Formation of an Unusual Product in the Reaction of a 1,2,5-Thiadiazolidine 1,1-Dioxide-Derived Thioether with Sulfuryl Chloride

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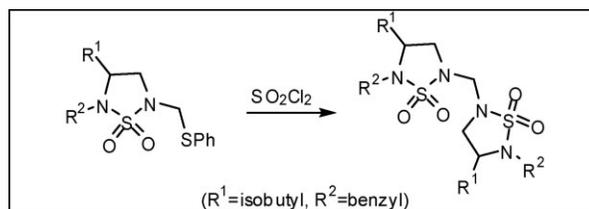David M. Eichhorn, and William C. Groutas*

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$(R^1 = isobutyl, R^2 = benzyl)$

The treatment of a 1,2,5-thiadiazolidine 1,1-dioxide-derived phenylthiomethyl ether with sulfuryl chloride yielded an unexpected dimeric product whose structure was determined using X-ray crystallography. A plausible mechanism for the formation of this product is proposed.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a multifactorial inflammatory disorder characterized by alveolar wall destruction, enlargement of the air spaces, and airflow obstruction due to chronic bronchitis and emphysema [1–3]. The treatment of COPD is symptomatic [4,5], and there are no drugs capable of halting the relentless progression of the disorder. Although the pathogenesis of COPD is poorly understood, recent ground-breaking studies indicate that the disorder involves the close interplay of oxidative stress [6], alveolar septal cell apoptosis [7–9], extracellular matrix destruction arising from a protease/antiprotease imbalance [10,11], and chronic inflammation [12]. Proteases implicated in COPD include serine (neutrophil elastase), cysteine (cathepsin S), and metallo-(MMP-2, MMP-9, and MMP-12) proteases [13]. Agents capable of modulating the aberrant activity of these enzymes may be of potential therapeutic value [14–16].

We have previously described the design, synthesis, and *in vitro* biochemical evaluation of a new and general class of mechanism-based inhibitors of serine proteases (structure (I), Figure 1) [17,18], and have recently demonstrated that the time-dependent inactivation of these enzymes by (I) proceeds through the initial formation of a Michael acceptor (a sulfonyl imine), ultimately leading to the formation of an inactive enzyme-inhibitor complex (or complexes) [19]. A key step in the multistep synthesis of (I) was the synthesis of a substituted *N*-chloromethyl sulfohydantoin via a sulfuryl chloride-mediated cleavage of a phenylthiomethyl ether (Scheme 1).

Based on the successful development of (I), we reasoned that the replacement of the C=O group by a CH_2 group would generate a 1,2,5-thiadiazolidine 1,1-dioxide (cyclosulfamide) and transform (I) into a new class of noncovalent inhibitors (II) (Figure 1) [20]. Accordingly, the appropriate substituted 1,2,5-thiadiazolidine 1,1-dioxide-derived phenylthiomethyl ether intermediate was synthesized and then treated with sulfuryl chloride to obtain the *N*-chloromethyl derivative (Scheme 2). Surprisingly, work up of the reaction mixture and subsequent purification of the product by flash chromatography afforded a solid which did not exhibit the spectral characteristics of the expected *N*-chloromethyl compound. Instead, an interesting dimeric product (7) was obtained, the structure of which and the mechanism leading to it constitutes the subject of the present article.

RESULTS AND DISCUSSION

The structure of product (7) was established on the basis of the following data: the molecular weight of the compound was determined by ESI-MS to be 549, corresponding to the molecular formula $C_{27}H_{40}N_4O_4S_2$, which was in agreement with the elementary analysis of the product. The structure of (7) was established unambiguously via single crystal X-ray crystallography. An ORTEP [21] view (Figure 2) and X-ray crystal structure data (Table 1) are shown below [22].

