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Reactions of Cyanomethanesulfonamides with Aldehydes and Synthesis of 2-Benzyl-2,3-dihydrobenzopyrano[3,2-*e*][1,2,4]thiadiazine 1,1-Dioxides

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Summary. Reactions of cyanomethanesulfonamides with aromatic aldehydes in the presence of *Ac*OH and piperidine produced the addition products, the 1-cyano-2-arylethenesulfonamides, whereas reactions with benzonitrile yielded the 2-amino-1-cyano-2-phenylethenesulfonamides only when done in *THF* with *Bu*Li. No addition products were isolated from the analogue reactions with 2-hydroxybenzaldehyde (salicylaldehyde). Instead, we obtained 2-imino-2*H*-chromene-3-sulfonamides with good to excellent yields. These 2*H*-chromene derivatives allowed a number of transformations, from which the reactions with orthoformates opened an approach to the hitherto unknown benzopyrano[3,2-*e*][1,2,4]thiadiazine ring system.

Keywords. Cyanomethanesulfonamide; Aldehyde; Condensation; Cyclization; Benzopyrano[3,2-*e*][1,2,4]thiadiazine 1,1-dioxide.

Introduction

In a preceding paper [1] we have reported about reactions of cyanomethanesulfonyl chloride with amines, and about the transformation of the obtained cyanomethanesulfonamides into various heterocyclic sulfonamides. These heterocycles exhibit interesting biological properties as diuretics, antihypertensives and others. In continuation, we report here about our results concerning the reactions of cyanomethanesulfonamides with aromatic aldehydes and related systems intending to find by this way an easy route to pharmacological active compounds, especially as some related compounds have been described [2] but prepared by a more complex way.

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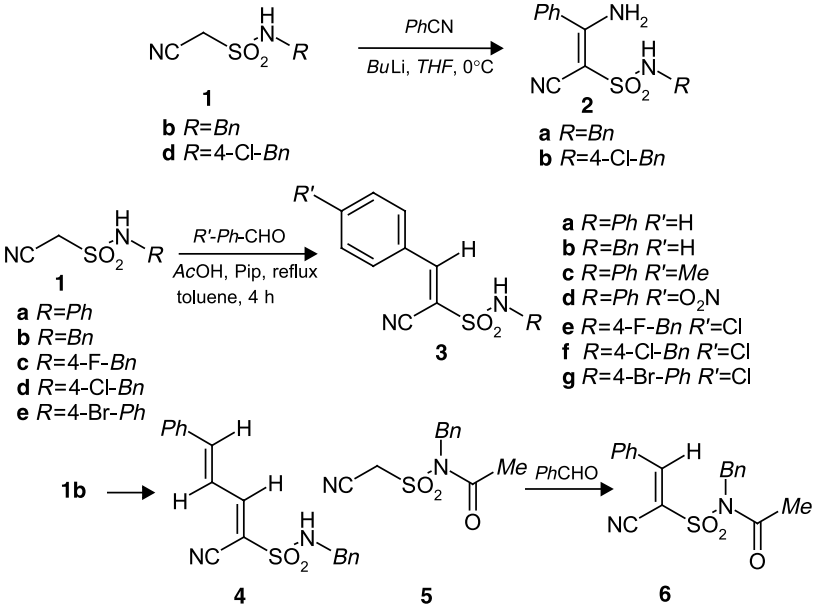
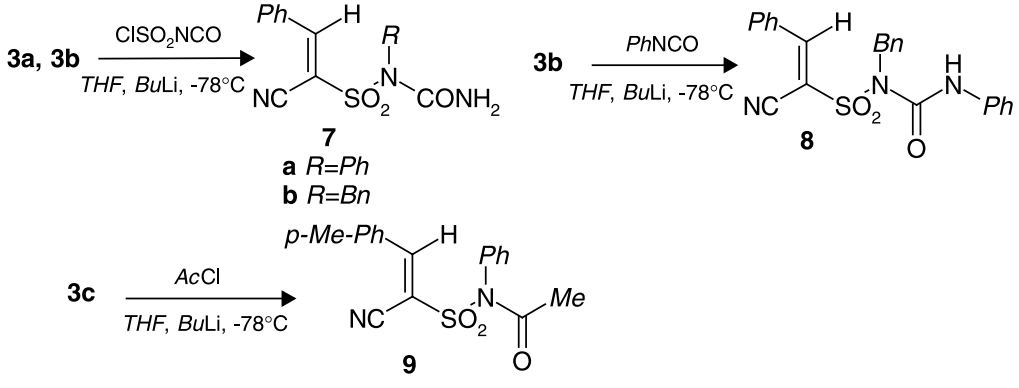
Results and Discussion

The methylene function of the cyanomethanesulfonamides **1** allowed not only condensation reactions with orthoformates or the parent N-derivatives as described [1] but also reactions with nitriles or aldehydes. For example, when **1b** or **1d** were reacted with benzonitrile and *Bu*Li in *THF* at 0°C, the expected 2-amino-2-phenyl-cyanoethenesulfonamides **2a** and **2b** became available as crystalline compounds with good yields (Scheme 1).

Experiments to use these conditions for reactions with aromatic aldehydes either failed completely or resulted in poor yields only. But when we performed the reactions between **1a**–**1e** and substituted benzaldehydes in the presence of a few drops of piperidine and a few drops of *Ac*OH in refluxing toluene until the sep-



Scheme 1



Scheme 2

aration of H_2O was completed, we isolated the substituted benzylidenecyanomethanesulfonamides **3a**–**3g** as crystalline compounds with yields up to 80%. The 1-cyano-4-phenylbutadiene-1-sulfonamide **4** was prepared from **1b** and cinnamic aldehyde, yield 60%. The formation of **6** from **5**, yield 80%, under these drastic conditions (reflux for 4 h) demonstrated the high stability of the *N*-acetyl-*N*-benzylsulfonamide structure of **5** (Scheme 1).

