Synthesis of Liquid Crystalline 4*H*-Benzo[1,2,4]thiadiazines and Generation of Persistent Radicals

Józef Zienkiewicz, Anna Fryszkowska,† Katarzyna Zienkiewicz, Fengli Guo,
Piotr Kaszynski,* Adam Januszko, and David Jones

*Organic Materials Research Group, Department of Chemistry, Vanderbilt University,
Nashville, Tennessee 37235*

piotr.kaszynski@vanderbilt.edu

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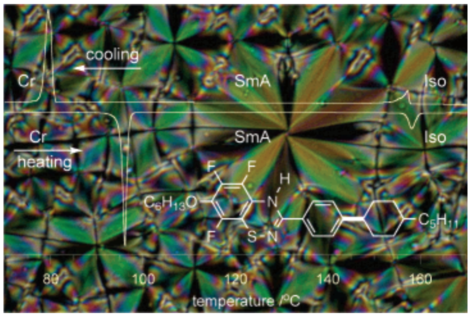

Four substituted 4*H*-benzo[1,2,4]thiadiazines **2** were prepared by condensation of the appropriate anilines and benzonitriles followed by oxidative cyclization. The preparation of three fluorinated derivatives **2b**−**2d** proceeded smoothly, while the synthesis of **2a** was problematic, presumably due to the relatively high electron density of the benzene ring. The four-ring derivatives **2c** and **2d** exhibited liquid crystalline properties (**2c**: Cr 95 SmA 158 I and **2d**: Cr 142 SmA 212 I). 4*H*-Benzo[1,2,4]thiadiazines **2** were oxidized with AgO to generate the corresponding persistent radicals **1** ($g = 2.0057$). The stability of the radicals followed the order **1b** ∼ **1d** > **1c** ≫ **1a**, and the two fluorinated radicals **1b** and **1d** were isolated as crude solids. The lower stability of **1c** is presumably due to the presence of the reactive benzylic CH position, and **1a** lacks the stabilizing effect of the three fluorine atoms. ESR spectra for **1** were simulated using DFT-derived hfcc as the starting point.

Introduction

Over the past two decades, there has been increasing effort to combine paramagnetic and liquid crystalline properties to enhance the effect of a magnetic field on optical properties (magnetooptics) and to elucidate fundamental aspects of molecular magnetism.[1] Liquid crystals (LCs) are partially oriented anisotropic fluids[2,3] that exhibit over two dozen distinct phases.[4] They offer access to a number of thermodynamically controlled spatial molecular arrangements and hence provide alternative types of intermolecular interactions either in the fluid phase (dynamic) or in the glass phase (static). Therefore, liquid crystals are an attractive vehicle to impose partial molecular order and to control intermolecular spin−spin interactions of paramagnetic mesogens.[5,6] To maximize these interactions, the spin source should be placed in the rigid core and the unpaired electron delocalized in the π-electron manifold.

The majority of paramagnetic LCs with permanent spins studied thus far are metallomesogens,[7] in which the spin

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[*] Corresponding author. Phone: (615) 322-3458. Fax: (615) 343-1234.

[†] Visiting graduate student from the group of Prof. R. Ostaszewski at Warsaw University of Technology, Poland.

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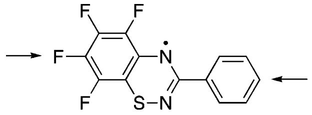
originates from transition metal centers. Many such compounds exhibit significant paramagnetic anisotropy due to the spin orbit coupling especially in the mesogenic complexes of some lanthanides.[8,9] Unfortunately, in metallomesogens, little spin is transferred from the metal to the π-framework,[10−12] which limits the extent of intermolecular spin−spin magnetic exchange. In contrast, properly designed all-organic paramagnetic mesogens are expected to provide significant delocalization of the spin, unfortunately at the expense of paramagnetic anisotropy. Such all-organic mesogens have been much more difficult to realize experimentally.[13]

There are very few LCs containing purely organic electrically neutral spin sources. To date, only nitroxyl and related nitronylnitroxide groups have been explored as spin sources for liquid crystalline radicals. Since for stability reasons the nitroxyl group must be substituted with quaternary centers, placing them in the rigid core without compromising mesogenic properties was a challenge for a long time.[14−18] Recently, the first such mesogens were prepared.[19,20] Although this constitutes a significant milestone in the investigation of all-organic paramagnetic mesogens, the new design[19] still has not addressed the issue of spin delocalization. The nitroxide group is a sterically and electronically isolated small spin source capable of very limited intermolecular spin−spin interactions.

A more effective way to design liquid crystals with π-delocalized spins is to use heteroaromatic radicals. In this context, we have focused on [1,2]thiazinyl as the fundamental structural element for calamitic and discotic mesogens.[13,21] We have prepared several of its hetera- and fused-ring analogues and investigated properties of such persistent radicals.[22−24] Many of these radicals exhibit a chemical stability sufficient for studying their liquid crystalline derivatives. In addition, the S atom provides a modest paramagnetic anisotropy[1] of the radicals,[25−27] which is greater than that of nitroxides.

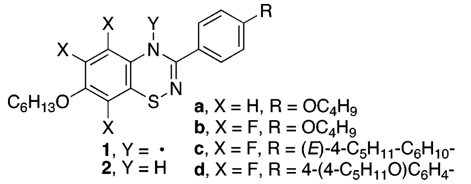


I

FIGURE 1. Persistent benzo[1,2,4]thiadiazinyl **I**. Arrows indicate the substitution sites to induce mesogenic behavior.

Recently, we developed a methodology for the synthesis of fused-ring 4*H*-benzo[1,2,4] thiadiazines[28] and for the efficient generation of the corresponding radicals.[23] Investigation demonstrated that the tetrafluoro derivative **I** (Figure 1) is moderately reactive toward oxygen but is sufficiently stable for isolation in the pure crystalline form and complete characterization. This prompted us to investigate **I** as a structural element for paramagnetic calamitic liquid crystals.[13]

To induce mesogenic properties, the anisometry of radical **I** was increased by substitution with a hexyloxy group in position 7 and introduction of a substituent in the para position of the phenyl ring (Figure 1). Therefore, we focused on a three-ring derivative **1b**, a trifluoro analogue of **1a**, and four-ring derivatives **1c** and **1d**, which could be available from the corresponding thiadiazines **2**.



Here, we report progress toward such a class of paramagnetic calamitic liquid crystals and describe the preparation and liquid crystalline properties of four substituted 4*H*-benzo[1,2,4]-thiadiazines **2**. We also report preliminary results on the generation and characterization of radicals **1**.

Results

Synthesis of 4*H*-Benzo[1,2,4]thiadiazines 2. Our initial approach to the preparation of thiadiazine **2a** followed the method of Gilchrist, which relies on electrophilic cyclization of *N*-arylbenzamidines with divalent sulfur electrophiles.[29] Thus, the reaction of amidine **3** with a bis(4-morpholinyl)chlorosulfonium intermediate followed by thermolysis of the resulting crude ylide **4** in chlorobenzene repeatedly gave disappointingly low yields (~5%) of the desired thiadiazine **2a** (Scheme 1). Separation of pure **2a** was complicated by the presence of benzothiazole **5**, which was formed presumably by thermolysis of **2a**, as was demonstrated for other benzo[1,2,4]thiadiazines.[30]

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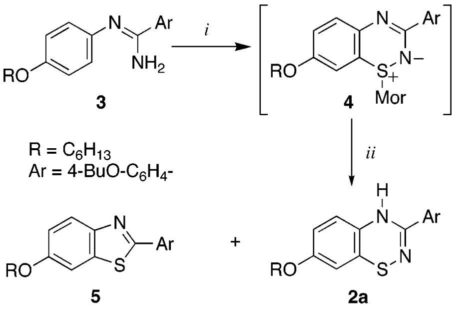
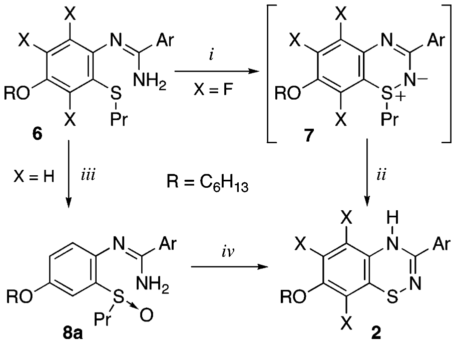
SCHEME 1[a]



[a] *i*: (1) (4-Morpholinyl)$_2$S, NCS and (2) 5% NaOH. *ii*: PhCl, reflux.

SCHEME 2[a]



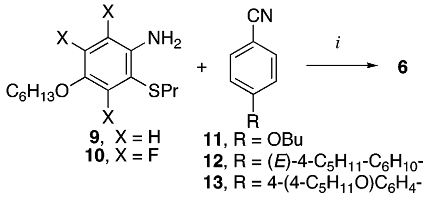
[a] *i*: (1) NCS, (2) 5% NaOH. *ii*: Toluene, reflux, **2b** 41−46%, **2c** 34%, **2d** 30%. *iii*: NaIO$_4$, 68%. *iv*: PhCl, reflux, 12%.

An analogous reaction[31] of amidine **3** with SCl$_2$ in the presence of pyridine resulted in partial chlorination of the ring and was not pursued further.

