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Synthesis and Structure of Novel 1λ^4,2,6-Thiadiazines

Wibke E. Diederich* and Manfred Haake

Institute of Pharmaceutical Chemistry at Philipps University, Marbacher Weg 6, 35032 Marburg, Germany

wibke.diederich@staff.uni-marburg.de

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S,S-Disubstituted sulfodiimines **9** are known to be versatile building blocks for the synthesis of various sulfur−nitrogen-containing heterocycles. Addition−condensation reactions of **9** with three different activated carbonylsubstrates **14**−**16** lead to several new 1λ^6,2,6-thiadiazine-3-ones **17**−**20**. S-Debenzylation via a novel synthetic approach utilizing different electrophiles such as TMSCl, $Alk_3O^+BF_4^-$, Tos_2O, and Mes_2O gives rise to a variety of so far hardly known 1λ^4,2,6-thiadiazine-3-ones **25** and **26**. Structure elucidation reveals NH/CH tautomers in solution as well as a tetrahedral asymmetric sulfur attached to the conjugated planar N/C skeleton. The structural features of the 1λ^4,2,6-thiadiazines **25** and **26** as well as their reactivity toward certain electrophiles will be discussed in detail. Alkylation with $Alk_3O^+BF_4^-$ preferably results in formation of the 3-alkoxy-1λ^4-2,6-thiadiazines **29**. In the presence of acid or base, also the *N*-2-alkyl isomers **30** are formed. Mesylation of **26** with methanesulfonic acid anhydride followed by aminolysis furnishes a variety of the desired heterocycles **5** in moderate overall yield.

Introduction

Selective herbicides have become the largest category among crop-protecting agents in the recent past. They are crop-specific and control targeted weeds without harming the crop itself, being used mainly on corn (the largest market), small grain cereals, soybeans, fruit and vegetables, and cotton.

In the class of the 1,3,5-triazines, especially the selective pre-emergence herbicides Simazine (6-chloro-*N*,*N*′-diethyl-1,3,5-triazine-2,4-diamine, **1**, Figure 1) and Atrazine (6-chloro-*N*-ethyl-*N*′-(1-methylethyl)-1,3,5-triazine-2,4-diamine, **2**, Figure 1) have gained worldwide attention. Atrazine is the most widely applied agricultural pesticide in the United States with approximately 65−80 million pounds used each year.[1]

In the 1990s, highly potent analogues such as Triaziflam {(*RS*)-*N*-[2-(3,5-dimethylphenoxy)-1-methylethyl]-6-(1-fluoro-1-methylethyl)-1,3,5-triazine-2,4-diamine, **3**, Figure 1} and related diaminotriazines were patented.[2,3] Recent results suggest that this class of compounds enantioselectively affect multiple sites of action that include photosystem II electron transport inhibitory activity, mitotic disruption by inhibiting microtubule formation, and inhibition of the cellulose synthesis of the crop.[4] In 1994 and 1996, 1λ^4,2,4,6-thiatriazines of type **4**, which are sulfur analogues of the 1,3,5-triazines, were patented.[5−8] They were found to act as novel cell wall biosynthesis inhibitors by causing accumulation of a noncrystalline form of β-1,4-glucan concomitant with inhibition of crystalline cellulose formation.[9]

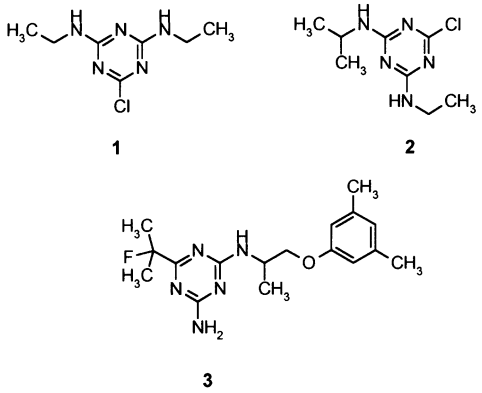

FIGURE 1. Structures of Simazine **1**, Atrazine **2**, and Triaziflam **3**.

Although the industry growth rate in this sector has recently slowed due to the advent of genetically modified crops, opportunities for new products with either a new mechanism of action, improved environmental profiles, or greater effectiveness are evident.

These facts prompted us to develop a synthetic route to the hitherto hardly known 1λ^4,2,6-thiadiazines **5**,

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(3) Idemitsu Kosan Company, Ltd. WO 96/25404, 1996.
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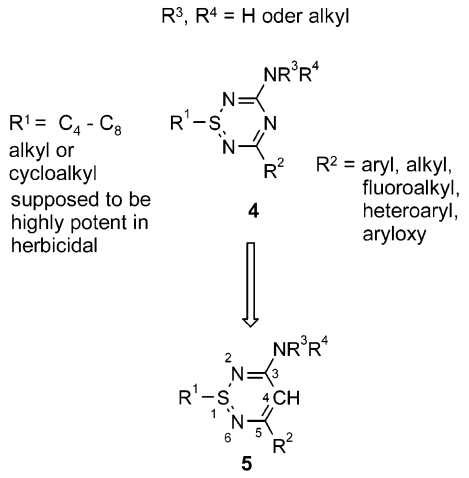
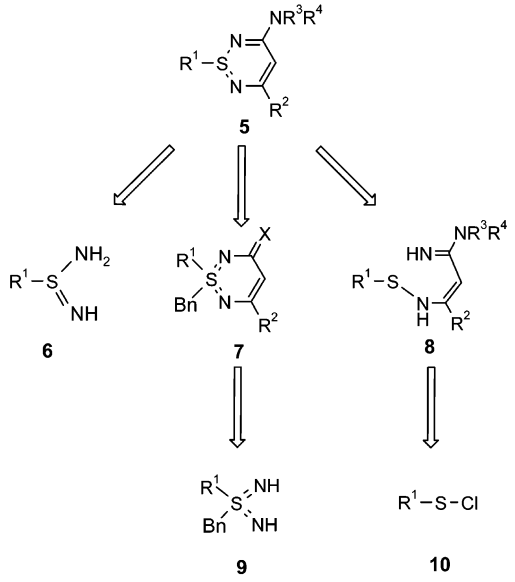
SCHEME 1



SCHEME 2. Retrosynthetic Analysis



which are carbon analogues of the related thiatriazines **4**, retaining the substitution pattern of the biologically active thiatriazines.[9]

It was found that for an optimal biological activity of the thiatriazines **4**, a C_4 to C_8 alkyl substituent at the sulfur atom (R^1) and a substituted or unsubstituted amino group at position 3 of the heterocycle are required. The substituent R^2 at position 5 is fairly variable but should preferably be lipophilic such as aryl, alkyl, or fluoroalkyl, as illustrated in Scheme 1.

The synthetic route leading to the thiadiazines **5** should therefore be as flexible as possible allowing the introduction of various substituents at the sulfur atom and position 5 as well as different amino residues at position 3 of this heterocyclic core structure.

Synthetic Strategy. 1λ^4,2,6-Thiadiazines **5** are in principle accessible via three different routes, as outlined in Scheme 2. The first one includes addition−condensation reactions (acr) of sulfinamidines **6** with appropriate building blocks. Although in this case the sulfur atom already bears the required oxidation level of +4, this route is not widely applicable because only two stable primary sulfinamidines are so far known in the literature.[10,11]

Starting from sulfenyl chlorides **10**, addition−condensation reactions to **8** followed by oxidative amination also lead to thiadiazines of type **5**. Similar to the sulfinamidines, however, drawbacks of this approach are the low stability and therefore limited accessibility of the sulfenyl chlorides.[12]

The third sequence applies S,S-disubstituted sulfodiimines such as *S*-alkyl-*S*-benzyl-sulfodiimines **9**.[13] Having the sulfur in the hexavalent tetracoordinated state, they are known to be versatile building blocks for the synthesis of various sulfur−nitrogen-containing heterocycles.[14,15]

S,S-Dialkyl-substituted sulfodiimines are characterized by a versatile and generally stable functional group. Under certain conditions, however, they are susceptible to C−S bond cleavage. Especially if a positive charge is built up on sulfur either by protonation or introduction of electron-withdrawing groups on one or both nitrogens, S-dealkylation accompanied by formation of a sulfur bearing the oxidation level of +4 is observed in the presence of nucleophiles.[14] This fact has led to a synthetic strategy that has already been successfully applied particularly in the synthesis of a large variety of 1λ^4,2,4,6-thiatriazines.[16−18] *S*-Alkyl-*S*-benzyl-sulfodiimines **9** were therefore considered to be excellent precursors for the synthesis of the desired 1λ^4,2,6-thiadiazines too, allowing the introduction of a large variety of alkyl substituents at the sulfur atom. Similar to the thiatriazines, addition−condensation reactions of **9** with suitable building blocks followed by subsequent cyclization should give rise to, at position 5, substituted 1λ^6,2,6-thiadiazines of type **7**, S-debenzylation of which would then lead into the new class of substituted 1λ^4,2,6-thiadiazines **13**. Alternatively, substitution at either of the nitrogens leading to **11** and subsequent S-debenzylation to **12** followed by intramolecular cyclization would also furnish the thiadiazines of type **13** (Scheme 3).

Results and Discussion

Synthesis of 1λ^6,2,6-Thiadiazine-3-ones. The *S*-alkyl-*S*-benzyl-sulfodiimines **9** employed in this study were synthesized via oxidative amination of the corresponding thioethers following the procedure by Haake.[14,19]

The addition−condensation reactions of **9** with the three different activated carbonyl substrates **14**−**16** enabled us to vary position 5 of the heterocycles of type

(10) Hänssgen, D.; Steffens, R. *Z. Naturforsch., B*: *Anorg. Chem., Org. Chem.* **1985**, *40 b*, 919−022.
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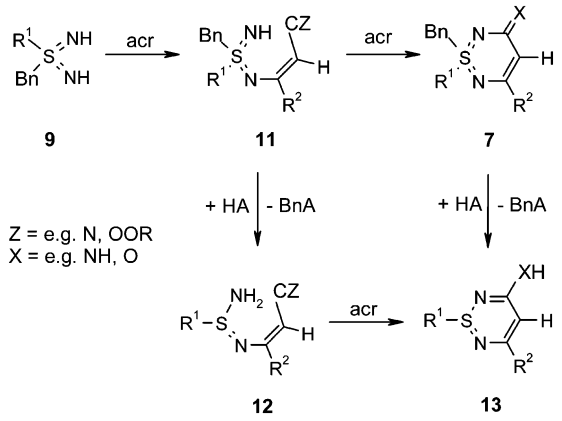
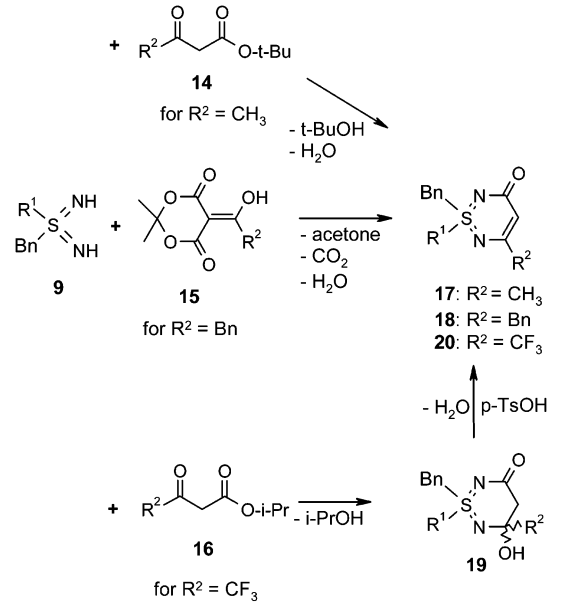
(19) Haake, M. *Tetrahedron Lett.* **1970**, *51*, 4449−4450.

SCHEME 3. Synthetic Route toward Position 5 Substituted 1-Alkyl-1λ⁴,2,6-thiadiazines



SCHEME 4. Synthesis of 1λ⁶,2,6-Thiadiazines via Addition−Condensation Reactions with *S*-Alkyl-*S*-benzyl-sulfodiimines



7 (X = O) as desired by introducing different lipophilic substituents with increasing electron-withdrawing character such as methyl, benzyl, and trifluoromethyl groups as well as the substituent R^1 at the sulfur atom simultaneously (Scheme 4; see Table 1 for details on substitution patterns and yields).

Reaction of *tert*-butylacetoacetate **14** with sulfodiimines of type **9** in refluxing toluene directly leads to the already dehydrated thiadiazines **17** in good yields. This type of reaction presumably proceeds via an acetylketene as the reactive intermediate.[20,21]

Acyl-meldrum's acids[22,23] have been widely utilized as acylacetylating agents throughout the past few decades. Analogously, reaction of **9** with 5-(1-hydroxy-2-phenylethyliden-2,2-dimethyl-1,3-dioxan-4,6-dione **15** (5-acyl-meldrum's acid)[24,25] in refluxing benzene directly gives rise to the heterocycles **18** bearing a benzyl group at position 5. Two different mechanisms are most likely for this reaction, both leading to the same intermediate, which upon intramolecular cyclization results in formation of the thiadiazines **18**. The first one involves the nucleophilic attack of **9** at one of the cyclic carbonyl functions of 5-acyl-meldrum's acid **15**, which is followed by the loss of acetone and carbon dioxide.[23,24] A second mechanism postulates intermediate conversion of 5-acyl-meldrum's acid into a highly reactive acylketene that subsequently reacts with **9** to yield **18**. [23,26,27]

TABLE 1. Synthesized 1λ⁶,2,6-Thiadiazine-3-ones via Addition−Condensation reactions of *S*-Alkyl-*S*-benzyl-sulfodiimines

	R^1	R^2	% yield
17a	CH_3	CH_3	70
17b	n-C_4H_9	CH_3	68
17c	i-C_4H_9	CH_3	55
17d	n-C_5H_{11}	CH_3	69
17e	c-C_6H_{11}	CH_3	54
18a	CH_3	Bn	71
18b	n-C_5H_{11}	Bn	73
18c	c-C_6H_{11}	Bn	73
19a	CH_3	CF_3	54
19b	n-C_5H_{11}	CF_3	76
19c	c-C_6H_{11}	CF_3	78
20a	n-C_5H_{11}	CF_3	67
20b	c-C_6H_{11}	CF_3	72

In the case of the related 4,4,4 trifluoroacetacidic acid isopropylester **16**, however, the nondehydrated 5-hydroxy-thiadiazines **19** are formed. Due to the resulting chiral centers at the sulfur atom and at C-5, they are obtained as a mixture of diastereoisomers. ^{1}H NMR spectroscopy revealed that one diastereoisomer is preferred by a ratio of approximately 8:1 (de 80%). Unfortunately, all attempts to separate the diastereomeric mixture by fractionate crystallization remained unsuccessful. Therefore, the diastereoisomers could not be assigned. Nevertheless, the desired trifluoromethylated thiadiazines of type **20** are readily accessible via dehydration of **19** using a catalytic amount of *p*-toluenesulfonic acid in methanol. As a side product, also the S-debenzylated 1λ⁴-2,6-thiadiazines **26h**,**i** are formed in small quantities.

