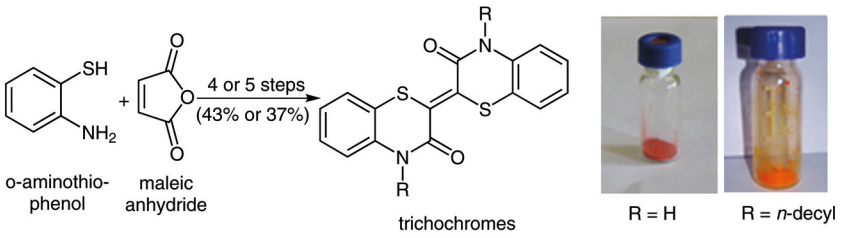
Synthesis R. Jangir et al. Paper

Sulfuryl Chloride Promoted *gem*-Dichlorination–Dehydrochlorination in Alkyl Benzothiazinylacetates: Synthesis of the Skeleton of Trichochrome Pigments

Ravi Jangir
Smita R. Gadre
Narshinha P. Argade*

Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune 411 008, India
np.argade@ncl.res.in



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Abstract Chemo- and stereoselective total synthesis of the basic trichochrome skeleton is described starting from *o*-aminothiophenol and maleic anhydride in very good overall yield. The process involves the synthesis of the corresponding 1,4-benzothiazin-2-ylacetates followed by their sulfuryl chloride induced dihalogenation–dehydrohalogenation and a second condensation with *o*-aminothiophenol as key steps.

Key words *o*-aminothiophenol, maleic anhydride, halogenation, condensations, trichochrome framework

Trichochromes bearing an indigoid chromophore have been isolated from human red hair, and such types of natural products are depicted in Figure 1. The presence of the indigoid chromophore in these systems is responsible for hair color even at very low concentrations.[1] Synthesis of such types of natural and unnatural safe coloring compounds would be useful to the flourishing dye industries. Kaul reported the one-pot synthesis of the trichochrome skeleton starting from *o*-aminothiophenol and dichloromaleic anhydride (Scheme 1),[2a] but this approach is limited for the synthesis of symmetrically substituted bibenzothiazine derivatives.[2] In continuation of our studies on cyclic anhydrides and derivatives in structurally interesting and biologically useful natural products and heterocyclic architectures,[3] we herein report the flexible stepwise synthesis of the trichochrome skeleton from readily available maleic anhydride via a novel sulfuryl chloride chlorination route.

The reaction of *o*-aminothiophenol (**2**) with maleic anhydride (**4**) in diethyl ether at room temperature gives the desired 1,4-benzothiazinylacetic acid **5** in 98% yield by a literature procedure (Scheme 2).[4] This reaction plausibly takes place via the Michael-type addition of the thiol unit of *o*-aminothiophenol (**2**) to the C=C bond in maleic anhydride, followed by regioselective in situ intramolecular aminolysis.[5]

