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Ethyl 1-fluoromethyl-5-(4,6-dimethoxypyrimidin-2-ylcarbamoysulfamoyl)pyrazole-4-carboxylate **1b**, a new fluoromethyl analogue of the herbicide pyrazosulfuron-ethyl **1a**, was prepared from ethyl 1-fluoromethylpyrazole-4-carboxylate **4b**. The difluoromethyl and trifluoromethyl analogues **1c,d** were also synthesized from ethyl pyrazole-4-carboxylate **2** via difluorocarbene reaction.

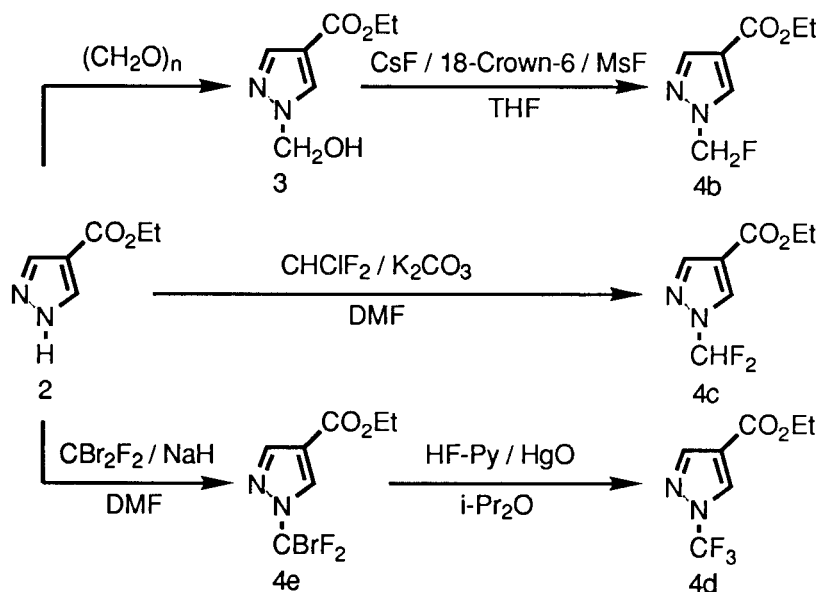
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The introduction of fluoromethyl, difluoromethyl and trifluoromethyl groups into heterocycles has become increasingly important because the incorporation of these functional groups has frequently produced much more potent activity than that of the parent compounds. The introduction of the above groups has generally been accomplished by the construction of the heterocycles using synthons originally containing a fluoromethyl, difluoromethyl or trifluoromethyl group [1,2]. However, little is known about the direct introduction of these groups onto an endocyclic sp^3 -nitrogen in azoles such as pyrazole, imidazole and triazole. Recently, Makino and Yoshioka [3] have reported a method for the introduction of the fluoromethyl group onto the endocyclic nitrogen of the pyrazole **2** (Scheme 1), while there is no paper on the introduction of the difluoromethyl and trifluoromethyl groups. In the present investigation, we found that the difluoromethyl and trifluoromethyl groups were conveniently introduced onto the endocyclic nitrogen of the pyrazole **2**, when utilizing

