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N-SULPHONYLFORMAMIDINES; PREPARATION AND CHARACTERISATION

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Abstract—N-Sulphonylformamidines have been prepared in a CuCl-catalysed α-addition reaction between sulphonamides and isocyanides. The actual tautomeric form present has been shown to be the N^2-sulphonylformamidine by ^{13}C NMR spectroscopy. Variable temperature NMR experiments show the existence of two rotamers.

In connection with our investigations on the reactivity of isocyanides towards nitrogen containing compounds,[1,2] the reaction with sulphonamides was of interest because of the difference in basicity compared to that of amines,[3] hydrazines[1] and semicarbazides.[2]

This paper reports the reaction between isocyanides and sulphonamides to form N-sulphonylformamidines **1**, and a discussion of the structure of the formamidines by means of IR, ^1H NMR and ^{13}C NMR spectroscopy.

$$RSO_2NH_2 + R'NC \rightarrow RSO_2NCHNHR'$$
1 a–d

Scheme 1. Compound (R, R'): **a** (Ph, Ph), **b** (*p*-$CH_3C_6H_4$, Ph), **c** (Me, Ph), **d** (*p*-$CH_3C_6H_4$, C_6H_{11}).

RESULTS

The formation of N-sulphonylformamidines **1** catalysed by CuCl proceeds on boiling isocyanide and sulphonamide for long periods in benzene solution. Aromatic isocyanides require boiling for about 14 days for the reaction with benzene- and *p*-methyl-benzenesulphonamide giving yields of 50–73%, while the reaction time is more than 25 days for the reaction between aromatic isocyanides and methanesulphonamide. The reaction between cyclohexyl isocyanide and aromatic sulphonamide gave less than 10% yield on prolonged heating.

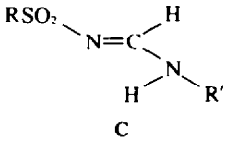
To establish the structure of the sulphonylformamidines the ^{13}C NMR spectra of the compounds and some model compounds (Table 1) were recorded to clarify which of the tautomers **A** or **B** was present in solution.

RSO_2–N = CH(NHR') **A** RSO_2–NH–CH = NR **B**

As is evident from Table 1, the chemical shift values of the imino carbon atom and the quaternary ring carbon atoms were of special value. For models with the tautomeric form **A** as well as for the prepared sulphonylformamidines the chemical shift value of the imino carbon atom is around 155–159 ppm while for the model **B** tautomer the value is 147 ppm. The chemical shift value of the quaternary carbon atoms in the *N*-phenyl group for model **A** tautomer **3** and **4** and the investigated formamidines **1a**, **b** and **c** are found to be 10 ppm lower than for model **B** tautomer **2**. The ^{13}C NMR data thus strongly indicate that the formamidines exist as the tautomeric form **A** in solution.

The infrared spectra of the compounds were of less conclusive value in determining which tautomer was present, as the position of the C–N stretching vibration, which is often used in structural proofs in amidine systems[6–9] is strongly influenced by the N–H bending vibration in the same region. The use of N-deuterated compounds did not give conclusive evidence either.

For the tautomer **A** there are at least 4 possible structures **C** – **F**, some of which might be in equilibrium mixtures. Recently there has been much discussion[10,11] about the structure of amidines but no data have been reported on sulphonylformamidines.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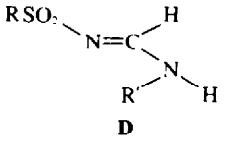
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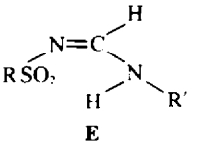
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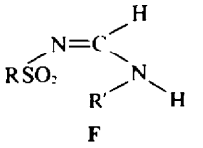
F

As is evident from Table 1, compounds **1a**, **b** and **d** show one set of signals for carbon atoms attached to the sulphonyl group while the rest of the molecule exhibits doubling of signals, especially for the imino carbon atom and the ortho carbon atoms in the phenyl group attached to the N^1-nitrogen atom. This indicates that there are different conformations in the part of the molecule near to the N^1-nitrogen atom while in the rest of the molecule (the sulphonyl part) very small effects could be detected only in compound **1c**. Consequently it is most likely that the existing forms are **E** and **F** or **C** and **D** as the presence of *ZE* isomers would have doubled all the carbon signals. This is in accordance with data found for *cis trans* isomers of some formamides.[12]

