Tetrahedron 65 (2009) 9280–9284

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Heterocyclic pentafluorophenyl sulfonate esters as shelf stable alternatives to sulfonyl chlorides

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ARTICLE INFO

Article history:
Received 22 June 2009
Received in revised form 21 August 2009
Accepted 3 September 2009
Available online 9 September 2009

ABSTRACT

Heterocyclic pentafluorophenyl sulfonate esters are shelf stable alternatives to the often less stable sulfonyl chlorides. They are easily prepared from thiols and react readily with primary and secondary amines to produce sulfonamides in high yields.

1. Introduction

The sulfonamide moiety has proven to be an important functionality in the drug development process during the past decades. Starting with the antibacterial sulfa drugs[1] and later incorporated into launched drugs with a variety of different pharmacological effects, like Argatroban (Thrombin inhibitor), Udenafil (PDE5 inhibitor), Sumatriptan (5-HT agonist) and Tipranavir (HIV protease inhibitor), see Figure 1. Furthermore, they are widely used in organic synthesis as nitrogen protecting groups.[2]

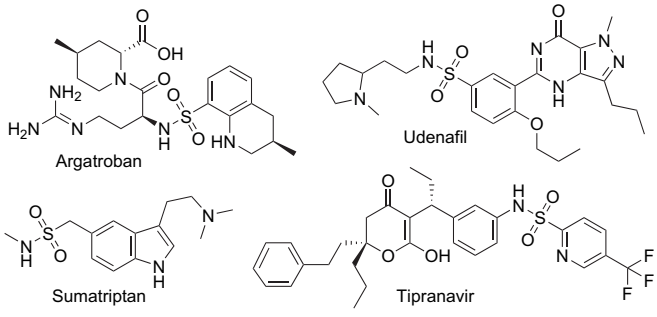

Figure 1. Selected examples of sulfonamide based drugs.

Sulfonamides can be prepared from the corresponding sulfonyl chlorides and amines, as this is a very efficient process in most cases.[3] However, some sulfonyl chlorides are difficult to prepare or unstable. This is particularly the case with electron deficient heterocyclic sulfonyl chlorides, which, depending on the electronic nature of the heterocycle, readily decomposes via extrusion of SO_2 to give the corresponding heteroaryl chloride.[4]

For this reason only a limited number of heterocyclic sulfonyl chlorides are commercially available as compared to arylsulfonyl chlorides. Thus, many heterocyclic sulfonyl chlorides have to be used immediately once prepared to prevent decomposition. Although this leads to the desired sulfonamides, it is inconvenient if a series of compounds are to be prepared. In this context a shelf stable reagent that can be used without any special precautions would be a major advantage.

We were interested in preparing a series of heterocyclic sulfonamides, and were faced with the problems outlined above. Herein, we wish to report that the corresponding pentafluorophenyl sulfonate esters (PFP sulfonate esters) are excellent surrogates for unstable heterocyclic sulfonyl chlorides. The PFP sulfonate esters are readily prepared from the corresponding thiols, and react with primary and secondary amines to give sulfonamides.

2. Results and discussion

Heterocyclic sulfonyl chlorides have traditionally been prepared via oxidation of the corresponding thiols with Cl_2,[5] although other reagents have also been developed.[6] Recently, Wright and Hallström described a very convenient procedure, where NaOCl was used as the oxidant.[7] They were confronted with the same problems of instability, and chose to react the sulfonyl chlorides directly with amines. Subsequently, they sought to convert the sulfonyl chlorides to a shelf stable entity that would react similarly. They converted six different heterocyclic sulfonyl chlorides to the corresponding sulfonyl fluorides, as sulfonyl fluorides previously have been reported to serve this purpose.[8] However, the sulfonyl fluorides proved to be quite difficult to handle, as they decomposed

