JOC Article

Fused-Ring Thiadiazines: Preparation and Crystallographic Characterization of 3-Phenyl Derivative of Benzo-, Pyridio[2,3-*e*]-, Pyrazino[2,3-*e*]-, and Tetrafluorobenzo-[1,2,4]thiadiazines

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Received December 17, 2003

Four bicyclic 4*H*-[1,2,4]thiadiazines **1a**−**d** were prepared in 74−88% yields in two steps from the corresponding amidines **2**. Three of them, **1a**, **1b**, and **1d**, were obtained by thermal elimination of propene from the intermediate *S*-propylsulfilimines **12**. The pyrazino derivative **1c** was formed upon thermolysis of sulfoxide **14c** obtained from **2c**. The E_i mechanism was investigated using DFT methods. The elimination in the sulfilimine appears to be more favorable by about 2 kcal/mol than in the analogous sulfoxide. Crystal and molecular structures of three out of the four thiadiazines were established by single-crystal X-ray analysis. All thiadiazines were found as the 4H tautomers with the heterocyclic ring puckered along the S(1)···N(4) line. The benzo derivative **1a** forms a unidimensional N(4)−H···N(2) chain, the pyrazino derivative **1c** forms dimeric pairs with two synergistic hydrogen bonds, and the crystal structure of **1d** is characterized by strong C_6F_4···C_6H_5 quadrupolar interactions.

Introduction

1,2,4-Benzothiadiazines[1,2] and several recently investigated pyridio analogues[3−5] belong to an important class of pharmacologically active compounds.[6] The most known and studied are the derivatives with hexavalent sulfur (e.g., cyclic sulfonamides), and much effort has been spent on the study of 1,2,4-benzothiadiazines with tetravalent sulfur. In contrast, only a handful of derivatives with divalent sulfur (general structure **I**) have been reported in the literature.[3,7−10] Such compounds with unsubstituted nitrogen atoms appear to be convenient precursors to persistent thiadiazinyl radicals.[11,12]

In the context of our interest in electrical and magnetic properties of free radicals in organized media, we focused on fused 1,2,4-thiadiazinyl radicals as the centerpiece of calamitic liquid crystals.[13,14] Initially, we concentrated on the development of convenient and general synthetic access to this class of heterocycles. In a subsequent publication, we will evaluate the stability of the corresponding 1,2,4-thiadiazinyl radicals as a function of the ring structure.[15]

1,2,4-Thiadiazine Ring-Closure Methods. The few known 1,2,4-benzothiadiazines were prepared using one of four synthetic methods shown in Scheme 1. The only direct method to **I** involves the condensation of *ortho*-aminothiophenols **II** with hydroxamoyl chlorides (Method A). A few reported examples show high yields of the thiadiazines and suggest generality of the method.[16,17]

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(1) Smalley, R. K. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 6, pp 645−680.

(2) Pfeiffer, W.-D. In *Hetarenes IV. Six-Membered and Larger Heterorings with Maximum Unsaturation*; Schaumann, E., Ed.; Thieme: New York, 1998; Vol. E9c, pp 522−524.

(3) Gilchrist, T. L.; Rees, C. W.; Vaughan, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 55−59.

(4) de Tullio, P.; Pirotte, B.; Dupont, L.; Masereel, B.; Laeckmann, D.; Podona, T.; Diouf, O.; Lebrun, P.; Delarge, J. *Tetrahedron* **1995**, *51*, 3221−3234.

(5) Neill, C. G.; Preston, P. N.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 13645−13654.

(6) Ref 1, pp 679−680 and references therein.

(7) Kresze, G.; Seyfried, C.; Trede, A. *Liebigs Ann. Chem.* **1968**, *715*, 223−237.

(8) Levchenko, E. S.; Borovikova, G. S.; Borovik, E. I.; Kalinin, V. N. *Russ. J. Org. Chem.* **1984**, *20*, 176−181.

(9) Finch, N.; Ricca, S., Jr.; Werner, L. H.; Rodebaugh, R. *J. Org. Chem.* **1980**, *45*, 3416−3421.

(10) Böhnisch, V. W.; Gilchrist, T. L.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2851−2854.

(11) Markovskii, L. N.; Talanov, V. S.; Polumbrik, O. M.; Shermolovich, Y. G. *J. Org. Chem. USSR* **1981**, *17*, 2338−2339.

(12) Shermolovich, Y. G.; Simonov, Y. A.; Dvorkin, A. A.; Polumbrik, O. M.; Borovikova, G. S.; Kaminskaya, E. I.; Levchenko, E. S.; Markovskii, L. N. *Russ. J. Org. Chem.* **1989**, *25*, 550−553.

(13) Patel, M. K.; Huang, J.; Kaszynski, P. *Mol. Cryst. Liq. Cryst.* **1995**, *272*, 87−97.

(14) Kaszynski, P. In *Magnetic Properties of Organic Materials*; Lahti, P. M., Ed.; Marcel Dekker: New York, 1999; pp 305−324.

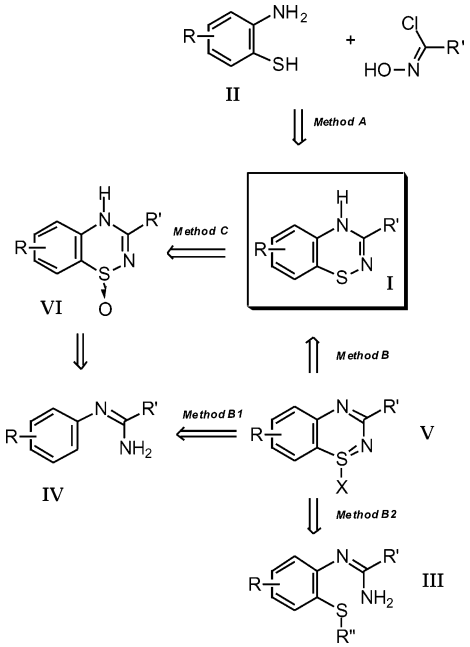
(15) Zienkiewicz, J.; Kaszynski, P.; Young, V. G., Jr. In preparation.

(16) Abdelhamid, A. O.; Khalifa, F. A.; Ghabrial, S. S. *Phosphorus Sulfur* **1988**, *40*, 41−46.

(17) Abdelhamid, A. O.; Negm, A. M.; Abdeen, T. M. S. *Arch. Pharm. (Weinheim Ger.)* **1988**, *321*, 913−915.

10.1021/jo035835h CCC: $27.50
Published on Web 03/09/2004

SCHEME 1



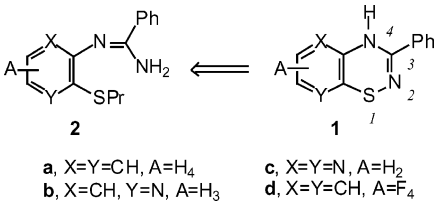
The remaining three methods involve transformations of tetravalent sulfur species, which are almost exclusively obtained by the double reaction of electrophilic sulfur species with amidines. The only exception is the reported[18] cyclization of *N*-(2-phenylthio)benzamidine (**III**, R″ = Ph, Method B2), but the product was not designed to be a substrate for **I**.

One of the most tested methods for preparation of **I** is the reaction of amidines **IV** with morpholine sulfide or disulfide in the presence of NCS followed by thermolysis of the resulting ylide **V** (X = 1-morpholinyl) at 140 °C.[3,19] The overall yields of the process are less than 35%. For example, 3-phenyl-4*H*-pyridio[2,3-*e*][1,2,4]thiadiazine was obtained in 24% yield.[3] Similar cyclization of amidine with methane- and ethanesulfenyl chloride gave the ylide **V** (X = Me and Et, respectively).[18] Only thermolysis of the *S*-methyl ylide was reported, and it gave **I** in 52% yield.[3] The relatively high temperatures required for the preparation of **I** in these reactions promotes ring contraction and formation of benzothiazole as byproducts.[3,10]

Cyclization of amidines[20] or *N*-chloroamidines[8,12] with SCl_2 in the presence of chlorine gave the corresponding sulfiliminyl chlorides **V** (X = Cl), which can be reduced to **I** with thiophenols.[8,15] The use of strongly chlorinating conditions (SCl_2 and Cl_2) limits the general use of this method.

The third method involves a cyclization of *N*-aryl benzamidines **IV** with two equivalents of *N*-sulfinylarenesulfonamide to form *S*-(*N*-sulfonylimine) derivative, which is hydrolyzed to form *S*-oxide **VI** in good overall yield.[7,9] Alternatively, the oxide was obtained from amidine **IV** with $SOCl_2$.[7] The *S*-oxide can be reduced to thiadiazine **I** with thionyl chloride[7] or with Bu_3P[9] in yields better than 70%. The use of $SOCl_2$ results in chlorination of the benzene ring,[7] and the reduction of **VI** with Bu_3P may lead to ring contraction as a side product.[9]

SCHEME 2



a, X=Y=CH, A=H_4 **c**, X=Y=N, A=H_2
b, X=CH, Y=N, A=H_3 **d**, X=Y=CH, A=F_4

The limited range of substrates (mostly *N*-phenyl benzamidine substituted with Cl or Me) used in the above investigations does not allow prediction of the generality of any of the methods. It is clear, however, that the strongly chlorinating conditions of Method B1 preclude it from use in more complex molecular systems. The regiospecificity of ring closure in amidines **IV** (Methods B1 and C) is largely governed by the nucleophilicity of the ring rather than by a molecular design. In contrast, the regiospecificity of ring formation is well defined in Method A, although the preparation and stability of the substituted thiophenols **II** can be problematic. Keeping in mind our future needs for more complex molecular systems with liquid crystal properties,[14] we focused on the development of Method B2. We adapted the method of Hori[21−23] for the formation of *S*-alkyl sulfilimines **V** by oxidative cyclization of amidines **III**. The thermal decomposition of the ylide **V** and the formation of thiadiazine **I** occurs readily for *S*-alkyl derivatives at temperatures as low as 80 °C.[23,24] The generally higher chemical stability of amino sulfides as compared to amino thiols and the facile and high yield of alkene elimination make this method particularly attractive and possibly general for the synthesis of substituted fused thiadiazines.

