Synthesis of 2-Alkoxy-Substituted Thiophenes, 1,3-Thiazoles, and Related S-Heterocycles via Lawesson's Reagent-Mediated Cyclization under Microwave Irradiation: Applications for Liquid Crystal Synthesis

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Introduction

Five-membered sulfur-containing heterocycles are important synthetic intermediates and have found a variety of applications in medicinal, agricultural, and materials chemistry.[1] We are interested in liquid crystals containing these heterocycles in order to obtain potential candidates for ferroelectric display applications.[2] S-Heterocycle-containing liquid crystals have been shown to have several beneficial physical characteristics when compared to their phenyl counterparts such as lower viscosity and fast switching times.[3] An additional feature of these *heterocyclic* ferroelectric materials is the high birefringence conferred by the heterocyclic core, which has been identified as being crucial for use in the latest complementary metal oxide semiconductor (CMOS)-based pixels. These are employed, for example, in optical-phase modulation devices, including holograms and telecommunication interconnects.[4]

Simple thiophenes,[5] 1,3-thiazoles,[6] and 1,3,4-thiadiazoles[7] have previously been prepared via sulfuration of the corresponding 1,4-dicarbonyl precursors using reagents such as H_2S/HCl, P_2S_5, and Lawesson's reagent. In contrast, the synthesis of 2-alkoxythiophenes and related alkoxy-substituted S-heterocycles is much less well developed. Treatment of a series of ethyl γ-aryl-γ-oxopropanoates with H_2S/HCl afforded the corresponding 5-aryl-2-ethoxythiophenes in very poor (10−20%) yield,[8] while analogous reactions of γ-alkyl-γ-oxo esters with H_2S/HCl[8] or P_2S_5[9] did not afford any alkoxythiophene products. The synthesis of short-chain 5-alkoxy-1,3-thiazoles from the corresponding alkyl β-acylaminoethanoate proceeds in moderate to good yield using P_2S_5.[10] A single high-yielding example was also reported using Lawesson's reagent,[7c] although full details of the scope and limitations of this chemistry were never published. In recent studies, we have shown that Lawesson's reagent can be used for the synthesis of alkoxythiophenes from γ-keto esters;[11] however, while the yields for longer-chain alkoxythiophenes were excellent, the yields for shorter-chain analogues were more modest (47−62%).

The above approaches for S-heterocycle synthesis typically suffer from one or more of the following drawbacks: moderate to low yields, extensive formation of byproducts, use of anhydrous hydrocarbon solvent, long reaction times at elevated temperatures, and/or use of a large excess of the sulfurization reagent. In this paper, we show that these drawbacks can be overcome by performing such cyclization reactions using Lawesson's reagent in the absence of solvent under microwave irradiation. Solvent-free reactions have many advantages (reduced pollution, low costs, and simplicity in processing and handling), which can make them attractive for large-scale (industrial) applications.[12] The use of microwave irradiation as a nonconventional source of energy has proven to be very beneficial in this area.[13]

Herein, we report that when the Lawesson's reagent-mediated cyclization of various 1,4-dicarbonyl compounds is performed under microwave irradiation conditions in a conventional microwave oven, high yields of the desired S-heterocycles are obtained, little or no byproduct is formed, reaction times are extremely short (3−13 min), and no solvent is needed for the reaction.

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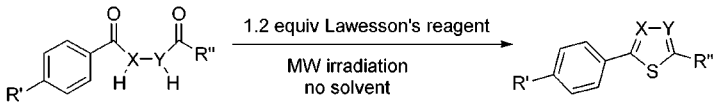
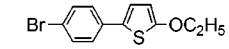
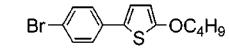
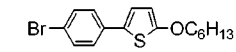
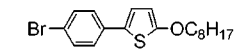
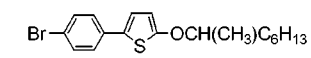
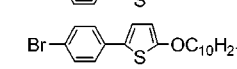
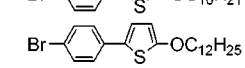
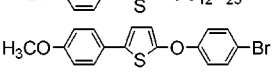
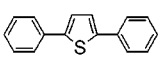
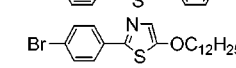
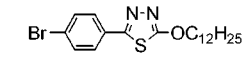
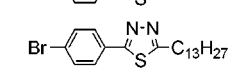
Table 1. Synthesis of Various S-Heterocycles via Lawesson's Reagent-Mediated Cyclization of 1,4-Dicarbonyl Compounds under Microwave Irradiation Conditions in the Absence of Solvent

