Comparative orienting effects of the methanesulfonamide group in aromatic nitration

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The methanesulfonamido group is shown to be a more powerful *ortho/para* directing group than the acetamido, methoxyl and methyl groups in aromatic nitrations.

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A number of substituted methanesulfanilides have useful biological activity. For example nimesulide (4-nitro-2-phenoxymethanesulfanilide)[1] is an anti-inflammatory agent which has formed the lead compound for more recent studies on the development of a series of selective cyclooxygenase-2 inhibitors.[2] Other methanesulfanilides such as sotalol have attracted interest in the treatment of ventricular arrhythmias.[3] It has been suggested that the acidic nature of the methanesulfanilide N–H may contribute to this biological activity.[3] This acidity may potentially be varied by the introduction of nitro substituents onto the aromatic ring. A methanesulfanilide is an *ortho/para* directing group.[4,5] It has been noted[6] that 'the toluene-*p*-sulfonamide group has a high orienting power compared with the acetamido group in nitration experiments.' There have been few comparable studies with methanesulfanilides and in the preparation of many substituted methanesulfanilides, the methanesulfonyl group is introduced after other substituents. In this paper, we describe the nitration of a series of substituted methanesulfanilides in order to assess the relative orienting effect of the methanesulfanilide group compared to other substituents.

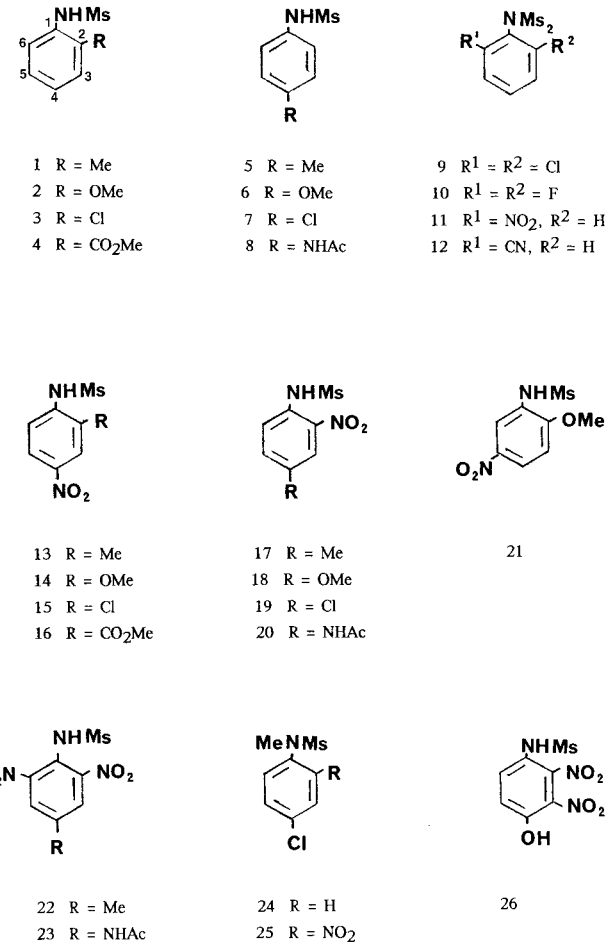
The methanesulfanilides **1**–**8**, **13**–**17**, **24** (Ms=methanesulfonyl) were easily prepared from the corresponding anilines by treatment with methanesulfonyl chloride in pyridine at room temperature for one hour.[7,8] Under these conditions 2-cyanoaniline, 2,6-dichloroaniline, 2,6-difluoroaniline and 2-nitroaniline readily formed dimethanesulfanilides (**9**–**12**). The ease with which diacetyl derivatives are formed, particularly of orthohaloanilines, has been noted previously.[9]

The monomethanesulfanilides possessed IR absorption at ν_{max}/cm^{-1} 3240–3288 and a ^1H NMR signal at δ_H 9.2–9.8 (determined in DMSO-d_6) assigned to the N–H group. In the monomethanesulfanilides, the $CH_3SO_2N<$ signal appeared in the range δ_H 3.0–3.1 whilst in the dimethanesulfanilides this methyl signal appeared in the range δ_H 3.4–3.8.

