Organometallics in Carbon–Carbon Bond Formation in 1,2,6-Thiadiazine 1,1-Dioxides

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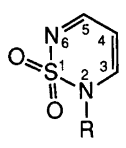
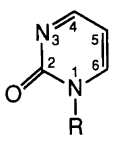
Carbon substituents have been introduced exclusively into the electrophilic 5-position in 1,2,6-thiadiazine 1,1-dioxides by 1,1-adduct formation with organomagnesium reagents followed by reoxidation by manganese dioxide to the conjugated, 5-substituted heterocycle. Pd(II)-catalyzed coupling reactions between organostannanes and the 4-bromo or 4-iodo derivatives have been used for the introduction of a 4-carbon substituent. Methods for chlorination, bromination or iodination in the 4-position are described.

Formation of adducts with organometallic reagents is a general property of π-electron deficient heteroarenes.[1] We have been especially interested in regioselective carbon–carbon bond formation in the pyrimidine system by addition of an organometallic reagent to an activated, electrophilic position. The dihydro adduct which is formed, is subsequently reoxidized to the carbon substituted heteroarene.[2] The N(3)–C(6) part of the pyrimidine **II** can be regarded as possessing electronic properties similar to an α,β-unsaturated carbonyl system, or more closely to the corresponding α,β-unsaturated imine system.[1] The same structural unit is seen in the N(6)–C(3) part of the thiadiazine **I**, and since the CO- and SO_2-groups in the two systems exert a similar electronic effect, the same type of addition to both systems was expected.

In an alternative and more general method which is applicable to any position in the heterocycle, the carbon substituent is introduced by a transition-metal-catalyzed coupling between a heteroaryl halide and an organometallic reagent such as a stannyl derivative.[3] The polarization of the reactants in this reaction may also be reversed in which case the heteroarene becomes the organometallic reactant.[4] In this report we describe studies of both methods in the carbon–carbon bond formation in 1,2,6-thiadiazine 1,1-dioxides, a relatively little explored π-electron deficient heterocyclic system.[5]



I

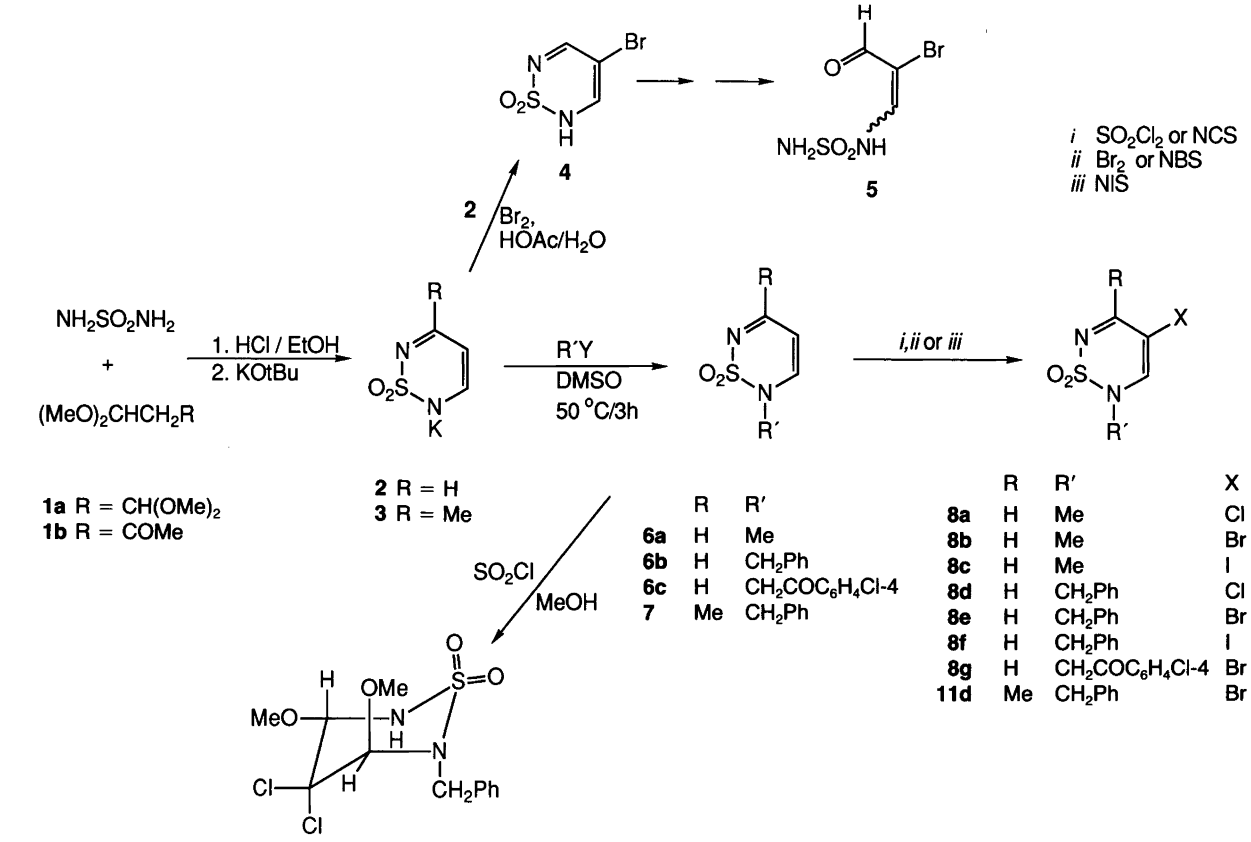


II

Scheme 1.