Synthesis of 1λ⁴,2,6-Thiadiazine-3-ones. Surprisingly, initial attempts to achieve S-debenzylation of 1λ⁶,2,6-thiadiazines **17**, **18**, and **20** according to literature procedures[28] employing a catalytic amount of *p*-toluenesulfonic acid in a protic solvent such as ethanol at elevated temperatures, a method that had proven to be extraordinarily useful in the synthesis of the related 1λ⁴,2,4,6-thiatriazines,[16−18] remained unsuccessful. Although during the synthesis of the trifluoro-substituted 5-hydroxy-1λ⁶,2,6-thiadiazines **19** S-debenzylation already occurred as a side reaction, all attempts to drive this reaction to completion failed. The conventional

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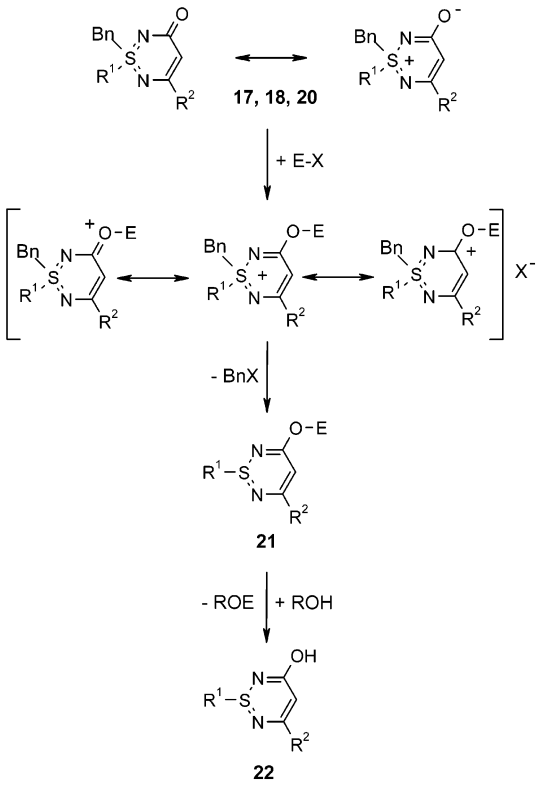
SCHEME 5



approach to accomplish S-debenzylation under various acidic reaction conditions seemed to cause stability problems, especially in the case of the 5-methyl-thiadiazine derivatives **17**. Our next objective was therefore the development of a new synthetic strategy for the S-debenzylation of **17**, **18**, and **20** employing milder reaction conditions. As already mentioned above, S-dealkylation of S,S-disubstituted sulfodiimines is observed in the presence of nucleophiles, if a positive charge is built up on sulfur.[14] This fact prompted us to subject the 1λ^6,2,6-thiadiazine-3-ones **17**, **18**, and **20** to an electrophilic attack at the carbonyl oxygen, thus generating a positively charged intermediate, which alike should facilitate the attack of a nucleophile causing C−S bond cleavage and therefore resulting in formation of 1λ^4,2,6-thiadiazines of type **21** as outlined in Scheme 5.

As an appropriate electrophile we chose TMSCl, hoping that after silylation of the carbonyl function the chloride ion itself could act as the required nucleophile, resulting in cleavage of the C−S bond by eliminating benzyl chloride. Subsequent deprotection of the formed TMS-ether **21** would then give rise to the thiadiazines of type **22** or corresponding tautomeric structures.

The reaction of 1λ^6,2,6-thiadiazine **17a** with just an equimolar amount of TMSCl in dry DCM at room temperature followed by the addition of methanol provided some unconverted starting material and a precipitate, the analytical data of which confirmed that the S-benzyl substituent had in fact been truncated. Surprisingly, the partly formed 1λ^4,2,6-thiadiazine was obtained in its protonated state. However, utilization of a slight excess of 2 equiv of TMSCl drove the reaction to completion, and the corresponding hydrochloride **25a** was obtained in a very good yield. Consequently, the S-debenzylation required at least 2 equiv of TMSCl. The

SCHEME 6. Postulated Reaction Mechanism for the S-Debenzylation of 1λ^6,2,6-thiadiazine-3-ones

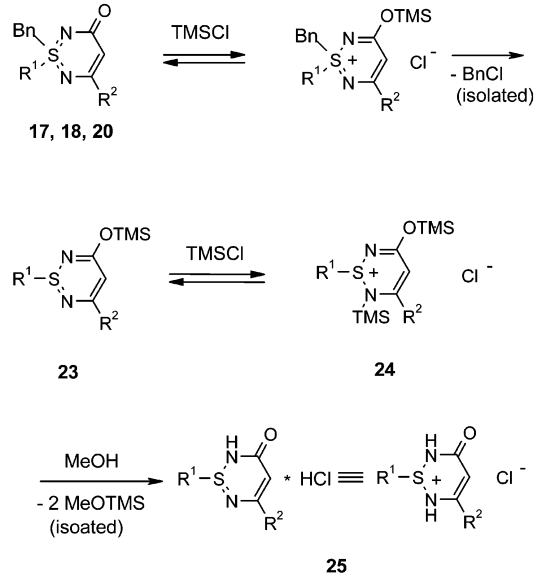


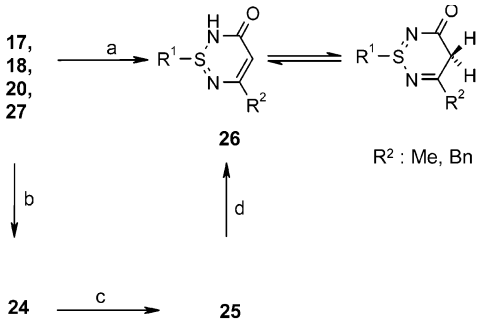
TABLE 2. 1λ^4,2,6-Thiadiazines-3-ones via S-Dealkylation of 1λ^6,2,6-Thiadiazines-3-ones 17, 18, 20, and 27

	R^1	R^2	% yield
25a	CH_3	CH_3	94
25b	CH_3	Bn	67
25c	n-C_5H_{11}	Bn	86
26a	CH_3	CH_3	76
26b	n-C_5H_{11}	CH_3	86
26c	c-C_6H_{11}	CH_3	72
26d	i-C_4H_9	CH_3	62
26e	CH_3	Bn	69
26f	n-C_5H_{11}	Bn	79
26g	c-C_6H_{11}	Bn	83
26h	n-C_5H_{11}	CF_3	64
26i	c-C_6H_{11}	CF_3	63
26j	$Cl(CH_2)_4$	CH_3	69
26k	$Cl(CH_2)_4$	Bn	37

S-benzyl substituent had been cleaved off by forming benzyl chloride, which was isolated and characterized by ^{1}H NMR. Cleavage of the TMS substituent by addition of methanol resulted in formation of the corresponding trimethylsilylmethyl ether, which was proved by its isolation and NMR characterization.

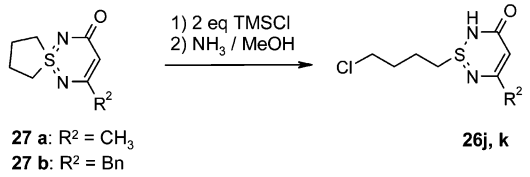
Therefore, benzylmethyl ether, which should have been formed in the case where methanol was the nucleophile in the S-debenzylation step, could not be isolated. As a result, the chloride ion turned out to be the only nucleophile involved in the C−S bond cleavage reaction. The formation of the 1λ^4,2,6-thiadiazines **25** can therefore be explained by the following reaction mechanism as illustrated in Scheme 6. The initial step should most likely be the silylation of the carbonyl function, which is followed by the nucleophilic attack of the herein created chloride ion giving rise to the monosilylated heterocycle **23**. In a subsequent competitive reaction, heterocycle **23** is again silylated at one of the nitrogens (presumably at N-6) to yield **24**, methanolysis of which finally results in formation of the corresponding hydrochlorides **25** in high yields (Table 2). These may be considered as a so far unknown type of cyclic *S*,*S*-diaminosulfonium salt.

SCHEME 7[a]



[a] Reagents and conditions: (a) (i) 2 equiv of TMSCl, (ii) MeOH/NH_3; (b) 2 equiv of TMSCl; (c) MeOH; (d) column chromatography (SiO_2).

SCHEME 8



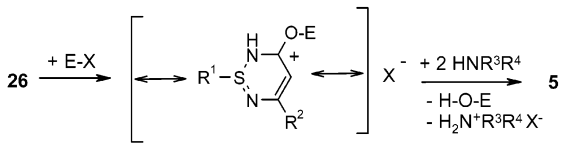
If in the desilylation step a methanolic solution of ammonia is applied instead of pure methanol, the deprotonated thiadiazines **26** are obtained in good yields too. They are also available by column chromatography of the hydrochlorides **25** on silica gel as outlined in Scheme 7. Overall, S-dealkylation of 1λ⁶,2,6-thiadiazine-3-ones **17**, **18**, and **20** with TMSCl as an activating agent gives rise to a broad range of novel 1λ⁴,2,6-thiadiazine-3-ones **26** under mild and convenient reaction conditions in good to excellent yields (see Table 2 for details on substitution patterns and yields).

Interestingly, thiadiazines **26** with a methyl or benzyl substituent present at position 5 showed a quite unusual NH/CH tautomerism in CH_2Cl_2 or $CHCl_3$ solution, which could be proved by ^{1}H NMR and ^{13}C NMR spectroscopy. The tautomerism is indicated by the additional appearance of two doublets for the corresponding two geminal protons attached to C-4 in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum displays the correlated CH_2 signal at about 40 ppm. However, at lower temperatures, the NH form is preferred in solution. In the solid state too, only the NH tautomer is present. X-ray analysis of **26b** revealed that this tautomer is stabilized by intermolecular hydrogen bonding.

Similar to the S-debenzylation discussed above, even the tetrahydrothiophen ring of **27**, accessible through addition−condensation reaction of tetrahydrothiophen-S,S-diimine with *tert*-butylacetoacetate **14** in refluxing toluene (**27a**[29]) or 5-acyl-meldrum's acid **15** in refluxing benzene (**27b**, 61%), can be cleaved easily by employing the same reaction conditions (Scheme 8). The nucleophlic attack of the chloride ion here leads to the corresponding *S*-4-chlorobutyl derivatives **26j**,**k**.

Synthesis of 3-Amino-Substituted 1λ⁴,2,6-Thiadiazines. Having synthesized a variety of 1λ⁴,2,6-thiadiazines **26** via a two-step protocol in good overall yields, our next objective was the introduction of the required amino substituent at position 3 of the heterocyclic core structure. As already discussed, the reaction of TMSCl with 1λ⁶,2,6-thiadiazines of types **17**, **18**, **20**, and **27** presumably leads to the intermediate **24**, which upon addition of ammonia renders the deprotonated thiadiazines **26**. Here the nucleophilic attack occurs not at position 3 but at the adjacent silicon itself.

SCHEME 9



Contrary to the silylation, our goal was the attack of an appropriate electrophile at the carbonyl oxygen, which should now direct the subsequent nucleophilic displacement toward the thus activated 3 position. Reaction of an amine was therefore believed to result in formation of the desired 3-amino-substituted heterocycles of type **5** as outlined in Scheme 9. In principle, this reaction is comparable to the transformation of an amide to an amidine, a reaction sequence well-known in organic chemistry.[30,31]

Prior to the intended sequence in Scheme 9, attempts to activate the carbonyl function by reaction of **26a** with a variety of chlorinating agents such as $SOCl_2$, PCl_5, $POCl_3$, and even triphenylphosphine/CCl_4[32,33] as an especially mild variation repeatedly resulted in a complex reaction mixture. Attempts to isolate the corresponding amidine even after immediate subsequent addition of an amine remained fruitless. Due to the tautomerism of **26a**, side reactions are likely. For instance, reaction as a secondary amide leads to the imidoyl chloride,[34] and reaction as a tertiary amide leads to the corresponding chloromethyleniminium salt.[35,36] In the case of *N*,*N*-dialkyl amides, the undesired α-chloro-*β*-(chloro-carbonyl)-enamines are also possible products.[37]

Another widespread synthetic approach toward amidines employs alkylation of amides with trialkyloxonium tetrafluoroborates,[38] providing alkoxymethyleniminium salts as reactive electrophilic intermediates that, upon addition of amines, yield the corresponding amidines.[39,40] Besides primary, secondary, tertiary, and cyclic amides,[41]

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SCHEME 10

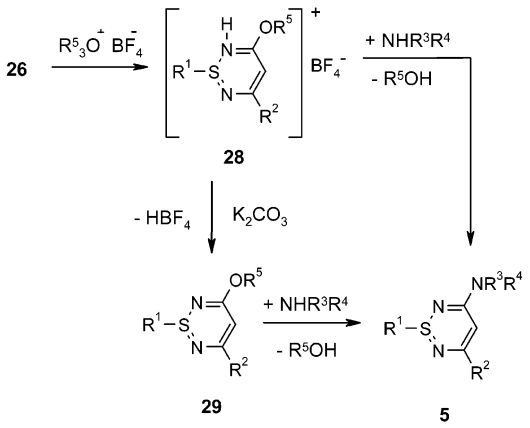


TABLE 3. 1-Alkyl-3-alkoxy-5-Substituted 1λ^4,2,6-Thiadiazines 29 and 1-Alkyl-2-alkyl-5-Substituted 3*H*-1λ^4,2,6-Thiadiazine-3-ones 30 via Alkylation of 26

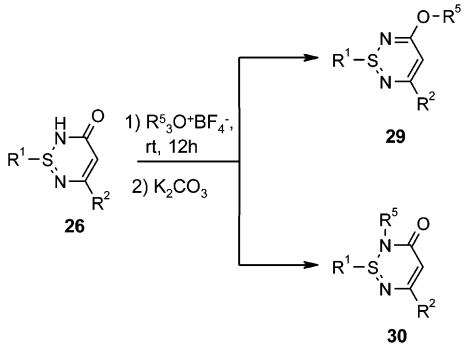
entry	compd	R^1	R^2	R^5	% yield
1	**29a**	CH_3	CH_3	Et	74
2	**29b**	n-C_5H_{11}	CH_3	Et	70
3	**29c**	n-C_5H_{11}	Bn	Me	48
4	**29d**	c-C_6H_{11}	Bn	Me	47
5	**29e**	c-C_6H_{11}	Bn	Et	79
6	**29f**	c-C_6H_{11}	CF_3	Et	24[a]
7	**29f**	c-C_6H_{11}	CF_3	Et	18[b]
8	**30a**	CH_3	CH_3	Et	40
9	**30b**	n-C_5H_{11}	CH_3	Et	29
10	**30c**	n-C_5H_{11}	Bn	Me	21
11	**30d**	c-C_6H_{11}	Bn	Me	15
12	**30e**	c-C_6H_{11}	CF_3	Et	7[a]
13	**30e**	c-C_6H_{11}	CF_3	Et	31[b]

[a] Compound prepared according to method a, Experimental Section. [b] Compound prepared according to method b, Experimental Section.

α,β-unsaturated amides[42] have also been successfully utilized in the synthesis of the analogous imidates. Accordingly, reaction of the heterocycles **26** with trialkyloxonium tetrafluoroborates should give rise to the oxonium salts **28**, which upon addition of an amine could possibly furnish the 3-amino-substituted heterocycles **5** (Scheme 10). Alternatively, basic workup of **28** forming the heterocyclic imidoester **29** and subsequent amine treatment would also lead to the desired thiadiazines **5**.