A plausible mechanism depicting the formation of (7) is outlined in Figure 3, line (a), whereby the initial formation of a chlorosulfonium salt proceeds further along
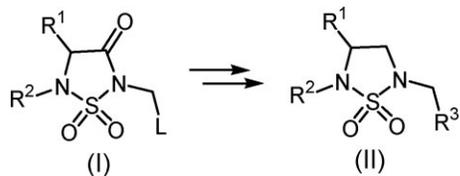
Figure 1. Design of noncovalent inhibitor (II).

two pathways: one leading to an iminium ion (A) [23], and the other leading to a sulfur ylide (B), probably favored by the high acidity of the methylene hydrogens in the moiety -N(SO$_2$N-)CH$_2$SClPh. This ylide subsequently undergoes rearrangement to α-chlorosulfide (C) in a process that is reminiscent of the Pummerer rearrangement [24,25]. When (C) dissociates into an ion pair (both ions are stabilized by resonance), anion (D) undergoes a Michael-type reaction with iminium ion (A) to afford the unusual dimeric product (7). The equilibrium leading to (A) will likely be more favorable for formation of (A) than (B), and hence more favorable for (A) than for (C) and (D). However, capture of (D) by (A) to produce (7) would shift the series of equilibria from (B) to (C) and (D), ultimately leading to (7).

It now becomes clear why such a dimeric product is not observed when the initial phenyl thiomethyl ether bears a carbonyl group at position 3 of the 1,2,5-thiadiazolidine 1,1-dioxide ring, but merely affords the chloromethyl derivative upon treatment with sulfuryl chloride (Figure 3, line (b)). The presence of a C=O group adjacent to nitrogen located at position 2 diminishes its nucleophilicity considerably (by virtue of being adjacent to a C=O group, as well as an SO$_2$ group), rendering path (a) in Figure 3 inoperative and blocking the formation of a dimer.

In summary, the structure of an unexpected dimeric product formed in the reaction of a 1,2,5-thiadiazolidine 1,1-dioxide-derived phenylthiomethyl ether with sulfuryl chloride was determined using X-ray crystallography. A

Scheme 1
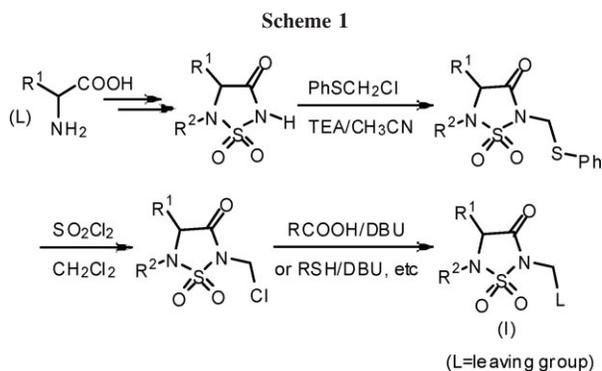
plausible mechanism leading to the formation of this product is proposed.

EXPERIMENTAL

General. The ^{1}H NMR spectra were recorded on a Varian XL-300 or XL-400 NMR spectrometer. Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were taken with a Nicolet FT-IR-Avatar 360 spectrometer. MS spectra were recorded with VARIAN 1200L mass spectrometer. Elemental analysis data were obtained from Columbia Analytical Services (Tucson, AZ). Reagents and solvents were purchased from various chemical suppliers (Aldrich, Acros rganics, TCI America, and Bachem). Silica gel (230–450 mesh) used for flash chromatography was purchased from Sorbent Technologies, Atlanta, GA. Thin layer chromatography was performed using Analtech silica gel plates. The TLC plates were visualized using iodine and/or UV light.