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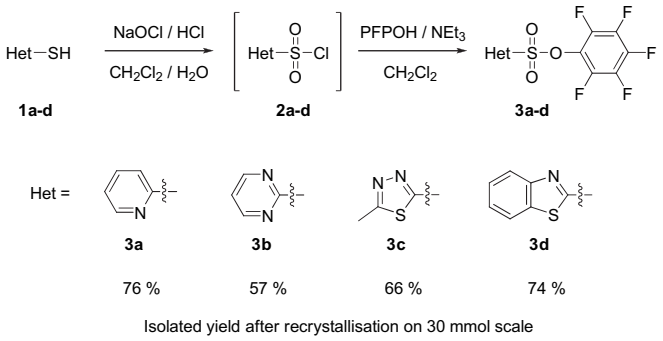
doi:10.1016/j.tet.2009.09.015

upon attempted chromatography on silica or alumina. Furthermore, no details were given on how these sulfonyl fluorides may be implemented in the synthesis of sulfonamides or other transformations. Other surrogates for sulfonyl chlorides have been developed, e.g., Katritzky's sulfonylbenzotriazoles, but they are not very reactive and require heating at 80 °C for extended periods of time to react with amines.[9]

Recently, Caddick et al. have described the synthesis and application of aryl PFP sulfonate esters (Ar-SO_2OPFP).[10] These esters are much less reactive than the corresponding arylsulfonyl chlorides, and as such also much more stable. Electron donating groups on the aromatic ring decrease the reactivity of these reagents toward amines, while electron withdrawing groups increase the reactivity. We believed that this concept would be ideally suited to electron deficient heterocyclic substrates. Heteroaryl PFP esters (Het-SO_2OPFP) would be expected to be more stable than the corresponding chlorides (Het-SO_2Cl) while maintaining a reasonable level of reactivity toward amines, therefore a good compromise between reactivity and stability.

We adopted Wright and Hallström's procedure with some minor improvements[11] to prepare four different heterocyclic sulfonyl chlorides **2a**–**d**, which were directly converted to the corresponding heterocyclic PFP esters **3a**–**d**, see Scheme 1.



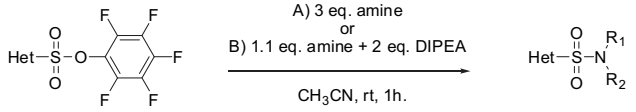
Scheme 1. Synthesis of pentafluorophenyl sulfonate esters.

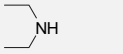
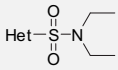
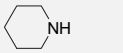
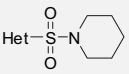
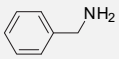
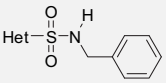
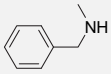
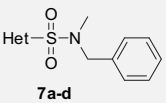
Pyridine-2-sulfonyl chloride (**2a**) is widely used to introduce the pyridine sulfonyl moiety, both as a protecting group and as a building block for medicinal chemistry programs.[12] It is moderately stable and can be stored for prolonged periods of time at low temperature.[13] We included this heterocyclic derivative in our survey to investigate if the corresponding PFP sulfonate ester (**3a**) would retain a reasonable level of reactivity, while at the same time demonstrating a higher stability than **2a**.

Starting from 2-mercaptopyridine (**1a**) the corresponding PFP sulfonate ester (**3a**) was isolated in 76% yield after recrystallization of the crude product, see Scheme 1. This material is very stable and **3a** can be stored at rt without special precaution.[14] Pyrimidine-2-sulfonyl chloride (**2b**) is of much lower stability than **2a**, and can only be handled at low temperatures.[15] Applying the same conditions to **1b** as described above provided **3b** in 57% yield after recrystallization.[14] Vedejs et al. showed that 5-methyl-1,3,4-thiadiazole-2-sulfonyl chloride (**2c**) (often abbreviated to ThsCl) and benzo[*d*]thiazole-2-sulfonyl chloride (**2d**) (often abbreviated to BtsCl) can be used to introduce the Ths- and Bts-group, respectively.[16] They are very useful nitrogen protecting groups, but their use have been quite limited presumably due to the limited stability of **2c** and **2d**[17] and the fact that Cl_2-gas was originally used in their preparation. In our hands, **1c** and **1d** were converted to the corresponding PFP sulfonate esters **3c** and **3d** in 66 and 74% yield after recrystallization. **3c** and **3d** are both stable materials that can be stored without any special precautions.[14]