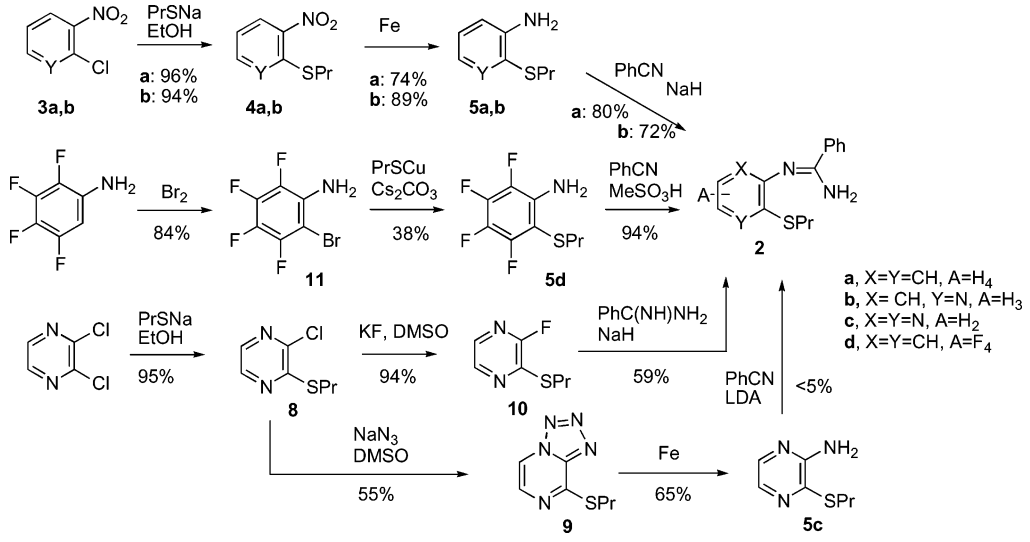
Here we report the synthesis of four thiadiazines **1** from amidines **2** using Method B2 (Scheme 2). We describe the mechanism for the formation of thiadiazines **1** supported by DFT calculations. The tautomerism of the thiadiazines is investigated with X-ray crystallography and computationally.

Results

Synthesis of Benzamidines 2. Synthesis of the *N*-phenyl and *N*-pyridyl benzamidines **2a** and **2b** was straightforward and is shown in Scheme 3. Thus, 2-chloronitrobenzene (**3a**) and 2-chloro-3-nitropyridine (**3b**) were reacted with 1-propanethiol in basic ethanol to form the corresponding propylthio derivatives **4a**[25] and **4b**, respectively. The pyridine derivative **4b** was reported only as a byproduct in a similar reaction of **3b**.[26] The nitro

(18) Gilchrist, T. L.; Rees, C. W.; Vaughan, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 49−54.
(19) Gilchrist, T. L.; Rees, C. W.; Vaughan, D. *J. Chem. Soc., Chem. Commun.* **1978**, 1049−1050.
(20) Markovskii, L. N.; Darmokhval, E. A.; Levchenko, E. S. *Russ. J. Org. Chem.* **1973**, *9*, 2055−2058.
(21) Hori, M.; Kataoka, T.; Shimizu, H.; Matsuo, K. *Tetrahedron Lett.* **1979**, 3969−3972.
(22) Shimizu, H.; Matsuo, K.; Kataoka, T.; Hori, M. *Chem. Pharm. Bull.* **1984**, *32*, 4360−4371.
(23) Shimizu, H.; Ikedo, K.; Hamada, K.; Ozawa, M.; Matsumoto, H.; Kamata, K.; Nakamura, H.; Ji, M.; Kataoka, T.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1733−1747.
(24) Benin, V.; Kaszynski, P. *J. Org. Chem.* **2000**, *65*, 8086−8088.
(25) Foster, D. G.; Reid, E. E. *J. Am. Chem. Soc.* **1924**, *46*, 1936−1948.

SCHEME 3



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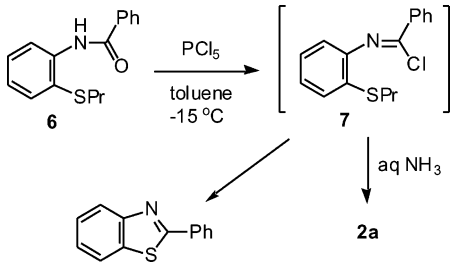


group was subsequently reduced with iron, and the resulting amines **5a**[25] and **5b** were condensed with benzonitrile in the presence of NaH to give the benzamidines **2a** and **2b**, respectively, in good yields.

Benzamidine **2a** was also prepared in an alternative way from amide **6** according to a similar synthesis[27] (Scheme 4). The crude imidoyl chloride **7** was generated from amide **6** with solid PCl_5 in toluene followed by a reaction with aqueous ammonia. At room temperature, a significant amount of 2-phenylbenzothiazole (1:1 with the amidine) was observed, presumably formed by intramolecular electrophilic attack on the sulfur center. At −15 °C, the cyclization was completely suppressed and the amidine **2a** was isolated in 78% yield.

The preparation of *N*-pyrazinyl amidine **2c** was more challenging. The commercially available 2,3-dichloropyrazine was thiolated in ethanol at ambient temperature to give sulfide **8** in high yield with only traces of the 2,3-bis(propylthio)pyrazine byproduct (Scheme 3). The amination step and the formation of **5c** was less straightforward. Following a general method for introduction of the amino group to the pyrazine ring,[28] chloride **8** was reacted with NaN_3 in DMSO to give azide tautomer **9** (Scheme 3). The reaction proceeded at an appreciable rate only above 120 °C, at which temperature the yield of **9** was partially compromised by thermal decomposition of the product. Reduction of triazole **9** was accomplished with iron, which offers mild reaction conditions as compared to some described in the literature.[28−30]

Each step of the synthesis, formation of the azide and its reduction, proceeded with about 60% yield, giving **5c** in an overall yield of 36% based on **8**.

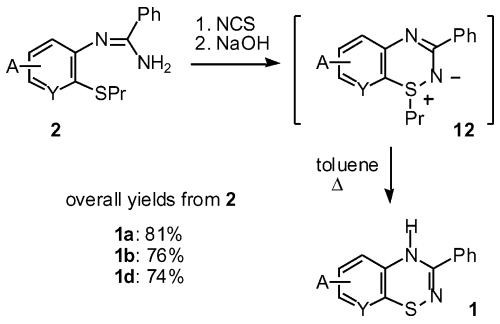
Several unsuccessful attempts were made to improve the yield of amine **5c**. In a reaction of the chloro derivative **8** with ammonia in dioxane at 120 °C, no product was observed. Similarly, a carbamination reaction[31] of **8** with *t*-$BuOCONH_2$ or amination with benzophenone imine[31,32] gave only the starting material recovered in over 80% yield.

Attempts at preparation of the amidine **2c** from amine **5c** and PhCN under conditions successfully used in the preparation of **2a** and **2b** (NaH/THF) did not work, and only unreacted starting amine **5c** was recovered. When LDA was used as the base following a general literature procedure,[33] the yield of *N*-pyrazine amidine **2c** was irreproducible and often less than 5%. In contrast, the literature preparation the parent *N*-pyrazinyl benzamidine from 2-aminopyrazine and PhCN in the presence of LDA was reproduced as reported.[33] Presumably, the failure of this base-assisted method is due to the extensive delocalization of the negative charge onto the ring nitrogen atom and chelation of the cation (Li^+ or Na^+) by the N and S atoms.

In search of a method to prepare amidine **2c**, we explored several other reactions. Thus, a direct reaction of the amidinyl anion,[27] generated in situ from benzamidine[34] and NaH in THF, with the chloride **8** at reflux gave no reaction. A similar negative result was obtained in the attempted Pd(0)-catalyzed amidination reaction of **8** under general conditions for amidation.[35]

(26) Lamotte, P. J.; Dupont, L.; Dideberg, O.; Dive, G.; Jamoulle, J. C. *Acta Crystallogr. Sect. B* **1980**, *B36*, 2157−2159.
(27) Linschoten, M. R.; Gaisser, H.-D.; van der Goot, H.; Timmerman, H. *Eur. J. Med. Chem.—Chim. Ther.* **1984**, *19*, 137−142.
(28) Shaw, J. T.; Brotherton, C. E.; Moon, R. W.; Winland, M. D.; Anderson, M. D.; Kyler, K. S. *J. Heterocycl. Chem.* **1980**, *17*, 11−16.
(29) Sato, N.; Matsuura, T.; Miwa, N. *Synthesis* **1994**, 931−934.
(30) Brown, D. J. In *The Chemistry of Heterocyclic Compounds*; Wiley & Sons: New York, 2002; Vol. 58, pp 272−273.
(31) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.
(32) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367−6370.
(33) Redhouse, A. D.; Thompson, R. J.; Wakefield, B. J.; Wardell, J. A. *Tetrahedron* **1992**, *48*, 7619−7628.
(34) Barker, J.; Phillips, P. R.; Wallbridge, M. G. H.; Powell, H. R. *Acta Crystallogr.* **1996**, *C52*, 2617−2619.

