Preparation of 1,5-Disubstituted 4-Sulfonylpyrazoles, β-Cyano-β-sulfonylenamines and 5-Substituted 4-Sulfonylisoxazoles from β-Keto-β-sulfonylenamines

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Reaction of β-keto-β-sulfonylenamines **1a,b** with *N*-substituted hydrazines gave 1,5-disubstituted 4-sulfonylpyrazoles **2a-h** in moderate yields, which were ring-opened on treatment with *n*-butyllithium to afford β-cyano-β-sulfonylenamines (**3a,b,d-f**). 5-Substitued 4-sulfonylisoxazoles **6a-d** were also prepared from **1a-d** and hydroxylamine.

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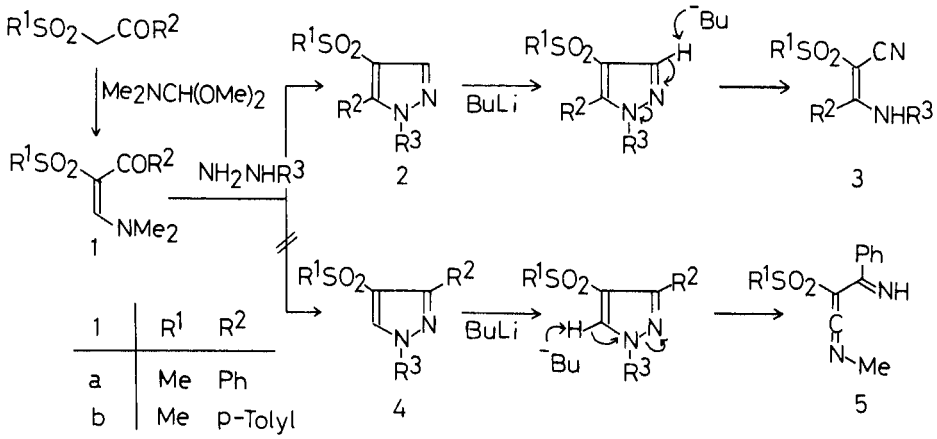
In the previous paper [1] we have shown the usefulness of β-keto-, β-ethoxycarbonyl-, and β-cyano-β-sulfonylenamines as synthons for 5-sulfonylpyrimidine derivatives. These enamines appear to serve also as the starting materials for the synthesis of five-membered heterocycles having sulfonyl substituents. We now report that β-keto-β-sulfonylenamines **1a-d** react readily with *N*-substituted hydrazines and hydroxylamine to give 1,5-disubstituted 4-sulfonylpyrazoles **2a-h** [2] and 5-substituted 4-sulfonylisoxazoles **6a-d** [3], respectively, in satisfactory yields.

β-Keto-β-sulfonylenamines **1a-d** were obtained from β-ketosulfones and *N,N*-dimethylformamide dimethylacetal [4] as described before [1] (Scheme 1). Treatment of **1a,b** with *N*-substituted hydrazines in refluxing ethanol for 4-11 hours gave 1,5-disubstituted 4-methanesulfonylpyrazoles in good yields (Tables 1 and 2). In contrast with the reaction with *N*-unsubstituted hydrazines [5,6], it seems possible to yield two regioisomers, 1,4,5-trisubstituted pyrazoles **2** and 1,3,4-trisubstituted pyrazoles **4**, as known in the synthesis of pyrazoles using β-halo- or β-amino-α,β-unsaturated carbonyl compounds and *N*-substituted hydrazines [2a]. It has been reported that 3-unsubstituted pyrzoles with electron with-drawing substituents at the 4-position were cleaved to yield the corresponding β-cyanoenamines on treatment with base [7]. On the other hand, 5-unsubstituted pyrazoles underwent ready lithiation followed by electrophilic attack to give 5-substituted pyrazoles [8,9]. When the present cyclized product, **2a** or **4a**, from **1a** and *N*-methylhydrazine was allowed to react with *n*-butyllithium in tetrahydrofuran, a ring-opened product was obtained in 49% yield. Its structure was assumed to be β-cyano-β-sulfonylenamine **3a** from **2a** or α-iminoketene imine **5** [10] from **4a** on the basis of the absorptions at 3250 (NH) and 2180 cm^{-1} (C=N or C=C=N) in the ir spectrum. Two singlets at δ 80.8 and 168.2 in the ^{13}C-nmr spectrum could be assigned to β- and α-carbons of β-cyanoenamine **3a**, respectively, by comparing with the known spectra of β-nitro, β-keto [11], and β-cyanoenamines [12]. A singlet at δ 116.4 was apparently attributable to CN group, whereas the presence of ketene imine moiety was excluded on the basis of the reported ^{13}C-nmr chemical shifts [13]. Thus, the structure **3a** is preferred to **5**, and accordingly a facile route to 1,5-disubstituted 4-sulfonylpyrazoles **2** from **1** has been established.

