A Facile Synthesis of Pyrazole-5-sulfonamide Derivatives [1]

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The reaction of the 5-unsubstituted pyrazoles **2a-k** with lithium diisopropylamide or *n*-butyllithium gave intermediary 5-lithiopyrazoles, whose reaction with sulfur dioxide afforded the lithium pyrazole-5-sulfinates **3a-k**. Subsequent reaction of **3a-k** with *N*-chlorosuccinimide followed by ammonolysis provided the pyrazole-5-sulfonamides **5a-k**.

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Many biologically active sulfonamide agents have been synthesized so far and reported in the journal or patent literatures. For example, tolbutamide [2], mefruside [3] and asulam [4] have been used as the antiadrenergic, diuretic and herbicidal agents, respectively. Since early 1980s, the research target has been directed toward the synthesis of heteroarylsulfonamide derivatives from the interest in search for new biologically active compounds [5,6], and a method for the introduction of the sulfamoyl group into various heteroaryl nuclei has been required for the design of new potent agents. Nowadays, the heteroarylsulfonamide derivatives are produced *via* the ammonolysis of a heteroarylsulfonyl chloride obtained by the direct chlorosulfonation between a heterocyclic compound and chlorosulfonic acid (method 1) [7], the reaction of a heteroarylthiol compound with chlorine water (method 2) [8] or with hydrogen peroxide/phosphorus pentachloride (method 3) [9] and the reaction of a heteroaryldiazonium salt derived from heteroarylamine with cuprous chloride/sulfur dioxide (method 4) [10]. Owing to the above method 4, we succeeded in the development of a potent rice paddy herbicide pyrazosulfuron-ethyl **1** (Figure 1), one of the heteroarylsulfonamides, which has the pyrazole-5-sulfonamide structure [11]. In continuation of this work, it is important and interesting for us to prepare the analogues of pyrazosulfuron-ethyl **1**. However, the above methods 1-4 were found to be inadequate for the comprehensive synthesis of various pyrazole-5-sulfonamides, when the functional groups of the pyrazole derivatives were unstable under acidic conditions, and when it was difficult to obtain the derivatives of 5-mercaptopyrazoles or 5-aminopyrazoles. Consequently, we had to devise a new route to pyrazole-5-sulfonamides, and our elaboration provided a convenient method for the synthesis of the various pyrazole-5-sulfonamides **5a-k** from the corresponding 5-unsubstituted pyrazoles **2a-k** (Scheme 1) which were easily prepared according to our previous study [12-14]. This paper describes a mild and efficient synthesis of **5a-k** from **2a-k** *via* the lithiation, sulfination, chlorination and then ammonolysis.

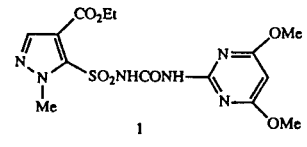

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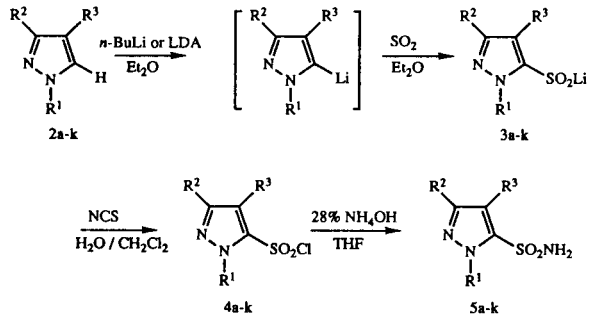
Figure 1

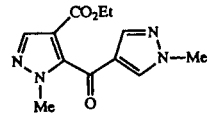
Scheme 1



a; R^1=Me, R^2=H, R^3=CO_2Et
b; R^1=Me, R^2=Cl, R^3=CO_2Et
c; R^1=Me, R^2=Br, R^3=CO_2Et
d; R^1=Me, R^2=OMe, R^3=CO_2Et
e; R^1=Me, R^2=CF_3, R^3=CO_2Et
f; R^1=Me, R^2=CH_2OMe, R^3=CO_2Et
g; R^1=*t*-Bu, R^2=H, R^3=CO_2Et
h; R^1=CH_2OMe, R^2=H, R^3=CO_2Et
i; R^1=$CONMe_2$, R^2=H, R^3=CO_2Et
j; R^1=Me, R^2=H, R^3=SO_2NMe_2
k; R^1=Me, R^2=H, R^3=Ph

