Synthesis of Halosulfuron-methyl *via* Selective Chlorination at 3- and/or 5-Position of Pyrazole-4-carboxylates

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Reactions of methyl pyrazole-4-carboxylates **4b-d** with *N*-chlorosuccinimide under heating conditions without a solvent gave methyl 3,5-dichloro-1-methylpyrazole-4-carboxylate **4a** in good yields. The reaction of **4a** with sodium hydrosulfide led to a nucleophilic substitution on the 5-position regioselectively to afford methyl 3-chloro-1-methyl-5-mercaptopyrazole-4-carboxylate **6a**, which was followed by oxidative chlorination and amination to obtain 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylate **2a**. Finally, the reaction of **2a** with phenyl 4,6-dimethoxypyrimidin-2-yl carbamate **7** provided methyl 3-chloro-5-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-1-methylpyrazole-4-carboxylate (halosulfuron-methyl) **1a** promising herbicide in corn.

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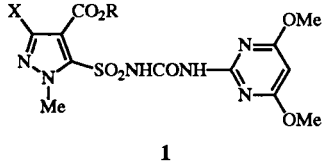
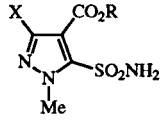
Sulfonylurea herbicides are a class of compounds having extremely low rates at pre- and post-emergence applications [1-3]. We were interested in their structures and herbicidal activity, and attempted to find new compounds with both high activity and excellent crop safety. Our previous study led us to the finding that sulfonylurea compounds in which the sulfonylurea bridge was bound to the 5-position of the pyrazole ring (pyrazole-5-sulfonylureas **1**) had high herbicidal activity [4]. In our continuing study of the structure-activity relationships of **1**, we introduced various substituents into the 3-position on the pyrazole ring of **1**, and found that methyl 3-chloro-5-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-1-methylpyrazole-4-carboxylate (halosulfuron-methyl) **1a** was a promising herbicide against broad-leaf weeds and sedges in corn fields [5]. We have reported two methods for the synthesis of pyrazole-5-sulfonamides **2** which are key intermediates for the synthesis of **1**; one of them is the method *via* dediazotization of pyrazole-5-diazonium salts prepared from 5-aminopyrazoles **3** [6], and another is the method *via* lithiation of 1-methylpyrazole-4-carboxylates **4** [7,8]. However, they are not suitable for a large scale preparation of methyl 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylate **2a**, because of the difficulty in the synthesis of methyl 5-amino-3-chloro-1-methylpyrazole-4-carboxylate **3a** as a starting material, or the use of expensive organolithium reagents such as lithium diisopropylamide.



1

a, X = Cl, R = Me (halosulfuron-methyl)



2

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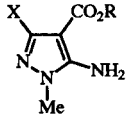
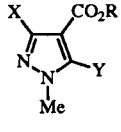


3

a, X = Cl, R = Me



4

a, X = Cl, Y = Cl, R = Me
b, X = Cl, Y = H, R = Me
c, X = H, Y = Cl, R = Me
d, X = H, Y = H, R = Me

Here, we wish to report a new method for the synthesis of **2a** *via* chlorination of 1-methylpyrazole-4-carboxylates **4b-d** with electrophilic chlorination reagents. Although an electrophilic chlorination of pyrazoles is [9,10], there is scarcely a preferential chlorination of pyrazoles with an electron withdrawing group such as a carboxylate group at the 4-position.

The results for the chlorination of methyl 3-chloro-1-methylpyrazole-4-carboxylate **4b** is shown in Scheme 1 and Table 1. Although a reaction of **4b** using an excess of chlorine in carbon tetrachloride at room temperature resulted in complete recovery of **4b** (Run 1), the reaction using chlorine (6.4 equivalents) without a solvent at 115° afforded methyl 3,5-dichloro-1-methylpyrazole-4-carboxylate **4a** in 44% yield together with the side chain-chlorinated pyrazoles **5a-d** as by-products detected by glc-mass spectrometer (Run 2). We screened various electrophilic chlorination reagents and reaction conditions to synthesize **4a** selectively (Run 3-8). *N*-Chlorosuccinimide was the most suitable reagent for the chlorination at 5-position of pyrazole ring of **4b**; the reaction of **4b** with *N*-chlorosuccinimide (1.8 equivalents) without solvent at 95° gave **4a** in 91% yield (Run 5). An increase in the amount of

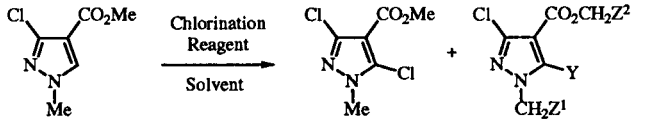
Table 1

Reaction of Methyl 3-Chloro-1-methylpyrazole-4-carboxylate **4b** with Chlorination Reagents

