Synthesis of 5-Chloropyrazoles by Chlorodediazoniation with Sulfur Dioxide

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A facile synthesis of 5-chloropyrazoles **4a-e** from 5-aminopyrazoles **2a-e** *via* diazotization followed by chlorodediazoniation is described. A new application of sulfur dioxide as a catalyst was demonstrated to be the best for the chlorodediazoniation of diazonium chlorides **3a-e**.

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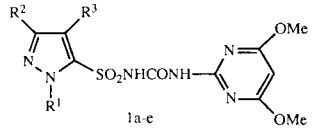
The selective introduction of a chlorine atom into heterocycles has become increasingly important because of its potential in applications for the syntheses of new bioactive molecules. It seems to date that one of the most convenient methods is the chlorination by the Sandmeyer reaction of an amino group on a heterocyclic ring, and in the field of azoles such as pyrazole, imidazole, isothiazole and thiazole, there exists only a few reports. For example, Reimlinger *et al.* reported the formation of 3-chloropyrazole by the Sandmeyer reaction in 32% yield [1]. O'Brien *et al.* also reported the formation of 5-chloro-3-methylisothiazole in 27% yield [2]. In the above reports, chlorodediazoniation as catalyzed with cuprous chloride was investigated, but the yields were unsatisfactory.

In connection with our continuing study on the synthesis of ethyl 5-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-1-methylpyrazole-4-carboxylate **1b** (code No. NC-311, pyrazosulfuron-ethyl), a selective herbicide for paddy rice and its derivatives **1a,c-e** [3], we now wish to report a new method for the synthesis of 5-chloropyrazoles **4a-e** from 5-aminopyrazoles **2a-e** *via* diazotization with sodium nitrite followed by chlorodediazoniation as catalyzed with sulfur dioxide in place of cuprous chloride.

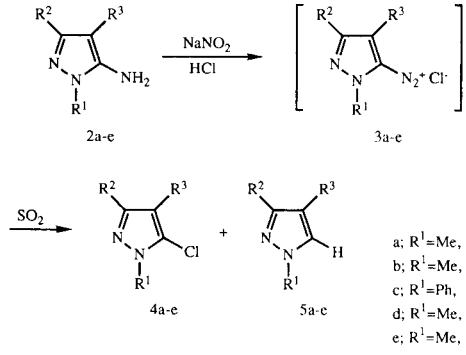


1a; R^1=Me, R^2=H, R^3=CO_2Me
1b; R^1=Me, R^2=H, R^3=CO_2Et
1c; R^1=Ph, R^2=H, R^3=CO_2Et
1d; R^1=Me, R^2=Me, R^3=CO_2Et
1e; R^1=Me, R^2=H, R^3=CN

Figure 1

First, ethyl 5-amino-1-methylpyrazole-4-carboxylate **2b** was chosen as a substrate and diazotized with sodium nitrite in hydrochloric acid. We preliminarily attempted chlorodediazoniation of the diazonium chloride **3b** in the presence of cuprous chloride, and obtained ethyl 5-chloro-1-methylpyrazole-4-carboxylate **4b** in 57% yield together with ethyl 1-methylpyrazole-4-carboxylate **5b** in 20% yield as a by-product (See run 2 in Table 1). Then, various inorganic substances were screened as the catalyst to synthesize **4b** selectively. As a result, we found that sulfur dioxide effectively promoted the chlorodediazoniation of **3b**. That is, chlorodediazoniation of **3b** derived from **2b** (1 equivalent) as catalyzed with sulfur dioxide (0.1 equivalent) in carbon tetrachloride yielded the 5-chloro derivative **4b** in 65% yield as the major product together with **5b** in 6% yield as the minor product (Run 3). The selectivity for **4b** was notably improved by the use of sulfur dioxide. The yield for **4b** was maximized up to 93% by increasing the amount of sulfur dioxide used in the chlorodediazoniation (Run 4). Carbon tetrachloride appears to be the best solvent for the current chlorodediazoniation, when compared with the cases in which toluene and hexane were used in Run 6 and 7. Also, chlorodediazoniation of **3b** smoothly proceeded without solvent and a result nearly equal to that seen in Run 5 was obtained (Run 8). Without a catalyst, this reaction did not occur (Run 1).