SCHEME 5



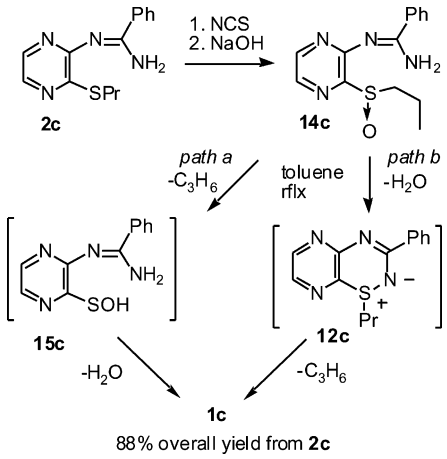
Finally, in a reaction[36] between amine **5c** and benzonitrile in the presence of $AlCl_3$ at 200 °C, only starting amine was recovered.

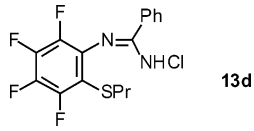
Since the chlorine atom in **8** showed low reactivity, it was converted into fluoride **10** using excess KF in hot DMSO. The reaction of crude fluoride **10** with sodium benzamidinate gave the desired amidine **2c** in good overall yield. The higher reactivity of fluoro derivative **10** than the chloro analogue **8** is consistent with previous findings for halopyrazines[37] and the generally greater mobility of F than Cl by a factor of 10^3 in nucleophilic aromatic substitution reactions.[38] The preparation of the *N*-tetrafluorophenyl benzamidine **2d** took advantage of the known[39] 2-bromo-3,4,5,6-tetrafluoroaniline (**11**), which was thiolated with cuprous propanethiolate in DMF to yield **5d** according to a similar reaction[39] (Scheme 3). Using Cs_2CO_3 as the base and 5 equiv of CuSPr added in portions over a 12 h period at 120 °C, the maximum yield of **5d** was about 40% and typically above 30%. (This is significantly lower than the yields of about 80% reported for analogous reactions with CuSPh.[39]) No other product was isolated in these reactions, also no reaction was observed in the absence of base. When a catalytic amount of $Pd(AcO)_2$ was added to the reaction mixture, the yield of **5d** decreased to about 20% and 2,3,4,5-tetrafluoroaniline, the debromination product, was observed in about the same amounts (~20%).

Initial attempts to condense amine **5d** with benzonitrile in the presence of NaH gave no reaction. An attempt to prepare amidine **2d** via amide **6d** as shown for **2a** in Scheme 4 proved to be impractical, and no desired product could be identified in the mixture of products. Finally, amidine **2d** was successfully prepared in about 94% by using the condensation of aniline **5d** with benzonitrile under acidic conditions.[40]

Formation of the Thiadiazines 1. With the exception of the pyrazine derivative, oxidative cyclization of the amidines **2** with NCS according to a general procedure[23] gave the corresponding unstable sulfilimines **12** (Scheme 5). This is evident from the diastereotopic splitting of the methylene group protons of the propyl group. When the amidine **2d** was reacted with NCS for only several hours, a significant amount (about 45% yield) of the *N*-chloroamidine **13d** was isolated chromatographically as the more mobile fraction and partially characterized. An NMR sample of **13d** in $CDCl_3$ was partially converted (about 50%) to the sulfilimine **12d** and subsequently to **1d** upon standing at ambient temperature for 24 h and almost completely transformed in 2 days. Thermolysis of sulfilimines **12** in boiling toluene gave the thiadiazines **1** in overall yields of about 80%. The yield of the thiadiazine **1d** was approximately the same using either pure **12d** or the *N*-chloroamidine **13d**.

SCHEME 6





The pyrazine amidine **2c** behaved differently than other amidines. Reaction of **2c** with NCS, followed by workup with 5% aq NaOH, did not give the expected sulfilimine **12c**. Instead, the product was identified as sulfoxide **14c** (Scheme 6) on the basis of spectroscopic data, which did not fit the general pattern for **12**. In the ^{1}H NMR spectrum, the S−C**H**$_2$ protons were shifted downfield by about 0.3 ppm relative to those in sulfilimines **12**. The adjacent CH_2 group showed an unusually strong diastereotopic splitting generally not observed in **12** but characteristic for sulfoxides.[41]

Both NMR and IR showed the presence of two N−H protons. IR also showed a strong absorption band at 1037 cm^{-1}, which can be attributed to the S═O stretching vibration. All this evidence is consistent with structure **14c**, whose thermolysis in toluene gave the desired thiadiazine **1c** in good yield. The reaction may proceed either through sulfilimine **12c** (path b) or sulfenic acid **15c** (path a in Scheme 6), and both paths are discussed below.

Mechanistic Investigations. The elimination of propene from the *S*-propyl sulfilimines **12** was investigated at the B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) level of theory. The sulfilimines were assumed to be at the syn-

(35) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104.
(36) Oxley, P.; Partridge, M. W.; Short, W. F. *J. Chem. Soc.* **1947**, 1110−1116.
(37) Chambers, R. D.; Musgrave, W. K. R.; Urben, P. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2584−2589.
(38) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968; Chapter 5.
(39) Yakobson, G. G.; Furin, G. G.; Korbina, L. S.; Vorozhtsov, N. N., Jr. *Russ. J. Gen. Chem.* **1967**, *37*, 1221−1224.
(40) Inukai, Y.; Oono, Y.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 516−520.
(41) For instance: Rudnik, M.; Maslankiewicz, A. *Heterocycles* **1999**, *51*, 2731−2738. Komeshima, N.; Osawa, T.; Nishitoba, T.; Jinno, Y.; Kiriu, T. *Chem. Pharm. Bull.* **1992**, *40*, 351−356.

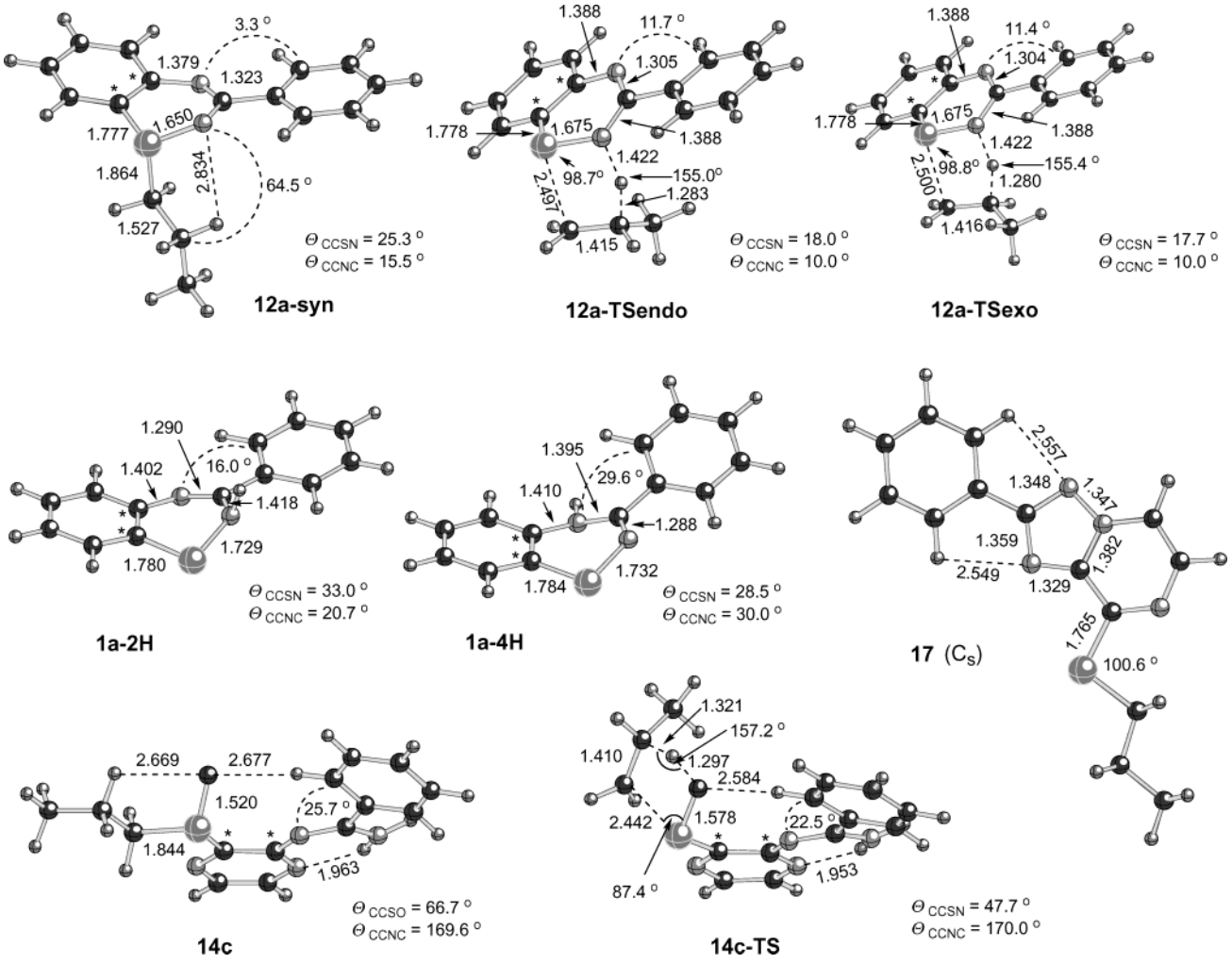


FIGURE 1. Optimized (B3LYP/6-31G(d,p)) geometries of ground- and transition-state structures for selected compounds. Atoms marked with an asterisk are used to define the dihedral angle θ.

clinal conformation on the basis of results for **12a** for which the syn orientation of the propyl group relative to the N(2) atom is more stable than the anti orientation by about 0.3 kcal/mol (Figure 1). Analysis of the theoretical models show that both conformers have almost identical geometrical parameters. The exception is the torsional angle about the exocyclic C−S bond: in the anti conformer, **12a-anti**, the dihedral angle is 177.5°, and in the syn conformer, **12a-syn**, the dihedral angle is 64.8°. In the latter, the distance between the ring nitrogen atom N(2) and the hydrogen atom, which is to be transferred from the propyl group to form **1a-2H**, is close to VDW separation and calculated to be 2.83 Å.