Methyl 2-(Benzylamino)-4-methylpentanoate (1). DL-Leucine methyl ester hydrochloride (43.6 g; 240 mmol) was suspended in 250 mL 1,2-dichloroethane, and then benzaldehyde (30.8 g; 270 mmol) and acetic acid (19.2 g; 320 mmol) were added, followed by sodium triacetoxyborohydride (71.2 g; 335 mmol). The reaction was stirred at RT overnight. The reaction mixture was adjusted to pH 10 using 20% sodium hydroxide, and then two layers were separated. The aqueous layer was extracted with 2 × 100 mL diethyl ether and the organic layers were combined and dried over anhydrous sodium
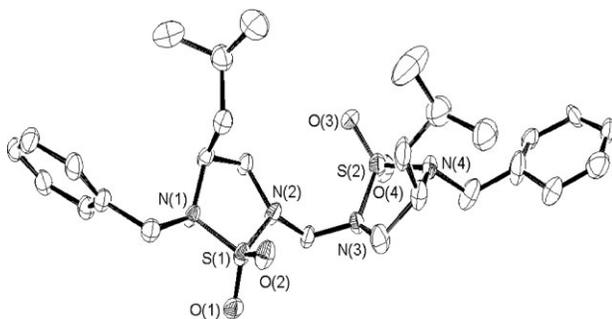
Scheme 2
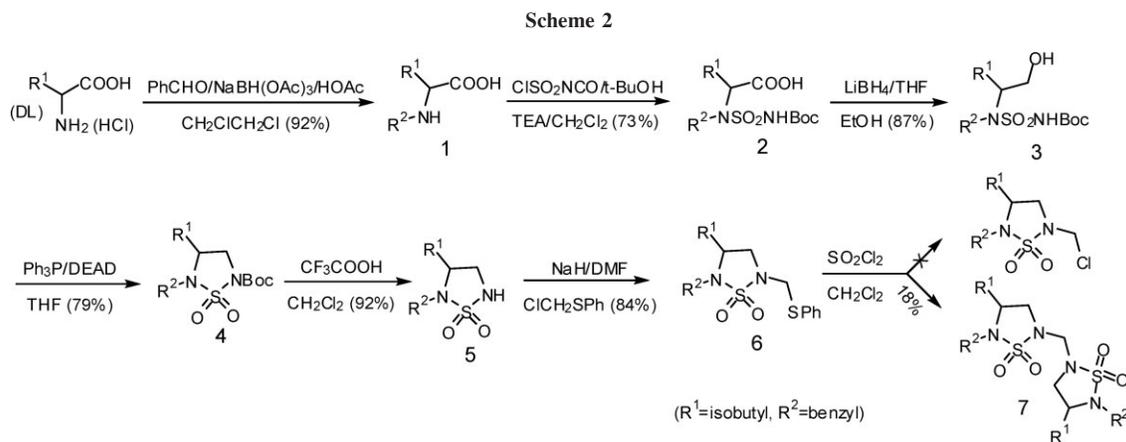
Figure 2. ORTEP drawing of compound **7** showing the 30% thermal ellipsoids. H atoms have been omitted for clarity.

sulfate. Removal of solvent yielded a crude product, which was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **1** as a colorless oil (27.0 g, 48.6% yield). ir (neat): 3333 (NH), 1735 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.88 (dd, 6H, 2CH$_3$, J = 6.6, 19.8 Hz), 1.48 (t, 2H, CH$_2$, J = 7.5 Hz), 3.31 (t, 1H, alpha-H, J = 7.5 Hz), 3.71 (dd, 2H, CH$_2$, J = 12.9, 60 Hz), 3.72 (s, 3H, OCH$_3$), 7.20–7.26 (m, 5H, phenyl protons); ms: m/z 258 (M$^+$+Na, 27%), 236 (M$^+$+1, 53%), 176 (M$^+$-C(O)OCH$_3$, 21%), 91 (phCH$_2^+$, 100%). Anal. Calcd. for C$_{14}$H$_{21}$NO$_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.19; H, 9.28; N, 5.94.

Methyl 2-(Benzyl(*N*-(*tert*-butoxycarbonyl)sulfamoyl)-amino)-4-methylpentanoate (2). A solution of *N*-chlorosulfonyl isocyanate (14.9 g; 103 mmol) in 130 mL dry methylene chloride cooled in an ice bath was added dropwise to a solution of *t*-butyl alcohol (7.72 g; 103 mmol) in 130 mL dry methylene chloride with stirring. After 15 min stirring, the resulting solution was added dropwise to a solution of compound **1** (24.24 g; 103 mmol) and triethylamine (10.6 g; 103 mmol) in 130 mL dry methylene chloride under an ice bath. The ice bath was removed after the addition and the reaction stirred at RT for 6 h. The reaction mixture was washed with 150 mL brine and the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product, which was purified by flash chromatography (silica