The reaction of ethyl 1-methylpyrazole-4-carboxylate **2a** with lithium diisopropylamide gave an intermediary 5-lithiopyrazole, whose reaction with sulfur dioxide afforded lithium 4-ethoxycarbonyl-1-methylpyrazole-5-sulfinate **3a**. The reaction of **3a** with *N*-chlorosuccinimide resulted in chlorination to provide ethyl 5-chlorosulfonyl-1-methylpyrazole-4-carboxylate **4a**, whose subsequent ammonolysis furnished requisite ethyl 1-methyl-5-sulfamoylpyrazole-4-carboxylate **5a** in 60% yield from **2a**. As a by-product, ethyl 1-methyl-5-(1-methylpyrazol-4-ylcarbonyl)pyrazole-4-carboxylate **6** (Figure 2) was obtained in 25% yield. The pyrazole-5-sulfonamides **5b-k** were synthesized from the pyrazoles **2b-k** in a similar manner to the above, although *n*-butyllithum was used as a base in the synthesis of **5k**. The yields of **5a-k** from **2a-k** are shown in the table, which exhibits no correlation between the yields and the substituent R^2. Namely, the electron-withdrawing (chloro, bromo, trifluoromethyl) and electron-donating (methoxy, methoxymethyl) substituents represented no appreciable tendency in the yields of **5b-f**. The 4-(*N*,*N*-dimethylsul-

famoyl)- and 4-phenylpyrazole-5-sulfonamides **5j** and **5k** were obtained in good yields, because bispyrazolyl ketone such as **6** (Figure 2) was not formed in the series of **j** and **k**.



6

Figure 2

Table

Preparation of Pyrazole-5-sulfonamides 5a-k

Substrate	Base	Product	(yield)
2a	LDA	**5a**	(60%)
2b	LDA	**5b**	(72%)
2c	LDA	**5c**	(45%)
2d	LDA	**5d**	(26%)
2e	LDA	**5e**	(29%)
2f	LDA	**5f**	(45%)
2g	LDA	**5g**	(30%)
2h	LDA	**5h**	(64%)
2i	LDA	**5i**	(27%)
2j	LDA	**5j**	(68%)
2k	*n*-BuLi	**5k**	(71%)

In conclusion, we succeeded in the synthesis of novel pyrazole-5-sulfonamides **5b-k** from the corresponding 5-unsubstituted pyrazoles **2b-k**. Especially, 1-(*t*-butyl)- and 1-(*N,N*-dimethylcarbamoyl)pyrazole-5-sulfonamides **5g,i** have seldom been obtained in a conventional procedure such as a diazotization method because of easy elimination of N_1-(*t*-butyl) or N_1-(*N,N*-dimethylcarbamoyl) group in the diazotization process under an acidic condition. Our method is convenient and effective when the synthesis of 5-amino- or 5-mercaptopyrazoles is difficult, troublesome or unknown in the literature. Moerover, our pyrazolylsulfonamide synthesis under mild reaction conditions should be widely utilized as a method for the introduction of the sulfamoyl group in various substituted heterocyclic nuclei.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a JASCO A-3 infrared spectrophotometer. The ^1H and ^{13}C nmr spectra were measured with a JEOL FX-90Q spectrometer using tetramethylsilane as an internal reference. The mass spectra were determined with a JMS-DX300/JMA-3100 spectrometer. Elemental analyses were performed on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione).

Ethyl 1-Methyl-5-sulfamoylpyrazole-4-carboxylate **5a**.