For some *N*-sulphonylbenzamidines it has been shown by IR measurements[9] that the dominating form is **E** with an intramolecular hydrogen bond. For compounds **1a–d** the NH stretching vibrations were found as two to three absorptions at rather low frequency (KBr), indicating the presence of inter- or intramolecular hydrogen bonding. Due to the very low solubility of the compounds it was not possible to obtain the IR spectra in normal IR solvents except for **1d**, where dilution experiments indicated that the relative intensity of the N–H stretching

Table 1. ^{13}C NMR chemical shift values (DMSO) in ppm (rel. TMS)

Compound		-NH-CH=N-	Quaternary ring C-atoms in the $R-SO_2$-group C(1)	C(4)	Quaternary ring C-atoms in the N-Ph-group	Methyl C-atoms	Tertiary ring C-atoms[a] $R-SO_2$-group meta	para	ortho	N-Ph-group meta	para	ortho
$C_6H_5SO_2NCHNHC_6H_5$ **1a**	*a*	157.2 154.8	141.9		138.0 137.4		128.9	132.1	126.1 126.2	128.9 129.5	125.2 125.0	120.8 118.0
	b	157.2 154.8	141.9		138.0 137.4		128.9 129.5	132.2 131.7	126.2 125.5	128.9 129.5	125.2 125.0	120.8 118.0
p-$CH_3C_6H_4SO_2NCHNHC_6H_5$ **1b**	*a*	157.0 154.7	142.5	139.1	138.1 137.6	20.8	129.5		126.3	128.9 129.5	125.2 125.0	120.8 117.9
	b	157.0 154.7	142.5	139.2	138.1 137.6	21.0	129.5 128.7		126.3 126.4	129.0 129.6	125.2 125.0	120.8 117.9
$CH_3SO_2NCHNHC_6H_5$ **1c**		157.5 154.8			138.3 137.7	41.6 41.5				129.6 128.9	124.9 124.8	120.7 117.8
p-$CH_3C_6H_4SO_2NCHNHC_6H_{11}$ **1d**		159.5 156.4	141.8	140.1			129.3		125.9			
p-$CH_3C_6H_4SO_2N(CH_3)CHNC_6H_5$ **2**		147.1	144.9	134.1	148.9	30.2 21.0	130.4		127.0	129.1	124.8	121.2
p-$CH_3C_6H_4SO_2NCHN(CH_3)_2$ **3**		159.6	141.8	140.3		40.8, 34.9 20.8	129.2		125.9			
p-$CH_3C_6H_4SO_2NCHN(CH_3)C_6H_5$ **4**		158.4	143.0	142.4	139.1	35.5 20.9	129.5		126.3	129.9	127.0	122.0
p-$CH_3C_6H_4SO_2NHCH_3$			142.6	136.5		28.6 20.9	129.5		126.8			
$C_6H_5NCHN(CH_3)_2$[4]		153.4			152.2					128.9	122.2	121.1
$C_6H_5NHCHNN(CH_3)_2$[5]		145.8			139.8					129.6	122.1	111.5

[a] Recrystallised from ethanol.
[b] Recrystallised from nitrobenzene.
[c] Recrystallised from DMSO.
[d] Assigned by means of spectra of model compounds.

vibration was not concentration dependant in $CHCl_3$ solution. This observation together with the very low frequency of the NH stretching vibration indicates that the structures are **E** and **F**. For some sulphonylbenzamidines[9] the presence of NH stretching bands at higher frequency than those assigned to intramoleculary hydrogen bonded NH groups is taken as evidence for the presence of both *syn* and *anti* isomers. For the sulphonylformamidines investigated here the ^{13}C NMR spectral data show that the isomers present in solution are not *syn anti* isomers but isomers arising due to hindered rotation around the C–N[-1] bond, an assignment which is supported by the ^1H NMR spectral data (Table 2).

From Table 2 it appears that compounds **1a–d** all showed two signals of different intensity for the CH=N proton and one or two broad signals for the NH proton. In compound **1c** both CH=N signals were doublets due to coupling (proved by spin decoupling experiments). The great difference in J_{CHNH} coupling constants (12.5 and 5.5 Hz) is in accordance with *trans* and *cis* structures respectively. Compound **1d** gave singlets somewhat broadened in DMSO solution for the CH=N signals while in $CDCl_3$ solution the two CH=N proton signals were doublets and the methyl signals were two singlets very close to each other.

