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Domino Reactions of 1,2-Diimidoyl-1,2-dichloroethanes. Synthesis of 3-Imino-1,2-dithia-3*H*-cyclopent-4-enes, 3-Amino-2-thioxo-2,5*H*-pyrrol-5-ones, 2,3-Diamino-4-thioxo-4*H*-thiopyrans, and 6-Imino-6*H*-1,3-oxazines

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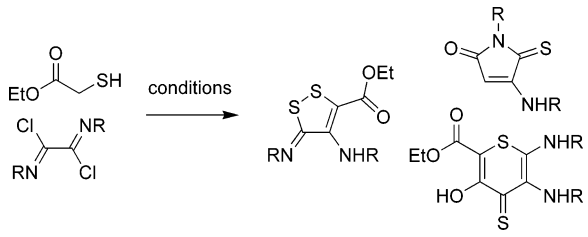

The reaction of mono- and dilithiated ethyl thioglycolate with 1,2-diimidoyl-1,2-dichloroethanes, aza-analogues of oxalyl chloride, afforded (depending on the reaction conditions) 3-imino-1,2-dithia-3*H*-cyclopent-4-enes, 3-amino-2-thioxo-2,5*H*-pyrrol-5-ones, and 2,3-diamino-4-thioxo-4*H*-thiopyrans. The reaction of the dianion of ethyl hippurate with 1,2-diimidoyl-1,2-dichloroethanes afforded 6-imino-6*H*-1,3-oxazines.

Introduction

1,2-Dithiacyclopent-4-ene-3-thiones represent an important class of anticarcinogenes, which selectively induce the cellular production of chemoprotective phase II detoxification enzymes.[1a−d] For example, synthetic oltipraz (Figure 1) possesses potent anticarcinogenic properties based on the cleavage of DNA and has been used as a cancer-preventive agent.[1d] The related 1,2-dithiacyclopentane-3-thiones occur in cruciferous vegetables (e.g., broccoli and cauliflower) and exhibit anticarcinogenic activity.[1a,e,2] Low molecular weight 1,2-dithiacyclopentan-3-one 1-oxides also exhibit antitumor activity based on DNA-cleaving properties;[3a] their heterocyclic core structure is present, for example, in the antitumor natural product leinamycin (Figure 2),[3] which is produced by *Streptomyces atroolivaceous*

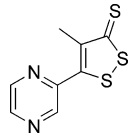

FIGURE 1. Oltipraz.

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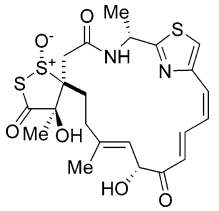


FIGURE 2. Leinamycin.

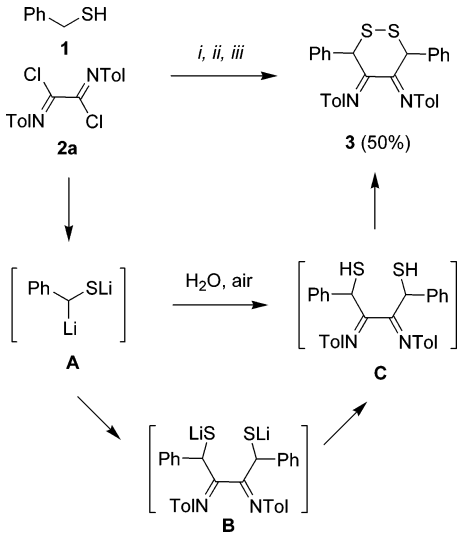
S-140.[3b,c] 1,2-Dithia-3*H*-cyclopent-4-enes are also found in nature, e.g., in the antibiotic natural product thiolutine.[4] Therefore, the synthesis of unsaturated 1,2-dithiacyclopentane derivatives is attractive from both a synthetic and medicinal standpoint. 1,5-Dihydropyrrol-2-ones also represent important synthetic building blocks which are found in a wide range of natural compounds with different biological activities.[5] For example, synthetic imrecoxib (also known as BAP-909) represents inhibitory effects on cyclooxygenase 1 and 2, and its antiinflammatory effect in vivo has been described.[6]

1,2-Dimidoyl-1,2-dichloroethanes[7] represent useful C_2-building blocks in cyclization reactions[8] with various dinucleophiles. Some years ago, we reported the synthesis of a 2,3-diiminothietane and of 1,2-dithia-3*H*-3-iminocyclopent-4-enes by cyclization of dilithiated ethyl thioglycolate with 1,2-diimidoyl-1,2-dichloroethanes.[9] Herein, we wish to report full details and studies related to the scope. With regard to our preliminary communication, the scope was significantly extended; in addition, it was found that the reaction conditions (amount of base, stoichiometry, concentration) have a dramatic influence on the course of the reaction and on the product distribution. In fact, the reaction of ethyl thioglycolate with 1,2-diimidoyl-1,2-dichloroethanes afforded (depending on the conditions) 3-imino-1,2-dithia-3*H*-cyclopent-4-enes, 3-amino-2-thioxo-2,5*H*-pyrrol-5-ones, or 2,3-diamino-4-thioxo-4*H*-thiopyrans. Recently, the synthesis of 3-imino-1,2-dithiacyclopent-4-enes based on ring-opening−ring-closing reactions of 2-alkylidene-4-oxothiazolidines with Lawesson's reagent has been reported.[10] 3-Amino-2-thioxopyrrol-5-ones and 3-aminopyrrol-2,5-dithiones have been prepared by transformation of the carbonyl groups of 3-aminopyrrol-2,5-diones into thiocarbonyl groups.[11] To the best of our knowledge, 2,3-diamino-4-thioxo-4*H*-thiopyrans have not yet been prepared. Synthetic approaches to 2-amino-4-thioxo-4*H*-thiopyrans have only scarcely been reported in the literature.[12,13] The reactions reported herein are useful, due to their operational simplicity. In addition, the starting materials are readily available.