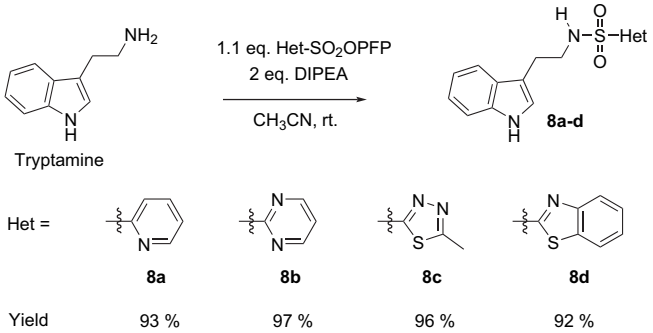
With the four different heteroaryl PFP sulfonate esters in hand we examined their reaction with amines, see Table 1. Treatment of **3a**–**d** with a slight excess of simple primary and secondary amines in CH_3CN at rt leads to full consumption of the Het-SO_2OPFP within 1 h. Two different conditions can be used: either 3 equiv of the amine (conditions A) or 1.1 equiv with 2 equiv of *N*,*N*-diisopropylethylamine (DIPEA) present to trap the pentafluorophenol produced (conditions B), see Experimental section for details. In all cases the resulting sulfonamides were isolated in good to excellent yields based on the pentafluorophenyl sulfonate esters, see Table 1.

Table 1
Reaction of Het-SO_2OPFP with amines



Amine	Het-SO_2OPFP	Conditions	Product	Yield (%)
	**3a**	**A**	 **4a-d**	93
	3b			98
	3c			92
	3d			95
	**3a**	**A**	 **5a-d**	95
	3b			93
	3c			93
	3d			94
	**3a**	**B**	 **6a-d**	91
	3b			92
	3c			90
	3d			92
	**3a**	**B**	 **7a-d**	92
	3b			89
	3c			97
	3d			91

Finally, as the Het-SO_2OPFP often would be used as a reagent, we also performed a series of experiments with an amine as the limiting factor. Tryptamine was reacted with 1.1 equiv of **3a**–**d** in the presence of 2 equiv DIPEA, which in all cases gave the corresponding sulfonamides **8a**–**d** in very good yields, see Scheme 2.



Scheme 2. Synthesis of tryptamine derived sulfonamides.

In conclusion, our results validate that heterocyclic pentafluorophenyl sulfonate esters are a synthetically useful compromise between reactivity and stability, and are ideally suited for the synthesis of heterocyclic sulfonamides in parallel synthesis and in general. Furthermore, the ease of preparation, high stability, and reactivity of **3c** and **3d** might encourage chemists to reexamine the utility of the Ths- and Bts-protecting groups in organic synthesis.

3. Experimental

3.1. General

Flash chromatography was performed on silica gel (Merck Kieselgel 60, mesh 230–400). Melting points were measured on an Optimelt automated melting point system using standard settings and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 DXP spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to Me_4Si and J values are given hertz. Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak (77.16 ppm for $CDCl_3$ and 39.52 ppm for DMSO-*d*). Chemical shifts (δ_C) for the pentafluorophenol part of the heterocyclic pentafluorophenyl sulfonate esters (**3a**–**d**) are not reported due to C–F couplings. The following compounds have previously been reported in the literature: **4a**, **4d**, **5a**, **5d**, **6a**, **6b**, **6d**, **7a**. NMR data of known compounds **4d**, **5d** and **7a** have been included here as they do not appear in the literature. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds are available as Supplementary data.