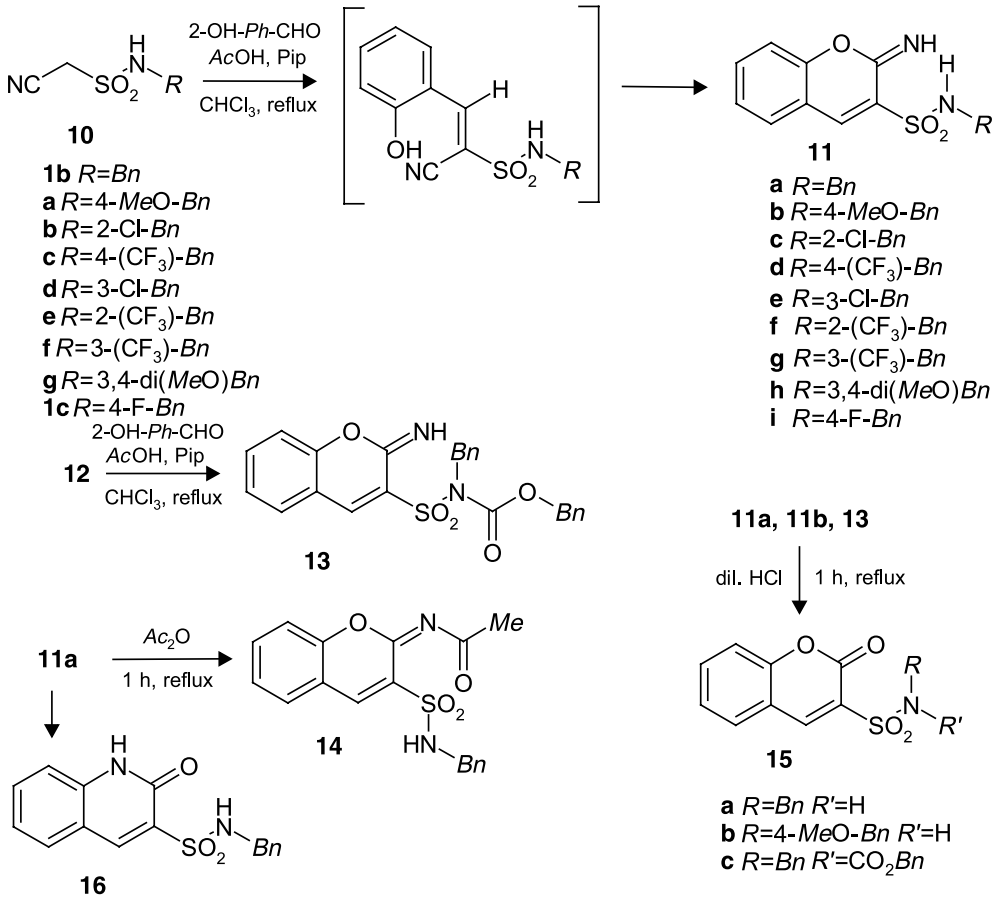
The synthesis of the sulfonylurea derivatives **7a** and **7b** was possible by the reaction of **3a** and **3b** with chlorosulfonyl isocyanate at −78°C in *THF* with *Bu*Li under a nitrogen atmosphere. Using analogue conditions, the derivative **8** was obtained from the reaction with phenyl isocyanate. Finally, the reaction between **3c** and acetyl chloride demonstrated the general possibility of N-acylation of these N-monosubstituted sulfonamide derivatives (Scheme 2).

The IR spectra of all benzylidene derivatives were characterized by a strong band at $\bar{\nu} = 2210$–$2230\,cm^{-1}$ indicating the conjugated C≡N group, two bands around 1350 and $1170\,cm^{-1}$ from the sulfonyl group, and the bands of H–N and other substituents. These bands are slightly shifted in the spectra of the aminobenzylidene derivatives **2a** and **2b**. The signal of the C≡N group was found at $2200\,cm^{-1}$, whereas the sulfonyl bands were detected at 1320 and 1150 (1130) cm^{-1}, indicating the influence of the amino group at C-2. The ^1H NMR spectra of the N-alkylated compounds **3a**–**3f** showed a sharp singlet at ∼8.0 ppm indicating the proton at C-2. This signal is shifted to ∼8.3 ppm in the spectra of the additionally acylated derivatives **7a**, **7b**, **8**, and **9**. We see the fact that the spectra exhibited only one sharp signal for 2-H as an indicator for the existence of only one diastereoisomer, and we deduce from calculations [3] and from the results of the following reactions with salicylaldehyde, that this isomer showed (*E*)-configuration.

Among the condensation reactions between the cyanomethanesulfonamides **1b**, **1c**, and **10a**–**10g** and aromatic aldehydes the reactions with salicylaldehyde gave the most interesting results. These reactions were performed in refluxing $CHCl_3$ in the presence of *Ac*OH and piperidine. After work-up we obtained the 2-imino-2*H*-chromene derivatives **11a**–**11h** as colorless to light yellow crystals with yields between 50 and 80%. Formation of these derivatives is best explained by an attack of the hydroxyl group to the nitrile after formation of the condensation product, which we could not isolate. Compound **13** was obtained from a reaction between the disubstituted sulfonamide **12** and salicylaldehyde (Scheme 3).