The difficulties with the isolation of pure thiadiazine **2a** and low yields of this process prompted us to develop a more reliable method involving regiospecific cyclization of amidines substituted with an alkylsulfanyl group.[28] According to this method, amidine **6a** was treated with NCS or with PhI(OAc)$_2$/K$_2$CO$_3$, but the formation of the expected ylide **7a** was not confirmed by NMR analysis (Scheme 2). It is possible that the oxidants preferentially attacked the electron-rich benzene ring rather than the amidinyl nitrogen atom. Therefore, the preparation of the desired thiadiazine **2a** was approached through sulfoxide **8a** following our success with an analogous synthesis of a pyrazine derivative.[28] Thus, thermolysis of **8a** in refluxing toluene showed a slow formation of the desired thiadiazine **2a** along with the thiazole **5** byproduct. The same reaction carried out in boiling chlorobenzene gave about 50% conversion of the starting **8a** after 16 h, and the product **2a** was isolated in 12% yield along with 8% of thiazole **5**. The required sulfoxide **8a** was smoothly obtained in 68% isolated yield by periodate oxidation[32] of either amidine **6a** or its hydrochloride **6a·HCl**. ^{1}H NMR and combustion analyses demonstrated that sulfoxide **8a** crystallizes with one molecule of water.

Preparation of the fluorinated thiadiazines **2b**−**2d** was more straightforward. They were obtained in 30−46% isolated yields by oxidative cyclization of amidines **6b**−**6d** in the presence of NCS and subsequent electrocyclic elimination of propene (Scheme 2).[28] In one instance, sulfoxide **8c** was isolated in 18% yield, presumably from hydrolysis of the unreacted chlorosulfonium intermediate. To increase the conversion, the NCS-assisted cyclization reaction of **6c** was first conducted at ambient temperature for 12 h and then in boiling methylene chloride for 1 h followed by the usual workup. Unfortunately, this led to the formation of a complex mixture of products, and the desired thiadiazine **2c** was isolated only in about 12% yield. This presumably resulted from temperature-enhanced reactivity of NCS toward the benzylic-type position in **6c** and also from partial decomposition of the thermally labile ylide **7c** to thiadiazine **2c** and its subsequent reaction with NCS.

SCHEME 3[a]



[a] *i*: NaH for **9**, MeSO$_3$H for **10**, 46−76%.

The preparation of the requisite amidines **6** was accomplished by condensation[28] of amines **9** and **10** with appropriate nitrile **11**−**13** either under basic (**6a**) or under acidic conditions (**6b**−**6d**) (Scheme 3). In the latter reaction, typically a 5-fold excess of nitrile was used to ensure the consumption of amine **10**. The unused nitrile was recovered in about 60% and reused for another condensation reaction with amine **10**. In one experiment, the amount of nitrile **12** was reduced to 2 equiv without significant compromising of the yield for **6c**. Experiments demonstrated that isomeric mixtures of amines containing 75−90% of **10** could be used successfully for the condensation reaction. In this case, pure amidines **6b** and **6c** were easily isolated by chromatography followed by recrystallization.

The required amines **9** and **10** were prepared from 2,4-dichloronitrobenzene (**14**) and pentafluoronitrobenzene (**15**), respectively, in a series of nucleophilic aromatic substitution reactions (Scheme 4). The order of introduction of the substituents was dictated by the demonstrated regioselectivity of alkylthiolation of **14**[33,34] and alkoxylation of **15**.[35] Thus, propylthiolation of **14** under PTC conditions gave the pure desired isomer **16**. Subsequent reaction of **16** with *n*-hexanol in DMSO in the presence of powdered KOH, according to an analogous procedure,[36] gave the nitro compound **17**, which was reduced to amine **9** with iron powder. The overall yield of the amine for the three steps was 38%.

Reaction of **15** with *n*-hexanol under PTC conditions, according to an analogous literature procedure,[37] gave 4-hexyloxytetrafluoronitrobenzene (**18**) and its ortho isomer in a 7:1 to 8:1 ratio. The structural assignment for the isomers was made on the basis of MS and NMR results. The formation of the

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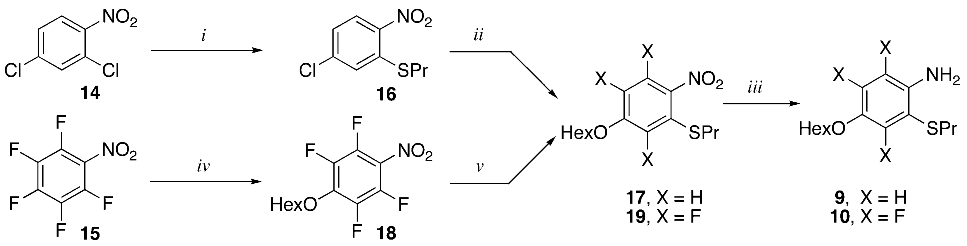
SCHEME 4[a]



[a] *i*: PrSH, NaOH, $Bu_4N^+Br^-$, benzene, 60%. *ii*: *n*-HexOH, KOH, DMSO, 67%. *iii*: Fe, AcOH, H_2O, **9** 94%, **10** 91%. *iv*: *n*-HexOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2, 76%. *v*: PrSH, NaOH, EtOH, 92%.

TABLE 1. Transition Temperatures and Enthalpies for Selected Compounds[a]

compound	phase transition
2a	Cr 133 I (*36.2*)
2b	Cr 93 I (*36.2*)
2c	Cr 95 SmA 158 I (*22.6*) (*3.75*)
2d	Cr 142 SmA 212 I (*31.6*) (*6.0*)
3	Cr 130 (SmX[b] 125 SmB 130)[c] SmA 136 I (*35.4*) (*0.1*) (*3.2*) (*7.3*)
5	Cr 99 N 125 I (*22*) (*0.9*)

[a] Transition temperatures (°C) and enthalpies (kJ mol^{-1}) were determined by DSC (5 °C min^{-1}) in the heating mode: Cr = crystal; Sm = smectic; and I = isotropic. [b] SmI or SmF phase. See text for details. [c] Monotropic transitions.

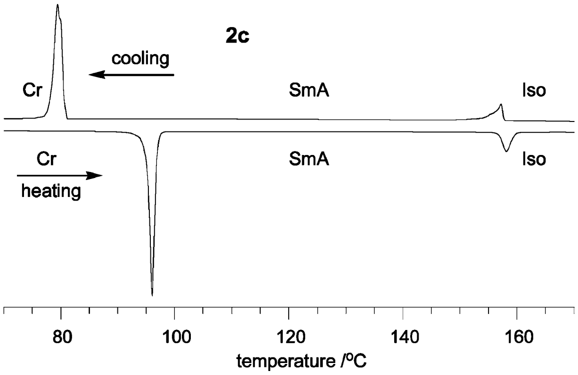


FIGURE 2. A DSC trace of **2c**. Heating and cooling rates are 5 °C/min.

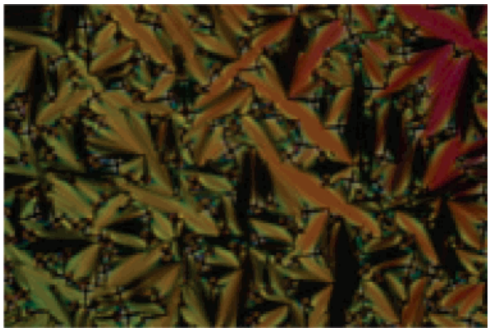


FIGURE 3. Optical texture for **2d** at 190 °C. Magnification 150×.

isomers and their ratio is consistent with other reports[38] on alkoxylation of **15** and the finding that the ratio of the two isomers is temperature-dependent.[35] Isomerically pure **18** was obtained by repeated fractional distillation. Propylthiolation of **18** gave **19**, which upon reduction with iron yielded amine **10** in good yield. Less satisfactory results were obtained with zinc/AcOH or zinc/NH_4Cl[39] as the reducing reagents, and the amine could not be separated from byproducts. For practical reasons, a large-scale synthesis could be carried out on the isomeric mixture of the nitrobenzenes and the isomers could be separated on later stages of the synthesis, as was demonstrated for amidines **6b** and **6c**. Thus, nitro derivative **18**, containing about 10% of the ortho isomer, gave amine **10** as a 9:1 mixture of two isomers, which was successfully used in the subsequent condensation reactions.

Liquid Crystalline Properties. Phase transition temperatures and enthalpies for 4*H*-benzo[1,2,4]thiadiazines **2**, amidine **3**, and benzothiazole **5** are collected in Table 1. Phase structures were assigned by comparison of microscopic textures observed under polarized light with those published for reference compounds.[40−42]

Out of the four thiadiazines, only the four-ring derivatives **2c** and **2d** exhibited liquid crystalline properties. The DSC trace for **2c** is shown in Figure 2. Optical microscopy for both thiadiazines revealed typical smectic A phases with the characteristic fan-shaped textures obtained upon cooling from the isotropic phase (Figure 3). The three-ring thiadiazines **2a** and **2b** showed only melting transitions and, upon cooling, crystallization at about 15 °C below the melting point. Interestingly, fluorination of **2a** results in a 40 °C lower melting point of **2b**.

Thermal and optical analysis of amidine **3** revealed the formation of a narrow temperature range enantiotropic SmA phase and two monotropic smectic phases. The first monotropic phase was identified as a SmB phase (hexatic) on the basis of a typical broken focal-conic texture and low viscosity (see Supporting Information). Upon cooling, the homeotropic regions of the SmB phase displayed a schlieren texture. This, combined with a very small enthalpy of transition (0.1 kJ/mol), suggested the formation of a tilted SmI phase, although a SmF phase cannot be excluded. None of the amidines **6** substituted with the PrS group exhibited mesogenic behavior.

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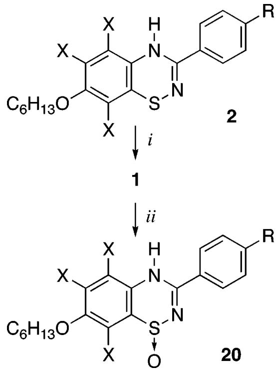
SCHEME 5[a]



[a] *i*: AgO, K_2CO_3, MeCN/toluene 1:1. *ii*: O_2.