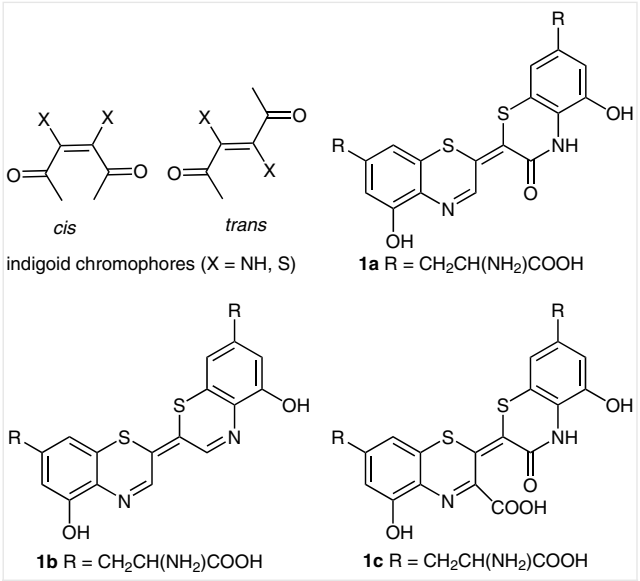
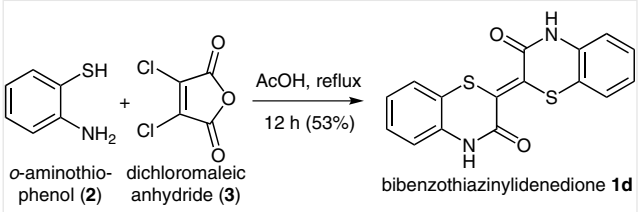
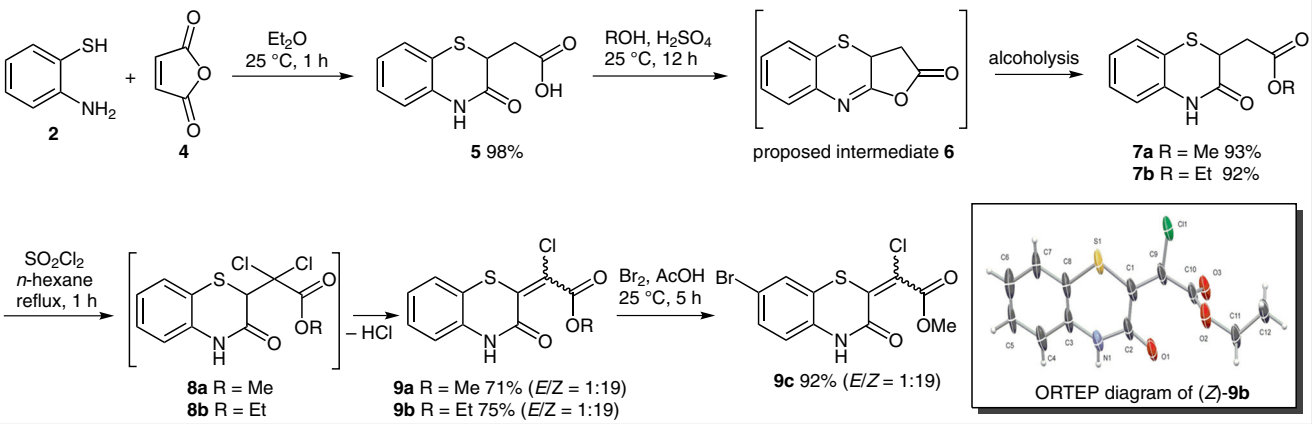


Figure 1 Indigoid chromophores and trichochromes from human red hair



Scheme 1 Kaul's one-pot synthesis of bibenzothiazinylidenedione

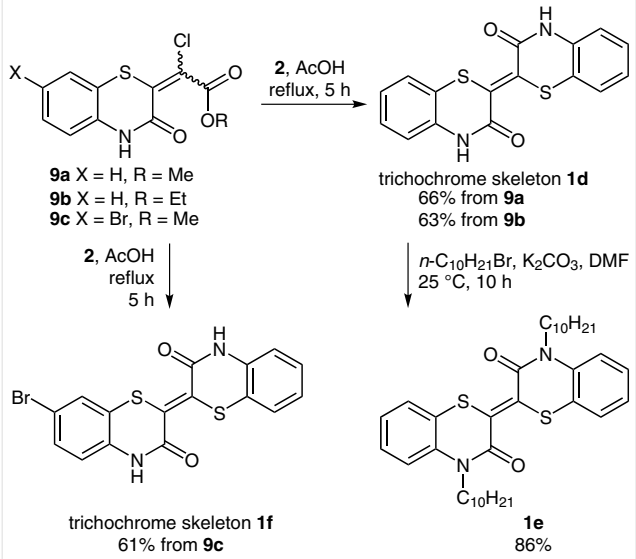


Scheme 2 Synthesis of trichochrome intermediates from *o*-aminothiophenol and maleic anhydride

The acid-catalyzed esterification of acid **5** with methanol or ethanol at room temperature smoothly delivered the corresponding methyl **7a** or ethyl ester **7b** in more than 90% yield. We presume that the esterification reactions take place via a reactive isosuccinimide intermediate **6** and hence do not demand reflux conditions.

