Studies on Pyrazines. 7 (1). The Synthesis of 5-Chloropyrazinecarboxylic Acid

Nobuhiro Sato* and Shinji Arai

Department of Chemistry, Yokohama City University,
Seto, Kanazawa-ku, Yokohama 236, Japan

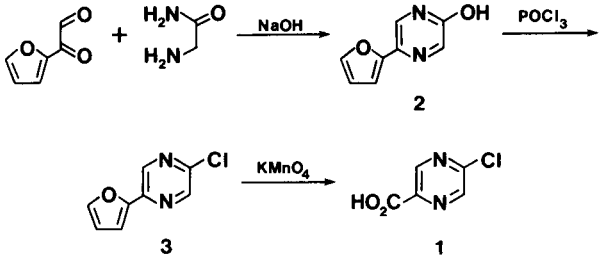
Received July 27, 1981

The titled carboxylic acid (**1**) was prepared by condensation of 2-furylglyoxal with aminoacetamide followed by chlorination of the resulting 2-hydroxy-5-(2'-furyl)pyrazine (**2**) and permanganate oxidation. The acid was further converted into methyl ester and 5-hydroxypyrazinecarboxylic acid.

J. Heterocyclic Chem., **19**, 407 (1982).

The earlier synthetic route to 5-chloropyrazinecarboxylic esters involves nitrosation-hydrolysis and esterification of 5-aminopyrazinecarboxylic acid followed by chlorination of the resulting 5-hydroxypyrazinecarboxylic esters with phosphoryl chloride (2,3). The aminocarboxylic acid has been prepared by a four-step sequence of reactions starting from 2,5-prazinedicarboxylic acid (4) or 2-aminoquinoxaline (5). We found a more direct synthetic method for the preparation of the parent 5-chloropyrazinecarboxylic acid (**1**) (6) (see Scheme I). This synthetic conception is based on the earlier observations that the condensation of phenylglyoxal with aminoacetamide affords almost exclusively 2-hydroxy-5-phenylpyrazine in two possible structural isomers (7-9), and that the permanganate oxidation of 2-substituted furan undergoes cleavage of the furan ring to produce the corresponding carboxylic acid (10).

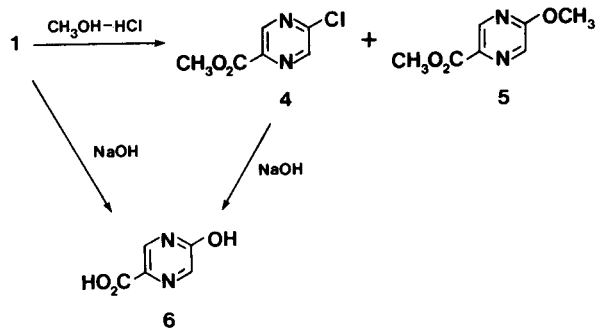
Scheme I



The condensation of 2-furylglyoxal and aminoacetamide with sodium hydroxide gave regiospecifically the expected 2-hydroxy-5-(2'-furyl)pyrazine (**2**) in 28% yield. The structure of **2** was conveniently confirmed by ^{1}H-nmr spectrum showing the characteristic coupling constant (1.2 Hz) of the 3,6 ring protons (11). Chlorination of hydroxypyrazine 2 was accomplished by refluxing in phosphoryl chloride for 3 hours to form chloropyrazine **3** in 52% yield. The prolonged heating and higher temperatures decreased the yield of **3**, *e.g.*, reaction conditions at 170° for 20 hours resulted in decomposition of **3** giving no desired product. Premanganate oxidation of **3** proceeded effectively in the presence of phase-transfer catalyst to give **1** in 76% yield.

The chloropyrazinecarboxylic acid **1** was further converted into the methyl ester **4** in 62% yield by refluxing in methanolic hydrogen chloride for 1 hour. The crude material was contaminated with a small amount of 5-methoxypyrazinecarboxylic methyl ester (**5**), the yield of which was increased by prolonged heating. Similar methoxylation of chloro substituent emerged in the esterification of 6-chloropyrazinecarboxylic acid with the same reagent (2).

Scheme II



An attempted conversion of **2** into 5-hydroxypyrazinecarboxylic acid (**6**) by permanganate oxidation failed although the potassium permanganate used was completely consumed, resulting in the formation of unidentified material. The hydroxycarboxylic acid **6**, however, was quantitatively obtained by refluxing **1** in 0.5*N* sodium hydroxide for 1 hour. Similarly, the methyl ester **4** underwent hydrolysis of the chloro substituent as well as the ester function to produce **6**.

EXPERIMENTAL

All melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded on a Hitachi EPI-G3 spectrometer, and nmr spectra on a JOEL JNM-MH-100 instrument with tetramethylsilane as an internal standard.

2-Hydroxy-5-(2'-furyl)pyrazine (**2**).