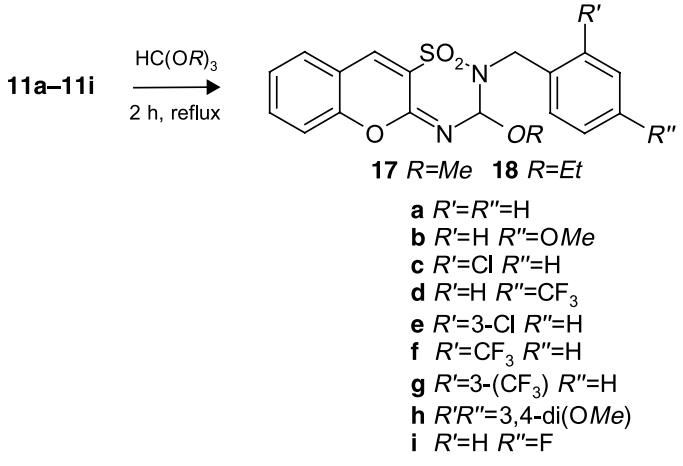
The 2-imino-2*H*-chromene derivatives **11a**–**11i** allowed some interesting transformations. Acylation of the imino group was demonstrated by refluxing of **11a** in Ac_2O yielding the crystalline derivative **14** with 90% yield. Refluxing of **11a** in *THF* under acidic conditions resulted in the isolation of the oxoisoquinoline derivative **16**, yield 50%, a reaction best understood as a *Dimroth* rearrangement. Three examples, starting from **11a**, **11b**, and **13** demonstrated the hydrolysis of the imino group yielding the coumarine sulfonamides **15a**, **15b**, and **15c**, stable, crystalline compounds with yields of *ca.* 90% (Scheme 3).

Structures of the 2*H*-chromene derivatives were established by spectroscopic data. The IR spectra of **11** were characterized by the absorption bands of the sulfonamide group at $\bar{\nu} = 1320$–1360 and 1160–$1130\,cm^{-1}$, and the imino band between 1630 and $1680\,cm^{-1}$, whereas the lactone group of **15a**–**15c** caused a strong band at $1730\,cm^{-1}$, and the oxo group of **17a** was identified by the band at $1725\,cm^{-1}$. The spectrum of **14** showed an amide band at 1650 and an H–N band at $3290\,cm^{-1}$ caused by the sulfonamide H–N. The ^1H NMR spectra contained all



Scheme 3

expected signals of the substituents and a sharp singlet at 7.96–7.98 (**11a**–**11i**), 8.34–8.47 (**15a**–**15c**), 8.50 (**16**), and 8.22 ppm (**14**), which was assigned to the proton at C-4.



Scheme 4

Finally, the iminochromene derivatives **11a–11i** were refluxed in an orthoformate solution, and we isolated from this reactions the benzopyrano[3,2-*e*][1,2,4]thiadiazine 1,1-dioxides **17a–17i** and **18a**, **18b**, and **18d–18h**. All derivatives were obtained as stable, crystalline compounds, the yields varied between 30 and 80% (Scheme 4). The pharmacological potency of these compounds was tested in different systems, and the most interesting aspect was the fact, that all compounds were able to lower high blood pressure in a way comparable to the so-called sartanes [4].

Experimental

For instrumentation details see Ref. [1]. Compounds **1a–1e**, **5**, **10a**, **10b**, and **12** were prepared as described in Ref. [1].

2-Amino-N-benzyl-2-phenyl-1-cyanoethenesulfonamide (**2a**, $C_{16}H_{15}N_3O_2S$)
At 0°C, *Bu*Li (7.5 cm^3, 10.5 mmol) was added to a solution of **1b** (1.0 g, 5 mmol) in *THF*, then, benzonitrile (1.63 cm^3, 16 mmol) was added, and the mixture was stirred for 1 h at 0°C and 12 h at room temperature. Then, the mixture was hydrolyzed with dil. HCl and an aqueous satd. NaCl solution, the organic layer was separated, dried ($MgSO_4$), and evaporated *in vacuo*. Yield 1.0 g (64%); colorless crystals; mp 132°C ($CHCl_3$); IR: $\bar{\nu} = 3320$, 3420 (NH_2), 2200 (CN), 1620 (C=C), 1320, 1150 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 4.4$ (s, CH_2), 7.2–7.6 (m, 10 *ar* H, NH_2, NH) ppm.

2-Amino-N-(4-chlorobenzyl)-1-cyano-2-phenylethenesulfonamide (**2b**, $C_{16}H_{14}ClN_3O_2S$)
From **1d** (1.2 g, 10 mmol) as described for **2a**. Yield 0.6 g (35%); colorless crystals; mp 156°C (*Me*OH); IR: $\bar{\nu} = 3460$, 3340 (NH), 2200 (CN), 1620 (C=C), 1320, 1130 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 4.4$ (d, $J = 6.6$ Hz, CH_2), 7.2–7.6 (m, 9 *ar* H, NH_2), 7.9 (s, NH) ppm.

*General Procedure for the Synthesis of **3**, **4**, and **6***
Compound **1** (**5**), the aldehyde, 4 drops of piperidine, and 2 drops of *Ac*OH were refluxed in 150 cm^3 toluene ($CHCl_3$ for salicylaldehyde) with a water separator until the reaction was complete (*ca.* 4 h). After cooling to room temperature, the mixture was washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was crystallized as noted.

1-Cyano-N-phenyl-2-phenylethene-1-sulfonamide (**3a**, $C_{15}H_{12}N_2O_2S$)
From **1a** (3.85 g, 20 mmol) and benzaldehyde (2.1 g, 20 mmol). Yield 2.1 g (75%); colorless crystals; mp 132°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3220$ (NH), 3040, 3060 (CH), 2220 (CN), 1360, 1170 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 7.0$–8.0 (m, 10 *ar* H), 8.10 (s, 2-H), 9.4 (s, NH) ppm.

N-Benzyl-1-cyano-2-phenylethene-1-sulfonamide (**3b**, $C_{16}H_{14}N_2O_2S$)
From **1b** (4.2 g, 20 mmol) and benzaldehyde (2.1 g, 20 mmol). Yield 4.8 g (80%); colorless crystals; mp 101°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3260$ (NH), 2215 (CN), 1350, 1170 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.3$ (s, CH_2), 5.4–5.5 (s, NH), 7.2–7.9 (m, 10 *ar* H), 7.90 (s, 2-H) ppm.

1-Cyano-2-(4-methylphenyl)-N-phenylethene-1-sulfonamide (**3c**, $C_{16}H_{14}N_2O_2S$)
From **1a** (1.9 g, 10 mmol) and 4-methylbenzaldehyde (1.4 g, 10 mmol). Yield 2.4 g (80%); colorless crystals; mp 132°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3260$ (NH), 2215 (CN), 1350, 1170 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 2.3$ (s, *Me*), 7.0–7.9 (m, 9 *ar* H), 8.0 (s, 2-H), 8.0–8.5 (s, NH) ppm.

