Preparation of 5-Sulfonylpyrimidines from β-Keto, β-Cyano-, and β-Ethoxycarbonyl-β-sulfonylenamines

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β-Keto-β-sulfonylenamines **2a,b** reacted with benzamidine or guanidines to give 2,4-disubstituted 5-methanesulfonylpyrimidines **3a-d**, whose methanesulfonyl groups were substituted by *n*-butyllithium or alkylmagnesium bromides to yield 2,4-disubstitued 5-alkylpyrimidines **6a-d**. 2-Substituted 4-amino-5-sulfonylpyrimidines **7a,b**, **8** and 2-substituted 5-benzenesulfonylpyrimidin-4-ones **9a,b** were similarly obtained from β-cyano-β-sulfonylenamines **2c,d** and β-ethoxycarbonyl-β-sulfonylenamine (**2e**), respectively.

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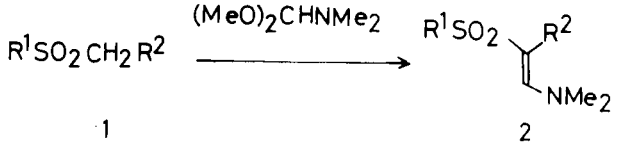
Several methods for the preparation of β-sulfonylenamines have been developed in recent years [1]. Little attention, however, has been payed to their synthetic utility. Alkylation and acylation of cyclic sulfonylenamines [2] and the formation of the ring-enlargement product in the reaction of the enamines with methanesulfonyl chlorides [3] were reported by Fatutta *et al.* Much more recently, the reaction of β-acetyl-β-sulfonyl or sulfenylenamines with acetamidine was described to give 2,4-dimethyl-5-sulfonyl- or sulfenylpyrimidines instead of the expected imidazoles [4]. This prompted us to report our results on the synthesis of 2,4-disubtituted 5-sulfonylpyrimidines starting from β-functionalized β-sulfonylenamines **2a-e**.

N,N-Dimethylaminomethylation of the active methylene compounds bearing sulfonyl group **1a-e** were readily accomplished on reacting with *N,N*-dimethylformamide dimethylacetal [5] in toluene or methanol at reflux or room temperature to yield the expected enamines **2a-e** in 48-91% yields (Table 1) (Scheme 1).

Scheme 1

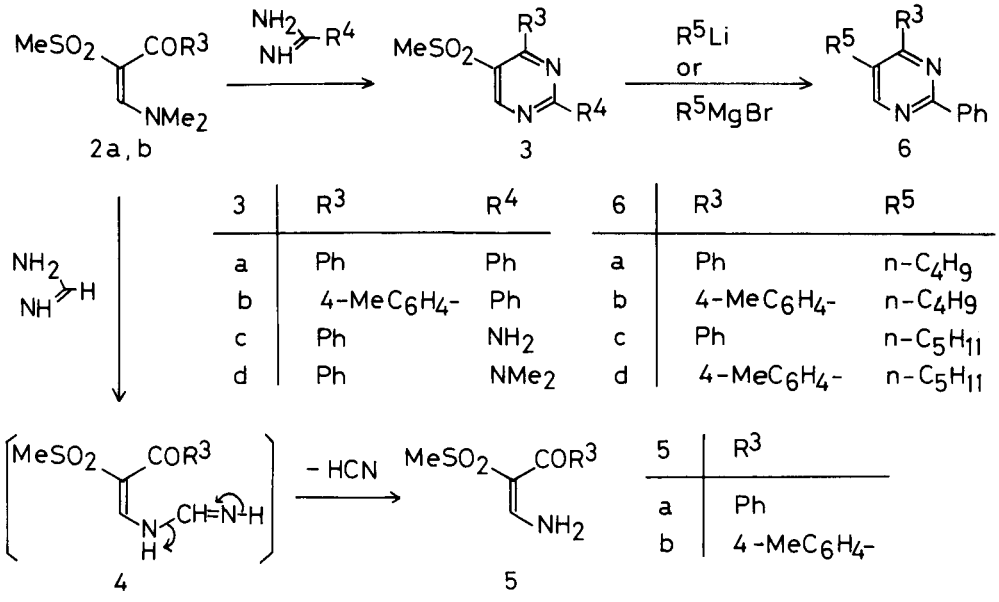


1 2

	R^1	R^2
1a , 2a	Me	COPh
1b , 2b	Me	4-MeC_6H_4CO-
1c , 2c	Me	CN
1d	CH_2CN	CN
2d	C(=CHNMe2)CN	CN
1e , 2e	Ph	CO_2Et