1,2,6-thiadiazine 1,1-dioxides in many reactions with electrophiles and nucleophiles behave similarly to the corresponding pyrimidines.[5,6] For our study of cross-coupling reactions and addition reactions, 1,2,6-thiadiazine 1,1-oxides were prepared by cyclization reactions and were halogenated and *N*-alkylated. 1,2,6-Thiadiazine 1,1-dioxide itself has been described as a non-crystalline compound; it was prepared by an acid-catalyzed cyclization reaction between sulfamide and 1,1,3,3-tetramethoxypropane.[7] We found the potassium salt **2** to be a readily purifiable solid. The 5-methyl homologue **3** was similarly prepared from 4,4-dimethoxy-2-butanone and sulfamide. It was needed as a reference in the structure analysis of the products after the introduction of carbon substituents into the thiadiazine, which is discussed below. Attempted bromination of the parent compound using bromine in acetic acid led to ring opening and formation of the α,β-substituted acrolein **5**. The ring-opening reaction is rationalized as being caused by addition of a hydroxy function to the highly electrophilic 3(5)-position in the 4-brominated 1,2,6-thiadiazine 1,1-dioxide **4** with a subsequent ring-opening. The 3,5-positions in the 1,2,6-thiadiazine 1,1-dioxides are probably more electron deficient than the corresponding 4,6-positions in 2-pyrimidinones as suggested by the σ_p values for $-SO_2NH_2$ and for $-CONH_2$, 0.57 and 0.26 respectively.[8] Halogenation in the 4-position in 1,2,6-thiadiazine 1,1-dioxides, however, was achieved after initial *N*-alkylation of the potassium salt **2**. The alkylating agents were methyl iodide, benzyl bromide or 4-chlorophenacyl bromide in dimethyl sulfoxide. The methyl derivative exists as an equilibrium mixture of the tautomers 5-methyl-2*H*-1,2,6-thiadiazine 1,1-dioxide and 3-methyl-2*H*-1,2,6-thiadiazine 1,1-dioxide,[7] but on benzylation only the the *N*-benzylated 5-methyl derivative **7** was obtained.

The *N*-alkylated derivatives **6** were chlorinated by sulfuryl chloride or *N*-chlorosuccinimide (NCS), iodinated by

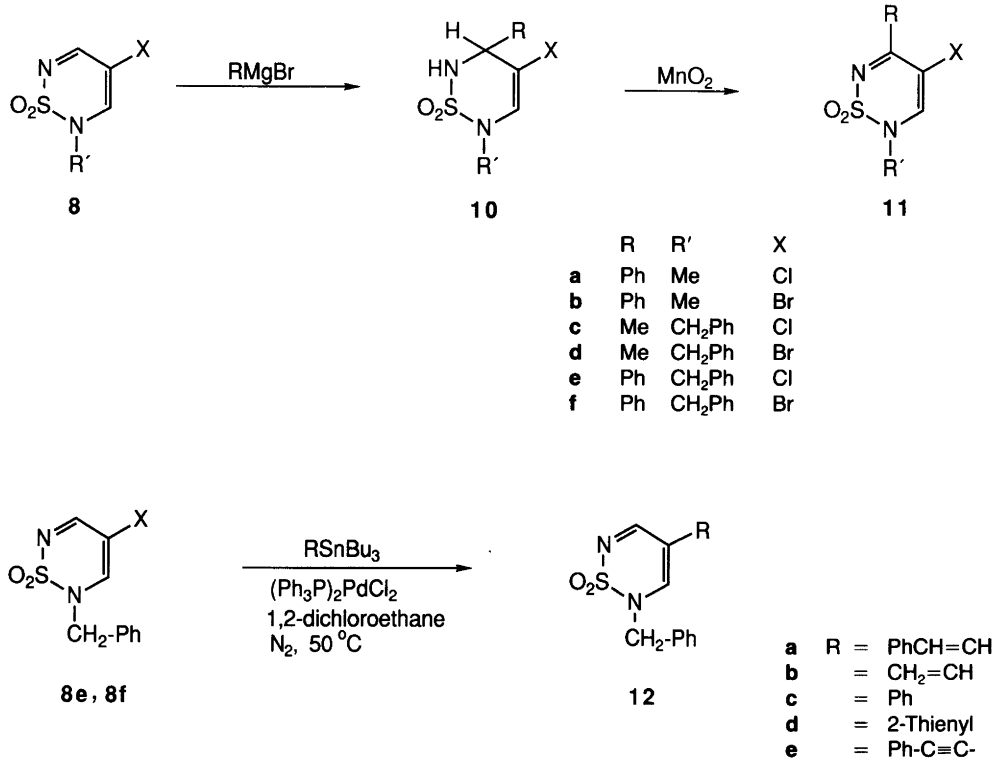


Scheme 2.

N-iodosuccinimide (NIS) or brominated by bromine or *N*-bromosuccinimide (NBS) in the 4-position. Sulfuryl chloride was the preferred reagent for chlorination, and bromine was the better reagent for bromination except in the case of the phenacyl derivative **6c** when NBS gave the better yield of the desired product. The solvent was either 1,2-dichloroethane or chloroform. The halogenated products readily add a molecule of methanol in a reversible manner. When the crude reaction product from the reaction between **6b** and sulfuryl chloride was heated in methanol, however, another product was obtained which was shown by X-ray analysis to have structure **9**.[9] It is probable that sulfuryl chloride remaining in the crude product reacted with methanol to provide the conditions for acid catalysis and formation of the saturated product **9**. No further study of the reaction was carried out. The course of this reaction, however, finds analogy in the bromination of 1,3-dimethyl-2(1*H*)-pyrimidinone under acidic conditions when the stable adduct, 5,5-dibromo-4,6-dihydroxy-1,3-dimethylhexahydro-2(1*H*)-pyrimidinone, was obtained.[10] The saturated product **9** assumes the chair conformation in the solid state, the 3,5-dimethoxy groups being *trans*. It is notable that the relatively large benzyl group is axial and has a *trans* relationship to the axial 3-methoxy group.[9]

The addition of organomagnesium derivatives to the 1,2,6-thiadiazines was found to be regiospecific. Carbon–carbon bond formation occurred exclusively in the 5-position (**10**), which corresponds to the 4-position in the pyrimidinones. For comparison, in the reactions of 2-pyrimidinones with these reagents mixtures of the 3,4- and the 3,6-isomeric adducts were formed.[2] The high regiospecificity observed in the reaction of organomagnesium reagents with the thiadiazines but not in the pyrimidines, may be rationalized in part as being due to the greater bulkiness of the SO_2 group compared with the CO group. The pyrimidine ring is planar and the oxygen of the CO group lies in the plane of the ring. The thiadiazine ring has an envelope conformation with the sulfur ca. 0.4 Å out of the plane of the other five ring atoms, and the oxygens in the SO_2 group lie below and above the ring plane.[11] The S–N bond in the thiadiazine is longer than the C–N bond in the pyrimidine.[7,12] The two ring systems therefore differ in their space requirements. Our results indicate that a non-bonded interaction between the *N*-substituent and the oxygens gives rise to stronger shielding of the 3-position in the thiadiazines than the shielding caused by the N-1 substituent of the corresponding 6-position in pyrimidinones.