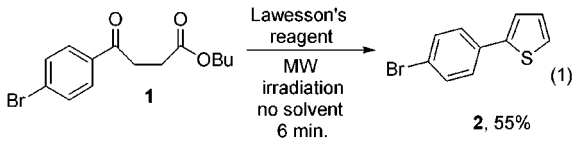


Entry	R'	X	Y	R''	Time (min)	Scale (mmol)	Product	Yield, %[a]
1	Br	CH	CH	C_2H_5O	3	1		90
2	Br	CH	CH	*n*-C_4H_9O	3	1		89
3	Br	CH	CH	*n*-$C_6H_{13}O$	3	1		94
4	Br	CH	CH	*n*-$C_8H_{17}O$	3	1		89
5	Br	CH	CH	$C_6H_{13}CH(CH_3)O$	3	1		89
6	Br	CH	CH	*n*-$C_{10}H_{21}O$	3	1		93
7	Br	CH	CH	*n*-$C_{12}H_{25}O$	3	1		87
8	CH_3O	CH	CH	4-BrC_6H_4O	3	1		65[b]
9	H	CH	CH	Ph	4	1		92
10	Br	N	CH	*n*-$C_{12}H_{25}O$	5	1		90
11	Br	N	CH	*n*-$C_{12}H_{25}O$	6.5	3	-//-	86
12	Br	N	CH	*n*-$C_{12}H_{25}O$	8	9.3	-//-	83
13	Br	N	N	*n*-$C_{12}H_{25}O$	[c]	1		0
14	Br	N	N	*n*-$C_{13}H_{27}$	7	1		95
15	Br	N	N	*n*-$C_{13}H_{27}$	13	20	-//-	91

[a] Isolated yield of product after chromatographic purification. [b] In addition, 11% of 2-(4-methoxyphenyl)thiophene was isolated as a byproduct. [c] A variety of irradiation times were explored (3−10 min).

Results and Discussion

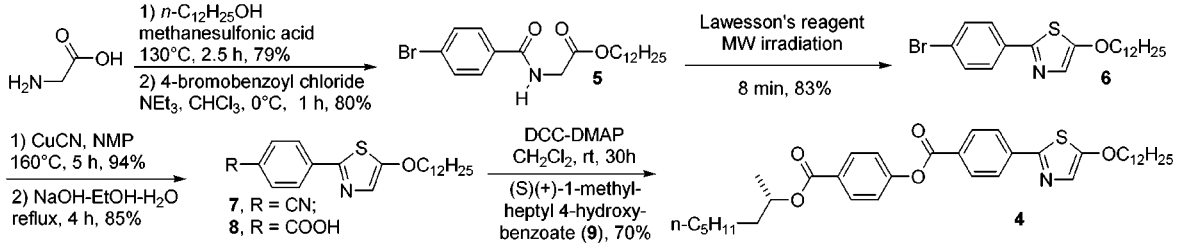
Our initial studies were focused on the synthesis of alkoxythiophenes as intermediates for liquid crystal synthesis, which we envisaged would be prepared from the corresponding γ-keto esters.[11] When these γ-keto ester derivatives were mixed with 1.2 equiv of solid Lawesson's reagent and subjected to microwave irradiation conditions, alkoxythiophenes were obtained in high yield (see Table 1, entries 1−7). Short-chain [ethyl (entry 1), *n*-butyl (entry 2)] esters as well as longer-chain [*n*-hexyl, *n*-octyl, *n*-decyl, and *n*-dodecyl (entries 3, 4, 6, and 7, respectively)] and branched-chain [1-methylheptyl (entry 5)] esters were used with equal success. The yields of alkoxythiophene products obtained from these microwave-mediated cyclization reactions are dramatically superior to those from the analogous solvent-based reactions for short-chain ester substrates. For example, 89−90% yields of the desired alkoxythiophene products along with only traces of byproduct were formed when ethyl and *n*-butyl ester substrates were employed in the present study (Table 1, entries 1 and 2). In contrast, the analogous solution-phase reactions provided the same products in only 47−62% yields, and formation of complex mixtures of byproducts was also observed.[11] It should be noted, however, that the yields from the two processes are more comparable for longer-chain ester substrates, although the much shorter reaction times and the avoidance of the need for an anhydrous solvent still confer a significant advantage on the microwave method. It was important to control the irradiation time precisely: to obtain optimal yields, the irradiation had to be stopped when the reaction mixture turned into an orange or red liquid. Prolonged irradiation of the reaction mixture gave a dark-brown tarry mixture, and product decomposition was observed. For example, when γ-keto ester **1** was allowed to react for 6 min, loss of the alkoxy chain occurred, resulting in the formation of monosubstituted thiophene **2** in 55% yield (eq 1).[14]