The compounds **1a** and **b** could both be obtained as two different isomers showing different patterns for the CHNH system in the ^1H NMR spectra. Thus use of ethanol, benzene or toluene as solvent for recrystallisation gave singlets for the two CH=N protons while for **1a** recrystallisation from DMSO or melting the compound gave doublets. The compound **1b** gave doublets when melted or recrystallised from nitrobenzene. Cooling experiments for **1b** (recrystallised from ethanol) in DMF solution showed a broadening of the CH=N singlets and at −41°C both CH=N signals were doublets with the same coupling constants as found for the isomer recrystallised from DMSO. The mass spectra of the two isomers were almost identical, so was the IR spectra except for a broadening of some bands in the modification recrystallised from DMSO. In the ^1H NMR spectra only the chemical shift value of the *trans* CH=N proton was different in the two isomers. Shaking with H_2O did not cause any change in any of the isomers exhibiting coupling. ^{13}C NMR spectral data for the two isomers showed very small changes in the chemical shift values of the benzenesulphonyl group, but practically no change in other parts of the molecule indicating that the difference in the two molecules is due to different conformations in the phenylsulphonyl part.

High temperature ^1H NMR experiments in DMSO solution also indicated that the presence of two forms was due to hindered rotation as the coalescence temperatures found (Table 2) indicated a barrier to rotation lower than that found for *ZE* isomerism[13] and in accordance with values found for amidine systems.[14,20,21] We found no differences in coalescence temperature for the different isomers of **1a** and **1b**.

DISCUSSION

The remarkable difference in reactivity between phenyl isocyanide and cyclohexyl isocyanide in the copper(I) chloride catalysed reaction with sulphonamides is analogous to the difference found for reactivity towards hydrazines.[1] It may probably be ascribed to the difference in complex bond strength in the isocyanide copper complex. The very long reaction time required compared to that of isocyanide reactions with amines[3] and hydrazines[1] may be explained by the low nucleophilicity of the sulphonamide.

In discussions on tautomerism and structure in amidine systems infrared spectroscopy[9,10] and acidity measurements[11] have been used especially in benzamidine and acetamidine systems. ^{13}C NMR spectroscopy has been used in some amidine systems.[4,15] This investigation shows that it is a very efficient tool for estimation of the structure of sulphonyl formamidines with the possibility for tautomerism, where IR and ^1H NMR spectra alone may be of less conclusive value. The explanation of the coupling and non-coupling isomers of **1a** and **b** is possibly also best explained by the ^{13}C NMR data. DMSO is known to be a solvent efficient for inducing coupling in alcohols[16,17] and amino compounds[22] due to solvent solute complex formation. The absence of coupling in some isomers may therefore be explained as a steric hindrance for the solvent to form this sort of complex due to the conformation of the phenyl groups. This is supported by the fact that compound **1c** with less steric hindrance always shows coupling. The ^{13}C NMR

Table 2. ^1H NMR chemical shift values[a] (δ, ppm) in DMSO solution

Compound	–N=CH–N=		–NH–		CH_3–		$J_{NH/CH(Hz)}$		Ratio[b] (E)/(F)	Coalescence Temp.[c]K
	(E)	(F)	(E)	(F)	(E)	(F)	(E)	(F)		
$C_6H_5SO_2NCHNHC_6H_5$ **1a**[d]	8.65(s)	8.21(s)	10.5–11.2						3/5	388
$C_6H_5SO_2NCHNHC_6H_5$ **1a**[f]	8.66(d)	8.21(d)	11.13(d)	10.71(d)			12.5	5.5	3/5	388
$4\text{-}CH_3C_6H_4SO_2NCHNHC_6H_5$ **1b**[d]	8.72(s)	8.25(s)	10.5–11.2		2.35(s)				3/4	383
$4\text{-}CH_3C_6H_4SO_2NCHNHC_6H_5$ **1b**[e]	8.73(d)	8.25(d)	11.35(d)	10.87(d)	2.35(s)		12.5	5.5	3/4	383
$CH_3SO_2NCHNHC_6H_5$ **1c**	8.52(d)	8.07(d)	10.98(d)	10.50(d)	3.00(s)		12.0	5.5	5/7	371
$CH_3SO_2NCHNHC_6H_5$ **1c**[x]	8.62(d)	8.23(d)	10.3		2.93	2.96	12.0	5.5	5/7	
$4\text{-}CH_3C_6H_4SO_2NCHNHC_6H_{11}$ **1d**[h]	8.28(d)	8.16(d)	6.8–6.6		2.406	2.399	12.0	5.5	1/3	
$4\text{-}CH_3C_6H_4SO_2NCHNHC_6H_{11}$ **1d**[x]	7.93(s)	8.10(s)	8.7–8.9		4.00				1/3	