Benzothiazole **5** exhibited only an enantiotropic nematic phase. It is a new member of a homologous series of benzothiazoles that exhibit nematic (lower homologues) and also SmA phases.[43]

Generation of Radicals. Radicals **1** were generated from the corresponding benzo[1,2,4]thiadiazines **2** using AgO in a MeCN/toluene or MeCN/benzene mixture according to an earlier established procedure[23] (Scheme 5). The three fluorinated radicals **1b**−**1d** were significantly more stable than **1a**. Their solutions were filtered through a Florisil pad to remove the inorganic salts, and solvents were removed from solutions of **1b** and **1d** under reduced pressure, leaving the black-green solid of the crude radicals. Radical **1c** appeared to be less stable than the two other fluorinated derivatives and decomposed in solution after filtration. Radical **1a** persisted in solution for a few hours but largely decomposed during the attempted filtration.

All three fluorinated radicals were moderately sensitive to molecular oxygen, and their solutions were bleached in air over several hours. In the case of radical **1b,** the *S*-oxide **20b** was isolated as the main decomposition product, which is consistent with the results for the parent radicals.[23]

Electron Spin Resonance. The room temperature benzene solution spectrum of radicals **1a** consists of a pseudo-quintet centered at about 3488 G, which arises from the principal coupling to the two nitrogen atoms and unresolved couplings to the hydrogen atoms (Figure 4, top). The solution spectra of **1b**−**1d** have more features due to the presence of the fluorine atoms. They appear similar to each other since the structural differences are in the remote part of the molecule. Spectra of **1b** and **1c** consist of 17 lines centered at about 3488 G, while the spectrum of **1d** exhibits several additional shoulder features (Figure 4, bottom). The measured *g* value for all four radicals **1a**−**1d** is 2.0057, which is practically the same as for the parent radicals.[23]

Simulations of the experimental spectra were performed using computed and appropriately scaled[23] hfcc values for two nitrogen, hydrogen or fluorine atoms in positions 5, 6, and 8, and also H atoms of the 3-phenyl substituent and the two hydrogens of the CH_2O group at the 7 position as the starting point (see Supporting Information). The resulting hfcc were structurally assigned on the basis of trends in the calculated values (Table 2).

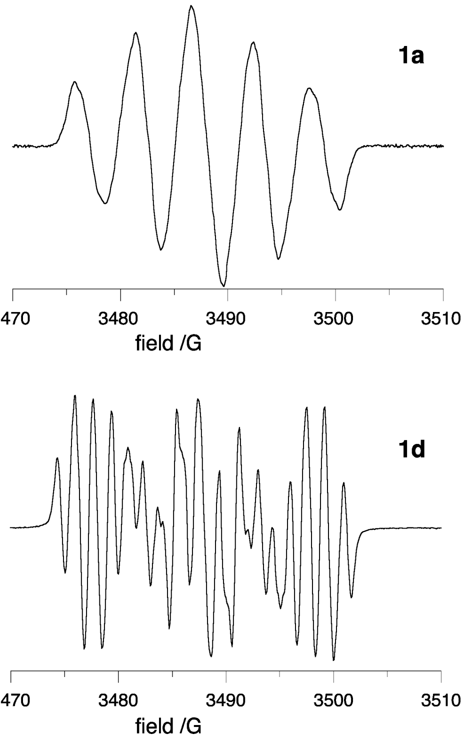


FIGURE 4. ESR spectra for **1a** (top) and **1d** (bottom) recorded in benzene at ambient temperature. The radicals were generated with AgO/K_2CO_3.

TABLE 2. Experimental Isotropic hfcc (G) for Radicals 1[a]

	1a	1b	1c	1d
aN2	5.82	5.91	5.86	5.83
aN4	5.04	4.87	4.92	4.90
aX5[b]	1.12	1.88	1.90	1.94
aX6[b]	0.76	1.42	1.44	1.38
aX8[b]	0.70	1.64	1.63	1.74
aH(Ph)[c] ortho	0.41	0.24	0.22	0.13
aH(Ph)[c] meta	0.34	0.23	0.12	0.05
aH(CH_2)[d]	0.76	0.44	0.40	0.30

[a] Obtained from simulation of the experimental spectra recorded in benzene solutions at ambient temperature ($g = 2.0057$). The correlation value $r^2 \geq 0.994$. [b] X is H (**1a**) or F (**1b**−**1d**). [c] Average value for the two hydrogen atoms. [d] Average value for two hydrogen atoms near the ring.

Results in Table 2 show that all four radicals exhibit two similar couplings a_N of about 6 and 5 G to the thiadiazinyl nitrogen atoms N(2) and N(4), which give the basic quintet in the spectrum of **1a** (Figure 4, top). Interestingly, the fluorine atoms decrease the spin density on the N(4) atom, and consequently, the a_{N4} for the fluorinated radicals is lower by about 0.15 G relative to that for **1a**. In radical **1a**, only one hydrogen atom, H(5), has a significant hfcc of 1.6 G, and the couplings to the remaining eight H atoms are ≤0.55 G. In contrast, in radicals **1b**−**1d**, there is a significant coupling to all three ^{19}F nuclei, and the a_F is in the range of 1.4−2.0 G. The a_F value for F(6) is markedly larger (~1.4 G) than that predicted by theory (0.16 G), which is consistent with our previous findings.[23] The couplings to the remaining six H atoms in **1b**−**1d** are similar to those observed for radical **1a** ($a_H \leq$ 0.6 G), and they contribute to the line broadening.

Computational Analysis. To provide the initial guess for the numerical simulation of the experimental ESR spectra, hyperfine coupling constants were calculated for model compounds **21** using the previously developed protocol.[44] For the purpose of calculations, the alkoxy groups in **1** were replaced with a methoxy group, and the 4-pentylcyclohexyl in **1c** was substituted with the isopropyl group. A model for **1d** was not

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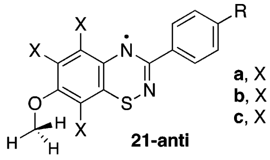
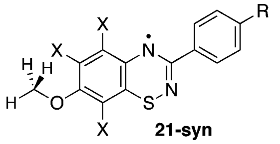
(43) Zhenrong, L.; Li, Y. *Thermochim. Acta* **1991**, *178*, 305−309.

considered. The orientation of the substituents in **21** was set in accordance with solid-state structures of compounds containing the relevant molecular fragments. Thus, the methoxy group at the 7 position of **21a** was fixed coplanar with the heterocyclic ring, and in **21b** and **21c**, it was initially set at about 60° to the heterocycle plane, in accordance with over two dozen solid-state structures featuring the 2,6-difluoroalkoxyphenyl fragment.[45] For all three compounds, two conformers were considered with the Me group syn and anti relative to the sulfur atom. The MeO group on the phenyl substituent in **21a** and **21b** was set to be coplanar, while the isopropyl group in **21c** was orthogonal to the benzene ring plane as it was found in the solid-state structures of simple 4-isopropylphenyl derivatives.[46] The geometries of syn and anti conformers of **21a** were optimized at the C_s point group symmetry and for **21b** and **21c** without symmetry constraints (C_1 symmetry) at the B3LYP/6-31G(d) level of theory. Results show that the 7-MeO group is oriented at about 10° for the anti and about 30° for the syn conformer relative to the heterocyclic ring in the equilibrium geometry of **21b** and **21c**. The 3-phenyl substituent remains coplanar with the thiadiazinyl ring, which is consistent with the solid-state structure for the parent radical **I**.[23]



a, X = H, R = OMe
b, X = F, R = OMe
c, X = F, R = CHMe$_2$

21-anti



21-syn

Single-point calculations at the B3LYP/cc-pVDZ level of theory gave the spin densities and Fermi contacts for each conformer. Inspection of the calculated coupling constants demonstrated that the orientation of the MeO group in the 7 position has an effect on all nuclei in the ring, but as expected, the most profound effect is on the methylene group and the atoms (H in **21a** and F in **21b** and **21c**) in the ortho positions. In the syn conformers, the two H atoms of the OMe group have approximately twice as large a_H values than in the anti conformers. This results from a balance of through bond and through space spin polarization induced by atoms X(6) and X(8) with spin densities of opposite signs. The X(6) and X(8) atoms are little affected (≤0.7 MHz) by the orientation of the OMe group. In contrast, the a_{X5} value varies significantly between the two conformers, and for **21a**, the difference between the syn and the anti form is 1.3 MHz, while for **21b**, it is 2.5 MHz. The a_{N2} value is also affected by conformational differences but to a smaller extent. The a_{N2} value is smaller in the syn conformer by 0.8 MHz for **21a** and by 0.5 MHz for the fluorinated radicals.

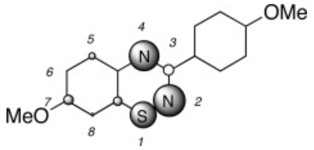


FIGURE 5. Total spin density map calculated for **21a** with the B3LYP/cc-DVZ//B3LYP/6-31G(d) method and averaged for two conformers. The numerals show the heterocycle numbering system.

The resulting hfcc values for pairs of conformers were averaged for each nucleus and appropriately scaled.[23] The values for hydrogen atoms on the 3-phenyl ring were obtained as an average of four hfcc (two ortho or two meta positions in two conformers). The average a_H values for the 7-MeO group were calculated using two hydrogen atoms closest to the ring in each conformer. These results served as starting points for the eight-parameter fitting of experimental spectra, and numerical values are listed in the Supporting Information.