As expected, alkylation of the 1λ^4,2,6-thiadiazine-3-ones **26** with triethyl- and trimethyloxonium tetrafluoroborates at room temperature in DCM indeed resulted in formation of the 3-alkoxythiadiazines **29**. Surprisingly, as side products, the structurally isomeric N-2-alkylated derivatives **30** are also formed. Especially under acidic (Table 3, entries 8−11) or basic (Table 3, entry 13) reaction conditions, **30a**−**e** are obtained in significant amounts. Yields vary from 15 to 40%. The formation of the N-alkylated side products can be diminished by employing freshly prepared trialkyloxonium tetrafluoroborates[43] that have been washed thoroughly with ether prior to use in order to remove traces of acid instead of utilizing commercially available alkyloxonium tetrafluoroborates. Thus, the alkoxy derivatives **29a**−**f** are obtained in good yields after workup with aqueous K_2CO_3 solution (Scheme 11 and Table 3, entries 1−6)

SCHEME 11



If the 1λ^6-thiadiazine **17d** is alkylated under the above reaction conditions followed by addition of a nucleophile, S-debenzylation is again observed in analogy to the related reaction utilizing TMSCl as an electrophile. After workup with aqueous K_2CO_3 solution, the O-alkylated thiadiazine **29b** was obtained in 70% yield.

X-ray analysis of the N-alkylated side product **30e** finally confirmed that the alkyl group is attached to N-2.

Furthermore, X-ray structure determination of differently substituted 1λ^4-thiadiazines (**26b**, **29f**, **30e**) revealed that the heterocyclic ring system is not planar. The sulfur atom, which is tetrahedrally configured, clearly sticks out of the plane of the N/C skeleton. Its fourth valence is occupied by the nonbinding lone electron pair. The position of the *S*-alkyl substituent is perpendicular to the plane. Both S−N bonds are almost the same length.

In contrast to the *N*-alkyl-substituted **30** and *NH*-1λ^4-thiadiazine-3-ones **26**, absorption maxima of the O-alkylated thiadiazines **29** are shifted to higher wavelengths (bathochromic effect). Therefore, crystals as well as solutions of these are yellow, whereas **26** and **30** both appear colorless, which is also confirmed by their UV spectra as illustrated in Figure 2.

In the case of the O-alkylation of **26** leading to **29**, the exocyclic double bond present in **26** is formally "shifted" into the heterocyclic ring system, thus enlarging the conjugated π-electron system. Yet, the tetrahedral-configured sulfur atom is not included in the ring delocalization. Consequently, even the O-alkylated thiadiazines **29** are nonaromatic heterocycles. The delocalized π-electron system may therefore be described as a 1,5-diaza-penta-1,3-diene anion that is analogous to the 1λ^4,2,4,6-thiatriazines.[44,45] The planar conjugated system also resembles the basic structure of a cyanine (in the case of **29**) or a merocyanine (in the case of **30**) system showing the characteristic absorption maxima for these types of chromophores (λ_{max} = 373 nm for a cyanine and λ_{max} = 335 nm for a merocyanine system, respectively). Contrary to the cyanines though, which bear a positively charged nitrogen, the conjugated system in **29** is negatively charged and may therefore be referred to as an inverse cyanine as illustrated in Figure 3.

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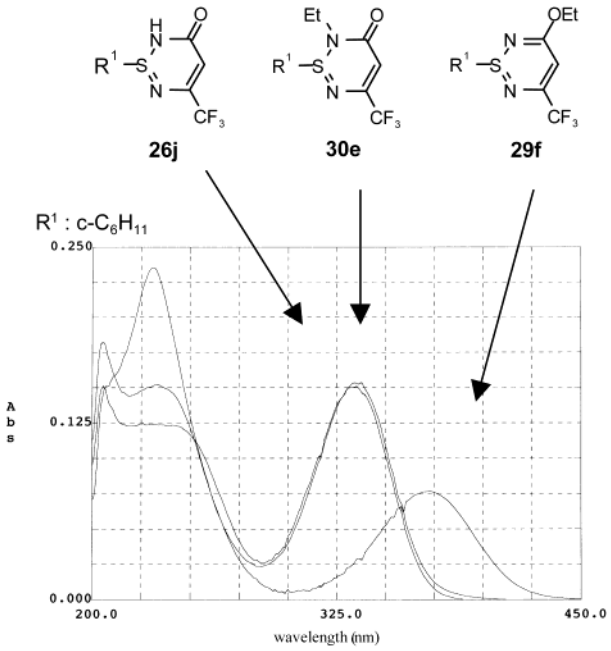


FIGURE 2. UV spectra of **26j**, **30e**, and **29f**.

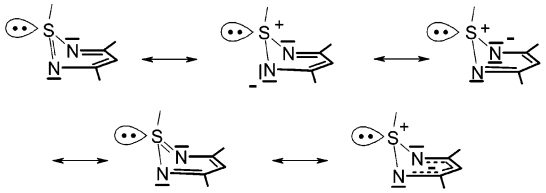


FIGURE 3. Resonance structures of 3-substituted 1λ⁴,2,6-thiadiazines **29**.

Either reaction of the in situ-formed oxonium salts **28** or of the isolated imidates **29** with different amines employing various reaction conditions such as stirring at 20 °C in $CHCl_3$, refluxing in toluene, or neat in benzylamine only resulted in formation of the imidates or even reisolation of starting material.

Due to the presence of the electron-withdrawing trifluoromethyl substituent in **26h** and **i**, the alkylation reaction is hampered, which is indicated by a prolonged reaction time and lower yields. Quenching of **28** with benzylamine as well as employing the above reaction conditions after isolation of the corresponding imidate led even in this case only to formation and reisolation of the deprotonated imidate **29f** accompanied by the isomer **30e**, suggesting that activation of the carbonyl functionality for the subsequent nucleophilic attack is still not sufficient.

We therefore decided to introduce a better leaving group than the ethoxy moiety to position 3 of the heterocycle, hoping that at least in the case of the trifluoromethylated derivatives, activation by the electron-withdrawing effects of substituents in positions 3 and 5 could facilitate the nucleophilic attack of an amine resulting in formation of the desired heterocycles of type **5**.

Treatment of the λ⁴-thiadiazines **26** with methane- and *p*-toluenesulfonic acid anhydride in DCM at 20 °C formed the sulfonates **31** and some **32** like the above-discussed alkylation reaction. After separation by flash column

SCHEME 12

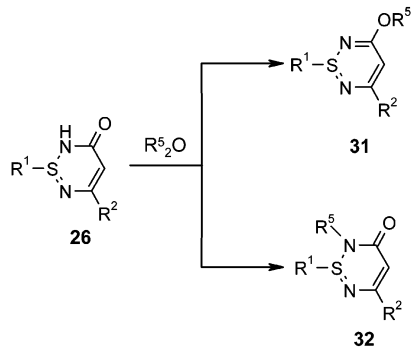


TABLE 4. (1-Alkyl-5-Substituted 1λ⁴,2,6-Thiadiazine-3-yl)-sulfonates 31 and 1-Alkyl-2-sulfonyl-5-Substituted 3*H*-1λ⁴,2,6-Thiadiazine-3-ones 32 via Sulfonylation of 26

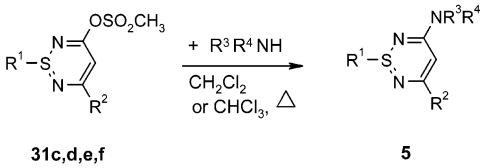
	R^1	R^2	R^5	% yield
31a	c-C_6H_{11}	CF_3	4-Ts	24
31b	n-C_5H_{11}	Bn	4-Ts	25
31c	n-C_5H_{11}	CF_3	Ms	20
31d	c-C_6H_{11}	CF_3	Ms	37
31e	c-C_6H_{11}	Bn	Ms	41
31f	n-C_5H_{11}	Bn	Ms	38
32a	c-C_6H_{11}	CF_3	4-Ts	5

TABLE 5. 1-Alkyl-2-amino-5-Substitued 1λ⁴,2,6-Thiadiazines 5 via Aminolysis of 31

5	R^1	R^2	R^3	R^4	% yield
5a	n-C_5H_{11}	CF_3	Bn	H	61
5b	c-C_6H_{11}	CF_3	Bn	H	64
5c	c-C_6H_{11}	CF_3	H	H	30
5d	c-C_6H_{11}	CF_3	X[a]	H	39
5e	c-C_6H_{11}	CF_3	C_2H_5	C_2H_5	31
5f	n-C_5H_{11}	Bn	Bn	H	45
5g	c-C_6H_{11}	Bn	Bn	H	35

[a] X = C_6H_5–(CH_3)CH–.

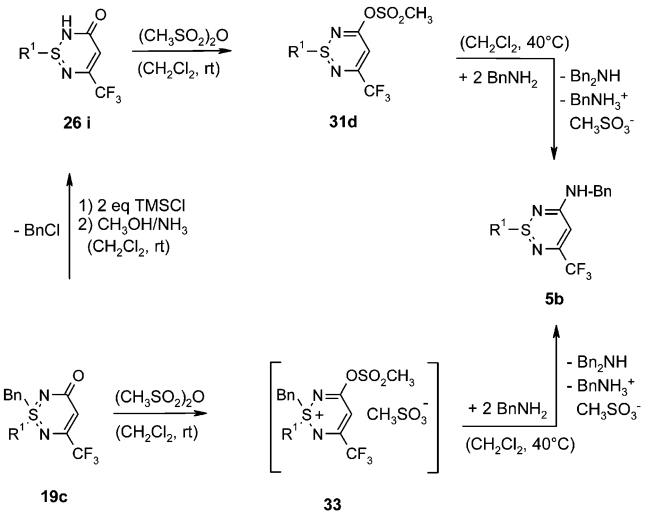
SCHEME 13



chromatography on silica gel, only in one case could the N-alkylated derivative **32a** be isolated, and the yield was low. Due to the relative instability of these compounds under such chromatography conditions (partial hydrolysis), the yields are moderate and range from 20 to 41% (see Scheme 12 and Table 4 for substitution patterns and yields).

Aminolysis of the sulfonates **31c** and **31d** in boiling DCM or **31e** and **31f** in $CHCl_3$ finally led to the desired amino-substituted thiadiazines of type **5** in good to moderate yields as illustrated in Scheme 13 (for substitution pattern and yields, see Table 3). In comparison to the CF_3-subtituted derivatives **31c** and **31d**, the reaction of the 5-benzyl-thiadiazines **31e** and **31f** with benzylamine not only required higher temperatures and longer reaction times but also gave lower yields. This result confirmed that the introduction of an electron-withdraw-

SCHEME 14



ing substituent like CF_3 indeed facilitates the nucleophilic attack at the conjugated carbonyl function of the sulfonylated thiadiazines.

Besides benzylamine, also sterically hindered secondary amines such as diethylamine as well as the less nucleophilic ammonia are suitable nucleophiles, although yields in the latter case are significantly lower. After reaction of **31d** with optically pure *S*-1-phenyl-ethylamine, the resulting diastereoisomers could be separated by column chromatography on silica gel, indicating that the tetrahedral configuration of the chiral sulfur is stable under these reaction conditions.

In an alternative approach, reaction of the 1λ^6-thiadiazine **19c** as a model substrate with methanesulfonic acid anhydride followed by subsequent addition of an excessive amount of benzylamine readily furnished the 3-amino-substituted thiadiazine **5b** in a slightly higher overall yield (17%) if compared to the stepwise synthesis described so far (14%). Generation of the sulfonylated sulfonium salt **33** followed by treatment with an excess of benzylamine truncated the *S*-benzyl moiety and converted the mesylated carbonyl function into the desired amino-substituted derivative, thus resulting in formation of **5a** via a one-pot reaction. Scheme 14 summarizes both reaction sequences leading to the new class of 3-amino-substituted 1λ^4-2,6-thiadiazines of type **5**.

Experimental Section

General Information. Melting points were measured according to the capillary method and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz in $CDCl_3$ and referenced to the residual $CHCl_3$ at 7.24 ppm (^{1}H) and $CDCl_3$ at 77.00 ppm (^{13}C) unless otherwise indicated. Mass spectra were obtained from a double-focusing sectorfield spectrometer. Infrared spectra were taken from a FT-IR spectrometer. Combustion analyses were determined on a CH analyzer or a CHN autoanalyzer (only nitrogen). Determination of sulfur and chlorine was accomplished manually according to the Schöniger method. UV spectra were recorded in MeOH at 20 °C unless otherwise indicated. Flash column chromatography was performed using silica gel 60 (63−200 ASTM mesh), silica gel 60 (50−100 ASTM mesh), or silica gel 60 (40−63 ASTM mesh), respectively. TLC was carried out using 0.2 mm aluminum plates coated with silica gel 60 F_{254}. All moisture-sensitive reactions were carried out using oven-dried glassware under a positive pressure of nitrogen. Solvents and reagents that are commercially available were used without further purification unless otherwise noted.

General Procedure for the Synthesis of 1-Alkyl-1-benzyl-5-methyl-3*H*-1λ^6,2,6-thiadiazine-3-ones 17: 1-Benzyl-1,5-dimethyl-3*H*-1λ^6,2,6-thiadiazine-3-one (17a). A solution of *S*-benzyl-*S*-methyl-sulfodiimine **9** (5.05 g, 30.0 mmol) and *tert*-butyl acetoacetate **14** (4.75 g, 30.0 mmol) in toluene (50 mL) was refluxed for several hours and monitored by TLC. After completion of the reaction, the solvent was concentrated in vacuo and the yellow to reddish oily residue solidified by the addition of diethyl ether. Recrystallization from dioxane gave pure **17a** (4.94 g, 70%) as colorless crystals: mp 162 °C (dioxane); ^{1}H NMR δ 7.45−7.41 (m, 5H), 4.77 (psd, J = 0.9 Hz, 1H), 4.56 (d, J = 13.2 Hz, 1H), 4.48 (d, J = 13.2 Hz, 1H), 3.32 (s, 3H), 1.89 (d, J = 0.9 Hz, 3H); ^{13}C NMR δ 168.6, 162.6, 131.4, 130.1, 129.0, 124.9, 95.4, 65.7, 43.1, 24.7. Anal. Calcd for $C_{12}H_{14}N_2OS$ (234.32): C, 61.51; H, 6.02; N, 11.96; S, 13.68. Found: C, 61.47; H, 5.92; N, 12.00; S, 13.66.

In analogy to the synthesis described for **17a**, the following compounds were obtained starting from *tert*-butyl acetoacetate and the respective *S*-alkyl-*S*-benzyl-sulfodiimines **9**.

1-Benzyl-1-butyl-5-methyl-3*H*-1λ^6,2,6-thiadiazine-3-one (17b): colorless solid after chromatography on silica gel (ethyl acetate/ethanol = 9/1), yield: 68%; mp 152 °C (diethyl ether); ^{1}H NMR (500 MHz) δ 7.46−7.37 (m, 5H), 4.67 (s, 1H), 4.43 (d, J = 13.1 Hz, 1H), 4.34 (d, J = 13.1 Hz, 1H), 3.33−3.26 (m, 2H), 1.98−1.88 (m, 2H), 1.86 (s, 3H), 1.52−1.45 (m, 2H), 0.96 (t, 3H); ^{13}C NMR (125 MHz) δ 169.1, 163.0, 131.4, 129.8, 128.8, 124.6, 94.4, 64.7, 54.7, 24.6, 22.0, 21.1, 13.5. Anal. Calcd for $C_{15}H_{20}N_2OS$ (276.40): C, 65.18; H, 7.29; N, 10.14; S, 11.60. Found: C, 65.30; H, 7.02; N, 10.20; S, 11.87.