A solution of 2-furylglyoxal hydrate (17.0 g, 0.12 mole) in 100 ml of methanol was added at a temperature below -30° to a stirred suspension of aminoacetamide hydrochloride (11.05 g, 0.10 mole) in 100 ml of methanol and 20 ml of water. To the mixture was added 12.5*N* sodium hydroxide (20 ml, 0.25 mole) at a temperature below -30° over a period of 5 minutes. The resulting solution was allowed to stand for 3 hours when the temperature raised to 10°. The solution was recooled to -10° and acidified at *p*H 3 with concentrated hydrochloric acid. The precipitated product was collected by filtration and air-dried to give 9.0 g of solid,

which was recrystallized from ethanol affording 4.54 g (28%) of **1** as yellow needles, mp 215° dec; ir (potassium bromide): 3000-2600 (broad), 1650, 1568, 1239, 1012 cm^{-1}; nmr (DMSO-d_6): δ 6.67 (dd, H-4', 1H, $J_{3',4'}$ = 3.4, $J_{4',5'}$ = 1.8 Hz), 6.76 (dd, H-3', 1H, $J_{3',5'}$ = 0.8 Hz), 7.71 (dd, H-5', 1H), 7.79 (d, H-3, 1H, $J_{3,6}$ = 1.2 Hz), 8.07 (d, H-6, 1H).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.37; N, 17.28. Found: C, 58.94; H, 3.62; N, 17.12.

2-Chloro-5-(2'-furyl)pyrazine (**3**).

A solution of **2** (5.02 g, 0.031 mole) in freshly distilled phosphoryl chloride (50 ml) was gently refluxed and stirred for 3 hours. Excess phosphoryl chloride was removed *in vacuo*, and the residue was worked up with ice-water. The mixture was basified with 20% aqueous sodium hydroxide at *p*H 9-10 and extracted with chloroform (4 × 80 ml). The extracts were washed with water, dried over magnesium sulfate and evaporated to give 3.70 g (66%) of crystalline product. Sublimation at 100° (0.1 mm) gave 2.91 g (52%) of **3**, mp 107-108°. Recrystallization from hexane gave colorless prisms, mp 107-108°; ir: (potassium bromide): 1609, 1497, 1303, 1138, 1028, 916, 758 cm^{-1}; nmr (deuteriochloroform): δ 6.54 (dd, H-4', 1H, $J_{3',4'}$ = 3.5, $J_{4',5'}$ = 1.8 Hz), 7.11 (dd, H-3', 1H, $J_{3',5'}$ = 0.9 Hz), 7.56 (dd, H-5', 1H), 8.50 (d, H-6, 1H, $J_{3,6}$ = 1.4 Hz), 8.80 (d, H-3, 1H).

Anal. Calcd. for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; N, 15.52; Cl, 19.63. Found: C, 53.09; H, 2.75; N, 15.31; Cl, 19.48.

5-Chloropyrazinecarboxylic Acid (**1**).

Chloropyrazine **3** (4.184 g, 0.023 mole) was added in small portions at temperature 15-20° (12) to a mixture of potassium permanganate (19.53 g, 0.124 mole) and tricaprylmethylammonium chloride (0.71 g, 1.8 mmoles) in 18 ml of water and 35 ml of benzene. The mixture was stirred at that temperature for 4.5 hours. Manganese dioxide which formed was removed by filtration and washed with water. The filtrate was washed with ether and the aqueous layer was treated with 95 ml of Amberlite 120B (hydrogen form). The resulting solution was evaporated to dryness *in vacuo* and the residue was sublimed at 120° (0.1 mm) to give 2.793 g (76%) of **1**, mp 152-153° dec. An analytical sample was obtained by recrystallization from water as colorless tiny needles, mp 153° dec; ir (potassium bromide): 3150-2500 (broad), 1730, 1620, 1390, 1252, 1200, 1138, 891, 639 cm^{-1}; nmr (DMSO-d_6): δ 8.94 and 9.04 (two doublets, H-3 and H-6, 1H + 1H, $J_{3,6}$ = 1.2 Hz).

Anal. Calcd. for $C_5H_3ClN_2O_2$: C, 37.87; H, 1.91; N, 17.67; Cl, 22.36. Found: C, 37.88; H, 1.90; N, 17.69; Cl, 22.34.

Methyl 5-Chloropyrazinecarboxylate (**4**).

A mixture of **1** (2.734 g, 0.0172 mole) in 50 ml of 10% methanolic hydrogen chloride was stirred under reflux for 1 hour. The resulting clear solution was evaporated to dryness *in vacuo*. The residue was basified with 5% aqueous sodium carbonate and the mixture was extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with water and dried over anhydrous sodium carbonate. Evaporation and sublimation at 100° (0.1 mm) gave 2.263 g of crude product, which was revealed by ^{1}H-nmr spectrum to be a mixture of **4** and methyl 5-methoxypyrazinecarboxylate (**5**) in ratio of about 8:1. Recrystallization from hexane gave 1.830 g (62%) of pure chloropyrazine **4** as colorless needles, mp 93-94° [literature (2) mp 90.5-91.5°]; ir (potassium bromide): 1727, 1438, 1343, 1290, 1153, 1026 cm^{-1}; nmr (deuteriochloroform): δ 4.04 (s, CH_3, 3H), 8.72 and 9.10 (two doublets, H-3 and H-6, 1H + 1H, $J_{3,6}$ = 1.2 Hz).