Interestingly, the use of smaller amounts of Lawesson's reagent (0.6 equiv) resulted in only a modest reduction

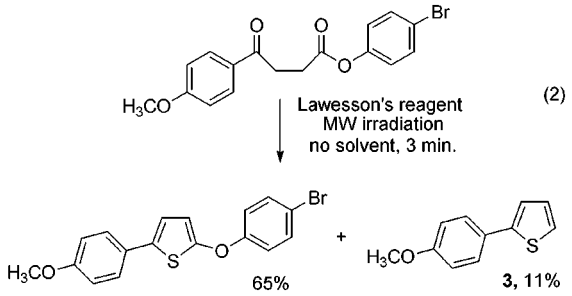
(14) An apparently related process was previously observed with γ-keto acid substrates: Noe, C. N.; Knolmuller, M.; Wagner, E. *Monatsh. Chem.* **1986**, *117*, 621−629.

Scheme 1



in yield and avoided byproduct formation even at these longer reaction times. Thus, prolonged irradiation (6 min) of a mixture of decyl 4-(4-bromophenyl)-4-oxobutanoate with 0.6 equiv of Lawesson's reagent afforded a dark-brown mixture that yielded ca. 70−75% of the desired alkoxythiophene product with little or no byproduct formation.

Application of the same microwave-mediated reaction conditions for the synthesis of aryloxythiophenes proceeded in somewhat lower yields (65%, entry 8), and formation of the monosubstituted thiophene byproduct **3** through loss of the aryloxy substituent competed with product formation even at short reaction times (eq 2).[15]



(2)

We next examined the use of these reaction conditions for the synthesis of 2,5-diarylthiophenes and found that 1,4-diphenylbutane-1,4-dione could be cyclized to 2,5-diphenylthiophene in 92% yield (entry 9). No product decomposition was observed even upon prolonged irradiation. Similarly high yields were obtained when this procedure was applied for the synthesis of 5-alkoxy-1,3-thiazoles (entries 10−12). When these conditions were employed in the attempted synthesis of 2-alkoxy-1,3,4-thiadiazoles, however, no product formation was observed and several byproducts were formed instead that were not characterized (entry 13). This result is in accordance with the original Lawesson's report for the analogous solution-phase reaction.[7d] However, *alkyl*thiadiazoles could be obtained using this procedure in high yield from the corresponding *N*,*N*′-diacylhydrazine precursor (entries 14 and 15).

It is noteworthy that a number of the reactions described above were scaled up to several grams without a significant reduction in yield (entries 11, 12, and 15).

This newly developed microwave-mediated closure of various 1,4-dicarbonyl compounds was successfully applied in the synthesis of several S-heterocycle-containing liquid crystalline targets. The thiazole-containing mesogen **4** was prepared as outlined in Scheme 1. Esterification of glycine with dodecanol[16] followed by N-acylation with 4-bromobenzoyl chloride[17] afforded the 1,4-dicarbonyl cyclization precursor **5**. Application of the aforementioned microwave-mediated cyclization using Lawesson's reagent afforded 5-alkoxy-1,3-thiazole **6** in 83% yield. Attempts to obtain the desired carboxylic acid **8** via lithiation with *n*-BuLi followed by quenching with excess CO_2 failed due to competing deprotonation of the thiazole ring next to nitrogen. To avoid this problem, bromide **6** was converted into the nitrile **7** using copper cyanide,[18] which was then hydrolyzed under basic conditions.[19] DCC−DMAP esterification[20] of the resulting carboxylic acid **8** with readily available phenol **9**[21] provided the target liquid crystal **4** in good yield.

The thiadiazole-containing liquid crystalline target **10** was prepared starting from commercially available 4-bromobenzohydrazide (Scheme 2). N-Acylation with myristoyl chloride[17] afforded the unsymmetrical *N*,*N*′-diacylhydrazine **11**, which was cyclized into the corresponding