Run	Chlorination Reagent (equivalent)	Solvent	Reaction Temperature (°)	Time (hour)	Relative Ratio [a] (%) 4b	4a	5a-d	Yield of **4a** (%)
1	Cl_2 (excess)	CCl_4	20	1	100	—	—	—
2	Cl_2 (6.4)	—	115	5	2	52	46	44
3	SO_2Cl_2 (2.4)	—	120	5	12	63	25	54
4	*t*-BuOCl (10)	—	reflux	5	100	—	—	—
5	NCS (1.8)	—	95	10	3	93	4	91
6	NCS (2.0)	—	110	8	3	87	10	82
7	NCS (3.0)	—	120	3	—	87	13	76
8	NCS (3.0)	—	140	3	—	81	19	67

[a] Relative ratio determined by glc method.

Scheme 1



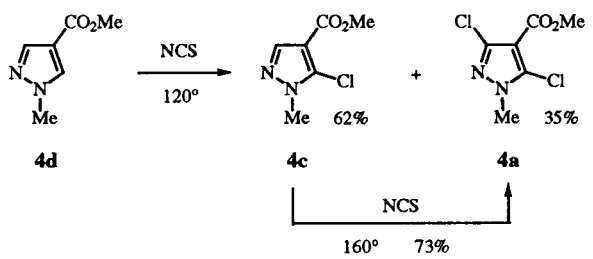
4b **4a** **5a-d**

a, Y = H, Z^1 = Cl, Z^2 = H
b, Y = H, Z^1 = H, Z^2 = Cl
c, Y = Cl, Z^1 = Cl, Z^2 = H
d, Y = Cl, Z^1 = H, Z^2 = Cl

N-chlorosuccinimide and/or an increase in the reaction temperature led to a reduced yield of **4a** (Runs 6-8).

Next, this method was applied to chlorination of other pyrazole-4-carboxylates **4c,d** as described in Scheme 2. The reaction of **4d** with *N*-chlorosuccinimide (3 equivalents) without solvent at 120° provided methyl 5-chloro-1-methylpyrazole-4-carboxylate **4c** in 62% yield together with **4a** in 35% yield, and **4c** underwent the chlorination

Scheme 2



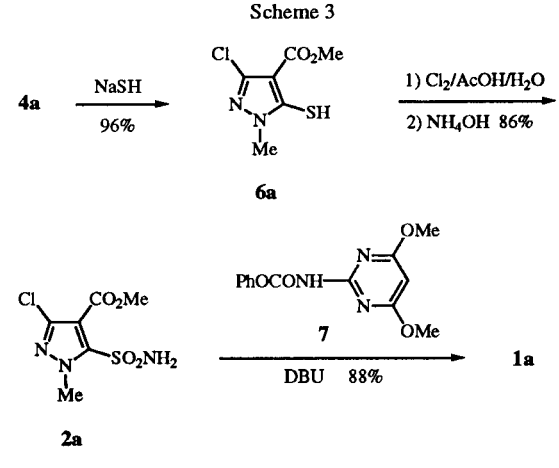
4d **4c** **4a**

at the 3-position by *N*-chlorosuccinimide (3 equivalents) at 160° to give **4a** in 73% yield.

As indicated below, **4a** was converted into halosulfuron-methyl **1a** *via* methyl 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylate **2a** (Scheme 3). The hydrosulfidation of **4a** with sodium hydrosulfide (2.5 equivalents) in *N,N*-dimethylformamide at 60° showed complete regioselectivity, yielding methyl 3-chloro-1-methyl-5-mercaptopyrazole-4-carboxylate **6a** in 96% yield. The mercaptopyrazole **6a** was treated with chlorine (4 equivalents) in aqueous acetic acid at 5°, and then with 28% aqueous ammonia at room temperature to give **2a** in 86% yield. The sulfamoylpyrazole **2a** was allowed to react with phenyl 4,6-dimethoxypyrimidin-2-yl carbamate **7** in acetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene at room temperature to obtain **1a** in 88% yield.

In this study, we demonstrated that pyrazole-4-carboxylates **4b-d** inactivated by a carboxylate group on the 4-position can be chlorinated at the 3- and/or 5-position by *N*-chlorosuccinimide without a solvent under heating conditions to give **4a** in good yields, the nucleophilic substitution of **4a** with sodium hydrosulfide occurs on 5-position regioselectively to afford **6a**, finally producing **1a** by reaction of **7** with **2a** formed by oxidative chlorination and amination of **6a**. The bulk production of **1a** for the evaluation of herbicidal activity in corn fields came to be possible by this process. From the field trials in the corn belt, **1a** completely controlled cocklebur (*xanthium strumarium*) and velvetleaf (*abutilon theophrasti*), they are troublesome weeds in corn fields, with the rates 18-70 g a.i./ha at early post- and post-emergence applications.