A search for the transition state for the elimination of propene from **12a-syn** to form the thiadiazine **1a-2H** resulted in both endo (**12a-TSendo**) and exo (**12a-TSexo**) transition structures (Figure 1). The DFT calculations slightly favor the endo TS by about 0.05 kcal/mol, which is about 22 kcal/mol above the starting **12a-syn** (Figure 2). The same small preference for the endo TS over the exo TS was calculated for an analogous transformation of **12c-syn**.

The elimination of propene from **12a-syn** and the formation of **1a-2H** thiadiazine is modestly exothermic and largely driven by the change in entropy. Additional

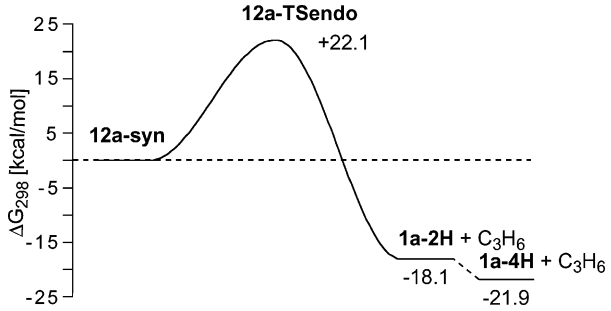


FIGURE 2. B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) Gibbs free-energy profile (298 K) for the formation of **1a-2H** and subsequently **1a-4H** thiadiazines in the gas phase. Transition- and ground-state structures are shown in Figure 1.

thermodynamic stabilization of about 4 kcal/mol is provided by tautomerization of **1a-2H** to **1a-4H**. The overall process is exoergic by about 22 kcal/mol or exothermic by 9.6 kcal/mol.

The endo TS was assumed for the formation of the remaining **1-2H** thiadiazines, and the activation parameters for all four processes are listed in Table 1. The calculated activation energies are generally about 22 kcal/mol, and all are within 0.5 kcal/mol. The highest value for $\Delta G^{\ddagger}$ of 22.1 kcal/mol was calculated for the benzo

TABLE 1. Calculated[a] Thermodynamic Parameters for Elimination of Propene

	$PhS(O)C_3H_7$			a		b		c		d	
	ΔH	ΔG_{298}		ΔH	ΔG_{298}	ΔH	ΔG_{298}	ΔH	ΔG_{298}	ΔH	ΔG_{298}
reactant	0.0	0.0	**12, 14**	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TS	23.0	23.6	**12-TSendo**	21.7	22.1	21.0	21.6	21.0	21.6	20.9	21.8
	25.9 ± 1.9[b]	30.4 ± 1.9[b]	**14-TS**					23.2	23.6		
products	[c]	[c]	**1-2H** + C_3H_6	−5.9	−18.1	−5.7	−17.7	−6.0	−18.0	−6.4	−18.2
	[c]	[c]	**1-4H** + C_3H_6	−9.6	−21.9	−8.3	−20.9	−14.5	−27.1	−10.1	−22.1

[a] B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) calculations. [b] Emerson, D. W.; Korniski, T. J. *J. Org. Chem.* **1969**, *34*, 4115−4118. [c] Not calculated.

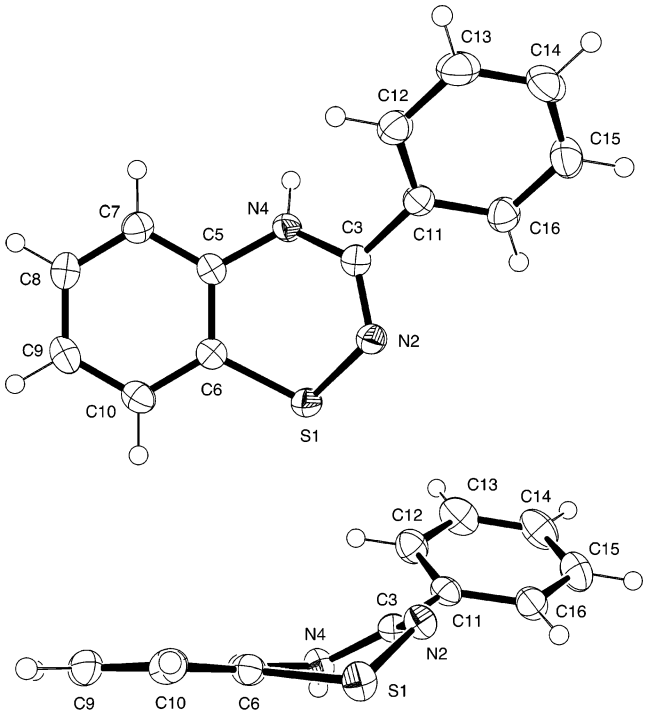


FIGURE 3. Thermal ellipsoid diagram of thiadiazine **1a** with the ellipsoids drawn at 50% probability. Hydrogen atoms are given arbitrary radii.

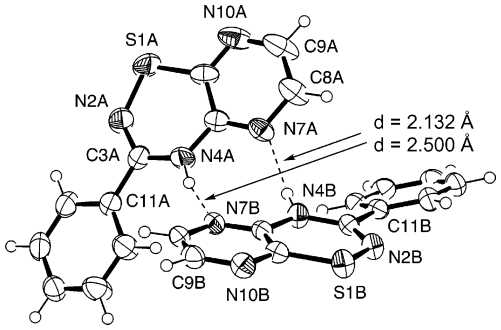


FIGURE 4. Thermal ellipsoid diagram of molecules A and B′ of thiadiazine **1c** with the ellipsoids drawn at 50% probability. Hydrogen atoms are given arbitrary radii.

derivative **12a**, which compares to 23.6 kcal/mol obtained for the analogous elimination of propene from phenyl propyl sulfoxide.

Analysis of the transition state **12a-TSendo** shows that the S−C bond is elongated by about 0.63 Å and the H···N distance is shortened by 1.41 Å relative to **12a-syn** (Figure 1). The N−S···C−C angle is changed from 65° in **12a-syn** to 6.8° in **12a-TSendo**, and all five atoms S−N···H···C−C involved in the transition state adopt an almost planar arrangement. The largest deviation from planarity of 10.4° is calculated for N···H···C−C atoms. The exo transition structure, **12a-TSexo**, is characterized by almost identical key geometrical parameters except for the orientation of the methyl group. The high degree of planarization in the TS is reflected in the negative activation entropy for the reaction.

Elimination of propene from **14c** to form the sulfenic acid **15c** was found to proceed through transition state **14c-TS** (Figure 1). The calculated activation energy $\Delta G^{\ddagger}$ is 23.7 kcal/mol, which is 2 kcal/mol higher than that calculated for the pyrazino derivative **12c** and nearly the same as that calculated for PhS(O)Pr (Table 1). A comparison of the geometrical parameters shows that the formation of propene in sulfoxide **14c-TS** is more advanced than in the sulfilimine **12c-TSendo**. This is evident from the slightly shorter C−C distance and the longer C···H separation in the transition state of **14c-TS**, both by about 0.04 Å. However, the S···C separation is more complete in the sulfilimine **12c-TSendo** than in sulfoxide **14c-TS**. The geometrical parameters for the pyrazine sulfilimine **12c-TSendo** are almost the same as those shown for the benzo analogue **12a-TSendo** in Figure 1.

The conformer of **14c** shown in Figure 1 in which the N−H interacts with the ring nitrogen atom was found to be more stable than the one in which the N−H forms a hydrogen bond with the sulfinyl group by more than 5 kcal/mol. In the former conformer, a close S−O···H−C_{Ph} interaction is maintained in the transition state **14c-TS**.

Crystal and Molecular Structures. Yellow, triclinic crystals of **1c** and monoclinic crystals of **1a** and **1d** were obtained by slow evaporation of CH_2Cl_2 solutions at ambient temperature, and their solid-state structures were determined by X-ray diffraction.[42]

Molecular structures for **1a** and **1c** are shown in Figures 3 and 4, and a partial packing diagram for **1d** is presented in Figure 5. Selected bond lengths and angles are shown in Table 2.