[a] Centers of multiplets, multiplicity given in parentheses.
[b] (E) and (F) refers to the two conformations.
[c] Coalescense of the N=CH–N proton signals (± 10 K).
[d] Recrystallised from ethanol.
[e] Recrystallised from DMSO.
[f] Recrystallised from nitrobenzene.
[x] Acetone-d_6-solution.
[h] 270 MHz data in $CDCl_3$, the tertiary cyclohexyl proton signals were found at 3.21–3.32 and 3.76–3.89 ppm, ratio 1/3.

data showing small changes only in the phenylsulphonyl group indicates that the two isomers differ in conformation in this part of the molecule, e.g. due to rotation around the N–S bond, one conformer being more open for NH solvent interaction than the other.

EXPERIMENTAL

Microanalyses were carried out in the Microanalysis Department of Chemical Laboratory II, The H. C. Ørsted Institute. ^{1}H NMR spectra were recorded on a Jeol JNM MH 60/II instrument (60 MHz) or a Bruker HX 270-S apparatus (270 MHz). ^{13}C NMR spectra were recorded on a Bruker WH 90 apparatus, IR spectra on a Perkin-Elmer model 225 grating spectrograph and Mass spectra on an AEI-902 instrument operating at 70 eV. Melting points are uncorrected.

N^2 - (4 - *Methylphenylsulphonyl*) - N^1 - *phenylformamidine* **1a** was prepared by refluxing phenyl isocyanide (0.1 mol), 4 - methyl - benzenesulphonamide (0.11 mol) and CuCl (1.5 mmol) in 100 ml benzene for 8 days. After cooling the precipitate was filtered off and recrystallised from ethanol (73%), m.p. 207°C. (Found: C, 61.40; H, 5.03; N, 10.12; S, 11.70. $C_{14}H_{14}N_2O_2S$ requires: C, 61.29; H, 5.14; N, 10.21; S, 11.69%). Recrystallisation from toluene, benzene, DMSO, nitrobenzene or DMF gave the same melting point and satisfactory analysis. Mass spectrum m/e (% of base peak): 274(38)M$^+$, 273(19), 155(29), 119(75), 118(21), 94(12), 93(33), 92(31), 91(100). IR (KBr, cm^{-1}): 3290w, 3235w, 3168w, 1655s, 1650s, 1590m, 1345m, 1306m, 1299s, 1148s, 930m. The IR spectrum of **1a** melted gave a shift of the 3168 cm^{-1} band to 3163 cm^{-1}, the position of the other bands were not changed. IR of a partially deuterated **1a** gave a shift of the NH stretching bands to 2341 and 2380 cm^{-1} and in the CN stretch region the band at 1650 decreased in intensity while a new band arose at 1618 cm^{-1} and the intensity of the 1590 cm^{-1} band increased.

N^2 - *Phenylsulphonyl* - N^1 - *phenylformamidine* **1b**. Phenylisocyanide (0.11 mol), benzenesulfonamide (0.11 mol) and CuCl (1.5 mmol) were refluxed in benzene (100 ml) for 14 days. The NC absorption in the IR spectrum of the reaction mixture had not completely disappeared. After cooling the precipitate was filtered off (50%) m.p. 242°C (from toluene). (Found: C, 60.25; H, 4.59; N, 10.87; S, 12.42. $C_{13}H_{12}N_2O_2S$ requires: C, 59.98; H, 4.65; N, 10.76; S, 12.32%). MS m/e (% of base peak): 260(31)M$^+$, 259(16), 141(25), 119(80), 118(20), 93(53), 92(49), 91(16), 78(16), 77(100), 51(34). IR (KBr, cm^{-1}): 3285w, 3228w, 3166m, 1655s, 1645s, 1599m, 1589s, 1345m, 1332m, 1300s, 1292s, 1145s, 1085s, 935s.