Scheme 3



EXPERIMENTAL

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

Methyl 3,5-Dichloro-1-methylpyrazole-4-carboxylate **4a**.

Method A.

N-Chlorosuccinimide (12 g, 90 mmoles) was added portionwise to melting **4b** (8.6 g, 49 mmoles) at 95° for 10 hours with stirring under nitrogen. After cooling to 60°, carbon tetrachloride (40 ml) was added and the insoluble solid was filtered off. The filtrate was washed twice with saturated aqueous sodium carbonate (20 ml), next with water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled to obtain 9.3 g (91%) of **4a**, bp 104-108°/0.25 Torr; mp 58-59°; ir (potassium bromide): ν cm^{-1} 1720, 1515, 1430, 1400, 1240, 1070, 770; ^1H nmr (deuteriochloroform): δ 3.82 (3H, s, NMe), 3.85 (3H, s, OMe); ms: m/z 208 (M^+), 177 (M^+-OMe, base peak).

Anal. Calcd. for $C_6H_6Cl_2N_2O_2$: C, 34.48; H, 2.89; N, 13.40. Found: C, 34.60; H, 3.14; N, 13.60.

Method B.

Chlorine (20 g, 282 mmoles) was introduced to melting **4b** (7.7 g, 44 mmoles) at 115° for 5 hours with stirring. After cooling to room temperature, chloroform (40 ml) was added to the mixture. The solution was washed with saturated aqueous sodium carbonate (20 ml), next with water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was analyzed by glc-mass spectrometer to detect **4a**; ms: m/z 208 (M^+), 177 (M^+-OMe, base peak), **4b**; ms: m/z 174 (M^+), 143 (M^+-OMe, base peak), **5a**; ms: m/z 208 (M^+), 177 (M^+-OMe, base peak), 173 (M^+-Cl), **5b**; ms: m/s 208 (M^+), 143 (M^+-OCH_2Cl, base peak), **5c**; ms: m/s 242 (M^+), 211 (M^+-OMe, base peak), 207 (M^+-Cl), **5d**; ms: m/s 242 (M^+), 177 (M^+-OCH_2Cl, base peak), and distilled to obtain 4.1 g (44%) of **4a**, bp 104-108°/0.25 Torr.

Method C.

To melting *N*-chlorosuccinimide (21 g, 157 mmoles) was added portionwise **4c** [6] (9.0 g, 52 mmoles) at 160° for 5 hours with stirring under nitrogen. After cooling to 60°, carbon tetrachloride (80 ml) was added and insoluble solid was filtered off. The filtrate was washed twice with saturated aqueous sodium carbonate (30 ml), next with water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled to obtain 7.9 g (73%) of **4a**, bp 104-108°/0.25 Torr.

Methyl 3-Chloro-1-methylpyrazole-4-carboxylate **4b**.

To a solution of methyl 3-amino-1-methylpyrazole-4-carboxylate [11] (50 g, 0.32 mole) in 35% hydrochloric acid (500 ml) was added portionwise a solution of sodium nitrite (29 g, 0.42 mole) in water (60 ml) at -5° with stirring, and the mixture was stirred for 1 hour at 0°. The mixture was added portionwise to a suspension of cuprous chloride (50 g, 0.51 mole) in chloroform (400 ml) at 30-40° with vigorous stirring. After additional stirring for 1 hour at room temperature, water (1000 ml) was added. The organic layer was washed twice with water (300 ml), dried over anhydrous sodium sulfate, and removed the solvent. The resultant residue was composed of **4b** as the major component and **4d** as the minor in a ratio 96:4 (by glc method). Chromatography of the residue on silica gel with chloroform gave 47 g (84%) of **4b**, mp 101-102°; ir (potassium bromide): ν cm^{-1} 3147, 2954, 1732, 1549, 1456, 1407, 1236, 1086, 770, 569; ^1H nmr (deuteriochloroform): δ 3.81 (3H, s, NMe), 3.85 (3H, s, OMe), 7.84 (1H, s, CH); ms: m/z 174 (M^+), 143 (M^+-OMe, base peak).

Anal. Calcd. for $C_6H_7ClN_2O_2$: C, 41.28; H, 4.04; N, 16.05. Found: C, 41.20; H, 4.10; N, 16.23.

Methyl 5-Chloro-1-methylpyrazole-4-carboxylate **4c**.