Spin densities calculated for **21a** are generally similar to those obtained for the parent radical[23] (Figure 5). The largest differences are observed for the sulfur atom and carbon atoms in positions 6, 7, and 8. The introduction of the MeO group to the parent radical decreases the spin density on the sulfur and C(7) atoms by 10 and 21%, respectively. At the same time, the small negative spin density on C(6) becomes positive and that on C(8) becomes more negative.

Discussion

Analysis of synthetic results reveals some limitations of the methods previously used for the 3-phenyl substituted parent heterocycles.[28] The NCS-assisted ring closure worked well for fluorinated thiadiazines **2b** and **2d**, but it proved to be problematic for **2c** and failed for **2a**. The difficulties with oxidative ring closure in **6c** to form **2c** presumably originate from the presence of the benzylic-type position, which is relatively reactive in free radical processes. Thus, higher temperature and presumably light may promote chlorination of the tertiary carbon in the phenylcyclohexane fragment by NCS and *N*-chloro intermediates. The failure of the formation of **2a** was at first surprising since the parent amidine, which lacks alkoxy substituents, was smoothly converted to the corresponding 3-phenyl-4*H*-benzo[1,2,4]thiadiazine.[28] Apparently, the presence of the hexyloxy substituent in **6a** increases the reactivity of the benzene ring toward electrophiles, and the oxidant attacks it preferentially to the amidine NH$_2$ group.

The high electron density of the benzene ring may also explain the low yield of **2a** obtained from sulfoxide **8a**. In this reaction, the formation of **2a** is slow and apparently comparable to the rate of its decomposition to benzothiazole **5**. A similar reaction of a pyrazine analogue of **8a** proceeded significantly faster and at lower temperatures, and no thiazole formation was observed. This difference in reactivity can be attributed to the dissimilarity in the electron density of the benzene and pyrazine rings in the two compounds. According to our postulate,[28] the first and also the rate-determining step in this process is the elimination of propene from the sulfoxide and the formation of sulfenic acid, which subsequently undergoes intramolecular condensation with the amidinyl NH$_2$ group to close the thiadiazine ring (Scheme 6). Thus, it appears that **8a** forms sulfenic acid **22a** at a slower rate than the pyrazine analogue

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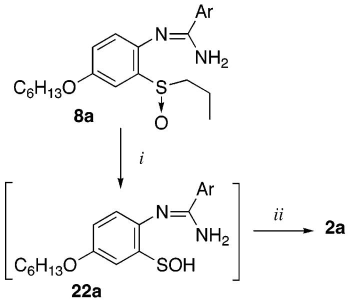
[44] Kaszynski, P. *J. Phys. Chem. A* **2001**, *105*, 7615−7625.

[45] For example: Smith, C. E.; Smith, P. S.; Thomas, R. L.; Robins, E. G.; Collings, J. C.; Dai, C.; Scott, A. J.; Borwick, S.; Batsanov, A. S.; Watt, S. W.; Clark, S. J.; Viney, C.; Howard, J. A. K.; Clegg, W.; Marder, T. B. *J. Mater. Chem.* **2004**, *14*, 413−420.

[46] (a) For example: Kravers, M. A.; Antipin, M. Y.; Struchkov, Y. T. *Cryst. Struct. Commun.* **1979**, *8*, 455−456. (b) Wójcik, G.; Holband, J. *Acta Crystallogr., Sect. B* **2002**, *B58*, 684−689. (c) Emsley, J.; Ma, L. Y. Y.; Bates, P. A.; Motevalli, M.; Hursthouse, M. B. *J. Chem. Soc., Perkin Trans 2* **1989**, 527−533.

SCHEME 6[a]



[a] *i*: Heat, -C_3H_6. *ii*: -H_2O.

does. This is consistent with results of previous studies for a series of para substituted phenyl propyl sulfoxides,[47] which demonstrated higher activation energies for the formation of sulfenic acid from substrates having electron donating groups relative to those with electron withdrawing substituents. Thus, for 4-methoxyphenyl propyl sulfoxide, $\Delta H^{\ddagger}$ is 2.4 kcal/mol higher than for the 4-nitro analogue, which translates to a nearly 4-fold difference in reaction rates.[47]

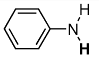
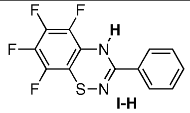
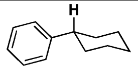
Overall, the present methods appear to be too harsh for the formation of electron-rich benzo[1,2,4]thiadiazines (such as **2a**), and careful control of reaction conditions must be used for substrates with groups susceptible to free radical processes (such as **2c**). The strongly basic or acidic conditions used for the formation of amidines **6** impose further restrictions on the type and variety of functional groups that can be introduced with this synthetic protocol.

The three-ring thiadiazines **2a** and **2b** do not form mesophases, although it is possible that longer alkyl chains may induce liquid crystalline behavior. In contrast, relatively wide-range enantiotropic SmA phases were observed for the four-ring derivatives **2c** and **2d** above 90 °C. As expected from general trends in mesogenic compounds,[48] the transition temperatures for the biphenyl derivative **2d** are significantly higher (by ~50 °C) than those for the less rigid cyclohexyl derivative **2c**. Similarly, high transition temperatures can be expected for radicals **1c** and **1d**, which is unfavorable for their stability and future magnetic investigation. Therefore, other substituents should be considered to induce a mesophase with the clearing temperature below 110 °C.

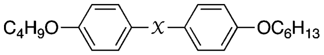
The finding that amidine **3** exhibits liquid crystalline behavior was unexpected and deserves comment. A comparison of **3**, the first mesogenic benzamidine,[48] to its Schiff base and ester analogues demonstrates the importance of intermolecular hydrogen bonding between the amidinyl groups in the stabilization of lamellar phases. The Schiff base and ester show only nematic phases with T_{NI} of 119[49] and 91.5 °C,[50] respectively. In contrast, the amidine exhibits three smectic polymorphs with a clearing temperature T_{SI} of 136 °C. Interestingly, the analogous *N*-phenylbenzamides appear to be much less mesogenic, and only the presence of a very long alkyl chain induces a monotropic mesophase.[51]

TABLE 3. Homolytic Bond Dissociation Enthalpy for Selected Compounds

$R\text{-}H \rightarrow R\bullet + H\bullet$

Compound	HBDE [kcal/mol]	
	Calcd[a]	exp
	88.4	88.0±2[b]
	72.2	–
	84.1	83.5±0.3[c]
PhOCH(Me)–**H**	92.6	–

[a] Calculated as ΔH for the reaction at the B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d) level of theory with B3LYP/6-31G(d) thermodynamic corrections. [b] Ref 52. [c] Ref 53.



3, X = -C(NH_2)=N-
X = -CH=N-
X = -COO-

The qualitative stability of the radicals follows the order **1b** ~ **1d** > **1c** ≫ **1a**. The observed difference in stability of **1a** versus its fluorinated analogue **1b** is consistent with our previous findings for the parent radicals and demonstrates again the significant stabilization effect of the fluorine atoms.[23]

The initial choice of the cyclohexyl substituent in **1c** was driven by a desire to obtain low transition temperatures and was based on general structure–property relationships in liquid crystals.[48] While this was accomplished, the presence of the cyclohexyl group appears to compromise the radical stability. For example, **1c** decays faster than the two other fluorinated radicals **1b** and **1d**, presumably via hydrogen abstraction from the benzylic position. To assess the H donor ability of **1c**, homolytic bond dissociation enthalpies (HBDE) were calculated for model compounds. Results collected in Table 3 show that the benzo[1,2,4]thiadiazinyl radical **I** is more stable by about 12 kcal/mol than the 1-phenylcyclohexyl relative to their R-H precursors, and consequently, the H donation by the benzyl group to the thiadiazinyl is not favorable. It is, however, more favorable by 8.5 kcal/mol than the H donation by the alkoxy group. In both cases, the abstraction leads to irreversible transformations, which result in slow decay of the thiadiazinyl.

The calculations reproduced well the experimental energies for aniline[52] and phenylcyclohexane,[53] lending credance to the results for the parent 5,6,7,8-tetrafluoro-3-phenyl-4*H*-benzo-[1,2,4]thiadiazine (**I–H**). Aniline is a close model for benzo-

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(47) Emerson, D. W.; Korniski, T. J. *J. Org. Chem.* **1969**, *34*, 4115–4118.

(48) Vill, V. *LiqCryst 4.6*; LCI Gmbh: Hamburg, 2004 and references therein.

(49) van der Veen, J.; Grobben, A. H. *Mol. Cryst. Liq. Cryst.* **1971**, *15*, 239–245.

(50) Steinsträsser, R. *Z. Naturforsch. B* **1972**, *27*, 774–779.

(51) (a) Mori, A.; Uno, K.; Kubo, K.; Kato, N.; Takeshita, H.; Hirayama, K.; Ujiie, S. *Liq. Cryst.* **2004**, *31*, 285–294. (b) Mori, A.; Hirayama, K.; Kato, N.; Takeshita, H.; Ujiie, S. *Chem. Lett.* **1997**, 509–510.

(52) McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493–532.

(53) Denisov, E. T. *Russ. J. Phys. Chem.* **1993**, *67*, 2178–2183.

[1,2,4]thiadiazines since both compounds form N-centered radicals with significant delocalization onto the adjacent benzene ring. Previously reported values for radicals were based on a reaction with MeO$^\bullet$, but this model was inadequate. The results in Table 3 suggest that the previously reported HBDE values[24] for **I−H** and other radicals are overestimated by about 7.5 kcal/mol, and the recalculated values are listed in the Supporting Information.