Scheme 1



1	R^1	R^2
a	Me	Ph
b	Me	p-Tolyl

Scheme 2

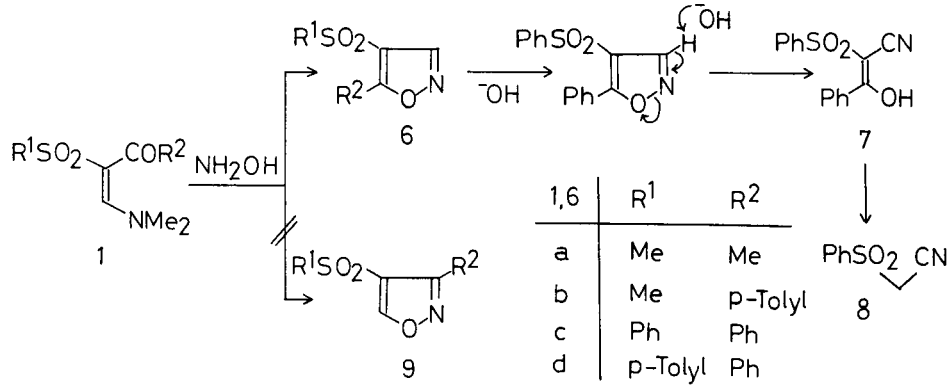


Table 1

Physical Properties of Compounds **2**, **3**, and **6**

Compound	R¹	R²	R³	Yield %	Mp °C (solvent)	Formula	Calcd % C	Calcd % H	Found % C	Found % H
2a	Me	Ph	Me	57	144-145 (A)	$C_{11}H_{12}N_2O_2S$	55.93	5.12	55.71	4.93
2b	Me	Ph	Ph	92	145-146 (B)	$C_{16}H_{14}N_2O_2S$	64.42	4.73	64.72	4.48
2c	Me	*p*-Tolyl	Me	60	159-160 (C)	$C_{12}H_{14}N_2O_2S$	57.59	5.64	57.75	5.74
2d	Me	*p*-Tolyl	Ph	81	130-131 (B)	$C_{17}H_{16}N_2O_2S$	65.37	5.16	65.17	5.23
2e	Me	Ph	*p*-ClC_6H_4	74	155-156 (B)	$C_{16}H_{13}ClN_2O_2S$	57.74	3.94	57.81	4.00
2f	Me	*p*-Tolyl	*p*-ClC_6H_4	74	183-185 (B)	$C_{17}H_{15}ClN_2O_2S$	58.87	4.36	59.13	4.36
2g	Me	Ph	*p*-$NO_2C_6H_4$	83	161-162 (B)	$C_{16}H_{13}N_3O_4S$	55.97	3.82	55.74	3.69
2h	Me	*p*-Tolyl	*p*-$NO_2C_6H_4$	87	209-211 (D)	$C_{17}H_{15}N_3O_4S$	57.13	4.23	57.31	4.21
3a	Me	Ph	Me	49	179-180 (E)	$C_{11}H_{12}N_2O_2S$	55.93	5.12	56.14	5.14
3b	Me	Ph	Ph	39	183-184 (A)	$C_{16}H_{14}N_2O_2S$	64.41	4.73	64.46	4.73
3d	Me	*p*-Tolyl	Ph	45	194-195 (F)	$C_{17}H_{16}N_2O_2S$	65.36	5.16	65.26	5.03
3e	Me	Ph	*p*-ClC_6H_4	42	179-180 (A)	$C_{16}H_{13}ClN_2O_2S$	57.74	3.94	57.63	3.83
3f	Me	*p*-Tolyl	*p*-ClC_6H_4	23	194-196 (A)	$C_{17}H_{15}ClN_2O_2S$	58.87	4.36	59.15	4.61
6a	Me	Ph		61	93-95 (B)	$C_{10}H_9NO_3S$	53.81	4.06	53.90	4.02
6b	Me	*p*-Tolyl		76	143-144 (B)	$C_{11}H_{11}NO_3S$	55.69	4.67	55.56	4.80
6c	Ph	Ph		43	79-80 (B)	$C_{15}H_{11}NO_3S$	63.16	3.89	63.34	3.82
6d	*p*-Tolyl	Ph		82	118-119 (B)	$C_{16}H_{13}NO_3S$	64.21	4.38	64.45	4.50