Electronic activation from a halogen in the 4-position seems to be a requirement for the reactions to proceed at a reasonable rate; in contrast with the 4-halogeno derivatives **8**, which readily formed adducts with organomagnesium reagents, the *N*-benzylated parent compound **6b** showed little reactivity (TLC). The adducts **10** are dihydro derivatives which have a chiral center at C-5. This explains



Scheme 3.

why the methylene protons of the benzyl group in **10c–10f** resonate in an AB pattern with J 15–18 Hz in the ^{1}H NMR spectra.

Dehydrogenation of the adducts **10** to the corresponding conjugated heterocycles **11** was effected by activated manganese dioxide. The dihydro derivatives were in most cases sufficiently stable for chromatographic purification on alumina. The stability of the methyl adducts **10c** and **10d**, however, was insufficient for purification, and the crude products were used for the dehydrogenation. The assignment of structure **10d** to the product from the Grignard-type reaction has been verified. Reoxidation of the other adduct gave **11d**, which was the same as the product from the bromination of the 5-methyl derivative **7**. The latter reaction is discussed above.

The 4-position in the thiadiazines is less electrophilic than the 5(3)-position, and carbon–carbon bond formation by the method of adduct formation can therefore not be applied to this position. The carbon bond formation, however, can be achieved by palladium-catalyzed coupling reactions between 4-bromo or 4-iodo derivatives with organostannanes in the manner shown previously for the coupling reactions of 5-bromo- or 5-iodo-pyrimidines.[3b] Thus coupling reactions with the 4-bromo derivative **8e** or the 4-iodo derivative **8f** proceeded readily with the introduction of carbon substituents at C-4 (**12**). Bis(triphenylphosphine)palladium(II) dichloride was the catalyst. For complete conversion of the halide an excess of the organostannyl reagent was required.

Preparation of **12e** was initially attempted using phenylacetylene, the Pd(II) catalyst, a tertiary amine and a Cu(I) salt, a method found useful for the introduction of acetylenic substituents in the pyrimidine series.[13] In the present case the reaction failed to give the desired product because the thiadiazine system was attacked by the copper reagent. A successful route for the preparation of the acetylenic derivative **12e**, however, was to couple the organostannyl derivative of phenylacetylene with the 4-bromo derivative **8e** using Pd(II) catalysis.

Experimental

The ^{1}H NMR spectra were recorded at 300 MHz and the ^{13}C NMR spectra at 75 MHz. The solvent was deuteriochloroform. The mass spectra were recorded at 70 eV. Isobutane was used for chemical ionization (CI). The spectra are presented as *m/z* (% relative intensity).

1,2,6-Thiadiazine 1,1-dioxide potassium salt **2**. Dry hydrogen chloride was bubbled through a solution of sulfamide (2.88 g, 30 mmol) and 1,1,3,3-tetramethoxypropane (4.93 g, 30 mmol) in ethanol at ambient temperature for 15 min and the reaction mixture heated under reflux for 6 h.

The solvent was then evaporated and the residue redissolved in ethanol (250 ml). Potassium *t*-butoxide (3.40 g, 30 mmol) was added at ambient temperature in small portions before the reaction mixture was heated at 80 °C for 10 min, filtered whilst hot, cooled and partially evaporated. The solution was kept in the refrigerator for 24 h and the precipitated product was filtered off and washed with diethyl ether; yield 2.70 g (68 %), m.p. 199–200 °C (EtOH). Anal. $C_3H_3KN_2O_2S$: C, H. ^{1}H NMR: δ 5.75 (H-4, t, *J* 5.5 Hz), 7.68 (H-3, H-5, d, *J* 5.5 Hz).

5-Methyl-1,2,6-thiadiazine 1,1-oxide potassium salt **3**. Compound **3** was prepared from 4,4-dimethoxy-2-butanone and sulfamide as above in 57 % yield, m.p. 249–250 °C (EtOH). Anal. $C_4H_5KN_2O_2S$: C, H. ^{1}H NMR: δ 2.10 (CH_3), 5.72 (H-4, d, *J* 5.7 Hz), 7.57 (H-3, d, *J* 5.7 Hz).

N-*(2-Bromo-3-oxo-1-propenyl)sulfamide* **5**. Bromine (1.56 g, 10 mmol) in acetic acid (4 ml) was added dropwise to a solution of the potassium salt of 1,2,6-thiadiazine 1,1-dioxide (1.70 g, 10 mmol) in a 1:6 mixture of water and acetic acid (14 ml). The reaction mixture was stirred at ambient temperature for 30 min, then heated slowly to 80 °C and stirred at 80 °C for 10 min, before the mixture was cooled and evaporated. The residue was extracted with water and with dilute hydrochloric acid, the solution kept in the refrigerator for 24 h, and the precipitated product was filtered off and dried; yield 1.10 g (48 %), m.p. 177–178 °C (H_2O). High resolution MS: Found 227.9185. Calc. for $C_3H_5BrN_2O_3S$: 227.9205. ^{1}H NMR: δ 3.95 (1 H, s), 8.13 (1 H, s), 9.11 (1 H, s). ^{13}C NMR: δ 102.1, 149.6, 185.0. IR (KBr): 3350, 3254, 3120, 1666, 1383, 1349, 1162 cm^{-1}. MS: 230/228 (20/19, *M*), 151 (53), 150 (32), 149 (77), 148 (30), 123 (30), 121 (36), 91 (22), 70 (91), 64 (44), 36 (100).