Conclusion

The facile preparation of three substituted 5,6,8-trifluoro-4*H*-benzo[1,2,4]thiadiazines **2b**−**2d** indicates straightforward access to other such derivatives from amine **10**, the common precursor, in an acid-promoted condensation with benzonitriles, followed by oxidative cyclization. Results of thermal analysis of **2a**−**2d** provide the starting point for further manipulation with the substituents in **2** to control the transition temperatures and the phase structure. The availability of the 4*H*-benzo[1,2,4]-thiadiazines **2** opened access to potentially liquid crystalline radicals **1**. Preliminary experiments demonstrated that some radicals **1** can be efficiently generated from **2** and presumably purified in a strictly anerobic atmosphere. Future studies will focus on **1d**, which appears to be particularly stable and likely mesogenic since **2d** exhibits a liquid crystalline phase. It is desirable, however, to lower transition temperatures through manipulation with the alkoxy substituents.

Experimental Section

4-(*E*-4-Pentylcyclohexyl)benzonitrile[54] (**12**) and 4′-pentyloxy-4-biphenylcarbonitrile[55] (**13**) were obtained commercially. 4-Butoxybenzonitrile[56] (**11**) was prepared by alkylation of 4-hydroxybenzonitrile in the presence of K_2CO_3 in MeCN.

Generation of Radicals 1. Benzo[1,2,4]thiadiazine **2** (0.1 mmol) was dissolved in dry toluene (3 mL), and dry MeCN (3 mL) was added. Solid AgO[57] (125 mg, 1 mmol) and K_2CO_3 (138 mg, 1 mmol) were added, and the mixture was vigorously stirred at ambient temperature for 90 s under Ar. The resulting black-green reaction mixture was diluted with toluene and filtered through a short jacketed column (5 cm of Florisil and 0.5 cm of silica) at 0 °C. Solvents were removed under reduced pressure (∼1 Torr) at temperatures below 0 °C, leaving a black-green solid of the crude radical.

3-(4-Butoxyphenyl)-7-hexyloxy-*4H*-benzo[1,2,4]thiadiazine (2a). Method A. A solution of NCS (134 mg, 1.0 mmol) in dry CH_2Cl_2 (2 mL) was added to a solution of dimorpholine sulfide[58] (204 mg, 1.0 mmol) in dry CH_2Cl_2 (4 mL) at −20 °C. After 1 h, a solution of amidine **3** (368 mg, 1.0 mmol) in CH_2Cl_2 (6 mL) was slowly added at −20 °C. The mixture was stirred at ambient temperature for 1 h, washed with 5% aqueous NaOH, and dried (Na_2SO_4). The solvent was evaporated, and the semicrystalline residue (525 mg) was crystallized (EtOH, −5 °C) to give 140 mg of starting amidine **3**. The filtrate was concentrated and dried under vacuum to give 380 mg of a brown oil, which was dissolved in dry PhCl (5 mL). The solution was gently refluxed for 4 h under N_2, and the solvent was removed. The viscous residue was dissolved in CH_2Cl_2 and passed through a silica gel plug. The resulting yellow solution was evaporated, and the solid was separated by column chromatography (SiO_2, hexane/CH_2Cl_2, 1:1). The crude product was recrystallized (hexanes) to give 20 mg (5% yield) of thiadiazine **2a** as yellow crystals. The second fraction contained benzothiazole **5**.

Method B. A solution of sulfoxide **8a** (166 mg, 0.362 mmol) in dry PhCl was refluxed for 16 h, and the solvent was evaporated. The resulting brown residue was separated by column chromatography (SiO_2, hexane/CH_2Cl_2, 1:1), and a yellow fraction containing **2a** and benzothiazole **5** was collected. Unreacted sulfoxide **8a** (81 mg, 48% yield) was eluted with AcOEt and recrystallized from AcOEt/hexane. Product **2a** was purified by PTLC (hexane/CH_2Cl_2, 3:2, multiple times reversed to separate the fluorescent benzothiazole **5**) and recrystallized (Et_2O/heptane) to give 17 mg (12% yield or 24% yield based on consumed **8a**) of thiadiazine **2a** as fine yellow crystals: mp 131−132 °C; ^{1}H NMR δ 0.90 (t, $J = 6.7$ Hz, 3H), 0.98 (t, $J = 7.4$ Hz, 3H), 1.20−1.42 (m, 6H), 1.49 (sextet, $J = 7.5$ Hz, 2H), 1.65−1.82 (m, 4H), 3.84 (t, $J = 6.6$ Hz, 2H), 3.97 (t, $J = 6.5$ Hz, 2H), 6.33 (d, $J = 2.5$ Hz, 1H), 6.36 (d, $J = 8.5$ Hz, 1H), 6.47 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.5$ Hz, 1H), 6.6 (bs, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.56 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR δ 13.8, 14.0, 19.2, 22.6, 25.6, 29.1, 31.1, 31.5, 67.8, 68.5, 109.3, 112.7, 114.4, 114.7, 122.6, 126.3, 127.5, 129.6, 156.9, 157.0, 161.2; IR (KBr) ν_{max} 3362, 1607, 1513, 1467; FAB-HRMS: Calcd for $C_{23}H_{30}N_2O_2S$ *m/z*: 398.2028; found: 398.2029. Anal. Calcd. for $C_{23}H_{30}N_2O_2S$: C, 69.31; H, 7.59; N, 7.03. Found: C, 69.09; H, 7.63; N, 7.02.

3-(4-Butoxyphenyl)-5,6,8-trifluoro-7-hexyloxy-4*H*-benzo[1,2,4]-thiadiazine (2b). A solution of NCS (326 mg, 2.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of amidine **6b** (1.190 g, 2.4 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was slowly warmed up and stirred for 12 h at ambient temperature. The mixture was washed with 5% aqueous NaOH; the organic layer was separated, washed with water, and dried ($MgSO_4$); and the solvent was evaporated. The resulting crude ylide **7b** (1.04 g) was dissolved in dry toluene, and the solution was stirred at reflux for 24 h. The solvent was removed under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and passed through a silica gel plug. The crude product was purified by column chromatography (SiO_2; hexane/CH_2Cl_2, 1:1) followed by recrystallization (hexane) to give 462 mg (43% yield) of pure thiadiazine **2b** as a yellow solid: mp 95 °C; ^{1}H NMR δ 0.90 (t, $J = 6.7$ Hz, 3H), 0.98 (t, $J = 7.4$ Hz, 3H), 1.29−1.36 (m, 4H), 1.44−1.56 (m, 4H), 1.70−1.81 (m, 4H), 4.00 (t, $J = 6.6$ Hz, 2H), 4.04 (t, $J = 6.7$ Hz, 2H), 6.6 (brs, 1H), 6.91 (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 8.8$ Hz, 2H); ^{19}F NMR δ −163.8 (dd, $J_1 = 20.9$ Hz, $J_2 = 9.9$ Hz, 1F), −153.4 (dd, $J_1 = 20.9$ Hz, $J_2 = 2.2$ Hz, 1F), −134.1 (dd, $J_1 = 9.9$ Hz, $J_2 = 2.2$ Hz, 1F); IR (KBr) ν_{max} 3198, 1590, 1437 cm^{-1}. Anal. Calcd. for $C_{23}H_{27}F_3N_2O_2S$: C, 61.04; H, 6.01; N, 6.19. Found: C, 60.77; H, 5.93; N, 6.10.

5,6,8-Trifluoro-7-hexyloxy-3-(4-(*E*-4-pentylcyclohexylphenyl)-4*H*-benzo[1,2,4]thiadiazine (2c). Benzo[1,2,4]thiadiazine **2c** was prepared as described for **2b**. The crude product was purified by flash chromatography (SiO_2; hexane/CH_2Cl_2, 4:1) and crystallization (hexanes) to give yellow crystals of **2c** in 34% yield: mp 98 °C; ^{1}H NMR δ 0.89 (t, $J = 7.0$ Hz, 3H), 0.90 (t, $J = 7.0$ Hz, 3H), 0.98−1.12 (m, 2H), 1.15−1.39 (m, 13H), 1.40−1.52 (m, 4H), 1.72 (quintet, $J = 7.0$ Hz, 2H), 1.87 (brd, $J = 11.3$ Hz, 4H), 2.51 (bt, $J = 12.0$ Hz, 1H), 4.04 (t, $J = 6.6$ Hz, 2H), 6.6 (brs, 1H), 7.27 (d, $J = 8.3$ Hz, 2H), 7.55 (d, $J = 8.3$ Hz, 2H); ^{19}F NMR δ −163.8 (dd, $J_1 = 20.6$ Hz, $J_2 = 10.2$ Hz, 1F), −153.4 (dd, $J_1 = 20.6$ Hz,

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(54) 4-(*E*-4-Pentylcyclohexyl)benzonitrile (**12**): ^{1}H NMR δ 0.89 (t, $J = 6.9$ Hz, 3H), 0.99−1.12 (m, 2H), 1.20−1.37 (m, 9H), 1.38−1.50 (m, 2H), 1.88 (brd, $J = 11.3$ Hz, 4H), 2.52 (tt, $J_1 = 12.2$ Hz, $J_2 = 3.0$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.57 (d, $J = 8.1$ Hz, 2H).

(55) 4′-Pentyloxy-4-biphenylcarbonitrile (**13**): ^{1}H NMR δ 0.93 (t, $J = 7.1$ Hz, 3H), 1.35−1.50 (m, 4H), 1.78 (quint, $J = 7.0$ Hz, 2H), 3.98 (t, $J = 6.6$ Hz, 2H), 6.98 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H).