The treatment of **2a,b** with benzamidine hydrochloride or guanidine hydrochloride in the presence of sodium carbonate in refluxing aqueous methanol led to 2,4-disubsti-

Scheme 2



3	R^3	R^4
a	Ph	Ph
b	4-MeC_6H_4-	Ph
c	Ph	NH_2
d	Ph	NMe_2

6	R^3	R^5
a	Ph	n-C_4H_9
b	4-MeC_6H_4-	n-C_4H_9
c	Ph	n-C_5H_{11}
d	4-MeC_6H_4-	n-C_5H_{11}

5	R^3
a	Ph
b	4-MeC_6H_4-

Table 1

Physical and Spectroscopic Data of Compounds **2-9**

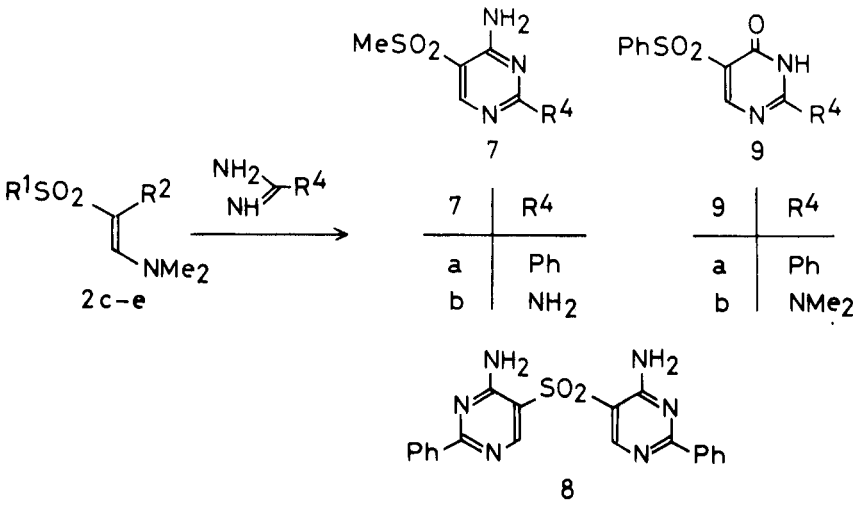
Compound	Yield %	Mp °C (Solvent)	Molecular Formula	Analysis % Calcd./(Found) C	H	MS M⁺, m/z	IR KBr, cm⁻¹		
2a	48	115-116 (MeOH)	$C_{12}H_{15}NO_3S$	56.91 (57.20)	5.97 (6.09)	253	1595 1410	1480 1370	1440 1305
2b	80	163-165 (MeOH)	$C_{13}H_{17}NO_3S$	58.41 (58.23)	6.41 (6.21)	267	1605 1380	1430 1280	1400 1245
2c	88	130-131 (MeOH)	$C_6H_{10}N_2O_2S$	41.37 (41.07)	5.79 (5.88)	174	2170 1375	1630 1295	1410 1135
2d	63	187-190 (MeOH)	$C_{10}H_{14}N_4O_2S$	47.23 (47.24)	5.55 (5.46)	254	2300 1360	1620 1310	1420 1285
2e	91	116-118 (MeOH)	$C_{13}H_{17}NO_4S$	55.11 (55.00)	6.05 (6.11)	283	1685 1440	1605 1430	1475 1380
3a	49	185-186 (CH_3CN)	$C_{17}H_{14}N_2O_2S$	65.80 (65.91)	4.55 (4.54)	310	1560 1430	1535 1315	1510 1160
3b	83	196-197 (CH_3CN)	$C_{18}H_{16}N_2O_2S$	66.65 (66.33)	4.97 (5.10)	324	1545 1410	1525 1370	1500 1300
3c	44	231-232 (MeOH)	$C_{11}H_{11}N_3O_2S$	53.01 (53.03)	4.45 (4.48)	249	3380 1630	3300 1555	3180 1520
3d	51	166-167 (MeOH)	$C_{13}H_{15}N_3O_2S$	56.31 (56.51)	5.45 (5.44)	277	1560 1400	1505 1300	1480 1130
5a	62	181-182 (MeOH)	$C_{10}H_{11}NO_3S$	53.33 (53.60)	4.92 (4.88)	225	3380 1630	3270 1580	3240 1560
5b	49	176-178 (MeOH)	$C_{11}H_{13}NO_3S$	55.23 (55.10)	5.48 (5.55)	239	3380 1640	3280 1580	3240 1550
6a	23 [a] 49 [b]	70-71 (MeOH)	$C_{20}H_{20}N_2$	83.29 (83.18)	6.99 (6.90)	288	2980 1575	2940 1535	1600 1420
6b	21 [a] 20 [b]	60-61 (MeOH)	$C_{21}H_{22}N_2$	83.40 (83.24)	7.33 (7.34)	302	2940 1565	2920 1525	1585 1415
6c	27	oil	$C_{21}H_{22}N_2$	83.40 (82.19)	7.33 (7.37)	302	2940 1565	2920 1530	1585 1370
6d	27	79-81 (MeOH)	$C_{22}H_{24}N_2$	83.50 (83.11)	7.64 (7.58)	316	2930 1565	2910 1525	1580 1420
7a	65	188-189 (MeOH)	$C_{11}H_{11}N_3O_2S$	53.01 (53.26)	4.45 (4.42)	249	3440 1560	3100 1530	1620 1410
7b	64	229-230 (MeOH)	$C_5H_8N_4O_2S$	31.91 (31.93)	4.28 (4.30)	188	3430 1620	3300 1560	3150 1530
8	80	>300 (DMF)	$C_{20}H_{16}N_6O_2S$	59.39 (59.65)	3.99 (4.12)	—	3450 1585	3100 1560	1620 1530
9a	74	>300 (DMF)	$C_{16}H_{12}N_2O_3S$	61.53 (61.21)	3.87 (3.87)	—	3050 1500	1655 1315	1535 1145
9b	62	297-300 (DMF)	$C_{12}H_{13}N_3O_3S$	51.60 (51.89)	4.69 (4.63)	279	3000 1590	2950 1535	1650 1500