(15) The loss of the alkoxy (aryloxy) side chain during the synthesis of 2-alkoxy- and 2-aryloxythiophenes has previously been noted by one of us under conventional solution-phase Lawesson's cyclization conditions, although no byproducts were characterized due to the complexity of the mixtures obtained.[11] The reduction byproducts **2** and **3** described above only form after a substantial amount of the desired alkoxy- or aryloxythiophene has accumulated and usually when almost no starting material remains. Therefore, it is very likely that the initially formed alkoxy- or aryloxythiophene products, and not the original γ-keto ester substrates, undergo reduction to these byproducts. Control experiments have shown that this reduction is not achieved by Lawesson's reagent alone.[11] Similarly, bubbling H_2S through a toluene solution of 2-(4-bromophenyl)-5-dodecyloxythiophene at reflux in the presence of 1.2 equiv of Lawesson's reagent also failed to effect this cleavage. Thus, it appears that the presence of some (presumably oxodesulfurized) Lawesson's reagent byproduct is a prerequisite for this reduction. The minimization of byproduct formation that occurs when the microwave procedure is used might then be explained by the rapid evolution of H_2S from the solvent-free reaction mixture (the amount of H_2S gas evolved during the microwave reaction was measured to be approximately 1 mmol for a 1 mmol scale reaction), effectively lowering the concentration of available reducing agent. The ease of the loss of the RO-substituent during our S-heterocycle ring-closure reactions seems to be in accordance with leaving group ability (4-bromophenoxy > ethoxy > butoxy). The fact that there is no byproduct generated during thiazole ring formation (Table 1, entry 10) might suggest that at least some carbocation character develops at C-2 during the loss of the RO-group. The electron-withdrawing nitrogen would then destabilize the positive charge at C-2 and account for the observed result. It is known that polar mechanisms tend to be favored under microwave irradiation.[13a] Hence, it is feasible that a protonated or Lewis acid-coordinated alkoxy or aryloxy group leaves to form a carbocation that is then reduced by some hydride source to form the byproduct **2** or **3**. Concomitant oxidation of some S−H-containing intermediate could conceivably facilitate such a hydride transfer mechanism.

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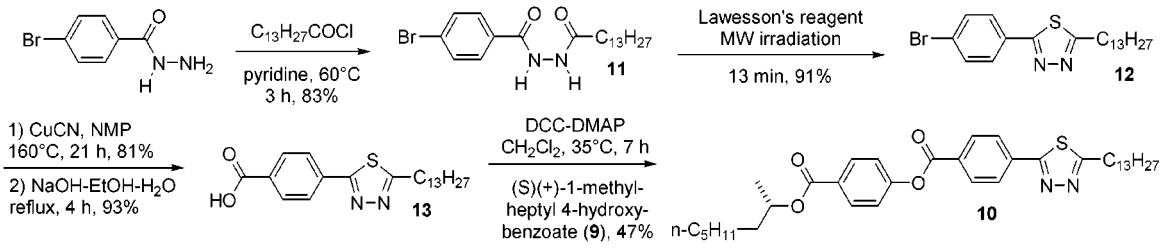
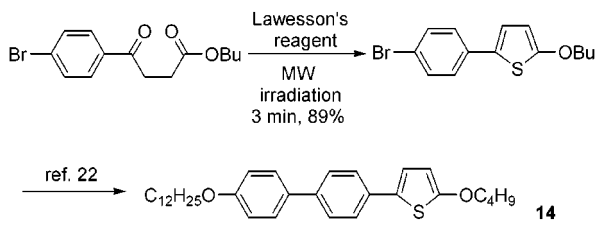
Scheme 2



Scheme 3



1,3,4-thiadiazole derivative **12** in 91% yield. The target liquid crystal **10** was then obtained via cyanation and basic hydrolysis to obtain the corresponding carboxylic acid **13** followed by DCC−DMAP esterification.

The new ring-closure methodology was also helpful in improving the yield of a previously synthesized liquid crystal **14**[22] as depicted in Scheme 3.

Each of the synthesized target materials **4**, **10**, and **14** possesses liquid crystalline properties. Of particular importance to us are compounds **4** and **10**, which have the desired ferroelectric and antiferroelectric phases. Materials exhibiting these phases may be useful in surface-stabilized ferroelectric and antiferroelectric liquid crystal displays.[23] A detailed study of the physical properties of these compounds is now in progress.

Experimental Section

General Procedure for Lawesson's Reagent-Mediated Cyclization Reactions. The 1,4-dicarbonyl compound (1.0 mmol) and Lawesson's reagent (0.486 g, 1.20 mmol) were mixed thoroughly in a glass reaction tube. The tube was placed in a beaker with a cover glass and irradiated using a commercial conventional microwave oven with a rotating tray (Samsung, MW6940W, 1000W) for 3−6 min until the evolution of gas ceased and the reaction mixture became an orange or yellow transparent liquid. It was then allowed to cool, and the resulting viscous mixture was dissolved in CH_2Cl_2 and evaporated on silica gel. Flash column chromatography on activated basic alumina (50−200 μm) or silica (200−425 mesh) provided the corresponding five-membered ring S-heterocycle, which was dried under vacuum (1.1 mmHg, P_2O_5, 24 h). *Caution*: these reactions must be performed in an efficient fume hood due to the generation of toxic H_2S gas.[24]

Synthesis of Liquid Crystals 4 and 10.