Sulfuryl chloride has been used for both *gem*-dichlorination of active methylene compounds and also for desulfurization reactions.[6,7] The reaction of benzothiazinylacetates **7a**,**b** with sulfuryl chloride under reflux conditions was highly chemo- and stereoselective and directly delivered the chlorobenzothiazinylideneacetates **9a**,**b** in more than 70% yield via the corresponding unisolable *gem*-dichloro intermediates **8a**,**b**. The mixtures of *E*- and *Z*-isomers of **9a**,**b** were inseparable by column chromatography on silica gel and their ratio was *E*/*Z* 1:19 by ^{1}H NMR. The geometry of the C=C bond in the major isomers of **9a** and **9b** was confirmed on the basis of X-ray crystallographic data obtained for ethyl ester **9b**. As expected the thermodynamically more stable *Z*-isomers were formed as the major product in both transformations due to the effective conjugation of lone pairs on the sulfur atom with the α,β-unsaturated ester moiety. This observation is in concurrence with our earlier studies on *N*-bromosuccinimide-induced isomerizations of C=C bonds bearing a methoxy substituent.[8] In the sulfuryl chloride promoted reaction of **7a**,**b** to **9a**,**b**; we did not notice any desulfurization taking place under the conditions used. The reaction of bromine in acetic acid with the methyl ester **9a** at room temperature was regioselective and exclusively delivered the corresponding 3-bromo ester **9c** in 92% yield.

As depicted in Scheme 3, the second coupling reactions of chlorobenzothiazinyl acrylates **9a**,**b** with *o*-aminothiophenol (**2**) in refluxing acetic acid furnished the desired dark red trichochrome product **1d** in more than 60% yield. Vinylic substitution of the chloride anion by the relatively more reactive thiol function in *o*-aminothiophenol (**2**) plausibly takes place initially by an addition–elimination pathway resulting in isomerization of the C=C bond together with subsequent concomitant lactamization. The trichochrome **1d** was poorly soluble in most organic solvents and hence its hydrocarbon character was enhanced by the preparation of its didecyl derivative **1e**. Finally the synthesis of an unsymmetrical trichochrome skeleton was planned from the corresponding bromochlorobenzothiazinylideneacetate **9c**.



Scheme 3 Synthesis of symmetrical and unsymmetrical skeletons of trichochrome pigments

Similarily, the second coupling reaction of precursor **9c** with *o*-aminothiophenol (**2**) in refluxing acetic acid furnished the desired unsymmetrical dark red trichochrome product **1f** in 61% yield. The analytical and spectral data obtained for all three trichochrome systems **1d**–**f** were in complete agreement with their assigned structures.

In summary, starting from inexpensive and readily available starting materials we have demonstrated a new efficient synthesis of trichochrome skeletons. The sulfuryl chloride mediated stereoselective halogenation of benzothiazinylacetates is noteworthy from the point of view of basic chemistry. The present approach to trichochrome is general in nature and it will be useful in the design of several symmetrical/unsymmetrical natural/unnatural congeners of bibenzothiazinylidenediones.

Melting points are uncorrected. ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz, and 700 MHz NMR spectrometers using TMS as an internal standard. ^{13}C NMR spectra were recorded on 200 (50 MHz), 400 (100 MHz), 500 (125 MHz), and 700 NMR spectrometers (175 MHz). Mass spectra were recorded on a MS-TOF mass spectrometer. HRMS (ESI) were recorded using a Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. IR spectra were recorded on an FT-IR spectrophotometer. Column chromatographic separations were carried out on silica gel (60–120 mesh). Commercially available *o*-aminothiophenol, maleic anhydride, SO_2Cl_2, and *n*-decyl bromide were used.