[a] Reaction with *n*-BuLi. [b] Reaction with *n*-BuMgBr.

tuted 5-methanesulfonylpyrimidines **3a-d** in the moderate yields (44-83%) (Scheme 2). In contrast to a number of 2-sulfonylpyrimidines, 5-sulfonyl derivatives seems to be limited [6]. α-(Alkoxymethylene)arylsulfonylacetonitrile [7, 8] and phenylsulfonylcyanoketene-*S*, *S*-acetal [9] appeared in the recent literatures as the starting materials for the cyclization to these pyrimidines. Thus, the present method, a modification of Pinner reaction [10], would serve as a new route to 2,4-disubstituted 5-sulfonylpyrimidines. On the other hand, when **2a** and **b** were allowed to react with formamidine acetate, *N*-unsubstituted β-keto-β-sulfonylenamines **5a,b** were formed unexpectedly in 62 and 49% yields, respectively. This reaction may be explained by assuming the intermediate **4** followed by the extrusion of hydrogen cyanide. The related series of *N*-unsubstituted β-sulfonylenamines was found to be synthesized by the reaction of sulfonyl carbanions with nitriles [11].

Substitution reactions at the 5-position of pyrimidines have not been studied extensively as compared with those at the 2- or 4-position [12]. Halogens at the 5-position were substituted by oxygen, sulfur, or nitrogen nucleophiles [6, 13] and by olefinic compounds in the presence of palladium acetate and triphenylphosphine [14]. However, it seems that the nucleophilic substitution reaction towards sulfonyl group at the 5-position has not been explored, although 2-sulfonylpyrimidines are known to be substituted

Scheme 3



[6,12] by nitrogen [15], sulfur [16] or carbanion [13,17] nucleophiles. Therefore, the nucleophilic substitution towards **3a** and **b** was undertaken. The reaction was carried out in two manners: a) pyrimidines **3a** and **b** were treated with *n*-butyllithium in tetrahydrofuran at −78° to room temperature, and b) with Grignard reagents (*n*-butyl and *n*-pentyl magnesium bromides) in refluxing ether-tetrahydrofuran. The results are summarized in the Table 1. The *n*-butyl and *n*-pentyl groups could be introduced to yield simple 2,4,5-trisubstituted pyrimidines **6a-d** in 20-49% yields. However, more higher alkyl, phenyl, or alkynylcarbanions showed less satisfactory results.