Dodecyl (4-Bromobenzoylamino)ethanoate (5). Glycine (3.80 g, 50.7 mmol) and dodecan-1-ol (23.25 g, 125.0 mmol) were stirred at 130 °C for 3 min. To this mixture was added methanesulfonic acid (3.56 mL, 55.0 mmol) over a period of 1 min. The reaction mixture was stirred vigorously at 130 °C for 2.5 h. The brown mixture was then cooled to room temperature, diluted with hexanes (250 mL), and cooled to 0 °C. The precipitate was filtered, washed well with hexanes, and suspended in ethyl ether (300 mL). It was then filtered again and air-dried to afford dodecyl 2-aminoethanoate hydromethanesulfonate as a white solid (13.33 g, 79%): ^{1}H NMR δ 7.91 (br s, 3H), 3.91 (m, 2H), 2.76 (s, 3H), 1.64 (quint, J = 6.8 Hz, 2H), 1.20−1.35 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 168.1, 66.5, 40.7, 39.2, 32.1, 29.8 (2), 29.7, 29.5, 29.4, 28.6, 25.9, 22.8, 14.3. Anal. Calcd for $C_{14}H_{31}NO_5S$: C, 51.66; H, 9.60; N, 4.30. Found: C, 51.32; H, 9.40; N, 4.57.

A solution of 4-bromobenzoyl chloride (4.39 g, 20.0 mmol) in $CHCl_3$ (15 mL) was added dropwise over a period of 3 min to a stirred, cooled (0 °C) solution of dodecyl 2-aminoethanoate hydromethanesulfonate (6.74 g, 20.0 mmol) and NEt_3 (6.10 mL, 44.0 mmol) in $CHCl_3$ (35 mL). The reaction mixture was stirred at 0 °C for 1 h, and the solvent was evaporated in vacuo. The residue was triturated with CH_2Cl_2 (100 mL), and the extract was passed through a short silica column (8 cm long, 4 cm in diameter). The solvent was evaporated to afford the title compound **5** as an off-white solid (6.85 g, 80%): ^{1}H NMR δ 7.67 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 6.92 (t, J = 4.7 Hz, 1H), 4.19 (d, J = 5.1 Hz, 2H), 4.17 (t, J = 6.7 Hz, 2H), 1.65 (quint, J = 6.9 Hz, 2H), 1.18−1.42 (m, 18H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 170.3, 166.7, 132.6, 132.0, 128.9, 126.7, 66.1, 42.0, 32.1, 29.8, 29.7 (2), 29.5, 29.4, 28.7, 26.0, 22.8, 14.3. Anal. Calcd for $C_{21}H_{32}BrNO_3$: C, 59.15; H, 7.56; N, 3.28. Found: C, 58.88; H, 7.58; N, 3.22.

2-(4-Bromophenyl)-5-dodecyloxy-1,3-thiazole (6). The title compound was prepared according to the general Lawesson's reagent-mediated cyclization procedure outlined above using 3.98 g (9.34 mmol) of compound **5** and 4.46 g (11.0 mmol) of Lawesson's reagent. An 8 min reaction time was employed. The cooled reaction mixture was dissolved in CH_2Cl_2 (250 mL) and evaporated onto silica gel (50 g). This was then placed on top of a silica column and chromatographed (140 g SiO_2, 4:1 hexanes−ethyl acetate). The product was then recrystallized from methanol (220 mL) and dried under reduced pressure (1.1 mmHg, P_2O_5, 20 h) to afford the title compound **6** as a white solid (3.30 g, 83%): ^{1}H NMR δ 7.67 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.12 (s, 1H), 4.09 (t, J = 6.5 Hz, 2H), 1.81 (quint, J = 6.9 Hz, 2H), 1.52−1.20 (m, 18H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 162.6, 154.1, 133.3, 132.1, 127.1, 123.4, 123.1, 75.6, 32.1, 29.8, 29.7 (2), 29.5, 29.4, 29.3, 25.9, 22.9, 14.3. Anal. Calcd for $C_{21}H_{30}BrNOS$: C, 59.43; H, 7.12; N, 3.30; S, 7.55. Found: C, 59.52; H, 7.20; N, 3.33; S, 7.95.