A solution of 15% *n*-butyllithium in hexane (20.5 g, 48 mmoles) was added to a solution of diisopropylamine (4.85 g, 48 mmoles) in dry ether (20 ml) under nitrogen below −65°. The solution was added *via* a syringe to a solution of ethyl 1-methylpyrazole-4-carboxylate **2a** (6.16 g, 40 mmoles) in dry ether (100 ml), maintaining the temperature below −65°. The resulting suspension was stirred for 1 hour and then excess sulfur dioxide was introduced to the mixture for 10 minutes at such a rate that the temperature was maintained below −55°. After stirring for 30 minutes at −65° the solution was allowed to warm to room temperature to precipitate lithium sulfinate **3a** which was filtered and washed with ether. The sulfinate **3a** was added to a two-phase solution of methylene chloride (50 ml) and ice-cold water (50 ml) and then *N*-chlorosuccinimide (5.34 g, 40 mmoles) was added portionwise with vigorous stirring at 5°. The organic layer was separated and the aqueous layer was extracted twice with methylene chloride (20 ml). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and then concentrated *in vacuo* to obtain crude oily ethyl 1-methyl-5-chlorosulfonylpyrazole-4-carboxylate **4a**. The oily product **4a** was dissolved in tetrahydrofuran (50 ml) to which 28% aqueous ammonia (9.7 g, 160 mmoles) was added and the mixture was stirred for 1 hour at room temperature. Concentration of the mixture *in vacuo* gave a solid, which was filtered and washed with water and then ether. Recrystallization of the solid from toluene gave **5a** (5.6 g, 60%), mp 113-114°; ir (potassium bromide): ν cm^{-1} 3320, 3220, 1700, 1522, 1355, 1215, 1185, 1165, 1042, 915, 774; ^1H nmr (deuteriochloroform): δ 1.38 (3H, t, J = 7.0 Hz, CH_3), 4.17 (3H, s, N-CH_3), 4.35 (2H, q, J = 7.0 Hz, CH_2), 6.40 (2H, bs, NH_2), 7.88 (1H, s, CH); ms: m/z 233 (M^+), 205, 188 (base peak).

Anal. Calcd. for $C_7H_{11}N_3O_4S$: C, 36.05; H, 4.75; N, 18.01. Found: C, 36.02; H, 4.71; N, 18.12.

The filtrate of lithium sulfinate **3a** was concentrated and then chromatographed on silica gel with hexane-acetone (4:1) to obtain a solid which was crystallized from toluene-heptane (2:1) and gave ethyl 1-methyl-5-(1-methylpyrazol-4-ylcarbonyl)pyrazole-4-carboxylate **6** (1.31 g, 25%), mp 107-108°; ir (potassium bromide): ν cm^{-1} 3400, 3100, 1700, 1650, 1535, 1384, 1238, 1218, 1158, 880, 780; ^1H nmr (deuteriochloroform): δ 1.11 (3H, t, J = 7.1 Hz, CH_3), 3.87 (3H, s, N-CH_3), 3.95 (3H, s, N-CH_3), 4.13 (2H, q, J = 7.1 Hz, CH_2), 7.81 (1H, s, CH), 7.82 (1H, s, CH), 7.92 (1H, s, CH); ^{13}C nmr (deuteriochloroform): δ 13.9 (q), 38.0 (q), 39.5 (q), 60.5 (t), 114.4 (s), 124.2 (s), 134.1 (d), 140.3 (d), 141.5 (d), 142.2 (s), 162.1 (s), 180.5 (s); ms: m/z 262 (M^+), 217, 109 (base peak).

Anal. Calcd. for $C_{12}H_{14}N_4O_3$: C, 54.95; H, 5.38; N, 21.36. Found: C, 54.95; H, 5.40; N, 21.32.

Ethyl 3-Chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylate **5b**.

This compound was obtained in 72% yield, mp 121-123° (toluene); ir (potassium bromide): ν cm^{-1} 3360, 3250, 1688, 1504, 1355, 1276, 1248, 1180, 625; ^1H nmr (deuteriochloroform): δ 1.41 (3H, t, J = 7.1 Hz, CH_3), 4.15 (3H, s, N-CH_3), 4.40 (2H, q, J = 7.1 Hz, CH_2), 6.28 (2H, bs, NH_2); ms: m/z 267 (M^+), 239, 222 (base peak), 107.

Anal. Calcd. for $C_7H_{10}ClN_3O_4S$: C, 31.41; H, 3.77; N, 15.70. Found: C, 31.36; H, 3.74; N, 15.72.

Ethyl 3-Bromo-1-methyl-5-sulfamoylpyrazole-4-carboxylate **5c**.

The compound was obtained in 45% yield, mp 107-108° (toluene); ir (potassium bromide): ν cm^{-1} 3355, 3250, 1692, 1505, 1354, 1242, 1178, 625; ^1H nmr (deuteriochloroform): δ 1.42 (3H, t, J = 7.1 Hz, CH_3), 4.17 (3H, s, N-CH_3), 4.41 (2H, q, J = 7.1 Hz, CH_2), 6.28 (2H, bs, NH_2); ms: m/z 311 (M^+), 283, 266 (base peek), 107.

