Syntheses and Reactions of Some 4,5-Dihaloimidazole-2-carboxylic Acid Derivatives

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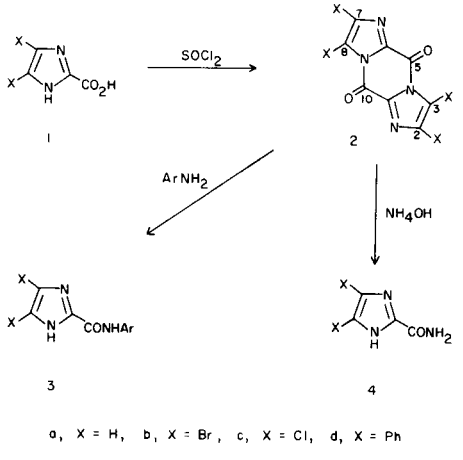
The preparation of 5*H*,10*H*-diimidazo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (**2a**) and its 2,3,7,8-tetrabromo- and 2,3,7,8-tetrachloro- analogs (**2b** and **2c**, respectively) is reported. These dimers, when allowed to react with various anilines, afford imidazole-2-carboxamides (**3a-c**).

J. Heterocyclic Chem., **17**, 409 (1980).

We sought to prepare *N*-substituted 4,5-dibromo- and 4,5-dichloroimidazole-2-carboxamides (**3b-c**). Although *N*-phenyl-4,5-diphenylimidazole-2-carboxamide (**3d**, Ar = Ph) had previously been synthesized from 2,3,7,8-tetraphenyl-5*H*,10*H*-diimidazo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (**2d**) (1), the parent structure (**3a**) (2) and the corresponding 4,5-dihalo-substituted derivatives (**3b-c**) were unknown at the time of this study. We now report the preparation of 5*H*,10*H*-diimidazo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (**2a**) (3) and its 2,3,7,8-tetrabromo- and 2,3,7,8-tetrachloro- analogs (**2b** and **2c**, respectively), which when allowed to react with anilines afford the desired imidazole-2-carboxamides (**3a-c**, Scheme I) (4).

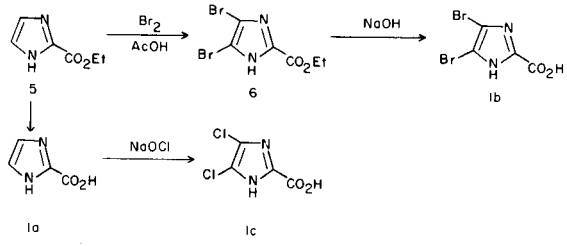
Scheme I



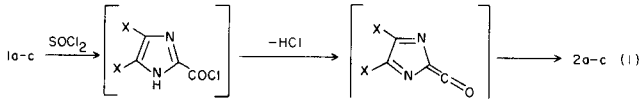
a, X = H, b, X = Br, c, X = Cl, d, X = Ph

The precursor imidazole-2-carboxylic acids (**1a-c**) were obtained from ethyl imidazole-2-carboxylate (**5**) (5) as outlined in Scheme II. Compound **5** was brominated using bromine-acetic acid to afford **6**, which on base hydrolysis gave 4,5-dibromoimidazole-2-carboxylic acid (**1b**). Imidazole-2-carboxylic acid (**1a**) was prepared by treatment of **5** with a 1 N sodium hydroxide solution (6). Chlorination of **1a** with sodium hypochlorite solution (7) afforded 4,5-dichloroimidazole-2-carboxylic acid (**1c**) in 52% yield.

Scheme II



As illustrated in Scheme I, the above imidazole-2-carboxylic acids (**1a-c**) were allowed to react with thionyl chloride and the resulting dimers (**2a-c**) were obtained in good yield. A plausible mechanism involves the intermediacy of a ketenelike species as in equation 1, followed by dimerization (8,9). Treatment of the dimers (**2a-c**) with two molar equivalents of various anilines in pyridine



X = H, Br, Cl

solvent at room temperature gave rise to the *N*-substituted imidazole-2-carboxamides shown in Table I (**3e-l**), with the exception of compound **3i**. The latter 4,5-dibromo analog was prepared by bromination of the parent imidazole-2-carboxamide **3f**. However, no suitable methods for 4,5-dichlorination could be found in analogous cases (10). When the dimer **2a** was allowed to react with ammonium hydroxide, the known imidazole-2-carboxamide **4a** was isolated in 86% yield (11).