Table 2

NMR Spectra of Compounds **2-9**

Compound	δ, ppm
2a [a]	2.72 (s, 6H), 3.17 (s, 3H), 7.38-7.85 (m, 6H)
2b [a]	2.40 (s, 3H), 2.73 (s, 6H), 3.15 (s, 3H), 7.23 (d, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.75 (s, 1H)
2c [a]	3.05 (s, 3H), 3.20 (s, 3H), 3.30 (s, 3H), 7.67 (s, 1H)
2d [a]	3.30 (s, 12H), 7.50 (s, 2H)
2e [a]	1.06 (t, J = 7 Hz, 3H), 3.16 (s, 6H), 4.00 (q, J = 7 Hz, 2H), 7.40-7.90 (m, 5H)
3a [a]	2.70 (s, 3H), 7.43-8.61(m, 10H), 9.40 (s, 1H)
3b [a]	2.45 (s, 3H), 2.70 (s, 3H), 7.29-8.67 (m, 9H), 9.46 (s, 1H)
3c [b]	2.82 (s, 3H), 7.46 (s, 5H), 7.69 (s, 2H), 8.71 (s, 1H)
3d [a]	2.63 (s, 3H), 3.30 (s, 6H), 7.22-7.75 (s, 5H), 8.89 (s, 1H)
5a [b]	3.12 (s, 3H), 7.38 (s, 5H), 8.02 (br s, 2H)
5b [b]	2.33 (s, 3H), 3.17 (s, 3H), 7.17-7.59 (m, 4H), 8.02 (br s, 2H)
6a [a]	0.97 (t, J = 6 Hz, 3H), 1.17-2.07 (m, 4H), 2.87 (t, J = 8 Hz, 2H), 7.36-8.62 (m, 11H)
6b [a]	0.99 (t, J = 7 Hz, 3H), 1.19-2.10 (m, 4H), 2.43 (s, 3H), 2.88 (t, J = 8 Hz, 2H), 7.24-8.70 (m, 10H)
6c [a]	0.93 (t, 6 Hz, 3H), 1.27-1.98 (m, 6H), 2.89 (t, J = 8 Hz, 2H), 7.44-8.71 (m, 11H)
6d [a]	0.92 (t, J = 7 Hz, 3H), 1.21-1.99 (m, 6H), 2.41 (s, 3H), 2.85 (t, J = 8 Hz, 2H), 7.24-8.70 (m, 10H)
7a [b]	3.23 (s, 3H), 7.52-8.18 (m, 7H), 8.68 (s, 1H)
7b [b]	3.00 (s, 3H), 6.87 (s, 4H), 8.07 (s, 1H)
8 [c]	7.19-7.96 (m, 14H), 8.80 (s, 2H)
9a [c]	7.25-7.86 (m, 11H), 8.78 (s, 1H)
9b [c]	3.06 (s, 3H), 3.12 (s, 3H), 7.19-7.69 (m, 5H), 8.37 (s, 1H)

[a] Measured in deuteriochloroform. [b] DMSO-d_6. [c] Trifluoroacetic acid.

Cyclization of β-cyano-β-sulfonylenamines **2c,d** to 4-amino-5-sulfonylpyrimidines **7a,b**, and **8** proceeded in 64-80% yields by reacting with benzamidine hydrochloride or guanidine hydrochloride in the presence of sodium carbonate (Scheme 3). The enamines behaved in the similar fashion as (α-alkoxymethylene)arylsulfonylacetonitriles [7,8].

Recently, isomeric 5-phenylsulfonylpyrimidin-2-ones and -4-ones have been prepared selectively by the reaction of alkyl *N*-cyanoimidates with phenylsulfonylacetonitrile and phenylsulfonylacetamide, respectively [18]. The use of β-ethoxycarbonyl-β-sulfonylenamine (**2e**) as the starting material seemed to be an unambiguous route to 5-phenylsulfonylpyrimidin-4-ones. In fact, the reaction took place smoothly on the same procedure as **2a-d** to give **9a** and **b** in 74 and 62% yields, respectively.

The structures of all compounds were established clearly on the basis of the elemental analysis, ir, nmr and mass spectra as shown in the Table 1 and 2.

EXPERIMENTAL

Melting points were uncorrected. The spectra were recorded on the following instruments; ir, JASCO A-102; ^{1}H-nmr, JEOL JNM-PMX and Hitachi R-20; ms, JEOL JMS-DX 300. Elemental analyses were performed on a Shimadzu UM-3B microanalyzer. The starting material **1a** [19], **c** [20], **d** [21], and **e** [22] were prepared by the literature methods. The compound **1b** was prepared according to the same procedure as **1a**, mp 118-119° (ethanol); ir (potassium bromide): 2990, 2960, 1660, 1600, 1320, 1300 cm^{-1}.

Anal. Calcd. for $C_{10}H_{12}O_3S$: C, 56.59; H, 5.70. Found: C, 56.32; H, 5.74.

1-Benzoyl-1-methanesulfonyl-2-(*N,N*-dimethylamino)ethene (**2a**).