All molecules in crystals of **1a**, **1c**, and **1d** are the 4H tautomers, which adopt a puckered conformation with the folding axis along the S(1)···N(4) line (e.g., **1a** in

(42) Crystal data for **1a**: $C_{13}H_{10}N_2S$ monoclinic, $P2_1/c$, $a = 6.932(3)$ Å, $b = 15.657(6)$ Å, $c = 10.350(4)$ Å, $\beta = 100.866(7)°$, $V = 1103.2(7)$ Å^3, $Z = 4$, $T = 173$ (2) K, $\lambda = 0.71073$ Å, R (F^2) = 0.0320 and $R_w(F^2)$ = 0.0845 (for 1789 reflections with $I > 2\sigma(I)$). Crystal data for **1c**: $C_{11}H_8N_4S$ triclinic, $P\bar{1}$, $a = 8.4404(14)$ Å, $b = 12.304(2)$ Å, $c = 20.759(3)$ Å, $\alpha = 80.261(3)°$, $\beta = 81.795(3)°$, $\gamma = 85.807(3)°$, $V = 2100.5(6)$ Å^3, $Z = 8$, $T = 173$ (2) K, $\lambda = 0.71073$ Å, R (F^2) = 0.0422 and $R_w(F^2)$ = 0.1007 (for 5737 reflections with $I > 2\sigma(I)$). Crystal data for **1d**: $C_{13}H_6F_4N_2S$ monoclinic, $C2/c$, $a = 14.189(5)$ Å, $b = 6.783(3)$ Å, $c = 24.549(9)$ Å, $\beta = 102.298(6)°$, $V = 2308.5(15)$ Å^3, $Z = 4$, $T = 173$ (2) K, $\lambda = 0.71073$ Å, R (F^2) = 0.0470 and $R_w(F^2)$ = 0.1200 (for 1462 reflections with $I > 2\sigma(I)$). For details, see Supporting Information.

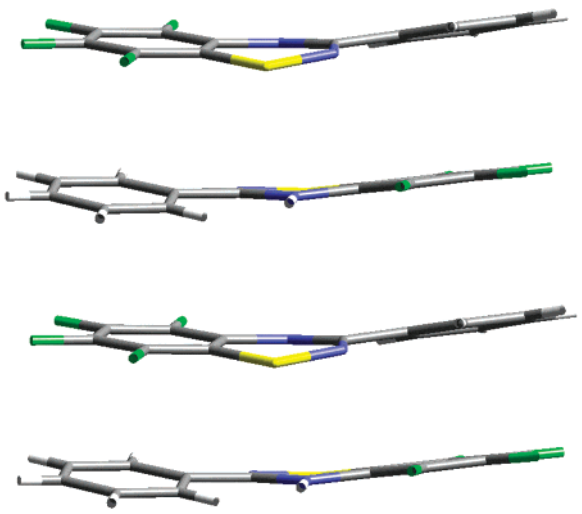


FIGURE 5. Partial packing diagram for **1d** showing molecular stacking along the *b* axis.

Figure 3). This is consistent with general trends in eight-π-electron six-membered heterocycles such as the [1,2,4,5]-thiatriazine[43] and related compounds.[44]

The unit cell of **1c** consists of four unique molecules in a pseudo-endo conformation in which the benzene ring interacts with H−N(4) in the endo face of the puckered thiadiazine ring (Figure 4). In contrast, only one unique molecule was found in crystal structures of **1a** and **1d**. The former adopts the pseudo-endo conformation (Figure 3), while the latter prefers the pseudo-exo conformation in the solid state (Figure 5). Calculations for **1d** show that both pseudo-endo and pseudo-exo conformers have almost identical interatomic distances and intra-ring angles, and their energies are within 0.1 kcal/mol. The heterocycle puckering angles α are calculated to be smaller in the pseudo-exo conformer by about 5° for the N center and 9° for the S center, which results in a higher degree of ring planarization. Similar calculations at the B3LYP/6-31G(d,p) level located only the pseudo-endo conformer of **1c**.

The intra-ring bond lengths and angles for the thiadiazine rings in **1** are typical for analogous compounds[43] and consistent with the 4H tautomer. The theoretical gas-phase geometry for the three molecules matches the experimental solid-state results, and the comparison is shown in Table 2. Generally, the calculations slightly overestimate the experimental C−C and C−N bond lengths by an average of 0.006 Å (std = 0.009 Å). In contrast, the bonds involving the sulfur atoms are overestimated by about 0.025 Å (std = 0.007 Å) except for the S−N bonds in the highly planarized **1d** and molecule A of **1c**. These two distances are shorter than calculated by about 0.04 Å, while in the more puckered **1a** this distance was only 0.008Å shorter than predicted. The difference between the experimental and calculated C−F distances is within the experimental error (mean = +0.003 Å and std = 0.001 Å). Overall, the mean difference between the two sets of data for all bonds is −0.009 with the std = 0.012.

The puckering of the thiadiazine ring is most pronounced in the benzo derivative **1a** (about 31° at the S(1) center, Figure 3), modest in molecule D of the pyrazo derivative **1c** (about 15°), and small, about 7°, in the tetrafluorobenzo **1d** (Figure 5) and molecules A−C of **1c** (Figure 4). These experimental angles are generally smaller than the values calculated for the molecules in the gas phase. Exceptions are **1a** and molecule D of **1c** for which the puckering angles are greater than calculated. This coincides with the largest observed torsional angles between the phenyl and the thiadiazine rings, which for **1a** significantly exceeds the calculated value of about 30°. These torsional angles are significantly smaller in the crystal of **1d** and close to 0° in molecule A of **1c**, which makes these molecules the most planar in the series. The observed planarization relative to the calculated values is most likely due to the compression of the puckering and torsional angles in the crystal.

The benzene ring in **1a** fused with the thiadiazine ring is slightly puckered with the largest deviation from planarity of 4.9(2)° observed for C(5)−C(6)−C(10)−C(9) atoms. In contrast, the tetrafluorobenzene ring in **1d** is planar within 1.5°, and the pyrazine rings in **1c** are planar within 2.2°.

Each unique molecule in the solid structure of **1** is related to its enantiomeric form through an inversion center. In the crystal structure of **1c**, four molecules are found per asymmetric unit. They form dimers through pairs of synergistic hydrogen bonds between N(4)−H and N(7). The N(4)···N(7) distances vary between 2.959 and 3.267 Å and the angles N(4)−H-N(7) between 152.5 and 168.3°, all observed in the A−B′ pair shown in Figure 4. The pyrazine rings in the A−B′ pair form an angle of 56° measured as C(9)C(8)N(7)−C(9)′C(8)′N(7)′ interplanar angle. The analogous value for the C−D′ pair is 43°. Some additional pseudosymmetry is observed, but no pseudo-inversion centers are apparent. Each unique molecule of **1c** is near a unique crystallographic inversion center.

In the crystal structure for **1a**, the molecules form one-dimensional hydrogen bonds between N(4)−H and N(2) parallel to the *c* axis. The N(4)···N(2) separation is 3.023 Å and the N(4)−H−N(2) angle is 147.9°.

No hydrogen bonding was found in **1d**. Instead, the molecules form approximately parallel stacks with alternating phenyl and tetrafluorobenzene rings as shown in Figure 5. The rings are approximately parallel to each other in the stack with the alternating separation between the rings of about 3.5 and 3.3 Å. The two sides of the individual rectangular stack are twisted relative to each other due to the conformational requirements of the molecules.

Discussion and Conclusion

Thiadiazines **1** were efficiently obtained from amidines **2** in a two-step process. The synthesis of thiadiazines **1a**, **1b**, and **1d** involved sulfilimines **12** and is a successful extension of the Hori and Gilchrist methods. In contrast, the preparation of the pyrazine derivative **1c** is the first example of a new method that involves a sulfoxide rather than a sulfilimine. Both of these methods simplify synthetic access to fused thiadiazines and offer a degree

(43) Farrar, J. M.; Patel, M. K.; Kaszynski, P.; Young, V. G. Jr. *J. Org. Chem.* **2000**, *65*, 931−940, and references therein.

(44) For example: Rees, C. W.; White, A. J. P.; Williams, D. J.; Rakitin, O. A.; Konstantinova, L. S.; Marcos, C. F.; Torroba, T. *J. Org. Chem.* **1999**, *64*, 5010−5016. Kim, D. C.; Yoo, K. H.; Shin, K. J.; Park, S. W.; Kim D. J. *J. Heterocycl. Chem.* **1997**, *34*, 57−63.

TABLE 2. Selected Experimental and Calculated Bond Lengths [Å] and Angles [deg] for Thiadiazines[a]

	1a		1c		1d	
	exp	calcd	exp	calcd	exp	calcd
S(1)−N(2)	1.7243(14)	1.732	1.687(2)[b]	1.719	1.677(2)	1.718
N(2)−C(3)	1.294(2)	1.288	1.283(3)[b]	1.286	1.285(3)	1.285
C(3)−N(4)	1.3785(19)	1.395	1.384(3)[b]	1.393	1.377(4)	1.401
N(4)−C(5)	1.416(2)	1.410	1.384(3)[b]	1.391	1.398(3)	1.404
C(5)−C(6)	1.393(3)	1.403	1.413(3)[b]	1.416	1.400(4)	1.402
S(1)−C(6)	1.7629(17)	1.784	1.762(3)[b]	1.787	1.763(3)	1.784
C(5)−X(7)[c]	1.393(2)	1.395	1.320(3)[b]	1.323	1.370(4)	1.392
C(6)−X(10)[c]	1.390(2)	1.394	1.314(3)[b]	1.317	1.372(4)	1.389
C(3)−C_{Ph}	1.489(2)	1.488	1.486(3)[b]	1.488	1.488(4)	1.487
S(1)···N(4)	2.910	2.943	3.018 [b]	3.033	3.039	3.031
S(1)−N(2)−C(3)	117.20(11)	118.6	122.6(2)[b]	122.3	124.4(2)	122.0
N(2)−C(3)−N(4)	125.14(14)	124.1	123.4(2)[b]	124.6	125.4(3)	125.7
C(3)−N(4)−C(5)	121.51(13)	122.2	124.4(2)[b]	124.9	123.7(2)	121.7
C(6)−S(1)−N(2)	101.96(7)	102.3	104.5(1)[b]	103.3	103.67(13)	102.7
X(7)−C(5)−N(4)−C(3)[c]	149.09(15)	149.2	169.0(2)[b]	166.5	171.4(3)	155.8
X(10)−C(6)−S(1)−N(2)[c]	147.85(13)	152.5	171.4(2)[b]	167.9	173.1(2)	160.3
N(4)−C(3)−C(11)−C(12)	43.7(2)	29.6	0.9(4), 23.5(3), 19.7(3), 25.8(3)	27.7	11.3(4)	25.0
S(1): α[d]	30.7	25.6	8.1, 5.3, 8.2, 15.5	12.2	7.5	16.8
N(4): α[d]	25.4	25.6	9.0, 5.5, 6.7, 15.1	12.1	7.5	18.9

[a] Gas-phase calculations at the B3LYP/6-31G(d,p) level of theory. [b] Average for four molecules. [c] X = C for **1a** and **1d** and X = N for **1c**. [d] Ring puckering angle defined as 180 − (X − * − *) angle in which asterisks are the midpoints between the C(6)···N(2) and C(5)···C(3) atoms.

