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

Józef Zienkiewicz, and Piotr Kaszynski*

Organic Materials Research Group, Department of Chemistry, Vanderbilt University, Box 1822 Station B, Nashville, Tennessee 37235

Victor G. Young, Jr.

X-ray Crystallographic Laboratory, Department of Chemistry, University of Minnesota, Twin Cities, Minnesota 55455

piotr@ctr.vax.vanderbilt.edu

Received December 17, 2003

Four bicyclic 4H-[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 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 C6F4⋯C6H5 quadrupolar interactions.

Introduction

1,2,4-Benzothiadiazines1,2 and several recently investigated pyrido analogues3,4 belong to an important class of pharmaceutically active compounds5. 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.6,7 Such compounds with unsubstituted nitrogen atoms appear to be convenient precursors to persistent thiadiazinyl radicals.8,9

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.10 I 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.11

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 1 involves the condensation of orthoaminothiophenols II with hydroxamoyl chlorides (Method A). A few reported examples show high yields of the thiadiazines and suggest generality of the method.12,13

* Phone: (615) 322-3458, Fax: (615) 343-1234.

10.1021/jo035833h CCC: $27.50 © 2004 American Chemical Society Published on Web 03/09/2004

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\textsuperscript{18} cyclization of N-(2-phenylthio)benzamidine (III, R\textsuperscript{+} = 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.\textsuperscript{3,19} The overall yields of the process are less than 35%. For example, 3-phenyl-4H-pyrid[2,3-e][1,2,4]thiadiazine was obtained in 24% yield.\textsuperscript{3} Similar cyclization of amidine with methane- and ethanesulfenyl chloride gave the ylide V (X = Me and Et, respectively)\textsuperscript{18}. Only thermolysis of the S-methyl ylide was reported, and it gave I in 52% yield.\textsuperscript{3} The relatively high temperatures required for the preparation of I in these reactions promotes ring contraction and formation of benzothiazole as byproducts.\textsuperscript{3,10}

Cyclization of amidines\textsuperscript{20} or N-chloroamidines\textsuperscript{8,12} with SCl\textsubscript{2} in the presence of chlorine gave the corresponding sulfimyl chloride V (X = CI), which can be reduced to I with thiophenols.\textsuperscript{8,15} The use of strongly chlorinating conditions (SCl\textsubscript{2} and Cl\textsubscript{2}) limits the general use of this method.

The third method involves a cyclization of N-aryl benzamidines IV with two equivalents of N-sulfanylarenosulfonamide to form S-(N-sulfonylimine) derivative, which is hydrolyzed to form S-oxide VI in good overall yield.\textsuperscript{7,9} Alternatively, the oxide was obtained from amidine IV with SOCl\textsubscript{2}.\textsuperscript{7} The S-oxide can be reduced to thiadiazole I with thionyl chloride\textsuperscript{7} or with Bu\textsubscript{3}P\textsuperscript{9} in yields better than 70%. The use of SOCl\textsubscript{2} results in chlorination of the benzene ring,\textsuperscript{7} and the reduction of VI with Bu\textsubscript{3}P may lead to ring contraction as a side product.\textsuperscript{9}

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,\textsuperscript{14} we focused on the development of Method B2. We adapted the method of Hori\textsuperscript{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.\textsuperscript{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 tautomericism 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 propyli derivatives 4a\textsuperscript{15} and 4b, respectively. The pyridine derivative 4b was reported only as a byproduct in a similar reaction of 3b.\textsuperscript{26} The nitro

---

\textsuperscript{25} Foster, D. G.; Reid, E. E. J. Am. Chem. Soc. 1924, 46, 1936–1948.
group was subsequently reduced with iron, and the resulting amines 5a and 5b were condensed with benzonitrile in the presence of NaH to give the amidines 2a and 2b, respectively, in good yields.

Benzamidine 2a was also prepared in an alternative way from amide 6 according to a similar synthesis (Scheme 4). The crude imidoyl chloride 7 was generated from amide 6 with solid PCl₅ 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)pyrazino byproduct. 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, chloride 8 was reacted with NaN₃ 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.

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 of 8 with t-BuOCN or amination with benzophenone imine 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, 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. 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, generated in situ from benzamidine 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.