Anal. Calcd. for $C_6H_5ClN_2O_2$: C, 41.76; H, 2.92; N, 16.24; Cl, 20.55. Found: C, 41.71; H, 2.88; N, 16.22; Cl, 20.58.

This compound was identified by comparison with ir and nmr spectra of the authentic sample (2) which was derived from 5-aminopyrazinecarboxylic acid (13).

The crude product which was obtained above (0.172 g) was treated with sodium methoxide (1.2 mmoles) in 5 ml of methanol by refluxing for 5 minutes was evaporated to dryness *in vacuo* and the residue was extracted with chloroform (2 × 10 ml). The extract was dried over magnesium sulfate and evaporated to give 0.139 g (78%) of **5**, 98-100°. Sublimation at 80° (0.1 mm) and recrystallization from hexane gave colorless tiny needles, mp 100-102°; ir: (potassium bromide): 1727, 1585, 1550, 1448, 1325, 1286, 1206, 1148, 1029, 804 cm^{-1}; nmr (deuteriochloroform): δ 4.00 (s, CH_3O, 3H), 4.05 (s, $CH_3OC=O$, 3H), 4.05 (d, H-6, 1H, $J_{3,6}$ = 1.2 Hz), 8.93 (d, H-3, 1H).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.91; H, 4.74; N, 16.56.

5-Hydoxypyrazinecarboxylic Acid (**6**).

A mixture of **1** (0.159 g, 1.0 mmole) in 10 ml of 0.5*N* sodium hydroxide (5.0 mmoles) was stirred under reflux for 1 hour. After cooling to room temperature, the solution was treated with 6 ml of Amberlite 120B (hydrogen form) and evaporated to dryness *in vacuo* giving 0.158 g (100%) of **6** as the monohydrate, which was recrystallized from water to give pale yellow crystals. Analytical sample was obtained by drying at 100° (0.1 mm) for 5 hours, mp 270° dec (unclear) [literature (5) mp > 300°]; ir: (potassium bromide): 3150-2500 (broad), 1730, 1620, 1390, 1252, 1200, 1138, 891, 639 cm^{-1}; nmr (DMSO-d_6): δ 8.00 and 8.08 (two doublets, H-3 and H-6, 1H + 1H, $J_{3,6}$ = 1.2 Hz), 12.7 (broad s, OH and CO_2H, 2H).

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.86; H, 2.88; N, 20.00. Found: C, 42.57; H, 2.84; N, 19.88.

Acknowledgment.

The authors wish to thank Drs. J. Adachi and T. Nakagawa for their helpful suggestions.

REFERENCES AND NOTES

(1) Part 6: N. Sato, *J. Heterocyclic Chem.*, **17**, 143 (1980).

(2) S. Okada, A. Kosasayama, T. Konno and F. Uchimaru, *Chem. Pharm. Bull.*, **19**, 1344 (1971).

(3) G. Palamidessi, A. Vigevani and F. Zarini, *J. Heterocyclic Chem.*, **11**, 607 (1974).

(4) W. J. Schut, H. I. X. Mager and W. Berends, *Rec. Trav. Chim.*, **82**, 282 (1963).

(5) E. Felder, D. Pitrè and E. B. Grabitz, *Helv. Chim. Acta*, **47**, 873 (1964).

(6) The synthesis of this compound by reaction of pyrazinecarboxylic acid 4-oxide with thionyl chloride was reported [L. Novacek, M. Celadnik, K. Palat and M. Holik, *Collect. Czech. Chem. Commun.*, **37**, 862 (1972); *Chem. Abstr.*, **76**, 153712 (1972)] but that compound was shown to be isomeric 6-chloropyrazinecarboxylic acid by other groups [ref 3 and F. Uchimaru, S. Okada, A. Kosasayama and T. Konno, *Chem. Pharm. Bull.*, **19**, 1337 (1971)].

(7) S. Sugiura, S. Inoue, Y. Kishi and T. Goto, *Yakugaku Zasshi*, **89**, 1646 (1969); *Chem Abstr.*, **72**, 90404 (1970).

(8) P. J. Lond and H. C. van der Plas, *Rec. Trav. Chim.*, **92**, 449 (1973).

(9) N. Sato, *J. Heterocyclic Chem.*, **15**, 665 (1978).

(10) C. A. Buehler and D. E. Pearson, "Survey of Organic Syntheses", Wiley-Interscience, New York, N.Y., 1970. p 770.

(11) G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocyclic Chem.*, **14**, 99 (1972).

(12) Higher temperatures decreased the yield of **1**.

(13) This compound was prepared by the procedure of Felder *et al.* (5) but decarboxylation of 5-amino-2,3-pyrazinedicarboxylic acid was achieved by refluxing in dimethylformamide for 1 hour (77% yield).