Preparation of 4,6-Disubstituted 5-Pyrimidinesulfonamides

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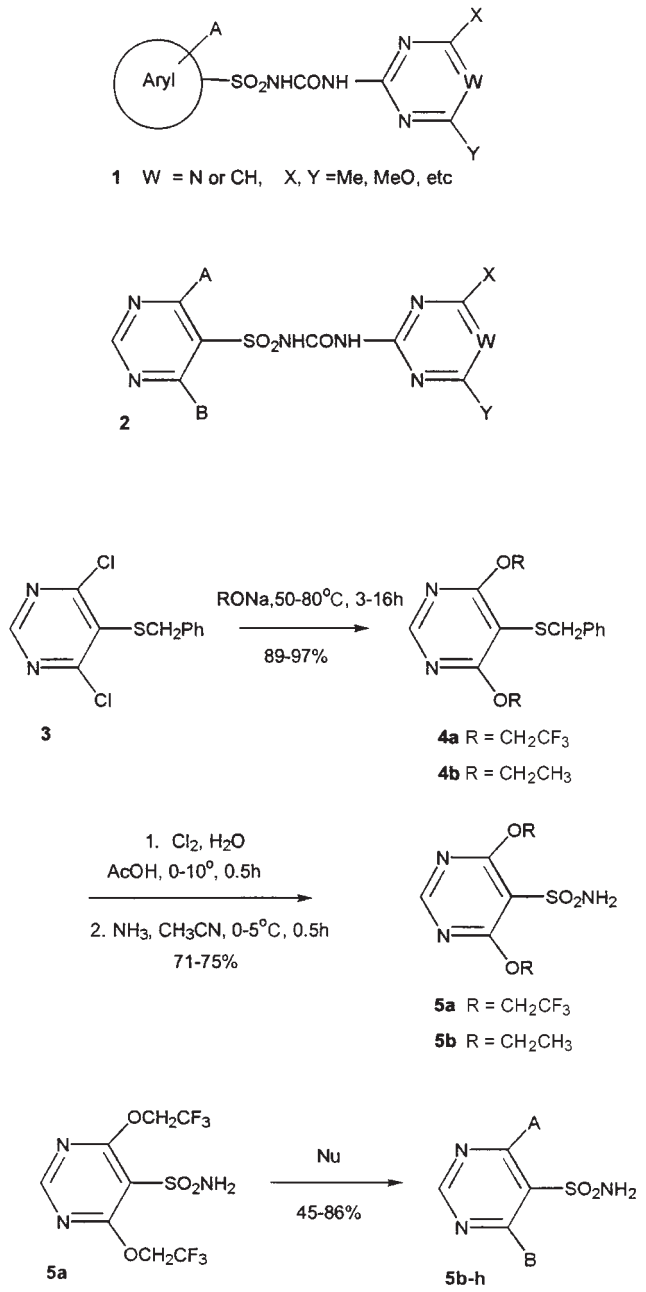
The first general synthesis of 4,6-disubstituted 5-pyrimidinesulfonamides is described. Treatment of 4,6-dichloro-5-benzylthiopyrimidine (**3**) with ethoxide or trifluoroethoxide, oxidation of the benzylthio group to a sulfonyl chloride and reaction with ammonia gave 4,6-dialkoxy-5-pyrimidinesulfonamides **5a,b.** Stepwise displacement of the trifluoroethoxy groups in **5a** gave a variety of symmetrical and non-symmetrical 4,6-disubstituted 5-pyrimidinesulfonamides **5b—h.**

The sulfonylurea herbicides represent a major development in agricultural chemistry, providing broad spectrum weed control at field rates as low as 2 to 5 grams/hectare. Since their discovery by DuPont chemists in 1976,[3] more than twenty different sulfonylurea herbicides have been commercialized for weed control in many important crops.[4] The requirements for activity have been well described by Levitt[5] and most herbicidal sulfonylureas fall into the general class of structure **1**. For high herbicidal activity it is important that the aryl ring contains a substituent ortho to the sulfonylurea bridge, but no substituent para to the bridge. There are commercial sulfonylurea herbicides in which the aryl ring in structure **1** is a substituted benzene (11 examples), pyrazole (4 examples), pyridine (3 examples) or a thiophene ring.[4]