Alkylation of 1,2,6-thiadiazine 1,1-dioxides. General procedure. The alkyl halide was added to a solution of the potassium salt of the thiadiazine in DMSO. The mixture was stirred at 50 °C for 3 h before water was added, and the product extracted into chloroform. The chloroform solution was washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether and purified by column chromotography or by recrystallization.

2-Methyl-1,2,6-thiadiazine 1,1-dioxide **6a**.[7] Compound **6a** was made from **2** (0.51 g, 3 mmol) and methyl iodide (1.42 g, 10 mmol); yield 1.73 g (59 %), m.p. 76–76 °C Et_2O).

2-Benzyl-1,2,6-thiadiazine 1,1-dioxide **6b**.[7] Compound **6b** was made from **2** (0.51 g, 3.0 mmol) and benzyl bromide (0.51 g, 3.0 mmol); yield 0.51 g (77 %), m.p. 91–92 °C (EtOH).

2-(4-Chlorophenacyl)-1,2,6-thiadiazine 1,1-dioxide **6c**. Compound **6c** was made from **2** (0.51 g, 3.0 mmol) and 4-chlorophenacyl bromide (0.70 g, 3.0 mmol); yield 0.62 g (74 %), m.p. 163–164 °C (MeOH). High resolution MS: Found 284.0012. Calc. for $C_{11}H_9ClN_2O_3S$: 284.0022. ^{1}H NMR (acetone-d_6): δ 5.51 (CH_2Ar), 6.12 (H-4, dd, *J* 6.0 Hz, *J* 2.4 Hz), 7.46 (2 H, *J* 8.8 Hz), 7.72 (H-3, dd, *J* 6.0 Hz, *J* 2.4 Hz), 7.95 (2 H, d, *J* 8.8 Hz), 8.10–8.16 (H-5, m). ^{13}C NMR (acetone-d_6): δ 54.5 (CH_2Ph), 100.4 (H-4), 129.4, 130.2, 133.2, 140.2 (Ph), 151.4 (H-3), 163.4 (H-5), 190.9 (C=O). MS: 286/284 (0.2/0.8, *M*), 220 (21), 141 (37), 139 (100), 113 (15), 111 (40), 81 (38), 80 (57).

2-Benzyl-5-methyl-1,2,6-thiadiazine 1,1-dioxide **7**.[7] Compound **7** was made from 5-methyl-1,2,6-thiadiazine 1,1-dioxide (**3**) and benzyl bromide (0.34 g, 2.0 mmol). The crude product was purified by chromotography on silica (CH_2Cl_2/EtOH 100:1); yield 1.63 g (86 %), m.p. 104–105 °C. MS: 236 (6, *M*), 171 (2), 103 (1), 95 (2), 92 (8), 91 (100), 89 (2), 65 (11).

4-Chloro-2-methyl-1,2,6-thiadiazine 1,1-dioxide **8a**. Sulfuryl chloride (0.30 g, 2.2 mmol) was added to a solution of 2-methyl-1,2,6-thiadiazine 1,1-dioxide (1.29 g, 2 mmol) in dry dichloromethane (4 ml). The reaction mixture was heated under reflux for 6 h, after which the solvent was evaporated and the residue was recrystallized from MeOH; yield 0.26 g (72 %), m.p. 112–114 °C. Anal. $C_4H_5ClN_2O_2S$: C, H. ^{1}H NMR: δ 3.55 (CH_3), 7.32 (H-3, d, *J* 3.0 Hz), 7.95 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 37.9 (CH_3), 106.7 (C-4), 146.9 (C-3), 161.9 (C-5). IR (KBr): 3050, 1620, 1340, 1170 cm^{-1}. MS: 182/180 (14/41, *M*), 118 (6), 117 (6), 116 (21), 115 (19), 88 (9), 81 (14), 74 (8), 42 (100).

4-Bromo-2-methyl-1,2,6-thiadiazine 1,1-dioxide **8b**. Bromine in dichloromethane (1 M, 2 ml, 2 mmol) was added dropwise with stirring to a solution of 2-methyl-1,2,6-thiadiazine 1,1-dioxide (0.29 g, 2 mmol) in dry dichloromethane (4 ml) at 0 °C. The mixture was stirred at ambient temperature for 30 min, before the solvent was evaporated and the residue triturated with diethyl ether; yield 0.40 g (88 %), m.p. 156–158 °C. Anal. $C_4H_5BrN_2O_2S$: C, H. ^{1}H NMR: δ 3.55 (CH_3), 7.38 (H-3, d, *J* 3.0 Hz), 7.98 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 37.8 (CH_3), 91.2 (C-4), 148.8 (C-3), 163.1 (C-5). IR (KBr): 3028, 1604, 1334, 1166 cm^{-1}. MS: 226/224 (54/52, *M*), 162 (23), 161 (13), 160 (24), 159 (12), 132 (4), 119 (6), 81 (16), 42 (100).

4-Iodo-2-methyl-1,2,6-thiadiazine 1,1-dioxide **8c**. *N*-Iodosuccinimide (0.44 g, 2 mmol) was added to a solution of 2-methyl-1,2,6-thiadiazine 1,1-dioxide (0.29 g, 2 mmol) in dry chloroform (4 ml). The mixture was stirred at ambient temperature for 3 h, before the solvent was evaporated and the residue recrystallized; yield 0.35 g (65 %), m.p. 193–194 °C (MeOH). Anal. $C_4H_5IN_2O_2S$: C, H. ^{1}H NMR:

δ 3.59 (CH_3), 7.90 (H-3, d, *J* 3.0 Hz), 8.04 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 37.6 (CH_3), 56.4 (C-4), 155.0 (C-3), 66.9 (C-5). IR (KBr): 3050, 1600, 1330, 1170 cm^{-1}. MS: 272 (82), 209 (1), 208 (33), 207 (9), 181 (3), 127 (11), 81 (26), 54 (43), 42 (100).