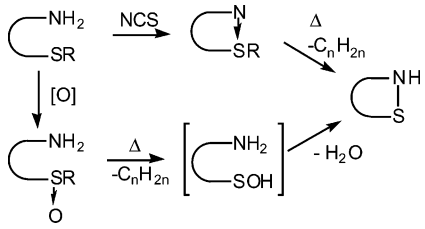


FIGURE 6. Two general methods for the formation of cyclic sulfenamides.

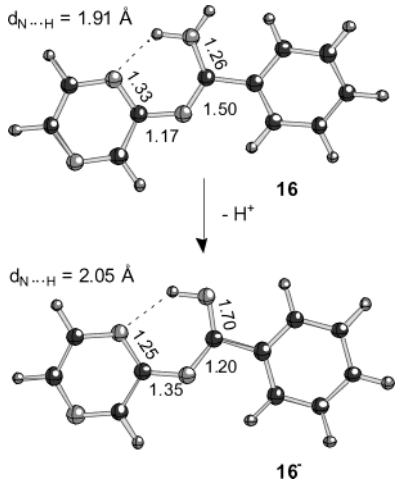


FIGURE 7. Optimized (B3LYP/6-31G(d,p)) geometries and calculated Wiberg bond order indices for amidine **16** and its anion **16**$^-$.

of regiochemical control in the ring closure, which is absent in Methods B1 and C (Scheme 1). The formation of the thiadiazines through sulfoxides is particularly valuable since the latter can be prepared from sulfides using a range of mild oxidants.[45]

These methods, schematically shown in Figure 6, can, in principle, be extended to other S−N systems and open new possibilities in synthesis of heterocyclic sulfenamides.

The formation of sulfilimines **12** most likely involves a chlorosulfonium cation generated either by direct chlorination with NCS or by chlorine transfer from nitrogen in *N*-chloroamidine, as suggested by the isolation of **13d**. The subsequent attack of the amidinyl nitrogen atom on the chlorosulfonium group results in the formation of the N−S bond and thiadiazine ring closure. This last step fails, however, for the pyrazine derivatives, and **12c** is not formed from **2c** under ordinary conditions. Instead, the chlorosulfonium cation derived from **2c** is hydrolyzed under workup conditions leading to the isolation of sulfoxide **14c** as the sole product. The problem with the formation of the N−S bond in **12c** presumably results from the strong intramolecular bonding between the ring nitrogen atom and the amidinyl group, which may deactivate the amidine as a nucleophile (see **14c** in Figure 1). Calculations for *N*-pyrazinobenzamidine (**16**) show a significant increase in the exocyclic C_{Pyraz}−N bond order upon deprotonation due to delocalization of the negative charge onto the pyrazine ring nitrogen atom in **16**$^-$ (Figure 7). Such an increase in the double-bond character further hinders the rotation about the C_{Pyraz}−N bond and makes the direct interaction between the chlorosulfonium cation and the amidinyl nitrogen atom inaccessible at ambient temperature.

The strong intramolecular hydrogen bonding and the high degree of conjugation with the pyrazine ring may also inhibit the N-chlorination of **2c**, and direct chlorination of the S center may occur instead. This is desired, since the generation of the *N*-chloro amidine **13c** could lead to the formation of the triazolopyrazine **17**, a more thermodynamically stable (by $\Delta H = 36.1$ kcal/mol) isomer of **12c** (Figure 1). Such triazolopyrazines are efficiently formed during pyrolysis of imidoyl azides,[46] oxidation of

(45) Kresze, G. In *Organische Schwefel-Verbindungen*; Klamann, D., Ed.; Verlag: New York, 1985; Vol. E11; pp 702−752.

amidines with $Pb(AcO)_4$,[47] or dehydration of *N*-hydroxyamidines.[48]

Elimination of propene from **12** proceeds through a concerted electrocyclic E_i mechanism characteristic for sulfilimines and sulfoxides among other functional groups.[49,50] The evidence for the concerted mechanism is provided by experimental data[50−52] and supported by recent computational results for sulfoxides.[53,54]

Our DFT calculations show that propene elimination from **12** requires lower activation energy than from phenyl propyl sulfoxide (Table 1). This is consistent with experimental data for sulfilimines and sulfoxides, which both typically easily eliminate in boiling toluene, as observed for **12**. Experimentally measured[55] activation energy and entropy for PhS(O)Pr are higher than calculated (Table 1), which suggests that the actual activation parameters for the formation of **1-2H** from **12** are also higher. A comparison of computational methods shows that MP2 level calculations give activation enthalpies close to the experimental values.[53] Also the use of perturbation methods may show significantly higher than 0.05 kcal/mol stabilization of the endo transition state **12-TSendo** relative to **12-TSexo**, as was found for Diels−Alder reaction.[56]

The formation of thiadiazine **1c** from sulfoxide **14c** most likely proceeds through elimination of propene and subsequent intramolecular condensation of the resulting unstable sulfenic acid **15c** to form **1c**. Our DFT calculations demonstrate that this is energetically possible under the reaction conditions, and sulfenic acids are known to react easily with nucleophiles.[57]

The alternative path b (Scheme 6), in which **14c** forms sulfilimine **12c**, is not plausible since sulfoxides do not readily undergo nucleophilic additions.

X-ray analysis of **1** provides the first experimental molecular structures for thiadiazines. To date, the only reported derivatives were 1,1-dioxides, which constitute an important class of biologically active compounds,[58] and one 1-oxide.[59]

The finding of **1-4H** tautomers in the crystal structures is consistent with their calculated higher thermodynamic stability as compared to the **1-2H** tautomers.

A comparison of the three experimental structures shows that the geometry of the thiadiazine ring is sensitive to the electronic structure of the fused ring. The N(4)−C(5) distance is shortened in the tetrafluorobenzo and pyrazino derivatives by 0.01 and 0.03 Å relative to that in **1a**. In the former, the shortening of the bond length occurs in response to the strongly electron-deficient benzene ring. In the pyrazino derivative **1c**, the large contraction of the N−C bond appears to be due to extensive conjugation with the pyrazine ring N atoms. At the same time, the pyrazine ring C(5)−N(7) distance is expanded relative to C(6)−N(10), and the C(5)−C(6) bond acquires more single-bond character relative to that in **1a**. These observed geometrical changes are consistent with the computational results. The shortening of the N(4)−C(5) distance also appears to parallel the increasing planarization of the N(4) center, which would be expected for strong interactions of the N(4) lone pair with the adjacent ring. Indeed, the sinus of the pyramidalization angle $\alpha_{N(4)}$ is approximately proportional to $d_{N(4)-C(5)}$ ($R^2 = 0.96$) for all four theoretical models **1** in the absence of crystal packing forces.

Crystal structures for the three thiadiazines show that hydrogen bonding and quadrupolar interactions between fluorinated and nonfluorinated rings are powerful tools for crystal engineering. The presence of the N(7) atom in the pyrazine ring makes it possible to form dimeric pairs with two synergistic interactions in **1c** similar to those in nucleic bases. In the absence of the nitrogen atom in position 7, thiadiazine **1a** forms an infinite hydrogen-bonded chain, which presumably causes a significant opening of the angle between the phenyl and the thiadiazine rings (Figure 3). Fluorination of the benzene ring in **1d** leads to changing of the packing diagram, and the hydrogen bond motif is replaced by quadrupolar interactions between π-faces of the fluorinated and nonfluorinated benzene rings as the main driving force in the molecular arrangement (Figure 5). Similar crystal packing is observed in the solid structure of a radical derived from **1d**.[15]

Experimental Section

3-Phenyl-4*H*-benzo[1,2,4]thiadiazine[3] (1a). A solution of crude sulfilimine **12a** (0.65 g, 2.3 mmol) in dry toluene (10 mL) was stirred at reflux for 12 h. The solvent was removed and the residue dissolved in CH_2Cl_2 and passed through a silica gel plug. The crude product was purified by silica gel column chromatography (CH_2Cl_2−hexanes in a 1:3 ratio) followed by recrystallization from a hexanes−toluene (9:1) mixture, which gave **1a** (0.44 g, 85% yield; other runs 79−85% yield) as a yellow solid: mp 119.5−120.5 °C (lit.[3] 119−120 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (dd, $J_1 = 7.0$ Hz, $J_2 = 2.0$ Hz, 1H), 6.59 (br s, 1H), 6.74 (dd, $J_1 = 7.0$ Hz, $J_2 = 2.0$ Hz, 1H), 6.89−6.99 (m, 2H), 7.39−7.47 (m, 3H), 7.63−7.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.1, 121.0, 122.9, 125.5, 125.8, 127.4, 128.6, 130.8, 133.8, 136.5, 156.8; IR 3239 (N−H), 1602 (thiadiazine C=N), 1461 and 1424 (ring in-plane) cm^{-1}; FAB *m*/*z* 226 (M^+, 100). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 69.11, H, 4.35, N, 12.33.