Arylsulfonylureas in which the aryl ring is pyrimidine are disclosed in the patent literature,[6] but the only example given was prepared from a 2-pyrimidinesulfonamide and is herbicidally inactive, probably because it has no substituents ortho to the sulfonyl group. We believed that it should be possible to achieve high herbicidal activity with pyrimidylsulfonylureas of general structure **2**, prepared from either 4-substituted or 4,6-disubstituted 5-pyrimidinesulfonamides. However, the only reported preparation of a 5-pyrimidinesulfonamide lacking a 2-substituent involved a low yielding and indirect synthesis of 4,6-diamino-5-pyrimidinesulfonamide.[7] We have now developed a more general synthetic route for the preparation of such pyrimidine derivatives and have confirmed that sulfonylureas prepared with these new sulfonamides have high herbicidal activity.[8]

Chlorosulfonation would appear to be the most direct method for the preparation of 5-pyrimidinesulfonamides. Thus, uracil is known to react at high temperatures to give 5-chlorosulfonyl-2,4-dihydroxypyrimidine,[9] but we have found that 4,6-dihydroxypyrimidine does not undergo chlorosulfonation under similar conditions,

We have recently reported[10] a convenient synthesis of 5-benzylthio-4,6-dichloropyrimidine (**3**) from the readily available 4,6-dihydroxypyrimidine and we now report that compound **3** is a useful precursor to a wide range of 4,6-disubstituted 5-pyrimidinesulfonamides. Thus, nucleophilic replacement of the 4,6-dichloro substituents on compound **3** with 2,2,2-trifluoroethoxy or ethoxy groups gave compounds **4a** and **4b**, and then oxidative chlorination[11] gave the corresponding sulfonyl chlorides, which were immediately converted to the sulfonamides **5a** and **5b**, in good overall yield (Scheme).



Scheme

It is well known[12] that activated 4-alkoxypyrimidines will undergo reactions such as transalkoxylation, alkaline hydrolysis and aminolysis, though in general fairly harsh conditions such as elevated temperatures are necessary. Trifluoroethoxy is known[13] to be a better leaving group than ethoxy and therefore we decided to test the use of compound **5a** as the key precursor to a variety of 4,6-disubstituted 5-pyrimidinesulfonamides. We have found that the bis(trifluoroethoxy)pyrimidinesulfonamide **5a** undergoes nucleophilic displacement of one or both of the trifluoroethoxy substituents under mild conditions and we have used **5a** to prepare the various other sulfonamides **5b–h** shown in the Table.

Table. Sulfonamides **5b–h** Prepared from **5a** by Reaction with Nucleophiles

Product	A	B	Nucleophile	Yield (%)
5b	OEt	OEt	EtO^-	72
5c	OEt	OCH_2CF_3	EtO^-	52
5d	SMe	OCH_2CF_3	MeS^-	73
5e	SMe	SMe	MeS^-	72
5f	HO	OCH_2CF_3	HO^-	86
5g	NH_2	OCH_2CF_3	NH_3	59
5h	NH_2	NH_2	NH_3	45

Melting points were determined using a Gallenkamp MFB-595 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer in DMSO-d_6 as solvent (unless otherwise specified), locked on solvent deuterium and referenced to residual solvent protons. Mass spectra were measured with a VG Trio-1 spectrometer at 70 eV. TLC was carried out on Whatman silica gel 60A plates and Merck silica gel 60 (0.063-0.20 mm) was used for column chromatography. Commercially available solvents and reagents were used without further purification.