gel/ethyl acetate/hexanes) to give compound **2** as a white solid (31.0 g, 72.6% yield), mp 95–96°C. ir (KBr pellet): 3355 (NH), 1740 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.68 (dd, 6H, 2CH$_3$, J = 6.0, 94.5 Hz), 1.40–1.60 (m, 3H, CH & CH$_2$), 1.50 (s, 9H, t-Butyl protons), 3.70 (s, 3H, OCH$_3$), 4.65 (t, 1H, alpha-H, J = 7.5 Hz), 4.71 (dd, 2H, CH$_2$, J = 16.5, 122.1 Hz, CH$_2$), 7.25–7.45 (m, 5H, phenyl protons); ms: m/z 437 (M$^+$+Na, 100%), 381 (M$^+$-OCH$_3$, 19%), 258 (M$^+$-SO$_2$NH-Boc+Na, 29%), 236 (M$^+$-SO$_2$NHBoc+1, 46%), 91 (PhCH$_2^+$, 19%). Anal. Calcd. for C$_{19}$H$_{30}$N$_2$O$_6$S: C, 55.05; H, 7.29; N, 6.76. Found: C, 55.13; H, 7.03; N, 6.62.

tert-Butyl *N*-Benzyl-*N*-(1-hydroxy-4-methylpentan-2-yl) sulfamoylcarbamate (3). To a solution of compound **2** (27.21 g; 65.5 mmol) in 100 mL dry THF, a solution of 2M lithium borohydride in THF (32.8 mL; 65.6 mmol) was added dropwise, followed by the dropwise addition of 197 mL absolute ethanol. The reaction mixture was stirred at RT overnight. The reaction mixture was cooled in an ice bath and neutralized to pH 4 using 5% aqueous HCl solution, and then the solvent was completely removed. Two hundred and fifty millilitres of water was added and extracted with 3 × 300 mL ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product, which was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **3** as a white solid (22.0 g, 86.7% yield), mp 107–109°C. ir (KBr pellet): 3217 (OH), 1733 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.82 (dd, 6H, 2CH$_3$, J = 6.3, 38.4 Hz), 1.05–1.35 (m, 2H, CH$_2$), 1.48 (s, 9H, t-Butyl protons), 1.56–1.65 (m, 1H, CH), 2.82 (t, 1H, OH, J = 5.4 Hz), 3.55–3.70 (m, 2H, CH$_2$), 4.03–4.17 (m, 1H, CH), 4.50 (dd, 2H, CH$_2$, J = 15.9, 29.7 Hz), 7.18–7.45 (m, 5H, phenyl protons); ms: m/z 409 (M$^+$+Na, 100%), 353 (M$^+$-*t*-Butene+Na, 12%), 230 (M$^+$-SO$_2$NHBoc+Na, 35%), 91 (PhCH$_2^+$, 9%). Anal. Calcd. for C$_{18}$H$_{30}$N$_2$O$_5$S: C, 55.94; H, 7.82; N, 7.25. Found: C, 56.11; H, 8.12; N, 7.18.

tert-Butyl 5-Benzyl-4-isobutyl-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide (4). A solution of compound **3** (21.54 g; 55.7 mmol) in 170 mL dry THF was treated with triphenyl phosphine (29.22 g; 111.4 mmol) and diethyl azodicarboxylate (DEAD, 19.4 g; 111.4 mmol) with stirring at RT for 4 h. Removal of the solvent left a crude product, which was purified

Table 1

Crystal data and structure refinement parameters for **7**.