(56) 4-Butoxybenzonitrile (**11**): ^{1}H NMR δ 0.97 (t, $J = 7.4$ Hz, 3H), 1.48 (sextet, $J = 7.6$ Hz, 2H), 1.78 (quintet, $J = 7.0$ Hz, 2H), 3.99 (t, $J = 6.5$ Hz, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 7.56 (d, $J = 8.8$ Hz, 2H). (a) Marquet, J.; Cayón, E.; Martin, X.; Casado, F.; Gallardo, I.; Moreno, M.; Lluch, J. M. *J. Org. Chem.* **1995**, *60*, 3814−3825. (b) Partridge, M. W. *J. Chem. Soc.* **1949**, 3043−3046.

(57) Hammer, R. N.; Kleinberg, J.; Holtzclaw, H. F., Jr.; Johnson, K. W. R. *Inorg. Synth.* **1953**, *4*, 12−14.

(58) The sulfide was prepared in 77% yield according to a literature procedure: ^{1}H NMR δ 3.28 (t, $J = 4.7$ Hz, 8H), 3.64 (t, $J = 4.7$ Hz, 8H); ^{13}C NMR δ 57.7, 67.8. Blake, E. S. *J. Am. Chem. Soc.* **1943**, *65*, 1267−1269.

J_2 = 2.5 Hz, 1F), −134.2 (dd, J_1 = 9.9 Hz, J_2 = 2.5 Hz, 1F); IR (KBr) ν_{max} 3335, 3133, 1443 cm^{-1}. Anal. Calcd. for $C_{30}H_{39}F_3N_2OS$: C, 67.64; H, 7.38; N, 5.26. Found: C, 67.26; H, 7.30; N, 5.26.

5,6,8-Trifluoro-7-hexyloxy-3-(4′-penyloxybiphenyl-4-yl)-4*H*-benzo[1,2,4]thiadiazine (2d). Benzo[1,2,4]thiadiazine **2d** was prepared as described for **2b**. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2) and crystallization (MeCN/toluene) to give yellow-orange crystals of **2d** in 30% yield: mp 143−144 °C; ^{1}H NMR δ 0.90 (t, J = 6.9 Hz, 3H), 0.94 (t, J = 6.9 Hz, 3H), 1.29−1.50 (m, 10H), 1.73 (quintet, J = 7.1 Hz, 2H), 1.82 (quintet, J = 7.1 Hz, 2H), 4.00 (t, J = 6.7 Hz, 2H), 4.05 (t, J = 6.7 Hz, 2H), 6.6 (brs, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H); ^{19}F NMR δ −164.2 (dd, J_1 = 20.5 Hz, J_2 = 10.2 Hz, 1F), −153.8 (d, J = 20.6 Hz, 1F), −134.6 (d, J = 9.6 Hz,1F); IR (film) ν_{max} 3335, 1442 cm^{-1}. Anal. Calcd. for $C_{30}H_{33}F_3N_2O_2S$: C, 66.40; H, 6.13; N, 5.16. Found: C, 66.33; H, 6.18; N, 5.11.

4-Butoxy-*N*-(4-hexyloxyphenyl)benzamidine (3). A mixture of 4-hexyloxyaniline (3.68 g, 20 mmol), nitrile **11**[56] (3.50 g, 20 mmol), dry benzene (20 mL), and 60% NaH (0.90 g, 22 mmol) was refluxed for 2 days. The resulting viscous mixture was poured into diluted HCl, and organic products were extracted (CH_2Cl_2). The organic layer was washed with sat. $NaHCO_3$ and dried (Na_2SO_4). The solvent was evaporated, and the residue was recrystallized (isooctane/toluene) to give 6.00 g (82% yield) of amidine **3** as an off-white solid: mp 132−133 °C; ^{1}H NMR δ 0.91 (t, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.30−1.39 (m, 4H), 1.42−1.57 (m, 4H), 1.78 (quintet, J = 7.0 Hz, 2H), 1.79 (quintet, J = 7.0 Hz, 2H), 3.94 (t, J = 6.6 Hz, 2H), 4.00 (t, J = 6.5 Hz, 2H), 4.8 (bs, 2H), 6.80−6.95 (m, 6H), 7.80 (d, J = 7.9 Hz, 2H); ^{13}C NMR δ 13.8, 14.0, 19.2, 22.6, 25.8, 29.4, 31.2, 31.6, 67.8, 68.3, 114.2-(2C), 115.5, 122.5, 128.1, 142.8, 154.6, 155.0, 161.0; IR (KBr) ν_{max} 1636, 1607, 1565, 1514, 1466, 1388, 1253, 1209. Anal. Calcd for $C_{23}H_{32}N_2O_2$; C, 74.96; H, 8.75; N, 7.60. Found: C, 74.85; H, 8.74; N, 7.57.

3-(4-Butoxyphenyl)-7-hexyloxybenzothiazole (5). Compound **5** was isolated as a less polar fraction (blue fluorescence on TLC) in chromatographic separation of **2a**. Colorless crystals (isooctane): mp 98−99 °C; ^{1}H NMR δ 0.92 (t, J = 6.6 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H), 1.30−1.42 (m, 4H), 1.45−1.57 (m, 4H), 1.76−1.87 (m, 4H), 4.02 (t, J = 6.6 Hz, 2H), 4.03 (t, J = 6.5 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 7.06 (dd, J_1 = 8.9 Hz, J_2 = 2.5 Hz, 1H), 7.32 (d, J = 2.5 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H); ^{13}C NMR (C_6D_6) δ 14.4, 14.7, 19.9, 23.4, 26.5, 30.0, 31.9, 32.4, 68.2, 69.0, 105.7, 115.6, 116.7, 124.5, 129.6, 137.3, 150.2, 153.2, 158.1, 162.0, 165.6; IR (KBr) ν_{max} 1606, 1453, 1254 cm^{-1}. Anal. Calcd. for $C_{23}H_{29}NO_2S$: C, 72.02; H, 7.62; N, 3.65. Found: C, 71.95; H, 7.70; N, 3.65.

4-Butoxy-*N*-(4-hexyloxy-2-(propylsulfanyl)phenyl)benzamidine (6a). Amidine **6a** was obtained in 50−60% yield from amine **9** and nitrile **11**[56] as described for **3** using either benzene or THF as the solvent. The oily crude product was crystallized (hexanes) and recrystallized (isooctane) to give amidine **6a** as a white solid: mp 76−77 °C; ^{1}H NMR δ 0.91 (t, J = 6.8 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H), 1.28−1.45 (m, 4H), 1.46−1.56 (m, 4H), 1.65−1.82 (m, 6H), 2.85 (t, J = 7.4 Hz, 2H), 3.94 (t, J = 6.6 Hz, 2H), 4.00 (t, J = 6.5 Hz, 2H), 4.7 (bs, 2H), 6.68 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 13.7, 13.8, 14.0, 19.2, 22.2, 22.6, 25.7, 29.3, 31.2, 31.6, 33.8, 67.8, 68.3, 111.4, 114.2, 121.8, 127.8, 128.3, 129.2, 129.9, 140.5, 154.6, 155.3, 161.0; IR (KBr) ν_{max} 3500, 3436, and 3349 (NH_2), 1636, 1607, 1466, 1253. Anal. Calcd. for $C_{26}H_{38}N_2O_2S$; C, 70.55; H, 8.65; N, 6.33. Found: C, 70.37; H, 8.64; N, 6.30.

4-Butoxy-*N*-(4-hexyloxy-2-(propylsulfanyl)phenyl)benzamidine Hydrochloride (6a·HCl). Acidic workup of a condensation reaction of amine **9** with nitrile **11** with dil HCl and without washing with sat. $NaHCO_3$ solution gave hydrochloride of benzamidine **6a** in 43% yield after crystallization from an AcOEt/hexane mixture: mp 150−152 °C; ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H), 1.21−1.41 (m, 4H), 1.42−1.86 (m, 10H), 2.85 (t, J = 7.2 Hz, 2H), 3.80−3.94 (m, 4H), 6.66−7.10 (m, 6H), 7.30−7.78 (m, 2H), 8.3 (bs, 1H).

4-Butoxy-*N*-(2,3,5-trifluoro-4-hexyloxy-6-(propylsulfanyl)phenyl)benzamidine (6b). Methanesulfonic acid (550 mg, 5.71 mmol) was added in one portion to a stirred solution of aniline **10** (355 mg, 1.11 mmol, 83% isomerically pure) and nitrile **11** (970 mg, 5.50 mmol) at 150 °C. The stirring was continued for 30 min. The mixture was cooled and neutralized with sat. $NaHCO_3$ (50 mL), and organic materials were extracted with Et_2O (3×). The combined extracts were washed with water, dried (Na_2SO_4), and passed through a silica gel plug. Crude product was recrystallized (hexane) to give 271 mg (50% yield) of isomerically pure amidine **6b** as white crystals: mp 91−93 °C; ^{1}H NMR δ 0.91 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H), 1.29−1.36 (m, 4H), 1.44−1.55 (m, 6H), 1.71−1.83 (m, 4H), 2.80 (t, J = 7.2 Hz, 2H), 4.02 (t, J = 6.4 Hz, 2H), 4.12 (t, J = 6.5 Hz, 2H), 4.75 (brs, 2H), 6.96 (t, J = 8.7 Hz, 2H), 7.87 (t, J = 8.6 Hz, 2H); ^{19}F NMR δ −150.9 (dd, J_1 = 21.9 Hz, J_2 = 10.9 Hz, 1F), −149.9 (dd, J_1 = 21.9 Hz, J_2 = 5.5 Hz, 1F), −124.9 (dd, J_1 = 10.9 Hz, J_2 = 5.5 Hz, 1F); IR (KBr) ν_{max} 3444 and 3123 (NH_2), 1640, 1601, 1446, 1403, 1253 cm^{-1}. Anal. Calcd. for $C_{26}H_{35}F_3N_2O_2S$: C, 62.88; H, 7.10; N, 5.64. Found: C, 63.00; H, 7.23; N, 5.60.