Recrystallization solvents: A = benzene, B = ethanol, C = ethyl acetate, D = methanol-acetonitrile, E = ethanol-benzene, F = chloroform.

2-Anilino-1-cyano-2-phenyl-1-(*p*-tosyl)ethane, a compound of a rare class β-cyano-β-sulfonylenamine, was reported to be obtained by treating 1,5-diphenyl-4-(*p*-tosyl)-pyrazole with potassium *t*-butoxide in refluxing *t*-butanol [7]. The present ring-opening process of **2a** to **3a** seems to provide a more applicable route to these enamines **3** because of ready access to the starting pyrazoles **3** and milder reaction conditions. The enamines **3b,d-f** were obtained expectedly under the similar reaction conditions, but some pyrazoles **2c,g,h** did not afford identifiable products (Tables 1 and 2).

The reaction of β-acylenamines with hydroxylamine is already known to afford isoxazoles [5,6]. Analogous treatment of **1a-d** with hydroxylamine hydrochloride and sodium acetate in aqueous methanol at room temperature led to the formation of 4-sulfonylisoxazoles in 43-82% yields (Scheme 2). A problem of regioselectivity, that is, 5-substituted 4-sulfonylisoxazoles **6** or 2-substituted 4-sulfonylisoxazoles **9**, was solved as follows; treatment of isoxazole **6c** or **9c** derived from **1c** with sodium hydroxide in aqueous methanol at room temperature gave benzenesulfonylacetonitrile (**8**) in 34% yield. It appears plausible, according to the well-documented ring-opening process in the chemistry of isoxazole [3], to assume that **6c** was cleaved by base to give an intermediate **7** which was further hydrolyzed to **8**. 5-Substituted 4-sulfonylisoxazoles **6a-d** thus prepared are summarized in the Tables 1 and 2.