5-Benzylthio-4,6-bis(2,2,2-trifluoroethoxy)pyrimidine (4a):
NaH (60% dispersion in oil, 1.8 g, 45 mmol) was added to a solution of 2,2,2-trifluoroethanol (3.25 mL, 45 mmol) in dioxane (30 mL) and the mixture was stirred at r.t. for 0.5 h, 5-Benzylthio-4,6-dichloropyrimidine (**3;** 3.0 g, 11 mmol) in dioxane (20 mL) was added slowly (15 min) and the resulting mixture was stirred for 3 h at 50°C. The solvent was evaporated and the residue was partitioned between EtOAc and dil aq 5% citric acid. The organic layer was washed with H_2O, separated, dried ($MgSO_4$) and evaporated to give the product (4.3 g, 97%) as a yellow oil which crystallized on standing to give compound 4**a** as pale yellow crystals; mp 57–58 °C.

$C_{15}H_{12}F_6N_2O_2S$	calc.	C	45.23	H	3.04	N	7.03
(398.3)	found		45.58		3.09		6.85

^1H NMR ($CDCl_3$): δ = 4.05 (2 H, s), 4.78 (4 H, q, J = 8.3 Hz), 7.19 (5 H, s), 8.26 (1 H, s).
^{13}C NMR: δ = 36.45, 62.90 (q, $J_{C,F}$ = 37 Hz), 98.85, 123.75 (q, $J_{C,F}$ = 276 Hz), 127.27, 128.38, 128.66, 137.31, 155.73, 168.28.

5-Benzylthio-4,6-bis(ethoxy)pyrimidine (4b):
5-Benzylthio-4,6-dichloropyrimidine (**3;** 2.7 g, 10 mmol) was added to a solution of sodium metal (0.7 g, 30 mmol) in EtOH (50 ml) and the solution was refluxed for 16 h. Most of the solvent was evaporated and the residue was partitioned between dil HCl (1 M, 100 mL) and $CHCl_3$ (2 × 100 mL). The combined $CHCl_3$ layers were dried ($MgSO_4$) and evaporated to give the crude product which was purified by chromatography on silica gel to afford **4b** (2.6 g, 89%) as a pale yellow solid; mp 59-61 °C.

$C_{15}H_{18}N_2O_2S$	calc.	C	62.06	H	6.25	N	9.65
(290.4)	found		62.19		6.03		9.51

^1H NMR ($CDCl_3$): δ = 1.35 (6 H, t, J = 7.1 Hz), 3.98 (2 H, s), 4.39 (4 H, q, J = 7.1 Hz), 7.16 (5 H, s), 8.25 (1 H, s).
^{13}C NMR: δ = 14.50, 36.59, 63.13, 97.26, 126.99, 128.20, 128.82, 138.03, 155,94, 169.47.

4,6-Bis(2,2,2-trifluoroethoxy)-5-pyrimidinesulfonamide (5a); Typical Procedure:
A suspension of **4a** (18.5 g, 47 mmol) in AcOH (270 mL) and H_2O (65 mL) was vigorously stirred and cooled to 5 °C. Cl_2 gas was bubbled into the reaction mixture for 20 min and stirring was continued while maintaining the reaction temperature below 10°C for a further 15 min. The reaction mixture was poured onto ice water (600 mL) and the crude sulfonyl chloride separated as a cream solid which was collected by filtration (15.9 g, 91%). The sulfonyl chloride (15.9 g) was dissolved in MeCN (160 mL) and the solution was cooled with ice and treated with a stream of gaseous NH_3 for 10 min. The mixture was stirred at 5 °C for a further 15 min and then the solvent and excess NH_3 were removed on a rotary evaporator. The residue was stirred with H_2O (50 mL) and filtered to give the product **5a** as a cream solid which gave colourless crystals (10.6 g, 71%) from EtOAc/hexane; mp 98–100°C.