1-Cyano-2-(4-nitrophenyl)-N-phenylethene-1-sulfonamide (**3d**, $C_{15}H_{11}N_3O_2S$)
From **1a** (1.9 g, 10 mmol) and 4-nitrobenzaldehyde (1.5 g, 10 mmol). Yield 2.65 g (80%); light yellow crystals; mp 138°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3260$ (NH), 3200, 3050 (CH), 2220 (CN), 1520 (NO_2),

1350, 1170 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 7.1–7.5$ (m, 5 *ar* H), 7.92 (s, 2-H), 8.0–8.5 (m, 4 *ar* H), 9.3–9.7 (s, NH) ppm.

2-(4-Chlorophenyl)-1-cyano-N-(4-fluorobenzyl)ethene-1-sulfonamide (**3e**, $C_{16}H_{12}ClFN_2O_2S$)
From **1c** (2.3 g, 10 mmol) and 4-chlorobenzaldehyde (2.8 g, 20 mmol). Yield 1.5 g (43%); colorless crystals; mp 130°C (*n*-hexane); IR: $\bar{\nu} = 3327$ (NH), 2223 (CN), 1364, 1159 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 4.4$ (s, CH_2), 7.0–7.7 (m, 8 *ar* H), 7.90 (t, $J = 1.8$ Hz, NH), 8.0 (s, 2-H) ppm.

N-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1-cyanoethene-1-sulfonamide (**3f**, $C_{16}H_{12}Cl_2N_2O_2S$)
From **1d** (2.4 g, 10 mmol) and 4-chlorobenzaldehyde (2.8 g, 20 mmol). Yield 1.7 g (46%); light yellow crystals; mp 140°C (toluene); IR: $\bar{\nu} = 3265$ (NH), 2230 (CN), 1353, 1156 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 4.4$ (s, CH_2), 7.20–7.70 (m, 8 *ar* H), 7.90 (t, $J = 1.9$ Hz, NH), 8.0 (s, 2-H) ppm.

N-(4-Bromophenyl)-2-(4-chlorophenyl)-1-cyanoethenesulfonamide (**3g**, $C_{15}H_{10}ClBrN_2O_2S$)
From **1e** (2.7 g, 10 mmol) and 4-chlorobenzaldehyde (2.8 g, 20 mmol). Yield 1.1 g (28%); light yellow crystals; mp 145°C (toluene); IR: $\bar{\nu} = 3234$ (NH), 2231 (CN), 1356, 1164 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 7.2–7.7$ (m, 8 *ar* H), 7.95 (t, $J = 1.6$ Hz, 2-H (E-Isomer)), 8.1 (d, $J = 1.6$ Hz, 2-H (Z-Isomer)), 8.2 (*s*, NH) ppm.

N-Benzyl-1-cyano-4-phenylbutadiene-1-sulfonamide (**4**, $C_{18}H_{16}N_2O_2S$)
From **1b** (2.1 g, 10 mmol) and cinnamic aldehyde (1.3 g, 10 mmol). Yield 1.9 g (60%); mp 175–177°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3320$ (NH), 2210 (CN), 1610 (C=C), 1350, 1160 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 4.4$ (d, $J = 6$ Hz, CH_2), 7.1–8.1 (m, 10 *ar* H, 3 = CH-), 7.7–8.7 (s, NH) ppm.

N-Acetyl-N-benzyl-1-cyano-2-phenylethene-1-sulfonamide (**6**, $C_{18}H_{16}N_2O_3S$)
From **5** (0.25 g, 1 mmol) and benzaldehyde (0.1 g, 1 mmol). Yield 0.27 g (80%); mp 102°C (*Me*OH); IR: $\bar{\nu} = 3030$, 2980, 2920 (CH), 2215 (CN), 1700 (CO), 1360, 1160 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.42$ (s, *Me*), 5.05 (s, CH_2), 7.1–8.2 (m, 10 *ar* H, 2-H) ppm.

N-Carbamoyl-1-cyano-N,2-diphenylethene-1-sulfonamide (**7a**, $C_{16}H_{13}N_3O_3S$)
At −78°C, *Bu*Li (6.5 cm^3, 10 mmol) was added to a solution of **3a** (2.8 g, 10 mmol) in 50 cm^3 *THF*. After 10 min, a solution of chlorosulfonyl isocyanate (1.45 g, 10 mmol) in 10 cm^3 *THF* was added, and after stirring for 0.5 h at −78°C the mixture was hydrolyzed with 2.5 cm^3 HCl (36%), washed with a satd. NaCl solution, the organic layer was separated, dried ($MgSO_4$), and evaporated *in vacuo*. Yield 2.7 g (85%); mp 129–131°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3490$, 3380 (NH_2), 2210 (CN), 1720 (CO), 1370, 1170 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 6.1–6.3$ (s, NH_2), 7.5–8.2 (m, 10 *ar* H), 8.32 (s, 2-H) ppm.

N-Benzyl-N-carbamoyl-1-cyano-2-phenylethene-1-sulfonamide (**7b**, $C_{17}H_{15}N_3O_3S$)
From **3b** (3.0 g, 10 mmol) and chlorosulfonyl isocyanate (1.45 g, 10 mmol) as described for **7a**. Yield 2.8 g (85%); mp 140–141°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3490$, 3380 (NH_2), 3050 (CH), 2220 (CN), 1720 (CO), 1360, 1170 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 5.05$ (s, CH_2), 6.5–7.2 (s, NH_2), 7.1–8.1 (m, 10 *ar* H), 8.24 (s, 2-H) ppm.