Results and Discussion

Treatment of 1,2-diimidoyl-1,2-dichloroethane **2a** with dilithiated benzyl mercaptane (**1**)[14] gave a complex reaction mixture from which 1,2-dithiane **3** was isolated in low yield (Scheme 1). The formation of **3** can be explained by initial condensation of **2a** with 2 equiv of **1** and subsequent oxidative cyclization. The yield of **3** was improved by employment of 2 rather than only 1 equiv of the dianion. However, a change of the reaction conditions (slow addition of the dianion to **2a**) and of the workup procedure (filtration under inert atmosphere rather than aqueous workup) did not provide the expected 1:1 cyclization product. The reaction of the dianion of allyl mercaptane with **2a** gave a complex mixture.

SCHEME 1. Synthesis of 1,2-Dithiane 3[a]



[a] Key: (i) 1 (2.0 equiv), THF; (ii) *n*-BuLi (4.4 equiv), −78 °C, 4 h; (iii) addition to **2a** (1.0 equiv), THF, −78 °C, −78 → +20 °C, 14 h, then at 20 °C, 2 h.

Synthesis of 3-Imino-1,2-dithia-3*H*-cyclopent-4-enes. The reaction of 1,2-diimidoyl-1,2-dichloroethane **2a** with the dianion of ethyl thioglycolate (**4**), generated according to a literature procedure,[15] resulted in formation of 3-imino-1,2-dithia-3*H*-cyclopent-4-ene **5a** (23%) and of side product **5a′** (9%) (Scheme 2, Table 1). The reaction was carried out by addition of the

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SCHEME 2. Cyclization of Lithiated Ethyl Thioglycolate with Oxaldiimidoyl Dichlorides

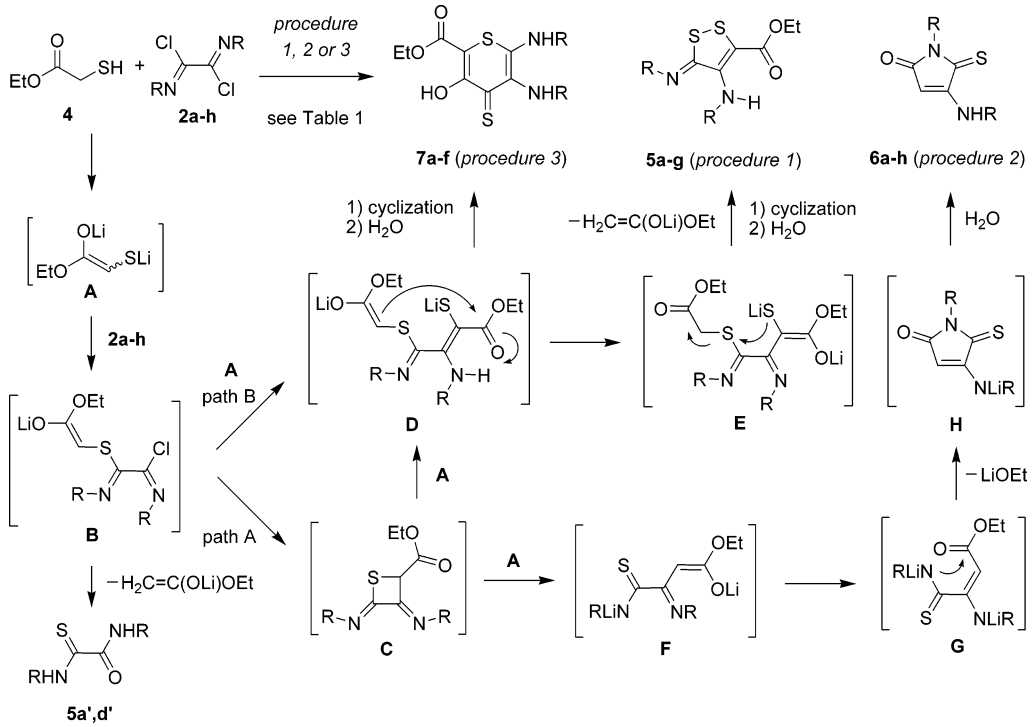
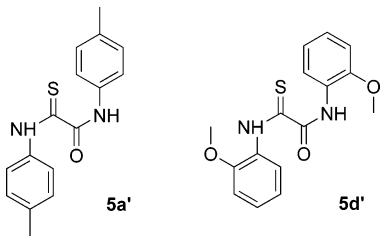


TABLE 1. Product and Yields

5, 6, 7	R	yield (%) (5)[a] procedure 1[b]	yield (%) (6)[a] procedure 2[c]	yield (%) (7)[a] procedure 3[d]
a	4-MeC_6H_4	23[e]	41[g]	79
b	Ph	32	40	62
c	2-MeC_6H_4	28	55	78
d	2-(MeO)C_6H_4	0[f]	55	46
e	4-(MeO)C_6H_4	30	38	69
f	1-naphthyl	28	63	54
g	2,4-$Me_2C_6H_3$	27	40	-
h	3,5-$Me_2C_6H_3$	-	52	-

[a] Yields of isolated products. [b] Procedure 1: (i) (1) LDA (2.3 equiv), TMEDA, **4** (1.0−1.2 equiv), THF, −40 → 0 °C, 1 h, (2) 0 °C, 1 h; (ii) addition to **2** (1.0 equiv, in THF), −78 °C, −78 → +20 °C, 14 h, then 20 °C, 2 h. [c] Procedure 2: (i) (1) LDA (5.0−5.5 equiv), TMEDA, **4** (2.0−2.2 equiv), THF, −40 → 0 °C, 1 h, (2) 0 °C, 1 h; (ii) addition to **2** (1.0 equiv, in THF), −78 °C, −78 → +20 °C, 14 h, then 20 °C, 24 h. [d] Procedure 3: (i) (1) LDA (6.0−9.0 equiv), TMEDA, **4** (5.0−7.0 equiv), THF, −40 → 0 °C, 1 h, (2) 0 °C, 1 h; (ii) addition to **2** (1.0 equiv, in THF), −78 °C, −78 → +20 °C, 14 h, then 20 °C, 48 h. [e] Besides, **5a′** (structure given below) was isolated (9%). [f] Only **5d′** was isolated (31%). [g] Product **5a** was isolated as a side product (24%).