Nitration of the methanesulfanilides was carried out under nitrosation:nitration conditions using nitric acid:sodium nitrite in aqueous acetic acid[10] and with nitric acid in acetic anhydride at room temperature.[5†] As noted previously[4] the dimethanesulfanilides were unreactive. The results are given in Table 1. In most cases the orientation of the substitution followed from the multiplicity of the aromatic proton signals and by comparison with authentic samples prepared by the methanesulfonation of the corresponding anilines. Where these were not available, the orientation was established by nuclear Overhauser effect studies.

The mononitration product (**17**) of the methanesulfonamide of *p*-toluidine was identical to the mesylation product of 2-nitro-4-methylaniline. When nitric acid:acetic anhydride was used, the methanesulfonamide (**22**) of 2,6-dinitro-4-methylaniline was obtained. Irradiation of the 4-methyl group resonance (δ_H=2.45) produced an nOe enhancement (9.4%) of the aromatic C–H signal (δ_H=8.14). There was also a long-range coupling (*J*=0.73 Hz) between these resonances. Hence the nitro groups are in the 2- and 6-positions. In a parallel experiment under these conditions, N-acetyl-*p*-toluidine gave only the N-acetyl derivative of 2-nitro-4-methylaniline.

In the case of the nitration of the methanesulfonamide (**2**) of *o*-anisidine, the ^1H NMR spectrum of the crude product showed that it was an 8:1 mixture of the methanesulfonamides of 2-methoxy-4- and 5-nitroanilines (**14** and **21**). This compares to *ca* 5:1 mixture obtained on nitrating *N*-acetyl-o-anisidine.[11] The orientation of the nitration product (**18**) of the methanesulfonyl derivative of *p*-anisidine[12] obtained under nitrosation:nitration conditions, was established by nOe studies. Irradiation of the methoxyl signal at δ_H 3.88 led to enhancements of the signals at δ_H=7.28 (double-doublet, *J*=3.0 and 9.1 Hz)(2.5%) and 7.71 (doublet, *J*=3.0 Hz)(5.7%). The product, obtained in rather poor yield with nitric acid:acetic anhydride was identified as the 2, 3-dinitrophenol (**26**). The ^1H NMR spectrum lacked the methoxyl signal but possessed two broad OH/NH signals



* Correspondence.

† See CAUTION in Experimental section

Table 1 Nitration of methanesulfonamides all compounds were used and isolated as their methanesulfonamides

Starting sulfonamide	Product (sulfonamide)	% Yield
Nitrosation-nitration reactions	($NaNO_2$,HNO_3,AcOH,H_20)	
o-toluidine	2-methyl-4-nitroaniline[a]	70
p-toluidine	4-methyl-2-nitroaniline	75
o-anisidine	2-methoxy-4-nitroaniline[b]	60
p-anisidine	4-methoxy-2-nitroaniline	75
o-chloroaniline	2-chloro-4-nitroaniline[a]	35
p-chloroaniline	4-chloro-2-nitroaniline	80
Methyl anthranilate	2-carbomethoxy-4-nitroaniline	51
p-acetamidoaniline	4-acetamido-2-nitroaniline	80
nitration reactions	(HNO_3,Ac_2O)	
p-toluidine	2,6-dinitro-4-methylaniline	65
p-anisidine	2,3-dinitro-4-hydroxyaniline	45
p-chloroaniline	4-chloro-2-nitroaniline	78
p-chloro-*N*-methyl aniline	4-chloro-2-nitro-N-methyl aniline	65
Methyl anthranilate	2-carbomethoxy-4-nitroaniline	85
4-acetamidoaniline	4-acetamido-2,6-dinitro- aniline	76

[a]The ^{1}H NMR spectrum of the crude product showed the presence of some 6-nitro compound. [b]The ^{1}H NMR spectrum of the crude product showed the presence of some 5-nitro compound.