***N*-(2,3,5-Trifluoro-4-hexyloxy-6-(propylsulfanyl)phenyl)-4-(4*E*-pentylcyclohexyl)benzamidine (6c).** Benzamidine **6c** was obtained in 66% yield from amine **10** and nitrile **12**[54] according to the procedure described for **6b**. Chromatographic separation recovered excess nitrile in 60% (SiO_2; hexane/CH_2Cl_2, 4:1) and gave amidine **6c** (hexane/CH_2Cl_2, 3:2). Using 2 equiv of **12** and 2.5 equiv of $MeSO_3H$, amidine **6c** was isolated in 76% yield. Analytical sample of isomerically pure **6c** was obtained by recrystallization from isooctane: mp 111 °C; ^{1}H NMR δ 0.90 (t, J = 6.9 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 1.00−1.12 (m, 2H), 1.18−1.39 (m, 11H), 1.40−1.65 (m, 8H), 1.77 (quintet, J = 7.0 Hz, 2H), 1.89 (brd, J = 9.9 Hz, 4H), 2.53 (bt, J = 12.0 Hz, 1H), 2.81 (t, J = 7.2 Hz, 2H), 4.11 (t, J = 7.2 Hz, 2H), 4.8 (brs, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H);^{19}F NMR δ −150.9 (dd, J_1 = 21.9 Hz, J_2 = 10.8 Hz, 1F), −149.8 (dd, J_1 = 21.9 Hz, J_2 = 5.5 Hz, 1F), −124.9 (dd, J_1 = 10.9 Hz, J_2 = 5.5 Hz, 1F); IR (KBr) ν_{max} 3413 and 3174 (NH_2), 1642, 1398 cm^{-1}; FAB-MS m/z: 577 ([M + H]$^+$, 68%), 257 (100%); FAB-HRMS: Calcd for $C_{33}H_{48}F_3N_2OS$ ([M + H]$^+$) m/z: 577.3439; Found: 577.3439. Anal. Calcd for $C_{33}H_{47}F_3N_2OS$: C, 68.72; H, 8.21; N, 4.86. Found: C, 68.05; H, 8.15; N, 4.78.

***N*-(2,3,5-Trifluoro-4-hexyloxy-6-(propylsulfanyl)phenyl)-4-(4-pentyloxyphenyl)benzamidine (6d).** Benzamidine **6d** was obtained in 46% yield from amine **10** (0.79 g, 2.45 mmol) and nitrile **13**[55] (1.30 g, 4.9 mmol) in the presence of $MeSO_3H$ (0.47 g, 4.9 mmol) as described for **6b**. Chromatographic separation on a silica gel plug recovered excess nitrile **13** (3.2 mmol; SiO_2, hexane/CH_2Cl_2, 2:1 eluent) as the first fraction, followed by amidine **6d** (0.78 g; CH_2Cl_2 eluent). The product was crystallized (hexane/toluene) and recrystallized (isooctane) to give 0.66 g (46% yield) of **6d** as a grayish solid: mp 115−116 °C; ^{1}H NMR δ 0.91 (t, J = 6.9 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H), 1.39−1.55 (m, 12H), 1.78 (quintet, J = 7.3 Hz, 2H), 1.82 (quintet, J = 7.0 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H), 4.01 (t, J = 6.6 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 4.8 (brs, 2H), 6.99 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H); IR (film) ν_{max} 3480 and 3396 (NH_2), 1633, 1605, 1450 cm^{-1}. Anal. Calcd for $C_{33}H_{41}F_3N_2O_2S$: C, 67.55; H, 7.04; N, 4.77. Found: C, 67.63; H, 7.02; N, 4.73.

4-Butoxy-*N*-(4-hexyloxy-2-(propylsulfinyl)phenyl)benzamidine (8a). Sodium periodate (290 mg, 1.36 mmol) was added to a solution of amidine **6a** (298 mg, 0.674 mmol) in MeOH (25 mL) and water (0.5 mL) at 0 °C. The mixture was stirred overnight at rt, diluted with water, extracted with CH_2Cl_2, and washed with sat.

$NaHCO_3$ solution. Combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to give the crude product as a light brown solid (100%). Crystallization (AcOEt/hexane) followed by recrystallization (MeCN) gave 210 mg (68% yield) of sulfoxide **8a** as white crystals: mp 163−164 °C; ^{1}H NMR δ 0.91 (t, $J = 6.8$ Hz, 3H), 0.99 (t, $J = 7.4$ Hz, 3H), 1.00 (t, $J = 7.4$ Hz, 3H), 1.31−1.36 (m, 4H), 1.41−1.55 (m, 4H), 1.57 (s, 2H), 1.74−1.95 (m, 6H), 2.79 (ddd, $J_1 = 13.1$ Hz, $J_2 = 8.9$ Hz, $J_3 = 5.1$ Hz, 1H), 3.08 (ddd, $J_1 = 13.1$ Hz, $J_2 = 9.1$ Hz, $J_3 = 7.1$ Hz, 1H), 4.02 (t, $J = 6.5$ Hz, 4H), 5.0 (bs, 2H), 6.88 (d, $J = 8.5$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.99 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.8$ Hz, 1H), 7.44 (d, $J = 2.8$ Hz, 1H), 7.77 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR δ 13.2, 13.8, 14.0, 15.8, 19.2, 22.6, 25.7, 29.2, 31.2, 31.6, 55.6, 67.9, 68.6, 109.4, 114.4, 118.9, 122.5, 126.9, 128.1, 136.5, 138.7, 154.8, 156.1, 161.5; IR (KBr) ν_{max} 3418 and 3220 (NH_2), 1630, 1610, 1251 cm^{-1}. Anal. Calcd. for $C_{26}H_{38}N_2O_3S$: C, 68.09; H, 8.35; N, 6.11. Calcd. for $C_{26}H_{38}N_2O_3S \cdot H_2O$: C, 65.51; H, 8.46; N, 5.88. Found: C, 65.59; H, 8.12; N, 5.92.

***N*-(2,3,5-Trifluoro-4-hexyloxy-6-(propylsulfinyl)phenyl)-4-(4*E*-pentylcyclohexyl)benzamidine (8c).** Compound **8c** was obtained as the second, more polar fraction in chromatographic separation of thiadiazine **2c**. Recrystallization from hexanes gave **8c** (18% yield) as white crystals: mp 135−136 °C; ^{1}H NMR δ 0.90 (t, $J = 7.0$ Hz, 3H), 0.91 (t, $J = 6.9$ Hz, 3H), 1.06 (t, $J = 7.4$ Hz, 3H), 1.15−1.42 (m, 13H), 1.40−1.52 (m, 4H), 1.76 (sextet, $J = 7.0$ Hz, 2H), 1.88 (d, $J = 11.0$ Hz, 8H), 2.52 (bt, $J = 11.0$ Hz, 1H), 3.15−3.29 (m, 1H), 3.46 (ddd, $J_1 = 14.7$ Hz, $J_2 = 8.6$ Hz, $J_3 = 6.3$ Hz, 1H), 4.13 (t, $J = 6.5$ Hz, 2H), 5.05 (s, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.76 (d, $J = 7.6$ Hz, 2H); IR (KBr) ν_{max} 3423, 3341, 3227, 1676, 1643, 1598, 1559, 1480, 1456 cm^{-1}; FAB-MS *m/z*: 593 ([M + H]$^+$, 68%), 163 (100%). FAB-HRMS: Calcd for $C_{33}H_{48}F_3N_2O_2S$ *m/z*: 593.3389; found: 593.3370.

4-Hexyloxy-2-propylsulfanylaniline (9). Amine **9** was obtained in 94% yield by reduction of **17** with Fe dust according to the procedure described for amine **10** (reaction time 1 h). Short-path distillation (175 °C/0.3 Torr) gave amine **9** as a colorless oil of purity >95% (by GCMS): ^{1}H NMR δ 0.90 (t, $J = 6.9$ Hz, 3H), 0.99 (t, $J = 7.3$ Hz, 3H), 1.28−1.38 (m, 4H), 1.39−1.52 (m, 2H), 1.60 (sextet, $J = 7.0$ Hz, 2H), 1.74 (quintet, $J = 7.0$ Hz, 2H), 2.74 (t, $J = 7.3$ Hz, 2H), 3.87 (t, $J = 6.6$ Hz, 2H), 4.0 (bs, 2H), 6.66 (d, $J = 8.7$ Hz, 1H), 6.72 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.7$ Hz, 1H), 6.96 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR δ 13.3, 14.0, 22.6, 22.9, 25.7, 29.4, 31.6, 36.7, 68.8, 115.9, 116.4, 119.5, 120.7, 141.7, 151.7; IR (neat) ν_{max} 3436 and 3345 (NH_2), 1590, 1492, 1472, 1268, 1229 cm^{-1}; MS *m/z* 267 (M$^+$, 71), 141 (100). Anal. Calcd. for $C_{15}H_{25}NOS$; C, 67.37; H, 9.42; N, 5.24. Found: C, 67.46; H, 9.43; N, 5.24.