2-(3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)acetic Acid (5)

To a stirred solution of maleic anhydride (**4**, 2.45 g, 25 mmol) in Et_2O (40 mL) was added *o*-aminothiophenol (**2**, 3.13 g, 25 mmol) in a dropwise fashion at 25 °C under argon; the mixture was stirred for 1 h. The separated precipitate was filtered on a Buchner funnel and washed with Et_2O (25 mL). The obtained product was dried under vacuum to give pure acid **5**; yield: 5.50 g (98%); mp 181–182 °C (MeOH).

IR ($CHCl_3$): 3204, 1699, 1662 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.43 (dd, *J* = 16, 8 Hz, 1 H), 2.85 (dd, *J* = 16, 8 Hz, 1 H), 3.79 (dd, *J* = 8, 8 Hz, 1 H), 6.99 (d, *J* = 8 Hz, 1 H), 6.70 (t, *J* = 8 Hz, 1 H), 7.21 (t, *J* = 8 Hz, 1 H), 7.33 (d, *J* = 8 Hz, 1 H), 10.67 (s, 1 H), 12.54 (br s, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 33.7, 37.5, 117.1, 118.2, 123.1, 127.3, 127.6, 136.9, 165.7, 171.1.

MS (ESI): *m*/*z* (%) = 246 (100) [M + Na]$^+$.

Methyl 2-(3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)acetate (7a); Typical Procedure

To a stirred solution of acid **5** (1.12 g, 5.00 mmol) in MeOH (25 mL) was added catalytic amount of concd H_2SO_4 at 25 °C. The mixture was stirred for 12 h and concentrated in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the organic layer was washed with water (25 mL) and brine (25 mL), and dried (Na_2SO_4). The organic layer was concentrated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–petroleum ether, 3:7) to give the methyl ester **7a** as a crystalline solid; yield: 1.10 g (93%); mp 142–143 °C.

IR ($CHCl_3$): 3200, 1745, 1668 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.62 (dd, *J* = 16, 8 Hz, 1 H), 3.08 (dd, *J* = 16, 8 Hz, 1 H), 3.74 (s, 3 H), 4.02 (dd, *J* = 8, 6 Hz, 1 H), 6.92 (dd, *J* = 8, 2 Hz, 1 H), 7.03 (dt, *J* = 8, 2 Hz, 1 H), 7.21 (dt, *J* = 8, 2 Hz, 1 H), 7.32 (dd, *J* = 8, 2 Hz, 1 H), 9.16 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.0, 38.0, 52.2, 117.3, 119.0, 124.0, 127.4, 128.1, 135.9, 167.2, 170.5.

MS (ESI): *m*/*z* (%) = 260 (100) [M + Na]$^+$.

Ethyl 2-(3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)acetate (7b)

Following the typical procedure for **7a** using acid **5** and EtOH gave a crystalline solid; yield: 1.15 g (92%); mp 122–123 °C.

IR ($CHCl_3$): 3206, 1739, 1670 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 8 Hz, 3 H), 2.61 (dd, *J* = 18, 8 Hz, 1 H), 3.07 (dd, *J* = 16, 6 Hz, 1 H), 4.03 (dd, *J* = 16, 6 Hz, 1 H), 4.21 (q, *J* = 8 Hz, 2 H), 6.91 (d, *J* = 8 Hz, 1 H), 7.03 (t, *J* = 8 Hz, 1 H), 7.20 (t, *J* = 8 Hz, 1 H), 7.32 (d, *J* = 8 Hz, 1 H), 9.12 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.2, 38.0, 61.2, 117.2, 119.1, 124.2, 127.4, 128.1, 135.9, 167.2, 170.1.

MS (ESI): *m*/*z* (%) = 274 (100) [M + Na]$^+$.