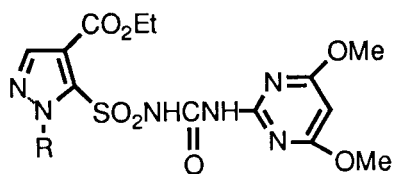
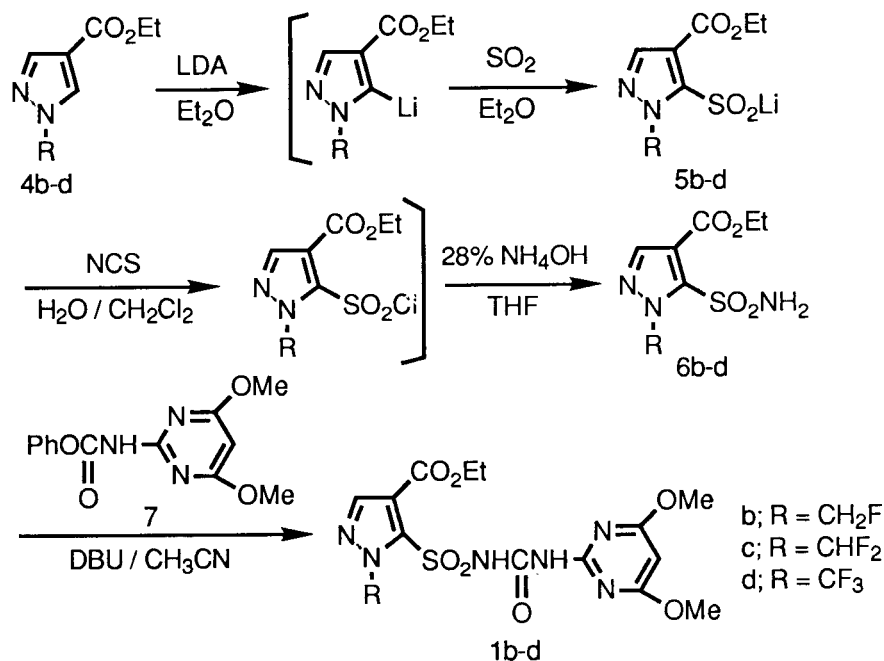
the difluorocarbene reaction [4-6] (Scheme 1). Thus, we have achieved the synthesis of the N_1 -fluoromethyl, -difluoromethyl and -trifluoromethylpyrazoles **4b-d**. Moreover, the success of the synthesis of **4b-d** enabled us to prepare new N_1 -fluoromethyl, -difluoromethyl and -trifluoromethyl analogues of pyrazosulfuron-ethyl **1a** (code No. NC-311) (Figure 1, Scheme 2) which was a selective herbicide for paddy weeds without phytotoxicity to the rice plant.

In connection with our continuing studies on the structure-activity relationship for pyrazosulfuron-ethyl **1a** and its related compounds [7], we now report the synthesis of new fluoromethyl, difluoromethyl and trifluoromethyl analogues of pyrazosulfuron-ethyl, ethyl 1-fluoromethyl-5-(4,6-dimethoxypyrimidin-2-ylcarbamoysulfamoyl)pyrazole-4-carboxylate **1b**, ethyl 1-difluoromethyl-5-(4,6-dimethoxypyrimidin-2-ylcarbamoysulfamoyl)pyrazole-4-carboxylate **1c** and ethyl 1-trifluoromethyl-5-(4,6-dimethoxypyrimidin-

Scheme 1



Scheme 2



- 1a; R = Me
 1b; R = CH₂F
 1c; R = CHF₂
 1d; R = CF₃

Figure 1

2-ylcarbamoylsulfamoyl)pyrazole-4-carboxylate **1d**, together with a new method for the synthesis of *N*₁-difluoromethyl and -trifluoromethyl pyrazoles **4c,d**.

As an evolution of the method for the synthesis of the difluoromethoxy and trifluoromethoxy groups *via* difluorocarbene reaction [5-7], difluorocarbenes derived from chlorodifluoromethane and dibromodifluoromethane were reacted with the pyrazole **2** as shown in Scheme 1. The reaction of **2** with an excess of chlorodifluoromethane and anhydrous potassium carbonate in *N,N*-dimethylformamide (DMF) at 95° did afford ethyl 1-difluoromethylpyrazole-4-carboxylate **4c** in 95% yield, while the reaction of **2** with dibromodifluoromethane and sodium hydride in DMF at room temperature provided ethyl 1-bromodifluoromethylpyrazole-4-carboxylate **4e** 45% yield together with **4c** in 6% yield as a by-product. The bromodifluoromethyl group of **4e** was readily converted into trifluoromethyl group with an excess of 70% poly(hydrogen fluoride)pyridine coupled with mercuric oxide in isopropyl ether at room temperature, yielding ethyl 1-trifluorometh-

ylpyrazole-4-carboxylate **4d** in 72% yield.