(δ_H=11.73 and 9.81 ppm) and two doublets (δ_H=7.37 and 7.63, *J*=9.1 Hz). This product had the same melting point as that assigned[12] the structure of the 2,6-dinitro-methanesulfonyl-*p*-anisidine. Under comparable conditions *N*-acetyl-*p*-anisidine afforded the 2,3-dinitro compound.[13]

Under both sets of conditions the methanesulfonamide of *p*-chloroaniline gave a 2-nitro derivative (**19**). The aromatic proton resonances comprised a doublet (δ_H 7.63, *J* 8.8 Hz), a double-doublet (δ_H=7.80, *J*=2.5 and 8.8 Hz) and a narrow doublet (δ_H=8.10, *J* 2.5 Hz). Irradiation of the methanesulfonyl group resonance (δ_H=3.14) gave an nOe enhancement of the doublet (δ_H=7.63, 3.6%). The methanesulfonamide (**24**) of *N*-methyl-*p*-chloroaniline was recovered unchanged from the nitrosation:nitration conditions but it was nitrated by nitric acid:acetic anhydride to give a mono-nitro compound (**25**). This possessed SO_2Me and N–Me ^{1}H NMR signals at δ_H 3.05 and 3.25 and aromatic signals at δ_H=7.84 (double-doublet, *J*=8.6 and 0.5 Hz), 7.86 (double–doublet, *J*=8.6 and 2.3 Hz) and 8.12 (double–doublet, *J*=2.3 and 0.5 Hz). Irradiation of each of the methyl signals enhanced the signal at δ_H=7.84 by 5%. Hence the nitro group is located at C–2.

The methanesulfonamide of methyl anthranilate gave the 4-nitro compound (**16**) under both sets of conditions. It was identified by comparison with an authentic sample. The orientations of the products (**20** and **23**) of nitration of *N*-methanesulfonyl-4-acetamidoaniline (**8**) were established by nOe studies. Irradiation of the $NHCOCH_3$ signal (δ_H=2.06) in the mononitration product, produced an enhancement (5.3%) of the N–H signal at δ_H=10.38 whilst irradiation of the $NHSO_2CH_3$ signal at δ_H-3.06 produced enhancements of the NH signal at δ_H=9.63 (0.5%) and the doublet at δ_H=7.53 (2.9%). Irradiation of the signal at δ_H=10.38 produced enhancements at δ_H 8.36(7.3%), 7.75 (7.7%) and 2.06(2.5%) whilst irradiation at δ_H=9.63 produced an enhancement at δ_H=7.53 (3.1%). Hence the mononitro compound is the 2-nitro compound (**20**). In the dinitro compound irradiation of the $NHCOCH_3$ signal (δ_H 2.10) enhanced the N–H signal at δ_H 10.77. Irradiation of this signal enhanced the aromatic singlet (δ_H=8.37, 8.0%) and the $NHCOCH_3$ signal (δ_H=2.10, 2.0%). Hence the dinitro compound is 4-acetamido-2, 6-dinitro-methanesulfanilide (**23**).

In conclusion, the methanesulfonamido group has dominated the orientation of nitration of these disubstituted aromatic compounds. Bearing in mind the ease with which the group may be removed by acidic hydrolysis, these substitution reactions may have some preparative value. The lack of reactivity of the methanesulfonamide of *N*-methyl-*p*-chloroaniline and of the dimethanesulfanilides under the nitrosation conditions suggests that the N–H may play a role in the nitrosation reaction possibly as part of a radical process.[14]

Experimental

General experimental details: IR spectra were determined as nujol mulls. ^{1}H NMR spectra were determined for solutions in DMSO-d_6 at 300 MHz; nuclear Overhauser effect enhancements were determined at 500 MHz. Accurate mass measurements were obtained by electrospray ionization on a Daltonics ApexIII mass spectrometer.