dianion (1.2 equiv) to a THF solution of **2a** (1.0 equiv) at −78 °C, warming of the reaction mixture to 20 °C within 14 h, and finally, addition of hydrochloric acid (10%) (procedure 1). The formation of **5a** can be explained by nucleophilic attack of the sulfur atom of the dianion (intermediate **A**) onto **2** to give intermediate **B**, cyclization to give 2,3-diiminothietane **C**, ring opening by attack of a second molecule of **4** (intermediate **D**) (path A), proton shift (intermediate **E**), cyclization with extrusion of lithiated ethyl acetate and subsequent protonation during the aqueous workup. Alternatively, a direct formation of intermediate **D** by addition of **A** onto **B** is possible (path B). However, path A is supported by the fact that the 2,3-diiminothietane (intermediate **C**, R = *p*-Tol, 30%) rather than **5a** could be isolated when the reaction mixture was warmed to 20 °C within 15 min (rather than 14 h), stirred for 2 h, concentrated, and directly purified by chromatography. Due to their ring strain, four-membered ring lactams and lactones readily undergo ring-expansion or -opening reactions[16,17] and the synthesis of iminothietanes has been previously reported.[18,19] Side product **5a′** was presumably formed by fragmentation of intermediate **B** by extrusion of lithiated ethyl acetate and hydrolysis of the imidoyl chloride upon aqueous workup.

The 1,2-dithia-3*H*-cyclopent-4-enes **5b**−**d** were prepared, according to the procedure as given for **5a**, from 1,2-diimidoyl-1,2-dichloroethanes **2b**−**d**. The reaction of **2e** with **4** gave *N*-(2-methoxyphenyl)-2-(2-methoxyphenylamino)-2-thi-

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oxoacetamide (**5e′**) rather than the expected 1,2-dithia-3*H*-cyclopent-4-ene (**5e**). The reaction of 1,2-diimidoyl-1,2-dichloroethanes **2f**,**g** with **4** afforded the 1,2-dithia-3*H*-cyclopent-4-enes **5f**,**g**. Unfortunately, the isolated yields of **5a**−**g** were rather low, due to incomplete conversion of the starting materials. In fact, significant amounts of diaryloxalamides (formed by hydrolysis of **2** during the aqueous workup) were isolated. In addition, the formation of side products of the type of **5a′** was observed in all reactions.

Synthesis of 3-Amino-2-thioxo-2,5*H*-pyrrol-5-ones. Studies related to the optimization of the cyclization of ethyl thioglycolate (**4**) with 1,2-diimidoyl-1,2-dichloroethanes **2** revealed that the reaction conditions (concentration, reaction time, stoichiometry) and the substituents of the 1,2-diimidoyl-1,2-dichloroethanes have a major influence on the mechanism and the course of the reaction. In fact, the employment of a 2-fold excess of ethyl thioglycolate (procedure 2) resulted in the formation of a new type of product rather than an increase of the yield of 1,2-dithia-3*H*-cyclopent-4-enes **5**. The reaction of dilithiated ethyl thioglycolate (2.0−2.2 equiv) with 1,2-diimidoyl-1,2-dichloroethane **2a** (1.0 equiv) afforded the 3-amino-2-thioxo-2,5*H*-pyrrol-5-one **6a** (41%) and 1,2-dithia-3*H*-cyclopent-4-ene **5a** (24%) (Scheme 2, Table 1). Likewise, the 3-amino-2-thioxo-2,5*H*-pyrrol-5-ones **6b**−**h** were prepared by reaction of **4** with 1,2-diimidoyl-1,2-dichloroethanes **2b**−**h**. In these reactions the respective 1,2-dithia-3*H*-cyclopent-4-enes **5b**−**h** were formed only in small quantities. The formation of **6a**−**h** can be explained by formation of intermediate **C**, reductive ring opening (to give intermediate **F**), protonation−deprotonation (intermediate **G**), and subsequent cyclization by attack of the nitrogen atom onto the ester group.

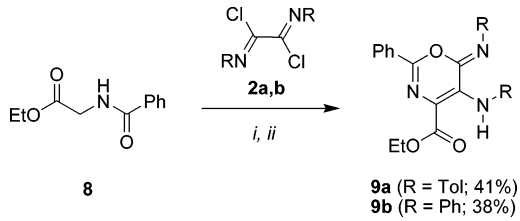
An independent and unambiguous proof of the structure was established by crystal structure analysis of **6g** (see supplementary information). All 3-amino-2-thioxo-2,5*H*-pyrrol-5-ones **6a**−**h** showed characteristic ^{13}C NMR resonances for O═C in the range of δ 173.5−174.0 and for S═C in the range of δ 194.5−195.7.

Synthesis of 2,3-Diamino-4-thioxo-4*H*-thiopyrans. During the variation of the reaction conditions, it was observed that the employment of a mono- rather than a dianion of ethyl thioglycolate again resulted in the formation of a different product. The reaction of a high excess of the *mono*anion of ethyl thioglycolate (5.0−7.0 equiv) with **2a** (procedure 3) afforded the 3-hydroxy-5,6-di(arylamino)-4-thioxo-4*H*-thiopyran-2-carboxylate **7a** (Scheme 2, Table 1). Likewise, heterocycles **7b**−**f** were prepared by reaction of lithiated ethyl thioglycolate with 1,2-diimidoyl-1,2-dichloroethanes **2b**−**c**,**e**−**g**. The formation of **7a**−**f** can be explained by formation of the open-chained intermediate **A** and subsequent cyclization. During the optimization, the use of an excess of monolithiated ethyl thioglycolate (5.0−7.0 equiv) proved to be important.