Subsequently, **4b-d** were converted into new fluoromethyl, difluoromethyl and trifluoromethyl analogues **1b-d** of pyrazosulfuron-ethyl **1a** *via* 5-sulfamoylpyrazole derivatives **6b-d** as described in Scheme 2. The lithiation of **4b** with lithium diisopropylamide (LDA) in ether at -78° followed by the reaction with sulfur dioxide below -40° yielded lithium 4-ethoxycarbonyl-1-fluoromethylpyrazole-5-sulfinate **5b**, whose treatment with *N*-chlorosuccinimide (NCS) in water-dichloromethane at 0° and then with 28% aqueous ammonia at room temperature did afford ethyl 1-fluoromethyl-5-sulfamoylpyrazole-4-carboxylate **6b** in 32% yield. Ethyl 1-difluoromethyl-5-sulfamoylpyrazole-4-carboxylate **6c** and ethyl 1-trifluoromethyl-5-sulfamoylpyrazole-4-carboxylate **6d** were similarly prepared from **4c** and **4d** in 17% and 9% yields, respectively.

Finally, **6b**, **6c** and **6d** were reacted with phenyl 4,6-dimethoxypyrimidin-2-yl carbamate **7** in acetonitrile in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at room temperature to obtain **1b**, **1c** and **1d** in 55%, 67% and 20% yields, respectively.

The growth inhibitory activity of **1a-d** to paddy weeds was found to increase in the following order: **1d** < **1c** < **1b** < **1a**.

In this study, it has been deduced that the difluorocarbene reaction can be applied to the synthesis of the *N*₁-difluoromethyl and -trifluoromethylpyrazoles and the *N*₁-

fluoromethyl, -difluoromethyl and -trifluoromethyl groups of the pyrazoles **4b-d** are enough stable to remain intact even under strongly basic conditions. Furthermore, the herbicidal activity of **1a** and its related compounds **1b-d** decreases in the increasing order of the electron-withdrawing effect of the N_1 -functional group of the pyrazole ring.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a JASCO A-3 infrared spectrophotometer. The ^1H and ^{19}F nmr spectra were measured with a JEOL FX-90 spectrometer using tetramethylsilane and trichlorofluoromethane as an internal reference, respectively. The mass spectra (ms and hrms) were determined with a JMS-D300/JMA-3500 and a JMS-DX300/JMA-3100 spectrometer, respectively. Elemental analyses were performed on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione).

Ethyl 1-Difluoromethylpyrazole-4-carboxylate **4c**.

Chlorodifluoromethane (80 g, 925 mmoles) was introduced to a suspension of **2** (6.0 g, 43 mmoles) and anhydrous potassium carbonate (18 g, 130 mmoles) in dry DMF (30 ml) at 90° for 2 hours. After cooling, the mixture was poured into water (100 ml) and extracted twice with benzene (50 ml). The benzene solution was washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain 7.0 g (95%) of **4c**, mp $31-32^\circ$; ir (neat): ν cm^{-1} 3100, 2960, 1713, 1555, 1439, 1413, 1380, 1365, 1255, 1210, 1170, 1130, 1080, 1018, 985, 955, 885, 835, 815, 760, 607; ^1H nmr (deuteriochloroform): δ 1.34 (3H, t, $J = 7.1$ Hz, CH_3), 4.31 (2H, q, $J = 7.1$ Hz, CH_2), 7.28 (1H, t, $J = 59.8$ Hz, CHF_2), 8.14 (1H, s, CH), 8.44 (1H, s, CH); ^{19}F nmr (deuteriochloroform): δ -92.35 (d); ms: m/z 190 (M^+), 162, 145 (base peak); hrms: m/z 190.0557 (M^+ , Calcd. for $\text{C}_7\text{H}_8\text{F}_2\text{N}_2\text{O}_2$: 190.0554).

Ethyl 1-Bromodifluoromethylpyrazole-4-carboxylate **4e**.