Table 2

Spectroscopic Data of Compounds **2**, **3**, and **6**

Compound	MS M⁺, m/z	IR (potassium bromide) cm⁻¹	NMR δ, ppm (Deuteriochloroform)
2a	236	3100, 2990, 2900, 1535, 1470, 1440	2.77 (s, 3H), 3.73 (s, 3H), 7.50 (s, 5H), 7.93 (s, 1H)
2b	298	3050, 2910, 2850, 1590, 1490, 1440	2.81 (s, 3H), 7.26-7.37 (m, 10H), 8.14 (s, 1H)
2c	250	3090, 2990, 2900, 1605, 1490, 1460	2.43 (s, 3H), 2.77 (s, 3H), 3.74 (s, 3H), 7.32 (s, 4H), 7.91 (s, 1H)
2d	312	3100, 3040, 2930, 1590, 1490, 1445	2.08 (s, 3H), 2.68 (s, 3H), 7.11-7.14 (m, 9H), 8.03 (s, 1H)
2e	332	3100, 2920, 1540, 1495, 1440, 1405	2.78 (s, 3H), 7.22-7.38 (m, 9H), 8.10 (s, 1H)
2f	346	3050, 2930, 1495, 1445, 1410, 1385	2.38 (s, 3H), 2.78 (s, 3H), 7.17 (s, 8H), 8.11 (s, 1H)
2g	343	3120, 2930, 1590, 1520, 1500, 1440	2.82 (s, 3H), 7.40 (d, J = 9 Hz, 2H), 7.43 (s, 5H), 8.15 (d, J = 9 Hz, 2H), 8.18 (s, 1H)
2h	357	3120, 3080, 3030, 2930, 1610, 1595	2.37 (s, 3H), 2.77 (s, 3H), 7.20 (s, 5H), 7.36 (d, J = 9 Hz, 2H), 8.12 (d, J = 9 Hz, 2H), 8.13 (s, 1H)
3a	236	3250, 3000, 2910, 2180, 1580, 1570	2.68 (s, 1.5 H), 2.75 (s, 1.5 H), 3.14 (s, 3H), 7.21-7.58 (m, 5H), 8.50 (br s, 1H)
3b	298	3280, 3050, 3010, 2930, 2190, 1550	3.31 (s, 3H), 6.67-7.40 (m, 10H), 10.22 (br s, 1H)
3d	312	3280, 3030, 2930, 2210, 1605, 1580	2.35 (s, 3H), 3.31 (s, 3H), 6.70-7.43 (m, 9H), 10.20 (br s, H)
3e	332	3270, 2200, 1600, 1560, 1495, 1425	3.27 (s, 3H), 6.57 (d, J = 9 Hz, 2 H), 7.03 (d, J = 9 Hz, 2H), 7.28 (s, 5H), 9.98 (br s, 1H)
3f	346	3260, 2930, 2200, 1590, 1560, 1515	2.32 (s, 3H), 3.25 (s, 3H), 6.53-7.26 (m, 8H), 9.92 (br s, 1H)
6a	223	3110, 1600, 1580, 1560, 1465, 1440	3.06 (s, 3H), 7.63-8.21 (m, 5H), 8.65 (s, 1H)
6b	237	3100, 3020, 2920, 1605, 1580, 1460	2.44 (s, 3H), 3.03 (s, 3H), 7.34 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 2H), 8.54 (s, 1H)
6c	285	3080, 1605, 1580, 1560, 1460, 1445	7.33-7.98 (m, 10H), 8.55 (s, 1H)
6d	299	3100, 1590, 1580, 1560, 1460, 1440	2.36 (s, 3H), 7.13-8.01 (m, 7H), 8.56 (s, 1H)

EXPERIMENTAL

Melting points are uncorrected. The spectra were recorded on the following instruments; ir, JASCO A102; ^{1}H-nmr, JEOL JNM-PMX; ms, JEOL JMS-DX 300. Elemental analyses were performed on a Shimadzu UM-3B microanalyzer. The starting materials **1a,b** were prepared according to the previous paper [1].

1-Benzenesulfonyl-1-benzoyl-2-(*N,N*-dimethylamino)ethene (**1c**).

A mixture of phenacyl phenyl sulfone [14] (248 mg, 1.0 mmoles) and *N,N*-dimethylformamide dimethylacetal (296 mg, 2.5 mmoles) in toluene (2 ml) was refluxed for 15 hours. After evaporation of the solvent the residue was recrystallized from chlorofom to give **1c** (243 mg, 77%), mp 162-163°; ir (potassium bromide): 2900, 1595, 1470, 1440, 1420, 1400 cm^{-1}; nmr (chloroform-d): δ 2.80 (s, 6H), 7.23-7.81 (m, 10H), 7.91 (s, 1H).