2-Benzyl-4-chloro-1,2,6-thiadiazine 1,1-dioxide **8d**. Sulfuryl chloride (0.30 g, 2.2 mmol) was added to a solution of 2-benzyl-1,2,6-thiadiazine 1,1-dioxide (0.44 g, 2 mmol) in dry dichloromethane (4 ml). The mixture was heated under reflux for 3 h, before the solvent was evaporated and the residue triturated with cold diethyl ether; yield 0.34 g (66 %), m.p. 90–91 °C. Anal. $C_{10}H_9ClN_2O_2S$: C, H. ^1H NMR: δ 4.91 (CH_2Ph), 7.22 (H-3, d, *J* 3.0 Hz), 7.4–7.5 (Ph), 7.92 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 53.5 (CH_2Ph), 107.2 (C-4), 128.5, 128.6, 129.3, 133.0 (Ph), 144.8 (C-3), 161.7 (C-5). MS: 258/256 (1.4/4.2, *M*), 92 (12), 91 (100), 90 (1), 89 02), 77 (2), 65 (13).

2-Benzyl-4-bromo-1,2,6-thiadiazine 1,1-dioxide **8e**. Bromine in dichloromethane (1 M, 2 ml, 2 mmol) was added dropwise to a solution of 2-benzyl-1,2,6-thiadiazine 1,1-dioxide (0.44 g, 2 mmol) in dry dichloromethane (4 ml). The mixture was stirred at ambient temperature for 30 min, before the solvent was evaporated and the residue triturated with diethyl ether; yield 0.54 g (90 %), m.p. 126–127 °C. Anal. $C_{10}H_9BrN_2O_2S$: C, H. ^1H NMR ($CDCl_3$): δ 4.92 (CH_2Ph), 7.24 (H-3, d, *J* 3.0 Hz), 7.4–7.5 (Ph), 7.96 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 53.6 (CH_2Ph), 92.2 (C-4), 128.7, 129.3, 129.4, 133.0 (Ph), 146.8 (C-3), 163.0 (C-5). IR (KBr): 3033, 2360, 1594, 1356, 1175 cm^{-1}. MS: 302/300 (2/2, *M*), 92 (7), 91 (100), 89 (1), 65 (8).

2-Benzyl-4-iodo-1,2,6-thiadiazine 1,1-dioxide **8f**. *N*-Iodosuccinimide (0.44 g, 2 mmol) was added to a solution of 2-benzyl-1,2,6-thiadiazine 1,1-dioxide (0.44 g, 2 mmol) in dry chloroform (4 ml). The reaction mixture was stirred at ambient temperature for 3 h, before the solvent was evaporated and the residue recrystallized; yield 0.42 g (60 %), m.p. 155–156 °C (MeOH). Anal. $C_{10}H_9IN_2O_2S$: C, H. ^1H NMR: δ 4.91 (CH_2Ph), 7.27 (H-3, d, *J* 2.7 Hz), 7.4–7.5 (Ph), 7.98 (H-5, d, *J* 2.7 Hz). ^{13}C NMR: δ 53.5 (CH_2Ph), 57.9 (C-4), 128.7, 129.3, 129.4, 133.1 (Ph), 151.4 (C-3), 166.6 (C-5). IR (KBr): 3021, 2351, 1581, 1351, 1172 cm^{-1}. MS: 348 (5, *M*), 300 (0.2), 181 (0.2), 166 (1), 92 (7), 91 (100), 89 (2), 77 (2), 65 (9).

4-Bromo-2-(4-chlorophenacyl)-1,2,6-thiadiazine 1,1-dioxide **8g**. *N*-Bromosuccinimide (0.21 g, 1.2 mmol) was added to a solution of 2-(4-chlorophenacyl)-1,2,6-thiadiazine 1,1-dioxide (0.36 g, 1 mmol) in dichloromethane. The mixture was stirred at ambient temperature for 5 h, before the solvent was evaporated. Water (5 ml) was added to the residue and the mixture heated for 5 min at 50–60 °C. The crude product was purified by chromatography on silica (CH_2Cl_2); yield 0.11 g (30 %), m.p. 90–91 °C. High resolution MS: Found 361.9118. Calc. for $C_{11}H_8BrClN_2O_3S$: 361.9128. ^1H NMR: δ 5.37 (CH_2Ar), 7.46 (2 H, d, *J* 8.8 Hz), 7.82 (H-3, d, *J* 2.7 Hz), 7.95 (2 H, d, *J* 8.8 Hz), 8.05 (H-5, d, *J* 2.7 Hz). ^{13}C NMR: δ 54.7 (CH_2), 91.6 (C-4), 129.0, 129.6, 132.3, 140.2 (Ar), 150.1 (C-3), 163.3 (C-5), 189.9 (CO). MS: 364/362 (2/2, *M*), 315 (3), 313 (3), 300 (6), 298 (6), 220 (7), 218 (9), 160 (11), 158 (10), 141 (33), 139 (100), 77 (12).