$C_8H_7F_6N_3O_4S$	calc.	C	27.05	H	1.99	N	11.82
(355.2)	found		27.20		1.95		11.57

^1H NMR ($CDCl_3$): δ = 4.87 (4 H, q, J = 8.2 Hz), 6.3 (2 H, br s), 8.38 (1 H, s).

^{13}C NMR: δ = 62.7 (q, $J_{C,F}$ = 37 Hz), 110, 123.3 (q, $J_{C,F}$ = 277 Hz), 157.9, 164,3.

4,6-Diethoxy-5-pyrimidinesulfonamide (5b):
Method A: Starting with compound **4b** and following essentially the typical procedure as described for compound **5a**, the sulfonamide **5b** was obtained in 75% yield as colourless crystals; mp 158–159°C.

$C_8H_{13}N_3O_4S$	calc.	C	38.86	H	5.30	N	17.00
(247.3)	found		38.82		5.13		16.77

^1H NMR : δ = 1.35 (6 H, t, J = 7.2 Hz), 4.49 (4 H, q, J = 7.2 Hz), 7.25 (2 H, br s), 8.52 (1 H, s).

^{13}C NMR : δ = 14.39, 63.94, 109.07, 158.38, 165.67.

Method B: Compound **5a** was treated with a solution of excess NaOEt in EtOH at r.t. following essentially the same procedure as described for compound **4b** from **3**. The reaction was monitored by TLC which showed complete reaction after 16 h and compound **5b** was isolated in 72% yield.

4-Ethoxy-6-(2,2,2-trifluoroethoxy)-5-pyrimidinesulfonamide (5c):
Compound **5a** (180 mg, 0,5 mmol) was added to a solution of Na (15 mg, 0.65 mmol) in EtOH and the solution was stirred at r.t. for 24 h. TLC showed the formation of compound **5b** plus a second, faster moving and major product. The solvent was evaporated and the residue was partitioned between H_2O (15 mL) and $CHCl_3$ (2 × 30 mL). The organic layers were combined. dried ($MgSO_4$) and evaporated to give a solid which was purified by chromatography on silica gel using $CHCl_3$ as eluent. Compound **5c** was obtained as colourless crystals (80 mg, 52%); mp 88–89 °C.

$C_8H_{10}F_3N_3O_4S$	calc	C	31.89	H	3.35	N	13.95
(301.2)	found		32.00		3.52		13.76

^1H NMR ($CDCl_3$): δ = 1.46 (3 H, t, J = 7.1 Hz), 4.61 (2 H, q, J = 7.1 Hz), 4.91 (2 H, q, J = 8.2 Hz), 5.4 (2 H, br s), 8.44 (1 H, s).

^{13}C NMR: δ = 14.30, 62.23 (q, $J_{C,F}$ = 37 Hz), 64.56, 109.52, 118.1 (q, $J_{C,F}$ = 256 Hz), 158.29, 163.94, 166.15.

4-Methylthio-6-(2,2,2-trifluoroethoxy)-5-pyrimidinesulfonamide (5d):
Compound **5a** (710 mg, 2 mmol) was added to a stirred suspension of NaOMe (140 mg, 2 mmol) in DMF (4 mL) at r.t. Stirring was continued for 4 h before the reaction mixture was poured into dil aq citric acid (10%, 50 mL) and the precipitate collected by filtration to give compound **5d** as a near white solid (440 mg, 73%); mp 151–l52°C.

$C_7H_8F_3N_3O_3S_2$	calc.	C	27.72	H	2.66	N 13.85
(303.3)	found		27.93		2.64	13.70

^{1}H NMR : δ = 2.48 (s, 3 H), 5.23 (q, 2 H, J = 8.3 Hz), 7.56 (br s, 2 H), 8.77 (s, 1 H).

^{13}C NMR : δ = 14.10, 61.80 (q, $J_{C,F}$ = 36 Hz), 120.19, 123.02 (q, $J_{C,F}$ = 284), 156.86, 162.90, 169.65.