EXPERIMENTAL (12)

Imidazole-2-carboxylic Acid (**1a**).

A mixture of 4.00 g. (0.029 mole) of ethyl imidazole-2-carboxylate (5) (**5**) and 40 ml. of 1*N* aqueous sodium hydroxide solution was heated under reflux for 4 hours, and the resulting solution was then chilled and made acidic (*p*H 1.5) with dilute hydrochloric acid. The product precipitated and was collected by suction filtration to afford 2.00 g. (64%) of **1a**, m.p.

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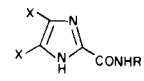
Table I

N-Substituted Imidazole-2-carboxamides (**3e-l**)



Compound No.	X	R	Yield, %	m.p. °C	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3e	H	Ph	74	215-217 (a)	$C_{10}H_9N_3O$						
3f	H	4-BrC_6H_4	75	261-262	$C_{10}H_8BrN_3O$	45.33	3.04	15.86	44.88	3.06	15.70
3g	H	3,4-$Cl_2C_6H_3$	34	233-234	$C_{10}H_7Cl_2N_3O$	46.92	2.76	16.41	46.88	3.14	16.22
3h	Br	Ph	76	252-254	$C_{10}H_7Br_2N_3O$	34.78	2.03	12.17	34.92	2.07	12.39
3i	Br	4-BrC_6H_4	89 (b)	268-269	$C_{10}H_6Br_3N_3O$	28.33	1.43	9.91	27.99	1.38	9.47
3j	Cl	4-ClC_6H_4	98	265-266	$C_{10}H_6Cl_2N_3O$	41.42	2.09	14.49	41.49	2.22	14.37
3k	Cl	3-$CF_3C_6H_4$	70	198-199	$C_{11}H_6Cl_2F_3N_3O$	40.78	1.86	12.97	40.76	2.24	12.75
3l	Cl	3-AcC_6H_4	65	272-273	$C_{12}H_9Cl_2N_3O_2$	48.37	3.06	14.10	48.43	3.07	14.10

(a) Lit. m.p. 218-219° (Reference 2). (b) Compound was obtained by bromination of **3f**.

169-170° dec (lit. (6) m.p. 163-164° dec.); ir (potassium bromide): 1640 cm^{-1} (C=O); ms: m/e 112 (M^+).

4,5-Dibromoimidazole-2-carboxylic Acid (**1b**).

Hydrolysis of ethyl 4,5-dibromoimidazole-2-carboxylate (**6**, 2.00 g., 6.71 mmoles) in the same manner as described for **1a** gave 1.66 g. (92%) of **1b**, m.p. 171-173° dec.; ir (potassium bromide): 1650 cm^{-1}; ms: m/e 272, 270, 268 (M^+).

Anal. Calcd. for $C_4H_2Br_2N_2O_2$: C, 17.79; H, 0.75; N, 10.38. Found: C, 17.62; H, 1.00; H, 9.93.

4,5-Dichloroimidazole-2-carboxylic Acid (**1c**).

To a solution of sodium hydroxide (4.30 g., 0.107 mole) in 300 ml. of sodium hypochlorite (5.25%, 0.214 mole) was added 12.0 g. (0.107 mole) of imidazole-2-carboxylic acid (**1a**) in one portion at room temperature (7). The reaction was exothermic and the temperature rose to 50°. After the reaction mixture returned to room temperature, it was cooled and acidified to *p*H 1.0 with concentrated hydrochloric acid. The resulting solid was collected by suction filtration and was added to water (500 ml.). Concentrated hydrochloric acid was then added dropwise to the slurry until all the solid went into solution. The aqueous solution was extracted with ethyl acetate and the combined extracts were dried and evaporated to afford a light yellow solid, which was washed with hexane (100 ml.) to give 10.0 g. (52%) of **1c**; m.p. 159-160° dec.; ms: m/e 184, 182, 180 (M^+).

Anal. Calcd. for $C_4H_2Cl_2N_2O_2$: C, 26.54; H, 1.11; N, 15.48. Found: C, 26.30; H, 1.32; N, 15.53.