Preparation of methanesulfanilides: The aromatic amine (3.5 g) was dissolved in pyridine (15 cm^3) and carefully treated with methanesulfonyl chloride (3 cm^3) in portions. The mixture was left to stand at room temperature for 1 h. The solution was then poured into dilute hydrochloric acid (100 cm^3) and stirred until the product had crystallised. The methanesulfanilide was filtered and recrystallised from methanol or aqueous methanol.

Nitration of the methanesulfanilides: (a) Sodium nitrite (1 g) was cautiously added to a solution of fuming nitric acid (d 1.5)(4 cm^3) in water (10 cm^3). The methanesulfanilide (2 g) was dissolved in glacial acetic acid (15 cm^3) and treated with the above nitrating mixture in portions. The mixture was left to stand at room temperature for 1–2 hours. It was then poured onto ice :water (100 cm^3). The product was filtered and recrystallised from aqueous methanol.

(b) The methanesulfanilide (1.5 g) was dissolved in acetic anhydride (15–25 cm^3) and treated with conc. nitric acid (3 cm^3) dropwise with stirring over a period of 15 min. The mixture was left to stand for 2–3 h. at room temperature. The mixture was then poured onto ice:water (100 cm^3). The product was filtered and recrystallised from aqueous methanol.

CAUTION: Mixtures of fuming nitric acid and acetic anhydride are known to be dangerously unstable and can detonate (*Brethericks Handbook of Reactive Chemical Hazards*, 6th edn. P.G. Urban (ed.), Vol.1 1568, Butterworth Heinemann, Oxford, 1999; see also G.A. Olah, *Chem.Brit.*, August 1996, **32**, 21). Although in the present case the acid used is not fuming, **caution is advised**.

The following compounds were obtained.

o-Toluidine monomethanesulfonamide (**1**): m.p. 106–108°C (lit.,[7] 103°C), ν_{max}/cm^{-1} 3244, 1596, 1375, 1152; δ_H=2.38 (3H,s,Ar–Me), 3.02 (3H,s, SO_2Me), 7.20 (2H,t, *J*=8.0 Hz), 7.32 (1H,d, *J*=8.0 Hz), 7.35 (1H,d, *J*=8.0 Hz), 9.03 (1H,s, NH).

p-Toluidine monomethanesulfonamide (**5**): m.p. 104–105°C (lit.,[7] 102°C), ν_{max}/cm^{-1} 3289, 1614, 1589, 1146; δ_H 2.35 (3H,s,Ar–Me), 3.05 (3H,s, SO_2Me), 7.25 (4H,br.s,), 9.55 (1H,s, NH).

o-Anisidine monomethanesulfonamide (**2**): m.p. 110°C (lit.,[7] 115°C), ν_{max}/cm^{-1} 3246, 1600, 1376, 1149; δ_H 3.05 (3H,s, SO_2Me), 3.90 (3H,s, OMe), 7.05 (1H,d, *J*=8.1 Hz), 7.15 (1H,d, *J*=8.1 Hz), 7.25 (1H,t, *J*=8.1 Hz), 7.35 (1H,t, *J*=8.1 Hz), 9.00 (1H,s, NH).

p-Anisidine monomethanesulfonamide (**6**): m.p. 116°C (lit.,[7] 116°C), ν_{max}/cm^{-1} 3250, 1600, 1149; δ_H=3.00 (3H,s, SO_2Me), 3.95 (3H,s, OMe), 6.88 (2H,d, *J*=8.2 Hz), 7.15 (2H,d, *J*=8.2 Hz), 9.50 (1H,s, NH).

o-Chloroaniline monomethanesulfonamide (**3**): m.p. 88°C (lit.,[7] 90.5°C), ν_{max}/cm^{-1} 3282, 1582, 1376, 1168; δ_H 3.05 (3H,s, SO_2Me), 7.25 (1H,t, *J*=7.5 Hz), 7.34 (1H,t, *J*=7.5 Hz), 7.42 (1H,d, *J*=7.5 Hz), 7.50 (1H,d, *J*=7.5 Hz), 9.45 (1H,s, NH).