Scheme 1



a; R^1=Me, R^2=H, R^3=CO_2Me
b; R^1=Me, R^2=H, R^3=CO_2Et
c; R^1=Ph, R^2=H, R^3=CO_2Et
d; R^1=Me, R^2=Me, R^3=CO_2Et
e; R^1=Me, R^2=H, R^3=CN

Next, we extended this chlorodediazoniation as catalyzed with sulfur dioxide to other substrates **2a,c-e** and the 5-chloro derivatives **4a,c-e** were obtained in good to moderate yields (Table 1), among which the steric hindrance of the phenyl group of **3c** was found to increase the amount of **5c**. Concerning the reaction mechanism, we guess that chlorodediazoniation is caused by electron donation from sulfur dioxide to the diazonium cation in the first reaction step.

In conclusion, this method should be of wide applicability to the selective introduction of a chlorine atom into

various heterocycles, and may provide us with an industrial pathway leading to a variety of chlorinated heterocycles because of the non-use of the environmentally toxic cuprous salts.

Table 1

Preparation of 5-Chloropyrazoles 4a-e by Chlorodediazoniation

Run	Substrate	Catalyst (eq)	Solvent	Product (Yield %)	
1	2b	–	CCl_4	4b (0%)	5b (0%)
2	2b	CuCl (0.7)	–	4b (57%)	5b (20%)
3	2b	SO_2 (0.1)	CCl_4	4b (65%)	5b (6%)
4	2b	SO_2 (0.5)	CCl_4	4b (93%)	5b (4%)
5	2b	SO_2 (1.0)	CCl_4	4b (92%)	5b (4%)
6	2b	SO_2 (0.5)	Ph-Me	4b (86%)	5b (7%)
7	2b	SO_2 (0.5)	n-C_6H_{14}	4b (84%)	5b (7%)
8	2b	SO_2 (1.0)	–	4b (89%)	5b (5%)
9	2a	SO_2 (0.5)	CCl_4	4a (93%)	5a (3%)
10	2c	SO_2 (0.5)	CCl_4	4c (79%)	5c (16%)
11	2d	SO_2 (0.5)	CCl_4	4d (93%)	5d (2%)
12	2e	SO_2 (0.5)	CCl_4	4e (85%)	5e (3%)

EXPERIMENTAL

All melting 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 (ms and hrms) were determined with a JMS-D300/JMA-3500 and a JMS-DX300/JMA-3100 spectrometer, respectively. Elemental analysis were performed on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione).

5-Chloropyrazoles **4a-d**. General Procedure.

Method A: (Runs 3-7, 9-11).

A solution of sodium nitrite (5.5 g, 79.7 mmoles) in water (11 ml) was added dropwise to a solution of 5-aminopyrazoles **2a-d** (59.2 mmoles) in 35% hydrochloric acid (50 ml), while maintaining the temperature below 10°. After stirring for 10 minutes, urea (1.0 g, 16.7 mmoles) was added to the solution to remove excess nitrous acid. Then, the solution was poured portionwise into sulfur dioxide in an appropriate organic solvent (50 ml) below 10° with efficient stirring. After stirring for 1 hour at room temperature, water (100 ml) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with chloroform (25 ml) and the combined organic layers were washed with water (50 ml), dried over sodium sulfate and then concentrated *in vacuo* to give crude products **4a-d** with a small amount of **5a-d**. Yields of **4a-d** and **5a-d** were determined by gc (OV-1) internal standard method. Recrystallization or chromatography on silica gel gave analytically pure samples of **4a-d**.

Method B: (Run 8).