N-Benzyl-1-cyano-2-phenyl-N-(phenylcarbamoyl)ethene-1-sulfonamide (**8**, $C_{23}H_{19}N_3O_3S$)
From **3b** (3.0 g, 10 mmol) and phenyl isocyanate (1.2 g, 10 mmol) as described for **7a**. Yield 2.6 g (80%); mp 120°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3370$ (NH), 3020 (CH), 2215 (CN), 1730 (CO), 1380, 1160 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 5.10$ (s, CH_2), 7.1–8.1 (m, 15 *ar* H), 8.27 (s, 2-H), 9.1 (s, NH) ppm.

N-Acetyl-1-cyano-2-(4-methylphenyl)-N-phenylethene-1-sulfonamide (**9**, $C_{18}H_{16}N_2O_3S$)
From **3c** (1.5 g, 5 mmol) and acetyl chloride (0.4 g, 5 mmol) as described for **7a**. Yield 0.8 g (50%); mp 141°C (*Me*OH); IR: $\bar{\nu} = 3040$ (CH), 2210 (CN), 1720 (CO), 1370, 1170 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.96$ (s, *Me*), 2.44 (s, *Me*), 7.2–8.0 (m, 9 *ar* H), 8.30 (s, 2-H) ppm.

*General Procedure for the Synthesis of **10***
At 0°C, a solution of cyanomethanesulfonyl chloride (1.4 g, 10 mmol) in 20–30 cm^3 Et_2O was slowly added to a solution of the amine (freshly distilled!) in 50–60 cm^3 Et_2O. The mixture was stirred for 2 h at room temperature, the precipitate was separated, and the filtrate was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was crystallized as noted.

N-[4-(Trifluoromethyl)benzyl]cyanomethanesulfonamide (**10c**, $C_{10}H_9F_3N_2O_2S$)
From 4-(trifluoromethyl)benzylamine (3.5 g, 20 mmol). Yield 1.1 g (40%); mp 89–92°C; IR: $\bar{\nu} = 3270$ (NH), 3090 (CH), 2988, 2938 (CH_2), 2268 (CN), 1338, 1147 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.9$ (s, CH_2), 4.45 (d, CH_2), 5.7 (s, NH), 7.6 (s, 4 *ar* H) ppm.

N-(3-Chlorobenzyl)cyanomethanesulfonamide (**10d**, $C_9H_9ClN_2O_2S$)
From 3-chlorobenzylamine (2.85 g, 20 mmol). Yield 1.3 g (53%); mp 90°C; IR: $\bar{\nu} = 3310$ (NH), 3090 (CH), 2991, 2935 (CH_2), 2265 (CN), 1341, 1148 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.95$ (s, CH_2), 4.45 (d, CH_2), 5.6 (s, NH), 7.4 (s, 4 *ar* H) ppm.

N-[2-(Trifluoromethyl)benzyl]cyanomethanesulfonamide (**10e**, $C_{10}H_9F_3N_2O_2S$)
From 2-(trifluoromethyl)benzylamine (3.5 g, 20 mmol). Yield 0.9 g (32%); mp 39–40°C; IR: $\bar{\nu} = 3282$ (NH), 3090 (CH), 2985, 2938 (CH_2), 2262 (CN), 1342, 1140 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.95$ (s, CH_2), 4.55 (d, CH_2), 5.6 (s, NH), 7.6 (m, 4 *ar* H) ppm.

N-[3-(Trifluoromethyl)benzyl]cyanomethanesulfonamide (**10f**, $C_{10}H_9F_3N_2O_2S$)
From 3-(trifluoromethyl)benzylamine (3.5 g, 20 mmol). Yield 0.9 g (32%); mp 59°C; IR: $\bar{\nu} = 3281$ (NH), 3080 (CH), 2990, 2931 (CH_2), 2267 (CN), 1327, 1139 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.95$ (s, CH_2), 4.5 (d, CH_2), 5.6 (s, NH), 7.6 (s, 4 *ar* H) ppm.

N-(3,4-Dimethoxybenzyl)cyanomethanesulfonamide (**10g**, $C_{11}H_{14}N_2O_4S$)
From 3,4-dimethoxybenzylamine (3.4 g, 20 mmol). Yield 0.5 g (18%); mp 125°C; IR: $\bar{\nu} = 3277$ (NH), 3060 (CH), 2968, 2921 (CH_2), 2260 (CN), 1341, 1148 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.73$ (s, CH_2), 3.85 (s, 2 CH_3), 4.4 (d, CH_2), 5.6 (s, NH), 6.95 (s, 3 *ar* H) ppm.

N-Benzyl-2-imino-2H-chromene-3-sulfonamide (**11a**, $C_{16}H_{14}N_2O_3S$)
From **1b** (2.1 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 2.5 g (80%); mp 123°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3310$, 3200 (NH), 3060, 2950 (CH), 1660 (C=NH), 1600 (C=C), 1330, 1155 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.20$ (s, CH_2), 5.7–6.5 (br, s, NH), 7.0–7.6 (m, 9 *ar* H, NH), 7.96 (s, =CH–) ppm.

2-Imino-N-(4-methoxybenzyl)-2H-chromene-3-sulfonamide (**11b**, $C_{17}H_{16}N_2O_4S$)
From **10a** (2.4 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 2.75 g (80%); mp 128°C ($CHCl_3$/cyclohexane); IR: $\bar{\nu} = 3300$, 3290 (NH), 3060, 2980, 2950, 2850 (CH), 1680 (C=NH), 1600 (C=C), 1320, 1160 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.55$ (s, *Me*), 4.2 (s, CH_2), 6.1–6.3 (br, s, NH), 6.6–7.5 (m, 8 *ar* H, NH), 7.88 (s, 4-H) ppm.

N-(2-Chlorobenzyl)-2-imino-2H-chromene-3-sulfonamide (**11c**, $C_{16}H_{13}ClN_2O_3S$)
From **10b** (2.4 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 2.1 g (57%); colorless to light yellow crystals; mp 114°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3310$ (NH), 3060, 2950 (CH),

1630 (C=NH), 1600 (C=C), 1330, 1155 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.20$ (s, CH_2), 6.0-6.5 (s, NH), 7.0–7.6 (m, 8 *ar* H, NH), 7.96 (s, 4-H) ppm.