p-Chloroaniline monomethanesulfonamide (**7**): m.p. 146°C (lit.,[7] 148°C), ν_{max}/cm^{-1} 3288, 1588, 1377, 1146; δ_H=3.00 (3H,s, SO_2Me), 7.20 (1H,d, *J*=8.5 Hz), 7.40 (2H,d, *J*=8.5 Hz), 9.90 (1H,s, NH).

p-Chloro-N-methylaniline monomethanesulfonamide (**24**) had m.p. 78°C (Found: M^+ 242.001 $C_8H_{10}ClNO_2SNa$ requires M^+ 242.001), ν_{max}/cm^{-1} 1553, 1172, 1146, 1060; δ_H=3.08 (3H,s, SO_2Me), 3.36 (3H,s,N-Me), 7.55 (2H,d, *J*=9.1 Hz), 7.60 (2H,d, *J*=9.1 Hz).

Methyl anthranilate monomethanesulfonamide (**4**): m.p. 92°C, (lit.,[8] 90.5–91°C), ν_{max}/cm^{-1} 3148,1694, 1602, 1584, 1376, 1258, 1159; δ_H=3.08 (3H,s, SO_2Me), 3.80 (3H,s, CO_2Me), 7.10 (1H,t, *J*=8.1 Hz), 7.55 (1H,t, *J*=8.1 Hz), 7.60 (1H,d, *J*=8.1Hz), 7.90 (1H,d, *J*=8.1 Hz), 10.05 (1H,s, NH).

4-Acetamidoaniline monomethanesulfonamide (**8**): m.p. 204–205°C, (Found: M^+ 251.046 $C_9H_{12}N_2O_3SNa$ requires M^+ 251.046), ν_{max}/cm^{-1} 3298, 3244, 1666, 1598, 1528, 1149; δ_H=2.18 (3H,s, $NHCOCH_3$), 3.07 (3H,s, SO_2Me), 7.28 (2H,d, *J*=8.8 Hz), 7.68 (2H,d, *J*=8.8 Hz), 9.70 (1H,s, NH), 10.14 (1H,s,NH).

2,6-Dichloroaniline dimethanesulfonamide (**9**): m.p. 174–176°C, (Found: M^+ 339.923 $C_8H_9Cl_2NO_4S_2Na$ requires M^+ 339.924), ν_{max}/cm^{-1} 1564, 1161; δ_H=3.62 (6H,s, SO_2Me), 7.52 (1H,t, *J*=7.8 Hz), 7.78 (2H,d, *J*=7.8 Hz).

2,6-Difluoroaniline dimethanesulfonamide (**10**): m.p. 164–166°C, (Found: M^+ 307.983 $C_8H_9F_2NO_4S_2Na$ requires M^+ 307.983), ν_{max}/cm^{-1} 1617, 1596, 1166, 1153; δ_H=3.45 (6H,s, SO_2Me), 7.35 (2H,t, *J*=7.5 Hz), 7.65 (1H,m).

o-Nitroaniline dimethanesulfonamide (**11**): m.p. 141°C, (Found: M^+ 316.987 $C_8H_{10}N_2O_6S_2Na$ requires M^+ 316.987), ν_{max}/cm^{-1} 1599, 1581,1536, 1165, 1149; δ_H=3.55 (6H,s, SO_2Me), 7.80 (3H,overlapping multiplets), 8.20 (1H,d, *J*=8.0 Hz).

o-Cyanoaniline dimethanesulfonamide (**12**): m.p. 166°C, (Found: M^+ 296.997 $C_9H_{10}N_2O_4S_2Na$ requires M^+ 296.997), ν_{max}/cm^{-1} 2229, 1592, 1163; δ_H=3.45 (6H,s, SO_2Me), 7.80 (1H,t,*J*=7.5 Hz), 7.95(2H,d, *J*=7.5 Hz), 8.05 (1H,d, *J*=7.5 Hz).