2-Benzyl-4,4-dichloro-trans-*3,5-dimethoxy-3,4,5,6-tetrahydro-1,2,6-thiadiazine 1,1-dioxide* **9**. Sulfuryl chloride (0.30 g, 2.2 mmol) was added to a solution of 2-benzyl-1,2,6-thiadiazine 1,1-dioxide (0.44 g, 2 mmol) in dry dichloromethane (4 ml). The mixture was heated under reflux for 3 h, before the solvent was evaporated and the residue dissolved by being heated in methanol. The product crystallized out on cooling; yield 0.24 g (47 %), m.p. 146–147 °C. Anal. $C_{12}H_{16}Cl_2N_2O_4S$: C, H. ^1H NMR: δ 3.50 (OCH_3), 3.66 (OCH_3), 4.34 (1 H, d, *J* 14.0 Hz), 4.41 (H-3, s), 4.74 (1 H, d, *J* 14.0 Hz), 4.92 (NH, d, *J* 11.3 Hz), 5.04 (H-5, d, *J* 11.3 Hz), 7.3–7.4 (Ph). ^{13}C NMR: δ 50.8 (CH_2Ph), 57.9 and 61.3 (OCH_3), 86.97 (CH), 87.02 (C-4), 94.0, 128.5, 128.8, 128.9, 134.0. MS: 376/374/372 (1/6/11, *M*), 342 (12), 340 (17), 323 (14), 276 (35), 275 (13), 274 (100), 108 (61), 91 (80).

Addition of organomagnesium reagents to 2-alkyl-4-halo-1,2,6-thiadiazine 1,1-dioxides. General procedure for the preparation of **10**. The organomagnesium reagent (4 mmol) was added to a solution of the 2-alkyl-4-halo-1,2,6-thiadiazine 1,1-dioxide (2 mmol) in dry THF (2 ml) under N_2 at 0 °C. The mixture was stirred at ambient temperature until the reaction was complete (TLC). Dilute hydrochloric acid was added carefully, and the solution extracted with chloroform (3×15 ml). The chloroform solution was washed with saturated sodium hydrogen carbonate (2×15 ml) and water (1×15 ml), then dried ($MgSO_4$) and evaporated. The crude product was purified by recrystallization or by chromatography on alumina (activity 2).

4-Chloro-5,6-dihydro-2-methyl-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **10a**. Compound **10a** was obtained in 65 % yield, m.p. 126–127 °C (EtOH). High resolution MS: Found 258.0223. Calc. for $C_{10}H_{11}ClN_2O_2S$: 258.0230. ^1H NMR: δ 3.08 (CH_3), 4.53 (NH, d, *J* 9.0 Hz), 5.25 (H-5, dd, *J* 9.0 Hz, *J* 1.8 Hz), 6.30 (H-3, d, *J* 1.8 Hz), 7.4–7.5 (Ph). ^{13}C NMR: δ 36.4 (CH_3), 63.9 (C-5), 113.5 (C-4), 128.4, 129.3, 129.6, 131.5, 135.4 (Ph, C-3). MS: 260/258 (9/27, *M*), 259 (4), 256 (2), 223 (15), 180 (35), 178 (93), 144 (18), 116 015), 115 (13), 42 (100).

4-Bromo-5,6-dihydro-2-methyl-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **10b**. Compound **10a** was obtained in 75 % yield, m.p. 137–138 °C ($EtOH/H_2O$). Found: C 40.96; H 3.98. Calc. for $C_{10}H_{11}BrN_2O_2S$: C 39.62; H 3.66. ^1H NMR: δ 3.09 (CH_3), 4.55 (NH, d, *J* 9.0 Hz), 5.28 (H-5, dd, *J* 9.0 Hz, *J* 1.7 Hz), 6.42 (H-3, d, *J* 1.7 Hz), 7.35–7.45 (Ph). ^{13}C NMR: δ 36.1 (CH_3), 64.8 (C-5), 102.0 (C-4),

128.3, 129.2, 129.5, 134.0, 136.1 (Ph, C-3). MS: 304/302 (35/37), 224 (96), 223 (40), 222 (92), 144 037), 115 (18), 102 (19), 77 (34), 42 (100).

2-Benzyl-4-chloro-5,6-dihydro-5-methyl-1,2,6-thiadiazine 1,1-dioxide **10c**. The crude product of **10c** was dehydrogenated to **11c** without further purification.

2-Benzyl-4-bromo-5,6-dihydro-5-methyl-1,2,6-thiadiazine 1,1-dioxide **10d**. The crude product of **10d** was dehydrogenated to **11d** without further purification.

2-Benzyl-4-chloro-5,6-dihydro-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **10e**. Compound **10e** was obtained in 69 % yield, m.p. 93–94 °C (EtOH/H_2O). ^{1}H NMR: δ 4.03 (NH, d, *J* 9.0 Hz), 4.38 and 4.81 (CH_2Ph, dd, *J* 14.9 Hz), 5.16 (H-5, dd, *J* 1.4 Hz, *J* 9.0 Hz), 6.32 (H-3, d, *J* 1.4 Hz), 7.0–7.1 and 7.3–7.4 (2×Ph). ^{13}C NMR: δ 53.3 (CH_2Ph), 63.8 (C-5), 116.5 (C-4), 128.0, 128.6, 128.7, 128.8, 129.0, 129.1, 129.4, 134.2 (2×Ph, C-3). MS: 336/334 (1.5/4, *M*), 254 (7), 225 (6), 220 (8), 164 (7), 115 (14), 92 (10), 91 (100).

2-Benzyl-4-bromo-5,6-dihydro-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **10f**. Compound **10f** was obtained in 71 % yield, m.p. 102–102 °C (EtOH/H_2O). Anal. $C_{16}H_{15}BrN_2O_2S$: C, H. ^{1}H NMR: δ 4.23 (NH, d, *J* 9.0 Hz), 4.4 and 4.8 (CH_2Ph, dd, *J* 15 Hz), 5.20 (H-5, dd, *J* 1.5 Hz, *J* 9.0 Hz), 6.43 (H-3, d, *J* 1.5 Hz), 7.05–7.1 and 7.3–7.5 (2×Ph). ^{13}C NMR: δ 52.9 (CH_2Ph), 64.7 (C-5), 104.8 (C-4), 128.1, 128.5, 128.7, 128.9, 129.2, 131.3, 134.2, 135.9 (2×Ph, C-3). MS: 380/378 (0.2/0.4, *M*), 302 (2), 300 (2), 104 (1), 102 (1), 92 (8), 91 (100), 89 (2), 77 (2).