1-Benzyl-1-isobutyl-5-methyl-3*H*-1λ^6,2,6-thiadiazine-3-one (17c): colorless crystals after recrystallization from dioxane; yield 55%; mp 148 °C (dioxane); ^{1}H NMR δ 7.45−7.35 (m, 5H), 4.65 (psd, J = 0.8 Hz, 1H), 4.40 (d, J = 13.0 Hz, 1H), 4.32 (d, J = 13.0 Hz, 1H), 3.27 (dd, J = 14.0 Hz, 5.8 Hz, 1H), 3.19 (dd, J = 13.8 Hz, 6.9 Hz, 1H), 2.59 (sm, 1H), 1.83 (d, J = 1.1 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ (125 MHz) 169.0, 162.7, 131.4, 129.8, 128.7, 124.5, 94.1, 66.0, 61.8, 24.6, 23.1, 22.7, 22.2. C/H−COSY−NMR (125/500 MHz): 61.8:3.27, 3.19; 23.1:2.59; 22.7, 22.2:1.13, 1.12. Anal. Calcd for $C_{15}H_{20}N_2OS$ (276.40): C, 65.18; H, 7.29; N, 10.14; S, 11.60. Found: C, 65.10; H, 7.08; N, 9.92; S, 11.47.

1-Benzyl-5-methyl-1-pentyl-3*H*-1λ^6,2,6-thiadiazine-3-one (17d): colorless crystals after rerystallization from DME; yield 69%; mp 150 °C (DME); ^{1}H NMR δ 7.43−7.36 (m, 5H), 4.67 (psd, J = 1.0 Hz, 1H), 4.45 (d, J = 13.1 Hz, 1H), 4.36 (d, J = 13.0 Hz, 1H), 3.33−3.21 (m, 2H), 2.02−1.84 (m, 2H), 1.86 (d, J = 1.0 Hz, 3H), 1.46−1.30 (m, 4H), 0.9 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 169.1, 163.0, 131.4, 129.9, 128.8, 124.6, 94.5, 64.8, 55.0, 29.9, 24.6, 22.1, 19.7, 13.6. Anal. Calcd for $C_{16}H_{22}N_2OS$ (290.43): C, 66.16; H, 7.64; N, 9.65; S, 11.04. Found: C, 66.21; H, 7.41; N, 9.75; S, 11.09.

1-Benzyl-1-cyclohexyl-5-methyl-3*H*-1λ^6,2,6-thiadiazine-3-one (17e): colorless crystals after recrystallization from dioxane; yield 54%; mp 152 °C (dioxane); ^{1}H NMR δ 7.45−7.35 (m, 5H), 4.53 (psd, J = 0.9 Hz, 1H), 4.38 (d, J = 13.0 Hz, 1H), 4.26 (d, J = 12.8 Hz, 1H), 3.27−3.20 (m, 1H), 2.30−2.20 (m, 2H), 2.08−2.01 (m, 2H), 1.93−1.68 (m, 4H), 1.80 (d, J = 0.9 Hz, 3H), 1.41−1.20 (m, 2H); ^{13}C NMR δ 169.4, 163.2, 131.6, 129.8, 128.7, 124.3, 94.1, 65.3, 60.5, 24.9, 24.7, 24.6, 23.8, 23.6. Anal. Calcd for $C_{17}H_{22}N_2OS$ (302.44): C, 67.51; H, 7.33; N, 9.26; S, 10.60. Found: C, 67.46; H, 7.06; N, 9.20; S, 10.46.

General Procedure for the Synthesis of 1-Alkyl-1,5-dibenzyl-3*H*-1λ^6,2,6-thiadiazine-3-ones 18: 1,5-Dibenzyl-1-methyl-3*H*-1λ^6,2,6-thiadiazine-3-one (18a). A solution of *S*-benzyl-*S*-methyl-sulfodiimine **9** (1.43 g, 8.5 mmol) and 5-(1-hydroxy-2-phenyl-ethyliden)-2,2-dimethyl-1,3-dioxane-4,6-dione **15** (2.2 g, 8.5 mmol) in benzene (75 mL) was refluxed for several hours and monitored by TLC. After completion of the reaction, the product precipitated upon cooling to room tem-

perature to yield **18a** as slightly yellow crystals (1.86 g, yield 71%): mp 153 °C (benzene/diethyl ether); ^{1}H NMR (CD_3CN) δ 7.42−7.17 (m, 10H), 4.51 (d, J = 13.5 Hz, 1H), 4.47 (d, J = 13.5 Hz, 1H), 4.45 (s, 1H), 3.39 (d, J = 14.7 Hz, 1H), 3.34 (d, J = 14.7 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.2, 164.2, 137.3, 131.4, 129.1, 128.9, 128.2, 128.0, 126.2, 125.9, 94.2, 63.2, 43.8, 42.6. Anal. Calcd for $C_{18}H_{18}N_2OS$ (310.41): C, 69.64; H, 5.84; N, 9.03; S, 10.33. Found: C, 69.70; H, 5.68; N, 8.87; S, 10.44.

In analogy to the synthesis described for **18a**, the following compounds were obtained starting from 5-(1-hydroxy-2-phenylethyliden)-2,2-dimethyl-1,3-dioxane-4,6-dione **15** and the respective *S*-alkyl-*S*-benzyl-sulfondiimines **9**.

1,5-Dibenzyl-1-pentyl-3*H*-1λ⁶,2,6-thiadiazine-3-one (18b): colorless crystals after recrystallization from ethyl acetate: yield 73%; mp 124 °C (ethyl acetate); ^{1}H NMR (500 MHz) δ 7.41−7.11 (m, 10H), 4.79 (s, 1H), 4.36 (d, J = 13.1 Hz, 1H), 4.28 (d, J = 13.4 Hz, 1H), 3.41 (d, J = 14.4 Hz, 1H), 3.38 (d, J = 14.4 Hz, 1H), 3.26−3.20 (sm, 2H), 1.91−1.78 (sm, 2H), 1.37−1.27 (m, 4H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz) δ 169.2, 165.0, 137.2, 131.4, 129.7, 129.2, 128.9, 128.3, 126.6, 124.5, 94.9, 65.6, 54.9, 45.0, 29.9, 22.1, 19.6, 13.6. Anal. Calcd for $C_{22}H_{26}N_2OS$ (366.52): C, 72.09; H, 7.15; N, 7.64; S, 8.75. Found: C, 72.18; H, 7.11; N, 7.54; S, 8.63.

1-Cyclohexyl-1,5-dibenzyl-3*H*-1λ⁶,2,6-thiadiazine-3-one (18c): colorless solid; yield 73%; mp 161 °C (benzene/diethyl ether); ^{1}H NMR δ 7.37−7.13 (m, 10H), 4.64 (s, 1H), 4.31 (d, J = 13.2 Hz, 1H), 4.23 (d, J = 13.0 Hz, 1H), 3.35 (s, 2H), 3.21−3.10 (m, 1H), 2.21−1.93 (m, 2H), 1.78−1.58 (m, 4H), 1.35−1.12 (m, 4H); ^{13}C NMR δ 169.5, 165.4, 137.3, 131.5, 129.6, 129.3, 128.7, 128.2, 126.5, 124.1, 94.3, 65.4, 60.1, 44.9, 27.8, 24.8, 24.7. Anal. Calcd for $C_{23}H_{26}N_2OS$ (378.53): C, 72.98; H, 6.92; N, 7.40; S, 8.47. Found: C, 73.04; H, 6.75; N, 7.68; S, 8.46.

General Procedure for the Synthesis of (5*R*,*S*)-1-Alkyl-1-benzyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-3*H*-1λ⁶,2,6-thiadiazine-3-ones 19: (5*R*,*S*)-1-Benzyl-5-hydroxy-1-methyl-5-trifluoromethyl-4,5-dihydro-3*H*-1λ⁶,2,6-thiadiazine-3-one (19a). A solution of *S*-benzyl-*S*-methylsulfodiimine **9** (840 mg, 5.0 mmol) and 4,4,4-trifluoroacidic acid isopropylester **16** (991 mg, 5.0 mmol) in toluene (50 mL) was refluxed for 60 min. After completion of the reaction, a white precipitate was formed that was separated by filtration from the hot reaction mixture, washed with diethyl ether, and dried to give pure **19a** (835 mg, 54%) as a mixture of diastereoisomers: mp 164 °C (toluene/diethyl ether); ^{1}H NMR (DMSO-d_6) δ *diastereomer a* 7.55−7.53 (m, 2H), 7.43−7.42 (m, 3H), 6.83 (s, 1H), 4.82 (d, J = 13.4 Hz, 1H), 4.65 (d, J = 13.2 Hz, 1H), 3.15 (s, 3H), 2.34 (d, J = 16.1 Hz, 1H), 1.96 (d, J = 16.1 Hz, 1H); *diastereomer b* 7.43−7.42 (m, 2H), 7.36−7.34 (m, 3H), 6.58 (s, 1H), 4.94 (d, J = 13.4 Hz, 1H), 4.78 (d, J = 13.7 Hz, 1H), 3.35 (s, 3H), 1.98 (d, J = 15.4 Hz, 1H), 1.16 (d, J = 15.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ *diastereomer a* 170.1, 131.8, 129.0, 128.4, 127.4, 125.3 (q, J = 286.7 Hz), 85.5 (q, J = 31.5 Hz), 64.4, 41.0, 37.7; *diastereomer b* 132.0, 129.2, 128.0, 125.4, 61.4, 45.3, 37.0 (C-3, CF_3, C-5 overlapped by the corresponding signals of diastereomer a). Anal. Calcd for $C_{12}H_{13}F_3N_2O_2S$ (306.31): C, 47.05; H, 4.28; N, 9.15; S, 10.47. Found: C, 47.07; H, 4.31; N, 9.22; S, 10.71.

In analogy to the synthesis described for **19a**, the following compounds were obtained starting from 4,4,4-trifluoroacidic acid isopropylester **16** and the respective *S*-alkyl-*S*-benzyl-sulfodiimines **9**.

(5*R*,*S*)-1-Benzyl-5-hydroxy-1-pentyl-5-trifluoromethyl-4,5-dihydro-3*H*-1λ⁶,2,6-thiadiazine-3-one (19b): colorless solid; yield 76%; mp 165 °C (toluene/diethyl ether); ^{1}H NMR (DMSO-d_6) δ *diastereomer a* 7.42−7.30 (m, 5H), 6.48 (bs, 1H), 4.85 (d, J = 13.0 Hz, 1H), 4.71 (d, J = 12.9 Hz, 1H), 3.48−3.44 (pst, 2H), 1.91 (d, J = 15.2 Hz, 1H), 1.96−1.90 (m, 2H), 1.60−1.20 (m, 4H), 0.99 (d, J = 15.5 Hz, 1H), 0.92−0.89 (pst, 3H); *diastereomer b* 8.30 (bs, 1H), 7.54−7.40 (m, 5H), 4.80 (d, J = 12.9 Hz, 1H), 4.66 (d, J = 13.4 Hz, 1H), 3.18−3.17 (pst, 2H), 2.25 (d, J = 16.3 Hz, 1H), 1.96−1.90 (d, 1H), 1.60−1.20 (m, 4H), 0.84−0.81 (pst, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ *diastereomer a* 170.7, 132.2, 129.2, 127.9, 125.2, 123.7 (q, J = 286.6 Hz), 85.3 (q, J = 30.7 Hz), 60.4, 55.7, 37.1, 29.6, 21.7, 19.3, 13.7; *diastereomer b* 132.0, 129.0, 128.5, 127.2, 63.8, 50.6, 37.7, 29.0, 21.5, 18.4, 13.5 (C-3, CF_3, C-5 overlapped by the corresponding signals of diastereomer a). Anal. Calcd for $C_{16}H_{21}F_3N_2O_2S$ (362.42): C, 53.02; H, 5.84; N, 7.73; S, 8.85. Found: C, 53.25; H, 5.63; N, 7.87; S, 8.98.

(5*R*,*S*)-1-Benzyl-1-cyclohexyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-3*H*-1λ⁶,2,6-thiadiazine-3-one (19c): colorless solid; yield 78%; mp 179 °C (toluene/diethyl ether); ^{1}H NMR (DMSO-d_6) δ *diastereomer a* 7.52−7.40 (m, 5H), 6.62 (s, 1H), 4.79 (d, J = 13.4 Hz, 1H), 4.67 (d, J = 13.3 Hz, 1H), 3.26−3.19 (m, 1H), 2.18 (d, J = 16.3 Hz, 1H), 2.11−2.09 (m, 2H), 1.87−1.82 (m, 2H), 1.67 (d, J = 16.3 Hz, 1H), 1.65−1.09 (m, 6H); *diastereomer b* could not be assigned properly; ^{13}C NMR (DMSO-d_6) δ *diastereomer a* 170.32, 131.7, 128.7, 128.1, 126.5, 123.7 (q, J = 286.5 Hz), 85.3 (q, J = 30.6 Hz), 61.3, 60.3, 37.9, 24.3, 24.1, 23.2, 23.1; *diastereomer b* 170.26, 132.2, 128.8, 127.5, 124.9, 64.9, 57.1, 37.0, 24.48, 24.46, 23.8 (CF_3, C-5 overlapped by the corresponding signals of diastereomer a). Anal. Calcd for $C_{17}H_{21}F_3N_2O_2S$ (374.43): C, 54.33; H, 5.65; N, 7.48; S, 8.56. Found: C, 54.49; H, 5.66; N, 7.41; S, 8.91.

General Procedure for the Synthesis of 1-Alkyl-1-benzyl-5-trifluoromethyl-3*H*-1λ⁶,2,6-thiadiazine-3-ones 20: 1-Benzyl-1-pentyl-5-trifluoromethyl-3*H*-1λ⁶,2,6-thiadiazine-3-one (20a). (5*R*,*S*)-1-Benzyl-5-hydroxy-1-methyl-5-trifluoromethyl-4,5-dihydro-3*H*-1λ⁶,2,6-thiadiazine-3-one 19b (1.81 g, 5.0 mmol) was suspended in methanol. After addition of a catalytic amount of 4-toluenesulfonic acid, the reaction mixture was stirred at room temperature. After completion was indicated by TLC, the solvent was removed under reduced pressure, suspended in chloroform, and treated with basic alumina. The filtrate was evaporated and solidified upon treatment with pentane to give pure 20a (1.15 g, 67%) as a colorless solid: mp 144 °C (chloroform/pentane); ^{1}H NMR δ 7.51−7.38 (m, 5H), 5.08 (s, 1H), 4.48 (d, J = 13.0 Hz, 1H), 4.43 (d, J = 13.0 Hz, 1H), 3.45−3.41 (sm, 2H), 2.04−1.97 (sm, 2H), 1.49−1.35 (m, 4H), 0.92 (pst, J = 7.2 Hz, 3H); ^{13}C NMR δ 167.1, 151.0 (q, J = 34.9 Hz), 131.7, 130.5, 129.1, 123.1, 120.2 (q, J = 275.2 Hz), 94.2 (psd, J = 3.8 Hz), 65.6, 55.9, 29.8, 22.0, 19.8, 13.6. Anal. Calcd for $C_{16}H_{19}F_3N_2OS$ (344.40): C, 55.80; H, 5.56; N, 8.14; S, 9.31. Found: C, 55.76; H, 5.66; N, 8.18; S, 9.96.