3.2. General procedure for the synthesis of heterocyclic pentafluorophenyl sulfonate esters

The following procedure is adapted from Wright and Hallström.[7] To a mechanical stirred mixture of 2 M HCl (76 mL) and CH_2Cl_2 (100 mL) cooled to −5 °C (internal temperature) was added a cold (5 °C) sodium hypochlorite (~10% solution, 1.55 M, 65 mL, 100 mmol, 3.3 equiv) at such a rate that the temperature was maintained below 0 °C. Thiol **1a**–**d** (30 mmol) was added in small portions while maintaining the internal temperature at −10 °C to −5 °C. The mixture was stirred for 15–20 min at −10 °C to −5 °C after the addition was complete. Excess chlorine was quenched by adding cold (0 °C) 1 M Na_2SO_3 or 1 M $Na_2S_2O_3$ until the yellow greenish color of the mixture disappeared and iodide paper (KI/starch) no longer gave a fast coloration.[18] The mixture was then transferred to a separating funnel (pre-cooled either in the freezer or with ice water) and the organic layer was rapidly separated and collected in a clean flask cooled in a dry ice-acetone bath. The aqueous phase was quickly extracted with cold (−10 °C) CH_2Cl_2 (40 mL). The organic extracts were combined and dried over $MgSO_4$ under N_2 atmosphere cooled in a dry ice-acetone bath. The mixture was filtered through a glass fritted funnel into a cold (−30 °C) stirred solution of pentafluorophenol (5.52 g, 30 mmol) and Et_3N (4.40 mL, 31.5 mmol) in 20 mL of CH_2Cl_2. The mixture was stirred for 1 h cooled in a salt-ice bath. The reaction mixture was washed with water (60 mL), 10% KH_2PO_4 (2×60 mL), saturated $NaHCO_3$ (2×60 mL), water (60 mL), and brine (60 mL). The organic fraction was dried ($MgSO_4$) and concentrated in vacuo.

*3.2.1. Pentafluorophenyl pyridin-2-sulfonate (**3a**).* Following the general procedure with the following exception: the reaction mixture was concentrated in vacuo, the residue was taken up in 200 mL of Et_2O, and worked up as described in the general procedure. The reaction of 2-mercaptopyridine (3.33 g, 30 mmol) gave 9.25 g of crude product. This was treated with activated carbon in EtOAc, filtered through Celite, and recrystallized from EtOAc/*n*-hexane giving 7.41 g (76%) of **3a** as large off white crystals, mp 64.8–66.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.83–8.79 (m, 1H), 8.16–8.13 (m, 1H), 8.06 (td, J=7.8, 1.7, 1H), 7.70 (ddd, J=7.5, 4.7, 1.2, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 150.9, 138.8, 129.0, 124.1. Anal. Calcd for $C_{11}H_4F_5NO_3S$: C 40.63; H 1.24; N 4.31. Found: C 40.41; H 1.10; N 4.13.

*3.2.2. Pentafluorophenyl pyrimidine-2-sulfonate (**3b**).* Following the general procedure, the reaction of 2-mercaptopyrimidine (3.36 g, 30 mmol) gave 7.89 g of a light yellow solid, which was recrystallized from EtOAc/*n*-heptane giving 5.93 g of **3b** contaminated by small amounts of Et_3NH–OPFP salt. The product was dissolved in EtOAc and filtered through a 3 cm plug of silica using EtOAc as eluent yielding 5.54 g (**57**%) of pure **3b** as a white solid, mp 85.9–86.7 °C. A further recrystallization from EtOAc/*n*-heptane gave **3b** as white needles, mp 85.9–86.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (d, J=4.9, 2H), 7.72 (t, J=4.9, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 159.4, 125.2. Anal. Calcd for $C_{10}H_3F_5N_2O_3S$: C 36.82; H 0.93; N 8.59. Found: C 36.64; H 0.95; N 8.44.

*3.2.3. Pentafluorophenyl 5-methyl-1,3,4-thiadiazole-2-sulfonate (**3c**).* Following the general procedure, the reaction of 2-mercapto-5-methyl-1,3,4-thiadiazole (3.97 g, 30 mmol) gave 9.47 g pale yellow solid, which was recrystallized from EtOAc/*n*-hexane yielding 7.66 g (73%) of **3c** as white crystals, mp 61.7–62.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 161.8, 16.3. Anal. Calcd for $C_9H_3F_5N_2O_3S_2$: C 31.22; H 0.87; N 8.09. Found: C 31.18; H 0.84; N 8.01.