N^2 - *Methylsulphonyl* - N^1 - *phenylformamidine* **1c** was prepared analogous to **1b**. After reflux for 25 days the solution was cooled and the precipitate filtered off (64%), m.p. 154°C (there was some unreacted isocyanide left). (Found: C, 48.60; H, 5.05; N, 13.98; S, 16.07. $C_8H_{10}N_2O_2S$ requires: C, 48.47; H, 5.08; N, 14.13; S, 16.17%). MS m/e (% of base peak): 198(40)M$^+$, 197(21), 119(100), 118(16), 93(93), 92(67), 91(10), 79(44), 77(21), 65(63), 51(16). IR (KBr, cm^{-1}): 3295w, 3220w, 3180m, 1650s (2–3 bands), 1599m, 1589m, 1478s, 1345s, 1280s, 1125s, 970m, 960m, 795s.

N^2 - (4 - *Methylphenylsulphonyl*) - N^1 - *cyclohexylformamidine* **1d**. Preparation analogous to **1a** using pyridine as solvent instead of benzene gave less than 10% yield of **1d**, after 4 weeks reflux. Preparation from the sodium salt of *p*-toluenesulphonamide (0.1 mol), phenyl isocyanide (0.1 mol) and CuCl (1.5 mmol) by reflux in 100 ml benzene for 14 days gave 12% yield of **1d**, m.p. 167–168°C. (Found: C, 59.75; H, 7.19; N, 9.98; S, 11.45. $C_{14}H_{20}N_2O_2S$ requires: C, 59.97; H, 7.19; N, 9.99, S, 11.44%). MS m/e (% of base peak): 280(11)M$^+$, 199(61), 155(46), 115(30), 104(39), 103(39), 91(100), 83(30), 77(46), 57(48), 56(92), 55(61), 54(46), 44(48), 43(46), 41(83). IR (KBr, cm^{-1}): 3305m, 3240w, 2935s, 2852m, 1640s, 1620s, 1610s, 1555w, 1452m, 1295m, 1271s, 1142s, 1089m, 882m, 815m, 690m, 678m, 554s.

N^1 - *Methyl* - N^1 - (4 - *methylphenylsulphonyl*) - N^2 - *phenylformamidine* **2** was prepared by stirring a mixture of *N*^{1} - methyl - *N*^{2} - phenylformamidine[5] (5 g), *p*-toluenesulphonylchloride (6.4 g) and triethylamine (6.7 g) in ethanol (100 ml) for 1.5 h at room temperature. After cooling the precipitate was filtered off, recrystallised from ethanol (40%), m.p. 102°C. (Found: C, 62.50; H, 5.73; N, 9.69. $C_{15}H_{16}N_2O_2S$ requires: C, 62.48; H, 5.59; N, 9.71%). MS m/e (% of base peak): 288(17)M$^+$, 224(12), 223(55), 184(17), 182(100), 155(10), 133(14), 104(35), 93(10), 92(36), 91(71), 77(55), 65(48), 51(22), 42(74). IR (KBr, cm^{-1}): 1635s, 1592s, 1380m, 1348s, 1288m, 1155s, 970s, 770m, 755m. ^{1}H NMR ($CDCl_3$) ppm: 2.42 (3H, s), 3.15 (3H, s), 6.7–7.8 (9H, m), 8.38 (1H, s).

N^1,N^1 - *Dimethyl* - N^2 - (4 - *methylphenylsulphonyl*) - *formamidine* **3**.[19] ^{1}H NMR ($CDCl_3$) ppm: 2.32 (3H, s), 2.87 (3H, s), 3.10 (3H, s), 7.1–7.7 (4H, m), 8.13 (1H, s). Cooling to −50°C ($CDCl_3$) or heating (DMSO) to 150°C caused no doubling or collapse of signals.

N^1 - *Methyl* - N^1 - *phenyl* - N^2 - (4 - *methylphenylsulphonyl*) - *formamidine* **4**[23] m.p. 108°C, yield 70%. (Found: C, 62.35; H, 5.53; N, 9.58; S, 10.97. $C_{15}H_{16}N_2O_2S$ requires: C, 62.48; H, 5.59; N, 9.71; S, 11.12%). MS m/e (% of base peak): 288(23)M$^+$, 287(28), 155(11), 134(12), 133(100), 132(28), 107(16), 106(35), 92(12), 91(51), 77(17), 65(17). IR (KBr, cm^{-1}): 1604m, 1575s, 1296m, 1148s, 1085m, 892m, 770s. ^{1}H NMR (DMSO) ppm: 2.36 (3H, s), 3.37(3H, s), 7.1–7.9(9H, m), 8.50(1H, s). Heating (DMSO) to 150°C or cooling ($CDCl_3$) to −50°C did not result in changes in the spectrum.

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