1-Benzyl-1-cyclohexyl-5-trifluoromethyl-3*H*-1λ⁶,2,6-thiadiazine-3-one (20b): colorless solid after crystallization from diethyl ether; yield 72%; mp 149 °C (chloroform/ diethyl ether); ^{1}H NMR (500 MHz) δ 7.48−7.36 (m, 5H), 4.96 (s, 1H), 4.44 (d, J = 12.8 Hz, 1H), 4.37 (d, J = 13.0 Hz, 1H), 3.43−3.37 (m, 1H), 2.30−2.28 (m, 2H), 2.07−2.04 (m, 2H), 1.90−1.74 (m, 3H), 1.44−1.24 (m, 3H); ^{13}C NMR (125 MHz) δ 167.5, 151.3 (q, J = 34.6 Hz), 131.9, 130.3, 128.9, 122.7, 120.2 (q, J = 275.4 Hz), 94.2 (psd, J = 3.8 Hz), 66.6, 61.2, 24.8, 24.5, 23.8. Anal. Calcd for $C_{17}H_{19}F_3N_2OS$ (356.41): C, 57.14; H, 5.37; N, 7.86; S, 9.00. Found: C, 57.24; H, 5.03; N, 7.85; S, 9.02.

Synthesis of 1,5-Dimethyl-2*H*,3*H*-1λ4,2,6-thiadiazine-3-one-hydrochloride (25a). To a solution of 1-benzyl-1,5-dimethyl-3*H*-1λ⁶,2,6-thiadiazine-3-one **17a** (1.17 g, 5.0 mmol) in dry DCM was added a solution of TMSCl (1.08 g, 10.0 mmol) in dry DCM over a period of 1 h under a nitrogen atmosphere, and the mixture was stirred for an additional 3 h. After completion of the reaction, the reaction mixture was carefully treated with methanol, at which time the product precipitated. The amorphous solid was collected, washed with DCM, and dried to give **25a** (904 mg, 94%) as a colorless solid: mp 141 °C (dichloromethhane); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.46 (bs, 2H), 5.45 (s, 1H), 3.03 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (CD_3-OD) δ 170.2, 157.8, 99.2 (pst, J = 26.9 Hz, partial H/D-exchange), 33.6, 21.5. Anal. Calcd for $C_5H_9ClN_2OS$ (180.74): C, 33.23; H, 5.02; N, 15.51; S, 17.75. Found: C, 33.21; H, 4.92; N, 15.55; S, 17.73.

General Procedure for the Synthesis of 1-Alkyl-5-benzyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one-hydrochlorides 25b and 25c: 5-Benzyl-1-methyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one-hydrochloride (25b). To a solution of 1,5-dibenzyl-1-methyl-3*H*-1λ^6,2,6-thiadiazine-3-one **18a** (621 mg, 2.0 mmol) in dry DCM was added a solution of TMSCl (478 mg, 4.4 mmol) in dry DCM over a period of 1 h under a nitrogen atmosphere. After completion of the reaction, the reaction mixture was concentrated in vacuo and the oily residue solidified by addition of DCM to give **25b** (345 mg, 67%) as a colorless solid: yield 67%; mp 138 °C (DCM); ^{1}H NMR (DMSO-d_6) δ 8.34 (bs, 2H), 7.34−7.22 (m, 5H), 5.21 (bs, 1H), 3.64 (d, J = 14.8 Hz, 1H), 3.60 (d, J = 15.1 Hz, 1H), 2.79 (s, 3H); ^{13}C NMR (CD_3OD) δ 169.7, 159.2, 135.7, 130.3, 130.1, 128.8, 99.7, 41.6, 33.1. Anal. Calcd for $C_{11}H_{13}ClN_2OS$ (256.75): C, 51.45; H, 5.10; N, 10.91; S, 13.81; Cl, 12.49. Found: C, 51.51; H, 5.12; N, 10.41; S, 13.85; Cl, 12.53.

In analogy to the synthesis described for **25b**, **5-Benzyl-1-pentyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one-hydrochloride 25c** was obtained utilizing 1,5-dibenzyl-1-pentyl-3*H*-1λ^6,2,6-thiadiazine-3-one **18b**. The resulting residue was solidified with diethyl ether to give pure **25c** as a colorless solid: yield 86%; mp 122 °C (diethyl ether); ^{1}H NMR δ 7.36−7.27 (m, 5H), 5.59 (s, 1H), 3.79 (d, J = 14.8 Hz, 1H), 3.70 (d, J = 15.0 Hz, 1H), 3.70−3.60 (m, 1H), 3.51−3.42 (m, 1H), 1.46−1.35 (bs, 1H), 1.10−0.87 (m, 6H), 0.80−0.76 (m, 3H); ^{13}C NMR δ 160.3, 156.0, 134.6, 129.2, 129.1, 127.8, 102.3, 46.5, 41.5, 29.7, 22.0, 21.9, 13.6. Anal. Calcd for $C_{15}H_{21}ClN_2OS$ (312.86): C, 57.88; H, 6.77; N, 8.96; S, 10.25; Cl, 11.33. Found: C, 57.67; H, 6.55; N, 8.83; S, 10.52; Cl, 11.31.

General Procedure for the Synthesis of 1,5-Dialkyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-ones and 1,5-Dialkyl-3*H*,4*H*-1λ^4,2,6-thiadiazine-3-ones 26a-26k: 1,5-Dimethyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer a*) and 1,5-Dimethyl-3*H*,4*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer b*) (26a). To a solution of 1-benzyl-1,5-dimethyl-3*H*-1λ^6,2,6-thiadiazine-3-one **17a** (1.64 g, 7.0 mmol) in dry DCM was added a solution of TMSCl (1.67 g, 15.4 mmol) in dry DCM over a period of 1 h under a nitrogen atmosphere. After completion of the reaction, the reaction mixture was treated with an excess of a methanolic ammonia solution and concentrated under reduced pressure and the oily residue treated with acetone, at which time ammonium chloride precipitated. Filtration followed by chromatography on silica gel (DCM/methanol = 95/5) gave pure **26a** (770 mg, 76%) as a colorless solid; mp 121 °C (DCM/methanol); ^{1}H NMR δ *tautomer a* 5.16 (s, 1H), 2.29 (s, 3H), 2.08 (s, 3H); *tautomer b* 3.32 (d, J = 20.0 Hz, 1H), 2.99 (s, 3H), 2.80 (d, J = 20.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR δ *tautomer a* 171.0, 163.8, 93.6, 32.0, 25.4; *tautomer b* 182.9, 166.5, 38.6, 36.7, 28.5. C/H−COSY NMR (125.8/500 MHz, $CDCl_3$): 93.6:5.16; 38.6:2.99; 36.7:3.32, 2.80; 32.0:2.79; 28.5:2.36; 25.4:2.08. HRMS calcd for $C_5H_8N_2OS$ 144.0357, found 144.0362. Anal. Calcd for $C_5H_8N_2OS$ (144.20): C, 41.64; H, 5.59; N, 19.43; S, 22.24. Found: C, 41.84; H, 5.49; N, 19.39; S, 21.69.

The following compounds were prepared as described above for **26a** utilizing the appropriate 1,5-dialkyl-1-benzyl-3*H*-1λ^6,2,6-thiadiazine-3-one **17**, **18**, **20**, or **27**.

5-Methyl-1-pentyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer a*) and 5-Methyl-1-pentyl-3*H*,4*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer b*) (26b). Chromatography on silica gel (ethyl acetate/ethanol = 9/1); colorless crystals; yield 86%; mp 75 °C (ethyl acetate/ethanol); ^{1}H NMR δ *tautomer a* 5.12 (s, 1H), 3.22 (pst, J = 7.8 Hz, 2H), 2.06 (s, 3H), 1.62−1.53 (m, 2H), 1.50−1.27 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); *tautomer b* 3.25 (d, J = 20.1 Hz, 1H), 3.17−3.12 (m, 2H), 2.77 (d, J = 20.0 Hz, 1H), 2.33 (s, 3H), 1.95−1.84 (sm, 1H), 1.80−1.68 (sm, 1H), 1.50−1.27 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ *tautomer a* 171.8, 163.6, 94.1, 44.8, 30.4, 25.5, 22.1, 20.6, 13.6; *tautomer b* 182.8, 166.2, 52.7, 36.8, 30.4, 28.6, 22.4, 20.6, 13.6; HRMS calcd for $C_9H_{16}N_2OS$ 200.0983, found 200.0983. Anal. Calcd for $C_9H_{16}N_2OS$ (200.13): C, 53.96; H, 8.05; N, 13.99; S, 16.01. Found: C, 54.14; H, 7.78; N, 13.10; S, 15.90.

1-Cyclohexyl-5-methyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer a*) and 1-Cyclohexyl-5-methyl-3*H*,4*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer b*) (26c): chromatography on silca gel (DCM/methanol = 9/1); colorless crystals; yield 72%; mp 77 °C (diethyl ether); ^{1}H NMR δ *tautomer a* 5.06 (s, 1H), 3.97−3.91 (m, 1H), 2.00 (s, 3H), 2.10−1.13 (m, 10H); *tautomer b* 3.16 (d, J = 20.3 Hz, 1H), 3.10−3.03 (m, 1H), 2.74 (d, J = 20.3 Hz, 1H), 2.27 (s, 3H), 2.10−1.13 (m, 10H); ^{13}C NMR δ *tautomer a* 171.9, 163.9, 94.8, 52.8, 26.8, 25.6, 25.5, 25.4, 25.3, 25.1, 24.7, 24.6, 24.0; *tautomer b* 182.9, 166.4, 62.1, 36.5, 28.6, 26.8, 25.6, 25.4, 25.3, 25.1, 24.7, 24.6, 24.0. Anal. Calcd for $C_{10}H_{16}N_2OS$ (212.32): C, 56.30; H, 7.60; N, 13.20; S, 15.03. Found: C, 56.03; H, 7.50; N, 13.10; S, 14.81.

1-Isobutyl-5-methyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer a*) and 1-Isobutyl-5-methyl-3*H*,4*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer b*) (26d): chromatography on silica gel (DCM/methanol = 95/5); colorless crystals; yield 62%; mp 75 °C (DCM/methanol); ^{1}H NMR δ *tautomer a* 5.09 (s, 1H), 3.15−2.95 (m, 2H), 2.06 (s, 3H), 2.01−1.88 (m, 1H), 1.05 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H); *tautomer b* 3.28 (d, J = 19.9 Hz, 1H), 3.24−3.19 (m, 2H), 2.78 (d, J = 19.9 Hz, 1H), 2.48−2.35 (m, 1H), 2.33 (s, 3H), 1.15 (pst, J = 6.7 Hz, 6H); ^{13}C NMR δ *tautomer a* 171.9, 163.8, 94.0, 53.0, 25.5, 23.9, 22.1, 21.8; *tautomer b* 182.5, 166.4, 63.2, 37.2, 28.6, 23.9, 22.1, 21.8. Anal. Calcd for $C_8H_{14}N_2OS$ (186.28): C, 51.58; H, 7.57; N, 15.04; S, 17.21. Found: C, 51.65; H, 7.32; N, 15.03; S, 17.10.

5-Benzyl-1-methyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (26e). After filtration of ammonium chloride and concentration of the filtrate, the product crystallized upon addition of diethyl ether to give pure **23e** (761 mg, 69%) as a colorless solid: mp 140 °C (diethyl ether); ^{1}H NMR (DMSO-d_6) δ 9.39 (bs, 1H), 7.31−7.18 (m, 5H), 4.94 (s, 1H), 3.50 (d, J = 14.3 Hz, 1H), 3.45 (d, J = 14.1 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.8, 162.6, 138.4, 129.1, 128.4, 126.4, 92.7, 44.6, 31.6; HRMS calcd for $C_{11}H_{12}N_2OS$ 220.067035, found 220.068428. Anal. Calcd for $C_{11}H_{12}N_2OS$ (220.30): C, 59.97; H, 5.49; N, 12.72; S, 14.56. Found: C, 60.03; H, 5.44; N, 12.30; S, 14.51.

5-Benzyl-1-pentyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer a*) and 5-Benzyl-1-pentyl-3*H*,4*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer b*) (26f): yield 79%; mp 107 °C (diethyl ether); ^{1}H NMR (500 MHz) δ *tautomer a* 7.35−7.21 (m, 5H), 5.17 (s, 1H), 3.57 (d, J = 14.2 Hz, 1H), 3.54 (d, J = 14.2 Hz, 1H), 3.23−3.17 (m, 1H), 3.16−3.07 (m, 1H), 1.46−1.17 (m, 6H), 0.85−0.83 (m, 3H); *tautomer b* 7.35−7.21 (m, 5H), 3.83 (d, J = 15.8 Hz, 1H), 3.80 (d, J = 15.8 Hz, 1H), 3.23 (d, J = 20.1 Hz, 1H), 2.93−2.67 (m, 2H), 2.69 (d, J = 20.1 Hz, 1H), 1.46−1.17 (m, 6H), 0.93−0.90 (m, 3H); ^{13}C NMR δ *tautomer a* 173.8, 164.0, 137.7, 129.0, 128.5, 126.6, 94.4, 48.3, 45.6, 30.2, 22.2, 22.1, 13.7; *tautomer b* 184.0, 166.3, 133.1, 129.3, 129.1, 127.9, 52.6, 44.9, 35.1, 30.3, 22.2, 20.4, 13.7. Anal. Calcd for $C_{15}H_{20}N_2OS$ (276.40): C, 65.18; H, 7.29; N, 10.14; S, 11.62. Found: C, 65.07; H, 7.02; N, 10.41; S, 11.62.

5-Benzyl-1-cyclohexyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer a*) and 5-Benzyl-1-cyclohexyl-3*H*,4*H*-1λ^4,2,6-thiadiazine-3-one (*Tautomer b*) (26g): yield 83%; mp 134 °C (acetone/diethyl ether); ^{1}H NMR (500 MHz) δ *tautomer a* 7.35−7.20 (m, 5H), 5.20 (s, 1H), 3.81−3.75 (m, 1H), 3.57 (d, J = 14.0 Hz, 1H), 3.52 (d, J = 14.0 Hz, 1H), 2.14−0.94 (m, 10H); *tautomer b* 7.35−7.20 (m, 5H), 3.83 (d, J = 14.0 Hz, 1H), 3.81 (d, J = 14.0 Hz, 1H), 3.18 (d, J = 20.4 Hz, 1H), 3.18−3.11 (m, 1H), 2.70 (d, J = 20.4 Hz, 1H), 2.14−0.94 (m, 10H); ^{13}C NMR (125.8 MHz) δ *tautomer a* 174.2, 164.2, 138.0, 129.0, 128.4, 126.6, 94.9, 52.6, 45.8, 26.5, 25.4, 25.1, 24.7, 24.6; *tautomer b* 184.2, 166.5, 133.3, 129.3, 129.1, 127.8, 62.3, 48.4, 35.0, 25.4, 25.3, 25.2, 24.8, 24.1. Anal. Calcd for $C_{16}H_{20}N_2OS$ (288.41): C, 66.63; H, 6.99; N, 9.72; S, 11.12. Found: C, 66.71; H, 6.91; N, 9.45; S, 11.11.