*3.2.4. Pentafluorophenyl benzothiazole-2-sulfonate (**3d**).* Following the general procedure, the reaction of 2-mercaptobenzothiazole (5.02 g, 30 mmol) gave 9.66 g crude product, which was recrystallized from EtOAc/*n*-heptane giving 7.50 g (66%) of **3d** as off white crystals, mp 94.7–96.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31–8.25 (m, 1H), 8.09–8.03 (m, 1H), 7.75–7.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 152.2, 137.4, 129.3, 128.5, 126.3, 122.4. Anal. Calcd for $C_{13}H_4F_5NO_3S_2$: C 40.95; H 1.06; N, 3.67. Found: C 40.87; H 0.98; N 3.47.

3.3. Synthesis of sulfonamides from PFP-sulfonates and amines

3.3.1. General procedure A. The heterocyclic pentafluorophenyl sulfonate ester (**3a**–**d**) (1 mmol) was dissolved in CH_3CN (3 mL) and the amine (3 mmol) was added. Stirring was continued at rt for 1 h before the mixture was diluted with aqueous KH_2PO_4 (10%, 20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo. Flash chromatography (heptane/EtOAc) gave the pure sulfonamides.

3.3.2. General procedure B. The pentafluorophenyl sulfonate ester (**3a**–**d**) (1 mmol) was dissolved in CH_3CN (3 mL) and the amine (1.1 mmol) and *N*,*N*-diisopropylethylamine (2 mmol) was added. Stirring was continued at rt for 1 h before the mixture was diluted with 10% KH_2PO_4 (aq) (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo. Flash chromatography (heptane/EtOAc) gave the pure sulfonamides.

3.3.3. General procedure C. Tryptamine (1 mmol) and the pentafluorophenyl sulfonate ester (**3a**–**d**) (1.1 mmol) were dissolved in CH_3CN (3 mL) and *N*,*N*-diisopropylethylamine (2 mmol) was added. Stirring was continued at rt for 1 h before the mixture was diluted with 10% KH_2PO_4 (aq) (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo. Flash chromatography (heptane/EtOAc) gave the pure sulfonamides.

*3.3.3.1. N,N-Diethyl-pyridine-2-sulfonamide (**4a**).* Following general procedure A: **3a** and diethylamine gave 199 mg (93%) of **4a** as a clear colorless oil. ^{1}H and ^{13}C NMR are in full agreement with previously reported values.[19]

*3.3.3.2. N,N-Diethyl-pyrimidine-2-sulfonamide (**4b**).* Following general procedure A: **3b** and diethylamine gave 210 mg (98%) of **4b**

as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90 (d, J=4.9, 2H), 7.49 (t, J=4.9, 1H), 3.47 (q, J=7.2, 4H), 1.19 (t, J=7.2, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 158.5, 123.0, 43.3, 14.6. Anal. Calcd for $C_8H_{13}N_3O_2S$: C 44.63; H 6.09; N, 19.52. Found: C 44.85; H 6.05; N 19.37.

*3.3.3.3. N,N-Diethyl-5-methyl-1,3,4-thiadiazole-2-sulfonamide (**4c**).* Following general procedure A: **3c** and diethylamine gave 216 mg (92%) of **4c** as white crystals, mp 47.6–48.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (q, J=7.2, 4H), 2.85 (s, 3H), 1.25 (t, J=7.2, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 168.6, 43.7, 16.0, 14.5. Anal. Calcd for $C_7H_{13}N_3O_2S_2$: C 35.73; H 5.57; N, 17.86. Found: C 35.77; H 5.27; N 17.59.

*3.3.3.4. N,N-Diethyl-benzo[d]thiazole-2-sulfonamide (**4d**).* Following general procedure A: **3d** and diethylamine gave 258 mg (95%) of **4d** as white crystals, mp 72.5–73.4 °C (lit. 167–168 °C).[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18–8.14 (m, 1H), 7.99–7.94 (m, 1H), 7.62–7.50 (m, 2H), 3.49 (q, J=7.2, 4H), 1.23 (t, J=7.2, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 152.7, 136.4, 127.5, 127.4, 125.2, 122.2, 43.3, 14.4.