***N*-(2-Propylthiophenyl)benzamidine (2a). Method A.** NaH (1.24 g of 60% suspension in mineral oil, 31.0 mmol) was washed with pentane (20 mL) and suspended in dry THF (20 mL). A solution of 2-propylthioaniline (**5a**, 5.00 g, 30 mmol) in THF (15 mL) was added dropwise within 10 min. The mixture was stirred at room temperature until no more gas evolved, and a solution of benzonitrile (3.20 g, 31.0 mmol) in

(46) Sambaish, T.; Reddy, K. K. *Indian J. Chem. Sect. B* **1992**, *31B*, 444−445.
(47) Badger, G. M.; Nelson, P. J.; Potts, K. T. *J. Org. Chem.* **1964**, *29*, 2542−2545.
(48) Tamura, Y.; Kim, J.-H.; Ikeda, M. *J. Heterocycl. Chem.* **1975**, *12*, 107−110.
(49) Oae, S.; Furukawa, N. *Tetrahedron* **1977**, *33*, 2359−2367.
(50) Oae, S.; Furukawa, N. *Sulfilimines and Related Derivatives*; ACS Monograph 179; Americal Chemical Society: Washington, DC, 1983.
(51) Kwart, H.; George, T. J.; Louw, R.; Ultee, W. *J. Am. Chem. Soc.* **1978**, *100*, 3927−3928.
(52) McNab, H. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Eds.; Pergamon: New York, 1995; Vol. 1, pp 778−780.
(53) Cubbage, J. W.; Guo, Y.; McCulla, R. D.; Jenks, W. S. *J. Org. Chem.* **2001**, *66*, 8722−8736.
(54) Jursic, B. S. *THEOCHEM* **1997**, *389*, 257−263.
(55) Emerson, D. W.; Korniski, T. J. *J. Org. Chem.* **1969**, *34*, 4115−4118.
(56) Calvo-Losada, S.; Suárez, D. *J. Am. Chem. Soc.* **2000**, *122*, 390−391.
(57) Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 65−181.
(58) Pirotte, B.; Ouedraogo, R.; de Tullio, P.; Khelili, S.; Somers, F.; Boverie, S.; Dupont, L.; Fontaine, J.; Damas, J.; Lebrun, P. *J. Med. Chem.* **2000**, *43*, 1456−1466 and references therein.
(59) Kresze, G.; Schwöbel, A.; Hatjiissaak, A.; Ackermann, K.; Minami, T. *Liebigs Ann. Chem.* **1984**, 904−910.

dry THF (10 mL) was added dropwise. Stirring was continued at room temperature for 2 h and at reflux for 10 h. Another portion of NaH (0.6 g) was added, and the mixture was stirred for additional 12 h. Most of the solvent was removed under reduced pressure. Ice−water (50 mL) was added, and the organic materials were extracted with diethyl ether (20 mL), dried (Na_2SO_4), and passed through a silica gel plug, which was washed with a hexanes−ethyl acetate mixture (2:1). Pure amidine **2a** was obtained by column chromatography (CH_2Cl_2) followed by recrystallization from hexanes−toluene (4:1) to give 6.5 g (80% yield; other runs 79−85% yield) of a white solid: mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.3 Hz, 3H), 1.69 (sextet, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 4.8 (s, 2H), 6.92 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.41−7.50 (m, 3H), 7.95 (d, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 22.3, 33.8, 121.2, 123.4, 126.1, 126.9, 127.6, 128.5, 129.5, 130.6, 135.5, 147.6, 154.5; IR 3460 and 3332 (N−H), 1632 and 1573 (amidine) cm^{-1}; MS m/z 270 (M^+, 25), 104 (100); FAB m/z 271 (MH^+, 100). Anal. Calcd for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; N, 10.36. Found: C, 71.17; H, 6.70; N, 10.57.

Method B. PCl_5 (0.11 g, 0.53 mmol) was added in one portion to a stirred solution of *N*-(2-propylthiophenyl)benzamide[60] (**6**, 0.136 g, 0.5 mmol), prepared from amine **5b**, in toluene (5 mL) at −15 °C. When PCl_5 completely dissolved, 30% aqueous ammonia (1 mL) was added in one portion and stirring continued for 15 min. The organic layer was separated and dried (Na_2SO_4) and solvent evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and passed through a silica gel plug. Column chromatography (CH_2Cl_2) followed by recrystallization from a hexanes−toluene mixture (in a 9:1 ratio) gave **2a** (0.105 g, 78% yield) identical with that prepared in Method A.

***N*-(3-Propylthiopyrazin-2-yl)benzamidine (2c).** NaH (0.12 g of 60% suspension in mineral oil, 3 mmol) was washed with pentane (10 mL) and suspended in dry THF (10 mL), and the suspension was warmed to 50 °C. Benzamidine hydrochloride (0.22 g 1.4 mmol) was added in one portion and stirring continued for 15 min until no more gas was evolving. A solution of 2-fluoro-3-propylthiopyrazine (**10**, 0.20 g, 1.2 mmol) in dry THF (2 mL) was added dropwise, and the mixture was stirred for 3 h. Most of the solvent was removed under reduced pressure; ice−water (20 mL) was added, and the organic material was extracted with diethyl ether (10 mL), dried (Na_2SO_4), and passed through a silica gel plug, which was washed with a hexanes−ethyl acetate mixture (2:1). Column chromatography (CH_2Cl_2) followed by recrystallization from hexanes−toluene (4:1) gave pure **2c** (0.18 g, 55% yield) as a yellow solid: mp 69.5−70.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J = 7.3 Hz, 3H), 1.78 (sextet, J = 7.3 Hz, 2H), 3.09 (t, J = 7.4 Hz, 2H), 6.2 (s, 1H), 7.42−7.54 (m, 3H), 7.86 (d, J = 2.9 Hz, 1H), 7.96 (d, J = 2.9 Hz, 1H), 8.02−8.05 (m, 2H), 10.2 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.3, 31.1, 127.1, 128.6, 131.2, 133.8, 135.9, 136.2, 154.6, 156.4, 159.7; IR 3460 and 3399 (N−H), 1615 (amidine), 1535, 1479, and 1370 (pyrazine in-plane) cm^{-1}; MS m/z 272 (M^+, 33), 104 (100). Anal. Calcd for $C_{14}H_{16}N_4S$: C, 61.74; H, 5.92; N, 20.57. Found: C, 62.00; H, 5.90; N, 20.74.

***N*-(2,3,4,5-Tetrafluoro-6-propylthiophenyl)benzamidine (2d).** Methanesulfonic acid (1.63 g, 17.0 mmol) was added in one portion to a stirred solution of 3,4,5,6-tetrafluoro-2-propylthioaniline (**5d**, 0.81 g, 3.4 mmol) and benzonitrile (1.75 g, 17.0 mmol) at 150 °C. After 30 min, the mixture was cooled and neutralized with a 5% solution of $NaHCO_3$ (10 mL). Organic materials were extracted with ethyl ether (2 × 20 mL), washed with water, dried (Na_2SO_4), and passed through a silica gel plug. The crude product was purified by column chromatography (CH_2Cl_2−hexanes in a 2:1 ratio) followed by recrystallization from a hexanes−toluene (4:1) mixture to give **2d** (1.09 g, 3.2 mmol, 94% yield; other runs 90%-94% yield) as a white solid: mp 93.5−94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.55 (sextet, J = 7.3 Hz, 2H), 2.84 (t, J = 7.2 Hz, 2H), 4.8 (s, 2H), 7.47−7.54 (m, 3H), 7.92 (d, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 23.2, 36.4, 111.9 (m), 127.0, 128.7, 131.3, 134.5, 156.3, (the ^{13}C−F signals were not located); ^{19}F NMR (282 MHz, $CDCl_3$) δ −132.3 (dd, J_1 = 24 Hz, J_2 = 10 Hz, 1F), −150.3 (dd, J_1 = 20 Hz, J_2 = 10 Hz, 1F), −156.0 (t, J = 21 Hz, 1F), −164.0 (t, J = 23 Hz, 1F); IR 3469 and 3314 (N−H), 1637 (amidine), 1493, 1456 cm^{-1}; MS m/z 342 (M^+, 20), 104 (100). Anal. Calcd for $C_{16}H_{14}F_4N_2S$: C, 56.13; H, 4.12; N, 8.18. Calcd for $C_{16}H_{14}F_4N_2S\cdot 0.5H_2O$: C, 54.69; H, 4.30; N, 7.97. Found: C, 54.90; H, 4.16; N, 7.71.