1-Pentyl-5-trifluoromethyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one (26h). The filtrate was concentrated until only a few milliliters of solvent remained and treated with pentane, at which time **26h** (865 mg, 64%) solidified: mp 117 °C (acetone/pentane); ^{1}H NMR δ 5.62 (s, 1H), 3.39−3.34 (m, 1H), 3.25−

3.20 (m, 1H), 1.64−1.60 (m, 2H), 1.43−1.31 (m, 4H), 0.92−0.88 (pst, 3H); ^{13}C NMR (125.8 MHz) δ 163.6, 158.7 (q, J = 33.6 Hz), 120.2 (q, J = 277.4 Hz), 93.4 (psd, J = 2.8 Hz), 44.9, 30.1, 22.1, 13.5; HRMS calcd for $C_9H_{13}N_2OS$ 254.0701, found 254.0654. Anal. Calcd for $C_9H_{13}F_3N_2OS$ (254.28): C, 42.51; H, 5.15; N, 11.02; S, 12.61. Found: C, 43.04; H, 5.23; N, 10.78; S, 13.04.

1-Cyclohexyl-5-trifluoromethyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one (26i): yield 63%; mp 141 °C (acetone/pentane); ^{1}H NMR δ 5.60 (s, 1H), 4.08−3.98 (m, 1H), 1.94−1.87 (m, 4H), 1.72 (m, 1H), 1.43−1.25 (m, 5H); ^{13}C NMR (125.8 MHz) δ 163.9, 158.9 (q, J = 33.6 Hz), 120.2 (q, J = 277.4 Hz), 94.0 (psd, J = 2.9 Hz), 53.5, 26.5, 25.1, 25.0, 24.6, 24.4; UV−vis (methanol) λ_{max} (ϵ) 337 nm (4096), 233 nm (4043). Anal. Calcd for $C_{10}H_{13}F_3N_2OS$ (266.29): C, 45.10; H, 4.92; N, 10.52; S, 12.04. Found: C, 45.05; H, 5.05; N, 10.38; S, 12.28.

1-(4-Chlorobutyl)-5-methyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one (*Tautomer a*) and 1-(4-Chlorobutyl)-5-methyl-3*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one (*Tautomer b*) (26j). Ammonium chloride was removed by filtration and the filtrate concentrated in vacuo to give pure **26j** after column chromatography on silica gel (ethyl acetate/ethanol = 5/1) (763 mg, 69%) as a colorless solid: mp 65 °C (ethyl acetate/ethanol); ^{1}H NMR (500 MHz) δ *tautomer a* 5.14 (s, 1H), 3.62−3.56 (m, 2H), 3.54 (t, J = 6.2 Hz, 2H), 2.01 (s, 3H), 2.05−1.74 (m, 4H); *tautomer b* 3.28 (d, J = 20.0 Hz, 1H), 3.31−3.16 (m, 4H), 2.78 (d, J = 20.0 Hz, 1H), 2.35 (s, 3H), 2.05−1.74 (m, 4H); ^{13}C NMR (125.8 MHz) δ *tautomer a* 171.7, 163.7, 94.3, 43.9, 43.8, 30.9, 25.5, 20.3; *tautomer b* 183.3, 166.1, 51.6, 43.8, 36.7, 30.7, 28.7, 18.5. C/H−COSY NMR (125.8/500 MHz): 94.3:5.14; 51.6:3.31−3.16; 43.9, 43.8:3.62−3.56, 3.54; 36.7:3.28, 2.78; 30.9, 30.7: 2.05−1.74; 28.7:2.35; 25.5:2.01; 20.3:2.05−1.74; 18.5:2.05−1.74. Anal. Calcd for $C_8H_{13}ClN_2OS$ (220.72): C, 43.53; H, 5.94; N, 12.69; S, 14.53; Cl, 16.06. Found: C, 43.92; H, 5.89; N, 12.20; S, 14.48; Cl, 15.94.

5-Benzyl-1-(4-chlorobutyl)-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one (26k) was obtained after column chromatography on silica gel (ethyl acetate/ethanol = 9/1) as a colorless solid: yield 37%; mp 137 °C (ethyl acetate/hexane); ^{1}H NMR (DMSO-d_6) δ 7.30−7.19 (m, 5H), 4.98 (s, 1H), 3.55−3.51 (sm, 2H), 3.49 (d, J = 14.1 Hz, 1H), 3.43 (d, J = 14.0 Hz, 1H), 3.20 (ddd, J = 12.4 Hz, 6.1 Hz, 9.2 Hz, 1H), 2.97 (ddd, 1H), 1.71−1.63 (m, 2H), 1.50−1.44 (m, 1H), 1.37−1.32 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 171.9, 162.0, 138.2, 128.9, 128.0, 126.1, 44.5, 44.4, 43.0, 30.2, 19.8. C/H−COSY NMR (125.8/500 MHz, DMSO-d_6): 128.9, 128.0, 126.1:7.30−7.20; 93.1:4.97; 44.5, 44.4:3.54, 3.49, 3.43; 43.0:3.25−3.15, 3.00−2.93; 30.2:1.71−1.63; 19.8:1.50−1.44, 1.37−1.32; 25.5:2.01; 20.3:2.05−1.74. Anal. Calcd for $C_{14}H_{15}ClN_2OS$ (296.82): C, 56.65; H, 5.77; N, 9.44; S, 10.80; Cl, 11.94. Found: C, 56.53; H, 5.68; N, 9.12; S, 10.99; Cl, 11.88.

Spiro-5-benzyl-3*H*-1λ⁶,2,6-thiadiazine-1,1′λ⁶-tetrahydrothiophen-3-one (27b). Colorless crystals after recrystallization from ethyl acetate, yield 61%; mp 174 °C (ethyl acetate); ^{1}H NMR (CD_3CN) δ 7.33−7.222 (m, 5H), 4.82 (s, 1H), 3.47 (s, 2H), 3.42−3.27 (m, 4H), 2.27−2.19 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 166.7, 164.2, 137.5, 128.8, 128.1, 126.3, 95.3, 57.6, 43.8, 22.3. Anal. Calcd for $C_{14}H_{16}N_2OS$ (260.36): C, 64.58; H, 6.20; N, 10.76; S, 12.32. Found: C, 64.54; H, 6.23; N, 10.50; S, 12.28.

General Procedure for the Synthesis of 1,5-Dialkyl-3-alkoxy-1λ⁴,2,6-thiadiazines 29a-29f: 3-Ethoxy-1,5-dimethyl-1λ⁴,2,6-thiadiazine (29a). To a solution of triethyloxonium tetrafluoroborate (712 mg, 3.75 mmol), carefully washed prior to use with dry diethyl ether to remove traces of tetrafluoroboronic acid, in dry DCM, was added a solution of 1,5-dimethyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one **26a** (360 mg, 2.5 mmol) in dry DCM over a period of 60 min. After completion of the reaction, the reaction mixture was quenched with saturated sodium carbonate solution and stirred for an additional 30 min. The organic layer was separated, washed with brine, and dried over sodium sulfate. Column chromatography on silica gel (hexane/ethyl acetate = 2/1) furnished **29a** as a slightly yellow oil (320 mg, 74%): ^{1}H NMR δ 5.16 (s, 1H), 4.25−4.17 (sm, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 1.31 (pst, J = 7.0 Hz, 3H); ^{13}C NMR (125.8 MHz) δ 172.6, 172.2, 86.8, 61.7, 28.8, 25.2, 14.4; HRMS calcd for $C_7H_{12}N_2OS$ 172.0670, found 172.0673.

In analogy to the synthesis described for **26a**, **3-ethoxy-5-methyl-1-pentyl-1λ⁴,2,6-thiadiazine (29b)** was obtained after column chromatography on silica gel (chloroform/ethyl acetate = 3/1) as a slightly yellow oil utilizing 5-methyl-1-pentyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one **26b (method a)**: yield 70%; ^{1}H NMR δ 5.12 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.05−2.86 (m, 2H), 2.04 (s, 3H), 1.56−1.48 (m, 2H), 1.42−1.28 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.0, 172.3, 87.2, 61.6, 42.1, 30.6, 25.2, 22.2, 22.0, 14.4, 13.7. C/H−COSY NMR (125.8/500 MHz, $CDCl_3$): 87.2: 5.12; 61.6:4.22; 42.1:3.05−2.86; 30.6:1.42−1.28; 25.2:2.04; 22.2, 22.0:1.56−1.48, 1.42−1.28; 14.4:1.31; 13.7:0.89. HRMS calcd for $C_{11}H_{20}N_2OS$ 228.1296, found 228.1309. Anal. Calcd for $C_{11}H_{20}N_2OS$ 228.36: C, 57.85; H, 8.83; N, 12.27; S, 14.04. Found: C, 57.47; H, 8.48; N, 12.12; S, 14.01. **Method b.** To a solution of triethyloxonium tetrafluoroborate (855 mg, 4.5 mmol), treated as described above, in dry DCM, was added a solution of 1-benzyl-5-methyl-1-pentyl-3*H*-1λ⁶,2,6-thiadiazine-3-one **17d** (871 mg, 3.0 mmol) over a period of 60 min. After stirring for an additional 16 h at room temperature, the reaction mixture was quenched with saturated sodium carbonate solution and stirred for an additional 30 min. The organic layer was separated, washed with brine, and dried over sodium sulfate. Column chromatography on silica gel (chloroform/ethyl acetate = 3/1) furnished **29b** as a slightly yellow oil. Analytical data were identical to those obtained by following method a.

In analogy to the synthesis described for **29a**, **5-benzyl-3-methoxy-1-pentyl-1λ⁴,2,6-thiadiazine (29c)** was obtained utilizing trimethyloxonium tetrafluoroborate and 5-benzyl-1-pentyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one **26f** after column chromatography on silica gel (hexane/ethyl acetate = 9/1) as a slightly yellow oil: yield 48%; ^{1}H NMR δ 7.29−7.26 (m, 5H), 5.13 (s, 1H), 3.76 (s, 3H), 3.59 (d, J = 14.3 Hz, 1H), 3.54 (d, J = 14.0 Hz, 1H), 3.04−3.00 (m, 1H), 2.67−2.61 (m, 1H), 1.41−1.21 (m, 6H), 0.88−0.83 (m, 3H); ^{13}C NMR δ 175.0, 173.0, 137.9, 129.0, 128.4, 126.5, 87.2, 53.1, 45.4, 42.2, 30.5, 22.2, 21.7, 13.7. C/H−COSY NMR (125.8/500 MHz, $CDCl_3$): 129.0, 128.4: 7.29−7.26; 87.2:5.13; 53.1:3.76; 45.4:3.59−3.54; 42.2:3.04−3.00, 2.67−2.61; 30.5, 22.2, 21.7:1.41−1.21; 13.7:0.88−0.83. HRMS calcd for $C_{16}H_{22}N_2OS$ 290.1453, found 290.1448. Anal. Calcd for $C_{16}H_{22}N_2OS$ (290.43): C, 66.16; H, 7.64; N, 9.65; S, 11.04. Found: C, 65.79; H, 7.53; N, 9.60; S, 11.11.

5-Benzyl-1-cyclohexyl-3-methoxy-1λ⁴,2,6-thiadiazine (29d) was obtained after column chromatography on silica gel (hexane/ethyl acetate = 9/1) as a slightly yellow oil utilizing 5-benzyl-1-cyclohexyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one **26g**: yield 47%; ^{1}H NMR δ 7.31−7.21 (m, 5H), 5.15 (s, 1H), 3.78 (s, 3H), 3.74−3.65 (m, 1H), 3.58 (d, J = 14.2 Hz, 1H), 3.54 (d, J = 14.2 Hz, 1H), 1.78−1.50 (m, 4H), 1.25−0.95 (m, 6H); ^{13}C NMR δ 175.4, 172.9, 138.2, 129.0, 128.3, 126.5, 87.8, 53.1, 50.5, 45.5, 25.6, 25.5, 24.8, 24.6. C/H−COSY NMR (125.8/500 MHz, $CDCl_3$): 129.0, 128.3:7.31−7.25; 87.8:5.15; 53.1:3.78; 50.5: 3.74−3.65; 45.5:3.58, 3.54; 25.6, 25.5, 24.8, 24.6:1.78−1.50, 1.25−0.95. Anal. Calcd for $C_{17}H_{22}N_2OS$ (302.44): C, 67.51; H, 7.33; N, 9.26; S, 10.60. Found: C, 67.55; H, 7.28; N, 9.25; S, 10.58.

5-Benzyl-1-cyclohexyl-3-ethoxy-1λ⁴,2,6-thiadiazine (29e). 29e was obtained according to the procedure described for **29a** after column chromatography on silica gel (hexane/ethyl acetate = 2/1) (1.36 g, 79%) as a slighly yellow oil: ^{1}H NMR δ 7.28−7.20 (m, 5H), 5.14 (s, 1H), 4.20 (q, J = 7.14 Hz, 2H), 3.75−3.65 (m, 1H), 3.57 (d, J = 14.0 Hz, 1H), 3.54 (d, J = 13.8 Hz, 1H), 1.82−1.49 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H), 1.22−0.99 (m, 6H); ^{13}C NMR δ 175.3, 172.4, 138.2, 129.0, 128.4, 126.4, 88.1, 61.8, 50.4, 45.5, 25.6, 25.5, 24.6, 14.5; HRMS calcd for $C_{18}H_{24}N_2OS$: 316.160935, found 316.159286. Anal. Calcd for $C_{18}H_{24}N_2OS$ (316.46): C, 68.31; H, 7.64; N, 8.85; S, 10.13. Found: C, 68.62; H, 7.62; N, 8.75; S, 9.66.

General Procedure for the Synthesis of 1,5-Dialkyl-2-alkyl-3*H*-1λ^4,2,6-thiadiazine-3-ones 30a−d: 2-Ethyl-1,5-dimethyl-3*H*-1λ^4,2,6-thiadiazine-3-one (30a). To a solution of 1,5-dimethyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one **26a** (415 mg, 2.88 mmol) in dry DCM was added a commercially available solution of triethyloxonium tetrafluoroborate (1 M, 4.32 mL) over a period of 60 min. After completion of the reaction, the reaction mixture was quenched with saturated sodium carbonate solution and stirred for an additional 30 min. The organic layer was separated, washed with brine, and dried over sodium sulfate. Column chromatography on silica gel (ethyl acetate/ethanol = 9/1) gave rise to **30a** (171 mg, 40%) as a colorless oil: ^{1}H NMR δ 5.23 (s, 1H), 3.79 (pssex, J = 14.3 Hz, 7.2 Hz, 1H), 3.49 (pssex, J = 14.3 Hz, 7.2 Hz, 1H), 2.68 (s, 3H), 2.04 (d, J = 0.6 Hz, 3H), 1.28 (pst, J = 7.1 Hz, 3H); ^{13}C NMR δ 168.4, 160.7, 96.0, 40.1, 30.7, 24.7, 14.7; HRMS calcd for $C_7H_{12}N_2OS$ 172.0670, found 172.0675. Anal. Calcd for $C_7H_{12}N_2OS$ (172.26): C, 48.81; H, 7.02; N, 16.27; S, 18.62. Found: C, 47.89; H, 7.04; N, 15.71; S, 18.44

In analogy to the synthesis described for **30a**, **2-ethyl-5-methyl-1-pentyl-3*H*-1λ^4,2,6-thiadiazine-3-one (30b)** was obtained after column chromatography on silica gel (ethyl acetate) as a colorless oil utilizing 5-methyl-1-pentyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one **26**: yield 29%; ^{1}H NMR (CD_3OD) δ 5.20 (s, 1H), 3.89 (pssex, J = 14.2 Hz, 7.1 Hz, 1H), 3.74 (ddd, J = 12.4 Hz, 7.1 Hz, 8.3 Hz, 1H), 3.42 (pssex, J = 14.2 Hz, 7.1 Hz, 1H), 3.01 (ddd, J = 12.4 Hz, 7.1 Hz, 8.3 Hz, 1H), 2.01 (d, J = 0.7 Hz, 3H), 1.62−1.51 (m, 2H), 1.44−1.27 (m, 4H), 1.23 (pst, J = 7.2 Hz, 3H), 0.92 (pst, J = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD) δ 171.2, 163.9, 97.7, 44.9, 42.9, 31.7, 25.1, 24.4, 23.4, 15.5, 14.3. C/H−COSY NMR (125.8/500 MHz, CD_3OD): 97.7:5.20; 44.9:3.74, 3.01; 42.9:3.89, 3.42; 31.7:1.44−1.27; 25.1:2.01; 24.4, 23.4:1.62−1.51, 1.44−1.27; 15.5:1.23; 14.3:0.92. H/H−COSY (500 MHz, CD_3OD): 5.20:2.01; 3.89:3.42, 1.23; 3.74:3.01, 1.62−1.51. HRMS calcd for $C_{11}H_{20}N_2OS$ 228.1296, found 228.1307.