A solution of **2** (30 g, 210 mmoles) in dry DMF (40 ml) was added to a suspension of 55% sodium hydride (10.5 g, 240 mmoles) in dry DMF (100 ml) at 4° . After stirring for 1 hour at room temperature, dibromodifluoromethane (54 g, 260 mmoles) in dry DMF (30 ml) was added dropwise below 25° , and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was poured into water (500 ml) and extracted three times with ether (300 ml). The solution was washed with water, next with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled to obtain colorless oil (23 g), bp $103-109^\circ/13$ Torr. It was composed of **4e** as the major component and **4c** as the minor in a ratio of 9:1. Preparative glc (OV-17) gave an analytically pure sample of **4e**; ir (neat): ν cm^{-1} 3100, 2960, 1715, 1560, 1395, 1230, 1065, 1019, 980, 870, 760, 635; ^1H nmr (deuteriochloroform): δ 1.33 (3H, t, $J = 7.1$ Hz, CH_3), 4.27 (2H, q, $J = 7.1$ Hz, CH_2), 7.96 (1H, s, CH), 8.15 (1H, s, CH); ^{19}F nmr (deuteriochloroform): δ -31.09 (s); ms: m/z 268 (M^+), 240, 223 (base peak); hrms: m/z 267.9669 (M^+ , Calcd. for $\text{C}_7\text{H}_7\text{BrF}_2\text{N}_2\text{O}_2$: 267.9660).

Ethyl 1-Trifluoromethylpyrazole-4-carboxylate **4d**.

Mercuric oxide (15 g, 69 mmoles) was added portionwise to a solution of crude **4e** (22.5 g) and 70% poly(hydrogen fluoride)pyridine (40 ml) in isopropyl ether (60 ml) at room temperature for 4 hours under stirring in nitrogen. After stirring at

room temperature for 5 hours, the mixture was poured into aqueous 25% potassium fluoride (200 ml), and the insoluble solid was filtered off. The filtrate was extracted three times with ether (200 ml), and the ether solution was washed twice with 5% hydrochloric acid (200 ml), twice with saturated aqueous sodium bicarbonate (200 ml), next with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled to obtain 13 g of **4d** (30% from **4c**), bp $78-79^\circ/18$ Torr; ir (neat): ν cm^{-1} 3110, 2970, 1725, 1565, 1430, 1405, 1290, 1255, 1183, 1060, 1020, 942, 760; ^1H nmr (deuteriochloroform): δ 1.32 (3H, t, $J = 7.1$ Hz, CH_3), 4.29 (2H, q, $J = 7.1$ Hz, CH_2), 7.98 (1H, s, CH), 8.18 (1H, s, CH); ^{19}F nmr (deuteriochloroform): δ -58.60 (s); ms: m/z 208 (M^+), 180, 163 (base peak); hrms: m/z 208.0474 (M^+ , Calcd. for $\text{C}_7\text{H}_7\text{F}_3\text{N}_2\text{O}_2$: 208.0460).

Ethyl 1-Fluoromethyl-5-sulfamoylpyrazole-4-carboxylate **6b**.