The solution of **3b** obtained by the method A was poured portionwise into liquid sulfur dioxide (3.79 g, 59.2 mmoles) below -10°. The mixture was warmed to room temperature, water added (100 ml) and extracted twice with chloroform (50 ml and 25 ml). The chloroform solution was washed with water (50 ml), dried over sodium sulfate and then concentrated *in vacuo* to give 11.3 g of an oil which contained 9.9 g (89%) of **4b** and 0.5 g (5%) of **5b**.

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

The crude solid **4a** was recrystallized from toluene to yield pure **4a**, mp 70-71°; ir (potassium bromide): ν cm^{-1} 3380, 2940, 1714, 1536, 1405, 1270, 1225, 1116, 1040, 982, 805, 770, 730, 565; ^1H nmr (deuteriochloroform): δ 3.85 (3H, s, CH_3), 3.87 (3H, s, CH_3), 7.91 (1H, s, CH); ms: m/z 174 (M^+), 143 (base peak), 109.

Anal. Calcd. for $C_6H_7ClN_2O_2$: C, 41.28; H, 4.04; N, 16.05. Found: C, 41.33; H, 3.91; N, 16.11.

The filtrate was concentrated and chromatographed on silica gel with hexane-acetone (4:1) to obtain **5a**, mp 63-64°; ir (potassium bromide): ν cm^{-1} 3370, 2940, 1703, 1546, 1425, 1392, 1358, 1294, 1226, 1110, 1006, 870, 760, 695, 598, 508; ^1H nmr (deuteriochloroform): δ 3.82 (3H, s, CH_3), 3.93 (3H, s, CH_3), 7.86 (1H, s, CH), 7.89 (1H, s, CH); ms: m/z 140 (M^+), 109 (base peak).

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.46; H, 5.71; N, 20.17.

Ethyl 5-Chloro-1-methylpyrazole-4-carboxylate **4b**.

The crude oil **4b** was chromatographed on silica gel with hexane-acetone (4:1) to give pure **4b** and **5b**. Compound **4b** had bp 104-107°/3 torr; ir (neat): ν cm^{-1} 3450, 2960, 1710, 1530, 1400, 1270, 1218, 1110, 1040, 978, 833, 770, 720, 638; ^1H nmr (deuteriochloroform): δ 1.36 (3H, t, J = 7.1 Hz, CH_3), 3.87 (3H, s, CH_3), 4.32 (2H, q, J = 7.1 Hz, CH_2), 7.91 (1H, s, CH); ms: m/z 188 (M^+), 160, 143, 126, 109 (base peak); hrms: m/z 188.0348 (M^+, Calcd. for $C_7H_9ClN_2O_2$: 188.0352).

Compound **5b** had bp 89-90°/3 torr; ir (neat): ν cm^{-1} 3450, 3110, 2940, 1705, 1548, 1442, 1400, 1292, 1218, 1114, 1025, 995, 876, 765, 695, 605; ^1H nmr (deuteriochloroform): δ 1.34 (3H, t, J = 7.1 Hz, CH_3), 3.93 (3H, s, CH_3), 4.29 (2H, q, J = 7.1 Hz, CH_2), 7.86 (1H, s, CH), 7.89 (1H, s, CH); ms: m/z 154 (M^+), 126, 109 (base peak); hrms: m/z 154.0702 (M^+, Calcd. for $C_7H_{10}N_2O_2$: 154.0742).

Ethyl 5-Chloro-1-phenylpyrazole-4-carboxylate **4c**.

The crude solid **4c** was recrystallized from hexane-ethanol (4:1) to yield pure **4c**, mp 62-63°; ir (potassium bromide): ν cm^{-1} 3370, 2960, 1700, 1530, 1400, 1248, 1222, 1160, 1060, 958, 768, 692, 554; ^1H nmr (deuteriochloroform): δ 1.39 (3H, t, J = 7.1 Hz, CH_3), 4.37 (2H, q, J = 7.1 Hz, CH_2), 7.48-7.55 (5H, m, Ph), 8.11 (1H, s, CH); ms: m/z 250 (M^+), 222, 205, 109 (base peak).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.75; H, 4.36; N, 11.14.