2-Imino-N-[4-(trifluoromethyl)benzyl]-2H-chromene-3-sulfonamide (**11d**, $C_{17}H_{13}F_3N_2O_3S$)
From **10c** (2.8 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 2.7 g (70%); colorless to light yellow crystals; mp 135°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3321$ (NH), 3060, 2950 (CH), 1630 (C=NH), 1611 (C=C), 1372, 1125 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.20$ (s, CH_2), 6.4–6.5 (s, NH), 7.0–7.6 (m, 8 *ar* H, NH), 7.98 (s, 4-H) ppm.

N-(3-Chlorobenzyl)-2-imino-2H-chromene-3-sulfonamide (**11e**, $C_{16}H_{13}ClN_2O_3S$)
From **10d** (2.4 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 2.0 g (57%); colorless to light yellow crystals; mp 85°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3335$ (NH), 3060, 2950 (CH), 1650 (C=NH), 1601 (C=C), 1339, 1160 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.20$ (s, CH_2), 6.4–6.5 (s, NH), 7.0–7.6 (m, 8 *ar* H, NH), 7.96 (s, 4-H) ppm.

2-Imino-N-[2-(trifluoromethyl)benzyl]-2H-chromene-3-sulfonamide (**11f**, $C_{17}H_{13}F_3N_2O_3S$)
From **10e** (2.8 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 2.0 g (52%); colorless to light yellow crystals; mp 50–53°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3294$ (NH), 3060, 2950 (CH), 1658 (C=NH), 1601 (C=C), 1341, 1162 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.30$ (s, CH_2), 6.4 (s, NH), 7.0–7.6 (m, 8 *ar* H, NH), 7.98 (s, 4-H) ppm.

2-Imino-N-[3-(trifluoromethyl)benzyl]-2H-chromene-3-sulfonamide (**11g**, $C_{17}H_{13}F_3N_2O_3S$)
From **10f** (2.8 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 2.5 g (65%); colorless to light yellow crystals; mp 103°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3342$ (NH), 3060, 2950 (CH), 1657 (C=NH), 1603 (C=C), 1330, 1162 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.20$ (s, CH_2), 6.45 (s, NH), 7.0–7.7 (m, 8 *ar* H, NH), 7.96 (s, 4-H) ppm.

N-(3,4-Dimethoxybenzyl)-2-imino-2H-chromene-3-sulfonamide (**11h**, $C_{18}H_{18}N_2O_5S$)
From **10g** (2.7 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 1.5 g (40%); colorless to light yellow crystals; mp 132°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3285$ (NH), 3060, 2934 (CH), 1659 (C=NH), 1603 (C=C), 1328, 1121 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.75$, 3.85 (2s, 2 CH_3), 4.20 (s, CH_2), 6.3 (s, NH), 6.5–7.6 (m, 7 *ar* H, NH), 7.96 (s, 4-H) ppm.

N-(4-Fluorobenzyl)-2-imino-2H-chromene-3-sulfonamide (**11i**, $C_{16}H_{13}FN_2O_3S$)
From **1c** (2.4 g, 10 mmol) and salicylaldehyde (1.2 g, 10 mmol) as described for **3**. Yield 1.4 g (42%); colorless to light yellow crystals; mp 69°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3310$ (NH), 3060, 2950 (CH), 1630 (C=NH), 1600 (C=C), 1330, 1155 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.20$ (s, CH_2), 6.0–6.5 (s, NH), 7.0–7.6 (m, 8 *ar* H, NH), 7.96 (s, 4-H) ppm.

N-Benzyl-N-(benzyloxycarbonyl)-2-imino-2H-chromene-3-sulfonamide (**13**, $C_{24}H_{20}N_2O_5S$)
From **12** (1.6 g, 5 mmol) and salicylaldehyde (0.6 g, 5 mmol) as described for **3**. Yield 1.65 g (75%); mp 143°C (*Me*OH); IR: $\bar{\nu} = 3500$–3300 (NH), 1730 (CO), 3060, 3020 (CH), 1600 (C=C), 1360, 1170 (SO_2) cm^{-1}; ^1H NMR: $\delta = 5.10$, 5.11 (2s, 2 CH_2), 7.0–8.2 (m, NH, 4-H, 14 *ar* H) ppm.

2-Acetylimino-N-benzyl-2H-chromene-3-sulfonamide (**14**, $C_{18}H_{16}N_2O_4S$)
Compound **11a** (1.6 g, 5 mmol) was refluxed in 20 cm^3 Ac_2O for 1 h, and then stirred at room temperature for 2 h. The mixture was evaporated *in vacuo*, the residue was dissolved in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and the solvent evaporated *in vacuo*. Yield 1.6 g (90%); mp 165–166°C (*Me*OH); IR: $\bar{\nu} = 3290$ (NH), 3060 (CH), 1650 (amide), 1340, 1180 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.27$ (s, *Me*), 4.4 (d, $J = 7$ Hz, CH_2), 5.9–6.1 (t, $J = 7$ Hz, NH), 7.2–7.8 (9 *ar* H), 8.22 (s, 4-H) ppm.

N-Benzyl-2-oxo-2H-chromene-3-sulfonamide (**15a**, $C_{16}H_{13}NO_4S$)
Compound **11a** (0.63 g, 2 mmol) was refluxed in 30 cm^3 dil. HCl, cooled to room temperature, and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), and evaporated *in vacuo*. Yield 0.6 g (95%); mp 115°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3300$ (NH), 3070, 2950 (CH), 1730 (CO), 1330, 1170 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.2$–4.3 (d, $J = 7$ Hz, CH_2), 5.6–5.8 (t, $J = 7$ Hz, NH), 6.9–7.8 (m, 9 *ar* H), 8.38 (s, 4-H) ppm.