A mixture of methyl phenacyl sulfone (**1a**) (598 mg, 3.0 mmoles) and *N,N*-dimethylformamide dimethylacetal (872 mg, 7.3 mmoles) in toluene (6 ml) was refluxed for 19 hours. After evaporation of the solvent the residue was recrystallized from methanol to give **2a** (370 mg, 48%). Compounds **2b-e** were similarly prepared under the following reaction conditions: **2b**, refluxed in toluene for 15 hours; **2c**, stirred in methanol for 2 hours at room temperature; **2d**, refluxed in methanol for 9 hours; **2e**, refluxed in toluene for 20 hours.

5-Methanesulfonyl-2,4-diphenylpyrimidine (**3a**).

A mixture of benzamidine hydrochloride (216 mg, 1.3 mmoles), sodium carbonate (71 mg, 0.67 mmole), and **2a** (244 mg, 0.96 mmoles) in aqueous methanol (water 0.5 ml and methanol 5 ml) was refluxed for 2 hours. After cooling the precipitates were collected by filtration, washed with water, and recrystallized from acetonitrile to give **3a** (146 mg, 49%). The compounds **3b-d** were prepared in the similar manner on treatment of **2a,b** with benzamidine hydrochloride, guanidine hydrochloride, or *N,N*-dimethylguanidine hydrochloride.

2-Amino-1-benzoyl-1-methanesulfonylethene (**5a**).

A mixture of **2a** (236 mg, 0.93 mmoles) and formamidine acetate (137 mg, 1.3 mmoles) in methanol (5 ml) was refluxed for 4 hours. After evaporation of the solvent the residue was recrystallized from methanol to give **5a** (131 mg, 62%). The compound **5b** was prepared on refluxing in a mixed solvent of chloroform-methanol (1:1) for 4 hours followed by collection of the precipitates.

5-(*n*-Butyl)-2,4-diphenylpyrimidine (**6a**).

To a stirred solution of **3a** (620 mg, 2.0 mmoles) in THF (30 ml) which was cooled at $-78°$ under nitrogen atmosphere was added a solution (3 ml) of 16% *n*-BuLi in hexane (4.6 mmoles). The resulting mixture was stirred for 20 hours at room temperature. After addition of a saturated ammonium chloride solution the organic layer was separated and the aqueous layer was extracted with chloroform. The combined extract was dried over magnesium sulfate and evaporated. The residue was subjected to bulb to bulb distillation (*ca.* 200°/2 mm Hg) and the solidified distillate was recrystallized from methanol to give **6a** (133 mg, 23%). The compound **6b** was prepared in the similar manner.

5-(*n*-Pentyl)-2-phenyl-4-(*p*-tolyl)pyrimidine (**6d**).

To a stirred solution of *n*-pentylmagnesium bromide in ether (5 ml) prepared from magnesium (243 mg, 10 mmoles) and *n*-pentyl bromide (1.2 ml, 10 mmoles) under a nitrogen atmosphere was added a solution of **3b** (649 mg, 2.0 mmoles) in THF (15 ml), and the resulting mixture was refluxed for 2 hours. After addition of a saturated ammonium chloride solution the organic layer was separated and the aqueous layer was extracted with chloroform. The combined extract was dried over magnesium sulfate and evaporated. The residue was subjected to bulb to bulb distillation (*ca.* 200°/2 mm Hg) and the solidified distillate was recrystallized from methanol to give **6d** (172 mg, 27%). The compounds **6a,b** were prepared in the similar manner. In the case of **6c** the residue was purified by column chromatography on silica gel with chloroform as an eluent.

Bis(4-amino-2-phenylpyrimidin-5-yl)sulfone (**8**).

A mixture of **2d** (254 mg, 1.0 mmoles), benzamidine hydrochloride (419 mg, 2.4 mmoles), and sodium carbonate (127 mg, 1.2 mmoles) in a mixed solvent of methanol (10 ml) and water (3 ml) was refluxed for 4 hours. After evaporation of the solvent, the residue was washed with water and recrystallized from DMF to give **8** (323 mg, 80%). The compounds **7a,b**, and **9a,b** were similarly prepared on treatment of **2c,e** with benzamidine hydrochloride, guanidine hydrochloride, or *N,N*-dimethylguanidine hydrochloride under the following reaction conditions: **7a**, refluxed in aqueous methanol for 10 hours, **7b**, refluxed in DMF for 24 hours; **9a**, refluxed in aqueous methanol for 20 hours; **9b**, refluxed in aqueous methanol for 20 hours.

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