The structure of **7c** was unambiguously and independently confirmed by crystal structure analysis (see the Supporting Information). The S═C and the hydroxy group are involved in an intramolecular hydrogen bond O−H···S. Characteristic ^{13}C NMR resonances in the range of δ 174.9−176.7 were observed for the C═S group of all 4-thioxo-4*H*-thiopyrans **7a**−**f**.

Synthesis of 6-Imino-6*H*-1,3-oxazines. The influence of the heteroatoms of the 1,2-dianion on the regiochemistry of cyclization was next studied. No cyclization could be induced in the reaction of 1,2-diimidoyl-1,2-dichloroethane **2a** with the dianion of ethyl lactate, presumably due to the lower nucleophilicity of the oxygen compared to the sulfur atom. In contrast, the reaction of **2a**,**b** with the dianion of ethyl hippurate (**8**)[20] afforded the 6-imino-6*H*-1,3-oxazines **9a**,**b** by regioselective cyclization via the carbon and the oxygen atom of the dianion (Scheme 3). A four-membered ring was not formed. Notably, a Dimroth rearrangement of the iminoether into an amide group was not observed.

SCHEME 3. Synthesis of 6-Imino-6*H*-1,3-oxazines 9a,b[a]



[a] Key: (i) (1) LDA (2.3 equiv), TMEDA, **8** (1.0 equiv), THF, −40 → 0 °C, 1 h, (2) 0 °C, 1 h; (ii) added into **2** (in THF), −78 °C, −78 → +20 °C, 14 h, then at 20 °C, 24 h.

The structure of **9a** was independently confirmed by crystal structure analysis (see the Supporting Information). Two out of three aryl groups are in plane with the heterocyclic core structure. The ester and the amino group are involved in an intramolecular hydrogen bond N−H···O.

In conclusion, the reaction of mono- and dilithiated ethyl thioglycolate with 1,2-diimidoyl-1,2-dichloroethanes afforded, depending on the reaction conditions, 3-imino-1,2-dithia-3*H*-cyclopent-4-enes, 3-amino-2-thioxo-2,5*H*-pyrrol-5-ones, and 2,3-diamino-4-thioxo-4*H*-thiopyrans. The reaction of the dianion of ethyl hippurate with bis(imidoyl)dichlorides afforded 6-imino-6*H*-1,3-oxazines.

Experimental Section

Synthesis of 4,5-Bis[(4-methylphenyl)imino]-3,6-diphenyl-1,2-dithiane (3). To a THF (20 mL) solution of benzyl mercaptane (**1**) (0.72 mL, 6.0 mmol) was added *n*-BuLi (8.25 mL, 13.2 mmol, 1.6 M in *n*-hexane) at −78 °C, stirred for 4 h, and subsequently transferred into a THF (80 mL) solution of oxaldi(4-tolylimidoyl) dichloride (**2a**) (0.90 g, 3.0 mmol) at −78 °C. The temperature was allowed to rise to 20 °C over 14 h, and the mixture was stirred at 20 °C for 2 h. To the reaction mixture was added an aqueous solution of HCl (10%, 100 mL) and extracted with diethyl ether (5 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/Et_2O = 10:1 → 3:1) to give **3** as a slightly brownish solid (0.717 g, 50%). ^{1}H NMR (THF-d_8, 200 MHz): δ 2.29 (s, 6 H, 2 × CH_3), 5.24 (s, 2 H, 2 × CH-S), 6.80−7.25 (m, 18 H, 18 × CH). ^{13}C NMR (THF-d_8, 50 MHz): δ_C 20.9, 54.5, 120.7, 128.6, 129.0, 129.6, 130.1, 138.1, 147.8, 156.8, 162.9. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3027 (w), 2921 (w), 1590 (s), 1502 (s), 1408 (m), 1218 (m), 1205 (m), 1114 (m), 824 (m). MS (CI, H_2O): *m*/*z* 479 ([M + 1]$^+$, 100).

Synthesis of Ethyl 2,3-Bis(*p*-tolylimino)thietane-4-carboxylate.[9] A THF solution of LDA was prepared by addition of *n*-BuLi (9.4 mL, 15.0 mmol, 1.6 M in *n*-hexane) to a THF (15 mL) solution of diisopropylamine (2.1 mL, 15.0 mmol) at 0 °C. To this solution were added TMEDA (2.3 mL, 15.0 mmol) and ethyl thioglycolate (**4**) (0.54 mL, 6.0 mmol) at −40 °C. The solution was stirred at 0 °C for 2 h and subsequently transferred into a THF (80 mL) solution of oxaldi(4-tolylimidoyl) dichloride (**2a**) (1.80 g, 6.0 mmol) at −78 °C. The temperature was allowed to rise to 20 °C within

(20) Krapcho, A. P.; Dundulis, E. A. *Tetrahedron Lett.* **1976**, 2205.

15 min, and the mixture was stirred at 20 °C for 2 h. The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, petroleum ether/Et_2O = 10:1 → 3:1) to give the product as a yellowish solid (0.634 g, 30%). Mp = 110 °C dec. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.98 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.32 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 4.94 (m, 2 H, OCH_2), 5.33 (s, 1 H, C*H*CO_2Et) 6.95−7.25 (m, 8 H, 8 × CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ_C 13.6, 21.0, 21.2, 54.5, 62.2, 121.4, 122.4, 129.8, 130.0, 136.7, 137.3, 143.0, 143.3, 157.0, 159.0, 167.4. IR (KBr, cm^{-1}): $\tilde{\nu}$ 2980 (w), 1738 (s), 1655 (m), 1641 (m), 1505 (s), 1268 (s), 1235 (m), 1125 (m), 1030 (m), 823 (m). MS (CI, H_2O): m/z 353 ([M + 1]$^+$), 236 ([M + 1]$^+$ − TolN≡C), 203 ([M + 1]$^+$ − TolN═C═S). Anal. Calcd for $C_{20}H_{20}N_2O_2S$ (352.450): C, 68.16; H, 5.72; N, 7.94. Found: C, 68.51; H, 5.79; N, 8.07.