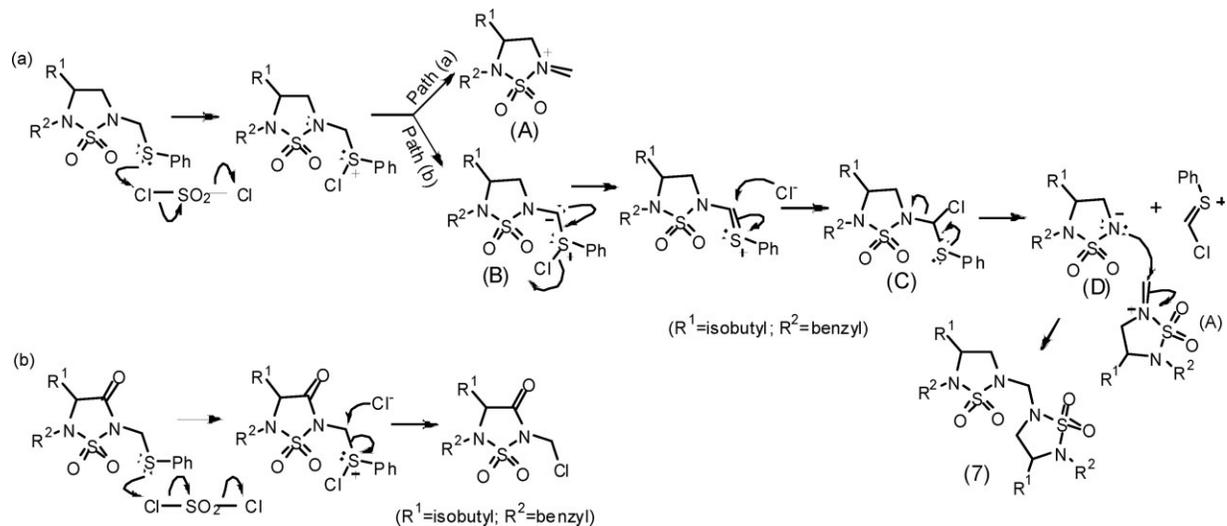|			
Empirical formula	C$_{27}$H$_{40}$N$_4$O$_4$S$_2$	Crystal habit	Needle
Formula weight	548.75	Crystal color	Colorless
Temperature	150 K	Θ range for data collection	2.04° to 26.00°
Diffractometer	Bruker Kappa APEX II		−50 ≤ h ≤ 50
Radiation	Mo Kα, 0.71073 Å	Limiting indices	−7 ≤ k ≤ 7
Crystal system	Monoclinic		−34 ≤ l ≤ 34
Space group	C2/c	Reflections collected/unique	50861/5705 [R(int) = 0.4278]
Unit cell dimensions	a = 40.714(7) Å	Completeness to θ = 26.00°	99.8%
	b = 6.2300(9) Å	Refinement method	Full-matrix least-squares on F^2
	c = 27.774(4) Å	Data/restraints/parameters	5705/0/367
	β = 124.547(9)°	Refinement threshold	$I > 2\sigma(I)$
Volume	5802.5(16) Å^3	Data > threshold	1681
Z	8	Goodness-of-fit on F2	1.021
Density (calculated)	1.256 Mg/m^3	Final R indices [$I > 2\sigma(I)$]	R1 = 0.0896, wR2 = 0.1829
Absorption coefficient	0.222 mm^{-1}	R indices (all data)	R1 = 0.3060, wR2 = 0.3004
F(000)	2352	Largest diff. peak and hole	0.491 and −0.400 e.Å^{-3}
Crystal size	0.43 × 0.06 × 0.05 mm^3		

Figure 3. Postulated mechanism for the formation of compound **7**.

by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **4** as a white solid (16.19 g, 79.0% yield), mp 81–82°C. ir (KBr pellet): 1721 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.79 (dd, 6H, 2CH$_3$, J = 6.3, 14.4 Hz), 1.35–1.60 (m, 3H, CH & CH$_2$), 1.56 (s, 9H, t-Butyl protons), 3.40–3.51 (m, 2H, CH$_2$), 3.80–3.88 (m, 1H, CH), 4.29 (dd, 2H, CH$_2$, J = 15.3, 48.3 Hz), 7.30–7.41 (m, 5H, phenyl protons); ms: m/z 391 (M$^+$+Na, 5%), 335 (M$^+$-t-Butene +Na, 42%), 176 (M$^+$-CH$_2$OH-SO$_2$NHBoc, 35%), 91 (PhCH$_2^+$, 100%). Anal. Calcd. for C$_{18}$H$_{28}$N$_2$O$_4$S: C, 58.67; H, 7.66; N, 7.60. Found: C, 58.85; H, 7.75; N, 7.53.

2-Benzyl-3-isobutyl-1,2,5-thiadiazolidine 1,1-dioxide (5). A solution of compound **4** (15.76 g; 42.8 mmol) in 40 mL dry methylene chloride was treated with trifluoroacetic acid (140 mL) at RT for 3 h. Removal of the solvent left a crude product, which was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **5** as a white solid (10.5 g, 91.5% yield), mp 60–62°C. ir (KBr pellet): 3225 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.80 (dd, 6H, 2CH$_3$, J = 6.3, 24.9 Hz), 1.38–1.58 (m, 3H, CH & CH$_2$), 3.12–3.20 (m, 1H, one proton of CH$_2$), 3.40–3.50 (m, 1H, one proton of CH$_2$), 3.50–3.60 (m, 1H, CH), 4.28(s, 1H, NH), 4.29 (dd, 2H, CH$_2$, J = 12.0, 45.6), 7.25-7.42 (m, 5H, phenyl protons); ms: m/z 291 (M$^+$+Na, 100%), 91 (PhCH$_2^+$, 20%). Anal. Calcd. for C$_{13}$H$_{20}$N$_2$O$_2$S: C, 58.18; H, 7.51; N, 10.44. Found: C, 58.09; H, 7.42; N, 10.20.