2-Methyl-4-nitroaniline monomethanesulfonamide (**13**): m.p. 195–196°C, (Found: M^+ 253.024 $C_8H_{10}N_2O_4SNa$ requires M^+ 253.025), ν_{max}/cm^{-1} 3290, 1590, 1519, 1161, 1150; δ_H=2.32 (3H,s,Ar–Me), 3.05 (3H,s, SO_2Me), 7.50 (1H,d, *J*=8.1 Hz), 8.00 (1H,dd, *J*=8.1 and 2.3 Hz), 8.05 (1H,d, *J*=2.3 Hz), 9.60 (1H,s, NH).

4-Methyl-2-nitroaniline monomethanesulfonamide (**17**): m.p. 120°C, (Found: M^+ 253.024 $C_8H_{10}N_2O_4SNa$ requires M^+ 253.025), ν_{max}/cm^{-1} 3289, 1585, 1500, 1161, 1150; δ_H 2.35 (3H,s,Ar–Me), 3.15 (3H,s, SO_2Me), 7.50 (1H,d,*J*=8.2 Hz), 7.58 (1H,dd, *J*=8.2 and 2.4 Hz), 7.83 (1H,d, *J*=2.4 Hz), 9.55 (1H,s, NH).

2-Methoxy-4-nitroaniline monomethanesulfonamide (**14**): m.p. 146°C, (Found: M^+ 269.019 $C_8H_{10}N_2O_5SNa$ requires M^+ 269.020), ν_{max}/cm^{-1} 3310, 1595, 1502, 1156, 1136; δ_H 3.15 (3H,s, SO_2Me), 3.90 (3H,s, OMe), 7.50 (1H,d, *J*=7.8 Hz), 7.80 (1H,d, *J*=2.0 Hz), 7.95 (1H,dd, *J*=7.8 and 2.0 Hz), 9.67 (1H,s, NH).

2-Methoxy-5-nitroaniline monomethanesulfonamide (**21**): m.p. 156°C, (Found: M^+ 269.019 $C_8H_{10}N_2O_5SNa$ requires M^+ 269.020), ν_{max}/cm^{-1} 3240, 1596, 1507, 1156; δ_H 3.15 (3H,s, SO_2Me), 3.95 (3H,s, OMe), 7.12 (1H,d,*J*=7.9 Hz), 8.10 (1H,d, *J*=7.9 Hz), 8.15 (1H,s,), 9.50 (1H,s, NH).

4-Methoxy-2-nitroaniline monomethanesulfonamide (**18**): m.p. 128°C, (lit.,[12] 123°C) ν_{max}/cm^{-1} 3245, 1576, 1525, 1499, 1160, 1139; δ_H=3.06 (3H,s, SO_2Me), 3.88 (3H,s, OMe), 7.28 (1H,dd,*J*=9.1 and 3.0 Hz), 7.71 (1H,d, *J*=3.0 Hz), 7.82 (1H,d, *J*=9.1 Hz), 9.22 (1H,s, NH).

2-Chloro-4-nitroaniline monomethanesulfonamide (**15**): m.p. 144°C, (Found: M^+ 272.971 $C_7H_7ClN_2O_4SNa$ requires M^+ 272.971), ν_{max}/cm^{-1} 3288, 1588, 1179; δ_H=3.15 (3H,s, SO_2Me), 7.70 (1H,d, *J*=8.1 Hz), 8.20 (1H,d, *J*=8.1 Hz), 8.30 (1H,s,), 10.1 (1H,s, NH).