2-(4-Cyanophenyl)-5-dodecyloxy-1,3-thiazole (7). A stirred solution of compound **6** (2.12 g, 5.00 mmol) and CuCN (0.586 g, 6.54 mmol) in anhydrous NMP (12 mL) was heated at 160 °C for 5 h. The cooled reaction mixture was poured into cooled (0 °C) 10% aq HCl (20 mL) and stirred for 0.5 h before it was extracted with ethyl ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residual dark-brown oil was purified by flash column chromatography (100 g of SiO_2, 10:1 hexanes−ethyl acetate) to afford the title compound **7** as a white solid (1.70 g, 92%): ^{1}H NMR δ 7.89 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.19 (s, 1H), 4.11 (t, J = 6.5 Hz, 2H), 1.82 (quint, J = 6.9 Hz, 2H), 1.23−1.51 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 163.9, 152.5, 138.2, 132.8, 125.9, 123.7, 118.8, 112.3, 75.8, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 25.9, 22.8, 14.3. Anal. Calcd for $C_{22}H_{30}N_2OS$: C, 71.31; H, 8.16; N, 7.56; S, 8.65. Found: C, 70.96; H, 8.28; N, 7.43; S, 8.89.

2-(4-Carboxyphenyl)-5-dodecyloxy-1,3-thiazole (8). A solution of compound **7** (1.46 g, 3.95 mmol) and NaOH (2.00 g, 50.0 mmol) in 1:1 ethanol−H_2O (20 mL) was heated under reflux for 4 h. The solvent was removed in vacuo (20 mmHg, 80 °C),

(22) Kiryanov, A. A.; Sampson, P.; Seed, A. J. *J. Mater. Chem.* In press.

(23) Lagerwall, S. T. *Ferroelectric and Antiferroelectric Liquid Crystals*; Wiley-VCH: Weinheim, 1999.

(24) For appropriate precautions when handling H_2S, see: *Prudent Practices in the Laboratory: Handling and Disposal of Chemicals*; National Research Council, National Academy Press: Washington, DC, 1995; pp 342−343.

and the residue was triturated with water (100 mL). The suspension was acidified with 10% aq HCl to pH 1 and stirred for 2 h at room temperature. The precipitate was filtered off, washed with water (200 mL), and dried under reduced pressure (1 mmHg, P_2O_5, 24 h) to afford the title compound **8** as a white solid (1.30 g, 85%): ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 6.7 Hz, 3H), 1.17−1.46 (m, 18H), 1.74 (quint, J = 6.8 Hz, 2H), 4.16 (t, J = 6.5 Hz, 2H), 7.38 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 2H), the carboxylic acid signal was not observed; ^{13}C NMR (DMSO-d_6) δ 14.0, 22.1, 25.2, 28.4, 28.6, 28.7, 28.9 (2), 29.0, 31.3, 75.1, 123.6, 125.1, 130.1, 131.3, 137.1, 152.4, 162.7, 166.8. Anal. Calcd for $C_{22}H_{31}NO_3S$: C, 67.83; H, 8.02; N, 3.60; S, 8.23. Found: C, 67.80; H, 8.24; N, 3.56; S, 8.60.

(*S*)-1-Methylheptyl 4-[4-(5-Dodecyloxy-1,3-thiazolyl-2-yl)phenylcarbonyloxy]benzoate (4). To a suspension of compound **8** (0.622 g, 1.60 mmol), DMAP (0.0490 g, 0.402 mmol), and phenol **9** (0.375 g, 1.50 mmol) in anhydrous CH_2Cl_2 (200 mL) was added DCC (0.340 g, 1.65 mmol) in one portion. The reaction mixture was stirred at room temperature for 30 h, diluted with hexane (50 mL), and filtered. The filtrate was washed with 10% aq HOAc (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (100 g of SiO_2, 12:1 petroleum ether−ethyl acetate (500 mL), followed by 9:1 petroleum ether−ethyl acetate) to afford the title compound **4** as a white solid (0.650 g, 70%): ^{1}H NMR δ 8.23 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.22 (s, 1H), 5.17 (app sext, J = 6.3 Hz, 1H), 4.13 (t, J = 6.6 Hz, 2H), 1.84 (quint, J = 7.0 Hz, 2H), 1.68−1.78 (m, 1H), 1.55−1.68 (m, 1H), 1.35 (d, J = 6.3 Hz, 3H), 1.24−1.53 (m, 26H), 0.89 (t, J = 6.7 Hz, 6H); ^{13}C NMR δ 165.6, 164.4, 163.7, 154.5, 153.4, 139.1, 131.3, 131.0, 129.3, 128.8, 125.6, 123.7, 121.8, 75.6, 72.1, 36.0, 32.1, 31.9, 29.8, 29.7 (2), 29.5, 29.4, 29.3, 29.2, 25.9, 25.6, 22.8, 22.7, 20.2, 14.3, 14.2. Anal. Calcd for $C_{37}H_{51}NO_5S$: C, 71.46; H, 8.27. Found: C, 71.47; H, 8.33. Transition temperatures: Cryst. 81.5 S_C*$_{ANTI}$ 89.0 S_C*$_{FERRI}$ 90.6 S_C*$_{FERRO}$ 94.9 S_A 99.6 Iso. Liq.

