The Synthesis of *N*-Alkylidene-*N*″-sulfonylformamidrazones

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As an extension of our investigations of the chemistry of *N*″-sulfonylformamidrazones [1-3] we became interested in the hitherto unknown *N*-alkylidene-*N*″-sulfonylformamidrazones. In these compounds presence of the fixed NC double bond might give additional information about the tautomeric and conformational properties of sulfonylamidrazones. The compounds may also have some interest as potential antitumor agents.[7]

This paper describes the preparation of *N*-alkylidene-*N*″-sulfonylformamidrazones. The structure of the compounds as deduced from their NMR spectral data is reported elsewhere.[4]

N-Alkylidene-*N*″-sulfonylformamidrazones may exist as either N^2-alkylideneformohydrazide sulfonylimides *1* or N^3-alkylidene-N^1-sulfonylformamide hydrazones *3*. Compounds *1a–s* were prepared by reacting the appropriate sulfonylformimidate with a slight excess of hydrazone (eqn. (1), Table 1).

Table 1. Yields and m.p.'s for compounds $R^1SO_2N{=}CH{-}NR^2{-}N{=}CR^3R^4$ (*1a–s*).

Compound	R^1	R^2	R^3	R^4	Yield %	M.p. °C
1a	Me	H	Me	Me	40	139–141
1b	Me	Me	Me	Me	50	98–99
1c	Me	H	Pr^i	Pr^i	63	88–89
1d	Me	H	Me	Ph	46	129–131
1e	Me	H	Ph	Ph	17	171–172
1f	Me	H	Et	Ph	40	130–131
1g	Me	Me	Me	Ph	26	175–176
1h	Ph	Me	Me	Me	40	79–80
1i	Ph	H	Et	Et	18	137–138
1j	Ph	H	Pr^i	Pr^i	46	114–119
1k	Ph	H	Me	Ph	45	182–184
1l	Ph	H	Ph	Ph	37	164–165
1m	*p*-MeC_6H_4	H	Me	Me	24	157–158
1n	*p*-MeC_6H_4	H	Et	Et	59	129–130
1o	*p*-MeC_6H_4	H	Pr^i	Pr^i	66	136–138
1p	*p*-MeC_6H_4	H	Me	Ph	40	177–178
1q	*p*-MeC_6H_4	H	Et	Ph	70	121–122
1r	*p*-MeC_6H_4	Me	Me	Ph	30	105–106
1s	*p*-MeC_6H_4	H	Ph	Ph	73	189–190

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$$R^1SO_2NCHOEt + R^2NHN{=}CR^3R^4 \rightarrow R^1SO_2N{=}CHNR^2N{=}CR^3R^4 \quad (1)$$
1a–s

The preparation of the sulfonylformamide hydrazones *3* was carried out by sulfonylation of the appropriate *N*-alkylidene formamidrazone *2* (eqn. (2)) or by reaction of *N*-sulfonylformamide, hydrazone, and $POCl_3$ (eqn. (3)).

$$R^1SO_2Cl + CH_3NHCH{=}N{-}N{=}CR^3R^4 \rightarrow$$
2c,d
$$R^1SO_2NCH_3CH{=}N{-}N{=}CR^3R^4 +$$
3d,o,p
$$R^1SO_2NHN{=}CR^3R^4$$
4c,d,o,p (2)

$$R^1SO_2NCH_3CHO + R^3R^4C{=}NNH_2 \xrightarrow{POCl_3} R^1SO_2NCH_3CH{=}N{-}N{=}CR^3R^4 \quad (3)$$
3p

The tosylation reaction gave mixtures containing compounds *3* and *4* as main products. The compounds *4* are probably formed from an *N*′-tosylated-*N*-alkylidene-formamidrazone which is hydrolyzed analogously to findings for other formamidrazones.[2] The $POCl_3$ method gave low yields and only compound *3p* was prepared by this method. The main product was the azine corresponding to the hydrazone. The new compounds *2* were prepared from N^2-alkylidene-*O*-ethyl formhydrazonate *5* and excess methylamine in methanolic solution (eqn. (4)).

$$R^3R^4C{=}N{-}N{=}CHOEt + CH_3NH_2 \rightarrow$$
5c,d
$$R^3R^4C{=}N{-}N{=}CHNHCH_3 \quad (4)$$
2c,d

The identity of all new compounds was proved by elemental analysis, IR, ^1H NMR, ^{13}C NMR and mass spectral data. Hydrolytic degradation of compounds *3* gave the expected *N*-methylsulfonamides. The identity of compounds *4* was ensured from the ^1H NMR spectra identical with those of authentic compounds.

Experimental. The experimental equipment was reported earlier.[1]

General procedure for preparation of N^2-*alkylideneformohydrazide sulfonylimides* 1. The hydrazone (0.06 mol) in ether (50 ml) was slowly dropped into a solution of *N*-sulfonylimidate (0.05 mol) in ether (50 ml). Stirring overnight at room temperature gave a crystalline compound which was filtered off and recrystallized from 99.5 % ethanol.

For compound *1r* this method gave a low yield. *1r* could be prepared by refluxing equimolar

amounts of hydrazone and sulfonylimidate (0.07) mol) in benzene (80 ml) overnight. The solvent was evaporated, 60 ml of NaOH (1 M) was added and the basic solution was extracted with CH_2Cl_2. The organic layer was dried (K_2CO_3), the solvent evaporated, and the compound recrystallized from ethanol.

N^2-Alkylidene-O-ethylformhydrazonates 5.[5] *5c*, b.p. 34–38 °C/0.1 mmHg, yield 60 %. *5d* b.p. 78–79 °C/0.05 mmHg, yield 69 %. Anal. $C_{11}H_{14}N_2O$: C, H, N.