4,6-Dimethylthio-5-pyrimidinesulfonamide (5e):
A solution of **5a (**355 mg, 1 mmol) in DMF (1 mL) was added to a stirred suspension of NaOMe (220 mg, 3.1 mmol) in DMF (3 mL) at r.t. The reaction mixture was stirred for 4 h and then poured into dil aq citric acid (10%, 50 mL) and the creamy precipitate was collected by filtration to give compound **5e (**182 mg, 72%); mp 200-201 °C.

$C_6H_9N_3O_2S_3$	calc.	28.67	H	3.61	N	16.71
(251.4)	found	28.57		3.48		16.41

^{1}H NMR : δ = 2.49 (s, 6 H), 7.78 (br s, 2 H), 8.81 (s, 1H).
^{13}C NMR : δ = 14.19, 131.66, 155.26, 167.86.

4-Hydroxy-6-(2,2,2-trifluoroethoxy)-5-pyrimidinesulfonamide (5f):
A solution of NaOH (0.91g, 23 mmol) in H_2O was added to **5a (**2.01 g, 5.7 mmol). The suspension was stirred and heated to 90°C, giving a clear solution which was heated for a further 2 h. The reaction mixture was cooled, acidified to pH 6 with concd HCl, and after standing at 0°C for 1 h the white precipitate was collected by filtration and air dried to give **5f (**1.33 g, 86%) as a colourless solid; mp 243.5–244.5°C.

$C_6H_6F_3N_3O_4S$	calc.	C	26.38	H	2.21	N 15,38
(273.2)	found		26.44		2.09	15.67

^{1}H NMR : δ = 5.09 (q, 2 H, J = 8.9 Hz), 6.96 (br s, 2 H), 8.42 (s, 2 H).
^{13}C NMR : δ = 62.86 (q, $J_{C,F}$ = 35 Hz), 109.91, 123.54 (q, $J_{C,F}$ = 277 Hz), 152.25, 159.57, 163.42.

4-Amino-6-(2,2,2-trifluoroethoxy)-5-pyrimidinesulfonamide (5g):
NH_4OH (15%, 5 mL) was added with stirring at r.t. to **5a (**710 mg, 2 mmol). The reaction mixture was stirred for 15 h at r.t. and then H_2O and excess NH_3 were removed on a rotary evaporator and the residue was partitioned between H_2O (5 mL) and EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a semi-crystalline solid which was purified by chromatography on silica gel using 95% $CHCl_3$/MeOH as eluent. Compound **5g** was obtained as colourless crystals (320 mg, 59%); mp 201–202°C.

$C_6H_7F_3N_4O_3S$	calc.	C	26.48	H	2.59	N 20.58
(272.2)	found		26.61		2.53	20.59

^{1}H NMR (acetone-d_6): δ = 5.13 (q, 2 H, J = 8.7 Hz), 6.63 (br s, 2 H), 7.06 (br s, 1 H), 7.50 (br s, 1 H), 8.23 (s, 1 H).

^{13}C NMR : δ = 61.53 (q, $J_{C,F}$ = 35 Hz), 102.39, 123.59 (q, $J_{C,F}$ = 278 Hz), 158.49, 160.36, 164.14.

4,6-Diamino-5-pyrimidinesulfonamide (5h):
NH_4OH (25%, 4 mL) was added with stirring to **5a (**350 mg, 1 mmol). The mixture was stirred and heated at 70°C for 6 h and then concentrated to dryness on a rotary evaporator. The residue was directly chromatographed on silica gel (10 g), starting with EtOAc as eluent to remove **5g (**70 mg) and then using 10% MeOH/EtOAc to give **5h** as a colourless solid (85 mg, 45%); mp 220–222°C (Lit.[7] mp 221–222°C).

^{1}H NMR : δ = 7.0 (br s, 4 H), 7.45 (s, 2 H), 7.81 (s, 1 H).
^{13}C NMR : δ = 96.53, 158.94, 159.46.

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