General Procedure for Compounds **2a-c**.

The imidazole-2-carboxylic acids (**1a-c**; 35 mmoles) and 35 ml. of thionyl chloride were heated under reflux for 2 hours. The reaction mixture was cooled and poured onto 125 ml. of benzene. The resulting precipitate was collected by suction filtration and washed with ether.

A. 5*H*,10*H*-Diimidazo[1,2-*a*:1′-2′-*d*]pyrazine-5,10-dione (**2a**).

This compound was obtained as a white dihydrochloride salt in 70% yield, m.p. 169-170°C dec.; ir (potassium bromide): 1755 cm^{-1} (C=O); nmr (DMSO-d_6): δ 7.34 (s); ms: m/e 188 (M^+), 94.

Anal. Calcd. for $C_8H_4N_4O_2 \cdot 2HCl$: C, 36.96; H, 2.33; N, 21.55. Found: C, 36.52; H, 2.82; N, 21.62.

B. 2,3,7,8-Tetrabromo-5*H*,10*H*-diimidazo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (**2b**).

This compound was obtained as a yellow dihydrochloride salt in 72% yield, m.p. 330-331°C dec.; ir (potassium bromide): 1755 cm^{-1} (C=O); ms: m/e 508, 506, 504, 502, 500 (M^+), 254, 252, 250.

Anal. Calcd. for $C_8Br_4N_4O_2 \cdot 2HCl$: C, 16.63; H, 0.34; N, 9.70. Found: C, 16.64; H, 0.24; N, 9.63.

C. 2,3,7,8-Tetrachloro-5*H*,10*H*-diimidazo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (**2c**).

This compound was isolated as a bright yellow solid in 68% yield, m.p. 310° dec., ir (potassium bromide): 1750 cm^{-1} (C=O); ms: m/e 332, 330, 328, 326, 324 (M^+), 166, 164, 162.

Anal. Calcd. for $C_8Cl_4N_4O_2$: C, 29.48; H, 0.00; N, 17.19. Found: C, 29.31; H, 0.25; N, 17.40.

General Procedure for Compounds **3e-h,j-l** (Table I).

A solution of 3 mmoles of **2a**, **2b** or **2c**, and 6 mmoles of the appropriate aniline in 10 ml. of pyridine was allowed to stir at room temperature for 4-18 hours. The reaction mixture was then poured into water and the resulting precipitate was collected by suction filtration. The solid was washed with water until the washings became colorless, and the product was then washed with a small amount of ethanol. Compounds **3j** and **3k** were recrystallized from ethanol-water. Nmr, ir and ms data were consistent with the structures shown in Table I.

N-(4-Bromophenyl)-4,5-dibromoimidazole-2-carboxamide (**3i**).

To a solution of **3f** (0.50 g., 1.8 mmoles) in acetic acid (10 ml.) was added dropwise bromine (0.57 g., 3.6 mmoles) in acetic acid (10 ml.). After 1 hour, the reaction mixture was poured into water and the resulting solid was collected by suction filtration to afford 0.68 g. (89%) of **3i**, m.p. 268-269°; ms: m/e 427, 425, 423, 421 (M^+) (see Table I for additional characterization data).

Imidazole-2-carboxamide (**4a**).

To a solution of ammonium hydroxide (50 ml.) at 10° was added 1.0 g. (3.8 mmoles) of 5*H*,10*H*-diimidazo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione dihydrochloride (**2a**) portionwise. The temperature was maintained at 10° for 1 hour and then allowed to come to room temperature. The precipitate was filtered and washed with water. After drying in a vacuum oven at 40° overnight 0.73 g. (86%) of **4a** was obtained: m.p. 312-313° dec. (lit. (11) m.p. 290° dec.); ms: m/e 111 (M^+).

Ethyl 4,5-Dibromoimidazole-2-carboxylate (**6**).

To a solution of ethyl imidazole-2-carboxylate (5) (**5**, 5.00 g., 35 mmoles) in acetic acid (25 ml.) was added dropwise bromine (12.4 g., 77

mmoles). The reaction mixture was slightly exothermic during the addition period (30 minutes). After 2 hours, the mixture was poured into water and the resulting solid was collected by suction filtration to afford 6.66 g. (63%) of **6**, m.p. 154-156°; ir (potassium bromide): 1740 cm^{-1}; nmr (deuteriochloroform): δ 1.40 (3H, t), 4.40 (2H, q), 12.3 (NH, bs); ms: m/e 300, 298, 296 (M^+).