*3.3.3.5. 2-(Piperidin-1-ylsulfonyl)pyridine (**5a**).* Following general procedure A: **3a** and piperidine gave 215 mg (95%) of **5a** as white crystals, mp 55.5–56.3 °C (lit. 55.2 °C).[21] ^{1}H and ^{13}C NMR are in full agreement with previously reported values.[21]

*3.3.3.6. 2-(Piperidin-1-ylsulfonyl)pyrimidine (**5b**).* Following general procedure A: **3b** and piperidine gave 210 mg (93%) of **5b** as a clear colorless oil that solidified on standing in the fridge giving **5b** as white crystals, mp 28.0–28.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (d, J=4.9, 2H), 7.51 (t, J=4.9, 1H), 3.46–3.40 (m, 4H), 1.71–1.62 (m, 4H), 1.61–1.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 158.5, 123.2, 47.6, 25.6, 23.7. Anal. Calcd for $C_9H_{13}N_3O_2S$: C 47.56; H 5.77; N, 18.49. Found: C 47.54; H 5.66; N 18.30.

*3.3.3.7. 2-Methyl-5-(piperidin-1-ylsulfonyl)-1,3,4-thiadiazole (**5c**).* Following general procedure A: **3c** and piperidine gave 230 mg (93%) of **5c** as white crystals, mp 98.7–99.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44–3.38 (m, 4H), 2.86 (s, 3H), 1.74–1.67 (m, 4H), 1.62–1.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 166.9, 47.6, 25.3, 23.5, 16.0. Anal. Calcd for $C_8H_{13}N_3O_2S_2$: C 38.85; H 5.30; N, 16.99. Found: C 38.85; H 5.09; N 16.99.

*3.3.3.8. 2-(Piperidin-1-ylsulfonyl)-benzo[d]thiazole (**5d**).* Following general procedure A: **3d** and piperidine gave 265 mg (94%) of **5d** as white crystals, mp 121.4–122.6 °C (lit. 112 °C).[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21–8.18 (m, 1H), 8.00–7.95 (m, 1H), 7.64–7.52 (m, 2H), 3.42–3.35 (m, 4H), 1.72–1.65 (m, 4H), 1.56–1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4, 152.8, 136.4, 127.6, 127.4, 125.3, 122.2, 47.6, 25.4, 23.6.

*3.3.3.9. N-Benzyl-pyridine-2-sulfonamide (**6a**).* Following general procedure B: **3a** and benzylamine gave 226 mg (91%) of **6a** as white crystals, mp 102.9–103.7 °C (lit. 102–103 °C).[7] ^{1}H and ^{13}C NMR are in full agreement with previously reported values.[7]

*3.3.3.10. N-Benzyl-pyrimidine-2-sulfonamide (**6b**).* Following general procedure B: **3b** and benzylamine gave 230 mg (92%) of **6b** as white crystals, mp 122.3–123.1 °C (lit. 117–118 °C).[7] ^{1}H and ^{13}C NMR are in full agreement with previously reported values.[7]

*3.3.3.11. N-Benzyl-5-methyl-1,3,4-thiadiazole-2-sulfonamide (**6c**).* Following general procedure B: **3c** and benzylamine gave 242 mg (90%) of **6c** as white crystals, mp 103.3–104.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.27 (m, 5H), 6.15 (br s, 1H), 4.43 (s, 2H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 168.6, 135.7, 128.9, 128.3, 128.2, 48.2, 15.9. Anal. Calcd for $C_{10}H_{11}N_3O_2S_2$: C 44.59; H 4.12; N, 15.60. Found: C 44.48; H 3.95; N 15.52.