***N*-(4-Bromobenzoyl)-*N*′-tetradecanohydrazide (11).** Myristoyl chloride (11.5 g, 46.7 mmol) was added dropwise to a solution of 4-bromobenzohydrazide (10.0 g, 46.5 mmol) in anhydrous pyridine (200 mL) at 10 °C under argon. The reaction mixture was heated at 60 °C for 3 h and then concentrated in vacuo at 70 °C. The crude residue was suspended in boiling water (600 mL) and heated at reflux for 0.5 h. Once all of the solid was finely suspended, the precipitate was filtered, air-dried, and suspended in hot petroleum ether (300 mL). The cooled suspension was filtered, and the precipitate was dried under reduced pressure (1.1 mmHg, P_2O_5, 24 h) to afford the title compound **11** as a white solid (16.4 g, 83%): ^{1}H NMR δ 8.92 (br s, 1H), 8.43 (br s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.70 (quint, J = 7.4 Hz, 2H), 1.49−1.23 (m, 20H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 170.8, 167.3, 132.5, 129.5, 129.3, 125.4, 32.0, 30.4, 30.2, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 22.8, 14.2. Anal. Calcd for $C_{21}H_{33}BrN_2O_2$: C, 59.29; H, 7.82; N, 6.59. Found: C, 59.28; H, 7.88; N, 6.52.

2-(4-Bromophenyl)-5-tridecyl-1,3,4-thiadiazole (12). The title compound was prepared according to the general Lawesson's reagent-mediated cyclization procedure outlined above using 8.50 g (20.0 mmol) of compound **11** and 8.91 g (22.0 mmol) of Lawesson's reagent. A 13 min reaction time was employed. The cooled reaction mixture was dissolved in CH_2Cl_2 (250 mL) and evaporated onto silica gel (50 g). This was then placed on top of a short silica plug (10 cm long, 6 cm wide) and chromatographed using 3:1 petroleum ether−ethyl acetate as an eluent. The filtrate was concentrated in vacuo, and the resulting solid was recrystallized from methanol (450 mL) to afford the title compound **12** as fine white needles (7.67 g, 91%): ^{1}H NMR δ 7.81 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H), 1.83 (quint, J = 7.5 Hz, 2H), 1.50−1.23 (m, 20H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 170.8, 167.3, 132.5, 129.5, 129.3, 125.4, 32.0, 30.4, 30.2, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 22.8, 14.2. Anal. Calcd for $C_{21}H_{31}BrN_2S$: C, 59.56; H, 7.38; N, 6.62; S, 7.57. Found: C, 59.53; H, 7.47; N, 6.51; S, 7.75.

2-(4-Carboxyphenyl)-5-tridecyl-1,3,4-thiadiazole (13). A stirred solution of compound **12** (6.35 g, 15.00 mmol) and CuCN (1.75 g, 19.5 mmol) in anhydrous NMP (36 mL) was heated at 160 °C for 21 h. The cooled reaction mixture was poured into cooled (0 °C) 10% aq HCl (20 mL) and stirred for a short time. The resulting mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and passed through a short silica plug (10 cm long, 4 cm wide). The filtrate was concentrated in vacuo; the residue was suspended in water (200 mL), and the resulting precipitate was filtered and air-dried. This solid was then triturated twice with boiling methanol (250 mL, 100 mL). The combined solutions were cooled and filtered to obtain 2-(4-cyanophenyl)-5-tridecyl-1,3,4-thiadiazole as a yellowish solid, which was dried under reduced pressure (1.1 mmHg, P_2O_5, 10 h) (4.13 g, 81%): ^{1}H NMR δ 8.07 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 3.17 (t, J = 7.6 Hz, 2H), 1.85 (quint, J = 7.5 Hz, 2H), 1.49−1.23 (m, 20H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 171.9, 166.4, 134.5, 133.0, 128.4, 118.2, 114.4, 32.0, 30.4, 30.2, 29.7 (2), 29.5 (2), 29.3, 29.1, 22.8, 14.2. Anal. Calcd for $C_{22}H_{31}N_3S$: C, 71.50; H, 8.45; N, 11.37; S, 8.68. Found: C, 71.38; H, 8.50; N, 11.15; S, 8.97.