Dehydrogenation of 2-alkyl-4-halo-5,6-dihydro-5-alkyl-(aryl)-1,2,6-thiadiazine 1,1-dioxides. General procedure for the preparation of **11**. Activated manganese dioxide[14] (15 mmol) was added to a solution of the 5,6-dihydrothiadiazine (1 mmol) in dry dichloromethane (4 ml). The mixture was stirred at ambient temperature under N_2 (**10a**, **10b**, **10e** and **10f** for 24 h; **10d** for 36 h; **10c** for 48 h), before the solid was filtered and washed with dichloromethane (×3). The solvent was evaporated, and the crude product purified by recrystallization or by chromatography on silica gel.

4-Chloro-2-methyl-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **11a**. Compound **11a** was obtained in 69 % yield, m.p. 143–144 °C (EtOH). Anal. $C_{10}H_9ClN_2O_2S$: C, H. ^{1}H NMR: δ 3.57 (CH_3), 7.4–7.6 (Ph, H-3), 7.7–7.8 (Ph). ^{13}C NMR: δ 37.3 (CH_3), 106.3 (C-4), 128.2, 129.7, 131.9, 134.3 (Ph), 147.6 (C-3), 169.3 (C-5). MS: 258/256 (30/73, *M*), 193 (15), 192 (27), 191 (31), 157 (27), 103 (17), 89 (19), 77 (46), 42 (100).

4-Bromo-2-methyl-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **11b**. Compound **11b** was obtained in 70 % yield, m.p. 144–145 °C (SiO_2: $CHCl_3$/EtOH 50:1). High resolution MS: Found 299.9579. Calc. for $C_{10}H_9BrN_2O_2S$: 299.9567. ^{1}H NMR: δ 3.59 (CH_3), 7.4–7.6 (Ph, H-3), 7.7–7.8 (Ph). ^{13}C NMR: δ 37.2 (CH_3), 91.8 (C-4), 128.0, 129.4, 131.6, 135.4 (Ph), 149.6 (C-3), 170.0 (C-5). MS: 302/300 (70/70, *M*), 301 (23), 299 (17), 236 (17), 159 (49), 156 (22), 116 (32), 89 (33), 42 (100).

2-Benzyl-4-chloro-5-methyl-1,2,6-thiadiazine 1,1-dioxide **11c**. Compound **11c** was obtained in 11 % yield. ^{1}H NMR: δ 2.4 (CH_3), 4.8 (CH_2Ph), 7.06 (H-3), 7.3–7.6 (Ph). MS: 272/270 (1/2, *M*), 104 (1), 92 (8), 91 (100), 77 (2), 65 (10).

2-Benzyl-4-bromo-5-methyl-1,2,6-thiadiazine 1,1-dioxide **11d**. *Method A as above.* Compound **11d** was obtained in 15 % yield, m.p. 125–126 °C. Anal. $C_{11}H_{11}BrN_2O_2S$: C, H. ^{1}H NMR: δ 2.44 (CH_3), 4.90 (CH_2Ph), 7.21 (H-3, s), 7.37–7.43 (m, Ph). ^{13}C NMR: δ 26.4 (CH_3), 52.9 (CH_2Ph), 94.3 (C-4), 128.7, 129.2, 129.3, 133.3 (2×Ph), 145.8 (C-3), 172.4 (C-5). MS: 316/314 (3/3, *M*), 207 (0.2), 104 (1), 102 (1), 92 (8), 91 (100), 77 (2), 65 (8).

Method B by bromination of **7**. *N*-Bromosuccinimide (0.39 g, 2.2 mmol) was added to a solution of 2-benzyl-5-methyl-1,2,6-thiadiazine 1,1-dioxide (0.47 g, 2.0 mmol) in dichloromethane. The mixture was stirred at ambient temperature for 5 h, before the solvent was evaporated. Water (10 ml) was added to the residue and the mixture heated for 5 min at 50–60 °C. The crude product was purified on a silica column; yield 67 %. Physical data are given below in the other method for the preparation of **11d**.

2-Benzyl-4-chloro-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **11e**. Compound **11e** was obtained in 70 % yield, m.p. 131–132 °C (EtOH). Anal. $C_{16}H_{13}ClN_2O_2S$: C, H. ^{1}H NMR: δ 4.97 (CH_2Ph), 7.3–7.5 and 7.7–7.8 (2×Ph, H-3). ^{13}C NMR: δ 53.1 (CH_2Ph), 107.0 (C-4), 128.1, 128.8, 129.3, 129.4, 129.7, 131.9, 133.2, 134.1 (2×Ph), 145.4 (C-3), 169.1 (C-5). MS: 334/332 (1/3, *M*), 333 (1), 232 (0.3), 104 (1), 103 (2), 102 (1), 92 (8), 91 (100), 89 (3), 74 (4), 65 (7).

2-Benzyl-4-bromo-5-phenyl-1,2,6-thiadiazine 1,1-dioxide **11f**. Compound **11f** was obtained in 70 % yield, m.p. 134–135 °C (EtOH). Anal. $C_{16}H_{13}N_2O_2SBr$: C, H. ^{1}H NMR: δ 4.97 (CH_2Ph), 7.4–7.5 and 7.7–7.8 (2×Ph, H-3). ^{13}C NMR: δ 53.2 (CH_2Ph), 92.9 (C-4), 128.1, 128.8, 129.3, 129.4, 129.6, 131.8, 133.4, 135.4 (2×Ph), 147.9 (C-3), 170.0 (C-5). MS: 378/376 (4/4, *M*), 232 (0.2), 104 (1), 103 (1), 102 (1), 92 (8), 91 (100), 82 (2), 77 (3), 65 (8).