N-(4-Methoxybenzyl)-2-oxo-2H-chromene-3-sulfonamide (**15b**, $C_{17}H_{15}NO_5S$)
From **11b** (0.65 g, 2 mmol) as described for **15a**. Yield 0.6 g (90%); mp 172°C (*Me*OH); IR: $\bar{\nu} = 3300$ (NH), 1730 (CO), 1330, 1160 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.5$ (s, O*Me*), 4.3 (d, $J = 6$ Hz, CH_2), 6.2–6.4 (t, NH), 6.6–7.8 (m, 8 *ar* H), 8.34 (s, 4-H) ppm.

N-Benzyl-N-(benzyloxycarbonyl)-2-oxo-2H-chromene-3-sulfonamide (**15c**, $C_{24}H_{19}NO_6S$)
From **13** (0.45 g, 1 mmol) as described for **15a**. Yield 0.35 g (80%); mp 174°C (*Me*OH); IR: $\bar{\nu} = 3060$, 3020 (CH), 1740, 1720 (CO), 1600 (C=C), 1370, 1170 (SO_2) cm^{-1}; ^1H NMR: $\delta = 5.05$ (s, CH_2), 5.17 (s, CH_2), 7.0–7.6 (m, 14 *ar* H), 8.47 (s, 4-H) ppm.

N-Benzyl-1,2-dihydro-2-oxoquinoline-3-sulfonamide (**16**, $C_{16}H_{14}N_2O_3S$)
Methyl chloroformate (1.2 g, 11 mmol) in 10 cm^3 *THF* was dropwise added to a solution of **11a** (3.1 g, 10 mmol) in 20 cm^3 *THF*. Then, the mixture was refluxed for 2 h, cooled to room temperature, washed with a satd. NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo*. Yield 1.55 g (50%); mp 120–121°C ($CHCl_3/CCl_4$); IR: $\bar{\nu} = 3300$ (NH), 3080, 2960 (CH), 1725 (CO), 1330, 1170 (SO_2) cm^{-1}; ^1H NMR: $\delta = 4.4$ (d, $J = 6$ Hz, CH_2), 5.9–6.1 (t, NH), 7.0–8.0 (m, 9 *ar* H, NH), 8.5 (s, 4-H) ppm.

(RS)-2-Benzyl-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17a**, $C_{18}H_{16}N_2O_4S$)
Compound **11a** (3.1 g, 10 mmol) was refluxed in 20 cm^3 $HC(OMe)_3$ for 2 h, and the formed *Me*OH was distilled off. After cooling to room temperature, the mixture was evaporated *in vacuo*. Yield 2.1 g (60%); mp 153°C (*Me*OH); IR: $\bar{\nu} = 1650$ (C=N), 1350, 1180 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (s, O*Me*), 4.3 (s, CH_2), 6.0 (s, 3-H) 7.0–7.7 (9 *ar* H), 8.0 (s, 10-H) ppm.

(RS)-2-(4-Methoxybenzyl)-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17b**, $C_{19}H_{18}N_2O_4S$)
From **11b** (3.5 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 1.4 g (36%); light yellow crystals; mp 147°C (*Me*OH); IR: $\bar{\nu} = 1650$ (C=N), 1350, 1180 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$, 3.8 (2s, 2 O*Me*), 4.2 (dd, $J = 2.2$, 17.6 Hz, 1H, CH_2), 4.6 (dd, $J = 1.1$, 17.6 Hz, 1H, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (s, 10-H) ppm.

(RS)-2-(2-Chlorobenzyl)-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17c**, $C_{18}H_{15}ClN_2O_4S$)
From **11c** (3.5 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 1.33 g (34%); light yellow crystals; mp 166°C (*Me*OH); IR: $\bar{\nu} = 1650$ (C=N), 1350, 1180 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (s, O*Me*), 4.2 (dd, $J = 2.2$, 17.6 Hz, 1H, CH_2), 4.6 (dd, $J = 1.1$, 17.6 Hz, 1H, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (*s*, 10-H) ppm.

(RS)-2-[4-(Trifluoromethyl)benzyl]-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17d**, $C_{19}H_{15}F_3N_2O_4S$)
From **11d** (3.8 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 1.9 g (45%); light yellow crystals; mp 175°C (*Me*OH); IR: $\bar{\nu} = 1657$ (C=N), 1601 (C=C), 1327, 1164 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (s, O*Me*), 4.3 (m, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (s, 10-H) ppm.

(RS)-2-(3-Chlorobenzyl)-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17e**, $C_{18}H_{15}ClN_2O_4S$)
From **11e** (3.5 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 2.6 g (67%); light yellow crystals; mp 99°C (*Me*OH); IR: $\bar{\nu} = 1654$ (C=N), 1599 (C=C), 1350, 1175 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (*s*, O*Me*), 4.2 (m, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (*s*, 10-H) ppm.

(RS)-2-[2-(Trifluoromethyl)benzyl]-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17f**, $C_{19}H_{15}F_3N_2O_4S$)
From **11f** (3.8 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 1.8 g (42%); light yellow crystals; mp 140°C (*Me*OH); IR: $\bar{\nu} = 1649$ (C=N), 1611 (C=C), 1354, 1172 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (*s*, O*Me*), 4.5 (dd, $J = 2.2$, 17.6 Hz, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (*s*, 10-H) ppm.

(RS)-2-[3-(Trifluoromethyl)benzyl]-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17g**, $C_{19}H_{15}F_3N_2O_4S$)
From **11g** (3.8 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 3.1 g (73%); light yellow crystals; mp 180°C (*Me*OH); IR: $\bar{\nu} = 1658$ (C=N), 1613 (C=C), 1365, 1197 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (s, O*Me*), 4.4 (dd, $J = 2.2$, 17.6 Hz, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (*s*, 10-H) ppm.

(RS)-2-(3,4-Dimethoxybenzyl)-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17h**, $C_{20}H_{20}N_2O_6S$)
From **11h** (3.7 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 3.3 g (80%); light yellow crystals; mp 147°C (*Me*OH); IR: $\bar{\nu} = 1647$ (C=N), 1597 (C=C), 1368, 1171 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (s, O*Me*), 3.7, 3.8 (2s, 2 O*Me*), 4.3 (s, CH_2), 6.0 (s, 3-H), 6.7–7.7 (m, 7 *ar* H), 7.9 (s, 10-H) ppm.