4-Chloro-2-nitroaniline monomethanesulfonamide (**19**): m.p. 144°C, (Found: M^+ 272.971 $C_7H_7ClN_2O_4SNa$ requires M^+ 272.971), ν_{max}/cm^{-1} 3240, 1610, 1568, 1146; δ_H=3.14 (3H,s, SO_2Me), 7.63 (1H,d, *J*=8.8 Hz), 7.80 (1H,dd, *J*=8.8 and 2.5 Hz), 8.10 (1H,d, *J*=2.5 Hz), 9.88 (1H,s, NH).

2-Carbomethoxy-4-nitroaniline monomethanesulfonamide (**16**): m.p. 166°C, (Found: M^+ 297.015 $C_9H_{10}N_2O_6SNa$ requires M^+ 297.015), ν_{max}/cm^{-1} 3148, 1694, 1602, 1584, 1258, 1146; δ_H=3.30 (3H,s, SO_2Me), 3.90 (3H,s, CO_2Me), 7.72 (1H,d,*J*=8.1 Hz), 8.42 (1H,dd, *J*=8.1 and 1.9 Hz), 8.67 (1H,d, *J*=1.9 Hz), 10.50 (1H,s, NH).

4-Acetamido-2-nitroaniline monomethanesulfonamide (**20**): m.p. 182°C, (Found: M^+ 296.032 $C_9H_{11}N_3O_5SNa$ requires M^+ 296.031), ν_{max}/cm^{-1} 3359, 3262, 1680, 1600, 1556, 1538,1157, 1146; δ_H=2.06 (3H,s, Ac), 3.06 (3H,s, SO_2Me), 7.53 (1H,d,*J*=8.8 Hz), 7.75 (1H,dd, *J*=8.8 and 2.5 Hz), 8.36 (1H,d, *J*=2.5 Hz), 9.63 (1H,s, $NHSO_2Me$), 10.38 (1H,s, NHAc).

2,6-Dinitro-4-methylaniline monomethanesulfonamide (**22**): m.p. 194°C, (Found: M^+ 298.011 $C_8H_9N_3O_6SNa$ requires M^+ 298.011), ν_{max}/cm^{-1} 3260, 1549, 1537, 1156; δ_H 2.46 (3H,s, ArMe), 3.03 (3H,s, SO_2Me), 8.14 (2H,s), 10.37 (1H,s, NH), Under high resolution conditions a coupling of 0.73 Hz was observed between the Ar–Me and H-3.

2,3-Dinitro-4-hydroxyaniline monomethanesulfonamide (**26**): m.p. 186°C (decomp.), (Found: M^+ 299.990 $C_7H_7N_3O_7SNa$ requires M^+ 299.990), ν_{max}/cm^{-1} 3270, 1629, 1552, 1536, 1146; δ_H=3.07 (3H,s, SO_2Me), 7.40 (1H,d, *J*=9.1 Hz), 7.65 (1H,d, *J*=9.1 Hz), 9.93 (1H,s, NH), 12.32 (1H,s, OH).

4-Chloro-2-nitro-N-methylaniline monomethanesulfonamide (**25**): m.p. 134°C, (Found: M^+ 286.986 $C_8H_9ClN_2O_4SNa$ requires M^+ 286.986), ν_{max}/cm^{-1} 1605, 1568, 1532, 1145; δ_H=3.05 (3H,s, SO_2Me), 3.25 (3H,s, NMe), 7.84 (1H,dd, *J*=9.6 and 0.5 Hz), 7.86 (1H,dd, *J*=8.6 and 2.3 Hz), 8.12 (1H,dd, *J*=2.3 and 0.5 Hz).

4-Acetamido-2,6-dinitroaniline monomethanesulfonamide (**23**): m.p.232–234°C, (Found: M^+ 341.017 $C_9H_{10}N_4O_7SNa$ requires M^+ 341.016), ν_{max}/cm^{-1} 3361, 3266, 1699, 1596, 1561, 1530, 1157; δ_H 2.10 (3H,s, Ac), 3.01 (3H,s, SO_2Me), 8.40 (2H,s), 10.20 (1H,s, $NHSO_2Me$), 10.80 (1H,s, NHAc).

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