General Procedure for the Synthesis of 3-Imino-1,2-dithia-3*H*-cyclopent-4-enes (5). A THF solution of LDA was prepared by addition of *n*-BuLi (2.5−3.0 equiv) to a THF (5 mL/mmol of **6**) solution of diisopropylamine (2.5−3.0 equiv) at 0 °C. To this solution were added TMEDA (2.5−3.0 equiv) and ethyl thioglycolate (**6**) (1.0−1.2 equiv) at −40 °C. The solution was warmed to 0 °C during 1 h, stirred at 0 °C for 1 h, and subsequently transferred into a THF (20 mL/mmol of **2**) solution of oxaldiimidoyl dichloride **2** (1.0 equiv) at −78 °C. The temperature was allowed to rise to ambient over 14 h, and the mixture was stirred at 20 °C for 2 h. To the reaction mixture was added an aqueous solution of HCl (10%, 25 mL/mmol) and the mixture extracted with diethyl ether (5 × 25 mL/mmol). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give **5**.

Ethyl 4-(*o*-Tolylamino)-3-(*o*-tolylimino)-1,2-dithia-3*H*-cyclopent-4-ene-5-carboxylate (5c). Starting with ethyl thioglycolate (**4**) (0.22 mL, 1.97 mmol), diisopropylamine (0.70 mL, 4.92 mmol), *n*-BuLi (2.0 mL, 4.92 mmol, 2.5 M in *n*-hexane), TMEDA (0.74 mL, 4.92 mmol), and *N*,*N*′-bis(2-methylphenyl)ethane−bis(imidoyl) dichloride (**2c**) (0.500 g, 1.64 mmol) in THF (15+35 mL), **5c** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → 3:1) as a brownish oil (0.178 g, 28%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.07 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 4.15 (q, J = 7.2 Hz, 2 H, OCH_2), 6.94−7.09 (m, 4 H, 4 × CH), 7.16−7.31 (m, 4 H, 4 × CH), 7.86 (broad s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 13.8, 17.7, 18.0, 61.9, 115.8, 117.4, 120.5, 123.7, 125.4, 125.8, 126.8, 129.7, 129.9, 130.4, 131.0, 140.0, 141.2, 148.7, 162.5, 162.7. IR (neat, cm^{-1}): $\tilde{\nu}$ 3293 (w), 3065 (w), 3018 (w), 2974 (m), 2961 (m), 2928 (m), 2870 (w), 1722 (m), 1686 (s), 1587 (s), 1574 (s), 1516 (s), 1497 (s), 1484 (s), 1459 (s), 1418 (m), 1394 (m), 1378 (m), 1329 (m), 1289 (m), 1243 (s), 1210 (s), 1185 (s), 1114 (s), 1098 (w), 1073 (m), 1049 (s), 1010 (w), 1000 (w), 760 (s), 749 (s), 724 (m), 715 (m), 587 (w). UV−vis (CH_2Cl_2, nm): λ_{max} (log ϵ) 229 (4.28), 420 (3.87). MS (EI, 70 eV): m/z 385 ([M + 1]$^+$, 5), 384 (M$^+$, 34), 351 (11), 311 (11), 291 (30), 284 (43), 251 (18), 193 (10), 161 (12), 148 (34), 118 (63), 91 (100), 77 (10). HRMS (ESI): calcd for $C_{20}H_{20}N_2O_2S_2$ [M$^+$] 384.09662, found 384.09606.

***N*-(2-Methoxyphenyl)-2-(2-methoxyphenylamino)-2-thioxoacetamide (5d′).** Starting with ethyl thioglycolate (**4**) (0.24 mL, 2.14 mmol), diisopropylamine (0.75 mL, 5.34 mmol), *n*-BuLi (2.2 mL, 5.34 mmol, 2.5 M in *n*-hexane), TMEDA (0.81 mL, 5.34 mmol), and *N*,*N*′-bis(2-methoxyphenyl)ethane−bis(imidoyl) dichloride (**2d**) (0.600 g, 1.78 mmol) in THF (15 + 35 mL), **5d′** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → 10:1) as a yellowish solid (0.173 g, 31%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.97 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 6.92−7.17 (m, 5 H, 5 × CH), 7.24−7.30 (m, 1 H, CH), 8.44 (dd, J = 8.1, 1.8 Hz, 1 H, CH), 9.26 (dd, J = 8.1, 1.8 Hz, 1 H, CH), 10.90 (broad s, 1 H, NH), 12.00 (broad s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 55.95, 56.00, 110.3, 110.4, 119.3, 120.3, 120.4, 120.9, 125.2, 126.6, 127.39, 127.44, 149.5, 150.2, 156.5, 180.6. IR (KBr, cm^{-1}): $\tilde{\nu}$ 3249 (m), 2966 (w), 2940 (w), 2839 (w), 1684 (s), 1600 (m), 1533 (s), 1529 (s), 1480 (s), 1464 (s), 1437 (m), 1397 (w), 1322 (w), 1294 (w), 1253 (s), 1113 (m), 1054 (w), 1043 (w), 1024 (m), 813 (w), 755 (s), 740 (m), 514 (w). MS (EI, 70 eV): m/z 316 (M$^+$, 21), 285 (23), 252 (35), 148 (100), 134 (35), 123 (76), 107 (52), 77 (21), 72 (22). HRMS (ESI): calcd for $C_{16}H_{16}N_2O_3S$ [M$^+$] 316.08816, found 316.08681.