*3.3.3.12. N-Benzyl-benzo[d]thiazole-2-sulfonamide (**6d**).* Following general procedure B: **3d** and benzylamine gave 280 mg (92%) of **6d** as white crystals, mp 131.6–132.9 °C (lit. 129–130 °C).[7] ^{1}H and ^{13}C NMR are in full agreement with previously reported values.[7]

*3.3.3.13. N-Benzyl-N-methyl-pyridine-2-sulfonamide (**7a**).* Following general procedure B: **3a** and *N*-methyl-benzylamine gave 228 mg (92%) of **7a** as white crystals, mp 52.9–53.9 °C (lit. 50–52 °C).[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76–8.71 (m, 1H), 8.03–7.97 (m, 1H), 7.92 (td, J=1.7, 7.7, 1H), 7.50 (ddd, J=1.2, 4.7, 7.4, 1H), 7.39–7.27 (m, 5H), 4.45 (s, 2H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 150.1, 138.0, 136.1, 128.7, 128.4, 128.0, 126.6, 122.9, 55.1, 35.2.

*3.3.3.14. N-Benzyl-N-methyl-pyrimidine-2-sulfonamide (**7b**).* Following general procedure B: **3b** and *N*-methyl-benzylamine gave 234 mg (89%) of **7b** as white crystals, mp 119.2–120.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (d, J=4.9, 2H), 7.52 (t, J=4.9, 1H), 7.41–7.27 (m, 5H), 4.53 (s, 2H), 2.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 158.6, 135.8, 128.8, 128.5, 128.0, 123.3, 55.2, 35.4. Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C 54.74; H 4.98; N, 15.96. Found: C 54.59; H 4.73; N 15.78.

*3.3.3.15. N-Benzyl-N,5-dimethyl-1,3,4-thiadiazole-2-sulfonamide (**7c**).* Following general procedure B: **3c** and *N*-methyl-benzylamine gave 275 mg (97%) of **7c** as white crystals, mp 88.8–89.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5H), 4.52 (s, 2H), 2.93 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 167.1, 135.0, 129.0, 128.6, 128.4, 55.1, 35.3, 16.0. Anal. Calcd for $C_{11}H_{13}N_3O_2S_2$: C 46.62; H 4.62; N, 14.83. Found: C 46.57; H 4.45; N 14.71.

*3.3.3.16. N-Benzyl-N-methyl-benzo[d]thiazole-2-sulfonamide (**7d**).* Following general procedure B: **3d** and *N*-methyl-benzylamine gave 290 mg (91%) of **7d** as white crystals, mp 95.9–96.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24–8.19 (m, 1H), 8.01–7.97 (m, 1H), 7.66–7.54 (m, 2H), 7.39–7.27 (m, 5H), 4.49 (s. 2H), 2.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 152.7, 136.4, 135.3, 128.9, 128.6, 128.3, 127.7, 127.5, 125.4, 122.3, 54.9, 35.2. Anal. Calcd for $C_{15}H_{14}N_3O_2S_2$: C 56.58; H 4.43; N, 8.80. Found: C 56.49; H 4.28; N 8.65.

*3.3.3.17. N-(2-(1H-Indol-3-yl)ethyl)-pyridine-2-sulfonamide (**8a**).* Following general procedure C: **3a** gave 281 mg (93%) of **8a** as white crystals, mp 95.6–96.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, J=4.6, 1H), 8.09 (s, 1H), 7.96–7.92 (m, 1H), 7.82 (td, J=7.7, 1.7, 1H), 7.43 (d, J=8.0, 1H), 7.38 (ddd, 7.6, 4.7, 1.1, 1H), 7.33 (d, J=8.1, 1H), 7.21–7.13 (m, 1H), 7.09–7.02 (m, 1H), 7.01 (d, J=2.3, 1H), 5.08 (t, J=5.9, 1H), 3.39 (q, J=6.6, 2H), 2.95 (t, J=6.7, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 150.0, 138.0, 136.5, 127.1, 126.6, 122.8, 122.3, 122.2, 119.5, 118.6, 111.9, 111.5, 43.7, 25.9. Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C 59.78; H 5.02; N, 13.94. Found: C 60.21; H 4.93; N 14.03.