(RS)-2-(4-Fluorobenzyl)-2,3-dihydro-3-methoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**17i**, $C_{18}H_{15}FN_2O_4S$)
From **11i** (3.3 g, 10 mmol) and 20 cm^3 $HC(OMe)_3$ as described for **17a**. Yield 1.6 g (43%); light yellow crystals; mp 104°C (*Me*OH); IR: $\bar{\nu} = 1650$ (C=N), 1350, 1180 (SO_2) cm^{-1}; ^1H NMR: $\delta = 3.4$ (*s*, O*Me*), 4.2 (dd, $J = 2.2$, 17.6 Hz, 1H, CH_2), 4.6 (dd, $J = 1.1$, 17.6 Hz, 1H, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (*s*, 10-H) ppm.

(RS)-2-Benzyl-2,3-dihydro-3-ethoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**18a**, $C_{19}H_{18}N_2O_4S$)
From **11a** (3.1 g, 10 mmol) and 20 cm^3 $HC(OEt)_3$ as described for **17a**. Yield 2.8 g (75%); mp 128°C (CCl_4); IR: $\bar{\nu} = 3040$, 2980 (CH), 1650 (C=N), 1350, 1180 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.0$–1.2 (t, $J = 8$ Hz, *Me*), 3.5–3.7 (q, $J = 3$ Hz, CH_2), 4.30 (s, CH_2), 6.08 (s, 3-H), 7.2–7.8 (m, 9 *ar* H), 8.00 (s, 10-H) ppm.

(RS)-2,3-Dihydro-3-ethoxy-2-(4-methoxybenzyl)benzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**18b**, $C_{20}H_{20}N_2O_5S$)
From **11b** (0.7 g, 2 mmol) and 20 cm^3 $HC(OEt)_3$ as described for **17a**. Yield 0.6 (75%); mp 134°C (*Me*OH); IR: $\bar{\nu} = 3040$, 2980, 2910 (CH), 1650 (C=N), 1350, 1170 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.1$–1.3 (t, $J = 7$ Hz, *Me*), 3.5–3.9 (m, O*Me*, CH_2), 4.27 (s, CH_2), 6.18 (s, 3-H), 6.7–8.5 (8 *ar* H), 7.89 (s, 10-H) ppm.

(RS)-2-[4-(Trifluoromethyl)benzyl]-2,3-dihydro-3-ethoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**18d**, $C_{20}H_{17}F_3N_2O_4S$)
From **11d** (3.8 g, 10 mmol) and 20 cm^3 $HC(OEt)_3$ as described for **17a**. Yield 1.7 g (38%); light yellow crystals; mp 144°C (*Et*OH); IR: $\bar{\nu} = 1654$ (C=N), 1615 (C=C), 1355, 1174 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.1$ (t, *Me*), 3.7 (m, CH_2), 4.4 (m, CH_2), 6.15 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (s, 10-H) ppm.

(RS)-2-(3-Chlorobenzyl)-2,3-dihydro-3-ethoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**18e**, $C_{19}H_{17}ClN_2O_4S$)
From **11e** (3.5 g, 10 mmol) and 20 cm^3 $HC(OEt)_3$ as described for **17a**. Yield 1.7 g (43%); light yellow crystals; mp 150°C (*Et*OH); IR: $\bar{\nu} = 1656$ (C=N), 1599 (C=C), 1347, 1175 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.05$ (t, *Me*), 3.5 (dd, $J = 2.2$, 17.6 Hz, CH_2), 4.2 (m, CH_2), 6.0 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (s, 10-H) ppm.

(RS)-2-[2-(Trifluoromethyl)benzyl]-2,3-dihydro-3-ethoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**18f**, $C_{20}H_{17}F_3N_2O_4S$)
From **11f** (3.8 g, 10 mmol) and 20 cm^3 $HC(OEt)_3$ as described for **17a**. Yield 1.5 g (34%); light yellow crystals; mp 133°C (*Et*OH); IR: $\bar{\nu} = 1649$ (C=N), 1599 (C=C), 1359, 1178 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.0$ (t, *Me*), 3.7 (m, CH_2), 4.5 (dd, $J = 1.1$, 17.6 Hz, CH_2), 6.2 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 8.0 (s, 10-H) ppm.

(RS)-2-[3-(Trifluoromethyl)benzyl]-2,3-dihydro-3-ethoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**18g**, $C_{20}H_{17}F_3N_2O_4S$)
From **11g** (3.8 g, 10 mmol) and 20 cm^3 $HC(OEt)_3$ as described for **17a**. Yield 2.3 g (53%); light yellow crystals; mp 173°C (*Et*OH); IR: $\bar{\nu} = 1658$ (C=N), 1613 (C=C), 1330, 1175 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.02$ (t, *Me*), 3.6 (q, CH_2), 4.3 (d, CH_2), 6.05 (s, 3-H), 7.0–7.7 (m, 8 *ar* H), 7.9 (s, 10-H) ppm.

(RS)-2-(3,4-Dimethoxybenzyl)-2,3-dihydro-3-ethoxybenzopyrano[3,2-e][1,2,4]thiadiazine 1,1-dioxide (**18h**, $C_{21}H_{22}N_2O_6S$)
From **11h** (3.7 g, 10 mmol) and 20 cm^3 $HC(OEt)_3$ as described for **17a**. Yield 2.8 g (64%); light yellow crystals; mp 167°C (*Et*OH); IR: $\bar{\nu} = 1646$ (C=N), 1614 (C=C), 1371, 1172 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.25$ (t, *Me*), 3.7, 3.8 (2s, 2 O*Me*), 4.3 (s, CH_2), 6.1 (s, 3-H), 6.7–7.7 (m, 7 *ar* H), 8.0 (s, 10-H) ppm.

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