Ethyl 4-(4-Methoxyphenylamino)-3-(4-methoxyphenylimino)-1,2-dithia-3*H*-cyclopent-4-ene-5-carboxylate (5e). Starting with ethyl thioglycolate (**4**) (0.54 mL, 6.0 mmol), diisopropylamine (2.1 mL, 15.0 mmol), *n*-BuLi (9.4 mL, 15.0 mmol, 1.6 M in *n*-hexane), TMEDA (2.3 mL, 15.0 mmol), and *N*,*N*′-bis(4-methoxyphenyl)-ethane−bis(imidoyl) dichloride (**2e**) (2.02 g, 6.0 mmol) in THF (30 + 100 mL), **5e** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → 5:1) as a yellowish oil (0.748 g, 30%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.16 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.15 (q, J = 7.2 Hz, 2 H, OCH_2), 6.78 (d, J = 11 Hz, 2 H, 2 × CH), 6.90 (d, J = 11 Hz, 2 H, 2 × CH), 6.98 (d, J = 11 Hz, 2 H, 2 × CH), 7.12 (d, J = 11 Hz, 2 H, 2 × CH), 7.95 (broad s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 13.4, 55.37, 55.41, 61.8, 113.7, 114.5, 121.5, 121.9, 124.2, 134.8, 141.1, 142.1, 155.7, 157.3, 161.0, 162.1. IR (KBr, cm^{-1}): $\tilde{\nu}$ 3360 (w), 2980 (w), 2928 (w), 1702 (s), 1638 (s), 1605 (s), 1532 (s), 1232 (s), 1130 (m), 1075 (s), 1043 (m). MS (EI, 70 eV): m/z 416 (M$^+$, 100). The exact molecular mass m/z = 416.0864 ± 2 ppm [M$^+$] for $C_{20}H_{20}N_2O_4S_2$ was confirmed by HRMS (EI, 70 eV).

General Procedure for the Synthesis of 3-Amino-2-thioxo-2,5*H*-pyrrol-5-ones (6). A THF solution of LDA was prepared by addition of *n*-BuLi (5.0−5.5 equiv) to a THF (10 mL/mmol of **4**) solution of diisopropylamine (5.0−5.5 equiv) at 0 °C. To this solution were added TMEDA (5.0−5.5 equiv) and ethyl thioglycolate (**4**) (2.0−2.2 equiv) at −40 °C. The solution was warmed to 0 °C during 1 h, stirred at 0 °C for 1 h, and subsequently transferred into a THF (20 mL/mmol of **2**) solution of the *N*,*N*′-diarylethane−bis(imidoyl) dichloride **2** (1.0 equiv) at −78 °C. The temperature was allowed to rise to ambient over 14 h, and the mixture was stirred at 20 °C for 24 h. To the reaction mixture was added an aqueous solution of HCl (10%, 30 mL/mmol), and the mixture was extracted with diethyl ether (2 × 30 mL/mmol) and then dichloromethane (4 × 30 mL/mmol). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give **6**.

1-(2-Methoxyphenyl)-3-(2-methoxyphenylamino)-2-thioxo-2,5*H*-dihydropyrrol-5-one (6d). Starting with ethyl thioglycolate (**4**) (0.10 mL, 0.90 mmol), diisopropylamine (0.30 mL, 2.1 mmol), *n*-BuLi (1.32 mL, 2.1 mmol, 15% in *n*-hexane), TMEDA (0.32 mL, 2.1 mmol), and *N*,*N*′-bis(2-methoxyphenyl)ethane−bis(imidoyl) dichloride (**2d**) (0.100 g, 0.30 mmol) in THF (10 + 10 mL), **6d** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 50:1 → 1:1) as an orange solid (0.056 g, 55%). Mp = 140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 5.64 (s, 1 H, CH═C), 6.94−7.14 (m, 5 H, 5 × CH), 7.23−7.31 (m, 2 H, 2 × CH), 7.41−7.45 (m, 1 H, CH), 8.55 (broad s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ_C 56.0, 56.2, 84.5, 111.0, 112.5, 117.2, 121.0, 121.3, 122.9, 124.6, 128.5, 130.3, 130.9, 144.4, 150.1, 155.7, 174.0, 195.7. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3274 (w), 2963 (w), 1723 (m), 1635 (s), 1596 (m), 1530 (s), 1509 (m), 1485 (w), 1463 (m), 1437 (w), 1411 (m), 1304 (m), 1280 (m), 1247 (s), 1175 (w), 1116 (w), 1052 (w), 1024 (m), 749 (m). UV−vis (CH_2Cl_2, nm): λ_{max} (log ϵ) 225 (4.16), 251 (4.18), 274 (4.13), 312 (4.09), 470 (3.52). MS (EI, 70 eV): m/z 340 (M$^+$, 68), 309 (100), 294 (8), 92 (20), 77 (25). The exact molecular mass m/z = 340.0882 ± 2 ppm [M$^+$] for $C_{18}H_{16}N_2O_3S$ was confirmed by HRMS (EI, 70 eV).

1-Naphthalen-1-yl-3-(naphthalen-1-ylamino)-2-thioxo-2,5*H*-dihydropyrrol-5-one (6f). Starting with ethyl thioglycolate (**4**) (0.18 mL, 1.6 mmol), diisopropylamine (0.6 mL, 4.0 mmol), *n*-BuLi (2.5

mL, 4.0 mmol, 15% in *n*-hexane), TMEDA (0.6 mL, 4.0 mmol), and *N*,*N*′-bis(1-naphthyl)ethane−bis(imidoyl) dichloride (**2f**) (0.300 g, 0.80 mmol) in THF (20 + 20 mL), **6f** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → 5:1) as an orange solid (0.190 g, 63%). Mp = 175 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.63 (s, 1 H, CH═C), 7.48−7.67 (m, 9 H, 9 × CH), 7.76−7.79 (m, 1 H, CH), 7.93−8.06 (m, 4 H, 4 × CH), 8.50 (broad s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 83.9, 116.9, 120.6, 122.5, 125.3, 125.5, 125.9, 126.5, 126.8, 126.9, 127.1, 127.1, 128.6, 128.8, 128.9, 129.9, 130.1, 130.7, 133.8, 134.30, 134.33, 146.0, 173.8, 195.5. IR (KBr, cm^{-1}): $\tilde{\nu}$ 3285 (w), 2983 (w), 1738 (s), 1635 (s), 1596 (w), 1576 (w), 1549 (w), 1503 (s), 1468 (w), 1444 (w),1420 (m), 1393 (w), 1370 (w), 1347 (w), 1288 (s), 1207 (w), 1183 (w), 1161 (m), 1124 (w), 1107 (w), 1028 (m), 1012 (w), 806 (w), 781 (m), 765 (m), 602 (w). UV−vis (CH_2Cl_2, nm): λ_{max} (log ϵ) 228 (4.67), 305 (4.31), 475 (3.53). MS (EI, 70 eV): *m*/*z* 380 (M^+, 100), 252 (11), 210 (12), 194 (51), 166 (55), 154 (35), 143 (24), 127 (82), 77 (12). The exact molecular mass *m*/*z* = 380.0983 ± 2 ppm [M^+] for $C_{24}H_{16}N_2OS$ was confirmed by HRMS (EI, 70 eV).