A solution of LDA (46 mmoles) in dry ether-hexane (70 ml, 4:3) was added dropwise to a solution of **4b** (6.2 g, 36 mmoles) in dry ether (70 ml) at -78° with stirring under nitrogen. After stirring for 1 hour at -78° , sulfur dioxide (5.0 g, 78 mmoles) was introduced below -40° , and then the reaction temperature was elevated to -10° . The resultant solid was gathered, washed sufficiently with ether, and dried *in vacuo* to obtain 9.7 g of crude **5b**. Next, **5b** (9.7 g) was dissolved in water (150 ml) and dichloromethane (100 ml) was added. Then, NCS (4.8 g, 36 mmoles) was added portionwise at 0° under vigorous stirring. After stirring for 0.5 hour at room temperature, the dichloromethane layer was separated and washed with saturated aqueous sodium bisulfite (50 ml), and with water. Then, 28% aqueous ammonia (6.0 g, 99 mmoles) was added dropwise to the dichloromethane solution at -5° , and the mixture was stirred for 0.15 hour at room temperature. After removal of the solvent, chloroform (50 ml) was added. The chloroform solution was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel with chloroform to obtain 2.9 g (32%) of **6b**, mp $92-93^\circ$; ir (potassium bromide): ν cm^{-1} 3300, 3225, 1705, 1535, 1380, 1360, 1245, 1215, 1180, 1165, 1105, 1025, 780, 760, 615, 510; ^1H nmr (deuteriochloroform): δ 1.39 (3H, t, $J = 7.1$ Hz, CH_3), 4.38 (2H, q, $J = 7.1$ Hz, CH_2), 6.38 (2H, d, $J = 50.1$ Hz, CH_2F), 6.48 (2H, brs, NH_2), 8.02 (1H, s, CH); ^{19}F nmr (deuteriochloroform): δ -164.45 (t); ms: m/z 251 (M^+), 223, 206 (base peak); hrms: m/z 251.0344 (M^+ , Calcd. for $\text{C}_7\text{H}_{10}\text{FN}_3\text{O}_4\text{S}$: 251.0376).

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{FN}_3\text{O}_4\text{S}$: C, 33.47; H, 4.01; N, 16.73. Found: C, 33.65; H, 4.08; N, 16.66.

Ethyl 1-Difluoromethyl-5-sulfamoylpyrazole-4-carboxylate **6c**.

This compound had mp $125-126^\circ$; ir (potassium bromide): ν cm^{-1} 3340, 3250, 1710, 1540, 1430, 1405, 1368, 1355, 1340, 1260, 1238, 1183, 1123, 1068, 825, 720, 520; ^1H nmr (deuteriochloroform): δ 1.38 (3H, t, $J = 7.1$ Hz, CH_3), 4.32 (2H, q, $J = 7.1$ Hz, CH_2), 6.40 (2H, brs, NH_2), 7.86 (1H, t, $J = 58.6$ Hz, CHF_2), 7.96 (1H, s, CH); ^{19}F nmr (deuteriochloroform): δ -94.18 (d); ms: m/z 269 (M^+), 241, 224 (base peak); hrms: m/z 223.9943 ($\text{M}^+ - \text{OEt}$, Calcd. for $\text{C}_5\text{H}_4\text{F}_2\text{N}_3\text{O}_3\text{S}$: 223.9942).

Anal. Calcd. for $\text{C}_7\text{H}_8\text{F}_2\text{N}_3\text{O}_4\text{S}$: C, 31.23; H, 3.37; N, 15.61. Found: C, 31.20; H, 3.33; N, 15.56.

Ethyl 1-Trifluoromethyl-5-sulfamoylpyrazole-4-carboxylate **6d**.

This compound had mp $131-132^\circ$; ir (potassium bromide): ν cm^{-1} 3340, 3240, 1713, 1540, 1375, 1358, 1255, 1218, 1180, 1103,

1010, 970, 780, 770, 630; ^1H nmr (deuteriochloroform): δ 1.37 (3H, t, $J = 7.1$ Hz, CH_3), 4.30 (2H, q, $J = 7.1$ Hz, CH_2), 7.40 (2H, brs, NH_2), 7.89 (1H, s, CH); ^{19}F nmr (deuteriochloroform): δ -51.80 (s); ms: m/z 287 (M^+), 260, 242 (base peak); hrms: m/z 287.0075 (M^+ , Calcd. for $\text{C}_7\text{H}_8\text{F}_3\text{N}_3\text{O}_4\text{S}$: 287.0187).

Anal. Calcd. for $\text{C}_7\text{H}_8\text{F}_3\text{N}_3\text{O}_4\text{S}$: C, 29.27; H, 2.81; N, 14.63. Found: C, 29.35; H, 2.72; N, 14.55.

Ethyl 1-Fluoromethyl-5-(4,6-dimethoxyypyrimidin-2-ylcarbamo-ylsulfamoyl)pyrazole-4-carboxylate **1b**.