*3.3.3.18. N-(2-(1H-Indol-3-yl)ethyl)-pyrimidine-2-sulfonamide (**8b**).* Following general procedure C: **3b** gave 293 mg (97%) of **8b** as white crystals, mp 152.8–155.0 °C. ^{1}H NMR (300 MHz, DMSO): δ 10.80 (s, 1H), 8.99 (d, J=4.9, 2H), 8.17 (s, 1H), 7.72 (t, J=4.9, 1H), 7.45 (d, J=7.7, 1H), 7.32 (d, J=8.0, 1H), 7.15 (d, J=2.3, 1H), 7.09–7.03 (m, 1H), 7.00–6.94 (m, 1H), 3.37–3.28 (m, 2H), 2.92–2.83 (m, 2H). ^{13}C NMR (75 MHz, DMSO): δ 165.8, 158.8, 136.2, 127.0, 123.6, 122.9, 120.9, 118.3, 118.0, 111.4, 110.9, 44.1, 25.9. Anal. Calcd for $C_{14}H_{14}N_4O_2S$: C 55.61; H 4.67; N, 18.53. Found: C 56.08; H 4.52; N 18.72. HRMS calcd for $C_{14}H_{15}N_4O_2S$ ($M+H^+$): 303.0916. Found 303.0892.

*3.3.3.19. N-(2-(1H-Indol-3-yl)ethyl)-5-methyl-1,3,4-thiadiazole-2-sulfonamide (**8c**).* Following general procedure C: **3c** gave 310 mg (96%) of **8c** as white crystals, mp 150.7–151.9 °C. ^{1}H NMR (300 MHz,

DMSO-*d*): δ 10.83 (s, 1H), 8.88 (s, 1H), 7.46 (d, J=7.8, 1H), 7.33 (d, J=8.0, 1H), 7.14 (d, J=2.3, 1H), 7.10–7.03 (m, 1H), 7.01–6.94 (m, 1H), 3.32 (t, J=7.5, 2H), 2.89 (t, J=7.5, 2H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*): δ 170.0, 168.6, 136.2, 126.9, 123.1, 120.9, 118.3, 118.0, 111.4, 110.5, 43.8, 25.4, 15.5. Anal. Calcd for $C_{13}H_{14}N_4O_2S_2$: C 48.43; H 4.38; N, 17.38. Found: C 48.76; H 4.21; N 17.51.

*3.3.3.20. N-(2-(1H-Indol-3-yl)ethyl)-benzo[d]thiazole-2-sulfonamide (**8d**).* Following general procedure C: **3d** gave 328 mg (92%) of **8d** as white crystals, mp 104.2–105.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–8.07 (m, 1H), 8.00 (s, 1H), 7.94–7.89 (m, 1H), 7.61–7.49 (m, 2H), 7.45 (d, J=8.0, 1H), 7.32–7.28 (m, 1H), 7.17–7.11 (m, 1H), 7.04–6.99 (m, 2H), 5.19 (t, J=5.9, 1H), 3.60 (q, J=6.5, 2H), 3.01 (t, J=6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 152.4, 136.5, 127.7, 127.5, 127.0, 125.1, 122.8, 122.4, 122.3, 119.7, 118.5, 111.41, 111.38, 44.1, 25.8. One carbon signal is missing. Judging from a DEPT spectrum of **8d** and the ^{13}C integrals, the peak at 136.5 ppm most likely consists of two coinciding signals. Furthermore, the tryptamine part in **8a**–**8c** and the benzo[*d*]thiazole-2-sulfonyl part in **4d**, **5d**, and **7d** both show ^{13}C NMR signals in the vicinity of 136.5 ppm. Anal. Calcd for $C_{17}H_{15}N_3O_2S_2$: C 57.12; H 4.23; N 11.76. Found: C 56.64; H 4.01; 11.59. HRMS calcd for $C_{17}H_{16}N_3O_2S_2$ ($M+H^+$): 358.0684. Found 358.0671.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.09.015.

References and notes

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