References:
Finally, in a reaction between amine 5c and benzonitrile in the presence of AlCl₃ 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 and the generally greater mobility of F than Cl by a factor of 10³ in nucleophilic aromatic substitution reactions. The preparation of the N-tetrafluorophenyl benzamidine 2d took advantage of the known 2-bromo-3,4,5,6-tetrafluoroaniline (Scheme 3). Using Cs₂CO₃ 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.) No other product was isolated in these reactions, 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.

**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 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 (45% yield) of the N-chloroamidine 13d was isolated chromatographically as the more mobile fraction and partially characterized. An NMR sample of 13d in CDCl₃ 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.

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 ¹H NMR spectrum, the S–CH₃ protons were shifted downfield by about 0.3 ppm relative to those in sulfilimines 12. The adjacent CH₂ group showed an unusually strong diastereotopic splitting generally not observed in 12 but characteristic for sulfoxides.

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-
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 thermodynamic stabilization of about 4 kcal/mol is provided by tautomerization of 1a-2H and subsequently 1a-4H thiadiazines in the gas phase. Transition- and ground-state structures are shown in Figure 1.

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.

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.
The largest deviation from planarization in the TS is reflected in the negative activation entropy for the reaction.

Comparison of the geometrical parameters shows that the S–C bond is elongated by about 0.63 Å relative to 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⋯H–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 ΔG‡ is 23.7 kcal/mol, which is 2 kcal/mol higher than that calculated for the pyrazine 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 sulfumine 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 sulfumine 12c-TSendo than in sulfoxide 14c-TS. The geometrical parameters for the pyrazine sulfumine 12c-TSendo are almost the same as those shown for the benzo analogue 12a-TSendo in Figure 1.

The conformation 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 conformation, a close S–O⋯H–CpH 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 CH2Cl2 solutions at ambient temperature, and their solid-state structures were determined by X-ray diffraction.

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

---

**Table 1. Calculated Thermodynamic Parameters for Elimination of Propene**

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>reactant</td>
<td>0.0</td>
<td>0.0</td>
<td>12, 14</td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>23.0 ± 1.9b</td>
<td>23.6</td>
<td>12-TSendo</td>
<td></td>
</tr>
<tr>
<td>products</td>
<td>25.9 ± 1.9b</td>
<td>30.4 ± 1.9b</td>
<td>1-2H + C3H6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-4H + C3H6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ΔH (kcal/mol)</th>
<th>ΔG298 (kcal/mol)</th>
<th>ΔH (kcal/mol)</th>
<th>ΔG298 (kcal/mol)</th>
<th>ΔH (kcal/mol)</th>
<th>ΔG298 (kcal/mol)</th>
<th>ΔH (kcal/mol)</th>
<th>ΔG298 (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>reactant</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TS</td>
<td>21.7</td>
<td>22.1</td>
<td>21.0</td>
<td>21.6</td>
<td>21.0</td>
<td>21.6</td>
<td>20.9</td>
<td>21.8</td>
</tr>
<tr>
<td>products a</td>
<td>-5.9</td>
<td>-18.1</td>
<td>-5.7</td>
<td>-17.7</td>
<td>-6.0</td>
<td>-18.0</td>
<td>-6.4</td>
<td>-18.2</td>
</tr>
<tr>
<td></td>
<td>-9.6</td>
<td>-21.9</td>
<td>-8.3</td>
<td>-20.9</td>
<td>-14.5</td>
<td>-27.1</td>
<td>-10.1</td>
<td>-22.1</td>
</tr>
</tbody>
</table>


---

**Figure 3.** Thermal ellipsoid diagram of thiazolium 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 thiazolium 1c with the ellipsoids drawn at 50% probability. Hydrogen atoms are given arbitrary radii.
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)–N(7)–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...
in principle, be extended to other S
using a range of mild oxidants.45
valuable since the latter can be prepared from sulfides
absent in Methods B1 and C (Scheme 1). The formation

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

of regiochemical control in the ring closure, which is
absent in Methods B1 and C (Scheme 1). The formation
of the thiadiazines through sulfides 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 sulfenam-
ides.