DBU (302 mg, 1.99 mmoles) was added to a suspension of **6b** (500 mg, 1.99 mmoles) and **7** (600 mg, 2.18 mmoles) in dry acetonitrile (5 ml) at room temperature. After stirring for 0.15 hour, water (20 ml) was added and insoluble solid was filtered off. The filtrate was acidified with 35% hydrochloric acid, and then extracted with chloroform (50 ml). The chloroform solution was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was treated with a small amount of ether and the resultant solid was gathered, washed with ether, and dried *in vacuo* to obtain 500 mg (58%) of **1b**, mp 190-192 $^\circ$; ir (potassium bromide): ν cm^{-1} 3400, 3300, 1725, 1605, 1570, 1585, 1435, 1355, 1233, 1216, 1195, 1160, 1018, 760, 618, 598, 515; ^1H nmr ($\text{DMSO}-d_6$): δ 1.31 (3H, t, $J = 7.1$ Hz, CH_3), 3.99 (6H, s, OCH_3), 4.26 (2H, q, $J = 7.1$ Hz, CH_2), 5.79 (1H, s, CH), 6.54 (2H, d, $J = 50.1$ Hz, CH_2F), 8.00 (1H, s, CH), 10.37 (1H, brs, NH), 13.30 (1H, brs, NH); ^{19}F nmr ($\text{DMSO}-d_6$): δ -166.07 (t); ms: m/z 433 ($\text{M}^+ + 1$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{FN}_6\text{O}_7\text{S}$: C, 38.89; H, 3.96; N, 19.44. Found: C, 39.12; H, 3.98; N, 19.21.

Ethyl 1-Difluoromethyl-5-(4,6-dimethoxyypyrimidin-2-ylcarbamo-ylsulfamoyl)pyrazole-4-carboxylate **1c**.

This compound had mp 184-187 $^\circ$; ir (potassium bromide): ν cm^{-1} 3400, 1730, 1715, 1605, 1570, 1495, 1441, 1360, 1245, 1220, 1200, 1165, 1120, 1090, 820, 620, 595, 515; ^1H nmr (deuteriochloroform): δ 1.34 (3H, t, $J = 7.1$ Hz, CH_3), 3.97 (6H, s, OCH_3), 4.29 (2H, q, $J = 7.1$ Hz, CH_2), 5.75 (1H, s, CH), 8.01 (1H, s, CH), 8.23 (1H, t, $J = 57.4$ Hz, CHF_2), 10.30 (1H, brs, NH), 13.30 (1H, brs, NH); ^{19}F nmr (deuteriochloroform): δ -95.30 (d); ms: m/z 451

($\text{M}^+ + 1$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_2\text{N}_6\text{O}_7\text{S}$: C, 37.34. H, 3.58; N, 18.66. Found: C, 37.18; H, 3.55; N, 18.60.

Ethyl 1-Trifluoromethyl-5-(4,6-dimethoxyypyrimidin-2-ylcarbamo-ylsulfamoyl)pyrazole-4-carboxylate **1d**.

This compound had mp 150-151 $^\circ$; ir (potassium bromide): ν cm^{-1} 3425, 1740, 1720, 1610, 1575, 1505, 1450, 1370, 1360, 1220, 1200, 1175, 640, 600; ^1H nmr (deuteriochloroform): δ 1.26 (3H, t, $J = 7.1$ Hz, CH_3), 3.92 (6H, s, OCH_3), 4.19 (2H, q, $J = 7.1$ Hz, CH_2), 5.69 (1H, s, CH), 7.51 (1H, brs, NH), 7.86 (1H, s, CH), 13.25 (1H, brs, NH); ^{19}F nmr (deuteriochloroform): δ -51.59 (s); ms: m/z 469 ($\text{M}^+ + 1$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{F}_3\text{N}_6\text{O}_7\text{S}$: C, 35.90; H, 3.23; N, 17.94. Found: C, 37.70; H, 3.18; N, 17.85.

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