General Procedure for the Synthesis of 2,3-Diamino-4-thioxo-4*H*-thiopyrans (7). A THF solution of LDA was prepared by addition of *n*-BuLi (6.0−9.0 equiv) to a THF (5 mL/mmol of **4**) solution of diisopropylamine (6.0−9.0 equiv) at 0 °C. To this solution were added TMEDA (6.0−9.0 equiv) and ethyl thioglycolate (**4**) (5.0−7.0 equiv) at − 40 °C. The solution was warmed to 0 °C during 1 h, stirred at 0 °C for 1 h, and subsequently transferred into a THF (50 mL/mmol of **2**) solution of *N*,*N*′-diarylethane−bis(imidoyl) dichloride (**2**) (1.0 equiv) at − 78 °C. The temperature was allowed to rise to ambient over 14 h, and the mixture was stirred at 20 °C for 48 h. To the reaction mixture was added an aqueous solution of HCl (10%, 30 mL/mmol), and the mixture was extracted with diethyl ether (2 × 50 mL/mmol) and then dichloromethane (4 × 50 mL/mmol). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give **7**.

Ethyl 5-Hydroxy-4-thioxo-2,3-di(*o*-tolylamino)-4*H*-thiopyran-6-carboxylate (7c). Starting with ethyl thioglycolate (**4**) (0.88 mL, 8.0 mmol), diisopropylamine (1.41 mL, 10 mmol), *n*-BuLi (6.3 mL, 10.0 mmol, 15% in *n*-hexane), TMEDA (1.5 mL, 10.0 mmol), and *N*,*N*′-bis(2-methylphenyl)ethane−bis(imidoyl) dichloride (**2c**) (0.500 g, 1.64 mmol) in THF (30 + 70 mL), **7c** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → EtOAc) as a dark reddish solid (0.542 g, 78%). Mp = 151 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 4.39 (q, *J* = 7.2 Hz, 2 H, OCH_2), 6.51 (d, *J* = 8.1 Hz, 1 H, CH), 6.65 (broad s, 1 H, NH), 6.91 (dt, *J* = 7.5, 0.6 Hz, 1 H, CH), 7.08 (dt, *J* = 7.5, 0.9 Hz, 1 H, CH), 7.19 (broad s, 1 H, NH), 7.22 (d, *J* = 7.2 Hz, 1 H, CH), 7.27−7.32 (m, 4 H, 4 × CH), 10.53 (broad s, 1 H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 14.2, 17.7, 17.9, 62.5, 99.7, 114.1, 122.1, 126.7, 126.8, 127.2, 127.7, 129.2, 131.0, 131.9, 131.9, 134.5, 135.3, 139.9, 153.4, 155.5, 164.0, 175.8. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3438 (m), 3267 (w), 3228 (w), 3193 (w), 2978 (w), 1729 (w), 1675 (s), 1581 (m), 1498 (s), 1476 (s), 1461 (s), 1442 (m), 1377 (m), 1365 (s), 1349 (s), 1301 (m), 1290 (m), 1249 (s), 1232 (m), 1211 (s), 1186 (m), 1161 (w), 1130 (w), 1117 (m), 1094 (w), 1063 (m), 921 (w), 755 (m), 745 (m). UV−vis (CH_2Cl_2, nm): λ_{max} (log ϵ) = 269 (4.14), 317 (4.02), 381 (3.89), 442 (3.91). MS (EI, 70 eV): *m*/*z* 426 (M^+, 100), 352 (15), 319 (17), 91 (27). The exact molecular mass *m*/*z* = 426.1072 ± 2 ppm [M^+] for $C_{22}H_{22}N_2O_3S_2$ was confirmed by HRMS (EI, 70 eV). The structure was confirmed by X-ray crystallography.

Ethyl 5-Hydroxy-2,3-di(4-methoxyphenylamino)-4-thioxo-4*H*-thiopyran-6-carboxylate (7e). Starting with ethyl thioglycolate (**4**) (0.45 mL, 4.15 mmol), diisopropylamine (0.75 mL, 5.34 mmol), *n*-BuLi (3.4 mL, 5.34 mmol, 15% in *n*-hexane), TMEDA (0.81 mL, 5.34 mmol), and *N*,*N*′-bis(4-methoxyphenyl)ethane−bis(imidoyl) dichloride (**2e**) (0.200 g, 0.59 mmol) in THF (30 + 35 mL), **7e** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 50:1 → 1:1) as a reddish solid (0.186 g, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.40 (q, *J* = 7.2 Hz, 2 H, OCH_2), 6.83 (d, *J* = 8.7 Hz, 4 H, 4 × CH), 6.95 (dd, *J* = 6.6, 2.2 Hz, 2 H, 2 × CH), 7.15 (dd, *J* = 6.6, 2.2 Hz, 2 H, 2 × CH), 7.33 (broad s, 1 H, NH), 10.51 (broad s, 1 H, OH), 12.68 (broad s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 14.3, 55.5, 55.6, 62.5, 99.2, 114.8, 115.4, 118.8, 121.9, 127.2, 132.6, 134.3, 135.1, 153.3, 155.48, 155.53, 164.1, 174.9. IR (neat, cm−^{1}): $\tilde{\nu}$ = 3447 (w), 3441 (w), 3274 (w), 2977 (w), 1726 (w), 1677 (w), 1509 (s), 1464 (w), 1440 (w), 1420 (w), 1407 (w), 1369 (m), 1349 (m), 1298 (m), 1244 (s), 1186 (m), 1113 (w), 1031 (m). UV−Vis (CH_2Cl_2, nm): λ_{max} (log ϵ) = 229 (4.26), 381 (3.97), 456 (3.96). MS (EI, 70 eV): *m*/*z* 458 (M^+, 22), 428 (29), 386 (8), 353 (17), 340 (73), 324 (13), 279 (14), 222 (9), 208 (37), 192 (22), 174 (74), 160 (20), 146 (44), 134 (100), 121 (82), 107 (62), 92 (34). The exact molecular mass *m*/*z* = 458.0970 ± 2 ppm [M^+] for $C_{22}H_{22}N_2O_5S_2$ was confirmed by HRMS (EI, 70 eV).