Anal. Calcd. for $C_6H_6Br_2N_2O_2$: C, 24.18; H, 2.03; N, 9.40. Found: C, 24.45; H, 2.07; N, 9.44.

REFERENCES AND NOTES

(1) R. Gompper, E. Hoyer, and H. Herlinger, *Chem. Ber.*, **92**, 550 (1959).

(2) Recently some *N*-substituted imidazole-2-carboxamides have been prepared in good yield from imidazole and isocyanate derivatives under reflux in a high boiling solvent: E. P. Papadopoulos, *J. Org. Chem.*, **42**, 3925 (1977). However, we obtained a complex mixture of products when we attempted this reaction with 4,5-dichloroimidazole.

(3) The closely related isomer of **2a**, *i.e.*, 5*H*,10*H*-diimidazo[1,5-*a*:1′,5′-*d*]pyrazine-5,10-dione, which is derived from imidazole-4-carboxylic acid, has been reported: (a)R. Buchman, P. F. Heinstein, and J. N. Wells, *J. Med. Chem.*, **17**, 1168 (1974); (b) K. Takahashi, N. Iguma, N. Kato, and K. Mitsuhashi, *J. Chem. Soc. Japan., Chem. Ind. Chem.*, 2244 (1975); (c) S. Kasina and J. Nematollahi, *Synthesis*, 162 (1975).

(4) After the completion of this study, a several-step synthesis of **2c** was reported starting from 2-methylimidazole, and numerous 4,5-dichloroimidazole-2-carboxanilides were synthesized from **2c**: G. Beck, K. Sasse, H. Heitzer, H. Eue, R. Schmidt, and H. Scheinpflug, German Offen., 2,610,527 (1977); *Chem. Abstr.*, **88**, P6886g (1978).

(5) Compound **5** was conveniently prepared from readily available starting materials in 35% yield by acid-promoted cyclization-ethanolysis of *N*-(2,2-diethoxyethyl)-2,2,2-trichloroacetamidine: G. Berkelhammer, W. H. Gastrock, W. A. Remers, and A. S. Tomcufcik, U. S. Patent 3,600,399 (1971).

(6) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).

(7) A. W. Lutz and S. DeLorenzo, *J. Heterocyclic Chem.*, **4**, 399 (1967).

(8) Alternatively, **2a-c** could arise from dimerization of the acid chlorides and subsequent intramolecular ring closure (reference 3a). In studies of closely related pyrrolecarboxylic acids, the pyrrole-2-carbonyl chlorides were isolated, and dimerization occurred when these were treated with triethylamine. Presumably the imidazole moiety is sufficiently basic to catalyze the loss of hydrogen chloride from the imidazole-2-carbonyl chlorides in the present examples: (a) D. M. Bailey, R. E. Johnson, and U. J. Salvador, *J. Med. Chem.*, **16**, 1298 (1973); (b) R. J. Boatman and H. W. Whitlock, *J. Org. Chem.*, **41**, 3050 (1976).

(9) A dimer from benzimidazole-2-carboxylic acid was obtained following treatment with thionyl chloride: R. A. B. Copeland and A. R. Day, *J. Am. Chem. Soc.*, **65**, 1072 (1943).

(10) Attempts were made to chlorinate the 4,5-positions of the imidazole ring of various *N*-phenyl-substituted imidazole-2-carboxamides with *N*-chlorosuccinimide, chlorine-acetic acid, or sodium hypochlorite solution, but were unsuccessful.

(11) P. J. Lont, H. C. van der Plas, and A. Koudijs, *Rec. Trav. Chim.*, **90**, 207 (1971).

(12) Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus or a Mel-Temp capillary hot stage apparatus (for compounds melting >250°C). Nmr spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as an internal standard. Ir spectra were determined with a Perkin-Elmer Model 21 spectrophotometer; and mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. All evaporations were conducted in vacuo using either a water aspirator or a vacuum pump.