1,2,5-Trifluoro-4-hexyloxy-6-(propylsulfanyl)aniline (10). To a vigorously stirred suspension of Fe dust (2.41 g, 43 mmol) in water (4 mL), acetic acid (0.25 mL) was added. The mixture was warmed up to 100 °C and nitro derivative **19** (1.427 g, 4.1 mmol) was added portionwise within 10 min. The mixture was stirred at 100 °C for 30 min and then cooled and poured to sat. $NaHCO_3$ (30 mL). Organic products were extracted with Et_2O (5×). Combined organic layers were dried ($MgSO_4$), the solvent was removed, and the resulting liquid residue was short-path distilled (150 °C/0.3 Torr) to give 1.19 g (91% yield) of amine **10** as a colorless liquid: ^{1}H NMR δ 0.90 (t, $J = 6.7$ Hz, 3H), 0.98 (t, $J = 7.3$ Hz, 3H), 1.27−1.35 (m, 4H), 1.40−1.47 (m, 2H), 1.53 (sextet, $J = 7.3$ Hz, 2H), 1.73 (quintet, $J = 7.2$ Hz, 2H), 2.67 (t, $J = 7.3$ Hz, 2H), 4.00 (t, $J = 6.5$ Hz, 2H), 4.45 (brs, 2H); ^{19}F NMR δ −161.7 (dd, $J_1 = 20.5$ Hz, $J_2 = 10.5$ Hz, 1F), −150.70 (dd, $J_1 = 20.5$ Hz, $J_2 = 5.9$ Hz, 1F), −126.6 (dd, $J_1 = 10.5$ Hz, $J_2 = 5.9$ Hz, 1F); IR (neat) ν_{max} 3480 and 3370 (NH_2), 1478 cm^{-1}; MS *m/e* (relative intensity) 321 (M$^+$, 17), 195 (100). Anal. Calcd. for $C_{15}H_{22}F_3NOS$: 56.05; H, 6.90; N, 4.36. Found: C, 56.31; H, 6.75; N, 4.48.

4-Chloro-1-nitro-2-(propylsulfanyl)benzene (16).[34] A mixture of 15% aqueous NaOH (20 mL), benzene (30 mL), 1-propanethiol (7.60 g, 100 mmol), 2,4-dichloronitrobenzene (**14**, 19.2 g, 100 mmol), and Bu_4NBr (1.0 g, 3.0 mmol) was vigorously stirred at ambient temperature for 45 min. The organic layer was separated, and the aqueous phase was extracted with hexanes. Combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue (25.0 g) was recrystallized (EtOH) to give 13.3 g of product **16** (60% yield) as yellow crystals: mp 76−77 °C (lit.[34] 74.5−75 °C); ^{1}H NMR δ 1.11 (t, $J = 7.4$ Hz, 3H), 1.78 (sextet, $J = 7.3$ Hz, 2H), 2.92 (t, $J = 7.1$ Hz, 2H), 7.17 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.1$ Hz, 1H), 7.32 (d, $J = 2.1$ Hz, 1H), 8.15 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR δ 13.7, 21.0, 34.4, 124.3, 125.9, 127.4, 140.3, 140.8, 144.0; IR (KBr) ν_{max} 1592, 1555, 1507, 1335, 1302, 1121; MS *m/z* 231 (M$^+$, 20), 125 (100). Anal. Calcd. for $C_9H_{10}ClNO_2S$; C, 46.65; H, 4.35; N, 6.05. Found C, 46.94; H, 4.38; N, 5.96.

4-Hexyloxy-1-nitro-2-(propylsulfanyl)benzene (17). Nitro compound **16** (2.02 g, 8.7 mmol) was added to a suspension of powdered KOH (0.85 g, 15.1 mmol) in DMSO (3 mL) and *n*-hexanol (0.92 g, 9.0 mmol). The mixture was stirred at 75 °C for 30 min, cooled, and poured into water. Organic products were extracted with Et_2O (2×), and combined extracts were dried ($MgSO_4$) and passed through a silica gel plug. The solvent was evaporated, and the oily residue was crystallized (EtOH) to give 1.72 g (67% yield) of **17** as yellow crystals: mp 53 °C; ^{1}H NMR δ 0.91 (t, $J = 6.8$ Hz, 3H), 1.12 (t, $J = 7.4$ Hz, 3H), 1.30−1.43 (m, 6H), 1.44−1.54 (m, 2H), 1.89 (sextet, $J = 7.3$ Hz, 2H), 2.90 (t, $J = 7.3$ Hz, 2H), 4.04 (t, $J = 6.5$ Hz, 2H), 6.68 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.5$ Hz, 1H), 6.79 (d, $J = 2.4$ Hz, 1H), 8.26 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR δ 13.8, 14.0, 21.1, 22.5, 25.6, 28.9, 31.5, 34.2, 68.8, 109.6, 111.6, 128.7, 139.0, 141.4, 163.0; IR (KBr) ν_{max} 1597, 1562, 1497, 1307, 1284, 1252 cm^{-1}; MS *m/z* 297 (M$^+$, 16), 149 (100). Anal. Calcd. for $C_{15}H_{23}NO_3S$; C, 60.58; H, 7.79; N, 4.71. Found: C, 60.95; H, 7.75; N, 4.73.

2,3,5,6-Tetrafluoro-4-hexyloxynitrobenzene (18). 1 M aqueous NaOH (100 mL) and $Bu_4N^+HSO_4^-$ (2.1 g, 6.1 mmol) were added to a solution of pentafluoronitrobenzene (**15**, 13.0 g, 61.0 mmol) and *n*-hexanol (6.20 g, 60.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred vigorously at 0 °C for 1.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried ($MgSO_4$), and passed through a silica gel plug. The solvent was evaporated, and the resulting crude product (18.0 g, 82% pure by GCMS) was fractionally distilled (94−99 °C/0.3 Torr) to give 12.70 g (76% yield) of 91% pure (by GCMS) product **18** as a yellow liquid. The product was redistilled, and pure **18** was obtained as a fraction boiling at 96 °C/0.2 Torr: ^{1}H NMR δ 0.90 (t, $J = 6.8$ Hz, 3H), 1.31−1.38 (m, 4H), 1.42−1.51 (m, 2H), 1.81 (quintet, $J = 7.0$ Hz, 2H), 4.39 (tt, $J_1 = 6.4$ Hz, $J_2 = 1.3$ Hz, 2H); ^{13}C NMR δ 13.9, 22.4, 25.1, 29.8, 31.3, 75.8 (t, $J = 4.1$ Hz), 124.5 (m), 140.5 (dm, $J_1 = 251$ Hz), 141.6 (dm, $J_1 = 262$ Hz), 141.7 (tt, $J_1 = 11$ Hz, $J_2 = 3$ Hz); ^{19}F NMR δ AA′XX′ −155.4 (d, $J = 16.2$ Hz, 2F), −147.6 (d, $J = 16.2$ Hz, 2F); IR (neat) ν_{max} 1550, 1498 cm^{-1}; MS *m/z* 295 (M$^+$, 3), 85 (100). Anal. Calcd. for $C_{12}H_{13}F_4NO_3$: C, 48.82; H, 4.44; N, 4.74. Found: C, 49.29; H, 4.38; N, 4.76.

3,5,6-Trifluoro-4-hexyloxy-1-nitro-2-(propylsulfanyl)benzene (19). A solution of 1-propanethiol (1.50 g, 19.7 mmol) and NaOH (0.786 g, 19.7 mmol) in EtOH (25 mL) was added dropwise within 15 min to a solution of nitro compound **18** (5.80 g, 19.7 mmol) in EtOH (20 mL) at 0 °C. The mixture was stirred for 45 min, the solvent was evaporated, and the oily residue was treated with water. Organic material was extracted with Et_2O (2×), dried ($MgSO_4$), and passed through a silica gel plug. The solvent was removed, and the crude mixture (6.82 g) was fractionally distilled collecting a fraction (148 °C/0.3 Torr) to give 6.36 g (92% yield) of pure **19** as a yellow liquid: ^{1}H NMR δ 0.90 (t, $J = 6.9$ Hz, 3H), 0.97 (t, $J = 7.3$ Hz, 3H), 1.31−1.37 (m, 4H), 1.42−1.50 (m, 2H), 1.52−1.60 (m, 2H), 1.79 (quintet, $J = 7.0$ Hz, 2H), 2.86 (t, $J = 7.3$ Hz, 2H), 4.27 (tt, $J_1 = 6.5$ Hz, $J_2 = 0.9$ Hz, 2H); ^{19}F NMR δ −148.5 (dd, $J_1 = 21.3$ Hz, $J_2 = 10.5$ Hz, 1F), −146.4 (dd, $J_1 = 21.3$ Hz, $J_2 = 8.7$ Hz, 1F), −122.1 (dd, $J_1 = 10.5$ Hz, $J_2 = 8.7$ Hz, 1F); IR (neat) ν_{max} 1547, 1492, 1454, 1371, 1122, 1063 cm^{-1}; MS *m*/*z* 351 (M$^+$, 7), 161 (100). Anal. Calcd. for $C_{15}H_{20}F_3NO_3S$: C, 51.27; H, 5.74; N, 3.99. Found: C, 51.52; H, 5.75; N, 4.03.

3-(4-Butoxyphenyl)-5,6,8-trifluoro-7-hexyloxy-1-oxo-4*H*-benzo[1,2,4]thiadiazine (20b). Compound **20b** was isolated as the sole product of decomposition of **1b** in air: ^{1}H NMR δ 0.92 (t, $J = 6.8$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H), 1.30−1.40 (m, 4H), 1.41−1.55 (m, 4H), 1.72−1.86 (m, 4H), 4.04 (t, $J = 6.6$ Hz, 2H), 4.09 (t, $J = 6.5$ Hz, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 7.93 (d, $J = 8.9$ Hz, 2H), 10.6 (brs, 1H); FAB-MS *m*/*z*: 469 ([M + H]$^+$, 100%), 210 (89%); FAB-HRMS: Calcd for $C_{23}H_{28}F_3N_2O_3S$ ([M + H]$^+$) *m*/*z*: 469.1773; found: 469.1780.

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Supporting Information Available: Computational details; general experimental methods; ESR experimental, simulated, and difference spectra for **1a**−**1d**; texture photomicrographs for **3**; and computational results for **21** and related compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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