General Procedure for the Synthesis of 6-Imino-6*H*-1,3-oxazines (9). A THF solution of LDA was prepared by addition of *n*-BuLi (2.5 equiv) to a THF (3 mL/mmol of **8**) solution of diisopropylamine (2.5 equiv) at 0 °C. To this solution were added TMEDA (2.5 equiv) and ethyl hippurate (**8**) (1.0 equiv) at − 40 °C. The solution was warmed to 0 °C during 1 h, stirred at 0 °C for 1 h, and subsequently transferred into a THF (13 mL/mmol of **2**) solution of *N*,*N*′-diarylethane−bis(imidoyl) dichloride (**2**) (1.0 equiv) at − 78 °C. The temperature was allowed to rise to ambient over 14 h, and the mixture was stirred at 20 °C for 2 h. To the reaction mixture was added an aqueous solution of HCl (10%, 20 mL/mmol of **8**) and the mixture extracted with diethyl ether (5 × 20 mL/mmol). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/Et_2O) to give **9**.

Ethyl 2-Phenyl-5-(*p*-tolylamino)-6-(*p*-tolylimino)-6*H*-1,3-oxazine-4-carboxylate (9a). Starting with ethyl hippurate (**8**) (1.24 g, 6.0 mmol), diisopropylamine (2.1 mL, 15.0 mmol), *n*-BuLi (9.4 mL, 15.0 mmol, 1.6 M in *n*-hexane), TMEDA (2.3 mL, 15.0 mmol), and *N*,*N*′-bis(4-methylphenyl)ethane−bis(imidoyl) dichloride (**2a**) (1.80 g, 6.0 mmol) in THF (15 + 80 mL), **9a** was isolated after chromatography (silica gel, petroleum ether/Et_2O = 10:1 → 3:1) as a yellowish solid (1.08 g, 41%). ^{1}H NMR (THF-d_8, 200 MHz): δ 1.10 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 2.26 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 3.92 (q, *J* = 7.2 Hz, 2 H, OCH_2), 6.95−7.45 (m, 11 H, 11 × CH), 7.95 (m, 2 H, 2 × CH), 8.60 (broad s, 1 H, NH). ^{13}C NMR (THF-d_8, 50 MHz): δ_C 14.4, 20.9, 21.1, 61.2, 119.1, 122.0, 123.6, 127.5, 129.2, 129.7, 130.0, 131.6, 131.7, 132.0, 133.4, 134.8, 140.1, 143.0, 144.9, 148.7, 166.2. IR (KBr, cm^{-1}): $\tilde{\nu}$ 3335 (m, br), 2980 (w), 1703 (s), 1680 (s), 1612 (w), 1512 (s), 1482 (m), 1380 (m), 1337 (m), 1100 (m), 1028 (m), 818 (m). MS (CI, H_2O): *m*/*z* 441 ([M+2]$^+$, 100), 440 ([M + 1]$^+$, 47). Anal. Calcd for $C_{27}H_{25}N_3O_3$ (439.506): C, 73.79; H, 5.73; N, 9.56. Found: C, 71.92; H, 6.33; N, 8.95. The structure was confirmed by X-ray crystallography.

Ethyl 2-Phenyl-5-phenylamino-6-phenylimino-6*H*-1,3-oxazine-4-carboxylate (9b). Starting with ethyl hippurate (**8**) (1.24 g, 6.0 mmol), diisopropylamine (2.1 mL, 15.0 mmol), *n*-BuLi (9.4 mL, 15.0 mmol, 1.6 M in *n*-hexane), TMEDA (2.3 mL, 15.0 mmol), and *N*,*N*′-diphenylethane−bis(imidoyl) dichloride (**2b**) (1.67 g, 6.0 mmol) in THF (15 + 80 mL), **9b** was isolated after chromatography (silica gel, petroleum ether/Et_2O = 10:1 → 3:1) as a yellowish solid (0.937 g, 38%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.98 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 3.78 (q, *J* = 7.2 Hz, 2 H, OCH_2), 6.95−7.55 (m, 13 H, 13 × CH), 7.82 (m, 2 H, 2 × CH), 8.72 (broad s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ_C 13.7, 60.6, 119.4, 119.9, 120.4, 122.29, 122.30, 124.5, 126.3, 128.5, 128.8, 131.4, 129.5, 130.0, 141.8, 144.8, 145.1, 148.2, 164.8. IR (KBr, cm−^{1}):

$\tilde{\nu}$ 3307 (w), 3060 (w), 2980 (w), 1740 (m), 1668 (s), 1590 (s), 1570 (s), 1520 (s), 1495 (m); 1450 (m); 1269 (s), 1210 (s), 1196 (m), 1138 (m), 1028 (m). MS (FAB): *m*/*z* 412 ($[M + 1]^+$, 100). Anal. Calcd for $C_{25}H_{21}N_3O_3$ (411.453): C, 72.98; H, 5.14; N, 10.21. Found: C, 72.52; H, 5.48; N, 9.90.

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Supporting Information Available: Copies of the NMR spectra, experimental procedures, and details of the crystal structure determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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