Pd-catalyzed coupling reactions. General procedure. The organostannyl reagent (2 mmol) was added to a mixture of 2-benzyl-4-bromo-1,2,6-thiadiazine 1,1-dioxide (0.30 g, 1 mmol) and bis(triphenylphosphine)palladium(II) dichloride (35 mg, 0.05 mmol) in dry 1,2-dichloroethane (2.5 ml). The reaction mixture was stirred under N_2 at 50 °C (**8b–8e** for 20 h) or at reflux temperature (**8a** for 7 h), until the

reaction was complete (TLC). The mixture was diluted with dichloromethane (10 ml) and the solution treated with saturated aqueous potassium fluoride (10 ml). The precipitated tributylstannyl fluoride was filtered off and the aqueous phase extracted with dichloromethane. The combined organic phase was washed with saturated aqueous sodium chloride (2×15 ml), dried ($MgSO_4$) and evaporated. The crude product was chromatographed and recrystallized from ethanol.

2-Benzyl-4-[(E)-β-styryl]-1,2,6-thiadiazine 1,1-dioxide **12a**. The yield of compound **12a** from (*E*)-β-styryltributylstannane[15] was 80 %, m.p. 161–162 °C (Silica; CH_2Cl_2). Anal. $C_{18}H_{16}N_2O_2S$: C, H. ^{1}H NMR: δ 4.97 (CH_2Ph), 6.55 (=C*H*, d, J_E 16.2 Hz), 6.63 (=C*H*, d, J_E 16.2 Hz), 7.19 (H-3, d, *J* 3.0 Hz), 7.2–7.4 (2×Ph), 8.28 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 53.4 (*C*H$_2$Ph), 113.6 (C-4), 120.8, 126.3, 127.7, 128.0, 128.7, 129.2, 129.4, 133.8, 136.3 (3×Ph, =*C*H), 144.1 (C-3), 161.7 (C-5). MS: 324 (14, *M*), 260 (1), 142 (1), 141 (1), 140 (1), 115 (6), 92 (8), 91 (100), 89 (2), 77 (2), 65 (8).

2-Benzyl-4-vinyl-1,2,6-thiadiazine 1,1-dioxide **12b**. The yield of compound **12b** from vinylstannane was 55 %, m.p. 106–107 °C (Silica; CH_2Cl_2). Anal. $C_{12}H_{12}N_2O_2S$: C, H. ^{1}H NMR: δ 4.95 (CH_2Ph), 5.07 (1 H, d, J_Z 11.1 Hz), 5.31 (1 H, d, J_E 16.1 Hz), 6.20 (1 H, dd, J_E 16.1 Hz, J_Z 11.1 Hz), 7.10 (H-3, d, *J* 3.0 Hz), 7.3–7.4 (Ph), 8.18 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 53.2 (*C*H$_2$Ph), 112.6 (=*C*H$_2$), 113.4 (C-4), 128.6, 128.8, 129.1, 129.3, 133.7 (Ph, =*C*H), 144.5 (C-3), 161.5 (C-5). MS: 248 (7, *M*), 128 (1), 92 (8), 91 (100), 89 (2), 77 (1), 65 (12).

2-Benzyl-4-phenyl-1,2,6-thiadiazine 1,1-dioxide **12c**. The yield of compound **12c** from phenyltributylstannane[16] was 45 %, m.p. 103–104 °C. Anal. $C_{16}H_{14}N_2O_2S$: C, H. ^{1}H NMR: δ 5.0 (CH_2Ph), 7.2–7.3 (Ph), 7.28 (H-3, d, *J* 3.0 Hz), 7.31–7.41 (Ph), 8.22 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 53.14 (*C*H$_2$Ph), 115.6 (C-4), 125.7, 127.8, 128.5, 129.0, 129.1, 129.2, 133.4, 133.6 (2×Ph), 144.8 (C-3), 162.3 (C-5). MS: 298 (11, *M*), 232 (1), 149 (1), 102 (2), 92 (7), 91 (100), 89 (3), 77 (2), 65 (8).

2-Benzyl-4-(2-thienyl)-1,2,6-thiadiazine 1,1-dioxide **12d**. The yield of compound **12d** from 2-thienyltributylstannane[17] was 56 %, m.p. 124–125 °C. Anal. $C_{14}H_{12}N_2O_2S_2$: C, H. ^{1}H NMR: δ 4.99 (CH_2Ph), 6.91 (H-3′, dd, *J* 3.6, 1.1 Hz), 7.0 (H-4′, dd, *J* 5.1, 3.6 Hz), 7.21 (H-5′, dd, *J* 5.1 Hz, *J* 1.1 Hz), 7.29 (H-3, d, *J* 3.0 Hz), 7.4–7.5 (Ph), 8.24 (H-5, d, *J* 3.0 Hz). ^{13}C NMR: δ 53.3 (*C*H$_2$Ph), 110.2 (C-4), 123.8, 124.8, 128.0, 128.6, 129.1, 129.3, 133.4, 135.6 (Ph, =*C*H), 144.0 (C-3), 161.9 (C-5). MS: 304 (8, *M*), 238 (2), 149 (2), 108 (2), 92 (8), 91 (100), 65 (11). When 2-benzyl-4-iodo-1,2,6-thiadiazine 1,1-dioxide (50 °C for 3 h) was used instead of the 4-bromo compound, the yield was 68 %.

2-Benzyl-4-phenylethynyl-1,2,6-thiadiazine 1,1-dioxide **12e**. The yield of compound **12e** from phenylethynylstannane[18] was 30 %, m.p. 106–107 °C. Anal. $C_{18}H_{14}N_2O_2S$: C, H. ^{1}H NMR: δ 4.97 (CH_2Ph), 7.32 (H-3, d, *J* 2.6 Hz), 7.3–7.4 (2×Ph), 8.11 (H-5, d, *J* 2.6 Hz). ^{13}C NMR: δ 53.4 (*C*H$_2$Ph), 81.2, 90.7 (C≡C), 98.8 (C-4), 122.0, 128.3, 128.6, 128.8, 129.3, 129.4, 131.2, 133.0 (2×Ph), 149.6, 164.0 (C-5). MS: 322 (13, *M*), 257 (1), 202 (1), 140 (1), 126 (2), 113 (4), 92 (8), 91 (100), 65 (8).

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