2-(4-Cyanophenyl)-5-tridecyl-1,3,4-thiadiazole (3.00 g, 8.13 mmol) was heated under reflux in a solution of sodium hydroxide (10.0 g, 0.250 mol) in ethanol (175 mL) and water (50 mL) for 3 h. A portion of the solvent (100 mL) was then distilled off at atmospheric pressure. The remaining solvent was evaporated in vacuo, and the beige mixture was suspended in water (350 mL). To this suspension was added 10% aq HCl (250 mL), and the resulting white mixture was stirred for 1 h. The precipitate was filtered off and dissolved in boiling acetic acid (100 mL). The resulting solution was cooled by addition of ice (100 g), and the precipitate was filtered and dried under reduced pressure (1.1 mmHg, P_2O_5, 14 h) to afford the title compound **13** as a white solid (2.94 g, 93%): ^{1}H NMR (DMSO-d_6) δ 8.07 (app s, 4H), 3.14 (t, J = 7.6 Hz, 2H), 1.76 (quint, J = 7.3 Hz, 2H), 1.42−1.19 (m, 20H), 0.84 (t, J = 6.7 Hz, 3H), the carboxylic acid signal was not observed; ^{13}C NMR (DMSO-d_6) δ 170.9, 166.5, 166.3, 133.3, 132.7, 130.0, 127.5, 31.0, 29.1 (2), 28.8, 28.7 (2), 28.6, 28.4, 28.3, 28.0, 21.8, 13.6. Anal. Calcd for $C_{22}H_{31}NO_3S$: C, 68.00; H, 8.30; N, 7.21; S, 8.25. Found: C, 67.86; H, 8.43; N, 7.09; S, 8.34.

(*S*)-1-Methylheptyl 4-[4-(5-Tridecyl-1,3,4-thiadiazolyl-2-yl)phenylcarbonyloxy]benzoate (10). To a suspension of compound **13** (0.776 g, 2.00 mmol), DMAP (0.0976 g, 0.800 mmol), and phenol **9** (0.391 g, 1.56 mmol) in anhydrous CH_2Cl_2 (150 mL) was added DCC (0.433 g, 2.10 mmol) in one portion. The reaction mixture was stirred at room temperature for 1 h and heated at reflux for 7 h. The reaction mixture was diluted with petroleum ether (100 mL) and cooled (0 °C). The precipitate was filtered off and washed with petroleum ether (50 mL) and CH_2Cl_2 (50 mL). The combined washings and the filtrate were evaporated in vacuo. The residue was recrystallized from 5:1 methanol−ethyl acetate (300 mL) to afford the title compound **10** as a white solid (0.530 g, 55%): ^{1}H NMR δ 8.30 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 5.17 (app sext, J = 6.2 Hz, 1H), 3.17 (t, J = 7.6 Hz, 2H), 1.86 (quint, J = 7.4 Hz, 2H), 1.80−1.68 (m, 1H), 1.68−1.54 (m, 1H), 1.35 (d, J = 6.1 Hz, 3H), 1.52−1.23 (m, 28H), 0.88 (t, J = 6.6 Hz, 6H); ^{13}C NMR δ 171.6, 167.1, 165.5, 164.0, 154.4, 135.3, 131.3, 131.1, 129.0, 128.1, 121.7, 72.1, 36.2, 32.0, 31.9, 30.4, 30.2, 29.7 (2), 29.6, 29.5, 29.3 (2), 29.1, 25.5, 22.8, 22.7, 20.2, 14.2, 14.1. Anal. Calcd for $C_{37}H_{51}NO_5S$: C, 71.57; H, 8.44; N, 4.51; S, 5.16. Found: C, 71.65; H, 8.46; N, 4.51; S, 5.22. Transition temperatures: Cryst. 93.5 S_C*$_{ANTI}$ 101.2 S_C*$_{FERRI}$ 102.0 S_C*$_{FERRO}$ 104.9 S_A 115.7 Iso. Liq.

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Supporting Information Available: General experimental procedures, procedures (or literature references) for the synthesis of 1,4-dicarbonyl compounds employed in Lawesson's reagent-mediated cyclization studies, and details of purification procedures and characterization data for all S-heterocycles produced during these cyclization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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