In analogy to the synthesis described for **30a**, **5-benzyl-2-methyl-1-pentyl-3*H*-1λ^4,2,6-thiadiazine-3-one (30c)** was obtained after column chromatography on silica gel (chloroform/ethyl acetate = 2/1) as a colorless solid utilizing trimethyloxonium tetrafluoroborate and 5-benzyl-1-pentyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one **26f**: yield 21%; mp 62 °C (ethyl acetate/chloroform); ^{1}H NMR δ 7.31−7.22 (m, 5H), 5.31 (s, 1H), 3.55 (d, J = 14.3 Hz, 1H), 3.50 (d, J = 14.0 Hz, 1H), 3.38−3.33 (m, 1H), 3.13 (s, 3H), 2.83−2.78 (m, 1H), 1.35−1.18 (m, 6H), 0.87−0.83 (m, 3H); ^{13}C NMR δ 171.0, 162.0, 137.8, 129.0, 128.4, 126.6, 96.9, 45.1, 43.2, 32.6, 30.4, 22.6, 22.1, 13.6. C/H−COSY NMR (125.8/500 MHz, $CDCl_3$): 129.0, 128.4:7.31−7.22; 96.9:5.31; 45.1:3.55, 3.50; 43.2:3.38−3.33, 2.83−2.78; 32.6:3.13; 30.4, 22.6, 22.1:1.35−1.18; 13.6:0.87−0.83. HRMS calcd for $C_{16}H_{22}N_2OS$ 290.145285, found 290.148926. Anal. Calcd for $C_{16}H_{22}N_2OS$ (290.43): C, 66.16; H, 7.64; N, 9.65; S, 11.04. Found: C, 66.56; H, 7.44; N, 9.55; S, 10.91.

In analogy to the synthesis described for **30c**, **5-benzyl-1-cyclohexyl-2-methyl-3*H*-1λ^4,2,6-thiadiazine-3-one (30d)** was obtained after column chromatography on silica gel (chloroform/ethyl acetate = 2/1) as a colorless solid utilizing 5-benzyl-1-cyclohexyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one **26g**: yield 15%; mp 95 °C (ethyl acetate/chloroform); ^{1}H NMR δ 7.29−7.20 (m, 5H), 5.33 (s, 1H), 4.05−3.92 (m, 1H), 3.55 (d, J = 13.9 Hz, 1H), 3.49 (d, J = 13.9 Hz, 1H), 3.17 (s, 3H), 1.79−1.57 (m, 4H), 1.28−0.85 (m, 6H); ^{13}C NMR δ 171.8, 162.1, 138.1, 129.0, 128.4, 126.5, 97.3, 53.2, 45.2, 34.7, 27.0, 26.1, 25.0, 24.8, 24.5; HRMS calcd for $C_{17}H_{22}N_2OS$ 302.145285, found 302.145378. Anal. Calcd for $C_{17}H_{22}N_2OS$ (302.44): C, 67.51; H, 7.33; N, 9.26; S, 10.60. Found: C, 67.65; H, 7.12; N, 9.34; S, 10.37.

1-Cyclohexyl-3-ethoxy-5-trifluoromethyl-1λ^4,2,6-thiadiazine (29f) and 1-Cyclohexyl-2-ethyl-5-trifluoromethyl-3*H*-1λ^4,2,6-thiadiazine-3-one (30e): Method a. To a solution of triethyloxonium tetrafluoroborate (570 mg, 3.0 mmol), carefully washed prior to use with dry diethyl ether to remove traces of tetrafluoroboronic acid, in dry DCM, was added a solution of 1-cyclohexyl-5-trifluoromethyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one **26i** (533 mg, 2.0 mmol) over a period of 30 min, and the mixture was stirred for 16 h; then the reaction was quenched with saturated sodium carbonate solution and the mixture stirred for an additional 30 min. The organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated in vacuo. Column chromatography on silica gel (hexane/ethyl acetate = 9/1) gave rise to **29f** (142 mg, 24%) as a yellow solid and **30f** (40 mg, 7%) as a colorless solid. **Method b.** To a solution of 1-cyclohexyl-5-trifluoromethyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one **26i** (533 mg, 2.0 mmol) in dry DCM was added *N*-ethyl-diisopropylamine (0.34 mL, 2.0 mmol), and the mixture was stirred for 5 min followed by the addition of a solution of triethyloxonium tetrafluoroborate (570 mg, 3.0 mmol) in dry DCM. After completion of the reaction, the reaction was quenched with saturated sodium carbonate solution and the mixture stirred for an additional 30 min. The organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated in vacuo. Column chromatography on silica gel (hexane/ethyl acetate = 9/1) gave rise to **29f** (104 mg, 18%) as a yellow solid and **30e** (185 mg, 31%) as a colorless solid.

29f: mp 27 °C (hexane/ethyl acetate); ^{1}H NMR (500 MHz) δ 5.51 (s, 1H), 4.31−4.25 (m, 2H), 3.87−3.83 (m, 1H), 1.91−1.85 (m, 4H), 1.69−1.65 (m, 1H), 1.34 (pst, J = 7.1 Hz, 3H), 1.29−1.23 (m, 5H); ^{13}C NMR (125.8 MHz) δ 172.8, 160.9 (q, J = 33.6 Hz), 120.2 (q, J = 277.4 Hz), 86.7, 62.7, 52.1, 25.5, 25.4, 25.1, 24.7, 24.5; UV−vis (methanol) λ_{max} (ϵ) 373 nm (2265), 231 nm (6912); HRMS calcd for $C_{12}H_{17}F_3N_2OS$ 294.1014, found 294.1007. Anal. Calcd for $C_{12}H_{17}F_3N_2OS$ (294.35): C, 48.96; H, 5.82; N, 9.52; S, 10.89. Found: C, 49.35; H, 5.99; N, 9.44; S, 11.00.

30e: mp 82 °C (ethyl acetate); ^{1}H NMR (500 MHz) δ 5.71 (s, 1H), 4.21−4.12 (m, 2H), 3.24−3.17 (m, 1H), 1.94−1.74 (m, 4H), 1.72−1.70 (m, 1H), 1.41−1.22 (m, 5H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125.8 MHz) δ 161.0, 156.5 (q, J = 33.6 Hz), 120.4 (q, J = 277.4 Hz), 96.9 (psd, J = 2.9 Hz), 53.1, 43.6, 27.2, 25.9, 24.9, 24.8, 24.5, 14.7; UV−vis (methanol) λ_{max} (ϵ) 335 nm (4441), 226 nm (3647). Anal. Calcd for $C_{12}H_{17}F_3N_2OS$ (294.35): C, 48.96; H, 5.82; N, 9.52; S, 10.89. Found: C, 49.10; H, 5.85; N, 9.45; S, 11.16.

(1-Cyclohexyl-5-trifluoromethyl-1λ^4,2,6-thiadiazine-3-yl)-4-toluenesulfonate (31a) and 1-Cyclohexyl-2-(4-toluenesulfonyl)-5-trifluoromethyl-3*H*-1λ^4,2,6-thiadiazine-3-one (32a). To a stirred solution of 4-toluenesulfonic anhydride (849 mg, 2.6 mmol) in dry DCM was added a solution of 1-cyclohexyl-5-trifluoromethyl-2*H*,3*H*-1λ^4,2,6-thiadiazine-3-one **26i** (533 mg, 2.0 mmol) in dry DCM at room temperature, and the mixture was stirred for 15 h. After addition of basic alumina, the resulting mixture was stirred for 5 min, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/ethyl acetate = 9/1) provided **31a** (199 mg, 24%) as a yellow solid and **32a** (40 mg, 5%) as a colorless solid.

31a: mp 74 °C (hexane/ethyl acetate); ^{1}H NMR (500 MHz) δ 7.90 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 5.53 (s, 1H), 4.01−4.00 (m, 1H), 2.47 (s, 3H), 1.87−1.83 (m, 4H), 1.68−1.66 (m, 1H), 1.30−1.24 (m, 5H); ^{13}C NMR (125.8 MHz) δ 168.9, 164.3 (q, J = 34.6 Hz), 146.0, 133.5, 129.7, 128.9, 119.5 (q, J = 278.3 Hz), 85.5 (psd, J = 3.8 Hz), 52.5, 25.3, 24.8, 24.5, 24.4, 24.2, 21.8; UV−vis (methanol) λ_{max} (ϵ) 396 nm (2143), 229 nm (14160). Anal. Calcd for $C_{17}H_{19}F_3N_2O_3S_2$ (420.47): C, 48.56; H, 4.55; N, 6.66; S, 15.25. Found: C, 48.69; H, 4.79; N, 6.78; S, 15.26.

32a: mp 145 °C (hexane/ethyl acetate); ^{1}H NMR (500 MHz) δ 7.90 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 5.53 (s, 1H), 4.24−4.18 (m, 1H), 2.45 (s, 3H), 2.13−2.02 (m, 1H), 2.00−1.91 (m, 3H), 1.74−1.71 (m, 1H), 1.60−1.50 (m, 2 H), 1.39−1.31 (m, 3 H); ^{13}C NMR (125.8 MHz) δ 157.4 (q, J = 33.8 Hz), 157.0, 146.5, 134.0, 129.9, 129.1, 119.9 (q, J = 277.4 Hz), 96.0 (psd, J = 3.8 Hz), 55.4, 27.7, 25.5, 24.9, 24.8, 24.7, 21.8; HRMS calcd for $C_{17}H_{19}F_3N_2O_3S_2$ 420.0789, found 420.0785. Anal.

Calcd for $C_{17}H_{19}F_3N_2O_3S_2$ (420.47): C, 48.56; H, 4.55; N, 6.66. Found: C, 48.41; H, 4.46; N, 7.05.

(5-Benzyl-1-pentyl-1λ⁴,2,6-thiadiazine-3-yl)-4-toluenesulfonate (31b). To a stirred solution of 4-toluenesulfonic anhydride (849 mg, 2.6 mmol) in dry DCM was added a solution of 5-benzyl-1-pentyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one **26f** (553 mg, 2.0 mmol) in dry DCM at room temperature, and the mixture was stirred for 3 h. After addition of basic alumina, the resulting mixture was stirred for 5 min, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) furnished **31b** (226 mg, 25%) as a yellow oil: ^{1}H NMR (500 MHz) δ 7.84 (d, J = 8.3 Hz, 2H), 7.32−7.21 (m, 5H), 7.20 (d, J = 8.2 Hz, 2H), 5.24 (s, 1H), 3.62 (d, J = 14.4 Hz, 1H), 3.57 (d, J = 14.2 Hz, 1H), 2.87 (pst, 2H), 2.44 (s, 3H), 1.42−1.23 (m, 6H), 0.88−0.86 (m, 3H); ^{13}C NMR (125.8 MHz) δ 179.3, 167.9, 145.3, 136.7, 134.0, 129.6, 129.0, 128.64, 128.62, 126.9, 88.1, 45.4, 41.5, 30.5, 22.1, 21.7, 20.8, 13.7; HRMS calcd for $C_{22}H_{26}N_2O_3S_2$ 430.1385, found 430.1388. Anal. Calcd for $C_{22}H_{26}N_2O_3S_2$ (430.58): C, 61.36; H, 6.09; N, 6.51. Found: C, 62.07; H, 6.34; N, 6.38.

General Procedure for the Synthesis of (1-Alkyl-5-trifluoromethyl-1λ⁴,2,6-thiadiazine-3-yl)-methanesulfonates 31c and 31d and (1-Alkyl-5-benzyl-1λ⁴,2,6-thiadiazine-3-yl)-methanesulfonates 31e and 31f: (1-Pentyl-5-trifluoromethyl-1λ⁴,2,6-thiadiazine-3-yl)-methanesulfonate (31c). To a stirred solution of methanesulfonic anhydride (1.13 g, 6.5 mmol) in dry DCM was added a solution of 1-pentyl-5-trifluoromethyl-2*H*,3*H*-1λ⁴,2,6-thiadiazine-3-one **26h** (1.27 g, 5.0 mmol) in dry DCM at room temperature, and the mixture was stirred for 12 h. After addition of basic alumina, the resulting mixture was stirred for 5 min, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/ethyl acetate = 8/1) furnished **31c** as a yellow oil (330 mg, 20%): ^{1}H NMR δ 5.64 (s, 1H), 3.45 (s, 3H), 3.31−3.24 (m, 1H), 3.17−3.10 (m, 1H), 1.70−1.60 (m, 2H), 1.44−1.31 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 169.5, 1164.8 (q, J = 35.3 Hz), 119.4 (q, J = 277.5 Hz), 85.5 (q, J = 2.3 Hz), 42.2, 41.9, 30.3, 22.0, 20.5, 13.6. C/H−COSY NMR (125.8:500 MHz, $CDCl_3$): 88.5:5.64; 42.2:3.45; 41.9:3.31−3.24, 3.17−3.10; 30.3, 22.0:1.44−1.31; 20.5:1.70−1.60; 13.6:0.91. Anal. Calcd for $C_{10}H_{15}F_3N_2O_3S_2$ (332.37): C, 36.13; H, 4.55; N, 8.43; S, 19.29. Found: C, 36.27; H, 4.82; N, 8.47; S, 19.22.

Analogously, **(1-cyclohexyl-5-trifluoromethyl-1λ⁴,2,6-thiadiazine-3-yl)-methanesulfonate (31d)** was prepared utilizing **26i**. Column chromatography (hexane/ethyl acetate = 9/1) afforded **31d** as a yellow oil: yield 37%; mp 49 °C (hexane/ethyl acetate); ^{1}H NMR (500 MHz) δ 5.61 (s, 1H), 4.18−4.13 (m, 1H), 3.45 (s, 3H), 2.08−2.05 (m, 1H), 1.91−1.86 (m, 3H), 1.69−1.67 (m, 1H), 1.37−1.26 (m, 5H); ^{13}C NMR (125.8 MHz) δ 169.3, 164.9 (q, J = 34.5 Hz), 119.4 (q, J = 278.3 Hz), 85.8 (q, J = 2.9 Hz), 52.2, 42.0, 25.3, 24.8, 24.4, 24.4, 24.2; UV−vis (methanol) λ_{max} (ϵ) 396 nm (4207). Anal. Calcd for $C_{11}H_{15}F_3N_2O_3S_2$ (344.38): C, 38.36; H, 4.39; N, 8.14; S, 18.62. Found: C, 38.62; H, 4.49; N, 8.11; S, 18.56.