2-Benzyl-3-isobutyl-5-[(phenylsulfanyl)methyl]-1,2,5-thia-diazolidine 1,1-dioxide (6). A solution of compound **5** (0.97 g; 3.6 mmol) in 4 mL dry DMF was cooled in an ice bath, and then sodium hydride (0.23 g; 60% w/w; 5.8 mmol) was added with stirring. Ten minutes later, chloromethyl phenyl sulfide (0.80 g; 5.0 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 2 h. DMF was removed by oil pump under 40°C. The residue was dissolved in 30 mL ethyl acetate and washed with 2 × 20 mL brine, and then the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent left a crude product, which was purified by flash chromatography (silica gel/ ethyl acetate/ hexanes) to give compound **6** as a colorless oil (1.18

g, 84.0% yield). ^{1}H NMR (CDCl$_3$): δ 0.75 (dd, 6H, 2CH$_3$, J = 6.0, 20.7 Hz), 1.35–1.50 (m, 3H, CH & CH$_2$), 2.95 (dd, 1H, one proton of CH$_2$, J = 7.2, 9.0 Hz), 3.32–3.43 (m, 1H, CH), 3.65 (m, 1H), 3.65 (dd, 1H, one proton of CH$_2$, J = 7.2, 9.0 Hz), 4.38 (dd, 2H, CH$_2$, J = 7.8, 15.0 Hz), 4.45 (dd, 2H, CH$_2$, J = 13.8, 156.9 Hz), 7.23–7.53 (m, 10H, phenyl protons); ms: m/z 391 (M$^+$+1, 78%), 281 (M$^+$-PhSH, 100%). Anal. Calcd. for C$_{20}$H$_{26}$N$_2$O$_2$S$_2$: C, 61.50; H, 6.71; N, 7.17. Found: C, 61.34; H, 7.04; N, 7.16.

2,2′-Methylenebis(5-benzyl-4-isobutyl-1,2,5-thiadi-azolidine) 1,1,1′,1′-tetraoxide (7). To a solution of compound **6** (1.18 g; 3.0 mmol) in 4 mL dry methylene chloride in an ice bath, a solution of sulfuryl chloride (0.82 g; 6.0 mmol) in 2 mL dry methylene chloride was added with stirring. The reaction was allowed to warm to RT and stirred for 2 h. The solvent was removed and the residue was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **7** as a white solid (0.15 g, 18.2% yield), mp 127–128°C. ^{1}H NMR (CDCl$_3$): δ 0.79 (dd, 12H, 4CH$_3$, J = 6.3, 24.0 Hz), 1.40–1.58 (m, 6H, 2CH & 2CH$_2$), 3.25 (dd, 2H, two protons of 2CH$_2$, J = 6.3, 9.6 Hz), 3.38–3.48 (m, 2H, 2CH), 3.72 (dd, 2H, two protons of 2CH$_2$, J = 6.9, 9.6 Hz), 4.26 (dd, 4H, 2CH$_2$, J = 14.7, 62.1 Hz), 4.60 (s, 2H, bridge CH$_2$), 7.25–7.41(m, 10H, phenyl protons); ms: m/z 549 (M$^+$+1, 76%), 281 (M$^+$-**5**, 100%), 91 (PhCH$_2^+$, 24%). Anal. Calcd. for C$_{27}$H$_{40}$N$_4$O$_4$S$_2$: C, 59.09; H, 7.35; N, 10.21. Found: C, 59.02; H, 7.15; N, 10.17.

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[22] The crystal structure shows disorder in one of the benzene rings. An alternate position for C(25), C(26), and C(27) was modeled with 47% occupancy. The majority component is shown in Figure 3. CCDC 683843 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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