Anal. Calcd. for $C_7H_{10}BrN_3O_4S$: C, 26.94; H, 3.23; N, 13.40. Found: C, 27.06; H, 3.30; N, 13.47.

Ethyl 3-Methoxy-1-methyl-5-sulfamoylpyrazole-4-carboxylate **5d**.

This compound was obtained in 26% yield, mp 134-135° (toluene); ir (potassium bromide): ν cm^{-1} 3260, 1682, 1540, 1510, 1352, 1300, 1262, 1178, 1138, 629; ^1H nmr (deuteriochloroform): δ 1.37 (3H, t, J = 7.1 Hz, CH_3), 3.97 (3H, s, CH_3), 4.04 (3H, s, N-CH_3), 4.34 (2H, q, J = 7.1 Hz, CH_2), 6.35 (2H, bs, NH_2); ms: m/z 263 (M^+), 235, 218 (base peak), 191, 138.

Anal. Calcd. for $C_8H_{13}N_3O_5S$: C, 36.50; H, 4.98; N, 15.96. Found: C, 36.50; H, 4.97; N, 15.89.

Ethyl 1-Methyl-5-sulfamoyl-3-trifluoromethylpyrazole-4-carboxylate **5e**.

This compound was obtained in 29% yield, mp 119-120° (toluene); ir (potassium bromide): ν cm^{-1} 3354, 3248, 1691, 1515, 1363, 1298, 1220, 1189, 1178, 1150, 618; ^1H nmr (deuteriochloroform): δ 1.38 (3H, t, J = 7.2 Hz, CH_3), 4.23 (3H, s, N-CH_3), 4.40 (2H, q, J = 7.2 Hz, CH_2), 6.25 (2H, bs, NH_2); ms: m/z 301 (M^+), 273, 256 (base peak), 236.

Anal. Calcd. for $C_8H_{10}F_3N_3O_4S$: C, 31.90; H, 3.35; N, 13.95. Found: C, 32.05; H, 3.35; N, 13.95.

Ethyl 3-Methoxymethyl-1-methyl-5-sulfamoylpyrazole-4-carboxylate **5f**.

This compound was obtained in 45% yield, mp 135-137° (toluene); ir (potassium bromide): ν cm^{-1} 3290, 1690, 1515, 1355, 1282, 1258, 1180, 1138, 1100, 615; ^1H nmr (deuteriochloroform): δ 1.40 (3H, t, J = 7.1 Hz, CH_3), 3.45 (3H, s, CH_3), 4.15 (3H, s, N-CH_3), 4.38 (2H, q, J = 7.1 Hz, CH_2), 4.62 (2H, s, CH_2), 6.37 (2H, bs, NH_2); ms: m/z 277 (M^+), 232, 216, 152 (base peak).

Anal. Calcd. for $C_9H_{15}N_3O_5S$: C, 38.98; H, 5.45; N, 15.15. Found: C, 38.79; H, 5.38; N, 15.12.

Ethyl 1-*t*-Butyl-5-sulfamoylpyrazole-4-carboxylate **5g**.

This compound was obtained in 30% yield, mp 105-107° (heptane-toluene, 4:1); ir (potassium bromide): ν cm^{-1} 3350, 1702, 1520, 1350, 1222, 1192, 1170, 603; ^1H nmr (deuteriochloroform): δ 1.38 (3H, t, J = 7.1 Hz, CH_3), 1.79 (9H, s, *t*-C_4H_9), 4.35 (2H, q, J = 7.1 Hz, CH_2), 6.60 (2H, bs, NH_2), 7.85 (1H, s, CH); ms: m/z 275 (M^+), 230, 220, 174 (base peak).

Anal. Calcd. for $C_{10}H_{17}N_3O_4S$: C, 43.62; H, 6.22; N, 15.26. Found: C, 43.51; H, 6.15; N, 15.45.

Ethyl 1-Methoxymethyl-5-sulfamoylpyrazole-4-carboxylate **5h**.