Methyl (*E*/*Z*)-2-Chloro-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylidene)acetate (9a); Typical Procedure

To a stirred slurry of methyl ester **7a** (118 mg, 0.50 mmol) in *n*-hexane (10 mL) was added SO_2Cl_2 (0.25 mL, 2.50 mmol) in dropwise fashion at 25 °C. The mixture was refluxed for 1 h and then allowed to cool to r.t. The mixture was slowly quenched with solid $NaHCO_3$ (250 mg) and it was further stirred for 1 h. The mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (25 mL). The organic layer was washed with water (25 mL) and brine (25 mL), and dried (Na_2SO_4). The organic layer was concentrated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–petroleum ether, 2:8) to give a yellow crystalline solid; yield: 95 mg (71%); ratio *E*/*Z* 1:19; mp 196–198 °C.

IR ($CHCl_3$): 3315, 1727, 1665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 3.91 (s, 3 H), 6.93 (d, *J* = 8 Hz, 1 H), 7.08 (t, *J* = 8 Hz, 1 H), 7.20 (t, *J* = 8 Hz, 1 H), 7.25 (d, *J* = 8 Hz, 1 H), 9.98 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*Z*-isomer) = 53.4, 115.8, 117.3, 124.3, 124.4, 124.7, 125.4, 127.2, 132.6, 156.9, 164.4.

MS (ESI): *m*/*z* (%) = 292/294 (9/5) [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8O_3NClNaS$: 291.9806; found: 291.9800.

Ethyl (*E*/*Z*)-2-Chloro-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylidene)acetate (9b)

Following the typical procedure for **9a** using ethyl ester **7b** gave a yellow crystalline solid; yield: 105 mg (75%); ratio *E*/*Z* 1:19; mp 151–153 °C.

IR ($CHCl_3$): 3191, 1734, 1669 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ (*Z*-isomer) = 1.37 (t, *J* = 8 Hz, 3 H), 4.38 (q, *J* = 8 Hz, 2 H), 6.95 (dd, *J* = 8, 2 Hz, 1 H), 7.07 (dt, *J* = 8, 2 Hz, 1 H), 7.20 (dt, *J* = 8, 2 Hz, 1 H), 7.25 (dd, *J* = 8, 2 Hz, 1 H), 10.27 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$,): δ (*Z*-isomer) = 13.8, 62.7, 115.8, 117.3, 123.9, 124.3, 125.1, 125.3, 127.1, 132.7, 157.1, 163.9.

MS (ESI): *m*/*z* (%) = 306/308 (52/18) [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{10}O_3NClNaS$: 305.9962; found: 305.9964.

Methyl (*E*/*Z*)-2-(7-Bromo-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylidene)-2-chloroacetate (9c)

To a stirred solution of methyl ester **9a** (50 mg, 0.185 mmol) in glacial AcOH (5 mL) was added Br_2 (148 mg, 0.92 mmol) at 25 °C and the mixture was stirred for 5 h. The mixture was concentrated in vacuo

and the obtained residue was dissolved in EtOAc (20 mL). The organic layer was washed with 5% aq $Na_2S_2O_3$ (10 mL), water (10 mL), and brine (10 mL), and dried (Na_2SO_4). The organic layer was concentrated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–petroleum ether, 2:8) to give **9c** as a yellow crystalline solid; yield: 60 mg (92%); mp 230–231 °C.

IR ($CHCl_3$): 3176, 1737, 1667 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ (*Z*-isomer)= 3.91 (s, 3 H), 6.76 (d, *J* = 10 Hz, 1 H), 7.31 (dd, *J* = 10, 2 Hz, 1 H), 7.41 (d, *J* = 2 Hz, 1 H), 9.18 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*Z*-isomer) = 53.5, 116.8, 117.9, 118.0, 118.3, 126.1, 127.9, 130.2, 131.8, 156.3, 164.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8O_3NBrClS$: 347.9091; found: 347.9091.