The filtrate was concentrated and chromatographed on silica gel with hexane-acetone (4:1) to obtain **5c**, mp 99-100°; ir (potassium bromide): ν cm^{-1} 3400, 3100, 2960, 1702, 1552, 1408, 1252, 1148, 1022, 952, 768, 752, 682; ^1H nmr (deuteriochloroform): δ 1.38 (3H, t, J = 7.1 Hz, CH_3), 4.33 (2H, q, J = 7.1 Hz, CH_2), 7.34-7.72 (5H, m, Ph), 8.10 (1H, s, CH), 8.41 (1H, s, CH); ms: m/z 216 (M^+), 171 (base peak), 109.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.65; H, 5.53; N, 13.16.

Ethyl 5-Chloro-1,3-dimethylpyrazole-4-carboxylate **4d**.

The crude solid **4d** was recrystallized from hexane-ethanol (4:1) to yield pure **4d**, mp 38-39°; ir (potassium bromide): ν cm^{-1} 3370, 2970, 1705, 1520, 1478, 1374, 1285, 1248, 1135, 1085, 1028, 850, 778, 635, 582; ^1H nmr (deuteriochloroform): δ 1.36 (3H, t, J = 7.1 Hz, CH_3), 2.43 (3H, s, CH_3), 3.80 (3H, s, CH_3), 4.31 (2H, q, J = 7.1 Hz, CH_2); ms: m/z 202 (M^+), 174, 157 (base peak), 109.

Anal. Calcd. for $C_8H_{11}ClN_2O_2$: C, 47.42; H, 5.47; N, 13.82.

Found: C, 47.52; H, 5.43; N, 13.91.

The gc/ms analysis of the filtrate detected **5d**. Compound **5d** had ms: m/z 168 (M^+), 140, 123 (base peak); hrms: m/z 168.0866 (M^+, Calcd. for $C_8H_{12}N_2O_2$: 168.0898).

5-Chloro-1-methylpyrazole-4-carbonitrile **4e** (Run 12).

A solution of sodium nitrite (5.5 g, 79.7 mmoles) in water (11 ml) was added dropwise to a solution of **2e** (7.22 g, 59.2 mmoles) in 35% hydrochloric acid (50 ml), while maintaining the temperature below 10°. The resulting solution was stirred for an additional 30 minutes and urea (1.0 g, 16.7 mmoles) was added to the solution to remove excess nitrous acid. After stirring for 30 minutes, the solution was poured portionwise into sulfur dioxide (1.89 g, 29.6 mmoles) in carbon tetrachloride (50 ml) below 5°. After stirring for 1 hour at room temperature, a small amount of insoluble solid was filtered off. After separation of the organic layer, the aqueous layer was neutralized with 20% aqueous potassium carbonate and extracted with chloroform (25 ml). The combined organic layers were washed with water (10 ml), dried over sodium sulfate and then concentrated *in vacuo* to give 7.6 g of the crude solid which contained 7.1 g (85%) of **4e** and 0.2 g (3%) of **5e**. Recrystallization of the solid from toluene gave pure **4e**, mp 63-64°; ir (potassium bromide): ν cm^{-1} 3400, 2220, 1520, 1392, 1352, 1190, 982, 860, 742, 660, 586; ^1H nmr (deuteriochloroform): δ 3.90 (3H, s, CH_3), 7.70 (1H, s, CH); ms: m/z 141 (M^+).

Anal. Calcd. for $C_5H_4ClN_3$: C, 42.42; H, 2.85; N, 29.68. Found: C, 42.64; H, 2.75; N, 29.97.

The gc/ms analysis of the filtrate detected **5e**. Compound **5e** had ms: m/z 107 (M^+); hrms: m/z 107.0452 (M^+, Calcd. for $C_5H_5N_3$: 107.0483).

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