This compound was obtained in 64% yield, mp 88-89° (toluene); ir (potassium bromide): ν cm^{-1} 3280, 1705, 1526, 1358, 1250, 1218, 1082, 612; ^1H nmr (deuteriochloroform): δ 1.38 (3H, t, J = 7.1 Hz, CH_3), 3.39 (3H, s, CH_3), 4.37 (2H, q, J = 7.1 Hz, CH_2), 5.84 (2H, s, N-CH_2), 6.40 (2H, bs, NH_2), 7.97 (1H, s, CH); ms: m/z 264 (MH^+), 232 (base peak).

Anal. Calcd. for $C_8H_{13}N_3O_5S$: C, 36.50; H, 4.98; N, 15.96. Found: C, 36.47; H, 4.94; N, 15.98.

Ethyl 1-Dimethylcarbamoyl-5-sulfamoylpyrazole-4-carboxylate **5i**.

This compound was obtained in 27% yield, mp 132-133° (toluene); ir (potassium bromide): ν cm^{-1} 3280, 1710, 1665, 1368, 1332, 1198, 1142, 1070, 612; ^1H nmr (deuteriochloroform): δ 1.36 (3H, t, J = 7.1 Hz, CH_3), 2.78 (3H, s, N-CH_3), 3.10 (3H, s, N-CH_3), 4.32 (2H, q, J = 7.1 Hz, CH_2), 6.30 (2H, bs, NH_2), 7.95 (1H, s, CH); ms: m/z 291 (MH^+), 246.

Anal. Calcd. for $C_9H_{14}N_4O_5S$: C, 37.24; H, 4.86; N, 19.30. Found: C, 37.15; H, 4.79; N, 19.35.

1-Methyl-4-dimethylsulfamoylpyrazole-5-sulfonamide **5j**.

This compound was obtained in 68% yield, mp 148-149° (toluene-ethanol, 2:1); ir (potassium bromide): ν cm^{-1} 3320, 3230, 1372, 1337, 1328, 1198, 1175, 1147, 958, 740, 625, 580; ^1H nmr (deuteriochloroform): 2.85 (6H, s, N-CH_3), 4.22 (3H, s, N-CH_3), 6.05 (2H, bs, NH_2), 7.76 (1H, s, CH); ms: m/z 268 (M^+), 224, 208, 189, 149 (base peak).

Anal. Calcd. for $C_6H_{12}N_4O_4S_2$: C, 26.86; H, 4.51; N, 20.88. Found: C, 26.96; H, 4.53; N, 20.79.

1-Methyl-4-phenylpyrazole-5-sulfonamide **5k**.

A solution of 15% *n*-butyllithium in hexane (20.5 g, 48 mmoles) was added dropwise to a solution of 1-methyl-4-phenylpyrazole **2k** (6.32 g, 40 mmoles) in dry ether (100 ml) under nitrogen below −65°. The resulting suspension was allowed to 0° over 1 hour and then cooled to −70°. Excess sulfur dioxide was introduced to the mixture for 30 minutes, while maintaining the temperature below −65°. After stirring for 1 hour at −65°, the solution was allowed to warm to room temperature to precipitate lithium sulfinate **3k**, which was filtered and washed with ether. The sulfinate **3k** was added to a two-phase solution of chloroform (150 ml) and ice-cold water (200 ml), and then *N*-chlorosuccinimide (5.34 g, 40 mmoles) was added portionwise with vigorous stirring at 5°. After stirring for 30 minutes at 5°, the organic layer was separated and the aqueous layer was extracted twice with chloroform (20 ml). The combined organic layer was washed with water, and then added to 28% aqueous ammonia (97 g, 1.6 moles) below 10°. The mixture was stirred for 1 hour at room temperature. Concentration of the mixture *in vacuo* gave a solid, which was filtered and washed with water and then ether. Recrystallization of solid from toluene gave **5k** (6.7 g, 71%), mp 163-165°; ir (potassium bromide): ν cm^{-1} 3350, 1560, 1342, 1170, 1138, 764, 610; ^1H nmr (deuteriochloroform): 4.19 (3H, s, N-CH_3), 4.95 (2H, bs, NH_2), 7.33-7.48 (5H, m, C_6H_5), 7.50 (1H, s, CH); ms: m/z 237 (M^+), 129, 89.

Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.73; H, 4.76; N, 17.70.

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