(*E*)-2,2′-Bi[1,4]benzothiazinylidene-3,3′(4*H*,4′*H*)-dione (1d); Typical Procedure

To a stirred solution of methyl ester **9a** (81 mg, 0.30 mmol) in glacial AcOH (5 mL) was added *o*-aminothiophenol (**2**, 75 mg, 0.45 mmol) at 25 °C under argon. The mixture was refluxed for 5 h. The separated solid product was filtered on Buchner funnel and it was washed with AcOH (5 mL) and then EtOAc (10 mL). The obtained product was recrystallized (DMF) to give analytically pure product **1d** as a dark red crystalline solid; yield: 65 mg (66%); mp >300 °C. It was also similarly obtained from the corresponding ethyl ester **9b**; yield: 62 mg (63%).

IR (neat): 3393, 1638, 1582 cm^{-1}.

^1H NMR (700 MHz, DMSO-d_6): δ = 6.99 (d, *J* = 7 Hz, 1 H), 6.99 (t, *J* = 7 Hz, 1 H), 7.14 (t, *J* = 7 Hz, 1 H), 7.26 (d, *J* = 7 Hz, 1 H), 11.16 (br s, 1 H).

^{13}C NMR (175 MHz, DMSO-d_6): δ = 116.2, 118.9, 123.2, 123.9, 124.9, 126.7, 133.6, 158.3.

MS (ESI): *m*/*z* (%) = 327 (30) [M + H]$^+$.

(*E*)-7-Bromo-[2,2′-bi[1,4]benzothiazinylidene]-3,3′(4*H*,4′*H*)-dione (1f)

Following the typical procedure for **1d** using bromo ester **9c** gave a dark red crystalline solid; yield: 31 mg (61%); mp >300 °C.

IR (Nujol): 3292, 3165, 1637, 1582 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 6.90 (d, *J* = 8 Hz, 1 H), 6.94–7.04 (m, 2 H), 7.15 (d, *J* = 8 Hz, 1 H), 7.28 (d, *J* = 8 Hz, 1 H), 7.32 (dd, *J* = 8, 2 Hz, 1 H), 7.52 (d, *J* = 2 Hz, 1 H), 11.23 (s, 1 H), 11.26 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.7, 116.4, 118.0, 118.9, 121.7, 122.8, 123.3, 124.9, 125.0, 126.9, 127.0, 129.5, 133.2, 133.6, 158.28, 158.33.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_9O_2N_2BrNaS_2$: 426.9181; found: 426.9178.

(*E*)-4,4′-Didecyl-[2,2′-bi[1,4]benzothiazinylidene]-3,3′(4*H*,4′*H*)-dione (1e)

To a stirred solution of dione **1d** (33 mg, 0.01 mmol) in dry DMF (5 mL) at 25 °C was added anhyd K_2CO_3 (6.90 mg, 0.05 mmol). After 15 min, *n*-decyl bromide (0.10 mL, 0.05 mmol) was added and the mixture was stirred for a further 24 h under argon. The mixture was diluted with EtOAc (20 mL) and the organic layer was washed with brine (3 × 25 mL) and dried (Na_2SO_4). The organic layer was concentrated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–petroleum ether, 1:9) to give pure **1e** as an orange crystalline solid; yield: 52 mg (86%); mp 82–83 °C.

IR ($CHCl_3$): 3394, 1633, 1587 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6 Hz, 6 H), 1.27 (br s, 24 H), 1.36 (br s, 4 H), 1.74 (quint, *J* = 8 Hz, 4 H), 4.07 (t, *J* = 8 Hz, 4 H), 6.90–7.10 (m, 4 H), 7.10–7.30 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 26.9, 27.3, 29.3 (2 C), 29.5, 29.6, 31.9, 45.3, 116.5, 122.5, 123.4, 126.5, 126.8, 126.9, 136.1, 159.2.

MS (ESI): *m*/*z* (%) = 606 (95%) [M]$^+$.

Anal. Calcd for $C_{36}H_{50}N_2O_2S_2$: C, 71.24; H, 8.30; N, 4.62. Found: C, 71.13; H, 8.54; N, 4.51.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378714.

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