 1.598$ mg/m^3, $R_1 = 0.0450$, $wR_2 = 0.0927$ [$I > 2\sigma(I)$]. CCDC 659069, 659070 and 659071 contain the supplementary crystallographic data for **2a**, **2b** and **4**.

11. Compound **4**: A solution of Hg(OAc)$_2$ (20.0 mg, 0.062 mmol) in DMF (1.0 mL) was added dropwise to a solution of **3b** (30 mg, 0.052 mmol) in DMF (1.0 mL). Single crystals suitable for X-ray crystallography were prepared by the vapor diffusion of diethyl ether into the solution in 40% yield: colorless crystal; mp 195–197 °C (decomp.); IR (KBr) 3442 mw (v_{O-H}), 3357 m (v_{N-H}), 1650 s ($v_{C=O}$), 1541 m (v_{N-H}), 1359 m (v_{C-O}) cm^{-1}; FAB-MS *m/z* 773 [M–OAc]$^+$.

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