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-chloroamide, as suggested by the iso-
lation 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 amide as a nucleophile

(45) Kresze, G. In Organische Schwefel-Verbindungen; Klamann, D.,


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

<table>
<thead>
<tr>
<th></th>
<th>exp</th>
<th>calcd</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)–N(2)</td>
<td>1.724(14)</td>
<td>1.732</td>
</tr>
<tr>
<td>N(2)–C(3)</td>
<td>1.294(2)</td>
<td>1.288</td>
</tr>
<tr>
<td>C(3)–N(4)</td>
<td>1.376(15)</td>
<td>1.395</td>
</tr>
<tr>
<td>N(4)–C(5)</td>
<td>1.416(2)</td>
<td>1.410</td>
</tr>
<tr>
<td>C(5)–C(6)</td>
<td>1.393(3)</td>
<td>1.403</td>
</tr>
<tr>
<td>S(1)–C(6)</td>
<td>1.762(17)</td>
<td>1.784</td>
</tr>
<tr>
<td>C(5)–X(5)F</td>
<td>1.383(2)</td>
<td>1.395</td>
</tr>
<tr>
<td>C(6)–X(6)F</td>
<td>1.390(2)</td>
<td>1.394</td>
</tr>
<tr>
<td>C(3)–C(6)</td>
<td>1.489(2)</td>
<td>1.488</td>
</tr>
<tr>
<td>S(1)–N(4)</td>
<td>2.910</td>
<td>2.943</td>
</tr>
<tr>
<td>S(1)–N(2)–C(3)</td>
<td>117.20(11)</td>
<td>118.6</td>
</tr>
<tr>
<td>N(2)–C(3)–N(4)</td>
<td>125.14(14)</td>
<td>124.1</td>
</tr>
<tr>
<td>C(3)–N(4)–C(5)</td>
<td>121.51(13)</td>
<td>122.2</td>
</tr>
<tr>
<td>C(6)–S(1)–N(2)</td>
<td>105.96(7)</td>
<td>106.3</td>
</tr>
<tr>
<td>X(7)–C(5)–N(4)–C(3)</td>
<td>147.09(15)</td>
<td>147.2</td>
</tr>
<tr>
<td>X(10)–C(6)–S(1)–N(2)</td>
<td>147.85(13)</td>
<td>152.5</td>
</tr>
<tr>
<td>N(4)–C(3)–C(11)–C(12)</td>
<td>43.7(2)</td>
<td>29.6</td>
</tr>
<tr>
<td>S(1):</td>
<td>30.7</td>
<td>25.6</td>
</tr>
<tr>
<td>N(4):</td>
<td>25.2</td>
<td>25.6</td>
</tr>
<tr>
<td>exp</td>
<td>calcd</td>
<td>exp</td>
</tr>
<tr>
<td>1a</td>
<td>1c</td>
<td>1d</td>
</tr>
</tbody>
</table>

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

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

(see 14c in Figure 1). Calculations for N-pyrazinobenz-
amidine (16) show a significant increase in the exocyclic
C_pyraz–N bond order upon deprotonation due to delocal-
ization 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 CPyraz–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 chlorina-
tion 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 ΔH = 36.1 kcal/mol) isomer
of 12c (Figure 1). Such triazolopyrazines are efficiently
formed during pyrolysis of imidoyl azides, oxidation of
amidines with Pb(AcO)₄, or dehydration of N-hydroxyamidines.

Elimination of propene from 12 proceeds through a concerted electrophilic E, mechanism characteristic for sulfillimines and sulfoxides among other functional groups. The evidence for the concerted mechanism is provided by experimental data and supported by recent computational results for sulfoxides.

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 sulfillimines and sulfoxides, which both typically easily eliminate in boiling toluene, as observed for 12. Experimentally measured activation energy and entropy for PhS(O)OPr 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 higher. A comparison of computational methods shows perturbation methods may show significantly higher than the computational results for sulfoxides.

The evidence for the concerted mechanism is provided by experimental data for sulfoxides among other functional groups. The evidence for the concerted mechanism is provided by experimental data and supported by recent computational results for sulfoxides.

The finding of the 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.