2-Propylthionitrobenzene (4a).[25] A solution of 2-chloronitrobenzene (**3a**, 15.7 g, 0.10 mol), 1-propanethiol (8.36 g, 0.11 mol), and NaOH (4.4 g, 0.11 mol) in EtOH (50 mL) was stirred for 2 h at room temperature, and EtOH was evaporated. Water was added, and organic materials were extracted with CH_2Cl_2, dried (Na_2SO_4), and passed through a silica gel plug. The solvent was removed, and the residue was Kugelrohr distilled (110 °C/0.3 Torr, lit.[25] 172 °C/7 Torr) to give **4a** (18.9 g, 96% yield) as a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J = 7.4 Hz, 3H), 1.75 (sextet, J = 7.4 Hz, 2H), 2.91 (t, J = 7.4 Hz, 2H), 7.21 (td, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.38 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.53 (td, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 8.14 (dd, J_1 = 8.3 Hz, J_2 = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 21.2, 34.1, 124.1, 125.9, 126.4, 133.3, 138.0, 145.8; MS m/z 197 (M^+, 62), 138 (100).

2-Propylthioaniline (5a).[25,61] This compound was prepared according to a modified literature procedure.[25] Nitro derivative **4a** (3.0 g, 15.2 mmol) was added to a stirred hot suspension of fine iron dust (5.6 g, 0.1 mol) in water (8 mL) containing AcOH (0.5 mL). The mixture was stirred at 100 °C for 30 min and cooled, and the product was extracted with hexanes. Organic extracts were dried (Na_2SO_4) and passed through a silica gel plug. Solvents were removed and the oily residue was Kugelrohr distilled (85 °C/0.3 Torr, lit.[62] 98 °C/1 Torr) to give **5a** (1.88 g, 74% yield) as a light yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.61 (sextet, J = 7.3 Hz, 2H), 2.75 (t, J = 7.3 Hz, 2H), 4.3 (s, 2H), 6.68−6.74 (m, 2H), 7.13 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.37 (dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H).

3,4,5,6-Tetrafluoro-2-propylthioaniline (5d). A mixture of 2-bromo-3,4,5,6-tetrafluoroaniline[39] (**11**, 3.2 g, 13.1 mmol), cuprous 1-propanethiolate (1.82 g, 13.1 mmol), and Cs_2CO_3 (0.85 g, 2.6 mmol) in dry DMF was stirred vigorously for 3 h at 120 °C. Additional portions of cuprous 1-propanethiolate (4 × 1.82 g) and Cs_2CO_3 (4 × 0.85 g) were added every 3 h. After 12 h the reaction mixture was cooled and passed through a Celite plug, which was washed with CH_2Cl_2. Most of the solvent was evaporated, and the residue was passed through a silica gel plug. The resulting solution was washed with water and dried (Na_2SO_4). The crude product was purified by column chromatography (hexanes−CH_2Cl_2, in a 4:1 ratio) followed by Kugelrohr distillation (108 °C/0.3 Torr) to give **5d** (1.2 g, 38% yield; other runs 32−38% yield) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.56 (sextet, J = 7.3 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 4.5 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 23.1, 36.7, 102.3 (d, J = 21 Hz), 132.7 (dddd, J_1 = 244 Hz, J_2 = 19 Hz, J_3 = 14 Hz, J_4 = 3 Hz), 134.6 (td, J_1 = 12 Hz, J_2 = 6 Hz), 136.1 (dddd, J_1 = 228 Hz, J_2 = 13 Hz, J_3 = 4 Hz, J_4 = 2 Hz), 141.4 (dtd, J_1 = 251 Hz, J_2 = 14 Hz, J_3 = 5 Hz), 149.0 (ddt, J_1 = 240 Hz, J_2 = 10 Hz, J_3 = 4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −133.3 (ddd, J_1 = 26 Hz, J_2 = 10 Hz, J_3 = 5 Hz, 1F), −156.6 (td, J_1 = 21 Hz, J_2 = 4 Hz, 1F), −161.3 (ddd, J_1 = 21 Hz, J_2 = 10 Hz, J_3 = 7 Hz, 1F), −173.1 (td, J_1 = 23 Hz, J_2 = 7 Hz, 1F); IR 3488 and 3369 (N−H) cm^{-1}; MS m/z 239 (M^+, 54), 197 (100). Anal. Calcd for $C_9H_9F_4NS$: C, 45.18; H, 3.79; N, 5.85. Found: C, 45.09; H, 3.75; N, 5.93.

(60) Heesing, A.; Homann, W. K.; Müllers, W. *Chem. Ber.* **1980**, *113*, 152−164.

(61) Takeuchi, H.; Hirayama, S.; Mitani, M.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 521−527.

(62) Parcell, R. F. U.S. Patent 2,836,595, 1956.

2-Chloro-3-propylthiopyrazine (8). This compound was prepared from 2,3-dichloropyrazine (5.0 g, 33.6 mmol) according to procedure as described for **4a**. Kugelrohr distillation (103 °C/0.3 Torr) gave **8** (6.03 g, 95% yield; other runs 93%-96% yield) as a bright yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.4 Hz, 3H), 1.72 (sextet, J = 7.3 Hz, 2H), 3.11 (t, J = 7.4 Hz, 2H), 7.96 (d, J = 2.6 Hz, 1H), 8.25 (d, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 22.1, 32.2, 137.4, 141.5, 146.3, 156.9; IR 1337, 1145 and 1053 (ring in-plane) cm^{-1}; MS *m*/*z* 191 and 188 (M^+, 17 and 45), 146 (100). Anal. Calcd for $C_7H_9ClN_2S$: C, 44.56; H, 4.81; N, 14.85. Found: C, 44.81; H, 4.80; N, 14.87.

8-Propylthiotetrazolo[1,5-a]pyrazine (9). A solution of NaN_3 (2.6 g 40 mmol) and 2-chloro-3-propylthiopyrazine (**8**, 3.75 g, 20 mmol) in dry DMSO (40 mL) was stirred at 120 °C for 12 h, cooled, and poured into ice water (50 mL). Organic materials were extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4), and passed through a silica gel plug. Solvents were removed, and the crude product was purified by column chromatography (hexanes−CH_2Cl_2 in a 1:1 ratio) to give **9** (2.15 g, 55% yield) as a dark yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J = 7.4 Hz, 3H), 1.84 (sextet, J = 7.2 Hz, 2H), 3.37 (t, J = 7.2 Hz, 2H), 8.02 (d, J = 4.6 Hz, 1H), 8.42 (d, J = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 22.0, 31.5, 113.6, 132.6, 143.0, 155.5; IR 1496, 1455, 1300, 1100 and 974 (all-in-plane ring) cm^{-1}; MS *m*/*z* 167 ($M^+ - N_2$, 22) 125 (100). Anal. Calcd for $C_7H_9N_5S$: C, 43.06; H, 4.65; N, 35.87. Found: C, 43.36; H, 4.64; N, 35.65.

2-Fluoro-3-propylthiopyrazine (10). A mixture of KF (2.1 g, 36 mmol) and 2-chloro-3-propylthiopyrazine (**8**, 1.35 g, 7.2 mmol) in dry DMSO (30 mL) was stirred for 12 h at 150 °C. Most of the solvent was removed under reduced pressure (22 Torr), and the residue was cooled and dissolved in water. Organic materials were extracted with diethyl ether (2 × 20 mL). Combined organic solutions were washed with water (2 × 20 mL), dried (Na_2SO_4), and passed through a silica gel plug, and solvent was removed. Kugelrohr distillation (90 °C/0.3 Torr) gave **10** (1.16 g, 94% yield) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7.4 Hz, 3H), 1.74 (sextet, J = 7.3 Hz, 2H), 3.17 (t, J = 7.3 Hz, 2H), 7.78 (dd, J_1 = 2.6 Hz, J_2 = 2.0 Hz, 1H), 8.24 (dd, J_1 = 4.4 Hz, J_2 = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 22.2, 30.6, 134.5 (d, J = 7 Hz), 140.7 (d, J = 4.5 Hz), 146.3 (d, J = 32 Hz), 156.2 (d, J = 253 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.4; IR 1324, 1141 and 1062 (ring in-plane) cm^{-1}; MS *m*/*z* 172 (M^+, 69), 130 (100). Anal. Calcd for $C_7H_9FN_2S$: C, 48.82; H, 5.27; N, 16.27. Found: C, 48.96; H, 5.39; N, 15.93.

3-Phenyl-1-propyl-1λ^4-benzo[1,2,4]thiadiazine (12a). A solution of NCS (0.41 g, 3 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of amidine **2a** (0.77 g, 2.9 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The solution was gradually warmed to room temperature (3 h) and stirred for an additional 22 h until no more starting amidine was detected by TLC. The mixture was washed with 5% aqueous NaOH (10 mL), and the organic layer was separated, washed twice with water, and dried (Na_2SO_4). The solvent was evaporated to give crude **12a** (0.73 g, 95% yield) as a dark brown oil, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 3H), 1.61 (sextet, J = 7.4 Hz, 2H), 2.58 (dt, J_1 = 12.4 Hz, J_2 = 7.7 Hz, 1H), 2.93 (ddd, J_1 = 12.4 Hz, J_2 = 8.0 Hz, J_3 = 6.9 Hz, 1H), 7.20−7.24 (m, 2H), 7.40−7.48 (m, 4H), 7.52−7.55 (m, 1H), 8.28−8.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, major signals) δ 12.9, 15.8, 50.7, 106.2, 125.1, 125.3, 126.4, 127.9, 128.4, 130.5, 133.0, 138.7, 144.8, 164.9.

Acknowledgment. Financial support for this work was received from the National Science Foundation (CHE-0096827).

Supporting Information Available: General experimental details, procedures, and characterization for other compounds (CuSPr, **1b**, **1c**, **1d**, **2b**, **4b**, **5b**, **5c**, **6**, **12b**, **12d**, **13d**, **14c**), domputational details, tables of computational results, crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035835H