N-Alkylidene formamidrazones 2. *2c* was prepared by stirring *O*-ethyl-*N^2*-(2,4-dimethyl-3-pentylidene) formhydrazonate (0.3 mol) with CH_3NH_2 in methanol solution (100 ml, 6 M) at room temperature for 14 days. The solvent was evaporated and the resulting liquid distilled *in vacuo*. B.p. 68–69 °C/0.05 mmHg, yield 70 %. Anal. $C_9H_{19}N_3$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 7.99 (1/3 H, d) $J_{CH/NH}$=3 Hz, and 6.94 (2/3 H, d) $J_{CH/NH}$=11.5 Hz; 5.8–4.5 (1 H, b); 3.63 and 2.66 (2 H, h); 2.93 (2 H, d) J(NH/CH_3)= 6 Hz, and 2.89 (1 H, d) J(NH/CH_3)=1 Hz; 1.17 (6 H, d) and 1.13, 1.09 (6 H, doublets). On cooling to −50 °C the NH proton signal appeared as two double quartets.

2d. Preparation analogous to *2c* with a reaction time of 30 days. B.p. 122–125 °C/0.05 mmHg, yield 70 %. ^{1}H NMR ($CDCl_3$): δ 8.23 (5/11 H, d) $J_{CH/NH}$=4 Hz, and 7.11 (6/11 H, d) $J_{CH/NH}$=11.5 Hz; 6.2–4.2 (1 H, b); 8.0–7.3 (5 H, m); 2.88 (18/11 H, d) J(NH/CH_3)=2 Hz and 2.87 (15/11 H, d) J(NH/CH_3)=6 Hz; 2.43 (18/11 H, s) and 2.41 (15/11 H, s). On cooling to −50 °C the NH signal appeared as two double quartets. Shaking with D_2O resulted in the disappearance of the NH signal and a collapse of the CH and CH_3 doublets.

N^3-Alkylidene-N^1-methyl-N^1-sulfonylformamide hydrazones 3. *2d* (0.045 mol), methanesulfonyl chloride (0.045 mol) and triethylamine (0.09 mol) were stirred in toluene (50 ml) for 3 days. The precipitate was filtered off, the filtrate washed with water, dried (K_2CO_3) and the solvent evaporated. The resulting crystalline mass was worked up by preparative TLC on silica gel plates using $CHCl_3$ as eluent. The main products isolated were *N'-(1-phenylethylidene) methanesulfonohydrazide* 4d (15 %) and *N^3-(1-phenylethylidene)-N^1-methyl-N^1-methanesulfonylformamide hydrazone* 3d. Yield 30 %, m.p. 87–88 °C. Anal. $C_{11}H_{15}N_3O_2S$: C, H, N. MS *m/e* (% of base peak): 253(32)M^+, 175(17), 174(89), 145(13), 133(15), 118(66), 92(13) 77(26), 42(100).

Treatment of *2d* with tosyl chloride and triethylamine analogous to the description above gave *N'-(1-phenylethylidene)-p-toluenesulfonohydrazide 4p* (yield 20 %) and *N^3-(1-phenylethylidene)-N^1-methyl-N^1-p-toluenesulfonylformamide hydrazone 3p*. Some *3p* could also be isolated by treating the crude product with ethanol. Yield 52 %, m.p. 135–136 °C. Anal. $C_{17}H_{19}N_3O_2S$: C, H, N. MS *m/e* (% of base peak): 329(9)M^+, 175(12), 174(80), 118(53), 105(14), 92(11), 91(26), 77(19), 65(11), 42(100). *3p* was prepared unambiquously from *N*-methyl-*N*-*p*-toluenesulfonylformamide[6] (0.06 mol) and acetophenonehydrazone (0.06 mol) in benzene (25 ml) which were slowly dropped into a refluxing solution of $POCl_3$ (0.06 mol) in benzene (50 ml). After reflux for 12 h, ice (50 g) was added and the solution made basic with 6 M NaOH. The mixture was extracted with ether, the ether phase dried (K_2CO_3) and the solvent evaporated. The resulting dark oil oil consisted mainly of acetophenone azine and some unreacted *N*-methyl-sulfonylformamide. Some crystals were formed from the oil on standing, these were isolated and recrystallized from ethanol giving a yield of *3p* on 5 %.

2c, treated with tosyl chloride and triethylamine as described above gave an oil, probably consisting of both an *N''*- and an *N'*-tosylated compound according to the NMR spectrum. Attempts to separate the components by distillation gave *p*-$CH_3C_6H_4SO_2NHCH_3$ and *p*-$CH_3C_6H_4SO_2NHNC(Pr^i)_2$ as decomposition products. A fraction b.p. 133–146 °C/0.05 mmHg was worked up by preparative TLC giving *3o*, yield 20 % (calculated from the ^{1}H NMR spectrum of the crude product), m.p. 82–83 °C, MS *m/e* (% of base peak): 323(29)M^+, 168(58), 139(60), 127(80), 91(100), 83(53), 55(44), 43(64), 42(69). ^{1}H NMR ($CDCl_3$): δ 8.60 (1 H, s), 7.2–8.0 (4 H, m), 3.25 (1 H, h), 3.12 (3 H, s), 2.59 (1 H, h), 2.45 (3 H, s), 1.0–1.2 (12 H, m).

2c and methanesulfonyl chloride gave analogously an oil. On standing a small amount of crystals was formed, these were filtered off and identified as $CH_3SO_2NHNC(Pr^i)_2$. Attempts to distil the filtrate resulted in decomposition.

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