Anal. Calcd. for $C_{17}H_{17}NO_3S$: C, 64.75; H, 5.43. Found: C, 65.03; H, 5.46.

The compound **1d** was prepared in 59% yield in the same manner from phenacyl *p*-tolyl sulfone, mp 145-146° (methanol); ir (potassium bromide): 2910, 1595, 1480, 1450, 1425, 1415 cm^{-1}; nmr (chloroform-d): δ 2.35 (s, 3H), 2.78 (s, 6H), 7.08-7.68 (m, 9H), 7.90 (s, 1H).

Anal. Calcd. for $C_{18}H_{19}NO_3S$: C, 65.64; H, 5.82. Found: C, 65.34; H, 5.82.

A General Procedure for the Preparation of 1,5-Disubstitued 4-Methanesulfonylpyrazoles **2a-d,g** and **h**.

A mixture of β-keto-β-sulfonylenamine **1** (1 mmole) and *N*-substituted hydrazine (1.2-5 mmoles) in ethanol (3-5 ml) was refluxed for 4-11 hours. After cooling the precipitates were collected by filtration and recrystallized from the appropriate solvents.

1-(*p*-Chlorophenyl)-4-methanesulfonyl-5-phenylpyrazole (**2e**).

To a solution of *p*-chlorophenylhydrazine hydrochloride (362 mg, 2.0 mmoles) in water (2 ml) were added sodium carbonate (109 mg, 1.0 mmoles), ethanol (15 ml) and **1a** (386 mg, 1.0 mmoles), and the mixture was heated at reflux for 15 hours. Upon cooling the precipitates were collected by filtration and recrystallized. The compound **2f** was prepared in the same manner.

A General Procedure for the Preparation of 1-Amino-1-aryl-2-cyano-2-methanesulfonylethenes **3a,b,d-f**.

To a stirred solution of pyrazole **1** (1 mmole) dissolved in dry tetrahydrofuran (5-10 ml), which was blanketed by nitrogen and cooled in a dry ice-acetone bath, was added excess *n*-butyllithium (3-5 mmoles) in hexane. The resulting mixture was stirred for several hours in the cooled bath, and then for an additional several hours at room temperature. A saturated aqueous solution of ammonium chloride was added to the mixture. The organic layer was separated and the aqueous layer was extracted with chloroform. After the combined extract was dried and evaporated, the residue was recrystallized from the appropriate solvents. In the case of **3d** the residue was purified by column chromatography on silica gel with chloroform; ^{13}C-nmr of **3a** (chloroform-d): δ 32.7 (CH_3-N), 43.9 (CH_3-SO_2), 80.8 (=C-SO_2), 116.4 (CN), 127.4, 129.4, 131.1 (aromatic carbons), 168.2 (=C-N).

A General Procedure for the Preparation of 5-Substituted 4-Sulfonylisoxazoles **6a-d**.

A mixture of β-sulfonyl-β-ketoenamine **1** (1 mmole), sodium acetate (1 mmole) and hydroxylamine hydrochloride (1 mmole) in methanol (4 ml) and water (2 ml) was stirred for 30 minutes to 22 hours at room temperature. The precipitates were collected by filtration and recrystallized from ethanol to give **6**.

Hydrolysis of **6c** to **8**.

To a solution of sodium hydroxide (100 mg) in methanol (9 ml) and water (1 ml) was added **6c** (240 mg, 0.8 mmole) and the mixture was stirred at room temperature for 19 hours. After evaporation of the solvent the syrupy residue was dissolved in water. The mixture was acidified with hydrochloric acid, evaporated, and subjected to column chromatography on silica gel with chloroform to afford **8** (53 mg, 34%), mp 111-113° (chloroform), identical with the authentic sample [15].

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