N-Chlorosuccinimide (2.8 g, 21 mmoles) was added portionwise to melting **4d** [6,12] (1.0 g, 7.1 mmoles) at 120° for 3 hours with stirring under nitrogen. After cooling to 60°, carbon tetrachloride (20 ml) was added, and insoluble solid was filtered off. The filtrate was washed twice with saturated aqueous sodium carbonate (10 ml), next with water, and dried over anhydrous sodium sulfate. After removal of the solvent, yellowish oil (1.3 g) was obtained. It was composed of **4c** as the major component and **4a** as the minor in a ratio of 60:40 (by glc method). Preparative glc (OV-17) gave an analytically pure sample of **4c**, mp 71-72° (lit 70-71° [6]); ir (potassium bromide): ν cm^{-1} 1724, 1545, 1236, 1047, 773; ^1H nmr (deuteriochloroform): δ 3.83 (6H, s, NMe, OMe), 7.84 (1H, s, CH); ms: m/z 174 (M^+), 143 (M^+-OMe, base peak).

Anal. Calcd. for $C_6H_7ClN_2O_2$: C, 41.28; H, 4.04; N, 16.05. Found: C, 41.43; H, 4.11; N, 16.31.

Methyl 3-Chloro-1-methyl-5-mercaptopyrazole-4-carboxylate **6a**.

To a solution of **4a** (19 g, 91 mmoles) in *N,N*-dimethylformamide (40 ml) was added portionwise 70% sodium hydrosulfide (18 g, 225 mmoles) at room temperature. After stirring for 0.5 hour at 60°, the mixture was cooled to room temperature, poured into water (350 ml), and insoluble solid was filtered off. The filtrate was acidified with 35% hydrochloric acid (20 ml). The resultant solid was gathered, washed with water, and dried *in vacuo* to obtain 18 g (96%) of **6a**, mp 84-85°; ir (potassium bromide): ν cm^{-1} 1685, 1505, 1385, 1300, 1260, 1070, 890, 765; ^1H nmr (deuteriochloroform): δ 3.74 (3H, s, NMe), 3.88 (3H, s, OMe), 6.64 (1H, s, SH); ms: m/z 206 (M^+), 174 (M^+-S, base peak).

Anal. Calcd. for $C_6H_7ClN_2O_2S$: C, 34.87; H, 3.41; N, 13.56. Found: C, 34.62; H, 3.57; N, 13.66.

Methyl 3-Chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylate **2a**.

Chlorine (27 g, 380 mmoles) was introduced to a suspension of **6a** (20 g, 97 mmoles) in a mixture of acetic acid (100 ml) and water (20 ml) for 3 hours at 5°. The reaction mixture was poured into iced water (350 ml), and extracted with 1,2-dichloroethane (300 ml). The 1,2-dichloroethane solution was washed with 5% aqueous sodium bisulfite (200 ml), next with water. Then, 28% aqueous ammonia (28 ml) was added dropwise to the 1,2-dichloroethane solution at -5°, and the mixture was stirred for 0.5 hour at room temperature. After removal of the solvent, ethyl acetate (200 ml) was added. The solution was washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was washed with diisopropyl ether to obtain 21 g (86%) of **2a**, mp 125-126°; ir (potassium bromide): ν cm^{-1} 3310, 3190, 1700,

1515, 1390, 1370, 1280, 1255, 1180, 1115, 615; ^{1}H nmr (DMSO-d_6): δ 3.83 (3H, s, OMe), 4.05 (3H, s, NMe), 8.10 (2H, br s, NH_2); ms: m/z 253 (M^+), 222 (M^+-OMe, base peak).

Anal. Calcd. for $C_6H_8ClN_3O_4S$: C, 28.41; H, 3.18; N, 16.57. Found: C, 28.39; H, 3.02; N, 16.46.

Methyl 3-Chloro-5-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-1-methylpyrazole-4-carboxylate (halosulfuronmethyl) **1a**.

To a suspension of **2a** (10 g, 39 mmoles) and **7** (12 g, 44 mmoles) in dry acetonitrile (50 ml) was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (5.9 g, 39 mmoles) at room temperature. After stirring for 0.5 hour, water (200 ml) was added, and insoluble solid was filtered. The filtrate was acidified with 35% hydrochloric acid, the resultant solid was washed with water, next with diisopropyl ether, and dried *in vacuo* to obtain 15 g (88%) of **1a**, mp 172-173°; ir (potassium bromide): ν cm^{-1} 3325, 1720, 1700, 1610, 1670, 1490, 1435, 1390, 1360, 1280, 1250, 1220, 1190, 1180, 1115, 625, 600; ^{1}H nmr (DMSO-d_6): δ 3.81 (3H, s, OMe), 3.98 (6H, s, OMe), 4.24 (3H, s, NMe), 5.90 (1H, s, CH), 10.76 (1H, br s, NH), 13.30 (1H, br s, NH); ms: FAB m/z 235 (M^++1).

Anal. Calcd. for $C_{13}H_{15}ClN_6O_7S$: C, 35.91; H, 3.48; N, 19.33. Found: C, 36.20; H, 3.46; N, 19.39.

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