The alternative path b (Scheme 6), in which 14c forms sulfillimine 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, and one 1-oxide.

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 tetrafluorobenzene 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 sinu of the pyramidalization angle δ(4) is approxiamately proportional to δ(4)–C(5) (R² = 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.

Experimental Section

3-Phenyl-4H-benzol[1,2,4]thiadiazine (1a). A solution of crude sulfillimine 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 CH₂Cl₂ and passed through a silica gel plug. The crude product was purified by silica gel column chromatography (CH₂Cl₂–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. 119–120 °C); 1H NMR (300 MHz, CDCl₃) δ 6.44 (dd, J₁ = 7.0 Hz, J₂ = 2.0 Hz, 1H), 6.59 (br s, 1H), 6.74 (dd, J₁ = 7.0 Hz, J₂ = 2.0 Hz, 1H), 6.89–6.99 (m, 2H), 7.39–7.47 (m, 3H, 7.63–7.68 (m, 2H); 13C NMR (75 MHz, CDCl₃) 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). Anal. Calcd for C₁₃H₁₀N₂S: C, 69.00; H, 4.45; N, 12.38. Found: C, 69.11, H, 4.35, N, 12.33.

N-(2-Propylthiophenyl)benzamidene (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-propylthiophenileine (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...
solid: mp 77 °C to give 6.5 g (80% yield; other runs 79–85% yield) of a white solid. mp 77–78 °C. 1H NMR (400 MHz, CDCl3, 0.085) t (J = 7.3 Hz, 2H), 4.8 (s, 2H), 7.47–7.54 (m, 3H), 7.92 (d, J = 7.3 Hz, 2H); 13C NMR (75 MHz, CDCl3) δ 13.1, 23.2, 36.4, 111.9 (m), 127.0, 128.7, 131.3, 134.5, 156.3. (the 13C−F signals were not located); 2F NMR (282 MHz, CDCl3) δ −132.3 (dd, J = 24 Hz, J = 10 Hz, 1F), −150.3 (dd, J = 20 Hz, J = 10 Hz, 1F), −165.0 (t, J = 21 Hz, 1F), −164.0 (t, J = 23 Hz, 1F); IR 3469 and 3314 (NH); MS m/z 342 (M+, 20), 104 (100). Anal. Calc'd for C14H14F2N2O: C, 71.07; H, 6.71; N, 10.36. Found: C, 71.17; H, 6.70; N, 10.57.


2d (1.09 g, 3.2 mmol, 94% yield; other runs 90–94% yield) as a white solid: mp 93.5–94.5 °C; 1H NMR (400 MHz, CDCl3) δ 0.96 (t, J = 7.3 Hz, 3H), 1.55 (sextet, J = 7.3 Hz, 2H), 2.8 (t, J = 7.2 Hz, 2H), 4.8 (s, 2H), 7.47–7.54 (m, 3H), 7.92 (d, J = 7.3 Hz, 2H); 13C NMR (75 MHz, CDCl3) δ 13.1, 23.2, 36.4, 111.9 (m), 127.0, 128.7, 131.3, 134.5, 156.3. (the 13C−F signals were not located); 2F NMR (282 MHz, CDCl3) δ −132.3 (dd, J = 24 Hz, J = 10 Hz, 1F), −150.3 (dd, J = 20 Hz, J = 10 Hz, 1F), −165.0 (t, J = 21 Hz, 1F), −164.0 (t, J = 23 Hz, 1F); IR 3469 and 3314 (NH); MS m/z 342 (M+, 20), 104 (100). Anal. Calc'd for C14H14F2N2O: C, 71.07; H, 6.71; N, 10.36. Found: C, 71.17; H, 6.70; N, 10.57.
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 (3.03 g, 95% yield; other runs 93%-96% yield) as a bright yellow liquid: \( ^1\)H NMR (400 MHz, CDCl3) \( \delta \) 1.03 (t, \( J = 7.4 \) Hz, 3H), 1.72 (sextet, \( J = 7.3 \) Hz, 2H), 1.31 (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, CDCl3) \( \delta \) 13.4, 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\(_7\)H\(_8\)ClN\(_2\)S: C, 44.56; H, 4.81; N, 14.85. Found: C, 43.36; H, 4.64; N, 35.65.