Analogously, **(5-benzyl-1-cyclohexyl-1λ⁴,2,6-thiadiazine-3-yl)-methanesulfonate (31e)** was prepared utilizing **26g**. The reaction was completed after 3 h at room temperature. Column chromatography (hexane/ethyl acetate = 5/1) afforded **31e** as yellow crystals: yield 41%; mp 114 °C (hexane/ethyl acetate); ^{1}H NMR (500 MHz) δ 7.32−7.22 (m, 5H), 5.29 (s, 1H), 3.97−3.92 (m, 1H), 3.67 (d, J = 14.2 Hz, 1H), 3.62 (d, J = 14.0 Hz, 1H), 3.40 (s, 3H), 1.97−1.96 (m, 1H), 1.79−1.71 (m, 2H), 1.62−1.59 (m, 2H), 1.28−1.07 (m, 5H); ^{13}C NMR (125.8 MHz) δ 180.1, 168.0, 136.8, 129.0, 128.6, 127.0, 88.9, 50.6, 45.5, 41.9, 25.5, 25.0, 24.8, 24.5, 24.5. Anal. Calcd for $C_{17}H_{22}N_2O_3S_2$ (366.50): C, 55.71; H, 6.05; N, 7.65; S, 17.50. Found: C, 55.69; H, 5.90; N, 7.70; S, 17.34.

Analogous to **31e**, **(5-benzyl-1-pentyl-1λ⁴,2,6-thiadiazine-3-yl)-methanesulfonate (31f)** was prepared utilizing **26f**. Column chromatography (hexane/ethyl acetate = 5/1) furnished **31f** as a yellow oil: yield 38%; ^{1}H NMR (500 MHz) δ 7.33−7.22 (m, 5H), 5.29 (s, 1H), 3.67 (d, J = 14.2 Hz, 1H), 3.62 (d, J = 14.2 Hz, 1H), 3.39 (s, 3H), 3.08−3.02 (m, 1H), 2.98−2.92 (m, 1H), 1.60−1.42 (m, 2H), 1.33−1.24 (m, 4H), 0.88−0.85 (pst, 3H); ^{13}C NMR (125.8 MHz) δ 179.9, 168.0, 136.6, 129.0, 128.7, 127.0, 88.4, 45.4, 41.9, 41.5, 30.4, 22.1, 20.8, 13.7. C/H−COSY NMR (125.8/500 MHz): 129.0, 128.7, 127.0: 7.33−7.22; 88.4:5.29; 45.4:3.67, 3.62; 41.9:3.39; 41.5:3.08−3.02, 2.98−2.92; 30.4, 22.1:1.33−1.24; 20.8:1.60−1.42; 13.7:0.88−0.85. Anal. Calcd for $C_{16}H_{22}N_2O_3S_2$ (354.49): C, 54.21; H, 6.26; N, 7.90; S, 18.09. Found: C, 54.39; H, 6.24; N, 7.66; S, 17.56.

General Procedure for the Synthesis of 1,5-Dialkyl-3-amino-Substituted 1λ⁴,2,6-Thiadiazines 5a,b and 5d−f: 3-Benzylamino-1-pentyl-5-trifluoromethyl-1λ⁴,2,6-thiadiazine (5a). A solution of the corresponding mesylate (**31c**) in dry DCM and an excess of the corresponding amine (benzylamine) were refluxed under a nitrogen atmosphere. After completion of the reaction (monitored by TLC), the solvent was removed in vacuo and the oily residue purified by column chromatography (hexane/ethyl acetate = 7/1) on silica to provide **5a** as slightly yellow crystals: yield 61%; mp 79 °C (hexane); ^{1}H NMR (DMSO-d_6) δ 8.27 (s, 0.5H), 8.24 (pst, J = 5.7 Hz, 0.5H), 7.35−7.23 (m, 5H), 5.59 (s, 1H), 4.52 (dd, J = 15.1 Hz, 5.7 Hz, 1H), 4.37 (dd, J = 15.1 Hz, 5.7 Hz, 1H), 2.91−2.83 (sm, 2H), 1.39−1.31 (m, 2H), 1.30−1.20 (m, 4H), 0.84−0.81 (pst, 3H); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 163.8, 154.6 (q, J = 32.6 Hz), 138.5, 128.0, 127.2, 126.7, 120.6 (q, J = 277.0 Hz), 85.2 (psd, J = 2.9 Hz), 43.5, 42.8, 29.7, 21.4, 21.3, 13.3. C/H−COSY NMR (125.8:500 MHz, DMSO-d_6): 128.0, 127.2, 126.7:7.35−7.23; 85.2:5.59; 43.5:4.52, 4.37; 42.8:2.91−2.83; 29.7:1.30−1.20; 21.4, 21.3:1.39−1.31, 1.30−1.22; 13.3:0.84−0.81. Anal. Calcd for $C_{16}H_{20}F_3N_3S$ (343.41): C, 55.96; H, 5.87; N, 12.24; S, 9.34. Found: C, 55.99; H, 5.88; N, 12.22; S, 9.50.

Analogous to **5a**, **3-benzylamino-1-cyclohexyl-5-trifluoromethyl-1λ⁴,2,6-thiadiazine (5b)** was prepared utilizing **31d** and benzylamine. Column chromatography (hexane/ethyl acetate = 7/1) afforded **5b** as slightly yellow crystals: yield 64%; mp 187 °C (hexane); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (t, J = 5.7 Hz, 1H), 7.33−7.22 (m, 5H), 5.56 (s, 1H), 4.54 (dd, J = 15.4 Hz, 5.7 Hz, 1H), 4.37 (dd, J = 15.1 Hz, 5.9 Hz, 1H), 3.55−33.50 (m, 1H), 1.70−1.48 (m, 5H), 1.20−1.05 (m, 5H); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 163.6, 154.9 (q, J = 31.7), 138.6, 128.0, 127.1, 126.7, 120.6 (q, J = 276.4), 85.8, 52.3, 43.5, 25.5, 24.8, 24.7, 24.1, 24.0; UV−vis (methanol) λ_{max} (ϵ) 356 nm (4626), 248 nm (11281). Anal. Calcd for $C_{17}H_{20}F_3N_3S$ (355.42): C, 57.45; H, 5.667; N, 11.82; S, 9.02. Found: C, 57.48; H, 5.68; N, 11.87; S, 9.34.

Analogous to **5a**, **(*R*)-1-cyclohexyl-3-[(*S*)-1-phenylethylamino]-5-trifluoromethyl-1λ⁴,2,6-thiadiazine** and **(*S*)-1-cyclohexyl-3-[(*S*)-1-phenylethylamino]-5-trifluoromethyl-1λ⁴,2,6-thiadiazine (5d)** were prepared utilizing **31d** and *S*-1-phenylethylamine. Column chromatography (hexanes/ethyl acetate = 8/1) gave rise to **5d** as yellow crystals: yield 39%; mixture of diastereoisomers. A sample (230 mg) of the diastereoisomers was separated by column chromatography (45 cm × 4 cm) on silica gel (40−63 ASTM mesh) with hexane/ethyl acetate = 9/1 to give rise to diastereomer a (75 mg, 33%), diastereomer b (80 mg, 35%), and 40 mg (17%) of mixed fractions.

Diastereomer a: mp 49 °C (hexane/ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 8.18 (d, J = 7.9 Hz, 1H), 7.33−7.19 (m, 5H), 5.58 (s, 1H), 5.07−5.04 (m, 1H), 3.66−3.53 (m, 1H), 1.83−1.72 (m, 4H), 1.57−1.55 (m, 1H), 1.42 (d, J = 7.0 Hz, 3H), 1.30−1.15 (m, 5H); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 162.8, 154.8 (q, J = 32.6 Hz), 143.9, 128.0, 127.1, 126.7, 120.6 (q, J = 277.0 Hz), 86.0, 52.2, 49.2, 25.6, 25.0, 24.9, 24.1, 24.0, 22.3; HRMS calcd for $C_{18}H_{22}F_3N_3S$ 369.1487, found 369.1475. Anal. Calcd for $C_{18}H_{22}F_3N_3S$ (369.47): C, 58.51; H, 6.00; N, 11.37. Found: C, 58.44; H, 6.08; N, 11.08.

Diastereomer b: mp 108 °C (hexane/ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 8.15 (d, J = 6.7 Hz, 1H), 7.34−7.18 (m, 5H), 5.60 (s, 1H), 5.08−5.01 (m, 1H), 3.35−3.25 (m, 1H), 1.59−1.57 (m, 2H), 1.45−1.35 (m, 2H), 1.38 (d, J = 7.1 Hz, 3H), 1.19−0.71 (m, 6H); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 162.9,

154.8 (q, J = 32.4 Hz), 144.5, 128.0, 126.3, 125.6, 120.6 (q, J = 276.7 Hz), 85.6, 52.5, 49.7, 25.2, 24.7, 24.3, 23.9, 22.2. C/H−COSY NMR (125.8/500 MHz, DMSO-d_6): 128.0, 125.6, 126.3: 7.34−7.18; 85.6:5.60; 52.5:3.35−3.25; 49.2:5.08−5.01; 29.7: 1.30−1.20; 25.2, 24.7, 24.3, 23.9:1.59−1.57, 1.45−1.35, 1.19−0.71; 22.2:1.38. HRMS calcd for $C_{18}H_{22}F_3N_3S$ 369.1487, found 369.1472. Anal. Calcd for $C_{18}H_{22}F_3N_3S$ (369.47): C, 58.51; H, 6.00; N, 11.37. Found: C, 58.36; H, 6.16; N, 11.28.

Analogous to **5a**, **(1-cyclohexyl-3-diethylamino-5-trifluoromethyl-1λ^4,2,6-thiadiazine (5e)** was prepared utilizing **31d** and diethylamine. Column chromatography (hexanes/ethyl acetate = 7/1) yielded **5e** as slightly yellow crystals: yield 31%; mp 49 °C (hexane/ethyl acetate); ^{1}H NMR δ 5.50 (s, 1H), 3.70−3.60 (m, 1H), 3.51−3.32 (m, 4H), 1.89−1.78 (m, 4H), 1.35−1.13 (m, 6H), 1.19 (pst, 6H); ^{13}C NMR (125.8 MHz) δ 162.8, 157.8 (q, J = 32.6 Hz), 120.9 (q, J = 277.4 Hz), 82.5 (psd, J = 3.8 Hz), 51.6, 42.7, 26.3, 25.9, 25.6, 24.9, 24.8, 13.4; UV−vis (methanol) λ_{max} (ϵ) 362 nm (3761), 288 nm (6881), 251 nm (6300). Anal. Calcd for $C_{14}H_{22}F_3N_3S$ (321.41): C, 52.31; H, 6.90; N, 13.07; S, 9.98. Found: C, 52.47; H, 6.74; N, 12.95; S, 10.13.

3-Amino-1-cyclohexyl-5-trifluoromethyl-1λ^4,2,6-thiadiazine (5c). Through a solution of (1-cyclohexyl-5-trifluoromethyl-1λ^4,2,6-thiadiazine-3-yl)-methanesulfonate **31d** in dry THF was passed a stream of carefully dried gaseous ammonia. After completion of the reaction (indicated by TLC), the solvent was removed in vacuo and the oily residue purified by column chromatography (hexane/ethyl acetate = 8/1) to yield **5c** as yellow crystals: yield 30%; mp 151 °C (hexane/ethyl acetate); ^{1}H NMR (500 MHz) δ 5.43 (s, 1H), 5.06 (bs, 2H), 3.79−3.74 (m, 1H), 1.90−1.83 (m, 4H), 1.43−1.24 (m, 6H); ^{13}C NMR δ 165.9, 159.2 (q, J = 33.1 Hz), 120.4 (q, J = 277.5 Hz), 84.8, 52.1, 26.0, 25.5, 25.2, 24.8, 24.7; UV−vis (methanol) λ_{max} (ϵ) 356 nm (2812), 242 nm (8037); HRMS calcd for $C_{10}H_{14}F_3N_3S$ 265.0861, found 265.0856. Anal. Calcd for $C_{10}H_{14}F_3N_3S$ (265.30): C, 45.27; H, 5.32; N, 15.84. Found: C, 45.35; H, 5.38; N, 15.25.

Analogous to **5a**, **5-benzyl-3-benzylamino-1-pentyl-1λ^4,2,6-thiadiazine (5f)** was prepared utilizing **31f** using $CHCl_3$ as a solvent. Column chromatography (hexane/ethyl acetate = 3/1) afforded **5f** as a colorless solid: yield 45%; mp 65 °C (hexane/ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 7.49 (pst, J = 5.5 Hz, 5.5 Hz, 1H), 7.35−7.16 (m, 10H), 5.07 (s, 1H), 4.46 (dd, J = 14.8 Hz, 5.7 Hz, 5.9 Hz, 1H), 4.26 (dd, J = 15.6 Hz, 6.0 Hz, 5.7 Hz, 1H), 3.42 (d, J = 14.8 Hz, 1H), 3.38 (d, J = 14.6 Hz, 1H), 2.76−2.71 (m, 1H), 2.63−2.52 (m, 1H), 1.23−1.15 (m, 6H), 0.79 (pst, 3H); ^{13}C NMR (DMSO-d_6) δ 169.3, 164.0, 139.6, 138.7, 128.6, 127.9, 127.9, 127.0, 126.4, 125.8, 86.4, 44.8, 43.1, 40.1, 29.9, 21.6, 21.5, 13.4; HRMS calcd for $C_{22}H_{27}N_3S$ 365.1926, found 365.1911. Anal. Calcd for $C_{22}H_{27}N_3S$ (365.53): C, 72.28; H, 7.45; N, 11.50. Found: C, 73.33; H, 7.60; N, 11.40.

Analogous to **5f**, **5-benzyl-3-benzylamino-1-cyclohexyl-1λ^4,2,6-thiadiazine (5g)** was prepared utilizing **31e** and benzylamine. Column chromatography (hexane/ethyl acetate = 3/2) provided **5g** as a colorless solid: yield 35%; mp 102 °C (ligroin); ^{1}H NMR (DMSO-d_6) δ 7.50 (pst, J = 5.7 Hz, 5.4 Hz, 1H), 7.31−7.15 (m, 10H), 5.09 (s, 1H), 4.74 (dd, J = 15.1 Hz, 5.7 Hz, 5.9 Hz, 1H), 4.26 (dd, J = 15.4 Hz, 5.8 Hz, 5.9 Hz, 1H), 3.82−3.42 (m, 1H), 3.38 (m, 2H), 1.57−1.39 (m, 5H), 1.05−0.92 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 169.7, 163.9, 139.7, 138.8, 128.6, 127.9, 127.8, 126.9, 126.3, 125.8, 87.2, 50.4, 44.9, 43.2, 25.7, 25.2, 25.0, 24.4, 24.2; HRMS calcd for $C_{23}H_{27}N_3S$: 377.1926, found 377.1933. Anal. Calcd for $C_{23}H_{27}N_3S$ (377.54): C, 73.17; H, 7.21; N, 11.13. Found: C, 72.17; H, 6.90; N, 10.92.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra of **17d**, **18a**, **19a**, **20a**, **26a**, **26h**, **26k**, **29a**, **29b**, **30b**, **31a**, **31b**, **31f**, **32a**, and **5b** and ORTEPs, cell packing diagrams, and crystallographic data of compounds **26b**, **29f**, **30e**, and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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