3-Phenyl-1-propyl-1H,1,2,4-benzothiadiazine (12a). A solution of NCS (0.41 g, 3 mmol) in dry CH\(_2\)Cl\(_2\) (5 mL) was added dropwise to a stirred solution of amidine 2a (0.77 g, 2.9 mmol) in CH\(_2\)Cl\(_2\) (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\(_2\)SO\(_4\)). 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, CDCl3) \( \delta \) 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, CDCl3) \( \delta \) 13.3, 22.0, 113.6, 132.6, 143.0, 155.5; IR 106.2, 125.1, 126.4, 127.9, 130.5, 133.0, 138.7, 141.5, 146.3, 156.9; IR 1323, 1134 and 1053 (ring in-plane) cm\(^{-1}\); MS m/z 172 (M\(^+\), 69), 130 (100). Anal. Calcd for C\(_7\)H\(_9\)FN\(_5\)S: C, 44.56; H, 4.61; N, 16.27. Found: C, 43.86; H, 4.98; N, 15.93.

8-Propylthiotetrazolo[1,5-a]pyrazine (9). A solution of Na\(_2\) (2.6 g 40 mmol) and 2-chloro-3-propylthiopyrazine (8, 3.75 g, 20 mmol) in dry DM\(_2\)O (40 mL) was stirred at 120 °C for 12 h, cooled, and poured into iced water (50 mL). Organic materials were extracted with CH\(_2\)Cl\(_2\), washed with water, dried (Na\(_2\)SO\(_4\)), and passed through a silica gel plug. Solvents were removed, and the crude product was purified by column chromatography (hexanes–CH\(_2\)Cl\(_2\) in a 1:1 ratio) to give 9 (2.15 g, 55% yield) as a dark yellow oil: \( ^1\)H NMR (400 MHz, CDCl3) \( \delta \) 1.16 (t, \( J = 7.4 \) Hz, 3H), 1.72 (sextet, \( J = 7.3 \) Hz, 2H), 8.24 (dd, \( J_1 = 4.4 \) Hz, \( J_2 = 2.7 \) Hz, 1H); \( ^{13}\)C NMR (75 MHz, CDCl3) \( \delta \) 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\(_7\)H\(_9\)ClN\(_2\)S: C, 44.56; H, 4.81; N, 14.85. Found: C, 43.36; H, 4.64; N, 35.65.

8-Propylthiotetrazolo[1,5-a]pyrazine (9). A solution of Na\(_2\) (2.6 g 40 mmol) and 2-chloro-3-propylthiopyrazine (8, 3.75 g, 20 mmol) in dry DM\(_2\)O (40 mL) was stirred at 120 °C for 12 h, cooled, and poured into iced water (50 mL). Organic materials were extracted with CH\(_2\)Cl\(_2\), washed with water, dried (Na\(_2\)SO\(_4\)), and passed through a silica gel plug. Solvents were removed, and the crude product was purified by column chromatography (hexanes–CH\(_2\)Cl\(_2\) in a 1:1 ratio) to give 9 (2.15 g, 55% yield) as a dark yellow oil: \( ^1\)H NMR (400 MHz, CDCl3) \( \delta \) 1.16 (t, \( J = 7.4 \) Hz, 3H), 1.72 (sextet, \( J = 7.3 \) Hz, 2H), 8.24 (dd, \( J_1 = 4.4 \) Hz, \( J_2 = 2.7 \) Hz, 1H); \( ^{13}\)C NMR (75 MHz, CDCl3) \( \delta \) 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\(_7\)H\(_9\)ClN\(_2\)S: C, 44.56; H, 4.81; N, 14.85. 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 DM\(_2\)O (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\(_2\)SO\(_4\)), 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, CDCl3) \( \delta \) 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, CDCl3) \( \delta \) 13.3, 22.0, 113.6, 130.5, 133.0, 138.7, 144.8, 154.8, 167 (100). Anal. Calcd for C\(_7\)H\(_9\)FN\(_5\)S: C, 43.06; H, 4.81; N, 35.87. Found: C, 43.36; H, 4.64; N, 35.65.